University of Regensburg

ISHC
International Society
of Heterocyclic Chemistry

Book of Abstracts

26th ISHC Congress

September 3 - 8, 2017

Regensburg, Germany

Karsten Dörre

International Society
of Heterocyclic Chemistry

President Prof. Oliver Reiser
Institute of Organic Chemistry
Universität Regensburg
D-93053 Regensburg

26th ISHC Congress

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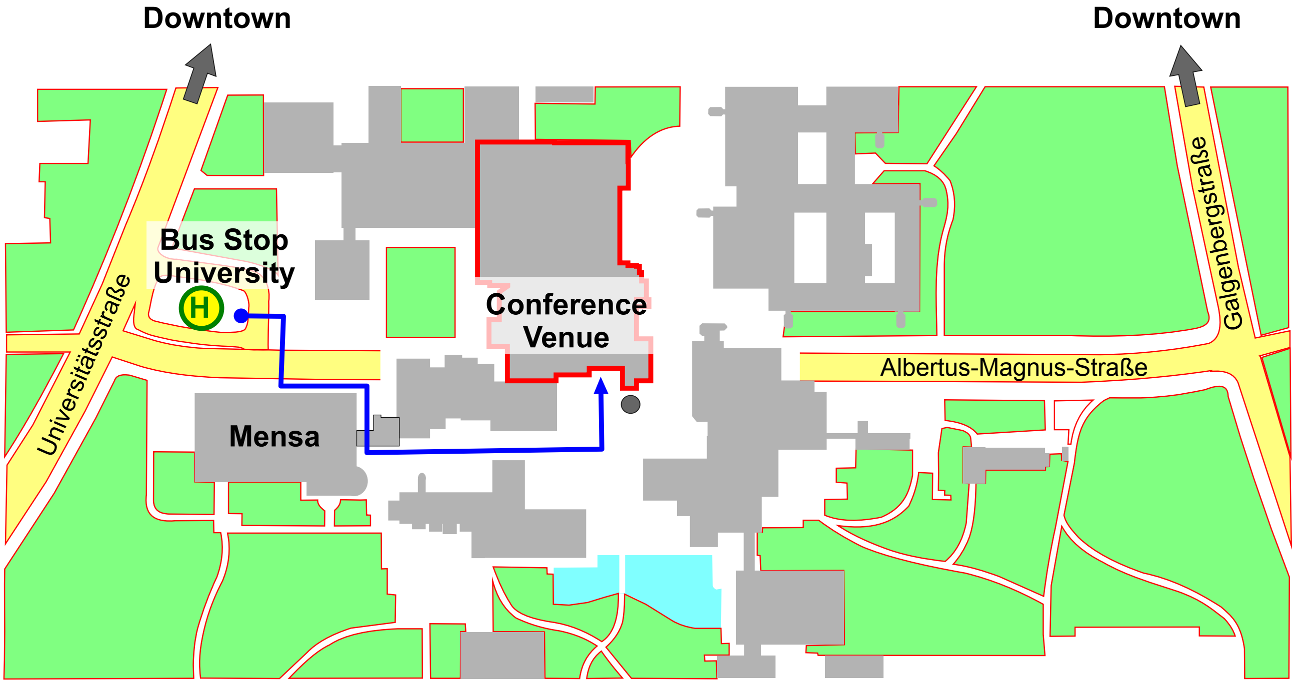
University of Regensburg, central campus



Bus lines from/to University

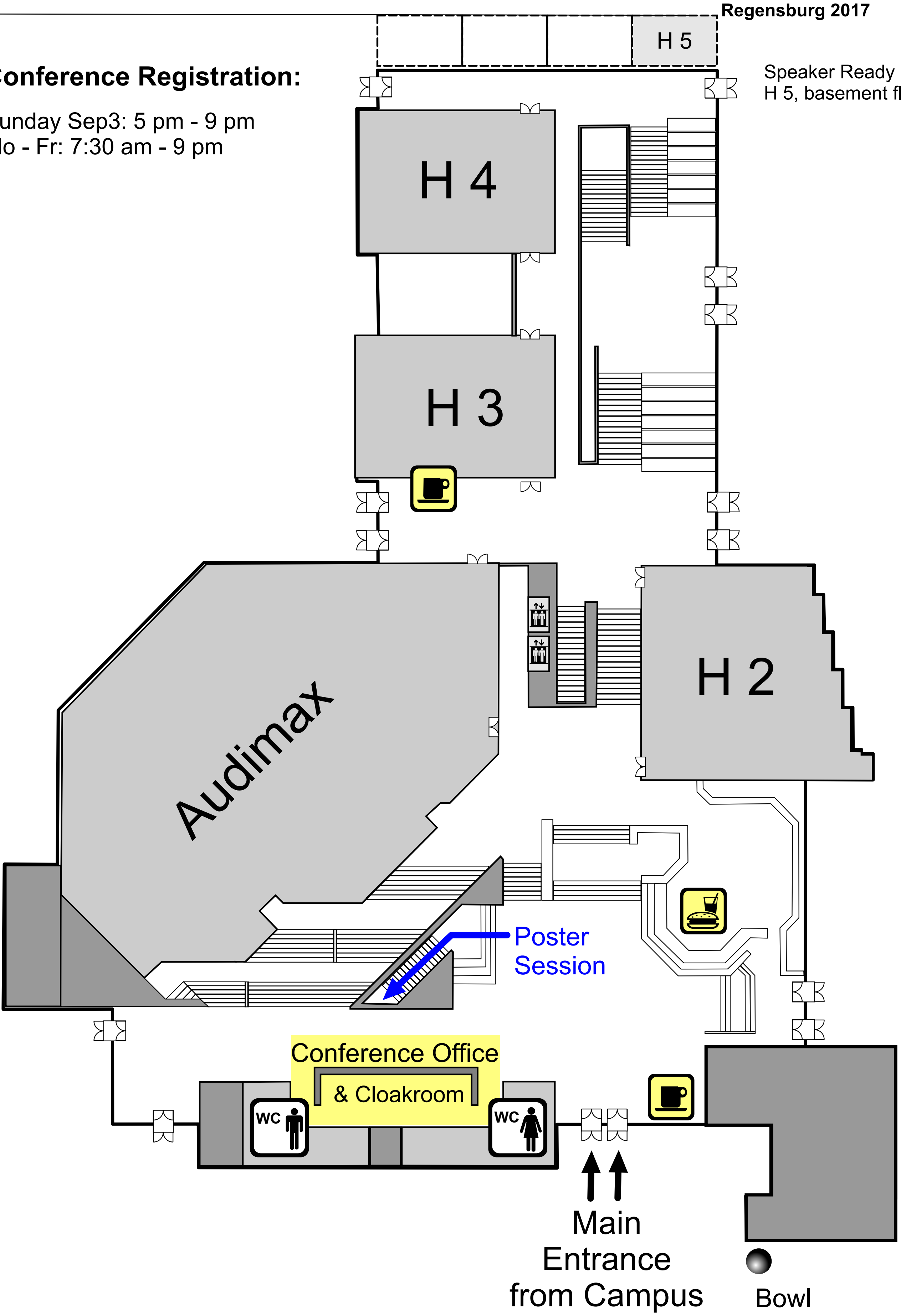
2B	Karl-Stieler-Straße - **University** - Albertstraße/Train Station - Schwabenstraße
6	Klinikum - **University** - Albertstraße/Train Station - Arnulfsplatz - Wernerwerkstraße
11	Hermann-Höcher-Str. - **University** - Albertstraße/Train Station - Roter Brach Weg

International Society
of Heterocyclic
Chemistry
ISHC
Regensburg 2017

Conference Venue - Central Lecture Hall

Conference Registration:

Sunday Sep3: 5 pm - 9 pm
Mo - Fr: 7:30 am - 9 pm



Speaker Ready Room
H 5, basement floor

Informations on Bus Lines

At the conference registration desk you will get a free bus ticket (valid from Sunday – Friday).

Please note: If you take the bus to the conference registration you have to buy a single ride ticket. Bus tickets can be purchased at ticket machines and bus drivers in the buses.*

* The fine costs € 60 if a passenger ride without a valid ticket

Recommended Bus Lines

Inner city hotels

Altstadthotel am Pach	Lines 6 and 11, bus stops Arnulfplatz, Dachauplatz or Albertstraße
Altstadthotel Arch	
Bohemian Hotel	
Brook Lane Hostel	
Hotel am Peterstor	
Hotel Bischofshof	
Hotel David	
Hotel Goliath	
Hotel Münchner Hof und Blauer Turm	
Hotel Roter Hahn	
Hotel Weidenhof	
Hotel zum fröhlichen Türken	

Other hotels:

Atrium im Park Hotel:	Line 8, bus stop Vilsstraße-Gewerbepark change on Dachauplatz or Albertstraße to lines 6 or 11
IBIS Style Hotel:	Line 12, bus stop Pfaffensteiner Brücke, change on Dachauplatz or Albertstraße to lines 6 or 11
B&B Hotel, Mercure Hotel	Line 11, bus stop Benzstraße
Hotel Wiendl Hansa Apart Hotel	Line 11, bus stop Oberer katholischer Friedhof or a 20 min. walk
St. Georg Business Hotel	Mo-Fr: Line 2, bus stop Karl-Stieler-Str. Line 2B: direct connection, Line 2A: change on Albertstaße to line 6 or 11 or a 20 min. walk
Hotel Apollo	A 15 min. walk, no bus
Youth hostel	Line 8 or 12, bus stop Wöhrdstraße change on Dachauplatz or Albertstraße to lines 6 or 11

For up to date bus schedules we highly recommend the RVV app: http://www.rvv.de/app

Bus Time Tables Sunday evening

Line 6, Sun, Final Destination: Klinikum				**Line 6, Sun, Final Dest.: Wernerwerkstraße**		
	10-23				10-23	
Arnulfsplatz	18	48		Universität	20	50
Dachauplatz	22	52		HBF/Albertstraße	30	00
HBF/Albertstraße	30	00		Dachauplatz	33	03
Universität	36	06		Arnulfsplatz	39	09

Line 11, Sun, Final Dest. Burgweinting - Herm.-Höcherl-Straße			**Line 11, Sun, Final Dest. Roter-Brach-Weg**	
	10-23			10-23
Arnulfsplatz	33		Benzstraße	26
Dachauplatz	40		Universität	35
HBF/Albertstraße	45		Oberer kath. Friedhof	37
Oberer kath. Friedhof	48		HBF/Albertstraße	42
Universität	51		Dachauplatz	48
Benzstraße	59		Arnulfplatz	54

Line 12, Sun, Final Dest. Hauptbahnhof					**Line 12, Sun, Final Dest. Pielenhofen**				
Pfaffensteiner Brücke	16:12	18:12	20:12		Hauptbahnhof	18:30	20:30	21:30	22:30
Wöhrdstraße	16:19	18:19	20:19		Dachauplatz	18:33	20:33	21:33	22:33
Dachauplatz	16:21	18:21	20:21		Wöhrdstraße	18:35	20:35	21:35	22:35
Hauptbahnhof	16:25	18:25	20:25		Pfaffensteiner Brücke	18:43	20:43	21:43	22:43

Line 8, Sun, Final Dest. Hauptbahnhof (HBF)			**Line 8, Sun, Final Dest. Grünthal**	
	10-23			19-23
Vilsstraße-Gewerbepark	30		HBF/Albertstraße	45
Wöhrdstraße	35		Dachauplatz	47
Dachauplatz	40		Wöhrdstraße	51
HBF/Albertstraße	42		Vilsstraße-Gewerbepark	58

Line 2, Sun, Final Dest. Graß				**Line 2, Sun, Final Dest. Schwabenstraße**				
	9-23				9-18		19-23	
HBF/Albertstaße	15	45		Karl-Stieler-Straße	07	37	09	39
Dachauplatz	17	47		Arnulfsplatz	19	49	19	49
Arnulfsplatz	23	53		Dachauplatz	25	55	25	55
Karl-Stieler-Straße	34	04		HBF/Albertstaße	27	57	27	57

Bus Time Tables Monday - Friday

Line 6, Mo-Fr, Final Destination: Klinikum

	7-17				18			19			20-22		23	
Arnulfsplatz	11	26	41	56	11	26	46	06	26	49	19	49	19	49
Dachauplatz	19	34	49	04	19	34	54	14	34	55	25	55	25	55
HBF/Albertstraße	23	38	53	08	23	38	58	18	38	00	30	00	30	00
Universität	30	45	00	15	30	45	05	25	45	06	36	06	36	06

Line 6, Mo-Fr, Final Destination: Wernerwerkstraße

	7-18				19				20			21-23		0
Universität	04	19	34	49	04	21	36	51	06	21	50	20	50	
HBF/Albertstraße	13	28	43	58	13	30	45	00	--	30	00	30	00	
Dachauplatz	16	31	46	01	16	33	48	03	--	33	03	33	03	
Arnulfsplatz	23	38	53	08	23	40	55	10	--	40	09	39	09	

Line 11, Mo-Fr, Final Destination Burgweinting - Herm.-Höcherl-Straße

	7-17			18		19		20		21-23	
Arnulfplatz	12	32	52	12	32	03	33	03	34	04	34
Dachauplatz	20	40	00	20	40	11	41	11	40	10	40
HBF/Albertstraße	24	44	04	24	44	15	45	15	45	15	45
Oberer kath. Friedhof	28	48	08	28	48	19	49	19	48	18	48
Universität	31	51	11	31	51	22	52	22	51	21	51
Benzstraße	40	00	20	40	00	31	01	31	59	29	59

Line 11, Mo-Fr, Final Destination Roter-Brach-Weg

	8-17			18			19		20-22		23
Benzstraße	11	31	51	11	31	54	24	54	27	57	27
Universität	22	42	02	22	42	05	35	05	36	06	36
Oberer kath. Friedhof	24	44	04	24	44	07	37	07	38	08	38
HBF/Albertstraße	32	52	12	32	52	12	45	15	45	15	45
Dachauplatz	35	55	15	35	55	15	48	18	48	18	48
Arnulfplatz	42	02	22	42	02	22	55	25	54	24	54

Line 12, Mo-Fr, Final Destination Hauptbahnhof (HBf)

	7	8	9-13	14	15-19	20
Pfaffensteiner Brücke	15	14	04	14	04	09
Wöhrdstraße	23	22	12	22	12	17
Dachauplatz	25	24	14	24	14	19
Hauptbahnhof	30	29	19	29	19	24

Line 12, Mo-Fr, Final Destination Pielenhofen / Heitzenhofen

	8-11	12	13-17	18-20	22
Hauptbahnhof	30	30	30	40	40
Dachauplatz	33	33	33	43	42
Wöhrdstraße	35	38	37	45	44
Pfaffensteiner Brücke	45	48	45	55	52

Line 8, Mo-Fr, Final Destination Albertstraße/HBF

	7			8-17			18			19	20		21-23
Vilsstraße-Gewerbepark	03	23	43	03	23	43	03	23	43	30	00	30	30
Dachauplatz	14	34	54	14	34	54	14	34	54	41	11	39	39
HBF/Albertstraße	16	36	56	16	36	56	16	36	56	43	13	42	42

Line 8, Mo-Fr, Final Destination Grünthal

	7-12			13			14-19			20		21-23
HBF/Albertstraße	10	30	50	10	30	50	10	30	50	15	45	45
Dachauplatz	12	32	52	12	32	52	12	32	52	16	47	47
Vilsstraße-Gewerbepark	23	43	03	23	43	03	23	43	03	24	58	58

Line 2B, Mo-Fr, direct connection from/to University

Final Destination Karl-Stieler-Str.

	7-18		19
Universität	10	40	10
Karl-Stieler-Straße	15	45	15

Final Destination Schwabenstraße

	7-18	
Karl-Stieler-Straße	19	49
Universität	23	53

Line 2A / 2B, Mo-Fr, Final Destination Karl-Stieler-Str. /Graß

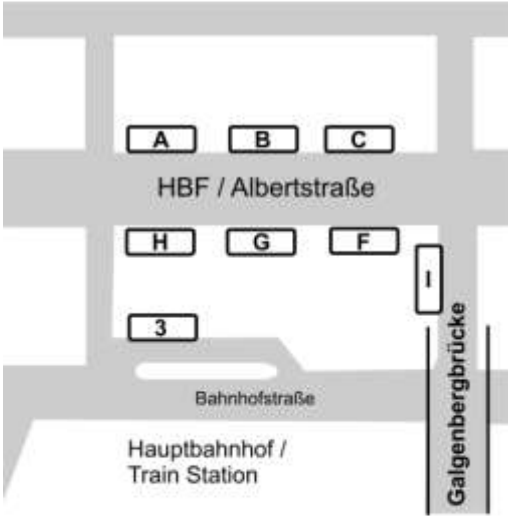
	8-14				15-18			19-23	
HBF/Albertstaße	04	19	34	49	04	19	34	15	45
Dachauplatz	06	21	36	17	06	21	36	17	47
Arnulfsplatz	13	28	43	58	13	28	43	23	53
Karl-Stieler-Straße	26	45	56	15	26	45	56	04	34

Line 2A / 2B, Mo-Fr, Final Destination Schwabenstraße

	8-14				15-18				19		20-23	
Karl-Stieler-Straße	07	19	37	49	07	19	37	49	06	36	06	39
Arnulfsplatz	19	34	49	04	19	34	49	04	18	48	18	49
Dachauplatz	26	41	56	11	26	41	56	11	25	55	25	55
HBF/Albertstaße	30	45	00	15	30	45	00	15	29	59	29	57

Platform map HBF/Albertstraße

Line	Direction	Platform
2	Schwabenstraße	B
2	Karl-Stieler-Straße	F
6	Wernerwerkstraße	C
6	Universität – Klinikum	I
8	Grünthal	G
11	Roter-Brach-Weg	C
11	Burgweinting /Hermann-Höcherl-Str.	I
12	Pielenhofen	3



More Information at www.rvv.de, RVV app and information desk

Sunday, Sep 3

17:00 – 18:30	Central Lecture Hall Building Conference Registration	
18:30 – 21:00		Central Lecture Hall Building Reception

Monday, Sep 4

7:30 – 9:00	Conference Registration
8:45 – 9:00	Audimax Conference Opening
9:00 – 10:55	Plenary Lecture 1 Audimax Benjamin List
10:00 – 10:30	Coffee Break
10:30 – 11:25	Plenary Lecture 2 Audimax Christina Nevado
11:30 – 12:25	Plenary Lecture 3 Audimax John Sutherland
12:30 – 14:00	Lunch

Monday, Sep 4 (continued)

14:00 – 14:40	Invited Lecture A1 Audimax Corey Stephenson	Invited Lecture B1 H2 Daniel Gryko	Invited Lecture C1 H3 Olga Garcia-Mancheno	
14:40 – 15:20	Invited Lecture A2 Audimax Lutz Ackermann	Invited Lecture B2 H2 Michail Hocek	Invited Lecture C2 H3 Shuji Akai	
15:20 – 15:40	Oral Presentation A1 Audimax Alan Aitken	Oral Presentation B1 H2 Shigeru Arai	Oral Presentation C1 H3 Vakhid Mamedov	Oral Presentation D1 H4 Fabio Marinelli
15:40 – 16:20	Coffee Break – THIEME SOS			
16:20 – 16:40	Oral Presentation A2 Audimax Mitsuru Kitamura	Oral Presentation B2 H2 Yongwen Jiang	Oral Presentation C2 H3 Stefan Kirsch	Oral Presentation D2 H4 Mitsuhiro Arisawa
16:40 – 17:00	Oral Presentation A3 Audimax Antonio C.B. Burtoloso	Oral Presentation B3 H2 Tetsuhiro Nemoto	Oral Presentation C3 H3 Jurij Svete	Oral Presentation D3 H4 Hiroyuki Suga
17:00 – 17:20	Oral Presentation A4 Audimax Richard Bunce	Oral Presentation B4 H2 Tun-Cheng Chien	Oral Presentation C4 H3 Leonid Voskessesnky	Oral Presentation D4 H4 Rodney Fernandes
17:25 – 18:05	Invited Lecture A3 Audimax Mike Doyle	Invited Lecture B3 H2 Wenjun Tang	Oral Presentation E1 H3 Jonathan Sperry	
17:25 – 18:05			Oral Presentation E2 H3 Andrea Penoni	

Tuesday, Sep 5

7:30 – 9:00	Conference Registration			
9:00 – 9:55	Plenary Lecture 4 Audimax Alois Fürstner MOLECULES LECTURE			
10:00 – 10:30	Coffee Break			
10:30 – 11:25	Plenary Lecture 5 Audimax Karl Anker Jørgensen			
11:30 – 12:25	Plenary Lecture 6 Audimax Sarah Reisman			
12:30 – 14:00	Lunch			
14:00 – 14:40	Invited Lecture A4 Audimax Nicolai Cramer	Invited Lecture B4 H2 Sergii Pazenok	Invited Lecture C4 H3 Jan Deska	
14:40 – 15:20	Invited Lecture A5 Audimax John Bower	Invited Lecture B5 H2 Benjamin Sherry	Invited Lecture C5 H3 C. Oliver Kappe	
15:20 – 15:40	Oral Presentation A5 Audimax Dorota Gryko	Oral Presentation B5 H2 Andreas Brunschweiger	Oral Presentation C5 H3 Suguru Yoshida	Oral Presentation D5 H4 Adrian Dobbs
15:40 – 16:20	Coffee Break			

Tuesday, Sep 5 (continued)

15:40 – 16:20	Coffee Break			
16:20 – 16:40	Oral Presentation A6 Audimax Till Opatz	Oral Presentation B6 H2 Keiichi Hirano	Oral Presentation C6 H3 Przemyslaw Boratynski	Oral Presentation D6 H4 Artur Silva
16:45 – 17:25	Invited Lecture A6 Audimax Akkattu Biju	Invited Lecture B6 H2 Guanglin Luo		
17:30 – 18:00	Audimax Flash Presentation TUE 1	H2 Flash Presentation TUE 2		
18:00 – 20:30	Poster Session TUE			

Wednesday, Sep 6

7:30 – 9:00	Conference Registration			
9:00 – 9:55	Plenary Lecture 7 Audimax Christopher Vanderwal			
10:00 – 10:30	Coffee Break			
10:30 – 11:25	Plenary Lecture 8 Audimax Karl Scheidt			
11:30 – 12:10	Invited Lecture A7 Audimax Mimi Hii	Invited Lecture B7 H2 Peter J. Stang		
12:15 – 12:35	Oral Presentation A7 Audimax Takashi Otani	Oral Presentation B7 H2 Simona Rizzo	Oral Presentation C7 H3 Craig Francis	Oral Presentation D7 H4 Malose Jack Mphahlele
12:40 – 14:00	Lunch			
14:00 – 14:40	Invited Lecture A8 Audimax Martin Eastgate	Invited Lecture B8 H2 Keisuke Suzuki		
14:40 – 15:20	Invited Lecture A9 Audimax Peter Meier	Invited Lecture B9 H2 Jeffrey Aube		
15:20 – 15:40	Oral Presentation A8 Audimax Hidetoshi Tokuyama	Oral Presentation B8 H2 Kiyosei Takasu	Oral Presentation C8 H3 Tonis Kanger	Oral Presentation D8 H4 Vasiliy Bakulev

Wednesday, Sep 6 (continued)

15:40 – 16:20	Coffee Break			
16:20 – 16:40	Oral Presentation A9 Audimax Donatella Giomi	Oral Presentation B9 H2 Daniel B. Werz	Oral Presentation C9 H3 Lwiza Chouguiat	Oral Presentation D9 H4 Saeed Balalaie
16:45 – 17:25	Invited Lecture A10 Audimax Peter Maienfisch	Invited Lecture B10 H2 Pauline Chiu		
17:30 – 18:00	Audimax Flash Presentation WED 1	H2 Flash Presentation WED 2		
18:00 – 20:30	Poster Session WED			

Thursday, Sep 7

7:30 – 9:00	Conference Registration		
9:00 – 9:55	Plenary Lecture 9 Audimax Ilhyong Ryu		
10:00 – 10:30	Coffee Break		
10:30 – 11:10	Invited Lecture A11 Audimax Burkhard König	Invited Lecture B11 H2 Mélanie Etheve-Quelquejeu	
11:10 – 11:50	Invited Lecture A12 Audimax Wen-Jing Xiao	Invited Lecture B12 H2 Ivone Carvalho	
11:50 – 12:20	Invited Lecture A13 Audimax Kirsten Zeitler	Invited Lecture B13 H2 Ullrich Jahn	
12:30 – 13:50	Lunch		Minisymposium Photocatalysis 13:00 – 18:00 H4 (see separate program)
14:00 –17:00	Sight seeing tours: Boat trip to Walhalla or City tour Regensburg or Thurn&Taxis palais		
19:30 – 22:00	**Conference Dinner** Restaurant St. Erhard, Kolpinghaus, Adolph-Kolping-Straße 1 Bus stop Dachauplatz		

Friday, Sep 8

9:00 – 9:55	Plenary Lecture 10 Yasuyuki Kita	Audimax
10:00 – 10:55	Plenary Lecture 11 Huw M.L. Davies	Audimax
11:00 – 11:20	Closing Remarks	Audimax
11:30 – 13:00	Lunch	

GRK 1626 Chemical Photocatalysis

Program of the 30th seminar day

September 7th, 2017

Minisymposium Photocatalysis

September 7th (lecture hall H4, University of Regensburg)

time	topic	Speaker
13:00-13:10	**Opening remarks**	Burkhard König
Chair	**Session I**	*Andreas Graml*
13:10-13:40	*Talk 1*	Leyre Marzo
13:40-14:00	*Talk 2*	Ethienne Brachet
14:00 -15:00	*Tutorial*	Wen-Jing Xiao
15:00-15:30	***Coffee break***	
Chair	**Session II**	*Simon Düsel*
15:30-15:50	*Talk 3*	Qing-Yuan Meng
15:10-16:30	*Talk 4*	Kirsten Zeitler
16:30-16:50	*Talk 5*	Indrajit Ghosh
17:00-18:00	*Tutorial*	Ilhyong Ryu

Plenary Speaker

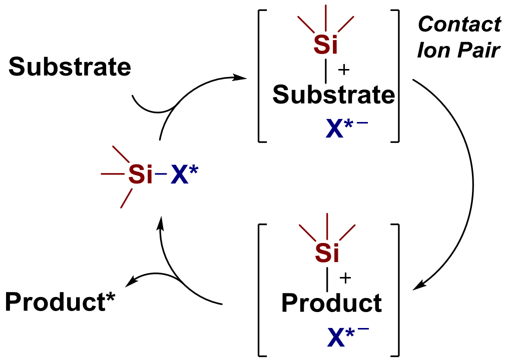
Davies, Huw M.L., Emory University C-H Functionalization with Carbenes Derived from N-Sulfonyltriazoles		**PL 11**
Fürstner, Alois, Max-Planck-Institut für Kohlenforschung Heterocycle Synthesis via π-Acid Catalysis	MOLECULES LECTURE	**PL 4**
Jørgensen, Karl Anker, Aarhus University Organocatalysis for the Construction of Chiral Heterocyclc Compounds		**PL 5**
Kita, Yasuyuki, Ritsumeikan University Metal-Free Oxidative Coupling Reactions Using Hypervalent Iodine Reagents		**PL 10**
List, Benjamin, Max-Planck-Institut für Kohlenforschung A New Concept for Asymmetric Lewis Acid Catalysis		**PL 1**
Nevado, Cristina, University of Zurich On mechanistic puzzles in metal catalyzed reactions		**PL 2**
Reisman, Sarah, California Institute of Technology Necessity is the Mother of Invention: Natural Products and the Chemistry They Inspire		**PL 6**
Ryu, Ilhyong, Osaka Prefecture University Cooperative Radical/Polar Annulation Approach to Nitrogen-Heterocycles		**PL 9**
Scheidt, Karl A., Northwestern University Cooperative Catalysis for Chemical Synthesis		**PL 8**
Sutherland, John, Medical Research Council Origins of Life Systems Chemistry		**PL 3**
Vanderwal, Christopher, University of California, Irvine Synthesis and Biological Evaluation of the Lissoclimide Cytotoxins		**PL 7**

ISHC 2017 Abstract (A New Concept for Asymmetric Lewis Acid Catalysis)

Prof. Dr. Benjamin List*
Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, Germany

As a fundamental activation mode, Lewis acid catalysis enables key reactions in chemical synthesis, such as the Diels–Alder and Friedel–Crafts reactions, and various aldol, Mannich, and Michael reactions. Consequently, substantial efforts have been directed towards the development of enantiopure Lewis acids, which have enabled important asymmetric variations of such reactions. Despite the plethora of elegant catalysts and methodologies developed in this context, a key limitation of enantioselective Lewis acid catalysis is the frequent need for relatively high catalyst loadings, which result from issues such as insufficient Lewis acidity, product inhibition, hydrolytic instability, and background catalysis.

We have recently developed in situ silylated disulfonimide-based organocatalysts, which address some of these problems in highly enantioselective Mukaiyama-type reactions involving silicon-containing nucleophiles with unprecedentedly low catalyst loadings. As an example of asymmetric counteranion-directed catalysis (ACDC), these reactions proceed via silylation of an electrophile, generating a cationic reactive species that ion-pairs with an enantiopure counteranion and reacts with a silylated nucleophile. We became interested in expanding this "silylium-ACDC" approach to, in principle, all types of Lewis acid catalyzed reactions, including those that do not involve silylated reagents. In my presentation, I will discuss how the concept evolved from our studies on ACDC. I will furthermore describe its first realization with the development of extremely active organic Lewis acid catalysts that enable new approaches to heterocycles and asymmetric versions of highly challenging Diels–Alder reactions.



Silylium-
Asymmetric Counteranion Directed Catalysis
(Si-ACDC)

On mechanistic puzzles in metal catalyzed reactions

Andrés García-Domínguez, Wei Shu, Zhaodong Li and Cristina Nevado*
University of Zurich, Department of Chemistry. Winterthurerstrasse 190, 8057 Zurich (Switzerland)
E-mail: cristina.nevado@chem.uzh.ch;

Intermolecular processes involving formation of new C-C bonds across multiple bonds are in high demand as they provide a fast access to complex molecules from readily available substrates.[1] Our efforts towards the development of metal catalyzed multicomponent dicarbofunctionalizations of alkynes and alkenes[2] as well as on the utilization of 1,n-H migration processes[3] to build up molecular complexity will be presented. The mechanistic lessons underpinning these transformations, most of which proceed via metal-catalyzed single electron transfer processes, will be discussed.

REFERENCES:

[1] a) E. Negishi, Z. Huang, G. Wang, S. Mohan, C. Wang, H. Hattori, *Acc. Chem. Res.* **2008**, *41*, 1474; b) A. B. Flynn, W. W. Ogilvie, *Chem. Rev.* **2007**, *107*, 4698; c) M. Ihara, K. Fukumoto, Angew. Chem. Int. Ed. **1993**, *32*, 1010; d) M. J. Chapdelaine, M. Hulce *Org. React.* **1990**, *38,* 225.

[2] a) Z. Li, A. García-Domínguez, C. Nevado, *J. Am. Chem. Soc.* **2015**, *137*, 11610; b) Z. Li, A. García-Domínguez, C. Nevado, *Angew. Chem. Int. Ed.* **2016,** *55*, 6938; c) A. García Domínguez, Z. Li, C. Nevado. *J. Am. Chem. Soc.* **2017**, *10.1021/jacs.7b03195*.

[3] a) W. Shu, A. Lorente, E. Gómez-Bengoa, C. Nevado, *Nature Commun.* **2017**, *8*, 13832; b) W. Shu, C. Nevado, *Angew. Chem. Int. Ed.* **2017**, *56*, 1881; c) W. Shu, C. Nevado, *Angew. Chem. Int. Ed.* **2017**, ASAP.

Origins of Life Systems Chemistry

John D. Sutherland*
MRC Laboratory of Molecular Biology, Cambridge UK

By reconciling previously conflicting views about the origin of life – in which one or other cellular subsystem precedes, and then 'invents' the others – we suggested a new *modus operandi* for its study. Guided by this, we uncovered a cyanosulfidic protometabolism which uses UV light and the stoichiometric reducing power of hydrogen sulfide to convert hydrogen cyanide, and a couple of other prebiotic feedstock molecules which can be derived therefrom, into nucleic acid, peptide and lipid building blocks. We are now considering the transition of systems from the inanimate to the animate state through intermediate stages of partial 'aliveness', and recent progress in the elaboration of building blocks into larger (oligomeric) molecules and systems in this context will also be described.

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MOLECULES LECTURE

Heterocycle Synthesis via π-Acid Catalysis

Alois Fürstner
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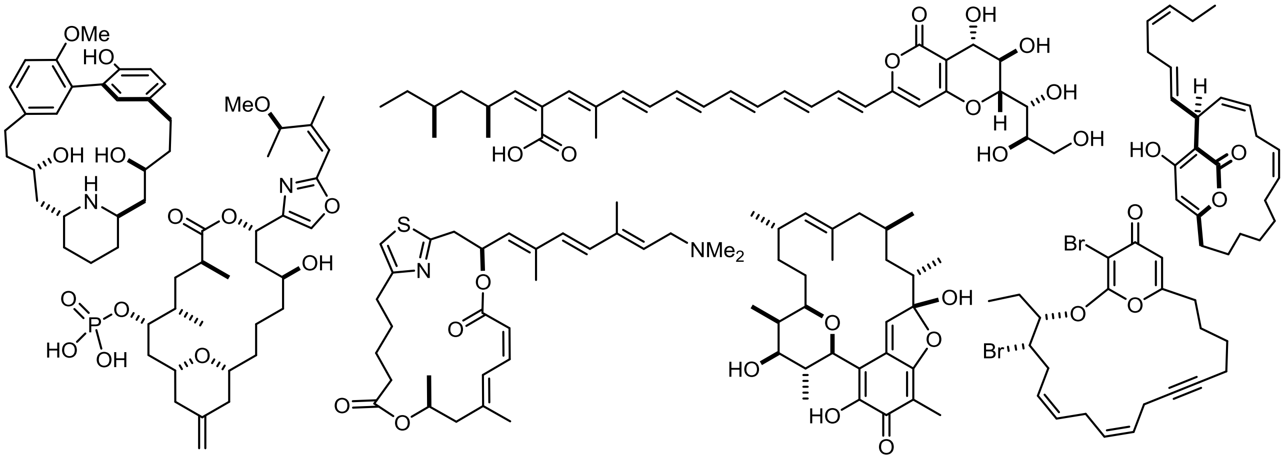
Email: fuerstner@kofo.mpg.de

A significant part of traditional heterocycle synthesis relies on carbonyl condensation reactions. Although the primacy of this chemistry is undisputed, it is worthwhile and necessary to contemplate possible alternatives. Since the C-atom of a carbonyl compound has formally the same oxidation state as that of an alkyne, any method that renders a triple bond susceptible to attack by a heteroatom nucleophile potentially opens orthogonal gateways.



It is in this context that the advent of π-acid catalysis in general and gold catalysis in particular have had a major impact. After a short discussion of the reasons for the exponential growth of this research area since the turn of the millennium, a few specific case studies will be outlined that are meant to illustrate the power of the concept [1]. Emphasis will be put on applications to the total synthesis of structurally complex heterocyclic targets of biological significance [2-6].

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[5] C.-X. Zhuo, A. Fürstner, *Angew. Chem. Int. Ed*. **2016**, *55*, 6051.
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Organocatalysis for the Construction of Chiral Heterocyclc Compounds

Karl Anker Jørgensen
Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

The lecture will demonstrate how organocatalysis has opened new avenues for the construction of chiral heterocyclic compounds.

Based on the activation of carbonyl compounds by primary and secondary amine catalysts it will be shown how various heterocyclic compounds, ranging from small to large ring-systems, can be constructed based on e.g. cycloaddition reactions.

Necessity is the Mother of Invention: Natural Products and the Chemistry They Inspire

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Abstract:

The chemical synthesis of natural products provides an exciting platform from which to conduct fundamental research in chemistry and biology. Our group is currently pursuing the synthesis of a number of structurally complex natural products, including the diterpenoids ryanodine and talatisamine, as well as the antibiotic pleuromutilin. The densely-packed arrays of heteroatoms and stereogenic centers that constitute these polycyclic targets challenge the limits of current technology and inspire the development of new synthetic strategies and tactics. This seminar will describe the latest progress in our methodological and target-directed synthesis endeavors.

Synthesis and Biological Evaluation of the Lissoclimide Cytotoxins

Christopher D. Vanderwal*
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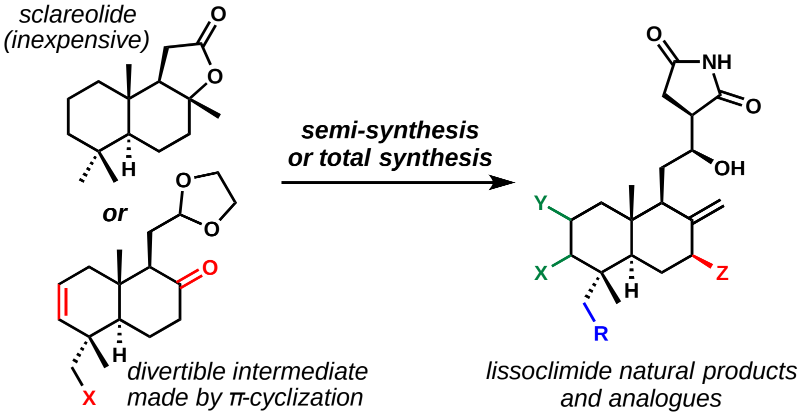
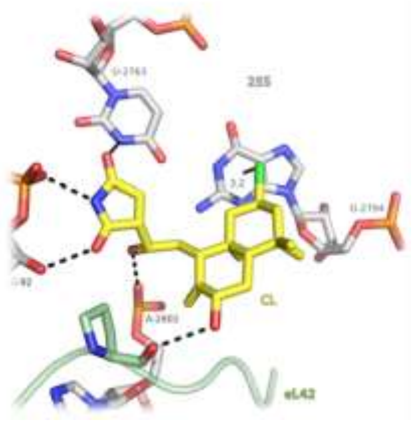
The lissoclimides are a family of labdane diterpenoids bearing an unusual succinimide motif, many of which were reported to have potent cytotoxic activity against representative mammalian cancer cell lines. Until recently, none of the 20+ natural products in this family have been made my chemical synthesis.





Our short semi-synthesis from sclareolide and our complementary analogue-oriented synthesis approach have provided a series of lissoclimide natural products and analogues that permitted expansion of the structure-activity relationships (SAR) in this family. The semi-synthesis approach yielded significant quantities of chlorolissoclimide that allowed us to obtain an X-ray co-crystal structure of the synthetic secondary metabolite with the eukaryotic 80S ribosome. While it shares a binding site with other imide-based natural product translation inhibitors, a particularly interesting and apparently novel attractive face-on halogen-π interaction between chlorolissoclimide's alkyl chloride and a guanine residue surfaced from this study. Our analogue-oriented synthesis supplemented our array of lissoclimide compounds, many of which were tested against aggressive human cancer cell lines, and whose cytotoxicity was correlated to their protein synthesis inhibitory activity. Computational modeling was used to explain the SAR of certain key compounds, setting the stage for structure-guided design of better translation inhibitors.

Finally, our efforts to synthesize the most potent known lissoclimide, haterumaimide J, led to the exploration of an underappreciated mode of cationic polycyclization, which is likely to have value outside of this small family of secondary metabolites. Our most recent results in each of these areas will be described.

Cooperative Catalysis for Chemical Synthesis

Karl A. Scheidt*
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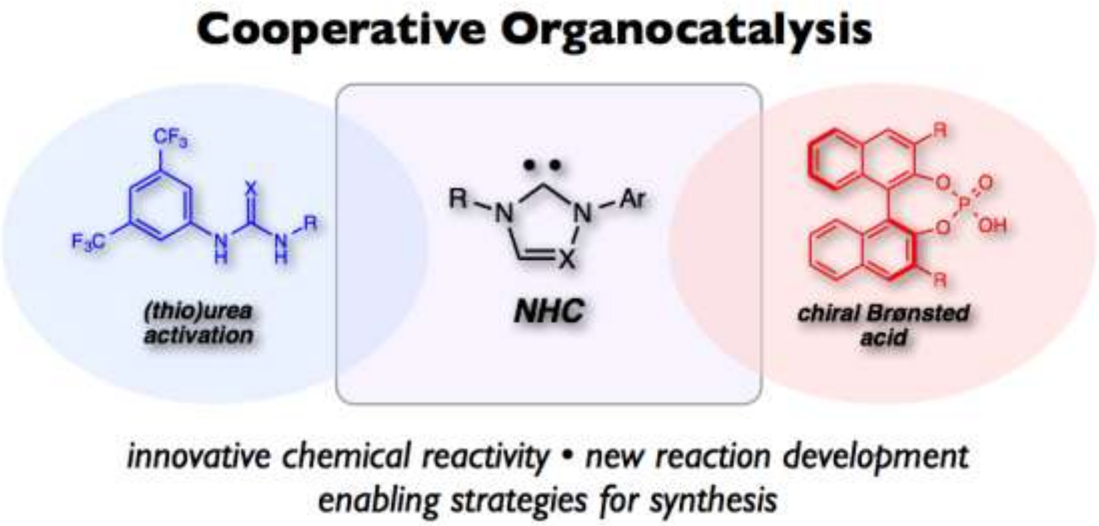
N-heterocyclic carbenes (NHCs) have tremendous versatility as ligands for transition metals and as highly selective organocatalysts. Our research program has pioneered the development of NHCs as unique Lewis base catalysts for stereoselective C–C and C–N bond forming processes involving unique homoenolate and enolate reactivity. These metal-free, catalytic reactions provide immense opportunities for development and application in target synthesis. This presentation will describe our recent discoveries in the area of cooperative catalysis and the applications to the synthesis of medically relevant natural products.



Acknowledgements: Financial support by the National Institutes of Health, National Institute of General Medical Sciences (NIGMS R01 073072) is gratefully acknowledged.

Cooperative Radical/Polar Annulation Approach to Nitrogen-Heterocycles

Ilhyong Ryu
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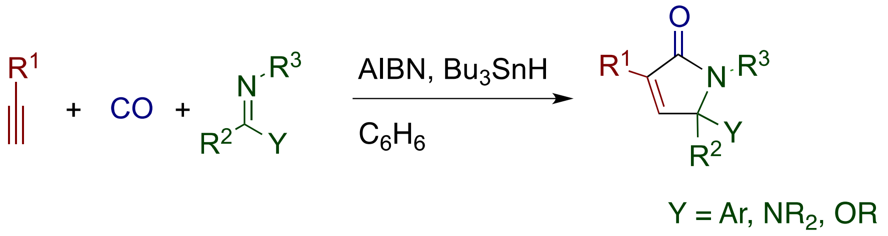
With a strong desire to develop radical carbonylation chemistry, we naturally focused our attention on the key reactive intermediates acyl radicals. Acyl radicals have been regarded as nucleophilic radicals towards electron-poor alkenes akin to vinyl radicals. However, deeming that acyl radicals may act as pseudo-carbonyl compounds, we observed acyl radicals to behave as electrophilic species, very unlike vinyl radicals. We reported that α,β-unsaturated acyl radicals, generated by the addition of alkenyl radicals to CO, underwent *N*-philic radical cyclization onto the nitrogen of N-C double bonds, providing a useful annulation method for the synthesis of lactams.[1] Intermolecular [2+2+1] cycloaddition reaction of acetylenes, amidines or the related compounds, and CO also proceeded well to give five membered α,β-unsaturated lactams (eq 1).[2] As an application of catalyst-free carbonylation of aromatic iodides,[3] we found that acyl radicals were successfully trapped by DBU, which gave ring-expanded *N*-heterocycles (eq 2).



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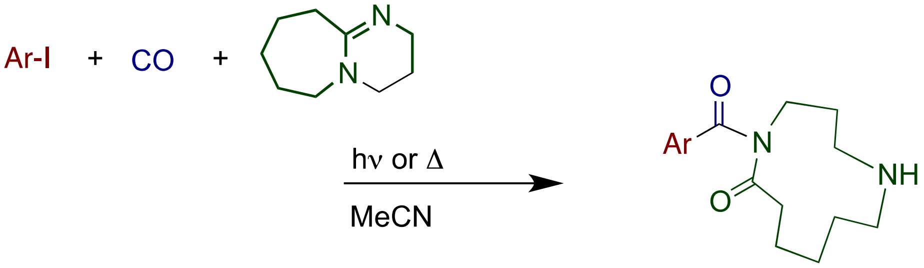

(2)

[1] (a) Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Ryu, I. *J. Am. Chem. Soc.* 2006, *128,* 7712. (b) Kyne, S. H.; Lin, C. Y.; Ryu, I.; Coote, M. L.; Schiesser, C. H. *Chem. Commun.* 2010, *46,* 6521. (c) Ryu, I., Fukuyama, T., Tojino, M., Uenoyama, Y., Yonamine, Y., Terasoma, N., Matsubara, H. *Org. Biomol. Chem.*, 2011, *9*, 3780. (d) Ueda, M., Uenoyama, Y., Terasoma, N., Doi, S., Kobayashi, S., Ryu, I., Murphy, J. A. *Beilstein J. Org. Chem.*, 2013, *9*, 1340.
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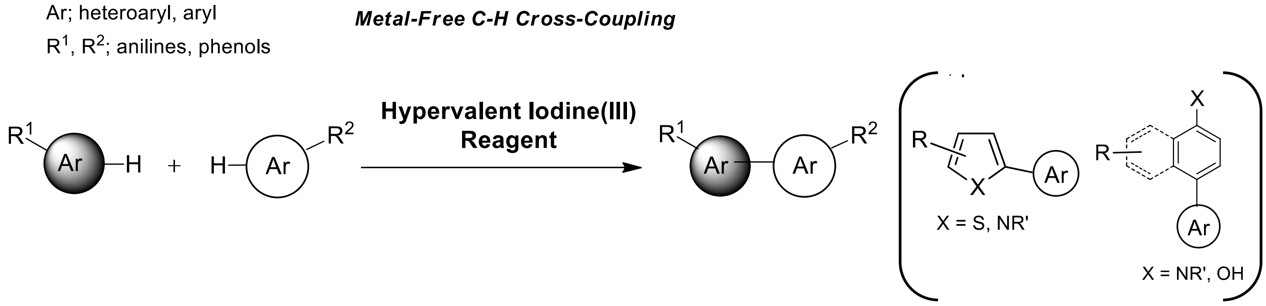
Metal-Free Oxidative Coupling Reactions Using Hypervalent Iodine Reagents

Yasuyuki Kita
Research Organization of Science and Technology, Ritsumeikan University,
Kusatsu, Shiga, Japan/ Country Code

We started our hypervalent iodine research about 30 years ago in the mid-1980's. We soon successfully developed the single-elecron-transfer oxidation ability of a hypervalent iodine reagent, specifically, phenyliodine(III) bis(trifluoroacetate) (PIFA), toward aromatic rings of phenyl ethers for forming aromatic cation radicals. This was one of the exciting and unexpected events in our research studies so far, and the discovery was reported in 1991. It also led to the next challenge, developing the metal-free oxidative coupling for C-H functionalizations and direct coupling between the C-H bonds of valuable aromatic compounds. In general, the methods for reacting non-activated aromatic substrates are known to have difficulty in achieving selective cross-biaryl-couplings because of the over-oxidation of the products and competitive homodimer formations by undesired coupling between the same aryl substrates. We have pioneered a number of new metal-free oxidative aromatic coupling methods for providing several types of mixed biaryls in high yields with perfect cross-coupling selectivities. They are classified into two types of aromatic ring activation modes based on the pattern of the reaction mechanisms, which involve i) the aromatic cation radicals and ii) diaryliodonium salts. [1]



These oxidative coupling reactions were successfully applied to other biaryl compounds having heteroatoms in and on the aromatic ring. [2]

In this lecture, I will explain about the background of our hypervalent iodine chemistry and then recent progress in the field of metal-free oxidative cross-coupling reactions of aromatic compounds having heteroatoms using hypervalent iodine(lll) reagents will be mainly presented.

[1] (a) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S., *J. Am. Chem. Soc.* **1994**, *116*, 3684~3691. (b) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T., *J. Am. Chem. Soc.* **2009**, *131*, 1668~1669. (c) Kita, Y.; Dohi, T., *Chem. Rec.* **2015**, *15*, 886~906.

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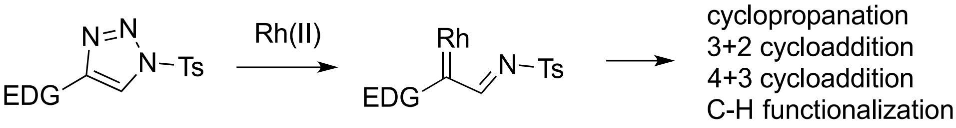
C-H Functionalization with Carbenes Derived from N-Sulfonyltriazoles

Huw M. L. Davies*
Department of Chemistry, Emory University, Atlanta, GA 30322, USA

N-Sulfonyltriazoles have been widely explored in recent years as precursors to reactive donor/acceptor carbene intermediates [1]. We have demonstrated that they can be used in cyclopropanations [2] , 3+2 cycloadditions [3,4], 4+3 cycloadditions [5], cyclization to pyrroles [6], and indole alkylations [7]. More recently, we have focused on applying the intermediates in site selective and stereoselective C–H functionalization [8]. This presentation will highlight our recent studies on expanding the scope of the C-H functionalization chemistry and some unusual transformations that were discovered during these studies.



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Invited Speaker

Ackermann, Lutz, Georg-August-Universität Göttingen **IL-A 2**
Selectivity Control in C–H Activation

Akai, Shuji, Osaka University **IL-C 2**
Arynes as Powerful Platforms for Regioselective Construction of Fused Heteroaromatic Compounds

Aube, Jeffrey, University of North Carolina **IL-B 9**
New Opioid Biology Arising From Heterocyclic Chemistry

Biju, Akkattu, Indian Institute of Science, Bangalore **IL-A 6**
Sustainable N-Heterocyclic Carbene (NHC) Organocatalysis

Bower, John, University of Bristol **IL-A 5**
Catalytic Chirality Generation: New Strategies for N-Heterocyclic Chemistry

Carvalho, Ivone, University of Sao Paulo **IL-B 12**
SYNTHESIS OF NEW QUINAZOLINE AND DIKETOPIPERAZINE SCAFFOLDS AND APPLICATIONS FOR MEDICINAL CHEMISTRY

Chiu, Pauline, University of Hong Kong **IL-B 10**
Applications of Intramolecular (4+3) Cycloadditions of Furans and Pyrroles to the Synthesis of Natural Products

Cramer, Nicolai, Ecole polytechnique fédérale de Lausanne **IL-A 4**
The Quest for Efficient Ligands in Asymmetric C-H Functionalizations

Deska, Jan, Aalto University, Department of Chemistry **IL-C 4**
Stereoselective Enzymatic Ring Expansion and Ring Contraction Reactions of O-Heterocycles

Doyle, Michael, University of Texas at San Antonio **IL-A 3**
New Constructions of Heterocycles and Carbocycles by Cycloaddition from Metallo-enolcarbenes

Eastgate, Martin, Bristol-Myers Squibb **IL-A 8**
Innovation in the Synthesis of Complex Pharmaceutical Compounds

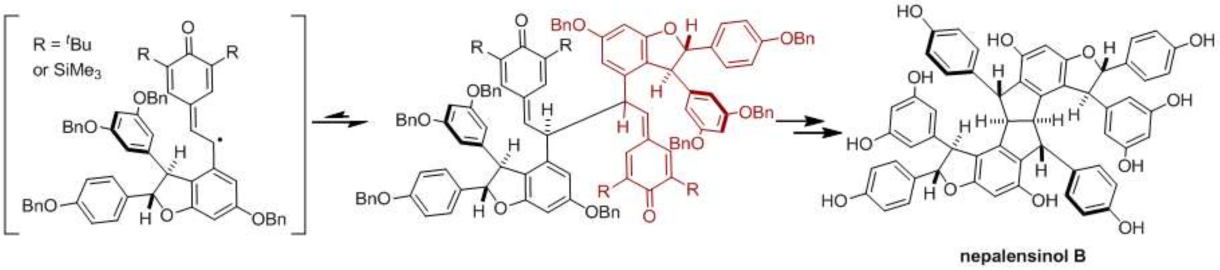
Etheve-Quelquejeu, Mélanie, University of Paris Descartes Post-functionalization of RNAs for specific conjugations with peptides and proteins	**IL-B 11**
Garcia Mancheño, Olga, University of Regensburg 1,2,3,-Triazoles: From Metal- to Supramolecular Organic Catalysis	**IL-C 1**
Gryko, Daniel T., Polish Academy of Sciences Diketopyrrolopyrroles - the Journey from Ferrari Pigments to Fluorescent Functional Dyes	**IL-B 1**
Hii, Mimi, Imperial College London Heterocycles for heterocycles: Synthesis of highly-substituted oxazolines using pyridines and N-heterocyclic carbene	**IL-A 7**
Hocek, Michal, Institute of Organic Chemistry and Biochemistry CAS Base-Modified Nucleosides, Nucleotides and Nucleic Acids. Synthesis, Medicinal Chemistry and Chemical Biology	**IL-B 2**
Jahn, Ullrich, IOCB Prague New Efficient Approaches to the Total Synthesis Piperazinone Alkaloids and Analogs	**IL-B 13**
Kappe, C. Oliver, University of Graz Going with the Flow – The Use of Continuous Processing in Organic Synthesis	**IL-C 5**
König, Burkhard, University of Regensburg Functionalization of 5- and 6-membered heteroarenes by visible light photocatalysis	**IL-A 11**
Luo, Guanglin, Bristol-Myers Squibb Evolution of Heterocyclic Replacements Led to a Potent Oral CGRP Receptor Antagonist for Migraine Treatment	**IL-B 6**
Maienfisch, Peter, Syngenta Crop Protection AG Synthesis and Properties of novel Spiroindoline Insecticides	**IL-A 10**
Meier, Peter, Novartis Pharma AG A Journey Through Heterocycles in Drug Discovery at Novartis	**IL-A 9**
Pazenok, Sergii, Bayer AG, Crop Science Division general approach towards the heterocyclic compounds bearing emergent fluorinated substituents	**IL-B 4**

Sherry, Benjamin, Merck Sharp & Dohme Corp. Development of Efficient Processes to Nitrogen Heterocycles	**IL-B 5**
Stang, Peter J., The University of Utah Abiological Self-Assembly: Predesigned Metallacycles and metallacages via Coordination	**IL-B 7**
Stephenson, Corey, University of Michigan Natural product synthesis leveraging persistent radicals	**IL-A 1**
Suzuki, Keisuke, Tokyo Institute of Technology Strategies in Total Synthesis of Polyketide-II Natural Products: Total Syntheses of Tetracenomycins C and X	**IL-B 8**
Tang, Wenjun, Shanghai Insititute Of Organic Chemistry, Chinese Academy of Sciences Natural Product Synthesis Facilitated by Ligand Design	**IL-B 3**
Xiao, Wen-Jing, Central China Normal University Construction of Heterocyclic Architectures through Reactions of Sulfur Ylides	**IL-A 12**
Zeitler, Kirsten, Universität Leipzig Multicatalytic Transformations in a New Light	**IL-A 13**

Natural product synthesis leveraging persistent radicals

Corey Stephenson*
Department of Chemistry, University of Michigan, Ann Arbor, MI, USA 48109

Single electron transfer (SET) processes – frequently utilized by Nature to activate its substrates – significantly enhance the reactivity of organic molecules. These SET reactions provide facile access neutral radicals – reactive intermediates that are particularly attractive for use in complex settings as a consequence of their general lack of reactivity with polar functional groups. The use of redox catalysis (e.g. photocatalysis and electrocatalysis) furthers the benefits of SET processes enabling the reduction of stoichiometric waste byproducts and toxic or hazardous reagents compared with classical approaches. The development of approaches to resveratrol derived natural products involving the selective generation of persisten radical intermediates underpinned on practicality and mechanistic understanding will be presented in this talk.[1,2,3]



[1] Keylor, M. H.; Matsuura, B. S.; Griesser, M.; Chauvin, J.-P. R.; Harding, R. A.; Kirillova, M. S.; Zhu, X.; Fischer, O. J.; Pratt, D. A.; Stephenson, C. R. J. *Science* **2016**, *354*, 1260.
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Selectivity Control in C–H Activation

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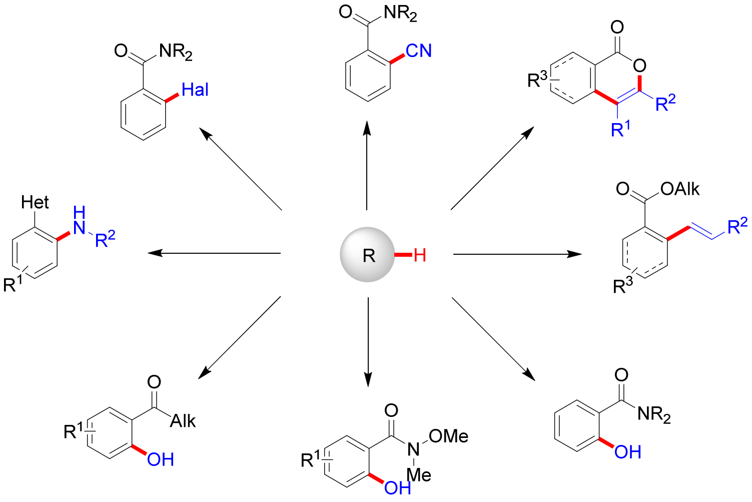
Institute for Organic and Biomolecular Chemistry, Georg-August-University Göttingen, 37077 Göttingen, Germany

C–H activation has surfaced as a powerful platform in molecular synthesis, with transformative applications to material sciences and drug discovery, among others.[1] Thus, we have introduced secondary phosphine oxides and carboxylates as additives for positional selective C–H arylations and alkylations with versatile ruthenium(II) complexes,[2] displaying complementary chemo- and site-selectivities as compared to palladium,[3a] nickel,[3b] cobalt,[3c] iron,[3d] copper[3e] or manganese[3f] catalysis. Detailed mechanistic insights into the working mode of the key C–H ruthenation step set the stage for ruthenium(II)-catalyzed twofold C–H bond functionalizations as well as step-economical oxidative alkyne annulations.[4,5] The oxidative C–H bond functionalization strategy proved broadly applicable and enabled, among others, ruthenium(II)-catalyzed oxygenations, nitrogenations, cyanations and halogenations, as well as *meta*-and *para*-selective arene diversification.[6]



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[2] Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345.

[3] Representative examples: (a) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem. Int. Ed*. **2009**, *48*, 201–204. (b) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem. Int. Ed*. **2014**, *53*, 2477–2480. (c) Li, J.; Ackermann, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 8551–8554. (d) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014,** *53*, 3868–3871. (e) Yang, F.; Koeller, J.; Ackermann, L., *Angew. Chem. Int. Ed.* **2016**, *55*, 4759–4762. (f) Ruan, Z.; Sauermann, N.; Manoni, E.; Ackermann, L., *Angew. Chem. Int. Ed.* **2017,** *56*, 3172–3176.

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New Constructions of Heterocycles and Carbocycles by Cycloaddition from Metallo-enolcarbenes

Michael P. Doyle, Yongming Deng, and Qing-Qing Cheng
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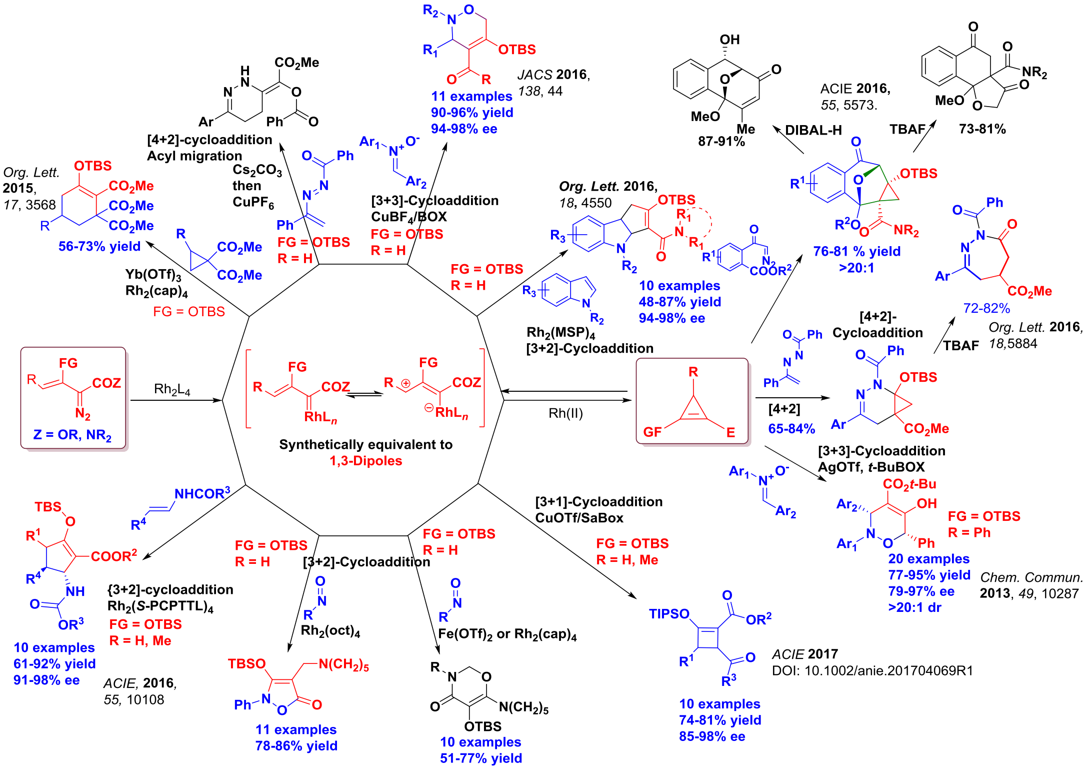
Enoldiazo compounds have proven to be one of the most versatile reagents for cycloaddition reactions in highly efficient constructions of various carbocycles and heterocycles. They have enormous flexibility in their chemical reactions for cycloaddition reactions of metal carbene intermediates. Applications of [3+3]-, [3+2]-, and [3+1]-cycloaddition reactions for highly selective asymmetric synthesis include dihydrooxazines, pyrazolidinones, quinolizidines, tetrahydropyridazines, cyclopentane amino acids, cyclobutenes and azacyclobutenes. Enoldiazoacetates and enoldiazoacetamides are stable at room temperature and below for weeks or months, yet they undergo thermal dinitrogen extrusion at temperatures as low as 50°C to quantitatively form donor-acceptor cyclopropenes that are precursors to the same metalloenolcarbenes that are formed from the corresponding enoldiazo compounds. These donor-acceptor cyclopropenes are themselves highly reactive dipolarophiles or dienophiles that form bi- or tricyclic structures which are subject to further transformations.



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Cheng, Q.-Q.; Doyle, M. P. in *Adv. Organometal. Chem., Vol. 66* Perez, P. J., Ed., Elsevier Limited. Oxford, United Kingdom, 2016. Chapter 1, pg. 1-26.

The Quest for Efficient Ligands in Asymmetric C-H Functionalizations

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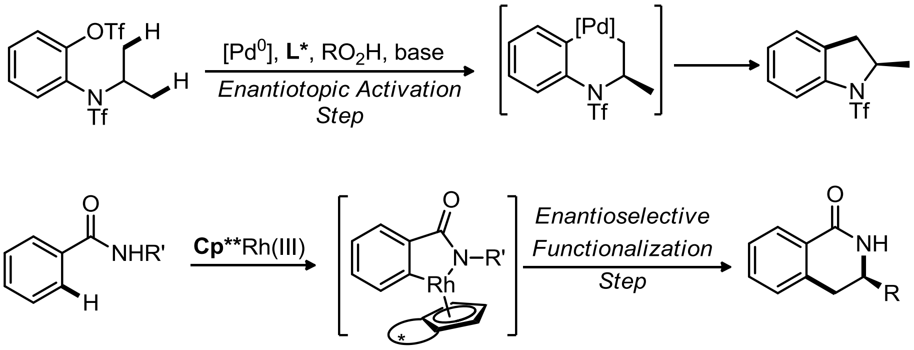
Reactions involving the selective activation and subsequent functionalization of C-H bonds have a high synthetic potential because of their economic and ecological benefits. Despite significant progress in addressing reactivity and selectivity issues, as well as refining mechanistic understanding of the different pathways, catalytic enantioselective transformations remain largely underdeveloped. Often harsh conditions, the use of uncommon ligand systems or bar metal salts as catalysts have hampered developments in this area. Therefore, the design and development of efficient ligand systems is critical to the success these transformations. The presentation will focus on our recent developments of activating enantiotopic C(sp^3)-H bonds using Pd(0)-catalysts.[1] The utility and versatility of chiral cyclopentadienyls as enabling ligands for a variety of late transition-metals for enantioselective C-H activations will be discussed, showcasing the use of these techniques for a streamlined access to relevant small molecules.[2]



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Catalytic Chirality Generation: New Strategies for N-Heterocyclic Chemistry

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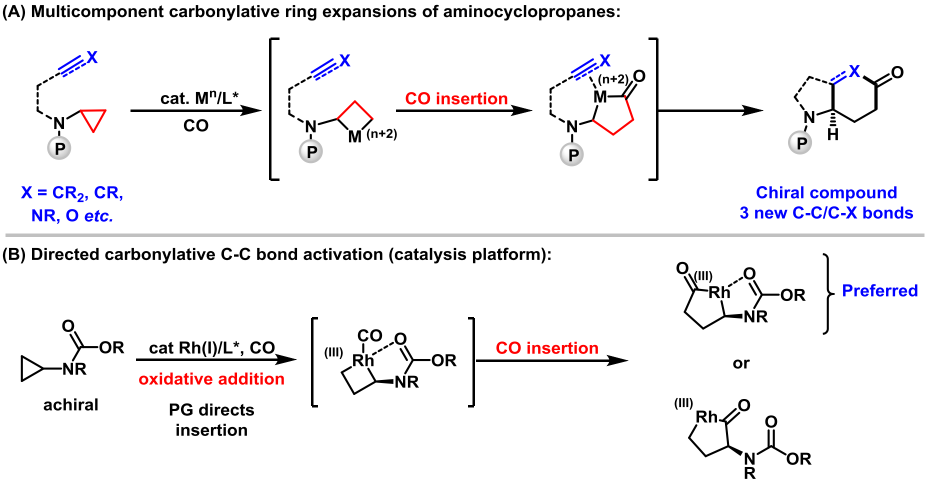
Our research programme is focussed upon the development of new catalysis platforms that enable direct access to medicinally valuable chiral scaffolds. Recently, we outlined a metal-catalysed (3+1+2) carbonylative cycloaddition strategy for the synthesis of complex nitrogen containing scaffolds (Scheme 1A).[1] The key metallacyclic intermediates are generated by Rh-catalysed carbonylative ring expansion of readily available amino-substituted cyclopropanes. To control the regioselectivity of this process we have developed a directing group strategy, which takes advantage of the N-protecting group (Scheme 1B). This approach controls (a) the regioselectivity of oxidative addition (into the more hindered cyclopropane C-C bond) and (b) the regioselectivity of CO insertion. Mechanistic aspects of this process will be discussed and prototypical catalytic processes that involve trapping of the metallacyclic intermediate with tethered alkynes or alkenes will be presented.[1-4]



Scheme 1

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Sustainable N-Heterocyclic Carbene (NHC) Organocatalysis

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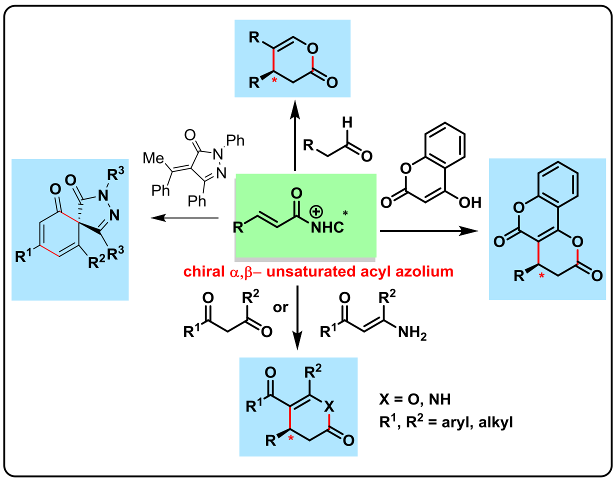

Catalysis is a fundamentally sustainable process, which can be used to produce a wide range of chemicals and their intermediates. Among the various catalytic methods, N-heterocyclic carbene (NHC)-catalyzed umpolung of aldehydes is widely used for the unconventional access to target molecules.[1] In this context, we have recently demonstrated, for the first time, the NHC-catalyzed umpolung of imines for the synthesis of 2,3-disubstituted indoles.[2] Moreover, NHC-catalysis is widely used for the generation of α,β-unsaturated acyl azoliums followed by their interception with various nucleophiles, the formal [3+3] annulation reactions. In this area, recently we have reported the enantioselective NHC-catalyzed annulations for the synthesis of dihydropyranones, dihydropyridinones, cyclopentenes, pyrazoles, spirocyclohexadienones and functionalized β-lactones.[3] The details of these works will be presented.

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Heterocycles for heterocycles: Synthesis of highly-substituted oxazolines using pyridines and *N*-heterocyclic carbenes

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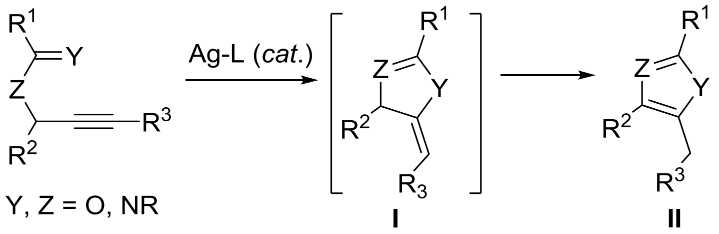

The KKH research group has a long-standing interest in heterofunctionalization reactions, particularly the addition of O-H and N-H to unsaturated carbon-carbon moieties, using group 11 metal catalysts such as copper and silver.[1] Intramolecular variants of these reactions can offer new routes to the synthesis of heterocyclic scaffolds.

In recent years, we have developed catalytic methodologies for the synthesis of highly-substituted oxazolines/oxazoles, based on silver complexes. [2] The discovery of some of these synthetic routes will be presented in this talk, including the synergistic effects between the nature of the heteroatoms present in the acyclic precursor (Y and Z in the above scheme) and the electronic and steric characteristics of the ligand (L), leading to the discovery of silver-NHC complexes as a novel class of catalyst for these reactions.[3]

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Innovation in the Synthesis of Complex Pharmaceutical Compounds

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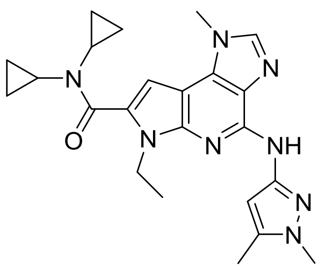
Modern pharmaceuticals are increasingly complex.[1] Todays clinical candidates often contain challenging stereochemistry, difficult molecular architectures and uncommon heterocyclic frameworks, wherein the disposition of ring heteroatoms produces unexpected reactivity patterns. Developing safe, scalable and innovative approaches to these molecules, in the context of increasingly short development timelines, requires an approach focused on creative chemical solutions – those that have significant impact to efficiency, greenness and cost – so called 'disruptive innovations'.[2]

This presentation will cover the strategies used to solve the synthetic challenges of molecules such as the nitrogen-rich JAK2 inhibitor BMS-911543,[3] and the HIV attachment inhibitor pro-drug, Fostemsavir, BMS-663068.[4] The commercially viable routes invented for these molecules led to the discovery of several new synthetic methods, such as a strategy for the regioselective synthesis of 1,4-disubstituted imidazoles,[5] the direct imidation of arenes[6] and the regioselective C2-halogenation of nitrogen containing heterocycles[7] – work which will be described in detail.



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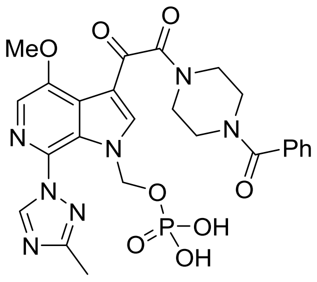

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A Journey Through Heterocycles in Drug Discovery at Novartis

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Heterocycles play a key role in drug discovery in the pharmaceutical industry. To cover the structural and property space in a most effective manner for the discovery of new leads, different strategies were applied for the selection of heterocycles and the scope of their variation. [1] Numerous examples will demonstrate these endeavors and show that these methodologies evolved over the years and led to the development of new concepts and technologies.

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Synthesis and Properties of novel Spiroindoline Insecticides

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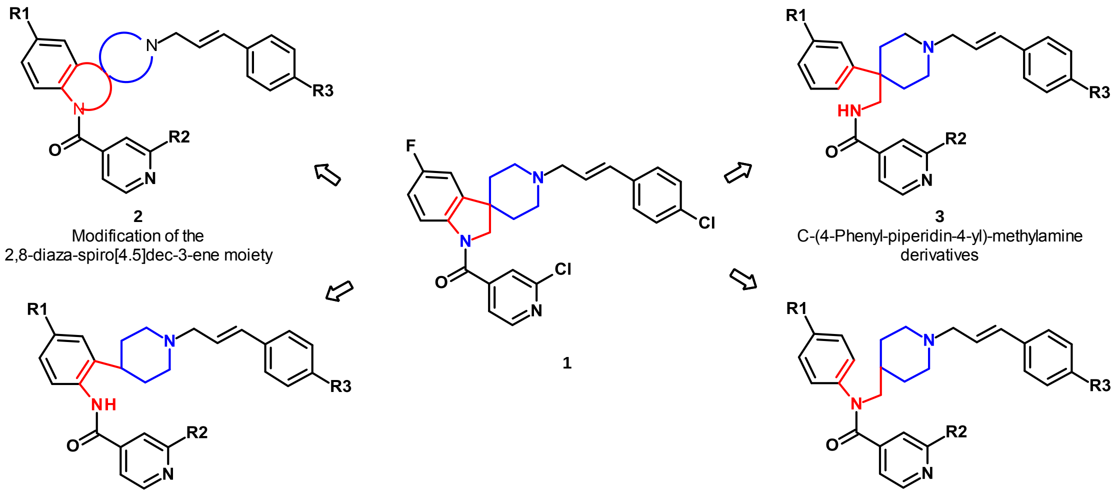
Increasing resistance risks, pest shifts and higher regulatory safety margins require further crop protection research with the aim to discovery newer, safer and more effective products. In the last two decades heterocycles have proven to be of tremendous value for the lead optimization of pharmaceuticals and agrochemicals. Today, the vast majority of insecticides introduced to the market bear at least one heterocyclic ring, and it is expected that this trend will continue.

Substituted spiro[indoline-3,4'-piperidine] compounds (spiroindolines) are a recently discovered class of insecticides acting at the vesicular acetylcholine transporter (VAChT) [1] and providing excellent activity against lepidopteran pests. An initial research program resulted in the discovery of the exploratory insecticide **1.** Further optimization was undertaken to identify even more potent compounds.



2
Modification of the
2,8-diaza-spiro[4.5]dec-3-ene moiety

1

3
C-(4-Phenyl-piperidin-4-yl)-methylamine
derivatives

4
2-Piperidin-4-yl-phenylamine
derivatives

5
N-Phenyl-piperidin-4-yl-methylamine
derivatives

As part of this program novel modification of the 2,8-diaza-spiro[4.5]dec-3-ene moiety were investigated. The presentation will report on the synthetic methodology applied to the preparation of the target compounds of types **2**, **3**, **4** and **5** as well as the biological activity and structure-activity relationships of spiroindoline insecticides. Our work resulted in the identification of the acyclic spiroindoline **4** (R^1=CF_3, R^2=Cl, R^3=Cl) - a compound with improved activity against lepidopteran pests.

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Functionalization of 5- and 6-membered heteroarenes by visible light photocatalysis

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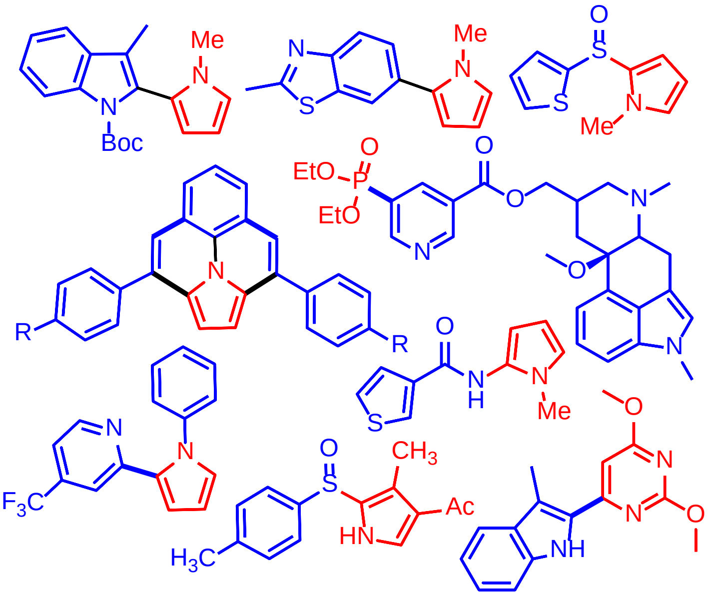
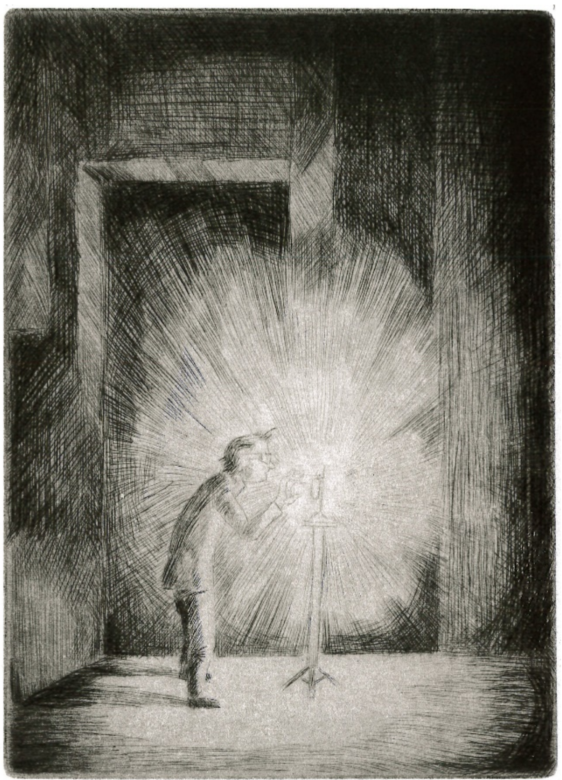
Light is a fascinating reagent for chemistry as it provides energy to drive reactions, but leaves no trace. The Italian chemist Giacomo Ciamician discovered and promoted the use of visible light in chemistry more than 100 years ago. In the last decade, photoredox catalysis has regained enormous interest. Colored, redox active dyes, metal complexes or organic heterocycles, convert visible light into redox energy allowing photoinduced electron transfer reactions.[1]



We have developed visible light photocatalytic protocols for C-H arylations, C-H amidations and sulfamidations, phosphorylations and sulfoxidations of arenes and heteroarenes.[3] The exceptionally mild reaction conditions allow for a broad tolerance of functional groups. We discuss the conditions, the scope, specific examples and proposed reaction mechanisms of the different reactions.



The illustration “The modern alchemist” (cold-needle etching, 2015, 19.5 x 13.5 cm) was created by Sebastian Dorn, art student at the University of Regensburg.

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Construction of Heterocyclic Architectures through Reactions of Sulfur Ylides

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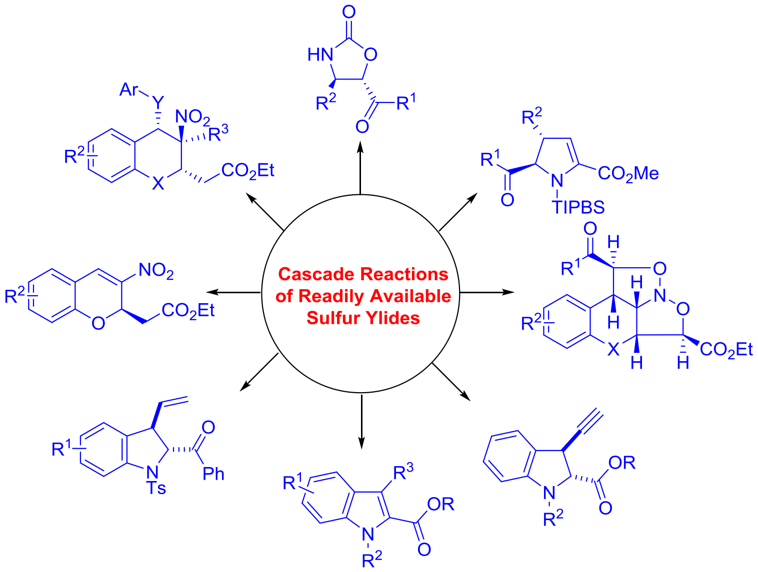
Heterocyclic compounds are a diverse class of organic molecules that have received extensive interest owing to their popularity in many natural products and synthetic drugs.[1] Although numerous methods exist to construct various heterocyclic systems,[2] new strategies with reduced numbers of transformation steps and purification procedures, lower costs and minimized chemical waste are still in high demand. We will describe a few new synthetic methods that are based on cascade strategies developed in our group. These cascade reactions aimed at the efficient construction of heterocyclic systems feature the following issues: 1) new understanding of sulfur ylides,[3] or designing new reagents based on catalyst character or retrosynthetic analysis of given structures; 2) in-depth investigations of reaction mechanisms and then designing novel cascade reactions; and 3) successful synthetic applications to access valuable synthetic building blocks, natural products, drugs and their analogs.



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Multicatalytic Transformations in a New Light

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Catalysis has been recognized as a key methodology for efficient and sustainable synthesis. Especially alternative approaches in the course of reactions, such as sequential, concerted or synergistic combinations of separate catalytic cycles enable previously unattainable transformations.[1]

However, in the context of such *multicatalytic* approaches concurrent activation of complementary reaction partners and the synchronization of the different catalytic cycles are major challenges. Umpolung strategies, including biomimetic NHC catalysis[2,3] and/or orthogonal activation such as by visible light,[4,5] which both represent non-traditional reaction manifolds, are among the activation modes to circumvent these inherent problems.

Our latest advances in developing new (multi)catalytic transformations for the activation of C–H and C–O bonds, both with and without the aid of light, will be discussed.

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Diketopyrrolopyrroles - the Journey from Ferrari Pigments to Fluorescent Functional Dyes

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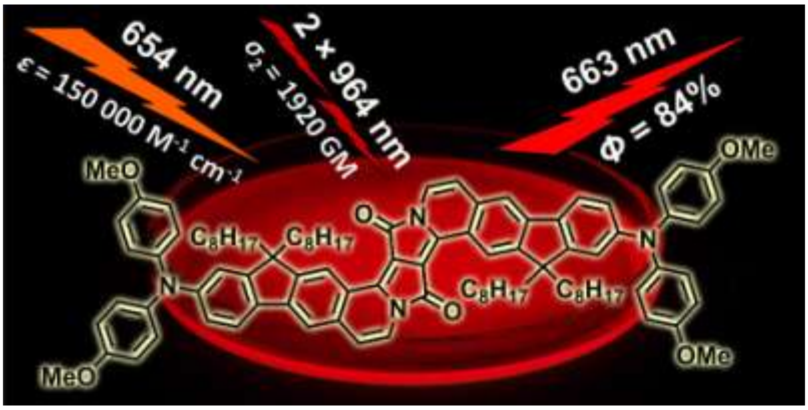
First reported by Farnum as long as 40 years ago, diketopyrrolopyrroles (2,5-dihydropyrrolo[4,3-*c*]pyrrolo-1,4-diones) are currently one of the most widely used dyes, with applications that span high-quality pigments, field-effect transistors, bulk-heterojunction solar cells, dye-sensitized solar cells, and fluorescence imaging. [1]

Structurally unique π-expanded diketopyrrolopyrroles were designed and synthesized. Strategic placement of a fluorene scaffold at the periphery of a diketopyrrolopyrrole *via* tandem Friedel-Crafts-dehydratation reactions, resulted in dyes with supreme solubility. Despite the extended ring system, the dye still preserved good solubility and was further functionalized using Pd-catalyzed coupling reactions, such as Buchwald-Hartwig amination. By placing two amine groups at peripheral positions of the resulting dyes, we have achieved values of two-photon absorption cross-section on the level of 2000 GM around 1000 nm, which generated a two-photon brightness of ~1600 GM. These characteristics in combination with red emission (665 nm) make these new π-expanded diketopyrrolopyrroles of major promise as two-photon dyes for bioimaging applications. [2,3]



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Base-Modified Nucleosides, Nucleotides and Nucleic Acids. Synthesis, Medicinal Chemistry and Chemical Biology

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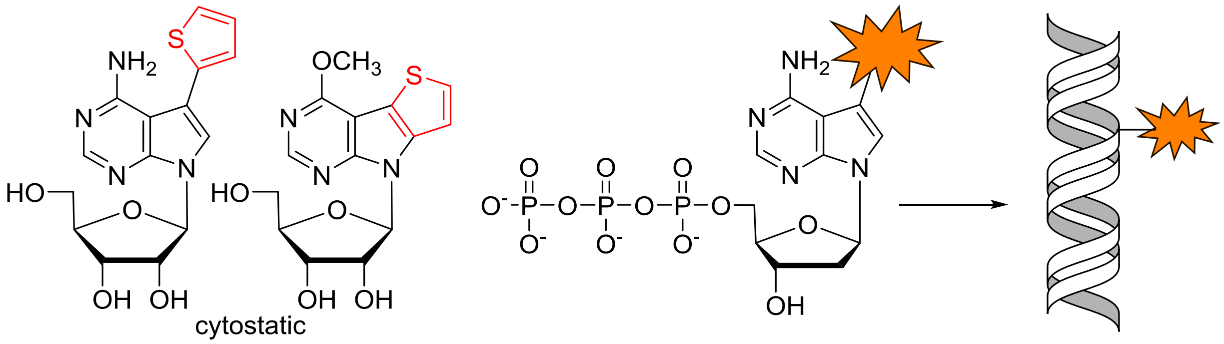
The talk will summarize our most recent findings in development of new methods of synthesis of modified nucleobases, nucleosides, nucleotides and oligonucleotides. The use of these methods will be demonstrated on the discovery and optimization of new deazapurine nucleoside cytostatics. [1] The second part of the talk will focus on synthesis of modified nucleotides and polymerase synthesis of base-modified DNA (and RNA) and applications in diagnostics (environment-sensitive fluorescent labelling, redox labelling etc.) and chemical biology (bioconjugations, cross-linking, regulation of protein-DNA binding and transcription). [2]



Medicinal chemistry

Chemical Biology

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Natural Product Synthesis Facilitated by Ligand Design

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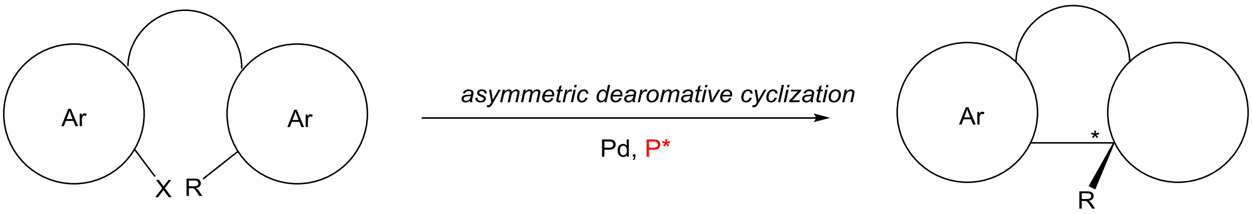
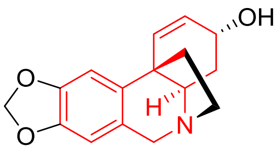
The asymmetric intramolecular Heck reaction have become one of most successful method for constructing polycyclic skeletons bearing an all-carbon chiral quaternary center in natural product synthesis. Despite its versatile synthetic utilities, the asymmetric Heck cyclization employs an olefinic starting material which often requires multiple synthetic steps to prepare. In addition, the transformation of its olefinic product to a target molecule is sometimes tedious. An attractive alternative is enantioselective intramolecular dearomative cyclization which employs an often more accessible substrate with an aryl moiety and leads to a multicyclic product bearing an all-carbon quaternary center. Because of the closer resemblance of the cyclic product to a variety of chiral natural products, this method offers advantages over the Heck reaction for the synthesis of a number of chiral polycyclic natural products. The key issue is how to achieve satisfactory reactivity, chemoselectivity, and enantioselectivity by employing an effective chiral phosphorus ligand. Herein we described the ligand design that have enabled an effective dearomative cyclization and the efficient asymmetric synthesis of several biologically important terpenes, alkaloids, and polyketides.





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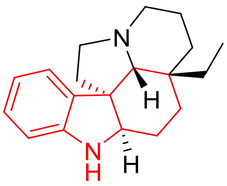

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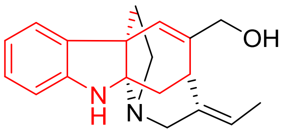

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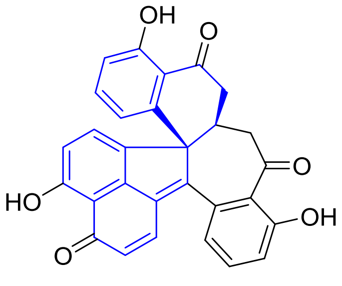

dalesconol A

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A general approach towards the heterocyclic compounds bearing emergent fluorinated substituents

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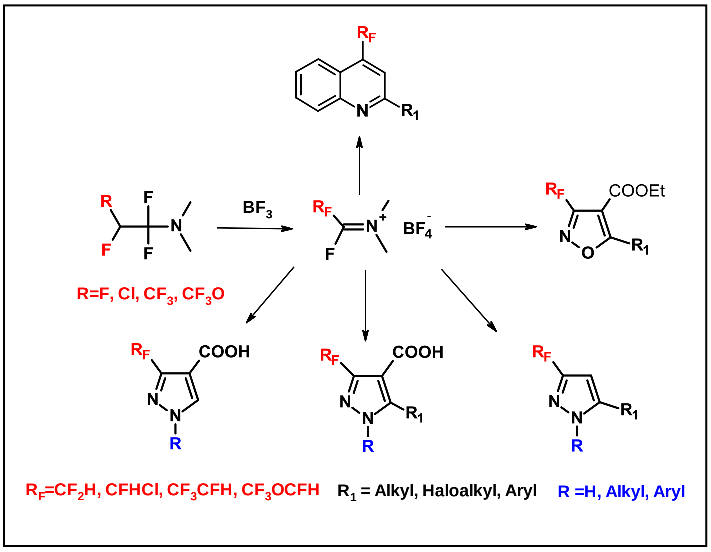
University of Strasbourg, UMR CNRS 7509, 25 Rue Becquerel, 67087 Strasbourg, France

Fluorinated heterocycles are important building block in pharmaceutical and agrochemical sciences and play a key role in modern Crop Protection. Fluoroalkyl- and fluoroalkoxy- groups are popular functional substituents and their introduction can significantly improve biological activity of active ingredients. α,α-Difluoroalkylamines belong to the so-called ***F***luoroalkyl ***A***mino ***R***eagents (**FAR**) and can be readily prepared from commercially available fluoro-olefins (monomers used for polymers production) and secondary amines. While these reagents have previously been used only for the replacement of OH with Fluorine in alcohols and carboxylic acids, we recently became interested in their use to prepare fluoroalkyl-containing heterocycles. It has been demonstrated that FARs, after activation with Lewis acids such as BF_3 and $AlCl_3$, afford iminium salts with Vilsmeier-type activity and with “unexhausted” potential for further transformations. We have exploited their reactivity to prepare diversity of fluorinated pyrazoles, isoxazoles, pyrimidines, quinolines, which are important building blocks for numerous modern agrochemicals.



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Development of Efficient Processes to Nitrogen Heterocycles

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Department of Process Research & Development, Merck Sharp & Dohme, Ltd.
Rahway, NJ 07065

Nitrogen heterocycles are prominent structural components in compounds of pharmaceutical relevance. The development of innovative and efficient means to construct these increasingly diverse motifs is a paramount problem in the field of pharmaceutical process research and development.

This seminar will describe three case studies in heterocycle synthesis applied to advanced clinical development candidates. The examples span planar aromatic comounds to more topologically complex saturated systems.

A focus throughout the discussion will be the discovery of new and enabling bond constructions or technologies that allow for the target structures to be prepared in an efficient and robust manner.

Evolution of Heterocyclic Replacements Led to a Potent Oral CGRP Receptor Antagonist for Migraine Treatment

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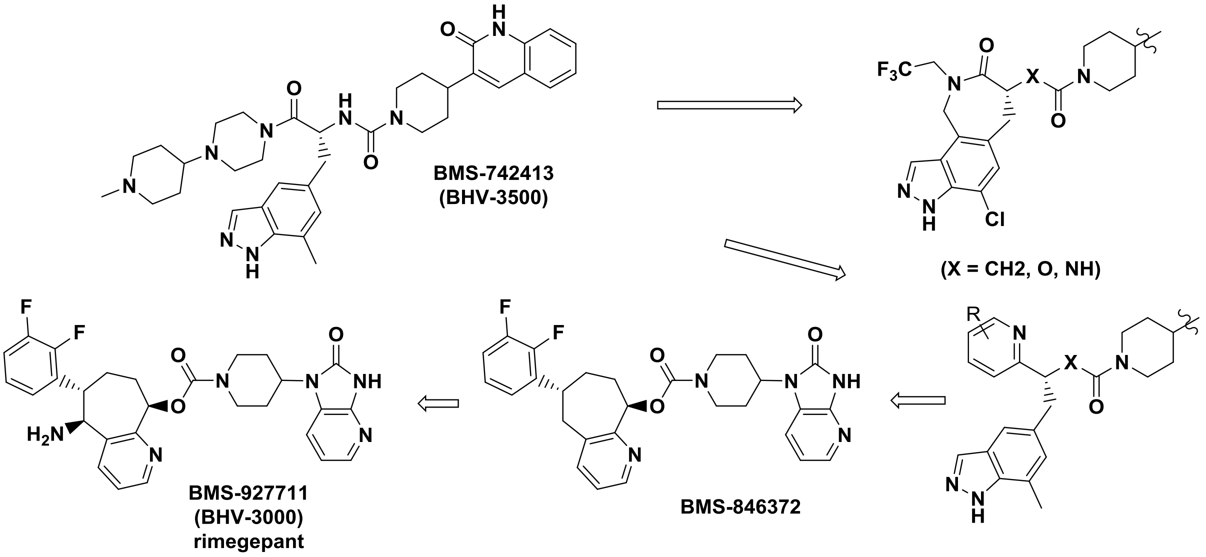
Bristol-Myers Squibb R&D
Wallingford, CT 06492, USA

Migraine is a painful and incapacitating disease that affects a significant portion of the adult population. CGRP receptor antagonists have been shown to be efficacious in treating migraine in clinical trials, but no marketed drugs in the CGRP area have yet been approved. Evolving from our intranasal lead, BMS-742413 (BHV-3500), through a series of heterocyclic replacements, we were able to discover a highly potent, orally bioavailable CGRP antagonist, BMS-927711 (BHV-3000)/rimegepant. This compound showed efficacy in a phase IIb clinical trial for acute migraine and is currently being progressed into further development..



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Abiological Self-Assembly: Predesigned Metallacycles and metallacages via Coordination

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The use of just two types of building blocks, linear and angular, in conjunction with symmetry considerations allows the rational design of a wide range of metallocyclic polygons and polyhedra via the coordination motif.[1-3] We have used this approach to self-assemble a variety of 2D supramolecular polygons such as triangles, rectangles, squares, hexagons, etc. as well as a number of 3D supramolecular polyhedra: truncated tetrahedra, triginal prisms, cubooctahedra4 and dodecahedra.[5] An example of the methodology is illustrated in Figure 1. More recently we have functionalized these rigid supramolecular scaffolds with different electroactive, host-guest, dendritic (Figure 2), and hydrophobic/hydrophilic moieties and have investigated the properties of these multifunctionalized supramolecular species.[6] Additionally, we have begun to explore the self-assembly of 2D polygons and 3D polyhedra on a variety of surfaces with the aim of developing their potential to be used in device settings.[7-12] These novel, supramolecular ensembles are characterized by physical and spectral means. The design strategy, formation, characterization and potential uses of these novel metallocyclic assemblies will be discussed, along with our very recent results.

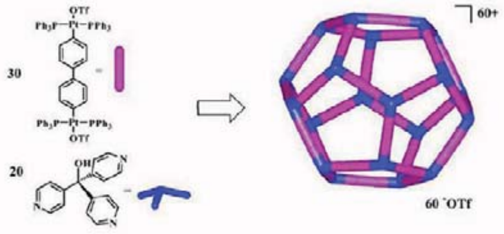

Figure 1: Self-assembly of a nanoscale dodecahedron.

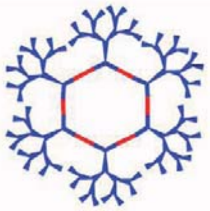

Figure 2: A cavity-cored dendritic hexagon.

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Strategies in Total Synthesis of Polyketide-II Natural Products: Total Syntheses of Tetracenomycins C and X

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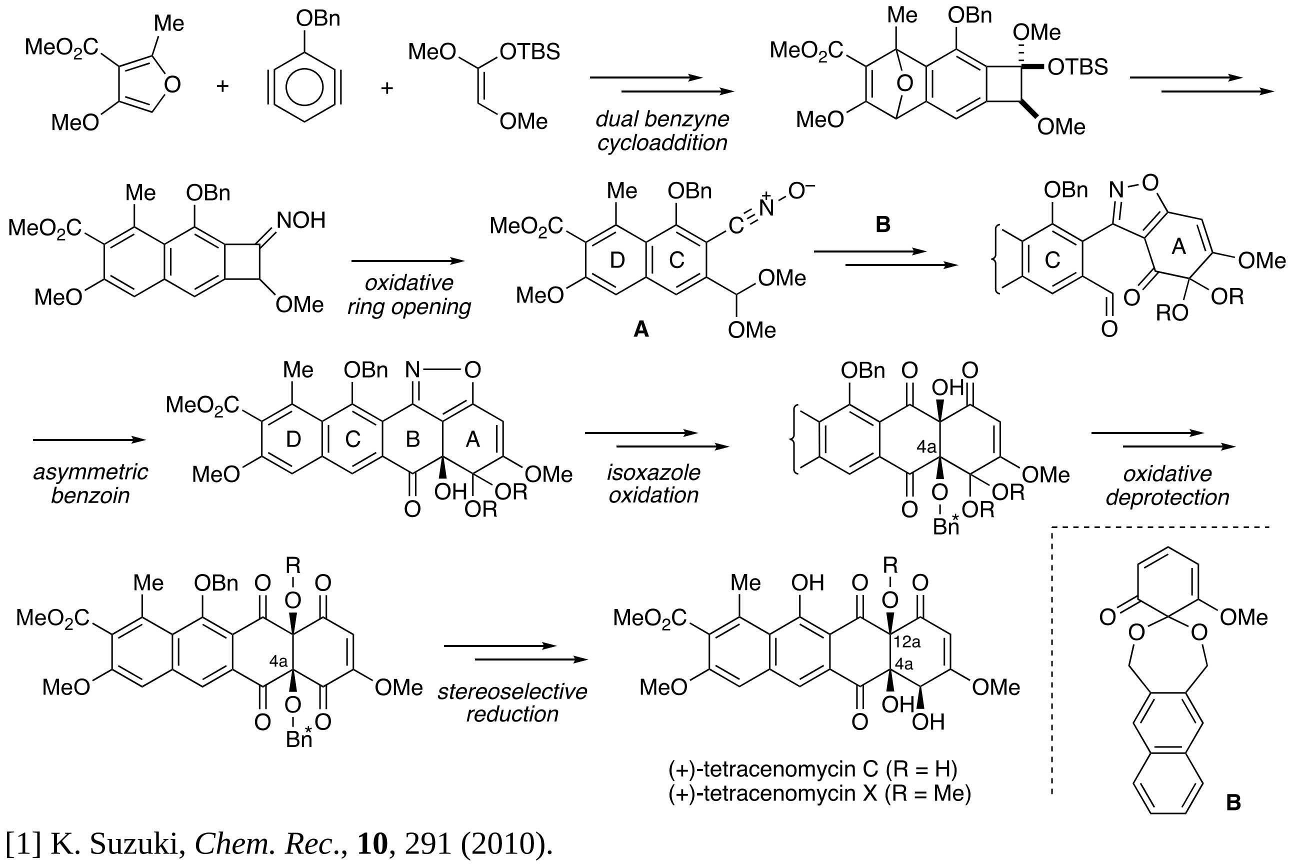
The polyketide-II biosynthetic pathway produces an impressive array of polycyclic architectures with functional and stereochemical complexity, thus serving as a rich source of biologically active molecules. Charmed by the challenges posed by such attractive structures, we have been engaged in the synthetic studies, centering attention to strategies and tactics that would enable rapid assembly of polycyclic scaffolds and also allow installation of multiple functionalities and stereogenic centers in a regio- and stereo-controlled manner.[1]

This talk will illustrate our approach by focusing on the recent total syntheses of tetracenomycins C and X, that feature 1) preparation of hexasubstituted naphthonitrile oxide **A** by successive benzyne cycloadditions and an oxidative ring-opening reaction; 2) a novel *ortho*-quinone mono-acetal **B** as the A-ring unit; 3) construction of three contiguous stereogenic centers by an asymmetric benzoin cyclization, an isoxazole oxidation, and a stereoselective reduction.[2]



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New Opioid Biology Arising From Heterocyclic Chemistry

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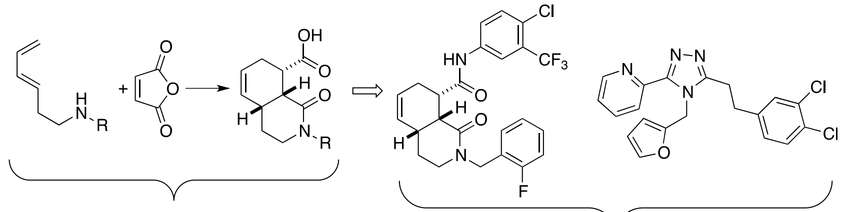
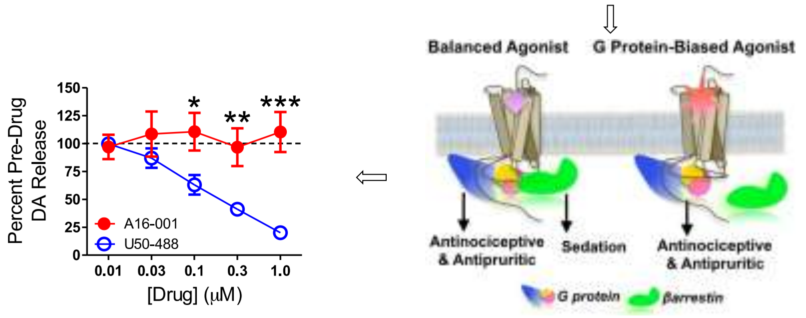
The worldwide opioid crisis has occasioned efforts to develop new opioids for both existing uses (pain control) as well as new indications (itch, addiction). We have focused on the discovery of compounds able to selectively activate one of the two main intracellular pathways associated with the kappa opioid receptor. This type of activity, called "functional selectivity" or "ligand bias", has the potential to segregate many of the ultimate biological effects of therapeutic opioids.

This project is an effort of a multidisciplinary, multi-institutional team led by the speaker and Professor Laura Bohn of the Scripps Research Institute.[1,2] It began with the development of a speculative library for screening against a range of potential biological targets based on a known but underexplored isoquinolinone synthesis. Applying this chemistry to library synthesis led to a hit compound that stoked our interest in biased ligand discovery, ultimately leading to the discovery of Triazole 1.1, a strongly biased KOR agonist with a fascinating in vitro and in vivo profile. These efforts and recent results will be described.



Library construction, methodology development

G-protein biased KOR agonists



New biology

New pharmacology

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Applications of Intramolecular (4+3) Cycloadditions of Furans and Pyrroles to the Synthesis of Natural Products

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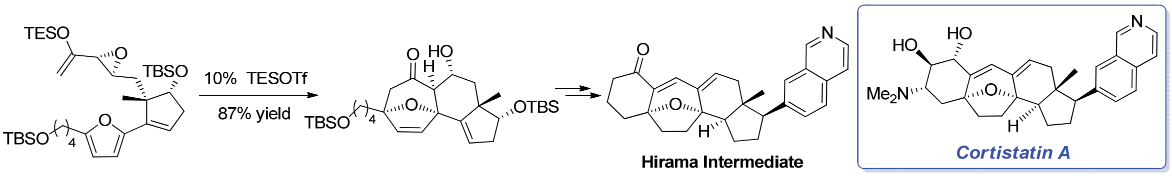
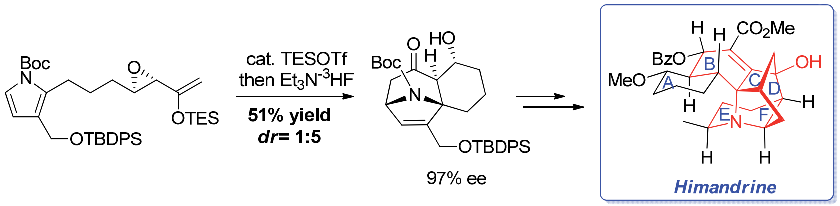
Department of Chemistry and State Key Laboratory of Synthetic Chemistry,
The University of Hong Kong, Hong Kong, P. R. China

Intramolecular cycloadditions are efficient reactions for the construction of polycyclic frameworks that are found in many bioactive compounds and complex natural products. However, heterocycles undergo cycloaddition reactions with different propensities.

We have developed an intramolecular (4+3) cycloaddition of epoxy enolsilanes and furan that afford products containing an oxabicyclic nucleus in good to excellent yields. The use of optically enriched epoxy enolsilanes affords cycloadducts as single enantiomers bearing multiple stereocenters.[1] We have applied this (4+3) cycloaddition as the key step in the asymmetric formal total synthesis of cortistatin A, which has been found to exhibit potent anti-angiogenetic, anti-HIV and anti-leukemic activity.[2]

Generally, (4+3) cycloadditions with pyrroles acting as dienes are far less common. This is because pyrroles tend to undergo Friedel-Crafts type of reactions, resulting in the restoration of aromaticity instead of cycloadditions. However, our studies have found that pyrroles also engage readily in intramolecular (4+3) cycloadditions with epoxy enolsilanes, resulting in optically active polycyclic structures harboring a tropane nucleus. Based on these results, we have applied this reaction as the key step for the construction of the BCDEF core common to the Type II galbulimima alkaloids.[3]





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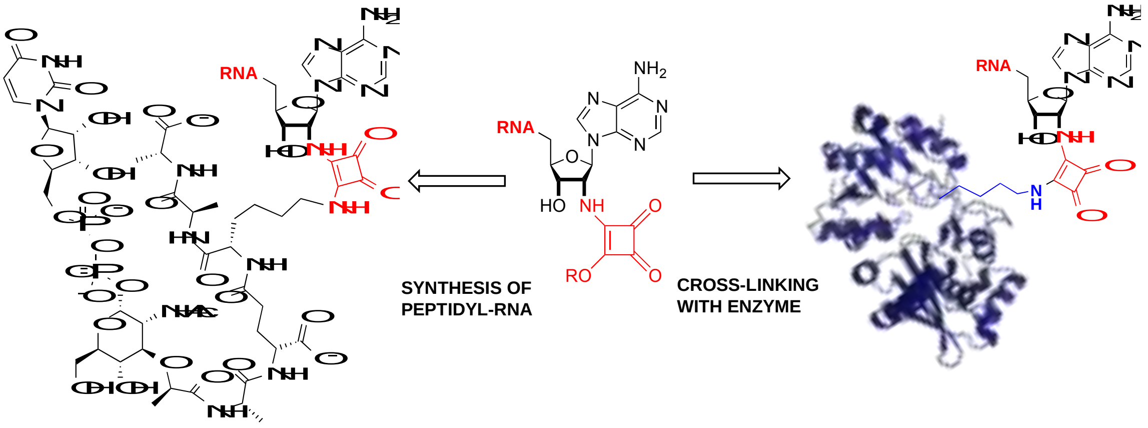
Post-functionalization of RNAs for specific conjugations with peptides and proteins

Nicolas Sakkas[a], Matthieu Fonvielle[b], Laura Iannazzo[a], Emmanuelle Braud[a], Michel Arthur[b] and Mélanie Etheve-Quelquejeu[a]*

a-Laboratoire de Chimie et de Biochimie Pharmacologiques et Toxicologiques, Université Paris Descartes, UMR 8601, Paris, F-75005 France ; CNRS UMR 8601, Paris, F-75006
b-Centre de Recherche des Cordeliers, Equipe 12, UMR S 1138; INSERM; Université Pierre et Marie Curie-Paris 6; Université Paris Descartes

RNA functionalization is challenging due to RNA instability and limited range of available enzymatic reactions. Since few years, we develop versatile methods for the synthesis of modified aa-tRNA[1]. We report here the synthesis of electrophilic RNAs based on post-functionalization of an azido group incorporated by SPS[2]. The post-functionalization step involved the addition of a squarate diester following reduction of the azido group. This strategy was fully compatible with the introduction of other functionalities in the RNA moiety, including a fluorescent probe for the detection of RNA-enzyme adducts and a hairpin loop linker for stabilization of RNA base-pairing. The squaramate-RNAs specifically reacted with the primary amine of unprotected UDP-MurNAc-pentapeptide. The squaramate unit also promoted specific cross-linking of RNA to the catalytic Lys of FemX_{Wv} but not to related transferases recognizing different aminoacyl-tRNAs. Thus, squaramate-RNAs provide specificity for cross-linking with defined groups in complex biomolecules due to its unique reactivity.

These modified RNAs are interesting tools to investigate in the field of RNA biology.



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SYNTHESIS OF NEW QUINAZOLINE AND DIKETOPIPERAZINE SCAFFOLDS AND APPLICATIONS FOR MEDICINAL CHEMISTRY

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Quinazolines represent one of the most widespread scaffolds among natural and synthetic bioactive compounds. In fact, the therapeutic relevance of quinazoline derivatives can be explained by a wide range of biological activities, such as anticancer, antiviral, antimicrobial, antiparasitic, anti-inflammatory etc. Over the past years, synthetic approaches toward this simple ring structure have been extensively investigated and advances have been made through novel and improved methods.[1-3] In this sense, we have designed a concise strategy to obtain 4-amino 6,7-disubstituted quinazoline rings bearing bioreductive groups as potential prodrugs to treat tumor hypoxia. Firstly, a quinazolinone nucleus was synthesized by regioselective demethylation of 4,5-dimethoxy-2-nitrobenzoic acid at position 5, followed by protection of the functional groups (carboxylic acid and phenol), one-pot reductive ring cyclization and replacement of the hydroxyl group at C-4 by amine derivatives. We have also explored the concept of click chemistry to obtain a diverse set of potential antitumoral compounds and have investigated a radiolabeling approach for hypoxia tumour imaging (unpublished results).

Just as important as, 2,5-diketopiperazines (2,5-DKPs) are abundantly found in nature and can be easily synthesized by the condensation of two α-amino acids. 2,5-DKPs are privileged scaffolds and became very attractive for drug discovery due to several characteristics, such as stability to proteolysis, conformational rigidity, three-dimensional shape, presence of donor and acceptor groups for hydrogen bond, peptide bond mimicking, convenient functionalization at different positions and configurations. These relevant chemical aspects favour interactions with different targets, thus resulting in a wide spectrum of biological activities.[4,5] Herein, we present a novel and facile solution-phase synthesis of 2,5-DKPs and *O*-glycosylated analogs.[6] Encouraged by these results, we have also addressed the synthesis and biological evaluation of some glycosyl diketopiperazines for the development of novel anti-trypanosomal agents and *Trypanosoma cruzi trans*-sialidase (TcTS) inhibitors.[7] Recently, we have designed 2,5-DKP derivatives as potential *h*AChE inhibitors exploring a moiety replacement approach based on donepezil drug used to treat Alzheimer's disease (unpublished results).

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New Efficient Approaches to the Total Synthesis Piperazinone Alkaloids and Analogs

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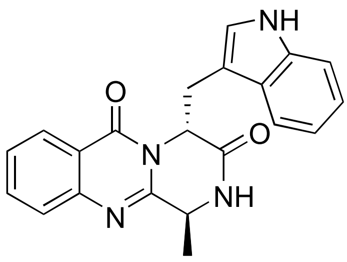
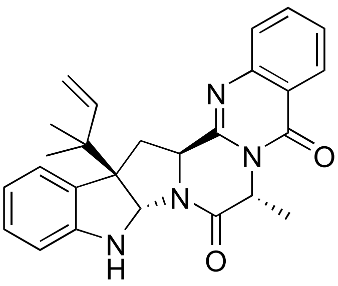
Bridged diketopiperazine alkaloids and their semi-reduced piperazinone congeners[1] as well as quinazoline-piperazinone alkaloids[2] are diverse classes of natural products displaying various biological activities. Their scarce occurrence in Nature and complex scaffolds serve as inspiration for the development of new efficient approaches for their total synthesis to provide sufficient material for their biological investigation.

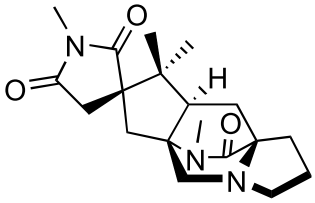
In this contribution, our progress toward simple and efficient total syntheses of alkaloids such as the fumiquinazolines, ardeemin or asperparaline C is reported.



Fumiquinazoline F



Ardeemin



Asperparaline C

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1,2,3,-Triazoles: From Metal- to Supramolecular Organic Catalysis

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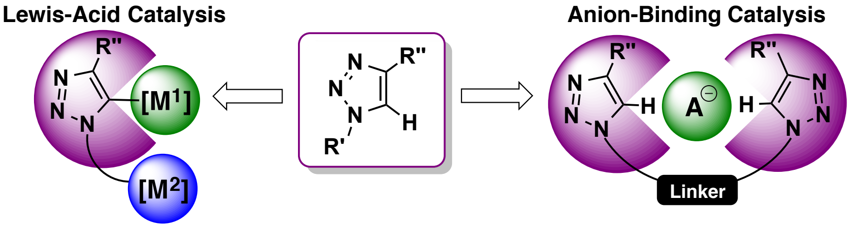
1,2,3-Triazoles constitute usual heterocyclic ligands in biology and coordination chemistry. Although such structure is well known since the 19th century, the main breakthrough in triazole chemistry was made by the introduction of the "click" chemistry concept by Kolb, Finn and Sharpless.[1] The 1,2,3-triazole is an intriguing heterocycle, with really interesting intrinsic properties such as a highly polarized C-H bond, a large dipole moment and a notable acidity character of the C-H bond. These special features make possible different supramolecular interactions: from metal (M) coordination to anion (A^-) complexation.[2]

Based on these properties, my group has recently designed novel 1,2,3-triazoles-based ligands and catalysts. In this lecture, some of our results on the use of triazole-based catalysts in Lewis acid metal catalysis,[3] counter-anion catalysis[4] and cooperative H-donor-based anion-binding organocatalysis[5] will be presented.



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[5] a) M. Zurro, S. Asmus, S. Beckendorf, C. Mück-Lichtenfeld, *J. Am. Chem. Soc.* **2014**, *136*, 13999-14002; b) O. García Mancheño, S. Asmus, M. Zurro, T. Fischer, *Angew. Chem. Int. Ed.* **2015**, *54*, 8823-8827; c) M. Zurro, S. Asmus, J. Bamberger, S. Beckendorf, O. García Mancheño, *Chem. Eur. J.* **2016**, *22*, 3785-3793; d) T. Fischer, J. Bamberger, O. García Mancheño, *Org. Biomol. Chem.* **2016**, *14*, 5794-5802; e) T. Fischer, Q.-N. Duong, O. García Mancheño, *Chem. Eur. J.* **2017**, *23*, 5983-5987.

Arynes as Powerful Platforms for Regioselective Construction of Fused Heteroaromatic Compounds

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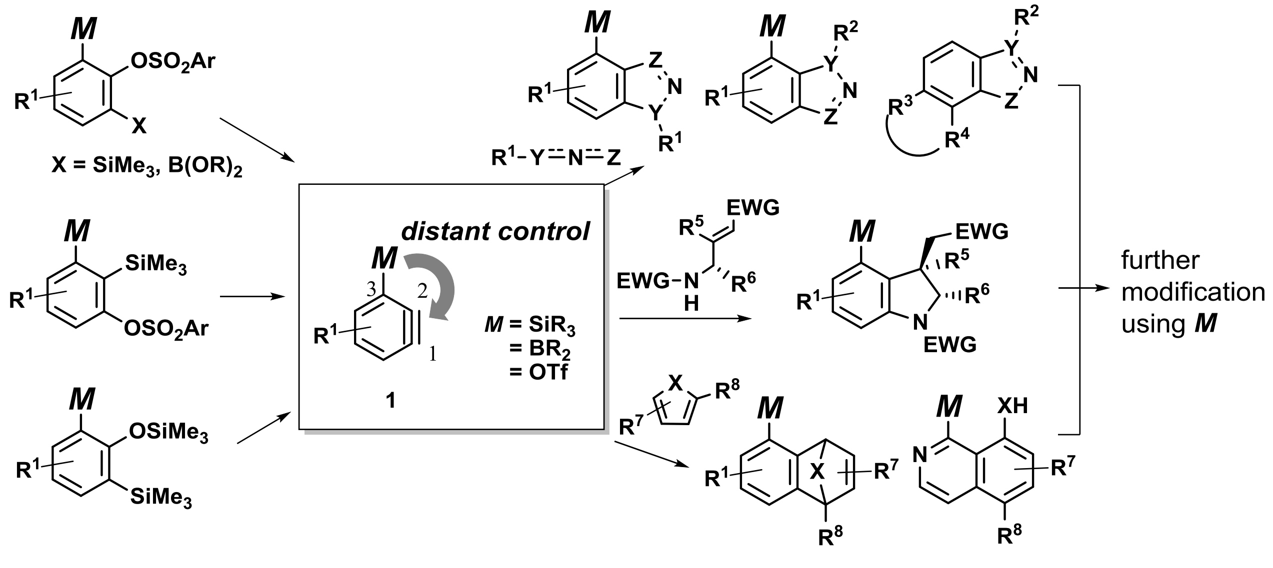
Suita, Osaka 565-0871, Japan

Benzo-fused nitrogen-containing heterocycles are abundant in biologically active compounds. One of the most effective methods for preparing such heterocycles is the cycloaddition reactions of benzynes with nitrogen-containing compounds. However, the reactions of unsymmetrically substituted benzynes generally show low regioselectivity to produce mixtures of two regioisomers. In this symposium, we present the synthesis of both regioisomers of multisubstituted benzo-fused azoles through the regiocomplementary (3 + 2) cycloaddition reactions of 3-boryl-, 3-silyl, and 3-triflyloxy-benzynes **1** with 1,3-dipoles, in which the substituent *M* at the C3-position effectively control the reaction site of **1**. Similar preparations of multisubstituted indolines and other fused nitrogen-containing heterocyclic compounds are also available by using **1**. The substituent *M* of the cycloaddition products is applicable to installation of a range of carbon-, nitrogen-, and oxygen-substituents at its ipso position. The improved generation of the functionalized benzynes **1** as well as benzdiynes from new precursors and the analysis of mechanisms for these regioselective cycloaddition reactions by density functional theory calculations will also be discussed.[1]



[1] Akai, Ikawa, et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 7673; *Angew. Chem. Int. Ed.* **2010**, *49*, 5563; *Org. Lett.* **2011**, *13*, 1730; *Angew. Chem. Int. Ed*. **2011**, *50*, 5674; *J. Synth. Org. Chem. Jpn.* **2012**, *70*, 1123 (Special Issue in English); *J. Org. Chem.* **2013**, *78*, 2965; *Tetrahedron* **2013**, *69*, 4338; *Org. Biomol. Chem*. **2013**, *11*, 8145; *Chem. Eur. J.* **2014**, *20*, 16228; *Aust. J. Chem*. **2014**, *67*, 475; *Org. Biomol. Chem*. **2015**, *13*, 526; *Adv. Synth. Cat*. **2015**, *357*, 2287; *Chem. Sci*. **2016**, *7*, 5206; *J. Org. Chem.* **2017**, *82*, 4242.

Stereoselective Enzymatic Ring Expansion and Ring Contraction Reactions of O-Heterocycles

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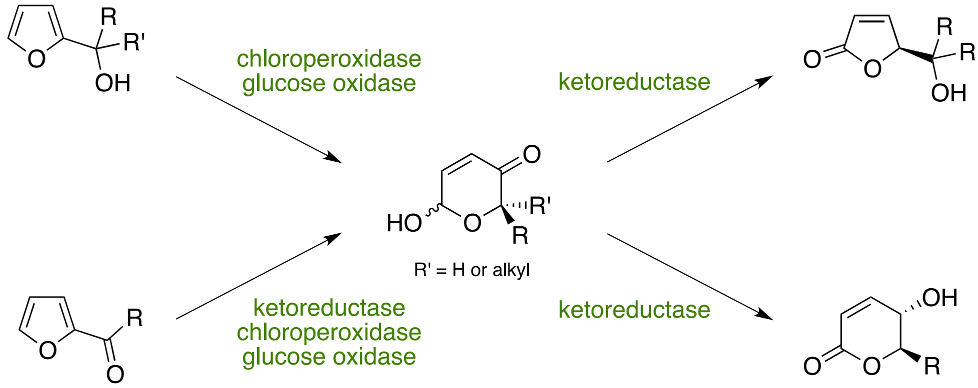
Biocatalysis is steadily gaining ground as module in the organic chemist's toolbox for the synthesis of well-defined building blocks. However, with regard to an even broader application of enzyme catalysts in classical synthetic chemistry, the lack of biosynthetic precedence for numerous synthetically relevant reactions and hence the consequent lack of biocatalysts to promote those reactions needs to be considered a major drawback. Since many years, catalytic promiscuity, the enzymes' ability to catalyze fundamentally different chemical interconversions, has been in the scientific focus,[1] however, just recently entirely abiotic transformations came within reach by means of specialized, evolved proteins.[2-4]

In our search of biological catalysts with abilities to address synthetically important reactions beyond the biosynthetic repertoire, a first breakthrough was achieved in form of non-natural ring-closing and ring-expanding transformations, respectively.[5,6] Wild-type metalloenzymes are not only qualifying as exquisite alternatives to chemical reagents or catalysts, but moreover, allow for the construction of short *ex vivo* metabolisms and thus for the stereoselective preparation of highly functionalized building blocks on basis of a biological synthetic-organic machinery.

Herein, we present a novel, fully biocatalytic toolkit for the synthesis and valorization of Achmatowicz-type pyranones including ring expansion, ring contraction and isomerization reactions, as well as their application in the creation of artificial metabolisms and total synthesis.



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Going with the Flow – The Use of Continuous Processing in Organic Synthesis

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Continuous flow processes form the basis of the petrochemical and bulk chemicals industry where strong competition, stringent environmental and safety regulations, and low profit margins drive the need for highly performing, cost effective, safe and atom efficient chemical operations. In contrast to the commodity chemical industry, however, the fine chemical industry primarily relies on its existing infrastructure of multipurpose batch or semi-batch reactors. Fine chemicals, such as drug substances and active pharmaceutical ingredients (APIs), are generally considerably more complex than commodity chemicals and usually require numerous, widely diverse reaction steps for their synthesis. These requirements generally make versatile and reconfigurable multipurpose batch reactors the technology of choice for their preparation. However, the advantages of continuous flow processing are increasingly being appreciated also by the pharmaceutical industry and, thus, a growing number of scientists, from research chemists in academia to process chemists and chemical engineers in pharmaceutical companies, are now starting to employ continuous flow technologies on a more routine basis [1].

In this lecture, contributions from our research group in the field of continuous flow processing will be highlighted. Emphasis will be given to highly atom efficient and process intensified chemical transformations useful for the synthesis of APIs or key heterocyclic intermediates that are often too hazardous to be executed in a batch reactor. These involve azide [2], diazomethane [3] and nitration chemistry [4], selective precious metal-free olefin [5] and nitrogroup [6] reductions, oxidation reactions involving pure oxygen [7], and flow photochemistry applications [8].

[1] Review: Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem. Int. Ed*. **2015**, *54*, 6688.
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[8] Cantillo, D.; de Frutos, O.; Rincon, J. A.; Mateos, C.; Kappe, C. O. *Org. Lett.* **2014**, *17*, 5590.

Oral Presentations – Speaker List

Aitken, Alan, University of St Andrews **Oral A 1**
A New Route to 3-Amino-2-arylbenzofurans and Related Heterocycles

Arai, Shigeru, Chiba University **Oral B 1**
Total Synthesis of Kopsia Alkaloids

Arisawa, Mitsuhiro, Osaka University **Oral D 2**
Synthesis of Novel Nitrogen-containing Polyheterocycles via Ruthenium-catalyzed One-pot Metathesis / Non-metathesis Reaction

Bakulev, Vasiliy, Ural Federal University **Oral D 8**
Switchable Rearrangements in 1,2,3-Thiadiazole and 1,2,3-Triazole series

Balalaie, Saeed, K. N. Toosi University **Oral D 9**
Synthesis of functionalized heterocyclic scaffolds using Post-Ugi transformations

Boratynski, Przemyslaw, Politechnika Wrocławska **Oral C 6**
Biheterocycles and linked heterocycles based on Cinchona alkaloids

Brunschweiger, Andreas, TU Dortmund **Oral B 5**
Access to DNA-encoded screening libraries of heterocycles through a tailored encoding strategy

Bunce, Richard, Oklahoma State University **Oral A 4**
Synthesis and Evaluation of Oxygen Analogues of a Promising Anticancer Drug

Burtoloso, Antonio C. B., University of São Paulo, Brazil **Oral A 3**
Towards the Total Synthesis of the Tetracyclic Core of Ergot Alkaloids

Chien, Tun-Cheng, National Taiwan Normal University **Oral B 4**
CuI-catalyzed Intramolecular Aminocyanation of Terminal Alkynes

Chouguiat, Lwiza, Université de Constantine 1, Algérie **Oral C 9**
The synthesis of new 1,4-benzoxazines via the Petasis multicomponent reaction

Dobbs, Adrian, University of Greenwich **Oral D 5**
The Asymmetric Aza-Prins Reaction

Fernandes, Rodney, Indian Institute of Technology Bombay **Oral D 4**
Allylic C-H Activation v/s Leaving Group Ionization for π-Allylpalladium: Unprecendented Bis-arylation

Francis, Craig, CSIRO Melbourne **Oral C 7**
Reactions of *N*,*N*-Dialkyl-*N'*-Chlorosulfonyl Chloroformamidines with 1,3-NCC Bis-Nucleophiles: Synthesis of New Fused Thiadiazine Ring Systems.

Giomi, Donatella, Università di Firenze **Oral A 9**
1-(2-Pyridyl)- and 1-(2-quinolyl)-2-propen-1-ol as useful reagents to access hydroxyindolizidine derivatives

Gryko, Dorota, Institute of Organic Chemistry Polish Academy of Sciences **Oral A 5**
Porphyrins as photoredox catalysts for efficient C-C bond forming reactions

Hirano, Keiichi, The University of Tokyo **Oral B 6**
Novel Accesses to Boron-containing Cycles and Related Structures

Jiang, Yongwen, Shanghai Institute of Organic Chemistry **Oral B 2**
Concise Construction of 3,3-Disubstituted-2-amino-3H-indoles via Copper-catalyzed Coupling of Aryl Chloride and ⍰-Alkyl Cyanoacetate

Kanger, Tonis, Tallinn University of Technology **Oral C 8**
TRIAZOLE-BASED HALOGEN BOND DONORS

Kirsch, Stefan, Bergische Universität Wuppertal **Oral C 2**
Geminal diazides: A versatile toolbox for the synthesis of heterocyclic entities

Kitamura, Mitsuru, Kyushu Institute of Technology **Oral A 2**
Azidoimidazolinium Salts: Safe and Efficient Diazo-transfer Reagents and Unique Azido-donors

Mamedov, Vakhid, A.E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Cente **Oral C 1**
Rearrangements of Quinoxalinones with “Outside” Group Participation Towards Benzimidazol(on)oes

Marinelli, Fabio, University of L'Aquila **Oral D 1**
β-(2-aminophenyl)-α-β-ynones as a valuable building blocks for the synthesis of heterocycles

Mphahlele, Malose Jack, University Of South Africa **Oral D 7**

2-Amino-5-bromo-3-iodoacetophenone and 5-bromo-2-hydroxy-3-iodoacetophenone as synthons for novel indoles and benzofurans and their annulated derivatives

Nemoto, Tetsuhiro, Chiba University **Oral B 3**

Synthesis of 3,4-Fused Tricyclic Indoles Using Transition Metal Catalysis

Opatz, Till, Johannes Gutenberg-University **Oral A 6**

The Magic of Light – Photochemistry in the Synthesis of Nitrogen Heterocycles

Otani, Takashi, National Institute of Technology, Anan College **Oral A 7**

Facile Two-step Synthesis of Highly Fluorescent Polyaza[7]helicenes

Penoni, Andrea, Università degli Studi dell'Insubria Como **Oral E 2**

Synthesis and Electrochemical Properties of Biindole Compounds

Rizzo, Simona, STM CNR Milano **Oral B 7**

Impressive enantiodiscrimination ability of 1,1'-bibenzimidazolium and 3,3'-bicollidinium salts in achiral ionic liquids

Silva, Artur, University of Aveiro **Oral D 6**

Oxygen and nitrogen heterocycles from 3-electron withdrawing substituted chromones

Sperry, Jonathan, University of Auckland **Oral E 1**

Natural Product Synthesis enabled by Ir-catalyzed C-H borylation

Suga, Hiroyuki, Shinshu University **Oral D 3**

Chiral Amine-urea Mediated Asymmetric Cycloadditions of Nitrile Oxides with o-Hydroxystyrenes and Their Computational Studies for Asymmetric Induction

Svete, Jurij, University of Ljubljana **Oral C 3**

Cu0-catalyzed azomethine imine-alkyne cycloadditions (CuAIAC), a fluorescent alternative to azide-alkyne cycloaddition (CuAAC)

Takasu, Kiyosei, Kyoto University **Oral B 8**

An Arylative Ring Expansion Cascade of Fused Cyclobutenes via Short-lived Cycloakladienes with Planar Chirality

Tokuyama, Hidetoshi, Tohoku University **Oral A 8**

Total Syntheses of (–)-Histrionicotoxin and (–)-Histrionicotocin 235A via Radical Translocation Cyclization Cascade

Voskessesnky, Leonid, RUDN University Moscow **Oral C 4**

Multicomponent and domino reactions of alkynes and benzynes in the synthesis of N-heterocycles. Recent advances.

