International Society of Heterocyclic Chemistry
ISHC

Book of Abstracts

27th International Society of Heterocyclic Chemistry Congress

September 1 [Sun] - 6 [Fri], 2019

ROHM Theatre Kyoto
& Miyakomesse
KYOTO, JAPAN

京都

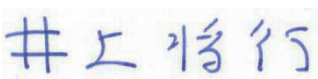
CONTENTS

A Message from the President of the International Society of Heterocyclic Chemistry (ISHC)

On behalf of ISHC, it is my pleasure to welcome all of you to the 27th International Society of Heterocyclic Chemistry (ISHC) Congress in Kyoto. This biennial symposium assembles national and international researchers to learn, discuss, and connect around our common interests. We are excited that you are here to share new advances in various facets of heterocyclic chemistry.

During this meeting, we will celebrate the achievements of outstanding scientists. I look forward to recognizing this year's recipient of our highest honor, E. C. Taylor Senior Award, Prof. Dale L. Boger (Scripps Research Institute). I also congratulate the recipients of Katritzky Junior Award, Prof. Richmond Sarpong (U. C. Berkeley), and ISHC Industrial Award, Dr. Guy Humphrey (Merck, Sharp & Dohme).

Our chairpersons Professors Shuji Akai and Yasuyuki Kita organized an outstanding program covering a breadth of exciting topics. I thank them for their tremendous dedication for chairing the symposium. The symposium could not also take place without considerable efforts of our executive committee members, Prof. Oliver Reiser (University of Regensburg), Prof. David Williams (Indiana University), and Prof. Fredrick Luzzio (University of Louisville), and Prof. Alan Aitken (University of St Andrews). I look forward to a stimulating week and hope everyone enjoys the symposium in Kyoto.



Masayuki Inoue, President

A Welcome Message from Chairpersons

Dear Participants,

It gives us great pleasure to welcome participants from all over the world to the 27th International Society of Heterocyclic Chemistry (ISHC) Congress in Kyoto.

Chemistry has always faced challenges and posed challenges. Many traditional fields of chemistry have evolved and mutated or have expanded and absorbed other fields, even from other traditional scientific disciplines. The Heterocyclic Chemistry has been not only one major branch of organic chemistry but also a foundation of a variety of sciences that has been able to adapt to the intellectual challenges of the sciences and also to provide solutions to the issues of current society throughout the world.

Under the theme of "Heterocycles for the Future", the 27th ISHC Congress is expected to have exciting discussions on the following three topics: 1) Heterocycles for Future Organic Chemistry, 2) Heterocycles for Future Life Sciences, and 3) Heterocycles for Future Material Sciences. The participants will witness the presentations filled with exciting new results at the forefront of different areas of Heterocyclic Chemistry and will enrich environment leading to rapid future development of a wide variety of sciences.

We wish you a very pleasant and memorable stay in Kyoto, a historical and beautiful city.

Shuji Akai, Chairperson

Yasuyuki Kita, Honorable Chairperson

History of
The International Society of Heterocyclic Chemistry

The first congress was held in Albuquerque, New Mexico, USA in 1967, and the President of the Congress was Raymond Castle. He also founded the "International Society of Heterocyclic Chemistry (ISHC)" next year.

ISHC Presidents:

1973–75 Raymond Castle (founder), Albuquerque, USA
1976–77 Edward Elslager, Warner–Lambert Parke–Davis Pharmaceuticals, USA
1978–79 Miha Tisler, University of Ljubljana, Slovenia
1980–81 Leroy Townsend, University of Michigan, USA
1982–83 Wolfgang Pfleiderer, University of Konstanz, Germany
1984–85 Stewart Schneller, University of South Florida, USA
1986–87 Henk van der Plas, University of Wageningen, Netherlands
1988–89 Yoshio Ban, Hokkaido University, Japan
1990–91 Victor Snieckus, University of Waterloo, Canada
1992–93 Jan Bergman, The Royal Institute of Technology, Sweden
1994–95 Albert Padwa, Emory University, USA
1996–97 Hal Moore, UC Irvine, USA
1998–99 Christopher Moody, University of Exeter, UK
2000–01 Yoshi Yamamoto, Tohoku University, Japan
2002–03 Steven Weinreb, Penn State, USA
2004–05 *Marco Ciufolini, University of British Columbia, Canada
2006–07 Margaret Brimble, University of Auckland, NZ
2008–09 Jeffrey Aube, Kansas University, USA
2010–11 Richard Taylor, University of York, UK
2012–13 Dawei Ma, Shanghai Institute of Organic Chemistry, China
2014–15 Daniel Comins, NCSU, Raleigh NC, USA
2016–17 Oliver Reiser, University of Regensburg, Germany
2018–19 Masayuki Inoue, The University of Tokyo, Japan

*Note: 2003, Alessandro Dondoni, University of Ferrara, Italy, was elected President–Elect but could not serve his term as President due to health problems.

ISHC Secretaries:

1973–1979 M. Malm
1980–1981 G. Cheeseman
1982–1989 Thomas Kappe
1990–2004 Hans Neunhoeffer
2005–2009 Johannes Froelich
2012–2015 Michael Kerr
2016– David Williams

ISHC Treasurers:

1973–1977 Leroy Townsend
1977–1979 Kevin Potts
1980–1989 Ludwig Bauer
1990–2011 Stan Lang
2012– Fred Luzzio

ISHC Publicity Chairs:

1994–1995 Willem Verboom
1996–1999 David StC Black
2000–2001 Dennis Liotta
2002–2009 C. Oliver Kappe
2010–2017 Tom Pettus
2018– R. Alan Aitken

ISHC Senior Fellows:

1995 Raymond Castle
1995 Alan Katritzky
1997 Thomas Kappe
2001 Henkvander Plas
2001 Charles W. Rees
2003 Albert Padwa
2005 Hans Neunhoeffer
2007 Victor Snieckus
2015 Margaret Brimble
2015 Yasuyuki Kita

ISHC Congresses:

1967 Albuquerque, NM, USA
1969 Montpellier, France
1971 Sendai, Japan
1973 Salt Lake City, UT, USA
1975 Ljubljana, Yugoslavia
1977 Tehran, Iran
1979 Tampa, FL, USA
1981 Graz, Austria
1983 Tokyo, Japan
1985 Waterloo, Ont, Canada
1987 Heidelberg, Germany
1989 Jerusalem, Israel
1991 Corvallis, OR, USA
1993 Antwerp, Belgium
1995 Taipei, Taiwan
1997 Bozeman, MT,USA
1999 Vienna, Austria
2001 Yokohama, Japan
2003 Fort Collins, CO, USA
2005 Palermo, Italy
2007 Sydney, Australia
2009 St. John's, Canada
2011 Glasgow, UK
2013 Shanghai, China
2015 Santa Barbara, CA, USA
2017 Regensburg, Germany
2019 Kyoto, Japan

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1967– Raymond Castle
1969– R. Jacquier and N. Cromwell
1971– Tetsuji Kametani
1973– Leroy Townsend
1975– Miha Tisler
1977– Iraj Lalezari
1979– Stewart Schneller
1981– Thomas Kappe
1983– Tetsuji Kametani and Yoshio Ban
1985– Victor Snieckus
1987– Richard Neidlein
1989– Alfred Hassner
1991– James D. White
1993– Frank Alderweireldt
1995– C. K. Sha
1997– Tom Livinghouse
1999– Fritz Sauter
2001– Masakatsu Shibasaki
2003– Robert M. Williams
2005– Girolamo Cirrincione
2007– David StC. Black and Roger Read
2009– Mohsen Daneshtalab
2011– Colin J. Suckling
2013– Biao Yu
2015– Tom Pettus
2017– Oliver Reiser
2019– Shuji Akai and Yasuyuki Kita

Awards:

E.C. Taylor Senior Awards in Heterocyclic Chemistry

2019 — Professor D. L. Boger
2017 — Professor Y. Kita
2015 — Professor J. Cossy

ISHC Senior Awards in Heterocyclic Chemistry

2013 — Professor S. F. Martin
2011 — Professor S.E. Denmark
2009 — Unclaimed
2007 — Professor K. C. Nicolaou
2005 — Professor L. E. Overman
2003 — Professor T. Fukuyama
2001 — Professor V. Snieckus
1999 — Professor A. Padwa
1997 — Professor A. I. Meyers
1995 — Professor C. W. Rees
1993 — Professor A. R. Katritzky
1991 — Professor W. Pfleiderer
1989 — Professor E. C. Taylor
1987 — Professor R. Huisgen
1985 — Professor T. Kametani
1983 — Professor R. Castle
1981 — Professor H. van der Plas

A.R. Katritzky Junior Awards in Heterocyclic Chemistry

2019 — Professor R. Sarpong
2017 — Professor C. Vanderwal
2015 — Professor H. Tokuyama
2013 — Professor T. Rovis
2011 — Professor P.S. Baran
2009 — Professor J.L. Wood
2007 — Professor D.W.C. Macmillan
2005 — Professor A. Fürstner
2003 — Professor P. Wipf
2001 — Professor W. H. Pearson
1999 — Professor T. Gallagher
1997 — Professor D. L. Boger

ISHC Industrial Award

2019 — Dr. G. Humphrey
2017 — Dr. M.D. Eastgate

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新学術領域研究 「ハイブリッド触媒」	MEXT Grant-in-Aid Project: Hybrid Catalysis for Enabling Molecular Synthesis on Demand
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■ Access to ROHM Theatre Kyoto

By Train

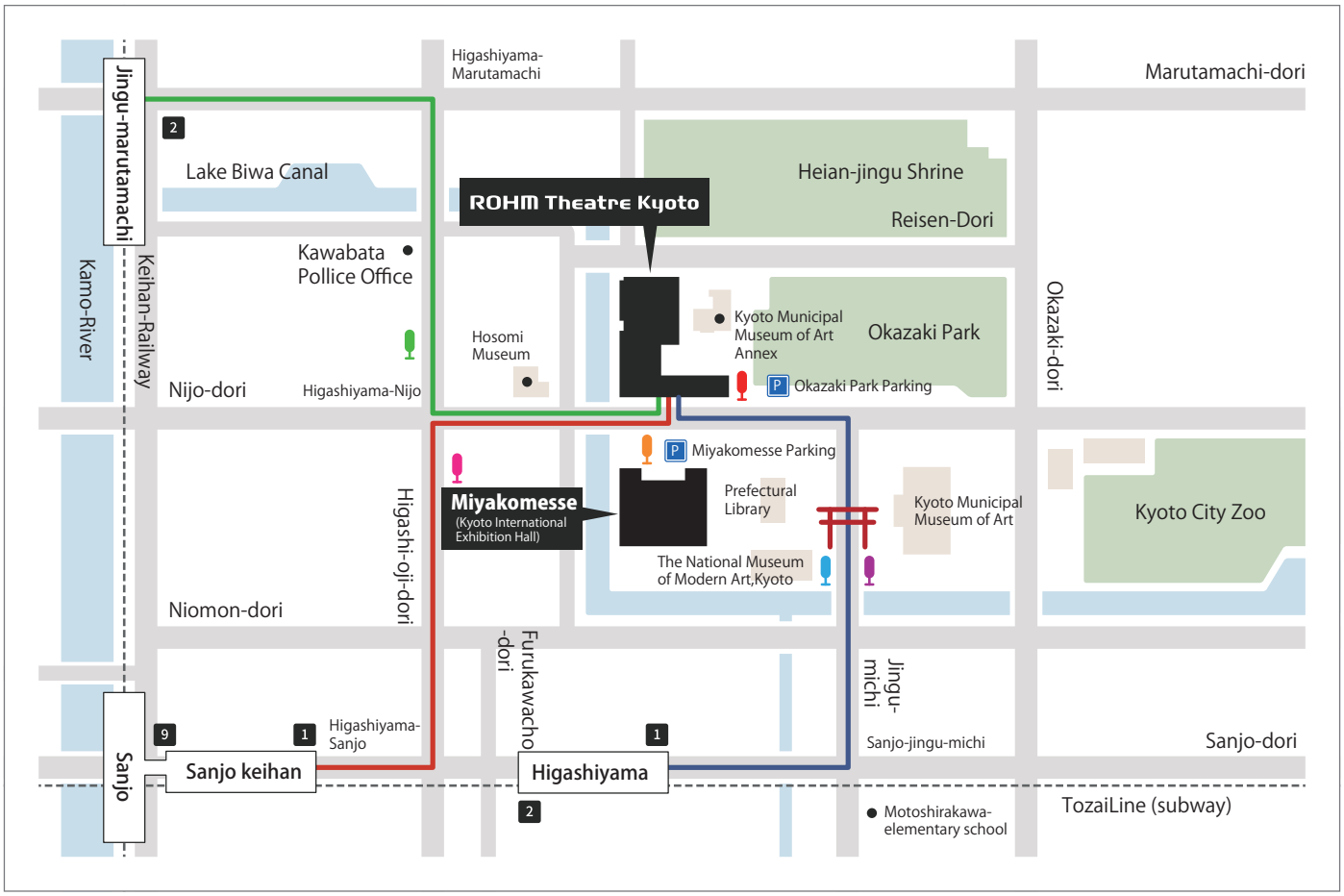
Line	Station	Direction	
Tozai Line (subway)	Higashiyama	Walking	Around 10 minutes from Exit 1.
Keihan	Jingu-marutamachi Station	Walking	Around 13 minutes from Exit 2.
	Sanjo	Bus	Take City Bus Line 5 bus from Sanjo-keihan-mae and alight at Okazaki koen/Bijutsukan/Heian-jingumae. The theater is a 5-minute walk
Hankyu	Kawaramachi	Bus	Take City Bus Line 32 bus or Heian Shrine-bound Line 46 bus from Shijo Kawaramachi. Alight at Okazaki koen/ROHM Theatre Kyoto/Miyako messe mae.
JR/Kintetsu	Kyoto	Bus	Take City Bus Line 5 bus from the A1 boarding point at the bus terminal. Alight at Okazaki koen/Bijutsukan/Heian-jingumae. The theater is a 5-minute walk.

By Bus

Route	Station
City Bus Line 32 Line 46 Kyoto-Okazaki Loop	Alight at Okazaki koen/ ROHM Theatre Kyoto/Miyako messe mae.
City Bus Line 5 City Bus Line 100 City Bus Line 110	Alight at Okazaki koen/Bijutsukan/Heian-jingumae.The theater is a 5-minute walk.
City Bus Line 31 City Bus Line 201 City Bus Line 202 City Bus Line 203 City Bus Line 206	Alight at Higashiyama Nijo/Okazakikoenguchi.The theater is a 5-minute walk.

There are no parking facilities at the theater.
Please use public transport or, if arriving by car, please use a nearby parking lot.

■ ROHM Theatre Kyoto Area Map



ROUTE A From Jingu-Marutamachi Station

Leave the station from Exit 2 and walk east along Marutamachi-dori, turning right at the Higashiyama-marutamachi intersection.
Proceed along Higashi-oji-dori and then turn left at the Higashiyama-nijo intersection.
Walk straight along Nijo-dori. ROHM Theatre Kyoto is on your left after you cross the canal.

ROUTE B From Sanjo Station

Leave the station from Exit 9 and walk east along Sanjo-dori,turning left at the Higashiyama-sanjo intersection.
Proceed along Higashi-oji-dori and then turn right at the Higashiyama-nijo intersection.
Walk straight along Nijo-dori. ROHM Theatre Kyoto is on your left after you cross the canal.

ROUTE C From Higashiyama Station

Leave the station and walk east along Sanjo-dori, turning left at the Sanjo-jingu-michi intersection.
Go straight up Jingu-michi, through the large shrine gate.
Turn left when you reach Okazaki Park and ROHM Theatre Kyoto is on the right.

Bus destinations from the nearest stations by the theatre

Okazaki koen/ROHM Theatre Kyoto/ Miyako messe mae

32 Ginkakuji Temple
46 Shijo Kawaramachi, Kamigamo-jinja Shrine
Kyoto-Okazaki Loop Nanzenji, Sosuikinenkan

Okazaki koen/ROHM Theatre Kyoto/ Miyako messe mae

32 Shijo Kawaramachi, Nishikyogoku

Okazaki koen/Bijutsukan/Heian-jingumae

5 Ginkakuji-Temple, Shugakuinmichi, Iwakura Soshajo-mae
100 Ginkakuji-Temple

Higashiyama Nijo/Okazakikoenguchi

32 Ichijoji Shimizucho, Kokusai Kaikan
201 Hyakumanben, Senbon Imadegawa
202 Kumano Jinja, Nishinokyo Enmachi
203 Kinrin Shako, Ginkakuji-Temple
206 Takano, Kitaoji Bus Terminal

Higashiyama Nijo/Okazakikoenguchi

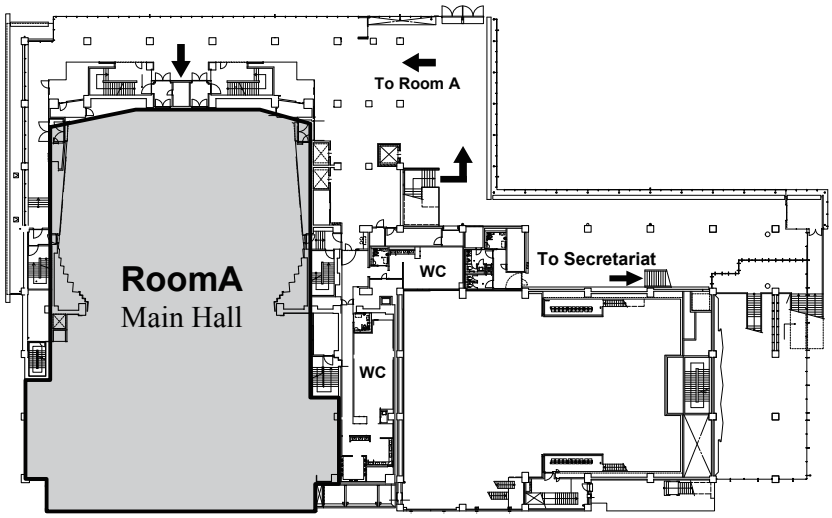
31 Gion, Shijo Karasuma
201 Gion, Shijo Omiya
202 Kiyomizudera Temple, Tofukuji Temple Kuji Shako
203 Gion, Nishioji Shijo
206 Kiyomizudera Temple, Higashiyama Nanajo, Kyoto Station

Okazaki koen/Bijutsukan/Heian-jingumae

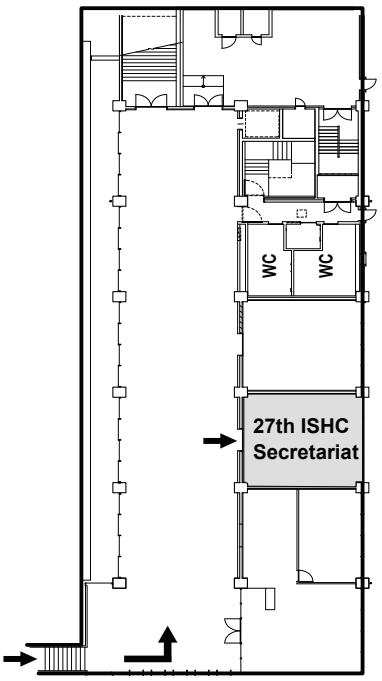
5 Kyoto Station
46 Shijo Kawaramachi, Kamigamo-jinja Shrine
100 Gion, Kiyomizudera Temple, Kyoto Station
110 Kiyomizudera Temple, Kyoto Station, Kyoto Railway Museum
Kyoto-Okazaki Loop
Shorenin Temple, Chionin Temple, Sanjo-Keihan

＜RoomA，RoomB，RoomC＞ ROHM Theatre Kyoto

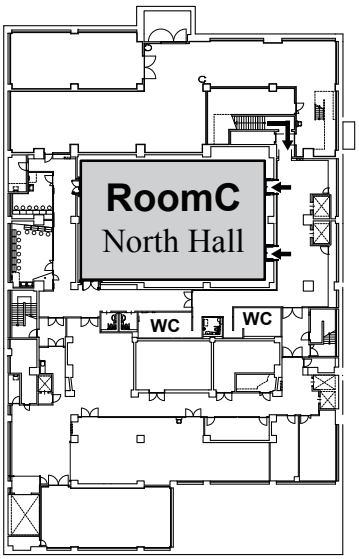
【*2nd floor*】*RoomA (Main Hall)*



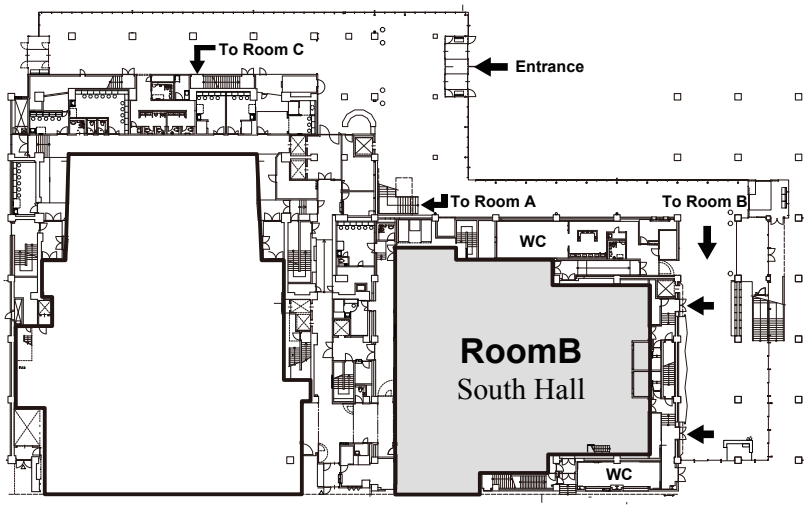
【*3rd floor*】



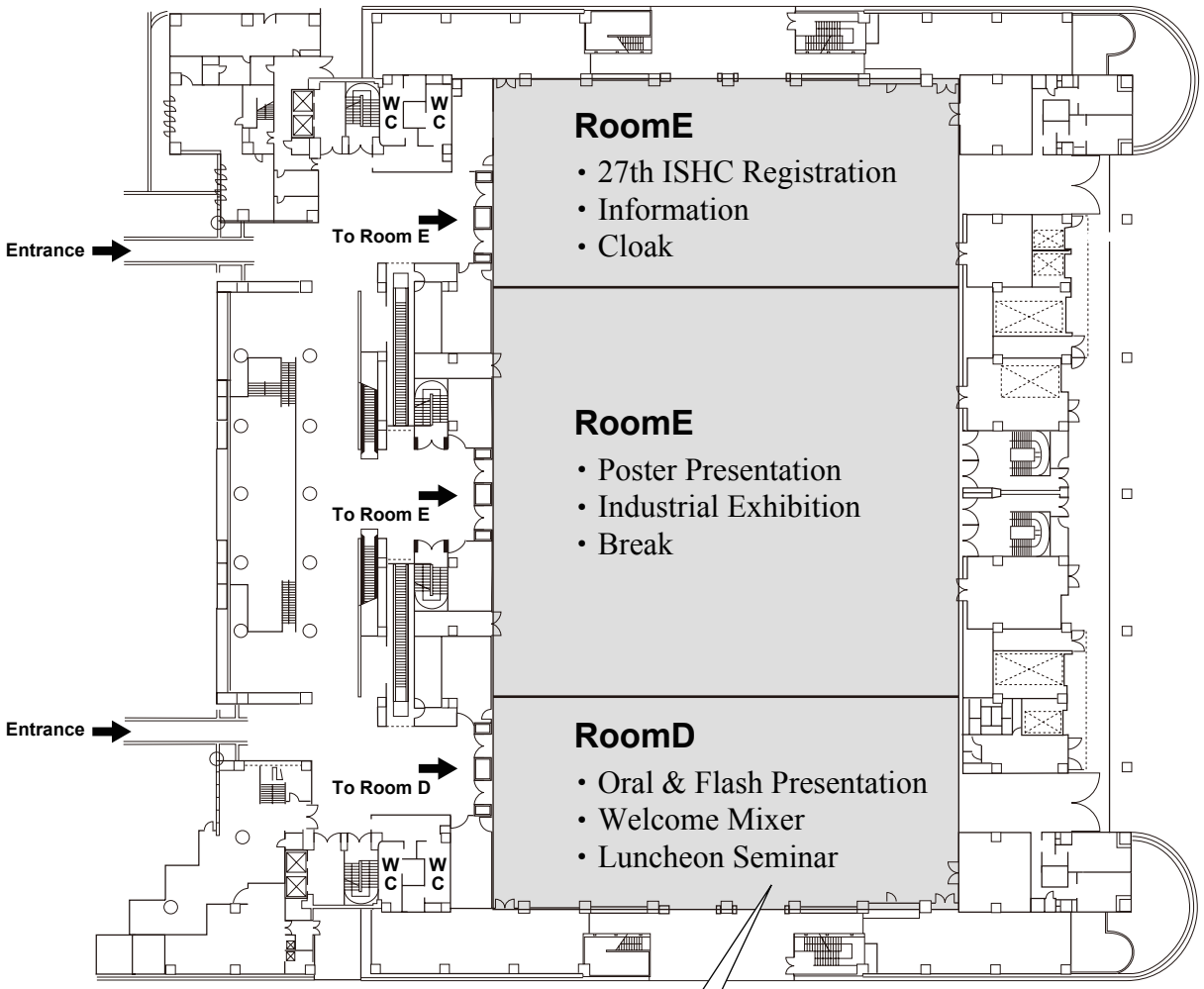
【*2nd basement*】*RoomC (North Hall)*



【*1st floor*】*RoomB (South Hall)*



＜RoomD，RoomE＞Miyako Messe
【*1st floor*】*2nd Exhibition Hall*



- **Welcome Mixer**
  Sep.1st, 18:00-20:00
- **Luncheon Seminar**
  Sep.2nd, 12:50-14:00
  Sep.3rd, 12:40-14:00
  Sep.5th, 12:45-14:00

Time Table of 27th ISHC Congress (2019)

Room A-C: ROHM Theatre Kyoto
Room D&E: Miyako Messe

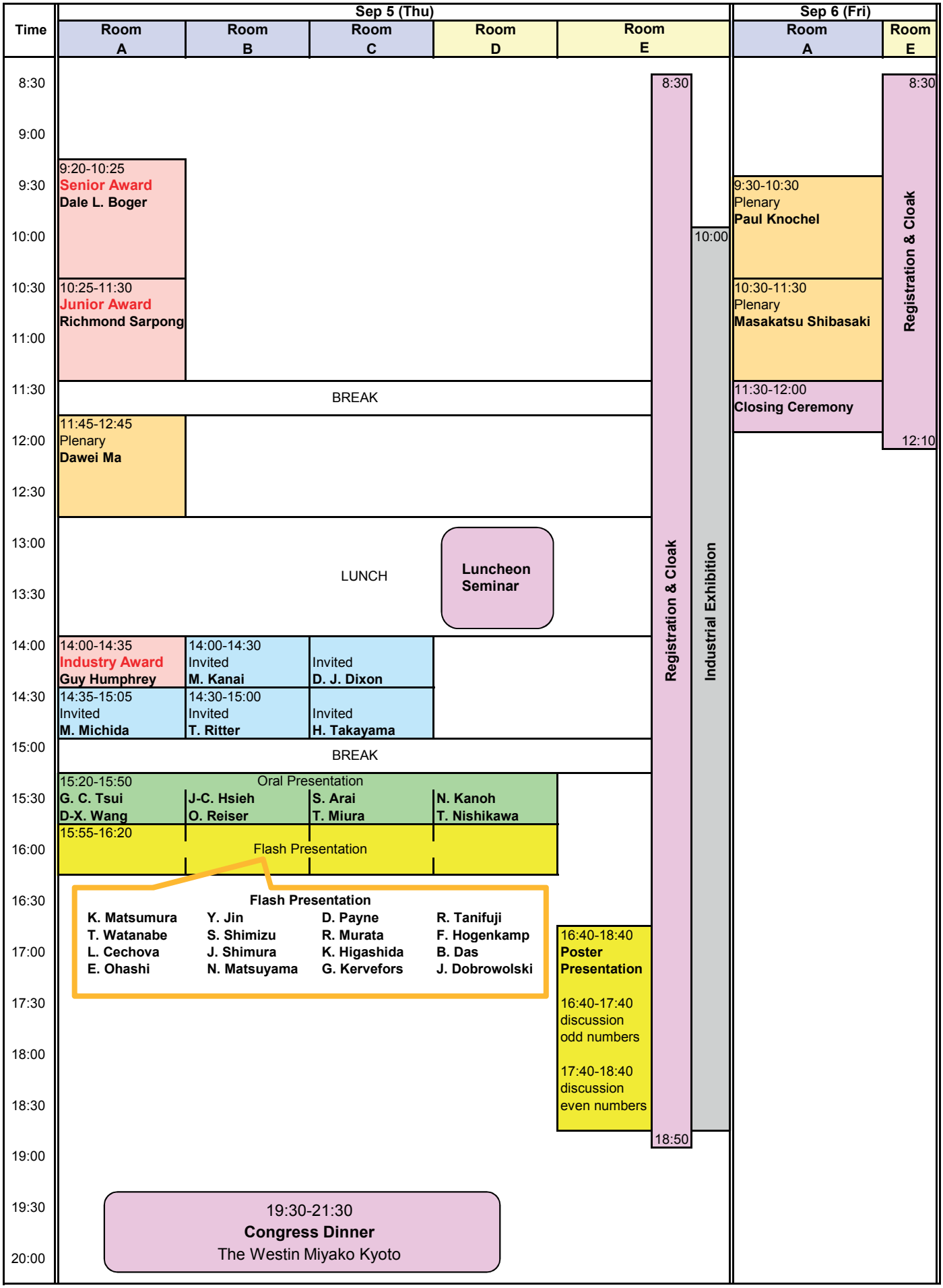
Time	Sep 1 (Sun) Room E	Sep 2 (Mon) Room A	Room B	Room C	Room D	Room E
8:30				Plenary Lecture 60 min Invited Lecture 30 min Oral Presentation 15 min Flah Presentation 6 min Award Lecture Senior Award 65 min Junior Award 65 min Industrial Award 35 min		8:30 Registration & Cloak
9:00		9:20-9:30 **Opening Ceremony**				
9:30		9:30-10:30 Plenary **Scott Miller**				
10:00						10:00 Industrial Exhibition
10:30		10:30-11:30 Plenary **Stefan Matile**				
11:30		BREAK				
12:00		11:50-12:20 Invited **S. Matsubara**	Invited **H. Kakeya**			
12:30		12:20-12:50 Invited **Y. -Y. Yeung**	Invited **J. Ohkanda**			
13:00		LUNCH		Luncheon Seminar		
13:30						
14:00		14:00-14:30 Invited **B. Bibal**	Invited **C. Chi**			
14:30		14:30-15:00 Invited **S. Ogoshi**	Invited **T. J. J. Müller**			
15:00		BREAK				
15:30		15:20-16:35 Oral Presentation				
16:00		**H. Tokuyama** **Y. Ando** **M. Dai** **F. Yoshimura** **A. Dobbs**	**Y. Takeda** **K. Tomooka** **D. Werz** **S. Arae** **J. Han**	**A. Taniguchi** **S. Aoki** **L. Zhai** **L. Brewitz** **R. T. Pardasani**	**N. Krause** **L. Liu** **N. Nishiwaki** **Y. Sohtome** **Y. Kobayashi**	
16:30		16:40-17:05 Flash Presentation				
17:00	17:00-20:00 **Registration**	BREAK				17:20-19:20 **Poster Presentation** 17:20-18:20 discussion odd numbers 18:20-19:20 discussion even numbers
17:30		**Flash Presentation** **S. Pagire** **K. Yamamoto** **T. Sawazaki** **P. Kramer** **K. Rakumitsu** **U. Sharma** **R. Hu** **S. Xu** **T. Ishii** **M. Sohail** **A. Kasahara** **M. Daniel** **S. Arikawa** **F. Ostler** **K. Aoki** **A. Sonawane**				
18:00	18:00-20:00 **Welcome Mixer**					
18:30						
19:00						
19:30						19:30
20:00						

Sep 3 (Tue)

Time	Room A	Room B	Room C	Room D	Room E
8:30					8:30 Registration & Cloak
9:00					
9:30	9:20-10:20 Plenary **Takuzo Aida**				
10:00					10:00 Industrial Exhibition
10:30	BREAK				
11:00	10:40-11:10 Invited **N. Shibata**	Invited **T. Ogoshi**	Invited **M. Wasa**		
11:30	11:10-11:40 Invited **D. Maiti**	Invited **M. A. Herranz**	Invited **S. Hirano**		
12:00	11:40-12:10 Invited **A. Aponick**	Invited **A. K. Yudin**	Invited **B. Liu**		
12:30	12:10-12:40 Invited **M. Kitamura**	Invited **T. Takata**			
13:00	LUNCH			**Luncheon Seminar**	
13:30					
14:00	14:00-15:15 Oral Presentation				
14:30	**B. Nachtsheim** **S. Takizawa**	**A. Nakayama** **T. Opatz**	**Q. Wang** **X. Xu**	**J. Pospíšil** **K. Hirano**	
15:00	**Y. Zhao** **F. Kakiuchi** **T. Ohmura**	**H. Takikawa** **J. Qu** **H. Ren**	**I. Nakamura** **T. Arai** **C. Wang**	**K. Okano** **M. Waser** **N. Hoffmann**	
15:30	BREAK				
16:00	15:35-16:35 Oral Presentation **C. Dohno** **K. Goto**	**A. Schmidt** **S. Jung**	**J-R. Chen** **K. Asano**	**M. Ito** **Y. Ueda**	
16:30	**C. Fruit** **J. Aubé**	**R. A. Aitken** **Y. Otani**	**S. Shirakawa** **Y. Nishimoto**	**S. Blakey** **K. Nozawa-Kumada**	
17:00	16:40-17:05 Flash Presentation				
17:30	BREAK				17:20-19:20 **Poster Presentation**
18:00	**Flash Presentation** **D. Zonidis** **Q-Q. Zhao** **T. Nagano** **P. Drelich**	**M. Petzold** **D-M. Yan** **C. Opie** **T. Murai**	**A. Bal** **K. Okada** **T. Asada** **K. Anderson**	**K. Choudhuri** **Y. Kakiuchi** **M. Paraja** **M. Fujie**	17:20-18:20 discussion odd numbers
18:30					18:20-19:20 discussion even numbers
19:00					
19:30					19:30
20:00					

Sep 4 (Wed)

Time	Room A	Room B	Room C	Room D	Room E
8:30					8:30 Registration & Cloak
9:00					
9:30	9:20-10:20 Plenary **Hiroaki Suga**				
10:00	9:20-10:20 Plenary **Herbert Waldmann**				10:00 Industrial Exhibition
10:30	BREAK				
11:00	11:40-12:10 Invited **K. Fukase**	Invited **M. S. Sherburn**	Invited **Y. Iwabuchi**		
11:30	12:10-12:40 Invited **D. Yang**	Invited **S. Kim**	Invited **R.-J. Chein**		
12:00					12:10
12:30	LUNCH				
13:00					
13:30					
14:00	**Excursion**				
14:30					
15:00					
15:30					
16:00					
16:30					
17:00					
17:30					
18:00					
18:30					
19:00					
19:30					
20:00					


Time
Sep 5 (Thu)
Room A
Room B
Room C
Room D
Room E
Sep 6 (Fri)
Room A
Room E
8:30
9:00
9:20-10:25
Senior Award
Dale L. Boger
9:30
10:00
10:25-11:30
Junior Award
Richmond Sarpong
10:30
11:00
11:30
BREAK
11:45-12:45
Plenary
Dawei Ma
12:00
12:30
13:00
LUNCH
Luncheon Seminar
13:30
14:00
14:00-14:35
Industry Award
Guy Humphrey
14:00-14:30
Invited
M. Kanai
Invited
D. J. Dixon
14:30
14:35-15:05
Invited
M. Michida
14:30-15:00
Invited
T. Ritter
Invited
H. Takayama
15:00
BREAK
15:20-15:50
Oral Presentation
15:30
G. C. Tsui
D-X. Wang
J-C. Hsieh
O. Reiser
S. Arai
T. Miura
N. Kanoh
T. Nishikawa
15:55-16:20
16:00
Flash Presentation
16:30
Flash Presentation
K. Matsumura
T. Watanabe
L. Cechova
E. Ohashi
Y. Jin
S. Shimizu
J. Shimura
N. Matsuyama
D. Payne
R. Murata
K. Higashida
G. Kervefors
R. Tanifuji
F. Hogenkamp
B. Das
J. Dobrowolski
16:40-18:40
Poster Presentation
16:40-17:40
discussion
odd numbers
17:40-18:40
discussion
even numbers
17:00
17:30
18:00
18:30
18:50
19:00
19:30
19:30-21:30
Congress Dinner
The Westin Miyako Kyoto
20:00
8:30
Registration & Cloak
10:00
Industrial Exhibition
9:30-10:30
Plenary
Paul Knochel
10:30-11:30
Plenary
Masakatsu Shibasaki
11:30-12:00
Closing Ceremony
8:30
Registration & Cloak
12:10

ABSTRACTS OF PLENARY LECTURES

Scott Joseph Miller

Irénée du Pont Professor of Chemistry
Department of Chemistry
Yale University
New Haven, CT 06520-8107 USA
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Scientific Vita

2008-Present	Irénée du Pont Professor of Chemistry, Yale University
2006-Present	Professor of Chemistry, Yale University
2002-2006	Professor of Chemistry, Boston College
1996-2002	Assistant/Associate Professor of Chemistry, Boston College
1994-1996	Postdoctoral Fellow, California Institute of Technology (Advisor: R. H. Grubbs)
1994	Ph.D. in Chemistry, Harvard University (Advisor: D. A. Evans)
1989	M.A. in Chemistry, Harvard University
1989	B.A. *magna cum laude* in Chemistry, Harvard College

Research Field

Organic Chemistry, Catalysis and Chemical Biology

Representative Publications

1 "Disparate Catalytic Scaffolds for Atroposelective Cyclodehydration" Kwon, Y.; Li, J.; Reid, J. P.; Crawford, J. M.; Jacobs, R.; Sigman, M. S.; Toste, F. D.; Miller, S. J. *J. Am. Chem. Soc.* **2019**, *141*, 6698-6705.

2 "Peptide-Based Catalysts Reach the Outer Sphere through Remote Desymmetrization and Atroposelectivity". Metrano, A. J.; Miller, S. J. *Acc. Chem. Res.* **2019**, *52*, 199-215.

3 "A Stereodynamic Redox-Interconversion Network of Vicinal Tertiary and Quaternary Carbon Stereocenters in Hydroquinone-Quinone Hybrid Dihydrobenzofurans" Storch, G.; Kim, B.; Mercado, B. Q.; Miller, S. J. *Angew. Chem. Int. Ed.* **2018**, *57*, 15107-15111.

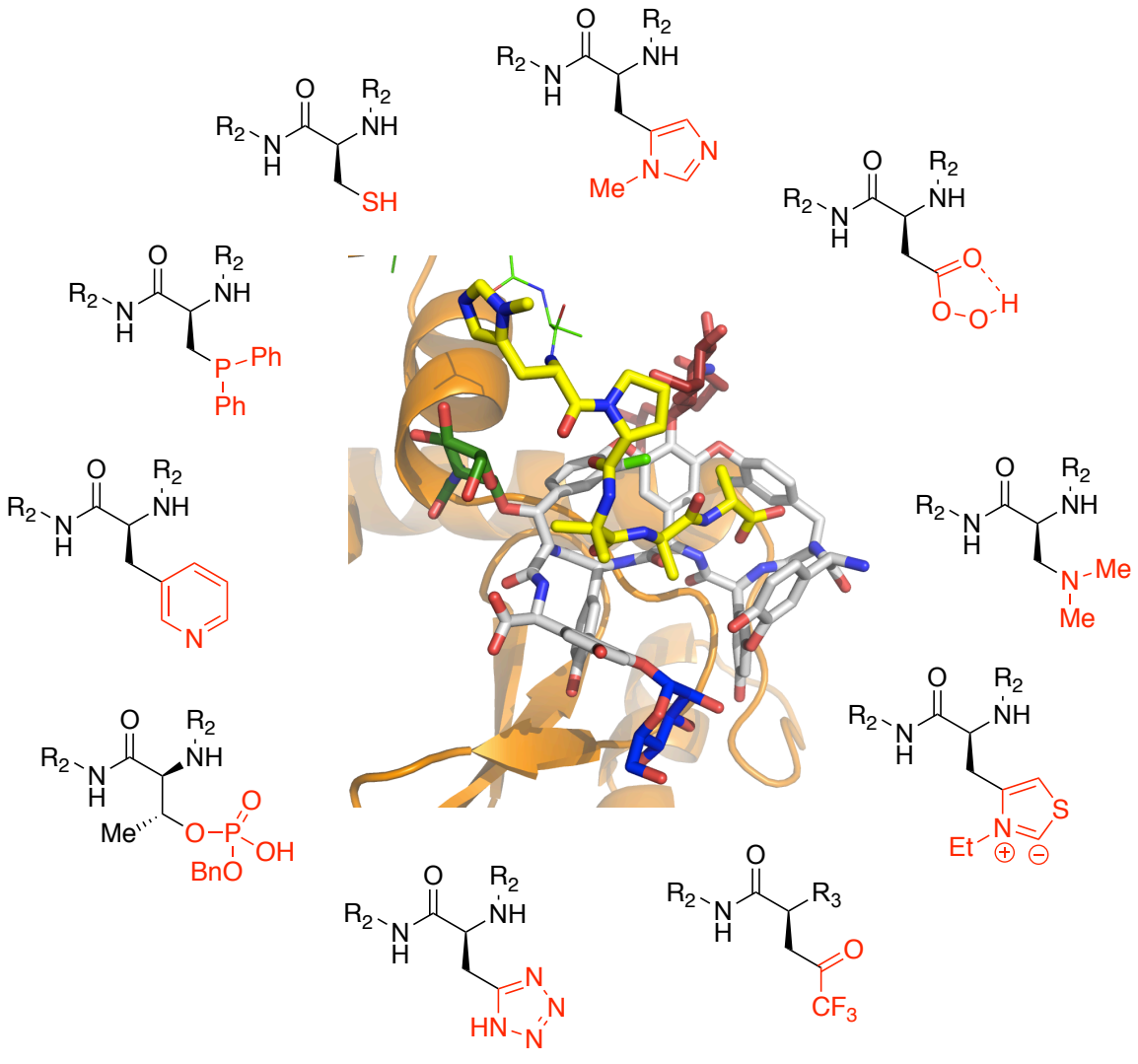
4 "Divergent Control of Point and Axial Stereogenicity: Catalytic Enantioselective C–N Bond-Forming Cross-Coupling and Catalyst-Controlled Atroposelective Cyclodehydration" Kwon, Y.; Chinn, A. J.; Kim, B.; Miller, S. J. *Angew. Chem. Int. Ed.* **2018**, *57*, 6251-6255.

5 "Site- and Stereoselective Chemical Editing of Thiostrepton by Rh-Catalyzed Conjugate Arylation: New Analogs and Collateral Enantioselective Synthesis of Amino Acids" Key, H. M.; Miller, S. J. *J. Am. Chem. Soc.* **2017**, *139*, 15460-15466.

Selective Catalytic Reactions in Complex Heterocyclic Scaffolds

Scott J. Miller*
Department of Chemistry, Yale University
New Haven, CT 06520-8107 USA
E-mail: scott.miller@yale.edu

This lecture will describe recent developments in our efforts to develop low-molecular weight catalysts for asymmetric reactions, in particular for the preparation of stereochemically complex heterocycles. Over time, our focus has been on enantioselectivity, site-selectivity and chemoselectivity. In most of our current work, we are studying issues of enantioselectivity as a prelude to extrapolation of catalysis concepts to more complex stereochemical settings where multiple issues are presented in a singular substrate. Moreover, we continuously examine an interplay between screening of catalyst libraries and more hypothesis-driven experiments that emerge from screening results. Some of the mechanistic paradigms, and their associated ambiguities, will figure strongly in the lecture.



2PL-A-2

Stefan Matile

University of Geneva, Switzerland

Professor Stefan Matile is a Full Professor at the University of Geneva and a founding member of the National Centre of Competence in Research (NCCR) Chemical Biology and the NCCR Molecular Systems Engineering. He is the co-author of more than 300 publications, many in top journals (57 *JACS*, etc), and has delivered more than 280 lectures all over the world. About half of the more than 100 junior researchers he has trained so far (PhD, postdoc) are now active in academia (China, France, Germany, India, Italy, Japan, Spain, Switzerland, USA, etc); others preferred a career in industry, or elsewhere. Educated at the University of Zurich (PhD, with Wolf Woggon) and Columbia University in New York (postdoc, with Koji Nakanishi), he started his independent academic career as an Assistant Professor at Georgetown University, Washington DC, before moving to Geneva.

His research interests are in functional supramolecular chemistry, supramolecular systems in action, at work, with emphasis on the integration of new or at least underrecognized concepts and principles into functional systems, particularly unorthodox interactions. The general expectation is that the integration of different ways to get into contact would ultimately yield new functions that will allow us to tackle challenges that are otherwise beyond reach. Current functions of interest are catalysis with anion-π interactions, chalcogen bonds and pnictogen bonds, the creation of mechanosensitive fluorescent probes to image physical forces in biological systems, and dynamic oligochalcogenide exchange chemistry to find new ways to enter into cells (tension, walkers, adaptive networks). Long-standing topics of interest also include transport across lipid bilayer membranes, sensors and artificial photosystems (molecular tongues, noses and leaves).

2PL-A-2

Functional Supramolecular Chemistry

Stefan Matile*
Department of Organic Chemistry, University of Geneva, Geneva, Switzerland

This lecture will focus on synthetic supramolecular systems with interesting functions. Particular emphasis will be on the integration of new (or almost new) concepts and principles from supramolecular chemistry into functional systems. The general expectation is that fundamentally new approaches to create function will ultimately allow us to tackle challenges in chemistry, biology and the materials sciences that are otherwise beyond reach. Functions of current interest include catalysis with anion-π interactions [1], chalcogen bonds [2] and pnictogen bonds, mechanosensitive fluorescent probes that change color like lobster during cooking to image forces in living cells [3], and repulsion-driven ion pairing and dynamic covalent exchange chemistry to find new ways into cells and deliver otherwise problematic substrates (e.g., quantum dots, artificial metalloenzyme). As a result of these lessons from supramolecular chemistry, new privileged scaffolds are emerging regularly, including cyclic oligochalcogenides (COCs; disulfides, diselenides, benzopolysulfanes [4]), naphthalenediimides (NDIs [1]), benzodiselenazoles (BDS [2]), dithienothiophenes (DTTs [3]), and other heterocycles.

For more, please visit: http://www.unige.ch/sciences/chiorg/matile/

[1] Zhao, Y.; Cotelle, Y.; Liu, L.; Lopez-Andarias, J.; Bornhof, A.-B.; Akamatsu, M.; Sakai, N.; Matile, S. *Acc. Chem. Res.* **2018**, *51*, 2255–2263.
[2] Benz, S.; Besnard, C.; Matile, S. *Helv. Chim. Acta* **2018**, *101*, e1800075.
[3] Strakova, K.; Soleimanpour, S.; Diez-Castellnou, M.; Sakai, N.; Matile, S. *Helv. Chim. Acta* **2018**, *101*, e1800019.
[4] Laurent, Q.; Sakai, N.; Matile, S. *Helv. Chim. Acta* **2019**, *102*, e1800209.

Takuzo Aida

Department of Chemistry and Biotechnology, School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan. RIKEN Center for Emergent Matter Science, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan.

Professional Appointments:
1984–1989: Assistant Professor, The University of Tokyo
1989–1991: Lecturer, The University of Tokyo
1991–1996: Associate Professor, The University of Tokyo
1996–Now: Professor, The University of Tokyo
2008–2012: Director, RIKEN Advanced Science Institute
2013–2013 Deputy Director, Riken Center for Emergent Matter Science
2009–Now Board of Reviewing Editors, *Science Magazine* (AAAS)
2014–Now Advisory Board, *Journal of the American Chemical Society* (ACS)

Recent Awards:
American Chemical Society Award in Polymer Chemistry (2009) / Chemical Society of Japan Award (2009) / Purple Ribbon (2010) / Alexander von Humboldt Research Award (2011) / Fujiwara Prize (2011) / Arthur K. Doolittle Award (2013) / Van 't Hoff Award Lecture 2013 (2013) / Leo Esaki Prize (2015) / Dean Award, U. Tokyo (2016), Chirality Medal (2017), Japan Academy Prize (2018)

Selected Publications:
(1) Nematic-to-Columnar Mesophase Transition by In situ Supramolecular Polymerization, *Science* **2019**, *363*, 161–165.
(2) Self-Assembly of Lattices with High Structural Complexity from a Geometrically Simple Molecule, *Science* **2018**, *361*, 1242–1246.
(3) Mechanically Robust, Readily Reparable Polymers via Tailored Noncovalent Cross-linking, *Science* **2018**, *359*, 72–76.
(4) Thermally Bisignate Supramolecular Polymerization, *Nature Chem.* **2017**, *9*, 1133–1139.
(5) An Autonomous Actuator Driven by Fluctuations in Ambient Humidity, *Nature Mat.* **2016**, *14*, 1084–1089.
(6) Sub-Nanoscale Hydrophobic Modulation of Salt Bridges in Aqueous Media, *Science* **2015**, *348*, 555–559.
(7) Selective-Assemblies of Giant Tetrahedra via Precisely Controlled Positional Interactions, *Science* **2015**, *348*, 424–428.
(8) A Rational Strategy for the Realization of 'Chain-Growth' Supramolecular Polymerization, *Science* **2015**, *347*, 646–651.
(9) Thermoresponsive Actuation Enabled by Permittivity Switching in an Electrostatically Anisotropic Hydrogel, *Nature Mat.* **2015**, *14*, 1002–1007.
(10) Ultrahigh-throughput Exfoliation of Graphite into Pristine 'Single-Layer' Graphene Using Microwaves and Molecularly Engineered Ionic Liquids, *Nature Chem.* **2015**, *7*, 730–736.
(11) Anisotropic Hydrogel with Embedded Electrostatic Repulsion among Cofacially Oriented 2D Electrolytes, *Nature* **2015**, *517*, 68–72.
(12) Manipulation of Discrete Nanostructures by Selective Modulation of Noncovalent Forces, *Science* **2014**, *344*, 499–504.

3PL-A-1

Noncovalent Design of Advanced Porous Materials

Takuzo Aida

Riken Center for Emergent Matter Science, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan
Department of Chemistry and Biotechnology, The University of Tokyo
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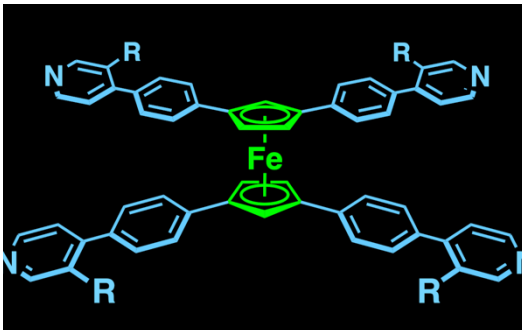
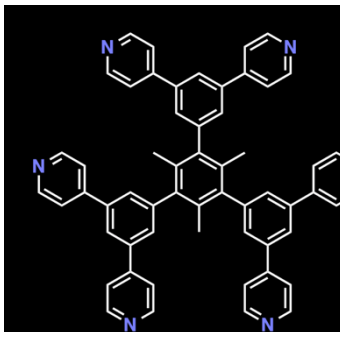
email: aida@macro.t.u-tokyo.ac.jp



In covalent organic synthesis, bond cleavage and formation are commonly employed for constructing complicated molecular structures. However, for noncovalent architectures, manipulation of the assembled structure is difficult because selective in-situ attenuation and/or enhancement of noncovalent forces is hard to achieve. Although a variety of beautiful nanostructures have been noncovalently synthesized, even more exotic or hardly accessible self-assembled motifs might become available if there were methods to cut, paste or merge assembled structures. By stepwise noncovalent synthesis, several exotic nanostructures were recently synthesized using inorganic clusters, block copolymers, and small organic molecules as assembling components, and some of those nanostructures were indeed shown to break up into thermodynamically inaccessible low-symmetry pieces. However, such selective cutting requires prior stabilization of parent nanostructures by partial crosslinking, so that cut pieces are covalently linked. Here we report that ferrocene-based tetratopic pyridyl ligands, which can dynamically change their geometry due to thermal rotation of their cyclopentadienyl rings in solution, assemble with $AgBF_4$ into discrete metal–organic nanotubes with large and uniform diameters [1–4]. The nanotubes can be cut into metal–organic nanorings by selective attenuation of the inter-nanoring interaction via ferrocene oxidation. The resultant nanorings can be transferred onto inorganic substrates electrostatically or allowed to reassemble to form the original nanotube by reductive neutralization of their oxidized ferrocene units.



We also report an anomalous porous molecular crystal built of 'C–H···N-bonded double-layered roof/floor components' and 'wall components of a segregatively interdigitated architecture' [5]. This complicated porous structure consists of only one type of fully aromatic multi-joint molecule carrying three identical dipyridylphenyl wedges. Despite its high symmetry, this molecule accomplishes difficult tasks by employing two of its three wedges for roof/floor formation and employing its other wedge for wall formation. Although a C–H···N bond is extremely labile, the porous crystal maintains its porosity until thermal breakdown of the C–H···N bonds at 202 °C to afford a non-porous polymorph. While this non-porous crystal survives even at 325 °C, it can retrieve the parent porosity under acetonitrile vapor. These findings show how one can translate simplicity into ultrahigh complexity.

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4PL-A-1

Hiroaki Suga

Department of Chemistry
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University of Tokyo

Hiroaki Suga is a Professor of the Department of Chemistry, Graduate School of Science in the University of Tokyo. He received Ph. D. at MIT (1994) followed by post-doctoral fellow in Mass General Hospital (1997). He was Assistant and tenured Associate Professor in the SUNY at Buffalo (1997-2003) and Professor in the Research Center for Advanced Science and Technology in the University of Tokyo (2003-2010). Since 2010, he has the present position. He is the recipient of Akabori Memorial Award 2014 (Japanese Peptide Society), Max-Bergmann Medal 2016 (German Peptide Society), Nagoya Medal Silver 2017, and Vincent du Vigneaud Award 2019 (American Peptide Society). He is also a founder of PeptiDream and MiraBiologics in Japan.

4PL-A-1

Revolutionizing the discovery processes of de novo bioactive peptides and biologics

Hiroaki Suga
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Macrocyclic peptides possess a number of pharmacological characteristics distinct from other well-established therapeutic molecular classes, resulting in a versatile drug modality with a unique profile of advantages. Macrocyclic peptides are accessible by not only chemical synthesis but also ribosomal synthesis. Particularly, recent inventions of the genetic code reprogramming integrated with an in vitro display format, referred to as RaPID (Random non-standard Peptides Integrated Discovery) system, have enabled us to screen mass libraries (>1 trillion members) of non-standard peptides containing multiple non-proteinogenic amino acids, giving unique properties of peptides distinct from conventional peptides, e.g. greater proteolytic stability, higher affinity (low nM to sub nM dissociation constants similar to antibodies), and superior pharmacokinetics. The field is rapidly growing evidenced by increasing interests from industrial sectors, including small start-ups as well as mega-pharmas, toward drug development efforts on macrocyclic peptides, which has led to several *de novo* discovered peptides entering clinical trials. This lecture discusses the aforementioned screening technology, the RaPID system, and several showcases of therapeutic potentials of macrocyclic peptides. This lecture also discusses an application of the RaPID peptides to biologics development.

A. Kawamura, M. Münzel, T. Kojima, C. Yapp, B. Bhushan, Y. Goto, A. Tumber, T. Katoh, O.N. King, T. Passioura, L.J. Walport, S.B. Hatch, S. Madden, S. Müller, P.E. Brennan, R. Chowdhury, R.J. Hopkinson, H. Suga*, C.J. Schofield “Highly selective inhibition of histone demethylases by de novo macrocyclic peptides” **Nature Communications**, (2017) Apr. 6, 14773.

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K. Ito; K. Sakai; Y. Suzuki; N. Ozawa; T. Hatta; T. Natsume; K. Matsumoto; H. Suga "Artificial human Met agonists based on macrocycle scaffolds" **Nature Communications**, 6, 6373 (2015)

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Y. Goto, T. Katoh, H. Suga “Flexizymes for genetic code reprogramming” **Nature Protocols** *6*, 779-790 (2011)

4PL-A-2

Herbert Waldmann

Max Planck Institute of Molecular Physiology, Germany

Herbert Waldmann was born in Neuwied, Germany and studied chemistry at the University of Mainz where he received his PhD in organic chemistry in 1985 under the guidance of Horst Kunz. After a postdoctoral appointment with George Whitesides at Harvard University, he completed his habilitation at the University of Mainz in 1991. In 1999 he was appointed Director at the Max Planck Institute of Molecular Physiology Dortmund and Professor of Organic Chemistry at the University of Dortmund. His research interests lie in the syntheses of signal transduction modulators and the syntheses of natural product inspired compound libraries and their biological evaluation. He is a member of several Editorial Boards of international journals and he is the Editor-in Chief for Bioorganic and Medicinal Chemistry. He also serves on various Advisory Boards including Max-Planck Innovation GmbH (Chairman) and Boehringer Ingelheim Foundation and he is member of the Scientific Committee of the Institut Européen de Chimie et Biologie, Bordeaux, France.

He has been the recipient of the Otto-Bayer-Award, the Max Bergmann Medal, the Hans-Herloff Inhoffen-Medal, the Emil-Fischer-Medal and the Paul Ehrlich Prize of the French Medicinal Chemistry Society. He is a Member of „Deutsche Akademie der Naturforscher Leopoldina, Halle/Saale“. In 2014 he received the Honorary Doctorate (Dr. h. c.) bestowed by Leiden University, NL.

Among his lectureships are the R. Raphael Lectureship, Glasgow, 2005, the Roessler Lectures, Cornell University, Ithaca, USA, 2006 as well as the Melvin Calvin Lecture, UC Berkeley, USA, 2007, the H.C. Brown Lectures, Purdue University, USA, 2013, the Mendel Lecture, Masaryk University, Brno, Czech Republic in 2015 and the Robert Robinson Lecture, University of Oxford in 2018.

4PL-A-2

Pseudo Natural Products

Herbert Waldmann*

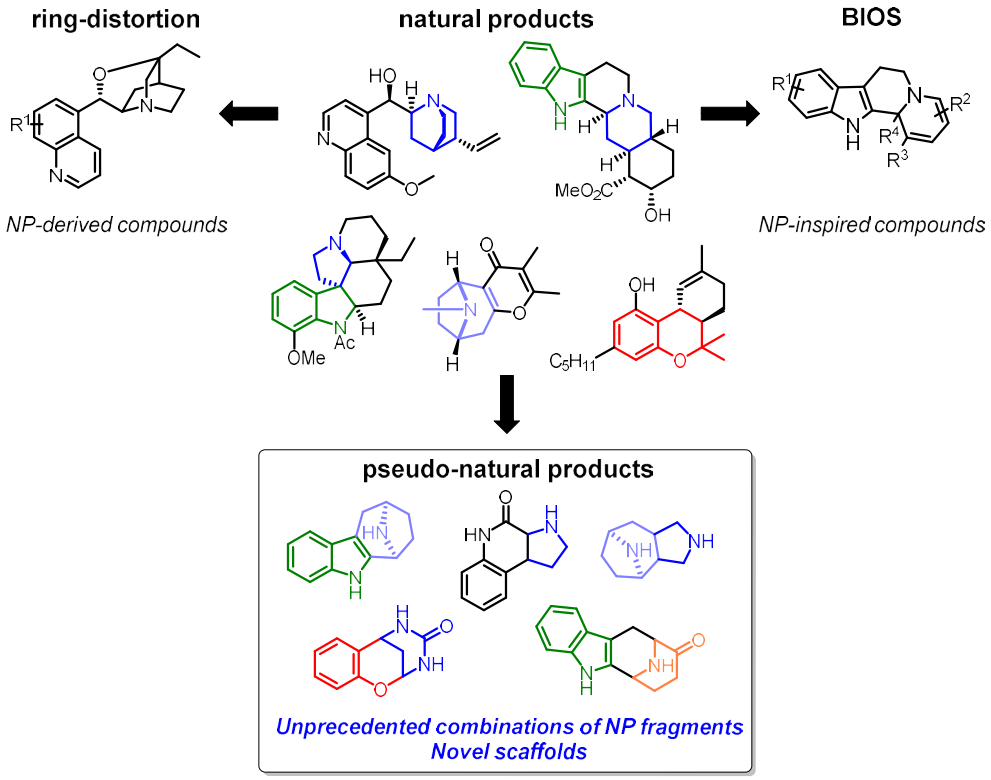
Max-Planck-Institut für molekulare Physiologie, Department of Chemical Biology, Otto-Hahn-Str. 11, D-44227 Dortmund, Germany, and TU Dortmund, Chemie und Chemische Biologie

Natural products have been invaluable sources of inspiration and of novel bioactive compounds for chemical biology and medicinal chemistry research. However, their often complex structure, and, therefore, demanding synthesis as well as their frequent unavailability in sufficient amounts, hamper their application.

This raises the fundamental question whether the particular structural properties of natural products leading to their pronounced bioactivity can be translated to structurally less demanding compound classes, readily accessible by chemical synthesis and yet still endowed with pronounced bioactivity.

The lecture will describe a logic for the simplification of natural product structure by means of "Biology Oriented Synthesis" (BIOS) and its evolution into the "Pseudo Natural Product" (PNP) concept. Application of natural product inspired compound collections designed and synthesized following these principles in cell-based phenotypic assays and subsequent identification of the cellular target proteins demonstrate that the BIOS and PNPs may enable innovation in both chemical biology and medicinal chemistry research.

Examples will include new modulators of and biological target proteins in major cancer-related cellular programs.



H. Waldmann et al., Nat. Chem. 2018, 10, 1103-1111

5PL-A-1

Dawei Ma

Shanghai Institute of Organic Chemistry
Chinese Academy
345 Lingling Lu, Shanghai 200032, China

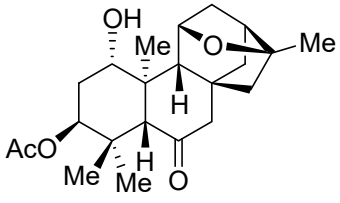
Dr. Dawei Ma received his PhD in 1989 from Shanghai Institute of Organic Chemistry (SIOC), and did his postdoctoral studies at the University of Pittsburgh and Mayo Clinic. He returned to SIOC in 1994, and was appointed as research professor in 1995. From 2001 to 2010 he was the director of State Key Laboratory of Bioorganic & Natural Products Chemistry. He is presently the deputy director of SIOC and an associate editor of Journal of Organic Chemistry. His research interests currently focus on the development of new synthetic methodologies, the total synthesis of complex natural products and their SAR and action mode studies, as well as the discovery of small modulators for target proteins and special biological processes.

5PL-A-1

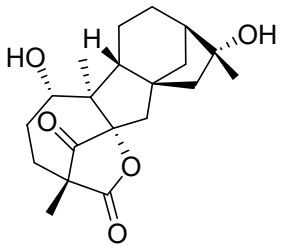
Total Synthesis of *ent*-Kauranes and Et-743

Xiangbo Zhao, Qifei Hu and Dawei Ma*
State Key Laboratory of Bioorganic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

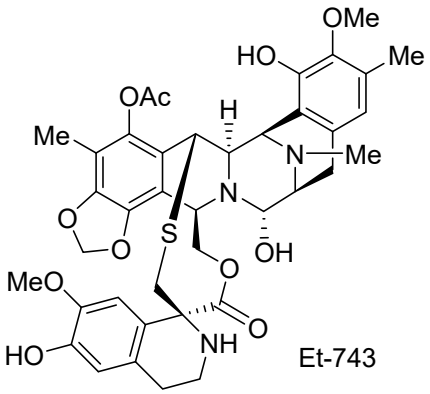
The *ent*-kaurane diterpenoids belong to an increasing family of natural products that contain over 1500 members. Most of them share the basic structure of *ent*-kaurane with diverse patterns of oxygenation, while a few possess quite different structures that might be generated from C-C bond cleavages or fragmentations of *ent*-kaurane precursors, which can be classified as rearranged *ent*-kaurane diterpenoids. In this lecture we describe the first asymmetric total synthesis of lungshengenin D[1] and pierisketolide A, in which their core structures were established via a homoaldol reaction of alkenyl carbamates with aldehydes and subsequent intramolecular Mukaiyama-Michael cyclization. Additionally, a short and scalable total synthesis of Et-743 is reported.[2]



Lungshengenin D



Pierisketolide A



Et-743

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Paul Knochel

Ludwig-Maximilians-Universität
Department of Chemistry

Birth Place and Date:	Strasbourg, France, November 15, 1955
1972 - 1979	Undergraduate Studies in Chemistry at the University of Strasbourg (ENSCS).
1982	Ph.D. ETH Zürich, Switzerland (Prof. D. Seebach): Nitroallylation Reagents.
1982 - 1986	Chargé de recherche at the CNRS in Paris, Université Pierre et Marie Curie, Paris, France (Prof. J. F. Normant): Allylzincation Reactions and Preparation of Bimetallic Reagents of Zn and Mg.
1986 - 1987	Post-doctoral research at the Princeton University, Princeton, New-Jersey, USA (Prof: M. F: Semmelhack): Arene-chromium complexes of indoles.
1988 - 1992	Assistant-professor, then full professor (1991) at the University of Michigan, Ann Arbor, Michigan (USA).
1992 - 1999	Professor of organic chemistry at the Philipps-Universität, Marburg (Germany).
1999 -	Professor of organic chemistry at the Ludwig-Maximilians-Universität München (Germany).

Honors:	1992 Berthelot Medal of the Academie des Sciences (Paris) 1994 IUPAC Thieme Prize 1995 European Chemical Society-Chiroscience Award for Creative Chemistry 1995 Otto-Bayer-Prize 1996 Leibniz-Prize 2004 Dr. Paul Janssen Prize for Creativity on Organic Synthesis 2005 Arthur C. Cope Scholar Award 2007 Lilly European Distinguished Lectureship Award 2009 Karl-Ziegler-Prize 2012 Nagoya Gold Medal 2014 ACS H.C.Brown Award for creative research in synthetic methods 2015 Paul Karrer Gold Medal for his work in organic chemistry 2018 Hispano-Alemán Elhuyar-Goldschmidt 2018 Prix franco-allemand Georg Wittig - Victor Grignard
Membership:	Member of the Académie des Sciences (Paris) 2007 Member of the Bavarian Academy of Science 2008 Member of the German Academy of Sciences Leopoldina 2009 Editor for “Synfacts” Chief-Editor for “Synthesis” Chief-Editor for “Comprehensive Organic Chemistry II”, Elsevier, 2014
Recent grant:	Advanced Investigator Grant from the European Research Council (ERC 227763) 2009-2014
Publication/Patent:	Author of more than 900 publications (including 34 books) and 40 patents – H-index: 90
Research Interests:	Development of new organometallic catalysts and reagents for organic synthesis. Preparation of polyfunctional organometallics, asymmetric synthesis, and natural product synthesis.

6PL-A-1

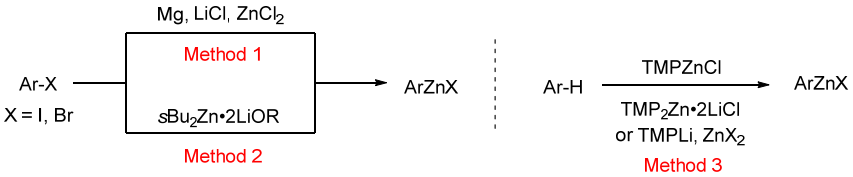
Polyfunctional Heterocyclic Organometallics in Synthesis

Prof. Dr. Paul Knochel*

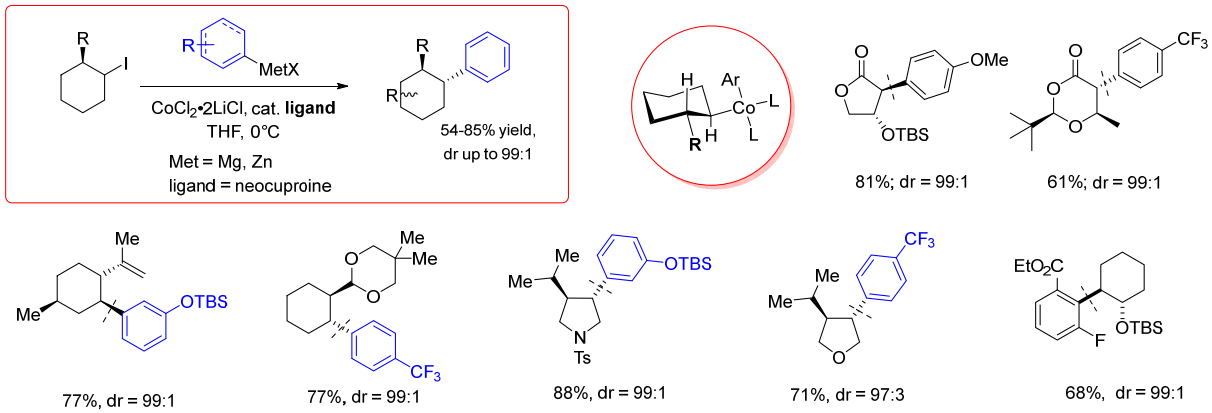
University Munich, Chemistry Department, Butenandtstr. 5-13 D-81377 Munich, Germany

Transition metal catalyzed cross-couplings are important tools for the pharmaceutical and agrochemical industries. Herein, we will first describe the most important methods for preparing polyfunctional organozinc and organomagnesium reagents and describe their use for performing cobalt-catalyzed cross-couplings and aminations.

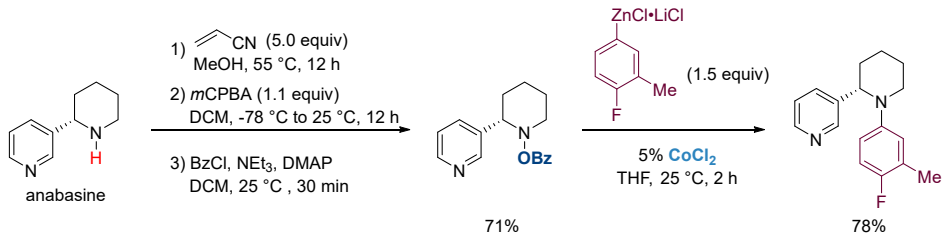
Scheme 1



Scheme 2



Scheme 3



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6PL-A-2

Masakatsu Shibasaki

Microbial Chemistry Research Foundation
Institute of Microbial Chemistry, Japan

1974	Ph. D., University of Tokyo (Professor Shun-ichi Yamada)
1974-1977	Post-doctoral Research Associate, Harvard University (Professor E. J. Corey)
1977-1983	Associate Professor, Teikyo University (Professor Shiro Ikegami)
1983-1986	Research Group Leader, Sagami Chemical Research Center
1986-1991	Professor, Hokkaido University
1991-2010	Professor, The University of Tokyo
2005.5-2006.3	Vice-president of The Pharmaceutical Society of Japan
2006.4-2007.3	President of The Pharmaceutical Society of Japan
2006.4-2008.3	Dean of the Graduate School of Pharmaceutical Sciences, The University of Tokyo
2006.4-2011.9	Member of Science Council of Japan
2010.4-	Director, Institute of Microbial Chemistry (BIKAKEN)
2013.4- 2015.3	President of The Pharmaceutical Society of Japan
2014.11-	Chairman of Board of Directors, Microbial Chemistry Research Foundation

Awards: The Pharmaceutical Society of Japan Award for Young Scientists, 1981 (Japan)
Inoue Prize for Science, 1994 (Japan)
Fluka Prize: Reagent of the Year 1996, 1996 (Switzerland)
Tetrahedron Chair, 1998 (Belgium)
The Pharmaceutical Society of Japan Award, 1999 (Japan)
Molecular Chirality Award, 1999 (Japan)
The Naito Memorial Award for the advancement of science, 2001 (Japan)
ACS Award: Arthur C. Cope Senior Scholar Award, 2002 (USA)
The Medal with Purple Ribbon 2003 (Japan)
Toray Science and Technology Prize, 2003 (Japan)
Japan Academy Prize, 2005 (Japan)
Sankyo Takamine Memorial Award, 2006 (Japan)
The Rare Earth Society of Japan Award (Shiokawa Prize), 2007 (Japan)
ACS Award for Creative Work in Synthetic Organic Chemistry, 2008 (USA)
Centenary Prize (Royal Society of Chemistry), 2008 (UK)
Prelog Medal (ETH), 2008 (Switzerland)
Special Award in Synthetic Organic Chemistry, Japan, 2010 (Japan)
Ryoji Noyori Prize 2012 (Japan)

6PL-A-2

Catalytic Asymmetric Synthesis of Heterocyclic Compounds through Cooperation Asymmetric Catalysis

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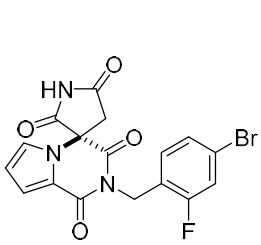
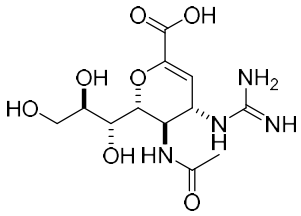
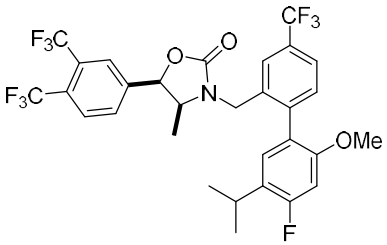
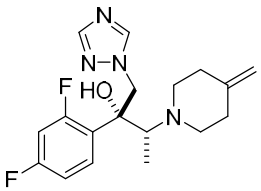
3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

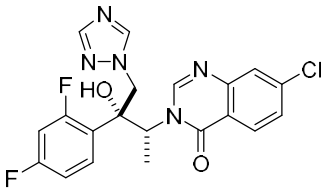
Our research focuses on the development of catalytic asymmetric C-C bond-forming reactions with particular emphasis on high atom economy and their application to the synthesis of biologically significant compounds. Thus, the concept of cooperative asymmetric catalysis such as Lewis acid-Brønsted base catalysis [1,2] and Lewis acid-Lewis base catalysis [3] plays the key role in our research paradigm. In this lecture, we report catalytic symmetric synthesis of heterocyclic compounds such as AS-3201(ranirestat), zanamivir(relenza), anacetrapib, efinaconazole, albaconazole, kainic acid and thuggacin B through cooperative asymmetric catalysis.

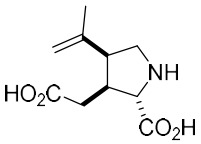

AS-3201
(ranirestat)

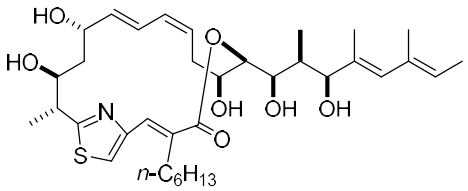

zanamivir
(relenza)

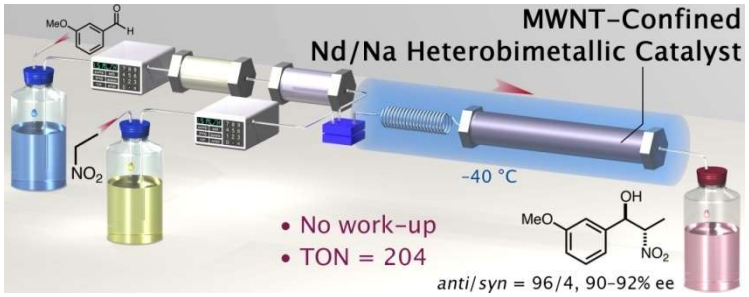

anacetrapib


efinaconazole


albaconazole


kainic acid


thuggacin B



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[3] M. Kanai, N. Kato, E. Ichikawa, and M. Shibasaki, "Power of Cooperativity: Lewis Acid-Lewis Base Bifunctional Asymmetric Catalysis", Synlett, 10, 1491-1508 (2005)

ABSTRACTS OF AWARD LECTURES

Senior Award Lecture
Sep. 5th, RoomA (ROHM Theatre Kyoto, Main Hall)
Boger, Dale L. (The Scripps Research Institute, USA) 5AL-A-1

Junior Award Lecture
Sep. 5th, RoomA (ROHM Theatre Kyoto, Main Hall)
Sarpong, Richmond (University of California–Berkeley, USA) 5AL-A-2

Industry Award Lecture
Sep. 5th, RoomA (ROHM Theatre Kyoto, Main Hall)
Humphrey, Guy (Merck Sharp and Dohme, USA) 5AL-A-3

5AL-A-1

Dale L. Boger

Department of Chemistry, The Scripps Research Institute
10550 N. Torrey Pines Road, La Jolla, CA 92037, USA

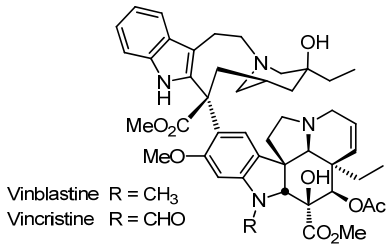
Dale Boger received his B.Sc. in chemistry from the University of Kansas (1975, with highest distinction and honors in chemistry) and Ph.D. in chemistry from Harvard University (1980) under the direction of E. J. Corey and supported by an NSF fellowship. He returned to the University of Kansas as a member of the faculty in the Department of Medicinal Chemistry (1979–1985), moved to the Department of Chemistry at Purdue University (1985–1991), and joined the faculty in the newly created Department of Chemistry at The Scripps Research Institute (1991–present) as the Richard and Alice Cramer Professor of Chemistry. From 2012–2018, he served as the Chairman for the Department of Chemistry. Professor Boger is internationally recognized for his work in organic synthesis, heterocyclic chemistry, medicinal chemistry, natural products total synthesis and their biological characterization, synthetic methodology development, and chemical biology, and has made seminal contributions to discovering new therapeutic targets (eg. FAAH, serine hydrolases), improving the glycopeptide antibiotics, and the understanding of DNA–drug interactions of naturally occurring antitumor-antibiotics. Among other honors, he is an elected member of the American Academy of Arts and Sciences and the National Academy of Sciences.

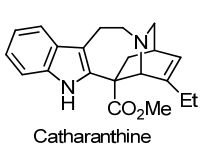
5AL-A-1

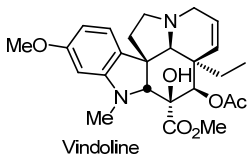
Vinblastine: Synthetic and Mechanistic Studies

Dale L. Boger*
Department of Chemistry, The Scripps Research Institute
10550 N. Torrey Pines Road, La Jolla CA, 92037

A brief introductory summary of studies providing a first generation and second generation asymmetric total synthesis of vindoline based on the implementation of a powerful [4+2]/[3+2] cycloaddition cascade of 1,3,4-oxadiazoles will be presented along with its extension to the preparation of a series of key analogs. The development of a single-step biomimetic Fe(III)-promoted coupling of vindoline with catharanthine and subsequent in situ oxidation to provide vinblastine, its extension to the total synthesis of related natural products and key analogs will be presented. Use of this technology in key studies addressing the structural features of vinblastine contributing to its tubulin binding and antitumor properties, and the synthesis, evaluation, and discovery of potent analogs will be summarized.




Catharanthine


Vindoline

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Richmond Sarpong

UC Berkeley, USA

Educational Background

Undergraduate Education:

Macalester College, St. Paul, MN.

B.A. Degree (Chemistry Major), May 1995 (Advisor Prof. Rebecca C. Hoye)

Graduate Education:

Princeton University, Princeton, NJ

Master of Science Degree (Organic Chemistry), May 1997

Ph. D. in Organic Chemistry, May 2001 (Advisor Prof. Martin F. Semmelhack)

Postdoctoral Institution:

California Institute of Technology, Pasadena, CA

UNCF•Pfizer Postdoctoral Fellow in Organic Synthesis, 2001–2004

(Advisor Prof. Brian M. Stoltz)

Professional Positions Held

University of California, Berkeley

Executive Associate Dean, College of Chemistry (July 2018–Present)

Full Professor, Department of Chemistry (July 2014–Present)

Associate Professor, Department of Chemistry (2010–June 2014)

Assistant Professor, Department of Chemistry (2004–2010)

Selected Honors and Awards

ISHC Alan R. Katrizky Award (2019)

Mukaiyama Award of the SSOCJ (2019)

John Simon Guggenheim Fellow (2017)

Noyce Prize for Excellence in Undergraduate Teaching (2016)

RSC Synthetic Organic Chemistry Award (2015)

ACS Arthur C. Cope Scholar (2015)

SSOCJ Lectureship Award (2011)

Camille Dreyfus Teacher-Scholar Award (2009)

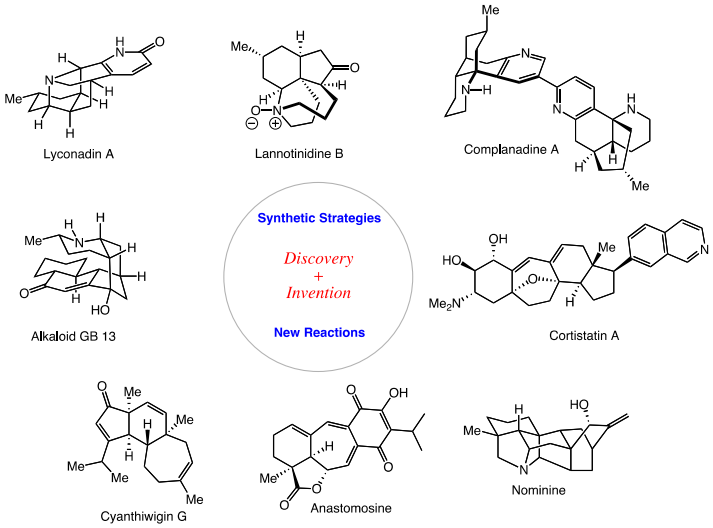
Alfred P. Sloan Foundation Fellow (2009)

5AL-A-2

Strategies and Methods for Synthesis Inspired by Complex Natural Products

Richmond Sarpong*
Department of Chemistry, University of California–Berkeley
Berkeley, California 94720, USA

Natural products continue to inspire and serve as the basis of new medicines. They also provide intricate problems that expose limitations in the strategies and methods employed in chemical synthesis. Several strategies and methods that have been developed in our laboratory and applied to the syntheses of architecturally complex diterpenoid alkaloids, indole alkaloids, and several *Lycopodium* alkaloids, will be discussed.



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5AL-A-3

Guy Humphrey

Merck, Sharp and Dohme (MSD), Rahway, USA

Dr. Guy Humphrey received his Ph.D. from the University of Southampton, UK in 1986. He joined the MSD process research group in Hoddesdon, UK and subsequently relocated, in 1990, to the MSD Department of Process Research in Rahway, USA. Throughout his career he has worked on multiple pipeline compounds, spanning many therapeutic areas, at all development stages. He has been involved in the design of manufacturing routes to a number of MSD compounds including Grazoprevir, Anacetrapib, Telcagepant, Tredaptive, Isentress, Odanacatib, and Montelukast. Most recently his group was responsible for the route design, development and regulatory filing for the approved drugs Letermovir (antiviral), Doravirine (HIV), and Ceftolozane (antibiotic).

His research interests are centered on the design and development of sustainable, practical synthetic methodologies and application to the efficient synthesis of drug intermediates and final drug substances. He is currently a distinguished scientist in the process research group at MSD in Rahway and leads the process chemistry department's scientific advisory council.

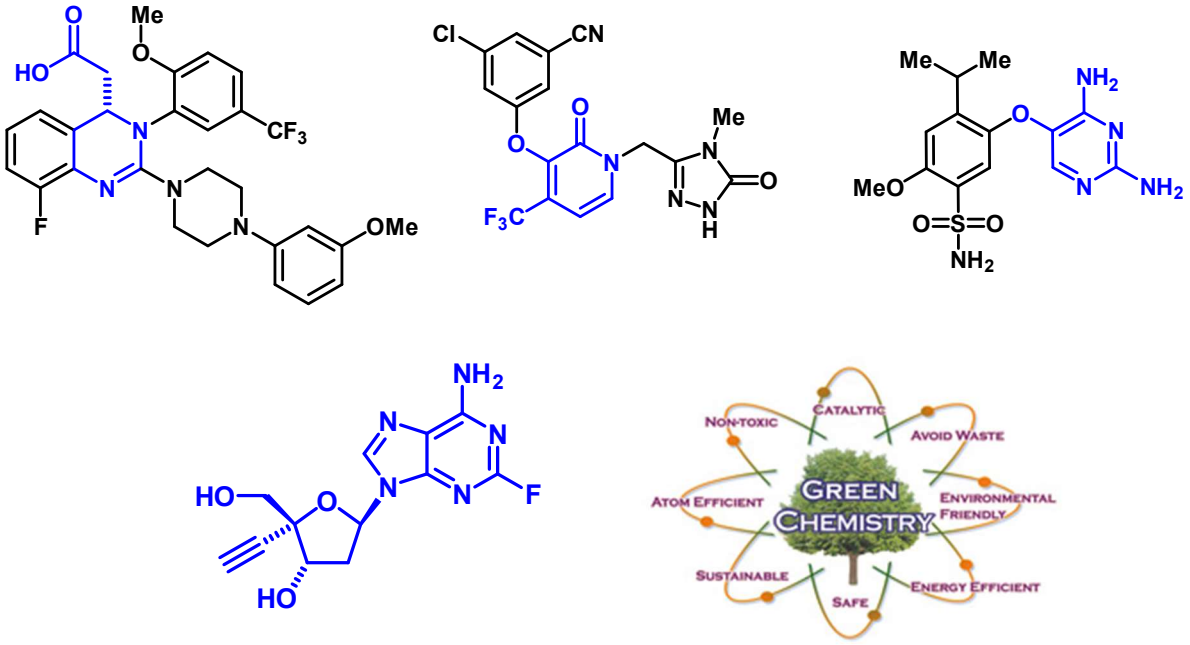
He received an ACS Heroes of Chemistry award in 2013 (Isentress), three consecutive EPA Green Chemistry Challenge awards for Letermovir (2017), Doravirine (2018) and Ceftolozane (2019) and the ACS Industrial Chemistry award in 2019. He is an advisory board member of Organic Process Research & Development Journal and member of the ACS Green Chemistry Institute Pharmaceutical Round Table.

5AL-A-3

Innovation: Key Enabler for the Development of Sustainable Commercial Manufacturing Processes at MSD

Guy Humphrey
Process Research and Development, Merck Sharp and Dohme,
Rahway, NJ, 07065, USA

Innovation is a key enabler in the design and development of highly efficient, green and sustainable commercial manufacturing processes for drug candidates. Several case studies from MSD's late-stage development and recent commercial product pipeline will be presented demonstrating innovative synthetic solutions as the key to enabling our 'best chemistry at first file' approach. Inherently green and sustainable technologies such as chemo- and bio-catalysis and continuous processing as well as process and mechanistic understanding will be highlighted with respect to efficient, large scale syntheses of a variety of heterocycles contained within medically useful bioactive molecules.



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ABSTRACTS OF INVITED LECTURES

Sep. 5th, RoomA (ROHM Theatre Kyoto, Main Hall)

Michida, Makoto (Daiichi Sankyo Co., Ltd., Japan) 5IL-A-1

Sep. 5th, RoomB (ROHM Theatre Kyoto, South Hall)

Kanai, Motomu (The University of Tokyo, Japan) 5IL-B-1

Ritter, Tobias (Max-Planck-Institut für Kohlenforschung, Germany) 5IL-B-2

Sep. 5th, RoomC (ROHM Theatre Kyoto, North Hall)

Dixon, Darren J. (University of Oxford, United Kingdom) 5IL-C-1

Takayama, Hiromitsu (Chiba University, Japan) 5IL-C-2

2IL-A-1

Preparation of Chiral Molecules for Pharmacophores

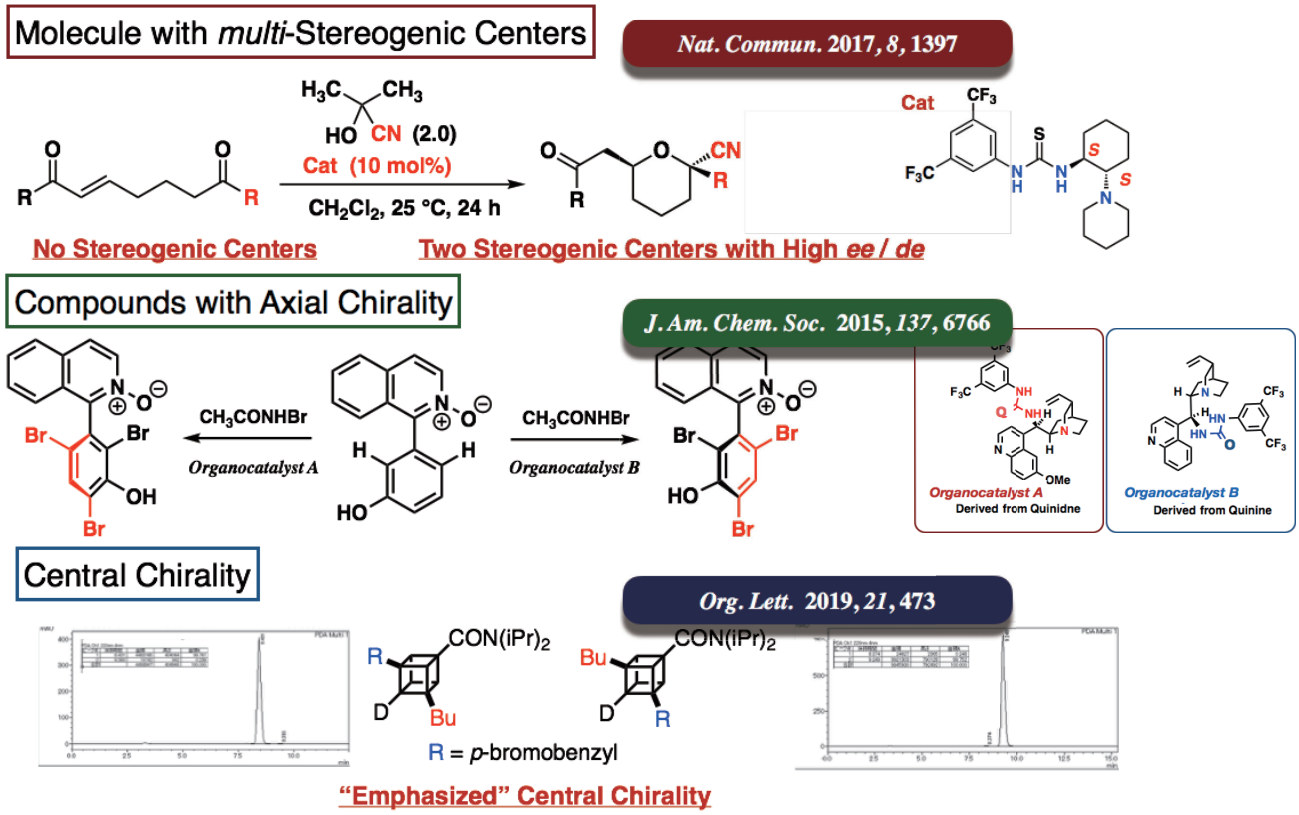
Seijiro MATSUBARA

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan

Interactions between proteins are known to trigger the onset of various diseases. Although relatively large molecules (middle-sized molecules) such as peptides are known to be effective in inhibiting these interactions, even small molecules have been found to be effective depending on the type of PPIs.

In this case, the small molecule is required to mimic various effective middle molecule structures, but above all it is necessary to enantioselectively control the configuration of several substituents in the molecule. To that end, we developed a method to simultaneously create several stereogenic centers and a method to create axially asymmetric compounds at once. As shown in the figure, a ζ-oxo-α,β-unsaturated ketone was converted into the disubstituted THP derivative stereoselectively in the presence of the amine-thiourea catalyst; axially chiral isoquinoline oxide derivatives were also obtained with high ee via bromination in the presence of the amine-thiourea catalyst.

In addition, cubane, which is considered to be an expanded molecular skeleton that emphasizes central asymmetry, was also converted into the chiral substituted derivatives. Although various elegant cubane syntheses have been studied since the synthesis of Eaton, we developed a method to synthesize 1,3,5-substituted cubane selectively by the newly developed protocol.

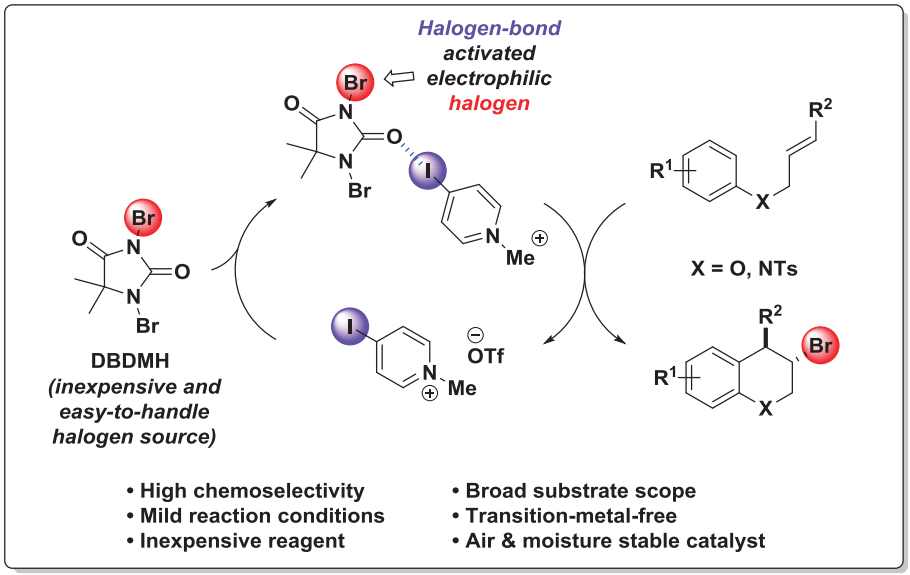


2IL-A-2

Recent Advances in Halocyclizations

Xiaodong Xiong, Zhihai Ke and Ying-Yeung Yeung*
Department of Chemistry, The Chinese University of Hong Kong, Shatin, NT, Hong Kong (China)

Electrophilic halocyclization reactions are an important class of organic transformation. Over the pass decades, reactions including cohalogenation, haloetherification, halolactonization and polyene cyclization are well documented. These reactions have been applied in many natural products and drug molecules synthesis. One of the research focuses in our research group is on the development of novel halogenation reactions using *N*-halosuccinimides, which are inexpensive and easy-to-handle halogen sources.[1] Recently, we have applied chiral cyclic selenide and sulfide catalysts in the asymmetric halocyclization reactions.[2] Various chiral, non-racemic pyrrolidines and lactones were prepared with good yields and ees. In this lecture, our recent progress in the development of organocatalytic and highly efficient halogenation reactions will be presented.[3]



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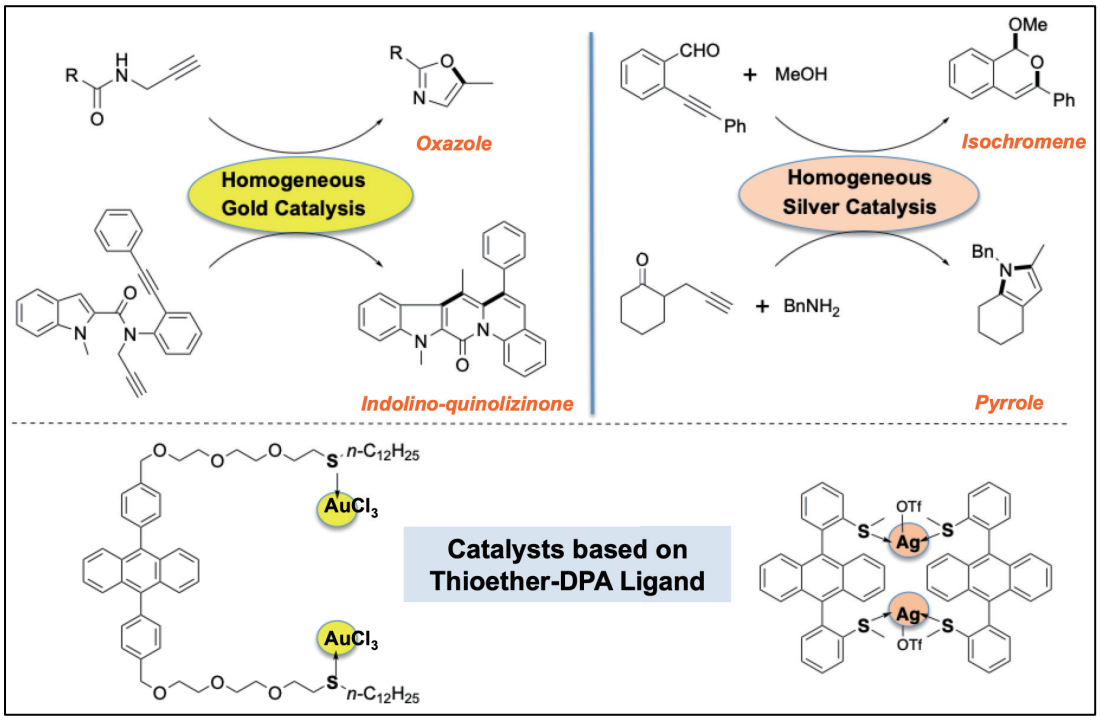
[3] (a) Xiong, X.; Yeung, Y.-Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 16101.(b) Liu, Y.; Tse, Y.-L. S.; Kwong, F. Y.; Yeung, Y.-Y. *ACS Catal.* **2017**, *7*, 4435. (c) See, J. Y.; Yang, H.; Zhao, Y.; Wong, M. W.; Yeung, Ke, Z.; Y.-Y. *ACS Catal.* **2018**, *8*, 850. (d) Chan, Y.-C.; Yeung, Y.-Y. *Angew. Chem. Int. Ed.* **2018**, *57*, 3483. (e) Gieuw, M. H.; Ke, Z.; Yeung, Y.-Y. *Angew. Chem. Int. Ed.* **2018**, *57*, 3782. (f) Xiong, X.; Yeung, Y.-Y. *ACS Catal.* **2018**, *8*, 4033.

2IL-A-3

9,10-diphenylanthracenes as scaffolds for metal coinage catalysts

B. Bibal*
Institut des Sciences Moléculaires UMR CNRS 5255, Université de Bordeaux, 33405 Talence, France

In recent years, gold and silver catalysis have enabled the efficient creation of C-C and C-X (X: O, N, S) bonds, by exploiting the redox and/or Lewis acid properties of these metals.
We are interested in the design of thioether ligands incorporated on 9,10-diphenylanthracenes (DPA), to benefit from the rigid architectures and the photophysical properties of these polyaromatic skeletons. The synthesis of silver (I) or photoreductible gold (III) chloride complexes using these thioether-DPA ligands will be presented, as well as their uses as catalysts for the synthesis of heterocycles and polaromatic compounds.[1]



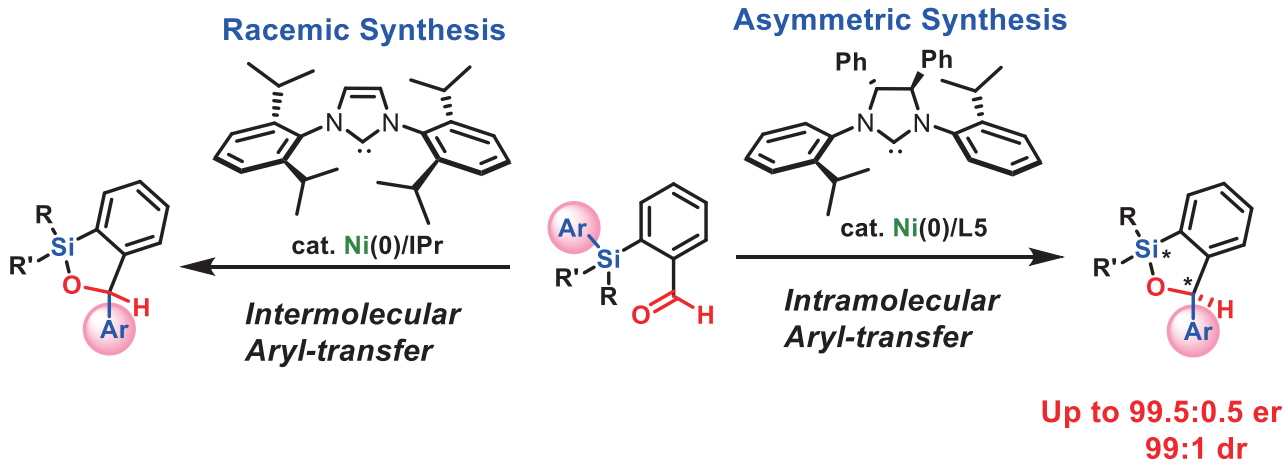
[1] (a) C. Mongin, I. Pianet, G. Jonusauskas, D. M. Bassani, B. Bibal, *ACS Catal*. **2015**, 5, 380-387; (b) Z. Cao, D. M. Bassani, B. Bibal, *Chem. Eur. J*. **2018**, 24, 18779-18787 (hot paper).

2IL-A-4

Nickel-catalyzed Synthesis of Benzoxasiloles: Ligand-Controlled Switching from Inter- to Intramolecular Aryl-Transfer Process

Sensuke Ogoshi*
Department of Applied Chemistry, Faculty of Engineering Osaka University, Suita, Osaka 565-0871, Japan

Chemists know that the changing ligands in the transition metal catalysis can change the reaction path to give a different product. In other words, chemists recognize the changing the reaction path based on the observation of the unexpected product. Previously we have reported the nickel-catalyzed synthesis of benzoxasiloles in the presence of IPr.[1] The reaction proceeds as an intermolecular reaction. Later, the asymmetric reaction in the presence of L5 has been also reported. In this reaction the reaction proceeds as an intramolecular reaction. [2] Although these two reactions afford absolutely same reaction product, the reaction is completely different. Details will be discussed at the presentation.



Reference

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[2] Kumar, R.; Hoshimoto, Y.; Yabuki, H.; Ohashi, M.; Ogoshi, S., Nickel(0)-Catalyzed Enantio- and Diastereoselective Synthesis of Benzoxasiloles: Ligand-Controlled Switching from Inter- to Intramolecular Aryl-Transfer Process. *J. Am. Chem. Soc.* **2015,** *137* (36), 11838-11845.

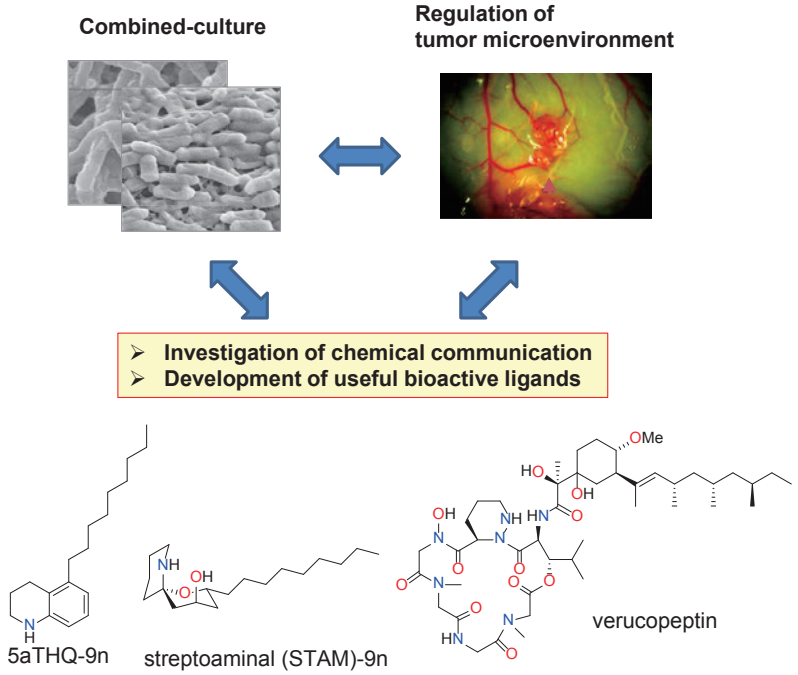
2IL-B-1

Frontier Research on Chemical Communications Unveils the Mystery of Life Science

Hideaki Kakeya*
Graduate School of Pharmaceutical Sciences, Kyoto University
Sakyo-ku, Kyoto 606-8501, Japan

The Scientific Research on Innovative Area "Frontier Research on Chemical Communications (Project Leader: Kakeya, H. (Kyoto Univ.), FY2017-2021)[1] " has started since June of 2017, which is supported by JSPS KAKENHI. This research project aims at not only developing innovative high-order analysis platforms, but also at clarifying essential roles of natural products as chemical communication molecules in the natural environment, leading to the development of useful chemical tools as well as pharmaceutical/agrochemical leads.

Our research group in this project has been challenging the development of chemical communication molecules among microbes including gut microbiota, as well as useful bioactive ligands such as pharmaceutical/agrochemical leads and chemical tools[2]. In this symposium, I will firstly introduce the outline of our project "Frontier Research on Chemical Communications" and then present our recent progress on antifungal 5-alkyl-1,2,3,4-tetrahydroquinoline (5aTHQs) and antimicrobial streptoaminals (STAMs)[3-5], produced by combined-culture of *Streptomyces nigrescence* HEK616 and *Tsukamurella pulmonis* TP-B0596, and anticancer verucopeptin[6] produced by *Steptomyces* sp. KUSC_A08.



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2IL-B-2

A Synthetic Molecule-based Approach Toward Controlling of Transient Protein Interactions

Junko Ohkanda*
Institute of Agriculture, Shinshu University, Minami-Minowa, Nagano 399-4598, Japan

Transient interactions of biomolecules play an essential role in the dynamic regulation of intracellular signaling machinery. The important components are intrinsically disordered proteins (IDPs) that are predicted in nearly 40% of all human proteins. Their structural flexibility allow the same proteins to interact with different partner molecules with different consequences, serving as hubs in protein interaction networks that regulate crucial cellular processes, including transcription, translation and the cell cycle. Recent advances in understanding of biological roles of IDPs have revealed that their dysregulation is associated with diseases, highlighting IDPs as a new class of therapeutic targets. However, development of clinical pharmaceuticals targeting IDPs remains a difficult challenge due to the diverse functions, complexity of their regulatory mechanism including post-translational modifications, and lack of binding sites for drug-like small molecules.

We are interested in developing a new methodology for developing synthetic molecules that are capable of controlling the function of IDPs. To this end, we envisioned that structure-based approach for inhibitors of IDP-binding proteins, or library screening-based approach for exploration of agents that directly bind and alter the function of IDPs would be possible. In this presentation, we will first describe a rational design of synthetic agents that disrupt protein-protein interactions (PPIs) of phosphorylated IDPs and their adopter proteins, a family of 14-3-3 proteins. Our results demonstrated that intracellular conjugation of a diterpene glycoside and a peptide fragment allowed for in situ generation of a mid-sized agent, which disrupts binding of c-Raf to 14-3-3, resulting in significant cytotoxicity. Interestingly, the cupper-free Huisgen cycloaddition between the azide-containing diterpene and the peptide fragment comprising cycloalkyne functionality proceeded regioselectively, suggesting the template effect of 14-3-3 upon the conjugate formation.

Second, we will describe our recent effort on developing an *in vitro* evaluation system for protein interactions of IDPs based on a conventional fluorescent polarization methodology. To this end, we designed truncated proteins of the transcription factor of the circadian clock machinery, and applied them for high-through-put screening of a heterocyclic library. As a result, several hit compounds were identified, and one of them was so far validated as a selective PPI inhibitor. The details of the design, and biological evaluation will also be discussed.

[1] H. Ruan, Q. Sun, W. Zhang, Y. Liu, L. Lai, *Drug Discov. Today* **2019**, *24*, 217-227.
[2] P. E. Wright, H. J. Dyson, *Nat. Rev. Mol. Cell. Biol.* **2015**, *16*, 18-29.
[3] J. Ohkanda, *Chem. Rec.* **2013**, *13*, 561-575.
[4] P. Parvatkar, N. Kato, M. Uesugi, S. Sato, J. Ohkanda, *J. Am. Chem. Soc.* **2015**, *137*, 156624-15627.
[5] J. Ohkanda, A. Kusumoto, L. Punzalan, R. Masuda, C. Wang, P. Parvatkar, D. Akase, M. Aida, M. Uesugi, Y. Higuchi, N. Kato, *Chem. Eur. J.* **2018**, 24, 16066-16071.

2IL-B-3

Heterocyclic Acenes and Quinodimethanes

Chunyan Chi*
Department of Chemistry, National University of Singapore
3 Science Drive 3, Singapore, 117543

Acene-based molecular materials have been demonstrated to be useful semiconductors and chromophores. For example, pentacene and rubrene are among the top most studied molecules used in active layer in organic field effect transistors (OFETs) with high hole mobilities. Longer acenes can be also used as model compounds to investigate zig-zag edges of graphene. However, one drawback which hampers their general applications is their intrinsic instability. Typical reactions of acenes related to the diene conjugation include addition with singlet oxygen to form endoperoxide and dimerization under light irradiation. In addition, parent acenes usually have poor solubility in common organic solvents. Therefore, we have developed several strategies to stabilize and solubilize acene based molecules, and a few kinds of acene derivatives have been prepared such as n-type acenes cyclopenta-fused acenes and quinoidal heteroacenes[1-5]. Heteroatom-containing quinoidal acene analogues and their charged forms could serve as good model compounds to understand the electronic properties of the all-carbon acenes. Some examples are shown below. Some of them also show open-shell diradical character and exhibit unique optical, electronic, and magnetic activity.

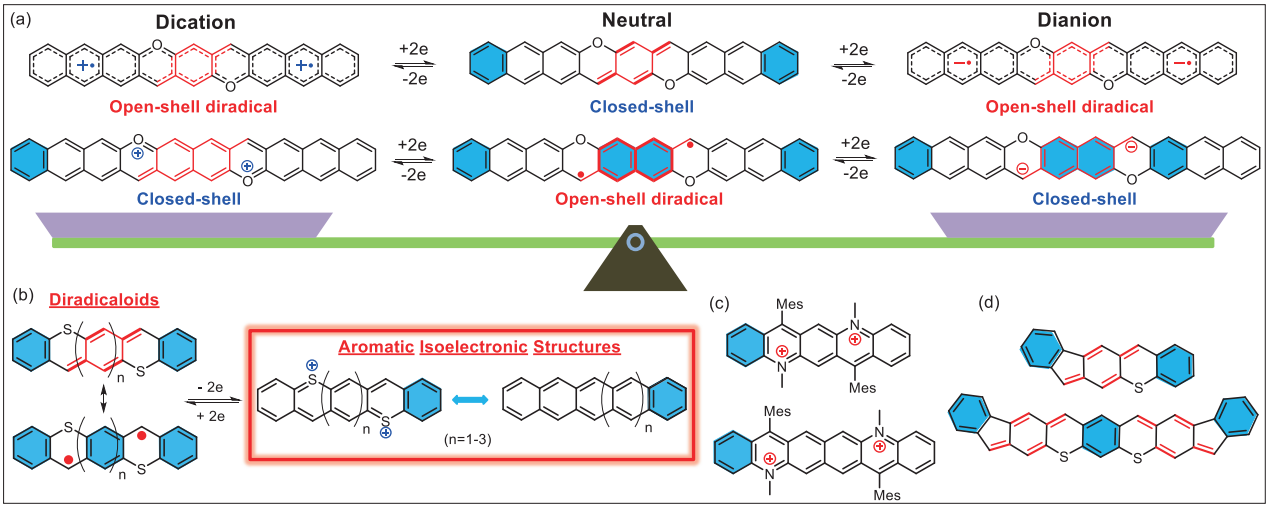

Figure 1. The examples of heterocyclic acenes and quinodimethanes.

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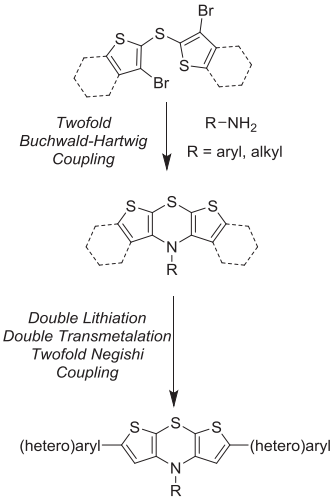
[2] Yuan, L.; Han, Y.; Tao, T.; Phan, H.; Chi, C. *Angew. Chem. Int. Ed*. **2018**, *57*, 9023.
[3] Wang, Q.; Gopalakrishna, T. Y.; Phan, H.; Herng, T. S.; Dong, S.; Ding, J.; Chi C. *Angew. Chem. Int. Ed.* **2017**, *56*, 11415.
[4] Dong, S.; Herng, T. S.; Gopalakrishna, T. Y.; Phan, H.; Lim, Z. L.; Hu, P.; Webster, R. D.; Ding, J.; Chi, C. *Angew. Chem. Int. Ed*. **2016**, *55*, 9316.
[5] Shi, X.; Kueh, W.; Zheng, B.; Huang, K.-W.; Chi, C. *Angew. Chem. Int. Ed*. **2015**, *54*, 14412.

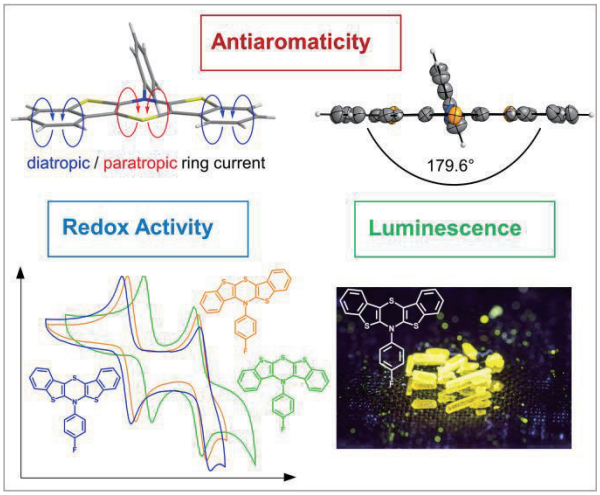
2IL-B-4

Dithieno-anellated [1,4]Thiazines – Redox Activity, Luminescence Characteristics and Antiaromaticity of Novel Congeners of Phenothiazine

Thomas J. J. Müller,[1]* Arno P. W. Schneeweis,[1] Simone T. Hauer,[1] and Catherine Dostert[1]
Institut für Organische Chemie und Makromolekulare Chemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, D-40225 Düsseldorf, Germany

Thieno [1-4] and benzothieno anellated [1,4]thiazines [5,6] can be readily accessed by twofold Buchwald-Hartwig aminations. These title compounds are significantly more electron rich than their more familiar congeners, i.e. phenothiazines, as supported by DFT calculations and cyclic voltammetry data [4]. While dithieno[1,4]thiazines are particularly interesting as strong donors due to their rich organometallic one-pot functionalization chemistry [2,3], *anti-anti* and *syn-anti* bis[1]benzothieno[1,4]thiazines reveal peculiar electronic properties [5,6]. *Anti-anti* bis[1]benzothieno[3,2-*b*:2',3'-*e*][1,4]thiazines display pronounced green luminescence in solution ($\Phi_F \approx 20\%$) and in the solid state, while *syn-anti* regioisomers are only weakly luminescent in solution, but show aggregation induced emission enhancement and solid state luminescence. X-ray structure analyses of *anti-anti* derivatives amazingly reveal coplanar arrangements of the pentacyclic anellated 1,4-thiazine system, emphasizing a structural similarity to heteroacenes. The calculated theoretical nucleus-independent chemical shifts (NICS) additionally confirm that these 8π-electron core systems can be considered as the first electronically unbiased anellated 1,4-thiazines with antiaromatic character.





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3IL-A-1

Synthesis of Trifluoromethylated Heterocycles under Palladium Catalysis

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Fluoro-functionalized heterocycles with diverse ring sizes and ring systems have been well studied in pharmaceuticals and agrochemicals. Thus, a remarkable number of publications have been dedicated to the development of efficient synthetic methods to construct fluoro-functionalized heterocycles. In particular, heterocyclic molecules with a trifluoromethyl carbinol moiety, i.e., $CF_3C(OR1)R^2R^3$, have gathered much attention on account of their promising biological properties. Efavirenz (anti-HIV), trifluoromethylated artemisinins (anti-malarial), and fluralaner (insecticide and acaricide) are representative examples (Figure 1).

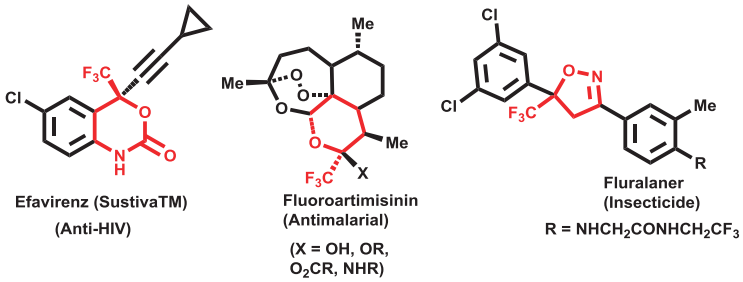
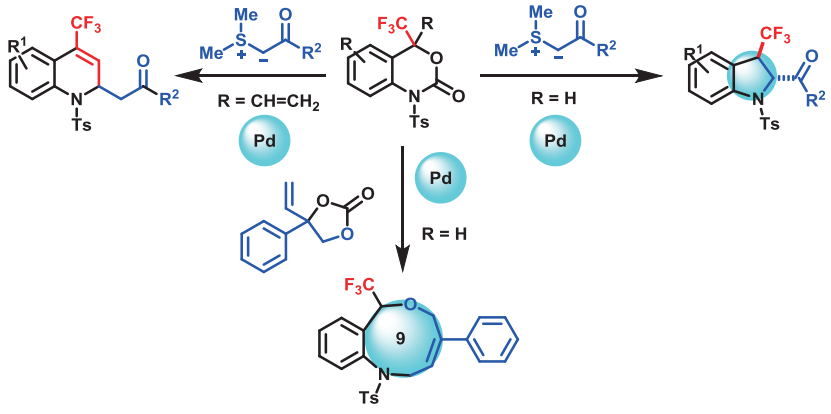


Figure 1.

In this presentation, our recent progress in the development of novel synthetic methodologies for fluorine-containing heterocycles will be discussed. The chemistry here will be focused on palladium-π-benzyl intermediates for the construction of trifluoromethyl-containing heterocycles (Scheme 1). [1]



Scheme 1.

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3IL-A-2

Designing of templates to reach the distal C–H bond

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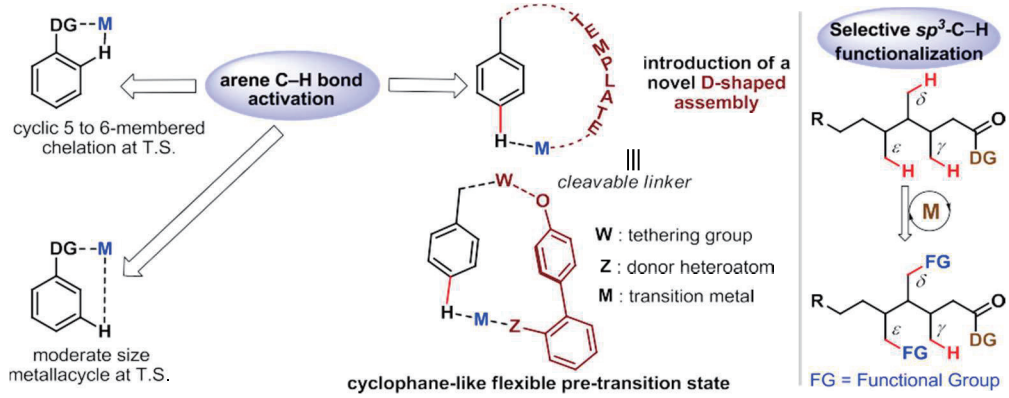
A practical protocol to simplify natural product synthesis by site selective C–H functionalization had always been a coveted target for chemists. Most often, directing group assisted metallacycle formation has served as an efficient strategy in ensuring promising regioselectivity. In this regard wide variety of *ortho*- functionalization stands as an archetype. Despite significant progress, directing group- assisted selective distal C–H functionalization in arenes (at *meta*- and *para*-positions) had remained an unexplored venture mainly due to the formation of a geometrically constrained metallacyclic transition state. To address these issues, a novel class of cleavable linker with nitrile based templates that direct efficient functionalization of distal *para*- and *meta*-C–H bonds are introduced. Recently, more robust heterocycle-based directing template has been designed to deliver the various and most useful functionalizations at remote *meta*-position. In addition, we have judiciously designed the directing group and substrate in a way which can selectively activate the distal aliphatic C(*sp3*)–H bond. Applicability of these template based strategies have been demonstrated by synthesizing various natural products and complex molecules through post synthetic modifications. In this talk, some of our recent efforts toward design of the novel templates and late-stage functionalizations and mechanistic elucidation will be discussed.



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3IL-A-3

Making Chiral Heterocycles Using Chiral Heterocycles as Ligands

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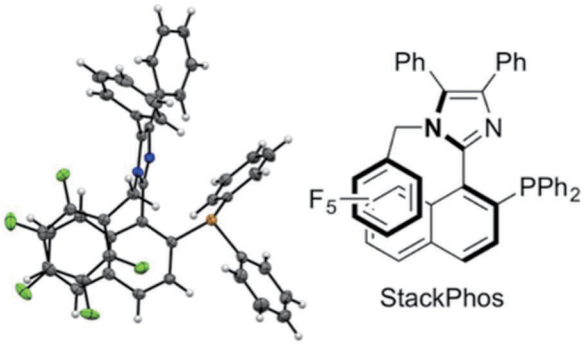
Enantioselective catalysis has been a mainstay of contemporary organic chemistry and, as such, the development of new ligands for transition metal catalysis is an important and active area of research. Finding new ligand archetypes enables the development of new reactions and new synthetic strategies. In this vein, we introduced imidazole-based chiral biaryl *P,N*-ligands[1,2] where the axial chirality is enabled by stabilizing pi-pi interactions. These ligands have proven to be excellent promoters for alkyne addition reactions and recent results in this area from our laboratory will be presented.[3,4]



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CpRu-catalyzed Enantioselective Dehydrative Cyclization of Protic Nucleophile tethered Allylic Alcohols

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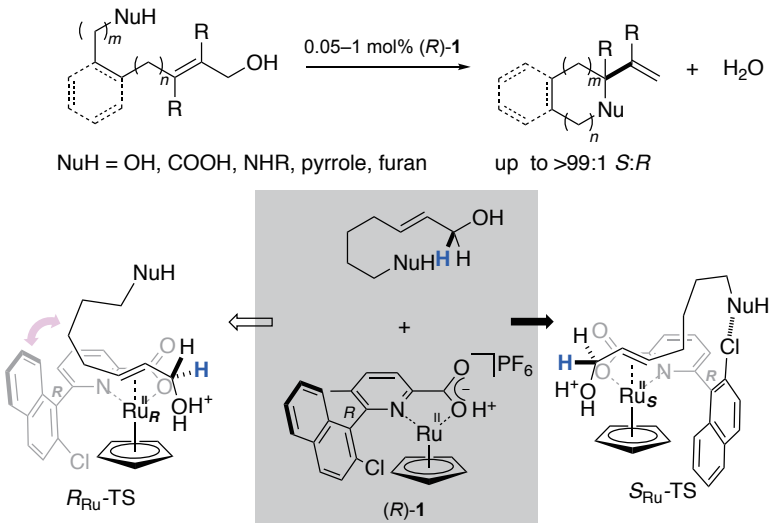
Tsuji-Trost allylation, which is one of the core Parts of catalytic asymmetric syntheses, is continuously expanded till now by using allyl esters or halides as the standard allyl donors. The number of the related papers now exceeds 3000. In this trend of asymmetric allylation history, we have established Cl-Naph-PyCOOH–Ru-catalysed dehydrative Tsuji-Trost-type allylation operating under slightly acidic conditions, realizing efficient asymmetric synthesis of various hetero- and carbo-cyclic compounds, all of which are important chiral intermediates for syntheses of natural products and pharmaceuticals.[1]–[3] Change from the salt liberating system to the water liberating system should be advantageous not only from the view points of the atom and step economy and environmental benignity but also from the retrosynthetic view point. Change in the conditions from basic to acidic should reverse the π allyl donicity, increasing flexibility in the synthesis of important compounds. [Ru(II)Cp((*R*)-Cl-Naph-PyCOOH)]PF_6 ((*R*)-**1**) activates the substrate by soft metal/proton cooperation mechanism, in which the ruthenium metal interacts with the double bond and the carboxylic proton interacts with the hydroxyl oxygen atom of the allylic alcohol moiety, facilitating oxidative addition. Complex (*R*)-**1** exists as two diastereomer mixtures, (*R*,R_{Ru})-**1** and (*R*,S_{Ru})-**1**, which have their own reactivity and selectivity and generate the two possible diastereomeric transition states, R_{Ru}-TS and S_{Ru}-TS. The energy levels of the TSs are highly affected by steric effect, hydrogen bond, halogen bond, CH/π interaction, and so on.[4] The details will be discussed in this paper.



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Pillar-Shaped Macrocyclic Compounds "Pillar[n]arenes": from Simple Molecular Receptors to Bulk Supramolecular Assemblies

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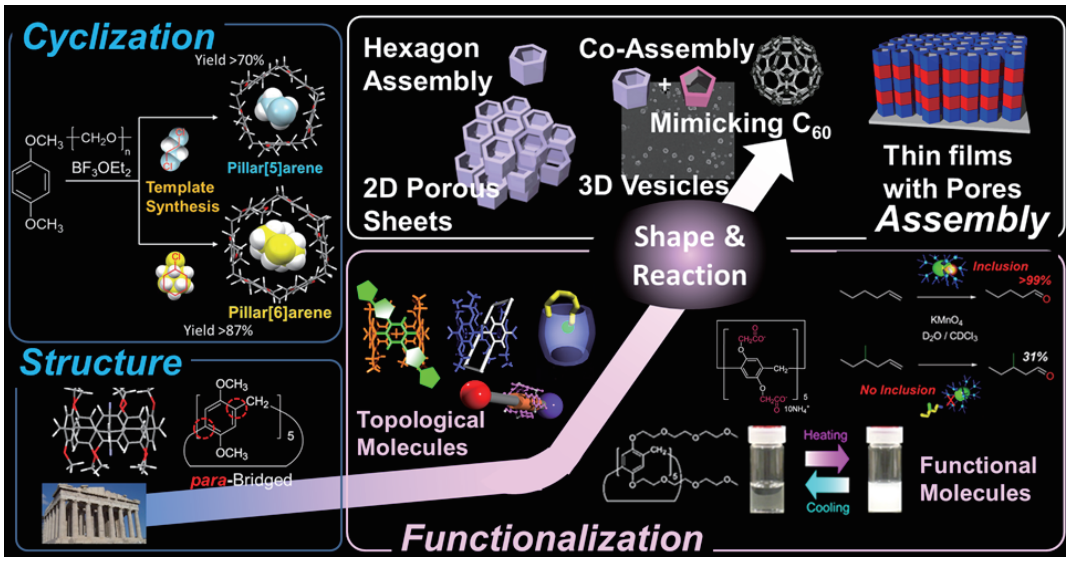
Macrocyclic compounds play a major role in supramolecular chemistry because of their beautiful shape, nano-scale size and molecular recognition ability. Numerous supramolecular architectures have been constructed and studied as new components of materials as well as entities related to biological structural formation and functions using various macrocyclic hosts. In 2008, we reported a new class of macrocyclic hosts named "pillar[n]arenes".[1,2] Linear 1,2-dichloroethane and bulky chlorocyclohexane acted as template solvents for high-yield synthesis of pillar[5]- and pillar[6]arenes, respectively. They have unique symmetrical pillar structures due to their para-bridge linkage. We have synthesized various topological and functional molecules based on functionality of pillar[n]arenes, and constructed 2D sheets and 3D vesicles based on geometric assemblies of their pentagonal and hexagonal structures.[3]



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3IL-B2

π-Extended Tetrathiafulvalenes (exTTFs): Versatile Heterocyclic Partners of Carbon Nanostructures in Donor-Acceptor Systems

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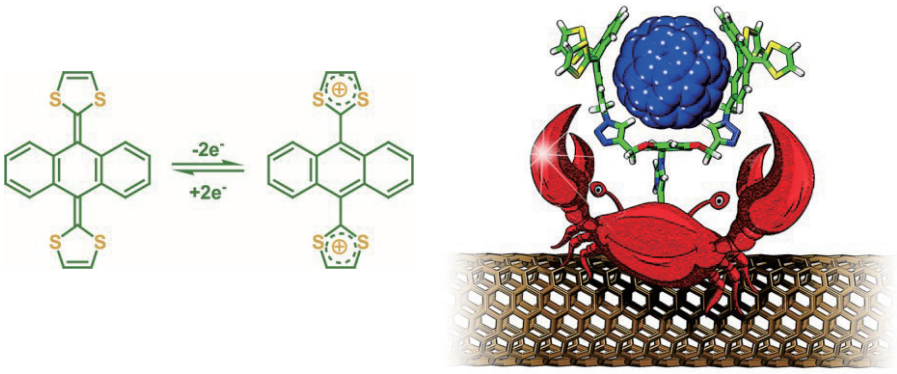
The *p*-quinoid analogue of tetrathiafulvalene (TTF), 2-[9-(1,3-dithiol-2-ylidene)anthracen-10(9H)-ylidene]-1,3-dithiole (exTTF), is a proaromatic heterocycle that undergoes aromatization upon oxidation, affording thermodynamically stable radical-cationic and dicationic species at relatively low oxidation potentials. Furthermore, the formation of aromatic species upon oxidation is accompanied by a dramatic geometrical change, which stabilizes the ion radical or the dication pairs.

Several synthetic approaches have been explored in the search for artificial photosynthetic models and photovoltaic systems, with a great deal of effort devoted to the preparation of π-conjugated donor-acceptor (D-A) organic molecules. In this regard, exTTFs have a beneficial effect in the charger transfer process by stabilizing the radical ion pairs generated upon light irradiation.[1]

As electron-accepting counterparts, carbon nanostructures such as fullerenes, carbon nanotubes, graphene or carbon-based dots, offer a whole plethora of nanomaterials with different morphologies and properties to be merged with exTTFs.[2-5] Recent examples of D-A systems based on the covalent and non-covalent combination of exTTFs and carbon nanostructures will be discussed (*e.g.* three-component assembly of exTTF receptors anchored to carbon nanotubes sidewalls for the recognition of C_{60} units).



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3IL-B-3

Dominant Rotors as a Tool to Control Macrocycles

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This lecture will describe my lab's emerging interest in non-equilibrium systems. I will use macrocycles as a way to showcase functionally rich molecules that suffer from a poor understanding of conformation. The emerging evidence suggests that a "butterfly effect" operates in large rings. It describes situations where a small change at a given position of a macrocycle may result in disproportional consequences at a distal location. Until recently, the available data had not translated into what matters most – a metric that describes the response of a given system to perturbation. To tackle this issue, we have implemented the concept of the dominant rotor, which corresponds to the bond that has the highest barrier to the rotation. This simple approach has allowed us to evaluate response factors in a wide range of rings and led to the creation of two-well systems with controlled conformational behavior. To reach our objectives, we have designed amino acids and other building blocks that offer varying degrees of control over rotors. The most exciting outcome of this work is our capability to detect, study, and isolate conformational isomers in the 0.5-3 kcal/mol energy range. Their unusual structural features suggest that there might be "hidden space" in the conformational analysis. Our work underscores that operations away from equilibrium offer an exciting possibility to control complex molecules.

Synthesis of Rotaxane Catalysts for Asymmetric and Processive Reactions

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Rotaxane can be characterized by dynamic nature of the components through the topological or mechanical linkage between them. Molecular switch, motor, and machine are typical application of rotaxane, as symbolized by the Nobel prize given for Prof. Stoddart and Prof. Sauvage in 2016. Another application is to utilize the cooperative effect of the rotaxane components in the reaction field. We have first reported the asymmetric reaction catalyzed by rotaxane, where catalytic asymmetric Benzoin condensation proceeded via effective through-space chirality transfer[1,2].
In this paper, we would like to discuss on the processive reaction, i.e. Pd macrocycle-catalyzed intramolecular cyclization of allylurethane moiety[3,4] and Pt macrocycle-hydrosilylation of diphenyl acetylene moiety of polymers, in which the formation of pseudorotaxane structure plays an important role as the key intermediate, in addition to the catalytic asymmetric reactions[5,6]. These reactions proceeded efficiently by the catalysts as shown below, two of which were prepared according to the typical rotaxane synthetic method[7].

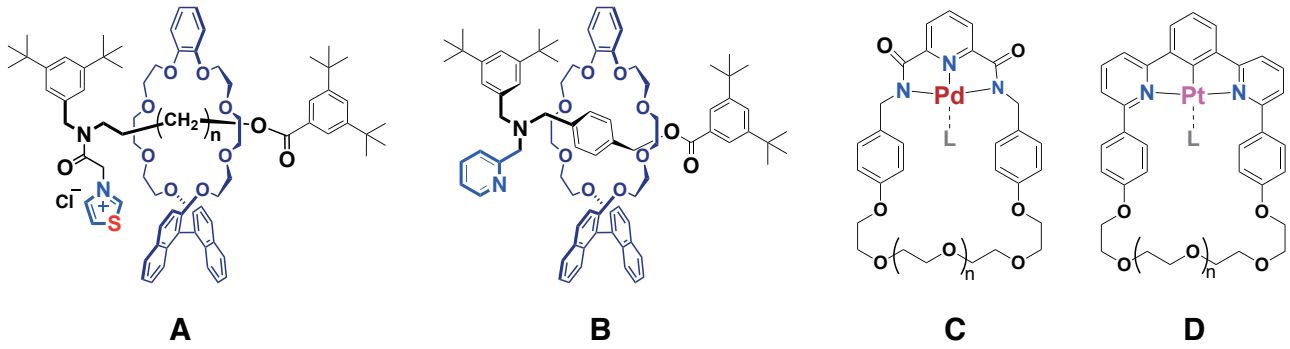

Figure. Structures of the catalysts for asymmetric benzoin condensation (**A**), *O*-acylative asymmetric desymmetrization of *meso*-1,2 -diol (**B**), processive intramolecular cyclization of allyurethane moiety of polymer (**C**), and processive hydrosilylation of diphenyl acetylene moiety of polymer (**D**).

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Enantioselective Cooperative Catalysis with Frustrated Acid/Base Complexes

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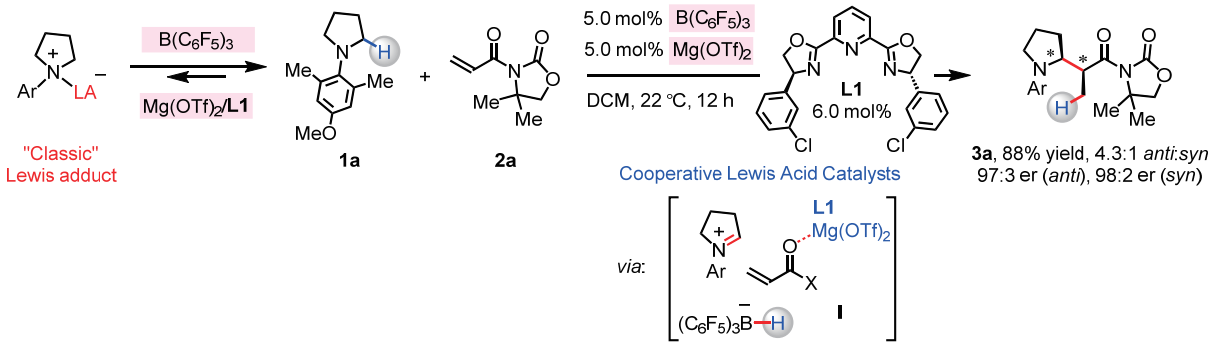
Cooperative enantioselective catalysis has previously been applied to the development of reactions between in situ generated, acid-activated electrophiles and base-activated nucleophiles. Nevertheless, notable shortcomings remain unaddressed. For instance, mutual quenching might occur in a mixture that contains an electrophile, a nucleophile, together with an acid and a base catalyst. One way to circumvent acid–base complexation is by avoiding a combination that exhibits high affinity (i.e., hard–hard or soft–soft pairing). However, this latter approach has thus far been limited to cases in which weakly to moderately acidic and/or basic promoters are involved, where only highly acid- or base-sensitive substrates can be used. Development of potent and unquenchable cooperative catalyst systems that facilitate reactions between unactivated substrates is an important and largely unresolved problem in enantioselective catalysis.

We have designed an enantioselective coupling of *N*-alkylamines (**1a**) and α,β-unsaturated compounds (**2a**) by implementing the cooperative action of two Lewis acid catalysts that possess overlapping functions (Scheme 1).[1] We have achieved this by developing catalyst/substrate combinations that form frustrated Lewis pairs (FLPs), namely, active acids and bases whose mutual quenching (formation of "classic" Lewis adduct) is sterically precluded. By tuning of different features of structurally and electronically different Lewis acids and substrates, the ability of Lewis acid catalysts to serve as a hydride acceptor from amines, or an activator of α,β-unsaturated compounds towards borohydride reduction to afford a chiral enolate, can be adjusted (**I**). Accordingly, enhancements in both the efficiency and stereoselectivity of C–C bond forming reactions between amines and α,β-unsaturated compounds can be attained without concomitant loss in enantioselectivity arising from any undesirable mode of catalysis by the achiral Lewis acid component. These principles serve as a conceptual framework for the development of new processes that demand separate and independently operational Lewis acidic co-catalysts whose functions might overlap and the simultaneous use may have a negative impact on enantioselectivity.

Scheme 1. Enantioselective C–H Functionalization of Amines by Cooperative Action of Chiral and Achiral Lewis Acid Catalysts



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Asymmetric route to chiral heterocyclic compounds toward efficient manufacturing process

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Asymmetric synthesis is pivotal methodology for manufacturing of drug substances (DSs) because about more than half of drugs currently used are chiral compounds. Manufacturing processes of chiral DSs become more efficient and atom economical as new asymmetric reactions have been developed in these decades. As one of the contracted development and manufacturing organizations (CDMO) for pharmaceutical industry, we would like to present our recent approaches toward several chiral heterocyclic compounds that overcome difficulties in manufacturing in a large scale.

1) Stereodivergent synthesis of cyclic 1,2-aminoalcohols

Cyclic 1,2-aminoalcohols are important building blocks because they are found in various pharmaceutical ingredients, biologically active compounds, and also used as ligands for metal-catalyzed reactions. Aside from their simple structure, there are scarce versatile and practical methods for all stereoisomers. As for *trans* isomer, the most reliable method is ring-opening of an epoxide followed by optical resolution with a corresponding chiral acid. However, it is not efficient because more than an equal amount of a chiral acid is required, and its theoretical yield is up to 50%. In the case of *cis* isomer, a few asymmetric synthetic methods[1] have been reported, but they are not suitable for the application of manufacturing in a large scale. We have developed an efficient and robust process for cyclic 1,2-aminoalcohols starting from cyclic ketones. Key reactions are: 1) Neber rearrangement; 2) Ru-catalyzed *cis*-selective dynamic asymmetric transfer hydrogenation; 3) Inversion on a hydroxy moiety under the mild conditions (for *trans* isomer). The developed process uses only readily available reagents, avoids harsh conditions and column purification step so that it is suitable for scale-up synthesis.

2) Synthesis of a heterocyclic amine via direct asymmetric reductive amination[2]

Direct asymmetric reductive amination (DARA) with an ammonia source has attracted much attention because it provides a chiral primary amine from a corresponding ketone in a single step. Since the first DARA was reported by Blaser *et al.* in 1999,[3] several elegant works have been reported, and currently aryl methyl ketones are able to be subjected to DARA.[4] However, there has been scarce report for heterocyclic amine especially for highly functionalized one. We have developed iridium-catalyzed DARA of 2-thiazolyl methyl ketone with ammonium salicylate as an ammonia source. It was found that both a reaction procedure and an additive were quite important to achieve high yield and enantioselectivity. The successful multi-kilogram manufacturing result of the chiral amine will also be presented.

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3IL-C-3

Total Synthesis of Natural Dimeric Terpenoids: Inspired but Not Limited by Biohypothesis

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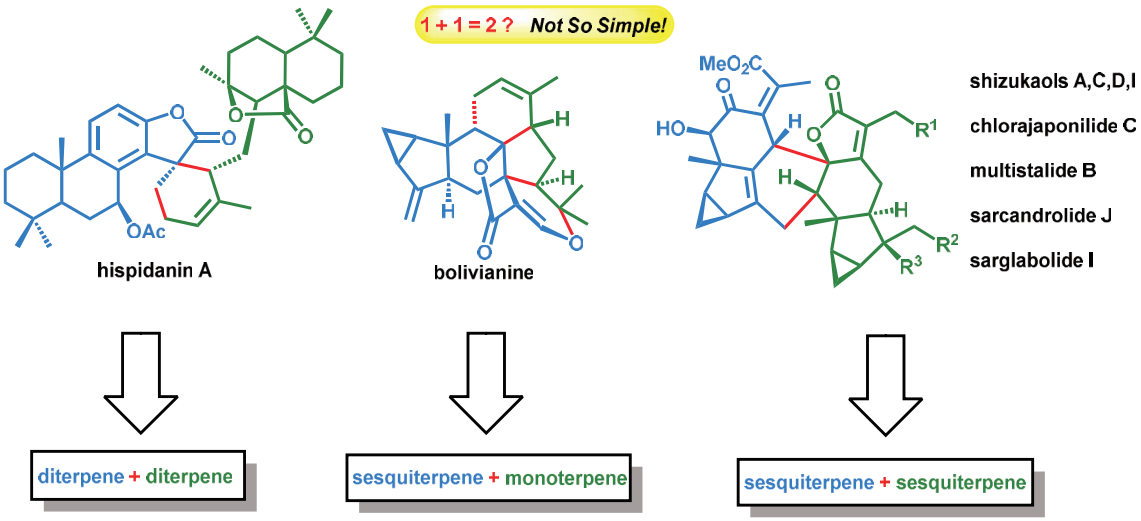
Generally, synthetic chemists can accomplish very concise and beautiful total syntheses inspired by biosynthetic information or just hypothesis of natural products. However, a detailed and reliable biosynthetic mechanism of a specific natural product requires a lot of time and endeavor for biochemists and molecular biologists. Hypothesis for biosynthetic pathway of natural products is very necessary and instructive to understand the machinery of their formation, but it could be modified in the practice of retrosynthetic analysis and chemical synthesis on the base of chemical reactivity of the proposed biosynthetic intermediate. We would like to present our recent studies on the total synthesis of several natural dimeric terpenoids on the basis of our modified biosynthetic hypothesis. Compared to the originally proposed biosynthetic hypothesis, the modified ones were proved more practicable for formation of hispidanin A,[1] bolivianine,[2] shizukaols A, C, D, I, chlorajaponilide C, multistalide B, sarcandrolide J, and sarglabolide I,[3-4] from a viewpoint of chemical reactivity.



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4IL-A-1

Synthesis and biofunctional studies of immunomodulating glycoconjugates

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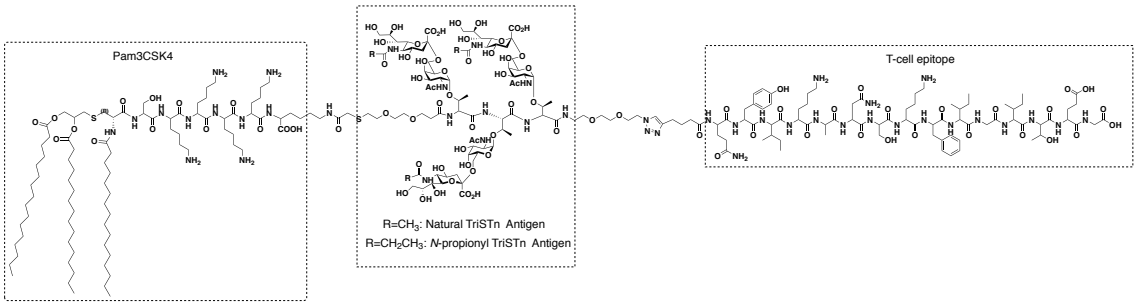
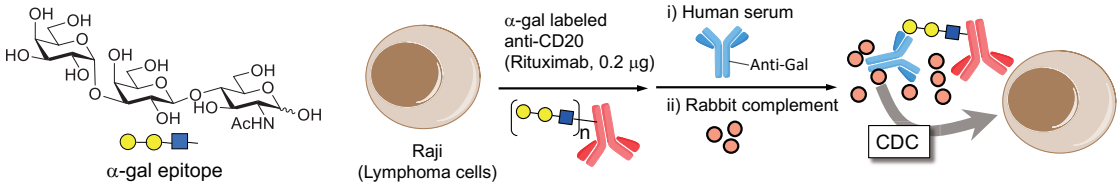
We have studied the synthesis of various microbial glycoconjugates such as peptidoglycans and lipopolysaccharides (LPS) to investigate their immunological functions. Here, we report on the application of their immunomodulatory effects to the developments of immune adjuvants and cancer vaccines. We found that LPS from *Alcaligenes faecalis*, a symbiotic bacterium inhabiting in dendric cells of Peyer's Patches, shows low inflammatory but effectively promotes antibody production.[1] The structural determination of *A. faecalis* LPS and its active entity lipid A and the synthesis and biological studies of *A. faecalis* lipid A will be reported.

Self-adjuvanting vaccines consisting in antigens and adjuvants have been investigated to improve vaccine efficacy and safety. We synthesized self-adjuvanting cancer vaccines composed of a trimeric tumor-associated carbohydrate antigen Sialyl-Tn (STn), a TLR2 agonist Pam3CSK4 as an adjuvant, and a T-helper epitope, since clustered STn antigens are highly expressed on many cancer cells. Immunization of vaccines in mice induced the anti-triSTn IgG antibodies, which recognized triSTn-expressing cell lines PANC-1 and HepG2.[2]



Humans do not have α-gal trisaccharide but have natural antibodies (Ab) against α-gal. The reaction of anti-Gal Abs with α-gal causes hyperacute rejection in xenogeneic organ transplantation. In this study, α-gal-Ab conjugates were developed that dramatically increased cellular cytotoxicity by recruiting natural Abs through the interaction between α-gal and anti-Gal Abs.[3]



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4IL-A-2

Novel Fluorescent Probes for Selective Detection and Imaging of Superoxide, Hydrogen Peroxide, Hypochlorous Acid, Hydroxyl Radical, and Peroxynitrite

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Reactive oxygen species and nitrogen species (ROS/RNS) play diverse roles in oxidative stress and redox signaling processes, which are regarded as key regulators in human health and disease. However, a lack of reliable molecular probes has hampered the mechanistic investigations in redox biology and medicine. Traditional probes with poor selectivity are no longer suitable to study individual ROS/RNS in complex biological processes, especially specific redox signaling. To address this gap, our lab has developed new chemical strategies with excellent selectivity and sensitivity toward superoxide, hydrogen peroxide, hypochlorous acid, hydroxyl radical, and peroxynitrite, respectively [1–5]. Those selective yet general sensing strategies could be extended to fluorescein, rhodol, rhodamine, naphthalimide, and BODIPY fluorophores, thus **HKSOX**, **HKPerox**, **HKOCl**, **HKOH**, **HKGreen**/**HKYellow** series probes have been developed as a comprehensive toolbox to detect individual species with different excitation/emission and organelle colocalization. Moreover, the photophysical properties of those probes could be modulated by chemical modifications of heteroaromatic fluorophores [6,7]. We anticipate that the **HK series** probes could provide robust tools to investigate complex ROS/RNS crosstalk and signaling process with spatial-temporal precision.

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4IL-B-1

Step Economic Total Synthesis of Heterocyclic Natural Products

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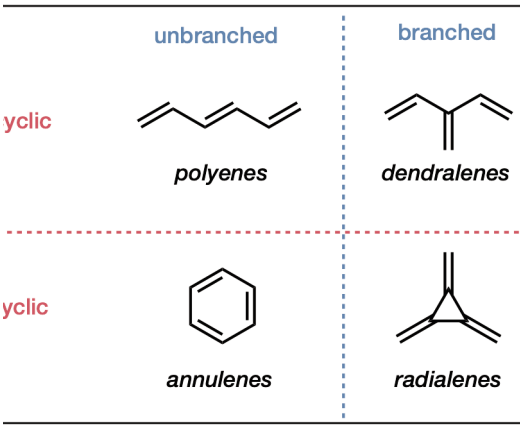
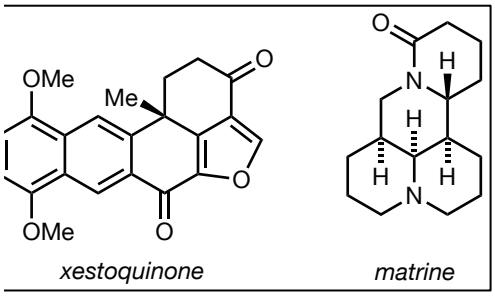
he two simplest acyclic branched hydrocarbons omprising only sp^2 carbons, namely]dendralene (3-methylene-1,4-pentadiene) and]dendralene (3,4-dimethylene-1,5-hexadiene), ere first reported in 1955 and 1962, respectively. o higher members of the series were described the literature until 2000.[1]



e played a dominant role in the push for a deeper nderstanding of these compounds and how to repare them, manipulate them, and best exploit eir virtually untapped synthetic potential.[2,3] These studies led to the successful synthesis of many nprecedented sp^2-C rich hydrocarbons, including [5]radialene, the simplest cyclic branched entaene.[4] These studies also involved the development of sp^2-C rich hydrocarbons as precursors r domino addition sequences that generate enormous amounts of structural complexity.[5]



This presentation will focus work involving the development of efficient new synthetic methods involving dendralenes, and the deployment of dendralenes in the most step economic total syntheses of bioactive natural products, including the pseudopterosins,[6] xestoquinone, and matrine.

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4IL-B-2

Asymmetric Total Synthesis of Heterocyclic Alkaloids with Chirality Economy

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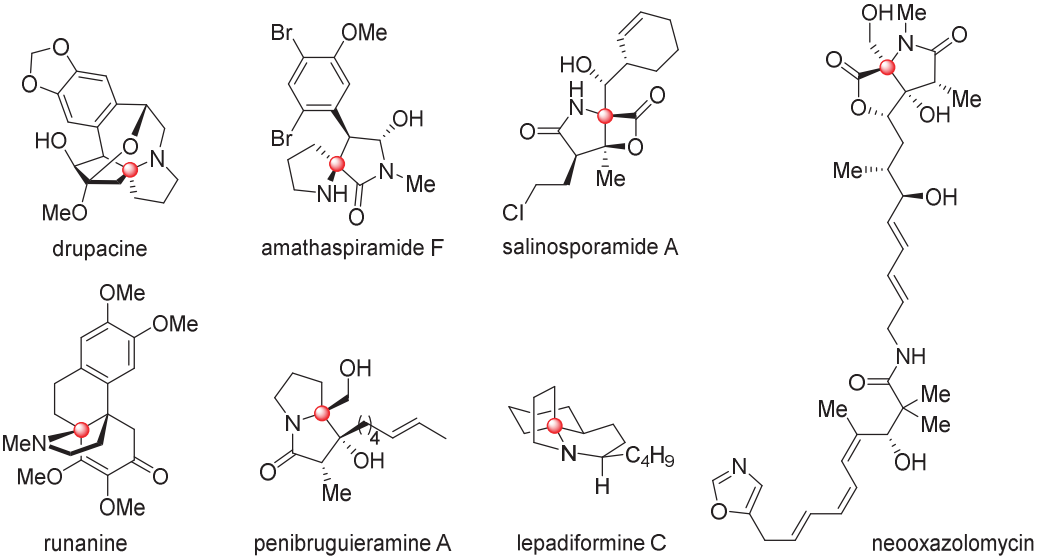
In recent years, we have been involved in the asymmetric total synthesis of biological interesting heterocyclic alkaloid natural products and their analogues without the aid of external chiral influences. Representative alkaloids of such interest include penibruguieramine, drupacine, lepadiformines, salinosporamides, cephalezomine, amathaspiramide, runanine, and neooxazolomycins. The common structural feature of these compounds is an asymmetric quaternary center bearing a nitrogen substituent (α-tertiary amines).

Amino acids was the staring material and the only source of chirality. Despite the possibility that the Cα-chiral center of amino acid might be destroyed by trigonalization during C-C bond formation, we have achieved an asymmetric synthesis without the aid of an external chiral influence. Towards this, we have utilized two strategies; Memory of Chirality and Carbon–to-Nitrogen-to-Carbon Chirality Transfer. These strategies was applied in a straightforward manner to the total synthesis of alkaloid natural products using an appropriate amino acid. In this presentation, I would like to share our old and new progress on this subject. A mechanistic rationale would be discussed for the excellent stereochemical outcome of reactions.



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4IL-C-1

Exploration and Exploitation of AZADO for Highly Selective Catalytic Oxidative Transformations

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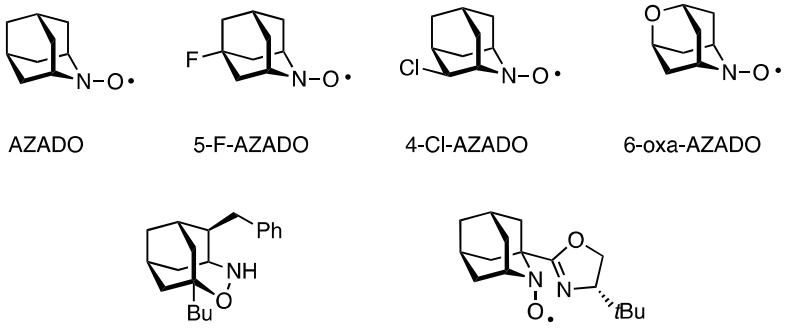
Nitroxyl radicals (*N*-oxyls or nitroxides), as exemplified by TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy) and PINO (phthalimidiy *N*-oxyl), represent a stable class of organic radicals that exhibit unique properties and reactivity. The diverse chemistry of these compounds has been found versatile use in electron spin resonance (ESR) studies as spin labels, in biological studies as antioxidants, as charge carriers for energy storage, as mediators in polymerization reactions, and as catalysts in chemical and electrochemical oxidation reactions. Our group has been focusing on the use of reversible redox properties to develop selective oxidative organic transformations employing caged-azacycles, specifically, AZADO (2-azaadamantane *N*-oxyl) [1] and the derivatives, [2-5] as the stereoelectronically modular platform. This lecture describes recent development of AZADO derivatives that enable highly chemo- and enantioselective aerobic alcohol oxidations.



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4IL-C-2

Chiral Tetrahydrothiophene Ligands in Asymmetric Catalysis

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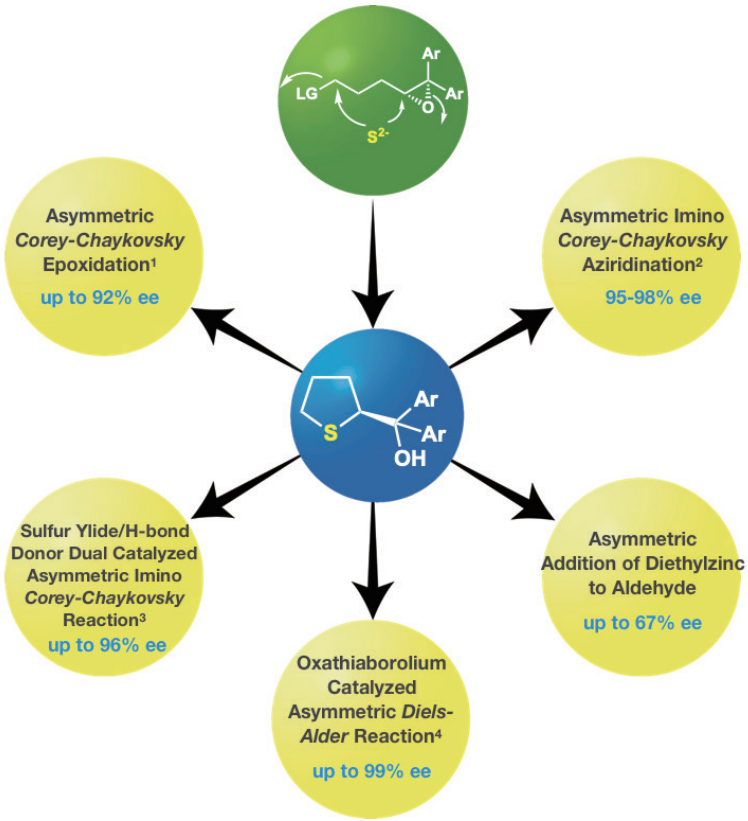
The fact that modern organic synthesis focus on the synthesis of enantiomerically pure molecules has made asymmetric catalysis an important art of organic synthesis. Continuous and all-around endeavors in this field are manifested in the discovery of new chiral organocatalysts or metal complexes with chiral ligands. Among such catalysts/ligands, chiral organosulfur compounds attracted much less attention than that of chiral phosphorus- or nitrogen-containing ligands although the number of studies with the former has increased considerably in recent decades. Here, we describe efficient and rapid procedures for the preparation of (*S*)-(thiolan-2-yl)diarylmethanols and demonstrate the applications of these chiral organosulfur ligands to the catalytic and asymmetric Corey-Chaykovsky epoxidation, the imino Corey-Chaykovsky aziridination, the Corey-Chaykovsky cyclopropanation, as well as the first oxathiaborenium catalyzed asymmetric Diels-Alder reaction.



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5IL-A-1

Development of an Efficient synthetic method for a Key Intermediate of Edoxaban

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Edoxaban is a once-daily direct oral anticoagulant (DOAC) that has been launched under the trade names Lixiana® and Savaysa® for the prevention of stroke in patients with atrial fibrillation (AF) and venous thromboembolism (VTE) recurrence.

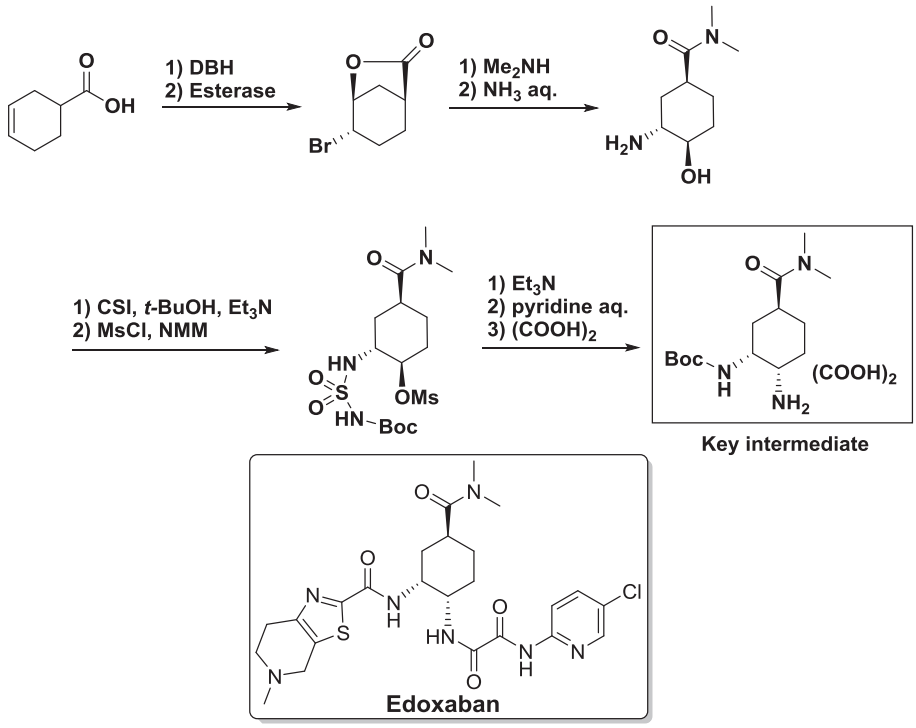
We developed a highly efficient synthetic method to access a key intermediate in the synthesis of Edoxaban which has three stereocenters including differencially protected 1,2-*cis*-diamine. The main features of the new synthetic method are

1) Enzymatic approach for the synthesis of chiral bromolactone

2) A unique cyclization reaction utilizing neighboring group participation to construct the *cis*-diamine

3) Implementation of plug-flow reactor technology for manufacturing scale

The overall yield for the preparation of Edoxaban was significantly increased by implementing these technologies and led to a more efficient and environmentally friendly manufacturing process. Herein, we would like to introduce our story of the development from the viewpoint of process chemistry.



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5IL-B-1

Aerobic Oxygen-Driven Functionalizations of Proteins

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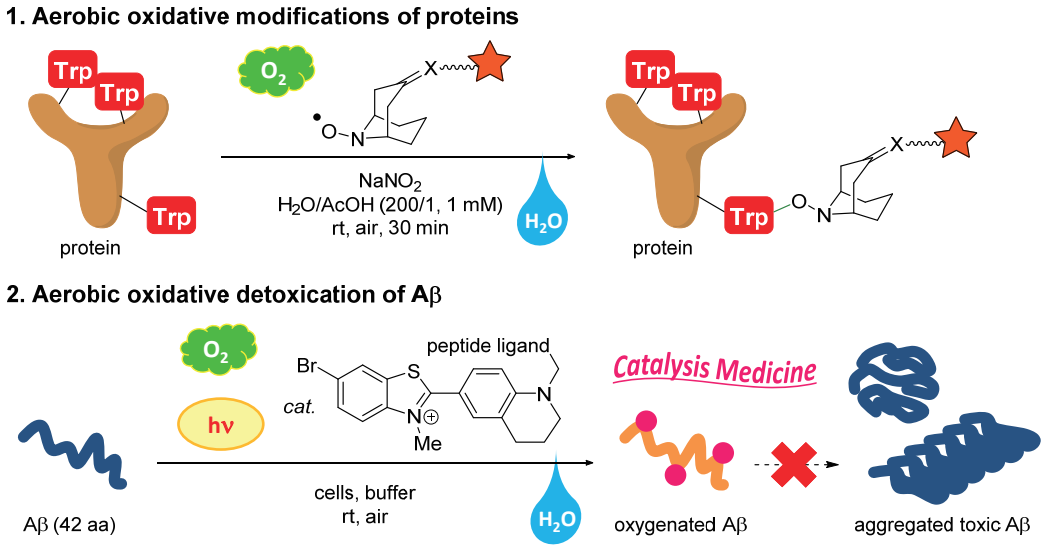
Our long-term research goal is developing synthetic catalysts that surrogate enzymes, and using the synthetic catalysis in our body as a new paradigm of medicine (catalysis medicine). Such a research direction should in turn contribute to green synthesis of functional molecules, including drugs. To do so requires powerful catalysts, which can functionalize stable, multifunctional organic molecules ranging from small molecules to biomacromolecules under mild conditions with synthetically valuable selectivity. I will present a tryptophan-selective protein functionalization [1] and catalytic detoxication of amyloid β (Aβ)/tau. [2] In both reactions, aerobic oxygen acts as a key driver. These two oxidative reactions may be useful for generating high-quality antibody–drug conjugates and treating Alzheimer disease, respectively.



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5IL-B-2

Late-Stage Functionalizations

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Late-stage functionalization reactions should reliably functionalize already complex molecules to quickly access value-added molecular diversity. Late-stage functionalization is desirable in many areas of discovery such as in drug or agrochemical development and a requirement in other areas such as the synthesis of positron-emission tomography (PET) tracers. I will describe the development of novel, modern highly selective reactions in late-stage functionalization, as well as their application in transition-metal-catalyzed and photoredox reactions, with a focus on the synthesis of ^{18}F and ^{19}F containing complex small molecules. In particular, I will describe the development of a broadly useful new C-H functionalization reaction to create molecular complexity for applications in catalysis, drug discovery, and medicine.

Nature **2011**, *473*, 470
Science **2011**, *334*, 639
Nature **2016**, *534*, 369
Nature **2018**, *554*, 551

5IL-C-1

Catalytic Approaches for Simplifying Complex Molecule Synthesis

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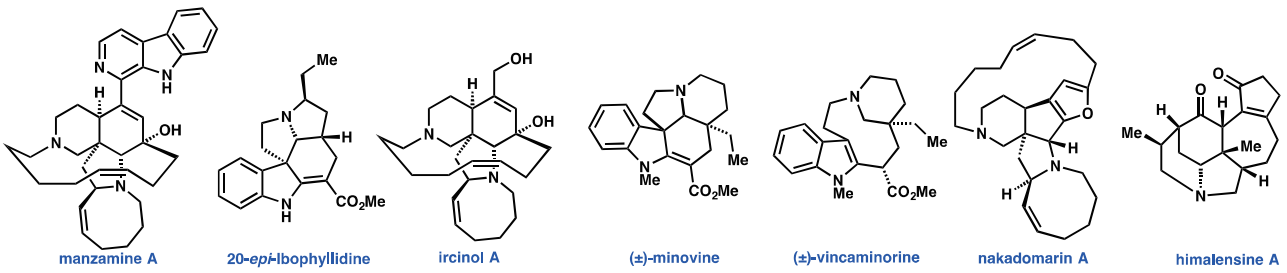
Catalysts that provide new reactivity and stereocontrol in efficient bond-forming reactions, are essential tools for converting low cost starting materials into high value, structurally complex, stereochemically defined product materials. In this presentation, new families of metal-free and metal-rich cooperative catalysts and their use in highly enantioselective C-C bond forming reactions and other relevant transformations, will be described.

Their strategic application to the discovery of new one-pot reaction cascade processes to generate novel, stereochemically defined scaffolds and architectures useful for library and target synthesis will also be discussed. Further application of selected methodologies as pivotal carbon-carbon bond forming steps in the total synthesis of a range of manzamine, aspidosperma, iboga, strychnos and daphniphyllum alkaloids will then be discussed. These syntheses serve to illustrate how complex molecular targets can be rapidly accessed when combinations of catalyst-controlled reactions, one-pot multistep procedures and powerful route-shortening cascades are designed into the overall synthetic sequence.[1-11]



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5IL-C-2

Asymmetric Total Syntheses of *Gelsemium* Alkaloids

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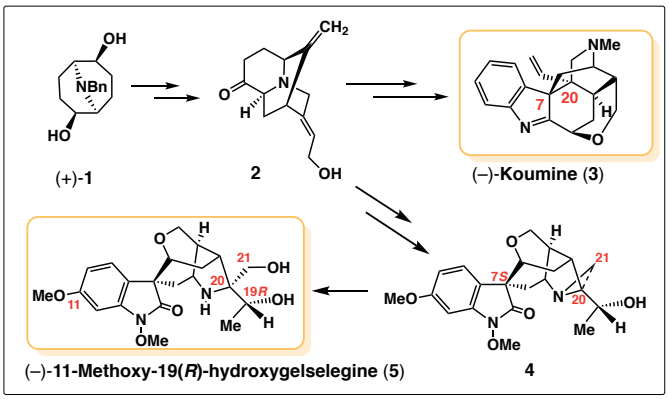
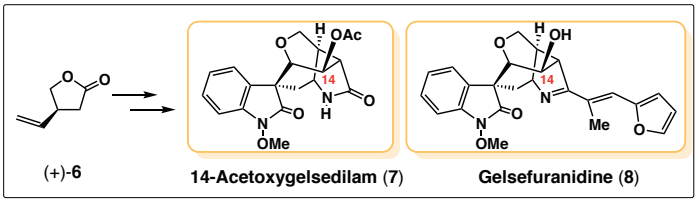
Graduate School of Pharmaceutical Sciences, Chiba University,
Chiba 260-8675, Japan

Gelsemium elegans is a toxic plant widely distributed in southeastern Asia and has been used as a traditional Chinese medicine for treatment of skin ulcers, cancer pains, *etc*.[1] We have investigated the ingredients of this plant resulting in the isolation of various skeletal types of indole alkaloids, and found that some of the gelsedine-type alkaloids exhibited potent cytotoxic effects against the A431 human epidermoid carcinoma cells.[2] This finding has prompted us to embark on the synthesis of *Gelsemium* alkaloids having unique structures and important biological activities. In this symposium, I present our recent results on asymmetric total syntheses of some *Gelsemium* alkaloids.

Koumine (**3**), one of the principle alkaloids of *G. elegans,* has a novel hexacyclic cage structure. Biogenetically, it would be derived from a simple Sarpagine-type alkaloid by intramolecular C-C bond formation at the C-7 and C-20 positions. By incorporating this hypothesis into the final stage of the chemical synthesis, we achieved total synthesis of koumine (**3**) starting from chiral diol (+)-**1** via an intermediate **2**.[3] Using the same intermediate **2**, 11-methoxy-19(*R*)-hydroxygelselegine (**5**), one of the gelsedine-type alkaloids with a hydroxymethyl group at the C-20 position, was also synthesized stereoselectively via a hypothetical biogenetic intermediate **4** with an aziridine function in the molecule.



By further chemical investigation of *G. elegans*, we found novel 14-hydroxylated gelsedine-type alkaloids, such as 14-acetoxygelsedilam (**7**) and gelsefuranidine (**8**).[4] Starting from the vinyl lactone (+)-**6**, the first asymmetric total syntheses of these alkaloids were accomplished. The synthetic studies concerning their related alkaloids will also be presented.



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ABSTRACTS OF ORAL PRESENTATIONS

Sep. 3rd, RoomB (ROHM Theatre Kyoto, South Hall)

Nakayama, Atsushi (Tokushima University, Japan)	3O-B-1
Opatz, Till (Johannes Gutenberg University, Germany)	3O-B-2
Takikawa, Hiroshi (Kyoto University, Japan)	3O-B-3
Qu, Jin (Nankai University, China)	3O-B-4
Ren, Hong (Merck Sharp & Dohme, USA)	3O-B-5
Schmidt, Andreas (Clausthal University of Technology, Germany)	3O-B-6
Jung, Sunna (Kwansei Gakuin University, Japan)	3O-B-7
Aitken, R. Alan (University of St Andrews, UK)	3O-B-8
Otani, Yuko (The University of Tokyo, Japan)	3O-B-9

Sep. 3rd, RoomC (ROHM Theatre Kyoto, North Hall)

Wang, Qiu (Duke University, USA)	3O-C-1
Xu, Xinfang (Soochow University, China)	3O-C-2
Nakamura, Itaru(Tohoku University, Japan)	3O-C-3
Arai, Takayoshi (Chiba University, Japan)	3O-C-4
Wang, Chao (The University of Tokyo, Japan)	3O-C-5
Chen, Jia-Rong (Central China Normal University, China)	3O-C-6
Asano, Keisuke (Kyoto University, Japan)	3O-C-7
Shirakawa, Seiji (Nagasaki University, Japan)	3O-C-8
Nishimoto, Yoshihiro (Osaka University, Japan)	3O-C-9

Sep. 3rd, RoomD (Miyako Messe 2nd Exhibition Hall ＜ D ＞)

Pospíšil, Jiří (The Czech Academy of Sciences, Institute of Experimental Botany, Czech Republic)	3O-D-1
Hirano, Koji (Osaka University, Japan)	3O-D-2
Okano, Kentaro (Kobe University, Japan)	3O-D-3
Waser, Mario (University of Linz, Austria)	3O-D-4
Hoffmann, Norbert (CNRS, Université de Reims, France)	3O-D-5
Ito, Mamoru (Waseda University, Japan)	3O-D-6
Ueda, Yoshihiro (Kyoto University, Japan)	3O-D-7
Blakey, Simon B. (Emory University, USA)	3O-D-8
Nozawa-Kumada, Kanako (Tohoku University, Japan)	3O-D-9

Sep. 5th, RoomA (ROHM Theatre Kyoto, Main Hall)

Tsui, Gavin Chit(The Chinese University of Hong Kong, Hong Kong)	5O-A-1
Wang, De-Xian (Institute of Chemistry, Chinese Academy of Sciences, China)	5O-A-2

Sep. 5th, RoomB (ROHM Theatre Kyoto, South Hall)

Hsieh, Jen-Chieh(Tamkang University, Taiwan)	5O-B-1
Reiser, Oliver (University of Regensburg, Germany)	5O-B-2

Sep. 5th, RoomC (ROHM Theatre Kyoto, North Hall)

Arai, Shigeru (Chiba University, Japan)	5O-C-1
Miura, Tomoya(Kyoto University, Japan)	5O-C-2

Sep. 5th, RoomD (Miyako Messe 2nd Exhibition Hall ＜ D ＞)

Total Synthesis of (–)–Dehydrobatzalladine C via Construction of Pyrrolopyrimidine Skeleton by Gold-Catalyzed Tandem Cyclization

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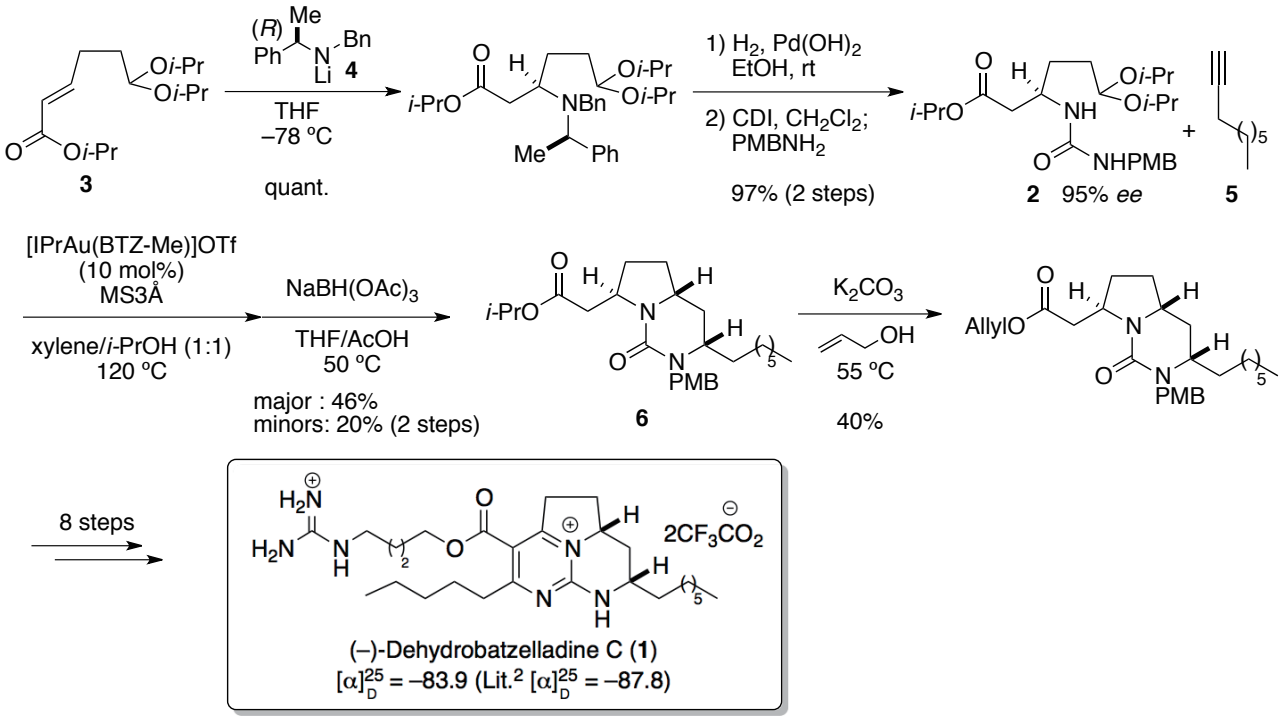
Graduate School of Pharmaceutical Science, Tohoku University
Sendai, Miyagi 980-8578, Japan

Dehydrobatzelladine C (**1**), isolated from the marine sponge *Monanchora arbuscula*, possesses a guanidine tricyclic skeleton and penta-substituted pyrimidine ring.[1] In addition to the characteristic structure, the potent anti-HIV and antibacteria activities of **1** has attracted considerable interest from synthetic chemists. Under these backgrounds, the first asymmetric total synthesis was achieved by Overman and co-workers in 2004.[2] Herein we describe a total synthesis of (–)-dehydrobatzelladine C via the newly developed pyrrolo[1,2-*c*]pyrimidine synthesis by gold-mediated auto-tandem catalysis.

Chiral urea **2** having acetal moiety was synthesized from α,β-unsaturated ester **3** via diastereoselective aza-Michael addition of (*R*)-α-phenethylamine (**4**). The key construction of pyrrolo[1,2-c]pyrimidine intermediate **6** proceeded upon treatment of urea **2** and alkyne **5** with catalytic amount of [IPrAu(BTZ-Me)]OTf, followed by reduction of imine moiety. After several step transformations including construction of core tricyclic skeleton of **1** via guanidinylation of the urea moiety and concomitant cyclization, the total synthesis of **1** was achieved by introduction of side chain having guanidine group at the terminus.



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Stereochemical Dichotomy in Two Competing Cascade Reactions: Enantio-divergent Total Syntheses of Spiroxin A

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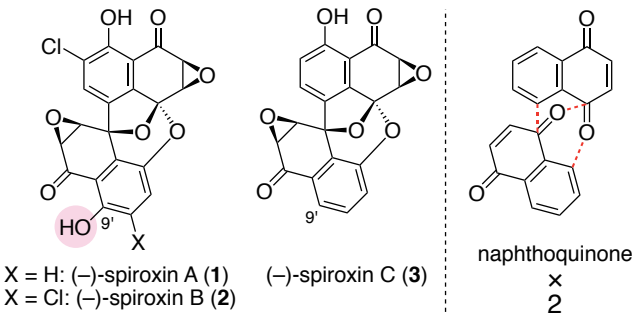
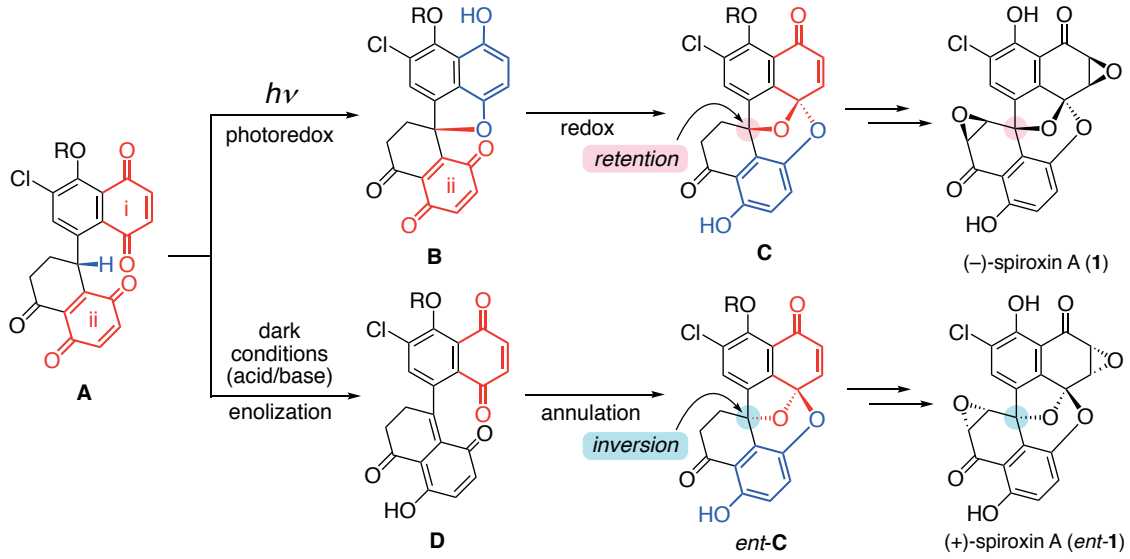
Department of Chemistry, Tokyo Institute of Technology, Tokyo/Japan 152-8551

Spiroxin A (**1**), the major constituent of the spiroxin-class marine natural products, sharing a unique dimeric naphthoquinone skeleton, and differing in the oxygenation and halogenation levels. Their highly complex architecture with sizable strain, plethora of sensitive functional groups, and multiple stereogenic centers present a challenge for chemical synthesis.



We recently reported the first enantioselective total synthesis of (–)-spiroxin C (**3**)[1] by expoiting a stereoretentive photoredox reaction[2,3] followed by oxidative spirocyclization as the two key steps. In addressing the synthesis of **1**, the presence of an additional hydroxy group at C9' in comparison with **3** gave us an idea: Given that the phtoredox reaction proceeds with substrate **A** having two quinones, i and ii, product **B** would be formed, which in turn would undergo an internal redox reaction spontaneously with the extra quinone ii, serving as an internal oxidant to give spiroacetal **C**. This idea worked very well, and the photoredox–redox reaction cascade proceeded in a *stereoretentive* manner. Furthermore, we serendipitously uncovered a chemically distinct pathway that is capable of converting **A** into *ent*-**C** with *stereoinvertive* manner via enol **D** in the dark conditions. These two cascade reactions enabled total syntheses of both enantiomers of spiroxin A.



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2O-A-3

Total Synthesis for Better and New Function: From Enabling Synthetic Methodology and Strategy to Novel Disease Target

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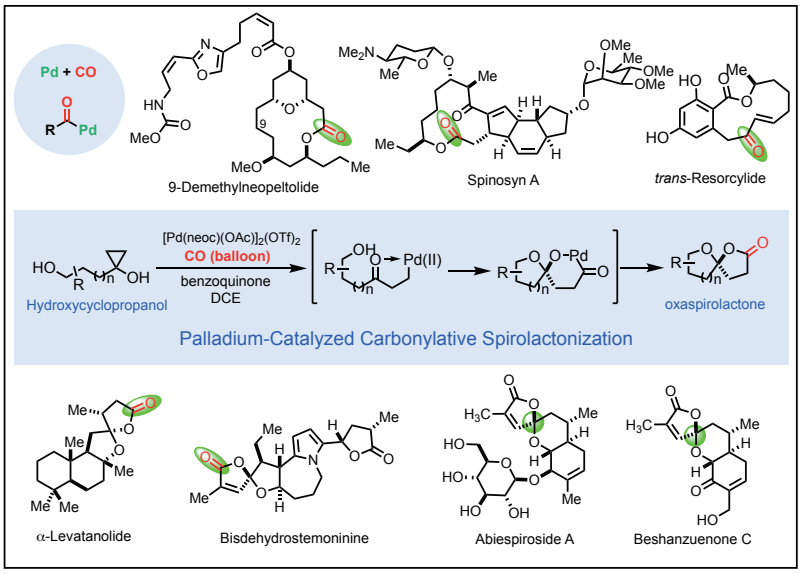
West Lafayette, Indian 47907, USA

One of our research programs focuses on developing novel palladium-catalyzed carbonylation reactions to (i) streamline the total synthesis of medicinally important natural products and (ii) facilitate comprehensive biological investigations and understanding of the target molecules' function. In these new enabling carbonylation reactions, cheap and abundant carbon monoxide was used as a one-carbon linchpin to quickly stitch relatively simple starting materials into complex structures, which in return significantly improves the overall synthetic efficiency.



Currently, we mainly work on macrocyclic [1-3] and spirocyclic [4-6] natural products. In this presentation, the ups and downs of our recent efforts in the total syntheses of oxaspirolactone-containing natural products by using a palladium-catalyzed carbonylative spirolactonization of readily available hydroxycyclopropanols will be highlighted. The target molecules include α-levantanolide [4], bisdehydrostemoninine [5], and two *abies* sesquiterpenoids abiespiroside A and beshanzuenone C [6]. Our chemical syntheses of the *abies* sesquiterpenoids further enabled (i) the validation of beshanzuenone C's weak PTP1B inhibiting potency, (ii) discovery of a new synthetic analog as a selective covalent inhibitor of oncogenic protein tyrosine phosphatase SHP2, (iii) identification of DNA polymerase epsilon subunit 3 (POLE3) as one of the novel cellular targets of these *abies* sesquiterpenoids, and (iv) evaluation of targeting POLE3 with small molecules as a novel strategy for chemosensitizing cancer cells to DNA damaging drugs such as etoposide.

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Total Synthesis of (+)-Laurallene

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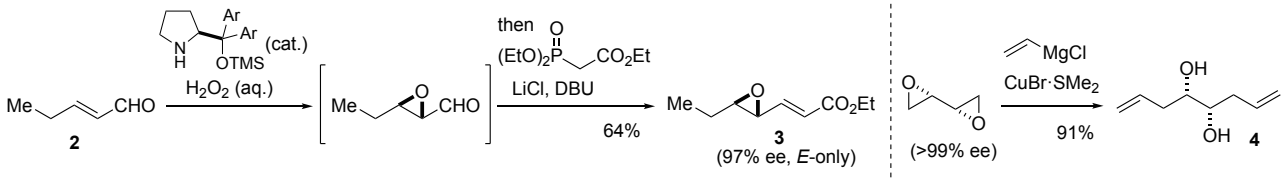
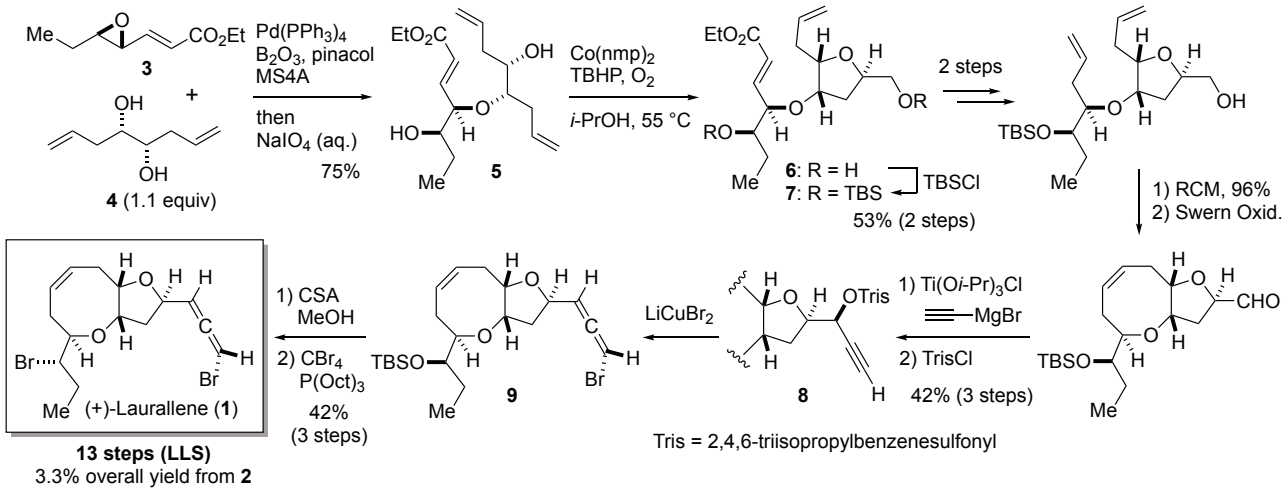
We report a concise asymmetric total synthesis of (+)-laurallene (**1**),[1] a unique and synthetically challenging lauroxane-type C_{15} acetogenin that possesses a 2,9-dioxabicyclo[6.3.0]undecene skeleton (8,5-fused bicyclic ether) containing an exocyclic chiral bromoallene unit.[2] The 13-step approach features a strategy that include early stage rapid construction of the 8,5-fused bicyclic ether skeleton and the late-stage installation of the sensitive bromoallene, thus allowed a high overall synthetic efficiency with minimal use of protecting groups in a redox economical manner. The key transformations in this synthesis include (1) facile construction of a branched ether system through a palladium-catalyzed alkoxy substitution reaction of γ,δ-epoxy α,β-unsaturated ester **3** with C_2-symmetric chiral diol **4** which was developed in our laboratory,[3] (2) cobalt-catalyzed Mukaiyama oxidative THF ring formation (**5→6**), and (3) stereoselective *anti*-S_N2' bromination reaction of propargylic torisylate **8** with bromocuprate reagent. Our approach should also allow rapid access to other lauroxane natural products and the related C_{15} acetogenins.

Synthesis of two optically active fragments



Completion of the total synthesis



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2O-A-5

Heterocycles and Neglected Diseases: still a role for total synthesis

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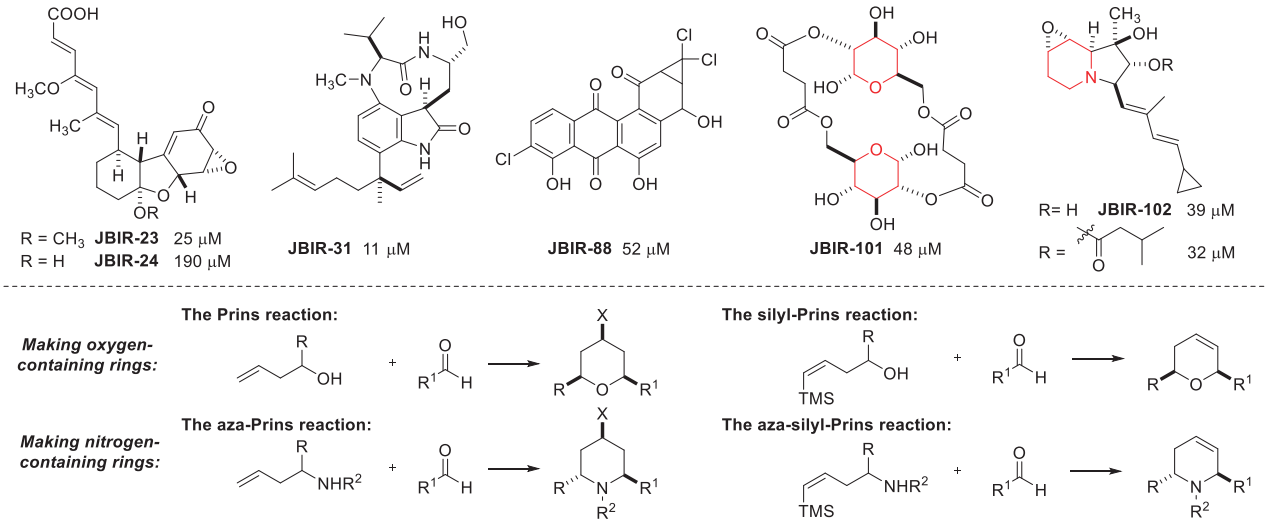
Human malignant pleural mesothelioma is a fatal lung cancer, associated with previous asbestos exposure. Typically symptoms do not appear until 30-40 years after the original exposure, with life expectancy then 12-18 months. Given the great use of asbestos during the 20th century and this long latency period, cases of mesothelioma continue to rise. There is no known cure for mesothelioma. However, very little in the way of mesothelioma research is taking place, as it is not considered to be a 'big market'. Consequently there are currently no new drugs in development for this disease. A second reason is that until recently there have been no reported lead compounds as a starting point for the drug discovery process; this has changed since 2010, with the reports of a small number of natural products which demonstrate activity against mesothelioma.[1]

The Prins and aza-Prins reactions are important methods for the preparation of 6-membered ring oxygen and nitrogen containing heterocycles.[2] The presentation will discuss the development and application of the Prins and aza-Prins reactions in the total synthesis and biological evaluation of a number of these potential anti-mesothelioma agents.



[1] M. Izumikawa, M. Takagi, K. Shin-ya, *J. Antibiot*. **2011**, *64*, 689; M. Izumikawa, T. Hosoya, M. Takagi, K. Shin-ya, *J. Antibiot*. **2012**, *65*, 41.
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2O-B-1

Dibenzo[*a,j*]phenazine-Cored Twisted Donor-Acceptor-Donor Triads: Promising Platform for Multi-Photofunctional Organic Materials

Youhei Takeda,[a,*] Przemyslaw Data,[b,*] and Satoshi Minakata[a,*]

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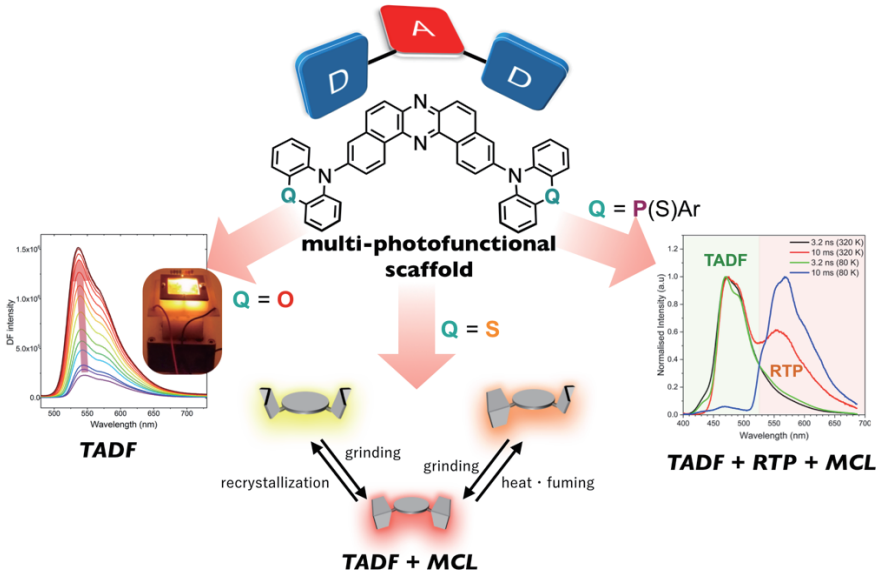
[b] *Department of Physical Chemistry and Technology of Polymers, Faculty of Chemistry, Silesian University of Technology, Gliwice 44-100, Poland*

Dibenzo[*a,j*]phenazine (DBPHZ)[1]-cored twisted donor-acceptor-donor (D-A-D) triads serve as a unique and promising platform for multi-photofunctional organic materials[2] such as efficient thermally activated delayed fluorescence (TADF),[3–5] high-contrast conformation-dictated multi-color-changing mechanochromic luminescence (MCL),[5–7] and room-temperature phosphorescence (RTP)[6,7] properties. In this presentation, the significant influences of the element (Q = O, S, and P(S)Ar) in a series of D-A-D compounds will be showcased and discussed.



[1] Takeda, Y.; Okazaki, M.; Minakata, S. *Chem. Commun.* **2014**, *50*, 10291–10294.

[2] For a review on multi-photofunctional organic emissive materials, see: Data, P.; Takeda, Y. *Chem. Asian J.* **2019**, *14*, 1613–1636.

[3] Data, P.; Pander, P.; Okazaki, M.; Takeda, Y.; Minakata, S.; Monkman, A. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 5739–5744.

[4] de Sa Pereira, D.; dos Santos, P. L.; Ward, J.; Data, P.; Okazaki, M.; Takeda, Y.; Minakata, S.; Bryce, M.; Monkman, A. P. *Sci. Rep.* **2017**, *7*, 6234/1–8.

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Chemistry of Planar Chiral Heterocycles

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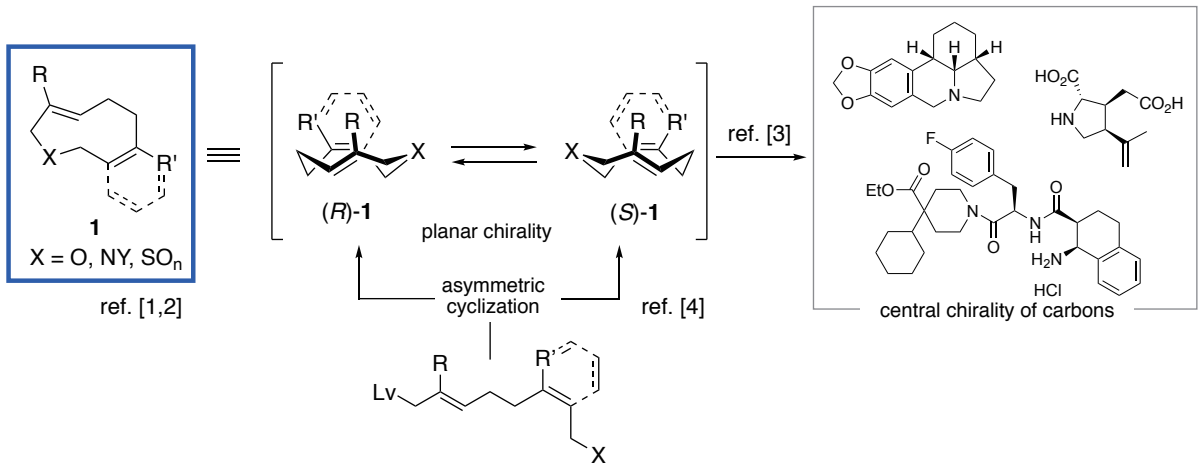
Institute for Materials Chemistry and Engineering,
Kyushu University, Fukuoka, Japan

Chiral molecules having conformational isomerism show an interesting dynamic stereochemical behavior and hence, they are important subject for study of structural organic chemistry, and an attractive motif of chiral technology. Recently, we have found novel chiral heterocycle **1** with planar chirality.[1,2] Their stereochemical stability is highly dependent upon the substituent R, R', and the embedded atom X. The planar chirality of properly designed heterocycle **1** is fairly stable at ambient temperature and can be transferred to a variety of central chiralities in a stereospecific fashion.[3] Furthermore, their enantioselective synthesis was achieved by the newly developed asymmetric cyclization protocol.[4] These results clearly show the synthetic potential of planar chiral heterocycles as useful chiral building blocks or key components of chiral reagents. Detailed stereochemical behavior of the planar chiral heterocycles and their synthetic utility will be presented.



References
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[2] (a) Tomooka, K.; Komine, N.; Fujiki, D.; Nakai, T.; Yanagitsuru, S. *J. Am. Chem. Soc.* **2005**, *127*, 12182-12183. (b) Tomooka, K.; Suzuki, M.; Shimada, M.; Yanagitsuru, S.; Uehara, K. *Org. Lett.* **2006**, *8*, 963-965. (c) Uehara, K.; Tomooka, K. *Chem. Lett.* **2009**, *38*, 1028-1029. (d) Tomooka, K.; Iso, C.; Uehara, K.; Suzuki, M.; Nishikawa-Shimono, R.; Igawa, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 10355-10358. (e) Tomooka, K.; Miyasaka, S.; Motomura, S.; Igawa, K. *Chem. Eur. J.*, **2014**, *20*, 7598-7602. (f) Igawa, K.; Machida, K.; Noguchi, K.; Uehara, K.; Tomooka, K. *J. Org. Chem.* **2016**, *81,* 11587-11593. (g) Machida, K.; Yoshida, Y.; Igawa, K; Tomooka, K. *Chem. Lett*. **2018**, *47*, 186. (h) Hayashi, J.; Uehara, K.; Ano, Y.; Kawasaki, Y.; Igawa, K.; Tomooka, K. *Heterocycles*, **2019**, *in press.*
[3] (a) Tomooka, K.; Suzuki, M.; Uehara, K.; Shimada, M.; Akiyama, T. *Synlett* **2008**, 2518-2522. (b) Tomooka, K.; Akiyama, T.; Man, P.; Suzuki, M. *Tetrahedron Lett.* **2008**, *49*, 6327-6329. (c) Tomooka, K.; Shimada, M.; Uehara, K.; Ito, M. *Organometallics*, **2010**, *29*, 6632–6635. (d) Tomooka, K.; Suzuki, M.; Shimada, M.; Ni, R.; Uehara, K. *Org. Lett.* **2011**, *13*, 4926–4929.
[4] (a) Tomooka, K.; Uehara, K.; Nishikawa, R.; Suzuki, M.; Igawa, K. *J. Am. Chem. Soc.* **2010**, *132*, 9232-9233. (b) Igawa, K.; Ichikawa, N.; Ano, Y.; Katanoda, K.; Ito, M.; Akiyama, T.; Tomooka, K. *J. Am. Chem. Soc.* **2015**, *137*, 7294–7297.

BOIMPYs and Oligomerized BODIPYs: A Key to Superfluorophors

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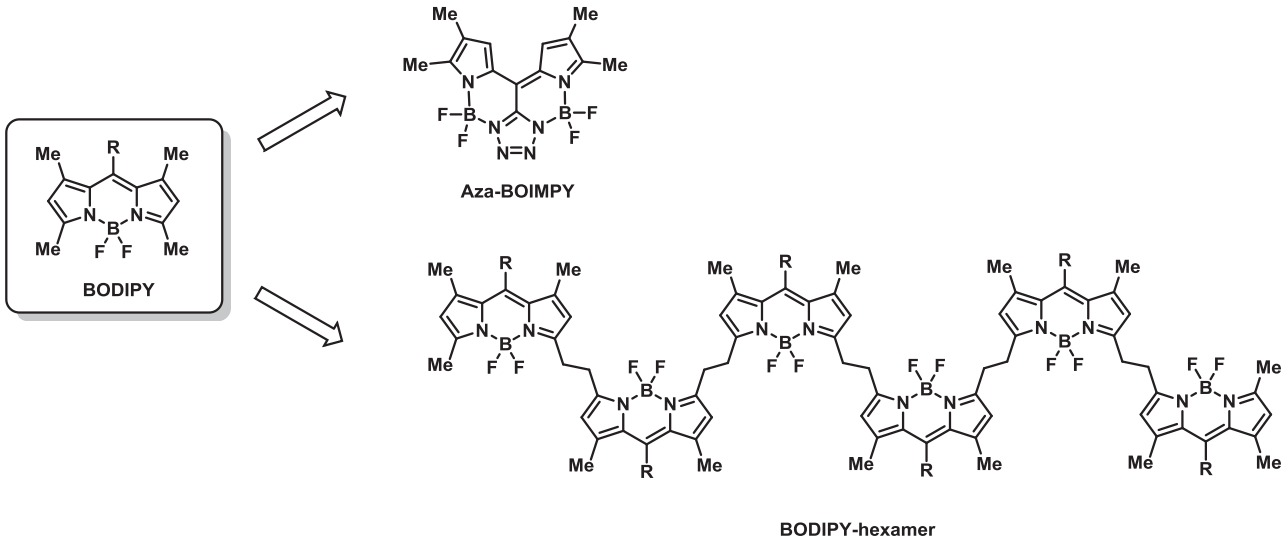
The rich chemistry of the BODIPY motif, together with its beneficial photophysical properties, has markedly boosted the popularity of this user-friendly fluorophore over the last few decades.[1] The diversity of easily incorporated fluorescence modulation modes has set the stage for a variety of sensorically active species.

This study describes which physical-organic rationalisation led to the development of the BOIMPY motif showing a significant red-shift with respect to the parent BODIPY.[2] In addition, a simple synthetic route to oligomerized ethano-linked BODIPYs (up to an octamer) is presented.[3] Photophysical properties are discussed by experimental and theoretical means. It is shown that the suprastructure of the oligomeric dyes plays a significant role for their absorption and emission properties.



Scheme 1: BODIPY, BOIMPY and oligomerized BODIPY.

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Regio- and Stereoselective Intramolecular Cyclization Reactions of Benzoheteroles and Alkynes through the Formation of Vinylidene *ortho*-Quinone Methide Intermediates

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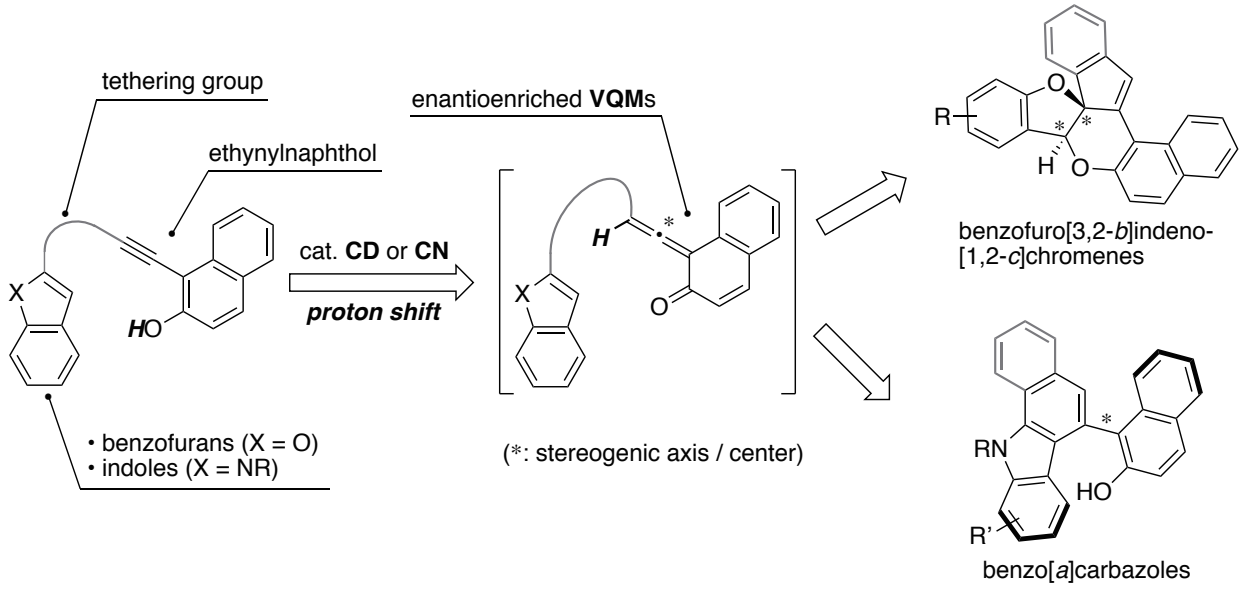
Vinylidene *ortho*-quinone methides (**VQM**s) are one-carbon elongated homologues of *ortho*-quinone methides, well-known as useful reaction intermediates in organic transformations. These related quinone methides are quite distinct in terms of stereochemistry. Namely, **VQM**s are characterized by an exocyclic allenyl ketone unit merged with a dearomatized ring system and thus, can be rendered axially chiral by locating a substituent properly at the terminal methylene group of the allene moiety. Focusing on these stereochemical and structural features, we have pursued the development of unprecedented asymmetric reactions involving enantioenriched **VQM** intermediates generated by chiral-base-catalyzed tautomerization of the ethynylphenol precursors.[1,2] Indeed, commonly used chiral base catalysts such as cinchonidine (**CD**) and cinchonine (**CN**) have been successfully demonstrated to be effective to this end. In this paper, we wish to present our recent studies on the asymmetric syntheses of optically active benzofuro[3,2-*b*]indeno[1,2-*c*]chromenes[3] and benzo[*a*]carbazoles[4] based on the catalytic enantioselective generation of **VQM**s with **CD** or **CN** and the stereocontrolled intramolecular follow-up cyclization with tethered benzofurans and indoles, respectively.



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2O-B-5

Photoluminescent 1,3,4-Thiadiazole-based Liquid Crystals with Wide Mesomorphic Temperature Ranges and Excellent Thermal Stability

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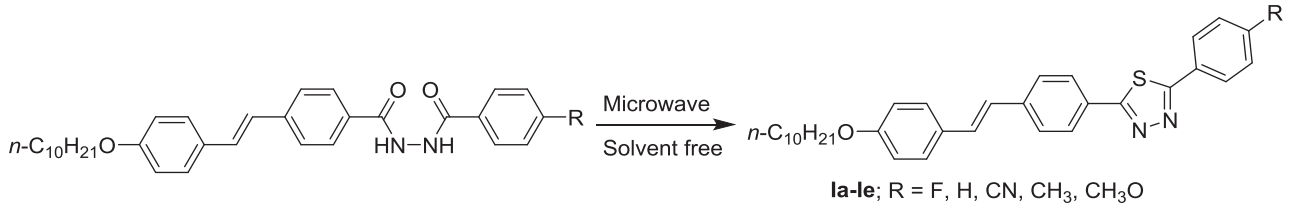
There is a continuing interest in luminescent liquid crystals due to the potential applications in optoelectronic devices.[1] Among many kind of luminescent liquid crytasls, those with 1,3,4-oxadiazole units in the aromatic core have been widely invesigated owing to the rich mesophases, high photoluminescence quantum yields and good electron transporting ability.[2] In contrast, the heterocyclic liquid crystals based on 1,3,4-thiadiazoles are known for their wide mesoporphic temperature ranges with good thermal stabilities.[3] In order to develop luminescent liquid crystals with wide mesomorphic temperature range and high thermal stability, a new series of 1,3,4-thiadiazole based mesogens **Ia-Ie** with ethylene links in the mesogenic core were prepared under microwave irradiation and solvent free conditions. The liquid crystalline properties were investigated by means of differential scanning calirometry(POM), polarizing optical microscopy (POM) and variable temperature X-ray diffraction. The natures of the mesophases are influenced greatly by the polarity of the terminal groups. Compound **Ia-Ie** display calamitic mesophases such as smectic C, smectic A and/or nematic phases in very wide mesomorphic temperature range (up to 234°C) with excellent thermal stability. In the solution of dichloromethane, all of the target compounds displayed a room temperature emission with λ_{max} at 460-516 nm and quantum yields with Φ = 0.10-0.38.



Ia-Ie; R = F, H, CN, CH_3, CH_3O

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Inactivation of Myostatin using Photooxygenation Catalyst-Peptide Conjugate

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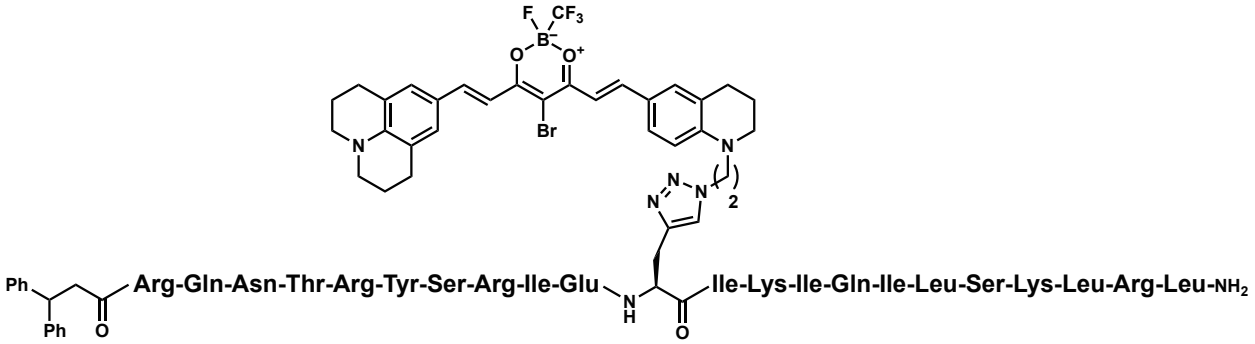
Myostatin, a member of the transforming growth factor-β (TGF-β) superfamily, negatively regulates the growth of skeletal muscle in the muscular homeostatic system.[1] The inhibition of myostatin can be a treatment for amyotrophic diseases including muscular dystrophy.[2]
Previously, we discovered a myostatin-binding peptide with 23 amino acid residues from a mouse propeptide sequence in promyostatin.[3] The peptide shows an inhibitory activity against myostatin due to its reversible binding with myostatin. In this study, to achieve a stronger inhibitory effect, the peptide was functionalized by the conjugation with photooxygenation catalyst.[4] As a catalyst, an "on/off" switchable photooxygenation catalyst was applied, which exhibits photooxygenation activity only when binding with a target protein.[5] The catalyst-peptide conjugate (**1**) selectively oxygenated myostatin under near-infrared irradiation. The oxygenated sites in myostatin were Trp, His and Met residues. Moreover, the oxygenated myostatin exhibited less bioactivity than native myostatin. Thus, conjugate **1** could irreversibly and catalytically inactivates myostatin. Therefore, the inhibitory effect of conjugate **1** was several orders of magnitude greater than that of the original peptide.



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Selective Substitution and Decomposition Reactions of Cyclometalated Iridium Complexes and Their Applications to Biomedical and Material Sciences

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Chemistry of cyclometalated iridium(III) (Ir(III)) complexes, in which Ir (III) ion is coordinated by cyclometalating ligands through Ir-C and Ir-N bonds, are strong triplet luminescent organometallics not only as organic light-emitting diodes (OLED) but also as chemosensors and bioimaging agents, due to their excellent photophysical properties and stability even in aqueous solution [1]. Besides, the cyclometalated Ir complexes possess C_3-symmetric structure and hence could be useful platform to mimic biomolecules that have the C_3-symmetric homotrimeric structures.

Previously, we found the regioselective electrophilic subtitution reactions of $Ir(tpy)_3$ (tpy: 2-(4'-tolyl)pyridine) and their applications to the design and synthesis of luminescence pH sensors [2], blue-color luminecence complexes [3], Ir complex-peptide hybrids (IPHs) as detectors of cancer cells and/or inducers of their cell death [4,5]. The IPHs linked with cationic peptides such as GGKK(K) sequences through appropriate linkers exhibit potent cytotoxicity against Jurkat cells and strong green emission from IPHs were observed in dead cells [4]. On the other hand, homotrimeric IPHs having cyclic peptides that had been reported to bind to death receptor (DR) of cancer cells bind to DR5 on cancer cells and induce their necrosis-type or apoptosis-type cell death [5]. We also report on the efficient synthesis of tris-heteroleptic Ir complexes (IrLL'A and IrLL'L'', in which L , L', and L'' are different cyclometalating ligands and A is an ancillary ligand) based on the selective degradation of tris-cyclometalated Ir complexes and their analogs promoted by Lewis acids such as ZnX_2 (X = Br or Cl), which affords the corresponding halogen-bridged Ir dimers (μ-complexes) [6].

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2O-C-3

Application of 7-azabicyclo[2.2.1]heptane derivatives to stabilize β-strand-like extended conformation of neighboring α-amino acids

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β-Strand is composed of an extended linear peptides that is usually paired to form β-sheet structures through inter-strand hydrogen bonding. A structured organic molecule can enforce or stabilize β-strand-like extended structures of the linked amino acids even in the absence of the inter-strand hydrogen bonding.(Figure 1 (a)) Spectroscopic and simulation studies indicated that the presence of a C-terminal 7-azabicyclo[2.2.1]heptane amine (Abh) favors a β-strand-like extended conformation of the adjacent α-amino acid on the N side (Figure 1 (b)). The bridgehead substitution of the Abh unit biases the amide *cis-trans* equilibrium of the adjacent α-amino acid residue to *cis* conformation. The proximity, a particular interaction between the bridgehead proton of Abh and the α-proton of the α-amino acid provides a driving force favoring the extended conformation (Figure 1 (b)), which is independent of solvents. These results provide a new strategy for *de novo* design of β-strand-mimicking extended peptides.

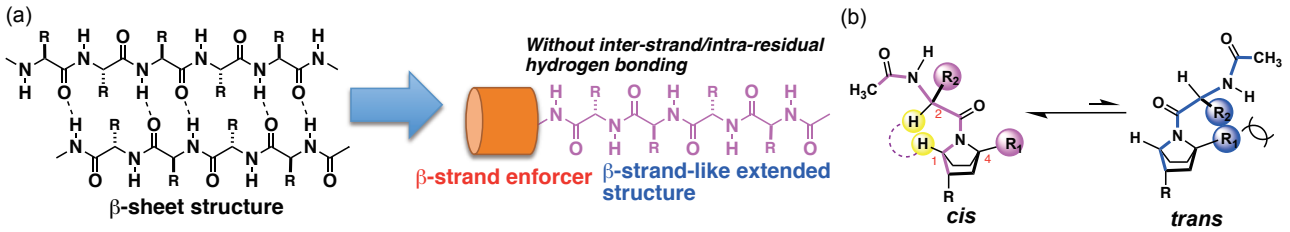

Figure 1 (a) β-Strand enforcer/stabilizer. (b) 2-C-terminal Abh favors a β-Strand-like extended conformation of the adjacent α-amino acid on the N side.

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Synthesis of 3- and 5-Substituted 2,4-Pyridinedicarboxylates which are Novel Potent and Selective Inhibitors of the Human Enzyme 'Aspartate/Asparagine-β-Hydroxylase'

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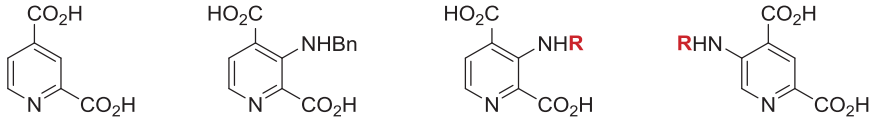
The human enzyme 'Aspartate/Asparagine-β-Hydroxylase' (AspH) is a 2-oxoglutarate (2OG)-dependent dioxygenase which catalyzes the posttranslational hydroxylation of specific Asp/Asn-residues in 'Epidermal Growth Factor' (EGF)-like domains.[1] AspH is overexpressed on the cell surface membrane of certain types of cancer cells and related to enhanced metastatic spread.[2] Recently, we developed the first *in vitro* assay to monitor AspH-activity and evaluate the therapeutic potential of AspH:[3] 2,4-Pyridinedicarboxylate (2,4-PDCA, **1**) and its 3-aminobenzyl substituted derivative **2**[4] were identified as potent small molecule AspH-inhibitors using this novel RapidFire mass spectrometry high-throughput assay.

In order to perform a comprehensive structure-activity relationship study, we developed a facile 3-step synthesis of 3-substituted 2,4-PDCA derivatives (**3**) as the previously reported synthesis of AspH-inhibitor **2** suffered from low overall yields due to harsh reaction conditions.[4] This novel synthesis is based on two consecutive Pd-catalyzed reactions: Both 3-aminoalkyl- and aryl-substituted 2,4-PDCA derivatives (**3**) were obtained in good overall yields under mild reaction conditions. Using this protocol, sufficient quantities of 2,4-PDCA derivatives (**3**) were synthesized to enable further biochemical experiments. Moreover, the first synthesis of 5-aminoalkyl- and aryl-substituted 2,4-PDCA derivatives (**4**) was achieved using the same reaction sequence but a different commercial starting material highlighting the versatility of this novel catalytic synthesis.



More than 20 novel 2,4-PDCA derivatives were synthesized and evaluated in the *in vitro* AspH-inhibition assay: The most potent AspH-inhibitor displayed an inhibitory concentration (IC_{50}) of 0.2 μM. Using a differential scanning fluorimetry assay, a significant shift of the AspH melting temperature was detected when exposing AspH to these inhibitors; This indicates that the inhibitors bind AspH (presumably by replacing 2OG in the AspH active site). A high selectivity of the novel inhibitors for AspH was observed when evaluating their inhibition of other human 2OG-dependent dioxygenases *in vitro* (PHD2, FIH, Jmjd5).

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Transition-metal mediated synthesis of complex *N*-heterocycles

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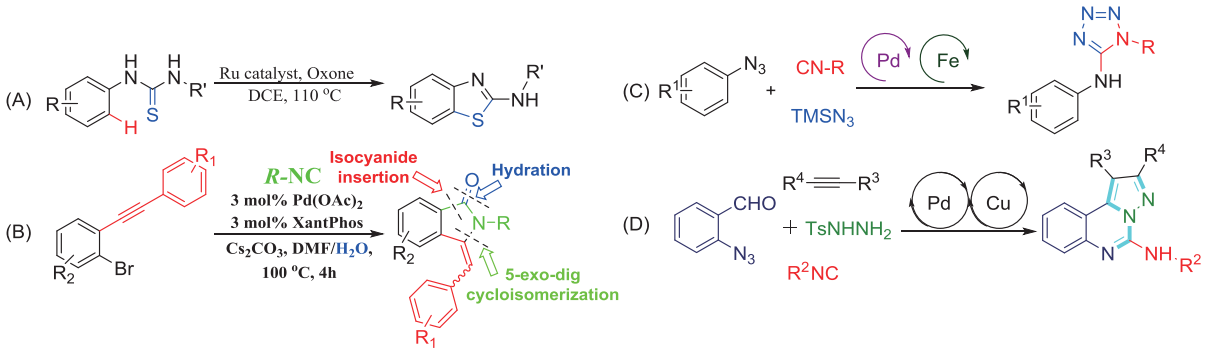
N-Heterocycles exhibit wide range of pharmaceutical and biological activities; thus play pivotal role in medicine, industry and life.[1] Recent advance in the field of synthetic organic chemistry has brought into light many techniques, such as transition metal-catalysed C-H activation,[2] cross coupling reactions, and multicomponent reactions[3] etc., which expanded the horizons in the field of heterocycles, a feat that was never envisaged before. The main aim of our research is to focus our attention on the application of these methodologies for the construction of diversified and complex heterocyclic molecules such as benzothiazole and isoindolinone, aminotetrazoles and pyrazolo[1,5-c]quinazolines for cancer therapy. Recently, we have reported the synthesis and mechanistic insights of 2-aminobenzothiazoles from N-phenyl thioureas by ruthenium catalysed C-H functionalization/ C-S bond formation (Scheme A).[4] Next, we also explored a simple and efficient Pd–catalysed tandem carboxamidation/hydroamidation of 2-bromophenylacetylene for the synthesis of 3-benzylidineisoindolin-1-one (Scheme B). Besides this, we also developed an easy access to the 5-amine[1*H*]tetrazole (Scheme C) and pyrazolo[1,5-c]quinazolines (Scheme D) framework by azide-isocyanide cross coupling reaction. The reaction is individually catalyzed by bimetallic dual catalyst system in a single pot (Scheme C & D). Salient features and detailed mechanistic study will be presented.



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Gold-catalyzed Synthesis of [N,N]-, [N,O]-, and [N,S]-Spiroacetals

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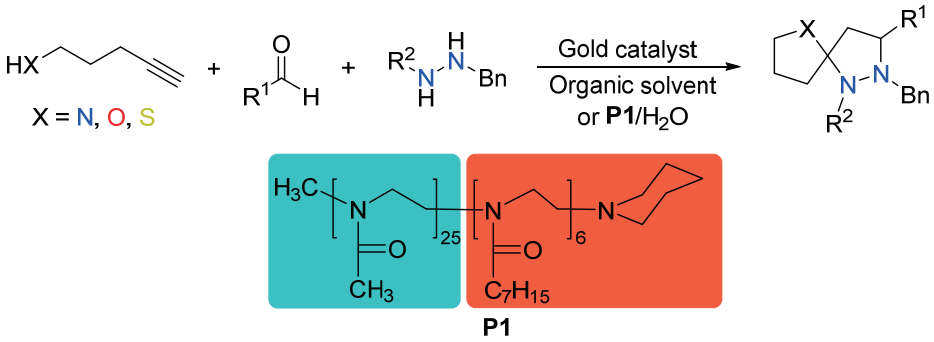
Spiroacetals appear in a wide range of natural products and biologically active molecules. Due to their unique three-dimensional, sp^3-rich structure, there is a high demand for efficient methods to synthesize these privileged scaffolds. Among these, gold-catalyzed spirocyclizations of acetylenic diols and related substrates in organic solvents are gaining importance.[1] In order to render these transformations more efficient and environmentally friendly, we have developed *recyclable* gold catalysts to afford saturated and unsaturated [O,O]-spiroacetals in *water* as bulk reaction medium.[2-4] A further step towards sustainable reaction conditions was taken by assembling nitrogen-containing spiroacetals from simple starting materials (aldehydes, hydrazines, and functionalized alkynes) in a gold-catalyzed *three-component* spirocyclization.[4,5] This opens an efficient and highly flexible access to new types of [N,N]-, [N,O]- and [N,S]-spiroacetals. These unique molecular scaffolds, which are of high interest in medicinal chemistry, can also be synthesized and evaluated on suitable DNA fragments starting from DNA-tagged aldehydes.[6] Performing these multicomponent reactions in bulk water using *micellar catalysis* is challenging due to the pronounced differences in polarity of substrates, catalysts, intermediates, and products. By using micelles derived from poly(2-oxazolines) of the type **P1**,[7] various substrate combinations afford the desired spiroacetals with high yield. The aqueous catalyst solution can be recycled with minimal loss of activity.



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2O-D-2

Asymmetric transformations of Morita-Baylis-Hillman adducts for construction of chiral aromatic heterocycles

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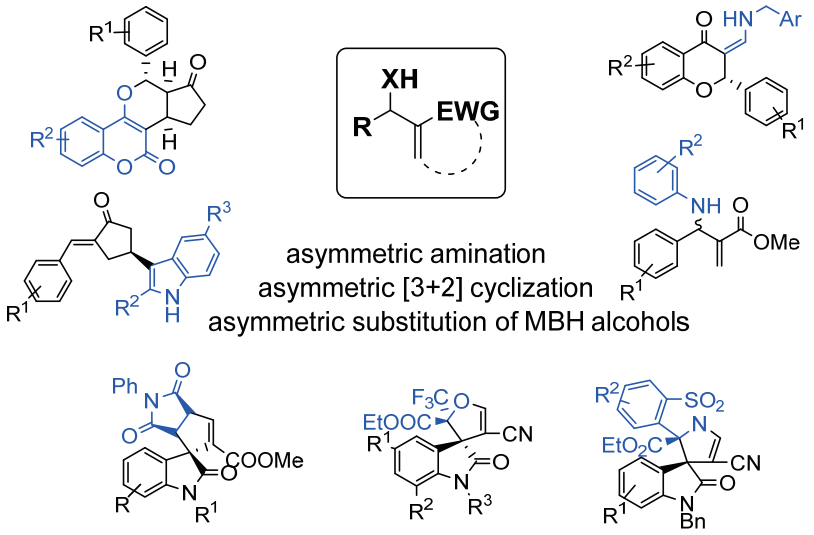
The Morita-Baylis-Hillman (MBH) adducts have attracted much attention in organic syntheses as valuable synthons and starting materials owing to their easy availability and versatile functionalities bearing allylic hydroxy and Michael acceptor units. We have developed a number of asymmetric transformations of MBH adducts for construction of chiral aromatic heterocycles. Highly enantioselective, diasteroselective and regioselective amination, [3+2] cyclization and direct substitution of MBH alcohols were achieved. [1]



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2O-D-3

Direct Synthesis of Nitroaziridines and the Subsequent Lewis Acid Mediated Isomerization to Nitroenamines

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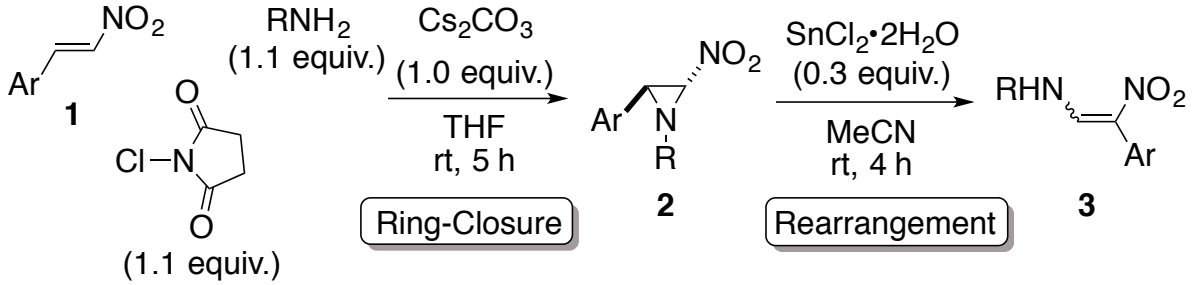
The aziridines are an important class of nitrogen-containing heterocyclic compounds and can be found in a number of biologically active compounds. Besides, functionalized aziridines also serve as versatile building blocks in organic synthesis. The ring-opening reaction of aziridines with nucleophiles affords various 1,2-difunctionalized compounds. A substantial number of functionalized aziridines can also be transformed into useful products through rearrangement, cycloaddition, and ring expansion reactions. Among the functionalized aziridines, *C*-nitroaziridines play an important role in chemical transformations because of the strong electron-withdrawing ability of the nitro group. Hence the development of efficient methods for the preparation of *C*-nitroaziridines has attracted much attention among organic chemists.



When β-nitrostyrene **1** was reacted with aliphatic amine and *N*-chlorosccuinimide at room temperature in the presence of a base, *N*-alkyl-*C*-nitroaziridine **2** was obtained. [1,2] Screening of the reaction conditions, such as solvents and bases, THF and Cs_2CO_3 were found to be suitable to increase the yield of **2** up to 85%. The aziridination proceeded stereoselectively to afford only *trans*-isomer. This reaction was applicable to other styrene derivatives to furnish the corresponding aziridines **2**, respectively, however, the isolated yields were considerably diminished because of instability under ambient conditions or on silica gel. Hence, conversion of unstable aziridine **2** into a useful and easily treatable reagents was studied.

Nitroaziridine **2** was found to isomerize into β-aryl-β-nitroenamine **3** in the presence of $SnCl_2 \cdot 2H_2O$. Notably, the aryl group rearranged to the adjacent carbon. [1] It was possible to synthesize nitroenamine **3** in one-pot. While electron-rich aromatic groups efficiently migrated, strongly electron-poor aromatic group did not migrate at all due to the low migratory ability. Since very few reports are focused on β-aryl-β-nitroenamines because of their poor availability, our method potentially yields a novel class of β-nitroenamines with structural diversity.

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Catalytic Asymmetric [3+2] Cycloadditions With α-Keto Ester Enolates

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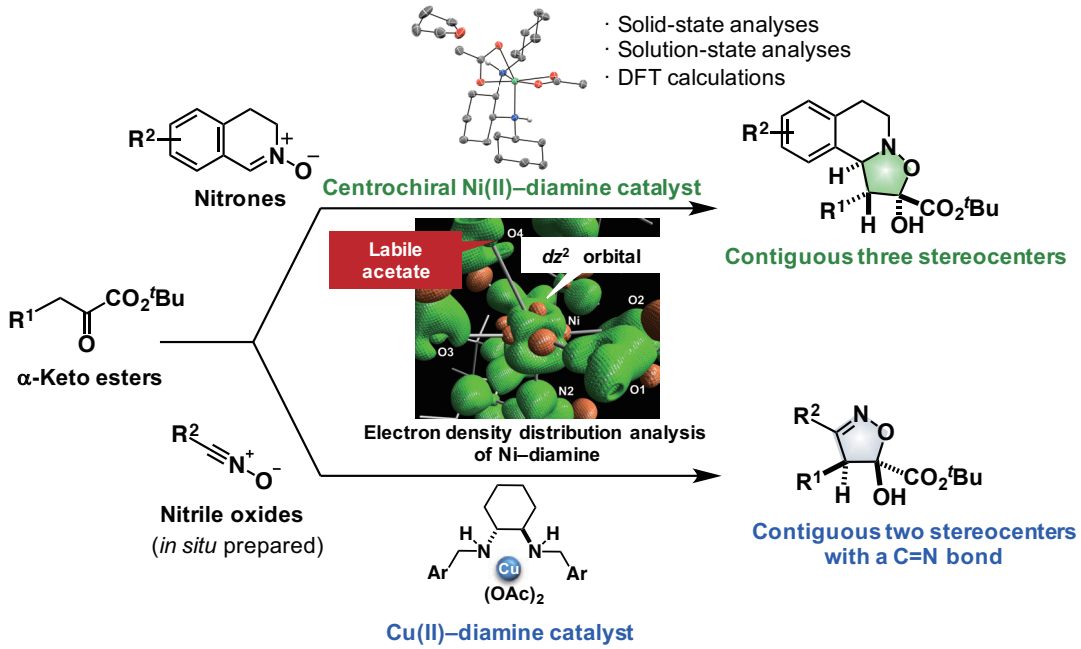
RIKEN Center for Sustainable Resource Science (CSRS), 2-1 Hirosawa, Wako, Saitama, Japan

Isoxazolidine and isoxazoline, containing adjacent nitrogen and oxygen atoms, represent important classes of the heterocycles. These heterocycles are typically synthesized through the [3+2] cycloaddition. However, there are only a few examples of inverse-electron-demand (IED) [3+2] cycloadditions using *electron-rich olefins*, which can be also categorized as type III cycloadditions according to Sustmann's classification. Here, we will present recent our efforts to use the Ni(II)–enolates[1] and Cu(II)–enolates[2] as formal 1,3-dipolarophiles, derived from α-keto esters, leading to the development of the catalytic asymmetric IED [3+2] cycloadditions. These catalytic IED [3+2] cycloadditions provided efficient access to stereochemically complex 5-membered heterocycles having contiguous stereocenters, in which a unique hemiketal structure is involved. We will also present structural characterization of a Ni(II) complex that involves metal centrochirality, in order to illustrate the relationship between the electronic structure of the Ni(II) complex and its catalytic activity. A plausible synergistic mode of action for ligand-induced metal centrochirality will be also discussed.



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2O-D-5

Direct addition of Amides to Glycals Enabled by Solvation-insusceptible 2-Haloazolium Salt Catalysis

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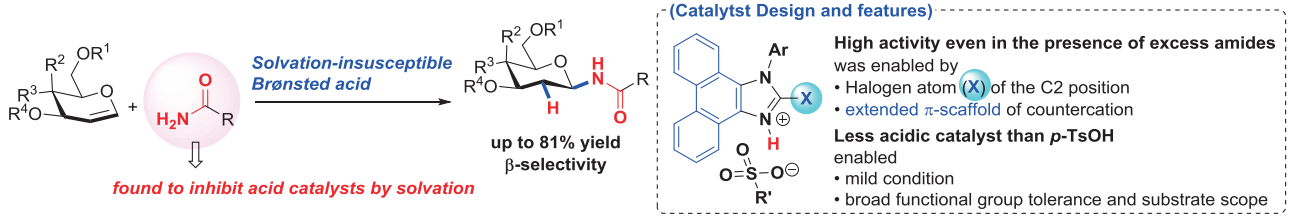
The oligosaccharides of natural glycoproteins play a key role in molecular recognition, and asparagine (Asn) residues are one of the major sites for glycosylation in glycoproteins. Glycoamidases hydrolyze the glycosylated amide bond of the asparagine side chain. Crystallographic analysis and site-directed mutagenesis have revealed that these enzymes require the 2-acetamide group on the Asn-linked GlcNAc for substrate recognition. Thus, a 2-deoxyglycosylation of the Asn residues could give the peptide chain stability against hydrolysis, resulting in enhanced biological activity and selectivity. [1] However, although the *N*-(2-deoxysugar)-amide structure is important in the fields of biochemistry and pharmacology, no straightforward synthetic methodology for this structure has been reported to date. We have recently reported a new methodology for the direct *N*-glycosylation of amide groups with glycosyl trichloroacetimidates, [2] and the product yields depended greatly on the structure of the countercations of ammonium salt as a Brønsted acid catalyst. In light of this observation, we envisioned an unprecedented concept that the designed ammonium salts could exhibit superior catalytic performance for the direct transformation of amides, such as in *N*-2-deoxyglycosylation.



Herein, we report the first example of the direct 2-deoxyglycosylation of an amide group with our newly designed 2-halogenated azolium salts as Brønsted acids. The salient features of this method are as follows: (1) the formation of the azolium salt enabled a mild condition, and this totally waste-free reaction was widely applied to various amides, including the asparagine residues, and (2) the 2-halogenated azolium salts improved the catalytic activity, whereas the ammonium salts have mainly been used just for improving the selectivity in catalytic asymmetric reactions. In addition, during the course of our investigations, it was found that the acid catalysts were deactivated by the amide groups. Mechanistic investigations suggested that the halogen atom and the extended π-scaffold of our new catalyst played an important role for the improved catalytic activity, even in the presence of amides. The detailed studies will be discussed in the presentation.

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3O-A-1

N-Heterocycle-Stabilized Hypervalent Iodine Compounds - Highly Modular Oxidation Catalysts with Unique Reactivities

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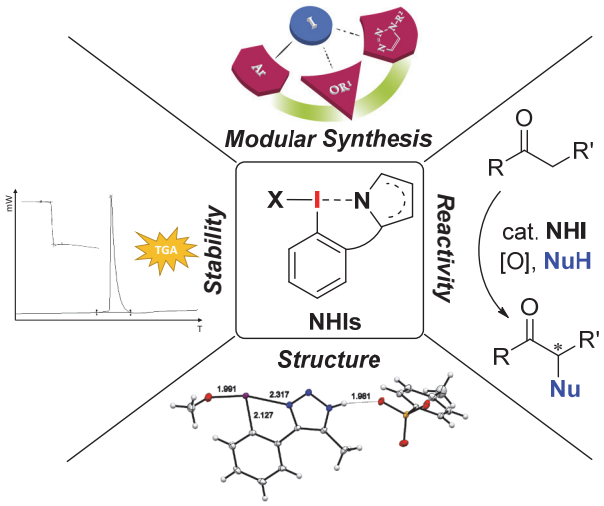
Hypervalent iodine compounds, in particular aryl-λ^3-iodanes, have found widespread applications as mild oxidants and group transfer reagents in natural product synthesis and reaction method development. [1] The stabilization of the hypervalent iodine atom by intramolecular donor ligands has been shown to be an important factor for the overall reactivity of these reagents. The most prominent examples are benziodoxol(on)es or pseudocyclic iodanes with stabilizing *O*-donors as used in electrophilic alkynylations, alkenylations or trifluormethylations. [2] Even though *O*-donor-stabilized iodanes are widely utilized, they have one major obstacle: The electron-donating properties of the *O*-donor are hard to modify and cannot be adapted to specific reactivity needs. Based on our heavy interest in C-H-activating arylations, alkenylations and alkynylations using iodanes as electrophilic group transfer reagents, [3] we profoundly investigate the influence of *N*-heterocycles as electronically easy to modify stabilizing donors in hypervalent iodine chemistry. We will present our recent results about robust and modular synthetic pathways leading to these novel ***N*-heterocycle-stabilized iodanes (NHIs)**. NHIs outperform most of the known *O*-stabilized iodanes in oxidation reactions and their reactivity is highly dependent upon the heterocyclic *N*-donor. Systematic investigations towards their stability, molecular structures as well as structure-reactivity relationships will be discussed. [4] Finally, the synthesis of highly modular chiral triazole-substituted aryl iodides and their application in enantioselective oxygenations are shown. [5] These chiral NHIs once again outperform most chiral hypervalent iodine compounds in terms of reactivity and enantioselectivity in a plethora of enantioselective C-O bond formations.



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3O-A-2

Enantioselective Synthesis of Highly Functionalized Heterocycles via Organocatalyzed Domino Reactions

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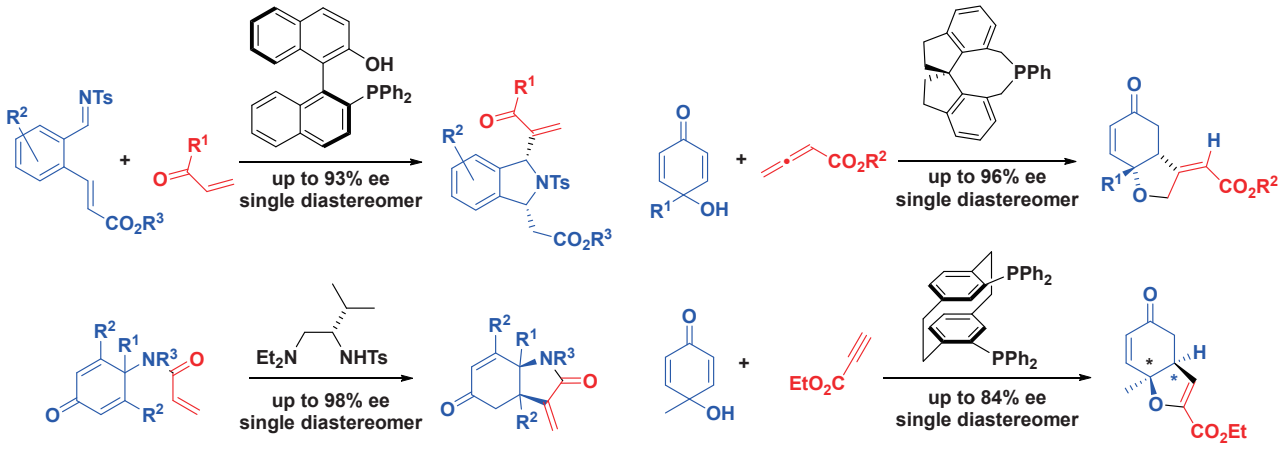
Highly functionalized heterocycles have been used as chiral building blocks for synthesis of biologically active compounds. Development of facile constructions of chiral heterocyclic skeletons is an important ongoing topic in the medical and agricultural fields. Among them, organocatalytic domino process is very attractive methodology due to its ability to construct the complex molecules from readily available substrates under mild reaction conditions without any purification of unstable synthetic intermediates. As our effort to explore enantioselective sequential processes, we were interested in designing organocatalyzed domino reactions to access isoindolines,[1,5] tetrahydrobenzofuranones,[2] α-methylidene-γ-lactams,[3] and hydrobenzofuran-2-carboxylates.[4] In the atom-economical domino reactions, chiral organocatalysts possessing two or more reaction-promoting units synergistically activate the substrates to realize the complicated sequential bond-forming reactions to provide highly functionalized chiral heterocycles with excellent enantioselectivities, some of which have tetrasubstituted and/or quaternary all carbon stereogenic centers. In this presentation, we will report an enantioselective organocatalyzed Rauhut-Currier/[3+2] annulation sequence by using flow system and machine learning-assisted reaction optimization.



