

Mangrolide A – A Novel Marine-Derived Antibiotic with Activity Against Gram-Negative Pathogens

Jef De Brabander

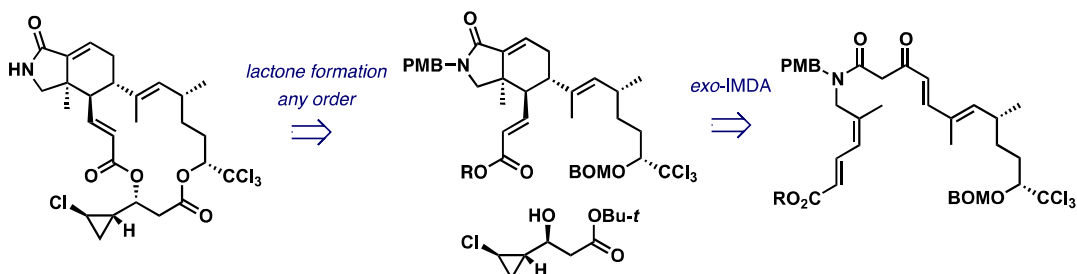
UT Southwestern Medical Center, Dallas, Texas, USA

I will present results related to a structurally novel antibiotic termed Mangrolide A, which was isolated from a marine actinomycete from the mangrove swamps in the Bahamas. Structurally, mangrolide A shares similarity to fidaxomicin ([®]Dificid), which is a clinically approved narrow-spectrum antibiotic used for the treatment of the Gram-positive pathogen *Clostridium difficile*. However, Mangrolide A exhibits potent and selective bactericidal activity against Gram-negative pathogens, including those associated with cystic fibrosis and hospital-acquired pneumonia infections. Mechanism of action studies revealed that Mangrolide interferes with the ribosomal [proofreading](#) process, leading to an increased rate of error in protein synthesis. This is the first example of a macrolide glycoside structure displaying the mechanism of action found for aminoglycosides. The frequency of antibiotic-resistant bacteria is currently rising at an alarming rate; therefore, the need to identify new antibiotics has reached a critical level. It is estimated that greater than 1.7 million hospital-acquired bacterial infections occurred in 2008 (4.5 per 1000 patients), resulting in more than 100,000 deaths. The estimated costs on the U.S. health care budget attributed to these infections are \$5 billion annually. Clinicians are increasingly concerned about the threat of Gram-negative pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and the Enterobacteriaceae, the main causes of hospital-acquired pneumonia. In a recent CDC survey 26% of *P. aeruginosa* isolates and 37% of *A. baumannii* hospital-isolates were resistant to the most common antibiotic treatments. While there have been a few approved clinical candidates for Gram-positive pathogens, new treatments for Gram-negative pathogens have stalled in recent decades. **Thus, the need for antibiotics that are effective against Gram-negative infections has become a medical necessity.**

Total Synthesis and Structural Revision of Muironolide A.

Kyle Young, Qing Xiao, Armen Zakarian

University of California, Santa Barbara, CA, USA



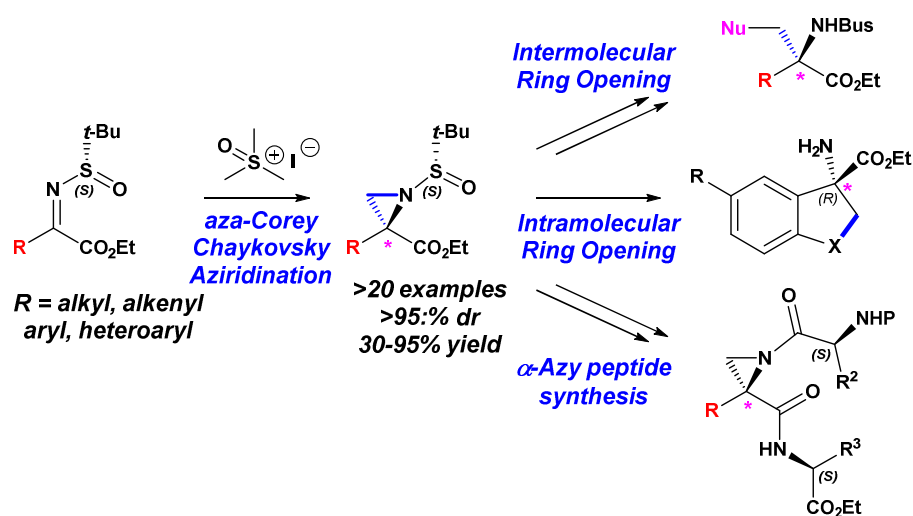
Muironolide A is a fascinating tetrachlorinated marine polyketide isolated from the sponge of *Phorbas* sp. Only 90 μ g had been isolated, and the structure was established by nanoscale NMR techniques. Herein we report the total synthesis of the substance with the assigned structure of muironolide A, propose a revised structure based on NMR data, and complete the enantioselective total synthesis of muironolide A.

Asymmetric Synthesis of α -Quaternary Substituted Aziridine-2-carboxylates and Application to Amino Acid Synthesis

Maurice Marsini

Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA

A general, scalable, and highly diastereoselective aza-Corey-Chaykovsky aziridination of *N*-tert-butanesulfinyl ketimino esters is described. The privileged, enantioenriched, and previously inaccessible α -quaternary aziridine-2-carboxylate products are densely functionalized compounds that provide straightforward access to novel, biologically relevant α -quaternary amino esters and derivatives starting from readily available precursors. The development of robust methodology and subsequent application via inter- and intramolecular ring opening will be presented.



A 50 Year Infatuation/Obsession with 1,3-Dipoles

Albert Padwa

Emory University, Atlanta, Georgia, USA

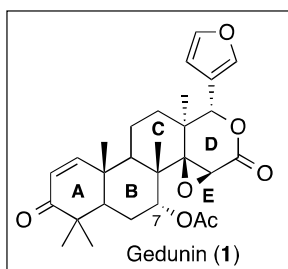
Part 1 of this presentation will provide a tribute to Professor Alan Katritzky's remarkable career in heterocyclic chemistry. In part 2, the chemistry of metal carbene complexes as a method to generate 1,3-dipoles is discussed. This approach bestows chemists with an exceptionally fertile ground for designing and developing new stereoselective bond construction for application toward the synthesis of various alkaloids. Due to their lability, metal carbene complexes are usually generated *in situ* from their corresponding diazo precursors prior to use. The reaction of α -diazo carbonyl compounds with transition metals such as rhodium(II) carboxylates constitutes a particularly powerful method for generating synthetically useful electrophilic carbene complexes. Earlier work by our group has shown that the rhodium(II) catalyzed reaction of α -diazo-3-oxobutanoates bearing tethered α -bonds represents a synthetically useful protocol for the construction of a variety of novel polycyclic skeletons. The Rh(II)-catalyzed reactions of the related 2-diazo-2-(1*H*-indol-2-yl)acetate system has now been examined as a potential route toward scandine, a member of the melodinus family of alkaloids. Attack of the neighboring carbonyl oxygen atom onto the rhodium carbenoid center produces a cyclic 1,3-dipole that undergoes cycloaddition with a tethered alkenyl group. The resulting cycloadduct corresponds to a potential intermediate in a planned synthesis of scandine.

Towards the Total Synthesis of the Tetranortriterpene Gedunin

Craig Williams

University of Queensland, Brisbane, Qld, Australia

Gedunin (1), which was first isolated from the West African timber *Entandrophragma angolense* in 1960, has been reported to exhibit a diverse range of biological activities, including antimalarial, antifungal, allergic response, peptic ulcer, anti-cancer, eryptosis, antifilarial, and insecticidal activity. In terms of anticancer activity, however, gedunin (1) was explored through the use of a connectivity map, and found to exhibit antiproliferative activity through the heat shock protein Hsp90. Such compelling biological interest in this compound inspired our group to investigate a synthetic route to gedunin so as to open opportunities for better understanding the underlying biochemical pathways. The lecture will describe our efforts in achieving the construction of a key advanced intermediate and subsequent activities towards total synthesis.

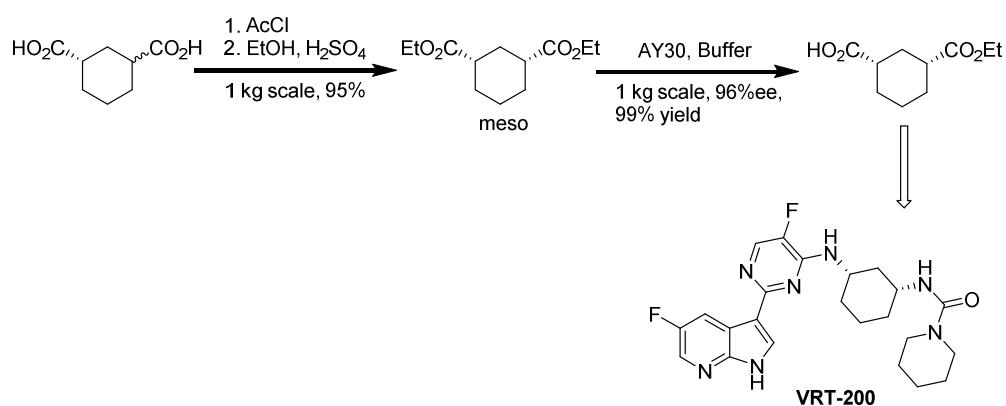


Scale Up of Azaindole Compound VRT-200: A Story of Synthetic Evolution

Colin Liang, Ed Dorsch, John Cochran, Ioana Davies, Huai Gao, Michael Clark, Paul Charifson

Vertex Pharmaceuticals, Boston, MA, USA

Azaindole compound **VRT-200** is a potent inhibitor of influenza PB2, and has complex structure which is a challenge for scale up. We use enzymatic desymmetrization of 1,3-bisester-cyclohexane to generate the two chiral centers with high yield (99%) and high ee (99%). The first generation of synthesis employs the displacement of chiral mono-Boc-diaminocyclohexane with sulfoxide, followed by urea formation (10 steps); The second generation of synthesis is racemic and need SFC separation (6 steps); The third generation of synthesis employs a Curtius rearrangement of acid to install morpholin urea in one step (7 total steps with 33% overall yield). All steps from last route are high yielding and easy to scale up

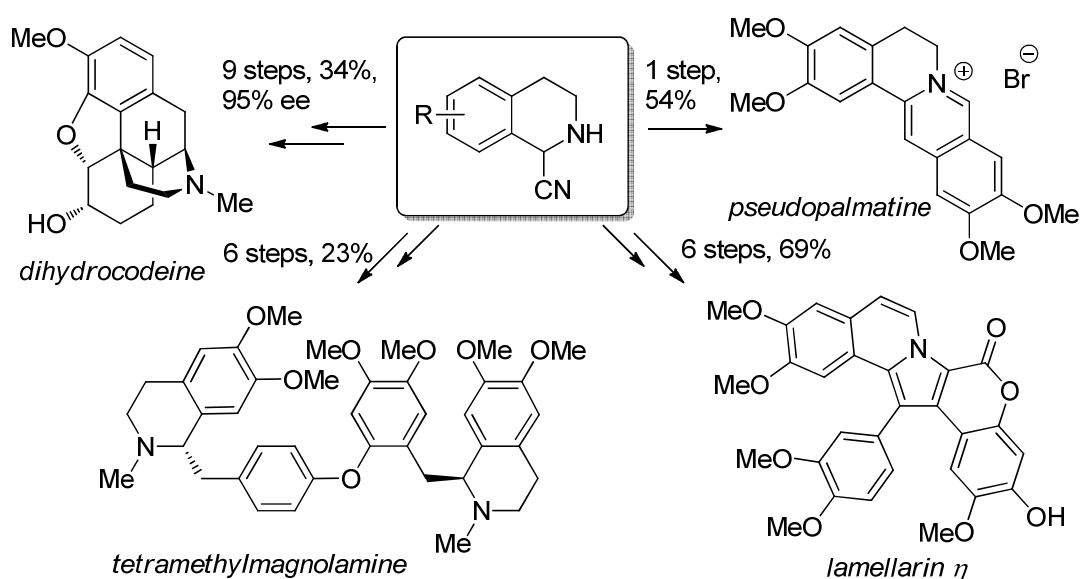


Deprotonated α -Aminonitriles as versatile Building Blocks for the construction of N-Heterocycles

Mario Geffe, Nancy Blank, Dennis Imbri, Günther Lahm, Till Opatz

Johannes Gutenberg-University, Mainz, Germany

The strong anion stabilizing capacity of the nitrile group permits α -aminonitriles with a primary or secondary amino group to be used as readily available α -aminocarbanion equivalents after deprotonation with a suitable base. These agents are versatile building blocks for the construction of highly substituted amines and N-heterocycles which can be obtained in very short reaction sequences or one-pot procedures. The related rearrangements of nitrile-stabilized ammonium ylides allow ring transformations such as the construction of protoberberine alkaloids in a single step.



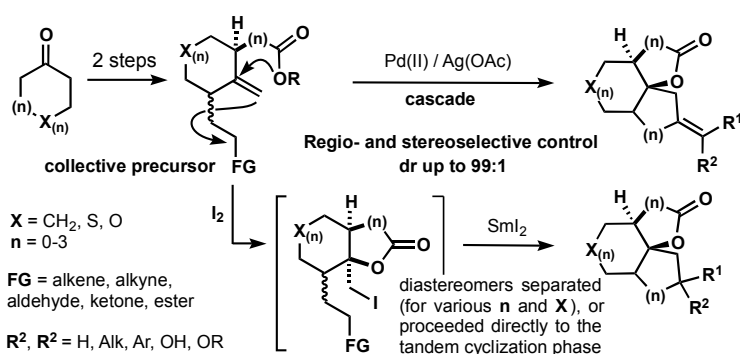
Rapid Composition of Tricyclic Spiranoid Lactones: Access to Natural and Unexplored Frames

Dmitry Tselikhovsky

Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

Many important biochemical compounds and drugs of natural origin contain tricyclic spirofuranone ring structures. Analysis of their molecular frames shows a compacted carbon skeleton with angularly fused tricycles of different oxidation states in each of the rings, which together present a real synthetic challenge.

Based on the remarkable core structure similarities among the natural products, we designed a rapid and practical collective synthesis strategy of complex functionalized natural and never-before explored frames. We devised a general and common synthesis of phylogenetically and structurally different tricyclic angularly fused systems via controlled cyclizations of simple key precursors. The novel strategy is short, regio- and stereoselective, and offers the possibility to access a broad spectrum of quaternary carbon-centered spiranoid lactone-based structures. Readily accessible key molecules, which are of lesser complexity than the target natural products, were elaborated by simple synthetic sequences. These yield a broad spectrum of spiranoid lactones of varying complexity.



Total and Formal Syntheses of Heterocyclic Natural Products and Drugs by MATSUDA-HECK-Reaction^[1]

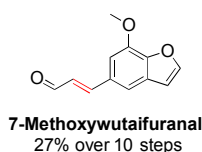
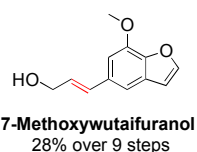
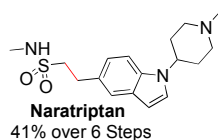
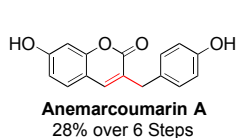
Felix Wolf, Bernd Schmidt

University of Potsdam, Potsdam, Germany

The palladium catalysed MATSUDA-HECK-Reaction or arene diazonium salts is a powerful synthetic tool for the coupling of olefins and (heterocyclic) aryl compounds. Highlighted by mild reaction conditions, convenient synthesis^[2,3] of very reactive and extremely useful electrophiles, this C-C-bond forming reaction is a highly versatile and efficient reaction for the synthesis of complex structures^[4].

To the best of our knowledge, we report the first total syntheses of three known bioactive heterocyclic natural compounds^[5,6] and one formal synthesis^[7] of the anti-migraine drug Naratriptan, which are presented below. Furthermore, we developed new synthetic pathways for the novel olefins and arene diazonium tetrafluoroborates required, optimized the systems and implement the results in very efficient and atom economic routes.

Our reaction conditions are distinguished by low catalyst loading of inexpensive Pd(OAc)₂, short reaction times, excellent functional group tolerance, absence of bases and ligands, full stereoselectivity and good to excellent yields.



¹manuscripts in preparation; ²B. Schmidt, R. Berger, F. Hölter *Org. Biomol. Chem.* **2010**, *8*, 1406-1414.; ³B. Schmidt, R. Berger, F. Hölter *Adv. Synth. Catal.* **2010**, *352*, 2463-2473.; ⁴J. G. Taylor, A.V. Moro, C. R. D. Correia *Eur. J. Org. Chem.* **2011**, 1423-1428.; ⁵J. Y. Ui, S. L. Seul, J. Hana, E.-K. Seo, *J. Nat. Prod.* **2009**, *72*, 1895-1898.; ⁶H.Y. Huang, T. Ishiwaka, I.-S. Chen *J. Nat. Prod.* **2008**, *71*, 1146-1151.; ⁷B. Pete, G. Simig, L. Toeke *Heterocycles* **2003**, *60*, 2441-2455.

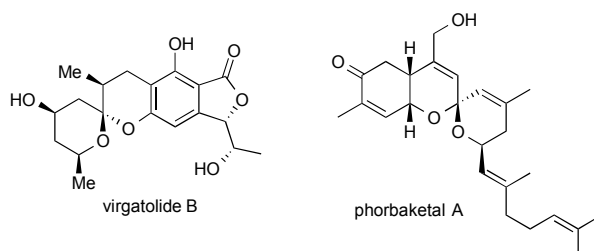
SYNTHESIS OF NATURAL PRODUCTS CONTAINING SPIROKETALS

Margaret Brimble

University of Auckland, Auckland, New Zealand

Natural products have long been regarded as “Nature’s medicine chest” providing invaluable platforms for developing front-line drugs. The chemical structures of natural products have evolved over several millennia for a specific biochemical purpose and their molecular frameworks can be considered “privileged scaffolds.” This lecture will showcase how natural products that contain intricate spiroketal scaffolds can be synthesized thus providing a platform to develop novel anticancer and anti-obesity agents.

The virgatolides are a family of natural products containing a rare benzannulated 6,6-spiroketal moiety isolated in 2011 from *Pestalotiopsis virgatula*.¹ Virgatolides A-C exhibit cytotoxicity against HeLa cells ($IC_{50} \sim 20 \mu\text{M}$). The first synthesis² of virgatolide B is described. Phorbaketal A and alotaketal A are two pseudoenantiomeric natural products, containing a unique spiro-esterterpenoid core structure.^{3,4} Phorbaketal A possesses moderate cytotoxicity against a range of cancer cell lines, as well as exhibiting osteoblast and mast cell differentiation activity and inhibition of fatty acid synthesis in the liver. Additionally, alotaketal A activates the cAMP signalling pathway at nanomolar concentrations. Our efforts directed towards the enantioselective syntheses of phorbaketal A and alotaketal A will be described.⁵



1. Li, J.; Li, L.; Si, Y.; Jiang, X.; Guo, L.; Che, Y. *Org. Lett.* **2011**, *13*, 2670.
2. Hume, P. A.; Furkert, D.P.; Brimble, M.A. *Org. Lett.* **2013**, *15*, 4588.
3. Rho, J.-R.; Hwang, B.S.; Sim, C.J.; Joung, S.; Lee, H.-Y.; Kim, H.-J. *Org. Lett.* **2009**, *11*, 5590.
4. Forestieri, R.; Merchant, C.E.; Matainaho, T.; Kieffer, T.J.; Andersen, R.J. *Org. Lett.* **2009**, *11*, 5166.
5. Hubert, J.G.; Furkert, D.P.; Brimble, M.A. *J. Org. Chem.* **2015**, *80*, 2231; *J. Org. Chem.* **2015**, *80*, 2715.