Werz, Daniel B., TU Braunschweig **Oral B 9**

Donor-Acceptor-Cyclopropanes as Unique Structural Units to Access Heterocyclic Compounds

Yoshida, Suguru, Tokyo Medical and Dental University **Oral C 5**

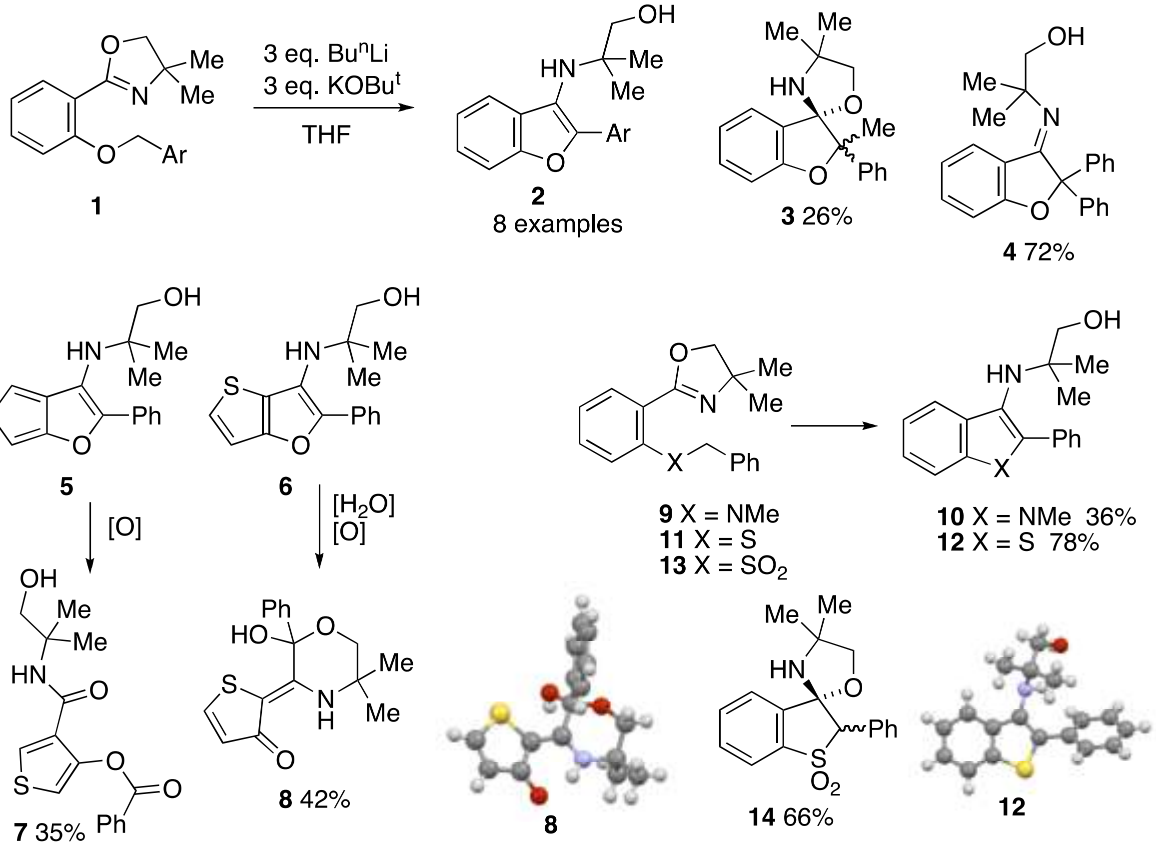
Synthesis of Aniline Derivatives via Aryne Intermediates Enabling Facile Preparation of Nitrogen-Containing Heterocyclic Compounds

A New Route to 3-Amino-2-arylbenzofurans and Related Heterocycles

R. Alan Aitken* and Andrew D. Harper
EaStCHEM School of Chemistry, University of St Andrews, St Andrews, UK

Treatment of *o*-benzyloxyphenyloxazolines **1**, readily prepared from methyl salicylate, with a mixture of BuLi and KOBu^t leads to intramolecular attack of the benzyl carbanion on the oxazoline, ring-opening and aromatisation to give the hydroxyalkylaminobenzofurans **2**. This reaction has been extended in several ways: the 2-allyloxy compound gives the 2-vinylbenzofuran while the α-methylbenzyloxy oxazoline gives a mixture of diastereomeric spiro compounds **3**. For the diphenylmethyl ether the iminodihydrobenzofuran **4** is produced.

The process is also possible for the corresponding benzyloxythienyloxazolines leading initially to the sensitive thienofuran products **5** and **6** with uncommon fused ring systems. However in each case hydrolytic or oxidative processes follow and the isolated products are respectively **7** and **8** (X-ray shown).

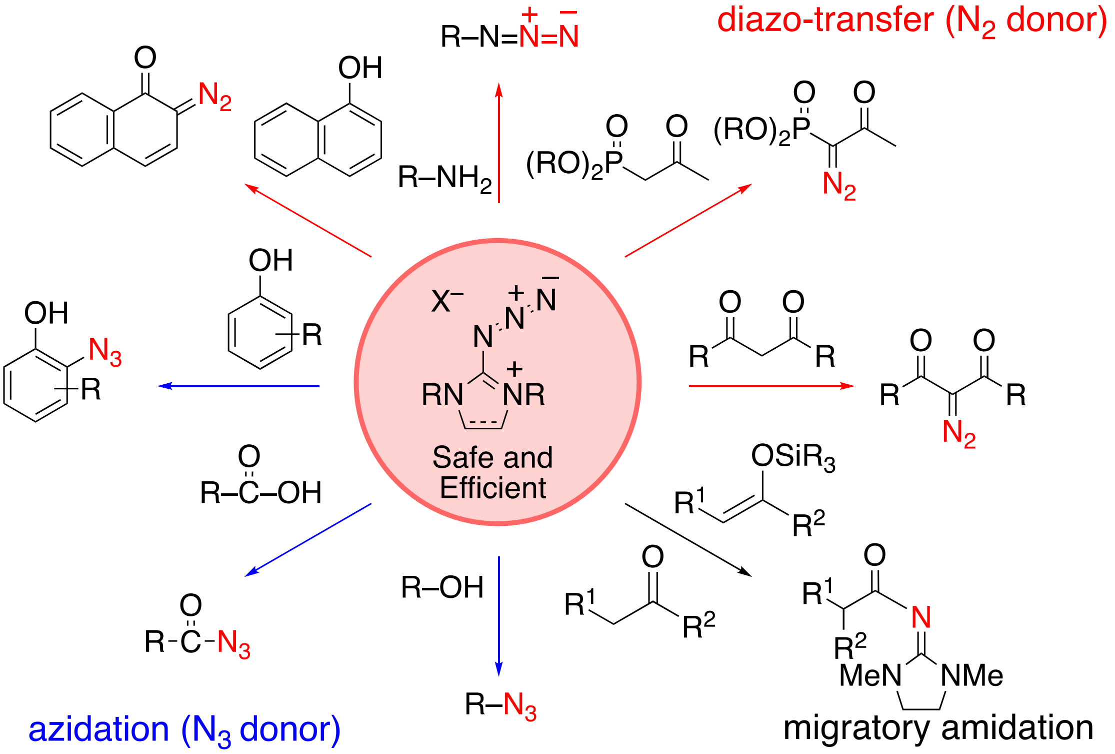


It can also be extended to formation of indoles such as **10** starting from the benzylic amine **9** and benzothiophenes **12** (for which an X-ray structure was obtained) starting from the sulfide **11**. The corresponding sulfone **13** gives a mixture of diastereomeric spiro compounds **14**.

Azidoimidazolinium Salts:
Safe and Efficient Diazo-transfer Reagents and Unique Azido-donors

Mitsuru Kitamura,* Norifumi Tashiro, Rie Sakata, Satoshi Miyagawa, Masakazu Yano, Tatsuya Koga, Kento Murakami, So Kato, Kazushige Konai, and Tatsuo Okauchi
Department of Applied Chemistry, Kyushu Institute of Technology
1-1 Sensuicho, Tobata, Kitakyushu 804-8550 Japan

2-Azido-1,3-dimethylimidazolinium chloride (ADMC) and its corresponding hexafluorophosphate (ADMP) were found to be efficient diazo-transfer reagents to various organic compounds.[1] ADMC was prepared by the reaction of 2-chloro-1,3-dimethylimidazolinium chloride (DMC) and sodium azide. ADMP was isolated as a crystal having good thermal stability and low explosibility. ADMC and ADMP reacted with 1,3-dicarbonyl compounds under mild basic conditions to give 2-diazo-1,3-dicarbonyl compounds in high yields, which were easily isolated in virtue of the high water solubility of the by-products. ADMP showed high diazo-transfer ability to primary amines even in the absence of metal salt such as Cu(II). Using this diazotization approach, various alkyl/aryl azides were directly obtained from their corresponding primary amines in high yields. Furthermore, naphthols reacted with ADMC to give the corresponding diazonaphthoquinones in good to high yields. In addition, 2-azido-1,3-dimethylimidazolinium salts were employed as azide-transfer and migratory amidation reagents.

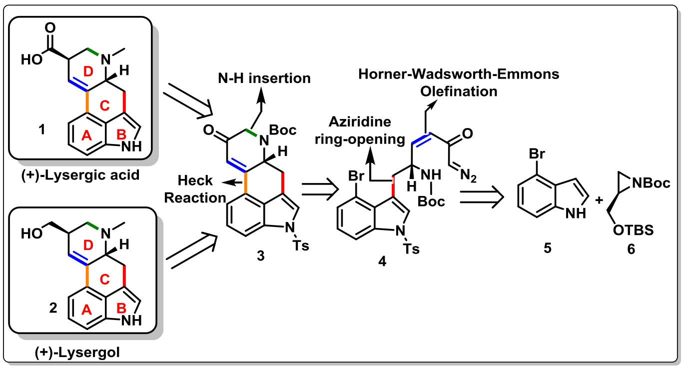


[1] M. Kitamura, *Chem. Rec.* **2017**, DOI: 10.1002/tcr.201600118.

Towards the Total Synthesis of the Tetracyclic Core of Ergot Alkaloids

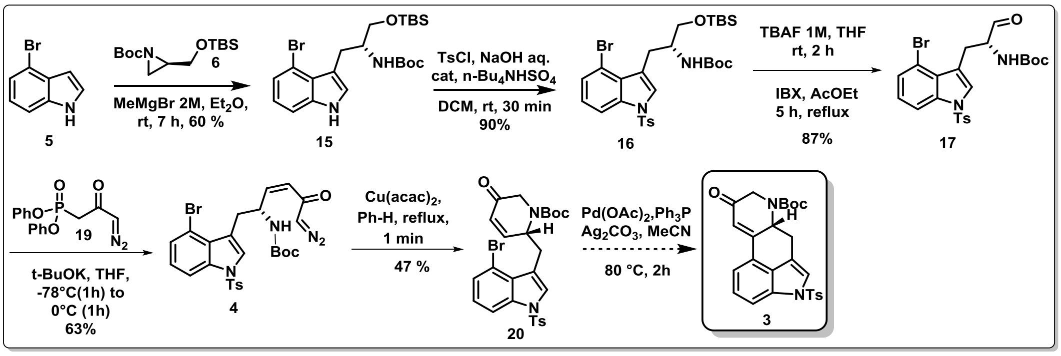
Edson G. Vilca and Antonio C. B. Burtoloso*
Chemistry Institute of São Carlos, University of São Paulo, Brazil

Ergot alkaloids are a class of compounds which were initially isolated from the fungus *Claviceps Purpurea.* For several decades, researches have shown that these natural products and its analogues have a wide spectrum of biological activity. In this work we report a direct and stereoselective synthetic route to build an advanced tetracyclic intermediate of these alkaloids, which can be used as key intermediates in the total synthesis of (+)-lysergic acid as well as other important ergot alkaloids such as Lysergol. Our strategy to build the tetracyclic core skeleton of ergot alkaloids consists in four key steps as shown in Scheme 1.



Scheme 1.

We started our work by the ring-opening of aziridine **6** with indole **5**, giving the desired intermediate **15** in 60% yield on a multigram scale (Scheme 2). After installation of the tosyl group and removal of TBS, followed by oxidation with IBX, aminoaldehyde **17** was obtained in 78% overall yield. Compound **17** was subjected to a HWE olefination, resulting in unsaturated diazoketone **4** in a 63% yield. Then, construction of D-ring by an N-H insertion reaction, gave **20** in 47% yield. Cyclization of **20** by an intramolecular Heck reaction to afford the desired tetracyclic core skeleton **3** is under investigation.

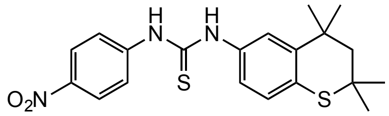


Scheme 2.

Synthesis and Evaluation of Oxygen Analogues of a Promising Anticancer Drug

Field M. Watts, Donghua Zhou, K. Darrell Berlin, Doris M. Benbrook[†] and Richard A. Bunce*
Department of Chemistry, Oklahoma State University, Stillwater, OK 74078, USA
[†]*Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA*

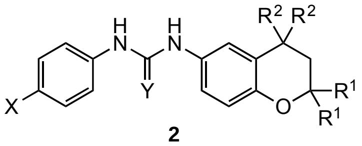
The thiochroman-based anticancer compound S-Het-A2 (**1**, NSC721689) has been shown to selectively induce apoptosis in cancer cells while leaving normal cells unharmed, and has been approved for development as a chemopreventive agent against ovarian cancer. This agent, however, possesses two metabolically reactive groups not normally valued in drug molecules, and could benefit from further improvements to its potency and efficacy.



1

S-Het-A2 (NSC721689)

In order to eliminate the reactive substituents as well as improve its drug properties, chroman-based analogues **2** of S-Het-A2, bearing nitro as well as less reactive functionality with similar donor/acceptor properties, have been prepared in seven steps from phenol and 3,3-dimethylacryloyl chloride. Based on the analogues prepared thus far, certain structural features have been identified as important to its drug interaction with HSPA9 in cancer cells. Additionally, important binding interactions have been ascertained by tracking chemical shift perturbations for amino acid residues when S-Het-A2 is bound to the active site of this protein. The presentation will include synthesis and activity data for 24 analogues of S-Het-A2 highlighting important substituent groups for optimal binding.



2

$X = NO_2, CO_2Et, CN, CF_3, OCF_3$
$Y = S, O$
$R^1 = H, Me, Et$
$R^2 = H, Me, Et$

During the course of this work, a new synthesis of 4-chromanones was discovered, and this will also be disclosed [1]

[1] Meraz, K.; Gnanasekaran, K. K.; Thing, R.; Bunce, R. A. *Tetrahedron Lett.*, **2016**, *48*, 5057-5061.

Porphyrins as photoredox catalysts for efficient C-C bond forming reactions

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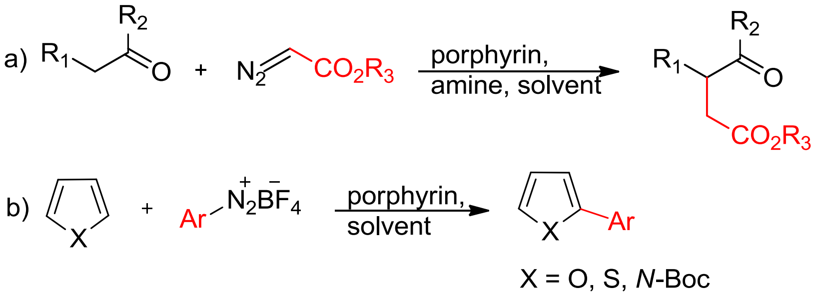
Porphyrins are natural functional dyes which are utilized by Nature as prosthetic groups of various enzymes not *per se* because of their coordination characteristic, but due to the combination of other properties with absorption of light (which translates to color) being the most important.
An efficient C−C bond formation in a green, nontoxic, and inexpensive way has always been a challenge and development of light-induced methodologies is one of the means to achieve such a goal.[1] Photoredox catalysis is based on a photoinduced electron transfer process (PET) between a substrate and a photoredox catalyst, commonly with Ru- or Ir-complexes.[2] Though organic dyes have been well-known for their ability to participate in photoinduced electron transfer processes, their use as catalysts in such reactions has been less explored as the replacement of Ir- and Ru-complexes with known organic dyes is not always possible.[3] We wondered whether simple porphyrins could be used as photocatalysts.

Herein, we demonstrate a successful application of these compounds as efficient photoredox catalysts for C-C bond forming reactions involving the reductive or oxidative quenching. Employing dual catalytic system – photocatalysis merged with enamine-iminium catalysis alkylation of carbonyl compounds at the α position was accomplished (a).[4] We have also found that porphyrins with tuned physicochemical properties, via tailoring various substituents at the periphery of the macrocycle, are also effective in catalyzing light-induced direct arylation of heteroarenes and cumarins with diazonium salts (b).[5]



a) Alkylation of carbonyl compounds at the α-position b) Arylation of heteroarenes

[1] a) M. Fintecave, *Angew. Chem. Int. Ed.* **2015**, *54*, 6946. b) Bucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. C) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, 116, 10035.
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[3] Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355.
[4] K. Rybicka-Jasińska, W. Shan, K. Zawada, K. M. Kadish, D. Gryko *J. Am. Chem. Soc.* **2016**, *138*, 15451.
[5] K. Rybicka-Jasińska, B. König, D. Gryko, *Eur. J. Org. Chem.* **2017**, 2104.

The Magic of Light – Photochemistry in the Synthesis of Nitrogen Heterocycles

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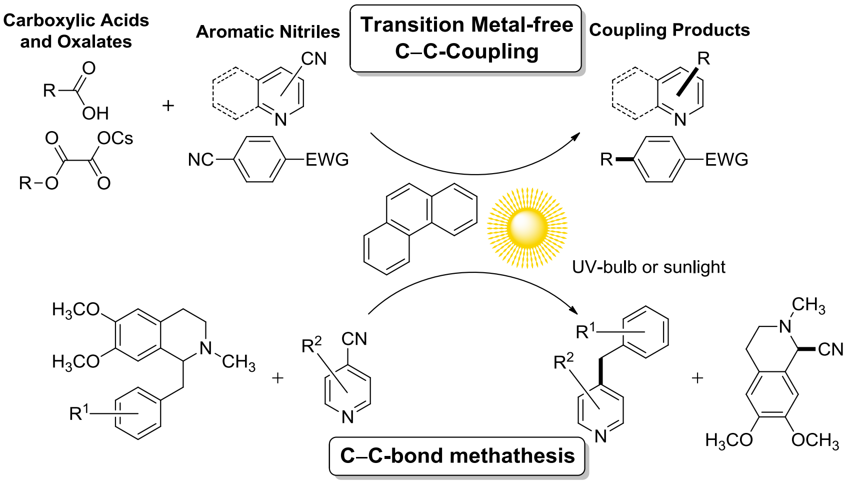
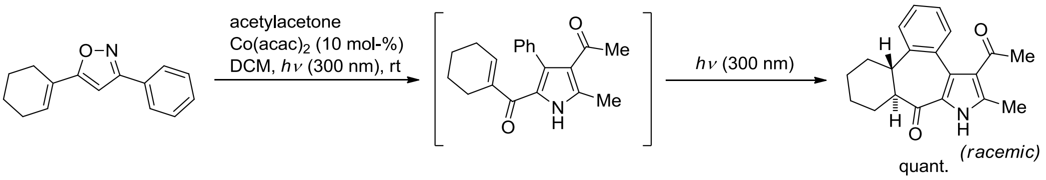
Institute of Organic Chemistry, Johannes Gutenberg-University, Mainz/D

Photoredox catalysis has become an attractive tool for synthetic organic chemistry and permits bond forming reactions under exceptionally mild conditions. While complexes of transition metals like Ru and Ir are frequently used in this context, simple and inexpensive organic compounds like phenanthrene can serve the same purpose. [1] Decarboxylative coupling reactions and a novel σ-bond metathesis in benzylisoquinoline alkaloids based on this concept will be presented. [2] These processes can be driven by sunlight in easy-to-build micro capillary photoreactors. [3]



Uncatalyzed photochemistry can be combined with bond forming reactions catalyzed by earth-abundant transition metals to build reaction cascades. As an example, the synthesis of pyrrolo-fused cycloheptadienones in a domino process involving two consecutive photochemical reactions (one of them being entirely unprecedented) and a new Co-catalyzed pyrrole synthesis will be discussed. [4]



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Facile Two-step Synthesis of Highly Fluorescent Polyaza[7]helicenes

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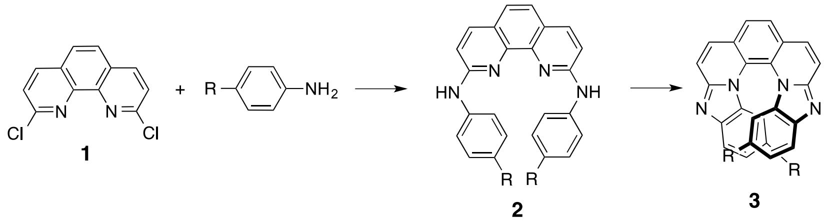
Helicenes have attracted considerable attention in material science and thus their syntheses have been widely studied. To the best of our knowledge, however, more than five steps were required for the synthesis of [7]helicene derivatives in all cases. We have developed a facile two-step synthesis of aza[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.[1,2]



hypervalent iodine reagent-mediated double NH/CH coupling

Single-crystal X-ray analyses of the helicenes revealed unique structures, including both a significantly twisted center and planar terminals of the skeleton. The azahelicenes show high fluorescent quantum yields (Φ) under both neutral (Φ: 0.25–0.55) and acidic conditions (Φ: up to 0.80 for **3a** (R = H)).

Enantiomers of **3a** (R = H), which were resolved from a racemic mixture using HPLC with a chiral column, showed high circularly polarized luminescence (CPL) activity under both neutral and acidic conditions (g_{lum}: up to 0.009). The high g_{lum} and Φ values suggest that **3** could be attractive for use as a CPL-emitting material.

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Total Syntheses of (–)-Histrionicotoxin and (–)-Histrionicotocin 235A via Radical Translocation Cyclization Cascade

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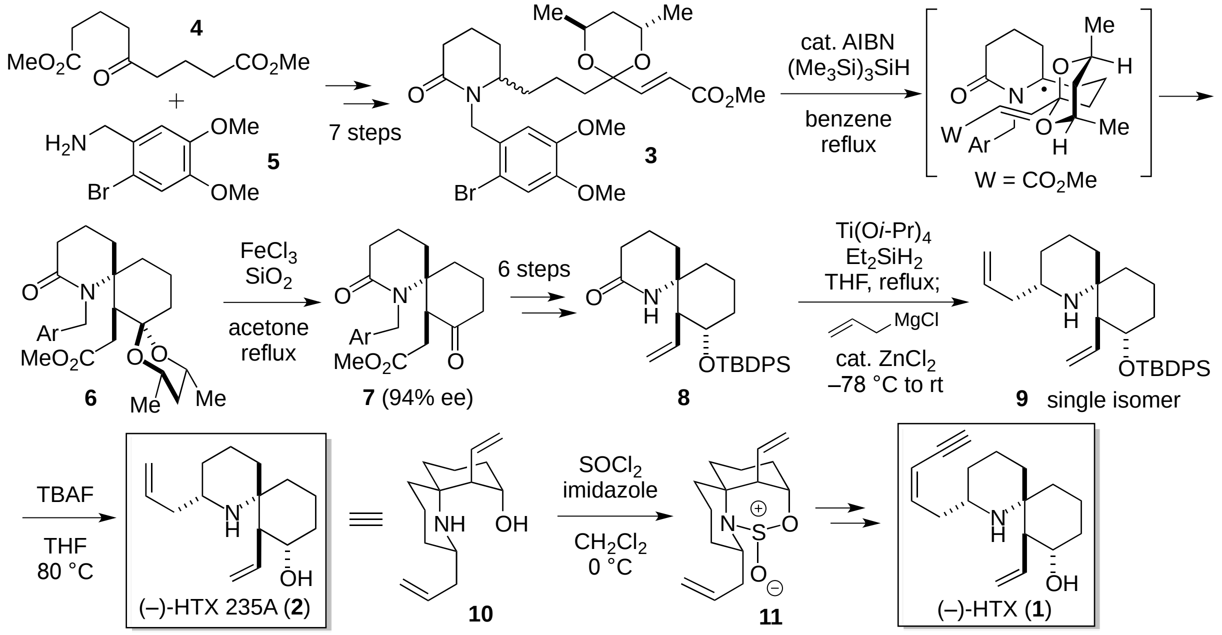
Histrionicotoxin (**1**, HTX) was isolated from the poison-arrow frog *Dendrobates histrionicus* by Daly and Witkop. This compound possesses a 1-azaspiro[5.5]undecane core with two (*Z*)-enyne side chains. We have demonstrated our radical translocation-cyclization strategy[1] was efficient for stereoselective construction of the 1-azaspiro[5.5]undecane core and accomplished total syntheses of (–)-HTX (**1**) and (–)-HTX 235A (**2**).[2] δ-Lactam **3** bearing an optically active cyclic acetal moiety was readily prepared as a 1:1 mixture of diastereomers from ketodiester **4** and benzylamine **5**. Under radical conditions using $(Me_3Si)_3SiH$, compound **3** underwent the radical translocation-cyclization to furnish spiro compound **6** in high diasterelselectivity. Optical purity of the major compound **6** was determined to be 94% ee after deacetalization. Stereoselective introduction of an allyl group on unprotected lactam **8** was achieved in a one-pot protocol by titanium hydride-mediated reduction to cyclic imine and subsequent allylation using ally zinc ate complex. The stereochemistry of **9** was confirmed by conversion to (–)-HTX 235A (**2**). Finally, two vinyl groups of **2** were converted to the (*Z*)-enyne side chains to complete the total synthesis of (–)-HTX (**1**).



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1-(2-Pyridyl)- and 1-(2-quinolyl)-2-propen-1-ol as useful reagents to access hydroxyindolizidine derivatives

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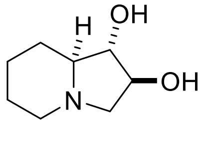
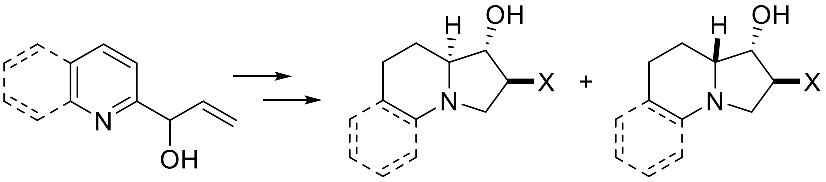
Nitrogen heterocycles are widely present in biologically active molecules and, in particular, polyhydroxylated alkaloids, usually referred as iminosugars, can act as potent and selective glycosidase inhibitors with important effects on glycoproteins as well as on cell-cell and cell-virus/bacteria recognition processes. Concerning 1,2-dihydroxyindolizidine systems, natural (+)-lentiginosine is a potent and selective inhibitor of fungal amyloglucosidases as well as Heat shock protein 90 (Hsp90), while the non-natural enantiomer acts as an apoptosis inducer on tumor cells of different origin. [1]



(+)-lentiginosine



X = OH, Br, I, OMe, OAc

In this context, 1-(2-pyridyl)- and 1-(2-quinolyl)-2-propen-1-ol, obtained by vinylation of commercially available 2-pyridine- and 2-quinoline-carboxaldehyde, behaved as useful reagents for the synthesis of indolizidine and benzo[*e*]indolizidine systems through a simple process involving bromination, reduction, and nucleophilic substitution (via elimination/addition). 1-(2-Pyridyl)-2-propen-1-ol afforded (±)–lentiginosine, in ca. 27% overall yield, as well as the non-natural diastereomer with inverted configuration at C-8a, [2] while 1-(2-quinolyl)-2-propen-1-ol allowed the synthesis of (±)–benzo[*e*]lentiginosine in 19% overall yield.
Mechanistic aspects and synthetic applications of this new approach will be discussed.

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Total Synthesis of Kopsia Alkaloids

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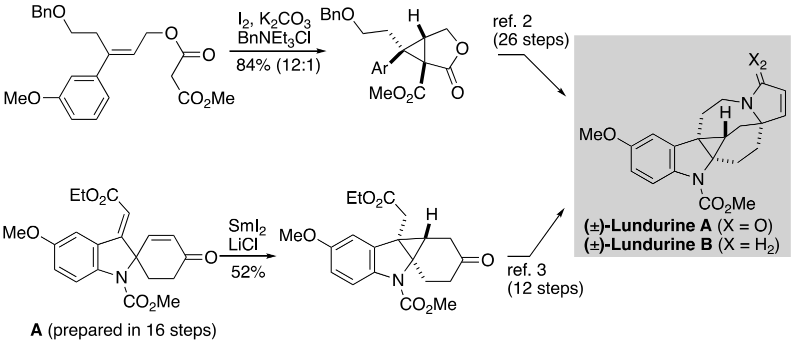
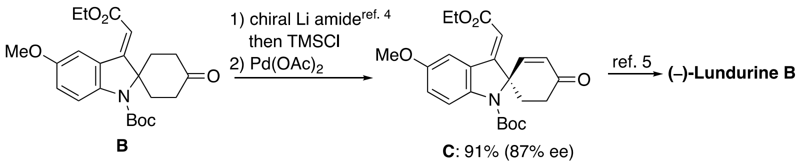
Graduate School of Pharmaceutical Sciences, Chiba University
Chiba, Japan, 2608675

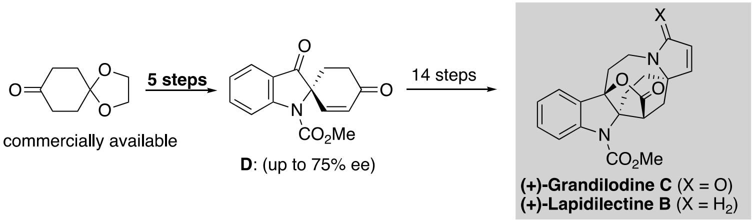
Scheme 1. Intramolecular Cyclopropanation[ref. 2,3]



Scheme 2 Asymmetric Total Sytnthesis of (–)-Lunduirine B



Scheme 3 Asymmetric Total Synthesis of Grandilodine C & Lapidilectine B[ref. 6]



Kopsia alkaloids have been attractive synthetic targets due to their structure and biological activities. Lundurine A and B have unique hexacyclic ring system including indoline cyclopropane, therefore their total synthesis has been major challenge in synthetic chemistry.

Recently, we have accomplished the total synthesis by two different strategies (Scheme 1).[1–3] The key cyclopropanations are 1) iodine-mediated cyclization using ketoester[2] and 2) Sm(II)-mediated radical cyclization using spiroenone **A**.[3] The symmetric spiroketone **B** is a suitable substrate to introduce chirality in spiroenone **C** by Koga's asymmetric deprotonation[4] and the total synthesis of (–)-lundurine B with determination of its absolute stereochemistry was achieved (Scheme 2).[5] A similar chiral spiroenone **D**, prepared in only 5 steps, was also applicable for the asymmetric total synthesis of (+)-lapidilectine B and (+)-grandilodine C and their absolute stereochemistry has been confirmed (Scheme 3).[6]

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Concise Construction of 3,3-Disubstituted-2-amino-3*H*-indoles via Copper-catalyzed Coupling of Aryl Chloride and α-Alkyl Cyanoacetate

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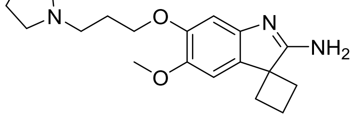
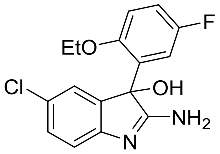
3,3-Disubstituted-2-amino-3*H*-indole and its analogues are an important class of pharmaceutical heterocycles that display a wide range of biological properties. A-366 is potent and selective inhibitors of histone methyltransferase G9a.[1] Genz-668764 inhibits P. falciparum in vitro.[2]

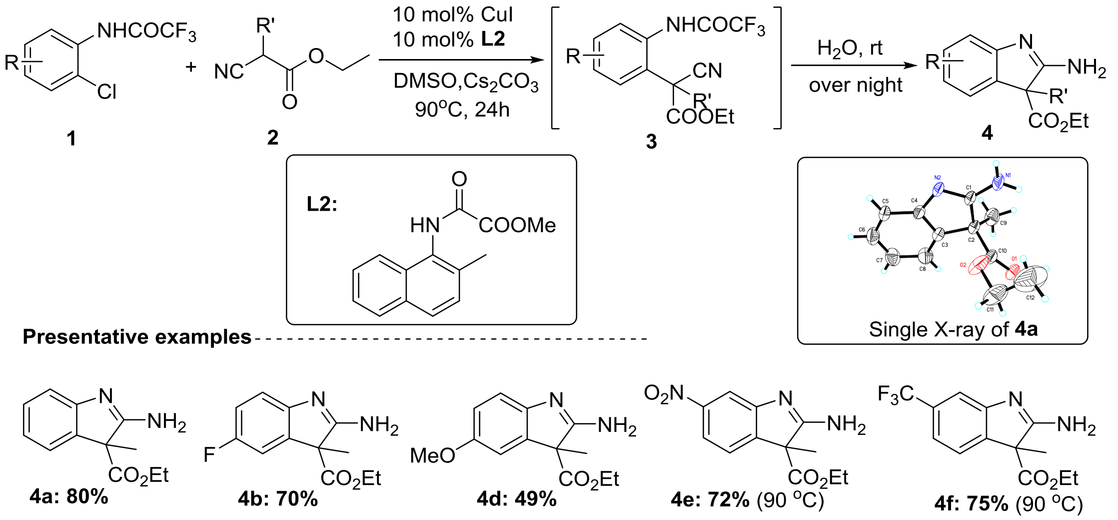


A-366



Genz-668764

Great progress in Cu-catalyzed coupling reactions provides abundant opportunity for discovering new methodologies to elaborate various heterocycles. Recently, we revealed that some oxalic diamides and related amides are very powerful ligands for copper catalysis, especially for coupling of less active aryl chlorides with some nucleophiles.[3-4] Herein, we described a concise method for the synthesis of 3,3-disubstituted-2-amino-3*H*-indoles based on copper-catalyzed C-C coupling of 2-chlorotrifluoroacetanilides **1** and α-alkyl cyanoacetate **2** under the promotion of methyl 2-((2-methylnaphthalen-1-yl)amino)-2-oxoacetate (**L2**).



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Synthesis of 3,4-Fused Tricyclic Indoles Using Transition Metal Catalysis

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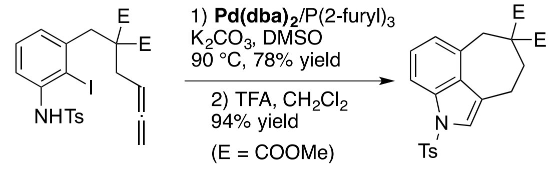
3,4-Fused tricyclic indole skeletons are found in various bioactive natural products and pharmaceuticals. Most of these molecules possess a functionalized medium-size ring bridging the C3 and C4 positions of the indole. This class of compounds is an attractive target in synthetic organic chemistry due to the ubiquity of the structural motif in bioactive molecules, as well as their characteristic structures. In this presentation, two-types of synthetic method of this structural motif will be discussed.

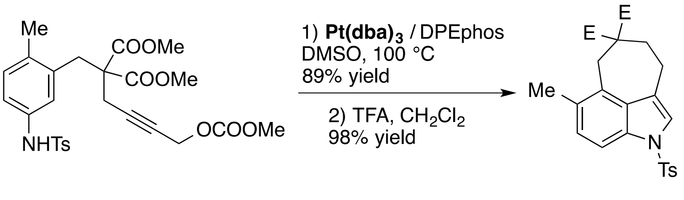
Allenes generally react with an aryl halide in the presence of a Pd(0) catalyst to give the corresponding π-allylpalladium(II) species through a Heck insertion process. We hypothesized that treatment of allenes tethered to *ortho*-iodoaniline derivatives at the *meta*-position with a Pd(0) catalyst in the presence of base would lead to the formation of 3,4-fused tricyclic 3-alkylidene indoline derivatives, which would be isomerized to 3,4-fused tricyclic indole skeletons. The corresponding substrates were reacted with 5–10 mol % of Pd catalyst and 4 equiv of K_2CO_3 in DMSO at 90 °C, producing 3,4-fused tricyclic 3-alkylidene indoline derivatives in moderate to excellent yield. The products were divergently transformed into three types of 3,4-fused tricyclic indole derivatives. [1]

Difficulty in preparing multi-substituted iodoaniline derivatives limited the flexibility to synthesize 3,4-fused tricyclic indoles with additional substituents on the aromatic ring using the developed Pd catalysis. Therefore, a novel Pt-catalyzed cascade cyclization reaction was developed by intramolecular Friedel-Crafts-type C–H coupling of aniline derivatives with a propargyl carbonate unit–allylic amination sequence. Treatment of various propargyl carbonates tethered to *meta*-aniline derivatives with a $Pt(dba)_3$/DPEphos catalyst system afforded the corresponding 3,4-fused tricyclic 3-alkylidene indolines, which could be transformed into the target compounds in excellent yield. [2]

*** Pd-catalyzed Heck Insertion-Allylic Amination Cascade**



*** Pt-Catalyzed C-H Coupling-Allylic Amination Cascade**



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CuI-catalyzed Intramolecular Aminocyanation of Terminal Alkynes

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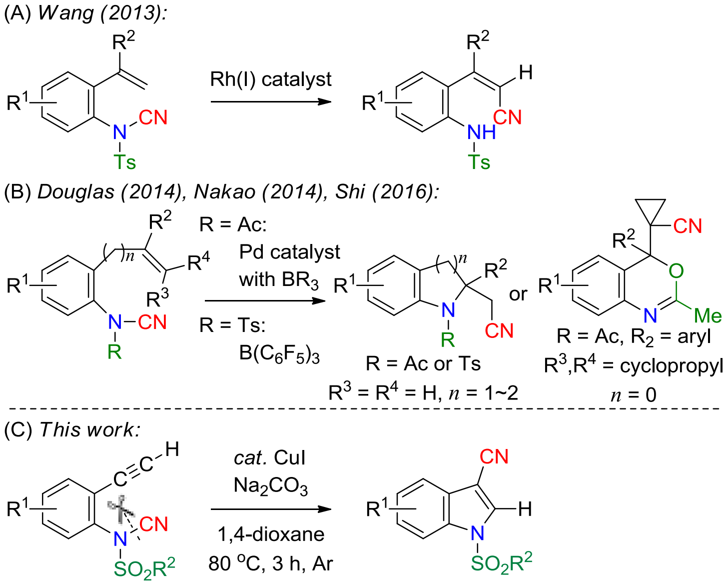
Cyanamide derivatives have been extensively used as reactive N-C-N building blocks in organic synthesis, and as ambidentate ligands in coordination chemistry. Recently, the use of *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS, **1**) and its derivatives as organic cyanating reagents has received considerable attention, of which the N-CN bond cleavage provided reactive CN species for expeditious synthesis of a wide variety of cyano-containing organic molecules.

Our attention was attracted by the intramolecular CN migration reaction of *ortho*-substituted NCTS derivatives, wherein the NCTS portion served as an internal cyano donor for intramolecular cyanation of unsaturated carbon-carbon bonds. Wang found that the Rh(I)-catalyzed reactions of *ortho*-vinyl substituted NCTS derivatives resulted in the intramolecular alkene-cyanation (**A**).[1] Douglas, Nakao and Shi, independently reported that *ortho*-allyl or homoallyl substituted NCTS derivatives or the *N*-acyl-*N*-phenylcyanamide congeners underwent intramolecular aminocyanation in the presence of boranes as activators (**B**).[2]



We herein reported a CuI-catalyzed intramolecular aminocyanation of terminal alkynes in *N*-(2-ethynylphenyl)-*N*-sulfonylcyanamides (**C**). The reaction was initiated by the formation of Cu-acetylide to trigger N-CN bond cleavage of the *N*-sulfonylcyanamide moiety followed by CN migration to form β-cyano Cu-vinylidene intermediate. Subsequently, the indole ring closure furnished the corresponding 1-sulfonyl-3-cyanoindoles.[3]

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Access to DNA-encoded screening libraries of heterocycles through a tailored encoding strategy

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DNA-encoded compound libraries (DELs) have found widespread use as screening technology for drug research.[1,2] Tagging compounds with genetic information allows for synthesis of very large screening collections, and for pooling these collections to mixtures. These are screened efficiently on disease-relevant target proteins by selection for bioactive compounds. Bioactive compounds are identified post-selection by PCR-amplification and next generation sequencing of the amplicon mixtures. Heterocycles are essential structures in the chemical space of bioactive compounds. Transition metal catalysts, and acid organocatalysts enable access to diverse drug-like heterocycles from simple starting materials, but interact or even react with purine bases eventually causing depurination of the DNA tag. To circumvent this impediment to methods development for DELs, we utilize a hexathymidine sequence “hexT” as an adapter oligonucleotide in the initial step of DEL synthesis (**Figure 1**).[3] The hexT tolerated several catalysts and harsh reaction conditions for heterocycle synthesis. The hexT-heterocycle conjugates were readily ligated to coding DNA sequences with a hexa-adenosine overhang.

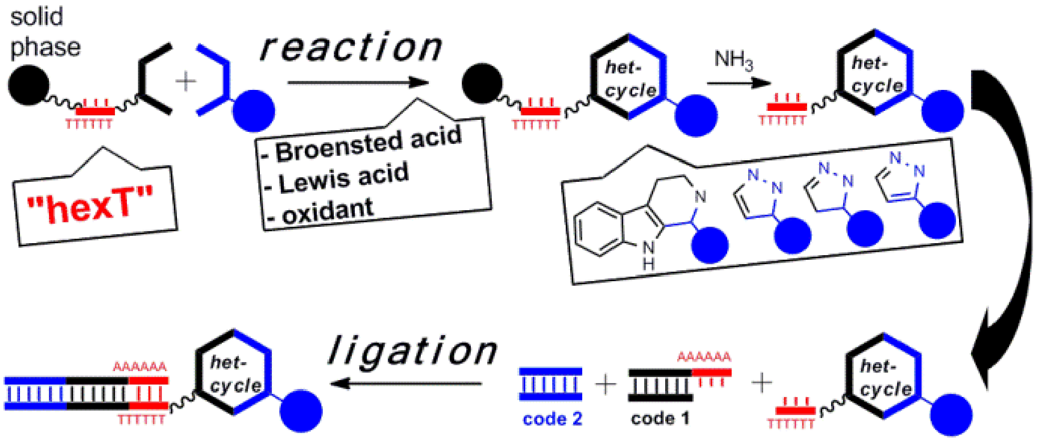

Figure 1: An access to DNA-encoded libraries based on the chemoresistant sequence “hexT”.

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Novel Accesses to Boron-containing Cycles and Related Structures

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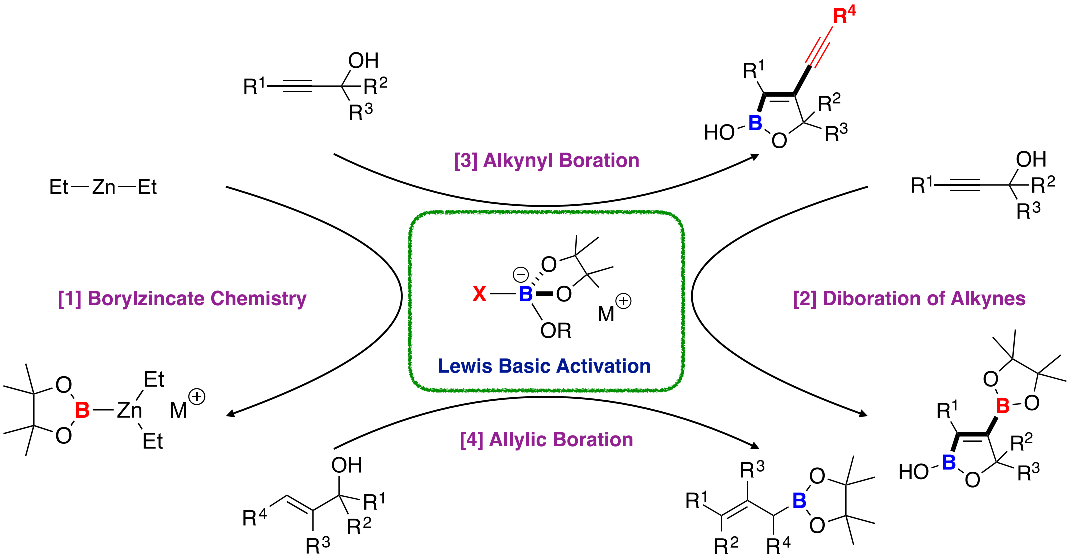
Organoboron compounds have been one of the most important classes of organic compounds owing to their flexibility in chemical synthesis enabling facile C–C bond formation as well as C–heteroelements bond formations. Recently, the preconception of toxicity of boron is being mended, and the utilization of organoborons in medicinal chemistry is actively developing. From these facts, efficient methodologies for regio-, stereo-, and chemoselective introduction of boron atom into organic molecules is eagerly anticipated.

We have been working on transition metal-free boration methodologies based on Lewis basic activation of boron reagents.[1] Taking advantage of the *pseudo*-intramolecular activation of boron atom by propargylic alcohols, we have established a novel and facile access to diverse oxaborolol structures *via* diboration[2] and carboboration[3] of the triple bond, which have been attracting much attention as novel pharmacophores. Oxaborolols are also useful synthetic building blocks providing regio- and stereocontrolled multiply substituted olefins. Using allylic alcohols instead of propargylic counterparts, allylic boronates are readily obtained, which are unless otherwise labor-intensive to synthesize.[4]



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Impressive enantiodiscrimination ability of 1,1’-bibenzimidazolium and 3,3’-bicollidinium salts in achiral ionic liquids

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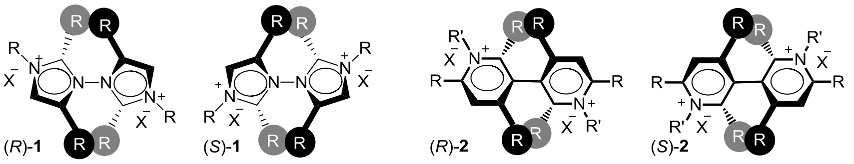
In "inherently chiral" materials the stereogenic element responsible for chirality coincides with the molecular portion responsible for their specific properties. This concept was successfully tested in designing chiral organic semiconductors employed by us as highly stereoselective electrode surfaces [1] and it is now applied to the preparation of inherently chiral ionic liquids (ICILs) and transport electrolytes.

According to this strategy, we synthesised the *N,N*’-dialkyl salts of bi-heteroaromatic systems characterized by atropisomeric 1,1’-biimidazole **1** and 3,3’-bipyridine **2** scaffolds. The enantiopure dialkyl salts were prepared by alkylation of the enantiopure antipodes of a series of 2-alkyl-1,1’-bibenzimidazoles and of 3,3’-bicollidine. They were obtained in an enantiopure state by resolution of the corresponding racemates by employing semi-preparative HPLC on CSP in the former case and by crystallization of the diastereomeric salts with the *O,O*-dibenzoyltartaric acids in the latter. [2], [3]



In particular, the long alkyl chain salts **2** are liquid at room temperature, therefore, they are the first atropisomeric ICILs. The new ICILs have been employed as additives to achiral ILs in cyclovoltammetric experiments devoted to check their enantiorecognition ability towards the antipodes of several probes differing in structure and stereogenic element on achiral electrodes. In particular, the selected probes are the *N,N’*-dimethyl-1-ferrocenyl-ethylamine (FcA), the 2,2‘-bis[2-(5,2'-bithiophenyl)]-3,3'-bithianaphthene (BT_2T_4), DOPA, DOPA Methylester, Ofloxacin and Thalidomide enantiomers, while $BMIMPF_6$ and $BMIMBF_4$ are the selected media.

The new chiral bis-onium salts provide outstanding differentiation of the oxidation or reduction peaks of the enantiomers of all the probes. [3]

These results appear indeed attractive on account of both the impressive enantiorecognition levels and the very small chiral inductor consumption.

Stereoselection mechanistic hypotheses are discussed.

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An Arylative Ring Expansion Cascade of Fused Cyclobutenes via Short-lived Cycloakladienes with Planar Chirality

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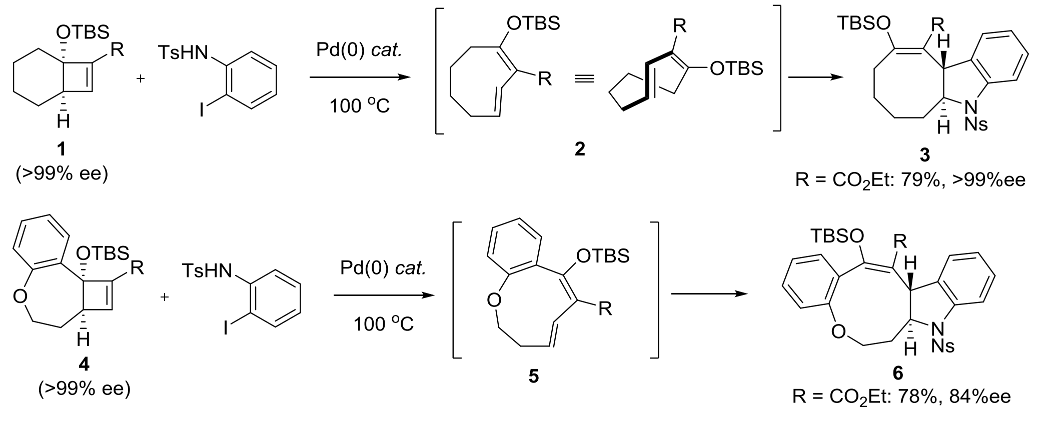
Yoshida, Sakyo-ku, Kyoto 606-8501, JAPAN

Thermal 4π electrocyclic reaction of cyclobutenes proceeds in a conrotatory manner to give 1,3-butadienes in accordance with Woodward-Hoffmann rules. Conrotatory electrocyclization of fused cyclobutene **1** generates highly strained *cis*,*trans*-cyclooctadiene **2**, which is unisolable due to the rapid reverse reaction to the starting material **1**. However, we envisioned trapping of this short-lived intermediate **2** by intermolecular reaction to provide access to medium ring compounds, which are generally difficult to construct by intramolecular cyclization strategy due to large entropy and enthalpy cost.

Moreover, our attention was directed to inherent planar chirality of the short-lived intermediate **2**. Certain medium ring *trans*-cycloalkenes are known to display planar chirality. For a representative example, *trans*-cyclooctene exhibits stable planar chirality at ambient temperature due to the highly rigid structure. We envisaged chirality transfer in a palladium-catalyzed ring expanding reaction of **1** to afford medium ring fused *trans*-indoline **3** through transient planar chirality of **2**.

When **1** (>99%ee) was treated with *o*-iodoaniline derivative in the presence of palladium catalyst and Ag_2CO_3 in toluene at 100 °C, indoline **3** was obtained in 79% yield as a single diastereomer without any loss of enantiopurity. Tricyclic cyclobutene **4** was also subjected to the reaction, which resulted in the isolation of **6** in 78% yield with 84%ee. The partial racemization was observed due to more facile ring flip of 9-membered transient intermediate **5**.[1]



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Donor-Acceptor-Cyclopropanes as Unique Structural Units to Access Heterocyclic Compounds

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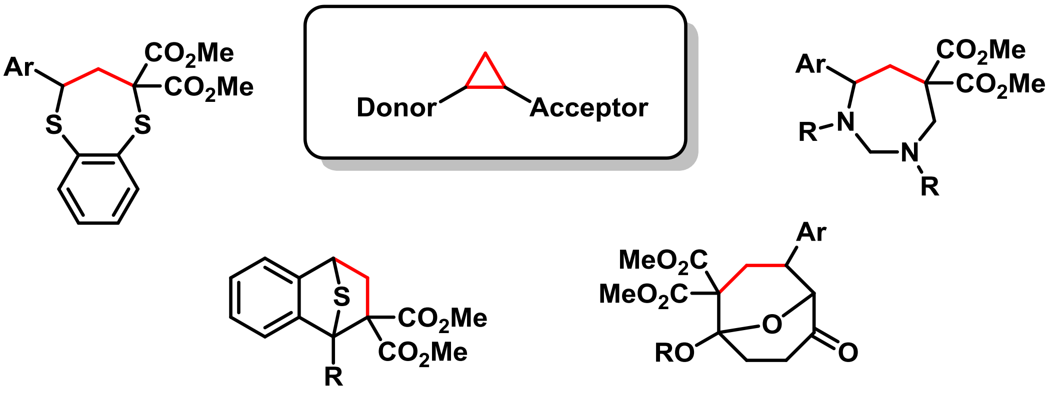
Donor-acceptor (DA) cyclopropanes are highly strained entities which are unique building blocks for heterocyclic and carbocyclic systems.[1,2] Our previous work was mainly focused on rearrangement reactions of DA cyclopropanes leading to spiroketals, oligoacetals,[3] pyrrols[4] and thiophenes. The recent developments in the lab deal with [3+n]-cycloaddition reactions (n = 1, 2, 3, 4).

Approaches to four-membered ring formation by insertion of one atom are presented. [3+3]-Cycloaddition reactions lead to tetrahydropyridazines.[5] Similar reactions using carbonyl ylides allow the preparation of complex bicyclic scaffolds in a simple manner. The formation of seven-membered rings with unusual 2-atom moieties being inserted are discussed. Such transformations pave the way to 1,4-bisamines by the formal addition of "NHR" and "CH_2NHR" to the 1- and 3-position of the cyclopropane.[7]



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Rearrangements of Quinoxalinones with “Outside” Group Participation Towards Benzimidazol(on)oes

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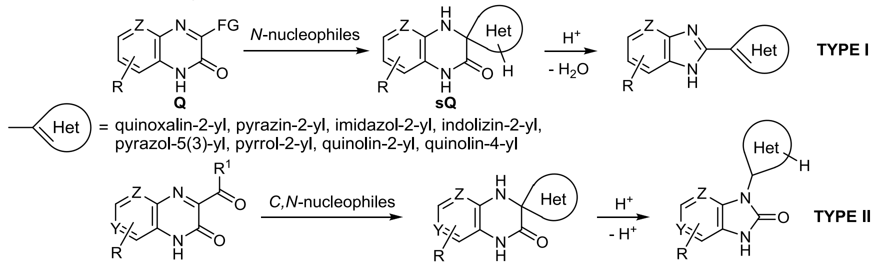
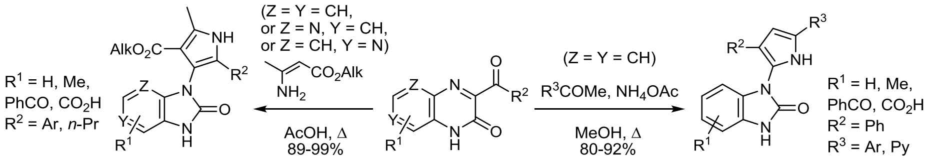
This report will focus on two aspects of our research program including reactions of quinoxalin-2(1*H*)-one derivatives when exposed to various *N*-nucleophilic reagents (TYPE I)[1,2] and C,*N*-nucleophilic reagents (TYPE II).[2,3] These functionalized quinoxalinones are suitable for ring transformations via spiro-quinoxalinone intermediates to afford a whole variety of 2-heteroaryl-bensimidazoles and 1-heteroaryl-benzimidazolones.



Note, when FG in structure **Q** (TYPE I) contains substituents of electrophilic character (centers), the *N*-nucleophiles can be not only aromatic diamines such as 1,2-diaminobenzenes, pyridine-2,3-diamine, pyrimidine-4,5-diamine, but also α-picolines and other amines – hydrazine, arylmethanediamines (prepared in situ), 2,3-diaminomaleonitrile. When FG in structure **Q** involves substituents of nucleophilic character (centers) the spiro-quinoxalinone **sQ** is formed either through the direct attack of the N atom of the amine group or via attack of C-2 of the enamine moiety formed in situ in the reaction of quinoxalines with ketones.[2]

When the reactions of aroyl- and alkanoyl- quinoxalinones and their azaanalogues were carried out with the commercially available enamines and enamines generated in situ this protocol reflected an effective strategy that enabled access to *N*-pyrrolylbenzimidazolones with good yields, while using environmentally friendly metal-free conditions.[4,5]



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Geminal diazides: A versatile toolbox for the synthesis of heterocyclic entities

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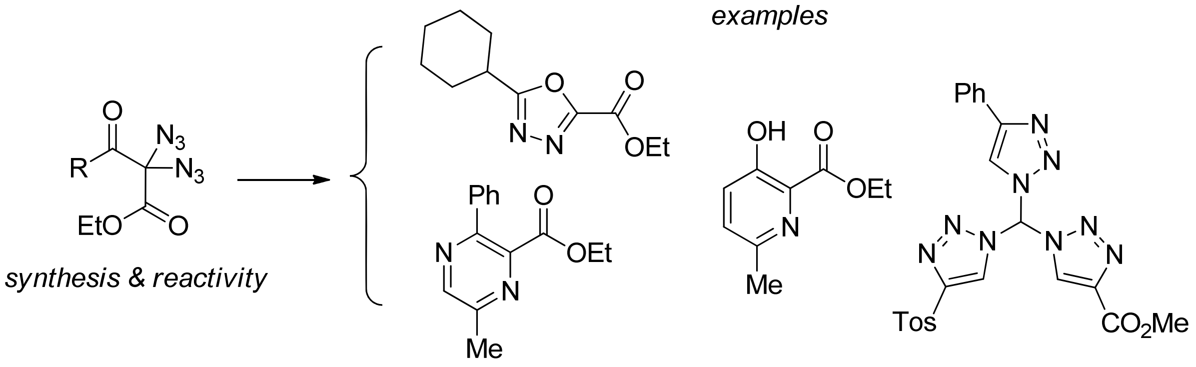
We present new studies on the synthesis and reactivity of geminal diazides, a mostly neglected class of compounds. The first geminal diazides were reported by Forster et al. in 1908.[1] However, the class of geminal diazides barely found attention in chemical sciences, and reports on their reactivity are rare.[2] It is now shown how geminal diazides (and even triazides) can be easily obtained from a range of highly functionalized starting compounds.[3] For example, 1,3-dicarbonyls undergo direct diazidation when treated with sodium azide and iodine in aqueous DMSO. Besides methods for their synthesis, new reactions with geminal diazides are discussed: In the realm of heterocycles, the thermolysis of geminal diazides can be used to access 3-hydroxypyridines, pyrazines or 1,3,4-oxadiazoles in a controlled way.[4] Unconventional bistriazoles and tristriazoles can be formed through sequential cycloaddition with alkynes.[5]



This presentation aims to make the class of geminal diazides more attractive to researchers by explaining the ease of their synthesis and the great potential of their reactions.

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Cu^0-catalyzed azomethine imine-alkyne cycloadditions (CuAIAC), a fluorescent alternative to azide-alkyne cycloaddition (CuAAC)

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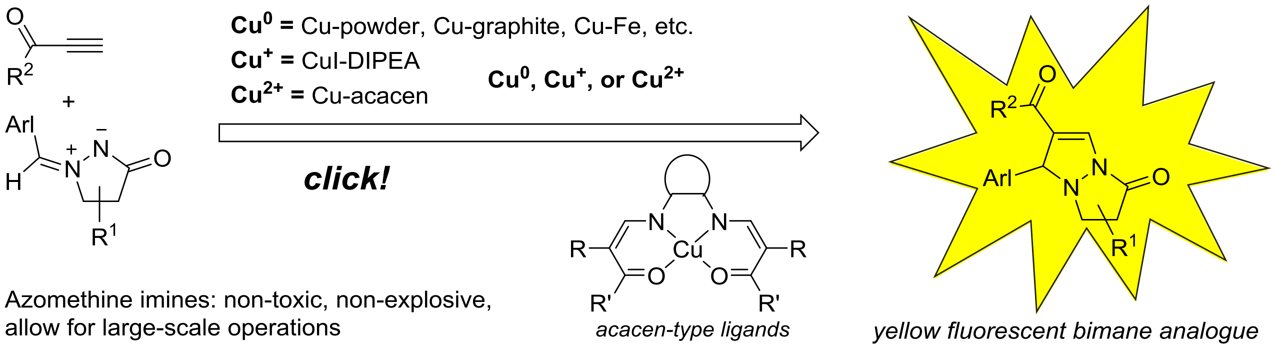
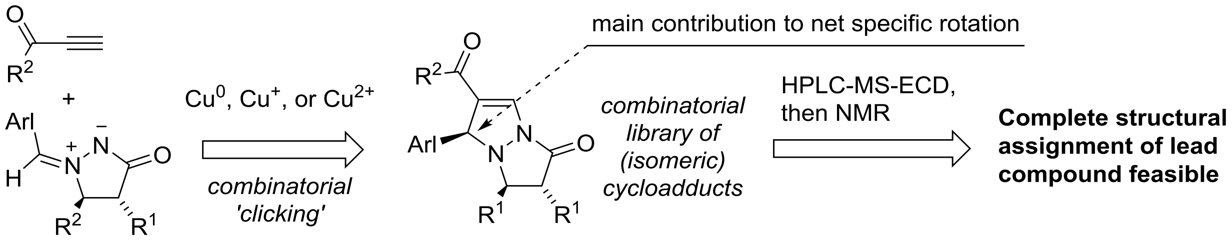
Copper-catalyzed cycloadditions of azomethine imines to acetylenes (CuAIAC) provide an easy access towards 2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles in a regio- and stereoselective manner and under mild conditions that are compliant with requirements of "click" chemistry. CuAIAC can also be catalyzed by copper metal (Cu^0), Cu^+, or Cu^{2+} to give fluorescent cycloadducts in very high yields. Availability of azomethine imines, mild reaction conditions, simple workup, and scalability make CuAIAC a viable supplement to CuAAC reaction in 'click' chemistry [1]. Recent combinatorial study also revealed promising activity of Cu(II)-acacen complexes in CuAIAC reaction [2].



In the non-racemic 2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole series the absolute configuration of representative compounds were determined by VCD and X-ray diffraction. A clear correlation between the sign of specific rotation and configuration at position C(1) allows for easy determination of the absolute configuration by ECD and NMR [3].



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Multicomponent and domino reactions of alkynes and benzynes in the synthesis of *N*-heterocycles. Recent advances.

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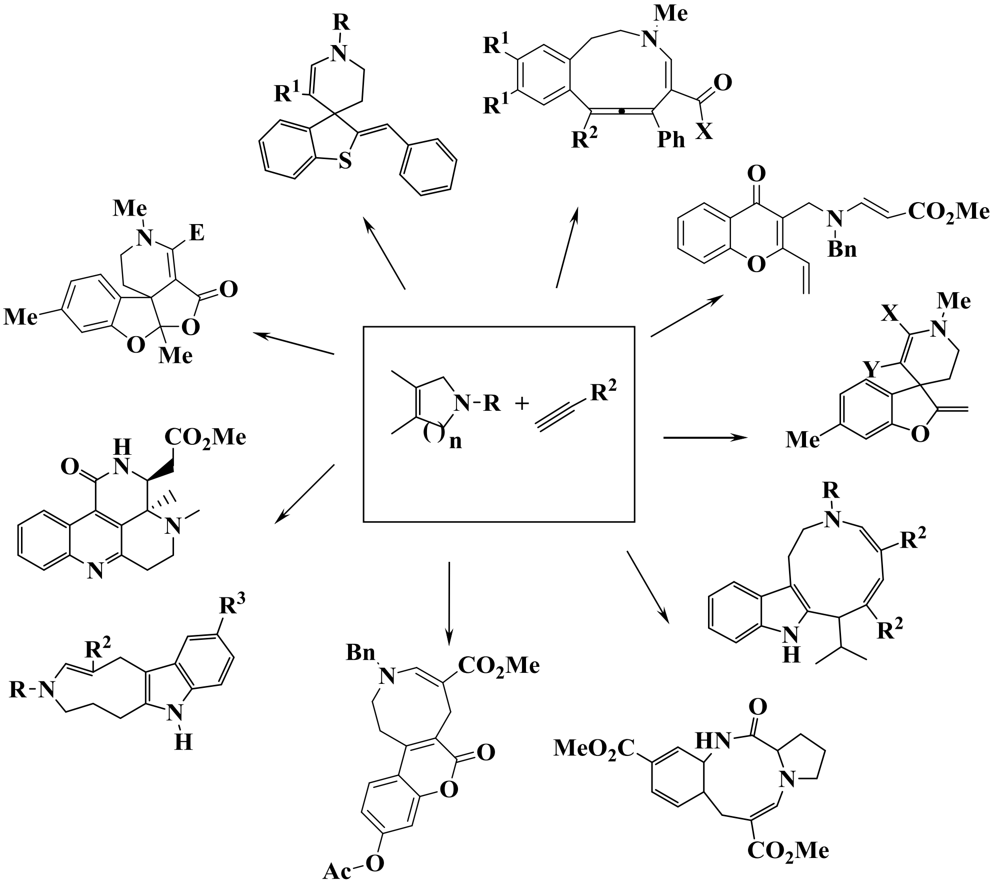
The development of new step-economical approaches to *N*-containing heterocyclic compounds, producing less waste and by-product, continues to be of considerable interest and important for modern organic and medicinal chemistry, particularly, for drug discovery and development. In the past several years, we and others have developed a series of Michael addition triggered domino reactions that provide easy access to multiple functionalized ring structures of chemical and pharmaceutical interest.



This presentation will cover recent results obtained in the synthesis of heterocyclic molecules based on MCR reactions initiated by the Michael addition with the emphasis on *N*- heterocycles reactions with alkynes and arynes.

This work was supported by the Russian foundation for basic research (grants # 17-03-00605 and 16-53-540004 viet-a)

Synthesis of Aniline Derivatives via Aryne Intermediates Enabling Facile Preparation of Nitrogen-Containing Heterocyclic Compounds

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Yoshihoro Misawa,[1] Yasuyuki Sugimura,[2] Kazunobu Igawa,[3] Shigeomi Shimizu,[2]
Katuhiko Tomooka,[3] Takamistu Hosoya[1,*]
[1] *Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Tokyo 101-0062*
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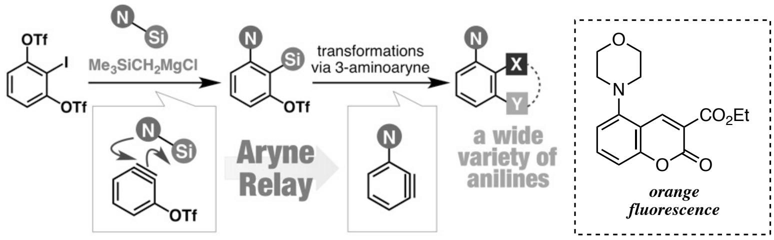
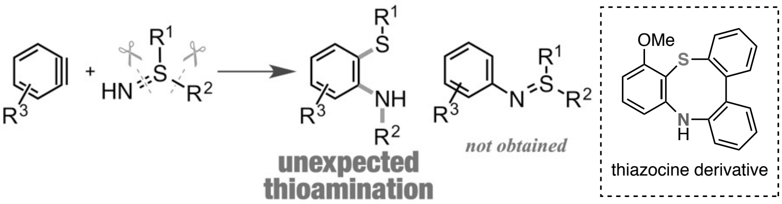
Aniline derivatives play an important role in various fields, including materials science and medicinal chemistry. In spite of the importance, synthesis of complex nitrogen-containing arenes including multisubstituted anilines and condensed organonitrogen compouds is not easy. Herein we disclose facile methods to prepare a variety of anilines via aryne intermediates.

We found that 3-amino-2-silylaryl triflates could be easily prepared via regioselective silylamination of 3-triflyloxyarynes, which were efficiently generated from *ortho*-iodoaryl triflate-type aryne precursors. 3-Aminoarynes were efficiently generated from the precursors synthesized by this method, which rendered a diverse range of aniline derivatives such as 5-aminocoumarins easily accessible, demonstrating the synthetic utility of aryne relay chemistry.



During the course of our studies to prepare anilines by the reaction between arynes and sulfilimines, we unexpectedly found that *o*-sulfanylaniline was produced instead of aniline. Based on this discovery, we have developed a novel method for preparing a diverse range of *o*-sulfanylanilines via direct thioamination of arynes, generated from *o*-silylaryl triflates, with sulfilimines, followed by migratory *N*-arylation. The reaction using a cyclic sulfilimine afforded a unique ring-expanded eight-membered thiazocine derivative in high yield.



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Biheterocycles and linked heterocycles based on *Cinchona* alkaloids

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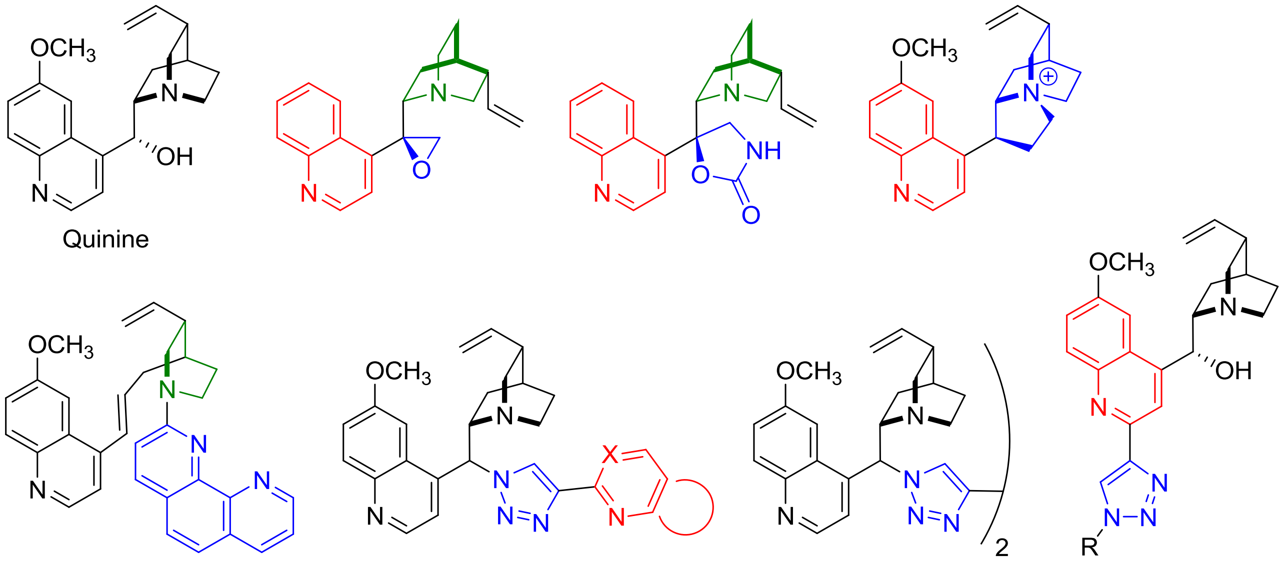
Cinchona alkaloids (e.g. quinine) and their derivatives are highly relevant to asymmetric catalysis and, now in diminishing extent, to medicine. In our laboratory, we have introduced various biheterocyclic systems to the *Cicnchona* alkaloids.[1-2] Alternatively we exploited the already present ring systems of quinoline and quinuclidine and made them linked directly to another heterocycle (Figure).[3-5] Perhaps the easiest way to obtain a new heterocycle is through copper-catalyzed 1,3-dipolar cycloaddition of azides and alkynes. The formed 1,2,3-triazoles were, however, seldom carrying "stand-alone" useful function but their combination with another heterocycle (such as pyridine, pyrimidine, quinoline, or an extra triazole) led to introduction of new interesting properties.



Some of the obtained products were found to form complexes with copper (II).[2] In case of bitriazole system, where the complexes are moderately stable, they catalyzed asymmetric Michael-hemiacetalization reaction providing up to 80%ee.[1] On the other hand, some other alkaloid-based biheterocycles gave promising *in vitro* results. The corresponding details will be presented.

Founded by National Science Center NCN, Poland (No. 2013/11/D/ST5/02909)

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Reactions of *N*,*N*-Dialkyl-*N*'-Chlorosulfonyl Chloroformamidines with 1,3-NCC Bis-Nucleophiles: Synthesis of New Fused Thiadiazine Ring Systems.

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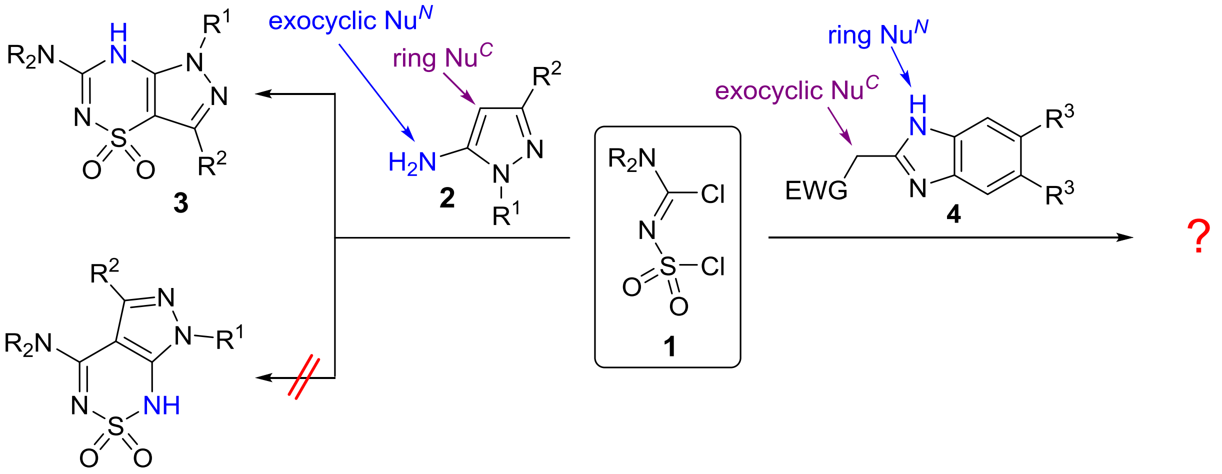
[1]*Flinders University, Adelaide, SA, Australia;* [2]*CSIRO, Melbourne, VIC, Australia*

N,*N*-Dialkyl-*N*'-chlorosulfonyl chloroformamidines **1** have proven to be highly versatile 1,3-bis-electrophilic intermediates for the synthesis of a wide variety of structurally unique heterocyclic ring systems.[1] Recently, we have been evaluating the reactions of dichlorides **1** with a range of 1,3-NCC dinucleophiles and the first example, the regioselective reaction with 1-substituted-5-aminopyrazoles **2** to afford derivatives of the new pyrazolo[3,4-*e*][1,2,4]thiadiazine ring system **3** (Scheme 1), has been reported.[2]



Scheme 1

It was of interest to investigate the effect of a reversed arrangement of nucleophilic centres in a 1,3-NCC bis-nucleophile, i.e. an exocyclic carbon nucleophile and a ring nitrogen nucleophile, on the regioselectivity of reactions with dichlorides **1**. Benzimidazole derivatives **4** (Scheme 1) were chosen to represent such a system and we will report the regioselective synthesis of a new benzimidazo-fused thiadiazine ring system bearing various electron withdrawing groups (EWG), as well as some substitution reactions, and other aspects of the reactivity of this new molecular scaffold.

We have also been investigating the reactions between the dichlorides **1** and 1,3-NCC bis-nucleophilic aniline derivatives. In addition to the expected benzothiadiazine products, we will report examples of a variety of unexpected, new and unusual heterocyclic systems generated from these reactions, particularly those involving electron-deficient aniline derivatives.

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TRIAZOLE-BASED HALOGEN BOND DONORS

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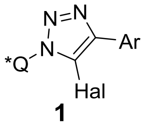
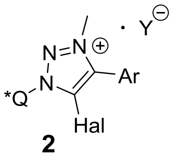
A halogen bond (XB) is a noncovalent interaction between an electrophilic halogen atom and some nucleophilic counterpart of the same or another molecule. [1] This concept has been widely used in crystal engineering, however, its application in solution, in particular, in catalysis, is scarce.

We have shown that enantiomerically pure triazole-based halides **1** or corresponding triazolium salts **2** are efficient XB donors in the solid state as well as in the solution. [2] The most intriguing property of these compounds were their ability to participate in the enantiodiscrimination of chiral thioureas in solution via XB formation. Our ongoing work is focusing on the use of these XB donors as organocatalysts. The rational design of the catalyst and tuning its properties will be discussed. Aza-Diels-Alder reaction was studied as a model reaction to address enantioselective catalysis and cooperative catalysis in the presence of XB donors.

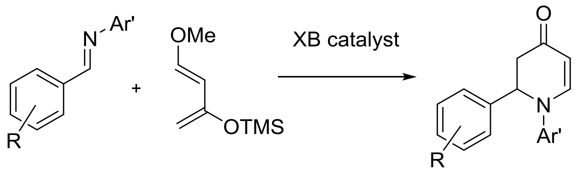


1



2

Q* = chiral substituent



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The synthesis of new 1,4-benzoxazines via the Petasis multicomponent reaction

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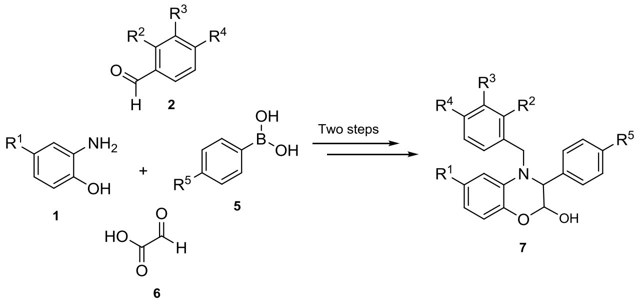
Laboratoire de synthèse de molécule d'intérêt biologique, Université de Constantine 1, Algérie, 25000.

Heterocycles constitute one of the biologically important classes of compounds in organic chemistry. [1,2] The selection of heterocycles by nature as the basis of most essential biological systems may be due to the fact that the introduction of heteroatom into cyclic compound imparts new properties and its chemical flexible nature leading to better response to the many demands of biochemical systems..

As part of our ongoing research towards the synthesis of heterocyclic compounds, [4,5] we wish to report herein, a protocol for the synthesis of new 2-hydroxy-1,4-benzoxazines via a Petasis multicomponent reaction in a single process. The protocol involves the use of secondary amines synthesized by the reaction between 2-aminophenols and aromatic aldehydes, via the reduction of the corresponding imines. The reaction between these secondary amines, phenylboronic acid and glyoxal gives the new corresponding 2-hydroxy-1,4-dihydrobenzoxazine derivatives in good to excellent yields.



The synthetic route to the benzoxazines **7** is shown in Scheme 1 mentioned above.

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[2] Baruah B, Prajapathi D, Baruah A, Sandhu JS (1997) Synthetic Commuication 27: 2563-2567 .

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[4] a) I Amine Khodja, R Boulcina, A Debache, (2015) Letters in Organic Chemistry 12:77-84,

β-(2-aminophenyl)-α–β-ynones as a valuable building blocks for the synthesis of heterocycles

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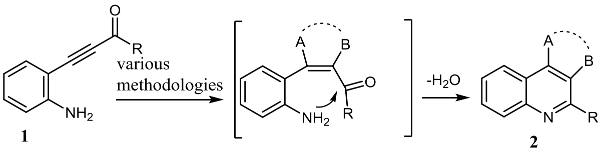
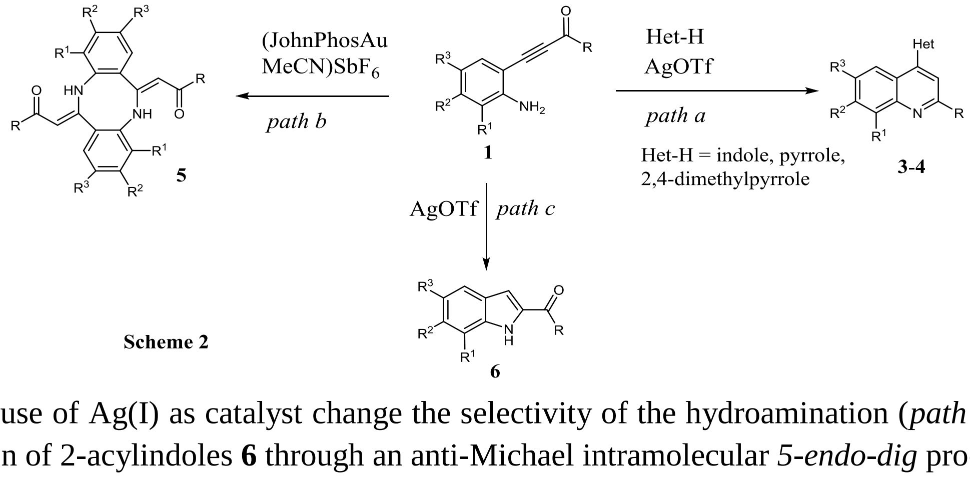
β-(2-Aminophenyl) α,β-ynones **1** represent useful starting materials for the synthesis of quinoline derivatives.[1] Over the years, we have developed various strategies for this transformation, including Pd-catalyzed transfer hydrogenation, Rh and Pd-catalyzed hydroarylation with organoboron derivatives, conjugate additions and cycloadditions. All these methodologies are based on the conversion of the C-C triple bond of the ynone into an alkene moiety, in which –NH_2 and carbonyl groups are in a cis relationship; sequential cyclocondensation results in the formation of quinolines **2** (Scheme 1).



Scheme 1

We have recently used this approach for the synthesis of 4-nitro, 4-sulfonyl, 4-aminoquinolines and 4-quinolones [2] by conjugate addition of nucleophiles to **1**. We wish to report here some new strategies for the synthesis of heterocycles from β-(2-aminophenyl) α,β-ynones**.** (Scheme 2). The reaction of **1** with electron-rich pyrrole and indole derivatives in the presence of Ag(I) catalyst results in the formation of pyrrolo- and indoloquinolines **3** and **4** (*path a*). Moreover, in the presence of a gold(I) catalyst, an unprecedented sequential intermolecular/intramolecular hydroamination allows the construction of challenging eight-membered dibenzo[1,5]diazocine structure **5** (*path b*).



Scheme 2

Finally, the use of Ag(I) as catalyst change the selectivity of the hydroamination (*path c*), allowing the formation of 2-acylindoles **6** through an anti-Michael intramolecular *5-endo-dig* process.

[1] For a review see: Abbiati, G.; Arcadi, A.; Marinelli, F.; Rossi, E. *Synthesis* **2014**, 687 and references therein.
[2] Rode, N.D.; Arcadi, A.; Chiarini, M.; Marinelli, F. *Synthesis* **2017**, *49*, 2501.

Synthesis of Novel Nitrogen-containing Polyheterocycles *via* Ruthenium-catalyzed One-pot Metathesis / Non-metathesis Reaction

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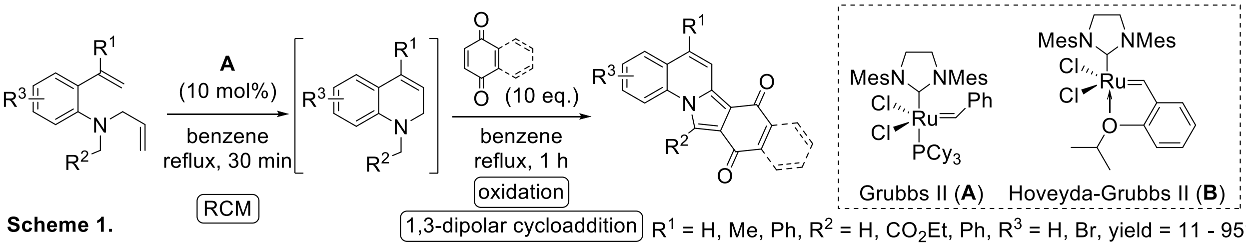
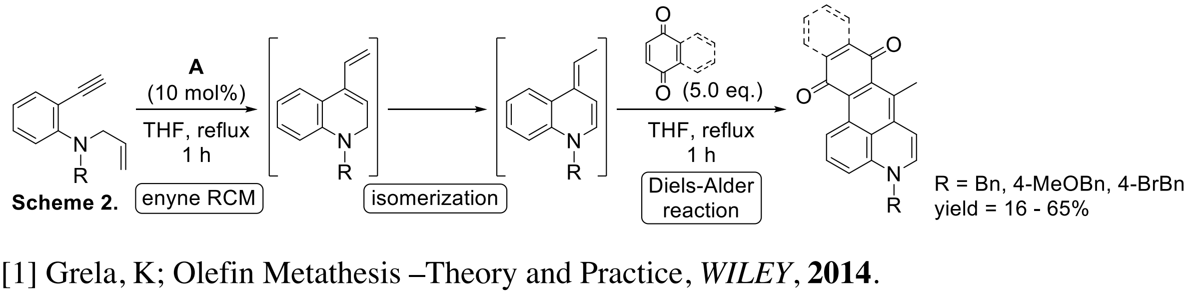
Olefin metathesis using ruthenium alkylidene catalysts were useful for the synthesis of medicine or functionalized molecules because of wide scope and easy handling. Over the past decade, several reaction sequences consisting of an olefin metathesis step and a subsequent non-metathesis transformation[1] were developed with using ruthenium alkylidene catalysts, such as ring-closing metathesis (RCM) / hydrogenation, RCM / radical cyclization, RCM / isomerizationor RCM / aromatization. Recently, we developed three ruthenium-catalyzed one-pot reactions for the synthesis of polycyclic nitrogen-containing compounds from simple aniline or benzylamine derivatives; RCM / 1,3-dipolarcycloaddition/ oxidation (Scheme 1)[2], olefin isomerization / enamine-RCM / 1,3-dipolar cycloaddition / oxidation[3] and enyne metathesis / olefin isomerization / Diels-Alder reaction / oxidation (Scheme 2)[4]. These reactions are useful to synthesize an isoindolo[2,1-*a*]quinoline core, an isoindolo[1,2-*a*]isoquinoline core and a naphto[*f*, *e*]quinolone core. We discovered these novel nitrogen-containing polyheterocycles are novel solution-processable pi-conjugated small molecules whose color can be altered dramatically by exchanging a substituent on the core. We also revealed some of these novel nitrogen-containing polyheterocycles have good absorbance or fluorescent properties in near-infrared (NIR) region. NIR dyes were more attractive in the field of electronic industry material or medicine.



Scheme 1. R^1 = H, Me, Ph, R^2 = H, CO_2Et, Ph, R^3 = H, Br, yield = 11 - 95%



Scheme 2. R = Bn, 4-MeOBn, 4-BrBn
yield = 16 - 65%

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[2] *Angew. Chem. Int. Ed.* **2013**, *52*, 1003-1007.
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Chiral Amine-urea Mediated Asymmetric Cycloadditions of Nitrile Oxides with *o*-Hydroxystyrenes and Their Computational Studies for Asymmetric Induction

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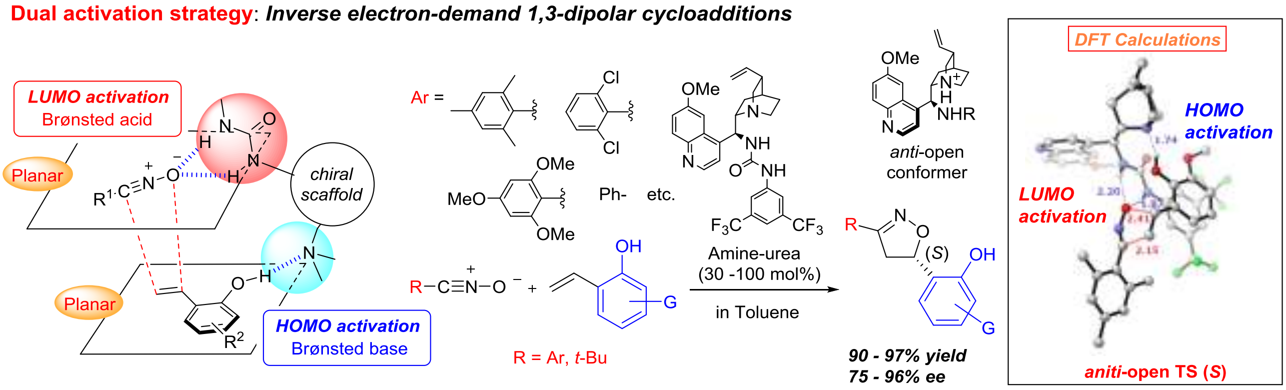
The nitrile oxide cycloadditons (NOCs) followed by reductive N-O bond cleavage sequence has been classically utilized for a number of natural product syntheses to construct stereogenic centers bearing nitrogen and oxygen functionalities. It is hence necessary to develop the enantioselective NOCs, as well as chiral substrate-based diastereoselective NOCs. However, up to date, only a few methodologies of enantioselective NOCs by using chiral Lewis acids [1] or metal catalysts [2] have been reported. This is probably due to their linear symmetrical structure that does not form an enantioface. Furthermore, enantioselective NOCs that involve organocatalytic variants or even in the presence of stoichiometric amount of chiral organic media have yet to be explored. To overcome the intrinsic challenge, we propose a novel dual-activation strategy involving LUMO activation by a Brønsted acid and HOMO activation by a Brønsted base in inverse electron-demand cycloadditions between nitrile oxides and *o*-hydroxystyrenes employing chiral amine-urea. In the congress, we describe the first example of cinchona alkaloid-based amine-urea-mediated asymmetric 1,3-dipolar cycloadditions between nitrile oxides and *o*-hydroxystyrenes, based on the dual activation methodology. In addition to stoichiometric asymmetric induction, catalytic amount of amine-urea enables the cycloadditions in an enantioselective manner. The high levels of asymmetric induction were strongly supported by DFT calculations of the energy differences between the *anti*-open TS (*S*) and *anti*-open TS (*R*). It has been also disclosed by the calculations that both the LUMO of nitrile oxides and HOMO of *o*-hydroxystyrenes can be activated by chiral amine-urea engaging the two reactants.



[1] Sibi, M.; Itoh, K.; Jasperse, C. *J. Am. Chem. Soc.* **2004**, *126*, 5366–5367.
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Allylic C-H Activation v/s Leaving Group Ionization for π-Allylpalladium: Unprecendented Bis-arylation

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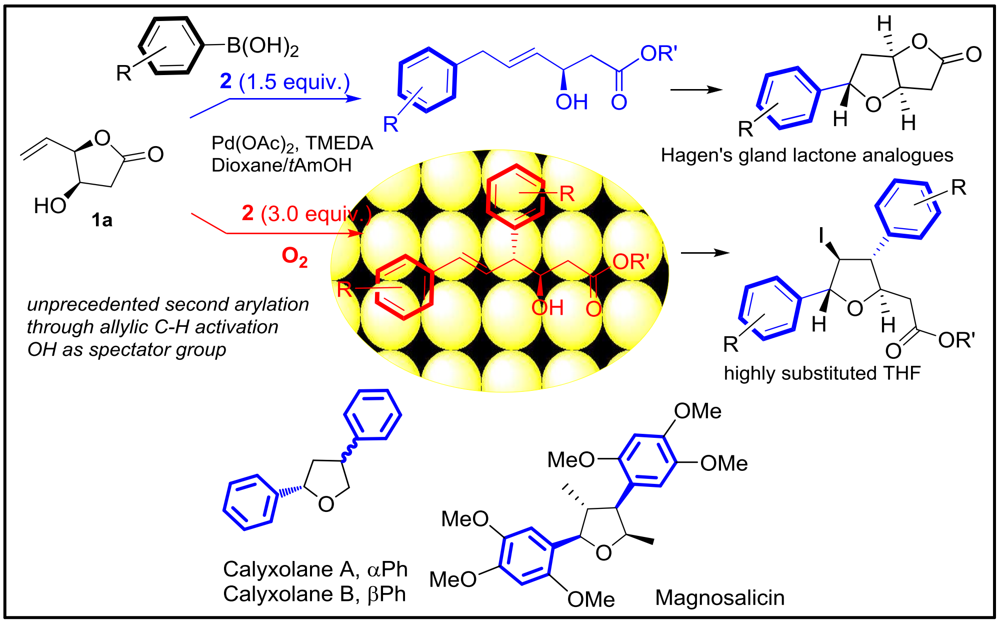
An efficient palladium-catalyzed site-selective arylation of γ-vinyl-γ-lactone by aryl boronic acid has been developed. An unprecedented allylic C-H activation[1] based π-allylpalladium formation was observed versus the allylic-OH based leaving group ionization.[2] The mono-arylation by allylic substitution was followed by site-selective second arylation by directed allylic C-H activation giving stereoselectively *anti*-γ-(aryl,styryl)-*β*-hydroxy acids. This methodology has been elaborated to synthesize highly substituted tetrahydrofurans including aryl-Hagen's gland lactone analogues via intramolecular iodoetherification.[3] The 2,4-biarylfuran moiety is present in calyxolanes A and B and magnosalicin. The insights of this work will be presented.



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[3] Nallasivam, J. L.; Fernandes, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 13238–13245.

The Asymmetric Aza-Prins Reaction

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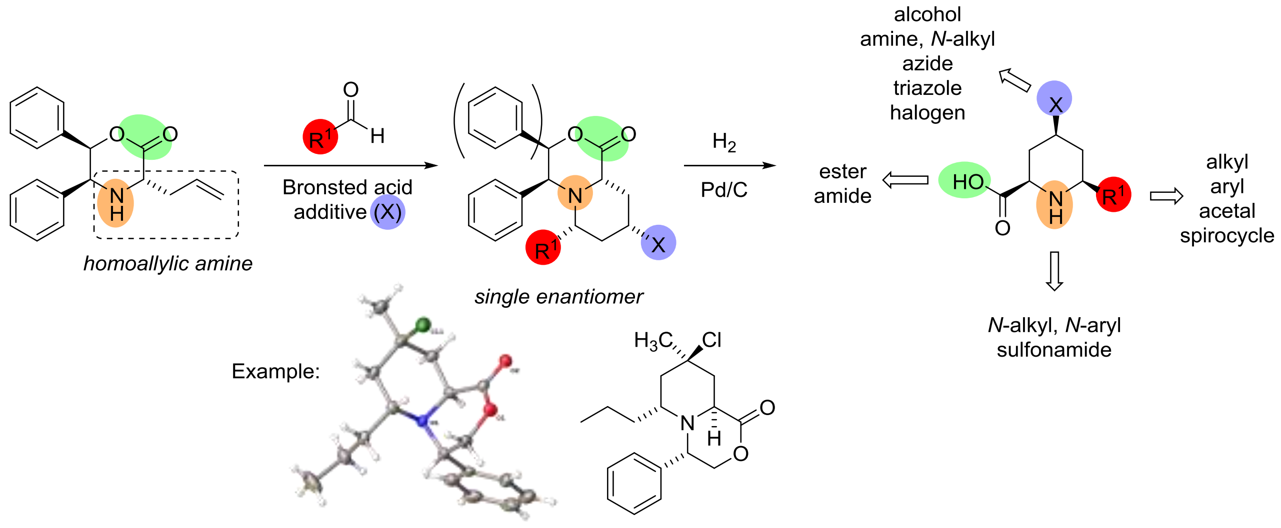
The acid catalyzed condensation between homoallylic alcohols and aldehydes – known as the Prins cyclisation – is a rapid and highly efficient method for the preparation of tetrahydropyrans. More recently, we (and others) have demonstrated the use of homoallylic amines in this reaction to generate substituted piperidines – the so called aza-Prins reaction. [1]

In 2015, List reported the first example of an asymmetric organocatalytic Prins reaction. [2] Herein, we report the development and first examples of an asymmetric aza-Prins reaction to generate substituted piperidines as a single enantiomer.



Furthermore, the piperidine structure is a highly targetted scaffold in drug discovery, as compound libraries are moving away from traditional (hetero)aromatic 2-dimensional compounds towards more structurally diverse and 3-dimensional sp^3-rich compounds. We shall additionally demonstrate the usefulness of our enantiopure bicyclic intermediates and piperidine products as 3D heterocyclic scaffolds. The libraries have been analysed by LLAMA [3] for their shape diversity, chemical space accessed and general lead-like properties.

[1] A. Dobbs *et al.*, *Org. Biomol. Chem*. **2010,** 1064; B.V.S. Reddy *et al.*, *Eur. J. Org. Chem*., **2017**, 1805.

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[3] https://llama.leeds.ac.uk/index.php

Oxygen and nitrogen heterocycles from 3-electron withdrawing substituted chromones

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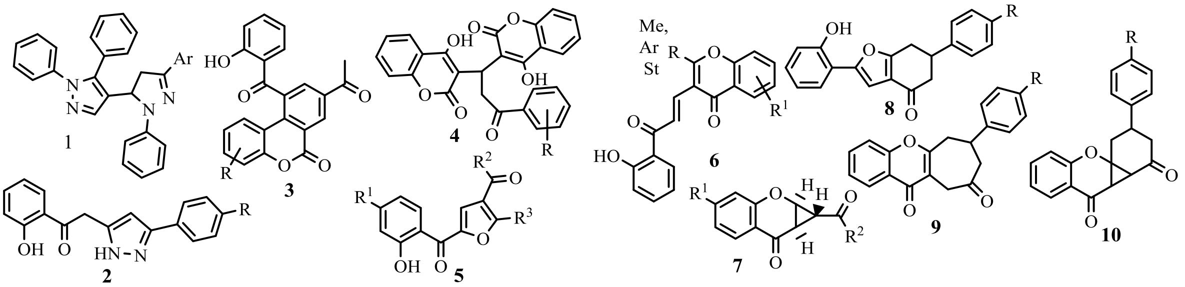
Oxygen and nitrogen heterocyclic compounds constitute the largest and most varied families of organic compounds, comprising a great number of classes according to the size, number of heteroatoms and heterocyclic ring oxidation. There is a huge number of marketed drugs, food additives and other industrial products based in these two types of compounds. These important industrial and biological applications and also some problems associated with their application, such as multiple drug resistance to some nitrogen heterocycles and potential carcinogenesis of high doses of oxygen heterocyclic-based antioxidants, led us to develop new synthetic methods for novel biologically active derivatives of both referred families of heterocyclic compounds.

This communication will be focused on the use of chromones bearing electron withdrawing substituents at position 3 as building blocks for the synthesis of several other nitrogen and oxygen heterocycles. These transformations involve one-pot reactions, conjugated and cycloddition reactions, oxygen heterocyclic ring opening, heterocyclisations, and tandem reactions and allowed us to prepare a plethora of different structures, such as pyrazoles **1** and **2** [1], coumarins **3** and **4** [2], furans **5** [3], polysubstituted chromones **6** [4], and polycyclic compounds **7-10** [5]. We will present and discuss the chemistry involved in each one of these synthetic routes and also some of the biological activities presented by some of those heterocycles.



Thanks are due to University of Aveiro and FCT/MEC for the financial support of the QOPNA research unit (FCT UID/QUI/00062/2013) through national founds and, where applicable, co-financed by the FEDER, within the PT2020 Partnership Agreement, and to the Portuguese NMR Network.

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[6]. a) J. L. C. Sousa, O. Talhi, R. F. Mendes, F. A. Almeida Paz, K. Bachari, A. M. S. Silva, *Eur. J. Org. Chem.* **2016**, 3949. b) J. L. C. Sousa, A. M. S. Silva, *Synlett* **2017**, *28*, 316.

2-Amino-5-bromo-3-iodoacetophenone and 5-bromo-2-hydroxy-3-iodoacetophenone as synthons for novel indoles and benzofurans and their annulated derivatives

M.M. Maluleka and M.J. Mphahlele*
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Specially prepared 2-amino-5-bromo-3-iodoacetophenone, 2-amino-5-bromo-3-iodobenzamide and 5-bromo-2-hydroxy-3-iodoacetophenone undergo sequential palladium catalyzed Sonogashira cross-coupling with terminal acetylenes followed by heteroannulation to yield novel 1-(2-aryl-1H-indol-7-yl)ethanones, 2-aryl-1H-indole-7-carboxamides and 7-amino-2-aryl-5-bromobenzofurans, respectively.

Molecular hybridization to append a chalcone moiety to these heterocyclic scaffolds was achieved via initial Claisen-Schmidt aldol condensation of 2-amino-5-bromo-3-iodoacetophenone and 5-bromo-2-hydroxy-3-iodoacetophenone with benzaldehyde derivatives followed by sequential palladium catalyzed Sonogashira cross-coupling and heteroannulation. Boric acid-mediated cyclocondensation of the 3-alkynyl-5-bromoanthranilamides with benzaldehyde derivatives followed by palladium chloride-mediated cyclization, on the other hand, afforded the 2,3-dihydro-1H-pyrrolo[3,2,1-ij]quinazolin-1-ones.[1]

The indole derivatives were transformed into the corresponding 3-trifluoroacetyl substituted derivatives, which were found by single crystal X-ray diffraction to exist as twin crystals.[2,3] The oximes derived from the 7-acetyl–substituted indoles and benzofurans were, in turn, subjected to Beckmann rearrangement followed by hydrolysis to afford the corresponding 7-amino–substituted derivatives. Amino-dechlorination of the 4-chloroquinazoline derivatives with the 7-aminoindoles and 7-aminobenzofurans afforded novel quinazoline-appended indoles and benzofuran hybrids. The anticancer properties of some of the prepared compounds will also be discussed.

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Switchable Rearrangements in 1,2,3-Thiadiazole and 1,2,3-Triazole series

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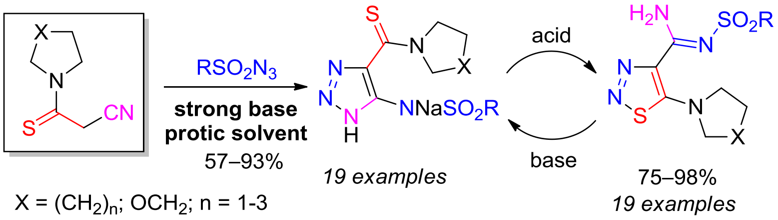
Tetyana V. Beryozkina[a], Mikhail S. Novikov[b]
[a] Ural Federal University, Yekaterinburg, Russia; 620002; [b] St. Petersburg State University, St. Petersburg, Russia, 199034



1,2,3-Triazoles and 1,2,3-thiadiazoles have been receiving permanent interest due to their exciting chemical reactivity including ring rearrangements and transformations to other heterocyclic compounds and valuable organic building blocks. [1,2]

We report here high yield solvent-base-controlled, transition metal-free synthesis of 4,5-functionalized 1,2,3-thiadiazoles and 1,2,3-triazoles from 2-cyanothioacetamides and sulfonyl azides. 2-Cyanothioacetamides were shown to operate under diazo transfer conditions in the presence of a base in an aprotic solvent as C–C–S building blocks produce 5-amino-4-cyano-1,2,3-thiadiazoles exclusively. The use of alkoxide/alcohol system completely switches the reaction course due to the change of one of the reaction centers in the 2-cyanothioacetamide (C–C–N building block) resulting in the formation of 5-sulfonamido-1,2,3-triazole-4-carbothioamide sodium salts as the only products. The latter serve as good precursors for 5-amino-1,2,3-thiadiazole-4-carboximidamides, the products of Cornforth-type rearrangement occurring in neutral protic medium or under acid conditions.

Authors thank RSF, project 15-13-10031 for financial support

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Synthesis of functionalized heterocyclic scaffolds using Post-Ugi transformations

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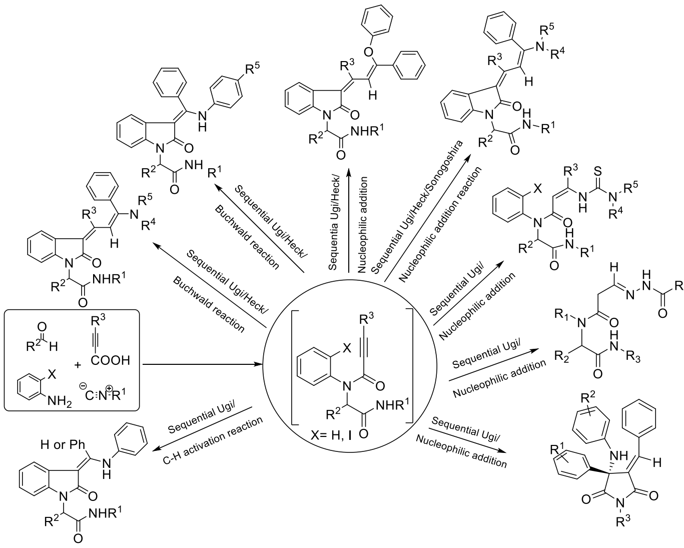
The combination of established isocyanide based multicomponent reactions (IMCR) with post-reaction transformations have become useful tools for generating complex and diverse molecular libraries with novel properties.[1] Among IMCRs, the Ugi-4CR has been used successfully to access α-acylamino-carboxamides. In this context, most noteworthy post-condensation modifications in the Ugi reaction include cycloadditions, cyclo-condensations, or ring-closure metathesises that perform on properly functionalized Ugi adducts to provide efficient routes to synthesize various cyclic scaffolds. Thus, the wise choice of starting materials is essential to providing scaffolds with appropriate functionalities paired for further transformations.[2-3]

In this lecture, an overview of post –Ugi transformation which makes some biologically active heterocyclic skeletons will be presented. Some important synthesized heterocyclic scaffolds such as 2-oxindoles, β-lactams, diketopiperazines, isoxazolino and isoxazolo benzazepines, and spiro compounds are illustratred.[4]



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Natural Product Synthesis enabled by Ir-catalyzed C-H borylation

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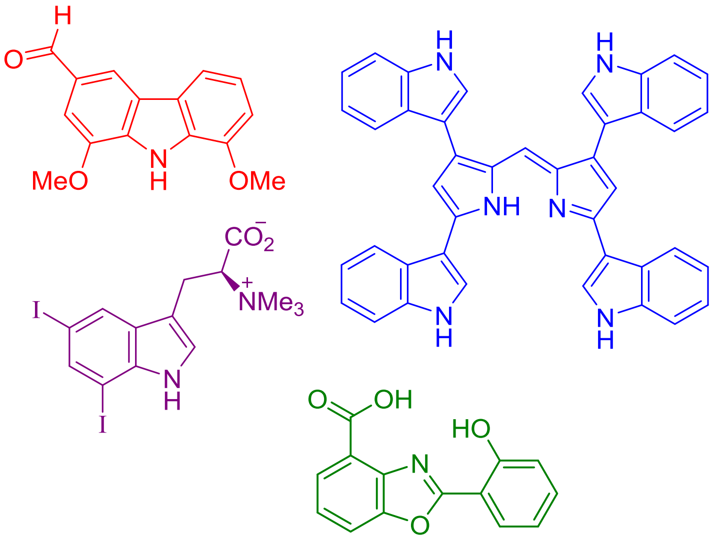
The vast majority of heterocycle syntheses are defined by a cyclization reaction that is typically the key synthetic step. These heterocyclizations require precursors that are not always readily available. A conceptually disparate approach to this traditional methodology would be to subject a simple, readily available heterocyclic scaffold to sequential C-H functionalization reactions,[1] thus avoiding any cyclisation steps. We have found the iridium-catalysed C-H borylation[2] to be successful in this regard and some ongoing natural product syntheses using this approach will be discussed.



[1] Eastabrook, A. S.; Sperry, J. *Aus. J. Chem.* **2015**, *68*, 1810; (b) Eastabrook, A. S.; Sperry, J. *Synthesis*. **2017**, *accepted.*

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Synthesis and Electrochemical Properties of Biindole Compounds

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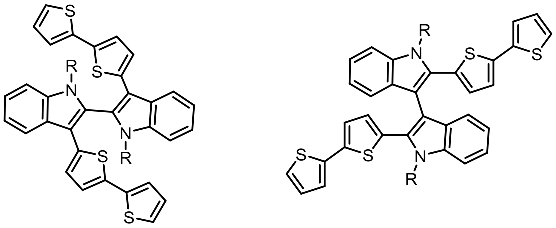
Very recently electroactive chiral polyheterocycles, where chirality is not external to the electroactive backbone but inherent to it, was investigated. Chirality results from a torsion generated by the periodic presence of atropisomeric, conjugatively active biheteroaromatic scaffolds, (3,3'-bithianaphthene).[1-3]



More recently, with the aim to investigate the properties of indole derivatives substituted with oligothiophene frameworks we afforded two different constitutional isomers by methodologies used by Arcadi and coworkers.[4-5]

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Abe, Kazumi **WED-P 56**

Development of Electron-Poor Phosphine Ligands Having 1,3,5-Triazinyl Groups

Agarwal, J. **Flash Presentation WED Track 1 WED-P 4**

First Enantioselective Synthesis of VAChT Inhibitors Vesamicol, Benzovesamicol, Spirovesamicols and Other Analogues

Akatsuka, Shuji **WED-P 107**

Conversion of Ester Moieties to Bromophenol

Akiyama, Toshiki **TUE-P 41**

Ruthenium nanoparticles-catalyzed ligand-free Suzuki-Miyaura Coupling

Al-Saedy, Muhannad Abdul-Redha **TUE-P 95**

Accounting for Different Reactivities of Sulfinate and Thiosulfate Salts in Regioselective Azetidine Coupling via C-H Sulfenylation of Indoles and First Formal Synthesis of Methyl Echinosulfone A Alkaloid.

Altmann, Lisa-Marie **TUE-P 142**

Development of Photochromic Kinase Inhibitors based on Fulgimides

Ambeu, N'ta Christelle Mélissa **WED-P 23**

Potential New Store-Operated Calcium Entry (SOCE) inhibitors from benzimidazole-azole linked derivatives for cancer

Ando, Yoshio **TUE-P 82**

Stereospecificity in Intramolecular Photoredox Reactions of Naphthoquinones: Enantioselective Total Synthesis of (–)-Spiroxin C

Ardkhean, Rchuta **WED-P 133**

Chiral ligand design for Copper catalysed conjugate addition with the aid of quantitative structure-selectivity relationship

Armitage, Georgina K. **WED-P 65**

Adapting The Zav’yalov Pyrrole Synthesis to Access 4-Acetoxy- and 4-Acetamido- Pyrrole-3-carboxylates

Arndt, Sebastian **TUE-P 18**

Simple Synthesis of Phosphindolium-Cored Structures

Aydiner, Burcu **Flash Presentation TUE Track 2 TUE-P 64**

Microwave-Assisted Synthesis of a Novel Series 2-(Coumarin-3-yl)imidazo[1,2-a]pirimidin Fluorophores as Water Soluble Fluorescent Light-Up pH Probe For Acidic Environment

de Azevedo, Orlando **WED-P 63**

Synthesis and Photoswitching of Naphthopyran Rhenium Complexes

Baaziz, Samira **WED-P 100**

Functionalization of dehydroacetic acid by electroactive moieties

Baba, Takumi **WED-P 81**

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Baker, Blake **Flash Presentation TUE Track 2 TUE-P 61**

A green, robust and scalable continuous-flow synthesis of fused 3-aminoimidazo-heterocycles

Bamberger, Julia **TUE-P 36**

Synthesis of 3-Benzazepines by Metal-Free Oxidative C–H Bond Functionalization–Ring Expansion Tandem Reaction

Banerjee, Arpan **Flash Presentation TUE Track 1 TUE-P 32**

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Synthesis of Spiropyrrolizines and Dihydro-1H-Pyrrolizines via [2+3] Cycloaddition Reactions

Bayer, Patrick **TUE-P 119**

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Baytas, Sultan **TUE-P 115**

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Bürger, Marcel **WED-P 131**

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Burtoloso, Antonio C.B. **WED-P 22**

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Byk, G. **TUE-P 11**

A NEW MULTICOMPONENT MCR4 REACTION FOR THE SYNTHESIS OF CHIRAL ANALOGS OF STAUROSPORINE

Capci Karagöz, A. **Flash Presentation WED Track 2 WED 112**

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Carmona Asenjo, Ana T. **TUE-P 132**

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Chandrasekhar, Attoor **WED-P 110**

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Chein, Rong-Jie **TUE-P 143**

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Da Silva Junior, Paulo Eliandro **WED-P 115**

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Didier, Dorian **Flash Presentation WED Track 2** **WED-P 130**

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A successful bioisosteric replacement in the design and synthesis of potent and selective HDAC6 inhibitors

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A novel [4+1]-cyclization using allenoates

Synthesis of 1,4-dihydropyridine linked bis-triazoles as fluorescent sensors for detection of iron(II) and iron(III)

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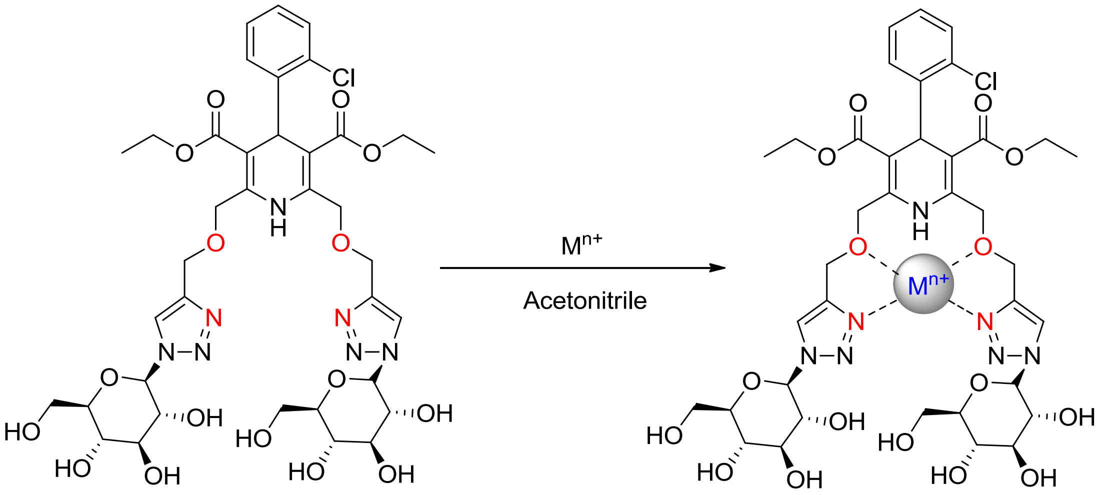
Abstract

Development of transition metal ion sensors has received a great deal of attention due to their relevance in environmental and biological processes. Copper and Iron ions play an important role in different biological processes. Balanced concentration of copper ions is required for smooth functioning of the liver and kidney whereas their accumulation leads to adverse effects on the gastrointestinal process in addition to damage to the liver and kidney.[1]while excess of iron(III) leads to cancer, hepatitis, hemochroma-tosis, and dysfunction of vital organs.[2]

This prompted us to synthesize a new class of water soluble Dihydropyridine – linked bis-triazoles as fluorescent sensors for recognition of metal ions. Presence of sugar or glycerol unit to enhances solubility of these fluorescent sensors. These bis–triazoles are also expected to be of pharmacological importance[3].



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Chemistry of Biologically Active Marine Natural 1,2,3,4-Tetrahydroisoquinoline. Unpredictable Photochemical Transformation of Renieramycin Type *p*-Quinone into Ecteinascidin Type Phenol

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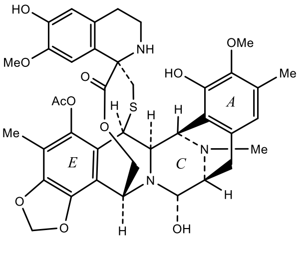
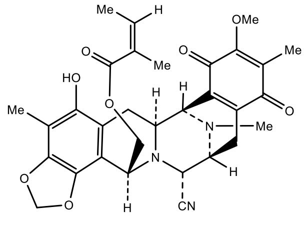
Bis-1,2,3,4-tetrahydroisoquinoline (THIQ) natural products along with their reduced form, such as renieramycins, jorunnamycins, cribrostatin 4, and ecteinascidins have persistently attracted considerable interest for more than three decades due to their novel structures and meagre availability in nature as well as their potent antitumor activity. Among them, ecteinascidin 743 (Et 743: **1**) is currently marketed in over seventy countries for the treatment of soft-tissue sarcoma and phase II/III clinical trials for the treating other cancers are ongoing.

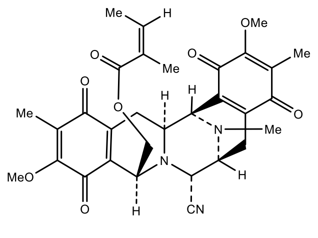
In the course of our research of new metabolites through the isolation and characterization of biologically active compounds together with many synthetic analogues, we have succeeded to isolate and elucidate the structures of renieramycins from Thai blue sponge, *Xestospongia* sp after stabilization of the marine organism homogenized in phosphate buffer solution by the addition of KCN. [1] We have also reported total synthesis of several renieramycin group of marine natural products along with identified the trace metabolite renieramycin T (**2**), which possesses a highly functionalized aromatic *E* ring bearing a characteristic substitution pattern as that of Et 743. [2] As it might be very interested in reneramycin T, we have recently finished total synthesis of **2**. [3] We report here an unpredictable photo-induced transformation of *p*-quinones into the ecteinascidin type arene at the *E* ring. This procedure is able to find that a diluted CH_2Cl_2 solution of renieramycin M (**3**) was stirred at 25°C with sun light afforded **2** in excellent yield.



ecteinascidin 743 (**1**)



renieramycin T (**2**)



renieramycin M (**3**)

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Ru(II)- or Rh(III)-Catalyzed Grignard-Type C−H Additions of Indolic Scaffolds with Activated Aldehydes and Ketones

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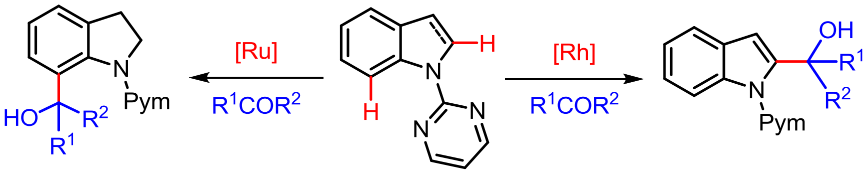
The indole heterocycle is among the most important structural motif found in natural products and pharmaceuticals with a broad spectrum of medicinal applications. In particular, many pharmaceutical agents include C7-substituted indoline and C2-substituted indole frameworks. With advances in catalytic C−H bond functionalization, it has been recognized as the most straightforward protocol leading to highly functionalized indoles and indolines. Recently, a great deal of effort has been made toward the directing-group assisted transition-metal-catalyzed C−H functionalization of indoles at the C2-position. In addition, the catalytic C−H bond functionalization of indolines at the C7-position has been intensively explored. For instance, arylation, alkenylation, alkylation, acylation, amidation, and alkynylation of indolines at the C7-position were investigated. Direct C−H additions to produce the desired alcohols can be realized by using electron-deficient aldehydes and ketones as the acceptors. To the best of our knowledge, there has been no example on the ruthenium-catalyzed nucleophilic addition of sp^2 C−H bonds to aldehydes and ketones.

Inspired by recent studies on the catalytic functionalization of indoles and indolines, we herein disclose the ruthenium(II)- or rhodium(III)-catalyzed site-selective C−H addition reactions of indolines and indoles to aldehydes and ketones via C–H bond activation.



Ruthenium(II)-Catalyzed Site-Selective Acylation of Indolinic C-H Bonds with Ethyl Glyoxalate

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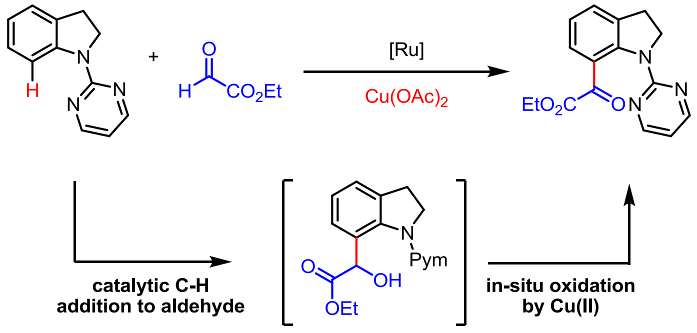
The C7-functionalized indolines have been recognized as important structural motifs found in a number of natural and synthetic products. With the development of catalytic functionalizations of inactive C-H bonds, it has become the most attractive strategy leading to C7-functionalized indolines. In this context, acylation, arylation, olefination, alkylation, amination, alkynylation and thiolation of indolines at the C-7 position were described bifunctional α-ketoesters can act as important backbones in some natural products, such as the 3-deoxy-2-ulosonic acids and their derivatives. In addition, aryl α-ketoesters have been used as useful intermediates for the synthesis of bioactive molecules such as potent inhibitors of proteolytic enzymes, inhibitors of leukotriene A4 hydrolase, photopolymerization initiators, and antisunburn agents.

Since α-ketoesters bear two vicinal functional groups, strongly electron-deficient carbonyls and neighboring binding-capable esters, it makes them useful synthons for asymmetric reduction, aminohydroxylation, fluorination, aldol reactions, lactonization, tandem heterocyclization and construction of various bioactive natural products. Due to the significance of α-ketoesters, various classical procedures have been reported including oxidation of a-hydroxyl esters using various kind of oxidants, Friedel-Crafts acylation, oxidation of methyl 2-phenylacetate, hydrolysis and esterification of acyl cyanides, and other methods. In addition, there have been numerous reports for the synthesis of α-ketoesters under metal catalysis or under metal-free conditions with different coupling partners.

Recently, the directing group-assisted catalytic addition reaction of inactive C(sp^2)-H bonds to carbonyl compounds has emerged as a green and atom economical strategy to afford the corresponding secondary or tertiary alcohols. Very recently, our research group disclosed the catalytic addition reaction of heterocyclic C-H bonds to activated aldehydes or ketones furnishing the corresponding secondary and tertiary alcohols. During the optimization of reaction conditions in the coupling of indolines and ethyl glyoxalate, we found that a Cu(OAc)$_2$ additive provided C7-indolinyl ketoesters as major products instead of alcohol compounds. Inspired by this interesting finding, we herein report the first Ru(II)-catalyzed site-selective acylation of indolinic C-H bonds with ethyl glyoxalate affording C7-indolinyl α-ketoesters.



Redox-Neutral Coupling Reaction of *N*-Acyl Ketimines with Maleimides under Rhodium Catalysis

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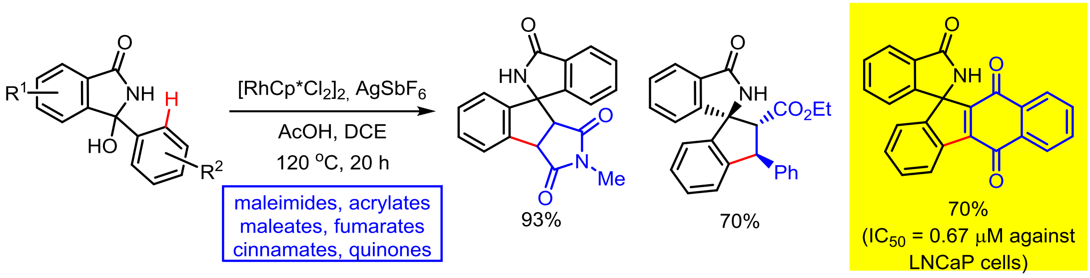
Isoindolinones are among the most interesting class of nitrogencontaining heterocycles, as they are found in various natural products and biologically active compounds. Among those, spiroisoindolinones also have their own importance as they exhibit various properties such as aldose reductase inhibition or can act as chemical sensors. imines have been utilized for the [3 + 2] cyclization reaction to provide aminoindanes or aminoindenes under transition-metal catalysis. In this context, cyclic imines are of prime importance as they could lead to the formation of spirocompounds via a [3 + 2] annulation reaction. In particular, a number of reactions have been carried out on cyclic N-sulfonylketimines under various transition-metal catalysts.

Herein, we report the [3 + 2] annulation reaction between cyclic N-acyl ketimines generated in situ by the dehydration of 3-aryl-3-hydroxyisoindolin- 1-ones and activated olefins for the formation of various spiroisoindolinone frameworks. Furthermore, the synthesized spiroisoindolinones have been evaluated for the cytotoxic effect against androgen-sensitive human prostate adenocarcinoma cells (LNCaP), human prostate adenocarcinoma cells (DU145), human endometrial adenocarcinoma cells (Ishikawa), human breast cancer cell (MCF-7), and triple negative human breast cancer cells (MDA-MB-231).



Rhodium(III)-Catalyzed Trifluoromethylallylation of Indolic Scaffolds with CF_3-Substituted Allylic Carbonates

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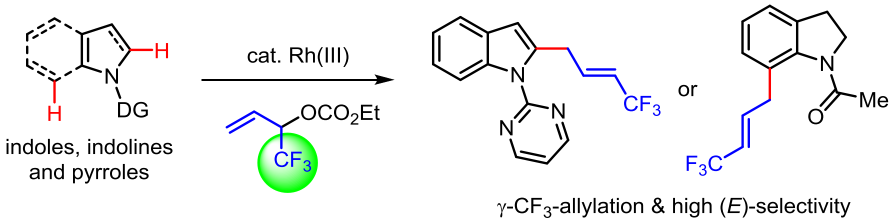
With considerable progress in medicinal chemistry, the incorporation of fluorine or fluoroalkyl groups in pharmaceuticals and biologically active molecules have gained increasing attention in the past decades. In particular, the trifluoromethyl group is prevalent in pharmaceuticals, agrochemicals, and functional materials. Owing to its unique characteristics such as high electronegativity, hydrophobicity, metabolic stability, bioavailability and binding affinity, trifluoromethyl groups into organic molecules can bring beneficial effects on pharmacokinetic properties. Recently, the directing group assisted trifluoromethylation of aromatic C–H bonds using various electrophilic and nucleophilic CF_3 sources has been disclosed. In addition, the photoredox catalysis and radical process also provided the facile access to the formation of aromatic $C(sp^2)–CF_3$ bonds. In contrast to aromatic C–H trifluoromethylation, the olefinic and alkynyl trifluoromethylations have been less explored. With the development of catalytic C–H bond functionalization, the direct C–H allylations have been performed using various metal catalysts. However, the CF_3-containing allyl substrates have rarely been explored in the C–H allylation strategy.

We herein present the first directing group assisted Rh(III)-catalyzed γ-trifluoromethylallylation of various heterocyclic C–H bonds with α-trifluoromethyl allyl carbonate.



Tandem C–H Olefination and Cyclization of Benzamides with Various Alkenes under Rhodium Catalysis

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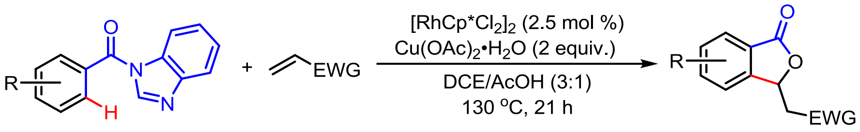
With considerable progress in medicinal chemistry, the construction of *O*-heterocycles has received increasing attention in the past decades. In particular, phthalides are widely found to be biologically relevant scaffold in natural products, pharmaceuticals, agrochemicals, and functional materials. For example, *n*-butylphthalide (NBP) is currently in the market as an antiplatelet drug for ischemia-cerebralapoplexy, and has led to the development of phthalides as a class of pharmaceutically important natural products. In addition, mycophenolic acid is under clinical trial for the prevention and reversal of transplant rejection and anticancer.
The transition-metal-catalyzed C–H activation reactions have been recognized as a powerful tool in organic and medicinal chemistry. In this context, the direct formation of heterocycles has recently been studied using various metal catalysts. Among them, secondary amide groups have been intensively used for the formation of isoindolinones, dihydroisoquinolones, 2-quinolinones, phenanthridinones, isoquinolones/pyridiones, azepinones, benzoisoxazoles, and etc.

In sharp contrast to annulation reaction of sencondary amide groups, tertiary amide groups have been rarely used for the formation of cyclic compounds. We herein described the synthesis of phthalides through tandem rhodium-catalyzed C-H olefination and annulation of benzamides.



Rhodium(III)-Catalyzed C(sp^3)–H alkylation of 8-Methylquinolines with Allylic Alcohols in Water

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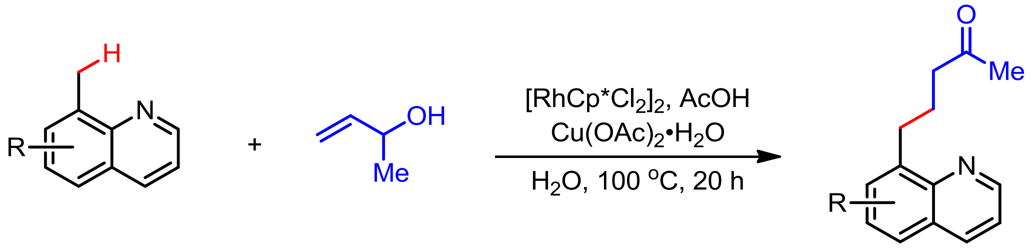
The rhodium(III)-catalyzed cross-coupling reaction of 8-methylquinolines with a range of allylic alcohols in water is described. This approach leads to the synthesis of various γ-quinolinyl carbonyl compounds, which are synthetically useful precursors for the construction of bioactive tetrahydroquinoline and azasteroid derivatives. Induced by the need to streamline the synthesis of valuable building blocks and complex molecules, the transition-metal catalyzed C–H bond activation has evolved as an important field in organic synthesis. It has attracted tremendous interest in developing cross-coupling reactions at low cost without the use of stoichiometric amounts of organometallic reagents.

In particular, C(sp^2)–H functionalization has been studied to a greater extent, whereas less research attention has been paid to the activation of C(sp^3)–H bonds. In this area, sp^3 C–H functionalizations have been executed with the assistance of a range of chelating auxiliaries such as amides, carboxylic acids, oximes, N-heterocycles, etc. In particular, 8-methylquinolines have been found to be good substrates for sp^3 C–H functionalization due to their ability to form cyclometalated complexes. In this context, amination, acylation and alkenylation reactions have been studied with various catalysts using different coupling partners. However, sp^3 C–H alkylation of 8-methylquinolines has rarely been explored. Although the catalytic C–H bond functionalizations provide atom economy, which constitutes a great contribution to the cross-coupling reaction, most of these reactions have been carried out in organic solvents. Thus, another important step to make these cross-coupling reactions more interesting is the use of water as a solvent. Undeniably, water as a solvent has many advantages over conventional organic solvents, because it is inexpensive, nontoxic, non-polluting, non-flammable and readily accessible.

In addition, the unique physiochemical properties of water such as the hydrogen-bonding effect and amphiphilicity can strongly influence the reactivity and selectivity of catalysts and reagents. As a result, various efforts have been made recently in the development of catalytic sp^2 C–H functionalization processes by employing water as a solvent or medium to accomplish efficient synthesis of organic compounds. In continuation of our Rh(III)-catalyzed sp^2 and sp^3 C–H alkylations, we herein report for the first time the C(sp^3)–H alkylation of 8-methylquinolines with allylic alcohols in water as a green solvent.