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Medium-Sized Heterocycles: Stereoselective Synthesis and Functionalization

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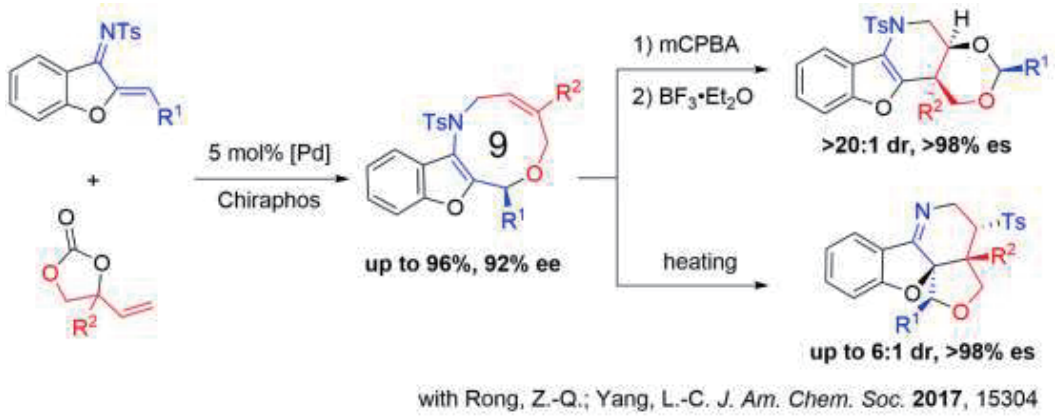
The efficient access to medium-sized rings remains a challenging goal in synthetic organic chemistry. The unfavorable entropy effect and transannular interactions are among the difficulties that have to be overcome in order to achieve such transformations. As a direct strategy for medium-sized ring formation from readily available building blocks, cycloaddition reactions have attracted much attention in recent years. We have developed the first formal [5 + 4] cycloaddition for the construction of nine-membered heterocycles using *N*-tosyl azadienes and substituted vinylethylene carbonates under palladium catalyzed conditions.[1] These medium-sized rings demonstrate highly intriguing reactivities such as diastereoselective peripheral functionalizations and transannular C-C bond formation-initiated rearrangement.[2] The related Pd-catalyzed synthesis of ten-membered heterocycles has also been achieved and will be discussed in this presentation.[3]



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3. "Pd-Catalyzed Enantioselective [6+4] Cycloaddition of Vinyl Oxetanes with Azadienes to Access Ten-Membered Heterocycles," Wang, Y. N.;† Yang, L. C.;† Rong, Z.-Q.; Liu, T.-L.; Liu, R.; Zhao, Y. *Angew. Chem. Int. Ed.* **2018**, *57*, 1596–1600.

Rhodium-catalyzed Deallylative Alkenylation via C–C Bond Cleavage

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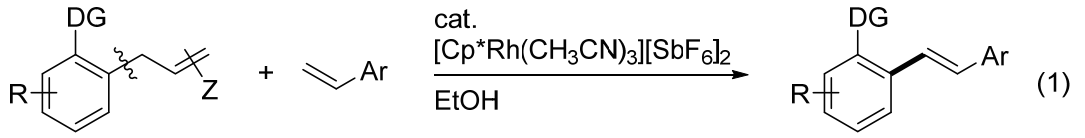
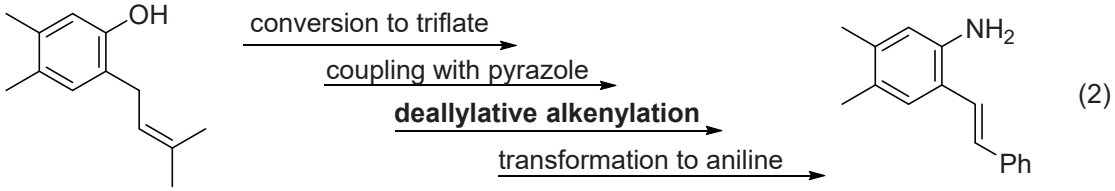
Transition-metal-catalyzed bond formation via cleavage of unreactive bonds has attracted much attention and has provided unconventional synthetic routes for complex organic molecules. Among these reactions, functionalizations of C–C bonds using transition metal complexes as catalysts have widely been studied. Especially, catalytic C–C bond formations via cleavage of unstrained C–C bonds have been recognized as one of the most challenging transformations. Chelation-assistance is important driving force for cleavage of unstrained C–C bonds and this strategy has been frequently used in the catalytic C–C bond functionalization. However, in these reactions, the cleavable bonds have been limited to those right next to a heteroatom such as ketones, imines, and alcohols.[1]
We recently found that the alkenylation of allylbenzene derivatives having a pyridyl or a pyrazolyl group as a directing group using styrenes was catalyzed by $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ efficiently to give β-styrylation products (eq 1). We also developed a new protocol for transformation of an ortho-prenylated phenol to an ortho-alkenylated aniline derivative through this deallylative alkenylation (eq 2).





In this presentation, scope and limitations of this direct transformation of allyl groups in allylbenzene derivatives to alkenyl groups via rhodium-catalyzed C–C bond cleavage will be discussed.

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3O-A-5

New Route to Indoles through Iridium-Catalyzed C(sp^3)–H Activation

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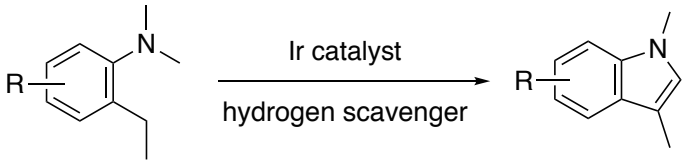
Use of transition-metal-catalyzed C–H activation in synthesis of heterocyclic compounds have received increasing attention, because it contributes to shorten the synthetic steps and reducing waste. We have reported on iridium-catalyzed cycloisomerization of 2-alkynylaryl methyl ethers to benzofurans, *N*-methyl-2-(2-alkenyl)anilines to indolines, and 2-(alkenyl)aryl methyl ethers to 2,3-dihydrobenzofurans, where the unsaturated C–C bond at the *ortho* position undergoes addition of the C(sp^3)–H bond of *O*-methyl and *N*-methyl groups. [1–3] Herein we describe an iridium-catalyzed direct conversion of 2-ethyl-*N*-methylanilines **1** into 3-methylindoles **2**. The initial step of this conversion is iridium-catalyzed transfer dehydrogenation of the ethyl group of **1** to form *N*-methyl-2-vinylaniline. The intermediate then undergoes iridium-catalyzed intramolecular addition of *N*-methyl C(sp^3)–H bond across the carbon–carbon double bond under the identical conditions to afford 3-methylindole **2**. This reaction is an efficient new route to indoles, because it allows participation of two alkyl groups into the construction of indole five-membered ring.



1 **2**

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3O-A-6

Modulation of ribozyme activity by conformational changes induced by a synthetic RNA binding molecule

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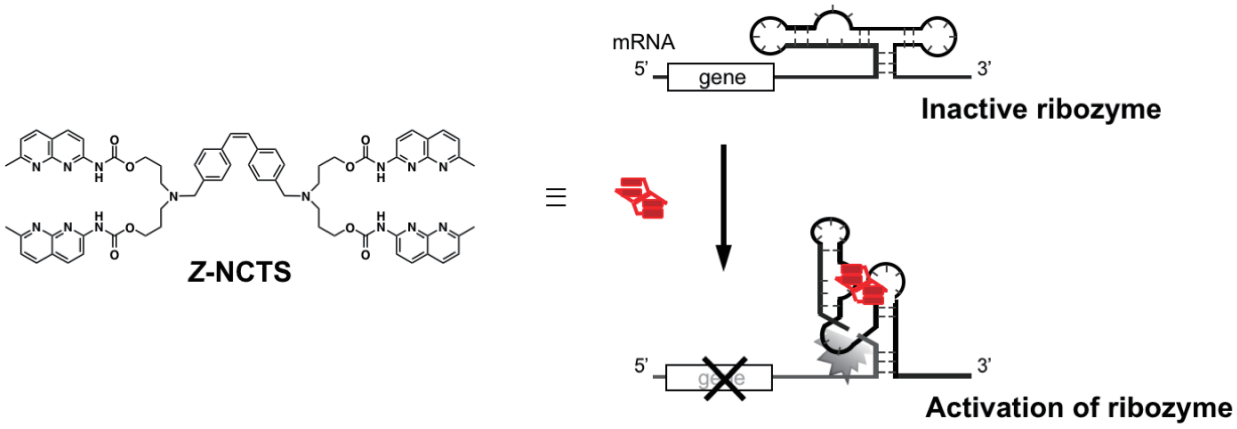
Functional RNA is an emerging target for small synthetic molecules to regulate biological functions. Some classes of RNAs form higher-order structures responsible for functions, reminiscent of folded proteins. These structured functional RNAs and other RNAs capable of forming such structures could be important targets for regulating biological reactions. We recently have demonstrated a concept of "molecular glue for RNA" that could modulate structure and function of RNAs. Molecular glue for RNA is a RNA binding molecule that can bring two distinct RNA domains into close proximity with each other. *Z*-NCTS, which consists of four naphthyridines with a *Z*-stilbene linker, is a RNA mismatch binding ligand and acts as a molecular glue for RNA. [1,2] *Z*-NCTS selectively binds to 5'-r(XGG)-3'/5'-r(XGG)-3' (X = U or A) by hydrogen bonding recognition between four guanines and four 2-acylamino naphthyridine moieties. [2] By introducing the *Z*-NCTS-recognition sites into functional RNA, we have created *Z*-NCTS-dependent functional RNAs whose structure and function could be regulated by *Z*-NCTS. [2,3]

Hammerhead ribozyme (HHR) is a well-studied RNA cleaving ribozyme whose higher-order structure is important for RNA-cleaving activity. *Z*-NCTS could induce the intended structural change in the RNA by bringing two particular domains into close proximity with each other, which allowed us to create a Z-NCTS-dependent HHR. [3] The RNA-cleaving activity of the engineered HHRs was regulated by *Z*-NCTS-induced conformational changes: binding of *Z*-NCTS could both activate and inhibit the RNA-cleaving activity depending on the HHRs. Incorporation of the *Z*-NCTS-dependent HHR sequence into 3′ untranslated region of the reporter gene allowed to create a ribozyme switch for conditional gene expression in cultured cells.



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3O-A-7

Model Study on the Formation of Cyclic *N*-Selenoamide Intermediates in Selenocysteine Oxidation in Glutathione Peroxidase Catalysis

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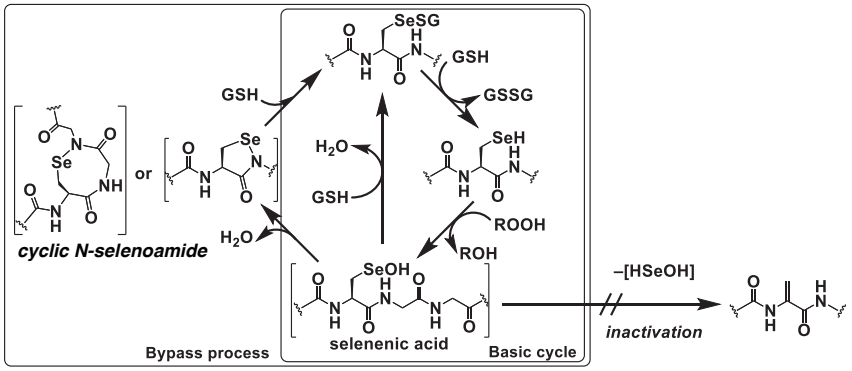
Glutathione peroxidase (GPx) is one of the most important antioxidant enzymes and plays a crucial role in biological defense. Although selenocysteine-derived selenenic acids (Sec-SeOHs) have been widely accepted as important reaction intermediates in the catalytic cycle of GPx, even observation of Sec-SeOHs has never been achieved experimentally because of their notorious instability both in proteins and in synthetic model systems. Recently, the formation of cyclic *N*-selenoamides with a 5-membered or 8-membered ring from Sec-SeOHs has been postulated as a key reaction in the bypass process for protection of GPx from irreversible inactivation caused by deselenation to produce the dehydroalanine form (Scheme 1).[1] However, essentially no chemical evidence has been available to date for this cyclization process of Sec-SeOHs to *N*-selenoamides. For modeling such reactive intermediates of enzymatic reactions, we have developed various types of nano-sized molecular cavities and applied them to stabilization of highly reactive species that have been difficult of access by conventional methods.[2] In this paper, we report the chemical demonstration of the elementary reaction processes proposed for the GPx catalytic cycle including the cyclization of a Sec-SeOH to a cyclic *N*-selenoamide. As a model system that can stabilize a Sec-SeOH intermediate, a selenopeptide incorporated in a nano-sized molecular cradle was developed (Figure 1). By utilizing this cradled selenopeptide model, spectroscopic observation of a Sec-SeOH was successfully achieved and its reactions including intramolecular cyclization to the corresponding isoselenazolidinone were demonstrated. The biological implication of these results will also be delineated.



Scheme 1. Proposed mechanism for GPx function.

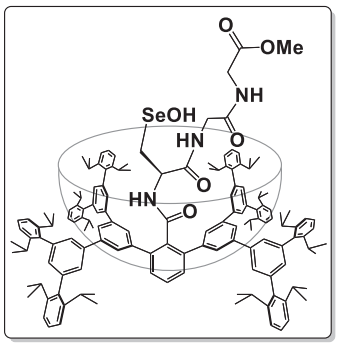


Figure 1. Cradled selenopeptide model.

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[2] For recent examples, see: (a) Sase, S.; Kakimoto, R.; Goto, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 901. (b) Sneeden, E.; Hackett, M.; Cotelesage, J.; Prince, R.; Barney, M.; Goto, K.; Block, E.; Pickering, I.; George, G. *J. Am. Chem. Soc.* **2017**, *139*, 11519. (d) Sase, S.; Kimura, R.; Masuda, R.; Goto, K. *New J. Chem.* **2019**, *43*, 6830.

3O-A-8

Promising DYRK1A inhibitor synthesized by late-stage C-H Arylation

Corinne Fruit,[1]* Florence Couly,[1] Marine Harari,[1] Pascal Bonnet,[2] Stefan Knapp,[3] Laurent Meijer,[4] John D. Crispino[5] and Thierry Besson[1]

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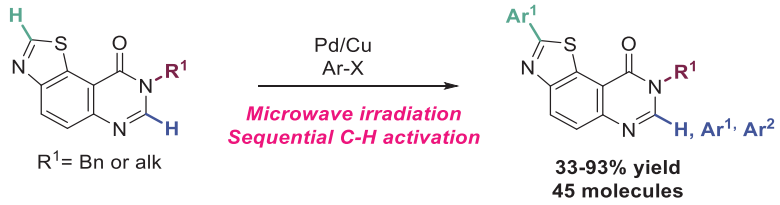
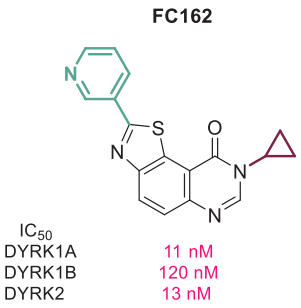
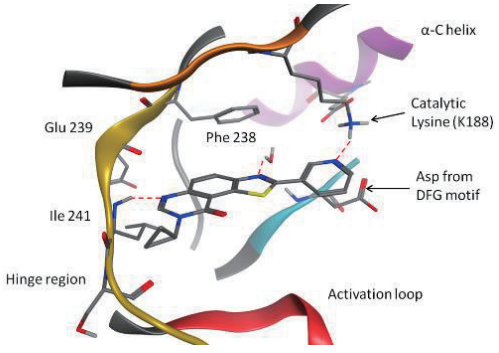
C-C Bond formation through a C-H bond activation emerged as a powerful tool for the late-stage diversification of complex nitrogen containing heterocycles.[1] Driven by the design of an efficient route allowing a direct transformation of lead molecules identified as kinase inhibitors,[2] the synthesis of an array of arylated compounds was further envisioned. Inspired by our study on C-H arylation of quinazolinone,[3] a selective C-H (hetero)-arylation of thiazolo[5,4-*f*]quinazolin-9(8*H*)-one has been developed under microwave irradiation. Electron-deficient heteroarenes are also readily introduced, a notable feature with respect to medicinal agent synthesis.[4]



Targeted molecules substituted by heteroarenes shown nanomolar IC_{50} values for DYRK kinases which are strongly involved in cellular cycle as well as in AD. In addition, the co-crystallized structure of **FC162** with DYRK1A revealed a new docking mode.[5] The *in vitro* and *in vivo* effects were also evaluated showing that **FC162** led to a reduction in cyclin D1 and D3 phosphorylation at Thr 286 and Thr283 respectively, in a dose-dependent manner. These results show that **FC162** recapitulates the effect of DYRK1A loss on cell cycle regulation.





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3O-A-9

Synthesis and applications of the MR1 ligand precursor 5-amino-6-D-ribitylaminouracil (5-A-RU)

Kelin Li,[1] Charles K. Vorkas,[2,3] Ashutosh Chaudhry,[3] Donielle L. Bell,[4] Richard A. Willis, [5] Alexander Rudensky,[3] John D. Altman,[4] Michael S. Glickman,[2,3,5] and Jeffrey Aubé[1*]

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[2] Division of Infectious Diseases, Weill Cornell Medicine, New York, New York, United States of America

[3] Immunology Program, Sloan Kettering Institute, New York, New York, United States of America

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Abstract

Mucosal-associated invariant T (MAIT) cells are an abundant class of innate T cells restricted by the MHC I-related molecule MR1. MAIT cells can recognize bacterially-derived metabolic intermediates from the riboflavin pathway presented by MR1 and are postulated to play a role in innate antibacterial immunity through production of cytokines and direct bacterial killing. MR1 tetramers, typically stabilized by the adduct of 5-amino-6-D-ribitylaminouracil (5-A-RU) and methylglyoxal (MeG), are important tools for the study of MAIT cells. In this presentation, a simple synthetic approach to the HCl salt of this ligand, which has improved stability during storage, will be disclosed, along with an overview of recent advances in immunology that have been enabled by broad access to this compound.

3O-B-1

Synthetic Studies on Chippiine-type alkaloids

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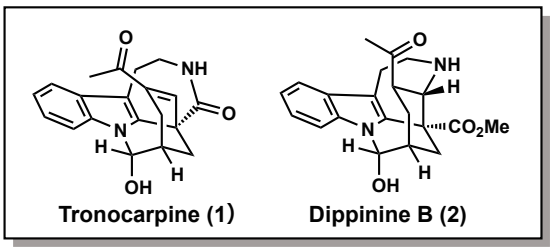
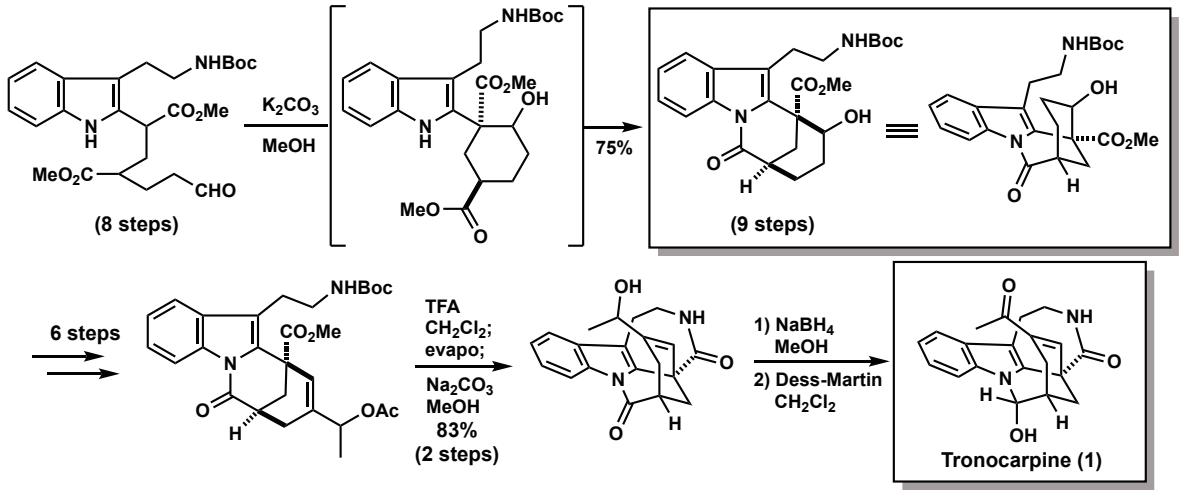
Graduate School of Pharmaceutical Sciences, Tokushima University, Tokushima, Japan 770-8505



Tronocarpine (**1**) and dippinine B (**2**) were isolated from the stem-bark of *Tabernaemontana corymbosa* as chippiine-type alkaloids by Kam and co-workers in 2000 and 2001, respectively [1,2]. The common structural features of these compounds are the pentacyclic skelton containing indole and 6-6-7 membered ring, a quaternary carbon center adjacent to the C2-position of indole, and hemiaminal moiety. Despite their attractive architecture and unique biological activity, there is no report of total synthesis of **1** and **2**. Thus, we initiated the synthetic studies on **1** and **2** to achieve the first total synthesis of **1** and **2**.

The most difficult issue in the synthesis of chippiine-type alkaloids is how to construct the quaternary carbon center adjacent to the C2-position of indole unit. Tandem cyclization would be useful for constructing this carbon center by using intramolecular Aldol reaction/6-membered lactam formation. We obtained the precursor of the tandem cyclization from the commercial available reagents in 8 steps, and examined the several condition for the tandem cyclization. Finally, we found the use of K_2CO_3 in MeOH at room temperature is effective to give the desired tetracyclic core skeleton of chippiine-type alkaloid in good yield. With the core structure of **1** and **2** in hand, we turned our attention to the total synthesis of **1**. After introduction of the C2 unit, removal of Boc group followed by base treatment occurred 7-membered lactam formation to afford the skeleton of **1**. Finally, reduction/oxidation sequence of the resultant pentacyclic skeleton gave tronocarpine (**1**). The attempt to synthesize dippinine B (**2**) by the use of the same intermediate is currently underway in our laboratory.



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3O-B-2

Xylochemistry and Photochemistry with Heterocycles –
Towards a Greener Synthesis

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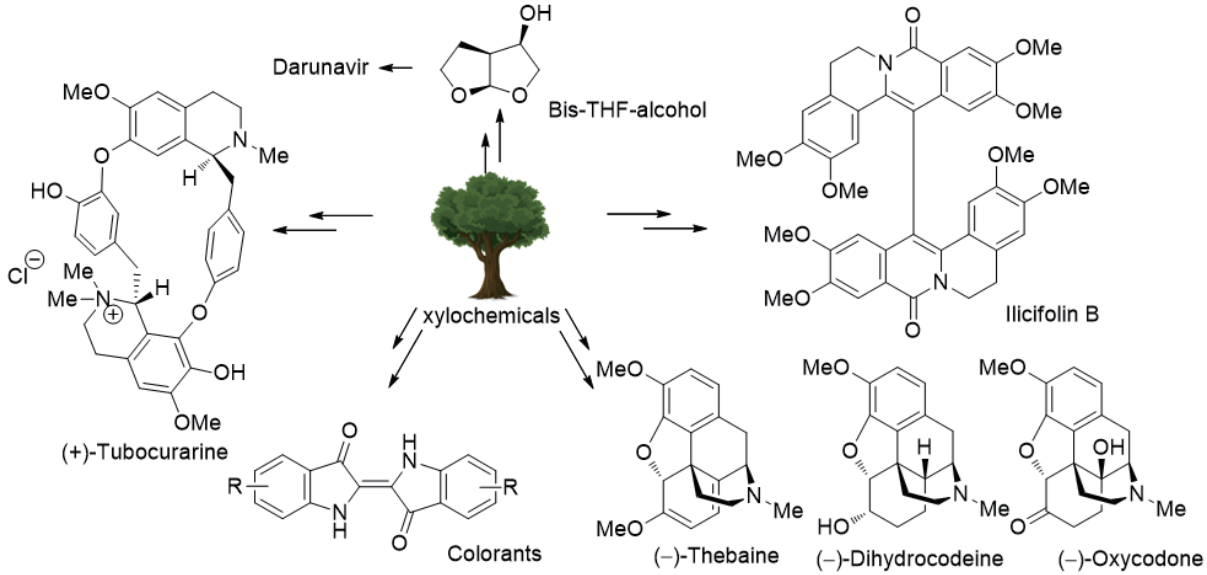
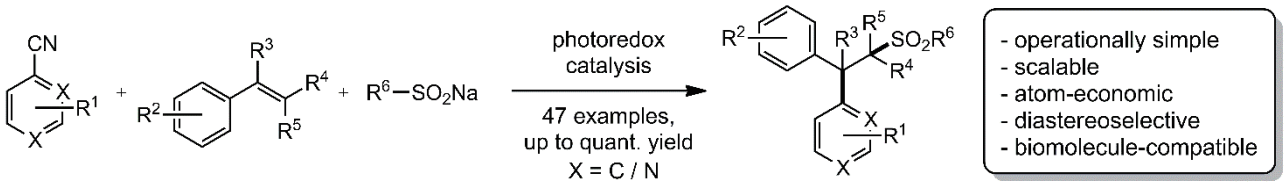
Institute of Organic Chemistry, Johannes Gutenberg University, Mainz/Germany, D-55128

Today's chemical synthesis largely relies on building blocks derived from petrochemical sources. Wood-based starting materials, the so-called xylochemicals, represent an interesting alternative. Their use for the synthesis of various compound classes will be demonstrated. All carbon atoms in the products are derived from renewable resources. [1,2]



Another option for improving the ecological footprint of chemical transformations is the use of light as an eco-friendly energy source. Even IR radiation can be employed and methods for the rapid modification of biomolecules have been developed. [3,4]



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3O-B-3

Synthetic Study on Helisorin, an Antiviral Neolignan Natural Product

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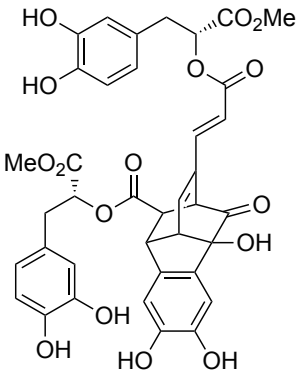
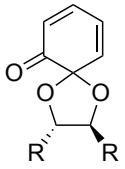
Among a vast array of neolignan natural products, helisorin (**1**) attracts attention of many synthetic chemists due to its unique caged structure as well as potent antiviral activity.[1] However, the asymmetric synthesis of **1** has remained elusive, which may be due to the formidable challenges posed by their stereochemical complexity of the tetracyclic core.[2]



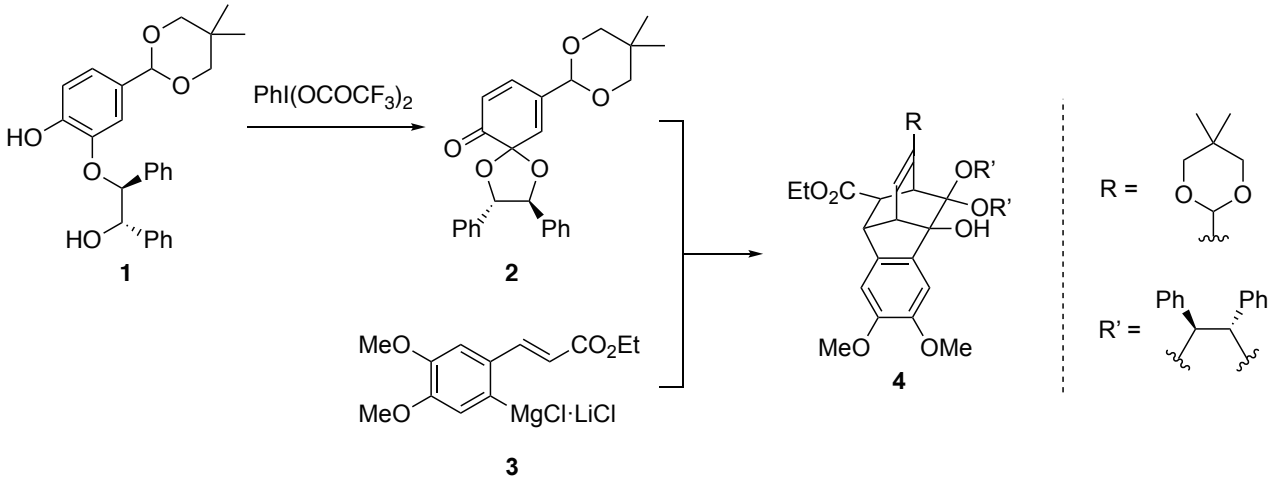
helisorin (**1**)



A

In our synthetic study toward this class of natural products, novel chiral *ortho*-quinone monoacetals (*o*-QMAs) **A** as a key platform was envisaged. We have developed a viable way to prepare **A** along these lines and the synthetic utility of **A** has been successfully demonstrated by the highly diastereoselective 1,2-addition with a broad scope. In this talk, we will report the preliminary model study towards the stereo-controlled synthesis of **1**, application to the construction of the characteristic tetracyclic skeleton of **1** by utilizing sequential 1,2-addition/intramolecular Diels–Alder reaction of chiral *o*-QMA **2**.

Upon treatment of *o*-QMA **2**, prepared by oxidative cyclization of diol **1**, with the Grignard reagent **3** the 1,2-addition proceeded in a highly diastereoselective manner to give the corresponding alcohol, which spontaneously underwent the subsequent intramolecular Diels–Alder reaction to afford **4** as a single diastereomer.



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Three Two-step Enantioselective Total Syntheses of (–)-Glabrescol

Implicate Alternative Biosynthetic Pathways Starting from Squalene

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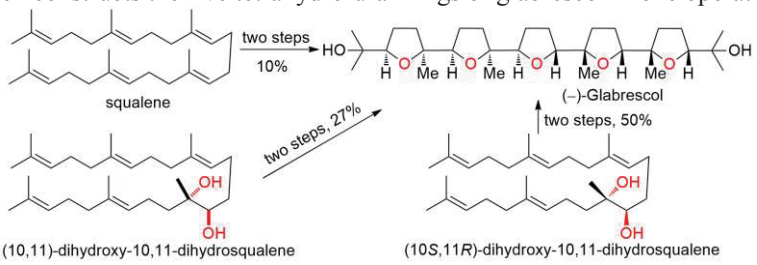
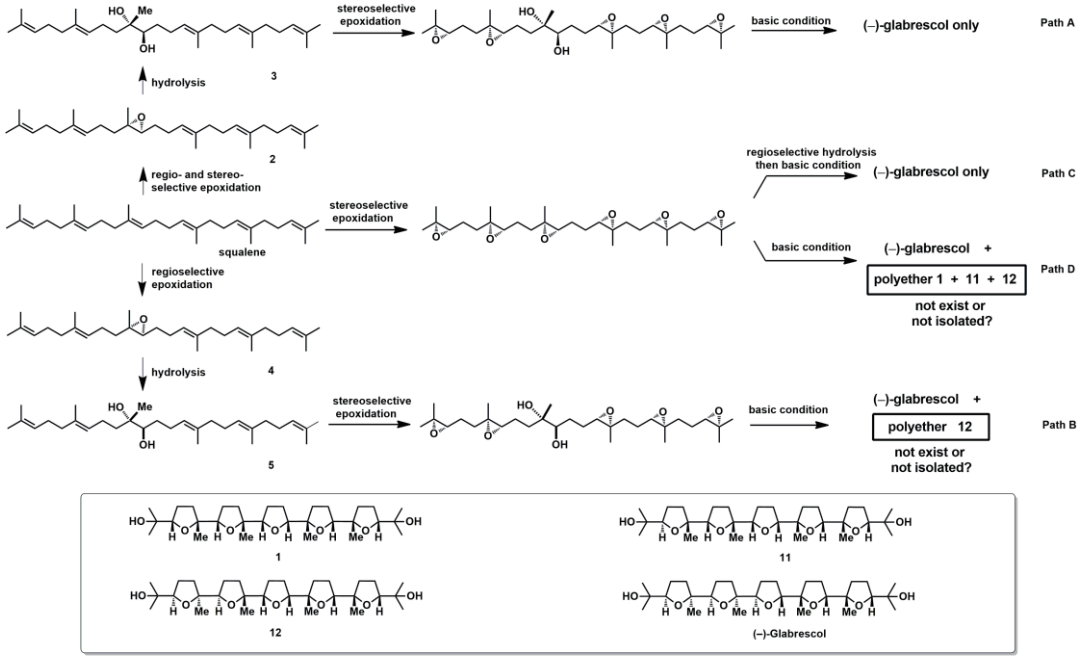
The squalene-derived (–)-glabrescol is the first reported penta-tetrahydrofuran polyether natural product with a novel C_2 symmetric structure. Its real structure was disclosed by Prof. Morimoto through the total synthesis in 2000 (10 steps, overall yield 3%).[1] Prof. Corey reported a biomimetic synthesis approach for (–)-glabrescol (6 steps, overall yield 5%) starting from squalene tetraol later in the same year.[2] We presented three much shorter total syntheses of (–)-glabrescol starting from (10*S*,11*R*)-dihydroxy-10, 11-dihydrosqualene (2 steps, total yield 50%), (10,11)-dihydroxysqualene (2 steps, total yield 27%), or squalene (2 steps, total yield 10%), respectively.[3] The key feature of these syntheses is the base-promoted middle-to-terminal epoxide-opening cascade, which constructs the five tetrahydrofuran rings of glabrescol in one operation.



We thereby proposed three alternative biogenetic pathways of (–)-glabrescol.



If compound 2 or 3, and only (–)-glabrescol were present in the crude extract, path A is the likely biosynthetic pathway
If compound 4 or 5 and (–)-glabrescol and polyether 12 were present in the crude extract, path B is the likely biosynthetic pathway
If only (–)-glabrescol was present in the crude extract, path C is the likely biosynthetic pathway
If (–)-glabrescol and polyether 1, 11, and 12 were all present in the crude extract, path D is the likely biosynthetic pathway

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3O-B-5

Development of a Commercial Manufacturing Process for Gefapixant

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Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States

MK-7264 (gefapixant) is a P2X3 antagonist currently in Phase III clinical trials for the treatment of chronic cough. The 1st generation manufacturing route consists of 11 steps with a PMI (process mass intensity) of ***366*** and overall yield of ***16%***. Therefore, Process Research & Development was tasked with the challenge of developing a robust and sustainable process with a low process mass intensity (PMI), short synthetic sequence, high overall yield, minimal environmental impact, and significantly reduced API costs. A 2nd generation manufacturing route has been developed with a PMI of ***76*** (a 5-fold reduction compared to the 1st generation route) and a significantly higher overall yield (16%→***60% yield***). The key breakthrough in the 2nd generation route was the development of a novel pyrimidine synthesis in flow to afford the core structure of MK-7264 in high yield. This presentation will detail the innovations made in synthetic chemistry, flow chemistry, and process chemistry in route to a commercial manufacturing route for MK-7264.

N-Heterocyclic Carbenes Derived from Sydnones in Heterocycle Synthesis and Catalysis

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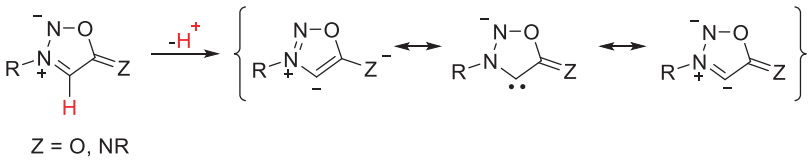
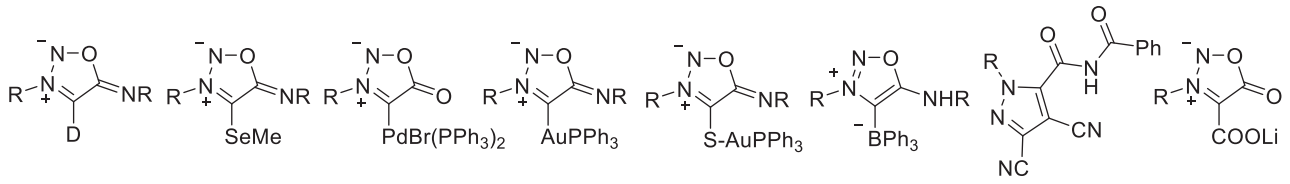
The anions of sydnones (Z = O) and sydnone imines (Z = NR) can be represented as anionic N-heterocyclic carbenes. Their highest occupied molecular orbitals are π-orbitals which possess considerable atomic orbital coefficients on the carbene carbon atom. The characteristic σ-type orbital of *N*-heterocyclic carbenes is the HOMO-1 or HOMO-2. As a consequence, the anions of sydnones and of their imines can be characterized as π-electron rich anionic *N*-heterocyclic carbenes. They display high calculated electron densities on the carbene carbon atom, the ^{13}C NMR resonance frequencies of which are shifted considerably upfield in comparison to other (anionic) NHCs.[1]



The anions of sydnones undergo characteristic trapping reactions and complex formations of NHCs (**1** - **6**).[2-5] Upon treatment with tetracyanoethylene they undergo reductive 1,3-dipolar cycloadditions,[6] induced by the attack of the NHC followed by interaction of the resulting terminal anion with the π-electron system, to form pyrazoles **7**. The lithium salts of the carbon dioxide adduct of sydnone anions **8** catalyze Suzuki-Miyaura reactions under acidic conditions.[7]



1 **2** **3** **4** **5** **6** **7** **8**

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3O-B-7

Syntheses of Isoanthracenoheteroles by Cycloaddition of Didehydroisobenzofuran

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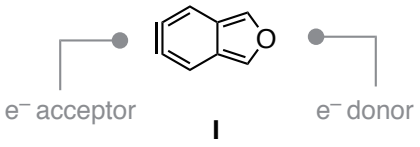
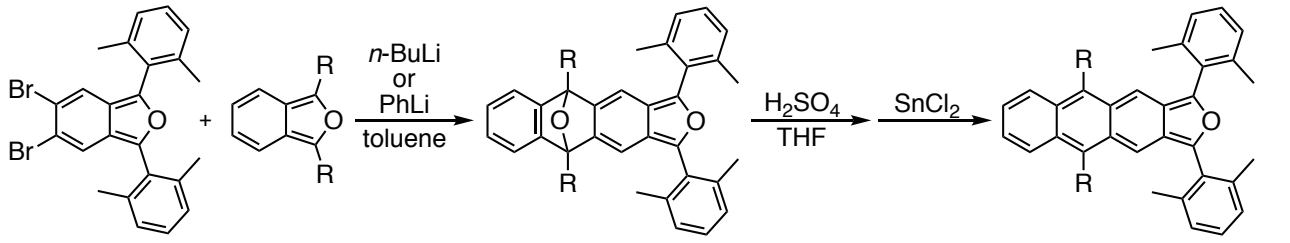
School of Science and Technology, Kwansei Gakuin University
Sanda, Hyogo, 669-1337, Japan



I

Isoanthracenoheteroles have potentially attractive reactivities and physical properties derived from the unique π-conjugated structure. Unfortunately, however, their syntheses have been quite limited due to the lack of practical method for preparing the highly condensed aromatic compounds. In this context, we focused on didehydroisobenzofuran (**I**), a new reactive intermediate possessing a highly strained cumulene structure in the isobenzofuran ring. Importantly, taking advantage of this unique electronic structure, possessing electron donor and electron acceptor moiety in one molecule, rapid construction of polycyclic framework would be realized via successive cycloadditions through the donor–acceptor interaction of **I**. Along these lines, we recently developed an efficient synthetic access to functionalized polycyclic aromatic compounds by using dibromoisobenzofuran as a synthetic equivalent to didehydroisobenzofuran **I**. [1]

As a further extension of this study, we report herein the syntheses of isoanthracenofurans and isoanthracenothiophenes by direct generation of didehydroisobenzofuran **I** via halogen–lithium exchange of dibromoisobenzofuran. Importantly, steric protection of the precursor around the furan moiety is key to control the reactivity of **I**, which enabled the mono-cycloaddition with various arynophiles, selectively affording functionalized diarylisobenzofurans. Moreover, the [4+2] cycloadducts **3**, thus obtained, was converted to isoanthracenofuran **4**, a novel class of heteroacene, by two-step aromatization.[2] Intriguing properties of **4** will also be discussed in the presentation.



1

2a (R = ·ϕ·Ph)
2b (R = ·ϕ·C≡C–Ph)

3a (R = ·ϕ·Ph)
3b (R = ·ϕ·C≡C–Ph)

4a (R = ·ϕ·Ph)
4b (R = ·ϕ·C≡C–Ph)

[1] Haneda, H.; Eda, S.; Aratani, M.; Hamura, T. *Org. Lett.* **2014**, *16*, 286−289.
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1,4-Thiazine

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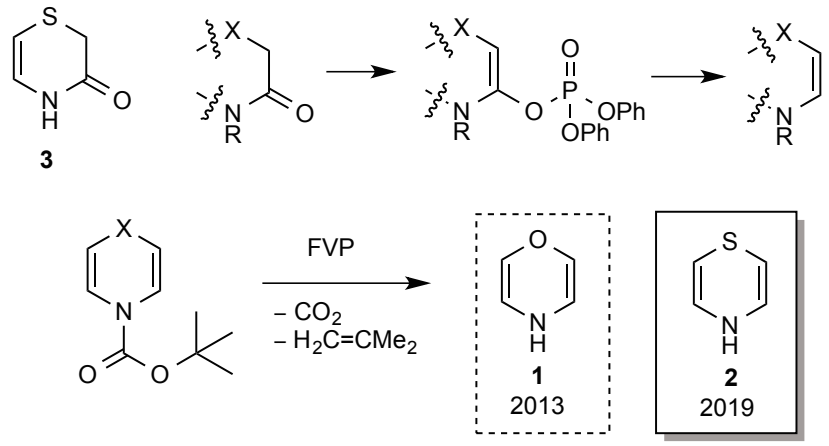
In 2013 we described the synthesis of the parent heterocycle 1,4-oxazine **1**.[1] Although it was the first, and so far only, fully unsaturated parent six-membered ring heterocycle containing a group 15 and a group 16 element to be spectroscopically characterized, it was unstable and slowly polymerized at RT. At that time, it was noted that there was an isolated early report[2] of formation of the related 1,4-thiazine **2** but this could not be reproduced and reliable generation as well as spectroscopic characterization of 1,4-thiazine has not been possible until now.



Herein we describe the successful rational synthesis of 1,4-thiazine **2** and its full characterization. The route is modelled on our oxazine synthesis but starting from the precursor **3**,[3] and applying first the enol phosphate method[4] to introduce the required double bond, followed by final deprotection of nitrogen under FVP conditions. The structure and properties of this important new heterocycle as well as some of the intermediates will be described.

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2. C. Barkenbus and P. S. Landis, *J. Am. Chem. Soc.*, 1948, **70**, 684–685.
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Chain Length-dependent Acceleration of Rotation of Lactams with Nitrogen-pyramidal Tertiary Amide

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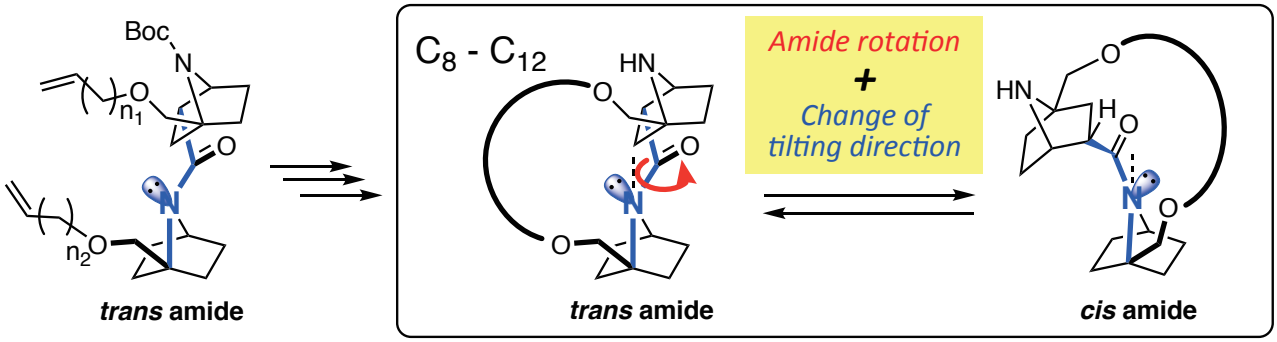
Rotation of tertiary amides in lactam is affected by the intervening chain and character of the rotatable bonds. In the homooligomers of the bicyclic β-proline, it was shown that the presence of the bridgehead substituent completely biases the amide *cis-trans* equilibrium to one side (*trans* amide). [1] Although the tertiary amide from the bicyclic amine takes nonplanar, i.e., nitrogen-pyramidal structure,[2] this amide is stable to hydrolysis and further synthetic transformation is feasible.[3] Therefore, we expected that this bicyclic system would provide a suitable scaffold to examine the stapling length dependency of lactam amide ratio and rotation.

We focused on cyclic lactams with two rigid bicyclic units. Cyclic dimer lactams with various lengths of alkyl chain (C_8-C_{12}) were synthesized by ring-closing metathesis (RCM) to staple the bridgehead alkenyl substituents of model bicyclic dimers, hydrogenation and deprotection of the Boc group. A consistent relationship was found between the amide *cis/trans* ratio and the linker length. We also found a consistent increase of *trans* ratio in accordance with a consistent deceleration of amide *trans* to *cis* rotation, together with concomitant acceleration of amide *cis* to *trans* rotation, as the side-chain staple length is increased in bicyclic dimers. Furthermore, Metadynamics simulations show that these lactam amides can spin through 360 degrees. The tilting direction of the pyramidal nitrogen atom of the bicyclic systems is synchronized with the direction of the semicircle-rotation of the amide. [4]



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Alkene Amino Difunctionalization as a Rapid Approach to Diverse Heterocycles

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ABSTRACT

1,2-Amino functionality-containing molecules are highly valuable as ligands, pharmaceuticals, and building blocks for organic synthesis, drug discovery and material science. Alkene amino difunctionalization represents a direct and powerful strategy to transform simple and readily available olefins into richly functionalized nitrogen-containing compounds of great value. Toward this, we have developed copper-catalyzed alkene amino difunctionalization reactions by exploring heteroatom-substituted nitrogen bonds as an electrophilic amino precursor in conjugation of nucleophiles. These methods afford a rapid and direct access to a diverse range of 1,2-diamines, 1,2-amino alcohol derivatives, including highly functionalized lactams and lactones. Importantly, mechanistic studies on these reactions reveal a novel electrophilic amination-initiated activation pathway for designing new alkene difunctionalization reactions that can incorporate diverse nucleophiles.

Catalytic Alkyne Functionalization *via* Metal Carbene Intermediate

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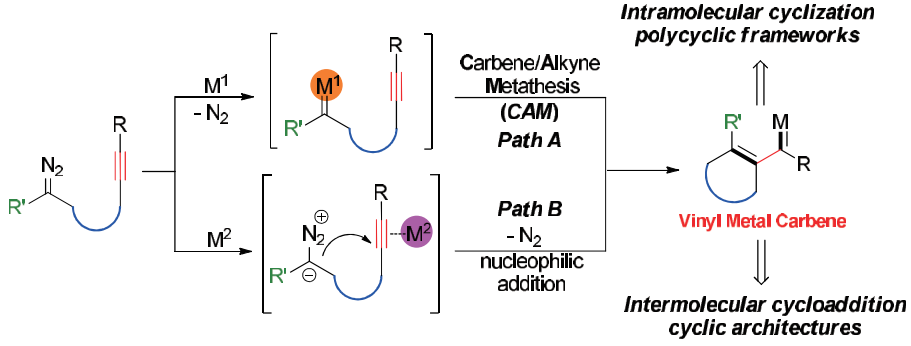
Heterocyclic and carbocyclic compounds are pervasive motifs in various areas of chemistry, medicinal chemistry, and material sciences. Therefore, efforts have been devoted to the construction of cyclic architectures in past decades. Catalytic alkyne transformation is a practical approach for the effective construction of functionalized cyclic frameworks.[1] Especially, the gold-catalyzed alkyne transformations.[2] It's noteworthy that Toste realized the first gold-catalyzed diazo-yne carbocyclization under mild conditions.[3] Inspired by those advances and as the continuation of our interest in alkyne bifunctionalization,[4] two distinct methodologies have been formulated with alkyne-tethered diazo compounds: the carbene/alkyne metathesis (CAM) transformation (Path A)[5] and the catalytic diazo-yne carbocyclization (Path B), both delivering the unique vinyl metal carbene intermediate which is accessible only with limited precursors. Herein, we would like to present the summary of our recent advances in this context, especially the catalytic diazo-yne carbocyclization process, which directly leads to the formation of the key vinyl metal carbene without going through the initial carbene species in CAM process, and to enable the intermolecular reaction in the terminating step of these cascade reactions.



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[2] (a) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. (b) Sohel, S. M.; Liu, R. *Chem. Soc. Rev.* **2009**, *38*, 2269. (c) Yeom, H.-S.; Shin, S. *Acc. Chem. Res.* **2014**, *47*, 966.

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Au-Catalyzed Skeletal Rearrangement of *O*-Propargylic Oximes via N-O Bond Cleavage with the Aid of a Brønsted Base Cocatalyst

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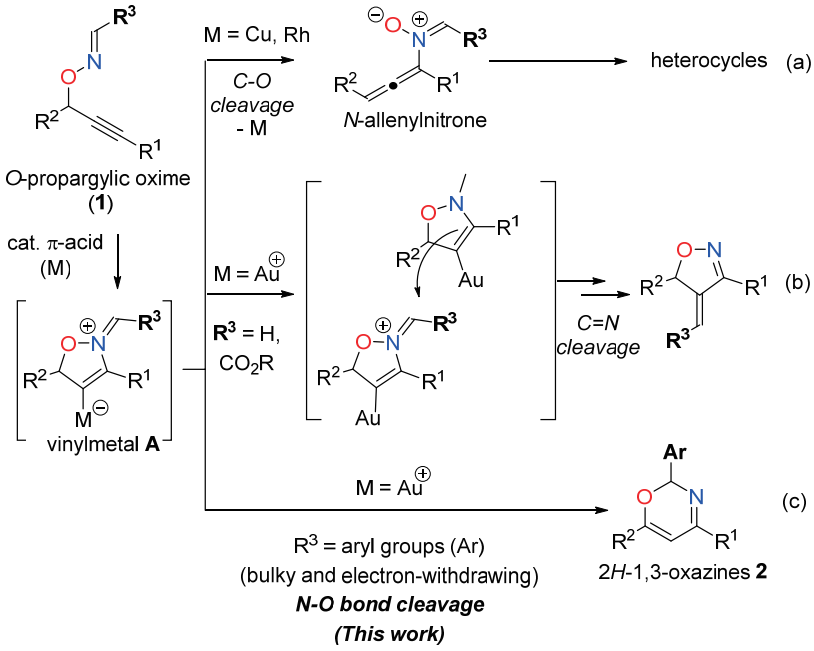
π-Acidic metal-catalyzed skeletal rearrangement reactions are a powerful method to construct highly elaborate heterocyclic compounds. We have recently disclosed that *O*-propargylic oximes **1** serves as an intriguing platform in catalytic skeletal rearrangement reactions (Scheme 1). For example, the copper- and rhodium-catalyzed reactions proceeds via C-O bond cleavage, generating *N*-allenylnitrone intermediate, which further undergoes favorable transformations to synthesize various heterocycles (Scheme 1a).[1] In contrast, the gold-catalyzed reactions of formaldoximes (R^3 = H) and glyoximes (R^3 = CO_2R) proceeds via C=N bond cleavage, presumably because of relativistic nature of the gold catalyst (Scheme 1b).[2] Our experimental results indicate that the reaction proceeds via intermolecular C-C bond formation between the iminium moiety of the long-lived vinylgold intermediate **A** and the olefin moiety of another vinylgold species. In this context, we envisioned that a bulky functional group at the oxime moiety would interrupt the C-C bond-forming process, resulting in different transformations. Herein, we report that the gold-catalyzed reactions of *O*-propargylic oximes **1**, which has a bulky and electron-withdrawing aryl group at the oxime moiety, proceeds via N-O bond cleavage, producing 2*H*-1,3-oxazine derivatives **2** in good to high yields (Scheme 1c).[3] It is noteworthy that the reaction of substrates having an alkyl group at the propargylic position (R^2) was dramatically accelerated by the use a Brønsted base cocatalyst.



Scheme 1. Catalytic Skeletal Rearrangement Reactions of *O*-Propargylic Oximes **1**

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Catalytic Asymmetric Synthesis of Thiochromanes

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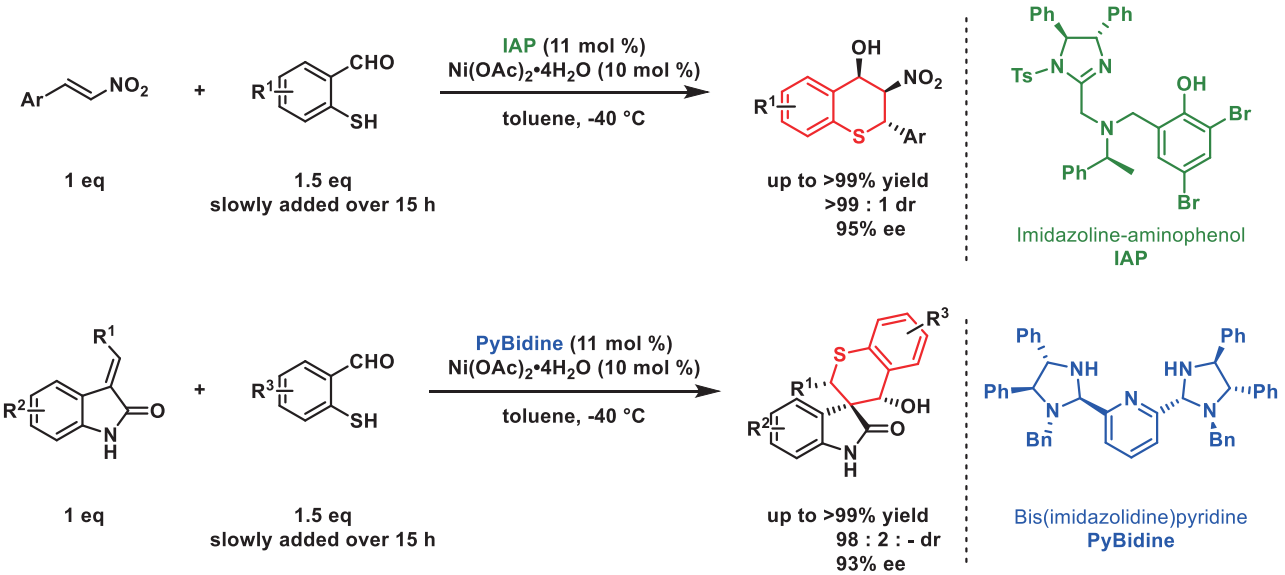
Chromane moieties are often found in various biologically significant compounds isolated from nature. The biological activity of these compounds following the replacement of the oxygen atom in the chromane group with sulfur to form thiochromanes has been studied with regard to research and development of pharmaceuticals. Here, two types of asymmetric metal cayalysts are reported for accessing the strereochemical divergent thiochromanes. A (*S*,*S*)-diphenylethylenediamine-derived imidazoline-aminophenol (IAP)-Ni complex catalyzed tandem asymmetric Michael/Henry reaction of 2-mercaptobenzaldehydes with β-nitrostyrenes to give the corresponding (2*S*,3*R*,4*R*)-2-aryl-3-nitrothiochroman-4-ols in up to 99% diastereoselectivity with 95% ee. [1,2] Reduction of the nitro group of the chiral thiochromanes gave a new series of (2*S*,3*R*,4*R*)-3-amino-2-arylthiochroman-4-ols with keeping the strereoselectivity. For the asymmetric Michael/aldol reaction of thiosalicylaldehydes with methyleneindolinones, (*S*,*S*)-diphenyldiamine-derived bis(imidazolidine)pyridine (PyBidine)-Ni(OAc)$_2$ complex was effective to provide (2'*R*,3*S*,4'*R*)-thiochromanyl-spirooxindole having three contiguous stereogenic centers.[3,4] Recent advances on the catalytic asymmetric synthesis of γ,δ,-unsaturated-β-ketoester will be also presented.



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Cross-Coupling via Ammonium or Pyridinium C–N Bond Cleavage

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Advanced Elements Chemistry Laboratory, Cluster for Pioneering Research (CPR), RIKEN
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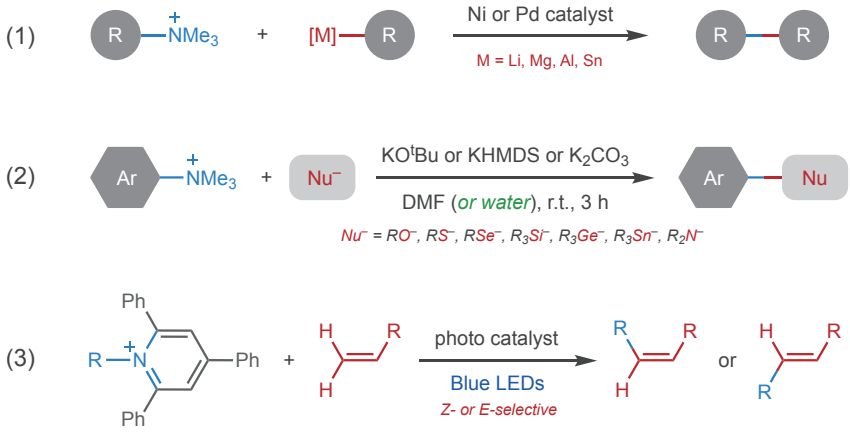
Amine groups occur widely in natural products, and are also found in many pharmaceuticals, dyes, and functional molecules. However, transformation of the NR_2 group is generally difficult, due to the chemical inertness of the C–N bond. Quaternary organo-ammonium/pyridinium salts can be easily prepared from various aryl/alkyl amines. Their potential usage in cross-coupling (Kumada-Tamao-type) was pioneered by Wenkert *et al.* in 1988.[1] Other protocols, such as Suzuki-Miyaura-type,[2] Negishi-type[3] an so on, have also been developed in recent years. While these advances of cross-coupling showed the synthetic utility of ammonium/pyridinium salts as efficient substitutes for halides, however, many other types still remained unknown despite that and novel protocols for functionalization of such C–N bonds are of great demands. Herein, we report our recent study on developing novel cross-coupling reactions of ammonium/pyridinium salts, including: 1) transition-metal-catalyzed cross-coupling reaction through ammonium C–N bond cleavage,[4-7] 2) nucleophilic aromatic substitution of aryl ammonium salts via C–N bond cleavage,[8-9] and 3) photo-induced stereo-selective Heck-type reaction via pyridinium C–N Bond cleavage.[10]



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Visible Light-driven Generation of N-Radicals and Application to N-Heterocycle Synthesis

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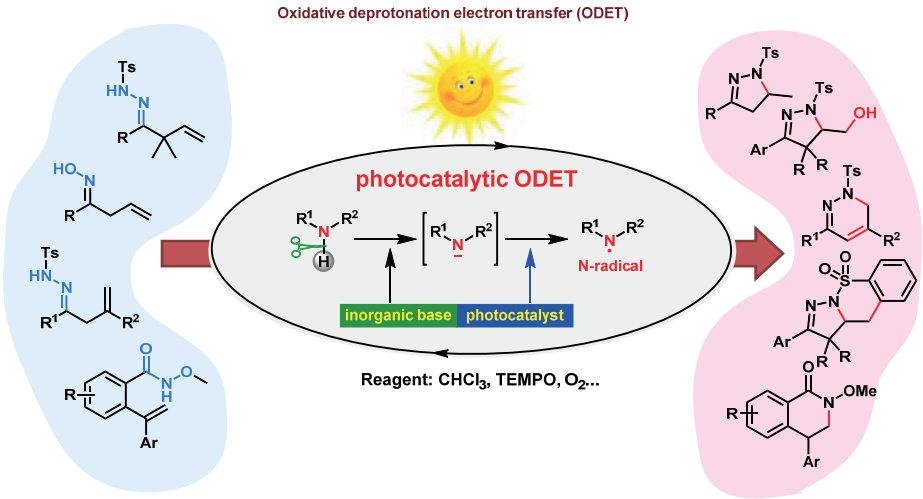
Wuhan, 430079, P. R. China (chenjiarong@mail.ccnu.edu.cn)

Because of the high bond dissociation free energy of the N-H bond, the generation of N-radicals from N-H bonds and their synthetic potential are still underexplored. Recently, the visible-light photocatalysis has emerged as an attractive tool for the catalytic formation of N-centered radicals, but the pre-incorporation of a photolabile groups at the nitrogen atom limited the substrate scope.[1]

Recently, we have developed a visible light-induced oxidative deprotonation electron transfer (ODET) strategy for direct conversion of the N–H bonds of hydrazones into the corresponding N-centered radicals. Employing this strategy, we have successfully developed a series of N-radical-based hydroamination, oxyamination of alkenes, as well as cascade reactions. DFT calculations and control experiments were also performed to investigate the reaction mechanisms and regioselectivity.[2-7] In this talk, I will present the details.



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Organocatalytic Enantio- and Diastereoselective Construction of *syn*-1,3-Diol Motifs via Dynamic Kinetic Resolution of In Situ Generated Chiral Cyanohydrins

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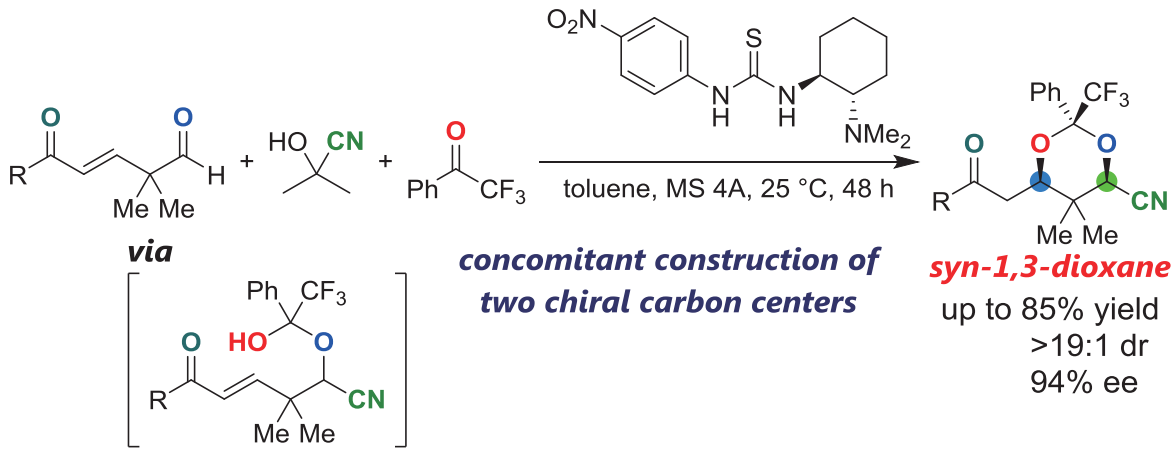
Due to the ubiquity in biologically active natural products and pharmaceuticals, chiral 1,3-diols have been gathered much attention as attractive synthetic targets. Although a number of stereoselective multistep syntheses of these structures have been reported to date, simultaneous catalytic construction of two stereogenic centers of chiral 1,3-diol structures is still challenging; especially an approach to *syn*-1,3-diol motifs from achiral substrates with high level of stereocontrol remained unexploited. In this study, we developed a catalytic asymmetric method for the synthesis of *syn*-1,3-dioxanes as acetal-protected *syn*-1,3-diol motifs. This method involves reversible formation of cyanohydrins enabling their racemization, thereby leading to dynamic kinetic resolution of in situ-generated chiral cyanohydrins;[1–3] a subsequent hemiacetalization/intramolecular oxy-Michael addition cascade[4,5] using chiral bifunctional organocatalysts enabled highly enantio- and diastereoselective construction of two stereogenic centers of desired *syn*-1,3-diol motifs.[6]



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Design of Chiral Bifunctional Sulfide Catalysts for Asymmetric Bromolactonizations

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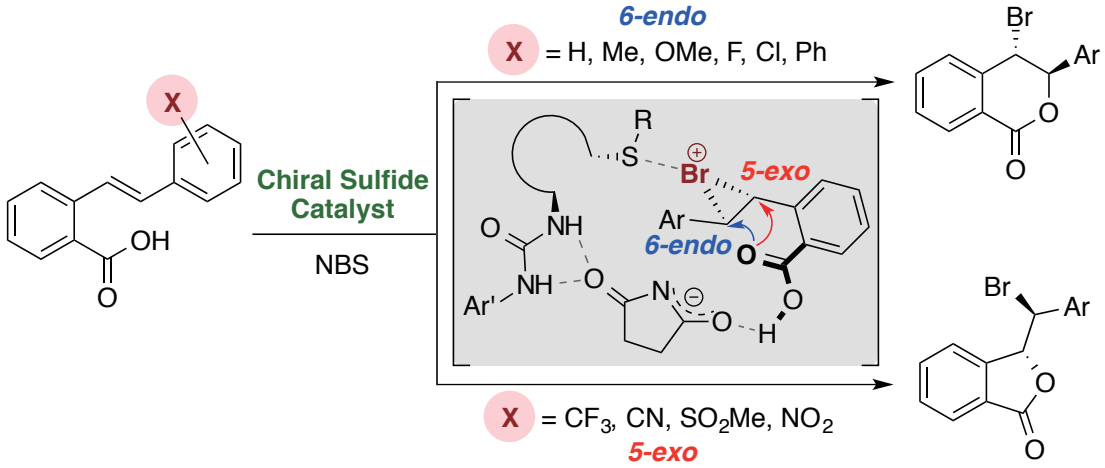
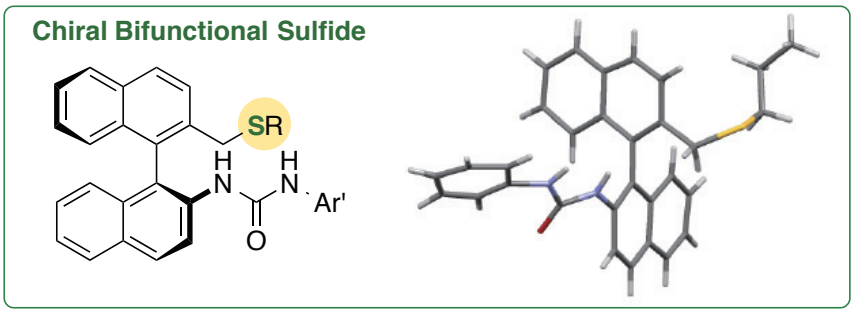
Although a wide variety of chiral organocatalysts have been developed for asymmetric transformations, effective chiral dialkyl sulfide organocatalysts remain relatively rare and under-developed, despite the potential utility of dialkyl sulfide catalysts. Herein, we report the development of chiral bifunctional dialkyl sulfide catalysts possessing a urea moiety for regio-, diastereo-, and enantioselective bromolactonizations. The importance of the bifunctional design of chiral sulfide catalysts was clearly demonstrated in the present work. The roles of both the sulfide and urea moieties of the catalyst were clarified based on the results of experimental and theoretical investigation.[1–3]





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Synthesis of Highly Coordinated Organoaluminum Complexes Bearing a Lewis Basic Substituent and Their Application to Catalytic Cycloaddition Reaction

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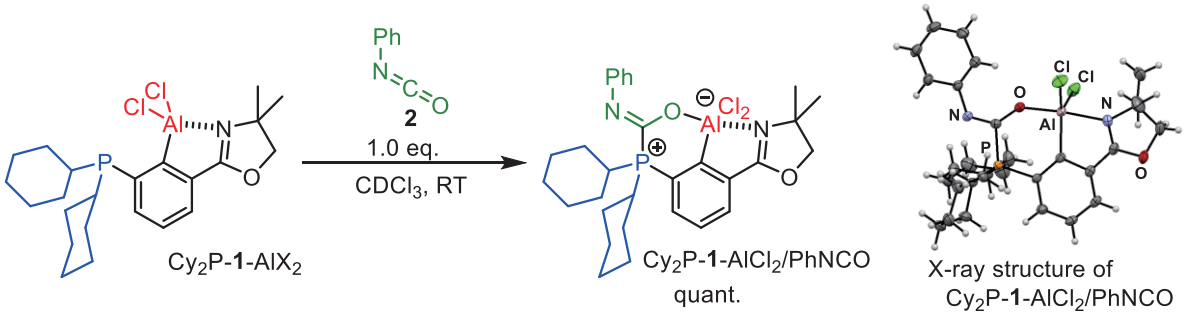
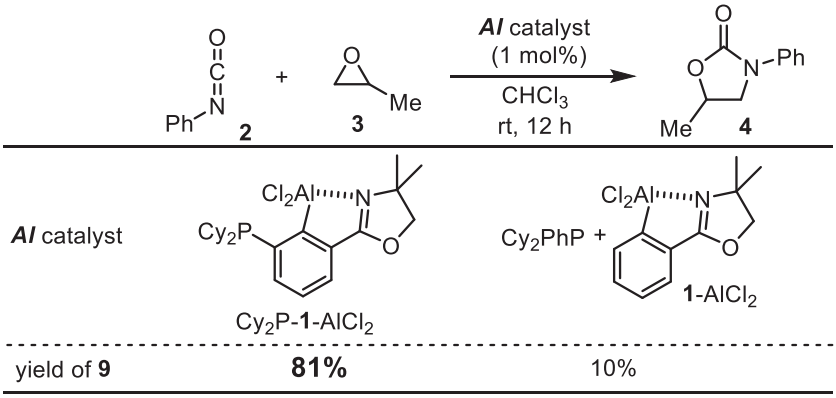
Aluminum is one of the most abundant metals in the earth's crust, and trivalent aluminum compounds have been used as important Lewis acids. A hydrocarbyl group is a promising ligand because modifications of the carbon framework could precisely control catalytic properties. Recently, we have developed Pheox- and Phebox-Al catalysts and the catalytic activity was successfully controlled using the Pheox and Phebox ligands.[1] Herein, we report the synthesis of Pheox-Al complexes bearing a Lewis basic moiety near the Al atom to create more functionalized Al-catalysts.

First, we synthesized Cy_2P-**1**-$AlCl_2$ bearing Cy_2P group as a Lewis basic moiety. When the reaction of Cy_2P-**1**-$AlCl_2$ with isocyanate **2** was examined, adduct complex Cy_2P-**1**-$AlCl_2$/PhNCO was obtained quantitatively. In this complex, Cy_2P group acted as a Lewis base to add to **2** and the aluminum group bound to the anionic oxygen atom.



The formation of the adduct between Cy_2P-**1**-$AlCl_2$ and PhNCO **2** encouraged us to investigate the cycloaddition of isocyanates and epoxides catalyzed by Cy_2P-**1**-$AlCl_2$. In the cycloaddition of isocyanate **2** with epoxide **3**, Cy_2P-**1**-$AlCl_2$ showed an excellent catalytic activity to afford **4** in 81% yield at room temperature. On the other hand, the combination of simple Pheox-Al complex (**1**-$AlCl_2$) and PPh_2Cy was not effective. Therefore, coexistence and cooperation of aluminum and phosphine moieties in a same molecule are important to the present catalytic cycloaddition.



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Benzo[d]thiazol-2-yl Sulfonyl Group – A new look for an old synthetic tool

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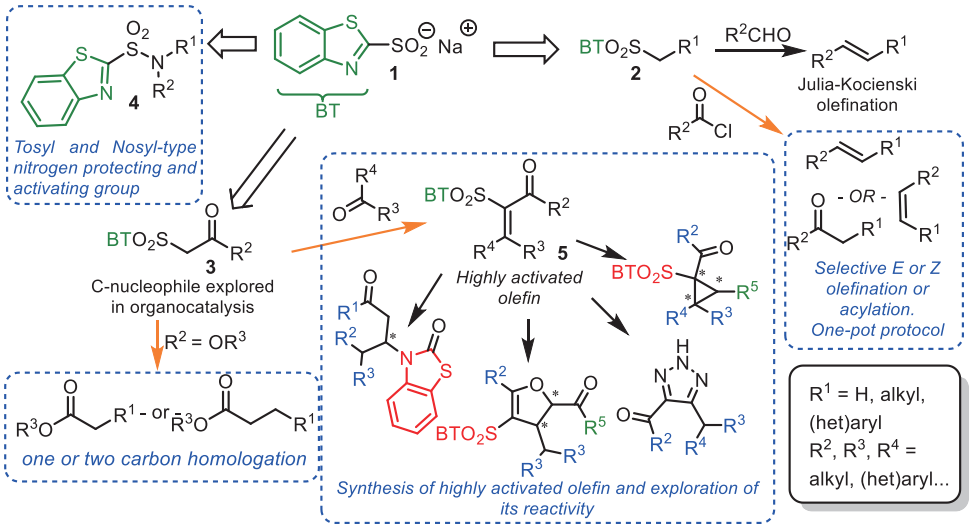
Benzo[*d*]thiazol-2-yl (BT) sulfones are indisputably connected in the organic synthetic community with Julia-Kocienski olefination reaction.[1] The use of BT group in this reaction allowed to transform two-pot Julia-Lythgoe olefination into one-pot protocol that proved to be not only more (*E*)-selective, but also proceeded under mild reaction conditions and possess broad functional group tolerance. The next important synthetic application of the BT group came a decade later, when Jørgensen et al. applied carbonyl derivative **3** as a C-nucleophile in the organocatalyzed Michael-type additions to various activated olefins.[2]



We have decided to extend the use of BT-sulfones even further, and demonstrated that the BT sulfonyl group can serve as (a) amine protecting/activating group with superior properties to tosyl and nosyl group; (b) C-nucleophiles **3** can be used in one and two carbon homologation reactions;[3] (c) reaction of alkyl BT-sulfones **2** and carboxylic acid derivatives yields carbonyl compounds, and (*E*) or (*Z*)-olefins; and finally (d) highly activated Knoevenagel-like olefins **5** can be used to produce in stereoselective fashion various carbo and heterocycles in enantioenriched manner and interesting products of intramolecular rearrangement.

Litterature

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Synthesis of Benzophospholes with Phosphenium Cations of Unique Reactivity

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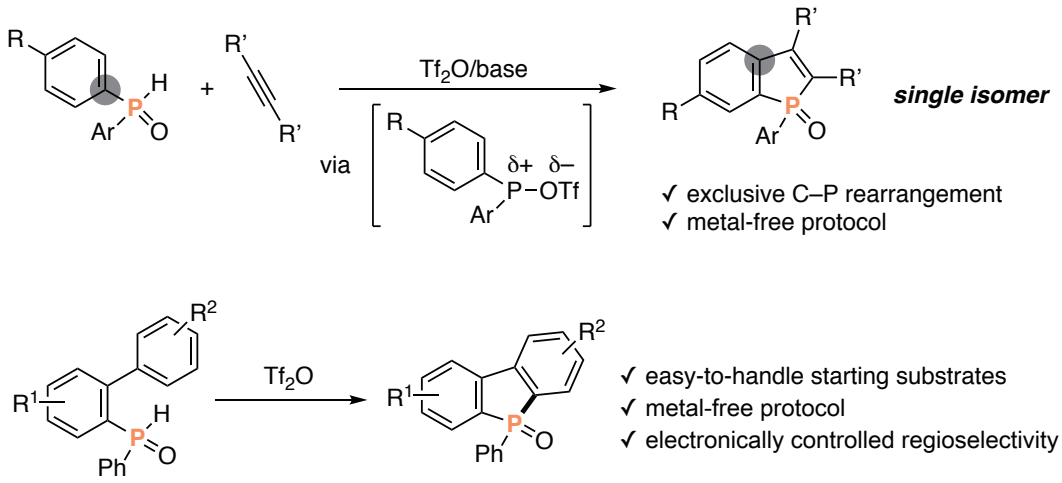
Osaka University, Suita, Osaka 565-0871, Japan

Benzophospholes and their derivatives have received significant attention in research fields of material chemistry because of their unique optical, electronical, and physical properties, as exemplified by potent applications in organic light-emitting diodes, photovoltaics, and cell imaging dyes. Accordingly, considerable attention has been focusing on the rapid and concise synthesis of the benzophosphole framework. However, the conventional synthetic procedures still required tedious and multistep sequences with complicated and unstable starting substrates and/or reagents.
On the other hand, our research group recently developed a new methodology for highly reactive and coordinatively unsaturated phosphenium cations from readily available secondary arylphosphine oxides and Tf_2O activator and succeeded in the development of metal-free phosphinative cyclization reaction of alkynes with pendant nucleophiles.[1] During continuous interest in this chemistry, we have now found a unique reactivity of in-situ generated phosphenium cations with simple internal alkynes: a formal [3+2]-cycloaddition occurs to deliver the corresponding benzophospholes in good yields. Additionally, different from the previous radical-promoted cycloaddition reactions,[2] the *ortho*- and *para*-substituted arylphosphine oxides undergo the reaction with concomitant C–P rearrangement to furnish the single regioisomers.[3] Related dibenzophosphole synthesis via the intramolecular phospha-Friedel-Crafts-type reaction will also be presented.[4]



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Termination of Halogen Dance by in situ Transmetalation

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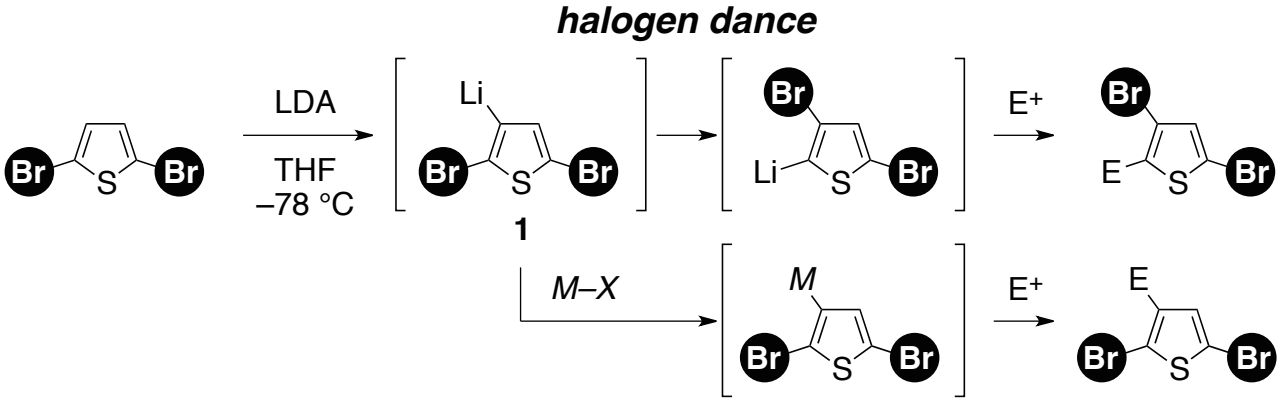
Multiply substituted heteroaromatic compounds are structural constituents of biologically active natural products, pharmaceuticals, and functional organic materials. The regiocontrolled synthesis of these heteroaromatic compounds remains important, because Paal–Knorr synthesis and Gewald thiophene synthesis require preparation of functionalized acyclic dicarbonyl compounds before cyclization under the harsh conditions, resulting in limited substrate scope.

A base-mediated halogen dance[1] allows forming two chemical bonds in one pot, which renders reduction of the number of reaction pots; however, synthetic application of the halogen dance as well as regiochemical control in the migration have not been fully investigated. Recently we succeeded in controlling the reactivity of the short-lived transient thienyl lithium species by transmetalation and achieved the regiocontrolled synthesis of multiply arylated thiophenes through Negishi coupling.[2] During the studies exploring substrate scope, a benzoxazole proved to be a superior directing group for a novel 1,3-migration of the bromo group.[3] Herein we disclose termination of halogen dance by trapping of the short-lived thienyllithium **1** through the finely tuned in situ transmetalation.[4]



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3O-D-4

Syntheses of Chiral Heterocycles Using Ammonium Ylides

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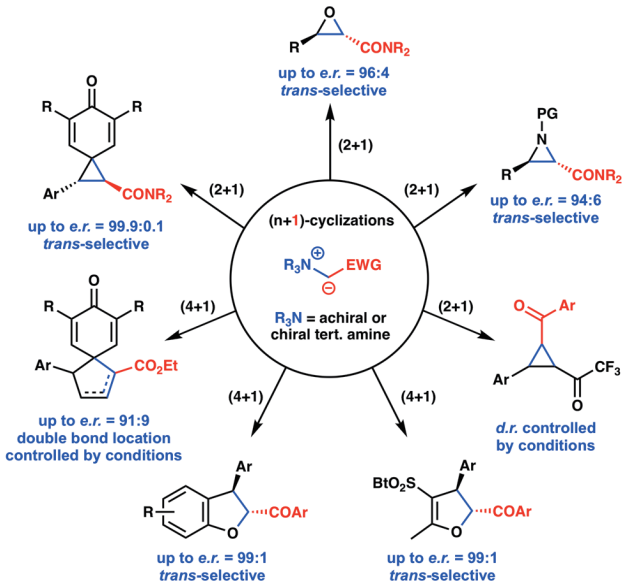
Ammonium ylides have emerged as very powerful C1-synthons for asymmetric formal (n+1)-cyclizations upon reaction with a broad variety of different acceptor molecules.[1]



Given the importance of the hereby accessible targets, we have recently started a detailed research program focusing on the systematic use of simple chiral ammonium ylides to access a broad variety of differently functionalized carbo- and heterocycles.[2] As outlined in the attached Scheme we succeeded in developing a variety of highly asymmetric protocols to access structurally diverse heterocycles (and carbocycles) under operationally mild conditions.

In the context of this presentation a detailed overview on the potential and the limitations of this methodology for heterocycle-forming formal (n+1)-cyclizations will be given.

In addition, we recently also discovered that allenoates may serve as C1 synthons for formal (4+1)-cyclization reactions under nucleophilic phosphine catalysis. This allowed for the highly enantioselective synthesis of densely functionalized dihydrobenzofuranes in an so far unprecedented manner and this novel approach will be presented as well.[3]

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3O-D-5

Photochemically induced electron and hydrogen transfer in heterocyclic chemistry

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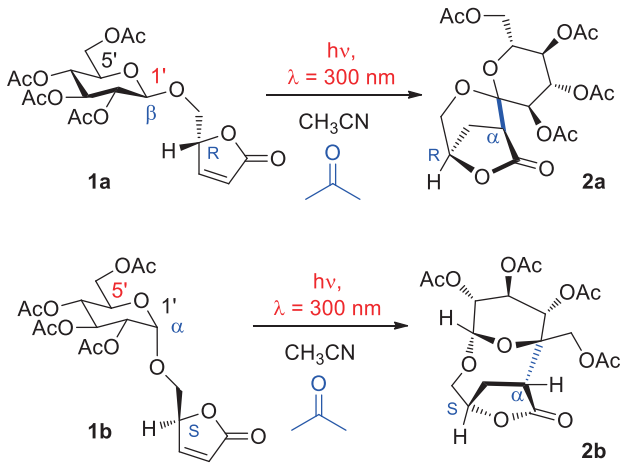
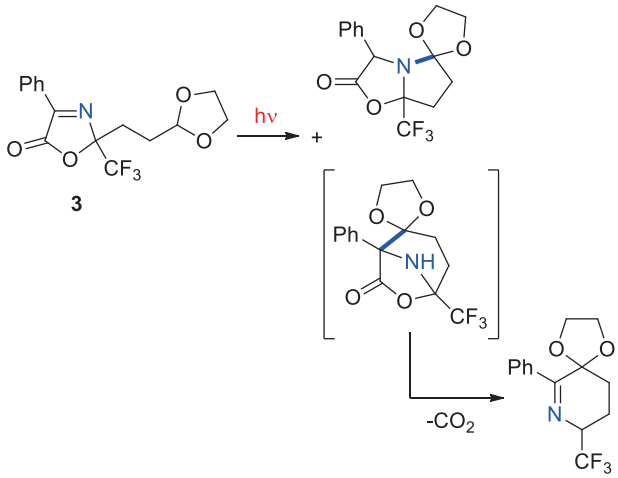
Electron and hydrogen transfer processes play an important role in many photochemical reactions. The mechanism of these processes has a significant influence on the regio- and stereoselectivity of such reactions.[1] Intramolecular reactions are used for the construction of unusual heterocyclic compounds. In such a reactions, α,β-unsaturated butyrolactones **1a,b** carrying glucose moieties are cyclized in two different positions involving C-C bond formation exclusively in the α-position of the unsaturated lactone chromophore (Scheme 1).[2] The reaction takes place at the anomeric center 1' or in position 5' of the glucose substituent depending on the relative configuration on both moieties. Compounds **2a** and **2b** are thus obtained.

Similar reactions have been carried out with imines (Scheme 2). [3] Formally, the oxazolones such as **3** are derived from α,β-unsaturated butyrolactones (compare **1a,b**) by replacing the carbon atom in β-position by a nitrogen atom. In this case, a competition between the formation of a C-C bond and the formation of a C-N is observed.



Scheme 1



Scheme2

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Construction of Nitrogen-Containing Medium-Sized Ring by Gold-Catalyzed Cycloisomerization

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Kyalo Stephen Kanyiva[2] and Takanori Shibata[1,*]
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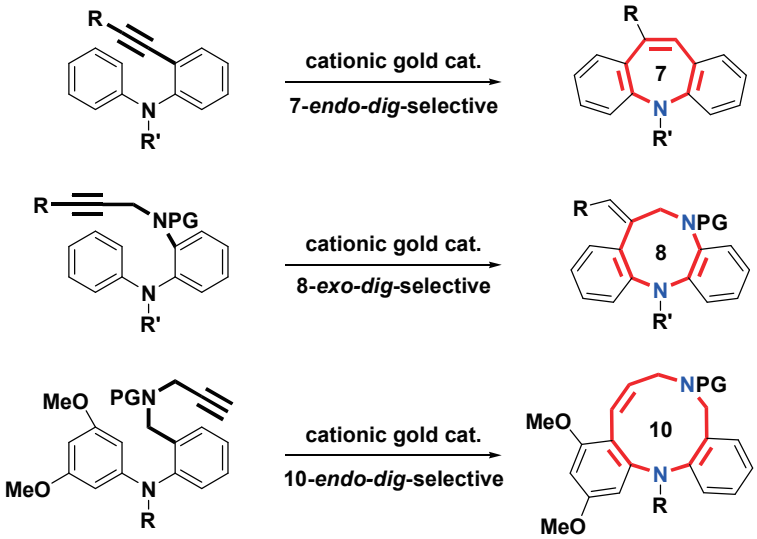
Gold-catalyzed cycloisomerization of 1,*n*-enyne provides a cyclic structure in high efficiency under mild conditions. Various types of cycloisomerizations have been reported and, in particular, 6-*endo-dig* type reaction is well-developed. While there are some examples of using part of benzene ring as an ene moiety to give various benzo-fused bicyclic compounds, only limited examples of benzo-fused medium-sized ring synthesis by cycloisomerization have been reported.

Agaisnt this background, we achieved cationic gold(I)-catalyzed 7-*endo-dig*, 8-*exo-dig,* and 10-*endo-dig*-selective cycloisomerization to give dibenzazepines, dibenzodiazocines, and dibenzodiazecines, respectively. The reaction of 2-alkynyldiphenylamines proceeded in 7-*endo-dig*-selective manner.[1],[2] When 2-propargylaminotriphenylamine derivatives were subjected to the reaction, 8-*exo-dig* products were obtained selectively.[3] In this reaction, the use of *o*-diaminobenzene tether and the electron-withdrawing protecting group were the key to the selective transformation. In order to construct 9 or 10-membered ring, the reaction of *N*-(2-anilinobenzyl)propargylamine derivatives was conducted. When phenyl group was used for the reaction site, no cyclization occurred. However, the reaction of highly nucleophilic 3,5-dimethoxyphenyl group-containing substrate proceeded 10-*endo-dig* selectively to give dibenzodiazecine derivatives.[4]



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β-Silicon Effect in Intermolecular Site-Selective C(sp^3)-H Amination Promoted by Dirhodium Nitrenes

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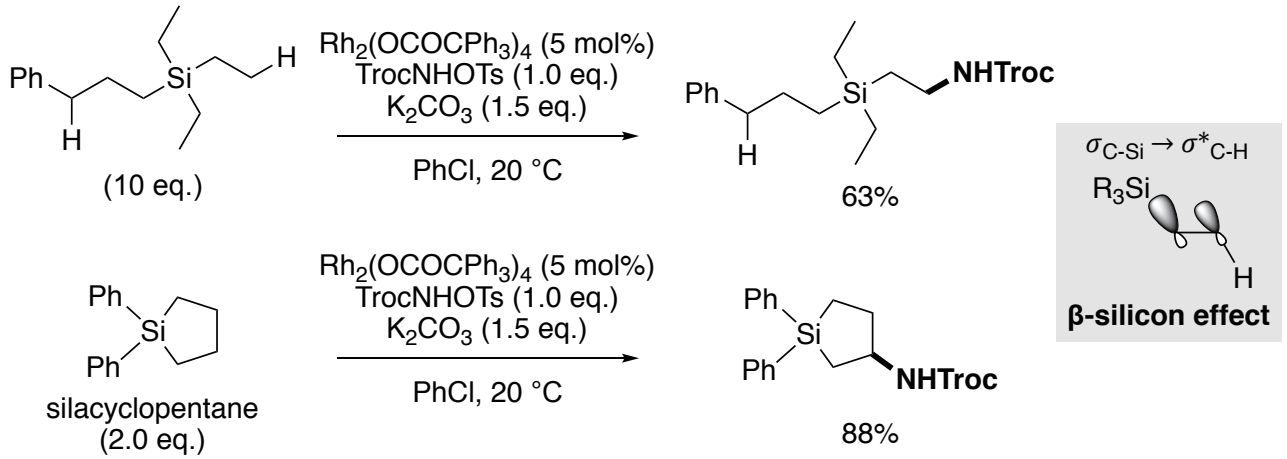
Metal-catalyzed nitrogen-group-transfer reaction via C-H bond cleavage has become an important technology for the construction of C-N bonds.[1] In particular, dirhodium nitrenes have emerged as powerful intermediates for C(sp^3)-H amination.[2] While cleavable C-H bonds are limited in intramolecular reaction, control of site-selectivity becomes a main issue in intermolecular reaction.[3] There are some examples that C(sp^3)-H bonds α to carbon-carbon multiple bonds or heteroatoms with lone pairs are selectively converted to C-N bonds in intermolecular manners. We recently reported chemo- and regioselective aromatic C(sp^2)-H amination of alkoxyarenes promoted by dirhodium nitrenes.[4] During the study, we unexpectedly found that the competitive C(sp^3)-H amination of silyl-group-substituted compounds took place at β-position of the silicon atoms.[5] Inspired from the phenomenon, we started investigation for β-position-selective C(sp^3)-H amination of organosilicon compounds to find that primary C(sp^3)-H bonds of silylethyl groups and endocyclic C(sp^3)-H bonds of silacycloalkanes have reactivity enough to be converted site-selectively. Kinetic studies indicated that the rate-determining step be the formation of the dirhodium nitrene species and the selectivity-determining step be the C-H insertion step. DFT calculation suggested that a C-Si σ bond could donate towards the reacting C-H σ* orbital in the transition state structure of the C-H bond cleavage step.



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3O-D-8

Development and Application of Allylic C-H Amidation Chemistry

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The development of new reactions and catalysts for the oxidative cross-coupling of C-H bonds with C-H, N-H and O-H bonds will be discussed. Strategically, these reactions allow for the synthesis of complex molecules from their constituent components, minimizing the need for functional group activation and manipulation. Specifically, rhodium and iridium catalysts for oxidative allylic C-H amidation of terminal, di- and trisubstituted olefins will be presented. Mechanistic insights leading to new reaction protocols for regiochemical control, and new catalyst designs that facilitate enantioselective reactions will be described. Illustrative examples of emergent applications will be provided.

Copper-Catalyzed Oxidative C(sp^3)−H Functionalization for the Synthesis of Heterocycles

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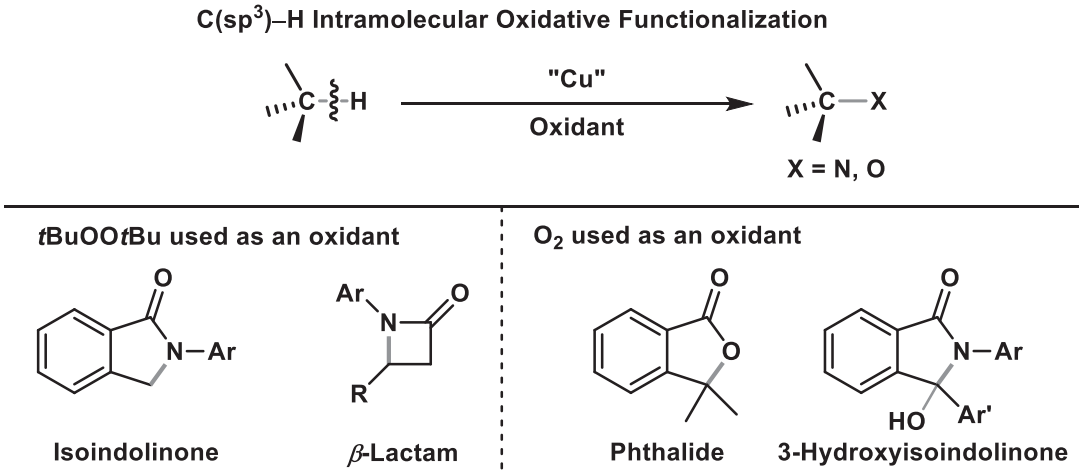
Transition-metal catalyzed direct functionalization of C(sp^3)−H bonds is one of the most attractive method to form C(sp^3)−N or C(sp^3)−O bonds because it does not require prefunctionalized starting materials. Therefore, this method can attain atom economy and step economy synthesis of organic compounds. Recently, copper-catalyzed C(sp^3)−H functionalizaion reactions using peroxides have been developed, which proceeds *via* hydrogen abstraction of C(sp^3)−H bonds by an oxy radical derived from the copper-initiated decomposition of peroxide.[1] This process is efficient due to an inexpensive nature of a copper catalyst and its applicability to a variety of C(sp^3)−H bonds, such as allylic, benzylic and aliphatic C−H bonds. However, there have been few reports of it being applied to intramolecular reaction. Herein we report a copper-catalyzed intramolecular C(sp^3)−H functionalization, which provides a new approach to synthesize isoindolinones[2] and *β*-lactams.[3] Furthermore, we found copper-catalyzed syntheses of phthalides and 3-hydroxyisoindolinones under molecular oxygen using 2-alkyl-*N*-arylbenzamides as substrates *via* benzylic C(sp^3)−H oxidative functionalization. In view of economical and environmental aspects, molecular oxygen is an ideal oxidant because of its low cost and lack of toxic byproduct. However, molecular oxygen mediated functionalization of C(sp^3)−H bonds, especially benzylic C(sp^3)−H bonds, has been hardly reported so far. We will also give a presentation for these reactions.



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5O-A-1

A Three-Pronged Approach to the Synthesis of Trifluoromethylated Heterocycles

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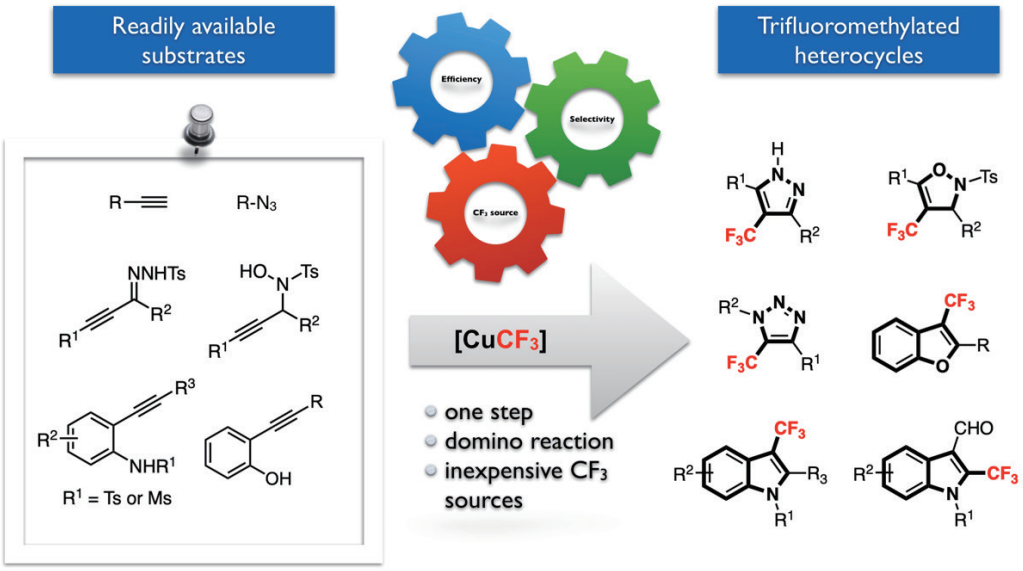
Trifluoromethylated heterocycles have found substantial applications in pharmaceuticals and agrochemicals. To address the synthetic challenges in the area of trifluoromethylation reactions, a three-pronged approach is needed to solve the problems of *efficiency*, *selectivity* and *CF_3-source*. We have recently developed a series of novel methods for the synthesis of diverse trifluoromethylated heterocycles *via* domino strategies with copper. An interrupted click reaction, using CuI/phen as the catalyst and (trifluoromethyl)trimethylsilane ($TMSCF_3$) as the nucleophilic CF_3 source, has been utilized to synthesize 5-trifluoromethyl 1,2,3-triazoles in one step from readily available terminal alkynes and azides.[1] Moreover, domino *5-endo-dig* cyclization/trifluoromethylation of *α,β*-alkynic tosylhydrazones and propargylic *N*-hydroxylamines allows convenient access to 4-(trifluoromethyl)pyrazoles and 4-trifluoromethyl-4-isoxazolines, respectively.[2-3] By employing easily accessible 2-alkynylanilines and the low-cost fluoroform(CF_3H)-derived $CuCF_3$ reagent, both 2- and 3-(trifluoromethyl)indoles can be prepared in good yields with no ambiguity of the CF_3 position.[4-5] Analogous cyclization/trifluoromethylation of 2-alkynylphenols can afford 3-(trifluoromethyl)benzofurans and one of the compounds was identified as a promising antibacterial and antifungal agent.[6]



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5O-A-2

Diversity-Oriented Construction of Multicavity-Containing Supermacrocycles

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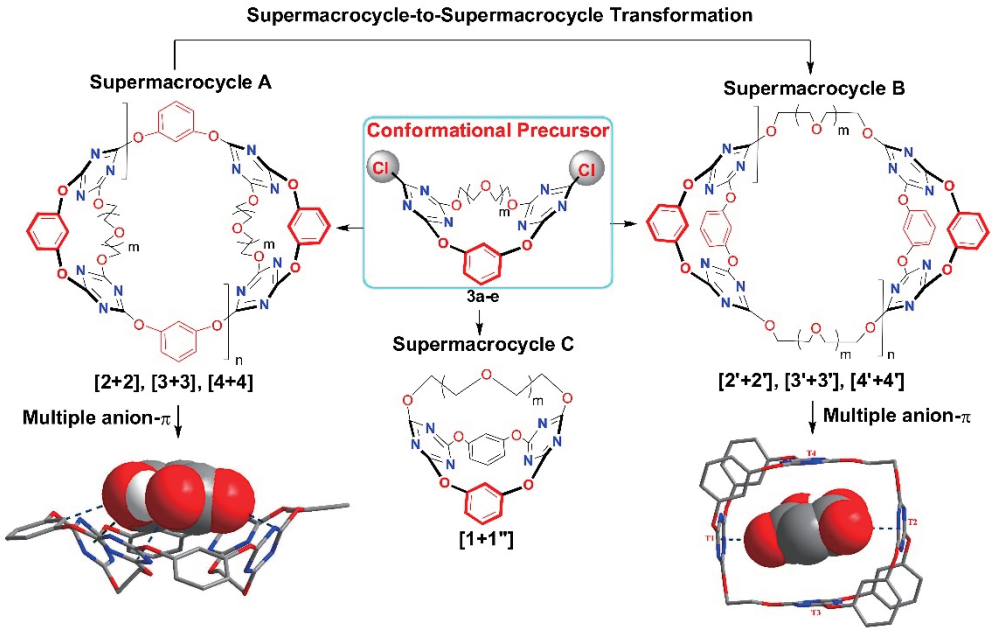
Anion-π interactions are a new emerging type of non-covalent motifs describing the interaction between electron rich anions and electron deficient aromatics.[1]Since the former theoretical works that predict such non-covalent interactions,[2] experimental results both in solid state and solution have exemplified the existence of anion-π interactions.[3] Anion-π interactions have recently been widely studied as new non-covalent driving forces in supramolecular chemistry.[4] Herein we presented the diversity-oriented construction of multicavity-containing supermacrocycles. A one-pot strategy for diverse construction of a series of supermacrocycles was realized from rationally designed macrocyclic precursors. The base was found to have a significant control on not only the size distribution but also the structure of the supermacrocycles formed. With large cavities and many electron-deficient triazines, the supermacrocyles can accommodate large organic anions via multiple anion-π interactions.



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5O-B-1

Synthesis of Heterocyclic Compounds through the Transition-Metal-Catalyzed Coupling Reactions of Benzoimine

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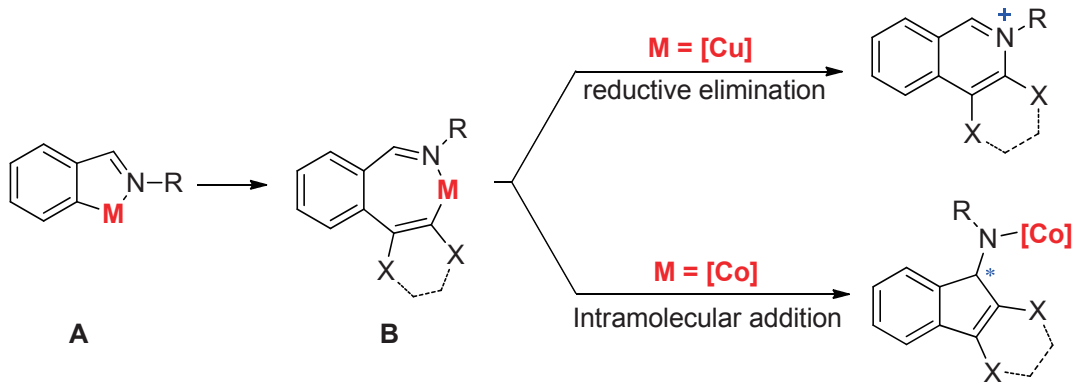
Department of Chemistry, Tamkang University, New Taipei City 25137, Taiwan (R.O.C.)

Our developed methods in the transition-metal-catalyzed C-C and C-N bond formation through the coupling reactions of benzoimines are illustrated below in two reaction types. By introducing the different transition-metal catalysts and reaction protocols, the complex **B** would execute either the reductive elimination[1] or intramolecular addition[2, 3] to provide the corresponding isoquinolinium salts or aminoindene derivatives. Further modifications, synthesis of polyheterocyclic compounds and the applications to prepare natural alkaloids, medicine candidates and bioactive compounds are also able to be carried out base on these methods.



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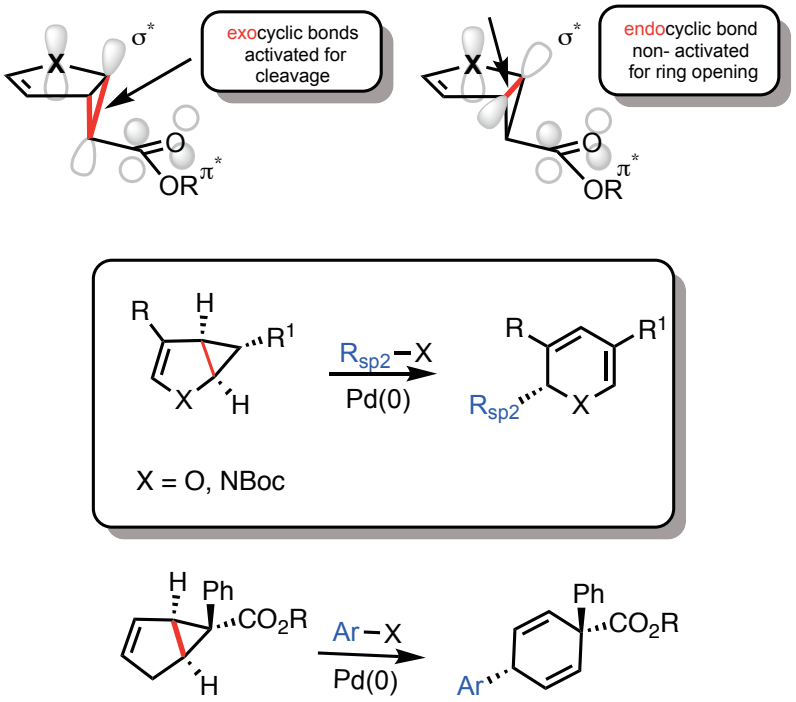
5O-B-2

Regio- and Stereoselective Synthesis of Functionalized Dihydropyridines, Pyridines, and 2H-Pyrans: Heck Coupling of Monocyclopropanated Heterocycles

Julietta Yedoyan, Nikolai Wurzer, Urszula Klimczak, Martin Stinglhamer, Riccardo Almir Agnes, Julia Rehbein and Oliver Reiser

The palladium-catalyzed coupling between aryl halides and monocyclopropanated pyrroles or furans has been developed leading to valuable six-membered N- and O-heterocycles. As the key step, a selective cleavage of the non-activated endocyclic C-C bond of the 2-heterobicyclo-[2.1.0]hexane framework is achieved. The developed method offers an access to highly functionalized piperidines, pyridines and pyrans that are challenging to access by traditional methods. Furthermore, the methodology can be extended to carbocylic starting materials, thus allowing the synthesis of functionalized 1,4-cyclohexadienes that cannot be accessed by Birch methodology. Computational studies are performed to shed light on the mechanism of this ring expansion reaction.



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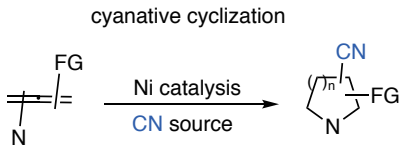
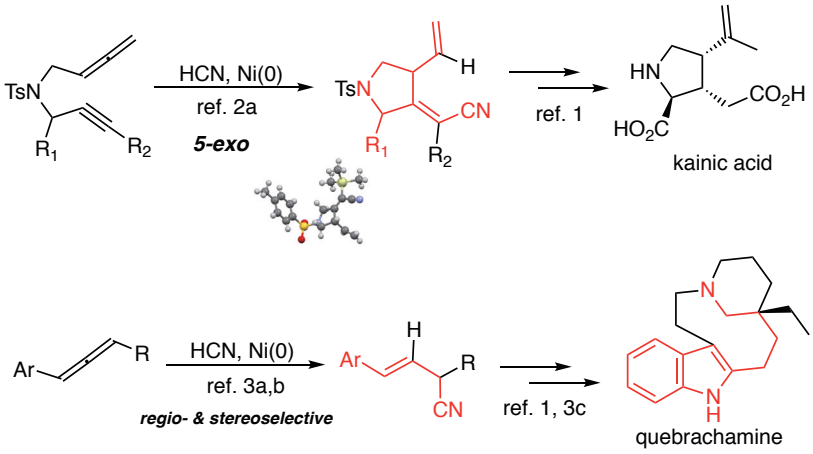
5O-C-1

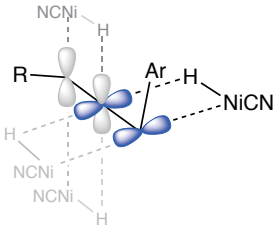
Synthesis of Nitrogen Heterocycles under Nickel Catalysis: Reaction Development and Its Application

Shigeru Arai,* Saki, Inagaki, Arisa Izaki, Yuka Amako and Atsushi Nishida
Graduate School of Pharmaceutical Sciences, Chiba University, Chiba/Japan 2608522

Metal-catalyzed cyclization and cycloaddition are one of the most efficient and reliable strategies to obtain highly functionalized heterocycles. We have focused on allenes (C=C=C) as building blocks to demonstrate regio- and stereoselective transformations[1] and found that the allene-ynes are key substrates for nickel-catalyzed hydrocyanative cyclization.[2] C-C multiple bonds in them were effectively discriminated to give the pyrrolidine derivatives in highly regioselective manner.[2a] The initial step is C-H bond formation on allenyl C_{sp} carbons. Its origin can be rationally understood by DFT calculation and this transformation is applicable for a formal synthesis of kainic acid.[1]







Arylallenes has been also suitable for regio- and stereoselective hydrocyanation,[3a,b] and the formal synthesis of quebrachamine has been accomplished.[1,3c] This hydrocyanation can be applied to axial chirality transfer using optically active allenes. Four possible π-faces were effectively discriminated to achieve up to 99% ee.[4] Another reactivity of allene-ynes is applicable to Ni-catalyzed cross coupling reaction and the results will be also discussed.[5]

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[5] Manuscript in preparation

Enantioselective Denitrogenative Annulation of 1*H*-Tetrazoles with Styrenes Catalyzed by Rhodium

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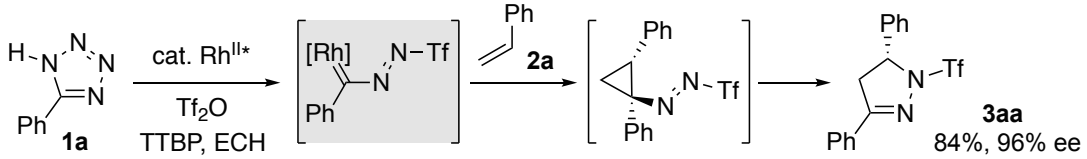
Katsura, Kyoto 615-8510, Japan

Metal carbene complexes have attracted much attention as the useful intermediates in organic synthesis. They are typically generated from diazo compounds by a denitrogenation reaction with transition-metal complexes. α-Diazocarbonyl compounds are most commonly used as the diazo compounds, generating α-oxo metal carbene complexes. On the other hand, *N*-sulfonyl-1,2,3-triazoles have emerged as latent precursors of α-imino metal carbene complexes. The electron-withdrawing sulfonyl group promotes ring-chain tautomerization to generate α-diazoiminyl compounds by equilibrium. The reactions of the α-imino rhodium(II) carbenoid species with various nucleophilic reagents have been extensively studied during the past decade.[1] Other than α-oxo or α-imino metal carbenoid species, however, related metal carbenoid species have remained unexplored. We now report an efficient method for the *in situ* generation of α-azo rhodium(II) carbenoid species from 5-substituted 1*H*-tetrazoles, which are readily prepared by 1,3-dipolar cycloaddition of nitriles and azides. The new α-azo carbenoid species react with styrenes to afford 3,5-diaryl-2-pyrazolines with induction of high levels of enantioselectivities.[2]

− We first examined a sulfonylation reaction of 1*H*-tetrazole with triflic anhydride according to the procedure reported by Fokin *et al.* for N*H*-1,2,3-triazoles,[3] and the resulting *N*-triflyl-tetrazole spontaneously collapsed into various compounds. Next, the *N*-triflyl-tetrazole *in situ* generated was directly subjected to a rhodium(II)-catalyzed reaction with styrene. Thus, 5-phenyl-1*H*-tetrazole (**1a**) was mixed with styrene (**2a**, 3.0 equiv), triflic anhydride (1.2 equiv), 2,4,6-tri(*tert*-butyl)pyridine (TTBP, 2.4 equiv), and Rh_2[(*S*)-TCPTTL]$_4$ (3.0 mol %) in ethylcyclohexane (ECH, 0.2 M). The resulting suspension was stirred at 0 °C for 22 h. The 2-pyrazoline **3aa** was isolated in 84% yield and its enantioselectivity was 96% ee. In a formal sense, the 2-pyrazoline **3aa** resulted from a [3+2]-type annulation of styrene (**2a**) with nitrile imine which was formed by denitrogenation of the tetrazole **1a**. The reaction mechanism is proposed as follows: *i*) The α-azo rhodium(II) carbenoid species undergoes asymmetric cyclopropanation of styrene (**2a**) to afford the cyclopropyldiazene stereoselectively. *ii*) A ring expansion reaction occurs with retention of stereochemistry to form 2-pyrazoline **3aa**.



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5O-D-1

Second-Generation Synthesis and Biological Evaluation of Heronamides, Naturally Occurring Polyene Macrolactams

Naoki Kanoh,[1,2,*] Ryusei Terashima,[2] Suguru Tanaka,[2] Yuta Terajima,[2] Hiromichi Nishiyama,[2] and Yoshiharu Iwabuchi[2]

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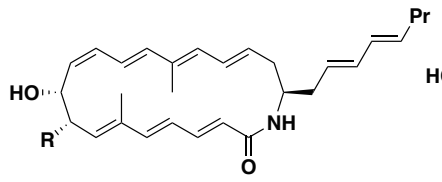
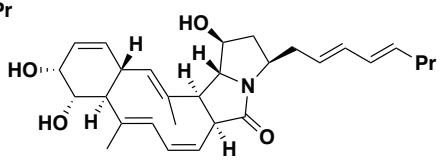
Polyene macrolactams are a glowing class of natural products possessing various biological activities, including antibacterial, antifungal, anticancer, and antitrypanosomal activities. Heronamides constitute an intriguing and remarkable class of polyene macrolactams because of their structural diversity, complexity, and potent antifungal activity.[1] Their biogenetic precursors 8-deoxyheronamide C (**1**) and heronamide C (**2**) are known to show potent antifungal activity by targeting membrane phospholipids possessing saturated hydrocarbon chains with an as-yet-unrevealed mode of action.[1b]

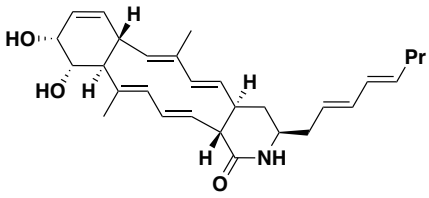
Intrigued by the chemistry and biology of heronamides, we have undertaken various synthetic and chemical biology programs. We have devised synthetic tactics towards heronamide C skeletons, culminating in the first total synthesis[2] and the structure revision of heronamide C (**2**),[2b] non-enzymatic transformation of heronamides A (**3**) and B (**4**) from heronamide C (**2**), the second-generation synthesis of heronamide C (**2**) and the first total synthesis of 8-deoxyheronamide C (**1**). The results of these efforts, as well as some biological and chemical studies, will be presented.



8-deoxyheronamide C (**1**): R = H
heronamide C (**2**): R = OH



heronamide A (**3**)



heronamide B (**4**)

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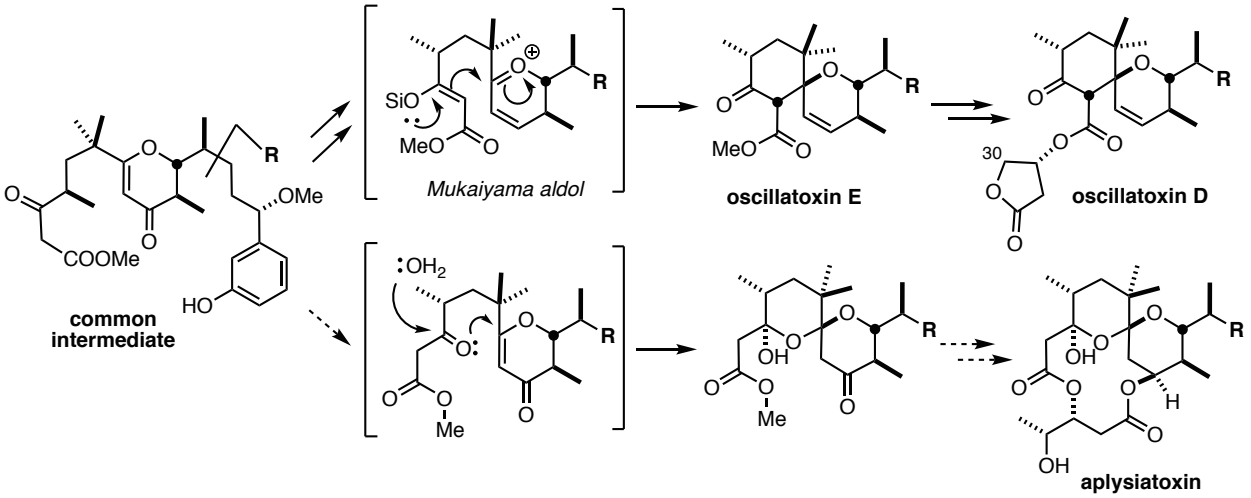
5O-D-2

Synthesis of Aplysiatoxin/Oscillatoxin Family of Marine Natural Products

Toshio Nishikawa,* Yusuke Hanaki, Yusuke Araki, Yoshihilko Nokura, and Atsuo Nakazaki

Graduate School of Bioagricultural Sciences, Nagoya University
Furo-cho, Chikusa, Nagoya 464-8601, Japan

Aplysiatoxin and oscillatoxin D belong to a small family of marine natural products isolated from cyanobacteria *Oscillatoriacea*.[1] Aplysiatoxin shows a variety of biological activities such as potent inflammation and tumor promotion and etc. through activation of protein kinase C. Recently, many new analogues of aplysiatoxin/oscillatoxin family have been isolated,[2] however, biological activities of the new analogs and oscillatoxin D have not yet been well investigated because of a limited amount of the compounds from natural sources. Despite of the intriguing biological profiles as well as the unique chemical structures, sole total synthesis of aplysiatoxin and oscillatoxon D was reported in 1987 and 1995, respectively. Under the situation, we initated to develop a unified route for collective synthesis of this class of natural products from a common intermediate, which was easily prepared in 13 steps from commercially available materials. Oscillatoxins E, F and D and its 30-methyl analogs were synthesized from the common intermediate by an intramolecular Mukaiyama aldol reaction as a key step for construction of a novel spiro-ether moiety.[3] On the other hand, the spiroacetal moiety of aplysiatoxin was preapred by oxy-Michael addition of the oxygen of the β-ketoester to the dihydropyrone moiety. Efforts towards the total synthesis of aplysiatoxin and other new analogs from the common intermediate will also be presented.



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ABSTRACTS OF FLASH PRESENTATIONS

Sep. 3rd, RoomD (Miyako Messe 2nd Exhibition Hall ＜ D ＞)

Choudhuri, Khokan (National Institute of Science Education and Research (NISER), Bhubaneswar, India)	3F-D-1
Kakiuchi, Yuya (Osaka University, Japan)	3F-D-2
Paraja, Miguel (University of Geneva, Spain)	3F-D-3
Fujie, Masaki (Osaka University, Japan)	3F-D-4

Sep. 5th, RoomA (ROHM Theatre Kyoto, Main Hall)

Matsumura, Kunihiro (Osaka City University, Japan)	5F-A-1
Watanabe, Takahiro (The University of Tokyo, Japan)	5F-A-2
Cechova, Lucie (IOCB Prague, Czech Republic)	5F-A-3
Ohashi Eisaku (Tokushima university, Japan)	5F-A-4

Sep. 5th, RoomB (ROHM Theatre Kyoto, South Hall)

Jin, Yuan (Nagoya University, Japan)	5F-B-1
Shimizu, Shinsuke (The University of Tokyo, Japan)	5F-B-2
Shimura, Jun (Tokyo Institute of Technology, Japan)	5F-B-3
Matsuyama, Naoki (Osaka University, Japan)	5F-B-4

Sep. 5th, RoomC (ROHM Theatre Kyoto, North Hall)

Payne, Daniel (National Institute for Materials Science (NIMS), Japan)	5F-C-1
Murata, Ryuichi (Kyoto University, Japan)	5F-C-2
Higashida, Keigo (Osaka University, Japan)	5F-C-3
Kervefors, Gabriella (Stockholm University, Sweden)	5F-C-4

Sep. 5th, RoomD (Miyako Messe 2nd Exhibition Hall ＜ D ＞)

Tanifuji, Ryo (Tokyo University of Agriculture and Technology, Japan)	5F-D-1
Hogenkamp, Fabian (Heinrich Heine University, Deutschland)	5F-D-2
Das, Bimolendu (Osaka University, Japan)	5F-D-3
Dobrowolski, Jeremy (The University of New South Wales, Australia)	5F-D-4

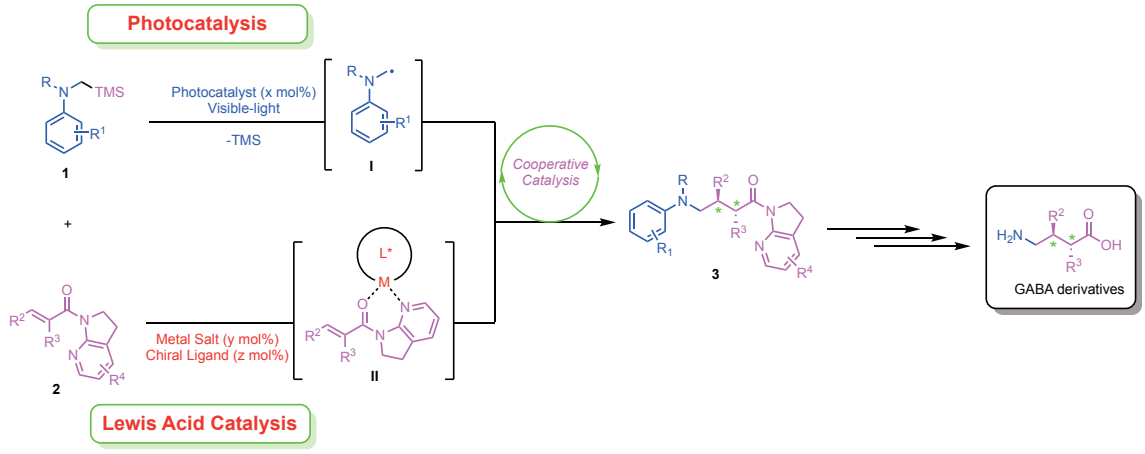
2F-A-1

Enantioselective Photocatalysis utilizing 7-Azaindolines as an Auxiliary: Challenges and Opportunities

Santosh. K. Pagire, Naoya Kumagai,* Masakatsu Shibasaki*
Institute of Microbial Chemistry (BIKAKEN), 3-14-23, Kamiosaki, Shinagawa-ku, Tokyo, 141-0021, Japan.

Recently, the area of visible-light photocatalysis has blossomed tremendously, which has been emerged into a handful tool in recent organic synthesis. The photocatalytic reactions are clean, waste reducing, proceeds under milder reaction conditions. Moreover, it can be coupled with asymmetric catalytic reactions to access the valuable chiral molecules. Arguably, the resulting molecules are typically difficult to accomplish utilizing other non-photocatalytic methods.

In this context, we envisioned to couple a photocatalytic cycle together with the Lewis acid catalytic cycle to achieve chiral γ-Amino Butyric Acid derivatives (GABA). They are important structural motif in many natural products and bioactive compounds. For example, (*S*)-Pregabalin, (*S*)-Baclofen, (*R*)-Rolipram, Arbaclofen Placarbil are important drug candidates, therefore, highly demanded as synthetic target.
Among many synthetic methodologies allowing creation of that structural pattern, direct *C*−*C* bond formation with simple starting materials and efficient catalytic systems remains an ideal. To achieve this synthetic goal, the metal catalyzed Michael reaction between amines 1 and 7-azaindolines 2 was utilized. However, there are several challenges to carry out these type reactions in a smooth way. This will be discussed in detail during the oral presentation.



2F-A-2

Total Syntheses of (–)-Secologanin, (–)-5-Carboxystrictosidine, and (–)-Rubenine

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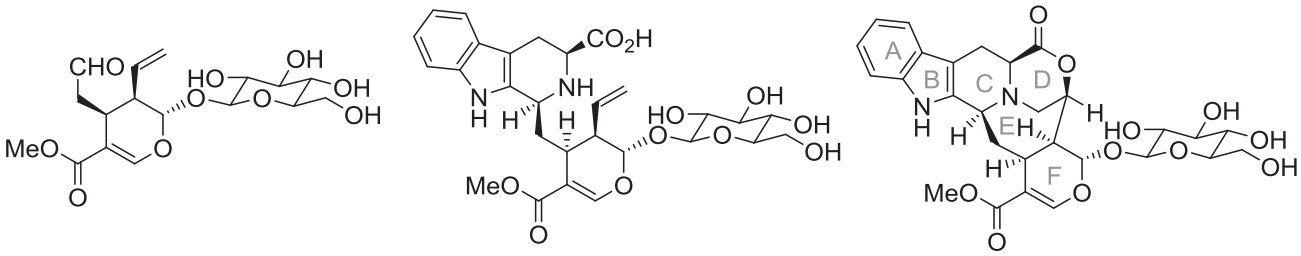
Monoterpenoid indole alkaloids form an important family of alkaloids, and over 3000 such alkaloids have been isolated from higher plants. Although a large number of total syntheses of non-glycosylated monoterpenoid indole alkaloids have been described, no glycosylated derivatives represented by (–)-5-Carboxystrictosidine (**1**)[1] have been reported. Among them, (–)-Rubenine (**2**)[2] possesses a complex ring system (rings A to F). The biosyntheses of monoterpenoid indole alkaloids are thought to proceed through Pictet–Spengler cyclization with either tryptophan or tryptamine, and (–)-secologanin (**3**)[3] as a common intermediate.

The first enantioselective total syntheses of **1**, **2**, and **3** were accomplished in 9, 14, and 10 steps, respectively. The key transformation in the synthesis of **3** was sequential *anti*-selective organocatalytic Michael reaction/Fukuyama reduction[4]/spontaneous cyclization to form an optically active dihydropyran ring. Subsequent seven-step transformations including diastereoselective glycosylation, hydroboration/oxidation, and sulfoxide elimination provided **3**. In addition, the secologanin tetraacetate, which is a potential key intermediate for bioinspired divergent syntheses of monoterpenoid indole alkaloids, was prepared in gram-scale quantities. Total syntheses of **1** and **2** were achieved through bioinspired transformations such as diastereoselective Pictet–Spengler reaction, site- and stereoselective epoxidation, and site-selective epoxide opening reaction followed by lactonization reaction.



secologanin
10 steps

5-carboxystrictosidine
9 steps

rubenine
14 steps

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2F-A-3

N-Heterocyclic Carbene-Catalyzed Decarboxylative Alkylation of Aldehydes

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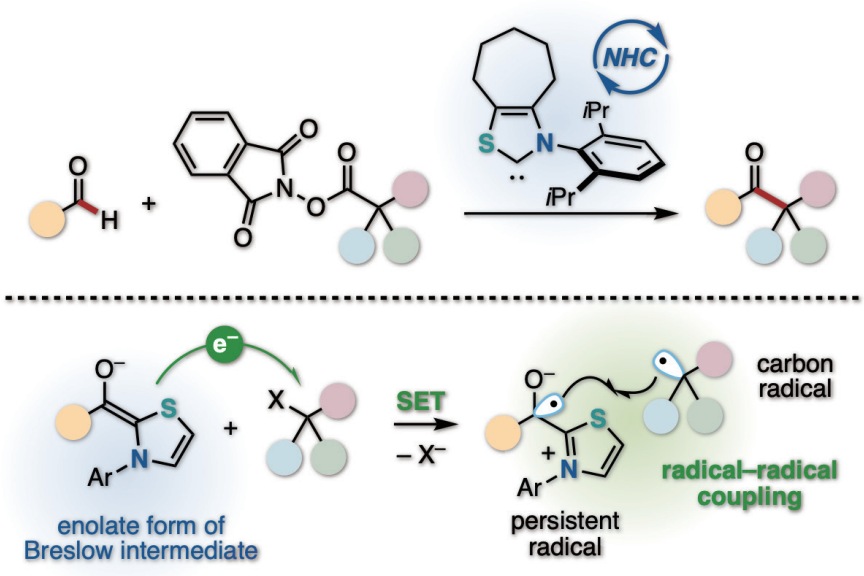
N-Heterocyclic carbene (NHC) catalysis, which exhibits a characteristic ability to access umpolung reactivity, has emerged as a powerful tool for challenging synthetic reactions. NHC catalysis involving a two-electron reaction pathway has been extensively studied. NHC-mediated radical reactions are also known. For example, there are a number of enzymes utilizing thiamine diphosphate (ThDP) as a coenzyme to catalyze the decarboxylation of pyruvate in nature. The resultant enamine, a so-called "Breslow intermediate," is known to perform single electron transfer to various electron acceptors such as lipoamides, flavin adenine dinucleotide and Fe_4S_4. Inspired by this process, *N*-heterocyclic carbene-catalyzed radical reactions have been developed. However, this area is still in its infancy with limited progress.[1]

This paper reports on our discovery of a new NHC radical catalysis that enables decarboxylative coupling reaction between aryl aldehydes and tertiary or secondary alkyl carboxylic acid-derived redox-active esters to deliver aryl alkyl ketones.[2] This protocol is first tertiary alkylation of aldehydes to construct quaternary carbon center. Due to the mild and transition-metal-free reaction conditions, this reaction tolerates a broad range of functional groups in the substrates. The power of this protocol was demonstrated by the functionalization of pharmaceutical drugs and natural product. Based on mechanistic studies, a reaction pathway involving the single electron transfer from an enolate form of Breslow intermediate to the redox ester followed by the recombination of the resultant radical pair is proposed.



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The First Synthesis and Characterization of a Polycyclic Zwitterion with Open-Shell Character

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Toyonaka, Osaka 560-8531, Japan

Recently, open-shell singlet biradicals have attracted much attention in the field of theoretical and materials chemistry due to their unique electronic structure.[1] Most open-shell singlet biradicals isolated to date are quinoidal singlet biradicals. On the other hand, only a few reports have been made on zwitterionic open-shell singlet biradicals, which limits structural diversity and hampers detailed understanding of their electronic structures and properties. Herein, we report the first synthesis and characterization of a polycyclic zwitterion with an open-shell character.[2]

We designed and synthesized zwitterion **1** (Figure 1a), which is kinetically stabilized by introducing bulky mesityl groups onto carbon atoms with large spin density (Figure 1b). Zwitterion **1** was isolated and characterized by X-ray crystal structural analysis. Based on bond lengths obtained by X-ray analysis, NMR studies, and DFT calculation, **1** can be described as the resonance structures in Figure 1a. **1** exhibited near infrared absorption and amphoteric redox properties originating from a small HOMO−LUMO energy gap. These results together with the observation of the thermally-excited triplet state by ESR (Figure 1c) and DFT calculations (Figure 1b) indicate that zwitterion **1** has an open-shell singlet ground state.

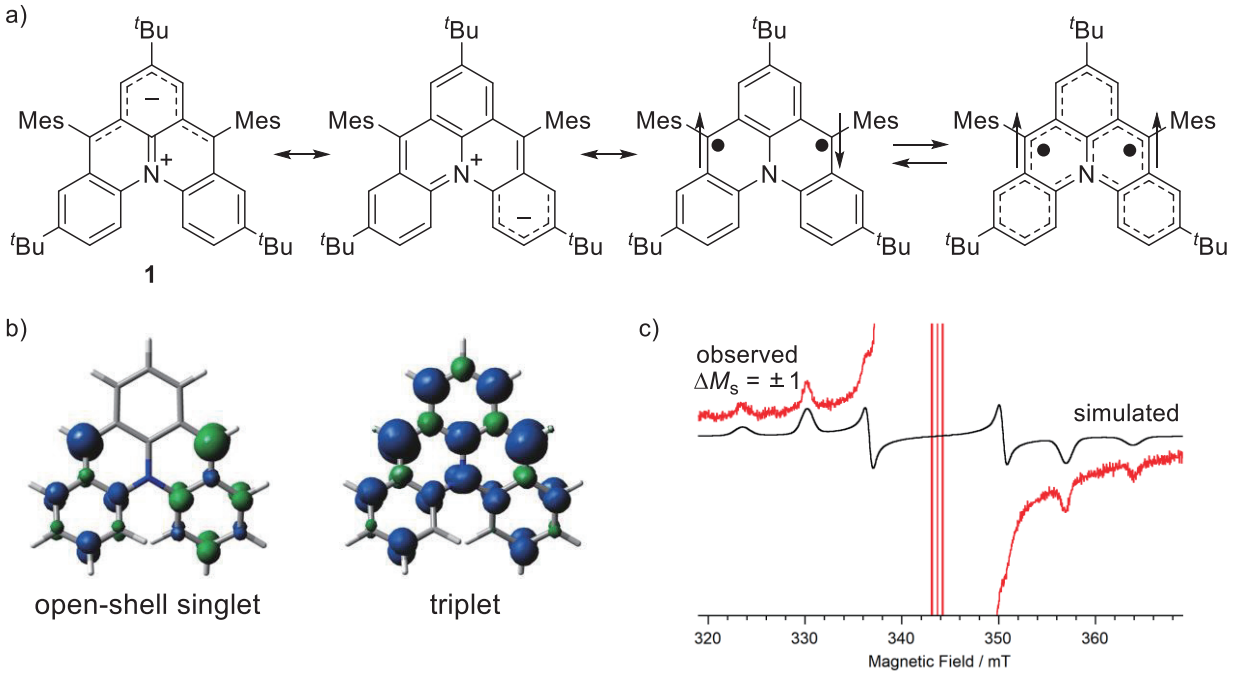

Figure 1. (a) Resonance structures, (b) Calculated spin densities, and (c) ESR spectrum of **1**.

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[2] Arikawa, S.; Shimizu, A.; Shintani, R. *Angew. Chem., Int. Ed.* **2019**, *58*, 6415.

Development of Quinoidal Oligothiophenes Having Fluorine Atoms

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Dicyanomethylene-substituted quinoidal oligothiophenes have been developed for use as n-type semiconductors in organic electronics.[1] Although it is well known that introduction of fluorine atoms into π-conjugated backbone increases its electron-accepting ability, quinoidal oligothiophenes having fluorine atoms are still rare.[2] In this research, we developed several quinoidal oligothiophenes having fluorine atoms (Figure 1) and investigated their structures, electrochemical behaviors, thin-film properties, and organic field-effect transistor (OFET) characteristics.

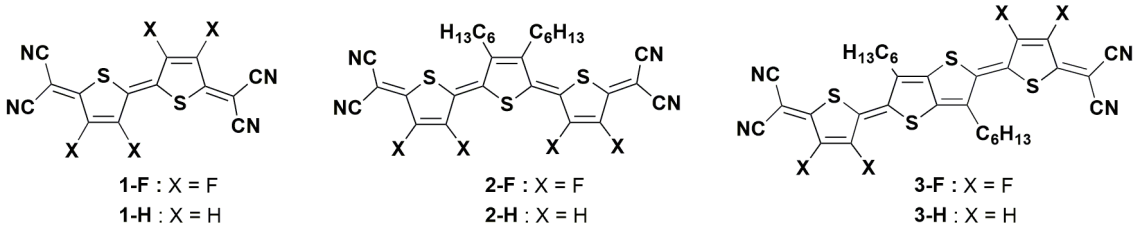

Figure 1. Chemical structures of compounds investigated in this study

The ^{19}F NMR spectra of **1-F**, **2-F** and **3-F** showed only two singlet signals, respectively. This result implies that these molecules have the stable conformation without *anti-syn* equilibrium, which is common for quinoidal oligothiophenes (**1-H** and **2-H**). The electrochemical properties of these compounds were investigated by cyclic voltammetry (CV) measurements in CH_2Cl_2. Cyclic voltammograms of **1-F**, **2-F** and **3-F** showed one reversible oxidation wave and two reduction waves. The lowest unoccupied molecular orbital (LUMO) energy levels of these compounds estimated from the first half-wave reduction potential were –4.69, –4.46, –4.50 eV, respectively. These values are lower than those of the reference compounds (**1-H**, **2-H** and **3-H**), indicating that the introduction of fluorine atoms into quinoidal oligothiophenes is effective to decrease the LUMO energy levels. OFET devices based on these materials showed typical n-type behavior even in the air condition. Furthermore**,** the blend films of this fluorinated quinoidal oligothiophene **2-F** and TIPS-pentacene showed ambipolar characteristics owing to the formation of co-crystal (Figure 2).

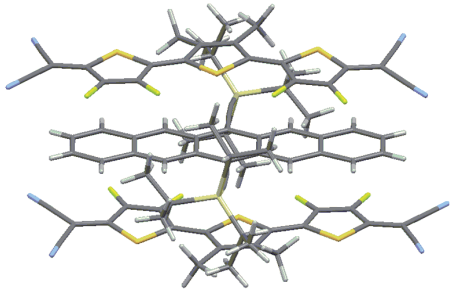

Figure 2. Co-crystal of n-type **2-F** and p-type TIPS-pentacene

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2F-B-2

Synthesis of Diversely Functionalized Heterocycles *via* Trapping of Transient σ- Alkyl/Vinyl-Palladium (II) Intermediates

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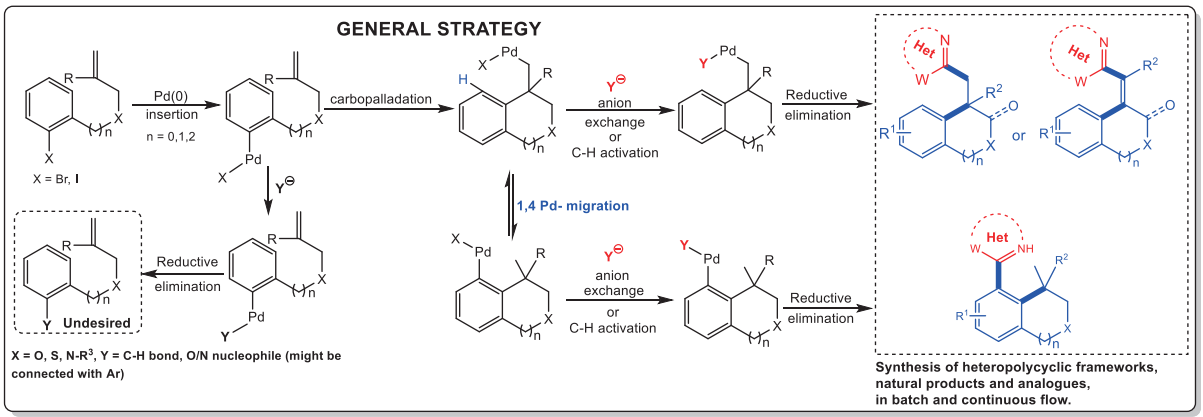
Despite the changing face of chemistry, the necessity to produce molecules in a controlled manner has not diminished. However, the increasingly complex synthetic problems being posed by nature, medicine and materials demand new reactivity concepts and strategies in order to meet these challenges. Domino reactions are one of the most attractive procedure for the synthesis of complex organic molecules, which according to Tietze, lead to the formation of "several bonds in one sequence without isolating the intermediates, changing the reaction conditions or adding the reagents".[1] It is already well-established that carbopalladation of acrylamides/propiolamides can generate the transient σ- alkyl/vinyl-palladium (II) intermediates.[2] The basic idea of the present work is to intercept the *in situ* generated σ- alkyl or vinyl palladium species *via* C-H functionalization including remote C-H functionalization, migratory insertion of isocyanide, anion capture etc to generate diversely functionalized heterocycles (Scheme 1). Such reactions will pave the way for the efficient synthesis of (poly)heterocyclic structures in batch as well as continuous flow. Many of these heterocyclic frameworks can already be seen in various alkaloids and pharmaceuticals.



Scheme 1: General strategy for the trapping of transient σ- alkyl/vinyl-palladium (II) intermediates.

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Dynamic Stereoselective Annulation to Afford Spirooxindole Pyran Polycycles

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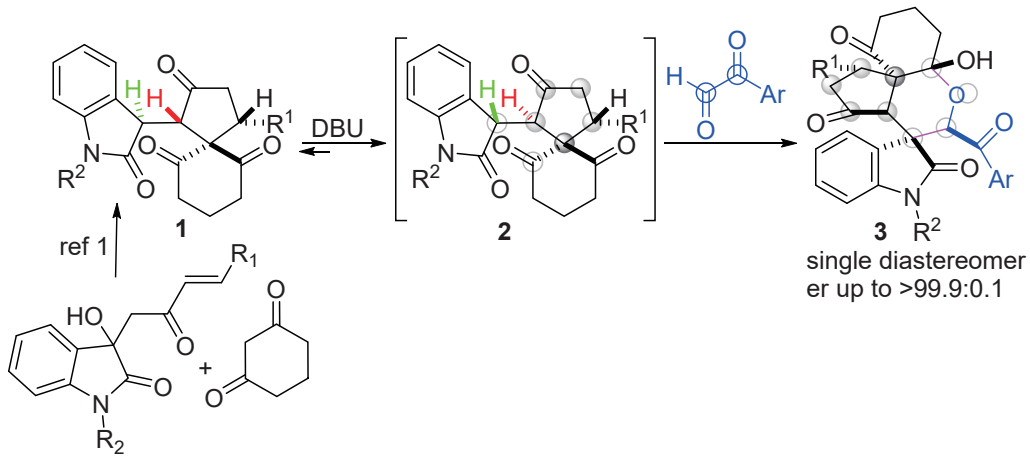
Onna, Okinawa 904-0495, Japan

Pyran-fused spiro polycycles are important biofuctional molecules. Synthesis of pyran-fused spiro polycycles is of interest in drug discovery efforts and related research. In this presentation, annulation reactions leading to spirooxindole pyran polycycles will be discussed.

We have developed catalytic stereoselective annulation reactions that afford spirooxindole pyran polycycles. In our strategy, a pyran ring in spiro polycycles is constructed via the formation of C-C and C-O bonds through dynamic aldol-oxa-cyclization cascade reactions. During the reactions, starting material **1**[1] was isomerized to diastereomer **2** with retention of the enantiopurity. Then, **2** was reacted with arylglyoxal to form **3**. With taking advantage of the feature of the isomerization, highly enantiomerically enriched forms of single diastereomers of spirooxindole pyran polycycles **3**, bearing six stereogenic centers, were obtained. Notably, the formation of the pyran ring resulting in the formation of the polycyclic system showed stereoselectivities distinct from the formation of the cyclohexane ring leading to the all-carbon polycycles.[1] We will discuss, these reactions including our strategy, the isomerization of **1** to **2**, and stereoselective formation of **3**.



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2F-B-4

Design & Synthesis of Novel Halogen-Bond-Donor Catalysts

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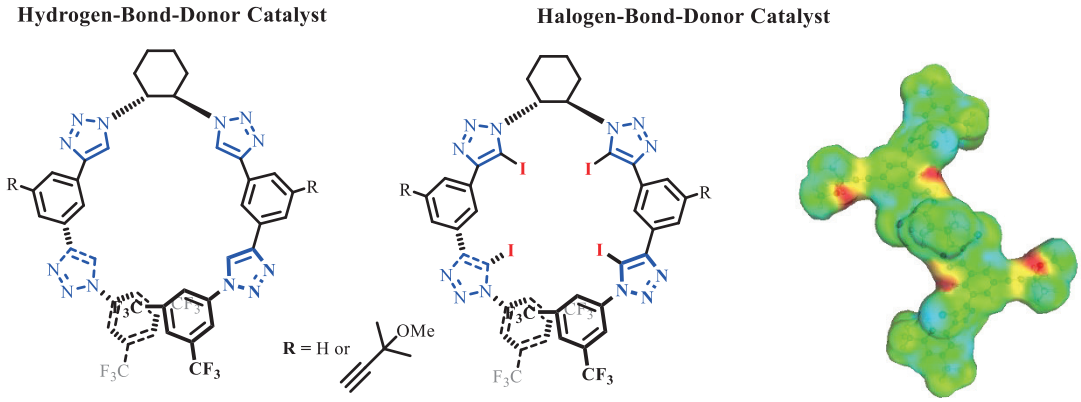
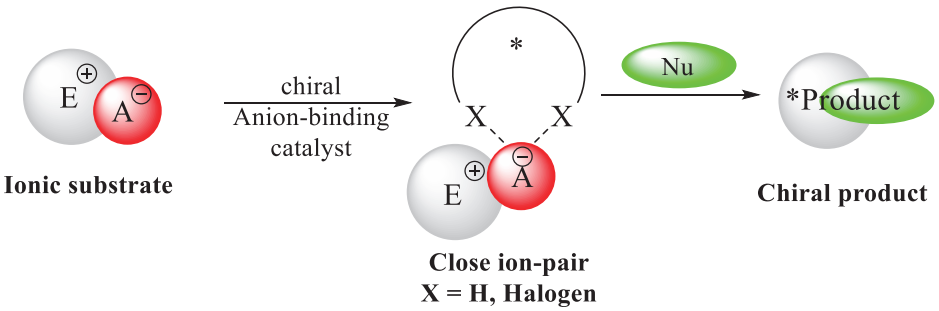


Asymmetric hydrogen-bond-donor catalysis has emerged as a powerful synthetic approach for the preparation of a variety of valuable chiral organic molecules. Our group successfully demonstrated that 1,2,3-triazoles are capable of promoting catalytic anion-binding processes and even surpass known thiourea or silanediol moieties.[1] The principle of halogen-bonding offers further possibilities to tune the properties of non-covalent organocatalysts, as polarized halides are able to act as electron accepting sites in a similar fashion as hydrogen-bond-donors.[2] To this day, enantioselective transformations, guided by halogen-bond-donor catalysts remain elusive.

Herein, we present the design and synthesis of new types of chiral organo-catalysts based on previously explored tetrakis-1,2,3-triazole structures. Different 5-iodo-1,2,3-triazole containing structures have been designed, presenting either both - hydrogen- and halogen-bond-donor properties - or just halogen-bond-donor properties.



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2F-C-1

Catalytic photo-oxygenation enables inhibition of tau amyloid formation

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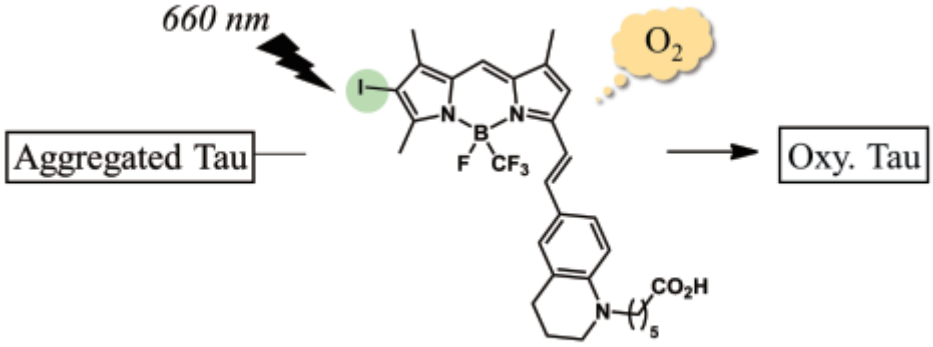
Alzheimer disease (AD) is caused by accumulations of amyloid proteins with a cross-β-sheet structure, which are composed of amyloid-β peptide (Aβ) and tau. Among these two types of amyloid accumulation, the distribution of tau amyloid is known to be associated with cognitive decline. Prion-like tau propagation is a mechanism involved in the spreading of tau pathology. Therefore, the inhibition of tau propagation might have therapeutic effects on AD. Previously, we developed photocatalysts, which selectively oxygenated Aβ amyloid upon light irradiation via binding to the cross-β-sheet structure. [1, 2]. The photo-oxygenation inhibited amyloid formation and the toxicity of Aβ. Here, we identified boron-dipyrromethene (BODIPY)-based photocatalyst **1**, which enabled efficient photo-oxygenation of tau amyloid. An iodine atom was introduced at the BODIPY, and tetrahydroquinoline-carboxylic acid was adopted at the electron donor part. In addition, a fluorine atom on the boron center was replaced with a more electron-withdrawing trifluoromethyl group to increase the photostability of the BODIPY core [3, 4]. Photo-oxygenation using **1** markedly reduced the seeding activity of tau, resulting in inhibition of tau amyloid formation *in vitro* and in cultured cells [5]. This study indicates the usefulness of photo-oxygenation to suppress tau propagation for AD therapy.



photocatalyst **1**

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Chemical synthesis and function of *Helicobacter pylori* peptidoglycan fragments

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Peptidoglycan, a major component of the bacterial cell wall, consists of polysaccharides and cross-linking peptides that forms a 3D mesh-like layer outside the plasma membrane. The polysaccharide chain is composed of alternating residues of β-(1,4) linked *N*-acetylglucosamine(GlcNAc) and *N*-acetylmuramic acid (MurNAc) attached by a peptide chain. Our group has revealed the immunostimulating mechanism of peptidoglycan by chemical synthesis of peptidoglycan fragments.[1]

Helicobacter pylori is a parasitic Gram-negative bacterium living in the stomach that causes chronic inflammation. It has recently been reported that *H. pylori* peptidoglycan modifications, i.e., *N*-deacetylation on GlcNAc and *O*-acetylation on MurNAc (Figure 1), confer lysozyme resistance and contribute to survival in the host.[2] In order to investigate whether these modifications also related to the immune regulation, we synthesized peptidoglycan fragments with different modifications.

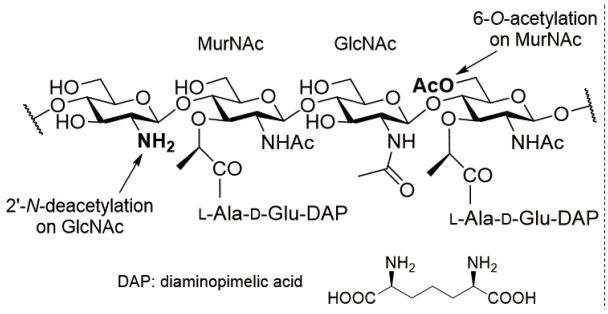

Figure 1: The chemical structure of *H. pylori* peptidoglycan and its modifications

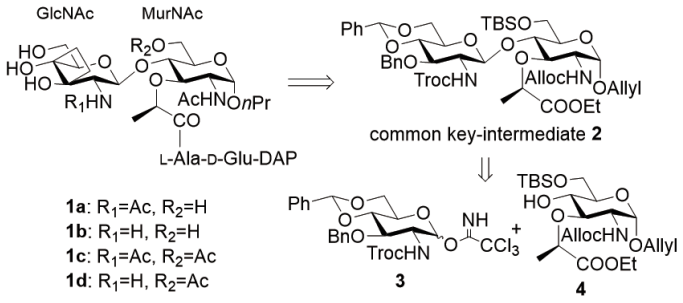

Figure 2: Target structures and synthesis strategy for *H. pylori* peptidoglycan fragments

In this work, we present the synthesis of *H. pylori* peptidoglycan fragments (**1a-d**) and elucidation of their immunological functions, especially effects of characteristic structural modifications. To construct diversity oriented synthetic route, common key-intermediate **2** with selectively removable protecting groups was developed via glycosylation of monosaccharide donor **3** and acceptor **4** (Figure 2). The conjugation of the peptide part to **2** and subsequent deprotection afforded *H. pylori* peptidoglycan fragments **1a-d**. The immunological activities of synthesized **1a-d** showed that *O*-acetylation reduces the immunostimulating activity, implying the association with immune escape mechanisms, while *N*-deacetylation has less influence on the immunostimulating activity.

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Conformational Analysis and *cis-trans* Control of Cyclized Tryptophan Tertiary Amides

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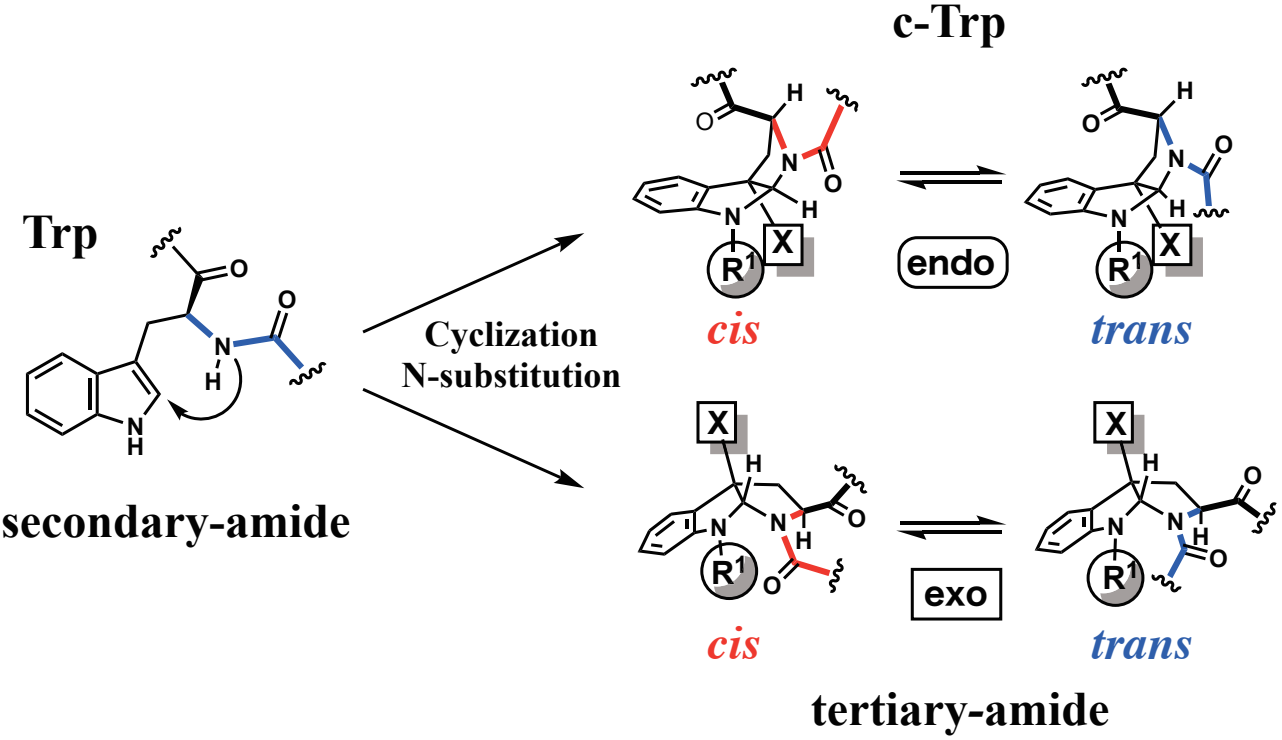
An amide bond is a kind of covalent chemical bond that links two amino acids to make peptides or proteins and has a partial double bond character. This double bond character makes amide structure planar and causes the rotational barrier between the two isomers, *cis* and *trans*. It is important to control the amide *cis-trans* equilibrium because it contributes to the three-dimensional structure of peptides, which is directly related to their bioactivity. In the case of a secondary amide, the *trans*-amide form predominates because the corresponding *cis*-amide is destabilized by steric repulsion. On the other hand, 10–20% of a tertiary amide can exist in its *cis*-form alongside the *trans*-form. It is known that of the natural α-amino acids, only α-proline can form a tertiary amide. While a tertiary amide can exist both in *cis*- and *trans*-amide forms, it is difficult to control the *cis-trans* ratio. So far, we have succeeded in controlling amide *cis-trans* ratios completely by using conformationally constrained bicyclic β-proline derivatives[1, 2].

In this study, we focused on cyclized tryptophan (c-Trp) as an α-amino acid derivative which can form a tertiary amide. There are two diastereomers of c-Trp, endo and exo, that are expected to have different *cis-trans* preferences. We have synthesized model compounds having tertiary amides of c-Trp (endo and exo) and analyzed their *cis-trans* ratios in order to reveal potential characteristic *cis-trans* equilibrium preferences.



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(Di-(2-picolyl)amino)quinazolines as Fluorescent Probes for ATP

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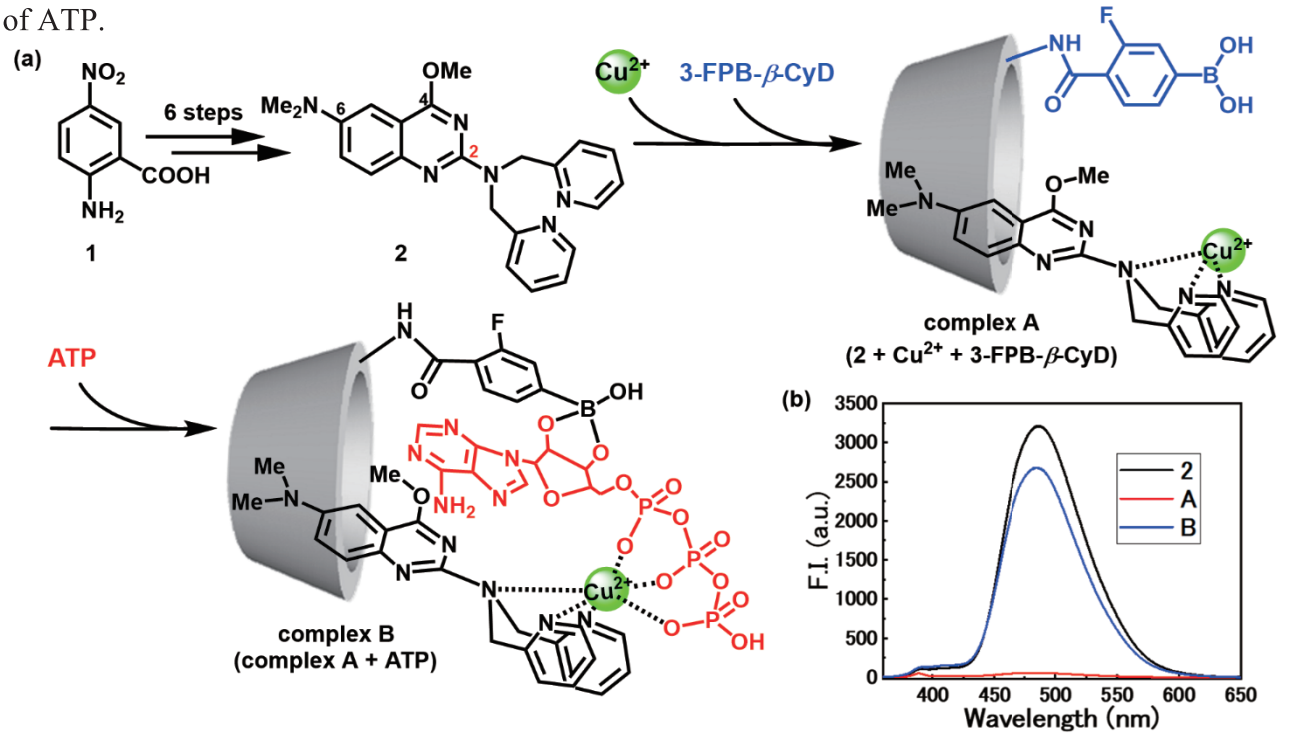
[Background] Adenosine triphosphate (ATP) is essential for life and the related cellular processes. Real-time monitoring of ATP levels can potentially help diagnose various diseases. However, there have only been a few precedents that enable ATP recognition with fluorescence enhancement using low-molecular weight probes. [1] Hence, we proposed to develop fluorescent probes for ATP detection using 2-aminoquinazolines, which were recently revealed to exhibit fluorescence. [2]

[Results and discussion] Di-(2-picolyl)amine (DPA) coordinates to various metal ions resulting in complexes that interact with phosphoric acids. To utilize this property, we prepared quinazoline probe **2** possessing a DPA moiety at position 2 from commercially available anthranilic acid **1** in 6 steps. When Cu^{2+} and *β*-cyclodextrin modified with 3-fluorophenylboronic acid (**3-FPB-*β*-CyD**) were added to a 1% DMSO solution of **2**, the fluorescence intensity was completely reduced by coordination of the DPA moiety to Cu^{2+} through ligand metal charge transfer (LMCT). This result indicates the formation of **complex A**. When ATP was added to the quenched solution, the fluorescence intensity recovered due to the interaction between Cu^{2+} and ATP which weakened the LMCT system (**Scheme 1**). Therefore, the novel quinazoline probe **2** enabled fluorescent detection of ATP.



Scheme 1. (a) Plausible mechanism of ATP detection and (b) fluorescence intensity of **2**, **A** and **B** (λ_{ex} = 345 nm).

[1] Fujita, K.; Fujiwara, S.; Yamada, T.; Tsuchido, Y.; Hashimoto, T.; Hayashita, T. *J. Org. Chem.* **2017**, *82*, 976.
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2F-D-1

Enamides as versatile tools for the stereoselective construction of heterocycles

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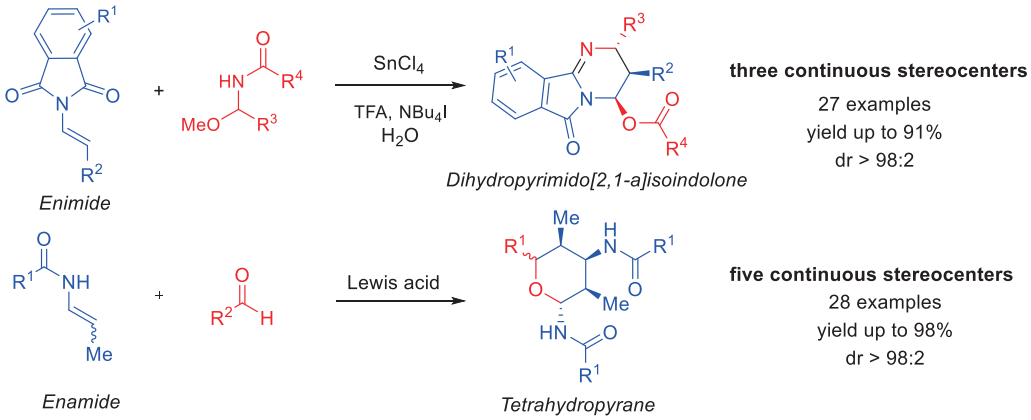
Heterocycles constitute the most common motif in natural products and biologically active molecules. Therefore, there is a sustained interest in novel methods for the efficient construction of all kinds of heterocycles, in particular for uncommon or so far inaccessible structures.[1] In the last few years enamides and enimides have become a useful tool for the synthesis of heterocyclic scaffolds and biologically active molecules.[2]

Herein we want to present two novel methods for the stereoselective construction of unusual heterocyclic scaffolds using enamides as central building block.

Based on our work on a stereodivergent synthesis of 1,3.-diamines[3], we could develop a stereoselective reaction sequence for the synthesis to highly substituted pyrimido[2,1-a]isoindolones.[4] Our reaction encompasses various substituted enimides and *N*-acyl-*N*,*O*-acetals to generate this so far inaccessible heterocyclic core. We could also extends the use of enamides towards a highly stereoselective synthesis of highly substituted tetrahydropyrans.[5] The reaction is based on the twofold addition of an enamide to an aldehyde followed by a ring closure. This novel transformation affords fully substituted tetrahydropyrans with five continuous stereocenters with an exceptional degree of diastereoselectivity.



Both reactions demonstrate the utility of enamides as tool for the construction of uncommon heterocyclic scaffolds with an excellent degree of stereoselectivity from simple building blocks.

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Synthesis of Six- and Seven-Membered Benzolactones by Nickel-Catalyzed C-H Coupling of Benzamides with Small-Sized Cyclic Ethers

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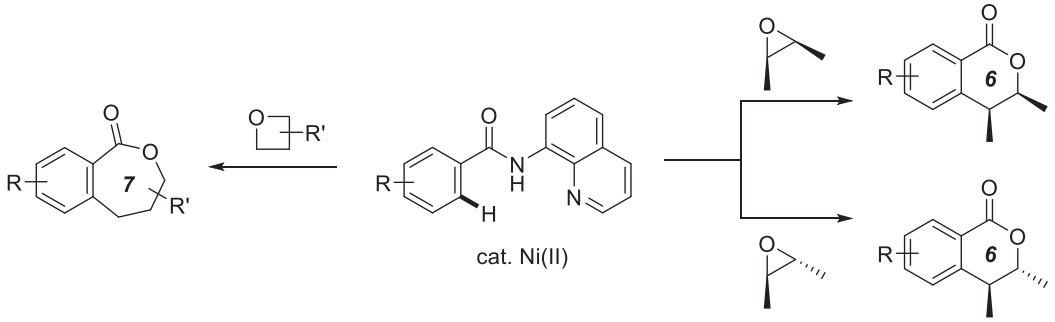
New strategies for the synthesis of oxygen-containing heterocycles have received significant attention in view of the fact that these compounds possess various biological activities. Among them, transition-metal-catalyzed C-H activation methods have played a dominant role because of their higher atom and step economies.[1]

Here, we present a convenient protocol to access six- and seven-membered benzolactones via Ni(II)-catalyzed C-H coupling of 8-aminoquinoline-derived benzamides with epoxides and oxetanes.[2] The N,N-bidentate coordination directed C-H alkylation is followed by an intramolecular esterification to deliver the corresponding lactones in one synthetic operation. The 8-aminoquinoline group is spontaneously removed and recovered. Additionally, in the reaction with epoxides, a unique stereospecificity is observed: the cis epoxide can be converted to the cis lactone whereas the trans isomer is selectively formed from the trans epoxide, which is complementary to that observed in previously reported Pd(II) catalysis.[3]



Scheme 1. Synthesis of six- and seven-membered benzolactones via Ni-catalyzed C-H coupling of benzamides with epoxides and oxetanes

[1] a) L. Yet, *Chem. Rev.* **2000**, *100,* 2963-3007; b) C.-Y. Huang, A. G. Doyle, *Chem. Rev.* **2014**, *114,* 8153-8198.
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2F-D-3

Hypervalent Iodine (III) in Direct Intramolecular N-N Bond Formation with Heteroaromatic Amines: Synthesis of Triazapentalene Derivatives

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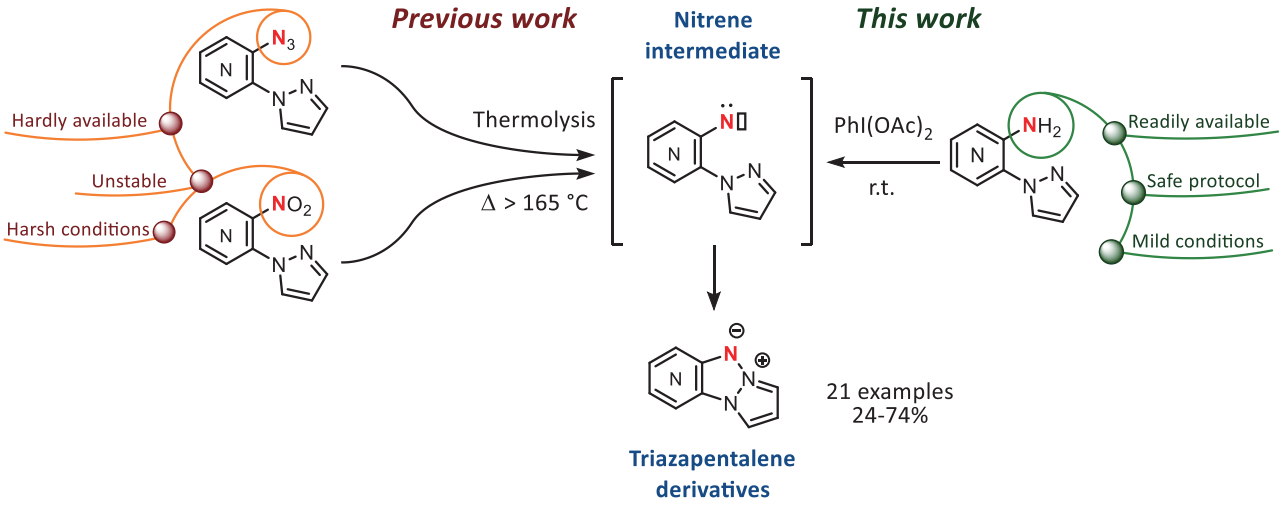
Triazapentalene derivatives exhibit an original structure, which confers them interesting fluorescent[1,2] and energetic[3,4,5] properties. Their synthesis used to rely on azido[3] or nitro[4,5] precursors, which required drastic experimental conditions to generate the nitrene intermediate. Furthermore, the azido and nitro derivatives are often unstable, potentially energetics and hardly available.

Consequently, we developed new conditions from heteroaromatic amines to provide an efficient and innovative approach for the formation of N-N bond in presence of iodine (III) reagent in mild conditions. This unprecedented method enables to synthesize nitrogen rich triazapentalene derivatives inaccessible with existing approaches. The fluorescent properties of the newly accessed triazapentalene derivatives will also be discussed.



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27-ISHC Abstract

Fe (III) Promoted Intramolecular Cascade Cyclization for the Synthesis of Quinoline fused Selenophene-based Heteroacene Scaffolds

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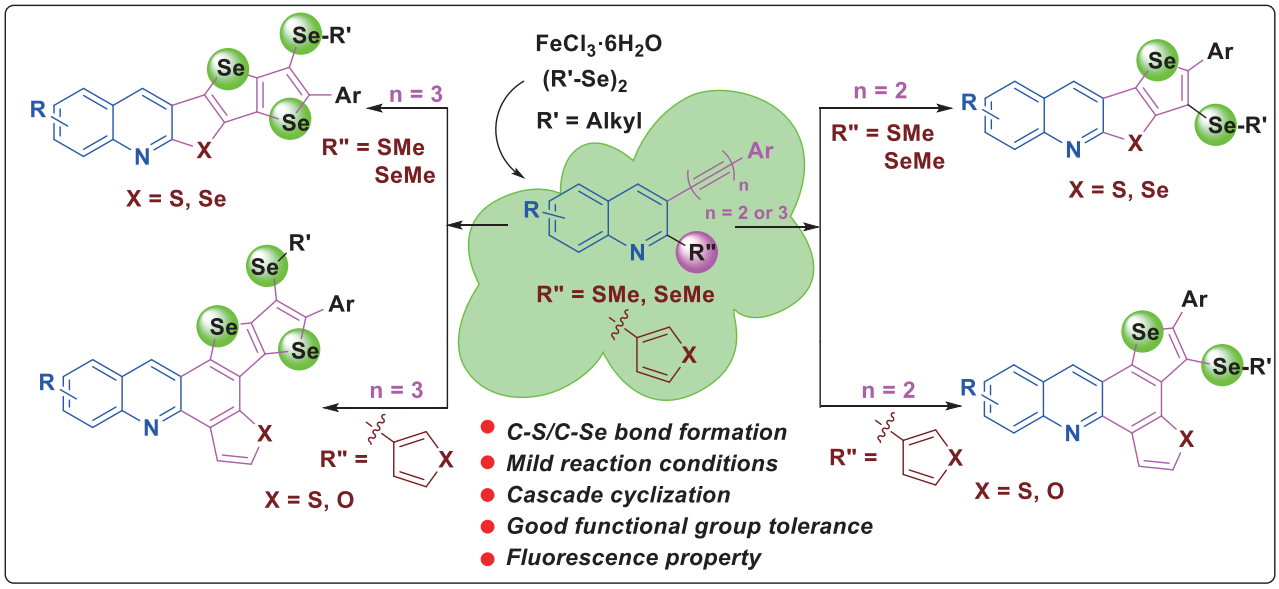
The Fe(III)-promoted linear intramolecular cascade cyclization of 1,3-diyne and 1,3,5-triyne for the construction of selenophene-fused, quinoline-based heteroacene scaffolds. In one step 1,3-diyne and 1,3,5-triyne were cyclized *via* diversified internal nucleophiles by using diorganyl diselenides. The diorganyl diselenide plays dual role, one as cyclizing agent and secondly insertion of one and / or two selenium atom and one R′-Se group in the final product. This is highly important in terms of atom economy. Diversified internal nucleophiles were used to afford quinoline and acridine based cores. The synthesized selenophene-fused derivatives showed λ_{max}, F_{max} and Φ_f values in the range from 370-411 nm, 427-472 nm and 0.003-0.059, respectively in dichloromethane solvent.



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Synthesis and Photochromism of Bis(Thienyl) Substituted 1,2-Oxathiine 2,2-dioxides

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Sulfenes, generated by the action of base upon sulfonyl chlorides, react smoothly with substituted enaminoketones **2**, derived from **1** and DMFDMA, to afford novel 3,4-dihydro-4-dimethylamino-1,2-oxathiine 2,2-dioxides **3** in good yield. As a consequence of the *transoid* relationship between the 3-aryl substituent and the 4-dimethylamino group (Figure 1) the 1,2-oxathiine 2,2-dioxides **4** were obtained for the first time by the use of a Cope elimination protocol on **3** (Scheme 1).

1a - d **2a - d** **3a - e** **4a - e**

Series **a**: $Ar^1 = Ar^2$ = 2,5-dimethylthiophen-3-yl, R = Ph; series **b**: Ar^1 = R = Ph, Ar^2 = 2,5-dimethylthiophen-3-yl; series **c**: Ar^1 = 2,5-dimethylthiophen-3-yl, Ar^2 = R = Ph; series **d**: $Ar^1 = Ar^2$ = R = Ph; series **e**: $Ar^1 = Ar^2$ = 2,5-dimethylthiophen-3-yl, R = H

Reagents: (i) DMFDMA, reflux; (ii) RCH_2SO_2Cl, Et_3N, THF; (iii) *m*-CPBA, CH_2Cl_2

Scheme 1

The application of the 1,2-oxathiine 2,2-dioxide scaffold in heterocyclic materials chemistry is exemplified by the efficient, reversible P-type photochromism observed for the 5,6-bis(2,5-dimethyl-3-thienyl) substituted oxathiine 2,2-dioxide **4a** (Figure 2 and 3). Exposure of a hexane solution of **4a** with UV irradiation (λ = 365 nm) promotes the electrocyclic ring closure to afford the coloured isomer **4a**' (image insert Figure 3). The reverse reaction was accomplished upon irradiation of **4a**' with visible light; the photochromic cycling could be repeated several times (insert Figure 3).

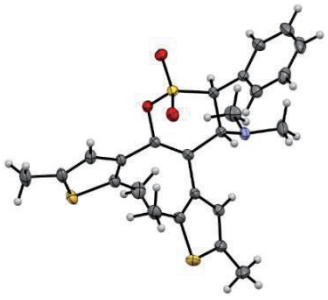

Figure 1: Crystal structure of **4a**

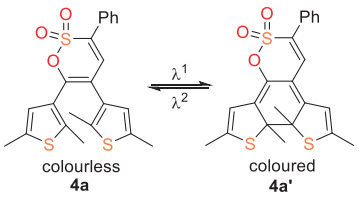

Figure 2: Reversible electrocyclization of **4a**

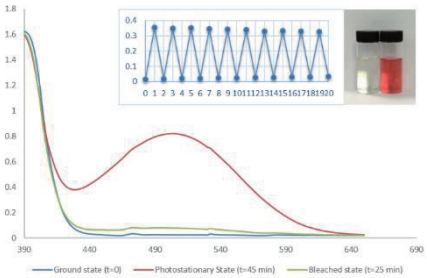

Figure 3: Photochromic response of **4a**

The synthesis of the precursor ketones **1** and novel photochromic dithienyl substituted 1,2-oxathiine 2,2-dioxides **3** and **4** together with their photochromic response will be discussed.

3F-A-2

Visible Light-driven Generation of Hydrazone Radicals for the Synthesis of Dihydropyrazoles and Tetrahydropyridazines

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Wuhan, 430079, P. R. China (zqqqhz@163.com)

In the past several years, with the development of visible light photoredox catalysis, the photocatalytic N-radical-mediated cascade reaction has been established as one of the most powerful tools for the construction of diversely functionalized N-heterocycles.[1-2]

Recently, we have developed a visible light-induced oxidative deprotonation electron transfer (ODET) strategy for the generation of N-centered radicals from the hydrazones.[3-4] Employing this strategy, a series of N-radical-mediated carboamination and carboallylation reactions of alkenes were achieved (Fig 1).[5-6] More recently, we also have extended this strategy to the N-centred radical catalysis, which enable an efficient bifunctionalization reaction of alkenes.[7]

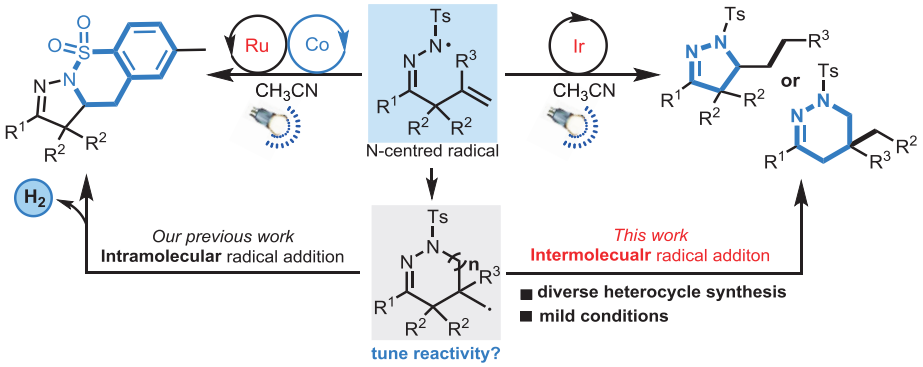

Fig. 1 Visible-light-driven N-centered radical-mediated synthesis of N-heterocycles

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Optically Active *trans*-Cyclooctene-pyridine Ligands in Rhodium-catalyzed Asymmetric 1,4-Addition

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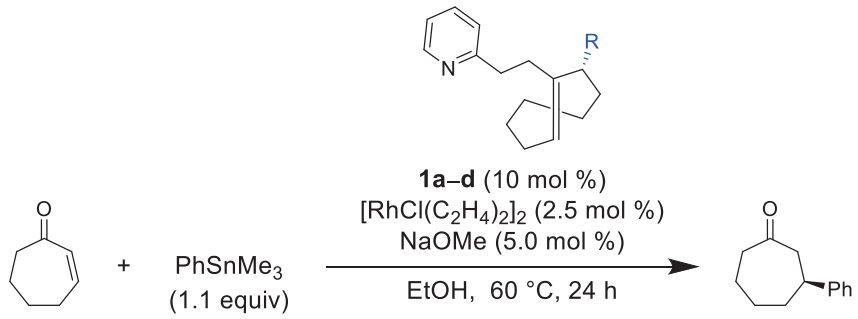
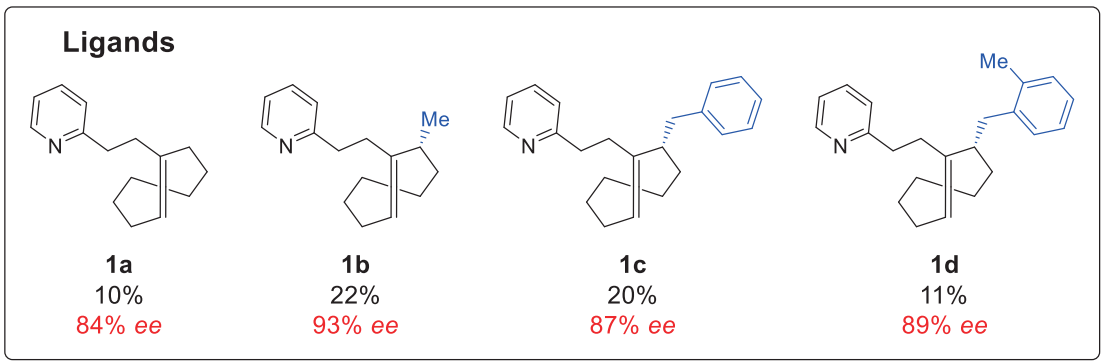
Chiral olefins such as optically active dienes are known to provide effective chiral environments and unique reactivities to some transition metal catalysts. Meanwhile, *trans*-cyclooctenes are planar chiral olefins, which are able to be isolated as optically active forms at ambient temperature, and the properties derived from their strained structures were revealed to be responsible for a strong coordination ability. However, their ability as chiral ligands of metal catalysts has not been investigated.

We have been interested in the catalytic behavior of *trans*-cyclooctenes.[1] Here, we present optically active *trans*-cyclooctene derivatives performed as ligands for rhodium-catalyzed asymmetric 1,4-addition. This is the first demonstration of their potential as chiral ligands to realize asymmetric catalysis. The pyridyl group is also essential for generating active catalytic species. Moreover, the introduction of substituents at the allylic position further improved the enantioselectivity.





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3F-A-4

Synthesis of γ,γ-Disubstituted Butenolides through a Doubly Vinylogous Organocatalytic Cycloaddition

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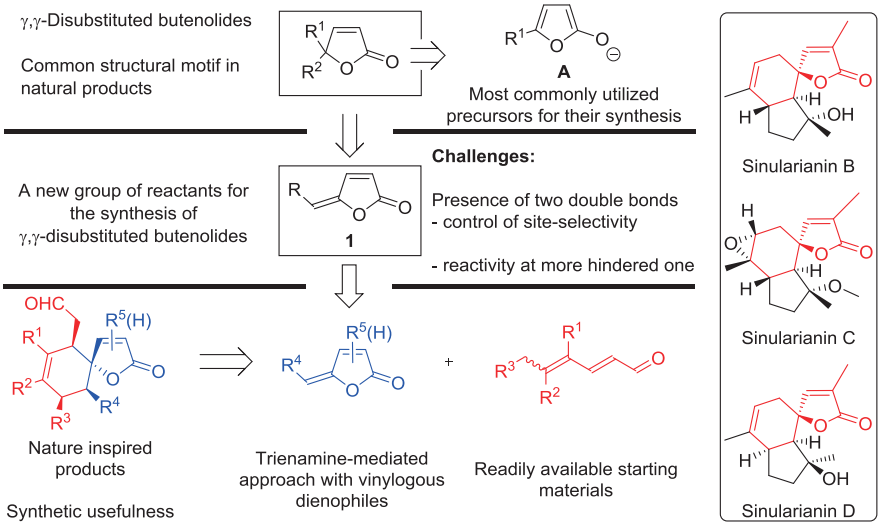
γ,γ-Disubstituted butenolides and related γ-lactones represent a common structural motif, found in wide variety of natural products relevant form the biological and medicinal chemistry point of view [1]. Therefore, much attention has been given to the development of synthetic methods allowing for their preparation, in a stereocontrolled manner. Within this research area, the asymmetric organocatalysis has proven highly useful, providing valuable solutions leading to enantiomerically enriched γ,γ-disubstituted butenolides [2].



|Herein a novel organocatalytic approach to γ,γ-disubstituted butenolides is described. It is based on a fully site-selective functionalization of 5-alkylidenefuran-2(5H)-ones via trienamine-mediated [4+2]-cycloaddition with α,β,γ,δ-diunsaturated aldehydes. The developed methodology proceeds with excellent stereocontrol and constitutes a unique example of trienamine chemistry with vinylogous dienophiles. Importantly, the reaction has very broad scope and allows for the introduction of substituents also in the α- or the β-position of the butenolide ring. [3].

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This project was realized within the Sonata Bis programme (grant number: 2015/18/E/ST5/00309) from the National Science Centre, Poland. The PROM project – "International scholarship exchange of PhD candidates and academic staff" is financed by the European Social Fund under the Operational Programme Knowledge Education Development, non-competitive project entitled International exchange of PhD candidates and academic staff, Agreement no. POWR.03.03.00-00-PN13/18

3F-B-1

(3+3)-Annulation of Carbonyl Ylides with Donor–Acceptor Cyclopropanes: Synergistic Dirhodium(II) and Lewis Acid Catalysis

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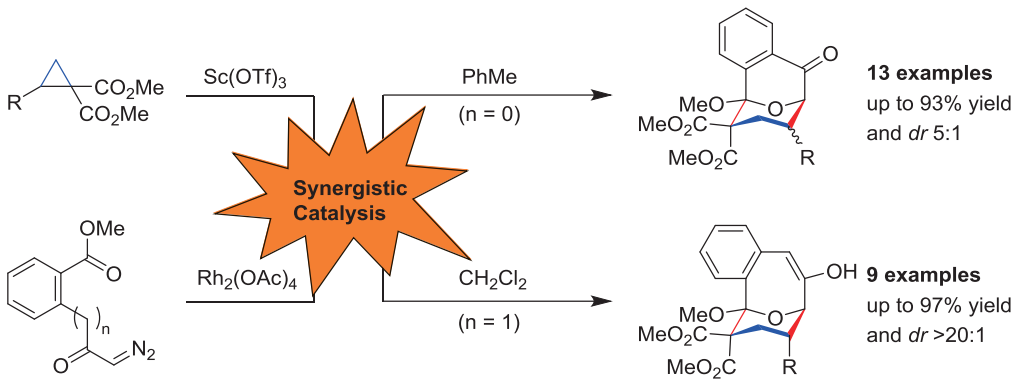
As versatile C_3-building blocks, donor-acceptor (D-A) cyclopropanes have found widespread application in organic synthesis. Their high ring strain (~115 kJ·mol^{-1}) and strongly polarized vicinal carbon-carbon bond offers unique 1,3-zwitterionic reactivity. In combination with carbonyl ylides, a high level of molecular complexity is achieved within one single synthetic step.[1,2]

This study describes the first (3+3)-annulation process of D-A cyclopropanes employing synergistic catalysis. The $Rh_2(OAc)_4$-catalyzed decomposition of diazo carbonyl compounds generated carbonyl ylides *in situ*. These 1,3-dipoles were converted with D-A cyclopropanes, activated by Lewis acid catalysis, to afford multiply substituted pyran scaffolds in high yield and diastereoselectivity (Scheme 1). Extensive optimization studies enabled access to 9-oxabicyclo[3.3.1]nonan-2-one and 10-oxabicyclo[4.3.1]decen-2-ol cores, exploiting solvent effects on intermediate reactivity. Mechanistic investigations led to a plausible concept, explaining diastereoselectivity and addressing the merging steps in the catalytic approach. [3,4]



Scheme 1: Construction of pyran scaffolds in nonan-2-one and decen-2-ol cores by synergistic catalysis.

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Dual Copper and Photoredox-Catalyzed Cross-Coupling of Alkenes, O-Benzoylhydroxylamines, and Sulfur Ylides

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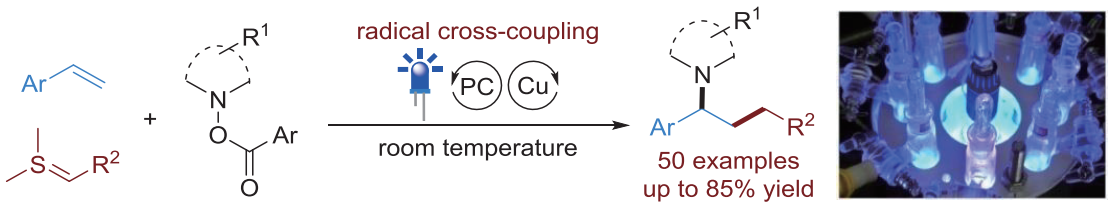
Nitrogen-containing compounds, especially the nitrogen heterocycles, are found in many biologically active synthetic targets, including natural products and designed pharmaceuticals, and they thus attract considerable attention from the synthetic community.[1,2] The development of efficient, practical and sustainable methods for direct functionalization of nitrogen heterocycles provides a powerful method to access structurally diverse nitrogen heterocycles.[3]

On the basis of our continuing interest in photochemistry,[4-5] recently, we have developed a dual copper and photoredox-catalyzed three-component radical cross-coupling of alkenes, O-benzoylhydroxylamines, and sulfur ylides. This mild protocol shows broad substrate scope and high functional group tolerance, giving the corresponding diversely functionalized nitrogen heterocycles with generally good yields and excellent selectivity. In the poster presentation, I will present the details.



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3F-B-3

Systematic examination of catalytic amide bond formation by the readily accessible B_3NO_2 heterocycle-containing molecule Pym-DATB

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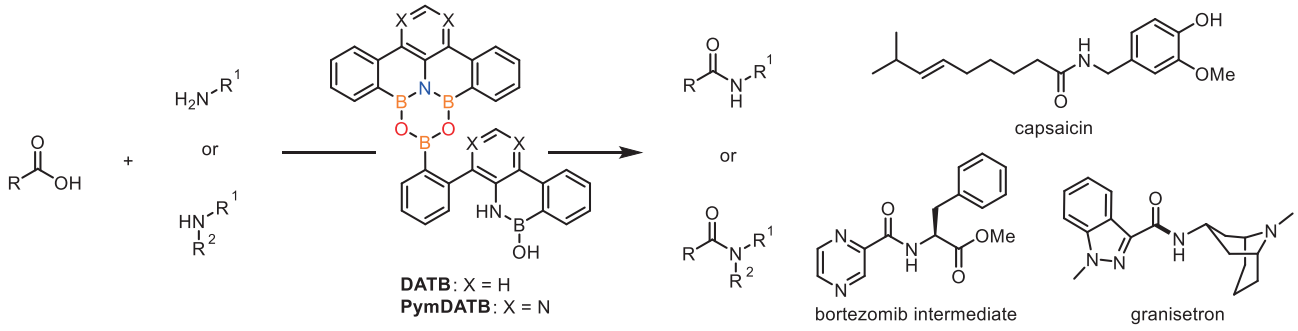
Although amide bonds are seen to be ubiquitous in organic chemistry, the main route to this functional group continues to be stoichiometric activation of a carboxylic acid prior to coupling with an amine, resulting in a large amount of waste material. We recently discovered that the heterocycle DATB (1,3-dioxa-5-aza-2,4,6-triborinane) can catalyze this reaction, employing a unique mode of action when compared with the more 'traditional' boronic acid-mediated amide bond catalysts. [1,2]

In order to provide a commercially appealing catalyst, we devised an expeditious route to a pyrimidine-containing analogue of the original DATB catalyst, Pym-DATB, using a pyrimidine-directed Bora-Friedel-Crafts reaction as a key step. The new catalyst retains catalytic activity and allows for an even greater substrate scope compared with the original catalyst. Various functional groups are tolerated without prior protection, and bulky candidates are well suited to the reaction. The utility was highlighted by the synthesis of several biologically relevant compounds, and catalyst loadings of even 0.5 mol % could be employed. [3]

The newly developed pyrimidine-directed DATB synthetic pathway opened the door for analogue synthesis, allowing for the production of a larger variety of DATB-containing compounds. The properties of the DATB ring could be moderated, and compounds with differing electronic properties as well as those with unprecedented solubility in organic solvents have allowed for more insight into this unusual heterocycle.



PymDATB is commercially available from Merck-Sigma-Aldrich (Catalog # 901627).

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Chalcogen-Bond Assisted Dirhodium Complex –Total Syntheses of Naturally Occurring γ-Lactones–

Takuya Murai[1], Wenjie Lu[1], Toshifumi Kuribayashi[1], Yongning Xing[1], Jingdong Guo[2], Shohei Hamada[3], Takahiro Sasamori[2], Norihiro Tokitoh[1], Takeo Kawabata[1] and Takumi Furuta[3,*]

[1]*Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan*

[2]*Graduate School of Natural Sciences, Nagoya City University, Nagoya 467-8501, Japan*

[3]*Kyoto Pharmaceutical University, Kyoto, Kyoto 607-8412, Japan*

Chalcogen bond between sulfur and oxygen atoms has been paid attentions as an attractive interaction, which contributes to conformational control of pharmaceuticals and organic materials. We recently reported dirhodium carboxylate catalyst **1** for asymmetric intramolecular C–H insertion of α-diazoacetates to α,β-disubstituted γ-lactones.[1)] We also applied this stereoselective C–H insertion to asymmetric total synthesis of cinnamomumolide (**2**). However, its steleoselectivity was found to be limited in a moderate level (in the case of cat. **3**: 67% ee) (Scheme 1).

In this study, we found that novel dirhodium complex **4** bearing chalcogen bonds, prepared from axially chiral binaphthothiophene dicarboxylic acid (**5**),[2)] was superior catalyst to improve its stereoselectivity (Figure 1).

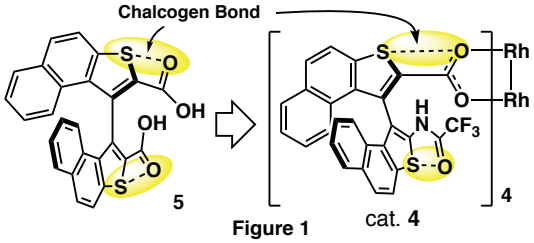
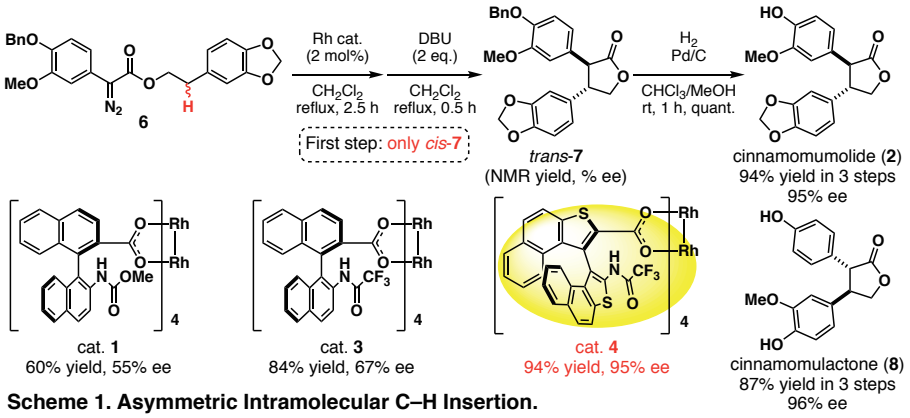


Figure 1

Upon treatment of **6** with cat. **4** (2 mol%) in CH_2Cl_2 under reflux conditions, intramolecular C–H insertion was proceeded smoothly to give *cis*-**7** as a sole isomer. The enantiomeric excess (95% ee) was determined in *trans*-**7** (94% yield in 2 steps) after epimerization with DBU. Deprotection of benzyl group of *trans*-**7** afforded **2** in 94% yield over 3 steps. In addition, we also achieved asymmetric total synthesis of cinnamomulactone (**8**) in short steps.



Scheme 1. Asymmetric Intramolecular C–H Insertion.

Chalcogen bonds between sulfur and oxygen atoms were thought to contribute for conformational lock of the carboxylate groups to lead well-defined D_2-symmetric structure of **4** as shown in the crystal structure (Figure 2). This could be the key for superior asymmetric induction of **4**.

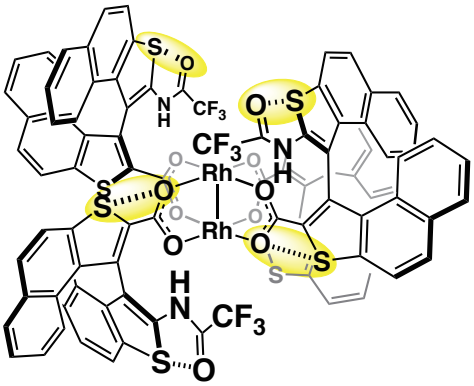


Figure 2. Crystal Structure of 4.

References

(1) W. Lu, T. Murai, T. Kawabata, T. Furuta *et al. Synlett* **2017**, *28*, 679–683. (2) T. Murai, T. Kawabata, T. Furuta *et al. Chem. Pharm. Bull.* **2018**, *66*, 1203–1206.

3F-C-1

Nitrenium Ion from λ^3-Iodanes

Ankita Bal, and Prasenjit Mal*

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Hypervalent iodine compounds are widely used as potential oxidant in organic synthesis. In spite of similar reactivity with transition metals, hypervalent iodine reagents[1] are more preferred because of their environmental sustainability. Among several types of hypervalent iodine reagents, trivalent organo iodine(III) reagents or λ^3- iodanes are popular due to their easy accessibility, stability and controlled oxidizing reactivity.[2] Amines react with iodine(III) oxidants in some specific way to provide divalent electrophilic ionic species, called as nitrenium ion. Depending on the nature and stability of nitrenium ion, numerous oxidative transformations are known to generate valuable functional molecules. In accordance with the above principle, biarylsulfonamides were used to generate nitrenium ion using the hypervalent iodine(III) reagent PIDA. Depending on the type of nucleophile, nitrenium ion is converted to carbenium ion which leads to synthesis of C-C or C-N bond.[4] The deciding factor in the outcome of a reaction is guided by the nucleophile available in the system. Herein, the role of hypervalent iodine(III) reagent in bringing about oxidative transformation for synthesis of carbazoles by distal (meta) C-H bond functionalization will be discussed.[3]

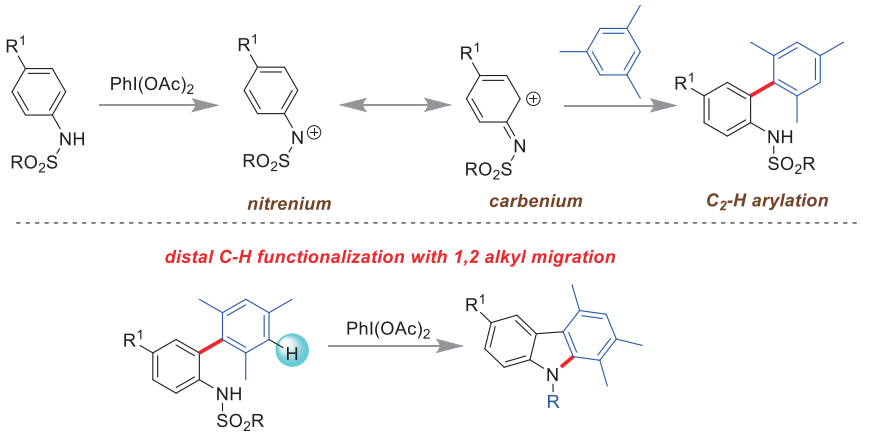

Figure 1: Nitrenium ion mediated synthesis of C-C and C-N bond.

References :

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[4] A. Bal, S. Maiti and P. Mal, *Communicated.*

Total Synthesis of (–)-Deoxoapodine

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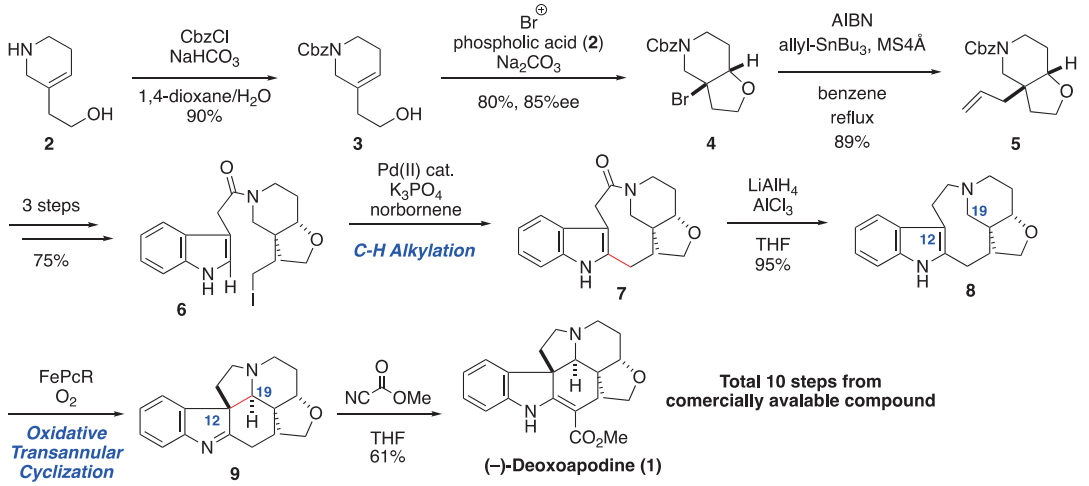
Sendai, Miyagi 980-8578, Japan

Aspidosperma alkaloids have attracted considerable attentions from the synthetic community due to their pharmaceutically important biological activities and unique structures, containing the pentacyclic core framework. Although a number of synthetic strategies for aspidosperma alkaloids have been reported, there is only one synthetic approach involving oxidative transannular bond formation between C12 and C19 positions, which used $Hg(OAc)_2$ as an oxidant.[1] However, this method resulted in a low yield due to over-oxidation, and required further reductive treatment. Recently, we have developed the aerobic oxidative modification of α-position of alkyl amines using phthalocyanine metal complex. Based on these backgrounds, we focused on (–)-deoxoapodine (**1**), containing a tetrahydrofuran ring, and undertook synthetic studies on **1** to demonstrate the utility of our oxidation reaction.

Our synthesis commenced with Cbz-protection of the commercially available amino alcohol **2**, which was followed by chiral phosphoric acid (**2**) catalyzed enantioselective 5-*endo*-*trig* bromocyclization to afford tertiary bromide **4** in optically active form. Then, construction of quaternary carbon center by Keck allylation, followed by a three-step conversion including ozonolysis of allyl group, provided alkyl iodide **6**. Next, the highly strained 9-membered ring system was successfully constructed by a direct C-H alkylation at the 2-position of indole based on Bach's method.[2] After reduction of lactam **7**, the resultant tertiary amine **8** was treated with the iron phthalocyanine complex under oxygen atmosphere to promote the transannular reaction starting from oxidation of the tertiary amine to give indolenine **9** possessing aspidosperma skeleton. Finally, we have achieved an enantioselective 10 step total synthesis of (–)-deoxoapodine (**1**) by introduction of methoxy carbonyl group.



References: [1] James, P. K.; Edward, P; Richard, T. B. *J. Am. Chem. Soc.* **1970**, *92*, 1700.
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Complexation between $Al(C_6F_5)_3$ and *N*-Phosphine Oxide-Substituted Imidazolidenes

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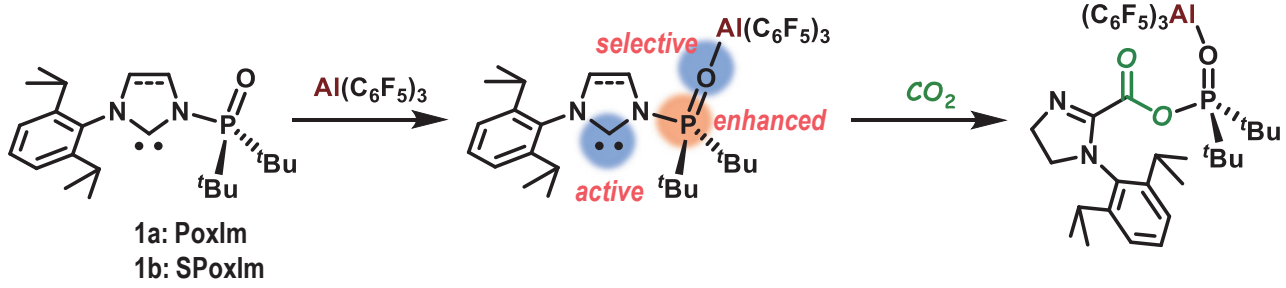
Department of Applied Chemistry, Faculty of Engineering, Graduate School of Engineering
Osaka University, Suita, Osaka 565-0871, Japan

N-Heterocyclic carbenes (NHCs) have found a multitude of applications in diverse research areas in organic, inorganic, and organometallic chemistry.[1] Applications of NHCs have been significantly furthered by the advent of multifunctional NHCs by the introduction of substituents on either the nitrogen atom(s) or on the backbone of the NHCs.[2] Recently, we have developed *N*-phosphine oxide-substituted imidazolylidenes (PoxIms) and the corresponding imidazolinylidenes (SPoxIms) through the direct introduction of the phosphinoyl group onto the nitrogen atom, which can work as a Lewis base and an electrophile showing multipurpose utility.[3a,b] Herein, we report the complexation between $Al(C_6F_5)_3$ and *N*-phosphinoyl groups in PoxIm **1a** or SPoxIm **1b** enhanced the electrophilicity on the phosphorus, hence the reactive carbene moieties are co-existed in these molecules.[4] Thus, a further use of the carbene was demonstrated by the preparation of a carboxylic-phosphinic mixed anhydride through the reaction between CO_2 and the phosphinoyl-coordinating complex comprising **1b** and $Al(C_6F_5)_3$. This CO_2-fixation was also promoted in the presence of 10 mol% $Al(C_6F_5)_3$, while $B(C_6F_5)_3$ did not show any catalytic activity.



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A new indole to benzoxazole rearrangement enabled by C-H borylation

Kirsty Anderson
Associate Professor Jonathan Sperry

Benzoxazoles are a class of aromatic compounds composed of a fused benzene and oxazole heterocycle. In particular, 1,3-benzoxazole with a 2-substituent are known pharmacophores and privileged structures in drug discovery due to a vast range of biological activity including antimicrobial, anticancer and antioxidant.[1] For example, caboxamycin[2] and nataxazole[3] are natural products containing the benzoxazole motif which exhibit cytotoxic activity through binding to metal ions in DNA and inhibiting human topoisomerase II; suvorexant[4] is a drug used to treat insomnia by working as an orexin receptor antagonist (Figure 1).

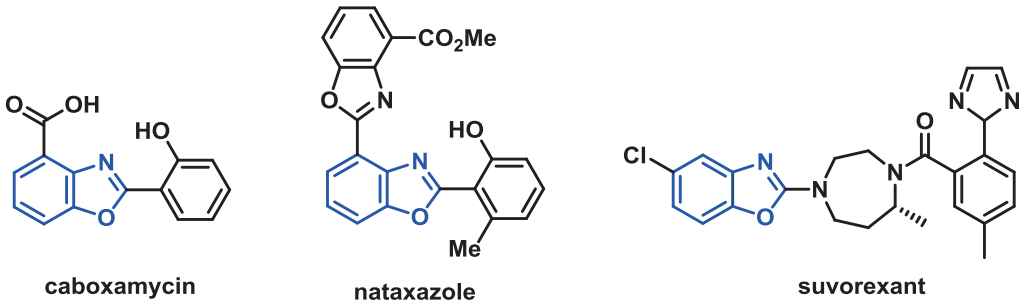
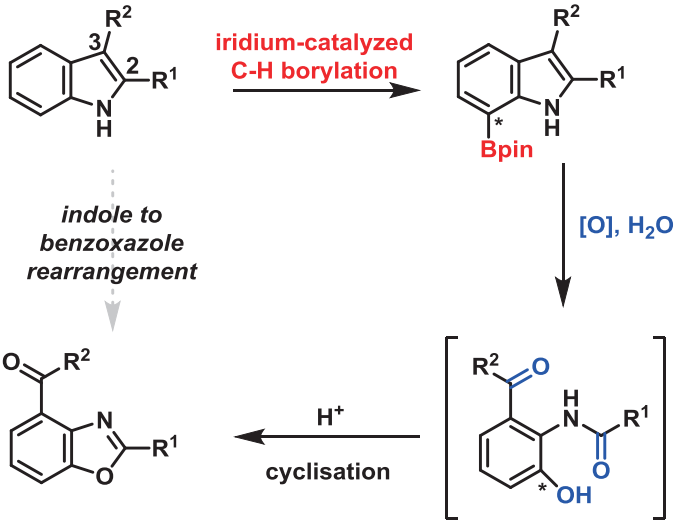


Figure 1: Examples of biologically active benzoxazole-containing molecules

Current methods to synthesise this important class of heterocycles are limited to cyclocondensation of *o*-aminophenols with carboxylic acid derivatives under relatively harsh conditions.[5] We envisage the straightforward conversion of commerically available indoles to benzoxazoles, utilising an iridium catalysed C7-borylation reaction followed by an oxidative hydrolysis/ring opening cyclisation cascade (Scheme 1).



Scheme 1: Conversion of 2,3-disubstituted indoles to benzoxazoles

[1] Rajasekhar, S.; Maiti, B.; Chanda, K. *Synlett*. **2017**, 28 (05), 521–541.
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3F-D-1

Advanced method for the construction of C-S bond via C-H functionalization

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C-S bonds are ubiquitously found in natural products. Many organosulfur compounds are widely used in medicinal, pharmaceutical and functional material science. Hence the C-S bond construction has become a significant research field in organic chemistry because of the tremendous importance of organosulfur compounds. To date, great developments have been made for erecting the C-S bonds including transition-metal-catalyzed [1] pathways but use of simple greener reagent [2] (base or organic reagent) is less explored. C-H bond is regarded as a non-functional group as it has high bond energy lacking reactivity. Hence functionalization of C-H bond is an emerging era in synthetic organic community. In continuation of our interest in C-S bond synthesis via C-H bond functionalization using the transition metal free inexpensive reagent is highly desirable. The evaluation of environmentally benign by-product makes these methodologies more fascinating. A detail study of our research for C-S bond [3-5]synthesis will be discussed here.

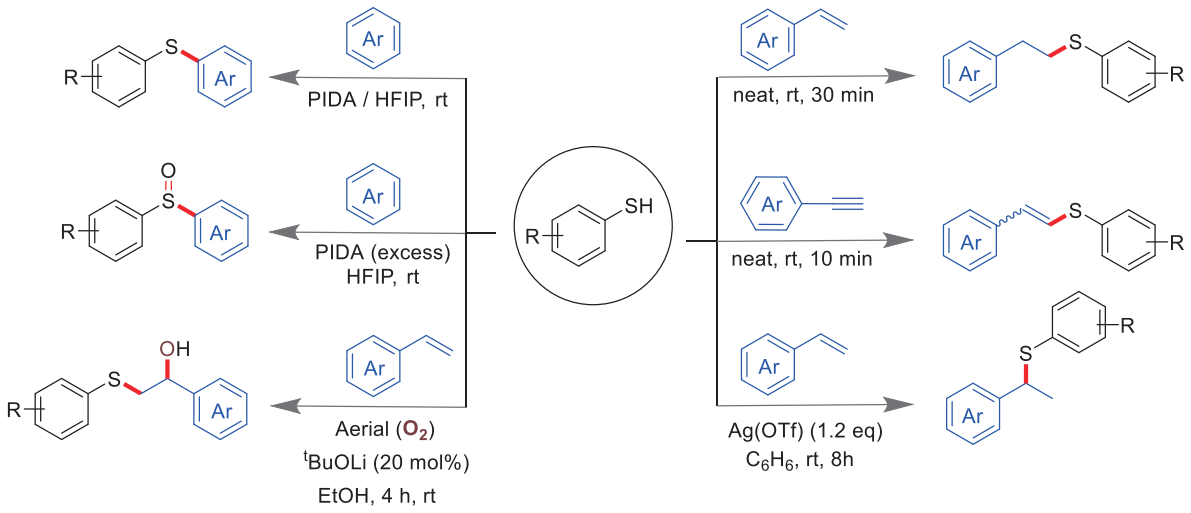

Figure 1: Thiophenol as sulphur surrogate for the regioselective C-H functionalization

Reference:

(1) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596.
(2) Kumar, R.; Saima; Shard, A.; Sinha, A. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 828.
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(4) Choudhuri, K.; Mandal, A.; Mal, P. *Chem. Commun.* **2018**, *54*, 3759.
(5) Choudhuri, K.; Maiti, S.; Mal, P. *Adv. Synth. Catal.* **2019**, *361*, 1092.

[2+2+1] Pyrrole Synthesis from Alkynes and Azobenzene via N=N Bond Cleavage Catalyzed by Vanadium Complexes

Yuya Kakiuchi,[1] Kento Kawakita,[1] Evan P. Beaumier,[2] Ian A. Tonks,*[,2]
Hayato Tsurugi,*[,1] and Kazushi Mashima*[,1]
[1]*Department of Chemistry, Graduate School of Engineering Science, Osaka University Toyonaka, Osaka 560-8531, Japan*
[2]*Department of Chemistry, University of Minnesota-Twin Cities, Minneapolis, Minnesota 55455, United States*

Multisubstituted pyrroles are synthetically valuable heteroaromatic compounds in terms of their versatility as building blocks of pharmaceuticals, natural products, functional materials, and dyes. Although cyclocondensation reaction such as the Paal-Knorr and Hantzsch reactions are well-established, transition metal-mediated [2+2+1] cycloaddition reaction of alkynes and primary amine have attracted great attention because of the substrate availability. One of us previously reported Ti-catalyzed [2+2+1] pyrrole formation reaction using alkynes and azobenzene as substrates.[1-2] We herein present that the combination of $VCl_3(thf)_3$ and *N,N*-bis(trimethylsilyl)aniline **1a** serves as an efficient catalyst for [2+2+1] cycloaddition reaction of alkynes **2** and azobenzene **3**, giving multisubstituted pyrroles **4**.[3] According to the ^1H NMR analysis of the reaction mixture, we found a generation of mono(imido)vanadium(III) species with concomitant release of 2 equiv of $ClSiMe_3$. Plausible reaction mechanism involves a generation of bis(imido)vanadium(V) species via N=N bond cleavage; in fact isolated bis(imido)vanadium complex **5** showed good catalytic activity for pyrrole formation reaction. Substrate scopes and a detailed reaction mechanism will also be discussed in this presentation.

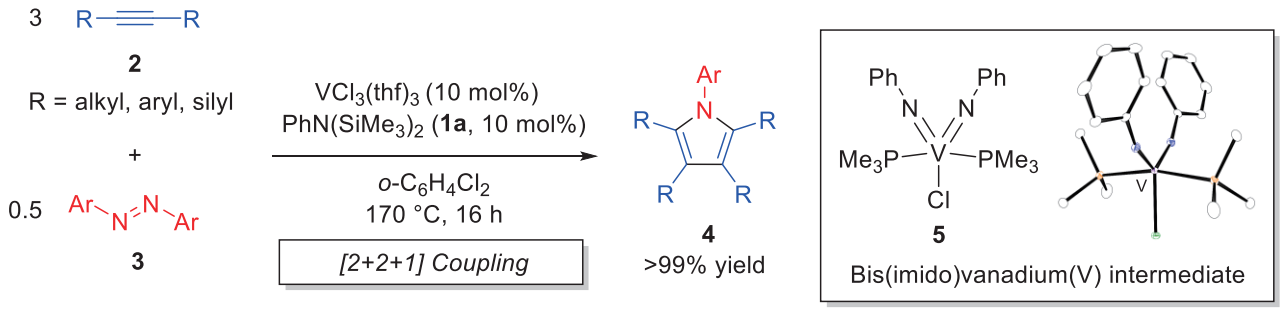

Figure 1. Vanadium-catalyzed [2+2+1] coupling of alkynes and azobenzene

[1] Davis-Gilbert, Z. W.; Hue, R. J.; Tonks, I. A. *Nat. Chem.* **2016**, *8*, 63.
[2] Davis-Gilbert, Z. W.; Kawakita, K.; Blechschmidt, D. R.; Tsurugi, H.; Mashima, K.; Tonks, I. A. *Organometallics* **2018**, *37*, 4439.
[3] Kawakita, K.; Beaumier, E. P.; Kakiuchi, Y.; Tsurugi, H.; Tonks, I. A.; Mashima, K. *J. Am Chem. Soc*. **2019**, *141*, 4194.

3F-D-3

Anion-π Catalysis for Epoxide-Opening Ether Cyclizations, from Monomers to Oligomers, Challenging Baldwin Rules

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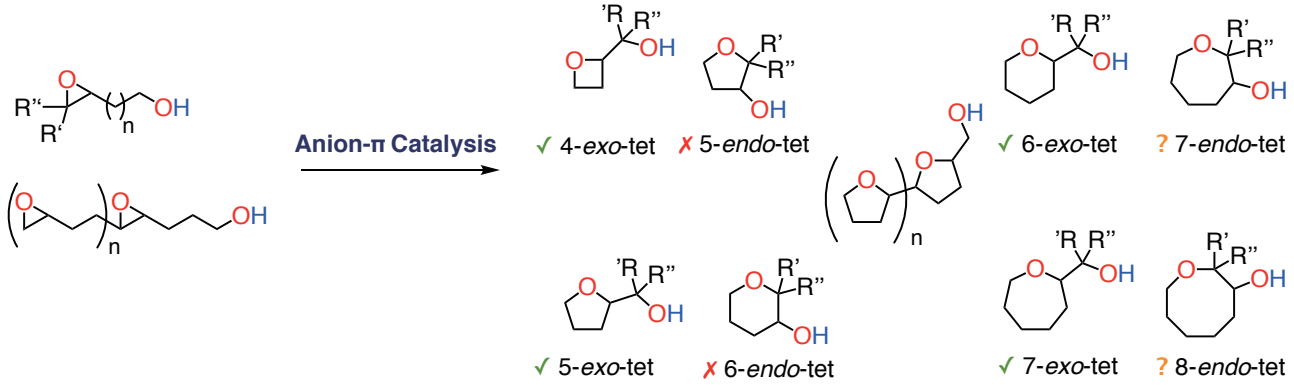
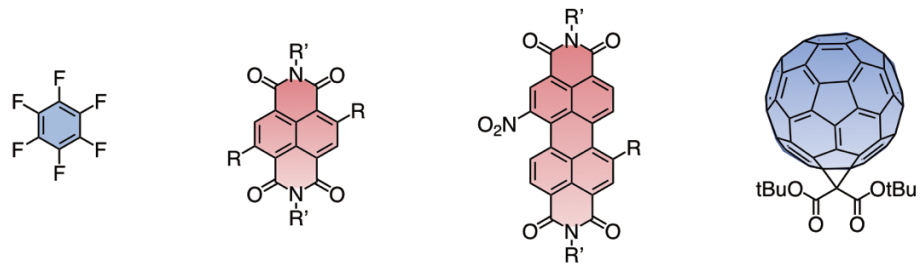
Department of Organic Chemistry, University of Geneva
Geneva, Switzerland

In recent years, it has been demonstrated that anion-π interactions can accelerate a wide variety of chemical transformations.[1] Particularly important has been the employment of primary anion-π catalysis to promote epoxide-opening cyclizations, reaction which shows an autocatalytic behavior. Preliminary studies showed that the use of anion-π interactions can enhance the formation of the 6-*endo*-tet product (anti-Baldwin) against the 5-*exo*-tet (Baldwin).[2] Considering the relevance of epoxide opening polyether cyclization in chemistry and biology we decided to analyze in depth this new primary anion-π catalytic reaction.[3] In this context, the next step was the evaluation of different lengths of the epoxide unit, making possible the access to different ring sizes. It was reviled that substitution on epoxide core as well as on the aliphatic chain (gem-dimethyl effect) can play a key role turning the epoxide more sensible against the anionic-π surface, and more important providing the anti-Baldwin rule product. The knowledge brought from the study of the monomers allow us to promote the cyclization of oligomers in a cascade opening-epoxide cyclization on different anionic-π surfaces.



Anion-π Catalysis



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[2] X. Zhang, X. Hao, L. Liu, A.-T. Pham, J. López-Andarias, A. Frontera, N. Sakai, S. Matile. *J. Am. Chem. Soc.* **2018**, *140*, 17867.
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3F-D-4

Synthesis of Hypervalent Iodine Reagents Bearing Cationic Heterocycles and Application to Oxidative Cyclization

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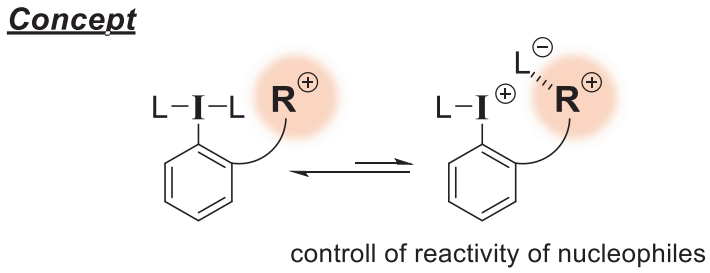
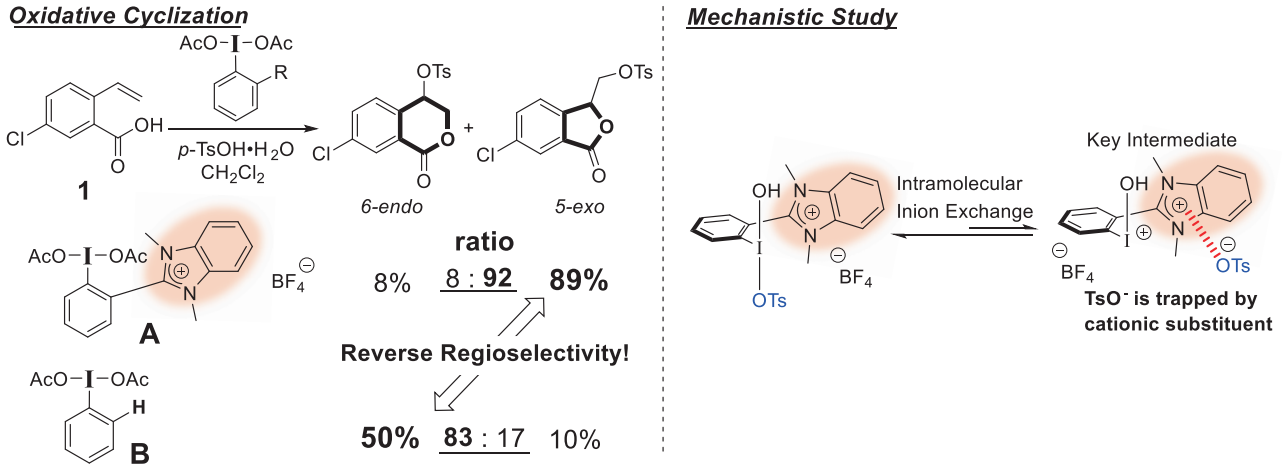
Hypervalent iodines are important oxidants in organic chemistry because they are metal-free reagents and their properties are controlled by organic ligands. However, controlling of reactivity depends on only electronic and steric effects of ligands [1]. In this study, we designed a new methodology employing an interaction of a nucleophile with an intramolecular cationic substituent (Concept).



We synthesized hypervalent iodines bearing a cationic nitrogen-containing heterocyclic moiety nearby the iodine center to control the reactivity by electrostatic interaction. The newly synthesized hypervalent iodine **A** caused 5-*exo* selective cyclization of 2-vinylbenzoic acids while typical iodobenzene diacetate **B** showed 6-*endo* selectivity (Oxidative Cyclization). These results suggested that the interesting reverse of the regioselectivity is ascribed to the cationic substituent. From NMR and UV-spectrum studies, it was found that nucleophilic TsO anion on iodine atom is trapped by cationic substituent which acts as an inhibitor to give Key Intermediate (Mechanistic Study).



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Total Synthesis of Histrionicotoxin 235A

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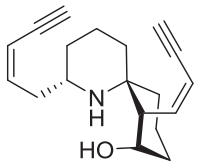
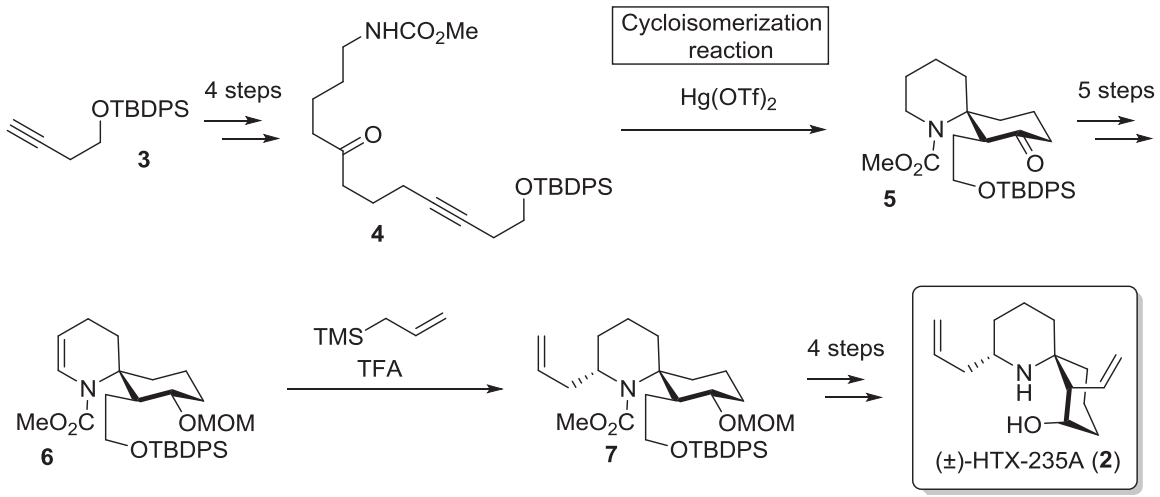
(−)-Histrionicotoxin (HTX-283A, **1**, Fig. 1), one of the azaspirocyclic alkaloids isolated from Colombian 'poison arrow' frog *Dendrobates histrionicus*, exhibits intent selective inhibition of the nicotinic acetylcholine receptors.[1] The chemical structure of **1** is characterized by a 1-azaspiro[5.5]undecane skeleton and two enyne side chains. The other members of this alkaloid family including (−)-HTX-235A (**2**) have also been identified;[2] however, biological activities of histrionicotoxin analogs remain unexplored due to paucity of the alkaloids in nature. In this presentation, we report the total synthesis of (±)-**2** using a $Hg(OTf)_2$-catalyzed cycloisomerization reaction[3] as a key reaction that directly constructs azaspirocyclic skeletons from linear substrates.



(–)-Histrionicotoxin
(HTX-283A, **1**)
Fig. 1

Our studies commenced with preparation of linear substrate **4** from alkyne **3** via 4 steps (Scheme 1). The cycloisomerization reaction of **4** stereoselectively afforded the desired spirocyclic compound **5**. Carbamate **6** was converted from **5** via 5 steps. Allylation of **6** with allyltrimethylsilane gave allylpiperidine **7**. Finally, (±)-**2** was synthesized through formation of a vinylic group and removal of protecting groups.



Scheme 1

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Synthetic Study of TPI 287

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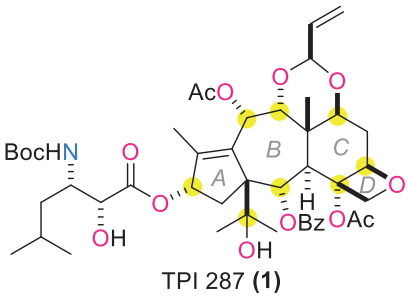
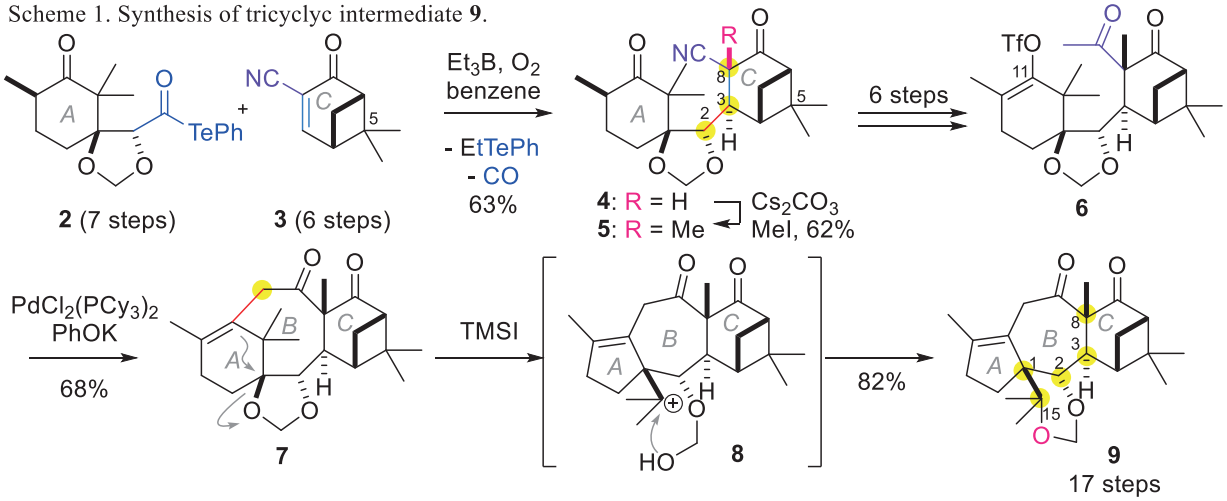
TPI 287 (**1**) belongs to an abeotaxane family and is clinically developed as an anti-cancer agent.[1] The 5/7/6-membered carbon skeleton (ABC-ring) of **1** with a bridgehead olefin and two quaternary carbons are substituted by eight oxygen functional groups, two of which form an oxetane ring (D-ring). Due to the intricately fused tricarbocyclic structure with the multi-oxygen functionalities, total synthesis of abeotaxanes including **1** has not been achieved. We embarked upon the study toward a convergent synthesis of **1** using decarbonylative radical coupling reaction. [2]



A-ring **2** [3] and C-ring **3** was prepared in 7 and 6 steps, respectively. Next, decarbonylative radical coupling reaction between α-alkoxyacyl telluride **2** and C-ring cyanocyclohexenone **3** was realized under mild conditions and adduct **4** was generated in the C2- and C3-stereoselective manners (Scheme 1). Methylation of **4** proceeded to avoid the C5 dimethyl group, and C8-quaternary carbon of **5** was stereoselectively constructed. The cyano group of **5** was converted to an acetyl group in six steps to afford **6**. The Pd(0)-mediated eight-membered cyclization of **6** delivered tricyclic intermediate **7**. When **7** was subjected to TMSI, Wagner–Meerwine rearrangement proceeded to afford **9**.

In summary, tricyclic intermediate **9** was obtained in 17 steps, which has the four contiguous stereocenters of **1** (C1, 2, 3, 8) on the 5/7-membered carbon skeleton and oxygen functional group at C15 position.

Scheme 1. Synthesis of tricyclyc intermediate **9**.



[1] Medina, M. *Int. J. Mol. Sci.* **2018**, *19*, 1160. [2] (a) Nagatomo, M.; Kamimura, D.; Matsui, Y.; Masuda, K.; Inoue, M. *Chem. Sci.* **2015**, *6*, 2765. (b) Matsumura, S.; Matsui, Y.; Nagatomo, M.; Inoue, M. *Tetrahedron* **2016**, *72*, 4856. [3] Matoba, H.; Watanabe, T.; Nagatomo, M.; Inoue, M. *Org Lett*, **2018**, *20*, 7554.

5F-A-3

5-Phenylazopyrimidines: A new class of orthogonal photoswitches?

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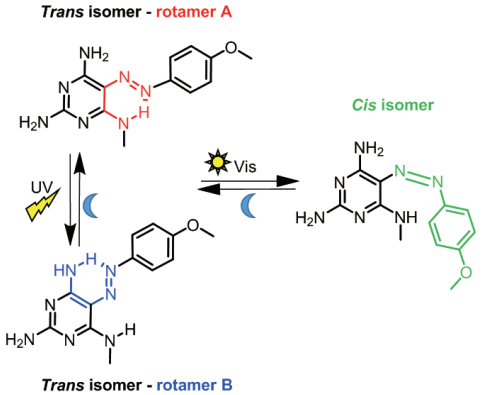
5-Phenylazopyrimidines are structurally close to the well-explored azobenzenes. Upon irradiation, they also undergo to the *trans-cis* isomerization. However, replacement of one phenyl ring with pyrimidine brings new prominent properties of such compounds, such as keto/enol tautomerism, biocompatibility or ability to form intermolecular hydrogen bonds[1].

We prepared three classes of new 5-phenylazopyrimidines, which are able to form none, one or two intramolecular hydrogen bonds (IMHBs). We used a unique combination of advanced experimental and theoretical methods to study their photochemical and physicochemical behaviour, namely 1) NMR with *in situ* irradiation, 2) optical spectroscopy, 3) mathematical fitting and 4) DFT calculations[2,3]. All prepared derivatives formed the *cis* isomer upon irradiation. Interestingly, some of them can be photoisomerized with visible light, which could be beneficial in applications, in which UV light is harmful. We were able to tune thermal relaxation rate and irradiation wavelength by suitable substitution. In compounds with two different hydrogen bond donors, we uncovered unique photoswitchable IMHBs. These derivatives can form two stable rotamers (A/B, both *trans* photoisomer). The rotamer ratio changed reversibly upon UV irradiation at low temperature. This photoinduced process as well as thermal relaxation is strongly substituent-dependent. The mechanism of these unique photoswitching processes was proposed by DFT calculations.

This detailed mechanistic study leads to a better understanding of the photochemical behaviour of azopyrimidines and gives an opportunity to designed new photoswitches, which could find a wide range of applications in optoelectronics, photobiology or material science.

Acknowledgements. Supported by the Czech Science Foundation (M.D., grant no. 18-11851S).



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5F-A-4

Studies on the Second Generation Synthesis of Palau'amine

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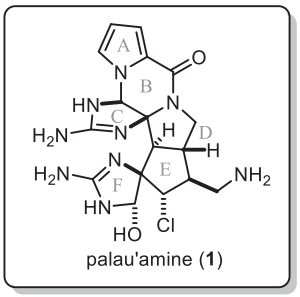
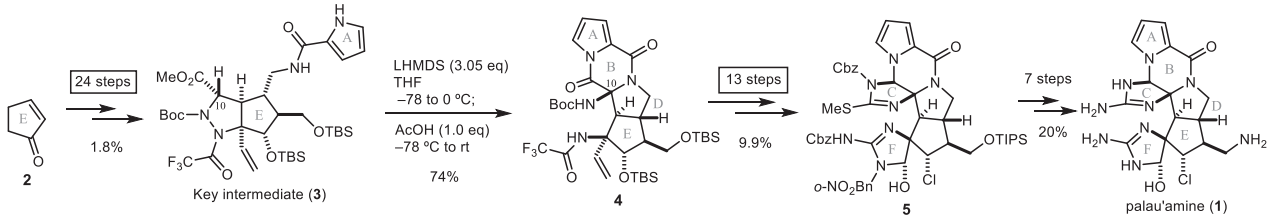


Palau'amine (**1**) was originally isolated from a sponge, *Stylotella agminate*, in 1993 by Scheuer and collegues, as a novel class of pyrrole-imidazole alkaloids.[1] We have recently reported the total synthesis of palau'amine characterized by the construction of ABDE tetracyclic ring core including a trans-bicyclo[3.3.0]octane skeleton at a middle stage of total synthesis. [2, 3] Starting from a commercially available compound (**2**), the key intermediate (**3**) was prepared. Treatment of **3** with LHMDS followed by AcOH afforded an ABDE tetracyclic compound (**4**). The construction of the C and F rings led to **5**. Subsequent transformations of functional groups afforded **1**. However, the synthesis needs long steps (45 steps from **2**). This problem was attributed to the many steps for the synthesis of **3** and the construction of the C and F rings. Therefore, we attempted to establish the second generation synthesis of **1** towards the short-step synthesis.

In order to verify the feasibility of short-step synthesis, we first addressed short-step synthesis of palau'amine analog (**6**) without aminomethyl and chloro groups of **1**. So far, key intermediate (**7**) has been successfully synthesized from **2** in only 9 steps. As a result of extensive investigation, a single step construction of the CDE ring system was achieved by the treatment of **7** with Ph_2NLi. At present, we are undergoing to construct the B and F rings from imine (**9**) that could be obtained from **8** in 3 steps. We will discuss these details in this presentation.



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[3] Namba, K. *et al*. *Nat. Commun.* **2015**, *6*, 8731.

5F-B-1

Synthetic Studies on Haliclonin A

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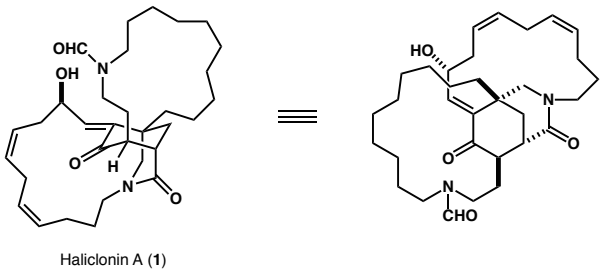
The group directed by Oh and Shin isolated haliclonin A (**1**, Figure 1) from *Haliclona* sp. (a marine sponge of Korea) and determined the structure of this compound by using a combination of spectroscopic and chemical analyses.[1]

Like sarain A and other bis-alkylpyridinium-derived compounds from sponges, haliclonin A possesses two macrocyclic rings. Nevertheless, its 3-azabicyclononane framework, also with the unprecedented enone part and two amide functionalities made this tetracyclic marine alkaloid extremely unique in terms of structure.



Haliclonin A (**1**)

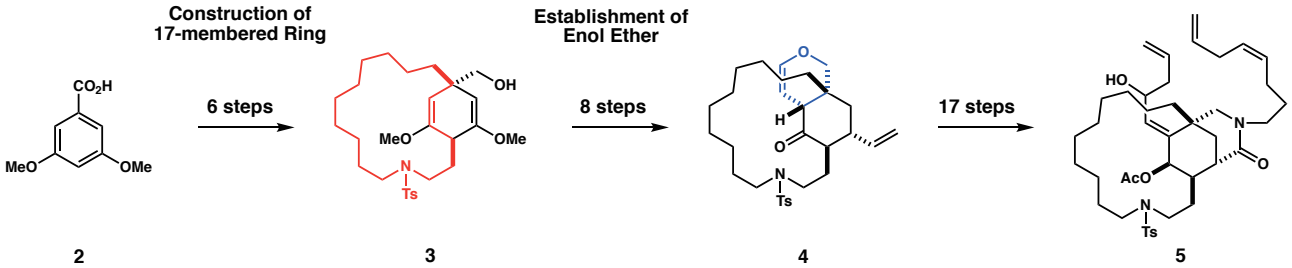
Figure 1. Haliclonin A

As to the biological activities, haliclonin A exhibited moderate cytotoxicity and antibacterial activity against diverse microbial strains. It also displayed moderate cytotoxicity against the K562 leukemia cell line, with an IC_{50} of 15.9 μg/mL.[1]

Not only the unparalleled structure but also the potent bioactivity made this tetracyclic marine alkaloid attract much attention, especially its fascination on the synthetic aspect.

As the synthetic studies in our laboratory (Scheme 1), starting with commercial available 3,5-dimethoxybenzoic acid **2**, construction of the 17-membered ring was achieved by only 6 steps (compound **3**). Whereafter, further 8 steps established the enol ether part (compound **4**) successfully.[2] After 17 steps of transformations, alcohol **5** was obtained as a single diastereomer, which means ring closing metathesis will be the last task before we accomplish the total synthesis of haliclonin A (**1**).

Scheme 1. Synthetic studies in our laboratory



[1] Jang, K. H.; Kang, G. W.; Jeon, J.; Lim, C.; Lee, H.-S.; Sim, C. J.; Oh, K.-B.; Shin, J. *Org. Lett.* **2009**, *11*, 1713.
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Total Syntheses of Bufadienolides

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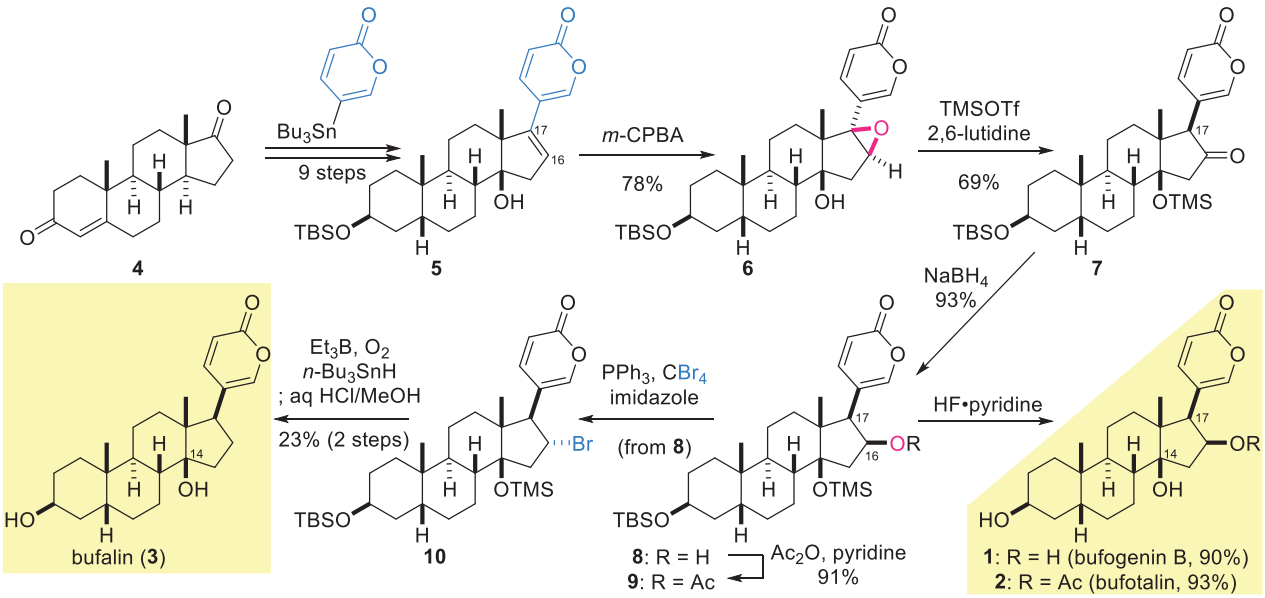
Bufadienolides (**1**, **2**, and **3**), steroidal natural compounds, were isolated from plants of the iris family and toads.[1] These structures possess a β-oriented hydroxy group at the C14 position and a β-oriented 2-pyrone at the C17 position. Several synthetic efforts have been reported, but no synthesis of highly functionalized bufadienolide has been achieved because of difficulty in introducing the β-oriented 2-pyrone under mild conditions. Herein, we describe the total syntheses of bufogenin B (**1**), bufotalin (**2**), and bufalin (**3**) by employing a new 2-pyrone installation strategy.