Hantzsch-type Reaction of β -Formyl- β -nitroenamine: Multi-component Synthesis of 4-Substituted-3,5-dinitro-1,4-dihydropyridine

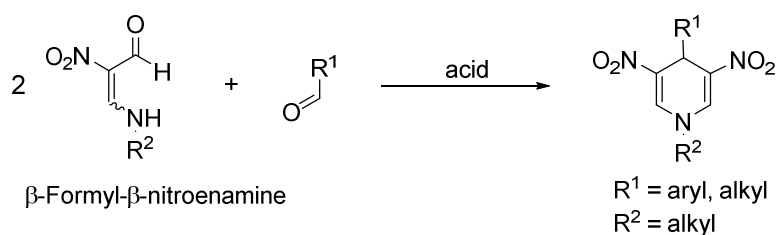
Haruyasu Asahara, Mai Hamada, Nagatoshi Nishiwaki

Kochi University of Technology, Kami/Kochi, Japan

1,4-Dihydropyridine (DHP) derivatives have attracted a considerable attention in medicinal chemistry and pharmacology due to the wide range of bioactivities, among which 4-arylated DHPs are also often found as the fundamental framework in drugs such as calcium antagonists and cardiovascular diseases.

On the other hand, we recently reported the novel method for construction of 4-arylated 3,5-dinitro-1,4-DHPs from β -formyl- β -nitroenamine as a reactive building block. Although this reaction serves as dinitro-DHPs that are not easily prepared by other method, the scope of the substrate is limited to highly electron-rich aromatics, and the theoretical maximum yield should be below 67%.

In this context, we have improved this reaction by using the strategy of Hantzsch-type multi-component reaction. Namely, a relevant multi-component reaction between two molecules of β -formyl- β -nitroenamine and an aldehyde is designed (Scheme), and we have succeeded to prepare various kinds of 4-aryl and 4-alkyl-3,5-dinitro-1,4-DHPs in high yields.



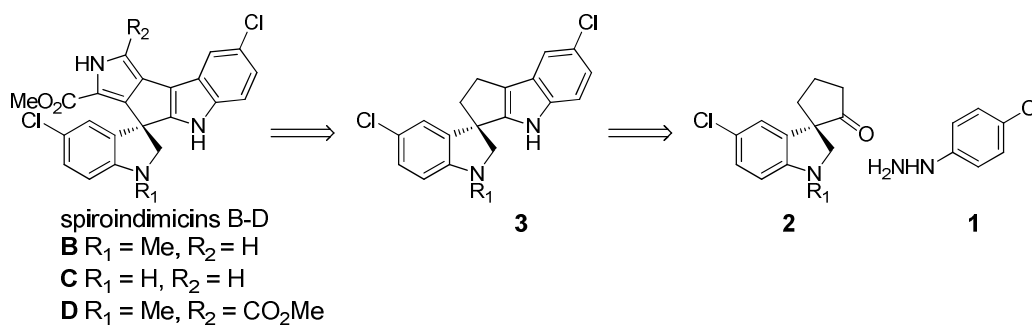
Scheme. Multi-component Synthesis of Dinitro-dihydropyridine

Synthetic studies towards spiroindimicins B-D

Lachlan M. Blair, Jonathan Sperry

The University of Auckland, Auckland, New Zealand

Spiroindimicins B-D were isolated in 2012 from *Streptomyces* sp. SCSIO 03032,¹ a deep-sea derived actinomycete collected from the Bay of Bengal. These hexacyclic natural products feature unprecedented [5,5] spirocyclic bisindole scaffolds, and exhibit moderate inhibitory activity and cytotoxicity against a series of cancer cell lines.¹ To date there are no reports on the synthesis of any member of this unusual family of natural products. Our synthetic strategy involves a Fischer indolization between phenylhydrazine **1** and ketone **2** to form the pentacycle **3**, to which we are currently attempting to append the pyrrole ring and hence complete the syntheses of spiroindimicins B-D.



1) Zhang, W.; Liu, Z.; Li, S.; Yang, T.; Zhang, Q.; Ma, L.; Tian, X.; Zhang, H.; Huang, C.; Zhang, S.; Ju, J.; Shen, Y.; Zhang, C., *Org. Lett.* **2012**, *14*, 3364-3367.

Synthesis of nitrogen analogues of bioactive lignans

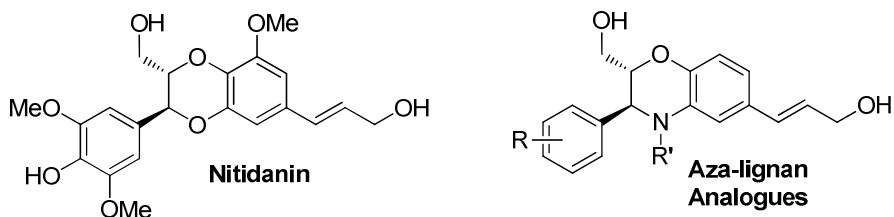
EunKyung Jung, David Barker

University of Auckland, Auckland, New Zealand

1,4-Benzodioxane neolignans are natural products that are a subclass within the lignan family that exhibit remarkable biological effects, including antimicrobial, hepaprotective and cytotoxic activities. In particular, 1,4-benzodioxane lignans with a 9-hydroxymethyl group such as silybin A, one of the components of silymarin (milk thistle extract), have shown inhibitory activity against hepatotoxicants. Nitidanin isolated from *Santalum album* is an antimalarial agent.

Previous work in our group has developed an enantioselective and flexible synthetic method to produce 1,4-benzodioxane lignans such as eusiderin and isoamericanin. We now report our efforts to synthesise nitrogen analogues of 1,4-benzodioxane lignans. The synthetic strategy is to convert the 1,4-benzodioxane skeleton into a benzomorpholine. The added nitrogen will allow an additional site for substitution which could allow bio-conjugation and also increase solubility.

We report our synthetic approach towards aza-lignans involving Mitsunobu reaction of an enantiopure secondary alcohol and an amino protected phenol, giving chirally pure aryl ethers which are converted into a benzomorpholine aminol. The N-Boc and O-Bn aminol was then subjected to N-acyliminium aryl addition, under acid condition. Aryl nucleophiles that are found in natural products were added to give a range of aryl benzomorpholine. Functionalization of the aryl bromide in these aryl benzomorpholines allows addition of the side chain.

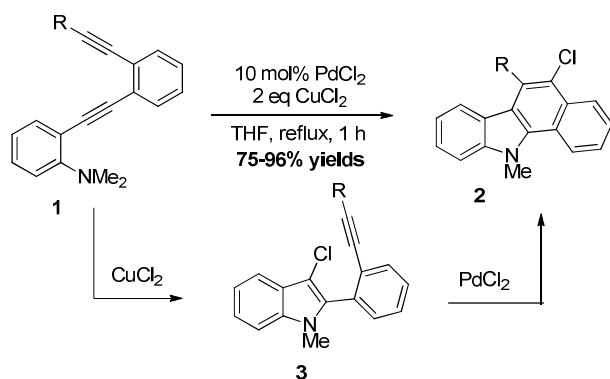


Transition Metal-Catalyzed Cyclization of Enediynes to Benzopyranones, Carbazoles and Benzothiophenes

Ming-Jung Wu

National Sun Yat-sen University, Kaohsiung, Taiwan

Recently, we found that treatment of *N,N*-dimethyl 2-[(2-(2-alkynylphenyl)ethynyl)anilines **1** with ten mol% of PdCl₂ and two equivalents of CuCl₂ at refluxing THF for one hour gave the chlorinated benzo[*a*]carbazoles **2** in excellent yields. The chloroindoles **3** was proposed as the key intermediate and can be prepared separately by reaction of **1** with two equivalents of CuCl₂ at refluxing THF. Treatment of **3** with various electrophilic transition metals, such as PdCl₂, Pd(OAc)₂ and PtCl₂, gave carbazoles **2** in good yields. Under the similar reaction conditions, methyl 2-[6-substituted 3(*Z*)-hexen-1,5-diynyl]benzoates and 2-(2-(2-(2-substituted ethynyl)phenyl)ethynyl)thioanisoles were converted to dibenzo[*b,d*]pyran-6-ones and benzo[*b*]naphtho[2,1-*d'*]thiophenes, respectively.



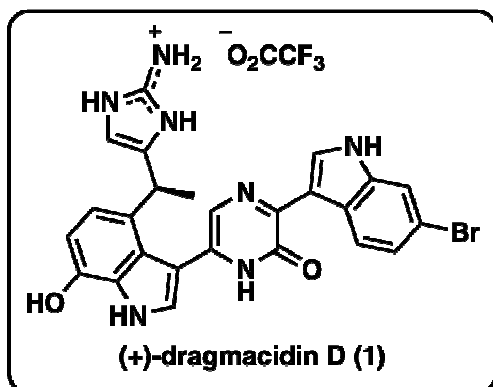
1. Chang, W. R.; Lo, Y. H.; Lee, C. Y.; Wu, M. J. *Adv. Synth. Catal.* **2008**, *350*, 1248.
2. Chen, C. C.; Chin, L. Y.; Yang, S. C.; Wu, M. J. *Org. Lett.* **2010**, *12*, 5652.
3. Chen, C. C.; Yang, S. C.; Wu, M. J. *J. Org. Chem.* **2011**, *76*, 10269.
4. Chen, C. C.; Chen, C. M.; Wu, M. J. *J. Org. Chem.* **2014**, *79*, 4704.

10 Step Asymmetric Total Synthesis and Stereochemistry of (+)-Dragmacidin D

Jeffrey Jackson, Armen Zakarian

UC Santa Barbara, Santa Barbara, CA, USA

The asymmetric total synthesis of (+)-dragmacidin D (1) has been completed in 10 steps. The lone stereocenter was set using a direct asymmetric alkylation procedure using a C₂-symmetrical tetramine in addition to lithium *N*-(trimethylsilyl)-*tert*-butylamide as the enolizing reagent. A regioselective Larock indole synthesis was employed as well as a copper-mediated acyl cross-coupling reaction to assemble the pyrazinone and aminoimidazole units. The stereochemical evidence from this work strongly supports the *S* configuration at the 6''' position consistent with other members of the dragmacidin family of natural products.

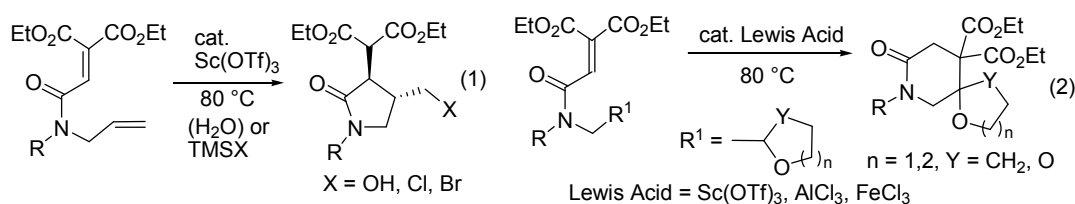


Lewis acid-catalyzed cyclization reactions of amides of ethenetricarboxylates

Shoko Yamazaki, Mamiko Niina

Nara University of Education, Nara, Japan

Nitrogen-containing heterocyclic systems are versatile core structures in organic chemistry because of their presence in many biologically active compounds. The development of new efficient synthetic strategies for the construction of nitrogen-containing heterocycles is of considerable interest. We have developed Lewis acid-promoted stereoselective five-membered ring formation of alkenyl ethenetricarboxylates.¹ To promote the cyclization/halogenation, 1-2 equivalents of Lewis acids such as AlCl₃, AlBr₃, TiCl₄, TiBr₄ and ZnI₂ are required. In this study, catalytic cyclization of allyl amides of ethenetricarboxylate leading to pyrrolidines has been examined. Reaction of allyl amides of ethenetricarboxylate with Sc(OTf)₃ (0.2 equiv.) gave 4-hydroxymethyl-2-oxopyrrolidine derivatives stereoselectively (eq 1). The formation of the hydroxymethylpyrrolidines may arise from participation of water in situ. Sc(OTf)₃-catalyzed cyclization reactions of the allyl amides with TMSX (X= Cl, Br) also proceeded efficiently to give halogenated 2-oxopyrrolidine derivatives. Catalytic cyclization of amides of ethenetricarboxylate bearing acetal and ether groups has also been examined. The reaction of the amides bearing cyclic acetal in the presence of Sc(OTf)₃ gave piperidine derivatives as major products (eq 2). The cyclized products may be formed via internal redox process.² Similarly, Lewis acid-catalyzed reaction of cyclic ethers gave spiro cyclic piperidine products selectively. The scope and the factors to control selectivities in the catalytic reactions of amides of ethenetricarboxylates are under investigation.



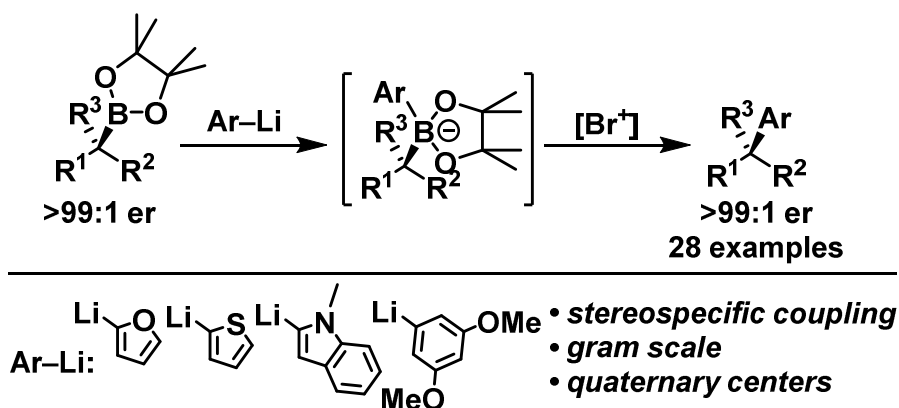
¹Yamazaki, S.; Fujinami, K.; Maitoko, Y.; Ueda, K.; Kakiuchi, K. *J. Org. Chem.* **2013**, *78*, 8405. ² Haibach, M. C.; Seidel, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 5010.

Enantiospecific couplings of secondary and tertiary boronic esters.

Marcin Odachowski

University of Bristol, Bristol, UK

A great amount of research has been dedicated in recent decade towards developing methods that facilitate the construction of 3D scaffolds of molecules. This comes as a direct consequence of a realisation that saturated molecules interact better with biological receptors than flat, unsaturated structures. There is a strong interest from pharmaceutical industry as it hopes to explore undiscovered chemical space using saturated molecules. Scientific community is investing a lot of effort to enable this goal, mainly by utilisation of established methods such as Suzuki-Miyaura cross-coupling. This Nobel Prize winning process has opened doors to a wide range of stereospecific reactions that enable the synthesis of tertiary carbon centres with high enantiomeric enrichment. This talk will focus on a new process developed in Aggarwal group that allows for the synthesis of tertiary and all-carbon quaternary centres in a transition metal free transformation.

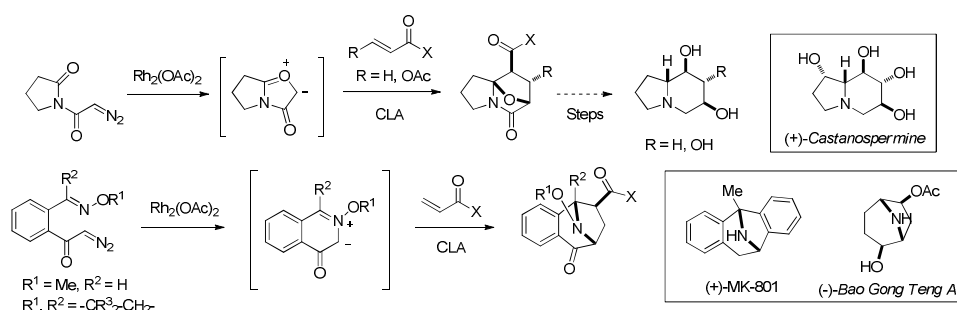


Asymmetric synthesis of heterocyclic compounds and their synthetic applications by cyclic ylides formation followed by enantioselective addition sequences

Hiroyuki Suga, Rinnosuke Oda, Takashi Bando, Takayuki Yoshida, Yasunori Toda

Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Nagano, Nagano, Japan

During the past decade, we developed enantioselective carbonyl ylide cycloaddition reactions featuring dual-activation methodology involving Rh-catalyzed cyclic carbonyl ylide formation followed by chiral Lewis acid-catalyzed cycloadditions, which have exhibited high levels of asymmetric induction.^{1,2)} To evaluate the efficiency of the dual-activation methodology for the asymmetric synthesis of several other biologically important heterocyclic compounds such as optically active polyhydroxy Indolizidine derivatives and 8-azabicyclo[3.2.1]octanes, we have investigated asymmetric cycloaddition reactions of the corresponding cyclic ylides derived from *N*-diazooacetyl lactams, 2-(2-diazoacetyl)-benzaldehyde *O*-methyloximes and related isoxazoline derivatives as diazo substrates based on the dual-activation methodology. Details of their enantioselectivities (good to high %ees) and synthetic applications will be reported.



This methodology could apply to the addition reaction of benzylalcohol to the cyclic carbonyl ylides derived from 2-diazo-3-alkanoyl-2-oxazolidinone derivatives. Relatively high enantioselectivities were observed for the addition products, which could be hydrolyzed to the corresponding water insertion products.

References

- 1) Suga, H. et al. *J. Am. Chem. Soc.* **2002**, 124, 14836. *J. Org. Chem.* **2013**, 78, 10840.
- 2) Suga, H. et al. *Org. Lett.* **2007**, 9, 4359. *Tetrahedron* **2010**, 66, 3070.

Vol. 9, No. 21

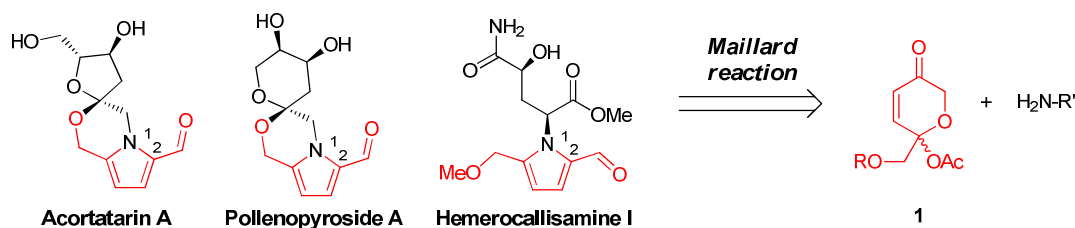
4359

Synthesis of 2-formylpyrroles using a Maillard approach: Elucidation of the bioactive pharmacophore in traditional Chinese medicines

James Wood, Daniel Furkert, Margaret Brimble

University of Auckland, Auckland, New Zealand

2-Formylpyrrole compounds have been isolated from a variety of plants with traditional medicinal uses. Among these compounds are the acortatarin family of natural products, which inhibit the production of high-glucose-induced reactive oxygen species in renal mesangial cells. This bioactivity has application in the treatment of diabetic nephropathy; the most common cause of chronic kidney failure. This project aims to explore the activity of the 2-formylpyrrole pharmacophore via library synthesis and SAR studies.



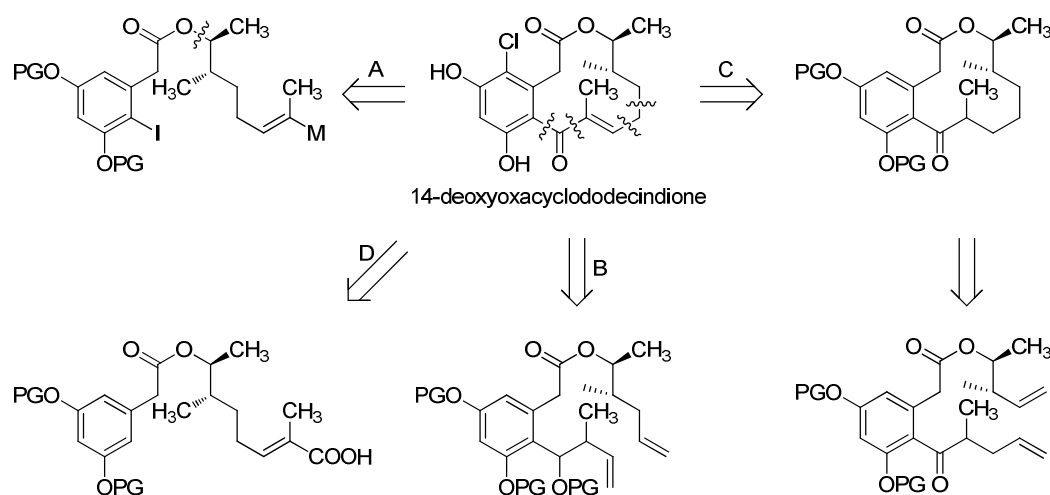
Our group has developed a novel Maillard-type reaction to synthesise 2-formylpyrrole natural products and their analogues; this reaction allows for the divergent synthesis of 2-formylpyrrole compounds from a single dihydropyranone intermediate **1**. Complexity is derived from the amine coupling partners, which have been prepared from amino acids and other chiral pool compounds. Herein, we present details of the total syntheses and compound library work for SAR bioactivity assays.