Synthesis of C7-Aminated Indolines with Anthranils under Rhodium Catalysis

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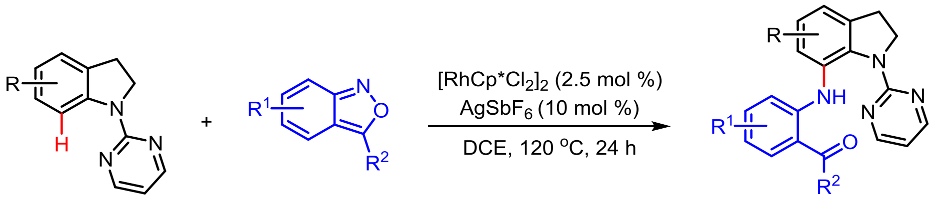
Transition-metal-catalyzed C–N bond formation reactions based on the C–H bond activation strategy have been of great significance in organic synthesis and medicinal chemistry due to the prevalence of nitrogen-containing bioactive molecules.[1] For the introduction of amino groups, various amino surrogates such as N-carboxylates, N-tosylates, N-fluorobenzenesulfonimide (NFSI), organic azides and dioxazolones have been investigated as relevant sources for C–H amination reactions. Very recently, anthranils have also been employed in the direct C–H amination reactions of sp^2 and sp^3 C–H bonds. Recently, the directing group-assisted C7-functionalization of indolines has been an interesting area due to the prevalence of a range of bioactive natural products and pharmaceutical agents. In this regard, acylation, arylation, alkylation, alkynylation, and olefination at the C7-position of indolines have been developed via the C–H activation protocol.

In continuation to our recent works on the rhodium(III)-catalyzed site-selective C–H functionalization of indolines, we herein report the Cp*Rh(III)-catalyzed direct amination of indolines with anthranils to afford C7-aminated indolines tethered to an electrophilic carbonyl group.[2] Particularly noteworthy was the resulting framework containing amino and carbonyl groups, which represents an important synthetic building block to readily convert to biologically interesting heterocycles.



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Cross-Coupling Reaction of 8-Methylquinolines with Maleimides under Rhodium Catalysis

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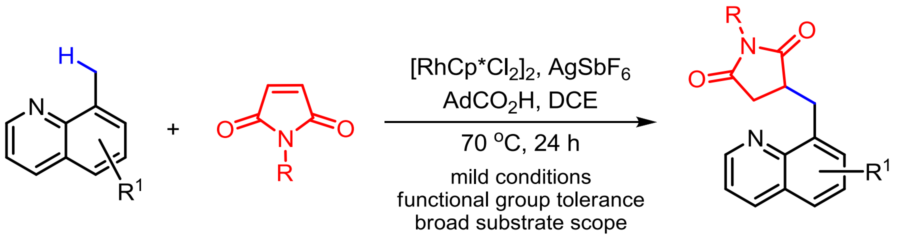
Transition-metal-catalyzed C–H bond activation and its subsequent functionalization has been one of the most attractive topics in organic synthesis because of its remarkable potential for atom economy and environmental sustainability. In this addition, a variety of C(sp^2)–H functionalization has been developed under metal catalysis in the past decade. Recently, much attention has been moved towards the C(sp^3)–H functionalization events, which continue to be a challenging issue. In this area, directing group assisted sp^3 C–H functionalization has been explored by use of amides, carboxylic acids, oximes, *N*-heterocycles, and etc. In particular, 8-methylquinolines have been found as good substrates for sp^3 C–H functionalization due to its ability to form cyclometalated complexes. Succinimides have been recognized as privileged structural cores found in a number of bioactive natural products, pharmaceuticals, and functional materials. Furthermore, the reduced derivatives such as pyrrolidines and γ-lactams have been also found in a large number of pharmaceutical relevant molecules, thus making them one of the most important and promising compounds.

We herein describe the first C(sp^3)–H activation of 8-methylquinolines and subsequent functionalization with maleimides to afford various succinimide derivatives.



A NEW MULTICOMPONENT MCR4 REACTION FOR THE SYNTHESIS OF CHIRAL ANALOGS OF STAUROSPORINE.

M. Gellman, T. Massarano, R. Lavi and G. Byk*
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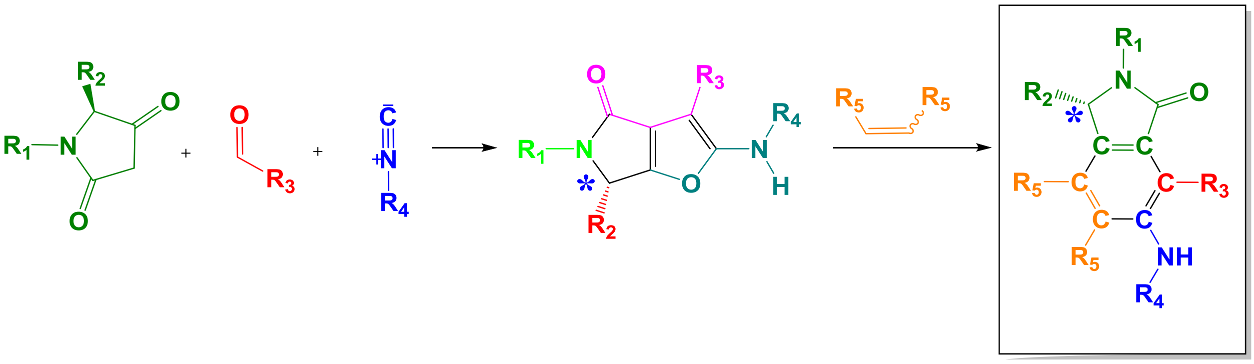
Multicomponent reactions are of special interest because they can generate in a single reaction complex molecules, such as hetero aliphatic and hetero aromatic polycyclic rings, and can be adapted to parallel automated synthesis. Special attention was devoted to Staurosporine, a natural alkaloid, which acts as non-selective inhibitor of protein kinases and induces apoptosis. Thus, its derivatives have potential applications for cancer treatment. This compound is characterized by a hexa-substituted benzene ring with a fused indole ring and a fused lactam ring. Two recent works deserved as driving forces for the synthetic strategy we present here: the first a conceptually new strategy for the synthesis of the hexa-substituted benzenes. The key-step of the reaction was the generation in situ of a furan intermediate which upon the presence of appropriate dienophiles undergoes Diels Alder reaction resulting in a non-stable intermediate that after rearrangement produces hexa-substituted benzenes [1]. The second, proposed the formation of substituted furans by reacting barbituric acid with isocyanides and aldehydes at room temperature [2]. Herein we combined both approaches for obtaining novel hexa-substituted benzenes. The advantage of the new approach is that chiral derivatives can be easily obtained. We have developed a new “Ugi like” MCR4 by using chiral β-keto-γ-lactams as precursors. The reaction can be performed both in solution and in solid phase. Products display significant biological activity in XTT viability assays in different cell lines. The mechanism of action will be discussed.



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Highly Enantioselective Allylation of Ketones – An Efficient Approach to all stereoisomers of Tertiary Homoallylic Alcohols

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im Forschungszentrum Jülich, Jülich/Germany
[b]*Department für Chemie, Universität zu Köln, Cologne/Germany*
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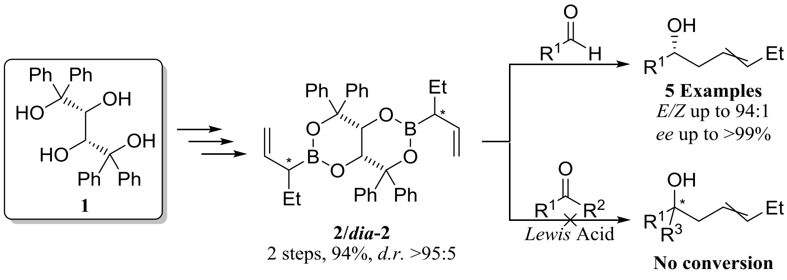
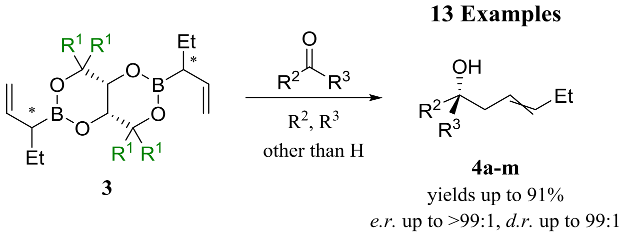
The boron based allylation of carbonyl compounds is an effective and reliable tool for the generation of enantiomerically pure homoallylic compounds, a moiety of widespread presence [1]. As a very potent agent on this behalf, we developed tartrate derived protecting group **1** providing an outstanding reactivity/stability balance. Thus, the convenient and highly selective syntheses of all four stereoisomers of secondary homoallylic alcohols depending on the configuration of the corresponding allylboronate **2/*dia*-2** could be demonstrated. However, due to their inherently lower reactivity, ketones remained inert to the systems established [2].



In order to overcome this problem, rational reagent design was employed 'tuning' the reagents' reactivity suitably. Herein we present new allylation reagents **3** enabling the very convenient and highly selective generation of all stereoisomers of tertiary homoallylic alcohols **4a-m**. Not only can the 2nd generation compounds be utilized without requiring inert conditions, but moreover highly selective access to *E*- and *Z*- configured tertiary homoallylic alcohols was given for the first time. Conclusively, all synthetic approaches and findings were investigated by DFT-calculations, revealing further mechanistic insight and rationalizing the presented methodology thoroughly.



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Synthesis of substituted octahydrochromenes, promising inhibitors of tyrosyl-DNA phosphodiesterase I

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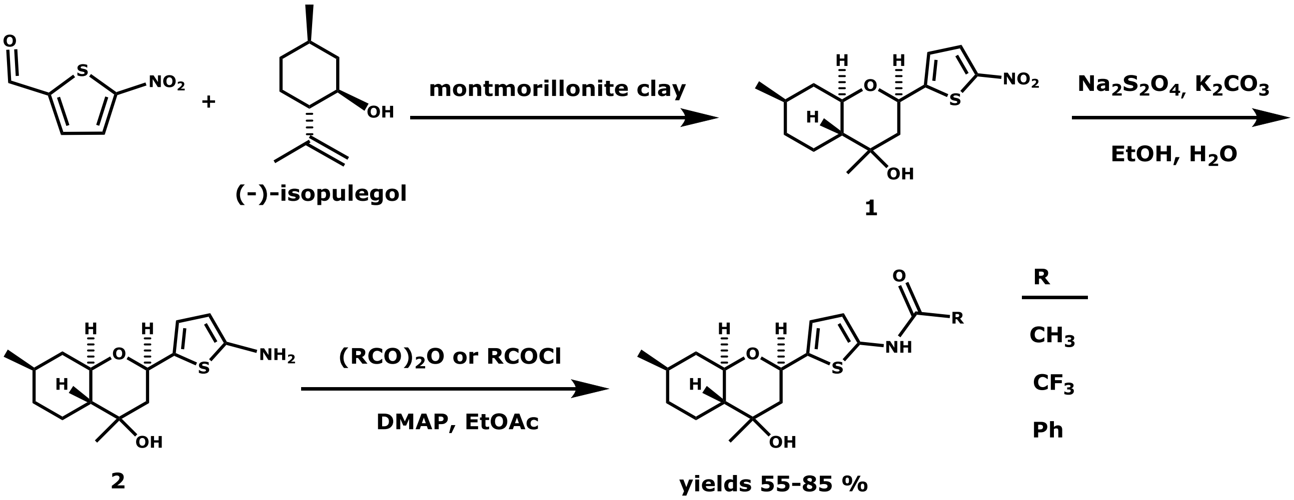
It was found earlier that reaction between (-)-isopulegol and heteroaromatic aldehydes in the presence of K10 montmorillonite clay led to formation of compounds with octahydrochromene framework [1]. Some products demonstrated promising biological activity, e.g. high analgesic activity [2].

In this work, we have developed a method for synthesizing octahydrochromenes containing an amide groups. We carried out the reactions of (-)-isopulegol and 5-nitrothiophene-2-carbaldehyde in the presence of K10 montmorillonite clay to get nitro compounds **1**. Successive reduction of compounds **1** to corresponding amines **2** and selective acylation of the amino groups results in the desired products.



It was found that the obtained products exhibit inhibitory activity in low micromolar concentration range against tyrosyl-DNA phosphodiesterase I (Tdp 1). Tdp1 plays a crucial role in the removal of DNA damage, caused by anticancer drugs, e.g. camptothecin and its derivatives. It is making it a perspective target to enhance anticancer treatment in combination with DNA damaging therapies.

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One-pot synthesis of 1,5,3-oxathiazepanes via the three-component condensation

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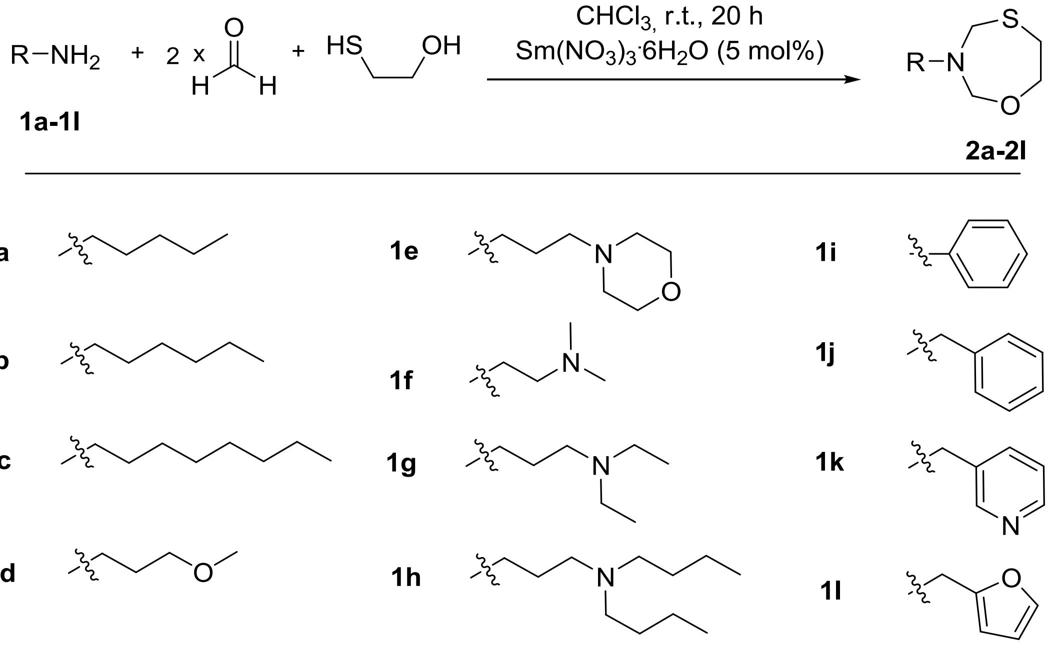
The development of new heterocyclic systems is of interest not only as examples of fundamental achievements in organic chemistry, but as valuable sources of pharmaceutical products and raw materials for various industrial sectors. The interest in multicomponent reactions (MCRs) has increased in recent years and are an area of focus in heterocyclic chemistry due to their atom economy, mild reaction conditions and high convergence. [1] The three-component condensation reaction of primary amines, formaldehyde and 2-mercaptoethanol using salts of transition and rare earth metals as catalysts was developed to obtain new 7-membered heterocyclic structural building block, 1,5,3-oxathiazepanes, in good to excellent yields. No reports have been published of the synthesis of this structural block. The structure of the heterocyclic fragment was confirmed by NMR spectroscopy.



This work was supported by Foundation by the Russian Foundation Research (N 15-03-00193A)

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New Azaheterocycle Derivatives of Phosphonic Acid as Perspective Bioactive Compounds and Polydentate Ligands

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L.I. Livantsova, V.I. Terenin, V.S. Petrosyan
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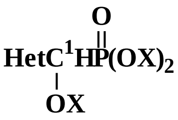
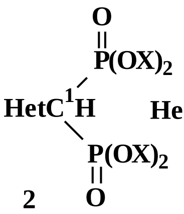
Functionalized organophosphorus acids and their derivatives with heterocyclic moieties are of great interest as effective chelating ligands and perspective bioactive substances with various properties. These acids are well-known biomimetics of hydroxy- or aminocarboxylic acids and natural pyrophosphates, and some of them such as zoledronic, risedronic, and minodronic acids are widely used in medicine [1]. We have synthesized the new functionalized phosphonic acids and their derivatives **1-5** including azaheterocycles *via* addition of tris(trimethylsilyl) phosphite to azaheterocyclic formamides and ketones. Trimethylsilyl-containing organophosphorus compounds easily react with methanol excess or with sodium methylate in methanol giving water soluble acids or their sodium salts in high yields [2,3].



$\mathrm{HetC^1H(OX)P(O)(OX)_2}$

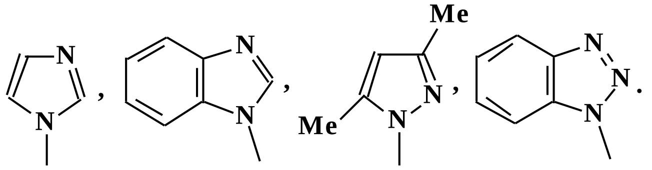
1

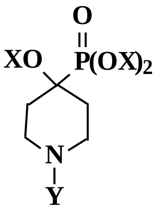


$\mathrm{HetC^1H[P(O)(OX)_2]_2}$

2

Het =





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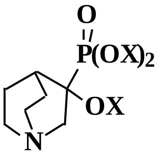

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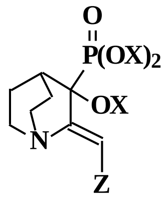

5

X = H, Me$_3$Si, Na; Y = H, Me, Bn, Ac, MeSO$_2$;
Z = 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, Fc.

The resulting compounds are the perspective biologically active substances and polydentate ligands with versatile properties as well as the promising precursors for multitarget drug discovery. This work was financially supported by the RFBR (grants numbers 15-03-00002 and 17-03-00169).

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Mono- and Bisorganophosphorus Proline Derivatives with P-C-N Moieties

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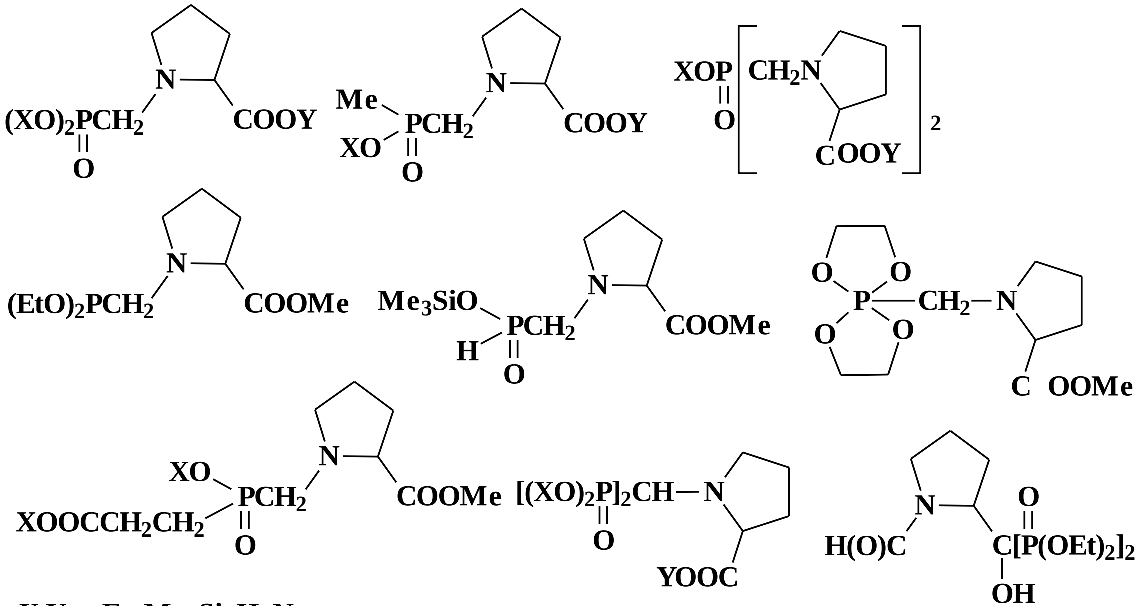
The functionalized organophosphorus derivatives of aminocarboxylic acids and their corresponding peptides are the perspective organophosphorus biomimetics of natural phosphates and hydroxy or amino acids. These compounds with nonhydrolysable P-C bonds interfere with various enzymatic processes and possess the antibacterial, antiviral, antibiotic, pesticidal, antitumor and enzyme inhibitory properties. Several phosphorus containing peptides with proline moieties have attached attention in the capacity of the competitive inhibitors of human immunodeficiency virus protease [1]. Recently the organophosphorus derivatives of glycine, β-alanine and γ-aminobutyric acid with PCH_2N moieties have been synthesized by us [2]. We have developed a convenient two- or three-component aminomethylation of varios PH-acids as the perspective method for synthesis of mono- and bisorganophosphorus proline derivatives with P-C-N moieties using proline or its highly reactive functionalized precursors. Trimethylsilyl-containing organophosphorus compounds easily react with methanol excess with formation of water soluble acids in high yields.



X,Y = Et, Me_3Si, H, Na

The resulting compounds are the promising synthons for preparation of various organophosphorus peptides with different arrangement of proline moieties as well as the perspective polydentate ligands and biologically active substances with versatile properties. This work was financially supported by the RFBR (grants numbers 15-03-00002 and 17-03-00169).

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One-pot synthesis of cyclic ethers using phosphonium salts

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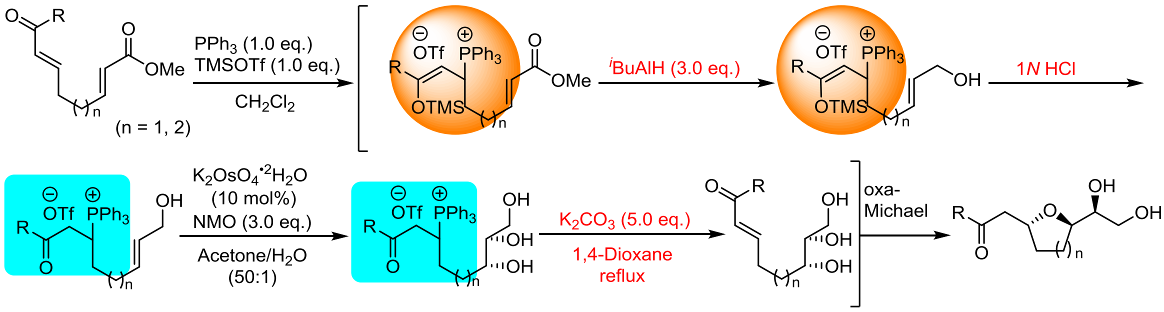
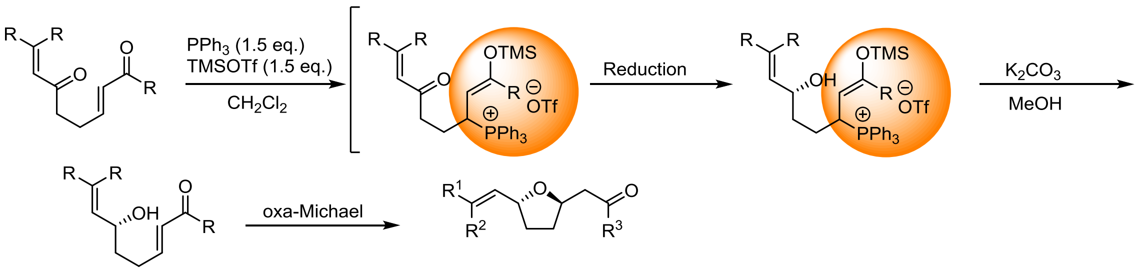
Discriminative transformation of one of the two functional groups having similar reactivity is important subject especially in the synthesis of multi-functional compounds such as natural products. We have been developing such transformation of carbonyl compounds using *in situ* protection methodology,[1] 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-disubsitututed enone in the presence of β-monosubsitututed 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 nice way for concise 6-steps one-pot synthesis 5-and6-membered oxacyclic compounds were in 57 to 68% yields (**Scheme 1**).



Scheme 1. One-pot synthesis of cyclic ethers using 2 types of phosphonium salts.

In relation to the substrates having β-monosubsitututed enone and β-disubsitututed enone in the same molecule afforded a nice way for concise 4-steps one-pot synthesis of 5 membered oxacyclic compounds in 62 to 71% yields (**Scheme 2**).



Scheme 2. One-pot synthesis of cyclic ethers using phosphonium salts.

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Simple Synthesis of Phosphindolium-Cored Structures

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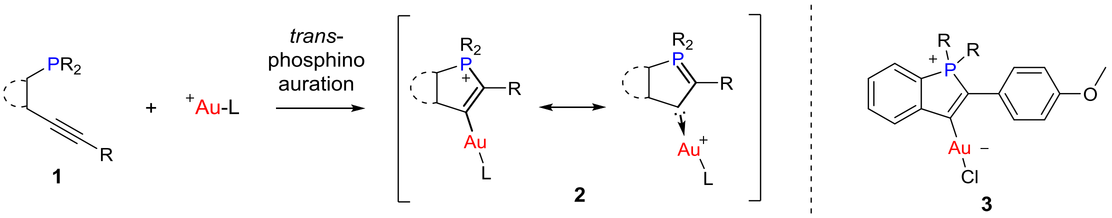
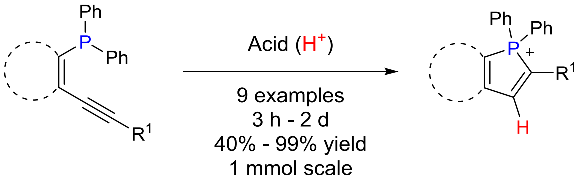
Organisch-Chemisches Institut Ruprecht-Karls-Universität Heidelberg, Heidelberg/69120

The intramolecular phosphinoauration of alkynes is presented comprising the synthesis of stable, aurated phosphindolium complexes **2** from easy accessible (*o*-alkynylphenyl)phosphines **1**. In order to overcome the strong bonding affinity of phosphine to gold, an FLP-motivated approach was attempted. Upon formation of a mixed phosphine NHC/phosphine phosphine gold species, elevated temperatures induced the cyclization to give **2**. This concept could furthermore be extended to overall neutral (phosphindolium)aurate complexes **3** featuring the yet unknown phosphindole ligand (Scheme 1).[1]



Scheme 1. Gold-mediated *anti*-phosphinoauration of unactivated alkynes.

The second part of the talk will focus on the synthesis of π-extended phosphindolium salts by simple proton-induced cyclization. During the course of our study the acid-mediated cyclization was discovered (Scheme 2). The process allows for a general metal-free and extraordinary simple protocol towards the target structures. The rearrangement proceeds in complete atom economy without the need for further purification. Photophysical measurements recorded quantum yields up to 97% in solution (Scheme 3) and fluorescence was observed in the solid state.[2]



Scheme 2. Protophosphonylation of (*o*-Alkynylphenyl)phosphanes.

Scheme 3. Fluorescence in solution.

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Synthesis and antibacterial activity of fluorinated oxazolopyridine from pentafluoropyridine

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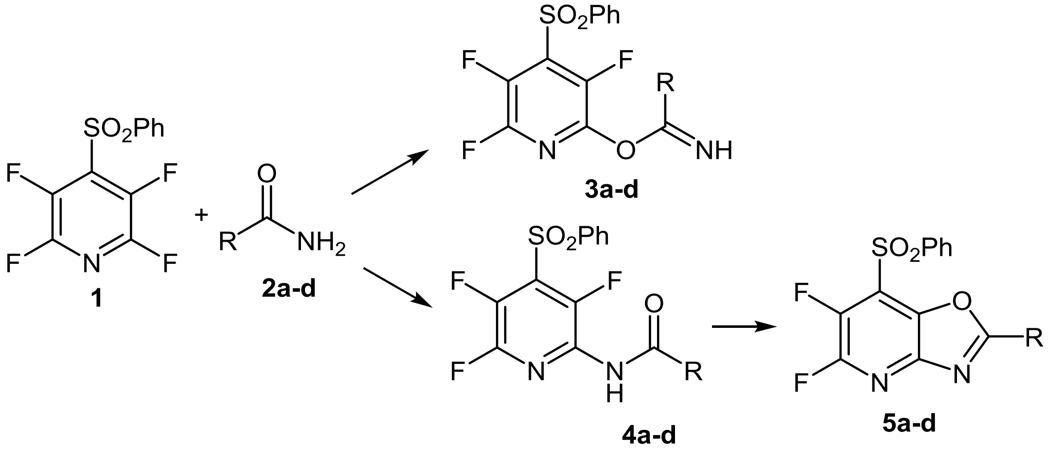
Perfluorinated heteroaromatics are useful scaffold for synthesis of a wide range of corresponding heterocycles because of their high reactivity toward nucleophilic attack that result from their electron-deficient nature [1]. The order of nucleophilic attack on pentafluoropyridine follows the sequence 4-F > 2-F > 3-F [2]. However, this site-reactivity order may be impressed by each substituent once attached to the heterocyclic ring and the nature of the attacking nucleophile.

Continuing our research on synthesis of new perhalo heterocyc;ic compounds, we investigate the reaction of amides with 4-phenylsulphonyl tetrafluoropyridine to synthesis of ozazolopyridine. Attempt to intrermolecular cyclization of **4a-d**, in the presence of potassium carbonate and in the DMF as solvent led to 4,6,7-trifluoro-2-methyloxazolo[5,4-c]pyridine **5a-d.** Two resonances by ^{19}F NMR (-92 and -149 ppm), indicate displacement of fluorine atom attached to the 2 and 3-position of the pyridine ring by the nitrogen and oxygen nucleophiles.



The Medium used for the antibacterial testing was nutrient agar media (NAM) of the following composition: peptone 10 g; beef extract 6 g; sodium chloride 10 g; agar 3% and final volume of the media was adjusted to 1 l with distilled water and autoclave at 15 lbs/in2.

The newly synthesized compounds **4a-d** were screened for their antibacterial activity against Gram-positive bacteria i.e. Staphylococcus aureus (MTCC 96) and Gram-negative bacteria i.e. Escherichia coli (MTCC 1652) using the disc diffusion assay technique and minimum inhibition concentration (MIC) method. Compounds **5a**, **5b** and **5d** showed moderate antibacterial activity against Gram-positive bacterium, Staphylococcus aureus.

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Ruthenium-catalyzed 1,6-enyne cycloisomerization of *o*-alkynyl phenyl enol ether; synthesis of 2,3-disubstituted benzo[*b*]furan

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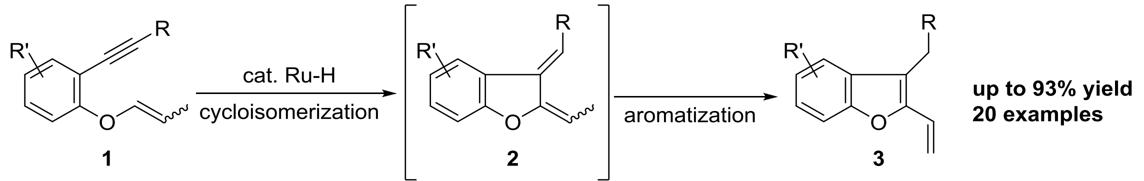
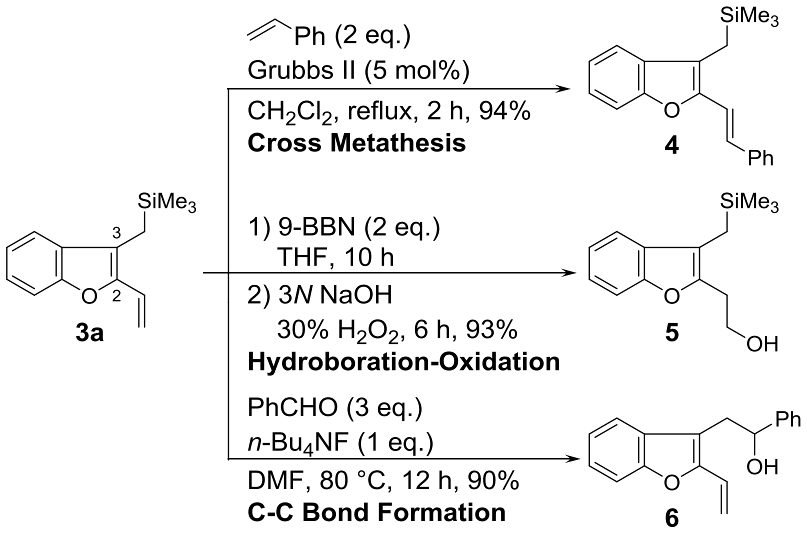
Enol ether has electron-rich nature which confers a very unique reactivity compared to other alkenes, and various types of valuable synthetic transformations are possible [1]. It’s reaction using a transition metal catalysts is limited to the Alder-ene reaction with rhodium catalyst [2], oxidative [2+2+1] annulation with copper catalyst [3], and the cycloisomerization reaction with triazole-gold catalyst [4]. Here, we investigated the novel reaction of *o*-alkynyl phenyl enol ether **1** with ruthenium hydride catalysts. As a result, 1,6-enyne cycloisomerization of **1** giving the cyclized **2** which were automatically aromatized, gave 2,3-disubsutituted benzo[b]furans **3** in excellent yields (up to 93% yield).



R = $SiMe_3$, $Si(i\text{-}Pr)_3$, $SiMe_2Ph$, $SiMe_2Bn$

Functional group transformations of the substituents of 2,3-disubstituted benzo[*b*]furan **3a** were possible. For example, cross metathesis reaction between the alkene unit at 2 position of **3a** and styrene proceeded to give **4** in 94% yield. Hydroboration-oxidation reaction of the alkene unit at 2 position of **3a** proceeded to give **5** in 93% yield. Moreover, fluoride anion promoted the formation of carbanion by detrimethylsilyl group at 3 position of **3a** followed by coupling reaction with benzaldehyde to give **6** in 90% yield.



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[4] S. Hosseyni, L. Wojtas, M. Li, X. Shi, *J. Am. Chem. Soc.*, **2016**, *138*, 3994.

Chiral pool based ionic liquids: Resourceful catalysts for asymmetric hydrogenation reactions

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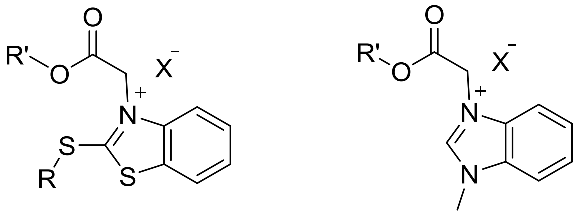
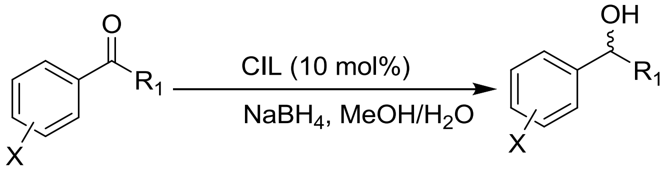
Recently, asymmetric synthesis gained much interest of the chemists due to the applications of the enantiopure products in pharmaceutical and other industries. Since two enantiomers of a compound can have different pharmacological activity and toxicity levels, so the synthesis of enantiopure compounds is of utmost importance. Chiral ionic liquids are well known for their use as reaction media and/or organocatalysts in many reactions. With low vapour pressure, excellent thermal stability and solvent potential these species are considered as the future solvents for organic synthesis [1,2]. These ionic species coordinates with substrates and led to stereoselectivity in many organic reactions, one such reaction is asymmetric hydrogenation. We have developed some new chiral ionic liquids based on benzimidazolium (or 2-mercaptobenzthiazolium) salts [3,4].



R'=Menthyl or Bornyl X= -Cl, -BF_4, -PF_6, -$OSO_2CH_2CH_2Br$

Fig. 1. Structure of the chiral ionic liquids synthesized from chiral pool

These chiral ionic liquids were employed in asymmetric reduction of prochiral ketones using sodium borohydride (illustrated in **Scheme 1**). Using both type of catalysts, moderate to excellent (ee>99%) enantiomeric excess was obtained. The chirality transfer is due to the formation of ionic intermediate between the ionic liquid catalysts and ketone substrates, in the solution. Furthermore, benzimidazolium based salts can be recycled and reused for three times.



Scheme 1: Asymmetric hydrogenation using chiral ionic liquids

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Expeditious and Divergent Total Syntheses of Aspidosperma Alkaloids Exploiting Iridium(I) Catalyzed Generation of Reactive Enamine Intermediates

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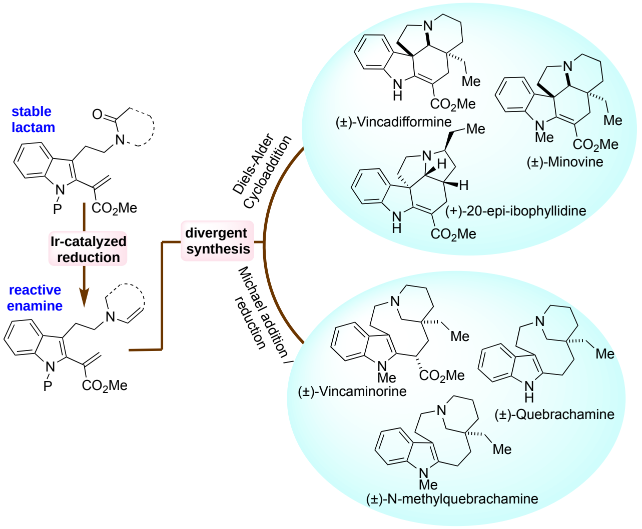
An expeditious approach for the divergent total syntheses of (±)-Vincaminorine, (±)-*N*-methylquebrachamine, (±)-Quebrachamine, (±)-Minovine and (±)-Vincadifformine, each in less than 10 linear steps starting from a single δ-lactam building block, is reported.[1] The late-stage generation of reactive enamine functionality from stable indole-linked δ-lactams via a highly chemoselective iridium(I) catalyzed reduction is the key to our route design. The efficiently formed secodine intermediates subsequently undergo either a formal *Diels-Alder* cycloaddition or a competitive Michael addition/reduction to access *Aspidosperma*-type alkaloids in excellent diastereoselectivities. Product selectivity could be controlled by subtly changing the indole *N*-protecting group in the reductive cyclization precursors. An asymmetric variant of this synthetic strategy for the synthesis of (+)-20-*epi*-ibophyllidine is also described.



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Facile synthesis of [1,2,4]triazolo[4,3-b][1,2,4,6]thiatriazine-1-oxides from N-triazol-3-yl imidate

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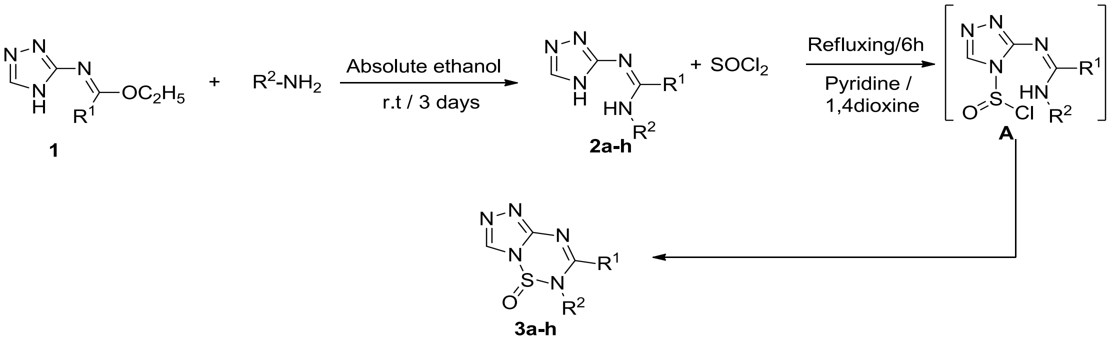
Abstract

A facile method for the synthesis of [1,2,4]triazolo[4,3-*b*][1,2,4,6]thiatriazine-1-oxides (**3a-h)** is presented. Our approach to access these triazolothiatriazine-oxides involves a cyclocondensation reaction between *N*-triazol-3-yl amidines (**2a-h)** and thionyl chloride in presence of pyridine. The *N*-triazol-3-yl imidate **1** were obtained by condensation of 3-amino[1,2,4]triazole with orthoesters according to a previously reported method [1]. The predicted structures of the synthesized compounds were confirmed by different spectral analysis studies including IR, ^{1}H NMR, ^{13}C NMR, elemental analyses and mass spectral analysis of (**3a-h)**.

Keywords: [1,2,4]triazole, thiatriazine-oxides, amidines, iminoester, synthesis, thionyl chloride.



3a : $R^1 = CH_3$, $R^2 = C_2H_5$; **3b** : $R^1 = C_2H_5$, $R^2 = C_2H_5$

3c : $R^1 = CH_3$, $R^2 = C_3H_7$; **3d** : $R^1 = C_2H_5$, $R^2 = C_3H_7$

3e : $R^1 = CH_3$, $R^2 = C_5H_9$; **3f** : $R^1 = C_2H_5$, $R^2 = C_5H_9$

3g : $R^1 = CH_3$, $R^2 = Ph\text{-}CH_2$; **3h** : $R^1 = C_2H_5$, $R^2 = Ph\text{-}CH_2$

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Insights into Aza-Indoles and Aza-Indazoles as Photoswitches

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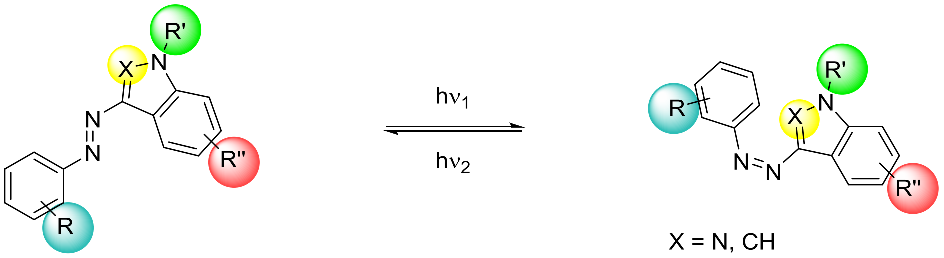
[b] *PhotoGreen Lab, Department of Chemistry, University of Pavia, Pavia I–27100*

In recent years, the field of *photopharmacology* expanded rapidly.[1] The usage of small, light-responsive molecule to generate enzyme inhibitors,[2] switchable antibiotics[3] and molecules, which cause light-induced apoptosis of single cells in tissue[4] illustrate the potential of the approach. Using light as an external stimulant adds an extrinsic parameter determining the selectivity of the compound. Furthermore, light is non-invasive, easy to apply, and offers an inimitable spatiotemporal control over the process of interest. Azobenzenes interconvert upon light irradiation between two structural isomers, which differ strongly in their physical properties, and thus also in their activity towards biomolecules.[1] However, they often suffer from low photoisomerization yields and insufficient thermal stability of the *cis*-isomer. Thus, there is a need to investigate novel azobenzene derivatives with improved properties.[5]

Both indoles and indazoles are nitrogen containing, bicyclic aromatic compounds. Indoles are widely spread scaffolds in natural compounds, various drugs and dyes. Indazoles occur rarely in nature, though, but also show potency as pharmaceuticals and are utilized pigments.



X = N, CH

We used a scaffold-hoping strategy and moved from azo-benzenes to aza-indoles and -indazoles. The presented molecules were investigated from a synthetical, spectroscopical and computational aspect to conclude a structure-activity relationship regarding the switching properties of the molecules.

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Construction of an Azasteroid Library

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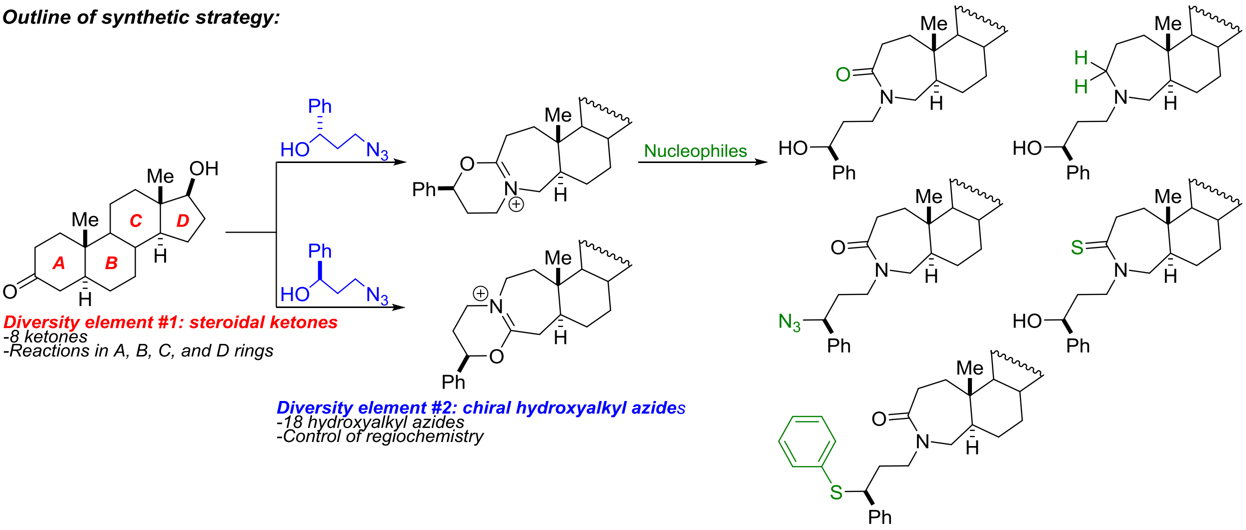
[b]*Division of Chemical Biology and Medicinal Chemistry,*
University of North Carolina, Chapel Hill, North Carolina

As screening collections remain an important aspect in early stage drug and probe discovery, access to diverse representations of chemical scaffolds is of considerable interest. Steroid natural products are attractive starting points for library construction because of their structural complexity and ability to interact with biological targets. Here, we describe a stereoelectronic approach towards regiochemical diversification of an azasteroid library using the azido-Schmidt reaction. This chemical method modifies steroidal ketones via a nitrogen insertion mechanism that enables predictable control of regiochemistry, and direct conversions to functionalized amino-steroids. The application of such a strategy has afforded access to a diverse collection of new steroid-like molecules that will be submitted for biological evaluation.

Outline of synthetic strategy:



Diversity element #1: steroidal ketones
-8 ketones
-Reactions in A, B, C, and D rings

Diversity element #2: chiral hydroxyalkyl azides
-18 hydroxyalkyl azides
-Control of regiochemistry

Diversity element #3: nucleophiles
-5 nucleophiles
-Ring opening using different nucleophiles

Ultrasound Promoted Facile One-Pot, Four-Component Synthesis of 2-Amino-3-Cyanopyridines Using Copper-Doped Silica Cuprous Sulfate(CDSCS)

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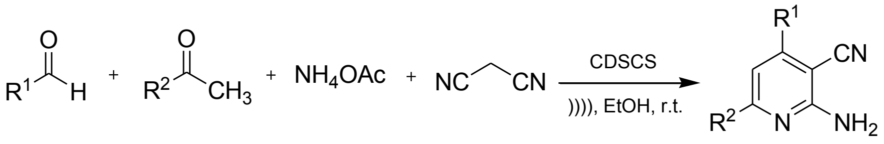
The pyridine substructure is a famous scaffold which found frequently in the structure of numerous natural and synthetic products exhibiting a wide range of biological and pharmacological properties. [1] Among pyridine derivatives, 2-amino-3-cyanopyridines have attracted considerable attention due to their remarkable biological properties. They exhibit diverse biological activities such as anticancer, anti-inflammatory, antiviral, antimicrobial, antihypertensive, antitubercular and antioxidant properties. Moreover, they have been frequently used as valuable intermediates for the construction of a variety of heterocyclic derivatives. [1] Given the significance of 2-amino-3-cyanopyridine derivatives, many synthetic approaches have been developed so far to access structurally diverse 2-amino-3-cyanopyridines. However, most of them are accompanied by one or more drawbacks such as harsh reaction conditions, complicated reaction procedures, the use of toxic solvents, utilizing expensive metal catalysts, multi-step syntheses, long reaction times, tedious work-ups, and unsatisfactory yield of the desired products. Consequently, the search for a simple, efficient, and practical synthetic strategy with suitable generality is still of great demand.

Nowadays, ultrasound-assisted organic synthesis has proved to be a clean and advantageous approach especially for the synthesis of heterocyclic compounds. [2] The ultrasound irradiation affords many important advantages in comparison with conventional thermal heating such as higher yield, the increment of the reaction rate, easier manipulation, minimizing the side-product, mild reaction condition, and higher selectivity. In light of the remarkable biological activities of 2-amino-3-cyanopyridines, hereby we would like to report an ultrasound-promoted synthesis of 2-amino-3-cyanopyridine derivatives **5** through one-pot, 4CR of different aldehydes, ketones, malononitrile, and ammonium acetate in the presence of copper-doped silica cuprous sulfate (CDSCS) in EtOH (Scheme 1).



1 **2** **3** **4** **5**

R^1, R^2= aryl and heteroaryl

CDSCS: $\boxed{SiO_2}$—OSO_3Cu

Scheme 1

[1] Allais, C.; Grassot, J.-M.; Rodriguez, J.; Constantieux, T. *Chem. Rev.* **2014**, *114,* 10829-10868.
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Ultrasound Promoted Facile Three-Component Synthesis of 1-Substituted Tetrazoles Using Cu/Graphene/Clay Nanohybrid as a Highly Efficient Heterogeneous Nano-Catalyst

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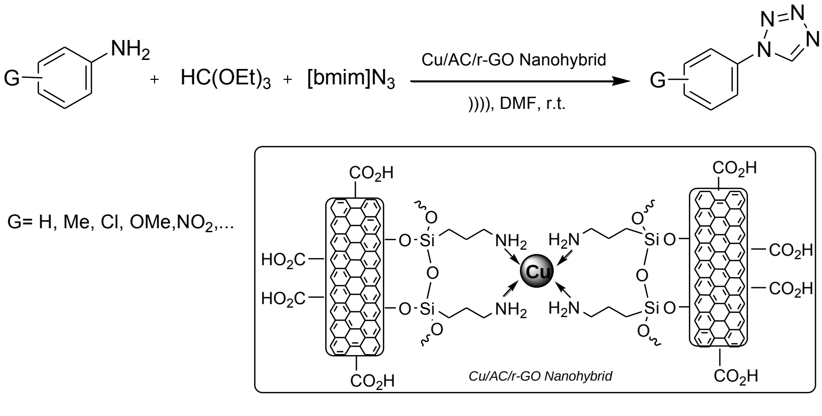
Tetrazoles are an important class of heterocyclic compounds with increasing applications in different research areas. In addition, tetrazole core is a key structural motif found in numerous biological active compounds and several famous drugs. [1] Due to their broad utility, the synthesis of tetrazole derivatives has attracted considerable attention, and several preparative methods have been established so far. The methods reported for the synthesis of 1-substituted tetrazoles involve acid-catalyzed cycloaddition between hydrazoic acid and isocyanides or trimethylsilylazide, cyclization between primary amines with an orthocarboxylic acid ester or ethyl orthoformate and sodium azide in the presence of acetic acid, acidic ionic liquid, ytterbium triflate and natrolite zeolite, etc. [2] However, most of these methods are accompanied by drawbacks such as long reaction times, harsh reaction conditions, the use of expensive and toxic reagents, and tedious work-up. To overcome these drawbacks, the search for mild and efficient synthesis of 1-substituted tetrazoles still remains as an important challenging subject in organic synthesis. Recently, we have reported the synthesis and application of Cu/aminoclay/reduced graphene oxide nanohybrid (Cu/AC/r-GO nanohybrid) as a highly efficient organic-inorganic hybrid nano catalyst for click synthesis of 1,2,3-triazolyl carboacyclic nucleosides. [3] Herein, we report the ultrasound-promoted three-component reaction of primary amines, triethyl orthoformate, and [bmim]N_3 catalyzed by Cu/AC/r-GO nanohybrid to afford the corresponding 1-substituted tetrazoles in good to excellent yields (Scheme 1).



Scheme 1

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[2] Naeimi, H.; Kiani, F. *Ultrason. Sonochem.* **2015**, *27*, 408-415 and references cited therein.

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Design and Synthesis of Novel Phenothiazine-Triazole Hybrids as Potential Chemotherapeutic Agents

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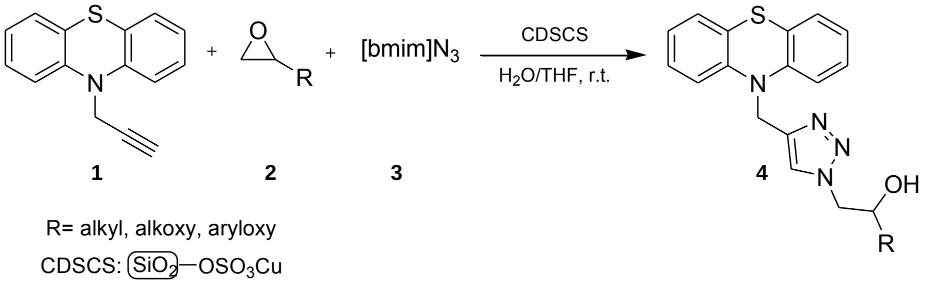
Phenothiazine derivatives are widely used in medicinal chemistry exhibiting diverse pharmacological activities such as antihistamines, analgesic, anti-inflammatory, anticonvulsants, antibacterial, antifungal, antipsychotic, anti-malarial, neuroleptics, diuretics, and sedative activity. [1] The most common route to obtain the new phenothiazine derivatives is the introducing a new substituent at the thiazine N(10) atom.

The 1,2,3-triazole derivatives has gained increasing attention in drug discovery since they can readily associate with biologically targets through the dipole interaction and hydrogen bonding. [2] Therefore, the incorporation of the 1*H*-1,2,3-triazolyl moiety into a molecular structure is a significant strategy in drug design. As a prototype of ‘click chemistry’, the Cu(I)-catalyzed Huisgen’s azide-alkyne cycloaddition (CuAAC) has emerged the powerful tool for introducing a 1,2,3-triazolyl residue into a molecule’s scaffold. [3]

Inspired by the remarkable biological activities of phenothiazine and 1,2,3-triazole derivatives, we now describe the design and synthesis of novel hybrid structure **4** having phenothiazine and 1,2,3-triazole residues. In this research, a variety of hybrid compound **4** analogues were efficiently synthesized through 3CR Huisgen 1,3-dipolar cycloaddition reaction between *N*-propargyl phenothiazine, structurally diverse epoxides, and [bmim]N_3 as a green source of azide in the presence of copper-doped silica cuprous sulfate (CDSCS) (Scheme 1). Thus, a variety of hybrid compounds **4** were obtained in good to excellent yields as potential chemotherapeutic agents. The structure of all synthesized compounds was confirmed by ^{1}H-NMR, ^{13}C-NMR, MS, and IR.



Scheme 1

[1] Kleeman, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical substances*; 3rd ed.; Thieme: Stuttgart, 1999.

[2] Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249-1262.

[3] M. Meldal, C.W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952-3015.

Synthesis and Biological Assessment of New 5-Substituted-1*H*-Tetrazole Derivatives Tethered to Bioactive *N*-Heterocyclic Cores Using Chitosan-Silica Sulfate Nano Hybrid (CSSNH) as a Novel Heterogeneous Nano Catalyst

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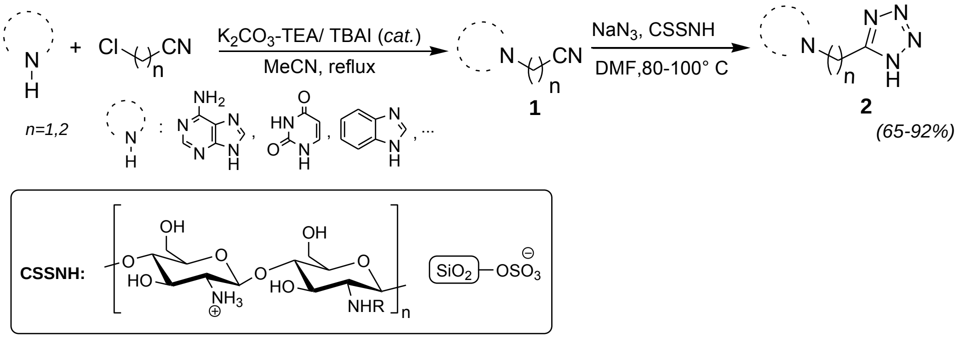
Tetrazoles are an important class of *N*-heterocyclic compounds exhibiting widespread applications in industries and medicine. Tetrazoles can be served as bioisosteres for the carboxylic acids. Additionally, the replacement of a carboxyl group with tetrazolyl moieties improved the metabolic stability, bioavailability and cell permeability of a drug molecule. [1]

The synthesis of tetrazoles has attracted considerable attention since the broad utilities found for tetrazoles. In this context, the different preparative methods have been emerged so far. Among them, the [3+2]-cycloaddition reaction of nitriles with azides is a well-known and most extensively studied and used procedure for synthesis of diverse 5-substituted-1*H*-tetrazoles. [2]

Nowadays, there has been a growing interest in the application of natural biopolymers as environmentally benign materials for preparation of heterogeneous catalysts. Along this line, polysaccharides like chitosan as one of the most abundant biomolecules in nature that extensively applied. In recent years, organic-inorganic hybrid materials or catalysts have gained particular attention. Regarding to benefits of biopolymers as the green catalysts, the use of biopolymer-inorganic hybrid catalysts have been emerged as an attractive strategy in preparation of new catalysts in organic reactions. Herein, the synthesis and characterization of chitosan-silica sulfate nano hybrid (CSSNH) as a novel heterogeneous nano catalyst has been described and this catalyst was used in synthesis of new 5-substituted-1*H*-tetrazole derivatives tethered to bioactive *N*-heterocyclic cores **2**. The synthesized tetrazoles were tested *in vitro* against some pathogenic fungal including *candida krusei*, *candida glabrata*, *aspergillus flavus* and *aspergillus fumigatus* in which some entries have displayed antifungal activity to some extent.



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Accessing Polyoxygenated Dibenzofurans via the Union of Phenols and *o*-Benzoquinones: Rapid Syntheses of Metabolites Isolated from *Ribes takare*

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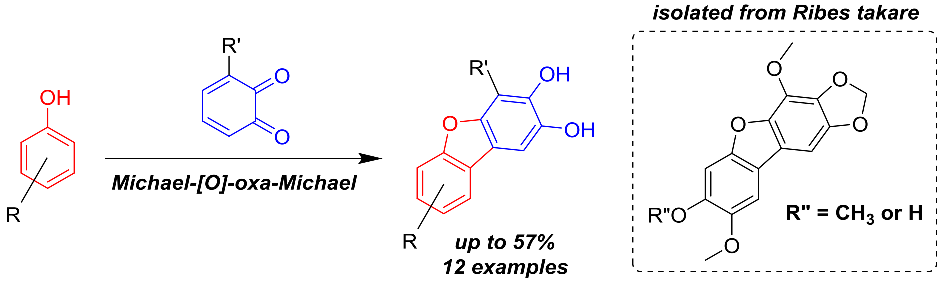
Oxygen-rich dibenzofurans are a class of compounds prevalent in nature.[1] The structural complexity and promising biological activity of dibenzofuran natural products have continuously inspired the development of methodology for the preparation of compounds and total syntheses of natural products bearing this structural motif.[2]



While various routes towards the syntheses of polyoxygenated dibenzofurans exist in the literature which traverse through biphenyl intermediates, we were interested in a complementary approach whereby the desired dibenzo[*b*,*d*]furan framework would be constructed in a single process from unprotected phenols/naphthols and *o*-benzoquinones via a Michael-oxidation-oxa-Michael cascade.[3] The utility of this transformation was demonstrated in the generation of a library of highly substituted dibenzofurans, featuring specifically substituted molecules containing broad ranges of functionality. The developed methodology was also applied to the total syntheses of two dibenzofurans recently isolated from *Ribes takare*, which possess mild α-glucosidase inhibitory activity.[4] Assemblage of the carbon scaffold of both natural products was achieved in a single operation, completing the syntheses in three and five steps.

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The synthesis and structure prove of 6-(bromomethyl)-3- substituted -5,6-dihydrothiazolo[2,3-c][1,2,4]triazole)

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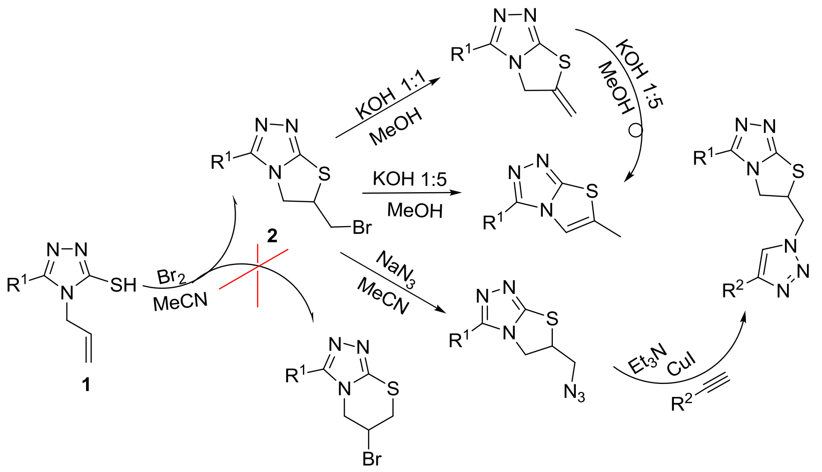
One of the most interesting heterocyclic compounds are triazoles. The different derivatives of which show important biological activities as antifungal, antibacterial, and antitumor etc[1-2]. Some derivatives are already used in drugs: Epoxiconazole, Fluconazol, Itraconazol etc[2]. The big field of using of thriazoles tell us to find both new derivatives and new methods of synthesis.

We tried to make new system, which contains triazol and other heterocyclic groups. For that on base of 4-allyl-5-substitited-4H-1,2,4-triazole-3-thiol (1) we successfully did some reactions which are presented here[3]:



R^1= benzyl; 2,4-dichlorophenoxymethyl; 2-chlorophenyl; 2-iodophenyl; 5-bromofuran-2-yl

The structure of final product of reaction of cyclization with halogenation was established with NMR and X-Ray methods. It is also proved, that the ring of triazole is fused with thiazole ring. The same prove the chemical reactions of that compounds. On the base of the **2** compounds we succeed in getting the new system, where the system of triazolothiazoles coupled with 1,2,3-triazole ring.

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Copper-Catalyzed Cascade Amination Route to *N*- Aryl Benzimidazoquinazolinones

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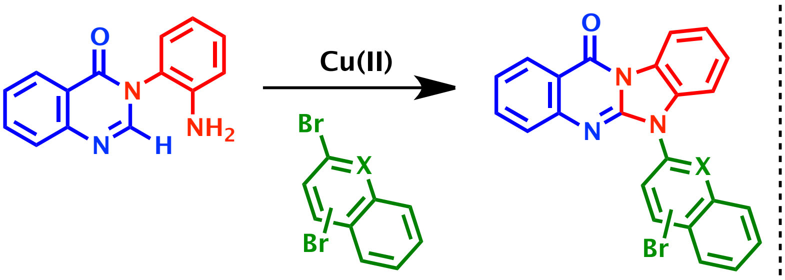
An efficient one-pot Cu-catalyzed C−H functionalization/two-fold C−N bond formation protocol for the syntheses of *N*-aryl benzimidazoquinazolinones has been reported. Our strategy involves a Cu-catalyzed C−N bond coupling reaction between *N*-anilinoquinazolinones and aryl/heteroaryl halides followed by acetate ligand-assisted intramolecular C−H amination. This reaction is high-yielding, has good functional group tolerance and straightforward for the synthesis of anti-cancer drug analogues of benzimidazo-quinazolinones.



Scalable
22 examples
High yield
Drug analogs
(Immunosuppressor
/Anti-tumor drug)
Excellent regioselectivity

[1] Banerjee, A.; Subramanian, P.; Kaliappan, K. P. *J. Org. Chem.* **2016**, *81*, 10424−10432.

Novel Pt(II) Coordination Complexes as Visible Light Photocatalyst

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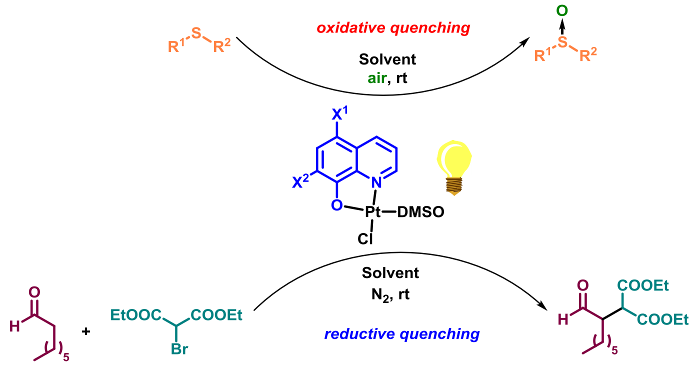
(2) Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Madrid, Spain

During last years, visible light photoredox catalysis has been established as a novel and powerful tool that aims to prepare diverse molecules under mild conditions through bond-selective activation.[1] The catalysts involved in most of the processes are Ru(II) and Ir(III) complexes or photoorganocatalysts such as eosyn Y or flavin. By contrast, few studies have focused on the development of photocatalysts based on other metal complexes.

Recently, our group has synthesized different coordination complexes relied on platinum(II) and hydroxyquinoline ligands which have proved to be excellent candidates as antitumoral complexes.[2] Their yellow-orange colour and their photophysical properties led us to postulate whether these platinum complexes could be used as visible light photocatalysts for different transformations.

Herein, we describe that hydroxyquinoline-Pt(II) complexes are capable of undergoing reductive and oxidative photocatalytic quenching pathways. We have developed the photooxidation of a large number of aryl and alkyl sulfides, as well as more complex structures such as heterocycles and methionine aminoacid, with complete chemoselectivity and without detection of other byproduct.[3] We have carried out mechanistic studies that suggest an electron-transfer process via oxygen radical anion as plausible mechanism. Also, we have obtained preliminary results in the α-alkylation of aldehydes using these platinum complexes in combination with the MacMillan's catalyst, affording the corresponding products in high yields and ee's.



Aknowledgment: the European Research Council (UNBICAT project number: 647550) and the Spanish government (project number: CTQ2015-64581-R) for the financial support.

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Atom Economic Oxidative Ugi-Type Reaction of Acridanes. Access to Novel Acridinium-Based Photocatalysts

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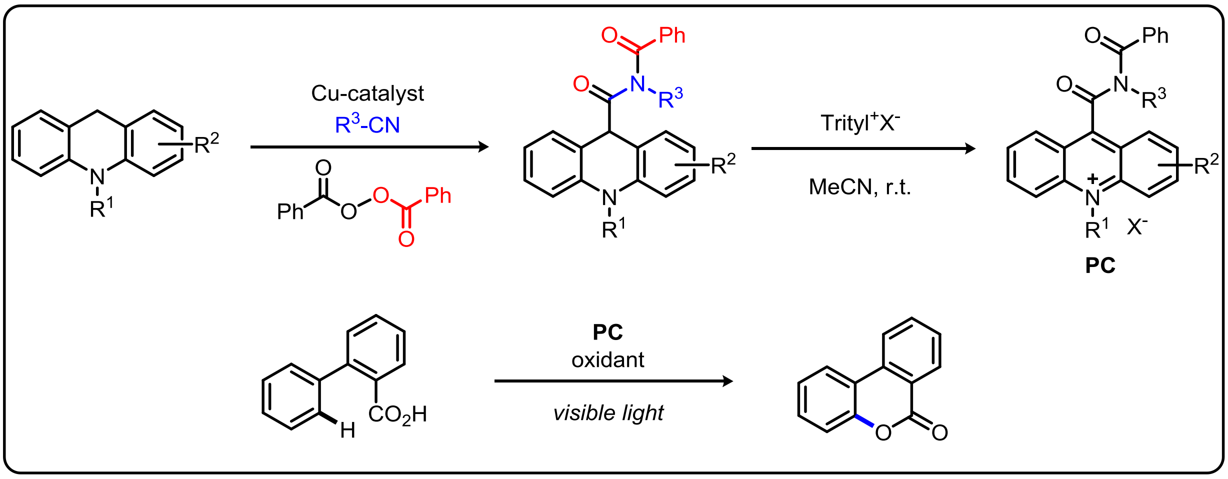
Acridinium-based photocatalysts belong to one of the most important groups of photooxidants and represent a cheap, bench-stable alternative to their transition-metal counterparts.[1] Their redox properties can be tuned by variation of the substituents at position C9 or at the acridinium core. However, only a few derivatives have been reported until now, in which only aromatic rests at the C9, such as mesityl for the commercially available Fukuzumi catalyst, are introduced.[1-2]



We herein report an effective and atom economic strategy for the construction of 9-substituted imido-acridanes by a Cu-catalyzed oxidative Ugi-type C-H functionalization in the presence of benzoyl peroxide as key oxidant. The obtained acridanes were further oxidized to the corresponding acridinium salts under mild conditions. Their photo- and electrochemical properties were determined by spectroscopic and cyclic voltammetric measurements and the novel catalysts were applied in visible light mediated dehydrogenative lactonization of biphenyl-2-carboxylic acid.

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Azaheterocycles for Multiple Tasks in Medicinal Chemistry

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"Alexandru Ioan Cuza" University of Iasi, Faculty of Chemistry; CERNESIM[†]; Bd. Carol 11, 700506 Iasi, Romania.

Over the past decades, five and six member ring azaheterocyclic compounds have received considerable attention due to their important applications from pharmacological, industrial, and synthetic points of view. Azaheterocyclic derivatives, especially azine, diazine and diazols, were reported as valuable scaffolds in medicinal chemistry, showing variously biological activities such as antiviral and anticancer, antituberculosis and other antimicrobials, etc.

As part of our ongoing research in the field of azaheterocycles derivatives, we present herein some core results obtained by our group in the field of nitrogen heterocycles derivatives, focused on chemistry and their pharmacological potential applications as anticancer, antituberculosis and other antimicrobials, leishmaniasis [1]. Our design has had in mind to get compounds with at least two biological activities.

As far for anticancer activity, several classes of azaheterocycles (diazols, fused azine and diazine, mono- and bis- indolizines, 1,10- 1,7- and 4,7- phenanthroline) was designed, synthesized, and tested. Some of the compounds have a significant and selective anticancer activity against Melanoma, Renal cancer, Brest cancer and Lung cancer. As to the mechanism, our classes of compounds belong to DNA-intercalators, either via covalent bonding interactions (alkylators) either via non-bonding interactions (intercalations between base pairs, minor/major groove binding, G-quadruplex interactions).

Design, synthesis and antimycobacterial activity of some new classes of nitrogen heterocycles (namely azine and bis-azine, diazine and bis-diazine, mono- and bis- indolizines, phenanthroline) is presented. The primary cycle high throughput screening reveals that some compounds are potent inhibitors against Mycobacterium tuberculosis (Mtb), their antitubercular activity being superior to the second-line antitubercular drug Pyrimethamine and Cycloserine. The MIC, MBC, LORA, intracellular (macrophage) drug screening, and MTT cell proliferation, indicate, for some of our compounds, the intracellular drug effectiveness against Mtb, the lack of toxicity, a significant activity against both replicating and non-replicating Mtb, a bactericidal mechanism of action, excellent solubility in microbiological medium. For the most active compounds, a complete ADMET studies have been performed (these including Plasma Protein Binding, Caco-2 Permeability, Cytochrome P450 Inhibition, In vitro microsomal Stability, HepG2 Cytotoxicity) with very good and promising results.

Design, synthesis and antileishmaniasis activity of three new classes of nitrogen heterocycles (imidazo- isoquinolines and phthalazine, (substituted)- bis-pyridazinone, PyrroloBenzoQuinone- pyridazine and phthalazine) is presented. The antileishmania assay against Leishmania donovani intramacrophage amastigote reveal a very good and promising activity for some compounds.

[1] Relevant literature data could be found to ORCID number 0000-0002-4632-5076.

Synthesis of 3-Benzazepines by Metal-Free Oxidative C–H Bond Functionalization–Ring Expansion Tandem Reaction

Julia Bamberger,[a] Andrea Gini,[a] Javier Luis,[b] Mercedes, Zurro,[a] Jose Aleman,*[b] Olga García Mancheño*[a]

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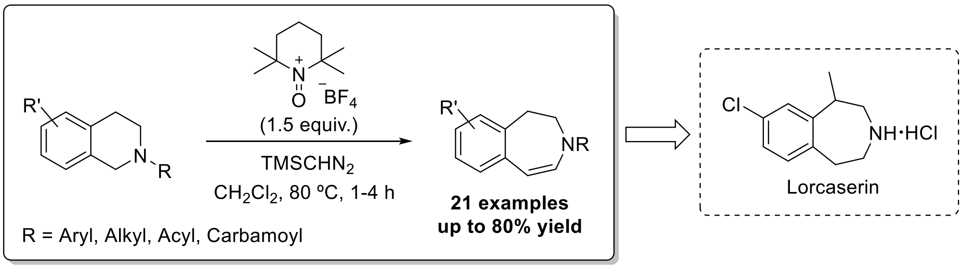
[b] *Department of Organic Chemistry, Universidad Autónoma de Madrid, Madrid/ES*

The nitrogen-containing seven-membered ring heterocycles 3-benzazepines are a unique class of compounds important in drug discovery. [1] The main strategy to synthesize the 3-benzazepine core is based on Lewis-acid mediated Friedel-Crafts-type cyclization approaches. However, in these cases multiple reaction steps or special substituted substrates are required. Therefore, more general and efficient synthetic strategies for this type of heterocycles are still needed.

Herein, we report a strong new methodology for the construction of the seven-ring structure by an oxidative C-H functionalization approach from readily available tetrahydroisoquinolines (THIQs). Based on our experience with trimethylsilyldiazomethane ($TMSCHN_2$) as nucleophile,[2] a straightforward one-pot synthesis of 3-benzazepines by an innovative, mild, metal-free, $T^+BF_4^-$-mediated oxidative C-H bond functionalization[3] – ring expansion process has been developed.[4] This methodology has proven to be quite general and functional group tolerant.



In order to gain insights into the mechanism, several experiments, including deuterium-labelling, and DFT calculations have been carried out. These investigations suggest an ionic oxidation and an aromatic driven ring-expansion step. Finally, the synthetic applicability of the developed methodology was demonstrated by the synthesis of the drug Lorcaserin.

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[4] A. Gini, J. Bamberger, J. Luis, M. Zurro, R. Mas-Ballesté, J. Alemán, O. García Mancheño, *Adv. Synth. Catal.* **2016**, *358*, 4049 –4056.

Synthetic approaches to indazole-based anthranilic diamides

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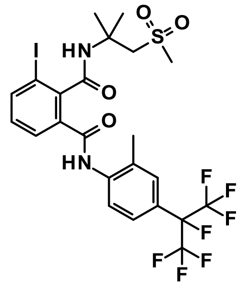
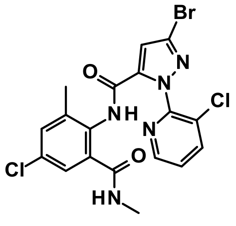
Modern farming relies a lot on chemical pest management. One of the recurrent problems in pest control is the adaptation of the pests to the methods used to limit them. Cross resistance may appear with the repeated use of different active ingredients showing the same mode of action. This reduces the usefulness of whole classes of compounds. For this reason it is very desirable to find substance classes that show new modes of action.

Recently, in the field of chemical insect control, new classes of diamides were found and made their way to the market. They modulate the insect ryanodine receptors (calcium channels), which was a new mode of action for commercial use [1].

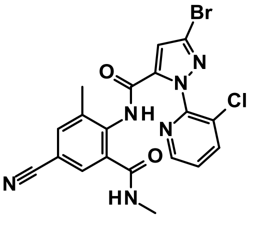
The first compounds of this class introduced to the market were the phthalamide, flubendiamide (Nyhon Nohyaku [2]) and the two anthranilic diamides, chlorantraniliprole (DuPont [3]) and cyantraniliprole (DuPont [4]). Syngenta, as a major player in crop protection, was also very active in this field. Syngenta's approach led to the discovery of novel insecticidally active bicyclic diamides. Especially interesting biological profile and efficacy were found in indazole based diamides, like compound (I) (Syngenta [5]).



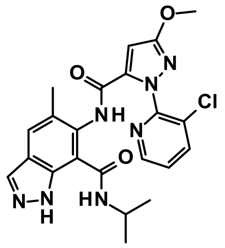
Flubendiamide



Chlorantraniliprole



Cyantraniliprole



Compound (I)

Polysubstituted indazole compounds can present a synthetic challenge, especially when a commercially viable access is sought for. A selection of synthetic strategies to access compound (I) will be presented.

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[5] PCT Int. Appl. (2007), WO 2007093402 A1 20070823.

Biphotonic Catalyzed C-C Coupling Reactions

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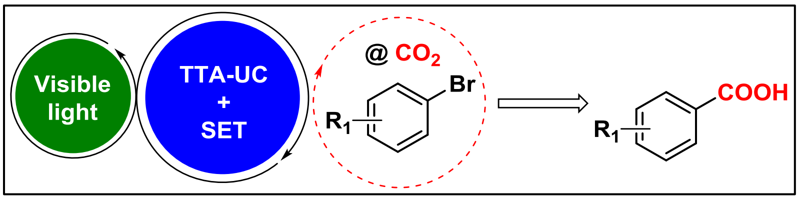
To achieve low energy demanding synthetic protocols using CO_2 as C1 building block, efficient interactions with the specific substrate is required. Furthermore, to use CO_2 in a more benign and practical manner, efficient transformations with less activated substrates under mild conditions have to be developed. In this context, the reduction of activated carbon halide (C-X) bonds has attracted considerable interest, especially in organic synthesis due to generation of carbon centered radical intermediates. Visible light photoredox catalysis is actually considered one of the most powerful tools in addressing these processes; it offers more effective and safer alternatives to traditional dehalogenation protocols involving metal halogen exchange, stoichiometric tin hydride and other highly toxic reagents. The scope of photocatalytic bond activations is generally limited by the energy of the visible photon, which in principle allows the cleavage of weak C–I, C(sp3)–Br and π bonds by energy or electron transfer mechanisms. However, a single visible photon does not provide sufficient energy for the dissociation of the stronger aryl–Br, C–Cl, C–O, and C–H bonds. Therefore, activation of higher energy aryl halides (Br, Cl) under mild conditions is found to be a significantly more challenging task. Among protocols using UVA (380 nm) light sources,[1] some recent examples have shown that upconversion processes (two-photons) are suitable techniques for the activation of aryl halides converting photoredox catalysts into "super reductants" using visible light. Hence, photogeneration of radical anions of aryl halides can be achieved by means of both a consecutive photoinduced electron transfer (conPET) process [2] and formation of a delayed fluorescence (higher energy) afforded by triplet-triplet annihilation, TTA (lower energy).[3] Related to the latter process, despite the fact that the use of low energy visible light ensures high functional group tolerance in chemical transformations, applications of photon upconversion (UC) based on TTA in C-C coupling reactions remain still missing. Thus, development of TTA-UC technology for addressing critical bond activations (*i.e.* CO_2 and hitherto unreactive aryl halides) or electron transfers in organic synthesis would be advantageous while retaining the benefit of mild reaction conditions by the use of lower energy visible light. Here, we will discuss the chemical transformation of CO_2 and its integration into synthetic organic molecules as well as generation of reactive aryl radical species through this novel combination of visible to UV photon up-conversion plus a SET initiated process and study subsequent C-C bond forming reactions.



[1] (a) *Chem. Commun.* **2015**, *51*, 11705; (b) *J. Org. Chem.* **2016**, *81*, 7155.
[2] (a) *Science* **2014**, *346*, 725; (b) *J. Am. Chem. Soc.* **2016**, *138*, 3958; (c) *Angew. Chem. Int. Ed.* **2016**, *55*, 7676; (d) *ACS Catal.* **2016**, *6*, 6780; (e) *ACS Catal.* **2016**, *6*, 8410.
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Triazole-Based Anion-Binding Catalysis for the Enantioselective Dearomatization of *N*-Heteroarenes with P-Nucleophiles

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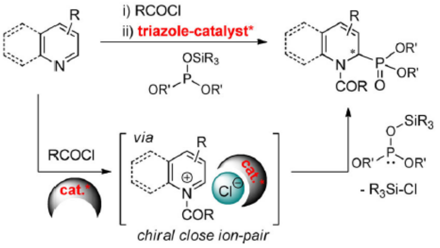
Organische Chemie,Chemie-Pharmazie Regensburg/DE

Chiral α-amino phosphonic acid derivatives are important bioactive structures in the pharmaceutical and medicinal industry, as well as valuable building blocks in organic synthesis.[1] Despite the extraordinary applicability of chiral *N*-heterocyclic α-amino phosphonic acids, there is still a demand for mild and simple synthetic methods. In this regard, the Mukherjee's group recently reported on a thiourea-based anion-binding-catalyzed asymmetric dearomatization of isoquinolines by acylation and subsequent reaction with trimethylsilyl-substituted phosphites.[2] Inspired by this work, and based on the observed superior performance of our recently developed triazole-based chiral H-donor catalyst[3] with the more challenging substrates quinolines and pyridines,[4] we decided to explore the enantioselective dearomatization of these heteroarenes with phosphorous nucleophiles.



Scheme 1. Dearomatization of *N*-heteroarenes with phosphorus nucleophiles.

The first enantioselective synthesis of chiral heterocyclic α-amino phosphonates by nucleophilic dearomatization of quinolines and pyridines using an anion-binding organocatalysis approach is described.[5] Chiral tetrakistriazoles were employed as efficient hydrogen-bond donor catalysts by the formation of a chiral close ion-pair with the *in situ* formed *N*-acyl salts with Troc-chloride and subsequent treatment with various phosphorous nucleophiles, such as silyl protected dialkyl phosphites and trialkylphosphites. Thus, the corresponding products were obtained in complete or high regioselectivities and up to 97:3 e.r. for quinolines or up to 89:11 e.r. for the more demanding pyridine substrates. This method allows the rapid access to substituted chiral cyclic α-amino phosphonates, which can easily further transform into phosphonic acid derivatives.

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[5] T. Fischer, Q.-N. Duong, O. García Mancheño, *Chem. Eur. J.* **2017**, DOI: 10.1002/chem.201605660.

New possibilities and features of synthesis of quinoxaline derivatives

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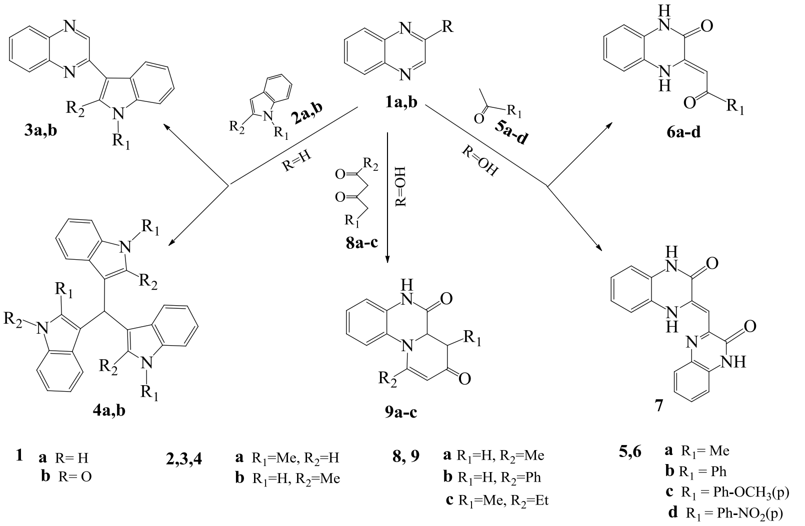
Quinoxaline derivatives possess various kinds of biological activity [1, 2]. For example, quinoxidine and dioxidine are used as antimicrobial agents[3]. The synthesis and biological activity of a large number of quinoxalin-2-one derivatives were reviewed in [4].

We have found that quinoxalines **1a,b** reacted with indoles **2a,b** heating in acetic acid to give the corresponding products of hydrogen substitution **3a,b** and tris(1-methyl-1H-indol-3-yl)methane **4a,b**.

Unusual transformations occurred during the reaction of quinoxalone **1b** with acetophenone derivatives **5a-d**. Beside of the products **6a-d**, (Z)-3-((3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)methyl)quinoxalin-2(1H)-one **7** was obtained.



The reaction of quinoxalone **1b** with β-dicarbonyl compounds **8a-c** yielded the derivatives of the new heterocyclic system 6a,7-dihydropyrido[1,2-a]quinoxalines-6,8-dione **9a-c**

Possible mechanisms of the discovered new chemical transformations of quinoxalines are considered. The diagnostic spectral characteristics of the compounds obtained were determined by using NMR and mass spectroscopy.

[1] *The Chemistry of Heterocyclic Compounds: The Pyrazines,* Barlin G.B., Ed., New York: Wiley, 1982,vol. 41.

[2] *The Chemistry of Heterocyclic Compounds: Condensed Pyrazines,* Cheeseman, G.W.N. and Cookson, R.F., Eds.,
New York: Wiley, 1979, vol. 35.

[3] Mashkovskii, M.D., *Lekarstvennye sredstva* (Medicines), Moscow: Meditsina, 1993, 12th ed., part II, p. 356.

[4] Sakata, G. and Makino, K., *Heterocycles*, 1988, vol. 27,p. 2481.

Ruthenium nanoparticles-catalyzed ligand-free Suzuki-Miyaura Coupling

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Transition metal catalyzed cross-coupling is an important reaction to make functional molecules. Especially, the development of immobilized transition metal nanoparticles (NPs) as catalysts for carbon-carbon (hetero) forming cross-coupling reactions is one of the most important areas in organic synthesis because these immobilized catalysts have several advantages such as recyclability and low metal contaminations. We developed a sulfur-modified Au-supported Pd catalyst (SAPd) and used it to catalyze Suzuki-Miyaura coupling, Buchwald-Hartwig coupling and C-H functionalization without any ligands.[1] However, recyclable and low-leaching non-palladium catalysis like ruthenium for ligand-free Suzuki-Miyaura coupling has not been developed very well.[2] To solve this problem, here we developed a conceptually and methodological novel ruthenium(0) NPs catalyst, sulfur-modified Au-supported Ru catalyst (SARu). SARu is easily prepared via three-steps; (i) sulfur modification, (ii) NPs immobilization and (iii) washing (**Scheme 1**). SARu is an ideal ruthenium catalyst for liquid-phase combinatorial synthesis, because SARu repeatedly catalyzes ligand-free Suzuki-Miyaura coupling of arylhalide, including heterocyclic arylbromide. The results are summarized in **Table 1**. It can be used for the reaction with various kinds of substituted aryl compounds in highly reliable yields (**Table 1**). In my poster presentation, I will report the result of screening of substrates including aryl boronic acids and arylchlorides, and the cahracterization of SARu.

Scheme 1. Preparation of SARu.

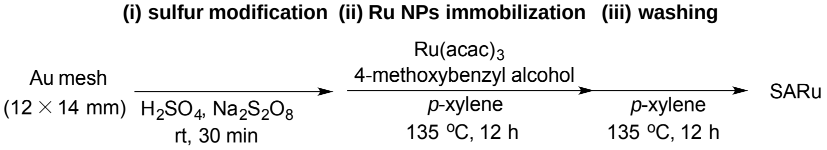
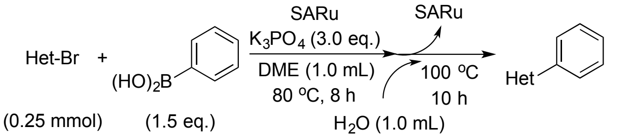
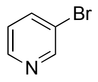
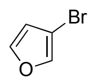
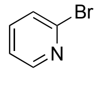
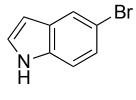
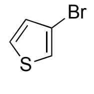
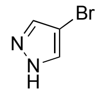
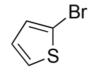
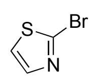
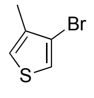
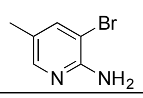


Table 1. SARu catalyzed Suzuki-Miyaura coupling of heterocyclic arylbromides.



Run	Het-Br	Yield (%)	Run	Het-Br	Yield (%)
1		87	6		82
2		89	7		95
3		92	8		88
4		90	9		85
5		89	10		78

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[1] (a) *J. Am. Chem. Soc*. **2010**, *132*, 7270-7272. (b) *Adv. Synth. Catal*. **2011**, *353*, 743-748. (c) *Adv. Synth. Catal*. **2012**, *354*, 1061-1068. (d) *J. Org. Chem*. **2013**, *78*, 7575-7581.
[2] (a) Y. Na, S. Park, S. B. Han, H. Han, S. Ko, S. Chang, *J. Am. Chem. Soc*. **2004**, *126*, 250-258. (b) M. Kawatsura, K. Kamesaki, M. Yamamoto, S. Hayase, T. Itoh, *Chem. Lett*. **2010**, *39*, 1050-1051.

Total Synthesis of (+)-Laurenidificin

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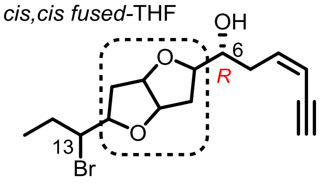
Mitsuhiro Arisawa, Hiromichi Fujioka

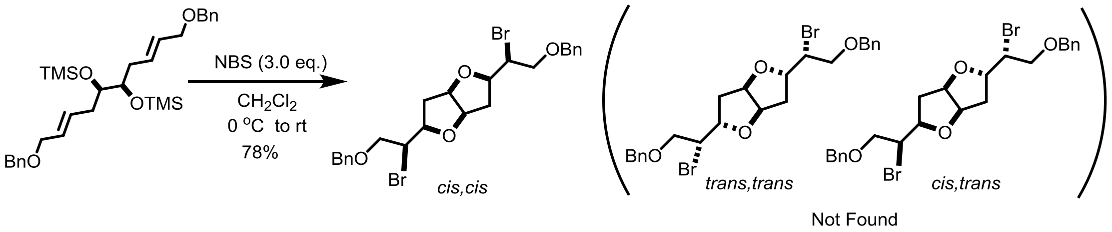
Graduate School of Pharmaceutical Sciences, Osaka University,1-6, Yamadaoka, Suita, Osaka 565-0871, Japan. yoshikawa-yu@phs.osaka-u.ac.jp



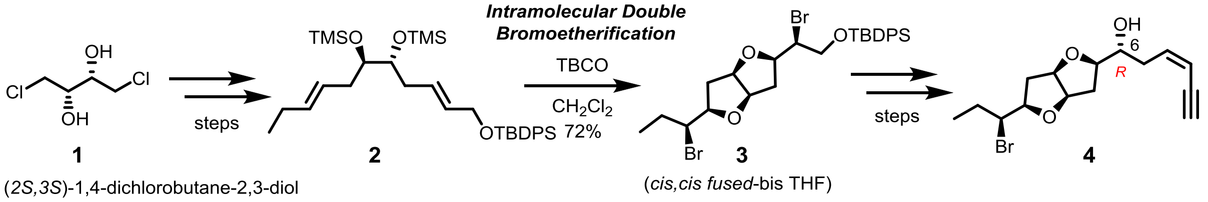
(+)-laurenidificin

(+)-Laurenidifcin was isolated from red algae *Laurencia nidifica* by Wang et al in 2010.1) It has *fused*-bis THF skeleton and enyne structure in its side chain. It is only shown that the relative configuration of the *fused*-bis THF skeleton is *cis,cis*-form, and the absolute configuration at C6 position is *R*.

In our laboratory we have recently developed the efficient method for construction of *fused*-bis THF skeletons stereoselectively in one pot operation.2) For example, *cis,cis fused*-bis THF can be constructed from TMS protected *E,E*-diene diol derivative efficiently in high yield by intramolecular double bromoetherification.



We synthesized one possible isomer of laurenidificin by using this reaction as a key step. Optically active **2** having the TMS protected *E,E*-diene diol was synthesized from commercially available (2*S*,3*S*)-1,4-dichlorobutane-2,3-diol **1**. Treatment of **2** with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) in dichloromethane afford *cis,cis fused*-bis THF **3** in good yield. Then, several transformations including the introduction of hydroxyl group at C6 position gave compound **4**, a possible isomer of laurenidificin, and it's ^{1}H- and ^{13}C-NMR data are in complete agreement with natural one.3) The details of its synthesis will be presented.



References:
1) B. G. Wang *et al*., *Chin. Chem. Lett.* **2010**, 1213.
2) *J. Org. Chem.* **2015**, *80*, 10261.
3) *Eur. J. Org. Chem.* in press.

Small Libraries of Bioactive Heterocycles from Dithiocarboxylates

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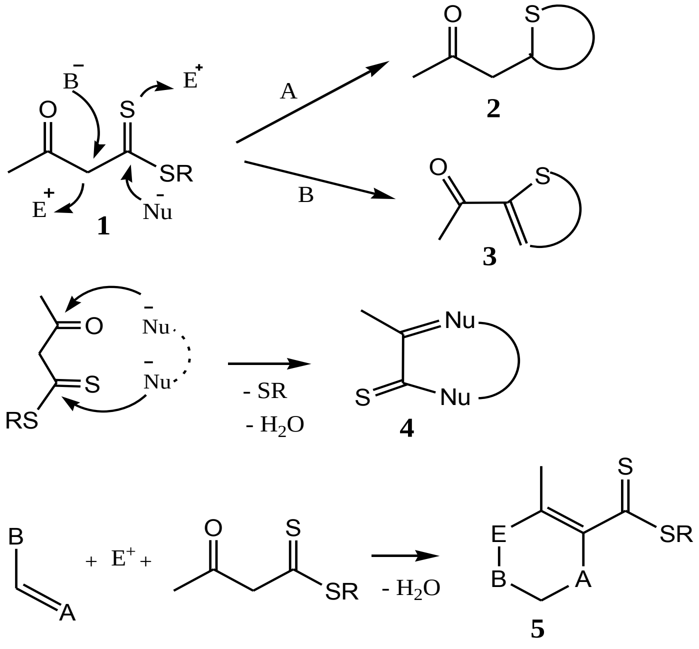
β-oxodithioesters are versatile multifunctional synthons in organic synthesis. A broad range of three- to six-membered, and several fused heterocycles have been synthesized using dithioesters.

β-Oxodithioesters **1**[1] exhibit intriguing nucleophilic reactivities as shown in Scheme **1**. Among the dithioesters, functionalized β-oxodithioesters have been recognized as potential C_3 fragments for the synthesis of diverse heterocyclic systems.[2-3] Possessing ambident electrophilicity at the 1,3-carbon centers due to the presence of carbonyl and thiocarbonyl functionalities, they can react with various dinucleophiles to afford a number of five- and six-membered heterocycles. In addition to this, they undergo cycloadditions, addition-elimination reactions, intramolecular ring cyclizations, and multicomponent reactions to generate libraries of bioactive heterocycles. In this presentation our recent developments on the synthesis of new bioactive heterocycles using this synthon will be highlighted.



Scheme 1

[1] Ramadas, S.R.; Srinivasan, P.S.; Ramachandran, J.; Sastry, V.V.S.K., *Synthesis*, **1983**, 605-622.

[2] Singh, O.M., *Dithiocarboxylates and related compounds in the synthesis of heterocycles,* in *Targets in Heterocyclic Systems: Chemistry and Properties* **2012**, Vol.16, 265-308. Attanasi, Orazio A.; Spinelli, Domenico (Eds.).

[3] Singh, T.P.; Bhattacharya, S.; Singh, O.M., *Org. Lett.* **2013**, *15*, 1974-1977

Hypervalent Iodine Promoted Organocatalytic Oxidative Ugi Reaction Under Metal-Free Condition

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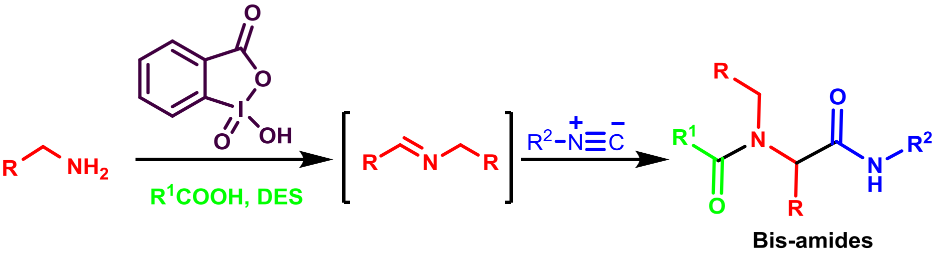
Department of Chemistry, Mohanlal Sukhadia University, Udaipur, India 313001



- **29 Examples**
- **Metal-free**
- **Operationally simple**
- **No chromatography**
- **Mild condition**
- **Environmentlly benign alternative to toxic organic solvents**
- **Catalyst recycle**
- **Solvent recycle**

Organocatalytic oxidations, the use of small organic molecules as catalysts for the oxidation reactions, are considered to be the major branch of organic synthesis along with transition metal catalysis. Despite their importance, oxidation reactions using organocatalysts have received limited synthetic attention with respect to their site-specific activity in asymmetric synthesis. We have developed a novel IBX-promoted oxidative coupling of primary amines and its utilization to Ugi reaction. Advantageously, the reaction could be carried out in choline chloride urea as a natural deep eutectic solvent. A range of imines and bisamides from pseudo-four-component oxidative Ugi reaction could be synthesized under mild and metal-free conditions.Advantageously, the oxidant (IBX) and solvent could be recycled up to five times with only a slight loss in activity

[1] Singh, Karandeep.; Kaur, A.; Mithu, V. S.; Sharma, S.; *J. Org. Chem*, ***2017***, http://dx.doi.org/10.1021/acs.joc.7b00594.

Enantioselective Access to Fragrances via An Asymmetric Prins Cyclization Reaction

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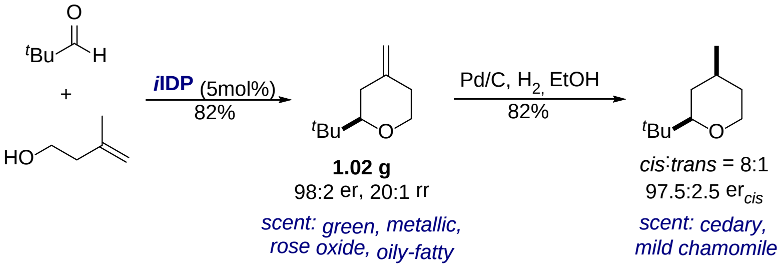
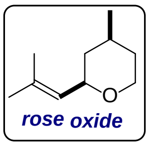
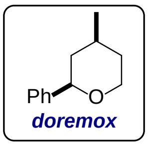
Mülheim an der Ruhr/45470

The Prins cyclization is an acid-catalyzed condensation of an aldehyde with a homoallylic alcohol. It is an efficient approach to construct functionalized tetrahydropyrans, which frequently present in natural products, pharmaceuticals and fragrances. Herein, we present a general Prins cyclization reaction, which provides an enantioselective access to perfumery ingredients, for example, rose oxide and doremox and a variety of scented compounds.[1]

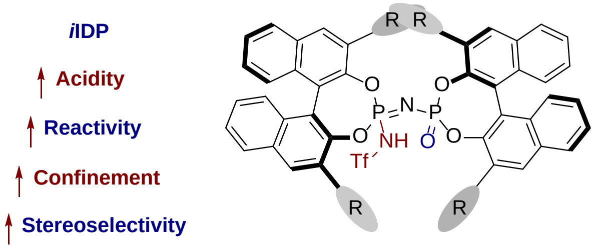



rose oxide


doremox

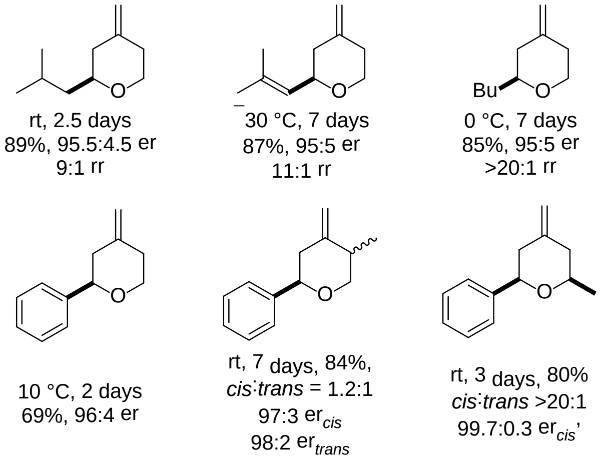
In 2015, the List group developed the first organocatalytic asymmetric Prins cyclization catalyzed by a chiral imidodiphosphate (IDP).[2] Functionalized 4-methylene tetrahydropyrans were afforded with moderate to good yields and excellent regio- and enantioselectivities. However, the scope of this reaction was limited to activated salicylaldehydes. We disclose that the development of new types of highly acidic and confined Brønsted acids imino-imidodiphosphates (*i*IDPs) enables a general catalytic asymmetric Prins cyclization here.

A New Highly Acidic and Confined Brønsted Acid



imino-imidodiphosphate (*i*IDP)

Selected examples catalyzed by *i*IDP



[1] L. Liu, P. S. J. Kaib, A. Tap, B. List *J. Am. Chem. Soc.* **2016**, *138*, 10822–10825.

[2] G. C. Tsui, L. Liu, B. List *Angew. Chem. Int. Ed.* **2015**, *54*, 7703–7706.

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF THE 3-NITRO ISOMER OF BIOREDUCTIVE TB DRUG PRETOMANID (PA-824)

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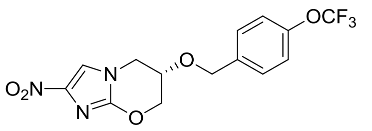
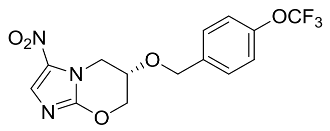
[c] Summit CMC Alliance LLC, 61 Hawthorne Place, Summit, New Jersey 07901, USA
[d] Global Alliance for TB Drug Development, 40 Wall Street, New York 10005, USA

Tuberculosis (TB) is still a major global public health threat – a persistent epidemic that currently afflicts over 11 million people worldwide[1]. Although TB can be treated, the lengthy and complex treatment regimens are inadequate to contain the disease, especially its multidrug resistant (MDR) forms. Very few new drugs have been developed in the past 50 years, and there is a need for anti-TB agents with different modes of action. The nitroimidazooxazine Pretomanid[2] (PA-824, **1**) is representative of a new class of bioreductive TB drugs and is currently undergoing Phase II/III clinical trials as part of a novel combination of agents (with bedaquiline, moxifloxacin and pyrazinamide) which can potentially reduce treatment duration and complexity[3].

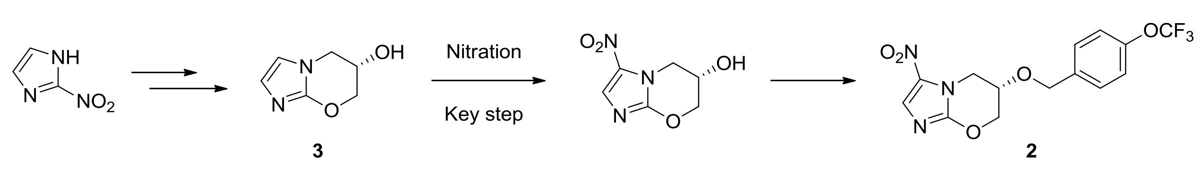


PRETOMANID (1)



3-NITRO ISOMER (2)

During the course of our studies, we became interested in the biological activity of the 3-nitro isomer of Pretomanid (**2**). The synthesis of **2** proved to be very challenging. The key and limiting step of the synthesis was a nitration reaction, involving the dihydro-imidazooxazinol intermediate **3**. We report here our optimization of the synthetic route, allowing us to prepare 10 g of the desired final target **2**. The structure of **2** was confirmed by X-ray crystallography. Preliminary data on its biological activity are also reported.



(1) *Global tuberculosis report 2016*; World Health Organization: Geneva, Switzerland, **2016**.
(2) Stover, C. K.; Warrener, P.; VanDevanter, D. R.; Sherman, D. R.; Arain, T. M.; Langhorne, M. H.; Anderson, S. W, Towell, J. A.; Yuan, Y.; McMurray, D. N.; Kreiswirth, B. N.; Barry, C. E.; Baker, W. R. Nature **2000**, *405*, 962-966.
(3) a) Kwon, Y.-S.; Koh, W.-J. *Expert Opin. Investig. Drugs* **2016**, *25*, 183-193. b) Global alliance for TB drug development [online] **2017**. Available: https://www.tballiance.org/portfolio/regimen/bpamz [Accessed 26 April 2017].

Synthesis of 2-arylquinoxaline via a triphenylstibane catalyzed oxidative cycloaddition of *α*-hydroxy ketones with 1,2-diamines

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and Shuji Yasuike[a,]*
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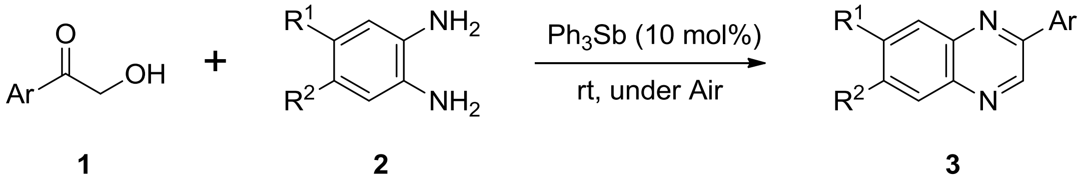
[b]*Faculty of Pharmaceutical Sciences, Hokuriku University, Kanazawa 902-1181*

Quinoxaline is an important building block for the synthesis of functional organic materials, and biologically active compounds. Among them, many synthesis methods of 2-arylquinoxalines have been reported, one of which is the oxidative cyclization of *α*-hydroxy ketones with 1,2-diamines in the presence of a transition metal or inorganic catalyst such as $CuCl_2$, MnO_2, CaO. Recently, we had reported triarylstibane to be a useful catalyst for the oxidation of benzoin to the corresponding benzyl derivative under mild conditions. [1] As a continuation of our studies on the promotion of oxidative catalytic reactions by organoantimony reagents, we report the one-pot tandem oxidative cyclization of *α*-hydroxy ketones with 1,2-diamines to afford the corresponding 2-arylquinoxalines under aerobic conditions. [2]

First of all, the reaction conditions such as antimony catalysts, solvents, and additives were studied using the oxidative cyclization of 2-hydroxyacetophenone (**1**; Ar = Ph) with 1,2-phenylendiamine (**2**; R^1, R^2 = H). The result showed that the reaction in the presence of triphenylstibane (10 mol%) as catalyst led to the formation of 2-phenylquinoxaline (**3**) in excellent yield under aerobic conditions. The sufficiency and generality of this protocol was evaluated by examining the reactions of various *α*-hydroxy ketones and *o*-phenylendiamines. *α*-Hydroxy ketones and *o*-phenylendiamines gave the corresponding 2-arylquinoxalines in moderate to good yields, whether bearing electron-donating or -withdrawing group on their aromatic ring. The reaction using aliphatic diamine was also gave the corresponding hexahydroquinoxaline. This reaction is the first example of oxidative cyclization catalyzed by organoantimony compounds. The possible mechanism of triphenylstibane catalyzed oxidative cycloaddition will be discussed.



Ar = 4-Tol, Ph, 4-CNC_6H_4, 2-Naphthyl, etc.
R^1, R^2 = H, OMe, Me, CN, etc.

[1] Yasuike, S.; Kishi, Y.; Kawara, S-i.; Kurita, J. *Chem. Pharm. Bull.* **2005**, *53*, 425-427.
[2] Matsumura, M.; Takada, R.; Ukai, Y.; Yamada, M.; Murata, Y.; Kakusawa, N.; Yasuike, S. *Heterocycles* **2016**, *93*, 75-83.

Synthesis and physico-chemical characterization of some thiazole aurones

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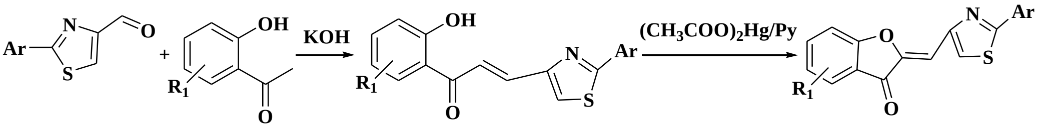
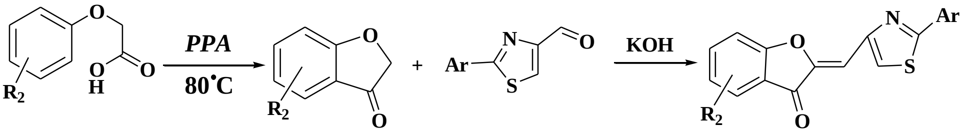
Daniela Hanganu[4], Valentin Zaharia[1]

[1]*Organic Chemistry, Department 1, Faculty of Pharmacy, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca*
[2]*Pharmaceutical Technology and Biopharmacy, Department 4, Faculty of Pharmacy, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca*
[3]*Biocatalysis and Biotransformation Research Group, Faculty of Chemistry and Chemical Engineering, Babeş-Bolyai University, Cluj-Napoca*
[4]*Pharmacognosy, Department 3, Faculty of Pharmacy, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca*

Aurones, 2-benzylidenebenzofuran-3-(2H)-ones, and chalcones, 1,3-aryl-2E-propene-1-ones, are natural compounds whose therapeutic potential has been highlighted with studies that revealed their anticancer, antimicrobial, antioxidant and anti-inflammatory properties (1, 2).
Based on these considerations and being aware of the biological potential of thiazole, our aim was to synthesize new thiazole *ortho*-hydroxychalcones and the corresponding aurones in order to evaluate their biological properties. The thiazole *ortho*-hydroxychalcones were synthesized *via* Claisen-Schimdt condensation of thiazole aldehydes with *ortho*-hydroxyacetophenones. By the oxidative cyclization of thiazole *ortho*-hydroxychalcones with mercury (II) acetate in pyridine, the corresponding aurones were synthesized.



Another series of aurones was synthesized by condensation between thiazole aldehydes and benzofuran-3-ones in basic media. The benzofuran-3-ones were synthesized by the cyclization of variously substituted phenoxyacetic acids in the presence of polyphosphoric acid (PPA).



The compounds were purified by column chromatography or recrystallization and their chemical structure was confirmed by ^{1}H NMR, ^{13}C NMR, IR and MS.
The thiazole *ortho*-hydroxychalcones were tested for their antioxidant activity using the DPPH free radical scavenging assay with ascorbic acid and butyl-hydroxytoluene as standards. The synthesized thiazole *ortho*-hydroxychalcones showed no inhibition towards the free radical DPPH, compared to the standards.

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One-pot and step-wise regioselective synthesis of polyfunctionalized thieno[3,2-c]pyridin-4-ones

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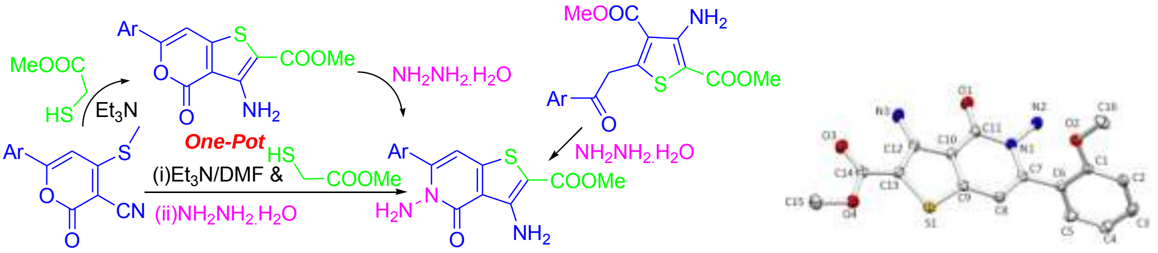
Abstract: One pot and step wise synthesis of methyl 3,5-diaminothieno[3,2-*c*]pyridine-4-one-2-carboxylates **3** has been delineated by reaction of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles **1**, methyl mercaptoacetate **2** and hydrazine hydrate.[1,2] During stepwise synthesis functionalized thieno[3,2-*c*]pyran-4-one **1** was isolated [3,4] and treated with hydrazine hydrate in further step to afford the desired product. Analogously, condensation-cyclisation of with hydrazine hydrate delivered identical product, thieno[3,2-*c*]pyridine-4-ones **3** in excellent yields. The structure of isolated product **3** was ascertained by spectroscopic and single crystal X-ray diffraction analyses.



Scheme 1- One pot synthesis of *N*-aminothieno[3,2-*c*]pyridin-4-ones.

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Synthesis of partially reduced imidazo[1,2-*a*]pyridines through unprecedented base mediated (4+2) cyclization

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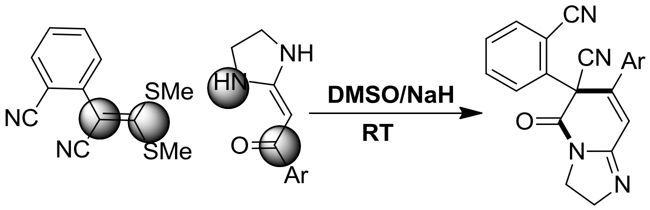

Abstract: A water-mediated regioselective synthesis of 6,7-diaryl-5-oxo-2,3,5,6-tetrahydro-imidazo[1,2 *a*] pyridine-6-carbonitriles have been developed by reaction of 2-[1-cyano-2, 2- bis (methylsulfanyl) vinyl]benzonitrile and 1-aryl-2-(imidazolidin-2-ylidene)ethanones[1-4] under basic conditions. This reaction involves unprecedented (4+2) annulations to yield sterically hindered compounds. The compound structure was confirmed by single crystal X-ray.

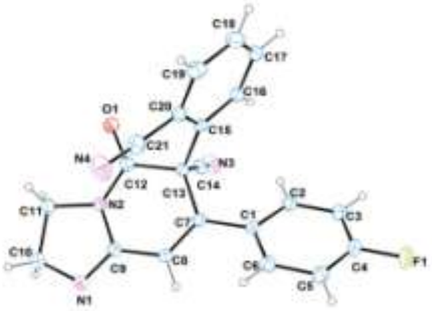

Fig. 1 ORTEP diagram of compound at 30% probability with atom numbering scheme. Only one molecule of the asymmetric unit comprising of two molecules is presented

References:

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Regioselective Ring-Opening Cyclization of Spirocyclopropanes with Amines: An Efficient Synthetic Method for Highly Substituted Indoles

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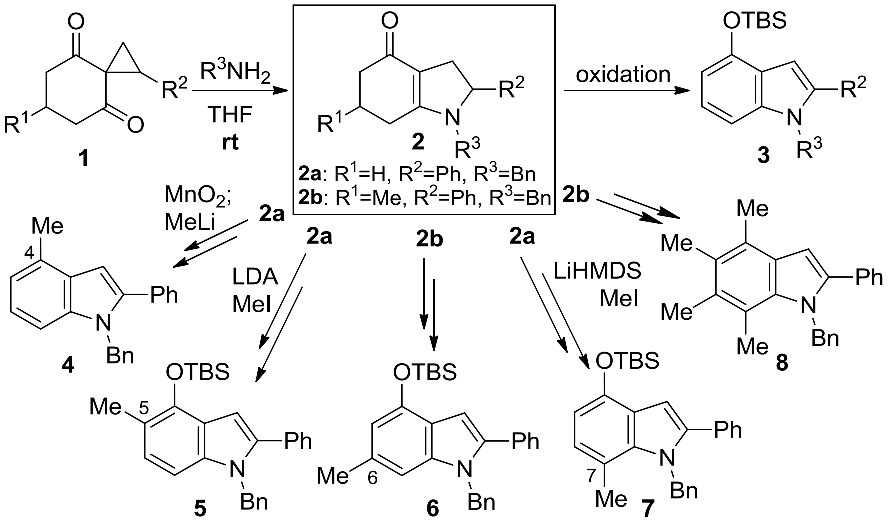
Cyclopropanes are extremely versatile building blocks in organic synthesis because of the high reactivity arising from their strong ring strain. Ring-opening cyclization of doubly activated cyclopropanes has emerged as a powerful method for the synthesis of a variety of carbo- and heterocyclic compounds. We herein report the ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes **1**[1] with primary amines as a potential route to highly substituted indoles.

The reaction of spirocyclopropanes **1** with primary amines at room temperature proceeded regioselectively to give tetrahydroindol-4(5*H*)-ones **2** without any 3-substituted isomers in good to excellent yields. A variety of primary amines and spirocyclopropanes **1** can be used in the reaction and **2** was readily converted into 4-hydroxyindole **3** by oxidation.[2]



Since **2** contains the enaminone moiety and has several reaction points, it would become a potential key synthetic intermediate for highly substituted indoles. 6-Methylindole **6** was synthesized from a readily available 6-methyltetrahydroindol-4(5*H*)-one **2b** by oxidation. Synthesis of 5- and 7-methylindoles **5** and **7** was achieved by regioselective methylation of **2a** followed by oxidation to indoles. 4-Methylindole **4** was synthesized by oxidation to pyrrole derivative, methylation with methyllithium, and oxidation to indole. Furthermore, synthesis of 4,5,6,7-tetramethylindole **8** was achieved from **2b** by using these regioselective alkylations.

Acknowledgements: This work was supported, in part, by JSPS Core-to-Core Program, B. Asia-Africa Science Platforms.

[1] (a) Nambu, H.; Fukumoto, M.; Hirota, W.; Ono, N.; Yakura, T., *Tetrahedron Lett.*, **2015**, *56*, 4312−4315. (b) Nambu, H.; Ono, N.; Hirota, W.; Fukumoto, M.; Yakura, T., *Chem. Pharm. Bull.* **2016**, *64*, 1763−1768.
[2] Nambu, H.; Fukumoto, M.; Hirota, W.; Yakura, T., *Org. Lett.*, **2014**, *16*, 4012−4015.

Stereoselective Total Synthesis of Myriocin and Related Natural Products through Oxathiazinane Intermediate

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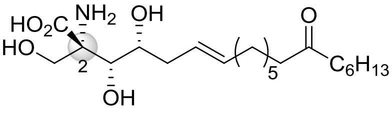
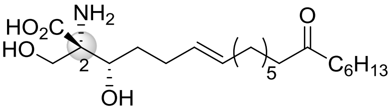
Toyama 930-0194, Japan

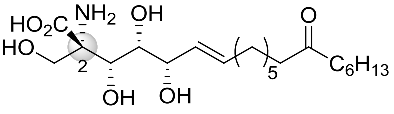
Myriocin (**1**), mycestericin D (**2**), and sphingofungin E (**3**) are complex *a*,*a*-disubstituted amino acid natural products structurally related to sphingolipids. Due to their challenging structural motif containing a quaternary chiral center and interesting biological activity, **1**−**3** are attractive targets for total synthesis. We herein report stereoselective total synthesis of **1**−**3** using a sequence of Rh(II)-catalyzed C−H amination to oxathiazinane *N*,*O*-acetal and the following its alkylation as a key step.



myriocin (**1**)

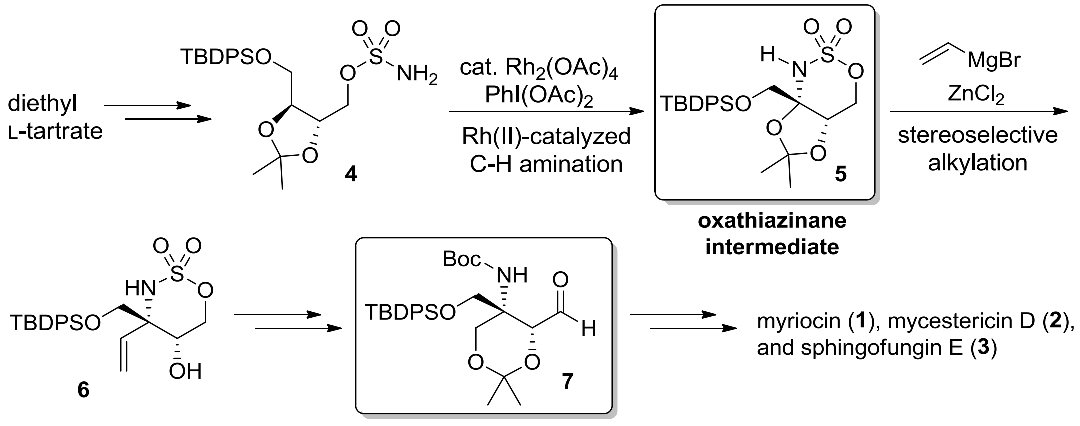


mycestericin D (**2**)



sphingofungin E (**3**)

Our synthesis started from diethyl L-tartrate, which was converted into sulfamate **4** in 4 steps. The reaction of **4** with $PhI(OAc)_2$ and MgO in the presence of $Rh_2(OAc)_4$ afforded stereospecifically oxathiazinane *N*,*O*-acetal **5** in high yield. Alkenylation of *N*,*O*-acetal **5** using vinylmagnesium bromide in the presence of zinc chloride proceeded stereoselectively to provide an oxathiazinane **6** bearing a quaternary chiral center in high yield. After conversion of **6** into aldehyde **7**, myriocin (**1**), mycestericin D (**2**), and sphingofungin E (**3**) were synthesized, respectively.[1]



Acknowledgements: This work was supported, in part, by JSPS Core-to-Core Program, B. Asia-Africa Science Platforms.

[1] (a) Nambu, H.; Noda, N.; Niu, W.; Fujiwara, T.; Yakura, T., *Asian J. Org. Chem.*, **2015**, *4*, 1246–1249. (b) Noda, N.; Nambu, H.; Ubukata, K.; Fujiwara, T.; Tsuge, K.; Yakura, T., *Tetrahedron,* **2017**, *73*, 868–878. (c) Noda, N.; Nambu, H.; Fujiwara, T.; Yakura, T., *Chem. Pharm. Bull.*, in press.

Acid-Catalyzed Ring-Opening Cyclization of Spirocyclopropanes: Total Synthesis of Benzofuran Natural Product Cuspidan B

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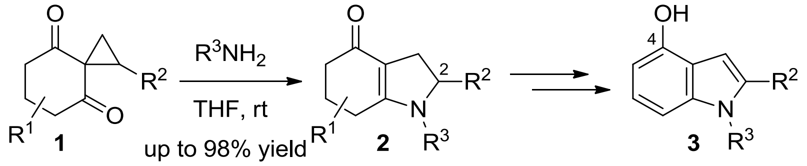
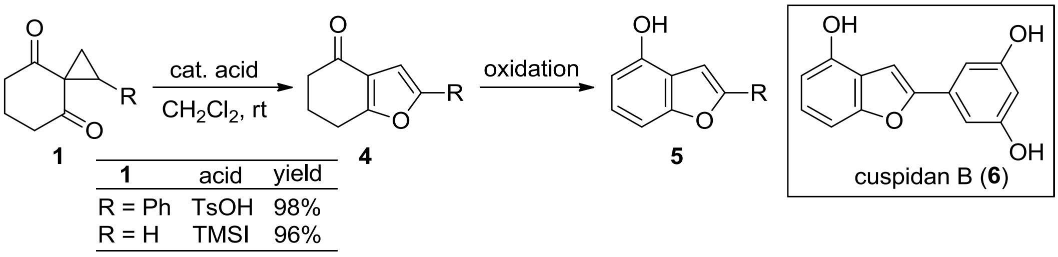
Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan

Recently, we reported a novel ring-opening cyclization of spirocyclopropanes **1**[1] with primary amines to generate 2-substituted tetrahydroindol-4(5*H*)-ones **2**, one of which was easily converted into 4-hydroxyindole **3**.[2] The reaction of **1** with a primary amine proceeded at room temperature without any additives in contrast to similar reactions of nonspirocyclopropanes. This high reactivity of spirocyclopropanes **1** stimulated us to investigate further development of the reaction using **1**. We herein reported acid-catalyzed ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes as a new route to benzofurans.



The reaction of 2-aryl- and 2-alkyl-substituted spirocyclopropanes **1** using a catalytic amount of TsOH proceeded at room temperature to provide 2-substituted 3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-ones **4** in high yields without the formation of 3-substituted isomers.[3] Although the reaction of nonsubstituted spirocyclopropanes **1** (R = H) did not proceed under the same conditions, the use of iodotrimethylsilane (TMSI) as a catalyst gave the corresponding product **4** in 96% yield. The obtained product **4** was converted into benzofuran **5** by oxidation. Furthermore, the first total synthesis of cuspidan B (**6**)[4] was achieved by using the present method.



1	acid	yield
R = Ph	TsOH	98%
R = H	TMSI	96%

Acknowledgements: This work was supported, in part, by JSPS Core-to-Core Program, B. Asia-Africa Science Platforms.

[1] (a) Nambu, H.; Fukumoto, M.; Hirota, W.; Ono, N.; Yakura, T., *Tetrahedron Lett.*, **2015**, *56*, 4312−4315. (b) Nambu, H.; Ono, N.; Hirota, W.; Fukumoto, M.; Yakura, T., *Chem. Pharm. Bull.* **2016**, *64*, 1763−1768.
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Synthesis of benzo[*b*]selenophene-fused imidazo[1,2-*a*]pyridines: Copper-catalyzed tandem cyclization of 2-(2-iodophenyl)imidazo[1,2-*a*]pyridine derivatives with selenium

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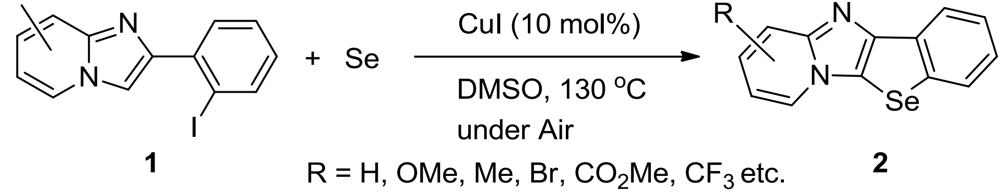
Organoselenium compounds have attracted significant interest because of their potential as important reagents in organic synthesis and biological activities. Transition metal-catalyzed cross-coupling reaction is one of the most popular methods to form C‑Se bonds. Herein, we report efficient and simple Cu-catalyzed tandem cyclization *via* one-step Ullmann-type *Se*-arylation and Csp^2–H selenation for the synthesis of novel benzo[4',5']selenopheno[3',2':4,5]imidazo[1,2-*a*]pyridines **2** from 2-(2-iodophenyl)imidazo[1,2-a]pyridine derivatives **1** and selenium powder in the absence of additives under aerobic conditions.$^{1)}$

We initially focused our attention on the determining the optimum conditions for the cyclization of 2-(2-iodophenyl)imidazo[1,2-*a*]pyridines **1a** (R= H) with Se powders. The best reaction condition was determined to be as follows: **1a** was treated with 1.0 eq. Se powder using 10 mol% CuI as catalyst in DMSO at 130 °C without the use of any ligand and/or inorganic reagent under aerobic conditions. To demonstrate the efficiency and versatility of the determined protocol, reactions of various iodides **1** with Se powder were investigated under the optimized reaction conditions. The substrates **1** bearing different functional groups with electron-donating and electron-withdrawing substituents at the 6-position on the imidazopyridine ring afforded the corresponding benzoselenophene-fused imidazopyridines **2** in good-to-excellent yields. The absorption maxima of **2a** (R= H), imidazopyridine, and benzoselenophene are 351.0, 302.5, and 305.0 nm, respectively. The maximum absorption of tetracyclic compound **2a** was red-shifted by 45-47 nm in comparison with those of the other two cyclic heteroles. These results suggest that the π-conjugated system of benzoselenophene-fused imidazopyridine **2a** is expanded.



1 R = H, OMe, Me, Br, CO_2Me, CF_3 etc. **2**

[1] Matsumura, M.; Sakata, Y.; Iwase, A.; Kawahata, M.; Kitamura, Y.; Murata, Y.; Kakusawa, N.; Yamaguchi, K.; Yasuike, S., *Tetrahedron Lett.*, **2016**, *57*, 5484-5488.

Synthesis of 5-organostibano-1*H*-1,2,3-triazoles by Cu-catalyzed azide-alkyne cycloaddition and their reactivity

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Naoki Kakusawa,[c] Kentaro Yamaguchi [b] and Shuji Yasuike [a,*]
[a]*School of Pharmaceutical Sciences, Aichi Gakuin University, Nagoya, 464-8650,*
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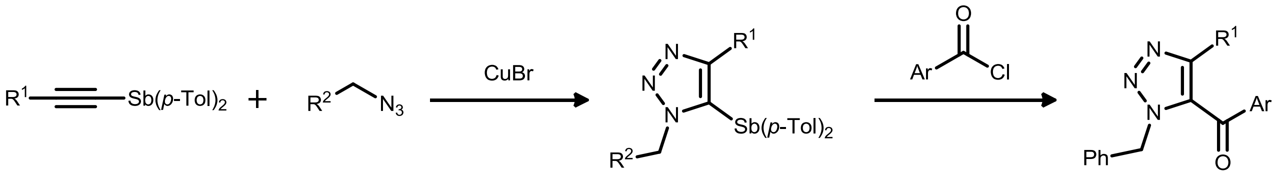
[c]*Faculty of Pharmaceutical Sciences, Hokuriku University, Kanazawa, 920-1181*

1,3-Dipolar azide-alkyne cycloaddition (AAC) has been effective for the synthesis of a wide variety of 1,2,3-triazoles. Recently, 1,4,5-trisubstituted-1,2,3-triazoles have been synthesized and applied for organic synthesis. To the best of our knowledge, there have been no reports concerning the systhesis of 1,4,5-trisubstituted-1,2,3-triazoles having antimony (Sb) atom at 5-position. Herein, we reported the synthesis of 5-stibanotriazole using the Cu-catalyzed AAC of various ethynylstibanes (**1**) with organic azide (**2**) and their reactivity. [1,2]

First, the optimal experimental conditions were determined for the regioselective Cu-catalyzed AAC reaction of di-*p*-tolylethynylstibane (**1a**) and benzyl azide (**2a**). The best reaction condition was determined to be as follows: **1a** was treated with **2a** using 5 mol% CuBr in THF at 60 ℃ under aerobic conditions. The reaction of **1** and **2** bearing various functional groups afforded the corresponding products (**3**) in good to excellent yields. We investigated reactivity of 5-position of triazole (**3a**) as an anion equivalent. The acyl-induced deantimonation of 5-stibanotriazole (**3a**) with acyl chlorides afforded the corresponding trisubstituted 5-acyltriazoles (**4**). **3a** was treated with an equimolecular amount of phenyllithium at -78 ℃. Sb-Li exchange reaction was proceeded and subsequent treatment with various electrophiles formed corresponding triazoles containing a benzyl moiety. These result indicate that functionalization of heterocycles are possible based on Sb side chain.



1 (0.5 mmol) **2** (1 eq.) **3** **4**

R^1 = **1a** : Ph
2a : 4-MePh
3a : *n*Bu

R^2 = **2a** : Ph
2b : cinnamyl
2c : CO_2Et etc.

Ar = **4a** : Ph
4b : 4-MeOPh
4c : 2-NO_2 etc.