First, **5** was synthesized from the commercially available compound **4** over nine steps, including installation of 2-pyrone moiety at the C17 position by using Stille coupling.[2] Oxidation of the C17-olefin of **5** proceeded chemo- and stereoselectively to give epoxide **6**. Lewis acid-promoted isomerization of **6** introduced the desired stereochemistry at the C17 position to afford ketone **7**. Next, stereoselective reduction of the carbonyl group of **7** proceeded to give alcohol **8**, and the TBS/TMS-removal provided **1**. Alternatively, acetylation of alcohol **8** led to **9**, and subsequent removal of the protecting groups afforded **2**. In addition, **8** was subjected to Appel reaction conditions to obtain bromide **10**. Finally, radical reduction of bromide **10**, followed by removal of the silyl protecting groups, provided **3**.

In conclusion, the chemo- and stereoselective 2-pyrone installation enabled the total syntheses of the three bufadienolides, bufogenin B (**1**), bufotalin (**2**), and bufalin (**3**). Because this strategy employs the mild conditions, it would be applicable to the synthesis of more oxygenated bufadienolides.



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[2] Mukai, K.; Urabe, D.; Kasuya, S.; Aoki, N.; Inoue, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 5300.

Total Synthesis of Saptomycin H

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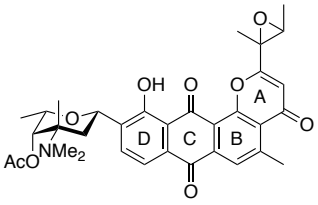
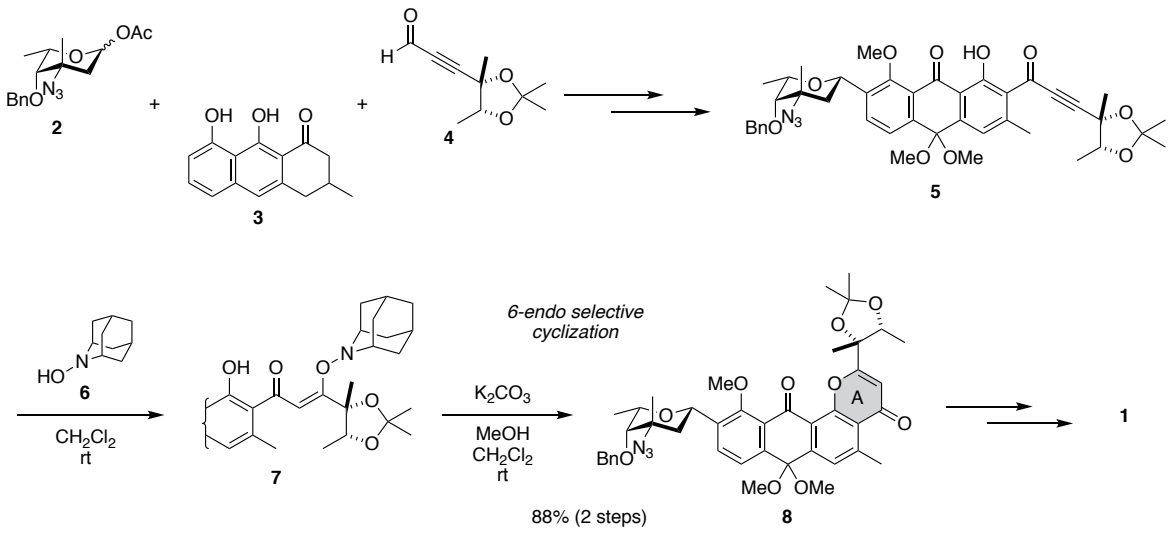
Saptomycin H (**1**), isolated from *Streptomyces* sp. HP530, is a member of the pluramycin-class antitumor antibiotics.(1) The structure features an anthrapyranone skeleton sharing the *C*-glycoside structure and an oxirane ring on the side chain. Although many synthetic studies have been reported, total synthesis of pluramycins having an oxirane ring is not achieved.



saptomycin H (**1**)

Herein, we will report a successful synthetic route to **1** via the 6-*endo* selective cyclization of anthraquinone acetal **5** by exploiting a particular reactivity of hydroxylamine **6**.

Anthrone **3** was combined with sugar **2** and aldehyde **4** to give anthraquinone acetal **5**. The A-ring formation from **5** to give **8** was not successful, and only the undesired 5-*exo* cyclization product was obtained. At this stage, we changed our strategy for the A-ring formation, focusing attention to the corresponding enone having a leaving group at the β position. Treatment of **5** with hydroxylamine **6** gave enone **7**, which smoothly underwent the desired reaction under basic conditions, giving only the desired 6-*endo* cyclization product **8**. Further transformations including removal of the protecting groups and construction of the oxirane ring culminated in the first total synthesis of saptomycin H (**1**).



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Facile Synthesis of Chiral Spirooxindoles *via* Pictet-Spengler/Oxidative Rearrangement

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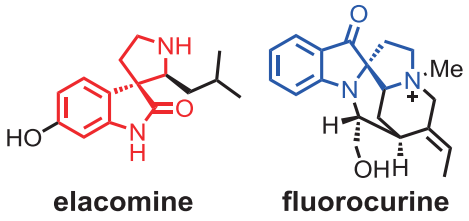
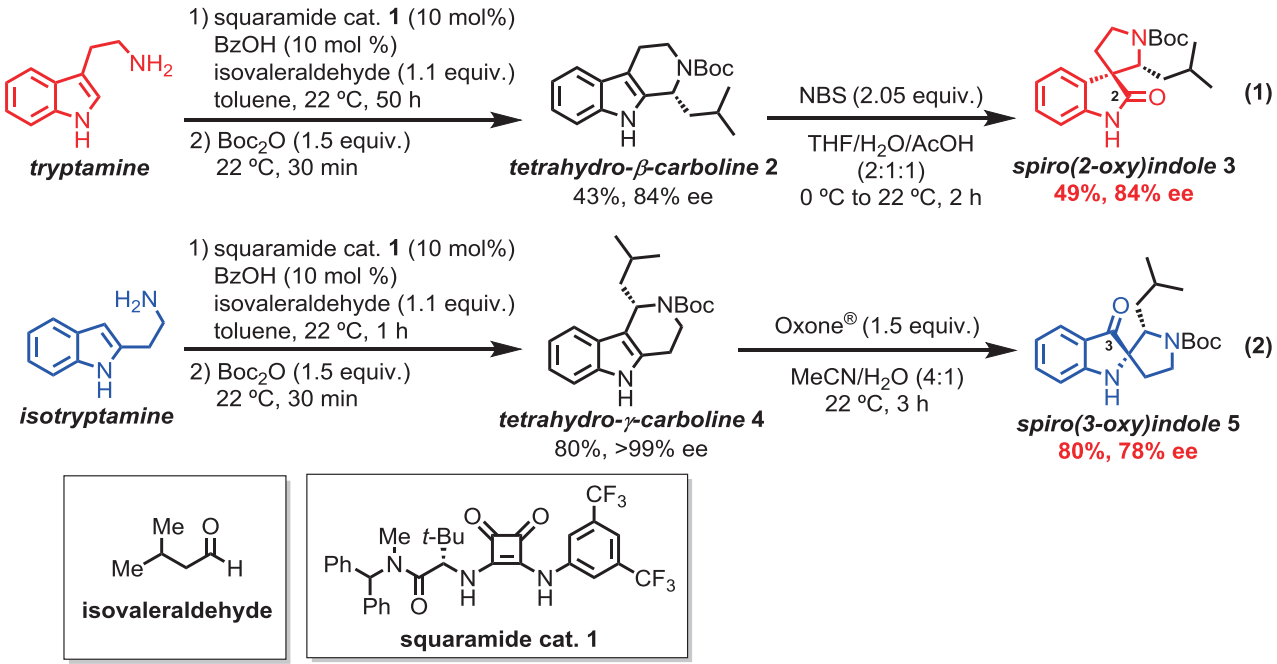
The chiral spirooxindole skeleton is recognized as an important substructure because the core motif can be seen in various biologically active compounds and natural products such as elacomine and fluorocurine. Although significant progress has been made in the asymmetric synthesis of diverse spirooxindoles, facile synthetic strategies capable of constructing multiple chiral centers from readily available substrates are still in high demand.[1,2]



Herein, we report the short enantioselective synthesis of spirooxindoles *via* organocatalyzed Pictet-Spengler reaction[3,4] and oxidative rearrangements of tryptamines. Initially, tryptamine, isovaleraldehyde and Boc_2O were treated with squaramide catalyst **1** (10 mol%) to afford tetrahydro-*β*-carboline **2** in 84% ee. Secondly, the oxidative rearrangement of **2** with *N*-bromosuccinimide (NBS) under acidic conditions provided spiro(2-oxy)indole **3** maintaining a high enantioselectivity. (eq. 1). Under the similar procedure, spiro(3-oxy)indole **5** was also obtained in 78% ee from isotryptamine *via* Pictet-Spengler reaction, followed by Oxone®-mediated oxidative rearrangement (eq. 2). In this presentation, the investigation of one-pot synthesis and substrate scope of Pictet-Spengler reaction and oxidative rearrangement will be also discussed.



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5F-C-1

Non-planar Porphyrinoids as Asymmetric Bifunctional Hydrogen-Bond Donor Catalysts

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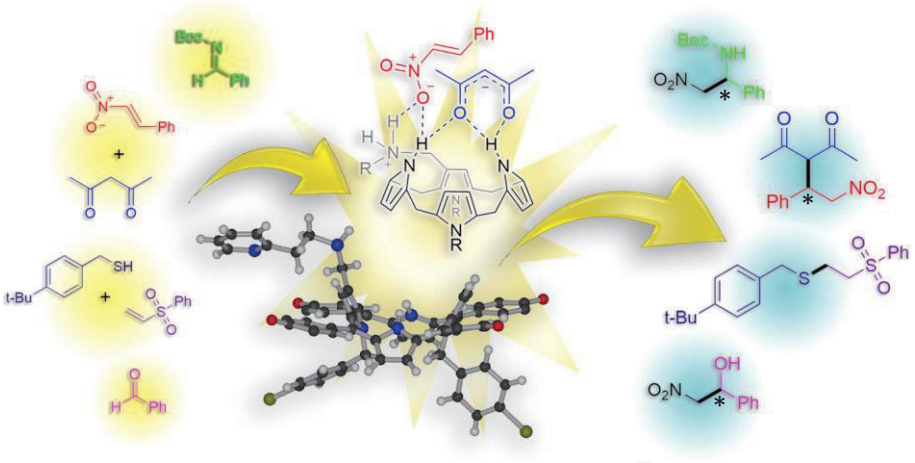

Porphyrins and related compounds have been extensively studied in catalysis as their metal complexes, indeed these type of complexes are key catalytic centres in 'nature's toolbox' carrying out a wide variety of transformations. On the other hand, their use as organocatalysts has been neglected because typically the porphyrin NH groups are internalized and therefore shielded by the macrocycle, inhibiting their use as catalysts [1]. In order to render porphyrins catalytically active non-planarity of the macrocycle must be induced in order to gain access to these NH moieties.

This presentation will outline the development and structure optimization of a new class of chiral macrocyclic hydrogen-bonding organocatalysts based on β-substituted oxoporphyrinogens and demonstrate their synthetic utility in a number of asymmetric transformations. Due to the inherent non-planarity and binding site rigidity of oxoporphyrinogens, alongside their ability to bind analytes including nitro and carbonyl species via hydrogen bonding interactions [2], these species have proven to be efficient organocatalysts. Spectroscopic investigation of the intermolecular interactions between the macrocycle and catalysis substrates have given us insight into the reaction mechanism and allowed for further optimization of catalytic activity.

Our results demonstrate the structural features required to render non-planar porphyrinoids catalytically active as hydrogen-bond donor catalysis and our studies have advanced this previously uninvestigated research area, demonstrating the first example of porphyrinoids as asymmetric organocatalysts [3].

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[3] M. K. Chahal, D.T. Payne, Y. Matsushita, J. Labuta, K. Ariga and J. P. Hill, *Manuscript submitted*

Desymmetrization of *gem*-Diols via Enantio- and Diastereoselective Cycloetherification Using Bifunctional Organocatalysts

Ryuichi Murata, Akira Matsumoto, Keisuke Asano,* and Seijiro Matsubara*
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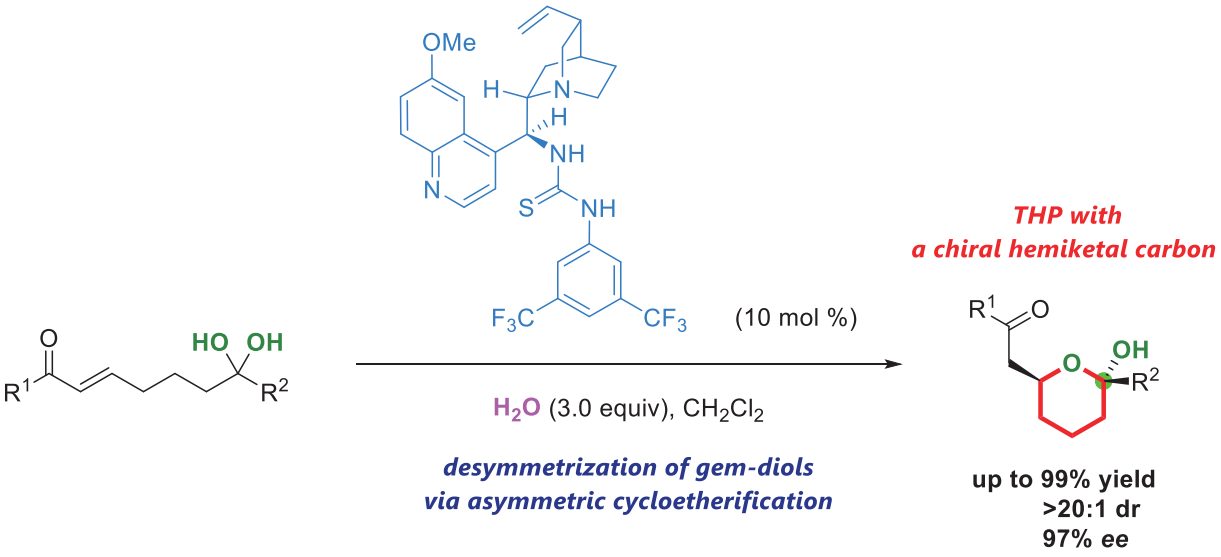
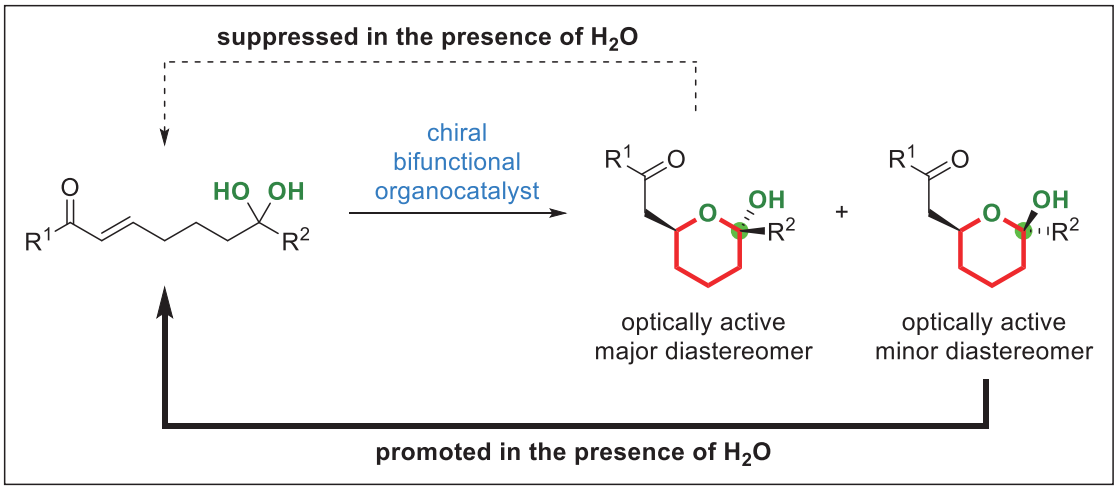
Desymmetrization of prochiral substrates is an efficient method for constructing tetrasubstituted chiral carbons; a number of methods for desymmetrization of diols were developed. However, desymmetrization of *gem*-diols forming chiral hemiketal carbons is unknown. In this study, the first desymmetrization of *gem*-diols was achieved via organocatalytic asymmetric intramolecular oxy-Michael addition. This transformation afforded an optically active tetrahydropyran skeleton bearing a chiral hemiketal carbon, which is a core structure in a range of bioactive compounds. The use of water enabled favorable isomerization between the diastereomers of the products, which was essential for the highly stereoselective desymmetrization.





5F-C-3

Chiral Vanadium Complex-catalyzed Enantioselective Oxidative Hetero-coupling Reactions of Arenols

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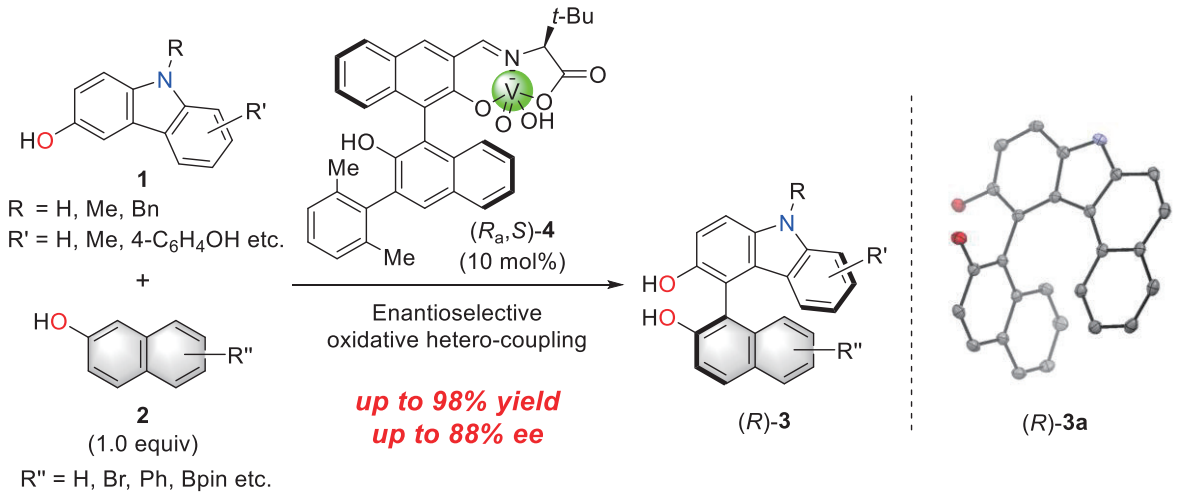
Optically active biarenol derivatives have played a significant role in the development of materials and pharmaceuticals due to their high potential as medicinal agents, chiral agents, and synthetic intermediates for natural products. Oxidative coupling reactions of arenols are powerful methods as a most straightforward synthetic tool for biarenols. To date, several enantioselective oxidative hetero-coupling reactions of arenols using copper, iron, and ruthenium catalysts have been reported, however, several issues have been remaining such as regio-, chemo- and enantioselectivity.

Herein, we report vanadium-catalyzed[1] enantioselective oxidative hetero-coupling reaction of 3-hydroxycarbazoles with 2-naphthols. When 3-hydroxycarbazole derivatives **1** and 2-naphthol derivatives **2** (1.0 equiv) were treated by mononuclear vanadium complex (R_a,*S*)-**4**[2] (10 mol %) in the presence of LiCl (3.0 equiv) under air, hetero-coupling product **3** was preferentially obtained in up to 98% yield with up to 88% ee. The homo-coupling products of **1** and **2** were obtained less than 5% yield, respectively. The present catalytic system exhibited good tolerance for functional groups such as free phenolic hydroxy, bromo, and pinacolate boryl groups. The absolute configuration of hetero-coupling product **3a** was determined to be *R* form by X-ray analysis. In this presentation, mechanistic studies for oxidative hetero-coupling reaction will also be discussed.



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Regiospecific *N*-Arylation of Aliphatic Amines under Mild and Metal-Free Reaction Conditions

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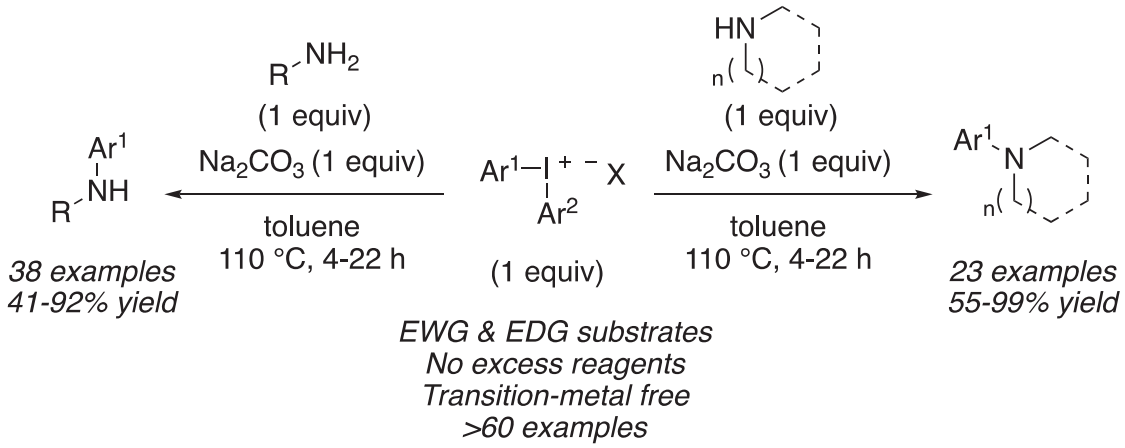
Stockholm University SE-106 91 Stockholm, Sweden

Diaryliodonium salts are versatile electrophilic arylating agents that are non-toxic, bench stable, and easily available via one-pot reactions from iodoarenes or arenes.[1] They can be applied in a variety of transition metal-free *C-, N-, O-* and *S*-arylations.[2] While the *N*-arylation of amides, anilines and some heterocycles has been reported,[2-3] aliphatic amines have been problematic substrates. To date, only the arylation of cyclic, secondary amines with electron deficient diaryliodonium salts has been established.[4]

Herein we present an efficient transition-metal free arylation of a wide range of primary and secondary amines with diaryliodonium salts.[5] Both acyclic and cyclic amines successfully provided a large set of *N*-alkyl anilines. The reactions are high yielding without excess reagents and diaryliodonium salts with both electron-withdrawing and electron-donating substituents could be employed (Scheme 1).



Scheme 1: N-arylation of primary and secondary amines with the aid of diaryliodonium salt and no excess reagents.

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5F-D-1

Chemo–enzymatic total synthesis of tetrahydroisoquinoline alkaloids exhibiting potent DNA alkylating ability

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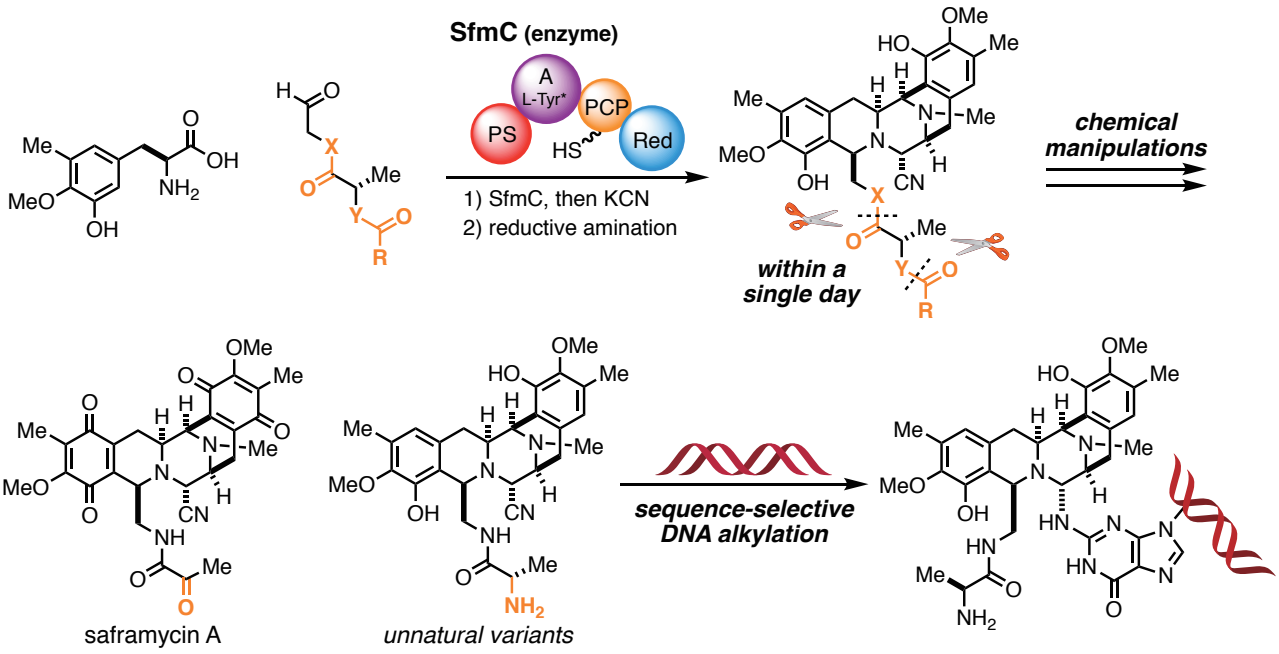
The anti-tumor tetrahydroisoquinoline (THIQ) alkaloids share a common pentacyclic scaffold. We previously revealed a unique biosynthetic mechanism to forge this scaffold catalyzed by SfmC, a module of non-ribosomal peptide synthetases.

Herein we report the chemo-enzymatic synthesis of saframycin A, saframycin Y3, jorunnamycin A and their variants. By streamlining the linkage between SfmC-catalyzed multi-step enzymatic conversions and chemical manipulations, we succeeded in efficient assembly of the appropriately functionalized pentacyclic skeleton within a single day from two simple synthetic substrates.

Further functional group manipulations involving removal of the side chain and oxidation allowed operationally simple and expeditious synthesis of THIQ alkaloids. Furthermore, we demonstrated that synthetic variants exhibit the potent DNA alkylating abilities superior to naturally occurring cyanosafracin B.



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5F-D-2

Heterocyclic Photocages for Carbohydrates

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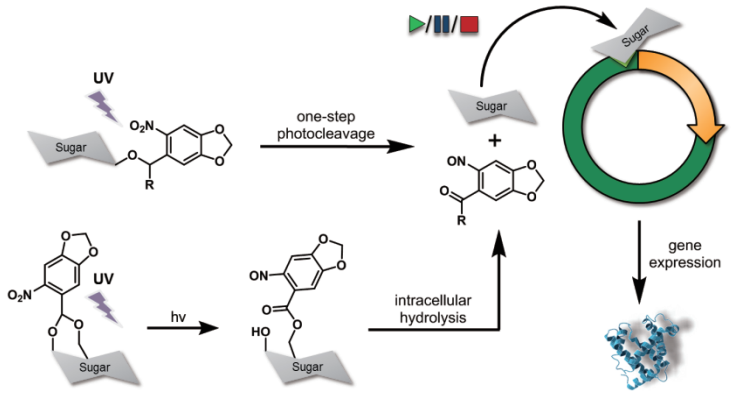
Photocaged compounds consist of an effector molecule and a photolabile protecting group, which enables the release of a biologically active substance by irradiation with a specific wavelength. Different heterocyclic compounds - coumarin and 6-nitropiperonyl derivatives – were utilized as photolabile protecting groups. The release of the effector molecule ensues with high spatiotemporal resolution, rendering the photolabile protecting groups not only beneficial for orthogonal deprotection in synthesis but also a crucial optogenetic tool for both biophysical and neurochemical examinations.[1-3] Our investigations focus upon the modification of the photolabile protecting group and in addition to it on the various types of biological effector molecules, giving us access to an extensive library of photocaged carbohydrates. A versatile toolbox was compiled und employed for a variety of synthetic biological and biotechnological applications.[4-6]



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5F-D-3

ANP77: A Three-carbon Atom Linked 2-Amino-1,8-naphthyridine Dimer that Recognizes Cytosine Rich Bulge-mismatched Sequences in Duplex DNA and RNA

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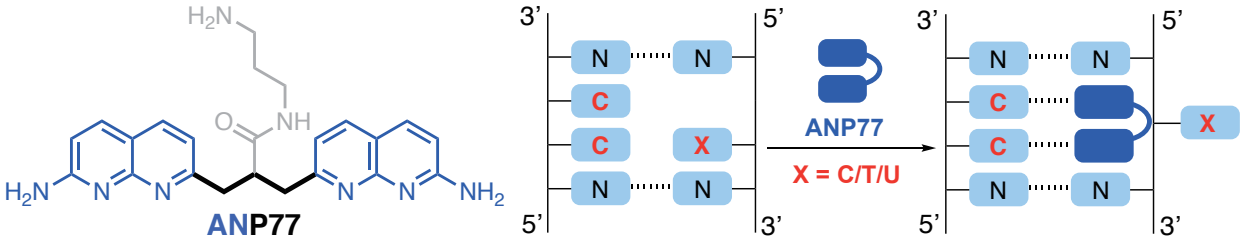
Bulged and mismatched structures in nucleic acids are of biological significance, arises as the consequence of replication or recombination errors and proposed to play crucial roles in many biomolecular processes that induce negative consequences on human health.[1-2] Sequence-specific recognition of these structures by small molecules is believed to be a promising tool for the development of novel chemotherapeutic agents. In continuation of our research on hydrogen-bonding-mediated sequence-specific recognition of the bulged and mismatched base pairs in duplex DNA and RNA by 2-amino-1,8-naphthyridine derivatives,[3-4] we have recently discovered a small molecule **ANP77**.[5]

ANP77 consists of two 2-amino-1,8-naphthyridine units, connected by a three-carbon atom linker that selectively recognizes the bulge-mismatched structures of dsDNAs and dsRNAs. The most efficient binding of **ANP77** to the bulge-mismatched site was observed for the sequences 5'-_C-3'/3'-CC-5' and 5'-_T(or U)-3'/3'-CC-5' with the formation of a 1:1 complex. Based on the binding studies and chemical analysis of the **ANP77** bound duplex DNA containing _T/CC site we proposed that two heterocycles in **ANP77** are supposed to be in folding orientation and stacks on to the bulge-mismatch site of the DNA helix with concomitant flip out of the thymine opposite to CC from the π-stack. Cytosine rich bulge-mismatched sites are a secondary structural element of many ncRNAs (such as pri-miRNAs or pre-miRNAs). ncRNAs play a crucial role in many biological processes and have functions in the regulation of gene expression. Therefore, **ANP77** could modulate the functions of ncRNAs by binding to r(_C/CC) or r(_U/CC).



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5F-D-4

Biologically Active Novel Nitrogen Heterocycles Containing the Benzoazepine Moiety

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Chemical compounds with the dibenzazepine moiety have found use in a range of areas, most prominently as drugs for the treatment of heart conditions, neuropsychiatric disorders, as well as in the search for novel structures for the treatment of cancer. However, access to azepine containing scaffolds with high degrees of substitution has remained a challenge and typically requires long synthesis strategies. The dihydrobenzo[6,7]azepino[3,2-*c*]quinolinones have remained largely unexplored with only a few examples in the literature showing the dihydrobenzazepine scaffold.

We report a robust and simple synthetic pathway to access a novel series of 7-phenyl-7,13-dihydro-8*H*-benzo[6,7]azepino[3,2-*c*]quinolin-8-one derivatives via an initial addition-oxidation-ring cleavage cascade reaction under basic conditions in the presence of NaOH in DMSO. A subsequent T3P® in DMF catalysed cyclisation reaction gave the fused quinoline ring incorporating the one carbon unit from the DMF (**Figure 1**). Reaction with aldehydes or ketones with T3P® in ethyl acetate as the catalyst, gave the corresponding C6 substituted compounds. The key feature of this synthetic pathway is that it provides rapid access to a new class of heterocyclic compounds, namely benzo[6,7]azepino[3,2-*c*]quinolin-8-ones. A high level of substitution is possible around the core scaffold allowing for diverse functionalisation to be achieved. Furthermore, this methodology can be applied to access a new class of indole-based derivatives that are yet to be reported. These compounds possess moderate anti-cancer activity and have significant potential for further development.[1]

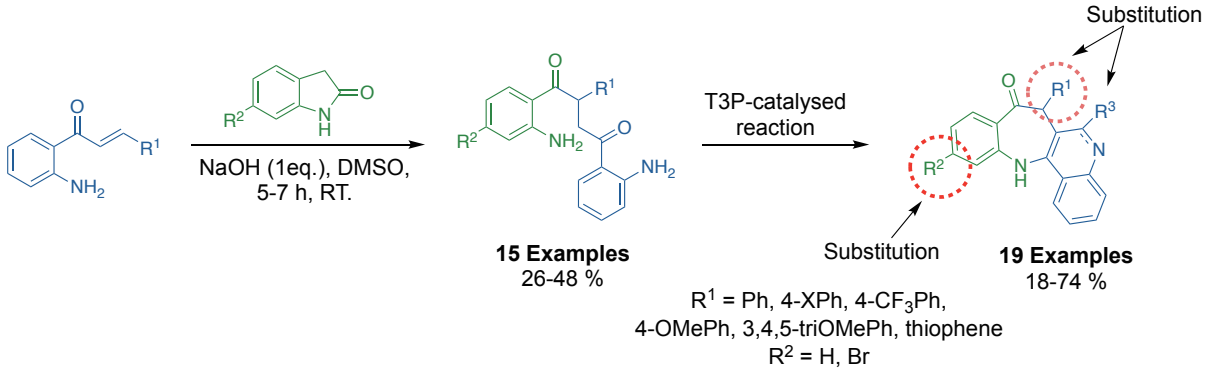

Figure 1: Novel highly functionalised 7-phenyl-7,13-dihydro-8*H*-benzo[6,7]azepino[3,2-*c*]quinolin-8-one derivatives.

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ABSTRACTS OF POSTER SESSIONS

Sep. 2nd, RoomE (Miyako Messe 2nd Exhibition Hall ＜ B/C ＞)

2P-001 ～ 2P-145

Sep. 3rd, RoomE (Miyako Messe 2nd Exhibition Hall ＜ B/C ＞)

3P-001 ～ 3P-145

Sep. 5th, RoomE (Miyako Messe 2nd Exhibition Hall ＜ B/C ＞)

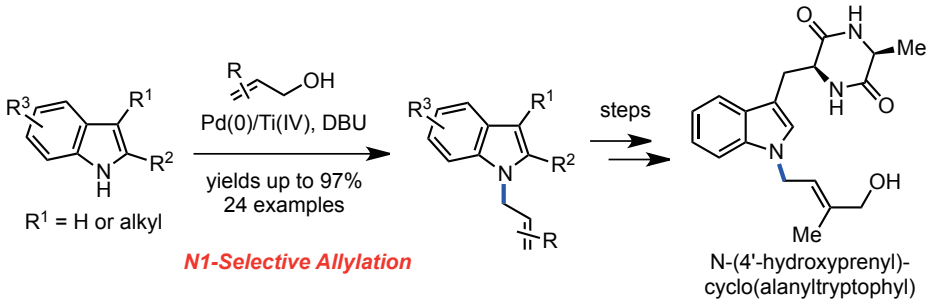
5P-001 ～ 5P-144

2P-001

Palladium-Catalyzed N1-Selective Allylation of Indoles with Allylic Alcohols

Chieh-Yu Chang, Yu-Huan Lin and Yen-Ku Wu*
Department of Chemistry, National Chiao Tung University, Hsinchu 30010, Taiwan

Indoles are prevalent structural motifs in natural products, pharmaceutical agents, and organic electronic materials. Catalytic selective functionalization of this privileged scaffold represents the focus of numerous synthetic studies. More specifically, extensive efforts have been undertaken to develop methods for the regioselective allylic alkylation of indole nucleophiles at N1 and C3 sites. Here we describe a direct N1-selective allylation of indoles with allylic alcohols enabled by synergistic functions of palladium catalysts and titanium tetraisopropoxide.[1-2] The site selectivity is notably different from that observed in other related transition metal-catalyzed approaches. This chemistry provides a facile route to a variety of allylated indoles in synthetically useful yields. The utility of this simple allylation reaction was demonstrated with the first total synthesis of (+)-N-(4′-hydroxyprenyl)-cyclo(alanyltryptophyl), which was completed in five steps, starting from L-tryptophan methyl ester hydrochloride.



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2P-002

Synthesis and plant growth stimulating activity of morpholine and piperidine ionic compounds

A. Zazybin[1,2]*, D. Zolotareva[2], Ye. Belyankova[1], A. Dauletbakov[1,2], V. Yu[3], B. Anapiyayev[2], S. Mergenbaeva[2], Zh. Tokenova[1], A. Tolstova[1]

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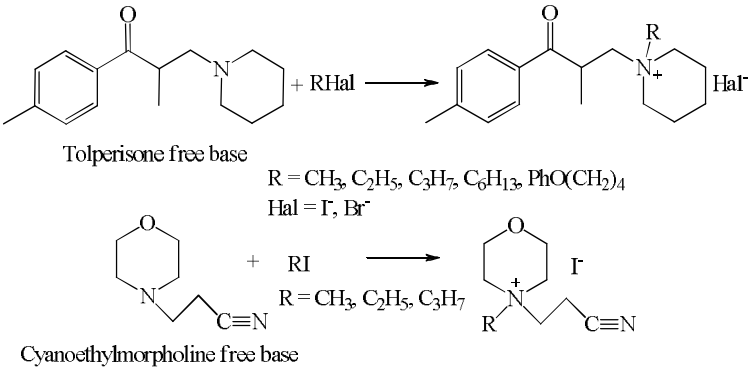
The range of N-alkyl derivatives of tolperisone and cyanomorpholine were synthesized via quaternization of tertiary amines:



New compounds have been experimentally studied for the following groups of biological activity: 1. Ecotoxicity (bioluminescence method); 2. Cytotoxicity (humans healthy and cancer cells); 3.Growth-stimulating activity (corn, wheat, sorghum).

Methyl derivative of tolperisone can be characterized (Passino and Smith, [1]) as relatively nontoxic compound against *Vibrio fischeri* bacteria. All tolperisone derivatives showed cytotoxic effect on Human ovarian cancer cell A2780, Human ovarian cancer cell A2780 CIS R and Human embryonic kidney cells HEK.

Tolperisone and cyanoethylmorpholine ionic derivatives showed higher plant growth stimulation activity in comparison with water. In addition, the studied compounds showed noticeable increase in seed germination, also the sprouts developed an extensive root system.

This work was financially supported by the Ministry of Education and Science of Kazakhstan [AP051032833/GF5, BR05236800/PTF, BR0526302/PTF, AP05131025/GF5, BR052344667/PTF].

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2P-003s

Synthesis of novel 2*H*-pyrazolo[4,3-*c*]pyridines and investigation of their anti-mitotic activity

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Pyrazole is a common structural unit in many pharmaceuticals and numerous ongoing studies are devoted to the synthesis and biological evaluation of novel pyrazole moiety-bearing molecules. Annelated pyrazoles are of particular interest as they constitute the core of several well-known drugs, including Sildenafil, Zaleplon and Allopurinol. Among the vast variety of up to now developed biologically active annelated pyrazole derivatives, 2*H*-pyrazolo[4,3-*c*]pyridines are, however, relatively understudied.

The aim of this study was to synthesize 2*H*-pyrazolo[4,3-*c*]pyridines, primarily varying by the substituents at the 2-, 4- and 6-positions. A Sonogashira-type cross-coupling reaction was employed to yield 3-alkynyl-1*H*-pyrazole-4-carbaldehydes, ethanones and propanones from the corresponding 1*H*-pyrazol-3-yl trifluoromethanesulfonates. Subsequent treatment of the coupling products with dry ammonia afforded a versatile library of 2*H*-pyrazolo[4,3-*c*]pyridines.

Newly prepared 2*H*-pyrazolo[4,3-*c*]pyridines were evaluated for their cytotoxicity against K562 and MCF-7 cancer cell lines. The most potent compounds displayed low micromolar GI_{50} values in both cell lines. The active compounds induced dose-dependent cell-cycle arrest in mitosis, as shown by flow cytometric analysis of DNA content and phosphorylation of histone H3 at serine-10. Moreover, biochemical assays revealed increased activities of caspases-3/7 in treated cells, specific fragmentation of PARP-1, and phosphorylation of Bcl-2, collectively confirming apoptosis as the mechanism of cell death. The mechanism of cellular action of these compounds, however, still remains unclear.

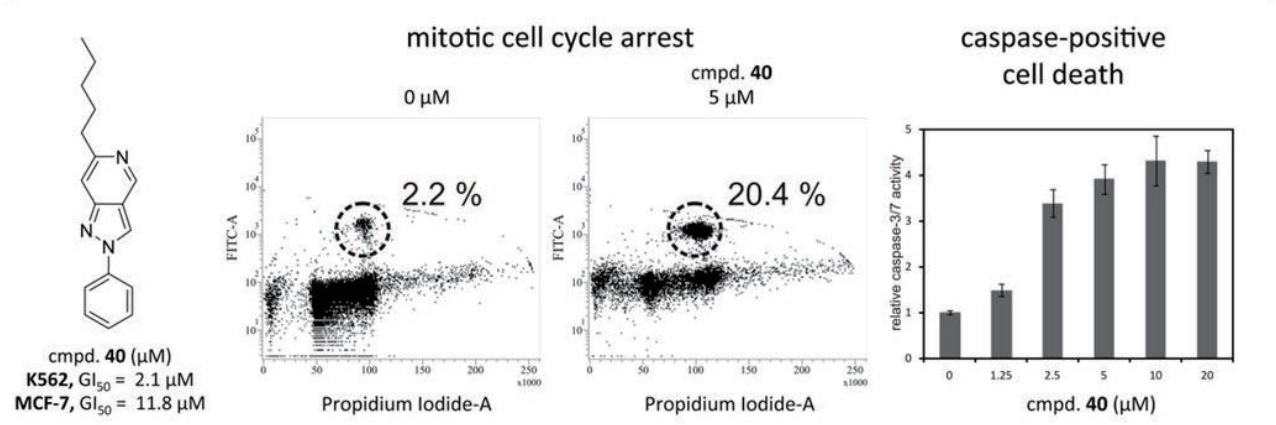

Fig. 1 Biological activity of the lead compound **40**

2P-004s

Enantioselective Photocatalysis utilizing 7-Azaindolines as an Auxiliary: Challenges and Opportunities

Santosh. K. Pagire, Naoya Kumagai,* Masakatsu Shibasaki*
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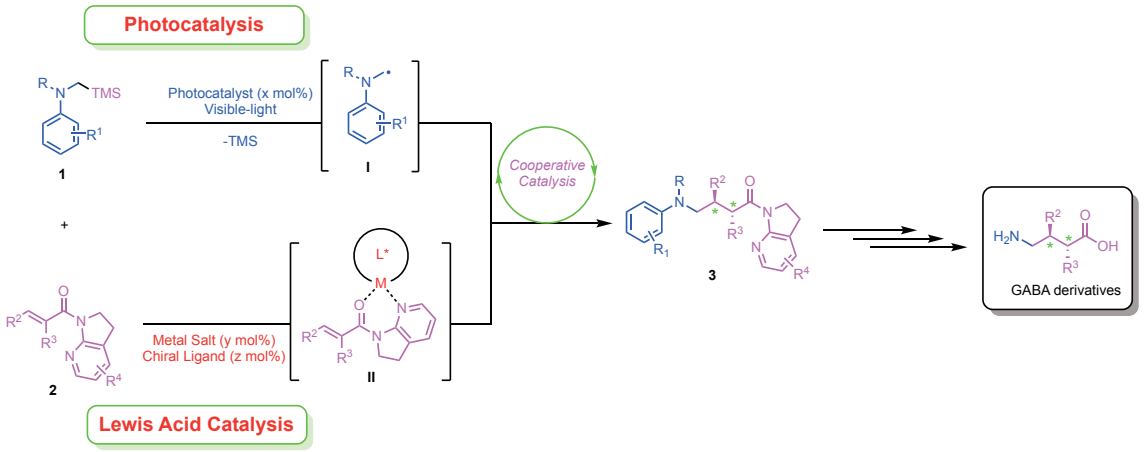
Recently, the area of visible-light photocatalysis has blossomed tremendously, which has been emerged into a handful tool in recent organic synthesis. The photocatalytic reactions are clean, waste reducing, proceeds under milder reaction conditions. Moreover, it can be coupled with asymmetric catalytic reactions to access the valuable chiral molecules. Arguably, the resulting molecules are typically difficult to accomplish utilizing other non-photocatalytic methods.

In this context, we envisioned to couple a photocatalytic cycle together with the Lewis acid catalytic cycle to achieve chiral γ-Amino Butyric Acid derivatives (GABA). They are important structural motif in many natural products and bioactive compounds. For example, (*S*)-Pregabalin, (*S*)-Baclofen, (*R*)-Rolipram, Arbaclofen Placarbil are important drug candidates, therefore, highly demanded as synthetic target.
Among many synthetic methodologies allowing creation of that structural pattern, direct *C*−*C* bond formation with simple starting materials and efficient catalytic systems remains an ideal. To achieve this synthetic goal, the metal catalyzed Michael reaction between amines 1 and 7-azaindolines 2 was utilized. However, there are several challenges to carry out these type reactions in a smooth way. This will be discussed in detail during the oral presentation.



2P-005s

Enamides as versatile tools for the stereoselective construction of heterocycles

P. Kramer, Prof. G. Manolikakes*
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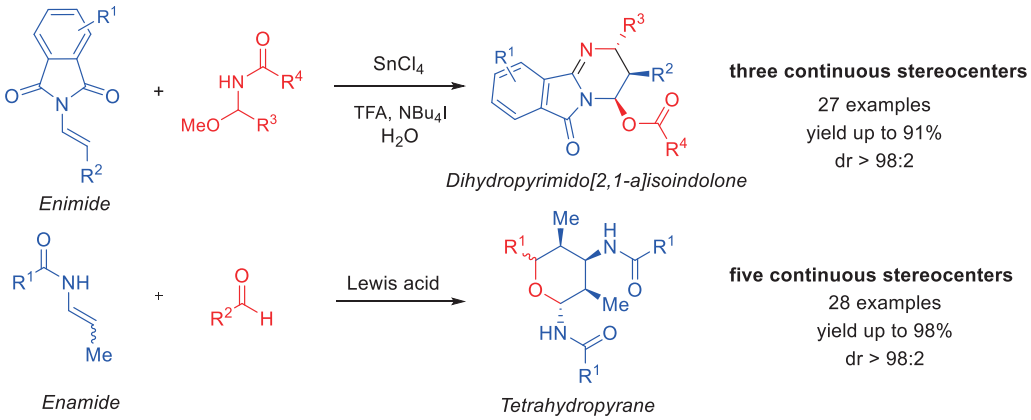
Heterocycles constitute the most common motif in natural products and biologically active molecules. Therefore, there is a sustained interest in novel methods for the efficient construction of all kinds of heterocycles, in particular for uncommon or so far inaccessible structures.[1] In the last few years enamides and enimides have become a useful tool for the synthesis of heterocyclic scaffolds and biologically active molecules.[2]

Herein we want to present two novel methods for the stereoselective construction of unusual heterocyclic scaffolds using enamides as central building block.

Based on our work on a stereodivergent synthesis of 1,3.-diamines[3], we could develop a stereoselective reaction sequence for the synthesis to highly substituted pyrimido[2,1-a]isoindolones.[4] Our reaction encompasses various substituted enimides and *N*-acyl-*N*,*O*-acetals to generate this so far inaccessible heterocyclic core. We could also extends the use of enamides towards a highly stereoselective synthesis of highly substituted tetrahydropyrans.[5] The reaction is based on the twofold addition of an enamide to an aldehyde followed by a ring closure. This novel transformation affords fully substituted tetrahydropyrans with five continuous stereocenters with an exceptional degree of diastereoselectivity.



Both reactions demonstrate the utility of enamides as tool for the construction of uncommon heterocyclic scaffolds with an excellent degree of stereoselectivity from simple building blocks.

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2P-006

Regioselective Addition of Quinoline Derivatives to Carbonyl Compounds via Pd-catalyzed Umpolung with Diethyl Zinc

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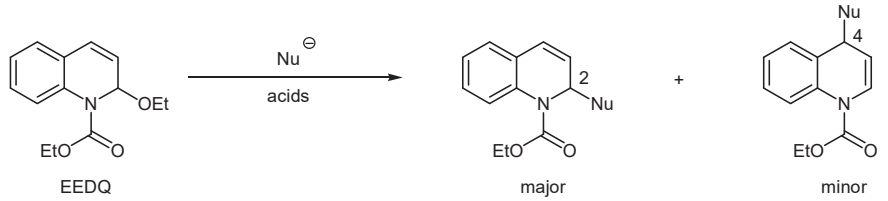
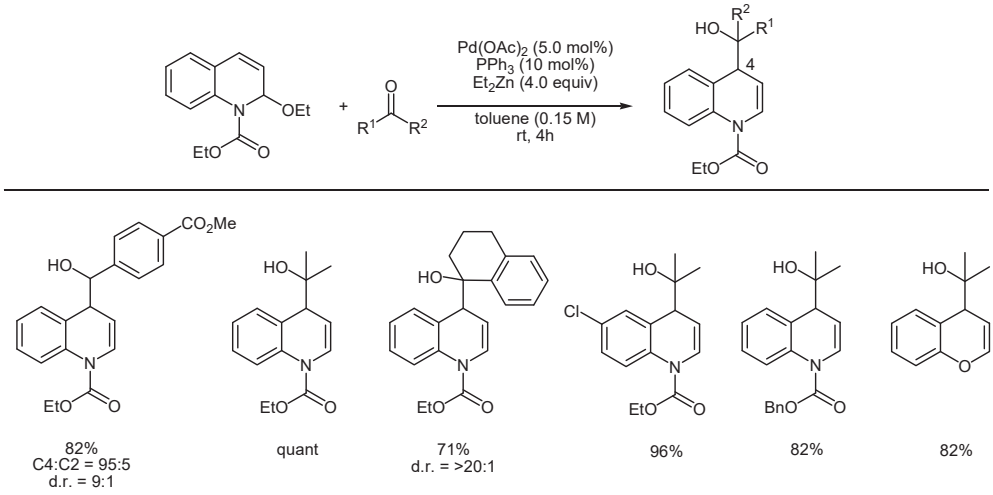
2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinolines (EEDQs) have been considered as useful *N*-acylquinolinium precursors, which have been substituted at the C-2 position by various nucleophiles. Under the reported reaction conditions, a small or negligible amount of C-4-substituted product was obtained, and C-4-selective reactions of EEDQs have not been disclosed, to the best of our knowledge.



In this abstract, an efficient method for the C-4-selective addition of quinoline derivatives to carbonyl compounds is described. Electrophilic Pd–allyl complexes are converted into nucleophilic allyl species in the presence of activating agents. The resultant nucleophilic Pd–allyl complexes are widely used for the allylation of a variety of electrophiles including aldehydes, ketones, and their equivalents. [1] In this context, we have developed C-4-selective substitution of piperidines with various electrophiles which involves the generation of the nucleophilic allyl species from 4-acetoxypiperidine derivatives with a Pd catalyst and Et_2Zn. [2] The combination of EEDQs with a palladium catalyst and Et_2Zn generates nucleophilic allyl species which undergo addition to various aldehydes and ketones. C-4-Substituted quinoline derivatives are obtained in high to excellent yields with high diastereoselectivities. [3]



[1] Tamaru, Y.; Tanaka, A.; Yasui, K.; Goto, S.; Tanaka, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 787.
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2P-007

Canceled

N,N'-Bis(trimethylsilyl)dihydropyrazine as a Salt-free Reductant for Ni-catalyzed Reductive C-C Bond Formation of Aryl Halides

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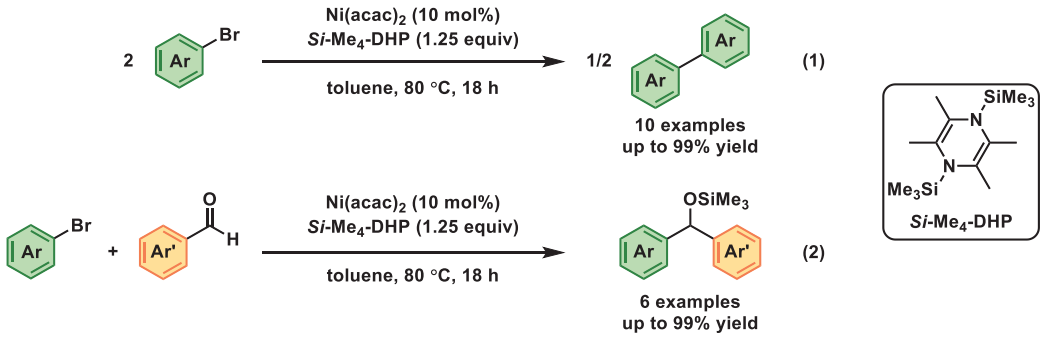
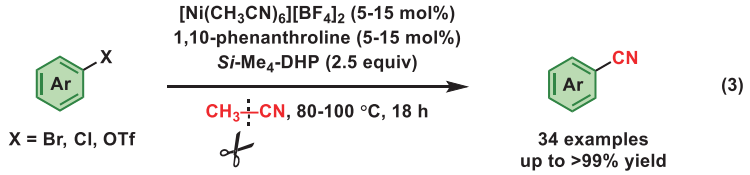
Chemical reduction of high-valent metal complexes provides low-valent transition metal species as a key step for generating catalytically active species in metal-assisted organic transformations. Improvement of a reductant is highly demanded in view of high reducing ability and removability of the reductant-derived waste from the reaction mixture. In this context, we have developed an organosilicon-based reductant, 1,4-bis(trimethylsilyl)-2,3,5,6-tetramethyldihydropyrazine (*Si*-Me$_4$-DHP), which served as two electron reductant for a variety of transition metal complexes with a release of easily removable 2,3,5,6-tetramethylpyrazine and trimethylsilyl derivatives.[1] Noteworthy is that *Si*-Me$_4$-DHP reduces halides, carboxylates, and acetylacetonates (acac) of several late transition metals for producing the corresponding metallic(0) NPs under mild conditions.[2] Among the NPs generated by this salt-free reduction method, we found that amorphous nickel(0) NPs showed high catalytic activity for the reductive C—C bond formation of aryl halides (eqs 1 and 2).



In addition to the aforementioned carbon—halogen bond cleavage reaction, our catalytic system can be applicable to the C-CN bond formation *via* cleavage of C-CN bond cleavage of acetonitrile: we found that a mixture of [Ni(CH$_3$CN)$_6$](BF$_4$)$_2$ and 1,10-phenanthroline became a catalyst for cyanation of aryl halides and aryl triflates using acetonitrile as a cyanide source in the presence of a stoichiometric amount of *Si*-Me$_4$-DHP, the latter of which functioned for reducing the nickel precursor and mediating the cyanation reaction (eq 3).[3]



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2P-009

Pyrrole Ring Formation from the Amido-substituted Benzoquinone Derivatives via Palladium Catalyzed Carbon-hydrogen Bond Functionalization

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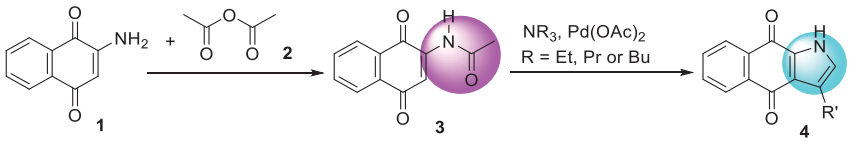
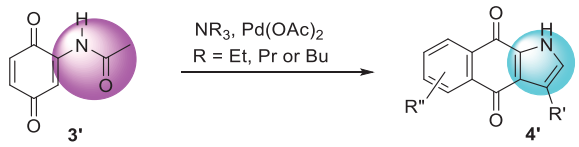
We have shown a fascinate pathway for the making of a new pyrrole ring in the product, **4**, from the reaction of an amido-substituted benzoquinone, **3**, with tertiary amines (Scheme 1).[1] The directing group amido-substituent in **3** is essential to the reaction. Here, tertiary amine plays two roles: as a reactant and base.

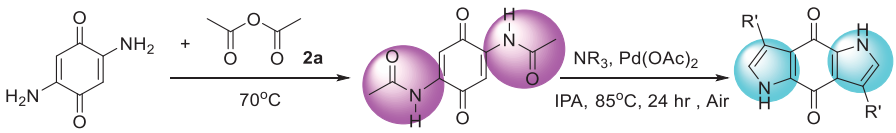


Scheme 1. The formation of a new pyrrole ring in **4** via palladium-catalyzed reaction of **3**

Our preliminary results also showed that unexpected extra benzene ring was formed from similar reaction (Scheme 2). The organic fragment of tertiary amine is incorporated to the newly-formed aryl ring. Based on the above results, it is expected that cyclization on both sides of the di-substituted benzoquinone to be occurred as proposed below (Scheme 3). More interesting results will be presented.



Scheme 2.



Scheme 3. Proposed pathways for the formations of double pyrrole rings

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2P-010

Hypoiodite-catalyzed Chemoselective Oxidative Generation of *ortho*-Quinone Methides and Tandem Reactions

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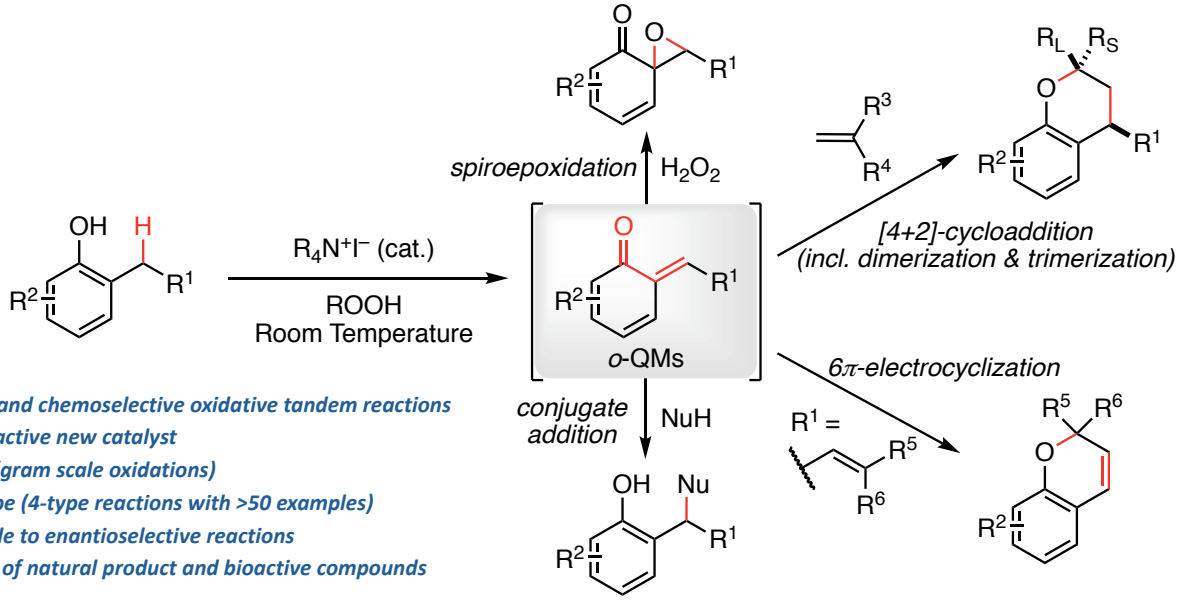
orho-Quinone methides (*o*-QMs) are extensively used as highly reactive transient intermediates in organic synthesis and biological processes.[1] *o*-QMs react with various classes of reagents by three typical reaction pathways: 1,4-addition of nucleophiles, [4+2]-cycloaddition with 2π dienophiles and oxa-6π-electrocyclization. Because most *o*-QMs are unstable and, therefore, nonisolable, the scope of these reactions generally depends on the reaction conditions used for the generation of *o*-QMs *in situ*. Conventionally, these unstable intermediates are generated *in situ* by thermolysis, photolysis, tautomerization, and acid- or base-promoted transformations of salicylic alcohol derivatives.[1] Biomimetic oxidative generation from the corresponding *ortho*-alkylphenols has also been developed, however, toxic heavy metal oxidants or transition metal complexes have been required.[1]
Recently, we have developed environmentally benign oxidative dearomatization of phenols catalyzed by hypoiodite salts,[2] which are generated *in situ* from the corresponding iodides with hydrogen peroxide or alkyl hydroperoxide (ROOH) as an oxidant.[3,4] Here, we report a new chemoselective *in situ* generation method of *o*-QMs through oxidation of *ortho*-alkylphenols using hypoiodite catalytic system, and synthetic application of *o*-QMs to tandem reactions such as spiroepoxidation, 1,4-addition, [4+2]-cycloaddition and 6π-electrocyclization.[5] Moreover, we investigated the reaction mechanism of the oxidative generation of *o*-QMs by kinetics studies and several control experiments.



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2P-011

A Rapid Synthesis of Substituted Oxazoles via PIFA-Mediated Oxidative Cyclization of Enamides

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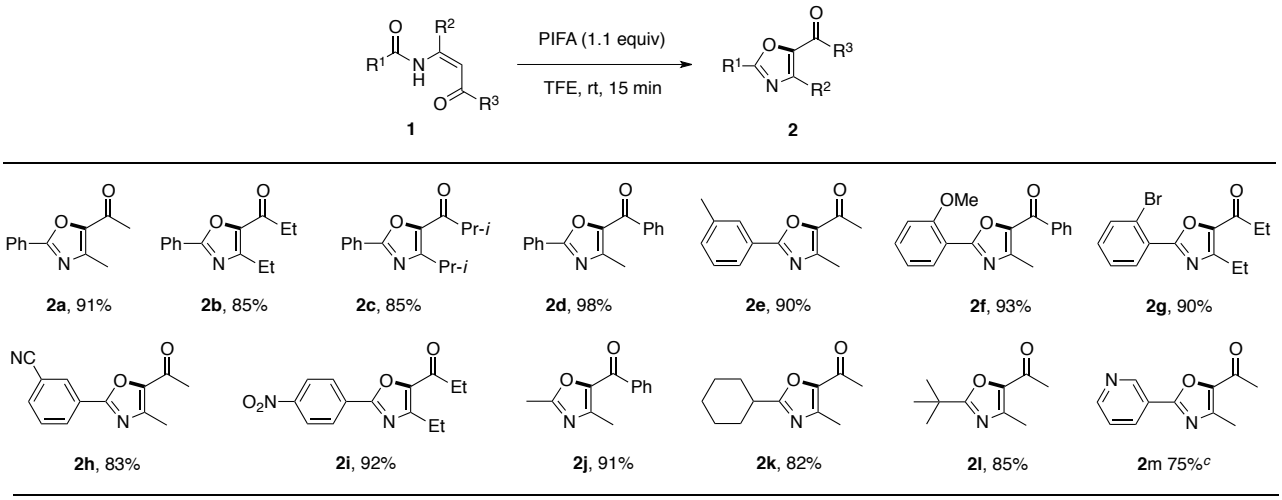
Oxazoles are one of the valuable scaffolds existing in a wide variety of biologically active compounds, such like pharmaceuticals and agrochemicals. Therefore, various synthetic methods have been developed for the synthesis of oxazoles. However, the existing methods suffer from some disadvantages, such as the requirement of Brønsted acid catalysts, transition-metal catalysts, Lewis acid reagents, or previously prepared substrates, which limit the overall functional group tolerance of the transformation. In this report, we disclose the successful phenylbis(trifluoroacetyl)iodine (PIFA)-mediated rapid and highly efficient access to substituted oxazoles with broad substrate scope by the use of trifluoroethanol (TFE) as solvent.

Reaction of enamide **1a** (R^1=Ph, R^2=R^3=Me) derived from benzamide and acetylacetone with PIFA (1.1 equiv) in TFE at room temperature for 15 min afforded the desired oxazole **2a** in 91% isolated yield. A reaction without the use of PIFA did not take place. Another solvents (CH_3CN, CH_2Cl_2, $(ClCH_2)_2$, and EtOH) with the use of PIFA resulted in the unsatisfactory yields (11-27%). Iodobenzene diacetate (PIDA) also afforded a good yield (81%) of product under the conditions.

We carried out the cyclization of several enamides under the optimized conditions. Regarding the R^2 and R^3 substitutions, alkyls (**2b** and **2c**) and aromatic (**2d**) accept the transformation. Substitutions at the aromatic ring did not influence the reactivity in spite of the electronic nature and positions (**2e**, **2f**, **2g**, **2h** and **2i**). Displacement of benzene ring to alkyls (**2j**, **2k**, and **2l**) including a sterically hindered (**2l**) and heteroaromatic one (**2m**) did not influence the reactivity.



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Trialkylborane-Mediated Propargylation of Aldehydes and New Synthetic Approach to 2,3,5-Trisubstituted Furans by Brønsted Catalysis

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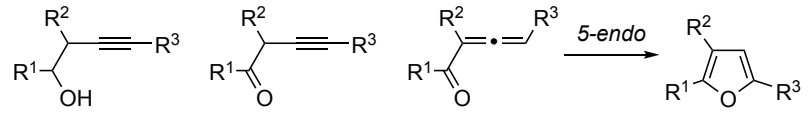
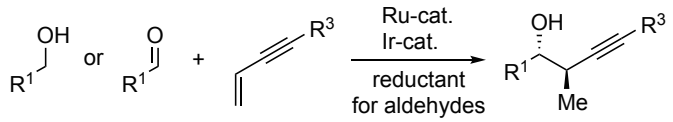
Graduate School of Science and Engineering, University of Toyama, 3190 Gofuku, Toyama 930-8555, Japan

The presence of furan scaffold in pharmaceuticals, bioactive natural products, and polymers is well-documented. Based on cycloisomerization and cyclization processes, hence, a range of transition metal-catalyzed furan syntheses have been developed (Scheme 1a).[1] Recent advances in the preparation of homopropargylic alcohols have contributed to the development of new methods of accessing to furans as the majority of those reported have used homopropargylic alcohols and their derivatives. However, most of these synthetic methodologies suffer from multistep routes to yield the 1,2,4-trisubstituted-homopropargylic alcohols and their derivatives. Although general synthetic methods for such compounds involve the addition reactions of propargyl/allenyl metal or metalloid to aldehydes, they are limited scope. While enyne-aldehyde reductive coupling (Scheme 1b)[2] and Marshall-Tamaru reaction (Scheme 1c)[3] constitute the most straightforward catalytic process to these compounds, the former relies on the enynes containing a terminal alkene and the latter suffers from poor functional-group-tolerance as well as regioselectivities of the reactions for allenyl versus propargyl products. Thus, devising new synthetic strategies for preparing homopropargylic alcohols from simple precursors is still of importance to provide more efficient approaches to substituted-furan synthesis. In our previous work, we disclosed a trialkylborane-mediated multicomponent reaction using aldehydes, 3-(tributylstannyl)propargyl acetates, and trialkylboranes, which provides *anti*-δ,δ-disubstituted homoallylic alcohols.[4] Herein, we report a trialkylborane-mediated three-component reaction to give a diverse range of homopropargylic alcohols (Scheme 1d). In addition, we also describe a successful development of DMP/Brønsted acid-promoted cascade oxidation/cyclization of homopropargylic alcohols to afford 2,3,5-trisubstituted furans.

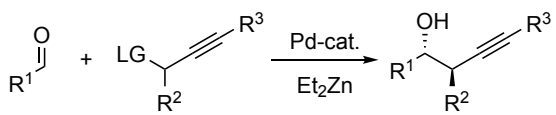
(a) ***Furan syntheis from homoallylic alcohols and their derivatives***



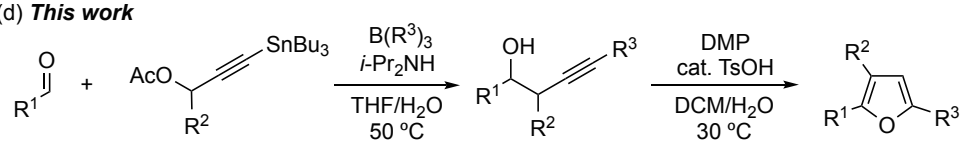
(b) ***Ru- or Ir-catalyzed enyne-aldehyde reductive coupling***



(c) ***Marshall-Tamaru reaction***



(d) ***This work***



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2P-013s

Catalytic photo-oxygenation enables inhibition of tau amyloid formation

Taka Sawazaki, Takanobu Suzuki, Yusuke Shimizu, Yu Nemoto, Atsuhiko Taniguchi, Shuta Ozawa, Yukiko Hori, Taisuke Tomita, Youhei Sohma, Motomu Kanai

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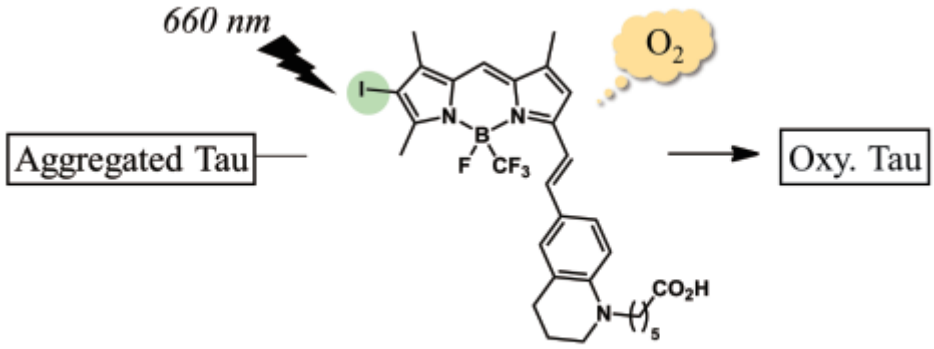
2. Laboratory of Synthetic Organic Chemistry, Graduate School of Pharmaceutical Sciences, The University of Tokyo,

Alzheimer disease (AD) is caused by accumulations of amyloid proteins with a cross-β-sheet structure, which are composed of amyloid-β peptide (Aβ) and tau. Among these two types of amyloid accumulation, the distribution of tau amyloid is known to be associated with cognitive decline. Prion-like tau propagation is a mechanism involved in the spreading of tau pathology. Therefore, the inhibition of tau propagation might have therapeutic effects on AD. Previously, we developed photocatalysts, which selectively oxygenated Aβ amyloid upon light irradiation via binding to the cross-β-sheet structure. [1, 2]. The photo-oxygenation inhibited amyloid formation and the toxicity of Aβ. Here, we identified boron-dipyrromethene (BODIPY)-based photocatalyst **1**, which enabled efficient photo-oxygenation of tau amyloid. An iodine atom was introduced at the BODIPY, and tetrahydroquinoline-carboxylic acid was adopted at the electron donor part. In addition, a fluorine atom on the boron center was replaced with a more electron-withdrawing trifluoromethyl group to increase the photostability of the BODIPY core [3, 4]. Photo-oxygenation using **1** markedly reduced the seeding activity of tau, resulting in inhibition of tau amyloid formation *in vitro* and in cultured cells [5]. This study indicates the usefulness of photo-oxygenation to suppress tau propagation for AD therapy.



photocatalyst **1**

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2P-014

Lewis Acid-Catalyzed Alcohol Addition Reactions to Cyclic Carbonyl Ylides Generated from Diazoacyloxazolidinones

Takayuki Yoshida,[†] Kaoru Arisue,[†] Hiroyoshi Esaki,[‡] Kazuaki Fukushima,[‡] Yasunori Toda,[†]and Hiroyuki Suga*,[†]

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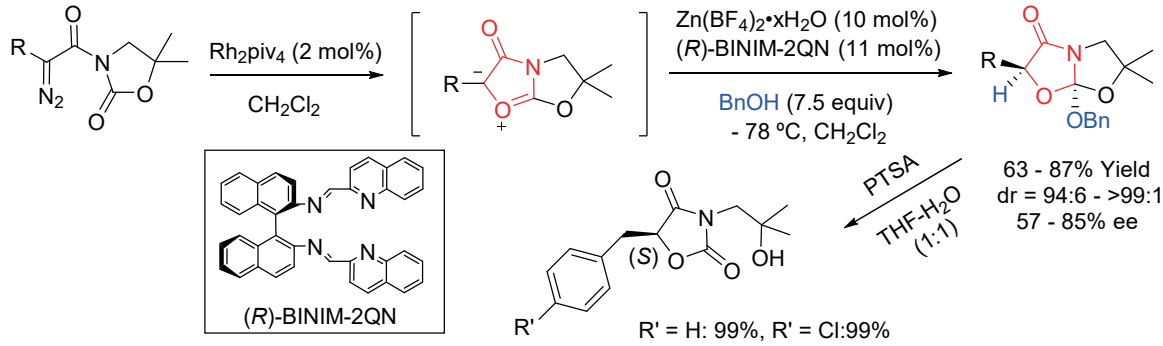
The Rh-catalyzed intramolecular carbenoid-carbonyl cyclization of diazocarbonyl compounds is known as one of the most efficient method for generating carbonyl ylides. The generated carbonyl ylides readily undergo cycloadditions with several dipolarophiles, such as olefins, acetylenes, aldehydes, and imines, to give complex epoxy-bridged compounds. For the past one and a half decades, we have demonstrated that the dual catalytic system consists of a Rh complex and a Lewis acid is effective in accelerating the cycloaddition and controlling the stereoselectivity.[1-4] However, a study on the effect of Lewis acids in carbonyl ylide reactions has been limited to the cycloadditions with dipolarphiles. In this symposium, we present the first example of Lewis acid-catalyzed alcohol addition reactions to cyclic carbonyl ylides and their asymmetric variants employing the dual catalytic system. The alcohol addition reactions to cyclic carbonyl ylides generated from α-alkyl-3-(diazoacetyl)-2-oxazolidinones were proceeded at -78 °C using the dirhodium tetrapivaloate/metal perchlorate system, affording unique heterobicyclic products with a quaternary heteroatom-substituted carbon and *trans* stereochemistry. An asymmetric variant of the reaction could be achieved with moderate to good enantioselectivities by using a Zn complex prepared from $Zn(BF_4)_2$•xH_2O and (*R*)-BINIM-2QN as a chiral Lewis acid. The conversion of the adducts to oxazolidine-2,4-dione derivatives and determination of the absolute configuration will also be reported.



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2P-015s

Total Syntheses of (–)-Secologanin, (–)-5-Carboxystrictosidine, and (–)-Rubenine

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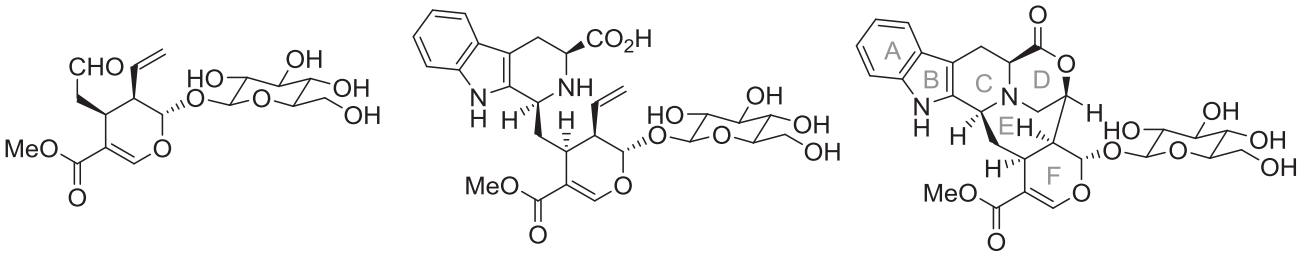
Monoterpenoid indole alkaloids form an important family of alkaloids, and over 3000 such alkaloids have been isolated from higher plants. Although a large number of total syntheses of non-glycosylated monoterpenoid indole alkaloids have been described, no glycosylated derivatives represented by (–)-5-Carboxystrictosidine (**1**)[1] have been reported. Among them, (–)-Rubenine (**2**)[2] possesses a complex ring system (rings A to F). The biosyntheses of monoterpenoid indole alkaloids are thought to proceed through Pictet–Spengler cyclization with either tryptophan or tryptamine, and (–)-secologanin (**3**)[3] as a common intermediate.

The first enantioselective total syntheses of **1**, **2**, and **3** were accomplished in 9, 14, and 10 steps, respectively. The key transformation in the synthesis of **3** was sequential *anti*-selective organocatalytic Michael reaction/Fukuyama reduction[4]/spontaneous cyclization to form an optically active dihydropyran ring. Subsequent seven-step transformations including diastereoselective glycosylation, hydroboration/oxidation, and sulfoxide elimination provided **3**. In addition, the secologanin tetraacetate, which is a potential key intermediate for bioinspired divergent syntheses of monoterpenoid indole alkaloids, was prepared in gram-scale quantities. Total syntheses of **1** and **2** were achieved through bioinspired transformations such as diastereoselective Pictet–Spengler reaction, site- and stereoselective epoxidation, and site-selective epoxide opening reaction followed by lactonization reaction.



secologanin 10 steps | **5-carboxystrictosidine** 9 steps | **rubenine** 14 steps

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2P-016

Formal Synthesis of (±)-Pentalenolactone A Methyl Ester

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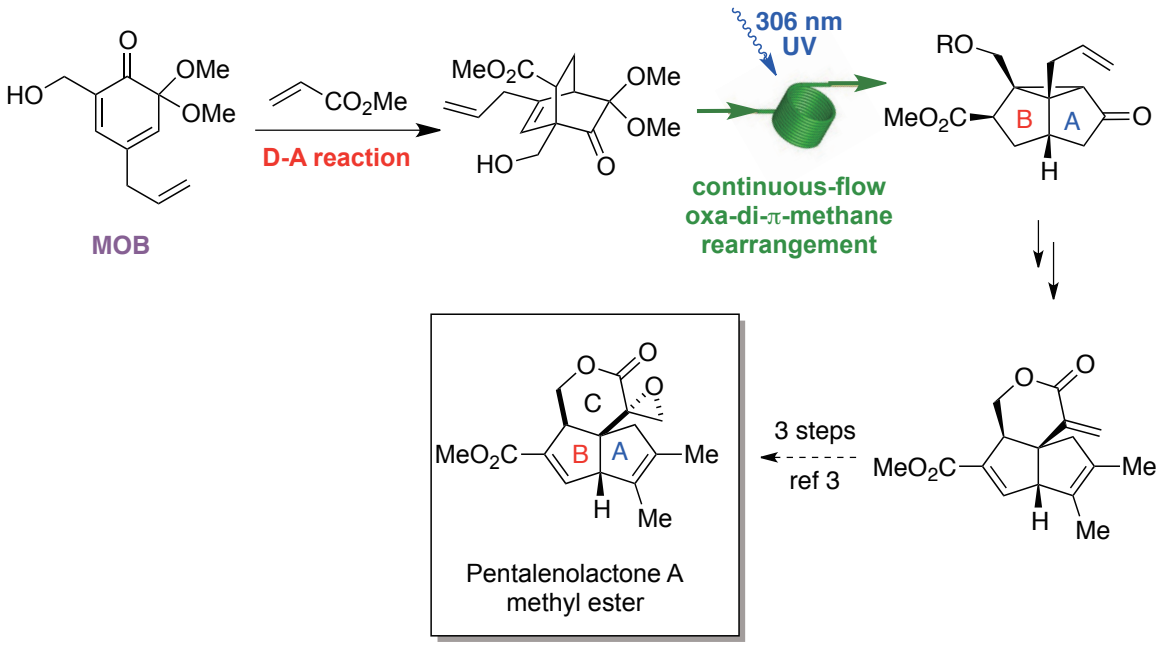
Pentalenolactone A, produced by prokaryotic organisms, was first isolated as a relatively stable methyl ester nearly twenty years ago by Cane *et al*.[1] As a member of the pentalenolactone family, its inherent biological activity makes it a potential candidate for use as an antibiotic agent. We here present our formal synthesis of (±)-penatalenolactone A methyl ester which was accomplished in 21 synthetic steps from a simple 2-methoxyphenol. The key features of our route are: a Diels-Alder reaction of masked *o*-benzoquinone (MOB) to assemble the functionalized bicyclo[2.2.2]octenone;[2] a continuous-flow oxa-di-p-methane (ODPM) rearrangement for construction of the diquinane core (AB ring); and, an oxidative cleavage/oxidation sequence for annulation of the d-lactone (C ring).[3]



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[4] manuscript submitted.

2P-017

Tricyclic Oxygen Heterocycles for Aqueous-Medium Thiol-Selective Modification

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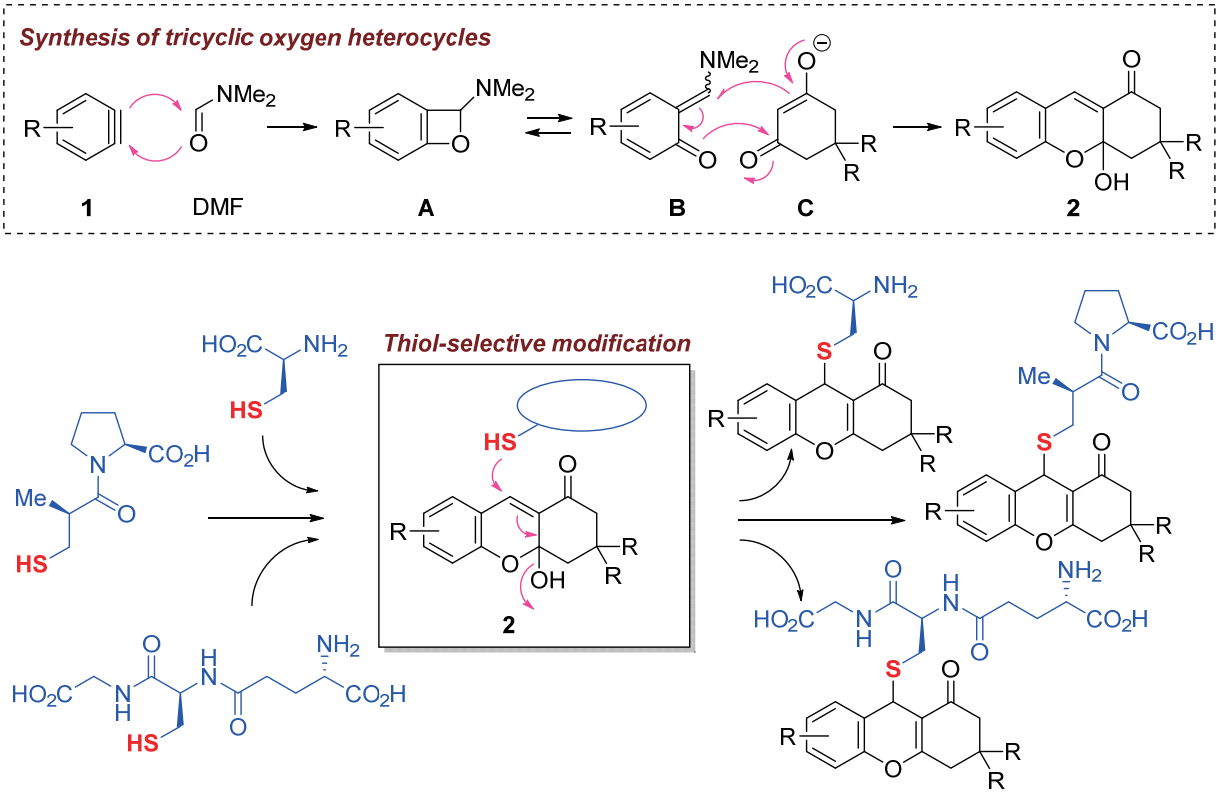
Chemical modification of proteins has played a significant role in the bioconjugation chemistry. In particular, thiol group of cysteine is the important targeting residue as a conjugation site owing to its low population and high nucleophilicity. Tricyclic oxygen heterocycles **2** worked as selective and reactive reagents for trapping thiols and cysteine via the S_N2' reaction.[1,2] Tricyclic oxygen heterocycles **2** were prepared by three-component coupling reaction of arynes **1** with *N*,*N*-dimethylformamide (DMF) and active methylenes such as cyclic 1,3-diketones.[3,4] The utility of tricyclic oxygen heterocycles **2** as a reagent for the thiol-selective modification toward bioconjugation was demonstrated by the use of L-cysteine, homocysteine, captopril and glutathione as a nucleophile having a thiol group. These trapping reactions proceeded under the mild and aqueous reaction conditions using MeCN-PBS (phosphate-buffered saline).



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2P-018

Synthesis of Diversely Functionalized Heterocycles *via* Trapping of Transient σ- Alkyl/Vinyl-Palladium (II) Intermediates

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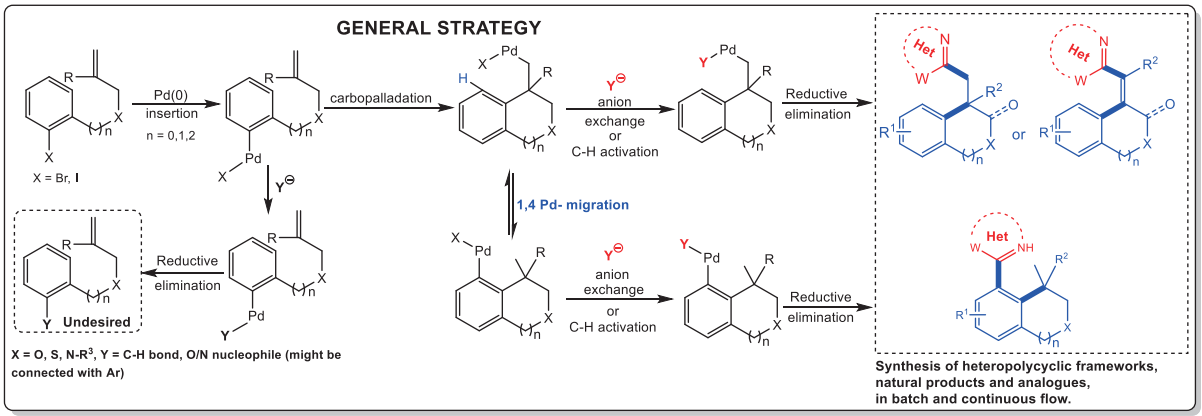
Despite the changing face of chemistry, the necessity to produce molecules in a controlled manner has not diminished. However, the increasingly complex synthetic problems being posed by nature, medicine and materials demand new reactivity concepts and strategies in order to meet these challenges. Domino reactions are one of the most attractive procedure for the synthesis of complex organic molecules, which according to Tietze, lead to the formation of "several bonds in one sequence without isolating the intermediates, changing the reaction conditions or adding the reagents".[1] It is already well-established that carbopalladation of acrylamides/propiolamides can generate the transient σ- alkyl/vinyl-palladium (II) intermediates.[2] The basic idea of the present work is to intercept the *in situ* generated σ- alkyl or vinyl palladium species *via* C-H functionalization including remote C-H functionalization, migratory insertion of isocyanide, anion capture etc to generate diversely functionalized heterocycles (Scheme 1). Such reactions will pave the way for the efficient synthesis of (poly)heterocyclic structures in batch as well as continuous flow. Many of these heterocyclic frameworks can already be seen in various alkaloids and pharmaceuticals.



Scheme 1: General strategy for the trapping of transient σ- alkyl/vinyl-palladium (II) intermediates.

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2P-019

Canceled

Synthesis of Six- and Seven-Membered Benzolactones by Nickel-Catalyzed C-H Coupling of Benzamides with Small-Sized Cyclic Ethers

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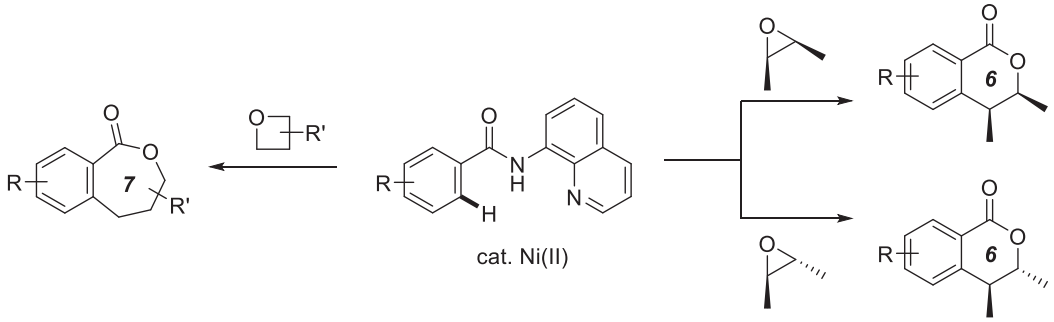
New strategies for the synthesis of oxygen-containing heterocycles have received significant attention in view of the fact that these compounds possess various biological activities. Among them, transition-metal-catalyzed C-H activation methods have played a dominant role because of their higher atom and step economies.[1]

Here, we present a convenient protocol to access six- and seven-membered benzolactones via Ni(II)-catalyzed C-H coupling of 8-aminoquinoline-derived benzamides with epoxides and oxetanes.[2] The N,N-bidentate coordination directed C-H alkylation is followed by an intramolecular esterification to deliver the corresponding lactones in one synthetic operation. The 8-aminoquinoline group is spontaneously removed and recovered. Additionally, in the reaction with epoxides, a unique stereospecificity is observed: the cis epoxide can be converted to the cis lactone whereas the trans isomer is selectively formed from the trans epoxide, which is complementary to that observed in previously reported Pd(II) catalysis.[3]



Scheme 1. Synthesis of six- and seven-membered benzolactones via Ni-catalyzed C-H coupling of benzamides with epoxides and oxetanes

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2P-021

Discovery of hydrazide derivatives as glycine *N*-methyltransferase (GNMT) inducers for the treatment of hepatocellular carcinoma

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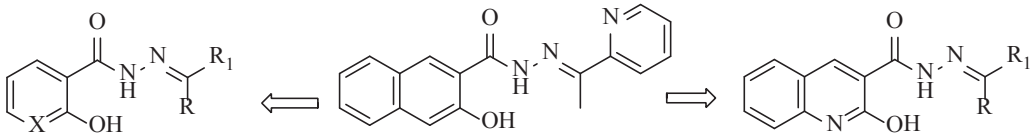
Glycine *N*-methyltransferase (GNMT) is one of the major enzymes in folate-mediated one-carbon metabolism and also an abundant cytosolic enzyme which catalyzes the transfer of a methyl group from *S*-adenosylmethionine (SAM) to glycine, generating *S*-adenosylhomocysteine and sarcosine (*N*-methylglycine). It affects genetic stability by regulating the ratio of SAM to *S*-adenosylhomocystine and is strongly down regulated in human cancers especially hepatocellular carcinoma (HCC) [1]. Therefore, discovery of small molecules that are able to enhance GNMT expression will have important implications for the treatment of HCC. Recently, we have identified a hydrazide derivative, 2-acetylpyridine-[*N*-(3-hydroxy-2-naphthoyl)]hydrazide (**1**), as the initial hit from a collective drug library containing more than 20,000 compounds using a GNMT gene expression-oriented screen platform. Compound **1** is a known compound, however, there is only four publications related to its properties and synthetic methods but no biological activity was reported [2-5]. Our preliminary results indicated that compound **1** is capable of inducing GNMT expression strongly with 7.57 folds to control in 2.5 μM.

In order to discover novel lead compounds based on the initial hit, we have synthesized more than 300 analogs of compound **1** and evaluated for their effects on GNMT promoter activity. Results indicated certain newly synthesized hydrazide derivatives (compounds **2** and **3**) are more active than compound **1**. A comprehensive SAR study will be presented.



2 **1** **3**

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2P-022s

Enantioselective Synthesis of Functionalized Decalins via Desymmetrization of Substituted Dihydropyrans and 1,3-Diketones

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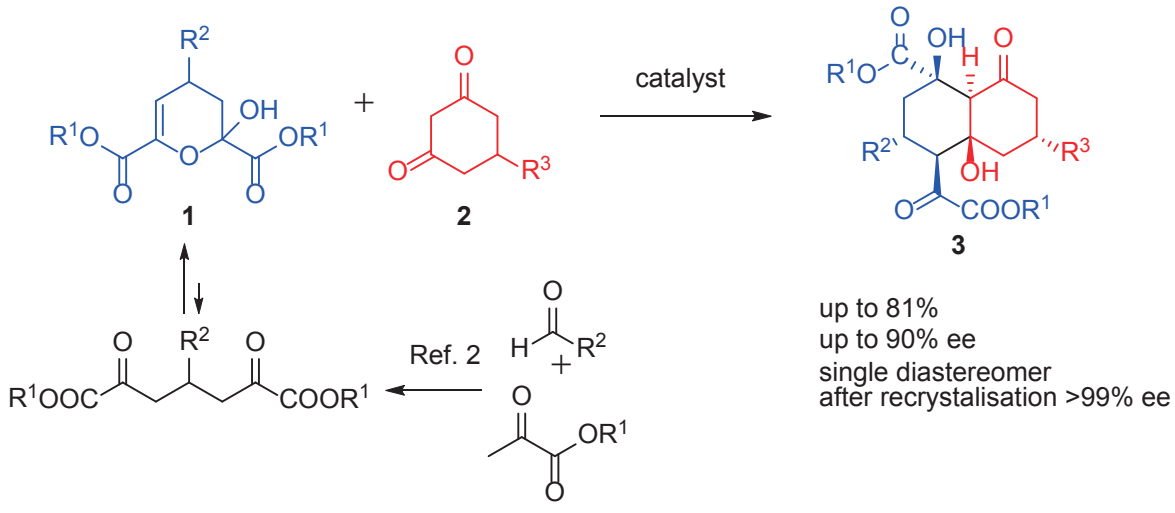
The decalin ring system is one of the most predominant structural units found in a wide variety of bioactive natural products such as diterpenoids and steroids. Diastereo- and enantioselective synthesis of densely functionalized decalin framework has been a challeng in synthetic chemistry. In this presentation, we present diastereo- and enantioselective reactions that afford polyfunctionalized decalins having five to six stereocenters.[1]

We have developed organocatalytic formal (4+2) cycloaddition reactions of dihydropyrans **1**[2] and 1,3-diketones **2** to provide densely functionalized decalins.[1] The reactions afforded *trans*-decalins **3** with high diastereo- and enantioselectivities in the presence of cinchona-derived catalysts under mild conditions. Double desymmetrization of dihydropyrans **1** and 1,3-diketones led to the exclusive formation of single diastereomer of *trans*-decalins bearing up to six stereogenic centers, including two tetrasubstituted chiral carbon centers, in high enantioselectivities. The product decalins were further transformed to various decalin derivatives. With our strategy, construction of five to six stereogenic centers was achieved from achiral starting materials with the formation of only two C-C bonds.



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2P-023s

Hepatoprotective activities of 3,5-dihydroxy-7-methoxy-2-(4-methoxyphenyl)-4-benzopyrone against CCl_4-induced liver fibrosis in mice

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The current study aimed to evaluate, for the first time, the possible hepatoprotective effects of 3,5-dihydroxy-7-methoxy-2-(4-methoxyphenyl)-4-benzopyrone against CCl_4-induced liver fibrosis in mice. Liver fibrosis was induced through intraperitoneal injection of CCl_4 (0.4 ml/kg) twice a week for six consecutive weeks. The treatment with benzopyrone derivative was started after fibrosis induction at dose 10 and 25 mg/kg twice per week for four consecutive weeks. Histological alterations in the liver were studied as well as oxidative stress, proliferation, and apoptosis. H&E staining indicated that benzopyrone derivative markedly reduced liver fibrosis induced by CCl_4. Furthermore, treatment with benzopyrone derivative increased SOD, CAT, and GPx activity and decreased lipid peroxidation and nitric oxide levels in liver tissue homogenates. Moreover, immunohistochemical analysis showed that Bcl-2, caspase-3, PCNA, CD31, and TGF-b1 expressions were downregulated after benzopyrone derivative treatment, while Bax expression was upregulated. The high dose of derivative was more effective than the low dose in all studied assays. In summary, benzopyrone derivative efficiently reduced CCl_4-induced live fibrosis in mice. Further pharmacological investigations are essential to determine the effectiveness of benzopyrone derivative in human.

2P-024s

Development of Carboiodination Reaction of Unsaturated Bonds Using Cationic Iodine

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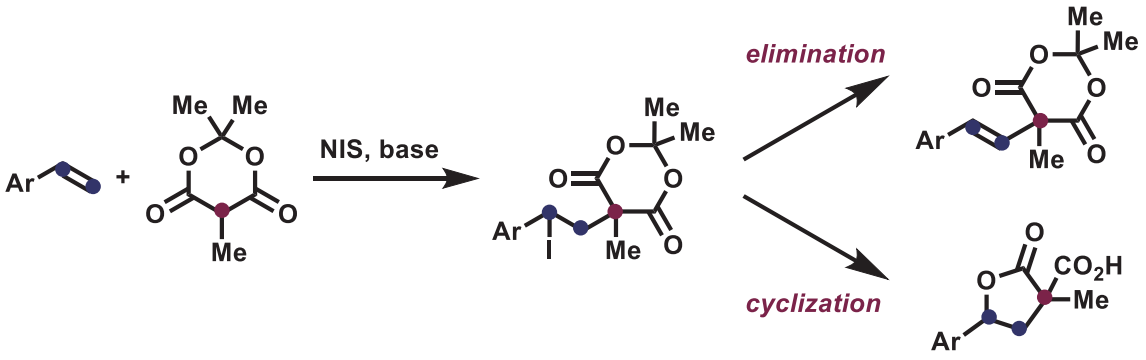
The carbohalogenation reaction using halogen source has been actively studied in recent years. Zhu and co-workers reported a redox neutral photocatalyzing divergent radical 1,2-carbohalogenation catalyzed by an iridium complex. [1] Mattos and co-workers also reported *vic*-haloformyloxylation reaction of alkenes using trichloroisocyanuric acid or *N*-bromosaccharin.[2] These reactions are versatile that the resulting alkyl halide can be used for further transformation. However, few cases have been reported that the carbohalogenation reactions with olefins under metal free condition and capable of various molecular transformations with inexpensive starting materials.

In our laboratory, it has been found that by reacting of styrenes with malonic acid derivatives in the presence of iodine, carbon–carbon bond and carbon–oxygen bond formation proceed in one step to give lactone. This reaction proceeds *via in situ* formed carboiodinated intermediate by the reaction of styrene, malonate with molecular iodine. [3]

In this research, we have developed that cationic iodine mediated carboiodination reaction using styrene derivatives with Meldrum's acid derivative. As a result of various examinations, by using NIS as a cationic iodine source at room temperature under an air atmosphere, the substrate was converted to the corresponding carboiodinated product. This reaction provides a carbon–iodine bond in one step without any metal catalyst, harsh reaction conditions or complex experimental operation. Furthermore, by using the generated alkyl halide as a substrate, the elimination of iodine can form a $C(sp^2)$–$C(sp^3)$ bond or a cyclization reaction can form a lactone. Currently, we are examining the development of conversion reaction to other compounds. These detailed results will also be discussed.



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Dynamic Stereoselective Annulation to Afford Spirooxindole Pyran Polycycles

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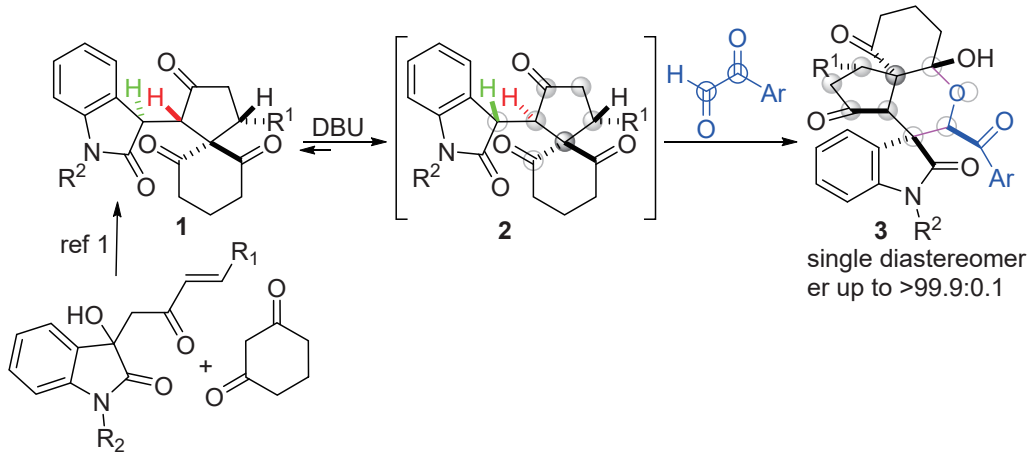
Pyran-fused spiro polycycles are important biofuctional molecules. Synthesis of pyran-fused spiro polycycles is of interest in drug discovery efforts and related research. In this presentation, annulation reactions leading to spirooxindole pyran polycycles will be discussed.

We have developed catalytic stereoselective annulation reactions that afford spirooxindole pyran polycycles. In our strategy, a pyran ring in spiro polycycles is constructed via the formation of C-C and C-O bonds through dynamic aldol-oxa-cyclization cascade reactions. During the reactions, starting material **1**[1] was isomerized to diastereomer **2** with retention of the enantiopurity. Then, **2** was reacted with arylglyoxal to form **3**. With taking advantage of the feature of the isomerization, highly enantiomerically enriched forms of single diastereomers of spirooxindole pyran polycycles **3**, bearing six stereogenic centers, were obtained. Notably, the formation of the pyran ring resulting in the formation of the polycyclic system showed stereoselectivities distinct from the formation of the cyclohexane ring leading to the all-carbon polycycles.[1] We will discuss, these reactions including our strategy, the isomerization of **1** to **2**, and stereoselective formation of **3**.



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2P-026

A Novel Higher-order Radical Cascade Provides Efficient Synthesis of a Variety of Heterocycles

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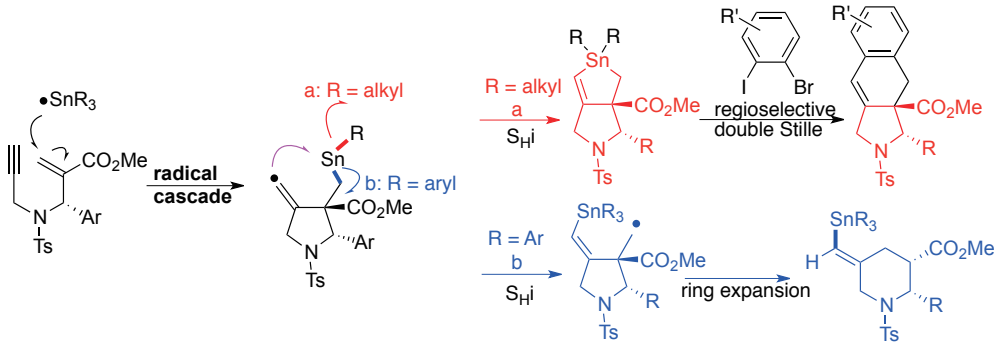
Radical cascade reaction provides useful methods for the formation of heterocyclic system. Recently, we found an efficient radical cascade reaction containing radical substitution at heteroatom such as tin, sulfur and silicon. In this presentation, we will show radical cascade provides a useful and highly efficient synthesis of heterocyclic compounds, and one-step preparation of piperidines, stannolanes, thiophenes, and siloles is achieved from 1,6-enyne precursors, which were readily prepared by Michael-iminoaldol process for chiral sulfinimines.[1] Treatment of chiral enyne compounds with Bu_3SnH gave bicyclic stannolanes in good yields. The reaction progressed through radical addition-cyclization-substitution reaction and the products were formed in a highly stereoselective manner.[2] This radical cascade also worked well when dimethylsulfide and tristrimethylsilylsilane were used.[3,4] Kinetic study reveled that the rate constant for the radical substitution on tin atom was as large as 4.2×10^8 sec^{-1}, and the substitution reaction was very fast.[5] When Ph_3SnH was used instead, higher-order radical cascade progressed to give piperidine in moderate yields. Stannolane underwent regioselective double Stille coupling with *o*-bromoiodobenzenes to give benzoisoindoles in good yields.[6] Homofugality between alkyl groups on tin atom will be discussed.[7]



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2P-027s

Cyclisations of 3-(*o*-Substituted-phenyl)penta-1,4-diyn-3-ols: Construction of Bicyclic, Tricyclic and Tetracyclic Rings Containing N, S and/or O

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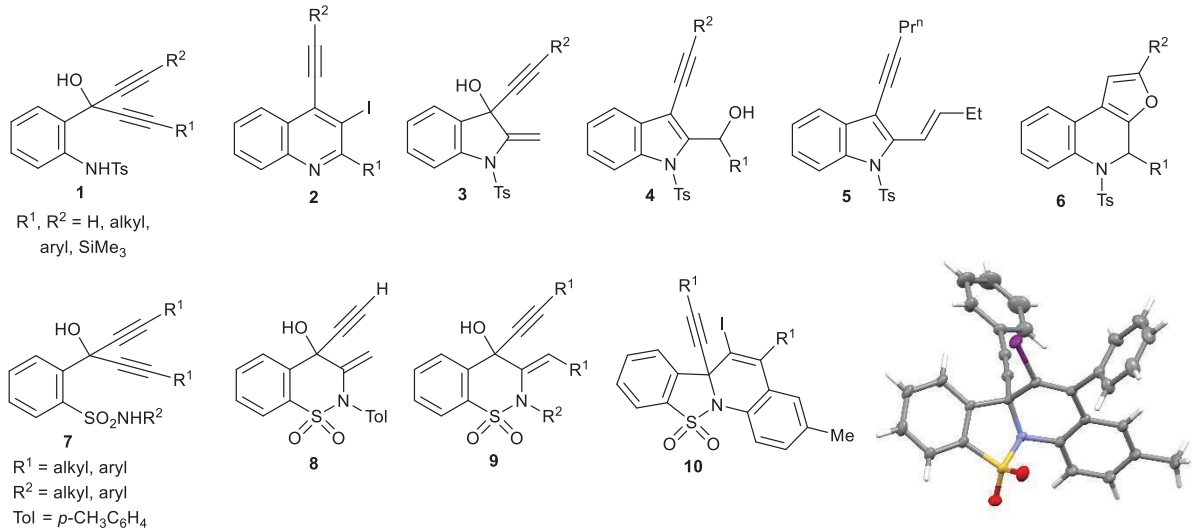
The use of an external electrophile to activate an alkyne, and so initiate cyclisation by interception with an internal nucleophile has been developed extensively for the synthesis of many types of heterocycle.[1] Depending on conditions 1-(2-aminophenyl)prop-2-yn-1-ol derivatives have been transformed to give 4-alkyl(aryl)-3-iodoquinolines, indoles, indolines or oxindoles.[2] Surprisingly, no iodo- or Lewis acid-induced cyclisations of 3-(2-aminophenyl)penta-1,4-diyn-3-ols have been reported. We have investigated the readily available diynols **1** for the synthesis of the hitherto unknown 4-alkynyl-3-iodoquinolines **2** and have also observed that mild base treatment of **1** (R^1 = H or $SiMe_3$) effects smooth cyclisation to the 3-ethynylindolines **3**. Treatment of **1** (R^1 = R^2 = alkyl or aryl) with AgOAc promotes cyclisation to the 3-alkynylindoles e.g. **4** and **5**, but with $In(OTf)_3$ an alternative cascade pathway supervenes leading to the novel furo[2,3-*c*]quinolines **6**. The behavior of isomeric sulfonamides **7**, available from saccharin, towards base or AgOAc or with ICl has been investigated and the 1,2-benzothiazines **8** and **9** and the novel tetracycle **10**, have been obtained. Solvent effects, mechanisms and extensions and applications of this chemistry will be described.



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2P-028s

Hypervalent Iodine (III) in Direct Intramolecular N-N Bond Formation with Heteroaromatic Amines: Synthesis of Triazapentalene Derivatives

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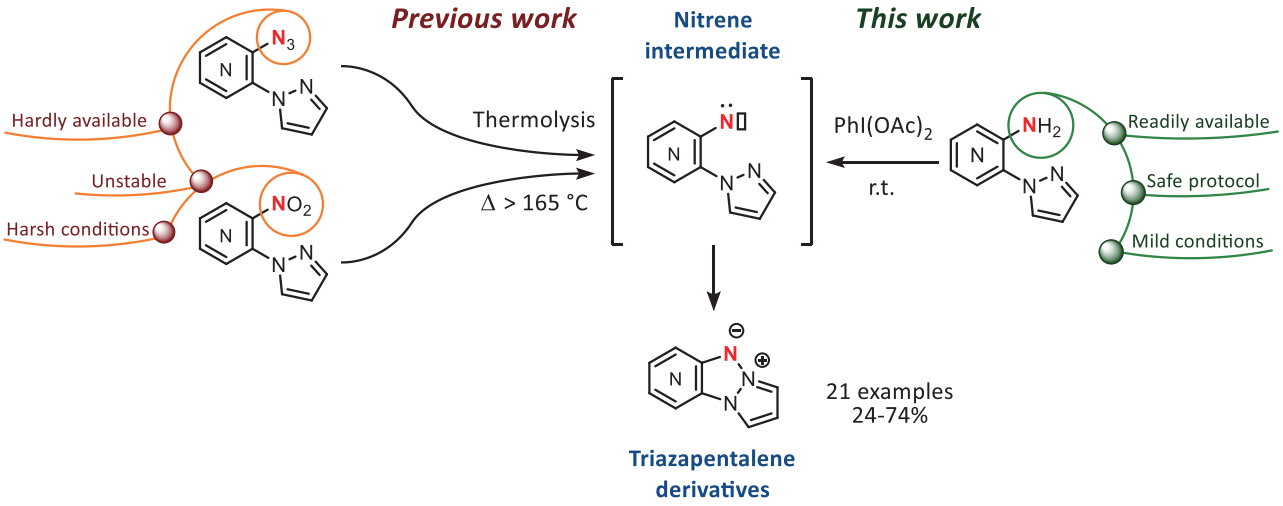
Triazapentalene derivatives exhibit an original structure, which confers them interesting fluorescent[1,2] and energetic[3,4,5] properties. Their synthesis used to rely on azido[3] or nitro[4,5] precursors, which required drastic experimental conditions to generate the nitrene intermediate. Furthermore, the azido and nitro derivatives are often unstable, potentially energetics and hardly available.

Consequently, we developed new conditions from heteroaromatic amines to provide an efficient and innovative approach for the formation of N-N bond in presence of iodine (III) reagent in mild conditions. This unprecedented method enables to synthesize nitrogen rich triazapentalene derivatives inaccessible with existing approaches. The fluorescent properties of the newly accessed triazapentalene derivatives will also be discussed.



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2P-029

Total Synthesis of Brussonol via Cross-Electrophile Coupling from Epoxides

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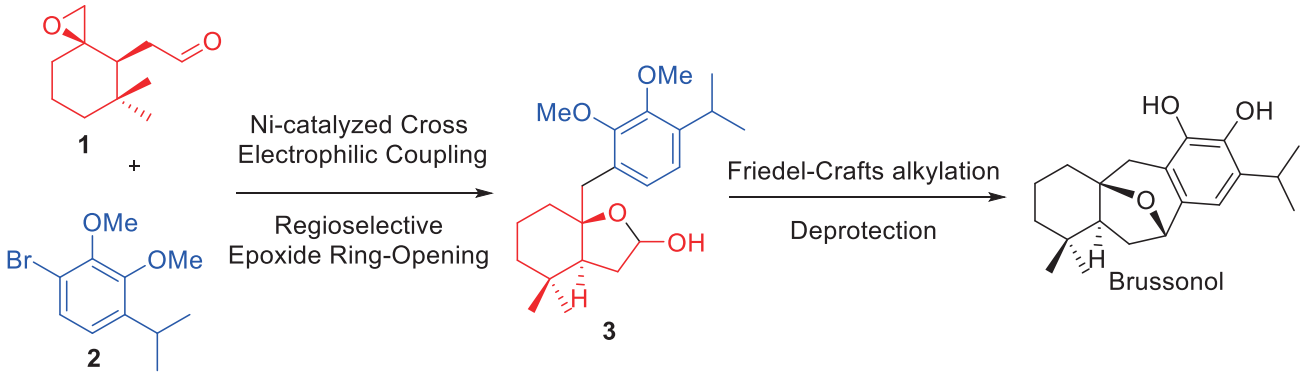
São Carlos, SP, 13560-970, Brazil

The icetexane diterpenes, isolated from a variety of terrestrial plant sources, have attracted considerable attention owing to their diverse structure features and broad range of biological activities [1]. For example, brussonol and komaroviquinone has received a great deal of attention from synthetic organic chemists due to its promising anti-cancer, cytotoxic and anti-protozoal activities. Herein, the shortest stereoselective convergent synthesis of natural product brussonol via a cross-electrophile coupling strategy is described. The chemistry features effective preparation of the challenging acetal intermediate **3** in a single step by Ni-catalyzed [2] regiodivergent epoxide **1** ring-opening approach [3] with aryl halide **2**, followed by highly efficient $BF_3.OEt_2$ catalyzed Friedel Craft alkylation to construct tricyclic skeleton. The synthetic approach might offer a unified approach for the synthesis of several natural products containing icetexane motifs.



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2P-030s

Formal Anti-Markovnikov Hydromethylation of Olefins

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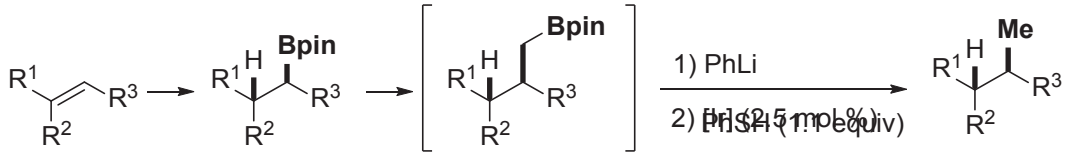
Pinacol boronic esters are highly valuable building blocks in organic synthesis.[1,2] The most important application to be named is the Suzuki-Miyaura-coupling.[3] In contrast to the many protocols available on the functionalizing deboronation of alkyl boronic esters like oxidations[4], aminations[5], halogenations[6] and C–C-bond-formations such as alkenylations[7] alkynylations[8] and arylations,[9] protodeboronation is not well developed.

Herein we report catalytic protodeboronation of 1°, 2° and 3° alkyl boronic esters utilizing a radical approach.[10] Paired with a Matteson-CH_2-homologation, our protocol allows for formal *anti*-Markovnikov alkene hydromethylation, a valuable but unknown transformation. The hydromethylation sequence was applied to a variety of substrates including methoxy protected (-)-Δ^8-THC and cholesterol. The protodeboronation was further used in the formal total synthesis of δ-(*R*)-coniceine and indolizidine 209B.



1° alkyl boronic ester

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2P-031

Nitrile Oxide Chemistry in a Renovate Use of Isoxazoles

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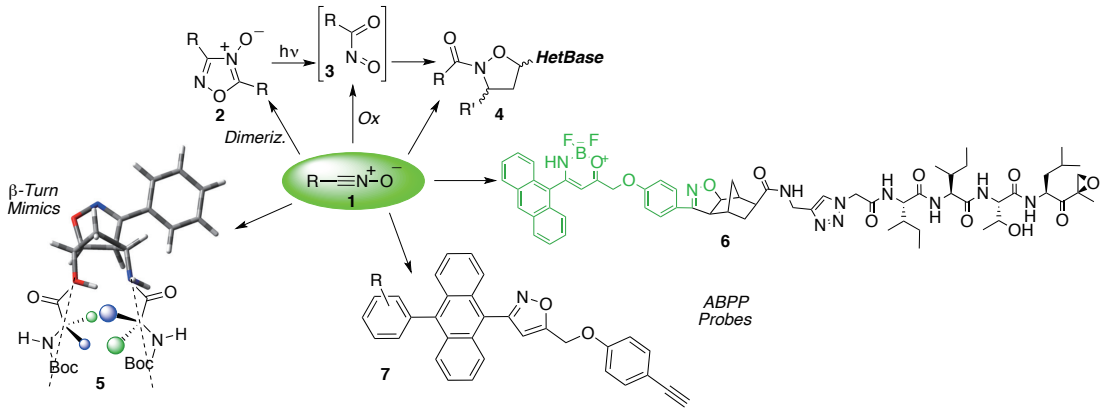
Nitrile oxides **1** represent the most traditional intermediates for the construction of heterocyclic compounds (isoxazoles, isoxazolines and isoxazolidines) via 1,3-dipolar cycloadditions. The chemistry of isoxazoles dates from 1888,[1] when Claisen proposed the correct structure for the product of the hydroxylamine - benzoylacetone reaction isolated years before. In 1891, he published the fundamental outline of the isoxazole chemistry.[2] After that seminal work, a few other authors explored the isoxazole chemistry; the reemergence of interest in these heterocycles must be ascribed to Quilico as a consequence of the research on the reaction of nitric acid with C≡C triple bonds.[3]



Somewhat, this chemistry never felt out of fashion. The oxidation of nitrile oxides were investigated, disclosing a new route to nitrosocarbonyls **3**, fleeting intermediates with a strong dienophilic and enophilic power.[4] With the help of the clean photochemical cleavage of 1,2,4-oxadiazole-4-oxides **2**,[5] the generation of these reactive species became the pivotal step in the synthesis of biologically active isoxazolidines **4** derivatives.[6] Furthermore, suitable derivatives of nitrosocarbonyl cycloadducts were elegantly elaborated to construct β-turn mimics of type **5**.[7] Fluorescent moieties attached to the nitrile oxide fragment are also at work to become competitive probes (compounds **6** and **7**) in Activity-Based Protein Profiling studies.[8]

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2P-032s

Synthesis of Functionalized Monoaryl Iodanes(III) via *ipso*-Substitution Reactions

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Masahiro Kojima, Tatsuhiko Yoshino* and Shigeki Matsunaga*
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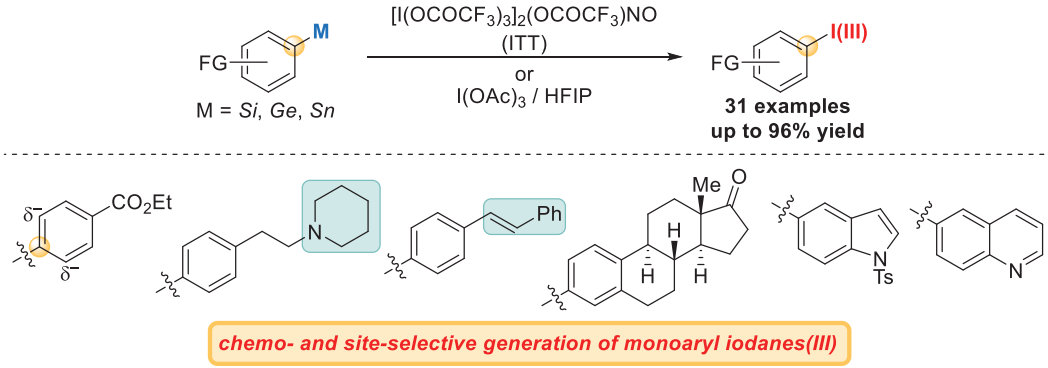
Kita-ku, Sapporo 060-0812, Japan

Monoaryl-λ^3-iodanes, hypervalent iodine(III) species bearing one aromatic substituent ($ArIX_2$), can serve as safe and less toxic oxidants and arylating agents. The typical synthesis of these compounds involves the oxidation of aryl iodides. The functional group compatibility is, however, of great concern when applied to oxidizable substrates. Although the direct introduction of a trivalent iodine moiety ($-IX_2$) in aromatic rings using electrophilic aromatic substitution reactions with $[I(OCOCF_3)_3]_2(OCOCF_3)(NO)$ (ITT) or $I(OAc)_3$ to avoid an oxidation step has been investigated [1], the scope of these reactions are limited to rather simple substrates. Moreover, the site selectivity of these electrophilic aromatic substitution reaction depends on the electronic nature of the substrates. In this symposium, we present the direct synthesis of monoaryl-λ^3-iodanes by chemo- and site-selective *ipso*-substitution reactions of stable aryl metal species (Ar-M, M = Si, Ge, Sn) with ITT and $I(OAc)_3$. Monoaryl-λ^3-iodanes provided in these reactions were converted to iodonium ylides or underwent further transformations in one pot. The *ipso*-substitution reactions selectively proceeded regardless of the electronic properties and orientation toward electrophilic aromatic substitution of the substrates. Substrates containing an aliphatic amine moiety and an olefin conjugated with aromatic rings and drug-like molecules afforded the corresponding products in moderate to good yield. [2] Furthermore, common oxidizable heteroaromatic compounds such as indoles and quinolines were also tolerated under the reaction conditions using $I(OAc)_3$ and HFIP. [3]



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2P-033

Cyclization of Spiro(Nitrocyclopropane)-oxindoles with Huisgen Zwitterions and Synthesis of Fused Pyrazole Derivatives

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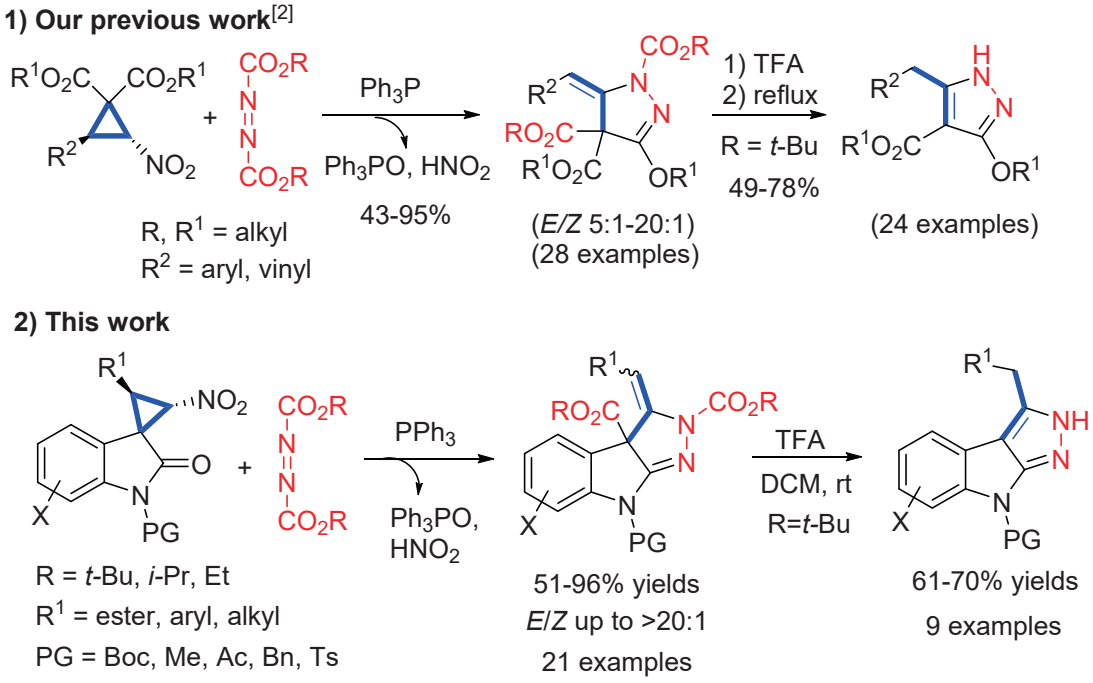
Pyrazoline and pyrazole are both privileged structural motifs frequently present in a large number of agrochemicals, pharmaceuticals and other bioactive molecules. Under this circumstance, the development of effective synthetic methods for pyrazolines and pyrazoles has therefore stimulated much interest from chemists.[1] In our previous report,[2] we realized a novel annulation reaction of *trans*-2-substituted-3-nitrocyclopropane-1,1-carboxylates with *in situ* generated Huisgen zwitterions, which provides facile access to 3-alkoxy pyrazolines and corresponding 3-alkoxy *1H*-pyrazoles. As continuation of our prior work, recently we successfully extended this cyclization strategy to spiro(nitrocyclopropane)-oxindoles and developed an efficient method for synthesis of complicated fused pyrazole derivatives like pyrazolo[3,4-*b*]indoles. Herein we present the relevant results.



Acknowledgement: Financial support from the National Natural Science Foundation of China (Grant Nos. 21272119, 21472096) is gratefully acknowledged.

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2P-034s

Development of lactamization reaction through three-components reaction using iodine and visible light

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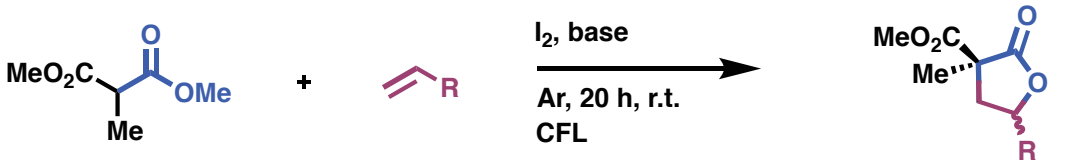
Gifu city, Gifu 501-1196, Japan

Lactams are one of the common functional structures in natural products and biologically active compounds. In particular, γ-lactams are widely present as pharmacophores in important pharmaceuticals. Therefore, development of a diversity-oriented synthesis methodology of γ-lactam derivatives in drug discovery chemistry is highly desired.

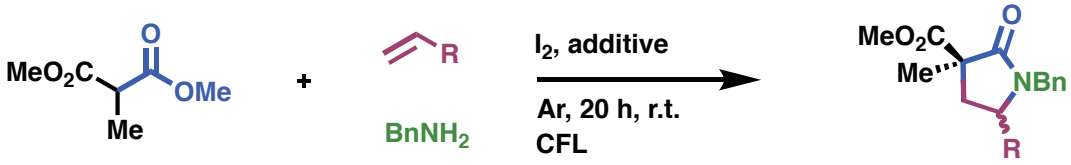
On the other hand, multi-component reaction (MCR) plays an important role in combinatorial chemistry because it can synthesize drug-like small molecules with structual-diversity. For example, the Passerini and Biginelli reaction are important to form amide and the synthesis of heterocycles. While γ-lactam are formed by MCR have been reported several methodology, it is many using aldehyde or carboxylic acid derivatives as reaction motifs.

Here in, we have developed intermolecular γ-lactamization through three-components reaction using olefin and molecular iodine under the visible light. Previously, we have developed rare metal-free method leading to lactones by forming C-C/C-O bond in the intermolecular reaction between malonate and styrene (Scheme 1). [1] During the course of this study, we have observed that the generated iodine radicals by cleavage of I-I bond under irradiation with visible light.

In this work, it found that iodine radical forms high reactivity intermediate with olefin, and it mediated reaction applied to three-component reaction of malonate derivatives and amine leading to γ-lactam (Scheme 2). Additionally, the reaction proceeded at room temperature and without using heavy metals or acids. These mechanisms proposed on the basis of control experiments and detailed results will also be discussed.



Scheme 1. Iodine radical mediated intermolecular lactonization



Scheme 2. Iodine radical mediated three-component lactamization reaction

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2P-035

Asymmetric Synthesis of Novel Fused Polycyclic 3,4-Dihydropyrano[4,3-*b*]pyran-5(2*H*)-ones via an Organocatalyzed Formal [3 + 3] Annulation

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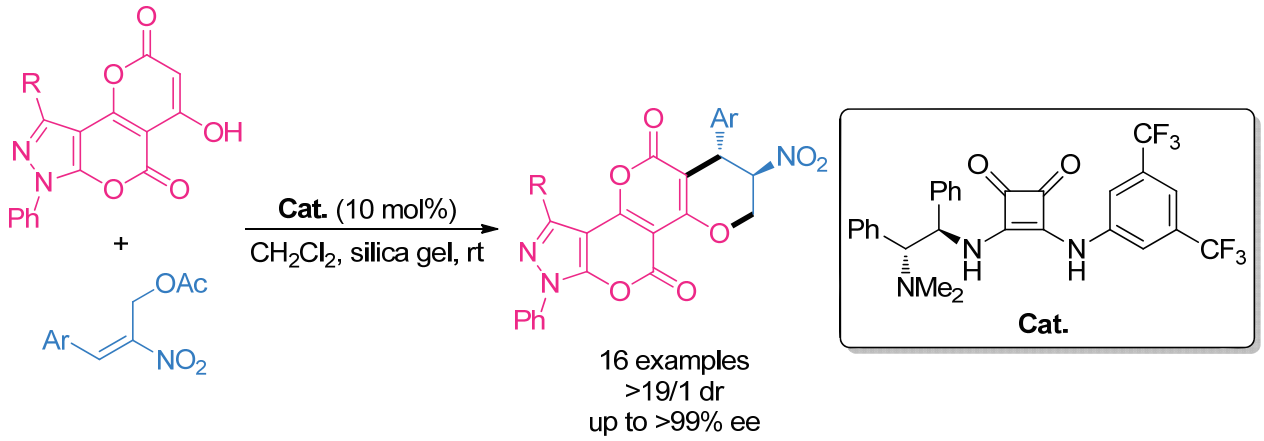
Both 3,4-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one[1] and pyrano[2,3-*c*]pyrazol-6(1*H*)-one[2] skeletons are common structural unit found in a number of biologically active naturally occurring and synthetic compounds. Over the past two decades, the privileged structures-based diversity-oriented synthesis has become a powerful and highly efficient tool for discovering biologically active small molecule.[3] In view of the interesting applications of 3,4-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one and pyrano[2,3-*c*]pyrazol-6(1*H*)-ones in the field of drug discovery, the fused-ring system consisting of a 3,4-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one skeleton and a pyrano[2,3-*c*]pyrazol-6(1*H*)-one skeleton will be an important structural motif that has potential among biological activities and synthetic applications. As a result, the development of efficient synthesis of chiral 7,8-dihydropyrano[2",3":4',5']pyrano[2',3':4,5]pyrano[2,3-*c*]-pyrazole-5,10(1*H*,6*H*)-diones with high levels of enantioselectivity will be of great importance and remains a challenge task. Herein, we report an organocatalytic [3 + 3] cascade reaction to access enantiomerically enriched novel fused polycyclic 3,4-dihydropyrano[4,3-*b*]pyran-5(2*H*)-ones in acceptable yields with high levels of diastereo- and enantioselectivity.



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2P-036s

Synthesis of 4-acetamido-octahydrochromene derivatives based on (-)-isopulegol *via* Prins-Ritter tandem reaction

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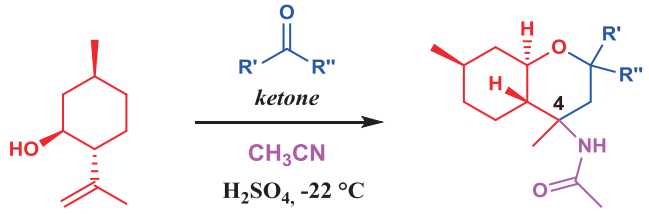
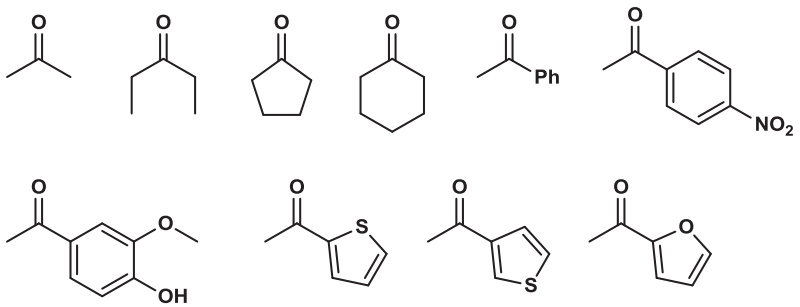
It was found earlier that some compounds with octahydro-2*H*-chromene scaffolds synthesized from monoterpenoid (-)-isopulegol demonstrated promising biological activity, e.g. analgesic and antiviral activities, inhibitory activity against DNA repair enzyme Tdp1 [1-3].
The flexible method for the synthesis of octahydro-2*H*-chromenes derivatives is the Prins cyclization. This reaction could serve also as an initiator of a tandem three-component reaction. For example, the sequence of the Prins and Ritter reactions is one of the best synthetic method to build efficiently in a one-pot single step reaction six-membered fragment of 4-amidotetrahydropyran.
In this work we have developed a method for synthesize of 4-acetamide derivatives of chiral octahydro-2*H*-chromenes. We used one-pot tandem Prins-Ritter reaction between monoterpenoid (-)-isopulegol and a set of ketones in acetonitrile. Desired products were formed as a mixture of 4*R*/4*S* diastereomers. Some of these compounds exhibit promising analgesic and antiviral activity in preliminary screening studies.



(-)-Isopulegol ***yields 10 - 65%***

Set of ketones



The research was financially supported by Russian Foundation for Basic Research (RFBR, grant 19-53-04005 Bel_mol_a).

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Pd-Catalyzed Intramolecular C–H Arylation of Aromatic Esters and Nitroarenes

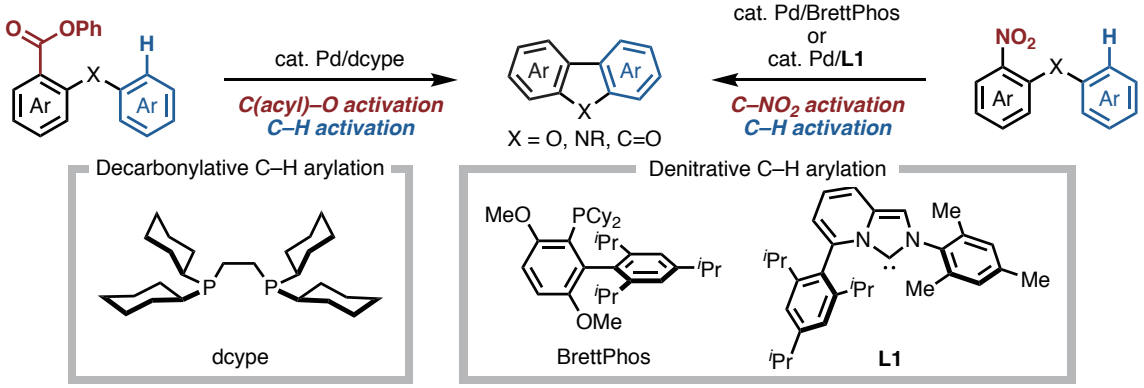
Toshimasa Okita,[a] Kitty K. Asahara,[a] Ami N. Saito,[a] Myuto Kashihara,[b] Kei Muto,[a] Yoshiaki Nakao[b] and Junichiro Yamaguchi*[a]

[a] *Department of Applied Chemistry, Waseda University, Tokyo 169-8555, Japan.*

[b] *Department of Material Chemistry, Kyoto University, Kyoto 615-8510, Japan*

Transition metal-catalyzed cross-coupling of haloarenes and metalloarenes is a reliable bond-forming reaction. For past decades, a C–H arylation of (hetero)arenes as aryl nucleophiles instead of metalloarenes have been reported. Additionally, various electrophiles for the C–H arylation have been developed such as arenols, aryl carboxylic acids, aromatic esters, and aromatic amides. These methods are quite effective in reducing number of steps and chemical waste. However, C–H nucleophiles have been limited, and the use of simple arenes continues to be a challenging issue. To circumvent this problem, an internal nucleophile can be used, changing the reaction mode from intermolecular to intramolecular. In this context, intramolecular C–H arylations of various "tethered" aryl electrophiles and arenes have been developed recently.

Herein, we have discovered two types of Pd-catalyzed intramolecular C–H arylations using aromatic esters and nitroarenes bearing tethered aryl group at *ortho*-position.[1,2] The key of the reaction is the choice of an appropriate ligand to activate inert chemical bonds. Successively, Pd/dcype catalyst enabled the cleavage of acyl C–O bond of aromatic ester followed by decarbonylation to afford the corresponding biaryl linkage. Similarly, a Pd/BrettPhos[3] and Pd/**L1** catalytic system activated a C–NO_2 bond, enabling the denitrative intramolecular C–H arylation. With the facile preparation of starting materials in one step from 2-halogenated benzoates and nitroarenes by a nucleophilic aromatic substitution (S_NAr), these methods realized the rapid synthesis of dibenzofuran, carbazole and fluorenone frameworks.



[1] Okita, T.; Komatsuda, M.; Saito, A. N.; Hisada, T.; Takahara. T. T.; Nakayama, K. P.; Isshiki, R.; Takise, R.; Muto, K.; Yamaguchi, J. *Asian J. Org. Chem.* **2018**, *7*, 1358.

[2] Asahara, K. K.†; Okita, T.†; Saito, A. N.; Muto, K.; Nakao, Y.; Yamaguchi, J. *Org. Lett.* ***2019,*** ASAP. DOI: 10.1021/acs.orglett.9b01593

[3] (a) Yadav, M. R.; Nagaoka, M.; Kashihara, M.; Zhong, R.-L.; Miyazaki, T.; Sakaki, S.; Nakao, Y. *J. Am. Chem. Soc.* **2017**, *139*, 9423. (b) Inoue, F.; Kashihara, M.; Yadav, M. R.; Nakao, Y. *Angew. Chem., Int. Ed.* **2017**, *56*, 13307. (c) Kashihara, M.; Yadav, R. M.; Nakao, Y. *Org. Lett.* **2018**, *20*, 1655.

The First Synthesis and Characterization of a Polycyclic Zwitterion with Open-Shell Character

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Toyonaka, Osaka 560-8531, Japan

Recently, open-shell singlet biradicals have attracted much attention in the field of theoretical and materials chemistry due to their unique electronic structure.[1] Most open-shell singlet biradicals isolated to date are quinoidal singlet biradicals. On the other hand, only a few reports have been made on zwitterionic open-shell singlet biradicals, which limits structural diversity and hampers detailed understanding of their electronic structures and properties. Herein, we report the first synthesis and characterization of a polycyclic zwitterion with an open-shell character.[2]

We designed and synthesized zwitterion **1** (Figure 1a), which is kinetically stabilized by introducing bulky mesityl groups onto carbon atoms with large spin density (Figure 1b). Zwitterion **1** was isolated and characterized by X-ray crystal structural analysis. Based on bond lengths obtained by X-ray analysis, NMR studies, and DFT calculation, **1** can be described as the resonance structures in Figure 1a. **1** exhibited near infrared absorption and amphoteric redox properties originating from a small HOMO−LUMO energy gap. These results together with the observation of the thermally-excited triplet state by ESR (Figure 1c) and DFT calculations (Figure 1b) indicate that zwitterion **1** has an open-shell singlet ground state.

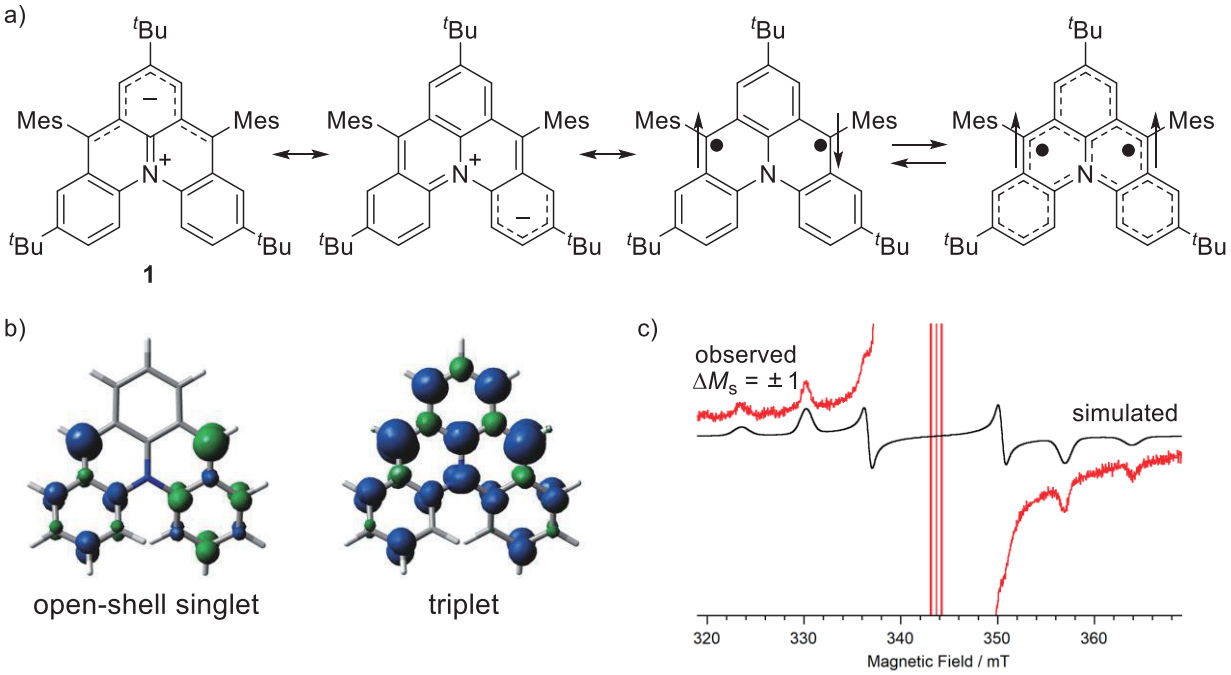

Figure 1. (a) Resonance structures, (b) Calculated spin densities, and (c) ESR spectrum of **1**.

[1] Abe, M. *Chem. Rev.* **2013**, *113*, 7011.
[2] Arikawa, S.; Shimizu, A.; Shintani, R. *Angew. Chem., Int. Ed.* **2019**, *58*, 6415.

2P-039s

Synthesis and Biological Evaluation of 3D Structure-Mimicked Apratoxin A Analogues

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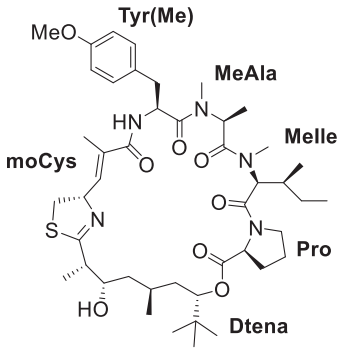
2) *Mitsubishi Tanabe Pharma Corporation*
3) *Department of Chemistry, University of Tsukuba*

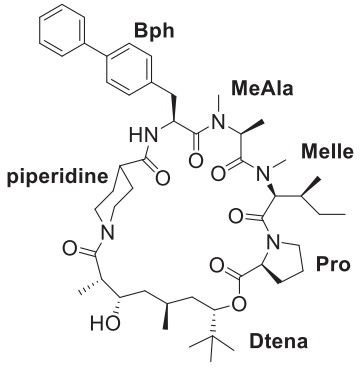
Apratoxin A (**1**) is a 25-membered cyclic depsipeptide, isolated from a marine cyanobacterium *Lyngbya majuscula* in 2001.[1] Total syntheses of **1** and its analogues have been accomplished by several groups including us.[2] This natural product has unique structural features such as a thiazoline-containing modified cysteine (moCys) moiety, three unnatural amino acids, and Dtena (3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid) possessing four chiral centers. **1** exhibits highly potent cytotoxicity against a variety of human cancer cells, indicating that **1** would be a promising lead compound for developing antitumor agents. However, it is difficult to apply **1** to the drug development because of its problematic structural complexity.

Recently, we have succeeded in development of apratoxin M16 (**2**),[3] which contains a piperidinecarboxylic acid moiety and biphenylalanine instead of the moCys moiety and Tyr(Me) residue, respectively, and exhibits highly potent cytotoxicity and growth inhibitory activity against various cancer cell lines as potent as apratoxin A. However, the structure of the Dtena moiety is still so complicated that a multi-step synthesis is required. Therefore, we designed new mimetics that have simpler structures and constrain their conformations similar to apratoxin M16.

In this study, we focused on the 3D structure of apratoxin M16 (**2**). We considered introducing a ring structure into the Dtena moiety to constrain its conformation like the stable conformation of **2**. In this presentation, the design and synthesis of four 3D structure-mimicked apratoxin A analogues and the results of biological evaluation will be discussed.



Apratoxin A (**1**)
HCT116 IC_{50} 2.8 nM



Apratoxin M16 (**2**)
HCT116 IC_{50} 1.1 nM

[1] Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J.; Corbett, T. H. *J. Am. Chem. Soc.* **2001**, *123*, 5418–5423.
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[3] Onda, Y.; Masuda Y.; Yoshida, M.; Doi, T. *J. Med. Chem.* **2017**, *60*, 6751–6765.

Chemical synthesis and function of *Helicobacter pylori* peptidoglycan fragments

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Toyonaka, Osaka 560-0043, Japan

Peptidoglycan, a major component of the bacterial cell wall, consists of polysaccharides and cross-linking peptides that forms a 3D mesh-like layer outside the plasma membrane. The polysaccharide chain is composed of alternating residues of β-(1,4) linked *N*-acetylglucosamine(GlcNAc) and *N*-acetylmuramic acid (MurNAc) attached by a peptide chain. Our group has revealed the immunostimulating mechanism of peptidoglycan by chemical synthesis of peptidoglycan fragments.[1]

Helicobacter pylori is a parasitic Gram-negative bacterium living in the stomach that causes chronic inflammation. It has recently been reported that *H. pylori* peptidoglycan modifications, i.e., *N*-deacetylation on GlcNAc and *O*-acetylation on MurNAc (Figure 1), confer lysozyme resistance and contribute to survival in the host.[2] In order to investigate whether these modifications also related to the immune regulation, we synthesized peptidoglycan fragments with different modifications.

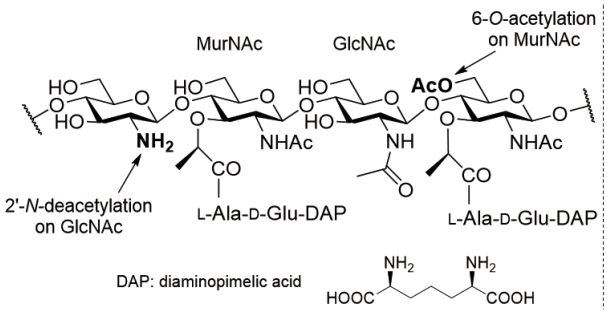

Figure 1: The chemical structure of *H. pylori* peptidoglycan and its modifications

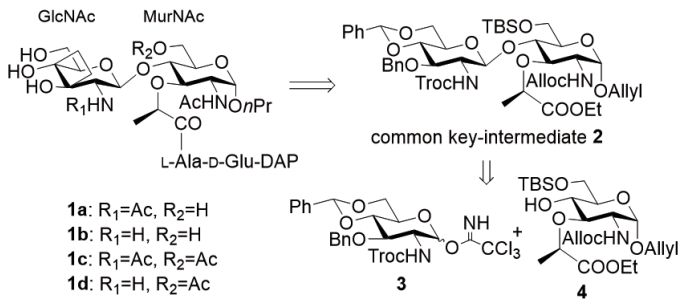

Figure 2: Target structures and synthesis strategy for *H. pylori* peptidoglycan fragments

In this work, we present the synthesis of *H. pylori* peptidoglycan fragments (**1a-d**) and elucidation of their immunological functions, especially effects of characteristic structural modifications. To construct diversity oriented synthetic route, common key-intermediate **2** with selectively removable protecting groups was developed via glycosylation of monosaccharide donor **3** and acceptor **4** (Figure 2). The conjugation of the peptide part to **2** and subsequent deprotection afforded *H. pylori* peptidoglycan fragments **1a-d**. The immunological activities of synthesized **1a-d** showed that *O*-acetylation reduces the immunostimulating activity, implying the association with immune escape mechanisms, while *N*-deacetylation has less influence on the immunostimulating activity.

[1] a) M. Chamaillard, K. Fukase, N. Inohara *et al.*, *Nature Immunol.,* **2003**, *4(7)*, 702. b) N. Inohara, K. Fukase, G. Nunez *et al.*, *J, Biol. Chem.,* **2003**, *278(8)*, 5509.
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2P-041

Electron-assisted tert-Alkylative Macrocylization

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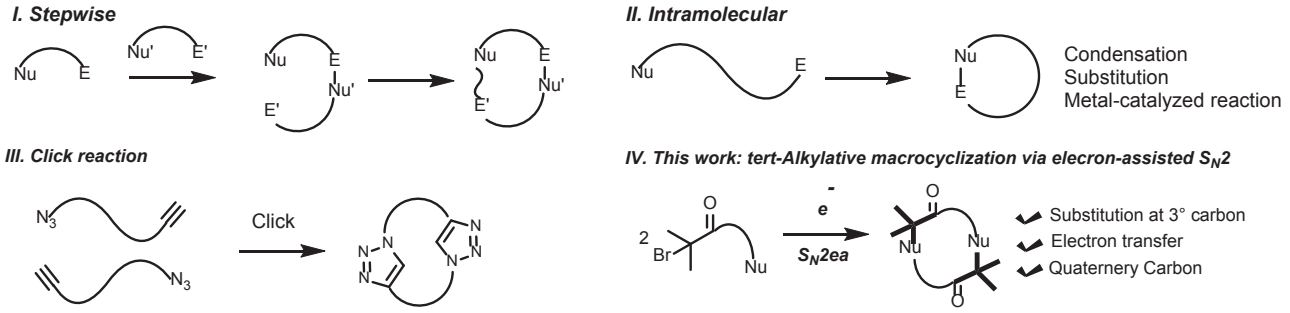
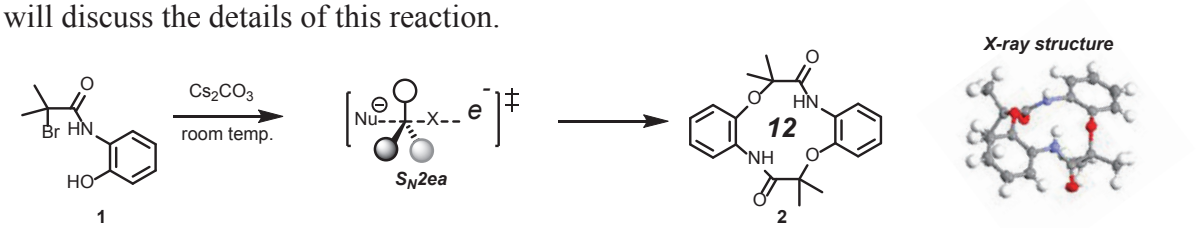
Macrocyclic compounds are important structure for pharmaceuticals and ligands for various elements. There are many reports on the synthesis of macrocycles[1]: I. stepwise construction via intermolecular reactions. II. Intramolecular reaction including condensation, substitutions, and metal-catalyzed reactions. III. Click reaction. By using those methodologies, the combinations of C(sp), C(sp^2) and 1° or 2° C(sp^3) are possible to form various C-C bonds. As the results, two- or three-dimensional structures possessing unique properties can be provided. Although interests of macrocycles in both medicinal chemistry and synthetic chemistry are increasing, a number of issues should be addressed including, (1) developing new methodology to construct macrocycles, and (2) incorporating a quaternary carbon in a macrocycle via tertiary alkylation. In this context, we envisaged to synthesize macrocycles including a quaternary carbon using alpha-bromocarbonyls that are a functionalized tert-alkyl source (IV).



We have studied the chemistry of alpha-bromocarbonyls in the presence of a copper catalyst [2]. During the course of our study, an electron-activated alpha-bromocarbonyl compound easily reacted with tert-BuOH to produce a highly congested ether bond, in which an electron could be coming from Cs_2CO_3 [3]. We call this reaction as electron-assisted S_N2 reaction (S_N2ea). When the reaction of **1** was carried out in the presence of Cs_2CO_3, we obtained 12-membered ring **2** in good yield at room temperature. This result shows that S_N2ea could be suitable for macrocyclizations. In this presentation, we will discuss the details of this reaction.



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[2] (a) Nishikata, T.; Noda, Y.; Fujimoto, R.; Sakashita, T. *J. Am. Chem. Soc*. **2013**, *135*, 16372. (b) Nakamura, K.; Nishikata, T. *ACS Catal*. **2017**, *7*, 1049. 4. (c) Nishikata, T.; Ishida, S.; Fujimoto, R. *Angew. Chem., Int. Ed*. **2016**, *55*, 10008. (d) Ishida, S.; Takeuchi, K.; Sunada, Y.; Nishikata, T. *Angew. Chem., Int. Ed*. **2017**, *56*, 11610.
[3] unpublished results.

2P-042

Intramolecular [2+2] photocycloaddition using chiral phosphoric acid as a template

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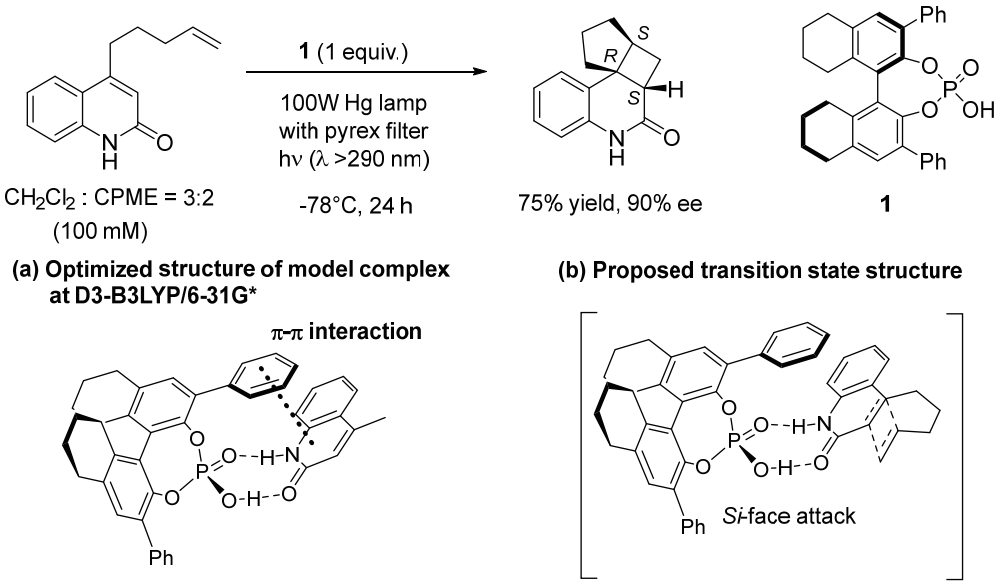
Recently, photochemical reactions have attracted considerable attention as a sustainable synthetic method with environmentally friendly and atomeconomy. However, it is not easy to control the high energy excitation state structure in the photochemical reaction, and achievement of enantioselective photochemical reaction is still difficult. [1] T. Bach and co-workers have developed chiral lactams as efficient templates for enantioselective photochemical reactions. The chiral templates eventually elevated to chiral sensitizers for catalytic enantioselective photochemical reactions.[1-3] In this research, intramolecular [2+2] photocycloaddition of quinolinone using chiral phosphoric acid[4] as a template was investigated. After several optimizations of reaction conditions, the corresponding [2+2] cycloaddition product was obtained in good yield (75%) with high enantioselectivity (90% ee). The theoretical calculation of model complex indicated the stabilization of the complex by π-π interaction between the phenyl group on phosphoric acid and the quinolinone ring. On the basis of the theoretical calculation, the transition state structure, in which [2+2] photocycloaddition proceeded from *Si*-face attack, was proposed.



[1] Brimioulle, R.; Lenhart, D.; Maturi, M. M.; Bach, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 3872-3890.
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2P-043

Synthesis of Benzo[*b*]thiophene-3-Carboxamides via Rhodium-Catalyzed Cyclization of (*ortho*-Alkynyl)phenyl Sulfides in the Presence of Isocyanates

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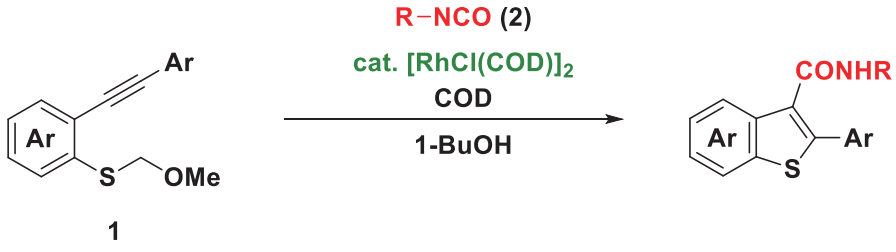
The benzo[*b*]thiophene framework occurs frequently in numerous biologically active compounds and designed medicinal agents, representing an important class of heterocycles. Therefore, the development of more practical and efficient procedures for preparing functionalized benzo[*b*]thiophenes has long been an area of intensive research. While a number of methods for the preparation of this class of compounds have recently been reported, versatile and applicable methods to access multi-substituted benzo[*b*]thiophenes are still limited. Amongst the various methods so far reported for the synthesis of benzo[*b*]thiophenes, several examples involve the cyclization of (*ortho*-alkynyl)phenyl sulfide derivatives. Despite potential effectiveness and applicability, however, the above-mentioned heteroannulation approach to benzo[*b*]thiophenes starting from (*ortho*-alkynyl)phenyl sulfides have not been well studied. In this symposium, we present a novel protocol for the construction of 2,3-disubstituted benzo[*b*]thiophenes via a heteroannulation process. The method involves a catalytic cyclization of (*ortho*-alkynyl)phenyl methoxymethyl sulfides **1** in the presence of isocyanates **2**. Use of a rhodium catalyst successfully effects the process, leading to the one-pot formation of benzo[*b*]thiophene-3-carboxamides.[1] Detailed results of the screening of reaction parameters as well as the substrate scope of the method will be discussed.



- *catalytic construction of 2,3-disubstituted benzo[b]thiophenes*
- *tandem-type, cyclization–addition process*
- *13 examples*
- *up to 80% isolated yield*
- *mild reaction conditions (rt to 50 °C)*

[1] Mizukami, A.; Tsugita, M.; Shimora, M.; Tanaka, S.; Hayama, N.; Kimachi, T.; Inamoto, K. *Chem. Lett.* **2019**, *48*, 468–470.

A new methodology to constructing axially chiral biaryls using organocatalyst

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Tohru Taniguchi,[2] Kenji Monde[2] and Yujiro Hayashi*,[1]
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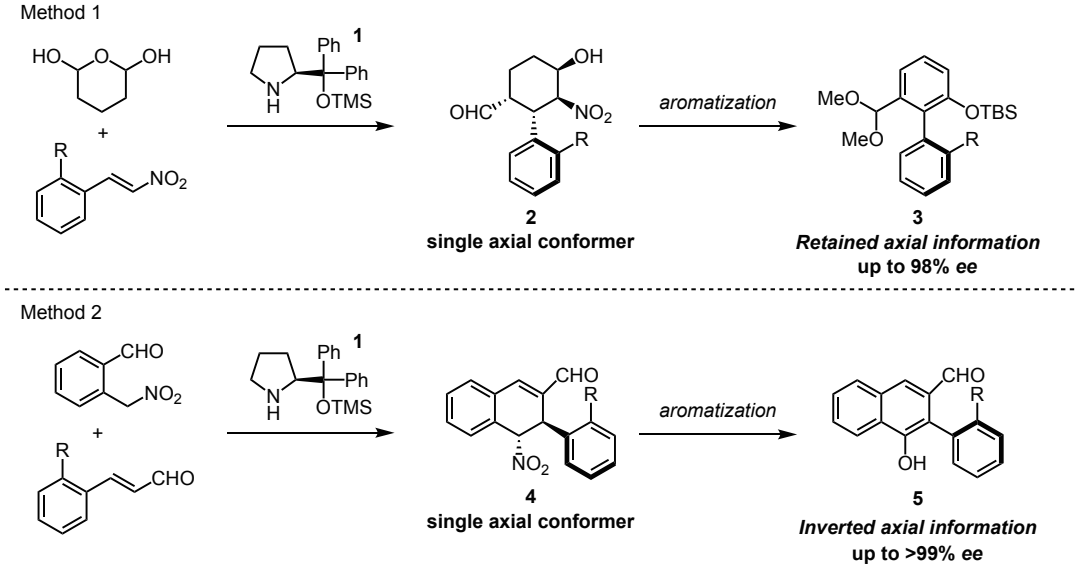
[2]*Faculty of Advanced Life Science, Hokkaido University, Sapporo, Japan*

Axially chiral biaryls are used as chiral ligands and organocatalysts, and also found in the biological active natural products. Thus, a development of the new methodology for the synthesis of axially chiral biaryls with high enantio-selectivity is important.

On the other hand, we have been investigating the construction of chiral carbocycles via domino reaction by the use of organocatalyst **1**. Diphenylprolinol silyl ether **1** is an effective catalyst with pyrrolidine core. Recently we found that some chiral carbocycles prepared by asymmetric domino reaction using organocatalyst exist as a single axial conformer, possessing not only central chirality but also axial information. If we remove central chirality without losing axial information, axial chiral molecules would be synthesized. Based on this idea, we developed two methods for the synthesis of axially chiral biaryls.

Method 1: Axially chiral biaryls **3** with excellent enantioselectivity were synthesized from domino reaction products **2.**[1)] The absolute configuration of the resulting biaryls reflected axial information of intermediate **2**, in which the axial information of intermediate **2** was retained.

Method 2: Axially chiral biaryls **5** with very high enantioselectivity were synthesized from the other domino reaction products **4,**[2)] in which the absolute configurations of biaryl **5** were completely inverted from the axial information of intermediate **4**. The reaction was investigated with experiments and computational method, and reaction mechanism will be discussed at the poster.



[1] Y. Hayashi *et al., Angew. Chem. Int. Ed.* **2007**, *46*, 4922.
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Design & Synthesis of Novel Halogen-Bond-Donor Catalysts

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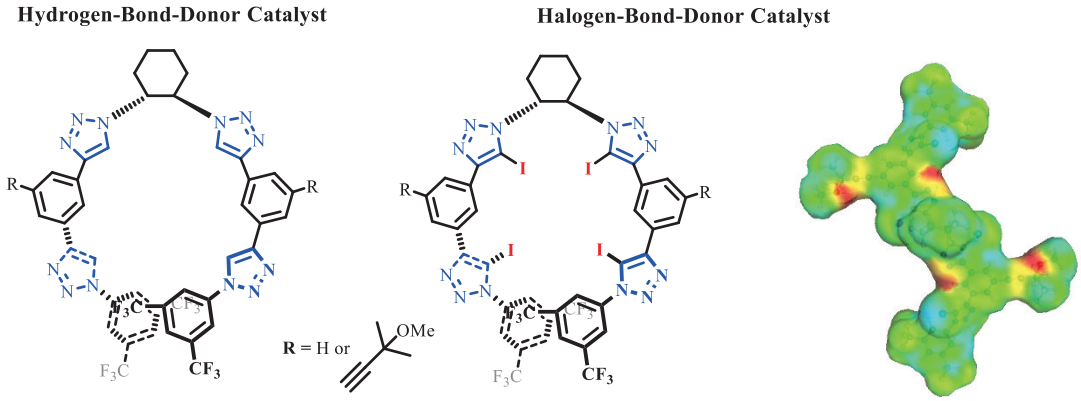
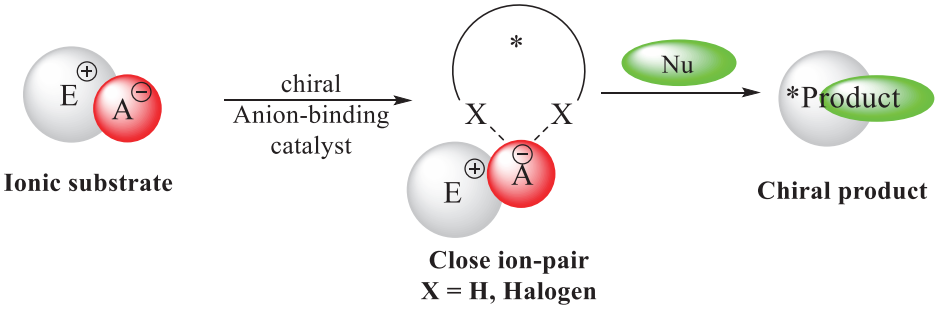
Institut für Organische Chemie, Westfälische Wilhelms-Universität Münster, Corrensstr. 40, 48149 Münster, Germany



Asymmetric hydrogen-bond-donor catalysis has emerged as a powerful synthetic approach for the preparation of a variety of valuable chiral organic molecules. Our group successfully demonstrated that 1,2,3-triazoles are capable of promoting catalytic anion-binding processes and even surpass known thiourea or silanediol moieties.[1] The principle of halogen-bonding offers further possibilities to tune the properties of non-covalent organocatalysts, as polarized halides are able to act as electron accepting sites in a similar fashion as hydrogen-bond-donors.[2] To this day, enantioselective transformations, guided by halogen-bond-donor catalysts remain elusive.

Herein, we present the design and synthesis of new types of chiral organo-catalysts based on previously explored tetrakis-1,2,3-triazole structures. Different 5-iodo-1,2,3-triazole containing structures have been designed, presenting either both - hydrogen- and halogen-bond-donor properties - or just halogen-bond-donor properties.



[1] (a) M. Zurro, S. Asmus, S. Beckendorf, C. Mück-Lichtenfeld, O. García Mancheño, *J. Am. Chem. Soc.* **2014**, *136*, 13999. (b) S. Asmus, M. Zurro, T. Fischer, O. García Mancheño *Angew. Chem. Int. Ed.* **2015**, *30*, 8823. (c) T. Fischer, J. Bamberger, M. Gómez-Martínez O. García Mancheño, *Angew. Chem. Int. Ed.* **2019**, *58*, 3217.

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27-ISHC Abstract

Fe (III) Promoted Intramolecular Cascade Cyclization for the Synthesis of Quinoline fused Selenophene-based Heteroacene Scaffolds

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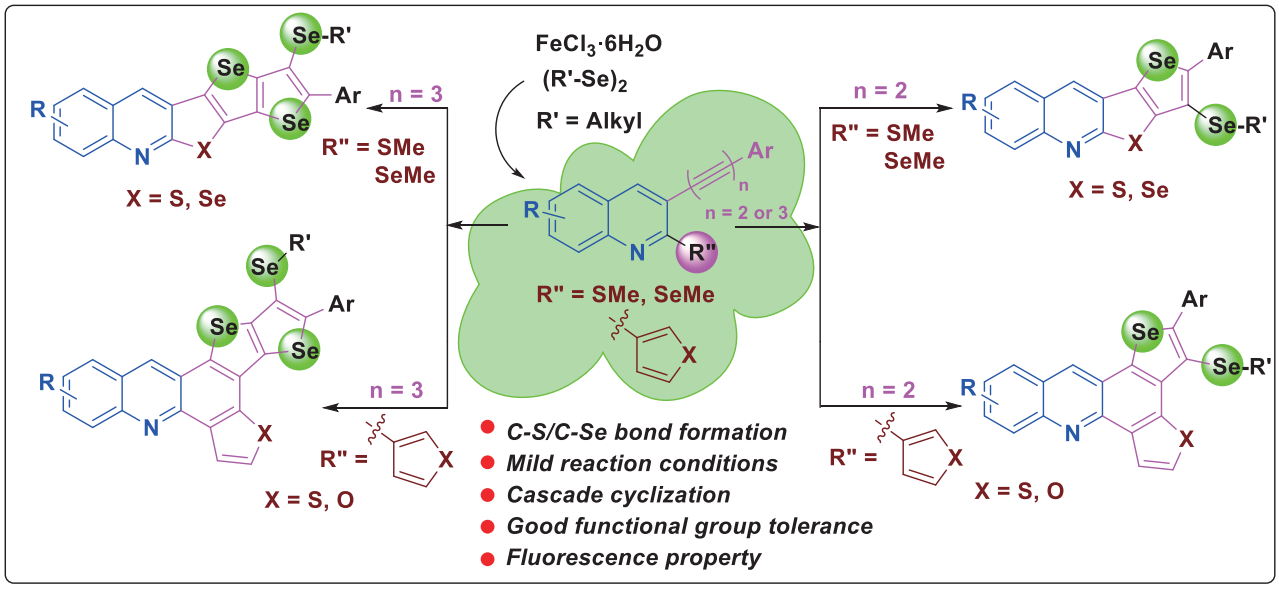
The Fe(III)-promoted linear intramolecular cascade cyclization of 1,3-diyne and 1,3,5-triyne for the construction of selenophene-fused, quinoline-based heteroacene scaffolds. In one step 1,3-diyne and 1,3,5-triyne were cyclized *via* diversified internal nucleophiles by using diorganyl diselenides. The diorganyl diselenide plays dual role, one as cyclizing agent and secondly insertion of one and / or two selenium atom and one R′-Se group in the final product. This is highly important in terms of atom economy. Diversified internal nucleophiles were used to afford quinoline and acridine based cores. The synthesized selenophene-fused derivatives showed λ_{max}, F_{max} and Φ_f values in the range from 370-411 nm, 427-472 nm and 0.003-0.059, respectively in dichloromethane solvent.



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[2] Banerjee, B.; Koketsu, M. *Coord. Chem. Rev.* **2017**, *339*, 104-127.
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2P-047

Synthesis of Tripodand- and Dicryptand-Type Compounds Using Mn(III)-Based Dihydrofuran-Clipping Reaction

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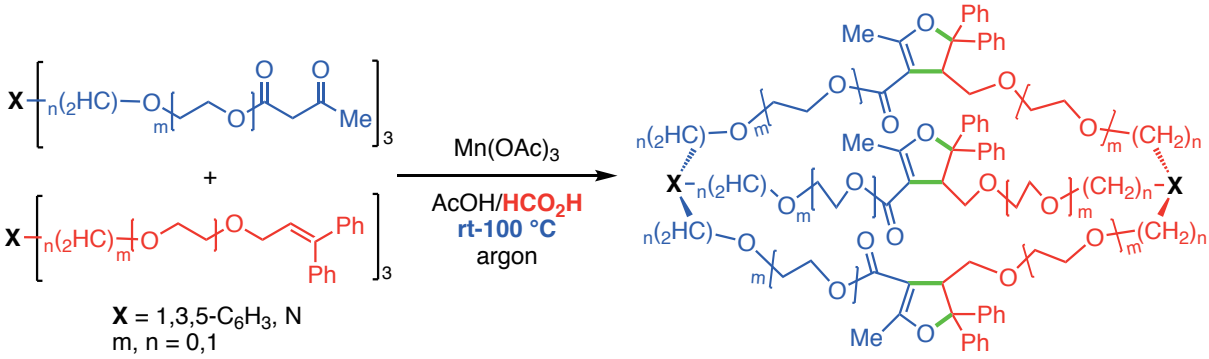
Kurokami 2-39-1, Kumamoto 860-8555, Japan

Dihydrofurans are one of the most important heterocycles as a building block for the synthesis of natural products and functional materials. One of the most efficient and convenient synthesis of the dihydrofuran is to use Mn(III)-based oxidation of alkenes with 1,3-dicarbonyl compounds.[1] The oxidation of 2,4-pentanedione with manganese(III) acetate in the presence of 1,1-diphenylethene in boiling acetic acid gave the corresponding dihydrofuran in 92% yield. The reaction starts from the formation of the Mn(III)-oxopentenolate complex, which constructs an electron donor-acceptor complex with alkene, and finally, carbon-carbon bond formation followed by cyclization via a single-electron transfer oxidation results in the dihydrofuran. Since a similar reaction of benzyloxyethyl 3-oxobutanoate with benzyloxyethoxypropene afforded the substituted dihydrofuran, the 1,4-disubstituted benzene bearing a terminal 3-oxobutanoate and alkene underwent the Mn(III)-based oxidation to produce the corresponding cyclophane-type dihydrofurans,[2] that is, the cyclophanes were constructed by *the dihydrofuran-clipping reaction*.[3] We then applied the reaction of amine and 1,3,5-trisubsutituted benzene having a terminal 3-oxobutanoate with alkene, giving tripodand-type dihydrofurans, while the reaction with amine and 1,3,5-trisubsutituted benzene having a terminal alkene afforded dicryptand-type dihydrofurans. Addition of formic acid was effective for the dihydrofuran-clipping reaction.[4] The obtained cage-type compounds are fascinating in biological and material science.[5]



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2P-048

Electrochemical Synthesis of Cyclic Oligosaccharides

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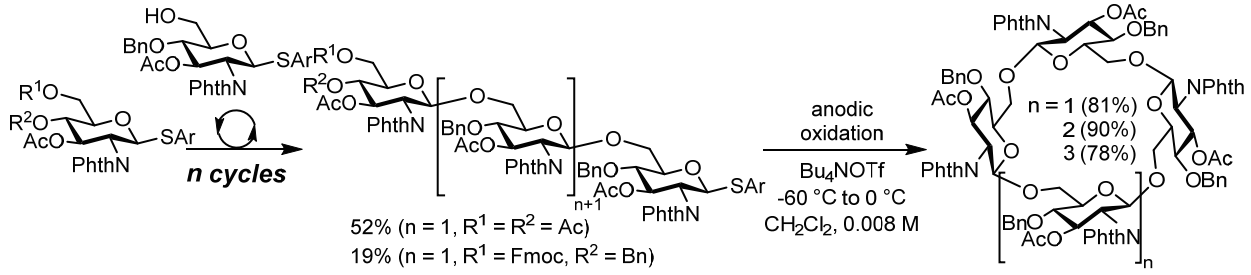
Tottori 680-8552, Japan

Cyclic oligosaccharides such as cyclodextrins and their derivatives have been paid attention as functional molecules. Various types of natural and unnatural cyclic oligosaccharides including the smallest cyclodextrins[1] and cyclic oligoglucosamines[2] have been reported. To investigate properties of these novel cyclic oligosaccharides and utilize them as functional materials, it is desirable to develop a method to prepare cyclic oligosaccharides in efficient and stereoselective manner.

We have developed "*automated electrochemical assembly*" which is an electrochemical method to synthesize oligosaccharides in an automated manner. Several oligosaccharides such as oligoglucosamines,[3] oligomannosides[4] and β-glucans[5] have been synthesized. Therefore, we envisioned that the electrochemical method may also be useful to convert linear oligosaccharides into cyclic oligosaccharides. Here we demonstrate that the electrochemical method enables stereoselective synthesis of cyclic oligosaccharides.

Precursors of cyclic oligosaccharides with a free hydroxy group was prepared by automated electrochemical assembly; however, the yield of the desired precursor was moderated with 6-*O*-Fmoc group. We improved the yield by starting from a disaccharide as a terminal building block. Thus-obtained precursors were cyclized by anodic oxidation under the conventional conditions of automated electrochemical assembly. Linear tetra-, penta-, and hexasaccharides were converted to the corresponding cyclic oligosaccharides in 81% (n = 1), 90% (n = 2) and 78% (n = 3), respectively. The primary alcohol at C-6 of the precursor is more reactive than other secondary alcohols. Therefore, deacetylation of the tetrasaccharide (R^1 = R^2 =Ac) was also converted to the cyclic tetrasaccharide under the same reaction condition.[6]



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2P-049

Novel approaches toward de novo syntheses of N-heterocycles triggered by gold(I)-catalyzed aza-enyne metathesis

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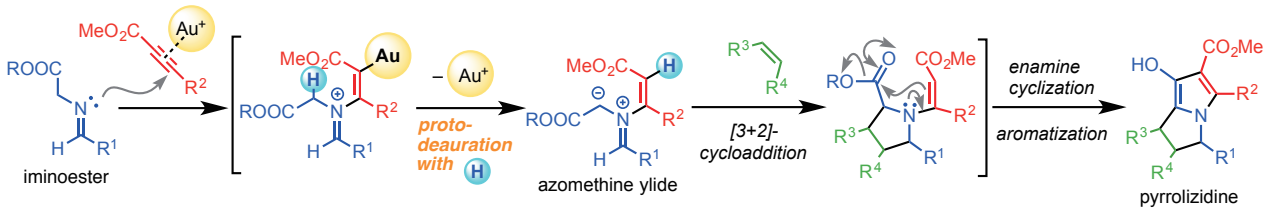
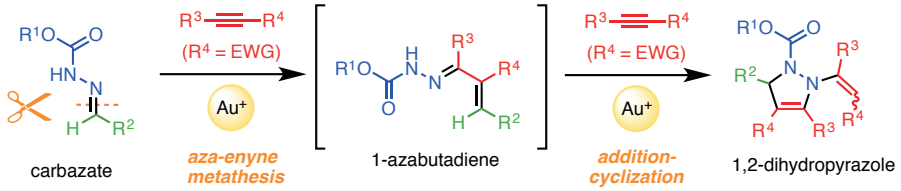
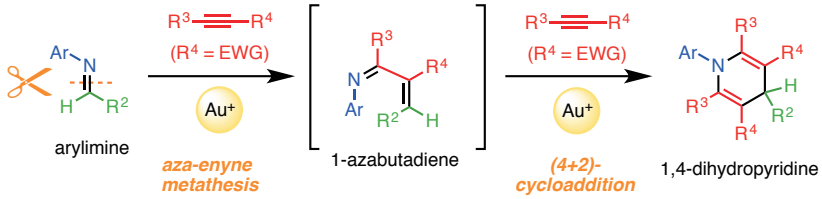
Multi-substituted nitrogen heterocycles are versatile and highly important skeleton in various scientific fields. Thus, diverse synthetic approaches toward such heterocycles have been studied for efficient and precise preparations avoiding circuitous site protection/deprotection manipulations of corresponding heterocyclic precursors. As a possible solution, we developed a novel multi-component synthesis of densely substituted pyrrolizidines via a gold(I)-induced azomethine ylide generation from glycine iminoesters and propiolates.[1]



During the study for an azomethine imine formation via the analogous reaction system, a reaction of carbazate instead of glycine iminoester, we unexpectedly found a novel reaction pathway to pyrazoles through a gold(I)-catalyzed aza-enyne metathesis and a hydroamination of another acetylene with the resultant 1-azabutadiene followed by a 6π-electrocyclization.



Further investigations on the substrate scope revealed that the aza-enyne metathesis was also induced from aryl imines and acetylenes to afford the corresponding 1-azabutadiene, which was then transformed into 1,4-dihydropyridines via a (4+2)-cycloaddition reaction with another molecule of acetylene activated by gold(I) catalyst.



In this conference, the above de novo syntheses of highly substituted N-heterocycles will be discussed regarding the scopes and reaction mechanisms including torquoselectivities observed in the ways to the common 1-azabutadiene intermediates. Moreover, recent studies with oxime ethers will be introduced briefly.

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2P-050

Oxidation of *p*-Methoxybenzyl Ethers by Electronically Tuned Nitroxyl Radical Catalysts

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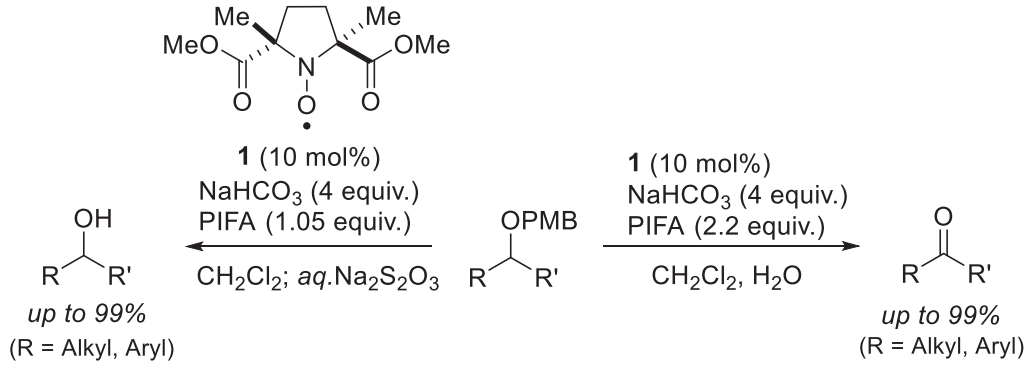
Oxidative deprotection of *p*-methoxy benzyl (PMB) groups for alcohols has been generally carried out with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) or ceric ammonium nitrate (CAN). However, these methods are not environmentally benign, because DDQ is known to produce toxic HCN, and the deprotection by CAN requires more than two equivalents of cerium, rare-earth metal. In addition, both reagents can not be applied for direct synthesis of carbonyl compounds from PMB ethers.

We have achieved chemoselective oxidation of an electron rich benzylic hydroxyl groups in the presence of electron deficient ones by nitroxyl radical catalyst **1**.[1] Mechanistic analysis revealed that the oxidation mediated by cat. **1** proceeded through rate determining hydride transfer. With this achievement, we extended the oxidation with cat. **1** to the oxidative deprotection of PMB ethers, as well as direct transformation of the alcohols produced by this oxidation to the carbonyl compounds.

The oxidative deprotection of PMB ethers bearing various functional groups in the presence of 10 mol% of cat. **1** and 1.05 equivalents of phenyliodinetrifluoroacetate (PIFA) gave the corresponding alcohols in up to 99% yield. With these substrates, TEMPO only gave the alcohols in low yield. Hammett substituent constant (ρ = –2.9) in the deprotection of *O*-benzylated-3-phenylpropanols supported cat. **1** catalyzed deprotection of PMB ethers also proceeded via hydride transfer.

The direct oxidation of PMB protected alcohols to carbonyl compounds was also achieved. A variety of ketones and aldehydes were prepared through the deprotection–oxidation process of PMB ethers derived from aliphatic and benzylic alcohols in the presence of cat. **1** (10 mol%), PIFA (2.2 equiv.), and H_2O in up to 99% yield.



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2P-051

Total Synthesis of Pseudouridine

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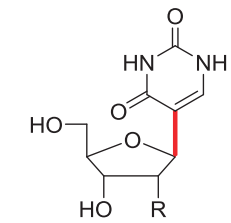
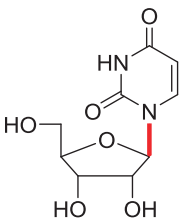
[b] *Faculty of Pharmacy, National Yang-Ming University, Taipei 11221, Taiwan*

C-Nucleosides belong to the category of nucleoside derivatives in which the ribofuranosyl moiety is linked to the heterocyclic base with a carbon-carbon bond. The first *C*-nucleoside found in nature is pseudouridine (ψ, **1**), which is the fifth abundant nucleoside component in RNA and the most abundant *C*-nucleoside. Pseudouridine (**1**) is the structural isomer of uridine (**2**) with identical uracil base and ribosyl sugar moieties but differ only in the nucleosidic bonds. It is formed by post-translational isomerization from uridine in RNA catalyzed by pseudouridine synthase. Due to the very limited commercial availability and expensive prices, chemical synthesis of pseudouridine continues to offer an alternative supply for this biological important molecule. Nevertheless, the chemical synthesis of *C*-nucleosides (and also *C*-glycosides) is perceived to be challenging and the development of efficient syntheses for *C*-nucleosides is still an ongoing task.

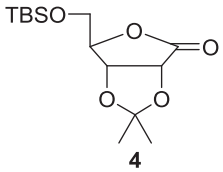
We first adopted the ribonolactone approach for the synthesis of pseudouridine (**1**). The addition of 5-lithiated 2,4-dimethoxypyrimidine to 5-*O*-*t*-butyldimethylsilyl-2,3-*O*-isopropylideneribonolactone (**4**) formed an anomeric mixture of the ribonolactols. Subsequent reductive dehydroxylation of ribonolactols followed by the deprotection afforded the desired pseudouridine accompanied with the α-isomer as the major product.[1] Alternatively, the Heck glycosylation approach was employed.[2] The palladium-catalyzed reaction of 5-iodouracil derivatives with 3,5-di-*O*-*t*-butyldimethyl ribofuranoid glycal (**5**) followed by the removal of protecting groups gave exclusively the β-anomer of 2'-deoxypseudouridine (**3**) in a good yield. Meanwhile, chemical elaboration of the Heck glycosylation adduct afforded the desired pseudouridine (**1**) in a good stereoselectivity.[3]



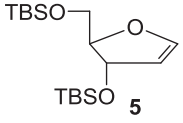
R = OH:
pseudouridine (**1**, Ψ)
R = H:
2'-deoxypseudouridine (**3**)



uridine (**2**, U)



4



5

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Regioselective Synthesis of Metalated 2-Pyrones by Intramolecular Oxymetalation Using Indium Trihalide

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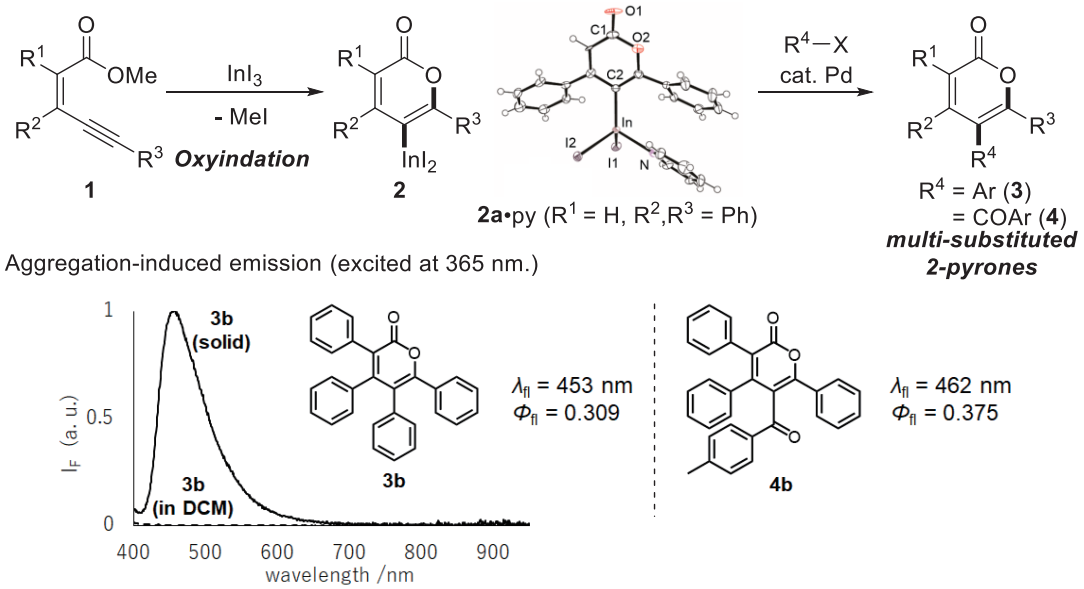
[2]*Frontier Research Base for Global Young Researchers Center for Open Innovation Research and Education, Graduate School of Engineering, Osaka University, Osaka 565-0871*

2-Pyrones are important oxygen-containing heterocycles because they have a broad range of biological activities and are versatile building blocks in organic synthesis. Therefore, the development of general synthetic methods of 2-pyrones has great significance. A metalated 2-pyrone, which bears a carbon-metal bond, has been used as a powerful synthetic precursor of 2-pyrones. However, there are few reports for tri- and tetrasubstituted metalated 2-pyrones in spite of their significant synthetic utility.[1] Herein, we present the regioselective synthesis of metalated 2-pyrones through oxymetalation using an indium salt.[2] The reaction of various carbonyl-ene-ynes **1** with InI_3 proceeded via oxyindation to give the corresponding 2-pyrone derivatives **2** including a C-In bond at the 5-position. The structure of **2a** (R^1 = H, R^2 = R^3 = Ph) was identified by X-ray crystal structure analysis as a pyridine complex. We applied the metalated 2-pyrones **2** to the synthesis of multi-substituted 2-pyrones. Palladium-catalyzed cross-coupling of **2** with an aryl iodide yields multi-substituted 2-pyrone **3**. The cross-coupling of **2** with an acid chloride also proceeded to give 2-pyrone **4** bearing four types of functional groups. Synthesized 2-pyrone derivatives **3b** and **4b** show intensefluorescence only in the solid state (aggregation-induced emission). Therefore, the present method established a modular synthesis of multi-functionalized 2-pyrones.



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[2] Our group has recently reported the intramolecular oxymetalation of 2-alkynylbenzoate with indium trihalides to afford isocoumarins including a C-In bond : Y. Kita, T. Yata, Y. Nishimoto, K. Chiba, M. Yasuda, *Chem. Sci.* **2018**, *9*, 6041.

2P-053s

Accessing Pyrrolodiazine Scaffolds for Kinase Inhibition

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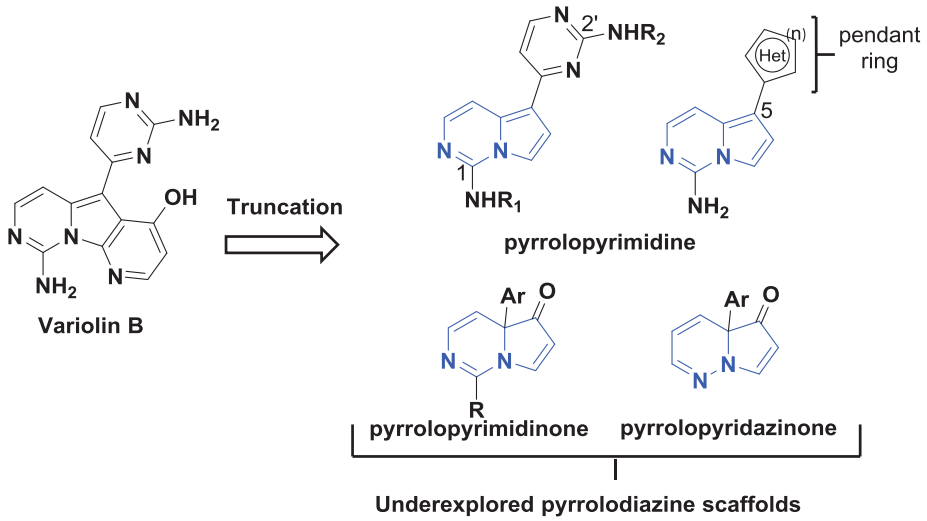
Sydney NSW, 2052

Variolin B is a marine alkaloid exhibiting potent kinase inhibitory activity.[1] Its utility is somewhat limited however, due to its low solubility and bioavailability. Work in the Morris group has shown that truncation of the tricyclic core to the simplified pyrrolo[1,2-*c*]pyrimidine scaffold retains the potent biological activity seen in the parent compound whilst improving its physicochemical properties.[2] Furthermore, differential substitutions at the C1 and C2′ positions of this scaffold can alter the selectivity profile of these molecules. Similarly, variations of the heteroaromatic C5-pendant ring have also shown to be significant in modulating the selectivity.[3]

Accessing analogues of these compounds in an efficient manner poses a synthetic challenge, as current approaches are limited due to their linear nature and challenging synthetic steps. This work aims to develop efficient protocols to the pyrrolodiazine scaffolds which allow for rapid, divergent generation of analogues for biological evaluation.



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2P-054

Development of Direct and Regioselective Monofluorination of 1-Isoquinolones and 2-Pyridones with *N*-fluorobenzenesulfonimide (NFSI)

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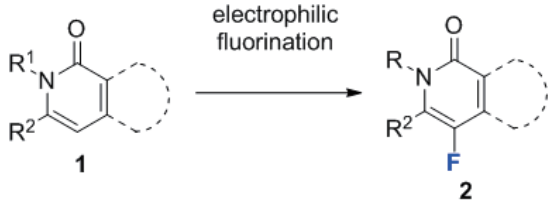
Fluorinated compounds have attracted for drug discovery by the feature of improving biological activity and physicochemical profiles. Although electrophilic fluorination reaction is one of the most useful and simple methodologies for synthesis of fluorinated heterocyclic compounds [1], there is still difficulty in fluorinating at the appropriate position of 1-isoquinolones and 2-pyridones as common scaffold in drug discovery. To date, few examples for the direct fluorination of 1-isoquinolones and 2-pyridones have been reported, but the regioselective monofluorination without overreaction still remains limited due to the difficulty of controlling the reaction.[2] We herein developed the direct and regioselective monofluorination of 1-isoquinolones and 2-pyridones using a stable and easy-handling electrophilic fluorinating reagent, *N*-fluorobenzenesulfonimide (NFSI).

The fluorination of 2-methylisoquinolin-1(2*H*)-one (**1a**) with Selectfluor™, the most commonly used as an electrophilic fluorinating reagent, afforded a complex mixture containing trace amount of desired 4-fluoro-2-methylisoquinolin-1(2*H*)-one (**2a**). On the other hand, when NFSI which shows lower reactivity compared to Selectfluor™ was used in the reaction, desired product **2a** was obtained in moderate yield as a single regioisomer. An appropriate balance between the substrate stability and the reactivity of fluorinating reagents is essential to achieve the regioselective fluorination. This NFSI method could be applied to the fluorination of some bicyclic and monocyclic pyridones, providing the corresponding desired monofluorinated products with high regioselectivity.



	NFSI	Selectfluor™
reagent		
reactivity	low	high
result	✓ *regioselective* ✓ *sole product 2*	✓ complex mixture

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2P-055

Structure-Activity Relationship Studies of Maitotoxin Based on the Chemical Synthesis of Partial Structures

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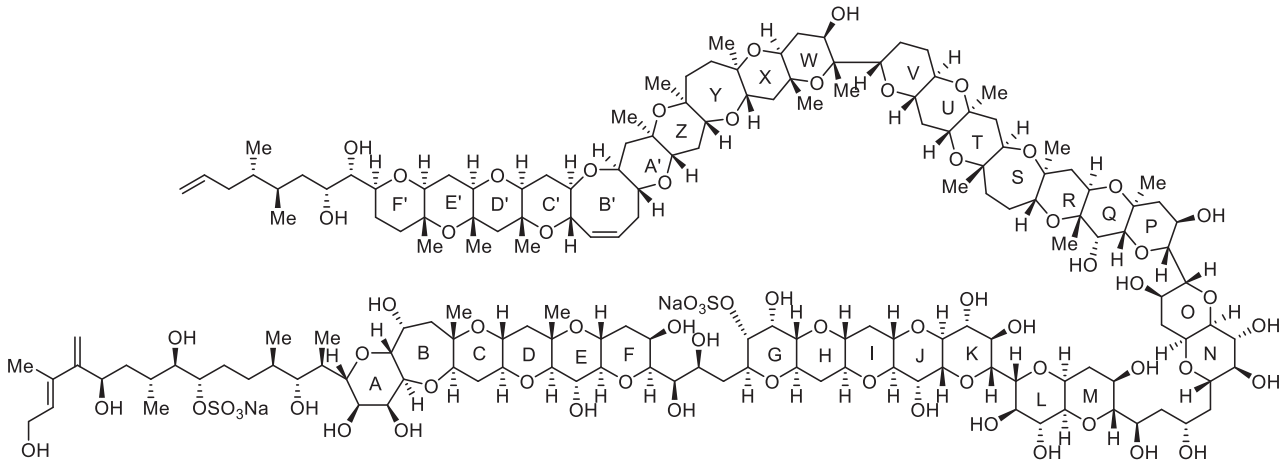
Maitotoxin (MTX) is a ladder-shaped polyether produced by dinoflagellate *Gambierdiscus toxicus*. MTX is a highly toxic compound against mammals (50 ng/kg), and it elicits potent calcium ion influx (0.3 nM) in all cell types examined to date. Despite a large number of pharmacological and biophysical investigations, the precise mode of action of MTX has not been elucidated at the molecular level, primarily due to the limited availability of MTX from natural sources. As a part of the structure-activity relationship studies of MTX based on the chemical synthesis of partial structures of MTX, the LMNO, *ent*-LMNO, NOPQR(S),[1] QRS,[2] WXYZ,[3] WXYZA'B'C',[4] C'D'E'F'[5] ring systems were synthesized. By using these fragments, inhibitory activity against MTX-induced calcium ion influx was evaluated. In this symposium, synthrsis of unified synthesis of the DEF and GHI ring systems, and highly convergent synthesis of the WXYZA'B'C'D'E'F'ring system based on the synthetic method developed in our laboratory will be reported.



Maitotoxin

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2P-056s

Synthesis of Biologically Active Molecules Based on Unique Right-Side Structure of Physalins

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Physalins (physalin B, **1**) are steroidal components of *Physalis* plants. The structure of physalins is characterized by a highly oxygenated and complex right-side structure. In addition to their structural complexity, physalins showed several unique biological activities, including inhibitory activity on NF-κB activation. We previously synthesized racemic right-side structure (DFGH-ring system, **2**) of physalins and revealed its biological function.[1-4] This time, we aim to synthesize enantiopure **2** bearing various hydrophobic groups R in order to develop structurally-novel NF-κB inhibitors with improved biological activities.

First, we developed a method to introduce a variety of hydrophobic group R to enantiopure tricyclic key intermediate **3**, which was prepared in 22 steps. The synthesis of DFGH-ring compound **2** with different R group were achieved through the following domino ring transformation. We found that the R group affected the yield of this transformation. The details will be disclosed in this congress.

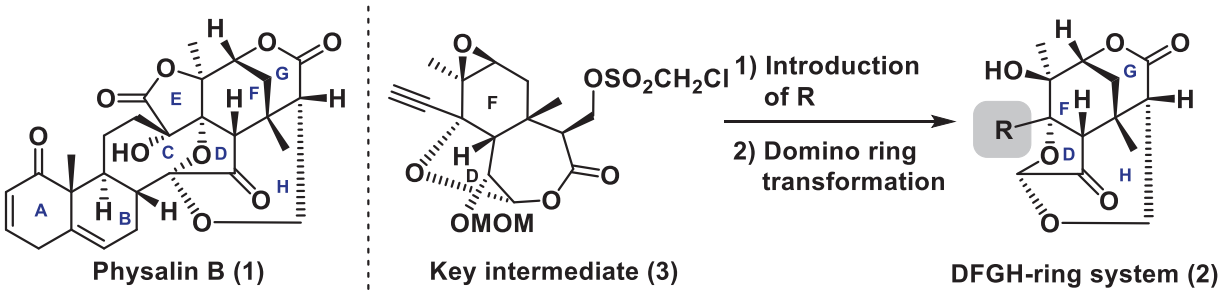

Figure 1. Structure of Physalin B **(1)**, DFGH-ring system **(2)** and key intermediate **(3)**

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2P-057

Divergent synthesis of methylene lactone- and methylene lactam-based spiro compounds

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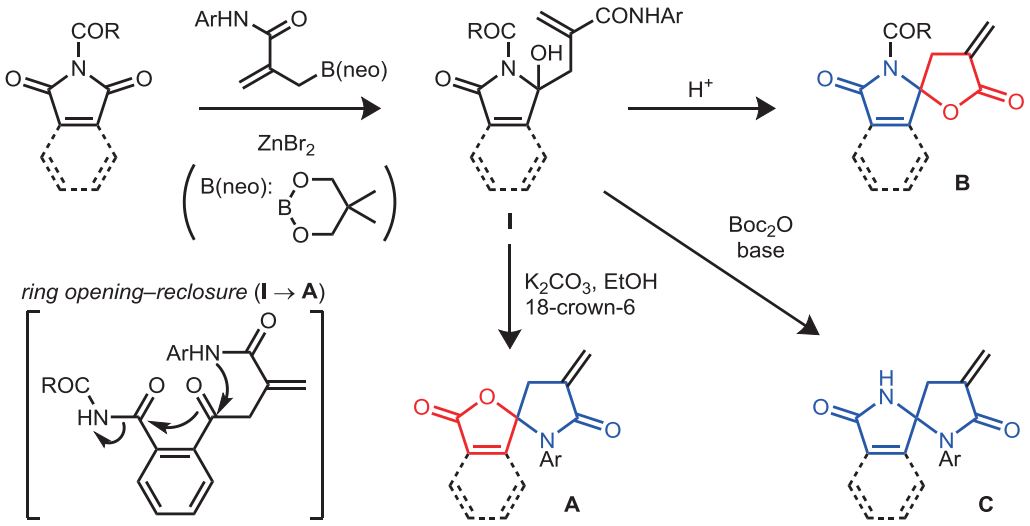
Compounds with a spiro center connecting to both heteroatoms of two heterocycles such as spiroketals are often found in bioactive natural products, and their structural complexity and unique bioactivities have attracted the interest of synthetic chemists.[1] Although synthetic methods of alcohol- or amine-derived spiroketals are well established, approaches toward spiro compounds consisting of lactone or lactam rings remain understudied. In this symposium, we report a divergent synthesis of methylene lactone- and methylene lactam-based new spiro compounds starting from *N*-carbonyl imides.

N,*O*-Spiro compounds **A** including both a lactam and a lactone were directly derived from *N*-carbonyl imides through a one-pot process involving $ZnBr_2$-mediated addition of β-amido allylboronate species followed by an irregular ring opening–reclosure.[2] On the other hand, regioisomeric spiro compounds **B** were prepared by treatment of isolated intermediates **I** under acidic conditions. Furthermore, new *N*,*N*-spiro compounds **C** could be obtained from the same intermediates through *N*-Boc protection followed by unusual lactam cyclization under basic conditions. We also report the advantage of our methodology on spacious cytotoxic evaluation of methylene lactone/lactam-based spiro compounds.



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2P-058s

Alkynoyl *o*-Iodo Anilides as Versatile Substrates for the Synthesis of Heterocyclic Luminophores

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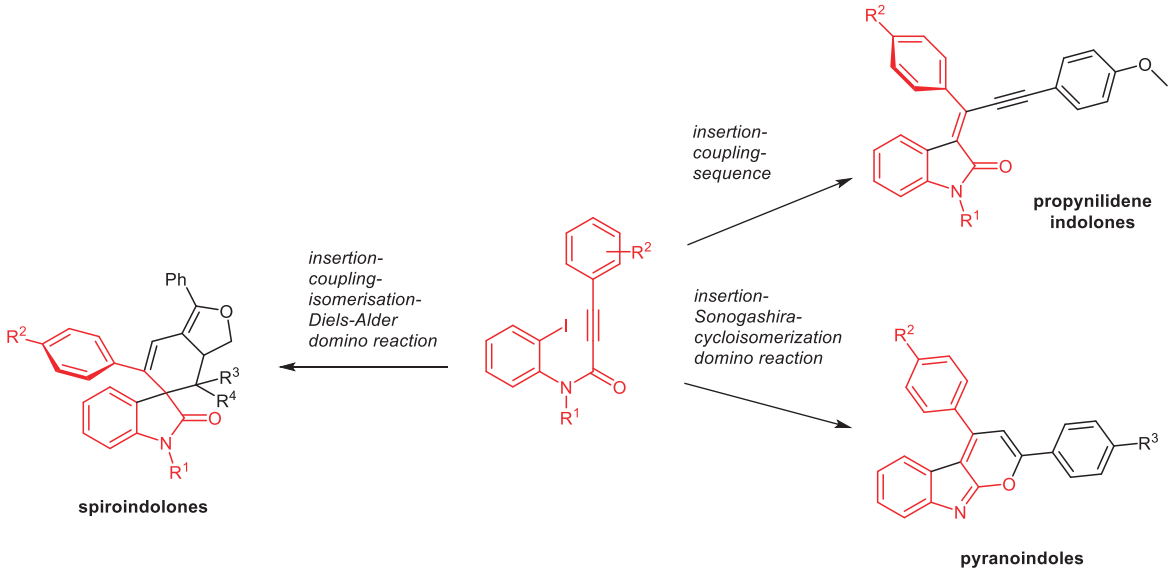
Organic chromophores are widely applied and used for instance in dye-sensitized organic solar cells, light-emitting diodes, or as chemosensors. Characterized by a functional π-electron system, absorption and emission of light at a specific wavelength belongs to one of their main features.[1-3] By modification of the chromophore through introduction of different functional groups, these properties can be tailored. To ensure structural and functional diversity of the target compound and thus its photophysical properties, domino syntheses can be employed. With this type of approach, large libraries of diverse scaffolds are accessible while using simple starting materials.[4]
Here, we report the palladium- and copper-catalysed syntheses of different, heterocyclic chromophores including (tetrahydroisobenzfuran)-spirodihydroindolones,[5] 2,4-diarylpyrano[2,3-*b*]indoles[3] and 3-arylpropynylidene indolones.[6] Furthermore, the versatility of substrate is highlighted as well as the peculiar emission characteristics of the different target compounds including large stokes-shifts,[5] high fluorescence quantum yields[5] and acidochromocity.[3]



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2P-059s

Synthesis of *ortho*-Aminoalkylated Pyridine Derivatives *via* Direct C–H Bond Aminoalkylation Catalyzed by Group 3 Metal Complexes

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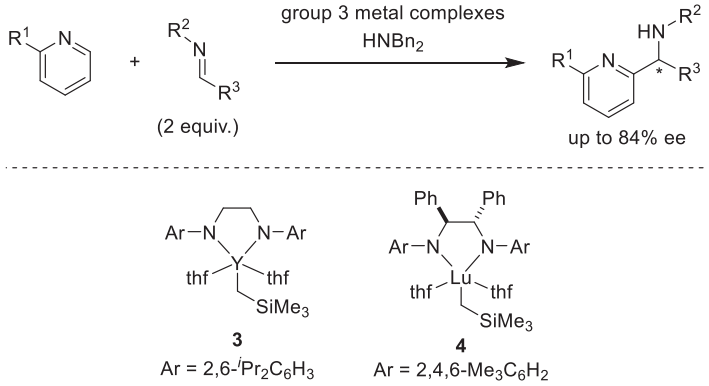
Pyridine is an important skeleton that exists in a large number of natural products, pharmaceuticals, ligands, and functional materials. Various synthetic protocols to introduce any functional groups in the pyridine skeleton have been intensively developed; metal catalyzed C–H bond activation followed by functionalization is one of the most atom- and step-economical processes. Although insertion of non-polar unsaturated substrates into a C–H bond of pyridine derivatives has been widely demonstrated,[1] the catalytic insertion of polar double bonds such as C=N, C≡N, and C=O is still challenging.[2] We previously reported that homoleptic tris(amido)lanthanum complexes, $Ln[N(SiMe_3)_2]_3$ (**1**), and a mixed-ligated $Y[N(SiMe_3)_2]_2(NBn_2)(thf)$ (**2**) became catalysts for the insertion of the polar C=N bond of imines in to the *ortho*-C–H bond of pyridine derivatives, producing aminoalkylated products.[3] Herein, we present superior catalytic performance of chelating diamido yttrium complexes such as $Y(\mathbf{L})(CH_2SiMe_3)(thf)_2$ [**3**: **L** = *N,N'*-bis(2,6-diisopropylphenyl)ethylenediamido)] for the aminoalkylation of 2-substituted pyridine derivatives.[4] Furthermore, we demonstrated the first example of asymmetric C–H aminoalkylation upon using a lutetium complex, $Lu(\mathbf{L^*})(CH_2SiMe_3)(thf)_2$ [**4**: **L*** = (1*S*,2*S*)-*N,N'*-dimesityl-1,2-diphenylethylethane-1,2-diamido], as a catalyst, and the enantioselectivity was up to 84% ee. We will discuss the details of the reaction mechanism based on the isolation and characterization of some intermediates as well as the kinetic study.



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Metathesis Cleavage of N=N Bond in Benzo[*c*]cinnolines and Azobenzenes by Ditungsten Complexes bearing a Metal-metal Triple Bond

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Transition metal-assisted metathesis reaction is one of the most important synthetic methodologies to catalytically cleave unsaturated multiple bonds of organic compounds such as C=C double bond as well as C≡C and C≡N triple bonds; however, metathesis cleavage of N=N double bond of azo compounds have hardly been investigated.[1,2] Herein, we describe that metathesis reaction of the N=N bond of benzo[*c*]cinnolines and azobenzenes occurred upon treated with the W≡W triple bond of $XY_2W{\equiv}WY_2X$ (X = Y = O^{t}Bu; X = OTf, Y = NMe_2), producing the corresponding terminal and μ_2-imido-ligated dinuclear tungsten complexes.[3]

Reaction of a ditungsten complex, $W_2(O^tBu)_6$ (**1**), with benzo[*c*]cinnolines proceeded smoothly at room temperature to give bis(imido)ditungsten complexes **2**—**4** in quantitative yields. The X-ray diffraction study of the complex **2** indicated that an N=N bond of benzo[*c*]cinnoline was cleaved by the metathesis reaction with the W≡W bond (Figure 1). In contrast, metathesis reaction of azobenzenes with $W_2(OTf)_2(NMe_2)_4$ (**5**) required blue-LED light irradiation, consistent with the *trans*/*cis* isomerization of azobenzene prior to be cleaved. In fact, under blue-LED light irradiation condition, azobenzene and its 4,4'-disubstituted derivatives reacted with **5** to give the corresponding bis(phenylimido)- and dimethylamido-bridged ditungsten complexes **6**—**8** (Figure 1).

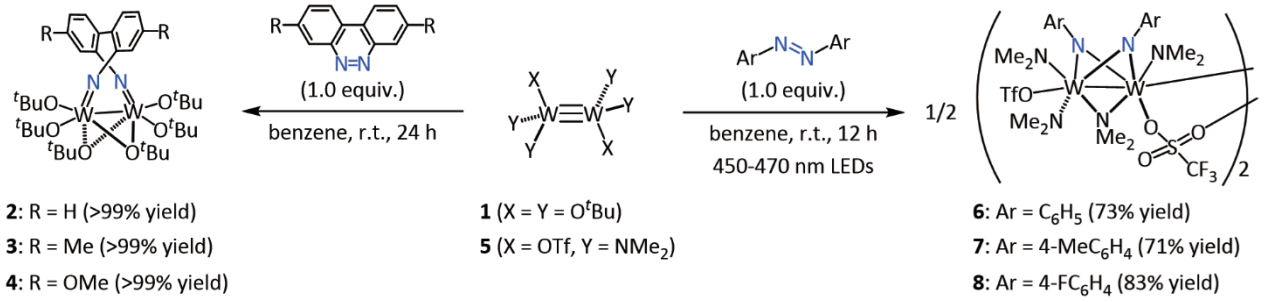

Figure 1. Metathesis Cleavage of N=N Bond in Benzo[*c*]cinnolines and Azobenzenes

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2P-061

Development of Catalytic *ortho*-Selective C–H Amination of *N*,*N*-Dialkylanilines with Rh(II)-Nitrene

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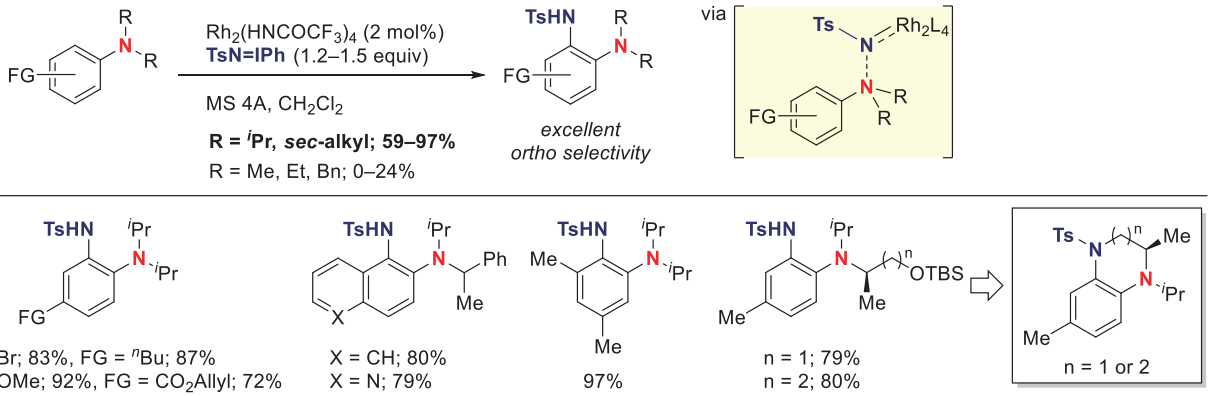
Rh(II)–nitrene species generated from dirhodium(II) complexes and (*N*-arylsulfonylimino) aryliodinanes are widely harnessed as the intermediates for C(sp^3)–H amination as well as aziridination of alkenes. In sharp contrast, there are very few examples of aromatic C–H amination in the literature.[1–3] The intermolecular reactions reported generally focused on amination at the *para*-position of electron-donating groups, and *ortho* C–H amination has still remained a major challenge. For example, *ortho* amination of *para*-substituted phenylethers gave a regioisomeric mixture in moderate selectivity,[2] or was scarcely favored over benzylic C–H amination.[3]

In this symposium, we present the *ortho* C–H amination of *N*,*N*-dialkylanilines using $Rh_2(HNCOCF_3)_4$ and TsN=IPh. In the reactions with *para*-substituted anilines, it was revealed that bulky secondary alkyl groups on the nitrogen atom were essential to accomplish the high product yields; conversely, methyl and primary alkyl groups led to undesired *N*-dealkylation, thus reducing the product yields. The *ortho* C–H amination displayed excellent compatibility with a range of functional groups including benzylic C–H and alkene moieties. Surprisingly, *para*-unsubstituted anilines also provided *ortho* C–H amination products up to 97% yield with no signs of the formation of *para* C–H amination products. To gain insight into the reaction mechanism, a series of competitive experiments were performed and the *ortho* selectivity observed was rationalized in terms of the coordination of the dialkylamino group to the Lewis acidic nitrogen atom of the Rh(II)–nitrene intermediate. Furthermore, the utility of the reaction was demonstrated by the elaboration of chiral heterocycles tetrahydroquinoxaline and 1,5-benzodiazepine from *ortho* C–H amination products.[4]



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2P-062

Enantioselective Total Synthesis of Diocollettines A

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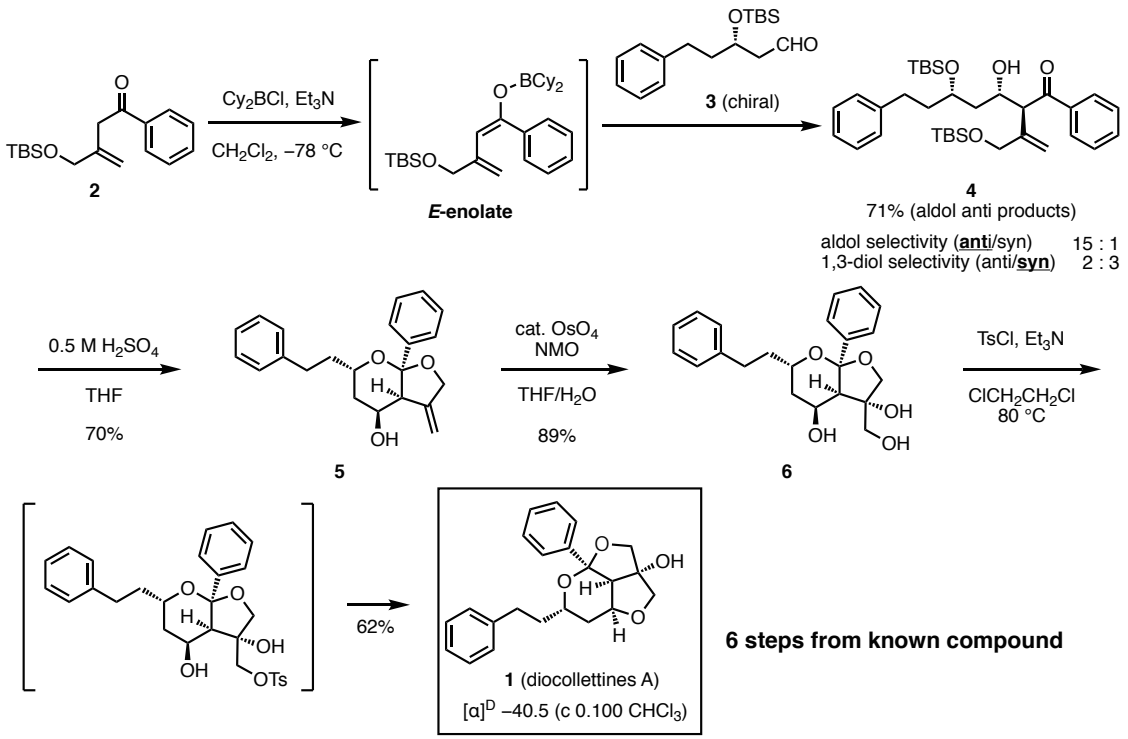
Diocollettines A (**1**) was isolated by Gao and coworkers in 2016 from the rhizomes *Dioscorea collettii*. [1] Compound **1** possesses a tricyclic skeleton with five stereogenic centers, two tetrahydrofuran rings and one tetrahydropyran ring fused to construct a complicated heterocyclic structure. In this presentation, the enantioselective total synthesis of diocollettines A was accomplished in only 6 steps from known compounds, featuring an intensive investigation of the stereoselective aldol reaction and an efficient stereocontrolled construction of the core skeleton. The synthesis commenced with the stereocontrolled aldol reaction using easily prepared ketone **2** and chiral aldehyde **3**. Thus, ketone **2** was subjected to the aldol condition using Cy_2BCl and Et_3N, which has been reported to generate *E*-enolate selectively, [2] followed by addition of aldehyde **3** to afford adduct **4** in a stereoselective manner. Treatment of **4** with 0.5 M H_2SO_4 triggered removal of the TBS groups followed by intramolecular acetal cyclization to yield compound **5**. The phenyl group was located at the more stable α face, the equatorial position. Furthermore, stereoselective dihydroxylation occurred exclusively from the convex face to afford triol **6**. Finally, TsCl and Et_3N induced the selective tosylation of the primary alcohol and the resultant tosylate was attacked by the secondary alcohol to build the last ring, completing the total synthesis of diocollettines A.



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Total Synthesis of Applanatumol B

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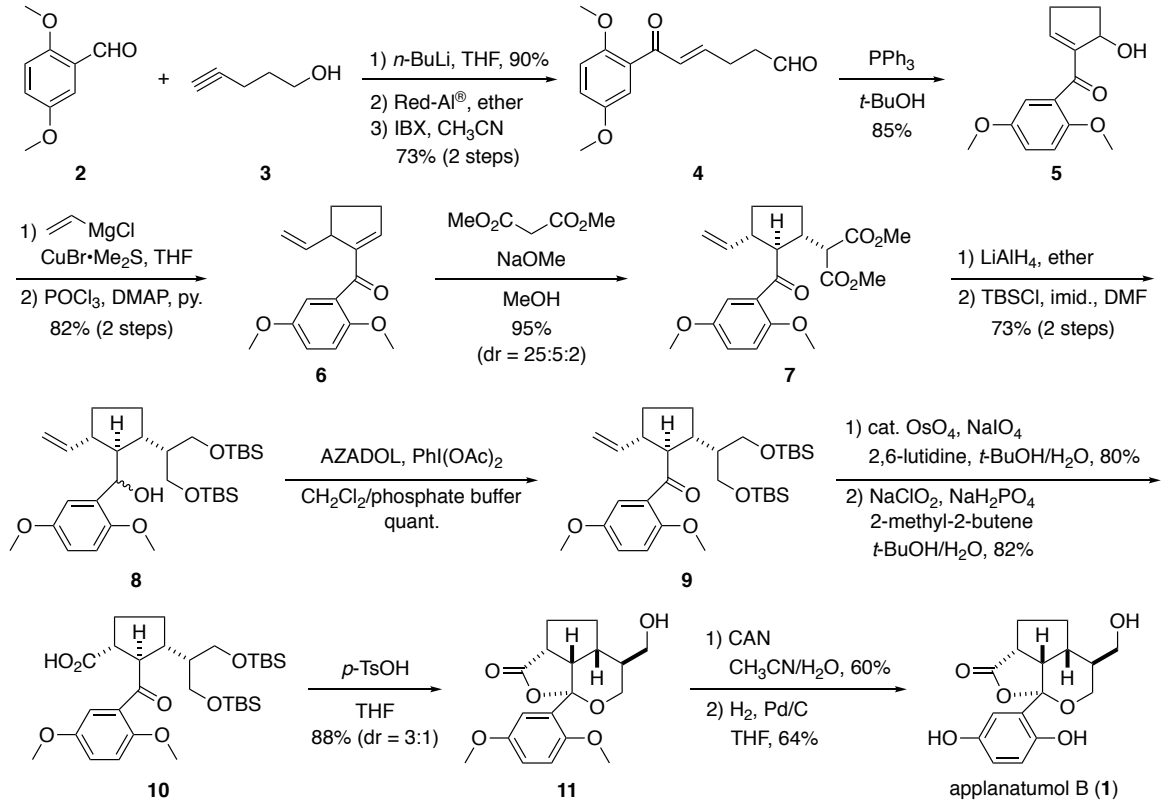
Applanatumol B (**1**) is a meroterpenoid isolated in 2016 from *Ganoderma applanatum*.[1] Compound **1** shows anti fibrogenic activity against NRK-52E cells in a dose dependent manner. No synthetic study of compound **1** has been reported. The unique structure and activity of compound **1** motivated us to start this synthetic study.

Compound **4**, which is derived from 2,5-dimethoxybenzaldehyde (**2**) and 4-pentyn-1-ol (**3**) as starting materials, was obtained through Red-Al® reduction followed by IBX oxidation. Intramolecular Morita-Baylis-Hillman reaction of **4** proceeded to afford **5** and then **6** was synthesized by 1,4- addition of vinylmagnesium chloride and dehydration. Michael addition of dimethyl malonate to **6** using NaOMe in MeOH under reflux condition gave all-*trans* configuration product **7** as a main diastereomer. Treatment of **7** with $LiAlH_4$ followed by protection with TBSCl produced **8** and then oxidation of benzylic position of **8** afforded **9**. Carboxylic acid **10** was synthesized by oxidative cleavage of vinyl group and subsequent Pinnick oxidation. Upon treatment of **10** with *p*-TsOH, cyclization to the tricyclic skeleton after epimerization of the α-position of the ketone proceeded to give compound **11**. Demethylation of **11** in 2-step procedure completed the total synthesis of applanatumol B (**1**).



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2P-064s

Synthesis of 2-Methylquinoxaline Derivatives from Glycerol and Diamines Catalyzed by Iridium Complex

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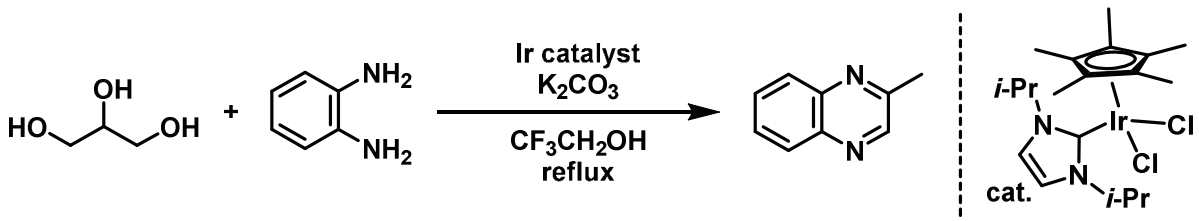
Substituted quinoxaline derivatives are known to exhibit interesting biological properties.[1] Among these compounds, 2-methylquinoxaline derivatives are widely used as intermediates for the synthesis of pharmaceuticals, natural products, and dyes.[2] Thus, it must be very important to develop a new and environmentally benign method for the synthesis of 2-methylquinoxaline derivatives from easily available starting materials.

2-Methylquinoxaline derivatives are conventionally synthesized via double condensation of 1,2-phenylenediamines with methylglyoxal. Although methylglyoxal is commercially available as aqueous solution, it has intrinsic difficulty in handling because of its high reactivity. Therefore, easily available and usable alternative is more desirable for the synthesis of 2-methylquinoxaline.

Meanwhile, glycerol can be obtained as a byproduct in the production of fatty acid or soap. Recently, it has also been obtained as a byproduct during production of biodiesel by ester exchange reaction of vegetable or animal oil with methanol.[3] In the last few decades, the production of glycerol has been increasing as the demand of biodiesel increases. In this context, the price of glycerol has become much lower, which renders the synthetic application of it much more attractive.

Herein, we report the synthesis of 2-methylquinoxaline derivatives from glycerol and diamines using iridium catalysts. This is cost-effective and environmentally friendly reaction due to the use of glycerol as starting material and high atom efficiency that only water and hydrogen gas are produced as byproducts.

For example, the reaction of glycerol with 1,2-phenylenediamine and K_2CO_3 in the presence of a catalytic amount of an *N*-heterocyclic carbene complex of iridium gave 2-methylquinoxaline. This catalytic system was applicable for the synthesis of various 2-methylquinoxaline derivatives. Scope of this catalytic system and the mechanism will also be presented.



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2P-065

Acylpyrazole as Carboxylic Acid Equivalent Platform for Chemoselective Catalysis

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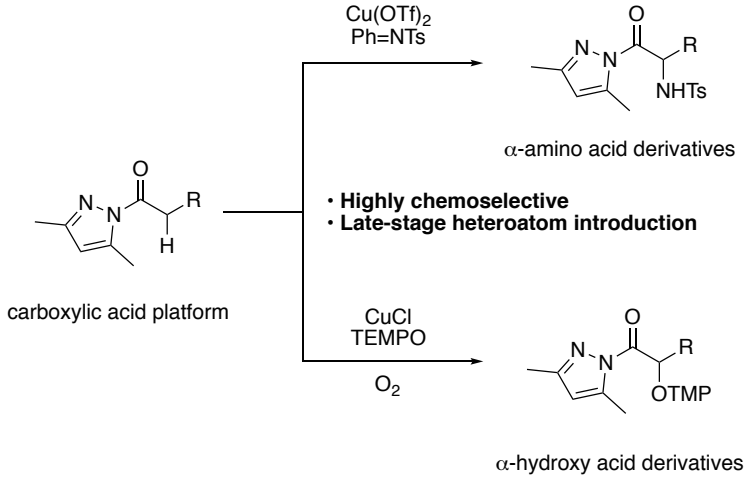
α-Amino and hydroxy acids are widely used as biologically active molecules and building blocks in synthetic organic chemistry and extensive efforts are focused on developing an efficient synthesis of unnatural α-amino and hydroxy acids. Late-stage oxidative heteroatom introduction at α-position of common readily available carboxylic acid platform offers expeditious access to a diverse set of unnatural α-amino and hydroxy acid derivatives. However catalytic generation of enolates derived from carboxylic acid oxidation state pronucleophiles and subsequent coupling with electrophiles remains a particularly difficult task due to the intrinsic low acidity of α-protons. Although a number of catalytic reactions using carboxylic acid oxidation state pronucleophiles with polar electrophiles, such as aldehydes, imines and electron-deficient olefins, have been reported, catalytic α-amination and hydroxylation is fairly rare.

As a carboxylic acid oxidation state pronucleophile, acylpyrazole[1,2] was selected for catalytic nucleophilic activation, due to a weak amide conjugation and bidentate coordination mode that enables chemoselective enolization over readily enolizable ketones, allowing for broad functional group compatibility. Herein we developed catalytic chemoselective synthesis of α-amino and hydroxy acid derivatives using acylpyrazole as a common carboxylic acid platform.[3-5] It is noteworthy that chemoselective activation of acylpyrazoles was achieved even in the presence of more reactive functionality.



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Gold-Catalyzed Cascade Cyclization of Anilines with Diynes: Controllable Formation of Eight-Membered Ring Fused Indoles and Propellane-Type Indolines

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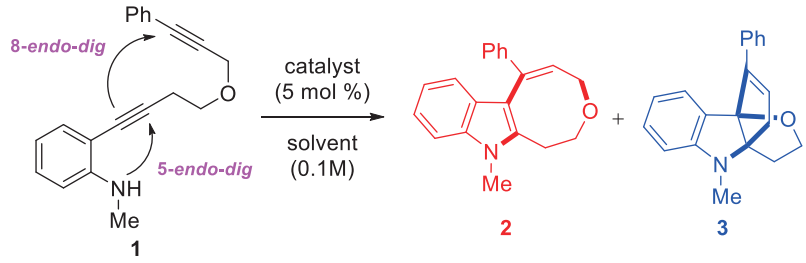
Kyoto 606-8501, Japan

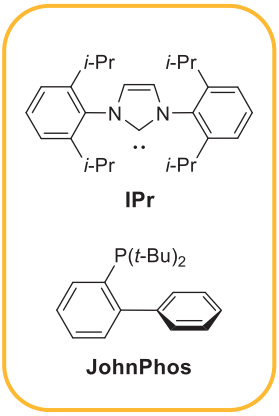
Cascade reactions are a powerful method for the syntheses of natural products and complex molecules. Gold catalysis is a useful tool for multiple carbon-carbon or carbon-heteroatom bond formation. We recently developed a gold-catalyzed reaction using diynes for construction of fused indoles through an intramolecular cascade 5-*endo-dig* hydroamination followed by a 6- or 7-*endo-dig* cycloisomerization.[1]

During our application studies of this reaction, we found that the reactions of **1** in the presence of 5 mol % of $IPrAuNTf_2$ gave an oxocine-fused indole **2** in 65% yield along with a propellane-type indoline **3**[2,3] in 27% yield. Further investigation revealed that the reaction with $JohnPhosAuNTf_2$ favored formation of the propellane-type indoline **3** in 88% yield. Interestingly, the use of 1,2-dichloroethane instead of 2-propanol selectively provided the propellane-type indoline **3** (86% yield) and **2** (4% yield). Thus, choices of the catalysts and/or solvents are important to regulate formation of the two different products, the oxocine-fused indole **2** and the propellane-type indoline **3**. The substrate scope and plausible reaction mechanism will also be discussed.



entry	catalyst [mol%]	solvent	temp. (°C)	**2** (%)	**3** (%)
1	**IPr**$AuNTf_2$ [5]	*i*PrOH	80	65	27
2	**JohnPhos**$AuNTf_2$ [5]	*i*PrOH	80	8	88
3	$IPrAuNTf_2$ [5]	**1,2-DCE**	80	4	86

Determined by ^1H NMR spectroscopy using 1,2,4,5-tetrachloro-3-nitrobenzene as an internal standard.



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2P-067

Fused Pyrrolidine and Piperidine Formation via Intramolecular Cycloadditions of Styrene-derived Ethenetricarboxylate Amides

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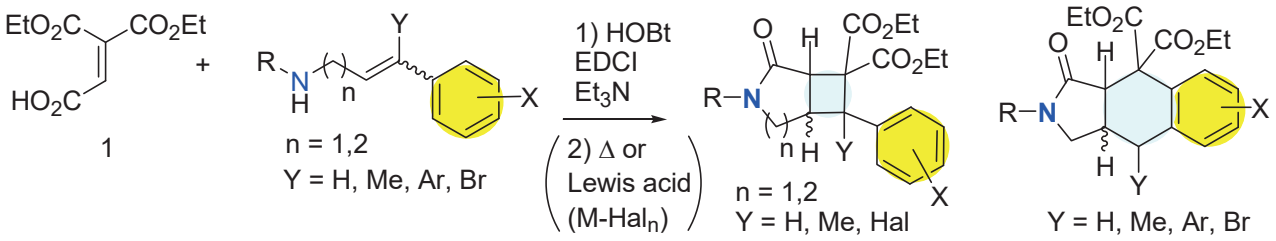
Intramolecular reactions of highly electrophilic ethenetricarboxylate with high selectivity are attractive in view of their wide applicability for various synthetic reactions. We have studied intramolecular cycloaddition reactions of styrene-derived ethenetricarboxylate amides. Reaction of ethenetricarboxylic acid 1,1-diester and cinnamylamines with EDCI/HOBt/Et_3N led to pyrrolidine products via intramolecular [2+2], [4+2] cycloadditions and HOBt-incorporated cyclization in sequential processes. The types of the products depend on the substituents on benzene ring. [1], [2]

Reaction of the acid and (Z)- and (E)-4-aryl-3-butenylamines with EDCI/HOBt/Et_3N gave the corresponding non-cyclized amides as isolable products. The reaction of (*Z*)-4-aryl-3-butenylamides of ethenetricarboxylate with 1-1.5 equiv. of Lewis acids such as $SnCl_4$ gave *cis*-cyclobutane fused piperidines as major products. On the other hand, (*E*)-4-aryl-3-butenylamides of ethenetricarboxylate with catalytic amounts of Lewis acids such as $InBr_3$ gave *trans*-cyclobutane fused piperidines.

Reaction of the acid and (*E*)-3-aryl-2-buten-1-amines with EDCI/HOBt/Et_3N led to pyrrolidine products in one pot, similar to the reaction of *E*-cinnamylamines. Reaction of the acid and (*E*)-3-phenyl-3-bromo-2-propene-1-amine with EDCI/HOBt/Et_3N at room temperature gave the corresponding amide as an isolable product. Heating the amide with Et_3N in benzene at 80 °C gave a *cis*-fused tricyclic compound via [4+2] cycloaddition/H-transfer. The reaction of the amide with $SnCl_4$ or $SnBr_4$ gave cyclobutane-fused pyrrolidines as major products. Halogen exchange was also observed. In order to obtain some insights for the mechanism, DFT calculations have been carried out.



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Convergent Synthesis and Growth Inhibitory Activity Evaluation of Stereoisomers around THF Ring of Acetogenin Thiophene Analogues

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Hiroki Iwasaki[1], Masayuki Yamashita[1], Naoto Kojima[1*]

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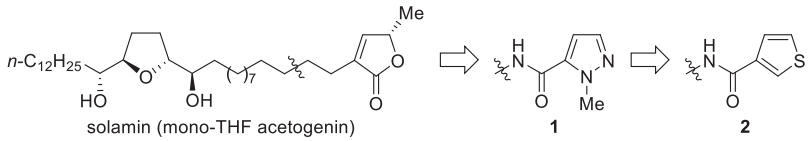
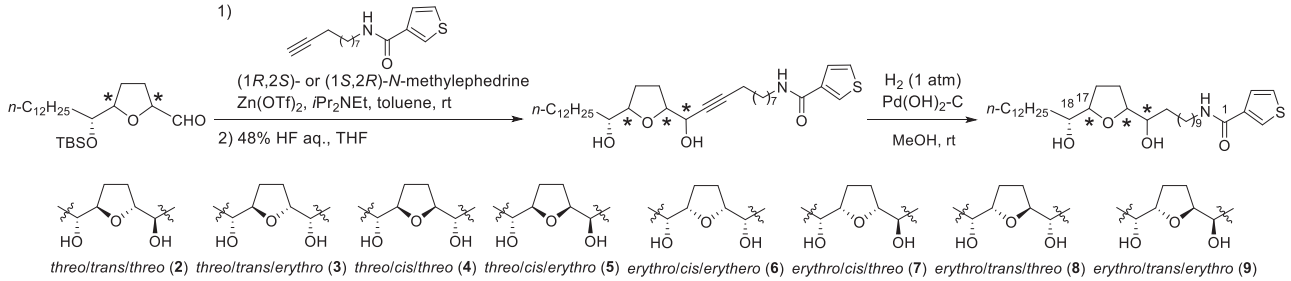
We are searching novel anititumor agents by structure-activity relationships (SAR) of annonaceous acetogenins. In our previous work, it was revealed that *N*-methylpyrazole-5-carboxamide analogue **1** has potent growth inhibitory activity toward human cancer cell lines,[1] but it is highly toxic in *in vivo* study. As a result of further examination, it was revealed that thiophene-3-carboxamide analogue **2** exhibit potent antitumor activity without critical toxicity in *in vivo* study.[2] However, SAR of stereoisomers around THF ring of **2** was unrevealed. Therefore, we planned to synthesize and evaluate the growth inhibitory activity of stereoisomers around THF ring of acetogenin thiophene analogue.



Now, the coupling reaction with THF-fragment and the alkyl chain with thiophene moiety was optimized to improve our previous synthetic route, and the convergent synthesis of eight stereoisomers **2**–**9** around THF ring by using stereoisomers of THF ring fragment[3] was accomplished. Their growth inhibitory activity toward 39 human cancer cell lines were also tested. The growth inhibitory profiles of three stereoisomers **3**–**5** with *threo* configuration between C-17 and 18 positions are very similar to that of the seed compound **2**, promising that they exhibit potent antitumor activity without toxicity.[4]



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Controlled Self-assembly of Porphyrins in Microflow Space

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[2]*Graduate School of Regional Development and Creativity, Utsunomiya University, Tochigi, 321-8585, Japan*
[3]*Department of Chemistry, Tokyo Institute of Technology, Tokyo, 152-8551, Japan*
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An overview of nature's self-assembly system reveals that energetically unfavourable molecular assemblies are accomplished in combination with energy consumption supplied from external systems. In artificial supramolecular systems, molecular assemblies occur generally under thermodynamic processes and structural varieties of the resultant assemblies are restricted. Herein, we demonstrate that use of microflow system to precisely regulate the self-assembling field enables control over the pathway for kinetic self-assembly processes.[1] In this study, we have employed tetrakis(4-sulfonatophenyl)porphyrin (TPPS, with H_2TPPS and H_4TPPS representing its free and protonated forms, respectively) as a model compound (Figure 1a). We designed three types of microchannels (Figure 1b). The time required for proton diffusion was directly correlated to the width of the TPPS layer (L) in the microflow, which we could control through the flow rate—a faster flow led to a narrower width (Figure 1c). We observed a direct correlation between the aggregation efficiency and the time required for proton diffusion (Figure 1d). AFM images revealed that length of the J-aggregate nanofibers was also controllable through controlling the proton diffusion time.

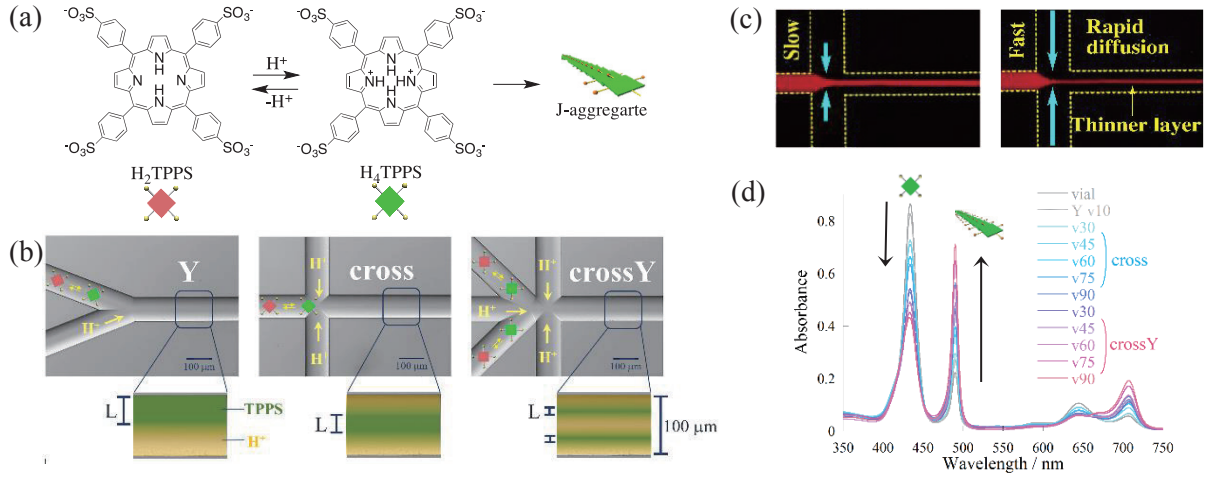

Figure 1: (a) Molecular structure of TPPS and a schematic representation of its J-aggregate formation. (b) Microscopy images of three types of microchannels and a schematic representation of laminer flow. (c) Fluorescence microscopy images of an aqueous solution of TPPS under different flow rates (cross type channel). (d) UV-Vis spectral changes recorded under various flow rates (0.267 mM; 0.1 mm cell, r.t.).

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Synthesis and Photophysical and Electrochemical Properties of Cationic Pyridinium-Chlorophyll Conjugates

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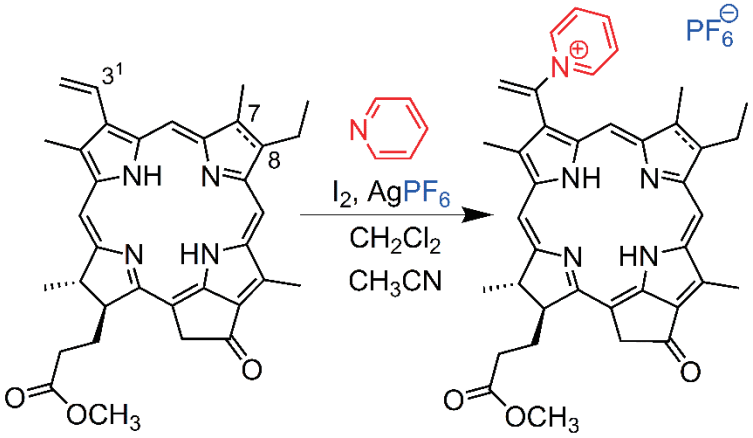
(Bacterio)chlorophylls [(B)Chls] are natural pigments that are engaged in photosynthesis oxygenic organisms. (B)Chls are porphyrinoids possessing a π-conjugated cyclic tetrapyrrole skeleton, including (bacterio)chlorins. Naturally occurring (B)Chls are neutral compounds without any charges in a molecule and its derivatives are usually neutral species. Due to less availabilities of cationic Chls, investigation on their chemical reactivities, photophysical properties, and electrochemical behaviors are limited. In this study, we report oxidative addition of pyridine to (B)Chl-*a* derivatives to give cationic pyridinium-chlorophyll conjugates, and their photophysical and electrochemical properties.