Synthesis of Potent Anti-Inflammatory Fungal Macrolactones

Johannes Tauber, Till Opatz

Johannes Gutenberg-University, Mainz, Germany

The secondary metabolite 14-deoxyoxacyclododecindione, isolated from *Exserohilum rostratum*, exhibits highly potent anti-inflammatory activity in the nanomolar range and may serve as a lead structure for new therapeutics for the treatment of chronic inflammatory and/or fibrotic diseases. While various synthetic approaches to the 12-membered skeleton like an attempted carbonylative ring closure (pathway A) or a ring-closing metathesis/double-bond isomerisation sequence (pathway B) were unsuccessful, a ring-closing metathesis/hydrogenation/unsaturation sequence (pathway C) furnished a highly potent analogue. Ultimately, an intramolecular Friedel-Crafts-acylation (pathway D) permitted the total synthesis of the natural product. The unknown relative stereochemistry was elucidated and initial structure-activity relationships were established for the oxacyclododecindione-type macrolactones.

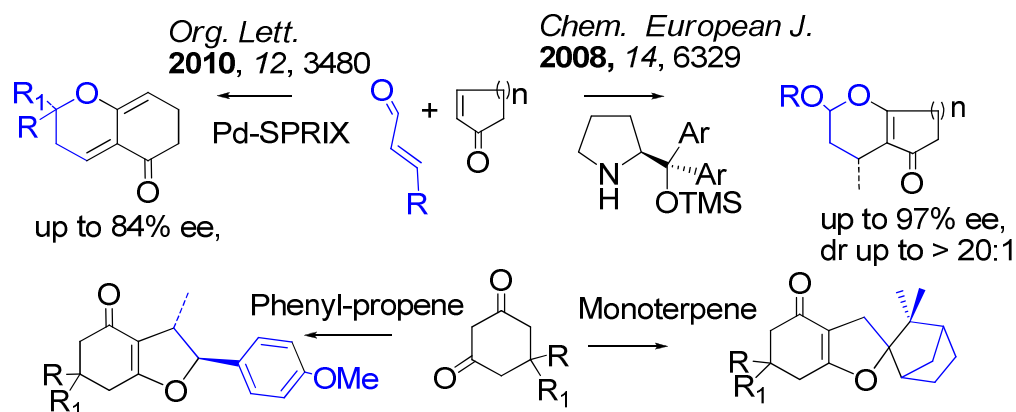


Novel syntheses of 5-oxo-benzopyran, 4-oxo-benzofuran and (1H)-isochromen-1-one derivatives through cyclization and coupling reactions

Sujata Bhat, Sylvia Fernandes

V. G. Vaze College, Mumbai University, Mumbai, Maharashtra, India

Benzopyranone, benzofuranone and (1H)-isochromen-1-one derivatives are important backbone in many natural products that exhibit interesting biological activities including immunomodulatory, cytotoxic, anti-inflammatory, anti-leukemic, antimicrobial, anti-allergic, and plant growth regulatory properties. In this presentation our recent efforts in synthesizing title compounds through the use of chiral LBA, Mn(OAc)₃ and related catalysts will be discussed.



1) Fernandes, S., Bhat, S. V. *Synthetic Commun.* **2014**, *44*, 2892-2898

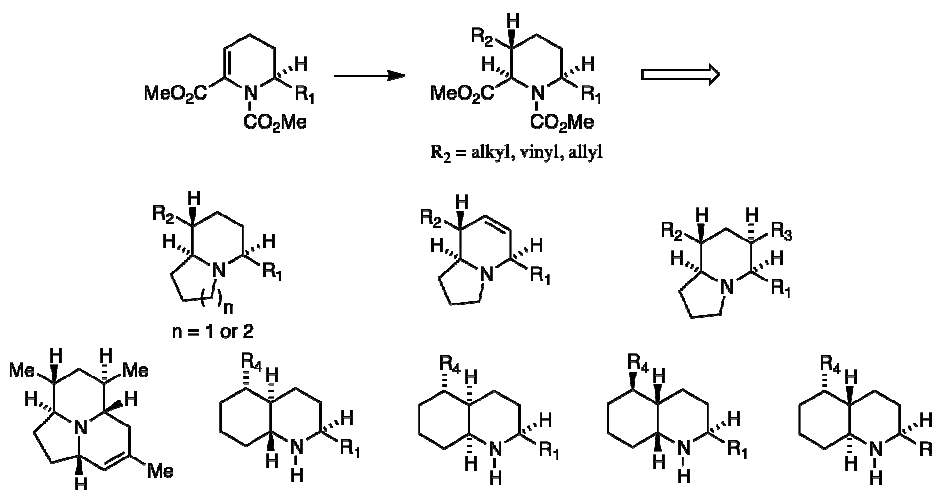
Synthesis of Poison-Frog Alkaloids

Naoki Toyooka

University of Toyama, Toyama, Japan

A variety of lipid-soluble alkaloids have been detected in amphibian skin, which contains over 20 structural classes and over 800 alkaloids. Many of these poison-frog alkaloids are expected to show interesting biological activities such as inhibitory effects on the neuronal nicotinic acetylcholine receptors (nAChRs).

We envisioned an efficient and flexible synthesis of 5,8-disubstituted, 6,7-dehydro-5,8-disubstituted, and 5,6,8-trisubstituted indolizidines, 1,4-disubstituted quinolizidines, decahydroquinoline-type poison-frog alkaloids using a Michael-type conjugate addition reaction of an enaminoester as the key step as shown below.



We will present our synthetic efforts toward the above alkaloids and the biological activity of the synthetic compounds on the nAChRs.

The title

Copper-Catalyzed Regioselective 2-Arylation of 5-Substituted Tetrazoles under Mild Conditions

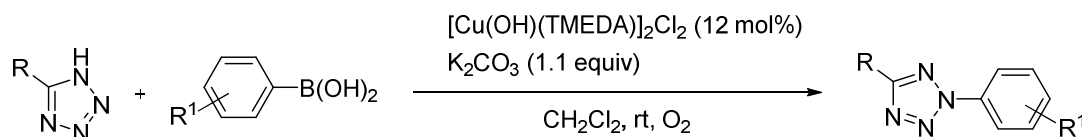
Takuya Onaka, Hideaki Umemoto

FUJIMOTO CHEMICALS Co., Ltd., Amagasaki, Hyogo, Japan

Tetrazoles are versatile, N-containing heterocyclic compounds used in pharmaceuticals, agrochemicals, and materials science. Moreover, 1-aryl-5-substituted tetrazoles are particularly useful as synthetic intermediates in biological research and medicinal chemistry. An efficient synthetic method of 1-aryl-5-substituted tetrazoles, therefore, has been developed.

Historically, 2-aryl-5-substituted tetrazoles have been regarded as less important than 1-aryl-5-substituted tetrazoles. However, the former have recently exhibited remarkable biological properties such as modulators of metabotropic glutamate receptors and G-protein-coupled receptor agonism. Despite these findings, however, reported methods for synthesizing 2-aryl-5-substituted tetrazoles are few. Several transition-metal-catalyzed direct 2-arylation of 5-substituted tetrazoles have been reported. Although 2-aryl-5-substituted tetrazoles were selectively obtained, these reported methods have been required a high reaction temperature and troublesome preparation of starting materials. It is known that tetrazoles are potentially explosive, and avoiding high reaction temperature is necessary. In addition, only 5-aryltetrazoles were used as substrates.

In this presentation, we report a novel method for the regioselective synthesis of 2-aryl-5-substituted tetrazoles by direct coupling of 5-substituted tetrazoles with arylboronic acids in the presence of a catalytic amount of $[\text{Cu}(\text{OH})(\text{TMEDA})]_2\text{Cl}_2$ in an O_2 atmosphere. The reaction can be conducted at room temperature and is applicable to both 5-aryltetrazoles and 5-alkyltetrazoles.



Applicable to Various Tetrazoles
(R = Alkyl, Thioalkyl, Halogen, Carbonyl, Aryl)

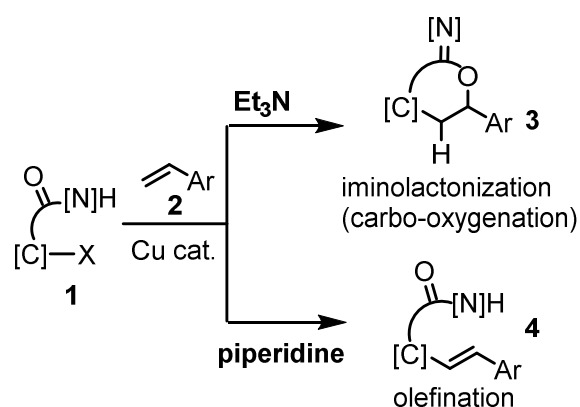
The title

Amine Enables the Switching between Iminolactonization and Olefination

Takashi Nishikata, Kohei Itonaga, Norihiro Yamaguchi, Yuki Inoue, Michinori Sumimoto

Yamaguchi University, 2-16-1 tokiwadai, Ube, Yamaguchi, 755-8611, Japan

The development of divergent reactions is one of the most challenging issues in metal-catalyzed reaction chemistry. Changing existing reaction patterns to other patterns by tuning the catalyst system suggests a new elemental step in the catalytic cycle. In this regard, we investigated a catalyst system that enables a perfect switch between iminolactonization and olefination. The reaction of alpha-bromoamides and styrenes underwent iminolactonization (carbo-oxygenation), in which simultaneous C–C and C–O bond formation occurred in the presence of a copper catalyst and triethylamine as a base, whereas olefination occurred in the presence of a copper catalyst and piperidine as a base.

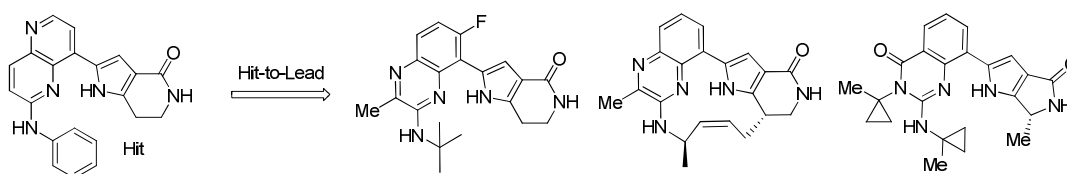


Optimization of Pim Kinase Inhibitors: Heterocyclic Chemistry and Macrocycles in a Pyrrole Series of Compounds

Victor Cee

Amgen, Inc., Thousand Oaks, CA, USA

Pim-1, -2, and -3 are highly homologous and constitutively active serine/threonine kinases. The three Pim isoforms phosphorylate a diverse group of proteins with known roles in proliferation, survival, apoptosis, and differentiation. The identification of oncogene-driven aberrant Pim kinase overexpression in subsets of B-cell malignancies including lymphomas, leukemias, and multiple myeloma, as well as in subsets of solid tumors, has led to intense efforts to identify small molecule Pim kinase inhibitors. A high-throughput screen of our corporate compound collection identified a hit composed of a 1,5-naphthyridine connected to a 6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one. A hit-to-lead optimization campaign resulted in the identification of improved inhibitors based on quinoxaline and quinazolin-4(3H)-one cores. A series of macrocyclic inhibitors in which the quinoxaline core and the dihydro-pyrrolo[3,2-c]pyridinone were connected was also found to possess improved properties. The heterocyclic chemistry of dihydro-pyrrolo[3,2-c]pyridinones, dihydropyrrolo[3,4-b]pyrrolones, and quinazolin-4(3H)-ones will be described, as well as the approaches used to synthesize macrocycles. Finally, the preclinical characterization of the lead molecules and their potential as treatments of Pim-driven malignancies will be presented.

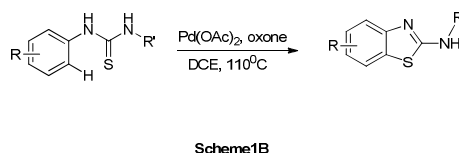
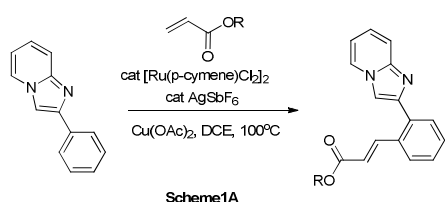


Exploration of new synthetic methodologies for the synthesis of heterocyclic scaffolds

R T Pardasani, Devesh Sawant, Shivani Sharma

Central University of Rajasthan, Bandarsindri, Rajasthan, India

Heterocyclic compounds are an important class of chemical compounds and are present in wide variety of drugs, photo-luminescent substances, agrochemical products, natural products etc.; thus play vital role in medicine, industry and life¹. Recent upsurge in the field of synthetic organic chemistry has brought into light many techniques, such as C-H activation,² transition metal-catalysed cross coupling reactions, multicomponent reactions³ etc., which expanded the horizons in the field of heterocycles, a feat that was never envisaged before. The main aim of our research is to focus our attention on the application of these methodologies for the construction of diversified and complex heterocyclic molecules. Recently, we published Ruthenium catalyzed C-H activation of the nitrogen containing heterocycles, wherein the innate reactivity of the heterocycle can be exploited for regioselective demonstrated C-2' alkenylation of 2-phenylimidazo[1,2-a]pyridine (Scheme 1A).⁴ Presently we are exploring synthesis of 2-aminobenzothiazoles from N-phenyl thiourea by palladium catalysed C-H functionalization/ C-S bond formation (Scheme1B). Salient features and mechanistic aspects will be presented.



References:

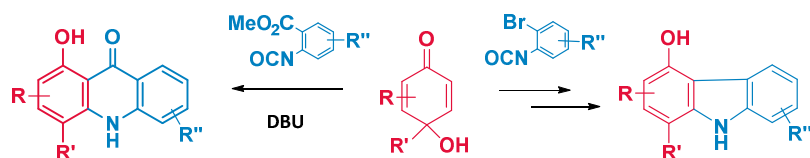
1. Pozharski, A. F.; Soldtenkov, A. T.; Katritzky, A. R. in *Heterocycles in Life and Society*, John Wiley and Sons, West Sussex, UK, **1997**.
2. Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169.
3. Sunderhaus, J. D.; Martin, S. F. *Chemistry* **2009**, *15*, 1300–1308.
4. Sawant, D.; Singh, I.; Tulsyan, G.; Abbagani, K.; Pardasani, R. T. *Synlett*, **2015**, in press.

Heterocycle Synthesis from Quinols

Jing Wu, Jinzhu Zhang, Shengping Zheng

¹Hunter College, New York, NY, USA, ²The Graduate Center, CUNY, New York, NY, USA

A variety of substituted 1-hydroxyacridones were synthesized in a one-pot carbamation/Michael addition/Claisen Condensation/decarboxylation cascade in two steps from commercial phenols in good to excellent yields (41-96%). Furthermore, synthesis of 4-hydroxycarbazoles from quinols was realized through a carbamation/Michael/enolate-aryl coupling/aromatization sequence. This methodology was also applied to a short total synthesis of carbazomycin B.



Reference

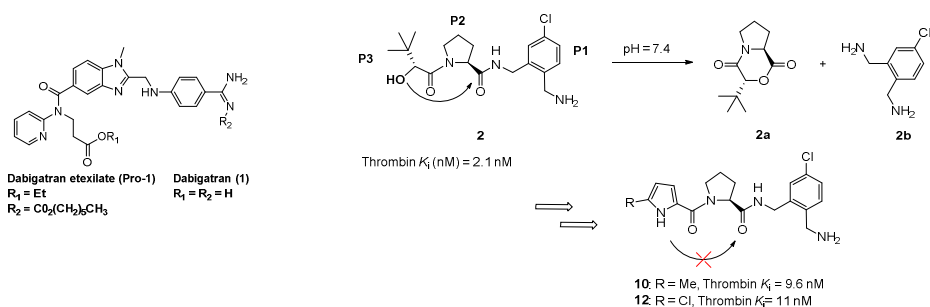
J. Zhang, J. Wu, Z. Yin, H. Zeng, K. Khanna, C. Hu, S. Zheng, *Org. Biomol. Chem.*, **2013**, 11, 2939.

Improved Stability of Proline-derived Direct Thrombin Inhibitors through Hydroxyl to Heterocycle Replacement

Harry Chobanian, Barbara Pio, Yan Guo, Hong Shen, Mark Huffman, Maria Madeira, Gino Salituro, Jenna Terebetski, James Ormes, Nina Jochowitz, Lizbeth Hoos, Yuchen Zhou, Dale Lewis, Brian Hawes, Lyndon Mitnaul, Kim O'Neill, Kenneth Ellsworth, Liangsu Wang, Tesfaye Biftu, Joseph Duffy

Merck and Co. Inc, Kenilworth, NJ, USA

Modification of the previously disclosed (*S*)-*N*-(2-(aminomethyl)-5-chlorobenzyl)-1-((*R*)-2-hydroxy-3,3-dimethylbutanoyl)pyrrolidine-2-carboxamide **2** by optimization of the P3 group afforded novel, low molecular weight thrombin inhibitors. Heterocycle replacement of the hydroxyl functional group helped maintain thrombin in vitro potency while improving the chemical stability and pharmacokinetic profile. These modifications led to the identification of compound **10**, which showed excellent selectivity over related serine proteases as well as in vivo efficacy in the rat arteriovenous shunt. Compound **10** exhibited significantly improved chemical stability and PK properties over **2**, and may be utilized as a structurally differentiated preclinical tool comparator to dabigatran etexilate to interrogate the on- and off-target effects of oral direct thrombin inhibitors.

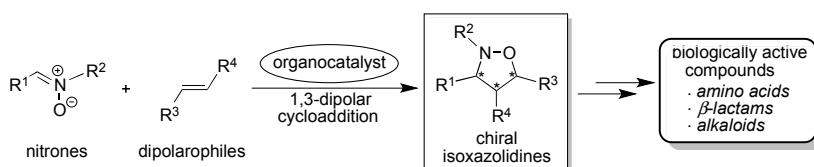


Enantioselective 1,3-dipolar cycloadditions reaction of nitrones with α,β -unsaturated aldehydes promoted by a primary siloxy β -amino alcohol organocatalyst

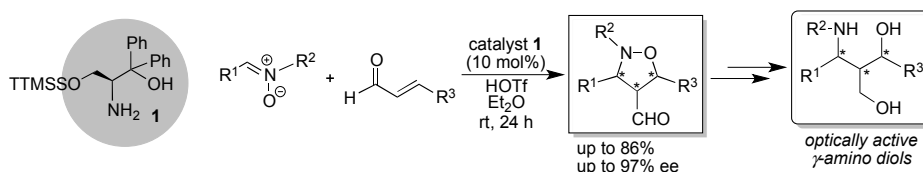
Tepei Otuki¹, Jun Kumagai¹, Yoshihito Kohari², Yuko Okuyama³, Eunsang Kwon⁴, Chigusa Seki¹, Koji Uwai¹, Yasuteru Mawatari¹, Nagao Kobayashi⁵, Tatsuo Iwasa⁶, Michio Tokiwa⁷, Mitsuhiro Takeshita⁷, Hiroto Nakano¹

¹Department of Bioengineering, Graduate School of Engineering, Muroran Institute of Technology, Muroran, Japan, ²Kitami Institute of Technology, Kitami, Japan, ³Tohoku Pharmaceutical University, Sendai, Japan, ⁴Research and Analytical Center for Giant Molecules, Graduate School of Sciences, Tohoku University, Sendai, Japan, ⁵Department of Chemistry, Graduate School of Science, Tohoku University, Sendai, Japan, ⁶Division of Engineering for Composite Functions, Graduate School of Engineering, Muroran Institute of Technology, Muroran, Japan, ⁷Tokiwakai Group, Iwaki, Japan

Organocatalyzed asymmetric 1,3-dipolar (1,3-DP) cycloaddition of nitrones with dipolarophiles¹ is an efficient reaction for the construction of optically active isoxazolidines, and the obtained isoxazolidines are valuable optically active chiral building blocks for the synthesis of various biological compounds.