[1] M. Yamada, M. Matsumura, Y. Uchida, M. Kawahata, Y. Murata, N. Kakusawa, K. Yamaguchi, S. Yasuike, *Beilstein J. Org. Chem.* **2016**, *12*, 1309-1313.

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Enantioselective C-H Photooxygenation of Aldehydes via Enamine Catalysis

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Maksymilian Karczewski and Dorota Gryko*
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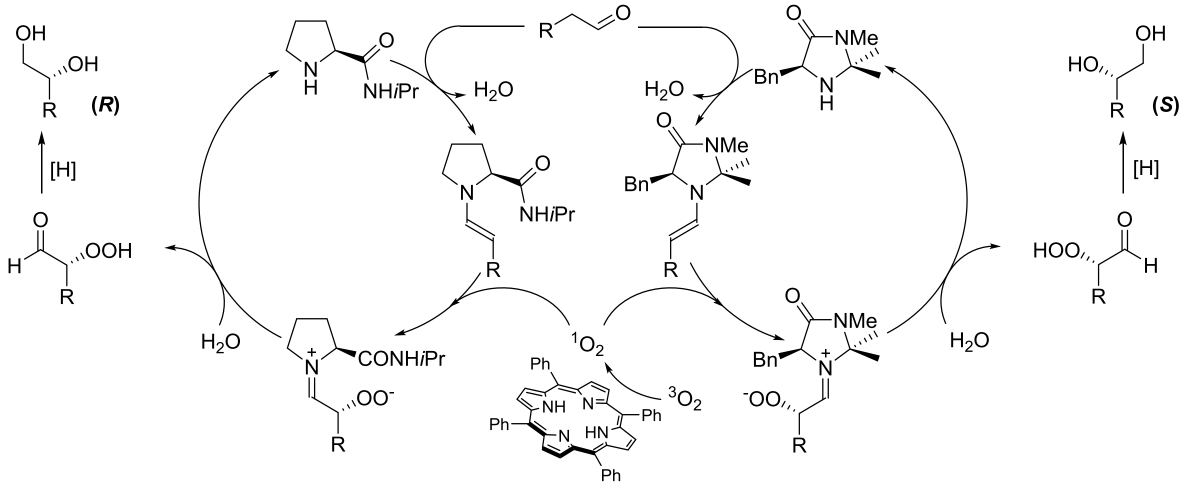
Singlet oxygen is an efficient and ecological tool for oxidation of organic compounds that can be easily generated by visible light *via* photosensitization of dyes (e.g. tetraphenylporphyrin). Despite high reactivity and small size of this reagent, there are many successful examples of using it in diastereoselective synthesis. On the contrary, enantioselective reactions are quite limited.[1,2] The interesting idea of the synergistic use of an organocatalyst and singlet oxygen in enantioselective α-oxygenation of carbonyl compounds, previously reported by Cordova,[3] was contradictory to the well established fact, that enamines can be easily oxidized by singlet oxygen to amides and carbonyl compounds.[4]

Our detailed optimization and wide organocatalyst screening allowed elaborating a method for efficient α-photooxygenation of aldehydes. We were able to obtain both enantiomers using catalysts easily derived from natural aminoacids. The (*R*)-enantiomer predominated in prolinamide-catalyzed reactions, while imidazolidinone assured the formation of the (*S*)-stereoisomer. Mechanistic studies, including DFT calculation and detailed analysis of the reaction mixture, confirmed the enamine mechanism of the reaction.[5]



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Stereoselective Non-covalent remote functionalization in the synthesis of tetrahydrothiophene derivatives

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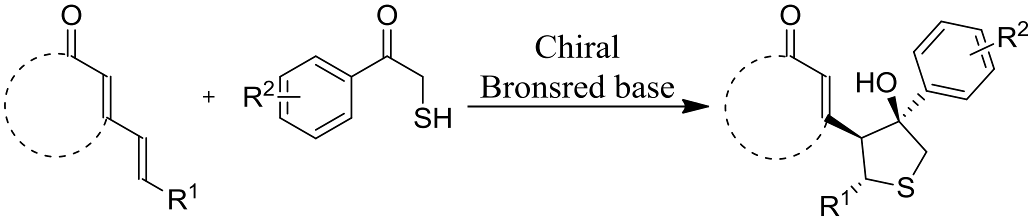
Possibility of stereocontrolled remote functionalization of organic compounds is one of the most interesting feature of modern asymmetric catalysis. Abovementioned term refers to a reaction which takes place on a distant site of the prochiral substrate *i.e.* a reaction site separated with at least 5 chemical bonds form the stereodifferentiating structural motif. First examples of such transformations were non-catalytic and very limited in terms of substrate scope [1]. Aminocatalysis overcame these limitations and became a tool of choice for the remote functionalization of carbonyl compounds [2]. Herein, we report a novel, non-aminocatalytic and non-covalent example of organocatalytic asymmetric remote functionalization of 2,4-dienones [3]. Developed reaction cascade proceeds in a sequence involving 1,6-conjugate addition followed by the intramolecular aldol reaction and leads to heterocyclic systems containing three contiguous stereocenters (including one quaternary) with high enantiomeric and diastereoisomeric ratios and good to high yields. Possible mechanism of the developed reaction is also proposed and rationalized.



up to 97:3 er
up to >20:1 dr
up to 98% yield

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Brønsted Acid-Catalyzed Addition of Enamides to *ortho*-Quinone Methide Imines – Efficient and Highly Enantioselective Synthesis of Chiral Tetrahydroacridines

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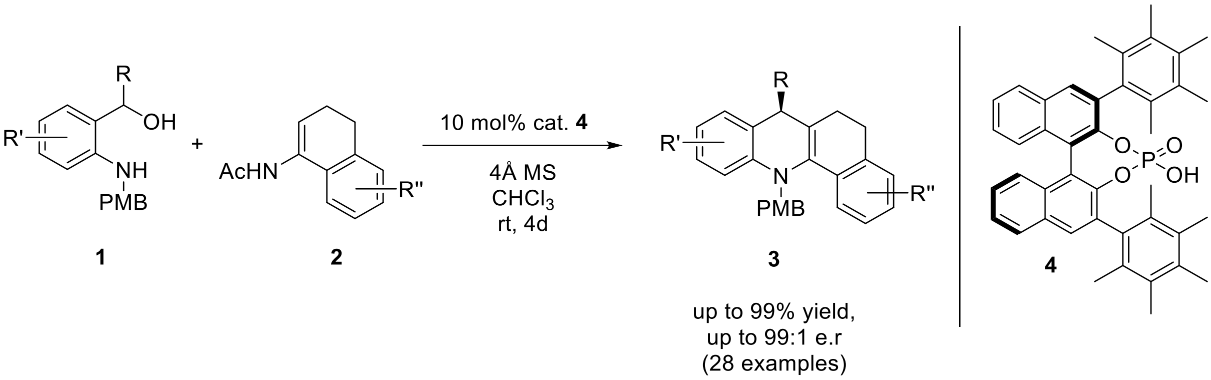
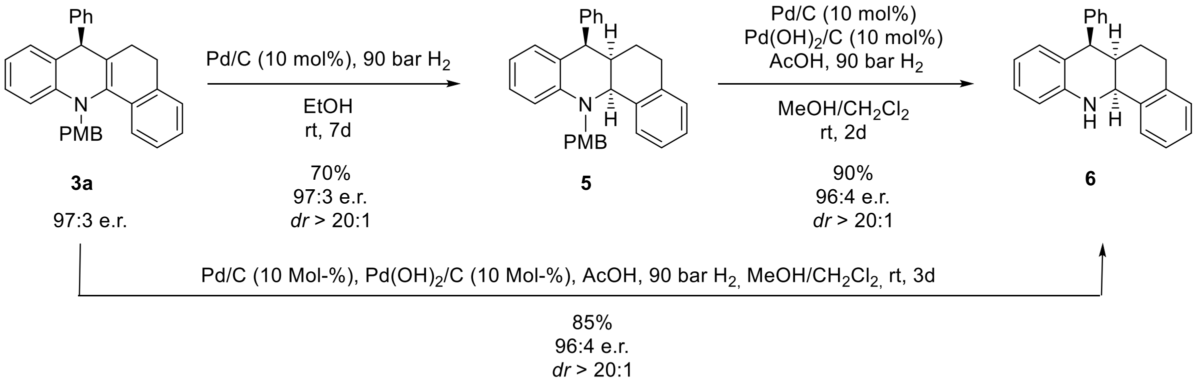
Due to their high biological activity 1,4-dihydroquinolines are priviliged structural motifs in the field of medicine and biology.[1] However, only a few direct syntheses towards this class of substances are currently known, which are also quite limited in their substrate scope.[2] Herein we report a conceptual novel, one-step synthetic strategy comprising a highly enantioselective, phosphoric acid-catalyzed formal cycloaddition of *in situ* generated *ortho*-quinone methide imines with enamides **2** as the central step.[3] The transient *ortho*-quinone methide imines whose synthetic potential was only discovered very recently were formed through acid-catalyzed dehydration of *ortho*-amino benzyl alcohols **1** and the initial cycloadducts were converted to the final tetrahydroacridines **3** by elimination of acetamide.



The tetrahydroacridines **3** were obtained with generally good yields and excellent enantioselectivity of up to 99:1 e.r. Furthermore, they could be readily converted into either protected or deprotected saturated hexahydroacridines **5**/**6** containing two new stereogenic centers with very high diastereoselectivity.



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Synthesis and Pharmacological Evaluation of Translocator 18 kDa Protein (TSPO) Ligands with Binding Sensitivity to Human Single Nucleotide Polymorphism rs6971.

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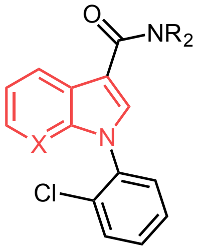
The increasing incidence of pathological conditions associated with neurodegeneration including Alzheimer's and Parkinson's disorders have prompted the need for novel therapeutic targets.[1-3] Since its discovery in 1977 and elucidation of its role in neurosteroid biosynthesis, the 18 kDa translocator protein (TSPO, formally known as the peripheral benzodiazepine receptor) presents a viable target for pharmaceutical intervention.[1] Furthermore, its upregulation within cancer has attracted considerable attention as a potential biomarker for neoplastic growth or as a novel receptor target for chemotherapy.[4]

The clinical utility of TSPO ligands currently available has been hindered by the presence of a polymorphism, rs6971, which causes a non-conservative substitution of alanine for threonine at amino acid residue 147 (TSPO A147T).[4] Efforts to develop a TSPO ligand that binds TSPO WT and TSPO A147T with similarly high affinity have been hampered by a lack of knowledge about how ligand structure differentially influences interaction with the two forms of TSPO. Whilst there are several distinctive chemical classes of TSPO ligands, there is no definitive chemotype. Each chemical class has different activity and selectivity profiles, making the characterisation of the TSPO binding sites a promising area of research. A series of novel TSPO ligands were developed based on the indole (**1**) and carbazole (**2**) heterocyclic core. To assess the potential of these analogues between the two TSPO isoforms, human embryonic kidney cell lines stably over-expressing human TSPO WT and TSPO A147T were established, and the analogues synthesised were tested to determine their binding affinity to both isoforms. Presently, the carbazole acetamides (**2**) are a class of high affinity TSPO ligands, displaying nanomolar binding affinities to both TSPO isoforms. Details of the current work on the synthesis and binding affinity of these analogues will be presented.



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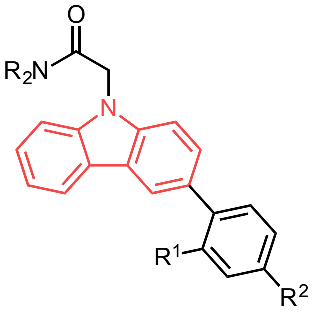

2

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Diverse and versatile synthesis of bioactive heterocyclic compounds from keto acids

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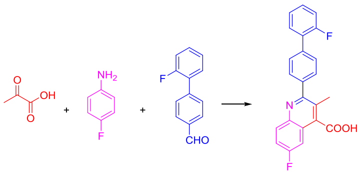
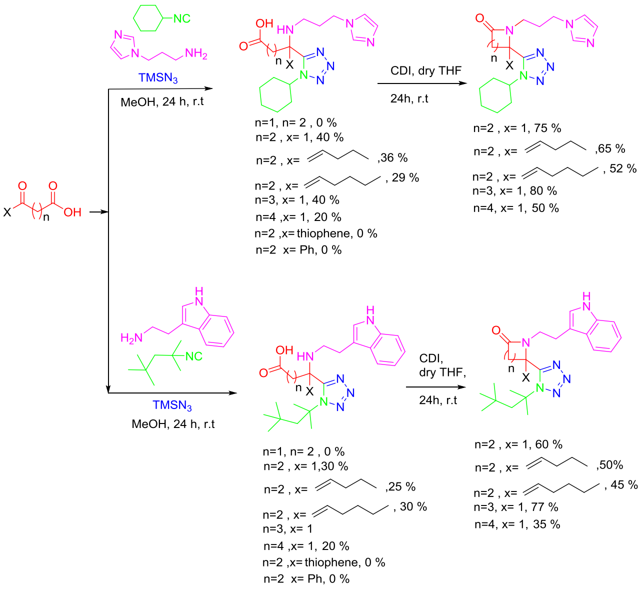
Sheffield, S3 7HF, U.K.

Keto acids or ketoacids are also called oxoacids that can be identified as organic compounds containing a ketone group and carboxylic acid group. Keto acids are employed to be bifunctional starting material in multicomponent reactions MCR. Keto acids are key components for preparing new heterocyclic using MCR.



Multicomponent Reactions (MCRs) are reactions that combine at least three starting materials in a one-pot reaction to produce a new product. MCR are more beneficial due to their tremendous atom efficiency and they have played a significant role in the synthesis of heterocyclic compounds. It has been observed that high diversity and complexity can be obtained by using post-multicomponent reactions. This approach is suitable to provide high functionalized compounds such as lactams involving sequential reactions with further post-transformation reactions for instance cyclization and nucleophilic addition. The lactams feature privileged moieties in medicinal chemistry, therefore flexible synthetic methods are in high demand. Further functionalization of multicomponent products were employed to synthesize new heterocyclic compounds such as diones, tetrazoles, isoquinolines, isoindoline, pyrazol and piperazine derivatives.



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A green, robust and scalable continuous-flow synthesis of fused 3-aminoimidazo-heterocycles.

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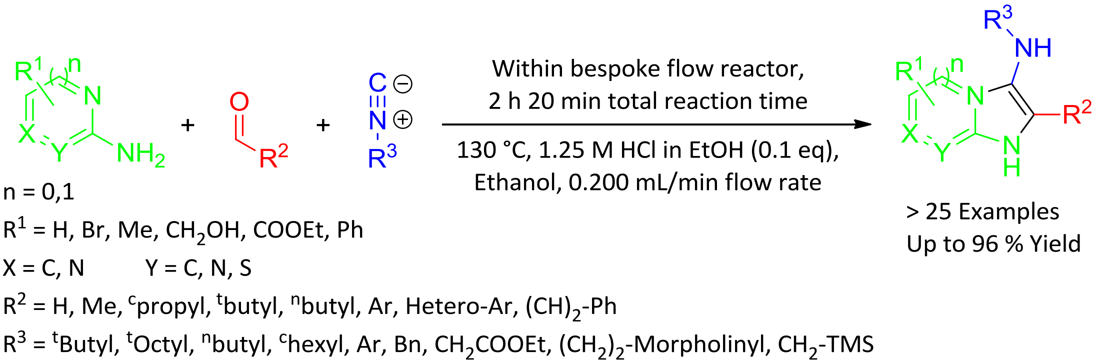
The Gröebke-Blackburn-Bienaymé reaction (GBBR) is an Ugi-like 3 component reaction, combining aldehyde, α-aminoazine and isocyanide reagents in a one-pot procedure to produce 3-aminoimidazo-heterocycles. [1][2][3]

Though there have been many developments since its discovery, use of the GBBR can still suffer from various problems using published procedures, including the use of chlorinated or hazardous solvents and expensive/environmentally unsustainable metal catalysts, limited substrate scope robustness, and long reaction times.[4][5]

Moreover, no currently published flow-based processes offer high yields across a broad substrate scope. [6][7] Aliphatic aldehydes and formaldehyde also have limited reported use in the GBBR. [8]

Our process delivers a flow-based, efficient, scalable and robust synthetic route towards a range of complicated heterocycles, utilising green conditions with ethanol as solvent, and only a dilute mineral acid catalyst.



n = 0,1

R^1 = H, Br, Me, CH_2OH, COOEt, Ph

X = C, N Y = C, N, S

R^2 = H, Me, ^{c}propyl, ^{t}butyl, ^{n}butyl, Ar, Hetero-Ar, $(CH)_2$-Ph

R^3 = ^{t}Butyl, ^{t}Octyl, ^{n}butyl, ^{c}hexyl, Ar, Bn, CH_2COOEt, $(CH_2)_2$-Morpholinyl, CH_2-TMS

The process tolerates various functional groups and substitution patterns on all reagents, and, crucially, enables the use of formaldehyde and aliphatic aldehydes. Over 25 examples have been synthesised in moderate to excellent yields.

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Towards an Asymmetric Synthesis of Tetrodotoxin

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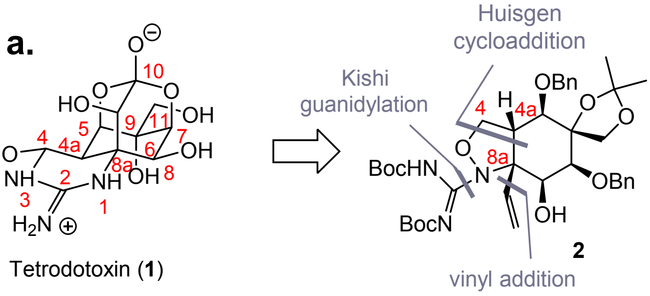
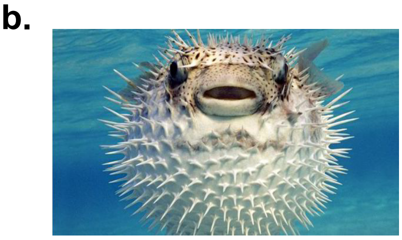
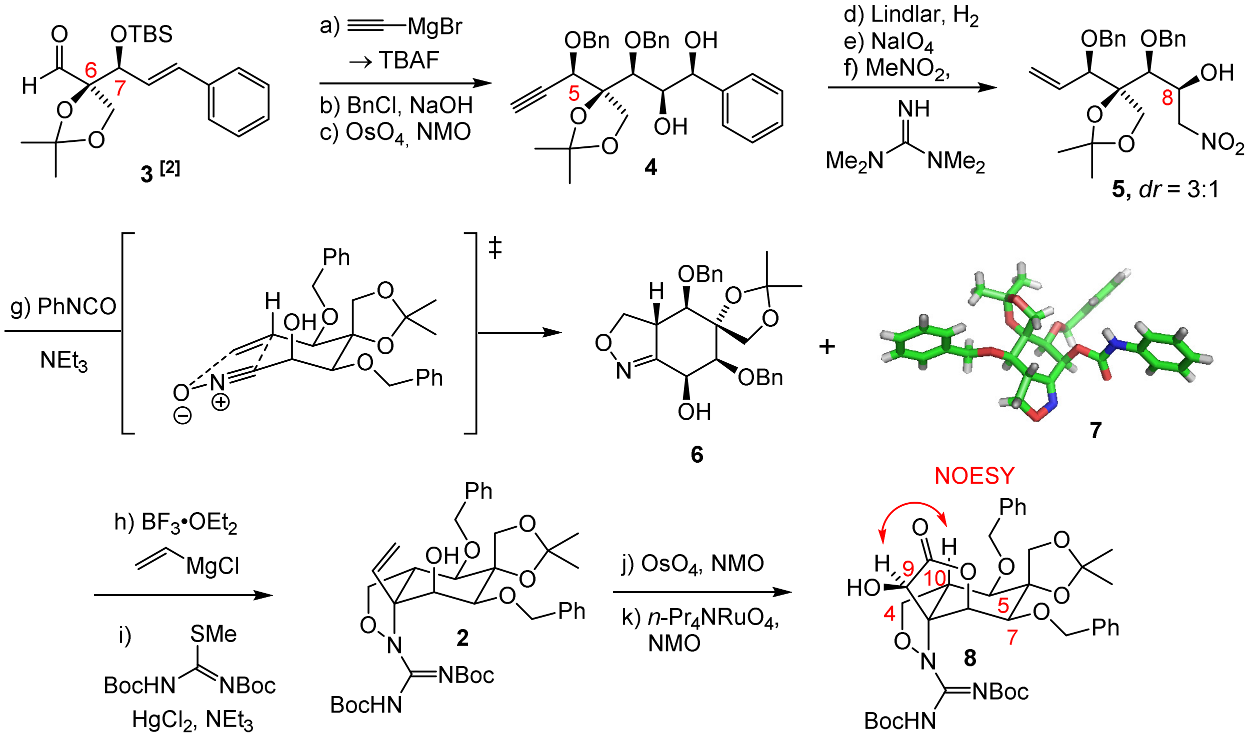
Tetrodotoxin (**1**, a) is one of the most toxic non-proteinaceous poisons with low molecular weight (M.W. = 319.3 g·mol^{-1}, LD$_{50}$ = 10.2 µg·kg^{-1}).[1] It is well-known as the toxin of the puffer fish (b), which has been a delicacy in Japanese cuisine for centuries and is renowned for its refined taste. The origin of its toxicity is the ability to selectively block voltage-gated sodium channels (Na$_V$1.1-1.9) with a preference for Na$_V$1.1-1.4 and Na$_V$1.6-1.7.





Our retrosynthetic analysis is based upon the premise that the latent C4 aldehyde and the C8a α-tertiary amine may arise from an isoxazolidine (**2**, a). This isoxazolidine moiety enables two reliable key retrons: a Huisgen 1,3-dipolar cycloaddition and a vinyl anion addition into the resulting oxime.



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Nitroso BODIPY dyes in the Development of Thiol Sensors

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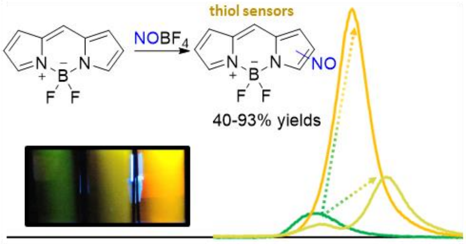
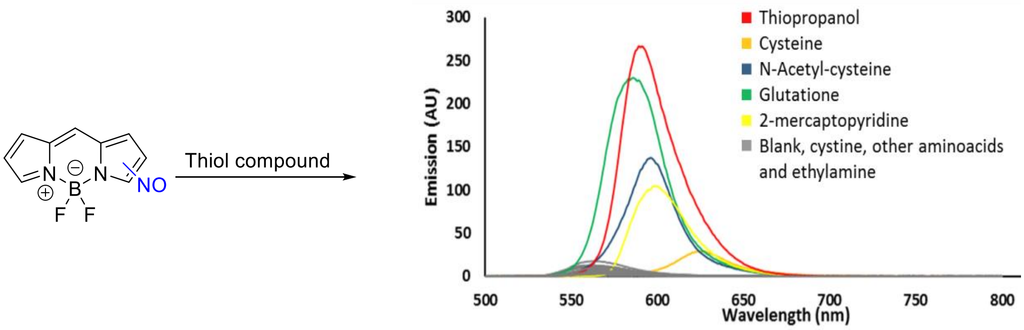
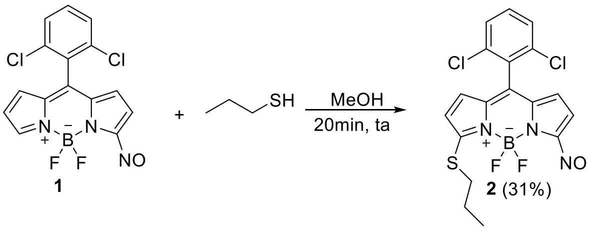
Departamento de Ciências Farmacêuticas, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil.



Previous work in our research group have explored nitrosation of BODIPY dyes[1], fluorophores with remarkable versatility concerning photophysical and reactivity properties[2]. Based on previously reported nitroso-dyes properties[3], we envisioned the application of nitroso BODIPYs as sensors for thiols. To test it, we analyzed the fluorescence of a solution of nitroso BODIPYs (0.5mM) in MeOH/Water 1:1 in the presence of thiopropanol, from which we observed an increased red-shifted emission. Similar emission changes were observed for solutions treated with cysteine (Cys), N-acetylcysteine (NAC), glutathione (GSH) and 2-mercaptopyridine while no relevant changes were observed for solutions treated with cystine, ethylamine or other amino acids.



To understand the underlying mechanism of the response of nitroso-substituted BODIPYs to thiol compounds, the reaction between **1** and thiopropanol was further investigated. Remarkably, TLC control showed the formation of a mixture of fluorescent red-shifted products. From this mixture, it was possible to isolate a major compound that was confirmed to be the thiopropyl-substituted BODIPY 2. Further studies will correlate structure and photophysical properties of this new compound to understand the mechanism involved in fluorescence changes while testing thiols.



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Microwave-Assisted Synthesis of a Novel Series 2-(Coumarin-3-yl)imidazo[1,2-a]pirimidin Fluorophores as Water Soluble Fluorescent Light-Up pH Probe For Acidic Environment

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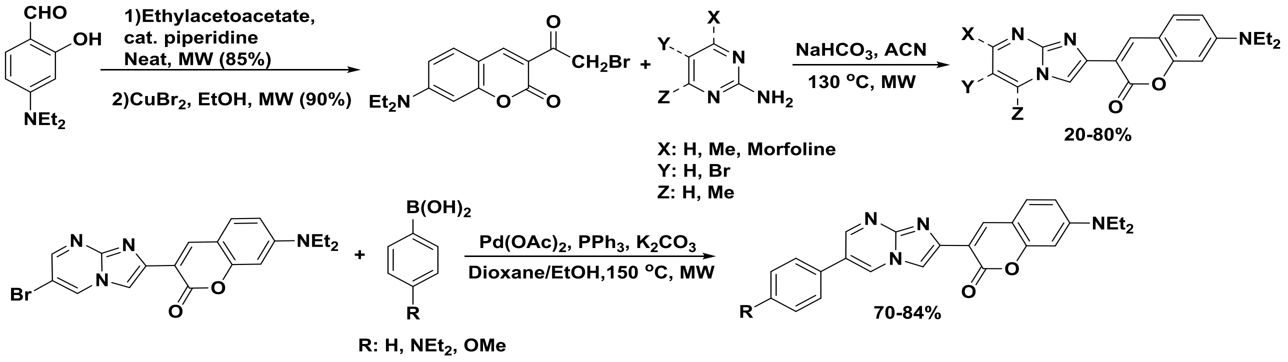
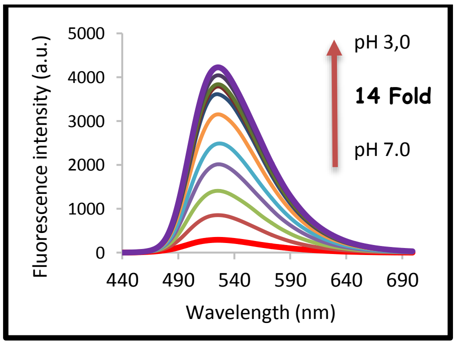
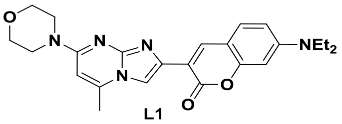
Detection of hydrojen ion by chemosensors is significant for biological environment. Especially, fluorescent chemosensors have several advantages due to their sensitivity, specificity, and real-time monitoring with fast response time. Main aim of this study, synthesis of new series 2-(coumarin-3-yl)imidazo[1,2-a]pyrimidine derivatives which are combined with coumarin ring, which is fluorophore group with well-known photophysical property, and imidazo[1,2-a]pyrimidine ring, which has potentially biological active, in the same molecule. Furthermore, titration studies were also investigated by UV-vis and fluorescence spectroscopy in the presence of trifluoroacetic acid (TFA) to determine the pH sensitivity of the compounds synthesized for their potential used as pH prob. Finally, acid dissociation constant (pKa) were determined by the UV-vis absorption spectroscopic method in buffer solution for selected three 2-(7-diethylaminocoumarin-3-yl)imidazo[1,2-a]pyrimidine derivatives.





Fluorescence emission spectra of probe (**L1**) (10 μM) in Na_2HPO_4-citric acid buffer solution at various pH values.



L1

pH-dependent photographs under day light (left) and UV light (right) (λ_{ex}:365 nm)

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Enzyme catalyzed multicomponent reactions as efficient tools for the synthesis of new N-phenyl-2-aminothiazole derived Mannich bases

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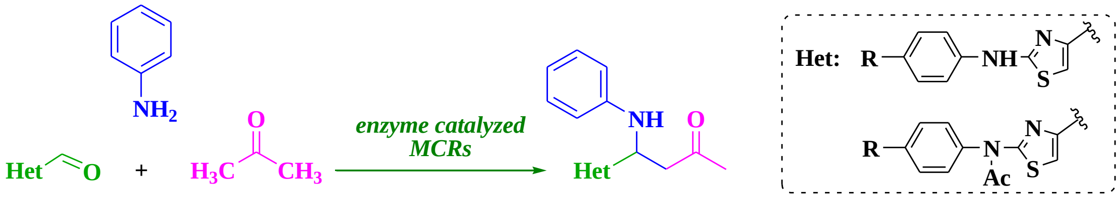
Mannich bases, also known as beta-amino ketones, are recognized to possess various biological activities such as antibacterial, antifungal, anti-inflammatory and anticancer properties.[1]
The 2-aminothiazole scaffold is an important pharmacophore which is currently found as central core in the structure of many bioactive compounds.
Multicomponent reactions (MCRs) have become powerful and versatile tools in drug discovery and modern synthetic chemistry because of their practical simplicity, rapidity and high atom economy. Enzyme catalyzed reactions represent a valuable green alternative in organic synthesis due to their low toxicity, mild reaction conditions and high chemo-, regio- and stereoselectivity. Lipases are versatile biocatalysts which, besides their natural role, are able to catalyze different multicomponent reactions, such as C-C and C-N bond forming, in Mannich type condensations.[2]
Being aware of the biological potential of Mannich bases and 2-aminothiazole derivatives, we decided to apply the lipase catalyzed multicomponent Mannich type condensation in order to access new thiazole derived Mannich bases for medicinal applications.
The thiazole aldehydes necessary as substrates in the enzymatic reactions were synthesized starting from different aryl isothiocyanates, by treatment with ammonia, followed by the Hantzsch condensation of the obtained N-aryl thioureas with 1,3-dichloracetone. The obtained 2-arylamino-4-chloromethylthiazoles were transformed into the corresponding aldehydes by N-acetylation with acetic anhydride, followed by Sommelet reaction.
The thiazole Mannich bases were synthesized by applying an enzymatic trimolecular condensation of thiazole aldehydes with aniline and acetone, using lipase B from *Candida antarctica* as biocatalyst, in acetone/water mixture as reaction media, at neutral pH.



The chemoenzymatic method allowed us to obtain new pharmacologically useful Mannich bases containing the 2-arylaminothiazole moiety, in good yields and by using mild and eco-friendly reaction conditions. Spectral analyses MS, ^{1}H NMR and ^{13}C NMR confirmed the structures of the obtained compounds.

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Stereoselective chemoenzymatic synthesis of chiral thiazole beta-amino acids

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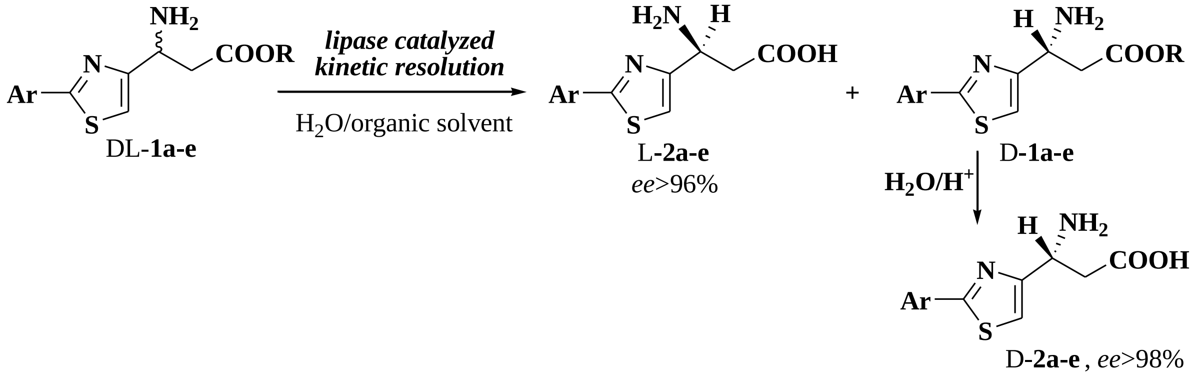
Enantiomerically pure β-amino acids and their derivatives are of great utility in medicinal chemistry, both individually as well as key-intermediates in the synthesis of new chiral bioactive compounds such as peptides, polymer materials and other functionalized compounds.

The thiazole ring, originally a naturally occurring heterocycle, is currently present as central core in the structure of many bioactive compounds with antiinflammatory, anticancer and antimicrobial properties.

Lipases are versatile biocatalysts with various applications in kinetic resolutions of racemic esters, alcohols, amides and other substrates, maintaining their selectivity even in organic solvents [1].

Based on these considerations, the aim of this study was to implement a stereoselective method for the efficient production of new enantiomerically pure β-amino acids containing the thiazole core, based on the enzyme catalyzed kinetic resolution of racemic β-amino esters.

Several lipases were tested as biocatalysts for the enantioselective hydrolysis of thiazole derived β-amino esters, in different reaction conditions, in order to find the optimal conditions for the enzyme performance. The reactions were monitored by RP-HPLC with chiral stationary phase.



The optimized kinetic resolution process was successfully applied at preparative scale, affording the thiazole derived L-β-amino acids with high enantiopurity (*ee*>96%), as well as their corresponding D-β-amino esters which remained untransformed during the kinetic resolution. The D-β-amino esters were hydrolysed in acid catalysis, leading the corresponding thiazole D-β-amino acids, without affecting the enantiopurity of the products (*ee*>98%).

Acknowledgments: The work described was performed under the research contract financed by "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania, by internal grant no. 4945/11/08.03.2016.

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Click chemistry and *in situ* biological screening in the discovery of glycosidase inhibitors

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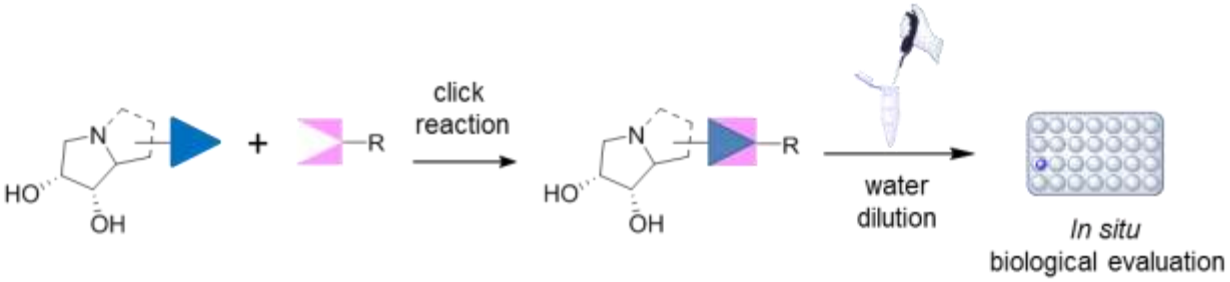
Glycosidases are enzymes that present a key role in the biosynthesis and processing of *N*-linked glycoproteins and oligosaccharide metabolism and, for this reason, their inhibitors have attracted considerable attention as potential drugs against diseases such as cancer, viral infections, diabetes or genetic disorders [1]. Iminosugars are polyhydroxylated saturated heterocycles that can be considered as carbohydrate mimics containing a nitrogen atom instead of an oxygen in the ring. They constitute the most important class of glycosidase inhibitors [2]. The inhibition properties of glycosidase inhibitors may be increased when an aromatic/aliphatic moiety is attached to the iminosugar backbone, as it has been observed in the case of fucosidase inhibitors [3].

Click chemistry followed by *in situ* biological evaluation appears as a tempting approach for the rapid identification of an optimal moiety attached to the hydroxylated heterocyclic core. This methodology implies the use of high-yield click organic reactions that can be carried out in water or water-miscible solvents on microscale without protecting groups, so that the product can be assayed directly *in situ* without isolation or purification. Based on our successful previous results in the identification of potent and selective α-fucosidase inhibitors [3], we report herein the extension of this methodology for the rapid discovery of α-galactosidase and β-glucosidase inhibitors based on pyrrolidine and pyrrolizidine iminosugars.



The authors acknowledge the Ministerio de Economía y Competitividad (CTQ2012-31247 and CTQ2016-77270-R) of Spain and Junta de Andalucía for financial support. M. M.-B. and P. E.-R. thank the Ministerio de Educación for FPU fellowships.

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Synthesis, anti-inflammatory and analgesic activities of new thiazolo[3,2,-b][1,2,4]triazoles bearing benzensulfonamide moiety

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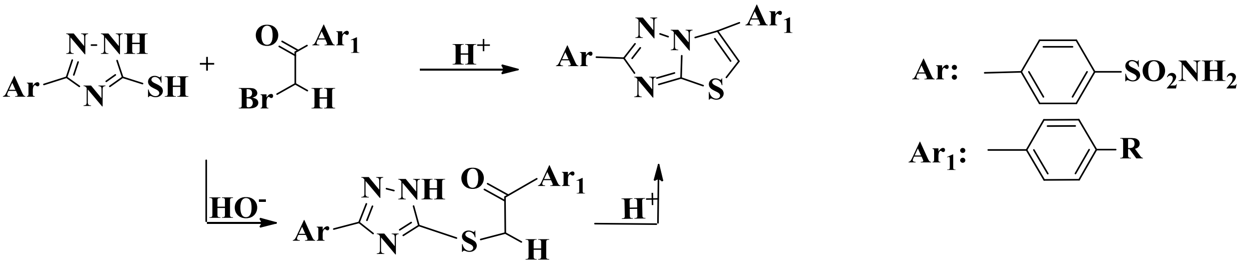
The aim of this study was the synthesis, characterization and biological evaluation of new thiazolo[3,2,-b][1,2,4]triazoles and their corresponding thioethers bearing benzensulfonamide as well as other adequate moieties which led to anti-inflammatory and analgesic activities.

Thiazolo[3,2-b][1,2,4]triazoles derivatives were synthesized from 3-thio-5-benzensulfonamide-1,2,4-triazoles, which underwent a condensation reaction with α–halogenocarbonyls. According to reaction conditions, thiazolo[3,2-b][1,2,4]triazole derivatives were obtained directly, or *via* acyclic thioether intermediates. [1]



The synthesized compounds, characterized by ^{1}H NMR, ^{13}C NMR, IR and MS, were evaluated *in vivo* for their biological activities, using a pharmacological model of acute inflammation induced in rats. The anti-inflammatory activity was evaluated by a pletismometric method and the analgesic activity was evaluated by Randall-Selitto test. The new synthesized heterocycles were evaluated for their gastric irritation side effect, by direct observation of the gastric mucosa. [2,3]

The spectral analysis confirmed the structures of the new polyheterocyclic compounds. All synthesized molecules showed good anti-inflammatory and analgesic activities compared to the positive control group, without any evidence of gastric toxicity.

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Deprotometallation of fluoro- and methoxypyridines using lithium-zinc combinations

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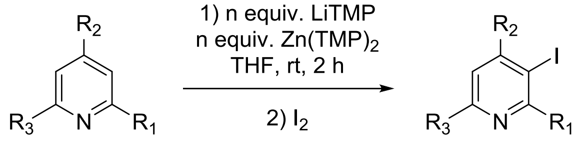
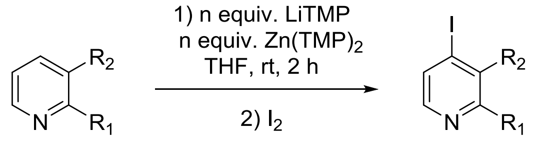
Aromatic heterocycles are present in numerous molecules of chemical or biological interest, as well as in organic materials for different applications. In particular, pyridines are key skeletons present in pharmaceuticals and in functional materials. Deprotonative metallation using polar organometallic bases is a powerful tool to functionalize such substrates.

Recently, pairs made of a monometallic base and a monometallic *in situ* trap were used to achieve deprotonative lithiation and subsequent "trans-metal trapping", and allowed sensitive substrates to be functionalized. Within this context, we have developed the putative 1:1 LiTMP-Zn(TMP)$_2$ (TMP = 2,2,6,6-tetramethylpiperidino) pair, generated *in situ* from ZnCl$_2$·TMEDA (TMEDA = *N,N,N',N'*-tetramethylethylenediamine) and LiTMP in a 1:3 ratio for the room temperature functionalization of numerous substrates including pyridines.

A series of fluoro- and methoxypyridines were deprotometallated in tetrahydrofuran by using this combination, and the metallated species were subsequently intercepted by iodine. Efficient functionalization was observed, either at the 3 position from 4-methoxy, 2-methoxy, 2,6-dimethoxy, 2-fluoro and 2,6-difluoropyridine, or at the 4 position from 3-methoxy and 2,3-dimethoxypyridine. Interestingly, clean dideprotonation was noticed from 3-fluoropyridine (at C2 and C4) and 2,6-difluoropyridine (at C3 and C5).



R_1 = OMe, R_2 = H, R_3 = H
R_1 = F, R_2 = H, R_3 = H
R_1 = H, R_2 = OMe, R_3 = H
R_1 = OMe, R_2 = H, R_3 = OMe
R_1 = F, R_2 = H, R_3 = F



R_1 = H, R_2 = OMe
R_1 = H, R_2 = F
R_1 = R_2 = OMe

M. Hedidi, G. Bentabed-Ababsa, A. Derdour, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, F. Chevallier, T. Roisnel, V. Dorcet, F. Mongin, *Tetrahedron*, **2016**, 72, 2196-2205

β-Lactam synthesis through diiodomethane addition onto amide dianions

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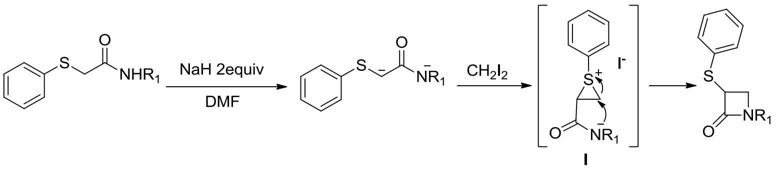
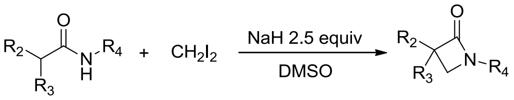
The [3+1] type cyclization of amide dianions with diiodomethane was first reported by Hirai et al. in 1979. [1]

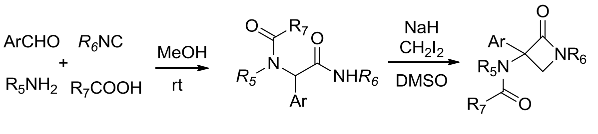


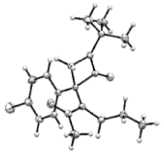
Despite a very simple and practical protocol, this approach didn't attract further interest probably due to very low reported yields and limited scope. Indeed, in agreement with the proposed episulfonium intermediate (**I**) in the reaction mechanism, the transformation was only described with thio derivatives. [2]

The biological importance of β-lactams inspired us to investigate further this reaction. Following our optimization, we were delighted to observe that the reaction could be transformed into a general access for β-lactams where the presence of the thio ether group is no more compulsory.



This methodology could be extended as well to afford β-lactams from Ugi adducts allowing a 4-component preparation of the former.





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Synthesis and Cycloaddition Reactions of Stabilized Münchnones

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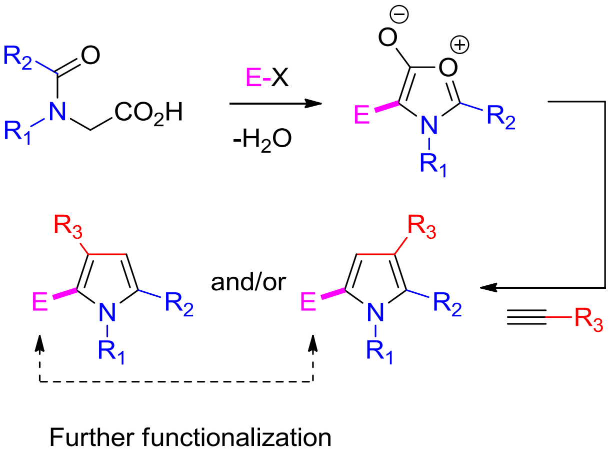
Chemistry department, Sheffield University

Sheffield, S3 7HF, U.K.

This poster will describe the synthesis and cycloaddition reactions of so-called ‘münchnones’, which are a class of mesionic compounds. These compounds have been shown to be involved in the synthesis of highly substituted pyrroles from simple starting materials. [1] We developed a family of stabilized münchnones bearing an acyl group at C4 and studied their behaviour in alkyne cycloaddition reactions. These reactions are highly regioselective, and this methodology represents a rapid and straightforward route to densely substituted pyrroles. Finally, the C4-stabilizing units can be further manipulated to furnish carboxylic acid and amide groups, or removed altogether to provide unsubstituted pyrroles (Scheme 1). [2]



Scheme 1. Use of stabilized münchnones in the synthesis of pyrrole.

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Syntheses and Electronic Properties of Di(benzothieno)thiazines

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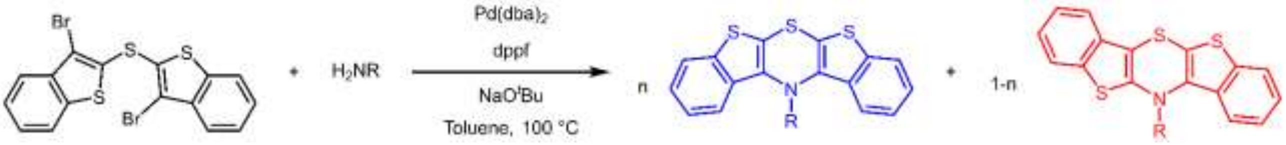
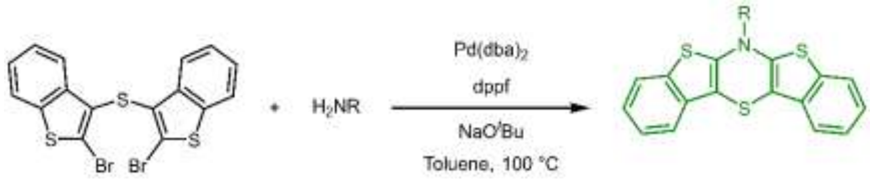
Dithienothiazines are tricyclic electron rich π-systems capable of reversible electron transfer processes. [1] The properties of the oxidised state, i. e. the radical cation, are the key to understanding the electronic characteristics of the neutral molecule. Therefore, we generated and studied the radical cation and dication of a dithienothiazine by spectroelectrochemistry. In addition, the radical cation salt was prepared and characterized. EPR-spectroscopy proves the stabilisation of the unpaired spin by extended delocalisation. [2]

The interesting electronic characteristics of the dithienothiazines prompted us to synthesise di(benzothieno)thiazines, annelated derivatives of the parent system. [3] Surprisingly, two regioisomers are formed under the same reaction conditions. The formation of the *syn-anti* isomer can be explained by a novel Pd-catalysed reaction mechanism.



Encouraged by the formation of the *syn-anti* regioisomer also the third possible regioisomer of di(benzothieno)thiazine was selectively prepared by *Buchwald-Hartwig* amination. [4] The three isomers display intriguing differences in their electronic properties, such as oxidation potentials and luminescence as a consequence of the variable annellation of the benzothiophene units.



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New Green Synthesis of 1.8-Dioxodecahydroacridine Derivatives and Polyhydroquinolines, Via Two Natural Catalysts in a Solvent-Free Medium

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Laboratory synthesis of molecules of biological interest, Department of Chemistry; Faculty of exact science; University of Constantine 1, Constantine, Algeria, 25000

Requirements of modern chemistry, including the development of new synthesis with new secure, economic and environmentally protocols guide us to the field of green chemistry [1]. The development of solvent-free organic synthetic methods has become an important research area, aiming to save energy and to prevent hazardous solvent waste and toxicity in chemical processes. On the other hand, the catalyst is the most important factor in organic synthesis for its important role in a reaction by its presence or by its intervention. Green chemistry has allowed the emergence of new horizons in the field of catalysis; it is now the ninth principle of green chemistry. Several green methods were applied as microwave , ultrasound , ionic liquids [2], nanoparticles. On our part we have contributed to this effect by the development of two new natural catalysts, inexpensive, non-toxic and very available, which are ascorbic acid and acetyl salicylic acid.

We applied our two new natural catalysts in the Hantzsch reaction (Figure:1), which is a multicomponent reaction, it is considered as a green reaction, by the fact they generate in record time and with good yields molecular structures with great complexity. The achieved results are remarkable, we could synthesize a range of 1.8-dioxodecahydroacridine derivatives (6), and polyhydroquinolines (7) with yields ranging between (47-99) % in the time range from (1.5-6) hours, we also enriched the bibliography molecules by synthesis of authentic molecules.

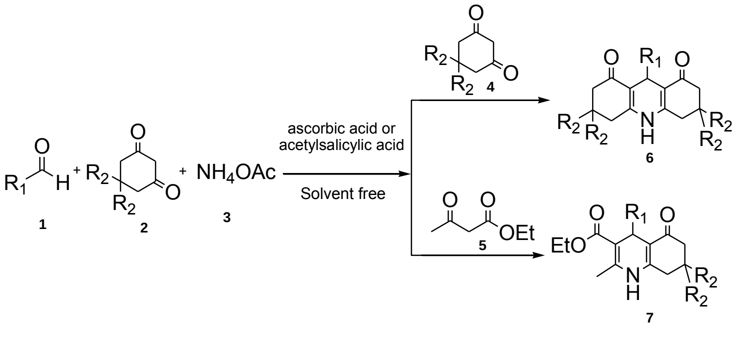

Figure : 1

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ISHC 2017

Nano-CuO catalyzed synthesis of 1-alkyl-3-aryl-4,5-bis(arylimino)-2-alkyliminoimidazolidines

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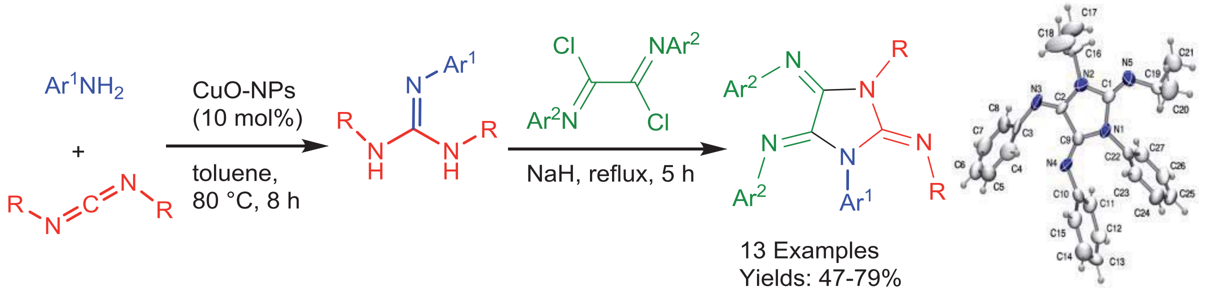
The imidazolidine nucleus, among the nitrogen heterocycles, is a prominent motif that exists in numerous natural products [1]. 2-Iminoimidazoles are important heterocycles endowed with a broad spectrum of biological activities, and are emerging as valuable pharmacophores for biomedical research. We prepared nano-CuO and used it as a new, simple and efficient catalytic system for guanylation of carbodiimides with amines to afford 1,3-dialkyl-2-arylguanidines [2]. Then, the reaction of these guanidine derivatives with bis(imidoyl) chlorides led to the synthesis of functionalized 4,5-bis(arylimino)-2-alkyliminoimidazolidines in moderate to good yields. The structures of the products were deduced from their IR and NMR spectroscopic data and a single crystal X-ray diffraction study.



13 Examples
Yields: 47-79%

References

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Synthesis of Spiropyrrolizines and Dihydro-1*H*-Pyrrolizines *via* [2+3] Cycloaddition Reactions

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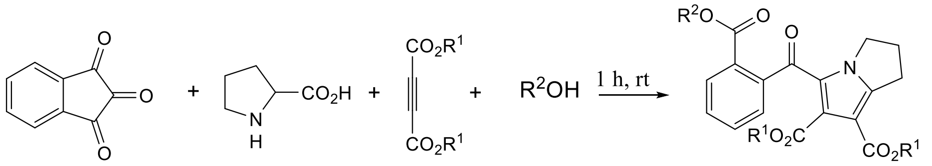
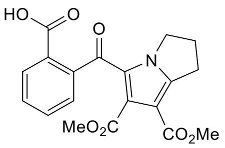
Pyrrolizines are bicyclic 5-5 systems with a nitrogen atom at the ring junction. They are the main part of numerous natural and non-natural products which show various biological activities. Several pyrrolizine derivatives, such as Ketorolac [1], is an important drug. The cycloaddition of azomethine ylides to alkenes and alkynes is an elegant entry to pyrrolidines. The required 1,3-dipoles can be produced from the reaction of α-amino acids with carbonyl compounds by eliminating carbon dioxide [2]. Herein, a one-pot synthesis of dihydro-1*H*-pyrrolizine derivatives *via* [2+3] cycloaddition reaction of azomethine ylides, prepared *in situ* from proline and ninhydrin, with dialkyl acetylenedicarboxylates, in alcohols, is described.

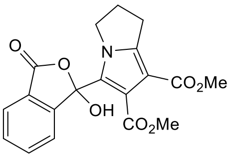


1 **2a** **3** **4** **5**

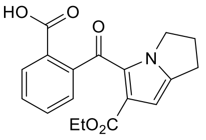
When the reaction of ninhydrin and proline was carried out with DMAD or ethyl propiolate in water, dimethyl 5-(1-hydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-2,3-dihydro-1*H*-pyrrolizine-6,7-dicarboxylate (**7a**) and ethyl 5-(1-hydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-2,3-dihydro-1*H*-pyrrolizine-6-carboxylate (**7b**) were obtained, respectively. The NMR spectra of products showed no signals for the keto tautomer **6**.



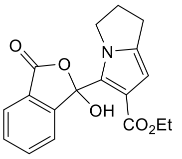
6a



7a (78%)

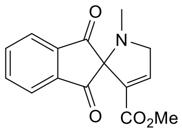


6b

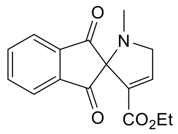


7b (62%)

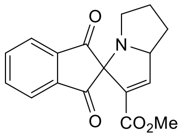
The reaction between ninhydrin and proline or sarcosine in the presence of alkyl propiolates in MeOH or EtOH, led to the formation of stable spirans **8a-c** in good yields.



8a (75%)



8b (69%)



8c (80%)

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New Chemistry of 1,2,6-Thiadiazines

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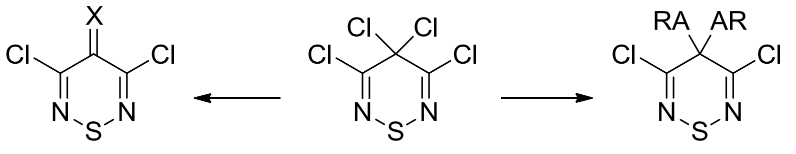
4*H*-1,2,6-Thiadiazines are important compounds as they find uses in the agrochemical[1] and material sciences.[2] While most syntheses of 1,2,6-thiadiazines rely on 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**1**)[3] as the thiadiazine starting material, we focused in developing the chemistry of 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine (**2**),[3] an overlooked but potentially versatile scaffold.

Tetrachlorothiadiazine **2** can be readily converted to 4-dicyanomethylene-1,2,6-thiadiazine **3**,[4] *N*-aryl-3,5-dichloro-4*H*-1,2,6-thiadiazin-4-imines **4**,[5] 3,5-dichloro-4,4-dialkoxy-4*H*-1,2,6-thiadiazines **5** and 3,5-dichloro-4,4-bis(alkylthio)-4*H*-1,2,6-thiadiazines **6**.[6]

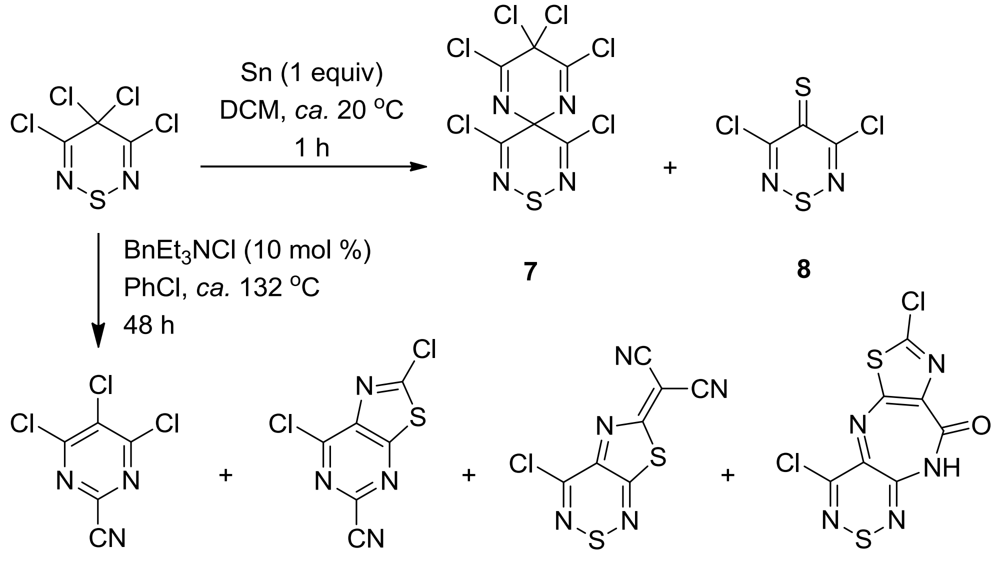


1 (X = O)
3 [X = C(CN)$_2$]
4 (X = NAr)

2

5 (A=O, R= Me, Ph, (CH$_2$)$_2$, 1,2-C$_6$H$_4$)
6 [A=S, R= Bn, Ph, 1,2-C$_6$H$_4$, Ac)

More recently, the degradation of tetrachlorothiadiazine **2** under reductive (dissolving Sn) or thermal conditions was investigated to reveal a plethora of interesting new fused heterocycles identifying new chemistry of this system.



7 **8**

9 **10** **11** **12**

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A Convergent, Efficient, and Scalable Total Synthesis of Halichondrins

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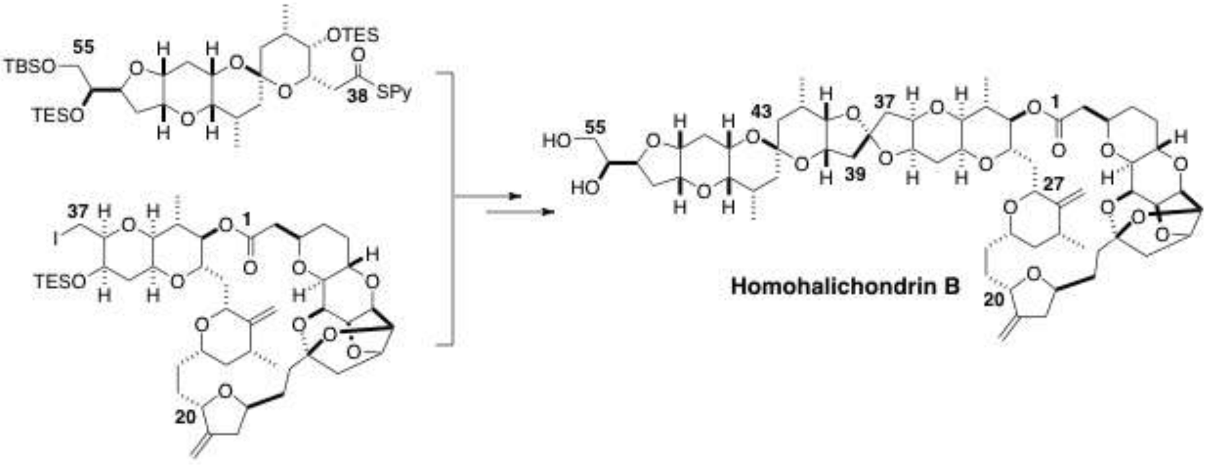
A convergent, efficient, and scalable total synthesis of all the members in the halichondrin class of natural products was accomplished. Newly designed left half and right half were synthesized stereoselectively from the same intermediate, which was prepared from D-galactal. New Zr/Ni-mediated one-pot ketone synthesis was developed to achieve the final assembly.[1]



Halichondrins are polyether macrolides, originally isolated from the marine sponge *Halichondria okadai* by Uemura, Hirata, and coworkers.[2] Due to their intriguing structural architecture and extraordinary antitumor activity, halichondrins have received much attention from the scientific community. Although we have previously reported efficient syntheses of halichondrins and norhalichondrins, an attempt of synthesizing homohalichondrins via the same route gave only a modest success.[3]

In this presentation, we report a convergent, efficient, and scalable synthesis of all the members, including homohalichondrins A~C, in the halichondrin class of natural produts, with use of newly developed Zr/Ni-mediated one-pot ketone synthesis as the final coupling reaction.

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Novel d^0 a^3 synthon equivalents for the stereocontrolled synthesis of functionalized 1,4-amino alcohol precursors

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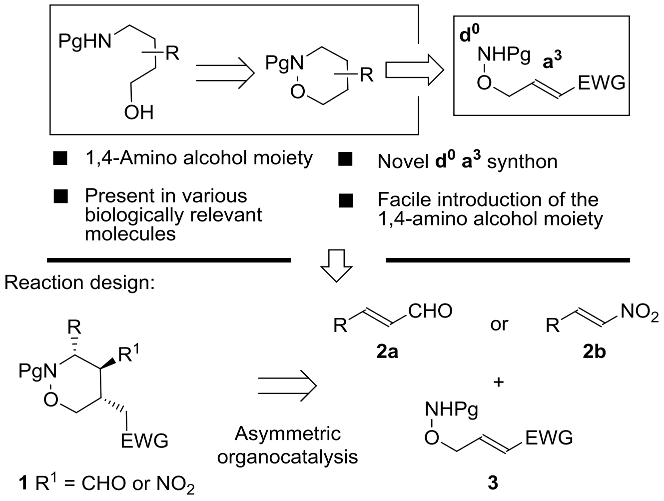
One of the most relevant topic in contemporary organic synthesis is the design of new stereoselective methods for the preparation of privileged structural motifs found in bioactive molecules [1]. The 1,4-amino alcohol framework, being of high importance for the life science industry, is readily available via the N–O bond cleavage in the corresponding tetrahydro-1,2-oxazines [2]. In this study, the synthesis and application of a novel group of aminooxylating reagents **3** has been demonstrated [3]. Due to their structural features, they can be considered as d^0a^3 synthon equivalents for organic synthesis. Their usefulness has been demonstrated in organocatalytic domino reactions, with either α,β-unsaturated aldehydes **2a** or nitroolefines **2b**, providing straightforward access to polysubstituted tetrahydro-1,2-oxazine derivatives **1**, serving as direct precursors of functionalized 1,4-amino alcohols. The tetrahydro-1,2-oxazines have been obtained with excellent stereoselectivity (>20:1 dr, >98% ee) and with high yields (up to 93%). Furthermore, the applicability of polysubstituted tetrahydro-1,2-oxazines have been presented in various chemoselective transformations.



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Preparation and Transformations of 1-Allyloxy-2-ethynylbenzene Derivatives for Synthesis of Oxygen-containg Heterocyclic Compounds

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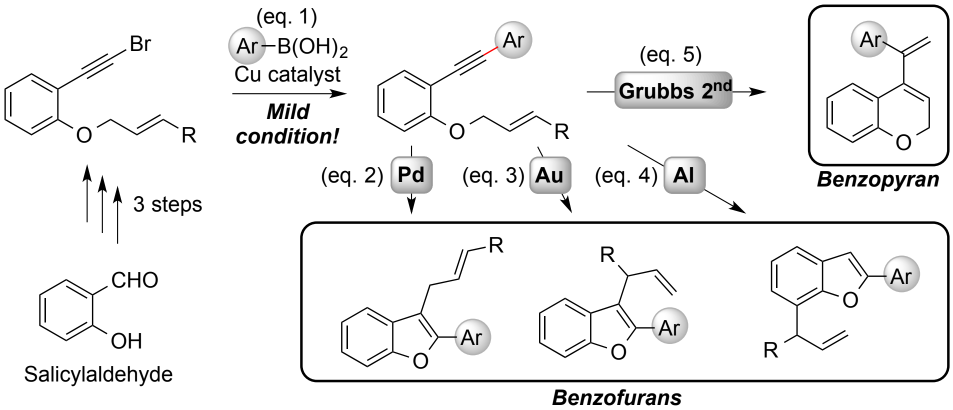
1-Allyloxy-2-ethynylbenzene derivatives were known as an effective precursor for oxygen-containg heterocyclic compounds such as benzofuran and benzopyran. For example, Tanaka's group reported the annulation of 1-allyloxy-2-ethynylbenzene derivatives using rhodium cartalyst afforded 3-benzylbenzofuran.[1] On the other hand, Lovely's group reported benzopyran derivatives could be obtained by Pauson-Khand reaction of 1-allyloxy-2-ethynylbenzene derivatives in the presence of cobalt catalyst.[2] Therefore, synthetic methodology of 1-allyloxy-2-ethynylbenzene derivatives is very important for the access to various oxygen-containg heterocyclic compounds.

Herein, we found that copper catalyzed Suzuki-Miyaura reaction of 1-(bromoethynyl)-2-allyloxybenzene, which was easily prepared from salicyaldehyde, with arylboronic acids afforded the corresponding 1-allyloxy-2-ethynylbenzene derivatives in effectively (eq. 1).[3] We further demonstrate that four types of transformation using 1-allyloxy-2-ethynylbenzene derivatives for the access to various heterocyclic compounds. At first, transformation of 1-allyloxy-2-ethynylbenzene derivatives in the presence of palladium catalyst led to 3-allylbenzofuran derivatives in excellent yields (eq. 2).[4] Second, using gold catalyst gave the branch type 3-allylbenzofuran derivatives from same substrate (eq. 3). Third, aluminium reagent caused claisen rearrangement followed by annulation afforded 7-allylbenzofuran derivatives (eq. 4). Finally, enyne metathesis reaction of 1-allyloxy-2-ethynylbenzene derivatives using Grubbs 2nd catalyst led to the corresponding benzopyran derivatives (eq. 5).



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Isocyanide as modern tool for the synthesis of diversified isoindolin-1-one derivatives via Pd-Catalysed insertion/cyclization reaction.

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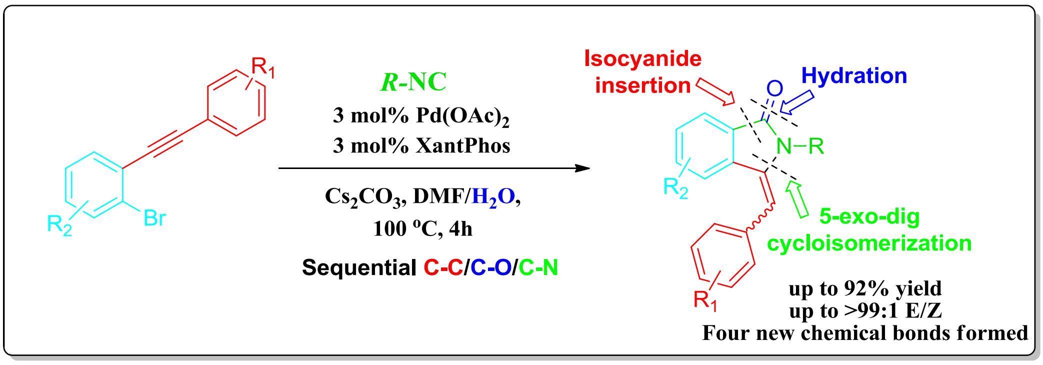
Isocyanides are widely explored as a versatile C1 building blocks via Pd-catalysis[1] and offer a vast potential for the synthesis of nitrogen containing heterocyclic molecules. A simple and efficient Pd–catalysed tandem carboxamidation/hydroamidation of 2- bromophenylacetylene has been developed for the synthesis of 3-benzylidineisoindolin- 1-one. The method developed demonstrated high substrate scope and diversity. The salient feature of the methodology involves formation of four chemical bonds and high regio- and stereo-selectivity with wide substrate scope. The mechanistic studies suggests that the reaction is following non-radical path. We also carried out controlled experiments to understand the both carboxamidation and hydroamidation step discretely. We also explore one pot protocol for the synthesis of complex isoindolinone derivatives starting from the simple 2-bromo iodobenzene substrate. The detailed mechanistic studies will be presented.



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Solvent-free synthesis of 2,4,5-trisubstituted-2,4-dihydro-3*H*-pyrrol-3-ones from alkyl 2-aminoesters

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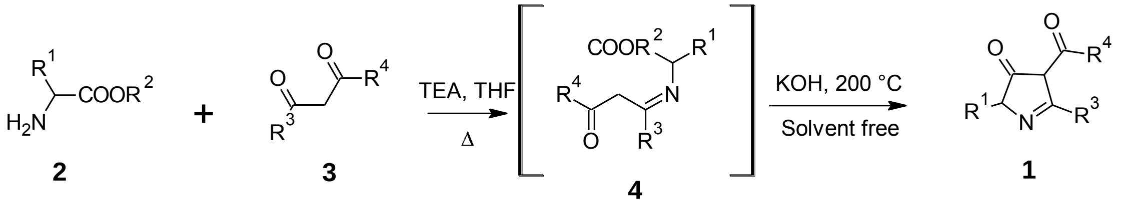
Phytoalexins are secondary metabolites which are produced by plants under exposure to physical, biological or chemical stress. Indole derivatives have received great attention for their potential application in the agricultural and pharmaceutical fields [1]. The application of bioisosteric compounds stimulates the design and production of new agrochemical agents based on the structural skeleton of phytoalexins. In the Bioorganic Chemistry Laboratory of Universidad Militar Nueva Granada, recent results have allowed to establish an efficient methodology for the synthesis of alkyl dithiocarbamates derived from *L*-tryptophan, which showed antifungal activity against *Fusarium oxysporum* [2]. With the aim to explore the feasibility to employ 2-aminoacids as precursors of new agrochemical agents, we continue the research on the derivatization of 2-aminoacids. In this paper, we presented the synthesis of 2,4,5-trisubstituted-2,4-dihydro-3*H*-pyrrol-3-ones **1**. The first step of the synthetic methodology involved the esterification of *L*-alanine, *L*-phenylalanine and *L*-tyrosine in excellent yields (93-98 %).



R^1= Me, R^2=Me, Et, 2-Pr, *n*-Bu
R^1= CH_2Ph, R^2=Me, Et, 2-Pr, *n*-Bu
R^1= CH_2-4-PhOH, R^2=Me, Et, 2-Pr, *n*-Bu

R^3= Me, R^4=Me
R^3= Me, R^4=OMe

R^1= Me, R^3=Me, R^4=Me
R^1= Me, R^3=Me, R^4=OMe
R^1= CH_2Ph, R^3=Me, R^4=Me
R^1= CH_2Ph, R^3=Me, R^4=OMe
R^1= CH_2-4-PhOH, R^3=Me, R^4=Me
R^1= CH_2-4-PhOH, R^3=Me, R^4=OMe

Reactions of **2** with carbonyl compounds **3** were carried out employing triethylamine and THF at reflux conditions to obtain alkyl 2-substituted[(*E*)-(1,3-disubstituted-3-oxopropylidene) amino]acetate **4** in good yields (72-85%). Compounds **4** were evaluated using EM-EI and NMR ^{1}H. All the mass spectra of **4** showed intense and characteristic signals which corresponded to the ion molecular for compounds **1**. These results suggested that compounds **4** could undergo 5-*exo-trig* cyclization towards **1**. Equimolar mixtures of **4** and KOH were heated employing solvent-free conditions. In all the cases, compounds **1** were obtained in moderate to good yields (45-81%), confirming the potential of 2-aminoacids as precursors of nitrogen-containing heterocyclic compounds. Product derived from the project IMP-CIAS-2294 funded by Vicerrectoría de Investigaciones at UMNG - Validity 2017.

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Stereospecificity in Intramolecular Photoredox Reactions of Naphthoquinones: Enantioselective Total Synthesis of (–)-Spiroxin C

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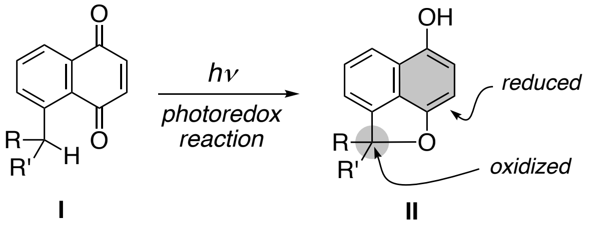
Takashi Matsumoto, Ken Ohmori, and Keisuke Suzuki*
Department of Chemistry, Tokyo Institute of Technology, Tokyo/Japan 152-8551

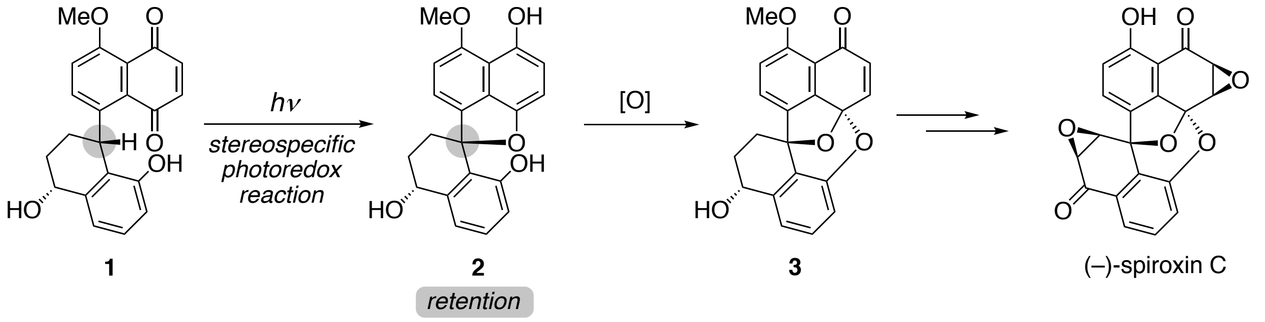
During the course of our synthetic study toward the *C*-glycosylated natural products, we discovered an intriguing photoreaction of naphthoquinone: The substituted naphthoquinone **I** is converted to an oxacycle **II** through Noriish-II-like reaction and cyclization under room light. This process corresponds to an intramolecular redox reaction, as its benzylic positions oxidized, while the quinone moiety is reduced into the hydroquinone.

In this presentation, we will discuss on the substrate scope and the mechanistic aspect of this photoreaction.[1] Also, the first asymmetric total synthesis of (–)-spiroxin C, one of the members of a class of marine natural products isolated from a fungal strain, by employing the photoredox reaction is discussed.



Several substituted naphthoquinones were subjected to the model study, which clarified that the presence of oxygen atom(s) or two alkyl groups at the benzylic position is essential in order for the photoredox reaction to proceed.[1] Interestingly, this transformation proceeds in a stereospecific manner when the naphthoquinone has a stereogenic center at the benzylic position.

Our synthetic strategy features the stereospecific photoredox reaction of naphthoquinone **1** to construct the key spiroether **2** with retentive manner, from which increase in the oxidation level and deprotection allowed the total synthesis. This synthetic route would be applicable to the other congenerts as well, which will be discussed in this presentation.



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Exploration of the P2X$_7$R pharmacophore using hybrid P2X$_7$R antagonists

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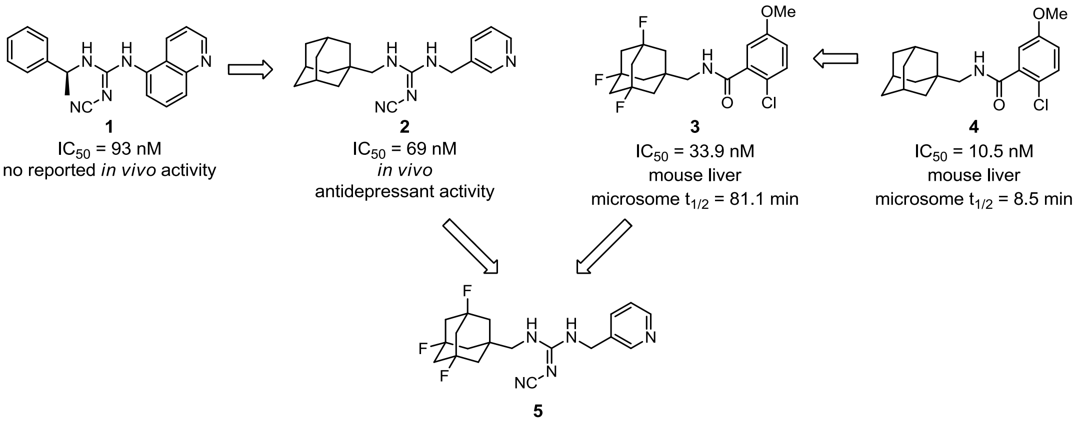
Sydney, NSW 2000, Australia

There is growing evidence suggesting that chronic inflammation is the underlying cause of several neurodegenerative and neuropsychiatric diseases, including Alzheimer's disease, Parkinson's disease, and major depressive disorder.[1,2] The P2X$_7$ receptor (P2X$_7$R) plays an essential role in the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β) within the central nervous system (CNS). [3] As such, inhibition of P2X$_7$R-mediated signaling is an attractive therapeutic target. However, the clinical development of a P2X$_7$R antagonist has remained elusive despite a persistent research effort by several major pharmaceutical organizations including AstraZeneca and Pfizer.

We have recently reported a structure-activity relationship (SAR) analysis of a series of adamantyl cyanoguanidines based on the aryl cyanoguanidine scaffold **1**.[4] These demonstrated potent P2X$_7$R inhibition, with heterocyclic derivatives displaying favorable drug-like properties and up to a five-fold increase in activity compared to **1**. The pyridyl analogue **2** displayed an anti-depressant phenotype in mice exposed to the forced swim test, providing evidence of CNS activity. We have also thoroughly explored the adamantyl benzamide **4** class, alternatively through the introduction of adamantane bioisosteres or with heteroaromatic isosteres of the benzene ring. Incorporation of the trifluoroadamantane polycycle **3** reduces lipophilicity to facilitate CNS-penetration and increase the metabolic stability of the hydrophobic adamantane moiety. In this presentation, we will describe recent progress made into exploring the common features of these discrete P2X$_7$R antagonist classes in order to better understand the P2X$_7$R pharmacophore. This insight will assist in the development of a CNS-permeable P2X$_7$R antagonist combining the optimal features from each class.



1
IC$_{50}$ = 93 nM
no reported *in vivo* activity

2
IC$_{50}$ = 69 nM
in vivo
antidepressant activity

3
IC$_{50}$ = 33.9 nM
mouse liver
microsome $t_{1/2}$ = 81.1 min

4
IC$_{50}$ = 10.5 nM
mouse liver
microsome $t_{1/2}$ = 8.5 min

5

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Gas-Phase Reaction of Heterocycles over Solid-Supported Molybdenum Trioxide

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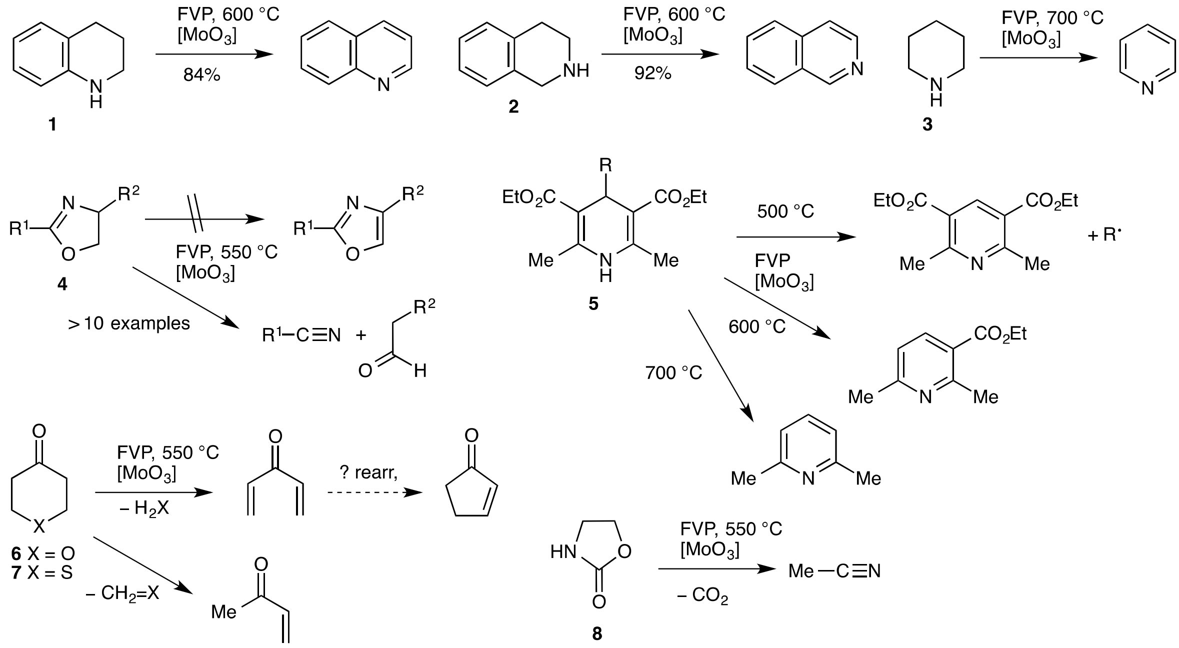
EastCHEM School of Chemistry, University of St Andrews, St Andrews, UK

Based on some unpublished preliminary studies [1] we have explored the use of MoO_3 supported on pumice stone chips as a solid reagent / catalyst in flash vacuum pyrolysis of heterocyclic compounds. This is a stable and relatively abundant metal oxide, which, once reduced, may be regenerated simply by heating in air. Aromatisation of tetrahydroquinoline and -isoquinoline **1** and **2** as well as piperidine **3** is easily achieved. Attempted extension to oxazolines **4** gave no oxazoles, but instead resulted in clean thermal cleavage into nitrile and aldehyde fragments, in what appears to be a previously unreported reaction.



The Hantzsch dihydropyridines **5** are readily aromatised at lower temperatures but as the temperature is raised first one and then the other ester group is lost as ethene and CO_2 to give the pyridine products shown. The pyranone and thiopyranone **6** and **7** undergo perhaps the most surprising process: loss of (thio)formaldehyde to give methyl vinyl ketone and also loss of water or H_2S to form divinyl ketone which is assumed to be the source of cyclopentenone, formed in an as yet unexplained isomerisation process. Finally the oxazolidinone **8** undergoes decarboxylation and oxidation to afford acetonitrile. Extension of many of these processes from the basic heterocycles to substituted examples is expected to lead to a range of new useful synthetic methods.

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Synthesis of sp^3 rich azepanes in an enantiomerically enriched fashion

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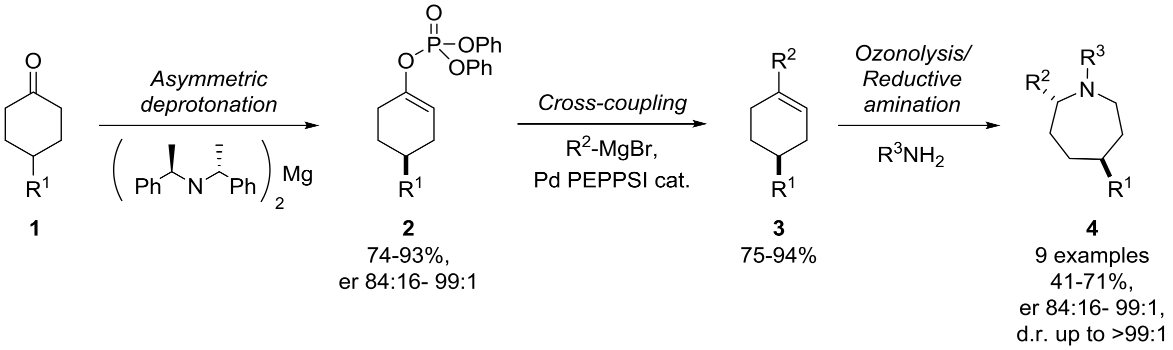
In 2009, Lovering *et al*. reported that the proportion of sp^3 centres in a target structure directly correlates with success rate in drug discovery.[1] Such structures are not readily achievable by traditional cross-coupling methods, therefore the synthesis of highly functionalized sp^3-rich scaffolds is highly desirable and warrants more extensive study.[2] Accordingly, the development of new synthetic strategies for the preparation of such molecules is required.

In our laboratory, a novel four-step sequence for the preparation of enantiomerically enriched azepane scaffolds was envisioned (**Scheme 1**). Employing chiral magnesium bases developed in the Kerr group, enol phosphates **2** were obtained in high enantioselectivities.[3b] Following this, a novel Pd PEPPSI catalyzed protocol for the cross coupling of enantiomerically enriched enol phosphates **2** with aryl Grignard reagents was developed, furnishing substituted chiral cyclohexenes **3** in high yield. Finally, the chiral trisubstituted alkenes **3** were oxidatively cleaved with ozone and the subsequent reductive amination of the intermediate keto-aldehyde was achieved in a one-pot fashion. The chiral, trisubstituted enantiomerically enriched azepanes **4** were obtained in good yields and high diastereomeric ratios. In this manner, a range of functionalized azepanes **4** were obtained, which will be presented in this poster.



Scheme 1

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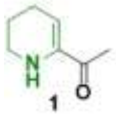
Stereoselective Synthesis of Tetrahydropyridine Derivatives via an Organocatalytic One-Pot Multicomponent Reaction

Radell Echemendía Pérez, [a,b] * Gustavo Piva da Silva, [a] Vitor Alcantara, [a] Marcio Weber Paixão, [a] and Daniel G Rivera [b]

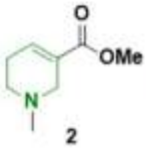
[a] *Department of Chemistry, Universidade Federal de São Carlos, São Carlos, 97105-900, São Paulo*

[b] *Center for Natural Products Research, Faculty of Chemistry, University of Havana, 10400, La Habana*

Tetrahydropyridines (THPs) are an important class of heterocycles that belongs to a widespread substructure in naturally occurring compounds and some synthetic bioactive molecules. They have recently attracted a lot of attention because of their widespread occurrence and their pronounced pharmacological properties.



1



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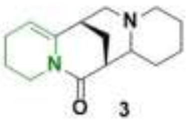
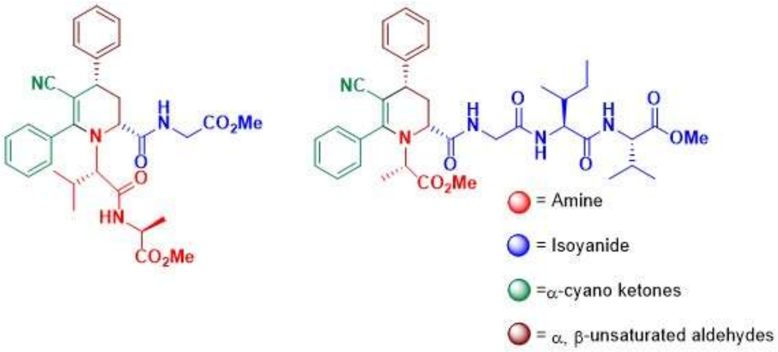


3

This work describes a highly stereoselective approach for the one-pot synthesis of complex natural product hybrids incorporating fragments such as THPs, peptides and lipids. The approach involves an asymmetric organocatalytic conjugate addition of α cyano ketones to α,β-unsaturated aldehydes, followed by an intramolecular 4-center 3-component reaction including amine and isocyanide components.



The strategy combines the stereocontrol of organocatalysis with the diversity-generating character of multicomponent reactions, thus leading to structurally unique peptidomimetics integrating heterocyclic (THP) and lipidic moieties.

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Metal-free regioselective tandem synthesis of functionalized benzimidazo-fused benzofuro[3,2-*c*]pyridines, ɣ-carbolines and benzofuro/thieno[2,3-c]pyridines in aqueous medium

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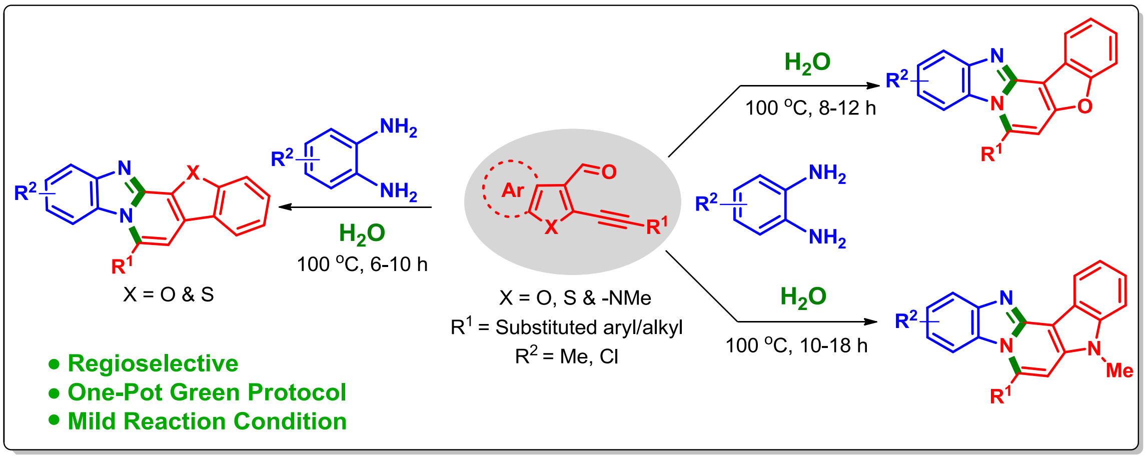
In the continuation of our ongoing lab work using *ortho*-alkynyl aldehydes,[1,2] we have design an operationally simple greener approach for the synthesis of broad range of functionalized benzimidazolo-fused benzofuro[3,2-*c*]pyridines, benzofuro/ thieno[2,3-*c*]pyridines and ɣ-carbolines under the metal-free condition in water has been described. The aqueous medium accelerates the formation of desired product by avoiding side-product as well as drastic reaction condition. The reaction proceed through inter and intramoleculer C-N bond formation in one-pot *via* 6-*endo-dig* cyclization. The deuterium labelling and X-ray crystallographic studies supported the proposed mechanistic pathway for the targeted cyclized product.



- Regioselective
- One-Pot Green Protocol
- Mild Reaction Condition

References:

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Total Synthesis of (–)-Codonopsinine using Chlorosulfonyl Isocyanate

Jun Min Jung[1], Yeon Su Kim, Da Eun Kim, Su Yeon Koh, Ki Min Park and Young Hoon Jung*[1]
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Polyhydroxylated pyrrolidine alkaloids have been frequently reported in nature and synthesized in laboratories. Moreover, these alkaloids have received considerable attention as potential medical agents because of their interesting pharmacological properties such as viral infections, cancer, malaria, insecticides, diabetes and cancer.

Among these, pyrrolidine alkaloids which have aryl substituent are rarely to be found. (–)-Codonopsinine and (–)-Codonoposine were isolated from Codonopsis Clematidea at 1969 and their structures and absolute stereochemistry were elucidated in 1972. These compounds have p-methoxyphenyl moiety in their pyrrolidine ring and exhibit antibiotic and hypotensive activities without affecting the central nervous system.

Due to the unique structural feature and interesting biological property, a number of efforts have been devoted to the development of various approaches for the efficient synthesis of (–)-Codonopsinine.

Recently, regioselective and diasteroselective amination of various 1,2-anti-dibenzyl ether using chlorosulfonyl isocyante(CSI) and its application to the synthesis of various biologically active alkaloids have been reported from our laboratory.

In this presentation, we describe a concise and efficient asymmetric synthesis of (–)-Codonopsinine. The total synthesis of (–)-Codonopsinine has been accomplished in 12 steps from readily available p-anisaldehyde, and the key steps in this route involve lithium enolate Aldol reaction, Lewis acid mediated chelation controlled Grignard reaction, CSI-mediated amination and intramolecular cyclization using amidomercuration.

DEOXYGENATION REACTION IN THE SYNTHESIS OF NEW AZOLYLSUBSTITUTED HETEROCYCLIC SYSTEMS

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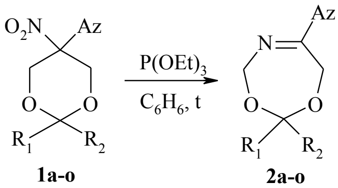
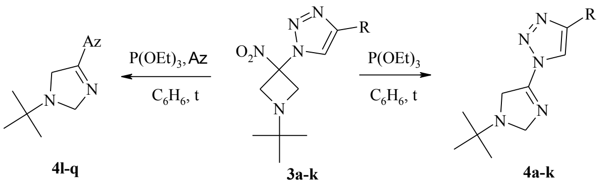
Several methods are currently known for deoxygenation of primary and secondary nitroalkanes with trivalent phosphorus compounds leading to the formation of nitriles, amines and derivatives of oximes. Recently we have shown that substituted 1-(5-nitro-1,3-dioxan-5-yl)-1*H*-1,2,3-triazoles **1a-o** easily transform into a new 4,7-dihydro-1,3,5-dioxazepine **2a-o** heterocyclic system by heating with triethylphosphite [1]. Also we had positive results when 1-(1-*tert*-butyl-3-nitroazetidine-3-yl)-1*H*-1,2,3-triazoles **3a-k** were used as start materials. We got a range of 1-(1-*tert*-butyl-2,5-dihydro-1*H*-imidazole-4-yl)-1*H*-1,2,3-triazoles **4a-k** with a good yield. We carefully studied the mechanism of this process and found that it occurred similarly to deoxygenation of germinal cloronitrocycloalkanes with triphenylphoshine [2]. Based on this information we created various imidazoles which contain different azoles **4l-q** in the fourth position.

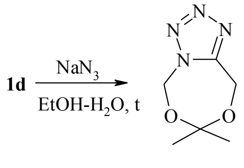


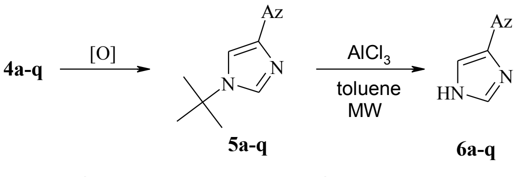


R_1=R_2= CH_3, Az = imidazole-1-yl (1**a**), pyrazole-1-yl (1**b**), benzoimidazole-1-yl (1**c**),
1,2,3-triazole-1-yl (1**d**), benzotriazole-1-yl (1**e**), 1,2,3-triazole-2-yl (1**f**), benzotriazole-2-yl (1**g**)
R_1 = R_2 = H, Az = 1,2,3-triazole-1-yl, (**1h**), R_1 = R_2 = Me, Az = 1,2,3-triazole-1-yl (**1i**),
R_1 = H, R_2 = Ph, Az = 1,2,3-triazole-1-yl (**1j**), R_1 = R_2 = Me, Az = 1,2,3-triazole-1-yl (**1k**),
R_1 = Me, R_2 = Et, Az = 1,2,3-triazole-1-yl (**1l**), R_1 = R_2 = Me, Az = 4-phenyl-1*H*-1,2,3-triazole-1-yl (**1m**),
R_1 = R_2 = -$(CH_2)_4$-, Az = 1,2,3-triazole-1-yl (**1n**), R_1 = R_2 = -$(CH_2)_5$-, Az = 1,2,3-triazole-1-yl (**1o**),
R_1 = R_2 = Me, Az = 4-trimethylsilyl-1*H*-1,2,3-triazole-1-yl (**1o**)

R = H (**4a**); $SiMe_3$ (**4b**); Cyclo-C_3H_5 (**4c**), C_6H_5 (**4d**),
2-FC_6H_4 (**4e**), 2-ClC_6H_4 (**4f**), 3-ClC_6H_4 (**4g**),
2,4-$Cl_2C_6H_3$ (**4h**), 4-$CF_3C_6H_4$ (**4i**), 3-$CF_3C_6H_4$ (**4j**),
3-$CH_3OC_6H_4$ (**4k**); Az = imidazole-1-yl (**4l**),
pyrazole -1-yl (**4m**), benzoimidazole-1-yl (**4**n),
benzotriazole-1-yl (**4o**), adenine-9-yl (**4p**), L-histidine (**4q**)

These structures could be interesting as new systems or as start materials for obtaining new heterocyclic systems such as **6a-q**:





Some of these molecules were tested on a range of phytophatogenic fungi.

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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL DIHYDROPYRANOINDOLE SYSTEMS FOR THE ENHANCEMENT OF ANTI-CANCER EFFECTS OF HDAC INHIBITORS

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Chemotherapy is one of the most common treatments for high-risk cancer patients. [1,2] A range of well-known agents have been used to combat to various cancers in modern chemotherapeutic approaches. [3,4] However, a major problem faced in chemotherapy is the resistance to commonly-used anti-cancer drugs. [5] Therefore, exploration of novel chemotherapeutic agents is in urgent demand in the area of drug discovery and development. The key objective of this research is to synthesize a range of novel indole-based heterocyclic molecules that can potentially be used for multi-targeted cancer therapies in combination with clinical doses of Histone deacetylase (HDAC) inhibitors. The work therefore consists of the design and synthesis of novel indole scaffolds as well as their systematic pre-clinical *in vitro* evaluation against human cancer cell lines in combination with HDAC inhibitors. A variety of unique indole-based fused dihydropyrano systems has been developed by using different synthetic methodology. Key tricyclic and tetracyclic pyranoindole systems have been prepared through treatment of dihydroxybenzaldehydes with haloalkynes to generate aryl ether benzaldehydes and the application of Hemetsberger indole synthesis allowed to build indole moiety. The Claisen cyclization of the alkyne indole ethers yielded the desired dihydropyranoindole systems. The cytotoxic profile of the novel compound was determined against a range of neuroblastoma (SH-SY5Y and Kelly) and breast cancer (MCF-7 and MBA-231) cells. The toxicity study for the healthy human cells was evaluated against the MRC-5 and WI-38 human fibroblast cells.

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A synthesis of functionalized indolizines by 1,3-dipolar cycloaddition reaction of azomethine ylides and phosphorylated hydroxyketenes

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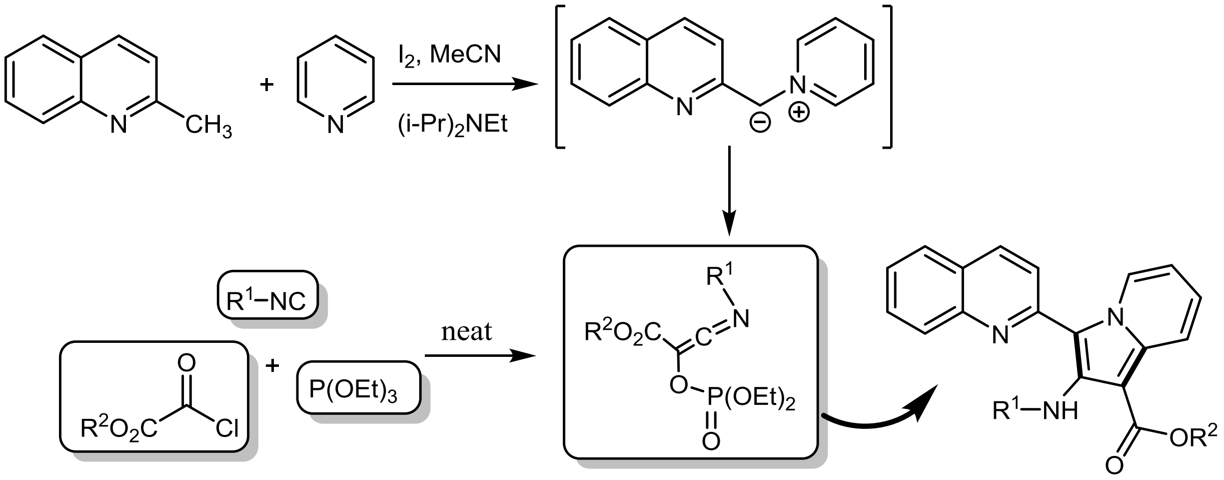
The 1,3-dipolar cycloadditions of azomethine ylides are generally stereospecific, with the stereochemistry of the dipole and dipolarophile retained in the cycloadduct. In this work, a method has been developed for the generation of azomethine ylides *via* C-H activation of unreactive C(sp^3)–H bonds of 2-methylazaarenes. Molecular iodine-promoted metal-free C–H activation of alkyl azaarenes has been described [1]. Herein, we represent a novel indolizine synthesis from the reaction of pyridinium ylides, generated from iodine-mediated reaction of 2-methylquinoline and pyridine, with phosphorylated hydroxyketenimines, formed *via* a Nef–Perkow cascade [2] involving isocyanides as starting material, in moderate to good yields. Various featurs of these transformations will be presented and discussed.



Scheme. One-pot multicomponent synthesis of indolizine derivatives.

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PTSA-catalysed Rearrangement Reaction of δ-Hydroxyalkynones to 6-Substituted 2,3-Dihydro-4*H*-pyran-4-one

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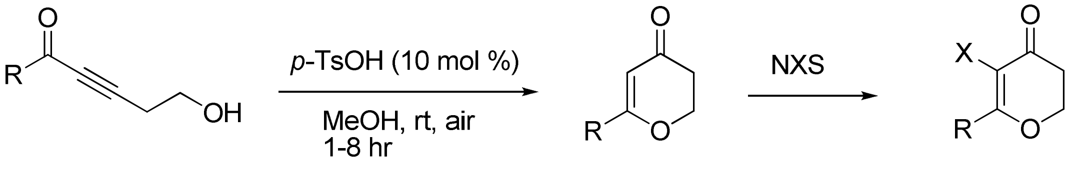
Pyrones are one of the important class of compounds which is present in various biological active molecule and natural products.[1-3] A PTSA-catalyzed intramolecular rearrangement reaction of δ-hydroxyalkynones to 6-substituted 2,3-dihydro-4*H*-pyran-4-ones has been developed. The desired rearranged product has been accomplished regioselectively over more conventional cyclization under mild and open-air conditions. The scope of the work has been illustrated by synthesizing a new class of aliphatic and aromatic 6-substituted 2,3-dihydro-4*H*-pyran-4-ones substrates in upto 96% yield with 100% atom economy and regiosectivity that can be used for constructing complex molecular targets.



-100 % Regioselectivity
-100 % Atom economy
-Upto 96 % yield
-Mild reaction condition
-Open air reaction
-Catalytic amount of PTSA used
-Low concentration of solvent

References:
[1] L. F. Cavalieri, *Chem. Rev.* **1947**, *41*, 525–584.
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Syntheses and Characterizations of Novel 6-(Pyridinyl)pyrimidine-2,4-diamines using Pd-catalysed Suzuki Cross-Coupling Reactions

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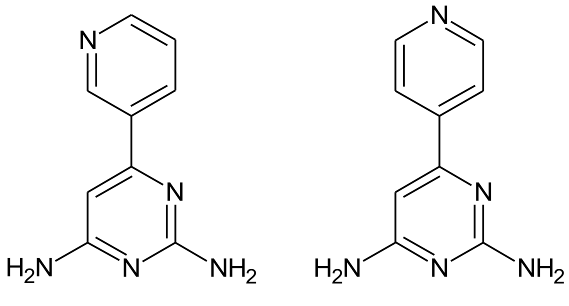
Suzuki cross-coupling reactions which involve Pd-catalysed cross-coupling reactions are useful for preparing hetero-aryl functionalised heterocyclic compounds. [1,2]

Some 6-aryl-2,4-diaminopyrimidine derivative compounds have been published with their potentially interesting molecular recognitions, agrochemical and pharmaceutical properties such as diarylamides derivatives have been highlighted as potential antiproliferative agents against a variety of cancer cell lines. [3]

We studied the reaction of between 6-chloro-2,4-diaminopyrimidine and 3- and 4- substituted pyridylboronic acids to give novel 6-(pyridinyl)pyrimidine-2,4-diamines.

During the literature searching, syntheses of similar compounds were resulted in lower yields. 6-(pyridinyl)pyrimidine-2,4-amines may be used as an easily synthesizable and functionalizable to prepare its derivatives via amino groups functionalizing. The amino group of 2-position is more reactive than 4-position, thus 2-position may be functionalized before addition on 4-position or they may be functionized with same reagent on both amino groups. Several of variety of functionalizing is open for free amino groups. [4,5]



Scheme 1: 6-(pyridin-3-yl)-2,4-diaminopyrimidine (left),
6-(pyridin-4-yl)-2,4-diaminopyrimidine (right)

The reaction conditions were optimized using different solvents. The novel 6-(pyridinyl)pyrimidine compounds were purified by flash column chramotography and characterized by NMR and X-ray studies.

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[5] I. H. Gilbert et al. *Journal of Medicinal Chemistry*, **2016**, 59, 6101–6120.

Synthesis, Characterization and NMR studies of Azahemiporphyrazines

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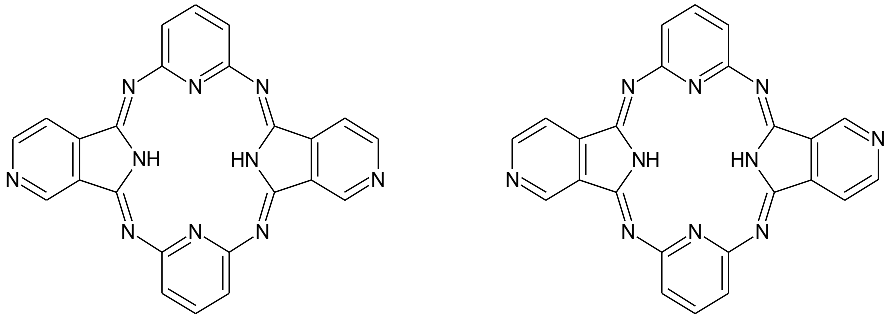
Hemiporphyrazines (Hps) are tetradentate, C_{2v} symmetric, nearly planar and with a cross-conjugated 20 π-electron macrocylic non-aromatic compounds. Hemiporphyrazines are also called analogues of phthalocyanines (Pc), in which two opposing (*trans*) isoindoline units are replaced by 2,6-diamino substituted pyridine rings. These macrocyclic molecules with a cross-conjugated 20 π-electron system, do not display aromatic behavior. The free base hemiporphyarzine (HpH_2) and metallo hemiporphyrazines (MHp) were first synthesized by Linstead in 1952. The simple hemiporphyrazine structure contains two co-facial isoindole and two co-facial 2,6-diaminopyridine that are linked through four aza bridges as benzo-fused porphyrazine (tetraazaporphine). [1,2,3]

In this study, 3,4-dicyanopyridine was synthesized from pyridine-3,4-dicarboxylic acid and reacted with 2,6-diaminopyridine to prepare the desired macrocyclic ring. The free base ring was purified by washing, dried and characterized by ESI-MS, UV-Vis, FTIR, EA, 1D and 2D-NMR spectroscopic techniques.

During the NMR studies, we realized that the two conformers as *cis* and *trans*-isomers are present in a 1:1 ratio of both conformers. The assignment of all proton (H) and carbon (C) atoms of both conformers as achived as well.



Scheme 1: *cis*-azahemiporphyrazine (left) and *trans*-azahemiporphyrazine (right).

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Accounting for Different Reactivities of Sulfinate and Thiosulfate Salts in Regioselective Azetidine Coupling via C-H Sulfenylation of Indoles and First Formal Synthesis of Methyl Echinosulfone A Alkaloid.

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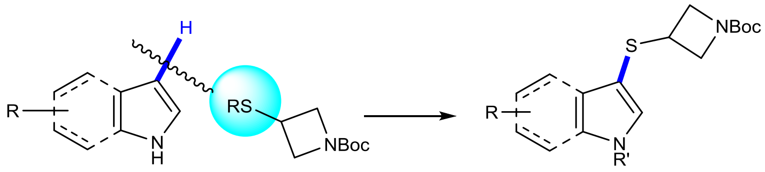
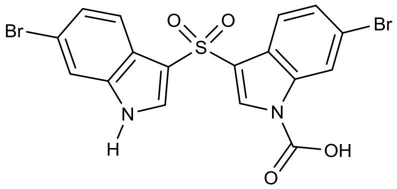
[a]*Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, U.K.*

[b]*Department of Chemistry, University of Al-Mustansiriyah, Baghdad, Iraq.*



SR = SO_2Na	SR = SSO_3Na
Narrow scope	***Broad scope***
via Az-S(O)-I	***via Az-S-I***



Echinosulfone A

Australian marine sponge
“ ***Echinodictyum sp.***”

The regioselective incorporation of azetidines into indoles, pyrroles and imidazo[1,2-a]pyridines is reported via a formal C-H sulfenylation reaction. While sodium sulfinate salts undergo C3 sulfenylation of electron rich indoles only, the corresponding thiosulfate salts have proved to be more general. In addition, thiosulfate salts have been shown to successfully couple to pyrroles and imidazo[1,2-a]pyridines. A mechanistic hypothesis for the different reactivities of sulfinate and thiosulfate salts is provided. The application of C-H sulfenylation chemistry using Bunte salt for the first formal synthesis of methyl **Echinosulfone A** alkaloid is described.

Base-catalyzed one carbon ring expansion of azetidin-2-ones

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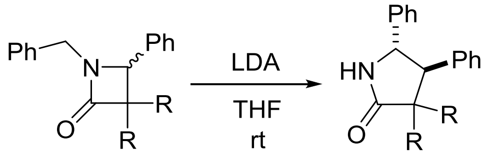
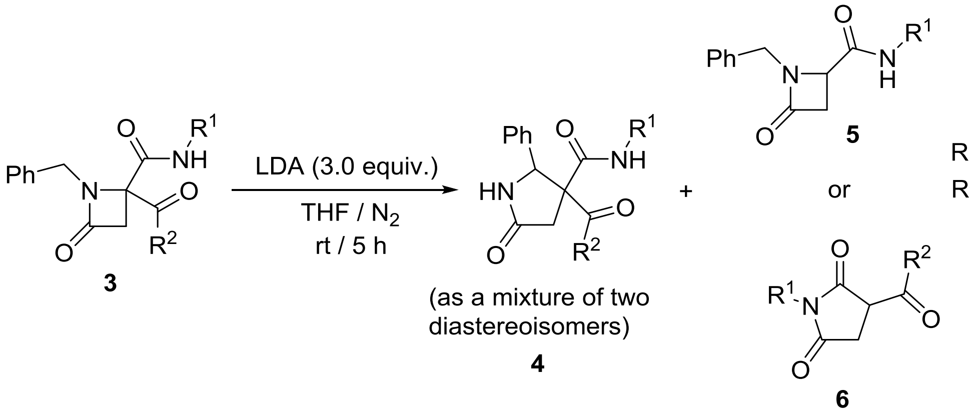
LDA- and *n*-BuLi-catalyzed one carbon ring expansion of β-lactams (azetidin-2-ones) **1** through the N(1)-C(4) bond cleavage followed by C(5) carbon insertion has been found a convenient method for the preparation of γ-lactams (pyrrolidin-2-ones) **2** with aryl substituents at positions 4 and 5.[1]



1a (R = Me)
1b (R = Ph)

2a (R = Me)
2b (R = Ph)

Our research interests include applications of the Ugi reaction and other multicomponent reactions in the synthesis of complex heterocyclic structures.[2] The reaction of azetidin-2-one **3** (synthesized by an Ugi/cyclization sequence) and LDA has been explored. Formation of pyrrolidin-2-one **4** as a product of one carbon ring expansion has been observed. Interestingly, either deacylated derivative **5** or pyrrolidin-2,5-dione **6** has been obtained as a side product.



R^1 = Bn, Cy, ^{t}Bu, *n*-Bu
R^2 = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, Ph, Me

Structural elucidation of the unexpected five-membered ring product **6** has been investigated and a suggested mechanism of its formation will be presented.

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[2] (a) Pertejo, P.; Corres, N.; Torroba, T.; García-Valverde, M. *Org. Lett.* **2015**, *17*, 612; (b) Pertejo, P.; García-Valverde, M.; Peña, P.; Cordero, N. A.; Torroba, T.; González-Ortega, A. *Org. Biomol. Chem.* **2014**, *12*, 4905.

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Dazine derivatives of potential interest in leishmaniasis

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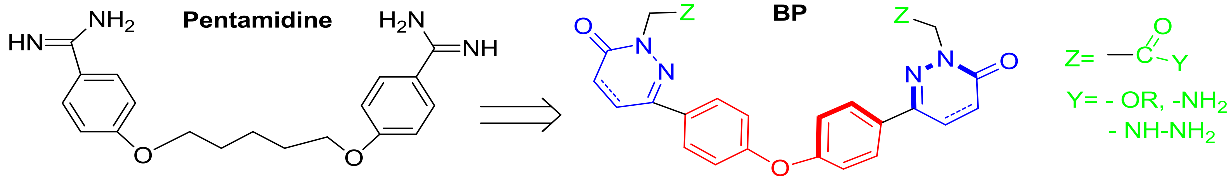
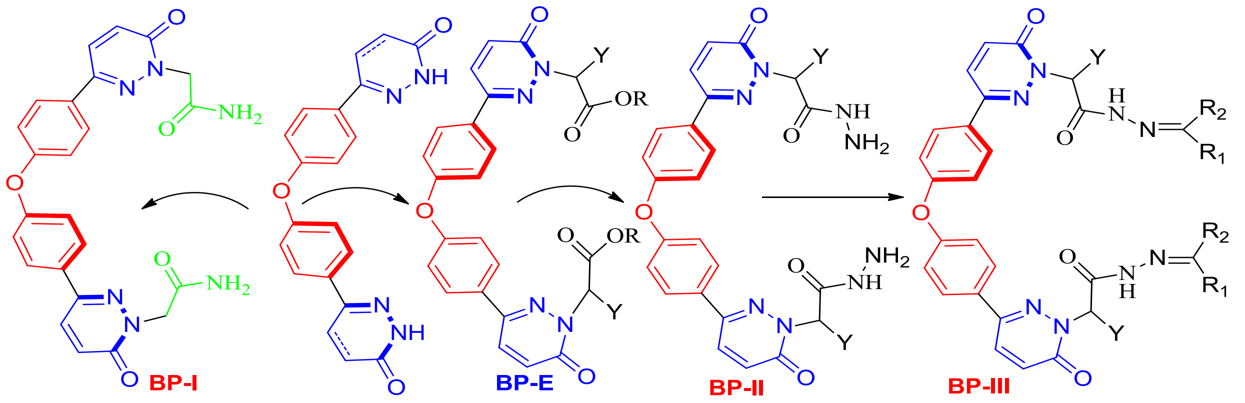
Cutaneous Leishmaniasis is the most common form of leishmaniasis. Current treatments for cutaneous leishmaniasis are performed with success using classical drugs such us pentamidine and imidazoquinolines. However, their use is limited by their toxicity, side effects, relatively high cost, discomfort and the emergence of drug resistance. This is why new approaches are urgently needed.

Nitrogen derivatives are "privileged structures" in drug design, optoelectronics, etc., the azaheterocycle scaffold being a core skeleton for multiple purposes. Pentamidine is a second-line drug largely used in treatment against cutaneous leishmaniasis caused by *Leishmania major* infection. The emphasis of this work consists in design, synthesis, characterization and determination of antileishmanial activity of new bis-pyridazine (BP) derivatives analogues of pentamidine.



The synthesis of our **BP** derivatives is straightforward and efficient, involving either a N-alkylation of BP (for BP-I class), either a N-alkylation followed by substitution with hydrazine for BP-II class, and finally, a condensation for BP-III class.



The structures have been elucidated by elemental and spectral analysis: IR, NMR (1H- , 13C- and 2D-experiments), X-ray analysis on monocrystal including.

The antileishmanial assay against *Leishmania donovani* intramacrophage amastigotes revealed a very good and promising activity for some **BP** compounds.

Acknowledgements. Authors are thankful to COST Action CM1307 and POSCCE-O 2.2.1, SMIS-CSNR 13984-901, No. 257/28.09.2010 Project, CERNESIM.

Competent route to Unsymmetric Dimer Architectures: Total Synthesis of (−)-Lycodine and (−)-Complanadines A and B

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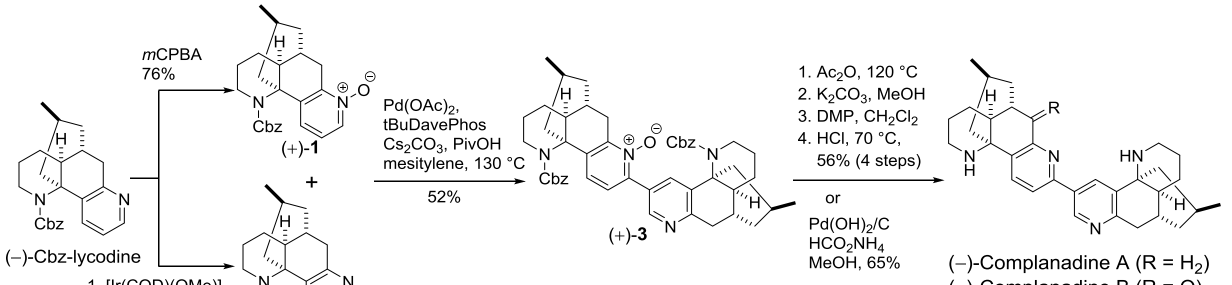
Complanadine A and B were isolated from club moss *Lycopodium complanatum* by Kobayashi and coworkers. Its structure was characterized by a dimeric motif of lycodine-type $C_{16}N_2$ skeleton. Interestingly complanadine A and B induced mRNA expression level for nerve growing factor (NGF) in 1321N1 human astrocytoma cells.[1] Because of the intriguing biological activity and complex structure, we started a synthetic program toward complanadines. Herein, we will present the total syntheses of lycodine, complanadines A and B.

In the synthesis of lycodine, diastereoselective Diels-Alder followed by Mizoroki-Heck reactions was employed for accessing a bicycle[3.3.1]nonane core in the skeleton. A key coupling reaction of the lycodine units, pyridine *N*-oxide (+)-**1** and bromopyridine derivative (+)-**2**, through C−H functionalization gave an unsymmetric dimer (+)-**3** at a late stage of the synthesis. The total synthesis of (−)-complanadine A and B was achieved from the intermediate (+)-**3**. We will report the detail of our total synthesis as well as biological studies. [2,3]



Scheme 1. Total Synthesis of Complanadine A and B.

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[2] Tsukano, C.; Zhao, L.; Takemoto, Y.; Hirama, M., *Eur. J. Org. Chem.*, **2010**, 4198.
[3] (a) Zhao, L.; Tsukano, C.; Kwon, E.; Takemoto, Y.; Hirama, M., *Angew. Chem. Int. Ed.*, **2013**, *52*, 1722. (b) Zhao, L.; Tsukano, C.; Kwon, E.; Shirakawa, H.; Kaneko, S.; Takemoto, Y.; Hirama, M., *Chem. Eur. J.*, **2017**, *23*, 802.

Towards the Total Synthesis of Divergolide Ansamycins: Preparation of macrocyclic precursors for the exploration of their biomimetic diversification

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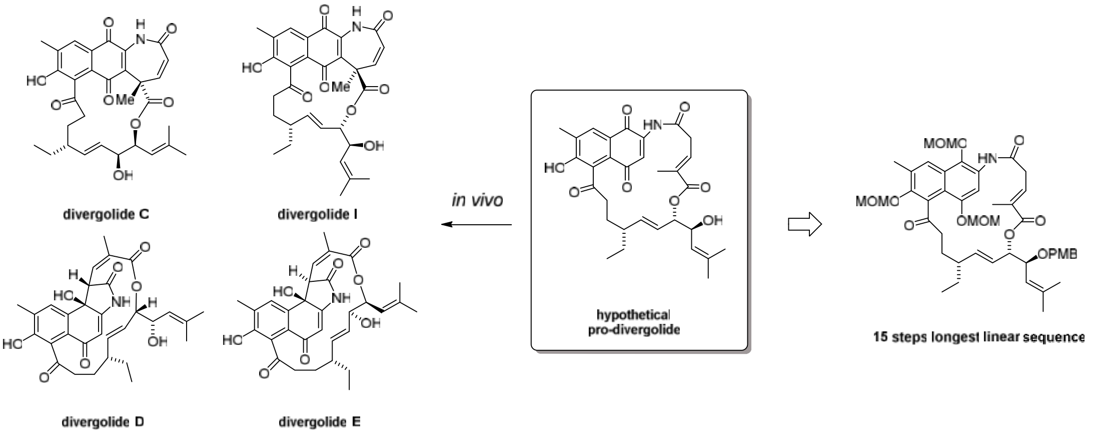
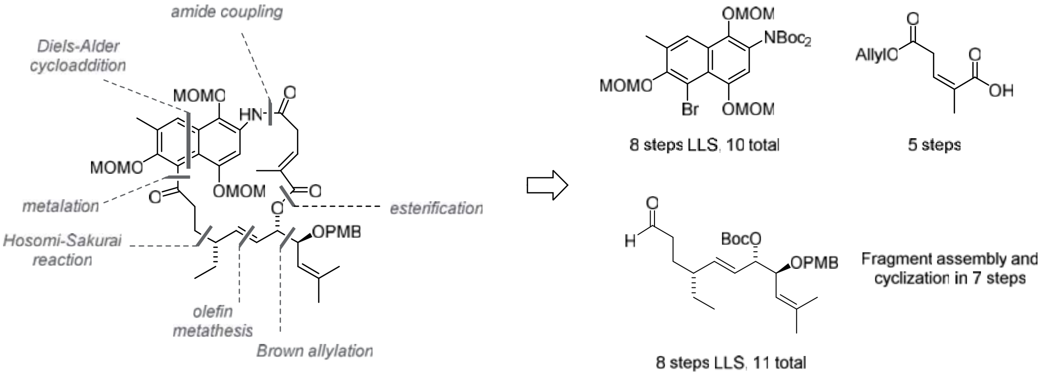
Ludwig-Maximilians-Universität, Munich, Germany

The divergolides represent strikingly diverse family of ansamycin polyketides. Studies on their biosynthesis reveal remarkable plasticity: a single molecule grants acts as a precursor to four different ring systems that resemble the skeletons of almost 20 different natural products.[1] Most of these show promising biological activity and have therefore evoked considerable interest in the synthetic community, yet no successful synthesis has been reported.



In our latest approach, we demonstrate how advanced macrocyclic compounds can be accessed in a rapid and convergent fashion, enabling us to explore the biomimetic endgame. We will present the evolution of this highly optimized synthesis as well as our forays into the final cyclization reactions.



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Synthesis of Functionalized Pyrazoles, Isoxazoles and Triazoles using 1,3-Dipolar Cycloaddition Reaction of Nitrile Imine and Nitrile Oxide

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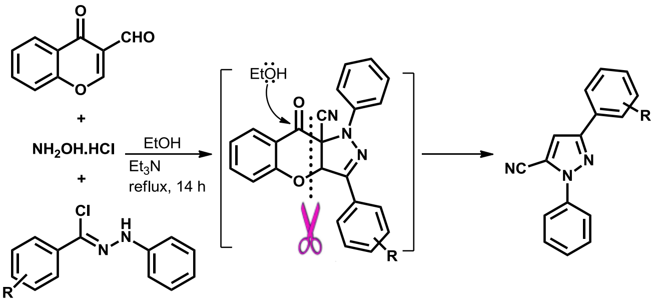
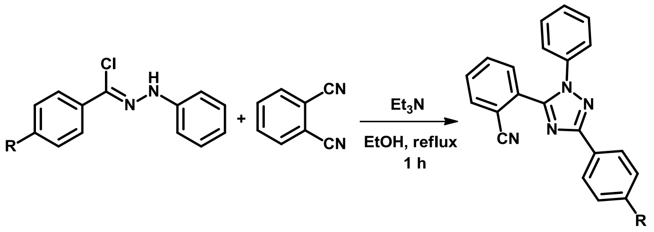
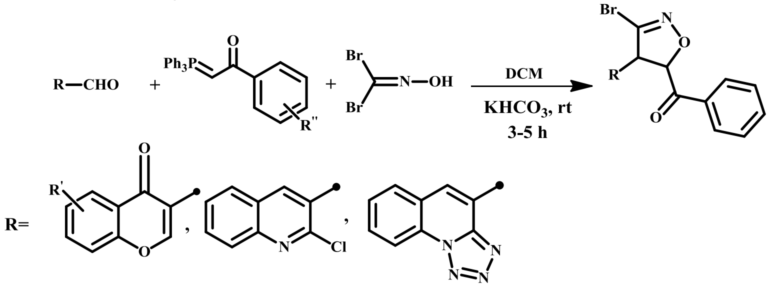
Development of versatile heterocycle synthesis has always been an important area in synthetic organic chemistry [1]. The 1,3-dipolar cycloaddition is a powerful approach for the construction of five-membered heterocycles since it was first reported by Huisgen in the 1960s [2]. The pyrazoles, 4,5-dihydroisoxazoles and 1,2,4-triazoles are found in natural and synthetic products that exhibit a wide range of biological activities [3]. Herein, we represent a novel method for the synthesis of these compounds by nitrile imine and nitrile oxide as 1,3-dipoles through a one pot procedure.



Scheme 1. Synthesis of 1,3-diphenyl-1*H*-pyrazole-5-carbonitrile *via* three-component reaction.



Scheme 2. Synthesis of 1,3,5-trisubstituted 1,2,4-triazoles.



Scheme 3. Synthesis of substituted 3-bromo-4,5-dihydro isoxazoles

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Optimization of fragment-like CsrA-RNA interaction inhibitors as potential anti-infectives

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The carbon storage regulator A (CsrA) is an astonishingly wide-spread bacterial RNA binding protein mediating global effects on translation by binding to GGA-motifs in mRNAs [1]. In pathogens, it is involved in regulation of pathogenicity traits rendering CsrA as a promising anti-infective drug target [2]. It is highly conserved in structure and RNA recognition [3] and is involved in virulence, motility, and biofilm formation [4]. Notably, a *CsrA* mutant of the pathogen *Yersinia pseudotuberculosis* displayed attenuated virulence in a murine infection model.

In a previous study, we discovered the first CsrA-RNA interaction inhibitors via biological and biophysical screenings of different small molecule libraries and the DZIF natural compound library [5]. From libraries of ~ 1000 molecules, 7 compounds were identified inhibiting the interaction by binding to CsrA, not to RNA. Among these hit molecules, we identified three promising heterocyclic scaffolds of fragment-like size suitable for facile medicinal chemistry optimization.

First, we elaborated synthetic routes to these compounds, which enabled us to introduce further modifications systematically. Then, we evaluated the hit scaffolds and their derivatives in a fluorescence polarization competition assay regarding their ability to disturb the RNA-protein interaction. The gained SAR insights will be exploited for future fragment-growing efforts.

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A Photocatalytic Meerwein Approach to the Synthesis of Isochromanones and Isochromenones

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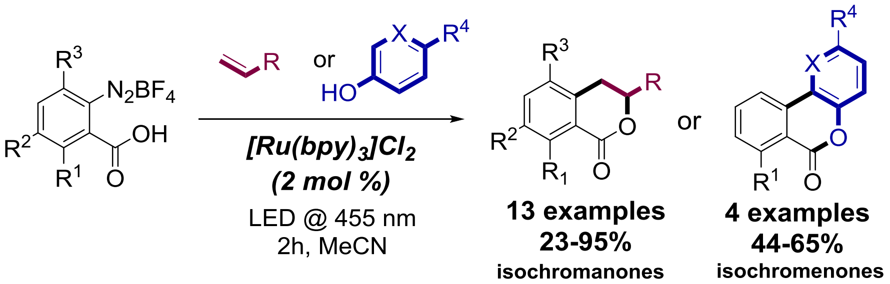
Isochromanones and isochromenones are molecules belonging to the isocoumarin–like product family. These molecules are commonly isolated from a wide variety of natural sources, such as plants, insects and microbes. [1] The interest regarding these classes of compounds is clearly witnessed by the vast number of reports regarding their activities, that span from antifungal to cytotoxic, antimalarial and anti–allergic properties. [2] In particular, heterosubstituted derivatives **B** have emerged as a class of iridium ligands in strongly emitting organometallic complexes that could find application in the development of tunable organic light-emitting diodes (OLEDs). [3] The large number of applications has triggered the development of various synthetic routes towards these compounds.

Herein we report a visible–light Ru^{II} photoredox Meerwein approach to the synthesis of isochromanones and isochromenones, [4] starting from diazonium salts of differently substituted anthranilic acids and various alkenes. This strategy is reliable and efficient, affording the desired products in good yields with high selectivity under mild conditions. The method allowed to build a small library of 3,4–dihydroisocoumarins. Both the presence of different substituents on the ring of the diazonium salt and modifications of the nature of the substituents on the unsaturated moiety do not affect the reaction outcome.



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Preparation of a Novel TetraPyrazinoPorphyrazine

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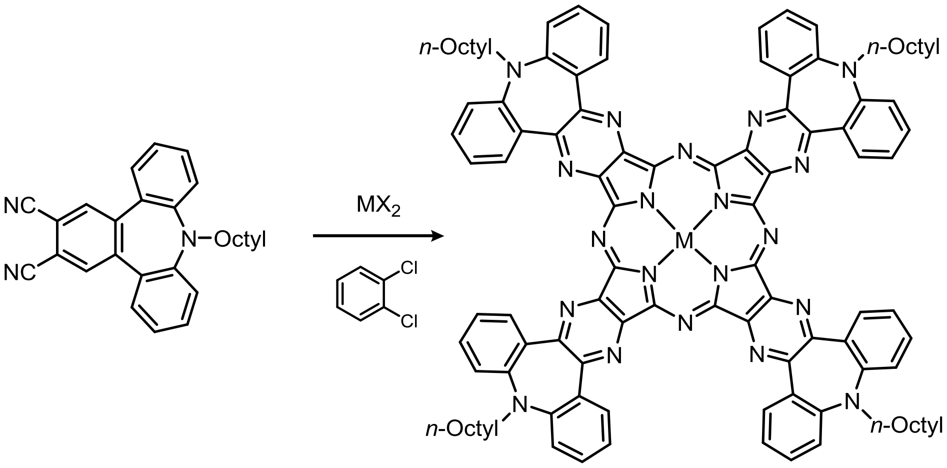
TetraPyrazinoPorphyrazines (TPyzPzs) are highly conjugated macrocyclic compounds that are particularly known, studied and used starting from the last century.[1] The ever growing interest in this class of compounds is connected with many potential applications in material science. Different TPyzPzs and their corresponding metal-complexes (TPyzPzsM) were illustrated as electronic devices, organic transitors, pigments, liquid-crystaline films.