Scheme 1. Synthesis of pyridinium−(B)Chl-*a* derivatives.

3-Vinyl-(bacterio)chlorins prepared by natural (B)Chls-*a* were transformed into the corresponding 3^1-pyridinio adducts, according to repoted procedures (Scheme 1).[1] Figure 1 shows the visible absorption spectra of methyl pyropheophorbide-*a* (Scheme 1, left, C7=C8) and its 3^1-pyridinio adduct (right, C7=C8) in CH_3CN. The substitution of the pyridinio group induced red-shifts of Qy bands, due to its electron-withdrawing effect: typically, 665 to 673 nm for Qy(0,0) maxima of Chl-*a* derivatives.

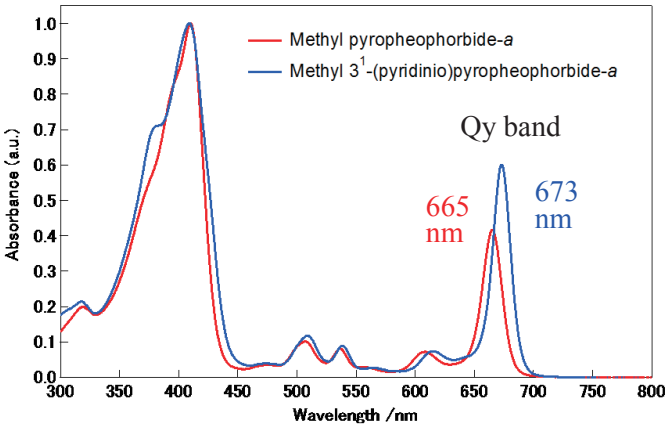


Figure 1. Visible absorption spectra in CH_3CN.

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2P-071s

Asymmetric (3+2) Annulations of Allenes with Alkylideneoxindoles Catalyzed by Planar Chiral [2.2]Paracyclophanol-based Phosphines

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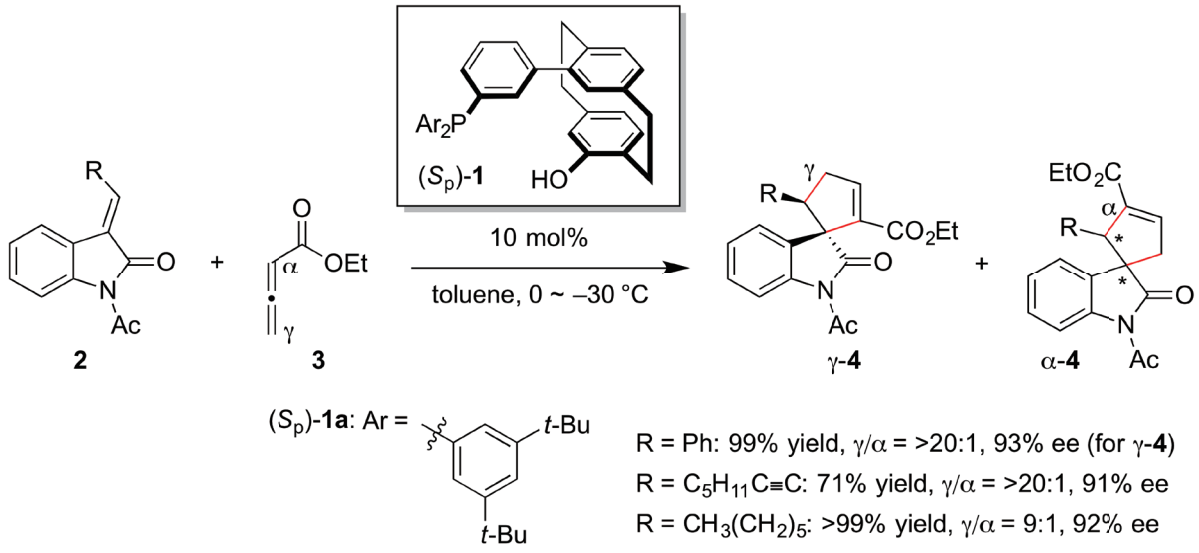
Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan[b]

Planar chiral ligands with a [2.2]paracyclophane (pCp) backbone have proven to be effective in many asymmetric catalysis.[1] However, the potential of pCp as a planar chiral organocatalyst backbone has yet to be sufficiently investigated. In this context, we recently developed pCp-based bifunctional phosphine-phenol catalysts, pCpOH-phosphines, in which one of the aryl groups on the phosphorus atom of the triarylphosphine had a pseudo-*ortho*-hydroxy-substituted pCp group at the *meta* position. The developed catalysts (S_p)-**1** worked well in the aza-Morita–Baylis–Hillman (MBH) reaction of *N*-tosylaldimines with various vinyl ketones[2,3] and in the (3+2) annulations of allenoates with *N*-tosylaldimines, affording 2,5-dihydropyrroles.[4] In this study, we found that the pCpOH-phosphines catalyzed the (3+2) annulation of allenoates **3** with alkylideneoxindoles **2** to produce 2,5-disubstituted spiro[cyclopent[2]ene-1,3'-oxindoles] γ-**4** in highly regio-, diastereo-, and enantioselective manner.



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2P-072

Pd(II) catalyzed ligand controlled synthesis of bis(3-furanyl)methanones and methyl 3-furancarboxylates

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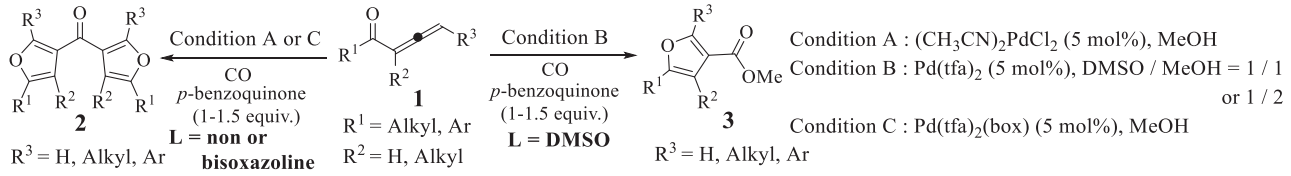
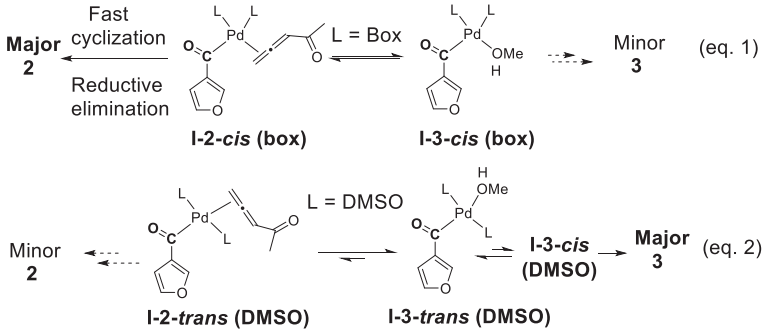
Furans are among the most important structural motifs, because they exist in a variety of natural products, agrochemicals, synthetic pharmaceuticals, and functional materials. Transition metal catalyzed cycloisomerization of allenyl ketones is an efficient way to build functional furans. [1] Previously, we reported the Pd^{II} catalyzed carbonylative dimerization of allenyl ketones. [2] Symmetrical ketones **2** bearing two furans were obtained in good to moderate yields. In all cases, 3-furancarboxylates **3** were minor products. The cyclization-carbonylation of allenyl ketones **1** to afford **3** as the major product has not been reported. Based on our preliminary results, we report here the Pd^{II} catalyzed ligand controlled synthesis of bis(3-furanyl)methanones **2** and methyl 3-furancarboxylates **3**. The reaction of **1** with $PdCl_2(CH_3CN)_2$ or $Pd(tfa)_2$(box) (5 mol%) and *p*-benzoquinone (1.5 equiv.) in methanol under a carbon monoxide atmosphere (balloon) afforded the **2** in 63-90% yield along with small amount of **3**. (conditions A or C) On the other hand, the use of DMSO strikingly changed the course of the reaction, affording methyl 3-furancarboxylates **3** in 76-94% yield along with small amount of **2**. (condition B)



The balance between reactivity (ease of cyclization) and stability of intermediates **I-2** and **I-3** determines the product selectivity. To estimate the stability of the intermediates, DFT calculations were performed. The allenyl ketone coordinated complex **I-2-*cis* (box)** is slightly favored over **I-3-*cis* (box)** (ΔG = -0.1 kJ mol^{-1}), and the high reactivity of the allenyl ketone allows fast cyclization leading to dimer **2**. (Eq. 1) In the case of the DMSO complex, the methanol coordinated **I-3-*trans* (DMSO)** is the more favored intermediate (ΔG = −48.4 kJ mol^{-1}), for the equilibrium with **I-2-*trans* (DMSO)**). Isomerization to **I-3-*cis* (DMSO)** (ΔG = +29.7 kJ mol^{-1}) followed by reductive elimination afforded the 3-furancarboxylate **3a** as the major product. (Eq. 2)



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2P-073s

Fluorescent Probes to Image Physical Forces in Biology

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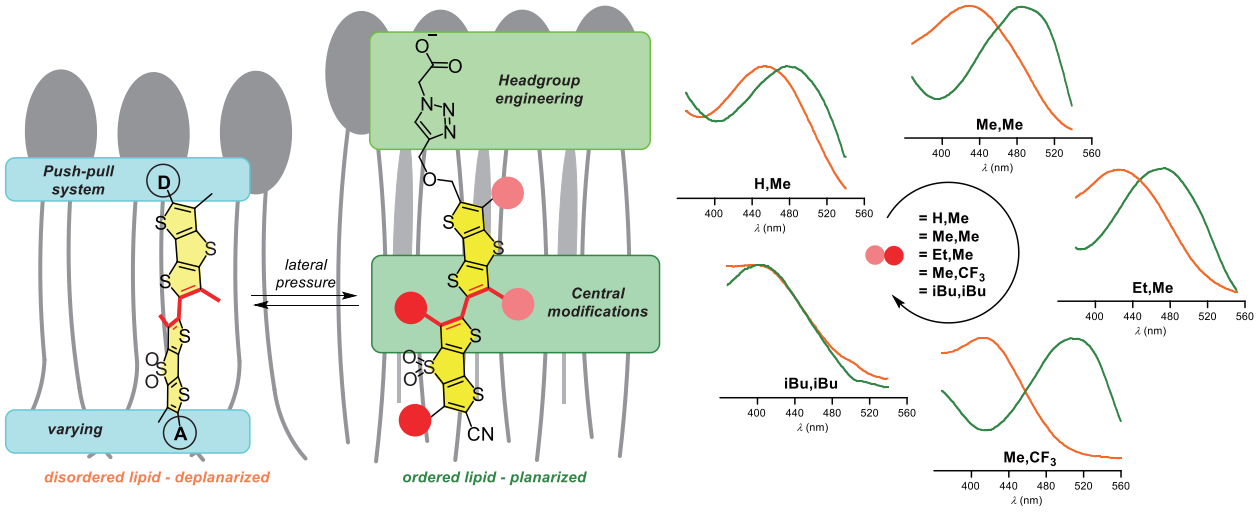
Aiming to provide better understanding of cellular membrane behavior, conceptually innovative mechanosensitive fluorescent "flipper" probes have been developed. These push-pull dithienothiophene dimers can respond to varying forces in membranes by a combined effect of ground state planarization and polarization, thus giving a direct fluorescent readout of tension and lateral organization of membranes.[1,2]

In past few years, our attention has been focused in two directions: a) improving the spectroscopic and mechanical properties of the fluorophore and b) attaching targeting groups to specifically reach desired cellular sites. By tailoring our flippers almost atom by atom, we have gained insight on the relationship between twist extent/push-pull strength and mechanosensitivity. Moreover, we have been able to specifically stain membranes of several cellular organelles and further studies involving protein tags are ongoing.[3] Our effort to bring our probes close to perfection continues also by investigating σ-hole interactions at the donor and acceptor site of the fluorophore.



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[3] Goujon, A.; Colom, A.; Straková, K.; Mercier, V.; Mahecic, D.; Manley, S.; Sakai, N.; Roux, A.; Matile, S *J. Am. Chem. Soc.* **2019**, *141*, 3380.

Reduction of Nitroarenes for Generating Arylnitrenes by 1,1'-Bis(trimethylsilyl)-1*H*,1'*H*-4,4'-bipyridinylidene

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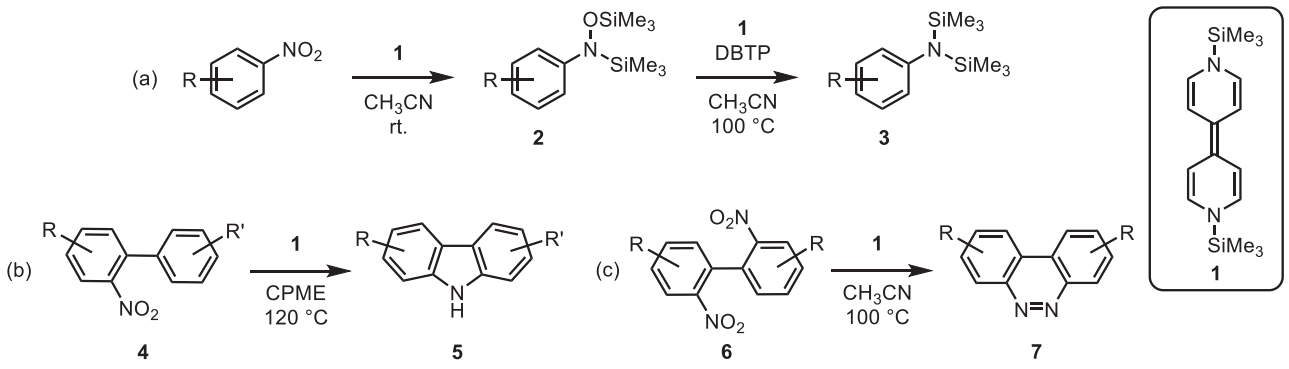
Reduction of nitroarenes is one of the important transformations for producing useful nitrogen-containing compounds such as hydroxyaniline and aniline delivatives, since nitroarenes are cheap, stable, and readily available nitrogen-containing feedstock. Combination of metals with strong acids as well as organic deoxygenation reagents have been utilized as standard synthetic protocols; however, rather harsh reaction conditions are inevitable, resulting in the lower functional group compatibility. Recent demands in synthetic organic chemistry is to develop any deoxygenation reagents for nitroarenes with a variety of functional groups. We previously reported that trimethylsilyl-substituted cyclohexadienes, dihydropyrazines, and 4,4'-bipyridinylidene served as organic reductants of transition metal complexes and organic halides in salt-free fashion.[1] In this contribution, we report that 1,1'-bis(trimethylsilyl)-1*H*,1'*H*-4,4'-bipyridinylidene (**1**) serves as a deoxygenation reagent of nitroarenes under mild reaction conditions.[2] Reaction of nitroarenes with **1** at room temperature afforded synthetically valuable *N*,*O*-bis(silylated)phenylhydroxylamine derivatives **2**, whose thermolysis in the presence of dibenzothiophene (DBTP) and an excess of **1** at 100 °C provided aniline derivatives **3** (Scheme 1-a). Reduction of 2-arylnitrobenzenes **4** by **1** followed by a subsequent thermolysis in cyclopentyl methyl ether (CPME) at 120 °C produced carbazole derivatives **5** *via* the insertion of nascent nitrene into a *ortho* C—H bond of the 2-aryl group (Scheme 1-b). In addition, reduction of 2,2'-dinitrobiphenyl derivatives **6** by **1** at 100 °C resulted in the formation of the corresponding benzo[*c*]cinnolines **7** in a selective manner (Scheme 1-c).

Scheme 1. Reductive Transformation of Nitroarenes by Organosilicon Reducing Reagent 1



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2P-075s

A One-Pot, Tandem-Sequential Approach for a Facile and Rapid Synthetic Access to 3-Hydroxyflavone Scaffolds

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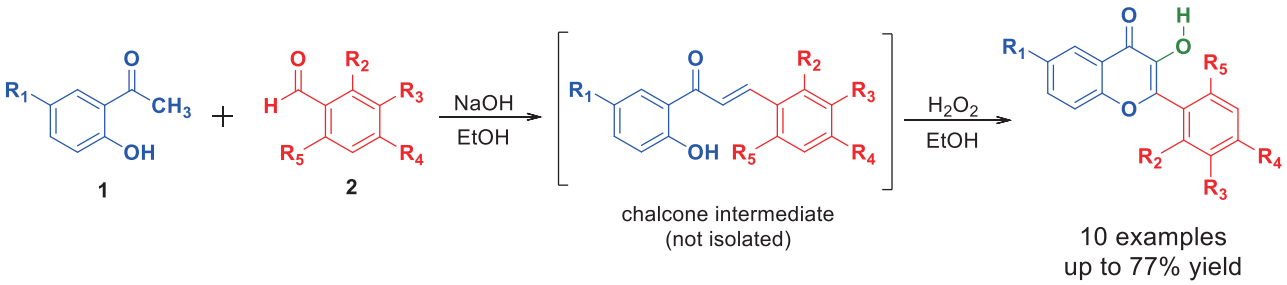
The 3-hydroxyflavone scaffold is an attractive synthetic target because of the considerable interest to their pharmaceutical use. In this study, we report a one-pot, two-step approach for the direct synthesis of the title compound involving *in situ* formation of 2'-hydroxychalcone from the Claisen-Schmidt condensation between **1** and **2**, and subsequent oxidative cyclization *via* a modified Algar-Flynn-Oyamada reaction using plain and dilute H_2O_2 under microwave irradiation. This method offers a more rapid and greener alternative access route to 3-hydroxyflavone moiety with simple operation and moderate to good yields in lieu of the conventional approach where requisite isolation of 2'-hydroxychalcone intermediates is needed.



2P-076s

Enantioselective *N*-alkylation of Nitroindoles

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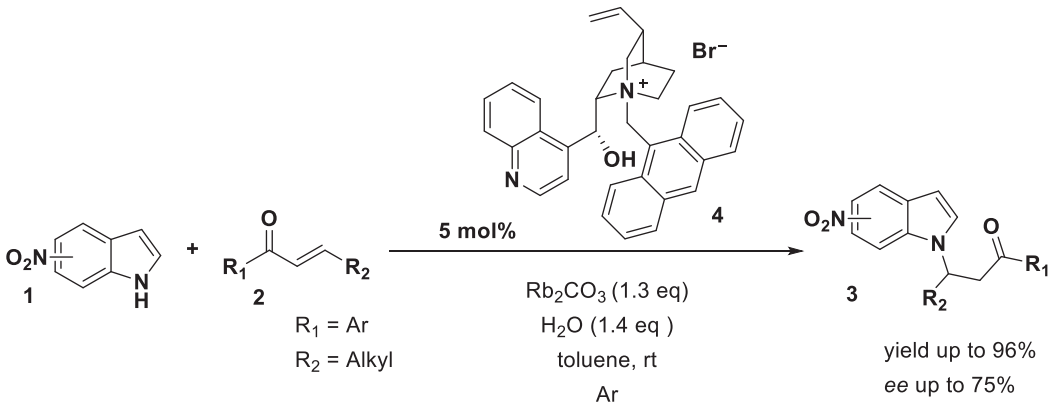
The indole core is present in a variety of natural products and pharmaceutical compounds.[1] The *N*-position of the indole framework has been used for the enantioselective alkylation reactions.[2-5] However, the asymmetric *N*-alkylation has been underdeveloped due to low acidity of the N-H proton.[6]

Herein, we report the enantioselective method to synthesize the aza-Michael products **3** from nitroindoles **1** and Michael acceptors **2** under phase-transfer catalysis. The reaction proceeded smoothly in the presence of catalyst **4** and rubidium carbonate providing desired Michael adducts **3** in moderate to high yields and good enantiomeric excesses.

The introduction of the electron-withdrawing nitro group in the indole core increases the acidity of the N-H proton. The position of nitro group determines the reaction rate and regio- and enantioselectivity of the reaction. At the same time, the higher acidity of the N-H proton does not increase the reaction rate.



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2P-077

Co-catalyzed deprotective cyclization affording cyclic carbamates, ureas, and isoureas

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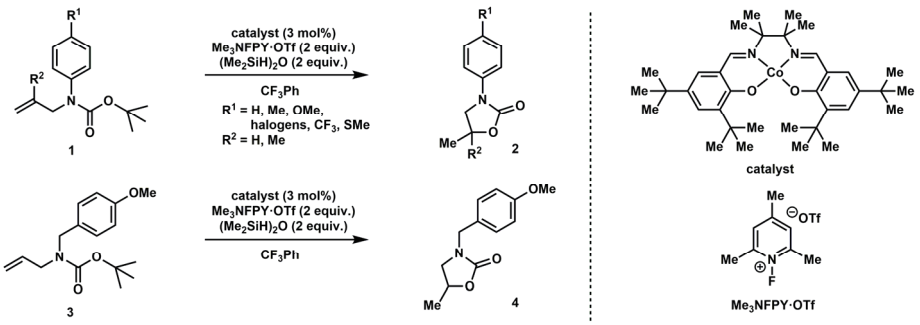
Cyclic carbamates and ureas are important structural motifs in biologically active compounds. Therefore, the construction of these frameworks has been extensively investigated in the field of synthetic organic chemistry. We previously reported a unique method for alkene activation using cobalt Schiff base catalyst, *N*-fluoropyridinium salt, and a silane reagent. The mechanism included a hydrogen atom transfer from cobalt hydride species to alkene generating radical intermediate, followed by radical-cation crossover generating a highly reactive cationic intermediate. The neutral and mild reaction conditions led to developing diverse reactions such as hydroalkoxylation, hydroacyloxylation, hydroamidation, and hydroarylation with excellent functional group tolerance. Herein, we present the cyclization of alkenyl carbamates to afford cyclic carbamates, the cyliczation of alkenyl isoureas to afford cyclic urea, and the cylization of alkenyl ureas to afford rare heterocycles, cyclic isoureas.

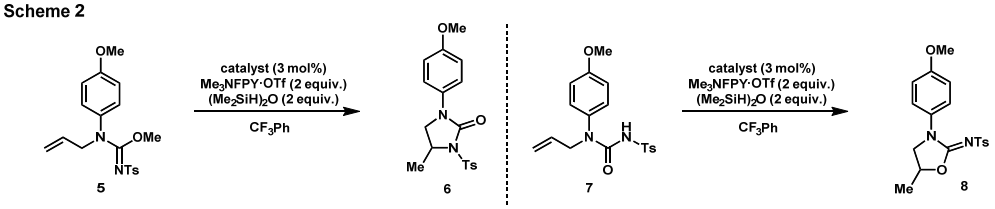
To our delight, simply applying the original reaction conditions to **1** provided **2** in excellent yield (Scheme 1). we examined the substrate scope with *t*-butyl carbamates. The electron density of the aromatic ring did not affect the reactivity. This method was also applicable to 2,2-disubstituted alkene using similar reaction conditions. Changing the aniline moiety to aliphatic amine also afforded excellent yield (**3** to **4**).

Scheme 1



Moreover, the application of a similar concept for substrate **5** and **7** afforded cyclic urea **6** and isourea, **8** respectively, in excellent yields (Scheme 2). The use of Ts group in **5** was unavoidable to obtain an acceptable yield. In the case of **7**, notably, the oxygen atom of urea moiety, which is an ambident nucleophile, connected to the activated alkene. We will present the origin of O/N selectivity and detailed substrate scope of these reactions in the poster presentation.

Scheme 2



[1] *Chem. Pharm. Bull.*, **2018**, *66*, 339-346. [2] in preparation.

Diastereoselective α-alkylation of Ammonium Salts

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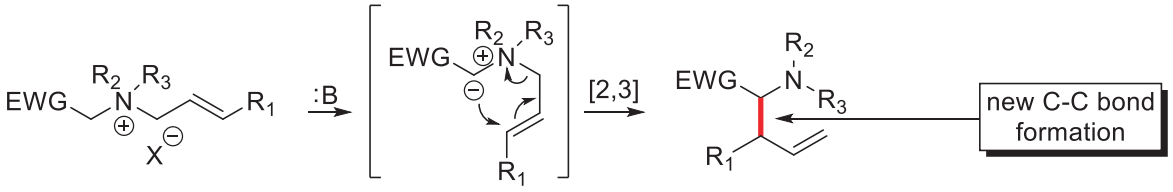
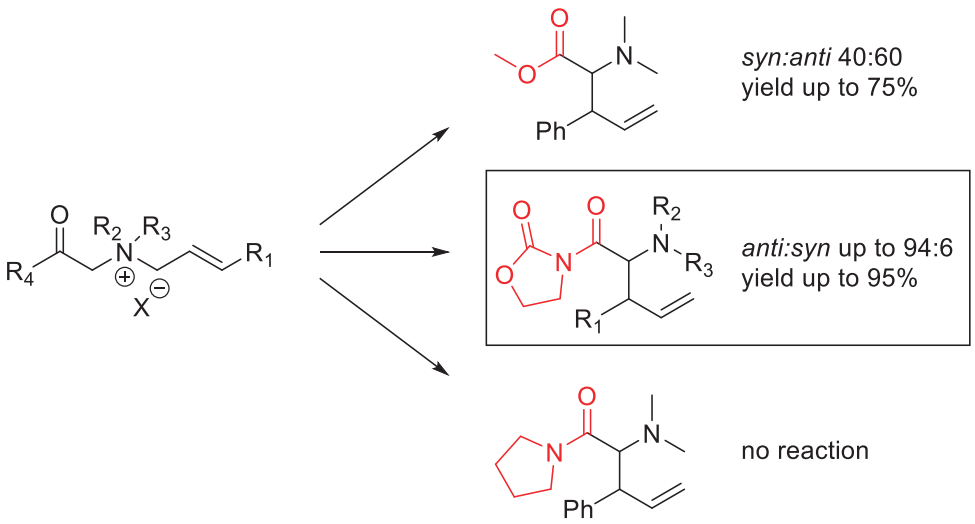
Pericyclic reactions are among the most useful organic reactions, as they give access to the generation of several new C-C or C-heteroatom bonds in a single step in 100% of atom-efficiency. Our research group has previously investigated enantioselective [2,3]-rearrangement of oxindoles[1] and allyloxymalonates[2]. In this work, we have studied Stevens [2,3]-sigmatropic rearrangement, which could be considered as formal α-alkylation of *N*-allyl ammonium salts. The formed homoallylic tertiary amines could be also regarded as α-amino acid derivatives.



We showed that depending on the structure of allyl ammonium salts and the reaction conditions, we could perform Stevens [2,3]-rearrangement rapidly in high diastereoselectivity and yield. To influence both reactivity of the substrate and the selectivity of the reaction, the oxazolidinyl moiety was introduced as EWG.



In order to achieve enantioselective outcome, we have utilized chiral (*S*)-4-benzyloxazolidin-2-one in the synthesis of ammonium salt. Under the optimized conditions, enantioselective product was generated with diastereomeric ratio of 84:8:7:1.

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2P-079s

Synthetic Studies of (–)-Callophycoic Acid A

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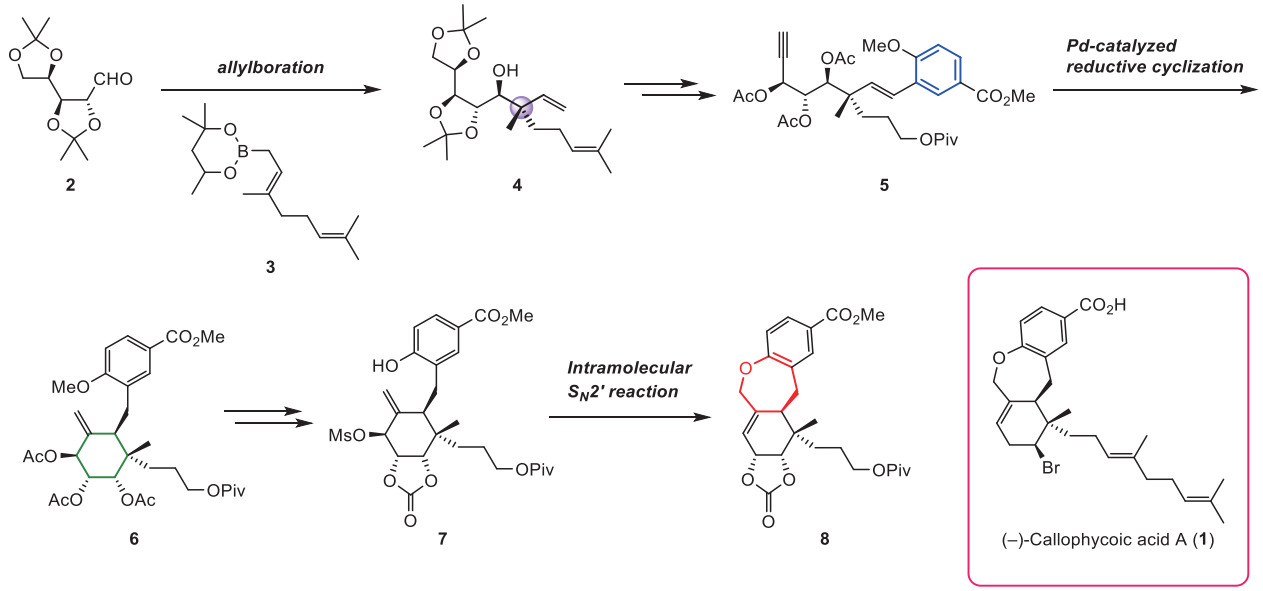
(–)-Callophycoic acid A (**1**) was isolated by Kubanek and co-workers in 2007 from extracts of the red alga *Callophycus serratus* (Solieriaceae), which was collected near Cakau-i-Ra Reef, Fiji.[1] This natural product is the first diterpene–benzoic acid found in macroalgae. The structure is characterized by a brominated tricyclic skeleton containing an all-carbon quaternary stereocenter. It showed antibacterial activity against vancomycin-resistant *Enterococcus faecium* (VREF) as well as antimalarial activity and cytotoxicity against human cancer cell lines.[2] Interested in these features, we have been involved in synthetic studies of **1**.

To construct the all-carbon quaternary stereocenter in **1**, carbonyl allylboration reactions were examined.[3] The reaction of D-xylose-derived chiral aldehyde **2** with geranylboronate **3** proceeded to give the desired γ-adduct **4** with highly stereoselective formation of a quaternary stereocenter. The γ-adduct **4** was converted into the enyne **5**, which possesses the benzoic acid moiety. Enyne **5** underwent a Pd-catalyzed reductive cyclization to provide the desired densely functionalized cyclohexane derivative **6** as a single isomer. After the transformation to phenol **7**, the tetrahydrooxepin ring was constructed by intramolecular S_N2' reaction. Thus, we achieved a stereocontrolled construction of the tricyclic skeleton of **1**.



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2P-080

Total Synthesis of Peroxide-bridged Jungermatrobrunin A

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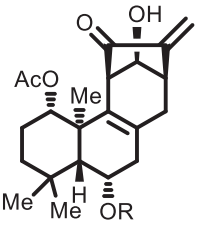
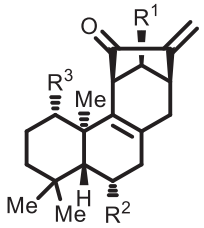
Our laboratory focuses on synthesis of bioactive molecules and elucidation of their biological functions. Diterpenoids are also attention-grabbing natural products because of their chemically attractive structures and biologically promised bioactivities. Recently, new rearranged ent-kaurene-type diterpenoids named Jungermatrobrunin A and several Jungermannenones were isolated from the liverwort Jungermannia species.[1-3] Jungermannenones share a unique bicyclic [3,2,1]octene backbone and several hydroxy groups. Furthermore, Jungermatrobrunin A possesses a peroxy ether hemiacetal (HO-C-O-O-C) structure on bicyclic [3,2,1]octane, which is rare structure in tetracyclic diterpenoids. The quite rigid and highly oxidized structure of Jungermatrobrunin A poses additional synthetic challenges. In this congress, I would like to disclose our recent work, total synthesis of peroxide-bridged Jungermatrobrunin A.



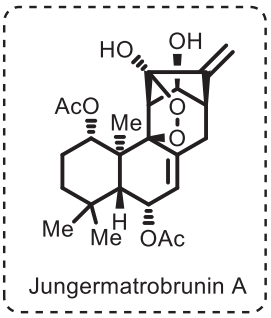
Acetoxy-hydroxy jungermannenone C (R = H)

Diacetoxy jungermannenone C (R = Ac)



Jungermannenone

A: R^1, R^2 = H; R^3 = OH
B: R^1, R^2, R^3 = H
C: R^1 = OH; R^2, R^3 = H
D: R^1, R^3 = OH; R^2 = H
E: R^1, R^3 = H; R^2 = OH



Jungermatrobrunin A

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2P-081

Concise Synthesis of Oxy-Functionalized Steroids through Intramolecular Diels-Alder Reaction of 2-Pyrone

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Oxy-functionalized steroidal skeleton can be found in a variety of natural steroids derived from plant or animal sources as well as clinical pharmaceuticals (Figure 1B). Especially, attention has been given to the cardiotonic steroids due to their prominent utilities for life science applications.[1] Therefore, a number of synthesis have been developed in pursuit of these skeleton. Recently, we have reported the synthesis of 2,14β-dihydroxyestradiol analogues from enantiomerically pure tricyclic alkene **2** (Figure 1A) to validate proposed structures of a candidate of endogenous digitalis-like factor (EDLF).[2,3] On the basis of our approach, we planned to construct estrogenic and cardiotonic steroidal skeletons through Mizoroki-Heck reaction and intramolecular Diels-Alder (IMDA) reaction using 2-pyrone[4] (Figure 1A). Simple modification of dienophile would enable to construct representative AB-ring systems both for estrogenic and cardiotonic steroids. Indeed, alkyne **4**, derived from **3** through Mizoroki-Heck reaction of known 2-pyrone triflate **1** and tricyclic alkene **2**, underwent IMDA reaction of 2-pyrone and alkyne to provide estrogenic compound **5**. In contrast, IMDA reaction of alkene **6** afforded cardiotonic compound **7** bearing a bridged lactone on the A-ring. Alkenes and hydroxy groups in obtained **5** and **7** allow to install oxy-functionalities in each ring to synthesize a wide variety of functionalized estrogenic and cardiotonic steroids, respectively.

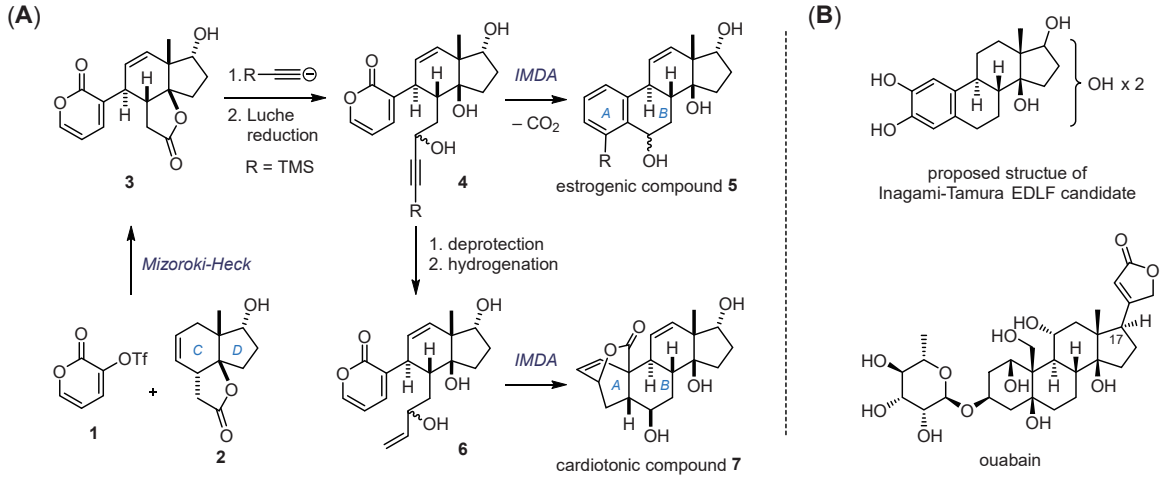

Figure 1. (**A**) Basic strategy for the construction of core frameworks of estrogenic and cardiotonic steloids. (**B**) Structures of estrogenic and cardiotonic steroids.

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2P-082s

Copper-Catalyzed Radical Cross-Coupling of Cycloketone Oxime Esters and Sulfinate Salts

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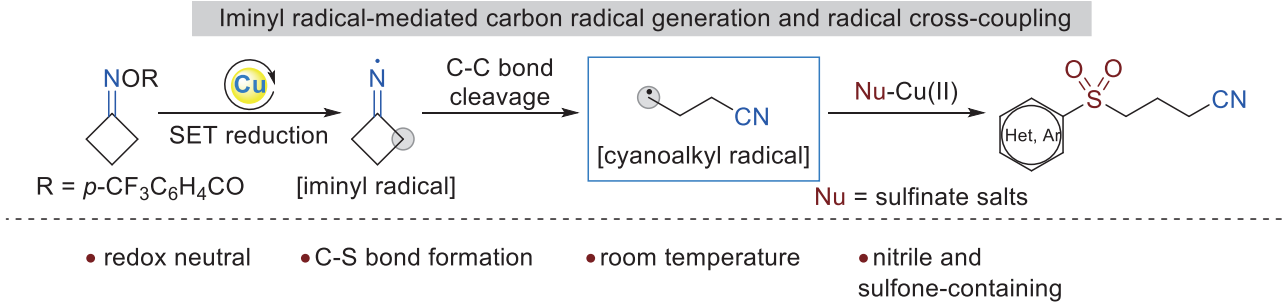
Alkylnitriles are a versatile class of synthetic building blocks in organic chemistry, because it could be easily transformed into various valuable functional groups, such as carboxylicacids, amidines and amines. Such type motifs are also widely found in many bioactive natural products and synthetic compounds. Thus the development of practical, effective and sustainable methods for synthesis of functionalized nitriles has attracted extensive attention from the synthetic community. In addition, sulfones are another class of important moieties with wide occurrence in numerous pharmaceuticals and bioactive compounds. Thus, incorporation of these two scaffolds into one compound would provide a new class of potentially useful structures that would be highly desirable for exploring new biologically relevant chemical space.

On the basis of our recent interest in nitrogen radical chemistry,[1-3] and the C-C bond cleavage/functionalizations of cycloketone oximes,[4-6] recently, we developed a copper-catalyzed radical cross-coupling of cycloketone oxime esters and sulfinate salts. This protocol provides a mild, practical and efficient approach to a series of compounds containing both cyano and sulfone functional groups. In the poster presentation, I will present the details.



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2P-083

A New Cascade Reaction for the Synthesis of 5,11-Dihydro-6*H*-indolo[3,2-*c*]quinolin-6-ones as Topoisomerase-I Inhibitors

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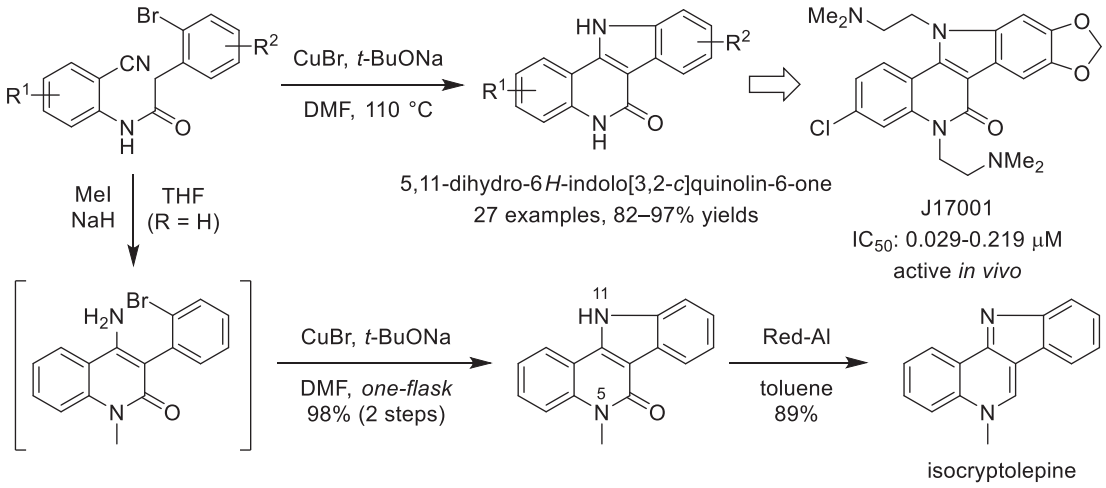
A copper(I)-catalyzed nitrile-addition/*N*-arylation ring-closure cascade was designed and developed for the synthesis of 5,11-dihydro-6*H*-indolo[3,2-*c*]quinolin-6-ones. The reaction was applicable to substrates having different substituents at the two phenyl subunits, including halo, methyl, methoxy, and methylenedioxy groups to provide the corresponding products in 82–97% yields. A plausible reaction mechanism was proposed for the cascade reaction. The cascade strategy was also applicable to the three-step total synthesis of natural product isocryptolepine (72% yield from commercially available starting materials). A series of 5,11-dihydro-6*H*-indolo[3,2-*c*]quinolin-6-ones were then di-alkylated and the antiproliferative activities of the di-alkylated products were evaluated on seven cancer cells. Among them, J17001 exhibited the best in vitro potency with IC_{50} values of 0.029–0.219 μM to inhibit the proliferation seven cancer cells. It demonstrated comparable efficacy to reduce the band intensity of Top1 to SN-38, which indicated that J17001 showed its antiproliferative activity through the stabilization of Top1 cleavable complex. J17001 showed low resistance to camptothecin-resistance HCT-116 cells and was active in vivo in mice bearing human HCT-116 and SJCRH30 xenografts. The spectrum of activity of J17001 was also evaluated on NCI-60 cancer cells. The 5,11-dihydro-6*H*-indolo[3,2-*c*]quinolin-6-one scaffold was a promising scaffold for Top1 inhibition and J17001 could be a suitable lead for further optimization.



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2P-084

Synthesis and Fluorescence Properties of the Diarylmethylene Analogs of the Green Fluorescent Protein Chromophore

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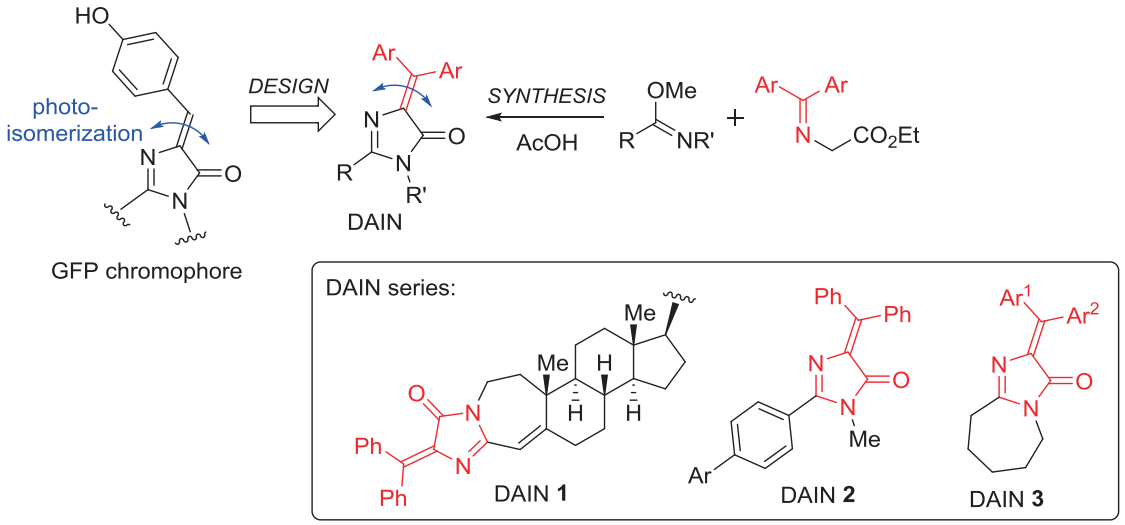
The green fluorescent protein (GFP) chromophore has an optical property of a fluorescent molecular rotor (motor), which rotates its C=C bond by photoabsorption and can emit fluorescence when the photoisomerization is restrained. We have developed a novel-type of GFP chromophore analog, diarylmethyleneimidazolinone (DAIN), which equips a diarylmethylene moiety instead of benzylidene in the chromophore.[1] DAIN behaves as a molecular rotor that can emit fluorescence in the powder form and in frozen solution but not in non-freezing solution. The DAIN synthesis was effectively performed by condensation with imidate and imino-acetate in the presence of acetic acid. This reaction notably accompanied the migration of the diarylmethylene moiety from nitrogen to α-carbon probably via an aziridine intermediate. The optical property of DAIN was applied for a fluorescent dye that can emit in response to the molecular motion control. For example, cholestene–hybrid DAIN **1** buried in lipid bilayers afforded an increase in the fluorescence intensity in relation to the phase transition temperature of the lipid. The intensity also nearly linearly increased as the amount of cholesterol in the lipid bilayer increased.[2] In the case of biaryl-conjugated DAIN **2**, the fluorescence wavelength widely shifted depending on the conditions (i.e., viscous solution, aggregation, and powder). The geometrical type of DAIN **3**, which was reversibly isomerized by the irradiation with UV and blue light, afforded different colors of emission between the *E*- and *Z*-isomers in the powder form.[3] We present the synthesis and fluorescence properties of DAINs in detail in this symposium.



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2P-085s

Synthetic study of suaveolindole and related indolosesquiterpenes

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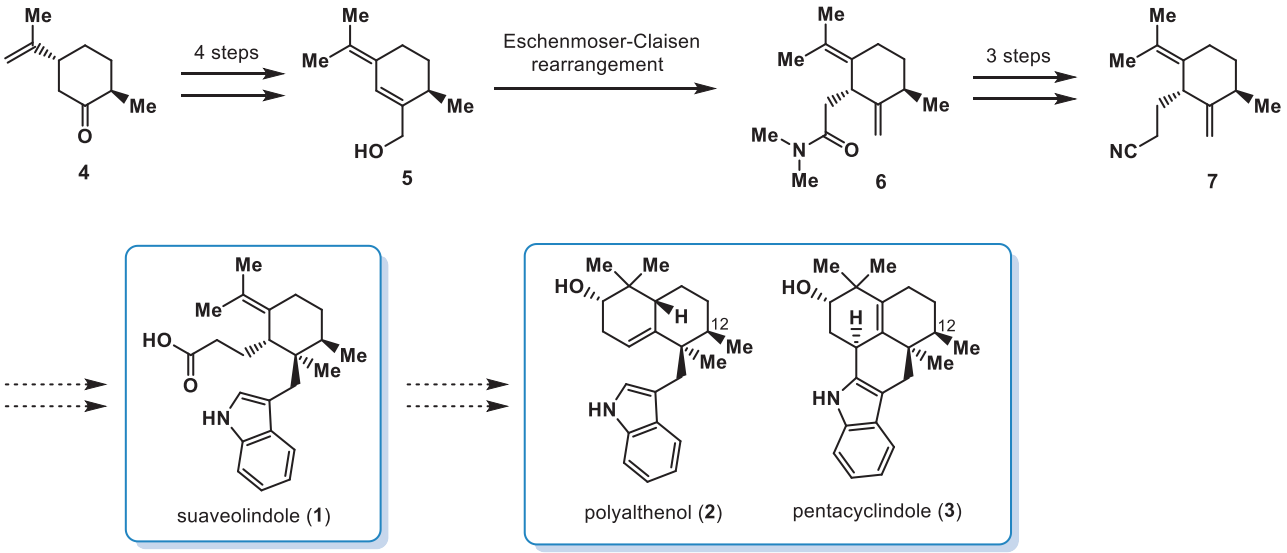
8916-5 Takayamacho, Ikoma, Nara 630-0192, JAPAN

Suaveolindole (**1**) is an indolosesquiterpene isolated from the fruits of *G. suaveolens*,[1] and **1** showed antibacterial activity against *Staphylococcus aureus* methicillin-resistant, *Staphylococcus aureus* and *Bacillus subtilis*. However, its total synthesis has been reported in only one case to date.[2] After the report of the total synthesis, similar analogues polyalthenol (**2**) and pentacyclindole (**3**), which also have antibacterial activity, were isolated.[3] Although 12-epimers of **2** and **3** have been synthesized,[4,5] total synthesis of **2** and **3** has not. For this reason, we planned an efficient synthetic route to **2** and **3** through **1**, which can lead various derivatives by late-stage heterocycle introduction.

The synthesis was commenced with (+)-dihydrocarvone (**4**) and was converted to alcohol **5** in 4 steps including palladium-catalyzed carbonylation reaction. The obtained pentadienyl alcohol **5** was submitted to Claisen rearrangement, and Eschenmoser-type reaction only gave rearranged product possessing sterically hindered alkyl chain at doubly allylic position. After three steps, nitrile **7** was synthesized, and further transformation is in progress.



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2P-086s

Rhodium-Catalyzed Selective C–H Alkylation of Benzenesulfonamide Derivatives with Alkenes and Investigation of Its Mechanistic Study

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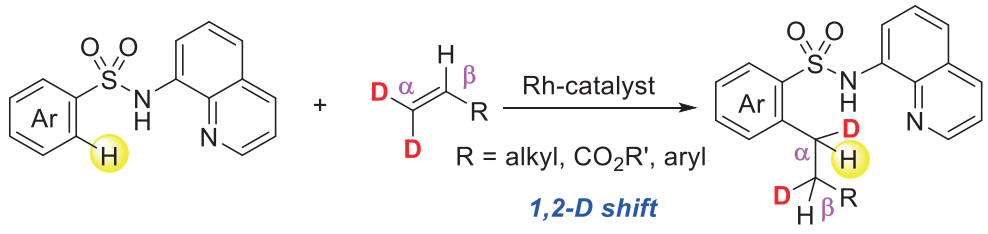
Sulfonamides are important structural motifs that are found in a variety of biologically active compounds such as azosemide, celecoxib, and gliclazide.[1] In the family of sulfonamide derivatives, sultams has one of the high significance in medicinal chemistry. Hence, the synthesis of sultams from sulfonamide derivatives has been extensively studied by various research groups.[2] However, the simple *ortho*-C–H functionalization of sulfonamides with olefins has not been extensively explored. To the best of our knowledge, only two examples of the *ortho*-C–H functionalization of sulfonamides in a form of alkenylation reaction with activated alkenes, such as acrylate esters and styrenes have been reported to date.[3] However, the selective C–H alkylation of benzenesulfonamides with alkenes has not been explored yet. Thus, a method for the alkylation of sulfonamide derivatives would be highly desirable. Given our long term interest in bidentate-chelation assisted Rh(I)-catalyzed C–H alkylation reactions,[4] we herein report on the Rh(I)-catalyzed *ortho*-alkylation of sulfonamides with various alkenes. The reaction is not only limited to the use of activated olefins, but unactivated olefins could also be used to produce the corresponding products even in higher yield as a mixture of linear and branched isomers. Moreover, deuterium labelling experiments and kinetics studies provided insights into the reaction mechanism, where two parallel catalytic cycles appear to be involved with an unusual 1,2-D shifting mechanism.



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2P-087s

Nickel(Ⅱ)-Catalyzed Reaction of Aromatic Amides with Bicyclic Alkenes through Carbon–Hydrogen and Carbon–Nitrogen Bond Cleavage

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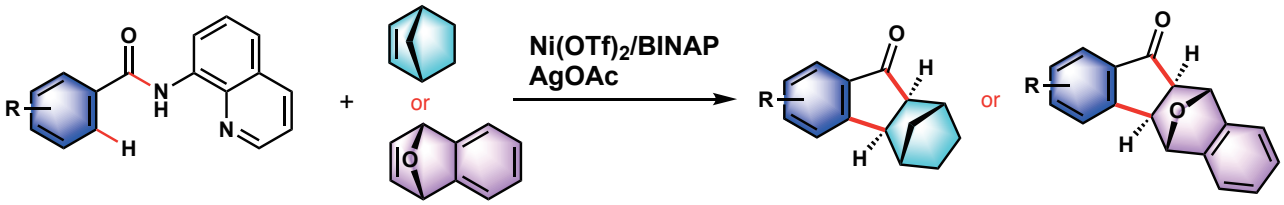
Fluorenone derivatives are naturally occurring active molecules.[1] Various types of hydrofluorenone derivatives were also isolated from natural sources.[2] Because of their potential bioactivities, the construction of the core fluorenone and hydrofluorenone are attracting considerable attention. In fact, many groups reported a synthetic method of hydrofluorenones using catalytic systems of noble metals.[3]

Recently, Cheng and coworkers reported the Co(II)-catalyzed [3+2] annulation of aromatic amides that contain an 8-aminoquinoline directing group with bicyclic alkenes as a coupling partner, in which the ortho C-H activation is involved as a key step.[4]

During the study of Ni-catalyzed C-H functionalization of aromatic amides, we found that Ni(II) complexes also show a high catalytic activity for a similar transformation. The nickel-catalyzed reaction of aromatic amides that contain an 8-aminoquinoline as a directing group with bicyclic alkenes, such as norbornene and 1,4-dihydro-1,4-epoxynaphthalene results in the cleavage of both the C-H bond at the ortho-position of the benzene ring and an amide C(O)-N bond to give methanofluoren-9-one and 1,4-epoxyfluoren-9-one derivatives.[5] In the meta-substituted aromatic amides, a less hindered C-H bond is exclusively functionalized in excellent selectivity.



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2P-088

An Immobilized Vanadium-Binaphthylbishydroxamic Acid Complex as a Reusable Catalyst for the Asymmetric Epoxidation of Allylic Alcohols

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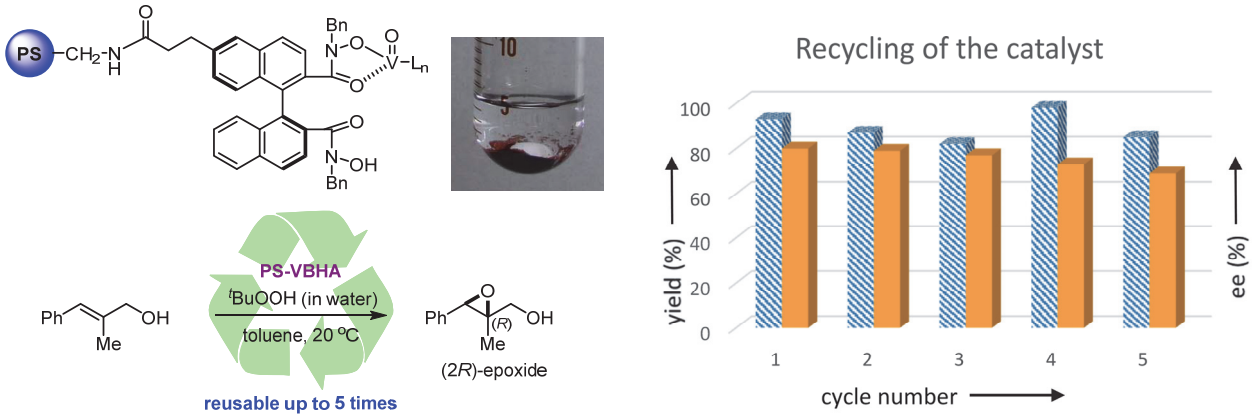
The immobilization of homogeneous catalysts has attracted growing attention in recent years. The potential advantages of immobilized catalysts include their rapid separation from reaction mixtures, facile recycling, and applicability to continuous-flow processes or high-throughput syntheses. Optically active epoxy alcohols are useful chiral building blocks for the synthesis of pharmaceuticals, fragrances, and agrochemicals. While various reliable methods exist, there is still room to further development of reusable catalytic system for the asymmetric epoxidation of allylic alcohols. Vanadium-hydroxamic acid-based catalyst systems have gained significant attention in the field of asymmetric epoxidations because of their lower catalyst loading, excellent moisture tolerance, and easier workup procedure.[1] Recently, we have developed a vanadium-binaphthyl-bishydroxamic acid (V-BBHA)-catalyst for the asymmetric epoxidation of allylic alcohols.[2] In this presentation, we wish to report our findings on the development of an immobilized polymer-supported VBBHA catalyst (PS-VBHA).[3] This catalyst can be easily recycled and reused over five consecutive runs with good to moderate chemical yields and enantioselectivities. The detail of the synthetic procedure of PS-VBHA will be also presented.



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2P-089

An Intermolecular [4+3] Cycloaddition Reaction Using 3-Hydroxy-2-Pyrone Derivatives with an Oxyallyl Cation

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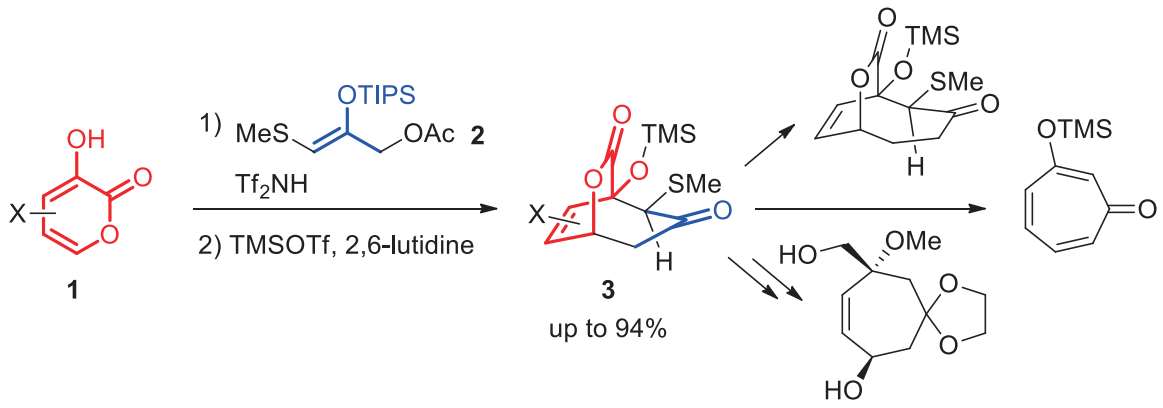
The [4+3] cycloaddition reaction is one of the most powerful tools for the construction of multi-functionalized seven-membered carbocycles, which are widely found in terpenoids and alkaloids. Much effort to investigate novel three-carbon units have been devoted during last two decades, however, the four-carbon units were limited to simple 1,3-dienes such as 1,3-butadienes, 1,3-cyclopentadiene, and furan. Therefore, the investigation of a novel four-carbon unit is an essential task to expand the utility of the [4+3] cycloaddition reaction. In this context, we focused on the intermolecular [4+3] cycloaddition reaction using 3-hydroxy-2-pyrone derivatives **1** as a four-carbon unit because we found that **1** were good substrates as a cyclic 1,3-diene of the intermolecular Diels-Alder reaction in our total synthesis of (−)-iso-A82775C.[1] We herein report the stereoselective intermolecular [4+3] cycloaddition of 3-hydroxy-2-pyrones and the oxyallyl cation prepared *in situ* from **2**, and the representative transformations of cycloadducts **3**, which enables easy access to various natural products.



We firstly examined the intermolecular [4+3] cycloaddition reaction using **1** and (2-silyloxy)allyl acetate **2** as the three-carbon unit[2] in the presence of Brønsted or Lewis acids. We found that the treatment of **1** with **2** and Tf_2NH afforded cycloadduct **3** in moderate to high yield, as a single diastereomer.[3] Because the cycloadduct **3** possesses the alley of functionality in the bicyclic framework, we demonstrated several transformations of the obtained cycloadducts **3**, such as ring-expansion reaction to 8-membered ring, troponization under mild conditions, and ring-opening reaction of the lactone ring.

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Synthesis of Nitrogen-Containing Seven-and Eight-Membered Compounds via Gold(I)-Catalyzed Cycloisomerization

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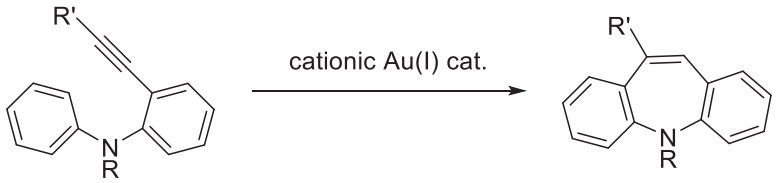
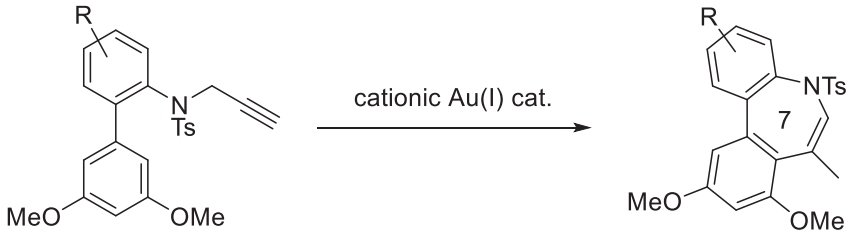
[b] *Global Center for Science and Engineering, Waseda University, Shinjuku, Japan*

Nitrogen-containing medium-sized ring is an important skeleton, which is contained in many bioactive compounds. Since the construction of heteroatom-containing medium-sized ring system is generally difficult, there are only limited examples. While transition metal-catalyzed cross coupling is generally used as a key reaction, halogen-derived wastes are problematic.[1] On the other hand, we reported gold(I)-catalyzed 7-*endo*-*dig*-selective cycloisomerization of *N*-alkyl-2-alkynylphenylanilne derivatives for the preparation of dibenzazepine derivatives (Eq. 1). [2]

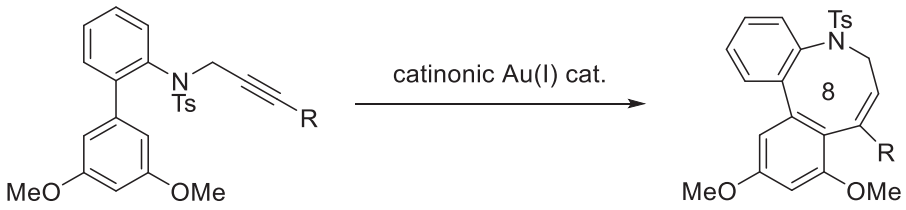


(1)

We here disclose the synthesis of seven- and eight-membered rings by the cycloisomerization of 2-(3,5-dimethoxyphenyl)-*N*-propargylaniline derivatives. In order to activate the arene moiety in cationic gold(I)-catalyzed reaction, 3,5-dimethoxyphenyl group was introduced.[3] The reaction of terminal alkyne-containing substrates proceeded 7-*exo*-*dig* selectively to give dibenzazepine derivatives (Eq. 2). In contrast, the internal alkynes underwent 8-*endo*-*dig*-selective cycloisomerization to give dibenzazocine derivatives (Eq. 3).



(2)



(3)

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Iodine-Catalyzed Asymmetric Synthesis of 4-Imidazolidinones via Dehydrogenative N-H/C(sp^3)-H Coupling Using α-Amino Acids and Amines

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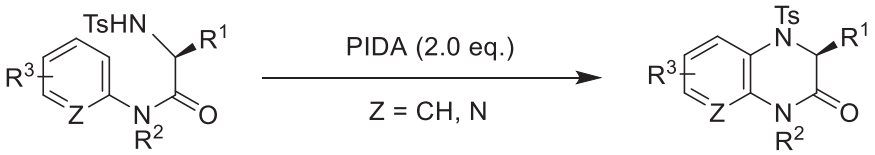
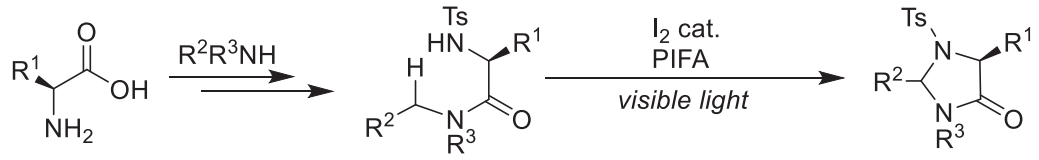
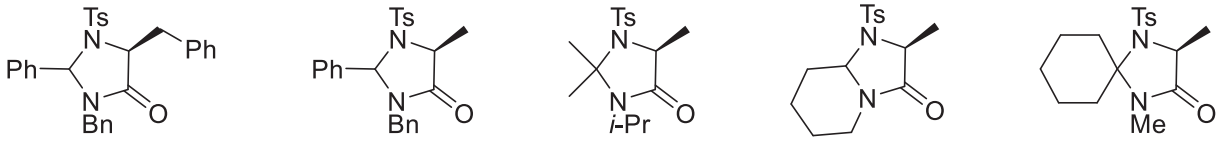
Dehydrogenative N-H/C-H coupling is a method of high atom efficiency capable of directly synthesizing a variety of nitrogen-containing compounds. It have been is mainly achieved using stoichiometric or catalytic amount of transition metal complexes, which are often toxic and costly. On the other hand, there are few examples using iodine or hypervalent iodine as a cheap and environment-friendly alternative to transition metals. We previously reported an asymmetric synthesis of dihydroquinoxalinone derivatives by N-H/C(sp^2)-H coupling with a stoichiometric amount of hypervalent iodine reagent using starting materials prepared from α-amino acid and aniline derivatives.[1]



Recently, a dehydrogenative N-H/C(sp^3)-H coupling reaction using iodine catalyst was reported.[2] Based on this background, we describe an efficient asymmetric synthesis of 4-imidazolidinones with iodine catalyst and hypervalent iodine under visible light irradiation.[3] The starting materials were conveniently synthesized from inexpensive and easily available α-amino acids and amines. The reaction proceeded in moderate to excellent yields to provide a variety of imidazolidinones, including spirocyclic derivatives.





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2P-092

Synthesis of Polycyclic Chromene Natural Products Based on Benzyne Cycloaddition Strategy

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[1]*Faculty of Pharmacy, Musashino University, Nishitokyo, Tokyo 202-8585, Japan*

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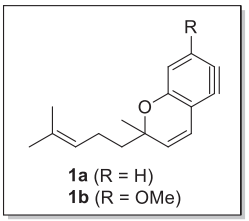
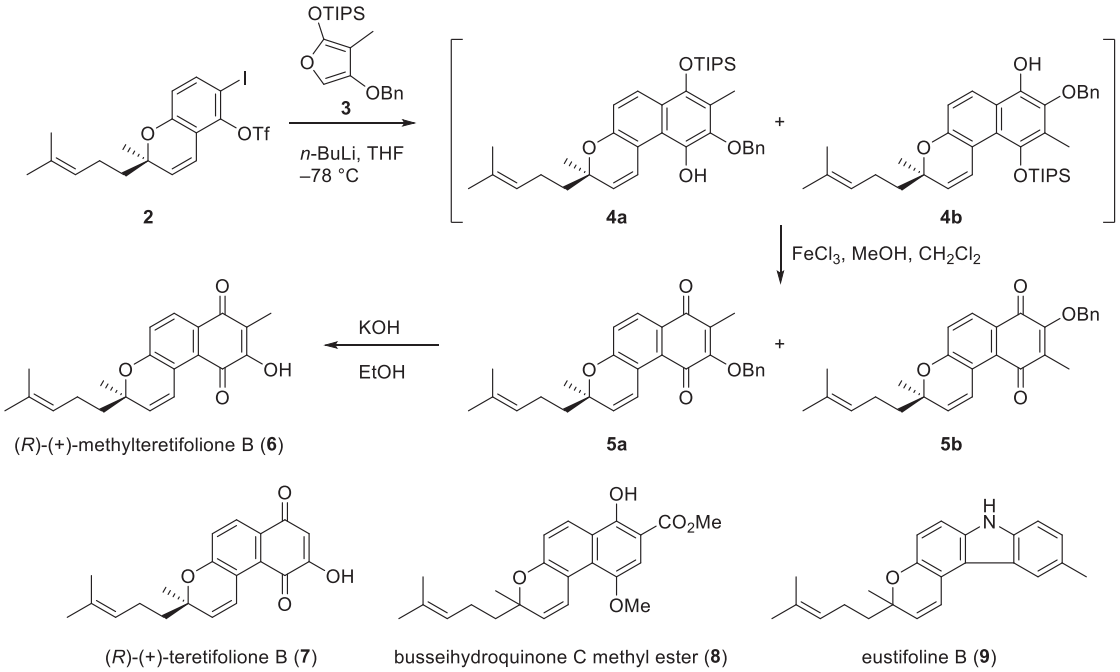
Owing to their unique structures and significant biological activities, angular polycyclic chromenes have been recognized as attractive targets for synthetic investigations.[1] We envisioned that such polycyclic skeletons could be constructed by a Diels–Alder reaction between benzyne intermediates **1** and electron-rich dienes.[2] Herein we addressed the synthesis of polycyclic chromene natural products via cycloaddition of pyranobenzyne intermediates.



The reaction of optically active (*R*)-2-iodophenyl triflate **2** with 2-silyloxyfuran **3** under halogen–lithium exchange conditions in THF at –78 °C afforded a mixture of desired cycloadduct **4a** along with its regioisomer **4b**. After separation, **4a** was treated with $FeCl_3$ in MeOH–CH_2Cl_2 followed by hydrolysis to complete the first asymmetric total synthesis of (*R*)-(+)-methylteretifolinone B (**6**).[3] The effectiveness of the present protocol has been demonstrated by the synthesis of polycyclic chromenes such as (*R*)-(+)-teretifolinone B (**7**) and busseihydroquinone C methyl ester (**8**). Further application of this method to the synthesis of eustifoline B (**9**) is now in progress.



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2P-093

Asymmetric Reactions Using Chiral Vanadium Complex as Acid Catalyst

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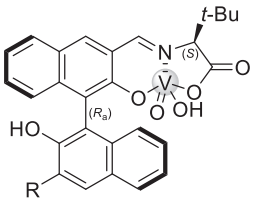
Harald Gröger,[2] Shinobu Takizawa,[1,*] and Hiroaki Sasai[1,*]
[1]*The Institute of Scientific and Industrial Research (ISIR), Osaka University, Ibaraki, Osaka 567-0047, Japan* [2]*Department of Chemistry, Bielefeld University, 33615 Bielefeld, Germany*

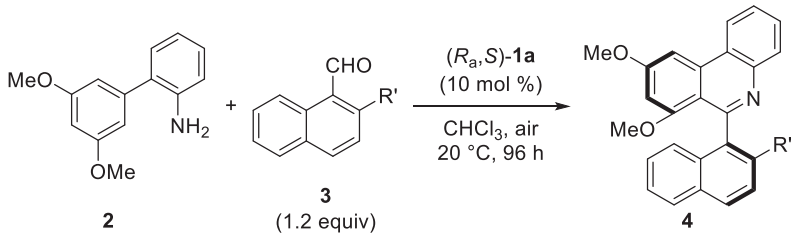
Vanadium complexes, as non-precious organometallic catalysts, have been utilized to develop a wide range of organic reactions by controlling the redox processes. So far, we have reported that a chiral oxovanadium complex promotes an enantioselective oxidative coupling of resorcinols, hydroxycarbazoles, and polycyclic phenols.[1] Moreover, with the Lewis acidity originated from the vanadium(V) complex, we have also achieved an enantioselective Friedel-Crafts type reaction.[2a] Our recent research discloses the Pictet-Spengler reaction/dehydrogenative aromatization sequence, and first enantioselective *oxa*-Piancatelli reaction using mononuclear vanadium catalysts (R_a,*S*)-**1** bearing a phenolic hydroxy group.[2b-c]



(R_a,*S*)-**1a** (R = H)
(R_a,*S*)-**1b** (R = 3,5-$(CF_3)_2C_6H_3$)

1) Pictet-Spengler reaction/dehydrogenative aromatization sequence

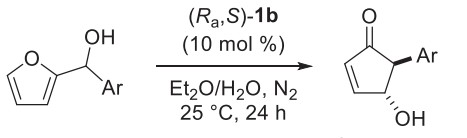
Axially chiral biaryl molecules are significantly useful as chiral reagents such as ligands and organocatalysts. A treatment of aniline derivative **2** and aldehyde **3** with 10 mol% vanadium catalyst (R_a,*S*)-**1a** under air afforded optically active phenanthridines **4** in one-pot system (Scheme 1). In this sequence, the vanadium catalyst acts as acid and oxidation catalyst.



Scheme 1

2) *oxa*-Piancatelli reaction

4-Hydroxy-2-cyclopentenones **6** have received a great deal of interest by organic chemists due to a useful building block in the various natural product synthesis. The vanadium catalyst (R_a,*S*)-**1b** efficiently promoted the reaction of furfuryl alcohols **5** to provide the desired product **6** in good yields with enantiomeric ratio of up to 93:7 and diastereomeric ratio exceeding 20:1 (Scheme 2).



Scheme 2

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2,6-Bis(trifluoromethyl)phenylboronic Esters as Protective Groups for Diols: A Protection/Deprotection Protocol for Use under Mild Conditions

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It is well-known that boronic acids form covalent bonds with 1,2- or 1,3- diols to generate five- or six-membered cyclic boronic esters under mild and neutral conditions. Therefore, boronic acids such as phenyl boronic acid and polymer-supported boronic acids have been used as protective or transient masking agents for diols.[1-2] However, cyclic arylboronic esters, except derived from highly hindered substrates, are susceptible to hydrolysis, even under neutral conditions (Figure 1a). Consequently, this poor stability limits the reaction conditions under which this protective strategy may be applied. In the present study, we demonstrate the stability of 2,6-bis(trifluoromethyl)phenyl boronic esters in aqueous media and, thus, the application of 2,6-bis(trifluoromethyl)phenyl boronic acid (*o*-FXylB(OH)$_2$) as an effective diol-protecting agent (Figure 1b).[3]

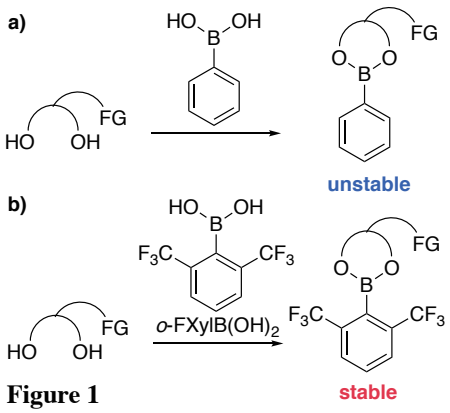

Figure 1

We initially investigated the formation of cyclic boronic esters between *o*-FXylB(OH)$_2$ and different diols (Figure 2). The reaction of an equimolar mixture of diol and *o*-FXylB(OH)$_2$ in dichloroethane proceeded smoothly to give the corresponding cyclic boronic ester in quantitative yield at a satisfactory level of purity. To demonstrate the utility of 2,6-bis(trifluoromethyl)phenyl boronic esters as a protective group for diols, we next explored several applicable chemical transformations. As a result, we found that the 2,6-bis(trifluoromethyl)phenyl boronic ester group can be used to protect diols and is tolerant against typical organic transformations such as oxidation, amide condensation, organometallic addition, and transition-metal-catalyzed cross coupling. Deprotection of the 2,6-bis(trifluoromethyl)phenyl boronic ester could be performed under mild conditions. Moreover, we found that *o*-FXylB(OH)$_2$ can be used as a recoverable and reusable protective agent for diols. Synthetic application for the total synthesis of sulfoglycolipid is now in progress and its detail will be reported in this presentation.

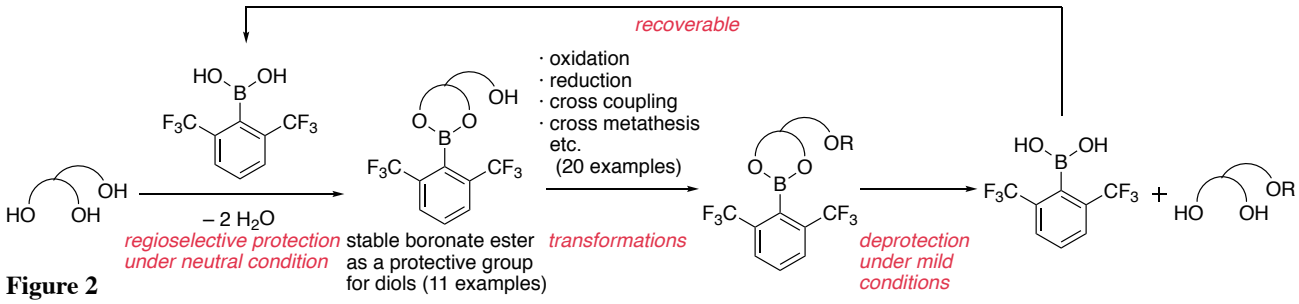

Figure 2

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2P-095

Iodocyclization of Ynamides for the Construction of Medium-Sized Oxacycles

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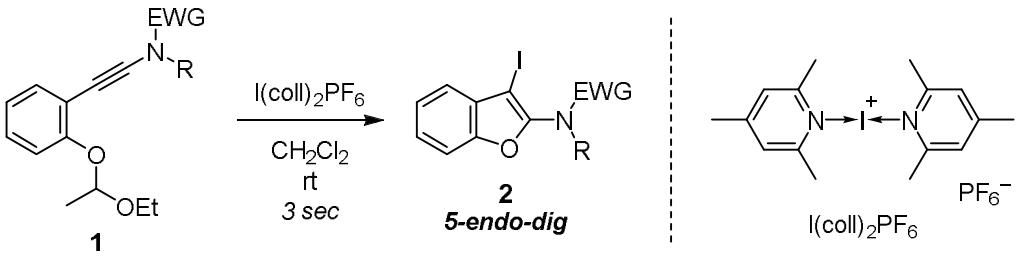
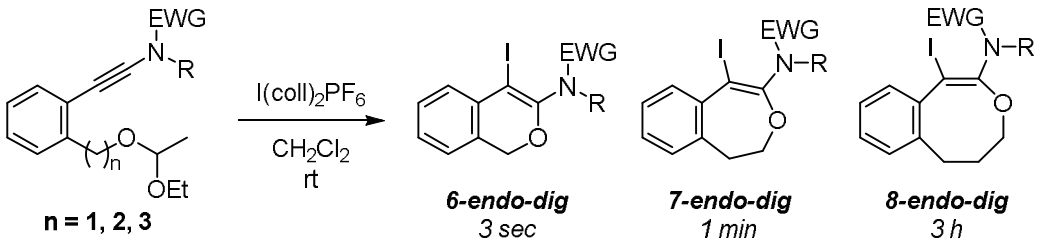
Iodocyclization, iodonium ion-mediated electrophilic cyclization, is one of the most efficient method for constructing ring architectures accompanied with iodo-component, that could be utilized for further functionalizations, such as cross-coupling reactions. We have already reported that 5-*endo-dig* iodocyclization of ynamides **1** finished within 3 seconds to afford benzofurans **2** in high yields (Scheme 1).[1] The reason why this reaction completes so fast is as follows: (1) electron-rich ynamides show high reactivity for electrophilic iodonium reagents; (2) ethoxyethyl group works as a good leaving group for iodocyclization; (3) $I(coll)_2PF_6$ is more reactive iodonium reagent than NIS and I_2.

Scheme 1. Immediate Construction of Benzofurans (Previous Work)



In this study, we adopted this highly reactive cyclization for larger-sized ring construction (Scheme 2). To our delight, 6-*endo-dig* iodocyclization of ynamides also completed for 3 seconds under the identical conditions to afford 1*H*-isochromenes in high yields. In a similar manner, 7-*endo-dig* iodocyclization finished for 1 minute. Surprisingly, even 8-*endo-dig* iodocyclization proceeded and eight-membered ether rings were obtained in moderate yields. This is the first report for the construction of medium-sized oxacycles by iodocylization of ynamides. These reactions underwent at room temperature albeit traditional methods for medium-sized rings closure needed high temperature.

Scheme 2. Six-, Seven-, and Eight-Membered Oxacycles Construction (This Work)



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Chemical synthesis of 4-azido-β-galactosamine derivatives for generation of compound library with inhibitory activity against GalNAc4S-6ST

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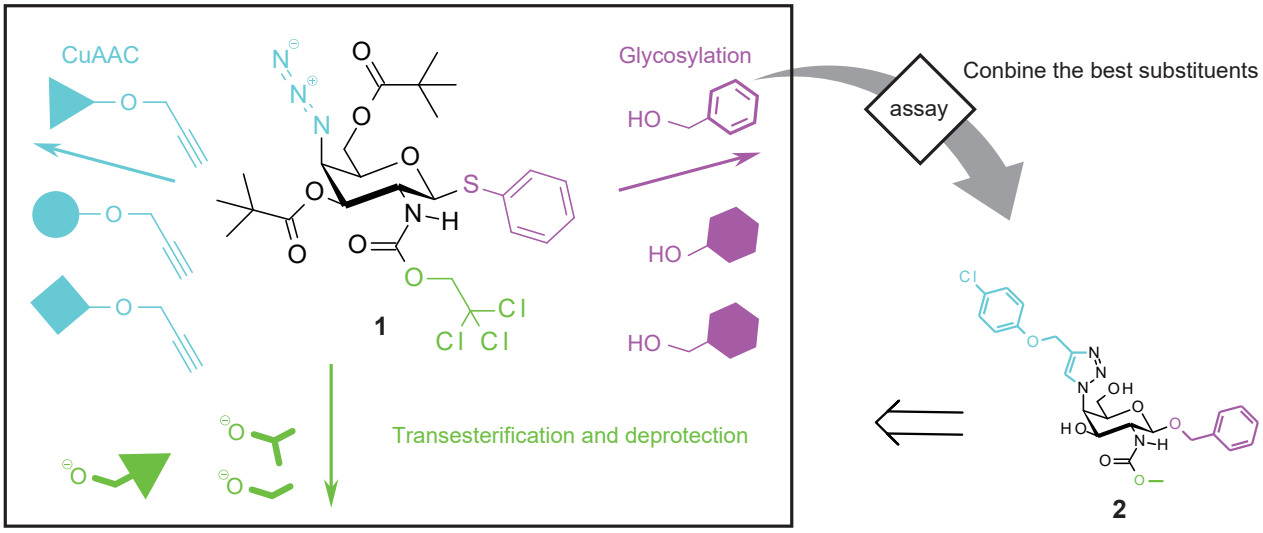
In our laboratory, we developed *N*-acetylgalactosamine (GalNAc) derivatives which can introduce various substituents for the purpose of constructing the "*N*-acetylgalactosamine 4-sulfate 6-*O*-sulfotransferase (GalNAc4S-6ST) inhibitor library" and also developed their practical synthesis. We have been focusing on GalNAc derivatives as candidates for GalNAc4S-6ST inhibitors.[1] Our aim is to find an excellent physiological active molecule efficiently with a combination of changing only one substituent at various positions. This time, we synthesized the 2,2,2-trichloroethoxycarbonylamino group-protected thioglycoside **1** having a building block that can selectively introduce various substituents. We developed a reaction for introducing and deprotecting substituents efficiently. We call this process the "fast track method". Compounds **2** was selected by a combination of the best substituents from the series of the inhibitory assay of the monosaccharides with changing only one substituent for the steps of glycosylation, transesterification, or CuAAC. The resulting compound **2** has two free hydroxy groups, in the future, it is considered to introduce a new substituent such as sulfate groups. This achievement of practicality can be expected to contribute to the construction of a high quality compound library and the search for new biologically active molecules.



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2P-097

Pd-Catalyzed Suzuki–Miyaura Cross-Coupling of α-Fluorinated Benzylic Triflones

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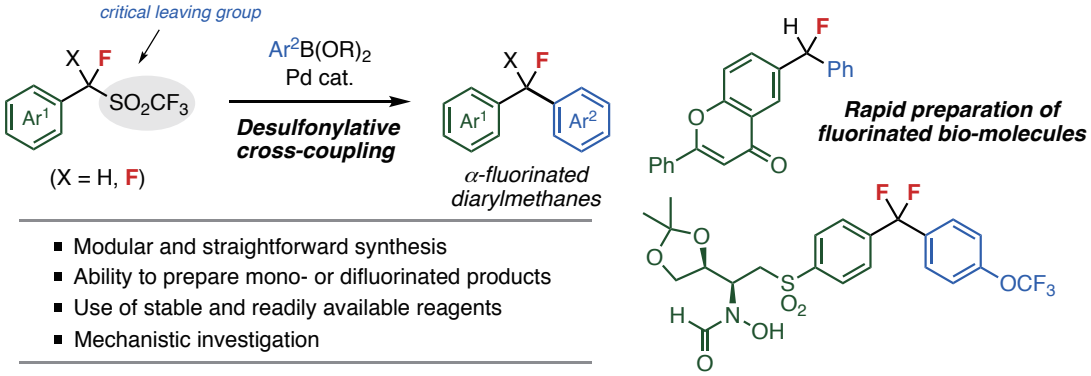
Fluorine is an important element in medicinal chemistry and material science because it can dramatically change chemical and physical properties of molecules. For example, the simple replacement of hydrogen with fluorine would enhance biological activities and metabolic stabilities. Thus, finding modular and straightforward syntheses of fluorinated molecules is still a challenge in synthetic organic chemistry. With the emergence of various fluoroalkylating agents in recent years, transition metal-catalyzed cross-coupling reactions of arene derivatives with fluorinated alkyl electrophiles or nucleophiles have been developed. Despite the recent advances in cross-coupling methodology, there are very few reports for the synthesis of α-fluorinated diarylmethanes.[1]

Our group have developed several cross-coupling reactions using benzylic sulfone derivatives as new electrophiles through carbon–sulfonyl bond activation by Pd, Ni, and Cu catalysis.[2] As part of our continuing studies, Herein, we report the Pd-catalyzed desulfonylative cross-coupling of α-fluorinated benzyltriflones with arylboronic acids to afford structurally diverse mono- and difluorinated diarylmethanes. The reactivity depended on the substituent on sulfonyl group, which was supported by theoretical calculations. Notably, sulfone substrates as versatile electrophiles are readily prepared by selective α-fluorination of benzylic triflones. To illustrate the utility of α-fluorinated benzylic triflones as new electrophiles, we attempted several transformations for the facile access to a variety of fluorinated compounds.



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[2] a) Nambo, M.; Crudden, C. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 742. b) Ariki, Z. T.; Maekawa, Y.; Nambo, M.; Crudden, C. M. *J. Am. Chem. Soc.* **2018**, *140*, 78. c) Nambo, M.; Tahara, Y.; Yim, J. C.-H.; Crudden, C. M. *Chem. Eur. J.* **2019**, *25*, 1923-1926.

2P-098

Total synthesis of 6-deoxydehydrokarafungin

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[2]*Research Institute of Pharmaceutical Sciences, Musashino University, 1-1-20 Shinmachi Nishotokyo-city, Tokyo, 202-8585 Japan*

Actinorhodin (ACT, **1**), produced by *Streptomyces coelicolor* A3(2), is a dimeric benzoisochromanequinone (BIQ) antibiotic, a class of aromatic polyketides. In the biosynthetic analysis of BIQs, 6-deoxydehydrokarafungin (DDHK, **2**) was assumed as biosynthetic intermediate between (*S*)-DNPA (**3**) and DHK hydroquinone (**4**) mediated by identified enzymes. However, **2** was not isolated from the fermentation broth meanwhile and the function is not clear (**Figure 1**).[1] We planned stereoselective synthesis of DDHK (**2**) via *trans*-selective reduction of tricyclic hemiacetal **5** providing basic carbon framework. MOM-protected lactone **6**, precursor of **5**, was prepared by tandem Michael–Dieckmann reaction of *o*-toluate **7** with β-alkoxydihdropyrane **8**.[2] After treatment of **6** with CH_3Li, reduction of the resultant hemiacetal **5** with Et_3SiH/TFA[3] gave BIQ **9** with undesired *cis*-stereochemistry exclusively and a small amount of enone **10**. **9** was temporarily subjected to further conversion to give epi-DDHK (**11**). Trials on reduction of hemiacetal **5** with other silanes did not afford desired *trans* isomer. Trials of simple MOM protection on the phenol part of **10** using NaH were unsuccessful, however, cyclic acetal **12** was obtained instead, when **10** was treated with excess amount of NaH. $NaBH_3CN$ reduction of **12** in acidic condition gave mainly *cis*-isomer **9** with desired *trans* isomer **13** as a minor component. Further trials using other reducing reagent resulted in the preferred formation of **13** (**13** : **14** = 7 : 3) with AlH_3 reduction. Following oxidation of **13** and deprotection lead to the total synthesis of DDHK (**2**) (**Figure 2**).

Figure 1

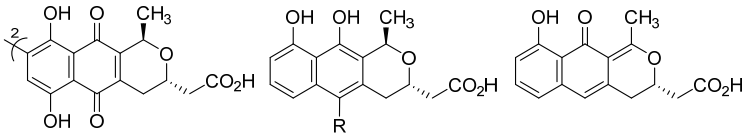
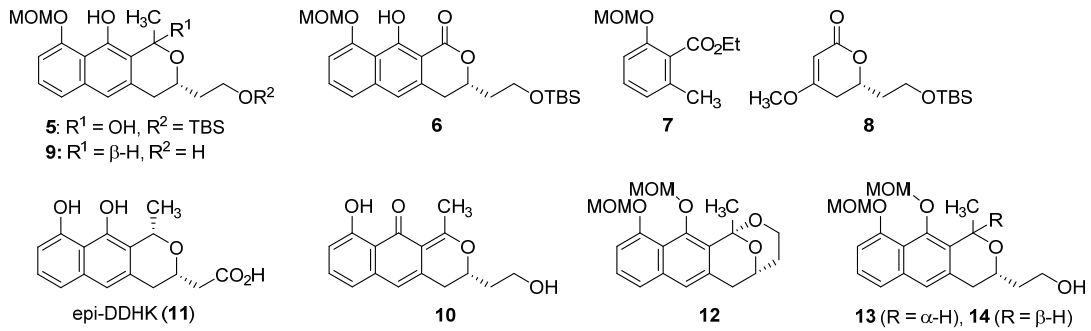


Figure 2



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Synthetic studies towards natural xanthones blennolides via spiro intermediates

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Naturally occurring xanthones have been isolated from a wide range of plants, bacteria, fungi, and lichens. (+)-Blennolides A (**1**) and C (**2**), partially hydrogenated xanthones, were isolated as secondary metabolites from an endophytic fungus *Blennoria* sp.[1] We have previously reported total synthesis of (+)-blennolide C (**2**).[2] In this synthesis, spirochromanone **3** was examined as key synthetic intermediate, which was prepared by aldol reaction of acetophenone **4** and cyclohexenone **5** followed by cyclization of **6** under acidic condition. Oxidative cleavage of the alkene moiety of **3** (R = Bn, $R^1 = CH_3$, R^2 = H) and following Dieckmann condensation of diester afforded desired (+)-blennolide C (**2**) (**Figure 1**). This methodology was applied for the synthesis of blennolide A (**1**). Racemic *cis*-disubstitttuted cyclohexenone **8** was prepared as followed: epoxybenzoate **9** derived from enone **10** was subjected to stereo- and regioselective reductive ring opening using $NaBH_3CN/BF_3{\cdot}OEt_2$[3] to give *cis*-substituted cyclohexanonol **11**. Benzyl protection in **11** and debenzoylation followed by sequential oxidation gave key cyclohexenone **8**. Following the pathway described above, enone **8** was subjected to aldol reaction with acetophenone **12**, however, desired aldol adduct was not obtained, and another synthetic pathway was examined. Propargyl alcohol **13** derived from enone **8** was subjected to Sonogashira coupling with iodoarene **14** followed by partial reduction to give Z-alkene **15**, which was treated with NaH to undergo S_NAr[4] to spirochromene **16**. Isomerization of **16** in thermal condition afforded spirochromene **17** with desired relative stereochemistry for the synthesis of blennolide A (**1**) (**Scheme 2**).

Scheme 1

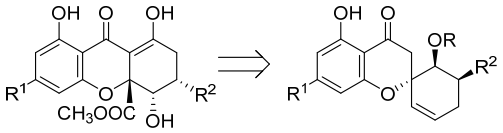
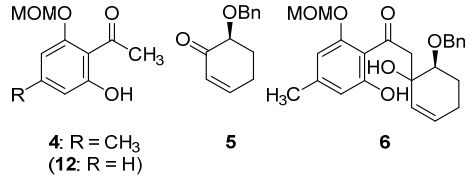
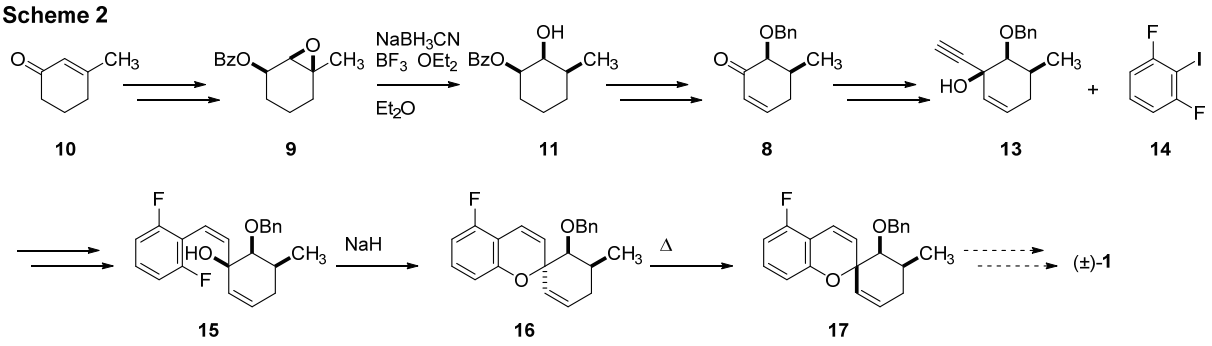


Figure 1



Scheme 2



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A Simple Protocol for the Synthesis of 4-Hydroxyquinolin-2(*1H*)-one and its Derivatization with Substituted Benzaldehydes

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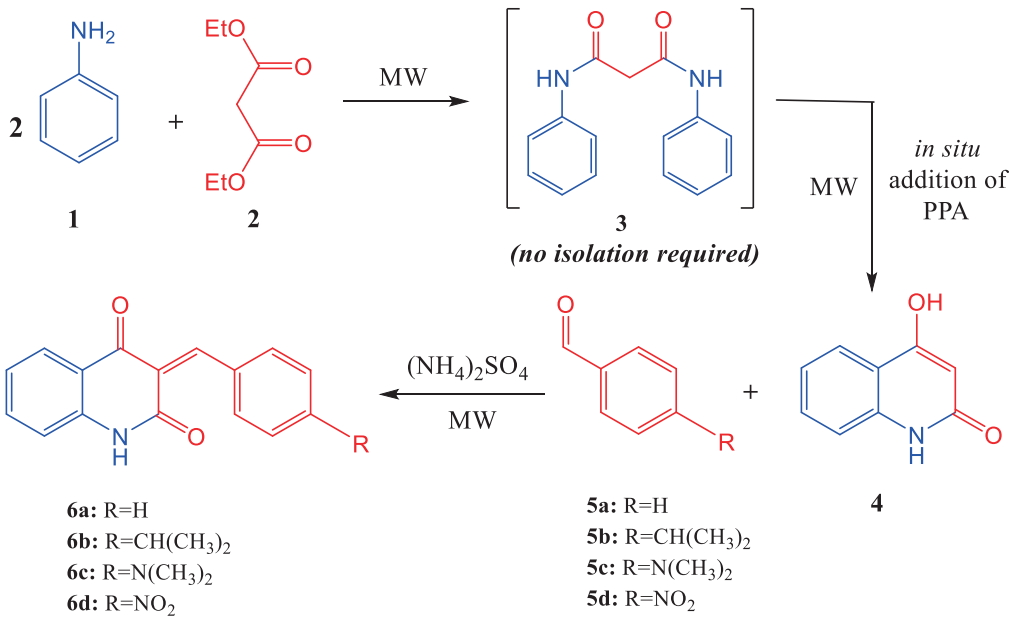
The quinoline derivative 4-hydroxyquinolin-2(*1H*)-one has caught the attention of numerous researchers due to its significance in natural products chemistry and the promising biological activities of its analogues.[1] The inherent reactivity of this compound has also allowed it to serve as a synthon for various types of functionalization.[2] However, traditional synthesis protocols utilize a two-step procedure where the intermediate is isolated. Such techniques require time-consuming procedures as well as harmful reagents.[3] This report presents a simple one-pot, two-step approach for the synthesis of 4-hydroxyquinolin-2(*1H*)-one from aniline and diethyl malonate. By employing microwave irradiation, total reaction time was reduced compared to conventional procedures while still affording the target compound in high yields. Moreover, performing the reaction using the one-pot protocol eliminated the necessity of intermediate isolation, thereby reducing the overall workup procedure as well as waste production. In addition, derivatization of the hydroxyquinolone framework with substituted benzaldehydes was also carried out. Incorporation of microwaves in the reaction and ammonium sulfate as catalyst produced 3-benzylidenequinolin-2,4(*1H,3H*)-diones in reasonable yields.



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Synthesis and Photophysical Properties of Flavylium Salts as Potential Bioinspired Dye Sensitizer

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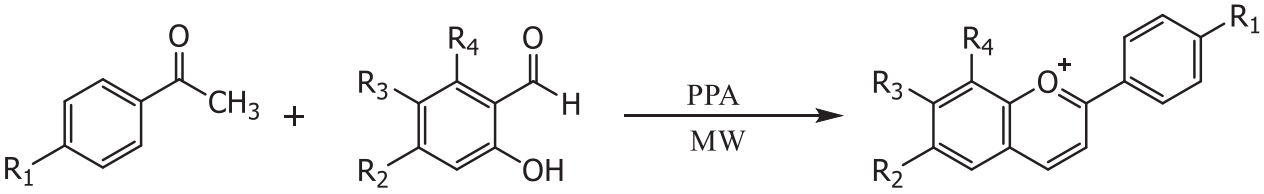
Iligan City, 9200, Philippines

Flavylium salts are the synthetic analogues of anthocyanin, the natural dye pigment in plants, which are widely used as sensitizers in various dye-sensitized solar cells (DSSC).[1-2] Traditionally, the synthesis of flavylium salts is commonly achieved through acid-catalyzed condensation of acetophenone and salicylaldehyde.[3] However, the traditional route uses harsh acidic conditions and longer reaction time. With the aim of developing a practical method under mild conditions and faster reaction time, a green synthetic approach was carried out. In this study, different flavylium salt compounds were synthesized under microwave irradiation from derivatives of acetophenone and salicylaldehyde using polyphosphoric acid (PPA) as catalyst. With microwave irradiation, shorter reaction time was achieved, while still giving sufficient yields for the synthesized flavylium salts. The photophysical properties of the synthesized compounds as potential new dye-sensitizers were also evaluated. Generally, introduction of electron-donating groups on ring A and ring B resulted in a bathoromic shift, and lower HOMO-LUMO band gaps. This was especially evident for flavylium salts containing a diethylamino- moiety at position-7 and a hydroxyl -moiety at position-4‘.



1: R_1= H
2: R_1= OH

3a: R_2, R_3, R_4= H
3b: R_2, R_4= H , R_3= $C_4H_{10}N$
3c: R_2= OCH_2CH_3, R_3, R_4=H
3d: R_2= H , R_3,R_4= CH=CH_2-CH-CH=CH_2

4a: R_1,R_2,R_3,R_4= H
4b: R_1,R_2,R_4 = H , R_3= $C_4H_{10}N$
4c: R_1,R_3,R_4 = H , R_2= OCH_2CH_3
4d: R_1,R_2,= H , R_3,R_4= CH=CH_2-CH-CH=CH_2
5a: R_1 = OH , R_2,R_4, R_3= H
5b: R_1 = OH , R_2,R_4 = H , R_3= $C_4H_{10}N$
5c: R_1= OH , R_3,R_4 = H , R_2= OCH_2CH_3
5d: R_1= OH, R_2 = H , R_3,R_4= CH=CH_2-CH-CH=CH_2

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2P-102s

Rhodium(III)-Catalyzed Direct C-H Bond Amidation of Aniline Derivatives Using a Pyrimidinyl Directing Group

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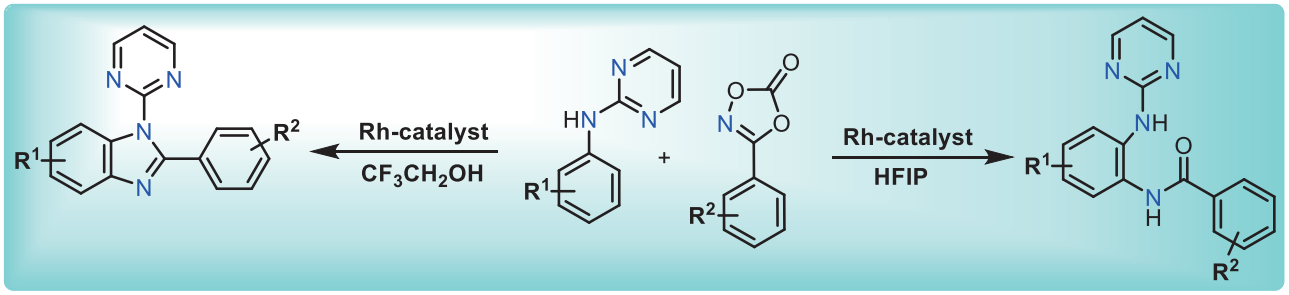
Direct C–H bond functionalization is most attractive field in organic chemistry because of it's step economical applications in synthetic field. The different types of C–H bonds present in organic compounds having utmost similar strength, which makes difficulty in regioselective C–H activation. In 1993, Murai group achieved the first regioselective C–H functionalization by ruthenium complex using ketone as a directing group.[1] Since Murai group dicovery, many reports appeared on C–H bond activation using a chelation assistance system and became common method for regioselective C–H bond activation using directing group strategy. Nitrogen containing compounds are important composition of many natural and synthetic compounds, and it shows broad applications in biological, pharmaceutical, and materials sciences.[2a] The efficient and selective catalytic conversion of C–H bond to C–N bond has been of much interest to researchers.[2b,2c] Direct amidation of C–H bond to form C–N has emerged as a step and atom-economical alternative to the convential C–N cross-coupling reactions. However, few examples are available for direct C–H amidation of aniline derivatives.[3]

Herein, we will present the Rh(III)-catalyzed regioselective C–H amidation of aniline derivatives with dioxazolone as an amidating reagent using pyrimidinyl as a directing group. This reaction provides broad substrate scope for aniline derivatives as well as dioxazolones. Also, the reaction tolerates various functional groups. This protocol shows solvent controlled monoamidation and amidation/cyclization. Preliminary mechanistic studies have been carried out to understand the working mode of catalysis.



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Iridium (III)- Catalyzed Direct C-H Alkynylation of Aromatic Acid Derivatives Using an Imidazole Directing Group

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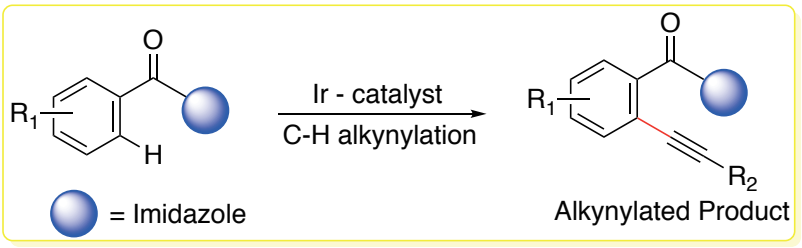
C-H functionalization reactions have made significant progress for last two decade after the first paper by Murai and co-workers was appeared in literature because the reaction is one of the effective and straight forward methods for introducing a functional group. [1] Alkynes are among the most unique functional groups and are widely present in natural products, drugs, and organic materials. It also permits to host of a broad range of C-C/ or C-hetero atom centered functional groups which can easily reassigned into various carbo-/heterocycles with diverse ring size. [2] However, a few examples are available for directed C-H alkynylation of aromatic acid derivatives by monodentate ligand. [3]
Herein, we introduce imidazole directed ortho C-H alkynylation of aromatic acid derivatives by iridium catalyst with bromoalkynes in very good to excellent yields. The detailed mechanism has been investigated and confirmed the intermediacy of six- membered iridocycle intermediates. This methodology is applicable for a wide range of carbocycles and heterocycles. The reaction tolerates a variety of functional group.



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Determining Nonempirical Absolute Configuration of Chiral Alkyl-substituted Epoxides Using Bis(zinc porphyrin) as a CD-Sensitive Bidentate Host Molecule

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Optically active epoxides are important and highly useful chiral building blocks in synthetic chemistry, and consequently, much effort has been devoted to the development of novel and efficient methods for their preparation, such as the catalytic asymmetric epoxidation reactions of olefins. The most commonly used technique for the determination of the absolute stereochemistry of optically active epoxides includes NMR analysis and exciton-coupled circular dichroism (ECCD) of appropriate derivatives of the corresponding ring-opened alcohols such as the Mosher esters and dibenzoates. However, very little is known about the direct and nonempirical determination of the absolute stereochemistry of chiral epoxides that do not require analyte derivatization.

Recently, our group has developed a direct nonempirical ECCD protocol to determine the absolute configurations of chiral monoalcohols with no chemical derivatization that employs bidentate bis(zinc porphyrin) host system **BP1** having a V-shaped structural motif as a circular dichroic (CD)-sensitive chirality probe (Figure 1).[1] As a new application of this bidentate host system **BP1**, we herein report a facile, direct assignment of the absolute stereochemistry of simple alkyl-substituted epoxides without other ligating functional groups based on a chemical derivatization-free supramolecular ECCD protocol (Figure 2).[2] A simple working model based on an MM2 optimized structure of the substrates is also proposed, which effectively enables the nonempirical prediction of the chirality of a variety of bound epoxides. The details of the working model and the analysis of various epoxides will be also presented.

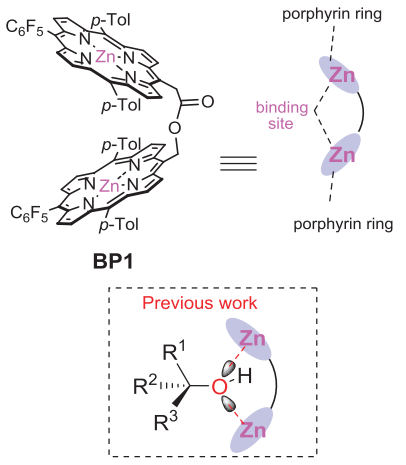

Figure 1. Structure of **BP1** and schematic of its simultaneous double coordination with monoalcohol (dashed box)

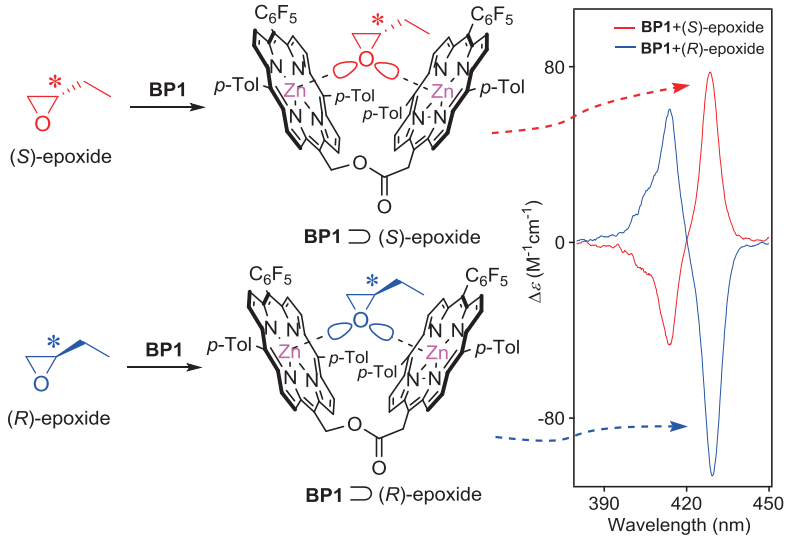

Figure 2. ECCD spectra of **BP1** in the presence of chiral epoxides.

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2P-105

First Total Synthesis of Antrimycin A and D

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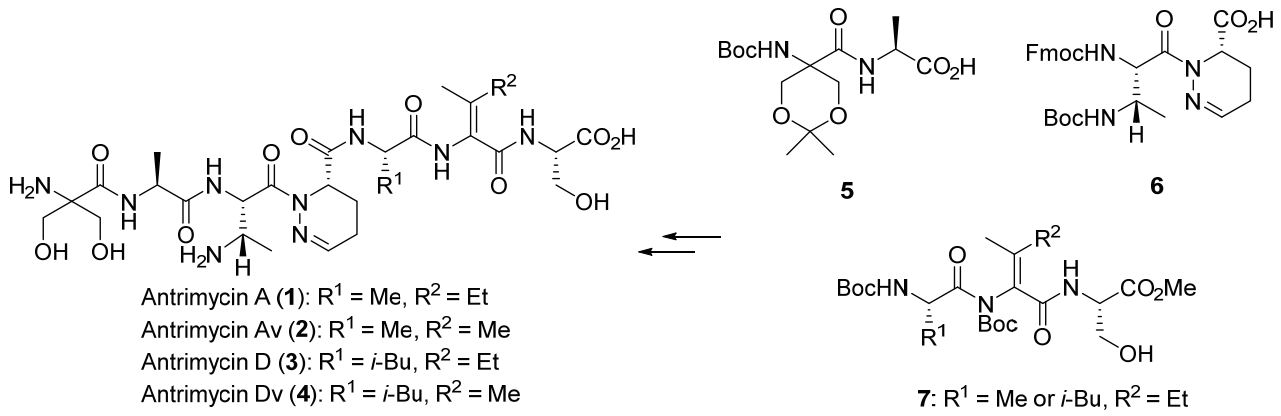
Antrimycins (**1**~**4**) were isolated from *Streptomyces* bacteria by Umezawa *et al*.[1] and Otake *et al*.[2] These natural products are rich in characteristic unusual amino acids: dehydropiperazic acid, α,β-dehydroamino acid, 2,3-daminobutyric acid, and α-hydroxymethylserine, and display a unique spectrum of antimicrobial activities for *Lactobacillus casei* and some strains of *Streptococci* and *Mycobacterium* sp. The structural and biological features made antrimycins attractive targets for total synthesis aiming to develop a new lead of antimicrobial agents. Schmidt[3] and Shin[4] independently achieved total synthesis of antrimycin Av (**2**) and Dv (**4**) bearing a dehydrovaline (ΔVal) moiety. On the other hand, total synthesis of antrimycin A (**1**) or D (**3**) in which ΔVal of **2** or **4** is replaced with *E*-dehydroisoleucine (ΔIle) has not been achieved. In this presentation, we report the first total synthesis of **1** and **3** by fragment coupling of **5**, **6**, and **7** via the stereoselective construction of *E*-ΔIle.[5] Efforts toward synthesis of natural congeners of **1** will be described.



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Synthetic Study of Sigillin A, Polychlorinated Polyketide

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Sigillin A is a unique polychlorinated natural product, which was isolated from the snow flea *Ceratophysella sigillata* in 2015,[1] and its structure was confirmed by X-ray crystallographic analysis (Figure 1). Sigillin A possesses *trans*-fused octahydroisocoumarin skeleton decorated with five chlorine atoms, and it has four consecutive stereocenters including two quaternary carbons. This molecule showed high repellent acivity in a bioassay with predatory ants. We were fascinated by these structural features to begin its total synthesis, although the structure of this molecule is quite simple.

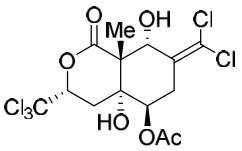
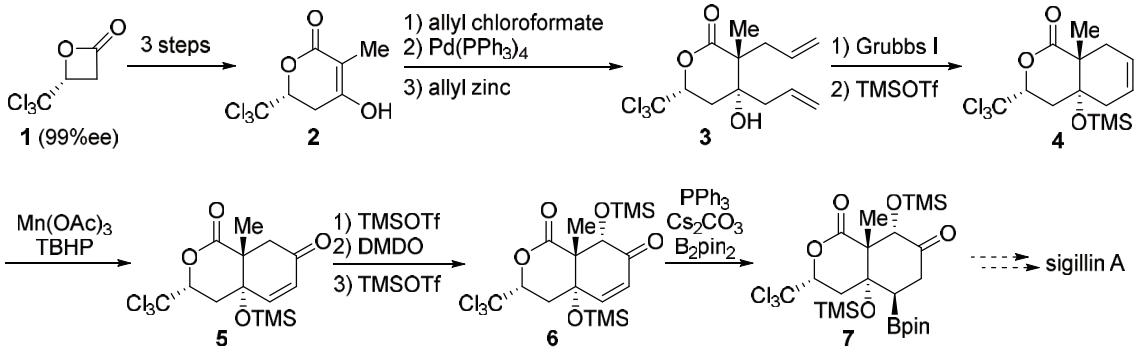


Figure 1. Sigillin A

The synthesis of octahydroisocoumarin core of sigillin A was started with known enantiopure β-lactone **1**. lactone **2** could be prepared from β-lactone **1** in three steps. Both electrophilic and nucleophilic allylations to lactone **2** afforded the desired compound **3** with high diastereoselectivity. RCM of **3** and silyl protection gave the carbon framework **4** (Scheme 1).



Scheme 1. Synthetic study of sigillin A

To increase in the proper oxidation level toward sigillin A, Mn-catalyzed allylic oxidation of **4**, followed by Rubottom oxidation of **5** led to enone **6**. Conjugate addition of boron pinacol ester to enone **6** was accomplished to give **7**, from which transformation into sigillin A is currently in progress.

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Spontaneous resolution of the chiral crystal and metal complex of *N,N′*-dimethylpyridine-2,6-dicarboxamides bearing pyrimidine

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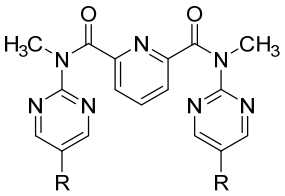
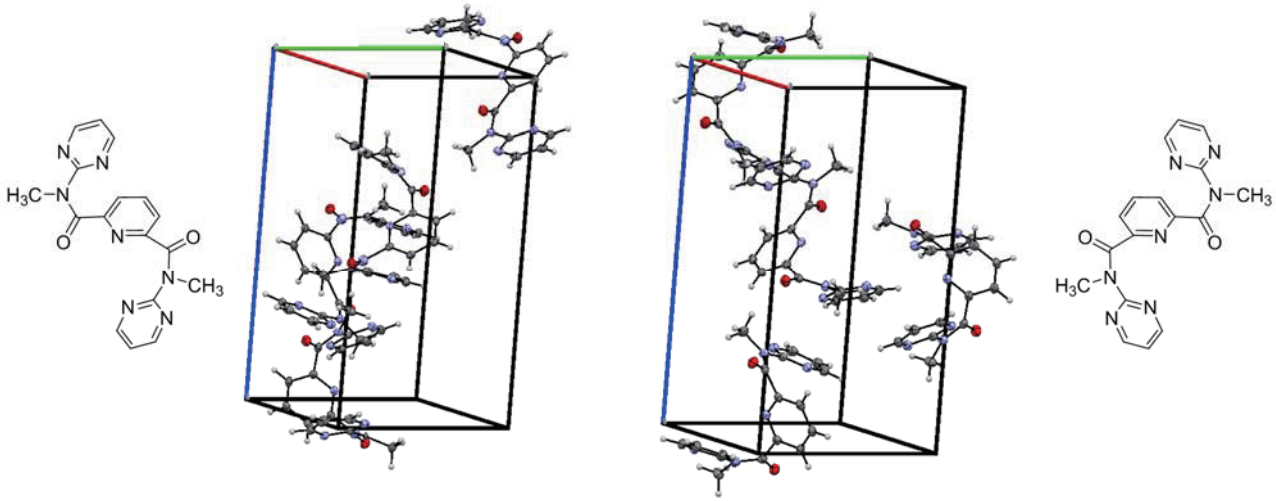
Pyridine is a well-known aromatic heterocycle that acts as a base and a ligand for various metals. In addition, many pyridine derivatives have important biological role or activities. On the other hand, most secondary amides, such as benzanilide and acetanilide, favor the *trans-form*, but *N*-methylation generally causes conformational alteration from *trans* to *cis* in crystal and solution. We focused on pyridine's properties and conformational preference of *cis-form* amides, we have synthesized unique *N*-alkyl aromatic amides containing pyridine. Previously, we have reported that the *N*-methyl amides bearing pyridine as outer stimuli, such as pH, responsive structural alteration units.[1,2] Furthermore, we synthesized *N,N′*-dimethylpyridine-2,6-dicarboxamides bearing pyrimidine **1**, and found that **1** have unique *cis*-amide structure in crystal. Among them, compound **1** (R=H) has the two pyrimidyl groups which are located on opposite sides of the central pyridine ring and is racemic in solution, but **1** (R=H) exhibits chiral properties in crystal.



1:R=H, alkyl, OCH_3, Br etc

In this study, we describe the more details of spontaneous resolution of chiral crystals of **1** (R=H) by means of X-ray and CD analysis. In addition, we report that the crystal structure of various *N*-methylpyridine-2,6-dicarboxamides and Pd-complex of these amides.



The crystal structure of the chiral crystal of **1** (R=H)

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Conformational Analysis and *cis-trans* Control of Cyclized Tryptophan Tertiary Amides

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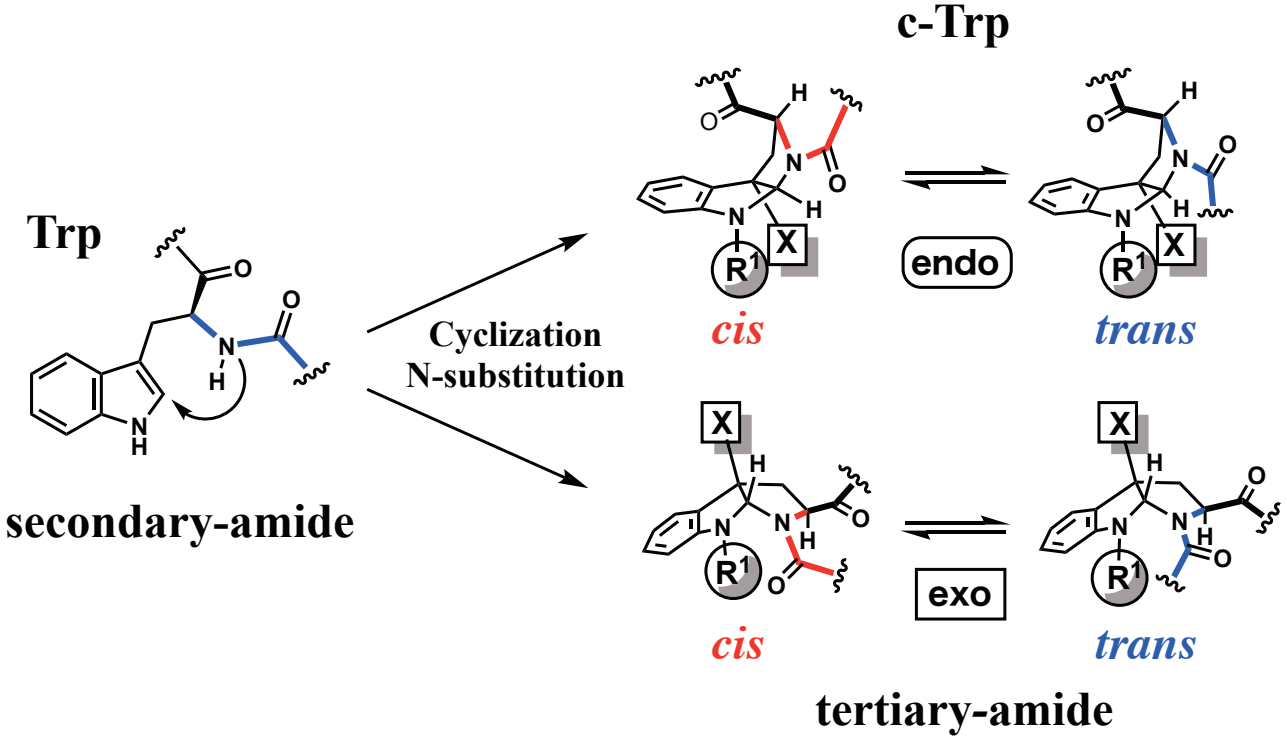
An amide bond is a kind of covalent chemical bond that links two amino acids to make peptides or proteins and has a partial double bond character. This double bond character makes amide structure planar and causes the rotational barrier between the two isomers, *cis* and *trans*. It is important to control the amide *cis-trans* equilibrium because it contributes to the three-dimensional structure of peptides, which is directly related to their bioactivity. In the case of a secondary amide, the *trans*-amide form predominates because the corresponding *cis*-amide is destabilized by steric repulsion. On the other hand, 10–20% of a tertiary amide can exist in its *cis*-form alongside the *trans*-form. It is known that of the natural α-amino acids, only α-proline can form a tertiary amide. While a tertiary amide can exist both in *cis*- and *trans*-amide forms, it is difficult to control the *cis-trans* ratio. So far, we have succeeded in controlling amide *cis-trans* ratios completely by using conformationally constrained bicyclic β-proline derivatives[1, 2].

In this study, we focused on cyclized tryptophan (c-Trp) as an α-amino acid derivative which can form a tertiary amide. There are two diastereomers of c-Trp, endo and exo, that are expected to have different *cis-trans* preferences. We have synthesized model compounds having tertiary amides of c-Trp (endo and exo) and analyzed their *cis-trans* ratios in order to reveal potential characteristic *cis-trans* equilibrium preferences.



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2P-109s

Synthesis of pyrazoles from conjugated hydrazone through acid-promoted β-protonation/ nucleophilic addition/cyclization/aromatization sequence

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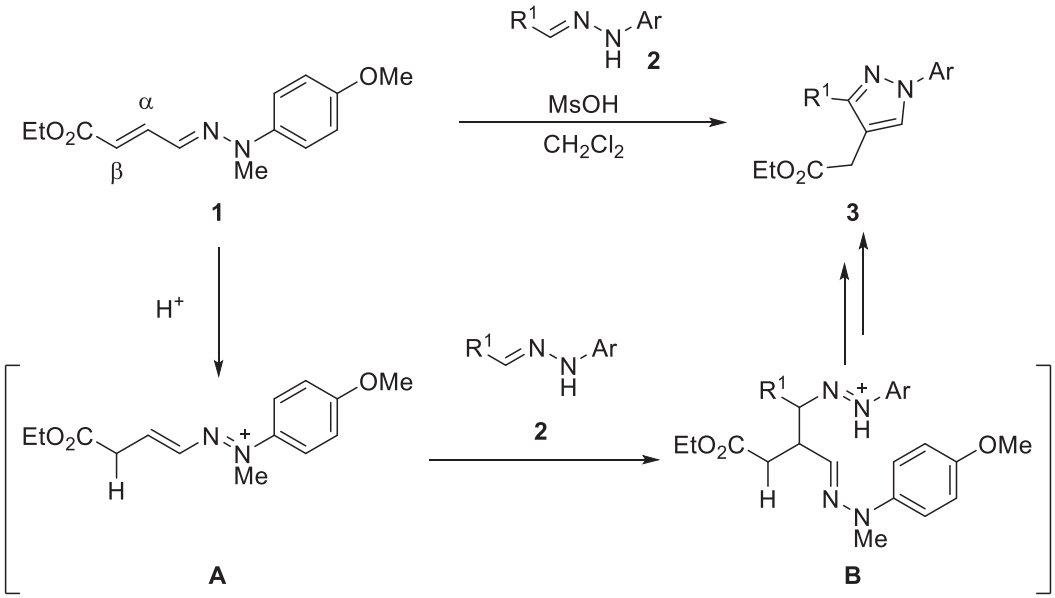
Intra- and intermolecular cyclization reaction utilizing conjugated imines is one of the most powerful strategies for the synthesis of aza-heterocycles. We have recently studied on the radical-mediated[1] and transition metal-catalyzed[2] cyclization reactions of conjugated imines to provide heterocyclic compounds. In the present study, we developed that the acid-promoted sequential reaction of conjugated hydrazone **1** with *N*-arylhydrazones **2** through an umpolung process provided various 1,3,4-trisubstituted pyrazoles **3**.

When the conjugated hydrazone **1** was treated with *N*-arylhydrazones **2** in the presence of methanesulfonic acid (MsOH) in CH_2Cl_2 at rt, the expected reaction proceeded smoothly to afford desired pyrazoles **3** in good yields. This sequential reaction would be triggered by the generation of 1,2-diazonium-1,3-diene **A** by protonation of **1** at the β-position. Then nucleophilic addition of *N*-arylhydrazones **2** to **A** and isomerization of intermediate **B** followed by cyclization-aromatization would give pyrazoles **3**. The substituent effects on the benzene ring of *N*-arylhydrazones were systematically examined. Further investigation of the reaction pathway and application to synthesis of Lonazolac, a nonsteroidal anti-inflammatory drug, will be presented.



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Copper-Catalyzed Synthesis of Multisubstituted Pyrroles by Cycloisomerization of Cyclopropenyl Oxime Ether

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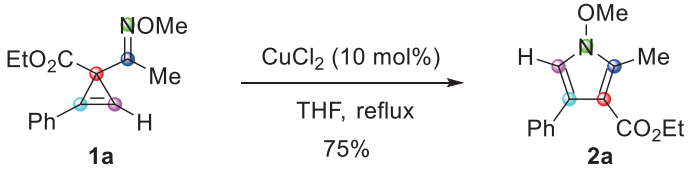
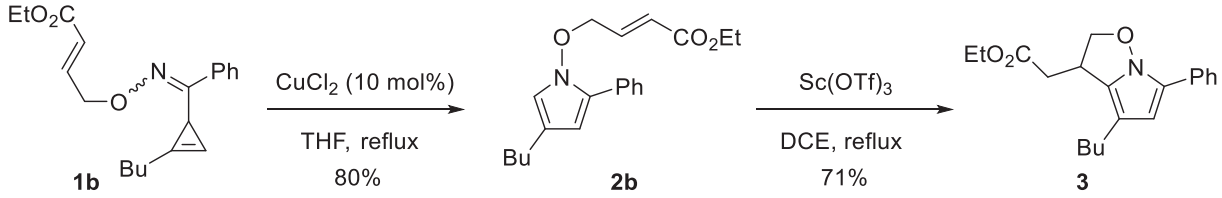
Transition metal-catalyzed cycloisomerization is highly effective methods for the construction of various heteroaromatic compounds with highly atom economical manner. Although cycloisomerization involving ring-opening of cyclopropene into aromatic hydrocarbons or furans has been reported, synthesis of pyrroles has not yet. [1-2] The development of synthetic methods of polysubstituted pyrroles is strongly desired because pyrroles are key structural units in many natural products and pharmaceuticals. We expected that cyclopropene bearing imine moiety would undergo cycloisomerization by transition metal to afford corresponding pyrrole. [3-5] Herein, we present a new synthetic strategy of polysubstituted pyrroles by copper-catalyzed cycloisomerization of cyclopropenyl oxime ether.

When oxime ether **1a**, which was easily prepared from corresponding cyclopropenyl ketone, was treated with 10 mol% of $CuCl_2$ under heating condition, the expected cycloisomerization effectively proceeded to afford pyrrole **2a** in 75% yield.



This synthetic method was successfully applied to the synthesis of fused heterocycles. Allylated oxime ether **1b** was smoothly converted to pyrrole **2b** in 80% yield by our copper-catalyzed cycloisomerization. The intramolecular cyclization of **2b** proceeded with $Sc(OTf)_3$ to produce 2,3-dihydropyrrolo[1,2-*b*]isoxazole **3** in 71% yield. It is note that the synthetic method of such unique fused pyrrole has not been reported so far.



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Four-component Coupling Strategy for 2,3,4-Trisubstituted 3,4-Dihydroquinoline

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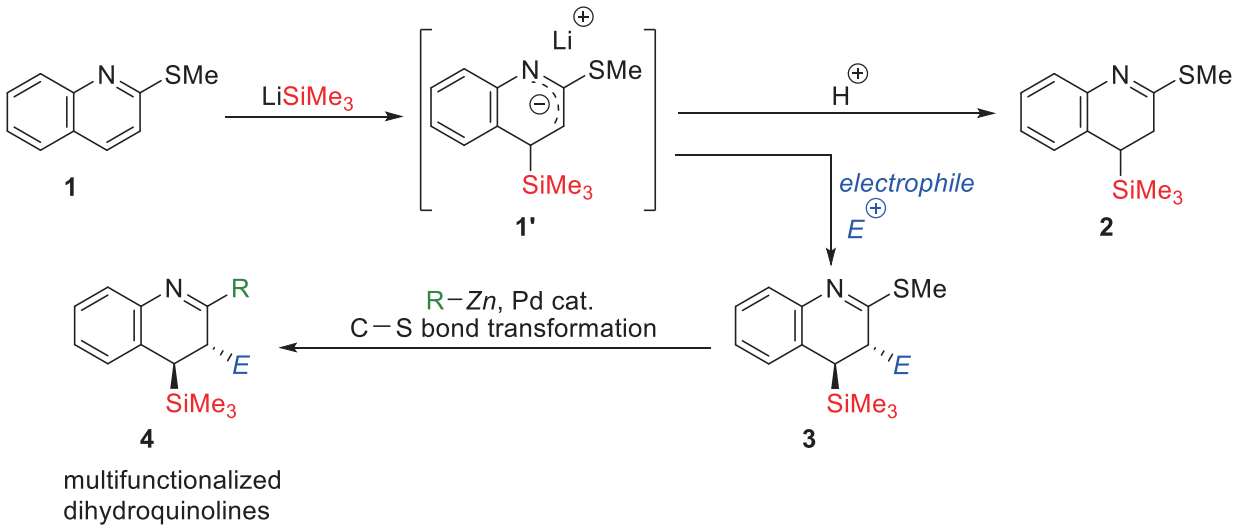
3,4-Dihydroquinoline skeleton is often found in the structure of biologically active compounds. In spite of the potential utility of these dihydroquinolines, a strategy for the synthesis of such a skeleton has rarely been investigated. In this symposium, we present a new synthetic strategy for 2,3,4-trisubstituted 3,4-dihydroquinoline through the regioselective attack of silyllithium to quinoline.[1]

The reaction of 2-methylsulfanylquinoline (**1**) with trimethylsilyllithium occurred selectively at the 4-position of the quinoline skeleton to afford 2-methylsulfanyl-4-trimethylsilyl-3,4-dihydroquinoline (**2**). The attack to the 4-position of the quinoline skeleton is unique to silyllithium, while the attack of a carbanion to the quinoline skeleton occurs at the 2-position selectively.[2] Lithium enamide intermediate **1'** could be trapped by electrophiles to give dihydroquinolines **3** in moderate to good yields. Palladium-catalyzed Negishi-type reaction of **3** afforded multifunctionalized 3,4-dihydroquinolines **4**.



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Studies on the Synthesis of Kadcoccilactone A

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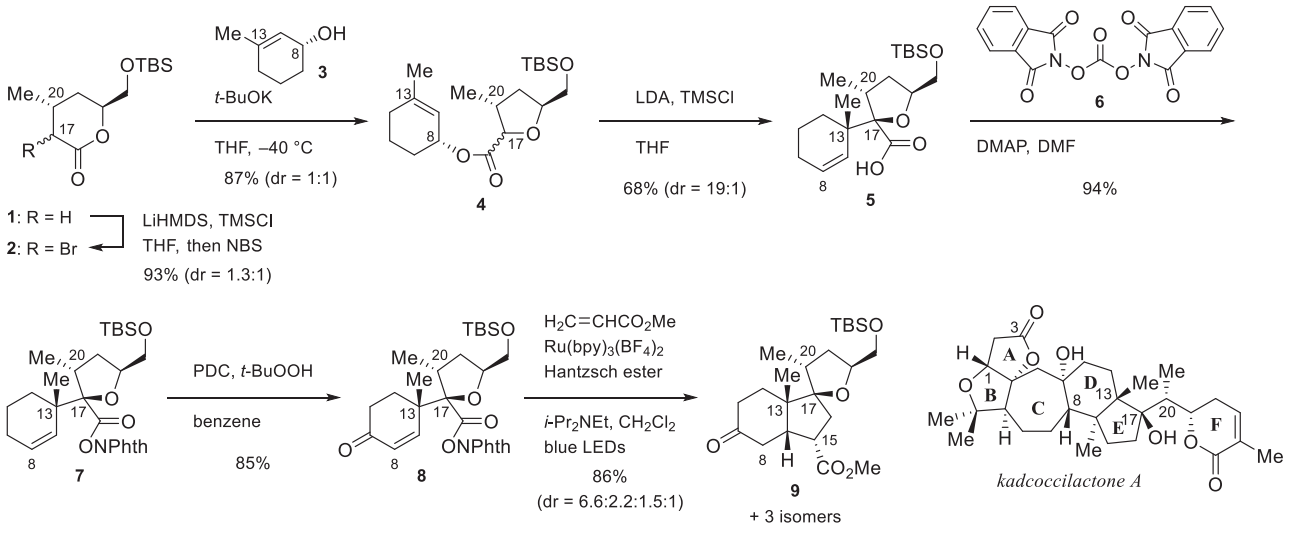
Kadcoccilactone A, isolated from *kadsura coccinea* by Sun and co-workers in 2008, is a unique polycyclic triterpenoid having a characteristic seven-membered ring.[1] Recently, we developed a method for the stereoselective synthesis of chiral building block **5** having contiguous quaternary stereocenters.[2] To demonstrate the synthetic utility of building block **5**, we planned to synthesize kadcoccilactone A.

At the outset of our study, we addressed a second-generation synthesis of ester **4** to improve the synthetic efficiency. Despite the lack of precedent for the use of secondary alcohols as nucleophiles, we found that ester **4** could be obtained by the ring-contractive transesterification of α-bromolactone **2**, prepared from known lactone **1**, with chiral secondary alcohol **3** when treated with *t*-BuOK in THF at −40 °C. Ireland−Claisen rearrangement of **4**, followed by esterification with **6** and allylic oxidation set the stage for the key radical addition/cyclization sequence. Gratifyingly, the expected ring formation occurred upon exposure of NHP ester **8** to the reductive photoredox reaction conditions in the presence of methyl acrylate to provide a separable mixture of four of the eight possible stereoisomers in 86% yield favoring desired isomer **9**.



[1] Gao, X.-M.; Pu, J.-X.; Huang, S.-X.; Lu, Y.; Lou, L.-G.; Li, R.-T.; Xiao, W.-L.; Chang, Y.; Sun, H.-D. *J. Nat. Prod.* **2008**, *71*, 1182−1188.

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[3] Saito, S.; Yamakoshi, H.; Nakamura, S. *Heterocycles* **2019**, *99*, 1086−1094.

2P-113

Stereoselective Synthesis of Regioisomeric 2,5-Disubstituted Thiazole Amino Acid Units for Dendroamide A Analogues

○Takuji Magata, Aya Furokawa, Kazuhisa Takeuchi, Yoshiaki Ohtomo, Yusuke Moriguchi, Ryosuke Yokoi, Shotaro Nojiri, Ryota Miyazaki, Yoshimi Hirokawa and Naoyoshi Maezaki*

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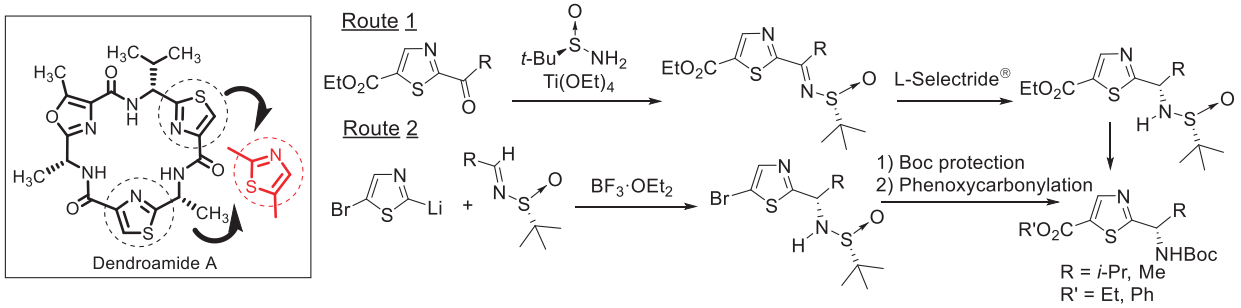
Dendroamide A is a thiazole–containing peptide isolated from terrestrial cyanobacteria. The peptide exhibits potent inhibitory activity against P-glycoprotein (P-gp), which plays an important role to multi-drug resistant (MDR) of cancer. To examine structure–activity relationship, we have synthesized 2,5-positional isomers of the natural thiazole and oxazole amino acid units for assembling dendroamide A analogues. We have previously reported a synthesis of the 2,5-disubstituted oxazole units.[1]

Here we will present two kinds of diastereoselective syntheses of the 2,5-disubstituted thiazole units utilizing chiral *N*-*tert*-butanesulfinyl imines, (1) diastereoselective hydride reduction of the chiral sulfinyl ketimines[2] and (2) diastereoselective addition of (5-bromothiazole-2-yl)lithium to the chiral sulfinyl aldimines.[3]

In the first approach, the thiazoyl ketones were converted into the ketimines with $Ti(OEt)_4$, followed by reduction with L-Selectride®, affording an amino stereogenic center with excellent diastereoselectivity.

In the second approach, the highly diastereoselective addition to the chiral sulfinyl aldimines was achieved on treatment of (5-bromothiazol-2-yl)lithium generated by selective lithiation of 2,5-dibromothiazole in the presence of $BF_3{\cdot}OEt_2$. After replacement of the sulfinyl group into a Boc group, a protected carboxyl group was introduced by Pd-catalyzed phenoxycarbonylation. This method can be applied to a synthesis of natural-type 2,4-disubstituted thiazole amino acid units. Detail of our research will be presented.



[1] Magata, T.; Nagano, S.; Endo, T.; Kawaida, J.; Nagaoka, S.; Hirokawa, Y.; Maezaki, N. *Tetrahedron Lett.* **2017**, *58*, 3628.

[2] Magata, T.; Hirokawa, Y.; Furokawa, A.; Takeuchi, K.; Ohtomo Y.; Kino T.; Kominami J.; Nakai Y.; Kitamura M.; Maezaki N. *Chem. Pharm. Bull.* **2018**, *66*, 416.

[3] Magata, T.; Hirokawa Y.; Moriguchi Y.; Yokoi R.; Nojiri S.; Miyazaki R.; Akasako S.; Takahashi R.; Nishida M.; Hakoda J.; Nakayama R.; Tanaka A.; Maezaki N. *Tetrahedron Lett.* **2019**, *60*, 718.

Total Synthesis of Tylophorine and Cryptopleurine

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Phenanthroindolizidine and phenanthroquinolizidine alkaloids,[1] such as tylophorine (**1**) and cryptopleurine (**2**), respectively, have been paid considerable attention not only by organic chemists but also medicinal chemists, because these alkaloids exhibit several interesting biological activities, such as antitumor and anti-inflammatory (Figure 1). Recently, we reported an efficient synthesis of preparing phenanthrenes via a KHMDS-promoted formal [2+2]-cycloaddition of 2'-vinylbiaryl-2-yl ketones, followed by a TfOH-promoted rearrangement.[2] We envisioned that this method could be applied to efficient synthesis of these alkaloids.

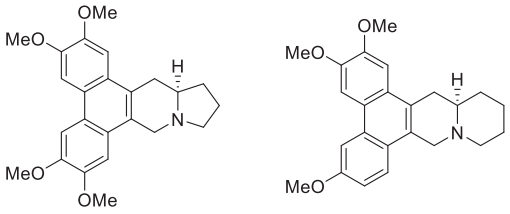
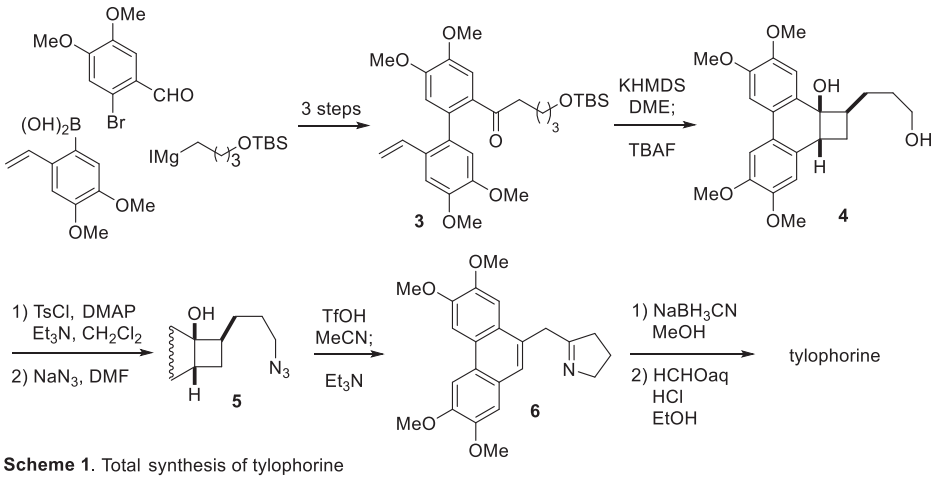


Figure 1. Structures of phenanthro-indolizine and -quinolizidine.



Scheme 1. Total synthesis of tylophorine

biaryl ketone **3** was prepared from readily available compounds in three steps. The key [2+2] cycloaddition followed by deprotection proceeded well to afford cyclobutanol **4**. Azide formation and acid-promoted rearrangement gave the desired phenanthrene **6**. Reduction of imine **6** followed by Pictet-spengler reaction led to tylophorine (Scheme 1).

In this poster session, the synthesis of phenanthroquinolizidine alkaloids such as cryptopleurine and our recent progress will be discussed.

[1] (a) R. Huang *et al*. *Synthesis* **2001**, 2365. (b) S. R. Chemler, *Curr. Bioact. Compd.* **2009**, *5*, 2.
[2] K. Takasu *et al. Org. Lett.* **2014**, *16*, 1008.

2P-115

Facile Synthesis of 3-Substituted 2-Trifluoromethylindoles from Trifluoroacetoanilides Bearing a Vinylogous Electron-withdrawing group

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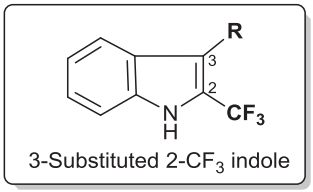
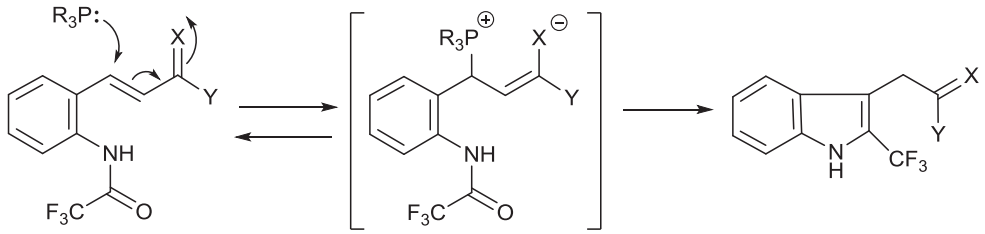
Indoles are a crucial class of heterocycles that can be seen in various structures of biologically active compounds, such as medicines and agrochemicals. Many of these indole derivatives that are biosynthesized from tryptophane have a significant substituent for the biological activity at the C-3 position of the indole skeleton as a common structural character. On the contrary, the introduction of a fluorine or trifluoromethyl group into organic molecules leads to a meaningful change in both the chemical and pharmaceutical properties of parent molecules. Therefore, we are particularly interested in the synthesis of 3-substituted indoles bearing a trifluoromethyl group at the C-2 position.

Two methods can be used for such purpose: 1) transformation from 2-trifluoromethylindole by the introducing the 2-substituent and 2) indole formation from a suitably substituted precursor for the 3-substituted 2-trifluoromethylindole. Regarding the first method, one of us reported the synthesis of 2-trifluoromethylindole by thermolysis of *o*-trifluoroacetoaminobenzylphosphonium salt and derived some 3-substituted 2-trifluoromethylindoles.[1] However, this method required longer steps, and was limited by the labile property of the trifluoromethyl group under conditions, such as hydrolysis and hydrogenation.



We considered the following method herein: trifluoroacetoanilides bearing a vinylogous electron-withdrawing group at the ortho-position could react with phosphine by the 1,4-addition mode to give phosphonium salt, which would subsequently give the 3-substituted indole under thermolytic conditions. We successfully performed a direct synthesis of the 3-substituted 2-trifluoromethylindoles, including the 2-trifluoromethyl analog of indomethacin (COX-2 selective inhibitor[2]).



[1] K. Miyashita et al. *J. Chem. Soc. Perkin. Trans 1* **1996**, 1261; *Chem. Pharm. Bull.* **1997**, *45*, 932.
[2] J. Marnett et al. *Med. Chem. Lett.* **2013**, *4*, 486.

Synthetic Study of 4″α-Substituted cyclic ADP Carbocyclic-ribose as a Target Identification Probe

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Cyclic adenosine diphosphate-ribose (cADPR, **1**) is a general second messenger involved in intracellular Ca^{2+} signaling. cADPR is involved in a variety of physiological processes, while these have not been fully clarified, in particular, the target proteins of cADPR must be identified. On the basis of cyclic adenosine diphosphate-carbocyclic-ribose (cADPcR[1], **2**), a stable equivalent of cADPR (Figure 1), which previously developed by us, considering the structure-activity relationship of cADPR-related compounds and three-dimensional structural modeling of cADPcR, we designed cyclic-ADP-4″α-azidopropyl carbocyclic-ribose (N_3-cADPcR, **3**). N_3-cADPcR can be a useful precursor for the preparation of biological tools effective to investigate cADPR mediated signaling pathways. For the synthesis of N_3-cADPcR, 4α-azidopropyl carbocyclic-ribosylamine **8** having a chiral quaternary stereogenic center was required as the key unit (Scheme 1). We planed to synthesize the desired unit **8** via construction of the quaternary stereogenic center by a radical cyclization with a silicon-tethered[2,3] substrate **6** as the key step. Introduction of the dimethylallylsilyl groups as the silicon-tether at the both 2,3-hydroxyl groups of the diol **5**, which was obtained from commercially available the bicyclic lactam **4**, gave **6**. When a solution of Bu_3SnH and AIBN in toluene was added slowly to a solution of **6** over a 4.0 h period under reflux, the reaction gave the cyclization product **7** with the desired quaternary stereogenic center in 94% yield. Tamao−Fleming oxidation of **7** to provide the 4α-hydroxypropyl triol, protecting the 2,3-cis-diol and subsequent introduction of the azido group at the terminal position of the 4α-branched-chain, followed by removal of phthaloyl and benzoyl groups produced the 4α-branched carbocyclic-ribosylamine **8**. Thus, the key unit **8** in hand, its treatment with the imidazole nucleoside derivative **9**, prepared from inosine, in the presence of K_2CO_3 in DMF/THF effectively induced adenine ring closure to produce the desired *N*1-carbocyclicribosyl adenosine derivative **10**. Synthesis of the target N_3-cADPcR (**3**) from **10** via a Ag^+-mediated intramolecular cyclization to form the 18-membered pyrophosphate ring as the key step, is under investigation.

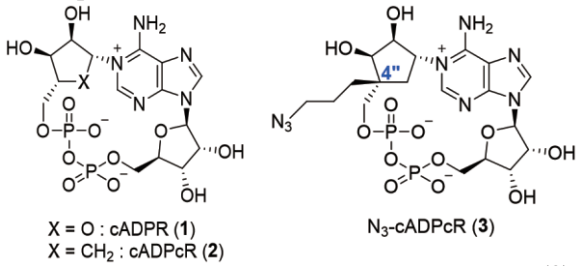
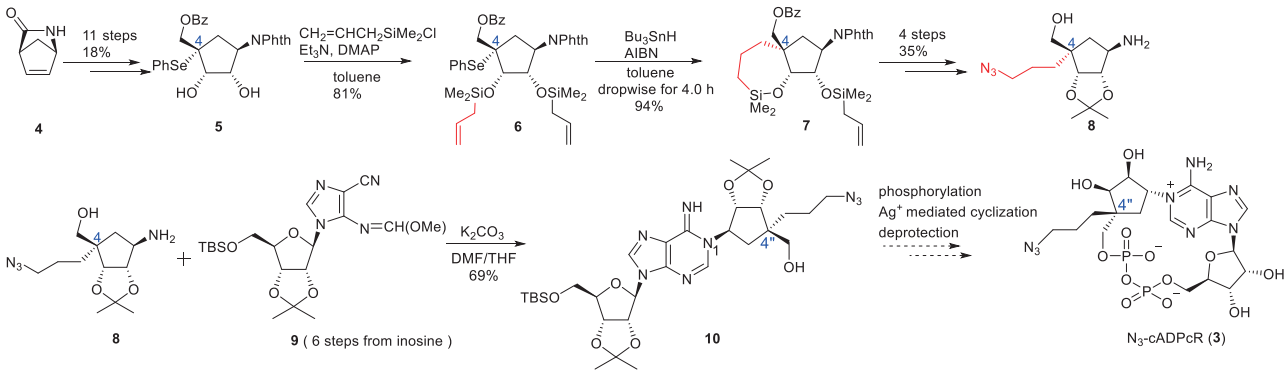


Figure 1 cADPR (**1**), cADPcR (**2**), and N_3-cADPcR (**3**)

Scheme 1



[1] Shuto, S.; Fukuoka, M.; Manikowsky, M.; Ueno, T.; Nakano, T.; Kuroda, R.; Kuroda, H.; Matsuda, A. *J. Am. Chem. Soc.* **2001**, *123*, 8750.

[2] Xi, Z.; Agback, P.; Plavec, J.; Sandstram, A.; Chattopadhyaya, J. *Tetrahedron,* **1992**, *48*, 349

[3] Terauchi, M.; Yahiro, Y.; Abe, H.; Ichikawa, S.; Tovey, S. C.; Dedos, G. S.; Taylor, C. W.; Potter, B. V. L.; Matsuda, A.; and Shuto, S. *Tetrahedron.* **2005**, *61*, 3697

Catalytic Asymmetric Dearomatization of Phenols Using Chiral Silver(I) Phosphate for Synthesizing Chiral Spirolactams

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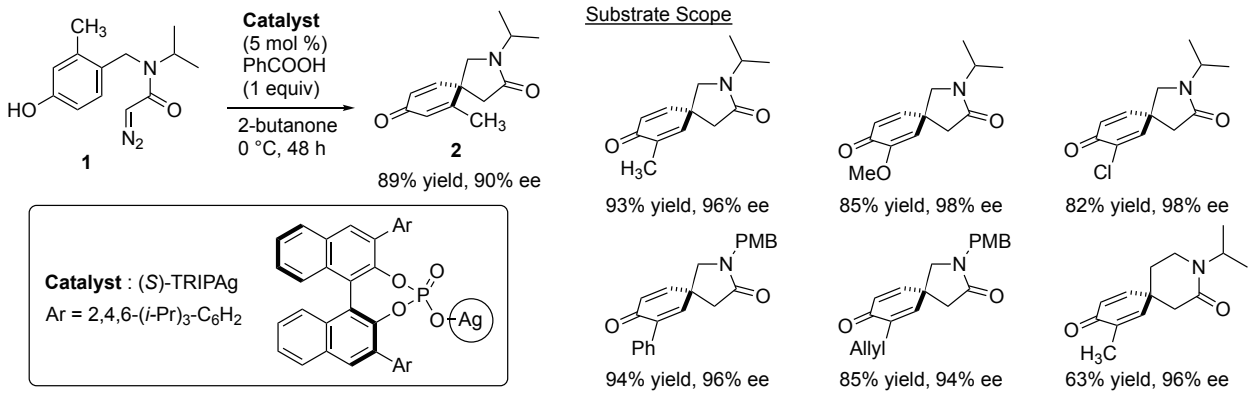
para-Substituted phenols can react with chirally-modified electrophiles at the *ipso*-position to give spirocyclohexadienones with a quaternary stereocenter. Recently, considerable efforts have focused on the development of catalytic asymmetric dearomatization reactions based on this strategy.[1] Chemo- and enantioselective reactions of arenes with metal carbenes remain a challenge in the field of organic synthesis because of the divergent reactivity of metal carbenes. We envisioned chemoselective dearomatization reactions of phenols could be realized by using an electrophilic metal carbene if the competing reactions such as C–H insertion and Büchner reaction could be controlled by selection of metal and ligands.

This hypothesis led us to examine the reaction using model substrate **1**. Metal screening revealed that, in contrast with the reactions using Rh or Cu catalysts, the reaction using Ag catalyst provided the dearomatized product in a chemoselective manner. Furthermore, when using 5 mol % of chiral Ag catalyst: (*S*)-TRIPAg in 2-butanone in the presence of 1 equiv of benzoic acid, the corresponding aza-spirocyclic compound **2** was obtained in 89% yield with 90% ee. Under the optimized conditions, various phenol derivatives were converted into the corresponding spirocyclic compounds in excellent yield with high ee. Mechanistic studies including a nonlinear effect study and a kinetic study suggested involvement of a single catalyst in the enantio- and rate-determining step. In addition, anisole derivative was not an effective substrate. These findings indicated that interaction between the phenolic hydroxyl group and catalyst via hydrogen bonding would play a key role for the stereocontrol.[2]



[1] For a review, see: You, S. L. *et al*. *Chem*. *Soc*. *Rev*. **2016**, *45*, 1570.
[2] Nakayama, H.; Harada, S.; Kono, M.; Nemoto, T. *J*. *Am*. *Chem*. *Soc*. **2017**, *139*, 10188.

Synthesis and function of *Alcaligenes faecalis* lipid A and its derivative

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Lipopolysaccharide (LPS) is one of the cell membrane components of Gram negative bacteria and activates innate immunity to induce strong inflammation. Glycolipid lipid A, located at the terminal of LPS, is its active principle. Low inflammatory lipid A and their derivatives have been expected as a novel vaccine adjuvant candidate.

Alcaligenes sp. is known as an opportunistic bacterium. Kiyono *et al.* showed that *Alcaligenes faecalis* inhabits human gut Peyer's patches and plays an important role in the immune response. We isolated *A. faecalis* LPS and found that *A. faecalis* LPS showed weaker inflammation than *E. coli* LPS. Interestingly, *A. faecalis* LPS promoted the IgA antibodies production at the same level as *E. coli* LPS.[1] We then determined the *A. faecalis* LPS structure by NMR and MS and found it to be a glycolipid composed of nona-saccharide and multiple acyl chains (Fig. 1).

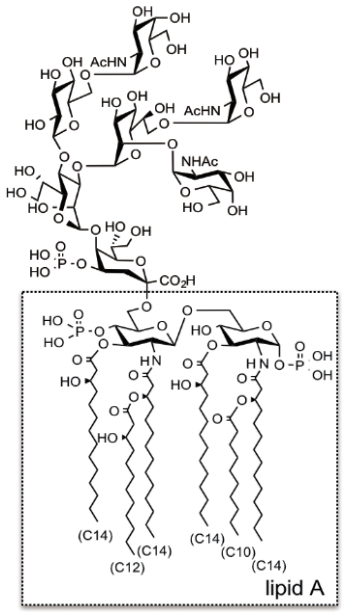

Fig 1. *A. faecalis* LPS/lipid A

In this work, for the structure-activity relationship studies, we synthesized *A. faecalis* lipid A **4a** and its derivative **4b** via key intermediate **1** from glucosamine hydrochloride.[2] After the introduction of acyl chain into the key intermediate **1**, two phosphate groups were simultaneously introduced into **1**, affording **3a** and **3b**. All protecting groups were removed to accomplish the *A. faecalis* lipid A **4a** and its derivative **4b** (Fig. 2). The immunological functions of synthesized **4a** and **4b** are now under investigations.

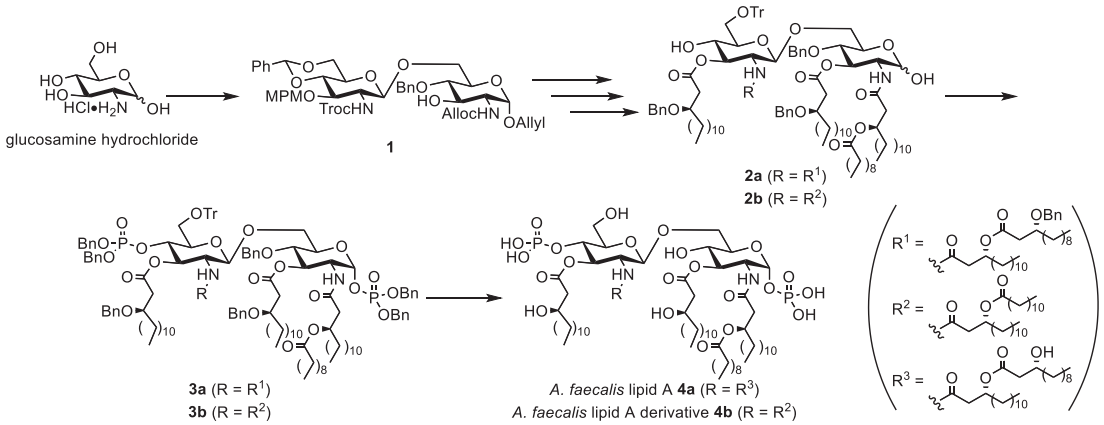

Fig 2. Synthetic scheme of *A. faecalis* lipid A **4a** and its derivative **4b**

[1] K. Fukase, H. Kiyono, *et al*., *Mucosal Immunol*., **2018**, 11, 693.
[2] A. Shimoyama, A. Saeki, N. Tanimura, H. Tsutsui, K. Miyake, Y. Suda, Y. Fujimoto, K. Fukase, *Chem. Eur.* J., **2011**, 17, 14464.

Synthetic study of 2”-fluoro analogues of cyclic ADP-ribose (cADPR), a Ca^{2+} mobilizing second messenger, as a stable equivalents of cADPR

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Cyclic ADP-ribose (cADPR) is a second messenger that regulates calcium ion release from intracellular vesicles in the mechanism of calcium ion-induced calcium ion release. Since the protonated adenine moiety works as an effective leaving group, cADPR is easily hydrolyzed by cADPR hydrolases under physiological conditions and also nonenzymatically even in neutral aqueous solution at the unstable *N*-1-glucosidic linkage to give inactivated ADP-ribose (ADPR) (Figure 1). Consequently, the biological as well as chemical instability of cADPR limits, to some extent, further studies of its physiological role. Therefore, we have designed and synthesized various cADPR derivatives with the aim of developing biotools that can be useful to elucidate the function of cADPR [1].

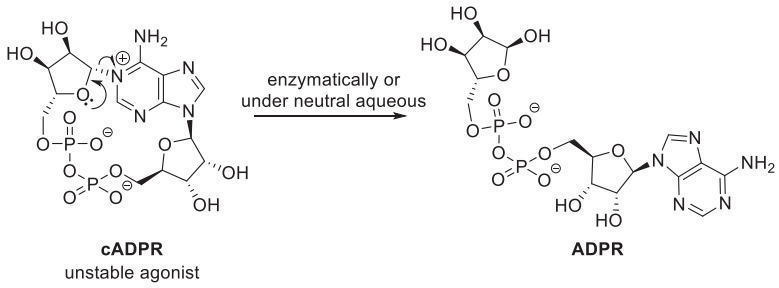

Figure 1: cADPR instability

As a cADPR antagonist, 8-amino-cADPR was reported, however, it would be unstable due to the charged *N*-1-ribosyl structure like cADPR [2]. To develop a stable antagonist of cADPR, we designed 2” α- or β-fluoro-8-amino-cADP-carbocyclic ribose (**3** or **5**) and its difluoro congener **7**, in which *N*-1-ribose ring oxygen was replaced by its bioisosteric monofluoromethylene or difluoromethylene group (Figure 2). I decided to synthesize fluoro-cADPcR **2** and **4** without the 8-amino group, which can be synthesized more easily that the corresponding 8-amino analogues. We will describe synthesis of **2** in this presentation.

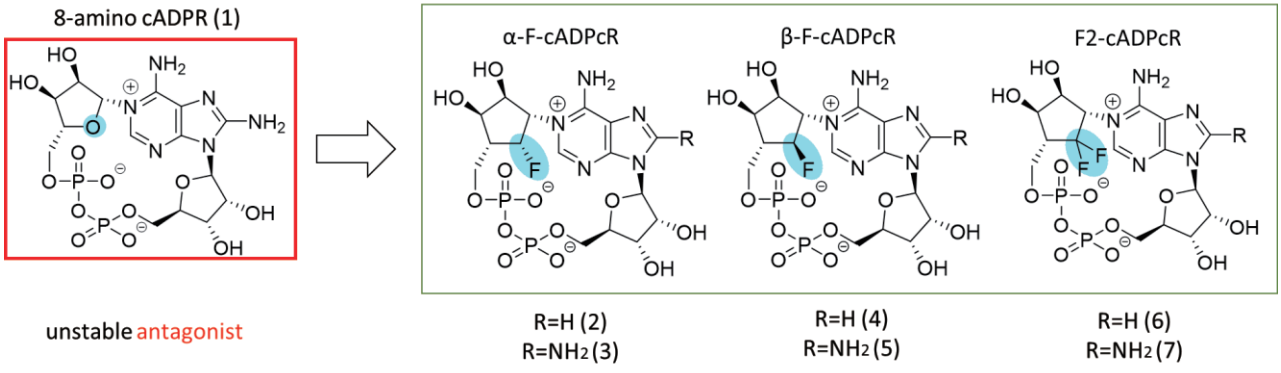

Figure 2 : Design of target compound of F-cADPcR

[1]S. Shuto, *Chem. Pharm. Bull.,* **2018**, *66*, 155
[2]T. F. Waleseth, *et al.*, *Biochim. Biophys. Acta.*, **1993**, *1178*, 235

Diversity-oriented synthesis of multi-antennary *N*-glycans containing sialic acid

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Asparagin linked glycans (*N*-glycans) are involved in various biological phenomena. Sialic acid is recognized by Siglec to regulate the immune system. In this study, we investigated the diversity-oriented synthetic route for the construction of the sialic acid containing *N*-glycan library to analize the interaction with Siglec (Fig. 1). We designed key intermediate **3**. Since four chain elongation sites of **3** were protected with orthogonal protecting groups, i.e. Fmoc, TBS, Proc, and Lev, di-, tri-, and tetra- antennary *N*-glycans can be efficiently synthesized from **3** by the glycosylation with sialic acid-containing trisaccharide **1** and **2**.

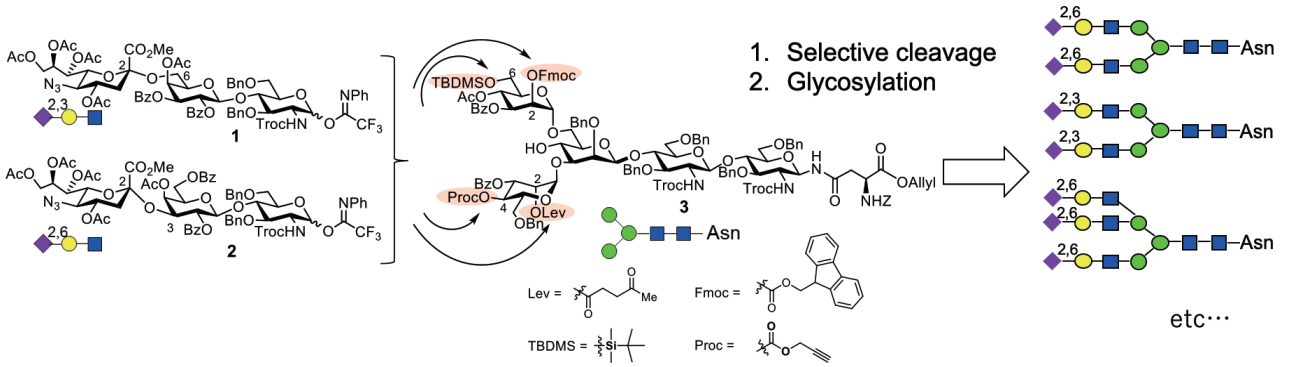
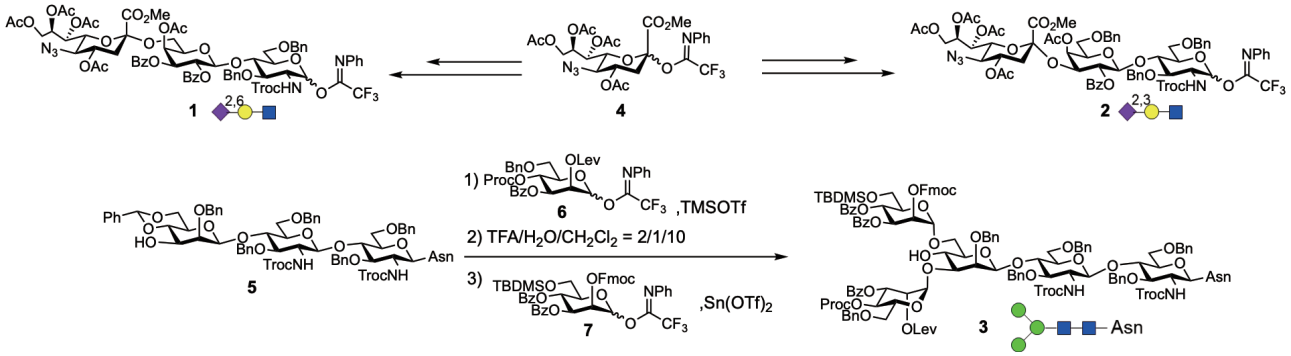


Fig. 1 diversity-oriented synthetic route for theconstruction of the sialic acid containing *N*-glycan library

Trisaccharides **1** and **2** having α2,6-sialylated galactose and α2,3-sialylated galactose, respectively, were synthesized via highly α-selective sialylation using C5-azide sialyl donor **4** (Scheme. 1). After the preparation of orthogonally protected mannosyl donors **6** and **7**, asparagine linked trisaccharide **5** was glycosylated with **6** followed by glycosylation with **7** to afford pentasaccharide **3**. Selective removal of the protecting groups of reducing end pentasaccharide **3** and glycosylation with **1** or **2** are under investigation.



Scheme.1 synthesis of non-reducing end trisaccharide **1**, **2** and reducing end pentasaccharide **3**

Synthesis of Highly Fluorescent Polyaza[7]helicenes

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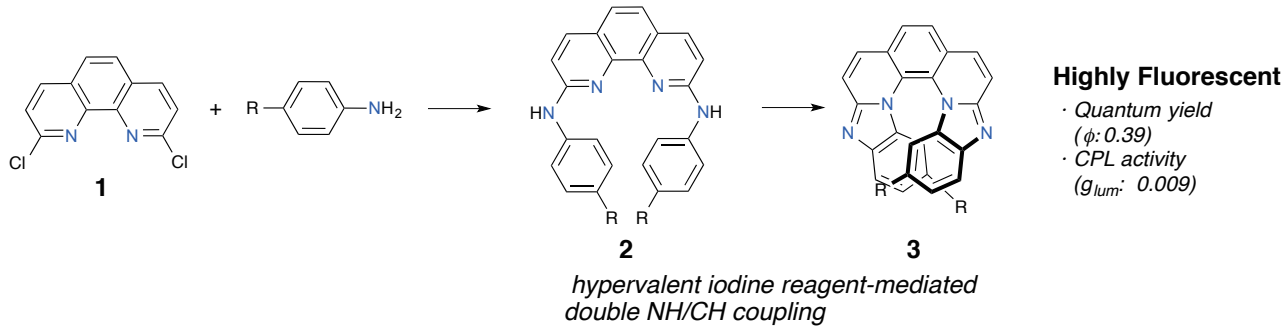
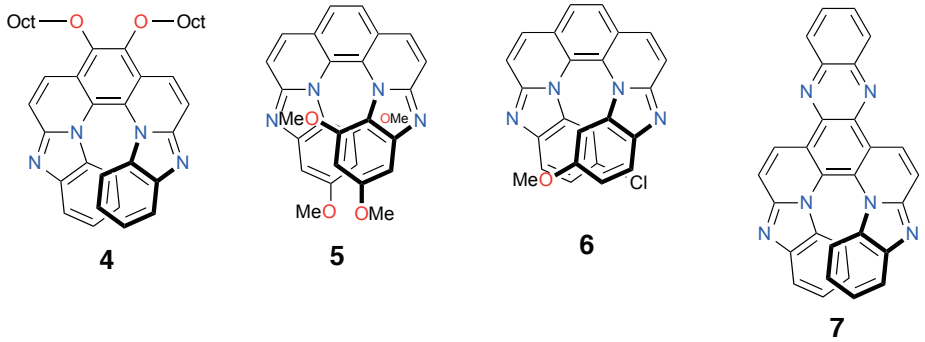
The twisted aromatic system in helicenes has been fascinating not only to synthetic but also material chemists. Although classical carbohelicenes are less fluorescent, the chiral pi-conjugated system is regarded as a potential motif to emit circularly polarized luminescence (CPL). In recent years, fluorescent heterohelicenes have attracted keen attention for their use of chiropotical material. We have reported a facile synthesis of tetraaza[7]helicenes **3** possessing a 6-5-6-6-6-5-6 skeleton from commercially available 2,9-dichloro-1,10-phenanthroline (**1**) via double-amination with aniline derivatives followed by hypervalent iodine reagent-mediated intramolecular double-NH/CH couplings.[1] Notably, the helicenes **3** exhibit high quantum yields and emit superior CPL.



We herein report synthesis of 3,4-dioctoxyhelicene **4**, 9,11,14,16-tetramethoxyhelicene **5**, and unsymmetrically 10,15-disubstituted helicene **6**, and quinoxaline-fused helicene **7**, along with their preliminary photophysical properties.



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2P-122

Investigation of reaction conditions to synthesize sulfated $GalN_3$ derivatives with various phenyls having methoxy groups at O-1 position using closed-vessel reactor

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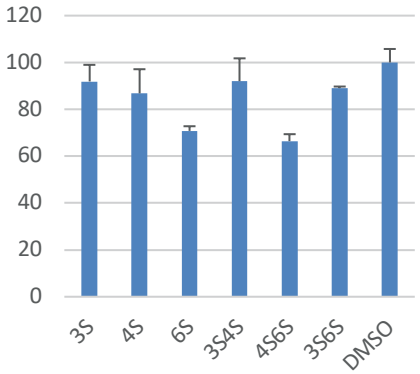
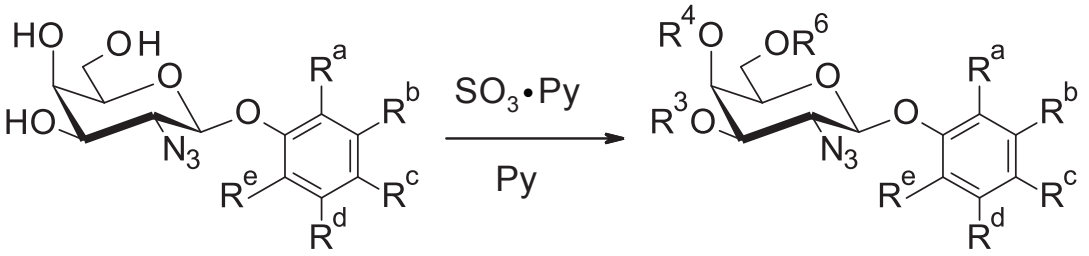
Japanese encephalitis virus (JEV) infection is considered a major public health concern. JEV has caused a major outbreak of viral encephalitis in south, southeast, and east areas of Asia. More than 67,000 cases, including approximately 20,000 deaths annually, occur from the viral infection. Since there are no clinically-approved anti-JEV drugs available, patients are confined to symptomatic alleviation and supportive care. Therefore, therapeutic use of anti-JEV drugs need to be developed. Heparin and chondroitin sulfate E (CS-E) are involved in host cell recognition in the early stage of JEV infection as host co-receptors. In previous our study, we confirmed that β-GalNAc6S and 4S6S derivatives having *p*-methoxyphenyl at O-1 own the inhibitory activity against JEV.[1] Substituenting NHAc group to N_3 group at C-2, $GalN_3$ 3S6S derivatives and 4S6S had higher inhibitory activity.[2]



Inhibitory actibity of GalNAc derivatives



R^a, R^b, R^c, R^d, R^e = H or OMe R^3, R^4, R^6 = H or SO_3^-

In this study, we aimed to synthesize $GalN_3$ derivatives in which one or several methoxy groups were introduced into phenyl group at O-1 position which is important part in the infection inhibitory effect. In the step of sulfation, we succeeded in improving selectivity by temperature control and shortening the reaction time by using closed-vessel reactor−Monowave 50. Furthermore, the equivalent of the sulfur trioxide pyridine complex and the reaction time were examined, and a practical method was developed to increase chemical libraries.

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Synthesis of Japanese encephalitis virus infection inhibitor with unsaturated bond introduced to glucuronic acid having hydroxy or acetamido group at C-2 position

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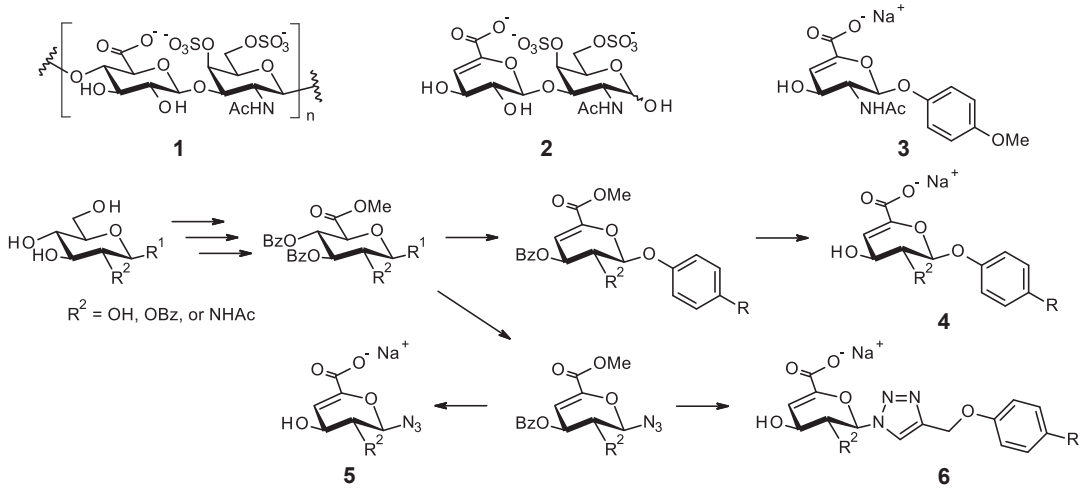
Japanese encephalitis virus (JEV) begins infection when the envelope glycoprotein on the viral membrane binds to receptor molecules on the host cell membrane. As a receptor molecule, sulfated glycosaminoglycans such as chondroitin sulfate E (CS-E) **1** and heparin are known. These compounds have been reported to have infection inhibitory activity against JEV.[1, 2]

CS-E has a repeating disaccharide unit composed of glucuronic acid (GlcA) and *N*-acetylgalactosamine (GalNAc). It is known that compound **2** having an uronic acid moiety which have an unsaturated bond between C-4 and C-5 can be obtained by digesting with CS-E by chondroitinase ACII. In our laboratory, we had synthesized uronic acid derivative **3** having 4-methoxyphenyl group at O-1 position and an unsaturated bond between C-4 and C-5, from GalNAc derivative. Compound **3** had infection inhibitory activity against JEV.

In this study, we focused on the uronic acid moiety and synthesized uronic acid derivatives **4**-**6** in expectation of having higher infection inhibitory activity against JEV. Two kinds of compounds having -OH or -NHAc group at C-2 position had been synthesized to compare the difference in the inhibitory activity. The substituent for para position of phenyl group at O-1 position was changed from electron donating group to electron withdrawing group to optimize the C-1 position. And, azido group was also substituted at C-1 position to introduce various substituents by CuAAC reaction.



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2P-124s

Total Synthesis of a Pentasaccharide Fragment from Arabinogalactan and its Application for Allergy Prevention

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[a]*Department of Organic Chemistry, Johannes Gutenberg-University, Mainz/Germany*
[b]*Department of Experimental Pneumology, Ruhr-University Bochum, Bochum/Germany*
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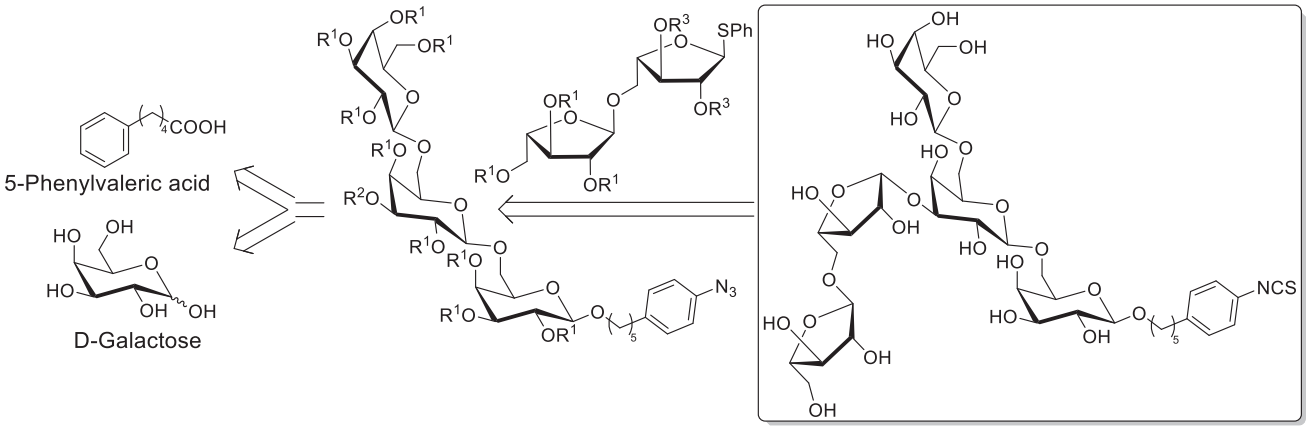
The impact of allergic diseases in industrial states is on a constant increase. Studies have shown that growing up in a traditional farming environment decreases the risk of developing allergies significantly.[1] It was also shown that arabinogalactan, a natural carbohydrate polymer occurring in plants, has allergy-protective activity.[2] Unfortunately, the exact structure of these carbohydrate polymers is complex and the exact mode of action on the immune system that leads to its allergy-preventive effect is not yet fully understood.[3] The aim of this work was therefore to simplify the complexity of arabinogalactan by the synthesis of a pentasaccharide partial structure. This synthetic oligosaccharide will afterwards be compared to its natural counterpart. The total synthesis was accomplished using a convergent strategy starting from D-galactose and 5-phenylvaleric acid. The galactose trisaccharide was synthesized with a (1→6)-linkage inbetween the galactose moieties. After glycosylation of the L-arabinose disaccharide in 3-position of the galactose moiety, the deprotected pentasaccharide was coupled to a carrier protein with the reactive isothiocyanate. The obtained neoglycoconjugate was afterwards evaluated for its allergy-protective activity.



[1] C. Braun-Fahrländer, J. Riedler, U. Herz, W. Eder, M. Waser, L. Grize, S. Maisch, D. Carr, F. Gerlach, A. Bufe, R. P. Lauener, R. Schierl, H. Renz, D. Nowak, E. von Mutius, *N. Engl. J. Med.* **2002**, *347*, 869-877.

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(Di-(2-picolyl)amino)quinazolines as Fluorescent Probes for ATP

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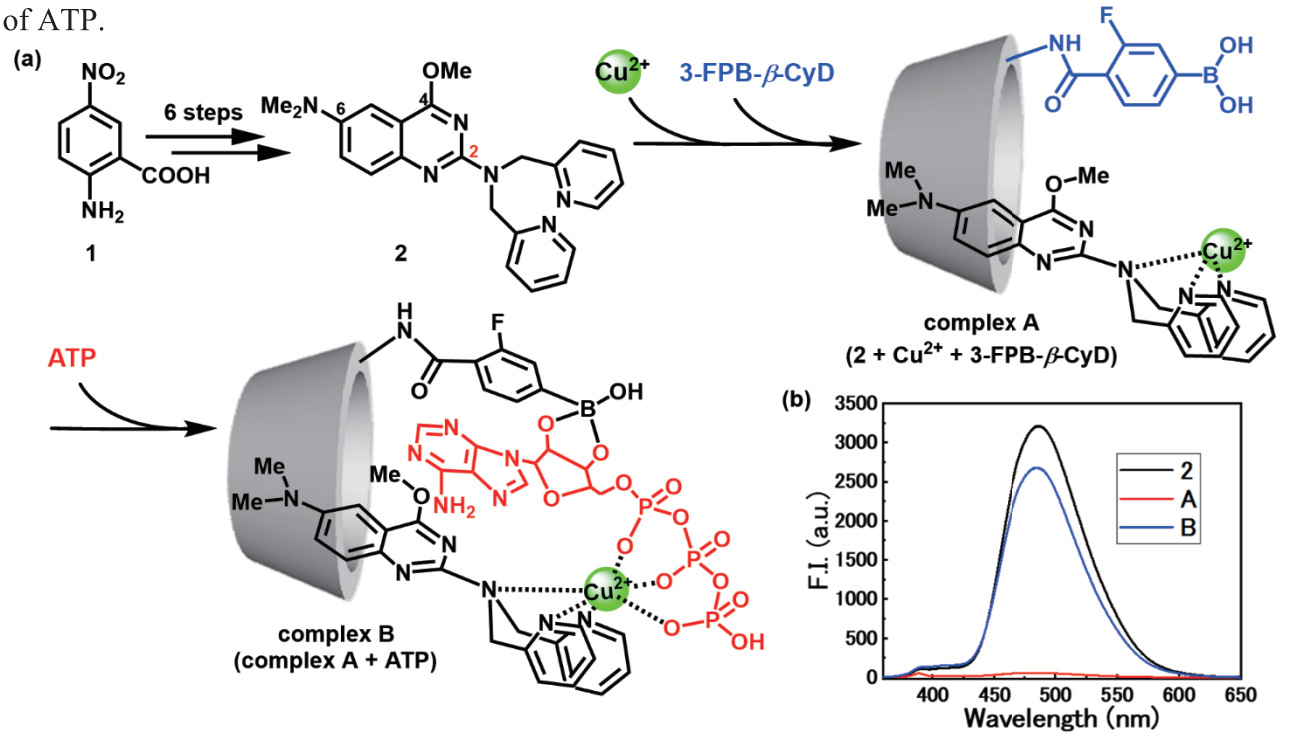
Kioi-cho 7-1, Chiyoda-ku, Tokyo 102-8554, Japan

[Background] Adenosine triphosphate (ATP) is essential for life and the related cellular processes. Real-time monitoring of ATP levels can potentially help diagnose various diseases. However, there have only been a few precedents that enable ATP recognition with fluorescence enhancement using low-molecular weight probes. [1] Hence, we proposed to develop fluorescent probes for ATP detection using 2-aminoquinazolines, which were recently revealed to exhibit fluorescence. [2]

[Results and discussion] Di-(2-picolyl)amine (DPA) coordinates to various metal ions resulting in complexes that interact with phosphoric acids. To utilize this property, we prepared quinazoline probe **2** possessing a DPA moiety at position 2 from commercially available anthranilic acid **1** in 6 steps. When Cu^{2+} and *β*-cyclodextrin modified with 3-fluorophenylboronic acid (**3-FPB-*β*-CyD**) were added to a 1% DMSO solution of **2**, the fluorescence intensity was completely reduced by coordination of the DPA moiety to Cu^{2+} through ligand metal charge transfer (LMCT). This result indicates the formation of **complex A**. When ATP was added to the quenched solution, the fluorescence intensity recovered due to the interaction between Cu^{2+} and ATP which weakened the LMCT system (**Scheme 1**). Therefore, the novel quinazoline probe **2** enabled fluorescent detection of ATP.



Scheme 1. (a) Plausible mechanism of ATP detection and (b) fluorescence intensity of **2**, **A** and **B** (λ_{ex} = 345 nm).

[1] Fujita, K.; Fujiwara, S.; Yamada, T.; Tsuchido, Y.; Hashimoto, T.; Hayashita, T. *J. Org. Chem.* **2017**, *82*, 976.
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2P-126s

Organic Dyes Containing non-Substituted Aryl Amino Moiety and Azobenzene Unit for Dye-Sensitized Solar Cell

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A series of novel sensitizers were successfully synthesized utilizing azobenzene as π-linkage unit for D-π-A structure. A slight red-shift on the absorption spectra and λ_{onset} of the sensitizers could be observed when thienyl group was introduced to the acceptor moiety (A). In addition, replacing the donor moiety (D) from carbazole to diarylamino could lead to a negative shift (~0.3 V) in the first oxidation potential. DFT calculation was also carried out and the trend of calculated HOMO-LUMO gaps was consistent to the experimental data obtained from the CV results (**DT1** < **DT2** < **DT3** < **DT4**). These sensitizers were then employed in dyesensitized solar cells to investigate their photovoltaic performances. Highest power conversion efficiency (PCE) of 0.84% was achieved for DT1-based DSSC according to its most bathochromic absorption spectrum.

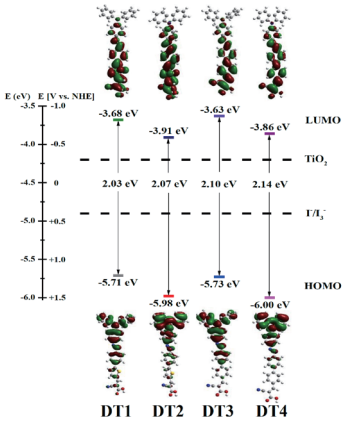

Figure 1. Calculated frontier molecular orbitals and experimental energy level diagram of **DT1**-**DT4**.

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[2] J. Preat, C. Michaux, D. Jacquemin, E. A. Perpe, *J. Phys. Chem. C*, **2009**, *113* (38), 16821–16833.
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Electrochemical Study of the imidazole-based star-shaped oligo(benzonitrile)s and application for inverted-type $MAPbI_3$ solar cells

Kuo Yuan Chiu, and Jiann-T'suen Lin*
Institute of Chemistry, Academia Sinica Taipei, Taiwan 115

A series of imidazole-based star-shaped oligo(benzonitrile) were easily prepared in good yields via the reaction of one precursor containing two or more aldehydes with dione compound having two bezonitrile. And these imidazole thin film was used as a functional electron transport layer (ETL) in inverted-type $CH_3NH_3PbI_3$ ($MAPbI_3$) solar cells. Comprehensive studies were carried out to explore the characteristics and functional capabilities of the graded ETLs in inverted-type $MAPbI_3$ solar cells, including the surface properties, electronic energy levels, molecular packing properties and energy transfer dynamics. This investigation also helps establish important tools for the characterizations of the ETLs in perovskite optoelectronic devices.

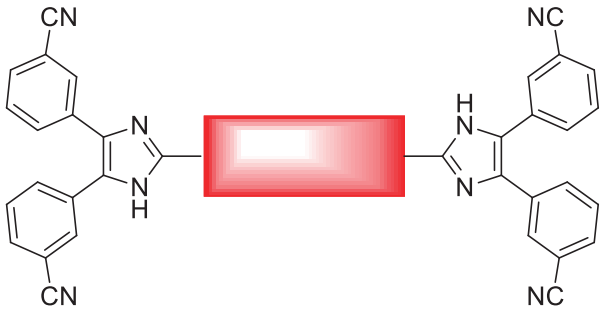

Figure1. The chemical structures of this study.

[1] W.S. Yang, J.H. Noh, N.J. Jeon, Y.C. Kim, S. Ryu, J. Seo and S. I. Seok *Science*, **2015**, *348*, 1234–1237.

[2] F. Wu, W. Gao, H. Yu, L. Zhu, L. Li and C. Yang, *J. Mater. Chem. A*, **2018**, *6*, 4443-4448.

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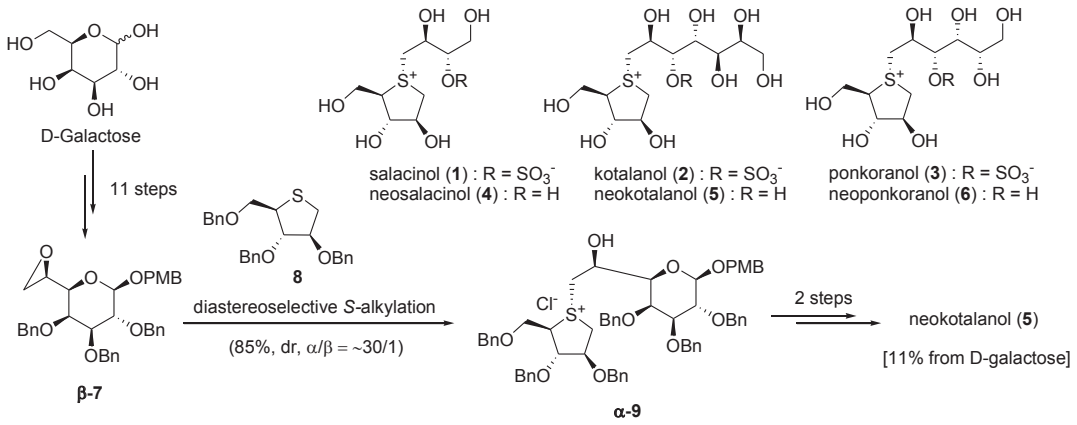
2P-128

Facile Synthesis of Neokotalanol, a Potent α-Glycosidase Inhibitor Isolated from the Ayurvedic Traditional Medicine "*Salacia*"

Genzoh Tanabe,[†, ‡,*] Satoshi Ueda,[†] Kazuho Kurimoto,[†] Naoki Sonoda,[†] Shinsuke Marumoto,[§] Fumihiro Ishikawa[†] and Osamu Muraoka[‡]

[†]Faculty of Pharmacy, [‡]Pharmaceutical Research and Technology Institute, and [§]Joint Research Centre, Kindai University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan.

Toward the end of the 1990s, a highly potent α-glucosidase inhibitor, salacinol (**1**), was first isolated from extracts of *S. reticulata*. The α-glucosidase inhibitory activity of **1** was revealed to be as potent as that of clinically used anti-diabetic drugs voglibose and acarbose.[1] Since the isolation of **1**, related sulfonium sulfonates, kotalanol (**2**) and ponkoranol (**3**), as well as their de-*O*-sulfonated analogs neosalacinol (**4**), neokotalanol (**5**), and neoponkoranol (**6**) were subsequently isolated from plants of the same genus as other sulfonium components exhibiting potent anti-diabetic activities. Among this series of sulfonium salts, neokotalanol (**5**) was proved to be the most active compound against rat intestinal α-glucosidas.[2a] Shortly thereafter, its activity intensity was revealed to be 2000-fold stronger against maltase-glucoamylase (MGA) than acarbose.[2b] Despite **5** having been recognized as the most active among this series of sulfonium salts, a facile and effective synthetic protocol leading to **5** has not been established to date because of the difficulty in selecting and designing a protected key intermediate. In this study, an appropriately protected epoxide (**β-7**) was successfully designed and diastereoselectively synthesized from the easily accessible D-galactose. By use of **β-7**, *S*-alkylation of sulfides (**8**) was successfully proceeded in a highly diastereoselective manner to afford **α-9** in good yield. Finally, **α-9** was converted to **5** *via* 2 steps. Total yield of **5** in the present study (11%, *via* 14 steps) far exceeded the yields previously reported (~1% *via* 15 steps[3a] , ~0.5% *via* 18 steps[3b], ~2% *via* 11 steps[3c]).



[1] Yoshikawa, M. *et al*., *Tetrahedron Lett*., **1997**, *38*, 8367.

[2] (a) Ozaki, S. *et al*., *J. Nat. Prod*., **2008**, *71*, 981; (b) Sim, L. *et al*., *Biochemistry*, **2010**, *49*, 443.

[3] (a) Jayakanthan, K. *et al*., *J. Am. Chem. Soc*., **2009**, *131*, 5621; (b) Xie, W. *et al*., *J. Nat. Med.*, **2013**, *11,* 676 (c) Huang, Y. *et al*., *Angew. Chem. Int. Ed*., **2019**, *58*, 6400.

Efficient Construction of Quaternary Carbon via Tandem Dibromocyclopropane Ring Opening/Wagner-Meerwein Rearrangement

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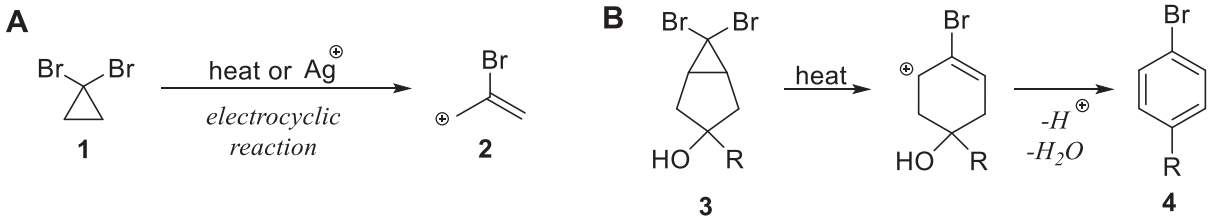
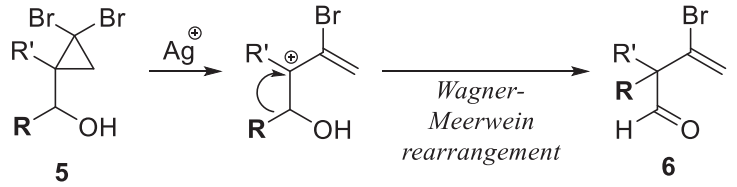
Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan

gem-Dihalocyclopropanes play an important role in organic synthesis due to high accessibility and a wide range of reactivities.[1] Especially, heat- or silver-induced electrocyclic reaction of dibromocyclopropane **1** affords 2-bromoallyl cation **2**, which allows facile synthesis of bromo compounds in combination with ensuing reactions (Scheme 1A). For example, we reported a synthesis of 4-bromobenzenes **4** via the electrocyclic reaction of **3**, followed by deprotonation and dehydration of the resulting allyl cation (Scheme 1B).[2]



Scheme 1. (**A**) Electrocyclic reaction of dibromocyclopropane. (**B**) Bromobenzene synthesis using dibromocyclopropane ring opening

In this symposium, we present a method for construction of quaternary carbon via the electrocyclic reaction of dibromocyclopropanes (Scheme 2). We found that treatment of dibromocyclopropanes **5** having a α-hydroxyalkyl group with silver salt, generated1 allyl cation, which underwent Wagner-Meerwein rearrangement to afford β-bromo-β,γ-unsaturated aldehyde **6** that has a quaternary carbon. Since the product has convertible functional groups such as formyl, bromo, and vinyl groups, the developed method would be applicable to syntheses of a variety of compounds bearing a quaternary carbon.



Scheme 2. This work

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[2] Ueda, K.; Umihara, H.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2015**, *17*, 3191.

Peptide modulating tension in cell membranes: the regulation of cell movement and morphology via actin remodeling

Toshihiro Masuda[1], Kentarou Baba[2], Tomo Murayama[1], Naoyuki Inagaki[2], Shiroh Futaki[1]*
[1]*Institute for Chemical Research, Kyoto University, Uji, Kyoto, 611-0011, Japan*
[2]*Division of Biological Science, Nara Institute of Science and Technology, Ikoma, Nara, 630-0192 Japan*

Membrane tension is closely related to a series of cellular events, including cell movement and morphology. Defects in these cellular events are linked to various pathological processes including neurodevelopmental disorders and tumor progression and metastasis. Therefore, development of new molecular tools that control cell movement and morphology can be expected via modulating membrane tension. However, few studies have been published on the regulation of cellular events by altering membrane tension. Here we report our approach to develop a new tool for regulating cellular events by changing membrane tension. Amphipathic regions of membrane remodeling proteins are known to insert themselves into membrane bilayers. We hypothesized that these amphipathic peptides can change membrane tension by the interaction with membrane. Several amphipathic peptides derived from membrane remodeling proteins were synthesized and the effects of these peptides on F-actin distribution were evaluated. An amphipathic peptide derived from Influenza M2 protein (M2) was thus selected which yielded a polarized actin distribution and a lamellipodia formation. FBP17 has been reported as a membrane tension sensor, involved in lamellipodia formation. The percentage of cells forming lamellipodia was reduced by FBP17 knockdown. This result suggested that lamellipodia formation by M2 was driven by FBP17. Wound healing assay was performed for investigation into influence of M2 on cell movement. Effect of M2 on neurite outgrowth from primary cultured neurons was also studied.

T. Masuda, K. Baba, T. Nomura, K. Tsujita, T. Murayama, T. Itoh, T. Takatani-Nakase, M. Sokabe, N. Inagaki, S. Futaki, *Commun. Biol.* in press.

2P-131s

Synthesis and structure–ATPase activity relationship of rhodamine derivatives against P-glycoprotein CmABCB1

Hiroshi Takikawa, Sorachi Miwa, Rina Takeuchi, Yousuke Yamaoka, Tomohiro Yamaguchi, Toru Nakatsu, Hiroaki Kato* and Kiyosei Takasu*

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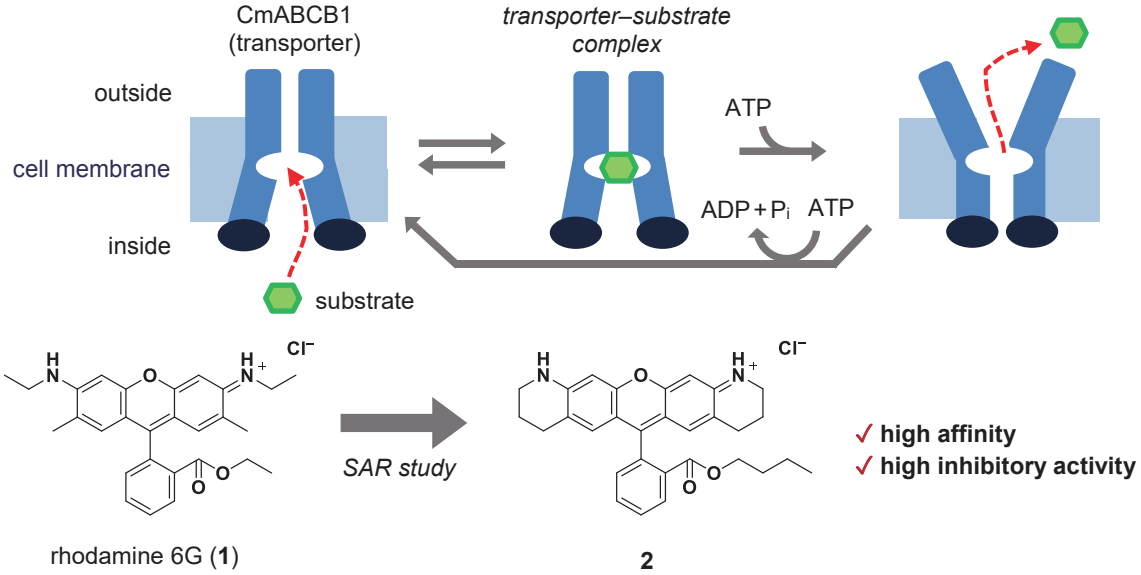
Understanding the function of ATP binding cassette subfamily B member 1 (ABCB1), a multidrug efflux transporter, is important to advance the research of drug resistance in many human cancers. However, the elucidation of the precise transport mechanisms has been hampered due to the pronounced instability of three-dimensional structure of ABCB1. Recently, we have determined the crystal structures of CmABCB1, a more thermo-stable homolog of ABCB1 exhibiting a similar substrate specificity and pharmacological behavior to those of ABCB1, which shed light on the whole architecture of CmABCB1.[1,2]

Among various potential substrates, CmABCB1 shows significant affinity for rhodamine 6G (**1**).[1] To gain further insight, we focused on the structure-ATPase activity of the rhodamine scaffold, which was conducted via the in-vitro assay using a range of rhodamine derivatives.

More than sixty rhodamine derivatives were synthesized and screened in vitro for their ability toward the ATPase activity. Among fifteen compounds with the superior affinity in comparison with the parent rhodamine **1**, we found that Q-rhodamine derivative **2**, which contained pentacyclic fused ring system and the butyl ester moiety, showed the highest affinity and the significant inhibitory activity.



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[2] Kodan, A.; Kato, H. *et al*., *Nat. Commun*. **2019**, *10*, 88.

2P-132

Molecular Imaging Utilizing Stimuli-Responsive Dyes Bearing Nucleophilic Substituents

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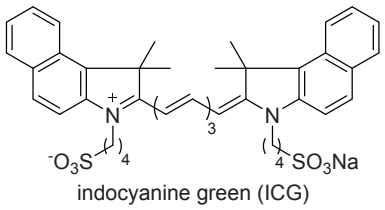
Fluorescent dye is one of the most powerful probes for visualizing target tissues and disease utilizing optical imaging devices. Indocyanine green (ICG), which was approved to be used for diagnosis of blood flow in organs, is well-known near-infrared fluorescent cyanine dyes. Because of its non-stimuli-responsive properties, ICG enables visualization of not only target tissues but also normal tissues and blood vessels, thereby providing low-contrast images. Based on this background, we developed a series of pH-responsive near-infrared (NIR) cyanine dyes having nucleophilic substituents for visualization of acidic microenvironment in cancer cells (Figure 1).[1] Under high pH conditions, the annulation of intramolecular nucleophilic moieties (YH = SH (**1a**), OH (**1b**), and NH_2 (**1c**)) smoothly proceeded to afford non-emissive dyes **1-C** having a closed-ring structure. In contrast, under low pH conditions, heteroatoms (Y) in the cyclic structures of **1-C** were protonated to form emissive **1-O** having an open-ring structure.



By conjugating cyclic RGD peptide, we prepared tumor-targeting pH-responsive dye, which could internalize into tumor cells bearing receptors and smoothly convert to its emissive open-ring structure.

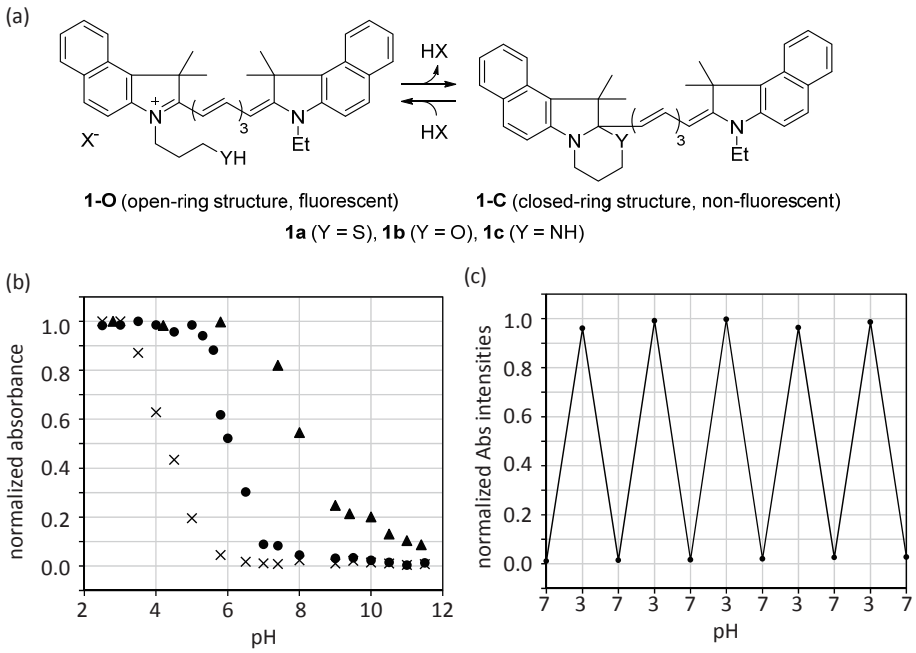


Figure 1. (a) pH-Responsiveness of dye **1**. (b) UV-vis absorbance of **1a** (cross), **1b** (circle), and **1c** (triangle). (c) pH-Dependent change of absorbance of **1a**. Absorbance were normalized by those measured at pH 3.0.

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Synthesis of Enantiomerically Pure 1,2,3-Trisubstituted Cyclopropane Nucleosides

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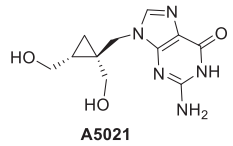
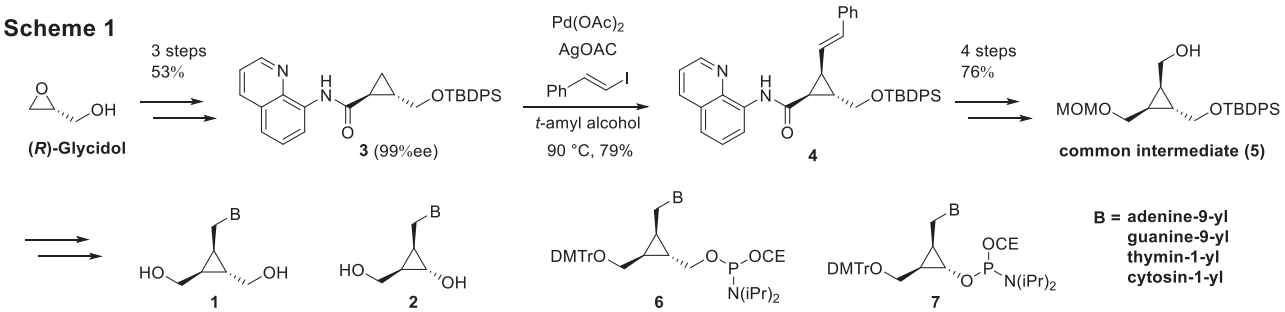
Much attention has been focused on carbocyclic nucleosides, e.g., entecavir and abacavir, lacking the biologically unstable *N*-ribosyl linkage in natural nucleosides, because of their significant antiviral activities. In the carbocyclic nucleosides, we are interested in cyclopropane nucleosides (CPNs) with the smallest carbocycle cyclopropane which having a characteristic sterically unhindered and rigid structural feature. Various CPNs have been reported, and their absolute configuration is known to affect the antiviral activity significantly. For example, a 1,1,2-trisubstituted CPN, A5021, shows approximately 100-fold antiviral activity versus its enantiomer. Therefore, the synthesis of enantiomerically pure CPNs is important; however, it is generally challenging to synthesize enantiomerically pure multi-substituent cyclopropane structures. Particularly, as for enantiomerically pure 1,2,3-trisubstituted CPNs, there is only one report. Thus, we tried to get a series of enantiomerically pure 1,2,3-trisubstituted CPNs (**1**, **2**, and their enantiomers) by using a Pd-catalyzed C(sp^3)–H activation reaction of cyclopropane.[1-3] Highly optical pure 1,2-*trans*-cyclopropane **3**, a substrate of the C(sp^3)–H activation reaction, was obtained in three steps from commercially available (*R*)-glycidol (**Scheme 1**). Treatment of **3** with $Pd(OAc)_2$, AgOAc and (*E*)-(iodovinyl)benzene in *t*-amyl alcohol at 90 °C successfully gave the desired 1,2,3-trisubstituted cyclopropane **4**. After the conversion of **4** to common intermediate **5** in four steps, the desired CPNs (**1**, **2**, and their enantiomers) were successfully synthesized.[4] We are now trying to obtain phosphoramidites (**6**, **7**) for making cyclopropane oligonucleotides.



Scheme 1



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[2] Hoshiya, N.; Takenaka, K.; Shuto, S.; Uenishi, J. *Org. Lett*. **2016**, *18*, 48.
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Facile Synthesis of 5-Hydroxycytidine Analogues: 2′-*O*-Me-RNA and scpBNA Bearing a 5-Hydroxycytosine Nucleobase

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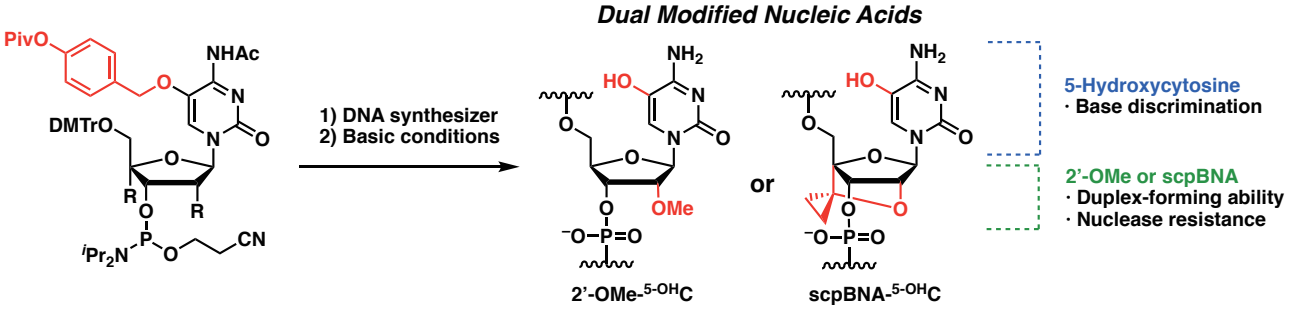
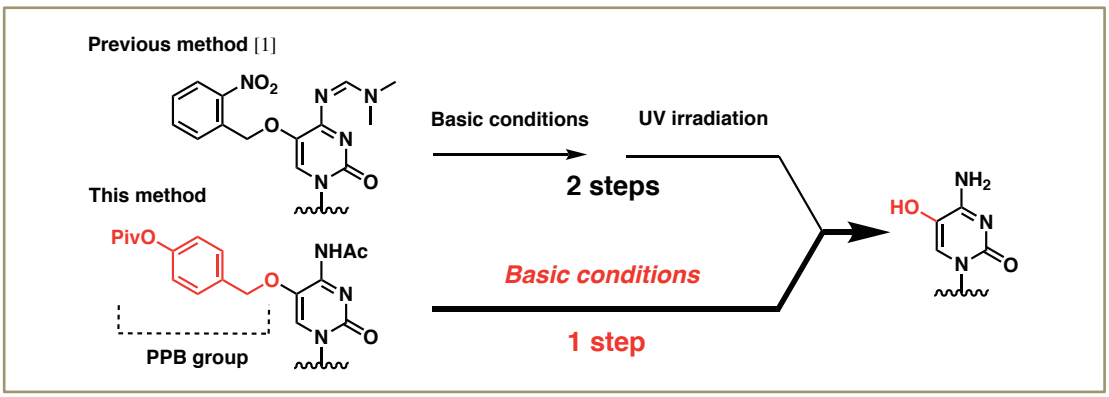
5-Hydroxycytosine ($^{5\text{-OH}}$C), an abundant nucleobase lesion, exhibits slightly higher base discrimination ability than natural cytosine.[1] On the other hand, oligonucleotides (ONs) modified with 2′-*O*-Me-RNA (2′-OMe) or 2′-*O*,4′-*C*-spirocyclopropylene-bridged nucleic acid (scpBNA) represent high duplex-forming ability toward single-stranded RNA and improved nuclease resistance. Taking into account the positive effects of these modifications to therapeutic antisense ONs, we recently designed and synthesized dual modified nucleic acids, 2′-OMe-$^{5\text{-OH}}$C and scpBNA-$^{5\text{-OH}}$C.

We have explored a facile synthetic route for 5-hydroxycytidine analogues. Leumann and co-worker used a photo-cleavable *o*-nitrobenzyl group for the 5-OH protection, but this required two-step deprotection protocol. We therefore newly designed *p*-pivaloyloxybenzyl (PPB) group for the 5-OH protection and synthesized 2′-OMe-$^{5\text{-OH}}$C and scpBNA-$^{5\text{-OH}}$C phosphoramidites, bearing a PPB group, in 5 steps and 16 steps, respectively. These phosphoramidites were successfully incorporated into ONs. As we had expected, the PPB group was easily removed under basic conditions. Both the 2′-OMe-$^{5\text{-OH}}$C-modified and scpBNA-$^{5\text{-OH}}$C-modified ONs showed excellent duplex-forming ability toward single-stranded RNA. The details of the other biophysical properties of these modified ONs will be presented.





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Theoretical Analysis of Absolute Configurations of Natural Organic Compounds

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Natural organic compounds are often useful to human beings in fields such as drug discovery. Some of the natural organic compounds have many asymmetric carbons. The absolute configurations of them are mainly determined by the NMR spectrum in solution. However, complicated compounds cannot be completely determined because only partial structural information can be obtained in NMR spectra. Therefore, theoretical calculation for analysis of the absolute configuration are required. In this study, we analyzed the absolute configurations of new natural organic compounds using the global reaction route mapping (GRRM) strategy.[1]

First, we analyzed the absolute configuration of a new alkaloid, *leucascine*, collected from sponges of Ginama in Okinawa. *Leucascine* has one asymmetric carbon on a long alkyl linear chain (Fig. 1). In order to clarify this absolute configuration, the NMR spectrum of the compound amidated with *R*/*S*-methoxyphenylacetic acid (MPA) was measured. However, the conformation around the amide bond is unknown. Our calculation revealed that the most stable conformation is *E* form for both amides, and that the asymmetric carbon has the *S* configuration by comparing the calculated NMR spectrum with the experimental one.

Next, we analyzed the absolute configuration of a new cyclic imine, *kabirimine*, collected from dinoflagellate in Ishigaki island. This heterocyclic compound has 8 asymmetric carbons (Fig. 2). In the experimental studies, the absolute configuration was limited to 16 isomers, though the full determination has not been achieved. We performed the conformation search for these 16 isomers, and calculated the thermally averaged optical rotation values. The optical rotations of structures of k03 isomer is most close to the experimental value. Therefore, we concluded that *kabirimine* has the k03 configuration, 3*S*, 4*R*, 8*R*, 11*R*, 13*R*, 14*R*, 15*S*, 16*R*, and 18*S*.[2]

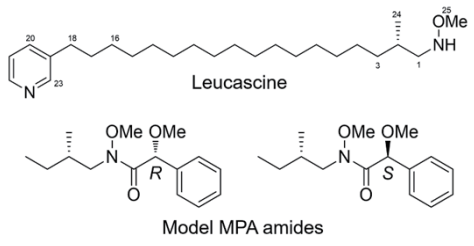

Fig. 1. *Leucasince* and model amides

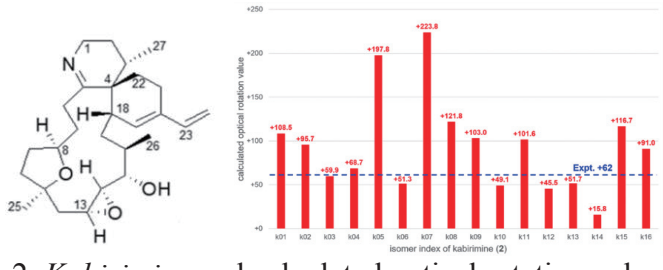

Fig. 2. *Kabirimine* and calculated optical rotation values.

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[2] Hermawan, I.; Higa, M.; Hutabarat, P. U. Basa, Fujiwara, T.; Akiyama, K., Kanamoto, A.; Haruyama, T.; Kobayashi, N.; Higashi, M.; Suda, S.; Tanaka, J. *Mar. Drugs* **2019**, *17*, 353.

2P-136

Development of On-Demand Bioconjugation/Deconjugation Platforms

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A practical method to conjugate functional small molecules to biomolecules through stable covalent bonds that are cleavable under specific conditions is anticipated in various fields, including chemical biology and drug discovery. In this context, disulfide linkages have been utilized to release bioactive thiols by treatment of external thiols.[1] However, the weak S–S bond often causes the undesired nonspecific release of thiols. One of the authors and Ohshima et al. recently developed a bioconjugation method using an indolylmethyl alcohol derivative.[2] A benzylic substitution with thiols proceeded under weak acidic conditions, enabling indolylmethylation at the cysteine residues of the proteins and peptides through C–S bond formation. We later found that this C–S bond could be cleaved under the strong acidic conditions (pH <1). To achieve the pH-dependent release of bioactive thiols, we commenced development studies particularly focusing on the design of heterocyclic core skeleton.

To begin with, we screened various heterocyclic compounds that undergo thiols exchange at their benzylic position in the presence of glutathione under weak acidic pH conditions. Based on the theoretical analysis that suggested several promising compounds, we synthesized some water-soluble compounds bearing azido or alkyne group, which are utilizable to introduce various functional molecules and biomolecules for further application. We also found that photoirradiation could trigger the degradation of these heterocyclic compounds resulting the desired release of bioactive compounds. The efficiency of conjugation and deconjugation of functional small molecules using our platform molecules will be presented.

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Asymmetric Aldol Reaction of Isatins with Carbonyl Compounds Using Diamino Alcohol Organocatalyst and Its Application to The Total Synthesis of Indoloquinazoline Alkaloids

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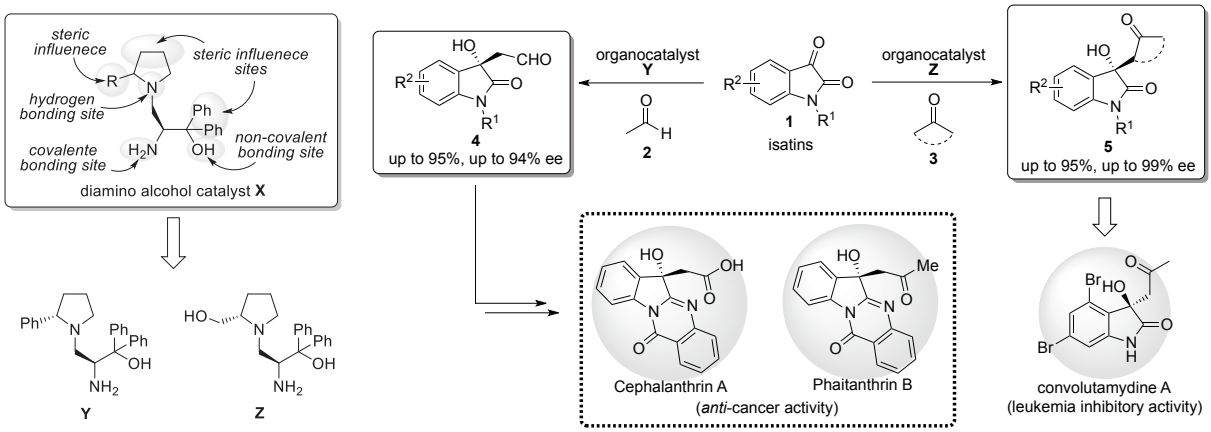
Asymmetric cross aldol reaction of isatins **1** with carbonyl compounds **2**,**3** respectively, are useful reactions for obtaining chiral 3-hydroxy-indolin-2-ones **4**,**5** which are versatile synthetic intermediates for deriving into various biologically active compounds including drugs. Several metal catalysts and organocatalysts have been developed for these reactions. In particular, organocatalyst is much attention as next generation environmentally friendly catalyst for reasons that they are stable in air, easy to handle, and inexpensive. We designed novel diamino alcohol organocatalyst **X**[1] for these reactions. Designed catalyst **X** contains amino covalent site for the formation of enamine, both *tert*-amino group and hydroxyl group acting as hydrogen bonding sites, and diphenyl group acting as steric influence site. Furthermore, *tert*-amino substituent may work as steric influence site for controlling the stereoselective reaction course.

New optically active diamino alcohols **Y**, **Z** were developed as new type organocatalyst and there catalytic activities were examined in the aldol reaction of **1** with **2** or **3** to obtain chiral aldol product **4** or **5**. As a result, catalyst **Y** showed good catalytic activity in this reaction and the corresponding product **4** were obtained in satisfactory chemical yields (up to 95%) and excellent enantioselectivities (up to 94% ee). And then, we tried total synthesis of both Phaitanthrin B and Cephalanthrin A having *anti*-cancer activity using this diamino alcohol organocatalyzed asymmetric aldol reaction using catalyst **Y** as a key step. Furthermore, aldol reaction of **1** with **3** using catalyst **Z** also showed good catalytic activity and the corresponding product **5** was obtained in satisfactory chemical yields and excellent enantioselectivities (up to 95%, up to 99% ee).



[1] Subba Reddy, U. V.; Chennapuram, M.; Seki, K.; Seki, C.; Anusha, B.; Kwon, E.; Okuyama. Y.; Uwai, K.; Tokiwa, M.; Takeshita, M.; Nakano. H. *Eur. J. Org. Chem*., **2016**, 24, 4124-4143.

[2] Seki, K.; Subba Reddy, U. V.; Keigo, Y.; Taniyuki, F.; Seki, C.; Kwon, E.; Okuyama. Y.; Uwai, K.; Tokiwa, M.; Takeshita, M.; Nakano, H. *submitted.*

Enantioselective Oxidation and Kinetic Optical Resolution of Carboxylic Acids by Chiral Lithium Amides

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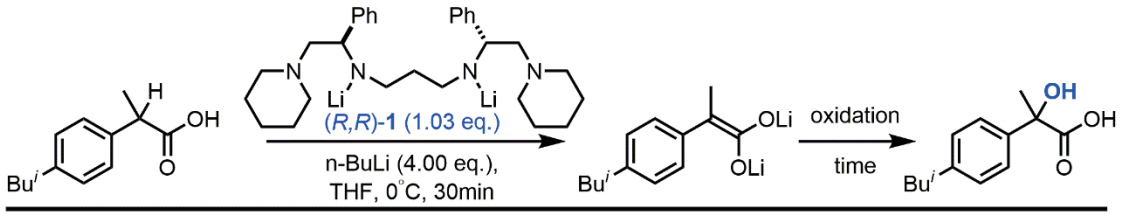
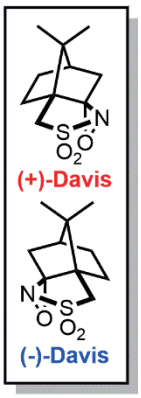
Chiral lithium amides are widely used as chiral bases in enantioselective deprotonation, including kinetic resolution of racemic carbonyl compounds. [1, 2] They are also utilized in enantioselective alkylation, aldol reaction, conjugate addition and protonation of the lithium enolates.

1. Enantioselective oxidation of carboxylic acids in the presence of chiral lithium amides

We found that lithium enolates of the carboxylic acids were oxidized by dissolved oxygen contaminated in anhydrous solvent. In the presence of chiral lithium amide (*R,R*)-**1**, oxidation of ibuprofen took place in 10%ee to give α-hydroxy acid. Surprisingly, when oxidized by (-)-Davis reagent along with (*R,R*)-**1**, significant synergistic effect by double stereodifferentiation was observed.

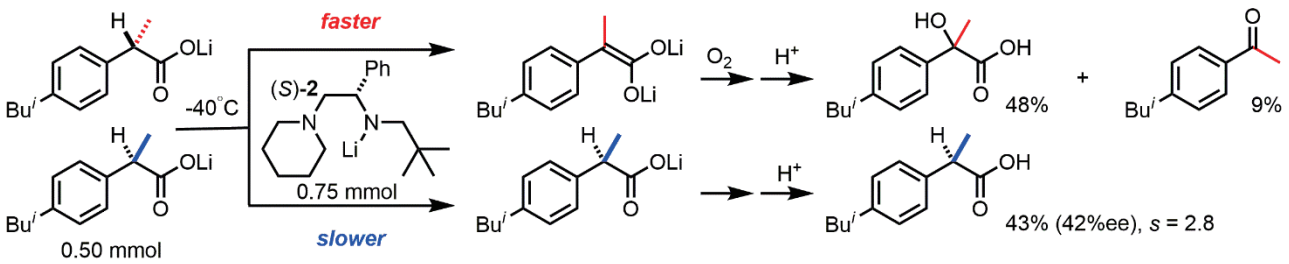


entry	base	oxidant	temp.(°C)	time (h)	yield(%)	%ee	*R* / *S*
1	(*R,R*)-**1**	dissolved O_2	0	24	100	**10**	*S*
2	Et_2NLi	**(+)-Davis**	-80	1	9	**20**	*R*
3	(*R,R*)-**1**	**(+)-Davis**	-80	1	34	**2**	*S*
4	(*R,R*)-**1**	**(-)-Davis**	-80	1	51	**65**	*S*



2. Kinetic optical resolution of carboxylic acids by chiral lithium amides

Direct kinetic optical resolution of carboxylic acids by chiral lithium amides is quite challenging. We thought that by use of *in situ* oxidation of the carboxylic acid enolates by dissolved oxygen, the carboxylic acids, not deprotonated by chiral lithium amides, could be isolated as optical active form as the result of kinetic optical resolution. As expected, enantioselective kinetic deprotonation of ibuprofen was performed to give 42%ee of the carboxylic acid with s value of 2.8.



[1] Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.*, **1986**, *108*, 543.
[2] Kim, H.; Kawasaki, H.; Nakajima, M.; Koga, K. *Tetrahedron Lett.*, **1989**, *30*, 6537.

New Amino Amide Alcohol Organocatalysts for Asymmetric Michael Addition of β-Keto Esters with Nitroolefins

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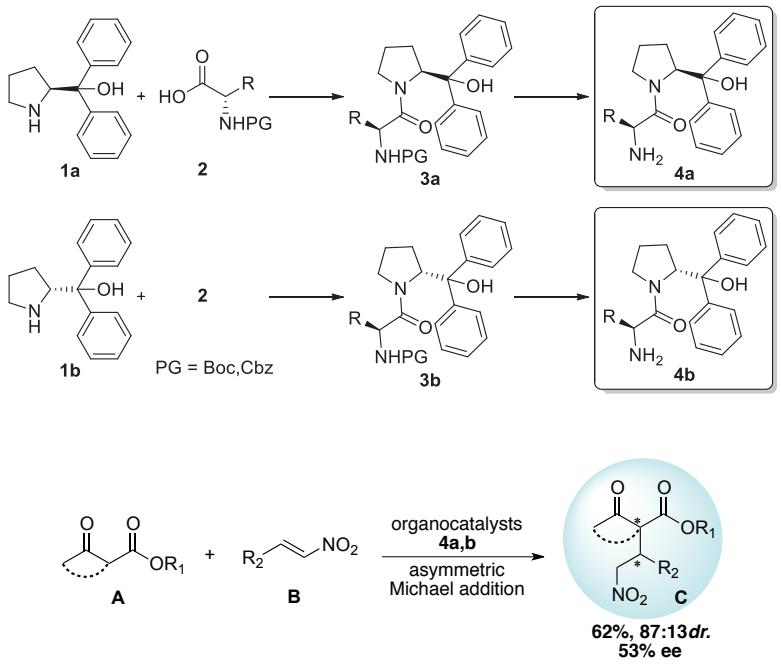
The development of new optically active organocatalysts for their use in asymmetric synthesis has attracted considerable interest in the scientific community over the last decade.[1] A simple and new pyrrolidine-based[2] amino amide alcohol organocatalysts[3] **4a**,**b** were developed for the asymmetric Michael addition of β-keto esters **A** with nitroolefins **B**. The organocatalysts **4a**,**b** were obtained by the condensation of (*S*) and (*R*)-diphenyl prolinols **1a**,**b** with *N*-protected amino acids **2**, followed by the deprotection of **3a**,**b** respectively, in good yields. This newly designed organocatalysts **4a**,**b** have primary amino basic site, hydroxyl non covalent hydrogen bonding site and steric influence sites in the single molecule. From these functionalities, this catalysts **4a**,**b** might show satisfactory catalytic activity in this reaction.



The organocatalysts **4a**,**b** were applied as an organocatalyst to asymmetric Michael reaction of β-keto esters **A** with nitroolefins **B**. As a result, these catalysts **4a**,**b** showed good catalytic activities in this reaction to afford the Michael adducts **C** with good chemical yields and moderate enantioselectivities (up to 62%, 87:13 *dr*, 53% ee). The detail of this work will be reported.

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Oxidative Rearrangement of Secondary Amines Using Hypervalent Iodine(III) Reagent

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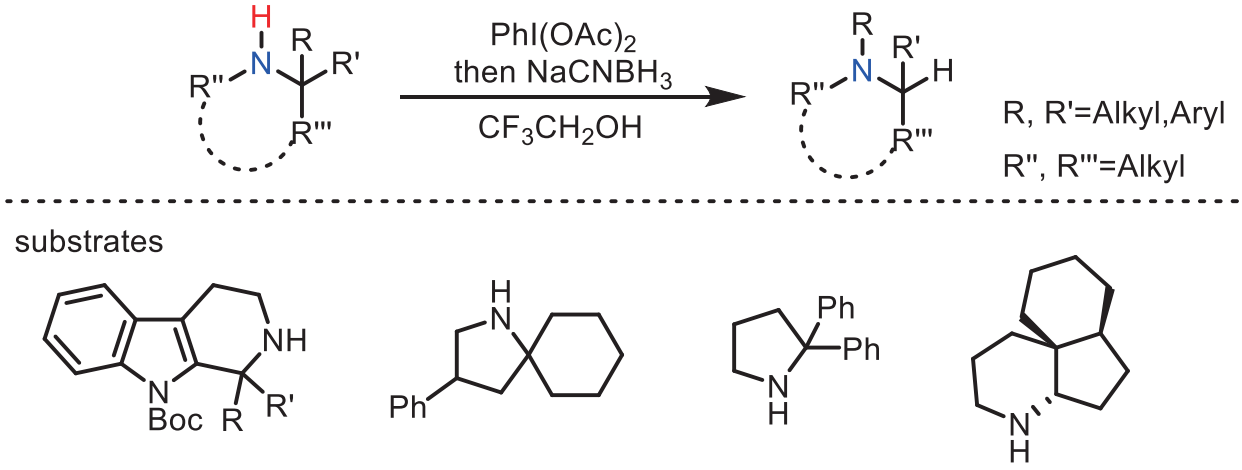
1,2-C to N rearrangement reactions have been playing an important role in organic chemistry to alter the molecular skeltons.[1] Especially, Hoffman , Beckmann, Stieglitz, Schmidt, and Curtius rearrangement are all well-known reactions and applied to synthesize various skeltons.[2] Among these rearrangement reactions, the 1,2-rearrangement reaction of amines bearing a leaving group on the nitrogen atom, such as azides, hydroxylamines, and *N*-chloroamines is known as Stieglitz rearrangement. In these reactions, the use of azides or the prior introduction of a leaving group to the nitrogen atom is necessary. However, the direct migration of amines has not well investigated. In this symposium, we will present direct 1,2-C to N rearrangement reactions of secondary amines by using $PhI(OAc)_2$ in CF_3CH_2OH.[3] This metal-free method provides facile and divergent access to the corresponding amine compounds via one-pot transformation. This protocol is also attractive because it can be readly carried out using a commercially available hypervalent iodine reagent. We demonstrated this new method to create nitrogen-containing macrocyclic indole-fused compounds and N-fused structures represented by the tricyclic marine alkaloids. A radical pathway is suggested to be involved in these transformations based on mechanistic investigation using radical scavengers.

This Work



[1] *Molecular Rearrangements in Organic Synthesis*; Rojas, C. M., Ed.; John Wiley & Sons, Inc: Hoboken, NJ, 2015.
[2] *Comprehensive Organic Name Reactions and Reagents*; Wang, Z.; John Wiley & Sons, Inc: Hoboken, NJ, 2010.
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Total Synthesis of (+)-CC-1065 via Two Directional Double Ring Expansion of Benzo-bis-Cyclobutenone Oxime Sulfonate

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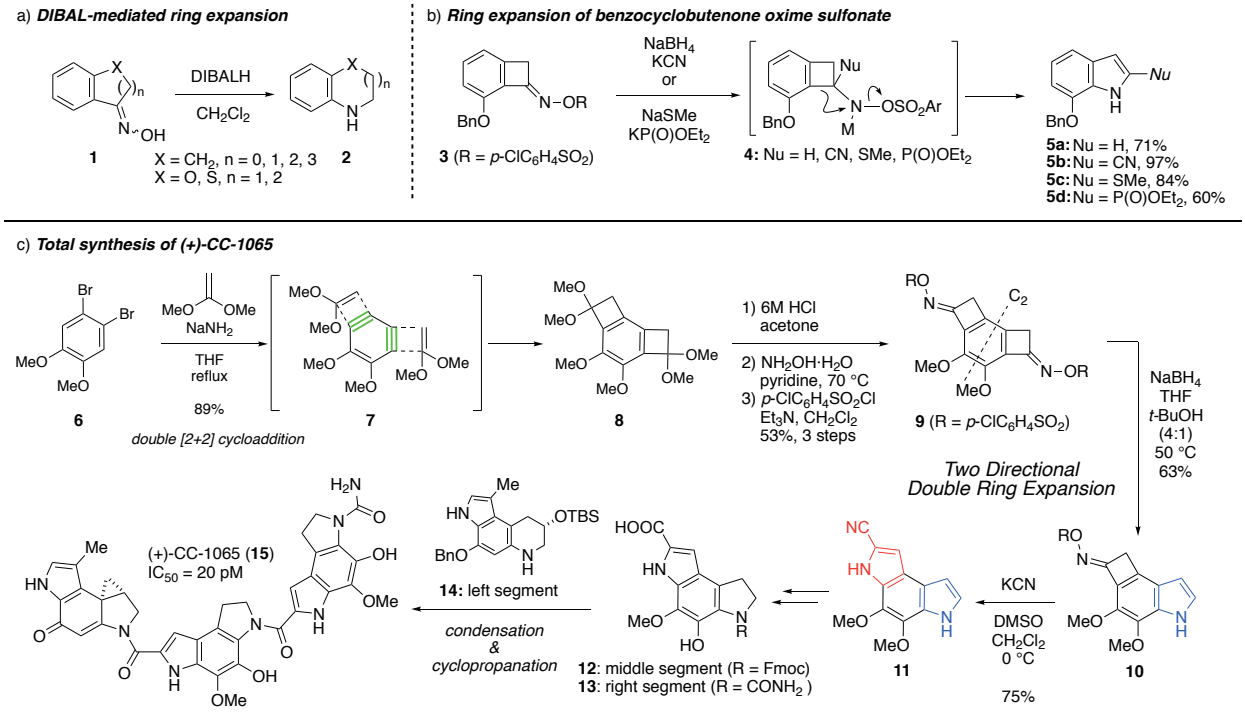
During the course of studies on DIBAL-mediated reductive ring expansion reaction of cyclic ketoxime **1**,[1,2] we recently developed a novel indole formation via analogous ring expansion reaction providing indole **5a** or 2-substituted indoles (**5b**–**d**) in good yields. To demonstrate utility of the novel indole synthesis, we planned to constructed the 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole segments of (+)-CC-1065 (**15**) via two directional double ring expansion strategy. Thus, double [2+2] cycloaddition between 1,3-benzdiyne generated from dibromoveratrole **6** and ketene dimethyl acetals provided tricyclic bis-acetal **8** in complete regioselectivity, which was then converted to C_2-symmetric benzo-bis-cyclobutenone oxime sulfonate **9**. The first ring expansion reaction of **9** with $NaBH_4$ smoothly proceeded to give indole **10** leaving the other cyclobutenone ring intact. Then, the second ring expansion reaction using KCN was conducted to provide pyrroloindole **11**. After conversion of **11** to the middle **12** and the right segment **13**, the total synthesis of (+)-CC-1065 (**15**) was accomplished by condensation of the left segment **9**, followed by the late-stage trans-annular cyclopropane formation.[3] In our presentation, we will discuss the scope and limitation of the indole synthesis, and the details on the total synthesis.



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[3] Imaizumi, T.; Yamashita, Y.; Nakazawa, Y.; Okano, K.; Sakata, J.; Tokuyama, H. *Org. Lett.* published online as ASAP (DOI: 10.1021/acs.orglett.9b01690).

N-Heterocyclic Carbene-Catalyzed Decarboxylative Alkylation of Aldehydes

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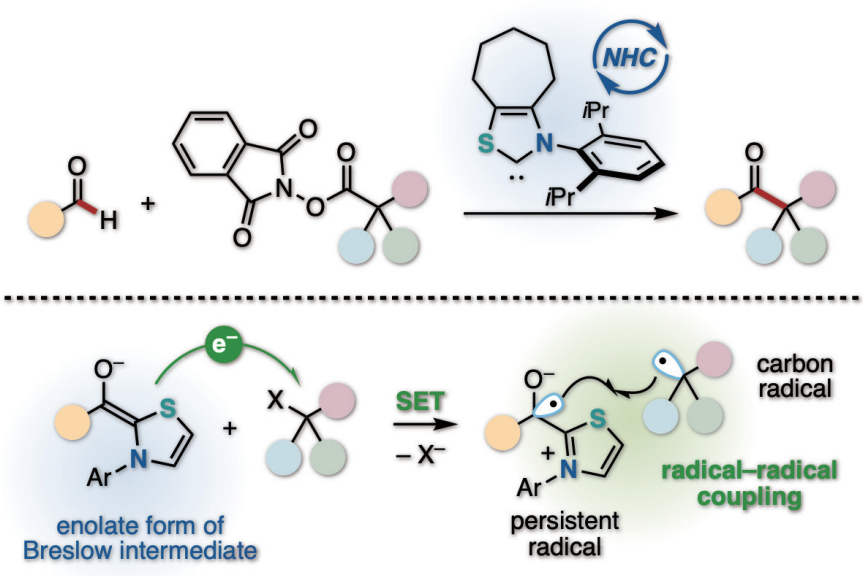
N-Heterocyclic carbene (NHC) catalysis, which exhibits a characteristic ability to access umpolung reactivity, has emerged as a powerful tool for challenging synthetic reactions. NHC catalysis involving a two-electron reaction pathway has been extensively studied. NHC-mediated radical reactions are also known. For example, there are a number of enzymes utilizing thiamine diphosphate (ThDP) as a coenzyme to catalyze the decarboxylation of pyruvate in nature. The resultant enamine, a so-called "Breslow intermediate," is known to perform single electron transfer to various electron acceptors such as lipoamides, flavin adenine dinucleotide and Fe_4S_4. Inspired by this process, *N*-heterocyclic carbene-catalyzed radical reactions have been developed. However, this area is still in its infancy with limited progress.[1]

This paper reports on our discovery of a new NHC radical catalysis that enables decarboxylative coupling reaction between aryl aldehydes and tertiary or secondary alkyl carboxylic acid-derived redox-active esters to deliver aryl alkyl ketones.[2] This protocol is first tertiary alkylation of aldehydes to construct quaternary carbon center. Due to the mild and transition-metal-free reaction conditions, this reaction tolerates a broad range of functional groups in the substrates. The power of this protocol was demonstrated by the functionalization of pharmaceutical drugs and natural product. Based on mechanistic studies, a reaction pathway involving the single electron transfer from an enolate form of Breslow intermediate to the redox ester followed by the recombination of the resultant radical pair is proposed.