We found that simple primary TTMSO- β -amino alcohol organocatalyst **1**² showed superior catalytic activity in 1,3-DP cycloaddition of nitrones with α,β -unsaturated aldehydes to provide high optically active isoxazolidines in good chemical yields (up to 86%) with excellent diastereoselectivities (up to *endo/exo* = 96/4) and enantioselectivities (up to 97% ee). Furthermore, the obtained optically active isoxazolidines were easily converted to β -amino diols having three successive stereogenic centers. This work will be presented and discussed in detail.



1. Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

2. (a) Kohari, Y.; Okuyama, Y.; Kwon, E.; Furuyama, T.; Kobayashi, N.; Otuki, T.; Kumagai, J.;

Seki, C.; Uwai, K.; Dai, G.; Iwasa, T.; Nakano, H. *J. Org. Chem.* **2014**, *79*, 9500. (b) Suttibut, C.;

Kohari, Y.; Igarashi, K.; Nakano, H.; Hiram, M.; Seki, C.; Matsuyama, H.; Uwai, K.; Takano,

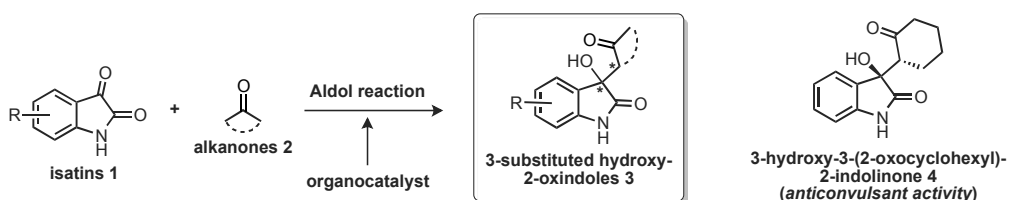
N.; Okuyama, Y.; Osone, K.; Takeshita, M.; and Kwon, E. *Tetrahedron Lett.* **2011**, *52*, 4745.

Asymmetric Aldol reaction of isatins with alkanones using an amino amide organocatalyst

Jo Kimura¹, Yoshihito Kohari², Yuko Okuyama³, Eunsang Kwon⁴, Chigusa Seki¹, Koji Uwai¹, Michio Tokiwa⁵, Mitsuhiro Takeshita⁵, Hiroto Nakano¹

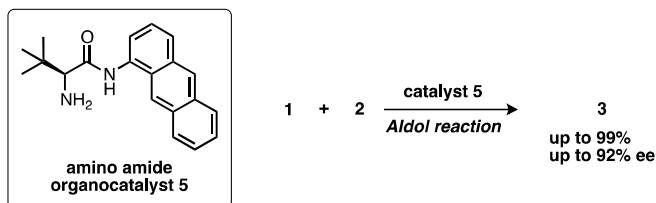
¹Department of Bioengineering, Graduate School of Engineering, Muroran Institute of Technology, Muroran, Japan, ²Kitami Institute of Technology, Kitami, Japan, ³Tohoku Pharmaceutical University, Sendai, Japan, ⁴Research and Analytical Center for Giant Molecules, Graduate School of Sciences, Tohoku University, Sendai, Japan, ⁵Tokiwakai Group, Iwaki, Japan

Organocatalyzed asymmetric Aldol reaction of isatins **1** with alkanones **2** is efficient reaction for the construction of optically active 3-substituted 3-hydroxy-2-oxindoles **3** and the resulted oxindoles can be used as useful synthetic intermediates for the synthesis of some biologically active compounds such as 3-hydroxy-3-(2-oxocyclohexyl)-2-indolinone **4** having anticonvulsant activity¹.



Chiral primary amino amide organocatalyst **5** was designed and synthesized as new organocatalyst for the asymmetric Aldol reactions of isatines **1** with alkanones **2** to produce chiral oxindoles **3**.

We found that amino amide organocatalyst **5** bearing a polycyclic aromatic hydrocarbon group showed superior catalytic activity in Aldol reaction for affording high optically active 3-substituted 3-hydroxy-2-oxindoles **3** (up to 99%, up to 92% ee). This work will be presented and discussed in detail.



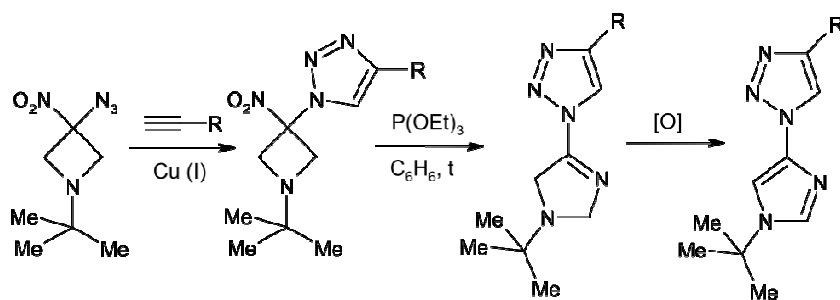
1. (a) M. Raj, N. Veerasamy, V. K. Singh, *Tetrahedron Lett.*, **2010**, 51, 2157-2159.

(b) Y. Tanimura, K. Yasunaga, K. Ishimaru, *Eur. J. Org. Chem.*, **2013**, 6535-6539.

Synthesis and Fungicidal Activity of Substituted 1-(1-tert-butyl-1H-imidazol-4-yl)-1H-1,2,3-triazoles

Mikhail Dubovis, Gennady Rudakov, Alexander Kulagin, Ksenia Tsarkova, Sergey Popkov, Victor Zhilin

Mendeleev University of Chemical Technology of Russia, Moscow, Russia



R = H, Me₃Si, cyclo-Pr, C₆H₅, 2-FC₆H₄, 2-ClC₆H₄, 3-ClC₆H₄, 2,4-Cl₂C₆H₃, 4-CF₃C₆H₄, 3-CF₃C₆H₄, 3-CH₃OC₆H₄

A series of new 1-(1-tert-butyl-1H-imidazol-4-yl)-1H-1,2,3-triazoles were prepared by reactions of corresponding 1-(1-tert-butyl-3-nitroazetidin-3-yl)-1H-1,2,3-triazoles with triethylphosphite with further oxidation. The 1,4-disubstituted triazoles were obtained by addition of azides to substitute acetylenes in the presence of ascorbic acid and copper(II) sulfate. Their structures were confirmed by ¹H, ¹³C NMR, IR, X-Ray, HRMS and elemental analysis. Most of the synthesized compounds were screened in vitro for their antifungal activity against *Rhizoctonia solani*, *Fusarium oxysporum*, *Fusarium moniliforme*, *Fusarium graminearum*, *Sclerotinia sclerotiorum*, *Venturia inaequalis* and *Bipolaris sorokiniana*. Some of the compounds displayed activities comparable with those of the commercial fungicide Triadimefon.

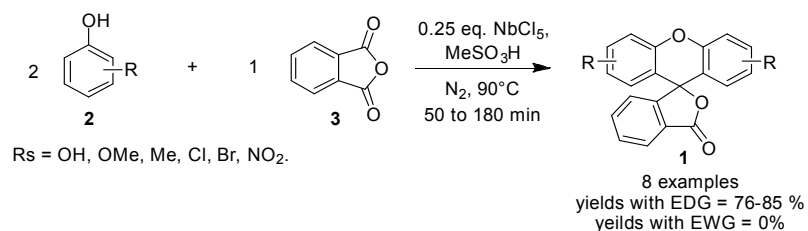
Synthesis of fluorescein derivatives by Multicomponent Friedel-Crafts reaction using Niobium pentachloride as Lewis acid

Bruno Henrique Sacoman Torquato da Silva, Lucas Michelão Martins, Luiz Carlos da Silva Filho

UNESP (Universidade Paulista "Júlio de Mesquita Filho"), São Paulo, Brazil

The fluorescein derivatives are an important class of heterocyclic compounds and has been attracting a large interest in the scientific community, taking several photochemistry and biochemical applications, such as: dyes in solar cells and other organic devices, and probes for use as cell biomarkers.[1] The Friedel-Crafts reaction is one of the most important reactions to formation of carbon-carbon bonds, leading to formation of aromatic ketones and alkylated rings.[2] Therefore, in this work we study the synthesis of fluorescein derivatives through Friedel-Crafts reaction using the niobium pentachloride as Lewis acid.

For the obtainment of fluorescein derivatives (**1**), the reactions were realized between 2,0 mmols of phenol derivatives (**2**) (substituted in *meta* or *para* position) and 1,0 mmol of phthalic anhydride (**3**), under inert atmosphere of N₂ and heating of 90 °C, using methanesulfonic acid as solvent and 0.25 eq. of NbCl₅. The adducts of fluorescein were obtained in reaction times ranging from 50 to 180 minutes and in yields ranging from 76 to 85% depending of the phenol derivative utilized. The results obtained, showed that the presence of electron-donating groups in the phenolic derivative favor the formation of the fluorescein derivative (**1**), while in the presence of electron-withdrawing groups wasn't observed the formation of products, with recovery of starting materials.



Acknowledgments: this work was supported by FAPESP, CAPES, CNPq and CBMM.

References: [1] Funabiki, K. et. al. *Journal of Fluorine Chemistry*. **2006**, 124, 257.

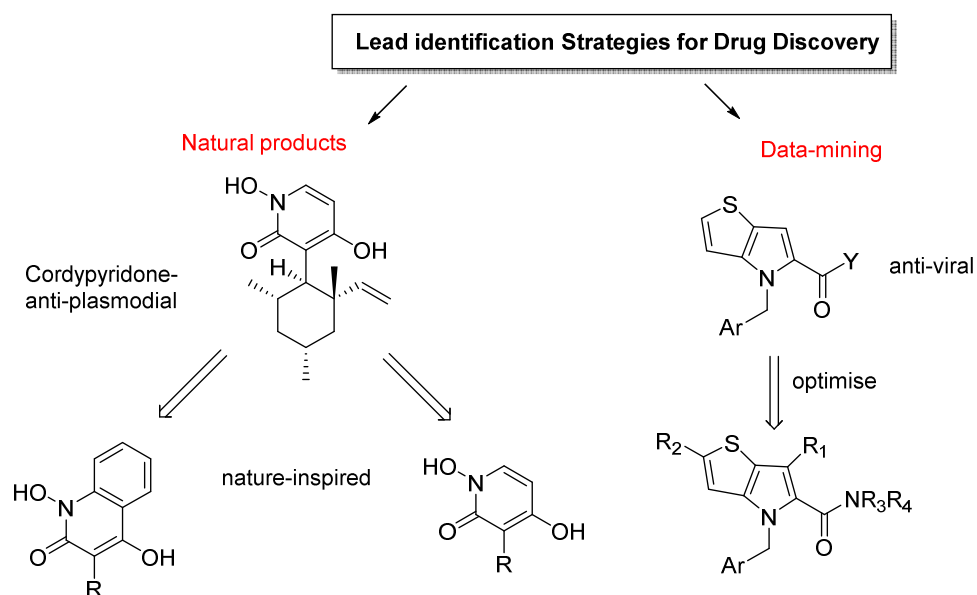
[2] Terrassom, V.; Figueiredo, R. M.; Compagne, J. M. *Eur. J. Org. Chem.* **2010**, 2635.

Targeting Tropical Vector Borne Infectious Diseases with Heterocyclic Compounds

Kuan Chieh Ching¹, Yanbo Teng¹, Yiu-Wing Kam³, Laurent Renia³, Lisa FP Ng^{3,1}, Christina LL Chai^{1,2}

¹National University of Singapore, Singapore, Singapore, ²Institute of Chemical and Engineering Sciences, Singapore, Singapore, ³Singapore Immunology Network, Singapore, Singapore

There is a pressing need to develop effective drugs for the treatment of vector borne infectious diseases such as malaria and chikungunya. In our research reported here, we utilise two strategies for lead identification. The nature products approach led to two heterocyclic scaffolds for anti-plasmodial drug development while data-mining identified thieno[3,2-b]pyrroles as potential anti-virals against chikungunya. This presentation will provide an overview of our synthetic and biological discoveries in this field.



Asymmetric Diels-Alder reaction of anthrones with dienophiles using a basic amino alcohol organocatalyst

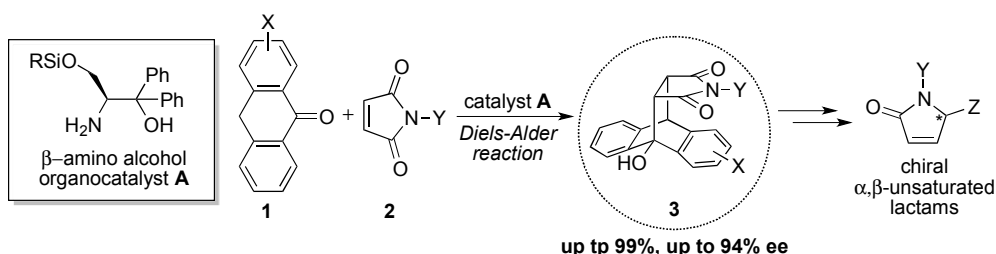
Jun Kumagai¹, Teppei Otuki¹, Yoshihito Kohari¹, Chigusa Seki¹, Koji Uwai¹, Yuko Okuyama², Eunsang Kwon³, Hiroto Nakano¹

¹Department of Bioengineering, Graduate School of Engineering, Muroran Institute of Technology, 27-1 Mizumoto, Muroran 050-8585, Japan, ²Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8585, Japan, ³Research and Analytical Center for Giant Molecules, Graduate School of Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

Asymmetric Diels-Alder (DA) reaction of anthrones with dienophiles using a basic organocatalyst is a useful reaction for the construction of optically active cage hydroanthracenes. The cage compounds could be easily converted to chiral α,β -unsaturated lactams, which are useful synthetic intermediate for many biologically active compounds.

Chiral primary amino alcohol¹ organocatalysts **A** bearing silyl group at β -position were designed and synthesized as new organocatalysts for the enantioselective DA reactions of anthrones **1** with maleimides **2** to produce chiral hydroanthracene DA adducts **3**.

We found that chiral primary amino alcohol organocatalysts **A** showed superior catalytic activity in DA reaction for affording high optically active hydroanthracenes **3** in excellent chemical yields (up to 99%) with high enantioselectivities (up to 94% ee). This work will be presented and discussed in detail.



- (a) Y. Sakuta, Y. Kohari, N. D. M. Romauli Hutabarat, K. Uwai, E. Kwon, Y. Okuyama, C. Seki, H. Matsuyama, N. Takano, M. Tokiwa, M. Takeshita, H. Nakano, *Heterocycles*, **2012**, *86*, 1379. (b) Y. Kohari, Y. Okuyama, E. Kwon, T. Furuyama, N. Kobayashi, T. Otuki, J. Kumagai, C. Seki, K. Uwai, G. Dai, T. Iwasa, H. Nakano, *J. Org. Chem.*, **2014**, *79*, 9500.

Synthesis of tetraaryl-1,4-dihydropyrrolo-[3,2-b]pyrroles derivatives using niobium pentachloride

Lucas Michelão Martins, Bruno Henrique Sacoman Torquato da Silva, Luiz Carlos da Silva Filho

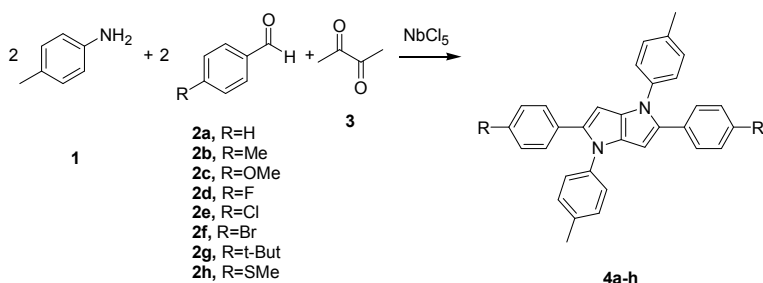
Universidade Estadual Paulista Júlio de Mesquita Filho, Bauru, São Paulo, Brazil

Heteropentalenes are aromatic compounds with 10π delocalized electrons in its structure. That characteristic make these compounds potential candidates as sensitizing dyes of organic electronic devices. Thieno[3,2-b]thiophene is a commercial available product that is used as basis for new compounds with the heteropentalene structure. The pyrrolo-[3,2-b]pyrroles derivatives are scarcely studied as sensitizing dyes in organic electronic devices.

Recently, a synthesis route was described for tetraaryl-1,4-dihydropyrrolo-[3,2-b]pyrroles derivatives (**4a-h**) through a multicomponent reaction between 2 moles of aldehydes derivatives, 2 moles of aniline derivatives and 1 mol of butanedione in the presence of acetic acid at 100°C , with low yields (5-34%).

Based on that, and in the objectives of our research group of applying the niobium compounds as catalyst in organic synthesis, we carried out the synthesis of tetraaryl-1,4-dihydropyrrolo-[3,2-b]pyrroles derivatives using niobium pentachloride as catalyst for the pentacomponent reaction among toluidine (**1**), benzaldehyde derivatives (**2a-h**), and 2,3-butanedione (**3**). The reactions proceeded in room temperature and in anhydrous solvent (CH_3CN). We could synthesize the products in a good reaction time (20-90 min) and with very good yields (49-98%). The products were purified by recrystallization and characterized by spectroscopic and spectrometric methods.

Acknowledgments: this work was supported by FAPESP, CAPES, CNPq and CBMM.

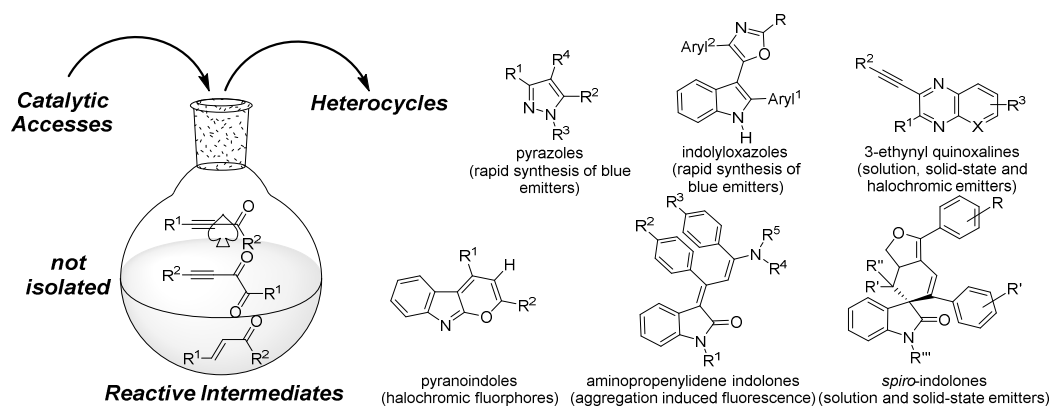


Functional Heterocyclic π -Systems by Multicomponent and Domino Syntheses

Thomas J. J. Müller

Heinrich-Heine-Universität, Düsseldorf, Germany

Multi-component and domino reactions are efficient and effective methods in the rapid and diversity-oriented synthesis of heterocycles. In particular, transition metal catalyzed multi-component sequences have recently gained a considerable interest.¹ Based upon transition metal catalyzed entries to ynones, diyones, and enones and sequentially Pd-catalyzed processes we have opened new avenues to one-pot syntheses of numerous classes of heterocyclic frameworks.² Among functional π -electron systems³ selected luminescent heterocycles are readily accessible in a modular fashion. They display peculiar photophysical properties, such as aggregation induced emission,⁴ pronounced emission solvochromicity, and photoinduced charge separation in DSSC.