Metal-complexes can be directly synthesized by the reaction of dinitrile precursors at high temperature in the presence of metal salts. Our studies in this class of compounds started with their use in catalytic procedures for the cyclopropanation of alkenes with EDA (EthylDiazo Acetate).[2] We started with this research following our previous interest in oxcarbazepine compounds and our particular attention was devoted to the preparation of a class of TPyzPzsM containing a dibenzoazepine moiety.[3]

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Chromones as versatile building blocks in cycloaddition reactions

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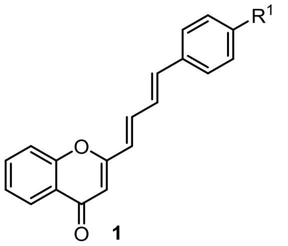
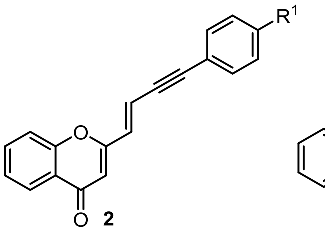
4*H*-Chromen-4-ones commonly referred as chromones are a class of naturally occurring heterocyclic compounds implicated in a series of biological and pharmacological properties.[1] It is also an interesting scaffold involved in a range of chemical transformations for the preparation of novel and more complex oxygen-containing heterocyclic derivatives.[2]

Following our interest in the chemistry of chromones, we design two different building blocks, 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones **1** and (*E*)-2-(4-arylbut-1-en-3-yn-1-yl)-4*H*-chromen-4-ones **2**, and explore the reactivity of the unsaturated systems in cycloaddition reactions. In the former case, chromones **1** were used as dienes in microwave-assisted Diels–Alder (DA) reactions with various electron-poor and electron-rich dienophiles to provide flavone-type compounds **3**.[3] In the latter case, the diene system of chromones **2** was involved in DA reactions with *N*-methylmaleimide whereas the acetylene moiety react with sodium azide, via 1,3-dipolar cycloaddition reaction, to afford xanthene-1,2,3-triazole dyads **4**.[4] In this communication, we will present and discuss the synthetic details and spectroscopic characterization of the main products and some interesting byproducts, as well as the intermediate compounds isolated in each case.



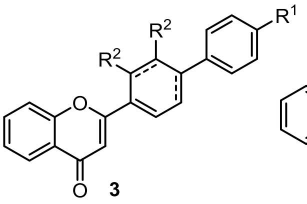
1

Diels-Alder reaction with electron-poor and electron-rich dienophiles



2

Diels-Alder reaction with *N*-methylmaleimide and 1,3-dipolar reaction with sodium azide



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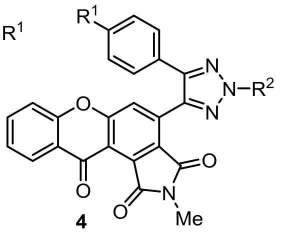

4

Thanks are due to University of Aveiro and FCT/MEC for the financial support of the QOPNA research unit (FCT UID/QUI/00062/2013) through national founds and, where applicable, co-financed by the FEDER, within the PT2020 Partnership Agreement, and to the Portuguese NMR Network, as well as to the Instituto Politécnico de Bragança. H.M.T.A. is grateful to FCT for their PhD grant (SFRH/BD/86277/2012).

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Synthesis of stable *trans*-cyclooctene containing amino acids for *in vivo* inverse-electron demand Diels-Alder cycloaddition with tetrazines.

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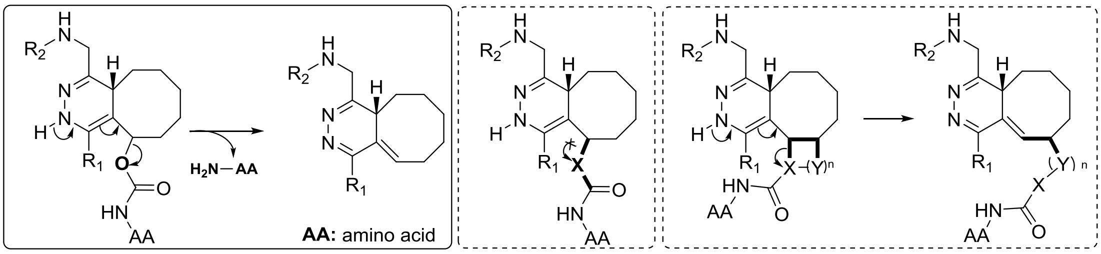
Bioorthogonal ligation strategies based on Diels-Alder cycloaddition are gaining widespread attention in the fields of chemical biology, medicine and diagnostics. In particular, specific and fast reactivity of strained *trans*-cyclooctenes with *1,2,4,5*-tetrazines in the inverse-electron demand Diels-Alder cycloaddition (IEDDAC) enabled selective tagging of biomolecules with small-molecule fluorophores suitable for *in vivo* super-resolution microscopy. [1] Notably, some *trans*-cyclooctene (TCO) based strained dienophiles can react rapidly with unhindered tetrazines exceeding reaction rates of enzymatic reactions. The high rate of the IEDDAC reaction is partly due to the ring strain induced by the *trans* geometry of the double bond. However, the induced strain makes *trans*-cyclooctenes containing probes susceptible to nucleophilic attack by thiols present in biological media. [2] Additionally, the dihydropyridazine product of IEDDAC reaction between *trans*-cyclooct-2-en-1-ol can undergo a side-reaction to eliminate a carbamate moiety under release of carbon dioxide and the linked amino acid. [3]



In the context of protein labelling such side-reaction lead to a drop in labelling efficiency when carbamate derivatives of (*E*)-cyclooct-2-en-1-ol are utilized. Therefore, there is a need in synthesis of new stable *trans*-cyclooctene containing amino acid side chains. We hypothesized that changing the carbamate to non-eliminating linker may suffice to overcome elimination problem. Stereoselective Mitsunobu-type displacement was used to install the desired linker onto (*E*)-cyclooct-2-en-1-ol. Synthesis of a new *trans*-cyclooctene containing unnatural amino acid is reported, as well as its genetic encoding into living mammalian cells. Furthermore, the stability of the conjugates with tetrazines was characterized by NMR and Förster resonance energy transfer studies.

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Chemoselective activation of amide carbonyls towards nucleophilic reagents

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Amides represent an important class of compounds in chemistry, chemical biology, and pharmaceutical industry. Their broad utility in many fields is closely tied to the structure of the amide moiety which endows these compounds with unique features. The low reactivity of amide carbonyls towards nucleophiles is a major obstacle to their further functionalization. Selective activation of amides and lactams enables access to novel reactivity pathways and opens up intriguing perspectives in synthesis.

Recently, we have demonstrated that upon treatment with $Cp_2Zr(H)Cl$ (Schwartz's reagent), five- and six-membered lactams, including sugar- and hydroxy acid-derived lactams,[1] can be easily converted into imines under mild conditions. In addition, in situ generated cyclic imines can be directly subjected to further reactions with nucleophilic reagents such as allyltributylstannane,[2] Grignard reagents,[2] enolates[2] or Danishefsky's diene[1] to afford α-functionalized pyrrolidines, piperidines, and polyhydroxylated pyrrolidine peptidomimetic[3] scaffolds in a one-pot manner.

The key advantage of the presented approach is the simplicity and convenience of generation of sugar-derived imines from readily available starting materials: sugar-derived lactams. The use of sugar-derived lactams as cyclic imine precursors is crucial to the efficiency of the described synthetic method. These compounds are more readily prepared, handled, and stored than the alternative precursors of cyclic imines such as nitrones, *N*-chloroamines, or azido aldehydes. In the second part of the presentation, a synthesis of previously inaccessible imines from readily available amides will be briefly presented.

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Synthesis of Novel RGD Peptides and Their Coupling with Bioactive Heterocyclic Skeleton

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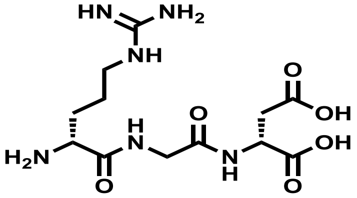
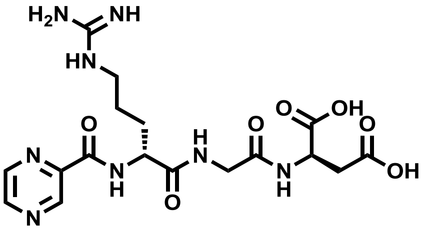
Arginine-glycine-aspartic (RGD), is a cell adhesion motif displayed on many extracellular matrix (ECM) and plasma proteins. RGD plays an important role in cell recognition and also tumor therapy and tissue engineering.



RGD peptide

Adding bioactive heterocyclic skeleton to the RGD peptides has an essential role in their conformation and also their biological activities. Meanwhile, there is some heterocyclic backbone that were selected as a candidate to add to the C- or N- terminal of synthesized RGD peptides such as pyrazine that exists in the structure of bortozomib as an anti-cancer drug.

Pyrazines are a class of compounds that occur almost ubiquitously in nature. Their effectiveness at very low concentrations and the ever increasing application of synthetic pyrazines in the food and pharmaceutical industries are responsible for the high interest in these compounds.[2] Herein, we wish to report the coupling of RGD peptides with 2-pyrazine carboxylic acid and other bioactive heterocyclic skeletons to access the novel peptides and show their effect to the conformation of the peptide. The structure of compounds was confirmed based on the HR-MS (ESI) data. The details about synthetic approach and structure of product will be further discussed in the conference.



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An Expedient Synthesis of CMF-019, a Potent Apelin Receptor (APJ) Agonist

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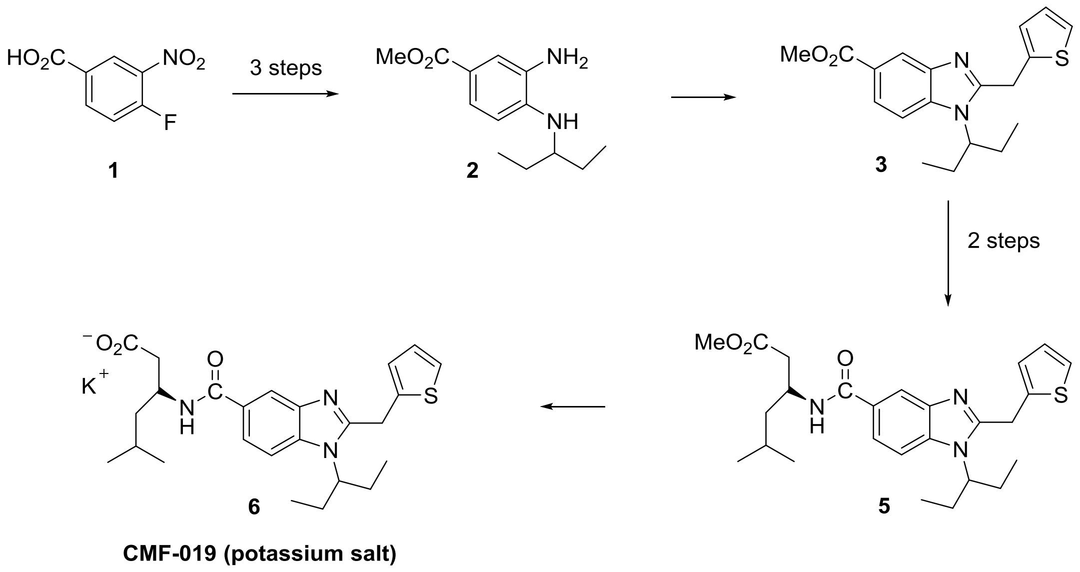
The apelin receptor (APJ) represents a recently identified G protein-coupled receptor,[1] that activates through a binding with an endogenous peptide apelin.[2] Nowadays, the apelin–APJ system has emerged as an important regulator of cardiovascular homeostasis.[3] In a some stage of our study on a heart failure chemotherapy an efficient non-peptidic agonist of the APJ-receptor was required. Recently, a series of benzimidazole-derived APJ-agonists was patented,[4a] and **CMF-019** was recognized as the lead compound.[4b] However, neither **CMF-019** nor it's more water-soluble potassium salt **6** were commercially available. Moreover, the reported synthesis suffered from the drawbacks associated with low yields in several key steps, luck of the spectroscopic data and detailed description of the synthetic procedures.[4] For preparation a considerable amount of **6** the previously described insufficient transformations of **2** → **6** were modified and improved. Particularly, the benzimidazole ring in **3** was better tailored by a condensation **2** with (thiophene-2-yl)acetimidate salt, prepared by a modified Pinner method (AcCl-MeOH in ether). Saponification of **3** and subsequent condensation of the free acid **4** with the corresponding enantiopure β-aminoacid methyl ester smoothly gave the precursor **5**. Treatment of the latter with methanolic KOH or with Me_3SiOK in THF followed by HPLC-purification afforded the desired product **6** in good yield.



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Construction of Hexahydrophenanthrenes by Rhodium(I)-Catalyzed Cycloisomerization of Benzylallene-Substituted Internal Alkynes through C-H Activation

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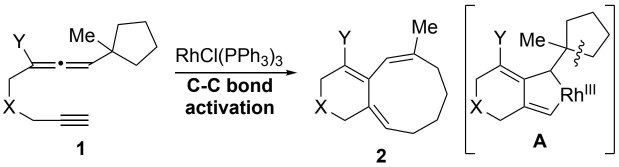
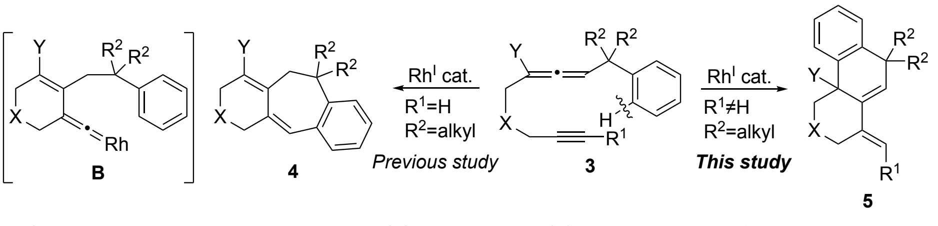
Cyclization reactions using transition-metal catalyzed C-H and/or C-C bond activation are powerful step- and atom-economic methods for the straightforward construction of complex polycyclic skeletons that are inaccessible by other conventional methods. These activation processes frequently require directing groups in the substrates, which bind the transition-metal catalyst at a position close to the reactive site. Relief of the high strain energy would be an alternative driving force to facilitate the cleavage of C-C bonds in cycloalkanes. We recently disclosed that the $RhCl(PPh_3)_3$ catalyzed intramolecular cycloisomerization of alkynes with a pendant allenylcyclopentane moiety **1** efficiently provides bicyclo[7.4.0]tridecatrienes **2**.[1] We presumed that this reaction occurred by the initial formation of rhodabicyclo[4.3.0] intermediate **A**, followed by β-carbon elimination and reductive elimination. The plausible key intermediate **A** could accelerate the unprecedented cleavage of the unactivated cyclopentane ring by releasing its low strain energy (6.3 kcal/mol). Thus this result allow for the assumption that the allene-alkyne unit functions as a highly reactive π component towards the Rh^I catalyst to form a rhodabicyclic intermediate, which would subsequently activate C-C and/or C-H bond near the Rh species.



While investigating the Rh^I-catalyzed cyclization of allene-alkynes, we observed a novel cycloisomerization for the benzylallene-substituted terminal alkynes **3** (R^1=H, R^2=alkyl) that proceeds through $C(sp^2)$-H bond activation on the benzene ring to produce **4**.[2] This reaction was assumed to proceed via the unique vinylidene carbene Rh intermediate **B**. Herein, we describe another type of C-H activation of benzylallene-alkyne species **3** (R^1≠H, R^2=alkyl); the replacement of the terminal alkyne with an internal one dramatically changed the ring-closing mode to furnish the hexahydrophenanthrene skeleton **5** in high yields.[3]



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Nucleobase azide–ethynylribose click chemistry contributes to stabilizing oligonucleotide duplexes and stem-loop structures

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and Yukio Kitade[1,2,5]
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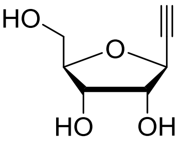
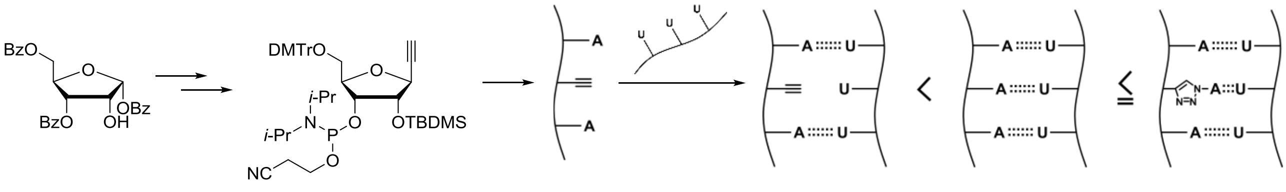
Copper-catalyzed azide-alkyne cycloaddition (CuAAC) has been widely used for the post-modification of oligonucleotides. Various nucleic acid mimics bearing ethynyl groups and their phosphoramidite derivatives have been developed to incorporate ethynyl residues into oligonucleotides by the standard phosphoramidite solid-phase method. We have also developed versatile probes possessing an ethynyl unit and post-labeling methods using CuAAC.[1–3] Here, we describe the synthesis of oligonucleotides with 1-deoxy-1-ethynyl-β-D-ribofuranose (R^E) using the corresponding phosphoramidite compound prepared by a method that is more practical and reliable than conventional methods.[4] Oligonucleotides bearing nucleobase-substituted 1,2,3-triazole nucleosides were synthesized by the CuAAC post-modification method. A thermal stability study showed that oligonucleotide-tethered base-pairing nucleobases introduced via CuAAC greatly stabilized the duplex. Moreover, 1,4-disubstituted 1,2,3-triazole units formed by CuAAC stabilized stem-loop structures. These findings could contribute to advancing the development of oligonucleotide-based medicine, including ribozymes and miRNA possessing stem-loop regions.



R^E



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Transition Metal-Catalyzed Regioselective Intramolecular Dehydrogenative C-5 and C-2 Cross Coupling in an *N*-substituted Pyrrole-Azole System

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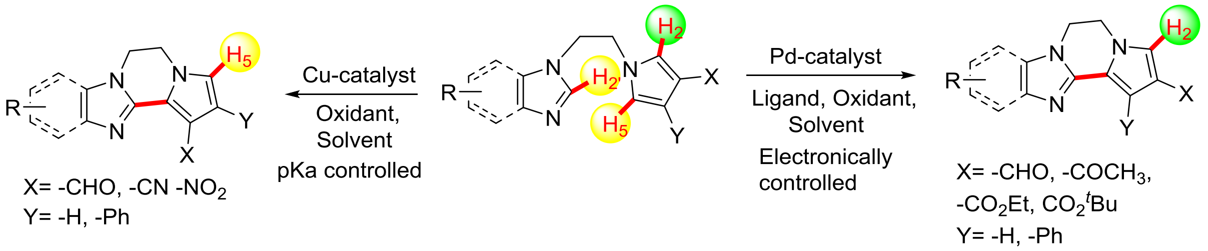
In recent years, transition-metal catalyzed direct C−C bond formation via oxidative C-H cross coupling reactions have emerged as one of the most important methodologies. The importance of heteroaromatic moiety lies in the fact that they are found in the core structure of several biologically active systems. The existing aim of synthesizing six membered and seven membered rings embedded in between the heterocycles through controlled site selective C-H activation provides significant attention to this methodology since this primary skeleton is found in certain natural products. Functionalized polycyclic pyrrole-azole structures possessing fused rings were directly synthesized via ligand-enabled Pd-catalyzed C-5 selective and Cu-catalyzed C-2 selective intramolecular cross coupling of N-substituted pyrrole-azoles. The Pd-catalyzed C5-H activation in the presence of reactive C2-H remains a challenge to be addressed, which was targeted to be resolved through the present approach by the use of apropriate pd-catalyst, ligand, oxidant and solvent, generating the cyclized products ranging from 83-100% selectivity. On the other hand, Cu-catalyzed, ligand free intramolecular site selective dehydrogenative cross coupling of unsymmetrically substituted pyrrole-azole systems, provides the C-2 selective polyheteroaromatic framework upto 88% yield and 95% selectivity.

The featured methodology provides a novel disconnection for the synthesis of pyrrole containing alkaloids and medicinal compounds.



Scheme 1: Regioselective C-2 and C-5 dehydrogenative cross coupling reactions

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Synthesis of 3,4,5-Trisubstituted-1,2,4-triazin- 6(1H)-one through Five-Component Sequential Ugi/Nucleophilic Reaction of 3-iminosaccharins with Hydrazine

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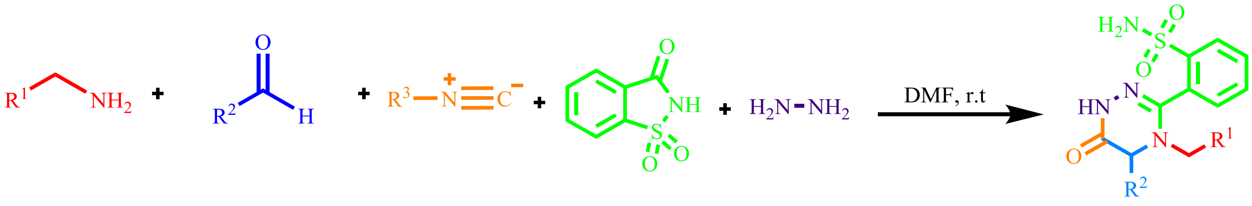
1,2,4-Triazinones are analogues of the pyrimidine bases of nucleic acids and an important class of molecules with several biological properties. For example, 1,2,4-triazin-3(2H)-ones have been shown to possess potential as anticancer,[1] antiviral[2] and antibacterial drugs.[3] However, to the best of our knowledge, no examples of 3,4,5-Trisubstituted-1,2,4-triazin- 6(1H)-one have been reported in the literature. Multicomponent reactions (MCRs) have become useful tools for diversity-oriented and complexity-generating synthesis of natural products and drug-like small molecules with novel properties.



Herein, we report a five component sequential Ugi/nucleophilic addition reaction of aromatic aldehydes, primary amines, Saccharin, isocyanides, and hydrazine has been developed in order to access 3,4,5-Trisubstituted-1,2,4-triazin- 6(1H)-one. The reaction may proceed through formation of 3-iminosaccharins as intermediates. The direct use of commercially available and inexpensive reagents, easy workup, short reaction times, and mild reaction conditions at room temperature make this domino reaction very attractive and practical.
The details about the synthesis will be further discussed in the conference.

Keyword: Multicomponent Condensation, Saccharin, 1,2,4-Triazinones.

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Modular Synthesis of Poly-substituted Pyridines *via* a Hydroamination of Alkynes and *N*-Silylamines

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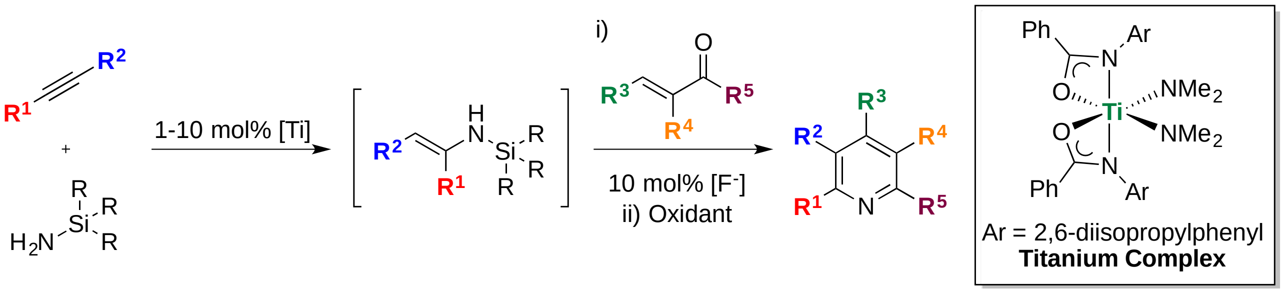
Hydroamination, the direct addition of an N-H bond across an unsaturation, such as an alkene or alkyne, is a powerful transformation towards the synthesis of nitrogen containing compounds. [1] The first example of a catalytically competent hydroamination of alkynes with *N*-silylamines has been developed. Using a bis(amidate)bis(amido)titanium(IV) precatalyst, the hydroamination reaction results in the formation of *N*-silylenamines with high to exclusive selectivity over the imine tautomer.



It has been previously shown that the additon of α,β-unsaturated carbonyls to bis-silylenamines in the presence of catalytic amounts of a fluoride source delivers pyridines. [2] A sequential hydroamination reaction/pyridine formation has been achieved. Addition of α,β-unsaturated carbonyls to the crude reaction mixtures in the presence of catalytic amounts of a fluoride source, followed by oxidation affords a variety of highly substituted pyridines in up to 96% yield.

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Diastereoselective Intramolecular (3+2) Cycloadditions of Epoxy & Aziridinyl Enolsilanes

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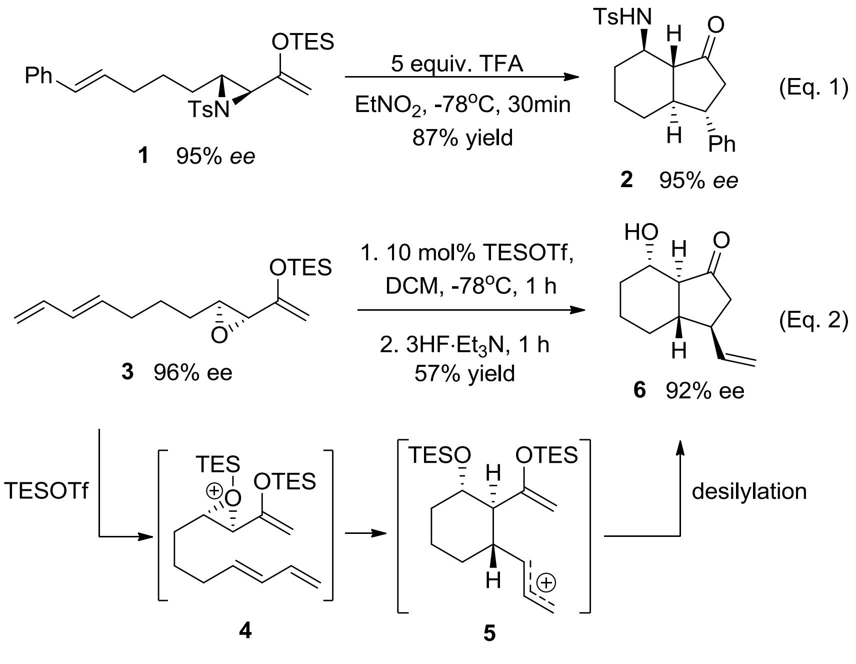
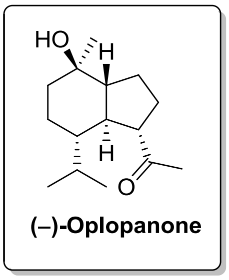
Department of Chemistry, the University of Hong Kong,
Pokfulam Road, Hong Kong

We have been studying and exploiting the reactivity of epoxy and aziridinyl enolsilanes for inter- and intramolecular (4+3) cycloadditions with dienes such as cyclopentadiene and furan, to produce cycloheptanoid cycloadducts in high yields and with good diastereo- and enantiomeric excesses.[1]

When we used open dienes in intramolecular reactions with aziridinyl enolsilanes or epoxy enolsilanes, diastereoselective (3+2) cycloadditions occurred instead to afford perhydroindanes bearing four contiguous stereocenters. These cycloadditions proceed by a stepwise mechanism, through an activated epoxide or aziridine **4** as intermediate. When the reaction was carried out with enantiomerically pure aziridines (Eq. **1**) and epoxides (Eq. **2**), cycloadducts were obtained with retention of *ee*. This reaction could be applicable as a key step in the asymmetric total synthesis of natural products such as (–)-oplopanone.





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Induction of Apoptosis in Hepatocellular Carcinoma Cell Lines by Novel Indolylacrylamide Derivatives: Synthesis and Biological Evaluation

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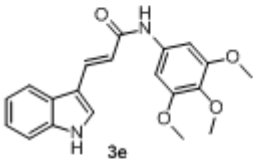
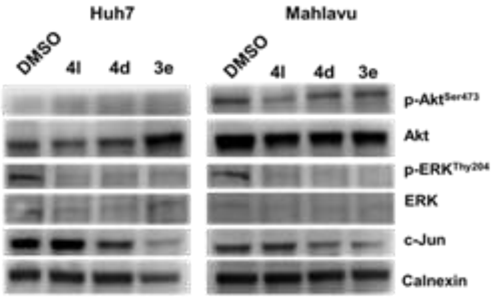
[3]*Cancer Systems Biology Laboratory, Informatics Institute, METU, 06800, Ankara, Turkey*

Hepatocellular carcinoma (HSC) is the sixth most common cancer and the second most common cause of cancer-related mortality. Each year, five hundred thousand new cases are diagnosed worldwide and about 85% of all cases come from developing countries. The 5-year survival rate of HSC patients is low and the incidence of HSC continues to increase (3-fold increase in 20 years). Hepatitis B virus (HBV) and hepatitis C virus (HCV), aflatoxin exposure, chronic alcohol intake and chronic infection caused by obesity are the etiologic factors associated with HSC. At present, the multikinase inhibitors Sorafenib and Regorafenib are drugs approved by the FDA for the treatment of HSC. Since liver cancer cells show resistance to conventional chemotherapy and radiotherapy, developing new therapeutic drugs against HSC is very important. We aimed to synthesize novel indole derivatives designed based on the structure of lead compound **SNB178** developed by our research group [1] and investigate their anticancer activity on the molecular level. In the first group, **3e**, **4l**, **4d**, which are the most active ones against Huh7, HCT116 and MCF7 cells among the synthesized 42 of the indole-3-yl-acrylamide derivatives, were tested by the SRB method in the liver cell panel. In flow cytometry analysis, **4l** caused G2/M arrest in Mahlavu and SNU475 cells while **3e** caused arrest in G2/M in all cells. Immunofluorescence staining technique has shown that **3e**, **4l** and **4d** cause apoptosis in liver cell lines. Western blot analysis showed that the level of CDK1 protein involved in the G2/M phase fell and cleaved-PARP bands were formed in the cells treated with the compounds. Furthermore, it has been determined that these three compounds cause reduction in phospho-ERK levels and decrease in level of c-Jun protein in ERK pathway in Mahlavu and Huh7 cells. (This study was supported by TUBITAK research grant 113S973).



3e



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Ring-Opening of Bicyclo[3.1.0]hexan-2-ones: Applications in Heterocyclic Synthesis

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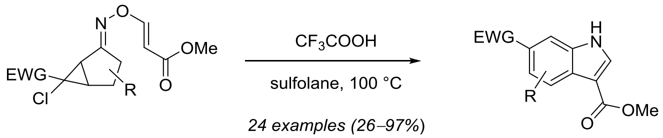
A new method for the synthesis of substituted indoles and indazoles will be presented based on our recently published ring-opening-aromatization reaction. [1]

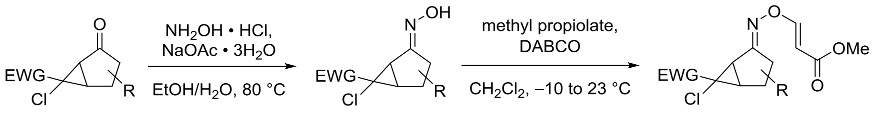
In our novel synthesis of substituted indoles, *O*-vinyl oxime **1** is converted to the corresponding substituted indole **2**. Mechanistically, we propose that **1** first undergoes a thermal 2π-disrotatory ring-opening-aromatization reaction to form an aryl-*O*-vinyl-oxime that affords the indole **2** via a facile acid-promoted [3,3] rearrangement.



1 2

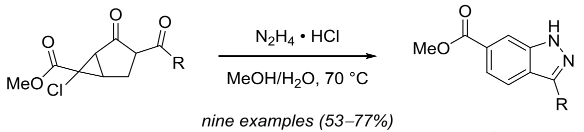
EWG = COOMe or Cl

O-Vinyl oxime **1** was synthesized in two steps from bicyclo[3.1.0]hexanones **3**. The first step of this reaction sequence is the condensation reaction of hydroxylamine hydrochloride with ketone **3** to give oxime **4**. Oxime intermediate **4** reacts with methyl propiolate under base-catalyzed conditions to give the corresponding *O*-vinyl oxime **1**.



3 4 1

In addition to our indole synthesis, we have also developed a one-pot strategy for the synthesis of indazoles from diketone **5**. Condensation of **5** with hydrazine monohydrochloride and subsequent ring-opening-aromatization reaction gave us the desired indazole **6** directly.



5 6

Using this method, simple variation of the diketone **5** allows us to gain access to a variety of C3-substituted indazoles.

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$PhB(OH)_2$-Mediated synthesis of 3-substituted isoindolin-1-ones *via* cascade Mannich/lactamization approach

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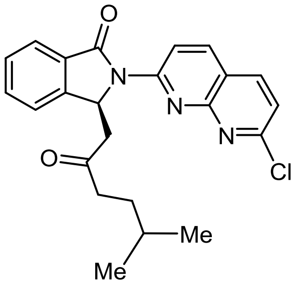
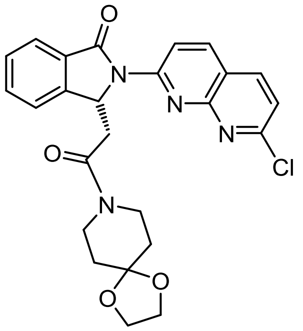
The 3-acyl substituted isoindolin-1-ones have attracted a great deal of attention because they have important pharmacological activities; for example, the pagoclone is a partial $GABA_A$ agonist[1] and the pazinaclone which act as an anxiolytic agent.[2]

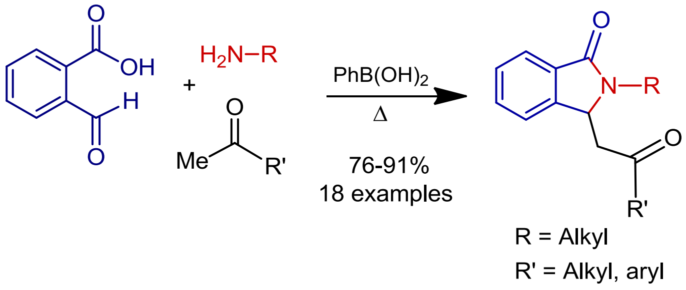


Pagoclone



Pazinaclone

Due to the valuable applications of 3-substituted isoindolin-1-ones, much effort has been devoted to the development of various synthetic methods for its preparation.[3] In this context, we herein report an efficient one-pot and eco-friendly approach for the synthesis of 3-functionalized isoindolin-1-ones by cascade Manich/lactamization reaction between 2-formylbenzoic acid, primary amines and several ketones under thermal and solvent free-conditions catalyzed by phenylboronic acid, providing the 3-acyl substituted isoindolin-1-one derivatives in 76-91% yield.



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A convenient synthesis of 1,2,3,4-tetrahydroisoquinoline-1-phosphonic and 1-phosphinic acids

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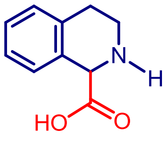
The 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (1-Tic) **1** core constitutes the skeleton of several compounds with a wide-ranging of therapeutic applications. The 1-Tic is also important as a conformationally constrained analogue of phenylglycine, present in several biologically active peptides.[1]

On the other hand, the α-aminophosphonic and α-aminophosphinic acids are probably the most important analogues of the α-amino acids,[2] these compounds are considered as stable mimetics of the tetrahedral transition state of peptide hydrolysis, providing greater bioavailability, stability and selectivity.[3]

Nevertheless, a small number of chemical methods are available for the synthesis of the conformationally constrained 1,2,3,4-tetrahydroisoquinoline-1-phosphonic acid **2**, whereas the synthesis of the 1,2,3,4-tetrahydroisoquinoline-1-phosphinic acid **3** has not yet been described in the literature.[4]



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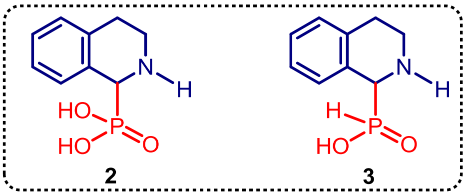
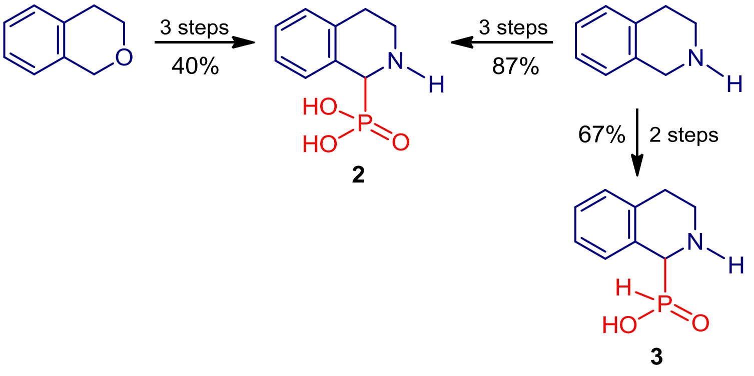


2 **3**

Due to the important properties of these organic compounds, here we report a new, practical and efficient method for the preparation of 1,2,3,4-tetrahydroisoquinoline-1-phosphonic acid **2** and the first synthesis of 1,2,3,4-tetrahydroisoquinoline-1-phosphinic acid **3** in excellent yield from cheap and commercially available isochroman and 1,2,3,4-tetrahydroisoquinoline.



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Investigation on Continuous-Flow Photooxidations of 1-Phenyl-1-cyclohexenes with Singlet Oxygen in a Micro Flow Reactor

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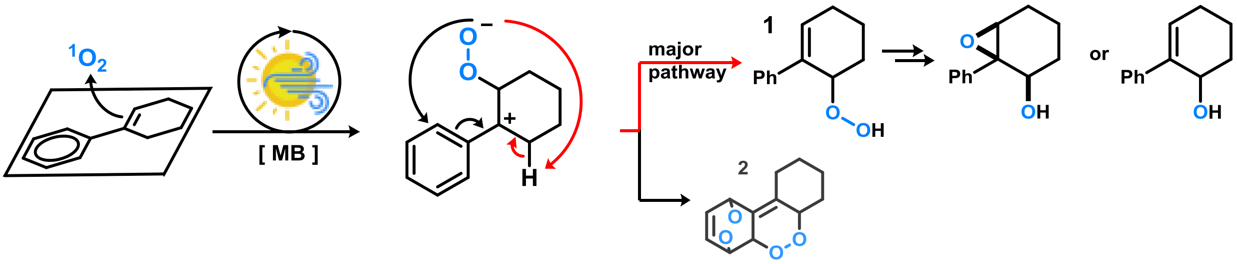
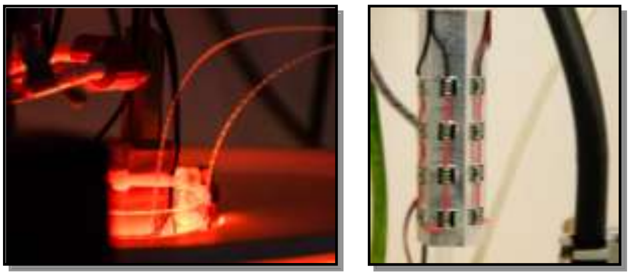
University of Regensburg, Institute of organic chemistry, Regensburg/D

As reactions of organic molecules with molecular oxygen in its ground state often show poor selectivity, protocols applying singlet oxygen are common. We used a home built photo-flow microreactor for these quasi tri-phasic reactions (gas, liquid, visible light). [1,2]

The combination of green reagents together with visible light within a safe, scalable, and efficient reactor technology is a promising approach towards environmentally benign reactions. We investigated the oxidation of phenylcyclohexenes with singlet oxygen, generated *via* photosensitization of oxygen with methylene blue (MB) under visible light:



in a photo-flow microreactor
capillary: 15 m
t_{rxn}: ~ 2 min



Depending on the substitution at the arene moiety, conversion of starting material and ratio between the two main oxidation products, hydroperoxide **1** and [4+2]-cycloaddition product **2**, were investigated in a Hammett study revealing two distinct reaction mechanisms. Interestingly, the hydroperoxides were stable enough be quantified *via* GC-FID, isolated, and stored for up to several months. To obtain even more stable products, the hydroperoxides were converted in Sharpless-type self-epoxidations [3] or efficiently reduced with PPh_3 to yield allylic alcohols without the need of intermediate work-up steps.

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Enantioselective Desymmetrization of para-Quinamines through an Aminocatalyzed Aza-Michael/Cyclization Cascade Reaction

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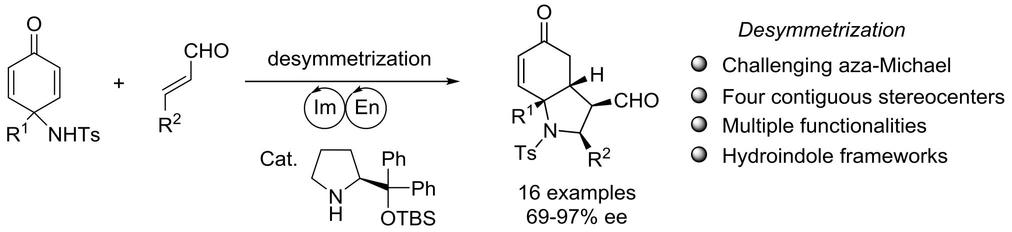
Desymmetrization processes are powerful means of transforming prochiral or meso-molecules into functionalized enantioenriched compounds. [1] The chief challenge facing the organic chemists within this field lies in the use of a catalyst enabling the discrimination between two enantiotopic atoms or groups during the symmetry-breaking transformation. Among the vast array of substrates available for such transformations, cyclohexadienone systems contain a rigid six-membered ring and functionalities, making them attractive starting materials to reach complex cyclic architectures via a desymmetrization process. [2] While several reports have described desymmetrization processes for which the nucleophile that attacks the dienone is already attached to the cyclohexadienone motif, bimolecular transformations have received less attention.



As part of our ongoing research into the development of organocatalytic methodologies, we wish to report herein the implementation of a novel dissymmetrical construction of functionalized nitrogen-containing polycycles via an aza-Michael/cyclization cascade reaction. [3] The ability of chiral secondary amines to promote iminium and enamine activation of α,β-unsaturated aldehydes in one catalytic cycle will be the centerpiece of our desymmetrization strategy toward hydroindole structures, which are common motifs in natural substances and biorelevant compounds such as alkaloids. [4]

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[2] For reviews, see: (a) Kalstabakken K. A., Harned, A. M., *Tetrahedron* **2014**, *70*, 9571; (b) Maertens G., Ménard M.-A., Canesi S., *Synthesis* **2014**, *46*, 1573; (c) Yang X., Wang J., Li P., *Org. Biomol. Chem.* **2014**, *12*, 2499;

[3] Pantaine L., Coeffard V., Moreau X., Greck C., *Org. Lett.* **2015**, *17*, 3674;

[4] (a) Fridrichsons J., Mathieson A.,*Tetrahedron Lett.* **1960**, *1*, 18; (b) Crow W. D., *Aust. J. Chem.* **1962**, *15*, 159; (c) Fridrichsons J., Mathieson A., McL. *Acta Crystallogr.* **1963**, *16*, 206; (d) Pfäffli P., Hauth, H., *Helv. Chim. Acta* **1978**, *61*, 1682; (e) Jepsen T. H., Jensen A. A., Lund M. H., Glibstrup E., Kristensen J. L., *ACS Med. Chem. Lett.* **2014**, *5*, 766.

Synthesis of (pyridin-3-yl)diindolymehtane derivatives through different energy sources

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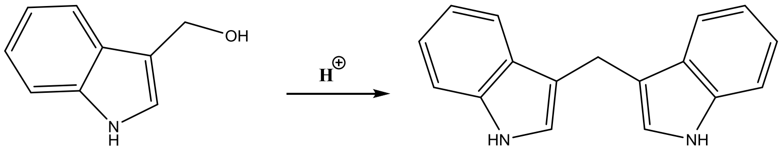
Cruciferae vegetables (eg. Cabbage, broccoli, cauliflower and Brussels sprouts, within others) contain phytochemical compounds which are precursors of indolyl-3-carbinol and 3,3'-diindolymethane (DIM-**I**). These precursors are either hydrolyzed by mirosinase enzyme or by the acidic media of stomach and their products are biologically actives, including indoles and isothiocianates. *[1]*

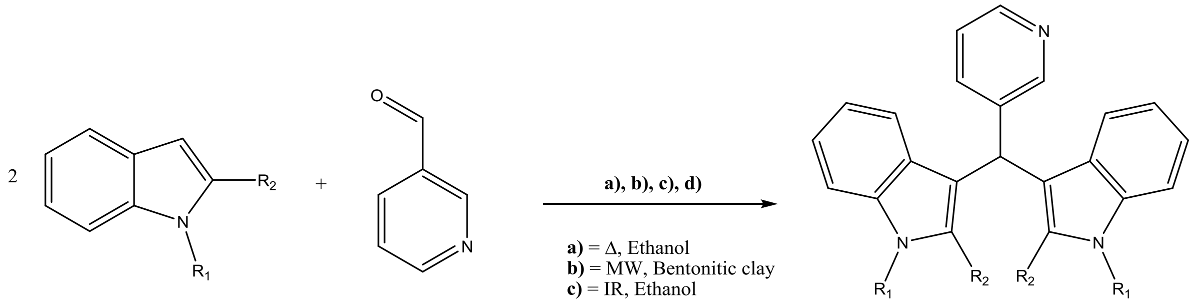
DIM is a dimer of indolyl-3carbinol (I3C) and it is known that it acts as prevention cancer moiety by induction of apoptosis on anticancer, Scheme 1.



I3C

I

Continuing our studies for the syntheses of DIM derivatives, in this work a study for the synthesis of a series of (pyridin-3-yl)diindolylmethanes by an ecological friendly methodology, using alternative energy sources (IR, US, MW), in short reaction times, with good yields and economic advantages*[2]* is presented. The results obtained with those generated with the use of conventional thermal energy are compared.



a) = Δ, Ethanol
b) = MW, Bentonitic clay
c) = IR, Ethanol
d) = US, Ethanol

1 R_1=H, R_2=H
2 R_1=Me, R_2=H
3 R_1=H, R_2=Me
4 R_1=H, R_2= ø

5

6 R_1=H, R_2=H
7 R_1=Me, R_2=H
8 R_1=H, R_2=Me
9 R_1=H, R_2= ø

1 Higdon, J.V.; Williams, D. E. et al. *Pharm Res,* **2007**, *55*, 224–236.

2 Penieres-Carrillo, J. G.; García-Estrada, J. G., et al. *Green Chem*, **2003**, *5*, 337-339.

Synthesis of new 5(6)-alkyl(aryl)amino-2-aryl-1*H*-benzimidazoles using alternative energy sources

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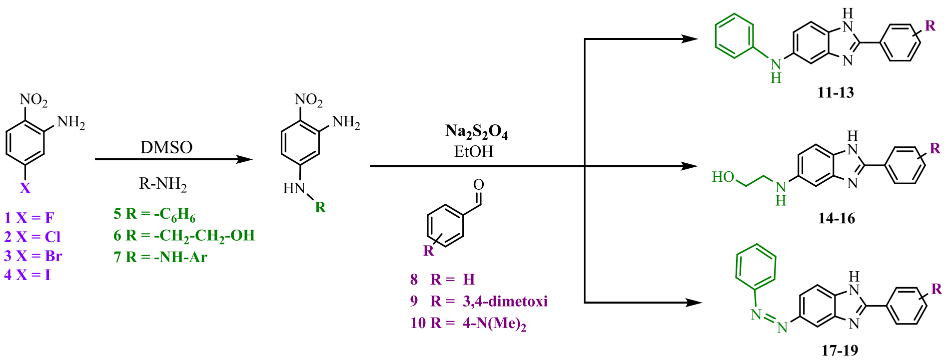
1)Sección Química Orgánica, Facultad de Estudios Superiores Cuautitlán-Universidad Nacional Autónoma de México (UNAM). Avenida 1 Mayo s/n, Cuautitlán Izcalli, Edo de México, C.P. 54740.

2) Instituto de Química, UNAM, Cd Universitaria, Coyoacán, Cd. De México, México, C.P. 04510

The structure of benzimidazole is a very versatile core contained in several substances that possess a wide range of pharmacological activities. Some applications are as anticancer,[1] antimicrobial[2] and antiviral,[3]within others. Therefore, the development of new synthetic methodologies of benzimidazoles is considered a goal by many organic chemists.

In this communication, conventional heating source *versus* eco-friendly energy sources (IR, US, MW) for preparation of a series of new 5(6)-alkyl(aryl)amino-2-aryl-1*H*-benzimidazoles with biological interest is presented. The synthetic pathway includes 5-halo-2-nitroaniline (X = F, Cl, Br, I) as start material and several alkyl(aryl)amines as nucleophilic agent for SNAr reactions and the products react with benzaldehyde derivatives and sodium dithionite as oxidizing agent to form the target molecules (Scheme 1) always with the best results using alternative energy sources.



Scheme 1.

1 Amal M. Y.; Ahmed M.; Mona H. B.; Rasha Y. E. and Ahmed S. S. *Med. Chem.* **2016**, *8*, 15-162.

2 Namrata S.; Annamalai P.; Kavita R.; Preeti A.; Arsad A.; Amit K. T. *Int. Curr. Pharm. J.* **2012**, *1*, 119-127.

3 Tonelli, M.; Paglietti, G.; Boido, V.; Sparatore, F.; Marongiu, F.; Marongiu, E.; La Colla, P.; Loddo, R. *Chem. Biodivers*. **2008**, *5*, 2386-2401.

Divergent carbonylative syntheses of functionalized benzimidazopyrimidinone and benzimidazimidazole derivatives

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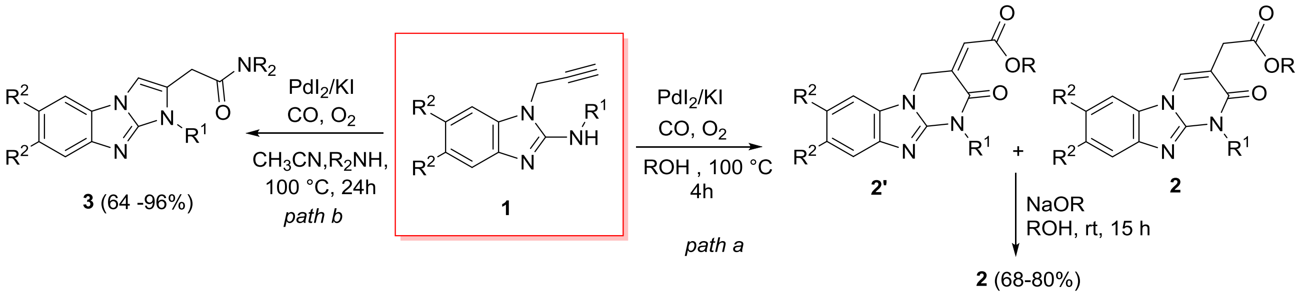
Benzo[4,5]imidazo[1,2-*a*]pyrimidin-2(1*H*)-one derivatives and imidazo[1,2-*a*]benzimidazole derivatives exhibit a wide spectrum of biological activities. In particular, their structural scaffold is present in drugs displaying analgesic, anti-inflammatory, hypotensive, anti-aggregant, hypoglycemic, and anti-cancer activities [1].

In this Communication, we report divergent carbonylative approaches for the direct synthesis of carbonylated benzimidazopyrimidinones and benzimidazimidazoles, starting from readily available (1-prop-2-ynyl-1*H*-benzimidazol-2-yl)amines **1**. When allowed to react with carbon monoxide (16 atm) and oxygen (4 atm of air) in the presence of the PdI_2/KI catalytic system [2] (PdI_2, 0.01-0.003 eq; KI, 0.3 - 1 eq), substrates **1** selectively afforded either benzo[4,5]imidazo[1,2-*a*]pyrimidin-2(1*H*)-ones **2** or 1*H*-benzo[*d*]imidazo[1,2-*a*]imidazoles **3** depending on reaction conditions. In particular, carrying out the reaction of **1** in an alcoholic solvent, at 100° C for 4 - 6 h, a mixture of **2** and *N*-substituted (*Z*)-2-(1-methyl-2-oxo-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-3(4*H*)-ylidene) esters **2'** was obtained, which was then quantitatively converted into benzimidazopyrimidinone **2** by base-promoted isomerization (Scheme 1, *path a*).

On the other hand, the same substrates were converted into **3** by performing the catalytic carbonylation reaction in CH_3CN at 100°C in the presence of an excess of a nucleophilic secondary amine (Scheme 1, *path b*).



Scheme 1

[1] P. N. Preston, D. M. Smith and G. Tennant (Eds.), *Benzimidazoles and its congeneric tricyclic compounds*, Part 2, Interscience, New York (1981).

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Nano Fe_3O_4-GO-SO_3H as a heterogeneous solid acid catalyst for the synthesis of 1′Hspiro[isoindoline-1,2′-quinazoline]-3,4′(3′H)-dione derivatives

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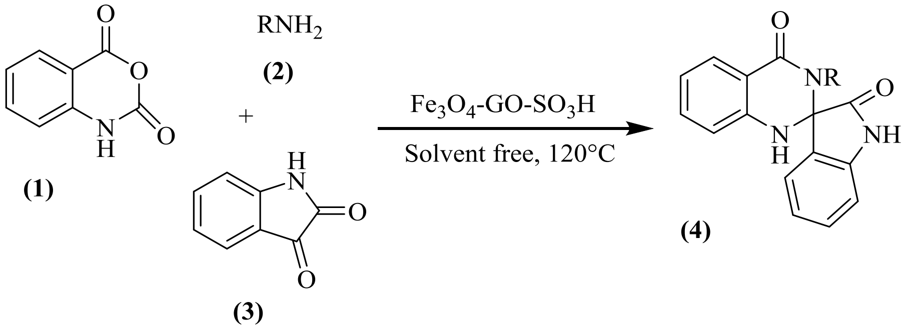
Spirooxindoles possess a wide range of biological and pharmaceutical activities.[1] These compounds have been prepared by different methods. One of which is from the reaction of isatoic anhydride, primary amines and isatin in the presence of a variety of catalysts such as $KAl(SO4)_2$. $12H_2O$.[2]

Graphene oxide, owing to abundant oxygen-containing functionalities (C–O, –OH) on their basal plane of sheet and carboxylic acids along the sheet edges, offers a wide range of routes to synthesize various functional catalysts.[3]

Herein, a facile procedure for the synthesis of 1′Hspiro[isoindoline-1,2′-quinazoline]-3,4′(3′H)-dione derivatives by one-pot reaction of isatoic anhydride (**1**), aliphatic or aromatic primary amines (**2**) and isatin (**4**) in the presence of nano Fe_3O_4-GO-SO_3H, as a magnetic, heterogeneous solid acid catalyst have been reported (Scheme 1).



Scheme 1. Synthesis of spirooxindoles in the presence of Fe_3O_4-GO-SO_3H nanocatalyst.

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Proline Catalysed Sequential Reactions for the Synthesis of 1,2-*syn,* 1,4-*anti* Diamino Alcohols

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Chemical Engineering & Process Development Division, National Chemical Laboratory
Dr. Homi Bhabha Road, Pune - 411008, Maharashtra, India.

Diamino alcohols are useful motifs present in many pharmaceutical compounds such as polyhydroxy alkaloids, azasugars, glycosphingolipids, amino acids and protease inhibitors. For instance, Sperabillins A–D (Fig. 1) with diamino units are potentially active against both Gram-positive and Gram-negative bacteria.

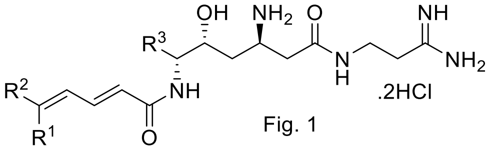
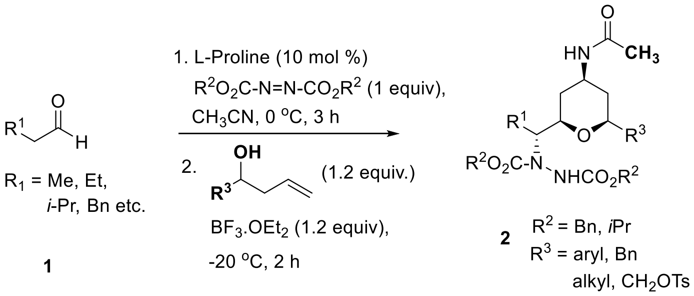


Fig. 1

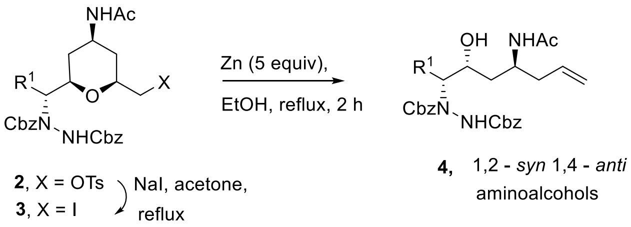
Sperabillin A: R^1 = Me, R^2 = H, R^3 = H
Sperabillin B: R^1 = Me, R^2 = H, R^3 = Me
Sperabillin C: R^1 = H, R^2 = Me, R^3 = H
Sperabillin D: R^1 = H, R^2 = Me, R^3 = Me

There is only one report available in the literature for the synthesis of 1,2-*syn*, 1,4-*anti* diamino alcohols (**4**) that uses toxic tin reagents. In continuation of our work on proline catalyzed sequential reactions, we present a new organocatalytic method for the synthesis of 1,2-*syn*, 1,4-*anti* diamino alcohols in high enantio- and diastereoselectivities. Firstly, the protocol involves a sequential L-proline catalyzed α-amination / Prins-Ritter amidation of aldehydes (**1**), all occurring in a single step, for the construction of tetrahydropyran (THP) units (**2**) (Scheme 1). This was followed by the Zn-mediated reductive ring opening sequence to produce 1,2-*syn*, 1,4-*anti*- amino alcohols (Scheme 2).



15 Examples
82-87 % yield
92-99 % ee
dr >99 %

Scheme1: Synthesis of THP units



82-90 % yield
> 98 % ee

Scheme 2: Synthesis of amino alcohols from THP units

Katayama, N.; Nozaki, Y.; Tsubotani, S.; Kondo, M.; Harada, S.; Ono, H. *J Antibiot* **1992**, *45*, 10.
Davies, S. G.; Haggitt, J. R.; Ichihara, O.; Kelly, R. J.; Leech, M. A.; Mortimer, A. J. P.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem*., **2004,** *2,* 2630.
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New method for post-functionalization of BODIPY dyes using nitrosation chemistry

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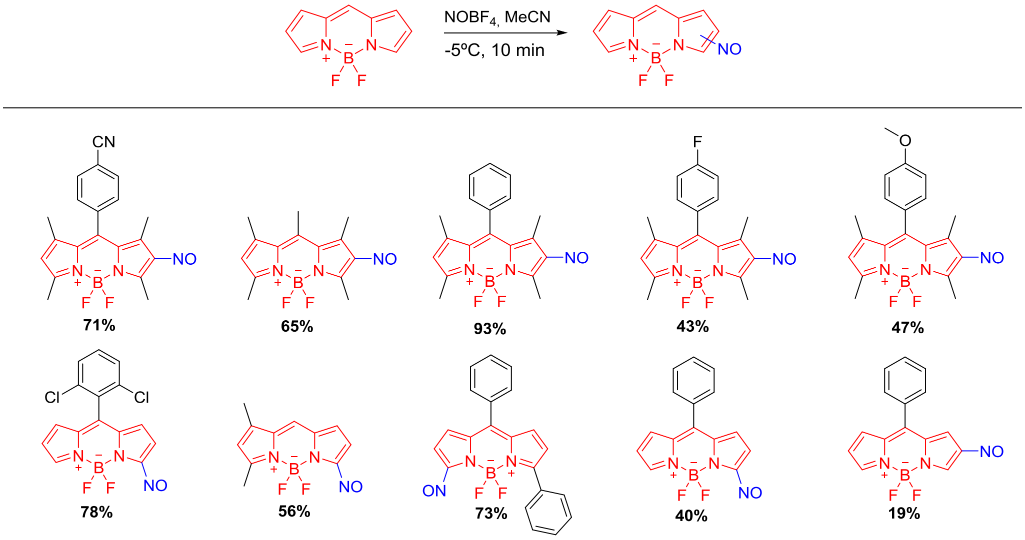
BODIPY is an outstanding class of fluorescent dyes with wide applications in biological research.[1] Innovations regarding the post-functionalization of this class of compounds are notorious and have received great prominence in the literature, which enables the development of libraries of new BODIPYs fluorophores with structure and fluorescence properties diversity.[2] Herein we show a new method for the post-funcionalization of BODIPY dyes by means of nitrosation with $NOBF_4$ in yields of 19 to 93%.



Nitroso substitution of BODIPYs is unprecedented in the literature, and not only due to originality regarding these fluorophores, but also because is not very common for five-membered rings. Furthermore, direct nitrosation opens opportunity for the development of new fluorescent probes.

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Facile One-Pot Synthesis of New Tricyclic 1,4-Benzodiazepines and Derivatives

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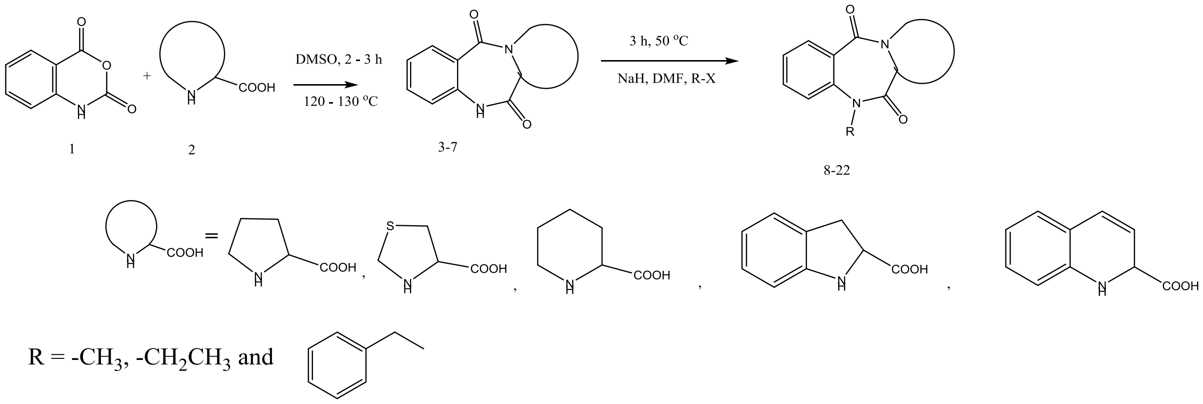
Abstract

Benzodiazepines have been used in the treatment of mental disorders. They act primarily on the Central Nervous System where they alter brain functions thereby resulting in temporary changes in perception, mood consciousness and behaviour.[1] Amongst the various psychiatric medications available, anxiolytics have been found to contain the benzodiazepine ring system. 1,4-Benzodiazepines are recognised as “privileged heterocyclic medicinal scaffolds” by virtue of their ability to provide ligands to a number of functionally and structurally discrete biological receptors. The fusion of a third ring system to the bicyclic 1,4- benzodiazepine scaffold has been shown to enhance biological activity.[2]

Novel tricyclic and tetracyclic benzodiazepines **3**–**7** were synthesised, in good yields, by the reaction of isatoic anhydride **1** with different cyclic amino acids **2**, such as **L**-proline, thiazolidine-4-carboxylic acid, pipecolinic acid, indoline-2-carboxylic acid and quinoline-2- carboxylic acid, in dimethyl sulphoxide at 120–130 ^{o}C for 2–3 hours. The resulting tricyclic benzodiazepines were also homologated with alkyl and aryl halides to furnish alkylated compounds **8**–**22**.

Keywords: alkylation, benzodiazepines, central nervous system (CNS) effectors, tricycles



R = $-CH_3$, $-CH_2CH_3$ and

X= -Cl, -Br

Scheme 1: One-pot synthesis of tricyclic and tetracyclic benzodiazepines

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Investigation of an Unexpected Anti-Baldwin Cyclization Leading to Chiral Pyrrolidinones

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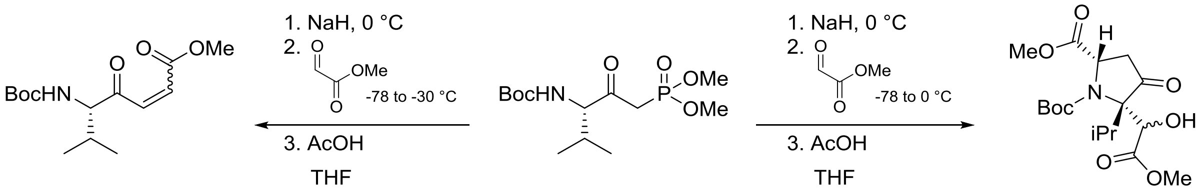
Cyclization reactions for the generation of heterocycles play an important role in organic synthesis. In 1976, J. E. Baldwin proposed rules describing the issue of favoured and disfavoured ring closure formations as a fundamental concept in organic chemistry. For trigonal systems 6 to 7-*endo-trig* cyclization reactions are favoured processes, while 3 to 5-*endo-trig* are disfavoured.[1,2] Indeed, there are couple of exceptions especially for 5-*endo-trig* cyclizations.[3-5] During the course of the development of specific inhibitors for the enzyme dipeptidyl-peptidase III, we used a standard Horner-Wadsworth-Emmons reaction for the synthesis of the core structure. Beside the expected product **2**, also a disfavoured 5-*endo-trig* cyclization could be observed at elevated temperatures leading to byproduct **3** with an interesting pyrrolidinone scaffold. We have explored the mechanism and synthetic potential of this unexpected Anti-Baldwin cyclization for the development of new interesting molecules.



2 **1** **3**

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Selective Chlorination of Benzimidazolone Ring: Practical Synthesis of a CRF$_1$ Receptor Antagonist

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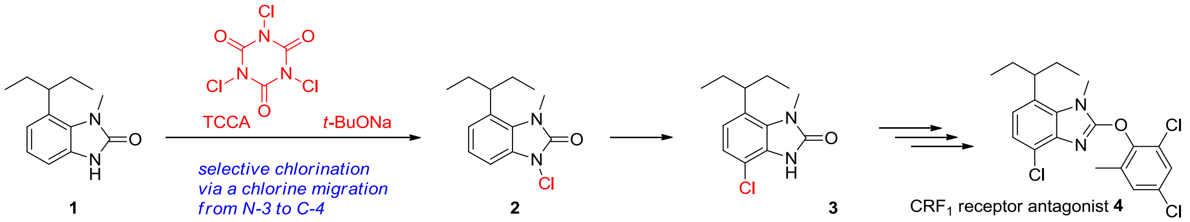
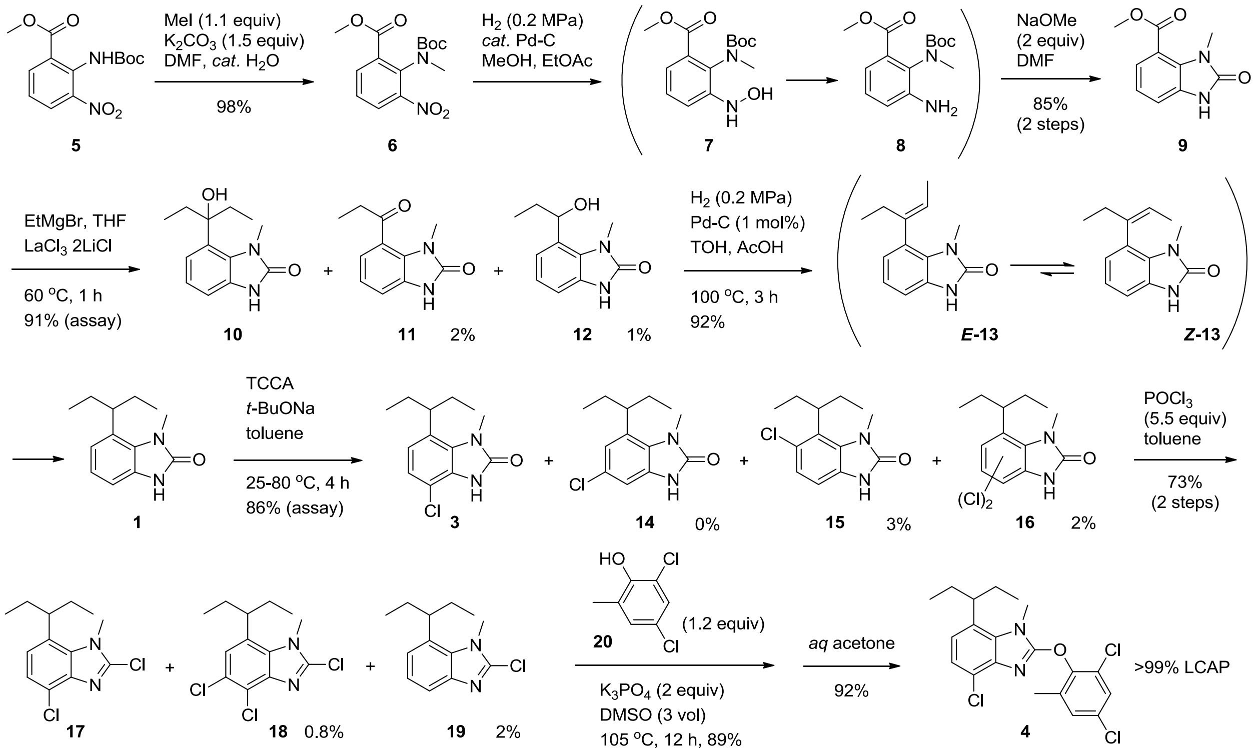
Process Chemistry, Pharmaceutical Sciences, Takeda Pharmaceutical Company Limited
Osaka, Japan



Novel selective chlorination of the 4-position of benzimidazolone **1** has been developed with chlorinating reagent 1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione (TCCA) in the presence of *t*-BuONa. [1] The selectivity was resulting from the chlorine migration mechanism, in which a chlorine atom migrated from the 3-position of the *N*-chloro intermediate **2** to the 4-position of **3**. The novel selective chlorination combined with other process improvements allowed the synthesis to produce quality Corticotropin-releasing factor 1 (CRF1) receptor agonist **4** with high >99% purity in 35 % yield over 6 steps on kilogram scale, compared to 10% yield in the literature. [2]



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Synthesis of Benzo[*d*]-3-aza-deca-4,6,7-trienes and its Thermolysis

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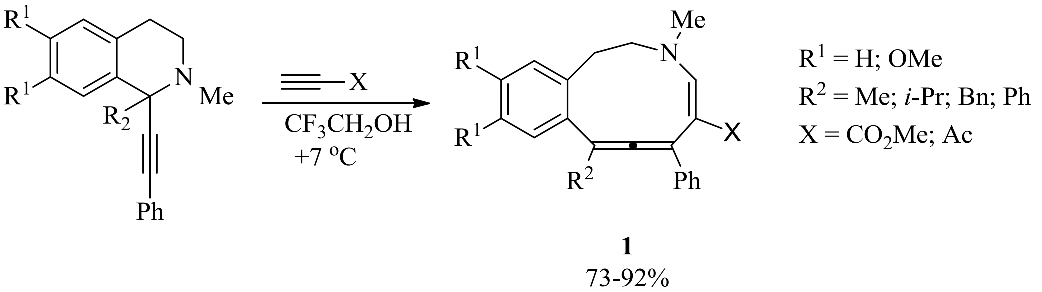
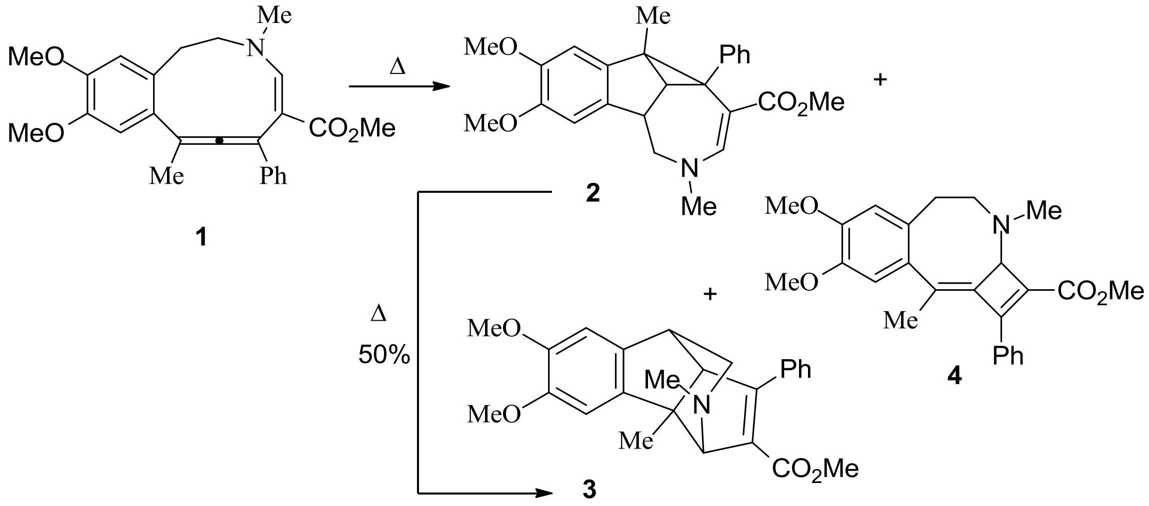
The first synthesis of cyclic ten-membered and eleven-membered allenyl lactams was described in 2011 [1]. For the first time our group prepared benzo[*d*]-3-aza-deca-4,6,7-trienes [2] via tandem reaction of 1-phenylethynyl-1-alkyl(aryl)-1,2,3,4-tetrahydroisoquinolines with methyl propiolate and acetylacetylene and studied thermolysis of the azacyclic allene on one example.





The main products of thermolysis were azabenzo[*a*]cyclopropa[*cd*]azulene **2** and (epiminomethano)cyclopenta[*a*]indene **3**, the cyclobutabenzazocine **4** was obtained in trace amounts. The azabenzo[*a*]cyclopropa[*cd*]azulene **2** was transformed to (epiminomethano)cyclopenta[*a*]indene **3** as a result of thermolysis. We suppose that **2** was formed due to the transformation of the allenyl system in azadecatriene **1**. It can be assumed that compounds **3** and **4** were formed through [2+2] cycloaddition of the enamine fragment to the bond of the 7,8 and 6,7-allene system.

The publication was financially supported by the Ministry of Education and Science of the Russian Federation (the Agreement № 02.A03.21.0008), the Russian Foundation for Basic Research (grants 17-03-00605, 17-53-540001).

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Synthesis of ethyl (5*S*)-2-hydroxy-2, 5-disubstituent-4-oxopyrrolidine-3-carboxylate type compounds: a DFT B3LYP computational study of the reaction mechanism

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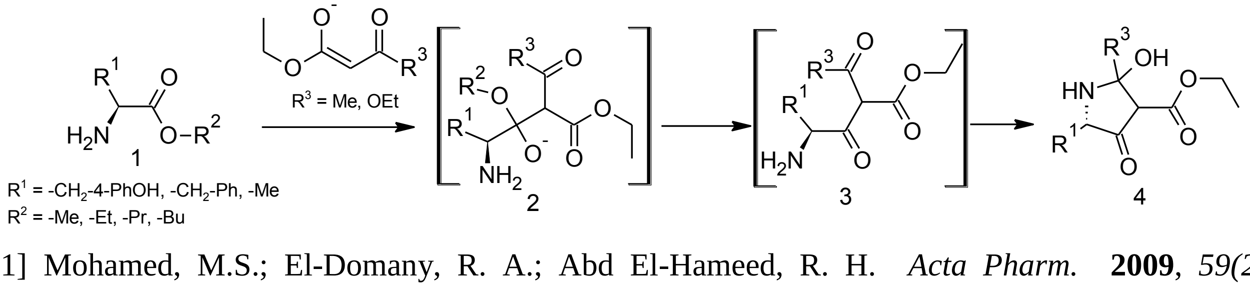
Heterocyclic systems such as pyrrole and indole are present in a broad family of natural products. These compounds have received a great interest due their wide range of biological activities, being employed for the design of new drugs and agrochemical agents. To obtain new biologically active molecules, InQuiBio group in Universidad Militar Nueva Granada have studied the reaction between some enolates and 2-aminoalkyl esters derived of common amino acids such as *L*-tyrosine, *L*-alanine and *L*-phenylalanine. We presented a DFT B3LYP computational study of the condensation reaction of enolates derived from diethyl malonate and ethyl acetoacetate against alkyl 2-aminoesters. Both, electrophilic and nucleophilic Fukui functions were calculated (f + and f-) using 6-31G(d,p) bases. These computational descriptors showed the (C=O)OR group in alkyl 2-aminoesters **1** have higher electrophilic character. These results are in agreement with the LUMO representation, which is located in the antibonding orbital π^* C = O. Moreover, enolate ions showed the highest nucleophilic character according the f- values (between 0.056-0.077). Thus, the first step in the reaction mechanism involves the attack of the enolate ion against the (C=O)OR group in **1** which leads to the formation of an alkoxide intermediate. The HOMO-LUMO GAP values were calculated for the mentioned nucleophilic and electrophilic reagents. These results showed decrease of the HOMO-LUMO GAP depending of the substituent R^1 in **1**. These results suggest the existence of anchimeric assistance due the existence of both, electronic inductive and mesomeric effects in the alkyl 2-aminoesters **1**. The second step of the reaction mechanism involves the formation of the intermediate **3**, which undergo intramolecular *5-exo-trig* cyclization towards **4**. According to the calculated Gibbs free energy values for the involved steps in the reaction mechanism, the cyclization to afford **4** consists in an equilibrium reaction at standard conditions. However, strong conditions such as strong bases and heating leaded to the formation of the product of interest in higher yields. Product derived from the project IMP-CIAS-2294 funded by Vicerrectoría de Investigaciones at UMNG - Validity 2017.



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Hydroxylated pyrrolidine-derived phosphines as organocatalysts in [3+2] cycloaddition reactions between allenoates and electron-deficient imines

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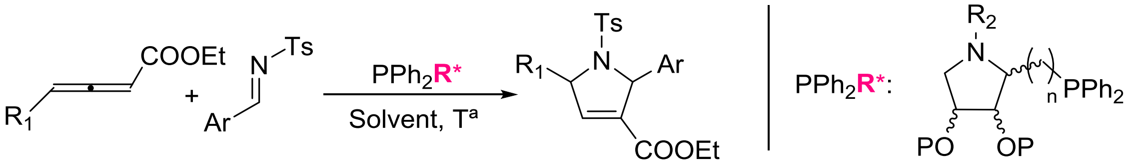
Chiral trivalent phosphines have recently found wide applications as nucleophilic catalysts in the enantioselective preparation of compounds of biological or synthetic relevance. In this context, phosphine catalyzed [3+2] cycloaddition reactions between allenoates and electron deficient alkenes and imines have been successfully used for the synthesis of highly functionalized carbo- and heterocycles [1]. Recently, chiral bidentate phosphines based on amino-acid scaffolds have proven to be efficient in the synthesis of these compounds [2].

We present the synthesis of several diastereomeric and enantiomeric hydroxylated pyrrolidine derivatives containing the amine-phosphine function using a multi-step synthetic route that employs carbohydrates as starting materials. These compounds have been used as organocatalysts in the [3+2] cycloaddition between alkyl allenoates and *N*-tosyl imines, affording 2,5-substituted-3-pyrrolines. The catalytic properties of these phosphines can be conveniently tuned with the appropriate substituents at the nitrogen atom and hydroxyl groups, configuration of the stereogenic centers and distance between the diphenylphosphine group and the pyrrolidine skeleton. The easy access to both enantiomeric forms of these organocatalysts has allowed the preparation of the corresponding enantiomeric 3-pyrrolines with similar yields, diastereo- and enantioselectivities.



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Generation and *in situ* screening of a library of dimeric pyrrolidine iminosugars as glycosidase inhibitors

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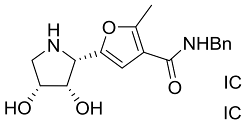
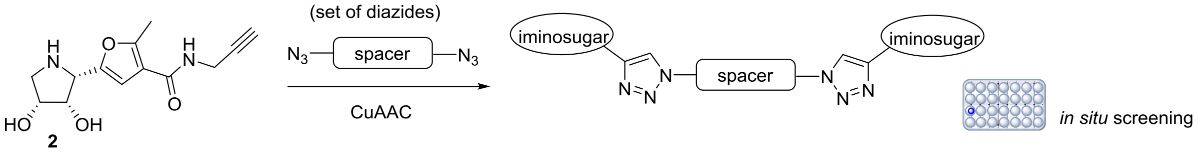
Multivalent glycosidase inhibitors with extremely enhanced activity respect to the monovalent parent have been successfully developed only for a selected group of these enzymes, such as α-mannosidases (Jack beans) and, to a lesser extent, β-glucocerebrosidases and hexosaminidases [1]. We have recently reported a methodology for the rapid discovery of α-fucosidase inhibitors based on the copper catalyzed azide alkyne cycloaddition (CuAAC) between an alkynyl-iminosugar and a set of azides followed by the *in situ* biological screening of the resulting (pyrrolidin-2-yl)triazole library [2a]. We show now the extension of this methodology to the discovery of divalent systems for the inhibition of β-galactosidases, enzymes directly related with some lysosomal storage diseases such as gangliosidosis GM1 and Morquio B. The divalent structures showed in this communication are inspired on the monovalent (pyrrolidin-2-yl)furan **1**, which is a moderate and selective inhibitor of β-galactosidases (bovine liver and *Aspergillus oryzae*) according to our previous findings [2b]. CuAAC reaction between pyrrolidine derivative **2** and a set of diazides followed by *in situ* screening of the resulting library towards β-galactosidases has allowed the selection of the best candidates for divalent interactions with the enzyme. The existence of a divalent effect was further evaluated by comparison of the inhibition data of the dimers with those of the adequate monovalent reference.



1

IC_{50} = 20 μM (β-galactosidases from *Aspergillus oryzae*)
IC_{50} = 120 μM (β-galactosidases from bovine liver)



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We acknowledge the Ministerio de Economía y Competitividad of Spain (CTQ2016-77270-R) and Junta de Andalucía for financial support. S. C.-J. thanks the Ministerio de Educación (Spain) for a FPU fellowship.

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γ-BUTYROLACTONES: A STEREOSELECTIVE CASCADE REACTION

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γ-Butyrolactones are common building blocks of various natural compounds showing diverse biological activities and are also known as flavour and fragrance compounds. Therefore, they are in great demand of food, fragrance as well as of pharmaceutical industries. For the synthesis of γ-butyrolactones several conventional chemical methods and in particular enzyme-catalysed approaches, using for example lipases or baker's yeast, are described in literature.[1, 2]

We will report on an alternative chemoenzymatic approach towards γ-butyrolactones: Different *α,β*-unsaturated *γ*-ketoesters (**1**), which are readily available by *Wittig*- or *Horner-Wadsworth-Emmons*-reactions, serve as a starting point for a consecutive one-pot enzyme cascade, first reducing with an ene reductase and then with an alcohol dehydrogenase, leading to various substituted *γ*-butyrolactones (**2**), e.g. the *quercus lactone* (**3**), in preparative scale (Figure 1).[3, 4]

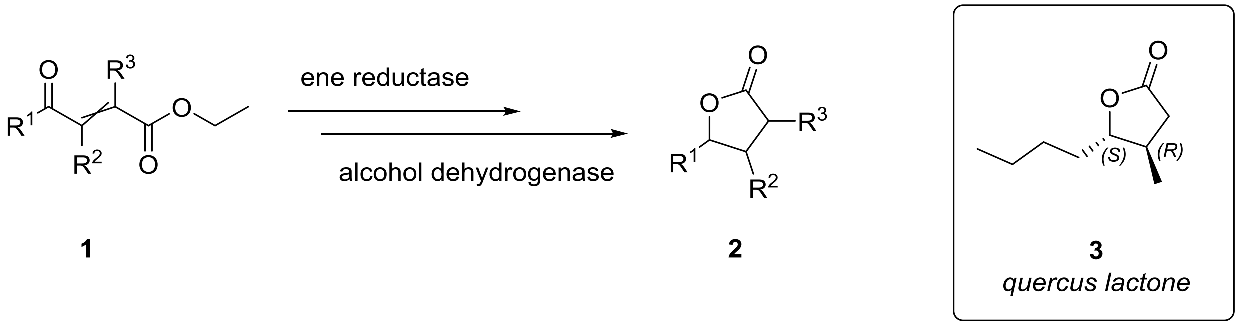

Figure 1: One-pot enzyme cascade towards several substituted γ-butyrolactones.

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A novel [4+1]-cyclization using allenoates

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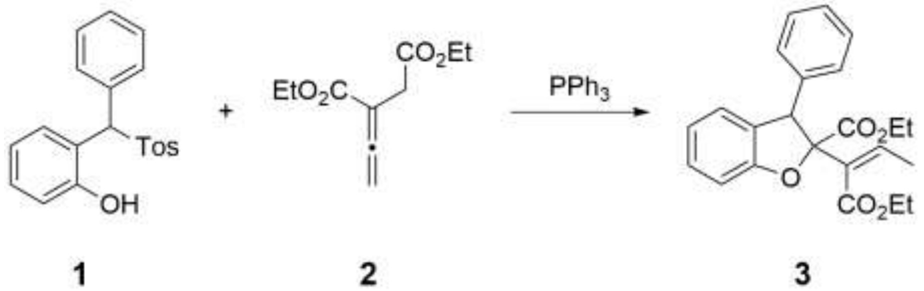
Phosphines and amines have been used previously as catalysts for reactions with allenoates for the generation of molecules with high molecular complexity starting from simple molecules. Since Lu`s pioneering studies on a phosphine catalyzed [3+2] annulation reaction, many useful reactions have been published. The coupling partners for allenoates range from electron-deficient olefins and imines to aldehydes, which allows for a large diversity in structure and reactivity of the products. There are many examples for [3+2] and [4+2] reactions with allenoates, which also include enantioselective versions, but [4+1] cyclizations remain scarce [1,2].

Herein we present a novel reaction using a disubstituted allenoate **2** and an in-situ-generated ortho-quinone-methide **1** which react under phosphine catalysis to the highly substituted product **3**.



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Unprecedented Base-Mediated Transformation of (Hetero)aromatic 1,2-Dinitriles into *vic*-Amidino Acids

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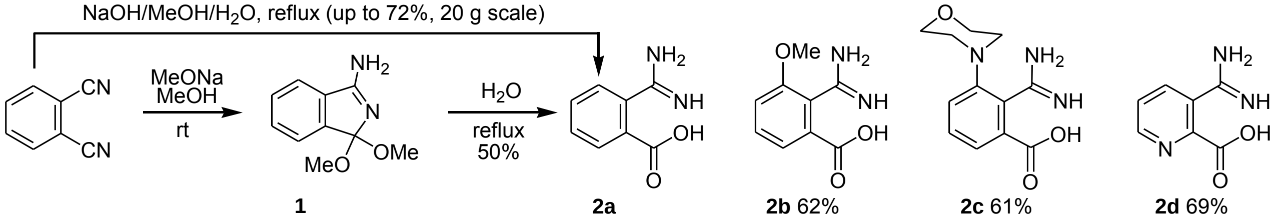
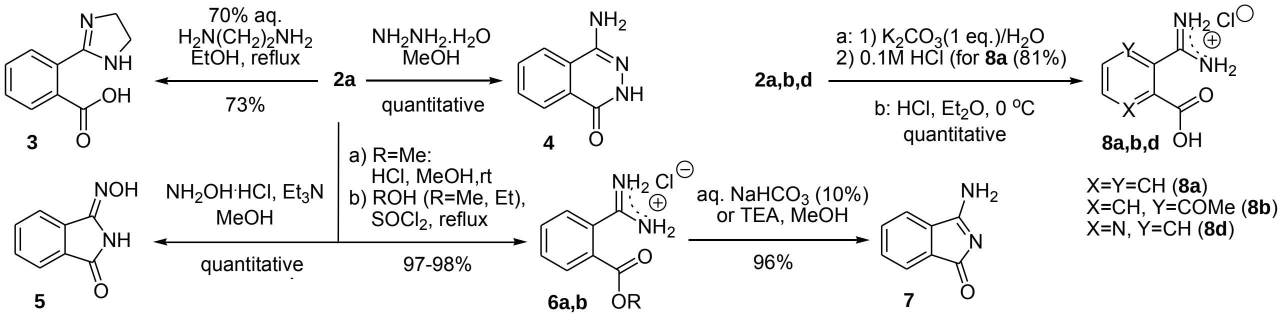
Reaction of phthalonitrile with ammonia is used for the synthesis of 1-imino-1*H*-isoindol-3-amine known as 1,3-diiminoisoindoline, one of the most important phthalogens. Recently, our group reported isolation of 2-carbamimidoylbenzoic acid (**2a**) as a by-product in its synthesis. [1]

We elaborated synthetic method of amidino acid **2a** preparation by phthalonitrile partial hydration in MeOH/H_2O media with an equimolar amount of NaOH in one step. Similar vic-amidino (hetero)aromatic acids **2b**-**d** also could be synthesized from corresponding 1,2-dinitriles by hydrolysis of in situ generated 1,1-dimethoxy-1*H*-isoindol-3-amine (**1**) analogs. In the crystal amidino acids exist in zwitterionic form. [2]



This transformation appears to be a general phenomenon which provides a simple direct synthetic entry to new type of 1,2-amidino acids from vic-dinitriles when steric arrangement of cyano groups would allow the pyrrole ring closure. Basic chemical properties of amidino acid **2a** were studied: protonation (for **2a**,**b**,**d**), esterification, re-amination with N-nucleophiles.



This new variety of compounds has a potential to be modified at both carboxylic and amidinic groups.

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Synthesis of γ-Cyclobutane Amino Acids via Visible Light

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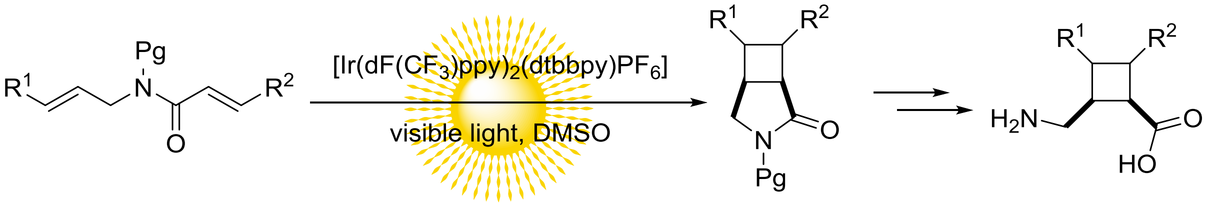
γ-aminobutyric acid (GABA) displays one of the major inhibitory neurotransmitter in the mammalian central nervous system. Therefore, this prominent representative plays an important role in the clinical treatment of diseases related to the central nervous system such as epilepsy, neuropathic pain or anxiety.[1] Over recent years a wide variety of GABA derivatives have been synthesized and investigated. Especially, cyclic GABA analogues have proven to be of significant therapeutic value.[2] Besides their own biological activity, γ-amino acids have been of great interest due to their potential application in the design and synthesis of oligopeptides, which adopt well defined secondary structures. Cyclic γ-amino acids seem to be promising building blocks for such peptides due to the limitation of their backbone torsional mobility.[3] The focus of this work is on the synthesis of cyclobutane containing γ-amino acids. In common procedures these compounds are synthesized *via* an UV-mediated [2+2] photocycloaddition. Herein, a variety of azabicyclo-heptanones were successfully synthesized *via* a photocatalytic [2+2] cycloaddition of amide-linked dienes by irradiation with blue LEDs (λ_{em} = 455 nm). The so obtained bicyclic compounds were transformed into the desired γ-amino acids. By derivatization and subsequent separation the γ-amino cyclobutane carboxylic acids were also prepared in enantiomerically pure form.



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Total synthesis of welwistatin using rhodium (II) catalyzed diazoketone rearrangement

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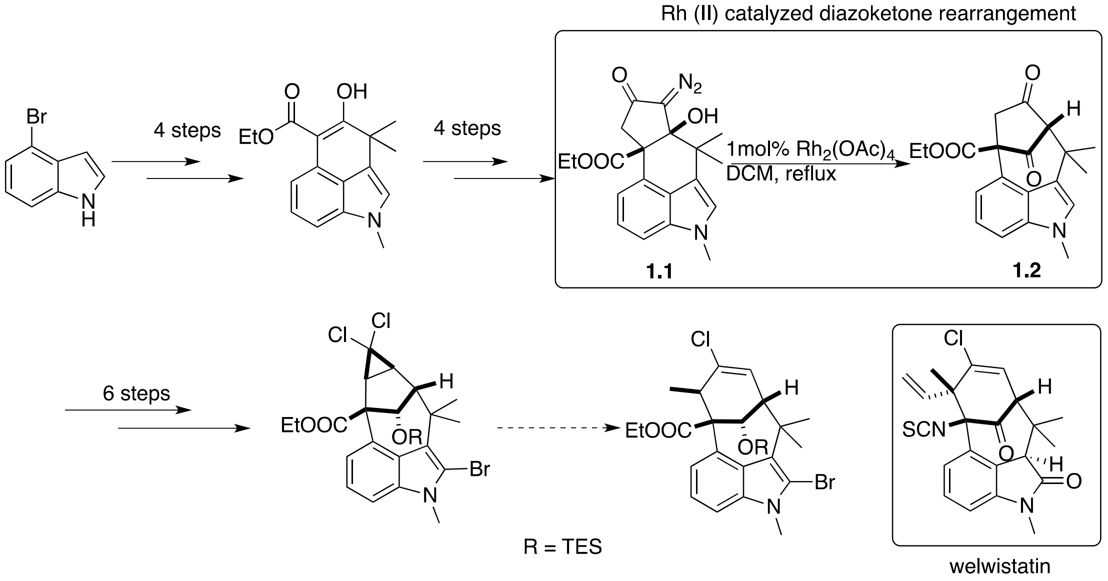
Abstract

(−)-Welwistatin is a natural product showing significant anti-multiple drug resistance (anti-MDR) activity. In 2012, Rawal[1] and Garg[2] independently published the total synthesis of welwistatin. As recent as 2015, Hatakeyama[3] developed a strategy to synthesize it in 24 steps.

The aim of this project is to utilize the rhodium (II) catalyzed diazoketone rearrangement as the key step in a synthetic approach to welwistatin. The α-diazo-β-hydroxyketone intermediate **1.1** has been synthesized to investigate the strategy. We found that the [4.2.1] bicyclic dione **1.2** was found as the sole product in good yield (77% brsm). Efforts to convert it to the welwistatin core structure are ongoing.



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Utility of benzyl substituted β,γ–unsaturated δ-lactams in the synthesis of alkaloid-like compounds with unique benzomorphan skeleton

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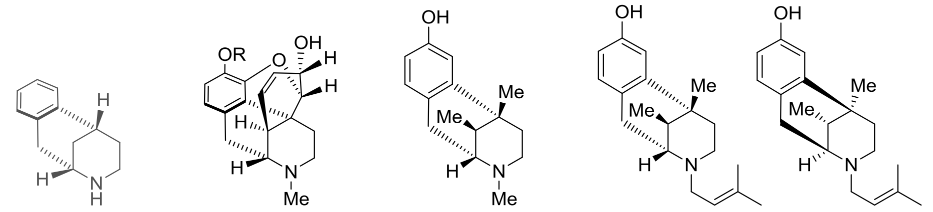
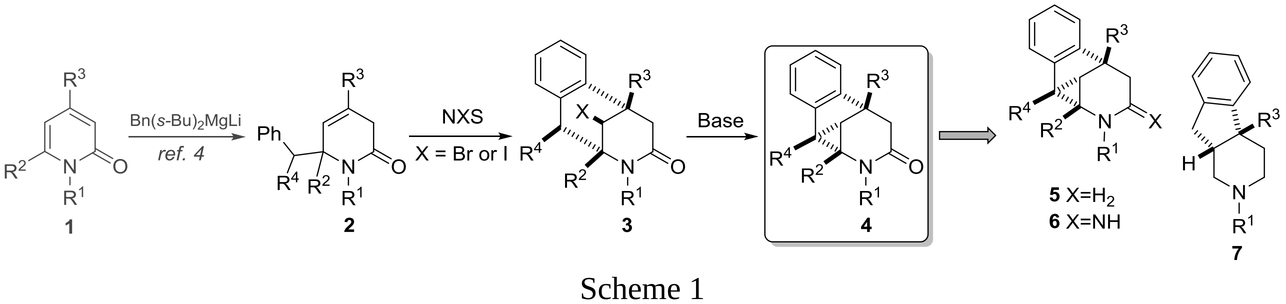
Piperidine alkaloids are one of the most important groups of compounds of natural origin. Probably the best known representatives of this group are Morphine or Codeine, which contain the benzomorphan skeleton in their structure [1]. Currently, benzomorphan skeleton became the basis for building a new, biologically active compounds such as Pentazocine or Metazocine [2]. Although δ–lactams are often used in the synthesis of piperidine derivatives, only α,β–unsaturated δ–lactams have been used in the synthesis of benzomorphanones [3].



Benzomorphan R=H: **Morphine** R=Me: **Codeine** **Metazocine** *(R)*-**Pentazocine** *(S)*-**Pentazocine**

In this communication we present the results of the utilization of benzyl substituted β,γ–unsaturated δ-lactams **2** in the synthesis of novel and unique alkaloid-like piperidine derivatives **4**, which structure can be considered as bridged benzomorphan skeleton. Our three-step synthesis strategy is based on the nucleophilic addition of lithium benzyl magnesiate to 2-pyridones (applied as simple precursors) [4], intramolecular halocarbocyclization and intramolecular cyclopropanation. In the preliminary attempts we found that products **4** are excellent starting materials for further transformations, leading e.g. to structures **5**, **6** and **7** (Scheme 1).



Scheme 1

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Synthesis of *N*-(azetidin-3-yl)pyrazolecarboxylates

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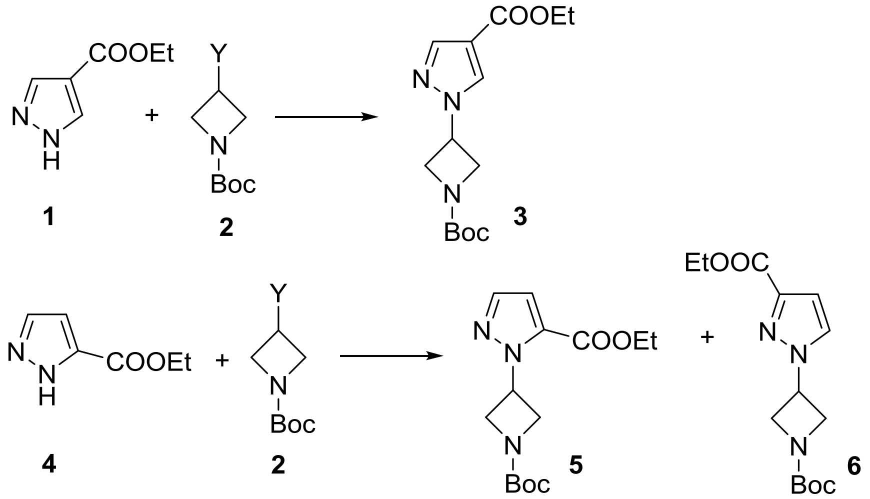
Pyrazole carboxylic acids have found wide application as building blocks in organic synthesis for designing of pharmaceuticals and agrochemicals [1].

The aim of the present work is the synthesis of pyrazolecarboxylates bearing an azetidin-3-yl substituent at the pyrazole nitrogen atom. The azetidine moiety has previously been identified as a privileged motif within medicinal chemistry [2-4]. The synthetic combination of two pharmacologically relevant pyrazole and azetidine motifs can provide interesting building blocks for developement of lead molecules. The synthesis strategy included coupling of various pyrazolecarboxylates with 3-hydroxy-, 3-mesyloxy- and 3-iodoazetidines. For example, treatment of structurally symmetrical ethyl pyrazole-4-carboxylate **1** with *N*-Boc protected 4-iodoazetidine **2** (Y = I) in the presence of cesium carbonate afforded compound **3** as a sole product in a good yield, while analogous reaction of unsymmetrical ethyl pyrazole-5-carboxylate **4** gave a mixture of isomeric compounds **5** and **6**. The Mitsunobu reaction of pyrazoles **1** and **4** with 4-hydroxyazetidine was carried out as well. The bromination of the obtained *N*-(azetidin-3-yl) substituted pyrazoles was performed and Pd-catalysed cross-coupling reactions of the corresponding bromo substrates were investigated.



Scheme 1. Y = OH, OMs, I

The structure of the synthesized new compounds was confirmed by data of the ^{1}H, ^{13}C and ^{15}N NMR spectroscopy and HRMS.

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Trifluoromethylation of Pyridines via *N*-methoxymethylpyridinium Salt Intermediate

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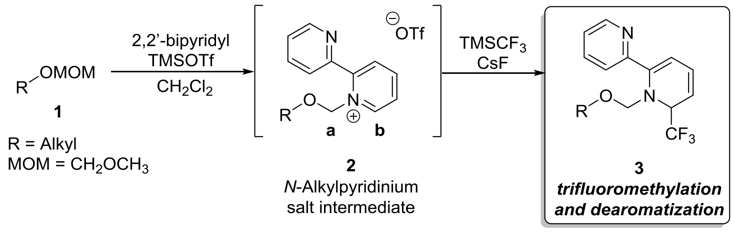
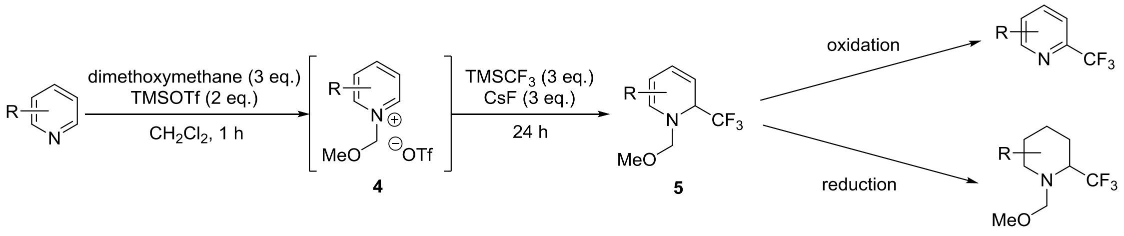
Molecules containing trifluoromethyl group have attracted attention in the field of agrochemical and medical drugs because of its high electron-withdrawing nature and high lipophilicity. Therefore, trifluoromethylation reactions have been extensively studied, and reported well. On the other hand, we previously discovered that treatment of alkyl methoxymethyl ethers (MOM ethers) **1** with 2,2'-bipyridyl and trimethylsilyl trifluoro-methanesulfonate (TMSOTf) gave a salt intermediates **2**, which were treated with nucleophile to give the corresponding compounds reacted at position **a**. [1] However, when trifluoromethylating reagents were used as nucleophile, the reaction occurred at position **b** and trifluoromethyled dihydropyridines **3** were obtained in high yields.



We herein report an effective method for trifluoromethylation of six-membered *N*-heteroaromatic compounds. *N*-methoxymethylpyridinium salt intermediates **4** were formed by treatment of pyridine derivatives with dimethoxymethane and TMSOTf. The reaction of **4** with trifluoromethylating reagents proceeded under mild conditions to give 2-trifluoromethyldihydropyridines **5** in high yields. Compounds **5** were further transformed to *N*-heterocycles. Thus, oxidation of **5** afforded pyridines and reduction of **5** gave piperidines. Both transformations proceeded smoothly without any problem.



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Development of Photochromic Kinase Inhibitors based on Fulgimides

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Kinases play an important role in signal transduction and in regulation of nearly every metabolic pathway. The dysregulation of kinases can lead to several diseases including diabetes and cancer. Therefore, kinase enzymes are a very popular target in the search for novel therapeutics.[1]

Gaining control over the activity of pharmaceuticals using light represents a very mild and selective method. Photoresponsive enzyme inhibitors which can change their binding properties when irradiated with light of specific wavelength can be used as a tool for controlling enzyme activity with high temporal and spatial resolution.[2,3]

For this reason, photochromic moieties have received remarkable interest. Fulgimides containing a heterocyclic ring undergo a pericyclic reaction between the closed and opened isomer when irradiated with light (Figure 1). They exhibit a good photochromism and a high fatigue resistance. Furthermore, fulgimides can switch in an aqueous environment which is crucial for pharmaceuticals.[1,4]

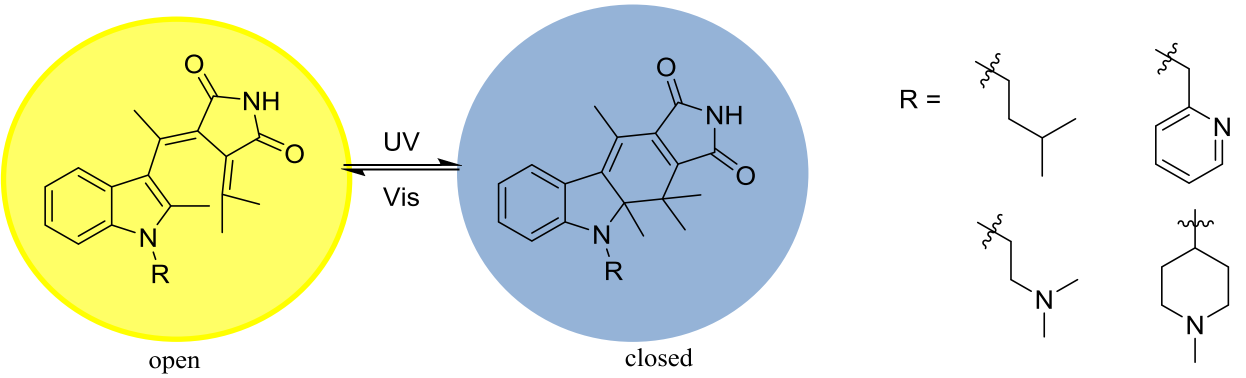

Figure 1: Reversible switching between the opened and closed isomer.

Herein, we describe the synthesis of different fulgimide-based kinase inhibitors (containing residues from already known kinase inhibitors) and the characterization of the photophysical properties. Therefore, light is used to switch reversibly between the more active and less active photo isomer.

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Chiral Tetrahydrothiophene Ligands in Asymmetric Catalysis

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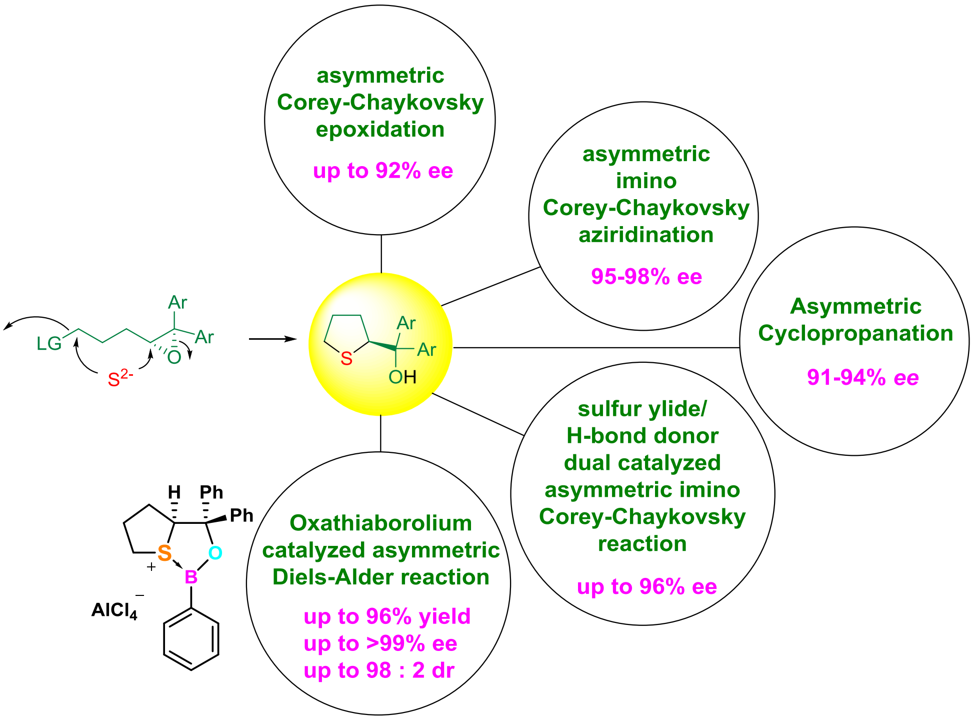
Chiral sulfur ligands are becoming a versatile tool in organic chemistry due to the blossomed development achieved in the past years. This presentation describes an expeditious and efficient preparation of enantiopure (thiolan-2-yl)diarylmethanols and the applications of their derivatives to the catalytic and asymmetric Corey-Chaykovsky epoxidation,[1] the imino Corey-Chaykovsky aziridination,[2,3] the Corey-Chaykovsky cyclopropanation,[4] as well as the first oxathiaborenium catalyzed asymmetric Diels-Alder reaction.[5]



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Asymmetric Conjugate Addition of Alkylzirconium Reagents to α, β-Unsaturated Thioesters: Access to fragrances and acyclic stereochemical arrays

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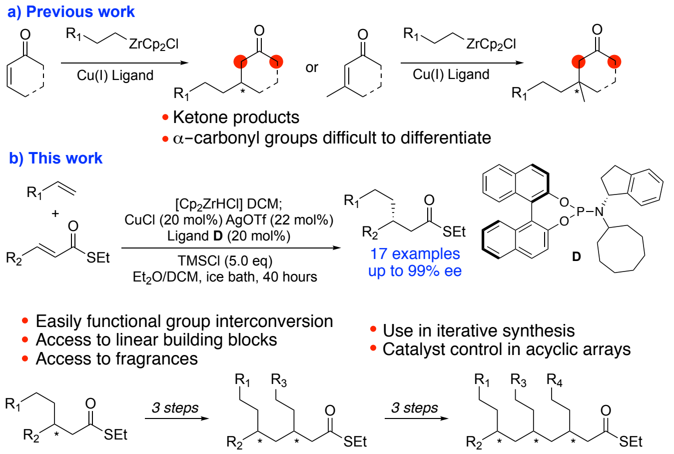
Copper-catalyzed asymmetric conjugate addition of alkylzirconium species to α, β-unsaturated thioesters is reported. A variety of functioanlized alkyl nucleophiles were introduced with yields around 70% and ee's over 92%. The method was applied to the straightforward syntheses of the commercially important fragrances phenoxanol (both enantiomers 97% ee), and hydroxycitronellal (98% ee). The 1,4-addition products can be converted to enantiomerically enriched linear building blocks bearing a terminal functional group. Formation of further α, β-unsaturated thioesters provides an iterative route for the stereocontrolled synthesis of functionalized acyclic arrays and we demonstrate almost complete catalyst control in the formation of additional stereocentres.



Scheme 1 a) Previous work on ACA of alkyl zirconium species to enones provides ketones b) This work, hydrozirconation / ACA of alkenes to α,β–unsaturated thioesters gives chiral products with an easily differentiated functional group and allows synthesis of functionalized acyclic stereochemical arrays.

Asymmetric addition of alkyl nucleophiles to α,β unsaturated aldehydes, esters and thioesters are high value transformations as enantiopure β -substituted carboxylic acid derivatives have enormous synthetic utility. While a great many non-enantioselective procedures have been developed and used in synthesis, there are only a few catalytic enantioselective methods, and these are limited to the addition of simple alkyl nucleophiles. The Loh group[1] used Grignard reagents to form stereogenic centres by ACA to esters, while the Minnaard/Feringa[2] and Alexakis[3] groups built tertiary centres from α, β-unsaturated thioesters and aldehydes respectively.

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Synthesis of Novel and Structurally Diverse Iminosugar *C*-glycosides

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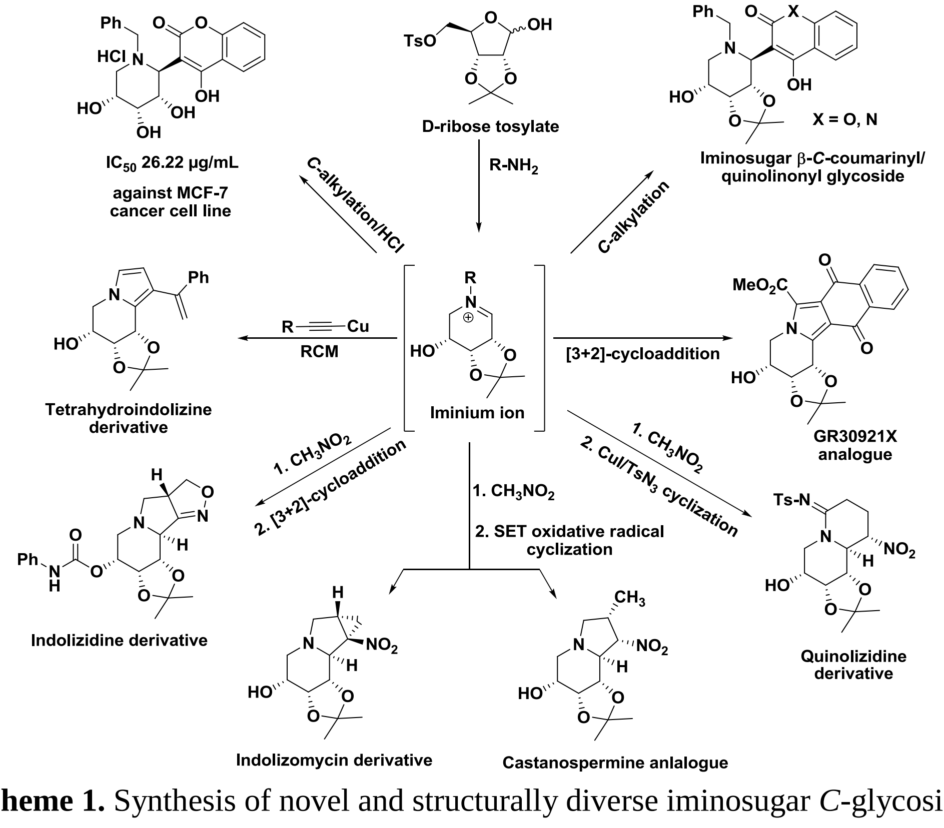
Iminosugars have served as lead molecules for treatment of various diseases, including cancer, diabetes, viral infections, and lysosomal storage disorders.[1] Slight modifications in both mono- and bicyclic iminosugars, including stereochemical changes and functional group variation like introduction of lipophilic substituents at the *N*-/*C*$_1$-position, alter their potency and specificity. As a consequence, there has been ever growing interest towards a simple, general and reliable synthesis of various *N*-/C$_1$-alkyl substituted iminosugars for wide spectrum of biological evaluations.[1]

We have developed an efficient one-pot method for stereoselective synthesis of hydrophobically modified iminosugar *C*-glycosides *via in situ* generated iminium ion with various carbon nucleophiles.[2-4] The synthetic utility of this methodology is further extended towards the synthesis of skeletally challenging bicyclic iminosugars and iminosugar hybrids.



Scheme 1. Synthesis of novel and structurally diverse iminosugar *C*-glycoside

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Transition Metal-free Cycloaddition of *N*-Boc Propargylenamine for the Synthesis of Functionalized Pyrroles

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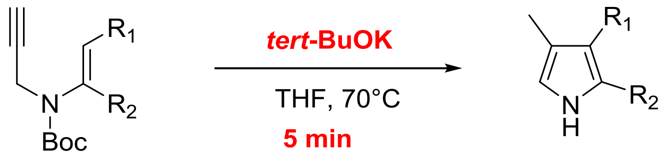
Of the many known pyrrole derivatives has always attracted the attention of chemists due to their many chemical and biological applications. Most of the cycloaddition is used transition metal catalyst, in particular gold and copper ion, as it can be activated alkenes and alkynes. Due to the cytotoxic properties of Au (I), (III), Cu (I) and (III), it is important to remove the metal catalysts from the reaction product. Recently, guideline for elemental impurities (Q3D) should enter into force by international council on harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use. This guideline presents a process and control elemental impurities in the drug product using the principles of risk management. This process provides a platform for developing a risk-based control strategy to limit elemental impurities in the drug product.

We will present our recent research into the 5-exo-dig cycloaddition of *N*-Boc propargylenamines under basic condition, resulting to give pyrroles in high yield. The intrinsic reactivity profiles of these enamines in a short time have been examined with a wide range of substrates. Interestingly, deprotection of *tert*-butoxycarbonyl group proceeded under sequential basic reaction.

This feature makes it possible to functionalize pyrrole derivatives by simple synthetic procedure that do not require toxic transition metal catalysts.



- ✓ mild and nontoxic condition
- ✓ simple operation and purification
- ✓ broad scope
- ✓ short time
- ✓ high yield

R_1; carbonyl, cyano, carboxyl
R_2; alkyl, aryl

LR-1 and LR-2 : Synthesis and its cytotoxic activity

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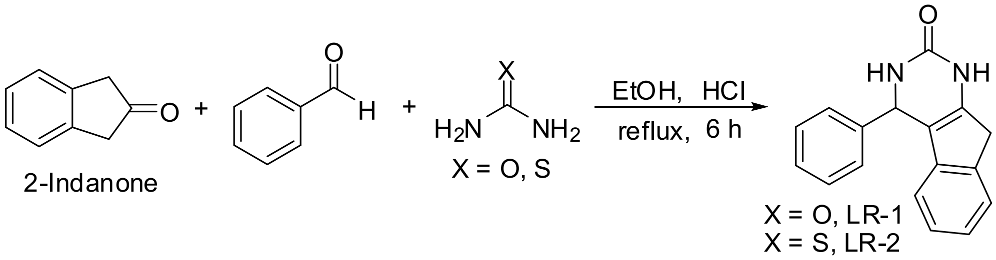
Multicomponent reactions (MCRs) is one of the important reaction in organic synthesis and medicinal chemistry. This kind of reaction can produce different kind of molecules with different kind of biological activities. Biginelli reaction is one of example of MCR. The modification on the Biginelli reaction has been made by most of researchers who worked in this kind of reaction for example by changing the startimg material of 1,3-dicarbonyl of the reaction. Our research is focused on the changing of the used of 1,3-dicarbonyl to 2-indanone.(**1**) This research is aimed to synthesis and evaluate the cytotoxic activity of 4-phenyl-3,4-dihydro-indeno[2´,1´]pyrimidin-2(1*H*)-one (LR-1) and 4-phenyl-3,4-dihydro-indeno[2´,1´]pyrimidin-2(1*H*)-thione (LR-2).

The synthesis is involved the reaction of 2-indanone, benzaldehyde and urea(thiourea) in acid condition. The reaction conditions have been optimised. The best reaction conditions are when the reaction run in phosphoric acid for 6 hours of the reaction time.



Scheme 1. Synthesis LR-1 and LR-2

The biological activity that is evaluated is its cytotoxicity activity based on the similar structure of LR-2 with monastrol, an anticancer agent. The cytotoxic activity of LR-2 has been studied on different cancer cell lines and gave LC_{50} as 159.5 µM, 65 µM, 268 µM to T47D (**2**), Myeloma and HeLa (**3**) respectively. The LC_{50} of Vero (normal) cell were undetermined, it means that LR-2 was not toxic to Vero cell, which indicates a good selectivity for anticancer drug candidate. The indeno-ring on LR-2 makes the molecule less polar or more non-polar (compared to monastrol) and makes the bioavailability of the drug in the body higher.

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Enantioselective Construction of Quaternary Stereocenters by 1,4-Addition of 3(2*H*)-Furanones to Alkynones

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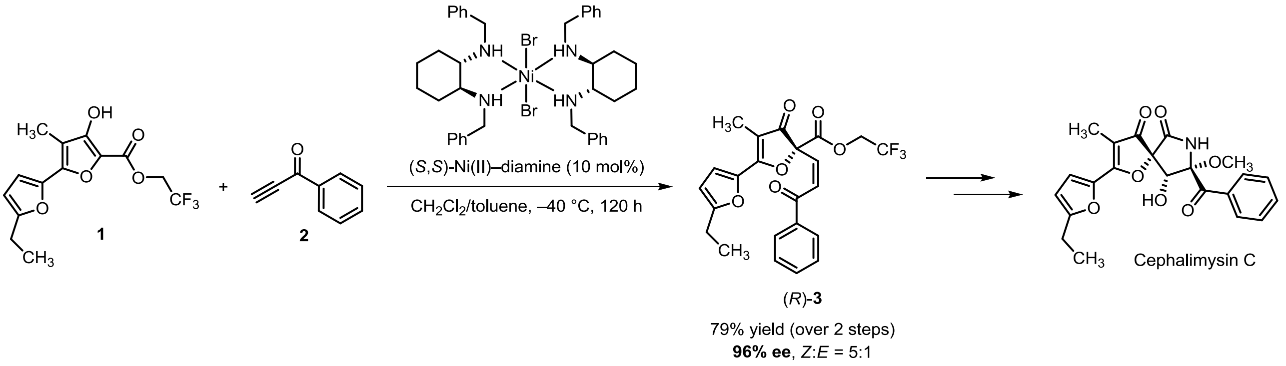
3(2*H*)-Furanone represents an important structural element found in many biologically active natural products. However, preparation and handling of 3(2*H*)-furanones can be challenging due to their limited stability including facile air oxidation. As part of our research on stereoselective synthesis of two natural spirocyclic alkaloids, cephalimysins B and C, we were led to study the enantioselective 1,4-addition between 2-(trifluoroethyloxycarbonyl)-3(2*H*)-furanone **1** and alkynone **2**.[1] In light of the fact that neither 2-(alkoxycarbonyl)-3(2*H*)-furanones nor alkynones feature frequently in enantioselective Michael additions, we performed a screen of common organocatalysts and selected organometallic complexes. Ni(II)–diamine complex developed by Evans et al.[2,3] emerged as a superior catalyst for this transformation, providing 1,4-adduct (*R*)-**3** in 96% ee. To our best knowledge, the Ni(II)–diamine catalyst has not been described in conjugate additions with alkynones or alkenones previously. Key reaction parameters and substrate scope of the Ni(II)–diamine-catalyzed 1,4-addition of *in situ* formed 3(2*H*)-furanones to alkynones will be presented.



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Trifluoroacetylation of indole-chalcones derived from the 2-amino-3-(arylethynyl)-5-bromo-iodochalcones

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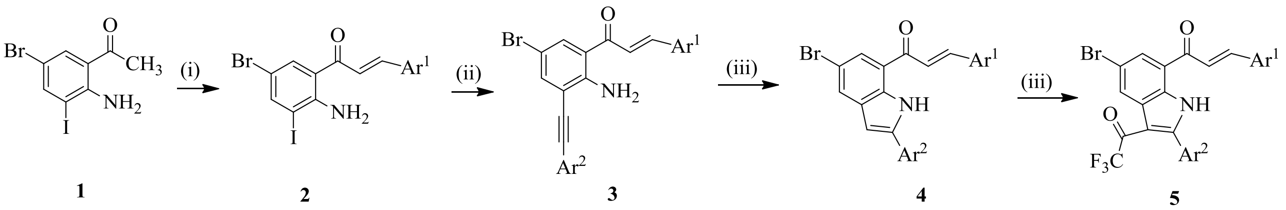
Indole-based compounds exhibit important biological properties such as antimicrobial, anti-oxidant, anticancer and antitubercular activities, and this moiety is widely distributed in numerous natural products.[1] Likewise, chalcone (1,3-diaryl-2-propen-1-one) moiety forms the central core for a variety of biologically active compounds with antimicrobial, antitumor, antioxidant, antimalarial, antiviral, antileishmanial and anti-inflammatory properties.[2,3] We became interested in the design and synthesis of indole-chalcone derivatives in which the five-membered moiety is fused to the 1,3-diaryl-2-propen-1-one framework on the aryl ring and bearing trifluoroacetyl group at the 3-position of the indole moiety.

We envisioned that molecular hybridization to construct an indole ring onto the 1,3-diaryl-2-propen-1-one framework through the standard indole synthesis would lead to the requisite indole-chalcones with potential to undergo trifluoroacetylation on the indole framework. In order to proof this assumption, we prepared 2-amino-5-bromo-3-iodoacetophenone **1** and subjected it to base-mediated Claisen-Schmidt aldol condensation with benzaldehyde derivatives. The prepared 2-amino-3-iodo-5-bromochalcones **2** were, in turn, subjected to Sonogashira cross-coupling with arylacetylenes followed by palladium chloride-mediated *endo-dig* Csp–N cyclization of the incipient 3-alkynyl-2-amino-5-bromochalcones **3** to afford novel indole-chalcones **4**. Further chemical transformation of these indole-chalcones via trifluoroacetylation afforded the corresponding novel 3-trifluoroacetyl–substituted indole-chalcones **5**.[4]



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First Enantioselective Synthesis of VAChT Inhibitors Vesamicol, Benzovesamicol, Spirovesamicols and Other Analogues

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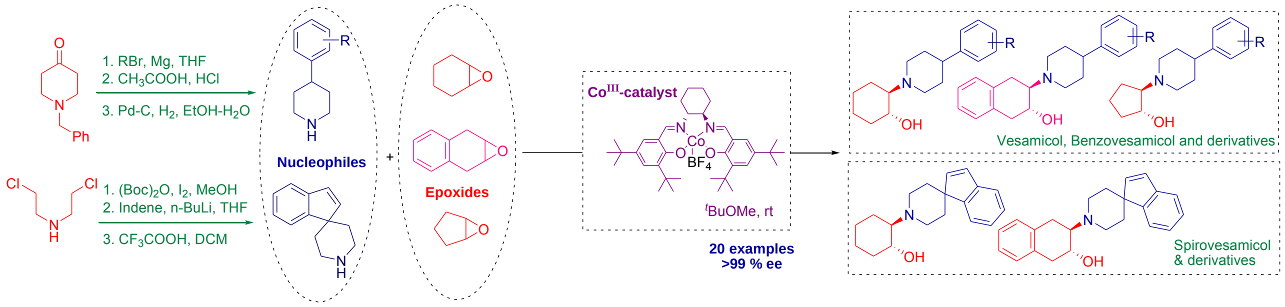
Chandigarh, INDIA, 160014

Vesamicol, a β-amino alcohol, is an important tool for physio-logical studies of cholinergic nerve terminals. It acts as an inhibitor for the transportation of neurotransmitter acetylcholine, and shows potential quantitative imaging in Alzheimer's disease.[1] The potency of one of its isomers is 500 times more than that of others. A kinetic resolution technique was applied to afford a single enantiomer of vesamicol and its derivatives;[2] however, to date, no reports are available for the direct enantioselective synthesis of vesamicol and its derivatives. Therefore, there is an urgent need to develop a convenient method for the enantioselective synthesis of vesamicols.

Chiral salen metal complexes are known as privileged catalysts for numerous asymmetric transformations such as asymmetric epoxidation, kinetic resolution of terminal epoxides, desymmetrization of meso-epoxides, polymerization, enantioselective Diels–Alder reactions, and other asymmetric transformations in organic synthesis.[3] The desymmetrization of meso-epoxides with different nucleophiles, such as nitrogen, sulfur, oxygen, halides, and selenium has been successfully accomplished and established as a key step in the enantioselective synthesis of many natural products and important biologically potent scaffolds. Herein, we report the first asymmetric aminolysis of meso-epoxides with 4-phenylpiperidine derivatives using a chiral [salenCo(III)] complex to afford vesamicol, benzovesamicol, and their derivatives with high enantioselectivities.[4]



Scheme 1: Asymmetric Synthesis of Vesamicol, Benzovesamicol and Spirovesamicol.

References:

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A very short synthesis of lythranidine

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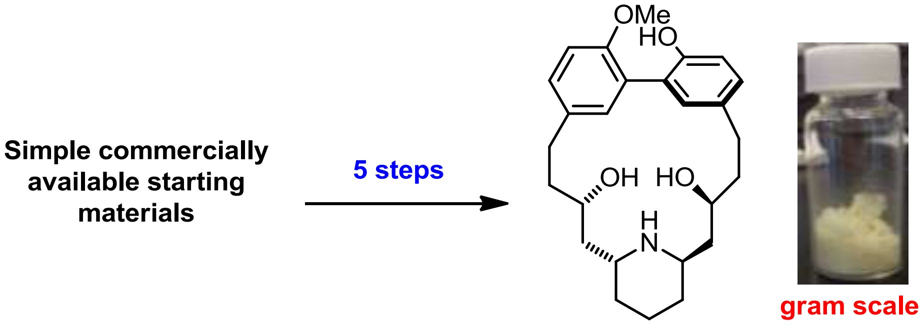
Of the many measures of efficiency in total synthesis, step economy is king. Thus, the exploitation of multi-bond forming reactions to rapidly generate molecular complexity is of paramount importance in total synthesis. This philosophy is exemplified by our remarkably short synthesis of a pseudopterosin natural product which was constructed in just ten steps using three multi-bond-forming Diels-Alder reactions.[1]

Our recent work extends the use of multi-bond-forming reactions to alkaloid synthesis, culminating in the step economical total synthesis of lythranidine, a macrocyclic alkaloid, isolated from the Japanese perennial plant Lythrum anceps Makino.[2] The previous shortest synthesis of this natural product was completed by Fürstner and co-workers, with a longest linear sequence of 15 steps, producing 8 mg of material.[3] This presentation will detail our exploitation of a (barely) hidden C2 symmetry in the structure to complete the first practical, gram scale, single digit step count synthesis of the natural product.



lythranidine

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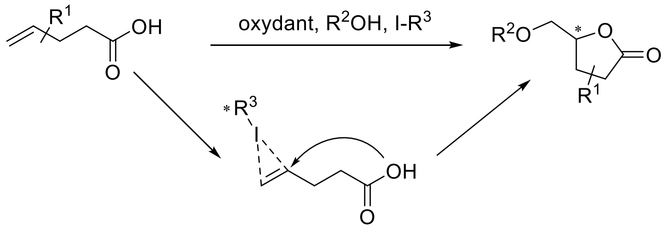
Chiral Hypervalent Iodine(III) Catalyst Promotes Highly Enantioselective Sulfonyl- and Phosphoryl-oxylactonizations

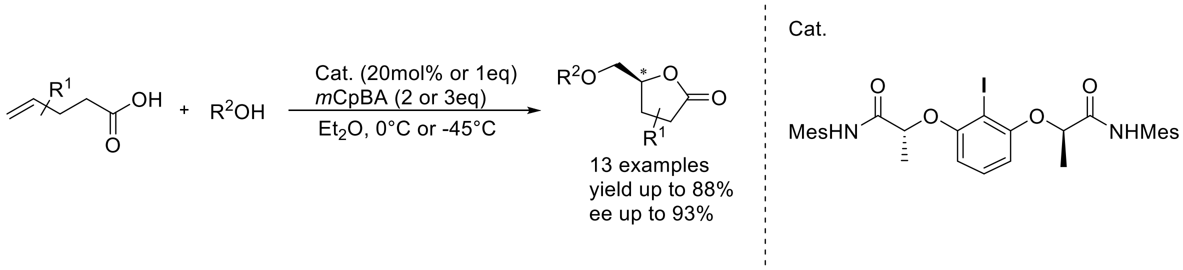
C. Gelis, A. Dumoulin and G. Masson*
ICSN-CNRS, 91198 Gif-sur-Yvette Cedex

Chiral γ-butyrolactones (dihydrofuran-2-ones) are prevalent motifs found in diverse biologically active natural and synthetic products. [1] In addition, γ-(hydroxymethyl)-γ-butyrolactones are valuable key building blocks for the synthesis of various natural products. [2] Direct oxycyclization of 4-pentenoic acids mediated by hypervalent iodine(III) represents one of the most straightforward approaches starting from readily available precursors (scheme 1). In spite of the recent developments, [3] few efficient enantioselective oxylactonizations have to date been recorded.