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Synthetic Study of (–)-A58365B via a Chiral 2-Pyridone Synthesis Using Conjugate Addition of β-Keto Ester to Chiral Alkynyl Imine as a Key Reaction

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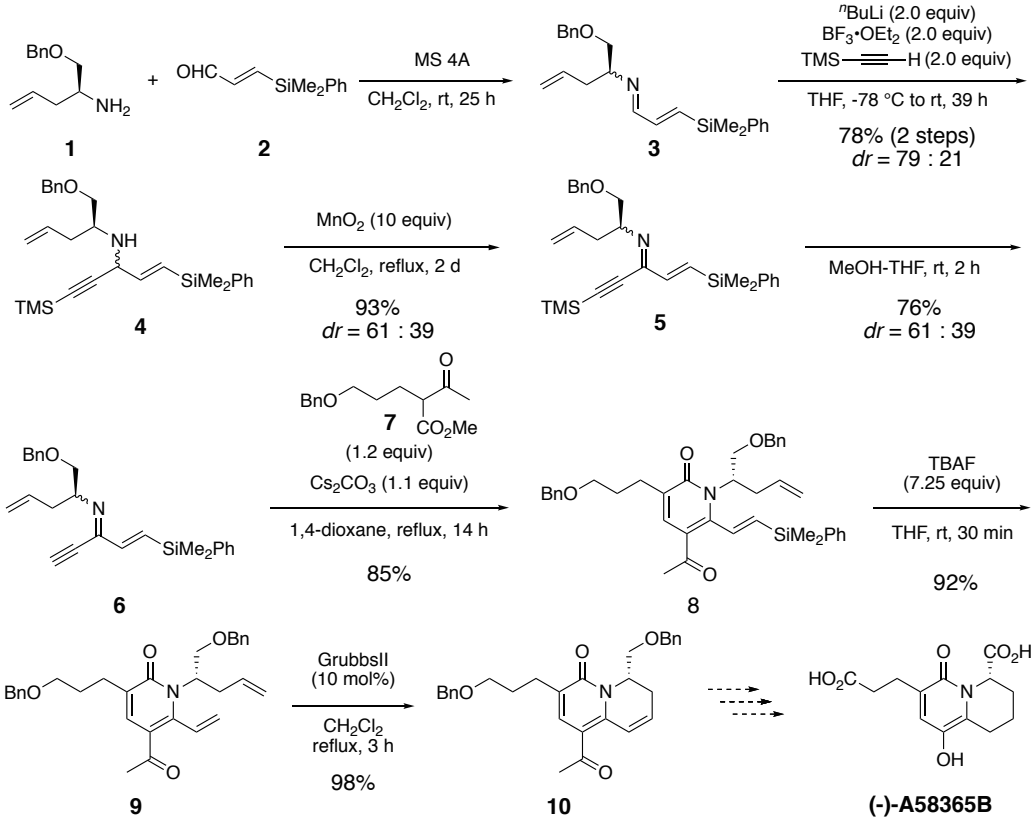
There are many biologically active compounds containing a 2-pyridone structure. (–)-A58365B having a 2-pyridone structure is one of them, which was obtained from a fermentation broth of the bacterium Streptomyces chromofucus in the Eli Lilly laboratories and found to be an angiotensin-converting enzyme inhibitors. Alkynyl imines are one of the most important nitrogen-containing starting materials because of their extensive use in the synthesis of nitrogen-containing compounds. We focused on the reactivity at the β-position of alkynyl imines and developed the efficient synthetic methods for several nitrogen-containing heterocycles such as 2-pyridones,[1] 2-iminopyridines,[2] 2-aminopyridines,[2] β-lactams,[3] and α-carbolines.[4] Herein, we report the synthetic study of (–)-A58365B via a chiral 2-pyridone **8** synthesis using conjugate addition of β-keto ester **7** to chiral alkynyl imine **6** as a key reaction.



[1] I. Hachiya, K. Ogura, M. Shimizu, *Org. Lett.* **2002**, *4*, 2755.
[2] I. Hachiya, Y. Minami, T. Aramaki, M. Shimizu, *Eur. J. Org. Chem.* **2008**, 1481.
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Synthesis and Evaluation of Chiral Spirooxindoles for Notch Signal Inhibitors

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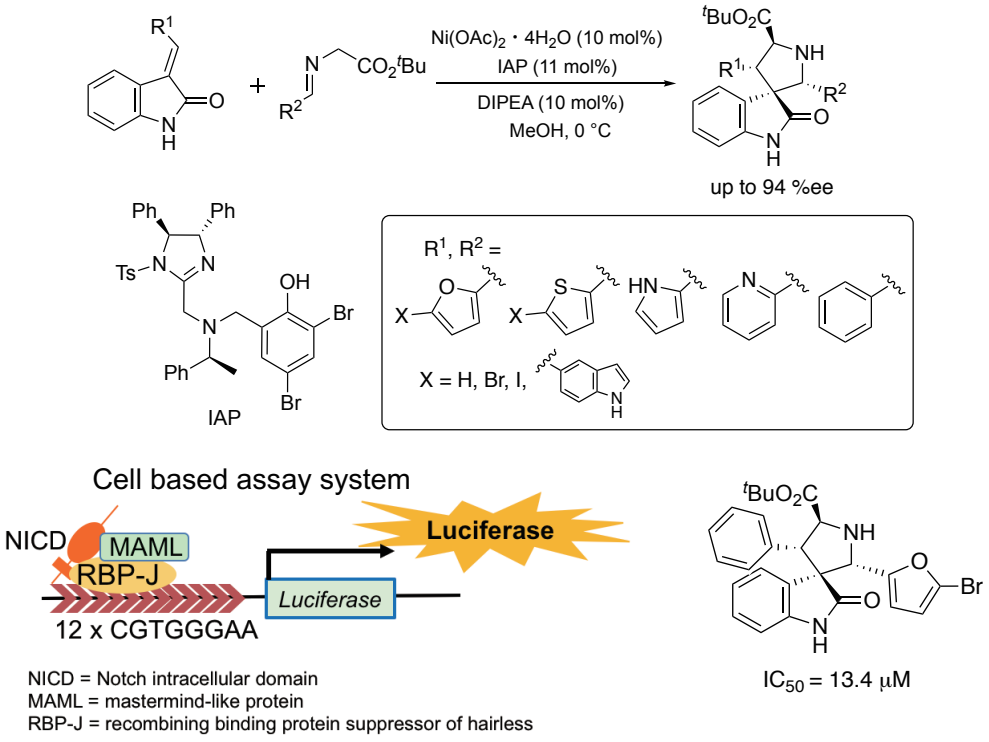
Notch signaling pathway has a crucial role in differentiation, cell proliferations and maintenance of stem cells. In neural stem cells, this signal inhibits cell differentiation to neurons by activation of hairy and enhancer of spilt 1 (HES1) expression, whereas this signal contributes to create cancer cells such as T-cell acute lymphoblastic leukemia (T-ALL), breast cancer and small cell lung cancer. Therefore, Notch signaling pathway could be a good therapeutic target of neurodegenerative diseases and new cancer therapy. Recently, we have developed an original cell based screening assay system for Notch signal inhibitors.[1a-c)] After screening small molecule library (Chiba Chemical Library), chiral spiro compounds were found to have inhibitory activity. To increase the activity, several chiral spirooxindoles bearing hetero cycles were synthesized using [3+2]cycloaddition by the imidazoline–aminophenol (IAP) catalyst **1**–$Ni(OAc)_2$.[2)] Evaluation of their inhibitory activity revealed that the derivative with Br-furan was most active (IC_{50} 13.4 μM). We will present synthesis of other chiral spiro compounds, effects of compound on neural stem cells and cancer cells.



[1] a) T. Yoneyama, M. A. Arai, *et al. J. Nat. Prod.* **2017**, *80*, 2453-2461, b) M. A. Arai, *et al. Sci. Rep.* **2018**, *8*, 5376, c) M. A. Arai, *et al. J. Nat. Prod.* **2018**, *81,* 1235-1240.
[2] T. Arai, *et al. Chem. Eur. J.* **2012**, *18*, 8278-8282.

Development of Quinoidal Oligothiophenes Having Fluorine Atoms

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[2]*Max Plank Institute for Polymer Research, Mainz/DEU*

Dicyanomethylene-substituted quinoidal oligothiophenes have been developed for use as n-type semiconductors in organic electronics.[1] Although it is well known that introduction of fluorine atoms into π-conjugated backbone increases its electron-accepting ability, quinoidal oligothiophenes having fluorine atoms are still rare.[2] In this research, we developed several quinoidal oligothiophenes having fluorine atoms (Figure 1) and investigated their structures, electrochemical behaviors, thin-film properties, and organic field-effect transistor (OFET) characteristics.

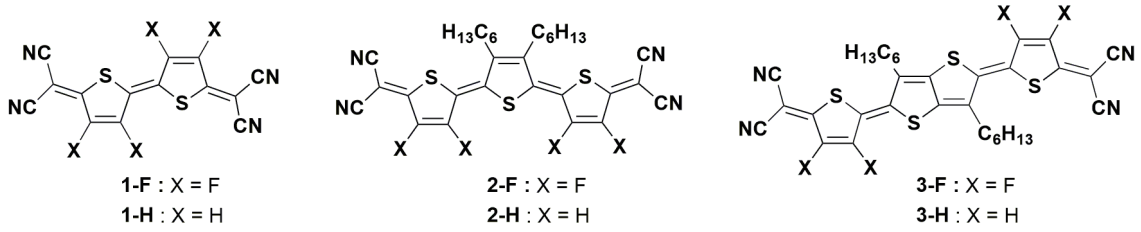

Figure 1. Chemical structures of compounds investigated in this study

The ^{19}F NMR spectra of **1-F**, **2-F** and **3-F** showed only two singlet signals, respectively. This result implies that these molecules have the stable conformation without *anti-syn* equilibrium, which is common for quinoidal oligothiophenes (**1-H** and **2-H**). The electrochemical properties of these compounds were investigated by cyclic voltammetry (CV) measurements in CH_2Cl_2. Cyclic voltammograms of **1-F**, **2-F** and **3-F** showed one reversible oxidation wave and two reduction waves. The lowest unoccupied molecular orbital (LUMO) energy levels of these compounds estimated from the first half-wave reduction potential were –4.69, –4.46, –4.50 eV, respectively. These values are lower than those of the reference compounds (**1-H**, **2-H** and **3-H**), indicating that the introduction of fluorine atoms into quinoidal oligothiophenes is effective to decrease the LUMO energy levels. OFET devices based on these materials showed typical n-type behavior even in the air condition. Furthermore**,** the blend films of this fluorinated quinoidal oligothiophene **2-F** and TIPS-pentacene showed ambipolar characteristics owing to the formation of co-crystal (Figure 2).

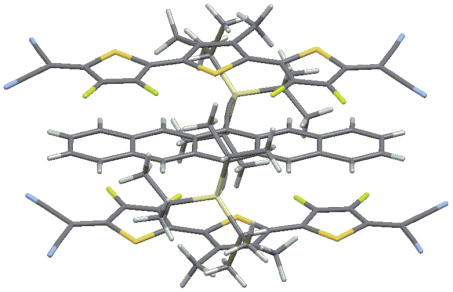

Figure 2. Co-crystal of n-type **2-F** and p-type TIPS-pentacene

[1] Pappenfus, T. M. *et al., J. Am. Chem. Soc.*, **2002**, *124*, 4184-4185; Handa, S. *et al.*, *J. Am. Chem. Soc.*, **2007**, *129*, 11684-11685.
[2] Yamamoto, K.; Ie, Y.; Aso, Y. et al. *J. Mater. Chem.C* **2018**, *6*, 7493.

3P-001

Synthesis and Photochromism of Bis(Thienyl) Substituted 1,2-Oxathiine 2,2-dioxides

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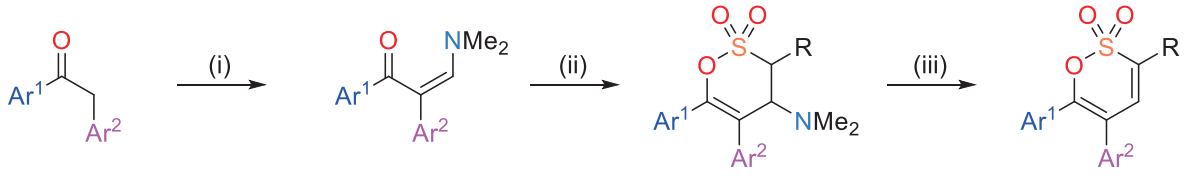
Department of Chemical Sciences, School of Applied Sciences, The University of Huddersfield, Queensgate, Huddersfield, HD1 3DH, UK

Sulfenes, generated by the action of base upon sulfonyl chlorides, react smoothly with substituted enaminoketones **2**, derived from **1** and DMFDMA, to afford novel 3,4-dihydro-4-dimethylamino-1,2-oxathiine 2,2-dioxides **3** in good yield. As a consequence of the *transoid* relationship between the 3-aryl substituent and the 4-dimethylamino group (Figure 1) the 1,2-oxathiine 2,2-dioxides **4** were obtained for the first time by the use of a Cope elimination protocol on **3** (Scheme 1).



Series **a**: $Ar^1 = Ar^2$ = 2,5-dimethylthiophen-3-yl, R = Ph; series **b**: Ar^1 = R = Ph, Ar^2 = 2,5-dimethylthiophen-3-yl; series **c**: Ar^1 = 2,5-dimethylthiophen-3-yl, Ar^2 = R = Ph; series **d**: $Ar^1 = Ar^2$ = R = Ph; series **e**: $Ar^1 = Ar^2$ = 2,5-dimethylthiophen-3-yl, R = H
Reagents: (i) DMFDMA, reflux; (ii) RCH_2SO_2Cl, Et_3N, THF; (iii) *m*-CPBA, CH_2Cl_2

Scheme 1

The application of the 1,2-oxathiine 2,2-dioxide scaffold in heterocyclic materials chemistry is exemplified by the efficient, reversible P-type photochromism observed for the 5,6-bis(2,5-dimethyl-3-thienyl) substituted oxathiine 2,2-dioxide **4a** (Figure 2 and 3). Exposure of a hexane solution of **4a** with UV irradiation (λ = 365 nm) promotes the electrocyclic ring closure to afford the coloured isomer **4a**' (image insert Figure 3). The reverse reaction was accomplished upon irradiation of **4a**' with visible light; the photochromic cycling could be repeated several times (insert Figure 3).

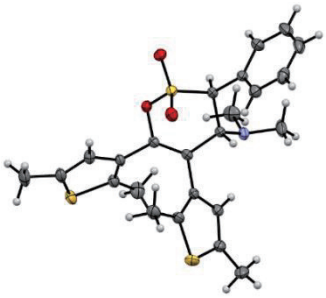


Figure 1: Crystal structure of **4a**

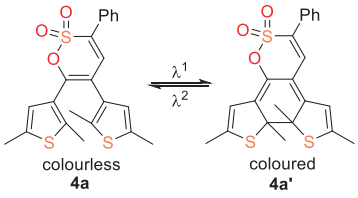


Figure 2: Reversible electrocyclization of **4a**

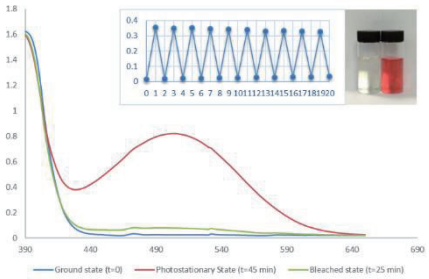


Figure 3: Photochromic response of **4a**

The synthesis of the precursor ketones **1** and novel photochromic dithienyl substituted 1,2-oxathiine 2,2-dioxides **3** and **4** together with their photochromic response will be discussed.

3P-002

Benzofuran synthesis from 2-hydroxychalcones via chloromethoxylation using hypervalent iodine reagent

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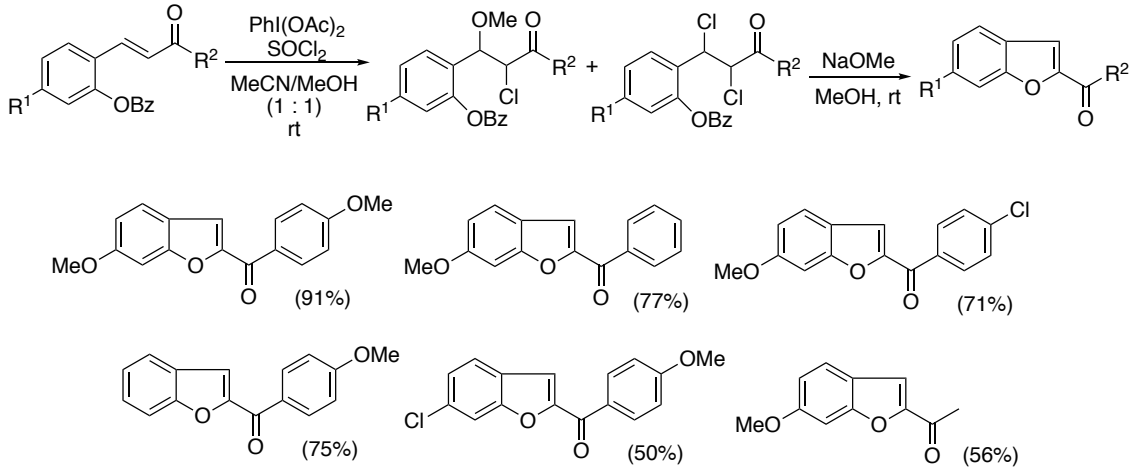
Benzofurans are important heterocyclic compounds and their skeletons are seen in many biologically active compounds. Among them, 2-acylbenzofurans are known to have a variety of biological activities such as anti-inflammatory and anti-proliferative and so on. Therefore, a number of synthetic methods for 2-acylbenzofurans have been reported. Rap-Stoermer synthesis is representative synthetic method for 2-acylbenzofurans from 2-hydroxybenzaldehydes. Synthesis from iodobenzene with alkynes via copper-mediated coupling reaction and concomitant cyclization has also been reported.

Recently, we have developed novel 2-acylindole synthesis from 2-aminochalcones using $PhI(OAc)_2$ and $SOCl_2$. The reaction proceeded via chloromethoxylation of chalcones as an intermediate and subsequent cyclization afforded 2-acylindoles. We herein report a 2-acylbenzofuran synthesis as an application of the synthesis of 2-acylindoles using 2-hydroxychalcone as a substrate. We first synthesize *O*-protected 2-hydroxybenzaldehyde with various protective groups, which were then coupled with phosphorus ylid to give the corresponding chalcones. Obtained chalcones were subjected to the chloromethoxylation using $PhI(OAc)_2$ and $SOCl_2$ under the optimized conditions reported in indole synthesis. The desired reaction proceeded but certain amount of starting materials remained as an inseparable mixture. Then we conducted the subsequent deprotection and cyclization reactions as a mixture. When benzoyl group was used as protective group, the best yield was obtained. We changed a solvent from MeOH to MeCN to improve solubility, however dichlorinated chalcone was obtained as a major product. This compound was attempted cyclization but yield was decreased compared with that of chloromethoxylated compound. Finally we employed the mixed solvent system and 1 : 1 of MeOH and MeCN afforded better result and chloromethoxylated compounds was obtained as major product. As an optimized reaction conditions in hand, the desired 2-acylbenofuran was obtained in 91% yield in 2 steps. Substrate scope is indicated below.



(3+3)-Annulation of Carbonyl Ylides with Donor–Acceptor Cyclopropanes: Synergistic Dirhodium(II) and Lewis Acid Catalysis

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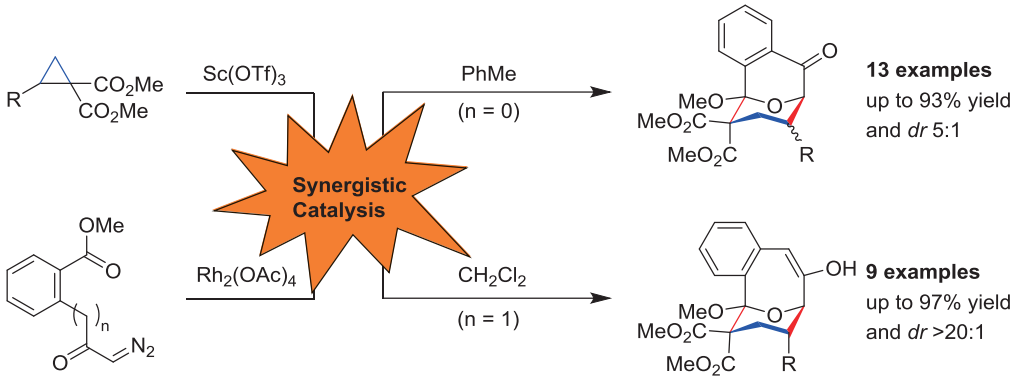
As versatile C_3-building blocks, donor-acceptor (D-A) cyclopropanes have found widespread application in organic synthesis. Their high ring strain (~115 kJ·mol^{-1}) and strongly polarized vicinal carbon-carbon bond offers unique 1,3-zwitterionic reactivity. In combination with carbonyl ylides, a high level of molecular complexity is achieved within one single synthetic step.[1,2]

This study describes the first (3+3)-annulation process of D-A cyclopropanes employing synergistic catalysis. The $Rh_2(OAc)_4$-catalyzed decomposition of diazo carbonyl compounds generated carbonyl ylides *in situ*. These 1,3-dipoles were converted with D-A cyclopropanes, activated by Lewis acid catalysis, to afford multiply substituted pyran scaffolds in high yield and diastereoselectivity (Scheme 1). Extensive optimization studies enabled access to 9-oxabicyclo[3.3.1]nonan-2-one and 10-oxabicyclo[4.3.1]decen-2-ol cores, exploiting solvent effects on intermediate reactivity. Mechanistic investigations led to a plausible concept, explaining diastereoselectivity and addressing the merging steps in the catalytic approach. [3,4]



Scheme 1: Construction of pyran scaffolds in nonan-2-one and decen-2-ol cores by synergistic catalysis.

[1] a) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804–818; b) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5504–5523; c) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151–1196.
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3P-004s

Nitrenium Ion from λ^3-Iodanes

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Hypervalent iodine compounds are widely used as potential oxidant in organic synthesis. In spite of similar reactivity with transition metals, hypervalent iodine reagents[1] are more preferred because of their environmental sustainability. Among several types of hypervalent iodine reagents, trivalent organo iodine(III) reagents or λ^3- iodanes are popular due to their easy accessibility, stability and controlled oxidizing reactivity.[2] Amines react with iodine(III) oxidants in some specific way to provide divalent electrophilic ionic species, called as nitrenium ion. Depending on the nature and stability of nitrenium ion, numerous oxidative transformations are known to generate valuable functional molecules. In accordance with the above principle, biarylsulfonamides were used to generate nitrenium ion using the hypervalent iodine(III) reagent PIDA. Depending on the type of nucleophile, nitrenium ion is converted to carbenium ion which leads to synthesis of C-C or C-N bond.[4] The deciding factor in the outcome of a reaction is guided by the nucleophile available in the system. Herein, the role of hypervalent iodine(III) reagent in bringing about oxidative transformation for synthesis of carbazoles by distal (meta) C-H bond functionalization will be discussed.[3]

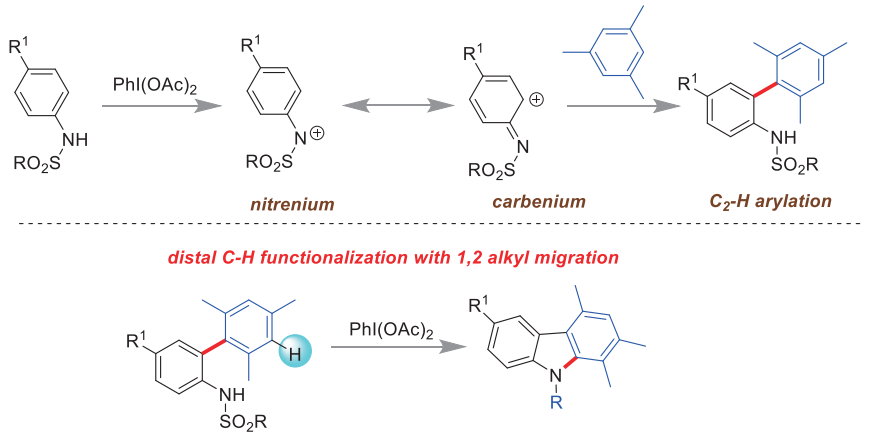

Figure 1: Nitrenium ion mediated synthesis of C-C and C-N bond.

References :

[1] T. Dohi and Y. Kita, *Chem. Commun.*, 2009, DOI: 10.1039/B821747E, 2073-2085.
[2] P. J. Stang and V. V. Zhdankin, *Chem. Rev.*, 1996, **96**, 1123-1178.
[3] A. Bal, S. Maiti and P. Mal, *J. Org. Chem.*, 2018, **83**, 11278-11287.
[4] A. Bal, S. Maiti and P. Mal, *Communicated.*

3P-005s

Advanced method for the construction of C-S bond via C-H functionalization

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C-S bonds are ubiquitously found in natural products. Many organosulfur compounds are widely used in medicinal, pharmaceutical and functional material science. Hence the C-S bond construction has become a significant research field in organic chemistry because of the tremendous importance of organosulfur compounds. To date, great developments have been made for erecting the C-S bonds including transition-metal-catalyzed [1] pathways but use of simple greener reagent [2] (base or organic reagent) is less explored. C-H bond is regarded as a non-functional group as it has high bond energy lacking reactivity. Hence functionalization of C-H bond is an emerging era in synthetic organic community. In continuation of our interest in C-S bond synthesis via C-H bond functionalization using the transition metal free inexpensive reagent is highly desirable. The evaluation of environmentally benign by-product makes these methodologies more fascinating. A detail study of our research for C-S bond [3-5]synthesis will be discussed here.

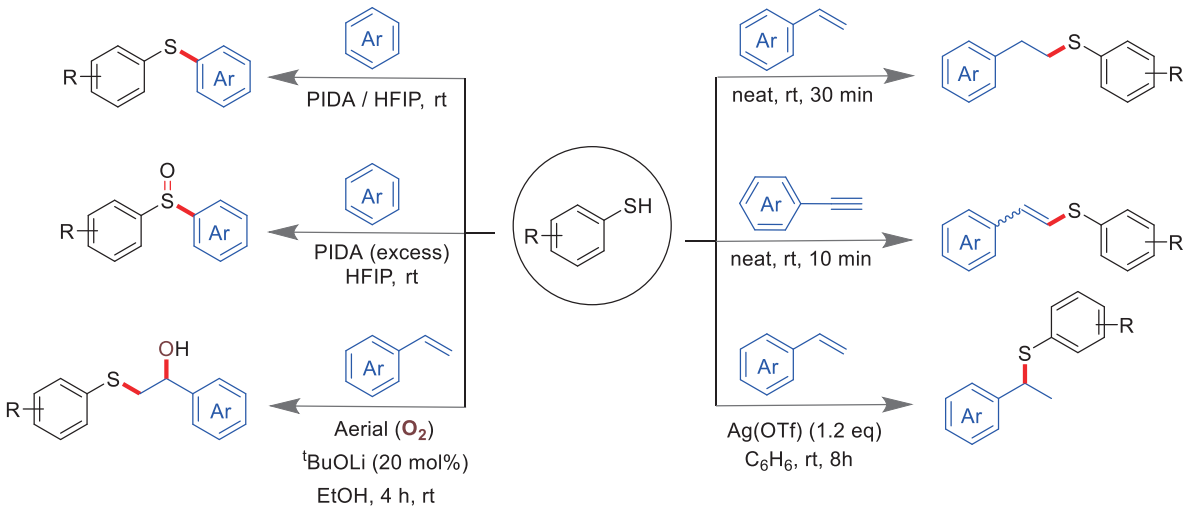

Figure 1: Thiophenol as sulphur surrogate for the regioselective C-H functionalization

Reference:

(1) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596.
(2) Kumar, R.; Saima; Shard, A.; Sinha, A. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 828.
(3) Choudhuri, K.; Achar, T. K.; Mal, P. *Adv. Synth. Catal.* **2017**, *359*, 3566.
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(5) Choudhuri, K.; Maiti, S.; Mal, P. *Adv. Synth. Catal.* **2019**, *361*, 1092.

Visible Light-driven Generation of Hydrazone Radicals for the Synthesis of Dihydropyrazoles and Tetrahydropyridazines

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In the past several years, with the development of visible light photoredox catalysis, the photocatalytic N-radical-mediated cascade reaction has been established as one of the most powerful tools for the construction of diversely functionalized N-heterocycles.[1-2]

Recently, we have developed a visible light-induced oxidative deprotonation electron transfer (ODET) strategy for the generation of N-centered radicals from the hydrazones.[3-4] Employing this strategy, a series of N-radical-mediated carboamination and carboallylation reactions of alkenes were achieved (Fig 1).[5-6] More recently, we also have extended this strategy to the N-centred radical catalysis, which enable an efficient bifunctionalization reaction of alkenes.[7]

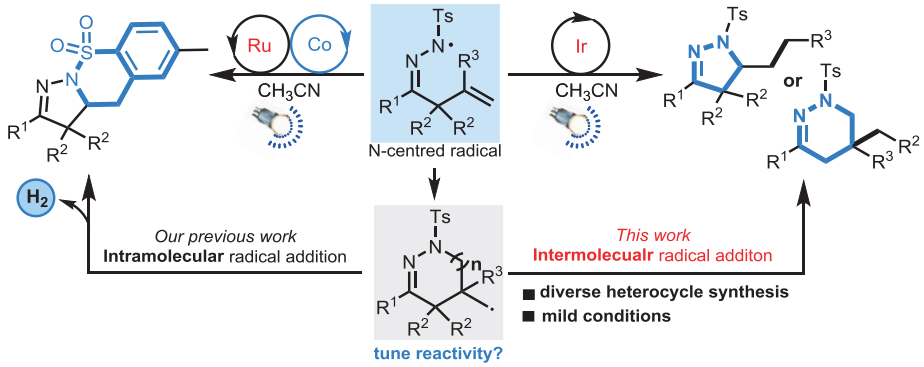

Fig. 1 Visible-light-driven N-centered radical-mediated synthesis of N-heterocycles

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Dual Copper and Photoredox-Catalyzed Cross-Coupling of Alkenes, O-Benzoylhydroxylamines, and Sulfur Ylides

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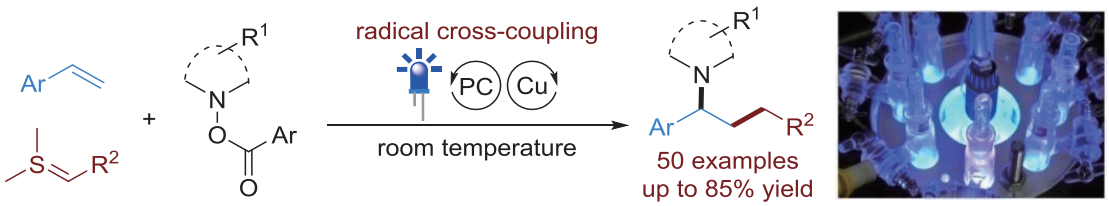
Nitrogen-containing compounds, especially the nitrogen heterocycles, are found in many biologically active synthetic targets, including natural products and designed pharmaceuticals, and they thus attract considerable attention from the synthetic community.[1,2] The development of efficient, practical and sustainable methods for direct functionalization of nitrogen heterocycles provides a powerful method to access structurally diverse nitrogen heterocycles.[3]

On the basis of our continuing interest in photochemistry,[4-5] recently, we have developed a dual copper and photoredox-catalyzed three-component radical cross-coupling of alkenes, O-benzoylhydroxylamines, and sulfur ylides. This mild protocol shows broad substrate scope and high functional group tolerance, giving the corresponding diversely functionalized nitrogen heterocycles with generally good yields and excellent selectivity. In the poster presentation, I will present the details.



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Total Synthesis of (–)-Deoxoapodine

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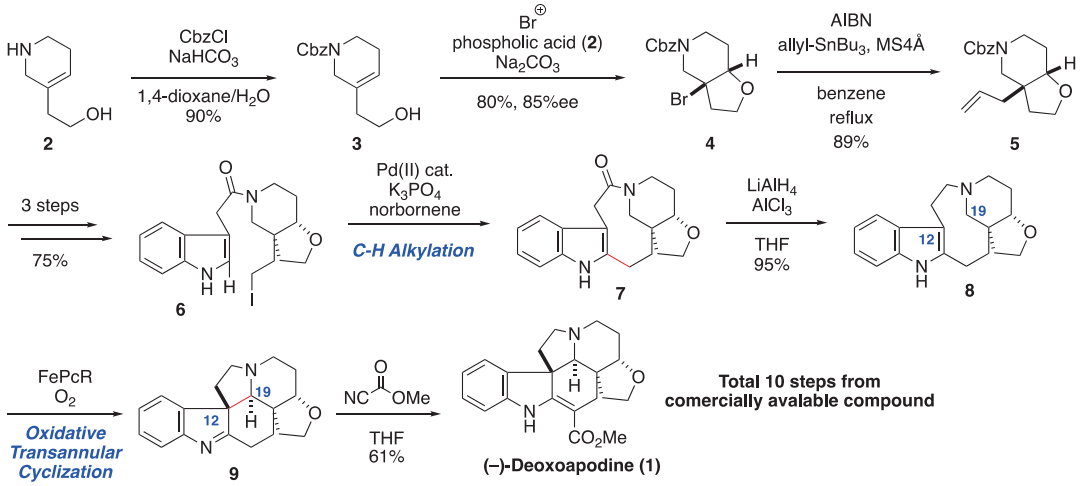
Aspidosperma alkaloids have attracted considerable attentions from the synthetic community due to their pharmaceutically important biological activities and unique structures, containing the pentacyclic core framework. Although a number of synthetic strategies for aspidosperma alkaloids have been reported, there is only one synthetic approach involving oxidative transannular bond formation between C12 and C19 positions, which used $Hg(OAc)_2$ as an oxidant.[1] However, this method resulted in a low yield due to over-oxidation, and required further reductive treatment. Recently, we have developed the aerobic oxidative modification of α-position of alkyl amines using phthalocyanine metal complex. Based on these backgrounds, we focused on (–)-deoxoapodine (**1**), containing a tetrahydrofuran ring, and undertook synthetic studies on **1** to demonstrate the utility of our oxidation reaction.

Our synthesis commenced with Cbz-protection of the commercially available amino alcohol **2**, which was followed by chiral phosphoric acid (**2**) catalyzed enantioselective 5-*endo*-*trig* bromocyclization to afford tertiary bromide **4** in optically active form. Then, construction of quaternary carbon center by Keck allylation, followed by a three-step conversion including ozonolysis of allyl group, provided alkyl iodide **6**. Next, the highly strained 9-membered ring system was successfully constructed by a direct C-H alkylation at the 2-position of indole based on Bach's method.[2] After reduction of lactam **7**, the resultant tertiary amine **8** was treated with the iron phthalocyanine complex under oxygen atmosphere to promote the transannular reaction starting from oxidation of the tertiary amine to give indolenine **9** possessing aspidosperma skeleton. Finally, we have achieved an enantioselective 10 step total synthesis of (–)-deoxoapodine (**1**) by introduction of methoxy carbonyl group.



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[2+2+1] Pyrrole Synthesis from Alkynes and Azobenzene via N=N Bond Cleavage Catalyzed by Vanadium Complexes

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Hayato Tsurugi,*[,1] and Kazushi Mashima*[,1]
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Multisubstituted pyrroles are synthetically valuable heteroaromatic compounds in terms of their versatility as building blocks of pharmaceuticals, natural products, functional materials, and dyes. Although cyclocondensation reaction such as the Paal-Knorr and Hantzsch reactions are well-established, transition metal-mediated [2+2+1] cycloaddition reaction of alkynes and primary amine have attracted great attention because of the substrate availability. One of us previously reported Ti-catalyzed [2+2+1] pyrrole formation reaction using alkynes and azobenzene as substrates.[1-2] We herein present that the combination of $VCl_3(thf)_3$ and *N,N*-bis(trimethylsilyl)aniline **1a** serves as an efficient catalyst for [2+2+1] cycloaddition reaction of alkynes **2** and azobenzene **3**, giving multisubstituted pyrroles **4**.[3] According to the ^1H NMR analysis of the reaction mixture, we found a generation of mono(imido)vanadium(III) species with concomitant release of 2 equiv of $ClSiMe_3$. Plausible reaction mechanism involves a generation of bis(imido)vanadium(V) species via N=N bond cleavage; in fact isolated bis(imido)vanadium complex **5** showed good catalytic activity for pyrrole formation reaction. Substrate scopes and a detailed reaction mechanism will also be discussed in this presentation.

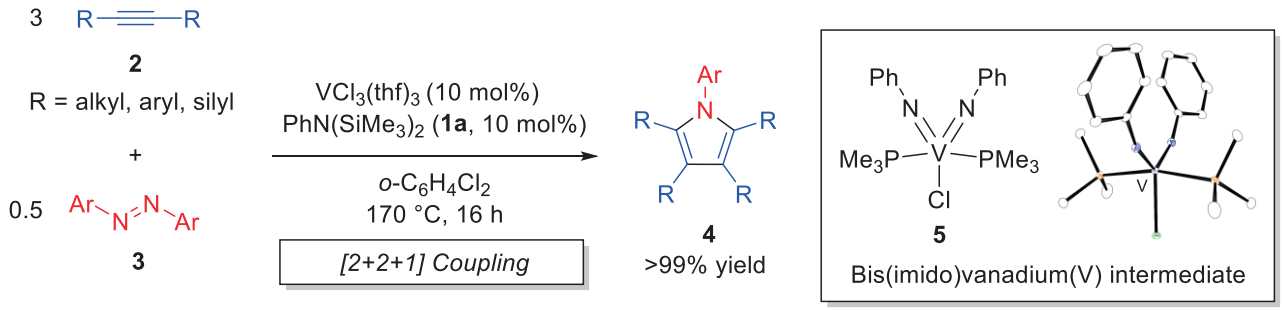

Figure 1. Vanadium-catalyzed [2+2+1] coupling of alkynes and azobenzene

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Optically Active *trans*-Cyclooctene-pyridine Ligands in Rhodium-catalyzed Asymmetric 1,4-Addition

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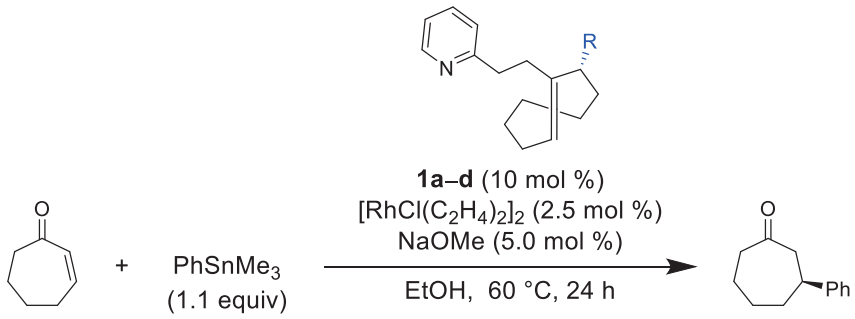
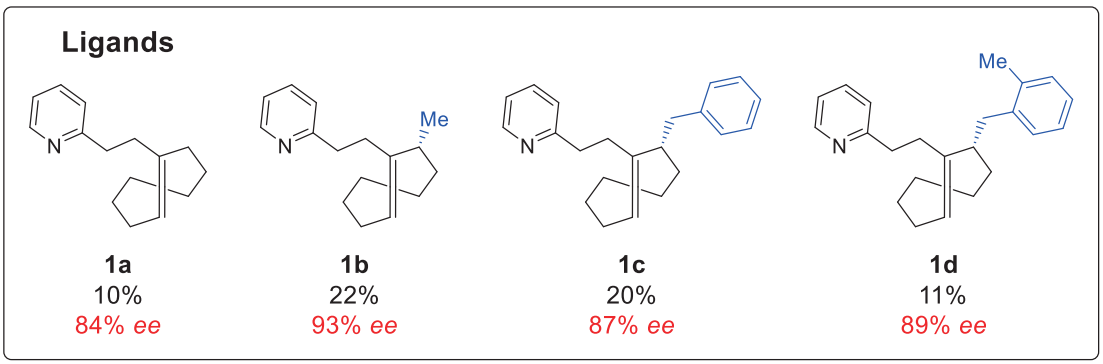
Chiral olefins such as optically active dienes are known to provide effective chiral environments and unique reactivities to some transition metal catalysts. Meanwhile, *trans*-cyclooctenes are planar chiral olefins, which are able to be isolated as optically active forms at ambient temperature, and the properties derived from their strained structures were revealed to be responsible for a strong coordination ability. However, their ability as chiral ligands of metal catalysts has not been investigated.

We have been interested in the catalytic behavior of *trans*-cyclooctenes.[1] Here, we present optically active *trans*-cyclooctene derivatives performed as ligands for rhodium-catalyzed asymmetric 1,4-addition. This is the first demonstration of their potential as chiral ligands to realize asymmetric catalysis. The pyridyl group is also essential for generating active catalytic species. Moreover, the introduction of substituents at the allylic position further improved the enantioselectivity.





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Systematic examination of catalytic amide bond formation by the readily accessible B_3NO_2 heterocycle-containing molecule Pym-DATB

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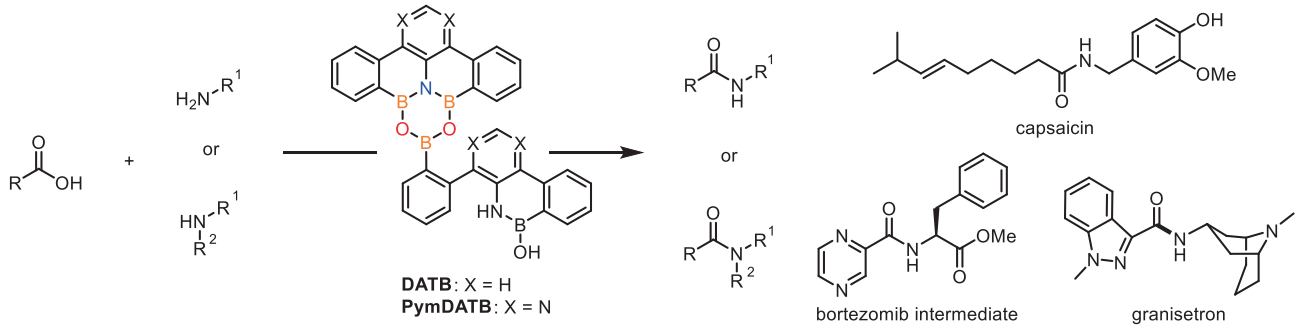
Although amide bonds are seen to be ubiquitous in organic chemistry, the main route to this functional group continues to be stoichiometric activation of a carboxylic acid prior to coupling with an amine, resulting in a large amount of waste material. We recently discovered that the heterocycle DATB (1,3-dioxa-5-aza-2,4,6-triborinane) can catalyze this reaction, employing a unique mode of action when compared with the more 'traditional' boronic acid-mediated amide bond catalysts. [1,2]

In order to provide a commercially appealing catalyst, we devised an expeditious route to a pyrimidine-containing analogue of the original DATB catalyst, Pym-DATB, using a pyrimidine-directed Bora-Friedel-Crafts reaction as a key step. The new catalyst retains catalytic activity and allows for an even greater substrate scope compared with the original catalyst. Various functional groups are tolerated without prior protection, and bulky candidates are well suited to the reaction. The utility was highlighted by the synthesis of several biologically relevant compounds, and catalyst loadings of even 0.5 mol % could be employed. [3]

The newly developed pyrimidine-directed DATB synthetic pathway opened the door for analogue synthesis, allowing for the production of a larger variety of DATB-containing compounds. The properties of the DATB ring could be moderated, and compounds with differing electronic properties as well as those with unprecedented solubility in organic solvents have allowed for more insight into this unusual heterocycle.



PymDATB is commercially available from Merck-Sigma-Aldrich (Catalog # 901627).

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Complexation between $Al(C_6F_5)_3$ and *N*-Phosphine Oxide-Substituted Imidazolidenes

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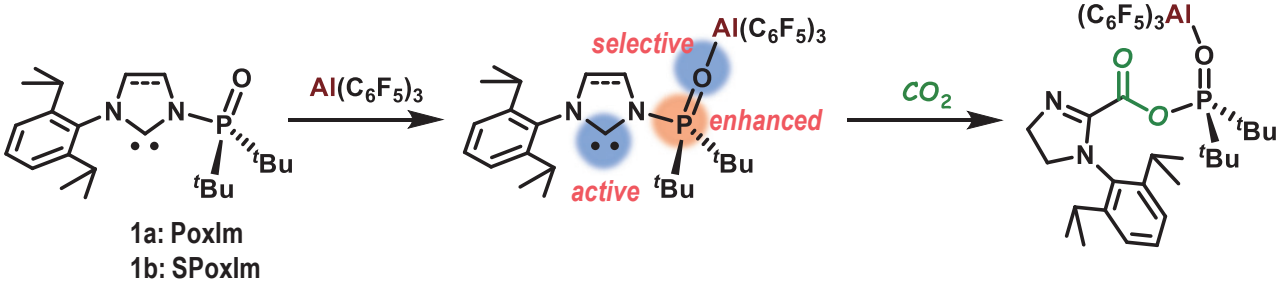
N-Heterocyclic carbenes (NHCs) have found a multitude of applications in diverse research areas in organic, inorganic, and organometallic chemistry.[1] Applications of NHCs have been significantly furthered by the advent of multifunctional NHCs by the introduction of substituents on either the nitrogen atom(s) or on the backbone of the NHCs.[2] Recently, we have developed *N*-phosphine oxide-substituted imidazolylidenes (PoxIms) and the corresponding imidazolinylidenes (SPoxIms) through the direct introduction of the phosphinoyl group onto the nitrogen atom, which can work as a Lewis base and an electrophile showing multipurpose utility.[3a,b] Herein, we report the complexation between $Al(C_6F_5)_3$ and *N*-phosphinoyl groups in PoxIm **1a** or SPoxIm **1b** enhanced the electrophilicity on the phosphorus, hence the reactive carbene moieties are co-existed in these molecules.[4] Thus, a further use of the carbene was demonstrated by the preparation of a carboxylic-phosphinic mixed anhydride through the reaction between CO_2 and the phosphinoyl-coordinating complex comprising **1b** and $Al(C_6F_5)_3$. This CO_2-fixation was also promoted in the presence of 10 mol% $Al(C_6F_5)_3$, while $B(C_6F_5)_3$ did not show any catalytic activity.



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Anion-π Catalysis for Epoxide-Opening Ether Cyclizations, from Monomers to Oligomers, Challenging Baldwin Rules

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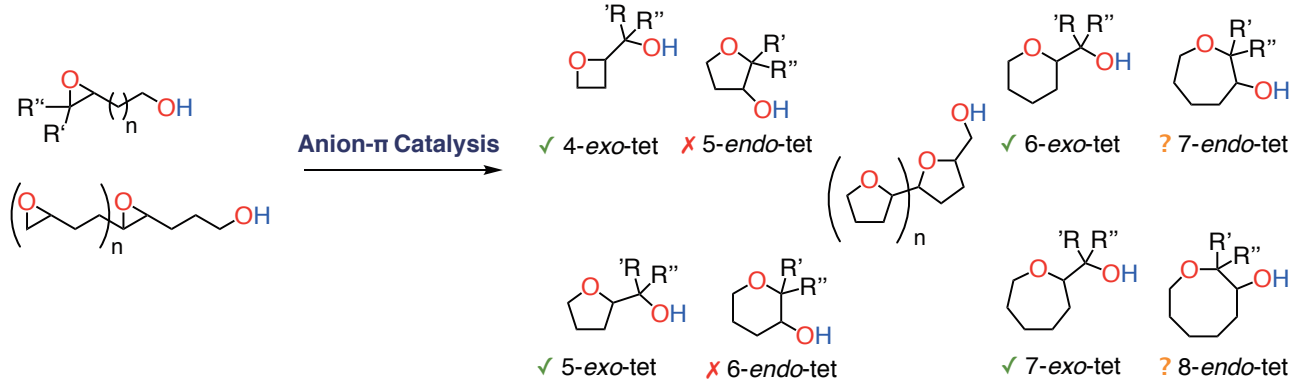
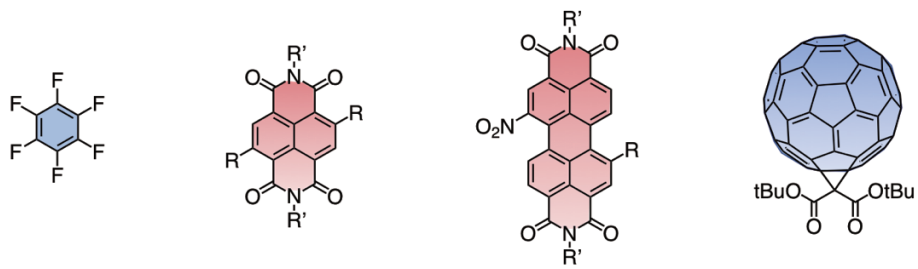
Geneva, Switzerland

In recent years, it has been demonstrated that anion-π interactions can accelerate a wide variety of chemical transformations.[1] Particularly important has been the employment of primary anion-π catalysis to promote epoxide-opening cyclizations, reaction which shows an autocatalytic behavior. Preliminary studies showed that the use of anion-π interactions can enhance the formation of the 6-*endo*-tet product (anti-Baldwin) against the 5-*exo*-tet (Baldwin).[2] Considering the relevance of epoxide opening polyether cyclization in chemistry and biology we decided to analyze in depth this new primary anion-π catalytic reaction.[3] In this context, the next step was the evaluation of different lengths of the epoxide unit, making possible the access to different ring sizes. It was reviled that substitution on epoxide core as well as on the aliphatic chain (gem-dimethyl effect) can play a key role turning the epoxide more sensible against the anionic-π surface, and more important providing the anti-Baldwin rule product. The knowledge brought from the study of the monomers allow us to promote the cyclization of oligomers in a cascade opening-epoxide cyclization on different anionic-π surfaces.



Anion-π Catalysis



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Synthesis of γ,γ-Disubstituted Butenolides through a Doubly Vinylogous Organocatalytic Cycloaddition

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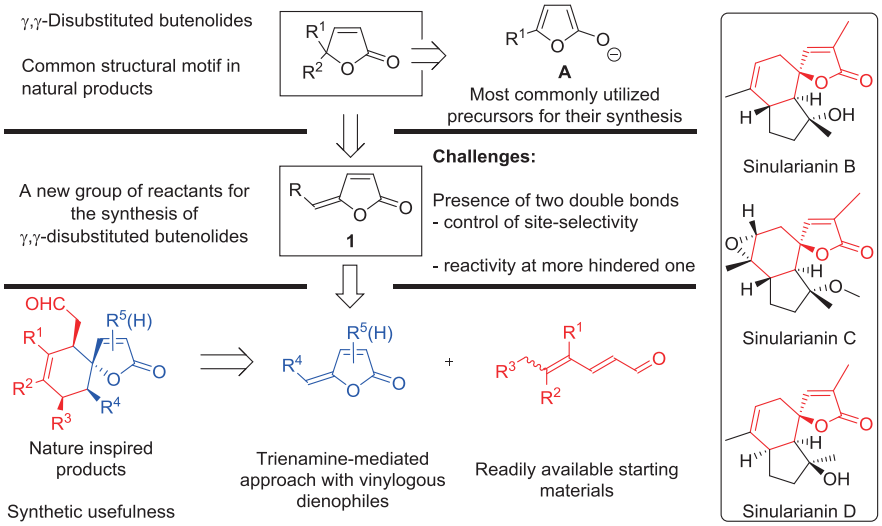
γ,γ-Disubstituted butenolides and related γ-lactones represent a common structural motif, found in wide variety of natural products relevant form the biological and medicinal chemistry point of view [1]. Therefore, much attention has been given to the development of synthetic methods allowing for their preparation, in a stereocontrolled manner. Within this research area, the asymmetric organocatalysis has proven highly useful, providing valuable solutions leading to enantiomerically enriched γ,γ-disubstituted butenolides [2].



|Herein a novel organocatalytic approach to γ,γ-disubstituted butenolides is described. It is based on a fully site-selective functionalization of 5-alkylidenefuran-2(5H)-ones via trienamine-mediated [4+2]-cycloaddition with α,β,γ,δ-diunsaturated aldehydes. The developed methodology proceeds with excellent stereocontrol and constitutes a unique example of trienamine chemistry with vinylogous dienophiles. Importantly, the reaction has very broad scope and allows for the introduction of substituents also in the α- or the β-position of the butenolide ring. [3].

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This project was realized within the Sonata Bis programme (grant number: 2015/18/E/ST5/00309) from the National Science Centre, Poland. The PROM project – "International scholarship exchange of PhD candidates and academic staff" is financed by the European Social Fund under the Operational Programme Knowledge Education Development, non-competitive project entitled International exchange of PhD candidates and academic staff, Agreement no. POWR.03.03.00-00-PN13/18

Chalcogen-Bond Assisted Dirhodium Complex –Total Syntheses of Naturally Occurring γ-Lactones–

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[1]*Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan*

[2]*Graduate School of Natural Sciences, Nagoya City University, Nagoya 467-8501, Japan*

[3]*Kyoto Pharmaceutical University, Kyoto, Kyoto 607-8412, Japan*

Chalcogen bond between sulfur and oxygen atoms has been paid attentions as an attractive interaction, which contributes to conformational control of pharmaceuticals and organic materials. We recently reported dirhodium carboxylate catalyst **1** for asymmetric intramolecular C–H insertion of α-diazoacetates to α,β-disubstituted γ-lactones.[1)] We also applied this stereoselective C–H insertion to asymmetric total synthesis of cinnamomumolide (**2**). However, its steleoselectivity was found to be limited in a moderate level (in the case of cat. **3**: 67% ee) (Scheme 1).

In this study, we found that novel dirhodium complex **4** bearing chalcogen bonds, prepared from axially chiral binaphthothiophene dicarboxylic acid (**5**),[2)] was superior catalyst to improve its stereoselectivity (Figure 1).

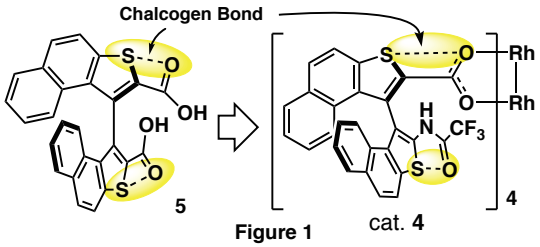
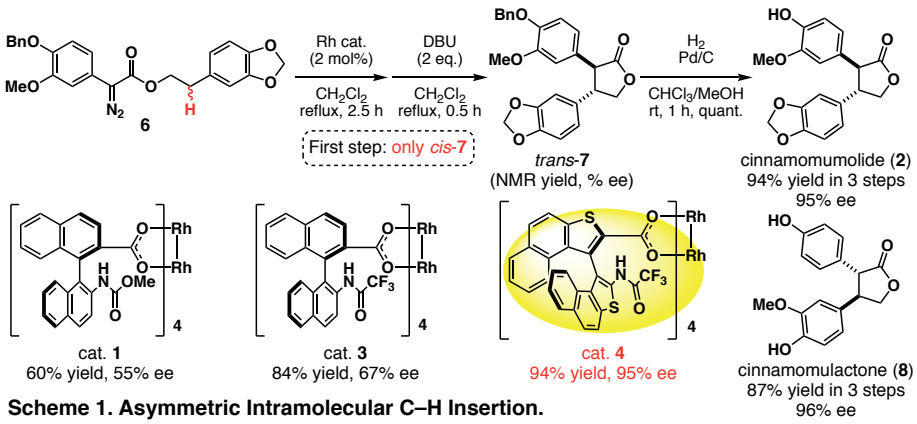


Figure 1

Upon treatment of **6** with cat. **4** (2 mol%) in CH_2Cl_2 under reflux conditions, intramolecular C–H insertion was proceeded smoothly to give *cis*-**7** as a sole isomer. The enantiomeric excess (95% ee) was determined in *trans*-**7** (94% yield in 2 steps) after epimerization with DBU. Deprotection of benzyl group of *trans*-**7** afforded **2** in 94% yield over 3 steps. In addition, we also achieved asymmetric total synthesis of cinnamomulactone (**8**) in short steps.



Scheme 1. Asymmetric Intramolecular C–H Insertion.

Chalcogen bonds between sulfur and oxygen atoms were thought to contribute for conformational lock of the carboxylate groups to lead well-defined D_2-symmetric structure of **4** as shown in the crystal structure (Figure 2). This could be the key for superior asymmetric induction of **4**.

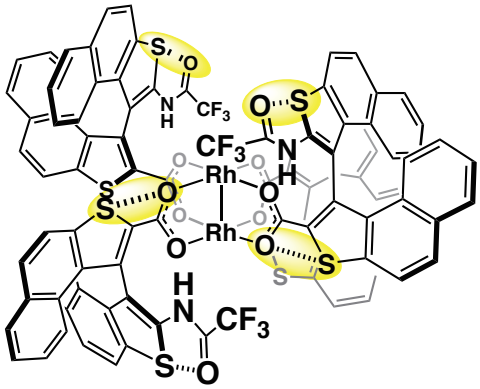


Figure 2. Crystal Structure of 4.

References

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3P-016s

Intramolecular cyclization of *o*-alkynylisocyanobenzenes: synthesis of 3-substituted quinolin-2(1*H*)-ones and 2-sulfonyl- and 2-thiocyanato-3-substituted quinolines

Onnicha Khaikate, Jatuporn Meesin, Ailada Charoenpol, Manat Pohmakotr, Vichai Reutrakul, Pawaret Leowanawat, Darunee Soorukram, and Chutima Kuhakarn*
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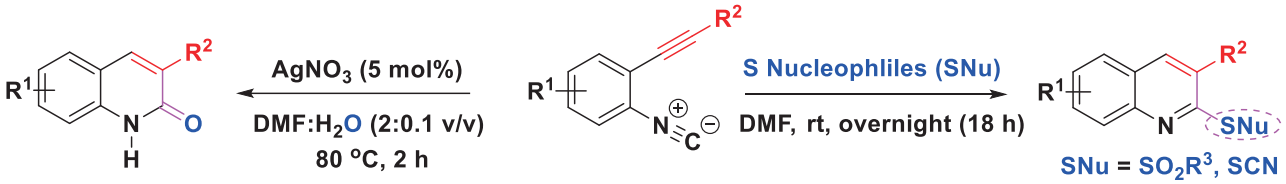
Facile methods for the synthesis of 3-substituted quinolin-2(1*H*)-ones, 2-sulfonyl- and 2-thiocyanato-3-substituted quinolines through cyclization of *o*-alkynylisocyanobenzenes employing water, sulfinate sodium salts and ammonium thiocyanates as nucleophiles were described. For the synthesis of 3-substituted quinolin-2(1*H*)-ones, water served as an oxygen and proton distributor and the reaction readily took place at 80 °C in the presence of catalytic amount of Ag(I) nitrate. The synthesis of 2-sulfonyl- and 2-thiocyanato-3-substituted quinolines was metal- and base-free, and the reaction proceeded under simple and mild reaction conditions. The reaction allows rapid and convenient access to numerous 3-substituted quinolin-2(1*H*)-one, 2-sulfonyl- and 2-thiocyanato-3-substituted quinoline derivatives in moderate to good yields. The electronic and steric effects of different substituents on the reaction efficiency were studied. Extensive experiments were also investigated toward plausible mechanistic pathways.



[1] Charoenpol, A.; Meesin, J.; Khaikate, O.; Reutrakul, V.; Pohmakotr, M.; Leowanawat, P.; Soorukram, D.; Kuhakarn, C. *Org. Biomol. Chem.*, **2018**, *16*, 7050.
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3P-017

Synthesis and Fluorescence Spectra of 5- or 6-Substituted 2-(4-Aminophenyl)-1,3-benzothiazole Derivatives

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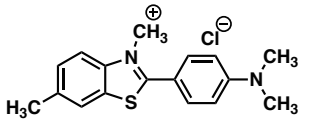
Molecular probes for detection of amyloid proteins would be useful for diagnosis and treatment of Alzheimer disease. 2-(4-Aminophenyl)-1,3-benzothiazole derivatives are known as such a kind of molecular tools. For example, Thioflavin T® (**1**) was developed in 1959,[1] and now is widely used for detection of amyloid proteins. Recently in Japan, ^{18}F-Flutemetamol® (**2**) has been approved for diagnosis of Alzheimer disease by PET. It was also reported that Thioflavin T® derivative with bromo group on 6-position has oxidative catalytic activity upon recognizing amyloid protein, that might lead to decomposition of amyloid.[2] We assumed that introduction of substituents with different electronic and/or steric nature in 2-(4-aminophenyl)-1,3-benzothiazole derivatives at 5- or 6-position might change their fluorescence wavelength, so might be possible to identify the accumulation state of amyloid protein by the change of fluorescence color. With the aim of developing a molecular probe with such a function, we synthesized a series of 2-(4-aminophenyl)-1,3-benzothiazole derivatives, and examined their changes in the fluorescence spectrum.

We selected methyl or methoxy group for electron-donating substituents, and nitro, boryl or halogen groups for electron-withdrawing substituents. 2-(4-Aminophenyl)-1,3-benzothiazole derivatives are synthesized from corresponding 2-aminothiophenol derivatives and 4-aminobenzoic acid derivatives by condensation reaction. Boryl group was introduced from corresponding halogen derivatives by palladium-catalyzed borylation reaction. Changes in UV and fluorescence spectra upon changing the position and the nature of substituents will be discussed.



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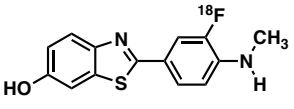

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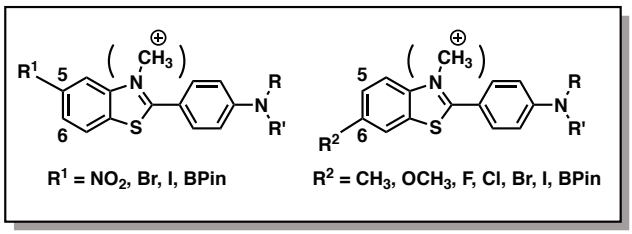

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3P-018

Concise Synthesis of Aspidospermidine from Spirocyclopropane through Ring-Opening Cyclization–Regioselective Alkylation Sequence

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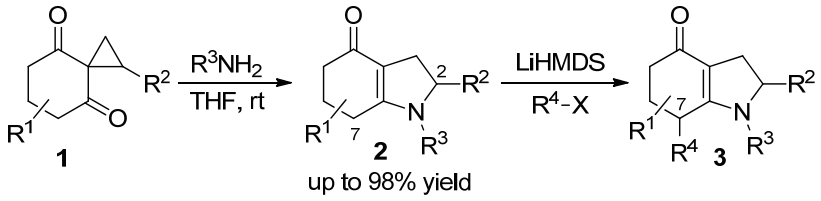
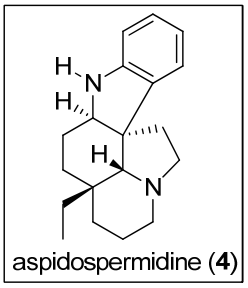
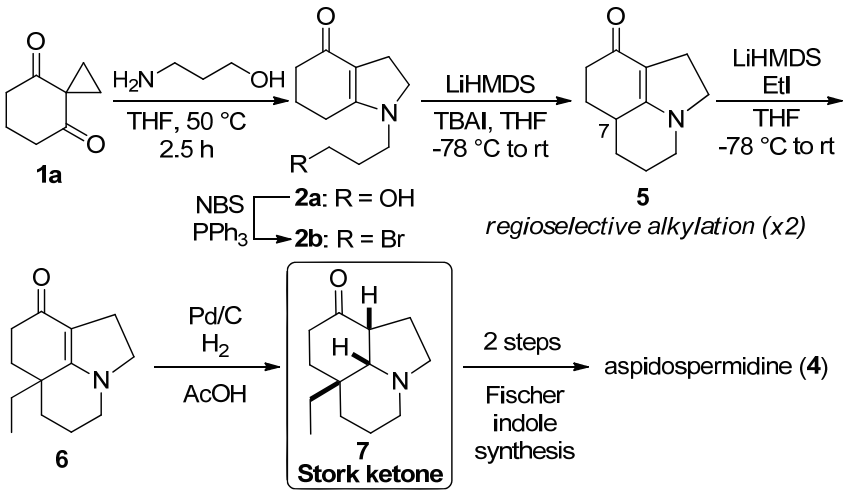
Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan

We previously reported a regioselective ring-opening cyclization of spirocyclopropanes **1** with primary amines to generate 2-substituted tetrahydroindol-4-ones **2** in up to 98% yield.[1] Furthermore, a regioselective alkylation of **2** at the C-7 position to **3** was achieved by using lithium hexamethyldisilazide (LiHMDS) as a base.[2] Herein, we report a concise route to *Aspidosperma* alkaloid aspidospermidine (**4**) using this sequential reaction.





Ring-opening cyclization of spirocyclopropane **1a**[3] with 3-amino-1-propanol proceeded smoothly to provide tetrahydroindol-4-one **2a** in high yield. After bromination of **2a**, intramolecular alkylation of **2b** using LiHMDS took place at C-7 to afford tricyclic product **5**. Introduction of ethyl group at C-7 was achieved by using intermolecular alkylation of **5** with ethyl iodide using LiHMDS to afford enaminone **6**. Stereoselective hydrogenation of **6** with a catalytic amount of Pd/C in acetic acid furnished the known Stork ketone **7**,[4] the key synthetic intermediate for *Aspidosperma* alkaloids. According to the previous work,[4] we completed total synthesis of **4** using Fischer indole procedure. Thus, the concise synthesis of **4** was achieved by using intra- and intermolecular regioselective alkylations.



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3P-019s

Stereoselective Synthesis of Actinoallolide A Furanone Fragment Using Rh(II)-Catalyzed *O*-Ylide Formation-Rearrangement Followed by C-H Amination

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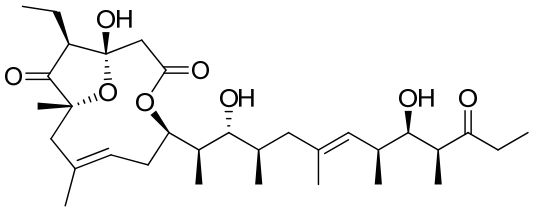
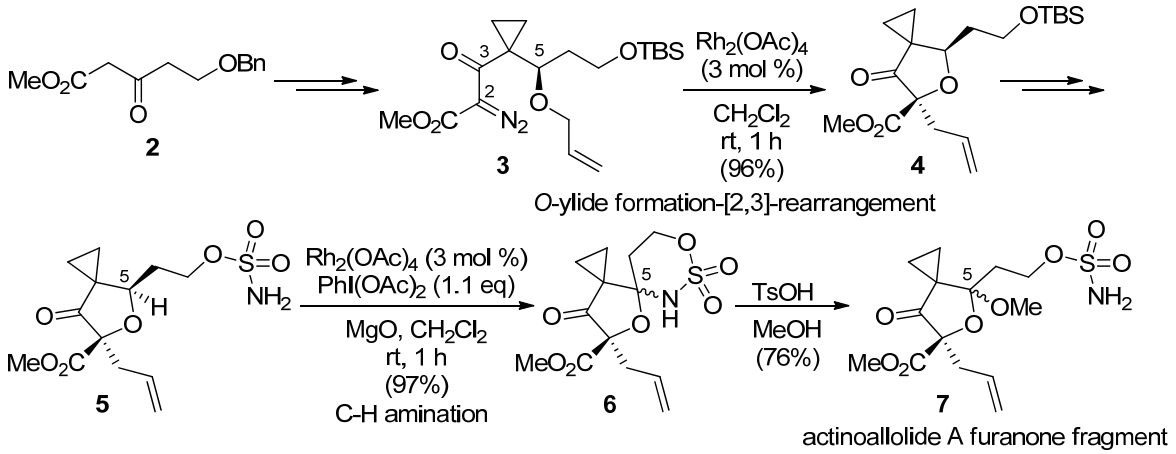
Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan



actinoallolide A (**1**)

Actinoallolide A (**1**), isolated from the cultured broth of *Actinoallomurus fulvus* MK10-036 by Ōmura, Sunazuka, and Iwatsuki, and exhibited a selective *in vitro* anti-trypanosomal activity without cytotoxicity.[1] The compound **1** was identified for the development of the drug for both sleeping sickness and Chagas disease. The structure of **1** has a 12-membered macrocycle including a highly substituted furanone skeleton. One of the key subjects in the total synthesis of this interesting natural product would be stereoselective constraction of the furanone system with a tetrasubstituted chiral center We herein report the preparation of the actinoallolide A furanone fragment by using rhodium carbenoid and nitrenoid chemistry.

Starting β-ketoester **2** was converted into 5-allyloxy-2-diazo-3-ketoester **3**, which has a cyclopropane moiety at C-4 position as an ethyl group equivalent. When **3** reacted with a catalytic amount of $Rh_2(OAc)_4$ in dichloromethane at room temperature for 1 h, stereoselective Rh(II)-catalyzed *O*-ylide formation−[2,3]-sigmatropic rearrangement[2] proceeded to provide tetrahydrofuran-3-one **4** as a single diastereoisomer in 96% yield. After leading to sulfamate **5**, oxidation of **5** at the C-5 position was achieved by employing $Rh_2(OAc)_4$-catalyzed C-H amination to generate spiro *N,O*-ketal **6**. Methanolysis of **6** under acidic conditions gave furanone fragment **7**.



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3P-020

Pyridyl and quinolyl methanols as valuable reagents for metal-free reductions of aromatic/heteroaromatic nitro compounds and imines

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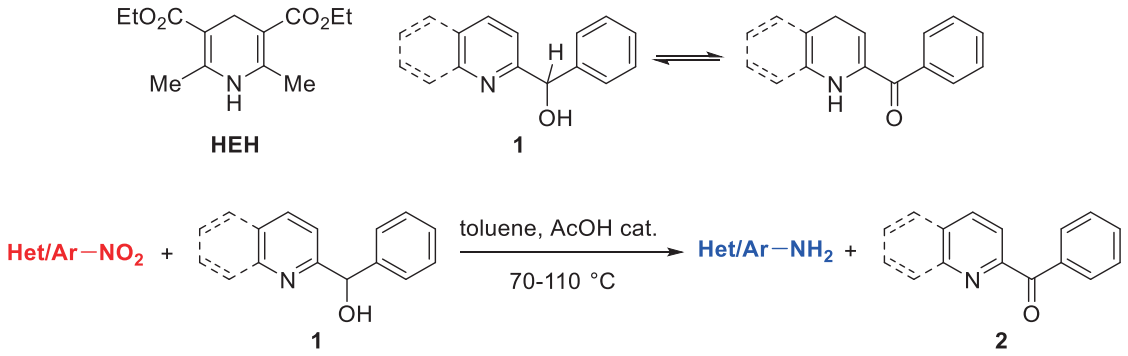
In the light of the great interest recently devoted to organocatalyzed transfer hydrogenation using Hantzsch ester (HEH) or other 1,4-dyhydropyridines, 2-pyridyl- and 2-quinolyl- methanols **1** were studied to evaluate their behavior as hydrogen donors. In particular, they showed a surprising reactivity in the metal-free reduction of aromatic and heteroaromatic nitro compounds to the corresponding amines.[1] The weak acidity of the 'picoline type' hydrogen atom in carbinols **1** is likely responsible for an easy access to 1,4-dihydropyridine forms certainly involved in the reduction process. On this ground, the low aromaticity of the quinolyl system with respect to the pyridyl one can justify a higher reactivity for the quinolyl carbinol allowing more efficient metal-free reductions of aromatic nitro compounds as well as activated imines.[2]



Ketones **2**, coming from oxidation of **1**, can be easily recovered and converted back to **1** by simple reduction, making possible the recycling of the reducing agent and ascribing the process to sustainable friendly reactions. Moreover, being HEH unable to reduce nitro compounds, carbinols **1** may play a complementary role in the panorama of metal-free reducing agents.

Mechanistic aspects as well as synthetic applications of these new reactions will be properly discussed.

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3P-021s

Concise Total Synthesis of Phenanthroindolizidine and Phenanthroquinolizidine Alkaloids

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Since phenanthroindolizidine and phenanthroquinolizidine alkaloids exhibit interesting biological activities, they have received increasing attention in the past decades. In addition to their interesting biological activities, these natural products display structural diversity; they possess the different number of methoxy groups around the phenanthrene ring and the different positions of the nitrogen atom in the indolizidine and quinolizidine rings, respectively. Thus, they have been considered synthetically challenging targets and many different synthetic routes have been developed. Despite these synthetic efforts, most previous approaches have been designed for the synthesis of each specific target molecule through an independent synthetic pathway, and there have been no general synthetic approaches to access these natural products. Thus, it is important to develop a novel synthetic route to approach the phenanthroindolizidine and phenanthroquinolizidine alkaloids with structural diversity.

Although these natural products exhibit the structural diversity, we recognized the structural similarity in these natural products.[1] Particularly, these two classes of natural products possess phenanthrene including a 1,2-dimethoxyphenyl ring structure, and have structurally similar pentacyclic skeletons, which could be constructed from the corresponding ortho-aza-terphenyl structures. Based on the structural similarity of these natural products, we envisioned that these natural products could be prepared via the iterative Suzuki-Miyaura reaction of three building blocks: aryl boronic acid, ortho-bromoaryl MIDA boronates, and pyridyl bromide with a suitable side-chain. In this poster presentation, we will describe the development of a general and concise synthetic route for phenanthroindolizidine and phenanthroquinolizidine alkaloids by the building block strategy.

[1] Jo, Y.-I.; Burke, M. D.; Cheon, C.-H. *Org. Lett*. **2019**, *20*, *ASAP*. DOI: 10.1021/acs.orglett.9b01397

3P-022s

Visible Light-Induced Sulfonylation/Arylation of Styrene Derivatives in a Double Radical Three-Component Photoredox Reaction

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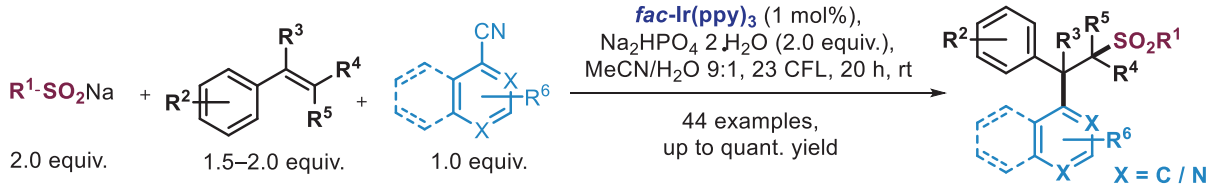
Multicomponent reactions (MCRs) are one-pot transformations of at least three substrates furnishing a product which ideally contains most of the atoms of the starting materials.[1] MCRs grant fast and easy access to scaffolds of elaborate molecular complexity.[2] They have thus become a paramount tool in drug discovery,[3] natural product synthesis,[4] heterocyclic chemistry,[5] and bioconjugation.[5]



A simultaneous sulfonylation and arylation of styrene derivatives was achieved in a photoredox-catalyzed three-component reaction under irradiation with visible light. The developed scalable reaction is wide in scope regarding all components and provides excellent yields. The method was also applied to the difunctionalization of biomolecules including peptides, carbohydrates and steroids and proceeds through a carefully designed and optimized sequence of radical formation and radical combination. It is among a very small number of double radical styrene-difunctionalizations which have been reported to date.[6-9] Usually, such transformations are achieved via a radical-polar crossover strategy in which the intermediate benzylic radicals are either oxidized or reduced prior to trapping.[10,11] As the limited portfolio of suitable nucleophiles and electrophiles is already well-explored, double radical strategies are highly desirable to expand the synthetic horizon of styrene-difunctionalizations.[6-9,12]

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3P-023s

Xylochemical Synthesis of Natural Products

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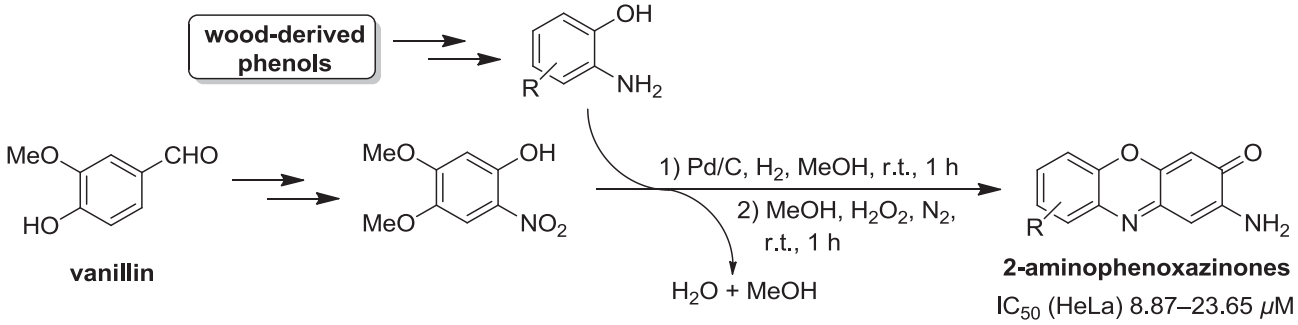
[b]*Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, 55128 Mainz, Germany.*
[c]*School of Chemical Engineering, University of New South Wales, Sydney NSW 2052, Australia.*

Today's starting materials for organic chemistry and in particular for the total synthesis of natural products are commonly derived from petrochemical resources. Due to the geological process of kerogenesis, they are poorly functionalized so that lengthy procedures are required to reintroduce heteroatoms and other chemical functionalities. We propose instead the use of biomass-based starting materials since they offer a higher degree of functionalization such as heteroatom substituents or stereocenters with defined chirality. Those chemical advantages add to the benefits of the sustainability of renewable resources.[1]
Herein, we present the use of wood-derived starting materials, the so-called xylochemicals,[2] for the synthesis of complex molecules in the form of 2-aminophenoxazinone-type natural products. In addition to the use of eco-friendly starting materials, we developed a new green oxidative coupling reaction to construct the 2-aminophenoxazinone nucleus.



With this approach, we were able to accomplish the first total synthesis of five natural products. Furthermore, the cytotoxic properties of these compounds were investigated and the results exhibit promising activities compared with established chemotherapeutic agents.[3]

[1] P. T. Anastas, J. C. Warner, *Green Chemistry Theory and Practice*, Oxford University Press, New York, **1998**.
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A new indole to benzoxazole rearrangement enabled by C-H borylation

Kirsty Anderson
Associate Professor Jonathan Sperry

Benzoxazoles are a class of aromatic compounds composed of a fused benzene and oxazole heterocycle. In particular, 1,3-benzoxazole with a 2-substituent are known pharmacophores and privileged structures in drug discovery due to a vast range of biological activity including antimicrobial, anticancer and antioxidant.[1] For example, caboxamycin[2] and nataxazole[3] are natural products containing the benzoxazole motif which exhibit cytotoxic activity through binding to metal ions in DNA and inhibiting human topoisomerase II; suvorexant[4] is a drug used to treat insomnia by working as an orexin receptor antagonist (Figure 1).

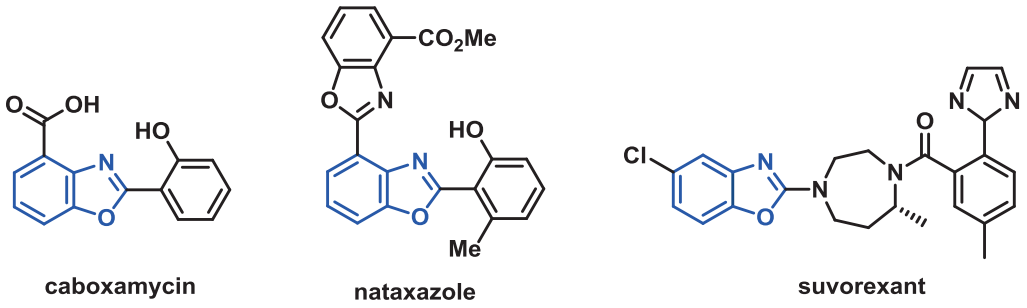
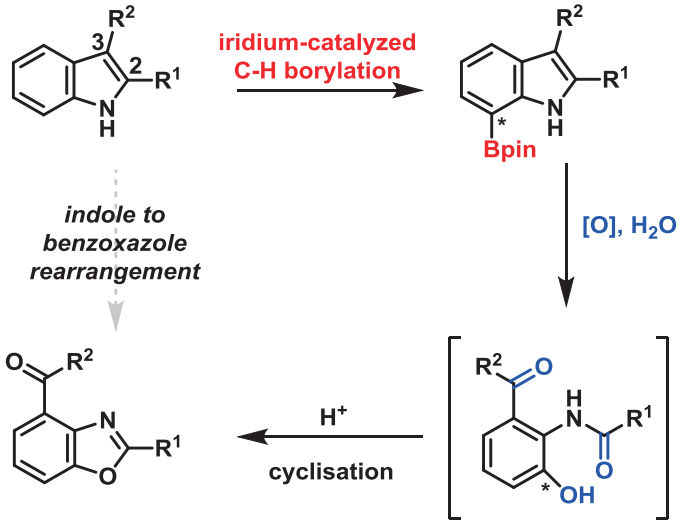


Figure 1: Examples of biologically active benzoxazole-containing molecules

Current methods to synthesise this important class of heterocycles are limited to cyclocondensation of *o*-aminophenols with carboxylic acid derivatives under relatively harsh conditions.[5] We envisage the straightforward conversion of commerically available indoles to benzoxazoles, utilising an iridium catalysed C7-borylation reaction followed by an oxidative hydrolysis/ring opening cyclisation cascade (Scheme 1).



Scheme 1: Conversion of 2,3-disubstituted indoles to benzoxazoles

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3P-025

CSTR Synthesis of Fairy Chemicals Using Fine Bubble and Flow Optimization Method

Nobuyuki Mase,* Keiya Matsuo, Takuya Kon, Junko Fujimoto,
Kohei Sato, Tetsuo Narumi, Kazuhiro Takeda
Research Institute of Green Science and Technology, Shizuoka University,
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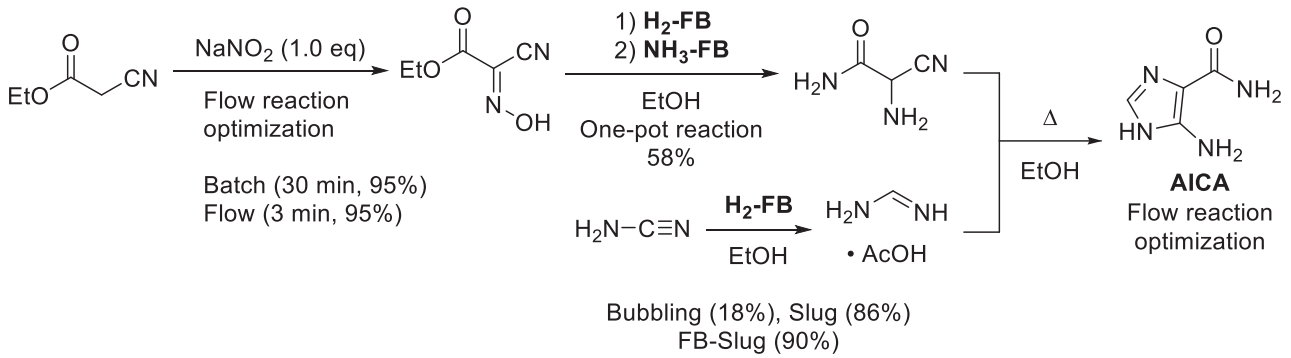
From a green sustainable chemistry (GSC) perspective, shifting from a batch process to a flow or continuous stirred-tank reactor (CSTR) process that can reduce waste and save energy is desired.[1] Reducing the number of post-treatment steps enables practical multi-step synthesis in the flow or CSTR method. The reaction involving the gas phase is a clean and simple initiated by simply injection of the gas, which can be stopped by removing the gas to save time for the post-treatment. In the present study, we report investigated improving the reaction efficiency by utilizing the fine bubbles (FB) by taking advantage of its excellent dispersibility and gas solubility in liquid reaction medium. In addition, we could conduct continuous reaction and post-treatment free reaction by identifying the reaction condition in the stoichiometric reaction to give the desired product in quantitative yield. We have previously developed a 9+4+1 method that combines design of experiments (DoE) and curved surface approximation using flow reactor.[2] Here, a new synthetic method of 5-aminoimidazole-4-carboxamide (AICA), which is an important intermediate of fairy compounds showing plant growth regulation,[3] was developed using FB and flow optimization method. As a result of applying the 9+4+1 method in the stoichiometric oximization, reaction conditions with a yield of 95% within 3 min residence time were identified in 14 experiments (180 min). Moreover, the H_2-FB hydrogenation reaction of the obtained oxime followed by the NH_3-FB amidation reaction of the ester could be carried out in a one-pot operation by readily changing the gas from H_2 to NH_3. Finally, AICA synthesis was achieved by H_2-FB hydrogenation reaction of cyano-group of cyanamide to imine and subsequent coupling reaction between amide and imine. All reactions except oximization were carried out in ethanol. Although a continuous process has not been achieved for all steps, a new synthetic scheme reported here has been established that significantly reduces the number of post-treatment steps.



[1] Fanelli, F.; Parisi, G.; Degennaro, L.; Luisi, R. *Beilstein J. Org. Chem.* **2017**, *13*, 520-542.
[2] Vámosi, P.; Matsuo, K.; Masuda, T.; Sato, K.; Narumi, T.; Takeda, K.; Mase, N. *Chem. Rec.* **2019**, *19*, 77-84.
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Preparation of Bicyclic Stannolanelactam via Radical Cascade Reaction

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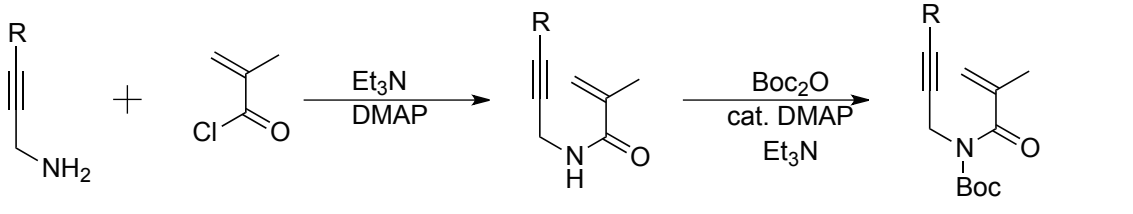
Radical cascade reactions provide efficient short-step synthesis for heterocyclic compounds. We have recently found a unique radical cascade reaction of chiral aza-1,6-enyne compounds triggered by tributyltin radical.[1] The reaction started by addition of tin radical to alkenyl site and the tin atom undergoes intramolecular radical substitution reaction by vinyl radical generated in the later stage of the cascade process. We thought that much simple precursor would progress a similar radical cascade and examined amide-type precursors, which is synthesized much shorter steps, for the reaction with tin radical. In this presentation, we will show one-step preparation of bicyclic stannolane-lactam from methacrylic enyne compounds.

The aza-1,6-enyne precursors **2** were readily prepared from propargylic amine and unsaturated methacryl chloride. Treatment of compound **2** with tributyltin hydride in the presence of catalytic amounts of AIBN at 80 °C resulted in the formation of desired bicyclic stannolane-lactam **3** in good yield. The reaction progressed smoothly when internal alkyne precursors such as **2b**, **2c**, **2d**, and **2e**, were employed, while terminal alkyne precursor such as **2a** gave poor yield of compound **3a**. The structure of the stannolane was confirmed by ^{13}C NMR spectra, which showed large ^{119}Sn-^{13}C and ^{117}Sn-^{13}C couplings between the vinylic and methylene carbons, supporting that stanollane structure was formed.

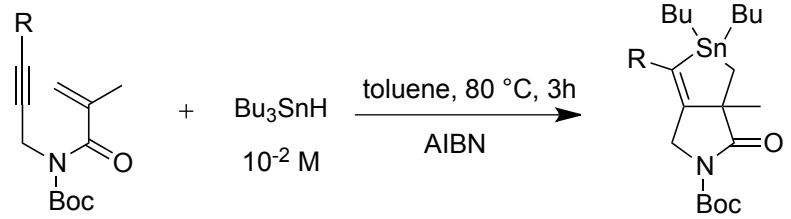


1

3a; R = H, 53%
3b; R = Me, 61%
3c; R = *n*-C_3H_7, 62%
3d; R = *n*-C_4H_9, 62%
3e; R = C_6H_{13}, 40%

2

4a; R = H, 94%
4b; R = Me, 60%
4c; R = *n*-C_3H_7, 81%
4d; R = *n*-C_4H_9, 54%
4e; R = C_6H_{13}, 82%



2 **3**

3a R = H, 16%
3b R = Me, 94%
3c R = *n*-C_3H_7, 75%
3d R = *n*-C_4H_9, 96%
3e R = C_6H_{13}, 92%

[1] Kamimura, A.; Ishikawa, S.; Noguchi, F.; Moriyama, T.; So, M.; Murafuji, T.; Uno, H. *Chem. Commun.* **2012**, *47*, 6592.

3P-027s

Synthesis of Hypervalent Iodine Reagents Bearing Cationic Heterocycles and Application to Oxidative Cyclization

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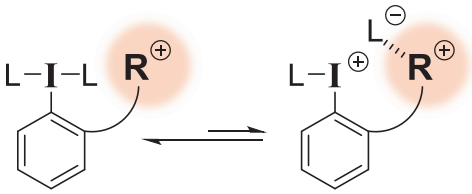
Hypervalent iodines are important oxidants in organic chemistry because they are metal-free reagents and their properties are controlled by organic ligands. However, controlling of reactivity depends on only electronic and steric effects of ligands [1]. In this study, we designed a new methodology employing an interaction of a nucleophile with an intramolecular cationic substituent (Concept).

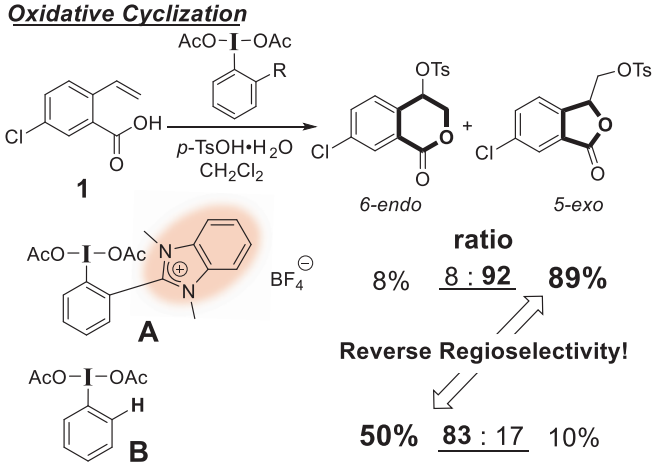
Concept



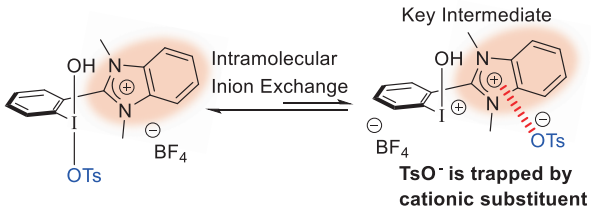
controll of reactivity of nucleophiles

We synthesized hypervalent iodines bearing a cationic nitrogen-containing heterocyclic moiety nearby the iodine center to control the reactivity by electrostatic interaction. The newly synthesized hypervalent iodine **A** caused 5-*exo* selective cyclization of 2-vinylbenzoic acids while typical iodobenzene diacetate **B** showed 6-*endo* selectivity (Oxidative Cyclization). These results suggested that the interesting reverse of the regioselectivity is ascribed to the cationic substituent. From NMR and UV-spectrum studies, it was found that nucleophilic TsO anion on iodine atom is trapped by cationic substituent which acts as an inhibitor to give Key Intermediate (Mechanistic Study).

Oxidative Cyclization



Mechanistic Study



[1] S. Ghosh, S, Pradhan, I. Chatterjee, *Beilstein J. Org. Chem.* **2018**, *14*, 1244.

3P-028

Gold(III)-Catalyzed Decarboxylative C3-Benzylation of Indole-3-carboxylic Acids with Benzylic Alcohols in Water

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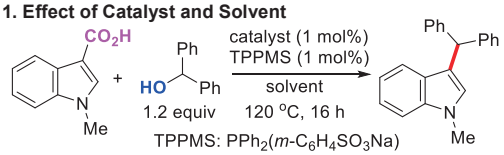
Funabashi, Chiba 274-8510, Japan

The indole scaffold is one of the most valuable synthetic targets since it is a common structural motif found in pharmaceuticals and functional materials. Therefore, a dehydrative coupling reaction for the direct introduction of diverse functionalities on indoles is gaining increasing interest. Recently, we developed a green and sustainable strategy for catalytic dehydrative C-C bond formation of indoles with benzylic alcohols.[1] Continuing our studies in the dehydrative coupling strategy, we envisioned its expansion to indole-3-carboxylic acids as a valuable coupling partner with its attractive features of low toxicity, high stability, and easy use. Recently, Miura *et al.* reported the Pd-catalyzed decarboxylative C3-arylation of 3-carboxyindoles with aryl bromides.[2]

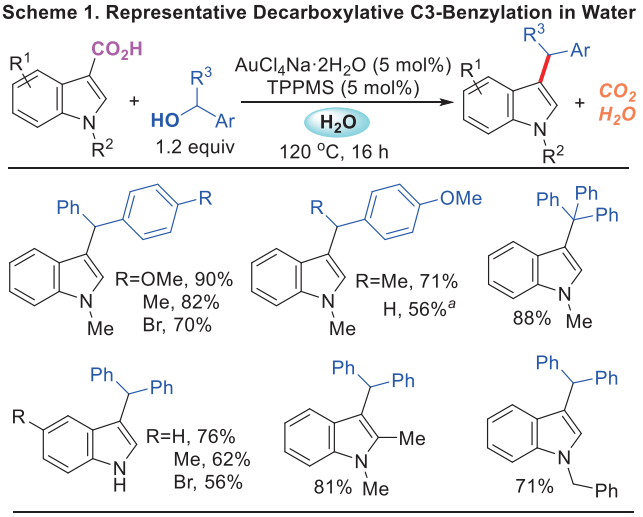
We herein present a strategy for the gold(III)-catalyzed decarboxylative and dehydrative coupling reaction of indole-3-carboxylic acids with benzylic alcohols in water (Table 1 and Scheme 1).[3] This cascade reaction is devised as a straightforward and efficient synthetic route for 3-benzylindoles in moderate to excellent yields. A Hammett study of the protodecarboxylation gives a negative ρ value, suggesting that there is a build-up of positive charge on the indole ring in the transition state. Furthermore, comparison of initial rates in H_2O and in D_2O reveals an observed kinetic solvent isotope effect (KSIE = 2.7). This simple protocol, which affords the desired products with CO_2 and water as the co-products, can be achieved under mild conditions without the need for base or other additives in water. To the best of our knowledge, this is the first example of using a gold(III) catalyst for the decarboxylative activation of carboxyindoles.

Table 1. Effect of Catalyst and Solvent



entry	catalyst	ligand	solvent	yield (%)
1	$NaAuCl_4{\cdot}2H_2O$	TPPMS	H_2O	61
2	$AuCl_4Na{\cdot}2H_2O$	TPPMS	DMF	0
3	HCl	none	H_2O	14
4	AuCl	TPPMS	H_2O	17
5	$CuCl_2$	TPPMS	H_2O	6
6	$PdCl_2$	TPPMS	H_2O	25
7	$FeCl_3{\cdot}6H_2O$	TPPMS	H_2O	18

Scheme 1. Representative Decarboxylative C3-Benzylation in Water



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[3] Hikawa, H.; Kotaki, F.; Kikkawa S.; Azumaya, I. *J. Org. Chem.* **2019**, *84*, 1972.

Intramolecular Hydroamination of *N*-Alkoxyamides under Blue LEDs Mediated Photoredox Catalyst Conditions

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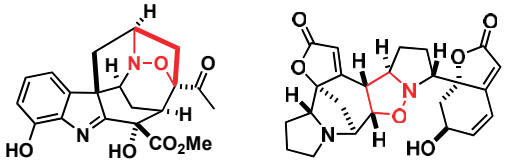
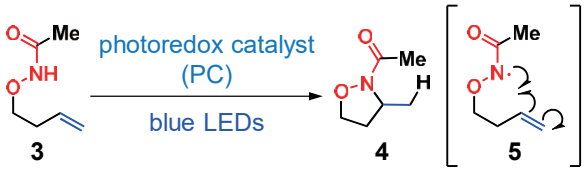
Tokyo Univercity of Agliculature and Technology,
Koganei, Tokyo 184-8588, Japan

The isoxazolidine moiety is the important building block for synthesizing natural products and biologically active molecules, such as Alsmaphorazine B (**1**) and Flueggine A (**2**) (Figure 1).[1] Recently, the visible light photoredox catalysis develops the direct transformation of an N-H bond into the nitrogen-centered radical under mild conditions. This high reactive *N*-radical is applied to the efficient construction of nitrogen-containing heterocycles. In this study, we attempted to examine the intramolecular hydroamination of *N*-alkoxyamides in the presence of a photoredox catalyst (PC) under blue LEDs irradiation to synthesize the isoxazolidines bearing an electron-withdrawing group on the nitrogen atom, which is difficult to obtain by classical methods (Scheme 1).



Alsmaphorazine B (**1**) Flueggine A (**2**)

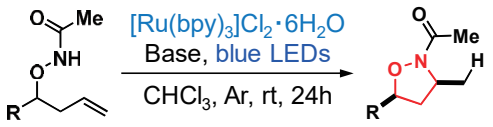
Figure 1. Representative natural products containing an isoxazolidine motif



Scheme 1. Intramolecular hydroamination of *N*-alkoxyamide **3** under blue LEDs mediated photoredox catalyst condition

We initially examined the photoredox cyclization reaction with *N*-alkoxyamide **6** in the presence of $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ (2 mol%) as a photoredox catalyst in chloroform (0.07 M) under irradiation (7 W) with blue LEDs using various bases (entries 1-3, Table 1). Within sodium hydroxide (2.0 equiv.) as a base, *N*-acetyl isoxazolidine **7** was obtained in 27% yield. Among the bases examined, potassium hydroxide gave the best results, and **7** was obtained in 38% yield (entry 2). Next, we performed the reaction at a lower concentration (0.01 M) than in entry 2. Under this condition, the yield was drastically improved and **7** was obtained in 61% yield (entry 4). With the optimal conditions in hand (entry 4), we next imvestigated the substrate scope for the photoredox cyclization of *N*-alkoxyamide **6** by varying an R group (entry 5-8). In all cases, *N*-acetyl isoxazolidine **7** was obtained in good yields.[2]

Table 1. Synthesis of *N*-acylisoxazolidine **7** from *N*-alkoxyamide **6**



entry	R	base	solv.(M)	yield(%)
1	Ph	NaOH	0.07	27
2	Ph	KOH	0.07	38
3	Ph	K_2CO_3	0.07	3
4	Ph	KOH	0.01	61
5	4-Me-C_6H_4	KOH	0.01	55
6	4-OMe-C_6H_4	KOH	0.01	66
7	4-Cl-C_6H_4	KOH	0.01	50
8	$(CH_2)_5CH_3$	KOH	0.01	78

[1] Berthet M.; Cheviet T.; Dujardin G.; Parrot I.; Martinez J.; *Chem. Rev.* **2016**, *116*, 15235-15283.
[2] Ishizuka H.; Adachi K.; Odagi M.; Nagasawa K.; *Bull Chem. Soc. Jpn.* **2019**, in press.

3P-030

Synthesis, Applications and Coordination Chemistry Study of water-tolerant organoantimony complexes

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Antimony has drawn considerable attention since Sb-containing compounds have a significant impact in the fields such as organic synthesis, catalysis, ligand chemistry and pharmaceutical chemistry. Over the past decades, there are significant progresses in the development of organoantimony chemistry. However, the problem of instability of Sb–C bonds and sensitivity to air and/or moisture severely restricts the applications of organoantimony complexes. The incorporation of a bidentate or tridentate ligand to the antimony center through the carbon atom of the aryl group as well as through the - intramolecular interaction with coordinate bond from donor atoms would result in organoantimony complexes with high stability and unique reactivity. Herein, I wish to present recent advances in applications of organoantimony complexes as water-tolerant Lewis acids and potential antineoplastic drugs by taking advantage of donor-acceptor interaction.[1-7]

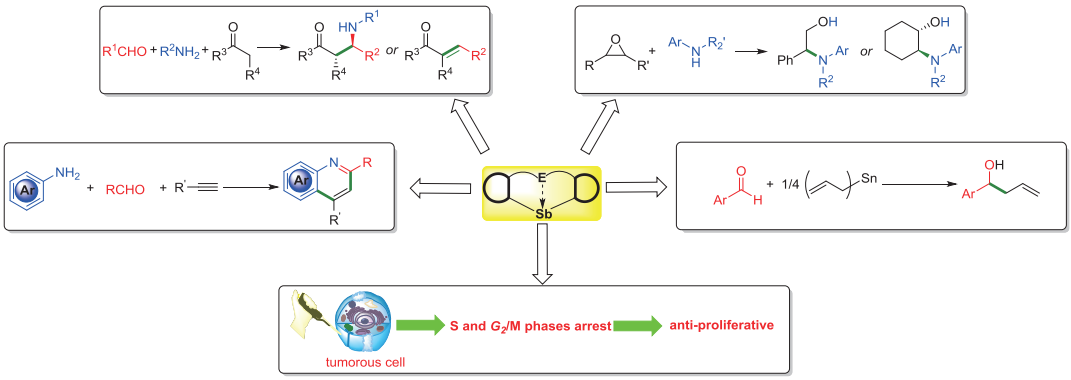

Figure 1. The applications of organoantimony complexes.

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3P-031s

Computational Study for the Selective Aromatic Nucleophilic Substitution on 4-Dimethylamino-2-methoxy-3-trifluoroacetylquinoline

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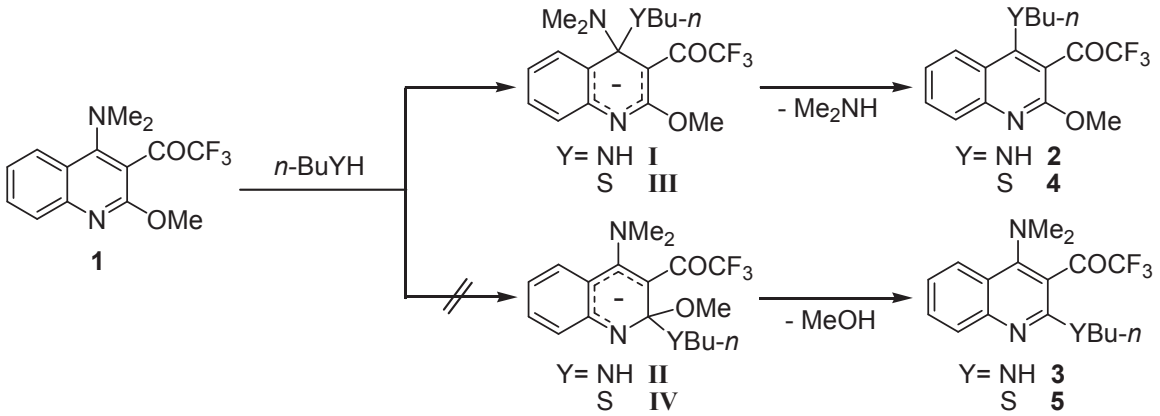
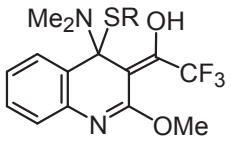
Kobe,Hyogo 657-8501,Japan

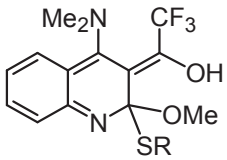
The nucleophilic aromatic substitution proceeds exclusively at the 4-position of 4-dimethylamino-2-methoxy-3-trifluoroacetylquinoline **1** by the reaction with various nucleophiles to give the corresponding *N*-*Y* exchanged products **2** and **4** solely, and no *O*-*Y* exchange reactions occur at the 2-position.[1,2]



Our DFT calculation study rationally explained the above unique selectivity on the substitution with amines based on the frontier electron densities (LUMO) of **1** and the relative stabilities of the Meisenheimer complexes **I**, **II** which are assumed to be formed as the intermediates on such substitution course.



III'



IV'

As to the substitution with thiols, in a reaction pathway from **1** to **III** and **IV** were required too much energies to make the reactions giving **4** and **5** proceed. In contrast, the processes from **1** to the intermediates **III'** and **IV'** were predicted to require much less energies than the cases from **1** to **III** and **IV**. The excellent selectivity affording the *N*-*S* exchanged products **4** solely is reasonably explained by much more stability of **III'** accessing **4** than **IV'** leading to **5**. It was also investigated about influences of the solvents on the present unique selective substitution with thiols by comparison with the analogous selective substitution on **1** using amine nucleophiles.

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3P-032

Fluorinated isoxazoles and isoxazolines: Synthesis, reaction and bioactive evaluation

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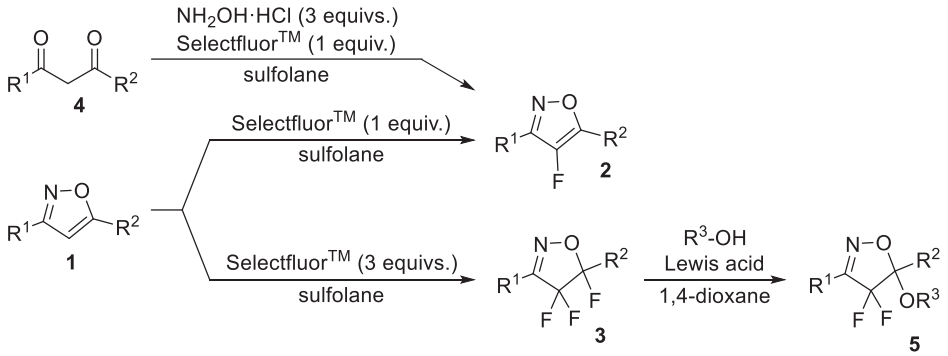
2) Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, UK

There is a continuing requirement for the synthesis of novel fluorinated heteroaromatic and heterocyclic systems, because many fluorinated pharmaceutical and agrochemical products have been reported containing these structural units, up to now. Among them, there are several researches of the synthesis, reaction and bioactive evaluation for fluorinated 6-membered heteroaromatic rings, but general methodology for the synthesis of fluorinated 5-membered heteroaromatic systems are rare. As part of a wider research program aimed to synthesize fluorinated heterocyclic systems, we reported a selective fluorination of pyrazoles to give fluorinated pyrazoles.[1, 2] In the expansion of this program, we herein report syntheses, reactions and bioactive evaluation of 4-fluorinated isoxazoles and fluorinated isoxazolines.

We recently reported a selective fluorination of isoxazoles (**1**) to give 4-fluoroisoxazoles (**2**) or 4,4,5-trifluorinated isoxazolines (**3**) using Selectfluor™, respectively (Scheme 1).[3] 4-Fluoroisoxazoles **2** were also synthesized from the corresponding β-diketones (**4**) via one-pot reaction. On the other hand, 4,4,5-trifluorinated isoxazolines **3** were easily converted to 5-hydroxylated or 5-alkoxylated difluoroisoxazolines (**5**) by treating with alcohols and Lewis acid.[4] To find the potential properties of fluorinated isoxazoles or fluorinated isoxazolines, we evaluated their bioactive properties, and a few fluorinated isoxazolines **3** or **5** were shown to have potent antifungal or miticidal activity.



Scheme 1. Syntheses and reactions of fluorinated isoxazoles.

[1] J. R. Breen, G. Sandford, D. S. Yufit, J. A. K. Howard, J. Fray, B. Patel, *Beilstein J. Org. Chem.* **2011**, *7*, 1048–1054.

[2] J. R. Breen, G. Sandford, B. Patel, J. Fray, *Synlett* **2015**, *26*, 51–54.

[3] K. Sato, G. Sandford, K. Shimizu, S. Akiyama, M. J. Lancashire, D. S. Yufit, A. Tarui, M. Omote, I. Kumadaki, S. Harusawa, A. Ando, *Tetrahedron* **2016**, *72*, 1690–1698.

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3P-033s

Synthetic Study of the C30–C63 Section of Karlotoxin 2

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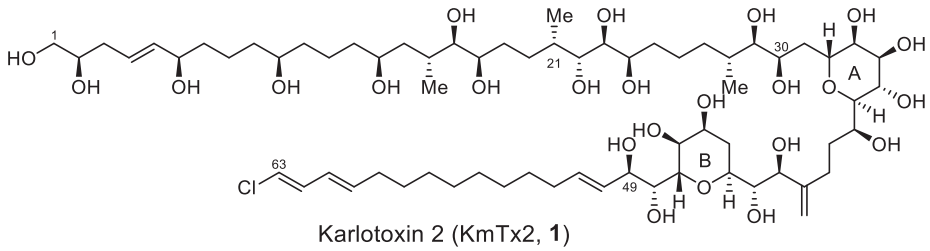
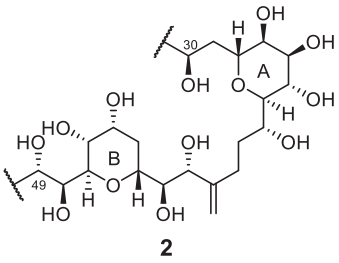
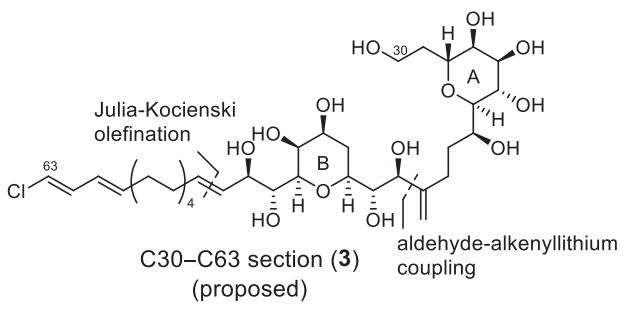
Fukuoka, Fukuoka 819-0395, Japan

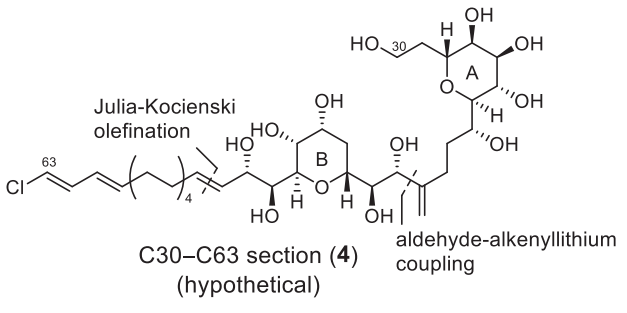
Karlotoxin 2 (KmTx2, **1**) is a cytotoxic natural product isolated from dinoflagellate *Karlodinium veneficum*. Although the stereochemistry of KmTx2 was determined by the JBCA method in 2010, the absolute configuration at C49 was revised in 2015 by caliculation using DP4 analysis.[1] Recently, we reported structural revision of amphidinol 3,[2] whose structure is similar to that of KmTx2, based on the chemical synthesis of partial structures. Therefore, we hypothesized that the absolute configuration of KmTx2 is to be revised as **2**.





To confirm the stereochemistry of KmTx2, we planned to synthesize the partial structure corresponding to the C30–C63 section of KmTx2. Both diastereomers, proposed (**3**) and hypothetical (**4**) structure, would be synthesized via aldehyde-alkenyllithium coupling and Julia-Kocienski olefination. Synthesis of the target compounds **3** and **4**, and comparison of the ^{1}H and ^{13}C NMR data with those of the natural product will be reported.





[1] (a) Peng, J.; Place, A. R.; Yoshida, W.; Anklin, C.; Hamann, M. T. *J. Am. Chem. Soc.* **2010**, *132*, 3277. (b) Waters, A. L.; Oh, J.; Place, A. R.; Hamann, M. T. *Angew. Chem., Int. Ed.* **2015**, *54*, 15705.

[2] Wakamiya, Y.; Ebine, M.; Murayama, M.; Omizu, H.; Matsumori, N.; Murata, M.; Oishi, T. *Angew. Chem., Int. Ed.* **2018**, *57*, 6060.

Acylative Desymmetrization of *meso*-1,3-Diols by Chiral DMAP Derivatives

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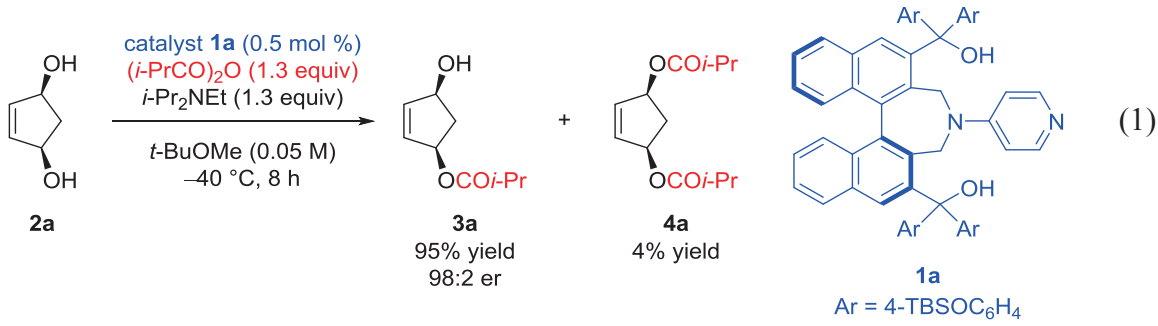
Enantiomerically pure 1,3-diols units are frequently found in various natural products including biologically active molecules. Enantioselective desymmetrization of *meso*-1,3-diols is one of the most useful and direct synthetic strategies to access such units. However, there are limited reports using organocatalysts to date, and problems of high catalyst loading and limitation of substrate scope remain to be solved.

Recently, we have developed highly active and enantioselective nucleophilic catalysts, binaphthyl-based *N*,*N*-dimethyl-4-aminopyridine (DMAP) for Steglich-type rearrangements,[1,2] acylation of various alcohols,[3–6] and dynamic kinetic resolution of azlactones.[7] Thus, we applied these catalysts to desymmetrization of *meso*-1,3-diols, and found that the reaction proceeded with only 0.5 mol % of catalyst **1a** to obtain the monoacylate **3a** in high yield with high enantioselectivity (95% yield, 98:2 er, eq 1). In this presentation, we report the details of optimizations of reaction conditions, substrate scope, and several control experiments for better understanding of the reaction mechanism.



[1] Mandai, H.; Fujii, K.; Yasuhara, H.; Abe, K.; Mitsudo, K.; Korenaga, T.; Suga, S. *Nat. Commun.* **2016**, *7*, 11294.
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[5] Mandai, H.; Yasuhara, H.; Fujii, K.; Shimomura, Y.; Mitsudo, K.; Suga, S. *J. Org. Chem.* **2017**, *82*, 6846.
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Synthesis of Silicon-Containing Fused Polycyclic Compounds by Consecutive Intramolecular Dehydro-Diels-Alder Reactions of Silicon-Tethered Tetraynes

Rikako Nagai,[a] Akihito Mitake,[a] Ayato Sekine,[a] Hideaki Takano,[a] Natsuhiko Sugimura,[b] Kyalo Stephen Kanyiva,[c] and Takanori Shibata[a,*]

[a] *Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, Shinjuku, Tokyo 169-8555, Japan*

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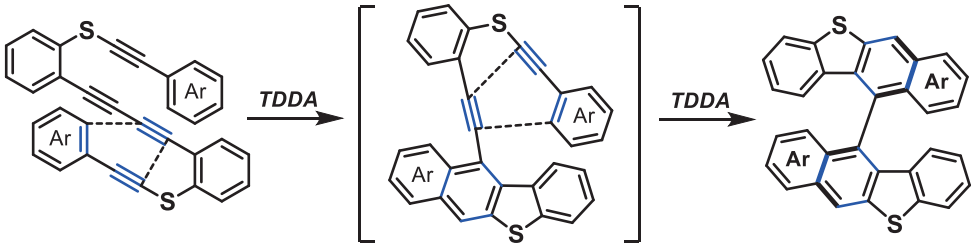
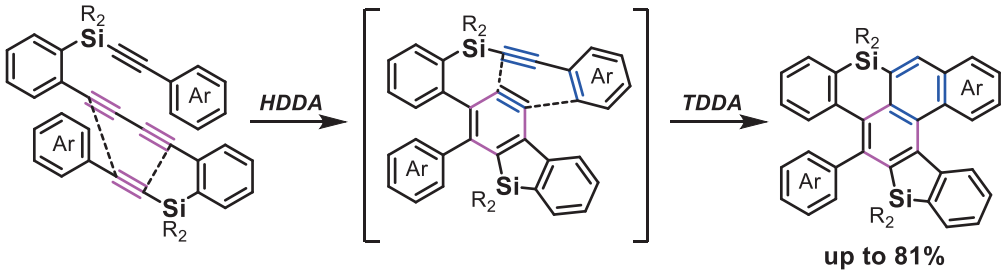
Dehydro-Diels-Alder reaction is [4+2] cycloaddition of alkyne-containing substrate(s) in place of the olefin(s). We already reported the consecutive intramolecular tetradehydro-Diels-Alder reactions of tetraynes having 1,3-diyne and *ortho*-phenylenethio moieties under heated conditions, and axially chiral bis(benzothiophene) derivatives were obtained.[1]



In this study, we examined thermal reaction of silicon-tethered tetraynes in place of sulfur. As a result, intramolecular hexadehydro-Diels-Alder reaction of 1,3-diyne and alkyne proceeded to give benzosilole-fuzed benzyne,[2] which further underwent intramolecular tetrahydro-Diels-Alder reaction with arylalkyne moiety. We disclose the scope of aryl moiety and the characteristic reactivity of obtained pentasilahelicene derivatives.[3]



We will discuss why silicon-tetherd tetraynes undergo HDDA reaction in place of TDDA reaction based on the DFT calculations.

[1] T. Shibata, A. Sekine, A. Mitake, K. S. Kanyiva, *Angew. Chem. Int. Ed.* **2018**, *57*, 15862.
[2] T. R. Hoye, B. Baire, D. Niu, P. H. Willoughby, B. P. Woods, *Nature* **2012**, *490*, 208.
[3] A. Mitake, R. Nagai, A. Sekine, H. Takano, N. Sugimura, K. S. Kanyiva, T. Shibata, *Chem. Sci. in press* (DOI: 10.1039/C9SC00960D).

3P-036

Isolation and Asymmetric Total Synthesis of New Biphenyl Quinolizidine Lactone Alkaloids from *Heimia salicifolia*

Mariko Kitajima, Haruka Kawabata, Taku Hirama, Tomomi Yanagisawa, Yasuka Yamaguchi, Noriyuki Kogure and Hiromitsu Takayama*

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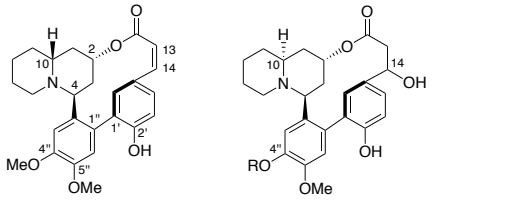
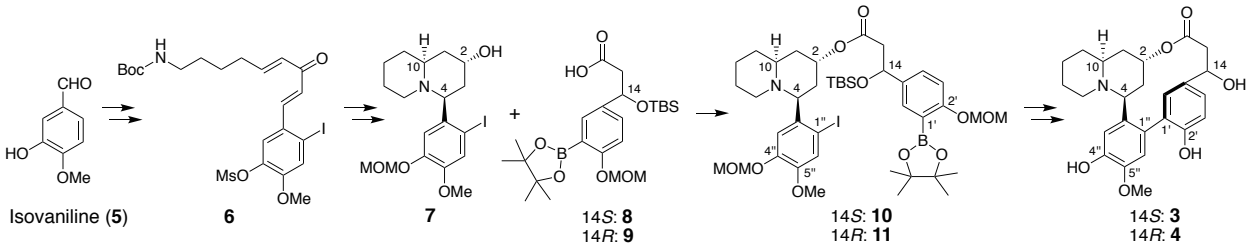
Heimia salicifolia (Lythraceae) is the main ingredient of the law-evading drug "sinicuichi", which produces psychoactive effects. This plant is known to contain biphenyl quinolizidine lactone alkaloids such as vertine (**1**) and lythridine (**2**), but the active principles responsible for the neurotropic effects and the mechanism of their action have not been clarified until now. In the course of our chemical studies on new and bioactive alkaloids, we investigated the alkaloidal constituents of *H. salicifolia*, resulting in the isolation of a number of new biphenyl quinolizidine lactone alkaloids including 4"-*O*-demethyllythridine (**3**) and 14-*epi*-4"-*O*-demethyllythridine (**4**).[1] To clarify the structures including the absolute configuration, the asymmetric total synthesis of **3** and **4** was carried out. Isovanillin (**5**) was converted to dienone **6**. Asymmetric intramolecular *aza*-Michael addition of **6** using the copper(I) alkoxide-chiral phosphine complexes as a chiral catalyst[2] constructed the chiral center at C-10 in good yield with high enantioselectivity. The resultant piperidine compound was converted to quinolizidine **7** with 2*S*,4*S*,10*S* configuration via the construction of quinolizidine ring, epimerization at C-4, and diastereoselective reduction of the ketone group at C-2. Condensation of **7** and chiral boronate ester **8** with 14*S* configuration or **9** with 14*R* configuration yielded ester **10** or **11**, respectively. Intramolecular Suzuki-Miyaura coupling of **10** or **11** followed by deprotection of MOM and TBS groups gave 4"-*O*-demethyllythridine (**3**) or 14-*epi*-4"-*O*-demethyllythridine (**4**), respectively. Synthetic **3** and **4** were identical in all respects with natural products, including optical rotation and experimental circular dichroism (ECD) data. Thus, the structures of **3** and **4** including the absolute configuration were confirmed.[3]





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[2] Shi, S.-L.; Wei, X.-F.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2012**, *134*, 17019.

[3] Kawabata, H.; Hirama, T.; Kogure, N.; Kitajima, M.; Takayama, H. manuscript in preparation.

3P-037s

Site-Selective Esterification of α- Hydroxyamides in Polyols by Metal Template Strategy

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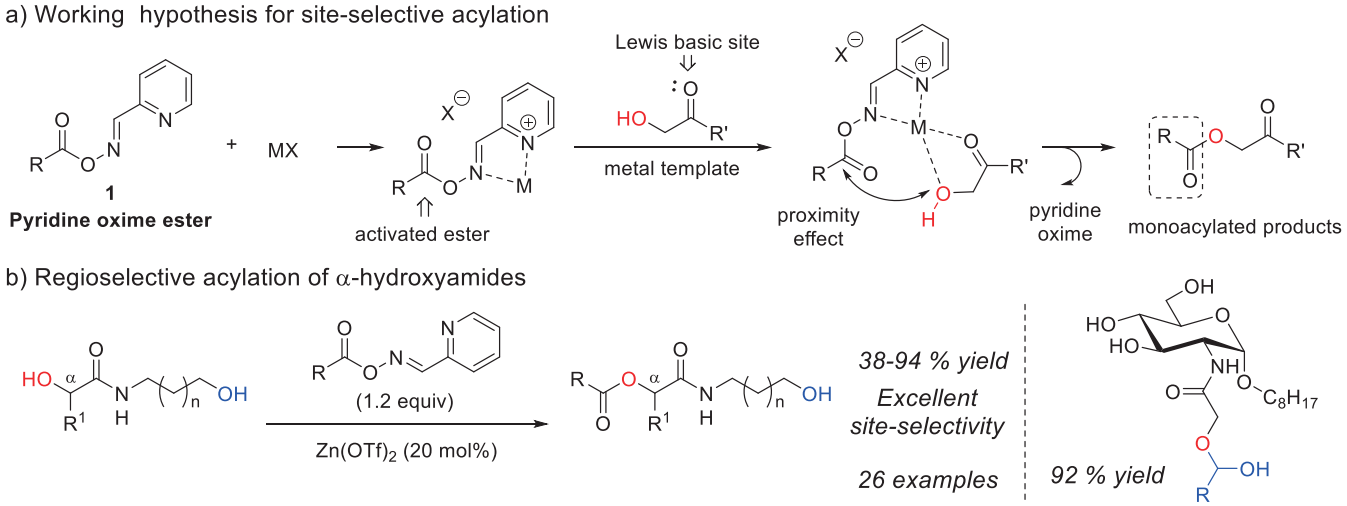
Carbohydrates remain important targets in various fields, such as synthetic organic chemistry and biochemistry because of their unique and specific bioactivities. They provide the core scaffolds for pharmaceutical agents and vaccines so that the chemical modification of carbohydrates should be highly important to create high value-added products. However, the differentiation of hydroxyl groups in complex molecules is a long-standing challenge due to requiring selective recognition of hydroxyl groups with very subtle steric and electronic differences. Although this research field has been widely studied, the current methods have limited ranges of applicable substrates respectively, so it is important to develop new methodologies for different ranges of substrates from the existing methods. We propose a new site-selective acylation procedure for α-hydroxyamides possessing other primary alcohols, such as seen in a variety of *N*-glycolyl amino sugars[1].



In this system, a catalytic amount of $Zn(OTf)_2$ acts as a key additive. Initially, the pyridine oxime ester **1** coordinates to $Zn(OTf)_2$ to form a complex. The cationic pyridinium moiety conjugated with the imine should activate the connected ester via an inductive effect. We envisioned that the metal complex attracted the hydroxyl group located in the vicinity of the amide preferentially to other hydroxyl groups due to its bidentate nature. The resulting metal complex can induce selective acylation to the coordinated hydroxyl group by the proximity effect. This metal template strategy showed excellent regioselectivity and good yield for various α-hydroxyamides. Efforts to further expand the substrate scope and the investigation of the mechanism are underway in our laboratories.

[1] Nishikawa, Y.; Takemoto, K.; Matsuda, K.; Tanaka, R.; Arashima, A.; Ito, K.; Kamezawa, Y.; Hori, Y.; Hara, O. *Org. Lett.* **2018**, *20*, 3367-3371.

Direct α-Heteroarylation of Heteroatom-Containing Aliphatic Compounds through a Radical Chain Mechanism

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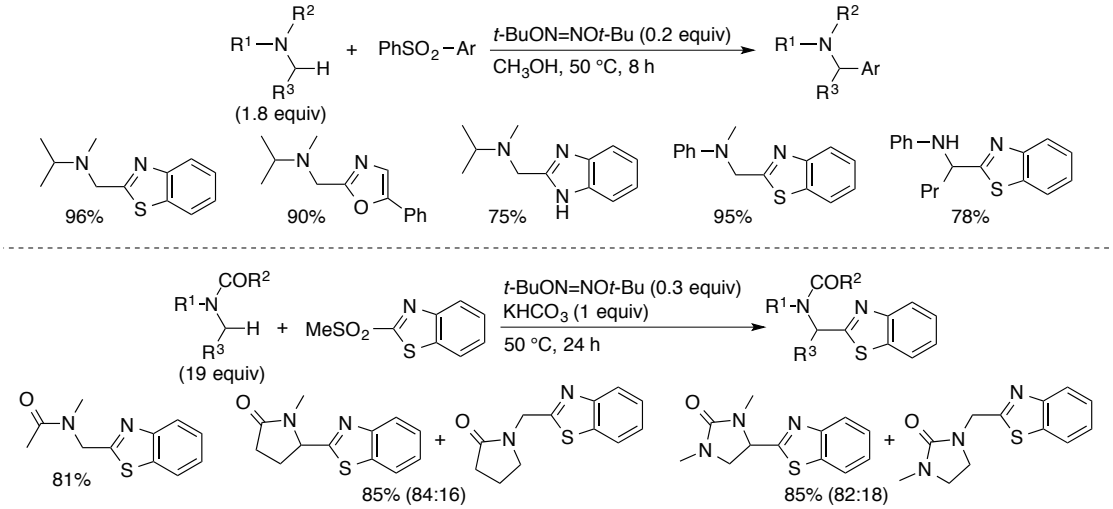
We have recently reported that alkylamines react with aryl halides in the presence of a stoichiometric amount of a *t*-BuO$^{\bullet}$ precursor to give α-arylalkylamines.[1] The reaction proceeds through a homolytic aromatic substitution (HAS) mechanism, consisting of addition of an α-aminoalkyl radical, generated through abstraction of α-hydrogen from an alkylamine by *t*-BuO$^{\bullet}$, to an aryl halide and elimination of the halogen radical (X$^{\bullet}$). However, a radical chain is not operative because termination through reduction of X$^{\bullet}$ into X^{-} by another molecule of the α-aminoalkyl radical is inevitable. The use of a leaving group that is sufficiently stable to leave as a radical and is sufficiently reactive to abstract a hydrogen from alkylamines makes a radical chain possible, and then we focused on a sulfonyl radical as a leaving group. Here we report direct α-heteroarylation of heteroatom-containing aliphatic compounds, such as alkylamines and alkylamides, with sulfonylheteroarenes in the presence of a substoichiometric amount of *t*-BuON=NO*t*-Bu through a radical chain mechanism.[2]

The reaction of 2-(benzenesulfonyl)benzothiazole with isopropyl(dimethyl)amine (1.8 equiv) and *t*-BuON=NO*t*-Bu (0.2 equiv) in methanol at 50 °C for 8 h gave (2-benzothiazolylmethyl)(isopropyl)(methyl)amine in 96% yield. The result that the yield exceeded the maximum amount (40%) of *t*-BuO$^{\bullet}$ generation shows the operation of a radical chain. The α-arylation with sulfonylheteroarenes is applicable also to alkylamides. For example, the reaction of 2-(methanesulfonyl)benzothiazole with *N*,*N*-dimethylacetamide (19 equiv) in the presence of *t*-BuON=NO*t*-Bu (0.3 equiv) and $KHCO_3$ (1 equiv) at 50 °C for 24 h gave *N*-(2-benzothiazolylmethyl)-*N*-methylacetamide in 81% yield.



[1] Ueno, R.; Ikeda, Y.; Shirakawa, E. *Eur. J. Org. Chem.* **2017**, 4188.
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3P-039s

Formal Synthesis of (−)-cephalotaxine via Proline Ester Enolate Claisen Rearrangement

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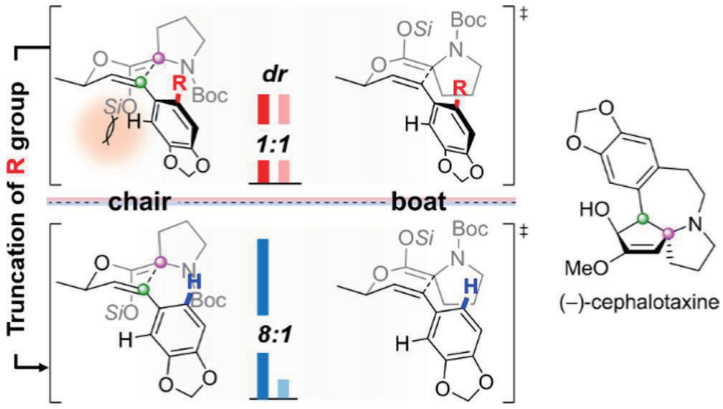
Cephalotaxus alkaloids exhibit potent cytotoxic activity against various human cancer cell lines.[1] Its azaspiranic tetracyclic backbone is structurally intriguing, which has attracted attention as a synthetic target for last three decades. Recently, we have achieved a concise formal total synthesis of (−)-cephalotaxine, a parent structure of *Cephalotaxus* alkaloids, via an ester enolate Claisen rearrangement (EECR). The EECR of α-amino acids has been utilized as a powerful strategy for the synthesis of complex nitrogen-containing molecules because this transformation can deliver densely functionalized amino acids with a defined stereochemistry.[2] A series of EECRs of proline allyl esters were examined to obtain the desired relative stereochemistry of an azaspiranic tetracyclic backbone. An unexpected reversal or low diastereoselectivity of (*Z*)-cinnamyl ester was observed. We discovered that the diastereoselectivity of EECR was shifted depending on the ortho-substitution pattern of the aromatic ring of the proline (*Z*)-cinnamyl ester substrate. This result represents a useful guide in aiding the prediction of stereochemical outcome of EECR of α-amino allylic esters.



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[2] Castro, A. M. M. Claisen Rearrangement over the Past Nine Decades. Chem. Rev. 2004, 104, 2939−3002.

3P-040s

Asymmetric synthesis of Cα-Quaternary Proline via Chirality Transfers: Application to the Total Synthesis of (–)-Amathaspiramide F

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Proline has been recognized as attractive substance in chemistry and biology owing to the distinct conformational properties. Thus, C→N→C chirality transfer strategy has been developed for the asymmetric synthesis of proline derivatives. However, the main limitation of this approach was the poor level of C→N chirality transfer. To overcome this circumstance, we decided to utilize conformationally restricted proline derivatives. Diastereomeric purity of quaternary ammonium salt was completely transferred to enantiomeric purity of α-carbon through [2,3]-Stevens rearrangement. An enantiopure synthesis of Cα-substituted prolines was successfully achieved via controlling the stereodynamics of proline by using a nitrogen-fused bicyclic system. This developed strategy was subsequently utilized in the total synthesis of (–)-amathaspiramide F.

Synthesis of Toxoflavin derivatives and Uracil derivatives

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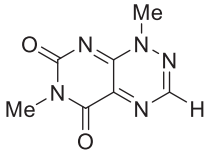
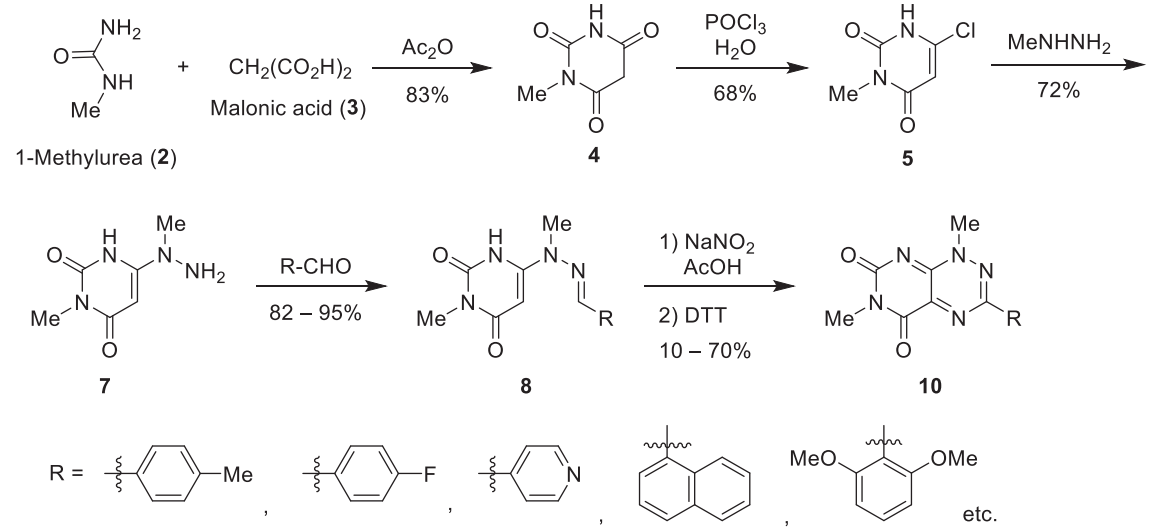
Toxoflavin (**1**) is one of a toxin produced by various bacterias including *Burkholderia gladioli.* This compound is known to have many useful physiological activity such as herbicidal activity, antiviral and anticancer. In this study, we focus on herbicidal activity and searched for molecules that is more useful as herbicides by synthesizing Toxoflavin derivatives.

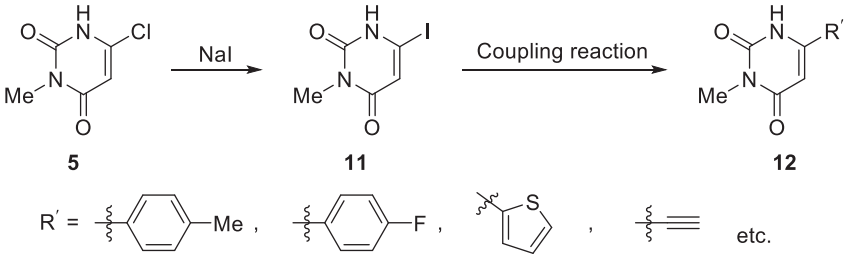


Toxoflavin (**1**)

Synthesis of pyrimidinetrione **4** was prepared by cyclization of 1-methylurea (**2**) and malonic acid (**3**) with acetic anhydride in 83% yield.[1, 2] The compound **4** was converted to the pyrimidinedione **5** by phosphorus oxychloride with small amount of water. Then, vinylchloride moiety of **5** was substituted by methylhydrazine to afford the amine **7** and subjected to imidation with various aldehydes to afford the imine **8** as good yields. Finally, cyclization of the imine **8** with $NaNO_2$/AcOH produced *N*-oxide, which upon reduction with dithiothreitol (DTT) afforded target molecules **10**.



In addition, we performed the synthesis from above key intermediate **5** to uracil derivatives **12**, which was known to have herbicidal activity.



[1] Mao, Y.; Tian, W.; Huang, Z.; An, J. *J. Heterocyclic Chem.* **2014**, *51*, 594-596.
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Total Synthesis of Diospyrodin

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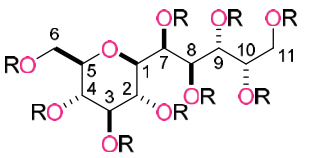
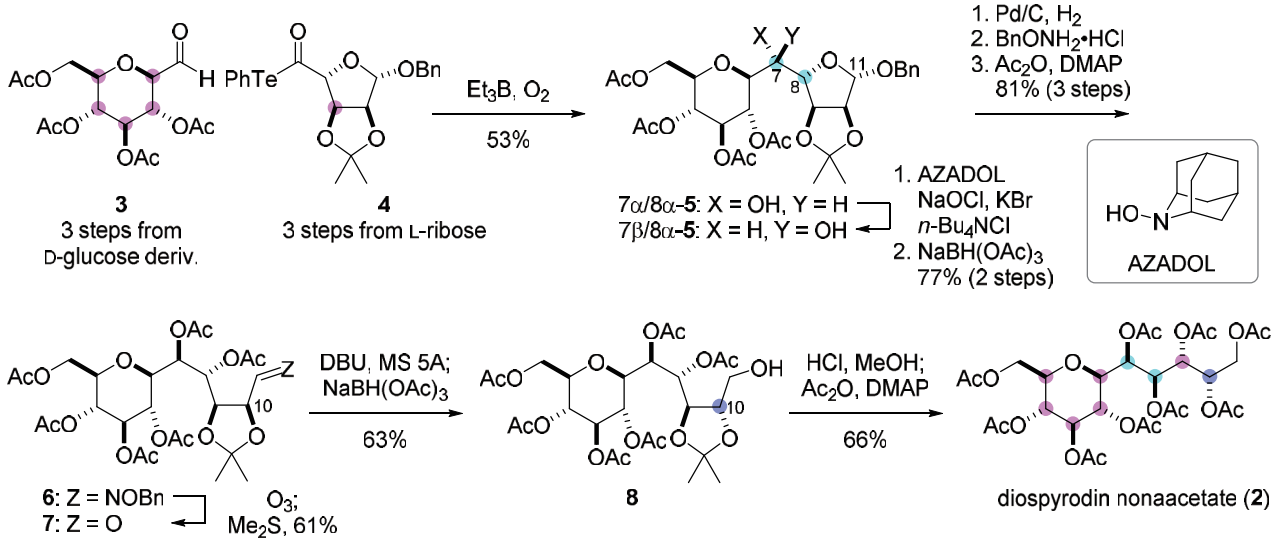
Graduate School of Pharmaceutical Sciences, The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033, Japan



Diospyrodin (**1**), the antibacterial natural product, was isolated from *Diospyros nigna*, a plant of the Ebenaceae family. Compound **1** is a unique *C*-glucoside with nine hydroxy groups and nine consecutive stereocenters. The optical rotation of the derivative of **1**, diospyrodin nonaacetate (**2**), was reported, but the absolute configuration has not yet been determined.[1] We devised a convergent strategy using addition of α-alkoxy carbon radicals to aliphatic aldehydes, achieved the total synthesis of **2**, and determined its absolute configuration.

First, aldehyde **3** and α-alkoxyacyl telluride **4** were prepared from D-glucose derivative and L-ribose, respectively, in three steps. Upon treatment with Et_3B and O_2, **3** and **4** were smoothly coupled to afford radical adducts 7α/8α-**5**.[2] Thus, we assembled the entire oxygenated carbon chain of **2** in one step. Alcohol 7α/8α-**5** was oxidized and the resultant ketone was reduced with $NaBH(OAc)_3$ to give the desired C7-diastereomer 7β/8α-**5**. Further three-step transformations from 7β/8α-**5** yielded oxime **6**. Then, oxidative cleavage of the C=N bond of **6** provided aldehyde **7**. Next, DBU-mediated C10-epimerization, followed by one-pot reduction of aldehyde converted **7** to **8**. Finally, removal of all the protecting groups of **8** in acidic conditions and acetylation of the nine hydroxy groups completed the total synthesis of **2**.

In conclusion, we have developed a novel radical-based synthesis of **2**. The present approach demonstrated the power and versatility of the radical reactions to realize the construction of highly oxygenated structures.



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3P-043s

Synthesis and Properties of Cup- and Bowl-shaped Cyclic Trilactams and Its Derivatives

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In order to build novel three-dimensional heterocyclic frameworks and to explore further functionalization, cup- and bowl-shaped cyclic trilactam derivatives, which are formed by complementary NH···O type hydrogen bonds are the good candidates to utilize the pore sizes. Here we report the synthesis and structural properties of two different chiral cyclic trilactams, the cup-shaped (**1**) and bowl-shaped (**2**) ones. **1** and **2** were synthesized via deprotection of *p*-methoxybenzyl (PMB) group from their corresponding derivatives[1,2]. Noteworthy is that the solubility of **1** and **2** are different. Bowl-shaped trilactam **2** was only soluble in highly polar solvent such as DMSO due to three lactam moieties at its peripheral positions. In contrast, cup-shaped trilactam **1** was dissolved not only in polar solvents but also in less polar solvents such as $CHCl_3$. X-ray single crystal analysis revealed that **1** formed the dimer structure by the formation of strong hydrogen bonds (Figure 1b). Further derivatization of **1** provided new cup-shaped compounds through $CuBr_2$-catalyzed *N*-arylation on amide moieties[2] (**3**)-(**5**) (Figure 1c). The unique capsule-like structure of cup-shaped **1** dimer as well as its derivatives may be the potential candidates to prepare the corresponding metal complex networks and/or porous materials.

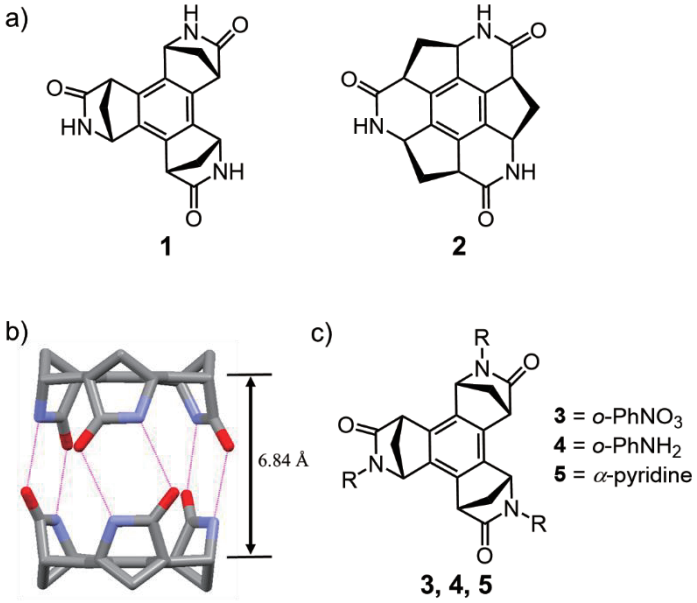

Fig. 1. a) Molecular structure of **1** and **2**. b) X-ray analysis showed dimer structure of **1**. c) Molecular structure of cup-shaped cyclic derivatives.

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3P-044

Total Synthesis of Antibiotic CJ-16,264

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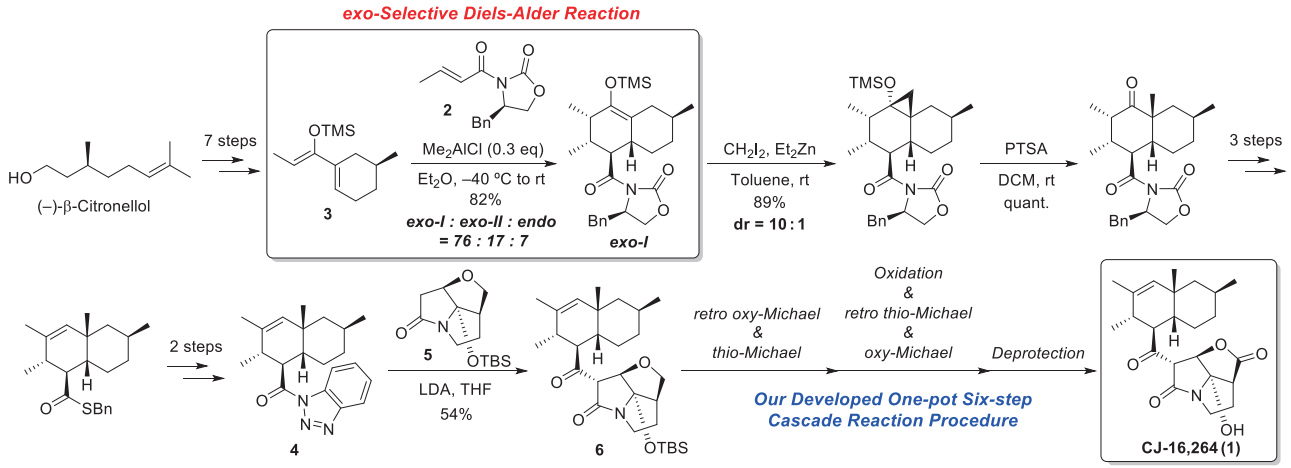
CJ-16,264 (**1**) is a unique naturally occurring tricyclic pyrrolizidinone, which was discovered in 2001 by the research group of Pfizer Inc. [1]. Compound **1** has received a lot of attention for its potent antibacterial activity against various multidrug-resistant strains. Nicolaou *et al*. reported the first total synthesis of **1** in 2015 [2]. The synthesis uses an effective an intramolecular Diels-Alder reaction involving a unique diolide-type precursor to construct the *cis*-decalin skeleton in **1**. To achieve a more efficient construction of this skeleton, we planned a novel synthetic strategy featuring an *exo*-selective Diels-Alder reaction between *N*-crotonoyl oxazolidone **2** and siloxydiene **3**, and the stereoselective introduction of the bridgehead methyl group. We have previously reported the total synthesis of UCS1025A, which contains a similar tricyclic pyrrolizidinone moiety [3]. Therefore, we envisaged that a new efficient total synthesis of **1** may be accomplished via a coupling reaction of independently synthesized *cis*-decalin fragment **4** and tricyclic lactam intermediate **5**. We initially investigated the above mentioned *exo*-selective Diels-Alder reaction, which was successfully carried out using Me_2AlCl in Et_2O as an effective catalyst system. Cyclopropanation of the silyl enol ether moiety and its subsequent ring-opening reaction proceeded stereoselectively to afford the desired *cis*-decalin intermediate. After the removal of the oxazolidone moiety via transformation into its corresponding thioester, reduction of the ketone and subsequent dehydrogenation, the fully elaborated *cis*-decalin fragment **4** was obtained. Fragment **4** was then coupled with tricyclic lactam intermediate **5** via a Claisen condensation reaction. The resulting α-acyllactam **6** was subjected to a one-pot, six-step cascade reaction procedure developed in our group to give the desired tricyclic pyrrolizidinone. Finally, a new efficient total synthesis of CJ-16,264 was successfully accomplished.



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Direct α-Heteroarylation of Alcohols with Heteroaryl Chlorides through a Radical Chain Mechanism

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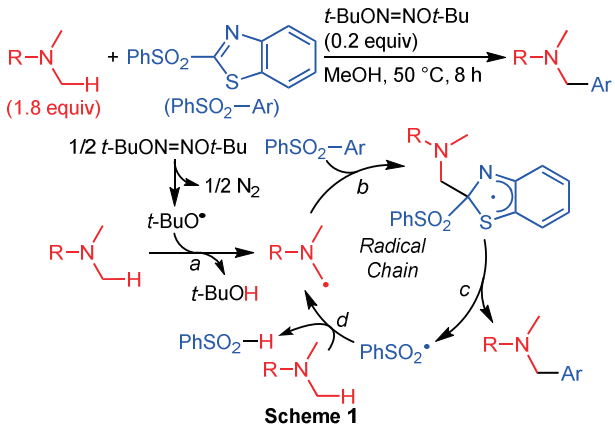
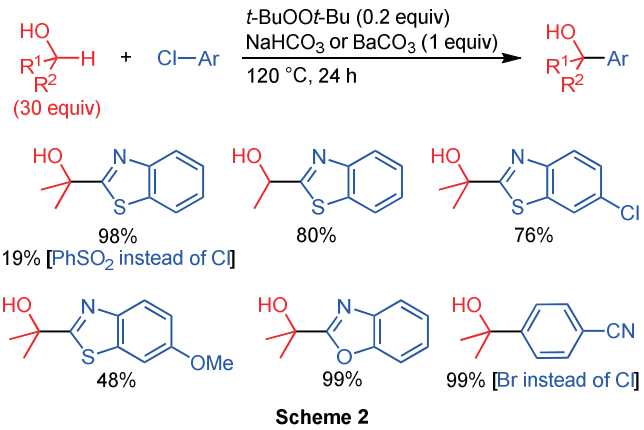
Direct introduction of an aryl unit to α-position of alcohols is one of the most straightforward methods to obtain α-aryl alcohols. However, only a few relevant reports are available in the literature.[1] On the other hand, we have reported the direct α-arylation of alkylamines using sulfonylarenes with the aid of a substoichiometric amount of a *t*-BuO$^{\bullet}$ precursor (Scheme 1),[2] proceeding through a homolytic aromatic substitution (HAS) mechanism consisting of abstraction of an α-hydrogen from an alkylamine by *t*-BuO$^{\bullet}$ (step *a*), addition of the resulting α-aminoalkyl radical to a sulfonylarene (step *b*), elimination of $PhSO_2^{\bullet}$ to give the α-arylation product (step *c*), and hydrogen abstraction from the alkylamine by the $PhSO_2^{\bullet}$ to propagate a radical chain (step *d*). Upon use of alcohols instead of alkylamines, step *d* does not proceed because $PhSO_2^{\bullet}$ is more stable than α-hydroxy radicals, and thus the radical chain would not work. We anticipated that use of heteroaryl chlorides makes the radical chain operative as unstable Cl$^{\bullet}$ can abstract an α-hydrogen of alcohols. Here we report the direct α-heteroarylation of alcohols using heteroaryl chlorides with the aid of a substoichiometric amount of a *t*-BuO$^{\bullet}$ precursor.

Treatment of 2-chlorobenzothiazole with *t*-BuOO*t*-Bu (0.2 equiv) and $NaHCO_3$ (1 equiv) in 2-propanol (30 equiv) at 120 ºC for 24 h gave 2-(2-benzothiazolyl)-2-propanol in 98% yield. The result that the yield exceeded the maximum amount (40%) of *t*-BuO$^{\bullet}$ generation indicates operation of a radical chain. As expected, use of 2-(benzenesulfonyl)benzothiazole scored a much lower yield (19%). This protocol is applicable to secondary and primary alcohols as well as 2-benzothiazolyl, 2-benzoxazolyl and electron-withdrawing group substituted phenyl halides.



Scheme 1



Scheme 2

[1] For examples, see: a) Twilton, J.; Christensen, M.; DiRocco, D. A.; Ruck, R. T.; Davies, I. W.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2018**, *57*, 5369; b) Niu, L.; Liu, J.; Liang, X.-A.; Wang, S.; Lei, A. *Nat. Commun*. **2019**, *10*, 467.
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3P-046s

Metathesis Reaction of Aryldimethylpropenylsilane

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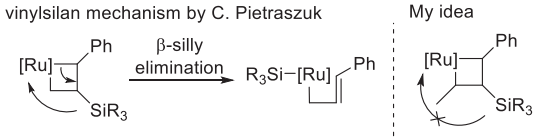
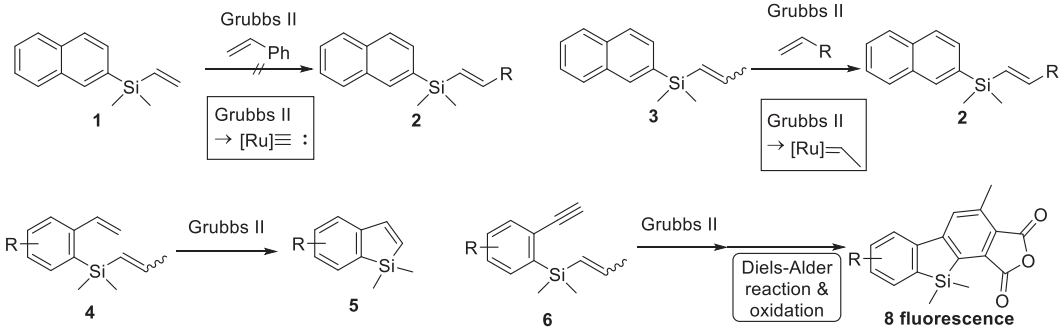
Silicon is different from carbon in several crucial aspects, for example, covalent radius and electronegativity. Thus, when a carbon atom is replaced with a silicon atom (the C/Si switch), the chemical and physicochemical properties of an organic compound are often dramatically changed. For example, the β-effect of silicon has the effect of stabilizing carbocations. This character is applied to Hosomi-Sakurai allylation and Peterson reaction. And as a functional molecule, it is used for medicine by improvement of lipid solubility, dyes utilizing the small difference of HOMO-LUMO and organic EL utilizing high electron acceptability of a silole ring [1]. However, there are few examples of synthetic methods for polycyclic silicon-containing compounds that are frequently used in the field of dyes and organic EL, it is limited to cyclization reactions using lithiation and so on [2].

The ruthenium carbene Grubbs catalyst, widely used in the synthesis of various heterocyclic compound, is a catalyst frequently used in metathesis reactions. However, metathesis reactions of hetero atom substituted olefins are difficult, and in particular, there have been no reports of metathesis reactions of trialkylvinylsilanes. Therefore, I set out to study an alternative metathesis reaction of trialkylvinylsilane with the aim of developing a new synthesis method for silicon-containing polycyclic compounds (three or more rings).

First, I tried cross metathesis reaction with vinylsilane **1** and styrene using a second-generation Grubbs catalyst, but the expected compound **2** was not obtained (Scheme 2). As the reason for this, Pietraszuk considered that β-silyl elimination occurs from rutenacyclobutane and the reaction stopped by the deactivation of the catalyst (Scheme 1) [3]. Therefore, I thought that it could be possible to suppress β-silyl elimination by introducing a substituent at the end of the vinyl group. In fact, as a result of examining various conditions using propenylsilane **3**, **2** was successfully obtained in 85% yield (Scheme 2). The method is also effective for ring closing metathesis reaction RCM, and benzosilole **5** was obtained from compound **4** in high yield. Furthermore, I succeeded in synthesizing a polycyclic silicon-containing fluorescent compound **8** from enyne compound **6** through one-pot enyne metathesis/Diels-Alder/oxidation.



Scheme 1. Proposed mechanism



Scheme 2. Metathesis of aryldimethylpropenylsilane

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3P-047s

Functionalization of Organic Azides *via* Generation and Reactions of Organolithiums bearing Masked Azides using Flow Microreactors

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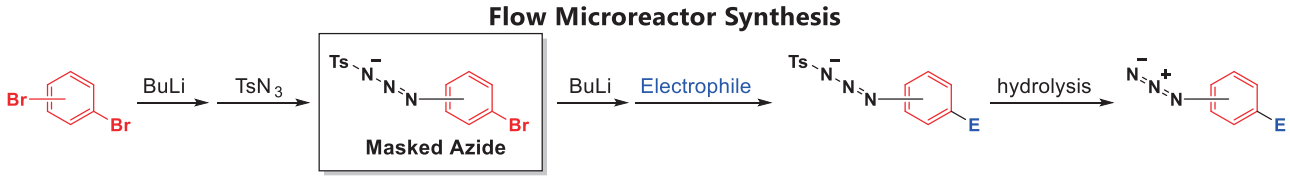
Organic azides are known as important targets and valuable intermediates in both organic and bioorganic chemistries. In particular, [3+2] cycloaddition of azides with dipolarophile such as alkynes and cyanides gives a wide range of heterocycles (1,2,3-triazoles, tetrazoles, *etc.*). Although late-stage incorporation of the azide group into aromatic rings have been utilized for generation of aryl azides, those conventional processes are often restricted because of poor functional-group compatibility and requirement of harsh reaction conditions.

We have developed flow microreactor chemistries, which are advantageous for reactions involving unstable reactive intermediates.[1] With flow microreactors, highly unstable organolithiums bearing electrophilic functional groups can be generated and be subsequently used before their decomposition by taking advantage of effective mixing and residence time control.[2] Although the flow microreactor system allows the generation and the reactions of aryllithiums with a broad range of functional groups, those of aryllithium species bearing an azide group were not achieved. Presumably it is due to the high reactivity of azide groups relative to aryl haride moiety.

In this presentation, we report "masked azide strategy," a novel approach for a generation of organolithiums bearing masked azides using flow microreactors. During the course of our present studies, we observed that tosyl triazene groups are more stable than azide groups for organolithium reactions. Since a tosyl group on the triazene moiety can be easily removed by hydrolysis, tosyl triazene salts work as synthetic equivalents of azides (masked azide). With this strategy, selectively lithiated dibromoarenes[3] were trapped with tosyl azide to generate the masked azide, whose subsequent Br-Li exchange reaction followed by a reaction with electrophiles gave a wide range of functionalized aryl azides after hydrolysis. The detail of those reactions and their synthetic utilities will also be discussed.



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3P-048s

Design, synthesis and biological evaluation of a novel library of antimitotic C_2-aroyl/arylimino tryptamine derivatives that are also potent inhibitors of indoleamine-2,3-dioxygenase (IDO)

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Abstract: C_2 substituted indole compounds are present in innumerable bioactive compounds, including pharmaceutical drug candidates and herbal remedies. Herein we have demonstrated a facile strategy to diversify C_2 position of indoles. Accordingly C_2-substituted tryptamines (C_2-aroyl/arylimino indoles and indole-diketopiperazine hybrids) were synthesized and screened for their inhibitory activity against tubulin polymerization, and also against proliferation of different cancer cell lines (A549 lung cancer, HeLa cervical cancer, MCF7 breast cancer and HePG2 liver cancer cell lines). A library was conceptualized were the design was inspired from natural products having antimitotic property. The molecular docking results indicated that C_2-substituted tryptamines compounds mimic the colchicin binding site in tubulin. They were synthesized by a unique iodine catalyzed oxidative ring opening reaction of 1-aryltetrahydro-β-carbolines and induced cytotoxicity on the cancer cells by disrupting the tubulin polymerization. They were found to be non-toxic for healthy cells. Immunofluorescence study for the most active molecules (between ~6 μM concentration) against A549 and HeLa cells demonstrated complete disruption and shrinkage of the microtubule structures.

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Oxidative Transformations of Alkenes Employing Azaadamantane-type Oxoammonium Salts

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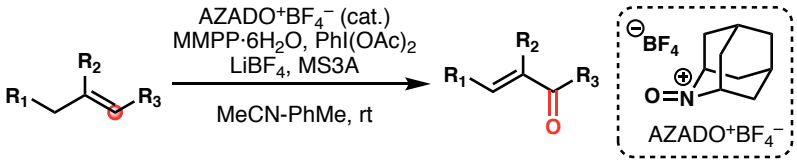
Alkene is an ubiquitous moiety in organic molecule and its selective transformation has been extensively investigated. Especially, oxidative transformation of alkenes gives synthetically useful molecules having oxygen or some other functionalities. Our research group has been focusing on a chemistry of azaadamantane-type nitroxyl radicals and its oxoammonium species, which act as an unique oxidant for various organic molecules (especially alcohols).[1] Herein, we describe novel oxidative transformations of alkenes employing these oxoammonium salts as a catalyst or reagent.

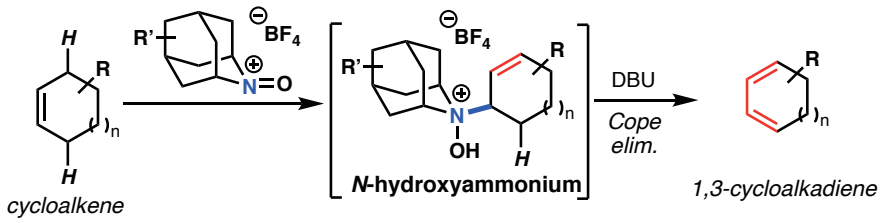
Allylic oxidation of alkenes is the most straightforward and ideal way to obtain enones. A direct oxygenation of the allylic position of alkene to give enones have been widely investigated and applied into complex molecule synthesis. Oxygenation of alkenes involving a migration of double bond (oxygenative allylic transposition) to give regioisomeric enones is also possible transformation but this have been rarely explored. We developed the oxygenative allylic transposition of alkenes into enones by using azaadamantane-type oxoammonium salt catalyst. This reaction system converts various tri- and trans-disubstituted alkenes into their corresponding enones with transposition of their double bond (**Scheme 1**). [2]

Scheme 1: Catalytic oxygenative allylic transposition of alkenes into enones with oxoammonium salt catalyst



During this project, we have unexpectedly found a new reactivity of oxoammonium species. Cycloalkenes was converted into 1,3-cycloalkadienes by treatment of azaadamantane-type oxoammonium salts. Mechanistic study revealed that an *N*-hydroxyammonium species formed in the reaction mixture and this was converted into 1,3-cycloalkadienes under basic conditions (**Scheme 2**). [3]

Scheme 2: Synthesis of 1,3-cycloalkadienes from cycloalkenes with oxoammonium salt



The detail of optimization of reaction conditions, substrate scope and mechanistic aspect of these transformations will be discussed.

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Synthesis of Metal-Free NIR Dye by One-Pot Ring-Closing Metathesis(RCM) /Oxidation/1,3-Dipolar Cycloaddition Reaction

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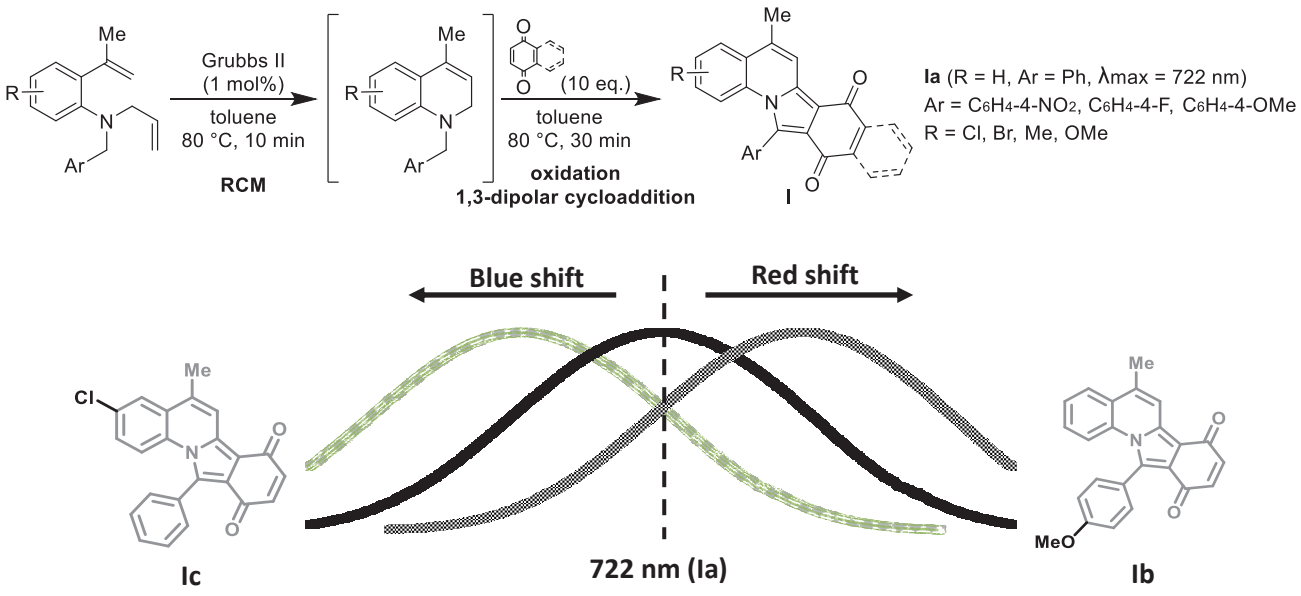
Near Infrared(NIR) absorption dyes which have maximum absorption wavelengths in NIR area have been attractive in industrial circles because they have been applied to CD-R and organic Els[1]. Recently, NIR dyes have been come into common use in bioimaging and photodynamic therapy so that NIR light can pass through our skins and leach to the deeper part of a biotissue than non-NIR area's light. The basic structures of these dyes, however, have been limited. That is why we tried to create new dyes which had new skeleton with high absorption or fluorescence. We previously developed a one-pot ring-closing metathesis(RCM)/oxidation/1,3-dipolar cycloaddition protocol, and we established a new skeleton, isoindolo[2,1-*a*]quinoline **Ia**, which is a NIR dye[2]. In this research, we aimed at better understanding the relationship between R and Ar substitutions and photoproperties.

We synthesized several analogues of compound **I** and investigated the absorption profiles of them. The maximum absorption wavelength was red-shifted when Ar has electron donating group (**Ib**). When we introduced electron withdrawing group as R, it was blue-shifted (**Ic**). We are going to show fluorescence feature of these analogues and change of maximum absorption wavelength by solvent[3].



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Design and Synthesis of Conformational Restricted Acetogenin Derivatives with *Fused*-bis THF Skeleton

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Acetogenins[1] are powerful inhibitors of complex I in mitochondrial electron transport systems. In addition, they are potent inhibitors of NADH oxidase of the plasmamembranes of cancer cells. These actions decrease cytosolic ATP production, then make cancer cell lead to apotosis.

In Miyoshi's research, the IC_{50} of acetogenin derivatives **1** with bis-THF rings was 280 nM in using the inhibition of complex I activity determined by NADH oxidaze assay.[2]

Bis-THF acetogenins have two THF rings united by single bond, so side-chains can move freely and flexibly. On the other hand, acetogenin derivatives are reported to make an internal chelation between THF rings and intracellular cation such as Ca^{2+}, which causes side effect. Lower calcium-chelation ability will display lower cytotoxicity.[3] In this back ground, we made a hypothesis that side effect may be related to chelating cation. In the presentation, we will discuss about design and synthesis acetogenin derivatives (**2-5**) in Figure 1, whose synthetic key intermediates having *trans,-trans fused*-bis THF skeleton was obtained by interarmolecular double bromoetheration developed in our laboratory.[4]

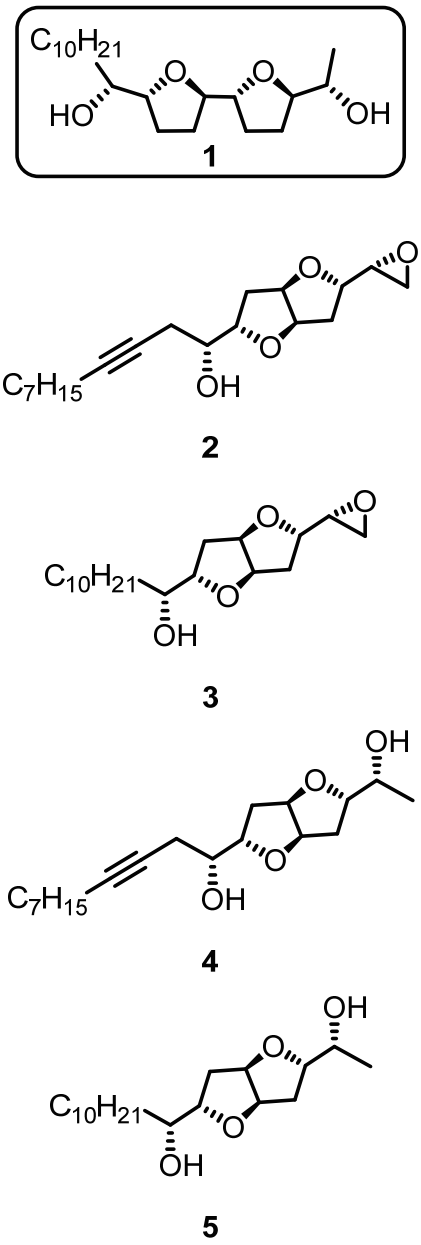

Figure 1.

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Cobalt-Catalyzed Acylation-Reactions of (Hetero)arylzinc Pivalates with Organic Thiopyridylester Derivatives

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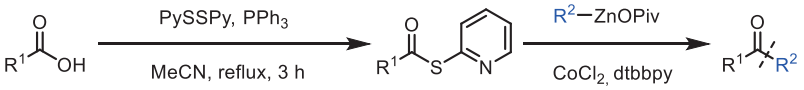
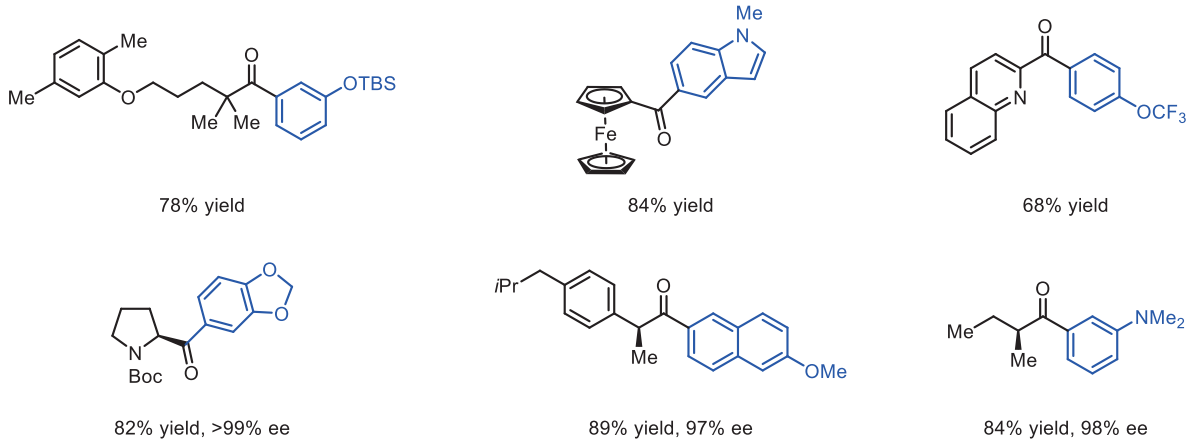
The carbonyl group is a central motif in organic chemistry. The performance of acylation reactions using organometallic reagents represents a general access to various ketones. A major drawback of these reactions is a restricted chemoselectivity and the use of expensive or toxic transition-metal catalysts. Whereas acid chlorides are broadly available acylating agents, their preparation requires harsh conditions, and thus lowering the functional group tolerance. Alternatively, thioesters readily react with organozinc halides in the presence of a palladium catalyst.[1] Recent advances have shown that solid arylzinc pivalates, displaying an enhanced stability towards moisture and air, are especially suited to undergo cobalt-catalyzed reactions.[2] We have developed a new cobalt-catalyzed synthesis of a variety of polyfunctional ketones by the acylation of aryl- and heteroarylzinc pivalates with various *S*-pyridylthioesters[3]. Furthermore, this cobalt-catalyzed acylation allows the preparation of several α-chiral ketones with very high stereoretention.[4]





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Stereoselective Cobalt-Catalyzed Cross-Couplings of α-Bromocarbonyl Compounds

Maximilian S. Hofmayer, Alisa S. Sunagatullina, Lucie Grokenberger, Ferdinand H. Lutter, and Paul Knochel*

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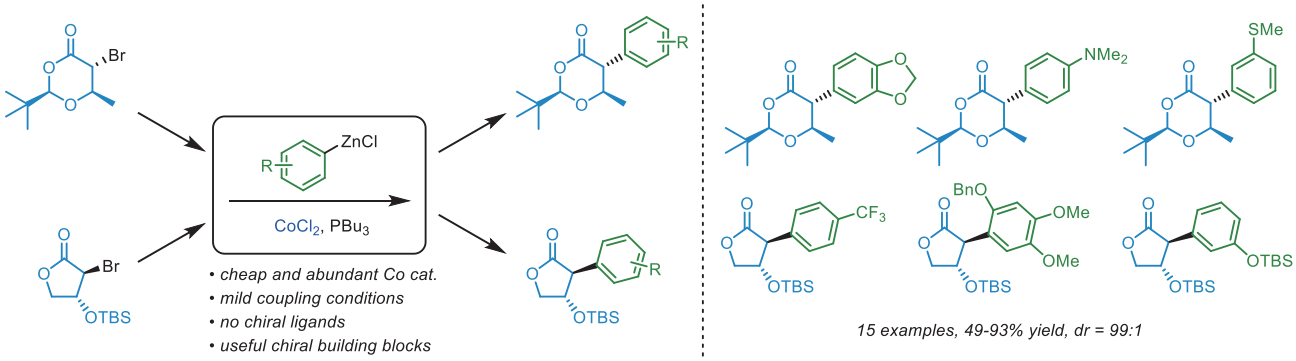
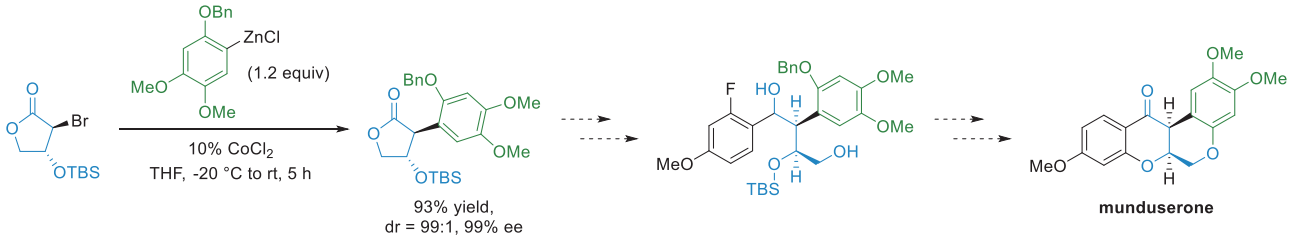
Transition metal-catalyzed C-C-bond forming reactions are valuable tools in organic synthesis. Pd- and Ni-complexes are most frequently used due to their high catalytic activity. However, drawbacks result from their high price, reasons of toxicity or a limited scope. Especially for couplings involving alkyl halides, decomposition of alkyl-metal intermediates via β-hydrogen elimination often occurs for Pd- and Ni-species.[1] These limitations can be circumvented by using Cobalt-catalysis.[1]

Zinc organometallics represent excellent reagents for cross-couplings, as a broad variety of sensitive functional groups is tolerated. Therefore, aldehydes, ketones, esters, and lactones can be employed in these Negishi-type couplings.[2]

Recently, we have developed a stereoselective cobalt-catalyzed cross-coupling reaction, involving arylzinc chlorides and chiral α-bromo substituted lactones.[3] The stereoinformation is controlled by the substitution of the cyclic bromides. This allows the efficient synthesis of valuable chiral building blocks for organic syntheses.



The synthetic value of this stereoselective cross-coupling can be demonstrated in the total synthesis of munduserone. This naturally occurring isoflavone belongs to the class of rotenoids. Many of them show insecticidal, pesticidal and biological activity.[4] This approach could allow the access to a broad range of optically active rotenoids as potential drug candidates.



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Novel Difluoropropargylation of Alcohols and Ketones with Difluoropropargyl Dicobalt Complexes; Access to Various Cyclic *a*-Fluoroethers

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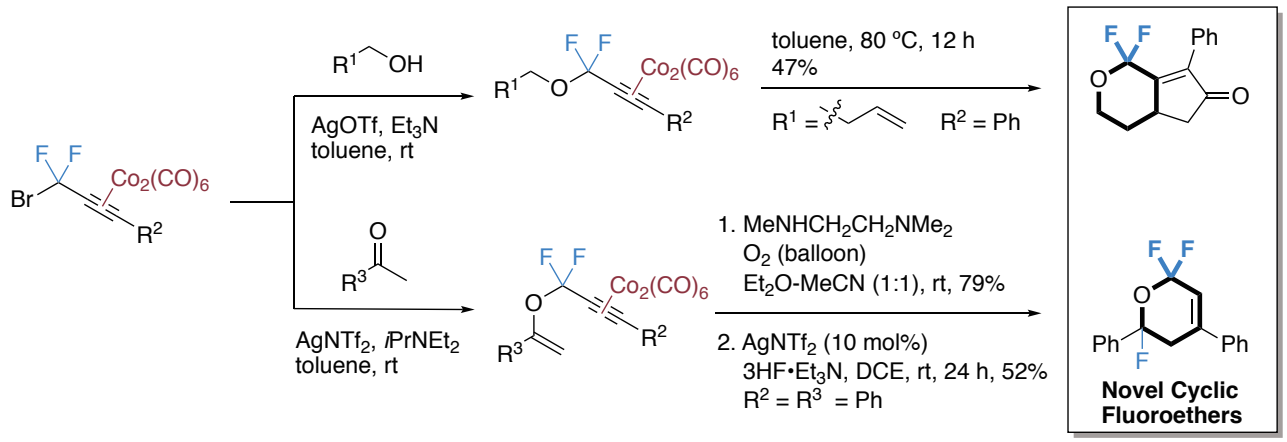
[b] *Institute of Medicinal Chemistry, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan*

Fluorine has been recognized as an indispensable element in medicinal chemistry because it enhances metabolic stability and improves membrane permeability of organic compounds. Therefore, various reactions have been developed to introduce fluorine or a fluoroalkyl group not only on carbon atoms but also on heteroatoms. [1]

Cyclic ethers are commonly found in bioactive molecules. Thus, novel methods to synthesize cyclic fluoroethers would be useful for drug development. However, such methods are limited.[2] Recently, we developed difluoropropargylation reactions of alcohols and ketones using bromodifluoropropargyl dicobalt hexacarbonyl complexes.[3] These complexes react with alcohols and ketones to give corresponding ethers and enol ethers in highly chemoselective manner. We also found that these fluoroethers and fluoroenolethers could be used to synthesize novel cyclic fluoroethers.

In this presentation, we will present the synthesis of various difluoropropargyl ethers as well as their application to the synthesis of various cyclic fluoroethers using Pauson-Khand reaction and metal-catalyzed cyclization.



[1] (a) C. Li and J. Hu, *Synthesis,* **2014**, *46*, 842-863. (b) C. Li, M. Hu and J. Hu, *Chem. Rev.*, **2015**, *115*, 765-825.

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[3] Manuscript in preparation

Palladium-catalyzed Stereoselective *Csp*^{3}-*Csp*^{2} Cross-Couplings of Chiral Secondary Alkylzinc Reagents with Alkenyl and Heteroaryl Halides

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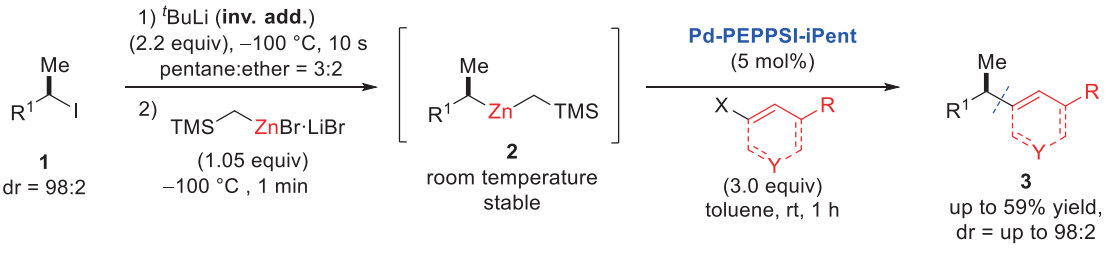
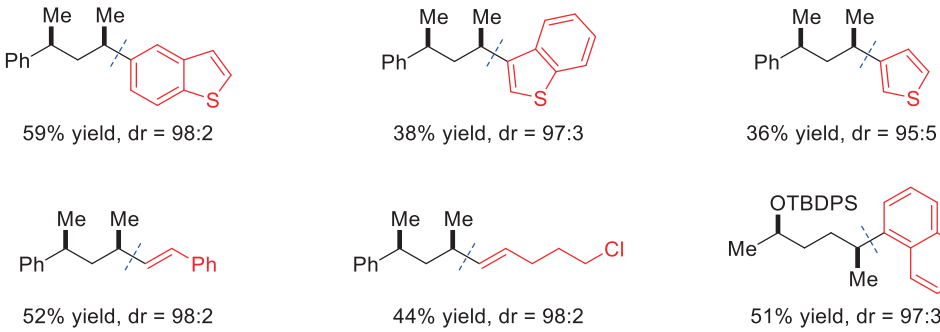
Organolithium reagents are important key intermediates and their exceptional high reactivity combined with new practical preparation methods has led to an increase in the use of these organometallic compounds in organic synthesis.[1] Stereodefined secondary alkyllithium reagents can be obtained by I/Li-exchange from the corresponding secondary alkyl iodides (**1**) with ^{t}BuLi at -100 °C. Direct transmetalation of these non-stabilized organolithium reagents to the corresponding secondary mixed dialkylzinc reagent afforded a room temperature stable organometallic reagent (**2**).[2] Subsequent palladium-catalyzed cross-coupling reaction with alkenyl and heteroaryl halides using Pd-PEPPSI-iPent[3] afforded α-chiral alkenes and heteroarenes (**3**) with high retention of configuration. Furthermore, the method was extended to various chiral secondary alkyl iodides and was used in the total synthesis of (*R*)- and (*S*)-curcumene. Computational studies were performed to explain the configurational stability of these mixed dialkylzinc species at room temperature.[4] Extensions of this method to *N*-heterocyclic electrophiles leading to α-chiral functionalized *N*-heterocycles are currently under investigation in our laboratories.





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[4] Skotnitzki, J; Kremsmair, A.; Keefer, D.; Gong, Y.; de Vivie-Riedle, R.; Knochel, P. *manuscript in preparation*.

3P-056s

Selective Synthesis of Benzonaphthosilines by Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition

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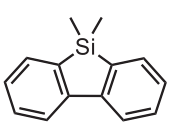
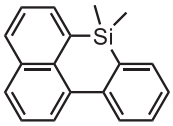
Silicon-bridged π-conjugated compounds have been widely investigated as potentially useful functional molecules in materials science based on their optoelectronic properties. Among them, 5*H*-dibenzo[*b*,*d*]siloles have been most extensively investigated and various effective synthetic methods are available to date. In contrast, other silicon-bridged π-conjugated compounds with different structural motifs are much less explored, presumably due to the lack of efficient synthetic methods. For example, 7*H*-benzo[*e*]naphtho[1,8-*bc*]silines belong to a class of compounds possessing promising optoelectronic properties, but their limited accessibility[1,2] significantly hampers the detailed studies toward discovery of their potential applications.



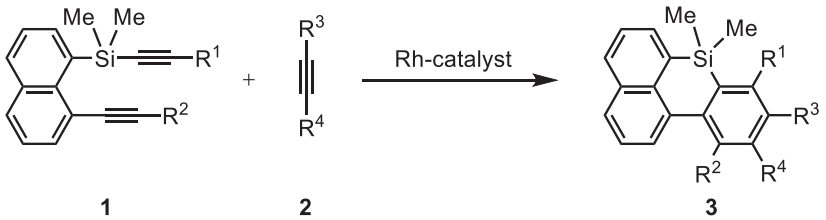
5*H*-dibenzo[*b*,*d*]silole



7*H*-benzo[*e*]naphtho[1,8-*bc*]siline

In this context, we decided to develop a new way of synthesizing benzonaphthosilines with high efficiency. Specifically, we chose to explore a rhodium-catalyzed [2 + 2 + 2] cycloaddition of naphthalene-based silicon-containing diynes **1** with alkynes **2**, and found that the use of a cationic rhodium catalyst having an appropriate ligand led to the formation of various benzonaphthosilines **3** in high yields (Scheme 1). Optical properties of these compounds were also investigated and some of them exhibited emission in a solid state. The details of synthesis and properties of benzonaphthosilines **3** will be presented in this Congress.

Scheme 1



1 **2** **3**

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Synthetic study of tubingensin B, a hexacyclic indole diterpenoid natural product

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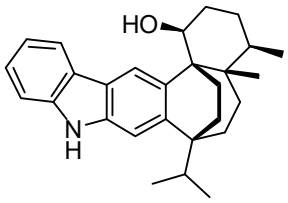
Keisuke Suzuki,[2] Kiyosei Takasu[1*]

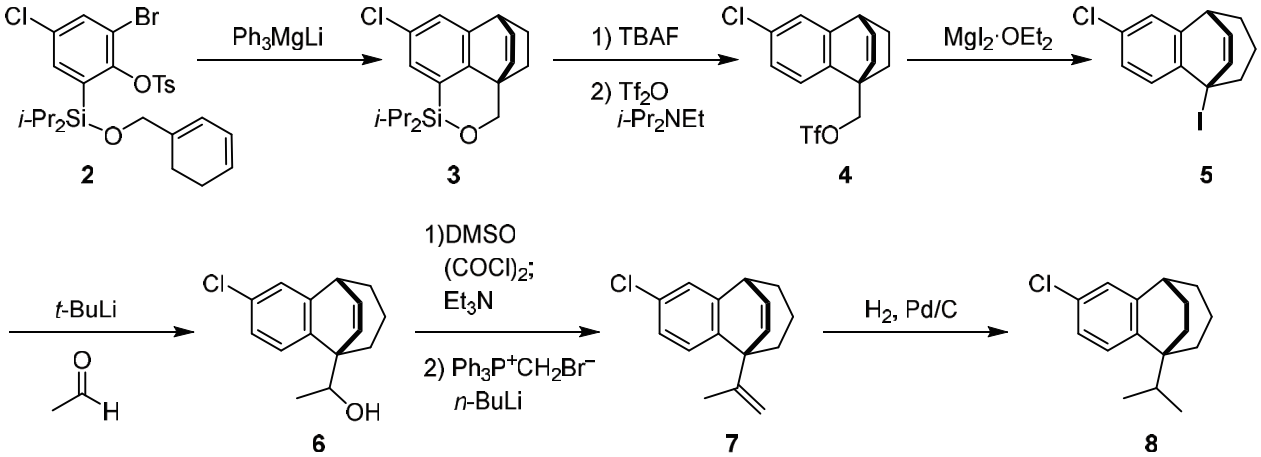
[1]*Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan*
[2]*Department of Chemistry, Tokyo Institute of Technology, 2-12-1 O-okayama Meguro-ku, Tokyo 152-8551, Japan.*



Tubingensine B

Tubingensin B (**1**), which exhibits potent antiviral and antitumor activities, is an indole diterpenoid isolated from the fungus *Aspergilus tubingensis*.[1] From a structural viewpoint, **1** showcases an exquisite molecular architecture, i.e., 1) bicyclo[3.2.2]nonane core fused to the carbazole ring and 2) five stereogenic centers, three of which are quaternary. Despite the rising interest in the total synthesis of **1** from the intriguing biological activities as well as the structural novelty, the total synthesis have been elusive due to the formidable challenges posed by the densely functionalized bridged structure.[2] Herein, we report the successful construction of the model tricyclic compound of **1** by exploiting (1) the sequential ring expansion/iodination, and (2) the introduction of carbon substituent via bridgehead anion.

Our synthesis commenced with the Diels–Alder reaction of benzyne precursor **2** with the cyclohexadiene moiety connected by the cleavable Si–O bond.[3] Upon treatment of **2** with Ph_3MgLi the generation of the benzyne followed by the cycloaddition smoothly proceeded to afford cycloadduct **3**, which was converted to triflate **4** via two steps, ready for the key ring expansion. Pleasingly, treatment of **4** with $MgI_2 \cdot OEt_2$ allowed the alkyl-selective ring expansion followed by the trapping of the intermediary bridgehead cation by iodide ion. Iodide **5**, thus obtained, underwent the clean iodide–lithium exchange with *t*-BuLi to generate a bridgehead anion, which was trapped with acetaldehyde to give adduct **6**. The synthesis of tricycle **7** was achieved via three functional group manipulations, including oxidation, methylenation, and saturation of the two alkenes.



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Synthesis of 2-Substituted Indoles and Benzofurans Using Carbozincation of Alkynyl Ethers

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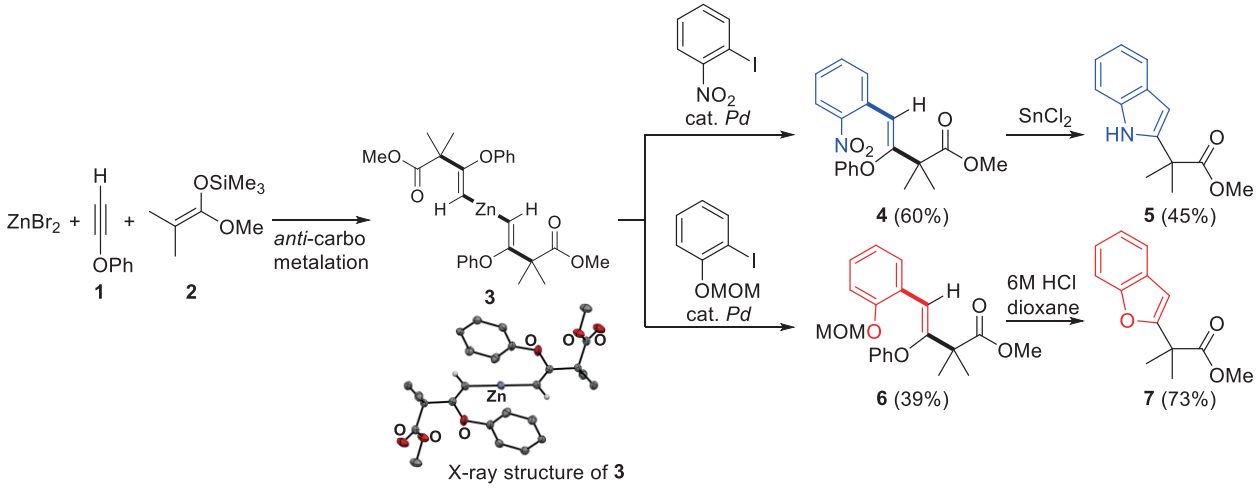
Department of Applied Chemistry and Frontier Research Base for Global Young Researchers Center for Open Innovation Research and Education (COiRE), Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871

One of the most active areas in heterocyclic chemistry is synthesis and application of indoles and benzofurans due to their structures found in many alkaloids and pharmacologically important substances.[1] Herein, we developed an approach using carbometalation of alkynyl ethers to 2-substituted indoles and benzofurans. [3] When treating alkynyl ether **1** with $ZnBr_2$ and silyl ketene acetal **2**, the carbometalation selectively gave *β*-alkoxyalkenyl zinc **3**. Synthesized alkenylzinc **3** was characterized by NMR spectra and X-ray crystal analysis, which supported the carbozincation occurred in *anti*-addition fashion. Alkenylzinc **3** was found to be a versatile reagent for reaction with electrophiles such as iodine, allylbromides and aldehydes. Especially, Negishi cross coupling using alkenyl zinc **3** and various aryl iodides proceeded efficiently. Introduce of 2-nitrobenzyl and 2-methoxymethyl group using Negishi coupling reaction with alkenyl zinc **3** was successful to give alkenyl ethers **4** and **6**, respectively. Reduction of nitro group of **4** using $SnCl_2$ directly gave indole compound **5** in 45 % yield, and deprotection/cyclization process of alkenyl ether **6** gave benzofuran compound **7** in 73 % yield. Our approach has the merit of synthesis 3-unsubstituted 2-substituted indoles and benzofurans, which are important building blocks for many medicinal compounds, hard to be synthesized by substitution of simple 3-unsubstituted indoles and benzofurans.



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3P-059

Room-Temperature, Metal-Free and One-Pot Preparation of 2*H*-indazoles *via* a Mills Reaction and Cyclization Sequence

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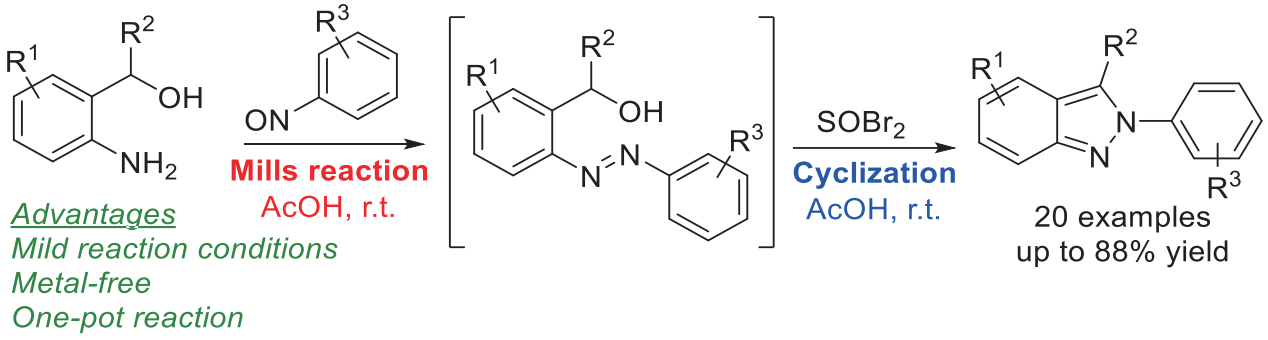
Mihogaoka, Ibaraki-shi, Osaka 567-0047, Japan

Indazoles are a useful class of *N*-heteroaromatic compounds because they have a crucial structural motif of various biologically active compounds, particularly, bioisosteres for indoles and benzimidazoles.[1] They are also utilized as fluorescent agents for cellular imaging in the field of chemical biology.[2] However, synthetic procedures of 2*H*-indazoles have inherent limitations such as the need for elevated temperatures, transition-metal reagents, multistep reactions and narrow substrate scope.[3] Herein, we demonstrate an operationally simple, one-pot, and metal-free synthesis of 2*H*-indazoles using 2-aminobenzyl alcohols, nitrosobenzenes, and brominating agents such as PBr_3 or $SOBr_2$ in acetic acid at room temperature. Mills reaction of 2-aminobenzyl alcohols with nitrosobenzenes efficiently furnish an azobenzene intermediate in acetic acid, which is converted into 2*H*-indazole *via* intramolecular cyclization by a brominating agent, along with easily removable side products such as H_2O, SO_2, or HBr. Our one-pot protocol afforded the desired 2*H*-indazoles in good yield with a broad substrate scope at room temperature (20 examples, up to 88% yield) (Scheme 1).[4] Further transformation of obtained 2*H*-indazoles and assumed reaction mechanism will be discussed.



Scheme 1. One-pot synthesis of 2*H*-indazoles *via* Mills reaction and cyclization sequence

[1] (a) Dong, J.; Zhang, Q.; Wang, Z.; Huang, H.; Li, S. *ChemMedChem* **2018**, *13,* 1490; (b) A. Schmidt, A. Beutler, B. Snovydovych, *Eur. J. Org. Chem.* **2008**, *23*, 4073.
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Catalyst-Free Aromatic C–H Amidation Using Newly Designed *N*-Acyliminoiodinanes

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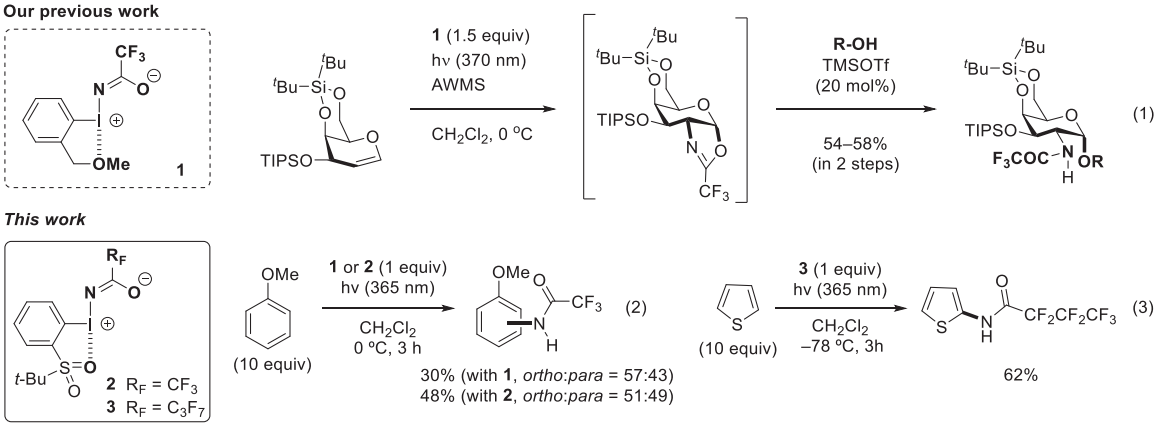
Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

Iminoiodinanes have been used as useful nitrogen sources for the synthesis or functionalization of natural products and pharmaceuticals via transition-metal-catalyzed aziridination, C–H amination, and trans-ylidation. Recently, new types of iminoiodinanes with *ortho*-coordinating substituents have attracted much attention due to their improved solubility in organic solvents.[1] However, most of the reported iminoiodinanes are limited to *N*-sulfonyl derivatives. In a previous report, we first succeeded in synthesizing *N*-trifluoroacetyliminoiodinane **1** bearing an *ortho*-methoxylmethyl group, and identified its unique structure by X-ray structural analysis. The most unique feature of **1** is the metal-free generation of the corresponding nitrene species by photo-irradiation at 370 nm, which allowed one-pot aminoetherification of galactals (eq. 1).[2]



To extend the utility of iminoiodinanes, we next investigated aromatic C–H amidation, because aromatic and heteroaromatic compounds bearing trifluoro- and perfluoro-acylamido groups are often found in various biologically active molecules. To our delight, similar to the metal-catalyzed reaction, catalyst-free C–H amination of anisole proceeded with **1** under photo-irradiation to give the corresponding adduct in 30% (eq. 2). Furthermore, the yield was improved to 48% using newly designed iminoiodinane **2** with an *ortho*-sulfonyl group. Under the optimized conditions, heteroaromatic compound such as thiophene was also functionalized with **3** to furnish the desired product in 62% yield (eq. 3). The details of the photo-induced amidation using **1**-**3** will be discussed in the presentation.

[1] For a review on *ortho*-coordinating groups, see: Zhdankin V. V., Protasiewicz J. D., *Coord*. *Chem*. *Rev*. **2014**, *275*, 54. [2] (a) Kobayashi, Y., Masakado, S., Takemoto, Y. *Angew*. *Chem*. *Int*. *Ed*. **2018**, *57*, 693. (b) Masakado, S., Kobayashi, Y., Takemoto, Y. *Chem*. *Pharm*. *Bull*. **2018**, *66*, 688.

Coinage Metal Catalyzed *7-Endo-Trig* Cyclization of Ene-Dios: Construction of 2,2-Dimethyloxepane Frameworks

Kakeru Maeda,[†] Ryo Murakami,[‡] Fuyuhiko Inagaki*[‡]

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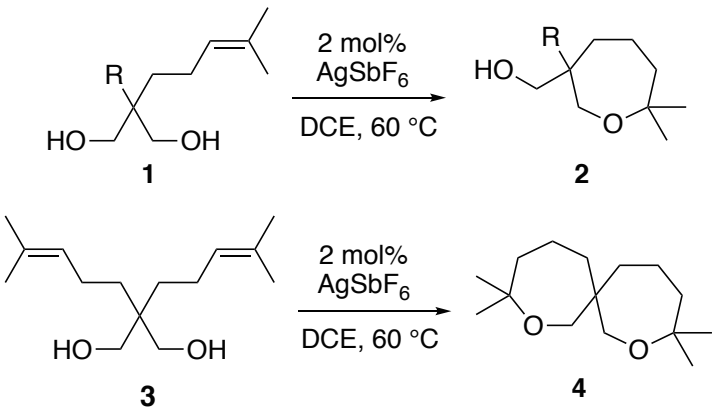
[‡]*The Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Minatojima 1-1-3, Chuoku, Kobe, 650-8586, Japan*

An oxygen-containing 7-membered ring having a quaternary carbon next to an oxygen atom, 2,2-dimethyl oxepane, is one of the important basic skeletons contained in natural products. As examples, Heliannuol C (allelopathic activity), Sodwanone S (possessing anticancer activity), Zoapatanol (menses-inducing effects of plant), Montanol (antifertility activity), Tomentol, and Tomentanol possess the common 2,2-dimethyl oxepane frameworks. Although various types of synthetic methods have already been reported for the oxepane frameworks, the synthesis of 2,2-dimethyl oxepane is still limited.

A recent effort in our laboratory focused on the development of an unprecedented reaction between a silver catalyst and alkenes. The treatment of a diene and the $AgSbF_6$ catalyst gave the cyclohexene derivative via cycloisomerization. [1] Also, selective C-N bond cleavage of the *N*-prenyl group occurred by the reaction between a sulfonyl amine and the $AgSbF_6$ catalyst. [2]

On these grounds, we developed the $AgSbF_6$-catalyzed *7-endo-trig* cyclization of an ene-diol **1** for the formation of the 2,2-dimethyloxepane frameworks **2**. In this reaction, the *spiro*-type dioxabicyclic products **4** were also derived from the diene-diols **3**. Also, a gold catalyst featuring the Z-ligand [3] was applicable for these cyclization reactions.



1 **2** **3** **4**

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Installation of O-Heterocycles to N-Heteroarenes via an Et_3B/O_2- Mediated Radical Reaction of α-Alkoxy and α-Alkoxyacyl Tellurides

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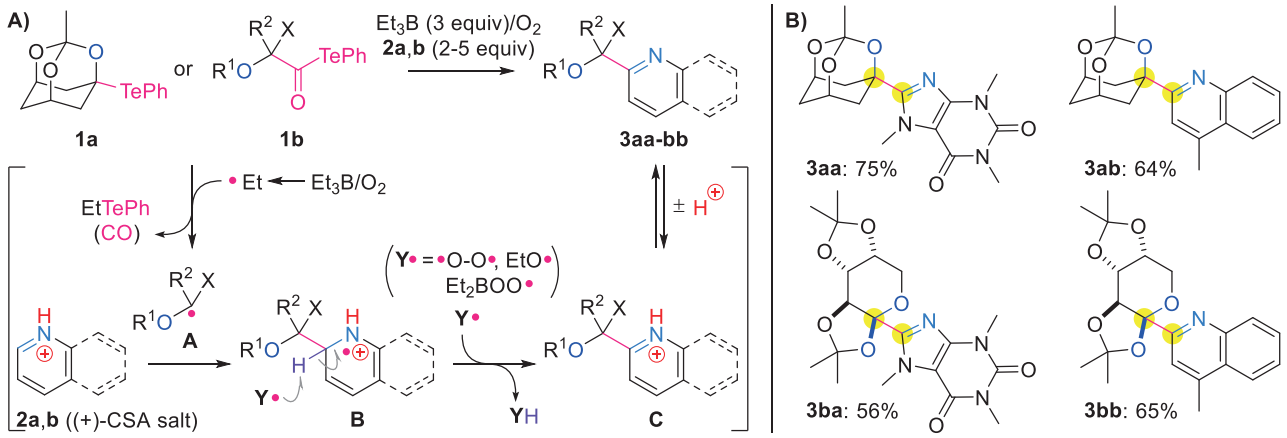
Nitrogen (N) and oxygen (O) heterocycles are among the most important structural components of pharmaceuticals. Hence, the development of coupling reactions of the two types of heterocycles has gained a great deal of interest for exploring new chemical space of pharmacologically important molecules. However, examples that can link highly oxygenated C(sp^3)-rich O-heterocycles and N-heterocycles are limited, and they also require harsh conditions, including high temperature, high-energy light, or potent oxidants.

We recently reported radical addition of highly oxygenated α-alkoxy tellurides or α-alkoxyacyl tellurides to C−N double bonds of imines and oximes.[1] Because of the compatibility of the reaction with various polar functional groups, we envisioned employing a combination of reactive radical precursors and mild reaction conditions to realize the coupling with N-heteroarenes (Scheme A). α-Alkoxy radicals **A** would be produced from α-alkoxy or α-alkoxy acyl tellurides **1a**,**b** by the action of Et_3B/O_2, and would react with the C−N double bonds of protonated N-heteroarenes **2a**,**b** to form radical cation intermediates **B**. We expected that oxyl radical species **Y** (e. g., triplet oxygen, oxyl, or peroxy radical) would abstract hydrogen from **B** to regenerate the aromatic rings. Finally, neutralization of **C** by work-up would afford O-heterocycle-functionalized N-heteroarenes **3aa-bb**.

The coupling reaction was performed using **1a**,**b** and (+)-camphor sulfonic acid (CSA) salt of N-heteroarenes (**2a**,**b**). As a result, the Et_3B/O_2 reagent system effectively promoted the radical formation, the coupling reaction, and the subsequent oxidative rearomatization without UV irradiation, heating, or external oxidants to produce **3aa-bb** in good yields (Scheme B).[2]

In conclusion, the present method enables the formation of hindered C(sp^3)−C(sp^2) bonds between O-heterocycles and N-heteroarenes under mild conditions.



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3P-063s

N-C Axially Chiral Quinazolinones with *ortho*-Fluorophenyl Group and the Application to Enolate Chemistry

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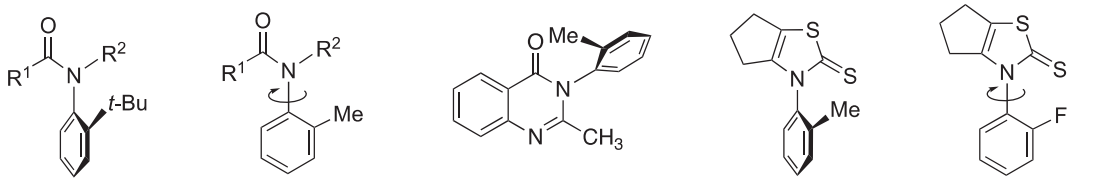
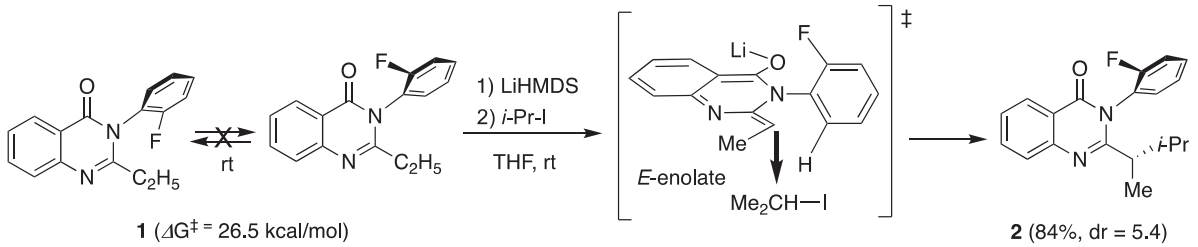
Recently, atropisomeric compounds owing to the rotational restriction around an N-Ar bond have been attracted remarkable attention as a new chiral molecule. Most of these N-C axially chiral compounds have an *ortho*-substituted aniline skeleton, and rotational stability around an N-Ar axis is influenced by the steric factor of an *ortho*-substituent and the structure on the nitrogen side. For example, in anilide derivatives **I**, a bulky *ortho*-substituent such as a *tert*-butyl group is required for a rotationally stable structure, while in 3-arylquinazolin-4-ones **II** and 3-arylthiazoline-2-thiones **III**, *orhto*-methyl derivatives **IIB** and **IIIB** also possess a stable atropisomeric structure. On the other hand, the N−C axially chiral compounds bearing an *ortho*-fluoro group have to date remained uncommon because the steric size of a fluorine atom is supposedly too small to restrict the rotation around the N−Ar bond. Indeed, in 3-arylthiazoline-2-thione **III,** the rotational barrier of *ortho*-fluoro derivative **IIIC** is significantly lower (14 kcal/mol) than that of *ortho*-methyl derivative **IIIB**.



We found that 2-ethyl-3-arylquinazolin-4-one **1** bearing an *ortho*-fluorophenyl group at N3 position are rotationally stable and the enantiomers can be isolated at rt ($\Delta G^{\ddagger}$ = 26.5 kcal/mol, $t_{1/2}$ = 17 days at 298 K). Furthermore, the reaction of *iso*-propyl iodide with lithium enolate prepared from quinazolinone **1** and LiHMDS proceeded in a diastereoselective manner to afford *iso*-propylation product **2** bearing (*P**,*S**)-configuration as a major diastereomer. The present α-alkylation is an unique stereoselective reaction which discriminates slight difference of steric factor between hydrogen and fluorine atoms.



1 ($\Delta G^{\ddagger}$ = 26.5 kcal/mol) **2** (84%, dr = 5.4)

3-Aryl-2-substituted quinazolin-4-one derivatives are pharmaceutically attractive compounds, and these results indicate that in any drug development with quinazolin-4-one derivatives bearing an *ortho*-substituted phenyl group at the N3 position, the N−C axial chirality should always be considered.

Synthesis of Optically Pure Bioactive N-C Axially Chiral Quinazolinone Derivatives

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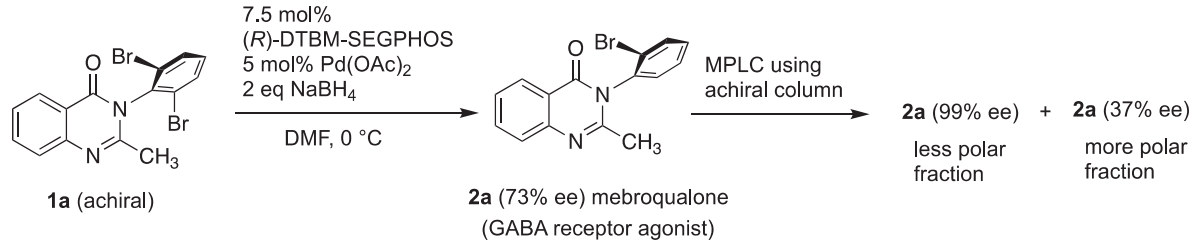
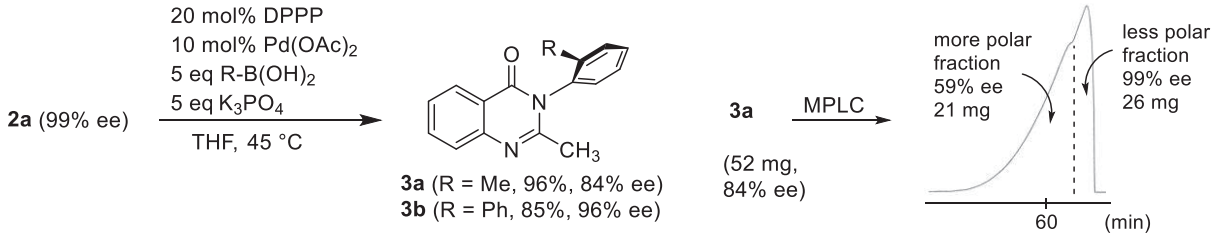
Quinazolin-4-one derivatives with ortho-substituted phenyl group at N3 position possess stable atropisomeric structure due to the rotational restriction around an N-Ar bond. In addition, some of these N-C axially chiral quinazolinones have pharmacological activity such as tranquilizing effect and anti-convulsant action. Recently we succeeded in the first catalytic enantioselective synthesis of mebroqualone **2a** (GABA receptor agonist) through chiral Pd-catalyzed reductive asymmetric desymmetrization of achiral quinazolinone substrate **1a**.[1] Furthermore, medium pressure liquid chromatography (MPLC) of optically active **2a** (73% ee) using an achiral SiO_2 column caused significant self-disproportionation of enantiomers (SDE) to bring about fractions containing enantiomerically pure **2a** and enantiomerically depleted **2a**.[2] We report here the conversion of mebroqualone **2a** to optically pure methaqualone **3a** (minor tranquilizer).



Suzuki-Miyaura coupling of optically pure mebroqualone **2a** with methyl and phenyl boronic acids gave methaqualone **3a** and *ortho*-phenyl derivative **3b** in good yields, while in these coupling reactions, decrease in the ee of the products **3a** and **3b** was observed. Especially, the conversion to methaqualone **3a** with methyl boronic acid led to considerable decrease in the ee (84% ee). Since mebroqualone **2a** and methaqualone **3a** have high rotational barrier ($\Delta G^{\ddagger}$ = ca. 35 kcal/mol and 32 kcal/mol), the decrease in the ee may be due to the lower rotational barrier of Ar-Pd-intermediate which resulted from the oxidative addition. On the other hand, MPLC of **3a** (84% ee) using an achiral SiO_2 column (eluent: hexane/AcOEt = 4) led to considerable SDE, and optically pure **3a** was obtained from less polar fraction.



[References]
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3P-065s

Selective Synthesis of 8*H*-Benzo[*e*]phenanthro[1,10-*bc*]silines under Palladium Catalysis

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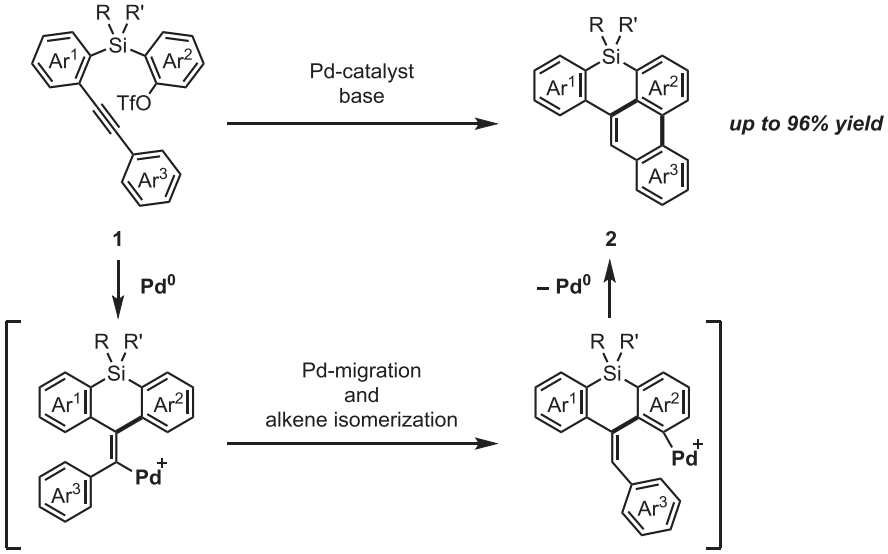
Silicon-bridged π-conjugated compounds such as dibenzosiloles and dithienosiloles have been intensively studied in the field of materials science because of their unique optoelectronic properties. Benzophenanthrosilines also belong to such compounds having a 6-membered silacycle and were reported as synthetic precursors of the corresponding benzophenanthroborinines, boron-containing polycyclic aromatic hydrocarbons, by a Si–B exchange reaction.[1] However, benzophenanthrosilines themselves have not been investigated in detail so far.

Recently, we reported palladium-catalyzed stereoselective synthesis of silacycles involving a C–H bond functionalization by employing 2-(arylsilyl)aryl triflates.[2,3] Based on these results, herein we devised a new way of synthesizing benzophenanthrosilines **2** from easily accessible 2-((2-arylethynyl)arylsilyl)aryl triflates **1** under simple palladium catalysis. The reaction presumably goes through a sequence of intramolecular *syn*-arylpalladation of alkyne/1,4-palladium migration with concomitant *E*/*Z*-isomerization of alkene/C–H arylation, and a variety of benzophenanthrosilines **2** could be obtained in high yields. In this Congress, the details on the scope and mechanism of this catalysis as well as physical properties of resulting benzophenanthrosilines **2** will be discussed.



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A Convenient Synthesis of Hemithioindigo by the Cyclization of 2'-Mercaptochalcone with NBS under Mild Conditions

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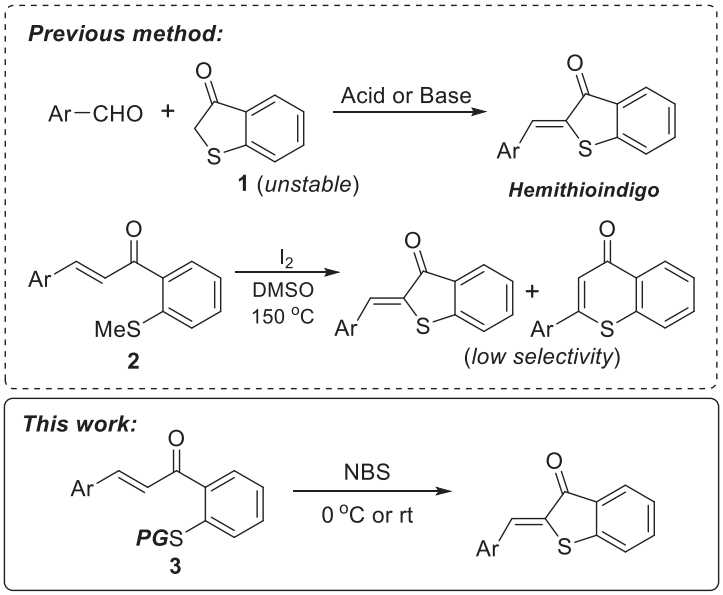
Higashi-osaka, Osaka 577-8502, Japan

Chalcones are very common in natural product and are cyclized into the corresponding chroman-4-one, also called flavanone, in biosynthesis. We have developed methods for the synthesis of heterocyclic compounds from a variety of chalcone, and recently the synthesis of azaisoflavones from 2'-nitrochalcones[1] and 3-acylindoles from 2-aminochalcones were reported.[2] For the application of this method, we next examined the synthesis of sulfur-containing heterocyclic compounds from mercaptochalcone and found a simple method for efficient synthesis of hemithioindigo. Hemithioindigo is unsymmetrical molecules consisting of a thioindigo fragment, which is connected to a stilbene fragment via a central double bond and its properties as photoswitches had been advanced in recent years. [3,4]



General synthetic method of hemithioindigo is the condensation of aldehydes with the unstable benzo-thiophen-3-one **1**. The only method to form hemithioindigo using 2'-mercapto-chalcone **2** was reported,[5] but high reaction temperature and low selectivity are the issues.

We first investigated cyclization conditions with 2'-mercaptochalcones **3** with several protecting groups (PG) and hemithioindigo can be predominantly obtained in high yield by treating with *N*-bromosuccinimide (NBS). A variety of 2'-mercaptochalcones were successfully converted into their corresponding hemithioindigos in moderate to high yields and one of the newly synthesized compound exhibits strong fluorescence properties.

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3P-067

Asymmetric Dearomatizing Fluorination of Indole Derivatives under Phase-Transfer Catalysis

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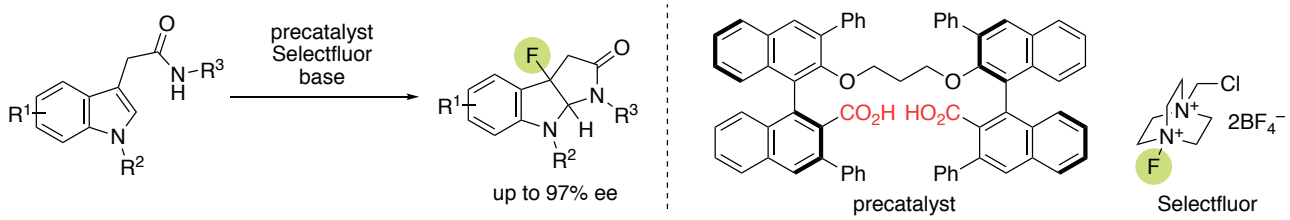
Since introduction of fluorine atom into an organic molecule often improves its property, such as metabolic stability and distribution, many medicinal drugs have fluorine atom(s) nowadays. Coupled with the chiral environment of the compounds present in nature, the development of efficient synthetic methods for chiral fluorinated compounds is a long-standing subject in the organic chemistry field. Therefore, asymmetric fluorinations including double functionalization of C=C bonds have been actively studied for nearly two decades. Inspired by Toste's pioneering work,[1] we have developed new chiral phase-transfer catalysts for asymmetric fluorolactonization[2] and 6-*endo*-fluorocyclization of allylic amides.[3,4] On the other hand, indoline framework could be found in many bioactive compounds, and the construction of chiral indoline derivatives including dearomatizing reactions of indole derivatives has been well studied. Therefore, we became interested in dearomatizing fluorination of indole derivatives and decided to utilize our phase-transfer catalyst to the fluorination.

After optimization of the reaction conditions, we were pleased to find that our dicarboxylic acid precatalyst provided the desired fluorinated indoline derivatives in a highly enantioselective manner.[5] Although the protective group (R^2) on the nitrogen atom of the indole unit was crucial for asymmetric induction, the removal of the protective group could be successfully demonstrated. The details of this reaction will be discussed in this presentation.



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3P-068

Asymmetric Synthesis of γ-alkoxybutenolides by the Thiourea-Ammonium salt-catalyzed Acetalization and Its Application

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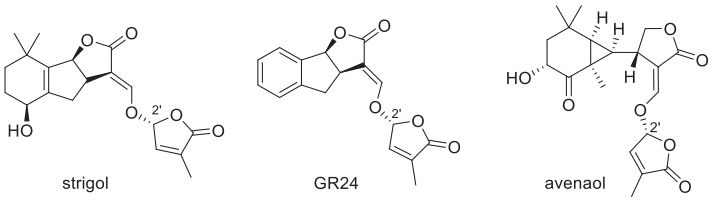
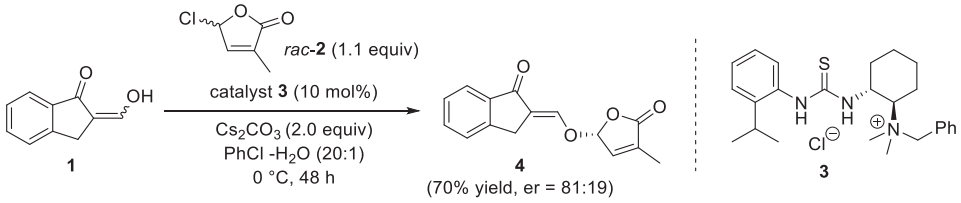
b. *Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan, 606-8501*

γ-Alkoxybutenolide is a common substructure of strigolactones which are plant hormones regulating shoot branching and stimulating seed germination of root parasitic plants. [1] Because of the significant and important biological activities of strigolactones such as strigol, GR24, and avenaol, they have been drawn attention from not only synthetic chemists but biologist. While there are various synthetic studies of strigolactones, the stereoselective introduction of the γ-alkoxybutenolide unit was limited. [2] Therefore, we have started to develop a highly general synthetic method for introducing this unit with high enantio- and diastereoselectivity.



Generally, intermolecular enantio- and diastereoselective acetalization with racemic electrophiles is challenging because it is necessary to control the approaching face of a nucleophile to an achiral electrophile. We envisioned that the organocatalyst having hydrogen bond donors as well as an electrostatic interaction would control this reaction to achieve high stereoselectivity. After extensive investigations, we found that the reaction of enol **1** with racemic chlorobutenolide **2** in the presence of 2 equivalent of Cs_2CO_3 as a base and 10 mol% of organocatalyst **3** having a quaternary ammonium unit proceeded to give compound **4** in 70% yield with high enantioselectivity. In this presentation, we will report the detail of the investigation of reaction conditions and catalysts as well as its application to the asymmetric synthesis of avenaol. [3]



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Synthesis of Ployoxy-Functionalized Piperidines via Mannich and Micheal Reactions of Carbohydrate Derivatives

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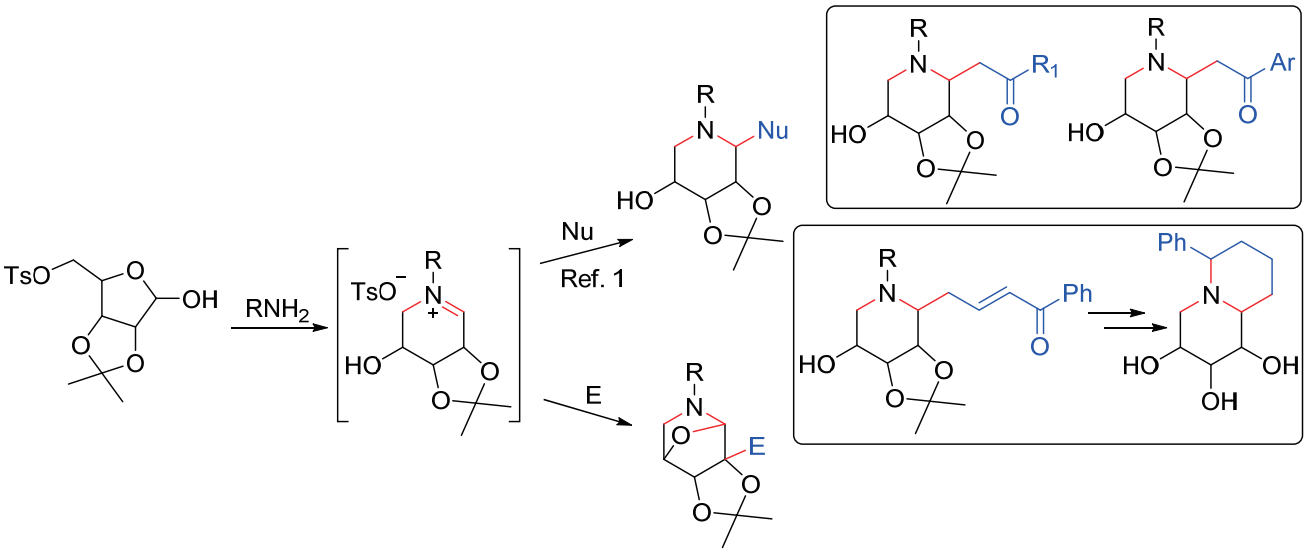
Onna, Okinawa 904-0495, Japan

Polyoxy-functionalized piperidine derivatives are found in pharmaceuticals, probes, and their building blocks. Therefore, the development of methods for the synthesis of polyoxy-functionalized piperidine derivatives is of interest in drug discovery and related areas. In this presentation, we present strategies involving Mannich and Michael reactions of iminium ions or enamines generated from carbohydrate derivatives that afford polyoxy-functionalized piperidines.

In the Mannich reaction strategy, ketone nucleophiles were generated in the presence of the amines used for the formation of iminium ions. Various carbohydrate derivatives were used along with the use of a series of ketones as nucleophiles resulted polyhydroxy-functionalized piperidine derivatives in high yields with high regio- and diastereoselectives in most cases. Further, the products from the reaction of allyl ketones were transformed to bicyclic (quinolizine) iminosugar derivatives.[1]

In the Michael reaction strategy, enamines were formed from the iminium ions in situ to react with electrophiles. The enamine formation pathway was demonstrated in the reactions with nitrostyrenes and α, β–unsaturated carbonyl compounds.



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Absolute Asymmetric Flavanone Synthesis involving Dynamic Enantioselective Crystallization Process

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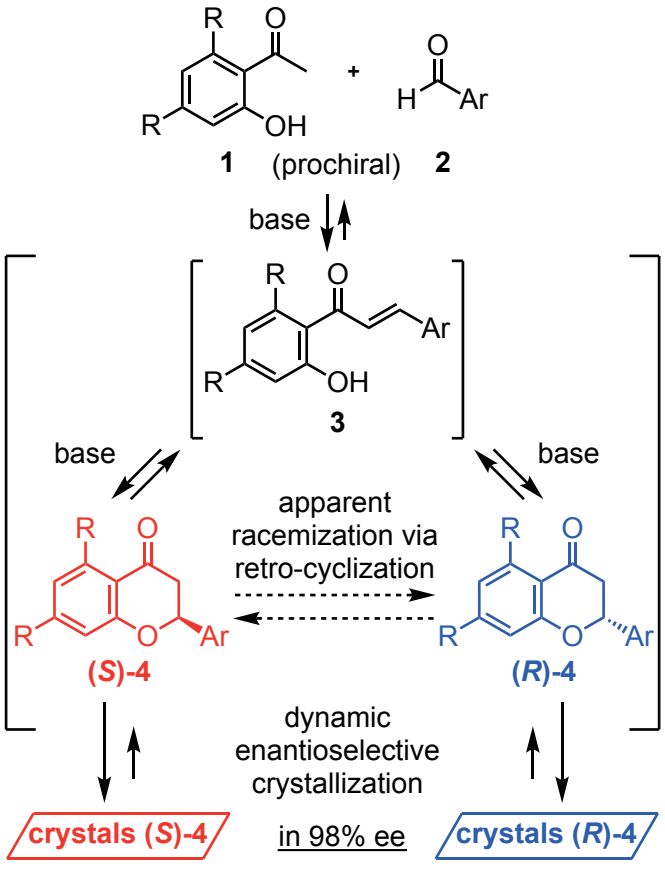
Asymmetric synthesis under absolutely achiral conditions is widely attractive and challenging topic, since this concept is closely linked to the origin of homochirality on the Earth. Flavanones are naturally occurring molecules in many plants and widely used for pharmaceutical materials. In this study, we developed a new absolute asymmetric synthesis of flavanones involving a combined methodology to generate chiral center from prochiral materials with dynamic enantioselective crystallization. Optically active flavanones **4** were obtained by condensation reaction of 2-hydroxyacetophenones and aromatic aldehydes in the presence of base followed by cyclization and dynamic crystallization.

The aldol condensation of prochiral acetophenones **1** and aromatic aldehydes **2** afforded adducts **3**, and was followed by cyclization leading to flavanones **4**. Single crystal X-ray structure analysis of **4** with various substituents revealed that **4a** (R = MeO, Ar = 2-naphthyl) afforded conglomerate crystal of chiral $P2_12_12_1$ space group. Flavanone **4a** did not racemize at room temperature; however, effective racemization through ring-opening and -closing reactions was promoted at high temperature under basic conditions. The half-life of racemization in 1-propanol in the presence of DBU (1.5 eq) was 12 min at 90ºC.

Next, we examined the asymmetric synthesis of **4a** by the dynamic crystallization. When prochiral **3a** or racemic **4a** was suspended in 1-propanol with glass beads in the presence of DBU over several days, deracemization occurred and flavanone **4a** was successfully obtained in 98% ee.



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Cu(I)-Catalyzed Pentafluoroethylation of Aryl Iodides Using Tetrafluoroethylene and CsF

Naoyoshi Ishida,[a] Kota Ando, [a] Yu Hashimoto, [a] Anna Shigaki, [a] Kotaro Kikushima, [a] Masato Ohashi*[b] and Sensuke Ogoshi*[a]

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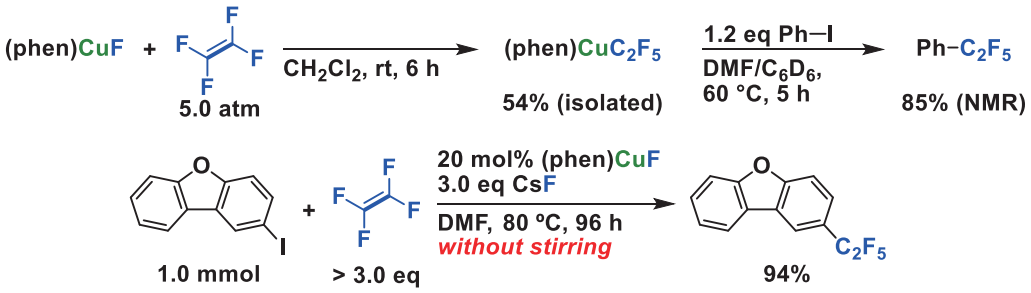
Organofluorine compounds have attracted much attention. Among them, trifluoromethylated aryl compounds (Ar–CF_3) are frequently encountered structural motifs in biologically active compounds. In comparison with Cu-mediated trifluoromethylation reactions, the introduction of a longer-chain perfluoroalkyl groups employing the corresponding Cu(I) species remains largely unexplored.[1]

Tetrafluoroethylene (TFE) should be an ideal starting material for the preparation of fluorinated compounds, considering that it is a cost-effective and environmentally benign feedstock with negligible GWP_{100} and ODP values. Recently, we have demonstrated that TFE can insert into a variety Cu(I)–X bonds (X = C, O, B, and Si) to furnish the corresponding fluoroalkylcopper(I) species, Cu–CF_2CF_2–X.[2] We subsequently envisioned that a pentafluoroethylcopper species (Cu–CF_2CF_3) should be generated from the fluorocupration of TFE. Thus, we have been focusing our attention on investigating if the fluorocupration of TFE affords a Cu–CF_2CF_3 species.[3]

We discovered that the fluorocupration of TFE occurs in the presence of phen as an auxiliary ligand, which resulted in the clear formation of (phen)CuC_2F_5 (Scheme 1). We also confirmed that the stoichiometric pentafluoroethylation of iodobenzene with (phen)CuC_2F_5 proceeded smoothly. In addition, we developed the first examples for a Cu(I)-catalyzed pentafluoroethylation of aryl iodides in the presence of TFE and CsF (Scheme 1), in which refraining from stirring the reaction mixture is the key to suppressing the competing oligomerization of TFE.[4]



(Scheme 1) Stoichiometric and Catalytic Pentafluoroethylation of Aryl Iodides

[1] (a) I. Popov, S. Lindeman, O. Daugulis, *J. Am. Chem. Soc.* **2011**, *133*, 9286. (b) K. Aikawa, Y. Nakamura, Y. Yokota, W. Toya, K. Mikami, *Chem. Eur. J.* **2015**, *21*, 96. (c) T. Schareina, X. F. Wu, A. Zapf, A. Cotte´, M. Gotta, M. Beller, *Top. Catal.* **2012**, *55*, 426. (d) T. Sugiishi, D. Kawauchi, M. Sato, T. Sakai, H. Amii, *Synthesis* **2017**, *49*, 1874.

[2] (a) H. Saijo, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.* **2014**, *136*, 15158. (b) M. Ohashi, T. Adachi, N. Ishida, K. Kikushima, S. Ogoshi, *Angew. Chem. Int. Ed.* **2017**, *56*, 11911. (c) H. Sakaguchi, Y. Uetake, M. Ohashi, T. Niwa, S. Ogoshi, T. Hosoya, *J. Am. Chem. Soc.* **2017**, *139*, 12855. (d) H. Sakaguchi, M. Ohashi, S. Ogoshi, *Angew. Chem. Int. Ed.* **2018**, *57,* 328.

[3] L. Li, C. Ni, Q. Xie, M. Hu, F. Wang, J. Hu, *Angew. Chem. Int. Ed.* **2017**, *56*, 9971.

[4] M. Ohashi, N. Ishida, K. Ando, Y. Hashimoto, A. Shigaki, K. Kikushima, S. Ogoshi, *Chem. Eur. J.* **2018**, *24*, 9794.

Enantioselective Synthesis of Chiral γ-Lactams by Ni(0)-Catalyzed Asymmetric Carbonylative Cycloaddition

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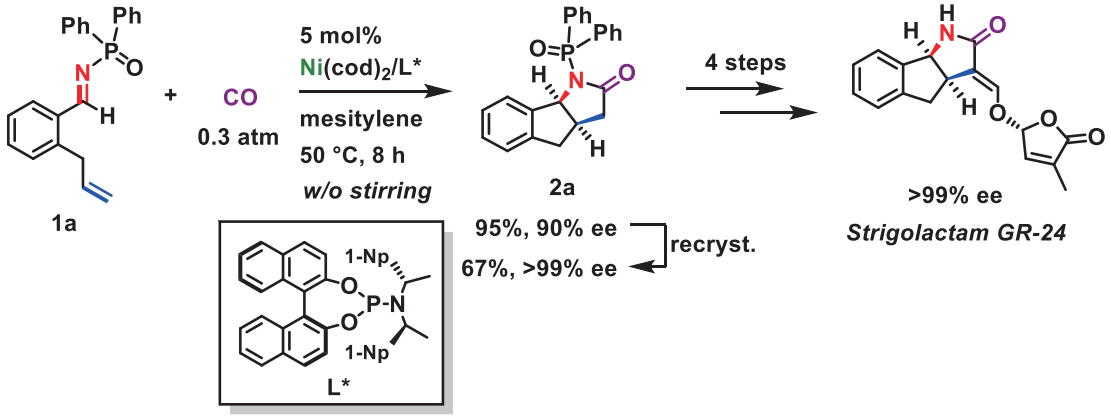
Chiral γ-lactam derivatives are ubiquitous in physiologically active compounds. The development of a straightforward and reliable synthetic method that affords chiral γ-lactam motifs in a stereocontrolled manner should be thus of importance. The transition-metal-catalyzed [2+2+1] carbonylative cycloaddition of imine, alkene, and carbon monoxide (CO) should represent an efficient method for the synthesis of the chiral γ-lactam motif;[1] however, such an asymmetric process has not been developed. Recently, we have developed the nickel-catalyzed carbonylative cycloaddition between ene-imines and CO, which proceeded in a completely diastereoselective manner to construct a tricyclic γ-lactam motif.[2] Herein, we demonstrate the first nickel-catalyzed asymmetric carbonylative cycloaddition between ene-imines and CO.

In the presence of 5 mol% of $Ni(cod)_2$ and chiral phosphoramidite **L***, the carbonylative cycloaddition between ene-imine **1a** and CO proceeded to afford tricyclic γ-lactam **2a** as a sole diastereomer with 90% ee (Scheme 1). The synthetic utility of the present nickel-catalyzed process was demonstrated by the first enantioselective synthesis of Strigolactam GR-24[3] from enantiopure **2a**, which was prepared by the present nickel-catalyzed reaction followed by recrystallization. Further synthetic utilities were demonstrated by the derivatizations of enantiopure **2a** into versatile chiral *N*-heterocycles.



Scheme 1. Ni-catalyzed asymmetric carbonylative cycloaddition between **1a** and CO

[1] (a) Chatani, N. *Chem. Rec*. **2008**, *8*, 201. (b) Hoshimoto, Y.; Ohata, T.; Sasaoka, Y.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc*. **2014**, *136*, 15877.
[2] Hoshimoto, Y.; Ashida, K.; Sasaoka, Y.; Kumar, R.; Kamikawa, K.; Verdaguer, X.; Riera, A.; Ohashi, M.; Ogoshi, S. *Angew. Chem., Int. Ed*. **2017**, *56*, 8206.
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Ni-Catalyzed Cleavage and Formation of C-O Bond to give Disubstituted Benzofurans

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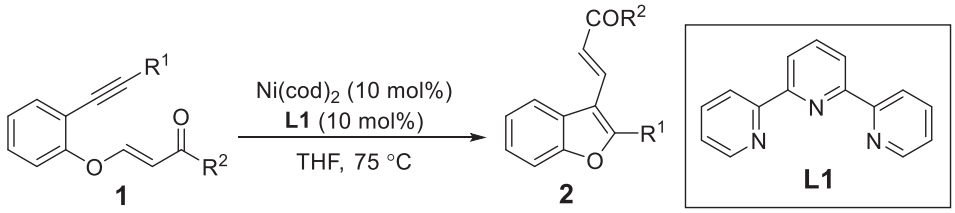
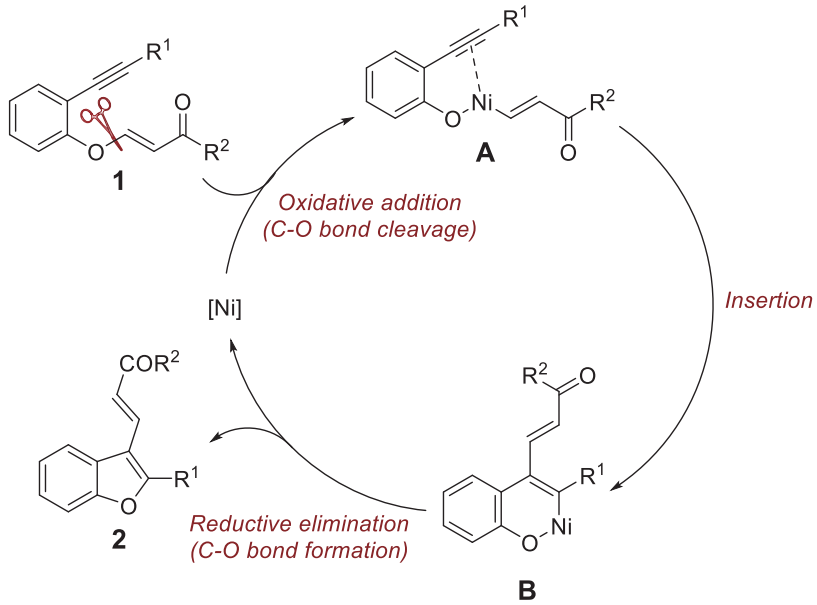
Suita, Osaka 565-0871, Japan

Novel reactions based on transition metal catalyzed C-O bond cleavage have attracted much attention in recent years as a new synthetic method.[1-2] Until now, several coupling reactions via C-O bond cleavage of aryl and vinyl ether[1] and ester[2] have been reported. Here we report the unprecedented C-O bond cleavage of 3-phenoxy acrylic acid derivatives, followed by intramolecular C-O bond formation with alkyne. We investigated substrate **1** was converted to 2,3-disubstituted benzofuran **2** in excellent yield in the presence of catalytic amount of $Ni(cod)_2$ and ligand **L1**.