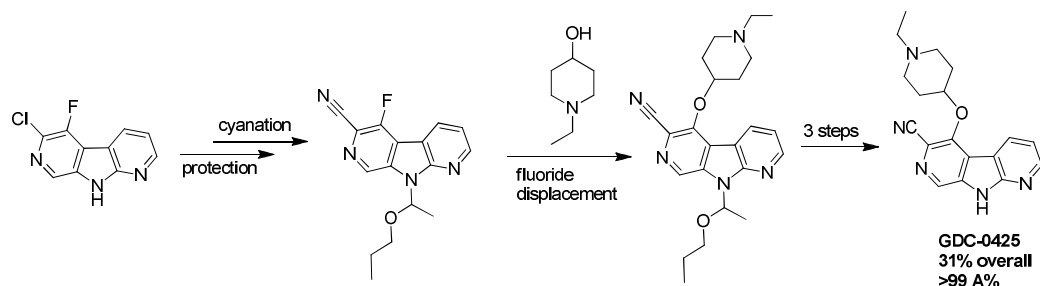


- 1 D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095.
- 2 a) Müller, T. J. J. *Top. Heterocycl. Chem.* **2010**, *25*, 25.94. b) Müller, T. J. J. *Top. Organomet. Chem.* **2006**, *19*, 149.
- 3 Müller, T. J. J.; D'Souza, D. M. *Pure Appl. Chem.* **2008**, *80*, 609.
- 4 Gers, C. F.; Nordmann, J.; Kumru, C.; Frank, W.; Müller, T. J. J. *J. Org. Chem.* **2014**, *79*, 3296.

Development of an Expedient Process for the Multi-Kilogram Synthesis of Chk1 Inhibitor GDC-0425

Andreas Stumpf, Zhigang Ken Cheng, Remy Angelaud, Lewis Gazzard

Genentech, San Francisco, CA, USA



As part of a recent drug development program for the orally active ChK1 inhibitor GDC-0425, we required multi kilogram amounts of active pharmaceutical ingredient (API) to support human clinical studies. The initial discovery chemistry synthesis involved a multi-step conversion from 6-chloro-5-fluoro-9H-pyrrolo[2,3-b:5,4-c']dipyridine **1**. This route effectively provided initial quantities of API but used undesirable reagents (SEM, NaH, TBAF), high catalyst loadings and required tedious workup and isolation procedures. We set out to develop a first generation process to manufacture ChK1 inhibitor GDC-0425 on multi-kilogram scale. An important part of our process development also needed to address the removal of heavy metals and the development of a crystallization process for the isolation of the penultimate API in high purity.

This presentation will discuss our efforts to secure an efficient and scalable route to the API and steps taken to lead us to the optimal route for GDC-0425 as shown in the scheme below. Highlights of the talk will be the discussion of the (1) carbazole protection strategy, (2) development of an efficient Pd catalyzed cyanation of aryl chloride **2**; (3) optimization of the S_NAr fluoride displacement of **3**; (4) development of the recrystallization process for GDC-0425. The optimized process delivered highly pure API (>99 A% by HPLC) with the desired crystal form in an overall yield of 31 %.

A Divergent Stereocontrolled Synthesis of the Enantiopure Tetracyclic Cores of Asparagamine A and Stemofoline via an Intramolecular 2-Propylidene-1,3-(bis)silane Bicyclization

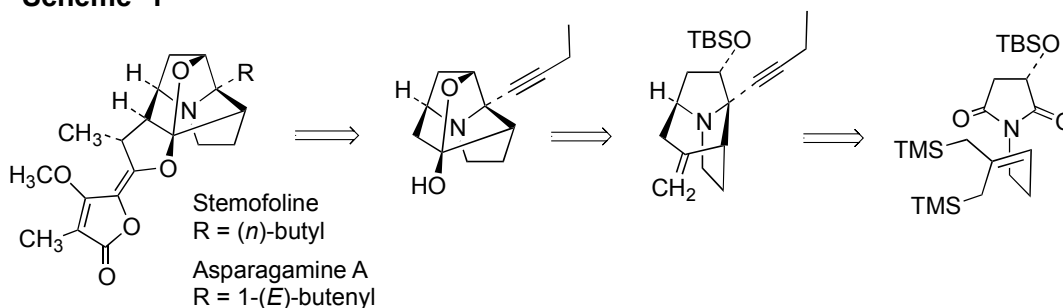
Thomas Livinghouse, Bryon Anderson, Bryce Sundahl

Montana State University, Bozeman, MT, USA

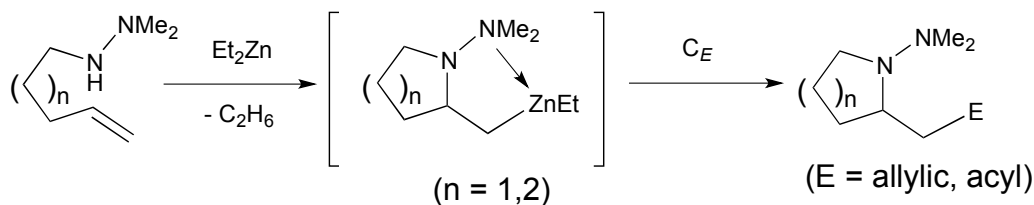
A concise and highly diastereoselective synthesis of the polyfused tetracyclic cores of the *Stemoa* alkaloids asparagamine A and stemofoline that relies on a 2-propylidene-1,3-(bis)silane bicyclization onto a enantiodefined pyrrolidine 2,5-di(cation) equivalent derived from L-malic acid will be described. A crucial feature of this divergent synthetic approach involves the solvolysis of a transient and highly labile tertiary-propargylic lactamol trifluoroacetate in the strongly ionizing medium 5M LiClO₄/Et₂O. The acyliminium ion generated in this manner undergoes stereospecific interception by the aforementioned (bis)silane nucleophile (Scheme 1).

The second topic of this discussion will be concerned with highly diastereoselective metalloamination/cyclizations of zinc(II) hydrazides derived from the reaction of diethylzinc and N,N-dimethylhydrazinoalkenes. The resulting organozinc intermediates have been found to undergo facile allylation and acylation, in-situ, to provide the corresponding functionalized piperidines and pyrrolidines respectively (Scheme 2).

Scheme 1



Scheme 2

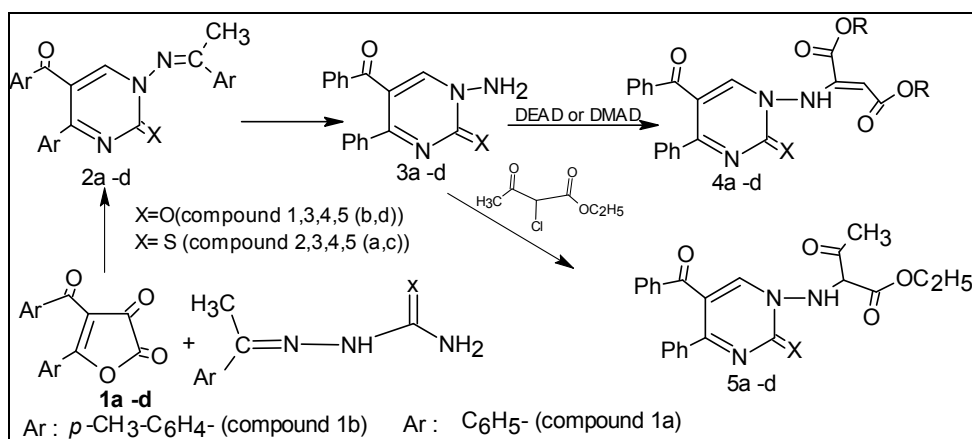


Investigation of Some Functionalization Reactions of 1-Amino-5-aryl-4-aryl-1H-pyrimidine-2-one/-thione Compounds with Dialkyl Acetylenedicarboxylates and Ethyl 2-chloroacetoacetate

Elif KORKUSUZ, Cihat Yüce

Erciyes University, Kayseri, Turkey

Pyrimidines in general have been found to be of much interest for biological and medicinal reasons, thus their chemistry has been extensively investigated. Some of these compounds have been shown to exhibit bactericide, antiviral and herbicide properties. In view of these important properties, we decided to extend our investigations related to preparing new heterocycles, which include the pyrimidine ring in their structure. Herein, we report the first synthesis of N-acyl pyrimidine derivatives 3a-d, 4a-d from the reaction of some 1-amino-5-aryl-4-aryl-1H-pyrimidine-2-one/-thione 3 with dialkyl acetylenedicarboxylates and ethyl 2-chloroacetoacetate.



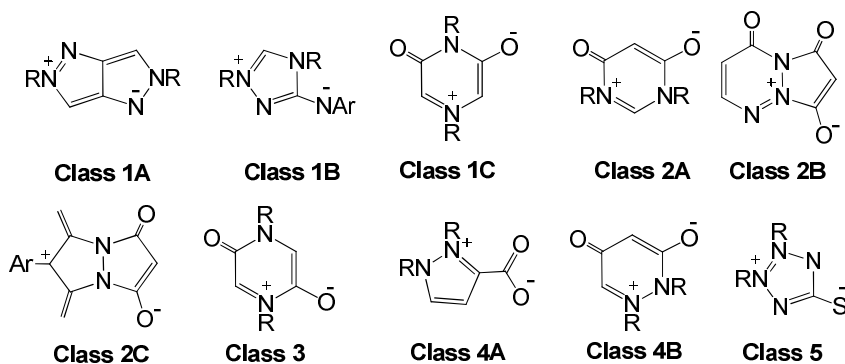
Acknowledgements. This study was financially supported by Research Foundation of Erciyes University. (FBA-2013-4215)

What are Heterocyclic Mesomeric Betaines?

Christopher Ramsden

Keele University, Keele, Staffordshire, UK

The structures shown below are all heterocyclic mesomeric betaines but they all have different general properties and they represent ten of the eleven distinct types of this class of heterocycle. Our systematic analysis identifies five discrete classes and associated subclasses. Each general class and subclass has different structural properties and reactivity profiles. In particular, it is important to distinguish between **Conjugated** (Class 1), **Cross-conjugated** (Classes 2 & 4) and **Semi-conjugated** (Classes 3 and 5) **mesomeric betaines**. Representatives of some classes are well known, others are rare and examples of a few are unknown. Together they account for a large area of heterocyclic chemistry. The common features and significant differences of the betaines shown will be discussed and our recent studies of (i) the aromaticity of semi-conjugated mesomeric betaines and (ii) mesomeric betaine/N-heterocyclic carbene tautomerism will be described.

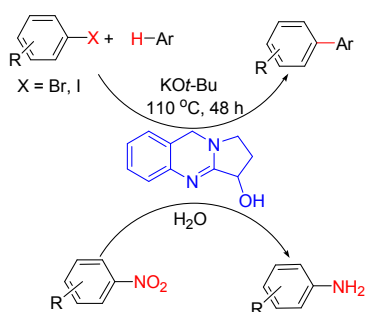


Unravelling the Organocatalytic Facet of Vasicine

Sushila Sharma^{1,2}, Neeraj Kumar^{1,2}

¹CSIR-Institute of Himalayan Bioresource Technology, Palampur, Himachal Pradesh, India,
²Academy of Scientific and Innovative Research, New Delhi, India

Organocatalysis has emerged as an attractive alternative to metalocatalysts in organic syntheses with regard to their selectivity, renewability and biodegradability. Owing to the functionalized structure and optically pure character of natural products such as carbohydrates, terpenes, alkaloids (proline and cinchona based organocatalyst), they have been efficiently utilized in various organocatalytic transformations.¹ Vasicine is an abundantly available quinazoline alkaloid mainly isolated from *Adhatoda vasica* leaves (present upto 1%) and is a privileged structure containing both Lewis acidic and basic sites, hence, able to activate both nucleophile and electrophile. Despite its medicinal importance in Ayurveda, its organocatalytic potential was not known before. Herein we disclose the prospects of vasicine as an efficient organocatalyst for transition metal free organic transformations viz. reduction and C-C bond formation reactions.²



References

1. a) L. Albrecht, H. Jiang, K. A. Jorgensen, *Chem. Eur. J.*, **2013**, DOI: 10.1002/chem.201303982; b) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 7496.
2. a) S. Sharma, M. Kumar, V. Kumar, N. Kumar, *Tetrahedron Lett.* **2013**, *54*, 4868; b) S. Sharma, M. Kumar, V. Kumar, N. Kumar, *J. Org. Chem.* **2014**, *79*, 9433.

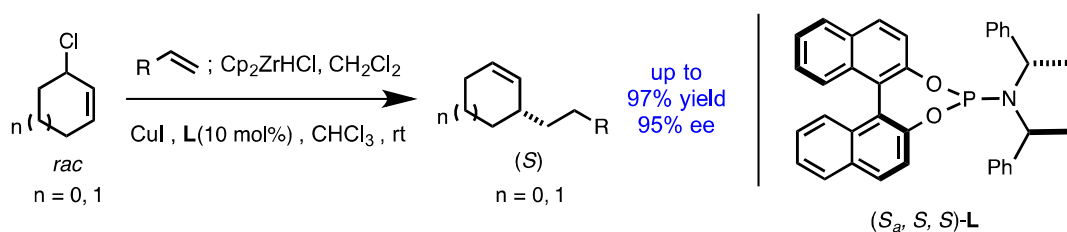
Non-stabilized Nucleophiles in Copper-Catalyzed Dynamic Kinetic Asymmetric Allylic Alkylation

Hengzhi You, Stephen.P. Fletcher

Oxford University, Oxford, UK

The development of reliable asymmetric methods to construct stereogenic centres from racemic starting materials would be powerful in synthetic organic chemistry. Over the past decades, the use of stabilized nucleophiles in dynamic kinetic asymmetric carbon-carbon formations, where both enantiomers of a starting material are converted to a single product, has proven to be a fruitful method.^{1,2} There have been significant difficulties in using non-stabilized nucleophiles in such processes, and this remains a key challenge.^{3,4}

Recently, we described a copper-catalysed enantioselective addition of alkyl zirconium reagents to racemic cyclic allylic chlorides (Figure 1). The reaction uses readily available starting materials and catalysts, tolerates a variety of functional groups and operates under convenient conditions.⁵ Here we will describe experimental work aimed at better understanding the mechanism of these reactions and at extending the scope of this chemistry.



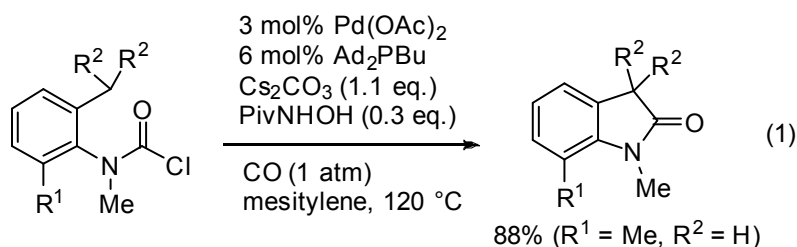
1. Trost, B. M., & Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–44.
2. Lu, Z., & Ma, S. *Angew. Chem. Int. Ed.* **2008**, *4*, 258–97.
3. Trost, B. M., & Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092–14093.
4. Sha, S.-C., Zhang, J., Carroll, P. J., & Walsh, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 17602–9.
5. You, H., Rideau, E., Sidera, M., Fletcher, S. P. *Nature*, **2015**, *517*, 351–355.

Palladium-Catalyzed Amidation by Chemoselective C(sp³)-H functionalization: Concise Route to Oxindoles and its application

Chihiro Tsukano, Masataka Okuno, Takeshi Nanjo, Nobusuke Muto, Yoshiji Takemoto

Kyoto University, Kyoto, Japan

The oxindole moiety is a core structure in many complex natural products; such natural products often possess interesting biological activities. This structure has also drawn the attention of medicinal chemists because of its potential as an important pharmacophore. In the course of the synthetic studies of spirooxindole skeleton, we focused on the utilities of carbamoyl chloride, which undergo oxidative addition to palladium catalyst. If C(sp³)-H bond activation is occurred after the oxidative addition, oxindoles would be accessed concisely. When we started the project, several groups reported the related cyclization using palladium catalyst via C(sp³)-H bond activation of a methyl group and the following reductive elimination. Thus we examined the formation of oxindoles from carbamoyl chloride bearing an alkyl group in proper position.



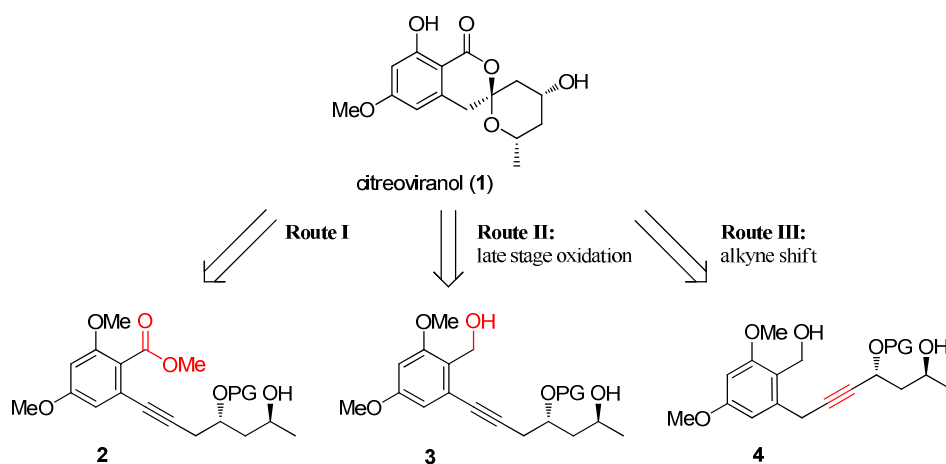
The cyclization of carbamoyl chloride (R¹ = Me, R² = H), which was prepared 2,6-dimethylaniline, proceeded smoothly under the conditions of palladium acetate (3 mol%), di(1-adamantyl)-*n*-butylphosphine (6 mol%), Cs₂CO₃ and *N*-hydroxypivalamide in mesitylene at 120 °C to give oxindole in 88% yield (eq. 1). These conditions could be applied to several substrates having chloro, methoxy groups and so on. Further studies to disclose the reaction scope and apply to the synthesis of natural products are currently underway and will be reported.

Synthetic Studies Towards Citreoviranol

Rachelle Quach, Daniel P. Furkert, Margaret A. Brimble

University of Auckland, Auckland, New Zealand

Citreoviranol (**1**) is a member of the biologically active resorcyclic lactone family, isolated from the fungus *Penicillium citreoviride*;¹ in addition to the characteristic resorcyclic lactone moiety, citreoviranol also contains a very rare 6,6-spiroketal lactone. To date, a total synthesis, and biological evaluation, of this unique molecule has yet to be undertaken. Herein, we endeavour to employ gold catalysis for construction of the spiroketal lactone core of citreoviranol from a functionalised alkyne precursor (**2-4**). Gold catalysis has proven to be a mild and efficient method for the synthesis of acid-sensitive spirocyclic heterocycles.²



(1) Shizuri, Y.; Shigemori, H.; Sato, R.; Yamamura, S.; Kawai, K.; Furukawa, H. *Chem. Lett.* 1988, 17, 1419.

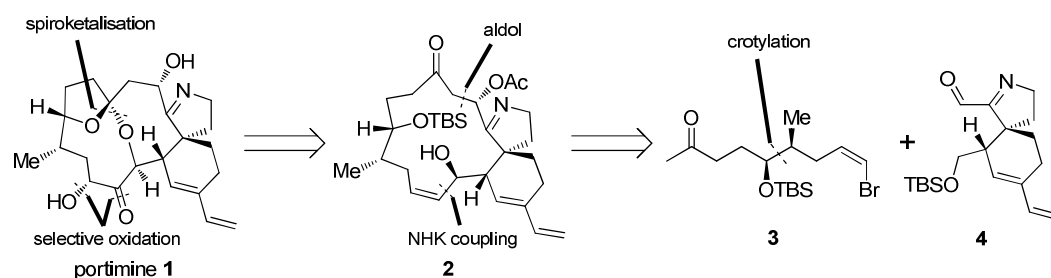
(2) Quach, R.; F. Chorley, D.; Brimble, M. A. *Org. Biomol. Chem.* 2014, 12, 7423.

Synthetic Studies Towards the Marine Toxin Portimine

Harry Aitken, Daniel Furkert, Margaret Brimble

University of Auckland, Auckland, New Zealand

Portimine (**1**) is a novel polycyclic marine toxin, containing spiroimine and bridged-spiroketal functionality, isolated from the dinoflagellate *Vulcanodinium rugosum* collected off the coast of Northland, New Zealand. Whilst the spiroimine motif is commonly observed in a number of algae-derived toxins the [4.5]-spiroimine ring system is unique to portimine, thus representing an intriguing synthetic challenge. Portimine is a potent inducer of apoptosis and confers high toxicity against leukaemia cells *in vitro* (P388 cells, $EC_{50} = 2.7$ nM).