Scheme 1

Within this context and in conjunction with our interest in enantioselective hypervalent iodine(III) catalysis,[4] we describe herein the first enantioselective sulfonyl- and phosphoryl-oxylactonization of nonrigid 4-pentenoic acid derivatives using stoichiometric or catalytic amounts of chiral hypervalent iodine precursors. This methods provides an efficient acces to various interesting enantioenriched γ-lactones through a tandem sequence, in acceptable yields and moderate to excellent enantioselectivity (scheme 2). [5]



Scheme 2

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Visible light triggers the direct C-H heteroarylation of anilines

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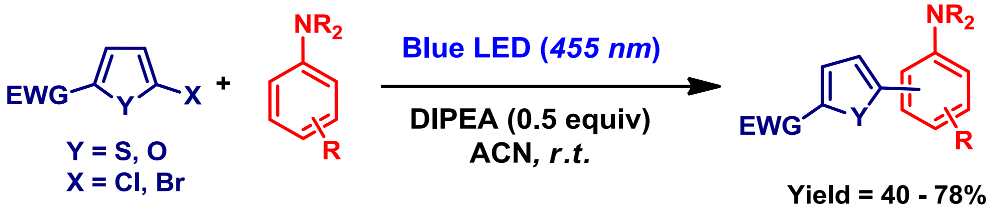
Aniline derivatives are important compounds for the society, present in our daily life. As an example, many pharmacologically active compounds present this moiety in their structure.[1] In addition , they are employed in industry as precursors for the obtention of pigments, dyestuffs, rubber products, etc.[2] Transition metal catalyzed cross-coupling approaches are probably the most common methodologies for their arylation.[3] However, prefunctionalized anilines are required as starting materials in these reactions. More direct approaches involved the direct C-H functionalization of anilines. So far, the approaches described require either the presence of stoichiometric amounts of the reductant or oxidant reagent, or the use of high temperatures in the reaction.[4] Here we present an alternative to the previous methods, that using visible light as the source of energy and allows the direct C-H heteroarylation of anilines from EWG-substituted thiophenes and furanes and anilines, using only DIPEA as sacrificial electron donor. A variety of anilines bearing substituents of different electronic nature can be heteroarylated under these conditions, and the method showed a broad functional group tolerance. Mechanistic studies of the reaction suggested the formation of a transient heteroaryl radical by excitation under blue LED irradiation followed by a single electron transfer from DIPEA, that is consecutively trapped by the aniline moiety present in the media.



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Preparation of Solid Organozinc Pivalates with Enhanced Air and Moisture Stability for Organic Synthesis

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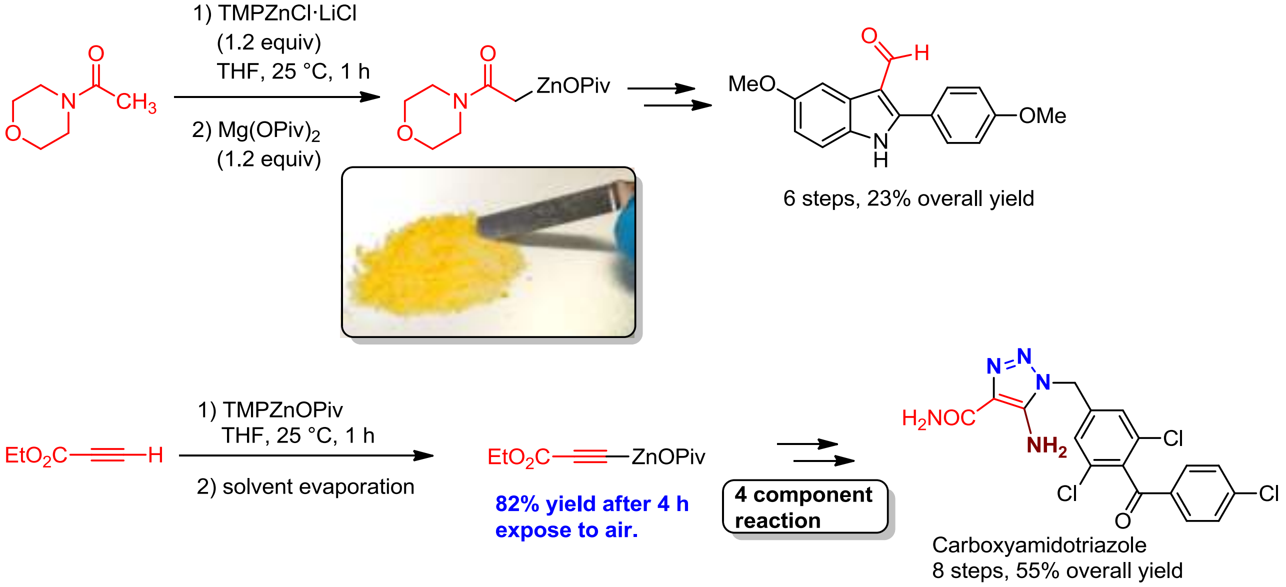
We have reported the preparation of solid and air-stable zinc amide enolates [1] and poly-functionalized alkynylzinc pivalates [2] from the corresponding morpholinoamides or alkynes using TMPZnX (TMP = 2,2,6,6-tetramethylpiperidyl) as base. These organozinc pivalates are obtained as powders under mild conditions in excellent yields that can be manipulated in air for several hours without significant decomposition. These zinc reagents show an excellent reactivity in various carbon-carbon bond forming reactions including 1,3-dipolar cycloaddition. And they have been used to prepare 3-formyl indole derivative and carboxyamidotriazole with crucial biological activity in concise way and good overall yield.



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Rhodium-Catalyzed Synthesis of Unsymmetric Di(heteroaryl) HetAr-X-HetAr' Compounds

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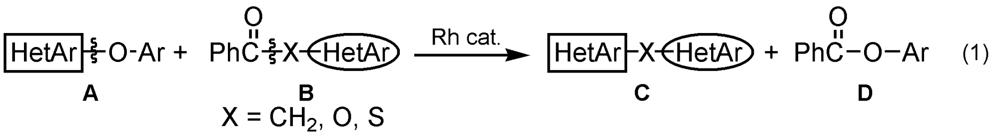
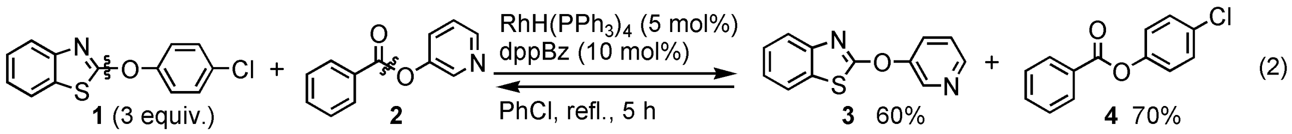
Di(heteroaryl) structure HetAr-HetAr is an important scaffold for drugs and functional organic materials, and the construction of its carbon framework has been extensively studied using the C–C coupling reactions between two aryl *sp*^{2}-carbons. On the other hand, the synthesis of di(heteroaryl) compound HetAr-X-HetAr' (X = O, S, CH_2, NH…) connected by a one-atom linker has been quite rare compared with HetAr-HetAr compounds. HetAr-X-HetAr' compounds are characterized by the flexible structure possessing two rotating *sp*^{2}-C/X bonds, and it is considered that HetAr-X-HetAr' can exhibit novel chemical and biological function not observed with HetAr-HetAr compounds. However, efficient and versatile synthetic method has not been known.

Recently, we developed rhodium-catalyzed synthesis of di(heteroaryl) ethers[1], di(heteroaryl) sulfides[2], and di(heteroaryl) methanes[3] from heteroaryl ethers by heteroaryl exchange reaction (Scheme1). The synthesis provides a diversity of unsymmetric five/six-membered di(heteroaryl) HetAr-X-HetAr' compounds, which were not known before.



For example, unsymmetric di(heteroaryl) ethers were synthesized by heteroaryl exchange between heteroaryl aryl ethers and heteroaryl esters[1]. When 2-phenoxybenzothiazole (**1**, 3 equiv.) was reacted with pyridin-3-yl benzoate (**2**) in the presence of $RhH(PPh_3)_4$ (5 mol%) and dppBz (10 mol%) in refluxing chlorobenzene for five hours, 2-(3-pyridinyloxy)benzothiazole (**3**, 60%) and phenyl benzoate (**4**, 70%) were obtained. No reaction occurred in the absence of $RhH(PPh_3)_4$ or dppBz (Scheme 2). The reverse reaction of **3** (1 equiv.) and **4** (1 equiv.) under the same condition gave **1** (39%) and **2** (40%), which indicated the equilibrium nature of the reaction.



Broad applicability of the rhodium-catalyzed method is due to the equilibrium nature of the exchange reaction using stable substrates, which do not employ metal bases.

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Synthesis, *In-vitro* antimycobacterial evaluation and docking studies of some new 2-heterostyrylbenzimidazole compounds as Inhibitors of *Mycobacterium tuberculosis* Pantothenate Synthetase

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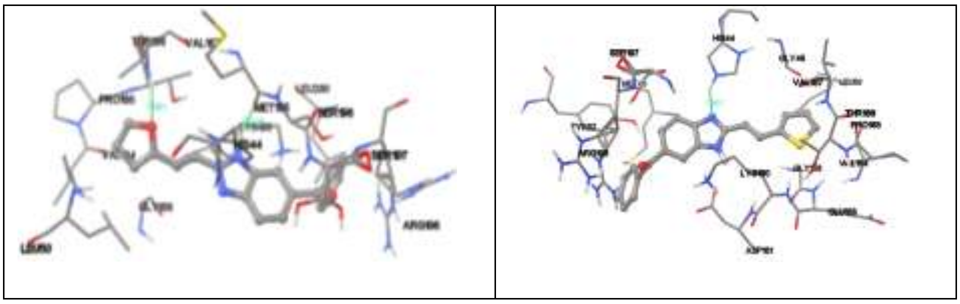
Tuberculosis is one of the oldest documented infectious disease and threat to worldwide public health, mainly caused by *Mycobacterium tuberculosis (M.tb.)* bacteria species. It is the only disease that does not require any vector for transformation from one person to another [1]. In 2010, there were around 8.8 million incident cases of TB, and around 1.1 million deaths from TB among HIV-negative people, and an additional 0.35 million deaths from HIV-associated TB [2].

Cinnamic acids, its derivatives such as ethyl cinnamate, sodium cinnamate, and benzylcinnamate have century old history as potential antituberculosis agents. 2-Styrylbenzimidazoles which were synthesized from these Cinnamic acids are also showed promising antituberculosis activity, but the practicable greener routes available for the synthesis of novel 2-heterostyrylbenzimidazoles are very less in the literature. Herein, we report the facile synthesis of some novel 2-heterostyrylbenzimidazoles using greener routes which were tested against *Mycobacterium Tuberculosis* and other Gram positive and Gram negative bacteria.

$R = H, NO_2, -COPh$
$X = H, CH_3, Cl, F, NO_2$

Figure 1: Synthesis of 2-heterostyrylbenzimidazoles (**3a-c**).

Pantothenate synthetase (PS) was considered as the target for the molecular docking studies and evaluated the binding pattern at active site, as PS plays a significant role in the biosynthesis of pantothenate in *Mycobacterium tuberculosis* (MTB).



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Unnatural Amino Acid Derivatives Through Click Chemistry: Synthesis of Triazolylalanine Analogues

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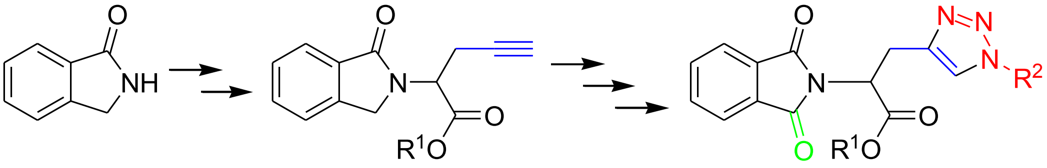
The synthesis and utilization of unnatural amino acids is a vital component of protein engineering, drug design and enzyme modification.[1] Most frequently, the preparation of many unnatural or otherwise non-proteinogenic amino acids begins with the preparation of so-called glycine equivalents and further manipulation through the installation of side chains.[2] In general the term 'glycine equivalent' infers a two-carbon fragment whereby the carboxyl group and the amino group bear suitable protection so that the methylene group may be activated as a nucleophile or electrophile to facilitate side-chain installation. A novel tert-butyl 2-(1-oxoisoindolin-2-yl) acetate derivative is selectively alkylated with propargyl bromide in the presence of lithium hexamethyldisilazide (LiHMDS). After removal of the *tert*-butyl protecting group, the resulting *N*-isoindolinyl (ethynylalanine) derivative is reacted with a series of azides under 'click' cycloaddition conditions. The click reactions afford an array of *N*-isoindolinyl- 1,2,3-triazolylalanine derivatives as the free carboxylic acids. Following esterification, the N-isoindolinone protecting group is transformed into the more easily-removable *N*-phthaloyl group by selective oxidation (Oxone®/KBr) at the benzylic position (7 examples). The benzylic oxidation of an isoindolinone to a phthalimide is a novel application of the Oxone system and was found to applicable to a range of isoindolinone-protected α–amino acid derivatives having alkyl and aromatic side chains.



R^1=*tert*-butyl, R^1=H, R^2=alkyl, benzyl
Click conditions: R_2-N_3/$CuSO_4.5H_2O$/Na accorbate/THF-H_2O; Yields, 67-95%; 7 Examples.
Benzylic oxidation conditions: Oxone®/KBr/MeCN-H_2O; Yields, 72-91%; 7 Examples.

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Axially Chiral Hemiaminals from α-Amino Acid Derivatives (Thiohydantoins): Nonracemic Synthesis and Stereodynamics

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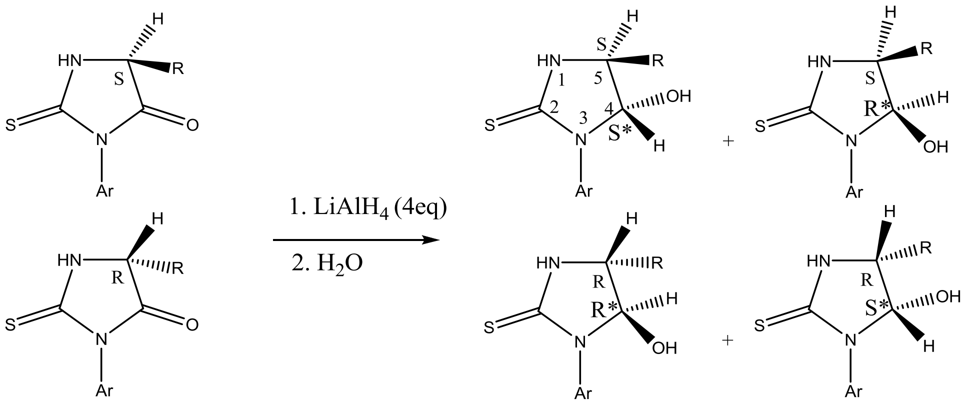
Stable, nonracemic axially chiral hemiaminals (O, N-hemiacetals) incorporated into cyclic thiourea structures have been synthesized stereoselectively from lithium aluminum hydride ($LiAlH_4$) reductions of previously synthesized [1] nonracemic 5-methyl- and 5-isopropyl-3-(*o*-aryl)-2-thiohydantoins in THF at room temperature in 10 minutes (Scheme 1). The **S** configuration at C-5 of the thiohydantoin ring was found to direct the reduction to produce predominantly **S** configured hemiaminals at C-4 of the heterocyclic ring (by 80% when the C5 substituent is methyl, by 97% when it is isopropyl). The stereochemical outcome of the axially chiral hemiaminals resulted from their conformational preferences which in turn arose from either a tendency for an intramolecular hydrogen bond formation or out of steric reasons. The stereodynamics of the axially chiral hemiaminals leading to their conformational preferences were investigated.



Ar = *o*-tolyl, *o*-fluorophenyl, *o*-chlorophenyl, *o*-bromophenyl,*o*-iodophenyl, 1-naphtyl and phenyl
R= CH_3 and isopropyl

Scheme 1 The reduction reaction of 5-methyl- and 5-isopropyl-3-(*o*-aryl)-thiohydantoins

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Synthetic Applications of γ-Benzyloxy Vinylogous Urethanes

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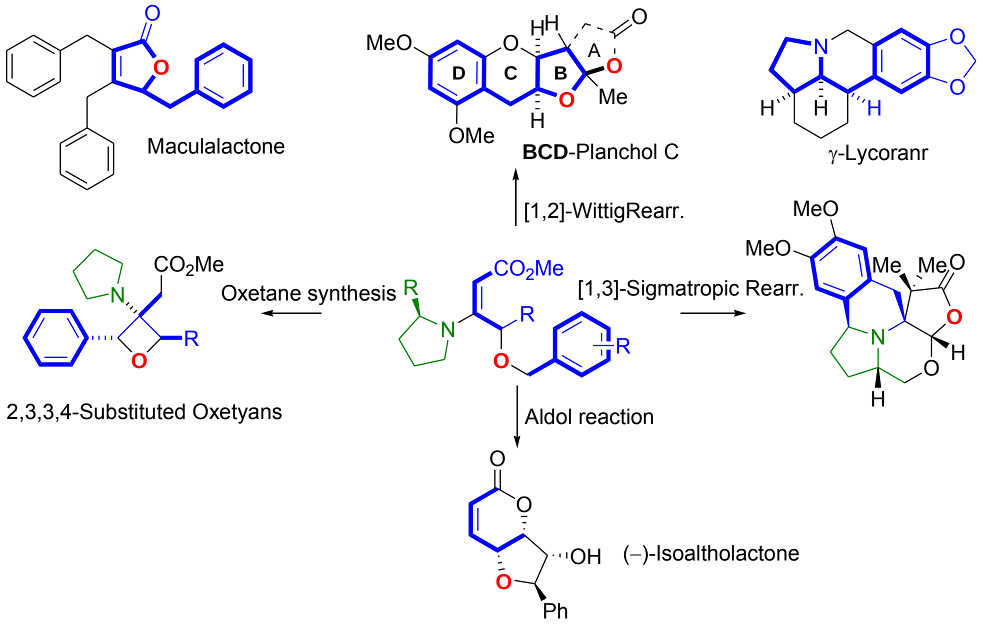
Chiayi City, Taiwan 60004

γ-Benzyloxy vinylogous urethanes were used in various studies including; 1) [1,2]-Wittig rearrangement, 2) 2,3,3,4-tetrasubstituted oxetane synthesis, 3) [1,3]-sigmatropic rearrangement followed by *m*-CPBA oxidation and rearrangement, 4) aldol reaction with cinnamaldehyde. [1] [2] Products generated from [1,2]-Wittig rearrangement studies were applied to complete the total synthesis of (±)-γ-lycorane, the formal synthesis of (±)-maculalactone and the B-C-D fragment of planchol C. Studies of [1,3]-sigmatropic rearrangement lead to the compound having crispin A core structure. Vinylogous urethane lactone obtained from aldol reaction was facilely transformed into (−)-isoaltholactone.



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Synthesis of 2-thioxo-quinazolidin-4-ones

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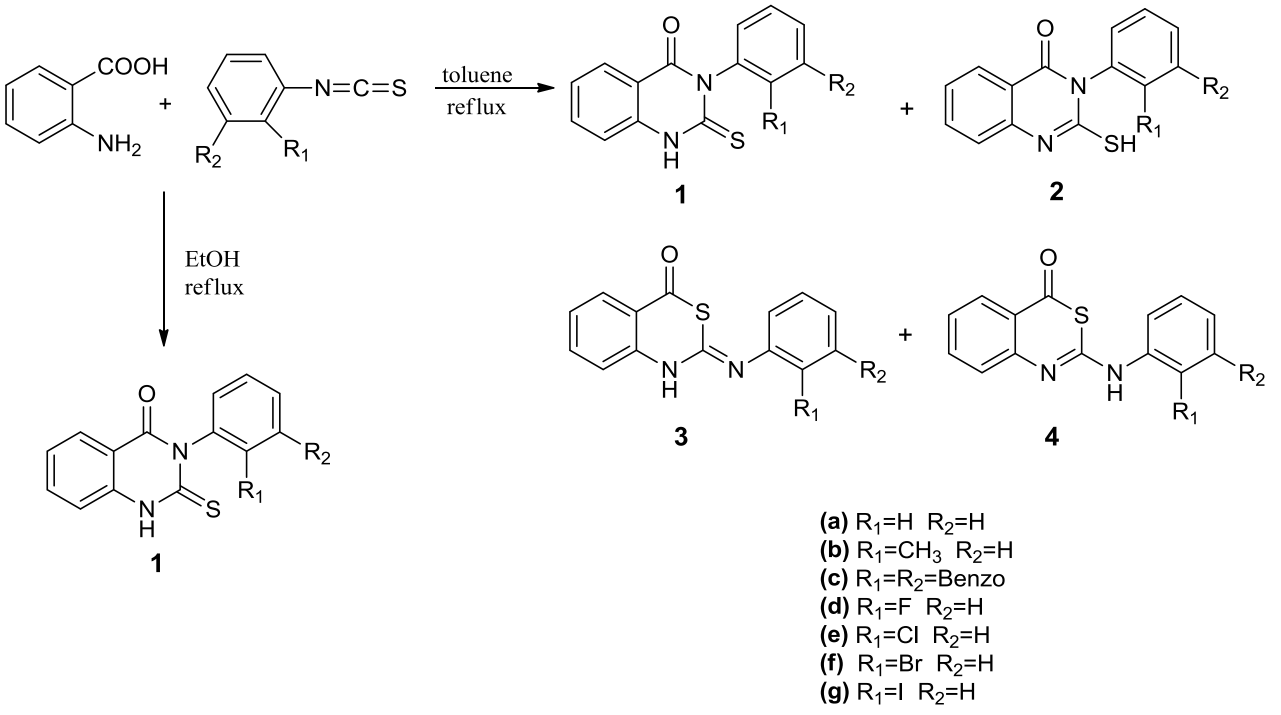
Quinazoline is one of the main classes of nitrogen-containing heterocycles. Its derivatives are versatile synthetic building blocks and precursors of many biologically active molecules [1-3]. Because of their great value, the synthesis of quinazoline derivatives has always received much attention. In order to synthesize 2-thioxo-quinazolidin-4-one derivatives, anthranilic acid was reacted with appropriate isothiocyanates in toluene, however the mixture of 3-aryl-2-thioxo-2,3-dihydroquinazolin-4(1H)-ones (**1**), 2-mercapto-3-aryl-quinazolin-4(3H)-ones (**2**), 2-(arylimino)-1H-benzo[d][1,3]thiazin-4(2H)-ones (**3**) and 2-(arylamino)-4H-benzo[d][1,3]thiazin-4-ones (**4**) were obtained. Their structures were identified by ^{1}H NMR. When the same reaction was carried out in ethanol, only 3-aryl-2-thioxo-2,3-dihydroquinazolin-4(1H)-ones (**1**) was obtained.



(a) R_1=H R_2=H
(b) R_1=CH_3 R_2=H
(c) R_1=R_2=Benzo
(d) R_1=F R_2=H
(e) R_1=Cl R_2=H
(f) R_1=Br R_2=H
(g) R_1=I R_2=H

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Synthesis of 2-Iminothiazolidine-4-one Derivatives as Single Enantiomers

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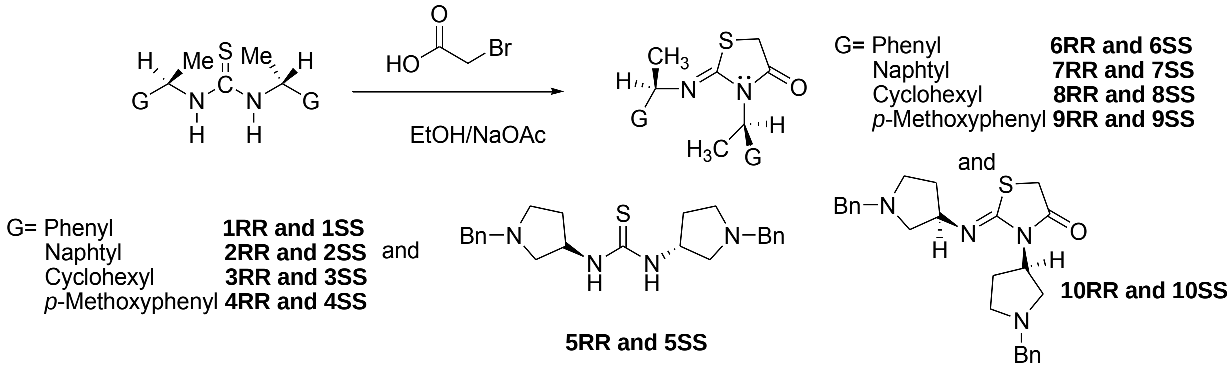
Istanbul/TURKEY ,34342

2-Iminothiazolidine skeleton finds a great application area not only on medicinal chemistry because of its various biological activities but also in synthetic organic chemistry due to the functionalization posibilities on its different positions. We have constructed 2-iminothiazolidine-4-one rings **6-10** as single enantiomers via cyclization of the corresponding N,N‘-bis thioureas **1-5** with an α-halo acid in the presence of a mild base (NaOAc) in a polar solvent (Scheme 1) and identified the products by NMR, polarimetry and HPLC on chiral stationary phases.



Scheme 1. Synthesis of chiral 2-imino thiazolidine-4-ones as single enantiomers

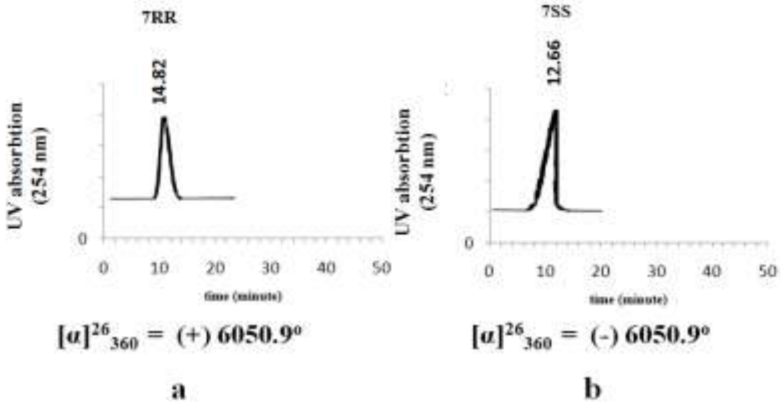


Figure 1. HPLC chromatograms of **7RR** and **7SS** on Chiralpak IC columnn, mobile solvent : Hexane:Ethanol (95:5), flow rate: 0.6 mL/min.

A General and Direct Reductive Amination of Aldehydes and Ketones with Electron-Deficient Anilines

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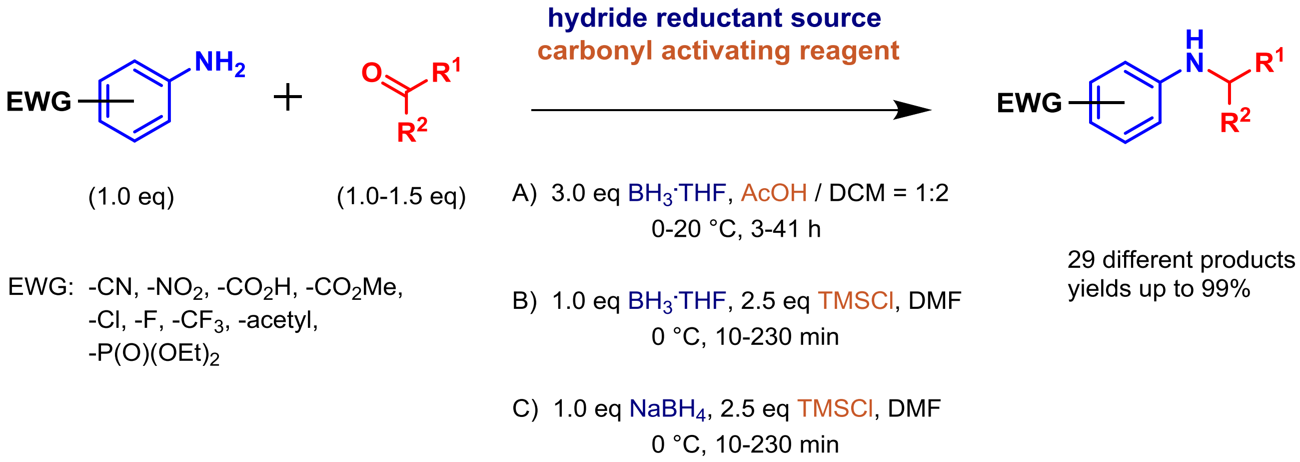

EWG: -CN, $-NO_2$, $-CO_2H$, $-CO_2Me$, -Cl, -F, $-CF_3$, -acetyl, $-P(O)(OEt)_2$

A) 3.0 eq $BH_3 \cdot THF$, AcOH / DCM = 1:2
0-20 °C, 3-41 h

B) 1.0 eq $BH_3 \cdot THF$, 2.5 eq TMSCl, DMF
0 °C, 10-230 min

C) 1.0 eq $NaBH_4$, 2.5 eq TMSCl, DMF
0 °C, 10-230 min

29 different products
yields up to 99%

In organic synthesis, reductive amination is the primary method for the generation of secondary or tertiary amines. During the design and synthesis of substrate analogues of intermediates of the PhzA/B catalyzed transformation occurring in the biosynthesis of phenazines by *Pseudonomas aeruginosa*,[1] we discovered limitations in current existing methods for C-N bond formation in reductive amination using electron-deficient anilines as substrates.[2] In order to overcome these constraints, we performed several screening experiments and report herein three scalable and robust methods with considerable substrate scope. Low-priced Method A using $BH_3 \cdot THF/AcOH/CH_2Cl_2$ gave full conversions in several hours while Method B ($BH_3 \cdot THF/TMSCl/DMF$) and Method C ($NaBH_4/TMSCl/DMF$) presented efficient reaction times of 10 to 230 min.[3] With these methods we tested 14 ketones, 3 aldehydes and 12 anilines in total, with functional group tolerance to acetyl, alkoxycarbonyl, halo, cyano, nitro, carboxy and diethylphosphonyl groups. Within this scope the coupling of heterocyclic aldehydes, ketones and amines was achieved. In experiments, where sterically hindered substrates were loaded the more reactive TMSOTf was used as an alternative to TMSCl to further increase reaction conversions.

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Radical Aromatic Substitutions Mediated by Very Weak Bases

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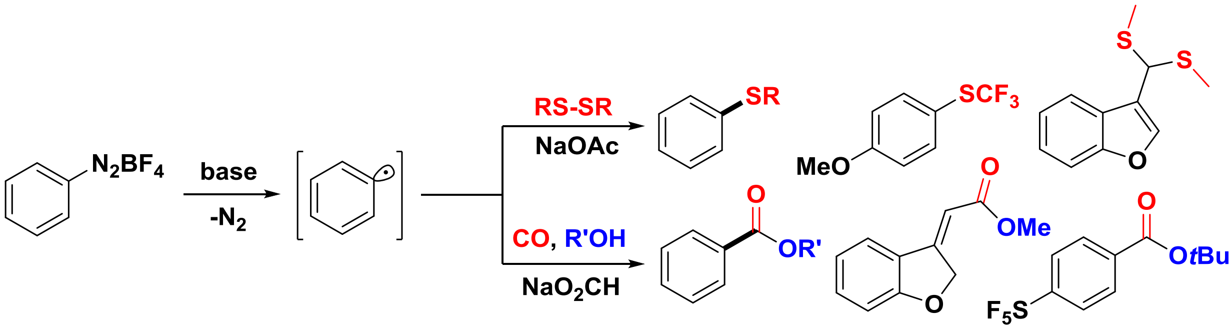
We have developed operationally facile protocols of radical aromatic substitutions which utilize simple sodium carboxylates as initiators. Such weak inorganic bases are cheap, environmentally benign, and easily removed from organic products while organic bases are mostly more expensive, hazardous, and miscible with organic phases. This general concept has been applied to metal-free thiolations (with disulfides) and alkoxycarbonylations (with carbon monoxide and alcohols).

Aromatic thioethers and analogous heavier chalcogenides were prepared by reaction of readily available arenediazonium salts with disulfides in the presence of NaOAc. The mild and practical reaction conditions (equimolar reagents, DMSO, r.t., 8 h) tolerate various functional groups (e.g. Br, Cl, NO_2, CO_2R, OH, SCF_3, furans). Mechanistic studies indicate the operation of a radical aromatic substitution mechanism *via* aryl, acetyloxyl, thiyl, and dimsyl radicals. [1]

Utilizing gaseous carbon monoxide, the base-mediated alkoxycarbonylation of arenediazonium salts affords benzoate esters in the presence of sodium formate at room temperature. Diverse *t*-butyl, alkyl, and *i*-propyl benzoates with electron-poor and electron-rich substituents were synthesized. Experimental and theoretical studies indicated the operation of an initial homolysis of the diazoformate that is followed by generation of an aryl radical, which subsequently reacts with carbon monoxide to provide the acyl radical. [2]



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Bio-inspired Total Synthesis of Pyrrolidine and Indolizidine Alkaloids

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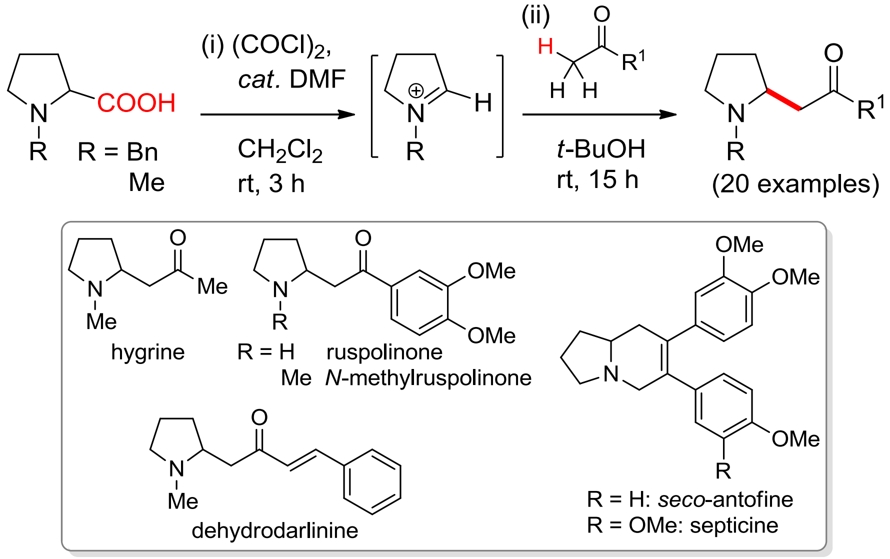
Department of Chemistry, National Taiwan Normal University, Taipei 11677, Taiwan

2-(Acylmethylene)pyrrolidine derivatives were synthesized *via* intermolecular decarbonylative Mannich reaction from various methyl ketones and 1-alkyl-1-pyrroliniums,[1] generated *in situ* from 1-alkylprolines.[2] This methodology features the advantages that direct formation of pyrrolinium intermediates from 1-alkylprolines and subsequent intermolecular Mannich reactions with methyl ketones could both be carried out under simple and mild conditions without the use of metal catalysts and other additives. This approach mimics the biosynthetic pathway and provides a direct access to a series of 2-(acylmethylene)-pyrrolidine alkaloids, including hygrine, *N*-methylruspolinone, dehydrodarlinine and ruspolinone. Further elaboration of the Mannich adducts can lead to a series of indolizidine alkaloids, such as septicine and *seco*-antofine.



Meanwhile, the decarbonylative Mannich reaction was also applicable to π-electron-excess heteroarenes as the nucleophilic counterparts. A series of pyrrole and indole derivatives underwent the decarbonylative Mannich reaction with 1-alkylprolines under the same condition to give the corresponding 1-alkyl-2-heteroarylpyrrolidines in very good yields. The reactions took place exclusively at the C2-position of pyrroles and C3-position of indoles. Further application of this methodology would be amenable to the synthesis of versatile 2-substituted pyrrolidine derivatives.

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Construction of Azabicyclo[6.4.0]dodecatrienes Based on Rhodium(I)-Catalyzed Intramolecular [6+2] Cycloaddition Between Azetidine, Allene, and Alkynes

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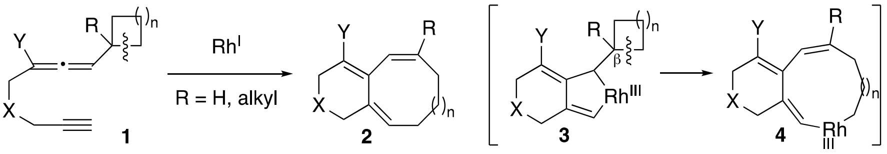
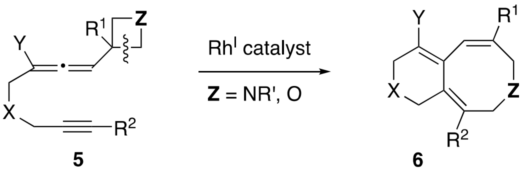
Small-sized cycloalkanes are often of significant use from synthetic points of view. We recently disclosed that the rhodium(I)-catalyzed cycloaddition of allenylcyclopropane-alkynes **1** (n=0) afforded the bicyclo[5.4.0]undecatrienes **2** (n=0)[1] in the [5+2] ring-closing manner. The reaction must have proceeded via cleavage of the cyclopropane ring due to of the relief of its high strain energy (27.5 kcal/mol). A similar ring construction could be realized using allenylcyclobutane-alkynes **1** (n=1) producing the eight-membered bicyclic compounds **2** (n=1)[2] in high yields ([6+2] cycloaddition). The unfunctionalized simple cyclobutane ring is generally known not to open, let alone being used as a C_4-building block. We tentatively interpreted that the production of **2** (n=1) would be initiated by the formation of the rhodabicyclo[4.3.0] intermediate **3** (n=1), which should be susceptible to β-carbon elimination, with release of the ring strain energy (26.3 kcal/mol) giving rise to the nine-membered rhodabicyclic species **4**. Reductive elimination would occur to provide the final products. The successful application of this methodology to the cyclopentane derivative **1** (n=2) afforded the nine-membered bicyclic compounds **2** (n=2).[3] This novel [7+2] cycloaddition involves the unprecedented cleavage of the normal-sized cyclopentane ring by releasing its strain energy (6.3 kcal/mol) via the intermediate **3** (n=2), similar to that of the cyclobutane derivatives.



We now report the application of a newly developed eight-membered ring formation method for the preparation of the bicyclic azocine derivatives **6** (Z=NR’) as well as the oxa analogue **6** (Z=O) from allenylheterocyclobutane-alkynes **5** (Z=NR’, O).[4] The polycyclic skeleton containing an eight-membered heterocycle has been found as the core structure in various natural products and biologically-active compounds.



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Total synthesis of Lamellarin G trimethyl ether

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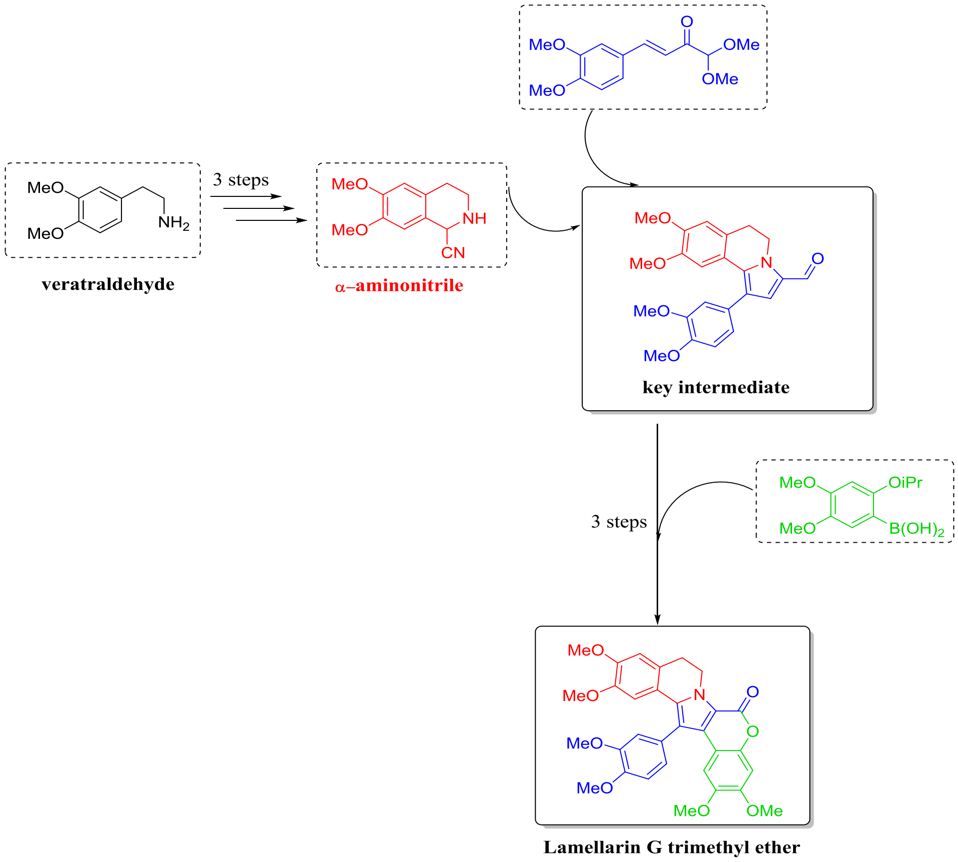
Lamellarins are a class of pyrrole alkaloids, which have been first isolated from the the prosobranch mollusc *Lamellaria sp.*, in 1985. These natural products have shown a remarkable variety of pharmacological features, such as inhibition of HIV-Integrase and type I topoisomerase and the initiation of natural cell death in *multi drug resistant* tumor cells.[1]

Starting from the commercially available veratraldehyde, the model compound lamellarin G trimethyl ether has been synthesised in seven steps with an overall yield of 14%. The key step is the deprotonation of an α-amino nitrile with KHMDS and a following *Michael addition* to an enone. This method has been devised in the Opatz group and since has found many applications in the synthesis of natural products.[2][3][4] The developed synthesis strategy potentially allows the access of every substitution pattern represented in the lamellarin classes IA and IB.[5]



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Light-Induced Alkylation of (Hetero)aromatic Nitriles in a Transition-Metal-Free C–C-Bond Metathesis

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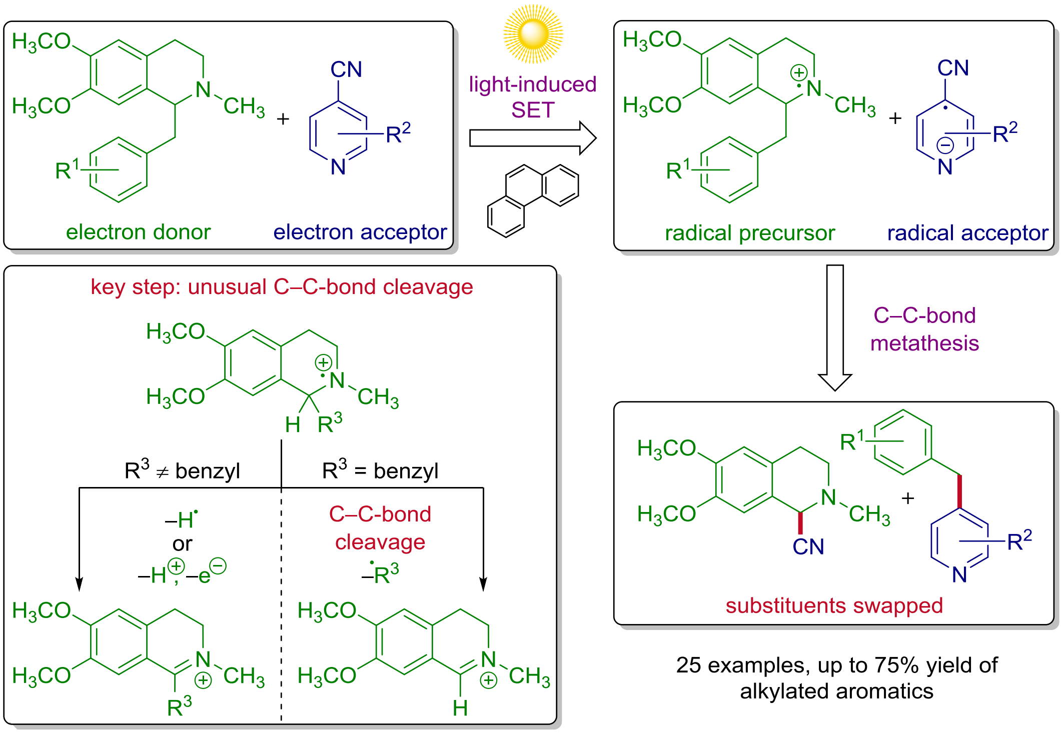
N-substituted 1,2,3,4-tetrahydroisoquinolines are among the most frequently used electron donors in photoredox-catalyzed transformations.[1] Upon oxidation, the initially formed amine radical cations are typically converted to the corresponding iminium ions by abstraction of a hydrogen atom or by deprotonation and subsequent one-electron oxidation of the resulting neutral radical.[1] However, for 1-benzyl-2-alkyltetrahydroisoquinolines abstraction of an electron from nitrogen is instead followed by the cleavage of the $C^1(sp^3)$–$C(sp^3)$-σ-bond giving rise to stabilized benzylic radicals. In the presented work[2], these radicals have been used for the *ipso*-substitution of (hetero)aromatic nitriles proceeding through another single-electron transfer-mediated C–C-bond cleavage and formation with concomitant elimination of cyanide. Trapping of the iminium ion generated upon liberation of the benzylic radical from the 1-benzyltetrahydroisoquinoline by cyanide gives rise to the corresponding *α*-aminonitrile, thereby completing a new type of σ-bond metathesis in which two C–C bonds are formed at the expense of two other C–C bonds. This constitutes the first report of a light-induced C–C-σ-bond metathesis.



25 examples, up to 75% yield of alkylated aromatics

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A New Entry for the Synthesis of Disubstituted Furanones Employing an Asymmetric Dihydroxylation of α,β-Unsaturated Diazoketones.

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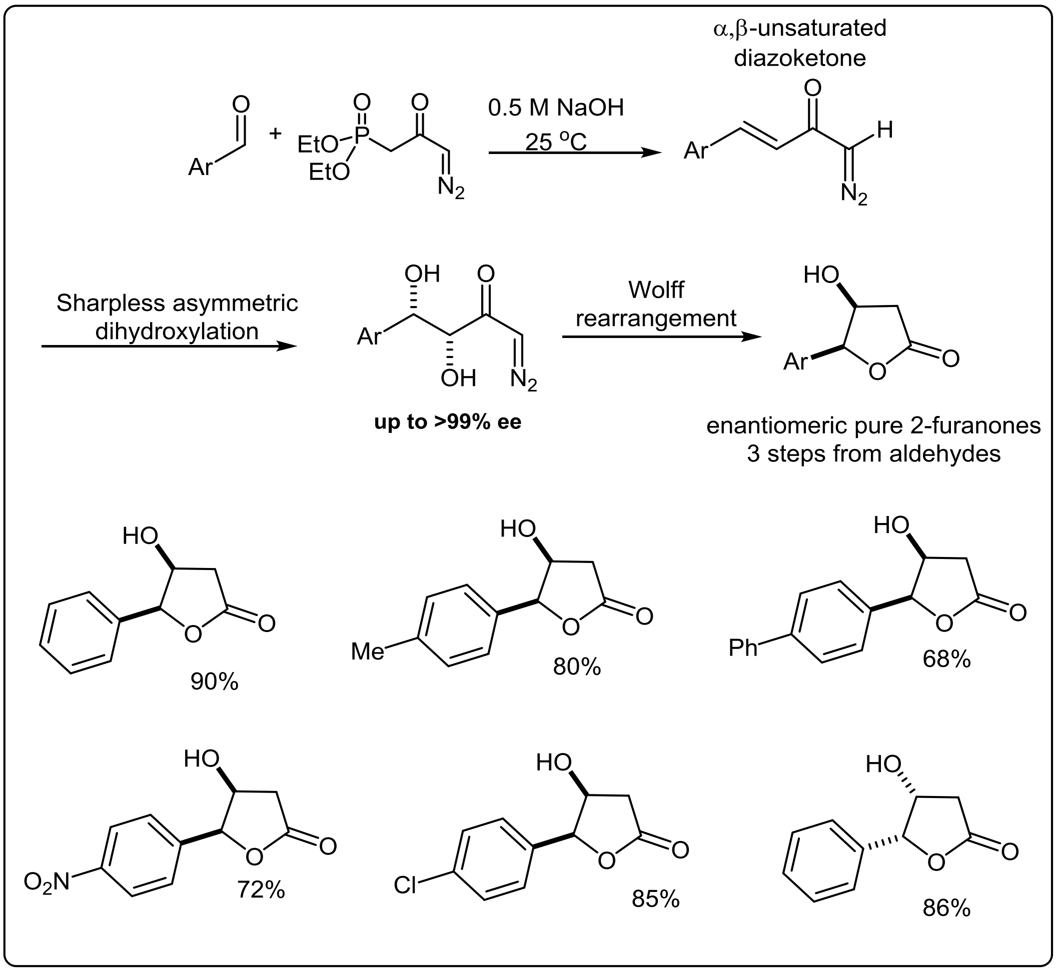
Chemistry Institute of São Carlos, University of São Paulo, Brazil

α,β-Unsaturated α'-diazoketones[1] have proven to be important building blocks in synthesis. Possessing a diazo group, a carbonyl and a double bond, unsaturated diazoketones can be important platforms for the direct synthesis of several molecules, including heterocycles. As a continuation of our studies with this class of diazocompounds, we would like to show our preliminary results in the asymmetric functionalization of some α,β-unsaturated diazoketones using a Sharpless Asymmetric dihydroxylation. After this study, moderate to good yields and excellent enantioselectivities were obtained in the synthesis of several α,β-dihydroxy α'-diazoketones. These intermediates were employed in the direct synthesis of chiral 2-furanones after a photochemical Wolff rearrangement. To the best of our knowledge, this sequence (3 steps starting from aldehydes) is among the shortest ways to prepare enantiopure 2-furanones.



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Potential New Store-Operated Calcium Entry (SOCE) inhibitors from benzimidazole-azole linked derivatives for cancer.

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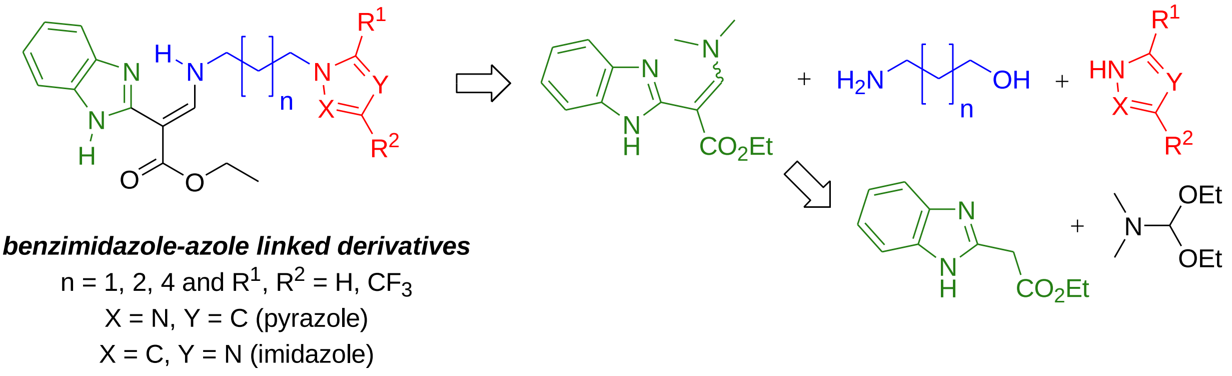
Ion channels are membrane proteins that control the passage of several ions [1]. They have a central role in the physiology of excitable cells for neurons or muscle and cardiac cells and also for ions. Ion channels are present in all tissues and cell types and their deregulation leads to many diseases [2]. The Store-Operated Calcium Entry (SOCE) inhibitors [3] are attractive as new generation of potential anti-cancer drugs [4]. In this context, we decided to investigate the multi-step synthesis of benzimidazole-azole derivatives [5] as alternative SOCE ligands to establish a preliminary relationship activity (RSA) study. For this presentation, we shall describe, for the first time, the total synthesis and biological properties with various tumor cells for these benzimidazole-azole linked or "aza azoles" derivatives.



benzimidazole-azole linked derivatives

n = 1, 2, 4 and R^1, R^2 = H, CF_3

X = N, Y = C (pyrazole)

X = C, Y = N (imidazole)

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Development of a Practical Process for the Synthesis of VEGF Inhibitors

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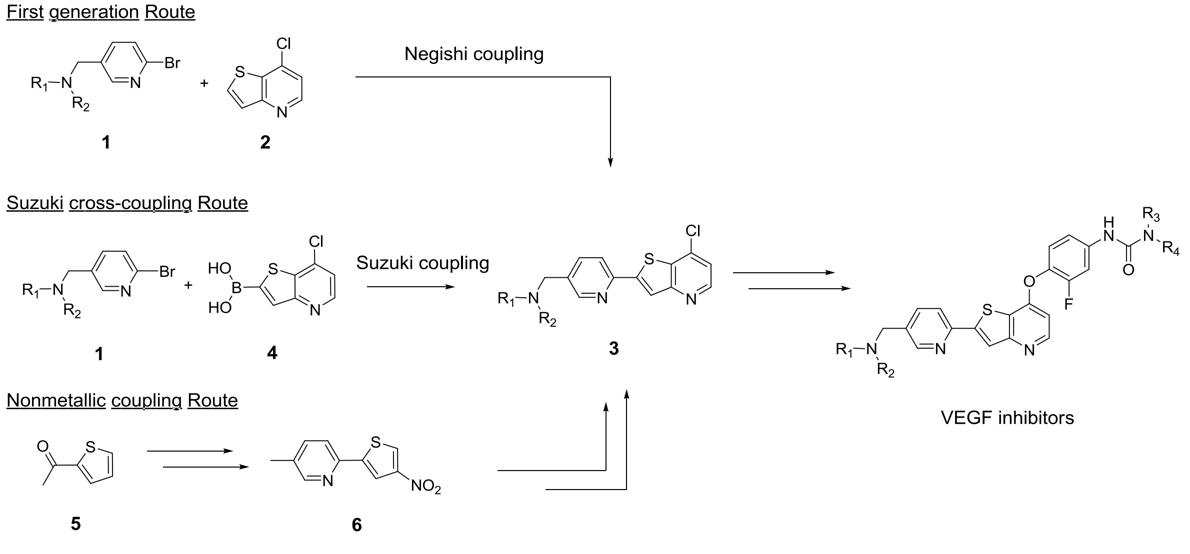
Two synthetic routes to VEGF inhibitors have been established for the practical process.

The first generation route utilizing a Negishi-coupling reaction requires a hazardous and expensive material (*n*-BuLi), and a low temperature condition (-78 °C) to prepare organozinc reagent derived from 7-chlorothienopyridine (**2**). Therefore we have investigated the following practical synthetic routes.

Suzuki cross-coupling route makes it possible to avoid a very low temperature used in Negishi-coupling. And we have also developed an efficient synthetic method for 6-bromopyridin derivatives (**1**) and 7-chlorothienopyridin-2-boronic acid (**4**).

The other synthetic route is via a nonmetallic coupling method. The synthesis begins with the nitration of commercially available 2-acetylthiophene (**5**). No metallic coupling reactions are involved in the process. This route is advantageous in costs and management of elemental impurities.



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Application of Vinylogous Mukaiyama-Mannich Reaction (VMMR) towards the synthesis of various Alkaloids

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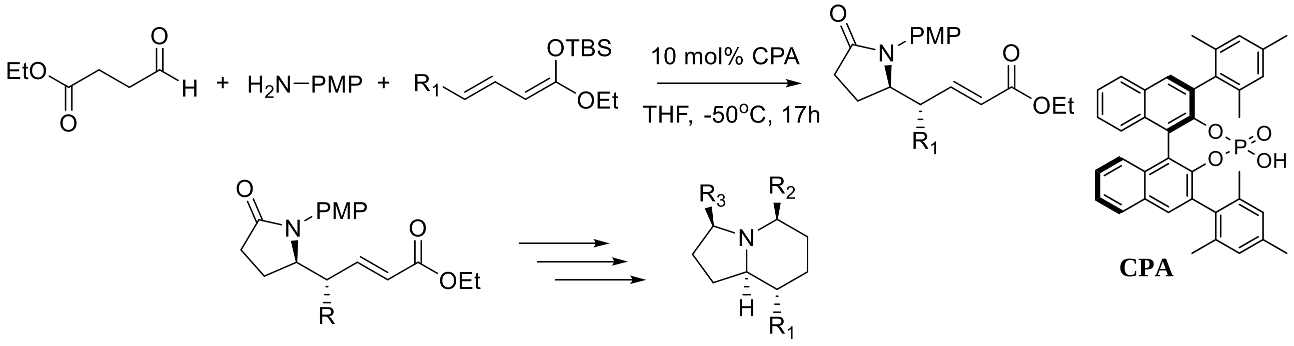
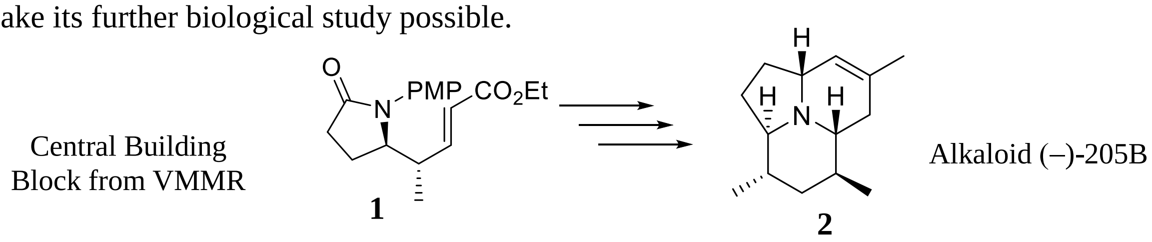
Our group has successfully established a versatile procedure for accessing various Indolizidine and Quinolizidine moieties through a highly enantio and diastereoselective VMMR.[1-2] The process involves the use of BINOL based phosphoric acids (**CPA**) as organocatalysts for the key reaction (**Scheme 1**).



***Scheme 1**: Versatile VMMR access to 16 alkaloids*

These alkaloids were discovered by John Daly and his co-workers from the skin of neotropical Panaemean Dendrobates frogs. Alkaloid (–)-205B (**2**) belongs to this family of lipid soluble alkaloids.[3] Its antipode has shown activity towards inhibition of $\alpha 7$ nicotinic acetylcholine receptor and could probably help to cure Alzheimer's and Parkinson's diseases. This alkaloid is present in miniscule quantity in nature because of which its applications have not been explored. Our target is to synthesize **2** in gram scale, by employing VMMR strategy as one of the key steps, to make its further biological study possible.



***Scheme 2**: Access to Alkaloid (–)-205B via VMMR*

In the present work, we have successfully synthesized the central building block in gram scales and the next target is to perform a substrate controlled alkylation followed by few chemical modifications to get the unique 8b-azaacenonaphthylene structure (**2**) (**Scheme 2**).

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Synthesis of π-Extended 9-Hydoroxyfluoranthenes by KHMDS-Promoted Domino Reaction

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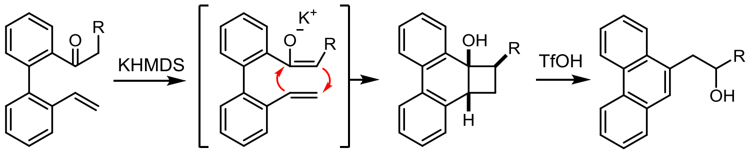
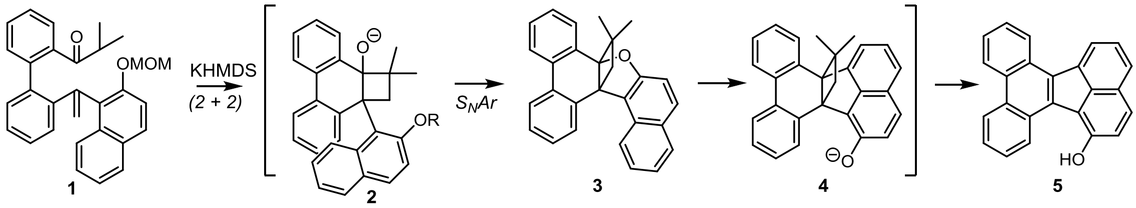
Polycyclic aromatic hydrocarbons (PAHs) are widely used as organic materials, hence developing new methodologies to synthesize PAHs are highly demanded. We previously reported a KHMDS-promoted (2 + 2)-cycloaddition of biaryl compounds bearing acyl and vinyl moieties to furnish fused cyclobutanols.[1] These cyclobutanols could be transformed into PAHs by acid-promoted ring-opening reaction (Scheme 1).



Scheme 1. KHMDS-Promoted (2 + 2)-Cycloaddition and Acid-Promoted Ring-Opening Reaction

We have developed a unique domino reaction furnishing π-extended fluoranthenes.[2] Biaryl compound **1** bearing naphthylalkenyl group was transformed into dibenzofluoranthene **5** by treating with KHMDS (Scheme 2). Oxapropellane **3** and carbopropellane **4** were found to be the intermediates in this reaction. Mechanistic studies suggested a unique reaction mechanism where KHMDS acts as both a base and a single-electron donor. First, oxapropellane **3** is formed via intramolecular S_NAr reaction of cyclobutanol **2**, which is produced via (2 + 2)-cycloaddition of biaryl **1**. Then, SET from KHMDS to **3** occurres and the resulting radical anion spices undergo a rearrangement reaction to furnish **4**. Finally, retro (2 + 2)-cycloaddition of **4** gives fluoranthene **5**. Synthetic applications of oxapropellane **3** for heterocyclic aromatic compounds will also be discussed.



Scheme 2. Formation of dibenzofluoranthene

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The Use of Derivatives of 8-Propyldithieno[3,2-*b*:2′,3′-*e*]pyridine-3,5-diamine (DITIPIRAM) for Molecular Recognition of Carboxylates

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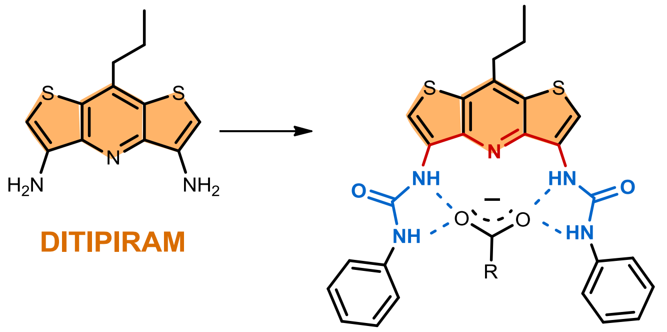
Anions play important role in many chemical and biological processes. Their complexation can be fundamental in catalysis,[1] pharmacy, and medicine.[2] For this reason, the design and synthesis of receptors that are capable of binding anions efficiently, is very important issue of modern supramolecular chemistry. Over the past two decades there has been an immense progress in the field of anion complexation, which resulted in development of many efficient and selective anion receptors. Moreover, the most effective among them possess rigid heteroaromatic central units.[3] Choice of such central unit (platform) plays a key role in the design of new anion receptors; given the importance of proper geometry of the binding site, even the small changes in arrangement of hydrogen bond donors may result in a different efficiency and selectivity of anion binding.[4]

Herein the synthesis and determination of anion binding properties of two novel receptors will be presented. These receptors incorporate a new and very promising heteroaromatic platform - 8-propyldithieno[3,2-*b*:2′,3′-*e*]pyridine-3,5-diamine (DITIPIRAM).[5]



- new rigid heteroaromatic platform
- unique geometry of binding pocket
- cooperative binding of carboxylates
($K_a > 10^4$, DMSO-d_6+0.5% H_2O)

References

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Polysubstituted pyrimidines with anti-inflammatory properties

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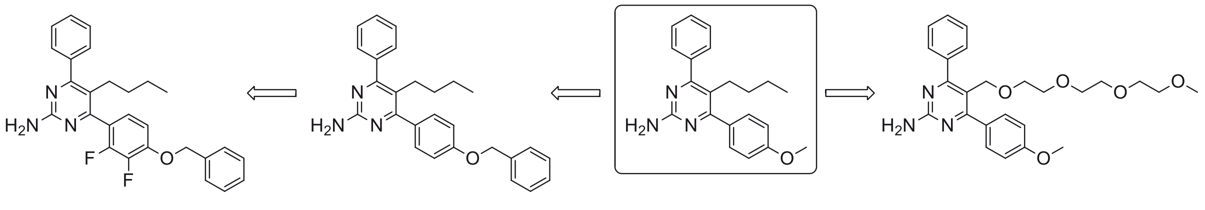
The main aim of this study was to design and synthesize new polysubstituted pyrimidines, derived from the current lead structure WQE-134, with improved biological properties, namely higher potency to inhibit prostaglandin E_2 (PGE_2) production and increased water-solubility.

The first structure-activity relationship study (SAR) was focused on enhancement of the anti-inflammatory efficacy (inhibition of PGE_2 production) through modifications of the phenyl moiety in the position C4 of pyrimidine. The key reaction was Suzuki-Miyaura cross-coupling. Firstly, eleven analogues were prepared which showed similar anti-inflammatory activity as WQE-134, but the most potent compound **9g** exhibited 62 times higher activity compared to the lead. Based on the results, ten additional derivatives bearing benzyloxy moiety were prepared, resulting in the discovery of **10d** with three orders of magnitude higher anti-inflammatory efficacy compared to the lead.

Further, a series of eleven WQE-134 analogues bearing a suitable moiety in the C5 position was prepared to increase their solubility. All prepared derivatives proved to be more soluble than WQE-134. Unfortunately, the biological data showed that this type of modification led to the decrease of anti-inflammatory efficacy. Nevertheless, the most soluble compound **25e** achieved two orders of magnitude higher solubility than WQE-134 while the biological activity decreased only slightly.



10d
three orders of magnitude
higher anti-inflammatory efficacy

9g

WQE-134

25e
two orders of magnitude
higher water-solubility

Since the mechanism of action of the studied pyrimidine derivatives remains unclear, biotinylated analogues of WQE-134 were also synthesized for subsequent pulldown experiments.

Acknowledgements. This work was supported by the Institute of Organic Chemistry and Biochemistry (RVO: 61388963) and by Technology Agency of the Czech Republic (TE01020028).

Heck Initiated Multicomponent Reactions for the Synthesis and Functionalization of Nitrogen Heterocycles

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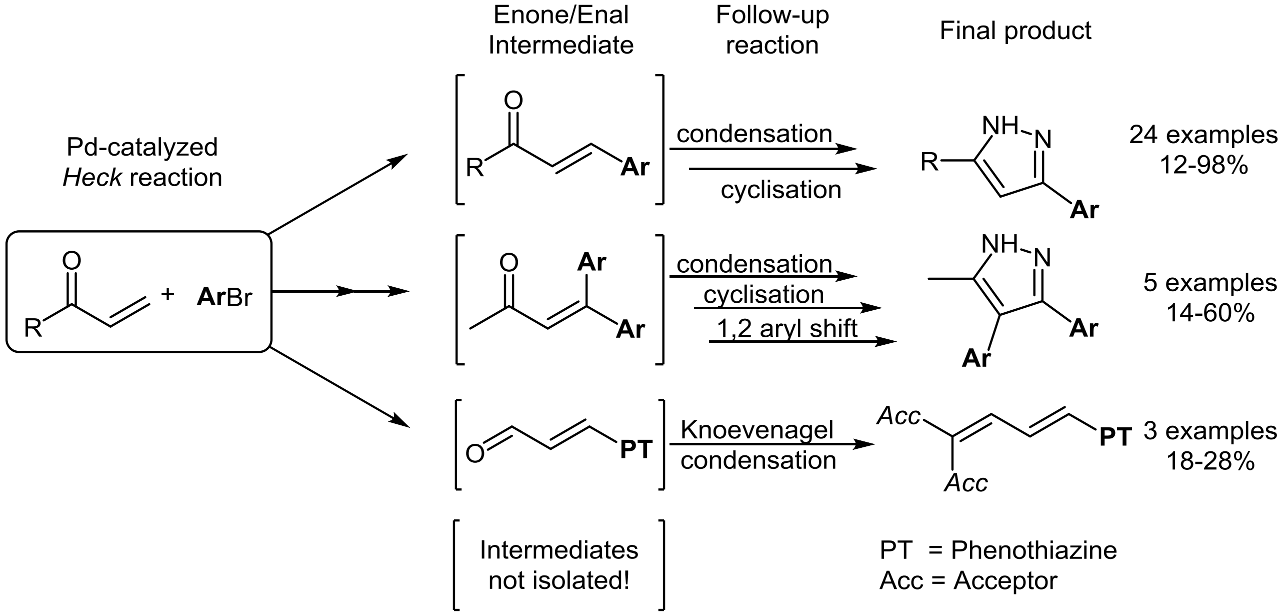
Heinrich Heine University, Düsseldorf/DE

Established already in the early days of organic chemistry,[1] the concept of multicomponent reactions (MCR) has changed the paradigm that only two component reactions could be reliably conducted. Consequently, MCR have become a general reactivity-based principle and synthetic concept.[2] Following this fundamental principle, our group has recently identified a novel catalytic system for the synthesis of *E*-configured *α,β*-unsaturated carbonyl derivatives by exploiting microwave assisted one-pot Pd-catalyzed *Heck* reactions.[3] This approach combines several advantages, such as short reaction times, minimal work up, cheap and commercially available starting materials. Applying microwave accelerated conditions allows low catalyst loading and prevents side reactions (e.g. polymerization of vinyl substrates). By the choice of the ligand aryl bromides can be transformed rapidly and under mild reaction conditions. Thereby cinnamaldehyde and chalcone derivatives are obtained in high yields, or they can subsequently undergo cyclocondensations to form pyrazoles in a one-pot fashion. Upon concatenating a subsequent *Knoevenagel* condensation merocyanine-type chromophores can be easily accessed.



While pyrazoles are known for biological and pharmacological activity,[4] phenothiazine based merocynine chromophores have successfully been applied in dye-sensitized solar cells (DSSCs). By expanding π-system, the bathochromic shift can be adjusted to reach the maximum efficiency of DSSC.[5],[6]

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A successful bioisosteric replacement in the design and synthesis of potent and selective HDAC6 inhibitors

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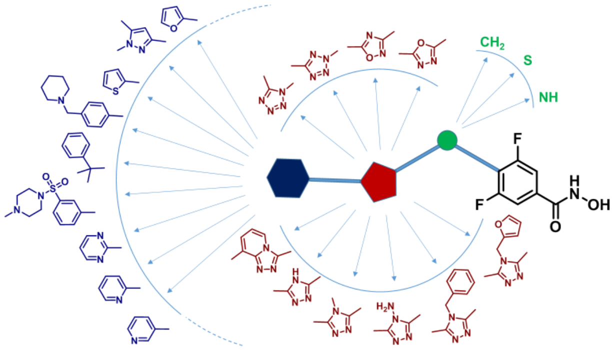
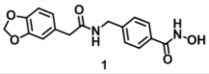
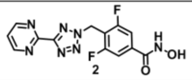
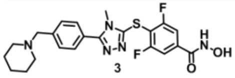
Zinc-dependent histone deacetylases (HDAC) are a class of 11 different enzymes, involved in regulating the acetylation status of histone and non-histone proteins. HDAC inhibitors were first developed in oncology based on the observation of frequent epigenetic defects in both solid and heme malignancies. These first-generation inhibitors however hit several, if not all, of the 11 Zn-dependent HDACs and suffer from a low therapeutic window that limits the possibility to target specific biological functions of individual HDAC subtypes. To further explore therapeutic opportunities in the HDAC field, there is a considerable interest in the development of isoform-selective HDAC inhibitors.[1]

HDAC6 appears to be a particularly attractive target, since its expression and function alterations have been correlated to a variety of pathologies, such as autoimmune disorders, neurodegenerative diseases and cancer. HDAC6 is primarily a cytoplasmic protein and its main deacetylase activity is on non-histone substrates, such as tubulin, HSP90 and cortactin. Moreover, selective inhibition of HDAC6 does not show cytotoxic effects.[2]
With the aim of ameliorating potency, HDAC6 vs HDAC3 selectivity and ADME of a series of amides of the *p*-amino methyl benzoic hydroxamic acid (see, for example, **compound 1**), we designed a library of 3,5-difluoro-benzohydroxamate-derivatives, bearing a 5-membered heterocyclic ring scaffold as a non-classical amide bioisostere.[3]



Compound	HDAC6 IC$_{50}$ [nM]	Selectivity vs HDAC3 [log(HDAC6/HDAC3)]
 **1**	199	-1,2
 **2**	5	-3,0
 **3**	5	-2,7
Tubastatin A	18,9	-2,4

We synthesized more than 200 compounds, most of them showing a relevant low nM HDAC6 inhibitory activity, with selectivity of up to 3 orders of magnitude vs HDAC3 and, in some cases, better ADME profiles when compared to other known HDAC6 inhibitors.[4]

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[4] M. Marchini et al, Italian Patent Appl. n. 102017000041723, 14 April 2017.

Synthesis and antiviral activities of trisubstituted pyrimidines

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Research of anti-HIV agents is still a promising field and substituted pyrimidines play key role as non-nucleoside reverse transcriptase inhibitors (NNRTIs), especially diarylpyrimidine (DAPY) derivatives[1]. We followed our previous research[2] and a new series of 2,4,6-trisubstituted pyrimidines derived from DAPY family was prepared as potential antiretroviral agents. Pyrimidine ring was substituted with 4-cyanophenylamino moiety, small group (NH_2, OCH_3 or CH_3) and aryl moiety attached through the carbonyl linker. 2,4,6-Trichloropyrimidine was used as a starting compound, therefore, three possible regioisomers were obtained (Fig. 1).

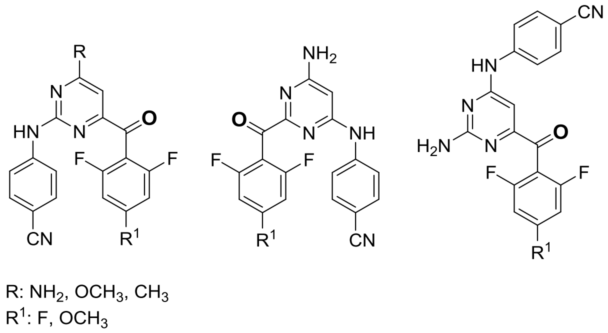

Fig. 1: Trisubstituted pyrimidines with the carbonyl linker.

The most potent candidate was expected to be the derivative with 4-cyanophenylamino arm in the C2 position as it is a structural analogue of approved antiviral drugs (etravirine and rilpivirine). This motive was used further and derivatives with O and NH linkers were synthesized after optimization of the synthesis (Fig. 2). Final products were tested on anti-HIV activities. The most potent compounds exhibited low nanomolar activity comparable with known anti-HIV drugs.

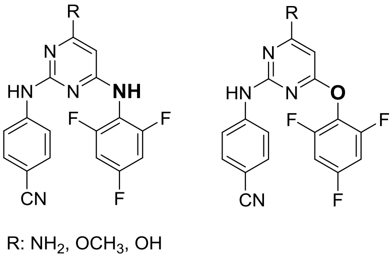

Fig. 2: Trisubstituted pyrimidines with the NH and O linkers.

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Generation of Arynes Triggered by Carbon–Carbon Bond Cleavage Reaction

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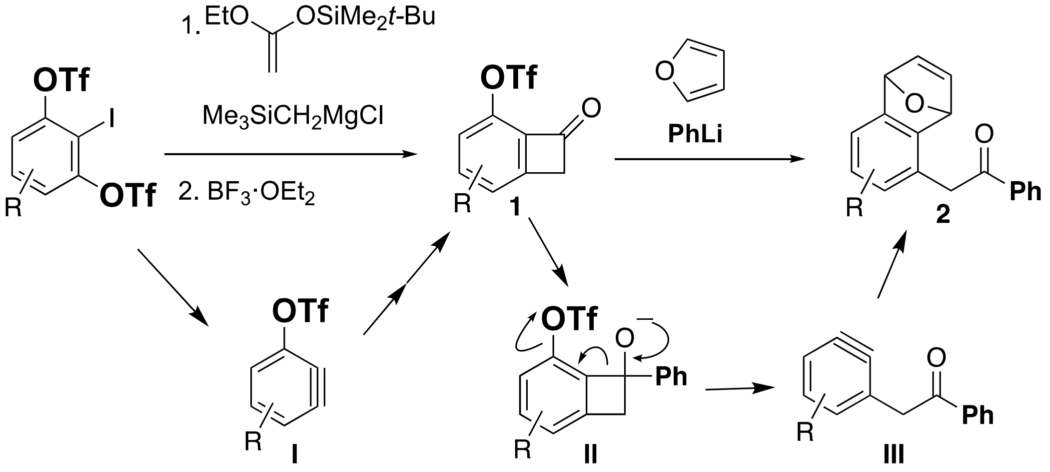
Aryne is a highly reactive intermediate useful in constructing complex aromatic compounds.[1] Previously, we disclosed an efficient generation method of 3-triflyloxyarynes **I** from 1,3-bis(triflyoxy)-2-iodoarenes using a trimethylsilylmethyl Grignard reagent. Various transformations via 3-triflyloxyarynes **I** enabled an efficient synthesis of a wide range of aryl triflates including benzocyclobutenones bearing a triflyloxy group.

During the course of the study to transform the products to benzocyclobutenols via the addition of organometallic reagents, we found that an aryne intermediate was generated efficiently via C–C bond cleavage of the four-membered ring. For example, the treatment of a mixture of benzocyclobutenones **1** and furan with phenyllithium provided three component-coupled α-aryl ketone **2** in high yield. Generation of arynes by this method allowed for modular synthesis of multisubstituted arenes from a variety of benzocyclobutenones, organolithium reagents, and arynophiles. In addition, mechanistic studies indicate that the reaction proceeds via generation of aryne **III** triggered by the carbon–carbon bond cleavage of benzocyclobutenoxide intermediate **II**, which led us to find a fluoride-mediated aryne generation method from triflyloxy-substituted benzocyclobutenone silyl acetal precursors.[3]



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Direct and divergent *N*-glycofunctionalization of amides utilizing halogenated azolium salts

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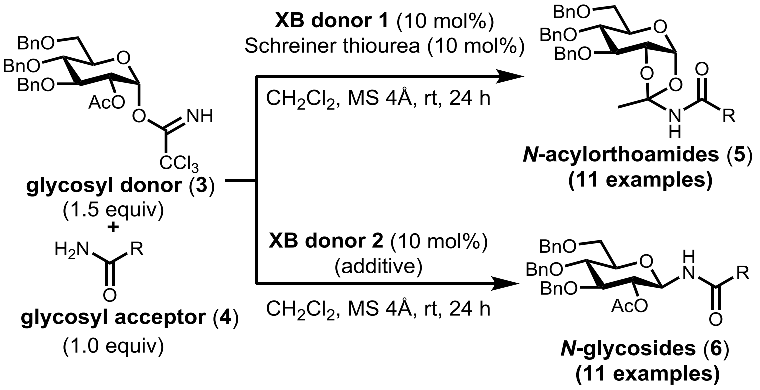
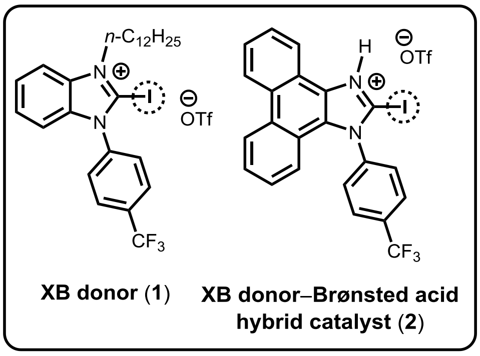
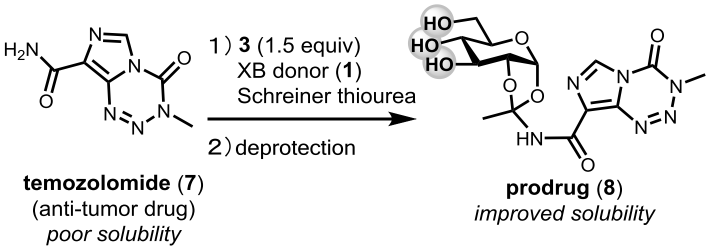
N-Glycosides are found in various pharmaceuticals, biologically active compounds, and natural products. However, synthetic methodologies for *N*-glycosylamides are not as well developed as those for nucleosides or *O*-glycosides. Among the reported synthetic methods for *N*-glycosylamides, direct *N*-glycosylation of amides is the most straightforward but challenging approach because of the poor nucleophilicity of the amides, and only limited catalytic conditions have been reported to date.[1]

During the course of the investigation on the halogen-bond (XB)-donor organocatalysis,[2] we found two types of direct *N*-glycofunctionalization of amides; 1) unique *N*-acylorthoamides (**5**) were obtained from Schmidt glycosyl donor (**3**) and various amides through Schreiner thiourea-XB donor (**1**) co-catalysis, and 2) the desired *N*-glycosides (**6**) were obtained from the same glycosyl donor (**3**) utilizing newly developed XB donor-Brønsted acid hybrid catalyst (**2**).[3]





The methodologies are particularly useful when the compound to be functionalized has only an amide group for a traceless modification. For example, the anticancer drug temozolomide (**7**) can be transformed into the corresponding *N*-acylorthoamide. After deprotection of the benzyl group of the product, the corresponding triol (**8**) was found to be soluble in protic solvents, such as methanol, while **7** itself is almost insoluble.



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[3] *to be Submitted.*

Lead Optimization of 2-Aminobenzothiazoles as Inhibitor of 3D Polymerase against Foot-and-Mouth Disease (FMD)

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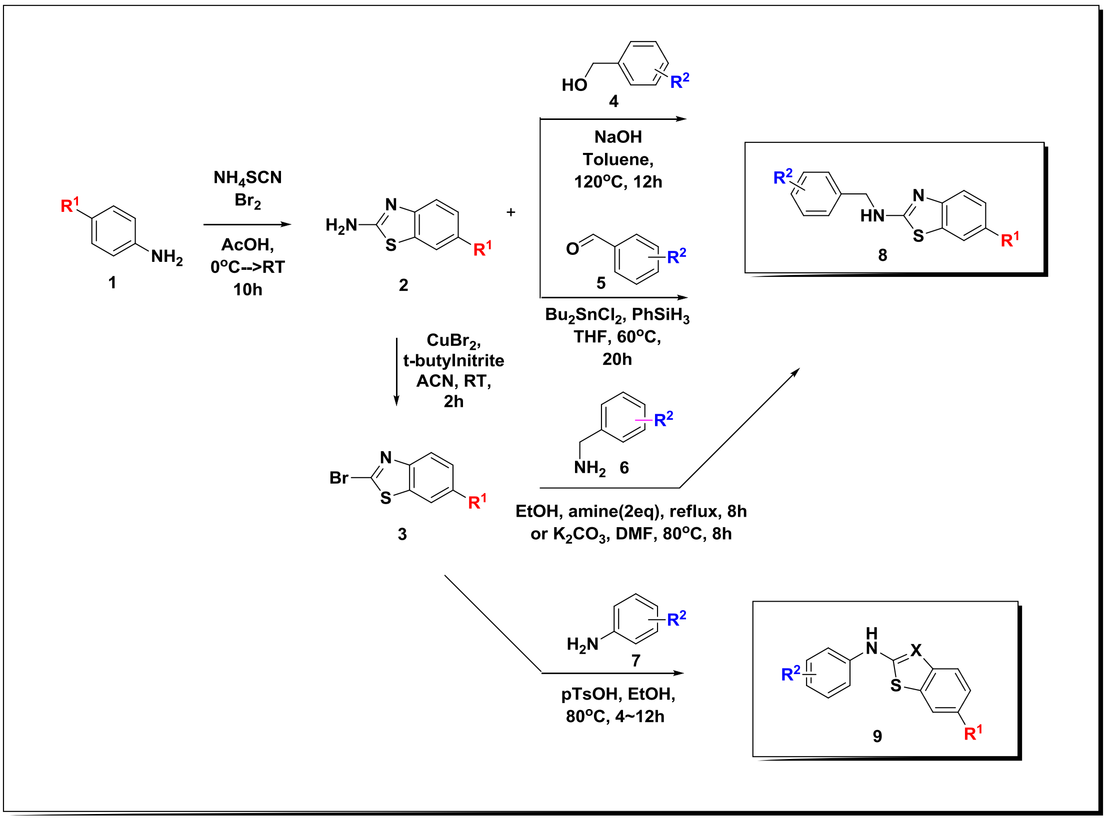
Foot-and mouth disease (FMD) has been described as the most contagious disease of livestock, such as cloven-hoofed animals. Because of its high morbidity and rapid spread to other animals, outbreaks of FMD have caused severe social and economic losses of stockbreeding. From the aspect of a drug target against Foot-and-mouth disease virus (FMDV), we chose 3D polymerase (non-structural protein) which is used to develop potent antiviral drugs because of their essential role in the viral life cycle. Inspired from 2-amino-4-arylthiazole which we had primarily studied, we modified its structure into 2-aminobenzothiazole via structure-activity relationship (SAR) as a second generation. The drug profiles including cytopathic effect (CPE; EC_{50}), selectivity index, physicochemical properties (i.e. pKa, LogP, S_k, S_{eq}, PAMPA), pharmacokinetic parameter (i.e. $t_{1/2}$, F, C_{max} and T_{max} etc.) and toxicity were provided for in-vivo model. We observed that 2-aminobenzothiazole (9u,BAMTI-299) increased survival rates of C57/BL6 mouse infected by the FMDV Asia1/Sharmir strain comparing with PBS control.



Scheme 1.General preparation of 2-Aminobenzothiazoles

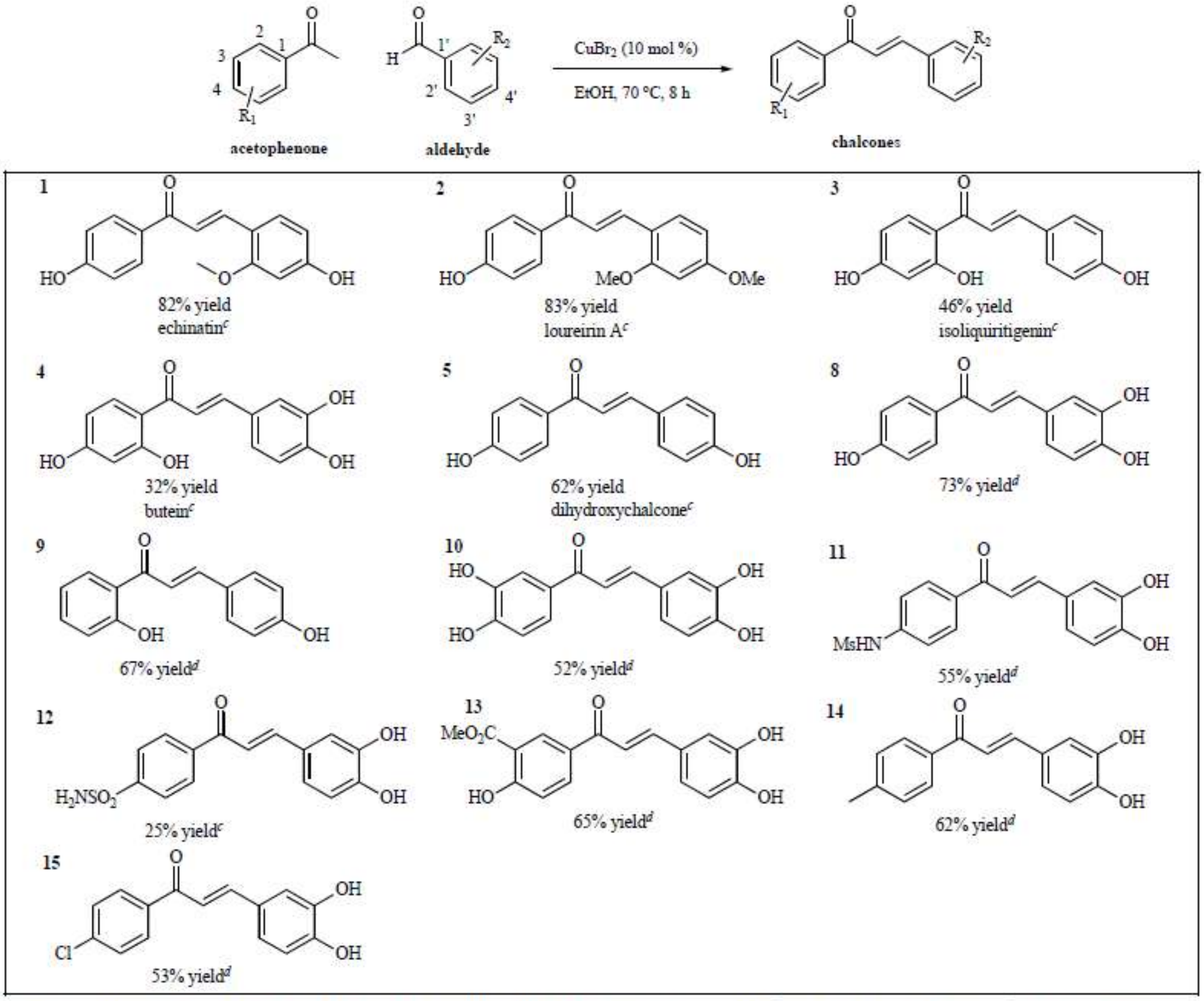
Cu(II) Mediated Chalcone Synthesis *via* α-bromocarbonyl Intermediate: A One-Step Synthesis of Echinatin

Jung-hun Lee[1], Dae-Youn Jeong[1], Seung-Young Jung[1], Sukchan Lee[3], Kye Won Park*[2] and Jin-Mo Ku*[1]

[1]Natural Product Research Team, Gyeonggi Bio-Center, Gyeonggi Institute of Science and Technology Promotion, 147 Gwanggyoro, Yongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea; [2]Department of Food Science and Biotechnology, Sungkyunkwan University,Suwon 16229, Republic of Korea [3]Department of Genetic Engineering, Sungkyunkwan University, Suwon, 16419, Republic of Korea

Since introduction of chalcones in 1899, chalcones have been considered as precursors of flavones in the biosynthesis of flavonoids. However, because the chalcones include multi-functional groups on aromatic rings, developments of efficient synthetic methodologies as well as synthetic strategies involving protection/deprotection should be considered.

Table 1. Scope of reaction and synthesis of natural products.



^{a}Reaction conditions: acetophenone (0.5 mmol), aldehyde (0.5 mmol), $CuBr_2$ (10 mol %) in ethanol at 70 °C for 8 h. ^{b}Isolated yields. ^{c}Natural products. ^{d}Synthetic compounds.

Biomimetic Synthesis of Thebaine via an Anodic Aryl-Aryl-Coupling

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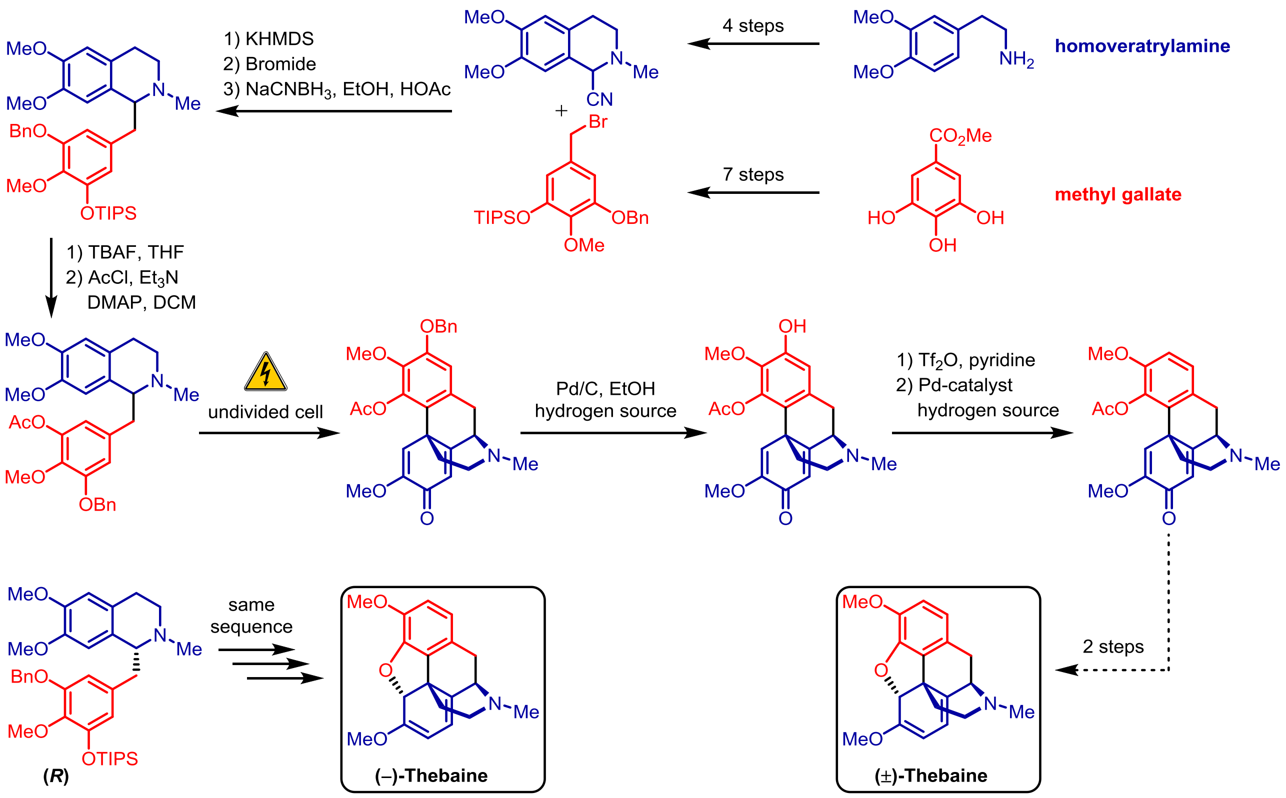
Department of Chemistry, Johannes Gutenberg-Universität, Mainz (55128), Germany.

Thebaine, a biosynthetic precursor of morphine, is used as starting material for the industrial semisynthetic production of multiple important drugs such as oxycodone, naloxone or buprenorphine and is thus unarguably of outstanding relevance for medicinal chemistry.[1] The key-step in the biosynthesis of thebaine and morphine is the intramolecular oxidative aryl-aryl-coupling of (*R*)-reticuline.[2] For decades, chemists have attempted to mimic this oxidative coupling using conventional chemical oxidants. However, their approaches were of limited success as they suffered from poor to moderate yields, required stoichiometric amounts of (often toxic and transition-metal based) oxidants and typically gave rise to mixtures of coupling products due to the lack of regio-selectivity in the aryl-aryl-coupling.[3] Based on the pioneering work of Schäfer,[4] we are currently developing a biomimetic approach to thebaine using an anodic, regio- and diastereoselective aryl-aryl-coupling of 1-benzyltetrahydroisoquinolines which are synthesized from inexpensive and naturally occurring starting materials.



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N-Cyanomethyl quaternary salts, *o*-hydroxybenzaldehydes and nucleophiles in synthesis of imidazo[1,2-*a*]pyridines annulated with chromene moiety

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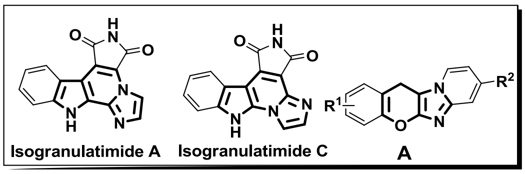
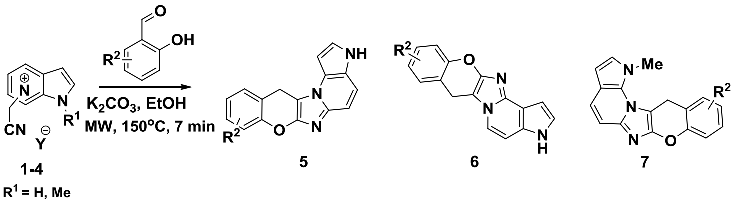
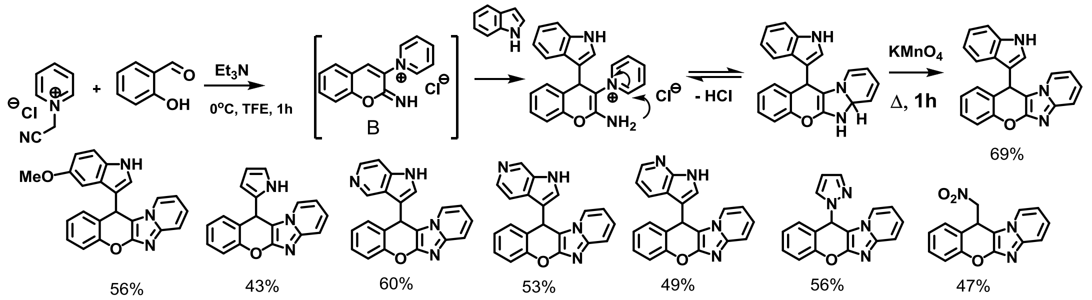
An imidazopyrrolopyridine fragment appears in the marine natural products isogranulatimides, isolated from the Brazilian ascidian *Didemnum granulatum*, which show high inhibitory activities against the G2 DNA damage checkpoint, the kinases Chk1 (IC50 = 0.1 μM) and GSK-3 beta and various other kinases[1]. The current project involves the preparation of imidazopyrrolopyridines fused with a chromene moiety through a base-promoted domino reaction of isomeric *N*-(cyanomethyl)azaindolium salts with *o*-hydroxybenzaldehydes, creating imidazole and pyran cycles in an effective manner[2].





Imidazoles annulated with chromenes **A** have recently been characterized as cytotoxic agents against HCT116 cancer cells due to their ability to induce cell cycle arrest and apoptosis without significant effects on normal cells[3]. Due to the useful biological activity of chromenoimidazopyridines **A** we decided to broaden the scope of such compounds through the introduction of different substituents at the methylene group. This has been successfully realized. At first step we generated iminochromenes **B**[4] and then added different nucleophilic agents such as indoles, azaindoles, pyrolle and nitromethane followed by an oxidant.



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Synthesis of a modular system for major groove sequence-selective DNA recognition

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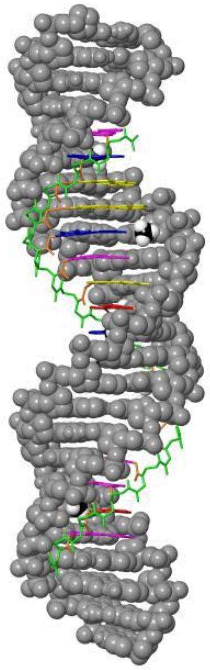

Nucleic Acid Recognition is a fundamental biological process. It is the basis of Central Dogma of Molecular Biology which allows for the flow of genetic information across all living organisms. Nature generally uses four different avenues for DNA recognition: intercalation into base pairs,[1] unspecific binding to the sugar phosphate backbone and minor[2] as well as major groove insertion.[3] For the purpose of addressing a specific gene, a ligand must be directed towards the minor or major groove, because here the base sequence becomes freely accessible - and readable.

Numerous efforts have been previously made towards achieving the goal of DNA recognition. However, they suffer from limitations like invasion of Duplex DNAs[4] due to extraordinary thermodynamic stability of the triplex, limited recognition up to only 7-10 base pairs [5,6], or being exclusive only to homopurines[7]. There exists therefore, necessity of creating a modular system which can bind sequentially to any given number of base pairs of a gene, specifically in the major groove of DNA.

We therefore, envisage the construction of synthetic sequence-selective Heterocyclic DNA ligands which operate by general base-pair recognition inside the major groove, thus providing a tool for Gene-specific manipulation of DNA. We intend to synthesize 4 hydrogen bonding ligands which would form a triplex with the each natural base pair (AT-, TA-, CG- and GC-) in a perpendicular orientation, fitting snuggly into the major groove side of base pairs respectively. These new ligands are intended to be covalently fused to a template strand, which directs the whole recognition module inside the major groove.

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Microporous organic polymers embedded with magnetic Co/C nanobeads and transition metal nanoparticles as recyclable multifunctional catalysts

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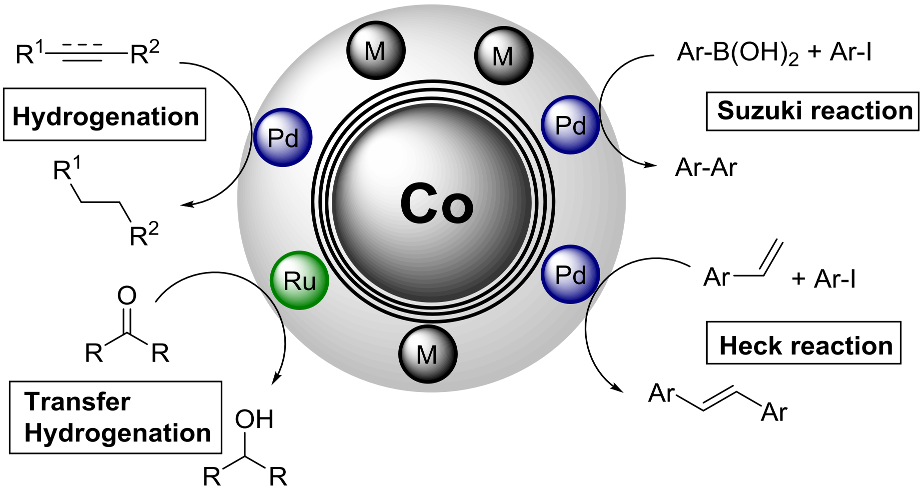
Microporous organic polymers (MOPs) embedded with metal nanoparticles (NPs) show a high potential with respect to their use in catalytic applications.[1,2] On the one hand, the polymer preserves the NPs from agglomeration or deactivation and, on the other, their size controlling effect positively influences the formation and homogeneous distribution of metal NPs over the MOPs.[2,3]
In this work, MOPs grown on magnetic carbon-coated cobalt (Co/C) nanobeads and are used after the incorporation of metal NPs. The overall effectiveness of the novel catalysts were evaluated regarding activity, stability, and especially, recyclability. Therefore, several reactions were chosen as model reactions, resulting in a good activity of the catalysts for several consecutive runs, displaying a low metal leaching and high recyclability of the catalysts. The developed catalytic systems were successfully applied in several cross coupling reactions such as Heck and Suzuki reactions, various hydrogenation reactions including a wide range of different substrates, as well as transfer hydrogenations of aromatic carbonyl compounds.



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Visible light mediated generation and trapping of vinyl radicals derived from α-halo chalcones and cinnamates

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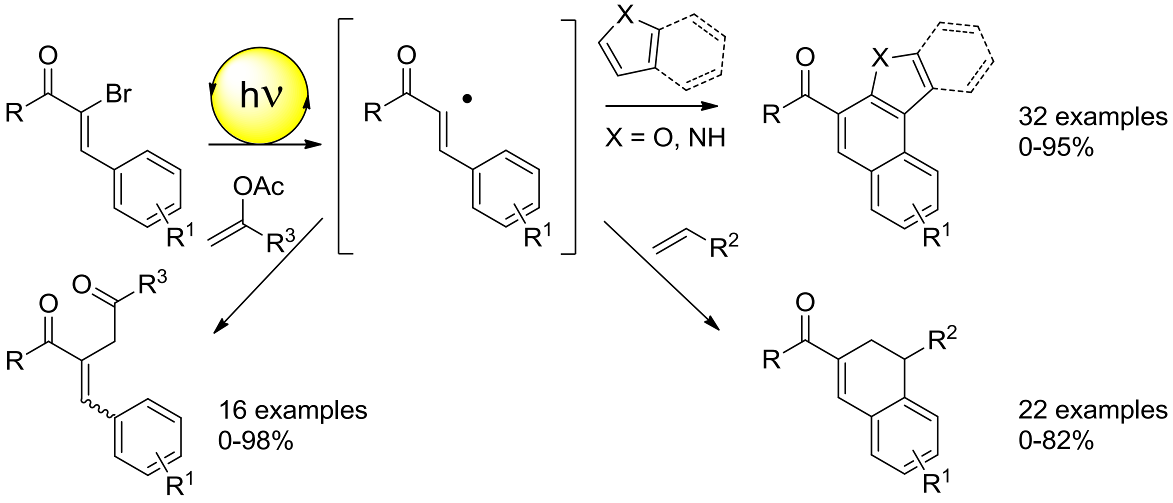
A photochemical approach for the generation of vinyl radicals is presented. Whereas previous reports were predominantly based on harsh and economically unfriendly reaction conditions which included highly toxic reagents like $SnBu_3H$ and AIBN,[1,2] we herein present a mild and environmentally benign protocol generating vinyl radicals derived from vinyl halides.[3-5] Using well established photoredox catalysts, these highly reactive radicals are easily accessible *via* SET (SET = single electron transfer) from bench stable precursors like α-bromo chalcones or α-chloro cinnamates. Careful trapping with a large set of different substrates gives access to powerful transformations and unprecedented bond formations.



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A Nef/Perkow access to imidazoles

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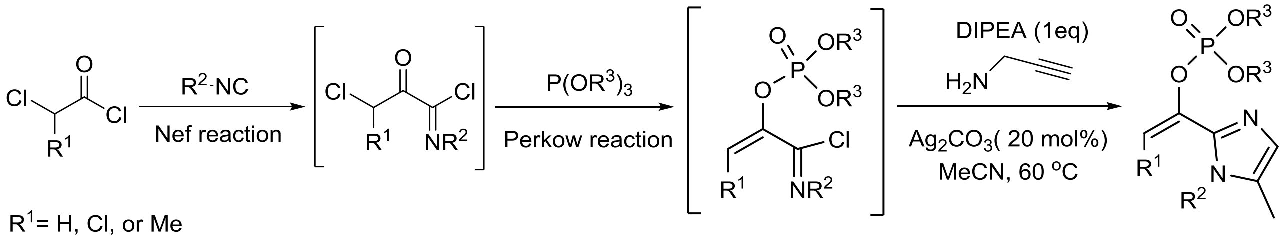
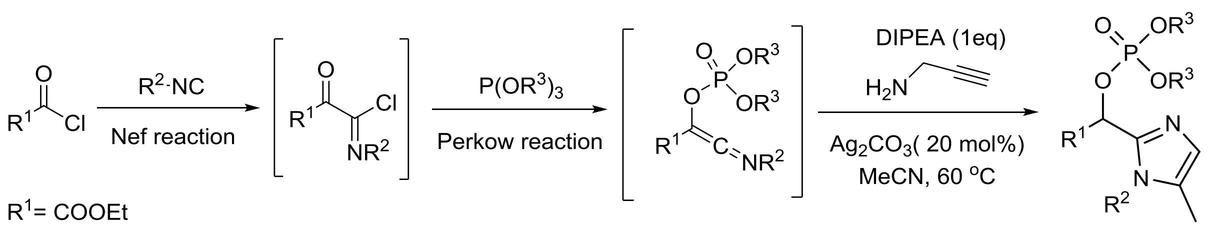
We report an efficient synthesis of imidazolyl vinyl phosphate and imidazolyl phosphate derivatives via a one-pot sequential four-component reaction. The addition of isocyanides to acyl chlorides (Nef reaction) [1] leads to imidoyl chlorides which can later be treated with trialkylphosphites in a Perkow-type reaction. [2] The outcome of this reaction step depends of the nature of the starting acyl chloride.

For acyl chlorides possessing chloride atoms at the 2 possition, the vinyl phosphate derivatives are obtained. However for acyl chlorides substituted by esters, the Perkow step leads to the formation of ketenimines phosphates. [3]

Vinyl phosphate imidoyl chlorides and ketenimine phosphates obtained in Nef/Perkow sequence may be easily converted to imidazolyl vinyl phosphate and imidazolyl phosphate derivatives under addition of propargyl amine in basic condition and in the presence of silver carbonate as a catalyst at 60℃.





We are currently exploring the potential addition of othere nucleophiles to these Nef-Perkow phosphate intermediates.

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Study on the photochemical decarboxylation of Asp and Glu derivatives: Optimized conditions and substrate scope

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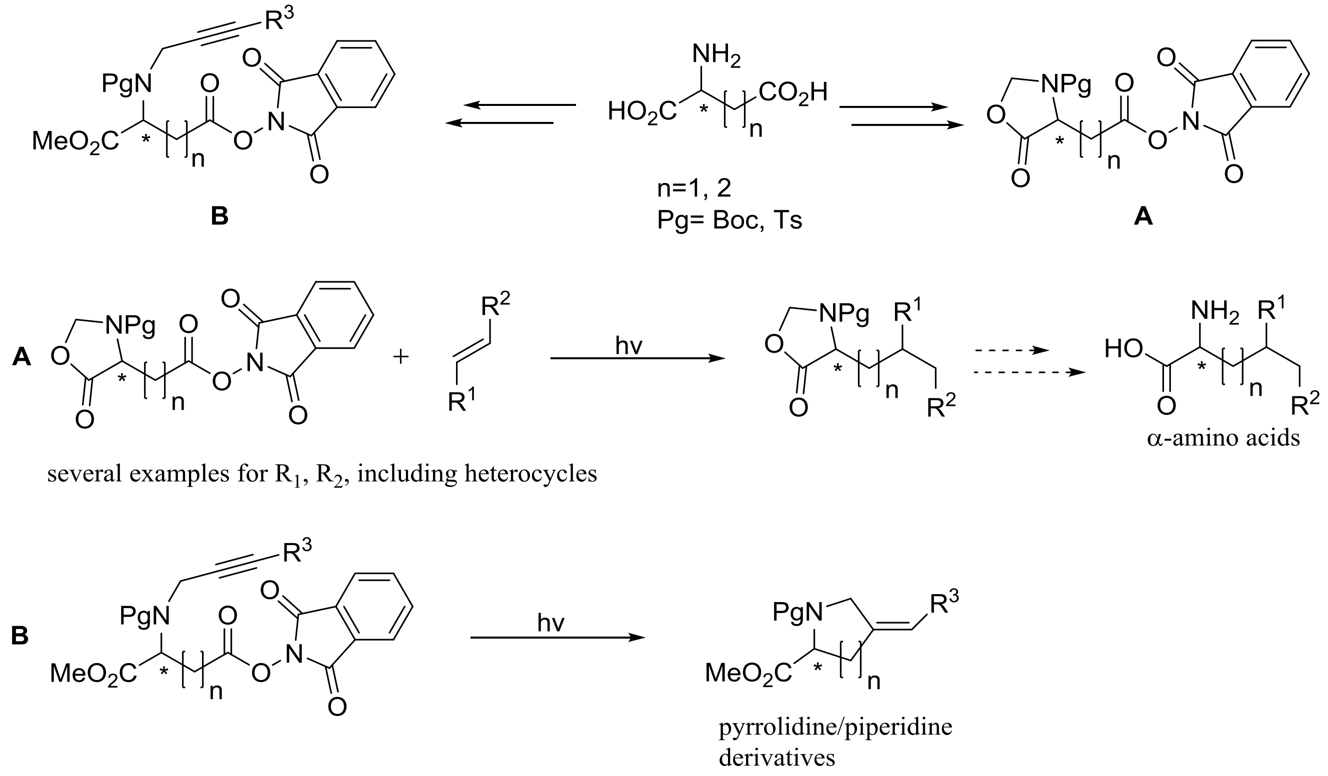
A study on the photochemical β/γ decarboxylation of aspartic/glutamic acid derivatives is presented. Therefore, the primary carboxylic acid was activated as N-acyloxyphthalimide[1-3], which undergoes decarboxylation upon visible light irradiation in the presence of a catalyst and a sacrificial electron donor. After decarboxylation, inter and intramolecular reactions of the resulting radical are feasible, depending on the structure of the derivatives. Hence, the reaction conditions were closely examined, and a variety of intra- and intermolecular reactions were tested with suitable aspartic/glutamic acid derivatives[4] to synthesize (un)natural amino acids or pyrrolidine/piperidine derivatives from inexpensive and abundant starting materials. Noteworthy, the stereocenter of the starting amino acid is conserved in the product.



Scheme 1: Synthesis of suitable precursors and intermolecular reaction of Glu and Asp derivatives upon visible light mediated decarboxylation.

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Ammonium ylide mediated synthesis of enantioenriched 2,3-dihydrofurans

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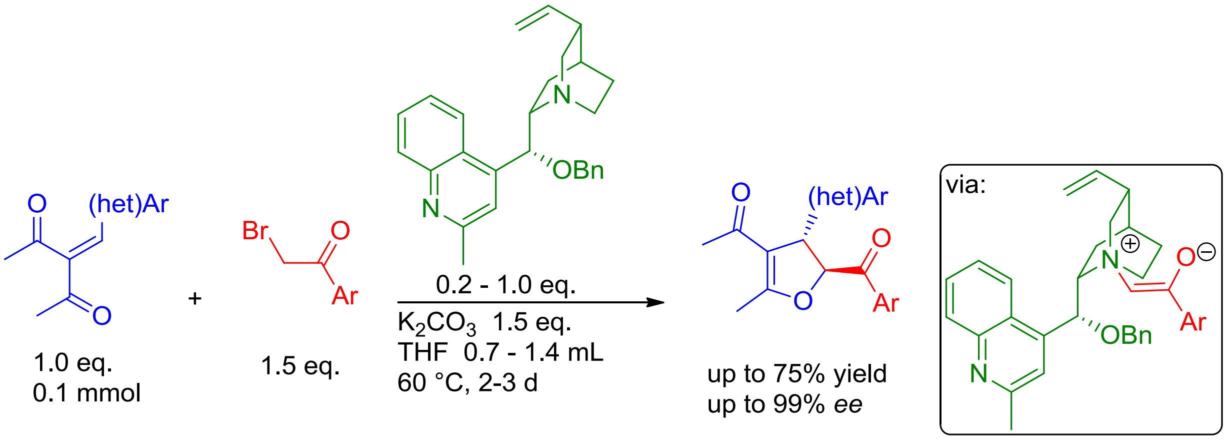
The application of ammonium ylides in asymmetric synthesis is rather limited in comparison to phosphorus or sulfur ylides. [1] Yet, a couple of transformations based on pyridinium and DABCO derived ylides leading to highly functionalized, racemic products have been described. [2] Chiral ammonium ylides were also used in asymetric [4+1] annulation reactions. [3]

Our research focuses on the development of novel methods for the generation of enantioenriched substances via chiral ammonium ylides. As a model reaction, we investigated the formation of tetrasubstituted 2,3-dihydrofurans. Employing modified cinchona alkaloids and cheap, commercially available phenacyl bromide or its derivatives, in combination with arylidendicarbonyl compounds gave access to the desired target molecules. The reactions proceeds via ammonium salt and ylide formation through a base, 1,4-addition and subsequent 5-*exo*-tet cyclization to exclusively yield the *trans*-2,3-dihydrofurans in up to 75% with good to excellent enantioselectivity.



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[2] (a) C. D. Papageorgiou, S. V. Ley, M. J. Gaunt, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 828. (b) C.-P. Chuang, K.-P. Chen, *Tetrahedron* **2012**, *68*, 1401. (c) M. J. Gaunt, C. C. C. Johansson, *Chem. Rev.***2007**, *107*, 5596. (d) K. Jiang, Y.-C. Chen, *Tetrahedron Lett.* **2014**, *55*, 2049.

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Pd-Catalyzed Heck Type Arylation of Alkenes with 1,5-Azastibocines

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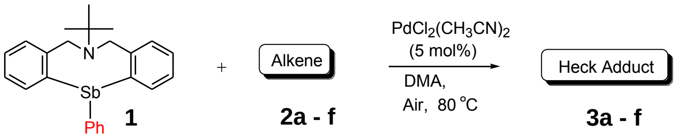
The Mizoroki-Heck reaction, Pd-catalyzed coupling reaction of alkenes with aromatic halides or triflates, have become a standard method for C-C bond formation in organic synthesis. The typical conventional reaction requires high temperature and prolonged heating with a base. In order to avert these drawbacks, various surrogates for aromatic halides have been investigated using highly reactive organometallic agents, such as boronic acids, arylsilanoles, organostannanes. [1]

As part of our continuing studies on organoantimony compounds[2], we have investigated Pd-catalyzed Mizoroki-Heck type arylation of alkenes with Sb-aryl-1,5-azastibocine (**1**) which is highly reactive *pseud*-hypervalent organoantimony compound with intramolecular N-Sb interaction.

Screening of various Pd catalysts and solvents was undertaken using **1** and methyl vinyl ketone (**2a**), which revealed that the reaction of **1** with **2a** gave Heck adduct (**3a**) in desirable yield (84%) under $PdCl_2(CH_3CN)_2$ (5 mol%) catalyst in DMA. Various aryl groups, other than phenyl substituents, were also coupled with **2a** in good yields using **1** bearing various aryl groups.

Table 1. Reaction of 1,5-azastibocine with various alkenes



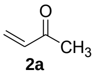
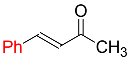
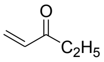
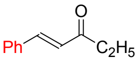
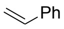
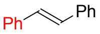
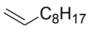
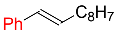
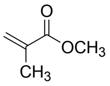
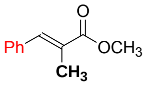
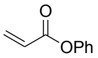
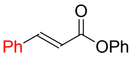
Entry	Alkene	Time (h)	Product	Yield (%)
1	 **2a**	6	 **3a**	84
2	 **2b**	5	 **3b**	87
3	 **2c**	3	 **3c**	70
4	 **2d**	12	 **3d**	76
5	 **2e**	5	 **3e**	62
6	 **2f**	9	 **3f**	77

Table 1 shows the results of the reaction of **1** with various alkenes. Enones (**2a, b**) were good substrates to give the adducts (**3a, b**) in high yields (entries 1, 2). Aromatic and aliphatic alkenes (**2c, d**) were applicable affording **3c, d** in good yields (entries 3, 4). Enoates (**2e, f**) also underwent arylation to gave the adducts (**3e, f**) in good yields (entries 5, 6).

Advantageous is that the reaction proceeds without a base in an ambient atmosphere under relatively mild condition.

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Application of Epoxy and Aziridinyl Enolsilanes in Dearomative (4+3) Cycloadditions

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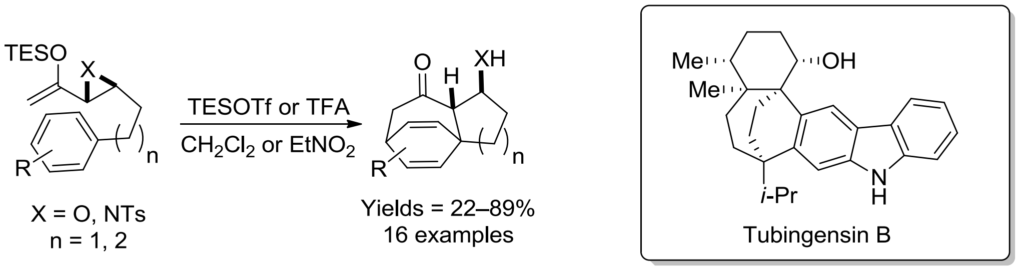
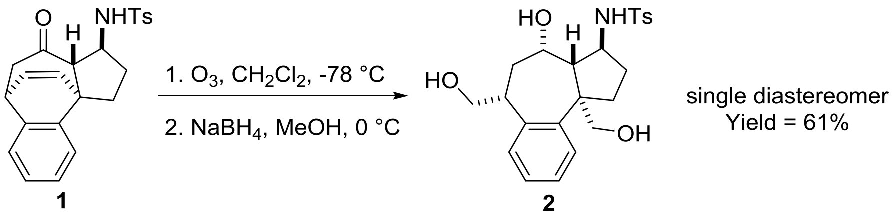
We have been using vinyl epoxide and aziridine derivatives, namely epoxy and aziridinyl enolsilanes, as dienophiles for diastereoselective (4+3) cycloadditions. They react with a wide range of dienes, including furans and pyrroles, to generate high yields of heterocycles embedded in seven-membered rings. This reaction has been applied to the synthesis of various heterocyclic bioactive molecules, such as cortistatin A.

Under suitable conditions, carbocyclic arenes also undergo (4+3) cycloaddition as dienes with epoxy/aziridinyl enolsilanes (Scheme 1). This intramolecular reaction, in effect a dearomatization, is surprisingly facile, and occurs even on benzene derivatives. The scope and the mechanism of the reaction have been studied. This dearomative cycloaddition may be applicable to the synthesis of polycyclic natural products such as tubingensin B.



Scheme 1

The olefin bridge of cycloadduct **1** can be cleaved under reductive ozonolysis to afford polycyclic triol **2** as a single diastereomer (Scheme 2). This demonstrates the potential of the dearomative (4+3) cycloaddition to synthesize bridged and non-bridged polycycles alike.



Scheme 2

Ling, J; Lam, S; Low, K.-H.; Chiu, P. *Angew. Chem., Int. Ed.* **2017**, *56*, 8879–8882.
Lam, S. K.; Lam, S.; Wong, W.-T.; Chiu, P. *Chem. Commun.* **2014,** *50* (14), 1738-1741.
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Kinetics and Mechanism of Oxirane-Formation by Darzens Condensation of Ketones

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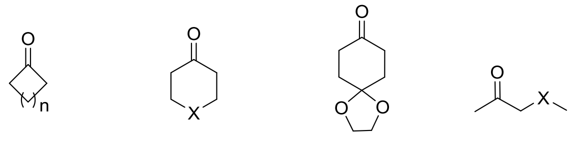
In order to quantify the electrophilic reactivities of aliphatic ketones (Scheme 1), we measured the rates of their reactions with arylsulfonyl-substituted halomethyl anions photometrically in DMSO at 20 ºC (Scheme 2).

Scheme 1. Cyclic Ketones 1a-h and Acyclic Ketones 1i-j



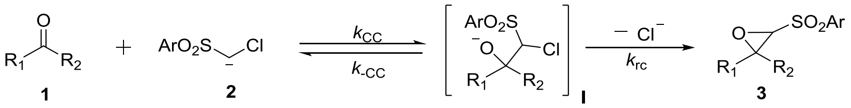
n=1 (**1a**)
n=2 (**1b**)
n=3 (**1c**)
n=4 (**1d**)

X=NMe (**1e**)
X=O (**1f**)
X=S (**1g**)

(**1h**)

X=CH_2 (**1i**)
X=S (**1j**)

Scheme 2. **Mechanism of the Reactions of Arylsulfonyl-Substituted Halomethyl Anions with Ketones**

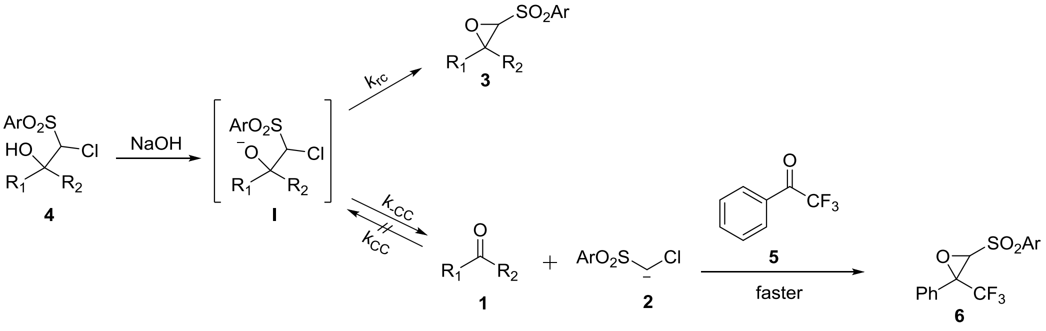


$$d[\mathbf{2}]/dt = -k_2^{\mathrm{exp}}[\mathbf{1}][\mathbf{2}] = -k_{\mathrm{CC}}[\mathbf{1}][\mathbf{2}]/(k_{\mathrm{-CC}}/k_{\mathrm{rc}} + 1) \quad (1)$$

$$\log k = s_{\mathrm{N}}(N + E) \quad (2)$$

We performed crossover experiments as described in Scheme 3 to elucidate the rate-determining step of this reaction cascade. For that purpose, the independently synthesized halohydrin **4** was treated with NaOH in the presence of a more reactive ketone **5**. The formed intermediate **I** then has the choice either to undergo ring closure with formation of the epoxide **3** or retroaddition with regeneration of **1** and **2**. As **5** is considerably more reactive than **1**, the carbanion **2** will exclusively be converted into the crossover product **6**, i.e. the ratio [**6**]/[**3**] equals the ratio $k_{\mathrm{-CC}}/k_{\mathrm{rc}}$. By combination of the measured second order rate constant k_2^{exp} with the ratio $k_{\mathrm{-CC}}/k_{\mathrm{rc}}$ according to eq 1, we can determine k_{CC}, the rate constant for the attack of **2** at the ketones **1**. By substitution of k_{CC} and the published parameters N and s_{N} for **2** into eq 2, it was possible to derive the electrophilicity parameters E of the ketones **1**. DFT calculations revealed a decent correlation of the electrophilicity parameters E with the methyl anion affinities calculated for DMSO solution.

Scheme 3. Crossover Reaction



[1] Li, Z.; Chen, Q.; Mayer, P.; Mayr, H. *J. Org. Chem.* **2017**, 82, 2011−2017.

[2] For a comprehensive database of nucleophilicity parameters N and s_{N} as well as electrophilicity parameters E, see http://www.cup.lmu.de/oc/mayr/DBintro.html.

Rational Design of Ready-to-Shape New Classes of Organo-Photocatalysts

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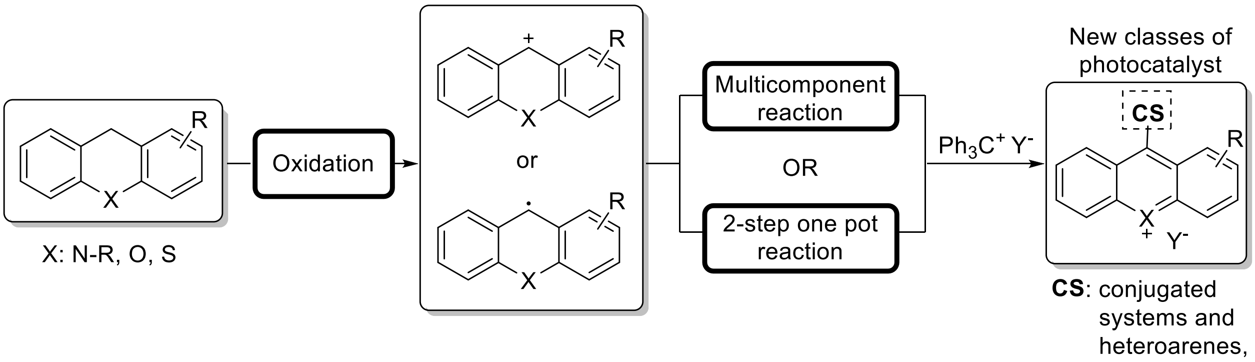
Over the past last decade, the renewed interest around photoredox catalysis resulted in a continuous flux of many valuable light-induced synthetic transformations.[1][2] Even though there are several advantages of a photoredox-mediated approach respect to standard thermal processes, most common catalysts are based on expensive nobel transition metals, such as iridium and ruthenium.[1] Moreover, they might contaminate the products, which is especially undesirable in the synthesis of pharmaceuticals. Thus, the use of organo-photocatalysts represents a valuable and attractive alternative, mainly because organic dyes are cheaper, harmless and easy to handle than the corresponding metal-based photocatalysts.[2] As follows, it is evident the advantage coming within the employment of such organic photosensitizers, but the exiguous variety of structures, which are based essentially on fluorescein, rhodamine, eosin and 9-mesityl-10-methylacridinium salt platforms, limit the possible applications. For this reason, new classes of organo-photocatalysts are highly demanding to both discover new synthetic solutions and improve the performance in standard catalytic photoredox reactions.

Following this perspective, we present herein several innovative one-pot strategies to achieve new classes of easily tunable and ready-to-shape (thio)xanthene or acridine-based photocatalysts, in which a Csp^3-H oxidative functionalization is involved as key step of the synthetic approach.[3][4] Furthermore, to show the potential and the versatility of such new structures, various applications in photoredox-catalysis are reported.



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Regioselective Transformation of Azido to Diazo Group

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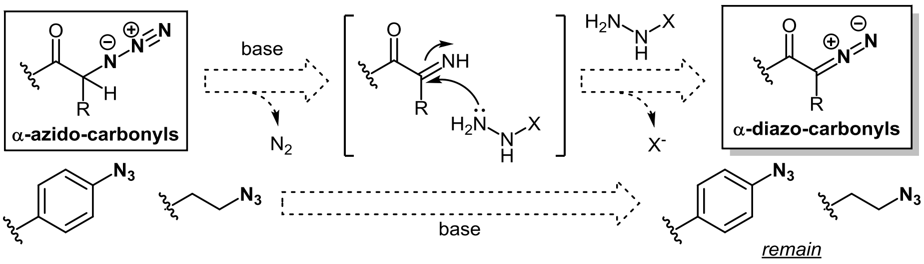
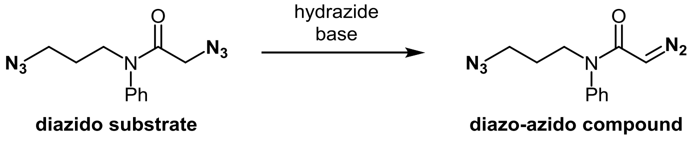
Azido group has been well used in wide research areas due to its valuable reactivity. Especially, azide-alkyne cycloaddition reactions which can combine two components through rigid triazole rings have been applied in chemical biology and polymer chemistry. Toward further development of azide chemistry, multi-azido compounds are attractive as platform molecules for synthesis of multi-functionalized molecules. However, regioselective transformation of specific azido groups in multi-azido molecules is still challenging problem because of the high reactivity. With this background, we designed selective transformation of azido group at α-carbonyl positions to diazo group (Scheme 1). We envisioned that acidic α-proton can proceed nitrogen gas elimination from azido group [1], and the generated imine could be transformed to diazo group thorough formation of hydrazone followed by Bamford-Stevens reaction, while other positions retain the azido moieties. Because diazo group was reported to have different reactivity on click reaction to azido group [2], our regioselective transformation of azido group can lead flexible functionalization using multi-azido compounds.