R^1 = $SiMe_3$, $SiEt_3$, $SiMe_2tBu$, *t*Bu, etc.
R^2 = Me, OMe, O*t*Bu, OPh, etc.

up to 99%



A possible catalytic cycle of this reaction is shown above. Ni complex was inserted to a C(vinyl)-O bond of substrate **1** to afford intermediate **A**. Product **2** was obtained by subsequent insertion and reductive elimination.

[1] (a) Cornella, A.; Zarate, C.; Matin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081. (b) Tobisu, M.; Takahira, T.; Morioka, T.; Chatani, N. *J. Am. Chem. Soc.* **2016**, *138*, 6711. (c) Zeng, H.; Qiu, Z.; D.-Huerta, A.; Hearne, Z.; Chen, Z.; Li, C.-J. *ACS Catal.* **2017**, *7*, 510.
[2] Takise, R.; Muto, K.; Yamaguchi, J. *Chem. Soc. Rev.* **2017**, *46*, 5864.

Ir-catalyzed Cycloisomerization between Aryl Enol Ether and Silylalkyne to Give 2,3-Disubstituted Benzofurans

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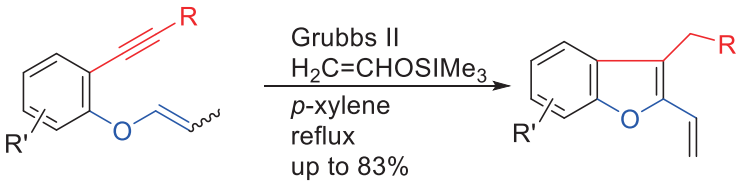
Suita, Osaka 565-0871, Japan

Transition-metal catalyzed cycloisomerization is a benign method, because all atoms contained in the starting material are retained in the final product.[1] Recently, we reported a ruthenium hydride catalyzed cycloisomerization between functionalized olefines, such as aryl enol ether and silylalkyne, to give 2,3-disubstituted benzofurans **[eq (1)]**.[2] The problems of this methodology are the use of expensive Grubbs II catalyst and requirement of high reaction temperature (150 ℃). To solve the above existing problems, we have screened catalyst systems in detail. Finally, we succeeded in finding that a cheaper pair of $[IrCl(cod)]_2$ and PCy_3 is suitable for this reaction {$[IrCl(cod)]_2$: 11,800 JPY/500 mg; Grubbs II: 41,300 JPY/500 mg} and got 96% yield of compound **2 [eq (2)]**.[3] To make matters better, the catalyst system also efficiently worked even at r.t.. This reaction is the first example of aryl enol ether and alkyne using Ir catalyst.

Previous Work : Ruthenium Hydride Catalyzed Cycloisomerization (2017)

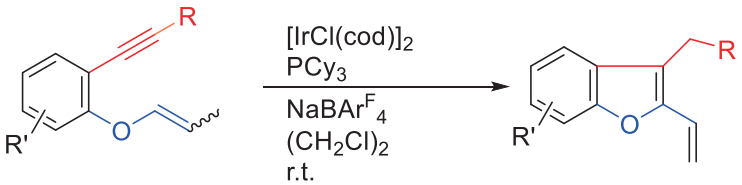


1 **2** **eq. (1)**

$R=SiMe_3$, $SiMe_2Ph$, $SiMe_2Bn$, etc.
R'=H, OMe, Cl.

Advantage: The first cycloisomerization between aryl enol ether and silylalkynes under Ru hydride catalysis.
Defects: 1) Expensive catalyst. (Grubbs II: 41,300 JPY/500 mg)
2) High temperature.

This Work : Iridium-Catalyzed Cycloisomerization (2019)



1 **2** **eq. (2)**

R = $SiMe_3$, $SiMe_2Ph$, $SiMe_2Bn$, etc.
R' = H, OMe, Cl.

[1] Fang, G.; Bi, X. *Chem. Soc. Rev.* **2015**, *44*, 8124-8173.
[2] Ohno, S.; Takamoto, K.; Fujioka, H.; Arisawa, M. *Org. Lett.* **2017**, *19*, 2422-2425.
[3] Referred the price from SIGMA-ALDRICH.

3P-075s

Novel synthesis method of γ-lactam from vinylketenimine-iron complexes

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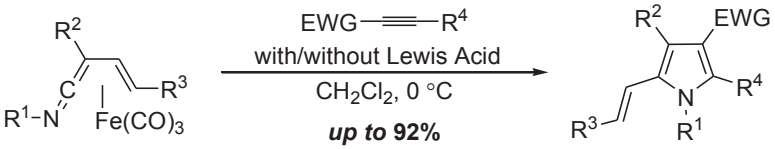
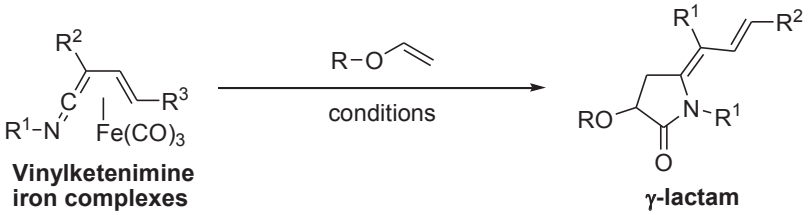
1-1 Sensuicho, Tobata, Kitakyushu, Fukuoka 804-8550, Japan

Vinylketenimine-iron complexes have interesting reactivity. We recently found that pyrroles were obtained from the complexes and an alkyne (Eq.1)[1]. Moreover, vinylketeneimine-iron complexes can be stored for a long time. We expected that vinylketenimine-iron complexes would be used for the synthesis of fine chemicals, pharmaceuticals and agrochemicals.



Vinylketenimine iron complexes **pyrrole** (1)

In this study, we have found that vinylketenimine-iron complexes reacted with a vinyl ether and γ-lactam were obtained (Eq.2). We considered that this reaction was Pauson-Khand type [2+2+1] cyclization of the complexes, vinyl ether and carbon monoxide. Pauson-Khand reaction using diene iron complexes and alkenes has not been reported yet. In the poster presentation, we will discuss the optimized conditions and propose the mechanism.



Vinylketenimine iron complexes **γ-lactam** (2)

Novel reaction of Pauson-Khand type

1) Unpublished data in our laboratory.

Organocatalyzed Enantioselective Addition of Glyoxylate Cyanohydrin to Imines for Divergent and Scalable Synthesis of α-Keto-β-Amino Acid Analogues

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β-Amino acid motif is an important non-proteinogenic amino acid, which can bring dramatic changes in a physical and bioactive property of a peptide. In particular, α-oxygenated β-amino acids are important fragments found in many bioactive compounds (Figure 1). In addition, α-keto-β-amino acids can be used for the decarboxylative condensation such as KAHA-ligation developed by Bode and coworkers[1]. For these reasons, a catalytic and stereoselective synthesis of a series of α-keto-β-amino acids is highly demanded.

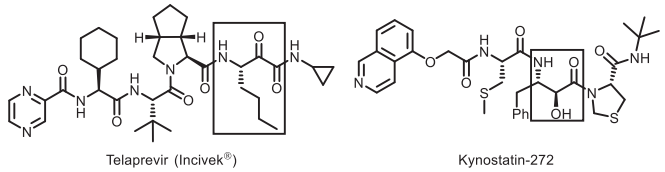
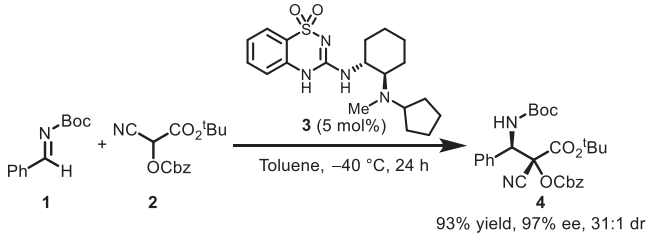


Figure 1. α-Oxygenated β-amino acid motif

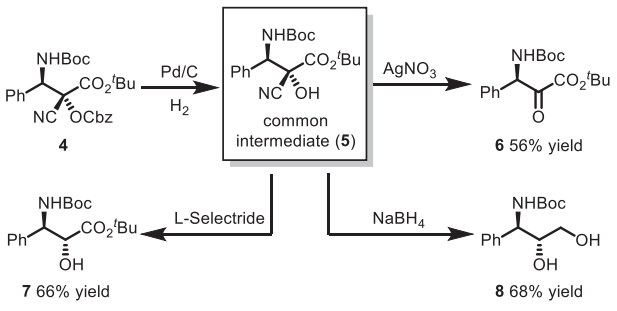
In order to establish a new method which allows divergent synthesis of protected α-keto-β-amino acid equivalents, we focused on glyoxylate cyanohydrin **2** as a C_2 nucleophile, and envisioned that the Mannich addition of cyanohydrin **2** to aldimines afforded the desired products **4**. On the basis of this concept, we screened various bifunctional hydrogen-bond donor catalysts for the reaction of *N*-Boc imine **1** and cyanohydrin **2**. As a result, benzothiadiazine catalyst **3** having an *N*-cyclopentyl-*N*-methylamino group provided the Mannich adduct **4** as an almost single stereoisomer in excellent yield (Scheme 1). In addition, this catalytic system is easily scalable, and the adduct **4** can be prepared on a gram-scale with even 1 mol% catalyst loading without a loss of yield and stereoselectivity.

Finally, we derivatized Mannich adduct **4** to β-amino acid analogues (Scheme 2). Deprotection of the Cbz group followed by treatment of the resulting **5** with aqueous silver nitrate afforded β-amino-α-ketoester **6** in 56% yield over two steps. Moreover, the hydride reduction of **5** with L-Selectride and $NaBH_4$ afforded *anti*-β-amino-α-hydroxyester **7** and *anti*-aminodiol **8** as single isomers, respectively. In all cases, the stereochemical information of products **6**-**8** was maintained during the transformation. These results show that the Mannich addition using glyoxylate cyanohydrin **2** is applicable to the efficient synthesis of various α-keto-β-amino acid congeners as chiral building blocks.

Scheme 1. Catalytic addition of cyanohydrin to imine



Scheme 2. Derivatization of the Mannich adduct



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3P-077

Various Tetrazoles Synthesis from Ketoximes Using DPPA : Substrate Scope and Limitations

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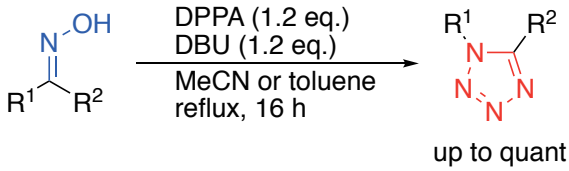
Tetrazoles are a significant class of synthetic heterocyclic compounds, and have been attracting increasing attention due to their wide range of applications in various scientific fields. Especially, among the tetrazole family, 1,5-disubstituted tetrazoles have been known to exhibit biological activity.

Some methods for the synthesis of 1,5-disubstituted tetrazoles from ketoxime esters *via* Beckmann rearrangement[1] or ketones *via* Schmidt rearrangement[2] have been reported. However, the utilization of these methods must be careful because of the use of toxic or explosive reagents.

On the other hand, diphenyl phosphorazidate (DPPA) is a less explosive azidating reagnet due to the stabilization by conjugation with the phosphorus atom. Recently, we have reported the synthesis of 5-substitured 1*H*-tetrazoles from aldoximes utilized DPPA.[3] This method improved the safety of azidation operation and utilized DPPA as both the activator and azide source. Therefore, 1,5-disubstitited tetrazoles could be synthesized safely from ketoximes if a Beckmann-type rearrangement proceeded by activation and azidation with DPPA.

Initially, we investigated whether the synthesis of a tetrazole *via* Beckmann rearrangement with DPPA was viable using acetophenone oxime. As a result, we found that the desired product was obtained in good yield by using DPPA in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Various ketoximes were able to be converted into the corresponding tetrazoles. No ketoxime isomerization occurred during the reaction, and rearrangement occurred stereospecifically with only the migration of *trans*-group. The advantages of this method include operational simplicity and increased safety as toxic or explosive reagents can be avoided.[4]

In this presentation, we will also report the details focusing on the substrate scope and limitations.



[1] Nishiyama, K. *et al*. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2419.
[2] (a) Suzuki, H. *et al*. *Synthesis* **1993**, 1218. (b) El-Ahl, A. S. *et al*. *Tetrahedron Lett.* **1995**, *36*, 7337. (c) Motiwala, H. F. *et al*. *J. Org. Chem.* **2016**, *81*, 1593.
[3] (a) Ishihara, K. *et al*. *Synlett* **2016**, *27*, 2225. (b) Ishihara, K. *et al*. *Synthesis* **2018**, *50*, 1293.
[4] Ishihara, K. *et al*. *Tetrahedron Lett.* **2019**, *60*, 1295.

3P-078s

Facile Synthesis of Diverse Heterocyclic Compounds via Au-Catalyzed Cyclization and Generation of Arynes

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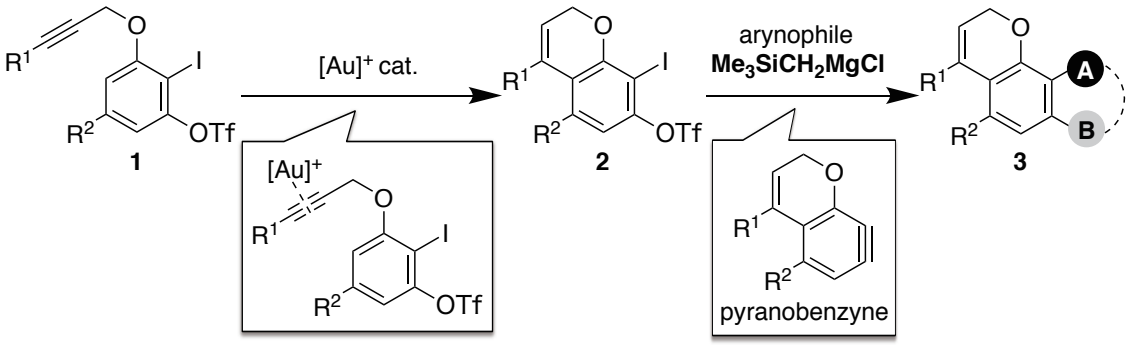
Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Tokyo/101-0062

Benzopyran derivatives are heterocyclic compounds that are often contained as a core skeleton in a wide range of molecules, including bioactive natural products and pharmacologically active compounds. Although the increasing importance of benzopyran derivatives, synthetic methods for multisubstituted benzopyrans are still limited. Recent advances in aryne chemistry have offered an easy access to a wide range of complex aromatic compounds. [1] We recently reported that ring-fused multisubstituted arenes were easily synthesized via heterocyclic-type arynes such as thiazolobenzynes, [2] thienobenzynes, [3] and furanobenzynes. [4]

Herein, we report a facile synthetic method for diverse multisubstituted benzopyran derivatives **3** via pyran-fused benzynes, which were generated from the corresponding benzyne precursors by treatment with a silylmethyl Grignard reagent as a mild activator. Pyranobenzyne precursors **2** were found to be easily prepared by the Au-catalyzed cyclization of 2-iodo-3-(propargyloxy)aryl triflates **1** leaving the iodo and triflyloxy groups untouched.



[1] Yoshida, S.; Hosoya, T. *Chem. Lett.* **2015**, *44*, 1450.
[2] Yoshida, S.; Yano, T.; Nishiyama, Y.; Misawa, Y.; Kondo, M.; Matsushita, T.; Igawa, K.; Tomooka, K.; Hosoya, T. *Chem. Commun.* **2016**, *52*, 11199.
[3] Morita, T.; Yoshida, S.; Kondo, M.; Matsushita, T.; Hosoya, T. *Chem. Lett.* **2017**, *46*, 81.
[4] Morita, T.; Nishiyama, Y.; Yoshida, S.; Hosoya, T. *Chem. Lett.* **2017**, *46*, 118.

3P-079

Imidazo[1,5-*a*]pyridine-derived NHC-type Carbenes as a Ligand for Catalysts: Characterization and Reactivity in Catalyses

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Since the first example of imidazo[1,5-*a*]pyridine-based *N*-heterocyclic carbenes (NHCs) (imidazopyridine carbenes: IPCs) was developed,[1] those carbenes have attracted much attentions as a new class of stabilized carbenes. Recently, particular interests were made to not only their structual features, but also their electronic properties. The efforts gradually revealed that the carbenes have non-negligible π-accepting character that is usually almost canceled by the internal stabilizing effect of vacant orbital by resonance effect in most conventional NHCs. Consequently, their transition metal (TM) complexes indicated rather different reactivities to the conventional NHC–TM complexes. In this regard, several researchers previously tested the IPCs as alternatives of conventional highly donating NHC ligands in such as cross-coupling type reactions, but those efforts resulted in only a few productive examples. Recently, we are curious about putative interaction of π*-orbital of the fused pyridine moiety and vacant p-orbital of carbene carbon on IPCs since those should overlap and make new accepting orbital that may show π-accepting character.[2,3] In fact, our previous theoretical and spectral studies indicated such orbital overlap and the actual π-accepting character based on the primary structural influence (Figure 1, left). Although Alcarazo and Fürstner pointed out a π-accepting character as well as σ-donating character of related IPC derivatives, the discussion was based on the orbital interaction of additional paracyclophane structure.[4] In addition, some of reports on the IPC-TM complexes used as a π-acidic catalyst usually indicated productive results, that is one of the weaker areas of catalyses with the conventional NHC ligands. Those observations encouraged us to further explore to use IPC-TM complexes as a π-acidic catalyst. In addition, the steric environment also important feature of IPC, and 5-aryl substituted compounds can be expected a similar and larger steric effect of series of Buchwald-type phosphine ligands (Figure 1, right), that may also affect the catalytic activities. Herein we report synthesis and structual investigation of IPC–TM complexes and their catalytic application, in particular, as a π-acidic catalyst.[5]

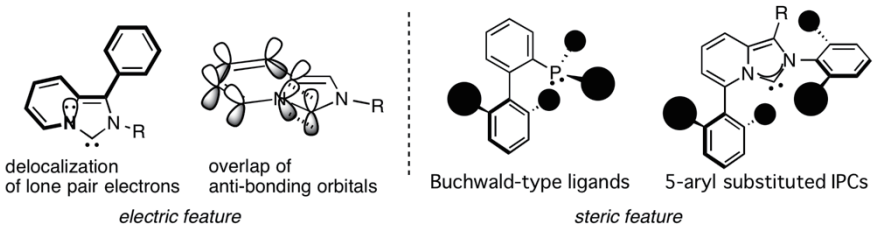

Figure 1. Features of Iimidazo[1,5-*a*]pyridine carbenes

[1] Alcarazo, M. ; Roseblade, S. J.; Cowley, A. R.; Fernández, R.; Brown, J. M.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3290.
[2] Koto, Y.; Shibahara, F.; Murai, T. *Org. Biomol. Chem.* **2017**, *15*, 1810.
[3] Koto, Y.; Shibahara, F.; Murai, T. *Chem. Lett.* **2016**, *45*, 1327.
[4] Alcarazo, M. ; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2542.
[5] *cf* Drost, R. M.; Bouwens, T.; van Leest, N. P.; de Bruin, B.; Elsevier, C. J. *ACS Catal.* **2014**, *4*, 1349.

3P-080

Synthesis of Aryl Esters through Accelerated Ligand Coupling of Diaryliodonium(III) Salts

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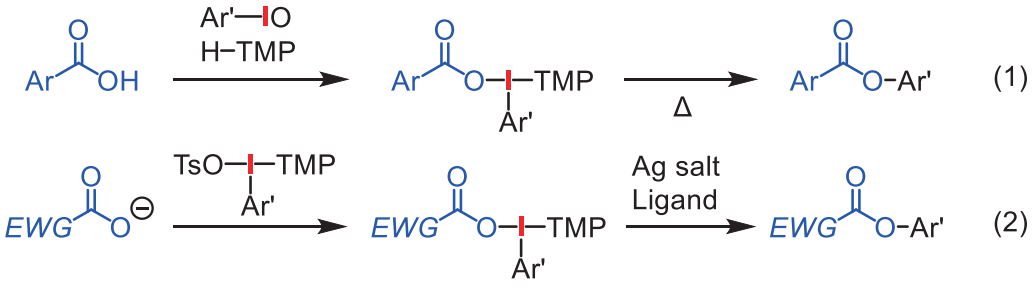
[1]*College of Pharmaceutical Sciences, Ritsumeikan University,*
[2]*Research Organization of Science and Technology, Ritsumeikan University,*
Kusatsu, Shiga 525-8577, Japan

Aryl esters are ubiquitous skeleton found in naturally occurring compounds, pharmaceuticals, agrochemicals, and functional polymers. General methods for the esterification of carboxylic acids with hydroxyarenes require an activation into acid derivatives including acyl chlorides and acid anhydrides. Condensation reagents, such as *N*,*N'*-dicyclohexylcarbodiimide (DCC), are also used for the esterifications. Recently, direct arylation reaction of carboxylic acids has been achieved by using transition-metal catalyst or diaryliodonium(III) salt,[1] wherein the carboxylic acids serve as a nucleophile. Our group has developed the metal-free oxidative coupling of diaryliodonium(III) salts with aryl nucleophiles producing biaryls. Herein, we demonstrate the synthesis of aryl esters through in situ generation of diaryliodonium(III) carboxylates followed by ligand coupling.[2]

Treatment of iodosoarenes with benzoic acid derivatives in the presence of 1,3,5-trimethoxybenzene afforded the corresponding diaryliodonium(III) benzoates, which successively underwent ligand coupling between the aryl group and the oxygen atom of benzoate to produce the arylative coupling products under heating conditions (eq 1). Various iodosoarenes including heteroaryl groups could be employed to afford the corresponding aryl esters. Introduction of carboxylic acid having low nucleophilicity, such as trifluoroacetic acid, instead requires silver catalysis. Thus, diaryliodonium(III) trifluoroacetates, prepared by anion exchange of diaryliodonium(III) tosylates with potassium trifluoroacetate, were converted into the corresponding hydroxyarenes in the presence of silver salt (eq 2). In this reaction, the ligand coupling of trifluoroacetoxy group proceeded to generate the corresponding aryl trifluoroacetates, which were converted into hydroxylarenes through hydrolysis during the isolation step. The uses of diaryliodonium(III) salts bearing heteroarenes for the present coupling strategy are also investigated.



TMP = 1,3,5-trimethoxyphenyl Ar, Ar' = aryl or heteroaryl

[1] (a) F. M. Beringer, A. Brierley, M. Drexler, E. M. Gindler, C. C. Lumpkin, *J. Am. Chem. Soc.* **1953**, *75*, 2708. (b) T. B. Petersen, R. Khan, B. Olofsson, *Org. Lett.* **2011**, *13*, 3462.
[2] T. Dohi, D. Koseki, K. Sumida, K. Okada, S. Mizuno, A. Kato, K. Morimoto, Y. Kita, *Adv. Synth. Catal.* **2017**, *359*, 3503.

Suppressing Decarbonylation with Silanes during Stille Coupling Reaction of Aromatic Acid Chlorides with Heterocyclic Stannane

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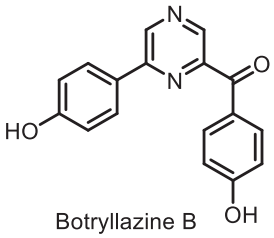
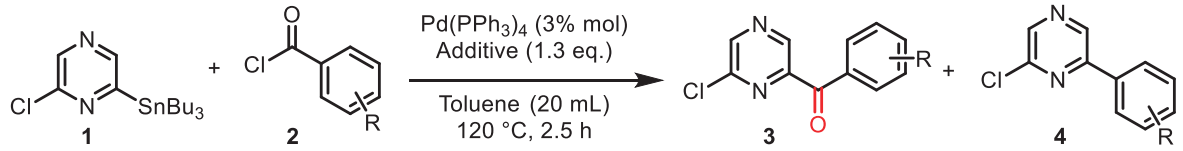
Stille coupling of arylstannanes with aromatic acid chlorides is a powerful tool for synthesizing aryl carbonyl compounds.[1] We previously utilized this reaction for preparing botryllazine B analogs as drug candidates for diabetic complications, and found that undesired decarbonylated byproducts were obtained with moderate yield when 2-chloro-6-(tri-*n*-butylstannyl)pyrazine **1** was reacted with substitutedbenzoyl chlorides. In this study, we have investigated the practical reaction conditions for suppressing the decarbonylation byproduct and obtaining the desired acylated compounds effectively.



Botryllazine B

We first examined the effect of CO sources, *N*-formylsaccharin or 2,4,6-trichlorophenyl formate and Na_2CO_3,[3,4] on the stille coupling reaction. Unfortunately, the CO sources applied were not effective to improve the ratio of **3** to **4**. In contrast, the formation of **4** was dramatically suppressed when triethylsiane was added to the reaction mixture (Table 1).

Table 1. The effects of triethylsilane on the Stille coupling of **1** with **2**



Entry	R	Additive	Yield (%)[a]	Ratio (**3** : **4**)[b]
1	3-OMe	—	96	3.8 : 1
2	3-OMe	**Et_3SiH**	97	34 : 1
3	3,4-OMe	—	84	2.8 : 1
4	3,4-OMe	**Et_3SiH**	95	2.3 : 1
5	3,5-OMe	—	78	5.5 : 1
6	3,5-OMe	**Et_3SiH**	89	17 : 1
7	4-CF_3	—	84	2.8 : 1
8	4-CF_3	**Et_3SiH**	80	7.8 : 1

[a]Determined from isolated weight of a mixture of **3** and **4**.
[b]Determined by ^{1}H NMR.

[1] D. Milstein, J. K. Stille, *J. Am. Chem. Soc.,* **1978**, *100,* 3636.
[2] B. Frederic, P. Nelly, T. Alain, Q. Guy. *J. Org. Chem.,* **2005**, *70*, 2616
[3] T. Ueda, H. Koyuki, K. Manabe, *Angew. Chem.,* **2013**, *52*, 8611.
[4] T. Ueda, H. Koyuki, K. Manabe, *Org. Chem.,* **2012**, *14*, 5370.

Catalytic Synthesis of Isoquinolines from 1,5-Yne-Imines through Migration of *N*-Aryl Sulfonyl Groups

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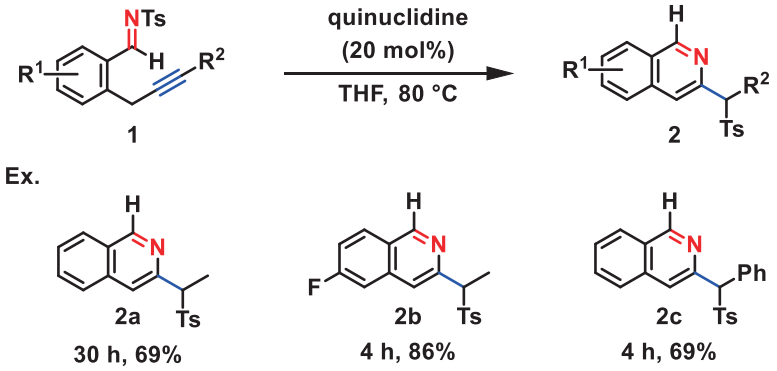
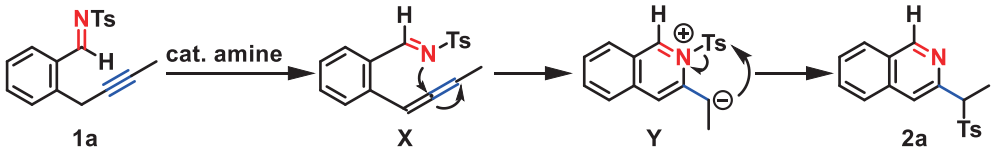
Isoquinoline represents a privileged core structural motif that occurs in biologically active alkaloids. Herein, we report a novel strategy for preparation of isoquinoline derivatives, which proceeds through the migration of aryl sulfonyl groups from the nitrogen to the carbon of alkyne moiety in 1,5-yne-imines.

In the presence of 20 mol% quinuclidine, transformation of **1a** took place to afford **2a** in 69% yield after 30 h at 80 ℃ (Scheme 1). Introduction of *meta*-fluorine with respect to the propargyl group accelerated the reaction progress to furnish **2b** in 86% after 4 h. The substrate **1c** including Ph group at the alkyne terminal afforded the corresponding isoquinoline **2c** in 69%. These results would indicate that the acidity of the benzyl proton in the propargyl moiety is important for the efficient formation of **2**.

A proposed mechanism is shown in Scheme 2. Firstly, intermediate **X** is generated by an amine-mediated isomerization of an alkyne unit from **1a**. Then an intramolecular cyclization occurs to yield intermediate **Y**. Finally, migration of an *N*-sulfonyl group affords isoquinoline **2a**.



Scheme 1. Ttansformation of **1** into **2** under quinuclidine catalyzed conditions.



Scheme 2. A proposed mechanism.

Dynamic Enantioselective Crystallization of Axially Chiral Nicotinamides

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Chiral symmetry breaking is widely interested about the origin of homochirality on the Earth, and also provides a practical methodology of total optical resolution of racemic compounds. Nicotinamide is known as a biomimetic model for asymmetric reduction in NAD/NADH systems, and also plays an important role in organic catalytic reactions.[1] Now, we focust on dynamic enantioselective crystallization of axially chiral nicotinamides.

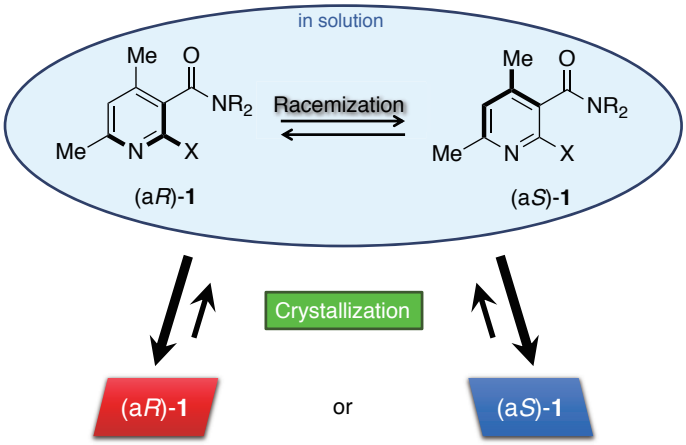
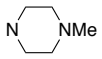


Figure 1. Chiral symmetry breaking of axially chiral nicotinamides.

N,*N*-Disubstituted aromatic amides can be generally solved into stable atropisomers when the substituents on both sides of the amide group are larger than hydrogen.[2] A variety of nicotinamides **1** with substituents at the 2- and 4-positions were synthesized, and the X-ray crystallographic analysis revealed that **1a** and **1b** afforded conglomerate crystals of $P2_1$ space group.

Table 1. Dynamic enantioselective crystallization of nicotinamides **1**.

1	NR_2	X	Space Group	Deracemization Conditions	Ee (%)
1a			$P2_1$	A[a]	6-42
				B[b]	96
1b	NBn_2	Cl	$P2_1$	A[a]	0-2
				B[b]	95

[a]Method A : crystallization from the melt.
[b]Method B : Viedma ripening.

Both nicotinamides have dynamic axial chirality, and the half-life of racemization at 25℃ in toluene was 24 min and 125 min, respectively. Crystallization of **1a** (mp 147-148℃) from the melt afforded optically active **1a** with 6-42% ee without seeding.[3] When a suspended solution of **1a** was kept stirring with glass beads at 70 ℃, chiral amplification was promoted by attrition-enhanced deracemization (Viedma ripening) leading to 96% ee after 10 days. Optically active **1b** (mp 83-84℃) was also obtained by crystallization from the melt; however, the optical purity was quite low. On the other hand, suspension of the racemic powder of **1b** in a mixed solvent of hexane and toluene with glass beads at 80 ℃ gave 95% ee of crystals after 12 days.

[1] Y. Mitaka *et al*., *J. Org. Chem.*, **2001**, *65*, 1590.
[2] M. Sakamoto *et al*., *Advances in Organic Crystal Chemistry, Comprehensive Reviews* 2015, **2015**, *443*.
[3] (a) M. Sakamoto *et al*., *Chem. Lett.*, **2013**, *42*, 1508. (b) *idem*, *molecules*, **2013**, *18*, 14430.

Synthetic Studies of Lyconesidines Based on Domino Ring-Transformation Strategy

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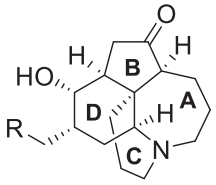
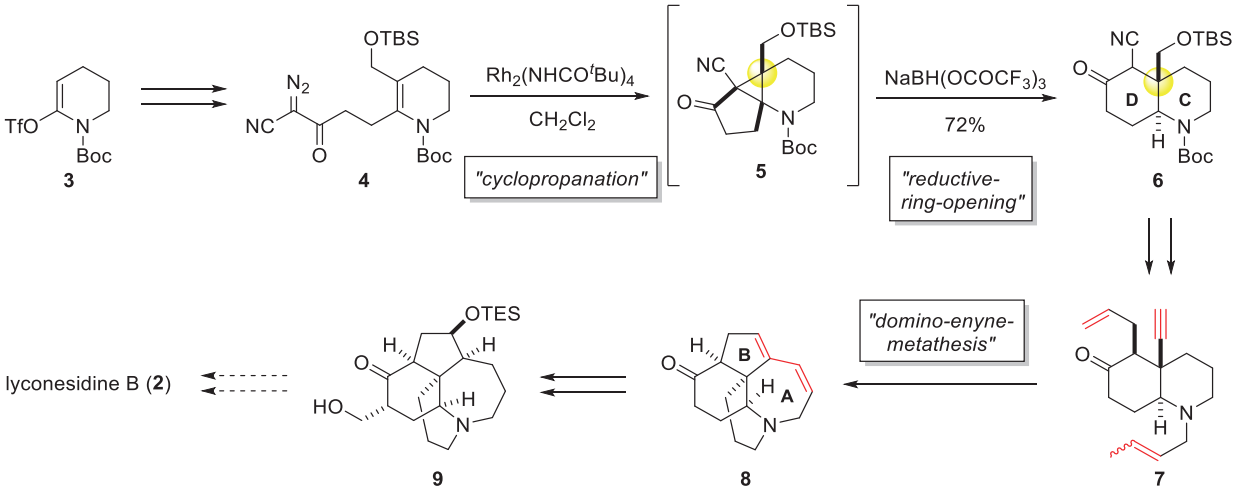
Lyconesidines (**1** and **2**), isolated from the club moss *Lycopodium chinense* by Kobayashi and coworkers, belong to *fawcettimine*-type lycopodium alkaloids possessing a complex tetracyclic skeleton with six continuous stereogenic centers containing a quaternary carbon. [1] These alkaloids exhibit cytotoxicity against murine lymphoma L1210 cells and an inhibitory effect on tubulin polymerization. Because of the intriguing structure and biological activity, we started the synthetic project of lyconesidines A and B.



lyconesidine A (**1**) (R = H)
lyconesidine B (**2**) (R = OH)

The key to the synthesis of lyconesidines is the construction of a complex tetracyclic skeleton with a quaternary carbon center. Recently, we developed a new synthetic strategy for hydroquinolines with a quaternary center at its angular position based on the domino cyclopropanation-reductive-ring-opening reaction.[2] This strategy has been successfully applied to the synthesis of decahydroquinoline **6** (CD ring) from diazoketone **4** via highly substituted cyclopropane **5**. After functional group transformations from **6**, the domino-enyne-metathesis of dienyne **7** was investigated under a variety of reaction conditions using different dienyne analogues to directly access tetracyclic diene **8**. We will report the details of these key transformations and further examinations toward the total synthesis of lyconesidines.



[1] Hirasawa, Y.; Morita, H.; Kobayashi, J. *Tetrahedron* **2002**, *58*, 5483.
[2] Kurose, T.; Tsukano, C.; Takemoto, Y. *Org. Lett*. **2017**, *19*, 4762.

Chemoselective, Decarboxylative Acylation of Amines.

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Development of efficient amidation reaction is still important area in organic synthesis due to the growing interest in peptide synthesis. In the course of investigations to find a different approach from a conventional dehydrative condensation reaction, we focused on decarboxylative condensation of α-ketoacids. α-Ketoacids are found in biochemical intermediates such as pyruvic acid and α-ketoglutaric acid which proceeds oxidative decarboxylation. This attractive functional group is also useful in synthetic organic chemistry considering α-ketoacids as a new type of acylanion equivalents by decarboxylative conversion.[1-3] Bode and coworkers have recently realized a decarboxylative amidation using α-ketoacids and hydroxylamines as known as KAHA ligation which proceeds without any condensation reagents.[1] Moreover, Lan and Lei also reported a visible light mediated decarboxylative amidation with aniline.[2] Although these brilliant preceding studies represent how useful α-ketoacids are as an acylating reagent, there is no report on high-yielding decarboxylative acylation of "normal" aliphatic amines. We envisioned that a highly electrophilic iminoacid derived from α-ketoacid and amine could smoothly react with nucleophilic oxidants such as hydroperoxide to provide corresponding amide. (Figure 1)

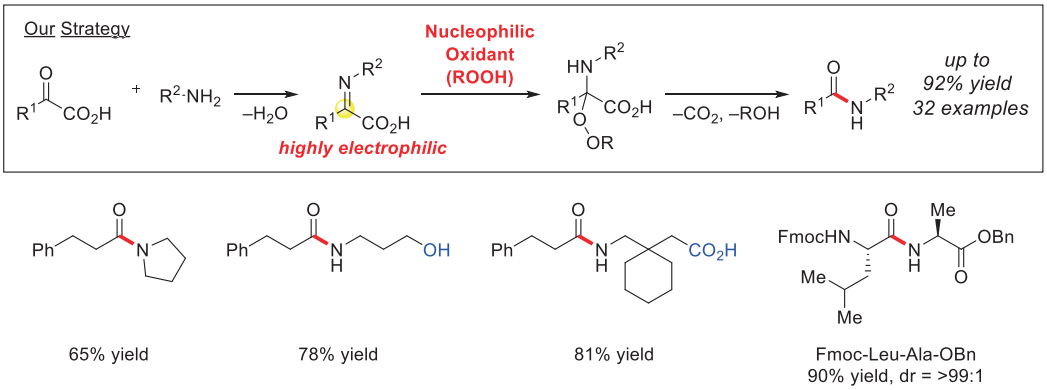

Figure 1. Strategy for Decarboxylative Amidation Mediated by Hydroperoxide.

On the basis of this strategy, we found that TBHP mediates decarboxylative acylation of both aliphatic and aromatic amine using α-ketoacids under mild condition. This reaction presents a unique chemoselectivity and a wide range of amides including peptides can be prepared in excellent yields.

[1] (a) J. W. Bode, R. M. Fox, K. D. Baucom, *Angew. Chem. Int. Ed.* **2006**, *45*, 1248. (b) N. Carrillo, E. A. Davalos, J. A. Russak, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 1452.
[2] J. Liu, Q. Liu, H. Yi, C. Qin, R. Bai, X. Qi, Y. Lan, A. Lei, *Angew. Chem. Int. Ed.* **2014**, *53*, 502.
[3] T. Nanjo, N. Kato, Y. Takemoto. *Org. Lett.* **2018**, *20*, 5766.

Borinic Acid Catalyzed Anomeric *O*-Alkylation for the Synthesis of 1,2-*cis*-Glycosides

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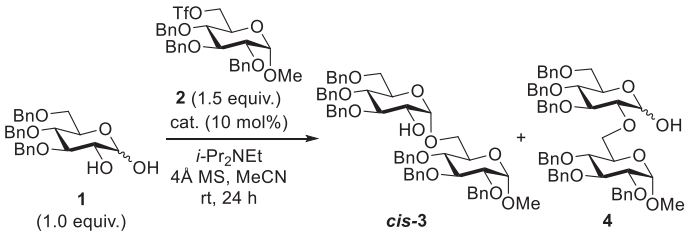
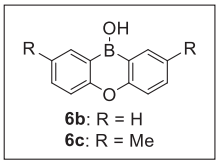
Chemical synthesis of oligosaccharides has attracted much attention for medical applications. To date, various synthetic strategies to control the selectivity have been developed. Whereas the neighboring-group participation of 2-*O*-acyl groups is a reliable method for *trans*-selective glycosylation, *cis*-selective glycosylation remains challenging. Therefore, recent synthetic efforts have been devoted to innovating new catalytic systems without relying on the directing and/or protecting groups. On the other hand, *O*-alkylation of anomeric hydroxy groups, in which oxocarbenium cations are not formed, is another approach for stereoselective synthesis of glycosides. Because of the high nucleophilicity of β-oxide anions of hexoses, the reaction generally provides kinetically controlled products such as 1,2-*trans*-β-glucosides.[1] Therefore, it seems difficult to apply this protocol to the synthesis of 1,2-*cis*-α-glucosides. So far, catalytic anomeric *O*-alkylation to form oligosaccharides has not been achieved due to the requirement of a stoichiometric amount of a strong base or organotin reagent. Recently, boronic acid or borinic acid has been reported as an effective catalyst for regioselective protection of 1,2- or 1,3-diols and regioselective glycosylation.[2,3] Inspired by these reports, we envisioned that the organoboron catalysts could promote the 1,2-*cis*-selective anomeric *O*-alkylation of 1,2-dihydroxyglucoses **1**.[4]

We initially examined the reaction of diol **1** and triflate **2** with commercially available boronic acid **5**. As expected, no 1,2-*trans*-product was detected and the desired product ***cis*-3** was obtained, albeit in low yield (21%), together with the 2-*O*-alkylated by-product **4** (entry 1). To improve the regioselectivity (***cis*-3**/**4**), various catalysts were screened, and borinic acids **6** showed superior catalytic performance. In particular, tricyclic borinic acid **6c** afforded ***cis*-3** in 92% yield with high selectivity (***cis*-3**/**4** = 12, entry 4). The mild reaction conditions allow the broad functional-group tolerance, including a free hydroxy group, which may enable the sequential synthesis of oligosaccharides by iterative manipulation. The details of condition optimization, substrate scope, and synthetic application will be shown in this presentation.



entry	cat.	*cis*-3	4	*cis*-3/4
1	$PhB(OH)_2$ **5**	21%	31%	0.7
2	Ph_2BOH **6a**	60%	32%	1.9
3	**6b**	82%	11%	7.2
4	**6c**	92%	7%	12



[1] Schmidt, R. R. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212.
[2] Gouliaras, C., Lee, D., Chan, L., and Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 13926.
[3] Nakagawa, A., Tanaka, M., Hanamura, S., Takahashi, D., and Toshima, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 10935.
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3P-087s

Bio- and Organocatalysts in Highly Enantioselective One-Pot-Cascades

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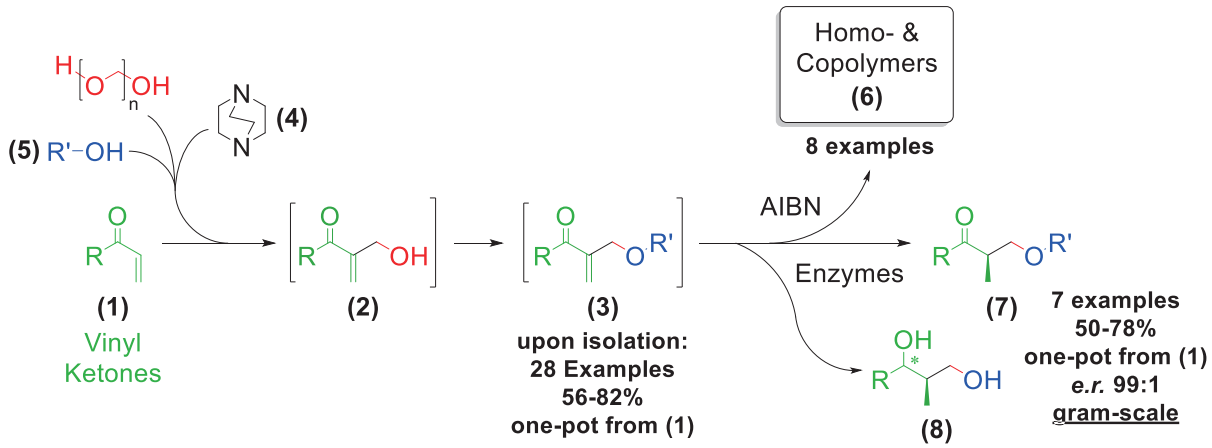
The α-hydroxymethylation of Michael-systems using formaldehyde has to be named as a simple, yet important reaction with respect to the products' vital role in total synthesis and polymer science. Additionally, not only the MBH-products themselves, but also their OH-protected analogues have proven to be valuable compounds for various purposes.[1-3] Nevertheless, a high yielding procedure towards vinyl-ketone **(1)** based MBH-etherification-products **(3)** without pre-activation of either one of the coupling partners remains unknown for the preparation of analogues based on primary and secondary alcohols.[2]



We herein present an approach not only granting one-pot access to a broad variety of non-pre-activatedly etherified MBH-products **(3)** simply using low catalyst-loadings of inexpensive DABCO **(4)** and easily accessible primary and secondary alcohols **(5)**, but implementing the further conversion of these into more complex final targets within our one-pot approach. Thus, next to e.g. sugar and steroid containing homo- and copolymers **(6)** prepared after isolation of monomers **(3)**, α-methyl ketones **(7)** and diols **(8)** were synthesized organo- and biocatalytically starting from vinyl ketones **(1)** in good to very good yields and excellent enantioselectivities on a gram-scale over at least three consecutive steps in the very same reaction vessel. The mild conditions used for the preparation of biocatalysis substrates **(3)** enable a rarely precedent, yet preparatively productive case of complexity in the combination of heterocyclic organocatalysts and enzymatic synthesis.

[1] Basavaiha D.; Veeraraghavaiah, G. *Chem. Soc. Rev.* **2012**, *41*, 68-78
[2] Bhowmik S.; S. Batra, S. *Curr. Org. Chem.* **2014**, *18*, 3078-3119
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[4] Mantel, M.; Guder, M.; Pietruszka J. *Tetrahedron* **2018**, *74*, 5442-5450

Facile Synthesis of *N*-Arylphenothiazines by Rearrangement of *o*-Sulfanylanilines

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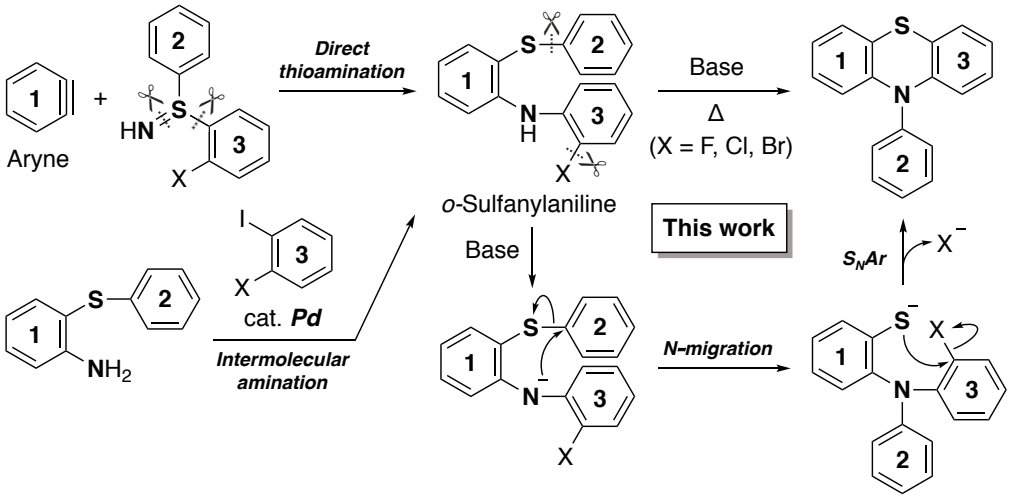
Phenothiazine derivatives are used in a wide range of fields, including medicinal chemistry and materials science. In particular, *N*-arylphenothiazines have been gaining much attention because they play versatile roles such as photoredox catalyst and organic light-emitting materials. [1] In general, *N*-arylphenothiazines have been synthesized from *N*-H phenothiazines by cross-coupling reactions with haloarenes. [2] However, synthesizable compounds by the conventional methods are limited, and a novel approach that can expand the scope of available compounds is eagerly anticipated.

Herein, we report an efficient synthesis of *N*-arylphenothiazines by heating *o*-sulfanylanilines in the presence of a base. Mechanistic studies suggested that this reaction proceeded through a C–S bond cleavage, intramolecular migratory *N*-arylation, and subsequent cyclization *via* dehalogenative S_NAr reaction. Moreover, multisubstituted *N*-arylphenothiazines were easily prepared by direct thioamination of aryne and subsequent migratory cyclization. [3]



[1] (a) H. Wang, N. Jui *J. Am. Chem. Soc.* **2018**, *140*, 163.
(b) H. Tanaka, K. Shizu, H. Nakanotani, C. Adachi *J. Phys. Chem. C* **2014**, *118*, 15985.
[2] J. Zhou, C. Hong, C. Pan *Mater. Chem. Front.* **2017**, *1*, 1200.
[3] S. Yoshida, T. Yano, Y. Misawa, Y. Sugimura, K. Igawa, S. Shimizu, K. Tomooka, T. Hosoya *J. Am. Chem. Soc.* **2015**, *137*, 14071.

Complexation between Lewis Acids and *N*-Phosphine Oxide-substituted Imidazolylidenes (PoxIms)

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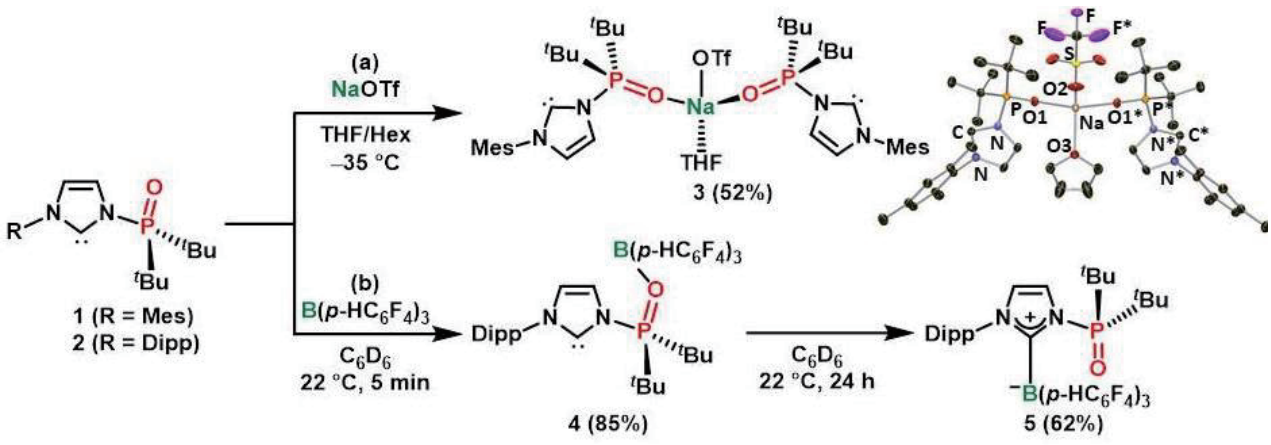
Recently, we have developed *N*-phosphine oxide-substituted imidazolylidenes (PoxIms) as a novel class of isolable, multifunctional *N*-heterocyclic carbenes,[1a,1b] and demonstrated their multipurpose utility.[2a-c] In this work, we report the complexation between PoxIms and Lewis acids such as NaOTf and triarylboranes, which dominantly proceeds via coordination of the phosphinoyl groups in the former case,[2d] yet affords both phosphinoyl- and carbene-coordinated Lewis pairs in the later case.

Firstly, we explored the reaction between **1** and NaOTf, and found that the complexation stoichiometry would depend on the reaction phase, i.e., **1**:NaOTf is 2:1 in the solid state, while it might be 3:2 in THF solution. Indeed, the solid state structure for [(**1**)$_2$Na(OTf)(THF)] (**3**) was directly confirmed by X-ray analysis by using a single crystal obtained from THF/hexane solution of **1** and NaOTf at –35 °C (Scheme 1a).

Next, the reaction of **2** with B(*p*-HC$_6$F$_4$)$_3$ was carried out in C$_6$D$_6$ at room temperature (Scheme 1b), affording the phosphinoyl-coordinated adduct **4** in 85% yield. A prolonged reaction time resulted in an intramolecular borane transfer to yield carbene–borane adduct **5**. The molecular structures of **4** and **5** were confirmed by NMR and X-ray analyses.



Scheme 1.

[1] Selected recent reviews on NHCs, see: (a) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485. (b) S. Hameury, P. de Frémont, P. Braunstein, *Chem. Soc. Rev.* **2017**, *46*, 632.
[2] (a) Y. Hoshimoto, T. Kinoshita, M. Ohashi, S. Ogoshi, *Angew. Chem. Int. Ed.* **2015**, *54*, 11666. (b) Y. Hoshimoto, T. Asada, S. Hazra, T. Kinoshita, P. Sombut, R. Kumar, M. Ohashi, S. Ogoshi, *Angew. Chem. Int. Ed.* **2016,** *55,* 16075. (c) S. Hazra, Y. Hoshimoto, S. Ogoshi, *Chem. Eur. J.* **2017**, *23*, 15238. (d) T. Kinoshita, M. Sakuraba, Y. Hoshimo, S. Ogoshi, *Chem. Lett.* **2019**, *48*, 230.

Total Synthesis of (-)-Aplysiallene and it's Biological Active Study

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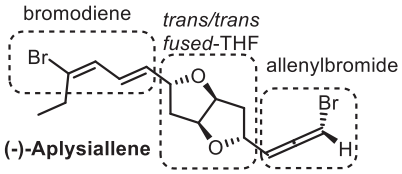
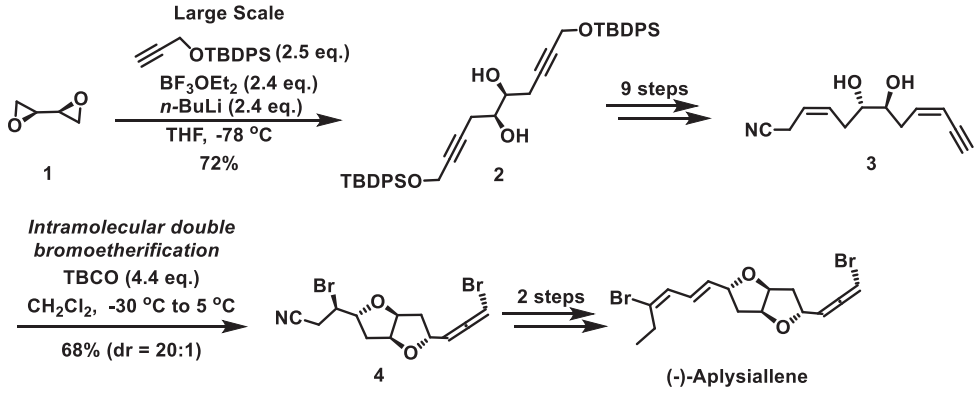
[2]*Graduate School of Dental Medicine, Hokkaido University, Kita-ku, Sapporo, 060-8586, Japan*



(-)-Aplysiallene was isolated from red algae *Laurencia Okamurai Yamada* by Kurosawa *et al* in 1985.[1)] It have *trans, trans fused*-bis THF, bromoarene and bromodiene units. This natural product was also isolated from *Aplysia Kurodai* by Okamoto *et al* in 2001, and it became clear that it has Na^+/K^+ ATPase inhibitory activity with IC_{50} = 0.7 mM.[2)] We have already synthesized (-)-aplysiallene and its analogues[3)] In this study, we developed new scalable synthesis method of (-)-aplysiallene and evaluated Na^+/K^+ ATPase inhibitory activity.

- **Total synthesis of (-)-aplysiallene**

Scheme 1 shows our synthesis study of (-)-aplysiallene. First, compound **1** was di-alkylnylated to C_2-symmetric **2** in large scale with high yield, then it was converted to diol **3** in 9 steps. Intramolecular double bromoetheration of compound **3** gave compound **4** having *trans, trans* fused-THF and bromoarene units. After construction of another side chain in 2 steps, we accomplished asymmetric total synthesis of (-)-aplysiallene.



Scheme 1

- **Activity study of (-)-aplysiallene**

As a result of the activity test of Na^+/K^+ ATPase purified from rat brain, natural products and part of their derivatives inhibited it in a concentration dependent manner (IC_{50} = 15.0 μM). On the other hand, no inhibitory activity was observed in derivatives without bromodiene structure. Next, we compared the Na^+/K^+ ATPase inhibitory activity of rat brain and pig kidney, as a result, the inhibitory activity was not observed in pig kidney (IC_{50} > 200 μM). On the other hand, ouabain (specific inhibitor of Na^+/K^+ ATPase) showed inhibitory activity (IC_{50} = 1.0 μM) in both organs (rat brain and pig kidney). This suggests that aplysiallene may show subtype selective inhibitory activity on Na^+/K^+ ATPase.

[1] M. Suzuki and E. Kurosawa, *Phytochemistry,* **1985**, *24*, 1999-2002. [2] Y. Okamoto, N. Nitanda, M. Ojika and Y. Sakagami*, Biosci. Biotchnol. Biochem*., **2001**, *65*, 474-476. [3] *J. Org. Chem.* **2015**, *80,* 10261-10277

3P-091s

Structural Properties and Antifungal Activities of Heterocyclic Compounds Bearing a Heavier Pnictogen(III) Center

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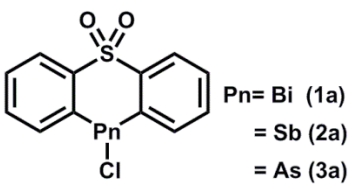
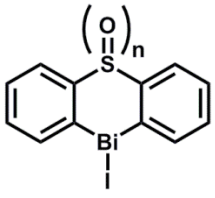
We have reported the synthesis and antifungal activity against the yeast *Saccharomyces cerevisiae* of heterocyclic organobismuth(III) compounds derived from diaryl sulfone derivatives. [1] The activity was estimated by measuring the diameter of the inhibition zone (IZ: [mm]) on agar plates in the growth inhibition test. We found that the IZ values showed a good correlation with the ClogP values of the bismuth compounds. Thus, the activity decreased as the ClogP value increased. Furthermore, DFT calculations suggested that the generation of antifungal activity of the bismuth compounds was well understood by the nucleophilic addition of a biomolecule at the bismuth atom to give an intermediate ate complex. [2] Although we have not identified the biomolecule to which these bismuth compounds bind, we expect that the Lewis acidic bismuth atom has a high affinity for thiol groups. Thus, the activity increased as the association energy (AE: kcal/mol) in the ate complex formation negatively increased, where the AE value is the calculated energy released when the organobismuth(III) compounds bind to methanethiolate anion (MeS^-) as a model nucleophilic biomolecule to form the ate complex.

It is an important issue for us to clarify the mechanism of action of heterocyclic organobismuth(III) compounds in the yeast cell and to find more active compounds. In the course of our study on the mechanism of action of **1a**, we sometimes encountered the undesired cleavage of the bismuth–carbon bond to give diphenyl sulfone. Hence, we synthesized **2a** and **3a**, the lighter pnictogen analogs of **1a**, and tested their activities and calculated their AE values. Furthermore, the activities of the heterocyclic organobismuth(III) compounds derived from diaryl sulfone derivatives were not as high as the standard antifungal drug, nystatin (IZ: 30 mm). There were no organobismuth(III) compounds exhibiting the IZ value over 20 mm. We synthesized **1b** and **2b** derived from diphenyl sulfide and diphenyl sulfoxide, respectively and found that they showed higher activities than **3b**. The structural properties and antifungal activities of **1a**–**3a** and **1b**–**3b** will be discussed from the viewpoint of ClogP and AE values.



Pn= Bi (1a)
= Sb (2a)
= As (3a)

1a-3a



n= 0 (1b)
= 1 (2b)
= 2 (3b)

1b-3b

[1] T. Murafuji *et al*., *Eur. J. Med. Chem*. **2011**, *46*, 51
[2] T. Murafuji *et al*., *Molecules* **2014**, *19*, 11077

3P-092

Development of Catalytic Oxidative Difunctionalization Reactions of Carbon-Carbon Double Bond Using Molecular Oxygens in Air

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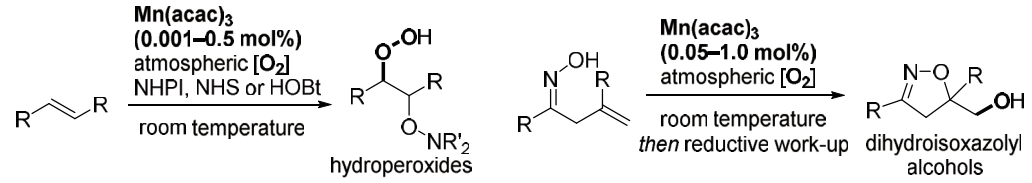
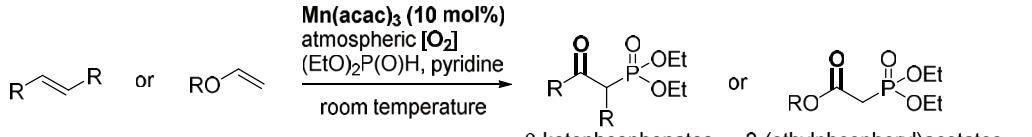
New methodologies for transition metal-catalyzed oxidation reactions have been extensively studied in the recent decade, and molecular oxygen is essentially recognized as an ideal oxidant. Despite developing the several elegant oxidation processes involving molecular oxygen as a sole oxidant, methodologies for directly incorporating molecular oxygen into organic substrates remain a major challenge in synthetic chemistry.

In continuation of our studies on manganese-catalyzed oxidative reactions, we have found that manganese(III) acetylacetonate ($Mn(acac)_3$) is a highly efficient catalyst for hydroperoxidation of carbon-carbon double bonds of enynes as well as styrene derivatives using *N*-hydroxyphthalimide, *N*-hydroxybenzotriazole or *N*-hydroxysuccinimide under mild reaction conditions (Scheme 1). We have also explored a manganese-catalyzed oxidative cyclization of unsaturated oximes to provide 4,5-dihydroisoxazolyl alcohols (Scheme 2). Notably, the unprecedentedly low catalyst loading of $Mn(acac)_3$ promoted the oxidative difunctionalization reactions of carbon-carbon double bond through the direct incorporation of molecular oxygen from air (pure oxygen is not required). To demonstrate the utility of this manganese-catalyzed reaction, we applied our method to the synthesis of a promising antitrypanosomal agent for the management of Chagas disease. On the basis of this knowledge on manganese-catalyzed oxidative difunctionalization reactions, we recently reported the aerobic oxophosphorylation of unactivated alkenes and acid-labile vinyl ether with diethyl *H*-phosphonates using the catalytic amount of $Mn(acac)_3$ (Scheme 3).



Scheme 1 $Mn(acac)_3$-catalyzed hydroperoxidation

Scheme 2 $Mn(acac)_3$-catalyzed oxidative cyclization



Scheme 3 $Mn(acac)_3$-catalyzed oxophosphorylation

[1] Yamamoto, D.; Ansai, H.; Hoshino, J.; Makino, K. *Chem. Pharm. Bull.* **2018**, *66*, 873–879.
[2] Yamamoto, D.; Soga, M.; Ansai, H.; Makino, K. *Org. Chem. Front.* **2016**, *3*, 1420–1424.
[3] Yamamoto, D.; Oguro, T.; Tashiro, Y.; Soga, M.; Miyashita, K.; Aso, Y.; Makino, K. *Eur. J. Org. Chem.* **2016**, 5216–5219.

3P-093s

Asymmetric Cyanation of Acylsilanes with Chiral Lewis Base Catalysts

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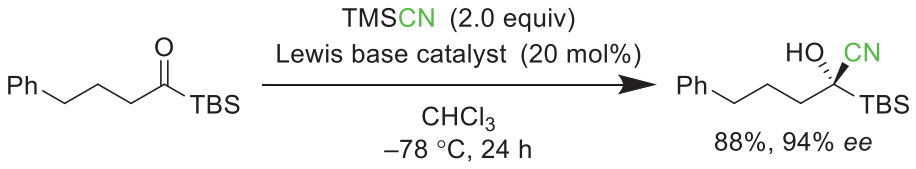
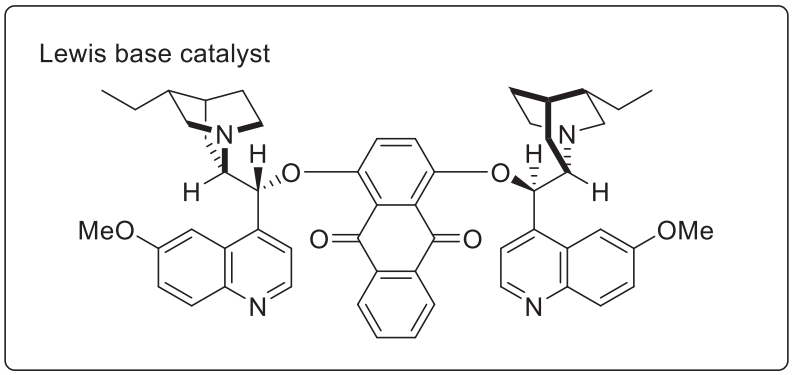
Cyanation of ketones is an efficient method for constructing tetrasubstituted chiral carbons. However, catalytic asymmetric cyanation of acylsilanes relied on an enzymatic reaction, in which only one substrate is applicable. Recently, we have accomplished catalytic asymmetric synthesis of acylsilane cyanohydrins via kinetic resolution,[1] which largely improved their synthetic approaches, however, the maximum yield is, in principle, 50%, and the substrate scope is still limited. Here we present chiral Lewis base catalysts in combination with a silyl cyanide allowed for asymmetric cyanation of various acylsilanes, affording optically active acylsilane cyanohydrins in up to a quantitative yield with high enantioselectivity.





[1] Matsumoto, A.; Asano, K.; Matsubara, S. *Chem.—Asian J.* **2019**, *14*, 116.

Studies on Total Synthesis of Polycitorol A Utilizing $Hg(OTf)_2$-Catalyzed Cycloisomerization Reaction

Priscilla Mei Yen Yoong, Keisuke Nishikawa and Yoshiki Morimoto*
Graduate School of Science, Osaka City University, Osaka 558-8585, Japan

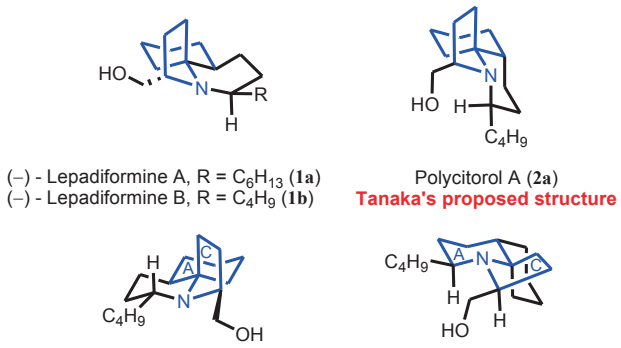
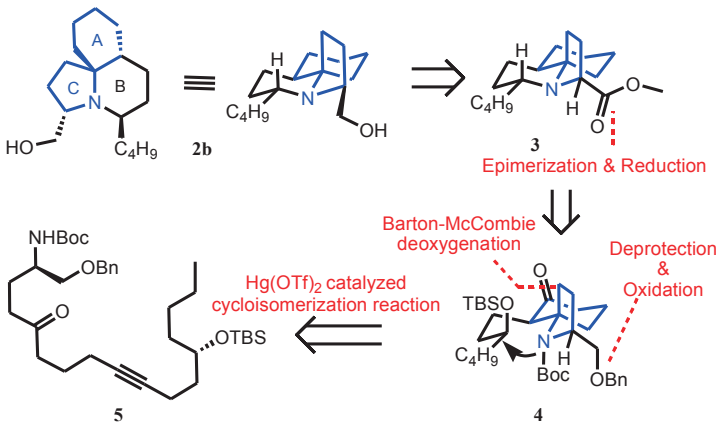


Figure 1. Representative tricyclic marine alkaloids.

Polycitorol A is one of the recent emerged new members of spirocyclic marine alkaloids (**Figure 1**), isolated from marine ascidians, *polycitoridae morph* blue.[1] In 2014, Kim and co-workers revealed that the originally proposed structure was incorrect by its total synthesis and speculated that the possible stereochemical identity of polycitorol A, is **2b** or **2c**, after a thorough comparison of its NMR spectroscopic data with the reported data of commonly related diastereomers of lepadiformine A, (–)-**1a**. Although with the convincing evidences on hand, the synthesis towards the revised structures of polycitorol A was forced to terminate because the construction of 1-azaspiro[4.5]decane (A/C-blue ring) ring system with desired stereochemical identities was a challenge in their synthetic approach.[2] Prompted by this problem, we had reported a $Hg(OTf)_2$-catalyzed cycloisomerization reaction, an effective and straightforward protocol to assemble the 1-azaspiro[4.5]decane.[3] With the idea in hand, we herein describe the studies of total synthesis of polycitorol A with the aim to elucidate the absolute configuration of polycitorol A and its biological properties owing to the strong cardiovascular effects and block of cardiac inward-rectifier potassium channel possessed by its congeners, lepadiformines.[4]

We first set **2b** as our target and the retrosynthetic analysis is summarized in **Scheme 1**. Noted that the spirocyclic product, **4** upon cycloisomerization has an opposite stereocenter at carbon linked to a methylene alcohol, reversing the stereocenter by epimerization of **3** is necessary and followed by reduction to generate **2b**. After Barton-McCombie deoxygenation of **4**, oxidation of the resultant primary alcohol and followed by Appel-like ring cyclization generates **3**. Finally, **4** could be traced back to the linear functionalized alkyne **5** by performing the $Hg(OTf)_2$-catalyzed cycloisomerization reaction.



Scheme 1. Retrosynthetic analysis of polycitorol A, **2b**.

[1] Tanaka, J *et al. Mar. Drugs* **2005**, *3*, 78.
[2] Kim, S. *et al. Chem. Eur. J.* **2014**, *20*, 17433.
[3] Morimoto, Y. *et al. Chem. Eur. J.* **2017**, *23*, 9535.
[4] M.-P. Sauviat, *et al. J. Nat. Prod.* **2006**, *69*, 558.

Development of a New Asymmetric α-Protonation in Aza-Michael Addition of α,β-Unsaturated Carboxylic Acids Catalyzed by Chiral Multifunctional Thiourea-Boronic Acid

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β-Peptides are generally stable toward enzymatic hydrolysis as compared to natural peptides. Therefore, incorporating β-amino acid units into biologically active peptides would enhance their stability and bioactivity. Due to the increasing demand for β-amino acids, various methodologies for preparing $\beta^{2,3}$- and β^3-amino acids have been established, while much less for β^2-amino acids (**Figure 1**).

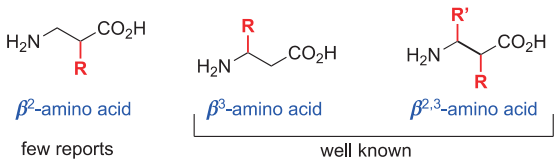
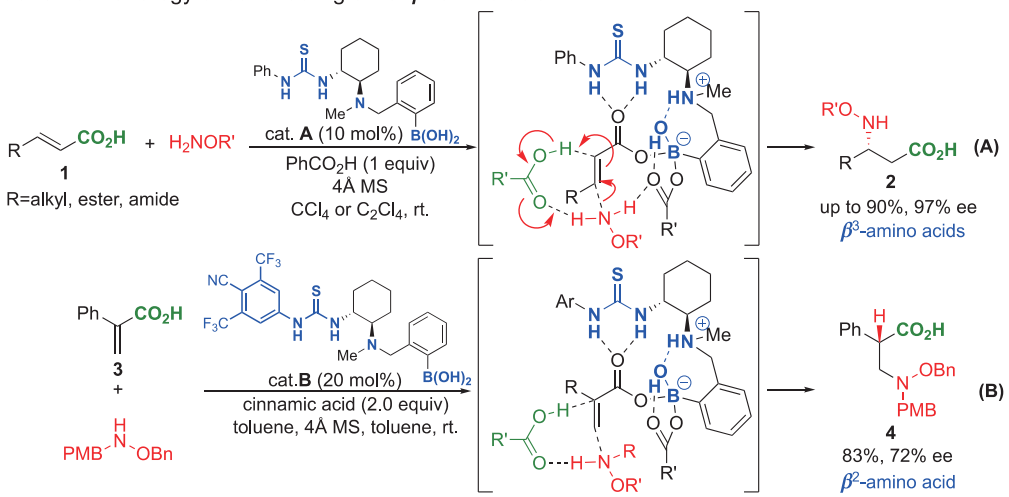


Figure 1. Structural classification of β-amino acids

We recently developed the asymmetric aza-Michael addition of $BnONH_2$ to α,β-unsaturated carboxylic acids **1** using chiral thiourea-boronic acid hybrid catalyst **A**[1,2]. Detail mechanistic analysis, including spectroscopic, experimental, and theoretical studies suggest asynchronous concerted face-selective nucleophilic addition and protonation to give product **2** (**Scheme 1A**)[3]. Based on the significant face selectivity of both two steps, we herein disclose a new catalytic synthesis of chiral *N*-hydroxy-β^2-amino acid derivatives **4** through asymmetric protonation of α-position in the aza-Michael addition (**Scheme 1B**). The above strategy led us to examine the reaction of atropic acid **3**, revealing that catalyst B and cinnamic acid efficiently controlled the stereoselectivity of α-protonation in the addition of PMBNHOBn to afford the (*S*)-**4** in 83% yield, 72% ee.

Scheme 1 Strategy of constructing chiral β^2-amino acid



[1] Hayama, N.; Kobayashi, Y.; Takemoto, Y. *Chem. Pharm. Bull.* **2016**, *64*, 704.
[2] Michigami, K.; Murakami, H.; Nakamura, T.; Hayama, N.; Takemoto, Y. *Org. Biomol. Chem.* **2019**, *17*, 2331.
[3] Hayama, N.; Kuramoto, R.; Földes, T.; Nishibayashi, K.; Kobayashi, Y.; Pápai, I.; Takemoto, Y. *J. Am. Chem. Soc.* **2018**, *140*, 12216.

3P-096s

Asymmetric Total Synthesis and Structural Elucidation of Marine Triterpene Polyethers (−)-Aplysiol B and (+)-Saiyacenol A with Potent Antitumor Activity

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Some bromine-containing polyethers, isolated from red algae and sea hares, exhibit potent cytotoxic activity against various cell lines. (−)-Aplysiol B, a marine squalene-derived triterpene polyether isolated from the sea hare *Aplysia dactylomela*, possesses feeding-deterrent and ichthyotoxic properties. As structural features, (−)-aplysiol B has a dioxabicyclo[4.4.0]decane ring system attached with a bromine-containing tetrahydropyranyl ring that is a common skeleton of triterpene polyethers produced from the genus *Laurencia*, and a tetrahydrofuran ring. However, the proposed structures **1**[1] and **2**[2] were in contradiction to the biogenetic hypothesis. Therefore, we reconsidered the biogenetic pathway of (−)-aplysiol B and synthesized the reasonable structure **3** through a key Shi epoxidation[3] followed by a 5-*exo* cyclization and a subsequent 6-*endo* bromoetherification using BDSB. The detailed comparison of the synthetic **2** and **3** with the natural product in the ^{1}H and ^{13}C NMR data and specific rotations has revealed the absolute configuration of (−)-aplysiol B to be that shown in **3**.

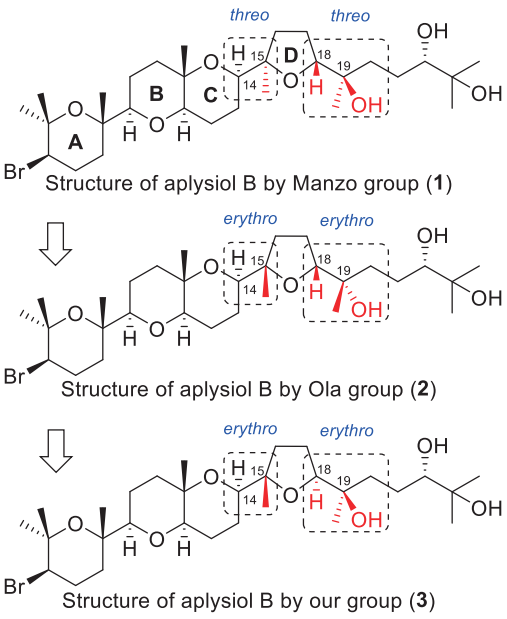

Figure 1

(+)-Saiyacenol A (**4**), a member of the thyrsiferol family, was isolated from the red alga *Laurencia viridis*. The first enantioselective total synthesis of **4** was achieved. The stepwise epoxidation followed by a 5-*exo* cascade cyclization and a 6-*endo* bromoetherification were utilized for the construction of DE-ring and bromine-containing tetrahydropyran ring, respectively. The absolute configuration of **4** was determined on the basis of the asymmetric synthesis.

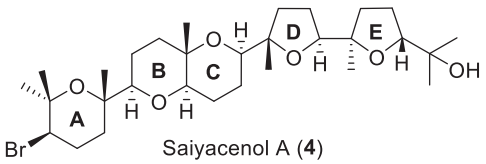

Figure 2

The antitumor activity of synthetic compounds **2**, **3**, **4**, and their analogues against HT-29, HeLa, and P388 cells was evaluated, clearly indicating that the stereochemistry of the D-ring moiety has little influence on the cytotoxic activity against P388.

[1] E. Manzo *et al. Tetrahedron* **2007**, *63*, 9970. [2] A. R. B. Ola *et al. Aust J. Chem.* **2010**, *63*, 903. [3] J. J. Fernández *et al. Tetrahedron* **2012**, *68*, 7275.

Highly Enantio- and Stereoselective Construction of *ent*-Atisane Scaffold via Organocatalytic Asymmetric Intramolecular Michael Reaction and [4+2] Cycloaddition

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Partial structure **I**, which is found in a variety of bioactive natural products such as *ent*-atisane and *ent*-kaurane diterpenes, features a *trans*-stereodiad consisting of an all-carbon quaternary and a tertiary stereogenic centers adjacent to a geminal dimethyl group (Fig. 1).

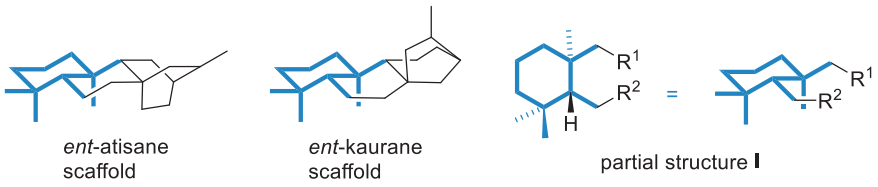
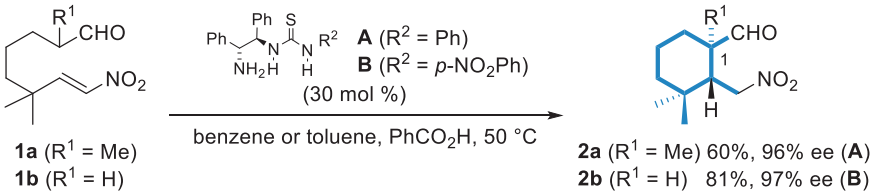


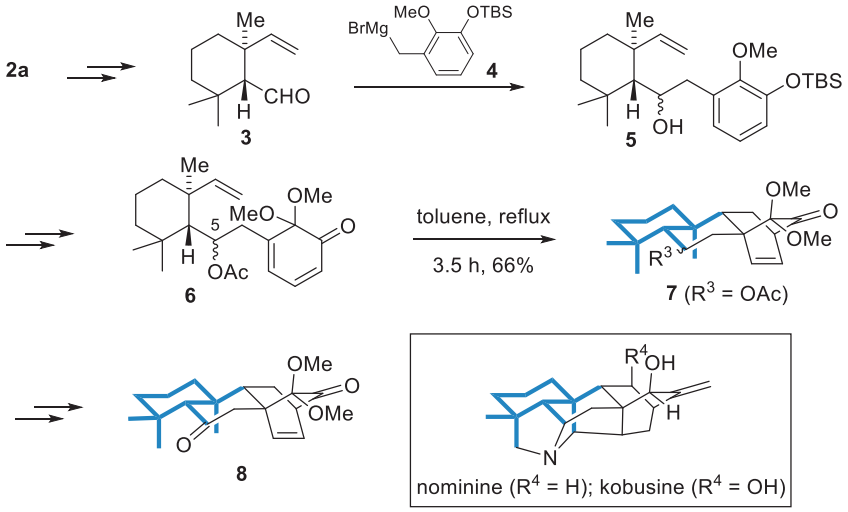
Figure 1. Structures of *ent*-atisane and *ent*-kaurane scaffolds, and their common scaffold **I**

Scheme 1. Catalytic Asymmetric Intramolecular Michael Reactions of **1a** and **1b**



We have found that the catalytic asymmetric intramolecular Michael reaction (CAIMR) of **1a** with **A** affords **2a** which possesses the *trans*-stereodiad with moderate yield and high enantio- and stereoselectivity (Scheme 1).[1] It was also found that the CAIMR of **1b** with a newly designed catalyst **B** afforded **2b** as a mixture of C1-epimers, both of which showed 97% ee, with a combined yield of 81%.[2]

Scheme 2. Construction of *ent*-Atisane Scaffold via Stereoselective [4+2] Cycloaddition of **6**



The prepared chiral building block **2a** was converted to **3**, followed by the reaction with **4** to afford **5**, which was further transformed to **6** via oxidative dearomatization (Scheme 2). The [4+2] cycloaddition of **6** proceeded in a highly stereoselective manner to give **7** as a mixture of C5-epimers, both of which were converted to **8** that possesses the *ent*-atisane ring system. The findings obtained in this research would be the basis for the enantioselective total synthesis of nominine and kobusine. The details about the highly enantio- and stereoselective CAIMRs of **1a** and **1b**, as well as the synthesis of **8** via the highly stereoselective [4+2] cycloaddition of **6** will be discussed.

[1] Sekita, H.; Adachi, K.; Kobayashi, I.; Sato, Y.; Nakada, M. *Org. Lett.* **2017**, *19*, 2390.
[2] Sato, Y.; Hosoya, Y.; Kobayashi, I.; Adachi, K.; Nakada, M. *Asian J. Org. Chem.* **2019**, in press.

Synthesis and Fluorescent Properties of 5-Phenylisoindolo[2,1-*a*]quinoline and Isoindolo[1,2-*a*]isoquinoline Dyes *via* One-pot Ring-closing Metathesis/ Oxidation/1,3-Dipolar Cycloaddition Reaction

[1]Ramon Avena, [1]Yuki Fujii,[2]Tsunayoshi Takehara, [2]Takeyuki Suzuki,[1]Kenichi Murai, [1]Hiromichi Fujioka and[1]Mitsuhiro Arisawa*

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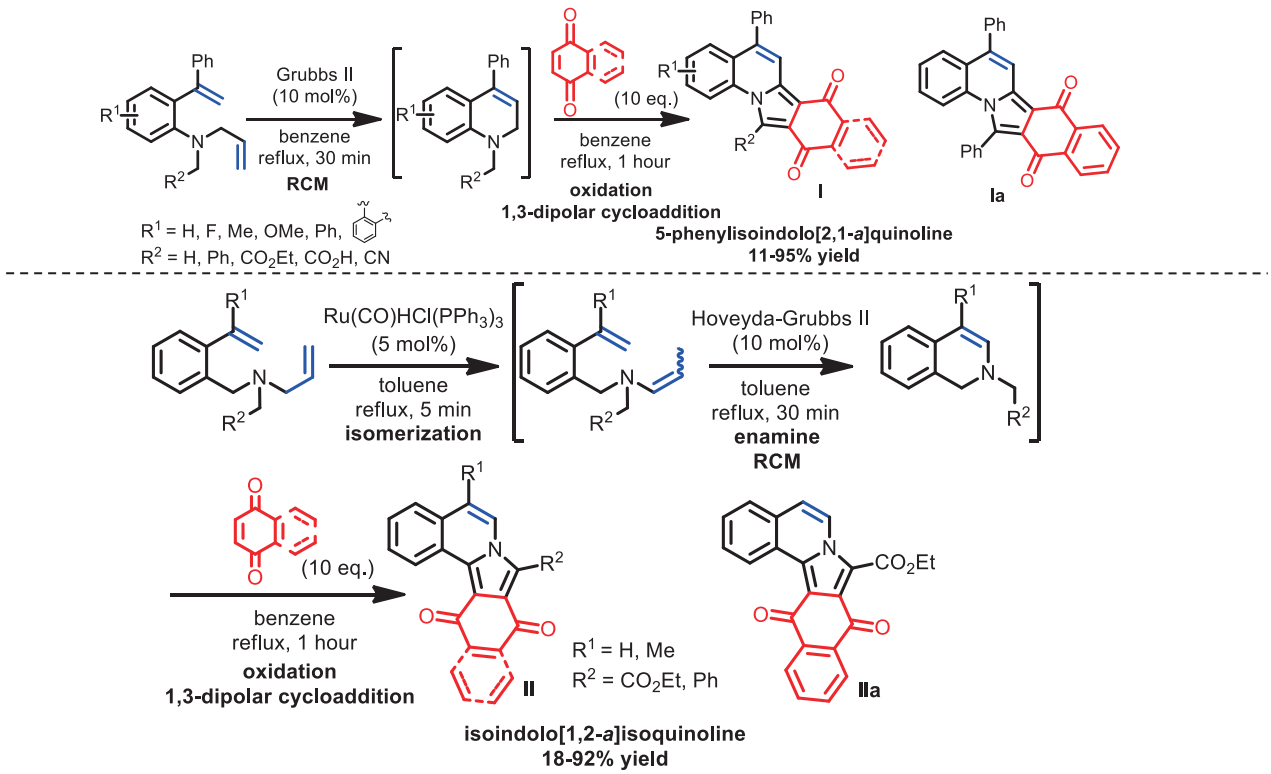
Fluorescence is one of the most frequently exploited chemical phenomena used for the study of various physiological functions using imaging techniques. Recently, the use of dyes exhibiting two-photon absorption have garnered a lot of interest due to their utility in two-photon microscopy which minimizes photodamage and allows a deeper penetration of the specimen while retaining a good optical resolution.[1] However, chemical scaffolds exhibiting this unique property remain scarce which gives impetus for the continuous development of new fluorescent probes. Previously, we have developed a methodology for the synthesis of 5-phenylisoindolo[2,1-*a*]quinoline and isoindolo[1,2-*a*]isoquinoline dyes *via* ring-closing metathesis followed by subsequent oxidation and 1,3-dipolar cycloaddition reaction.[2-3] Surprisingly, some of the dyes exhibited both one-photon and two-photon absorption properties, particularly, dyes **Ia** and **IIa** gave remarkable results. In this research, we aimed to further modify the 5-phenylisoindolo[2,1-*a*]quinoline dye and establish a structure-activity correlation to further improve its photochemical properties.



[1] Suzuki, S.; Yokoyama, K. *Biosensors*. **2015**, *5*, 337.

[2] *Angew. Chem. Int. Ed*. **2013**, *52*, 1003.

[3] *Adv. Synth. Catal*. **2015**, *357*, 4055.

Construction of 4,6-*O*-(*R*)-HHDP Group by Intramolecular Oxidative Coupling

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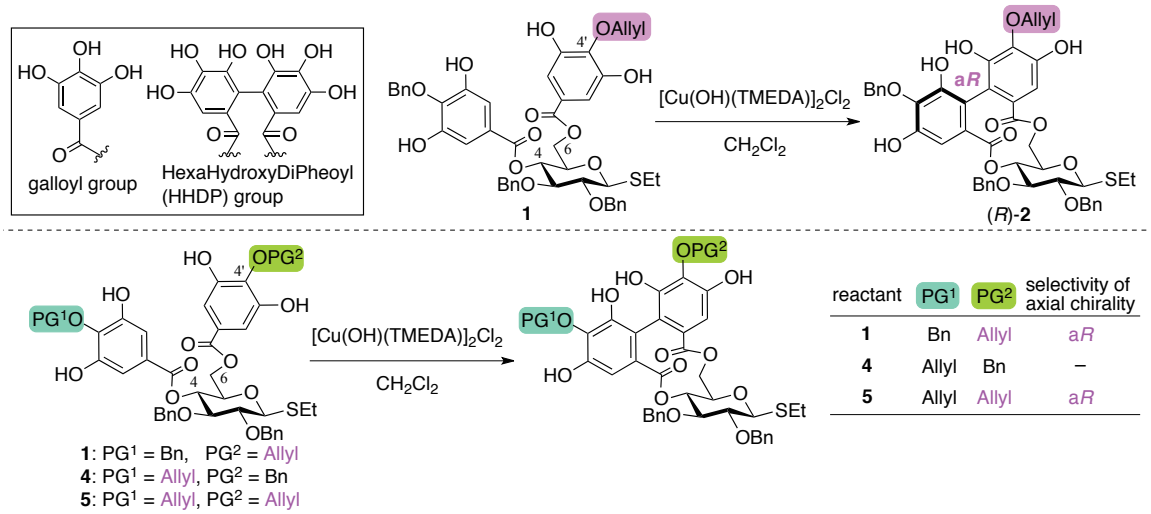
Ellagitannins are a class of hydrolysable tannins. The most basic ellagitannins consist of D-glucose core with esterified galloyl and hexahydroxydiphenoyl (HHDP) groups. Compounds of the class have structural diversity as more than 1000 are known. One of the factors of the diversity is the axial chirality of the HHDP group.[1] The axial chirality is roughly dependent on the bridging position of glucose. For example, the axial chirality of compounds which have the HHDP group bridged between 4-O and 6-O of glucose is overwhelmingly *S*. The tendency is similar in chemical synthesis of the HHDP group.[2] However, four natural ellagitannins including the 4,6-*O*-(*R*)-HHDP group, where the axial chirality is disadvantageous, have been known.[3]

In this context, we synthesized the (*R*)-HHDP group by oxidative coupling of partly protected galloyl groups on the 4- and 6-O of glucose. Specifically, the intramolecular oxidative coupling of **1** provided (*R*)-**2**, selectively. The comparative experiment using **1**, **4**, and **5** revealed that the (*R*)-selectivity appeared when the 4'-O of the galloyl group on the 6-O of glucose was protected by the allyl group.



reactant	PG¹	PG²	selectivity of axial chirality
1	Bn	Allyl	*aR*
4	Allyl	Bn	–
5	Allyl	Allyl	*aR*

[1] a) O. T. Schmidt, W. Mayer, *Angew. Chem. Int. Ed.* **1956**, *68*, 103. b) E. Haslam in *Plant Polyphenols* (Eds.: R. W. Hemingway, P. E. Laks), Springer US, New York, **1992**, pp. 169.
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[3] a) M. Era, Y. Matsuo, T. Shii, Y. Saito, T. Tanaka, Z.-H. Jiang, *J. Nat. Prod.* **2015**, *78*, 2104. b) A. Itoh, T. Tanahashi, S. Ikejima, M. Inoue, N. Nagakura, K. Inoue, H. Kuwajima, H.-X. Wu, *J. Nat. Prod.* **2000**, *63*, 95. c) T. Tanaka, S. Kirihara, G.-I. Nonaka, I. Nishioka, *Chem. Pharm. Bull.* **1993**, *41*, 1708.

Studies on stereoselective synthesis of lactonamycin

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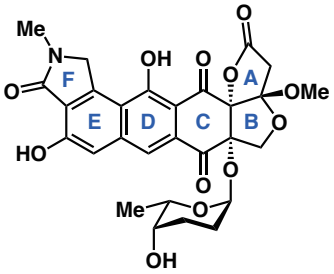
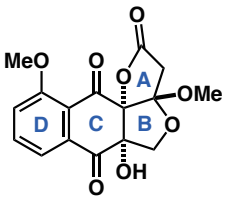
Lactonamycin (**1**) is an antibiotic isolated from *Streptomyces* species,[1] which exhibits potent antimicrobial activity against MRSA and VRE as well as strong antitumor activity.[2] The structure of **1** features a hexacyclic fused ring system, which is decorated by multiple oxygen functionalities, including an angular *cis*-diol. In connection with our synthetic study directed toward **1**, we have developed a viable route for the construction of the DEF ring system of **1**.[3] In this talk, we will report a model study for the synthesis of the ABCD ring system by setting **2** as the model target.



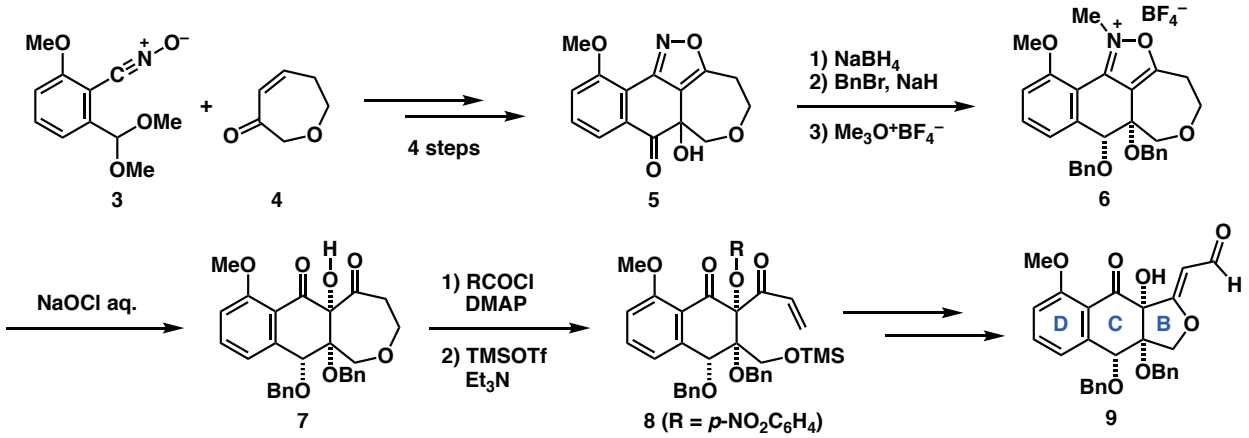
lactonamycin (**1**)



2

Starting from regioselective 1,3-dipolar cycloaddition of benzonitrile oxide **3** and cyclic enone **4**, ketol **5** was prepared via the four-step sequence involving an NHC-catalyzed benzoin cyclization. The angular hydroxylation was achieved at the stage of isoxazolium salt **6** by treatment with NaOCl, giving alcohol **7** as a single diastereomer.[4] After the *tert*-hydroxy group in **7** was protected by a benzoyl, an eliminative ring opening using TMSOTf and Et_3N gave enone **8**, which was further transformed to enal **9**.

The presentation will address further progress of the synthetic venture.



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Metal-Free and One-pot Synthesis of *β*-Lactam Derivatives via 4,6-Dihydroxysalicylic Acid-Catalyzed Oxidative Coupling of Amines to Imines under Mild Conditions

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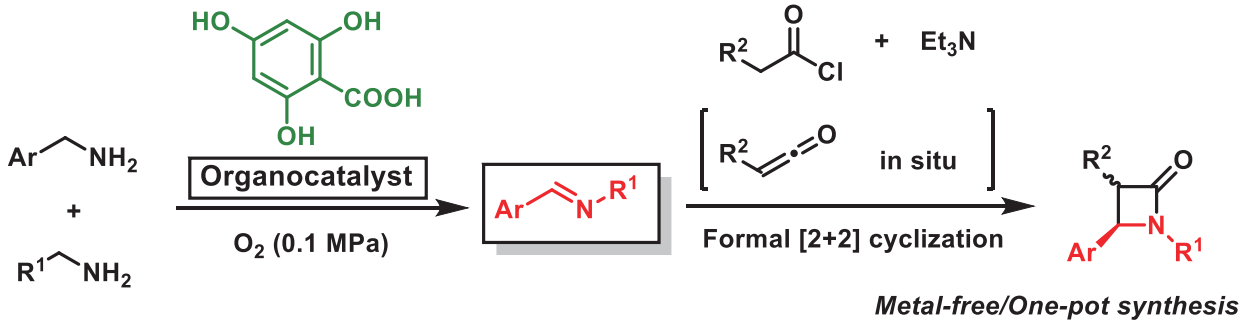
Oxidation plays an important role to produce key intermediates and materials in the chemical industry. However, most of these processes are conducted with stoichiometric amount of heavy metals or peroxides as oxidants under harsh conditions, resulting in the environmental load. Since oxidation is used frequently for the synthesis of pharmaceuticals and functional materials, it is important to reduce metal residues from the final products. Therefore, the development of metal-free, catalytic, and selective oxidation methods using molecular oxygen as an eco-oxidant for the production of these useful compounds, is strongly desired from the viewpoint of green chemistry. In this study, we have focused on a metal-free and eco-friendly synthesis of imines by the oxidation of amines under mild conditions. Imines are one of the most important intermediates for the construction of nitrogen-containing substances. We recently developed a novel efficient method for oxidation of benzylamines to the corresponding imines using 4,6-dihydroxysalicyclic acid as an organocatalyst with oxygen.[1] Since this reaction system can be conducted under mild conditions without any metal reagents, we attempted to apply this method to metal-free and one-pot approaches toward pharmaceuticals synthesis.[2–3] In this symposium, we present a metal-free and one-pot synthetic method of *β*-lactam derivatives, which are found in many pharmaceutically active compounds, via 4,6-dihydroxysalicyclic acid-catalyzed oxidative coupling of two molecules of amines to the corresponding imines. The reaction of imines, in situ generated through the catalytic oxidation of amines, with ketenes formed from acyl chlorides in the presence of base gives the corresponding *β*-lactam derivatives in excellent yield with *cis*-selectivity. This method provides a convenient approach to synthesize novel *β*-lactams under mild conditions.



[1] Dong, C-p.; Higashiura, Y.; Marui, K.; Kumazawa, S.; Nomoto, A.; Ueshima, M.; Ogawa, A. *ACS Omega* **2016**, *1*, 799.
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3P-102

Theoretical Study on Self-assembly process of Octahedron-shaped Molecular Capsule

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[2]*Element Strategy for Catalysis and Battery (ESICB), Kyoto University, Kyoto, 615-8510, Japan*
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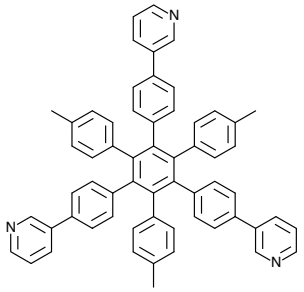
Self-assembly is a process, in which the components spontaneously assemble to form an order-structure. An octahedron-shaped molecular capsule $[M_6L_8]^{12+}$ developed by Professor Hiraoka and coworkers is one of the examples. It consists of six metal ions (M) and eight disk-shaped tris-monodentate ligand (L) (Scheme) [1]. The time evolution of the assembly process was experimentally observed by utilizing a novel method called QASAP (quantitative analysis of self-assembly process). Therefore, in order to clarify the intermediates, we computed the process based on master equations between transitional states consisting of a set of compositional formula of intermediates. The method enables us to understand intermediates and conversions among them. It is interesting that this approach successfully describes the overall trend of the time evolution of chemical species though it adopts only simple rules for ligand-exchange-type reaction.



Scheme 1

We also introduced a quantum effective Hamiltonian model to compute the geometrical structures of transient species [3]. The obtained binding energies for the intermediates agree very well with those from standard DFT computations in a wide range of interaction, indicating that our model is capable to adequately describe the interaction energy with much lower computational costs. The present model makes it possible to explore the potential energy surface. Because there is a huge number of intermediates and their conformers, a rapid computation is vital to properly understand the system. At the final stage of assembly studied with this model, two different reaction pathways were found that were derived from the ligand chirality [4].

[1] Y. Tsujimoto, T. Kojima, S. Hiraoka, *Chem. Sci.* **5**, 4167 (2014); S. Hiraoka, *Bull. Chem. Soc. Jpn.* **91**, 957 (2018).
[2] Y. Matsumura, S. Hiraoka, H. Sato, *Phys. Chem. Chem. Phys.* **19**, 20338 (2017).
[3] Y. Matsumura, S. Iuchi, H. Sato, *Phys. Chem. Chem. Phys*. **20**, 1164 (2018).
[4] Y. Matsumura, S. Iuchi, S. Hiraoka, H. Sato, *Phys. Chem. Chem. Phys*. **20**, 7383 (2018).

Theoretical study on the isomerization mechanism of α-acids

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[1]*Undergraduate School of Industrial Chemistry, Kyoto University, Kyoto 615-8510, Japan*
[2]*Department of Chemistry, Biology, and Marine Science, University of the Ryukyus, Nishihara, Okinawa 903-0213, Japan*
[3]*Department of Molecular Engineering, Kyoto University, Kyoto 615-8510, Japan*

Hops are main ingredients of beer. The principal bitter taste of beer comes from iso-α-acids, which are obtained from thermal isomerization of α-acids extracted from hops during the wort boiling process [1]. The isomerization of α-acids leads to two epimeric iso-α-acids: *trans*-iso-α-acids and *cis*-iso-α-acids (Fig. 1). The ratio of *cis*/*trans* isomerization strongly depends on the reaction conditions. It is experimentally known that the *trans*-iso-α-acids are kinetically favored products whereas the *cis*-iso-α-acids are thermodynamically favored ones [2]. Furthermore, metal cations such as Mg^{2+} and Fe^{3+} accelerate the isomerization of α-acids [3]. However, the detailed molecular mechanism is unknown. In this study, we theoretically investigated the isomerization of cohumulone, a kind of α-acids, and the metal ion effect with the density functional theory. We employed the B3LYP/6-31+G(d) functional with the SMD solvation model. The calculated activation free energy of *trans*-isocohumulone is 3.63 kcal/mol lower than that of *cis*-isocohumulone whereas the reaction free energy of *trans*-isocohumulone is 2.15 kcal/mol higher than that of *cis*-isocohumulone. This result is in good agreement with the experimental one. The reaction free energy of Mg-*cis*-isocohumulates is about 4 kcal/mol lower than that of *cis*-isocohumulone, which is consistent with the experimental result. Further analysis will be demonstrated in the poster presentation.

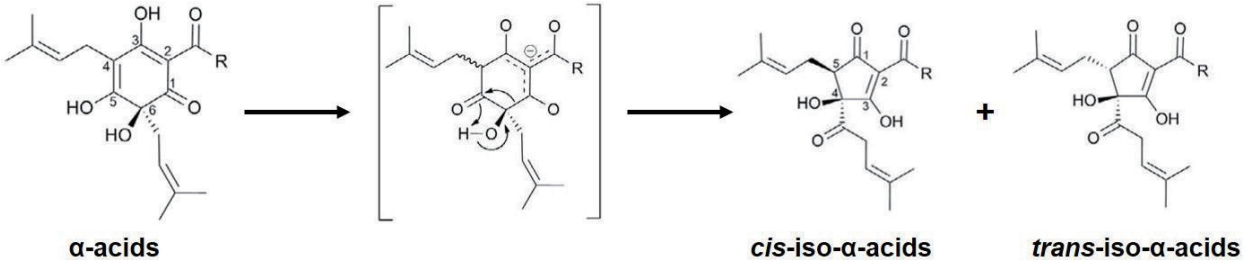

Fig. 1. Isomerization of α-acids [1].

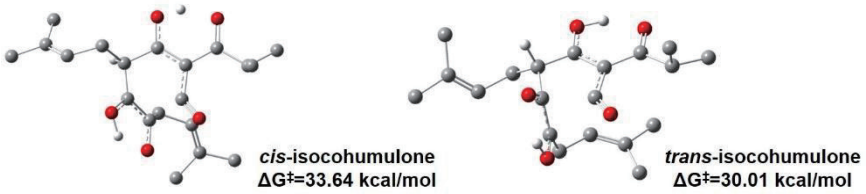

Fig. 2. Calculated transition-state geometries leading to the *cis*/*trans*-isocohumulone.

[1] Steenackers B.; De Cooman, L.; De Vos, D. *Food Chem*. **2015**, *172*, 742.
[2] Jeskula, B.; Kafarski, P.; De Cooman, L. *J. Agric. Food Chem*. **2008**, *56*, 6408.
[3] Kostrzewa, D. et al. *J. Inst. Brew*. **2016**, 122, 493.

Pd-Catalyzed Acetalization with Diazoquinone

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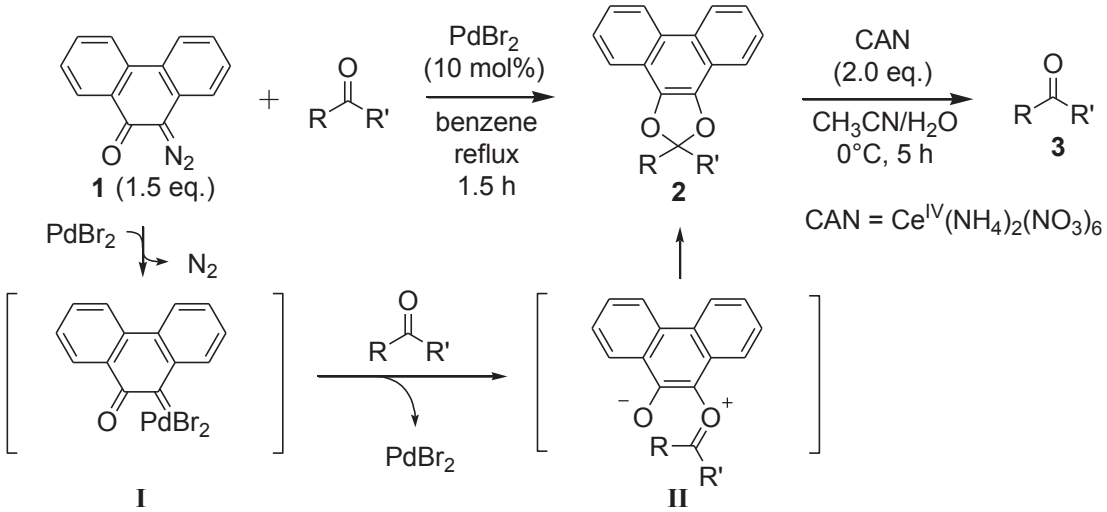
For the synthesis of complex organic compounds such as natural products and its derivatives, protection of functional groups is often required. Acetal is common protective group of carbonyl groups, and acetalization of carbonyl groups is generally conducted under acidic conditions. Therefore, when the compounds have acid sensitive functional groups, such as silyloxy groups and trityloxy group, direct introduction of acetal group is difficult. Development of acetalization under neutral conditions solve the problem and would offer a new strategy for the synthesis of target molecules.

We developed a new neutral acetalization using Pd(II) catalyst and diazophenanthquinone **1** (Scheme 1). When 10 mol % of $PdBr_2$ and diazophenanthquinone **1** were treated to carbonyl compounds in benezene at reflux, corresponding acetals were obtained in good yields. The reaction would be proceeded as follows. First, diazophenanthquinone **1** reacted with $PdBr_2$ to form Pd-carbene **I** with releasing nitrogen. Next, carbonyl compounds attacked Pd-carbene **I** to generate oxonium ylides **II**. Finally, intramolecular cyclization proceeded to form acetal **2**.

Deprotection of acetal **2** successfully proceeded by treating $Ce^{IV}(NH_4)_2(NO_3)_6$ in aqueous acetonitrile.



Scheme 1 Pd(II)-catalyzed acetalization

Synthesis of Distorted 1,8,13-Trisilyltriptycenes and its Transformation into Heterocyclic Cage Molecules

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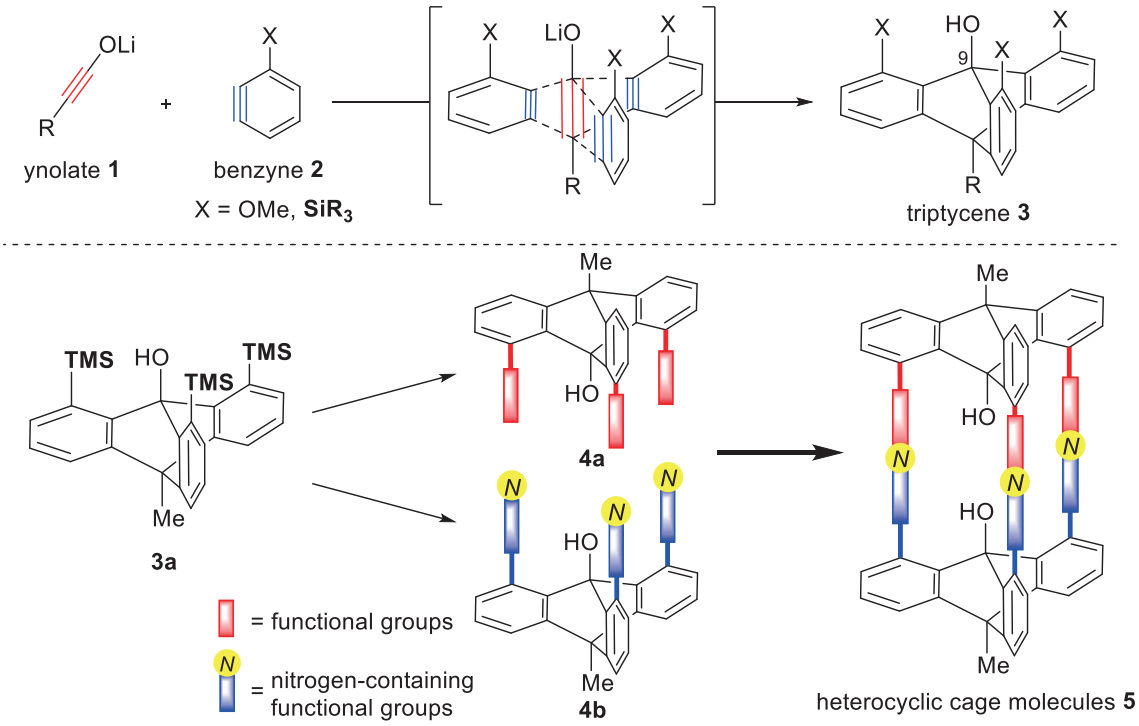
[1] *Institute for Materials Chemistry and Engineering, Kyushu University,*
[2] *Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasuga, Fukuoka 816-8580, Japan*

Triptycenes, which have three fixed benzene rings, have been increasingly used in material science and supramolecular chemistry. We have recently developed a novel synthesis of triptycene **3** using triple cycloaddition of ynolates **1** to benzynes **2**.[1] It was also found that 3-methoxybenzyne selectively gives *syn*-substituted triptycenes where three methoxy groups are placed with same side of C9-hydroxy group. In this study, ynolate-aryne triple cycloaddition using 3-silylbenzynes was investigated.

Benzynes bearing silyl groups such as TMS, TBS, TIPS groups were treated with ynolate, which regioselectively afforded trisilyltriptycenes. X ray crystallographic analysis revealed that the compounds have distorted benzene rings due to steric congestion among silyl groups. Tri(TMS)triptyene **3a** was then converted into halogenated triptycenes which was used as a versatile intermediate for *syn*-substituted triptycenes **4** with phenyl, vinyl and alkynyl groups.[2] Furthermore, the *syn*-substituted triptycenes were employed for synthesis of heterocyclic cage molecules such as **5**.



[1] Umezu, S.; Gomes, G. P.; Yoshinaga, T.; Sakae, M.; Matsumoto, K.; Iwata, T.; Alabugin, I.; Shindo, M. *Angew. Chem. Int. Ed*. **2017**, *56*, 1298.
[2] to be submitted

Synthesis and Properties of Sumanene-Ruthenium Complex

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Bis(2,2′:6′,2″-terpyridine)-ruthenium (II) has gained much attentions as functional templates in the fields of supramolecular chemistry, [1] basic photochemistry and photophysics [2] due to the strong coordination ability based on the lone pairs of three nitrogen atoms with Ru and long-range electron or energy transfer. Meanwhile, bowl-shaped π-conjugated molecule, sumanene, [3] which possesses concave and convex faces with different electrostatic potentials, tends to form a one-dimensional π-stacking columnar structure in the solid state. [4] Therefore, sumanene grafting with terpyridine may be the potential candidate for terpyridine complex-based electroluminescence and photovoltaic materials. Here we show the preparation of new supramolecular building block, sumanenylterpyridine (**1**), sumanenyl-Ph-terpyridine (**3**), bis(sumanenylterpyridine)-Ru complex (**2**) and bis(sumanenyl-Ph-terpyridine)-Ru complex (**4**). The complex **2** and **4** display a strong absorption peak in the visible region corresponding to a metal-to-ligand-charge-transfer (MLCT) transition, as well as the emission band arising from the lowest lying triplet excited MLCT state.

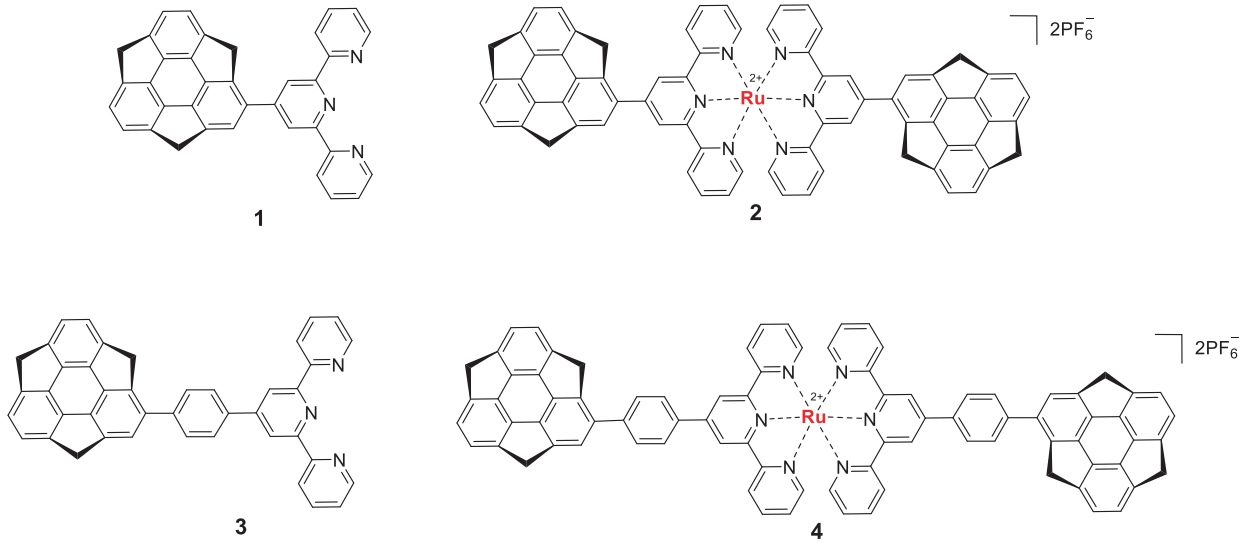

Figure 1. Molecular structure of **1**, **2**, **3** and **4**.

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[3] Sakurai, H.; Daiko, T.; Hirao, T. *Science* **2003**, *301*, 1878.
[4] Mebs, S.; Weber, M.; Luger, P.; Schmidt, B. M.; Sakurai, H.; Higashibayashi, S. *Org. Biomol. Chem.* **2012**, *10*, 2218.

Efficient Synthesis of Azatriphenylenes by Iridium-Catalyzed [2+2+2] Cycloaddition of Biaryl-Linked Diynes with Nitriles

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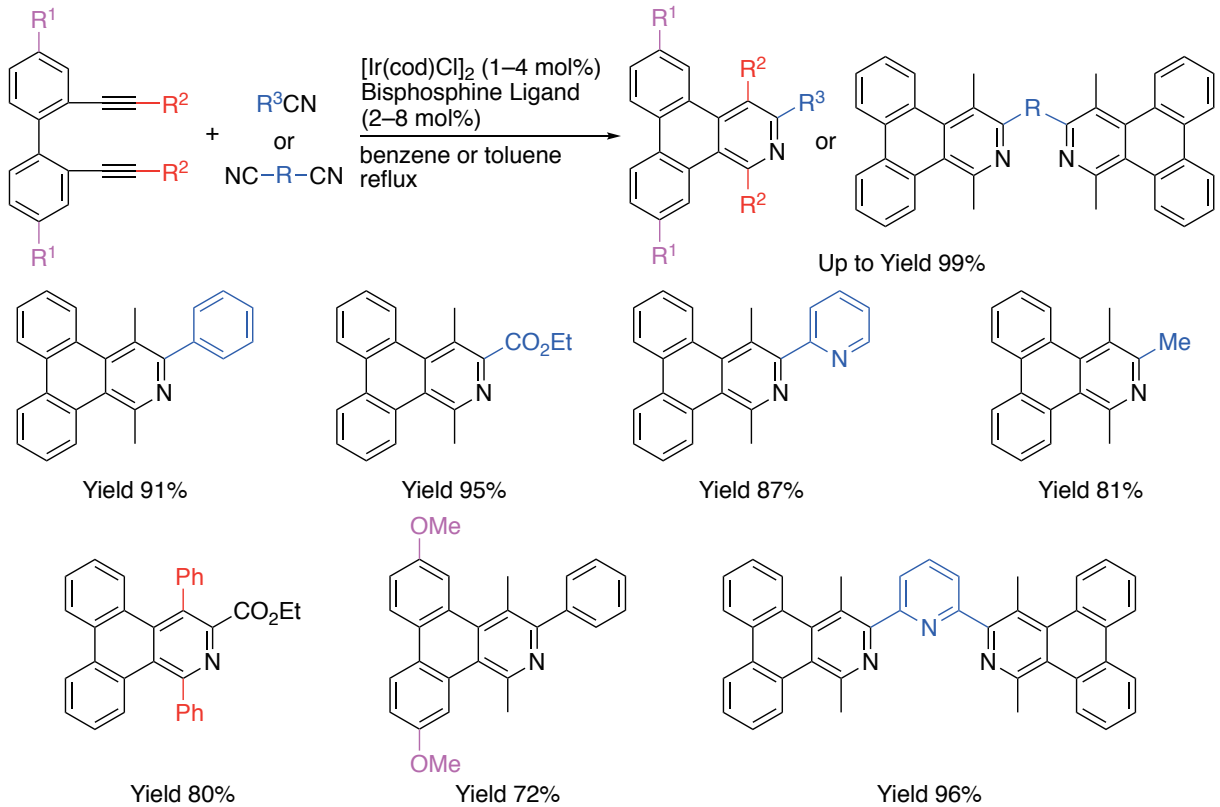
Polycyclic aromatic compounds show the excellent electrochemical and photochemical properties, and therefore have received much attention as the important basic structures of organic functional materials. In particular, triphenylenes are fascinating compounds due to the rigidity and planarity, and various efficient methods for the synthesis of triphenylenes have been reported. However, in contrast to triphenylenes, the synthetic methods of nitrogen-containing analog of triphenylene, azatriphenylenes, have not been well-developed.

Transition-metal catalyzed [2+2+2] cycloaddition is atom-economical and straightforward method for the systematic synthesis of heteroaromatic rings and have been used for the formation of electronically and photochemically useful heteroaromatic compounds. Our group has recently developed a Ir/bisphosphine complex-catalyzed [2+2+2] cycloaddition between biaryl-linked diynes and nitriles to provide a variety of multi-substituted azatriphenylenes in high yields.[1] Various nitriles including aromatic nitriles, heteroaromatic nitriles, aliphatic nitriles, and functionalized nitriles can be applied for the reaction. High yields of oligoheteroarenes were also obtained with dicyanides through double cyclization.



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Concise total synthesis of haouamine A·B and their derivatives

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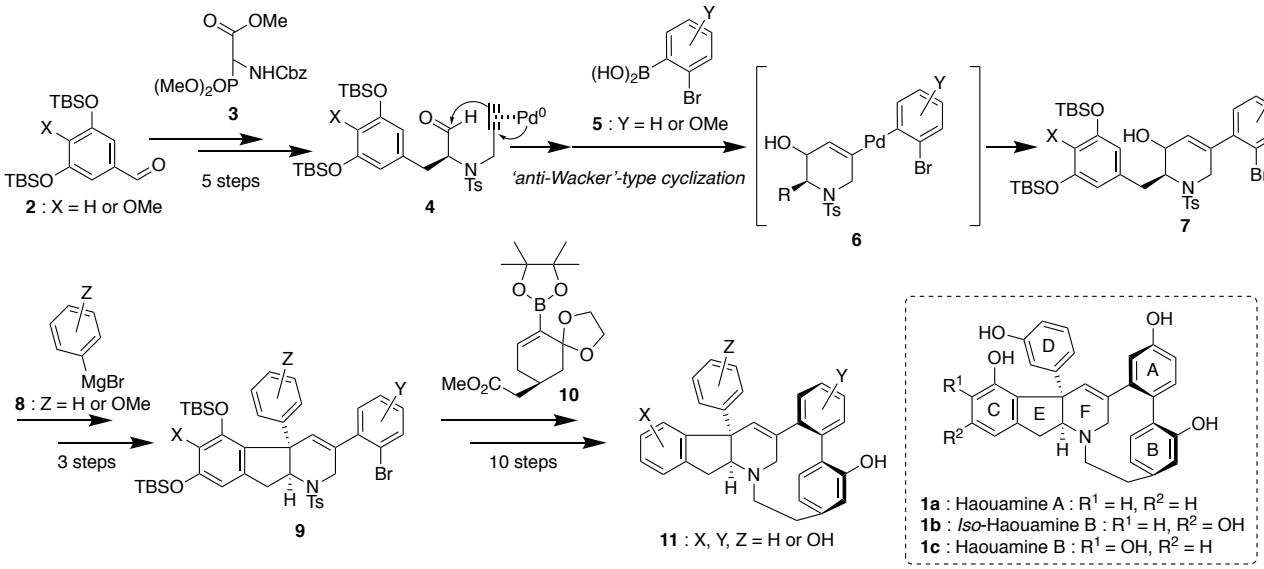
Haouamines (**1**) are polycyclic marine alkaloids isolated from *Aplidium haouarianum* collected off Tarifa Island in southern Spain [1]. Their unique structural features including an indeno-tetrahydropyridine and a strained aza-paracyclophane with an axial chirality attracted considerable attention in the chemical community and several researchers have achieved their total syntheses [2]. Haouamine A (**1a**) exhibits strong and selective cytotoxicity against human cancer cell line HT-29 (IC_{50} 0.1 μg/mL) whereas haouamine B (**1c**) is much less cytotoxic than **1a**, probably due to its instability. To understand the effect of phenolic hydroxyl groups in haouamines on the biological activity, we started to establish a concise synthetic route for haouamine derivatives.

Our own palladium-catalyzed arylative cyclization [3] of alkyne-aldehyde **4** with arylboronic acid **5** followed by oxidation, 1,2-addition of Grignard reagent **8**, and 'Friedel-Crafts'-type cyclization provided indeno-tetrahydropyridine **9** with a wide variety of substituents on the A, C, and D rings (Scheme 1). Subsequent Suzuki-Miyaura cross-coupling reaction with cyclohexenylboron reagent **10**, monodeoxygenation of the C ring, macrocylization, and oxidative aromatization developed by Baran's group [2b] afforded haouamine derivatives including natural haouamine B (**1c**), which was successfully isolated as a relatively stable acid salt.



Scheme 1

[1] Garrido, L.; Zubía, E.; Ortega, M. J.; Salva, J. J. *J. Org. Chem.* **2003**, *68*, 293–299.
[2] (a) Baran, P. S.; Burns, N. S. *J. Am. Chem. Soc.* **2006**, *128*, 3908–3909; (b) Burns, N. Z.; Krylova, I. N.; Hannoush, R. N.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 9172–9173; (c) Matveenko, M.; Liang, G.; Lauterwasser, E. M. W.; Zubía, E.; Trauner, D. *J. Am. Chem. Soc.* **2012**, *134*, 9291–9295; (d) Momoi, Y.; Okuyama, K.; Toya, H.; Sugimoto, K.; Okano, K.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 13215–13219.
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Enantiodivergent and Quantitative Conversion of Racemic Propargyl Alcohols into Their Both Enantiomers Using Lipase-Catalyzed Dynamic Kinetic Resolution

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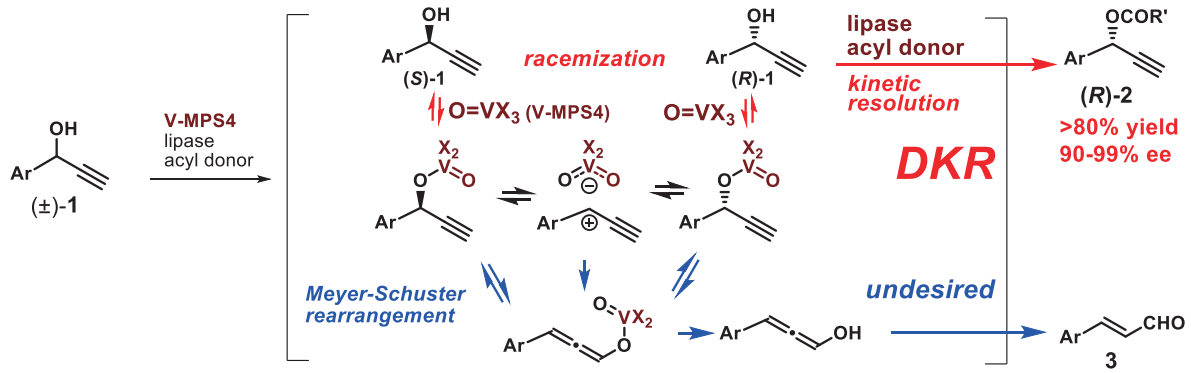
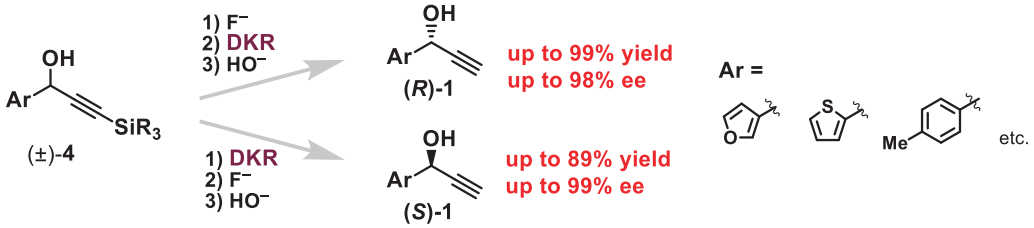
Very recently, we have applied our V-MPS4/lipase co-catalyzed dynamic kinetic resolution (DKR)[1] to racemic propargyl alcohols **1** to produce the corresponding optically active esters (*R*)-**2** in >80% yields with 90-99% ee.[2] The success is owed to our investigation of solvents that accelerated the racemization while sufficiently suppressing the common oxovanadium-catalyzed rearrangement of **1** to irreversibly produce enals **3** (Meyer-Schuster rearrangement). The relative rates of rearrangement and racemization were found to be significantly dependent on solvents. In particular, (trifluoromethyl)benzene effectively suppressed the rearrangement while enhancing the racemization, and acetonitrile was another option for decelerating the rearrangement.



As shown in the above Scheme, most of natural lipases tend to selectively acylate (*R*)-secondary alcohols by recognizing the size difference of two substituents adjacent to the hydroxyl group. We next focused on the quantitative production of (*S*)-**1** from racemic **1** using our lipase-catalyzed DKR. For this purpose, we considered that the attachment of a removable dummy substituent to the smaller substituent could change it to the larger one leading to the acylation of the original (*S*)-**1**. Actually, we could produce enantiomer (*S*)-**1** by DKR of (±)-**4** bearing a trialkylsilyl group at the ethyl moiety followed by cleaving the silyl and acyl substituents.

In conclusion, the V-MPS4/lipase co-catalyzed DKR has been applied for racemic propargyl alcohols to produce their both enantiomers in >80% yields with 90−99% ee in many cases.



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[2] S. Akai, et al., *Org. Lett.*, **2019**, *21*, 2978.

Chiral Symmetry Breaking of Spiropyrans and Spirooxazines

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Spiropyrans and spirooxazines belong to a series of valuable organic dyes by the integrity of their thermochromic and photochromic properties (**Figure 1**). The spiro-carbon compounds are chiral; however, their asymmetric synthesis has not been achieved except by optical resolution using a chiral HPLC stationary phase.[1] We focused on the development of optically active spiropyrans and spirooxazines via dynamic enantioselective crystallization. Total optical resolution by dynamic crystallization is widely interested because optically pure materials were easily obtained by one crystallization from a racemic mixture.[2] Now we applied this methodology to the total optical resolution of these valuable spiro compounds.

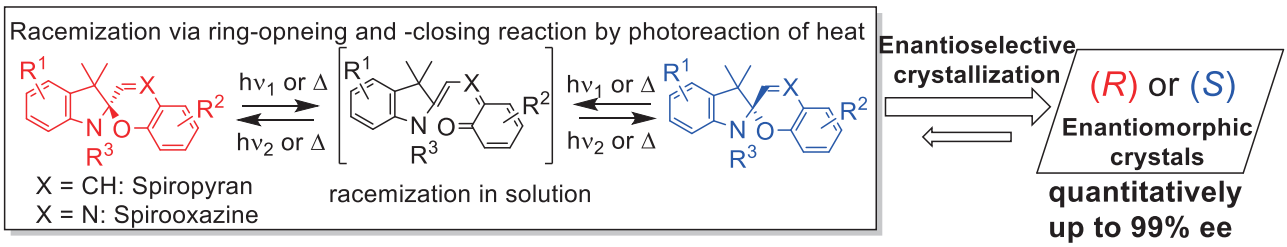

Figure 1. Chiral symmetry breaking of spiropyrans and spirooxazines by dynamic enantioselective crystallization.

Chiral symmetry breaking by the solvent evaporation method and Viedma's ripening for three racemic conglomerate crystals including two spiropyrans and one spirooxazine was performed.[3] All enantiomorphic crystals were obtained by dynamic crystallization in pure form, and the chirality was established by the solid-state CD spectra and the HPLC analysis using chiral column. Two spiropyrans racemized even at room temperature; however, the activation free energy of racemization of spirooxazine in methanol was 23.0 kcal mol^{-1} and the half-life was 63 min at 25 degrees.

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[3] H. Ishikawa, N. Uemura, R. Saito, Y. Yoshida, T Mino, Y. Kasashima, M Sakamoto, *Chem. Eur. J.*, **2019**, *in press*.

Regio- and Stereoselective Hydroarylation of Alkynes with Azoles

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Thiazole-containing π-conjugated moieties are important structural units in the development of new electronic and photo-chromic materials. We have developed a palladium-catalyzed *syn*-hydroarylation reaction of diaryl alkynes with thiazoles, which provides access to thiazole-containing triarylethylenes. Pd(II) complexes derived from Pd(0) species and carboxylic acids facilitated C–H functionalization of the unsubstituted thiazole with high C5 selectivity. The catalytic system was also compatible with other azoles, allowing the stereoselective syntheses of various trisubstituted olefins.

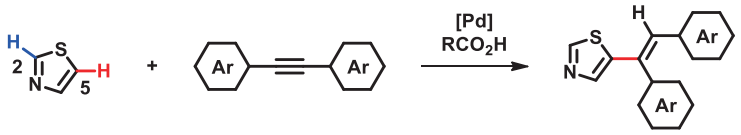

Figure 1. Hydroarylation of diaryl alkynes with thiazole

3P-112s

Synthesis of Polycyclic Heterocycles by Annulation with Alkenes

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In continuation of our research interest on C–H functionalization,[1] herein we developed a new palladium-catalyzed annulation strategy of pyrazoles using different alkenes. This transformation provides a variety of polycyclic compounds having a pyrazole core in a single step, where the molecular complexity was dramatically increased. The resulting polycycles further functionalized at a later stage to afford different types of heterocyclic systems and pyrazole-containing polymers.

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3P-113

Nickel-Catalyzed Regioselective Olefin Migration Reaction

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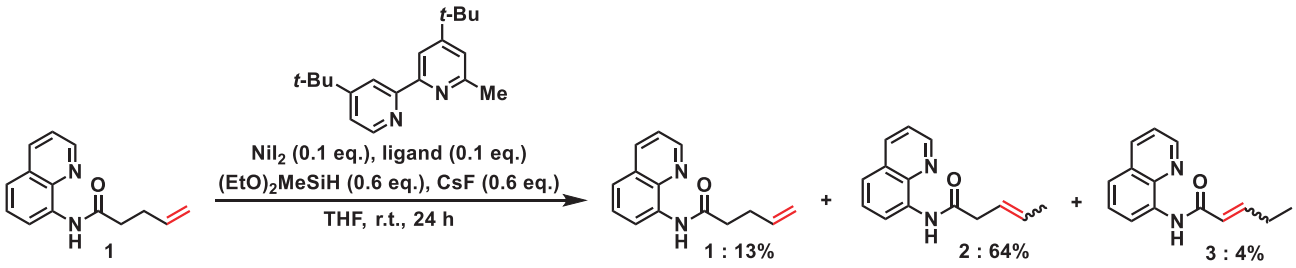
There are various lipid molecules in human beings, and unsaturated fatty acids play a central role as its basic component and the precursor of lipids. Unsaturated fatty acids are known to exhibit different physiological activities and functions depending on the length of the alkyl side chain and the degree of unsaturation. From the viewpoint of synthesis, unsaturated fatty acids having carbon-carbon double bonds, useful for functionalization, have high value as building blocks.

In this study, the author is developing a methodology to synthesize selectively regioisomers of double bond of unsaturated carboxylic acids by controlling olefin migration reaction (chain walking reaction) using transition metal catalyst. Specifically, in the process of the olefin migration reaction, the position of double bond is controlled regioselectively to some extent by trapping metal-carbon species on the alkyl chain with the directing group.

At first, preliminary experiments using a model substrate were carried out to address this research. As a model substrate, the amide **1**, prepared from 4-pentenoic acid with 8-aminoquinoline, was selected. As a result of examinations (transition metal catalyst, bipyridyl ligand, hydride source, etc.), the desired internal olefin **2** was obtained in 64% yield(NMR analysis). Generally, in the chain walking reaction system, generation of α, β-unsaturated ester is the most possible major product. Therefore, this result is a very important finding for this research project aiming at "control of the regioselective olefin migration by directing group". In this poster presentaion, the author will discuss recent approaches to regioselective olefin migration reaction for other analogs of unsaturated carboxylic acid using various reaction conditions.



$Fe(PMe_3)_4$-Catalyzed C–H Alkylation of Aromatic Ketones with *N*-Alkenylindoles and Partial Indolylation via 1,4-Iron Migration

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C–H functionalizations using catalysts containing iron has attracted particular attention and has been widely studied by many research groups,[1,2] but expansion of its scope is still desired. For example, there have been only two reports on iron-catalyzed ketone-directed C–H functionalizations.[2,3] Our group recently found that C–H/olefin coupling of aromatic ketones proceeds using $Fe(PMe_3)_4$ catalyst.[3]

Here we report that the C–H alkylation of aromatic ketones with *N*-alkenylindoles also proceeds in the presence of only a simple $Fe(PMe_3)_4$ catalyst (Figure 1). In addition, the reaction provided ortho C–H indolylation products as minor products. The indolylation products are considered to be formed via C–H oxidative addition and hydrometalation to form intermediate **A**, followed by rarely-observed 1,4-iron migration[4] to provide indolyliron complex **B** before reductive elimination from the alkyliron intermediate **A**. For example, when the reaction of pivalophenone with *N*-vinylindole was carried out using 5 mol % $Fe(PMe_3)_4$ at 60 °C for 20 h, the alkylation and the indolylation proceeded in 77 and 11% NMR yields, respectively.

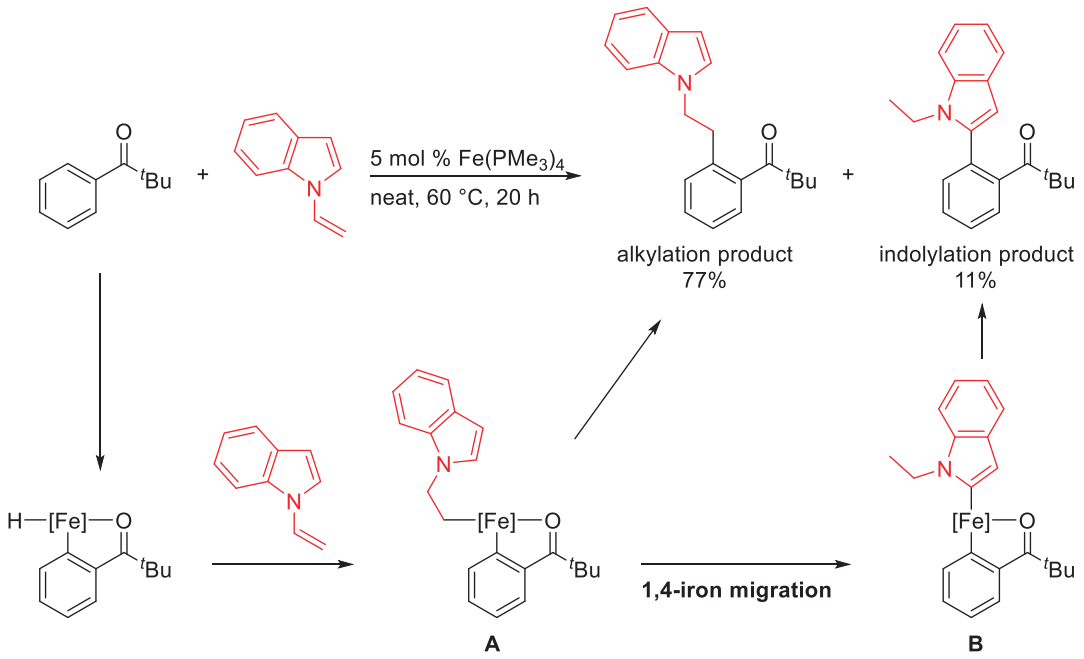

Figure 1. Iron-Catalyzed C–H Alkylation and Indolylation with *N*-Vinylindole.

[1] Shang, R.; Ilies, L.; Nakamura, E. *Chem. Rev*. **2017**, *117*, 9086.
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C4-Functionalization of Pyrazoles by Buchwald-Hartwig Coupling Reaction

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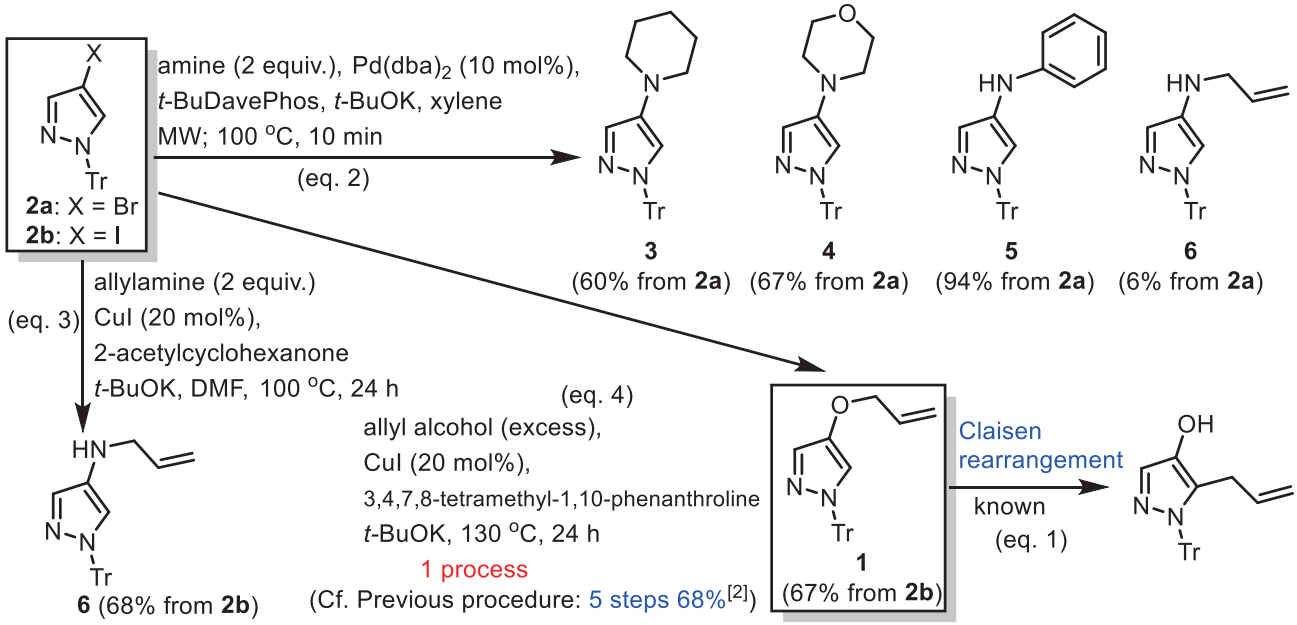
Various functionalized pyrazoles are important components in clinical drugs or agricultural chemicals. Therefore, developments of synthetic methods for pyrazoles are one of the most important tasks of organic chemists. However, most of them have been based on the cyclization of already prepared functions. Hence, we have been studied direct functionalizations of pyrazoles via various coupling reactions.[1] We recently reported the synthesis of pyrazole-fuzed heterobicyclic compounds.[2] In these works, 4-allyloxy-1*H*-1-tritylpyrazole (**1**) played an important role as a substrate for Claisen rearrangement (eq. 1). However, it required 5 steps for the preparation of **1** from 4-halo-1*H*-1-tritylpyrazole (**2**). To obtain **1** directly from **2**, Buchwald-Hartwig coupling reaction of **2** was investigated.[3] At first, we searched coupling conditions between **2** and piperidine in the presence of a palladium catalyst. After a lot of trials in various combinations of parameters, the optimum condition was obtained as shown in eq. 2, but it resulted in a low yield of **6** (6%) in case of allylamine. Alternatively, changing of catalyst to CuI improved the chemical yield of **6** (68%) (eq. 3). Furthermore, for the preparation of **1**, dual use of inexpensive allyl alcohol as reagent and solvent gave a moderate yield of **1** (67%) (eq.4).



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[3] Surry, D. S.; Buchwald, S. L. *Angewante Chem. Intn. Ed.* **2008**, *47*, 6338; Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046.
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Diazotization of phenol using azido imidazolinium salt

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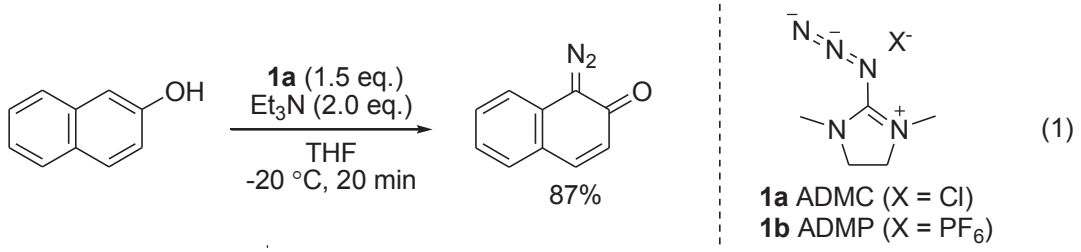
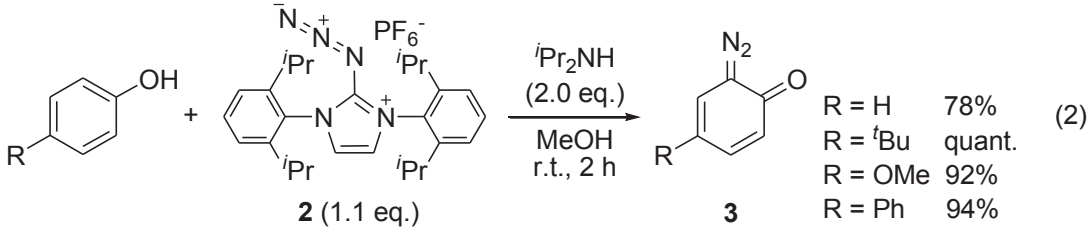
There have been reported various diazo transfer reactions. Diazo-transfer reaction to active methylene compounds and primary amines are typical reactions, and sulfonyl azides are used as the diazo-transfer reagent in general. We have developed new diazo-transfer reagent, 2-azido-1,3-dimethylimidazolinium salts **1a** and **1b**, which were found to show efficient diazo-transfer ability to active methylene compounds and primary amines[1]. In addition, diazo-tranfer reaction of **1a** to naphthol proceeded giving diazonaphthoquinone (Eq.1)[2]. However, phenol could not be diazotized by the 2-azido-1,3-dimethylimidazolinium salt **1**. In a further study, we synthesized a new azido imidazolinium salt **2** having bulky aryl groups on its nitrogen in the ring and **2** was found to show diazo transfer ability to simple phenols.



(1)

When azido imidazolium salt **2** was added to a methanol solution of unsubstituted phenol in the presence of $^{i}Pr_2NH$, corresponding diazotized compound **3** was obtained in 78% yield (Eq.2). In the reaction of *p*-tertiary butyl, *p*-methoxycarbonyl and *p*-phenyl phenols, corresponding diazoquinones were obtained in high yields.



(2)

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3P-117

Synthesis of Pyrazole-3-triflones via [3+2] Cycloaddition Reaction

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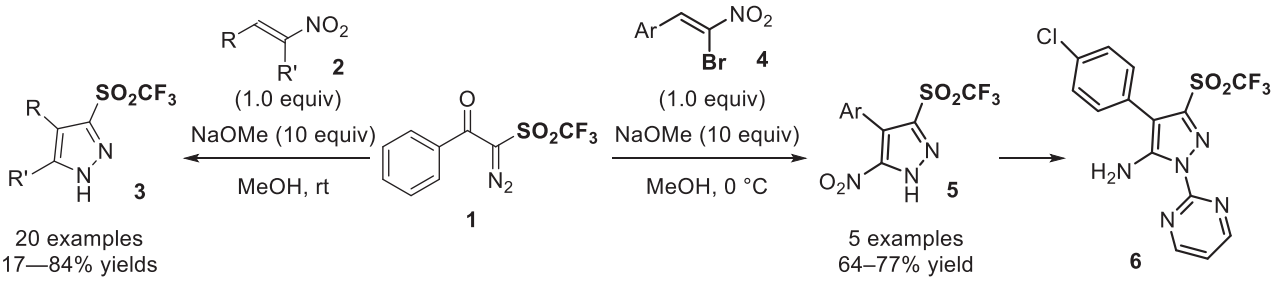
Pyrazoles are often found as an integral part of biologically active molecules, and the fluorine substitution containing pyrazoles have gathered much attention in the development of pharmaceuticals and agrochemicals. In particular, trifluoromethanesulfonyl (triflyl, SO_2CF_3) substituted pyrazoles might be attractive drug candidates, due to those high electron-withdrawing ability and mild lipophilicity ($\sigma_m = 0.79$, $\sigma_p = 0.93$, $\pi = 0.55$). We recently reported a diazo-triflone (**1**) as an electrophilic trifluoromethylthiolation reagent. [1] Furthermore, we reported that **1** can be used as a building block for the synthesis of heteroaryl tryflon with or without copper catalyst. [2] As an extension of reactivity of **1**, we herein disclose the synthesis of pyrazole-3-triflones by the reaction of **1** with nitroalkenes via [3+2] cycloaddition under basic condition.

After screening of the reaction conditions of **1** with nitroalkenes, we found that the use of 10 equiv of NaOMe in MeOH afford the desired pyrazole-3-triflon in high yield. A variety of nitroalkene derivatives (**2**) containing electron-donating, electron-withdrawing and halogenyl substituents could be applicable for this [3+2] cycloaddition to furnish the corresponding pyrazole triflones (**3**) in good to high yields. [4]
Next, α-bromonitrostyrene derivatives (**4**) were attempted this [3+2] cycloaddition. The reaction of **1** with **4** were also proceeded smoothly at lower temperature to provide the 5-nitro-pyrazole triflones (**5**) in good yield. Moreover, the agrochemically attractive 5-amino-*N*-pyrimidinyl-pyrazole triflone (**6**) could be obtained by 2 steps conversion from **5**. [5]



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Reaction of Aromatic Methoxymethyl Ethers with Trialkylsilyl Triflate and 2,2'-Bipyridyl: Deprotection and Direct Conversion to Aromatic Triethylsilyl Ethers

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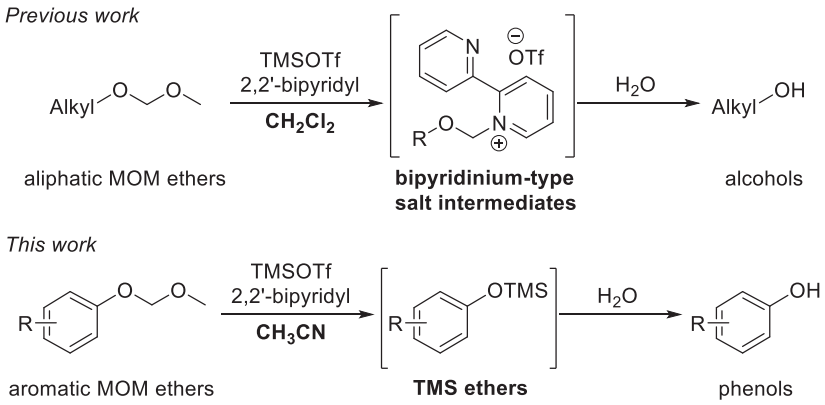
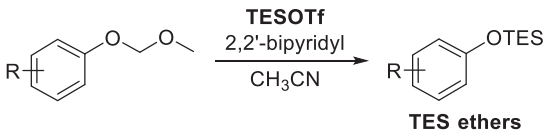
Methoxymethyl (MOM) group is widely used hydroxyl protecting group due to the resistance in strongly basic to weakly acidic conditions. Therefore, the deprotection of the MOM group generally needs strongly acidic conditions. Then, the substrates with acid-labile functional groups usually need other protective groups, whose deprotection doesn't need such acidic conditions. However, a development of new mild deprotection method of MOM ether, which doesn't affect the substrates having labile functional groups, can broaden the range of the use MOM group.

We have recently reported that aliphatic MOM ethers form bipyridinium salt intermediates upon treatment with trimethylsilyl triflate (TMSOTf) and 2,2'-bipyridyl in CH_2Cl_2 (Scheme 1, Previous work).[1] The intermediates susceptible to nucleophilic attack by H_2O which affords the corresponding deprotected products via hemiacetal intermediates. However, aromatic MOM ethers have reduced reactivity under the same conditions compared with that of aliphatic MOM ethers.

We then explored the reaction of aromatic MOM ethers with TMSOTf and 2,2'-bipyridyl in detail, and found the remarkable effect of CH_3CN as a reaction solvent and the reaction pathway of deprotection of aromatic MOM ethers is completely different from that of aliphatic ones (Scheme 1, This work). Also, this difference in reactivity also allowed us to develop an unprecedented conversion of aromatic MOM ethers directly to TES ethers (Scheme 2). Additionally, these observations allowed us to develop a chemoselective transformation on molecules containing both aromatic and aliphatic MOM ethers.[2]



Scheme 1. Deprotection of MOM ethers with TMSOTf and 2,2'-bipyridyl



Scheme 2. Direct conversion to aromatic TES ethers from aromatic MOM ethers

[1] H. Fujioka *et al*. *Tetrahedron*, **2011**, *67*, 2949-2960.
[2] H. Fujioka *et al*. *ACS Omega*, **2019**, *4*, 8465-8471.

Synthetic Study of Bryostatins

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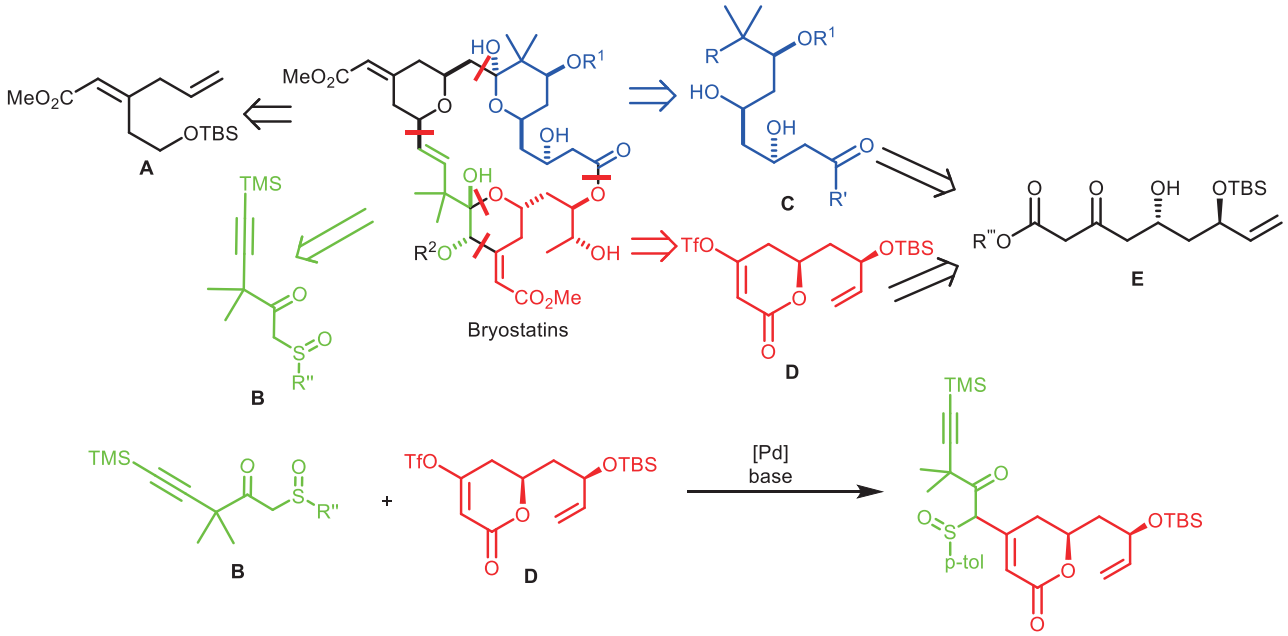
Bryostatins are macrolide compounds derived from the marine organism *Bugula neritina* and are reported to exhibit diverse biological activities; anti-neoplastic activity, eradiction of AIDS and treatment of Alzeimer's disease[1][2]. Since it is difficult to obtain a stable supply from natural sources, many researches on the toltal synthesis of bryostatins and the synthesis of its analogues have been reported. However, the syntheses of bryostatins with dense oxygen functionality and multiple stereocenter require multiple steps in all cases (29-90 total steps)[3]. For this reason, it is practically difficult to make each derivative separately in conducting structure-activity relationship studies of bryostatins. With these backgrounds, this study is aimed at comprehensive short-step synthesis of bryostatins and its derivatives.

In this study, 4 fragments of **A**, **B**, **C**, and **D** are synthesized, and bryostatins are synthesized by coupling of them. Two of these four fragments were synthesized from the common intermediate **E**, thereby achieving fragment synthesis efficiently.

Now, we are studying the conditions for the coupling reaction of the synthesized fragment **B** and fragment **D** with palladium. This coupling reaction will also be dicussed in this presentation.



[1] George R. P.; Cherry L. H.; Dennis L. D.; Delbert L. H.. *J. Am. Chem. Soc.* **1982**, *104*, 6846
[2] Peter K.; Josef R.; Zuzana B.; Jiří P. *Pharmaceutical Biology*, **2014**, *52*, 237
[3] Yuebao Z.;Ji L.;Hongze L.;Xianwei S.;Lu GZ. S. *Synlett*, **2019**, *30*, 753

gem-Diboronic Acid-Catalyzed Dehydrative Peptide Synthesis

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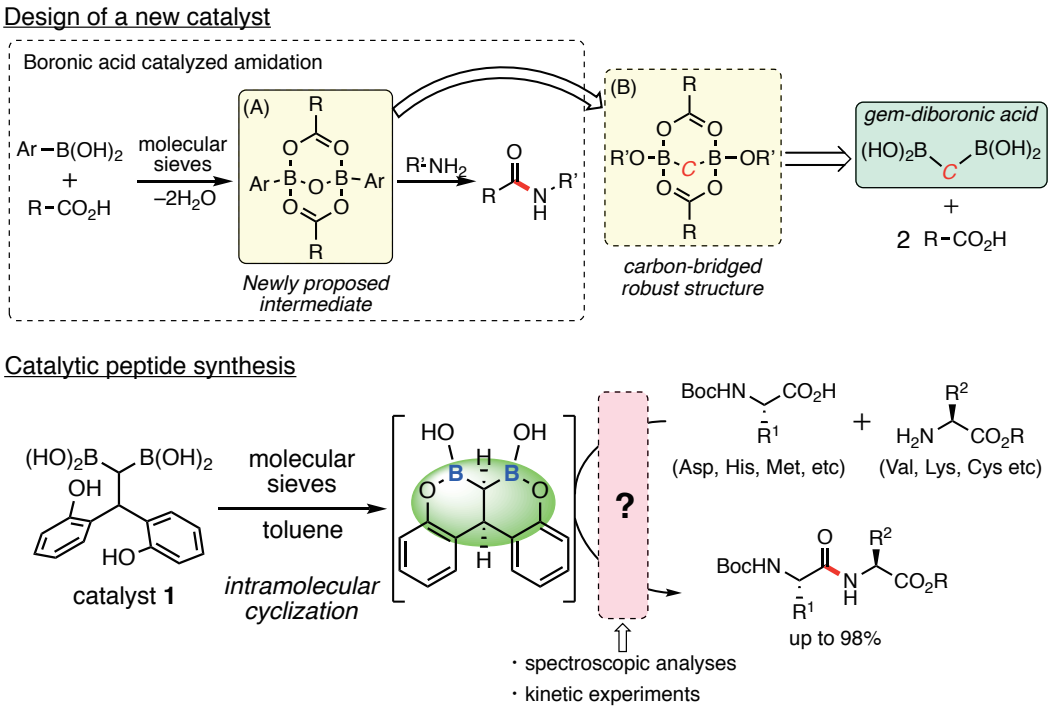
Peptide bond is a fundamental structure that connects amino acids to form a main chain in protein molecules. Solid-phase peptide synthesis has been established as a practical method of forming peptide bonds, but excess amounts of coupling reagents are irreversibly converted into chemical wastes. To circumvent this problem, catalytic dehydrative peptide synthesis has attracted significant attention and some examples using boron-containing catalysts have been reported[1]. However, heating conditions are required in any case and catalytic dehydrative peptide synthesis at ambient temperature has never been achieved. We thus focused on the development of a novel catalysts applicable to a broad range of substrates under milder conditions without epimerization.

The recent reports regarding bidentate activation mode (A) of carboxylic acids by boron-containing catalysts[2] led us to design a new activation mode (B) including robust carbon-bridged structure. The activation mode (B) is formed by the condensation of *gem*-diboronic acid catalyst and carboxylic acids. The catalyst modification successfully provided highly active catalyst **1** capable of dipeptide synthesis from various *O*-, *N*-, and *S*-functionalized α-amino acids. The intramolecular cyclization of catalyst **1** quickly proceeds under the reaction condition. To elucidate the actual mechanism, we performed some spectroscopic analyses and kinetic experiments.



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1) a) Fatemi, S.; Gernigon, N.; Hall, D. G. *Green. Chem.* **2015**, *17*, 4016. b) Wang, K.; Lu, Y.; Ishihara, K. *Chem. Commun.* **2018**, *54*, 5410. c) Liu, Z.; Noda, H.; Shibasaki, M.; Kumagai, N. *Org. Lett.* **2018**, *20*, 612.
2) Arkhipenko, S.; Sabatini, M. T.; Batsanov, A. S.; Karaluka, V.; Sheppard, T. D.; Rzepa, H. S.; Whiting, A. *Chem. Sci.* **2018**, *9*, 1058.

Synthesis of Sulfur-Containing Fused Ring Compounds Using Thionyl Chloride as a Sulfur Source

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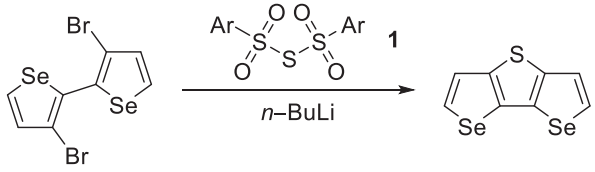
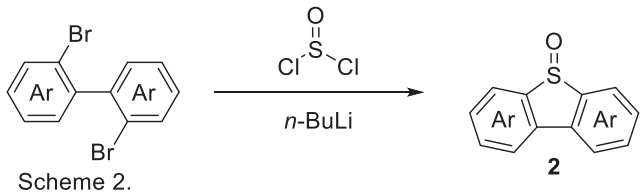
Highly π-extended polyacenes widely opened up a field of organic electronic devices, in particular, organic semiconducting materials, but those are usually troublesome to handle and unstable without some techniquesas introduction of bulky substituents. Also, diversity of the compound is limited. One of the ways to development of such diverse and stable π-extended compounds with suitable functionality for the materials, the use of ladder-type heteroarenes, especially containing thiophene ring in place of simple benzene ring are attracting significant attentions. Recently, a lot of compounds were developed and applied to several organic electronic devices such as organic field effect transistors, solar cells, and light-emitting diodes to result in high efficiency. However, there still remain synthetic issues such as separation of the compounds and impurities from reagents used, cost of the reagents, and efficiency of synthetic route itself. For example, bis(arylsulfonyl)sulfide **1** are usually used as a sulfur electrophile (ring closing reagent) but the cost and availability need improvement (Scheme 1). [1]

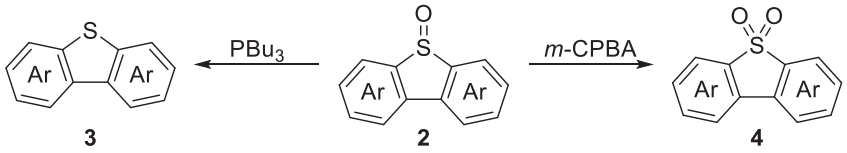


Scheme 1.

Herein, we found that very cheap and common thienyl chloride can be used as a surrogate of such sulfur electrophile. Generally, thienyl chloride is considered as not a sulfur introducing reagent but chlorinating reagent at C-O bond with oxophilicity of sulfur atom (Scheme 2). The reaction of 2,2'-lithiated biaryl and thienyl chloride under cryogenic conditions to give the corresponding cyclized aryl-thiophene oxide **2** ring-fused compound in good to high yield. The obtained thiophene oxide group could be reduced and oxidized by treatment of tributylphosphine and *m*-CPBA to give the corresponding aryl-thiophene **3** and aryl-thiophene dioxide **4** ring-fused compounds. Some of the obtained ring-fused compounds showed unexpected fluorescent character (Scheme 3). In this presentation, those will be deeply discussed.



Scheme 2.



Scheme 3.

[1] Xu, W.; Wang, M.; Ma, Z.; Shan, Z.; Li, C.; Wang, H. *J. Org. Chem.* **2018**, *83*, 12154.

3P-122

Essential structure of orexin 1 receptor antagonist YNT-707

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Orexin receptors are G-protein coupled receptors (GPCR) classified into two subtypes, orexin 1 receptor (OX_1R) and orexin 2 receptor (OX_2R). Orexin system is important for regulation of sleep/wake cycle and arousal. Additionally OX_1R has been reported to regulate reward-related behaviors and motivation. Many orexin ligands have been reported, and the OX_1R/OX_2R dual antagonist suvorexant was launched for the treatment of insomnia.

Recently, we found that the κ opioid receptor agonist nalfurafine showed moderate antagonistic activity and high selectivity for OX_1R (OX_1R: K_i = 250 nM, OX_2R: Not active), and synthesized the more potent OX_1R antagonist YNT-707 (OX_1R: K_i = 8.14 nM, OX_2R: Not active). [1] In the course of the above optimization study, we found that the specific character of the morphinan skeleton would greatly contribute to the remarkable OX_1R selectivity. Therefore, we examined the roles in the orientations of each functional groups of YNT-707 to the activity and selectivity for OX_1R.

We synthesized several YNT-707 derivatives to examine the roles of the C4,5-epoxy ring and the C14-hydroxy group in the orientations of the C6-amide side chain, the C14-hydroxy group in the orientation of the N17-benzenesulfonyl group, and the C3-methoxy group and the A-ring on the activity for orexin receptors (OXRs), respectively. Then, we evaluated the activities of these derivatives for OXRs. As a result, we found that the N17-benzenesulfonyl group and the C6-amide side chain were essential for the activity for OX_1R, while the C14-hydroxyl group, the C4,5-epoxy ring, the C3-methoxy group, and the A-ring were dispensable (Figure 1). Moreover, the docking simulation and the conformational analyses suggested that the adequate orientations of the N17-benzenesulfonyl group and the C6-amide side chain were important for the activity for OX_1R. [2], [3], [4]

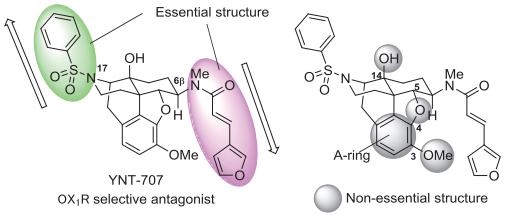

Figure 1. Essential structure of YNT-707

[1] *J. Med. Chem.* **2017**, *60*, 1018-1040. [2] *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4176-4179. [3] *Bioorg. Med. Chem. Lett.* **2018**, *28*, 774-777. [4] *Bioorg. Med. Chem.* **2019**, *27*, 1747-1758.

Nickel Nanoparticle-catalyzed Ligand-free C(sp^2)-C(sp^3) Kumada Coupling

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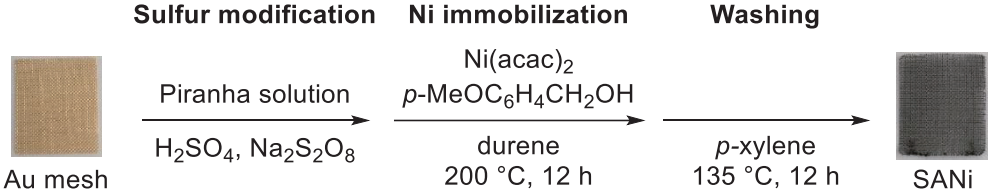
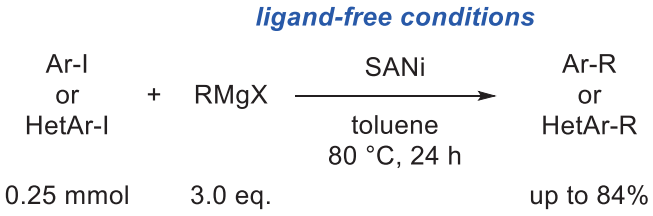
Transition metal catalyzed cross-coupling reactions of aryl halides with alkyl organometallic reagents play an important role in the formation of C(sp^2)-C(sp^3) bonds. However, these reactions generally require ligands which are difficult to remove.[1]

We developed a unique and novel nickel nanoparticles catalyst, Sulfur-modified Au-supported Nickel (SANi). SANi is easily prepared via three-steps; (i) sulfur modification, (ii) Ni immobilization and (iii) washing (Scheme 1), and it could be applied to the ligand-free C(sp^2)-C(sp^2) Kumada coupling and Negishi coupling. However, SANi-catalyzed ligand-free cross-coupling reactions of aryl halides with alkyl organometallic reagents have not been developed.[2] As a result of optimizations of reaction conditions on ligand-free C(sp^2)-C(sp^3) Kumada coupling, we found that the desired product can be obtained in high yield, and heteroaromatic halides are applicable to our reaction system (Scheme 2). In the presentation, we will discuss about substrate scopes of aryl or heteroaromatic halides and alkyl Grignard reagents, and the structural analysis of SANi.

Scheme 1. Preparation of SANi



Scheme 2. SANi-catalyzed ligand-free C(sp^2)-C(sp^3) Kumada coupling



[1] Jana R.; Pathak P. T.; Sigman S. M. *Chem. Rev.* **2011**, *111*, 1417-1492.
[2] *Adv. Synth. Catal.* **2016**, *358*, 2449-2459.

Ligand-free Suzuki-Miyaura Coupling of Chlorinated Heterocycles using Continuously Irradiating Microwave and Glass-Supported Palladium Nanoparticle Catalyst

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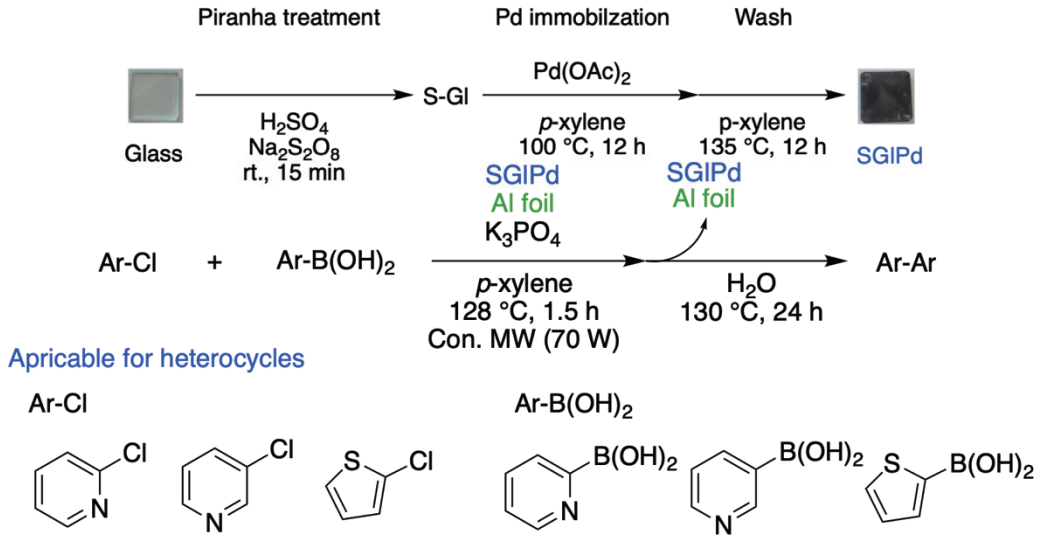
Suzuki-Miyaura coupling is widely utilized in the synthesis of functional organic molecules used in pharmaceuticals, functional materials and agricultural agents[1]. In the reaction, aryl iodides and aryl bromides have been generally used as substrates. Aryl chlorides can also be used but usually requires sophisticated and expensive ligands due to their lower reactivity in the oxidative addition step. However, the contamination of the product by the metal catalyst and the ligand poses a problem in the purification step in the synthesis of functional compounds which is comprised of several heteroatoms[2].

Previously, we developed gold-supported Pd or Ru nanoparticle catalysts: SAPd[3] and SARu[4] ; and glass-supported Pd nanoparticle catalyst, SGlPd[5]. In this presentation, we will discuss our results on the ligand-free Suzuki-Miyaura coupling of aryl chlorides using SGlPd and continuously irradiating microwave. We will also introduce a modified reaction procedure using an additional aluminum foil resulting to milder reaction conditions.



[1] (a) Goutam, B. *RSC Adv.* **2016**, *6*, 64676-64725. (b) Alan, H. C.; Nathaniel, T. K.; Sarah E. R.; *Chem. Rev.* **2015**, *115*, 9587-9652. [2] Garrett E.; Prasad K. *Adv. Synth. Catal*. **2004**, *346*, 889-900. [3] (a) Hoshiya N.; Shimda M.; Yoshikawa H.; Yamashita Y.; Shuto S.; Arisawa M., *J. Am. Chem. Soc.* **2010**, *132,* 7270-7272. [4] Akiyama T.; Taniguchi T.; Saito N.; Doi R.; Honma T.; Tamenori Y.; Ohki Y.; Takahashi N.; Fujioka H.; Sato Y.; Arisawa M., *Green Chem.* **2017**, *19*, 3357-3369. [5] Xiao M.; Hoshiya N.; Fujiki K.; Honma T.; Tamenori Y.; Shuto S.; Fujioka H.; Arisawa M., *Chem. Pharm. Bull.* **2016**, *64*, 1154-1160.

Total Synthesis of JBIR-126 toward Elucidation of Structure Activity Relationships

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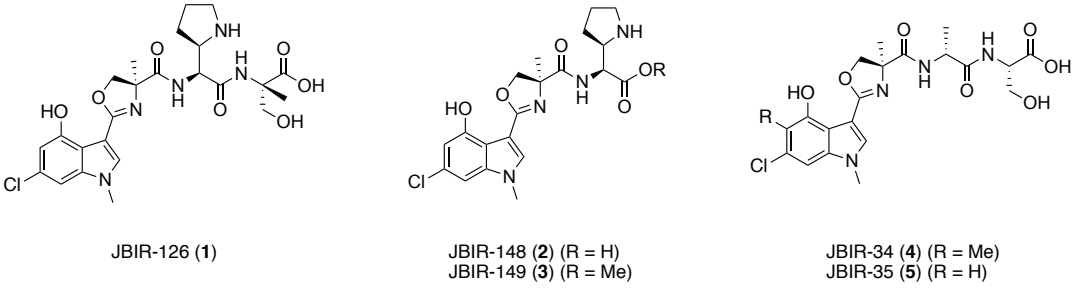
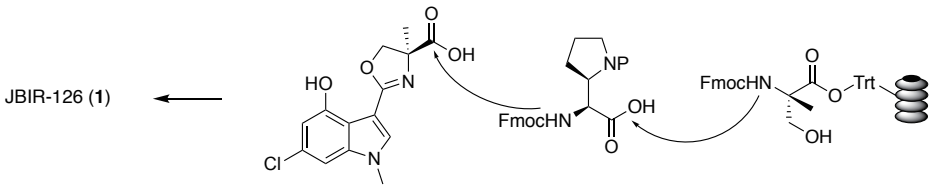
2) Graduate School of Pure and Applied Sciences, University of Tsukuba
3) National Institute of Advanced Industrial Science and Technology

JBIR–126 (**1**), isolated from a culture of *Streptomyces sp.* NBRC 111228 obtained from soil collected in the Okinawa Prefecture, is a biologically active linear tetrapeptide consisting of unique unusual amino acids (*S*)-α-methylserine and (2*S*, 3*R*) pyrrolidinoglycine (Figure 1).[1)] In addition, JBIR–148 (**2**) and JBIR–149 (**3**) were isolated, and their structures are lack of α-methylserine at the C-terminus of JBIR–126. In 2010, Shin-ya also reported the isolation of JBIR–34 (**4**) and JBIR–35 (**5**), which did not exhibit cytotoxicity agianst cancer cells.[2)] As **1** exhibited weak cytotoxicity against leukemic cells, the pyrrolidinoglycine moiety in JBIR–126 (**1**) is expected to be indispensable for biological activity. Toward elucidation of structure activity relationships, total synthesis of JBIR-126 (**1**) was carried out to establish a synthetic route for the synthesis of various analogues.



(Figure 1)

An efficient solid phase total synthesis of JBIR-126 (**1**) was achieved. Sequential peptide coupling using unusual amino acids was performed by a solid phase peptide synthesis using a Fmoc strategy. Cleavage from the polymer-support, removal of all protecting groups afforded the desired JBIR–126 (**1**) (Scheme 1). Details of the synthesis of JBIR-126 and its analogs will be presented.



(Scheme 1)

References

[1] Izumikawa, M.; Kawahara, T.; Kagaya, N.; Yamamura, H.; Hayakawa, M.; Takagi, M.; Yoshida, M.; Doi, T.; Shin-ya, K. *Tetrahedron Lett*. **2015**, *56*, 5333-5336.
[2] Motohashi, K.; Takagi, M.; Shin-ya, K. *J. Nat. Prod.* **2010**, *73*, 226–228.

Efficient Synthesis of *N*-Trifluoromethylthiomethyl Indoles: Physical Property, Metabolism and IDO Inhibitory Activity Evaluation of Substituted Indoles

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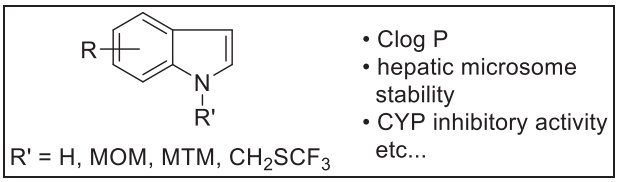
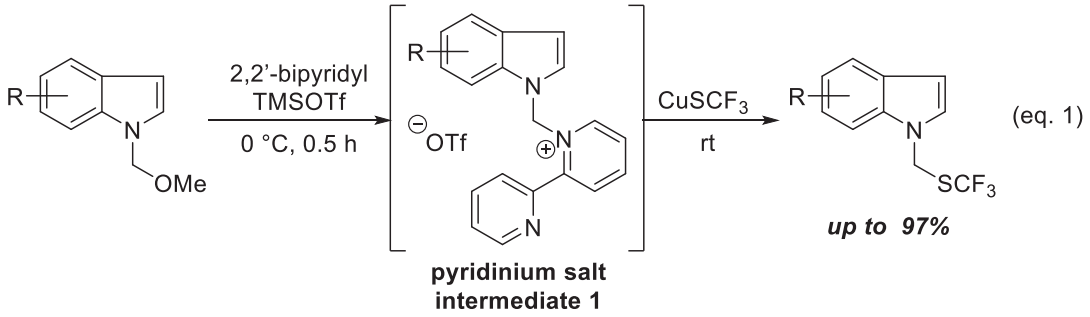
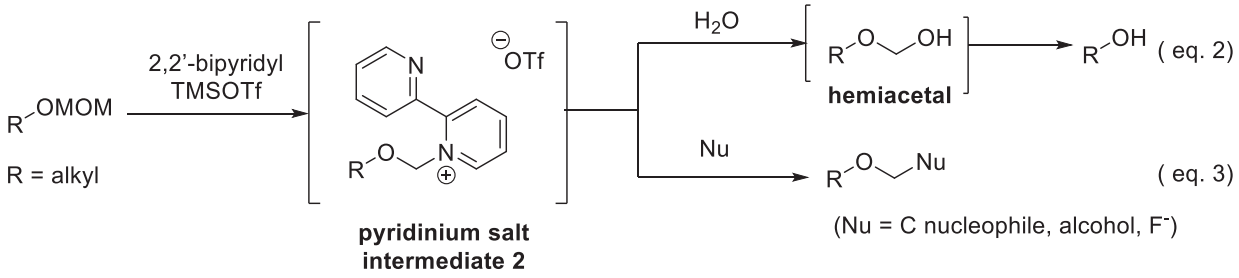
[2]*School of Pharmacy, Shizuoka University*

Drug discovery heavily relies on the systematic synthesis of lead compounds. Hence, evaluation of absorption, metabolism and biological activities of heterocyclic compounds to form chemical library of drug-like substances is essential. We therefore synthesized various substituted indole derivatives, and evaluated their absorption, metabolism, and indoleamine 2,3-dioxygenase (IDO) inhibitory activity.



In this presentaion, we will also discuss the synthesis of *N*-CH_2SCF_3 indole derivative from *N*-MOM indole compound *via* pyridinium salt intermediate **1** formed by the treatment of *N*-methoxymethyl (MOM) indole with TMSOTf and 2,2'-bipyridyl (eq. 1). This methodology is a good application of our previously reported findings.[1)] We have reported a mild deprotection of alkyl MOM ether to give the correspondig alcohol *via* pyridinium salt intermediate **2** and subsequent hemiacetal intermediate (eq. 2). Aside from water, other nucleophiles such as alcohol, Gilman reagent, or fluoride anion can be utilized to obtain their corresponding ethers (eq. 3).





1) *Adv. Synth. Catal.* **2012**, *354*, 1861.; *J. Synth. Org. Chem.* **2013**, *7*, 694.

3P-127

Strong acid-promoted C-N bond cleavage of tetrahydroisoquinoline derivatives

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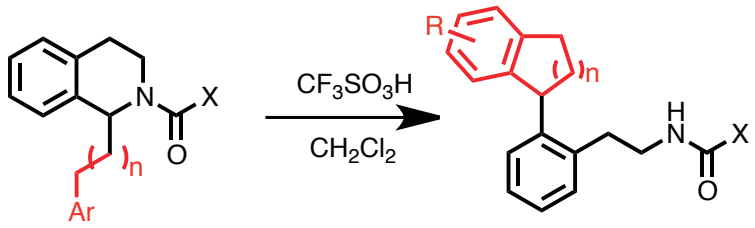
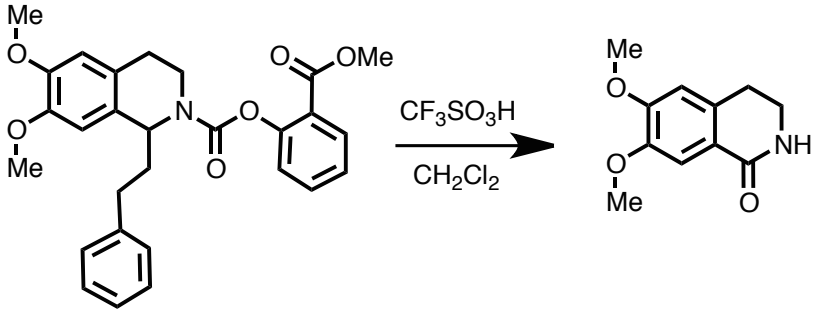
Tetrahydroisoquinoline skeleton is present in a large number of natural products and drugs.[1] Because of its pharmaceutical utility, the synthetic method of the skeleton has attracted great interest. Electrophilic aromatic substitution methods, such as Pictet-Spengler reaction from phenethylamine derivatives in acidic condition, have been one of the most useful methods in the construction of the structure. However, the ring-fused system is so rigid that inverse approach for *destruction* has been rarely investigated, even though this approach enables us to obtain *ortho*-substituted phenethylamine derivatives. In the limited number of successful destruction examples, most of them employed oxidative condition.[2] We have recently found that the N-acylated tetrahydroisoquinoline derivetives proceed a C-N bond cleavage reaction under strong acidic condition without oxidation. In this presentation, we will discuss the reaction mechanism and substrate generality of the reaction.



In the course of this research, we also investigated the reaction of electron-rich substrates, which afforded a product which is generated as a result of oxidation at a glance. The mechanistic study showed that the reaction proceeds in sequential cationic reactions starting from C-N bond cleavage reaction, in which no oxidation occurs. We also present the generality of this alkyl chain-loss process.



[1] J. D. Scott, R. M. Williams, *Chem. Rev.*, **2002**, *102*, 1669-1730.
[2] S.-T. Lu, Y.-C. Wu, *Heterocycles*, **1985**, *23*, 3085-3094.

Synthesis of *cis*-3,4-disubstituted piperidines

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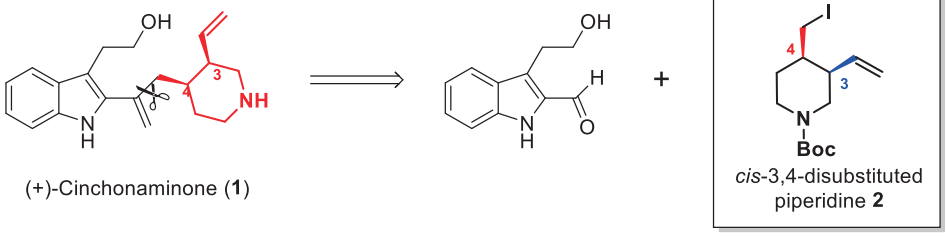
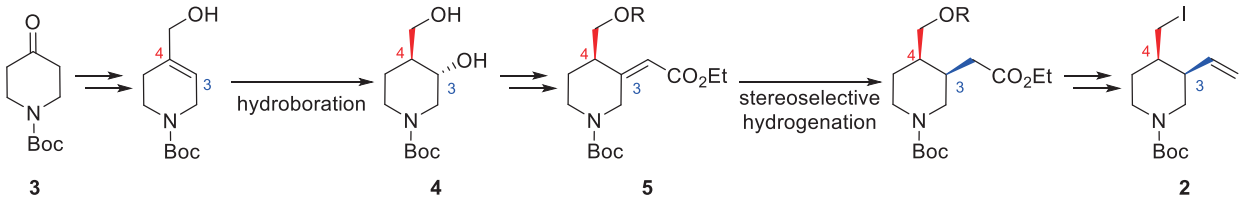
Cis-3,4-disubstituted piperidines are worthy structures in medicinal chemistry and found in natural products and drugs. [1]

(+)-Cinchonaminone **1**, one of the alkaloid compounds, also contains *cis*-3,4-disubstituted piperidines. It was isolated from *Cinchonae Cortex* in 1989, and reported to have an inhibitory activity against monoamine oxidase (MAO) from bovine plasma (IC_{50} = 31.7 μm). [2] Previously, we reported synthesis of (±)-**1**, however an asymmetric synthesis of (+)-**1** has not been reported yet. [3] In previous work, there are several problems about synthesis of *cis*-3,4-disubstituted piperidine derivative (±)-**2**. Especially, total yield of (±)-**2** is low (8%) and enantioselective synthesis is difficult. In order to solve these problems, new approach to synthesis of *cis*-3,4-disubstituted piperidine derivative (±)-**2** is necessary.

In this presentation, we will report a novel synthesis of (±)-**2** by 12 steps in 33% overall yield, from commercially available 1-Boc-4-piperidone **3**. Hydroboration of allyl alcohol (±)-**4** and stereoselective hydrogenation of unsaturated ester (±)-**5** enables stereoselective synthesis of (±)-**2**. We will also discuss about asymmetric synthesis of both (+) and (-) **2**, enantiomers.





[1] a) Igarashi, J.; Katsukawa, M.; Wang, Y.; Acharya, P. H.; Kobayashi, Y. *Tetrahedron Lett.* **2004**, *45*, 3783. b) Sarkar, M. S.; Taira, Y.; Nakano, A.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Tetrahedron Lett.* **2011**, *52*, 923. c) Narhea, D. B.; Bremana, C. A.; Padwala, J.; Vandenputb, A. L. D.; Scheidtb, M. S.; Benningshofb, C. J. J.; Marela, A. G.; Overkleefta, S. H.; Stelta, M.; Filippov, V. D. *Bioorg. Med. Chem.* **2017**, *25*, 5160.

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3P-129

Design and synthesis of the vitamin D receptor ligand containing three-membered heterocyclic ring

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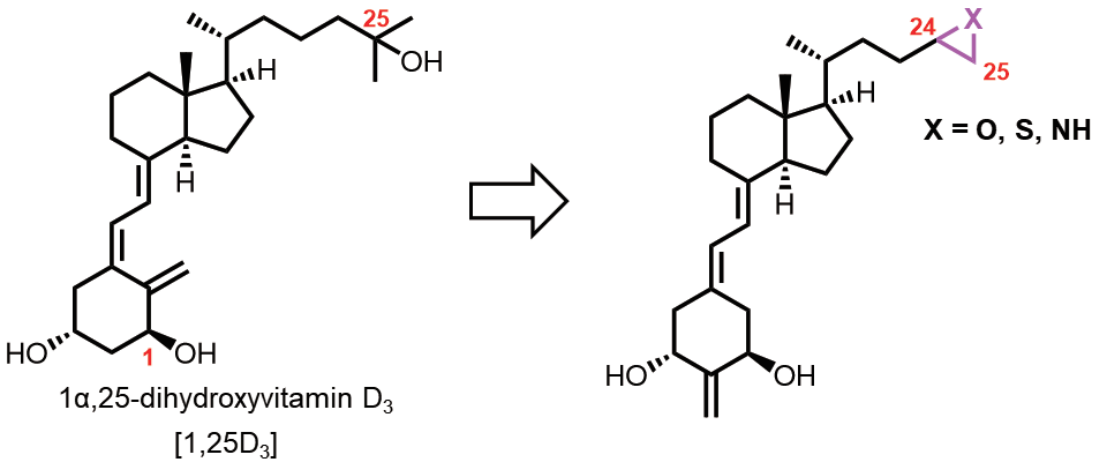
A number of popular covalent drugs are used in clinical treatment. The advantage of covalent drugs is that the pharmacological activity after binding persists until turnover of the target molecules occurs. On the other hand, covalent modifiers have specific feature. A covalent bond has large energy, which exceeds van der Waals forces and hydrogen bonds, it is considered possible to regulate molecular dynamics of the target molecule with a wide range. However, covalent modifiers have been excluded from high throughput screening and chemical libraries due to the risks of off-target and false-positive results. Therefore, it is important that covalent drugs show binding selectivity to target molecules as well as high activity at low doses.

1α,25-Dihydroxyvitamin D_3 ($1,25D_3$) is a hormone that plays significant roles in calcium metabolism, immunomodulation, cellular differentiation, and cellular proliferation. Various vitamin D receptor (VDR) ligands have been developed and several vitamin D analogues are used in clinical applications, such as osteoporosis. Recently, we have reported VDR ligands having enone group as a covalent modifier. These synthetic ligands had agonistic activity, and also they were shown to covalently bind to the VDR-LBD (ligand-binding domain) by ESI-MS and X-ray crystallographic analysis. [1]

For the purpose of being free from drug design restrictions, we focused on heterocyclic ring which have small reactive moiety with sp^3 atom. Among them, by its ring strain, three-membered heterocycles can be expected as hydrogen bond acceptors as well as covalent modifiers. So, we designed and synthesized novel VDR ligands with three-membered heterocycles at the side chain, which are expected nucleophilic substitution by from His301 or His393 in the VDR.



1α,25-dihydroxyvitamin D_3
[$1,25D_3$]

[1] Yoshizawa, M. *et al*., *J. Med. Chem.* **2018**, *61*, 6339.

A facile synthesis of coumarin conjugated PPARγ Ligand

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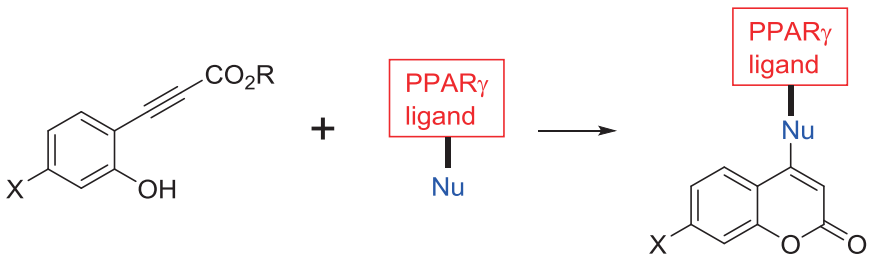
Functional analysis of proteins is important to elucidate the mechanisms in life science. A coumarin skeleton is smaller in structure compared to that of other fluorophores, so this feature is an advantageous in probes. Also many coumarin-type fluorescent probes have been developed because the coumarin can be control fluorescence properties by introducing substituents.

Previously, we reported a Turn-on type fluorescent probe in which a coumarin skeleton is formed by the conjugate addition of nucleophilic amino acid residues in a protein to an inoate. [1] Coumarin construction methods have been reported in many ways, however, we thought that this method could be applied to the fluorescence of ligands. The facile synthesis of a fluorescent coumarin ligand is expected by using a nucleophilic addition reaction with heteroatom of the ligand. We examine the reaction conditions for the appropriate constructing coumarin skeleton. Using optimized condition synthesis of coumarin conjugated PPARγ ligand has been achieved. We are studying the effects on the fluorescence properties and protein function of protein ligands introducing a coumarin skeleton.



[1] Kojima, H. *et al*. *submitted*.

Synthesis and Aggregation Properties of Deazahypoxanthine Derivatives Bearing Multiple Hydrogen-Bonding Sites

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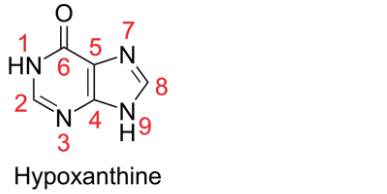
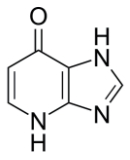
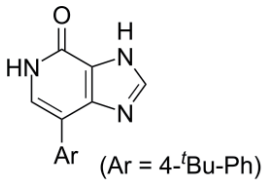
Hypoxanthine as a purine analogue exists naturally in the form of nucleoside inosine. Hypoxanthine has a number of tautomers based on the isomerization equilibrium between pyridone and pyridinol and based on the proton transfer at the imidazole ring. In addition, it possesses several proton-donor and proton-acceptor sites, leading to a formation of hydrogen-bonded pairs with other nucleobases. In this work, we designed and synthesized two deazahypoxanthine derivatives, 1-deazahypoxanthine and 3-deazahypoxanthine. To our knowledge, while various 7- and 9-deazahypoxanthine derivatives have been synthesized and extensively studied for biomedical applications such as inhibitors of several enzymes and antiviral agents, few reports about the preparation and properties of 1- and 3-deazahypoxanthine were presented. Besides that, little is known about their hydrogen bond donating and accepting abilities. This study aims to explore the synthetic methods of 1- and 3-deazahypoxanthine and to construct high dimensional hydrogen-bonded networks from them toward application to bio-inspired organic functional materials for strongly correlated electron systems.

In this symposium, we present the synthesis of 1-deazahypoxanthine **1** and 3-deazahypoxanthine derivative **2**. We also mention the single crystal structure of **1** determined by the X-ray crystal analysis. Deazahypoxanthine **1** is a planar π-conjugated molecule, and has two proton donating sites and two proton accepting sites. Therefore, it gave strongly self-aggregated crystals by hydrogen bonding and π-π stacking. We explain these strong intermolecular interactions characteristic of **1** through the hypotheses based on the resonance assisted hydrogen bonding (RAHB) [1] model and the proton delocalization model.

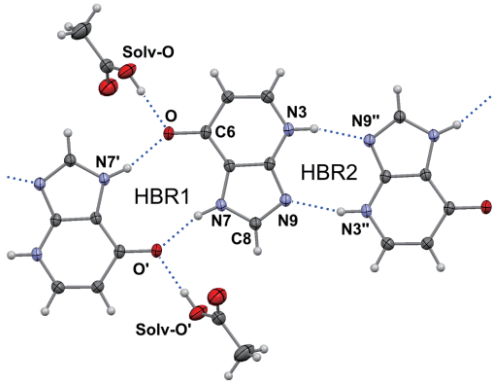




1-Deazahypoxanthine **1**



3-Deazahypoxanthine **2**



Hydrogen-bonded network of **1**

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Synthetic Study of Blespirol Using a Novel Rearrangement Reaction

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Ayumi Imayoshi,[1] Kazunori Tsubaki [1]
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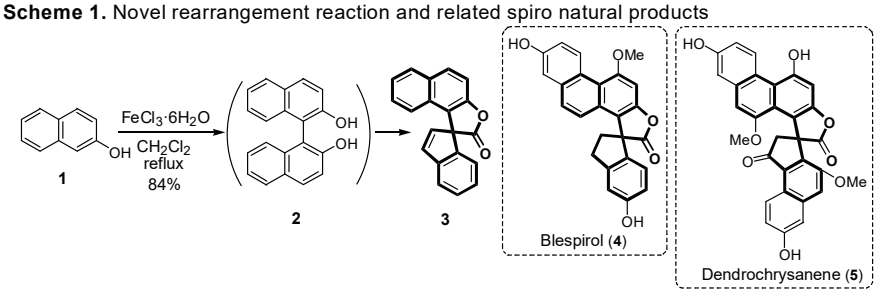
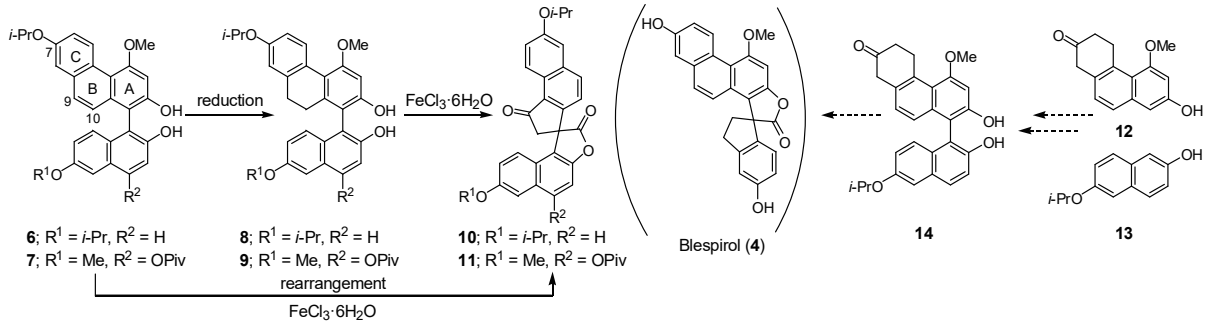
Scheme 1. Novel rearrangement reaction and related spiro natural products



We previously developed a novel rearrangement reaction, in which naphthol (**1**) was converted to spiro compound **3** via binaphthol (**2**) in the presence of $FeCl_3 \cdot 6H_2O$ (Scheme 1).[1] On the other hand, blespirol (**4**)[2] and dendrochrysanene (**5**), isolated from plants of the Orchidaceae family, are known to have the spiro skeleton. Interestingly, the corresponding binaphthol and naphthol derivatives have also been isolated from the same orchid plant. We believe that the series of compounds should be linked to this unique rearrangement reaction. Recently, we have achieved total synthesis of dendrochrysanene (**5**) using this rearrangement reaction as a key step.[3] In this poster, we will talk about the construction of blespirol (**4**), another spiro natural product, using this rearrangement reaction.

First, the rearrangement reaction of **6**, **7** was investigated (Scheme 2). However, the desired rearrangement did not proceed. The phenanthrene ring, instead of the naphthalene ring, collapsed to give spiro compounds **10** and **11**. In order to achieve the rearrangement reaction on the naphthalene ring, we synthesized compounds **8** and **9** that the phenanthrene ring at 9 and 10 positions were selectively reducted. Although the key reaction of **8**, **9** was performed, compound **10** and **11** were again obtained. In the presence of $FeCl_3 \cdot 6H_2O$, compounds **8**, **9** were reoxidized to regenerate compounds **6** and **7**, then undesired direction of the rearrangement seemed to have proceeded. Based on these results, we proposed a new synthetic strategy. We expected that compound **14** would proceed desired rearrangement reaction. In compound **14**, the C ring of compound **6** is reduced and isopropyl ether at position 7 is converted into a ketone in order to equalize the reactivity between **12** and **13**. We are now synthesizing compound **12** to prepare rearrangemnt precursor **14**.

Scheme 2. Synthesis of Blespirol



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3P-133

Selective Synthesis of Disubstituted Isoxazole Isomers by the Rearrangement of Chalcones Mediated by Hypervalent Iodine Reagents

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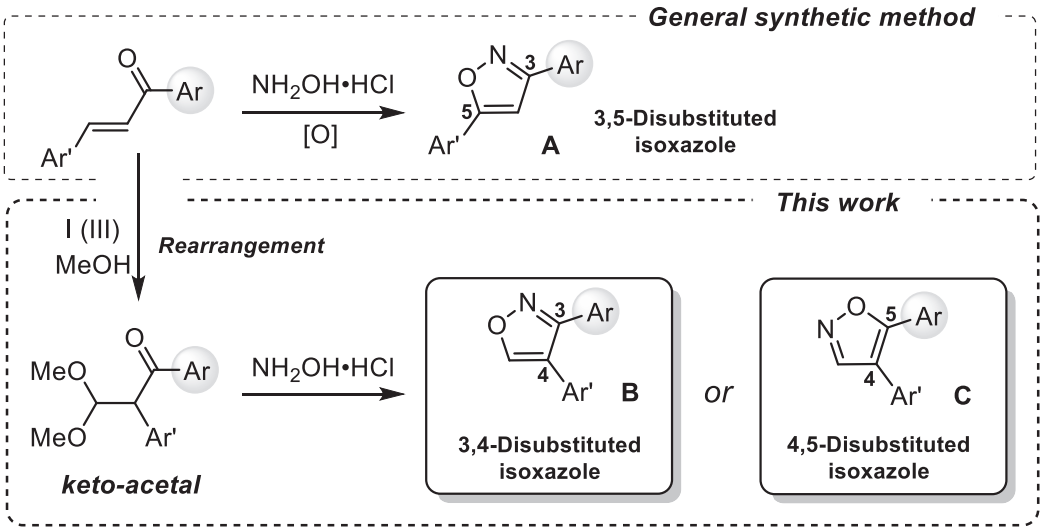
Isoxazole is an important structure for biological or pharmacological interaction and various approaches have been developed for the synthesis and functionalization of isoxazoles in recent years. We have developed the synthetic methods of heterocyclic compounds via rearrangement reaction of the chalcones by using hypervalent iodine reagent.[1] As an extension of this method, we next investigated the synthesis of disubstituted isoxazole derivatives.

Chalcones were generally used for the synthesis of 3,5-disubstituted isoxazoles **A** with hydroxyamine hydrochloride and oxidants.[2] In our approach, keto-acetals obtained by the rearrangement of chalcones mediated by hypervalent iodine reagent was used for the synthesis of 3,4-disubstituted isoxazoles **B**. The reactions of keto-acetals with hydroxyamine hydrochloride under the several reaction conditions for the synthesis of **A** were found to be ineffective, and mixture of isoxazole isomers were formed with low yields. After further optimization, keto-acetals could be converted to the cyclized acetal intermediates in the presence of pyridine, and isoxazoles **B** were formed after acidic work-up. On the other hand, the 4,5-disubstituted isoxazole **C** was directly obtained from keto-acetals in moderate yields by using strong base such as DBU instead of pyridine. Under these reaction conditions, both disubstituted isoxazole isomers could be synthesized selectively. We will show more details at the poster session.



[1] Nakamura A.; Tanaka S.; Imamiya A.; Takane R.; Ohta C.; Fujimura K.; Maegawa T.; Miki Y. *Org. Biomol. Chem.* **2017**, *15*, 6702–6705. Nakamura A.; Takane R.; Tanaka J.; Morimoto J.; Maegawa T. *Heterocycles* **2018**, *97*, 785.
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(2*Z*,4*E*)-3-Hydroxy-1,5-diarylpenta-2,4-dien-1-ones in the reaction of [3+2] cycloaddition with stabilized azomethine ylides

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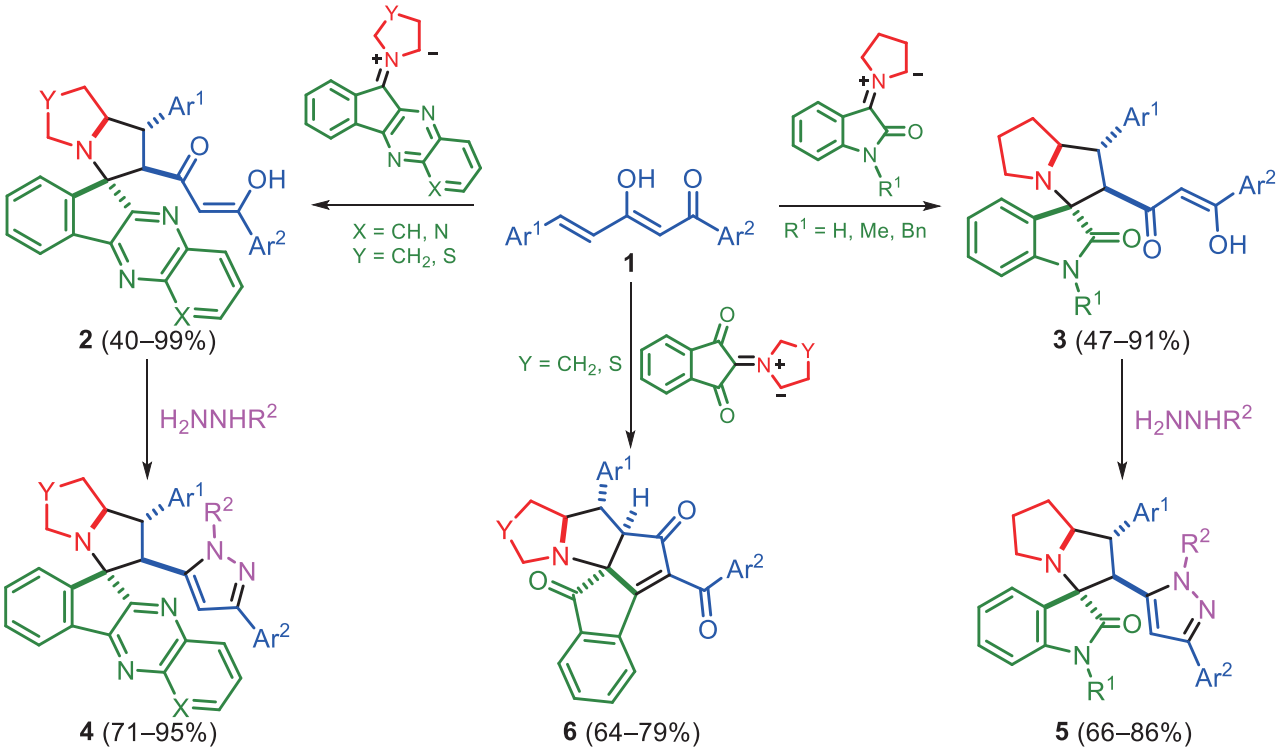
Russia, Ekaterinburg, 620002, Mira str. 19

The 1,3-dipolar cycloaddition reaction of azomethine ylides at the activated double bond of various alkenes is an effective one-step method for regio- and stereoselective synthesis of spiropyrrolidines and spiropyrrolizidines with several chiral centers.
In the present work we have studied [3+2] cycloaddition of stabilized azomethine ylides derived *in situ* from 11*H*-indeno[1,2-*b*]quinoxalin-11-ones, ninhydrin or isatins and α-amino acids (proline, thiaproline) with (2*Z*,4*E*)-3-hydroxy-1,5-diarylpenta-2,4-dien-1-ones **1**. Reactions of indenoquinoxalinone and isatins-based ylides led to the formation of corresponding spiroadducts **2**, **3**, that were further transformed into the spiropyrrolizidine-pyrazol conjugates **4**, **5** under the action of hydrazine hydrate or arylhydrazine hydrochloride. Due to the presence of two active carbonyl groups, cycloadduct formed from the ninhydrin-based ylide underwent *in situ* intra-molecular condensation into the hexahydrobenzo[4,5]pentaleno[1,6a-*b*]pyrrolizine-6,12-diones **6**.



All reaction proceeded under mild conditions, giving corresponding products as single diastereo- and regioisomers with good yields. Structures of the obtained compounds have been unambiguously confirmed by X-ray diffraction analysis.

This work was supported by the Russian Foundation for Basic Research (grant № 18-33-00635).

An Efficient Method for the Construction of *cis*-1,2-oxazadecaline Skeleton and its Application to Formal Enantioselective Synthesis of Trichodermamide B and C

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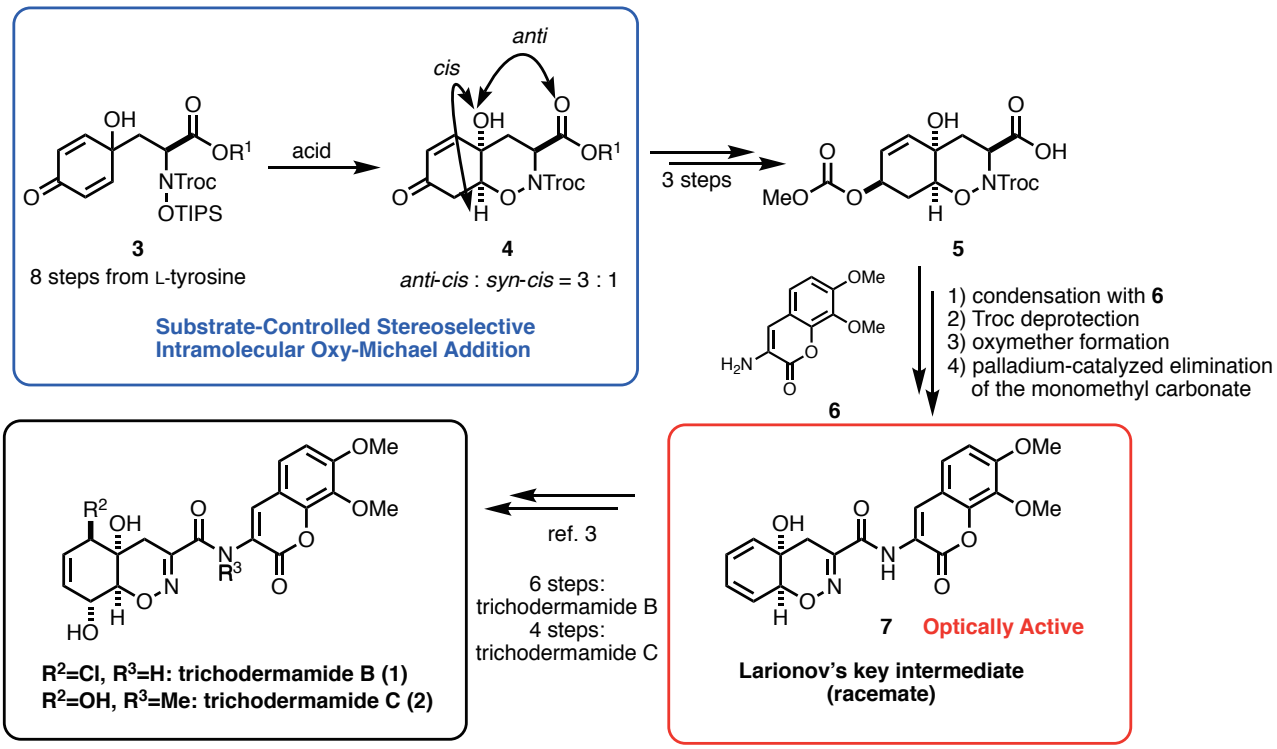
Trichodermamides exhibit potent bioactivity and possess a highly functionalized *cis*-1,2-oxazadecaline skeleton and therefore have attracted both of medicinal and synthetical interest. However, to date, two racemic[1,2] and only a single enantiselective[3] syntheses of trichodermamides have been reported. In this symposium, we present the development of an efficient and enantioselective synthesis of the *cis*-1,2-oxazadecaline skeleton via acid-mediated intramolecular oxy-Michael addition and its application to the formal enantioselective synthesis of trichodermamide B (**1**) and C (**2**). Our synthesis commenced with the stereoselective construction of *cis*-1,2-oxazadecaline enone **4**. After optimizing the reaction conditions, we found that hydroxydienone **3**, obtained in eight steps from L-tyrosine, underwent desilylation-triggerd spontaneous cyclization to furnish the desired **4**, *anti-cis* isomer, and *syn-cis* isomer at a ratio of 3 to 1. Following a three-steps manipulation of the functional groups of **4** gave carboxylic acid **5**. Next, a condensation of **5** with aminocoumarin **6**, which was prepared by following a reported procedure[1], a Troc-deprotection/oxymether formation sequence, followed by a palladium-catalyzed elimination of the monomethyl carbonate afforded the desired dienol **7**. As this compound was optically active and its spectral data were identical to the key intermediate used by Larionov and co-workers in their synthesis of **1** and **2**[3], a formal enantioselective synthesis of these natural products have been accomplished.



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3P-136

Formal Synthesis of Haliclonin A Using Tandem Radical Reaction

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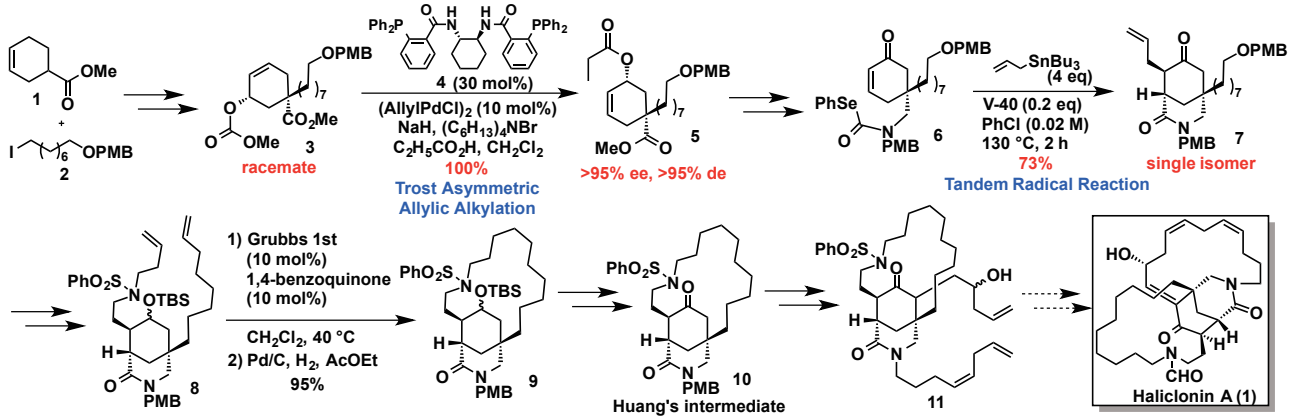
Haliclonin A (**1**) is a macrocyclic alkaloid, which was isolated from the marine sponge *Haliclona sp.* in Korea[1]. This natural product exhibits moderate cytotoxicity and antibacterial activity against various microbials. The structure possesses an unprecedented azabicyclo[3.3.1]nonane core having two ansa chains. We planned to construct the intriguing bicyclic core by a tandem radical reaction to aim the total synthesis of **1**.

Our initial efforts focused on the stereoselective formation of cyclohexenol derivative **5** possessing a quaternary center by Trost asymmetric allylic alkylation[2] of allyl carbonate **3**. The palladium-catalyzed deracemization of **3** with Trost ligand **4** afforded chiral quaternary synthon **5** in 98% yield with excellent selectivity. The resulting **5** was converted to selenocarbamate **6**, precursor of radical reaction. Next, the tandem radical reactions of **6** were explored. After various conditions were examined, we successfully found the reaction of **6** in the presence of allyltributyltin and V-40 under high dilution condition afforded the desired product **7** in 73% yield with excellent selectivity.

The bicyclic product **7** was transformed to diene **8**, which underwent RCM and hydrogeneration to afford macrocyclic compound **9** in excellent yield. The removal of TBS group, followed by oxidation provided Huang's intermediate **10**[3]. Resulting compound **10** was converted to key intermediate **11**, which is regarded as one of the most promising precursors of RCM reaction.



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Iron(0) Nanoparticle-catalyzed Ligand-free C-C/C-N Bond Forming Tandem Reaction

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[2]*Japan Synchrotron Radiation Research Institute, Sayo-gun, Hyogo 679-5198, Japan*

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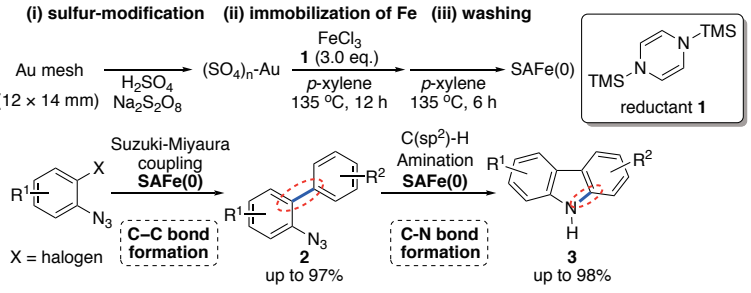
The development of immobilized transition metal nanoparticles (NPs) as catalysts for carbon-carbon (heteroatom) forming cross-coupling is one of the most important areas in organic synthesis, because these immobilized catalysts have several advantages such as recyclability and low metal contaminations.[1] We developed a sulfur-modified Au-supported Pd catalyst (SAPd) and used it to catalyzed Suzuki-Miyaura coupling and C-H functionalization without ligands.[2] In our latest report, we succeeded in preparation of iron(II) NPs immobilized catalyst sulfur-modified Au-supported Fe(II) catalyst, SAFe(II), and its application to ligand-free Kumada coupling.[3] However, it has been challenging to prepare iron(0) NPs catalyst because of its higher reductive potential and instability. Here, we succeeded in preparation of iron(0) NPs catalyst, SAFe(0), by combining our original catalyst preparation method with a silicon-containing heterocyclic compounds[4] (**1**), and its application to ligand-free carbon-carbon and carbon-nitrogen bond forming reactions.

SAFe(0) is easily prepared *via* three steps; (i) sulfur-modification, (ii) NPs immobilization and (iii) washing (**Scheme 1**). In the second step, we found that silicon-containing pyrazine derivatives **1**[4] was the best to prepare SAFe(0). Catalytic activity of SAFe(0) is summarized in **Scheme 1**. SAFe(0) catalyzed ligand-free Suzuki-Miyaura coupling of iodobenzene with phenylboronic acid to give a biaryl compound **2** in 97% yield. Moreover, SAFe(0) catalyzed ligand-free C(sp^2)-H amination to give carbazole **3** in 98% yield. In the presentation we will report the screening of substrates including aryl iodides, aryl bromides, arylboronic acids, and the characterization of SAFe(0).



Scheme 1. Preparation of SAFe(0) and SAFe(0) catalyzed C-C/C-N bond forming reactions

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[2] a) Hoshiya, N.; Shimoda, M.; Yoshikawa, N.; Yamashita, Y.; Shuto, S.; Arisawa, M. *J. Am. Chem. Soc.* **2010**, *132*, 7270. b) Al-Amin, M.; Arisawa, M.; Shuto, S.; Ano, Y.; Tobisu, M.; Chatani, N. *Adv. Synth. Catal*. **2014**, *356*, 1631.

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3P-138s

A Pot-Economical Approach for Accessing Pyrimidines *via* a Chalcone Intermediate

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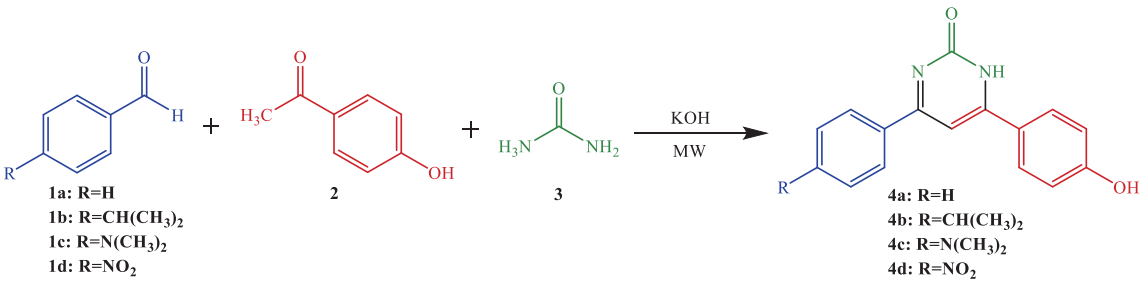
Pyrimidine is an essential heterocyclic moiety which possesses a wide spectrum of biological activities upon derivatization. Among such are 4,6-diphenylpyrimidin-2(*1H*)-ones which have been reported to exhibit anti-tubercular, antihypertensive, anthelmintic, antifungal and antimicrobial activities. [1,2] Synthetic approaches for accessing the heterocyclic moiety have been reported which primarily involve annulation reactions. However, these methods utilize various multi-step reactions where intermediates are isolated. Additionally, such protocols require long reaction time, harsh conditions and to some extent, inaccessible and harmful reagents. [3,4] This account presents a method for the synthesis of 4,6-diphenylpyrimidin-2(*1H*)-ones from different benzaldehyde analogues, 4'-hydroxyacetophenone and urea by employing a one-pot protocol under microwave irradiation. Furthermore, isolation of the chalcone intermediates was no longer performed which reduced the use of chemicals and reagents by eliminating the workup procedure for the isolation of the intermediate. Reaction time employed in the synthetic method was also reduced due to the influence of microwave radiation, which afforded 4,6-diphenylpyrimidin-2(*1H*)-one derivatives in good yields.



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Asymmetric Desymmetrization of 1,3-Alkane Bisphenols via Organocatalytic Aromatic Bromination

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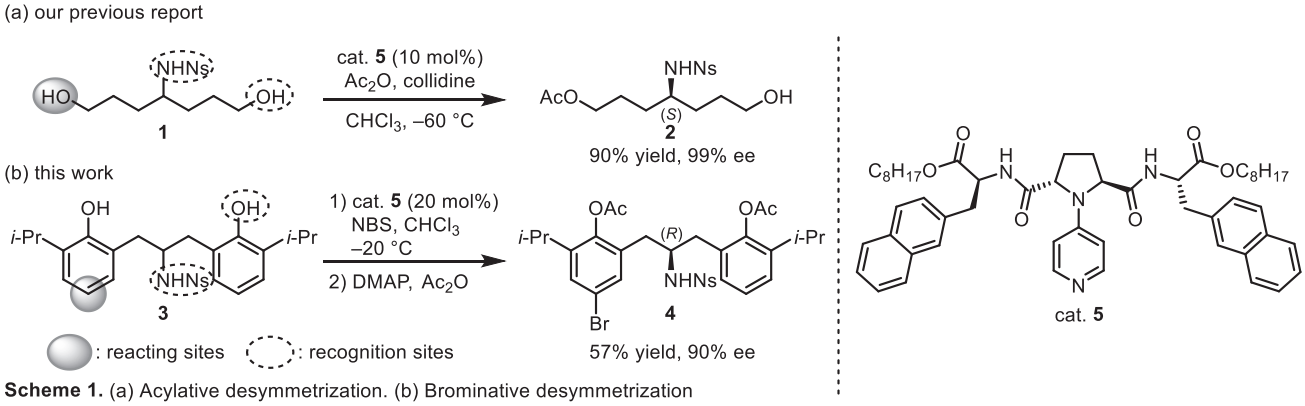
Catalytic asymmetric desymmetrization of prochiral compounds is powerful method for preparation of optically active compounds.[1] Remote asymmetric desymmetrization, in which reacting sites exist far from a prochiral center, is challenging task because of the difficulty in discriminating one reacting site from the other due to the similarity of the steric microenvironments around the potential reacting sites.[2] Since bromoarenes are expected to be useful building blocks for the development of bioactive compounds and functional materials, methods for asymmetric synthesis of bromoarenes by brominative desymmetrization of prochiral compounds have recently been reported.[3-6] All of these examples have been limited to asymmetric desymmetrization of prochiral arenes whose reacting aromatic rings are directly connected to the prochiral axis or carbon. Here, we report the first example of catalytic asymmetric brominative discrimination of prochiral arenes, in which a prochiral center locates through one carbon from the reacting arenes.

We previously achieved acylative remote asymmetric desymmetrization of σ-symmetric 1,7-diols by a C_2-symmetric chiral 4-pyrrolidinopyridine-type catalyst via H-bond mediated molecular recognition (Scheme 1a).[7] Based on this result, we envisioned that the molecular recognition strategy could be applied for remote asymmetric desymmetrization of σ-symmetric 1,*n*-bisarylalkanes by catalytic aromatic bromination. Asymmetric bromination of 1,3-bisphenol **3** with NBS in $CHCl_3$ at −20 °C in the presence of catalyst **5** followed by acetylation gave mono-brominated product (*R*)-**4** in 57% yield and 90% ee (Scheme 1b). NMR studies suggested that formation of a complex between substrate **3** and catalyst **5** seems to be the key for efficient asymmetric induction.



Scheme 1. (a) Acylative desymmetrization. (b) Brominative desymmetrization

[1] D. J. Dixon *et al. J. Chem. Soc. Rev.*, **2016**, *45*, 5474-5540. [2] For pioneering examples, see: (a) S. J. Miller *et al*. *J. Am. Chem. Soc*., **2006**, *128*, 16454-16455. (b) S. J. Miller *et al*. *J. Am. Chem. Soc*., **2008**, *130*, 16358-16365.[3] T. Akiyama *et al*. *J. Am. Chem.Soc*., **2013**, *135*, 3964-3970. [4] S. J. Miller *et al*. *J. Org. Chem*., **2017**, *82*, 11326-11336. [5] S. J. Miller *et al*. *Science*, **2010**, *328*, 1251-1255. [6] S. Matsubara *et al*. *J. Am. Chem. Soc.*, **2015**, *137*, 6766-6769. [7] Unpublished results.

One-pot synthesis of THF rings using phosphonium salts : Formal synthesis of AmphidinolideF

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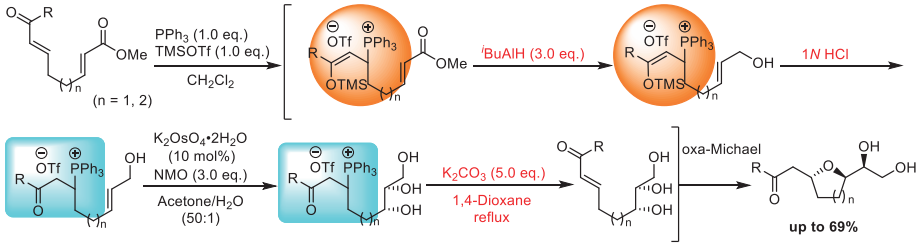
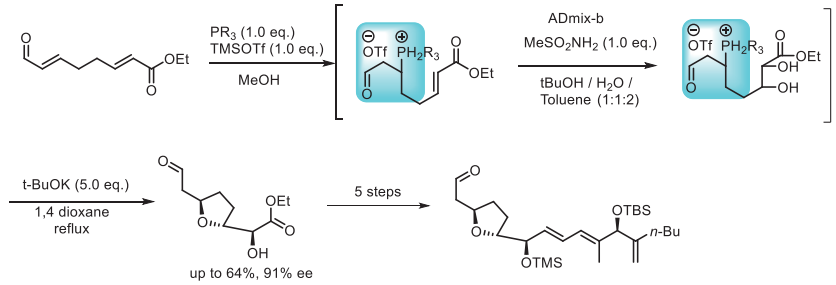
Discriminative transformation between two functional groups having similar reactivities is an important subject especially in the synthesis of multi-functional compounds such as natural products. We have been developing such transformation of carbonyl compounds using an *in situ* protection methodology,[1] and recently reported two-type transformations of α,β-unsaturated ester, transformation of ester moiety and transformation of olefin moiety in the presence of enone using two-type phosphonium salts.[2] Furthermore, we have developed highly chemoselective one-pot transformation of β-disubsitituted enone in the presence of β-mono disubsitituted enone by using phosphonium salts. Application of these two-type transformations to the substrates having α,β-unsaturated ester and enone in the same molecule afforded a decant way for the concise 6-steps one-pot synthesis of five and six-membered oxacyclic compounds were in 57 to 69% yields (**Scheme 1**).



Scheme 1. One-pot synthesis of cyclic ethers using 2 types of phosphonium salts.

In addition, it succeeded in synthesizing the fragment of Amphidinolide F[3] in only 5 steps from the obtained THF ring (**Scheme 2**).



Scheme 2. Fragment synthesis of Amphidinolide F

[1] a) Fujioka, H.; Yahata, K.; Kubo, O.; Sawama, Y.; Hamada, T.; Maegawa, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 12232. b) Yahata, K.; Minami, M.; Watanabe, K.; Fujioka, H. *Org. Lett.* **2014,** *16***,** 3680.
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[3] Ferrié, L.; Fenneteau, J.; Figaderè, B. *Org. Lett*. **2018**, *20*, 3192.

Pd-Catalyzed Migratory Cycloisomerization of *N*-Allyl-*o*-allenylaniline Derivatives

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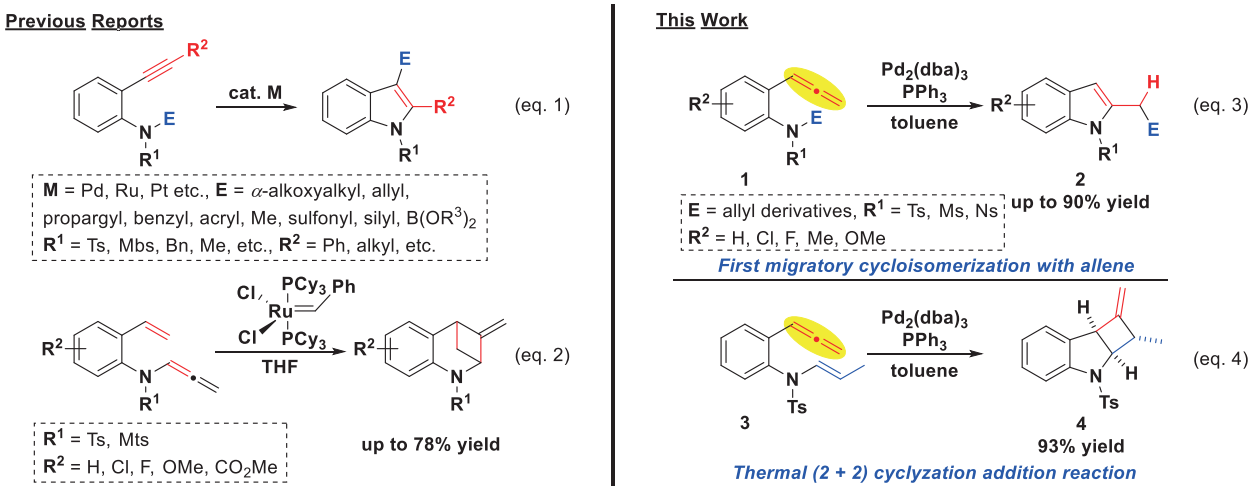
Transition-metal-catalyzed migratory cycloisomerization provides a powerful approach in organic synthesis. In particular, migratory cycloisomerizations of *o*-alkynylaryl amines having a migrating group on the heteroatom have been used to the synthesis of 2,3-disubstituted indoles (eq. 1). [1]

Allenes, a class of readily accessible, air- and water-stable compounds, show interesting and varied reactivity patterns as a result of their unique chemical properties. So, allenes are now becoming an integral part of modern synthetic methods in cyclization to yield complex skeletons. [2]

Recently, we reported the Ru-catalyzed (2 + 2) reaction of *N*-allenyl-*o*-vinyl aniline derivatives (eq. 2). However, there have been no reports of migratory cycloisomerizations between allenes and amines having a migrating group on the heteroatom leading to various substituted heterocycles. [3]

In this presentation, we will report the unprecedented Pd-catalyzed migratory cycloisomerization of *N*-allyl-*o*-allenyl aniline derivatives **1** to give 2-substituted indoles **2** (eq. 3). And also, we show the thermal (2 + 2) cyclization addition reaction of compound **3**, containing allene and vinyl amine moieties, proceeded preferentially over the migratory cycloisomerization (eq. 4). [4]



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3P-142

Regioselective Synthesis of 3-Aroylindoles by Cycloaddition of *C*-Nitrosoaromatics with Alkynones

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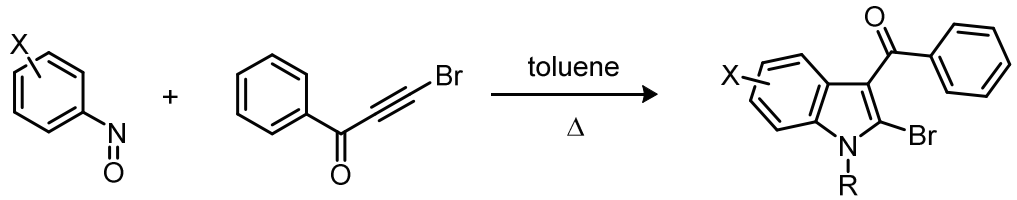
[c] *Department of Chemistry, College of Arts, Science and Humanities, Mody University of Science and Technology, Lakshmangarh 332311, Rajasthan, India*

[d] *Department of Chemistry and Biochemistry, University of Oklahoma, Stephenson Life Sciences Research Center, 101 Stephenson Parkway, Norman, OK 73019-5251, USA*

Indole compounds are deeply studied because of their biological activity and continue to capture the attention of synthetic organic chemists. A large number of original indole ring syntheses and applications of known methods to new problems in indole chemistry have been reported so far.[1] Our general interest in the chemistry of indoles led us to introduce in the past years a synthetic approach to the formation of the indole ring by cycloaddition of nitro- and nitrosoarenes with alkynes.[2] A straightforward indole synthesis via annulation of *C*-nitrosoaromatics with conjugated terminal alkynones was realised achieving a simple, highly regioselective, atom- and step economical access to 3-aroylindoles in moderate to good yields.[3]



X = 4-NO_2, 4-Br, 2-CO_2CH_3, H; R = H, OH

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[4] G. Ieronimo, G. Palmisano, A. Maspero, A. Marzorati, L. Scapinello, N. Masciocchi, G. Cravotto, A. Barge, M. Simonetti, K. L. Ameta, K. M. Nicholas, A. Penoni *Org. Biomol. Chem.* **2018**, *16*, 6853.

3P-143

Development of Active and Stable Hydrotalcite–supported Pd and Pd/Ag Bimetallic Nanocluster Catalysts for Reactions under Mild Conditions

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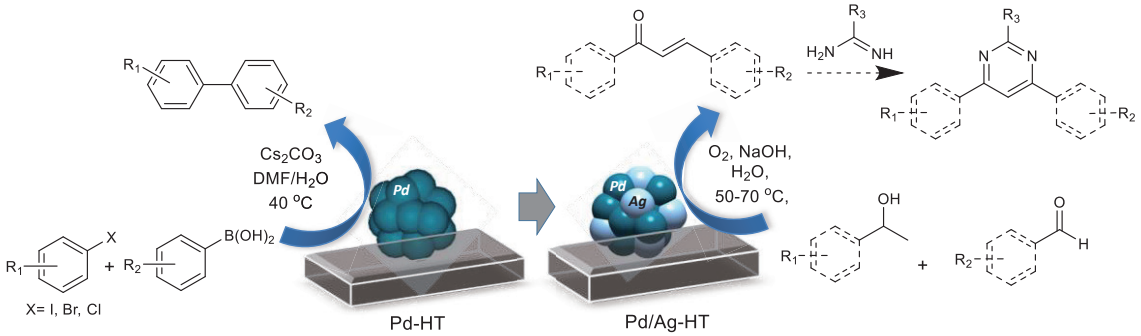
[c]*Department of Advanced Materials Science, Graduate School of Frontier Sciences, The University of Tokyo, 5-1-5 Kashiwanoha, Kashiwa, Chiba 277-8561, Japan.*

The Pd-catalyzed reactions have very high impact on organic synthesis, medicinal chemistry and pharmaceutical industry. Due to the serious economic, environmental and reusability issues, stabilization of Pd by heterogenization and bimetallization has attracted much attention. These processes enhance catalytic properties of Pd based on the high dispersibility and combined action of two or more chemically different metals. The strength of the metal-support interactions considerably influences the stability and catalytic properties. So, recently, we prepared very small highly active palladium nanoclusters (NCs) stabilized on hydrotalcite (Pd-HT) by chemical reduction method. The catalyst worked efficiently for Suzuki coupling reactions of aryl halides (I, Br and Cl) under very mild reaction conditions, affording excellent yield with good reusability of the catalyst.[1]

Bimetallic catalysts have attracted much attention because of their high catalytic activity providing mild and favorable condition to perform a chemical transformation. In addition, the use of water as a reaction medium for transition-metal-catalyzed reactions is very attractive for organic synthesis due to environmental, economic, and safety reasons. But, the incompatibility of various ligands with water and air limits their utility in various solvents, including water in synthetically important reactions. Herein, we present our recent results on preparation of HT-supported bimetallic Pd/Ag NC and its catalytic activity for the oxidation reaction. The Pd/Ag-HT showed very good oxidation ability of alcohols to aldehydes in water and oxygen as a mild oxidant. Under the optimized reaction condition, one pot aldol condensation with various aldehydes were successfully carried out with good to moderate yields. In addition, one pot transformations of alcohols, aldehydes and amidines to pyrimidine derivatives are underway.



1. S. Karanjit, M. Kashihara, A. Nakayama, L. K. Shrestha, K. Ariga, K. Namba, *Tetrahedron* **2018**, *74*, 948.

Fluorescence properties of push-pull type benzoquinoline derivatives

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Push-pull type fluorophores have environmental response property such as the solvatochromism corresponding to solvent polarity. We have already reported that "**TFMAQ**" (2,4-bis-trifluoromethyl-7-amino quinoline) as the push-pull type fluorophore exhibited some unique fluorescence properties. For example, the fluorescence colour change was observed due to the thermal single-crystal-to-single-crystal transformations [1]. Recently, the **TFMAQ** group was further applied for thermo-responsive nanomaterials as the *in vivo* tumour-imaging agent [2], [3]. Currently, we are developing several fluorophores with trifluoromethyl groups to acquire higher quantum yield (ϕ) and longer emission wavelength. In this study, we synthesized and evaluated fluorescence properties of the new tricyclic amino-benzoquinoline (BQ) derivatives (Figure 1) based on ring-expansion of the **TFMAQ** framework.

The synthesis of BQ derivatives was performed from diaminonaphthalene by Combes synthesis condition. Remarkably, unexpected angular-type BQ (**BQA**) was obtained in higher yield than desired linear-type BQ (**BQL**). These structures were revealed by single-crystal X-ray structure analysis. The planarity of the aromatic rings within **BQL** was high, whereas the rings within **BQA** were distorted due to an intramolecular steric repulsion. Both of **BQA** and **BQL** exhibited longer emission wavelength than the **TFMAQ**, accompanied by a noticeable solvatochromic effect (Figure 2 and Table). Notably, the higher planarity of **BQL** led to display longer emission wavelength (536 nm in hexane) and higher ϕ value (0.67 in hexane) in low polar solvents than those of **BQA** (FL:λ_{max}= 475 nm, ϕ= 0.08 in hexane). Phenyl-substituted BQ derivatives were synthesized by cross-coupling reaction to a primary amino group of **BQA** or **BQL**. **BQA** and **BQL** derivatives with mono- or diphenyl groups showed also higher ϕ values in solutions. In this presentation, we will report and discuss the structures and the physical properties of BQ derivatives in detail.

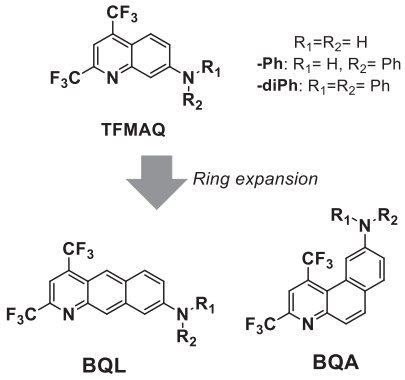
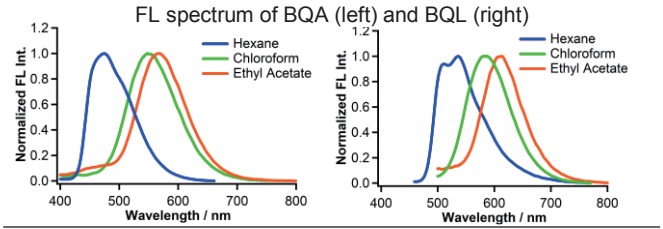


Figure 1 TFMAQ and **BQ** derivatives



	Fluorescencce λ_{max} / nm (ϕ)			
	Hexane	$CHCl_3$	AcOEt	DMSO
TFMAQ	418 (0.23)	458 (0.45)	489 (0.61)	535 (0.23)
BQA	475 (0.08)	548 (0.07)	568 (0.06)	-
BQL	536 (0.67)	583 (0.08)	614 (0.03)	-

Figure 2 and **Table** Fluorescence spectral data of **TFMAQ** and **BQ**

[1] Abe, Y.; Karasawa, S.; Koga, N. *Chem. Eur. J.* **2012**, *18*, 15038–15048.
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[3] Araki, T.; Fuchi, Y.; M.; Aoki, I.; Yamada, K.; Karasawa, S. *et al*., *Nanomaterials* **2018**, *8*, 782.

3P-145

Cu-Catalyzed Stereoselective Formation of 2,5-Dihydro-1,2-oxaborole from Alkyne, Aldehyde, and Organoborane

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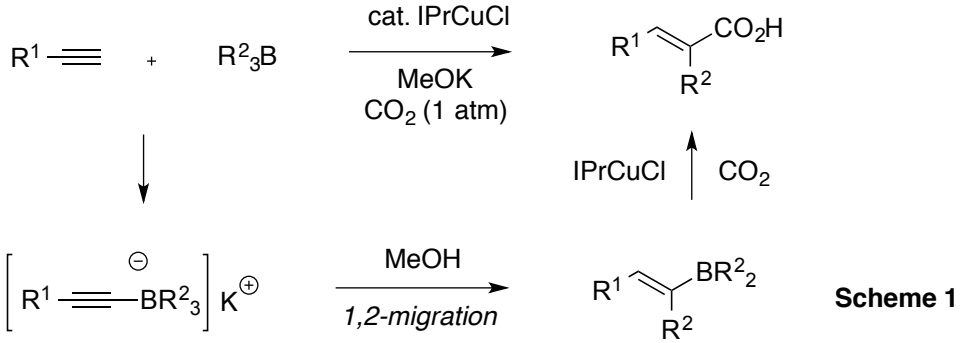
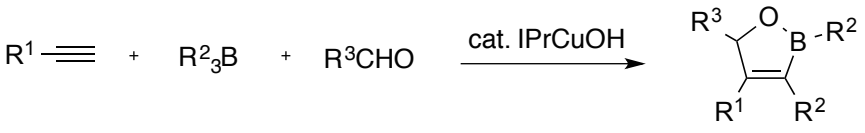
Akynylborate is an efficient key intermediate for construction of the stereodefined substituted alkenylboranes. Recently, we have developed the Cu-catalyzed highly regio- and stereoselective formation of α-alkylated acrylic acids from terminal alkynes with trialkylboranes under CO_2 atmospheric pressure[1]. Alkynylborates were produced in the presence of Cu-catalyst, trialkylborane, terminal alkyne in situ, and then underwent the protonation at β-position. Thus, the formed alkenylboranes reacted with CO_2 smoothly promoted by Cu(I) catalyst to provide the α-substituted acrylic acids with high regio- and stereoselectivities (Scheme 1).