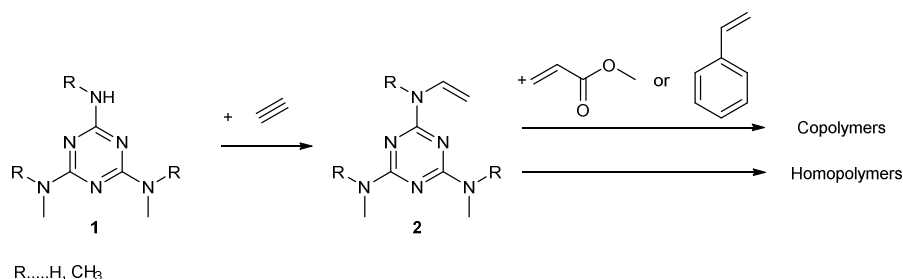
The synthesis of portimine (**1**) has been designed to provide structural analogues of portimine for biological evaluation. The carbon framework of portimine will be accessed by aldol addition of Leighton crotylation-derived polyketide **3** to spiroimine **4**. Subsequent macrocyclisation using a Nozaki-Hiyama-Kishi reaction will provide tricyclic intermediate **2**; finally, spiroketalisation and selective oxidation—to the unusual α,α' -dihydroxyketone moiety—will complete the synthesis of portimine.

***N*-methylmelamines as precursors for new polymers**

Herbert Gabriel, Martin Irrgeher, Manuela List, Clemens Schwarzinger

Johannes Kepler University Linz, Linz, Austria

Methylated melamines are widely used as anti-tumor drugs, insect sterilants, and as monomers for modified melamine-formaldehyde-polymers. Methylol(methylmelamines) are metabolites of antitumor agents such as altretamine (hexamethylmelamine) and trimelamol (trimethylol(trimethylmelamine)), formed by oxidation of a methyl group and subsequent elimination of formaldehyde. *N*-vinylmelamine derivatives **2** offer a broad range of industrial applications, not only homopolymerization but also copolymerization with other monomers currently being under investigation. Our recent studies have used methylmelamines **1** as building blocks for the synthesis of functional acrylate monomers for coatings or in the synthesis of polymer additives.



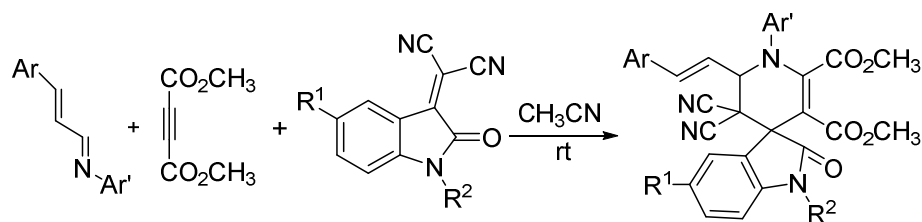
In attempt to produce new melamine polymers we have prepared different functional triazine compounds for further vinylation and then polymerization with commercially available monomers, such as ethylene, styrene, or methylmethacrylate. The vinylgroup is usually attached to a free NH-group – the influence of different substituents on the nitrogen on the rate of vinylation has been investigated and found to be of great importance. At the moment copolymerization of the vinyl melamines is being done. Depending on the selected melamine derivative basic polymerization parameters have been studied and optimized.

Synthesis of spiro[indoline-3,4'-pyridines] and spiro[indene-2,4'-pyridines] via three-component reaction

Chao-Guo Yan, Jing Zhang

Yangzhou University, Yangzhou, China

In the diverse polycyclic 1,4-dihydropyridines (1,4-DHPs), spiro[indoline-3,4'-pyridine] is now recognized as one of the privileged heterocyclic scaffold, which attracted everlasting interests in organic synthesis, chemical biology and pharmaceutical chemistry. The cycloaddition reaction of isatinylidene malononitrile with the dipolar intermediates derived from nucleophilic additions of N-heterocyclic arenes and arylamines to electron-deficient alkynes such as acetylenedicarboxylate or propiolate provided a convenient synthetic protocol for spiro[indoline-3,4'-pyridine] derivatives. Here we developed another elegant synthetic methodology by using the 1,4-dipoles generated from N-aryaldimines and acetylenedicarboxylates. The three-component reaction of α,β -unsaturated N-aryaldimines, dialkyl acetylenedicarboxylate (alkyl propiolate) and isatinylidene malononitriles (ethyl cyanoacetates) in dry acetonitrile at room temperature afforded polysubstituted spiro[indoline-3,4'-pyridines] in good yields and with high diastereoselectivity. Under similar reaction conditions, the corresponding spiro[indene-2,4'-pyridines] were obtained from the three-component reactions containing 2-(1,3-dioxo-1H-inden-2(3H)-ylidene)malononitrile.



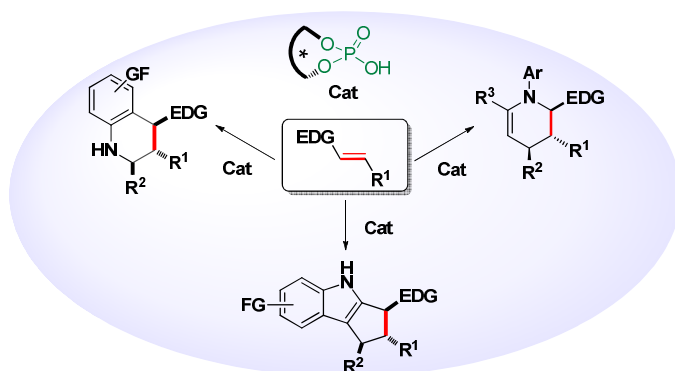
ENANTIOSELECTIVE ORGANOCATALYTIC CYCLOADDITIONS VIA HYDROGEN BOND CATALYSIS

GERALDINE MASSON

INSTITUT DE CHIMIE DES SUBSTANCES NATURELLES (CNRS), GIF-SUR-YVETTE, FRANCE

Asymmetric Brønsted acid catalysis has rapidly emerged as a powerful strategy for the synthesis of chiral, biologically relevant compounds, complementing enzymes and metal complexes. For the past five years we have been interested in developing enantioselective cycloadditions catalyzed by chiral Brønsted acid catalysts.¹

This talk will present our work in this area, which includes the asymmetric cycloaddition syntheses of various six- and five-membered nitrogen-containing heterocycles.² We also applied these methodologies in the synthesis of biologically active natural and non-natural products.



References

1) (a) Masson, G. ; Lalli, C.; Benohoud, M. ; Dagousset, G. *Chem. Soc. Rev.* **2013**, 42, 9023; (b) Bernadat, G. ; Masson, G. *Synlett* **2014**, 25, 2842.

2) (a) Lebée, C. ; Kataja, A. ; Blanchard, F. ; Masson, G. *Chem. Eur. J.* **2015** DOI : 10.1002/chem.201500749; (b) Dagousset, G. ; Erb, W. ; Masson, G. *Org. Lett.* **2014**, 16, 2554; (c) He, L.; Laurent, G.; Retailleau, P.; Folléas, B.; Brayer, J.-L.; Masson, G. *Angew. Chem. Int. Ed.* **2013**, 52, 11088; (d) He, L., Bekkaye, M., Retailleau, P.; Masson, G., *Org. Lett.* **2012**, 14, 3158; (e) Dagousset, G., Zhu, J.; Masson, G., *J. Am. Chem. Soc.* **2011**, 133, 14804; (f) Liu, H., Dagousset, G., Masson, G., Retailleau, P., Zhu, J., *J. Am. Chem. Soc.* **2009**, 131, 4598.

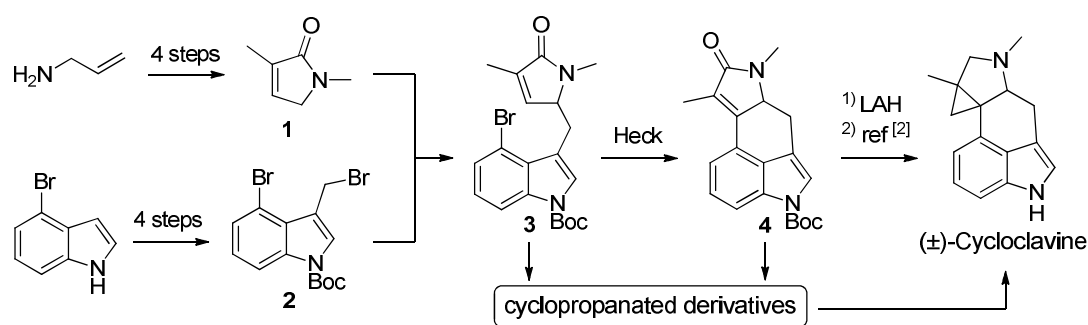
Formal Total Synthesis of (±)-Cycloclavine

Natalie Netz, Till Opatz

University of Mainz, Mainz, Germany

Among the ergot alkaloids, which are known for their various potent biological activities, the clavine-type alkaloid cycloclavine is noteworthy because of its unique pentacyclic structure.^[1]

We here report a short convergent route to (±)-cycloclavine, which contains only eight linear steps and requires only four chromatographic purifications. The two building blocks **1** and **2** are synthesized in four linear steps from commercially available starting materials. They are linked by two consecutive coupling reactions, including a selective alkylation of a dienolate, which is the key step.



Compound **4** is easily reduced to complete the formal total synthesis of (±)-cycloclavine employing the cyclopropanation step by *Incze et al.*^[2]. In order to improve the overall yield, we are currently working on the alternative cyclopropanation of amide precursors **3** and **4**, with a samarium-mediated process showing the most promising results so far.

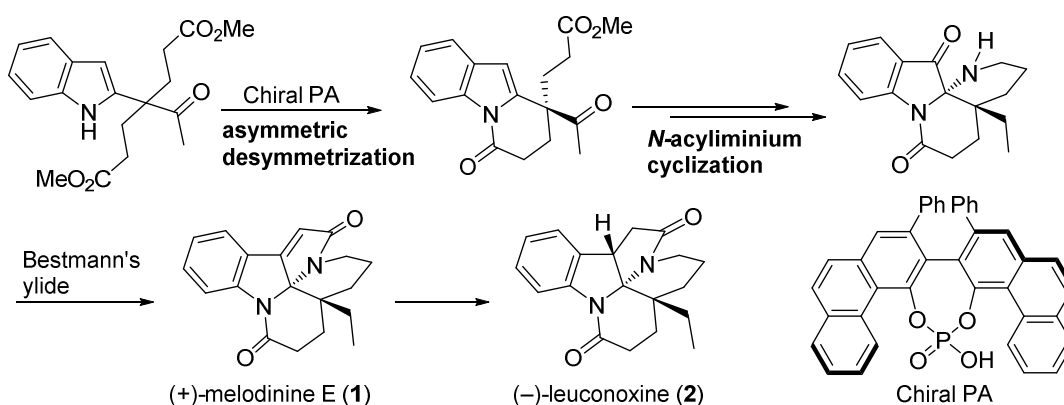
References:

- [1] D. Stauffacher *et al.*, *Tetrahedron* **1969**, *25*, 5879-5887.
- [2] M. Incze *et al.*, *Tetrahedron* **2008**, *64*, 2924-2929.

Total Synthesis of (–)-Leuconoxine Featuring Mannich-type Intramolecular Cyclization and Chiral Phosphoric Acid-Catalyzed Desymmetrization

Kazuhiro Higuchi, Shin Suzuki, Reeko Ueda, Norifumi Oshima, Emiko Kobayashi, Masanori Tayu, Shigeo Sugiyama, Tomomi Kawasaki

Meiji Pharmaceutical University, Kiyose, Tokyo, Japan



We have accomplished the asymmetric total synthesis of (–)-leuconoxine (2). In the presence of a chiral phosphoric acid catalyst (VAPOL-PA), the desymmetrization of prochiral diester produced highly-enantioenriched lactam (75%ee) in excellent yield. Ring construction steps featuring the *N*-acyliminium mediated intramolecular piperidine cyclization with Tf_2O and subsequent the one-step pyrrolidone formation using Bestmann's ylide were achieved successfully.

Development and application of 2-azanorbornylmethanols as a cage type amino alcohol organocatalyst

Ayumi Ogasawara¹, Yoshihito Kohari¹, Chigusa Seki¹, Koji Uwai¹, Eunsang Kwon², Yuko Okuyama³, Hiroto Nakano¹

¹Department of Bioengineering, Graduate School of Engineering, Muroran Institute of Technology, 27-1 Mizumoto, Muroran 050-8585, Japan, ²Research and Analytical Center for Giant Molecules, Graduate School of Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan, ³Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku Sendai 981-8585, Japan

Cage type amino alcohol, with 2-azanorbornylmethanol framework **1**, is well known molecule and efficiently used as chiral ligand for organometallic catalyst.¹⁾ This amino alcohol (Fig. 1) has bulky 2-azanorbornane backbone, which contain nitrogen atom that need for the formation of enamine moiety. Furthermore, the molecule has a hydroxy group for a hydrogen bonding with a substrate as the side chain on the 2-azanorbornane backbone. Considering these abilities, it is expected that this type of amino alcohol might show an efficient functionality as an organocatalyst.

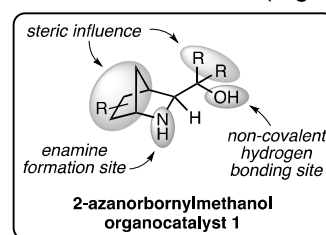
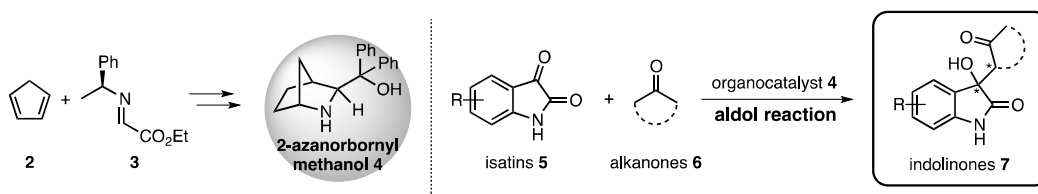


Fig. 1

2-azanorbornylmethanol **4**²⁾ was designed and synthesised as a new chiral cage type amino alcohol organocatalyst, and the functionality as a catalyst was examined in the asymmetric aldol reactions of isatins **5** with alkanones **6** (Scheme 1).

We found that 2-azanorbornylmethanol **4** showed highly catalytic activity in the aldol reaction for affording chiral indolinones **7**.

This work will be presented and discussed in detail.



Scheme 1

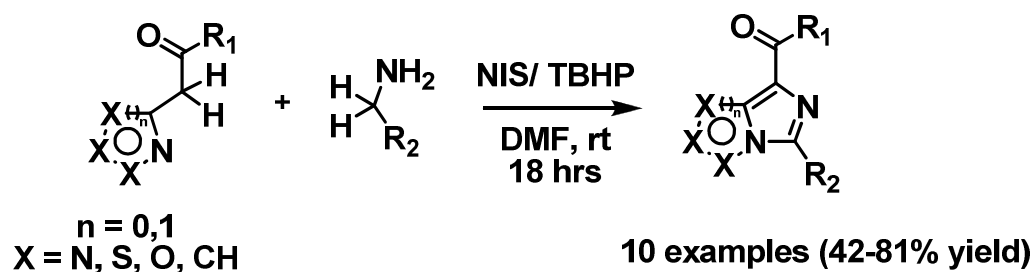
- 1) D. Guijarro, P. Pinho, P. G. Andersson, *J. Org. Chem.*, **1998**, *63*, 2530-2535.
- 2) H. Nakano, N. Kumagai, H. Matsuzaki, C. Kabuto, H. Hongo, *Tetrahedron: Asymmetry*, **1997**, *8*, 1391-1401.

Efficient Synthesis of Fused Imidazole Containing Ring Systems via Dual Oxidative Amination of C(sp³)-H bonds

Georgette M. Castanedo, Marie-Gabrielle Braun, James Crawford

Genentech, Inc, South San Francisco, CA, USA

Fused heterocyclic ring systems containing bridgehead nitrogens are valuable building blocks in medicinal chemistry and represent a persistent synthetic challenge. Existing methods suffer from several issues including lack of availability of starting materials, long synthetic routes and harsh reaction conditions. Herein we report a mild and robust method for their synthesis in a one-pot fashion from commercially available starting materials. Construction of a variety of poly-substituted fused 5,5 and 5,6 imidazole containing ring systems with wide functional group tolerance are described using this process. Moreover, some 5,5 systems that have not been previously reported in the literature can now be accessed.



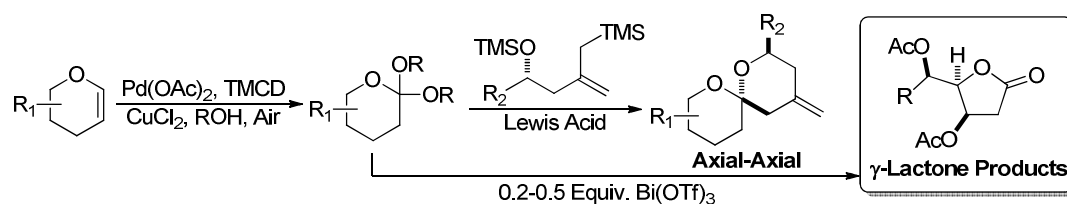
Ortholactone Spiroketal Fragment Couplings: A Convergent Approach to Complex Natural Products.

Matthew Cook, Kate Baddeley

Queen's University Belfast, Belfast, UK

Spiroketals are ubiquitous in nature occurring in many complex macrolides which exhibit potent biological activity. Most methods for their construction are linear approaches requiring long synthetic sequences to install functional groups prior to a cyclization to form the spiroketal. Although effective, these methods are not convergent and lead to high linear step counts and issues with both material throughput and structure diversification.¹ Our approach was to develop a modular fragment-coupling based strategy whereby the spiroketalization is also the fragment coupling step. This convergent approach uses the coupling of an ortholactone and a δ -hydroxyallylsilane to form the spiroketal in a single step, a strategy reported by Markó on very simple substrates.²

The major synthetic challenges were to develop an efficient and functional group tolerant synthesis of ortholactones followed by optimization of the fragment coupling in complex systems. The ortholactone synthesis was achieved through a palladium catalyzed Wacker-type oxidation of dihydropyrans.³ This method was particularly efficient for the construction of both methoxy and spirocyclic variants. These ortholactones could be coupled very efficiently with the allylsilanes to form the spiroketals in high yields as a single stereoisomer. When $\text{Bi}(\text{OTf})_3$ was used as a Lewis acid, a fragmentation reaction occurred to form a rearranged γ -lactone product which occurs with a wide range of functionality.⁴



[1] Review: Yeung, K. -S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237.

[2] Markó: *Tetrahedron Lett.* **1991**, *32*, 4783; *J. Org. Chem.* **1992**, *57*, 2211;

[3] Baddeley, K. A.; Cao, Q.; Muldoon, M. J.; Cook, M. J. *Chem. Eur. J.* **2015**, *21*, 7726.

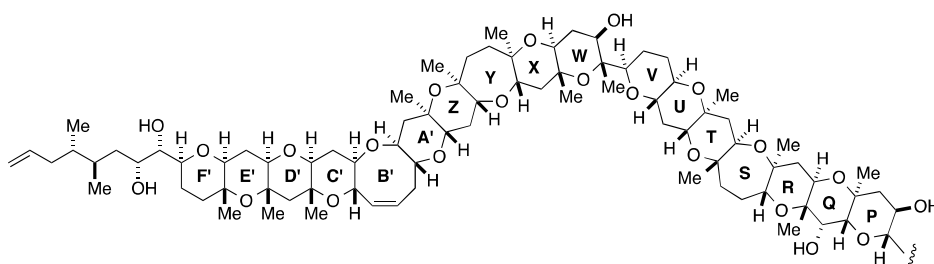
[4] Baddeley, K. A.; Cook, M. J. *Submitted for Publication*.