Scheme 1. Regioselective transformation of azido to diazo group

With tetrabutylammonium fluoride as base, regioselective conversion of azido to diazo group at α-carbonyl was achieved in the presence of alkyl azide (Scheme 2). Addition of pyrrolidine as second base for Bamford-Stevens reaction sequence, the isolated yield of desired product was improved. Comparing amides and ketones, ketones with more acidic α-protons were successfully transformed under mild conditions. With these results, the regioselective transformation reaction of other di-, and triazido substrates was investigated.



Scheme 2. Regioselective transformation of diazido substrate

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Stereoselective Cobalt-Catalyzed Halofluoroalkylation

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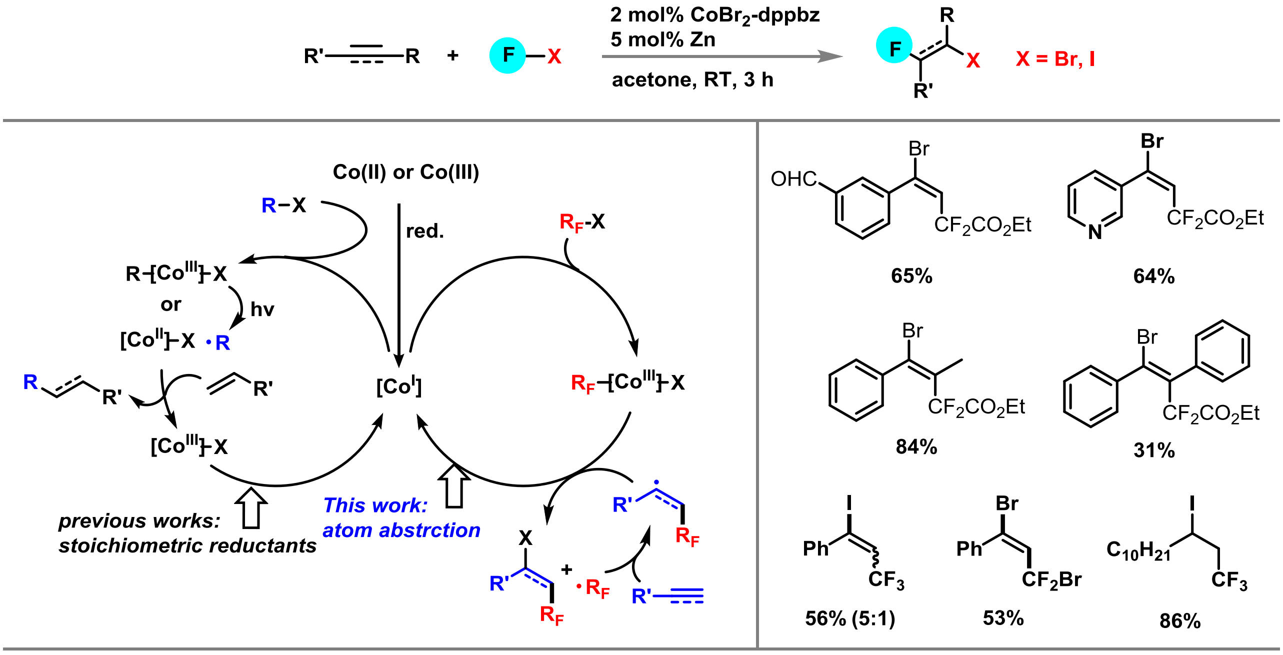
Fluorinated hydrocarbons constitute key structural motifs in many bioactive molecules, agrochemicals, and pharmaceuticals due to their high metabolic stability, lipophilicity, and bioavailability compared with the parent compounds.[1] As a result, the development of efficient process for fluoroalkyl groups introduction has been a significant issue in organic synthesis. An efficient and robust method that operates at mild conditions and low catalyst loading and is applicable to various difluoro and perfluoroalkyl bromides would have considerable use in the synthesis of densely functionalized fluorinated building blocks.

The utility of alkyl halide building blocks in organic synthesis programs has recently been greatly enhanced by the advent of new cross-coupling protocols catalyzed by low-valent metal catalysts (Fe, Co, Ni).[2] Among them, efficient cobalt catalysis has been reported for reductive couplings and Heck-type reactions between alkyl halides and alkenes. Herein, we reported the low-valent cobalt-catalyzed halofluoroalkylation of alkynes, which enabled the highly regio- and stereoselective synthesis of halofluoroalkenes under mild conditions



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[2] a) G. Cahiez, Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435; b) A. Guérinot, J. Cossy, *Top Curr Chem. Lett.* **2016**, *374*: 49; c) T. Iwasaki; N. Kambe, *Top Curr Chem. Lett.* **2016**, *374*: 66.

C-H Functionalization of deazapurine nucleobases

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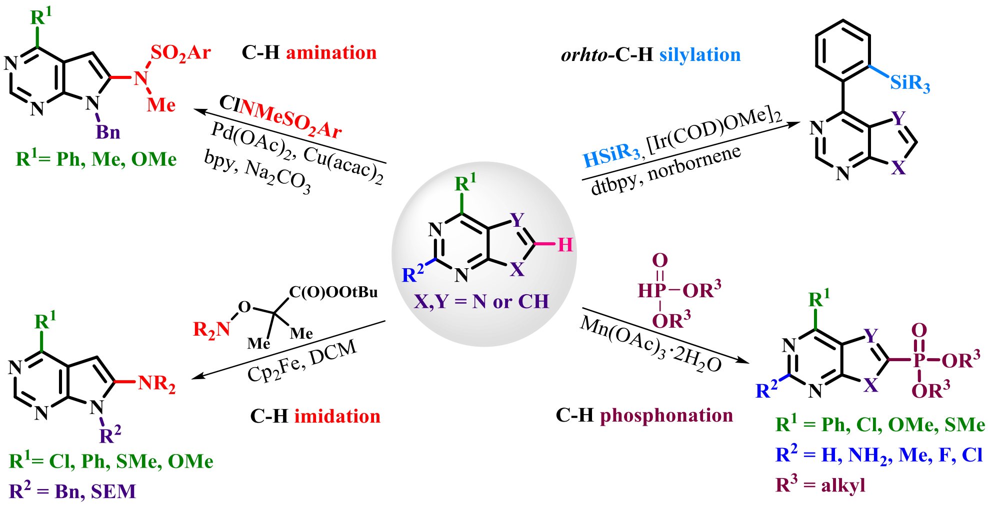
[b] *Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Gilead & IOCB Research Center, Flemingovo nam. 2, CZ-16610 Prague 6, Czech Republic*
e-mail: sabat@uochb.cas.cz, hocek@uochb.cas.cz

Modified pyrrolo[2,3-*d*]pyrimidine (7-deazapurine) bases and nucleosides display a variety of biological effects. [1] Therefore, development of chemo- and regioselective synthesis of deazapurines bearing diverse substituents is a worthwhile goal.

Here we report on complementary C-H activation methods for the modification of deazapurine nucleobases. Protocols for selective direct C-H imidation, C-H amination, [2] C-H silylation and C-H phosphonation [3] of deazapurines have been developed (Scheme 1). The scope and limitations of the methods, as well as synthesis of series of multifunctionalized deazapurine bases and their possible further transformations are presented.

Scheme 1



This work was supported by the institutional support of the Charles University and Academy of Sciences of the Czech Republic (RVO: 61388963), by the Czech Science Foundation (P207/12/0205, 16-0011785) and by Gilead Sciences.

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Synthesis and Optical Properties of Novel 1,2,3-Triazole – (7-Deaza)purine Conjugates

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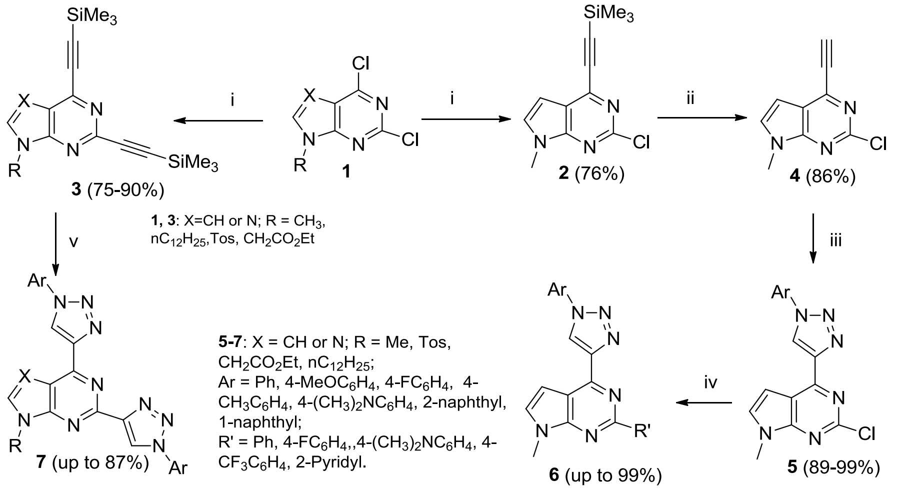
Heterocycles containing 1,2,3-triazole moiety have found application in fields of bioconjugation, material science, chemical sensors, drug discovery and related areas [1]. Recently, we have shown that 2,6-bis(1,2,3-triazol-1-yl)-7-deazapurines exhibit strong fluorescence and are promising candidates as functional materials [2]. In this report we present the synthesis and photophysical properties of novel triazole − 7-deazapurine and purine conjugates.

Synthetic pathway to the target (1,2,3-triazol-4-yl)-7-deazapurines and purines (**6**, **7**) is depicted in Scheme 1.



Scheme 1. *Reagents and conditions*: i -Me_3SiCCH, $Pd(PPh_3)_2Cl_2$, CuI, Ph_3P, Et_3N, 45-50 °C, argon; ii - KF, MeOH, r.t.; iii - Ar-N_3, CuI, DIPEA, AcOH, CH_2Cl_2, r.t., argon; iv - Bu_3SnR', $Pd(PPh_3)_2Cl_2$, $AsPh_3$, dioxane, MW, 180 °C, argon; v - Ar-N_3, KF, $CuSO_4$, Na ascorbate, THF:H_2O:^tBuOH.

Peculiarities of reactivity of (7-deaza)purines (**1**, **5**) in the alkynylation and arylation cross-coupling reactions and fluorescence properties in conjunction with DFT calculations of the synthesized molecules will be discussed.

Acknowledgements

The research was funded by a grant (No. TAP-LLT-01/2015) from the Research Council of Lithuania.

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Halogenation of Dimethyl Indole-2,3-dicarboxylate Using Phenyliodine Diacetate and Alkali Metal Halides

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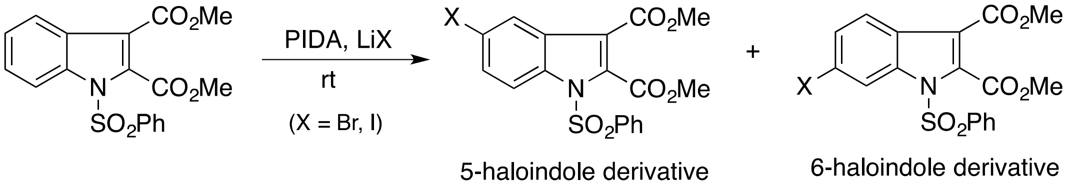
Halogenated indoles with novel biological activities have been found as secondary metabolites of marine organisms. [1] Most bromoindole alkaloids have a bromine atom at the 5- or 6-position. Chae and co-workers reported the selective bromination of dimethyl indole-2,3-dicarboxylate using bromine in the presence of sodium acetate in acetic acid to give dimethyl 5-bromoindole-2,3-dicarboxylate as the sole product. [2] We then investigated the bromination of various *N*-protected dimethyl indole-2,3-dicarboxylates using pyridinium hydrobromide perbromide (PHPB) and bromine in the presence of Lewis acid. Interestingly, the introduction of a protective group on the indole nitrogen affected the selectivity of bromination position, and an electron-withdrawing group resulted in preferential bromination of the 6-position. [3] Here, we investigated bromination and iodination of *N*-protected dimethyl indole-2,3-dicarboxylates using phenyliodine diacetate and alkali metal halide.

Treatment of dimethyl 1-benzenesulfonylindole-2,3-dicarboxylate with a combination of PIDA (1.5 eq) and LiBr (1.5 eq) in the presence of $ZnCl_2$ (2 eq) in CF_3CH_2OH to give a mixture of dimethyl 1-benzenesulfonyl-5-bromoindole-2,3-dicarboxylate (28%) and dimethyl 1-benzenesulfonyl-6-bromoindole-2,3-dicarboxylate (65%).

The reaction of dimethyl 1-benzenesulfonylindole-2,3-dicarboxylate was conducted using PIDA and LiI instead of LiBr in the presence of $BF_3 \cdot Et_2O$ (5 eq) in CH_2Cl_2 to provide a mixture of dimethyl 1-benzenesulfonyl-5-iodoindole-2,3-dicarboxylate (52%) and dimethyl 1-benzene-sulfonyl-6-iodoindole-2,3-dicarboxylate (47%).



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Synthesis of Altersolanol Derivatives

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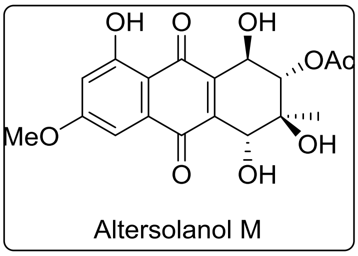
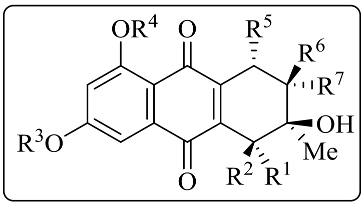
The chemical synthesis of natural antibiotics has been a challenge for many years. One example of bioactive natural products is the polyketide family of tetrahydroanthraquinones - Altersolanols -. [1] In nature Altersolanols and derivatives are a class of secondary metabolites produced in endophytic fungi such as *Alternaria solani* or *Stemphylium globuliferum* and provide the basis of symbiotic interactions between plants and fungus. It protects the plant against microbial infections, bacteria and dryness without having any toxic effects on the eukaryote. [2] Structure determination and antimicrobial activity tests were clarified by Proksch and co-workers in the Heinrich-Heine University of Düsseldorf. [3] A first test has shown that Altersolanol M has an increased antimicrobial activity and the position of the acetate group has a specific importance. [4] This project is focusing on the total synthesis of Altersolanol derivatives and clarification of ring-opening reactions of epoxides by 2D-NMR studies.



Altersolanol M



Altersolanol	R^1	R^2	R^3	R^4	R^5	R^6	R^7
A	OH	H	Me	H	OH	OH	H
B	H	H	Me	H	H	H	OH
C	OH	H	Me	H	H	H	OH
D	OH	H	H	Me	OH	H	OH
E	OH	H	Me	H	OH	H	OH
F	H	OH	H	Me	OH	H	H
G	OH	H	Me	H	Me	H	OH
H	OH	H	Me	H	H	OH	H

We will present our recent findings toward the total synthesis of Altersolanol M and derivatives based on synthesized precursors from Brassard's diene.

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Orthogonal two wavelength regulation by coumarinylmethyl caging groups

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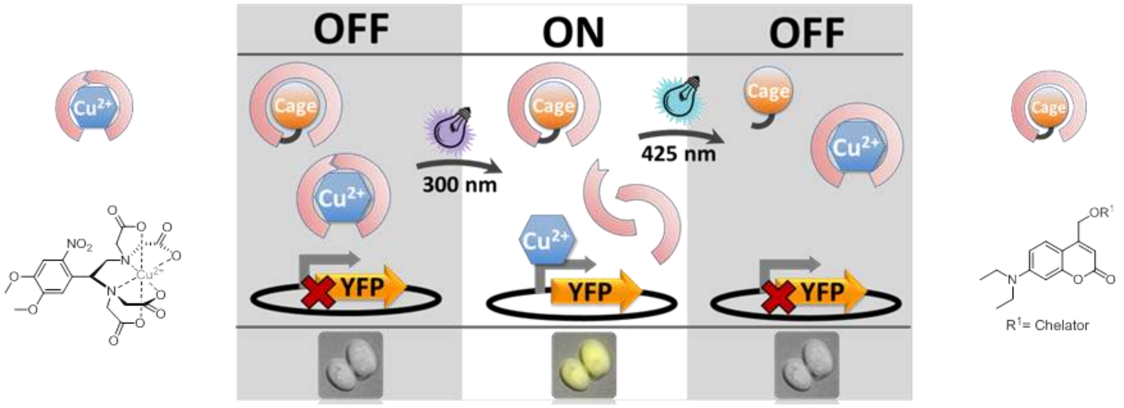
In recent years, the photolytic regulation of cellular functions, also known as optogenetics, proved to be useful in many biotechnological applications. The combination of photolabile protecting groups and small effector molecules enables the masking of their biological activity until the irradiation with light of a specific wavelength releases the caged molecule. [1] We present the utilisation of the versatile photolabile chelator DMNP-EDTA to control Cu^{2+} release upon UV-A irradiation, resulting in the first example of a caged metal ion to regulate recombinant gene expression. [2] We endeavour to cage the previously released Cu^{2+}-ions through use of different chelators. The applied chelators are caged by aminocoumarin derivatives, which can orthogonally be addressed by higher wavelengths. We present the synthesis and characterisation of these coumarin derivatives and the hopeful application in this biological system.



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Tandem One-pot Synthesis of Triaryl Cyclopentenones: Access to Enantioselective Combretastatin A-4 Analogues

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The development of convergent and enantioselective methods for the synthesis of biologically active molecules is of high importance in fields of both synthetic and medicinal chemistry. Cyclopentenones are important structural scaffolds which are extensively found in natural products as well as biologically active molecules, used as versatile synthetic intermediates for the assembly of complex natural products and bioactive molecules,[1] such as cyctotoxic agents Rocaglamide and Chamaecypanone C (Figure 1).[2] Moreover, Among the naturally occurring compounds, Combretastatin A-4 (Figure 1) is one of the best characterized antimitotic agents. When the alkenyl motif of Combretastatin A-4 was replaced by cyclopentenone, the analogues show enhanced activity compared to parent compound.[3]

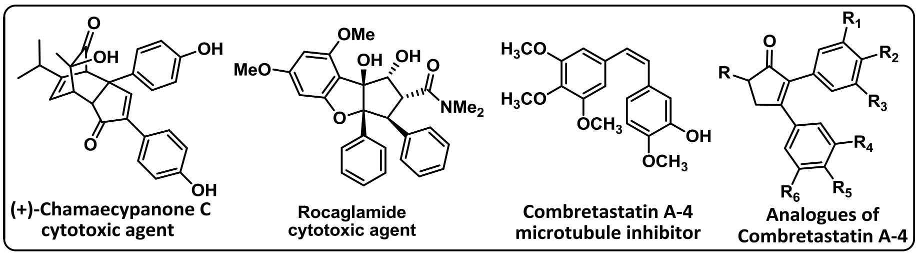
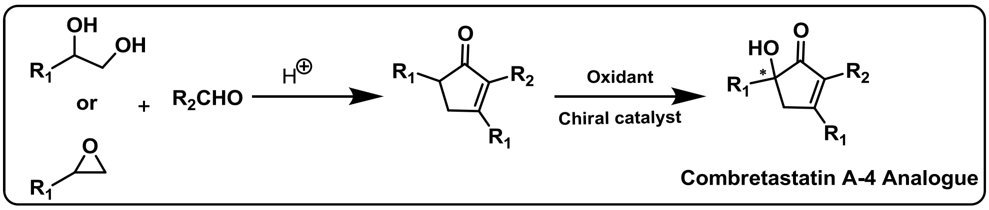


Figure 1. Representative molecules show anticancer activity

We have developed a tandem one-pot method for the facile synthesis of triaryl substituted cyclopentenones (scheme 1).[4] Our synthetic strategy has successfully exploited in the enantioselective synthesis of 5-hydroxy substituted Combretastatin A-4 analogues which displayed promising microtubule inhibitor activity against various cancer cell lines.



Scheme 1. Enantioselective synthesis of 5-hydroxy cyclopentenones

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Development of Electron-Poor Phosphine Ligands Having 1,3,5-Triazinyl Groups

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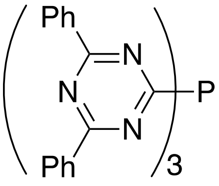
Introduction: Many phosphine ligands developed hitherto are generally more electron-rich than triphenylphosphine (PPh_3) because they promote the oxidative addition. Although electron-poor phosphine ligands are considered to accelerate the reductive elimination, transmetalation, and insertion reaction,1) there is still room to further investigate those ligands. Because 1,3,5-triazine, which is part of the structure of reagents for condensations2) or *O*-alkylations3) developed by us, shows highly π-electron-deficient property, we are interested in reactivity of 1,3,5-triazin-2-ylphosphines as a ligand for metals. However, to the best of our knowledge, there are a few reports of the reactions using triazinylphosphines as a metal ligand, all of which are limited to mono(triazinyl)phosphines.4) Here, we report the synthesis of several types of triazinylphosphines and the use of them as a ligand for the Stille cross-coupling.

Results & Discussion: Tris(4,6-diphenyl-1,3,5-triazin-2-yl)phosphine (**1**) has been successfully synthesized in a good yield (Figure 1). The effect of the triazinylphosphine ligands on the catalytic activity for the Stille cross-coupling reaction was examined. Stille coupling is performed better with less σ-donating ligands such as tri(2-furyl)phosphine [P(2-furyl)$_3$], because the rate-determining step of the reaction is the transmetalation step.5) In the cross-coupling reactions between 4-(trifluoromethyl)iodobenzene and tributyl(phenylethynyl)tin, **1** gave a higher yield compared to those using P(2-furyl)$_3$ and PPh_3 (Scheme 1). The highly electron-withdrawing character of **1** was confirmed by IR spectrum, ^{31}P NMR, and X-ray single crystal structure analysis. In this presentation, we will also discuss the synthesis and ligand activity of other triazinylphosphines.

Figure 1



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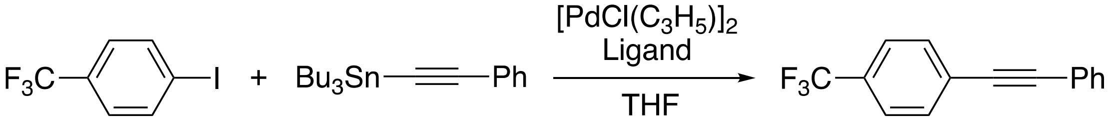
Scheme 1



Ligand	**1**	P(2-furyl)$_3$	PPh_3
Yield (%)	93	57$^{6)}$	1$^{6)}$

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Different Monomers– Containing Microporous Organic Polymers Encapsulated with Pd Nanoparticles and CO/C nanobeads for Hydrogenation

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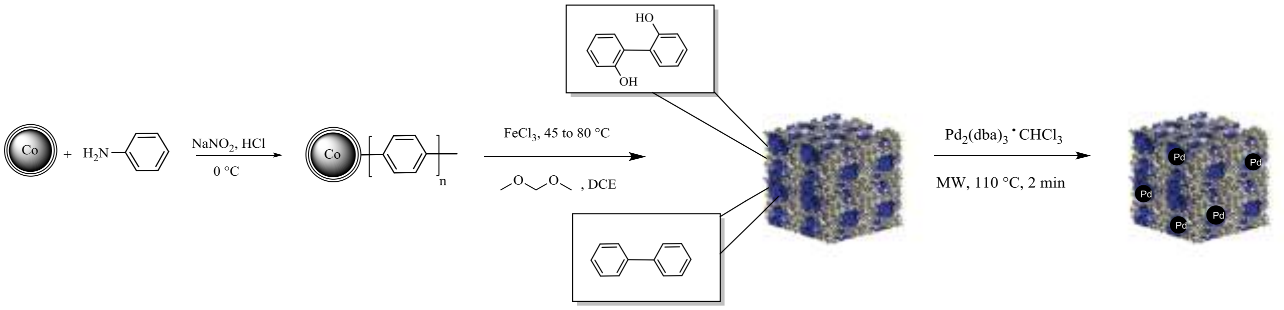
Owing to the specified chemical structure and rich functionality, microporous organic polymers (MOPs) confer flexibility immobilizing catalytic sites. Metal nanoparticles like Pd is embedded in the interior MOPs in order to produce recyclable heterogeneous catalyst. Hence, desire surface area and pore size could impact the catalyst activity efficiently by preventing nanoparticles (NPs) from agglomeration and leaching. [1] Herein, we report the synthesis of two different polymer of this type, using aromatic building blocks such as biphenyl and bisphenol. MOPs were synthesized by formaldehyde dimethyl acetal (FDA) as an external cross-linker in the presence of the Lewis acid ($FeCl_3$). One advantage of MOPs is the low-cost synthesis and the cost-effective of starting materials. In order to find the impact of active functional group such as –OH to encage Pd nanoparticles, we evaluated the catalysts in hydrogenation reactions with respect to activity, selectivity, and recyclability.



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Synthesis of pyrrole-fused 7-deazapurine ribonucleosides

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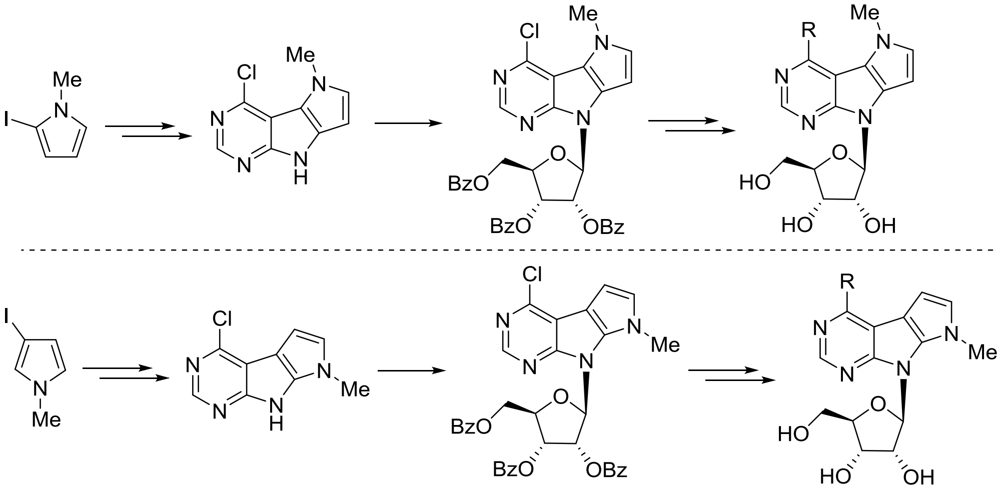
Substituted 7-deazapurine nucleosides exert diverse biological activities, but, despite extensive systematic study of this type of compounds, there is still potential for the development of new anticancer and antiviral drugs. Recently, our group discovered a new class of cytostatic compounds – 4-substituted (het)aryl-fused 7-deazapurine ribonucleosides with a fused benzene or thiophene ring. Some of these derivatives displayed nano- to micromolar anticancer and antiviral activities. [1]

Based on these results, we decided to synthesize and investigate biological activities of similar *N*-methylpyrrole-fused 7-deazapurine ribonucleosides. Desired nucleobases were prepared starting from a corresponding halopyrrole and 4,6-dichloropyrimidine, and then were subjected to Vorbrüggen glycosylation to yield the key benzoylated β-nucleosides. Target free nucleosides were prepared using various palladium-catalyzed coupling reactions and nucleophilic substitutions with subsequent deprotection.



This work was supported by the institutional support of the Charles University, by the Academy of Sciences of the Czech Republic (RVO 61388963), by the Czech Science Foundation (16-0011785), and by Gilead Sciences, Inc.

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High-pressure mediated 1,4-conjugated addition of diethyl malonate to heterocyclic nitroolefins: The combination of high hydrostatic pressure and thiourea based catalysis

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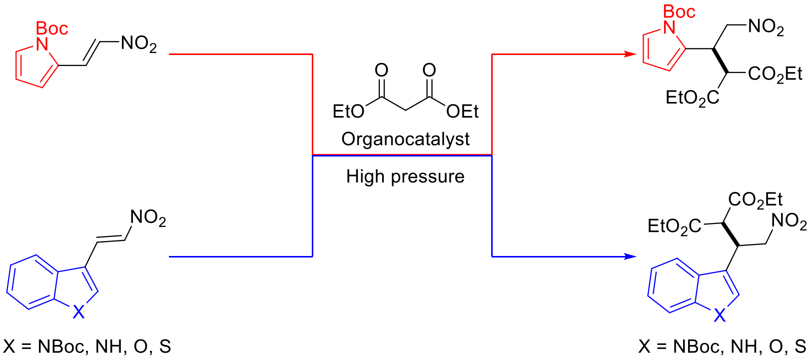
The field of organocatalysis, which was successfully established at the turn of the millennium, is developing as an important tool for organic chemistry, competing with metal- and biocatalysis. [1,2] Especially the low price of organocatalysts and their accessibility through easy preparatory routes make them beneficial in contrast to metal-based catalysts. Furthermore, organocatalytic methods seem to be very attractive for the synthesis of e.g. pharmaceutical agents, due to the fact that metal contamination of the final product can be avoided. [3] High pressure acts as a mild and non-destructive activation mode for chemical reactions. Surprisingly, the combined effects of catalysis and high pressure activation, although known for a long time, has not been investigated to a larger extent until now. This is unfortunate, as this strategy can lead to significant rate acceleration, increased selectivity and the possibility of suppressing side product formation. [4] Catalytically active thiourea derivatives have been investigated in the area of molecular recognition due to their strong hydrogen bonding activity, making them to outstanding organocatalysts. The catalyzed Michael reactions of nitroolefins represent a convenient access to nitroalkanes, which are key compounds in organic synthesis. [5] We present our recent results using thiourea derivatives in the asymmetric 1,4-Michael addition of diethyl malonate to *N*-, *S*- and *O*-heterocyclic nitroolefins under ambient as well as high pressure conditions. In this reactions yields up to 99% and *ee* up to 94% could be achieved. The pressurized reactions showed a dramatically increase in reactivity by stabilizing the hydrogen-bond scaffolds. [6]



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Visible light mediated synthesis of polysubstituted *N*-heterocycles via deoxygenative radical formation

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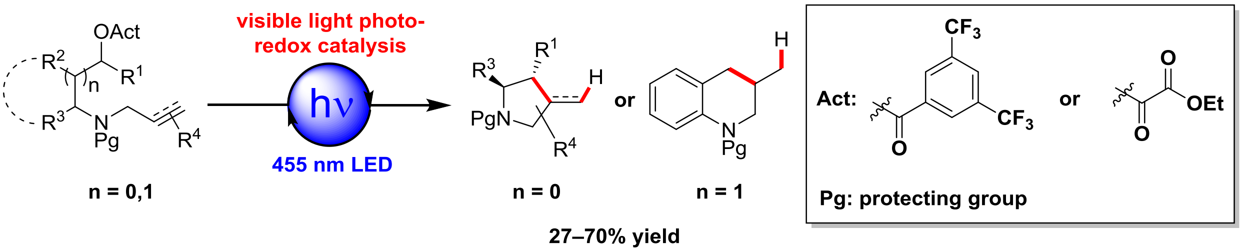
A variety of natural products and pharmaceutical agents contain *N*-heterocycles such as pyrrolidines and tetrahydroquinolines. [1] The activation of the strong C-O bond, which plays a crucial role in functional behavior of different renewable resources, is a big challenge due to the environmental aspect. Based on the previous work of our group on deoxygenation of alcohols via visible light photoredox catalysis, we present a strategy for the construction of polysubstituted *N*-heterocycles via intramolecular C–C bond formation. [2] The transformation of the hydroxy group of the easily accessible mono-allylated/propargylated and *N*-protected amino alcohols into inexpensive ethyl oxalates or recyclable 3,5-bis(trifluoromethyl)benzoates gives access to a broad range of substrates. Under irradiation with blue light (LED 455 nm) in the presence of *fac*-Ir(ppy)$_3$ as photocatalyst the intermediary radical is formed which undergoes intramolecular cyclization reaction to form polysubstituted pyrrolidines and tetrahydroquinolines in moderate to good yields.



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Enantioselective Synthesis of 2-Cyclopentenones: Total Synthesis of Phomapentenone A

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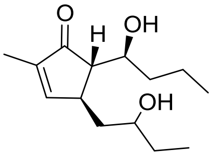
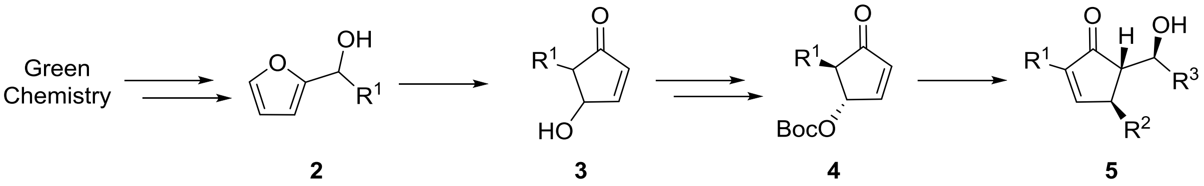
The core structure of cyclopentenones is present in various pharmaceutical drugs and natural products and therefore a valuable building block for synthesis. [1] The synthesis of enantiopure 4,5-disubstituted cyclopent-2-en-1-ones, that are suitable for synthesis of prostaglandine derivatives, was published by our group in 2015. [2] Referring to this publication synthesis of trisubstituted cyclopentenones seemed attractive in terms of the natural product Phomapentenone A (**1**). [3]



Phomapentenone A (**1**)

For the synthesis of 2,4,5-trisubstituted cyclopent-2-en-1-ones various substituted 2-furylcarbinols **2**, outcoming from Green Chemistry, were employed as precursors. Subjecting the substituted furylcarbinols **2** to a continuous flow system or microwave-assisted reaction the 5-substituted 4-hydroxycyclopentenones **3** were efficiently obtained as *anti*/*syn* diastereomers via Piancatelli rearrangement. Subsequent Boc-protection of the hydroxy group led to an activated compound that is suitable for kinetic resolution. Via asymmetric Tsuji-Trost allylation the kinetic resolution of the activated Boc-compound is carried out giving rise to an optically active product **4**. Finally, various 2,4,5-trisubstituted cyclopent-2-en-1-ones **5** were received via directed aldol type reaction and consecutive elimination of the *O*-Boc group employing compound **4** as starting material. This reaction showed excellent enantio- and diastereocontrol including the C1'-position.



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Synthesis of negatively photochromic spirooxazines

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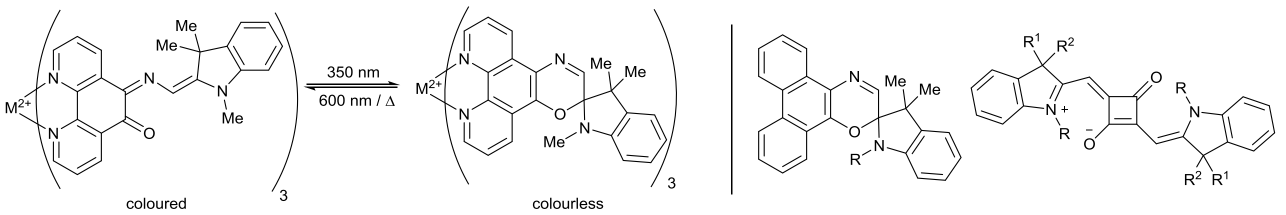
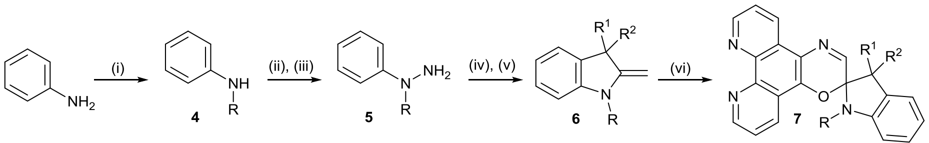
The phenomenon of negative photochromism remains little explored.[1] This study involves the influence of structural diversity upon the photochromic response of one of the few known negative photochromic systems, the transition metal complexes of spiro[indoline-2,2'-[1,4]oxazino[2,3-*f*][1,10]phenanthrolines] (Figure 1).[2]



1 **2** **3**

Figure 1. Negative photochromism of complex 1

Variation of the indoline unit at the 1-position of **1** with variously branched alkyl chains has been accomplished and this chain branching has a significant impact on the photochromic cycling and physical properties of the system. The *N*-alkylated indolenines **6** required for the preparation of **1** were synthesised either using a five-step sequence which utilized benzotriazole (Bt) as a synthetic auxillary and terminates with a Fischer indolisation or in the case of **8** and **9** by direct Fischer indolisation (Scheme 1). Condensation of **6** with 6–nitroso-1,10-phenanthrolin-5-ol affords the positively photochromic oxazines **7** which are then complexed with a metal (M^{2+}) salt leading to **1**. The versatility of the novel Fischer bases **6** has been demonstrated by their conversion to novel positively photochromic phenanthrene derived oxazines **2** and squaraine dyes **3**.



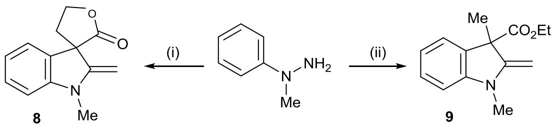
4a R = *i*-but (79%)
4b R = 3,5,5-trimethylhexyl (89%)
4c R = neopentyl (76%)
4d R = cyclohexylmethyl (88%)
4e R = butyl (81%)
4f R = Me R_1+R_2 =cyclohexyl

5a R = *i*-but (81%)
5b R = 3,5,5-trimehtylhexyl (74%)
5c R = neopentyl (78%)
5d R = cyclohexylmethyl (72%)
5f R = Me R_1 + R_2 = cyclohexyl (64%)

6a R = *i*-but (44%)
6b R = 3,5,5-trimethylhexyl (54%)
6c R = neopentyl (33%)
6d R = cyclohexylmethyl (64%)
6e R = butyl (56%)
6f R = Me R_1+R_2 (67%)

7a R = *i*-but (68%)
7b R = 3,5,5-trimethylhexyl (32%)
7c R = neopentyl (57%)
7d R = cyclohexylmethyl (71%)
7e R = butyl (69%)
7f R = Me R_1+R_2 = cyclohexyl (77%)

Reagents: (i) Btz, R-CHO, $NaBH_4$, THF ; (ii) $NaNO_2$, HCl, H_2O; (iii) Red-Al, PhMe; (iv) 3-methyl-2-butanone; (v) CH_3COOH (vi) 6-nitroso-1,10-phenanthrolin-5-ol, EtOH.



8 (11%) **9** (8%)

Reagents: (i) 3-acetyldihydrofuran-2(3*H*)-one; PhMe; CH_3SO_3H (ii) ethyl 2-methyl-3-oxobutanoate; Et_2O; H_2SO_4

Scheme 1. Fischer base synthesis

References

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Synthesis and Photoswitching of Naphthopyran Rhenium Complexes

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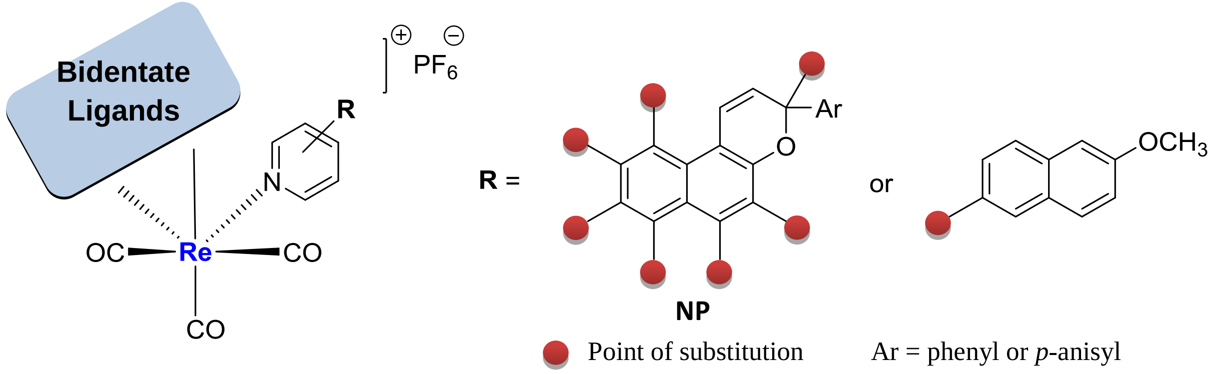


Figure 1.

This project explores the synthesis of photochromic naphthopyrans (NP) [1] which have been decorated with pyridine units that serve as ligands in luminescent rhenium complexes (**Figure 1, 2**). It is envisaged that cycling the NP will not only generate the coloured photomerocyanines but will also modulate the luminescence of the derived Re complexes [2].

Preliminary spectroscopic data has shown that the novel Re complexes exhibit P-type photochromism with variable half-lives depending on the point of attachment on the NP core and the nature of the bidentate ligands. Emission profiles and lifetimes (τ_e) were measured. 2-Methoxy-6-(4-pyridyl)naphthalene-Re complexes were prepared and their luminescence profiles acquired so providing an insight to the energy-transfer processes in a model system.

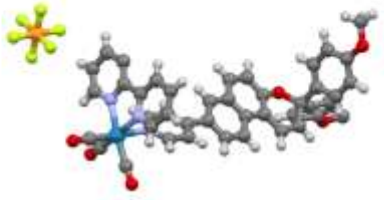
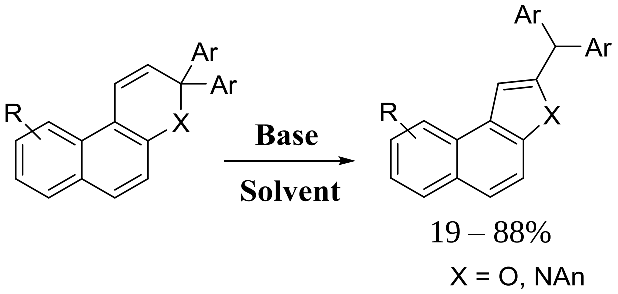


Figure 2.

Diverse synthetic strategies were employed to access the Re complexes depending on the position and the orientation of the pyridyl substituent on the NP ring. During Suzuki coupling of the pyridine unit to the NP nucleus a ring contraction was observed. This reaction has been developed into an efficient base-mediated protocol to access multiple naphthofurans, naphthodifurans and benzo-fused indoles (**Scheme 1**) in generally good yields.



Scheme 1.

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Synthesis of Novel Electrochromic Materials

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Christopher D. Gabbutt, and B. Mark Heron
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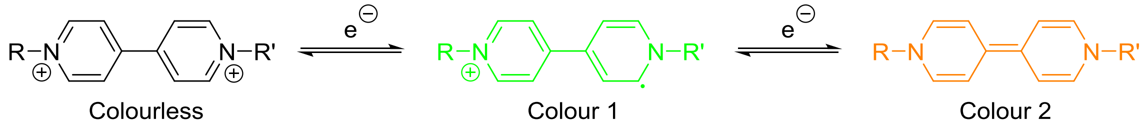
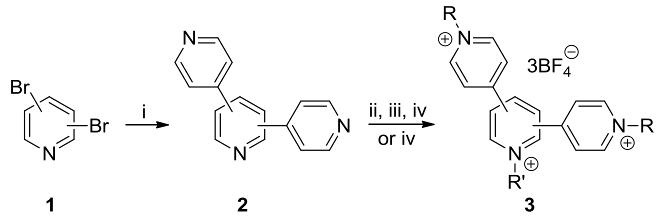
Electrochromism is a phenomenon exhibited by certain molecules whereupon a reversible colour change is observed by way of an electrochemical reaction induced by application of an electrical current.[1] Electrochromism has been harnessed in a variety of multifunctional devices [2] and is displayed by several polymer systems [3]. An interesting and very active area of electrochromism is the study of compounds known as viologens which are founded on a diquaternised 4,4'-bipyridinium core. These structures can form highly coloured radical cations upon application of either a negative voltage or reaction with an appropriate reducing agent (**Scheme 1**).



Scheme 1: Electrochemical transformation of viologen-type dications.

In order to extend the currently limited range of properties associated with simple viologens a series of terpyridines and their derived salts, which may be considered as pyridine core extended viologens, were synthesised and studied. The synthesis commenced from a series of readily available dibromopyridines **1** which were subject to poly-functionalisation involving either a one-pot double Suzuki coupling reaction or sequential, selective Suzuki – Negishi reactions to access the isomeric terpyridines **2**. Subsequent *N*-alkylation (or *N*-arylation) afforded the novel electrochromic terpyridinium (1,1',1"-trialkyl(aryl)[terpyridine]-1,1',1"-triium) tetrafluoroborates **3** (**Scheme 2**). One unexpected observation was that the tris-*N*-hexylated 4,3':5',4"-terpyridine salt was strongly emissive in solution yet also displayed electrochromism comparable to that of the other terpyridine isomers investigated.



Reagents: i) 4-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine, K_2CO_3, $Pd(PPh_3)_4$, PhMe, EtOH, reflux; ii) 1-iodohexane, MeCN, reflux; iii) $NaBF_4$, aq. MeOH; iv) Me_3OBF_4, CH_2Cl_2

Scheme 2: Synthesis of terpyridinium salts **3**

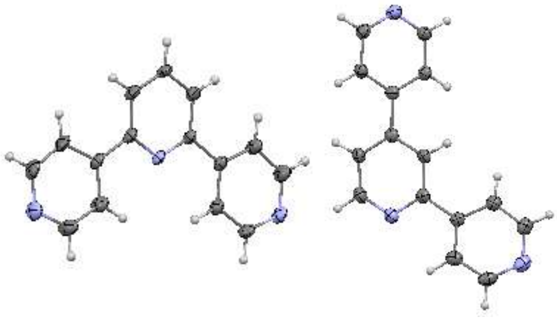


Figure 1: Selected structures of terpyridines **2**

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Adapting The Zav'yalov Pyrrole Synthesis to Access 4-Acetoxy- and 4-Acetamido- Pyrrole-3-carboxylates

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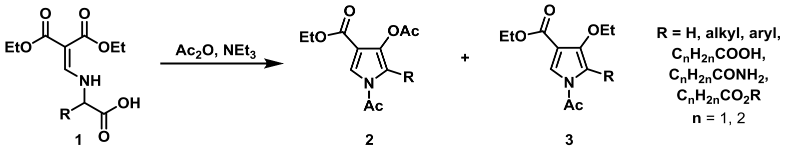
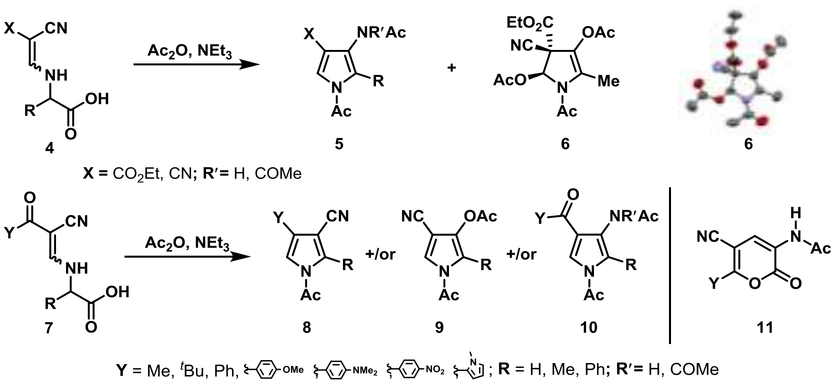
Pyrroles are of fundamental academic and industrial interest. [1] In spite of significant accessibility to structural diversity, access to certain pyrrole substitution patterns, in particular 2,5-unsubstituted systems, remains difficult. [2] In this study we extend our earlier investigations [3a)] of the little-known Zav'yalov pyrrole synthesis. [3b)] Thus, we have investigated the anhydride-mediated cyclisation of a variety of enamino acids **1**, derived from α-amino acids, to obtain substituted pyrrole-3-carboxylates **2** and **3** (Scheme 1).



Scheme 1

This cyclisation chemistry has been extended to enaminonitriles **4**, which when cyclised provided novel pyrroles **5** (Scheme 2). Derivatives of enaminonitrile **7** were synthesised with substituents Y chosen for their steric and electronic properties. Interestingly, varying Y had little effect on the distribution of products and rather the R group dictates the outcome of the reaction. When R = Me, the product from the reaction is mainly **9**, whereas when R = Ph the product is usually **10**. In contrast, when R = H the reactions produce a range of products (**8**–**10**); interestingly an alternate mechanistic pathway provided novel pyranones **11** (R = H, Y = Ph or An).



Scheme 2

The Zav'yalov pyrrole synthesis has been utilised to produce a wide range of substituted pyrroles. The mechanism has been thoroughly investigated through means including ^{13}C-labelling and trapping of mesoionic intermediates and these findings will be presented. In addition, C–H functionalistion reactions of the novel pyrroles will be described.

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Brønsted-Acid catalyzed enantioselective intramolecular Povarov reaction

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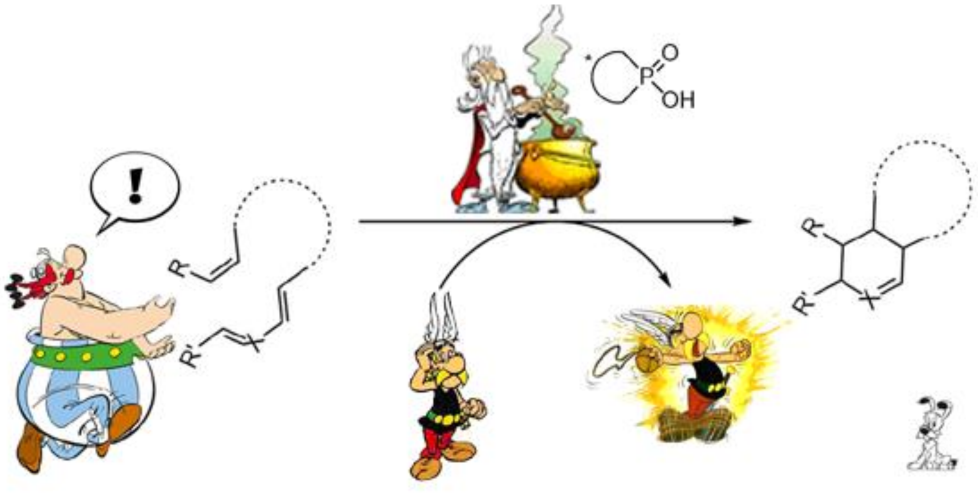
Highly substituted heterocyclic rings are key structural features in a wide range of natural bioactive products. Heterocycles are also common structural units in marketed drugs and in medicinal chemistry targets in the drug discovery process. Over 80% of top small molecule drugs by US retail sales in 2010 contain at least one heterocyclic fragment in their structures. [1] Therefore, the development of an efficient catalytic asymmetric method for the preparation of heterocycles is still an unmet need with potentially wide-ranging utilities.

The stereoselective cycloaddition is one of the most convergent strategies for the synthesis of chiral heterocycles. Although the utility of these reactions has been explored fruitfully over the past two decades,[2] quite limited progress has been made in catalytic asymmetric variants.

On the basis of these facts, we describe a chiral Brønsted acid-catalyzed enantioselective synthesis of original functionalized heterocycles. With a very simple and rapid process, a wide range of new molecules can be prepared with excellent results in reactivity as well as selectivity. Evaluation of biological activities of synthetized compounds are currently in progress. [3]



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Continuous Flow Synthesis of Indoles by Pd-catalyzed Deoxygenation of 2-Nitrostilbenes with Carbon Monoxide

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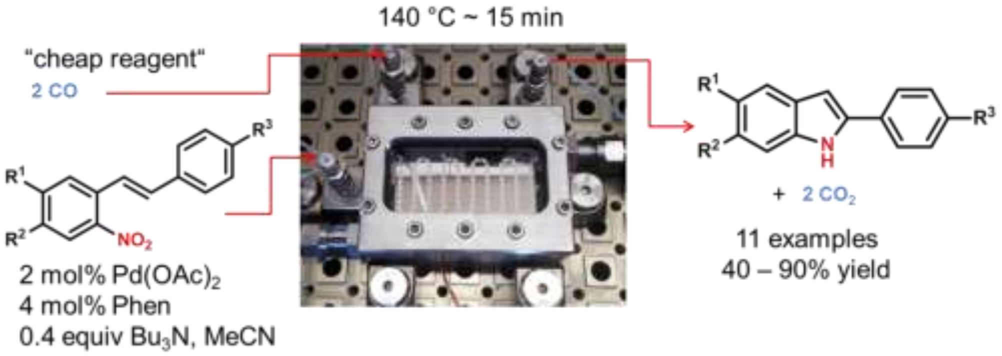
Indoles are among the most abundant heterocycles in nature and a vastly diverse array of natural and synthetic compounds contain the indole scaffold. Even though first methods for the generation of indoles were discovered well over a century ago, the ubiquity and structural diversity of biologically active indoles has continued to drive research towards their synthesis and functionalization. In particular, the development of regioselective methods for the construction of indoles with complex substitution patterns has remained an active area of research [1].

Herein we present an intensified and scalable continuous flow protocol for the palladium-catalyzed deoxygenation of *o*-vinylnitrobenzenes to produce indoles employing carbon monoxide as terminal reductant (Scheme). The reaction proceeds with catalyst loadings of 1 to 2 mol% Pd(OAc)$_2$ in the presence of suitable ligands/additives and generates carbon dioxide as the only stoichiometric side-product. The reductive cyclization proceeds in a clean fashion with high initial reaction rates in the pressurized flow reactor, ultimately leading to deposition of catalytically inactive palladium(0) inside the channels of the flow device, allowing for an efficient catalyst recovery. A variety of *o*-vinylnitrobenzenes (*o*-nitrostilbenes and –styrenes) were converted to the corresponding indoles within 15 to 30 min at a reaction temperature of 140 °C to furnish products in good to excellent yields (10-20 bar CO pressure). Mechanistic aspects and the scope of the transformation are discussed [2].



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Temperature Controlled Selective C-S bond formation: First Photocatalytic Sulfonylation of Unactivated Heterocycles utilizing Aryl Sulfonyl Chlorides

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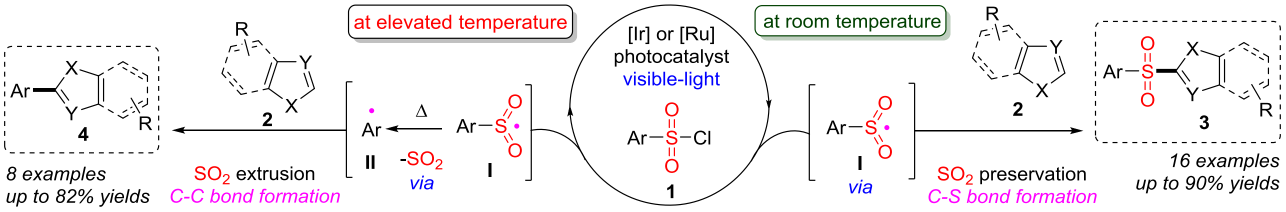
Abstract: We report a new, facile, and efficient method for heterocyclic sulfonylation by employing visible-light-induced oxidative quenching cycle of Iridium or Ruthenium photocatalysts at room temperature conditions. This protocol provides a direct access to the novel class of sulfonyl substituted heterocycles in excellent yields. Furthermore, this transformation also offers a straightforward route for the synthesis of corresponding sulfonyl-containing biologically active molecules. On another hand, the C-C bond formation reaction proceeds with the extrusion of the SO_2 group at elevated temperature conditions.

Notably, sulfur-containing organic compounds have been recognized as important building blocks in synthetic as well as in medicinal chemistry.[1] The introduction of a sulfur group on the aryl or heteroaryl moiety either in the form of sulfanyl, a sulfinyl, or a sulfonyl tremendously enhances the synthetic utility and biological activity of the resulting organic compounds.[2,3] Consequently, numerous and elegant synthetic approaches have been developed in this direction.[4,5]

Herein, we also present our strategy for direct C-H functionalization of heteroaromatics utilizing bench stable sulfonyl chlorides and unactivated heterocycles under different temperatures conditions operated by visible-light photocatalysis (Scheme 1).



Scheme 1: Temperature controlled C-C or C-C bond formations by visible-light photocatalysis

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Synthesis of Novel Heteropropellanes

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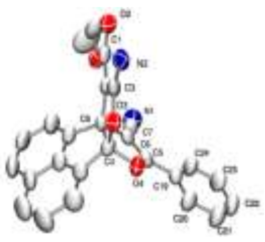
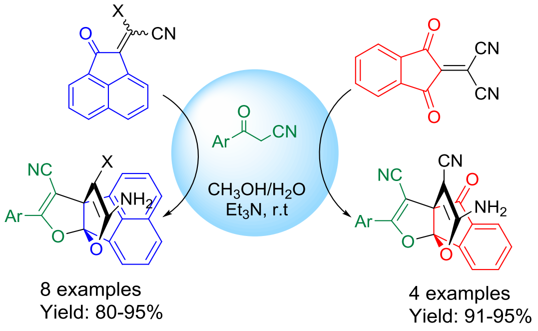
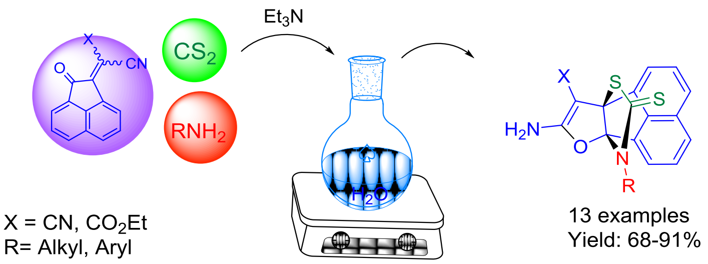
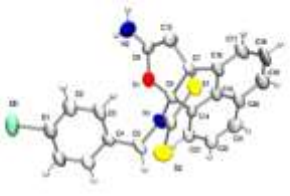
Propellane is a special kind of fused tricyclic system containing three non-zero bridges and one zero bridge between a pair of bridgehead carbon atoms. Although the first propellanes were synthesized in 1930s, the term propellane was proposed in 1966 by Ginsburg because of the characteristic propeller shape of these molecules. Propellane skeletons have received much attention in synthetic organic chemistry due to their fascinating topology and significant chemical and physical properties.

Highly chemoselective and regioselective methods for the synthesis of dioxopropellanes, thioxo[3.3.3]propellanes, and oxo-thioxo[3.3.3]propellanes have been developed by reaction of the Knoevenagel adducts of acenaphthoquinone (or ninhydrin) and malononitrile, with various nucleophiles.

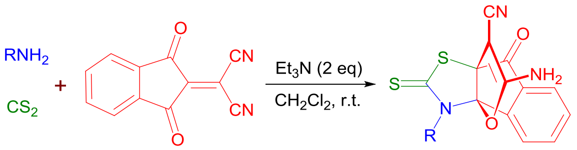








X-ray structure of **6l**



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Yavari, I.; Khajeh-Khezri, A., *Mol. Divers.*, **2017**,

Total Synthesis of Hippolachnin A

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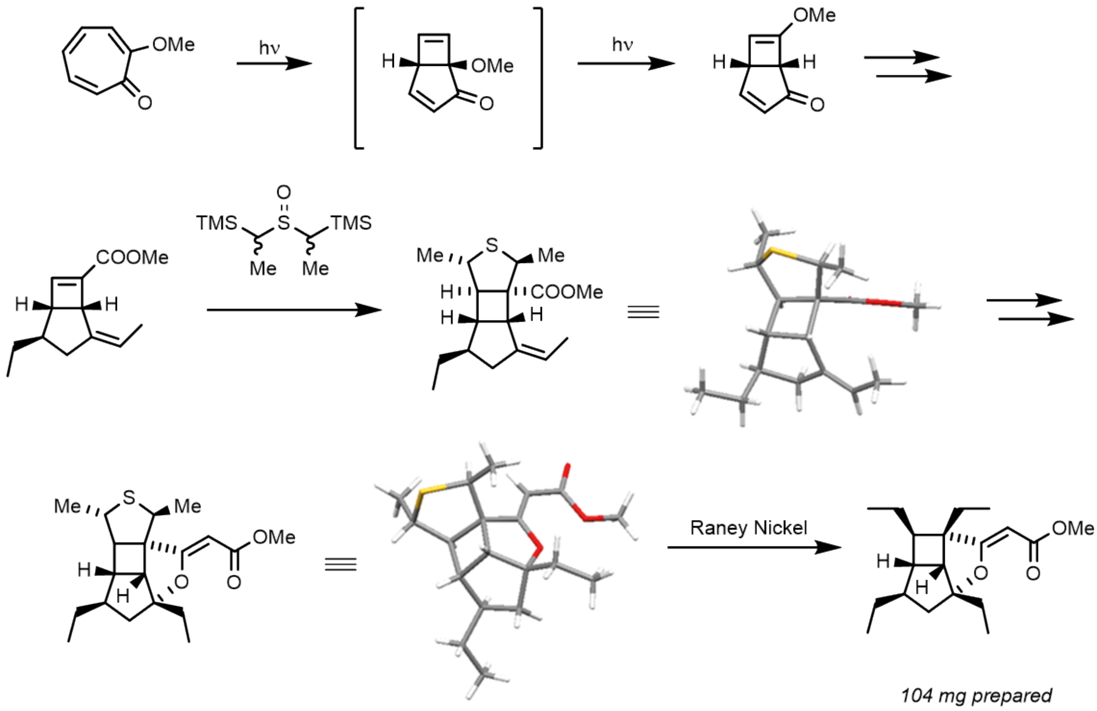
[##]*Department of Chemistry, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, 81377 Munich, Germany*

Hippolachnin A is an antifungal molecule that bristles with ethyl groups mounted on a caged heterotricyclic core. It has shown potent activity against *Cryptococcus neoformans*, a fungus that affects immunocompromised patients as an opportunistic pathogen.[1] Herein we describe a concise and scalable synthesis of (±) hippolachnin A. It features a powerful photochemical opening step,[2] a diastereoselective addition of an ethyl cuprate and a strategical sequence to install two additional ethyl groups on the convex face of the molecule[3] as well as a chelate-controlled alkylation of a tin enolate[4] to generate the thermodynamically less stable (Z)-double bond of the natural product.



104 mg prepared

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Serendipitous Synthesis of Isatogen Compounds by Reaction of *C*-Nitrosoarenes with Alkynes

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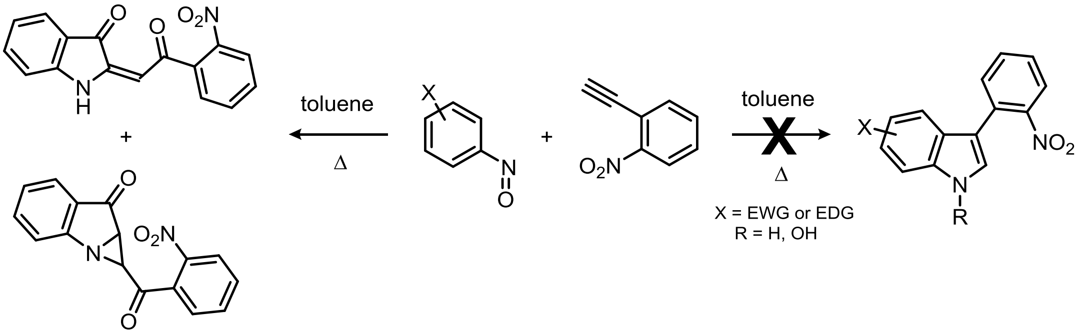
Indole derivatives are probably the most diffuse and important heterocyclic compounds studied by many research groups both in academy and industry.[1] Recently, we developed a novel indolization procedure by using nitrosoarenes and alkynes.[2] This reaction led us to afford a wide library of different indole compounds by cycloaddition of *C*-nitrosoaromatics with conjugated aromatic terminal alkynes in moderate to good yields.[3] This synthetic protocol was used even to achieve marine alkaloids containing indole fragment like the meridianins.[4]



In a very recent study, in the aim to expand the synthetic scope of the reaction, we tried to use the nitroso-alkyne cycloaddition reaction using 2-nitrophenylacetylene as starting material. Surprisingly the reaction, carried out without any metal catalyst, shows the presence of isatogen compounds as major products and no traces of indole derivatives.

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A Revisited Survey of the Synthesis of CR-1015

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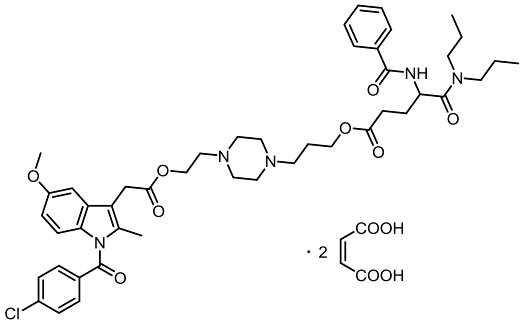
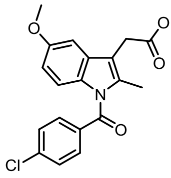
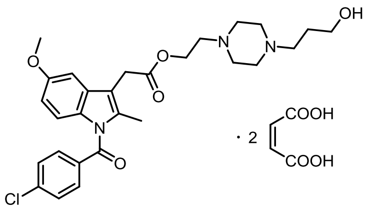
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are pharmaceutical agents that show anti-inflammatory, analgesic and antipyretic effects.[1] All of them work by blocking cyclo-oxygenase (COX-1 and COX-2) enzymes. Both types produce prostaglandins that have a number of different effects, one of which is to regulate inflammation. Proglumetacin is one of the most popular pharmaceutical agents that belongs to NSAID list and contains two fundamental moieties like Indomethacin that plays the role of anti-inflammatory drug and proglumide that inhibits gastrointestinal motility and reduces gastric secretions.[2]



Proglumetacin



Indomethacin



CR-1015

In a very recent study, in the aim to synthesize CR-1015, that is known as a side product in the large scale production of Proglumetacin, we tried to repeat some procedures reported in literature to afford CR-1015 and we detected controversial results that will be discussed.

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New synthesis of carbamoyl and thiocarbamoyl derivatives of chromones

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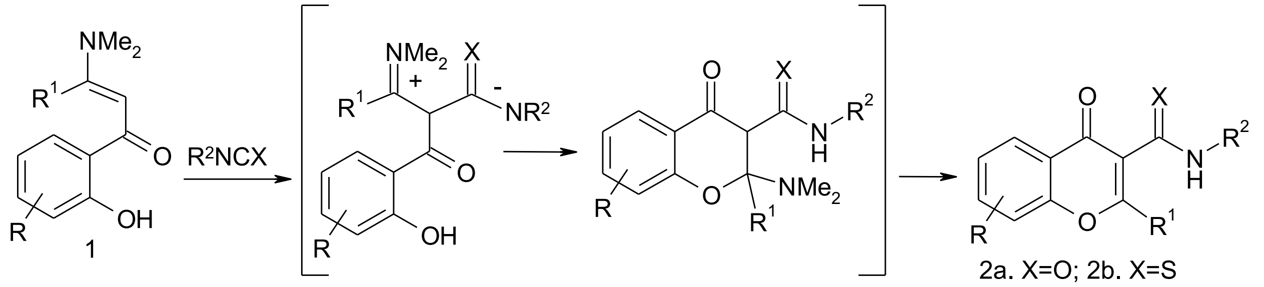
N. D. Zelinsky Institute of Organic Chemistry, Moscow,
Russian Federation, 119991

Chromones and their derivatives are very important heterocyclic compounds, which is a common and integral feature of a variety of natural products and medicinal agents. These heterocycles show a variety of pharmacological properties, and change of their structure offers a high degree of diversity that has proven useful for the search of new therapeutic agents. A large volume of research has been carried out on chromones, which has proved the pharmacological importance of this heterocyclic nucleus.

The present work focuses on the synthesis and some properties of carbamoyl- and thiocarbamoylchromone derivatives. It should be noted that replacement of the carbonyl function for the thiocarbonyl one can result in drastic increasing biological activity. These chromones have a very high synthetic potential but practically unknown in the literature.

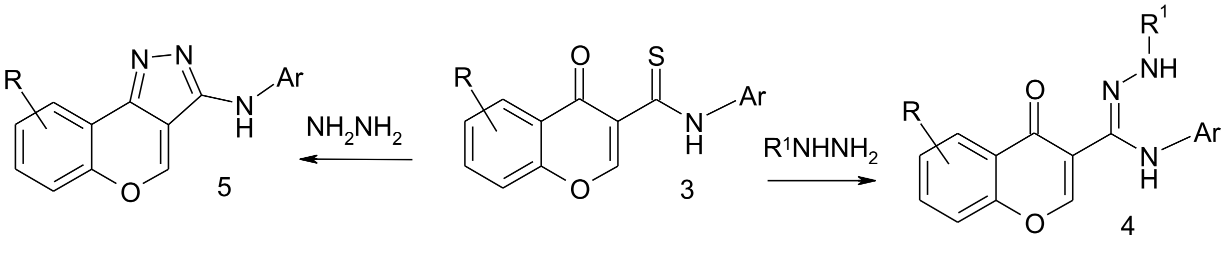
We worked out a very simple and convenient method for synthesis of 3-carbamoyl- and 3-thiocarbamoylchromones (2a, 2b) from available enaminones 1 and isocyanates and isothiocyanates.



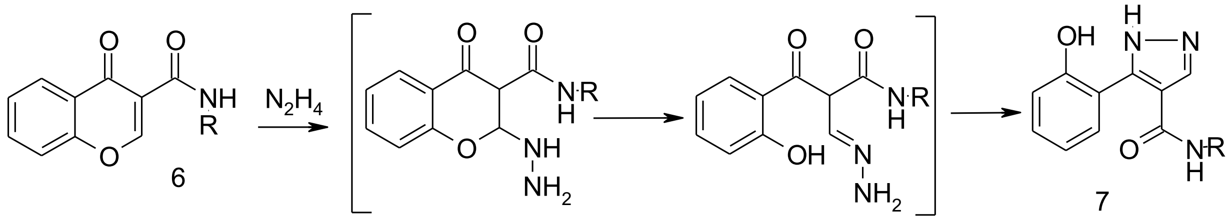
2a. X=O; 2b. X=S

X = S,O; R = R^2 = FG, Ar,Het; R^1 = H,Ar,Het

Some reactions of chromones will be presented. Thus, compounds 3 react with hydrazines to give both linear amidrazones 4 and condensed pyrazoles 5.

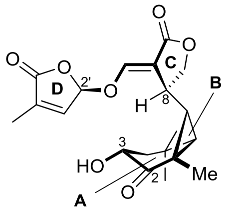


Unlike thioderivatives 3 carbamoylchromones 6 interact with hydrazine with splitting benzopyrane cycle that is an evidence of some peculiarity of these thioamides.

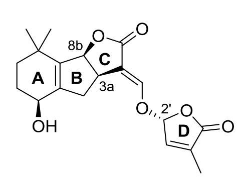


First Total Synthesis of Avenaol: New Strategy for Synthesis of All-*cis*-Substituted Cyclopropane Natural Products

Motohiro Yasui, Rina Ota, Chihiro Tsukano* and Yoshiji Takemoto*
Graduate School of Pharmaceutical Sciences, Kyoto University,
46-29 Yoshida-Shimo-Adachi-cho, Sakyo-ku, Kyoto 606-8501, Japan



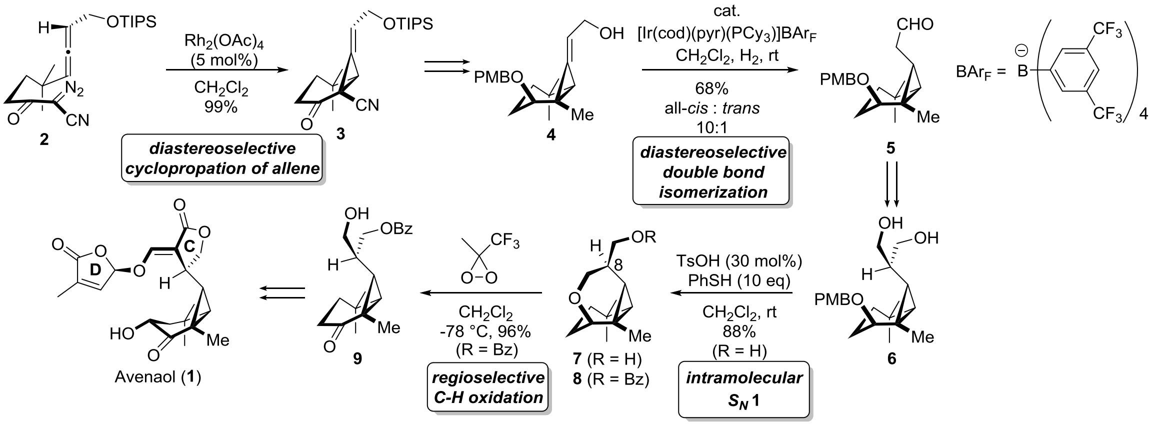
Avenaol (**1**)
(atypical SL)



Strigol
(typical SL)

Avenaol (**1**), which was isolated from the allelopathic plant black oat (*Avena strigosa* Schreb.) by Yoneyama and coworkers, is the first reported natural C$_{20}$ germination stimulant structurally related to strigolactones (SLs)[1]. The structure of avenaol is characterized by a bicyclo[4.1.0]heptanone skeleton with an all-*cis* substituted cyclopropane on which the three main substituents are positioned in the same direction. Avenaol shows potent germination-stimulating activity for *Phelipanche ramose* seeds, but low activities for *Striga hermonthica* and *Orobanche minor*. To date, no total synthesis of avenaol (**1**) has been reported. Because of its unique structure, important biological activity, and limited availability from the natural source, we started a synthetic project of avenaol.

In this presentation, we would like to present the first total synthesis of avenaol (**1**), which features the following reactions: (i) Rh-catalyzed intramolecular cyclopropanation of an allene (**2** → **3**), (ii) Ir-catalyzed stereoselective double-bond isomerization (**4** → **5**), (iii) differentiation of two hydroxymethyl groups by intramolecular S$_N$1 reaction (**6** → **7**), and (iv) regioselective C-H oxidation of tetrahydropyran (**8** → **9**). This synthetic route through an alkylidenecyclopropane effectively avoids undesired side reactions including ring-opening of a cyclopropane. The proposed structure of avenaol, especially the all-*cis*-substituted cyclopropane was confirmed to be correct by our total synthesis.



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The application of cyclopropanated pyrrroles: the synthesis of non-proteinogenic pyrrolidine- and piperidine-based amino acids

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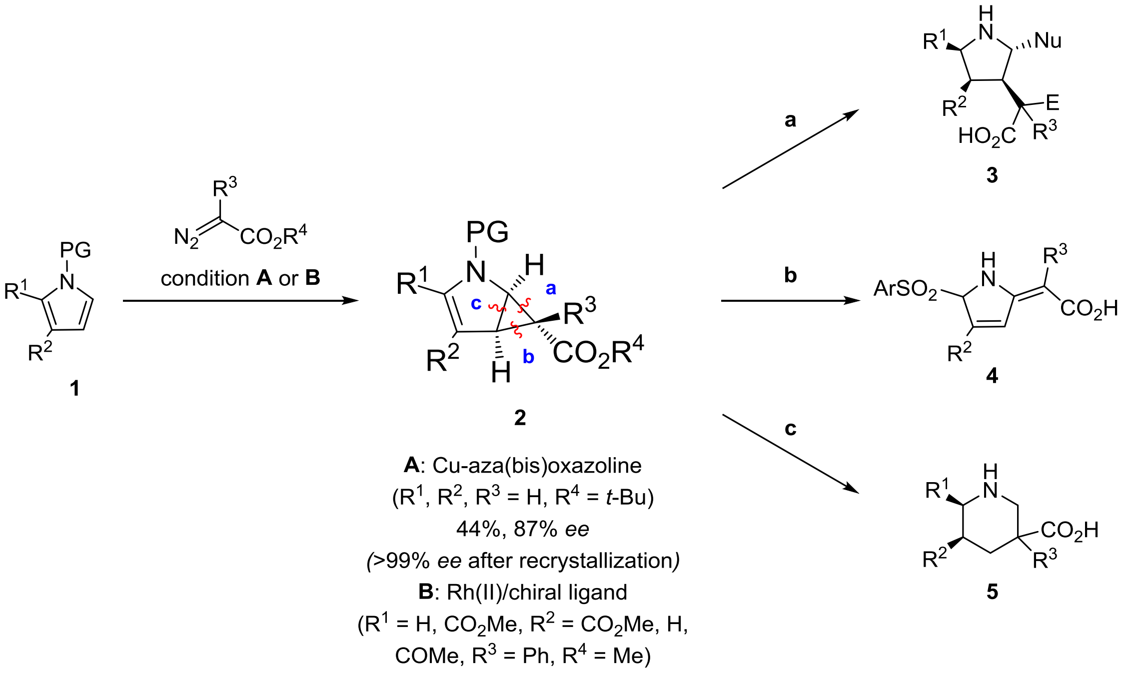
Monocyclopropanated pyrroles **2** constitute useful building blocks in organic synthesis: they can be readily obtained from the corresponding pyrroles **1** in moderate to good yields with high enantiomeric excess and the presence of the double bond and the donor-acceptor cyclopropane ring system in **2** enables a broad range of transformations.[1] Through the selective cleavage of the cyclopropane ring, **2** can be converted to amino acids **3** without loss of *ee*, pyrrolines **4** *via* radical pathway and finally substituted piperidine derivatives **5** under hydrogenation conditions.[2] Pyrrolidine- and piperidine-based amino acids resulting from these transformations play an important role in medicinal and organic chemistry i.e. as structural elements of peptide analogues, organocatalysts or intermediates in the synthesis of more complex molecules.



A: Cu-aza(bis)oxazoline
(R^1, R^2, R^3 = H, R^4 = *t*-Bu)
44%, 87% *ee*
(>99% *ee* after recrystallization)
B: Rh(II)/chiral ligand
(R^1 = H, CO_2Me, R^2 = CO_2Me, H,
COMe, R^3 = Ph, R^4 = Me)

[1] Reiser, O. *Isr. J. Chem.* **2016**, *56*, 531–539.

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The furo[2,3-*b*]furan motif as core structure of natural products

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Prof. Dr. Oliver Reiser, Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31,
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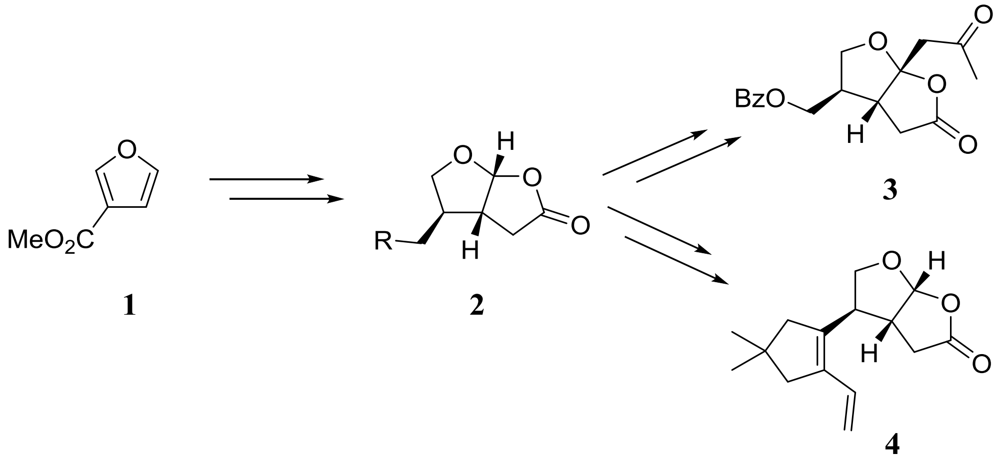
The furo[2,3-*b*]furan motif can be found in a variety of natural products, especially in a group of spongiane diterpenes. Members of this hardly explored subgroup of marine diterpenes are, e.g., norrisolide, dendrillolide A and macfarlandin C.[1-3] Moreover, the fused tetrahydrofuran-γ-lactone scaffold is also present in (+)-Paeonilide **3** and the fungal metabolite dermatolactone **4**.[4-5] (+)-Paeonilide **3** is a highly oxygenated monoterpenoid, which was first isolated from the roots of *Paeonia delavayi* in 2000. It is selectively inhibiting the PAF (platelet activating factor) induced platelet aggregation with an IC_{50} value of 25 μM (8 μg/mL).[4]

The novel sesquiterpene dermatolactone **4** shows nematicidal and cytotoxic activity. It was first isolated in 1996 from the extracts of an ascomycete (strain A4990) belonging to the Dermateaceae. Up until now no total synthesis is known in the literature.[5]

Starting from commercially available 3-furoic methyl ester **1** the substituted tetrahydrofuro[2,3-*b*]furan-2(3*H*)-one core structure **2** of these two natural products can be obtained via a cyclopropanation and acid-catalyzed ring expansion sequence.[6]

The synthesis of a library of (+)-Paeonilide **3** derivatives and subsequent biological evaluation as well as studies towards the total synthesis of dermatolactone **4** are currently ongoing.



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Synthesis of Pyrazines from Vinyl Azides utilizing a Visible-Light-Mediated Photocascade Process

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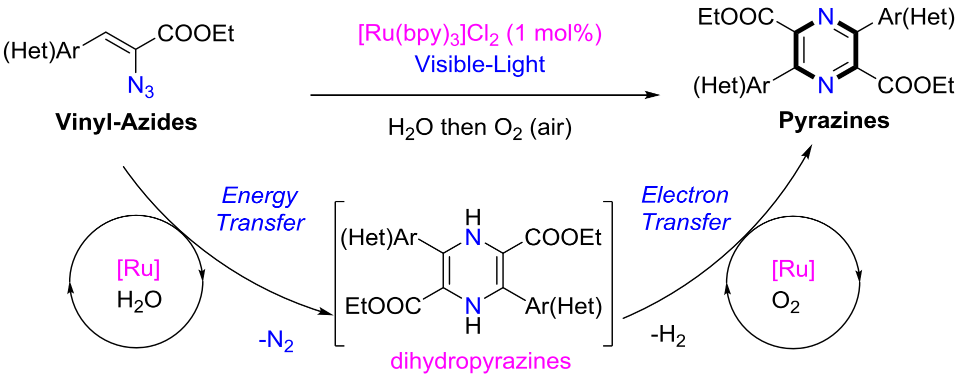
Abstract: A convenient method for the synthesis of substituted pyrazines from vinyl azides has been developed utilizing a dual energy transfer and electron transfer strategy enabled by visible-light photocatalysis. Initially, vinyl azides are activated by a triplet sensitization process from an excited [Ru]-photocatalyst under the aqueous conditions to form dihydropyrazines, followed by a single electron transfer (SET) process under oxygen (air) atmosphere leads to the tetrasubstituted pyrazines in good to excellent yields under mild reaction conditions (Scheme 1).



Scheme 1: Synthesis of pyrazines from vinyl azides by a photocascade process

Recently, many photocatalytic organic transformations have been achieved by activating the colorless organic substrates in two different pathways. The substrate can either be activated by direct energy transfer (ET) or single-electron-transfer (SET) from the excited state photocatalyst.[1] However, the utilization of both ET followed by SET (a photocascade process) together is not well established with only a few examples are known.[2] Following our recent report of activation of vinyl bromides by the photocascade process,[3] herein, we extend the scope of such a dual activation strategy for the synthesis of pyrazines from corresponding vinyl azides. This method is very successful for the synthesis of desired *N*-containing heterocycles in good to excellent yields at room temperature conditions.

References:
[1] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322.
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Synthesis of *tetra*-Substituted Thiophenes via Direct Metalation

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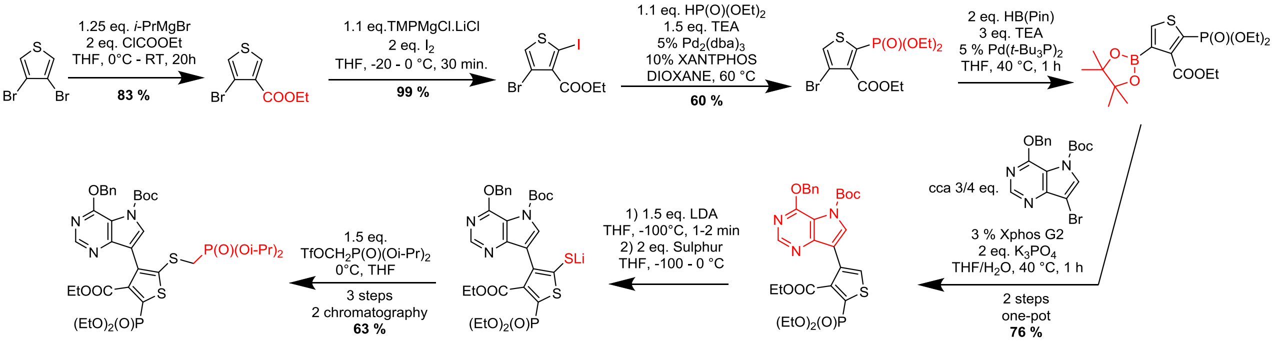
Thiophenes are important heterocyclic building blocks in many parts of an industry (e.g. pharma industry). Thiophenes can be easily derivatized with direct or halogen-exchange metalation, yet, there are only a few metalation examples of highly substituted thiophenes with reactive functional groups in the literature.[1,2] In this work, *tetra*-substituted thiophenes were synthesized by combination of several approaches with direct metalation as the most important one.

As the scheme below shows, several metal-introducing reagents were used in both high and low temperature metalations. Then, organometallic intermediates allowed reactions with required electrophiles. The reactivity and the compatibility of the function groups as well as the proper reaction condition requirements will be discussed.



Scheme 1: Example of the synthesis

Acknowledgment: This work was supported by the Institute of Organic Chemistry and Biochemistry CAS (RVO61388963), Czech Science Foundation (16-06049S), and Gilead Sciences (Foster City, CA, USA).

Reference:

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Ir(I)-Catalyzed Enantioselective Formal C-H Conjugate Addition of Acetanilides to *β*-Substituted-*α*,*β*-Unsaturated Esters

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Takanori Shibata[a,c]
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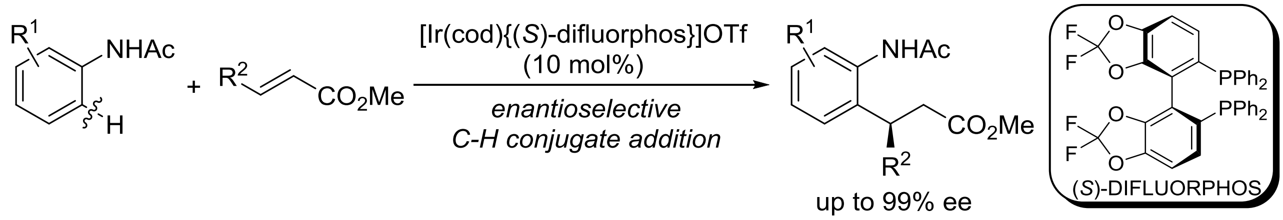
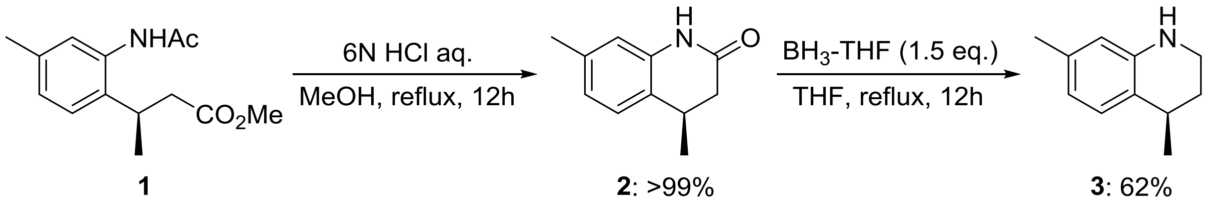
[b] *International Center for Science and Engineering Programs (ICSEP), Waseda University, 3-4-1 Okubo, Shinjuku, Tokyo 169-8555, Japan*
[c] *JST, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama, 332-0012, Japan*

C-H bond functionalization is a straightforward transformation because it is efficient and atom-economical. Therefore, it is the most important strategy in organic synthesis. While sp^2 C-H alkylation with alkenes, such as styrenes, has been studied comprehensively, sp^2 C-H alkylation with *α*,*β*-unsaturated carbonyl compounds, namely formal C-H conjugate addition has recently attracted research interest.[1] However, there were few examples of enantioselective formal C-H conjugate addition. We have already reported enantioselective sp^2 C-H bond activation of ferrocenes[2] and sp^3 C-H bond activation of *γ*-butyrolactams along with the reactions with acrylates.[3]

Next, we focused on sp^2 C-H bond activation at the *ortho*-position of anilide derivatives by chiral Ir catalysts and recently achieved the first example of enantioselective formal C-H conjugate addition to *β*-substituted-*α*,*β*-unsaturated esters.[4]



The obtained product **1** was transformed into chiral *δ*-lactam **2** by acidic hydrolysis and tetrahydroquinoline **3** by subsequent boran-reduction. This protocol can be useful because pharmaceutical agents often include optically active tetrahydroquinoline moiety.



References

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PIDA-Mediated Efficient Synthesis of Dihydroquinoxalinones by Oxidative Intramolecular N-H/C-H Coupling

Masashi Horiuchi,[a] Kyalo Stephen Kanyiva,[b] and Takanori Shibata[a,c]
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[b] *International Center for Science and Engineering Programs (ICSEP), Waseda University, 3-4-1 Okubo, Shinjuku, Tokyo 169-8555, Japan*
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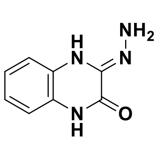
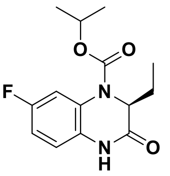
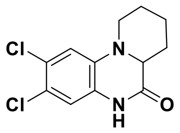
Quinoxalinone derivatives including dihydroquinoxalinones have various bioactive properties such as anti-cancer, anti-HIV and absorption inhibitory actions. In addition, quinoxalinone derivatives are versatile intermediates for the synthesis of useful organic compounds. Therefore, development of new and efficient methods for their synthesis is strongly desired in organic chemistry.



WO2011103028
anti-cancer agent

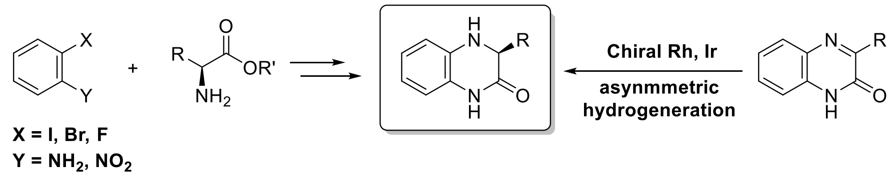


GW420867X
anti-HIV agent

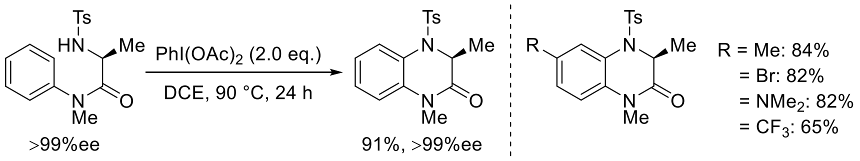


WO 2014195695
absorption inhibitory action

In the past, dihydroquinoxalinones were synthesized using two main strategies. One of them involves the reaction of 1,2-disubstituted benzenes with amino acids or their derivatives in two or more steps. In addition, 1,2-disubstituted benzenes are often expensive and/or difficult to prepare. The other strategy is the asymmetric hydrogenation of quinoxalinone derivatives using transition metal catalysts such as rhodium and iridium. But from the viewpoint of pharmaceutical synthesis, the use of transition metals is undesirable.



Recently, hypervalent iodine has attracted much attention as a substitute for transition metals in various coupling reactions.[1] We considered that dihydroquinoxalinones could be synthesized by direct intramolecular N-H/C-H bond formation using hypervalent iodine. We established a method for the synthesis of dihydroquinoxalinones by simple operation from readily available anilines and amino acid derivatives. For example, when *N*-methyl-*N*-phenyl-2-(tosylamino) propanamide reacted with (diacetoxy)iodobenzene (PIDA) in dichloroethane at 90 ºC for 24 h, intramolecular N-H/C-H coupling proceeded smoothly to give the desired dihydroquinoxalinone in high yield with perfect retention of enantiometric excess. The reaction tolerates a wide scope of functional groups, as well as amino acids.



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Intramolecular C-H Activation at the C-2 Position of Indoles: *Exo* and *Endo* Selective Alkenylation by the Choice of Metal Catalyst

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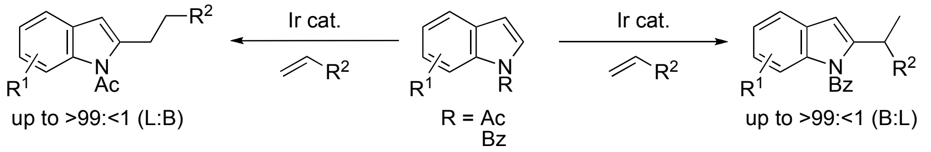
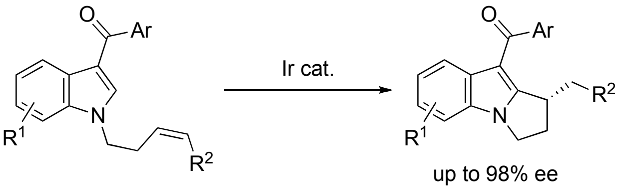
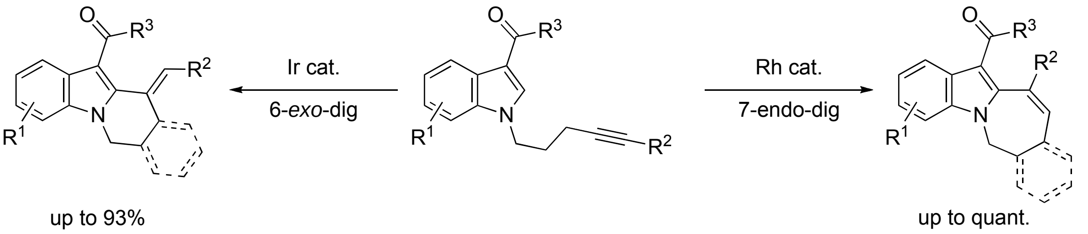
Transition metal-catalyzed C-H bond activation is the most important reaction in modern organic chemistry. Especially, direct C-H functionalization of heterocycles, which are often found in bioactive molecules, is strongly desired in pharmaceutical and agricultural chemistry. We have comprehensively studied the C-H functionalization of indole skeletons. For example, we reported linear/branch selective intermolecular C-H alkylation at the C-2 position of indole derivatives.[1]



We further reported an intramolecular C-H alkylation at the C-2 position of indole. This reaction of *N*-alkenylindole derivatives proceeded with high enantioselectivity by using a chiral Ir catalyst, but the Rh counterpart was ineffective for this transformation.[2]



We here examined an intramolecular C-H alkenylation of *N*-alkynylindole derivatives. In this transformation, Ir catalyst promoted 6-*exo*-dig cyclization to give pyrido[1,2-*a*]indole derivatives. On the other hands, Rh catalyst did 7-*endo*-dig cyclization to give azepino[1,2-*a*]indole derivatives. These reactions have wide substrate scope. For example, both electron-donating and -withdrawing groups could be available as a substituent on the indole ring (R^1), and the corresponding tri- and tetracyclic compounds were obtained in good to excellent yields.[3]



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Alkenes as functionalised nucleophilic surrogates and a journey towards the synthesis of Taxol® core

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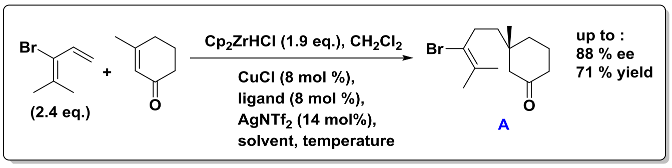
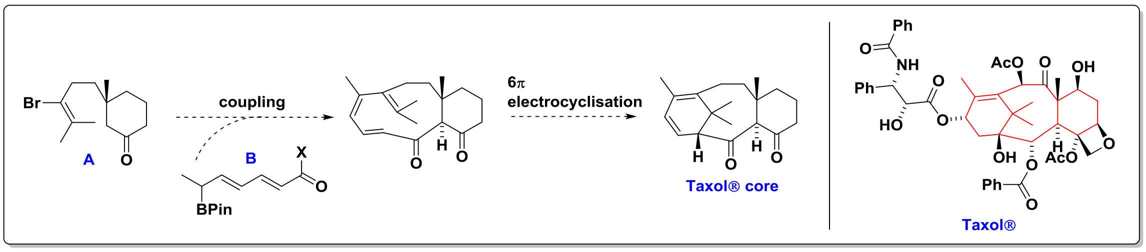
Our group has developed methodology which uses hydrozirconated terminal alkenes/alkynes as nucleophilic surrogates. Using a Cu(I) source and a chiral phosphoramidite system, 1,4-addition products can be prepared from cyclic enones with high yield and enantioselectivity (up to 97 % yield and 95 % ee) [1]. This methodology also tolerates a wide variety of functional groups, allowing for rapid generation of molecular complexity in short steps. As a consequence, this leads to increased efficiency and elegance of the overall chemical synthesis.

The purpose of this poster is two-fold. We showcase the use of a new functionalised diene that would give products not previously available and then apply this newly developed methodology towards the chemical synthesis of the Taxol® core.



The development of an end game strategy is currently underway. It is envisaged that a coupling between fragments **A** and **B**, followed by a 6π electrocyclic ring closure will give access to the final core structure.



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A Biosynthetically Inspired Route to Substituted Furans Using the Appel Reaction: Total Synthesis of F-Acid F_5[1]

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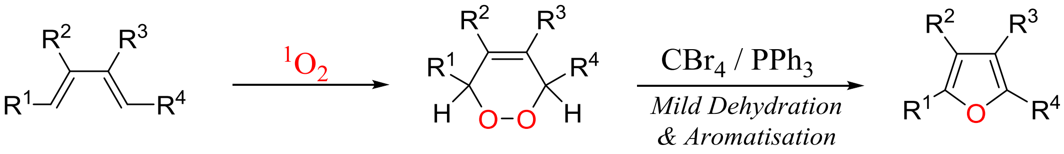
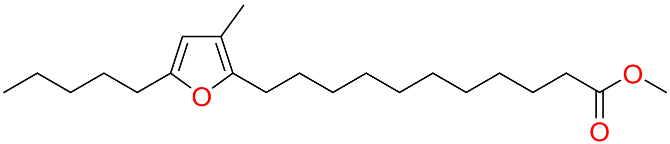
Furan fatty acids (F-Acids) are widely distributed in nature, and are present in high concentrations in several marine lipid sources. The isolation of single F-Acids from natural sources is a difficult task due to their susceptibility to oxidation and degradation by enzymes present in the sources; however, a consequence of this instability is the powerful antioxidant and radical-scavenging properties of F-Acids.[2] Such characteristics may prove beneficial in the resolution of diseases with an inflammatory response.



The conditions of the Appel reaction[3] have been harnessed to affect a mild, biosynthetically inspired, dehydration of endoperoxides allowing for the preparation of multi-substituted furans. Unlike traditional dehydrative procedures, this method is metal and acid free, and can be achieved under redox neutral conditions. It is general for a range aryl and alkyl substituted endoperoxides, and is tolerant of both a range of functional groups, and unstable furans which may be generated. Furthermore, the mild reaction conditions allowed for the total synthesis of a highly electron rich F-Acid (F_5), which due to its reactivity cannot be prepared *via* classical means.



Furan Fatty Acid F_5

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Aromatic substitutions of aryl halides enabled by dual photoactivation of a small organic dye

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Raúl Pérez-Ruiz[c]
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[b]Department of Chemistry, CISQ, University of La Rioja, Madre de Dios 53, 26006, Logroño, Spain
[c]Photoactivated Processes Unit, IMDEA Energy Institute, Ramón de la Sagra 3, 28935, Móstoles, Spain
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Metal-free photocatalytic activations of aryl halides are generally limited by the photonic energy and the efficiency of energy and electron transfer processes. While two-photon processes would provide sufficient photonic energy, the ultra-short lifetimes of the excited states prohibit chemical reactions. We were able to utilize 9,10-dicyanoanthracene (DCA), a simple organic dye, for the photocatalytic aromatic substitution of non-activated aryl halides.[1] This reaction operates under VIS irradiation via sequential photonic, electronic, and photonic activation of the organic dye and greatly expands the scope of current photoorganocatalysis.[2,3]

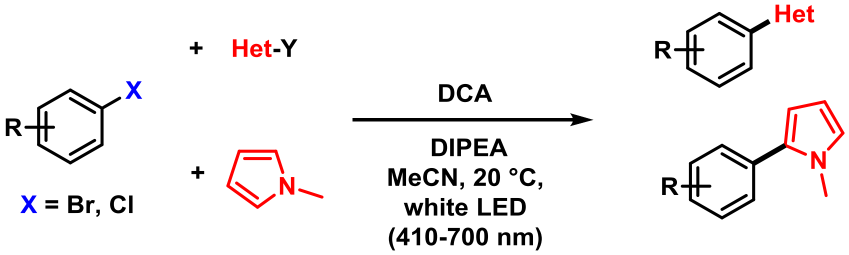

Figure 1. Abstract scheme of the presented project.

The ultimately formed excited radical anion DCA•−* enables the reductive activation of various aryl bromides and aryl chlorides under mild conditions and the application to hetero-biaryl cross-coupling and heteroatom functionalization reactions. Detailed spectroscopic and theoretical studies support the postulated dichromatic photocatalytic mechanism.[1]

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Organo-Iodine(III) Catalyzed Oxidative Cross-Coupling Reaction of Phenols

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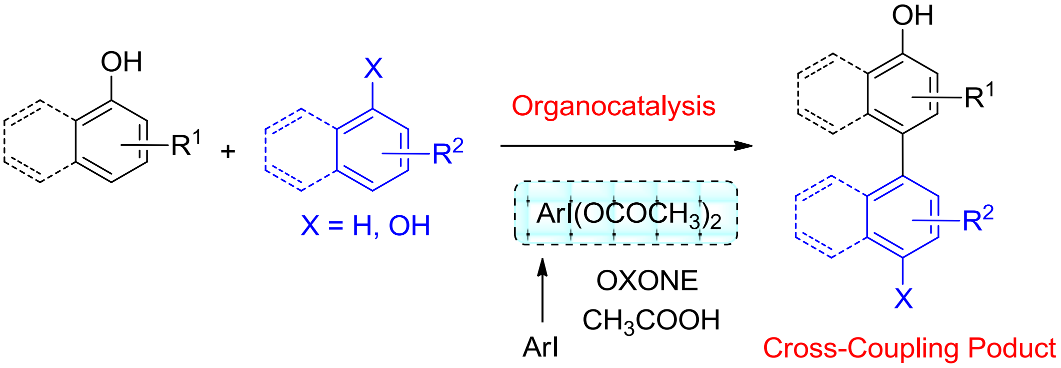
Phenol biaryls are important cores found in a wide range of compounds such as natural products, and ligands for transition-metal catalysts. Therefore, the development of the oxidative cross-coupling of unprotected phenols is important because of their environmentally-friendly processes and economical advantages. However, the catalytic oxidative cross-coupling reaction of phenols by C-H/C-H' coupling has remained challenging because of the formation of the undesired homo-coupling as a by-product and over-oxidation of the coupling products.

Recently 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] and then reported the oxidative cross-coupling reaction of phenols using stoichiometric hypervalent iodine reagents.[2] However, the hypervalent iodine(III) catalyzed cross-coupling reaction of phenols still remains to be realized. In this poster session, we present an organo-iodine(III) catalyzed oxidative cross-coupling reaction of phenols using Oxone® as a terminal oxidant (Scheme 1).[3]



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Hypervalent iodine as an Excellent Promoter of Thioglycosides in Glycosylation Reaction

Tetsuya Kajimoto*, Koji Morimoto, Kana Yanase, Ibuki Odaka, Yasuyuki Kita
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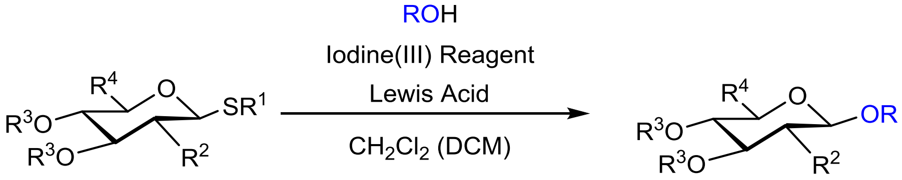
Thioglycosides are available donors in glycosylation due to the stability of the anomeric C-S bond under general reaction conditions of protection and deprotection as well as orthogonality in their activation. Thus, the tunable reactivity of thioglycosides has often been used for the synthesis of various oligosaccharides. The conventional glycosylation of thioglycosides was performed using a mercury salt, such as $HgSO_4$, $HgCl_2$, $Hg(OBz)_2$, or $Hg(NO_3)_2$. The use of $Cu(OTf)_2$ (Mukaiyama) or $CuBr_2$-Bu_4NBr-AgOTf (Ogawa and Ito) as an activator was further explored. However, these methods for the glycosylation of thioglycosides have relied on a toxic heavy metal oxidant for glycisidic bond formation.

The hypervalent iodine(III) reagents have been widely applied to useful organic transformations due to their mild oxidation abilities, low toxity, easy handling, and an alternative to toxic heavy metal reagents. Recently, we have reported reactions of hypervalent iodine-induced glycosylation reaction of thioglycoside.[1] In the present poster session, we present a glycosylation reaction of *thio*-glycosides with various alcohols using a combination of hypervalent iodine(III) reagent and Lewis acid. The reaction proceeds in a very short time in excellent yields at room temperature.

Glycosylation of thioglycosides using hypervalent iodine(III) reagent .



R^1 = Me, Ph, p-$C_8H_{17}O$-Ph
R^2 = OAc, NPhth, R^3 = Ac, Bn etc.
R^4 = CH_2OAc, CO_2Me etc.

Scheme 1. Hypervalent iodine induced metal-free glycosylation

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First Enantioselective Syntheses of Blennolides D, E and F

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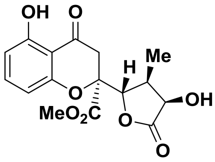
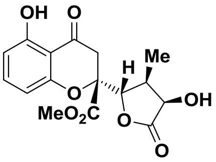
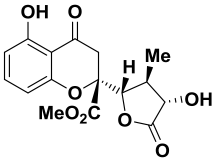
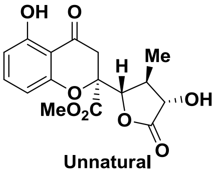
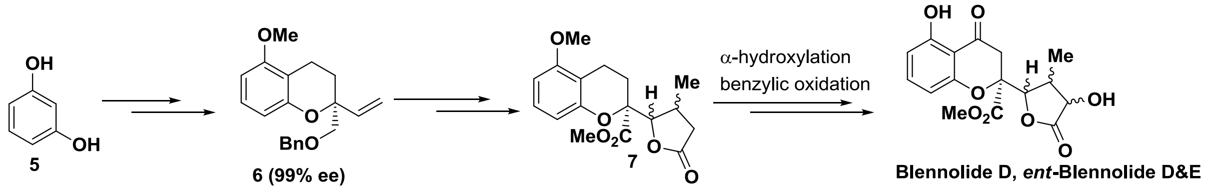
Natural products are very important as lead structures in the development of drugs and agrochemicals. Xanthones and chromanones are common skeletons present in a vast amount of natural products predominantly isolated from different types of fungi.[1] Moreover, many of the naturally occurring xanthone and chromanone derivatives as well as artificial derivatives exhibit various bioactivities.[1] Recently, new interesting chromanone containing natural products, namely blennolides D-F, have been isolated from *Blennoria sp.*, an endophytic fungus from *Carpobrotus edulis*.[2]


Blennolide D (1)


Blennolide E (2)


Blennolide F (3)


Unnatural Blennolide (4)



5
6 (99% ee)
7
Blennolide D, *ent*-Blennolide D&E as well as unnatural blennolide

Our sustained interest in the design and synthesis of natural products using domino process has resulted in the enantioselective total syntheses of several complex and structurally diverse natural products such as (−)-blennolide A, (−)-diversonol, (+)-linoxepin, and (+)-dicerandrol C, and secalonic acid E.[3] Here we describe the first enantioselective total syntheses of blennolide D, E, and F as well as of an unnatural diastereomer starting from resorcinol. The procedure is based on an enantioselective Wacker-type cyclization which allows us to obtain compound **6** with 99% ee. It follows a diastereoselective dihydroxylation, formation of a protected hydroxy aldehyde, Wittig reaction, Michael addition, lactonisation, hydroxylation and benzylic oxidation to obtain the desired natural products.

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Construction of Dibenzazepine Skeleton via Au(I)-Catalyzed Cycloisomerization on 7-Position of Indoline

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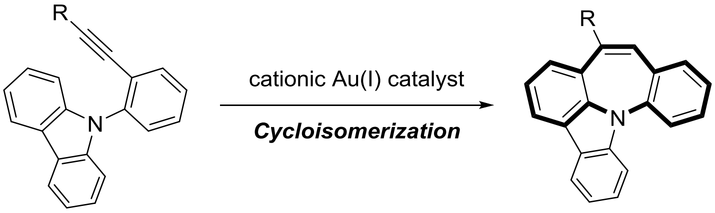
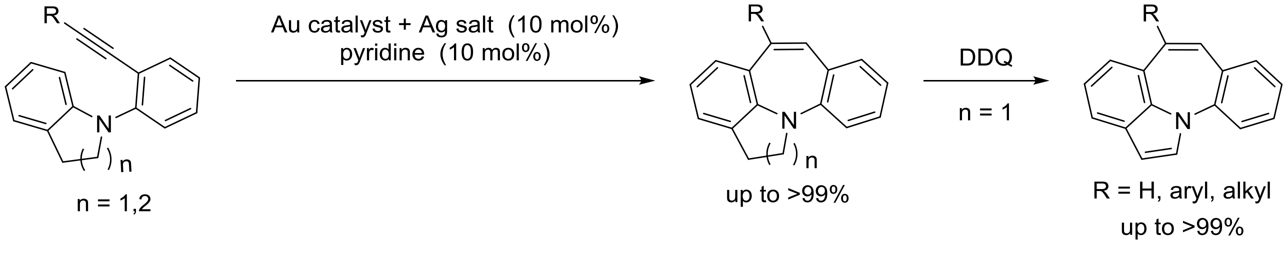
Dibenzazepine is a compound, where two benzene rings fuse with seven-membered azepine core. The dibenzazepine skeleton is found in various medicines, therefore, many stoichiometric or catalytic synthetic methods have been already reported. For example, palladium-catalyzed tandem intermolecular coupling of 2-bromostylene and 2-chloroaniline is a successful example.[1]

We recently achieved an atom-economical synthesis of dibenzazepine derivatives by cationic Au(I)-catalyzed cycloisomerization. The intramolecular reaction of *N*-(2-alkynylphenyl)carbazoles gave dibenzazepine derivatives containing a carbazole skeleton.[2]



We further examined the cycloisomerization of *N*-(2-alkynylphenyl)indoline (n = 1) in order to expand the substrate scope. As a result, dibenzazepine derivatives could be obtained by cationic Au(I) catalyst, and the addition of a catalytic amount of pyridine was critical for the high yield different from the previous reaction of carbazole-containing substrates. The obtained cycloadducts could be characterized by NMR analyses, but were unstable for the silica gel purification. Subsequent dehydrogenation by DDQ gave stable tetracyclic compounds where indole fuses with azepine skeleton. We also achieved to synthesize azepine derivatives fused with tetrahydroquinoline (n = 2).



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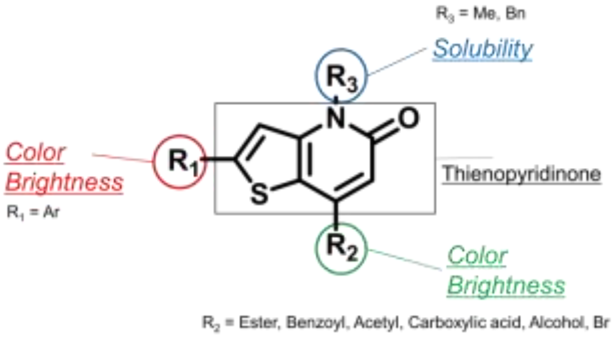
Synthesis and Photophysical Properties of Fluorescent Thieno[3,2-b]pyridin-5(4*H*)-ones

Dan-Bi Sung†, Bo Hyun Mun†, Sol Park‡, Hyi-Seung Lee†, ‡, Jihoon Lee†, Yeon-Ju Lee†, ‡, Hee Jae Shin†, ‡, and Jong Seok Lee*,†, ‡

†Marine Natural Products Chemistry Laboratory, Korea Institute of Ocean Science and Technology (KIOST), Ansan, Republic of Korea, 15627

‡Department of Marine Biotechnology, Korea University of Science and Technology, Daejeon, Republic of Korea, 34113

Molecular fluorescence is a rapidly growing research field, which has significant applications in physical, chemical, material, and biomedical sciences. In our continued efforts to construct a small molecular library of natural product-inspired fused heterocylic ring systems, thieno[3,2-*b*]pyridine-5(4*H*)-one has been recognized as a novel fluorescent scaffold. In this presentation, we demonstrate the synthesis of highly fluorescent thieno[3,2-b]pyridine-5(4H)-one derivatives and the photophysical properties of the resulting products.



The chemical synthesis of these novel fluorophores employs a series of subsequent reactions employing the Suzuki-Miyaura cross-coupling reaction, and a regioselective aza-[3 + 3] cycloaddition reaction of 3-aminothiophenes with α,β-unsaturated carboxylic acids promoted by BOP ((benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate). The structure-property relationship study of this novel fluorescent scaffold revealed that the introduction of a specific functional group to the thieno[3,2-*b*]pyridine-5(4*H*)-one scaffold enables the photophysical properties to be finely tuned. Consequently, significant hypsochromic and bathochromic shifts with large Stokes shifts up to 7672 cm^{-1} were observed and high quantum yields up to 99% were obtained in dichloromethane. The inherent ease of chemical modification of this fluorescent scaffold would bestow a tailor-made function into a molecule of choice.

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Total Syntheses of (–)-Rotenone and (–)-Deguelin

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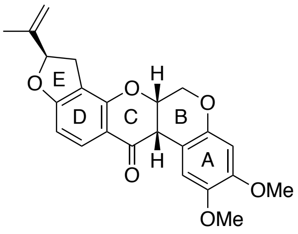
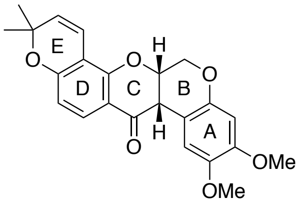
Rotenoids, as represented by (–)-rotenone (**1**) and (–)-deguelin (**2**), constitute a class of isoflavonoids with insecticidal and fish poison activities. These compounds possess a unique pentacyclic skeleton, composed of two aromatic and three oxacyclic rings. Herein, we will report an efficient synthetic approach to this class of molecules by way of stereospecific 1,2-rearrangement[1)] and S_NAr oxycyclization.[2)]

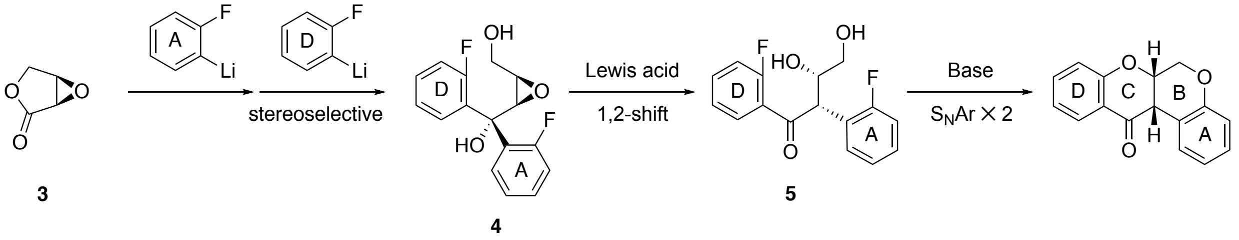


(–)-rotenone (**1**)



(–)-deguelin (**2**)

Scheme 1 illustrates the key aspects of our synthetic strategy.[3)] Two aromatic units were successively installed into epoxylactone **3**, giving the corresponding *tert*-alcohol **4** in rigorous stereoselectivity. Epoxyalcohol **4** was subjected to Lewis acid-promoted 1,2-rearrangement to give aldol **5** where only the aryl unit **A** underwent the 1,2-migration. Sequential S_NAr oxycyclizations constructed the rotenoid skeleton. By exploiting this unified strategy, we have achieved the asymmetric total syntheses of **1** and **2**.



Scheme 1

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Catalyst-free synthesis of 2,2-bis(pyridin-2-ylamino)cyclobutanols and their application in 5-(pyridin-2-ylamino)dihydrofuran-2(3H)-ones synthesis

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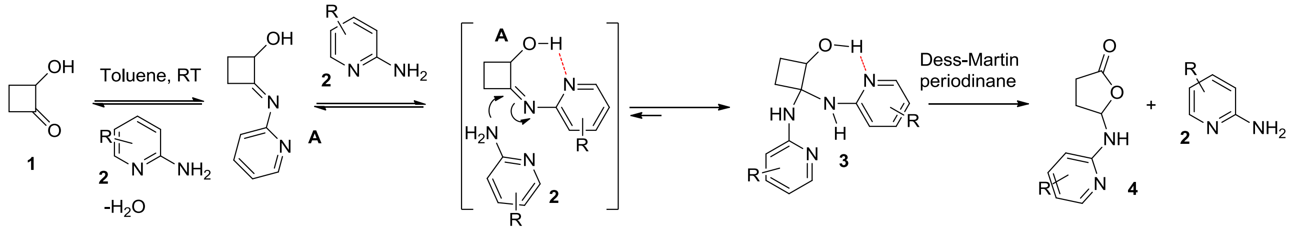
As part of our continuing interest in the chemistry of cyclobutanes,[1] in order to gain access to new molecular functions, we were curious if α-hydroxy cyclobutanone (given its chemical reactivity bestowed by the presence of two adjacent functional groups on a strained four-membered-ring)[2] could be harnessed to participate in reversible intermolecular bond-forming reactions, and therefore, as a versatile platform for the creation of aminal[3] based cyclobutanes **3**. In this respect, intramolecular hydrogen bonding could be used as a driving force to stabilize the reaction adduct. With this strategy in mind, the reaction of α-hydroxy cyclobutanone **1** and 2 equiv. of 2-aminopyridines **2** was screened. Under the optimum conditions, various substituents that differentiate the stereoelectronic nature of the starting 2-aminopyridines including methyl, ethyl, benzoyloxy, chloro, bromo could be applied with a general good efficiency of the process.



During the course of our studies, after the successful achievement of **3**, we decided to employ them as starting materials for the synthesis of the corresponding α,α-diamino cyclobutanones by Dess-Martin periodinane oxydation. Surprisingly, we found that **3** in the presence of Dess-Martin periodinane underwent unexpected ring expansion process providing functionalized 5-(pyridin-2-ylamino)dihydrofuran-2(3H)-ones **4**.

On the basis of the abovementioned results, a novel periodinane-mediated ring expansion was established, providing a range of novel γ-lactones bearing an amino pyridine unit.

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Reaction of Dehydroacetic Acid *N*-Acyl Hydrazones with Phenylboronic Acid. Synthesis of Novel Tetrahedral Boron Heterocycles with Antioxidant and Anti-inflammatory Activities.

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Ewa Różycka-Sokołowska,[c] Piotr Bałczewski,[c,d] John A. Joule,[e]
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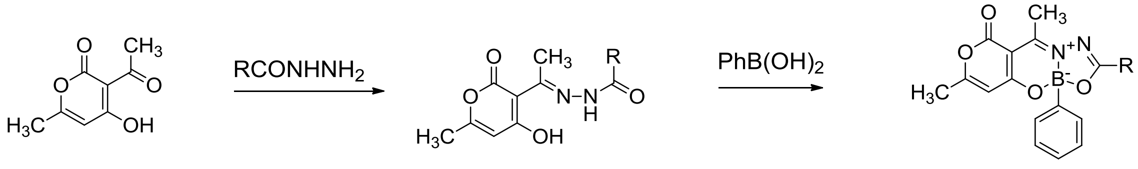
Our interest in boron heterocycles [1] as well as in the biological activity of small molecules [2] prompted us to design a synthesis of tetrahedral boron heterocycles **3** and investigate their antioxidant and anti-inflammatory activity. The presence of a pyrone ring, hydrazone moieties and a boron atom in compounds **3**, makes them potential candidates to possess antioxidant properties.

The new compounds **3** have been synthesized in good yields *via* cyclocondensation of dehydroacetic acid *N*-acyl hydrazones **2** with phenylboronic acid. Their characterization was achieved by their spectroscopic data and an X-Ray analysis for a representative example **3g** (R=2-thienyl).

Subsequently, their reducing activities as % interaction with the free stable radical DPPH and their % anti-lipid peroxidation activities (anti-LP %) using the assay of lipid peroxidation induced by AAPH has been studied according to our protocol [2]. Compounds have been tested as lipoxygenase inhibitors to define their anti-inflammatory activity. It was found that derivatives **3c** and **3e** are excellent inhibitors of lipid peroxidation (93% and 92% respectively). Among the tested compounds, the 4-Cl-substituted phenyl **3c** was found to highly inhibit LOX (100%) at 100μM, followed by 2-furyl derivative **3f** (88%) and the derivative **3a** (84%). Thus, derivative **3c** exhibits a very interesting biological profile combining antioxidant as well as anti-inflammatory activities and could be used as lead molecule for the design of LOX inhibitors.



1 **2** **3**

a: R = Ph, b: R = 4-MeC$_6$H$_4$, c: R = 4-ClC$_6$H$_4$, d: R = 4-O$_2$NC$_6$H$_4$, e: R = 2-O$_2$NC$_6$H$_4$, f: R = 2-furyl, g: R = 2-thienyl, h: R = CH$_2$Ph

Acknowledgement: The authors are grateful to the Alan and Linde Katritzky Foundation for financial support.

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Copper-Catalysed Asymmetric Allylic Alkylation of Alkylzirconocenes with Racemic Chloro-Tetrahydropyridines

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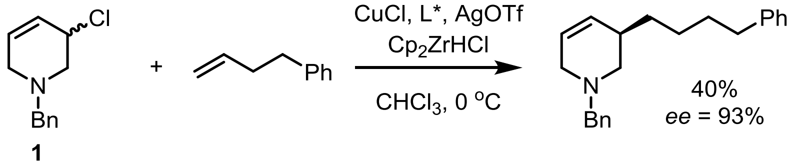
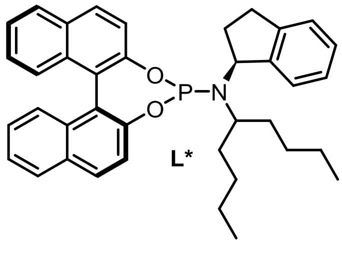
Asymmetric synthetic methods are important as they produce new organic scaffolds with desired stereostructures. Achieving enantiomerically enriched outcomes via stereoselective transformations of racemic substrates is especially valuable. Among those transformations asymmetric allylic alkylation (AAA) has been proven to be one of the most efficient and useful. We have developed copper catalysed-AAA's of *in situ* formed, non-stabilized alkylzirconocene nucleophiles with various cyclic allylic halides and pseudohalides. Racemic 3-chloro-1,2,3,6-tetrahydropyridines (**1**) were also tested as substrates and shown to go through kinetic resolution.

1,2,3,6-Tetrahydropyridines constitute an important subgroup of heterocycles as they are found in a wide range of biologically active compounds including alkaloids and iminosugars. Therefore, chemists have worked on development of new stereoselective strategies to afford these heterocycles. Here we report the successful kinetic resolution of racemic 3-chloro-1,2,3,6-tetrahydropyridines in Cu-catalysed reactions with alkylzirconocenes leading to formation of novel, enantiomerically enriched 1,2,3,6-tetrahydropyridines.





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Dual Copper/Proline Catalysis Towards Dynamic Kinetic Asymmetric Transformations

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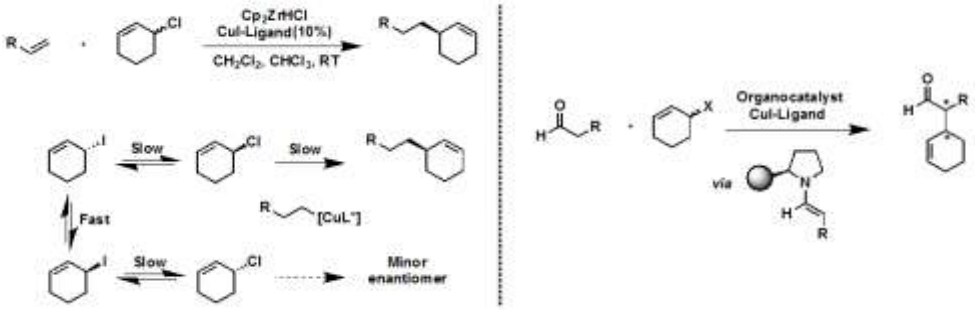
Oxford, United Kingdom

The ability to make carbon-based compounds efficiently is essential for the development of new medicines, fragrances, polymers, materials, catalysts and the study of biological and physical properties. Asymmetric C–C bond formation generates single enantiomers of chiral molecules at the same time as the molecular framework is assembled and is therefore strategically powerful in synthesis design. In this context, the use of racemic mixtures of chiral starting materials in dynamic kinetic asymmetric transformations (DYKATs) allows to access highly enantiomerically enriched products in yields superior to 50%.[1] This approach constitutes a complementary strategy to the more widely embraced use of prochiral starting materials or kinetic resolutions. However, the development of efficient DYKAT processes is rather limited.

Our research group has recently found that alkylzirconium reagents can be used in highly efficient DYKATs with racemic allyl chlorides in the presence of 10 mol% of a CuI-phosphoramidite complex.[2] Mechanistic studies suggest that this process takes place through the racemization of the allyl chloride via succesive S_n2'reactions with CuI (see scheme below). Selective nucleophilic attack on one of the enantiomers leads to enantioenriched products.[3]

Based on this principle, we envisioned that this copper-catalyzed racemization could be carried out in the presence of other nucleophiles, such as enamines. In this way, by using a chiral organocatalyst (i.e. proline) and if a selective nucleophilic attack takes place we could generate two enantioenriched contiguous stereocentres.



Herein we will describe our efforts toward the implementation of this strategy as well as the problems encountered so far.

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Divergent synthesis of 2,3-disubstituted indoles

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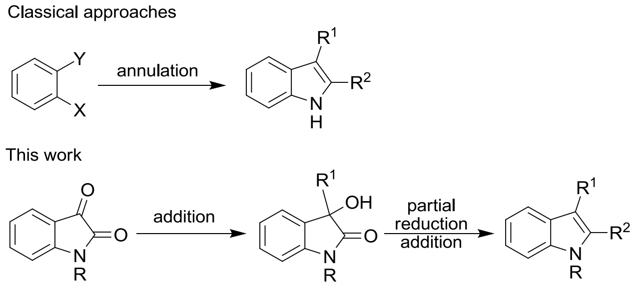
Compounds containing an indole moiety are very valuable due to their diverse biological properties. A number of methods for their synthesis are known. However, these are often hampered by certain limitations: poor regioselectivity and non-ideal functional group tolerance. We have designed and developed an approach to the synthesis of 2,3-disubstituted indoles in a manner which overcomes these obstacles.[1] The selective activation of the amide carbonyl in isatin-derived oxindoles by Schwartz's reagent-mediated reduction has allowed us to obtain the title compounds regiospecifically and with excellent functional group tolerance.



The obtained compounds were investigated for acetylcholinesterase (AChE) inhibitory activity as the indole skeleton is often seen in the structure of enzyme inhibitors. All of the compounds inhibited AChE isolated from *Electrophorus electricus* (electric eel). The determined IC_{50} values were in the range of 2.69-279.7 μM. Moreover, such properties as logP, blood-brain barrier transport parameters, and Caco2 permeabilities were also calculated. The inhibitory potency towards AChE activity and the ability to penetrate into the central nervous system (CNS) illustrate their potential *in vivo* activity.

Additionally, investigations into the divergent synthesis of biindoles utilizing the described methodology will be described.

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Vinylogous type of Ferrier-Petasis rearrangement of vinyl ethers and alkoxydienes

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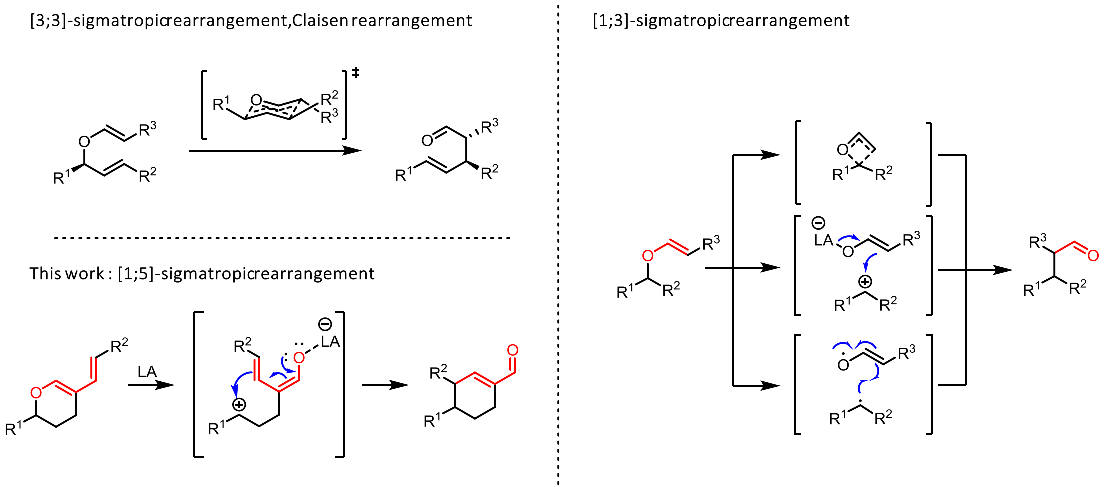
Vinyl ethers undergo two particular transformations. One of them is the [3,3] sigmatropic rearrangement of allyl vinyl and allyl aryl ethers, known as the Claisen rearrangement, which leads to γ,δ-unsaturated carbonyl compounds. On the other hand, a less well-known transformation of vinyl ethers is the Lewis acid-catalyzed [1,3] rearrangement. [1]



Pioneering investigations of the [1,3] rearrangement have been made by the Ferrier group in the 1970s.[2] They've shown that enol ethers, furanose and pyranose derivatives undergo smooth reorganization with a catalytic amount of mercury salts. This process, called the Ferrier carbacyclization, leads to polyhydroxylated cyclohexenes and cyclopentenes.[3] In later years, Petasis and co-workers have demonstrated that the rearrangement of vinyl ethers, called the Ferrier-Petasis rearrangement, is a useful tool in the synthesis of stereochemically defined natural products and biologically active compounds.