Based on these results for the coupling reactions with alkynylborates, we could acheive the coupling reactions with an aldehyde as an electrophile instead of proton. Three-component coupling reactions of terminal alkyne, organoborane, and aldehyde combined with high regio- and stereoselectivities to form the 2,5-dihydro-1,2-oxaboroles under nitrogen atmosphere (Scheme 2). These transformations are convenient and straightforward synthetic methodologies for the stereodefined construction of 2,5-dihydro-1,2-oxaboroles in a single operation. In this presentation, we disclose the scope and limitations for the three-component coupling reactions with a wide variety of terminal alkynes, organoboranes, and aldehydes as well as the applicable expansion reactions involving the oxaborole derivatives as synthetic key intermediates.



Scheme 1

This work



Scheme 2

[1] Kuge, K.; Luo, Y.; Fujita, Y.; Mori, Y.; Onodera, G.; Kimura, M. *Org. Lett.,* **2017**, *19*, 854.

5P-001s

Biologically Active Novel Nitrogen Heterocycles Containing the Benzoazepine Moiety

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Chemical compounds with the dibenzazepine moiety have found use in a range of areas, most prominently as drugs for the treatment of heart conditions, neuropsychiatric disorders, as well as in the search for novel structures for the treatment of cancer. However, access to azepine containing scaffolds with high degrees of substitution has remained a challenge and typically requires long synthesis strategies. The dihydrobenzo[6,7]azepino[3,2-*c*]quinolinones have remained largely unexplored with only a few examples in the literature showing the dihydrobenzazepine scaffold.

We report a robust and simple synthetic pathway to access a novel series of 7-phenyl-7,13-dihydro-8*H*-benzo[6,7]azepino[3,2-*c*]quinolin-8-one derivatives via an initial addition-oxidation-ring cleavage cascade reaction under basic conditions in the presence of NaOH in DMSO. A subsequent T3P® in DMF catalysed cyclisation reaction gave the fused quinoline ring incorporating the one carbon unit from the DMF (**Figure 1**). Reaction with aldehydes or ketones with T3P® in ethyl acetate as the catalyst, gave the corresponding C6 substituted compounds. The key feature of this synthetic pathway is that it provides rapid access to a new class of heterocyclic compounds, namely benzo[6,7]azepino[3,2-*c*]quinolin-8-ones. A high level of substitution is possible around the core scaffold allowing for diverse functionalisation to be achieved. Furthermore, this methodology can be applied to access a new class of indole-based derivatives that are yet to be reported. These compounds possess moderate anti-cancer activity and have significant potential for further development.[1]

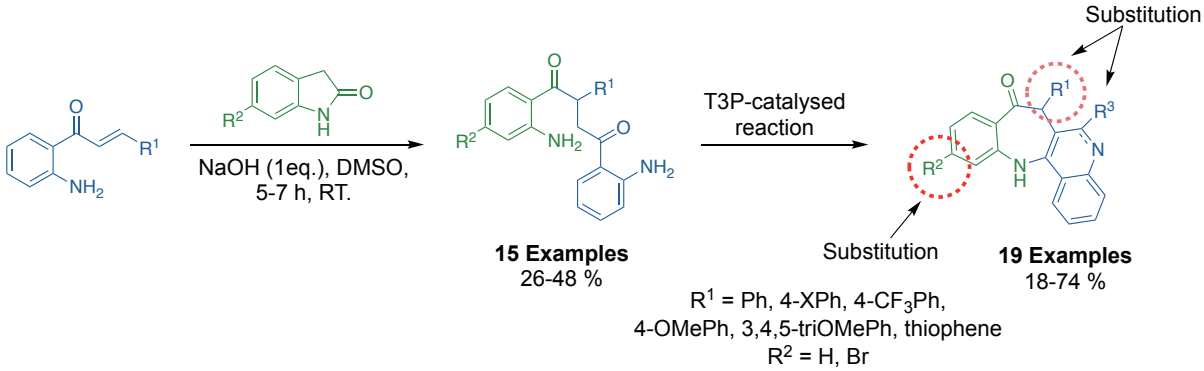

Figure 1: Novel highly functionalised 7-phenyl-7,13-dihydro-8*H*-benzo[6,7]azepino[3,2-*c*]quinolin-8-one derivatives.

[1] **Dobrowolski, JC**; Nguyen, DHT; Fraser, BH; Bhadbhade, M; Black, DS; Kumar, N. **2019**. A general synthesis of 7-phenyl-7,13-dihydro-8H-benzo[6,7]azepino[3,2-c]quinolin-8-ones. *Synlett* **2019**, 30(05), 567–572. DOI: 10.1055/s-0037-1612106

5P-002

Regio-divergent Syntheses of Heteroatom-Substituted 1,2,3-Triazoles via Copper-Catalyzed Click Reaction of Phosphorylethynes

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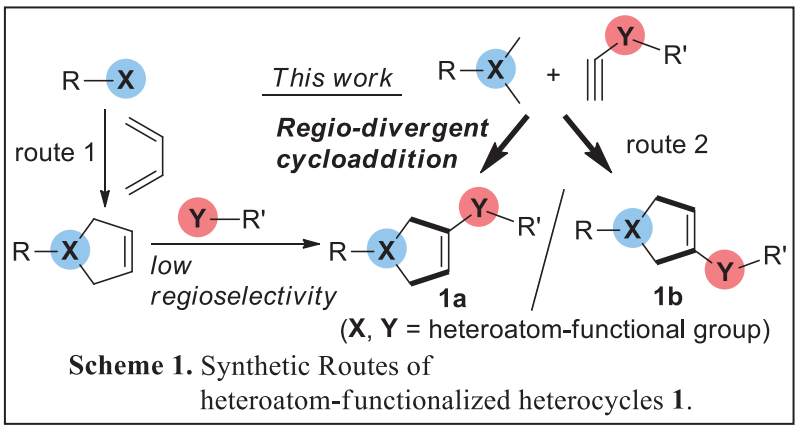
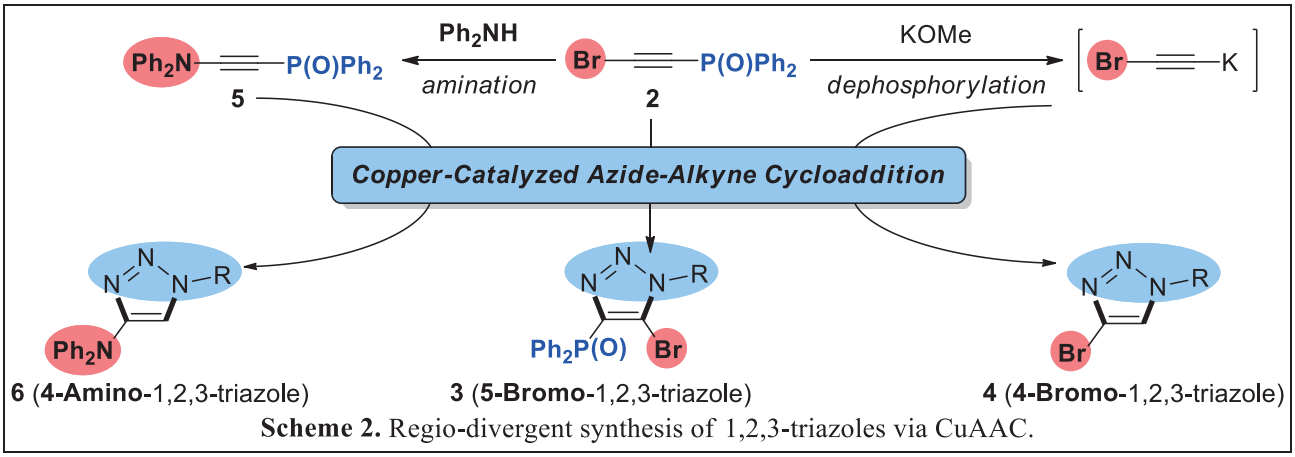
Heteroatom-functionalized heterocycles **1** are of great importance in the fields of pharmaceutical, agricultural and biological chemistry. Although stepwise strategies, consecutive construction of heterocycles and installation of heteroatom-functional groups, are conventional synthetic route of **1**, it often suffers from a low regioselectivity in the heteroatom-functionalization (Route 1 in Scheme 1). We herein describe regio-switchable synthetic routes using bromo(phosphoryl)ynamine **2** as staring compound (Route 2 in Scheme 1). When ynamine **2** was subjected to copper-catalyzed azide-alkyne cycloaddition (CuAAC), 5-bromotriazole **3** was obtained (Scheme 2). [1,2] In contrast, subjection of **2** to MeOK-mediated dephosphorylation and CuAAC afforded 4-bromotriazole **4** with a high regioselectivity. The dephosphorylative CuAAC protocol enabled transformation of amino(phosphoryl)ynamine **5** to 4-aminotriazole **6**. In this presentation, we also describe further functionalization of bromotriazoles **3** and **4**.



Scheme 1. Synthetic Routes of heteroatom-functionalized heterocycles **1**.



Scheme 2. Regio-divergent synthesis of 1,2,3-triazoles via CuAAC.

[1] Peng, L.; Xu, F.; Suzuma, Y.; Orita, A.; Otera, J. *J. Org. Chem.* **2013**, *78*, 12802.
[2] Peng, L.; Xu, F.; Shinohara, K.; Nishida, T.; Wakamatsu, K.; Orita, A.; Otera, J. *Org. Chem. Front.* **2015**, *2*, 248.

5P-003s

Perylene Photocatalyst-Promoted Desulfonylation of Ethenyl Sulfones

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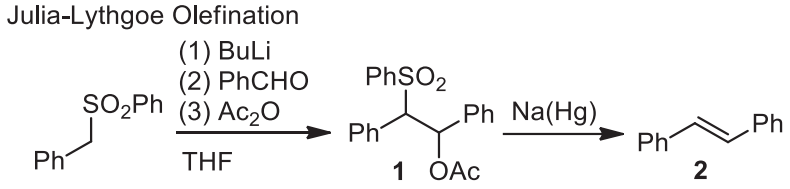
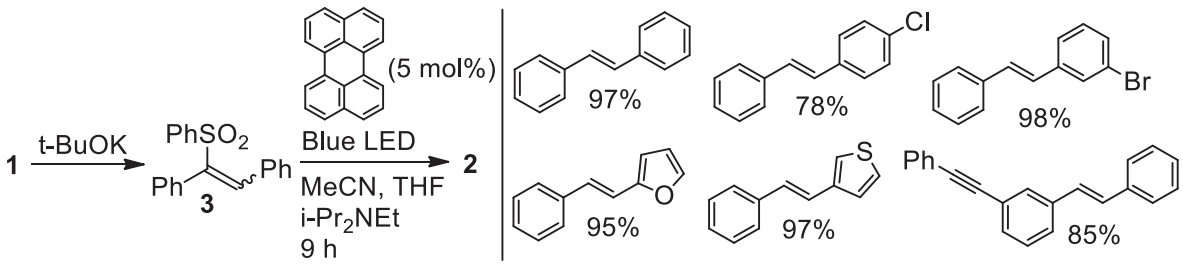
A double bond between carbons is one of fundamental arrays in organic compounds, and a number of synthetic protocols of alkenes have been developed so far: for instance, Wittig reaction, Peterson olefination and Mizoroki-Heck reaction. Julia-Lythgoe olefination is another protocol for syntheses of alkenes which employs sulfones and aldehydes as starting compounds, and this olefination is composed of two-step reaction: (i) C-C bond formation to give β-acetoxy sulfone **1** and (ii) Na(Hg)-promoted reductive desulfonylation to give the desired alkene **2**.[1]



Although Julia-Lythgoe olefination is indeed of great use because this protocol can be applied to construction of sterically congested C-C double bond, use of Na(Hg) is required in the desulfonylation step to produce hazardous metal mercury as a byproduct. In order to overcome this drawback, we developed an alternative synthetic method for transformation of β-acetoxy sulfones to alkenes by taking advantage of photocatalyst-promoted reduction system. When **1** was treated with t-BuOK, ethenyl sulfone **3** was obtained, and the consecutive irradiation of visible light to an MeCN/THF solution of **3** in the presence of perylene photocatalyst and i-Pr_2NEt as a sacrificing reagent provided **2**. The photoreduction protocol could be applied to other ethenyl sulfones bearing functional groups such as halogens, heteroaromatic rings and acetylene. In this presentation, we will show a plausible reaction mechanism.



[1] Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, 4833.

5P-004

Inverse-Electron-Demand Diels–Alder Reactions of α,β-Unsaturated Hydrazones with α-Pyrones Having Electron-Withdrawing Group

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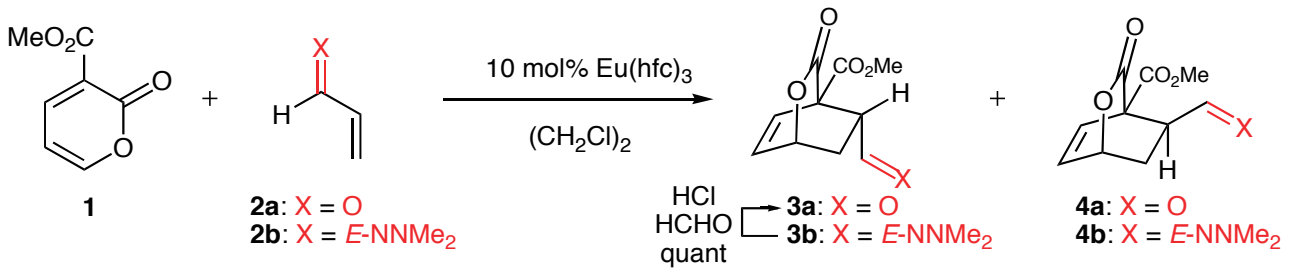
Carbonyl umpolung (polarity inversion) using hydrazone, which has an electron-donating nitrogen atom in an imine functionality, is often applied in synthetic chemistry.[1] Additionally, there are a few reports on its electron-donating ability extension to conjugated olefins. For example, a Povarov-type inverse-electron-demand aza-Diels–Alder reaction of α,β-unsaturated hydrazones with aromatic imines afforded tetrahydroquinolines.[2] Recently we focused on application of this type umpolung approach of α,β-unsaturated oximes and hydrazones to inverse-type cycloadditions.[3,4] Here, we report inverse-electron-demand Diels–Alder reactions of electron deficient α-pyrones with α,β-unsaturated hydrazones to afford cycloadducts with high syn and endo selectivity.[5] For example, α-pyrone **1** failed to react with acrolein (**2a**) in the presence of 10 mol% of Eu(hfc)$_3$ even at 80 °C and none of cycloadduct **3a** or **4a** was obtained. In contrast, the reaction with the corresponding dimethylhydrazone derivative **2b** proceeded with the same catalyst at room temperature to provide a 92 : 8 mixture of **3b** and **4b** in 86% yield. Next, we examined the indirect synthesis of aldehyde **3a** that could not be obtained by the cycloaddition of **1** and **2a**. Thus, **3b** was exposed to hydrazone exchange conditions (HCl and aq. HCHO) to give **3a** quantitatively.



Other examples will be also presented.

[1] For a review, see: Lazny, R.; Nodzewska, A. *Chem. Rev.* **2010**, *110*, 1386.
[2] For examples, see: (a) Bianchini, G.; Ribelles, P.; Becerra, D.; Ramos, M. T.; Menéndez, J. C. *Org. Chem. Front*. **2016**, *3*, 412. (b) Sridharan, V.; Ribelles, P.; Estévez, V.; Villacampa, M.; Ramos, M. T.; Perumal, P. T.; Menéndez, J. C. *Chem. Eur. J*. **2012**, *18*, 5056.
[3] Hashimoto, Y.; Ishiwata, H.; Tachikawa, S.; Ban, S.; Morita, N.; Tamura, O. *Chem. Commun*. **2017**, *53*, 2685.
[4] Hashimoto, Y.; Ikeda, T.; Ida, A.; Morita, N.; Tamura, O. *Org. Lett*. in press.
[5] Hashimoto, Y.; Abe, R.; Morita, N.; Tamura, O. *Org. Biomol. Chem*. **2018**, *16*, 8913.

5P-005

Chemoselective demethylation of methoxypyridine

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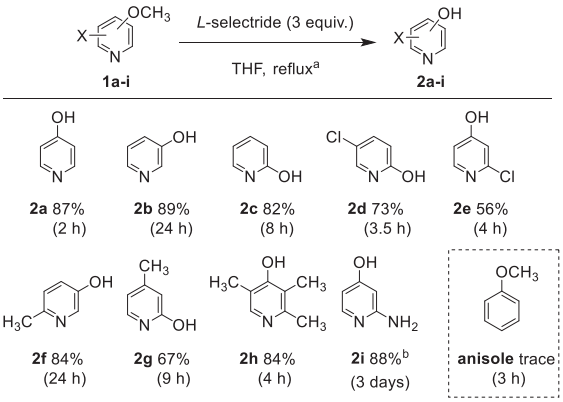
[b]*Faculty of Pharma Sciences, Teikyo University, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan.*
[c]*Research Institute of Pharmaceutical Sciences, Musashino University, 1-1-20 Shinmachi, Nishitokyo-shi, Tokyo 202-8585, Japan.*
[d]*Faculty of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.*

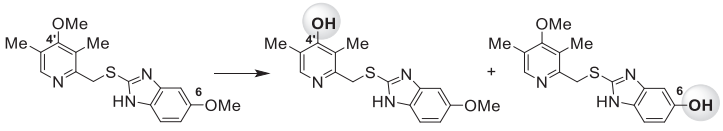
Methyl ether is considered to be useful and effective protective group for phenols in synthetic chemistry because of a tolerance to a variety of reaction conditions. We found a chemoselective demethylation for various methoxy pyridines. Treatment of 4-methoxypyridine with *L*-selectride in THF for 2 hours at reflux temperature afforded 4-hydroxypyridine in good yield, while no reaction occurred to anisole (Scheme 1).[1] Intriguingly, the position of the -OCH_3 group has a profound influence on the reactivity for demethylation, and the reaction was completed in 2 h for **2a**, while 24 h was needed for **2b**. Other methoxypyridines, irrespective of their electronic nature (electron-rich/electron-poor), furnished the corresponding demethylated compounds **2c**–**2i** in 56–84% yields. The utility of our method was demonstrated by the efficient synthesis of the metabolites of anti-ulcer agent, omeprazole (**3**-**5**). A chemoselective demethylation at the site of 3,5-dimethyl-4-methoxypyridine in the presence of 4-methoxybenzimidazole was achieved (Table 1). We anticipate this method would be useful to prepare biologically active heterocyclic compounds.

Scheme 1



a) Reaction times are shown in parentheses. b) 6 equiv. of *L*-selectride were used.

Table 1



Entry	Reagents	Equiv.	Solvent	Temp.	Time	**4** (%)	**5** (%)
1	*L*-selectride	3	THF	reflux	3 h	94	—
2	BBr_3	2.5	CH_2Cl_2	0 °C	12 h	—	79

[1] Makino, K.; Hasegawa, Y.; Inoue, T.; Araki, K.; Tabata, H.; Oshitari, T.; Ito, K.; Natsugari, H.; Takahashi. H. *Synlett* **2019**, *30,* 951－954.

5P-006

Palladium-Catalyzed Oxidative Cyclization: Application to the Synthesis of Lapidilectine B

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Motoki Ito and Shigeo Sugiyama
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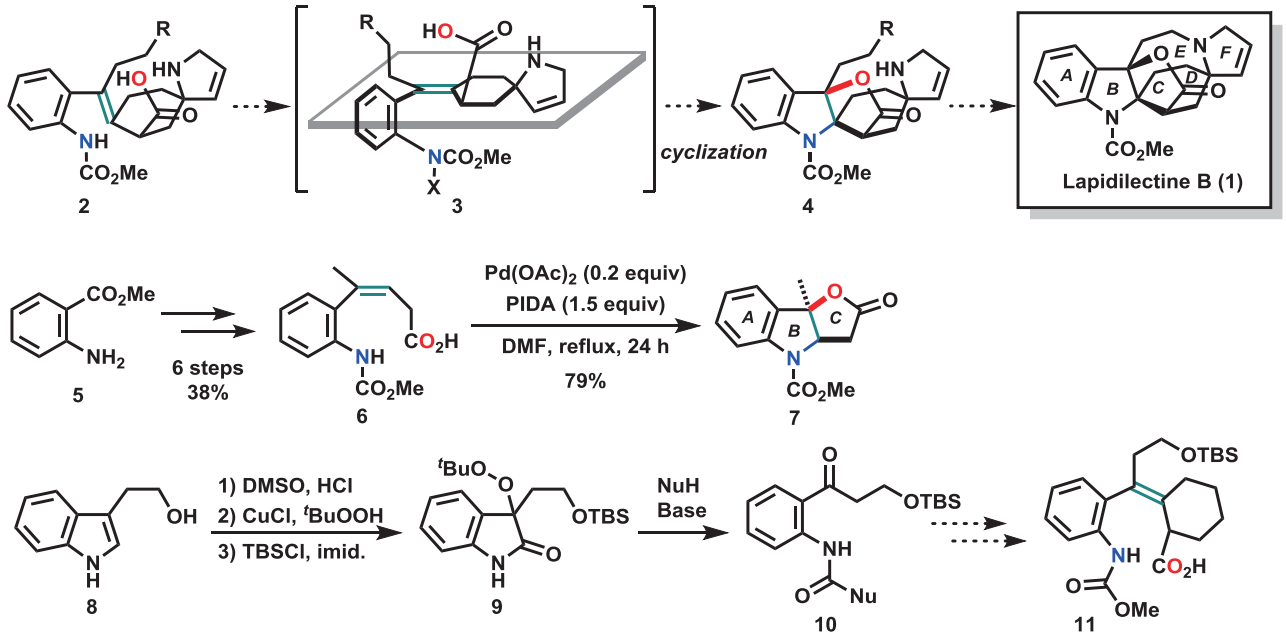
Kiyose, Tokyo 204-8588, Japan

Lapidilectin B (**1**) was isolated by Awang in 1992 from the leaves of *Kopsia lapidilecta*.[1] One of the unique biological activity of **1** is the multidrug resistance reversing effect toward vincristine-resistant KB cancer cells.[1] As the structural features of **1**, B, C and E rings constitute a propellane skeleton, and further B, D and F rings are each joined by the spiro centers. For the unique biological activity and structure, a lot of synthetic studies have been investigated and the total syntheses of **1** were achieved by Pearson[2], Nishida[3] and Ma[4] groups.

We planned an alternative approach to synthesize tricyclic skeleton corresponding to the rings A to C of lapidilectin B (**1**) by the palladium-catalyzed oxidative cyclization[5] of the tetra-substituted alkene **3**. Firstly, the tri-substituted alkene **6** was synthesized in 6 steps from methyl anthranilate (**5**). When the alkene **6** was treated with catalytic amounts of $Pd(OAc)_2$ and $PhI(OAc)_2$, the cyclized compound **7** was obtained in a yield of 79%. We will report the synthetic study of the tetra-substituted alkene **11** via oxidative fragmentations of oxindole[6] derived from tryptophol (**8**).



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[2] Pearson W. H.; Mi, Y.; Lee, I. Y.; Stoy, P. *J. Am. Chem. Soc.* **2001**, *123*, 6724.
[3] Nakajima, M.; Arai, S.; Nishida, A. *Angew. Chem. Int. Ed.* **2016**, *55*, 3473.
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[5] Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542.
[6] Klare, H. F. T.; Goldberg, A. F. G.; Duquette, D. C.; Stoltz, B. M. *Org. Lett.* **2017**, *19*, 988.

Synthetic Study of Phomopsin A : Catalytic Asymmetric Synthesis of β-OH-DOPA

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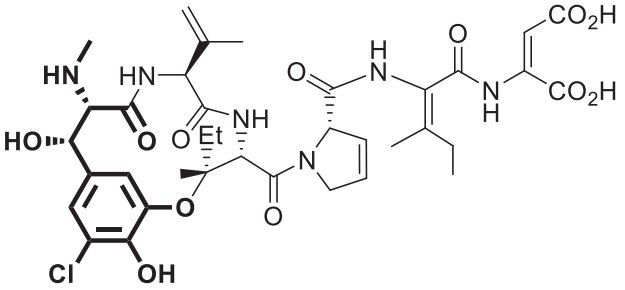
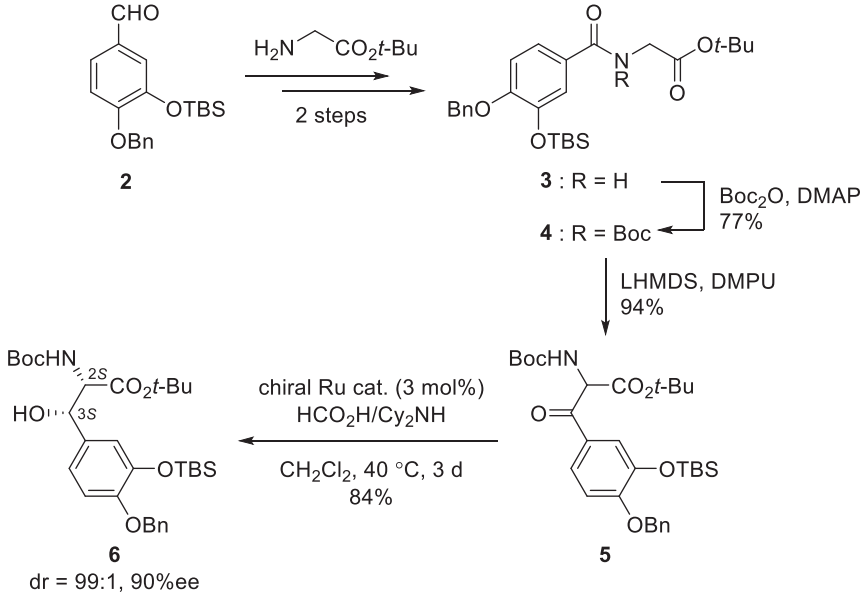
Osaka 558-8585, Japan

Phomopsin A (**1**), isolated from *Diaporthe toxica* as a mycotoxin, exhibits potent tubulin polymerization inhibitory activity.[1] This natural product consists of six unnatural amino acids. Three of the six participates in the formation of a heterocyclic 13-membered cyclophane ring. Due to its complex structure and bioactivity, **1** has attracted much attention as a synthetic target. In this presentation, we would like to report our synthetic efforts toward development of the β-OH-DOPA derivative in an optically active form by asymmetric transfer hydrogenation reaction via dynamic kinetic resolution of **5**.[2]



Phomopsin A (**1**)

Amide **3** was synthesized from aldehyde **2**[3] by oxidation and condensation with glycine, and subsequently converted to ketone **5** via acyl rearrangement of **4**. Asymmetric transfer hydrogenation of **5** gave (2*S*,3*S*)-alcohol **6** with high diastereo- and enantioselectivity. Recent progress toward total synthesis of **1** from **6** will be descrived.



[1] Culvenor, C. C. J.; Beck, A. B.; Clarke, M.; Cockrum, P. A.; Edgar, J. A.; Frahn, J. L.; Jago, M. V.; Lanigan, G. W.; Payne, A. L.; Peterson, J. E.; Petterson, D. S.; Smith, L. W.; White, R. R. *Aust. J. Biol. Sci.* **1977**, *30*, 269.
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5P-008

Dramatic Enantioselectivity Reversal in the Propargylation of Aldehyde with Alkynyllithium Catalyzed by Dilithium Binaphtholate Derivatives

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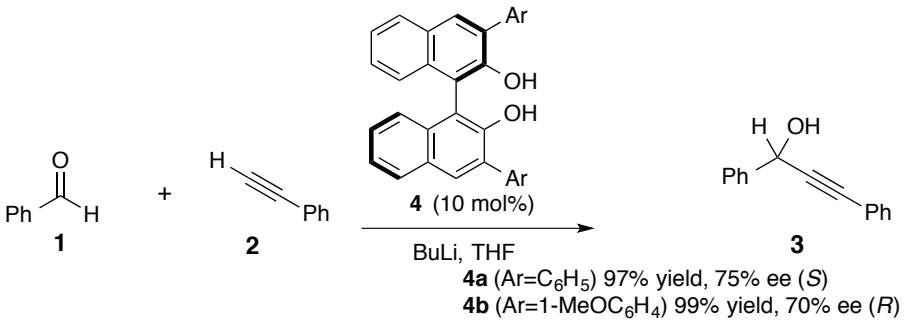
The enantioselective propargylation of carbonyl compounds is an important process for the preparation of optically active propargylic alcohols. We previously reported an enantioselective propargylation of carbonyl compounds catalyzed by dilithium binaphtholate derivatives. [1] In an effort to develop more effective propargylation methods, we found dramatic enentioselectivity reversal by the introduction of ether group on the catalyst.

We found that 3,3'-diphenylbinaphthol (**4a**) as a precatalyst gave the corresponding propargylic alcohol with the *S*-configuration with a 75% ee in the reaction of benzaldehyde and phenylacetylene, whereas introduction of methoxy group at the *ortho* position on the phenyl ring on the precatalyst (**4b**) gave the alcohol in *R*-configuration with a 70% ee. [2]

After screening of the structure of the precatalyst and the reaction conditions to obtain (*R*)-alcohol in high enantiomeric excess, we found that the catalyst precursor **4c** is the precatalyst of choice. Table 1 shows the selected data for the enantioselective alkynylation of aldehydes catalyzed by **4c**-Li. Introduction of methoxy group to the phenyl ring of benzaldehyde increased the enantioselectivity; 4-Methoxybenzaldehyde or 3,4,5-trimethoxy-benzalhdehyde gave the corresponding product in high enantiomeric excess of 93% ee. [3]



4a (Ar=C_6H_5) 97% yield, 75% ee (*S*)
4b (Ar=1-$MeOC_6H_4$) 99% yield, 70% ee (*R*)

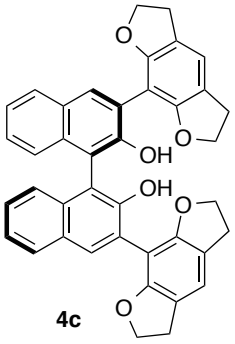


Table 1 Enantioselective Phenylethynylation Catalyzed by **4c**-Li

aldehyde	chemial yield, %	ee, % (conf)
PhCHO	99	87 (*R*)
2-NapCHO	94	86 (*R*)
1-$Me_2NC_6H_4CHO$	76	84 (*R*)
4-$MeOC_6H_4CHO$	97	93 (*R*)
3,4,5-$(MeO)_3C_6H_2CHO$	97	93 (*R*)

[1] Tanaka, K.; Kukita, K.; Ichibakase, T.; Kotani, S.; Nakajima, M. *Chem. Commun.* **2011**, *47,* 5614-5616.
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5P-009s

Total Syntheses of Pleiocarpamine, Normavacurine, and *C*-Mavacurine

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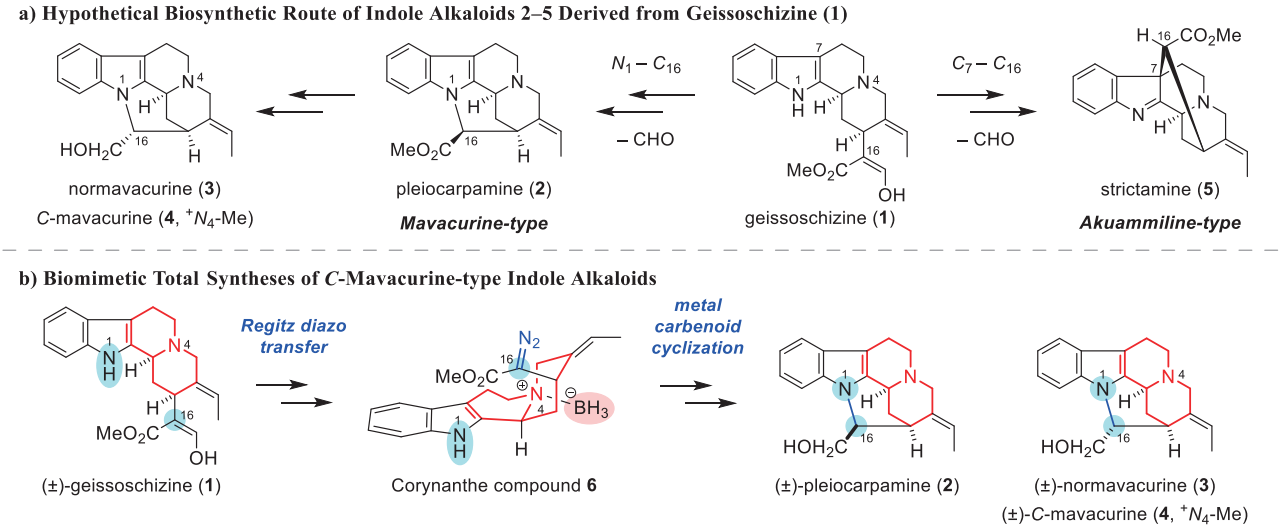
C-Mavacurine-type alkaloids, such as pleiocarpamine (**2**), are considered to be biogenetically derived from geissoschizine (**1**) by the ring closure between the C_{16} and N_1 positions.[1] Geissoschizine (**1**) is also supposed to be a biogenetic common intermediate to provide akuammiline-type alkaloids, such as strictamine (**5**).[1] A number of total syntheses of akuammiline-type alkaloids was reported in the past decade.[2,3] On the other hand, synthetic studies of *C*-mavacurine-type alkaloids are quite limited[4] and there is no report on the synthesis of those alkaloids by the direct coupling between the C_{16} and N_1 positions in the Corynanthe skeleton.

Recently, we have achieved the biomimetic total syntheses of (±)-pleiocarpamine (**2**), (±)-normavacurine (**3**), and (±)-*C*-mavacurine (**4**)[5] via a direct cyclization by a carbene N–H insertion reaction between the C_{16} and N_1 positions in Corynanthe compound **6** that was equipped with a diazo function. For this key cyclization, the N_4 modification of the substrate using an amine–borane complex was indispensable to fix the molecular conformation to a robust *cis*-quinolizidine structure.



[1] Atta-ur-Rahman; Basha, A. *Biosynthesis of Indole Alkaloids*; Clarendon Press: Oxford, **1983**.
[2] Adams, G. L.; Smith, A.B., III. *The Alkaloids: The Chemistry of the Akuammiline Alkaloids*; Knölker, H.-J., Ed.; Academic Press, Inc.: Amsterdam, **2016**; Vol. 76, pp 171.
[3] Zhang, X.; Kakde, B. N.; Guo, R.; Yadav, S.; Gu, Y.; Li, A. *Angew. Chem., Int. Ed.* **2019**, *58*, 6053, and references cited therein.
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[5] Sato, K.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2019**, *21*, 3342.

5P-010s

Synthesis of Pemetrexed Medoxomil Ester Prodrugs Aiming for the Oral Administration

K. Miyoshi[1], N. Hayama[1], K. Inamoto[1], A. Miyazaki[1], A. Nakamura[2], T. Maegawa[2], T. Otori[2], K. Matsuyama[3] and T. Kimachi[1]*

1 School of Pharmacy and Pharmaceutical Sciences, Mukogawa Women's University, Nishinomiya 663-8179, Japan

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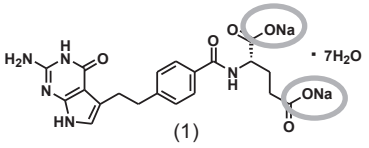
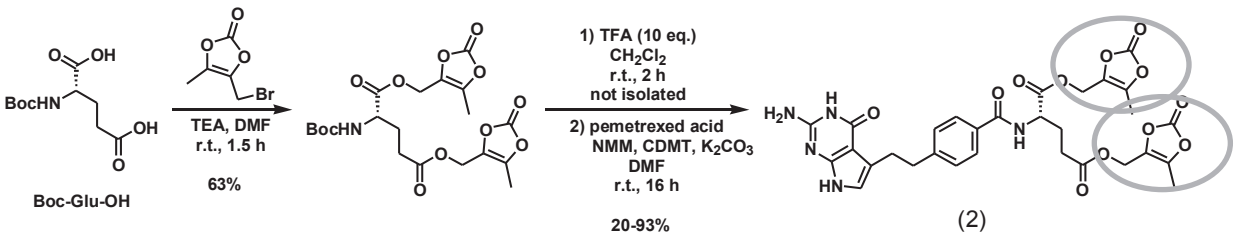
3 Hanshin Dispensing Pharmacy, Akashi 673-0005, Japan

Pemetrexed (1) is an excellent anticancer agent having inhibition of DNA synthesis. At present, it is used in combination with platinum perparation for malignant mesothelioma and unresectable advanced / recurrent non-small cell lung cancer. High polarity in its structure causes the poor membrane permeability and is limited to be used by intravenous infusion therapy in clinical site. The oralization of pemetrexed as a prodrug is considered to be an important issue in order to advance the aging of medical care and the expansion of home care in Japan. We chose the medoxomil group as an ester protecting group for prodrug synthesis. It is known as a substituent that is rapidly hydrolyzed after absorption in the digestive tract. Direct dimedoxomil ester formation to obtain pemetrexed dimedoxomil ester (2) was attempted using pemetrexed disodium salt, but the reaction did not proceed. Therefore, a dimedoxomil ester precursor of glutamic acid was synthesized, and coupled with pemetrexed acid with the help of condensing agents.[1] The pemetrexed monomedoxomil ester prodrug (3) was prepared using monobenzyl ester of glutamic acid as a starter, coupling with pemetrexed acid and the subsequent debenzylation by catalytic hydrogenation. The oral administration experiment to rats was performed using the obtained pemetrexed prodrugs (2, 3), and the pemetrexed concentration in blood was measured.



(1)



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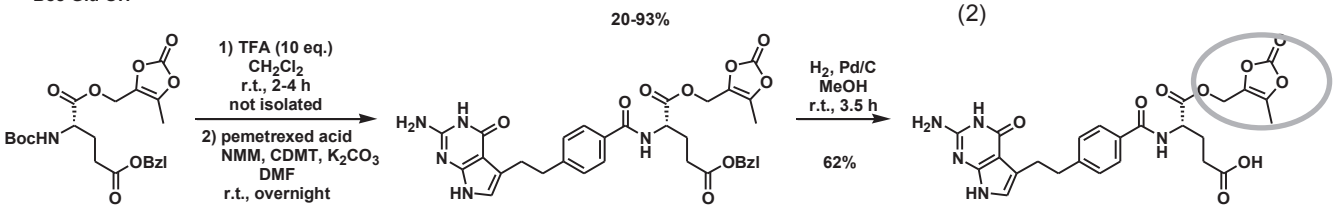

(3)

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5P-011s

New Polyazahelicenes: Facile Synthesis by Consecutive N-H/C-H Coupling with Hypervalent Iodine and Evaluation of Their Photophysical Properties

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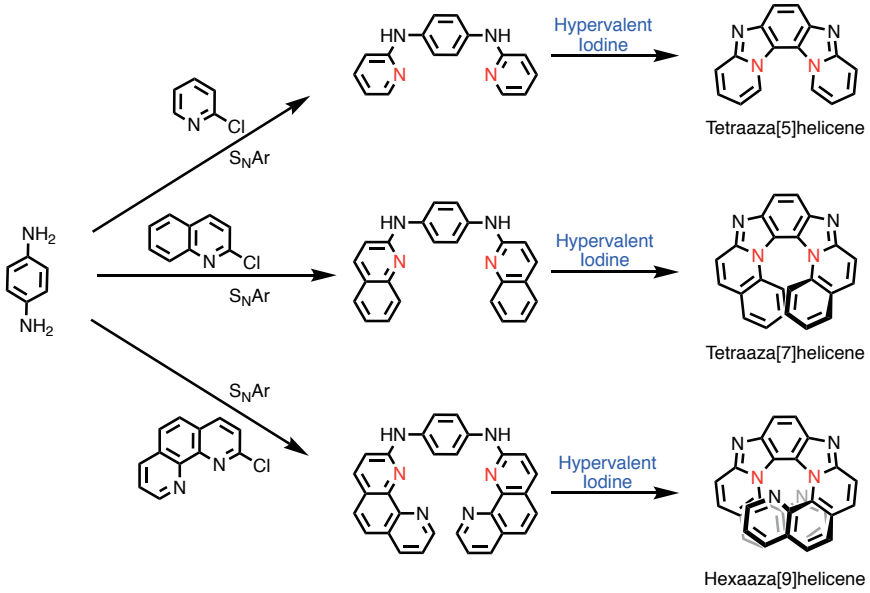
Helicene is a generic term for nonplanar polyaromatic compounds in which aromatic rings are fused by sharing a side bond, and has helical chirality derived from steric hindrance. Chiral helicenes are interested in unique optical properties due to extended π electron interactions, for example, optically active helicenes have circularly polarized light emission properties (CPL) in addition to strong circular dichroism (CD) and extremely large optical rotation. Therefore, their application to functional organic materials is expected. However, helicene synthesis generally requires multiple steps, and the fluorescence quantum yield is low. In this research, we used the commercially available *p*-phenylenediamine as a starting material and synthesized azahelicene precursors by S_NAr reaction or Buchwald-Hartwig amination of halogenated nitrogen arenes. New polyaza[5], [7] and [9]helicenes were synthesized by consecutive N-H/C-H coupling with hypervalent iodine.− Polyazahelicenes showed higher fluorescence quantum yield than carbohelicenes.



Since polyaza[7]- and [9]helicenes have helical chirality, optical resolution was conducted by HPLC using a chiral column, and their photophysical properties were measured. We will discuss the chiroptical characteristics of these polyazahelicenes.

[1] T. Otani, A. Tsuyuki T. Iwachi, S. Someya, K. Tateno, H. Kawai, T. Saito, K. S. Kanyiva, T. Shibata, *Angew. Chem. Int. Ed*. **2017**, 56, 3906-3910.

5P-012s

New catalytic hydroboration with pinacolborane and NaH as catalyst

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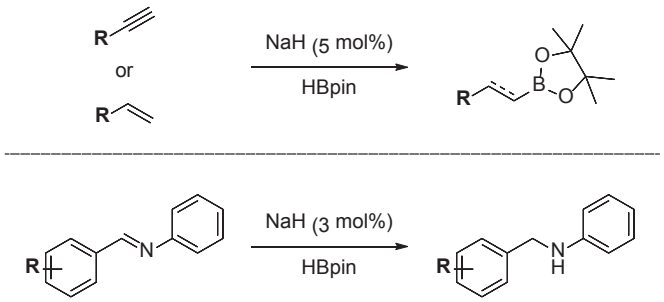
Hydroboration is an important and fundamental reaction system in organic chemistry for the reduction of unsaturated compounds (C=C, C=O, and C=N bonds). The organoboranes obtained from hydroboration are remarkably valuable precursors for various chemical transformations and cross-coupling reactions. [1,2] Borane reducing agents such as $LiBH_4$ have been utilized for the stoichiometric hydroboration. Making the reactions more selective and economical, research on the catalyzed hydroboration is continuously increasing and of present interest that leading to its rapid application with various catalytic systems like transition metals, main metal, non-metal, and Lewis acid/Lewis acid–base pairs.

Recently, we have reported NaH catalyzed hydroboration of carbonyl compounds such as aldehydes ketones. In addition, aldehydes were selectively reduced in the presence of ketones. This method was convenient, economical and a valuable alternative for highly expensive, precious transition metals catalyzed hydroboration of aldehydes and ketones. [3]

Further, the catalyzed hydroboration of alkenes and alkynes are economical and straight-forward reactions for functionalized alkyl and alkenyl boronate esters than the stoichiometric reactions. In continuation of our research; with modified and optimal conditions, we successfully obtained catalyzed hydroboration of alkenes, alkynes, and imines with pinacolborane and NaH system under suitable reaction conditions.



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[2] Obligacion, J. V.; Chirik, P. J. *Nat. Rev. Chem*. **2018**, *2*, 15.
[3] Shin. W. K.; Kim, H.; An. D. K. *Tetrahedron.* **2018**, *74*, 6310.

5P-013

Conformational properties based on the axis of 6*N*-benzoyl- and 6*N*-p-tosyl-1,6-benzodiazocines: Comparison with those of 1,5-benzodiazepines

Hidetsugu Tabata,[a] Kaoru Funaki,[a] Kazuya Murai,[a] Chihiro Takemae,[a] Tomohiko Tasaka,[b] Tetsuta Oshitari,[a] Hideyo Takahashi,[c] Hideaki Natsugari[a,b,d]

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Benzo-fused seven-membered-ring nitrogen-heterocycles are found as the scaffolds of many biologically active molecule. Thus far, we have investigated the conformation based on axial chirality of 5*N*-benzoyl derivatives of several seven-membered-ring nitrogen-heterocycles (**1A**) and its relation with the biological activities.[1-4] Recently, we investigated the congener 5*N*-*p*-toluenesulfonyl derivatives (**1B**) and revealed that **1B** also possess the atropisomeric properties caused by the Ar–N(SO_2) axis similar to **1A**.[5]

In this study, the atropisomeric and conformational properties of the eight-membered 1,6-benzodiazocines (**2**) with 6*N*-benzoyl- (**A**) and 6*N*-*p*-tosyl- (**B**) groups were examined by comparing with those of the seven-membered 1,5-benzodiazepine congeners (**1**) (**A**,**B**) (Fig.1).[6] The conformation (orientation) of the benzene ring in benzoyl and tosyl groups differed depending on the ring size (7/8) and *N*-substituent (-CO-/-SO_2-). A typical example is illustrated for (+)-(a*R*)-**1B** and (+)-(a*R*)-**2B** in Fig. 2: the benzene ring of **1B** locates over the diazocine ring (folded form), whereas that of **2B** locates *anti* to the diazocine ring (extended form). The activation free-energy barrier to rotation of the axes ($\Delta G^{\ddagger}$) in the *N*-*p*-tosyl derivatives (**1B,2B**) (R = CH_3) was shown to be extremely high (~130 kJ/ml) .

Fig. 1

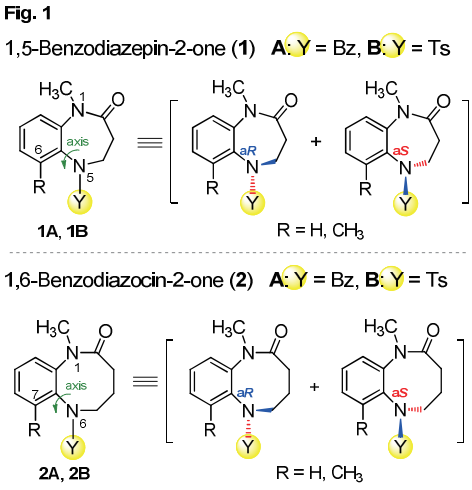
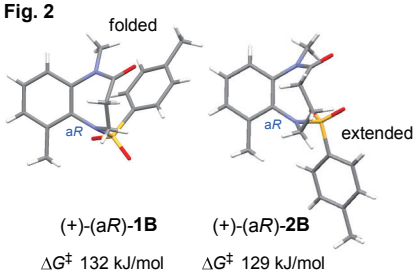


Fig. 2



Ref. [1] H. Tabata, et al., *Angew. Chem. Int. Ed.* **2011**, *50*, 3075–3079.
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[3] T. Yoneda, et al., *J. Med. Chem.* **2015**, *58*, 3268–3273.
[4] H. Tabata, et al., *J. Med. Chem.* **2017**, *60*, 4503–4509.
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[6] H. Tabata, et al., *Heterocycles*, **2019**, *99*, 566–581.

5P-014

ORAL PRESENTATION
27-ISHC Abstract

Synthesis of diverse heterocyclic library consisting macrocyclic moieties

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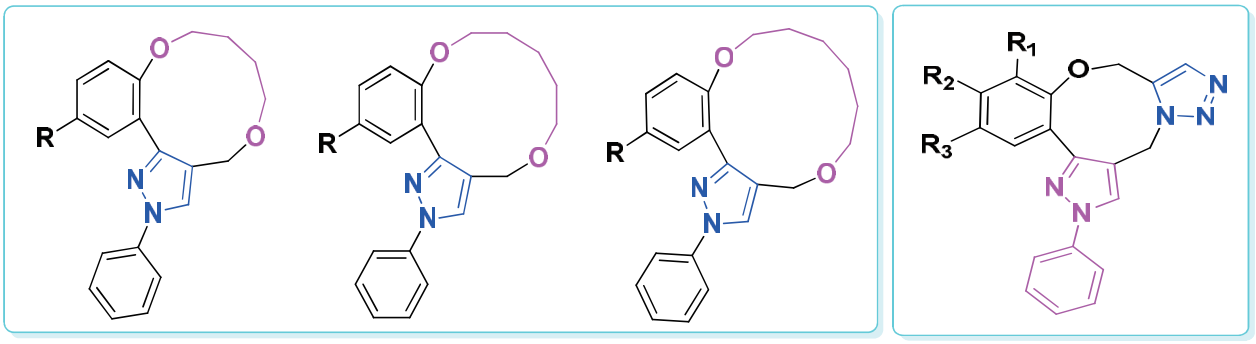
Heterocycles and macrocycles are the most often encountered scaffolds in pharmaceutically relevant substances and are essential for the human well being.[1-2] The remarkable ability of heterocyclic nuclei to serve as reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs. Certain possible modifications on the heterocyclic moiety may lead to new compounds with better biological profiles. Macrocyclic rings are commonly found structural units within the frame work of a variety of natural products, which is the main reason for the growing importance of such class of compounds. Moreover for an equal number of atoms, cyclic analogues inherently possess a lower number of rotatable bonds than their acyclic analogues. As a result cyclic counterparts are more conformationally restricted than their acyclic analogues, which potentially can impart higher target binding, selectivity and improved oral bioavailability. As a part of our research program towards the synthesis of bioactive molecules and above observations prompted us to take up the synthesis of diverse heterocyclic library consisting macrocyclic moieties.



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5P-015

Triazine-Based Dehydrative Condensing Reagents Bearing Carbon-Substituents

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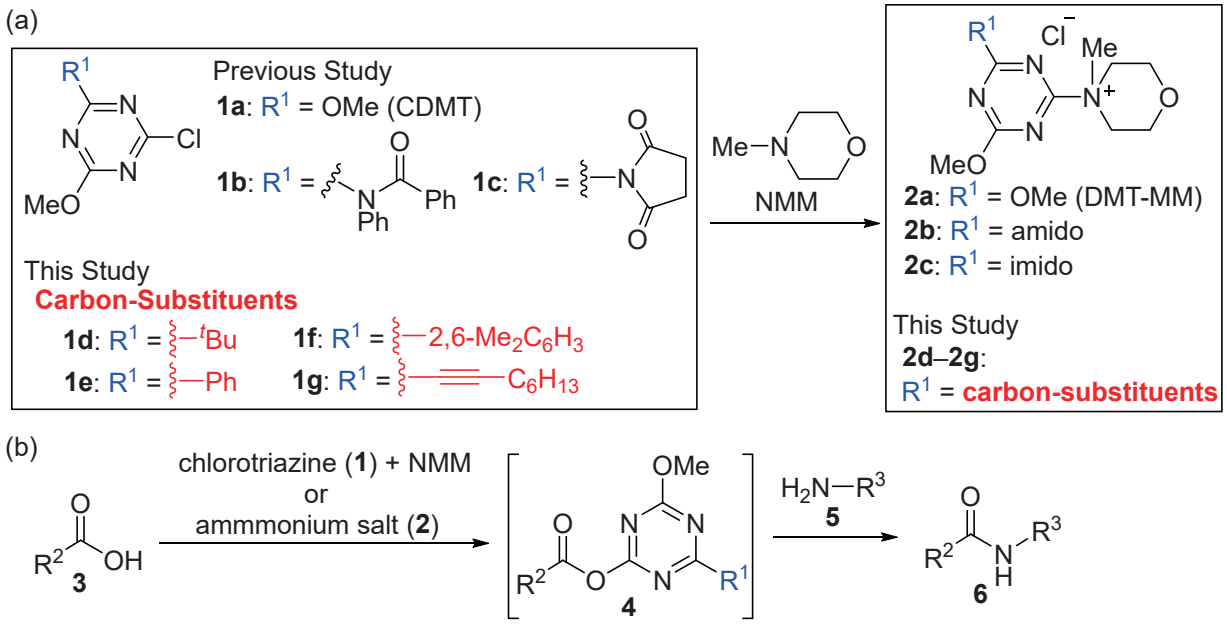
We have reported dehydrative condensing reagents that are chlorotriazines (**1b**–**1c**) and their ammonium salts (**2a**–**2c**).[1–3] Using these reagents, carboxylic acids (**3**) are converted to activated esters (**4**) which then react with amines (**5**) to give amides (**6**), even in the presence of hydroxy-groups[3] or in aqueous- or alcoholic solvents[1,2]. More electron-withdrawing amido- or imido-substituents (**1b**–**1c** or **2b**–**2c**) instead of methoxy groups of **1a** (CDMT) or **2a** (DMT-MM) were examined based on the ideas that electron deficiency of the triazine ring is driving force of condensing reactions. It is unambiguous that the significant reactivity is induced by competing-strong electron-withdrawing inductive effect and strong electron-donating resonance effect of oxygen and nitrogen atoms. Therefore, we were interested in carbon-substituents that have slight inductive and resonance effect because comparable electron withdrawing effect of the triazine would be expected. In this study, we investigated the effect of carbon substituents on the reactivity of the triazine-based dehydrocondensing reagents. Indeed, amide-forming reactions with **1d**–**1g** and **2d**–**2g** proceeded in good yields which are almost identical or superior in some cases to that with **1a** (CDMT) or **2a** (DMT-MM). We will discuss details of structures, dehydrocondensing reactions, and kinetic studies of these triazine-based reagents.



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5P-016

Gold-catalyzed One-Pot Synthesis of Oxazoles from 3-Trimethylsilyl Propargylic Alcohols and Amides

Nobuyoshi Morita*. Aoi Sano, Ayako Sone, Shino Aonuma, Arisa Matsunaga, Yoshimitsu Hashimoto, and Osamu Tamura*
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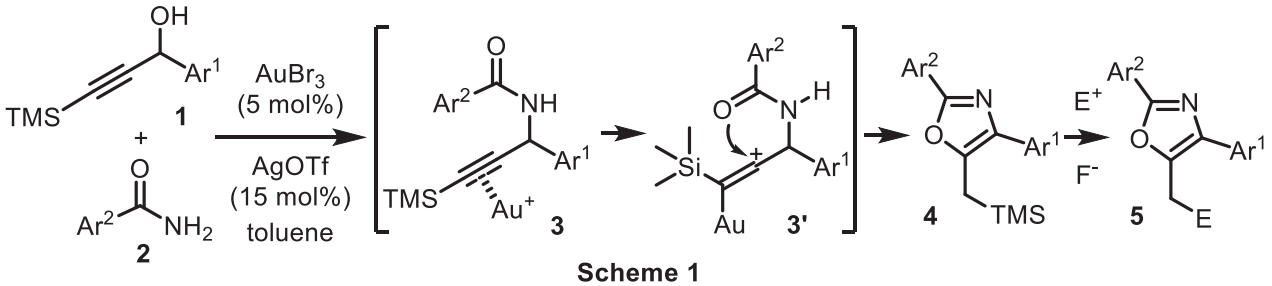
Oxazole is a structural motif in huge number of natural products and biologically active compounds,[1] as well as in various reagents/intermediates used in organic synthesis.[2] Among the numerous procedures reported for the synthesis of substituted oxazoles, cycloisomerization of propargylic amides to substituted oxazoles has attracted much attention. On the other hand, the one-pot synthesis of substituted oxazoles directly from propargylic alcohols and amides via propargylic amides as intermediates remains a challenging task, although both propargylic substitution and subsequent cycloisomerozation might proceed effectively under the same reaction conditions.[3] Herein, we present the one-pot synthesis of substituted oxazoles by gold-catalyzed propargylic substitution followed by cycloisomerization promoted by β-cation-stabilizing effect (**3'**) of the silicon atom of 3-trimethylsilyl propargylic alcohols (Scheme 1).[4] Treatment of 3-trimethylsilyl propargylic alcohols **1** with amides **2** as nucleophile in the presence of $AuBr_3$ (5 mol%) and AgOTf (15 mol%) in toluene at reflux afforded the desired oxazoles **4** in good yields. In addition, the trimethylsilylmethyl group in oxazole **4** synthesized in this procedure was smoothly transformed into carbon-functional group **5**.



Scheme 1

[1] (a) Yeh, V. S. C. *Tetrahedron* **2004**, 60, 11995. (b) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115.
[2] (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (b) Wasserman, H. H.; Mccarthy, K. E.; Prowse, K. S. *Chem. Rev.* **1986**, *86*, 845.
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5P-017

Development of visible light/iodine mediated inter/intramolecular CDC type reaction of heteroarenes

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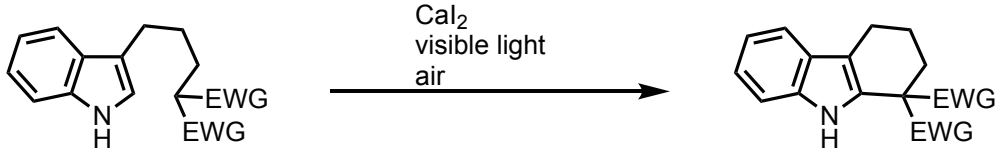
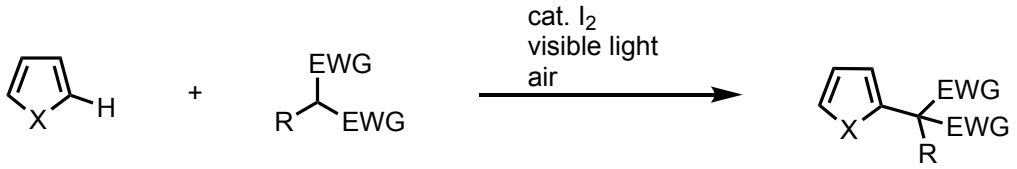
Polycyclic indole skeletons are a common structural motif in various naturally occurring products, pharmaceuticals, agricultural chemicals and organic functional materials. In this regard, numerous methods have been developed to synthesize these compounds, such as Friedel–Crafts alkylation, transition metal-catalyzed cyclization and radical cyclization reactions. However, the straightforward synthesis of these compounds presents challenges, especially in a catalytic system.
We have studied aerobic photo-oxidative reactions mediated by a halogen source. During the course of this study, we have developed a practical method for a photo-aerobic intramolecular dehydrogenative cyclization reaction using a catalytic amount of calcium iodide.[1]



During the investigation of intramolecular reaction, we have observed a rare-metal-free catalytic photoaerobic intermolecular dehydrogenative C−C bond-forming reaction from two C−H bonds of heteroarenes with malonate. This system proceeded at room temperature under visible light irradiation from CFL with aerobic oxygen as a terminal oxidant.[2]



In this presentation, we will show the detailed results of these intra/intermolecular CDC type reaction catalyzed by iodine under visible light irradiation.

[1] Yamaguchi, E.; Sudo, Y.; Tada, N.; Itoh, A. *Adv. Synth. Catal.* **2016**, *358*, 3191-3195.
[2] Sudo, Y.; Yamaguchi, E.; Itoh, A. *Org. Lett.* **2017**, *19*, 1610-1613.

Highly-Functionalized Pyrrole Synthesis via 3,6-Dihydro-1,2-oxazines using Heterogeneous Copper Catalyst

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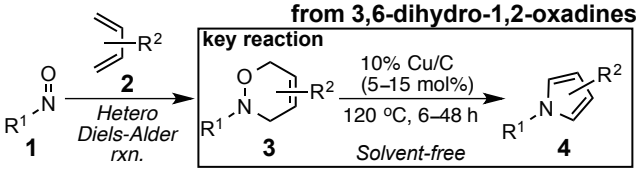
Gifu, Gifu 501-1196, Japan.

Pyrrole is a crucial chemical scaffold of various functional materials, such as biologically active compounds, pharmaceuticals, electrical conductors, *etc*. 3,6-Dihydro-1,2-oxazines (**3**), which are easily prepared by a hetero Diels–Alder reaction between nitroso dienophiles (**1**) and 1,3-dienes (**2**), can be transformed to the corresponding pyrroles (**4**) through the stepwise processes comprised of the reductive *N–O* bond cleavage requiring stoichiometric reductant or metal reagent to form *δ*-amino alcohol and the subsequent oxidative annulation. We have newly developed a direct transformation of 3,6-dihydro-1,2-oxaziens (**3**) to the corresponding pyrrole derivatives (**4**) using heterogeneous copper on carbon (Cu/C) under solvent-free conditions.[1]

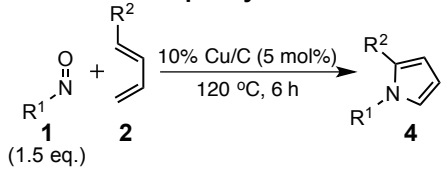
The pyrrole ring was effectively constructed from *N*-phenyl-6-phenyl-3,6-dihydro-1,2-oxazine (**3aa**) in the presence of 10% Cu/C under neat conditions at 120 °C for 6 h to give *N*-phenyl-2-phenyl pyrrole (**4aa**) in 84% yield (Table 1). The present reaction conditions were applicable to synthesize various 2-aryl, heteroaryl or benzyl-substituted *N*-phenyl pyrroles (**4ab**-**4ag**), and trisubstituted pyrrole (**4ah**). *N*-Aryl or *N*-benzyl 3,6-dihydro-1,2-oxazines (**3ba**-**3da**) could be also converted into the corresponding pyrroles (**4ba**-**4da**). Furthermore, nitroso dienophiles (**1**) and 1,3-dienes (**2**) could be directly transformed to the pyrrole derivatives (**4**) via a hetero Diels–Alder reaction to give 3,6-dihydro-1,2-oxazines (**3**) following by Cu/C-catalyzed pyrrole construction in a one-pot manner (Scheme 1). The present neutral and solvent-free method using an easily-removable and reusable heterogeneous Cu/C is valuable from the viewpoint of green sustainable chemistry and novel synthetic methodologies of pyrrole derivatives.

Table 1. Cu/C-catalyzed pyrrole synthesis from 3,6-dihydro-1,2-oxadines



substrate (**3**)	product (**4**)	substrate (**3**)	product (**4**)
R= Ph (**3aa**)	**4aa**: 84%	**3ah**	**4ah**: 49%
4-$MeOC_6H_4$ (**3ab**)	**4ab**: 72%		
4-BrC_6H_4 (**3ac**)	**4ac**: 79%		
3-$MeOC_6H_4$ (**3ad**)	**4ad**: 67%		
2-$MeOC_6H_4$ (**3ae**)	**4ae**: 61%		
2-thienyl (**3af**)	**4af**: 88%		
Bn (**3ag**)	**4ag**: 58%		
R^1= 4-MeC_6H_4 (**3ba**)	**4ba**: 71%		
4-BrC_6H_4 (**3ca**)	**4ca**: 66%		
Bn (**3da**)	**4da**: 46%		

Scheme 1. One-pot synthesis



4aa: R^1= Ph, R^2= Ph (60%)
4ab: R^1= Ph, R^2= 4-$MeOC_6H_4$ (46%)
4ba: R^1= 4-MeC_6H_4, R^2 = Ph (46%)
4ca: R^1= 4-BrC_6H_4, R^2 = Ph (42%)

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5P-019

Synthesis of aggregation inductive luminous organic fluorescence dyes, and evaluation of their fluorescence properties

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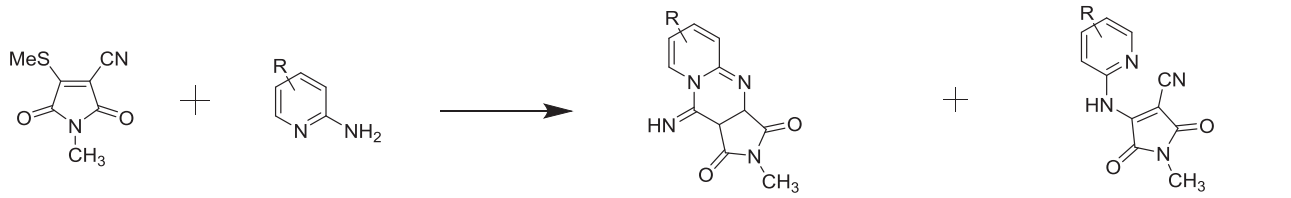
The organic fluorescent dyes which absorbs and emits light energy efficiently are widely used in the industrial field or the life-science field. However, in the high concentration solution or solid state, molecules each other causes stacking because of the aggregation, and fluorescence properties such as the luminous efficiency, chromogenic, light sensitivity and photosensitivity is significantly reduced. Previously, a method of preventing aggregation by improving the molecular structure of the dye has been attempted. Conversely, a new functional dye showing the aggregation induced emission (Aggregation-Induced Emission Enhancement: AIEE) phenomenon when the compound is aggregated and the emission is increased has been reported. However, detailed studies on characteristics such as luminous efficiency and chromogenic by molecular aggregation has not been fully examined. Therefore, we worked on the development of an organic fluorescent dye with AIEE characteristics for the purpose of constructing a new luminescent compound. As a general feature of the fluorescent dye, it is known empirically that the molecular structure involved in the emission is required to be a plane. In our preliminary study, we found that a secondary amine derivative in the figure below showed AIEE characteristics. Here, by synthesizing secondary amine derivatives having various substituents, fluorescence characteristics, wavelength and fluorescence intensity, in the solid state and solution states was analyzed. We also discuss the geometry and electronic structures of these derivatives using density functional theory (DFT) calculations.



Maleimides 2-aminopyridines Cyclized pyridazino[1,2-a]pyridazines Pyridine-amino-maleimides

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[3] Shigemitsu, Y. *et al*., *Heterocycles* 2001, 55(12), 2257-2260

5P-020s

Total Synthesis of Hinckdentine A

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Hinckdentine A was isolated from the bryozoan *Hincksinoflustra denticulate* by Blackman, Taylor and co-workers in 1987. It has a unique architecture consisting of seven-membered lactam ring fused to tribromoindolo[1,2-c]quinazoline. Since its extremely low bioavailability (0.0005%), its bioactivity has not been explored yet. Because of its interesting structure and the demand for exploring biological activities, there have been considerable effects on the development of an efficient synthetic route to this natural product, and three total syntheses, including two asymmetric total syntheses, of this natural product have been reported.

We recently developed an efficient method for the synthesis of 2-substituted indole-3-acetic acid derivatives from aldimines derived from 2-aminocinnamic acids and aldehydes via the cyanide-catalyzed imino-Stetter reaction. We envisioned that 2,2-disubstituted indol-2-one, a key intermediate in the synthesis of hinckdentine A, could be synthesized by oxidative rearrangement of 2-arylindole-3-acetic acid derivative. The indole compound could be prepared from an aldimine derived from 4,6-bromo-2-nitrocinnamic acid and 5-bromo-2-nitrobenzaldehyde via the cyanide-catalyzed imino-Stetter reaction. The corresponding indole compound already has three bromines and an amine functional group for the D-ring formation, which could allow us to complete the total synthesis of the natural product via a completely different strategy from the previous syntheses. In this poster presentation, we will disclose the total synthesis of Hinckdentine A using 2-arylindole derivatives as a key intermediate prepared via the cyanide-catalyzed imino-Stetter reaction from readily available starting materials.

5P-021s

Development of Novel Protocols for Synthesis of 2-Arylquinolines from 2-Aminochalcones *via* Nucleophile-catalyzed Dehydrative Cyclization

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2-Substituted quinolines are important scaffolds found in biologically active natural products and pharmaceuticals, as well as key building blocks in materials science. Due to their importance, considerable effort has been made for the development of novel protocols for the synthesis of 2-arylquinolines. Among the protocols developed, the intramolecular cyclization of (*E*)-2-aminochalcones is one of the conventional methods. However, (*E*)-2-aminochalcones cannot undergo the dehydrative cyclization due to its restricted configuration of the double bond, and thus, most of the previous methods have been developed based on the conversion (*E*)-alkene into (*Z*)-isomer *via* either photoisomerisation or the use of a stoichiometric amount of chemical reagents, such as I_2 and PhSeCl, in the presence of a base.

We hypothesized that 2-arylquinolines could be prepared from 2-aminochalcones using a nucleophilic catalyst. Conjugate addition of the nucleophile to 2-aminochalcones would provide their saturated ketones bearing the nucleophile at the β-position. Conformational change from *s*-trans to *s*-cis about the C_α-C_β single bond allows the proximity of the two functional groups, and following condensation reaction would afford dihydroquinoline intermediates. Subsequent elimination of the nucleophile could provide the desired 2-arylquinolines. Based on this hypothesis, we developed a series of protocols for 2-arylquinolines starting from 2-aminochalcones in the presence of a nucleophile catalyst. Furthermore, we expanded this synthetic method to prepare 2-arylquinolines *via* palladium-catalyzed Heck reaction between 2-iodoaniline and β-chloropropiophenone, more readily available starting materials. In this poster presentation, the recent progress of 2-arylquinoline synthesis from 2-aminochalcone *via* dehydrative cyclization will be disclosed.

5P-022

Unified Total Synthesis, Stereochemical Elucidation, and Antifouling Activity of Sarcophytonolides

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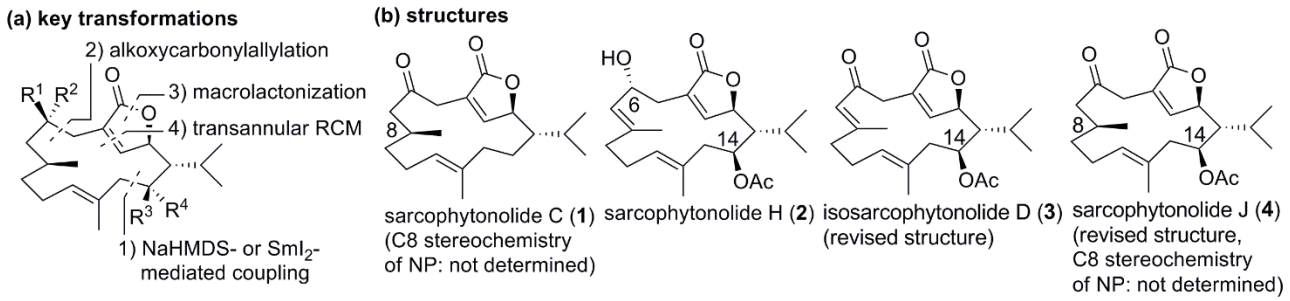
[1]Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530, Japan, [2]Himeji EcoTech Co., Ltd., 841-49 Koh, Shirahama-cho, Himeji 672-8023, Japan, [3]Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Zhangjiang Hi-Tech Park, Shanghai 201203, China

Sarcophytonolides are cembranolide diterpenes isolated from the soft corals of genus *Sarcophyton*. These natural products have a 14-membered carbon framework and butenolide moiety as common structures. Among sarcophytonolides, sarcophytonolides H and J are reported to inhibit the larval settlement of barnacle. In this presentation, we report unified total synthesis, stereochemical elucidation, and antifouling activity of sarcophytonolides.[1–3]

Because the stereochemistry at the C8 position of natural sarcophytonolide C was not clarified, we decided to synthesize two C8-stereoisomers toward the stereostructural determination of this natural product. Total synthesis of **1** and its C8-epimer was achieved by using NaHMDS-mediated coupling, alkoxycarbonylallylation, macrolactonization, and transannular ring-closing metathesis (RCM) as key steps. This total synthesis revealed the absolute configuration of natural sarcophytonolide C to be that described in **1**. Sarcophytonolides E, F, and G were also synthesized by the same synthetic strategy. The oxymethyne moiety at the C14 position of sarcophytonolide H (**4**) was successfully introduced by utilizing SmI_2-mediated coupling between allylic bromide and aldehyde in place of NaHMDS-mediated reaction. Asymmetric alkoxycarbonylallylation furnished the C6 chiral alcohol portion of **2**, which led to the total synthesis of **2**. Total synthesis of isosarcophytonolide D (**3**) and sarcophytonolide J (**4**) was also accomplished, which resulted in the stereochemical revision of these natural products. In addition, antifouling activity and toxicity of the synthetic sarcophytonolides H (**2**) and J (**4**) and their analogues against the larvae of the barnacle *Balanus* (*Amphibalanus*) *amphitrite* will be discussed.



[1] Takamura, H.; Iwamoto, K.; Nakao, E.; Kadota, I. *Org. Lett.* **2013**, *15*, 1108.
[2] Takamura, H.; Kikuchi, T.; Endo, N.; Fukuda, Y.; Kadota, I. *Org. Lett.* **2016**, *18*, 2110.
[3] Takamura, H.; Kikuchi, T.; Iwamoto, K.; Nakao, E.; Harada, N.; Otsu, T.; Endo, N.; Fukuda, Y.; Ohno, O.; Suenaga, K.; Guo, Y.-W.; Kadota, I. *J. Org. Chem.* **2018**, *83*, 11028.

Au(I)-Catalyzed Sequential Reaction of Ynamide for Synthesis of γ,δ-Unsaturated Amides and Polysubstituted Furans

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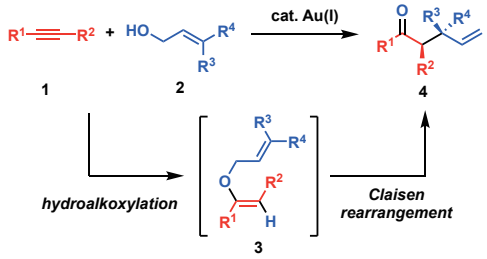
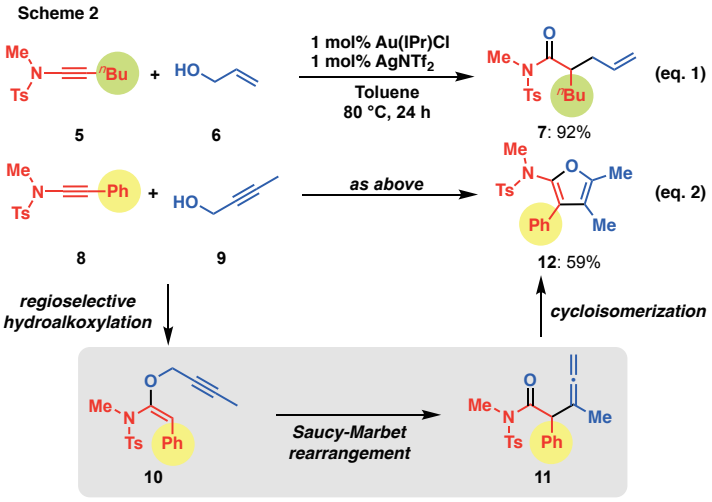
Au(I)-catalyzed reactions through activation of C-C multiple bond have been received much attention from synthetic organic chemists over the past few decades due to its unique transformation, broad scope, and high tolerance of functional groups. Recently, Au(I)-catalyzed sequential reaction of alkyne **1** with allylic alcohol **2** was reported by Aponick and Nolan, in which hydroalkoxylation followed by Claisen rearrangement proceeded to give γ,δ-unsaturated ketone **4** in good to high yields in one-pot (Scheme 1).[1] In this context, we examined Au(I)-catalyzed sequential reaction using ynamide instead of simple alkyne as a substrate (Scheme 2, eq. 1).[2] The reaction of ynamide **5** with allyl alcohol (**6**) was carried out at 80 °C in toluene in the presence of 1 mol% of Au(IPr)Cl and $AgNTf_2$. We were very pleased that γ,δ-unsaturated amide **7** was obtained in 92% yield as a sole product. On the other hand, when the reaction of propargylic alcohol **9** instead of allyl alcohol (**6**) with ynamide **8**, having an aromatic ring at the terminus of alkyne, was carried out under the same conditions (Scheme 2, eq. 2). Interestingly, it was found that polysubstituted furan **12** instead of γ,δ-unsaturated amide **11** was obtained in good yield. In this reaction, nucleophilic addition of **9** to **8** followed by Saucy-Marbet rearrangement of **10** proceeds, giving γ-alleneyl amide **11**. Subsequently, cycloisomerization of **11** takes place to give **12**.[3] Further studies to determine the scope, limitations, and the detail mechanism of this reaction are in progress.

Scheme 1



Scheme 2



[1] (a) Ketcham, J. M.; Biannic, B.; Aponick, A. *Chem. Commun.* **2013**, *49*, 4157. (b) Gómez-Suárez, A.; Gasperini, D.; Vummaleti, S. V. C.; Poater, A.; Cavallo, L.; Nolan, S. P. *ACS Catal.* **2014**, *4*, 2701.
[2] Oonishi, Y.; Misawa, S.; Miyairi, A.; Nolan, S. P.; Sato, Y. *manuscript in preparation.*
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5P-024s

Synthesis and Properties of Ethene-Bridged Terthiophene Multi-Oxides

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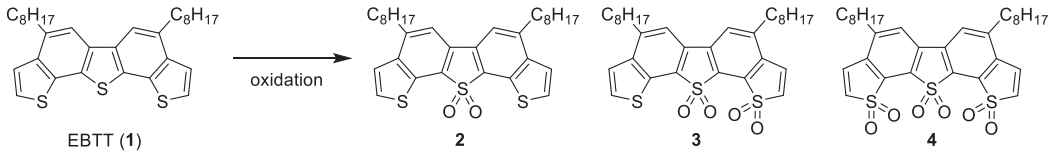
In order to realize excellent organic functional materials, it is quite significant to easily access both an appropriate electron-donating molecule having a high HOMO level and an electron-accepting molecule having a low LUMO level. As good donor molecules, a variety of thienoacene derivatives, acenes including a thiophene ring(s), have been reported. In contrast, since the thiophene dioxide skeleton obtained by oxidation of the thiophene ring has acceptor ability, a molecule incorporating this skeleton is expected to be an acceptor molecule.

Meanwhile, we recently reported an efficient synthesis of ethene-bridged terthiophene (EBTT) which is expected to act as a donor molecule.[1] In this study, we succeeded in the selective synthesis of three kinds of oxides (which are expected to be acceptors) by oxidizing in part or all of thiophene rings on EBTT (Scheme 1). Their fundamental physical properties were compared with calculated data (Figure 1). We also report the synthesis of π-extended EBTT oxides by further derivatization.



Scheme 1. Synthesis of EBTT oxides **2**–**4** from EBTT (**1**)

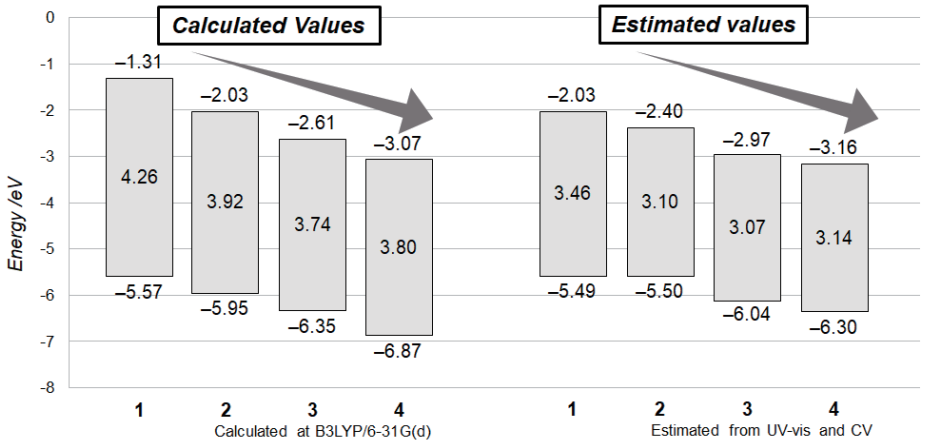


Figure 1. Calculated and Estimated HOMO–LUMO Levels of **1**–**4**

[1] Mitsudo, K.; Sato, H.; Yamasaki, A.; Kamimoto, N.; Goto, J.; Mandai, H.; Suga, S. *Org. Lett.* **2015**, *17*, 4858–4861.

5P-025s

Transition Metal-Catalyzed Electrophilic Amination of Organozinc Reagents

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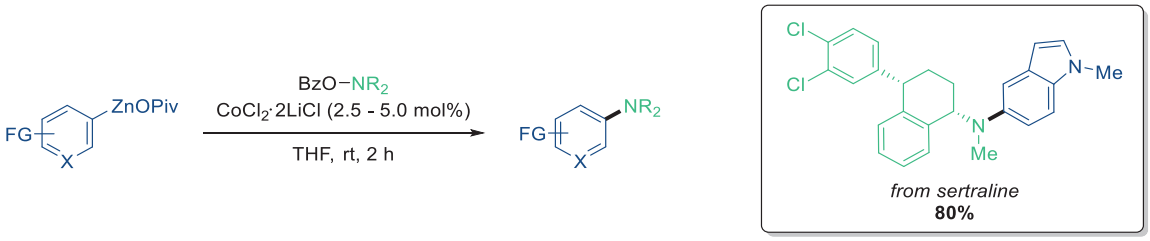
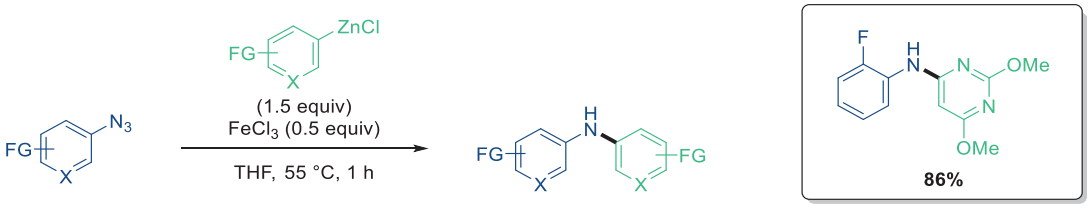
Over the past two decades, the development of palladium catalyzed Buchwald-Hartwig nucleophilic aminations allowed a facile synthesis of aryl amines. However, these reactions usually require expensive catalysts and ligands. Moreover, elevated temperatures and stoichiometric amounts of base are often necessary. We reported two electrophilic amination protocols, using polyfunctional organozinc reagents as nucleophile, which combined enable the excess to various secondary and tertiary (hetero)aryl amines.

First, we developed a ligand free cobalt-catalyzed electrophilic amination of organozinc pivalates with *O*-benzoylhydroxylamines under mild conditions.[1] Aryl- and heteroaryl-zinc pivalates are aminated with *O*-benzoylhydroxylamines at 25 °C within 2-4 h in the presence of 2.5-5.0% $CoCl_2$·2LiCl furnishing the corresponding tertiary arylated or heteroarylated amines in good yields. In combination with an optimized procedure to access the required hydroxylamine benzoates, the utility of this electrophilic amination was demonstrated in the late stage functionalization of complex molecules (drugs and peptidic substrates) in high yields.[2, 3]



The second protocol uses organic azides as electrophilic nitrogen sources. Without any additive, azides are tolerated by organozinc reagents. However, in the presence of $FeCl_3$ (0.5 equiv) the addition of the organozinc reagent to the azide, forming a secondary diaryl amine, was observed. Thus, a broad range of functionalized diaryl and heteroaryl amines were prepared in good yields. This method was extended to optically enriched substrates (e.g. amino acids), providing under retention of the stereo center the arylated amines in high yields and enantiomeric access.



Literature:

[1] Y.-H. Chen, S. Graßl, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 1108.
[2] I. A. O'Neil, D. J. Tapolczay, *Tetrahedron Lett.* **2001**, *42*,8247-8249.
[3] S. Graßl, Y.-H. Chen, C. Hamze, C. P. Tüllmann, P. Knochel, *Org. Lett.* **2019**, *21*, 494–497.

5P-026s

Simple magnesium catalyzed hydroboration of various carbonyl compounds

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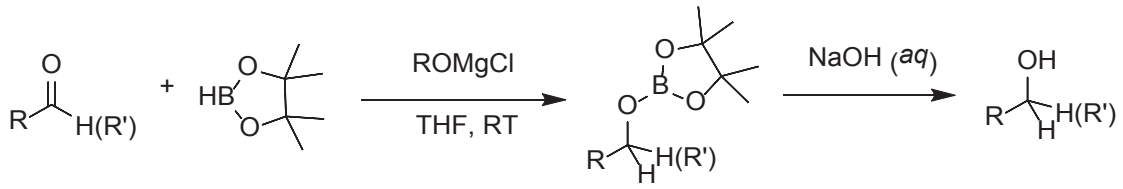
Chuncheon 24341, Republic of Korea

In organic synthesis, catalytic reaction has more advantageous than conversion stoichiometric reactions in terms of cost, environmental pollution and selectivity of the reaction. Hydroboration is one such transformation due to their mild nature and versatile utility as building blocks for various chemical reactions.

In addition, reduction of carbonyl groups like aldehyde and ester to alcohol is a fundamental and useful transformation in organic synthesis, with industrial applications. we try to make catalytic hydroboration more simple and economical by using chloroalkoxymagnesium as a catalyst and succeeded with commercial bench top catalyst with good yields. [1,2,3]



[1] Wu, Y.; Shan, C.; Ying, J.; Liu, L. L.; Zhao, Y. *Green Chem.* **2017**, *19*, 4169-4175.
[2] Query, I. P.; Isley, N. A.; Clark, T. B. *J. Org. Chem.* **2011**, *76*, 6452-6456.
[3] Yang, S. J.; Jaladi, A. K.; Kim, J. H.; An, D. K. *Bull. Korean Chem. Soc.* **2019***, 40*, 34-38.

5P-027s

A new one pot synthesis of ester to α,β-unsaturated esters from esters

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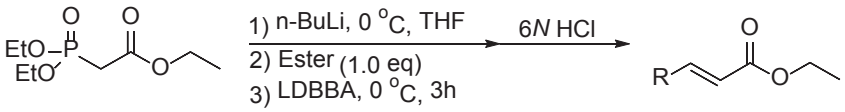
For the preparation of α,β-unsaturated esters, Horner–Wadsworth–Emmons (HWE) reaction is a widely used method in organic synthesis. Especially, this reaction is popular for stereoselective olefination of carbonyl compounds which are useful in the synthesis of complex natural products. however most of the conditions demonstrated for aldehyde and ketone functional group. [1] only few reports demonstrated with ester group [2,3], with harsh conditions.

Given our interest in finding selective and one pot reactions, and the above situations was prompted us to carry out reductive-HWE reaction with ester group. Recently, we have identified reductive-HWE olifination from ester group via partial reduction. Accordingly, up on reduction of an ester with lithium diisobutyl-*t*-butoxy aluminum (LDBBA) and in one pot reaction with phosphate ester, could easily access the desired HWE product under mild conditions.



[1] *Tetrahedron Letters*. **2018**, *59*, 568-582
[2] *Org. Lett.* **2015**, *17*, 5792-5795.
[3] *Tetrahedron Letters*. **1986**, *27*, 1257-1260

5P-028s

Catalyst and solvent-free hydroboration of alkynes

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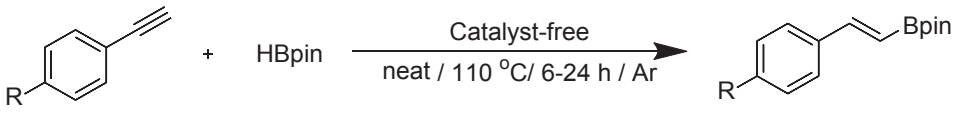
Chuncheon, Gangwon, 24341, Republic of Korea

Organoboranes are versatile building blocks for various chemical transformations in organic synthesis. Hydroboration is the straight-forward reaction to prepare these valuable synthetic synthons. Hydroboration of unsaturated hydrocarbons (C=C, C=O) bonds have been reported catalytically with numerous metal catalysts. Practically, however metals are expensive, sensitive and their by-products make significant environment pollution. To eliminate these issues arising from the use of complex metal catalysts, interest in finding environmentally benign methods for hydroboration increased recently. For example, catalyst free hydroboration of aldehydes [1] and carboxylic acids. [2]

With the aim of identifying robust and economically viable methods, in this present study, we have chosen synthesis of various alkenyl boronates via hydroboration of alkynes under catalyst and solvent free condition.



[1] *Green Chem*. **2018**, *20*, 1738-1742
[2] *Org. Biomol. Chem*., **2019**, *17*, 3604-3608

5P-029s

Partial reduction of isopropyl esters to aldehydes using MeLi catalyzed hydroboration

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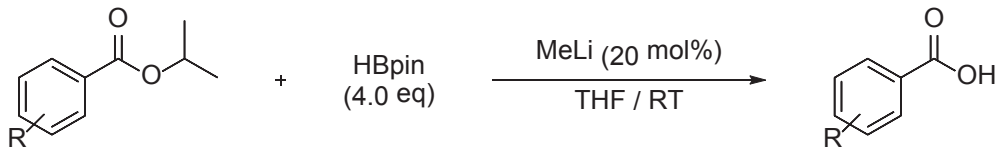
Reduction of ester to aldehyde is a fundamental and useful transformation in organic synthesis. A large number of reducing agents for this purpose have been reported. Among which DIBALH is the well-known reagent, however reaction proceeds under cryogenic conditions (-78 ℃).

In our continuation efforts to identify selective, partial reducing agents, recently we have developed several reagents for partial reduction of carbonyl compounds. In the present abstract we wish to explore our novel findings for the partial reduction of ester to aldehydes via catalyzed hydroboration under mild conditions for the first time. [1]



[1] Yang, S. J.; An, D. K.; *Bull. Korean Chem. Soc.* **2019**, *40*, 34-38.

5P-030

Formal Synthesis of (±)-Morphine via Tandem Oxidation/Cycloaddition Sequence

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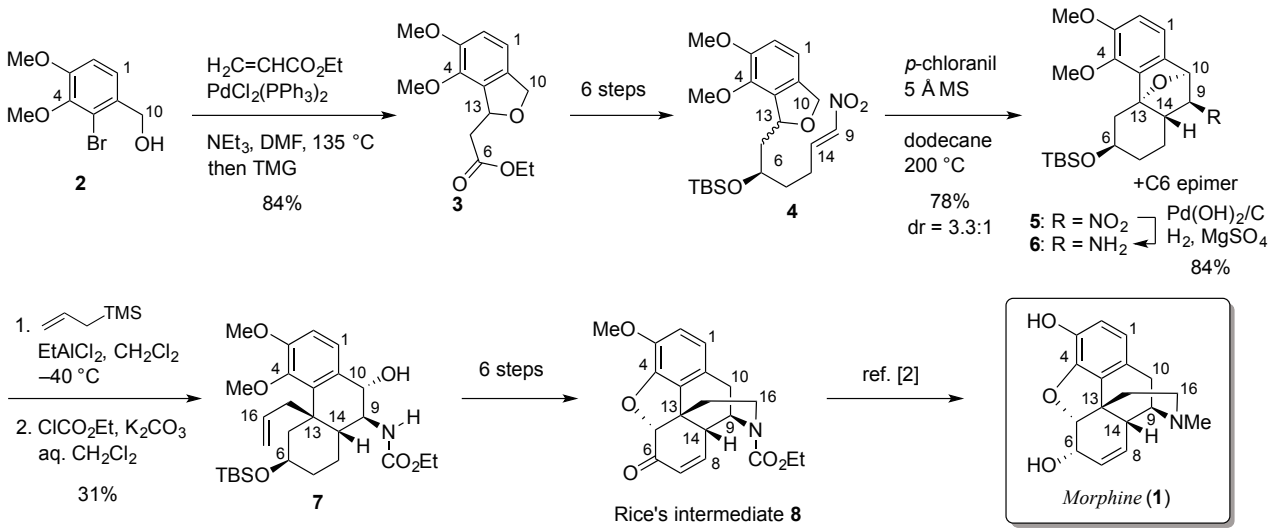
Morphine (**1**) is an attractive synthetic target due to its unique fused structure and potent analgesic activity. Since its first synthesis by Gates and Tschudi in 1952, six groups accomplished the total syntheses and formal syntheses were reported by 23 groups.[1] Herein, we describe the formal synthesis of (±)-**1**, wherein the hydrophenanthrene skeleton was constructed from readily available phthalan derivative by a novel tandem oxidation/intramolecular Diels–Alder sequence as a key step. Phthalan **4** having a nitroalkene moiety was synthesized through a six-step sequence from ester **3**, prepared from bromide **2** by a sequential Heck/intramolecular oxa-Michael reaction. Upon heating with *p*-chloranil in the presence of 5 Å MS in dodecane at 200 °C, oxidation of phthalan **4** and intramolecular Diels–Alder reaction of the resulting isobenzofuran proceeded to provide cyclo-adducts in 78% yield as a mixture of *endo*-adducts (dr = 3.3:1). The nitro group of major isomer **5** was reduced under hydrogen atmosphere with the aid of $Pd(OH)_2$/C. After considerable experimentation, it was found that regioselective C–C bond formation at C13 could be achieved by the nucleophilic substitution reaction with allyltrimethylsilane in the presence of $EtAlCl_2$, providing desired alcohol **7** after *N*-protection with $ClCO_2Et$. A six-step sequence involving construction of the pyrrolidine ring and the cyclic ether completed the synthesis of pentacyclic compound **8**, known synthetic intermediate in Rice's synthesis of morphine (**1**).[2]



[1] For a recent review, see: Reed, J. W.; Hudlicky, T. *Acc. Chem. Res.* **2015**, *48*, 674.
[2] Iijima, I.; Rice, K. C. *Heterocycles* **1977**, *6*, 1157.

5P-031s

Total syntheses of (±)- and (+)-Goniomitine

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Goniomitine, isolated from the root bark of Gonioma Malagasy, has interesting biological activity such as antiproliferative activity in several cancer cell lines. In addition, although it belongs to aspidosperma alkaloids, it possesses unique structural features such as aminal-containing tetracyclic core and β-hydroxyethyl side chain at the 3-position of the indole. These intriguing characters of the goniomitine sparked interest within the synthetic community and there have been seven asymmetric total syntheses of this natural product along with five total syntheses of (±)-goniomitine to date.
According to the proposed biosynthetic pathway, this natural product might be generated from vincadifformine through a series of fragmentation/rearrangement through a tryptophol intermediate bearing ethyl-3-piperidinium, which could be generated from the corresponding lactam, at the 2-position. Although biomimetic synthesis could significantly streamline the synthetic approach for the natural product, most of the previous total syntheses of goniomitine have been developed through a different synthetic strategy and the total synthesis of goniomitine, particularly the asymmetric total syntheses, have not been well developed based on this biogenetic synthetic route. As part of our interest in the total synthesis of indole alkaloids based on the cyanide-catalyzed imino-Stetter reaction, we envisioned that the proposed key intermediate, tryptophol bearing ethyl piperidinone ring at the 2-position, could be prepared via the cyanide-catalyzed imino-Stetter reaction of 2-aminocinnamic acid derivatives and aldehyde bearing a piperidinone ring. In this poster presentation, we will describe the highly concise total syntheses of (±)- and (+)-goniomitine using the cyanide-catalyzed imino-Stetter reaction as the key step.

5P-032

The Utilization of Enzyme-mediated Acylation and De-acylation in the Transformation of Heterocycles

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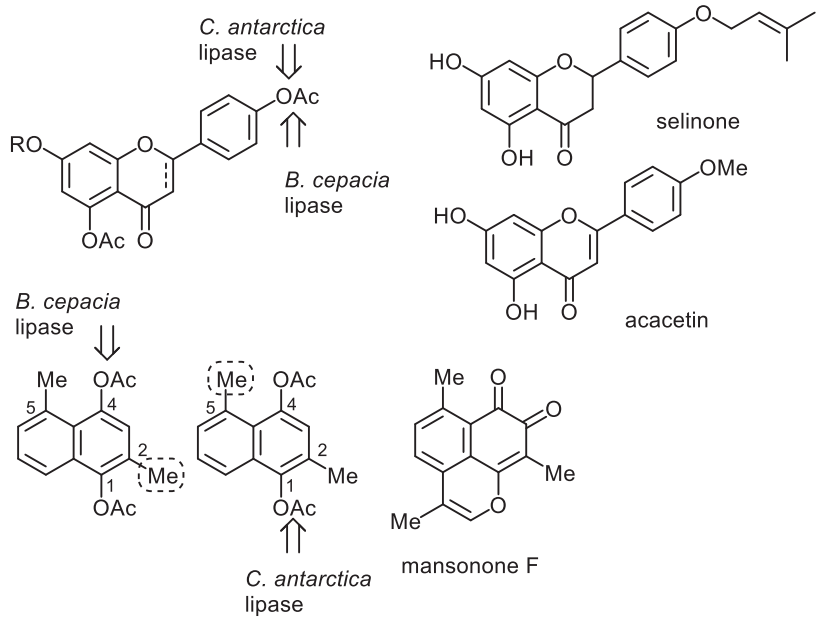
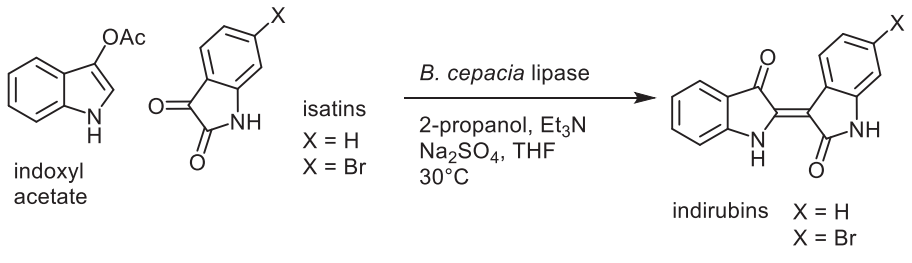
The rate of lipase-catalyzed reactions on polyphenolic substrates such as hydrolysis, transesterification, and acylation are effected by the neighboring steric hindrance. When flavonoid acetates and their glycosylated forms were submitted to lipase-catalyzed transestericiation conditions, deacetylation preferentially occur at C-4‘ position, the least hindered phenolic acetates [1-3]. The products were derived to physiologically active substances such as acacetin and selinone. We then examined lipase-catalyzed deacetylation of severely sterically hindered diacetate with both *ortho*- and *peri*- substituent. With *Burkholderia cepacia* lipase, the deacetylation proceeded on 4-position. On the contrary, with *C. antarctica* lipase B, the suppressing effect of a methyl substituent at the *peri*-position over that at the *ortho*-position was significant [4]. From the resulting monoacetate, mansonone F, a bioactive sesquiterpenoid heterocyclic quinone of *Mansonia altissima*, was synthesized.





Indoxyl acetate was a good substrate for the deacetylation with *B. cepacia* lipase (Amano PS-IM). The syntheses of indirubin and 6-bromoindirubin were achieved *via* the aldol condensation between isatins and an indoxyl anion in tetrahydrofuran under anhydrous and anaerobic conditions as the key step. The aldol donor was generated *in situ* by that lipase-catalyzed deacetylation of indoxyl actate in the presence of triethylamine.

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5P-033s

A Self-Assembled Polymeric Pyridine Copper Catalyst for the Huisgen Cycloaddition of Alkynes and Acetylene Gas: Application in Synthesis of Tazobactam

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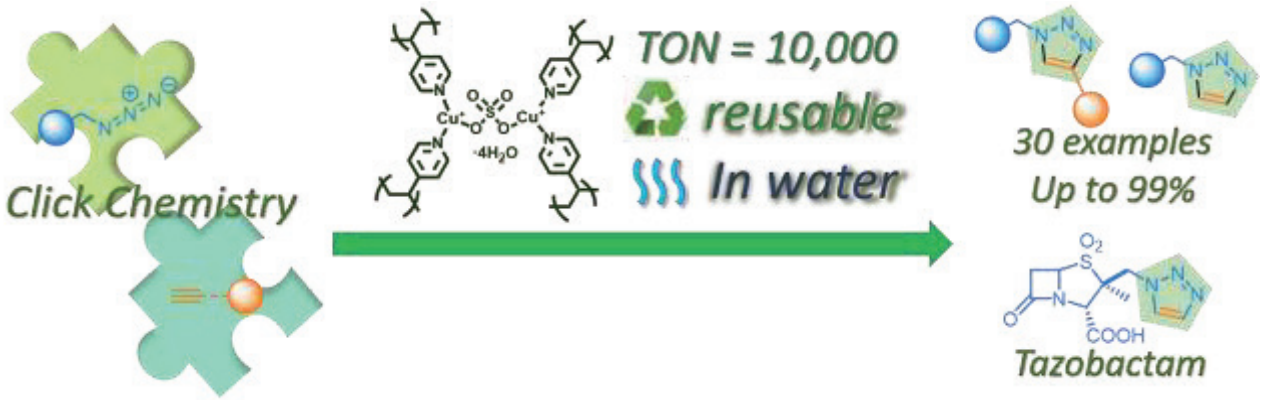
Copper-catalyzed azide-alkyne cycloaddition (CuAAC) is an efficient reaction to afford 1,4-substituted 1,2,3-triazoles in which various biologically active compounds were found. Recently, our research team has reported highly active copper(II) catalysts[1] and copper-containing polymeric-membrane-installed microflow catalytic reactors.[2] However, use of organic solvents and low catalytic performance were still unsolved problems.

In this symposium, we present a highly active and reusable polymeric copper catalyst that works in water at the mol ppm of Cu level.[3] Thus, the molecular convolution of $CuSO_4 \cdot 5H_2O$ and poly(4-vinylpyridine) (PVPy) in the presence of sodium ascorbate with/without sodium salts afforded various PVPy-Cu composites. Whose structures of Cu atoms and their surroudings were investigated with XANES, EXAFS and DFT calculation. SO_4^{2-} was found to be the most appropriate anion which can increase the activity of the polymeric Cu catalyst in CuAAC. The CuAAC of a variety of alkynes including acetylene gas proceeded smoothly with 100 to 800 mol ppm Cu of PVPy-Cu in water. The turnover numbers reached up to 100,000. This catalyst was readily reused without significant loss of catalytic activity. Furthermore, the reaction was also applied to the total synthesis of tazobactam, an inhibitor of bacterial *β*-lactamases.



[1] Yamada, Y. M. A.; Sarkar, S. M.; Uozumi, Y. *J. Am. Chem. Soc.* **2012,** *134,* 9285; Yamada, Y. M. A.; Yoshida, H.; Ohno, A.; Sato, T.; Mase, T.; Uozumi, Y. *Heterocycles* **2017,** *95,* 715.

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5P-034

Development of oxidative N-N coupling reaction of carbazole alkaloids by using NaOCl・$5H_2O$

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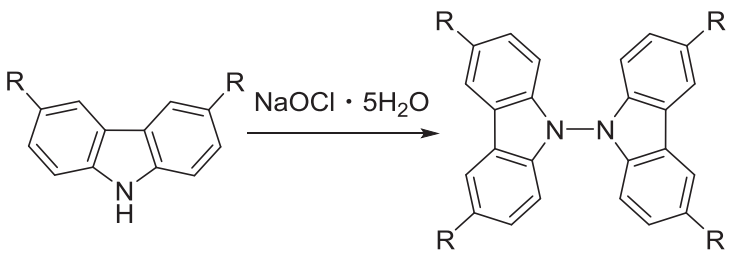
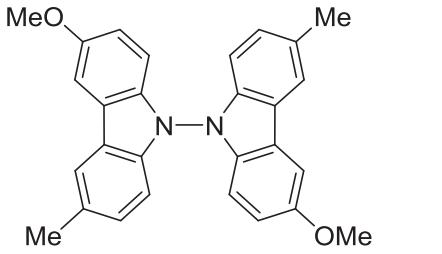
N-N linked homodimeric 9,9′-bicarbazoles, such as Dixiamycin B, are found in nature and have attracted much attention in materials chemistry. Although some methods such as stoichiometric $KMnO_4$, [1] Ag_2O, [2] dichromate, [3] or Cu-catalyzed aerobic oxidation, [4] or electrochemical oxidation [5] have been reported for the preparation of these compounds, the effective chemical synthesis to construct the various 9,9′-bicarbazoles except 3,6-disubstituted carbazoles is limited. In this symposium, we present the oxidative N-N coupling reaction of carbazole alkaloids by using NaOCl・$5H_2O$ to access 9,9′-bicarbazoles. The developed reaction proceeded under mild conditions (ambient atmosphere, room temperature and transition metal free) and afforded various 9,9′-bicarbazoles in moderate to excellent yield. Furthermore, we applied the reaction to the synthesis of structure-undefined 9,9′-biscarbazole due to the small amount which was isolated from Glycosmis pentaphyllia, and we succeeded structure elucidation of novel 9,9′-bicarbazole alkaloid.





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5P-035s

Synthesis of optically active pharmaceuticals by using recyclable catalytic asymmetric trnsfer hydrogenation in ionic liquid

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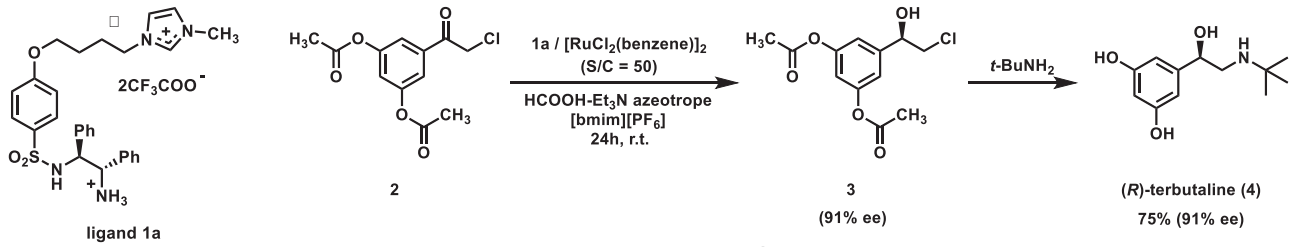
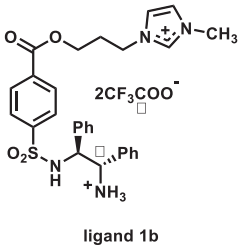
In previous work, we have developed that recyclable catalytic asymmetric transfer hydrogenation (RCATH) can be performed in an ionic liquid [bmim][PF_6] using HCOOH as a hydrogen sauce in the presence of the chiral catalyst constituted of the ionic chiral ligand **1a** and the Ru(II) catalyst.[1-2]

In this time, we present RCATH using ligand **1a** for the asymmetric synthesis of (*R*)-terbutaline (**4**) (Scheme 1).[3] Especially, in the transformation of **3** to **4**, use of acetyl group as a protecting group of OH groups was essential to obtain **4** by treating with *t*$BuNH_2$ in single step.



Scheme 1

Next, our aim was improving reactivities of the ligand **1a** by modification of its structure. After several investigations, we succeeded in developing a crystalline ligand **1b**, enabling to obtain the optically active secondary alchol derivatives with high yields, high enantioselectivities and excellent recycling efficiency in RCATH.[4]



Furthermore, synthesis of optically active pharmaceuticals such as (*R*)-terubutarine (**4**) by the present RCATH using **1b** is currently in progress.

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[4] Uchimoto H., Ikeda M., Tanida S., Ohhashi K., Chihara Y., Shigeta T., Arimitsu K., Yamashita M., Nishide K., Kawasaki I., *Chem*. *Pharm*. *Bull*., **2017**, *65*, 389-395.

5P-036s

Synthesis of 15*E-anti* Phytochrome Chromophore Derivatives

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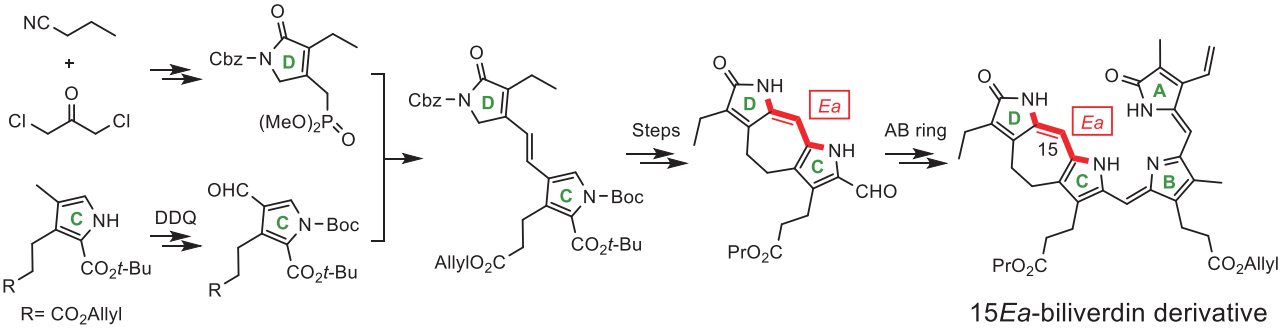
Kanazawa, Ishikawa 920-1192, Japan

Phytochrome is a photoreceptor present in microorganisms such as plants, bacteria, fungi, and simple molds. They consist of photosensory input and regulation output modules, function as bimodal photo switches and play an important role in controlling various light control processes of bacteria and plants. Upon absorption of light, linear tetrapyrrole cofactors contained in phytochromes are known to undergo isomerization via photoconversion between the red light-absorption state (Pr) and the far-red light-absorption state (Pfr).

In order to analyze the structure and function of chromophores in phytochrome, we focused on the stereochemistry around the C15 position and studied the synthesis of non-natural bilin chromophores. In our laboratory, we successfully synthesized the sterically locked 15*Z-syn*, 15*Z-anti*, 15*E-syn*, and 15*E-anti* 18Et-biliverdin derivatives. [1] Among them, 15*E-anti* biliverdin derivatives corresponding to far-red light absorption state (Pfr) is very important for the study on the properties of phytochrome. However, the synthesis of 15*E-anti* biliverdin derivatives required multi-steps linier synthetic schemes. Therefore, a simple strategy for synthesis of 15*E-anti* biliverdin derivatives in large scale in shorter steps was desired.

The new convergent approach via coupling of CD ring using Horner-Wadsworth-Emmons (HWE) reaction was designed. First, the D ring phosphite was prepared in 6 steps starting from butyronitrile and dichloroacetone. Next, C ring aldehyde was prepared by DDQ oxidation, [2] followed by Boc protection. Then, the coupling reaction was performed by the HWE reaction to bind C and D ring. Subsequently, hydrogenation reaction using palladium carbon, deesterification, formylation, and cyclization using DBU were successfully carried out to give *E-anti* CD ring. Finally, a coupling reaction was achieved with AB ring synthesized separately to afford 15*E-anti* biliverdin derivative.



Scheme 1. Synthesis of 15*E-anti* biliverdin derivative

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5P-037s

Synthesis of 3-Allylindole Derivatives Using Palladium Catalyst with P,Olefin Type Ligand

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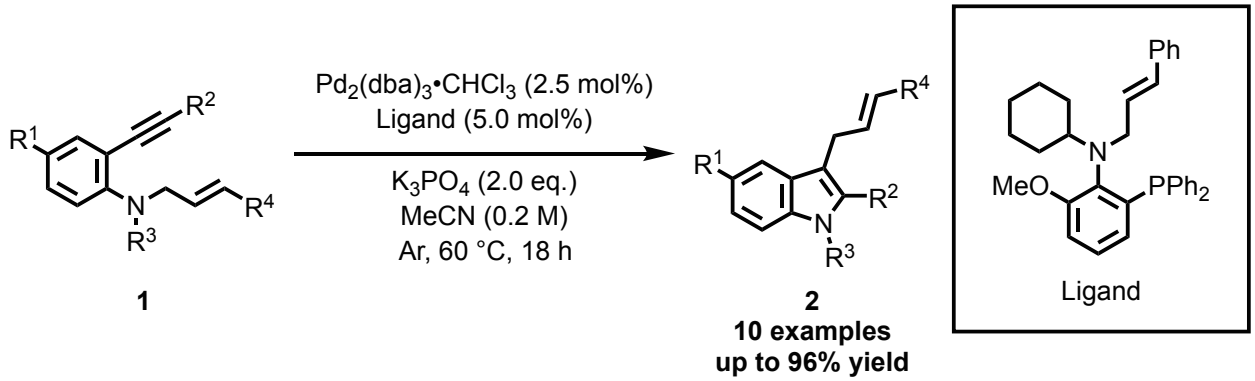
Yasushi Yoshida, Masami Sakamoto
Graduate School of Engineering, Chiba University, Chiba, 263-8522, Japan

Indole structure is included in many biologically active natural organic compounds and medicines. So, the development for constructing indole structure is expected. One of the effective methods based on the cyclization of 2-ethynylaniline derivatives has been so far reported by Cacchi's group.[1] In this case, the reaction is limited to reflux conditions in acetonitrile, and the products cannot hold substituents on nitrogen. On the other hand, Liu's group and Kato's group independently reported the cyclizations without elimination of substituents on nitrogen.[2,3] However, both reactions are also under reflux conditions. In this study, the reaction of compound **1a** (R^1 = H, R^2, R^4 = Ph, R^3 = Ts) as a 2-ethynylaniline derivative was carried out using 2.5 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$, 5.0 mol% of P,olefin type ligand, and 2 eq. of K_3PO_4 at 60 ºC. The corresponding product such as indole derivative **2a** retaining the substituent on nitrogen was obtained in 96% isolated yield under mild conditions. Moreover, we evaluated the substrate scope for this reaction, it was observed that a wide range of substrates could be adapted.



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5P-038s

Synthesis of Trifluoromethyl Nine-Membered Heterocycles via a Double Decarboxylative Ring-Expansion under Palladium Catalysis

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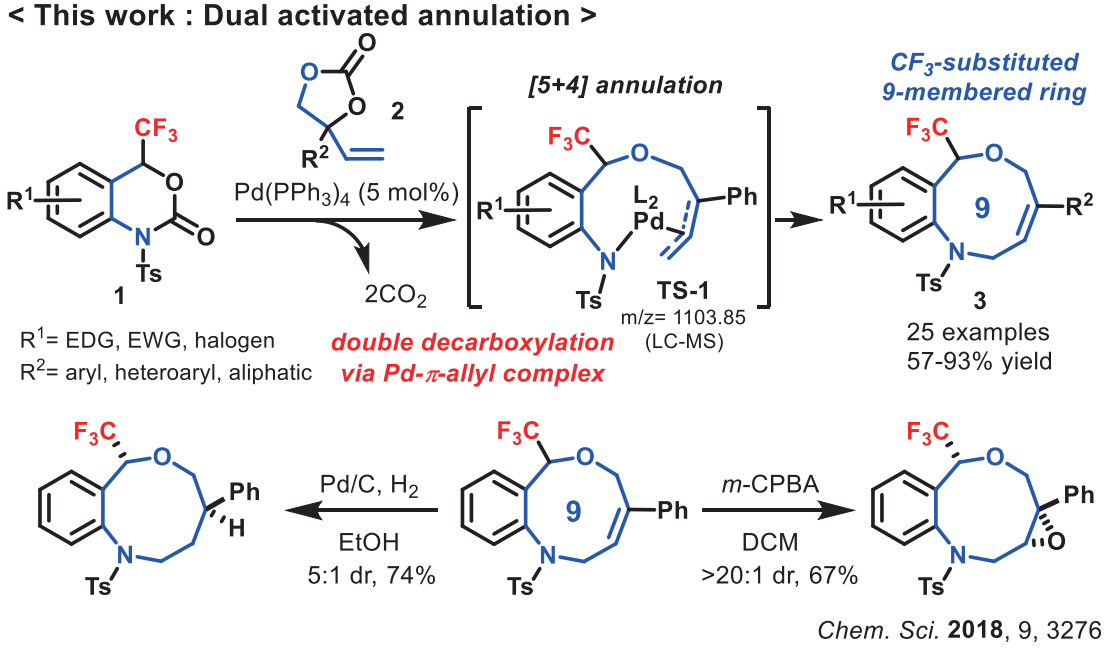
Heterocyclic molecules with a trifluoromethyl carbinol moiety, i.e., $CF_3C(OR^1)R^2R^3$ have gathered much attention as bioactive compounds, for example, Efavirenz (anti-HIV). In this work, we developed the synthetic methodologies for fluorine-containing heterocycles via a palladium-catalyzed double-decarboxylation process. Recently, we reported the reaction of trifluoromethylated benzoxazinanones **1** with sulfur ylides to afford trifluoromethyl-substituted indolines.[1] As an extension of this work, we examined the ring-expansion reaction of **1** with vinyl ethylene carbonate **2** through a formal double-decarboxylative [5+4] annulation under Pd-catalysis. As our expectation, pharmaceutically attractive benzo-fused nine-membered heterocyclic alkenes **3** having a trifluoromethyl carbinol moiety were successfully obtained in good to excellent yield.[2] While the reaction mechanism is not precise, we proposed the generation of a Pd-π-allyl zwitterionic intermediate, and the CF_3 substituent at the C-4 position of **1** plays an essential role for this transformation. Diastereoselective derivatizations of the benzo-fused nine-membered heterocyclic alkene **3**, such as epoxidation and H_2 reduction, were demonstrated to show the synthetic utility of the products. The enantioselective variant of reaction is under investigation.



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5P-039s

Ring-Opening Cyclization of Spirocyclopropanes with Sulfonium Ylides for the Construction of a Chromane Skeleton

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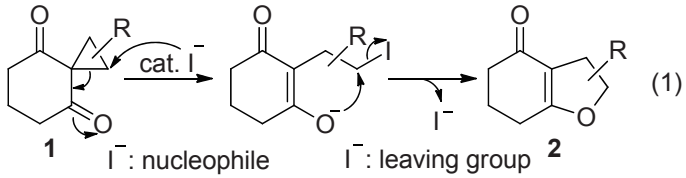
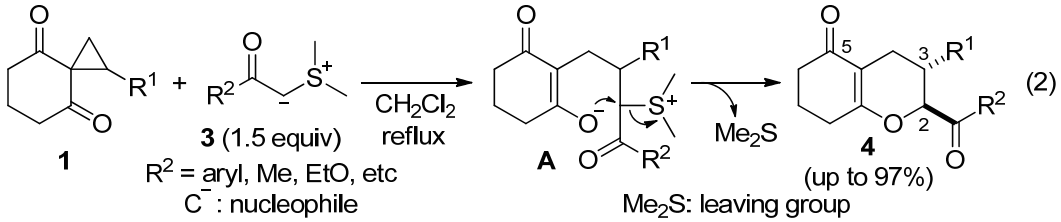
Recently, we reported that iodide-catalyzed ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes **1**[1] proceeded in a regioselective manner to afford 3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-ones **2** with excellent yields (eq. 1).[2] In this catalytic system, an iodide ion acts as a nucleophile for the ring opening of cyclopropane and subsequently as a leaving group for the cyclization to provide dihydrofuran. Herein, we report the ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes **1** using sulfonium ylides for the construction of a chromane skeleton.[3]



(1)

Reaction of spirocyclopropanes **1** with carbonyl-substituted sulfonium ylides **3**, which have nucleophilic site and good leaving group, afforded 2,3-*trans*-hexahydrobenzopyran-5-ones **4** in up to 97% yields with no evidence of the formation of any diastereoisomers or regioisomers (eq. 2). In this reaction, the carbanion in **3** attacks as a nucleophile for the ring opening of cyclopropane to form the betain intermediate **A** and subsequent S_N2-type cyclization of **A** occurs to afford the *trans*-product **4** with the concomitant release of dimethyl sulfide. To the best of our knowledge, this is the first example of a ring-opening cyclization of cyclopropanes with sulfonium ylides. This reaction can be regarded as a formal [5+1] cycloaddition and it would serve a stereoselective construction method for a chromane skeleton. We would like to discuss the stereoselectivity.



(2)

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[3] Nambu H., Onuki Y., Ono N., Yakura T., *Chem. Commun.,* in press (DOI: 10.1039/c9cc03023a).

Total Synthesis of Histrionicotoxin 235A

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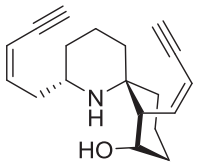
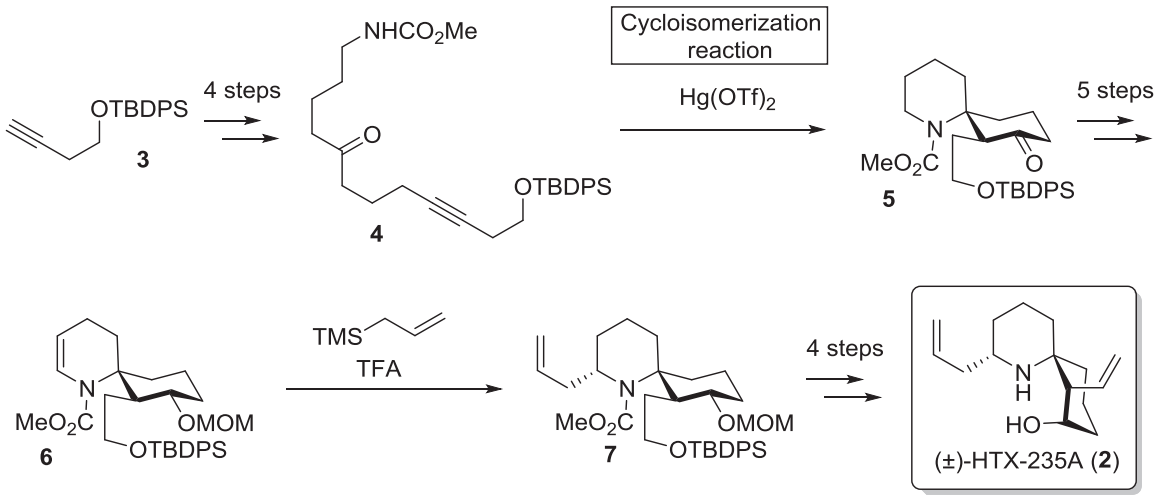
(−)-Histrionicotoxin (HTX-283A, **1**, Fig. 1), one of the azaspirocyclic alkaloids isolated from Colombian 'poison arrow' frog *Dendrobates histrionicus*, exhibits intent selective inhibition of the nicotinic acetylcholine receptors.[1] The chemical structure of **1** is characterized by a 1-azaspiro[5.5]undecane skeleton and two enyne side chains. The other members of this alkaloid family including (−)-HTX-235A (**2**) have also been identified;[2] however, biological activities of histrionicotoxin analogs remain unexplored due to paucity of the alkaloids in nature. In this presentation, we report the total synthesis of (±)-**2** using a $Hg(OTf)_2$-catalyzed cycloisomerization reaction[3] as a key reaction that directly constructs azaspirocyclic skeletons from linear substrates.



(–)-Histrionicotoxin
(HTX-283A, **1**)
Fig. 1

Our studies commenced with preparation of linear substrate **4** from alkyne **3** via 4 steps (Scheme 1). The cycloisomerization reaction of **4** stereoselectively afforded the desired spirocyclic compound **5**. Carbamate **6** was converted from **5** via 5 steps. Allylation of **6** with allyltrimethylsilane gave allylpiperidine **7**. Finally, (±)-**2** was synthesized through formation of a vinylic group and removal of protecting groups.



Scheme 1

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[2] Shimada, A. et al. *Tetrahedron* **1992**, *48*, 1823.
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5P-041s

Chemo–enzymatic total synthesis of tetrahydroisoquinoline alkaloids exhibiting potent DNA alkylating ability

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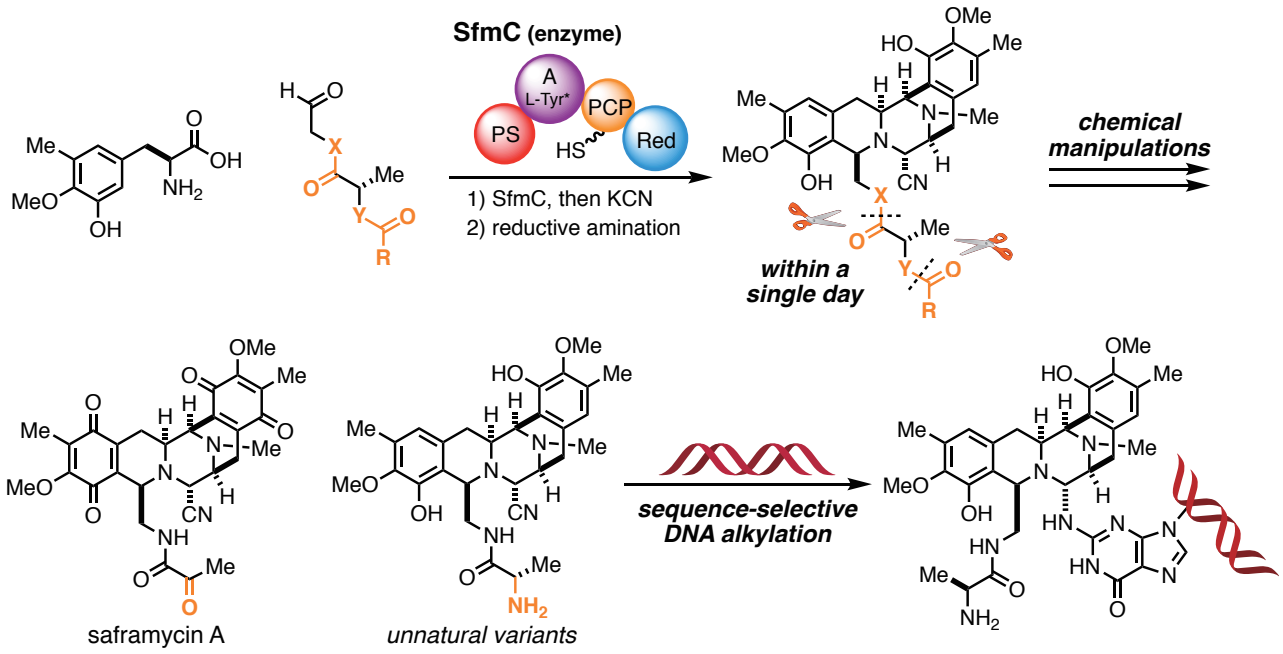
The anti-tumor tetrahydroisoquinoline (THIQ) alkaloids share a common pentacyclic scaffold. We previously revealed a unique biosynthetic mechanism to forge this scaffold catalyzed by SfmC, a module of non-ribosomal peptide synthetases.

Herein we report the chemo-enzymatic synthesis of saframycin A, saframycin Y3, jorunnamycin A and their variants. By streamlining the linkage between SfmC-catalyzed multi-step enzymatic conversions and chemical manipulations, we succeeded in efficient assembly of the appropriately functionalized pentacyclic skeleton within a single day from two simple synthetic substrates.

Further functional group manipulations involving removal of the side chain and oxidation allowed operationally simple and expeditious synthesis of THIQ alkaloids. Furthermore, we demonstrated that synthetic variants exhibit the potent DNA alkylating abilities superior to naturally occurring cyanosafracin B.



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5P-042s

Synthetic Studies on Haliclonin A

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The group directed by Oh and Shin isolated haliclonin A (**1**, Figure 1) from *Haliclona* sp. (a marine sponge of Korea) and determined the structure of this compound by using a combination of spectroscopic and chemical analyses.[1]

Like sarain A and other bis-alkylpyridinium-derived compounds from sponges, haliclonin A possesses two macrocyclic rings. Nevertheless, its 3-azabicyclononane framework, also with the unprecedented enone part and two amide functionalities made this tetracyclic marine alkaloid extremely unique in terms of structure.

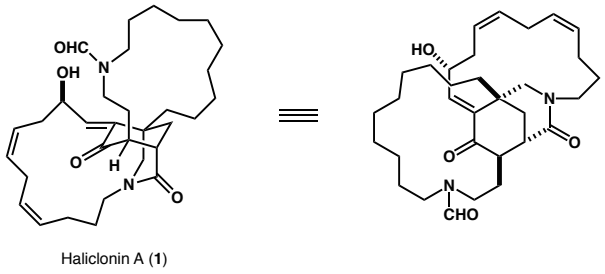


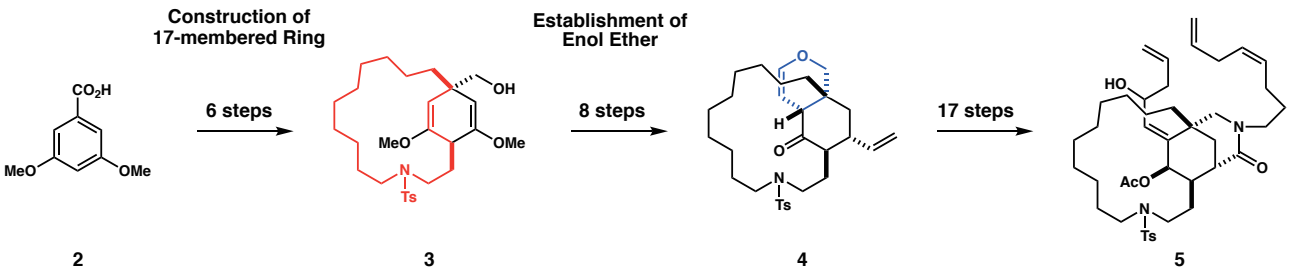
Figure 1. Haliclonin A

As to the biological activities, haliclonin A exhibited moderate cytotoxicity and antibacterial activity against diverse microbial strains. It also displayed moderate cytotoxicity against the K562 leukemia cell line, with an IC_{50} of 15.9 μg/mL.[1]

Not only the unparalleled structure but also the potent bioactivity made this tetracyclic marine alkaloid attract much attention, especially its fascination on the synthetic aspect.

As the synthetic studies in our laboratory (Scheme 1), starting with commercial available 3,5-dimethoxybenzoic acid **2**, construction of the 17-membered ring was achieved by only 6 steps (compound **3**). Whereafter, further 8 steps established the enol ether part (compound **4**) successfully.[2] After 17 steps of transformations, alcohol **5** was obtained as a single diastereomer, which means ring closing metathesis will be the last task before we accomplish the total synthesis of haliclonin A (**1**).

Scheme 1. Synthetic studies in our laboratory



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5P-043s

Non-planar Porphyrinoids as Asymmetric Bifunctional Hydrogen-Bond Donor Catalysts

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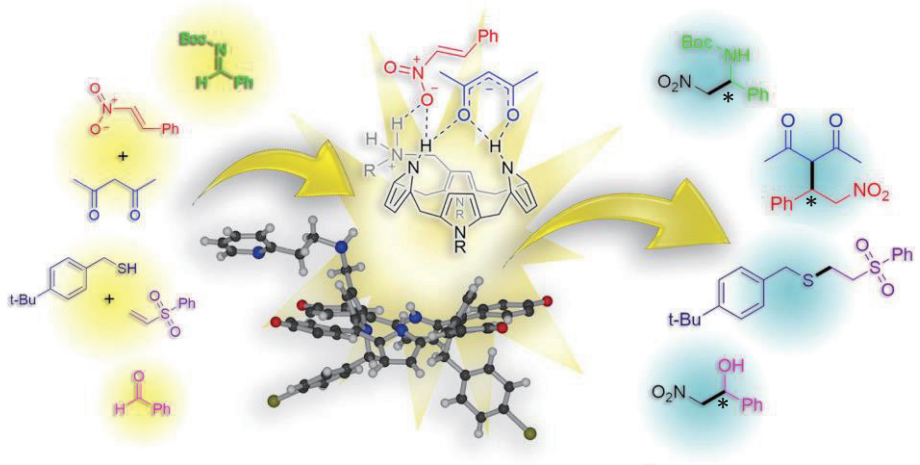
WPI-MANA, National Institute for Materials Science, Tsukuba, 305-0044, Japan



Porphyrins and related compounds have been extensively studied in catalysis as their metal complexes, indeed these type of complexes are key catalytic centres in 'nature's toolbox' carrying out a wide variety of transformations. On the other hand, their use as organocatalysts has been neglected because typically the porphyrin NH groups are internalized and therefore shielded by the macrocycle, inhibiting their use as catalysts [1]. In order to render porphyrins catalytically active non-planarity of the macrocycle must be induced in order to gain access to these NH moieties.

This presentation will outline the development and structure optimization of a new class of chiral macrocyclic hydrogen-bonding organocatalysts based on β-substituted oxoporphyrinogens and demonstrate their synthetic utility in a number of asymmetric transformations. Due to the inherent non-planarity and binding site rigidity of oxoporphyrinogens, alongside their ability to bind analytes including nitro and carbonyl species via hydrogen bonding interactions [2], these species have proven to be efficient organocatalysts. Spectroscopic investigation of the intermolecular interactions between the macrocycle and catalysis substrates have given us insight into the reaction mechanism and allowed for further optimization of catalytic activity.

Our results demonstrate the structural features required to render non-planar porphyrinoids catalytically active as hydrogen-bond donor catalysis and our studies have advanced this previously uninvestigated research area, demonstrating the first example of porphyrinoids as asymmetric organocatalysts [3].

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Synthetic Study of TPI 287

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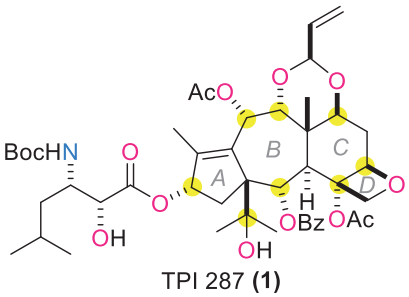
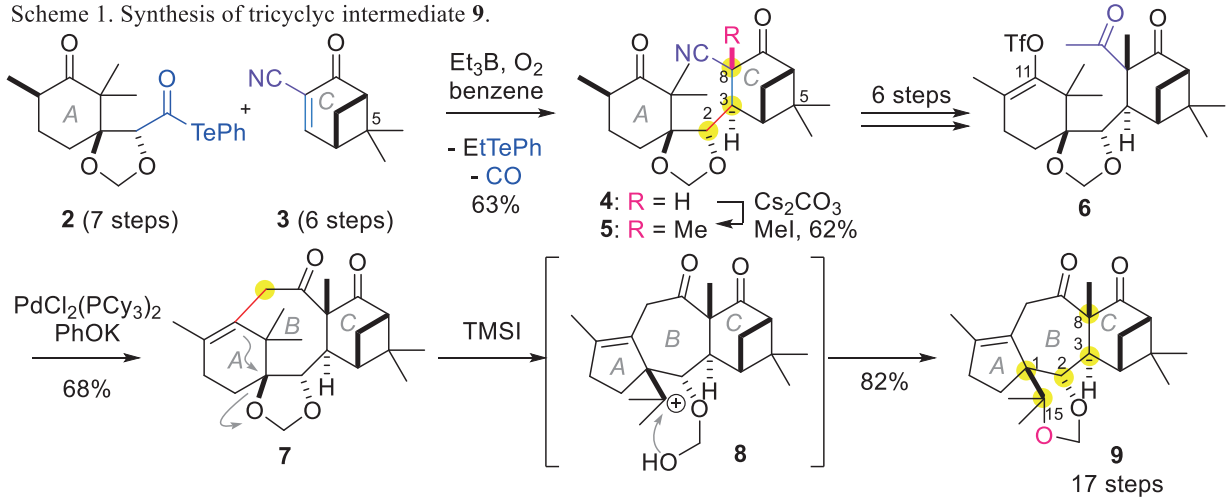
TPI 287 (**1**) belongs to an abeotaxane family and is clinically developed as an anti-cancer agent.[1] The 5/7/6-membered carbon skeleton (ABC-ring) of **1** with a bridgehead olefin and two quaternary carbons are substituted by eight oxygen functional groups, two of which form an oxetane ring (D-ring). Due to the intricately fused tricarbocyclic structure with the multi-oxygen functionalities, total synthesis of abeotaxanes including **1** has not been achieved. We embarked upon the study toward a convergent synthesis of **1** using decarbonylative radical coupling reaction. [2]



A-ring **2** [3] and C-ring **3** was prepared in 7 and 6 steps, respectively. Next, decarbonylative radical coupling reaction between α-alkoxyacyl telluride **2** and C-ring cyanocyclohexenone **3** was realized under mild conditions and adduct **4** was generated in the C2- and C3-stereoselective manners (Scheme 1). Methylation of **4** proceeded to avoid the C5 dimethyl group, and C8-quaternary carbon of **5** was stereoselectively constructed. The cyano group of **5** was converted to an acetyl group in six steps to afford **6**. The Pd(0)-mediated eight-membered cyclization of **6** delivered tricyclic intermediate **7**. When **7** was subjected to TMSI, Wagner–Meerwine rearrangement proceeded to afford **9**.

In summary, tricyclic intermediate **9** was obtained in 17 steps, which has the four contiguous stereocenters of **1** (C1, 2, 3, 8) on the 5/7-membered carbon skeleton and oxygen functional group at C15 position.

Scheme 1. Synthesis of tricyclyc intermediate **9**.



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Total Syntheses of Bufadienolides

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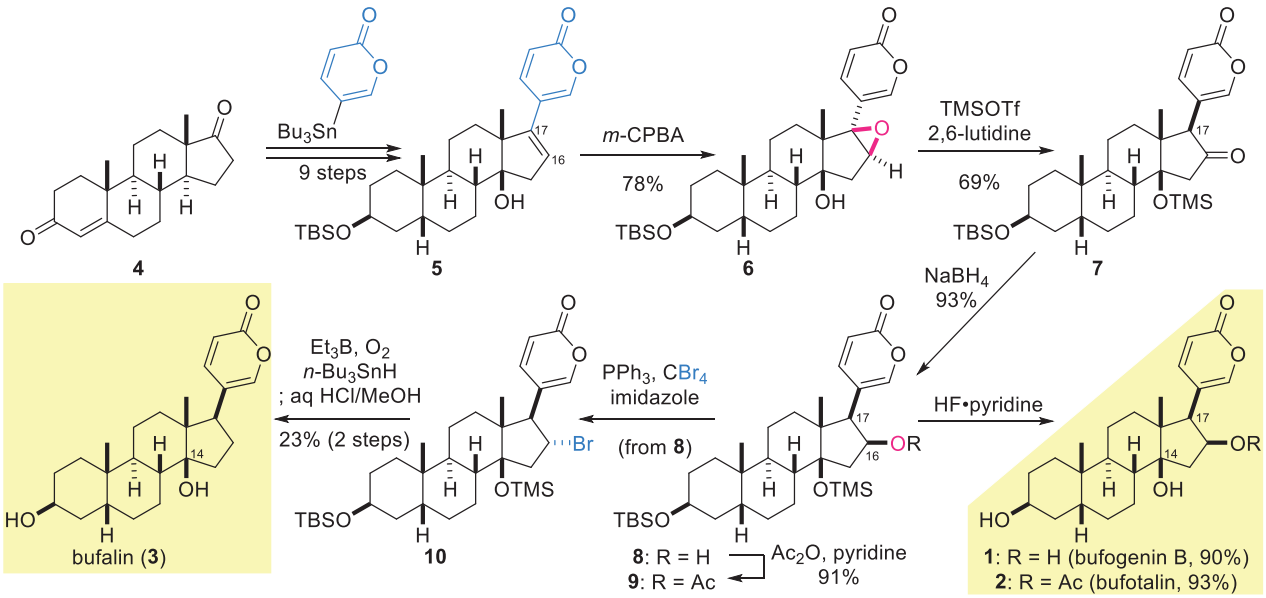
Bufadienolides (**1**, **2**, and **3**), steroidal natural compounds, were isolated from plants of the iris family and toads.[1] These structures possess a β-oriented hydroxy group at the C14 position and a β-oriented 2-pyrone at the C17 position. Several synthetic efforts have been reported, but no synthesis of highly functionalized bufadienolide has been achieved because of difficulty in introducing the β-oriented 2-pyrone under mild conditions. Herein, we describe the total syntheses of bufogenin B (**1**), bufotalin (**2**), and bufalin (**3**) by employing a new 2-pyrone installation strategy.

First, **5** was synthesized from the commercially available compound **4** over nine steps, including installation of 2-pyrone moiety at the C17 position by using Stille coupling.[2] Oxidation of the C17-olefin of **5** proceeded chemo- and stereoselectively to give epoxide **6**. Lewis acid-promoted isomerization of **6** introduced the desired stereochemistry at the C17 position to afford ketone **7**. Next, stereoselective reduction of the carbonyl group of **7** proceeded to give alcohol **8**, and the TBS/TMS-removal provided **1**. Alternatively, acetylation of alcohol **8** led to **9**, and subsequent removal of the protecting groups afforded **2**. In addition, **8** was subjected to Appel reaction conditions to obtain bromide **10**. Finally, radical reduction of bromide **10**, followed by removal of the silyl protecting groups, provided **3**.

In conclusion, the chemo- and stereoselective 2-pyrone installation enabled the total syntheses of the three bufadienolides, bufogenin B (**1**), bufotalin (**2**), and bufalin (**3**). Because this strategy employs the mild conditions, it would be applicable to the synthesis of more oxygenated bufadienolides.



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5P-046s

Desymmetrization of *gem*-Diols via Enantio- and Diastereoselective Cycloetherification Using Bifunctional Organocatalysts

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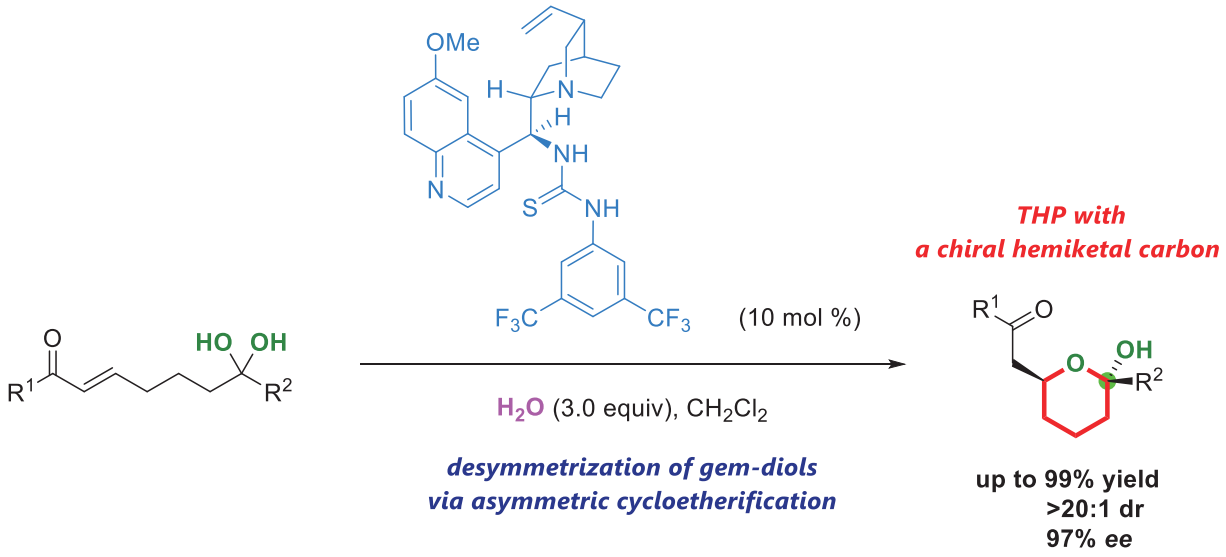
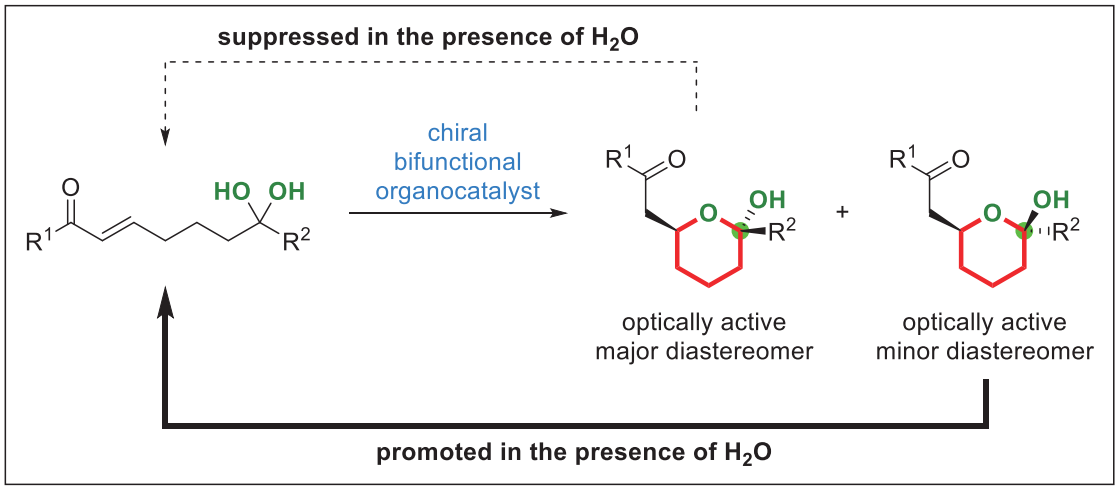
Desymmetrization of prochiral substrates is an efficient method for constructing tetrasubstituted chiral carbons; a number of methods for desymmetrization of diols were developed. However, desymmetrization of *gem*-diols forming chiral hemiketal carbons is unknown. In this study, the first desymmetrization of *gem*-diols was achieved via organocatalytic asymmetric intramolecular oxy-Michael addition. This transformation afforded an optically active tetrahydropyran skeleton bearing a chiral hemiketal carbon, which is a core structure in a range of bioactive compounds. The use of water enabled favorable isomerization between the diastereomers of the products, which was essential for the highly stereoselective desymmetrization.





5P-047s

Heterocyclic Photocages for Carbohydrates

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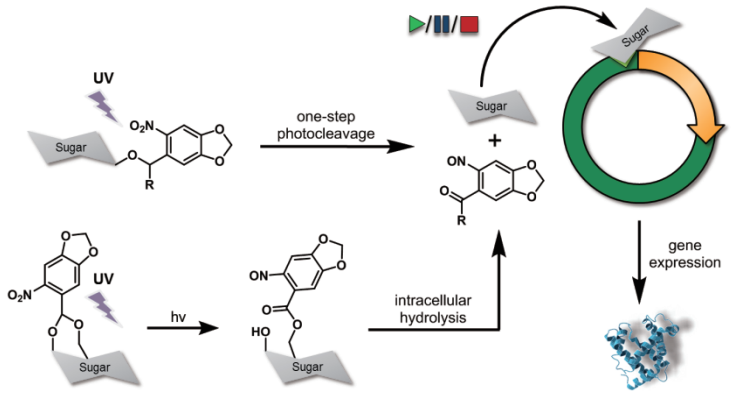
Photocaged compounds consist of an effector molecule and a photolabile protecting group, which enables the release of a biologically active substance by irradiation with a specific wavelength. Different heterocyclic compounds - coumarin and 6-nitropiperonyl derivatives – were utilized as photolabile protecting groups. The release of the effector molecule ensues with high spatiotemporal resolution, rendering the photolabile protecting groups not only beneficial for orthogonal deprotection in synthesis but also a crucial optogenetic tool for both biophysical and neurochemical examinations.[1-3] Our investigations focus upon the modification of the photolabile protecting group and in addition to it on the various types of biological effector molecules, giving us access to an extensive library of photocaged carbohydrates. A versatile toolbox was compiled und employed for a variety of synthetic biological and biotechnological applications.[4-6]



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Synthetic Study on Zinc(II) Complexes of 3-Hydroxy-5-(*p*-substituted)phenylthiazole-2(3*H*)-thiones toward the Development of New Antidiabetic Agents

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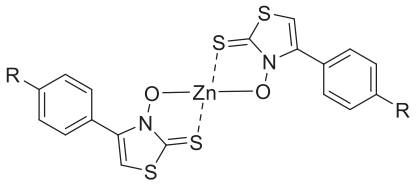
Zinc(II) ion has attracted increasing attention of medicinal chemists because of its insulin-mimetic activity. During the last two decades, many organozinc complexes with heterocyclic compounds as ligands have been synthesized to exhibit higher insulin-mimetic activities than inorganic $ZnSO_4$.In this context, we have synthesized zinc(II) complexes with 3-hydroxy-4-(*p*-substituted) phenylthiazole-2(3*H*)-thiones (**1**) and evaluated their insulin-mimetic activity to demonstrate that these complexes are potent antidiabetic agents.[1] In the present study, as part of structure-activity relationship study of zinc(II) complexes with 3-hydroxythiazole-2(3*H*)-thiones as antidiabetic agents, we have developed synthetic route to novel 3-hydroxy-4-(*p*-substituted)phenylthiazole-2(3*H*)-thiones (**2a**–**e**), and the synthesized **2a**–**e** were successfully converted into the corresponding zinc(II) complexes (**3a**–**e**).



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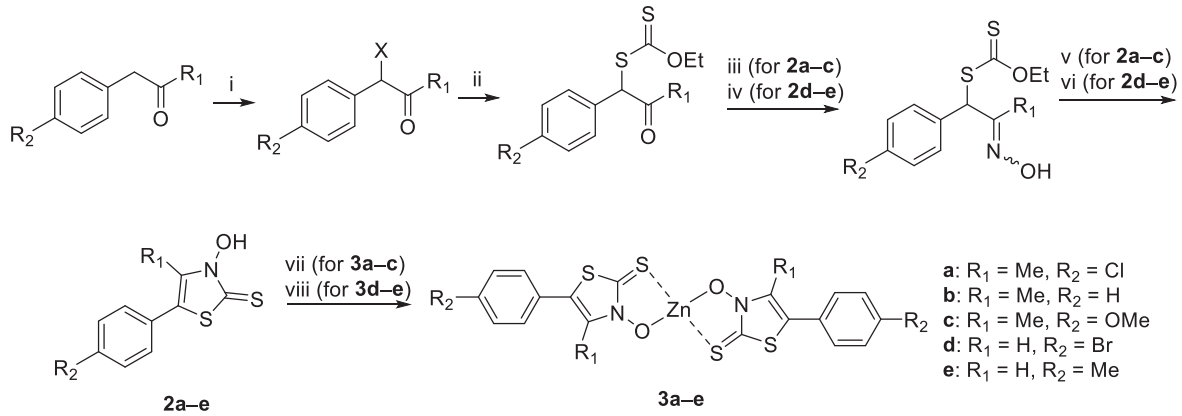

2a–e **3a–e**

Scheme 1. *Reagents and conditions*: (i) NBS, AIBN, CCl_4 reflux; (ii) potassium *O*-ethyl dithiocarbonate, aqueous acetone, r.t.; (iii) NH_2OH•HCl, aqueous ethanol, r.t.; (iv) pyridine, NH_2OH•HCl, methanol, r.t.; (v) KOH, aqueous CH_2Cl_2, r.t.; (vi) $ZnCl_2$, Et_2O, 0 ºC to r.t.; (vii) $ZnSO_4$, LiOH, aqueous THF, r.t.; (viii) $Zn(OCOCH_3)_2$, aqueous ethanol, r.t.

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5P-049s

5-Phenylazopyrimidines: A new class of orthogonal photoswitches?

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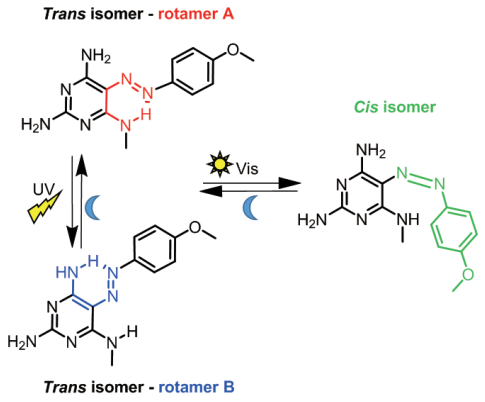
5-Phenylazopyrimidines are structurally close to the well-explored azobenzenes. Upon irradiation, they also undergo to the *trans-cis* isomerization. However, replacement of one phenyl ring with pyrimidine brings new prominent properties of such compounds, such as keto/enol tautomerism, biocompatibility or ability to form intermolecular hydrogen bonds[1].

We prepared three classes of new 5-phenylazopyrimidines, which are able to form none, one or two intramolecular hydrogen bonds (IMHBs). We used a unique combination of advanced experimental and theoretical methods to study their photochemical and physicochemical behaviour, namely 1) NMR with *in situ* irradiation, 2) optical spectroscopy, 3) mathematical fitting and 4) DFT calculations[2,3]. All prepared derivatives formed the *cis* isomer upon irradiation. Interestingly, some of them can be photoisomerized with visible light, which could be beneficial in applications, in which UV light is harmful. We were able to tune thermal relaxation rate and irradiation wavelength by suitable substitution. In compounds with two different hydrogen bond donors, we uncovered unique photoswitchable IMHBs. These derivatives can form two stable rotamers (A/B, both *trans* photoisomer). The rotamer ratio changed reversibly upon UV irradiation at low temperature. This photoinduced process as well as thermal relaxation is strongly substituent-dependent. The mechanism of these unique photoswitching processes was proposed by DFT calculations.

This detailed mechanistic study leads to a better understanding of the photochemical behaviour of azopyrimidines and gives an opportunity to designed new photoswitches, which could find a wide range of applications in optoelectronics, photobiology or material science.

Acknowledgements. Supported by the Czech Science Foundation (M.D., grant no. 18-11851S).



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Total Synthesis of Saptomycin H

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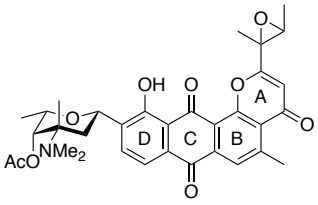
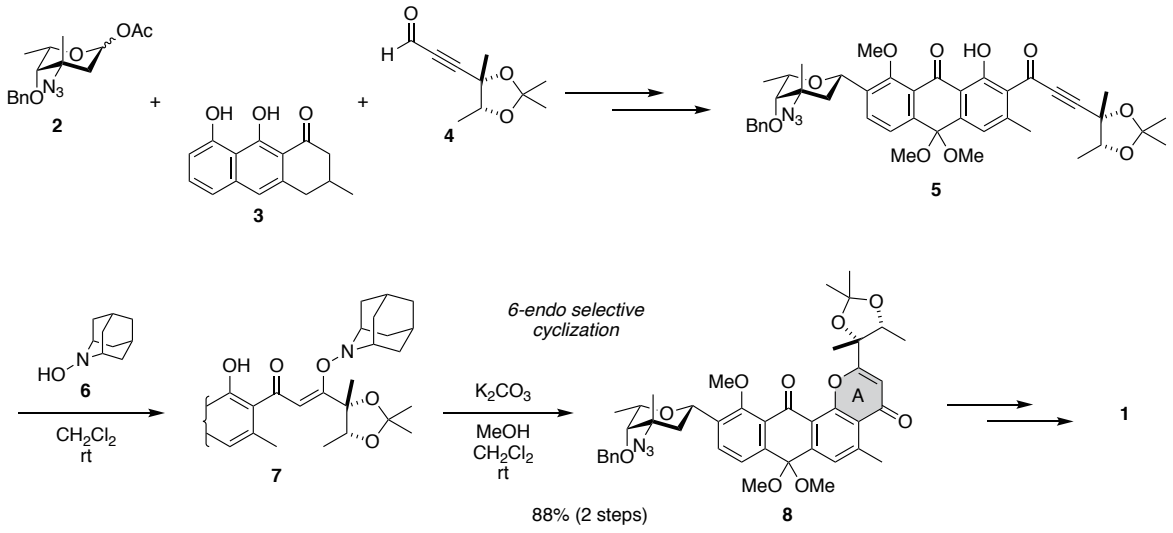
Saptomycin H (**1**), isolated from *Streptomyces* sp. HP530, is a member of the pluramycin-class antitumor antibiotics.(1) The structure features an anthrapyranone skeleton sharing the *C*-glycoside structure and an oxirane ring on the side chain. Although many synthetic studies have been reported, total synthesis of pluramycins having an oxirane ring is not achieved.



saptomycin H (**1**)

Herein, we will report a successful synthetic route to **1** via the 6-*endo* selective cyclization of anthraquinone acetal **5** by exploiting a particular reactivity of hydroxylamine **6**.

Anthrone **3** was combined with sugar **2** and aldehyde **4** to give anthraquinone acetal **5**. The A-ring formation from **5** to give **8** was not successful, and only the undesired 5-*exo* cyclization product was obtained. At this stage, we changed our strategy for the A-ring formation, focusing attention to the corresponding enone having a leaving group at the β position. Treatment of **5** with hydroxylamine **6** gave enone **7**, which smoothly underwent the desired reaction under basic conditions, giving only the desired 6-*endo* cyclization product **8**. Further transformations including removal of the protecting groups and construction of the oxirane ring culminated in the first total synthesis of saptomycin H (**1**).



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5P-051s

Chiral Vanadium Complex-catalyzed Enantioselective Oxidative Hetero-coupling Reactions of Arenols

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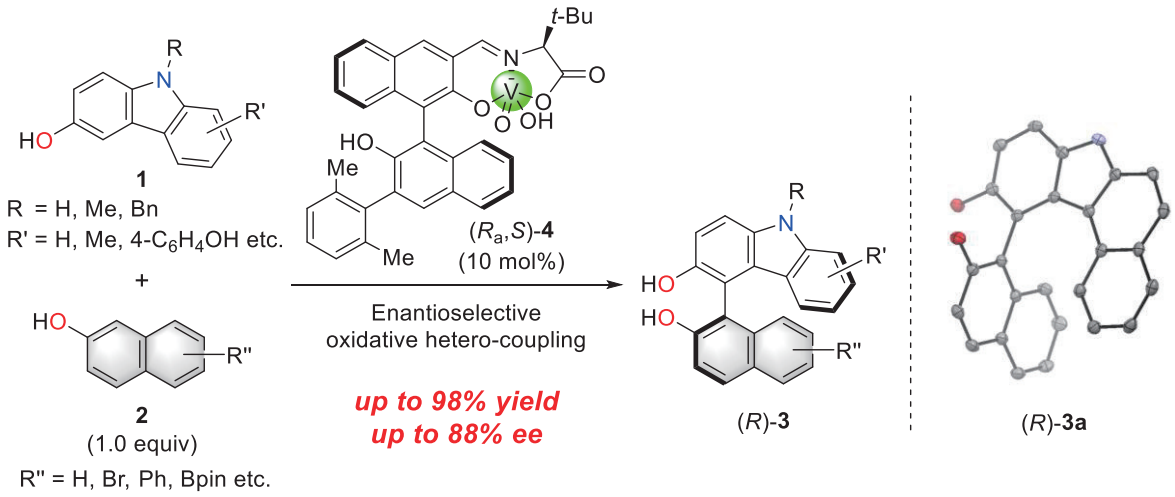
Optically active biarenol derivatives have played a significant role in the development of materials and pharmaceuticals due to their high potential as medicinal agents, chiral agents, and synthetic intermediates for natural products. Oxidative coupling reactions of arenols are powerful methods as a most straightforward synthetic tool for biarenols. To date, several enantioselective oxidative hetero-coupling reactions of arenols using copper, iron, and ruthenium catalysts have been reported, however, several issues have been remaining such as regio-, chemo- and enantioselectivity.

Herein, we report vanadium-catalyzed[1] enantioselective oxidative hetero-coupling reaction of 3-hydroxycarbazoles with 2-naphthols. When 3-hydroxycarbazole derivatives **1** and 2-naphthol derivatives **2** (1.0 equiv) were treated by mononuclear vanadium complex (R_a,*S*)-**4**[2] (10 mol %) in the presence of LiCl (3.0 equiv) under air, hetero-coupling product **3** was preferentially obtained in up to 98% yield with up to 88% ee. The homo-coupling products of **1** and **2** were obtained less than 5% yield, respectively. The present catalytic system exhibited good tolerance for functional groups such as free phenolic hydroxy, bromo, and pinacolate boryl groups. The absolute configuration of hetero-coupling product **3a** was determined to be *R* form by X-ray analysis. In this presentation, mechanistic studies for oxidative hetero-coupling reaction will also be discussed.



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5P-052s

Studies on the Total Synthesis of Hamigeran B

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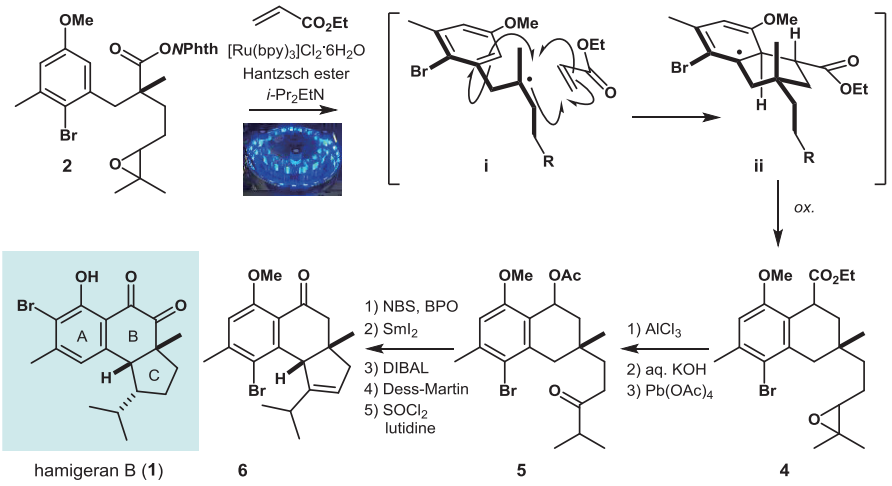
Hamigeran B (**1**), a marine natural product isolated from the sponge *Hamigera tarangaensis*, has been shown to exert a potent inhibitory activity against herpes and polio viruses. [1] In addition to the biological activity, its unique molecular architecture that features the highly substituted carbocycle fused to an aromatic ring has attracted considerable attention from synthetic chemical community. [2] In this presentation, we will discuss our endeavors to establish a new synthetic approach to this natural product (Scheme 1).

Scheme 1. *Synthetic approach to hamigeran B*



Our approach features a redox radical cascade process under visible light irradiation conditions to access tetralin skeleton, which constitutes a core motif of hamigeran B. Thus, *N*-hydroxyphthalimide ester **2** was subjected to the radical decarboxylation with Ru(II) catalyst in the presence of ethyl acrylate to afford tetraline **4**. Then, tetralin **4** was converted to ketone **5** that possesses all the functionalities necessary for constructing the C ring. Ketone **5** was subjected to five-step manipulations including benzylic functionalization and cyclization to furnish tricyclic compound **6**. With this compound **6** in possession, further studies to complete the total synthesis of hamigeran B are currently underway.

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5P-053

In situ click reaction activated by a metal ion in targeted proteins: Identification of a triazole compound as a lysine demethylase 5C inhibitor

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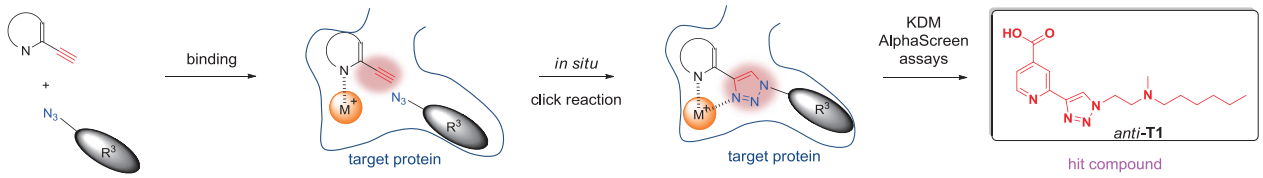
In situ click chemistry is a target-guided synthesis technique for discovering highly potent ligands by assembling azides and alkynes into triazoles inside the affinity site of a target protein. In conventional *in situ* click chemistry, the *in situ* generated triazoles are detected by LC-MS analysis, which makes it low-throughput screening.[1] In addition, hit compounds in LC-MS-based conventional *in situ* click chemistry are not always highly active toward the target proteins. Therefore, activity-based high-throughput *in situ* click chemistry screening methodologies are desired, although it is difficult to use activity-based high-throughput screening in *in situ* click chemistry because the cycloaddition is quite slow and produces only very small amounts of triazole.

To overcome these drawbacks of conventional *in situ* click chemistry, we developed a modified *in situ* click chemistry that can be used to discover inhibitors of metalloproteins. In the modified *in situ* click chemistry, 2-etynyl *N*-hetero rings are used as alkyne fragments. The ethynyl group becomes electron-poor only when the nitrogen is coordinated to a metal ion in a target protein,[2] which accelerates the formation of the triazoles that are expected to show potent activity by binding to the metal ion in the protein in a bidentate fashion through their two nitrogen atoms of triazole and hetero ring (Figure). This makes it possible to perform activity-based high-throughput *in situ* click chemistry screening.

In this study, we used the modified *in situ* click chemistry to identify *anti*-**T1** as an inhibitor of lysine demethylase 5C (KDM5C), a Fe(II)-dependent protein. The details will be presented in the congress.



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Facile Synthesis of Chiral Spirooxindoles *via* Pictet-Spengler/Oxidative Rearrangement

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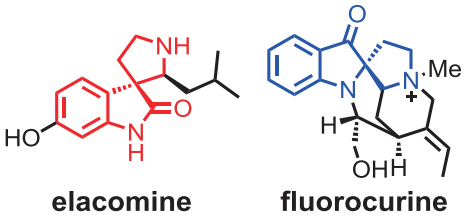
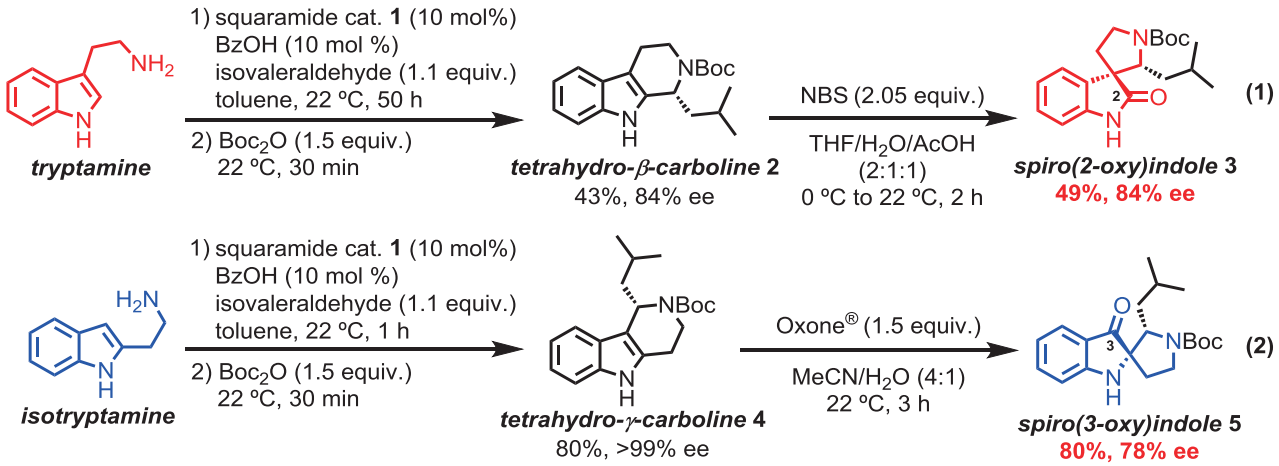
Ibaraki, Osaka 567-0047, Japan

The chiral spirooxindole skeleton is recognized as an important substructure because the core motif can be seen in various biologically active compounds and natural products such as elacomine and fluorocurine. Although significant progress has been made in the asymmetric synthesis of diverse spirooxindoles, facile synthetic strategies capable of constructing multiple chiral centers from readily available substrates are still in high demand.[1,2]



Herein, we report the short enantioselective synthesis of spirooxindoles *via* organocatalyzed Pictet-Spengler reaction[3,4] and oxidative rearrangements of tryptamines. Initially, tryptamine, isovaleraldehyde and Boc_2O were treated with squaramide catalyst **1** (10 mol%) to afford tetrahydro-*β*-carboline **2** in 84% ee. Secondly, the oxidative rearrangement of **2** with *N*-bromosuccinimide (NBS) under acidic conditions provided spiro(2-oxy)indole **3** maintaining a high enantioselectivity. (eq. 1). Under the similar procedure, spiro(3-oxy)indole **5** was also obtained in 78% ee from isotryptamine *via* Pictet-Spengler reaction, followed by Oxone®-mediated oxidative rearrangement (eq. 2). In this presentation, the investigation of one-pot synthesis and substrate scope of Pictet-Spengler reaction and oxidative rearrangement will be also discussed.



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Synthesis and evaluation of novel artificial nucleic acid having an oxanorbornane skeleton

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[1]*Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan,*
[2]*Graduate School of Engineering, The University of Tokyo, komaba, Tokyo 153-8904, Japan,*
[3]*National Institutes of Biomedical Innovation, Health and Nutrition, Ibaraki, Osaka, 567-0085, Japan*

Natural oligonucleotides have many rotatable single bonds, and thus their secondary structures are generally flexible. The structural flexibility results in the entropic penalty when forming a duplex with single-stranded RNA or DNA. It is also known that natural oligonucleotides are prone to rapid degradation in the body; thus they have limited therapeutic applications. To reduce the entropic penalty of natural oligonucleotides in the duplex formation and improve the enzymatic stability, we designed a novel artificial nucleic acid having an oxanorbornane skeleton (OxNorNA). The OxNorNA-uracil (OxNorNA-U) phosphoramidite was synthesized in 14 steps from known compound **1** and incorporated into oligonucleotides. As we had expected, the OxNorNA-U-modified oligonucleotides reduced the entropic penalty in the duplex formation, although they showed lower duplex-forming ability than the natural counterparts. It was notable that the OxNorNA-U-modified oligonucleotide had a markedly enhanced nuclease stability as compared to the corresponding 2',4'-BNA/LNA-modified or phosphorothioate-modified oligonucleotide. The results of the molecular dynamics simulation will also be presented.

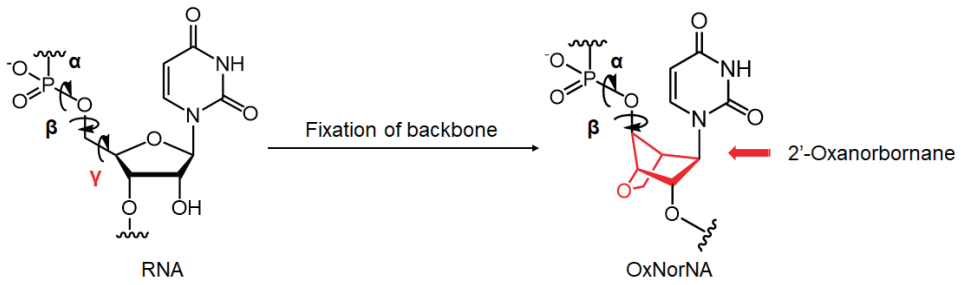
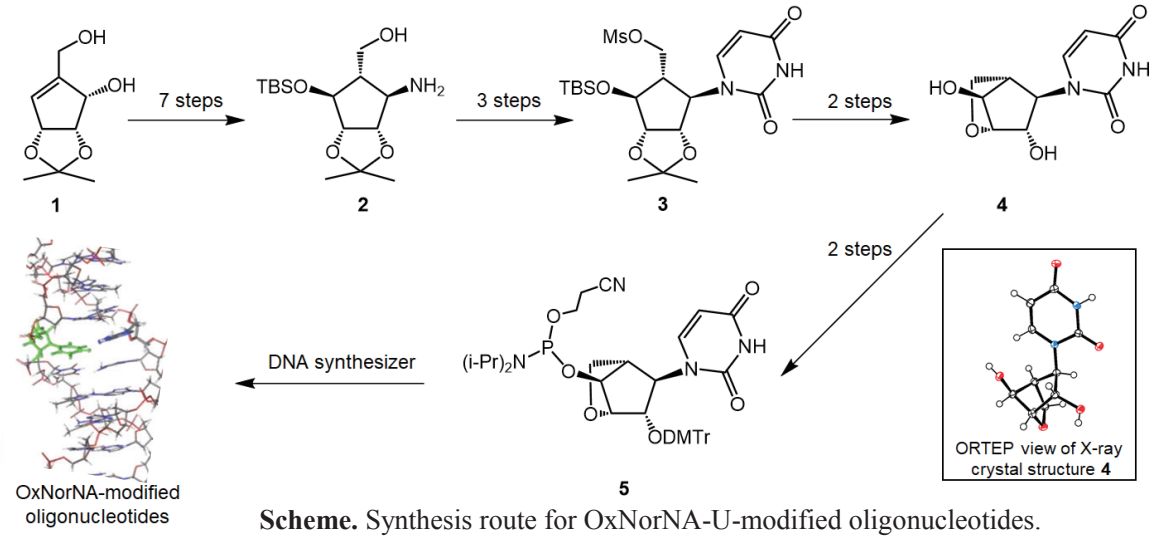


Figure. Molecular design of OxNorNA.



Scheme. Synthesis route for OxNorNA-U-modified oligonucleotides.

5P-056

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5P-057s

Regiospecific *N*-Arylation of Aliphatic Amines under Mild and Metal-Free Reaction Conditions

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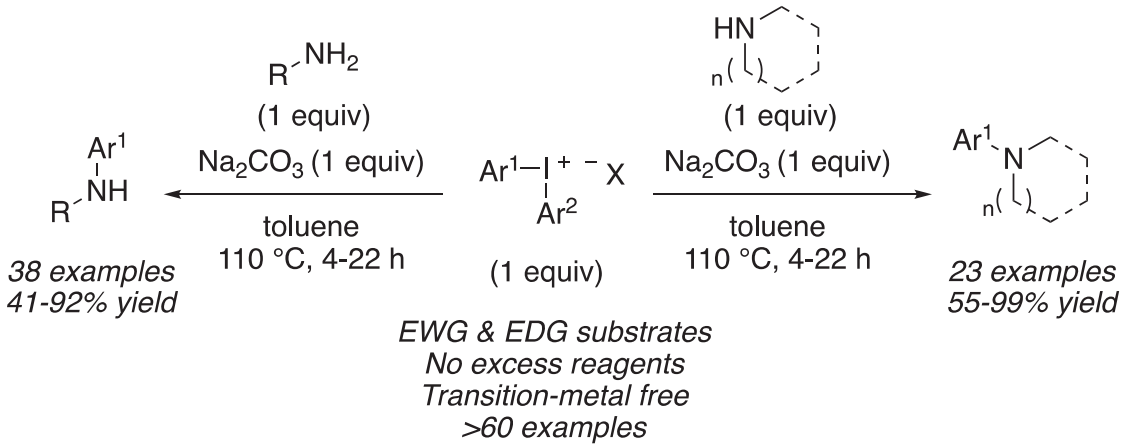
Stockholm University SE-106 91 Stockholm, Sweden

Diaryliodonium salts are versatile electrophilic arylating agents that are non-toxic, bench stable, and easily available via one-pot reactions from iodoarenes or arenes.[1] They can be applied in a variety of transition metal-free *C-, N-, O-* and *S*-arylations.[2] While the *N*-arylation of amides, anilines and some heterocycles has been reported,[2-3] aliphatic amines have been problematic substrates. To date, only the arylation of cyclic, secondary amines with electron deficient diaryliodonium salts has been established.[4]

Herein we present an efficient transition-metal free arylation of a wide range of primary and secondary amines with diaryliodonium salts.[5] Both acyclic and cyclic amines successfully provided a large set of *N*-alkyl anilines. The reactions are high yielding without excess reagents and diaryliodonium salts with both electron-withdrawing and electron-donating substituents could be employed (Scheme 1).



Scheme 1: N-arylation of primary and secondary amines with the aid of diaryliodonium salt and no excess reagents.

References

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[5] N. Purkait, G. Kervefors, E. Linde, B. Olofsson, *Angew. Chem. Int. Ed.* **2018**, *57*, 11427-11431.

Promoting accumulation of curvature-inducing peptides on cell membranes

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Membrane curvature plays important roles in various aspects in cellular life such as cell movement and cell growth. Approaches to modulate membrane curvature are expected to provide novel means in understanding and manipulating these cellular events.

Epsin-1 is a protein involved in the formation of positive curvature necessary for clathrin-coated pit formation. We previously reported that an amphipathic helical peptide corresponding to the N-terminus 18 residues (EpN18) has an ability to induce positive curvature [1] and to loosen lipid packing of cell membranes [2]. However, EpN18 has low affinity to cell membranes.

Here, we report a novel approach for facilitating the interaction of EpN18 with membranes at a lower concentration. EpN18 was conjugated with a probe peptide (K4), which specifically recognizes E3 tag of a membrane protein expressed on cell surface. Binding of E3/K4 promoted accumulation of EpN18 onto cell membranes, probably resulting in efficient enhancement of loosening lipid packing by EpN18 (Fig.1).

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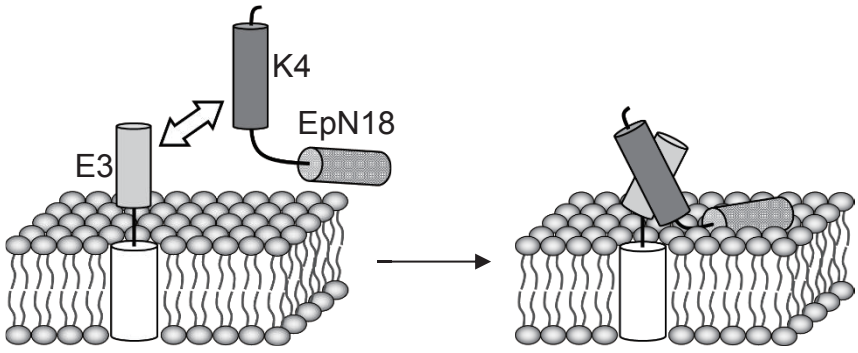

Fig.1 Accumulation of EpN18 on cell membranes with binding of E3/K4

5P-059s

Synthetic Study of Pyridone-embedded Analogs of Cortistatin A

Saki Watanabe [a], Yuki Tsujimura [b], Kanako Mizuno [c], Hirokazu Matsumoto [c], Aoi Ito [c], Motomasa Kobayashi [c] and Naoyuki Kotoku [a,b,c,*]

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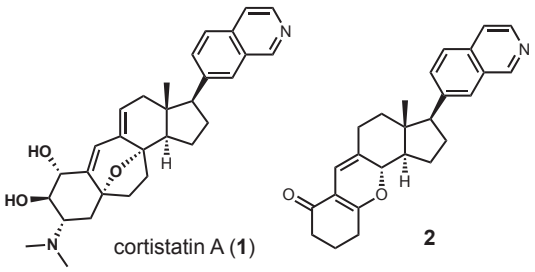
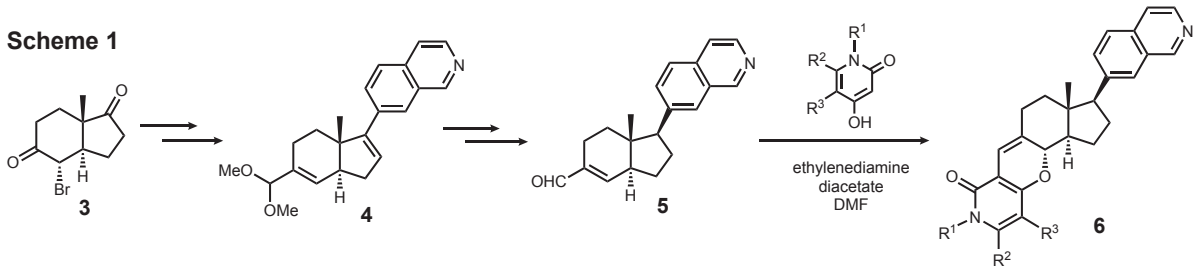
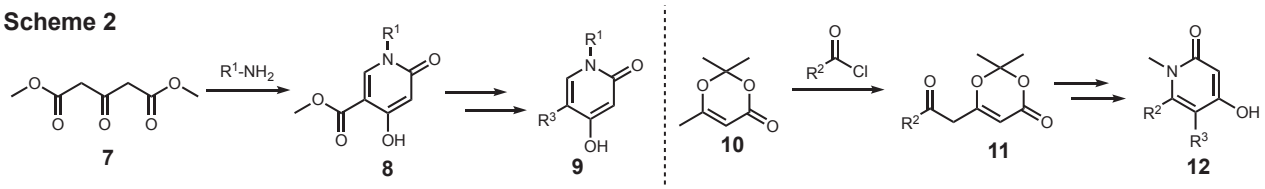
Cortistatin A (**1**), a steroidal alkaloid isolated from the Indonesian marine sponge, shows potent and highly selective anti-angiogenic activity. [1-2] As quite limited supply of **1** from natural sources hampered further development to be an attractive anti-cancer drug lead, we designed and synthesized the simplified analogs of **1** instead of the total synthesis and resulted in developing an analog **2** which shows comparable activity and selectivity with those of **1**. [3] As partial structure-activity relationship study of **2** revealed that the structural modification of A-ring affects the activity and selectivity, we focused to synthesize analogs with various substituents in A-ring using 4-hydroxy-2-pyridones as A-ring precursor.



Corresponding pyridones having the substituents in 1- and 5-position were prepared through cyclization of **7** with various amines[4], and 5- or 6-substituted pyridones were synthesized by acylation of 1,3-dioxin-4-one derivative **10** and subsequent intramolecular cyclization[5] (Scheme 2). Then, amine-catalyzed condensation/cyclization between the pyridones and aldehyde **5** provided the desired analogs **6** possessing various functional groups on A-ring (Scheme 1). The detail of the synthesis and biological evaluation of the analogs will be presented at the poster session.





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5P-060s

Synthesis and Evaluation of Novel Analogs of Arenastain A

Koki Fujimoto [a], Maho Kishimoto [b], Shinya Nakamura [c], Isao Nakanishi [c] and Naoyuki Kotoku [a,b,*]

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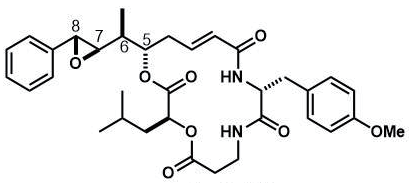
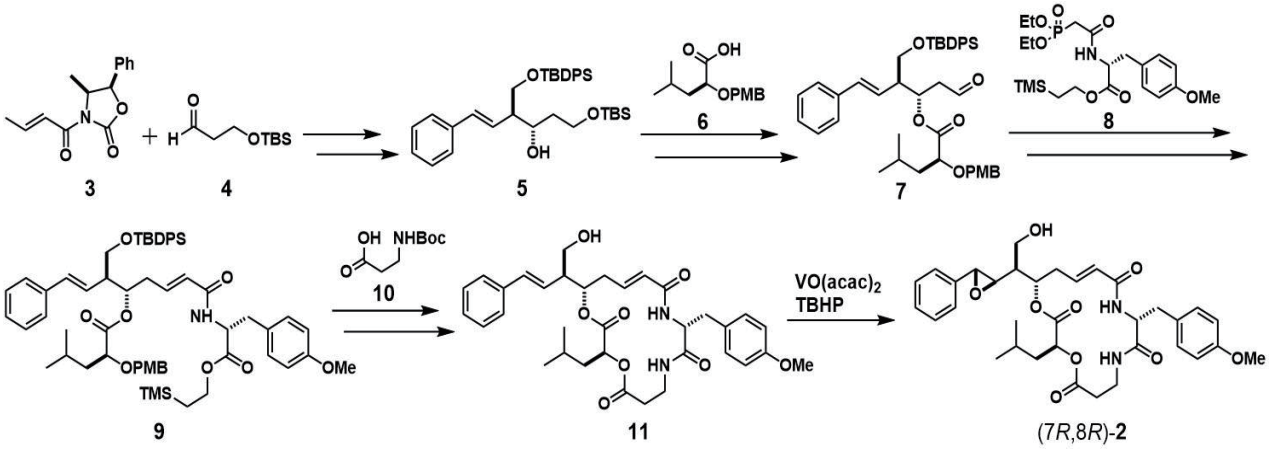
Arenastatin A (**1**), a cyclic depsipeptide isolated from Okinawan marine sponge, shows potent cytotoxicity against cancer cells.[1] In order to analyze more detailed structure-activity relationship of **1** [2], total synthesis and biological evaluation of a novel analog (**2**), in which a methyl group at C-6 position is converted to a hydroxymethyl group, is executed in this study.



The Evans' asymmetric aldol reaction with acyl oxazolidinone **3** and aldehyde **4**, and the following introduction of benzene ring by Heck reaction gave **5**. Subsequent conversions including the condensation reaction with a known carboxylic acid **6** provided an aldehyde **7** in good yield, which was then subjected to Horner-Emmons reaction with phosphonate **8**. After the resulting product **9** was coupled with carboxylic acid **10**, the intramolecular macrolactamization provided compound **11**. Then, epoxidation reaction proceeded from β-side stereoselectively by the treatment with $VO(acac)_2$ and TBHP, to give the desired analog **2**. The stereoselectivity (β:α = 5:1 by ^{1}H-NMR) was significantly improved compared with the reported one in the total synthesis of **1**, which implies that the newly introduced hydroxymethyl group at C-6 might work as a directing group against $VO(acac)_2$–TBHP complex at the moment. [3]

The detail of the synthesis of **2** and some other analogs, as well as and the results of the biological evaluation of them or the docking simulation with tubulin, will be discussed in the poster session.



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β-Amino Alcohol Organocatalyst for Asymmetric Hetero Diels-Alder Reaction of Isatins with Enones

Perumalsamy Parasuraman,[1] Madhu Chennapauram,[1] Chigusa Seki,[1] Koji Uwai,[1] Yuko Okuyama,[2] Michio Tokiwa,[3] Suguru Tokiwa,[2] Mitsuhiro Takeshita,[3] Hiroto Nakano,*[1]

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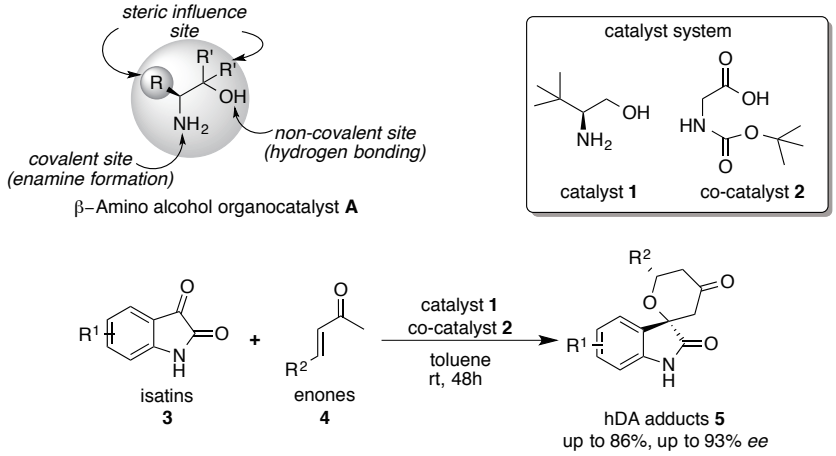
The development of asymmetric organocatalysis has emerged as one of the most intensively investigated area in synthetic organic chemistry. We are currently conducting the research of chiral amino alcohol organocatalyst that shows high level of catalytic activity in some asymmetric reaction. This catalyst has two advantages feature of easy preparation and desirable structural characteristics. Namely, catalyst **A** can be derived easily from the corresponding amino acid and contain both amino group acting as covalent site for enamine formation and hydroxyl group acting as non-covalent site for hydrogen bonding. Furthermore, the steric influence of α and *β*-position in **A** also might for controlling stereoselective reaction course.[1] The asymmetric hetero Diels–Alder (hDA) reaction is one of the important tool to construct biologically active chiral heterocycles.[2] In this study, we examined the asymmetric hDA reaction of isatins **3** with enones **4** using *β*-amino alcohol **A** as catalyst along with amino acid as co-catalyst. As a result, two component catalytic system of amino alcohol **1** with *N*-proteced amino acid **2** as co-catalyst showed a good catalytic activity in this reaction and the corresponding DA adducts **5** were obtained with good chemical yields (up to 86%) and good enantioseectivities (up to 93% ee). The obtained chiral DA adducts **5**, including spiro structure are efficient synthetic intermediates **5** for converting many biologically active compounds including drugs.[2] The detail of this work will be reported.



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[2] (a) H.-L. Cui, F. Tanaka, *Chem. Eur. J.* **2013**, 19, 6213-6216. (b) H.-L. Cui, P. V. Chouthaiwale, F. Yin, F. Tanaka, *Asian J. Org. Chem*. **2016**, 5, 153-161.

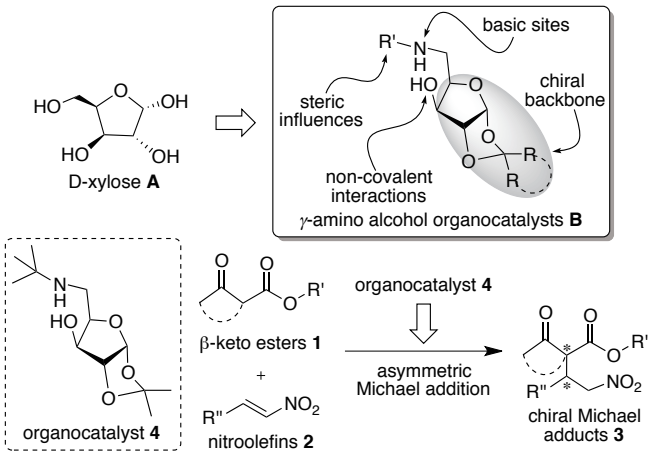
5P-062s

Xylofuranose Based γ-Amino Alcohol Organocatalysts for Asymmetric Michael Addition of β-Keto Esters with Nitro Olefins

Divakar Ganesan,[a] Madhu Chennapuram,[a] Chigusa Seki,[a] Koji Uwai,[a] Yuko Okuyama,[b] Michio Tokiwa,[c] Suguru Tokiwa,[c] Mitsuhiro Takeshita [c] and Hiroto Nakano*[a]

[a]*Graduate School of Engineering, Muroran Institute of Technology, 27-1 Mizumoto-Cho, Muroran* 050-8585*, Japan,* [b]*Tohoku Medical and Pharmaceutical University, 4-4-1 Komatsushima, Aoba-Ku, Sendai 981-8558, Japan,* [c]*Tokiwakai Group, 62 Numajiri, Tsuduri-chou, Uchigo, Iwaki 973-8053, Japan*

The asymmetric organocatalysis has emerged as one of the most prominent field in synthetic organic chemistry to prepare biologically active chiral synthetic intermediates and natural products templates.[1] In our continuation efforts in exploration of chiral amino alcohol and their derivatives as an organocatalysts for asymmetric reactions, we designed the xylofuranose-based γ-amino alcohol organocatalyst **B** from readily available simple D-xylose **A** by facile transformations.[2]



The prepared γ-amino alcohol organocatalyst **B** has essential modes for chiral activation such as chiral backbone to express steric influence, basic amino group and hydroxyl group for making hydrogen bonding in the single molecule. Based on those functionalities, γ-amino alcohol **B** is expected to work as superior catalyst in asymmetric reactions.

Asymmetric Michael addition is widely recognized as one of the most powerful tools to achieve carbon-carbon bond formation in synthetic organic chemistry. Especially, asymmetric Michael addition of β-keto esters **1** with nitroolefins **2** afford chiral Michael adducts **3** contains contiguous stereocenters.[3]

In this study, xylofuranose based organocatalysts **B** were applied to this reaction of **1** with **2** to afford the corresponding chiral adducts **3**. As a result, Michael adducts **3** were obtained with excellent chemical yields (up to 96%) and good stereoselectivities (up to 95:5% *dr*, up to 84% *ee*) when this reaction was carried out in the presence of catalyst **4**.

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[2] H. Nakano, J. Yokoyama, Y. Okuyama, R. Fujita, H. Hongo. *Tetrahedron*: *Asymmetry,* **2003**, 14, 2361-2368.
[3] M. S. Ullah, S. Itsuno. *ACS Omega,* **2018**, 3, 4573-4582.

5P-063s

Synthesis and Property of Propeller-Shaped Isoacenoheteroles

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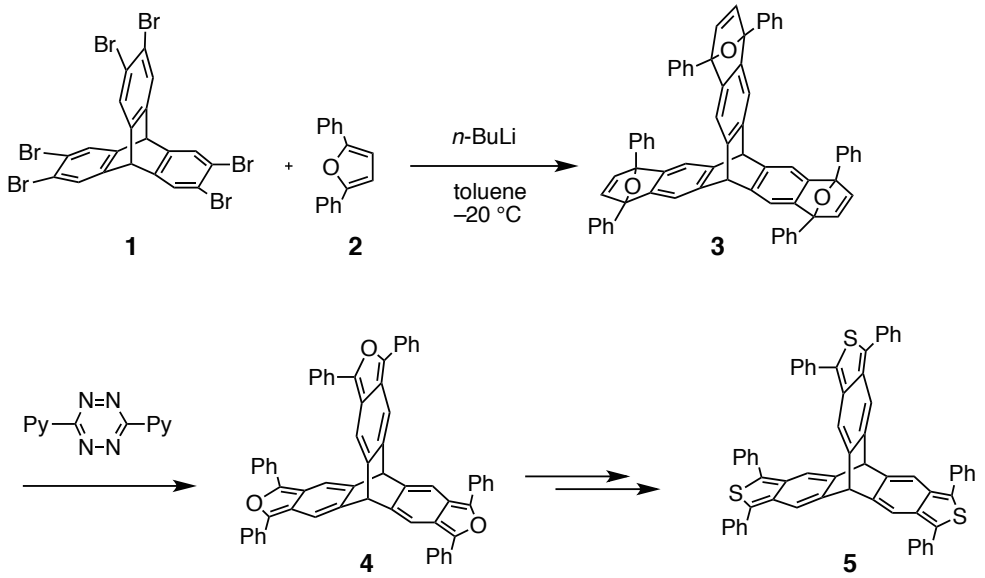
Sanda, Hyogo, 669-1337, Japan

Design and generation of a new reactive molecule is an important subject, because discovery of a novel reactivity inherent in its unique structure would lead to develop a new reaction, which opens a way to access to various functionalized organic molecules. In this context, we previously developed an efficient synthetic method of functionalized isobenzofurans,[1] which served as a reactive platform for construction of highly condensed aromatic compounds.[2] Further investigation along these lines revealed that linearly fused bis-isobenzofuran[3] and tris-isobenzofuran with a planar form[4] could be generated under the suitable conditions and trapped with various dienophiles to give novel 2D and 3D polycyclic compounds. We now develop a synthetic access to propeller-shaped isobenzofuran **4** and isobenzothiophene **5** as high-ordered iptycene derivatives possessing unique three-dimensional conjugated system.

One of the synthetic examples of propeller-shaped isobenzoheteroles was shown below. Upon treatment of hexabromotriptycene **1** with *n*-BuLi in the presence of diphenylfuran **2**, triple cycloadditions occurred smoothly to give three-fold cycloadduct **3**. Subsequent treatment of **3** with tetrazine gave 3D isobenzofuran **4**, which was converted to 3D isobenzothiophene **5** by reaction with Lawesson's reagent.



[1] Kudo, R.; Kitamura, K.; Hamura, T. *Chem. Lett.* **2017**, *46*, 25-28.
[2] Kitamura, K.; Asahina, K.; Nagai, Y.; Sugiyama, H.; Uekusa, H.; Hamura, T. *Chem. Eur. J.* **2018**, *24*, 14034–14038.
[3] Akita, R.; Kawanishi, K.; Hamura, T. *Org. Lett.* **2015**, *17*, 3094−3097.
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5P-064

Theoretical Analysis of Water Effect on a Stereoselective Fluorination Reaction

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We investigated the mechanism of water effect on a highly regio- and stereoselective fluorination reaction with amine and acid catalysts (Fig. 1)[1].

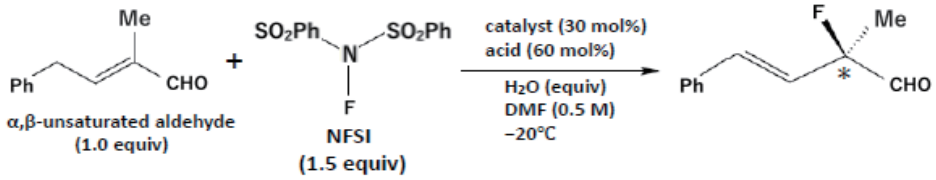

Figure 1. Fluorination of α,β-unsaturated aldehyde

In this reaction, adding some water to DMF solution significantly improves the reactivity, e.g., shortening the reaction time, whereas too much water decreases the enantiomeric excess. To elucidate the details of this water effect, we analyzed the activation free energies in various mixture ratio of DMF and water solutions by means of 3D-RISM-SCF method, which is an effective method to analyze the solvation free energy of a solute in a mixed solvent. The calculated results show that as the ratio of water is increased, the activation free energy decreases (Fig. 2). In addition, the free energy differences between transition states which give major and minor products are decreased as water is increased. These results are in good agreement with the experimental ones. Further analysis shows that the former is caused by the reactant destabilization, and that the latter is due to the difference of hydration free energy.

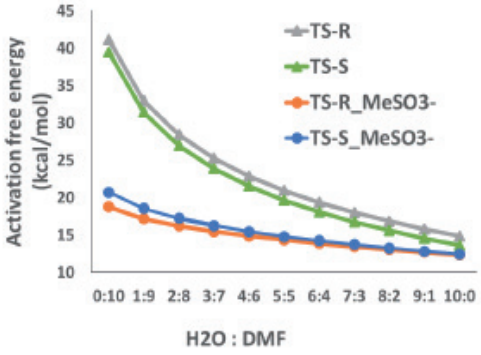

Figure 2: Calculated Activation Free Energies

References

[1] Arimitsu, S.; Yonamine, T.; Higashi, M. *ACS Catal.* **2017,** *7,* 4736-4740.

5P-065s

Asymmetric Catalysis of Racemization-Free Planar-Chiral Pyridinophanes Including Hemiacetal and Acetal Skeletons

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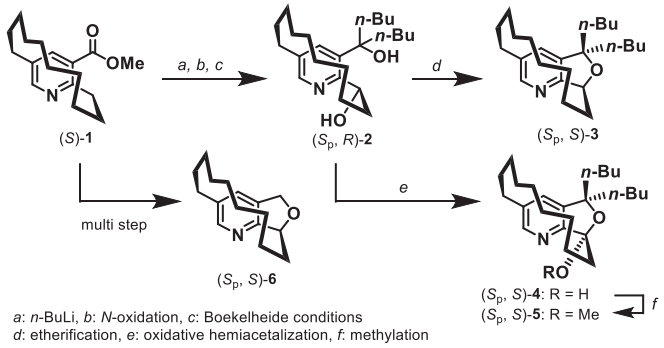
Planar-chiral pyridinophanes are structurally unique and useful chiral sources for asymmetric reactions.[1] Rope-skipping isomerization is a distinguishing property of pyridinophanes bearing appropriate length ansa-bridge, which induces racemization at high temperatures to restrict the scope of asymmetric reactions under heating conditions. We have designed and synthesized a new type of pyridinophanes having a tethered ansa-bridge and investigated asymmetric cyclopropanations with such racemization-free catalysts.

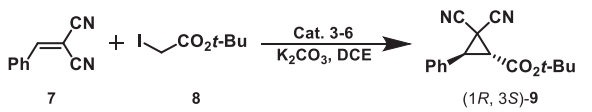
Syntheses of the racemization-free pyridinophanes **3**-**5** were achieved from optically active nicotinate (*S*)-**1** in excellent yield via nucleophilic addition of *n*-butyl lithium, *N*-oxidation, and Boekelheide transformation giving the common diol intermediate **2**, and the following intramolecular etherification to **3** or oxidative (hemi)acetalization to **4** and **5** (**Scheme 1**).

The pyridinophane-catalyzed asymmetric cyclopropanation proceeded to give the desired *trans*-cyclopropane product **8** exclusively by the reaction of malononitrile **6** with iodoacetate **7** in the presence of K_2CO_3 upon heating in 1,2-dichloroethane (DCE) (**Table 1**). The racemization-free catalyst **9**, independently synthesized from **1**, afforded cyclopropane **8** in 68% *ee*. The enantioselectivity increased to 84% *ee* by using ether catalyst **3** bearing di-butyl substituents, the steric demand of which extrudes the ansa-bridge toward pyridine nitrogen or the reaction site of the catalyst. Though hemiacetal catalyst **4** exhibited a comparable level of enantioselectivity, acetal catalyst **5** remarkably increased the stereoselectivity to provide the highly enantioenriched cyclopropane **8** with 95% *ee*. These findings are compatible with our proposed transition state: steric repulsion between a methoxy group and a bulky *tert*-butyl ester moiety in **7** is predominant to determine the lower transition state energy leading to the major stereoisomer, (1*R,* 3*S*)-**8**.



Scheme 1. Synthesis of pyridinophane catalysts

Table 1. Catalytic asymmetric reactions



7 8 (1*R*, 3*S*)-**9**

Entry	Cat.	Yield (%)	*ee* (% *ee*)
1	(S_p, *S*)-**6**	84	68
2	(S_p, *S*)-**3**	71	84
3	(S_p, *S*)-**4**	43	82
4	(S_p, *S*)-**5**	43	95

[1] N. Mugishima; N. Kanomata; N. Akutsu; H. Kubota, *Tetrahedron Lett.* **2015**, *56*, 1898-1903.

Highly Efficient Asymmetric Total Synthesis of (–)-Dehydro-*exo*-Brevicomin via Photoisomerization-Acetalization Strategy

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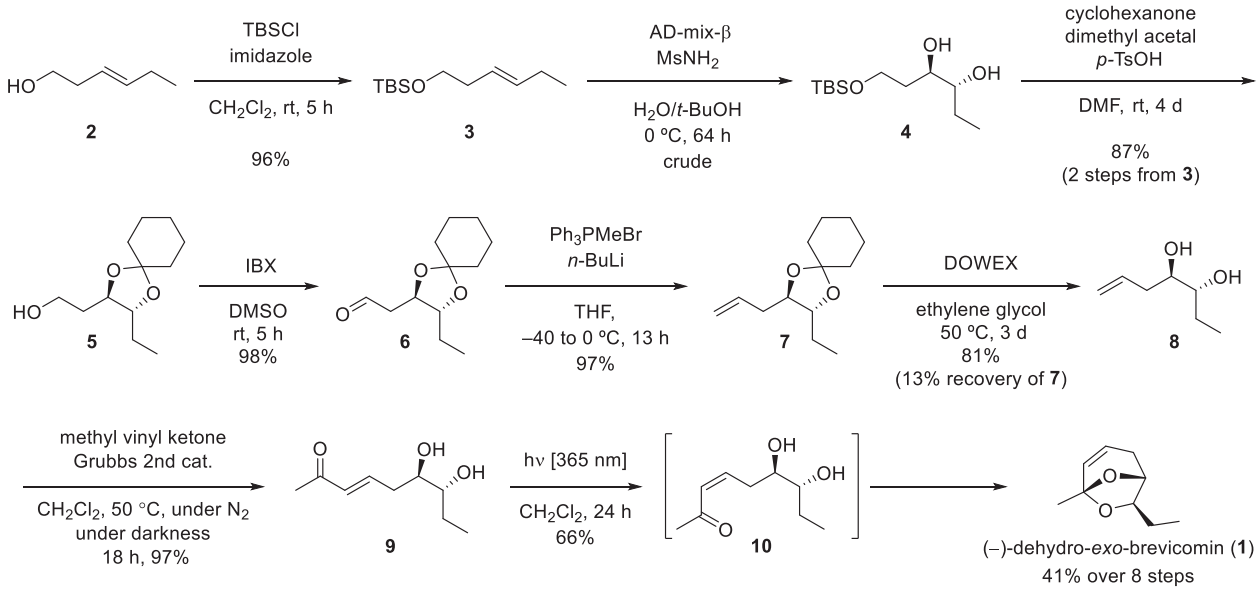
(–)-Dehydro-*exo*-brevicomin (DHB, **1**), a sex pheromone isolated from the urine of an adult male house mouse by Novotny in 1984, has an unique bicyclo[3.2.1] skeleton having three stereogenic centers.[1,2] In 1986, asymmetric total synthesis was reported independently by Wasserman, and Mori[3,4] We will present herein the highly efficient total synthesis of (–)-**1** via photoisomerization of *trans*-enone **9** and the following intramolecular acetalization *in situ* (**Scheme 1**).
We prepared the key precursor *trans*-**9** stereoselectively in 62% yield over 7 steps from commercially available *trans*-3-hexen-1-ol (**2**) via Sharpless asymmetric dihydroxylation. The characteristic bicyclo[3.2.1] skeleton of DHB **1** was established in the final step of the total synthesis by intramolecular acetalization of *cis*-**10** generated *in situ* as a photoisomer [5] of *trans*-**9**. The computed transition states of both *cis*- and *trans*-enones suggested that the intramolecular hydrogen bonding plays a key role to preferentially stabilize the desired regioisomer, *cis*-**10**. Each reaction step was extensively optimized to easily handle some volatile synthetic intermediates. Overall, the asymmetric total synthesis of (–)-dehydro-*exo*-brevicomin **1** was achieved over 8 steps in 41% total yield.



Scheme 1. Total synthesis of (–)-dehydro-*exo*-brevicomin (**1**)

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[5] Li, B.; Williams, D, B.; Smith, B. A. *Org. Lett*. **2015**, *17*, 3-5.

5P-067s

Synthesis and Structure-Activity Relationship Study of 1-(4-Methoxyphenyl)-1-(quinazolin-4-yl)ethanols as Anticancer Agent

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[2]*School of Pharmaceutical Sciences, University of Shizuoka 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan.*

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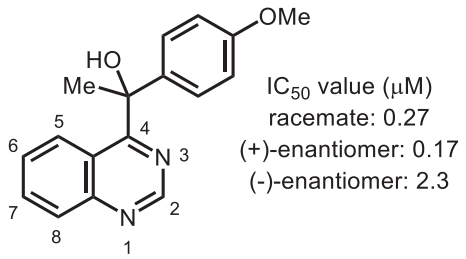
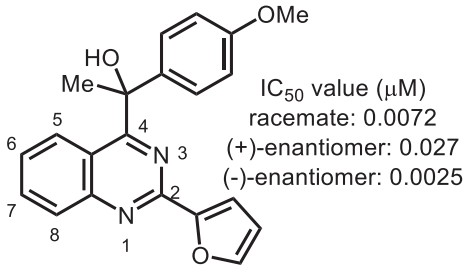
Quinazoline derivative PVHD121 (**1**) possesses antiproliferative activity against cancer cell lines such as HeLa, A549, and PC3. As a structure activity relationship study, derivatives of PVHD121 bearing various substituents at position 2, 5, 6, 7, or 8 of the quinazoline core were **s**ynthesized, and their antiproliferative activities against A549 cell line were evaluated.

Derivatives of PVHD121, compounds **B** were synthesized from halo-quinazolines **A** through NHC-catalyzed aroylation reaction and the subsequent Grignard reaction. S_NAr reaction or Suzuki-Miyaura cross coupling reaction of 2-chloroquinazoline derivative (**B**: R^1 = H, R^2 = Cl) produced 2-substituted quinazolines **C** (Scheme 1). In MTS cell proliferation assay with the A549 cell line, 2-furyl derivative **2** (PVHD303) showed an approximately 38-fold higher activity (7.2 nM) than the lead compound **1**. The enantiomers of **1** and **2** were separated by chiral column chromatography. (+)-**1** showed higher activity than (–)-**1**, whereas (–)-**2** exhibited higher activity than (+)-**2**. (Figure 1).

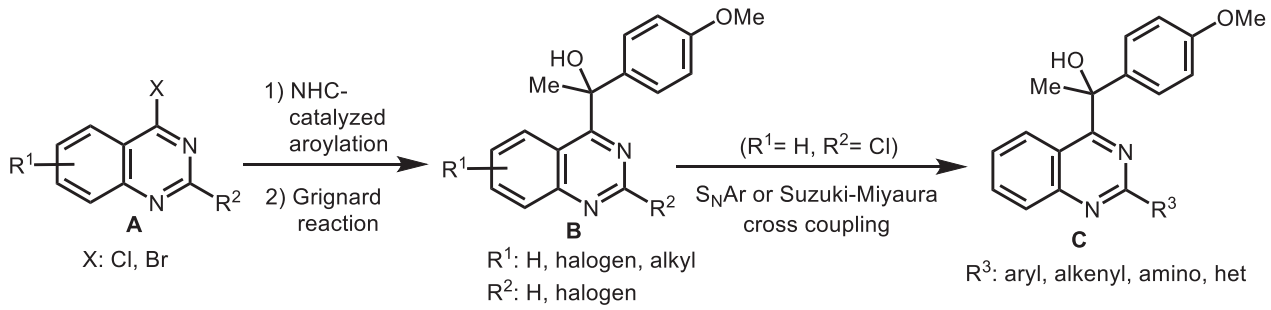


PVHD121 (1)



PVHD303 (2)

Figure 1: Structure and activity of PVHD121 and PVHD303



Scheme 1: Synthesis of PVHD121 Derivatives

[1] Kuroiwa, K. *et al., ACS Med. Chem. Lett.* 2015, 6, 287-291.

5P-068

Cycloaddition of alkynes and nitriles to heterocyclic N-imines as a tool for functionalized pyrazolo[1,5-a]pyridines and 1,2,4-triazolo[1,5-a]pyridines synthesis

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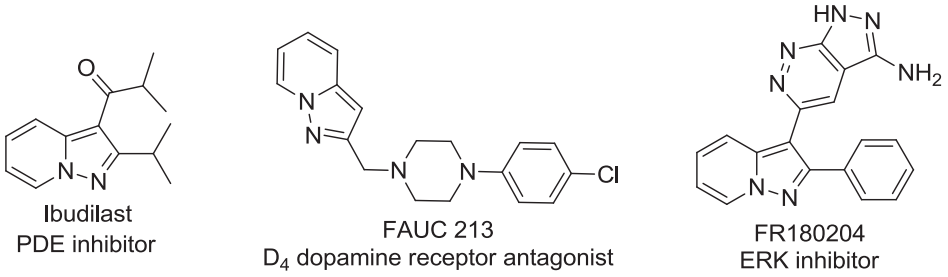
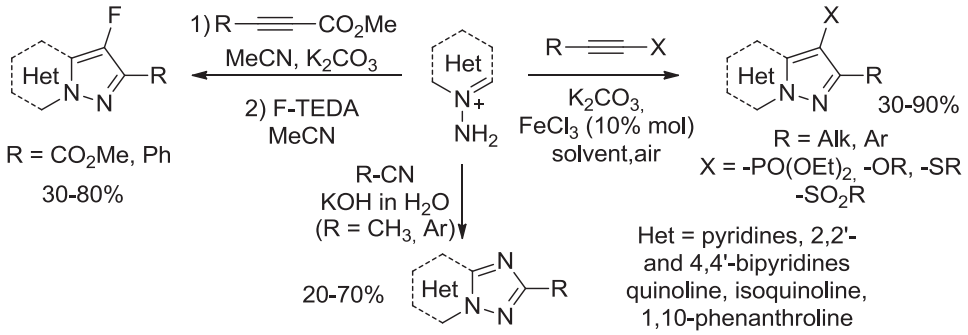
Pyrazolo[1,5-*a*]pyridines have attracted much attention from the medicinal chemistry community due to their various biological activities, such as anti-inflammatory, antiviral, anticancer. Numerous pyrazolo[1,5-*a*]pyridine derivatives act as PDE, ERK, p38 kinase inhibitors and dopamine receptors ligands. PDE4 inhibitor Ibudilast has been marketed in Japan for over 25 years as anti-inflammatory drug. One of the main routes to pyrazolo[1,5-*a*]pyridines is the 1,3-cycloaddition reaction of EWG-substituted alkynes to heterocyclic *N*-imines. In this work, approaches to 3-F, -$PO(OEt)_2$, -OR and -SR substituted pyrazolo[1,5-*a*]pyridines based on 1,3-dipolar cycloaddition are described.



Addition of CO_2Me-substituted acetylenes to pyridinium-*N*-imines is well known method for pyrazolo[1,5-*a*]pyridine-3-carboxylates preparation. Further fluorination of these compounds with F-TEDA unexpectedly led to 3-fluoro-derivatives with good yields. Mechanism of this transformation will be discussed.



Using $PO(OEt)_2$-substituted acetylenes, ynols of thioynols as dipolarophiles corresponding 3-substituted pyrazolopyridines were obtained. However, for such alkynes reaction proceeded much slower than in case of CO_2Me analogs and requiered $FeCl_3$ as catalyst. Aromatic nitriles and acetonitrile also could undergo cycloaddition reaction with pyridinium, bipyridinium and phenanthrolinium-*N*-imines to afford corresponding 2-substituted 1,2,4-triazolo[1,5-*a*]pyridine derivatives with moderate to good yields. Mechanism of this reaction will be discussed on the basis of DFT calculations.

This work was supported by Russian Scientific Foundation (grant # 18-73-00133).

5P-069s

Reaction of (Hetero)aryl Tetrafluoro-λ^6-Sulfanyl Chlorides with Alkynes and Alkenes under Visible Light

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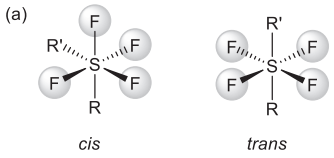
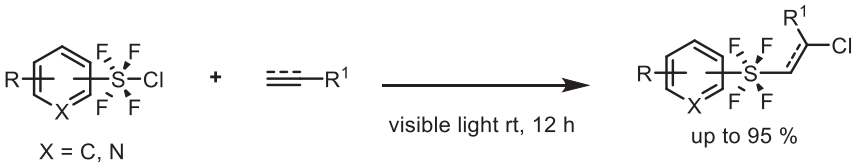
More and more attention has been focused on the research of fluorinated functional groups due to the success of the fluoro-pharmaceuticals on the market. Among a variety of fluorinated functional groups such as fluoro (F) and trifluoromethyl (CF_3), pentafluoro-λ^6-sulfane (pentafluorosulfanyl, SF_5) group has just recently turned out in the front of the research, since chemists have noticed the varied potentials of this moiety. Our group has also joined in this area for a decade and several papers concerning the development of an efficient methodology for SF_5-containing molecules [1]. On the other hand, the tetrafluoro-λ^6-sulfane (tetrafluorosulfanyl, SF_4) moiety, with equally robust functionality, has not been exploited enough and is highly underdeveloped. The SF_4 moiety has not only unique physiochemical properties such as high electronegativity, lipophilicity, and membrane permeability but also has exciting geometric features that enable it to connect two independent functional groups via the central hypervalent sulfur atom in either the *cis* or *trans* configuration of R-SF_4-R'. The *trans*-SF_4 configuration is particularly of high significance, as it functions as a building block in the construction of linear structures. The vital importance of the SF_4 moiety was also reported by our group [2], where we reported the radical addition reaction of pyridine tetrafluorosulfanyl chlorides (Py-SF_4Cl) to alkynes catalyzed by triethylboran (Et_3B) to furnish pyridine *trans*-SF_4-alkenes [3]. As an extension of this method, we report herein the visible light induced radical addition reaction of (hetero)aryl tetrafluorosulfanyl chlorides ((Het)Ar-SF_4Cl) to alkynes.



A wide variety of ((Het)Ar-SF_4Cl) is nicely converted to the corresponding (Het)Aryl-*trans*-SF_4-alkenes at room temperature under irradiation of visible light. Not only alkynes but also alkenes were reacted under the same conditions. Reaction mechanism will be discussed in the poster session.



[1] (a) N. Shibata *et al*., *Angew. Chem. Int. Ed.* **2016**, *55*, 10781; (b) *Chem. Commun*. **2017**, *53*, 3850; (c) *Chem. Commun.* **2017**, *53*, 5997; (d) *Tetrahedron Lett.* **2017**, *58*, 4803; (e) *Chem. Commun.* **2017**, 53, 12738; (g) *Beilstein J. Org. Chem.* **2018**, *14*, 364; (i) *Phosphorus, Sulfur Silicon Relat. Elem.* **2019**, *in press*.

[2] N. Shibata *et al*., *Chem. Sci.* **2018**, *9*, 4931.

[3] N. Shibata *et al*., *Org. Chem. Front.* **2018**, *5*, 719.

5P-070

Simultaneous binding of Chromomycin A_3 to the CGG repeat of DNA

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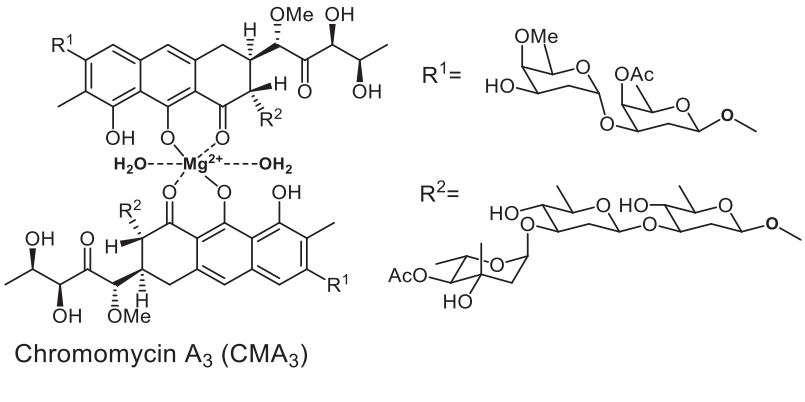
Chromomycin A_3 (CMA_3) is an aureolic acid-type antitumor antibiotic. CMA_3 forms dimeric complexes with divalent cations, such as Mg^{2+}, which strongly binds to the GC rich sequence of DNA to inhibit DNA replication and transcription.[1] In this study, the binding property of CMA_3 to the DNA sequence containing CGG repeat was investigated by measuring the protection from hydrolysis by the restriction enzymes.

The hydrolysis of the DNA containg d(CGG) repeat by the restriction enzyme *Fnu*4HI[2] was investigated in the presence or absence of CMA_3, and the produced DNA fragments were analyzed by gel-electrophoresis using denaturing PAGE. The conformation of duplex formed with $d(CGG)_n$ was confirmed to be the B-type by its CD spectrum. The $d(CGG)_{16}$ duplex was completely digested by *Fnu*4HI in the absence of CMA_3 to produce a number of fragment bands. Remarkably, full-length bands appeared in the presence of CMA_3, albeit with a few DNA fragments, suggesting that CMA_3 molecules simultaneously bind to the CGG repeat sequence.[3]

This study has shown the ability of CMA_3 to simultaneously bind to the CGG, which may account for an aspect of varied bioactivities of CMA_3. Development of small molecular ligands to the DNA repeat is now on-going based on the simultaneous binding mode of CMA_3.



Chromomycin A_3 (CMA_3)

Figure 1. The structure of Chromomycin A3

Figure 2, CMA_3-Dimer-Mg^{2+}-DNA Complex

[1] Hou, M. H.; Robinson, H.; Gao, Y. G.; Wang, A. H. J. *Nucleic Acids Res*. **2004**, 32, 2214.
[2] Leung, D. W.; Lui, A. C. P.; Merilees, H.; McBride, B. C.; Smith, M. *Nucleic Acids Res.* **1979**, *6*, 17.
[3] Murase, H.; Noguchi, T. and Sasaki, S., *Bioorg. Med. Chem. Lett*., **2018**, *28*, 1832–1835.

5P-071

Reaction of 2-Phenylbenzo[1,3,2]dioxaboridines with Various Oxidants

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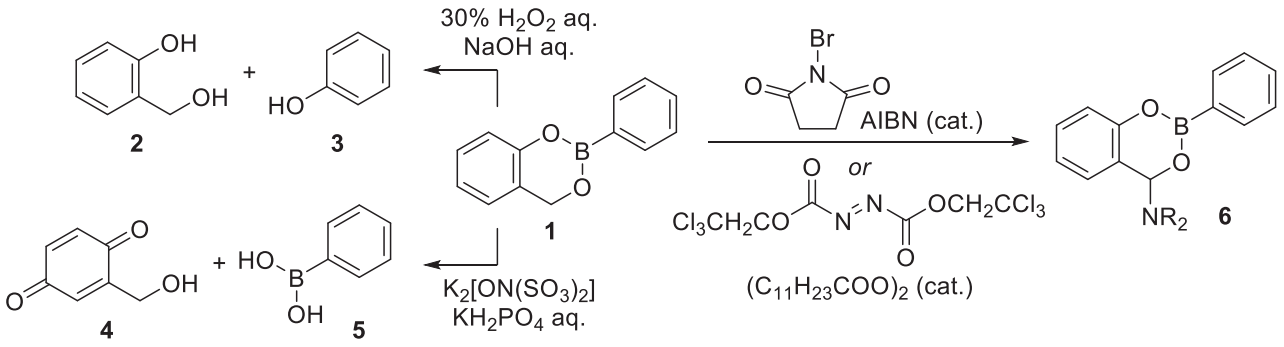
Boron-containing compounds, typically boronate esters, are used as important partners for the Suzuki-Miyaura coupling reactions. While boronate esters may be utilized as protective groups, organoboranes are known to be oxidized to the corresponding alcohols. To elucidate stability against oxidation, salicyl alcohol ester of phenylboronic acid **1** was chosen as substrate and oxidation reactions of **1** with various oxidants were examined.



Reaction of **1** with basic hydrogen peroxide underwent smoothly to produce salicyl alcohol **2** and phenol **3**. As seen in the synthesis of alcohols from alkenes, oxidation of the boron-carbon bond *via* the 1,2-miglation was preferred process compared with oxidation of salicyl alcohol. When **1** was reacted with the Frémy's salt, dipotassium nitrosodisulfonate,[1] on the other hand, 2-hydroxymethyl-1,4-benzoquinone **4** was produced along with phenylboronic acid **5**. The Frémy's salt has radical on the oxygen of the central hydroxylamine group and is known for the good reagent to produce benzoquinones from phenols. As we expected, oxidation of salicyl alcohol part was faster than that of the boron-carbon bond. On the other hand, radicals on the nitrogen atoms which were produced by *N*-bromosuccinimide in the presence of catalytic amount of azoisobutyronitrile abstracted hydrogen at the benzylic position of salicylic esters to produce **6** with the hemiaminal structures. The same type of reaction was also carried out by using bis(trichloroethyl) azodicarboxylate in the presence of catalytic amount of lauroyl peroxide.[2] The resulting hemiaminals **6** were not stable and were decomposed into phenylboronic acid **5** and salicylaldehyde when solution of **6** were washed with water. The results of oxidation of **1** with various substituents by *N*-bromosuccinimide will be presented in this symposium.

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5P-072s

IBS-catalyzed Highly Efficient and Selective Oxidation of Alcohols with Oxone

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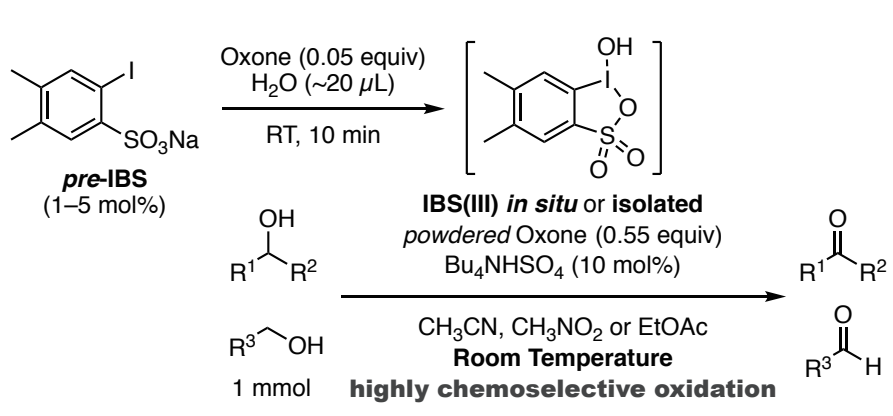
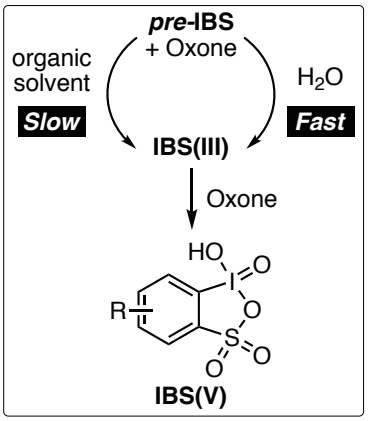
The oxidation of alcohols to the corresponding carbonyl compounds is one of the most fundamental and important transformations in synthetic organic chemistry. Transition metal-catalyzed oxidation process has attracted great attention because even gaseous O_2 can be use as a stoichiometric oxidant. However, there are great needs for more efficient, chemoselective and greener methods without any heavy metallic species for such transformations, particularly in the pharmaceutical industries. Over the past two decades, hypervalent organoiodine compounds have been focus of great attention due to their mild and chemoselective oxidizing properties and their environmental benign character in contrast to toxic metal reagents.[1] However, the use of hypervalent iodine reagents as a stoichiometric oxidant has been limited because some are shock-sensitive or explosive, and/or show poor solubility in organic solvents. Therefore, the catalytic use of hypervalent iodine is strongly in demand from both economic and environmental perspectives.[2]

We have previously developed selective oxidation of alcohols using 2-iodoxybenzenesulfonic acid (IBS), which is generated *in situ* from catalytic amount of 2-iodobenzenesulfonic acid (*pre*-IBS) and Oxone as an oxidant.[3–5] However, harsh reaction conditions (i.e., high temperature) were required for efficient oxidation reaction that leading a limited substrate scope. Here, we succeeded in the IBS-catalyzed highly efficient and chemoselective oxidation of alcohols at room temperature by using tetraalkylammonium hydrogen sulfates as solid-liquid phase transfer catalysts under optimized conditions. The investigation of catalytic mechanism revealed that the generation of IBS(III) from *pre*-IBS was slow under non-aqueous conditions, which is essential for the catalytic use of IBS. Therefore, the reaction rate of the present oxidation could be improved by using isolated or *in situ*-generated IBS(III) instead of *pre*-IBS.





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5P-073

Synthesis of Azepino[1,2-a]indoles by the [6+1] Annulation Reaction of Ynenitriles

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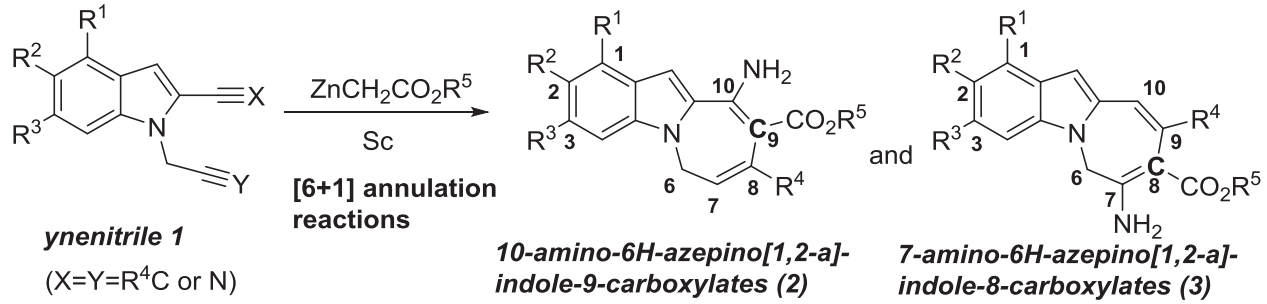
Azepino[1,2-a]indoles are seven-membered heterocycles connected to the N1–C2 face of indoles. These heterocycles display important pharmacological activities. Some synthetic methods for preparing azepino[1,2-a]indoles have been reported in the literature.[1] However, presenting new methodologies for preparing functionalized azepinoindoles is necessary owing to their potential role in anticancer activities against cholagiocarcinoma, hepatocellular carcinoma, lung carcinoma, and lymphoblastic leukemia.[2]

Recently, we reported the [6+1] annulation reaction of ynenitriles with Reformatsky reagents, which is a useful protocol for directly synthesizing various 3-amino-2,7-dihydro-1*H*-azepine-4-carboxylates.[3] Herein, we synthesize azepino[1,2-a]indoles via Lewis acid-catalyzed [6+1] annulation reactions of both 2-cyano-1-propargyl-indoles and 2-alkynyl-1-cyanomethyl-indoles with the Reformatsky reagents.

First, we reacted 2-cyano-1-propargylindole **1a** (R^1=R^2=R^3=H, X=N, Y=CEt) with the Reformatsky reagent, which was prepared from zinc and ethyl bromoacetate in 1,4-dioxane under reflux conditions. The optimized scandium triflate-catalyzed reaction succeeded in yielding azepino[1,2-a]indoles through the Blaise-type reaction and successive 7-endo-mode cyclization of the β-aminoacrylate intermediates. Then, we examined similar reactions of **1a** with other Reformatsky reagents (R^5=Me, *t*-Bu). The reaction with methyl ester afforded a good result. However, the bulky *t*-butyl ester did not yield pure products. In addition, we performed the [6+1] annulation reactions of other indoles having substitutions on the aromatic ring (R^1–R^3). Most annulation reactions of the substituted indoles afforded azepino[1,2-a]indoles **2** in good yields.

Similar annulations of 2-alkynyl-1-cyanomethylindoles with the Reformatsky reagents successfully yielded 7-amino-6*H*-azepino[1,2-a]indole-8-carboxylate **3**. Interestingly, pyridoindoles were not detected in this annulation reaction. Furthermore, the antiproliferative activity of the obtained compounds against the HCT-116 cells is also reported.



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5P-074s

μ-Oxo Hypevalent Iodine(III)-Catalyzed Oxidative Aryl Amination for Synthesis of *N*-Heterocycles

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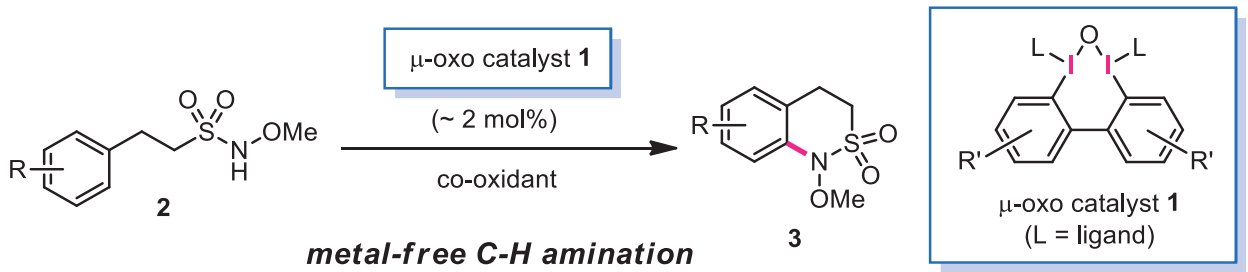
For the synthesis of *N*-heterocyclic compounds, intramolecular metal-catalyzed reactions, such as Ullmann amination and Buchwald-Hartwig amination, are the promising methods. Although these aminations are the useful and practical strategy, the use of pre-functionalized aromatic compounds is usually required for performing the C–N bond formation and cyclization. Therefore, chemists have pursued a direct amination method that can convert the aromatic C–H bond into C–N bonds to construct *N*-heterocyclic structures. For this purpose, several direct C–N bond-forming reactions using metal catalysts in combination with oxidizing agent have been reported in recent years.[1] However, these reactions often required high catalyst loadings and the use of toxic heavy metal co-oxidants at elevated temperatures.

Hypervalent iodine reagents are the low-toxic and safe reagents having reactivities similar to those of heavy metal oxidants. Our group previously reported hypervalent iodine-catalyzed dearomative spirocyclization of amides to provide *N*-fused spirolactams.[2,3] We have now examined the reactivity of hypervalent iodine catalysts **1**[4] in the synthesis of *N*-heterocycles, such as cyclic sulfonamides **3** by the oxidative cyclization of sulfonamides **2**.[5]

Based on the screening of the iodine catalysts, the desired cyclized products **3** were effectively obtained when a small amount of oxygen-bridged highly reactive biaryl iodine(III) catalyst (~2mol%) was employed in the presence of suitable oxidant, such as peracetic acid and *m*-chloroperbenzoic acid. The present research has thus revealed that μ-oxo iodine(III) catalyst **1** shows higher catalytic activities compared with the conventional metal oxidants and catalysts. Using this new C–N bond formation protocol, cyclic sulfonamides **3** can be synthesized by direct transformation of the aromatic C–H bond into new C–N bond under mild and metal-free conditions.



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Synthetic Study of Aspidophylline A Based on Gold(I)-Catalyzed Cascade Cyclization

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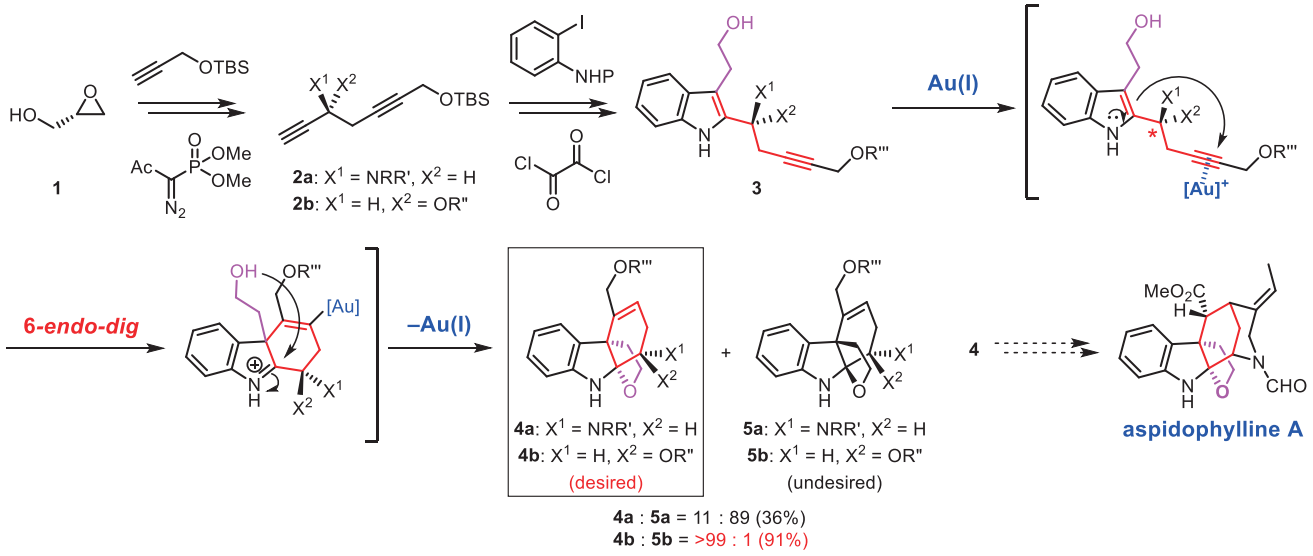
Aspidophylline A is a cage-like pentacyclic compound isolated by Kam and co-workers in 2007 and was found to exhibit reverse drug resistance activity toward resistant KB cells.[1] The intricate pentacyclic framework of aspidophylline A represents synthetic challenges, including the tricyclic furoindoline motif, a densely substituted cyclohexane ring containing five contiguous stereogenic centers, and [3.3.1]bicyclic structure. We recently reported the construction of a cyclohexane ring of strictamine by the use of gold(I)-catalyzed cyclization.[2] Based on this result, we designed a novel method for construction of cyclohexane-fused furoindoline scaffold via a gold(I)-catalyzed cascade cyclization for total syntheses of aspidophylline A.

Using a racemic substrate **3a** bearing a nitrogen functional group, we investigated the gold-catalyzed cyclization. Although the cascade cyclization proceeded to give the fused furoindolines **4a** (desired) and **5a** (undesired), the control of the stereoselectivity was difficult (**4a**:**5a** = 11:89; 36% yield). Therefore, we investigated the cyclization reaction using **3b** bearing an oxygen functional group instead of a nitrogen group and obtained promising results (**4b**:**5b** = >99:1; 91% yield). In this presentation, the change in stereoselectivity will also be discussed.



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Chemoselective Nucleophilic Functionalizations of Aromatic Aldehydes / Acetals via Pyridinium Salt Intermediates

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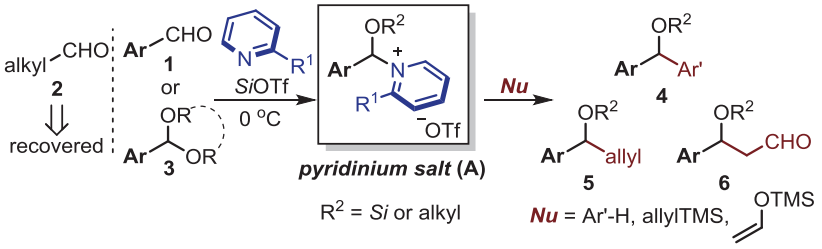
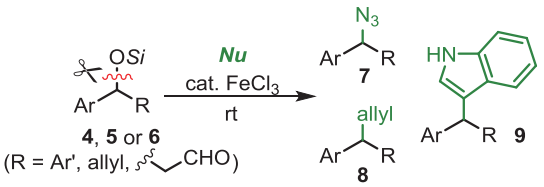
Aldehydes are widely utilized as reactive electrophiles toward carbon nucleophiles to form carbon-carbon bonds in organic synthesis. However, the perfect chemoselectivity between aromatic and aliphatic aldehydes is difficult to be achieved by the previous methods. Herein, we demonstrate an aromatic aldehyde-selective nucleophilic functionalization using silyl triflate and a pyridine derivative via the pyridinium-type salt intermediates.[1] Moreover, the aromatic acetals as protected aldehydes could be directly transformed to similar pyridinium salt intermediates, which selectively reacted with various nucleophiles in the presence of the aliphatic aldehydes.[2]

The pyridinium-type salt intermediate (**A**; R^2 = *Si*), generated from aromatic aldehydes (**1**) in the presence of the pyridine derivative and *Si*OTf, efficiently reacted with electron-rich arene (Ar'-H), allyl silane and silyl enol ether derivatives to give the corresponding benzyl silyl ethers (Scheme 1; **4**, **5** and **6**). Although aliphatic aldehydes (**2**) were also transformed to the corresponding pyridinium-type salt intermediates, the aliphatic aldehyde **2** was completely recovered after aqueous work-up due to their low reactivities toward the nucleophiles. The aromatic acetals (**3**) as the protected form of aldehydes were also converted into the similar pyridinium salt (**A**; R^2 = alkyl), which could undergo the subsequent chemoselective transformation in the presence of aliphatic aldehyde (**2**). Moreover, the resulting secondary benzyl silyl ether moieties in the obtained products (**4**, **5** and **6**) were chemoselectively transformed to the functionalized products (**7**, **8** and **9**) via the $FeCl_3$-catalyzed nucleophilic substitution[3] accompanied with the elimination of the siloxy group (Scheme 2). The present unprecedented and chemoselective carbon-carbon bond formations are useful to diversify the synthetic strategies for target organic molecules.



Scheme 1. Aromatic aldehyde/acetal selective functionalizations.



Scheme 2. Further chemoselective functionalizations.

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5P-077s

Approach to Spirocyclohexadiene through Visible Light-Mediated *ipso* Cyclization of Biaryls

Haruka Takeuchi[1], Shinsuke Inuki[1]*, Takashi Miyagawa[1], Yukari Fujimoto[2], Shinya Oishi[1], and Hiroaki Ohno[1]*

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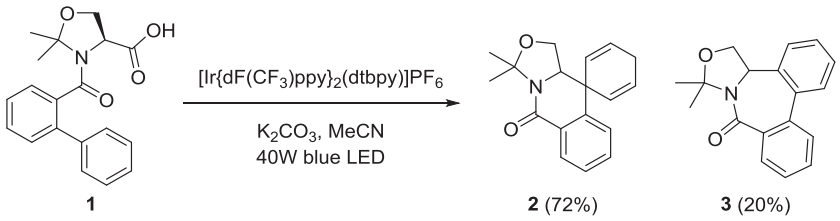
[2]*Graduate School of Science and Technology, Keio University, Kanagawa 223-8522, Japan*

Spirocycle is an important structural motif found in a variety of pharmaceutical products and biologically active natural compounds.[1] Thus, considerable efforts have been made to explore efficient strategies for the synthesis of those scaffolds. One representative method for construction of spirocycles relies on the intramolecular radical *ipso*-cyclization onto various functionalized aromatic rings. Our group also has reported a samarium(II)-mediated spirocyclization onto aromatic rings.[2]

On the other hands, visible light-mediated decarboxylative functionalizations of carboxylic acids employing photoredox catalysts have received considerable attention, and now recognized as a promising approach to new carbon–carbon or carbon–heteroatom bond formation.[3] These types of reactions enable mild and efficient transformations using a commercially available household light bulb. We envisaged that visible light-mediated decarboxylative reaction of serine derivatives bearing biaryl groups could allow construction of spirocycles via intramolecular radical *ipso*-cyclization. During the course of this study, decarboxylative functionalizations of amino acid derivatives with a high-pressure mercury lamp was reported by Yoshimi et al.[4]

After the investigation of reaction conditions, we found that the reaction of L-serine derivative **1** with $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ and K_2CO_3 in MeCN under visible−light irradiation afforded the desired spirocycle **2** in 72% yield. The unanticipated side-product **3** was also observed in 20% yield. In this presentation, the substrate scope and plausible reaction mechanism will also be discussed.