Convergent synthesis of the *ent*-ZA'B'C'D' ring system of maitotoxin

Tatsuo Saito^{1,2}, Tadashi Nakata^{1,3}

¹RIKEN, Saitama, Japan, ²The University of Tokyo, Tokyo, Japan, ³Tokyo University of Science, Tokyo, Japan

Maitotoxin (MTX) was first found from the surgeonfish *Ctenochaetus striatus* in 1976, and later isolated from cultured cells of the dinoflagellate *Gambierdiscus toxicus*. MTX is the most toxic and largest natural product (MW 3422) known to date, except for biopolymers. It is implicated in ciguatera food poisoning and is involved in Ca^{2+} -dependent mechanisms over a wide range of cell types. The full structure and partial relative configuration of MTX were reported by Yasumoto et al., and then the relative configuration of the remaining parts and the absolute configuration were determined independently by the Tachibana and Kishi groups. The unusual molecular structure of MTX contains 32 fused ether rings, 28 hydroxyl groups, 21 methyl groups, 2 sulfate esters, and 98 chiral centers (Figure 1). The skeletal novelty, complexity, and biological activity of MTX have attracted the attention of synthetic organic chemists, and the syntheses of several fragments of MTX have been reported by the Nicolaou, Oishi, and our groups. We report the synthesis of *ent*-ZA'B'C'D'-ring system based on convergent synthesis using Suzuki-Miyaura cross coupling of alkylborane with (*Z*)-vinyl iodide.



Lipophilic part of maitotoxin (1)

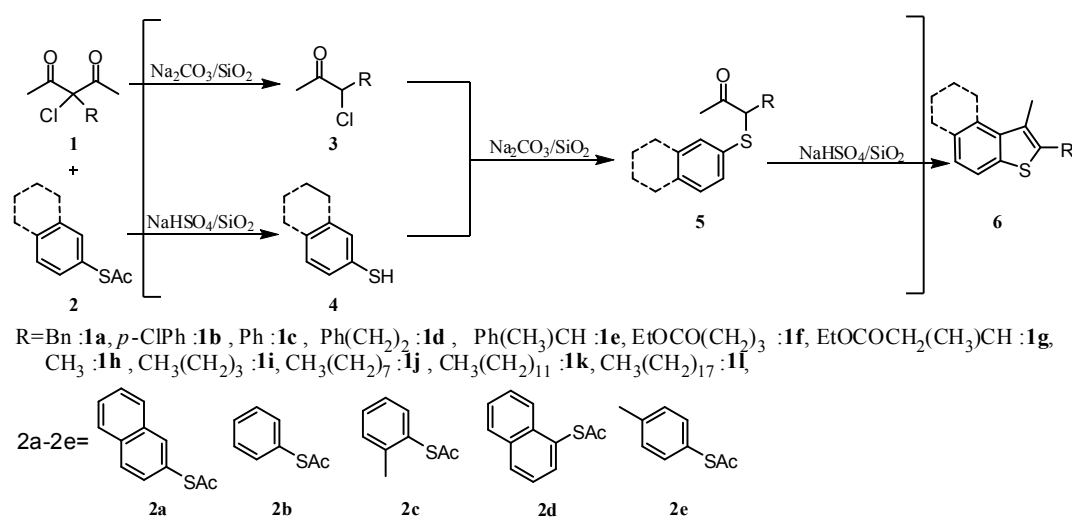
The title

One-pot synthesis of aryl thiophenes using NaHSO₄/SiO₂ and Na₂CO₃/SiO₂

Mamiko Hayakawa, Tadashi Aoyama, Akihiko Ouchi

Nihon University, Tokyo, Japan

A novel one-pot reaction was developed for the synthesis of aryl thiophenes [6] from 3-substituted-3-chloro-pentanediones [1] and aryl thioacetates [2] using NaHSO₄/SiO₂ and Na₂CO₃/SiO₂. The reaction proceeded by initial conversion of 1 and 2 to α-halo ketones [3] and aryl mercaptans [4], respectively, using corresponding base and acid catalysts, followed by the reaction of 3 and 4 to give α-sulfanyl ketones [5] by Na₂CO₃/SiO₂, and successive cyclization to 6 by NaHSO₄/SiO₂; e.g. 2-benzyl-1-methyl-naphtho[2,1-b]thiophene [6aa] was obtained quantitatively from the reaction of 1a (1.0 mmol) and 2a (1.1 mmol) at 135 °C for 1 h in chlorobenzene. More than 40 aryl thiophenes were easily synthesized by using this method.



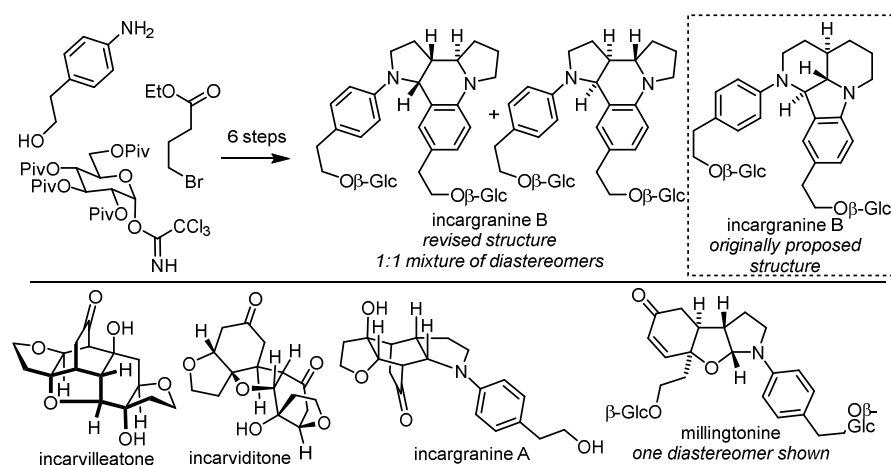
Scheme 1

Biomimetic Synthesis of Phenylethanoid Alkaloids

Patrick Brown¹, Andrew Lawrence^{1,2}

¹University of Edinburgh, Edinburgh, Scotland, UK, ²Australian National University, Canberra, ACT, Australia

The phenylethanoids are a diverse group of shikimic acid derived natural products, characterised by the presence of a C₆C₂ moiety. These compounds are of great interest for their structural complexity and wide range of biological functions. Incargranine B is a dimeric phenylethanoid alkaloid, originally assigned an unprecedented indolo[1.7]naphthyridine structure. As a result of biosynthetic speculation, we proposed a dipyrroloquinoline core as a plausible alternative structure. Following a biomimetic strategy, the proposed structure of incargranine B was accessed in six steps, confirming the suggested structural revision and indicating the natural product likely exists as a mixture of two *pseudo*-enantiomeric diastereomers. Extending upon this biomimetic synthesis, we now propose a unified biosynthetic hypothesis for the entire family of phenylethanoid natural products isolated from plants of the genus *incarvillea*. Studies towards the biomimetic synthesis of millingtonine and incargranine A will also be presented.



Carbaporphyrins and Beyond: The Quest for Quatyrin

Timothy Lash

Illinois State University, Normal, Illinois 61790-4160, USA

Carbaporphyrins are porphyrin analogues where one of the interior nitrogens has been replaced by a carbon atom. In addition to true carbaporphyrins, which possess a cyclopentadiene unit, many related systems are known including N-confused porphyrins, benziporphyrins, azuliporphyrins and tropiporphyrins. These monocarbaporphyrinoid systems have unique reactivity and unusual spectroscopic properties. They range from fully aromatic macrocycles that resemble the porphyrins to nonaromatic systems, and indeed antiaromatic systems have also been noted. Many of these systems are superior organometallic ligands that form complexes with many late transition metal ions under mild conditions. For instance, azuliporphyrins have been reported to form stable complexes with Ni(II), Pd(II), Pt(II), Ir(III), Rh(III) and Ru(II). Carbaporphyrins also form organometallic derivatives with Ag(III), Au(III) and Pd(II). Given the unique and insightful properties exhibited by monocarbaporphyrinoid systems, syntheses of dicarbaporphyrinoids and further heterocycle-diminished species have been investigated. In these studies, porphyrinoid systems with two pyrrolic units and two carbocyclic moieties have been prepared. These include structures with two azulenes, two indenenes, two cyclopentadiene rings, two benzenes, mixed benzene and azulene structures, and mixed indene and azulene macrocycles. These systems again demonstrate a wide range of aromatic properties and in some cases afford organometallic derivatives. The extent of aromatic character in these structures provides insights into the origins of aromaticity in the porphyrins. It is noteworthy that while some of these porphyrinoids retain highly diatropic characteristics, the stability of many dicarbaporphyrinoids is reduced compared to monoporphyrinoid systems. Hence, the pyrrole units in porphyrin appear to play an important role in stabilizing these macrocycles. Nevertheless, this work may lead to the development of synthetic routes to quatyrins, theoretically important hydrocarbon analogues of the porphyrins.

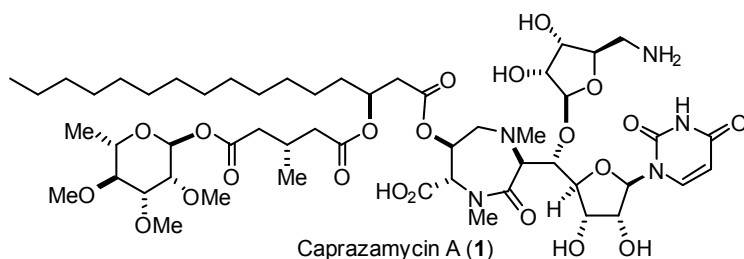
Total Synthesis of (-)-Caprazamycin A

Hugh Nakamura, Chihiro Tsukano, Motohiro Yasui, Yoshiji Takemoto

Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan

Caprazamycin A (**1**) was isolated from *Streptomyces* sp. by Igarashi and co-workers, which shows antibacterial activity against *Mycobacterium tuberculosis* including multidrug-resistant *tuberculosis*. So far, thirteen analogues were isolated by two groups, independently. The structure is characterized by a seven-membered diazepanone core, amino ribose, uridine, and a fatty-acid side chain. The complex structure and significant biological activities of caprazamycins have drawn much attention from synthetic chemists.

The first total synthesis of caprazamycin A (**1**) is herein reported and features (1) the scalable preparation of the syn- α -hydroxy amino acid with a thiourea catalyzed diastereoselective aldol reaction, (2) construction of a diazepanone with an unstable fatty-acid side chain, and (3) global deprotection by hydrogenation. This report provides a route for the synthesis of related liponucleoside antibiotics with fatty-acid side chains.



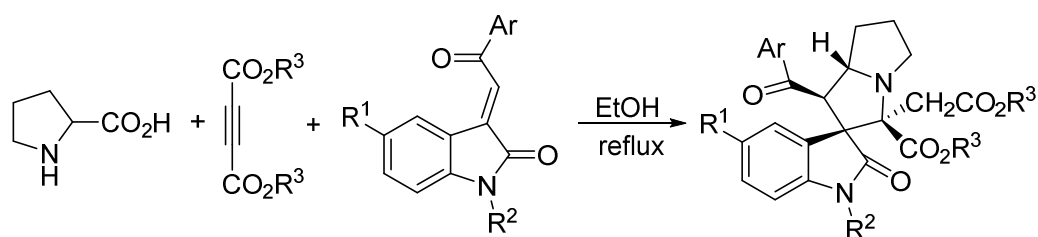
H. Nakamura, C. Tsukano, M. Yasui, S. Yokouchi, M. Igarashi, Y. Takemoto, *Angew. Chem. Int. Ed.* **2015**, *54*, 3136.

Diastereoselective synthesis of functionalized spiro[indoline-3,2'-pyrrolizines] and spiro[indoline-3,3'-pyrrolidines] via multicomponent reactions

Jing Sun, Liang Chen, Hui Gong, Chao-Guo Yan

Yangzhou University, Yangzhou, China

1,3-Dipolar cycloaddition reaction of azomethine ylides with alkenes is one of the most extensive studied organic reactions. In these years, extensive studies have been performed on the employing 1,3-cycloaddition reactions of azomethine ylides for the synthesis of spirocyclic pyrrolidines, especially spiro[indoline-3,3'-pyrrolidines] and polycyclic derivatives. In these works, azomethine ylides were usually generated from the condensation of an amine with an carbonyl compounds such as aromatic aldehyde and isatins, followed by deprotonation of the iminium ion or prototropic shift of the imine. Herein, we described for the first time the *in situ* generation of new-type azomethine ylide by the reaction of α -amino acids with dialkyl acetylenedicarboxylates and its sequential 1,3-dipolar cycloaddition reaction. The three-component reaction of secondary α -amino acids including proline, sarcosine, thiazolidine-4-carboxylic acid with dialkyl acetylenedicarboxylate and 3-methyleneoxindoles in refluxing ethanol afforded the functionalized spiro[indoline-3,2'-pyrrolizines], spiro[indoline-3,3'-pyrrolidines] and piro[indoline-3,6'-pyrrolo[1,2-c]thiazoles] in good yields and with high diastereoselectivity. Furthermore, the similar multicomponent reactions containing primary α -amino acids such as glycine, alanine and phenylalanine resulted in (spiro[indoline-3,3'-pyrrolidine]-1'-yl)maleates.



Fragment-Based Approach Toward Lactate Dehydrogenase A (LDHA) Inhibitors

Jacques Briand², Kristin Brown¹, Nino Campobasso², Kevin Duffy², Mark Elban¹, Don Huddler², Terry Hughes¹, Beth Knapp-Reed¹, Yiqian Lian², Angela Smallwood²

¹GlaxoSmithKline, King of Prussia, PA, USA, ²GlaxoSmithKline, Collegeville, PA, USA

A fragment based approach was used to identify a unique series of LDHA inhibitors with good ligand efficiencies. Subsequent optimization delivered a novel lead series with LDHA cellular activity of 10 μ M, selectivity against LDHB, and good physicochemical properties. The overall strategy of identification and optimization, lessons learned, and some guiding principles of the FBDD effort will be presented in the context of the discovery of a fragment-derived lead series for the inhibition of LDHA.

“All studies were conducted in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals and were reviewed the Institutional Animal Care and Use Committee either at GSK or by the ethical review process at the institution where the work was performed.”

Convenient Synthesis of Triphenylphosphanylidene Spiro[cyclopentane-1,2'-indenes] via Three-Component Reactions

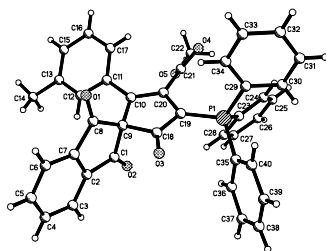
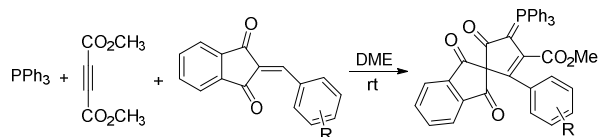
Ying Han, Wen-Jie Qi, Jing Sun, Chao-Guo Yan

Yangzhou University, Yangzhou, Jiangsu Province, China

Three-component reactions of triphenylphosphine, but-2-yne-1,3-diolate, and 2-arylidene-1,3-indandiones in dimethoxyethane resulted in methyl 1',3',5-trioxo-2-phenyl-4-(triphenylphosphanylidene)-1',3'-dihydrospiro[cyclopentane-1,2'-inden]-2-ene-3-carboxylate in satisfactory yields with mild conditions and simple operation methods.

Entry	Compd	R	Yield (%) ^b
1	1a	p-OCH ₃	75
2	1b	p-CH ₃	73
3	1c	p-NO ₂	70
4	1d	P-C(CH ₃) ₃	85
5	1e	m-OCH ₃	69
6	1f	m-Cl	62
7	1g	m-F	65
8	1h	m-NO ₂	72

Table 1. Three-Component Reaction for Spiro[cyclopentane-1,2'-indenes] 1a-1h^a



^aReaction conditions: DMAD (1.2 mmol), 2-arylidene-1,3-indandiones (1.0 mmol), PPh₃ (1.0 mmol) in DME (10.0 mL), 0–rt, 2 h. ^bIsolated yields.

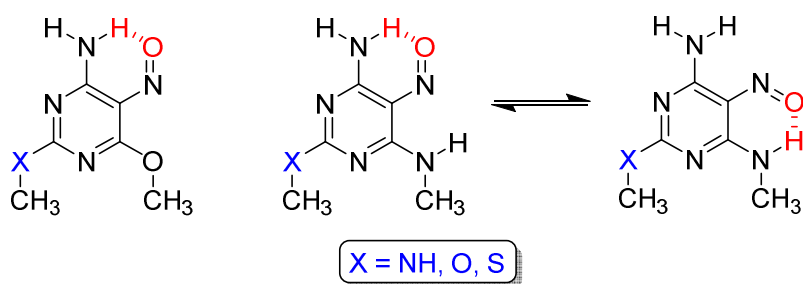
Novel 5-nitrosopyrimidines and their physicochemical properties

Lucie Cechova^{1,2}, Eliska Prochazkova¹, Zlatko Janeba¹, Martin Dracinsky¹

¹IOCB AS CR, v.v.i., Prague, Czech Republic, ²UCT Prague, Prague, Czech Republic

5-Nitrosopyrimidine derivatives are not naturally occurring compounds, but their interesting physicochemical and biological properties have been reported. The cytostatic, antifungal or antibacterial effects of these compounds are well known.

2,4,6-Triamino-5-nitrosopyrimidines can form strong intramolecular hydrogen bonds between the 5-nitroso group and amino groups in positions C-4 and C-6, and so, two rotamers can be observed. In our previous work we have reported separation of such rotamers, as planamers, by chromatography at room temperature. The rotational barrier of the nitroso group is unusually high (more than 20 kcal/mol) and thus, resonance-assisted hydrogen bonding is expected to play a key role in the stability of the rotamers. To further study the described phenomenon, novel series of 5-nitrosopyrimidines with different substituents in position C-2 (namely methylamino, methoxy and methylthio group) was prepared and influence of these substituents on the rotational barrier of the 5-nitroso group was studied.



Acknowledgments. The study was supported by IOCB AS CR (RVO61388963), by the

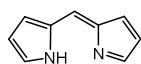
Ministry of Interior of the Czech Republic (VG20102015046) and by the Czech Science Foundation (grant no. 15-11223S).

Talkative Molecules: Design and Synthesis of Functional Bodipy Compounds

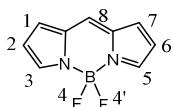
Neelam Shivan¹, S. Chattopadhyay²

¹Indian Institute of Science Education and Research, Pune, India, ²Bhabha Atomic Research Centre., Mumbai, India

Among many dipyrin complexes the difluoro-boraindacene family (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene, Bodipy) has gained recognition as one of the more versatile fluorophores since it has emerged as a frontrunner for lasing, imaging, sensing and opto-electronic applications. The basic Bodipy unit can be readily functionalized and shift the absorption maxima over a wide spectral range. The major objective of our study is to develop Bodipy-based functional materials for various applications such as photostable laser dyes, Bodipy based organoelectronic materials and photosensitizer for Photo-Dynamic Therapy (PDT). This warrants synthetic modifications of the Bodipy core, available commercially or synthesized in-house so as to impart the desirable attributes to the newly developed molecules/assemblies. To this end, various sites of the Bodipy cores viz. different positions of the dipyrrole moieties and/or the *meso*-position are innovatively used for introduction of different functional groups. Several new Bodipy-O-glycosides were synthesized by incorporating the glucose unit at meso-phenol or C-3/C-5 hydrostyryl moieties. Subsequent attachment of a glucose unit to the phenolic function of the conjugated dyes furnished the photosensitizers. All the compounds showed impressive good photo-toxicity to the human lung cancer A549 cells, without any dark toxicity due to their accumulation in cytoplasm. The efficacy of the protocols in designing new molecules and the potential functional applications along with their biomedical usefulness will be emphasized in the talk.



Dipyrromethene (dipyrin)



4,4-difluoro-4-bora-3a,4a-diaza-s-indacene
BODIPY

References:

1. Loudet, A.; Burgess, K. *Chem. Rev.* **2007**, *107*, 4891.
2. Ulrich, G.; Ziessel, R.; Harriman, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 1184.

Polysubstituted pyrimidines: biological and chemical properties

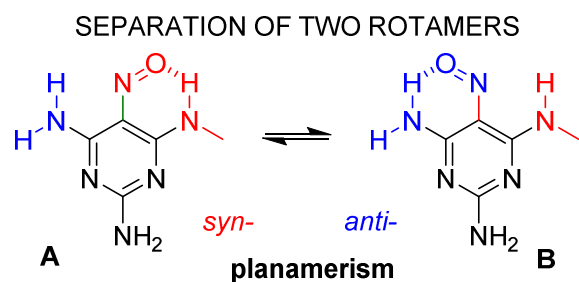
Zlatko Janeba

Institute of Organic Chemistry and Biochemistry, AS CR, Prague, Czech Republic

The pyrimidine ring represents an important pharmacophore and a key structural motif of numerous natural, as well as synthetic biologically active compounds. Various polysubstituted pyrimidines were studied in our team for their interesting and miscellaneous properties, namely antiviral (as non-nucleoside reverse transcriptase inhibitors), anticancer (as inhibitors of cyclin-dependent kinases), and anti-inflammatory (as inhibitors of nitric oxide and/or prostaglandin E2 production).