While conducting research on the modification of the transformation described above, we discovered that alkoxydienes undergo a smooth rearrangement in a vinylogous manner with a catalytic amount of titanium (IV) chloride, which leads to highly substituted cyclohexenes.

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Synthesis and Transformation of 1,2-Diketones *via* Sequential Catalysis

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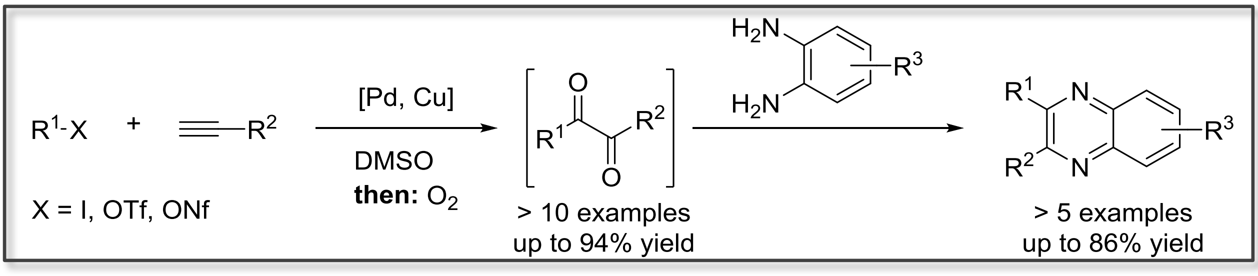
1,2-Diketones are very important structural units in biologically active molecules[1] that can be transformed into complex structures in organic synthesis.[2] A number of methods for the synthesis of 1,2-diketones have been developed where the Pd(II)- and Cu(II)-catalyzed oxidation of alkynes is considered to be one of the most practical strategies.[3]

The aim of the present work is the preparation of the 1,2-diketone moiety *via* a consecutive *pseudo*-four-component reaction while a single catalyst system is reused, without isolation of the intermediate alkyne. The sequence starts with a Pd(0)/Cu(I)-catalyzed *Sonogashira* coupling of a terminal alkyne and an aryl (pseudo)halide in DMSO. Subsequently, the solvent serves as an oxidant, whereas the catalyst system is reoxidized by molecular oxygen furnishing the desired product. Due to its modular nature the reaction sequence offers quick access to a broad range of variably substituted 1,2-diketones by virtue of the terminal alkyne and aryl (pseudo)halide. Electron releasing as well as withdrawing substituents are equally well tolerated.

1,2-Diketones can be transformed into quinoxalines, which are of interest as an important class of stable fluorescent heterocycles, finding use in several practical applications, such as laser dyes, emitters in light-emitting diodes, and as fluorescent sensors.[4] Based upon this strategy, we also report a one-pot synthesis of quinoxalines in a consecutive *pseudo*-five-component process. This sequence additionally includes a cyclocondensation transforming the 1,2-diketone to the corresponding heterocyclic compound (Scheme 1).

Moreover, different binucleophiles can also be employed in the one-pot sequence furnishing other heterocyclic systems. These processes are currently under investigation.



Scheme 1: Multi-component one-pot procedures for the synthesis of 1,2-diketones or quinoxalines.

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Development of new scaffolds for chiral diene-ligands

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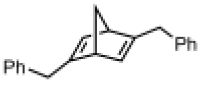
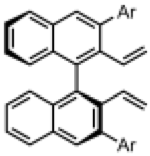
More than a decade ago, first examples of chiral diene-ligands were developed and applied successfully in the asymmetric addition of boronic acids to conjugated enones. More recent advances in this field extended the applicability of this ligand class to a variety of transformations, however, the use of such chelating diene-ligands remains restricted to Rhodium or Iridium catalyzed transformations. The design of these chiral diene-ligands is limited to the asymmetric substitution of a rigid core structure, such as bicyclic dienes, and to binaphtyl-based ligands.

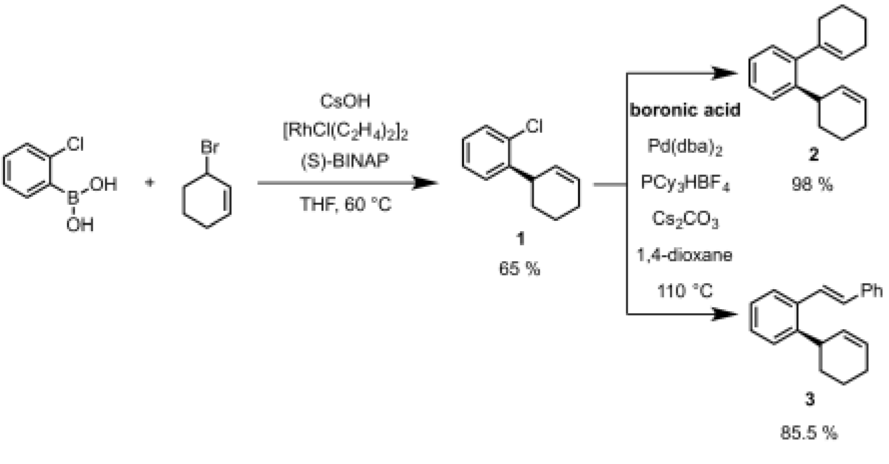


Hayashi, 2003



Du, 2010

We envision overcoming these structural limitations of chiral diene-ligands by designing suitable dienes with asymmetric quaternary centers as a source of chirality. The synthesis strategy applies the recently reported asymmetric allylic arylation of racemic halides with boronic acids as the key step to create chiral olefins, e.g. **1**. This approach allows us to subsequently modify these compounds to access a range of dienes such as **2** or **3** and test them as potential diene ligands.



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Manganese(I)-Catalyzed C–C/C–H Activation

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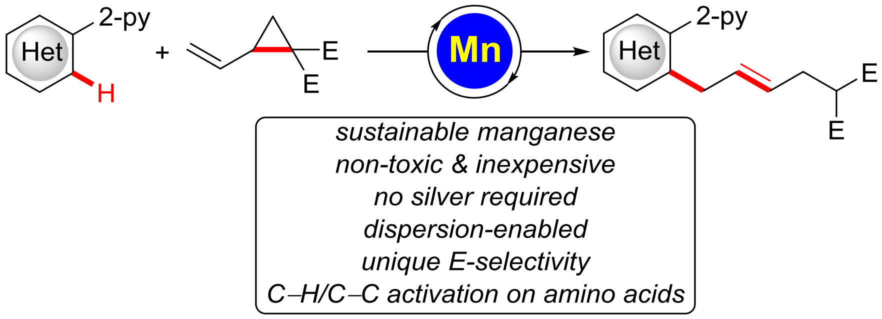
The functionalization of unreactive C–H bonds has emerged as a powerful tool for molecular synthesis.[1] Although notable progress has been achieved for precious 4d and 5d transition-metal catalysts, focus has shifted towards the use of more sustainable base-metal compounds.[2] In recent years, non-toxic and inexpensive manganese catalysis has gained a significant impetus in C–H functionalizations.[3] Furthermore, as a new strategy for organic synthesis, challenging C–C bond cleavage reactions have a great potential to gain future interest in academic and industrial research. In spite of these undisputed advances, catalytic C–H/C–C activations continue to be scarce, with all the reported examples requiring the precious metal rhodium,[4] whereas only one example used a cobalt(III)-based catalyst in the presence of silver salts as additives.[5]

In sharp contrast, we have developed a simple manganese(I) catalyst for C–H activation of different heteroarenes, followed by C–C activation with good to excellent yields. The reaction occurred with high regio- and *E*-diastereoselectivity.[6] Detailed mechanistic studies provided strong support for a facile C–H activation and a rate determining C–C cleavage, with key contributions of London dispersion[7] interactions. The power of this method has been highlighted with a broad substrate scope, including the racemization-free transformation of amino acids *via* C–C/C–H activation.



sustainable manganese
non-toxic & inexpensive
no silver required
dispersion-enabled
unique E-selectivity
C–H/C–C activation on amino acids

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Functionalization of dehydroacetic acid by electroactive moieties

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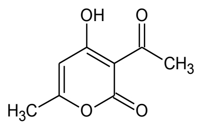
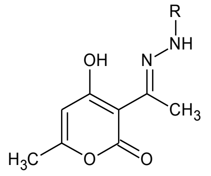
Dehydroacetic acid (DHA) is a versatile starting material for the synthesis of a wide variety of heterocyclic ring systems. Moreover, DHA and its Schiff base can complex difluoroboron moiety and such difluoroboron complexes present two advantages: (i) it enhances the reactivity of DHA itself and (ii) some of these derivatives can exhibit fluorescence properties. We report in this work the functionalization of DHA-BF_2 and its Schiff base by a phenyl ring or an electroactivecore (tetrathiafulvalene or ferrocene) in order to analyze the influence of the electrophore on the fluorophore properties.

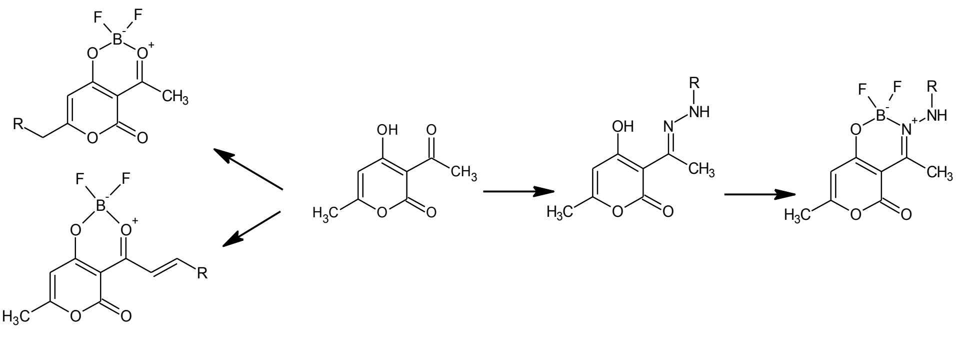


DHA



Shiff base of DHA

For that purpose, three approaches were used: i) Wittig reaction at the 6 position involving aldehydes bearing an electroactive unit and a phosphonium salt of DHA, ii) condensation reactions of these aldehydes with DHA BF_2 at the acetyl position and iii) condensation of the aldehydes on the DHA-hydrazone as demonstrated below. Depending on the reaction used, the spacer group between the DHA moiety and the electroactive part will be different as well as the position of the connecting part on the DHA core. The redox and the photophysical properties of obtained derivatives have been studied. [1]



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Synthesis of Acridines *via* Micellar Open Air Palladium Catalyzed Amination in Water

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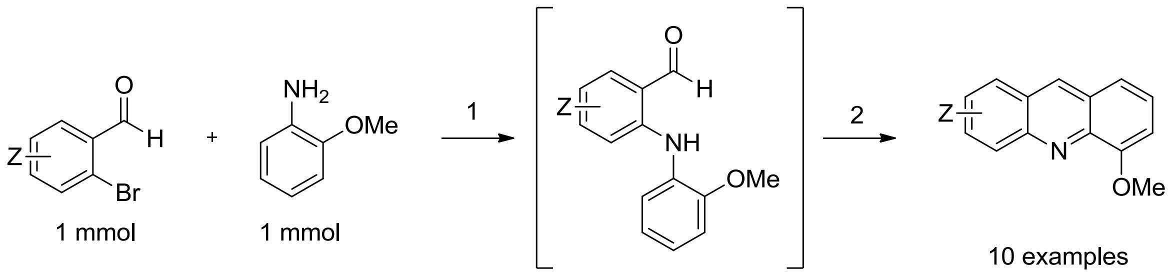
Department of Material Science, University of Milano-Bicocca, Milano/Italy 20125

Acridines displayed interesting properties in biological active applications, like antibacterial, antimicotic and anticancer agents, mainly owing to their inhibition of DNA-related enzymes, such as topoisomerases, by intercalation. [1] Fluorinated acridines were also successfully used in material science, as additives in intraocular lens to prevent the calcium containing deposit. [2] A recently reported methodology for the synthesis of unsymmetrical acridines involves a tandem coupling-cyclization approach under Pd(0)-catalysis by using readily available 2-bromobenzaldehydes and anilines as starting materials. [3] One of our main research activity entail the synthesis of fluorinated hydroxy aza heterocycles to be tested against resistant bacteria, we decide to apply the amination-electrocyclization synthetic strategy to the synthesis of acridines intermediates.



1) Pd(0), Diphosphine Ligand, Base, Kolliphor (1.97% H_2O) / cosolvent 9:1, open air, 60 °C, 2h.
2) TFA, r.t., 12h.

The use of an innovative micellar catalysis method in water for the palladium catalyzed amination step, with Klolliphor® EL as surfactant agent, allowed us to obtain excellent yields, lowering by more than ten fold the reaction times respect to the classical organic solution process, without the need of an inert atmosphere.

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Desymmetrisation of *Meso*-Cyclic Dialkylphosphates via Cu-Catalysed Allylic Alkylation

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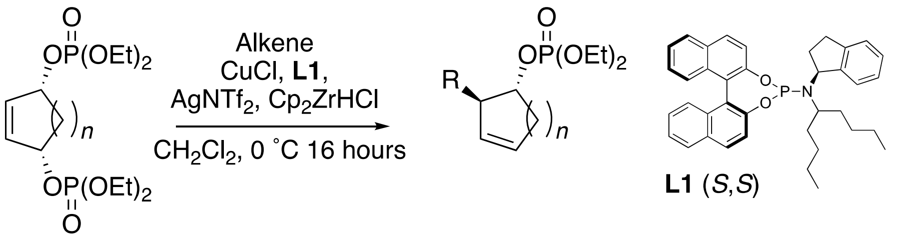
Desymmetrisation reactions of *meso*-compounds derived from simple starting materials can provide highly functionalised building blocks for the synthesis of chiral molecules.[1] These valuable transformations are often limited by poor functional group compatibility. We report here a novel Cu(I)-catalysed asymmetric allylic alkylation procedure that involves hydrozirconated alkenes generated *in situ*.[2] Phosphoramidite ligands are used as a source of asymmetric induction and the electrophile is a bis-dialkylphosphate easily accessed from a *meso*-diol.



L1 (*S*,*S*)

n = 1, 2 and 3
32 examples
>20:1 *trans*:*cis*
up to 82% yield and 97% e.e

This carbon-carbon bond forming reaction provides cyclic compounds bearing 2 stereocentres with an alkene and phosphate group for further functionality. In addition the procedure consistently demonstrates high enantioselectivity and diastereoselectivity.

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Molecular and Chiral Recognition of Anions Using Diamidonaphthalenedipyrrole-Derived Fluorescent Sensors

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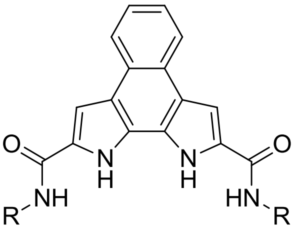
The spectroscopic properties of bisamide derivatives of naphthalenedipyrrole (**1**) can be fine-tuned through small modifications of the structure at the sensor periphery.



1a: R=n-Bu
1b: R= Ph

We will show that the strong fluorescence of these compounds is perturbed through the binding of anionic species in the binding pocket through four hydrogen bonds. Importantly, these effects depend on the nature of the anionic guest, its concentration, and the specific structure of the receptor host. As shown in Fig. 1, in the case of one derivative (**1a**) the fluorescence is selectively quenched upon addition of $PhCO_2^-$, while other anions do not have an effect on its spectral properties. In another case (**1b**), only $H_2PO_4^-$ triggers a spectacular enhancement of fluorescence (more than five times higher intensity), while other anions do not change its spectral properties. Such selective responses are related to the selectivity of the anionic species binding, which can be controlled with the structure of the binding pocket. In this poster we demonstrate that a diamidonaphthalenedipyrrole platform can be used to construct selective sensors for anions that allow for fast and efficient identification of the desired anion present in the analytical samples [1], and we provide results of recent studies on chiral recognition abilities of this platform.

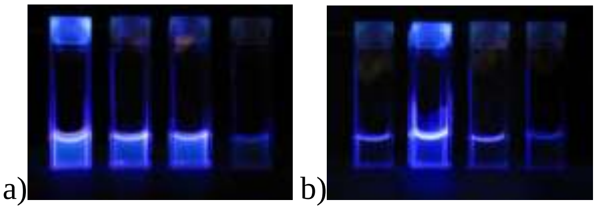


Fig. 1 Fluorescence of receptors **1a** (a) and **1b** (b) in DMSO.

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Reversible Folding of a β-hairpin peptide by a metal chelating amino acid

Jan Reutzel, Timm Marian Diogo and Armin Geyer
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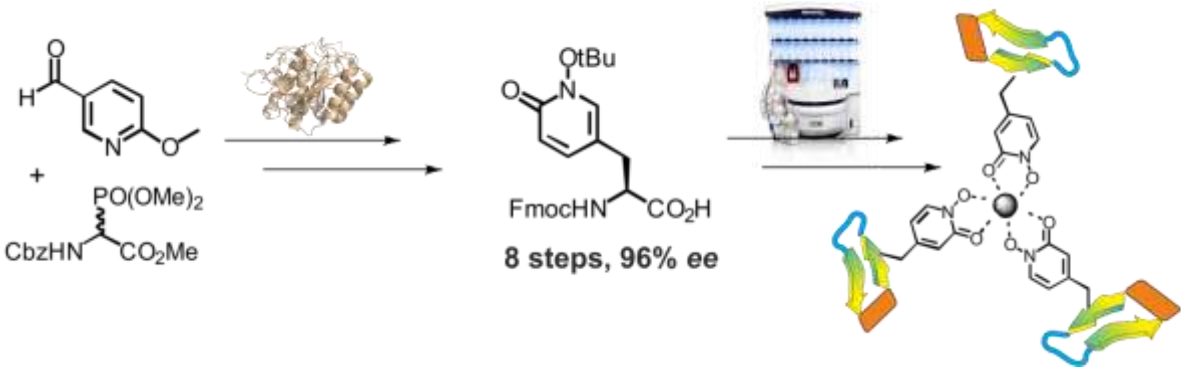

5-(1-Hydroxy-pyridin-2(*1H*)-onyl) L-alanine (Hop)is a *N*-hydroxy-1,2-pyridone functionalized α-amino acid with the desired metal chelating properties of DOPA but without its unwanted redox activity. The Fmoc-protected amino acid Fmoc-L-Hop(*t*Bu)-OH was synthesized from glycine phosphonate followed by enzymatic hydrolysis of the methyl ester yielding the Hop L-isomer in 96% *ee*. The Hop amino acid is used in automated peptide synthesis for the assembly of a 14mer β-hairpin peptide with the sequence [dsb^{1,14}]H-CH**X**ETGKHGHKLVC-OH (X = W, L-Hop). While the 10 π electron containing indol side-chain of L-Trp in peptide completes the formation of a hydrophobic cluster and results in 90% folding, the folded fraction is significantly decreased to approximately 30% for the 6 π electron L-Hop side chain. Metal chelation of Ga^{3+} reconstitutes the folding oft the Hop-peptide to above 60% due to the formation of a trimer. The chelating process of is monitored by NMR spectroscopy and the subsequent release of Ga^{3+} by a competitive metal chelator exemplifies the reversible oligomerization of peptide epitopes by metal chelation, bearing the opportunity to synthesize protein-sized aggregates on the basis of reversible chemistry in water.[1]

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Luminescent Quinoxaline and Phenazine Dyes One-pot Syntheses, Photophysics and Electronic Structure

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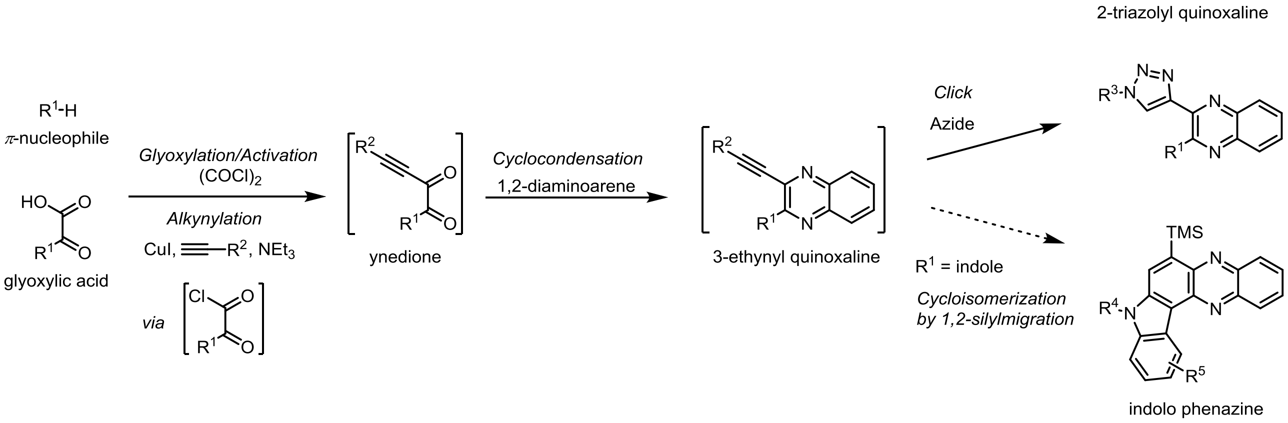
Especially in today's times, the concept of one-pot and multicomponent reactions (MCR) adopts a central position in modern synthetic chemistry. Particularly the formation of fluorophores and chromophores *via* a rapid and elegant MCR approach remains a paramount challenge for organic and materials chemists.[**1**] Ultimately, with adequate reflection of this issue a crucial aspect of the one-pot fashion is the diversity-oriented nature. With the aid of this methodology substance libraries can be set up. These conceptual approaches has already found its way into the construction of highly luminescent and stable heterocycles. For this purpose, our group has recently developed a set of complementary one-pot syntheses of fluorescent and solvatochromic 3-ethynyl quinoxalines and 2-triazolyl quinoxalines (Scheme 1) [**2**,**3**] based on intermediary ynediones.[**4**] Interestingly, the indole substituted 3-trimethylsilyl quinoxaline undergoes an cycloisomerization and leads to indolo phenazine derivatives.



Scheme 1: Diversity-oriented multi-component procedures for the synthesis of 3-ethynyl-, 2-triazolyl quinoxalines and indolo phenazines.

Consequently, we set out to investigate the reaction scope as well as the photophysical and chemical properties of the synthesized compounds.

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Design of Novel Mixed Thiourea-Triazole H-Donor and H-Donor/Halogen-Donor Catalysts

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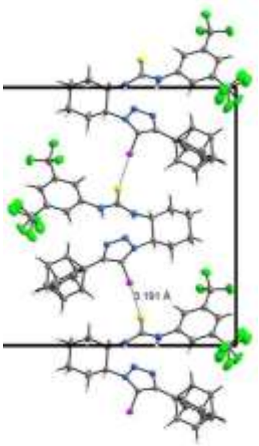
In the past years, asymmetric hydrogen-donor catalysis has emerged as a powerfull synthetic approach for the preparation of a variety of valuable chiral organic molecules. Among the different types of H-donors, (thio)ureas represent the most exploited active moieties.[1] Alternatively, our group recently demonstrated that 1,2,3-triazoles, which present an intrinsically weaker H-donor character via their less polarized C-H bonds, are also excellent structures for catalytic anion-binding processes.[2] Furthermore, 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.[3]

Herein, we present the design and synthesis of new types of chiral bifunctional catalysts, based on a thiourea and a 1,2,3-triazole active moieties. In addition, 5-iodo-1,2,3-triazole-containing structures have been designed, presenting both hydrogen- and halogen-donor properties. In these cases, the iodo-triazole moiety enhances the hydrogen-donor properties of the thiourea-moiety of another catalyst-molecule by intermolecular I—S halogen-bonding.



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Conversion of Ester Moieties to Bromophenol

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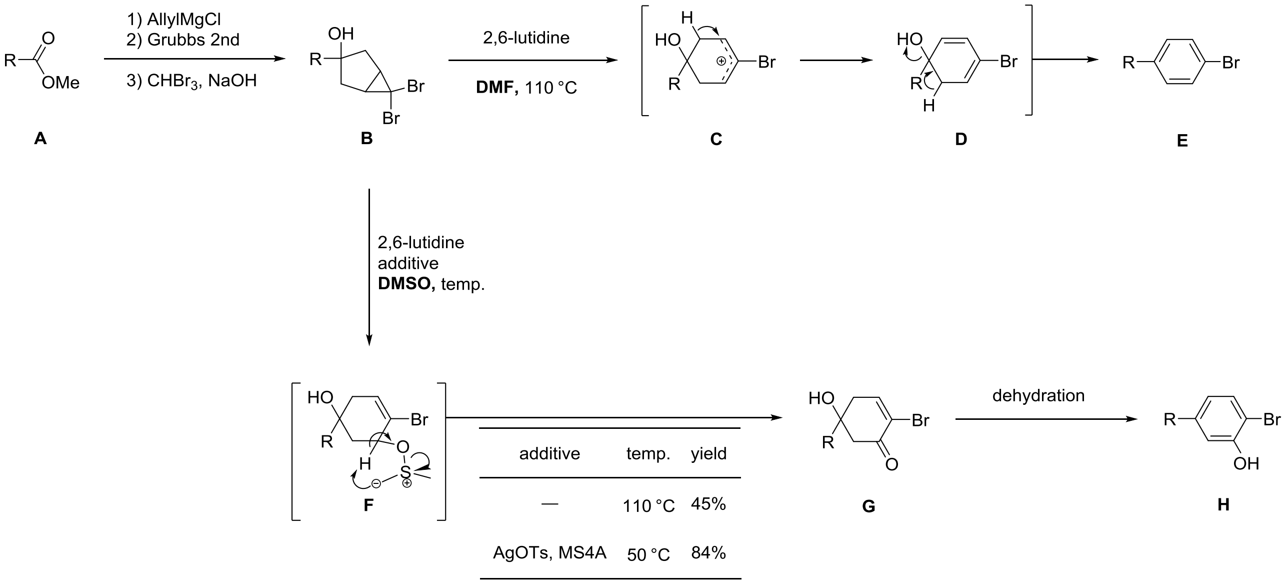
Furo-cho, Chikusa-ku

We have reported a reaction to synthesize bromobenzene **E** from ester **A** via dibromocyclopropane **B**. When **B** was heated in DMF, ring opening of **B** proceeded to generate allyl cation intermediate **C**. Deprotonation of **C**, followed by dehydration of the resulting diene **D**, afforded **E**. When DMSO was used as a solvent for the ring opening instead of DMF, hydroxyketone **G** was obtained in a moderate yield. Mechanism of the production of **G** is considered as follows. Ring opening of the dibromocyclopropane generated the same intermediate **C**, which was captured by DMSO to give sulfonium intermediate **F**. Then, deprotonation at α-position of the oxygen atom and elimination of dimethyl sulfide gave **G**. By addition of silver tosylate, the ring opening reaction of **B** could be run at a lower temperature, resulting in improvement of the yield. The resulting hydroxyketone **G** could be converted into bromophenol **H**. In this congress, we will present the details of this transformation, including the substrate scope.



additive	temp.	yield
—	110 °C	45%
AgOTs, MS4A	50 °C	84%

K. Ueda, H. Umihara, S. Yokoshima, and T. Fukuyama, *Org. Lett.*, **17**, 3191 (2015)

Membrane-Spanning Building Blocks for Artificial Signal Transduction

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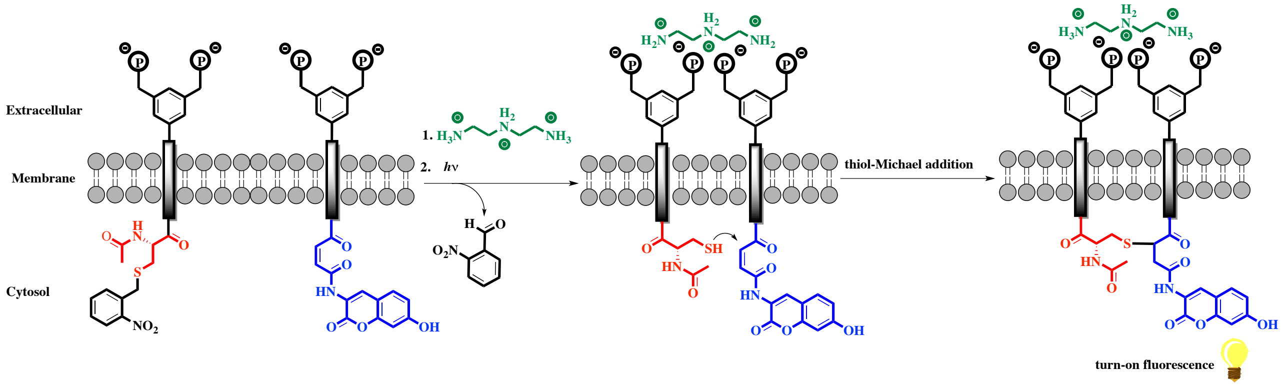
Signal transduction is the intercellular communication initiated by signaling molecules and prerequisite for all living organisms. Despite the enormous importance of signal transduction in nature, only very few entirely artificial transduction systems have been reported, which were designed by chemists.[1], [2]

Inspired by nature, we now present a chemical model that mimics the entire process from receptor docking, over signal transmission, to the chemical reaction on the intracellular side of the membrane. Our concept imitates the signaling principle of receptor tyrosine kinases: Two rigid lipophilic transmembrane (TM) units, which are made from steroids, both carry bisphosphonate receptor head groups for the ditopic recognition of small triammonium cations. This recognition event brings also the opposite ends of both TM units in close proximity, so that a chemical reaction can be triggered inside. Since thiols play crucial roles in biological systems, we envisage the use of a pair of tail moieties, which are capable of performing a thiol-Michael addition reaction. Here, on the one end of the TM unit, we decided to use a coumarin-based fluorescent probe with an "open" maleimide as the thiol acceptor, which will be specifically attacked by a cystein thiol linked to the other end of the second TM unit. The maleimide moiety efficiently quenches the coumarin fluorescence, which is, however, immediately restored after thiol addition. This leads to a drastic increase in fluorescence quantum yield – the output signal. [2], [3]



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Electrophilic Activation of Iodonium Ylides by Halogen-Bond-Donor Catalysis for Cross Enolate Coupling

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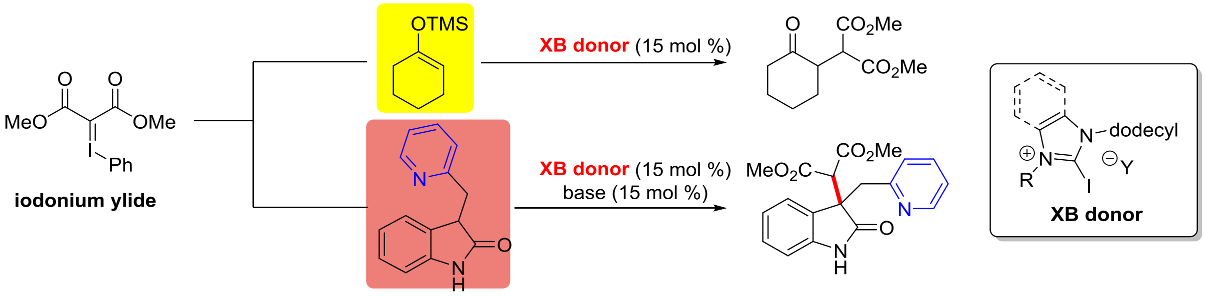
Halogen bonding (XB) is known as the non-covalent interactions between an XB donor (Lewis acidic moiety of an electron deficient haloalkene or -arene) and an XB acceptor (Lewis base). Despite many reports on XB interactions in the areas of crystal engineering and supramolecular chemistry, the utilization in synthetic organic chemistry is still developing research area. Recently, we have developed several reactions utilizing the unique properties of XB interaction.[1–3] In particular, we focused on the soft Lewis acidity of XB donors, which would allow them to preferentially interact with soft co-catalyst[2] and electrophiles,[3] enabling otherwise inaccessible transformation.

Very recently, we found that an iodonium(III) ylide was effectively activated by an XB-donor catalyst, and the umpolung alkylation of silyl enol ethers proceeded under mild conditions to afford various 1,4-dicarbonyl compounds in high yields.

Unlike typical transition-metal activation processes of such ylide precursors, which tend to proceed via carbenoid intermediates, experimental and computational studies indicate that halogen bonding between the XB donor catalyst and the iodonium ylide plays a crucial role in promoting the reaction. To make the reaction direct and more atom-economical, the identification of a compatible Brønsted base catalyst enabled the extension of this method to enols generated in situ to give the corresponding adducts in good yields.[3]



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Pd(0) catalyzed carbonylative annulation of 1,3-diphenyltriazene derivatives for facile and highly selective synthesis of 3-arylbenzo[1,2,3]triazin-4(*3H*)-ones.

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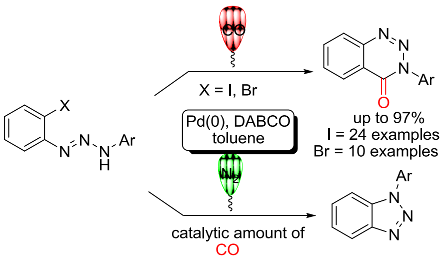
1,2,3-triazin-4-one is an important heterocyclic scaffold in medicinal chemistry. Derivatives of 1,2,3-triazin-4-ones exhibit a wide variety of biological activities such as sedative, diuretic, anesthetic, antiarthritic, antitubercular and antitumor activities[1]. Benzo-1,2,3-triazin-4-ones are also useful starting materials in organic synthesis for the synthesis of isoquinolones by metal catalyzed denitrogenative transannulation reactions with allenes and alkynes[2]. Conventionally 1,2,3-benzotriazin-4(*3H*)-ones were synthesized through a multistep synthesis from methyl anthranilates and anthranilamides using diazotization of the amino functional group[3]. Pd catalyzed denitrogenative carbonylation of aryltriazenes in acidic conditions yields amides[4].

Although transition metal catalyzed carbonylative annulation reaction has been applied to the synthesis of a variety of heterocyclic scaffolds[5], it has not been applied to the synthesis of 1,2,3-benzotriaz-4(3*H*)-ones. Our interest in Pd(0) catalyzed carbonylation reactions[6] using carbon monoxide led us to the investigation of carbonylative annulation of 1-(2-X-phenyl)-3-phenyltriaz-1-ene (X = Br, I). Using the carbonylative annulation strategy a facile synthetic method has been developed for the synthesis of 3-arylbenzo[1,2,3]triazin-4(3*H*)-ones. Interestingly in the presence of catalytic amount of carbon monoxide the reaction led to the formation of benzotriazoles. A probable mechanism for these reactions has been proposed by investigation of control experiments.



Pd catalyzed carbonylative annulation of iodo and bromo 1,2,3-triazenes

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New Photosensitizers with extended 1,4-dithiin ligand

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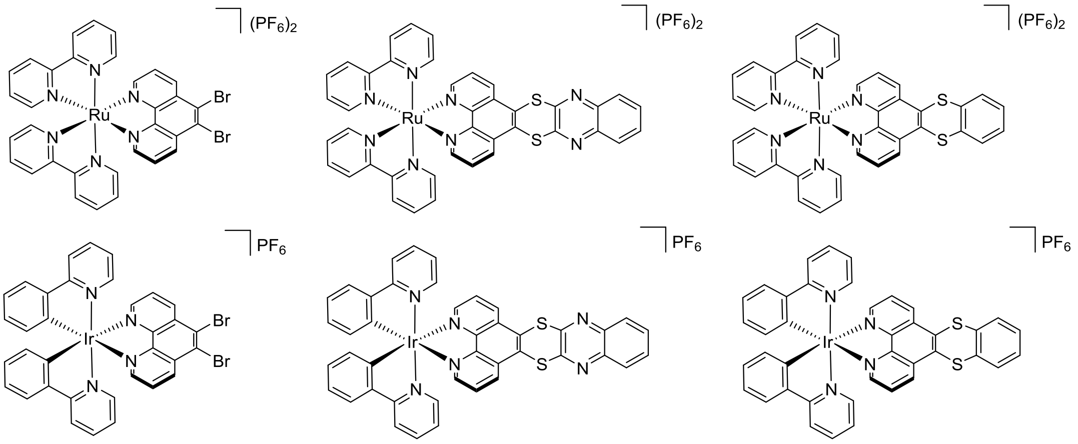
Sun-powered photophysical processes can contribute to an environmentally friendly supply of fuel or valuable substances in the future. Charge- and energy transfer are the key elements in photocatalysis and their understanding and optimization are of crucial importance. A variety of polynuclear complexes with Ru(II) or Ir(III) chromophores have shown remarkable potential of charge separation or energy transfer. [1] A 1,4-dithiine moiety is nonplanar (however, the activation barrier of the swinging-through via a planar conformation is very low). On the other hand, the oxidized 1,4-dithiin structure is planar. Therefore, an electron transfer might be accelerated, or delayed, by the oxidation state of the 1,4-dithiine moiety.

We present a row of new Ru(II) and Ir(III) photosensitizers with a new ligand system expanded with a 1,4-dithiine structure. Furthermore, we investigated the photophysical properties and compared the photocatalytic applications with a benchmark system. [2]



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Synthesis of New 1,2,4-Trioxane-Chloroquinoline Hybrids via Organo- and Cu(I)-catalyzed Click Reactions and their Biological Evaluation

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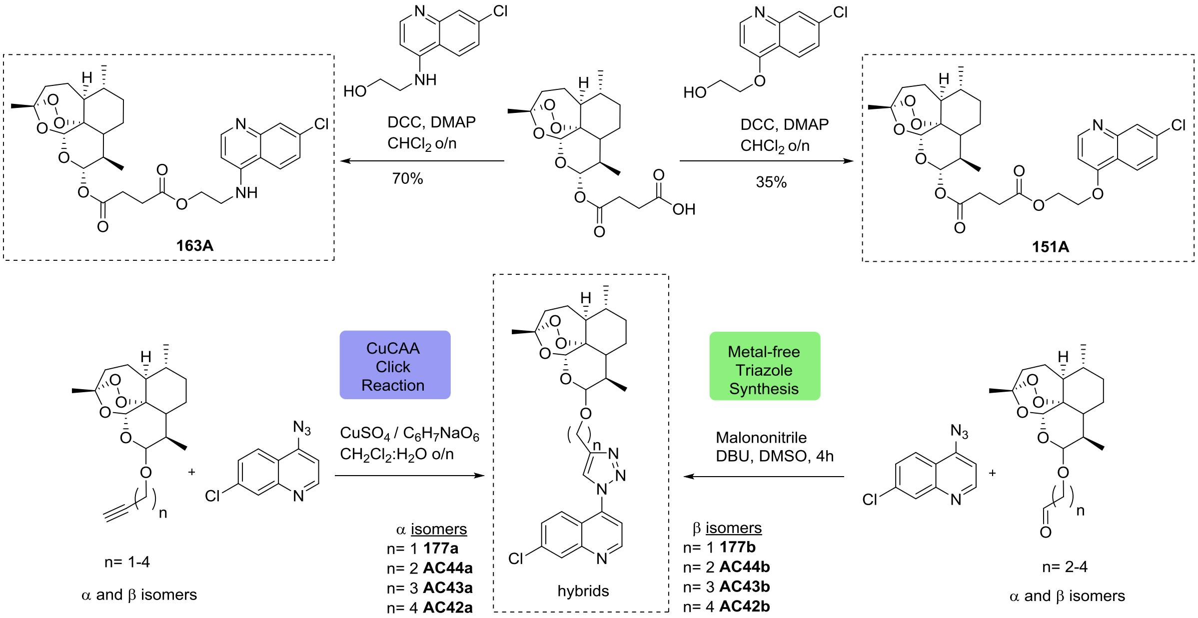
The natural sesquiterpene artemisinin and its derivatives have proven to be versatile antimalarial, anticancer and antiviral agents.[1] Recently, we have reported a series of 1,2,4-trioxane hybrid molecules obtained via various domino and one-pot transformations.[2] Notably, our results have shown that the new molecular structures, prepared via hybridization, demonstrate strongly improved properties compared to their parent compounds. In this study, artemisinin and chloroquinoline derivatives have been chosen due to their highly antimalarial activity. Moreover, comparative synthesis of triazole-linked hybrids via Cu(I)-catalyzed and organocatalyzed click reactions have also been carried out.



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Synthesis of tryptophan-derived α-Amino Acids via directed C-H Activation

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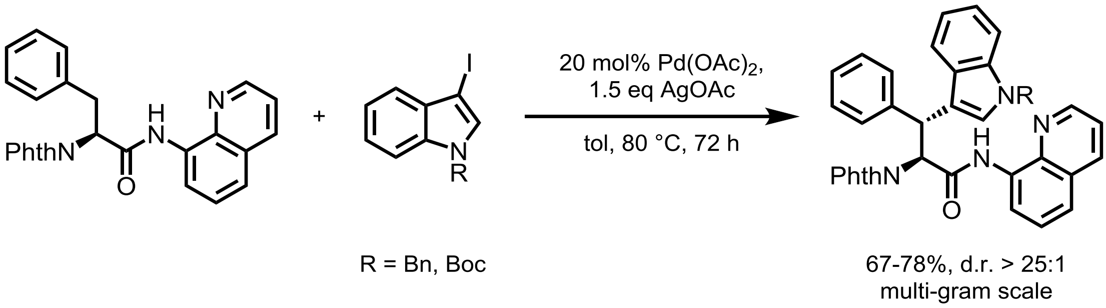
The increasing desire for unnatural α-amino acid building blocks for the synthesis of bioactive and well-structured peptides made us investigate in the derivatization of canonic amino acids by the means of directed β-C-H activation. Especially the need for bulky tryptophan derivatives encouraged us to study the β-indoylation of a suitable protected phenylalanine with 8-aminoquinoline as the directing group.



The well-established β,β´-diarylation of amino acids was to this point not expanded towards the use of 3-iodoindoles,[1,2] which display a reasonable challenge in Pd(II)/Pd(IV) catalyzed C-H activation due to their high steric demand because of the adjacent benzoannelation to its pyrrole core. Also, the lability of the 3-iodoindole compound makes the use of inert gas atmosphere crucial which stands in sharp contrast to other Pd(II)/Pd(IV) catalyzed, directed C-H activation reactions.

[1] E. J. Corey *et al.*, *Org. Lett.* **2006**, *8 (15)*, 3391.
[2] J.-Q. Yu *et al.*, *Sciene* **2014**, *343*, 1216.

Synthesis of Anti-Inflammatory Oxacyclododecindione-Type Macrolactones

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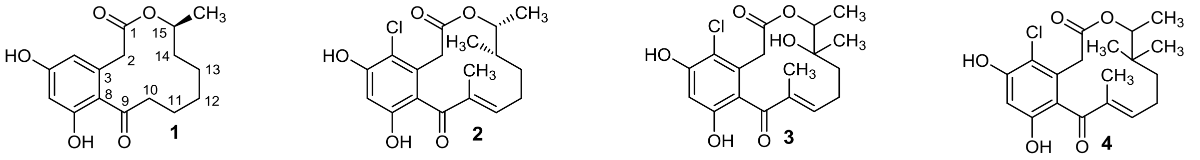
The fungal secondary metabolite oxacyclododecindione (**3**), a 12-membered macrolactone, and its derivatives such as (*S*)-curvularin (**1**) and (14*S*, 15*R*)-14-deoxyoxacyclododecindione (**2**), exhibit highly potent anti-inflammatory activities in cell culture and were successfully used in an *in vivo* mouse model of systemic lupus erythematodes (SLE). [1]

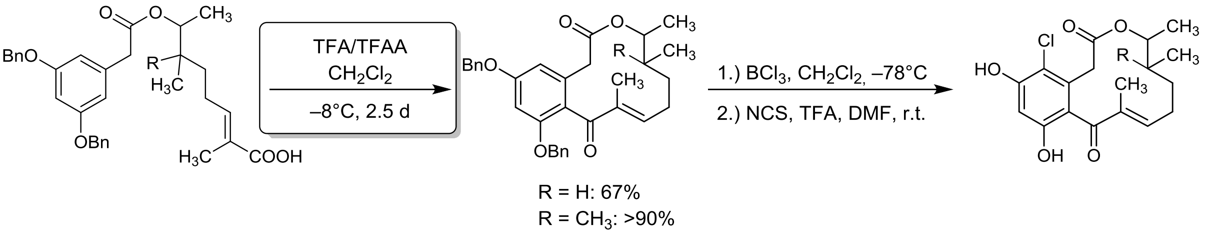
Oxacyclododecindione-Type Macrolactones



To identify the biological targets and to gain a better understanding of structure-response relationships, we strive for the total syntheses of the above named natural products and some synthetic derivatives. Since the 12-membered ring bears intense ring strain, a ring closing method with correct double bond and substituents positions poses the crucial step. We recently found a Steglich esterification/intramolecular Friedel-Crafts acylation sequence to be suitable for the racemic syntheses of 14-deoxyoxacyclododecindione (**2**) and the C-14 *gem*-dimethyl derivative **4**. [2,3]

The transfer of this ring closing method to the synthesis of oxacyclododecindione (**3**) and the elucidation of its absolute configuration at C-14 and C-15 is still subject of ongoing research.

Key Step: Intramolecular Friedel-Crafts acylation



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Synthesis and functionalization of promising heteroaromatic ring of the future for medicinal chemistry applications

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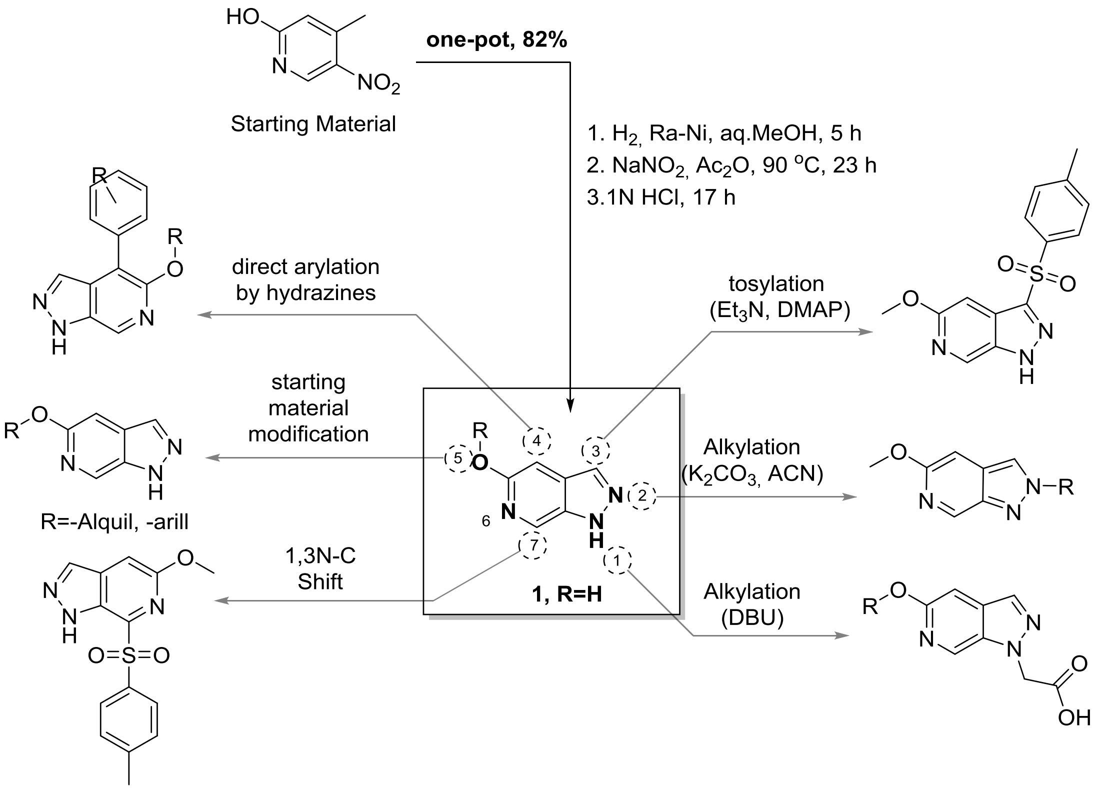
[b] *Institute of Organic Chemistry, Johannes Gutenberg-University,Mainz, Germany*
[c] *School of Pharmacy, University of East Anglia, Norwich, UK*

Heterocycles are an indispensable component of life occurring in a vast array of natural small molecules as well as biopolymers including proteins and nucleic acids. Consequently, it is not surprising that medicinal chemists are heavily dependent on heterocycles for drug discovery. Inspired by the computational study by UCB Celltech to identify 'Heteroaromatic Rings of the Future', here we describe our efforts to synthesize and explore the reactivity of a scaffold that fall under the underprivileged category, 1,6 -dihydro-5*H*-pyrazolo[3,4-c]pyridin-5-one **1**. [1]

The synthesis of **1** is based on a one-pot strategy that consists of subsequent reactions: reduction, acetylation, nitrosation and hydrolysis to afford **1** [2]. Once established the synthesis of **1** in multigram scale, we carried out a reactivity study, that resulted in regioselective strategies to acess several positions of these complex heterocyclic system, **1**.



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One-Pot synthesis of pyrimido[2,1-a]isoindoles

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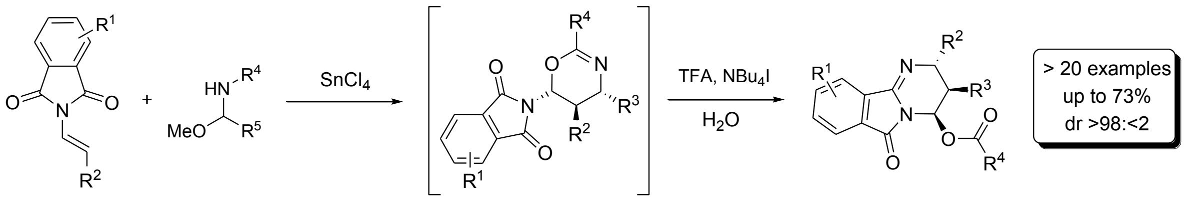
Nitrogen-containing heterocycles are abundant structural elements of a myriad of natural products and biologically active compounds. Therefore, there is a sustained interest in the efficient construction of these heterocycles. New methods for the synthesis of uncommon or so far inaccessible heterocyclic cores are of particular interest for medicinal chemistry. [1]

In the last few years Enamides and Enimides have become a useful tool for the synthesis of many different nitrogen-containing molecules.[2] In the course of our work on a stereodivergent synthesis of 1,3-diamines[3], we serendipitously discovered an unprecedented, highly stereoselective reaction sequence of enimides with N-acylimines leading to novel, highly substituted pyrimido[2,1-a]isoindoles with up to three continuous stereogenic centers.[4]



> 20 examples
up to 73%
dr >98:<2

This transformation is based on the hetero-Diels-Alder reaction of an *in situ* formed acylimine with an enimide. The formed oxazin then undergoes a Brønsted-acid-catalyzed rearrangement to the final pyrimido[2,1-a]isoindole. The scope of the reaction is broad and encompasses various substituted enimides and N-acyl-N,O-acetals. The tricyclic products were obtained in good yields and excellent stereoselectivities. In summary we developed a novel reaction sequence for the synthesis of pyrimido[2,1-a]isoindoles. Our method offers an efficient access to this of uncommon heterocyclic scaffold and can provide an entry to new biologically active compounds.

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[4] P. Kramer, G. Manolikakes, *Manuscript in preperation.*

Synthesis of *p*-methoxyphenyl sulfated 2-acetamido-2-deoxy-β-D-galactopyranoside derivatives with inhibitory activity against Japanese encephalitis virus

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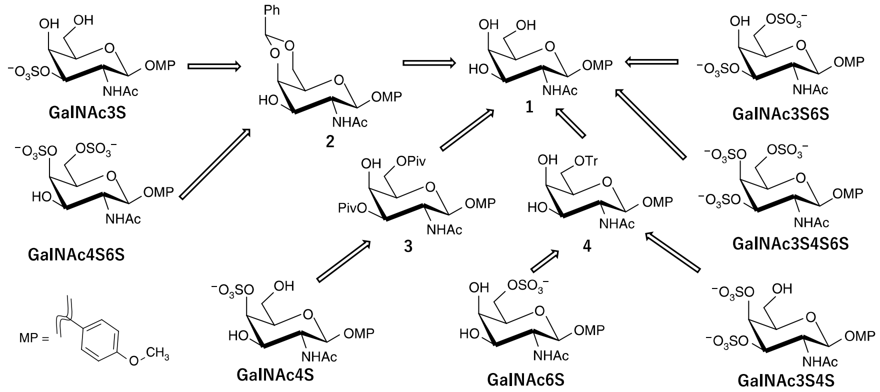
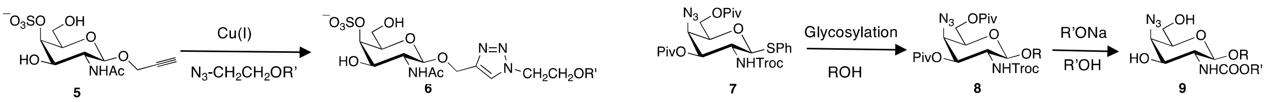
[1]Department of Chemistry, Aichi University of Education, Kariya, Aichi, Japan 448-8542; [2]Junior College Division, University of Aizu, Ikki-machi, Aizuwakamatsu, Fukushima, Japan 965-8570; [3]Epizootic Research Center, Equine Research Institute, Japan Racing Association, 1400-4 Shiba, Shimotsuke, Tochigi, Japan 329-0412

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. Vaccination is the most effective way to prevent JEV infection. JEV is not fully controlled in areas with relatively lower vaccine coverage. 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. [1] In this study, we focused on the structure of *N*-acetylgalactosamine (GalNAc) in CS-E because CS-E shows strong inhibitory activity against JEV infection. We designed, chemically synthesized, and characterized GalNAc derivatives with different numbers and positions of sulfate groups that showed effective inhibitory activity against JEV infection. The synthesis of a series of *p*-methoxyphenyl β-GalNAc derivatives (**GalNAc3S** – **GalNAc3S4S6S**) with a sulfate group at 3-, 4-, and/ or 6-positions was carried out using an efficient route through a common synthetic intermediate **1**. [2]



In order to introduce various substituent to GalNAc, Cu(I)-catalyzed cycloaddition of propargyl glycoside **5** with azide derivatives to give 1,2,3-triazoles and glycosylation of **7** having azide group at 4-position followed by deprotection to give **9** were carried out. In the latter synthesis, Troc group at 2-position was converted to alkoxycarbonyl group by treatment of the corresponding alkoxide with removal of Piv groups. We also present their inhibitory activity against JEV.



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Enantioselective synthesis of 1,4-dihydroquinoline-3-carboxylates via *in situ* generated *ortho*-quinone methide imines

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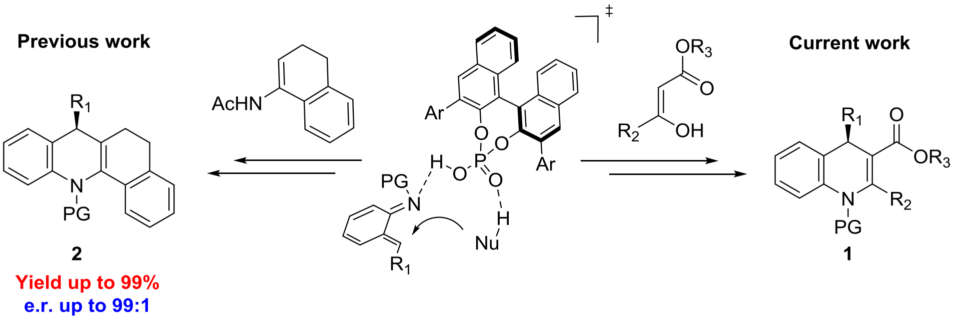
The 1,4-dihydroquinoline architecture **1** represents an important structural motif of various natural products and pharmaceutically active compounds.[1] Classical methods to synthesize this heterocycle are mainly based on annulation reactions typically requiring harsh reaction conditions.[2]

Recently, we have developed a phosphoric acid-catalysed strategy to form *ortho*-quinone methide imines (*o*-QMIs) *in situ* from *N*-protected 2-aminobenzhydryl alcohols upon dehydration (**Fig. 1**). The hydrogen-bonded *o*-QMIs thus formed reacted with enamides in a formal [4+2]-cycloaddition through a well-organised transition state assembly to form tetrahydrobenzo[*c*]acridines **2** with good chemical yields and excellent enantioselectivity in just one step.[3]

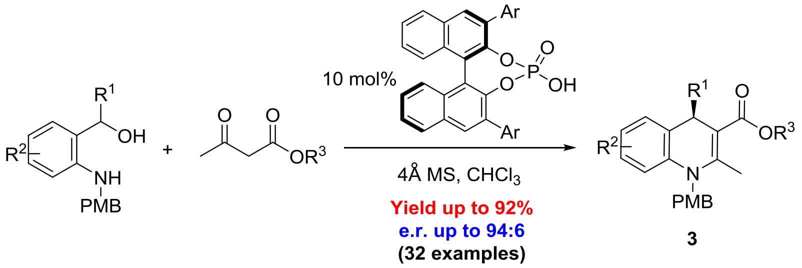


2
Yield up to 99%
e.r. up to 99:1

1

Fig.1: The use of *o*-QMIs in the synthesis of enantiomerically enriched heterocycles

We have now extended that concept to the enantioselective conjugate addition of β-keto esters toward *o*-QMI furnishing 1,4-dihydroquinoline-3-carboxylates **3** in one step after ensuing cyclodehydration.[4] The desired heterocycles were obtained with good chemical yields and enantioselectivity under ambient reaction conditions.



Yield up to 92%
e.r. up to 94:6
(32 examples)

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Selective C-5 iodination of furo[2,3-*b*]pyridine core and use thereof

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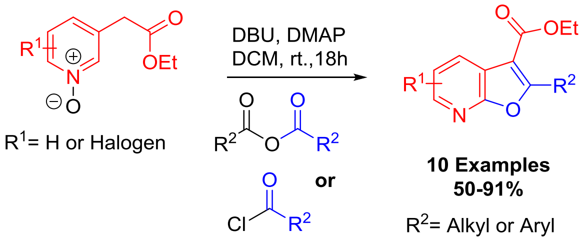
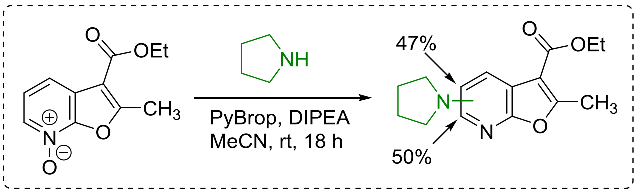
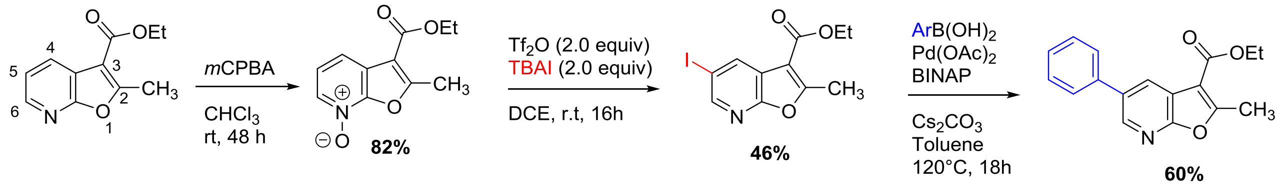
+*Institut für Organische und Biomolekulare Chemie Georg-August-Universität Göttingen, Tammannstrasse 2, 37077 Göttingen (Germany)*

We recently reported an efficient strategy for the synthesis of 2,3-substituted furo[2,3-*b*]pyridines,[1] an fused heterobicyclic ring system with potential utility as a core unit for the development of medicinal chemistry compound libraries.[2] We mapped the reactivity of the relatively underexplored heterocyclic core in various reaction sequences, including C–H amination. In this case, we first described the *β*-amination of the pyridine moiety, which can be largely influenced by the fused furan ring.[1]





Considering this unique reactivity, we explore other type of reaction, with different activating agent and nucleophile. Based on recently described regioselective C-4 bromination of thieno[2,3-*b*]pyridine,[3] we used triflic anhydride to activate the furopyridine *N*-oxide derivative and tetrabutylammonium iodide, as nucleophile source. The product obtained in moderated yield (46%, isolated) showed the selectivity for iodination at C-5. It was not observed product with iodine at C-4, as described for thieno[2,3-*b*]pyridine,[3] and just traces of C-6 iodine substituted furopyridine was observed. Therefore we could active selective functionalization at C-5, which still will be optimized.



The reactivity at C-5 is important to synthesize some biological active compounds.[4] Therefore we also performed one example of use of this iodine derivative trough Suzuki coupling reaction. It was possible to obtain the desired product in good yield.

These findings showed to be promising, but to the better understand of the pathways involved in this selective C-5 activation reaction, other nucleophiles and activated agents will be tested.

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Synthesis and transformations of aryl-functionalized 6-benzyl-3,6-dihydropyridin-2-ones upon treatment with halogen- containing reagents as an example of Diversity-Oriented Synthesis

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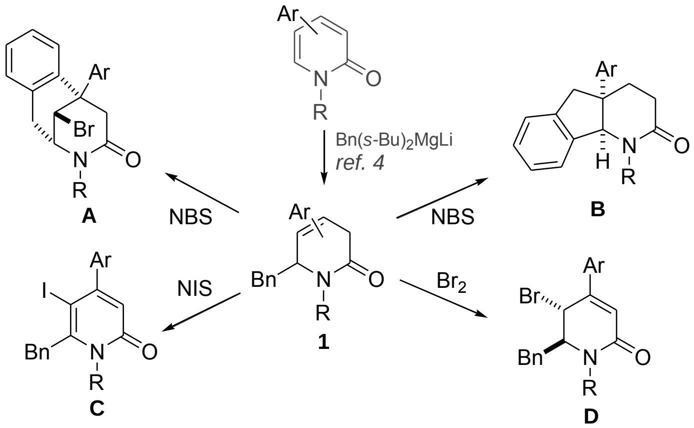
On the one hand, aryl substituted 2-pyridones and their fully or partially saturated derivatives, including natural compounds such as camptothecin [1] and clausenamide [2] have been recognized as promising pharmacophores showing a wide range of pharmacological activities [3].

On the other hand, 4(5)-aryl-functionalized 6-benzyl-3,6-dihydropyridin-2-ones (**1**), obtained by us recently *via* the addition of benzyl magnesiate to corresponding aryl-pyridones [4], were found to be suitable starting materials for halocarbocyclisation reactions, which deliver various products, dependently on reagents and conditions used. For example, upon treatment of **1** with NBS, one of the products formed belongs to bromo-benzomorphan derivatives (products **A**). The other products (**B**) are derivatives of hexahydroindenopyridin-2-ones, resulted from the new aza-pinacol rearrangement, which could be applied as a new synthetic tool to obtain natural alkaloids and nitrogen-containing heterocyclic compounds [5].

Herein, we just present the preliminary results of halocarbocyclisation of **1** as an example of Diversity-Oriented Synthesis, providing quick access to the libraries of structurally different molecules (such as **A**, **B**, **C**, **D**) from simple precursors.



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[4] J.G. Sośnicki, T.J. Idzik, A. Borzyszkowska, E. Wróblewski, G. Maciejewska, Ł. Struk, *Tetrahedron*, **2017**, *73*, 481-493.
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The Best Use of Acyl Groups Installed by Dynamic Kinetic Resolution for Asymmetric Total Synthesis of Heterocyclic Natural Products

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1-6 Yamadaoka, Suita, Osaka 565-0871, Japan

Recently we developed a new method for dynamic kinetic resolution (DKR) of racemic allylic alcohols using a combination of lipases and our original racemization catalyst, V-MPS, in which oxovanadium moieties were covalently bound on the inner surface of mesoporous silica (MPS) to achieve perfect compatibility between the lipase and the oxovanadium moiety due to its narrow pore. The DKR proceeds by the lipase-catalyzed kinetic resolution (KR) of the allylic alcohols outside of MPS and the V-MPS-catalyzed racemization of remaning alcohols via 1,3-transposition of the hydroxyl group inside of MPS to provide optically active allylic esters in quantitative yields (Fig. 1a).[1] On the other hand, there are very few examples which utilize the acyl groups installed by KR or DKR. In most cases, the acyl groups are removed or converted into other functional groups during subsequent transformations. In this symposium, we present asymmetric total synthesis of heterocyclic natural products, (–)-crinane and (–)-himbacine, by making best use of the acyl groups installed by DKR of racemic alcohols (**1a** and **1b**) (Fig. 1b). The presentation includes the following topics:

I. An optically active allyl acetate (*R*)-**3a**, generated by DKR of a cyclic alcohol (±)-**1a**, with vinyl acetate **2a**, was converted into the cycloalkene **4** bearing all-carbon quaternary stereogenic centers via the Ireland–Claisen rearrangement. Further chemical transformation of **4** achieved the asymmetric total synthesis of (–)-crinane.[2]

II. DKR of a dienol (±)-**1b** with an acyl donor **2b** possessing a reactive dienophilic moiety produced an optically active ester **3a**, which caused an intramolecular Diels–Alder reaction in a one-pot procedure to afford an optically-active lactone-fused decalin derivative **5**. This method was successfully applied to the asymmetric total synthesis of (–)-himbacine.[3]

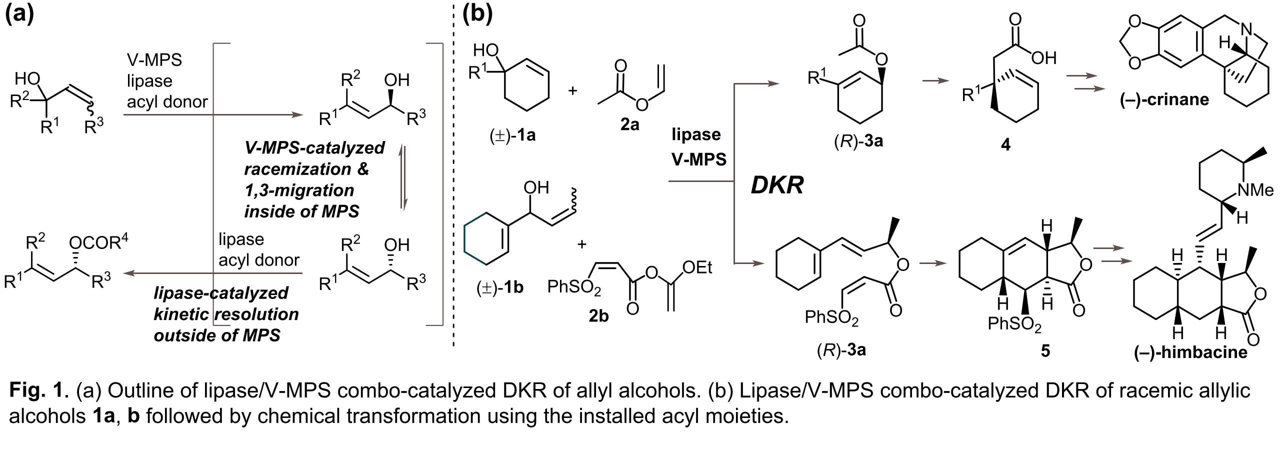

Fig. 1. (a) Outline of lipase/V-MPS combo-catalyzed DKR of allyl alcohols. (b) Lipase/V-MPS combo-catalyzed DKR of racemic allylic alcohols **1a**, **b** followed by chemical transformation using the installed acyl moieties.

1) (a) S. Akai, et al., *Angew. Chem. Int. Ed.* **2013**, *52*, 3654. (b) S. Akai, et al., *Catal. Sci. Technol.* **2016**, *6*, 5023. 2) S. Akai, et al. *Green Chem.* **2017**, *19*, 411. 3) S. Akai, et al. manuscript submitted.

Syntheses of C4/C5 Cyclopropanated Uridine Analogues

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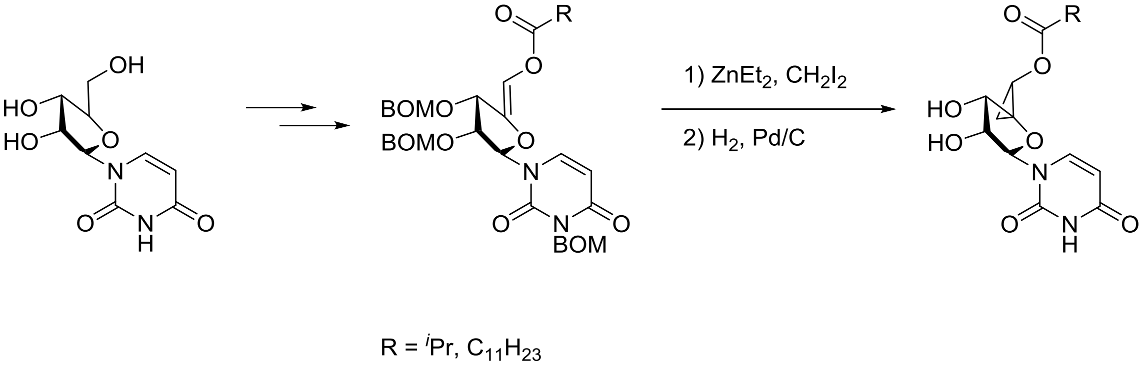
Institut für Organische Chemie, Technische Universität Braunschweig, Braunschweig/DE

Nucleoside analogues proved to be a strong tool for anti-viral and anti-cancer therapy since the late 1960s. [1] Spirocyclopropanes are enhancing rigidity and conformational confinement of nucleosides making protein interactions with these compounds more likely and feature drug applicability. Up to now, only syntheses of difluorospirocyclopropanated nucleosides have been performed by transfer of difluorocarbenes to an exocyclic terminal alkene. This method yielded nucleoside analogues lacking the natural polarity and biological recognizable substitution pattern of nucleosides at the C5. [2]

Recently our group developed a suitable diastereoselective cyclopropanation method to generate spirocyclopropanated pyranoses by using the Furukawa procedure of the Simmons-Smith reaction. [3] Further we established a novel class of C4/C5 cyclopropanated uridine analogues conserving the natural nucleoside core structure (Scheme 1). [4] Finally an appropriate protection strategy offers access to interesting unprotected spirocyclopropanated uridine analogues.



Scheme 1: Abridgement of the C4/C5 cyclopropanated uridine synthesis.

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Catalytic Asymmetric Synthesis of Geminal Dicarboxylates (Acylals)

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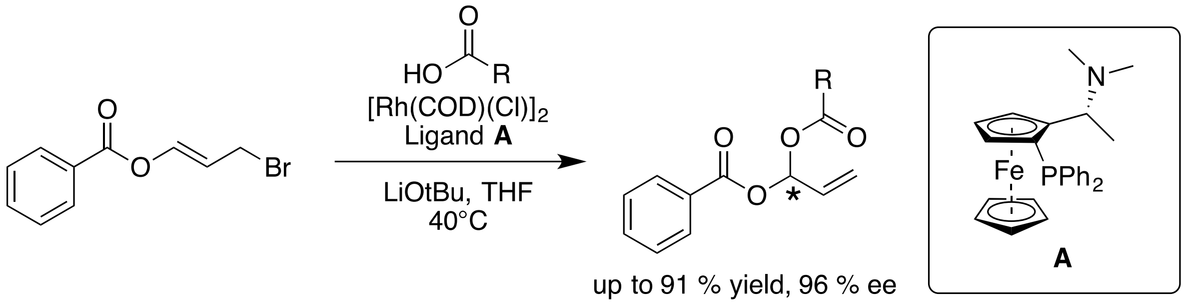
Geminal dicarboxylates, also known as acylals, are a relatively under-explored class of compounds. The diacetate derivative of these compounds is mostly used as a protecting group for aldehydes.[1] It has been shown that prochiral *gem*-dicarboxylates can be used in an asymmetric Pd-catalysed allylic substitution reaction to give allylic esters in high ee.[2] However, to the best of our knowledge, there has only been one asymmetric synthesis of a *gem*-dicarboxylate, in which only 10 % ee was achieved.[3] We have developed a rhodium-catalysed asymmetric synthesis of *gem*-dicarboxylates starting from a prochiral starting material. The method uses common and readily available carboxylic acids as nucleophiles, forming a new C–O bond enantioselectively. Preliminary studies have shown the method can be applied to both aromatic and aliphatic carboxylic acids giving both high yields and excellent enantioselectivities.



up to 91 % yield, 96 % ee

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Tris(triazolyl)methanols: A potential new class of triazole-based H-donor catalysts

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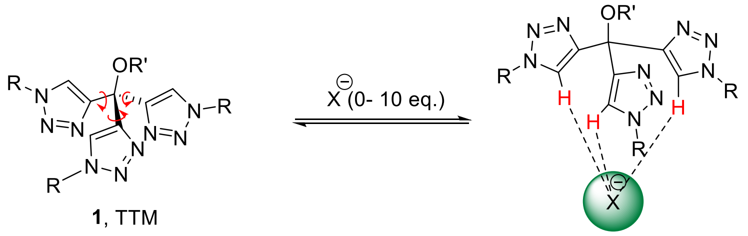
In the past years, hydrogen-bonding catalysis has been consolidated as a powerful synthetic tool. It constitutes an important research field in asymmetric catalysis, in order to efficiently prepare enantioenriched products. Typically, H-donor catalysts bear strong polarized O-H or N-H bonds, such as in (thio)ureas or diols like BINOL. However, recent studies from our group showed that 1,2,3-triazole- structures are also suitable as C-H-based H-donors in anion-binding catalysis. [1]

Pericàs et al. recently designed tris(triazolyl)methanol derivatives (TTM) as a new family of asymmetric tridentate ligands for copper(I) catalysis. They were already efficiently employed in several reaction types like cyclopropenation, insertion into a C-H bond, aziridination, allylic- or sulfide oxidation, α-amination and the Henry reaction. [2] Furthermore, these structures show a similar geometry like thiophosphoramides (TPA), which were presented by Nagorny in 2013 as efficient three-hydrogen bond organocatalysts. [3] Thus, the three triazole rings in the TTM-structures could also interact as a hydrogen-bond donor catalyst.

Herein, we present the first study of tris(triazolyl)methanol derivatives as potential new hydrogen donor organocatalysts, in which the anion-binding activity is based on three 1,2,3-triazole moieties.



2
Anion - TTM - complex

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Tetrasubstituted Enol Ethers via an *anti*-Carbopalladation/Alkoxylation Cascade

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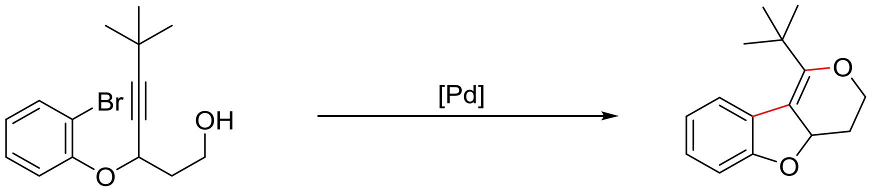
The formation of two or more bonds in one single step is becoming more and more relevant, especially in terms of efficiency and atom economy. Such transformations are named domino reactions, when they take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions are a consequence of the functionality formed in the previous step. [1] Recently, our group developed a formal *anti*-carbopalladation of alkynes. [2] Since such a process leads to a tetrasubstituted vinyl palladium species a terminating step, e.g., a Heck reaction, needs to be added. [3]

In the present study, a nucleophilic attack by a hydroxyl group is used as terminating process. By this *anti*-carbopalladation/alkoxylation cascade tetrasubstituted enol ethers are easily available (Scheme 1). [4]



Scheme 1: Example of an anti-*carbopalladation/alkoxylation cascade.*

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[4] T. Schitter, P. G. Jones, D. B. Werz, *unpublished results*.

Chemoenzymatic Synthesis of Heterobiaryl Natural Products and their Derivatives

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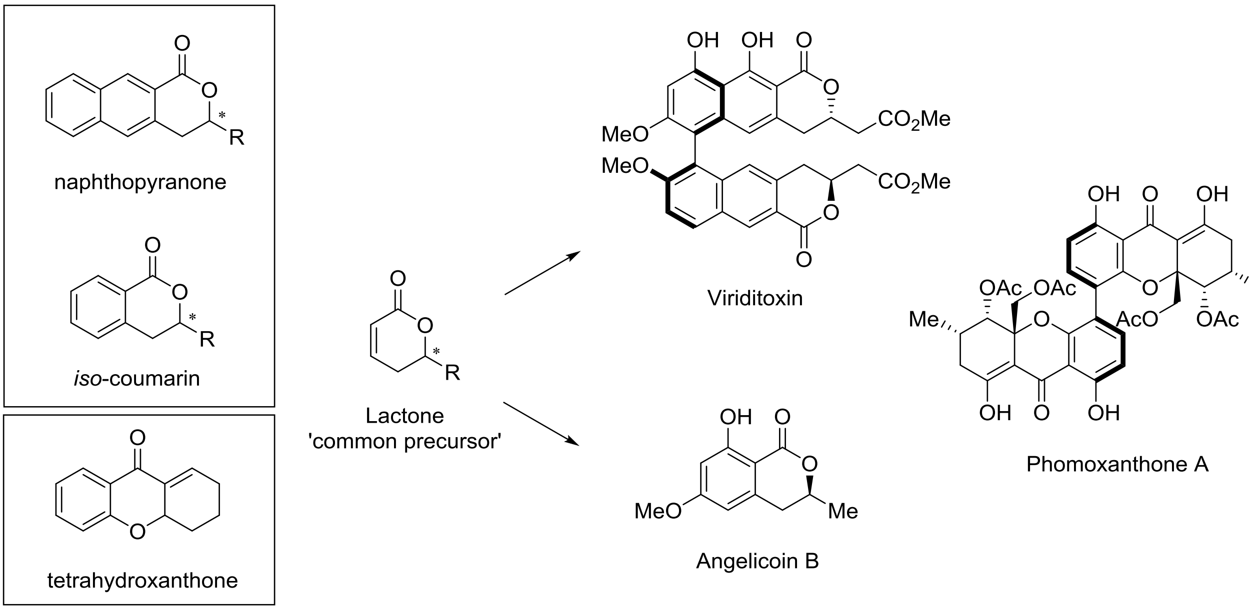
As multi drug resistance (MDR) of cancer cells and pathogens has become an increasingly pressing problem for the pharmaceutical treatment of diseases in the recent years, there is a growing demand for novel drug-like molecules and lead structures. Therefore, modern natural product synthesis has partly shifted its focus away from a ‘classical’, purely target-oriented approach towards more diversity-oriented strategies [1]. Among the broad variety of bioactive natural products – from which medicinal chemists draw their inspiration – dimeric heterobiaryls exhibit remarkable bioactivities and an intriguing chemistry. Some prominent representatives are Phomoxanthone A [2], which belongs to the diverse class of tetrahydroxanthone dimers [3], or the naphthopyranone biaryl Viriditoxin [4] as well as related *iso*-coumarin dimers or monomers like Angelicoin B [5].



Here, we will present our findings towards the syntheses of these complex compounds based on common precursors, which should enable a rapid diversity generation.

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Reactions of Donor-Acceptor Cyclopropanes with Carbonyl Ylides

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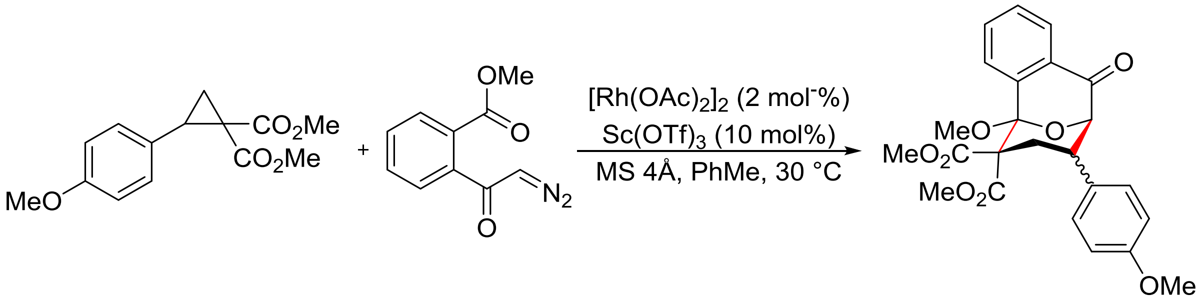
The formation of complex structural motifs within one step is the key to many synthetic strategies. Donor-acceptor (DA) cyclopropanes are of high value for this effort. Due to their high ring strain (~115 kJ·mol^{-1}) and a strongly polarized vicinal carbon-carbon-bond they offer unique reactivity and it is possible to unleash their full synthetic potential as C_3-building blocks in various transformations. [1-3]

In this study DA cyclopropanes were reacted with carbonyl ylides. These 1,3-dipoles are well known in literature for cycloadditions with *e.g.* olefins, alkynes, imines or carbonyls. [4,5] They can be easily prepared *in situ* from the corresponding diazo compounds. The reaction with DA cyclopropanes results in oxygen-bridged carbocycles (Scheme 1) with tunable substitution pattern. [6]



Scheme 1: [3+3]-Cycloaddition of a DA cyclopropane with an *in situ* generated carbonyl ylide.

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Synthetic Strategy of Fused Benzofurans by using Quinone Monoacetals

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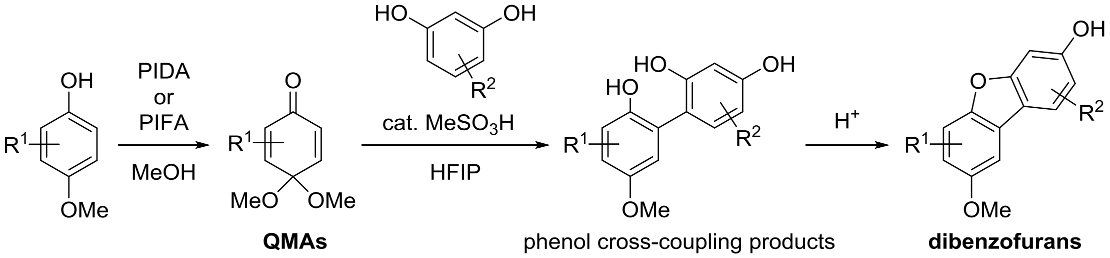
Kusatsu, Shiga, Japan 525-8577

Highly functionalized fused-aromatic compounds widely exist in nature, pharmaceuticals, agrochemicals and functional materials. These skeletons are generally constructed by the transition metal-catalyzed reactions using the metal- or halogen-functionalized aromatic compounds as the starting materials. Recently, direct coupling reactions of unfunctionalized aromatics by C-H activation have been reported as atom-economical reaction by various research groups. However, significant problems, such as regioselectivity and over reaction, are still remain in direct coupling reactions. To dissolve these problems, we have focused on quinone monoacetals (QMAs) as aryl equivalent. QMAs can be easily synthesized by the oxidation of phenols using hypervalent iodine reagents, such as phenyliodine diacetate (PIDA) and phenyliodine bis(trifluoroacetate) (PIFA). Regarding the reactivity, QMAs can be functionalized by various nucleophiles, because all ring carbon atoms have electrophilic nature due to α,β-unsaturated carbonyl and allyl acetal moieties. A number of 1,2- or 1,4-addition reactions to the α,β-unsaturated carbonyl moiety have been reported, whereas substitution reactions to the allyl acetal moiety have been rarely reported.

Meanwhile, we have developed the regioselective substitution reactions to the allyl acetal moiety by the aid of suitable acid promotors in 1,1,1,3,3,3-hexafluoroisopropanol. For example, electron-rich aromatic compounds, such as alkoxy arenes, were introduced into the α-position of carbonyl on QMAs, and *o*-substituted phenols were efficiently obtained,[1] and alkene nucleophiles afforded dihydrobenzofurans by Brønsted acid-catalyzed [3+2] coupling reaction.[2] Moreover, we have recently reported the synthesis of phenol cross-coupling products by the regioselective substitution of phenols into the α-position of carbonyl.[3] In this conference, we report the application of this cross-coupling reaction to the synthesis of highly functionalized fused-benzofurans. This strategy can afford the highly functionalized dibenzofurans without any transition-metal catalyst and pre-functionalized aromatic compounds.



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Synthesis of Medium-sized *trans*-Cycloalkenes by Domino 4π-Electrocyclization—Alkylation of Fused Cyclobutenes

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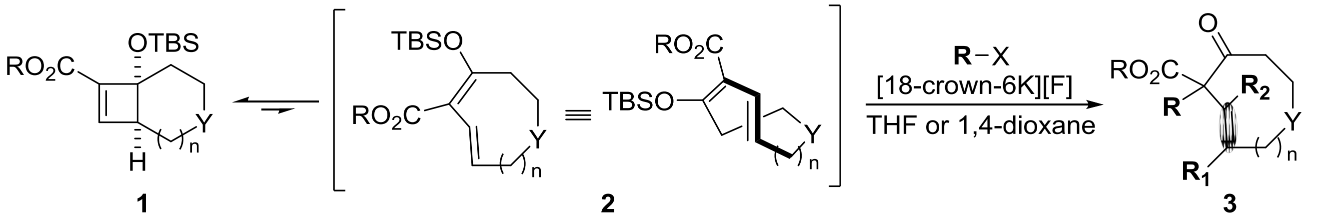
Yoshida, Sakyo-ku, Kyoto 606-8501, JAPAN

A thermal 4π-electrocyclization of cyclobutenes stereospecifically proceeds in a conrotatory manner to give 1,3-butadienes in accordance with the Woodward-Hoffmann rule. The thermal electrocyclic ring-opening reaction of fused cyclobutenes **1** might generate *cis,trans*-cycloalkadienes **2**. When the size of the fused ring of **1** is not enough large, equilibrium of the electrocyclization must be unfavorable for the production of **2** due to its severe ring strain. Despite the latent planar chirality and the synthetic utility of the *trans*-cycloalkenes, the chemistry has been rarely developed.

We have reported a domino reaction involving 4π-electrocyclization of **1** with chirality transfer of the short-lived planar chiral intermediate **2,** followed by Heck reaction to give fused Indolines.[1] In present work, we focused on the high reactivity of the silyl enol ether moiety of intermediate **2**, and planned to synthesize the medium-sized *trans*-cycloalkenes with highly strain as isolable products. When cyclobutenes **1** were treated with [18-crown-6K][F] and electrophiles (**R**-X) at the appropriate temperature, *trans*-cycloalkenones **3** were obtained in good to excellent yield. Stereoselective synthesis of tri-substituted *trans*-cycloalkene was also achieved. Medium-sized ring synthesis using hetero-atom-containing fused cyclobutens and the chirality transfer experiment will be discussed. The strategy would be a powerful and facile method for the formation of medium-sized rings.



planar chiral intermediate

up to 96% yield

Reference

1. Arichi, N., Yamaoka, Y., Yamada, K. Takasu, K. *J. Am. Chem. Soc.* **2015**, *137*, 9579-9582.

Unsaturated N-Containing Four-Membered Heterocycles – A Versatile Building Block for Drug Discovery

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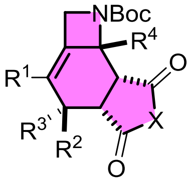
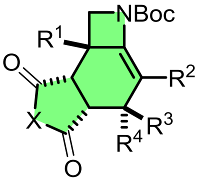
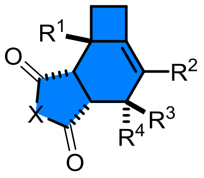
Small, strained ring systems have recently received increased attention due to their large applicability in drug discovery and development. However, generating these systems is often limited by the restricted number of efficient and available methods. Spurred on by the recent emerging interest that the chemical community has shown for unsaturated four-membered heterocycles, we designed an unprecedented approach to nitrogen-containing four-membered rings.



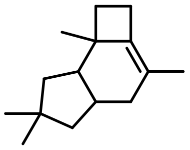
fused 3-alkylidene-azetidines



fused 2-alkylidene-azetidines



bioactive fused alkylidenecyclobutane



natural protoilludane skeleton

After having established a solid base for the efficient and stereoselective synthesis of their carbonated analogues: cyclobutenes (CBs)[1] and alkylidenecyclobutanes (ACBs),[2-4] we took on the challenge of opening a new route toward substituted azetines.[5] A step further was then taken by developing a stereo- and regioselective access to fused alkylideneazetidines,[6] N-containing analogues of biologically active fused ACBs.[7]

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Palladium activates thiocyanates:
Sulfur-carbon bond cleavage for the intramolecular cyanothiolation of internal alkynes

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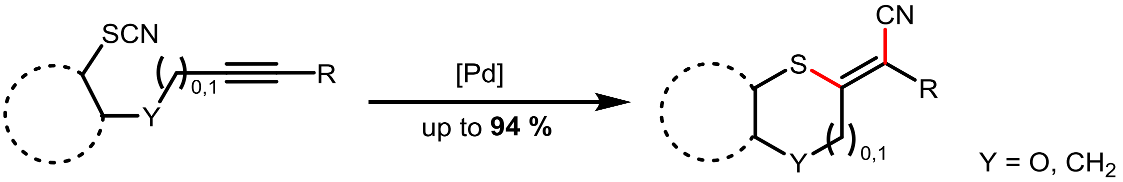
marcel.buerger@tu-braunschweig.de

Palladium-catalyzed cross-coupling reactions have been established as essential tools in organic chemistry and are also of high importance in pharmaceutical and material science.[1] While in the beginning primarily carbon-carbon bond formation has been investigated nowadays also carbon-heteroatom bond construction plays a significant role. Besides C-X, C-O and C-N bond functionalization the coupling of C-S bonds is only little investigated. An interesting approach is the activation of Het-CN moieties as it was shown for oxycyanation, aminocyanation and also for the reaction between aryl thiocyanates and terminal alkynes or arynes, respectively.[2]

As our group continuously strives for new methods to build up complex and valuable structures or key scaffolds in a single synthetic step, we developed a methodology for the intramolecular cyanothiolation of internal alkynes. This transformation leads to novel compounds with a heterocyclic backbone (e.g. 1,4-benzoxathiines, thiopyranes or thiophenes) bearing a tetrasubstituted exocyclic double bond (Scheme 1).[3]



Scheme 1: Intramolecular cyanothiolation of an internal alkyne.

In our initial studies, we show that the activation of the sulfur-cyano bond of an aromatic or aliphatic thiocyanate enables the cyanothiolation of an internal triple bond. This transformation includes a thiopalladation and the associated dislocation of the released cyanide as straightforward termination step of the catalytic cycle.

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Design and synthesis of chiral ligands using multivariate modelling

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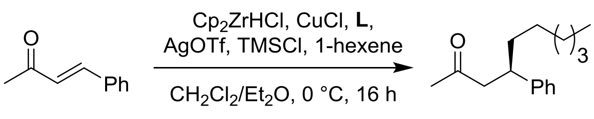
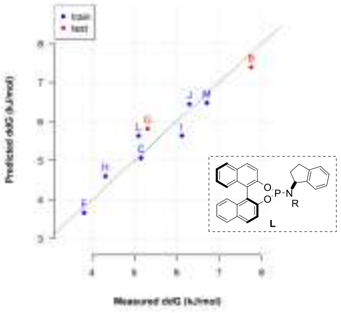
Asymmetric catalysis is at the core of modern synthetic chemistry but catalyst design has been driven by trial-and-error processes for decades. New techniques have recently emerged such as high-throughput experimental screening[1,2] and physical-organic approaches.

The latter is expected to give a faster and systematic route to new catalysts. In particular, the statistical analysis of multivariate models coupled with synthetic and mechanistic expertise shows promise.[3] Combining these separate areas will permit the development of more valuable and time effective approaches to design new ligands in asymmetric catalysis.

In this work, we present the elaboration of experimentally validated quantitative structure selectivity relationships in order to discover, design and synthesize new chiral ligands for asymmetric catalysis.

This general rational approach to improve asymmetric induction has been applied to a copper-catalysed asymmetric conjugate addition of alkylzirconium nucleophiles. The addition initially proceeded in 59% yield with 33% ee[4] and it now gives up to 99% yield and 94% ee. Our work shows that a systematic approach to catalyst design can be straightforward and effective.





Previous work
59% yield, 33% ee
This work
~20 Ligands
up to 99% yield and 94% ee

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ISHC 2017 Abstract

Chiral ligand design for Copper catalysed conjugate addition with the aid of quantitative structure-selectivity relationship

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Cyclopentenones are challenging substrates for enantioselective conjugate addition reactions.[1,2] We developed a mild and effective protocol for the synthesis of all-carbon quaternary centres using copper catalysed asymmetric conjugate addition (ACA) of alkylzirconocenes derived from readily available alkene starting materials.[3] To aid the design of the chiral phosphoramidite ligands for this transformation, we used quantitative structure-enantioselectivity relationship and computational calculations. The model showed correlations of electronic terms of the aryl moiety of the ligand and the steric terms with the enantioselectivity observed.

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Cyclization of some bioisosteres of brassinin towards 1,3-thiazinane-2-thiones and 1,3-thiazolidine-2-thiones

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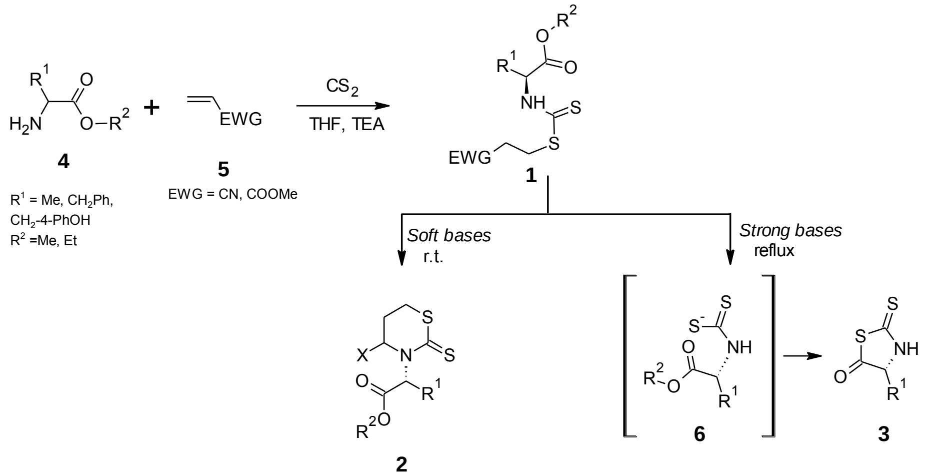
Phytoalexins are secondary metabolites which are produced by plants for protecting against microbial pathogens, heavy metals and UV irradiation. Among the cruciferous (Brassicaceae) phytoalexins, brassinin has a fundamental role due to its central position in the biosynthetic pathway of phytoalexins [1]. Some brassinin bioisosteres **1** have been synthesized from *L*-tryptophan [2]. Antifungal activities showed the potential application of **1** as agrochemical agents. To explore the cyclization reaction of **1** to 4-substituent-3-alkyl-1,3-thiazinane-2-thiones **2**, some reactions of **1** were carried out. We presented the synthesis of **2** and 4-alkyl-1,3-thiazolidine-2-thiones **3** showing the dependence of the reaction conditions in the reaction pathway. The first step of the synthetic methodology involved the esterification of *L*-alanine, *L*-phenylalanine and *L*-tyrosine in excellent yields (93-98 %) to afford alkyl 2-aminoesters **4**. Reactions of **4** with carbon disulfide and Michael acceptors **5** were carried out using triethylamine and THF at room temperature to obtain **2** in good yields (87-92%). The basicity of the reaction medium was modified using triethylamine (TEA), potassium carbonate, potassium hydroxide and potassium methoxide, respectively. When the reactions were performed at room temperature, compounds **3** were detected using NMR ^{1}H and ^{13}C. However, the presence of compounds **2** was also detected in $CDCl_3$ solutions. These results suggested the existence of opening-closure ring reactions. The major yields for **2** were detected using soft bases such as TEA and potassium carbonate. The yield of **2** decreased using stronger bases. Moreover, when the reactions were performed at reflux conditions, compounds **3** were obtained as majority products in all the cases. These results suggested compounds **1** could undergo collateral reactions with C-S bond cleavage. Then, ionic dithiocarbamates **6** suffer ring cyclization to afford compounds **3**. Product derived from the project INV-CIAS-2043 funded by Vicerrectoría de Investigaciones at UMNG - Validity 2017.



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Total Synthesis of Echinocidin D

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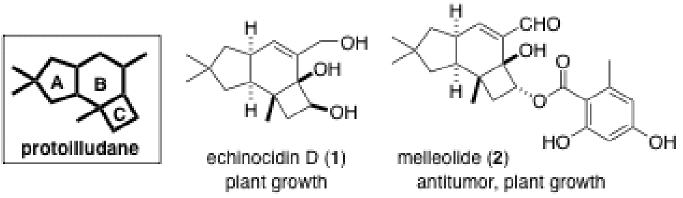
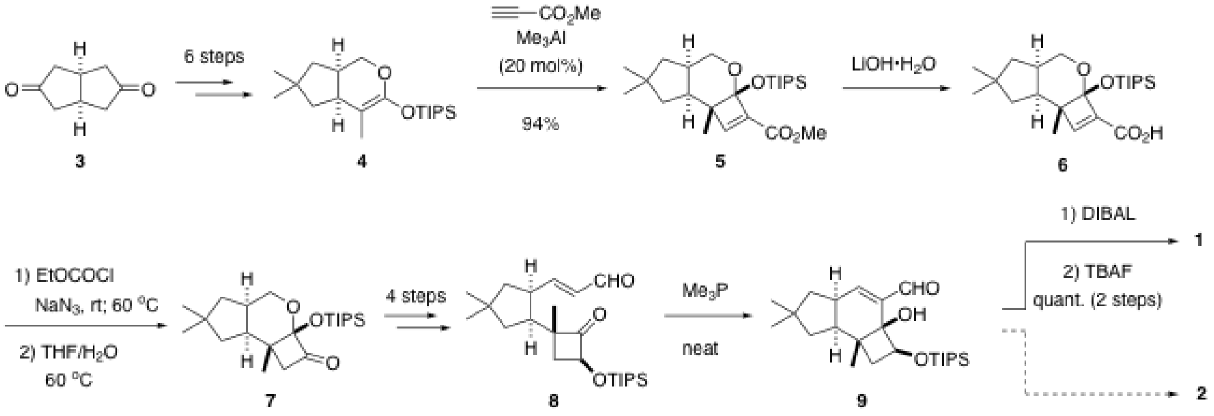


Figure 1 Protoilludanes which has hydroxy group at B/C ring juncture.

Protoilludane sesquiterpenoids, having 5-6-4 tricyclic skeleton with various oxidative statuses., are frequently found in nature. Among them, ones that have a hydroxy group at the ring juncture between B- and C-rings, such as echinocidin D (**1**) and melleolide (**2**), display attractive biological activities (Figure 1). Echinocidin D, isolated from *Echinodontium tsugicola,* was reported to accelerate plant growth process[1]. We will discuss about total synthesis of echinocidin D and the synthetic study towards melleolide by using a new cyclobutene formation reaction.

Cyclic ketene silyl acetal **4** was synthezed from known diketone **3** in several steps. $AlMe_3$ catalyzed [2+2] cycloaddition of **4** with propiolate, which was recently reported by us,[2] gave tricyclic cyclobutene **5** in 94% yield. Transformation of α,β-unsaturated ester **5** into cyclobutanone **7** was nicely achieved by Curtius rearrangement followed by hydrolysis. Intramolecular Morita-Baylis-Hillman reaction was attempted to construct of the protoilludane skeleton. After several exploration, the reaction of α,β-unsaturated aldehyde **8** with trimethylphosphine as a solvent gave the desired tricyclic aldehyde **9**. Further transformation provided echinocidin D (**1**). The synthesis of melleolide (**2**) will be also presented.



Scheme 1 Total synthesis of echinocidin D

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Nitrosoallenes: Inter- and Intramolecular Reaction for Heterocycles Synthesis by Their Strong Reactivities

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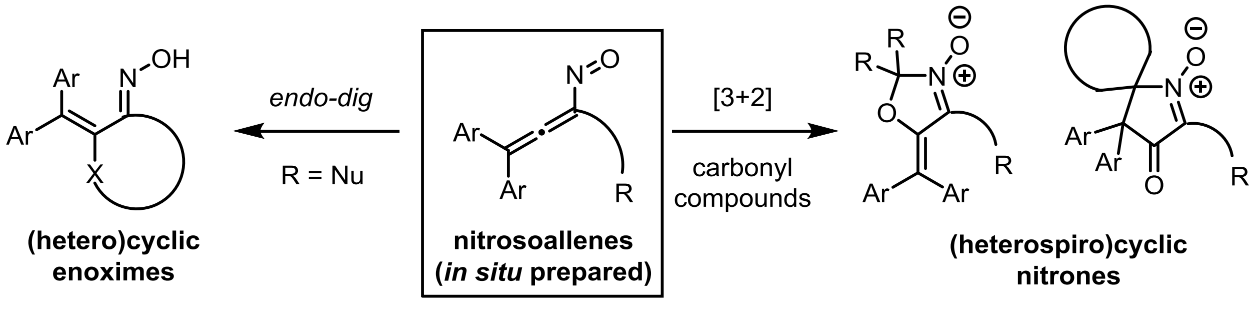
Nitroso compounds are well known to be highly fascinating reactive species to construct nitrogen-containing cyclic structures of various alkaloids and bioactive heterocycles. However, due to the instability and synthetic difficulty, reaction potentials of nitroso compounds is to be further developed.

Emerged from our research of azido cyclization with propargyl cations,[1] we have developed the unique reactive intermediate nitrosoallenes. These showed strong electron-withdrawing character by the presence of nitroso group, and α-substituted enoximes were rapidly obtained in the presence of heteronucleophilic reagents through 1,4-addition to nitrosoallenes.[2] With these strong electron-withdrawing ability, we envisioned that the high reactivity of nitrosoallenes could give various heterocycles. We present synthesis of heterocyclic compounds by intermolecular [3+2] reactions, and intramolecular *endo-dig* type cyclizations reactions on ISHC congress.

With carbonyl compounds like ketones, formal [3+2] reactions rapidly occurred to give oxacyclic nitrones.[3] Among them, spirooxacyclic nitrones proceeded further unique skeletal rearrangement to give densely substituted spirocarbocyclic nitrones. Ester and nitrile nucleophiles showed different reactivities to produce azacycles.

On the other hand, with substrates possessing internal nucleophilic sites, intramolecular *endo-dig* type cyclizations, which were usually disfavored cyclization manners, were smoothly carried out to afford exo-methylene enoximes of 5–7 membered rings, which contained S, O, and N atoms, as well as carbocycles by C-C bond formations. The exo-methylene enoxime positions in these (hetero)cyclic products are very efficient for further construction of the heterocycle structures.



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Synthesis of alkyl 5-(furan-2-yl)-3-oxo-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carboxylate type compounds from heterocyclic chalcones

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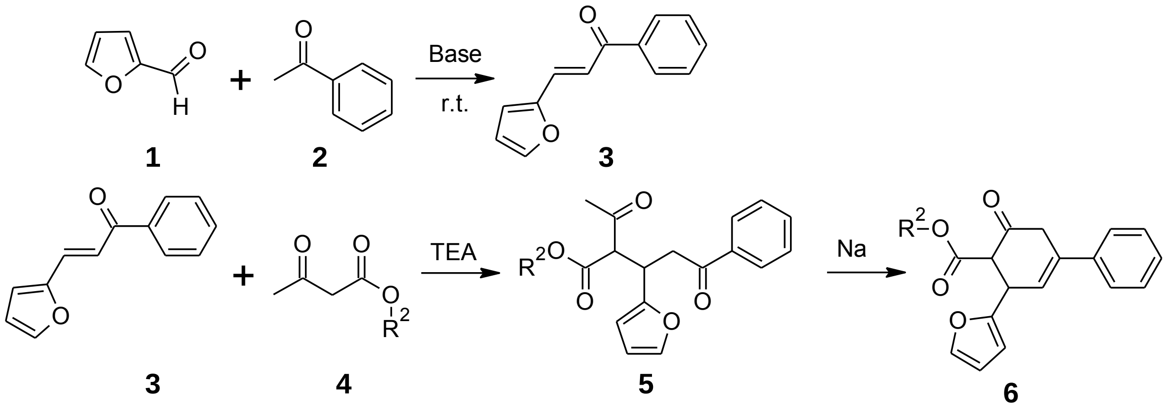
Chalcone derivatives have been of great interest in the plant metabolism research, especially due their importance in the biosynthesis of secondary metabolites such as flavonoids [1]. Moreover, compounds with chalcone skeleton have shown an interesting behavior as antimicrobial, anti-inflammatory, analgesic and anticancer agents [2]. Recently, chalcone type compounds have been employed as reagents for the synthesis of various heterocyclic compounds such as flavones and chromenes [3]. Exploring the potential application of chalcone derivatives as precursor of biologically interest heterocyclic systems, we present the synthesis and application as synthetic precursor of (2*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-ones **3**. First, compound **3** was synthesized starting from furfural **1** and acetophenone **2** in mild conditions. Then, compound **3** was evaluated as precursor of alkyl 5-(furan-2-yl)-3-oxo-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carboxylate type compounds **6**. Some reactions between **3** and enolates derived from alkyl acetoacetates were studied varying the reaction conditions such as base strength, temperature and solvent. NMR ^{1}H experiments in $CDCl_3$ showed Michael addition reaction is the first step in the reaction mechanism. This reaction only occurs under TEA catalysis, forming intermediate **5** in all the cases. When stronger bases were used as catalysts, self-condensation reaction of carbonyl compounds occurred. To avoid self-condensation reaction, **3** and **4** reacted using TEA as catalyst. Then, addition of stronger bases in the reaction media leaded to the formation of **6** through Robinson annulation reactions with moderate yields (45-63%). Some experiments were performed employing alkaline metals as catalysts. Sodium-catalyzed reactions carried out to the compounds **6** formation in good yields (79-87 %). Product derived from the project IMP-CIAS-2294 funded by Vicerrectoría de Investigaciones at UMNG - Validity 2017.



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Ru-catalyzed 1,6-enamide-yne cycloisomerization for 2,3-disubstituted indoles synthesis

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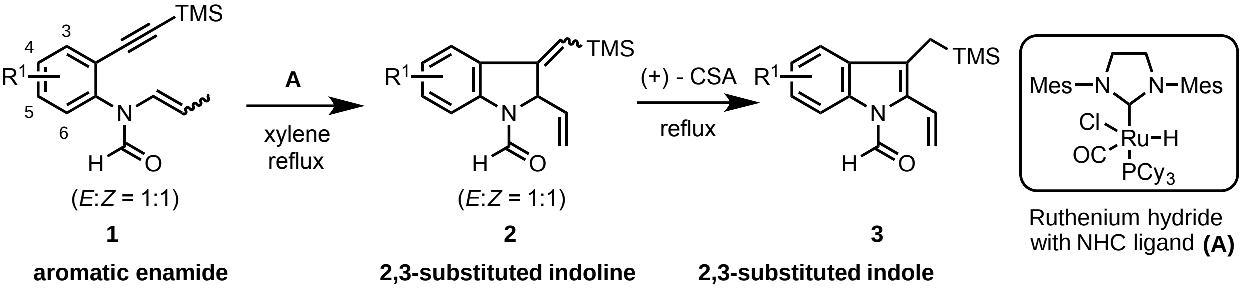
A substituted indole, including a 2,3-disubstituted indole, is a key component of natural products with bioactivities, and the synthesis of this important structure has been a research topic for many years. Although several sophisticated methods for the synthesis of indole have been developed, it is still challenging to construct a 2,3-disubstituted indole with a proper substituent at a desired position.

Enamide in which the nitrogen atom of enamine is used as an amide has attracted in recent years, because reactions of enamide with organometallic catalysts is useful for heterocycles synthesis. For example, reactions of aliphatic enamide with organometallic catalyst (Co, Ru, Pd, etc.) gave substituted pyrrole and pyridine [1, 2].

Here, we demonstrate ruthenium hydride catalyst **A** catalyzed 1,6-enamide-yne cycloisomerization of **1,** and subsequent aromatization to give a 2,3-disubstituted indole **3** (**Fig. 1**) [3].

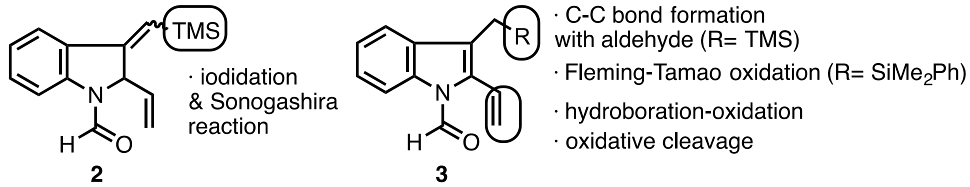
Fig. 1 1,6-Enamide-yne cycloisomerization for 2,3-disubstituted indoles



Yield of **3** from **1** R^1 = H (92%), 3-Cl (60%), 4-Cl (73%), 5-Cl (85%), 6-Cl (69%), 4-OMe (81%)

We will also discuss chemical conversions of compounds **2** and **3** (**Fig. 2**).

Fig. 2 Examples of chemical conversions of compounds 2 and 3



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Visible light catalyzed [2+2] cycloadditions of α,β-unsaturated esters by energy transfer.

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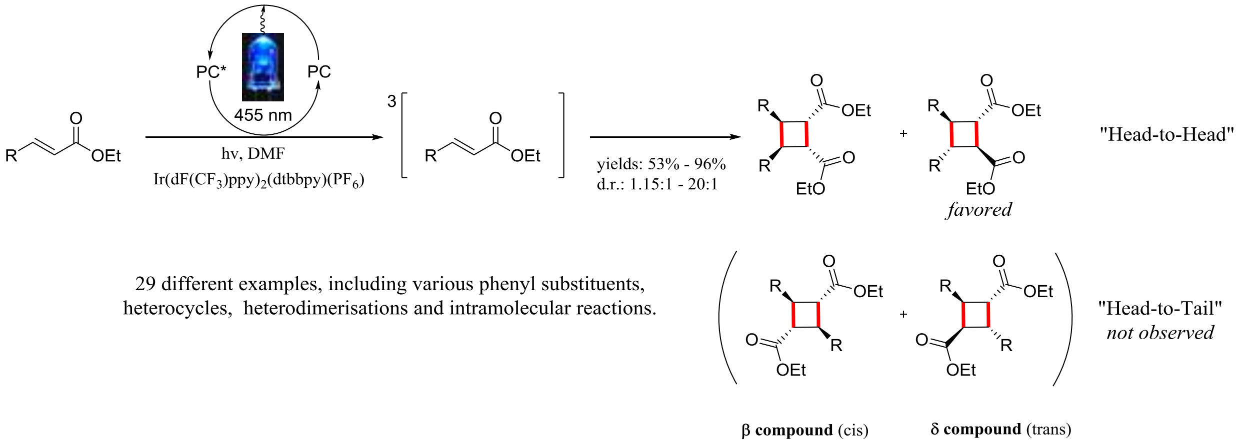
Cyclobutanes are a recurring structural motive in natural product synthesis. In the past, direct triplet sensitization of π-systems by UV light enabled [2+2] cycloadditions for a variety of cyclobutane derivatives.[1] Starting from 2012, Yoon et al. developed intramolecular [2+2] cycloadditions catalyzed by visible light by an energy transfer mechanism.[2] However, the substrate scope up to this point has been limited to styrene, diene and chalcone derivatives to achieve suitable triplet energy levels.[3]



29 different examples, including various phenyl substituents, heterocycles, heterodimerisations and intramolecular reactions.

Scheme 1: A general overview for dimerization of α,β-unsaturated esters.

A more diverse substrate scope with a variety of α,β-unsaturated esters for visible light catalyzed [2+2] cycloadditions was accomplished. The substrate scope demonstrated tolerance towards multiple different heterocycles, substituted cinnamates, chalcones and styrenes. Additionally, hetero dimerizations with asymmetric products were explored and optimized. Moreover, selectivity for the head-to-head product in intermolecular dimerization reactions was obtained using π-stacking interactions.

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Directed C−H Functionalization of Chromones, 1,4-Naphthoquinones, and Xanthones with Maleimides under Rhodium(III) Catalysis

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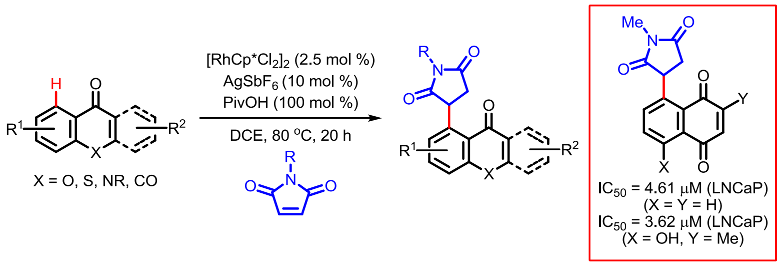
The weakly coordinating ketone group-directed C–H functionalizations of chromones, 1,4-naphthoquinones and xanthones with various maleimides under rhodium(III) catalysis are described. These protocols efficiently provide a range of succinimide-containing chromones, naphthoquinones and xanthones with excellent site-selectivity and functional group compatibility. All synthetic compounds were screened for in vitro anticancer activity against human breast adenocarcinoma cell lines (MCF-7). The ketone-containing bi- and tricyclic scaffolds have been recognized as ubiquitous frameworks found in a large number of chromones, naphthoquinones and xanthones. Particularly this class of compounds has attracted considerable attention by virtue of their diverse and interesting biological activities, i.e. anticancer activity, antioxidant activity, α-glucosidase inhibitory activity, antibacterial activity and antifungal activity. As a consequence, various synthetic derivatives have been synthesized and evaluated for clinical applications. We herein report the rhodium(III)-catalyzed C–H alkylation of chromones, naphthoquinones and xanthones with maleimides affording various succinimide derivatives. In addition, all synthetic compounds have been screened for the cytotoxic activity against human breast adenocarcinoma MCF-7 cell lines. Moreover, compounds selected from initial activity screening were further tested against various cancer cell lines, such as human prostate adenocarcinoma cells (LNCaP), human liver carcinoma cells (HepG2), human lung carcinoma cells (A549) and human ovarian carcinoma cells (SKOV3), and were found to exhibit promising anticancer properties competitive with anticancer doxorubicin.



Rhodium(III)-Catalyzed C7 Functionalization of Indolines with 1,4,2-Dioxazol-5-Ones

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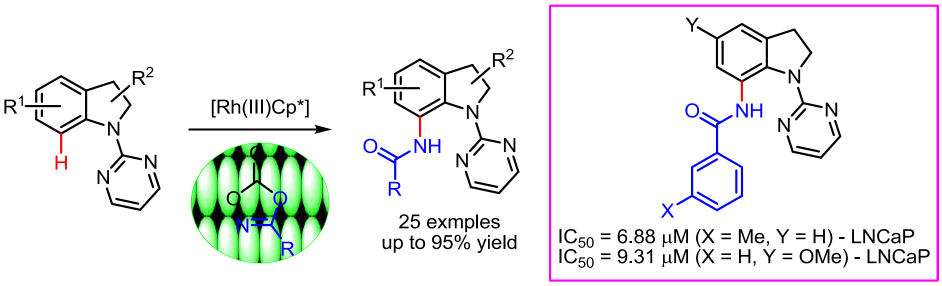
Indolic scaffolds are recognized as ubiquitous structures found in a large number of natural products and pharmaceuticals. Particularly, C7-amidated indolines and indoles have attracted considerable attention by virtue of the discovery of interesting biological properties. In fact, this class of compounds is known to display diverse biological profiles, such as tublin polymerization inhibition, histone deacetylase (HDAC) inhibitory activity, acyl CoA-monoacylglycerol acyltransferase-2 (MGAT2) inhibition for hypocholesterolemic action, and antiproliferative activity. The biological activities of these compounds are closely associated with C7-amino functionality but vary depending on the nature and/or position of the substituents on indolic scaffolds.

The past decade witnessed the transition-metal-catalyzed C−H functionalization as a powerful method for the efficient construction of structurally diverse molecules in organic and medicinal chemistry. In this context, a great deal of effort has been devoted to the C−H functionalization of indolic scaffolds with various coupling partners. In particular, the directing group-assisted C-7 functionalizations of indolines have been of intensive research area due to prevalence of many pharmaceutical agents. We herein disclose the Rh(III)-catalyzed direct C−H amidation of indolines with dioxazolones under mild reaction conditions. Also, our synthetic compounds have been evaluated for the cytotoxic effect against human prostate adenocarcinoma cells (LNCaP), human endometrial adenocarcinoma cells (Ishikawa) and human ovarian carcinoma cells (SKOV3), and were found to have promising anticancer properties competitive with that of anticancer agent doxorubicin.



25 exmples
up to 95% yield

IC_{50} = 6.88 μM (X = Me, Y = H) - LNCaP
IC_{50} = 9.31 μM (X = H, Y = OMe) - LNCaP

Synthesis of Bioactive Indazole Compounds via C–H Addition and Cyclization of Azobenzenes under Rhodium Catalysis

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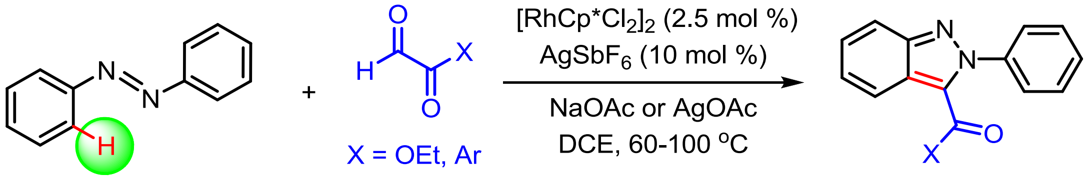
The indazole heterocycle has been recognized as a crucial structural core found in natural products and pharmaceuticals with a broad spectrum of medicinal applications.[1] In particular, the 3-acyl indazole motif is present in molecules that possess anticancer, antiemetic, viral polymerase inhibition, and anti-inflammatory activities.[2] The classical routes to 3-acyl indazoles involve (i) *N*-nitrosation of acetanilides followed by intramolecular cyclization onto the ortho-methylene group, (ii) multistep synthesis from isatins via hydrolysis of the amide unit, diazotization and reduction, and (iii) direct lithiation at the C3-position followed by the addition of electrophiles.

In continuation of our recent studies on the rhodium-catalyzed C−H functionalization and heterocycles synthesis,[3] we herein present the Rh(III)-catalyzed direct C−H addition followed by intramolecular cyclization of azobenzenes with α-keto aldehydes, such as ethyl glyoxalate and aryl glyoxals, affording 3-acyl-(2H)-indazoles.[4]



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Efficient PhB(OH)$_2$-catalyzed synthesis of 3-substituted isobenzofuran-1-ones *via* aldol-lactonization reaction under solvent-free conditions.

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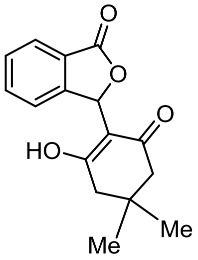
Isobenzofuran-1-ones or phthalides, are considered as internal esters of the corresponding γ-hydroxycarboxylic acids. Within this class of compounds, the 3-substituted isobenzofuran-1-ones have shown several important biological activities. For example, the isobenzofuran-1-one **1** exhibit significant antiproliferative active against two cancer cells (lymphoma and leukemia),[1] and **2** is a precursor of *n*-butylphalide (NBP), which is currently in the market as an antiplatelet drug for ischemia-cerebral apoplexy.[2]



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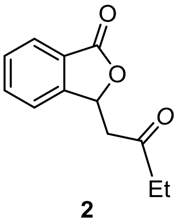
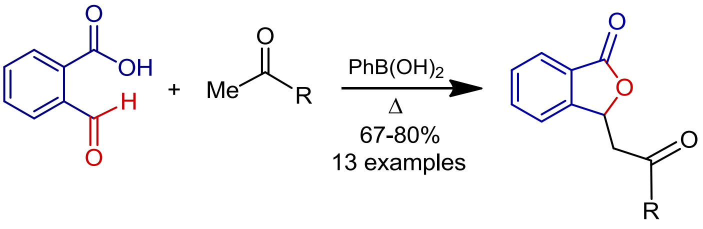


2

Although, exist a large number of protocols for the synthesis of 3-acyl substituted isobenzofuran-1-ones, most of these methods involve the use of strong, corrosive and harmful acids and bases.[3] For this reason, the introduction of an efficient, environmentally friendly, water resistant and recyclable catalyst for the synthesis of these compounds under solvent free conditions is still a challenge. Therefore, in connection with our program on the development of novel organic synthetic methodologies, herein we report our results on the synthesis of 3-acyl substituted isobenzofuran-1-ones in 67 to 80% yield *via* an aldol-lactonization reaction between 2-formylbenzoic acid and ketones catalyzed by PhB(OH)$_2$ under solvent-free conditions.



2; R = Alkyl, aryl

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Convenient one-pot synthesis of 2,3-disubstituted isoindolin-1-ones promoted by $PhB(OH)_2$

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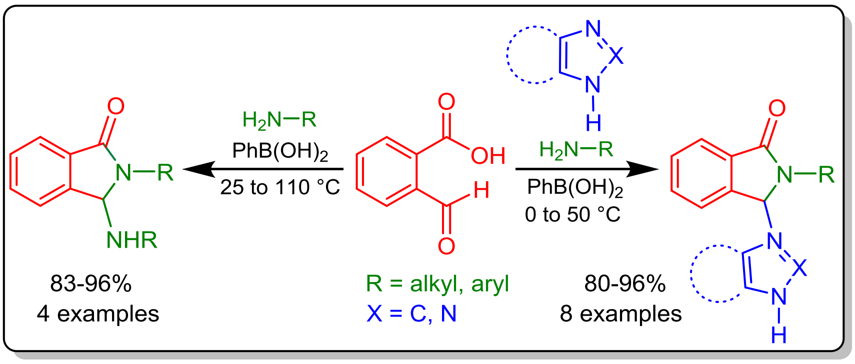
The isoindolin-1-ones (2,3-dihydro-1*H*-isoindol-1-ones) constitute a very interesting class of organic compounds due to their attractive pharmacological properties, including antiinflamatory, antitumor, antibacterial and antihypertensive activities. Additionally, the isoindolin-1-ones are key intermediates for the synthesis of many naturally occurring bioactive compounds.[1] As result, different methods have been developed for the preparation of these heterocycles, which suffer various drawbacks such as long reaction times, high temperatures, unsatisfactory yields and the use of expensive reagents.

In accordance with the increasing need to develop new methods to prepare these active compounds, in this communication we report a straightforward, efficient and sustainable method for the one-pot synthesis of new isoindolin-1-ones derivatives. The methodology involves the one-pot reaction of 2-formylbenzoic acid and aromatic or aliphatic amines in the presence of phenylboronic acid $PhB(OH)_2$ as a nontoxic, cheap and reusable catalyst, providing an important library of 2,3-disubstituted isoindolin-1-ones in excellent yields (Scheme 1).[2]



These new isoindolin-1-ones may find useful applications in organic synthesis, medicinal chemistry and for the development of chemosensors.

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Efficient allylic substitutions catalyzed by bifuntional nanoparticles

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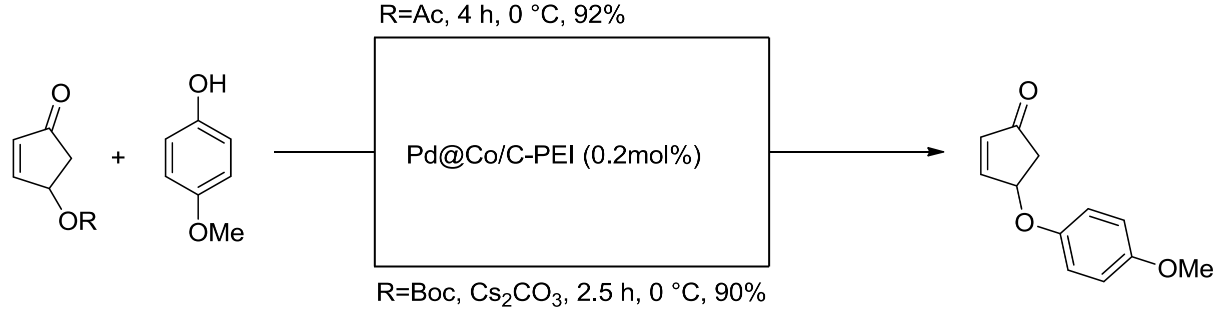
The well-established Tsuji-Trost reaction is one of the most important protocols to form new C-C/C-O bonds via introducing an allylic group into organic molecules.[1] As both base and palladium catalyst are required and have to be selected carefully to avoid self-quenching, it would be desirable to find an easy system which combines both active species in one catalyst and does not face those problems. In this work we describe the PEI-system[2] (polyethylenimine) on magnetic carbon-coated nanoparticles (Co/C) as scavenger for palladium nanoparticles and its use in Tsuji-Trost reactions.[3] The tertiary amine groups in the particles should act as base and the Pd(0) nanoparticles as palladium catalyst. Recycling of the base is done via stirring the particles in a K_2CO_3-solution. The new hybrid material was applied successfully in the reaction of *Ac*- and *Boc*-protected (±)-4-hydroxycyclopenten-1-one with *p*-methoxyphenol.[4,5]



The Pd@Co/C-PEI nanoparticles showed high activity in five consecutive cycles and could be recycled successfully without any significant loss in activity.

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Sustainable synthesis of 3-substituted phthalides from pyrones

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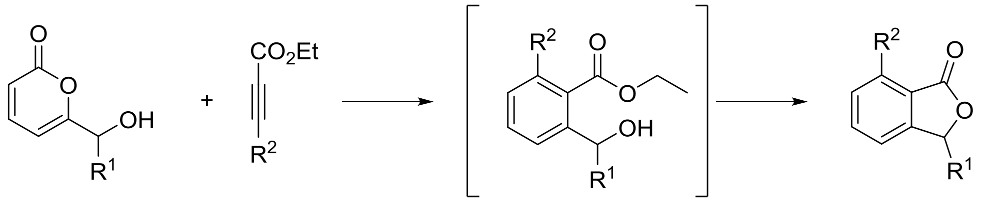
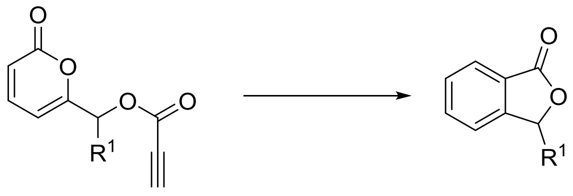
The structural motif of phthalides (3*H*-isobenzofuran-1-ones) is a key structure in many natural products isolated from plants and microorganisms.[1] Especially, 3-substituted phthalides are important heterocycles that possess a broad range of biological activities and significant pharmacological potentials.[2] Furthermore, phthalides bearing an alkyl or aryl substituent at the C-3 position are valuable building blocks for the synthesis of plenty natural products and pharmaceutical agents.[3] Therefore, the synthesis of those target molecules is an interesting research field. The focus of this work is to prepare a variety of 3-substituted phthalides and derivatives *via* a Diels-Alder reaction of 6-substituted 2-pyrones and alkynes. We present a synthetic route to different 6-α-hydroxyalkyl 2-pyrones **A** starting from 4-hydroxy-2-cyclopentenone, which can be obtained from agricultural waste products.[4,5] Although 2-pyrones are known to undergo [4+2]-cycloaddition with alkynes to give rise to benzene derivatives, no cycloaddition reactions of 6-α-hydroxyalkyl 2-pyrones **A** are reported to date.[6] During the investigations of the Diels-Alder reaction of those pyrones **A** with alkyne esters **B**, the formation of phthalide derivatives **D** were observed. In addition, also an intramolecular Diel-Alder reaction was developed yielding 3-substituted derivatives **F**. Studies towards an enantioselective synthesis of those compounds are currently ongoing.



A **B** **C** **D**



E **F**

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ISOCYANIDES IN NEW THREE-COMPONENT REACTIONS

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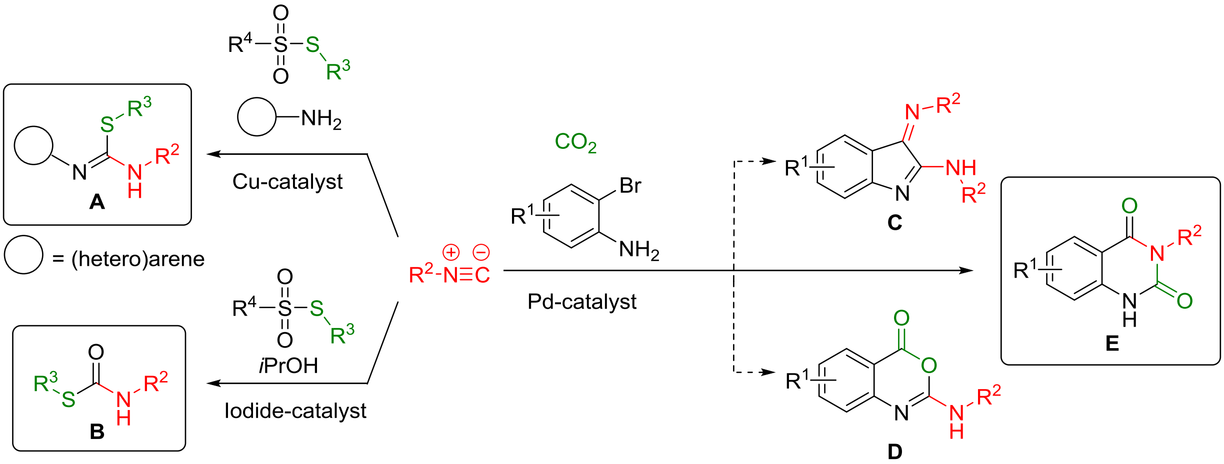
Isocyanides (R^2NC) are readily available and valuable C_1-reactants for organic synthesis.[1] They are especially valuable in the context of multicomponent reactions as they allow library synthesis in a rapid and step-efficient manner. The *one-pot* nature of these reactions avoids multiple work-ups, which is important in the context of sustainable chemistry.[2] Our laboratories have explored the combination of R^2NC with $R^4SO_2SR^3$ (thiosulfonates) in three-component reactions which gave access to new methods for isothiourea (**A**) and thiocarbamate synthesis (**B**).[3] More recently, the combination of R^2NC and CO_2 was studied. Their simultaneous use in transition-metal catalyzed reactions is a challenge due to the difference of these C_1-reactants in kinetic and thermodynamic stability. The Pd-catalyzed three-component reaction of 2-bromoanilines, CO_2 and RNC yielded *N*3-substituted quinazoline-2,4(1*H*,3*H*)-diones (**E**). While two other heterocycles (**C, D**) can potentially be formed, the three-component reaction delivered **E** in a completely regio- and chemoselective manner.



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