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5P-078s

Total Synthesis of Dictyodendrins by the Gold-Catalyzed Cascade Cyclization of Conjugated Diynes with Pyrroles

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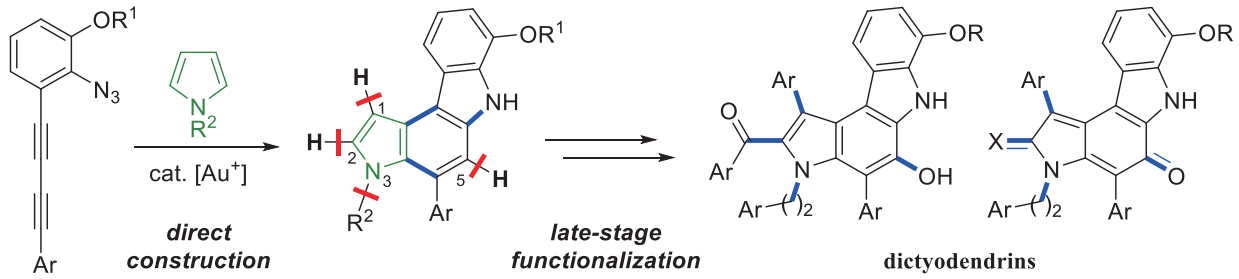
Dictyodendrins consist of a highly substituted pyrrolo[2,3-*c*]carbazole core, the complexity of which has attracted considerable interest of synthetic chemists. Several total syntheses of dictyodendrins have been reported to date, which rely on the introduction of several optimally placed substituents prior to the construction of the pyrrolo[2,3-*c*]carbazole core. We envisaged that the development of a diversity-oriented synthesis for the construction of these natural products based on the early-stage construction of the core structure would be more amenable to medicinal applications.
In this presentation, we will present total and formal syntheses of dictyodendrins based on the direct construction of the pyrrolo[2,3-*c*]carbazole core by the gold-catalyzed annulation of a conjugated diyne with a pyrrole to form three bonds and two aromatic rings. The subsequent introduction of substituents at the C1 (Suzuki–Miyaura coupling), C2 (addition to aldehyde), N3 (alkylation) and C5 (Ullman coupling) positions led to total syntheses of dictyodendrins B, C (formal), D (formal), E (formal), and F.[1, 2]



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5P-079

Synthetic Study of Fairy Chemicals

Hitoshi Ouchi[1], Takuya Namiki[1], Tomohiro Asakawa[2], Makoto Inai[1],
Fumihiko Yoshimura[1], Jae-Hoon Choi[3], Hirokazu Kawagishi[3] and Toshiyuki Kan[1,*]

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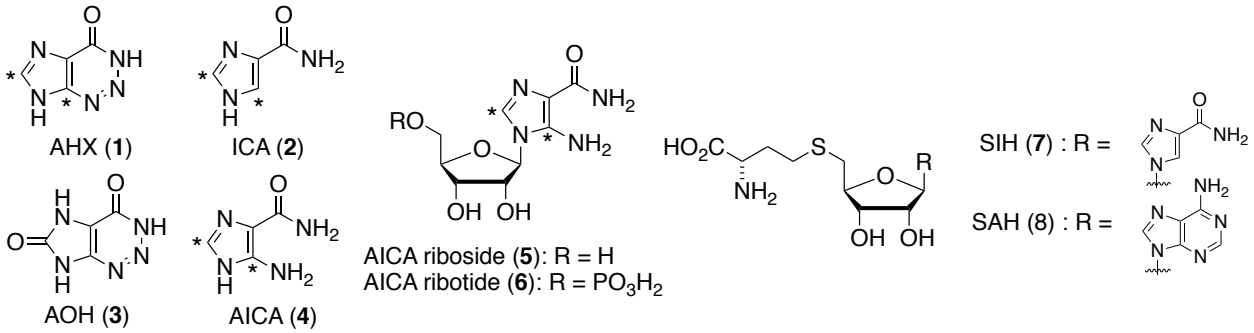
Rings or arcs of fungus-stimulated plant growth occur often on the floor of woodlands, in agricultural areas and in grasslands worldwide, which are commonly called "fairy rings". Recently, Kawagishi and co-workers identified 2-Azahypoxanthine (AHX, **1**), imidazole-4-carboxamide (ICA, **2**) and 2-aza-8-oxohypoxanthine (AOH, **3**) as specific plant growth regulators in a fairy-ring forming fungus *Lepista sordida*. They also found that these three compounds, called fairy chemicals (FCs), endogenously exist not only in specific fungi, but also in various plants and are biosynthesized via a new purine metabolic pathway. [1-3]

Our research group synthesized FCs and its derivatives for the purpose of various investigation of FCs. At first, we examined about large-scale synthetic method of FCs to carry out field experiment and achieved to develop a hundred gram scale synthetic method. Next, we synthesized some expected biosynthetic intermediate such as riboside (**5**), ribotide (**6**) and its ^{13}C-labeled compounds (**1**,**2**,**4**-**6**) to reveal the actual biotransformation in plants. Using our synthetic compounds as authentic samples of LC-MS analysis or as substrate of uptake examinations, we proved new purine metabolic pathway connect with FCs.[4] Furthermore, we synthesized the metabolite of FCs, *S*-ICA ribosyl homocysteine (SIH, **7**), due to the structural similarity of *S*-adenosyl homocysteine (SAH, **8**), which has important pharmaceutical activity. The bioactivities of synthesized **7** and its derivatives are under investigation.



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A Biocatalytic Highly Enantioselective Synthesis of Axially Chiral Bihydroxycarbazoles

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[b]*The Institute of Scientific and Industrial Research (ISIR), Osaka University, Mihogaoka, Ibaraki, Osaka 567-0047, Japan*
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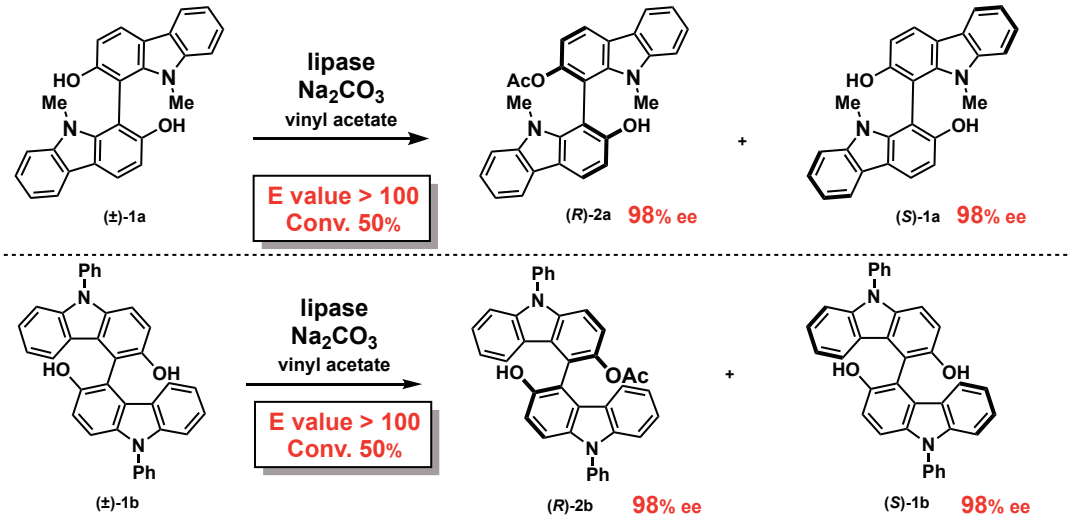
Bihydroxycarbazoles are found in various natural products and have a variety of biological activities such as anti-biotic, anti-bacterial, anti-yeast activities, and free-radical scavenging acitivity.[1] Many efforts have been made to develop the synthesis of these compounds, whose majority include the oxidative coupling of hydroxylcarbazoles using metal catalysts containing V, Fe, etc.,[2] however, only few reports have been made regarding the asymmetric synthesis of bihydroxycarbazoles.[3]

Very recently, we have developed lipase-catalyzed acylative kinetic resolution of axially chiral biaryl diols, in which the use of Na_2CO_3 was essential to dramatically enhance the reactivity of the lipases.[4] In this symposium, we will report the first example of an efficient lipase-catalyzed kinetic resolution of racemic bihydroxycarbozoles to prepare their optically active enantiomers with up to 98% ee.



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[4] a) S. Akai et al., *RSC Adv.* **2019**, *9*, 1165. See also: b) S. Akai et al., *Angew. Chem. Int. Ed.* **2018**, *57*, 10278.

5P-081

Planar-Chiral Phosphine-Olefin Ligands Exploiting a (Cyclopentadienyl)manganese(I) Scaffold: Application in Asymmetric Catalysis

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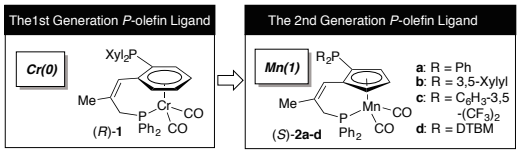
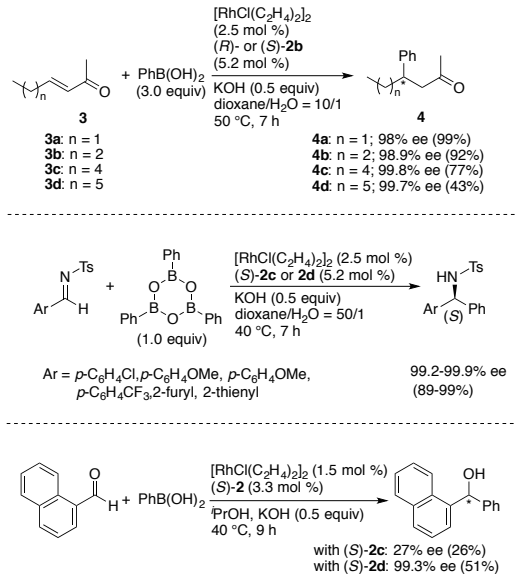
Enantioselective reactions catalyzed by chiral transition-metal complexes are very powerful methods to supply various chiral building blocks in modern organic synthesis. The most common method for chiral modification of transition-metal catalysts is introduction of appropriate chiral ligands onto a metal center, and thus, design and synthesis of new chiral ligands, which could provide high activity and high enantioselectivity for the metal catalysts, has been a central subject in the development of asymmetric reactions. In 2014, we developed highly effective chiral phosphine-olefin ligand (*R*)-**1** which was based on the planar-chiral (arene)chromium scaffold. Ligand (*R*)-**1** showed very high enantioselectivity and reactivity in the rhodium-catalyzed asymmetric 1,4-addition reaction of cyclohexenone with phenylboronic acid (99.5% ee, 98%).[1] While planar-chiral (arene)chromium-based ligands (*R*)-**1** showed the very high performance in the series of cyclic enones and related substrates, it was realized that (*R*)-**1** had some drawbacks in terms of the substrate scope and its robustness. Thus, we next developed a new family of chiral phosphine-olefin bidentate ligands **2**, whose chirality is based on a planar-chiral (η^5-cyclopentadienyl)manganese(I) dicarbonyl scaffold.[2] Ligand **2** shows the better robustness as well as the higher enantioselectivity over homologous (η^6-arene)chromium(0)-based ligands **1**. Ligand **2b**, which is with bis(3,5-dimethylphenyl)phosphino group on the cyclopentadienyl ring, shows very high enantioselectivity in the rhodium-catalyzed asymmetric 1,4-addition reactions of arylboronic acids to various cyclic and acyclic enones to give the corresponding arylation products in up to 99.9% ee. Ligands **2c** and **2d** are suited for the rhodium-catalyzed asymmetric 1,2-addition reactions of the arylboron nucleophiles to imines or aldehydes showing up to 99.9% ee selectivity.

Figure 1. Design of second-generation phosphine-olefin ligands (*S*)-**2** based on the (cyclopentadienyl)manganese(I) framework



Scheme 2. Rhodium-Catalyzed Asymmetric 1,2-/1,4-Addition of Phenyl Nucleophile



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5P-082s

Benzylic Oxidation and C-H Functionalization of Xanthenes using Hypervalent Iodine(III) Reagents

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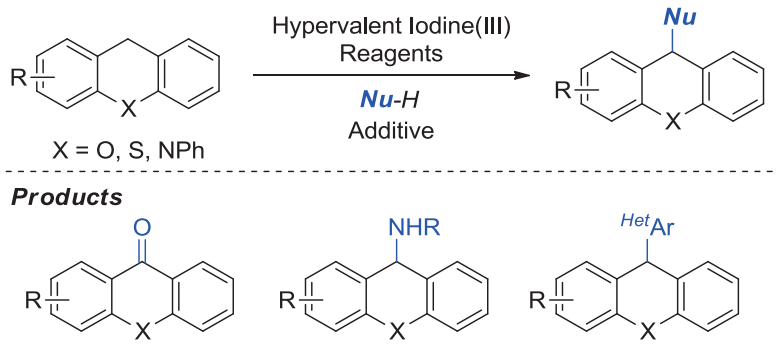
Xanthenes and their benzyl-functionalized derivatives are widely found in biologically active compounds, organic functional materials and dyes. So far, some groups have developed direct functionalizations at the reactive benzylic positions; The C-C bond formations with carbonyl compounds via radical species were reported using suitable oxidant.[1] Arylation of xanthenes has been achieved by combination of palladium catalyst and copper oxidant.[2] Very recently, de Bruin et al. reported the oxidative benzylic C-H amination of xanthene derivatives by using tetrachloro-*p*-benzoquinone as the oxidant,[3] while development of a more unified method for installing various functionalities into xanthene derivatives is strongly desired. On the other hand, our group previously reported aqueous benzylic C-H oxidation to give aryl ketones utilizing hypervalent iodine(III) reagents in the presence of potassium bromide and montmorillonite-K10.[4] In this reaction, reactive hypervalent iodine(III) species from water-insoluble polymeric iodosobenzene $[PhIO]_n$ and KBr[5] are considered as the key radical initiator.

To expand this reaction to xanthene functionalizations, we have investigated benzylic oxidation and sulfonamidation using $[PhIO]_n$ and phenyliodine(III) diacetate (PIDA) using water and sulfonamides as nucleophiles. The use of thienyl and indolyl iodonium(III) salts with Lewis acid has also caused heteroarylation at benzylic position of xanthenes to produce heteroaryl-functionalized compounds. We present in this conference the details about these oxidative C-H functionalizations utilizing hypervalent iodine(III) reagents.



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Tertiary Alkylations of Aldehydes, Ketones, or Imines Using Organoboronates and Base Catalyst

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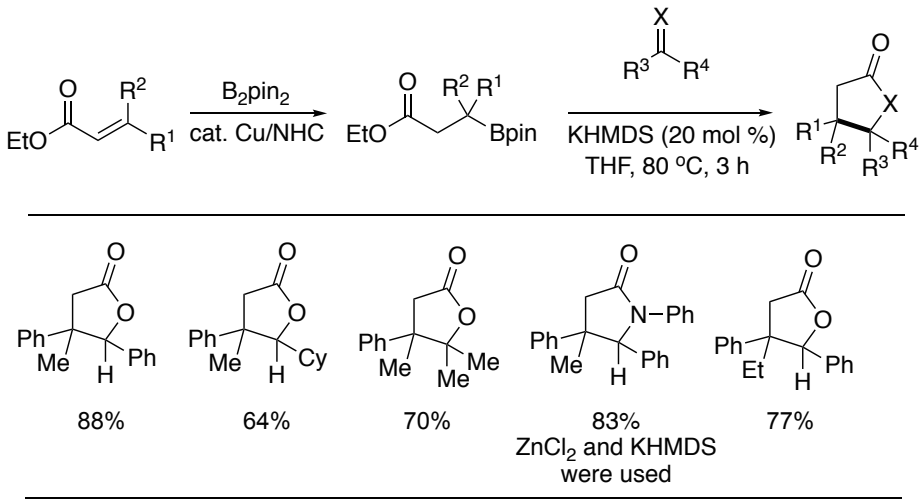
The demand for construction of sp^3-carbon-rich chemical scaffolds in pharmaceuticals and bioactive natural products has been recently increased. The C(sp^3)–C(sp^3) bond formation using tertiary alkyl organometallic nucleophile is a direct and reliable approach for highly congested sp^3-carbon-rich chemical scaffolds. Tertiary alkylboron compounds are particularly attractive organometallic reagents because of their high chemical stability and broad availability. Recent progress in the catalytic preparation of tertiary alkylborons from various simple organic molecules is remarkable. Nevertheless, the catalytic C(sp^3)–C(sp^3) bond formation using tertiary alkylborons is still in its infancy with limited progress.

In our study on new methodology based on the formation of a secondary α-alkoxyalkyl anion from aldehyde,[1,2] we have turned our attention to the generation of a tertiary alkyl anion and its application to C(sp^3)–C(sp^3) bond formation. This paper reports tertiary alkylations of aldehydes, ketones, or imines using organoboronates and base catalyst. The reaction involves the generation of tertiary alkyl anions from organoboronates under mild and transition-metal-free reaction conditions. The protocol allowed the simple and efficient construction of highly congested contiguous sp^3-carbon centers. The tertiary alkylboronates are available through the established catalytic conjugate borylation of β,β-disubtituted α,β-unsaturated carbonyls, and thus the overall process represents a reductive umploung β-functionalization of the α,β-unsaturated carbonyls.



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An Iridium-Catalyzed Reductive Nucleophilic Addition to Amides

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Amide has been recognized as a ubiquitous chemical structure often seen in natural products and pharmaceuticals. Recent extensive study of peptide drugs renders amides more important targets for the synthetic research. In this presentation, we report an iridium-catalyzed reductive nucleophilic addition to tertiary amides, *N*-alkoxyamides and secondary amides.

Treatment of tertiary amide **1** with a catalytic amount of the Vaska complex [IrCl (CO)(PPh_3)$_2$] and TMDS [$(Me_2HSi)_2O$] initiated hydrosilylation of the amide carbonyl forming enamine **2** via the *N*,*O*-acetal. [1] Subsequent addition of the silyl ketene acetal and PPTS to enamine **2** gave multi-substituted amine **3**. [2] The developed conditions were applicable to *N*-alkoxyamides **4** (**4**→**5**→**6**).

The hydrosilylation of secondary amide **7** took place with [Ir(COE)$_2$Cl]$_2$ and Et_2SiH_2 to form imine **8**, which underwent nucleophilic addition to give secondary amine **9**.

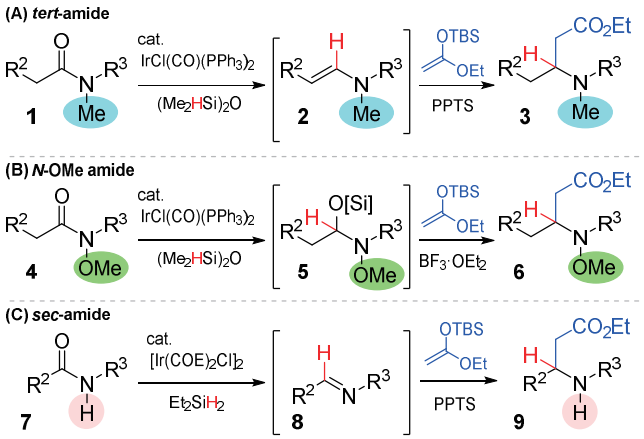

Fig. 1 Reductive nucleophilic addition to amides

Considering the application to peptides, we investigated differentiation of two types of amides in a single molecule. Amide **10** possessing tertiary- and *N*-alkoxyamides was subjected to the reductive Mannich reaction with the Vaska complex and TMDS. The reaction proceeded with complete tertiary amide selectivity to give aminoester **11** in 90% yield. Subsequent reductive Strecker reaction with TMSCN and $BF_3 \cdot OEt_2$ afforded aminonitrile **12** in 96% yield.

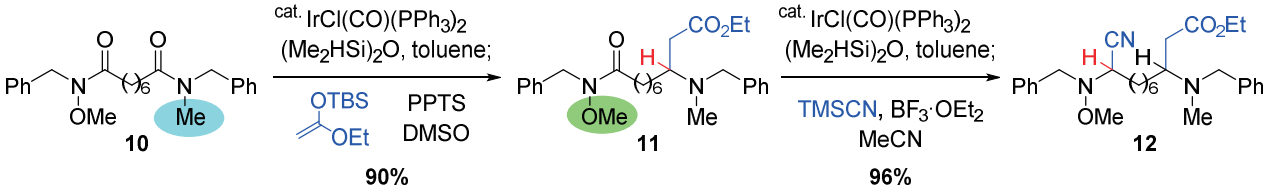

Fig. 2 Site selective transformation in the presence of tertiary amide and *N*-alkoxyamide

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5P-085s

N^2-Selective Alkylation of Benzotriazoles via Cobalt Catalyzed Hydroamination Reaction of Non-Activated Olefins

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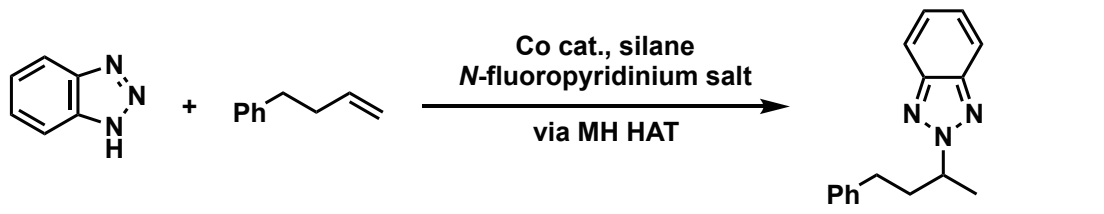
Suita, Osaka 565-0871, Japan

Benzotriazole and its derivatives are important skeletons found in medicines with a variety of biological activities, and their functional group introduction and/or conversion reactions are important research subjects in synthetic organic chemistry and medicinal chemistry. Among them, N^2-alkylated benzotriazoles have various biological activities. To obtain the N^2-alkylated benzotriazoles, alkylation of benzotriazoles is one of the simplest methods. Unfortunately, in contrast to N^1-selective alkylation, N^2-selective alkylation is so difficult due to a decrease in the aromaticity of the N^2-alkylated benzotriazoles, and there have been few reports to date.[1] Most reported alkylation occur at the N^1-position or in a non-selective manner. Therefore, the N^2-selective alkylation is a challenging research theme.

Metal hydride hydrogen atom transfer (MH HAT) is a synthetically useful method for the Markovnikov-selective hydrofunctionalization of olefins.[2] This reaction generally proceeds chemo- and regioselectively under mild conditions. Various hydrofunctionalization of olefins via MH HAT have been developed, but there are few examples of intermolecular hydroamination.[3] Therefore, we decided to study the hydroamination reaction of olefins via MH HAT to achieve N^2-selective alkylation of benzotriazole.

We started our project on the MH HAT reaction of benzotriazole and 4-phenyl-1-butene. After screening a range of conditions, we found that the reaction proceeds by using a cobalt-salen catalyst, silane and an *N*-fluoropyridinium salt. Fortunately, we obtained the alkylated benzotriazole as a single regioisomer, in which a coupling reaction proceeded regioselectively between the 2-position nitrogen of benzotriazole and the inner carbon of the olefin. The details of this reaction, the substrates scope and application of this method will be discussed.



N^2-Alkylated Benzotriazole

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5P-086s

Nonmetal-Catalyzed Skeletal Reorganization of 7-En-2-ynones into 3-Alkylidenecyclohexenes

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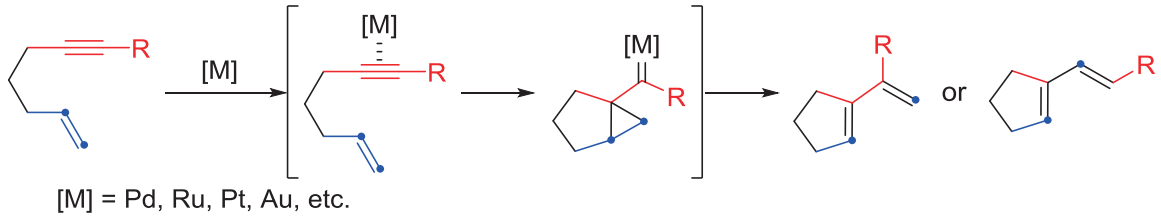
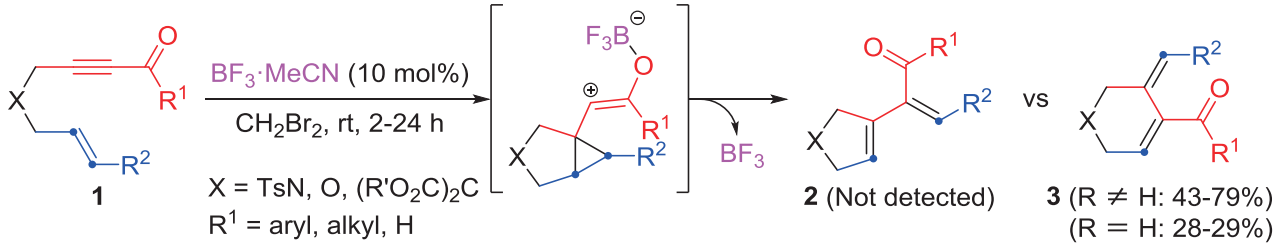
Koganei, Tokyo 184-8588, Japan

The skeletal reorganization of 1,6-enynes, which is regarded as a formal metathesis, allows an atom economical method for the construction of the cyclic conjugated dienes.[1] This reaction has been reported to be catalyzed by various π-acidic metal complexes (Scheme 1). Interestingly, Fürstner *et al.* disclosed the synthesis of the cyclic dienes by the skeletal reorganization of 1,6-enynes having cyclooctene with HBF_4 or $BF_3 \cdot OEt_2$. However, the systematic studies on the skeletal reorganization using nonmetal-catalysts have been unknown.[2]



Scheme 1

As a novel extension of our researches on the metathesis reactions between alkynes and heteroenes,[3] we examined the skeletal reorganization of enynes bearing electron-deficient alkynes by nonmetal-catalysts. As a result, in the presence of $BF_3 \cdot MeCN$ (10 mol%), the desired reactions of 7-en-2-ynones **1** smoothly proceeded in dibromomethane at room temperature to afford the corresponding 3-alkylidenecyclohexenes **3** in good yields. Since the synthesis of 3-alkylidenecyclohexene from 7-en-2-ynone derivatives via such a cleavage of carbon-carbon double bonds has not been reported, the present results would provide useful findings in organic synthesis chemistry.



Scheme 2

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5P-087

Synthesis of 4-Aroyl-5-arylpyrazoles and 4-Aroyl-3-arylpyrazoles via the Reaction of Enaminodiketones with Substituted Hydrazines

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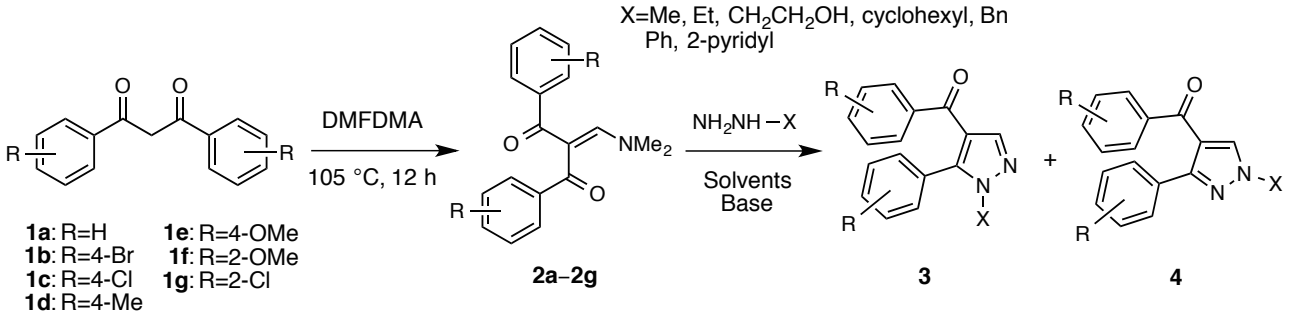
[a]*Graduate School of Pharmacy Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-0292, Japan.*
[b]*Department of Biochemistry, Kawasaki Medical School, Kurashiki, Okayama, 701-0192, Japan.*
[c]*Faculty of Pharmaceutical Sciences, Yokohama University of Pharmacy, 601 Matano, Totsuka-ku, Yokohama 245-0066, Japan.*

Pyrazole, as well as other five-membered heterocyclic compounds, is an important heterocycle in the medicinal field. In fact, owing to this diversity of biological activities, pyrazole and its derivatives have attracted much attention from medicinal chemists.[1] Many efforts for synthesis have been reported in review articles thus far concerning pyrazole and its derivatives.[2] Among these, many synthetic approaches for a pyrazole ring included the reaction of either 1,3-dicarbonyl compounds or their synthetic equivalents with hydrazine derivatives.[3] We previously reported the synthesis of symmetrical 1,3-dicarbonyl compounds, which are dibenzoylmethane derivatives, for the assay of antimutagenicity.[4] We planned a new way to utilize these symmetrical 1,3-dicarbonyl compounds, dibenzoylmethanes **1a**-**g**, and found that the enaminodiketone **2a**-**g** derived from dibenzoylmethanes **1a**-**g** with dimethylformamide dimethyl acetal (DMFDMA) is of interest as a precursor for a new mode of substituents of five-membered pyrazole derivatives. We here describe the regioselective synthesis of two isomers, 4-aroyl-5-arylpyrazoles **3** and 4-aroyl-3-arylpyrazoles **4**, which are provided by the reaction of symmetrical enaminodiketones **2a**-**g** with substituted hydrazines.[5]



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5P-088

Synthetic Strategy for Highly Substituted Indoles based on Regioselective Coupling of Iminoquinone Monoacetals

Tohru Kamitanaka,[1] Natsuki Toda,[2] Yuriko Fujita,[2] Yusuke Tsunoda,[2] Toshifumi Dohi,[1,2] and Yasuyuki Kita[1]

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[2] *College of Pharmaceutical Sciences, Ritsumeikan University*

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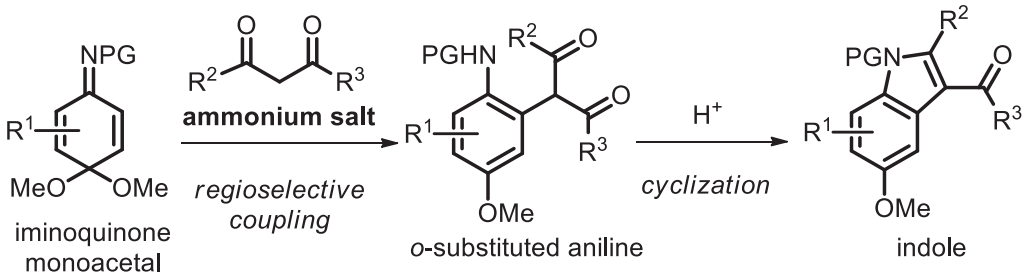
Iminoquinone monoacetals exhibit various unique reactivities arising from the two electrophilic functional groups, α,β-unsaturated imine and allyl acetal moieties, in one ring skeleton. Therefore, iminoquinone monoacetals represent the versatile precursor for the synthesis of nitrogen-containing aromatic compounds. However, control of the regioselectivity is somewhat difficult because all the ring carbon atoms have electrophilic nature. On the other hand, our group reported the utilization of iminoquinone monoacetals in the early 1990s, that is, the synthesis of indoles by the intramolecular condensation of the nitrogen group with the carbonyl group of quinone monoacetals (QMAs) followed by aromatization.[1] Moreover, our group reported the oxidative coupling of aniline derivatives with π-carbon nucleophiles for the synthesis of indoline and indole derivatives.[2] We now extend the strategy to regioselective coupling of iminoquinone monoacetals with nucleophiles for the synthesis of nitrogen-containing aromatic compounds. As the regioselective introduction of nucleophiles into quinone derivatives, we developed the coupling reactions of QMAs promoted by Brønsted acids in 2011,[3] and subsequently applied them to the synthesis of various aromatic compounds.[4,5] Based on these reactions, we tried the regioselective introduction of 1,3-dicarbonyl compounds into iminoquinone monoacetals. As a result, *ortho*-substituted aniline derivatives could be obtained by the aid of specific ammonium salt as the mild acid promotor. Subsequent acid-catalyzed cyclization of the coupling products could afford the highly functionalized indoles.



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5P-089s

Synthetic study of silybins

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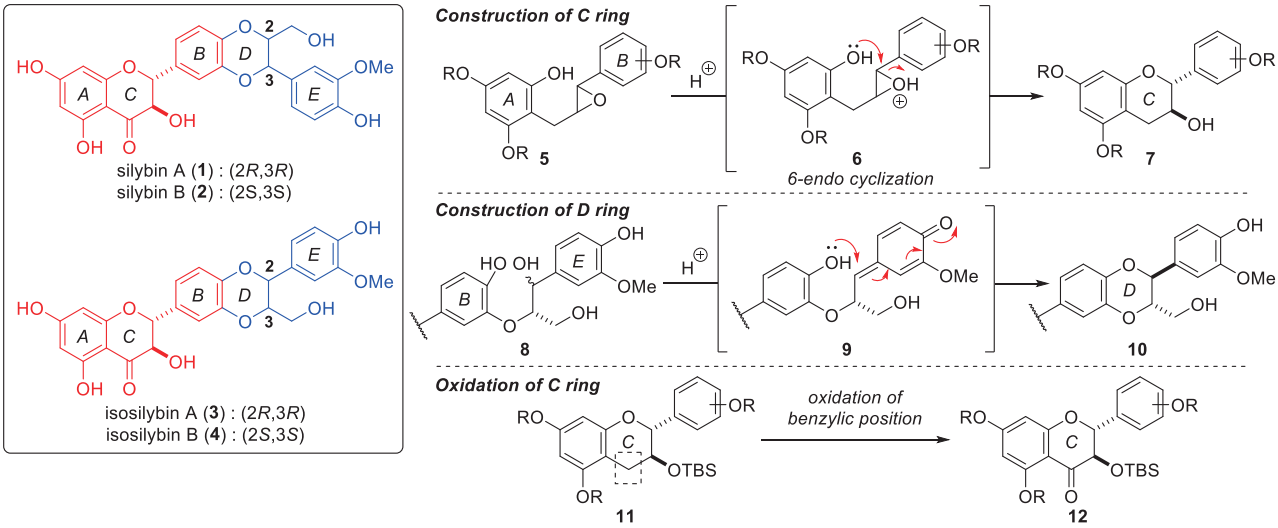
Flavonolignans, silybins A (**1**) and B (**2**) and isosilybins A (**3**) and B (**4**) are isolated from the seeds of milk thistle (*Silybum marianum*), [1] which possessed strong hepatoprotective activity. These unique hybrid polyphenols are composed from hydroxyflavanone and 1,4-benzodioxane lignan. Structure determination of the relative stereochemistry of these hybrid polyphenols was performed by detailed NMR analysis and the absolute configuration was estimated by comparison of the CD values with similar monomer lignans. During the course of our synthetic investigation of hybrid polyphenols, combination of stereoselective synthesis and comparison with CD values including the theoretical simulation was enable for the confirmation of absolute configuration. Encouragement with these backgrounds, we started synthetic study of flavonolignans silybins.

For the total synthesis of silybins, we envisioned that construction of dihydrobenzopyran ring (C-ring) and 1,3-benzodioxane ring (D-ring) would be accomplished by an application of our synthetic methods[2],which were developed by polyphenol synthesis. During the course of our tea catechin synthesis, we found that 6-endo cyclization of **6** proceeded smoothly by acid treatment of epoxy-phenol **5** to provided **7** in stereoselective manner. In our princepin synthesis[3], the diastereoselective construction of 1,3-benzodioxane ring was performed by cyclization of the quinonemethide intermediate **9** which was generated by the acid treatment of benzyl alcohol **8**. Oxidation of benzylic position of dihydrobenzopyran ring was suitable for the combination DDQ and AZADO oxidation of **11** provided flavanone **12**.



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5P-090

Hypervalent Iodine(III) Induced Oxidative Cross-Coupling of Phenols

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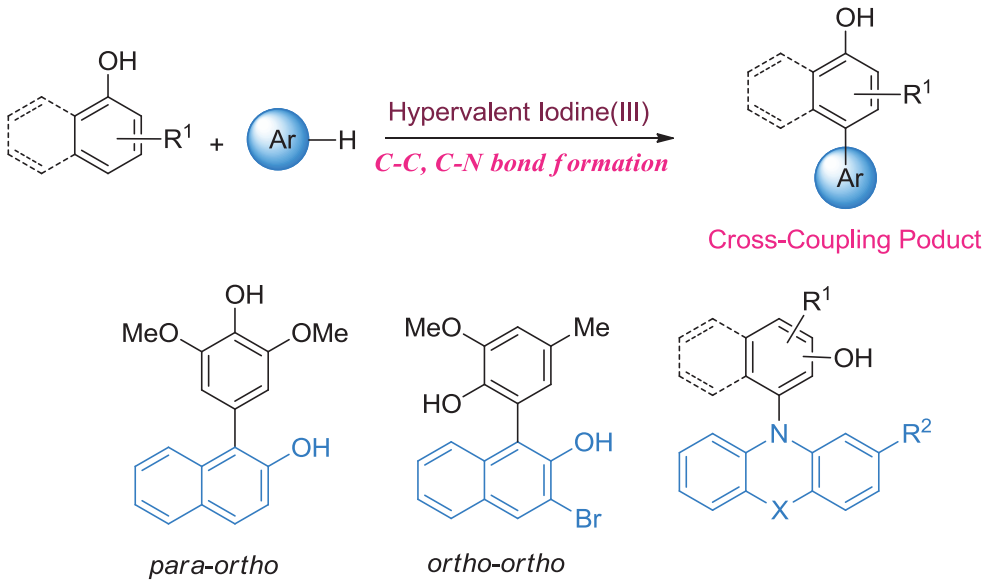
Phenol biaryls are important fragments found in a wide range of compounds such as natural products, and ligands for transition-metal catalysts. Therefore, the oxidative cross-coupling reaction by activation of the C-H bond of phenols is an attractive method for the synthesis of biaryls that avoids prefunctionalization of the starting material as compared to transition metal catalyzed cross-coupling reactions. However, oxidative cross-coupling of phenols has several difficulties. That is, the oxidation of starting material forms undesirable homo-coupling product, and over-oxidation of the coupling product sometimes occurs because of the lower oxidation potential of the product than that of the starting material. Therefore, development of an efficient oxidative cross-coupling reaction of phenols is challenging in organic synthesis. In our previous work, we developed a new synthetic method that enables the metal-free C-H/C-H' cross-coupling of two aromatic compounds using hypervalent iodine(III) reagents.[1] In this poster session, we present the recent progress in the oxidative cross-coupling reaction of phenols using hypervalent iodine reagent (Scheme 1). [2,3]



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5P-091s

Efficient *N*-Arylation of Azole Compounds utilizing Designer TMP-Iodonium(III) Salts

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Yasuyuki Kita[2] and Toshifumi Dohi[1, 2]

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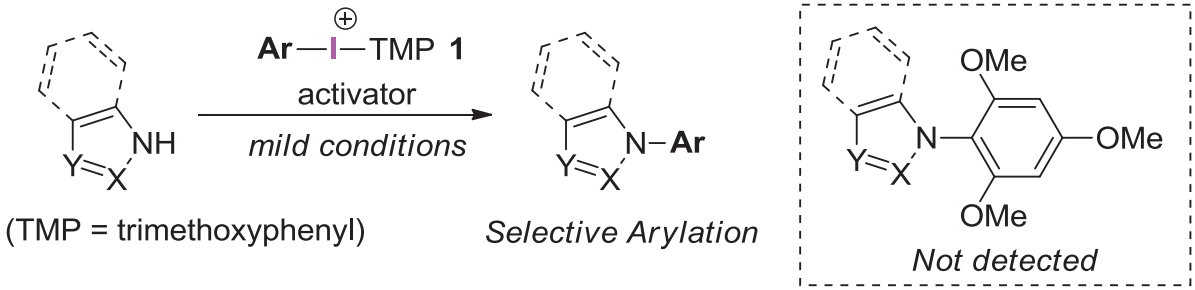
The C-N bond-forming reaction is an important strategy for constructing *N*-aryl azole structures, which are found in not only bioactive compounds, but also functional molecules and valuable ligands. Despite harsh reaction conditions, Ullmann-type aminations were typically used for this purpose. Buchwald-Hartwig amination is more recently used, while the reaction requires pre-functionalized aryl compounds. Other aryl sources, such as arylboronic acid, aryllead, arylbithmuth, arylsiloxane, are also used in Chan-Lam-type coupling reactions for realizing mild reaction conditions.

Diaryliodonium(III) salts represent a class of useful aryl sources with practical applications in synthetic chemistry, polymer synthesis, and materials sciences. These iodonium(III) salts are useful for the coupling reactions with metal catalyst and nucleophilic substitution reactions because of their high reactivities.[1] In these reactions, diaryliodonium(III) salts are more reactive than aryl halides toward nucleophiles, bases, and organometallic reagents. Recently, their high reactivities drew a considerable attention from synthetic chemists working on challenges in the practical applicability of the aryl-coupling processes. We previously developed a convenient procedure for synthesizing diaryliodonium(III) salts in fluoroalcohol solvent, in which a variety of symmetrical and unsymmetrical salts can be prepared under mild conditions.[2]

In 2000, Kang and co-workers reported the first example of preparation for *N*-aryl azoles for limited numbers of diaryliodonium(III) salts.[3] We recently found that aryl(TMP)iodonium(III) salts **1** (TMP: 2,4,6-trimethoxyphenyl) show high reactivity accompanied with complete aromatic ring-selectivity in metal-free coupling reactions.[4] We now present selective *N*-arylation of azole compounds utilizing designer TMP-iodonium(III) salts **1** to give *N*-aryl azole compounds under mild conditions.



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5P-092s

N-Glycosylation Reaction of Thioglycoside using Hypervalent Iodine(III) Reagent

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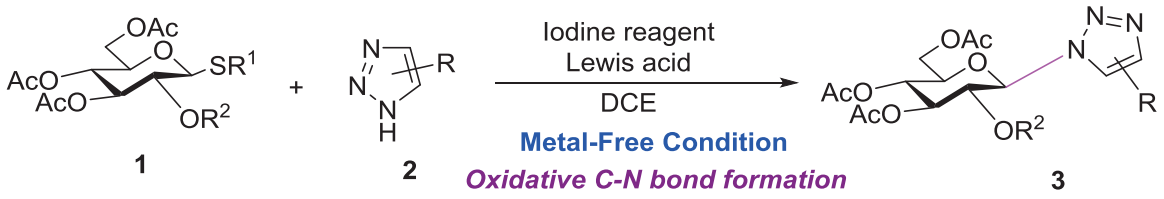
Glycosyl triazoles are used as inhibitors against glycosyltransferases and a part of complex neoglycoconjugates. In the latter, triazole groups are mostly defined as biologically inactive linkers. Moreover, various glycosyl triazoles have been employed as useful glycosyl donors in glycosylation reaction. Thus, the development of efficient methods for targeting the glycosyl triazoles via formation of C–N bonds is highly fascinating for organic chemistry. To date, 1,4,5-trisubstituted 1,2,3-triazoles have been prepared through the classical Huisgen [3+2] cycloaddition of glycosyl azides and activated symmetrical alkynes such as dimethyl acetylene dicarboxylate. Recently, oxidation with the environmentally-benign hypervalent iodine(III) reagent has witnessed profound progress in organic chemistry. The low toxicity, ready availability, and easy handling of the reagents are expected to be useful feature for the activation of sulfur atom. We have been engaged in the development of the oxidation of the sulfur atom utilizing hypervalent iodine(III) reagents and reported, recently, glycosylation reaction of thio–glycoside using hypervalent iodines.

During the study on the glycosylation reaction, we found the reaction of phenyl thio–glycoside and triazoles in the presence of hypervalent iodine(III) and Lewis acid. The C-N bond formation reaction proceeded to give β-glycosyl azoles in a good yield. Details will be discussed in the presentation.



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5P-093s

Glucuronidation Reaction Using Odorless Thio-glycoside and Hypervalent Iodine Reagent

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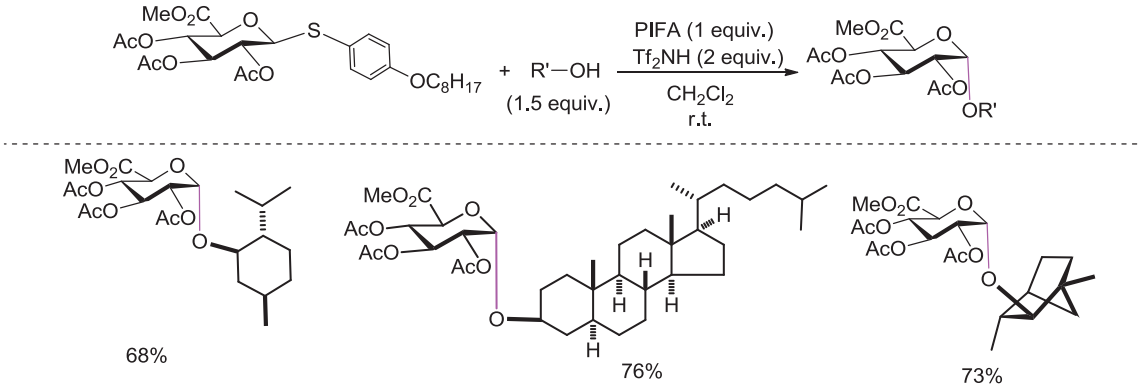
Recent development of glycosciences revealed that complex oligosaccharides on cell surfaces play important roles in biological events concerning cell-cell adhesions. Moreover, medicines having glycosidic bonds or glycosyl structures have become widely used to treat some specific diseases such as diabetes and influenza virus infection. To synthesize the glycosyl derivatives, the chemistry of thioglycosides has been well developed in the past two decades because of their stability and easiness of preparation; however, the large scale preparation of thioglycosides and glycosylation reaction requires quite tedious procedures on handling odorous organo sulfur compounds, *e.g.*, trimethylsilylmethyl sulfide or benzenethiol in each steps. Therefore, we tried to replace the aglycone source of thioglycosides with odorless *p*-octyloxybenzenethiol to solve the problem. On the other hand, N-iodosuccinimide (NIS)/TfOH has been widely used to promote the thioglycosides, while few were reported on glycosylation using hypervalent iodines reagent, which are environmentally-benign and bear much more diverse reactivities than NIS. On the basis of these background, we have reported glycosylation reactions using hypervalent iodine reagents.[1] Herein, we embarked on glucuronidation reaction which has been performed via oxidation of the C–6 hydroxyl group of glucosides. As a result, glucuronidation reaction using *p*–octyloxyphenyl thio-glucuronide as a glycosyl donor and 1 equivalent of phenyliodine bis(trifluoroacetate) (PIFA) with 2 equivalent of Tf_2NH as an activator afforded desired glucuronides with α–configuration in good yields.[2] Details will be discussed in the presentation.



[1] T. Kajimoto, K. Morimoto, R. Ogawa, T. Dohi, Y. Kita, *Eur. J. Org. Chem.*, **2015**, 2138.; *Chem. Pharm. Bull.*, **2016**, *64*, 838.

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5P-094s

Cholesterol Dependent Membrane Interaction of Diosgenyl Saponins

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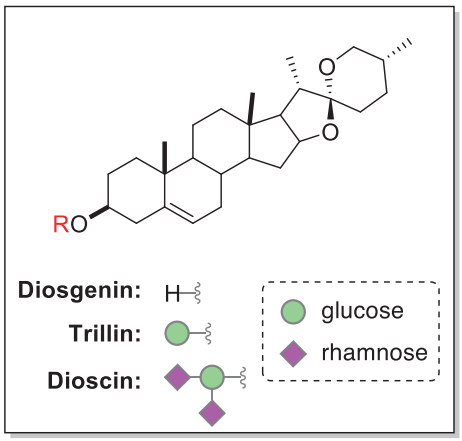
Toyonaka, Osaka 560-0043

The diosgenyl saponins (DG) can be obtained abundantly in plants such as *yams (Dioscorea* sp.) and *fenugreek (Trigonella foenum-graecum)*. These saponins possess a diosgenin (DS) aglycone with a spirostanol structure (Fig. 1) and have been studied extensively for their pharmacological benefits [1]. Previously, our group studied a unique saponin, OSW-1, as well as a steroidal saponin, digitonin. Both the saponins require membrane Cho to exert their activities. In the presence of cholesterol, OSW-1causes deformation yet preserves the overall integrity of the membrane, while digitonin strongly disrupts membrane integrity.[2]



The aims of this study are to extend the understanding of the membrane activities of saponins with more general steroidal core, particularly their interaction with Cho in the membrane environment and to elucidate the structural effect of the aglycone as well as the sugar residues on the activity. A host of biophysical techniques such as solid-state NMR, differential scanning calorimetry (DSC) and fluorescence spectroscopy were used to study the interactions of DS with Cho and evaluate the effect of these compounds towards membrane dynamics.

Solid-state ^{2}H NMR verified the membrane-activity dependence of saponin on the Cho content in POPC membranes as well as the escalating strength of saponin-Cho interaction as the number of sugar units of the saponin increased. ^{31}P NMR showed the partial membrane deformation induced by trillin with one sugar residue, but a more pronounced membrane curvature was facilitated by dioscin with three sugars. Interestingly, trillin has shown to increase the rigidity of the membrane more strongly compared with dioscin as revealed by Laurdan GP fluorescence results. DSC measurements revealed that 1) the interaction of diosgenin (DS) with DMPC was similar to that of Cho, and 2) in the presence of DG, membrane perturbation was augmented by an increasing Cho content.

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5P-095

Limonoids from Andiroba (*Carapa guianensis*) Improve Glucose and Lipid Metabolism in Hepatocytes

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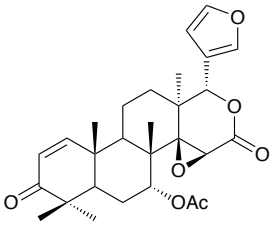
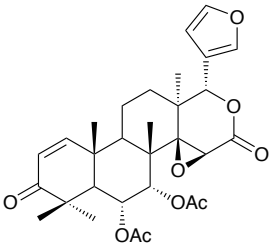
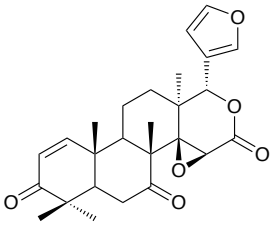
Carapa guianensis Aublet (Meliaceae), known locally as andiroba, is distributed in the tropical rainforests of countries such as Brazil and Colombia. In the course of our studies on the chemical constituents from *C. guianensis*, we have isolated several limonoids, such as gedunin (**1**), 6α-acetoxygedumin (**2**), 7-deacetoxy-7-oxogedunin (**3**), and 7-deacetoxy-7α-hydroxygedunin (**4**), from the seed oil. We have also reported that several limonoids from *C. guianensis* showed cytotoxic, antimalarial, anti-inflammatory, hepatoprotective activities.[1-4] Fatty liver is recognized as a significant risk factor for life style-related disease. There is a strong causal linkage between fatty liver disease and hyperinsulinemic insulin resistance. Thus, fatty liver is considered to be highly associated with obesity and type 2 diabetes. We further evaluated the effect of principal gedunin-type limonoids from the oil of *C. guianensis* on triglyceride content in human hepatoblastoma HepG2. In results, 7-deacetoxy-7-oxogedunin (**3**) and 7-deacetoxy-7α-hydroxygedunin (**4**) showed to reduce triglyceride content markedly. Additionally, peroxisome proliferator-activated receptor (PPAR) a and peroxisomal acyl-coenzyme A oxidase 1 (ACOX1) were found to be upregulated. Limonoids from *C. guianensis* seem to be useful for prevention or improvement of life style-related disease.



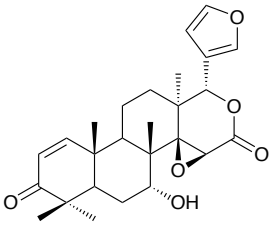
gedunin (**1**)



6α-acetoxygedunin (**2**)



7-deacetoxy-7-oxogedunin (**3**)



7-deacetoxy-7α-hydroxygedunin (**4**)

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5P-096s

Synthetic study of the furanosteroid, viridin

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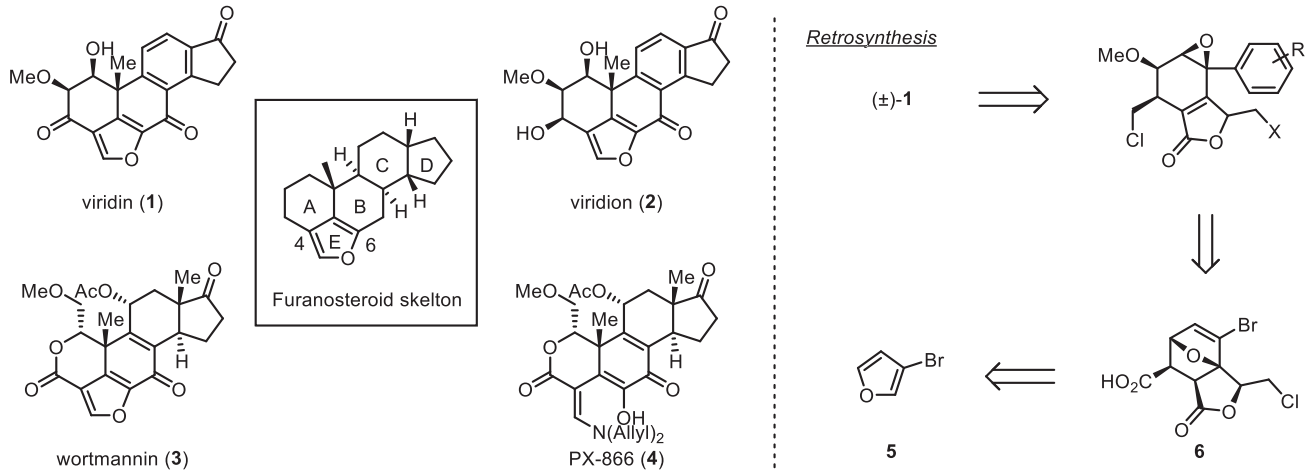
The furanosteroids, viridin (**1**), viridiol (**2**) and wortmannin (**3**), have a characteristic common structure; the steroid scaffold with a furan fused at the C4 and C6 positions. In 1994 and 1996, biological investigations on wortmannin revealed a selective and irreversible inhibition of phosphatidylinositol 3-kinases (PI3Ks).[1-2] PI3K is a family of enzymes located in the upstream of intracellular signaling pathway and is essential for cell growth and development. PI3K gene mutation causes cancer development and progression. A wortmannin derivative, PX-866 (**4**), has advanced to Phase II clinical trials.[3] That have brought the increase of interest in the other furanosteroids, which includes viridin having a potentially higher inhibition effect (IC_{50}=2 nM; wortmannin, IC_{50}=4 nM).[3] Sorensen completed the first total synthesis of viridin and viridiol, in racemic forms [4], and Gurrero succeeded the first enantioselective synthesis of (–)-viridin and (–)-viridiol.[5]

Our synthesis features the utilization of the multi-functionalized tricyclic compound **6**, which is readily available from commercial 3-bromofuran **5**. Some of the worth noting steps include the installation of an aryl moiety on the bromo olefin by Suzuki-Miyaura coupling, stereoselective epoxidation, and the regio- and stereoselective epoxide-ring opening using $AlMe_3$ to construct the consecutive stereogenic carbon centers. Further details of this study will be discussed at the symposium.



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5P-097

Neokotalanol, a Principal Thiosugar Sulfonium Constituent in *Salacia chinensis*, Suppresses HbA1c Levels in Genetically Obese-hyperglycemic *ob*/*ob* Mice

Masakazu Kobayashi[1], Junji Akaki[1,2], Yasuyo Yamaguchi[1], Hiroo Yamasaki[1], Kiyofumi Ninomiya[2,3], Yutana Pongpiriyadacha[4], Masayuki Yoshikawa[2], Osamu Muraoka[2,3], and Toshio Morikawa*[2,3]

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Thiosugars, containing a sulfur atom as heteroatom or a disaccharide linked *via* a sulfur bridge, possess unique physicochemical and biological properties. We have investigated a new class of 1,4-thioanhydrosugar sulfonium, neokotalanol (**1**), and their related analogues from several *Salacia* genus plants, such as *S. raticulata*, *S. oblonga*, and *S. chinensis*. Administration of 0.50% of *S. chinensis* extract for three weeks in KK-A^y mice were found to significantly suppress both blood glucose and HbA1c levels without changes of the body weight and food intake. The mechanism of this effect was revealed to be α-glucosidase inhibition, and neokotalanol (**1**, IC_{50} = 4.0 μM for human small intestinal maltase) and their related analogues were found to be the principal active ingredients.[1] In this study, neokotalanol (**1**) significantly suppressed the postprandial blood glucose in maltose-loaded mice in a dose-dependent manner. To further evaluate their antidiabetic effect, HbA1c levels after chronic administration of **1** in *ob/ob* mice were also examined. As the result, administration of the diet containing 0.0003% neokotalanol (**1**) for 20 days was found to cause significant suppression of HbA1c levels without significantly changes in body weight.[2] On the basis of this evidence, a potent α-glucosidase inhibitor neokotalanol (**1**) was revealed to be the active constituents improving the progress of diabetic symptoms in the obese-hyperglycemic *ob/ob* mice model.

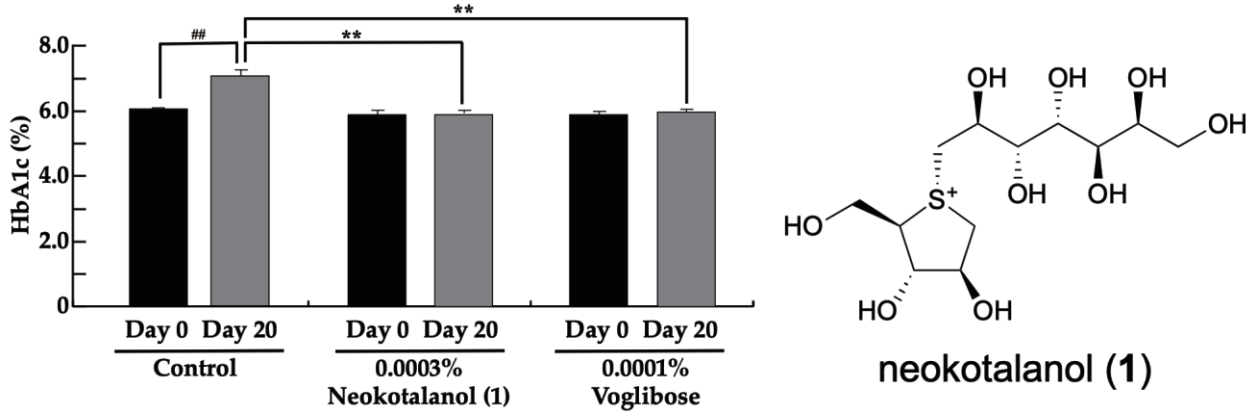

Fig. 1. Effects of **1** and voglibose on HbA1c levels after 20 days administration in ANI-93M purified diet-fed *ob*/*ob* mice
All values are means ± SEM (n = 6), Significantly different from control at day 0, $^{\#\#}p < 0.01$ or from control at day 20, $^{**}p < 0.01$ (Dunnett's test).

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5P-098

Development of novel acyl-transfer catalysts for protein modification

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Chemical modifications of proteins, particularly those of lysine residues, play an important role in the life science. For example, introduction of a fluorescent label or a purification tag enables visualization, functional elucidation, and proteomics analysis of the proteins in cells. In addition, acetylation and methylation of histone lysine residues are important post-translational modifications, and constitute the fundamental regulatory element of the cellular functions via gene transcription. A chemical means to enable the protein modifications is, therefore, highly desirable.

In 2017, we reported two chemical catalyst systems to introduce lysine acylations into histones (SynCAc[1] and DSH[2]) based on an *N*,*N*-dimethylaminopyridine (DMAP) skeleton as an acyl transfer nucleophilic catalyst center. Although these catalyst systems can acylate lysine residues of the histone proteins under physiological conditions, more active catalysts have been desired especially for in-cell histone acylation reactions. In organic solvents, higher electron density of the pyridine ring of DMAP derivatives leads to higher nucleophilicity, resulting in more active catalysts. Under physiological conditions, however, DMAP is protonated, and increasing the electron density of the pyridine ring would lead to inactivation of the catalyst due to its increased basicity and protonation. It is, thus, difficult to separate basicity and nucleophilicity of the DMAP derivatives[3].

Herein, we present the novel hydroxamic acid acyl-transfer catalysts for protein modifications. On the contrary to DMAP, this hydroxamic nucleophilic center would be activated through deprotonation and worked as a better nucleophilic catalyst for lysine acetylation under physiological conditions than DMAP. Details of the analysis, a plausible reaction mechanism, and an application to protein modification by a ligand-conjugated hydroxamic acid catalyst will be discussed.

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5P-099

Ent-Kaurane Type Diterpenoids from the Aerial Part of *Isodon trichocarpus* as Proproliferative Agents on Human Follicle Dermal Papilla Cells

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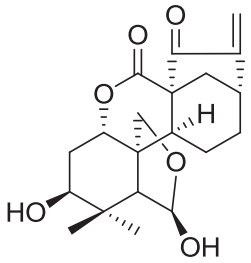
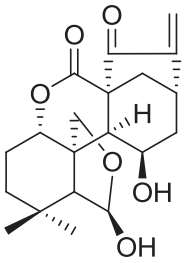
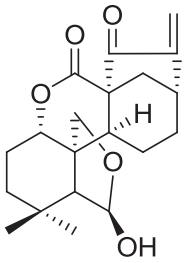
Plants of the genus *Isodon* (syn. *Rabdosia,* Labiatae) are widely distributed and the source of popular folk medicines in Japan and China. In Japan, the aerial parts of *I. japonicus* Hara and *I. trichocarpus* Kudo (common name "enmei-so" in Japanese), which are listed in "The Japanese Standard for Non-Pharmacopoeial Crude Drugs" as the source plants of Isodonis Herba, are used for the treatment of gastrointestinal disorders.[1] We previously reported inhibitory effect of the isolates from the aerial part of *I. trichocarpus* on melanogenesis in theophylline-stimulated B16 melanoma 4A5 cells.[2] In our continuing studies on this natural medicine, we found that the methanol extract showed a significant proproliferative activity against human follicle dermal papilla cells (HFDPCs) at a concentration of 2.5 μg/mL. Through bioassay-guided separation, 14 *ent*-kaurane type diterpenoids, two abietane type diterpenoids and four triterpenoids were isolated. Among the isolates, enmein (**1**), nodosin (**2**), isodocarpin (**3**), and oridonin (**4**) showed the significant activity at 2.5 μM.



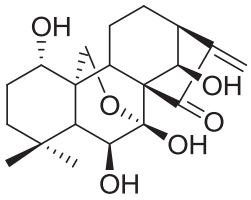
enmein (**1**)



nodosin (**2**)



isodocarpin (**3**)



oridonin (**4**)

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5P-100

Copper-mediated Ring Opening of Thiazolidine Derivative for Protein Chemical Synthesis

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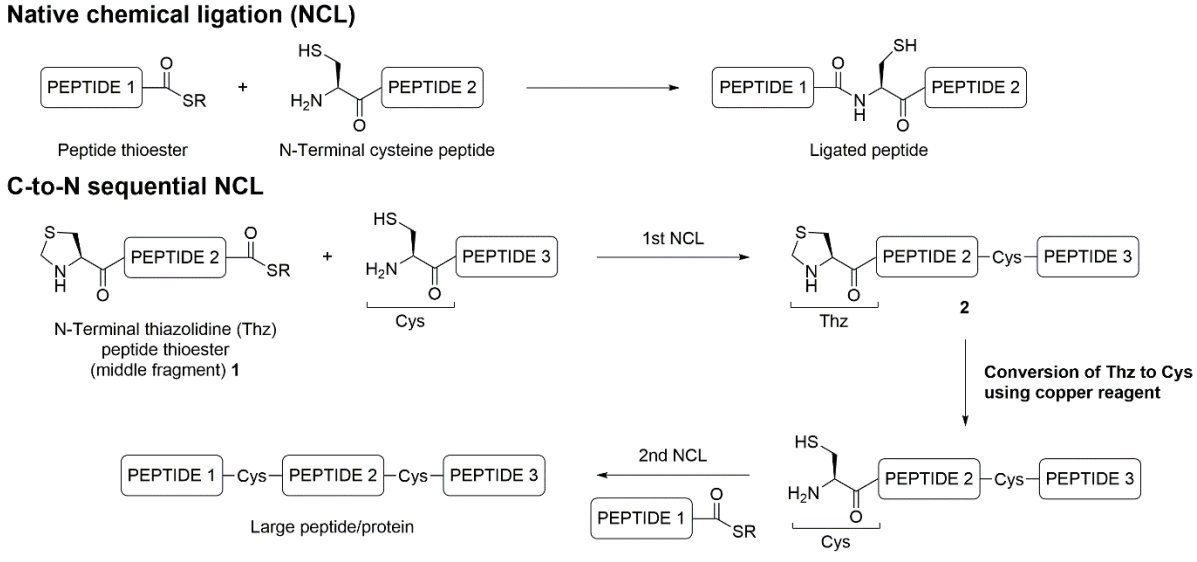
Recent protein chemical synthesis uses the native chemical ligation (NCL) protocol which features chemoselective condensation between thioester and N-terminal cysteine fragments prepared by solid-phase peptide synthesis (SPPS) [1]. One NCL coupling generally affords proteins up to about 100 residues, which is due to the fact that SPPS-affordable residue number of peptide fragments for NCL is about 40–50 residues. Therefore, chemical synthesis of proteins over 100 residues requires the NCL-mediated coupling of more than two peptide fragments where middle fragments have to possess the cysteine and thioester structures in their N- and C-terminal ends, respectively. And peptide fragments are condensed by intermolecular NCL in the N–to–C- or C–to–N-directed manner. In both manner, formation of cyclic peptides derived from intramolecular NCL reaction of the middle fragments is issue of special concern. Therefore, N-terminal thiazolidine peptide thioester **1** has been utilized in the C–to–N-directed protocol for suppression of the concerned side reaction [2]. Use of fragment **1** in the C–to–N-protocol requires the ring-opening of the thiazolidine product **2** which has been performed by treatment with methoxylamine or palladium salts [3] in aqueous solution. However, time-consuming reaction (methoxylamine) or air-sensitive expensive reagent (Pd) is needed for the ring-opening. In this context, we attempted to reexamine the thiazolidine-opening which was found as a side reaction in the copper-mediated Huisgen cycloaddition reaction [4].



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Regioselective Dienone-phenol Rearrangement of 4,4-Disubstituted 2-Hydroxycyclohexa-2,5-dienones into 3,4-Disubstituted Catechols

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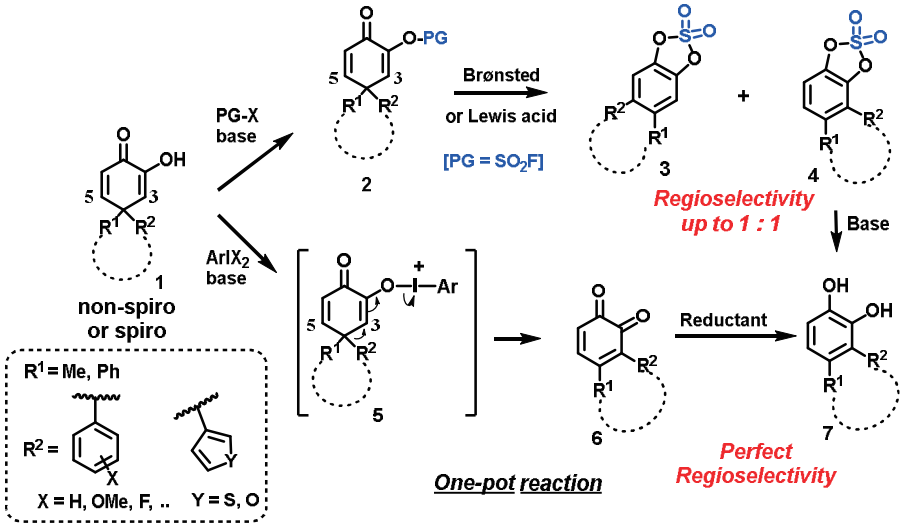
During our recent studies on the dienone-phenol rearrangement of 4,4-disubstituted 2-hydroxycyclohexa-2,5-dienones **1** under acidic conditions, we found that the migration always proceeded towards their C5-carbon affording 4,5-disubstituted catechols exclusively[1,2] and also have learned that no other methods are available for the regioselective migration of **1** towards their C3-carbon. If we could obtain the C3-migration products, 3,4-disubstituted catechols, in a separate way, a set of these transformations would be a useful tool to produce a range of disubstituted catechols with different substitution pattern, which are important structural motifs involved in various pharmaceuticals and agrochemicals. In this symposium, we present our efforts to control the migration of **1** towards the C3-carbon affording the desired **7** for the first time in a high yield and regioselectivity.

Our first trial was to unveil effects of protecting groups (PGs) attached to the C2-hydroxyl moiety of **1** on the migration regioselectivity, which has not been studied before. It was found that the electron-withdrawing groups increased the ratio of the C3-migration products and that a combination of a fluorosulfonyl group (PG = SO_2F) with a suitable Brønsted acid or Lewis acid afforded the 3,4-disubstituted catechols **4** in up to 50% yield for the first time. However, they were always obtained along with **3** in up to 1:1 regioselectivity. In order to increase the electron-withdrawing effect of PG, we attempted a reaction of **1** with hypervalent iodine reagents to find that the desired **7** was obtained in up to 81% yield with exclusive regioselectivity after the one-pot reduction of the in situ generated *ortho*-quinones **6**. Applicability of the last methodology to different substrates will be discussed.



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Platinum on carbon-catalyzed aqueous oxidative lactonization of diols using molecular oxygen

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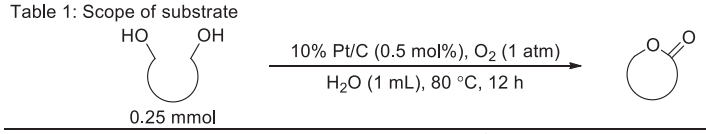
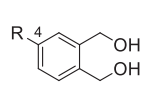
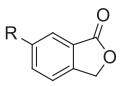
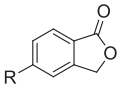
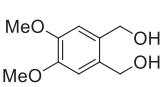
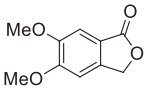
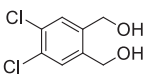
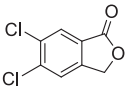
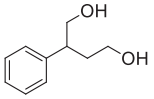
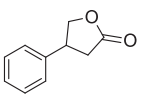
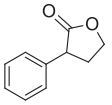
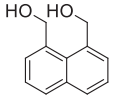
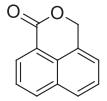
1-25-4 Daigaku-nishi, Gifu 501-1196, Japan

Lactones are important frameworks in organic, pharmaceutical, and industrial chemistries. Among the versatile lactone syntheses, the oxidative lactonization of easily-available diol is eagerly investigated. In particular, the lactonization of diols using molecular oxygen (O_2) as an oxidant in the presence of transition metal catalysts is valuable from the viewpoint of atom economy and green sustainability due to the advantage that the only by-product is water. Although various homogeneous and heterogeneous catalytic lactonization of diols have been reported, the organic solvents were required to facilitate the desired lactonization. We have also previously developed the oxidation of primary and secondary alcohols catalyzed by ruthenium on carbon (Ru/C) in toluene under an oxygen atmosphere.[1] Herein, we newly report the platinum on carbon (Pt/C)-catalyzed oxidative lactonization of diols using O_2 as a green oxidant in water to provide the corresponding lactones.

The desired lactonization was carried out in the presence of 10% Pt/C (0.5 mol%) in water under atmospheric O_2 at 80 °C for 12 h, and the scope of substrates is shown in Table 1. 1,2-Benzenedimethanol (**1a**) was effectively converted to phthalide (**2a**) in 88%. The derivatives (**1b** and **1c**) bearing a substituent at the 4-position of the aromatic nuclei underwent the lactonization to the corresponding phthalide derivatives (**2b** and **2c**) as isomeric mixtures. The lactonization of 2-phenyl-1,4-butanediol (**1d**) gave the γ-butyrolactones as an 88:12 mixture of isomers (**2da** and **2db**) in good yields under the optimal conditions. 4,5-Dimethoxy and dichloro 1,2-benzenedimethanol derivatives (**1e** and **1f**) were also transformed to phthalides (**2e** and **2f**). 1,8-Bis(hydroxymethyl)naphthalene (**1g**) was smoothly converted to 1,8-naphthalide bearing a six-membered lactone moiety (**2g**).

Table 1: Scope of substrate



substrate	product		substrate	product
				
R = H (**1a**)	88% (**2a**)	–	(**1e**)	43% (**2e**)
R = Me (**1b**)	26% (**2ba**)	56% (**2bb**)		
R = F (**1c**)	26% (**2ca**)	66% (**2cb**)	(**1f**)	40% (**2f**)
				
(**1d**)	69% (**2da**)	9% (**2db**)	(**1g**)	70% (**2g**)

The present catalytic method using molecular oxygen in water is valuable from the viewpoint of green sustainability and atom-efficiency. Additionally, the use of water as a solvent was an advantage as it also suppressed the potential ignition property of Pt/C.

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5P-103s

One-Pot Incorporation of Nucleophiles to Cyclic Hemiacetal Aldols: Ring Opening Strategy Promoted by Amine Pendant Boronic Acid

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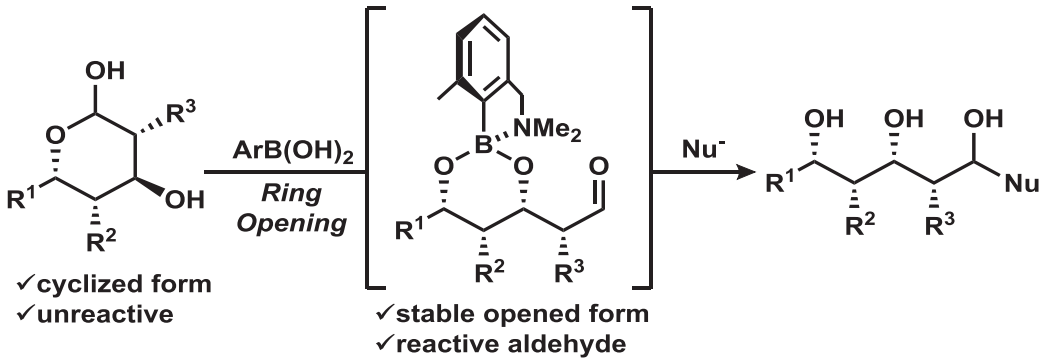
Rapid and stereoselective polyketide synthesis has been one of the key challenges in organic chemistry due to their highly promising ability as drugs. For the synthesis of 1,3-polyols, a catalytic asymmetric aldehyde cross-aldol reaction would be an ideal method.

Our group previously reported syn-selective copper-catalyzed aldehyde cross-aldol reaction[1] and applied this strategy to iterative double aldol reaction. For the iterative 1,3-polyol synthesis of more than double aldol product, however, current strategies cannot be applied because aldol products quickly cyclize to form unreactive hemiacetals.

Direct transformation of unprotected cyclic hemiacetals to reactive linear aldehyde would be a promising approach for introduction of various nucleophiles into 1,3-polyol units. However, such efficient ring opening process has been limited to only several precedents for one-step ring-opening reaction of a tetrahydropyranol.

Herein we reported that linear aldehydes transiently generated in equilibrium could be trapped as thermodynamically stable boron ester using amine-pendant boronic acid. One-pot introduction of several additional modules into unreactive cyclic hemiacetals is possible by this ring opening strategy[2].



[1] L. Lin, K. Yamamoto, H. Mitsunuma, **Y. Kanzaki**, S. Matsunaga and M. Kanai, *J. Am. Chem. Soc.* **2015,** *137,* 15418.

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5P-104s

Improvement of Peptide-Mediated Cytosolic Delivery of Macromolecules

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Development of systems that effectively bring macromolecules into cytosol should be beneficial for the understanding of biological significance of cytosolic components by modulating their functions using macromolecules, and for developing therapeutic systems based on these understandings. Our laboratory developed a peptide "L17E" that delivers macromolecules into cytosol, by modifying the sequence of a hemolytic spider venom peptide M-lycotoxin [1]. L17E is capable of efficiently delivering various bioactive proteins, including IgG, into cytosol. Specific recognition of cytosolic proteins and suppression of glucocorticoid receptor-mediated transcription were thus achieved using the targeting IgGs in the presence of L17E.

Yet, to effectively deliver macromolecules into cytosol, use of ~40 μM L17E is suggested. To improve the endosomolytic activity, we focused on the helical structure formation of the peptides dependent on endosomal pH decrease, in accord with hydrophobic interaction of peptides with membranes. We have succeeded in obtaining a peptide named "HAad", yielding a significantly improved cytosolic appearance of polydextran (a model macromolecule). HAad yields a marked pH-dependent helical switch and membrane perturbation, which are absent for L17E and may be a possible explanation for the enhanced endosomolytic activity of the peptide.

[1] Akishiba, M. et al. Nat. Chem. 9, 751-761 (2017).

Structural Modification and Biological Evaluation of Quinomycin Antibiotics Focusing on Cross-bridge Structures of Bicyclic Depsipeptide

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[2] *Department of Chemistry, The University of Tokyo, Bunkyoku, Tokyo 113-0033, Japan*

[3] *Faculty of Engineering, Gifu University, Gifu-city, Gifu 501-1193, Japan*

Triostin A (TA) and Echinomycin (Ec), which are naturally occurring quinoxaline antibiotics isolated from *Streptomyces aureus*, are C_2-symmetric cyclic octadepsipeptide with a disulfide (TA) and a thioacetal (Ec) cross-bridge, respectively (**Figure 1**). We recently established a useful liquid-phase procedure of total synthesis of TA and found that it has an antitumor effect (IC_{50}: 211.6 nM) and an inhibitory effect of hypoxia-inducible factor (HIF)-1α transcriptional activity (IC_{50}: 26.9 nM). Furthermore, it was shown that Ec has highly potent antitumor activity (IC_{50}: 2.0 nM) and HIF-1 inhibitory effect (IC_{50}: 0.35 nM) at concentrations 2 orders of magnitude higher than those of TA.[1] These data suggested that the cross-bridge structure had a great influence on antitumor activity in quinomycin antibiotics. Therefore, we performed structural modification studies based on the bicyclic depsipeptide scaffold focusing on the cross-bridge moiety in particular.

All compounds were synthesized by the liquid phase procedure efficiently (**Scheme 1**) and evaluated for their cytotoxicity on various tumor cells, transcriptional activity of HIF-1α, and anti-angiogenic activity (**Table 1**). These results suggested that there was a significant correlation between conformational change induced by modification of the cross-bridge structure and the biological activities. Consequently, it was revealed that enhancing ring strain by the structural modification of cross-bridge moiety was especially critical to potentiate the cytotoxicity and HIF-1 inhibitory activity of quinomycin antibiotics. We also discuss the structure-activity relationship and molecular modeling studies of the newly obtained conformationally constrained cyclic octadepsipeptides to elucidate the structural requirements of potent antitumor and HIF-1 inhibitory effects.

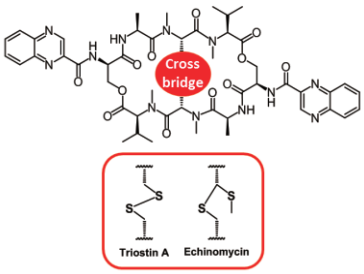


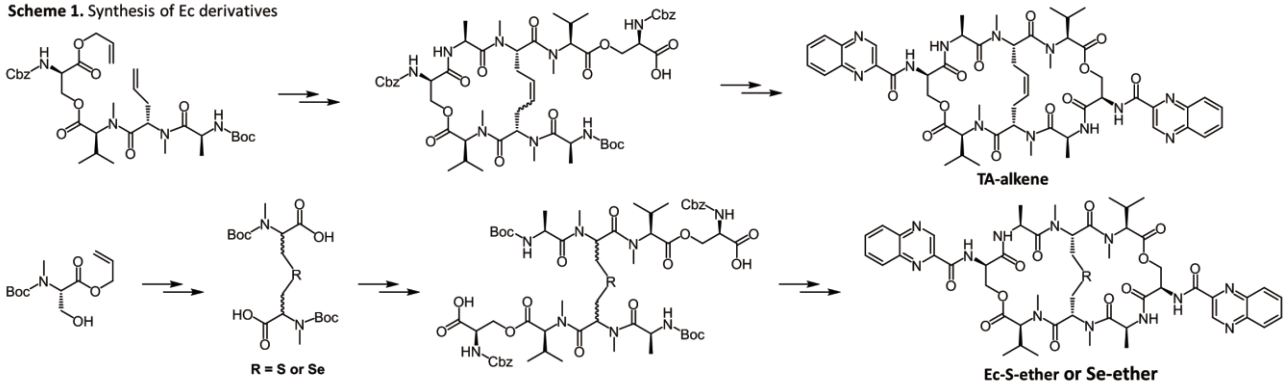
Figure 1. Structure of Triostin A and Echinomycin

Table 1. Half maximal inhibitory concentration (IC_{50}) on hypoxia-induced HIF-1 activation and cytotoxicity treated with Triostin A and its analogues.

Crross bridge	Triostin A (disulfide)	Echinomycin (thioacetal)	alkene	alkane	S-ether	Se-ether
Cytotoxicity[a] [nM]	211.6 ± 14.0	2.0 ± 0.14	2.9 ± 0.27	23.5 ± 0.08	9.7 ± 1.2	7.1 ± 0.55
HIF-1 suppression[b] [nM]	26.9 ± 1.3	0.35 ± 0.03	1.0 ± 0.2	6.3 ± 1.2	2.4 ± 0.3	2.0 ± 0.1

a: MTT assay for MCF-7 cells, *b*: Luciferase assay for transfected HEK293 cells

Scheme 1. Synthesis of Ec derivatives



[1] K. Hattori, K. Koike, K. Okuda, T. Hirayama, M. Ebihara, M. Takenaka and H. Nagasawa, *Org. Biomol. Chem.* **2016**, *14*, 2090–2111

Synthesis and Evaluation of Heterocyclic Rocaglamide Derivatives with Wnt Signaling Inhibition

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Rocaglamide derivatives are naturally occurring compounds, which are discovered in medicinal plants of the genus *Aglaia* (Meliaceae). These compounds contain a unique cyclopenta[*b*]benzofuran skeleton and show various and potent biological activities (*anti-tumor, anti-viral, anti-inflammatory, etc.*). In our laboratory, we have synthesized heterocyclic rocaglamides *via* [3+2] photocycloaddition[1] of 3-hydroxychromones and cinnamic acid derivatives (Fig. 1), and discovered their Wnt signaling inhibitory activity for the first time.[2] This time, we aimed to enhance rocaglamides' biological activity and to reveal a mechanism of their Wnt signal inhibition. We focused on a derivative with bromothiophene moiety ((±)-**1**, IC_{50} against Wnt signaling: 78 nM) and further derivatized this compound. Wnt signaling inhibitory activities of derivatives were evaluated with a cell-based luciferase reporter assay system, and a structure-activity relationship (SAR) was studied, which led to the synthesis of a very potent derivative (-)-**2** (IC_{50} 8.7 nM). (-)-**2** showed strong cytotoxicity against a Wnt-upregulated human gastric adenocarcinoma (Fig. 2). Taking account of the report that rocaglamides inhibit a protein translation[3], mechanism study of (-)-**2** is ongoing and will be discussed in this symposium.

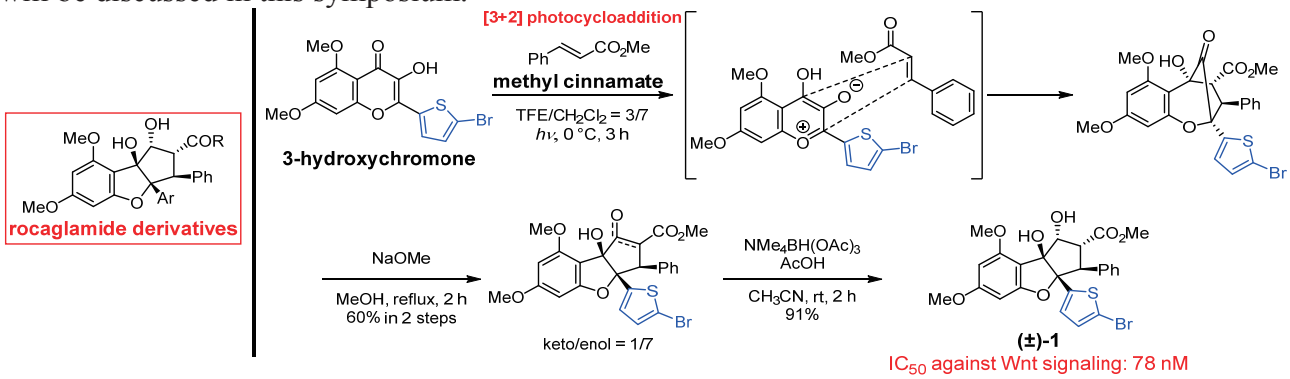

Fig. 1 left) A general structure of rocaglamides. right) The synthetic pathway.

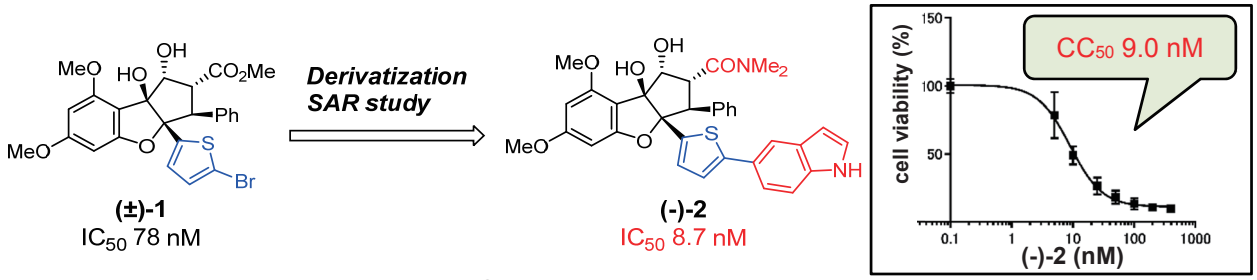

Fig. 2 Synthesis of a potent derivative (-)-**2**, and its cytotoxicity against AGS cells (gastric adenocarcinoma).

[1] Gerard, B.; Jones, G., II; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 13620−13621.
[2] Arai, M. A.; Kofuji, Y.; Tanaka, Y.; Yanase, N.; Yamaku, K.; Fuentes, R. G.; Karmakar, U. K.; Ishibashi, M. *Org. Biomol. Chem.* **2016**, *14*, 3061-3068.
[3] Iwasaki, S.; Floor, S. N.; Ingolia, N. T. *Nature* **2016**, *534*, 558-561.

5P-107

Photooxygenation of Aromatic Substrates using Azafluorenone Derivatives as Photocatalysts

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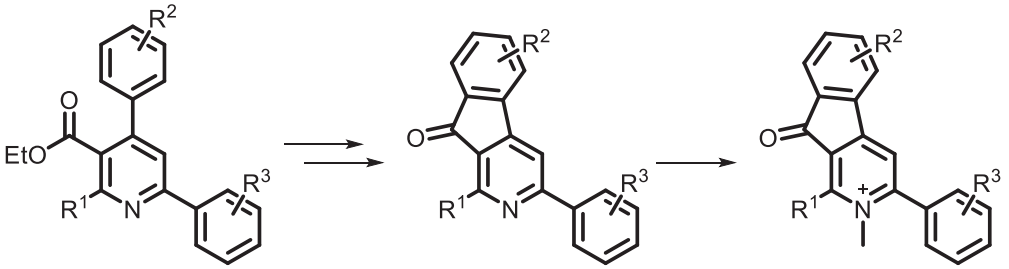
The oxidation reaction of hydrocarbons well-known as industrially important process, contributing about 30% of all chemical processes. In general, the oxidation processes require the use of expensive transition metal catalyst and proceed under severe reaction conditions such as high temperature and high pressure. In addition, there are also the problems of equivalent-molar heavy metal oxidizing agents. Based on these backgrounds and green chemistry, the photochemical reaction process has attracted much attention in recent years. Because this process uses relatively inexpensive catalyst, mild reaction conditions, and does not use heavy metals. Therefore, the developments of novel photocatalysts are widely studied.

On the other hand, azafluorenone derivatives, which have a carbonyl group and a ring nitrogen, are expected to be applied as photocatalyst due to its properties such as visible light absorption, tuning property and high oxidizing ability. Recently, we have developed a facile method for synthesizing polysubstituted nicotinates, which are the key precursors for azafluorenones.[1] Indeed, the intramolecular cyclization of 4-aryl nicotinates affords the substituted 2-azafluorenone derivatives on demand (Scheme (a)). We also studied the application of azafluorenones as photocatalyst for photooxygenation of toluene to benzaldehyde with molecular oxygen under visible-light irradiation (Scheme (b)).

(a) Synthesis of azafluorenone derivatives used in this study



(b) Photooxyegenation of toluene using azafluorenone as photocatalyst

[1] S. Hirai, Y. Horikawa, H. Asahara, N. Nishiwaki, *Chem. Commun.* **2017**, *53*, 2390.

Design and synthesis of novel transthyretin amyloidogenesis inhibitors

Kishin Inui[1], Takuya Okada[1], Wakana Katayama[2], Ayaka Shimane[2], Ryota Kitakami[3], Takeshi Yokoyama[3], Mineyuki Mizuguchi[3,4] and Naoki Toyooka[1,4]*

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Faculty of Pharmacy and Pharmaceutical Sciences, University of Toyama[2], 2630 Sugitani, Toyama 930-0194, Japan
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3190 Gofuku, Toyama 930-8555, Japan, 2630 Sugitani, Toyama 930-0194, Japan

Transthyretin (TTR) is a homotetrameric protein involved in human hereditary amyloidoses. TTR-related amyloidosis is caused by mutations in the TTR gene. The mutations destabilize the tetramer of TTR, and cause familial amyloidotic polyneuropathy (FAP) via the formation of amyloid fibrils and the deposition to peripheral tissues and heart. Thus, the stabilization of TTR is a key strategy for the treatment of TTR-related amyloidosis.

Previously, it has been reported that γ-mangostin[1] and naringenin[2] have inhibitory activities against the amyloid fibril formation of mutant (V30M) amyloidogenic TTR (**Figure 1**). To obtain the more potent inhibitor, we designed and synthesized the xanthone and flavanone derivatives as shown in **Scheme 1**. Xanthone derivatives **3** were synthesized from *o*-chloro- or *o*-nitro-nitrobenzaldehydes **1** and phenols **2** in the presense of $CuCl_2$, Ph_3P, and K_3PO_4 in single step.[3] 2-Hydroxyacetophenones **4** and benzaldehydes **5** were converted to the corresponding chalcones, which were transformed into the flavanone derivatives **6**. The effects of synthesized compounds were evaluated using thioflavin T assay. Some of the synthesized compounds shows higher inhibitory activities than γ-mangostin and naringenin, respectively, with the IC_{50} value around 5.3 μM.

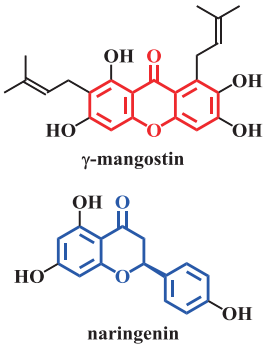
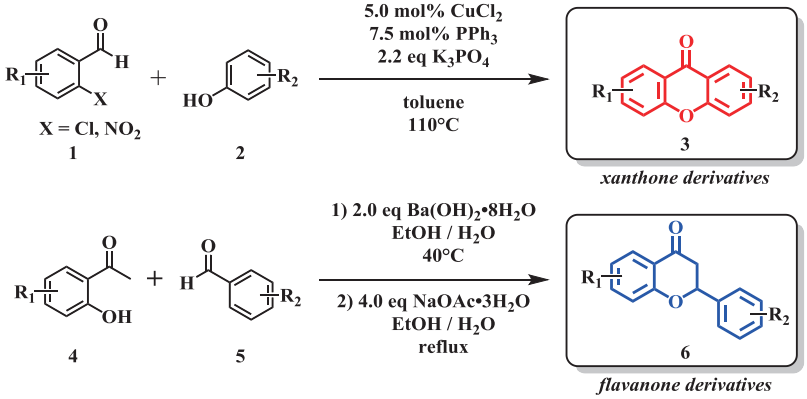


Figure 1. Chemical structures of γ-mangostin and naringenin



Scheme 1. Synthesis of target compounds

Details of the synthesis of xanthone and flavanone derivatives and their evaluation on Thioflavin T assay will be reported.

[1] Yokoyama, T.; Ueda, M.; Ando, Y.; Mizuguchi, M. *Sci. Rep.* **2015**, *5*, 13570
[2] Trivella, D. B.B.; Reis, C. V.D.; Lima, L. M. T. R.; Foguel, D.; Polikarpov, I. *J. Struct. Biol.* **2012**, *180*, 143
[3] Menendez, C. A.; Nador, F.; Radivoy, G.; Gerbino, D. C. *Org. Lett.* **2014**, *16*, 2846

A Concise Asymmetric Total Synthesis of (+)-Epilupinine

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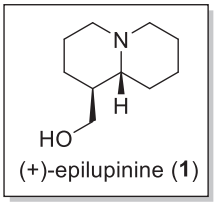
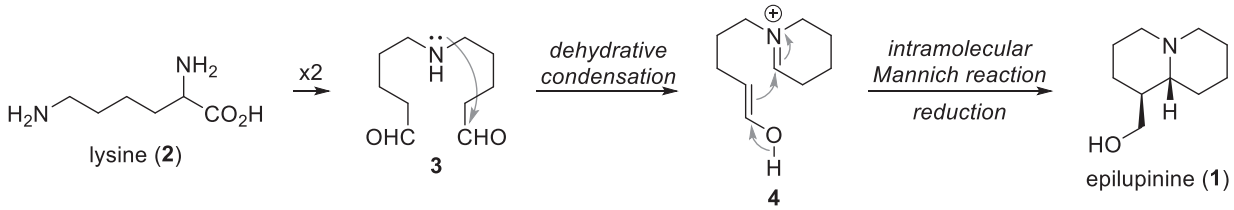
Shomachi, Tokushima 770-8505, Japan

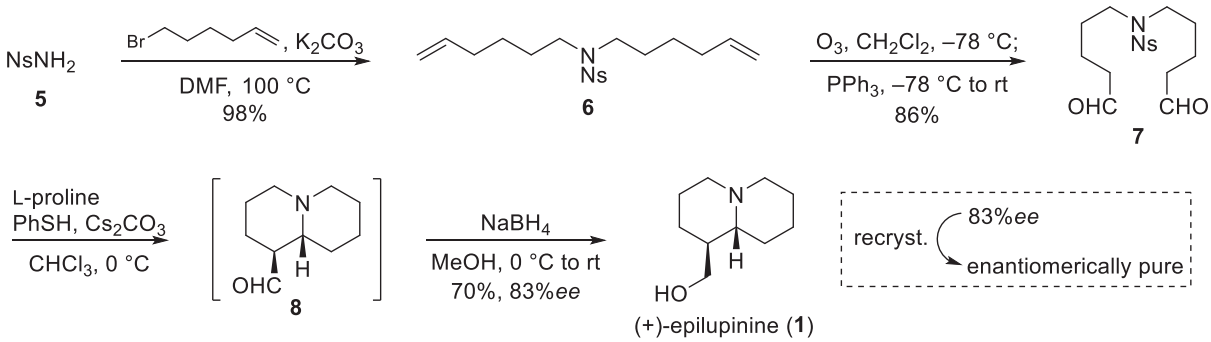
(+)-Epilupinine (**1**) is quinolizidine alkaloid which have the octahydro-2*H*-quinolizine (quinolizidine) skeleton as a structural unit. **1** was found mostly in genus *Lupinus* and known to exhibit *in vitro* inhibitory activity against Leukaemia.[1] To date, 15 asymmetric total syntheses and more than 30 racemic total syntheses have been reported.



The biosynthetic pathway of epilupinine (**1**) is proposed as follows.[2] Starting from the dimerization of lysine (**2**), the resulting dialdehyde **3** undergoes dehydrative condensation to form iminium salt **4**. Subsequent intramolecular Mannich reaction followed by reduction affords epilupinine (**1**). We thought that development of an asymmetric version of this cascade reaction would be the most efficient approach to **1**.



Treatment of *N*-nosylamide **5** with 6-bromo-1-hexene and K_2CO_3 in DMF at 100 °C afforded the diene **6** in 98%. Ozone oxidation of the diene **6** in dichloromethane at −78 °C proceeded smoothly to give the dialdehyde **7** in 86% yield. Finally, treatment of dialdehyde **7** with L-proline, PhSH and Cs_2CO_3 in $CHCl_3$ at 0 °C followed by a reduction with $NaBH_4$ afforded (+)-epilupinine (**1**) in 70% yield with 83% *ee*. Enantiomerically pure **1** was obtained by recrystallization. In this presentation, we will discuss the details of the three-step total synthesis of (+)-epilupinine (**1**).[3]



[1] Hua, D. H.; Miao, S. W.; Bravo, A. A.; Takemoto, D. J. *Synthesis* **1991**, 970−974.
[2] Robinson, R. *The Structural Relations of Natural Products*; Oxford University Press: London, **1955**.
[3] Tsutsumi, T.; Karanjit, S.; Nakayama, A.; Namba, K. *Org. Lett.* **2019**, *21*, 2620.

Stereodivergent asymmetric synthesis of DHQ-type poison-frog alkaloids for SAR study to inhibitory effect of nicotinic acetylcholine receptors

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[1]Graduate School of Innovative Life science, University of Toyama [2] Graduate School of Science and Engineering, University of Toyama [3]Faculty of Engineering, University of Toyama [4] Graduate School of Medicine and Pharmacutical Sciences, University of Toyama [5] Toyama Prefectural University

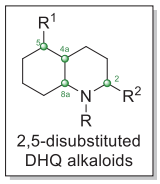
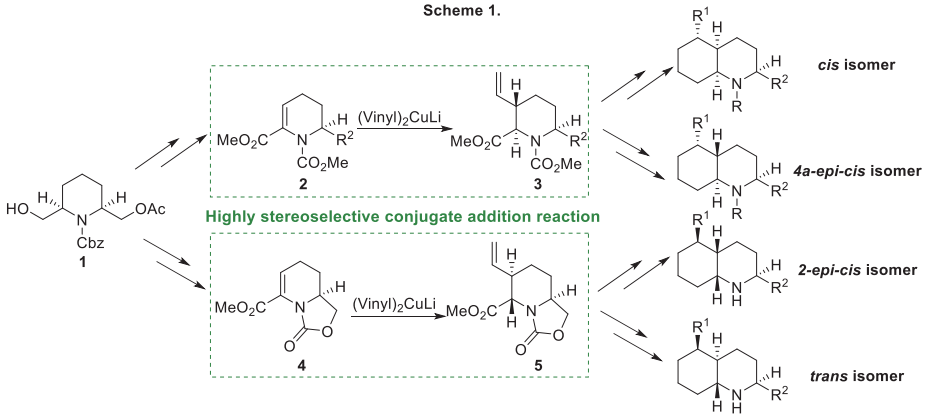


Figure 1.

The skin extracts of the neotropical poison frogs contain a remarkable diversity of alkaloids, and the 2,5-disubstituted decahydroquinolines (DHQ) represent one of the major class of these amphibian alkaloids (**Figure 1**).[1] The parent member of the DHQ class of alkaloids *cis*-**195A** has known as noncompetitive blockers of nicotinic acetylcholine receptors.[2] However, biological activity of other compounds in this class has not been elucidated. So, we carried out stereodivergent synthesis of DHQ-type poison-frog alkaloids for the structure–activity relationship (SAR) studies for the subclass selective inhibitory effect of nicotinic acetylcholine receptors.

The synthesis began with known chiral acetate **1**[3], which was converted to enaminoester **2**. The key highly stereoselective conjugate addition reaction to enaminoester **2** gave adduct **3** as a single isomer. Synthesis of *cis*- and *4a-epi-cis*-isomer were accomplished via several steps from adduct **3**. Enaminoester **4**, which was synthesized from **1**, was transformed into the adduct **5** in the similar manner as the above conjugate addition reaction. Synthesis of *2-ep-cis*- and *trans*-isomer was achieved via several steps from adduct **5** (**Scheme 1**). Our key reaction can be shown difference stereoselectivity by substrate control. We already synthesized 14 compounds according to the above strategy. Furthermore, we tested inhibitory effect of several compounds on [^{3}H] nicotine uptake by TR-BBB13 cells and [^{3}H] verapamil uptake by TR-BBB2 cells, and details will be reported.

Scheme 1.



[1] Daly, J. W. *et al*. *J. Nat. Prod.* **2005**, *68*, 1556.
[2] Daly, J. W. *et al*. *Neurochem. Res.* **1991**, *19*, 1207.
[3] Chênevert, R. *et al*. *Tetrahedron: Asymmetry.* **1999**, *10,* 3117.

5P-111s

Access to trisubstituted piperidines using an organocatalyst-mediated asymmetric conjugate addition of aldehydes and β-substituted-α-cyano ethyl acrylates as a key step

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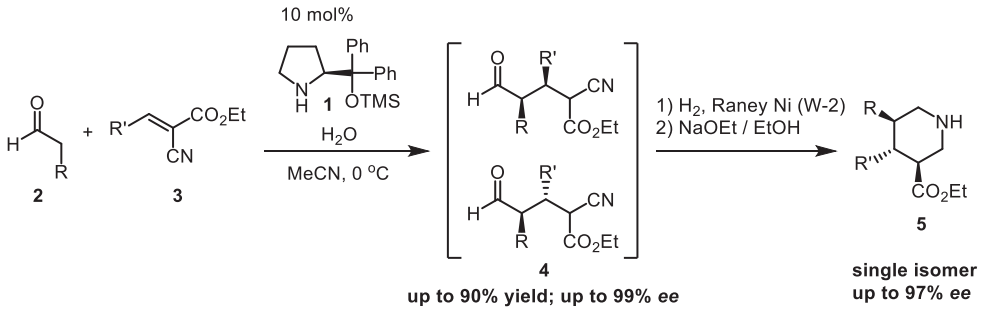
Piperidine motifs are present in a vast range of alkaloids, biomolecules, and natural products. A large portion of therapeutic agents and pharmaceuticals that are used as drugs usually contain the piperidine scaffold.[1] Therefore, new and efficient methods for the preparation of multi-substituted piperidine scaffolds especially with enhanced regio- and stereo-control from achiral precursors are highly desirable.

Our group developed diphenylprolinol silyl ether **1** as an efficient organocatalyst, and it has been shown to effectively catalyze the asymmetric Michael reactions of a variety of Michael acceptors and aldehydes containing active methylene units.[2,3] Given the far-reaching success of this organocatalyst, we further investigated its use in the asymmetric Michael reaction of aldehydes **2** and β-substituted-α-cyano ethyl acrylates **3**. Our interest in this class of Michael acceptor is based on the idea that a successful conjugate addition would generate enantiomerically enriched Michael adduct **4** that presents a suitable handle for further transformation into single isomers of trisubstituted piperidine.

Herein, we present the results of our investigation into the diphenylprolinol silyl ether-mediated asymmetric conjugate additions, as well as the outcome of a subsequent reductive cyclization using the obtained Michael adducts **4** to furnish the corresponding equatorially-oriented 3,4,5-trisubstituted piperidines **5** as single isomers with excellent enantiopurity. Notably, the conjugate addition was predominantly syn-selective for aldehyde precursors with small R-substituents (e.g. R=Me), and anti-selective for aldehyde precursors with large R-substituents (R=Et, Bn, etc.).



[1] Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem*. **2014**, *57*, 10257.
[2] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 4212.
[3] Hayashi, Y.; Kranidiotis-Hisatomi, N.; Sakamoto, D.; Oritani, K.; Kawamoto, T.; Kamimura, A. *Eur. J. Org. Chem*. **2018**, 6843, and references cited therein.

5P-112s

Dianionic phase transfer catalyst for asymmetric fluorofunctionalizations

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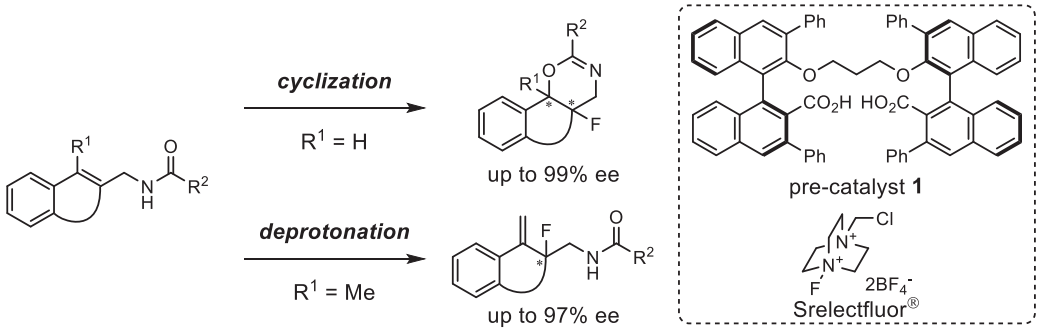
Fluorinated compounds are widely used in pharmaceutical, agrochemical and material sciences. Thus, the development of asymmetric fluorinations is highly desirable but still remains a lot of challenges. We reported asymmetric fluoro-lactonization with a hydroxyl carboxylate catalyst as an anionic phase-transfer catalyst in 2015.[1] Taking the mechanistic studies of the fluoro-lactonization into account, we considered that a dianionic catalyst would strongly interact with Selectfluor, which is insoluble in nonpolar solvents due to its dicationic property. Based on this hypothesis, we designed a novel linked dicarboxylate catalyst, which could be synthesized via our reductive CO_2 fixation.[2] As the result of the optimizations, it was found that the linked dicarboxylate pre-catalyst **1** promoted 6-*endo*-fluorocyclization of allyl amides to give the corresponding fluorinated dihydrooxazine compounds with excellent enantioselectivity (up to 99% ee).[3] We thought that this reaction proceeded via a carbocation intermediate and the amide group underwent hydrogen bond interaction with the carboxylate of the catalyst. Subsequently, we investigated cyclic tetrasubstituted allyl amide substrates that can give a more stable carbocation intermediate. Fluorodeprotonation reaction proceeded preferentially and allyl fluoride compounds were obtained with high enantioselectivity (up to 97% ee). As fluorocyclized products were obtained mainly without the catalyst, this catalyst is thought to control the reaction pathway as well as the facial selectivity of C=C bond.[4] The details will be presented.



[1] Egami, H.; Asada, J.; Sato, K.; Hashizume, D.; Kawato, Y.; Hamashima, Y. *et al. J. Am. Chem. Soc.* **2015**, *137*, 10132–10135.
[2] Egami, H.; Sato, K.; Asada, J.; Kawato, Y.; Hamashima, Y. *et al. Tetrahedron* **2015**, *71*, 6384–6388.
[3] Egami, H.; Niwa, T.; Sato, H.; Hotta, R., Rouno, T., Kawato, Y.; Y. Hamashima *et al. J. Am. Chem. Soc.* **2018**, *140*, 2785–2788.
[4] Niwa, T.; Ujiie, K.; Sato, H.; Egami, H.; Y. Hamashima *et al. Chem. Pharm. Bull.* **2018**, *66*, 920–922.

Synthetic Studies on Iridoids: Construction of a *cis*-Fused Cyclopenta[*c*]pyran Ring via Pauson-Khand Reaction

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[2]*Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan.*

【Introduction】 Iridoids are monoterpenoid natural products, which exhibit various biological activities, such as anti-inflammatory, anti-microbial, anti-tumorigenic, and neurotrophic effects, so the core bicyclic structure would be important for multiple biological functions. Among them, catalpol (**1**) and aucubin (**2**) (Figure 1) show anti-aging effects that are not found in other iridoids.[1)] This biological activity is intriguing, however, the detailed mechanisms of action (MOAs) remain unknown. Hence, we aimed to establish an efficient synthetic route for **1** and **2** for the purpose of elucidating the anti-aging MOAs.

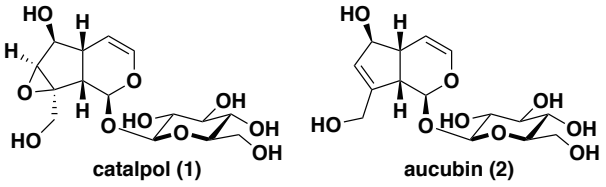
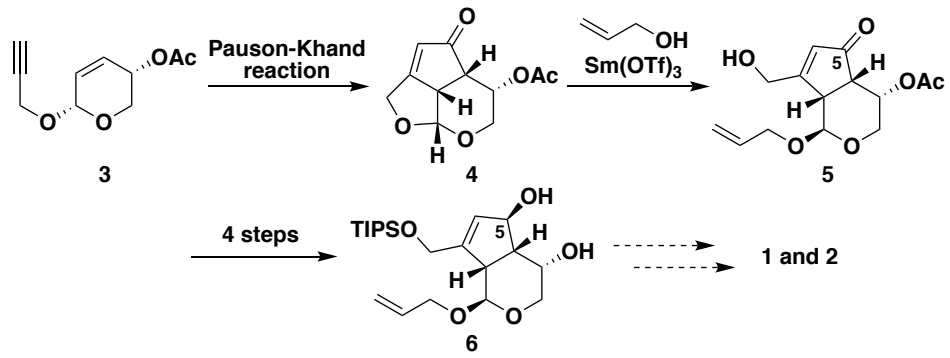


Figure 1. Structures of catalpol (1) and aucubin (2).

【Results and Discussion】 First, the Pauson-Khand reaction (PKR) was examined with reference to Ruiz's method (Scheme 1).[2)] Using substrate **3**, which was prepared from 3,4-di-*O*-acetyl-L-arabinal, the desired tricyclic enone **4** possessing the *cis*-fused ring system was produced by the PKR. Interestingly, the stereochemistry of the acetoxy group of **3** affected yields of this reaction. Then, the acetal moiety of tricyclic enone **4** was quantitatively cleaved upon exposure to allyl alcohol and a catalytic amount of $Sm(OTf)_3$ to obtain **5**. After protecting the primary alcohol of **5**, DIBAL reduction gave a diol that had an opposite stereochemistry at C5. Then, the selective oxidation of the resulting allylic alcohol followed by the reduction from the *concave* surface using $NaBH(OAc)_3$ successfully generated the diol **6**. In this presentation, we discuss our synthetic efforts toward the total synthesis of **1** and **2** including examination of dehydration and glycosylation reactions.

Scheme 1. Synthetic approach toward catalpol (1) and aucubin (2).



[1] Jensen, C. J. *et al*. *Glycoconj. J.* **2016**, *33*, 671.

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5P-114

Synthesis of Quinolines *via* Friedländer Reaction under One-pot-one-step, Solvent-free, Microwave-assisted Conditions

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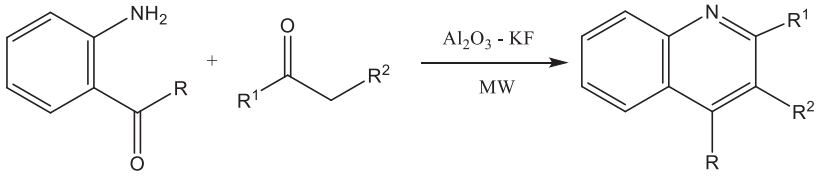
[2]*Department of Chemistry, Faculty of Science, Niigata University, Japan*

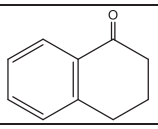
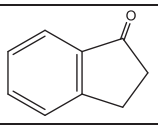
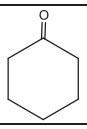
Quinolines are one of the most well-known *N*-heteroaromatic compounds found in the structures of many pharmaceuticals. Quinolines are not only known for their significant biological activities but also for their formation of conjugated molecules and polymers that combine enhanced electronic, optoelectonic, or nonlinear optical properties with excellent mechanical properties.[1,2,3,4] Thus, a number of methods for the synthesis of quinolines are available. However, many of these methods are not satisfactory because they involve harsh reaction conditions, poor yields, long reaction time, and the use of hazardous and expensive reagents and catalyst.[4]

In this project, we report a straightforward reaction route for the synthesis of quinolines carried out under a one-pot-one-step, solvent-free, and microwave-assisted conditions. The workup is quite facile and the product yields are moderate to very good.



1a-c **2a-c** yield = 46 - 96%

	R
1a	Ph
1b	CH_3
1c	H

R	**2a**	**2b**	**2c**
			

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5P-115s

Dihydrobenzofuran Synthesis by [3+2] Coupling of Quinone Monoacetals with Vinyl Ethers

Yusuke Tsunoda[1], Tohru Kamitanaka[1], Yuriko Fujita[2], Toshifumi Dohi[1,2], Yasuyuki Kita[1]
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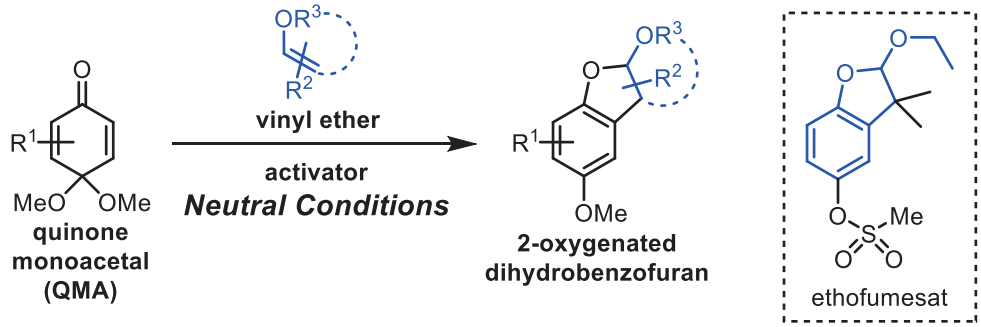
Highly oxygenated aromatic compounds exist as building blocks in natural products, pharmaceuticals, and functional materials. These compounds are generally synthesized by the transition metal-catalyzed methods using pre-functionalized aromatic compounds. Although these methods can be utilized in various fields due to their high reliability, more alternative greener methods are desired. Recently, direct coupling of unfunctionalized substrates based on C-H activation has been actively investigated as a step- and atom-economical strategy. However, their applications to the natural product synthesis are somewhat limited because of the problems on reaction control, such as over-reaction and generation of regioisomers. To exclude these concerns, we have recently reported new approaches to the synthesis of highly oxygenated aromatic compounds using quinone monoacetals (QMAs) as the key intermediate. These QMAs could be easily obtained by the oxidation of phenols using hypervalent iodine(III) reagents, such as phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA).[1]

In 2011, we developed the regioselective nucleophilic substitution into the α-position of carbonyl by the aid of suitable acid promotors.[2-4] Based on these methods, aromatic and alkene nucleophiles could be introduced in a regiospecific manner, and biaryls and dihydrobenzofurans were obtained. However, the utility of alkene nucleophiles was limited to acid-stable ones, while acid-labile nucleophiles, e.g., vinyl ethers, were not tolerated to the reaction condition because of the rapid decomposition of the nucleophiles. We have now found the new activation method of QMAs under nearly neutral conditions for specific organic salt-catalyzed reactions. This new strategy enables the coupling of QMAs with acid-labile vinyl ethers to afford 2-oxygenated dihydrobenzofurans that are found in the core structure of natural products and pharmaceutical compounds.



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Pd-Catalyzed Asymmetric Allylic Alkylation of Tryptamine for Construction of Pyrroloindole Alkaloids

Riho Korogi, Shieri Yamauchi and Masanari Kimura*
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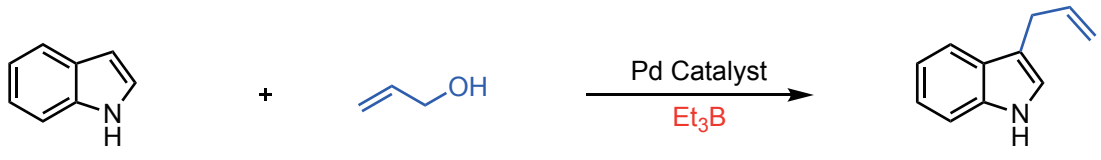
1-14 Bunkyo, Nagasaki 852-8521, Japan

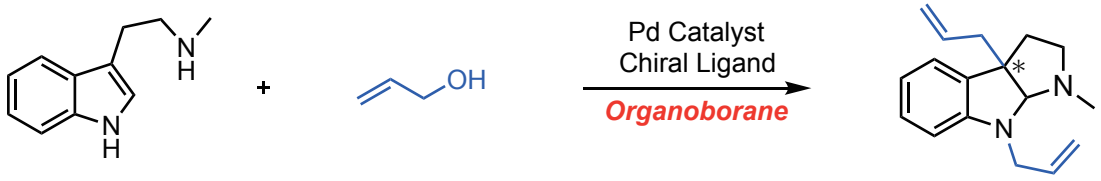
Allylic alkylation is among the most efficient C-C bond transformations for the construction of physiologically active molecules. We have developed the first direct allylic alkylation of indoles with allyl alcohols to provide C-3 allylated indoles in the presence of Pd catalyst and triethylborane (equation 1).[1] In this case, triethylborane can serve as a Lewis acid to promote the oxidative addition of allyl alcohols toward Pd(0) metals, and can also accelerate to proceed the electrophilic allylation.

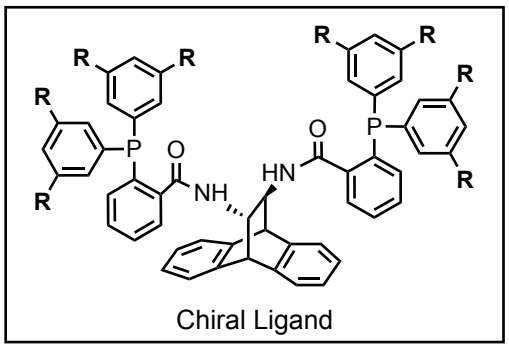
Furthermore, B. M. Trost et al. also reported Pd-catalyzed asymmetric allylic alkylation of substituted indoles with allylic alcohols[2] and vinylcyclopropanes[3] in the presence of organoboranes with asymmetric ligands based on our previous report.

According to our previous Pd/Et_3B promoted allylic alkylation protocol and Trost's asymmetric allylic alkylations, we could succeed in the asymmetric one-pot synthesis of debromoflustramine B from tryptamine and allyl alcohol under Pd-catalyst/organoboranes with asymmetric bidentate phosphine ligands.



This work





Chiral Ligand	*Organoborane*	Yield (%)	ee (%)
R = H	Et_3B	91	56
R = Me	Et_3B	44	65
***R* = Me**	***C_6H_{13}-9-BBN***	***90***	***81***

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5P-117

The Specific Reactivity of Pyrrolo[2,1-f][1,2,4]triazines and the Synthesis of Rogaratinib (BAY 1163877)

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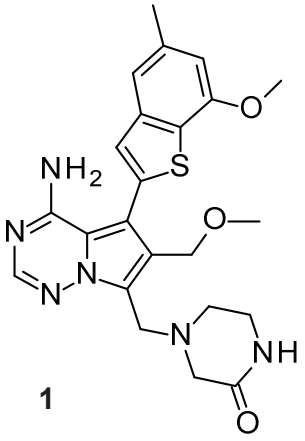
Department of Medicinal Chemistry, Drug Discovery, Bayer AG,
P.O. BOX 101709, 42096 Wuppertal, Germany

Rogaratinib (BAY 1163877) **1**[1] is a highly potent and selective pan-fibroblast growth factor receptor (FGFR) inhibitor (FGFR1–4) for oral application currently being investigated in clinical trials for the treatment of cancer.
The pyrrolo[2,1-f][1,2,4]triazin ring system exhibits a specific chemical reactivity. For instance, the 4-amino-pyrrolo[2,1-f][1,2,4]triazin **2**, is primarily attacked in a bromination reaction in position 5 and 7 by the electrophile and it is challenging to avoid mixtures and dibromination. [2] To introduce all substituents on the pyrrole ring of Rogaratinib special synthetic strategies have to be applied.



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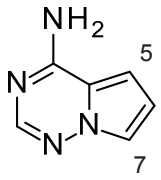

2

[1] Marie-Pierre Collin; Mario Lobell; Walter Huebsch; Dirk Brohm; Hartmut Schirok; Rolf Jautelat; Klemens Lustig; Ulf Böhmer; Verena Vöhringer; Melanie Heroult; Sylvia Grünewald; Holger Hess-Stumpp ChemMedChem 2018, 13, 437 – 445
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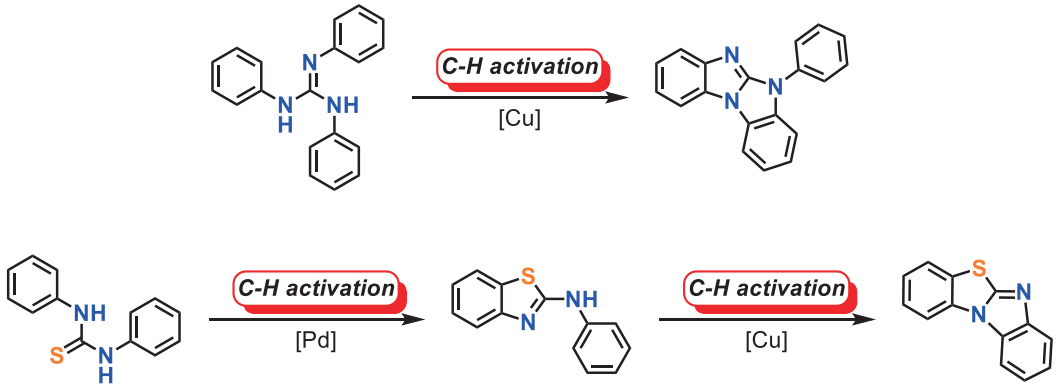
The Tandem Cyclization Reaction to Form Heteroatoms-Containing Tetracyclic Compounds

Madoka Waku[1], Yuki Akamatsu[1], Shinichiro Kamino[1,2] and Daisuke Sawada[1,2,*]
[1]Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama 700-8530, Japan; [2]RIKEN-CPR, Wako, Saitama 351-0198, Japan

The carbon nanomaterials including heteroatoms have unique properties and functions, therefore, the modification of carbon nanomolecules with heteroatoms receives much attention. This time, we designed and synthesized new heteroatoms-containing carbon nanomolecules by bottom-up strategy. This strategy makes it possible to control the positions of introduced heteroatoms in synthesis of the molecules. In our synthetic plan, tetracyclic compounds were constructed through a metal-catalyzed direct C-H functionalization/C-heteroatom (nitrogen and sulfur) bond formation with intramolecular directing group.

As a directing group including nitrogen, we selected guanidino group, and using triphenylguanidine as a substrate, we tried cyclization reaction with $Cu(OAc)_2$ as a catalyst. After extensive screening of solvents, oxidants, and ligands, the tetracyclic compound containing three nitrogen atoms was obtained in moderate yield through the tandem cyclization reaction in one pot operation.[1] Based on this reaction, the synthesis of larger molecules containing many fused rings are on-going.

As a directing group including nitrogen and sulfur, we chose thiourea group. By using a sulfur atom, improvement in the reactivity of substrate was expected. According to the precedent of palladium-catalyzed C-S bond formation from thiourea via C-H functionalization,[2] we attempted a catalytic cyclization reaction using 1,3-diphenylthiourea, to obtain 2-phenylaminobenzothiazole in 50% yield. Then, we explored the cyclization reaction of 2-phenylaminobenzothiazole to afford a tetracyclic compound. On the basis of the tandem cyclization reaction of triphenylguanidine, the reaction was first carried out in the presence of $Cu(OAc)_2$ and K_2CO_3 in DMF at 100 °C under an O_2 atmosphere, and we were able to obtain the desired compound in 6 % yield. After investigation, the yield of the compound has been improved to 15 %.



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Total Synthesis of (–)-Emestrin H and (–)-Asteroxepin

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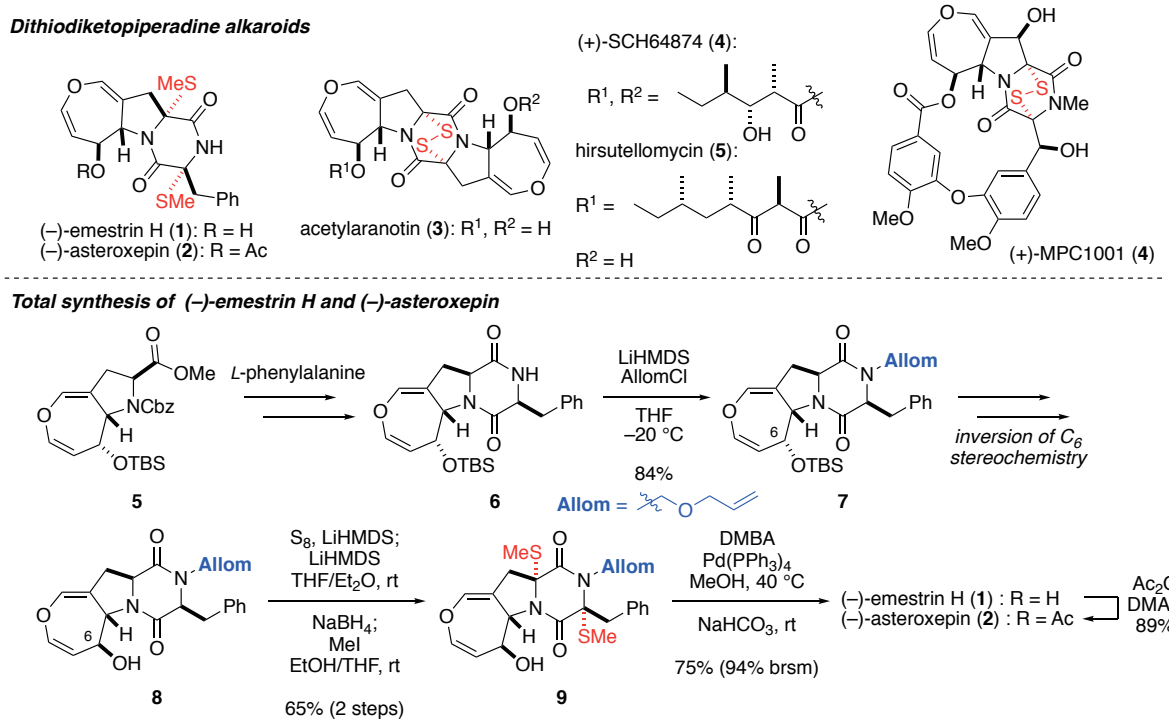
Graduate School of Pharmaceutical Science, Tohoku University
Sendai, Miyagi 980-8578, Japan

Sulfur-containing diketopiperazine alkaloids have received a great deal of attention from the synthetic community due to their broad range of structural diversity and fascinating biological activities. Our group completed total syntheses of a series of the diketopiperazine alkaloids having dihydrooxepine moiety, such as acetylaranotin (**3**),[1] (+)-SCH64874 (**4**),[2] hirsuteromycin (**5**),[2] and (+)-MPC1001 (**6**).[3] In connection with these researches, we recently accomplished total syntheses of (–)-emestrin H (**1**) and (–)-asteroxepin (**2**). The key synthetic issue to be addressed in the total syntheses of **1** and **2** was to choose an appropriate protecting group for the amide nitrogen of the diketopiperazine intermediate **6**. The protecting group should be robust enough to tolerate the sulfenylation under highly basic conditions (**8**→**9**), and cleavable easily in the final stage of the total synthesis without affecting acid and oxidant labile dimethylthio groups (**9**→**1**). After the extensive investigations, we eventually discovered that allyloxymethyl (Allom) group was the suitable protecting group for these purposes. In our presentation, we will discuss the details of the total syntheses.[4]



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[4] Manuscript in preparation.

Studies on the Second Generation Synthesis of Palau'amine

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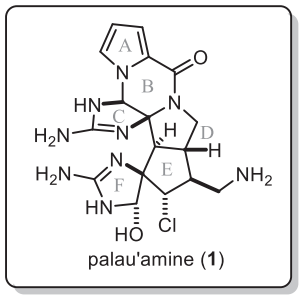
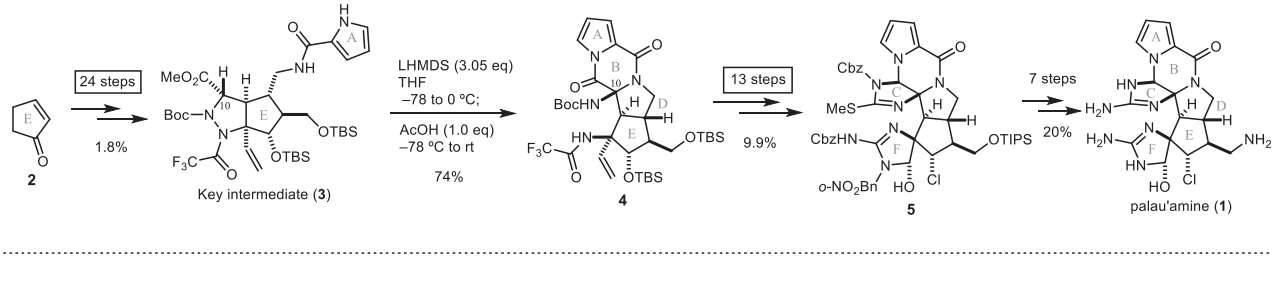


Palau'amine (**1**) was originally isolated from a sponge, *Stylotella agminate*, in 1993 by Scheuer and collegues, as a novel class of pyrrole-imidazole alkaloids.[1] We have recently reported the total synthesis of palau'amine characterized by the construction of ABDE tetracyclic ring core including a trans-bicyclo[3.3.0]octane skeleton at a middle stage of total synthesis. [2, 3] Starting from a commercially available compound (**2**), the key intermediate (**3**) was prepared. Treatment of **3** with LHMDS followed by AcOH afforded an ABDE tetracyclic compound (**4**). The construction of the C and F rings led to **5**. Subsequent transformations of functional groups afforded **1**. However, the synthesis needs long steps (45 steps from **2**). This problem was attributed to the many steps for the synthesis of **3** and the construction of the C and F rings. Therefore, we attempted to establish the second generation synthesis of **1** towards the short-step synthesis.

In order to verify the feasibility of short-step synthesis, we first addressed short-step synthesis of palau'amine analog (**6**) without aminomethyl and chloro groups of **1**. So far, key intermediate (**7**) has been successfully synthesized from **2** in only 9 steps. As a result of extensive investigation, a single step construction of the CDE ring system was achieved by the treatment of **7** with Ph_2NLi. At present, we are undergoing to construct the B and F rings from imine (**9**) that could be obtained from **8** in 3 steps. We will discuss these details in this presentation.



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[3] Namba, K. *et al*. *Nat. Commun.* **2015**, *6*, 8731.

N-Aryl Effect on the Enhanced Catalytic Activity of Imidazolium-Salt Derived NHCs

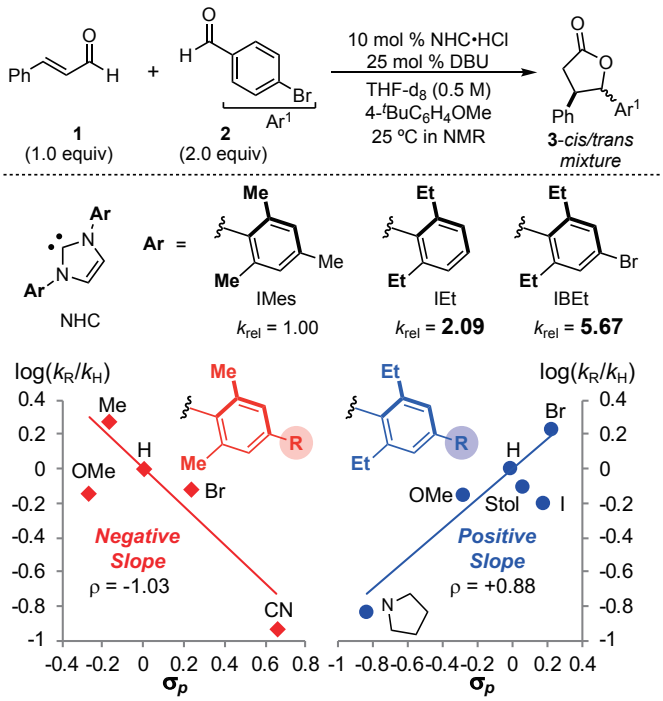
Ryuji Kyan[a], Kohei Sato[b], Nobuyuki Mase[a,b,c], Tetsuo Narumi[a,b,d]

[a] Graduate school of Science and Technology, Shizuoka University; [b] Graduate School of Integrated Science and Technology, Shizuoka University; [c] Green Chemistry Research Division, Research Institute of Green Science and Technology; [d] Green Energy Research Division, Research Institute of Green Science and Technology, Shizuoka University, 3-5-1 Johoku, Naka-ku, Hamamatsu, 432-8561 Japan;

N-heterocyclic carbenes (NHCs) have been widely employed as organocatalysts for the C-C bond formation via umpolung of carbonyl compounds.[1] Especially, the conjugated Breslow intermediate which can be generated by NHCs and α,β-unsaturated aldehyde acts as a homoenolate equivalent for β-functionalization to provide a wide range of heterocyclic and carbocyclic compounds.[2] Despite these important catalytic systems, there are few methods for tuning the catalyst reactivity of NHCs. In fact, imidazolylidene catalysts which have 2,4,6-trimethylphenyl (mesityl, Mes) groups or 2,6-bis(2-propyl)phenyl (Dipp) group as N-aryl groups have been utilized effectively.

Recently, our study including the structural and kinetic investigation of a series of imidazolylidene catalysts for homoenolate-mediated γ-butyrolactone formation revealed that catalyst activity can be clearly increased by introducing 2,6-diethylphenyl groups as N-aryl groups.[3] The imidazolylidene catalysts derived from IEtCl bearing 2,6-diethylphenyl groups showed *ca.* 2.0-fold higher reactivity than IMes. Moreover, we found that *para*-bromo-substituted catalyst (IBEt) showed over 5.0-fold higher reactivity than IMes.

As an extension of this work, we performed the Hammett study on *para*-substituents of the 2,6-dimethylphenyl and 2,6-diethylphenyl groups, revealing that the effect of the 2,6-substituents is likely to affect the trend of substituent effect for the catalyst activity. Details of the kinetic studies and several mechanistic investigations including parallel experiments of H/D kinetic isotope effect will be discussed.



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Asymmetric Total Synthesis of Diatretol, A Potent Antimalarial Agent

Shu Takahashi, Tomoyasu Hirose, Aoi Kimishima, Masato Iwatsuki, Hokari Rei, Aki Ishiyama, Takeshi Yamada, Akihiro Sugawara, Satoshi Omura, and Toshiaki Sunazuka
Kitasato Institute for Life Sciences and Graduate School of Infection Control Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan.

Malaria, which is caused by species of *Plasmodium* parasites, is one of the world's three gravest infectious diseases, and remains a major global health problem. Although many antimalarial agents have been continually developed, drug-resistant Plasmodia rapidly and increasingly appear. Therefore, the development of novel antimalarial drugs with new modes of action and structures is urgently and constantly required. In the course of our screening program of metabolites of microorganisms to discover antimalarial agents that are active against drug-resistant parasites *in vitro* and *in vivo,* we have discovered various compounds with potent antimalarial properties. Diatretol was isolated from a culture broth of *Metarhizium anisopliae* FKI-7223, having been originally discovered in a culture broth of the fungus *Clitocybe diatreta* by Nasini and co-workers in 1996.[1] It was known to exhibit weak antibacterial activity against *Bacillus cereus* but Diatretol possesses a diketopiperazine (DKP) framework, consisting of characteristic *N,O*-acetal, and shows potent antimalarial activity *in vitro* and *in vivo*. Therefore we decided to synthesize Diatretol to investigate its structure-activity relationships. For total synthesis of Diatretol, the key is way to construct *N,O*-acetal stereoselectively. With regard to conformation, several DKPs bearing a benzyl moiety have been reported to adopt a folded conformation in which the benzyl moiety is folded over the DKP.[2] We considered that *N,O*-acetal could be constructed by stepwise stereoselective oxidation and regioselective transacetalization using this folded conformation. At this congress, we are going to report the first total synthesis of Diatretol in addition to total synthesis of three Lepistamides.

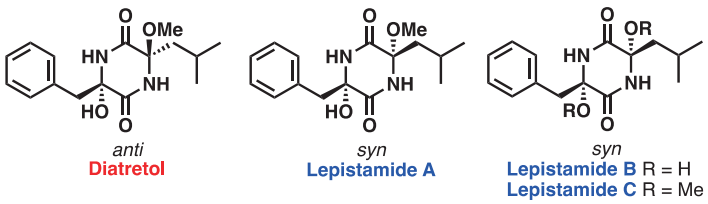
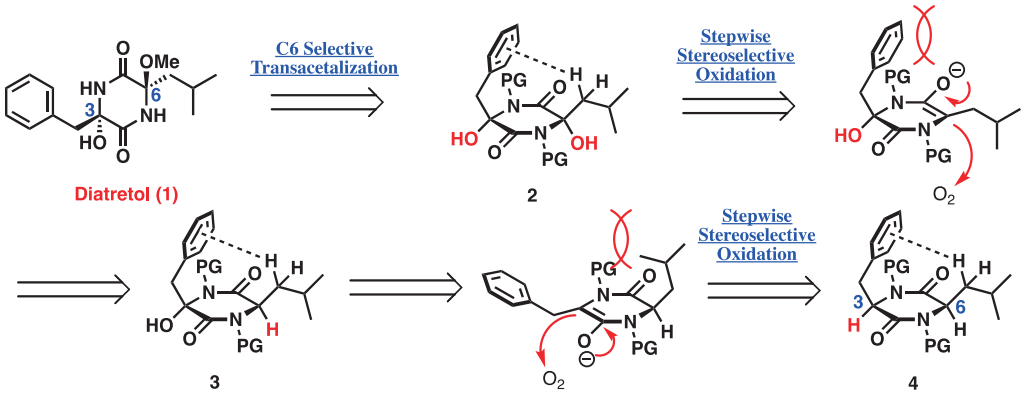


Figure 1. Structures of Diatretol and Lepistamides



Scheme 1. Synthetic Strategy of Diatretol

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Synthetic Study of TIGIT Protein for Mirror-Image Screening

Keisuke Aoki, Jumpei Sasaki, Naoya Iwamoto, Yusuke Usui,
Shinsuke Inuki, Hiroaki Ohno and Shinya Oishi*
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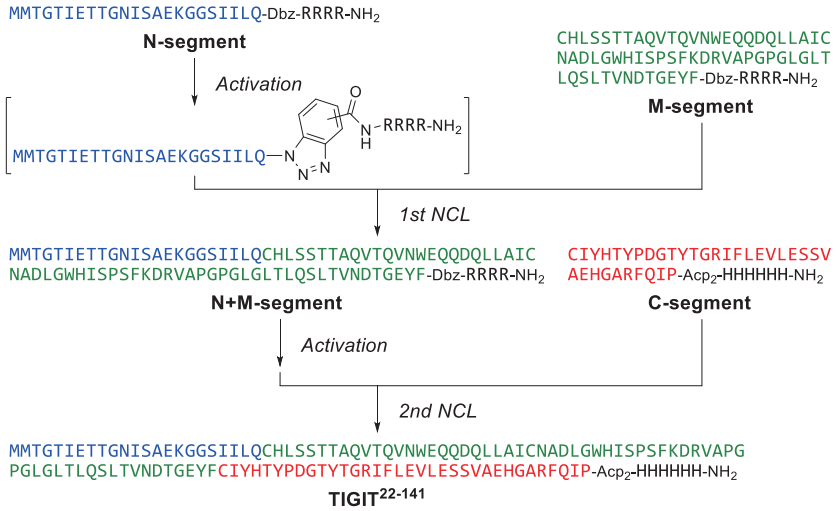
T cell immunoreceptor with Ig and ITIM domains (TIGIT) is a coinhibitory receptor expressed by $CD8^+$ T cells, which infiltrates into various tumor tissues and suppresses immune responses via interaction with CD155. Because the inhibitory molecules against TIGIT-CD155 interaction can reactivate the immune responses, TIGIT is an attractive drug target for cancer immunotherapy. In our screening campaign from virtual mirror-image library of natural products,[1] we selected the extracellular domain of TIGIT ($TIGIT^{22\text{-}141}$) as a target protein. In this study, we investigated the chemical synthesis of TIGIT proteins via stepwise native chemical ligations (NCLs).

Initially, we synthesized three peptide segments (N-, M-, and C-segments) by a standard Fmoc-based solid-phase synthesis. Because the N-segment and M-segment were less soluble in solvents for HPLC purification, a soluble peptide sequence was appended at the C-terminus via the Dbz linker. In the first NCL by nitrate-mediated activation of the N-segment to provide *N*-acylbenzotriazole intermediate,[2] HPLC purification of the product (N + M segment) failed, although various conditions were investigated. To overcome this problem, size-exclusion separations such as dialysis and ultrafiltration were attempted to remove the unreacted substances and by-products. The desired TIGIT protein was obtained by the second NCL between N + M segment and C-segment; however, the yield and purity were low. The optimization of the reaction conditions and purification processes are now ongoing to improve the preparation of $TIGIT^{22\text{-}141}$.



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ANP77: A Three-carbon Atom Linked 2-Amino-1,8-naphthyridine Dimer that Recognizes Cytosine Rich Bulge-mismatched Sequences in Duplex DNA and RNA

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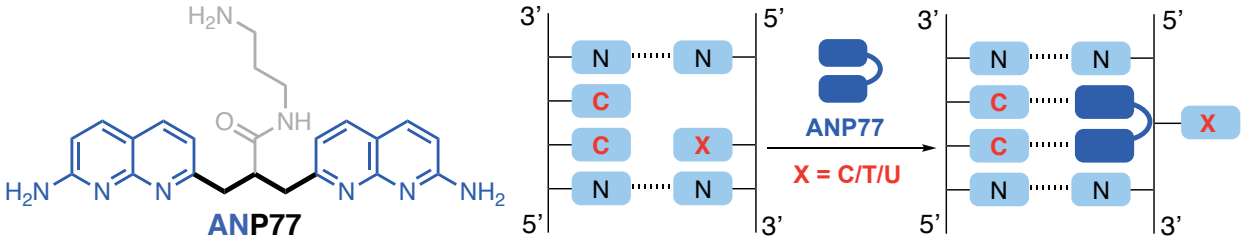
Bulged and mismatched structures in nucleic acids are of biological significance, arises as the consequence of replication or recombination errors and proposed to play crucial roles in many biomolecular processes that induce negative consequences on human health.[1-2] Sequence-specific recognition of these structures by small molecules is believed to be a promising tool for the development of novel chemotherapeutic agents. In continuation of our research on hydrogen-bonding-mediated sequence-specific recognition of the bulged and mismatched base pairs in duplex DNA and RNA by 2-amino-1,8-naphthyridine derivatives,[3-4] we have recently discovered a small molecule **ANP77**.[5]

ANP77 consists of two 2-amino-1,8-naphthyridine units, connected by a three-carbon atom linker that selectively recognizes the bulge-mismatched structures of dsDNAs and dsRNAs. The most efficient binding of **ANP77** to the bulge-mismatched site was observed for the sequences 5'-_C-3'/3'-CC-5' and 5'-_T(or U)-3'/3'-CC-5' with the formation of a 1:1 complex. Based on the binding studies and chemical analysis of the **ANP77** bound duplex DNA containing _T/CC site we proposed that two heterocycles in **ANP77** are supposed to be in folding orientation and stacks on to the bulge-mismatch site of the DNA helix with concomitant flip out of the thymine opposite to CC from the π-stack. Cytosine rich bulge-mismatched sites are a secondary structural element of many ncRNAs (such as pri-miRNAs or pre-miRNAs). ncRNAs play a crucial role in many biological processes and have functions in the regulation of gene expression. Therefore, **ANP77** could modulate the functions of ncRNAs by binding to r(_C/CC) or r(_U/CC).



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Synthesis of Helicenes Using Diels–Alder Reactions of Fused Benzynes with Furans

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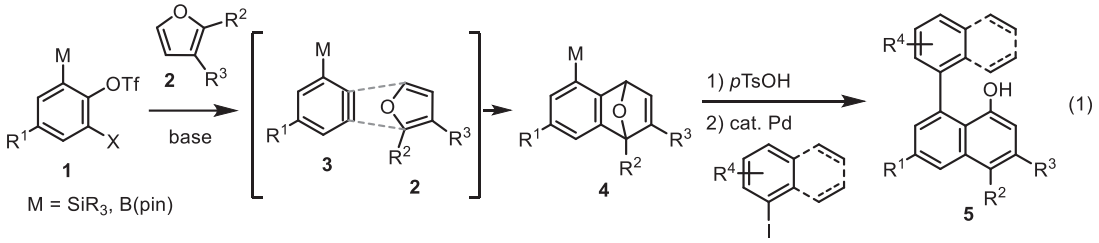
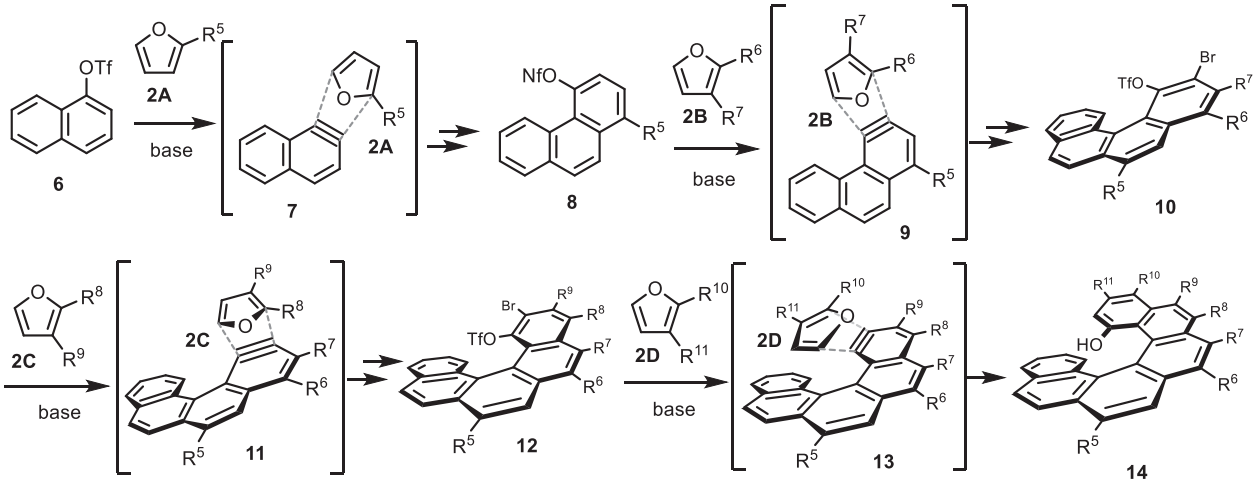
Helicenes have been studied extensively in chiral catalysts, tools for material science and chemical biology, etc. because of their anomalous feature. However, most helicene syntheses require multiple steps and are hard to functionalize on their skeleton. Recently, we have reported the regioselective Diels–Alder reactions of 3-silyl and 3-borylbenzynes **3** with furans **2** for the synthesis of naphthalene derivatives **5** (eq 1).[1] In this conference, we are going to present the diversity-oriented synthesis of functionalized helicenes through consecutive Diels–Alder reactions of fused benzynes with furans.



First, 1,2-naphthalyne (**7**) was generated from 1-naphthyl triflate (**6**) in the presence of 2-substituted furans **2A** using lithium tetramethylpiperidide (LTMP) at –78 °C in THF (Scheme 1). Then, the obtained Diels–Alder cycloaddition products were transformed to nonaflates **8** in 2- steps. The 3-membered fused benzynes **9** were generated in the presence of furans **2B** and the produced adducts were functionalized to give triflates **10** in 3- steps. Interestingly, 4-membered fused benzynes **11** generated from **10** reacted with furans **2C** in toluene but not in THF to provide desired Diels–Alder adducts. Finally, the reaction of triflates **12** converted from adducts gave helicenes **14** via 5-membered fused benzynes **13** in toluene. The distal/proximal regiochemistry of each Diels–Alder reaction was more influenced on C3-sbstituents (R^7, R^9, R^{11}) of furans **2** than C2-substituents (R^6, R^8, R^{10}).



Scheme 1. Synthesis of Helicenes through Consecutive Diels–Alder Reactions of Fused Benzynes

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5P-126s

Drug Discovery of Pyrilamine Derivatives as Blood-Brain Barrier Permeable Histone Deacetylase Inhibitors

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Histone deacetylases (HDACs) are enzymes repressing gene expression through deacetylating acetyl lysine of histone protein. HDAC inhibitors are considered to be therapeutic drugs for the treatment of cancer and central nervous system (CNS) diseases because overexpression of HDACs are observed in these diseases. Although some HDAC inhibitors are marketed as anti-cancer drugs, there is no HDAC inhibitors targeting CNS diseases due to their low permeability to blood-brain barrier (BBB). It is because HDAC inhibitors need polar zinc binding groups such as hydroxamic acid and *N*-(2-aminophenyl)benzamide. To overcome the problems, we focused on hybridization of HDAC inhibitors and pyrilamine which is known as a substrate of pyrilamine-sensitive proton-coupled organic cation antiporter (PYSOCA) on the BBB vascular endothelial cells. Based on this strategy, we designed and synthesized pyrilamine-based HDAC inhibitor **1** (Figure 1). As we hypothesized, biological evaluations showed that compound **1** was a substrate of PYSOCA and showed class I preferring HDAC inhibitory activity and high BBB permeability in rats.[1] For further optimization of compound **1**, we synthesized pyrilamine derivatives for acquiring structure-activity relationship information. As a result, we identified compound **2** with potent HDAC1 inhibitory activity (IC_{50} = 2.2 μM) (Figure 1).

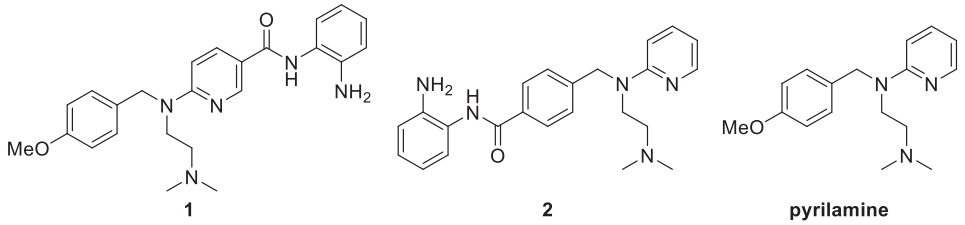

Figure 1. Chemical structures of pyrilamine and pyrilamine-based HDAC inhibitors **1** and **2**.

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5P-127

Total Synthesis of Sophoraflavanone H

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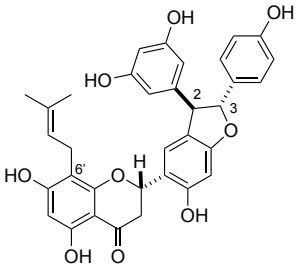
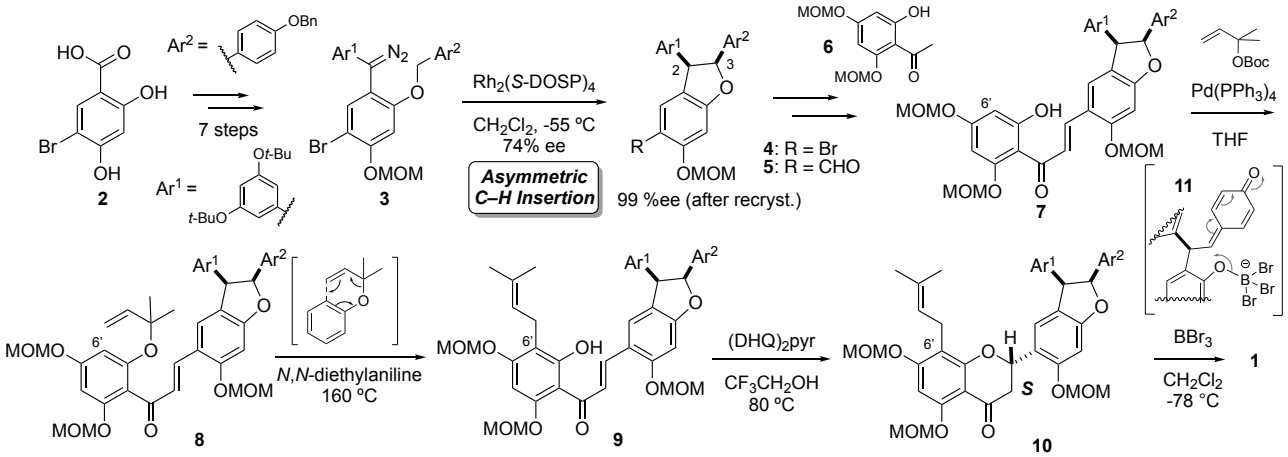
Sophoraflavanon H (**1**), which is a unique polyphenol isolated from *Sophora moorcroftiana* [1], has a hybrid-type structure containing 2,3-diaryl-− dihidorobenzofuran and flavanone ring. On the other hand, **1** has special activities derived from the unique structure, such as an antibiotic activity toward drug-resistant bacteria and antitumor activity. Thus, 1 is expected to constitute a lead compound for drug development. Here, we report that the total synthesis and determination absolute configuration of **1**.



Sophoraflavanon H (**1**)

During the synthesis of 1, structurally unique 2,3-diaryldihidorobennzofuran and flavanone ring were constructed by our developed Rh-catalyzed C-H insertion reaction and flavonoid chemistry. The diazomethane **3** was synthesized by the position-controlled conversion of benzoic acid **2**. The C-H insertion reaction of **3** proceeded smoothly to afford **4** with high enantiomeric excess. The absolute configuration of **4** was determined by X-ray crystallographic analysis. After the conversion into **7** through the formylation and the aldol condensation with **6**, the installation of 8'-prenyl group was performed by reverse-prenylation of free hydroxyl group followed by Claisen condensation. The flavanone ring was constructed by treatment with $(DHQ)_2$pyr in TFE to give **10** with its diastereomer. With the comparison between the CD spectrum of the synthetic and the model flavanone, the absolute configuration of **10** was determined as *S* form. Finally, the total synthesis of **1** was achieved by the deprotection of **10** and the isomerization via quinone methide intermediate **11**.



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One-Pot Synthesis of Highly Functionalized 2-Chloroaziridines for Stereoselective Synthesis of (*Z*)-Chloroalkene Dipeptide Isosteres Containing α,α-Disubstituted Amino Acids

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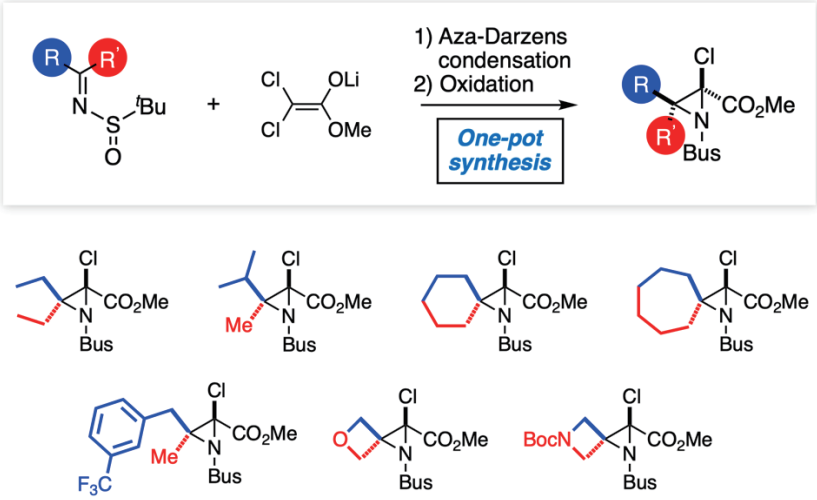
Substituted aziridines are useful building blocks employed widely for the synthesis of bioactive molecules, pharmaceuticals, and materials because of the high ring strain energy delivering their unique reactivity. As part of our program on developing novel peptidomimetics including chloroalkene-type dipeptide isosteres (CADIs),[1] one of the useful dipeptide mimetics in the fields of medicinal chemistry and chemical biology, containing α,α-disubstituted amino acids (ααAA),[2] we envisioned that a stereoselective ring opening of 2-chloroaziridines would be highly useful for those synthetic purposes.

In this symposium, we will report a one-pot stereoselective synthesis of a highly functionalized 2-chloroaziridines by aza-Darzens condensation from readily available *tert*-butanesulfinyl imines and methyl dichloroacetate. Various imines react smoothly, enabling the synthesis of a variety of highly functionalized 2-chloroaziridines including spirocyclic aziridines. The resulting, spirocyclic aziridines are in great demand as scaffolds for the synthesis of ααAA-containing (*Z*)-CADIs. Details of the design of the strategy, substrate scope, and application studies of those aziridines to synthesize ααAA-containing (*Z*)-CADIs will be discussed.



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5P-129

Gold-Catalyzed Indenone Synthesis from 2-Alkynylaldehyde Cyclic Acetal

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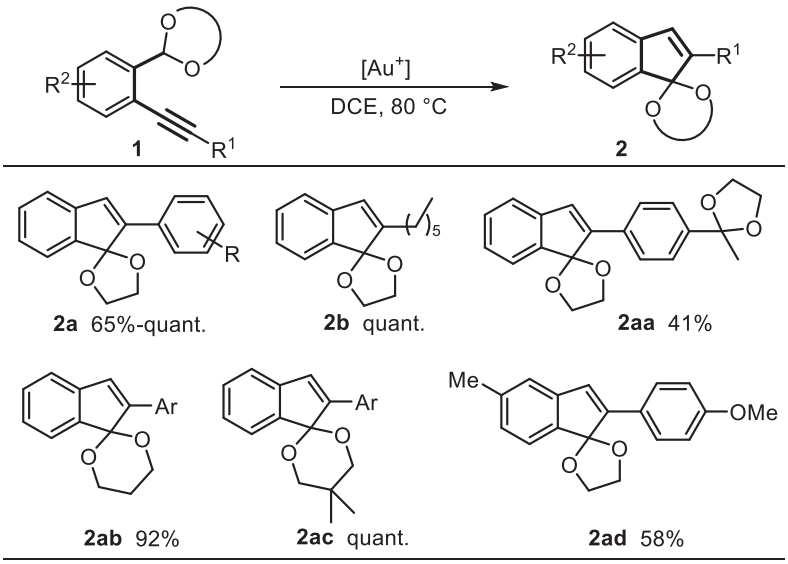
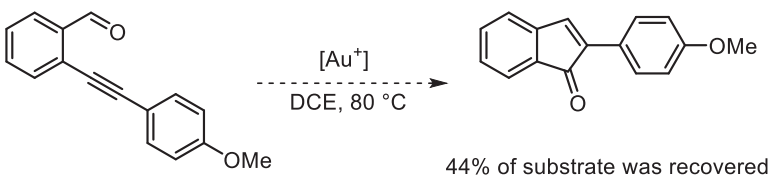
Gold-catalyzed intramolecular cyclization reactions through activation of alkynes using by π-acidic gold (I) cation complex is the powerful tool for the synthesis of various hetero and carbocyclic compounds under mild reaction conditions. Since the indenone skeleton is frequently included as the partial structures in various medicines, natural products, and functional materials, the development of an efficient synthetic method of indenone derivatives is essential. Although indenone structures could be prepared by the oxidation of indene or transition metal-catalyzed inter- or intramolecular cyclization of various alkynyl compounds, these reported synthetic methods required stoichiometric amounts of oxidants, reoxidant of the metal catalysts, or organometal reagents, and so on.

We present the development of the novel gold-catalyzed intramolecular cyclization of 2-alkynylaldehyde cyclic acetal (**1**) for the synthesis of indenone derivatives (**2**). Various 2-alkynylaldehyde cyclic acetals are efficiently cyclized in the presence of gold(I) complex without any additives (Scheme 1). The NMR analysis of asymmetrically substituted indenone ethylene ketal (**2ad**) indicated that the acetal unit of the substrate might be migrated to the opposite position of the fused ring during the reaction, although the further structural determination is now in progress. The cyclization reaction is also applicable to various cyclic acetals such as 1,3-dioxane acetal and 2,2-dimethyl-1,3-dioxane acetal to obtain corresponding cyclic ketals (**2ac** and **2ad**). Since the cyclization of 2-alkynylbenzaldehyde (**3**) never proceeded (Scheme 2), the acetal unit is essential for the present carbocyclization reactions. In this symposium, we will discuss the development of the gold-catalyzed indenone synthesis and the detailed reaction mechanisms, including the structural determination of asymmetrically substituted indenone ethylene ketal.

Scheme 1. Scope of substrates



Scheme 2. Comparative experiment



Genome mining of hydrazine-forming machinery identified novel natural products with unique dihydropyridazinone rings

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Natural products containing a nitrogen-nitrogen (N-N) bond are scares but they exhibit wide structural diversity and various biological activity. Although recent studies unveiling several different biosynthetic mechanisms for N-N bond formation, they have not been fully understood in most cases. In our previous study, we identified a novel biosynthetic route to form N-N bond.[1] In this route, methionyl-tRNA synthetase (metRS)-like enzyme; Spb40 catalyze N-N bond formation between two amino acids to generate hydrazine. Most recently, it was found that this hydrazine-forming machinery is also utilized in the biosynthesis of other natural products such as triacsins[2] and formycins.[3] Although the number of N-N bond containing natural products is still limited, database search revealed that this hydrazine-forming machinery widely distributes across several bacterial phyla including *Actinobacteria, Proteobacteria, Cyanobacteria*, *Firmicutes* and *Deinococcus-Thermus*. This fact indicates the overlooked biosynthetic potentials of these bacteria to produce natural products with N-N bond, and the large portion of these compounds remain unidentified. Here in this study, we screened the actinomycetes possessing metRS-like gene to select strains with potentials to produce natural products containing N-N bonds. This genome-mining approach led to the identification of g1-p1 with dihydropyridazinone ring that is unprecedented in natural products.

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5P-131s

Design and Synthesis of Inhibitors of Enzymes of Purine Metabolism – Application of Direct Metalation of Heterocycles

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Hypoxanthine-guanine-(xanthine) phosphoribosyltransferase (HG(X)PRT) and purine nucleoside phosphorylase (PNP) are important enzymes involved in the purine salvage pathway and it was shown that inhibition of them could be used as a potential target for treatment of bacterial and/or parasitic infections. Inhibitors, which mimic transition state of the reaction catalyzed by HG(X)PRT (Fig. 1), effectively arrest the growth of protozoan parasites of the genus *Plasmodium*, which causes malaria[1].

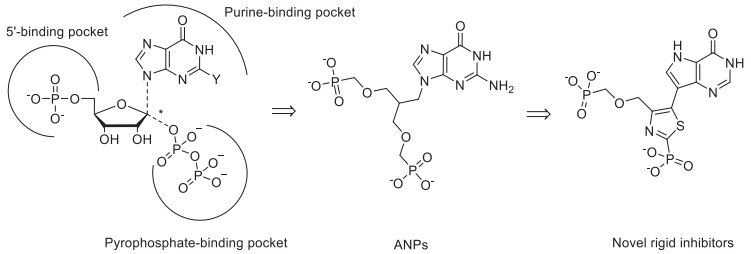

Fig. 1. HG(X)PRT transition state and structures of ANPs.

Inhibitors of HG(X)PRT and PNP based on acyclic nucleoside phosphonates (ANPs) were previously developed in our research group[2] (Fig. 1). HG(X)PRT inhibitors can bind into all three binding pockets of the enzyme – purine-base pocket, 5'-phophate pocket and pyrophosphate-binding pocket. New compounds, where acyclic moiety was replaced with rigid aromatic heterocycles, were designed and synthesized as mimics of the transition state of the enzyme.

For example, thiophenes can be easily derivatized by direct or halogen-exchange metalations, yet, there are only a few reported metalation examples of highly substituted thiophenes with reactive functional groups[3]. In this work, *tetra*-substituted thiophenes were synthesized by combination of several approaches with direct metalation as the most important one.

This work was supported by the IOCB CAS (RVO61388963), Czech Science Foundation (16-06049S), NHMRC Australia (1147368), and the Technology Agency of the Czech Repulic (NCK 1, TN01000013).

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Functionalized Lactone Formations on the Basis of Halogen-Controlled Rapid Cyclization of Haloketo Acids under Mild Conditions

Hideyasu China, Nami Kageyama, Hotaka Yatabe, Kaishi Nishiguchi, Yusuke Kojima, Kotaro Kikushima and Toshifumi Dohi

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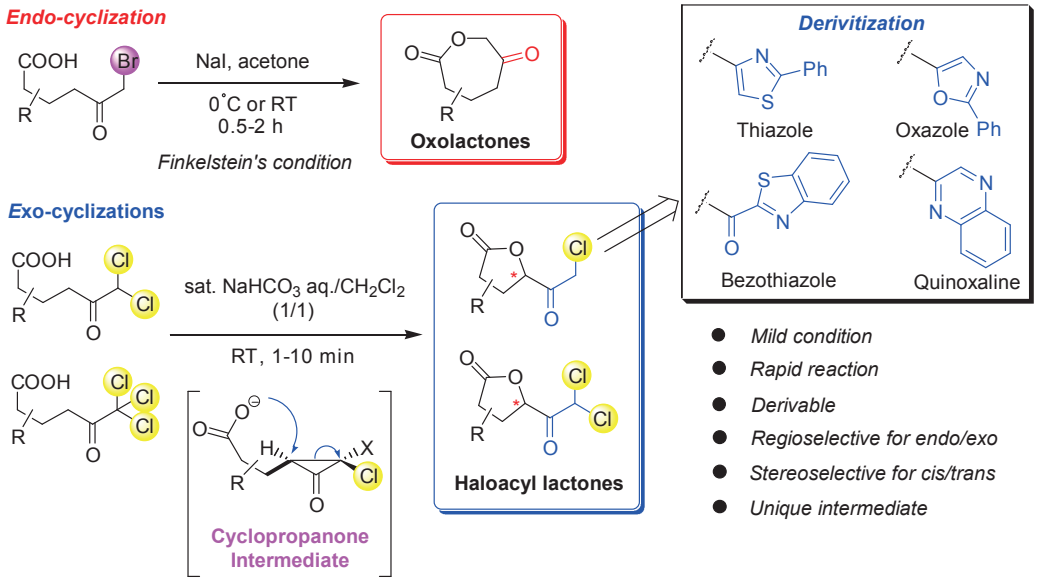
Functionalized lactones are useful for the synthesis of various heterocyclic compounds. Although the halogen atoms are a typical activating factors for organic compounds, they have not been effectively utilized for lactone formation. In this study, we present halogen-controlled selective synthesis of functionalized lactones from haloketo acids under mild conditions, which were found during monochlorodimedone assay for evaluation of the oxidative bromination activity of haloperoxidases.[1]

The reaction of monobromo keto acids with sodium iodide underwent *endo*-cyclization to afford the corresponding oxolactones. On the other hand, di- and tri-chloro keto acids were unexpectedly converted into chloro acyllactones through the *exo*-cyclization in aqueous solution of weak inoganic base without any sacrificial reagent. The different ring sizes were selectively constracted under mild conditions, wherein the high regioselectivities were controlled by the halogen atoms in halo keto acids. Reaction mechanism for the *exo*-cyclization is suggested to involve the Favorskii cyclopropanone intermediate generated by the intramolecular catalysis of the carboxylate anion of di- and tri-halo keto acids. Regarding the haloacyl lactone products, the chloroacyl group with the lactone structure can be successively transformed into various heterocycles.



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5P-133

Synthetic Studies Towards Broussonetine N

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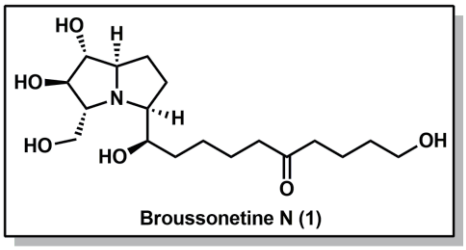
Broussonetines are a family of naturally occurring iminosugars or polyhydroxylated alkaloids, isolated from the branches of the deciduous tree *Broussonetia kazinoki* SIEB.[1] To date, about 30 congeners of broussonetine alkaloids have been isolated by Kusano and co-workers.[2] Most of these alkaloids show potent glycosidase inhibitory activities and have therapeutic potential as antitumor and anti-HIV agents.[3] Therefore, the synthesis and biological evaluation of these alkaloids could lead to the creation of molecules applicable for drug development.

While most of these alkaloids have a pyrrolidine core, broussonetine N (**1**), isolated and determined the structural elucidation in 1999, possesses unique structure having a polyhydroxylated pyrrolizidine skeleton with six stereogenic centers and a long hydrocarbon chain (**Figure 1**).[4] However, the total synthesis of broussonetine N (**1**) has not been reported, and the absolute configuration is only predicted by Mosher's method. In addition, iminosugers having a pyrrolizidine skeleton, including broussonetine N (**1**), have high potential as pharmaceuticals, but reserach on synthesis and biological evaluation of these alkaloids is not sufficient. Therefore, we aimed at establishing a flexible and efficient synthetic route to broussonetine N (**1**) and its derivatives for the structure-activity relationship studies of pyrrolizidine-type iminosugars.



Biological activity : β-Glu : IC_{50} = 6.7 μM
β-Gal : IC_{50} = 2.9 μM
β-Man : IC_{50} = 3.3 μM

Figure 1. Structure of Broussonetine N (1)

Details of the synthetic studies on broussonetine N (**1**) and its derivatives will be presented.

[1] Shibano, M.; Kitagawa, S.; Kusano, G. *Chem. Pharm. Bull.* **1997**, *45*, 505.
[2] Shibano, M.; Tsukamoto, D.; Kusano, G. *Heterocycles* **2002**, *57*, 1539.
[3] Winchester, B.; Fleet, G. W. J. *J. Carbohydr. Chem.* **2000**, *19*, 471.
[4] Shibano, M.; Tsukamoto, D.; Kusano, G. *Chem. Pharm. Bull.* **1999**, *47*, 907.

Development of an efficient synthetic method for α-methylene γ-butyrolactone skeleton and its application to total synthesis of arglabin and ludartin

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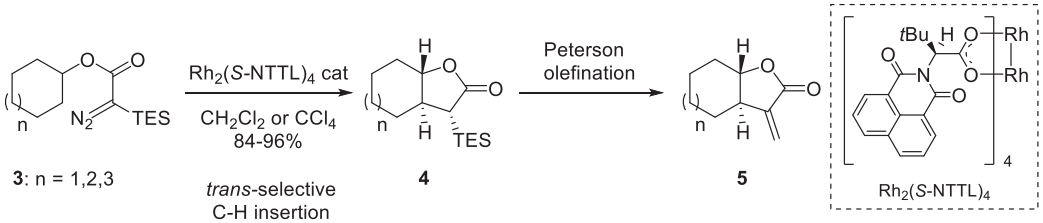
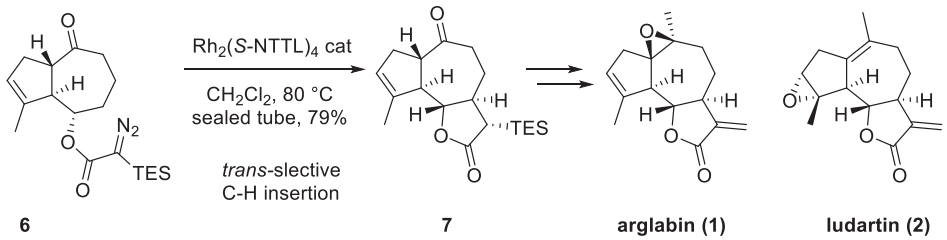
α-Methylene-γ-butyrolactone skeleton has recently attracted much attention in medicinal chemistry as a pharmacophore that undergoes Michael reaction with nucleophilic amino acid residues to exhibit various biological activities.[1] However, methods capable of constructing the skeleton efficiently are limited: the most conventional method is a sequence of lactonization of hydroxy acids and α-methylenation. Here we develop an efficient synthetic method for α-methylene γ-butyrolactone, featuring intramolecular C–H insertion of α-diazoesters. The synthetic use is demonstrated by the total synthesis of antitumor sesquiterpenes, namely, arglabin (**1**) and ludartin (**2**).

We envisaged that Rh-catalyzed intramolecular C–H insertion of α-diazoesters would be effective for rapid construction of γ-butyrolactone from appropriate alcohols. The effects of α-substituents of α-diazoesters and Rh catalysts were screened employing diazoester **3** and its derivatives as model substrates. As a result, it was found that *trans*-fused compound **4** was efficiently obtained by the use of Rh_2(*S*-NTTL)$_4$ catalyst and a substrate with a bulky substituent such as a triethylsilyl group (**3**). α-Methylenation of the γ-lactone was achieved via Peterson olefination to establish a method for construction of α-methylene-γ-butyrolactone skeleton (**Scheme 1**).



Scheme 1

This method was applied to total synthesis of arglabin (**1**) and ludartin (**2**). Diazoester **6** with a bicyclo[5.3.0]decane skeleton successfully underwent Rh-catalyzed intramolecular C–H insertion to construct *trans*-γ-butyrolactone. Thereafter, total synthesis of **1** and **2** was achieved via several conventional transformations (**Scheme 2**).



Scheme 2

[1] R. J. K. Taylor *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 9426-9451

Parallel Kinetic Resolution of Various rac-Allylic Amides via Asymmetric Bromocyclization

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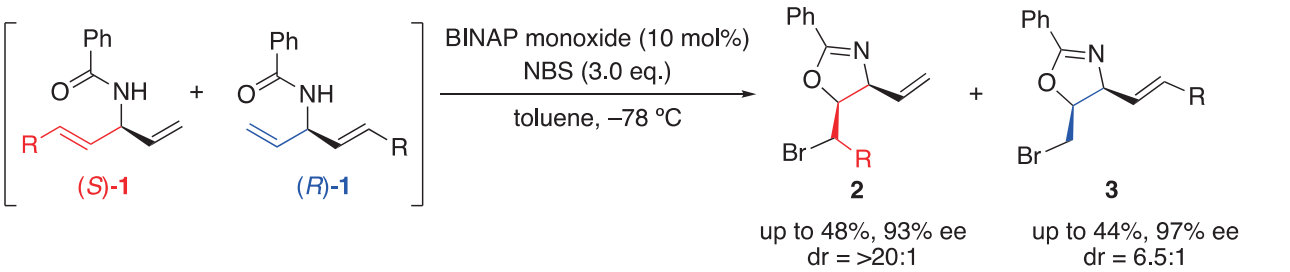
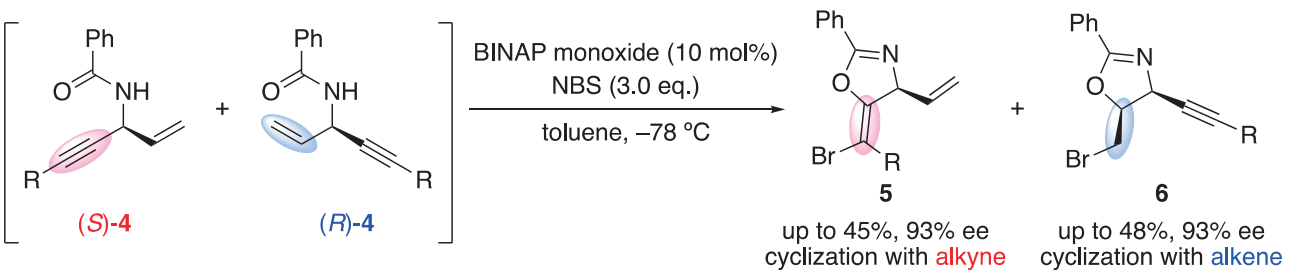
Enantioselective halocyclizations are important methods for synthesizing chiral halogen-containing compounds, which are versatile building blocks for the synthesis of natural products and pharmaceuticals. In this context, we have developed the catalytic desymmetrization of bisallylic amides through a highly enantioselective bromocyclization with BINAP monoxide as a catalyst.[1–3] Here we report the first parallel kinetic resolution (PKR) of racemic allylic amides (**1**) via asymmetric bromocyclization catalyzed by the BINAP monoxide. The catalyst could recognize both enantiomers of the substrate, converting them into regioisomeric products **2** and **3** in a highly stereoselective manner. This catalytic system could be applicable to various allylic amide substrates. In particular, the substrates having both alkene and alkyne moieties (**4**) were also efficiently transformed to the corresponding cyclized products **5** and **6** in high yields with high enantioselectivities, respectively. Overall, we achieved regio- and chemodivergent PKR of racemic allylic amides with the use of a simple chiral BINAP monoxide catalyst. In this presentation, we will also discuss the active catalytic species for the bromocyclizations and a possible resolution mechanism.

■ *Regiodivergent* parallel kinetic resolution



■ *Chemodivergent* parallel kinetic resolution



[1] Nagao, Y.; Hisanaga, T.; Egami, H.; Kawato, Y.; Hamashima, Y. *Chem. Eur. J.* **2017**, *23*, 16758.
[2] Nagao, Y.; Hisanaga, T.; Utsumi, H.; Egami, H.; Kawato, Y.; Hamashima, Y. *J. Org. Chem.* **2018**, *83*, 7290.
[3] Kawato, Y.; Hamashima, Y. *Synlett* **2018**, *50*, 2948.

5P-136s

Synthetic studies on GPR35 agonist without species-specificity

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Activation of orphan G protein-coupled receptor GPR35 suppresses the production of inflammatory cytokines IL-4, therefore GPR35 agonist is expected as an antiallergic drug. There is no compound under clinical trial because the most of known GPR35 agonists demonstrate species-specificity between human and rodent. We have already developed the potent GPR35 agonist **1** without the species-specificity by docking studies, namely two acidic substituents might settle the species-specificity (Figure 1A). Moreover, docking studies of compound **1** to GPR35 homology model reconciled with the SAR of COOH position. Therefore, we designed and synthesized compound **2** (scanning substituents on chromone ring) and compound **3** (replacement of chromone ring by quinolone ring) to elucidate the structure-activity relationship (SAR) and to diversify potent GPR35 agonist (Figure 1B). As a result of the biological evaluations, methyl ester **2b** was unexpectedly found to be a potent agonist without species-specificity. It is speculated that compounds with a hydrogen bond accepter (HBA) such as OMe, CN and F exhibit also potent GPR35 agonistic activity without species-specificity. On the course of the synthesis, we found that chromone ring with an electron-withdrawing substituent at 6-position is easily cleaved by alkaline hydrolysis. In this presentation, synthesis, biological evaluations and docking study of compound **1**-**4** will be reported.

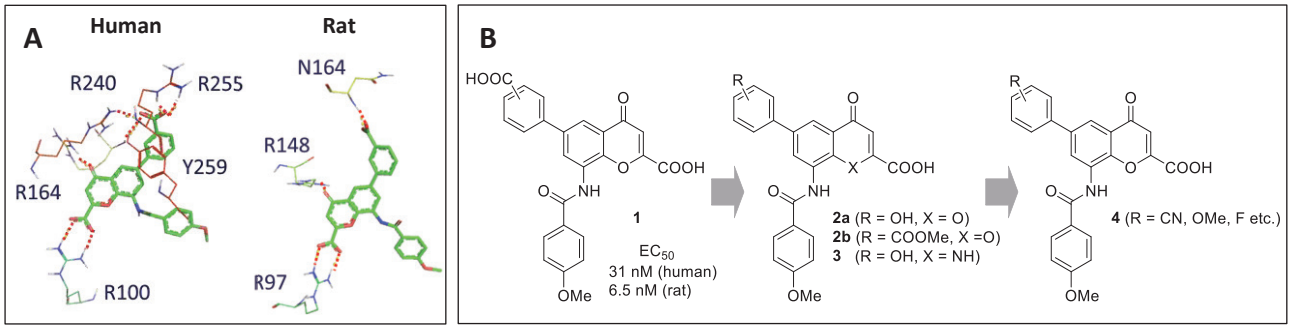

Figure 1. (A) Docking studies of cpd. **1** with GPR35 homology model. (B) Design of GPR35 agonist without species-specificity.

5P-137

Rational design of bis-2-aminothiazoline as a new chiral scaffold beyond bisoxazoline

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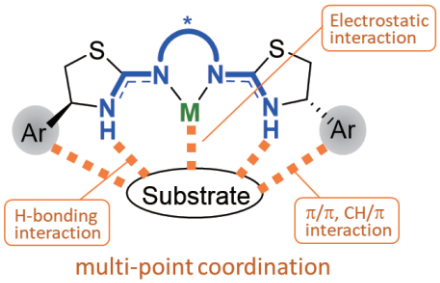
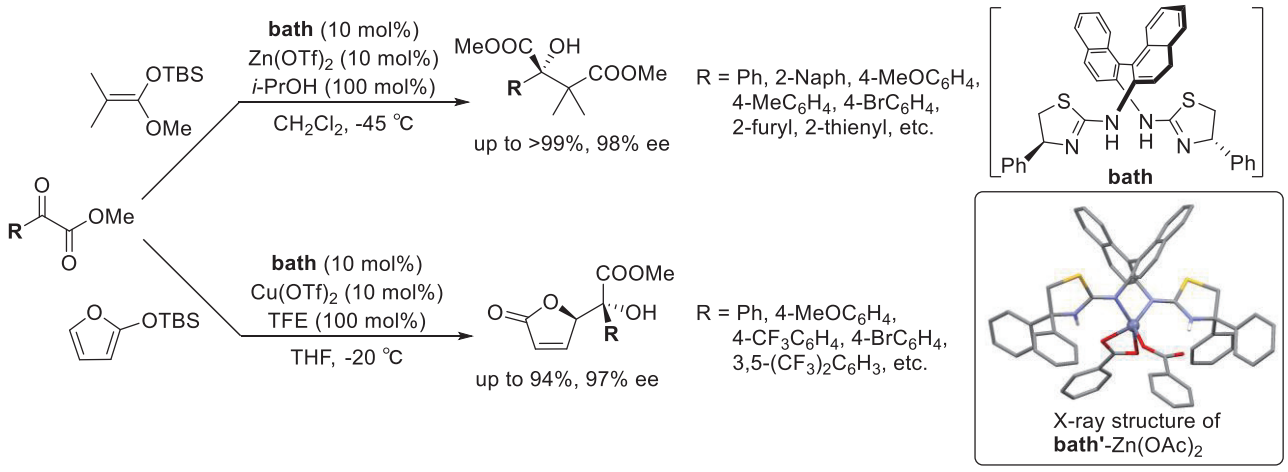
Development of chiral catalyst with valuable impact on asymmetric synthesis has continuously attracted much attention over the past decades. Recent progress of computational chemistry motivated us to establish a guideline for the rational design of new catalyst. We herein develop a new chiral scaffold, bis-2-amino-thiazoline, through the interplay between computation and experiment.



Chiral bisoxazolines (box) are one of the most efficient privileged ligand for asymmetric catalysis. The box-Cu(II) complex has been developed for asymmetric aldol reaction of enolsilanes with pyruvate esters, pioneered by Evans in 1997, but substrate scope was still rather limited. Computationally supposed TS models of box-Cu(II) catalyzed aldol reaction suggested that the lack of substrate generality would be attributed to the narrow chiral space of box. To improve substrate generality with keeping high stereocontrol ability, bis-2-amino-thiazoline (bath) was rationally designed. The corresponding metal complex (bath-M) provides a wider chiral space in which the sterically hindered α-ketoesters would be efficiently captured. In addition, bath-M is supposed to achieve high stereoselectivity through the multi-point coordination consisting of electrostatic interaction (M: Lewis acid), hydrogen bonding interaction (NH residue), and dispersive interaction (Ar group). In sharp contrast to box-Cu(II), bath-Zn(II) promoted asymmetric Mukaiyama aldol reaction of dimethylketene silyl acetal with a wide variety of α-ketoesters to afford the aldol products having continuous quaternary carbon center with high yields and enantioselectivities. DFT calculation of transition state indicates that the predicted multi-point coordination plays a crucial role in the high enantioselectivity. In addition, bath-Cu(II) was also successfully utilized for asymmetric vinylogous aldol reaction of α-ketoesters, achieving high yield and enantioselectivities.



5P-138

Parapyrazinophane - An Intrinsically Chiral Diazine-cyclophane and the Kinetics of Its Racemization

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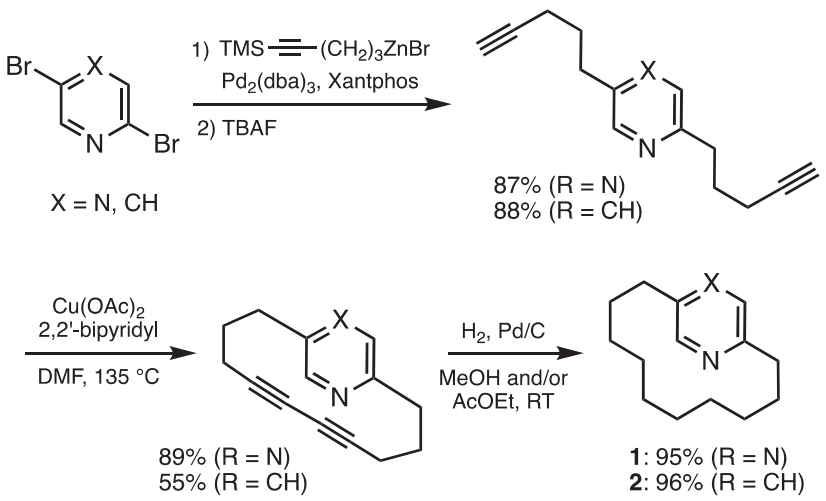
Parapyrazinophane is an intrinsically chiral diazine-cyclophane having a C_2-symmetric planar-chirality. [1] Although its physical properties must be dependent on the nature of the pyrazine core, nothing is known because the synthetic method of parapyrazinophane has not been reported yet. For investigating the physical properties of such a unique heterocyclic molecule, we have targeted [10]parapyrazinophane **1** to develop an efficient synthetic protocol for studying the stability of each enantiomer from the kinetics of racemization.

Synthesis of a parent [10]parapyrazinophane **1** and its reference molecule, [10]parapyridinophane **2**, was achieved in four steps each from the corresponding 2,5-dibromides followed by double Negishi coupling of TMS-protected pentynylzinc bromide, successive Glaser coupling after deprotection, and hydrogenation of the resulted diyne moieties of cyclophane precursors. Their kinetic properties of activation were measured by monitoring their rope-skipping racemization from enantio-enriched **1** and **2** obtained by HPLC resolution using chiral stationary phases. Surprisingly, further nitrogen incorporation onto an aromatic core of pyridinophane **1** was found to decrease the rate of racemization against our expectations. The isomerization of pyrazinophane **1** was suppressed as compared with that of pyridinophane **2** ($\Delta\Delta G^{\ddagger}_{1\text{-}2}$ = +3.4 kJ/mol) as shown in Figure 1, although $\Delta H^{\ddagger}$ indicates that planar-chirality of **1** is energetically less stable than that of **2** ($\Delta\Delta H^{\ddagger}_{1\text{-}2}$ = –20.0 kJ/mol). This sign inversion is ascribed to a more significant negative value of $\Delta S^{\ddagger}$ for **1** (–125.0 J/mol•K), suggesting that its intrinsic C_2 symmetry enhances dynamic flexibility at an initial state such as more active pseudo rotations of its ansa-bridge to equilibrate geometrically stable conformers.



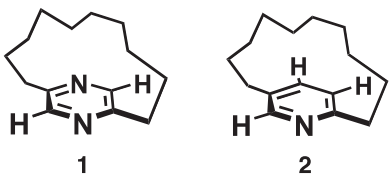


Table 1. Kinetic parameters of racemization for **1** and **2**

	1	**2**
$\Delta G^{\ddagger}$ [kJ/mol]	126.3	122.9
$\Delta H^{\ddagger}$ [kJ/mol]	89.1	109.1
$\Delta S^{\ddagger}$ [J/mol•K]	-125.0	-46.1

[1] Mugishima, N.; Kanomata, N.; Akutsu, N.; Kubota, H. *Tetrahedron Lett*. **2015**, *56*, 1898-1903.

Synthetic Study of Aloin through Regioselective Diels-Alder Reactions of Benzaines

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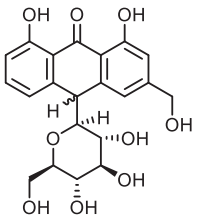
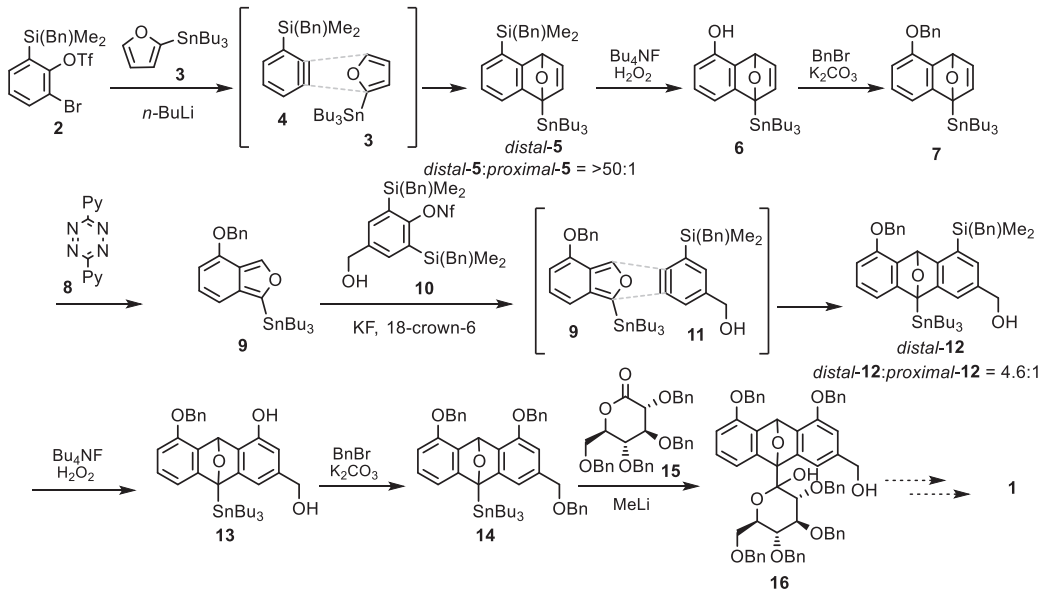

aloin (**1**)

Aloin (**1**), contained in aloe, has long been used as a traditional laxative. Recently, various biological activities of **1**, such as inhibitory effects against cardiovascular and Alzheimer disease, have been reported. However, the total synthesis of **1** has not been reported yet, and its structure-activity relationship has hardly been studied.

We have reported the Diels–Alder reactions of benzynes with furans which proceed regioselectively using a silyl or boryl group as a directing group.[1,2] In this conference, we are going to report our synthetic study of **1** using the consecutive and regioselective Diels–Alder reaction of benzynes to build up its aglycone framework.

First, the Diels–Alder reaction of **2**-(tributylstannyl)furan (**3**) and **3**-silylbenzyne **4**, generated from its precursor **2**, provided the cycloaddition product **5** with perfect regioselectivity (distal-**5**: proximal-**5** = > 50 : 1).[1] Next, distal-**5** was converted to benzyl ether **7** by the Tamao oxidation and the following protection of the hydroxyl group. The obtained **7** was subjected to one-pot isobenzofuran preparation using tetrazine **8** and the Diels–Alder reaction of silylbenzyne **11**, generated from a precursor **10**, to produce distal-**12** in good selectivity (distal-**12**: proximal-**12** = 4.6: 1). Another Tamao oxidation of distal-**12** and the hydroxyl group protection provided **14**, which was lithiated using MeLi, and the resultant anion was captured by lactone **15** to generate **16** having all carbon skeletons of **1**. Further transformations of **16** to complete the total synthesis of **1** are now ongoing.



[1] Akai, S.; Ikawa, T.; Takayanagi, S.; Morikawa, Y.; Mohri, S.; Tsubakiyama, M.; Egi, M.; Wada,Y.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 7673.
[2] Ikawa, T.; Takagi, A.; Kurita, Y.; Saito, K.; Azechi, K.; Egi, M.; Kakiguchi, K.; Kita, Y.; Akai, S. *Angew. Chem., Int. Ed.* **2010***, 49,* 5563.

5P-140

The Enhancement of Enantio-recognition in Kinetic Resolution of Chiral Secondary Alcohols with Chiral Acyltriazolium by Formation of Alcohol–Carboxylate Complexes

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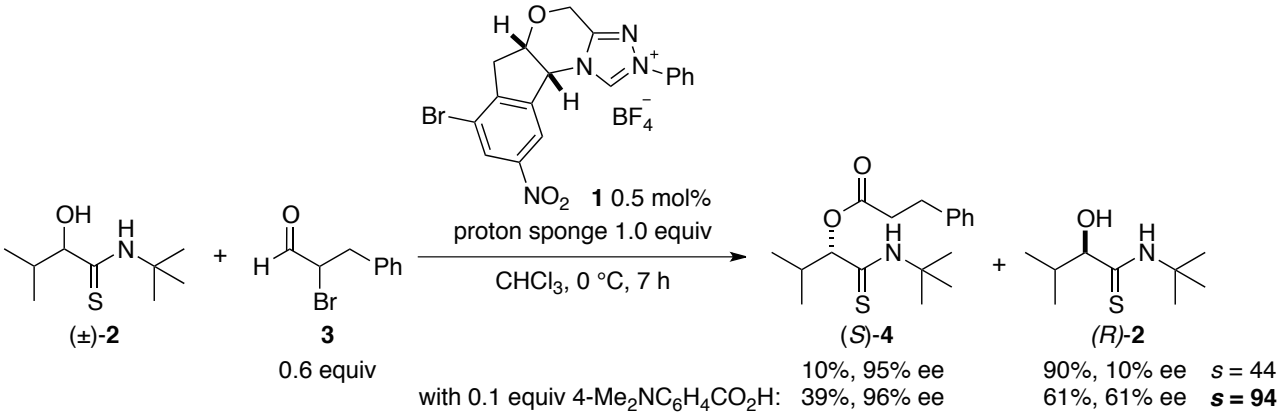
Kinetic resolution of racemic secondary alcohols via enantioselective acylation is an important method in synthetic chemistry.[1] Recently, we found that the rates and enantioselectivities of chiral NHC-catalyzed asymmetric acylation of alcohols bearing an adjacent H-bond donor functionality are remarkably enhanced in the presence of a carboxylate cocatalyst. The degree of the enhancement is correlated with the basicity of the utilized carboxylate. Using a cocatalyst and newly developed electron-deficient chiral NHC, generated from triazolium **1**, kinetic resolution of α-hydroxy thioamide **2** was achieved with high enantioselectivity (s = 94) with low catalyst loading (0.5 mol %), while the significantly decreased selectivity (s = 44) was observed in the absence of the cocatalyst (Scheme 1). The methodology was also applicable to kinetic resolution of cyclic diols and amino alcohols as well as desymmetrization of a meso compound.[2]



Scheme 1: NHC–Carboxylate Catalyzed Kinetic Resolution of α-Hydroxy Thioamide.

[1] Müller, C. E.; Schreiner, P. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 6012.
[2] Kuwano, S.; Harada, S.; Kang, B.; Oriez, R.; Yamaoka, Y.; Takasu, K.; Yamada, K. *J. Am. Chem. Soc.* **2013**, *135*, 11485.

Regioselective Synthesis of Fused Heterocycles Using 2-Silyl-3,4-pyridyne

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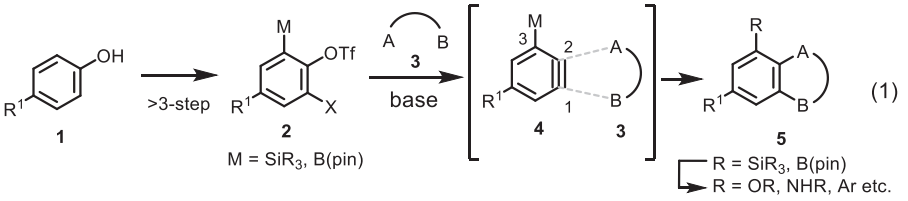
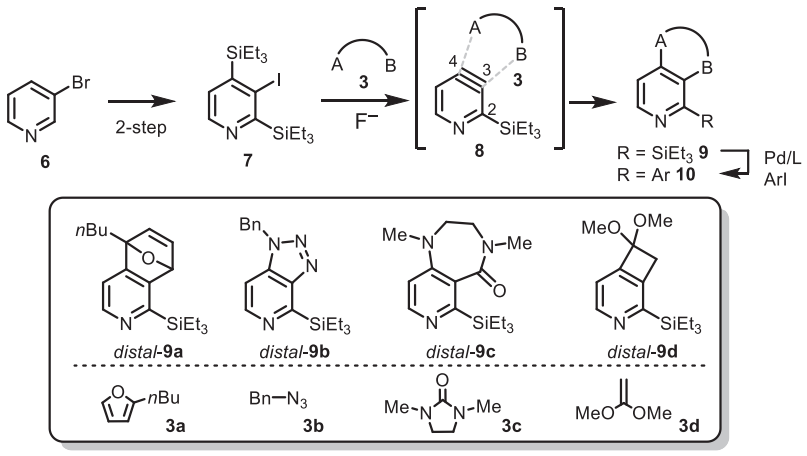
Benzynes are distorted and highly reactive intermediates bearing an endocyclic triple bond and are being used for the synthesis of a wide variety of aromatic compounds. Recently, we have reported the regioselective cycloaddition reactions of 3-silyl- and 3-borylbenzynes **4** with arynophiles **3** (eq 1).[1] These benzynes **4** were generated from precursors **2**, which were prepared from phenol derivatives **1** in over 3 steps. Additionally, the directing groups (M) of the obtained cycloaddition products **5** were converted to other substituents such as oxygen, nitrogen and carbon functional groups. On the other hand, one of the aza-benzynes, 3,4-pyridynes generated from 3-bromopyridine was first reported by Leake in 1955.[2] However, yields and regioselectivities of 3,4-pyridyne reactions with arynophiles were low in most cases. In this conference, we are going to present regioselective cycloadditions of 3,4-pyridyne with various arynophiles using triethylsilyl group as a directing group (Scheme 1).



(1)

We first developed a synthetic method of 2-silyl-3,4-pyridyne precursor **7** from commercially available 3-bromopyridine (**6**) only in 2 steps (overall 80%). The reaction of **7** with 2-butylfuran **3a** in the presence of CsF in MeCN at 60 °C produced the fused pyridine, *distal*-**9a** in 93% yield and regioselectivity (*distal*-**9a**:*proximal*-**9a** = 2.3:1). This result indicated that 2-(triethylsilyl)-3,4-pyridyne **8a** was successfully generated in-situ and the silyl group of **8a** controlled the orientation of the reaction and improved the yield of **9a**. Other arynophiles **3b**–**3d** were also applied to reactions with **8** to produce corresponding cycloadducts, *distal*-**9b**–**9d** in good to excellent yields and regioselectivities. Moreover, the remaining silyl groups on the adducts **9** were replaced with other functional groups. This method would be useful for the synthesis of a variety of fused pyridines.



Scheme 1. Regioselective cycloaddition of 3,4-pyridyne **8**

[1] a) S. Akai, T. Ikawa et al. *Angew. Chem. Int*. Ed. **2008**, *47*, 7673–7676. b) *Angew. Chem. Int. Ed.* **2010**, *49*, 5563–5566. c) *J. Org. Chem.* **2013**, *78*, 2965–2983.
[2] W. W. Leake et al. *Science* **1955**, *121*, 780.

5P-142

Development of Drugs for Modulating Endoplasmic Reticulum Stress Response

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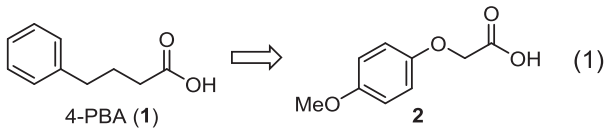
Endoplasmic reticulum (ER) is the organelle that performs appropriate modification and folding of newly made proteins following protein biosynthesis. When cells were exposed to hypoxia or low nutrition environment, the accumulation of unfolded and/or misfolded proteins in the ER induced apoptosis and led to cell death. ER stress response (UPR) is a protecting pathway which removes and refolds abnormal proteins. In several studies, 4-phenylbutylic acid (4-PBA) was shown to be a chemical chaperone that eliminates the accumulation of unfolded proteins in the ER. But its chaperone activity was not potent. Kitamura and co-workers had developed new chemical chaperones which suppressed UPR better than 4-PBA (Eq. 1).[1] They also found that these compounds blocked IRE1 and ATF6 pathways among three UPR branches.

Meanwhile, we have been interested in the tumor microenvironments which are characterized as low-nutrient and hypoxia. Such microenvironments cause UPR upregulation to lead cancer malignant. Therefore, small molecular compounds that modulates UPR will be useful for therapeutic intervention in refractory cancers.

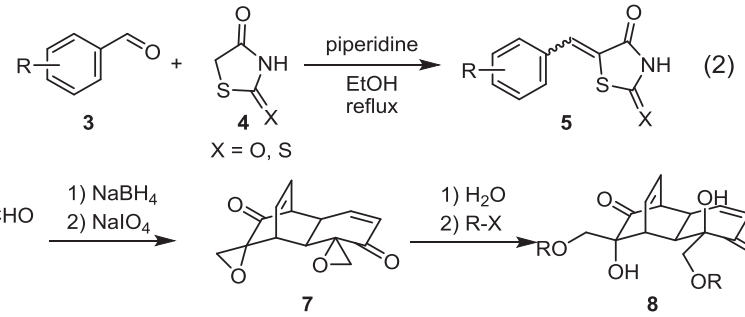


(1)

We first prepared compounds **5**, which were carboxylic acid isostere of **2**. Knoevenagel condensation with benzaldehydes (**3**) and thiazolidines (**4**) afforded compounds **5** in one step procedure (Eq. 2). Second, we synthesized (±)-grandifloracin, which is known to an antiausterity agent, and its derivatives **8**. According to Stoltz's procedure,[2] Bis-spiroexpoxydiendione **7** was obtained by reduction of salicylic aldehyde **6** with $NaBH_4$ followed by oxidative dearomatization. After epoxide opening of **7** by H_2O, primary alcohols were esterified to provide (±)-grandifloracin derivatives **8** (Eq. 3).

Synthesized compounds were screened by the morphology assessment and cytotoxicity assay under ER stress conditions. Furthermore, selected compounds were evaluated with reporter gene luciferase assays which depended on HIF-1 transactivation or grp78 promoter activity.

In this symposium, we will show recent results of synthetic study and biological assay for modulating UPR.



[1] M. Kitamura, *et al*. *Br. J. Pharmacol.* **2013**, *170*, 822−834.
[2] B. M. Stoltz, *et al. Org. Lett.* **2015**, *17*, 3008−3010.

5P-143

Transformations of *N*-(allenyl)indoles: syntheses of pyrazino[1,2-*a*]indoles and vinylsulfones

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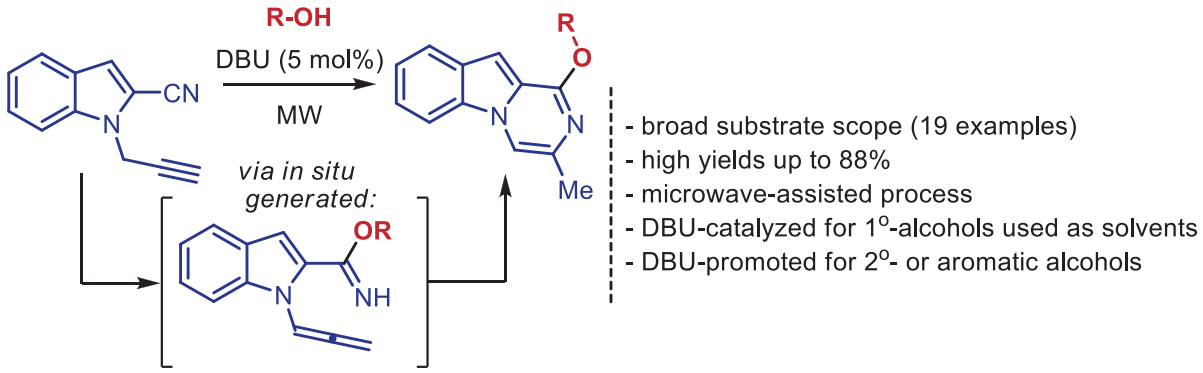
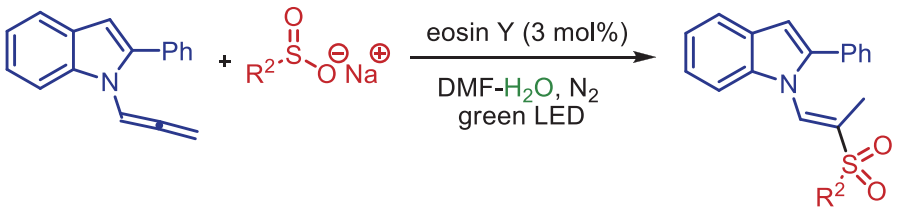
1-(Propargyl)indol-2-carbonitriles react with alcohols to afford 1-alkoxypyrazino[1,2-*a*]indoles under DBU-catalyzed microwave-assisted conditions. The reaction scope includes a wide range of indoles, primary and secondary alcohols, and a thiol. The initial mechanistic study shows that the domino process presumably proceeds through an alkyne−allene rearrangement, imidate formation, and nucleophilic cyclization reaction sequence.



We have developed an effective microwave-assisted route toward the 1-alkoxypyrazino[1,2-*a*]indole scaffold through a DBU-catalyzed isomerization/double nucleophilic addition reaction sequence in an alcohol medium [1]. The reaction tolerated a wide range of indoles and primary alcohols. We also elaborated on analogous transformations for secondary alcohols and alcohols which were difficult to use as solvents, including thiol. We envision that the reaction will be interesting in the field of medicinal chemistry for the synthesis of drug like structures. A more extensive study using a wider range of nucleophile initiators will follow in due course.

We have recently developed a photocatalyzed hydrosulfonylation of *N*-(allenyl)indoles.



References

[1] Alexey A. Festa, Rajesh R. Zalte, Nikita E. Golantsov, Alexey V. Varlamov, Erik V. Van der Eycken, and Leonid G. Voskressensky *J. Org. Chem.* **2018**, *83* (16), pp 9305–9311.

The work was prepared with the support of the "RUDN University Program 5-100" and RFBR grant 18-33-20040.

5P-144

Nucleoside Antibiotic Support Studies: Uridine-Based Homologation Strategies Using the Nitroaldol Approach

Frederick A. Luzzio* and Paige J. Monsen
Department of Chemistry, University of Louisville,
Louisville, Kentucky 40292 USA

Nucleoside antibiotics may emerge as the last remaining bastion toward the world pandemic of antibiotic-resistant infection. Owing to the ever-increasing threat posed by the rise of multi-drug resistant bacteria toward established antibiotics, there is a need to develop new anti-infective therapies with novel mechanisms of action. Critical for bacterial growth and survival are the glycoconjugates that compose the bacterial cell walls and the proteins responsible for the biosynthesis of those glycoconjugates.[1] The tunicamycins (TM), liposidomycins (LM) and mureidomycins are nucleoside antibiotics which inhibit the membrane cycle (Translocase I catalysis) of reactions in peptidoglycan biosynthesis. All the antibiotics have a uridine residue in common and two (TM and LM) possess the uridine homologated to a central scaffold or torus which bears both sugar and lipid residues [Figure 1]. Our present work involves strategies toward C-C bond homologation of uridine to provide a central scaffold whereby both lipid and sugar and even peptide components may be attached to provide a complete experimental antibiotic. The discussion will focus on the methodology surrounding the nitroaldol reaction[2] and uridine-compatible reactions which involve the ensuing nitro alcohol functional group.

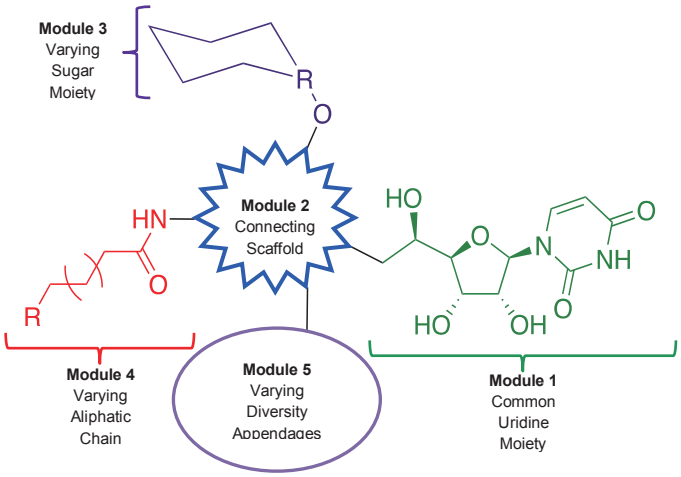


Figure 1. Structural components of an experimental nucleoside antibiotic

[1] Brandish, P. E.; Kimura, K.-I.; Inuaki, M.; Southgate, R.; Lonsdale, J. T.; Bugg, T. D. H. *Antimicrob. Agents Chemother.* **1996**, *40*, 1640.
[2] Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915.

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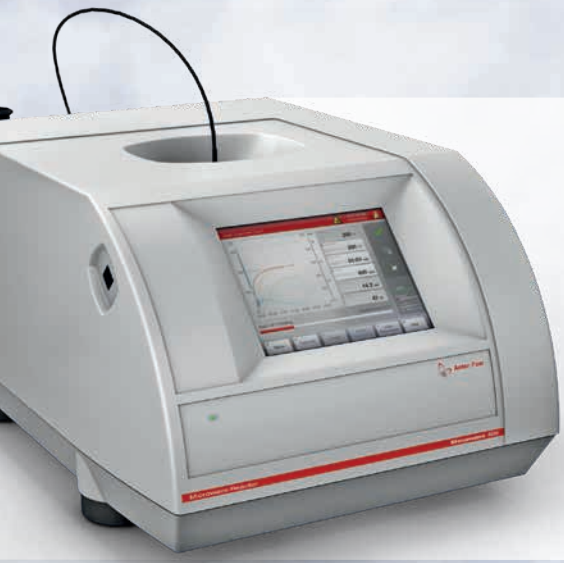

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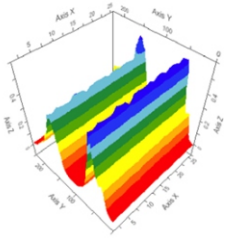

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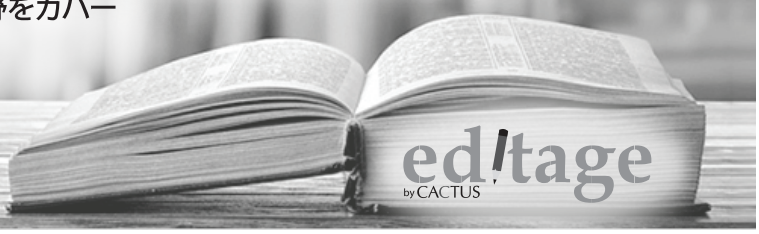

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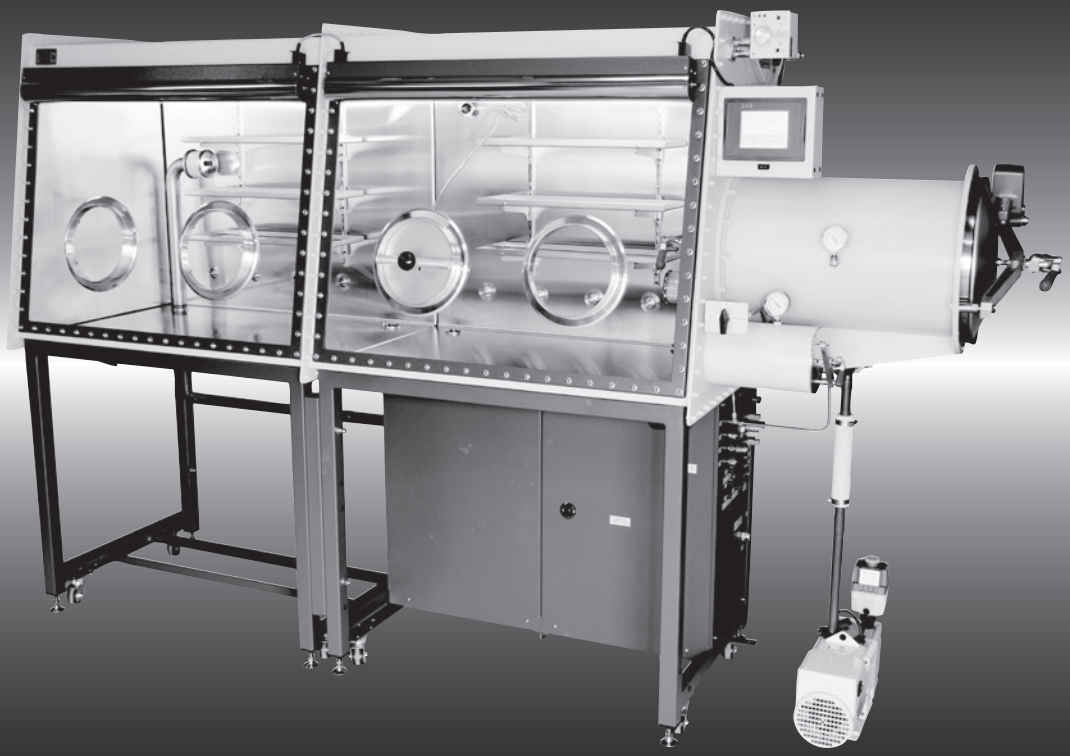

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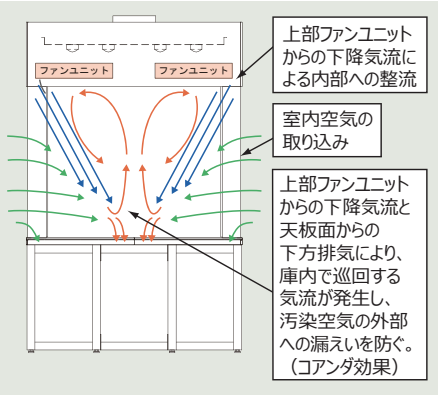

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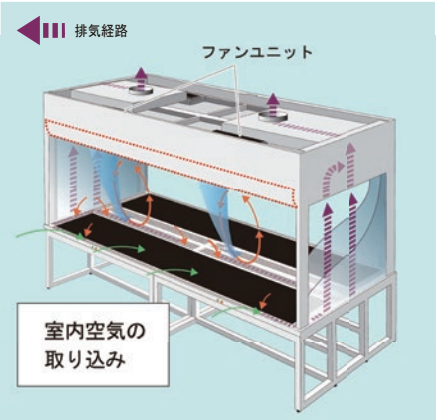

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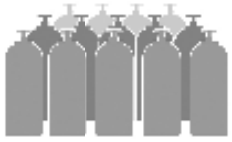
災害の原因となる
危険性があります。



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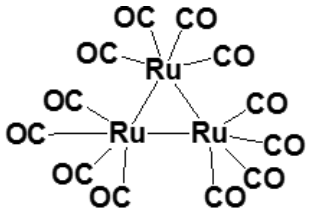
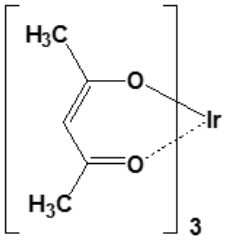


$Ru_3(CO)_{12}$



$Ir(acac)_3$

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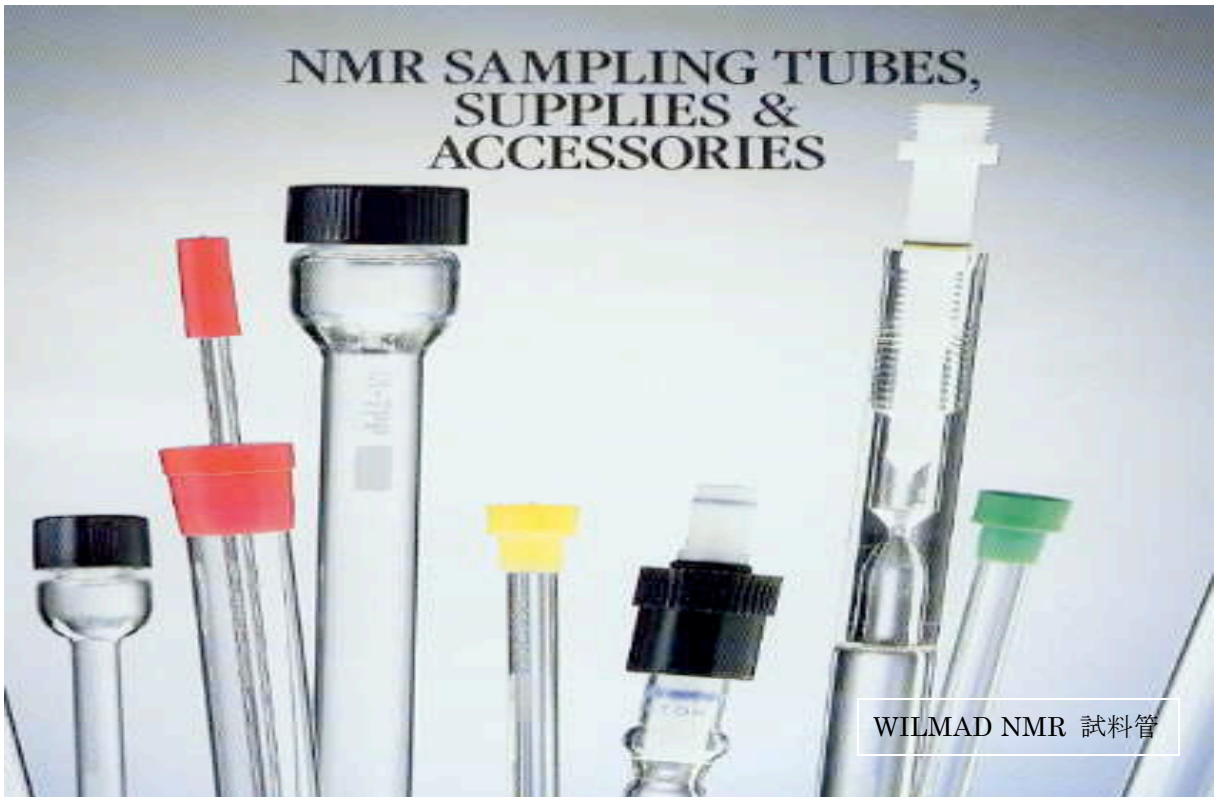

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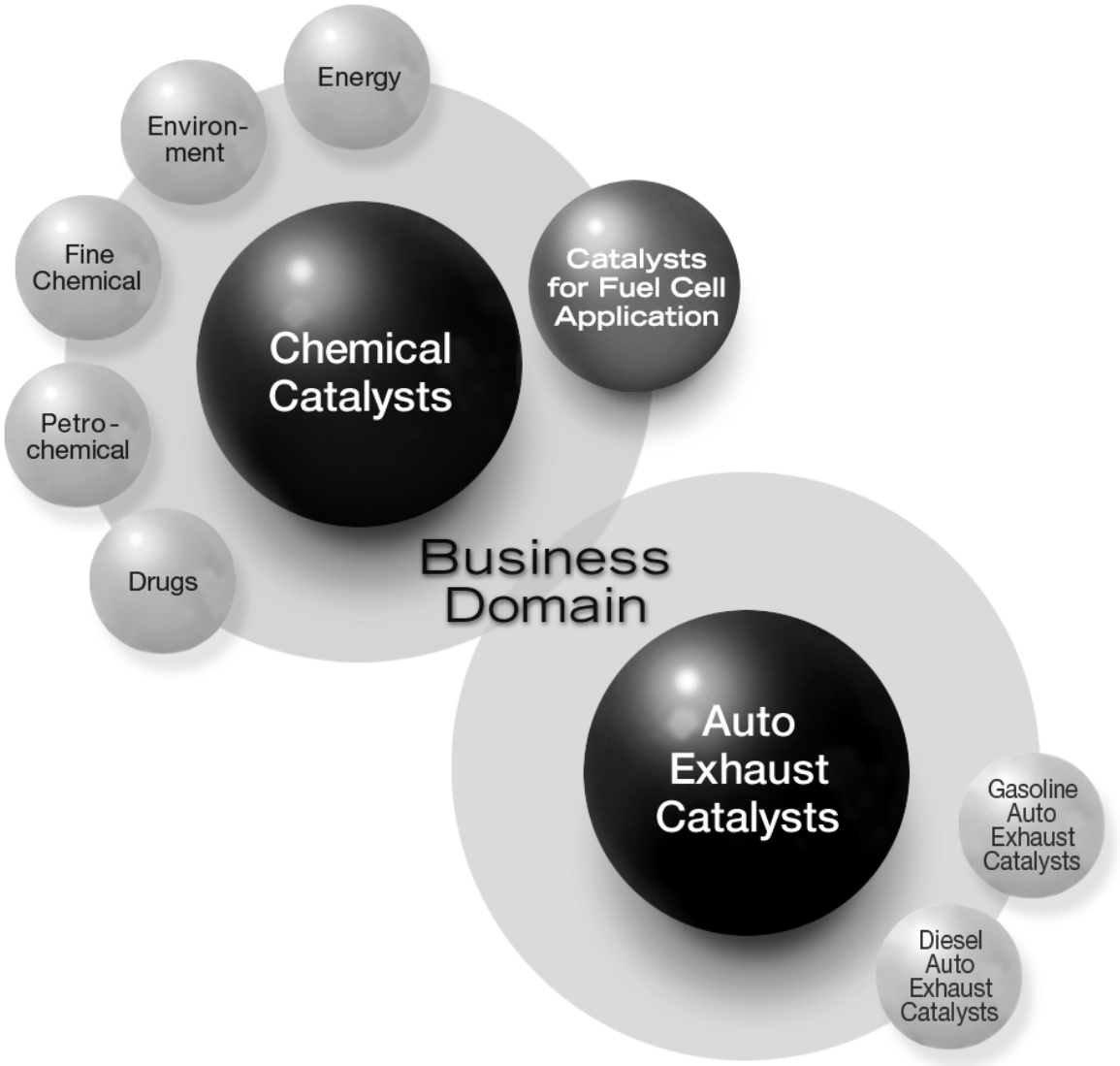

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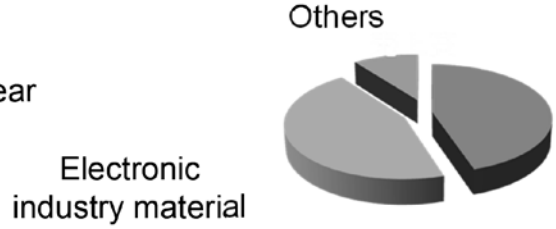
Outline of Business

- Synthesis of functionality organic material for pharmaceutical field, fine chemicals, and electronic device etc.
- Making of chemicals high purity, Optical division, and Extraction separation refinement of active ingredient in culture liquid.
- Supply of biotechnology materials such as peptide, proteins, and nucleic acids (DNA, RNA).

Company Profile

Trade Name	KNC Laboratories Co., Ltd.
Established	February 1, 1985
Capital	1.9 billion yen
Employees	280 people (As of April, 2019)
Activities	Contract Research & Development, Manufacture of Organic Chemicals, Purification and Extraction

Feature
- Technological staff of about 70%
- Contract with about 150 companies/year
- Contract with about 800 themes/year



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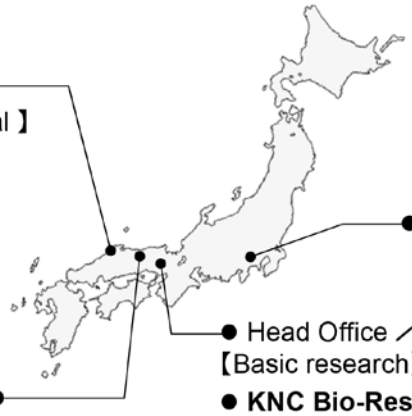
Business Location



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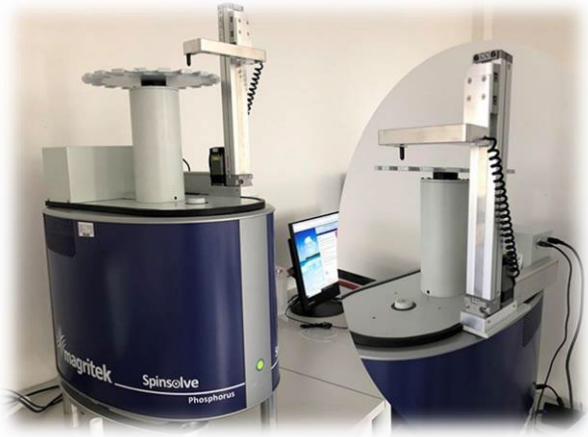
卓上型NMR Spinsolve



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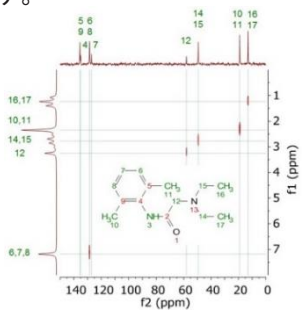
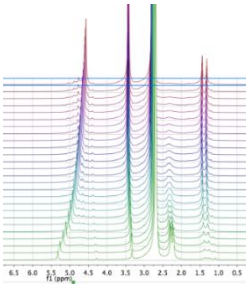
❒軽溶媒使用。
❒通常5mmガラス管で測定します。
❒精密な温度制御・安定した磁場。
❒COSY等の2次元測定も可能です。
❒核種：H, F, C, P , N , Li, Si, B他
❒50%半値幅：＜0.5Hz。
❒操作は簡単、自動シム調整。
❒重量：55Kg（43MHzの場合）
❒寸法：58(L) x 43(W) x 40(H) cm



❒オプションのオートサンプラーには、サンプル管を20本セットできます（左上の写真はオートサンプラーを装着した状態です）。
❒オプションのリアクションモニタリングキットにより、オンラインで化学反応の追跡が可能です（左下の写真は、リアクションモニタリングキットを装着した状態です）。



Waterfall plot showing NMR spectra acquired as a function of time during the reaction

YHCHEM®

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「テフロン内筒型密封加熱SUSリアクター」は、特定の温度および圧力条件下で化学物質を合成するための反応容器です。大学や研究機関で、新素材、金属蛍光材料、パーティクル実験、合成反応実験等に広く使用されています。

❒貴重なサンプルのロスはありません。
❒ SUS304製リアクターは、200℃、3Mpaの高温高圧に耐えることができます。
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シェル直径	53mm	58mm	79mm	87mm	87mm	108mm
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チャンバー高さ	60mm	73mm	91mm	103mm	113mm	146mm
チャンバー直径	35mm	44mm	54mm	69mm	69mm	83mm
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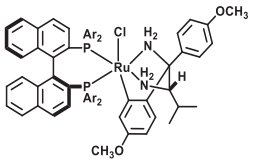

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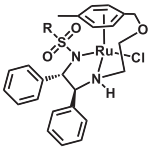

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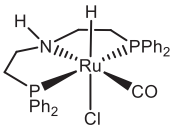

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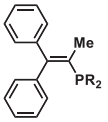

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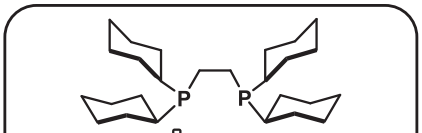


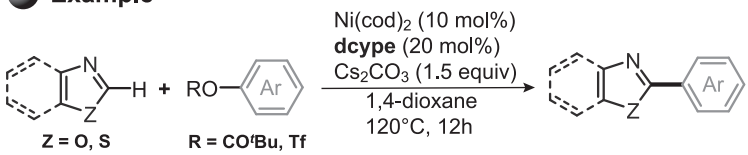
dcype

1,2-Bis(dicyclohexylphosphino)ethane

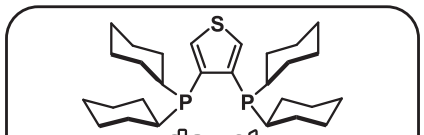
CAS RN® : 23743-26-2

Ni-Catalyzed C-H Coupling of 1,3-Azoles
Pd-Catalyzed Decarbonylative Cross-Coupling

Example



Nickel-catalyzed C-H/C-O coupling of azoles with phenol derivatives
Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169.



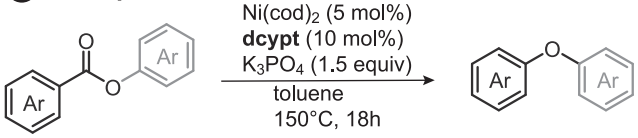
dcypt

3,4-Bis(dicyclohexylphosphino)thiophene

CAS RN® : 1638677-61-8

Ni-catalyzed α-alylation of carbonyl compound with phenol derivatives
Ni-catalyzed Decarbonylative Diaryl Ether Synthesis

Example



Decarbonylative Diaryl Ether Synthesis by Pd and Ni Catalysis
Takise, R.; Isshiki, R. Muto K.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2017**, *139(9)*, 3340-3343.

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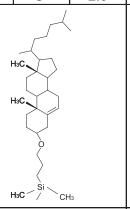
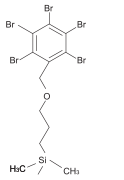
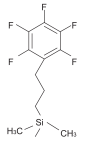
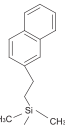
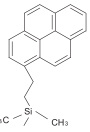
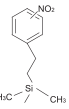
- 保持がなくて困った → 親水性化合物分離用逆相カラム COSMOSIL PBr
  → 親水性相互作用クロマトグラフィー用カラム COSMOSIL HILIC

●充填剤の物性と特長

充填剤名称	Cholester			PBr		PFP	πNAP		PYE	NPE	HILIC	
分離モード	逆相										親水性相互作用	
シリカゲル※	全多孔性		Core-Shell	全多孔性	Core-Shell	全多孔性	全多孔性		全多孔性	全多孔性	全多孔性	
平均粒子径(μm)	2.5	5	2.6	5	2.6	5	2.5	5	5	5	2.5	5
固定相構造												
化学結合基	コレステリル基			ペンタブロモベンジル基		ペンタフルオロフェニルプロピル基	ナフチルエチル基		ピレニルエチル基	ニトロフェニルエチル基	トリアゾール	
主な相互作用	・疎水性 ・分子形状認識能			・疎水性 ・分散力		・疎水性 ・π - π ・双極子 - 双極子	・疎水性 ・π - π		・疎水性 ・π - π ・分散力 ・分子形状認識能	・疎水性 ・π - π ・双極子 - 双極子	・親水性 ・陰イオン交換能	
特長	・C18と同一移動相で分析可能 ・高い分子形状認識能			・分散力による分離 ・親水性化合物を逆相条件で分析可能		・弱く双極子を識別	・フェニルカラムよりも強いπ - π 相互作用		・最強のπ - π 相互作用	・強く双極子を識別	・C18で保持のない化合物に有効	

※シリカゲル：全多孔性…全多孔性球状高純度シリカゲル　Core-Shell…Core-Shellシリカゲル、平均細孔経（2.5 μm：約130 Å, 5 μm：約120 Å, 2.6 μm：約90 Å）
比表面積（2.5 μm：約330 m²/g, 5 μm：約300 m²/g, 2.6 μm：約150 m²/g）

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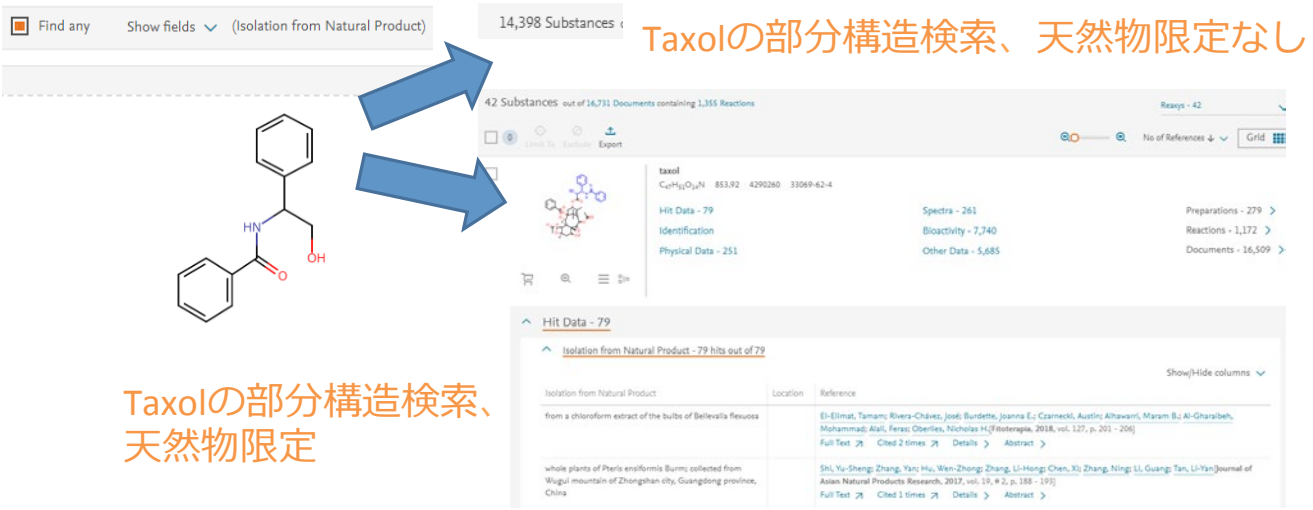

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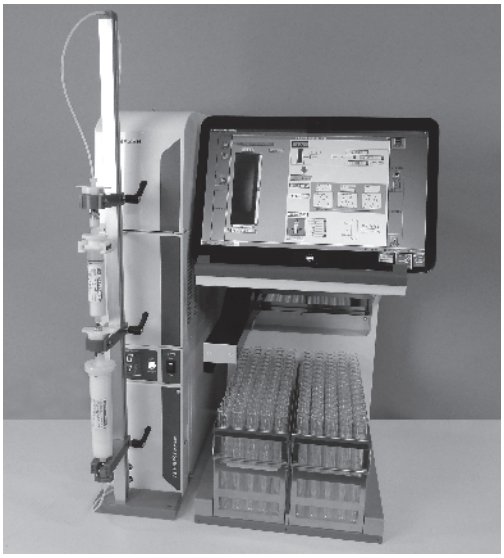

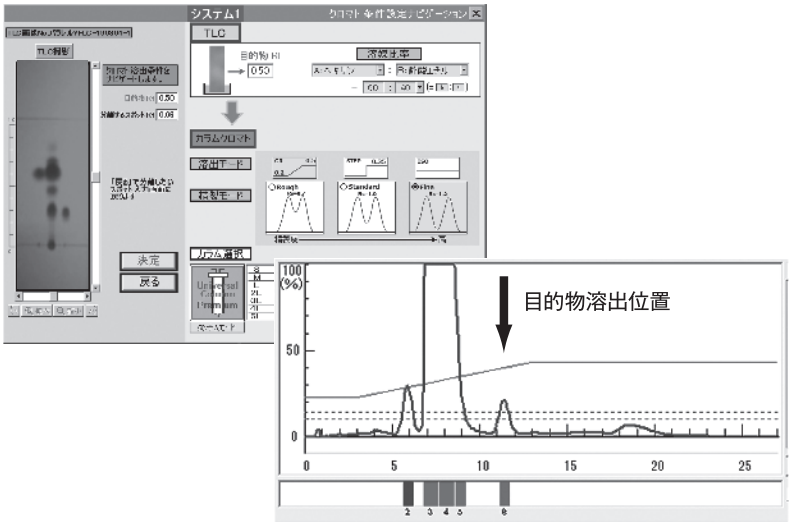

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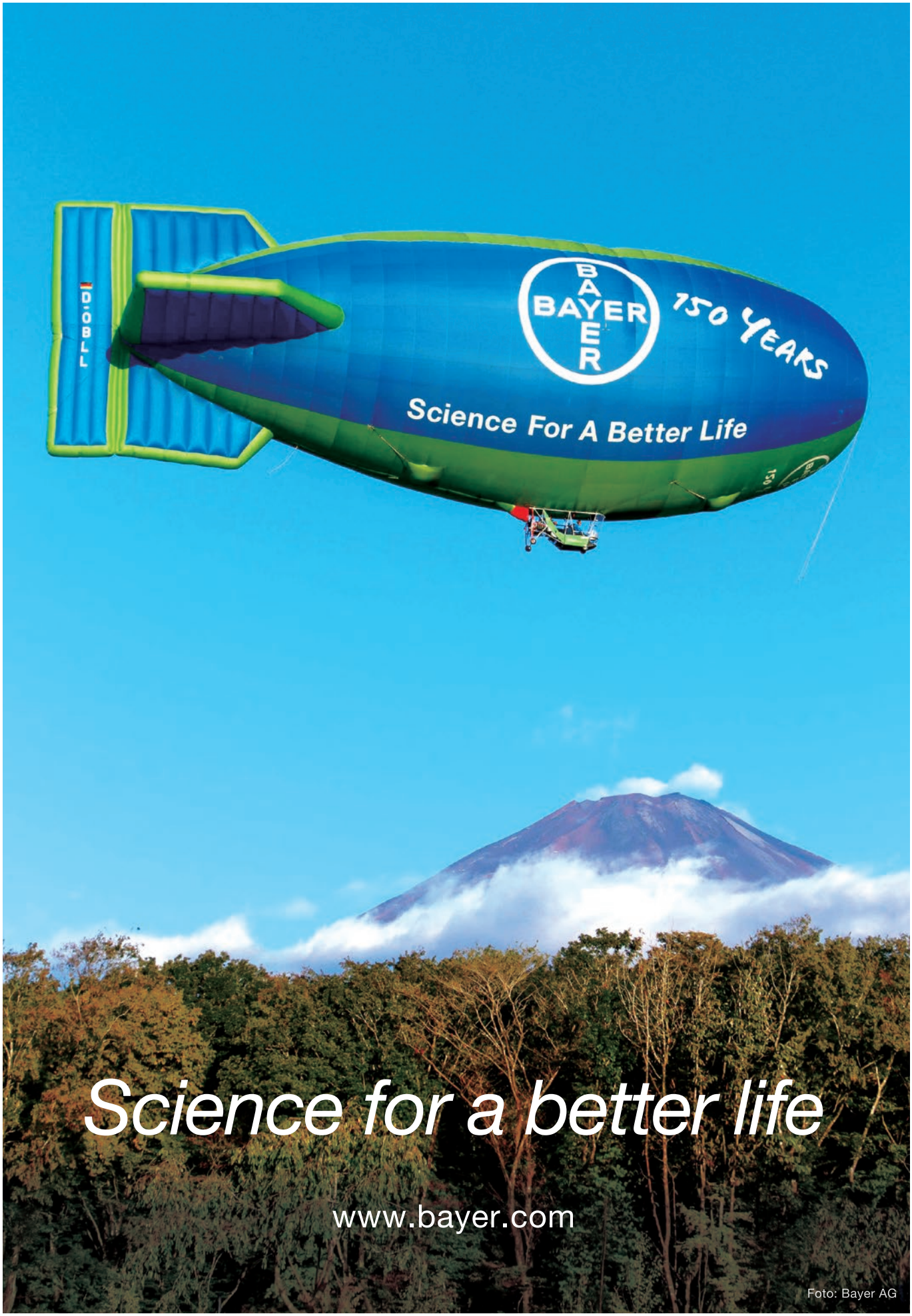
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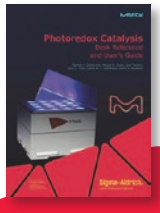

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