Some derivatives, e.g. polysubstituted 5-nitrosopyrimidines, were studied for their ability to form strong intramolecular hydrogen bonds. Such compounds were suggested to structurally (and hopefully also biologically) mimic bicyclic heterocycles like purines or pteridines.

Two possible rotamers were often observed depending on other substituents attached to the pyrimidine moiety and in several cases, they could even be isolated as chemical species.



Acknowledgments. The study was supported by IOCB AS CR (RVO61388963), by the Ministry of Interior of the Czech Republic (VG20102015046) and by the Czech Science Foundation (grant no. 15-11223S).

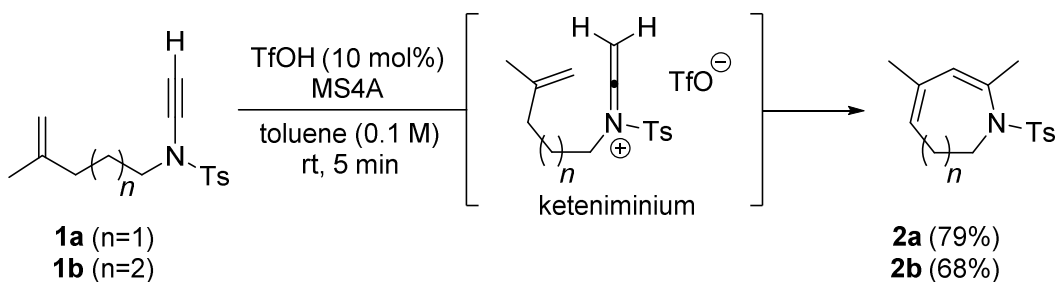
The title

Yousuke Yamaoka, Nao Takeuchi, Ken-ichi Yamada, Kiyosei Takasu

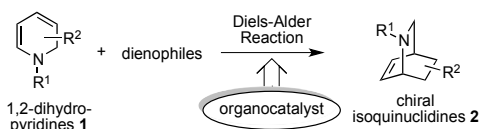
Kyoto University, Kyoto, Kyoto, Japan

Nitrogen-containing medium rings are important and attractive class of compounds for natural products and pharmaceuticals. However, the synthesis of heterocyclic medium rings remains a challenging task due to entropic and enthalpic factors for cyclization approaches. General strategies to the synthesis of medium rings, such as ring-closing metathesis and the Yamaguchi esterification, are often required precious transition metals or high dilution condition to prevent the undesired dimerization. In this poster session, we would like to present the efficient synthesis of nitrogen-containing medium rings with ynamides catalyzed by a strong Brønsted acid.

We anticipated that cyclization of ynamides **1** would afford the nitrogen-containing medium rings **2** through the highly reactive keteniminium intermediate. After several screening, the cyclization of ynamide **1** occurred with 10 mol% TfOH in the presence of MS4A to give the 7- and 8-member heterocycles in good yields. It is noteworthy that this reaction instantly proceeded and high dilution is not necessary.



Development of new antiviral candidate molecules using organocatalyzed asymmetric Diels-Alder reaction of 1,2-dihydropyridines with dienophiles as a key reaction



Ryohei Takagi¹, Yoshihito Kohari¹, Chigusa Seki¹, Koji Uwai¹, Eunsang Kwon², Yuko Okuyama³, Mitsuhiro Takeshita⁴, Michio Tokiwa⁴, Hiroto Nakano¹

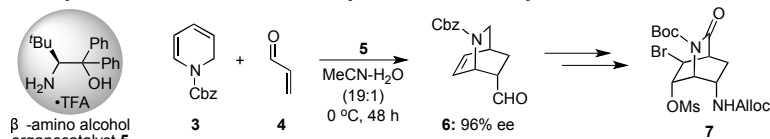
¹Department of Bioengineering, Graduate School of Engineering, Muroran Institute of Technology, 27-1 Mizumoto, Muroran 050-8585, Japan, ²Research and Analytical Center for Giant Molecules, Graduate School of Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan, ³Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8585, Japan, ⁴Tokiwakai Group, 62 Numajiri Tsuduri-chou Uchigo Iwaki 973-8053, Japan

Asymmetric Diels-Alder (DA) reaction of 1,2-dihydropyridines **1** with dienophiles using an organocatalyst is an important reaction for the construction of chiral isoquinuclidines (2-azabicyclo

[2,2,2]octanes) **2**, can be used as the synthetic intermediates for the synthesis of biological active molecules such as oseltamivir phosphate.

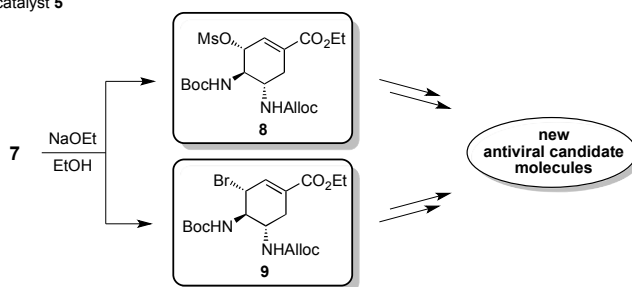
In this presentation, we introduce that simple primary α -aminoalcohol **5** acts as an efficient chiral organocatalyst for the enantioselective DA reactions of *N*-Cbz-1,2-dihydropyridine **3** with acrolein **4**. In addition, we also describe the utilization of both the new chiral building blocks **8** and **9** that were obtained from the intermediate **7** for the preparation of new antiviral candidate molecules.

1. Y. Kohari, Y. Okuyama, E. Kwon, T. Furuyama, N. Kobayashi, T. Otuki, J. Kumagai, C. Seki, K. Uwai, Iwasa, H. *J. Org. Chem.* **2014**, *79*, 9511.



G. Dai, T. Nakano, *Chem.* **9500-**

2. N. Satoh, S.



T. Akiba,

Yokoshima, T. Fukuyama, *Tetrahedron*, **2009**, *65*, 3239-3245.

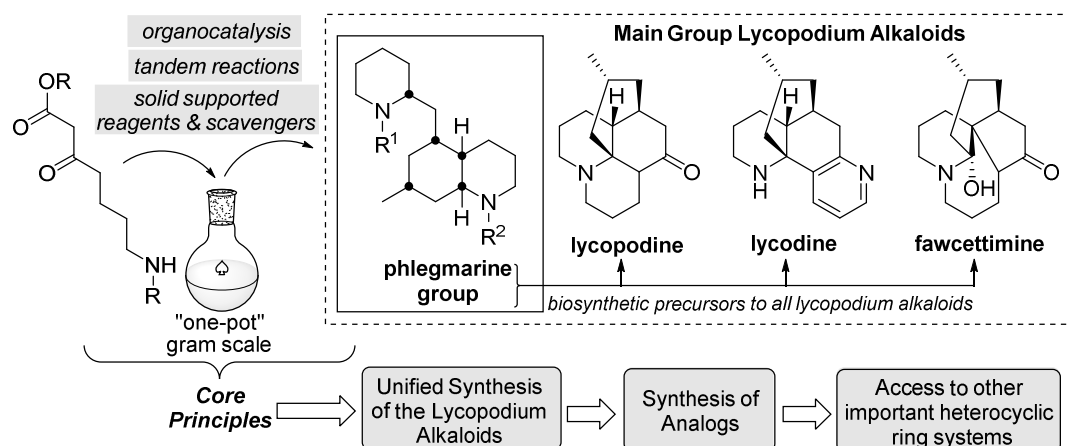
To Phlegmarines and Beyond - Strategies for Efficiency and Diversity in Natural Product Synthesis

Ben Bradshaw, Caroline Bosch, Carlos Luque-Corredera, Claudio Parra, Gisela Saborit Villarroja, Josep Bonjoch

University of Barcelona, Barcelona, Spain

The Lycopodium alkaloids have attracted enormous attention in recent years for their medicinal properties as well as the synthetic challenges they present.¹

We have used the stereochemically diverse phlegmarine group as a platform to develop new synthetic methods including the use of organocatalysis,² tandem reactions and stereocontrolled reductions based on radical, homogeneous and directed heterogeneous catalysis. The use of these methods in conjunction with solid supported reagents and pot economy strategies have allowed for easy gram scale synthesis of these compounds in a single flask.³ This presentation will give an overview of this work and illustrate the potential of the underlying strategies to access all of the other Lycopodium alkaloids, their analogs as well as a diverse portfolio of other important heterocyclic nuclei.



¹ Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752.

² Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Org. Lett.* **2013**, *15*, 326.

³ Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Chem Commun.* **2014**, *50*, 7099.

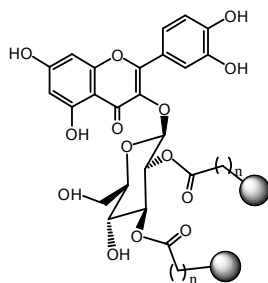
The title

Novel quercetin diacylglycosides as potent anti-MRSA and anti-VRE agents

Abugafar M L Hossion¹, Yoshito Zamami², Kenji Sasaki^{2,3}

¹The University of Kansas, Department of Medicinal Chemistry, 2034 Becker Dr., Lawrence, Kansas 66047, USA, ²Okayama University, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 1-1-1, Tsushima-Naka, Kita-Ku, Okayama 700-8530, Japan, ³Okayama University, Center for Faculty Development, 2-1-1, Tsushima-Naka, Kita-Ku, Okayama 700-8530, Japan

Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections (Threat report 2013). Vancomycin is an FDA approved antibiotic and is growing importance in the treatment of hospital infections, with particular emphasis on its value to fight against methicillin-resistant *Staphylococcus aureus* (MRSA). The increasing use of vancomycin to treat infections caused by the Gram-positive MRSA in the 1970s selected for drug-resistant enterococci, less potent than staphylococci but opportunistic in the space vacated by other bacteria and in patients with compromised immune systems. Over the past few years, we developed novel quercetin diacylglycoside analogues as potent antibacterial agents. The significant enzymatic inhibition of both *Escherichia coli* DNA gyrase and *Staphylococcus aureus* topolV suggest that these compounds are dual inhibitors. Most of the investigated compounds exhibited pronounced inhibition with MIC values ranging from 0.13 to 128 µg/mL toward the growth of multidrug-resistant Gram-positive methicillin-resistant *S. aureus*, methicillin sensitive *S. aureus*, vancomycin-resistant enterococci (VRE), vancomycin intermediate *S. aureus*, and *Streptococcus pneumoniae* bacterial strains. The synthesis and properties of these compounds will be described.

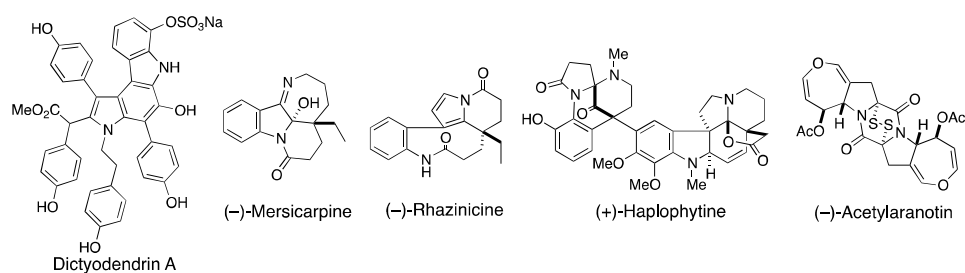


Synthetic Studies on N-Heterocyclic Natural Products

Hidetoshi Tokuyama

Tohoku University, Sendai, Miyagi, Japan

Since nitrogen-containing heterocyclic rings are common structural motifs in biologically important natural products, development of new synthetic methodologies for construction of these structures have been one of the important research topics in synthetic chemistry. In this lecture, our recently completed total syntheses of polycyclic alkaloids featuring new synthetic strategies will be discussed. We investigated a reductive ring expansion of cyclic ketoximes and applied to a concise total synthesis of (–)-mersicarpine.¹ For formation of substituted indolines, we developed a benzyne-mediated cyclization-functionalization sequence and applied this reaction to total syntheses of dictyodendrins A–E.² A protective group free total synthesis of (–)-rhazinicine was accomplished based on the development of a gold-catalyzed double cyclization cascade.³ In the first total synthesis of (+)-haplophytine, we constructed the characteristic spiroaminal by an oxidative semi-pinacol type rearrangement.⁴ Dihydrooxepin rings in (–)-acetylaranotin was formed by combination of the vinylogous Rubottom oxidation and the Baeyer-Villiger ring expansion of an enone intermediate.



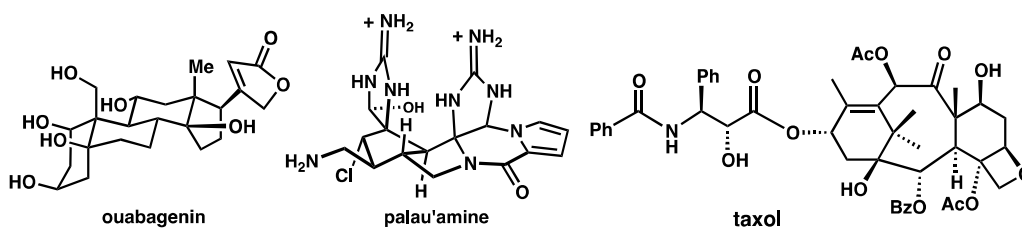
1) Iwama, Y.; Okano, K.; Sugimoto, K.; Tokuyama, H. *Org. Lett.* **2012**, *14*, 2320. 2) Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 5925. 3) Sugimoto, K.; Toyoshima, K.; Nonaka, S.; Kotaki, K.; Ueda, H.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7168. 4) Ueda, H.; Satoh, H.; Matsumoto, K.; Sugimoto, K.; Fukuyama, T.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 7600. 5) Fujiwara, H.; Kurogi, T.; Okaya, S.; Okano, K.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 13062.

Studies in Natural Product Synthesis

Phil Baran

The Scripps Research Institute, La Jolla, CA, USA

There can be no more noble undertaking than the invention of medicines. Chemists that make up the engine of drug discovery are facing incredible pressure to do more with less in a highly restrictive and regulated process that is destined for failure more than 95% of the time. How can academic chemists working on natural products help these heroes of drug discovery – those in the pharmaceutical industry? With selected examples from our lab and others, this talk will focus on that question highlighting innovation in fundamental chemistry and new approaches to scalable chemical synthesis.

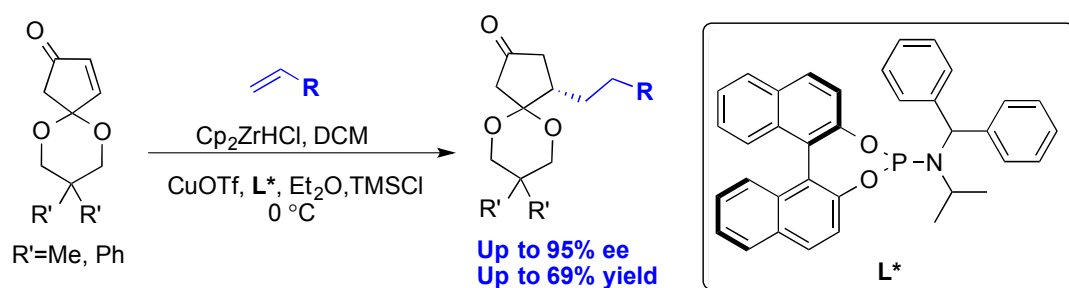


Asymmetric Conjugate Addition of Alkylzirconocenes to Cyclopentene-3,5-dione Monoacetals.

Emeline Rideau, Florian Maesing, Stephen Fletcher

University of Oxford, Oxford, UK

The asymmetric conjugate addition of organometallics to cyclopentenones is highly desirable.¹ Many methodologies have been developed in recent years but fail to address the challenges of cyclopentenones.² Our group demonstrated that the conjugate addition of alkylzirconocenes to cyclohexenone derivatives is advantageous.³ However, when applying the methodology conditions to cyclopentenones, the yield was poor (23%) and the ee dropped (to 75%). Feringa *et al.* reported⁴ the derivatisation of cyclopentene-3,5-dione monoacetal with dialkylzinc reagents in moderate yield (40%) and high ee (90%). We decided to examine the hydrozirconation/asymmetric conjugate addition of alkenes to cyclopentene-3,5-dione monoacetal. After extensive screening, we have demonstrated that functionalized, enantioenriched cyclopentanone derivatives can be successfully prepared in that way. Further studies are currently undergoing to apply this methodology to the synthesis of prostaglandins.



(1) (a) Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12904 (b) Jansen, D. J.; Shenvi, R. A. *J. Am. Chem. Soc.* **2013**, *135*, 1209. (2) (a) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (3) Maksymowicz, R. M.; Roth, P. M. C.; Fletcher, S. P. *Nat. Chem.* **2012**, *4*, 649. (4) (a) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841.

Synthesis of hybrid 1-5 disubstituted Tetrazoles by Ugi-azide reaction

ROCIO GAMEZ-MONTAÑO

UNIVERSIDAD DE GUANAJUATO, GUANAJUATO, Mexico

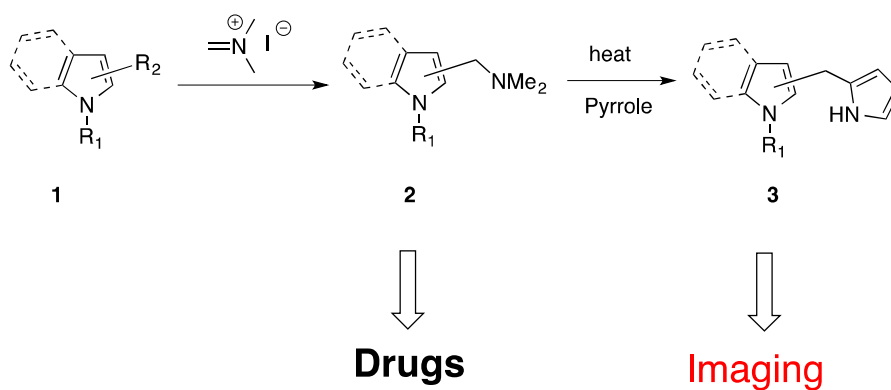
Multicomponent reactions (MCR) are powerful tools toward the synthesis of a large variety of interesting scaffolds even heterocycles. MCR are defined as one pot processes in which three or more reagents are sequentially combined to afford products having the majority of the atoms present in the starting reagents. The main applications of MCR are in Diversity Oriented Synthesis (DOS) and Combinatorial Chemistry (CC). The most important MCR are the isocyanide-based multicomponent reactions (I-MCR) such as Ugi reactions e.g. the classic Ugi-4CR, Ugi-3CR, Ugi-Smiles, Ugi-Nenajdenko, Ugi-Interrupted (Groebke-Blackburn-Bienaymé), and Ugi-azide. This latter allows the synthesis of 1,5-disubstituted Tetrazoles of high interest in medicinal chemistry because their ability to adopt conformations of *cis*-amide bond of peptides. On this occasion, I will show my results lately published just regarding the use of the Ugi-azide reaction towards the synthesis of 1,5-disubstituted Tetrazole-based hybrid compounds and some of their applications, mainly in medicinal chemistry.

Building blocks for the synthesis of oligopyrroles and indolo analogues

Ruisheng Xiong, Eszter Borbas

Uppsala University, Uppsala, Sweden

Pyrrole and its oligomeric derivatives have played important roles in bio-imaging and drug discovery. However, their potential is limited by the poor accessibility of the target compound. We have developed a method to synthesize *N,N*-dimethylamino-methylated pyrroles and indoles in good to excellent yields with good tolerance of functional groups. Dimethylaminomethyl pyrroles and indoles are useful building blocks for the synthesis of anti-cancer drugs. Furthermore, the application of these intermediates was investigated in the formation of dipyrromethane and analogues thereof, which are precursors of various porphyrinoids and BODIPY dyes.

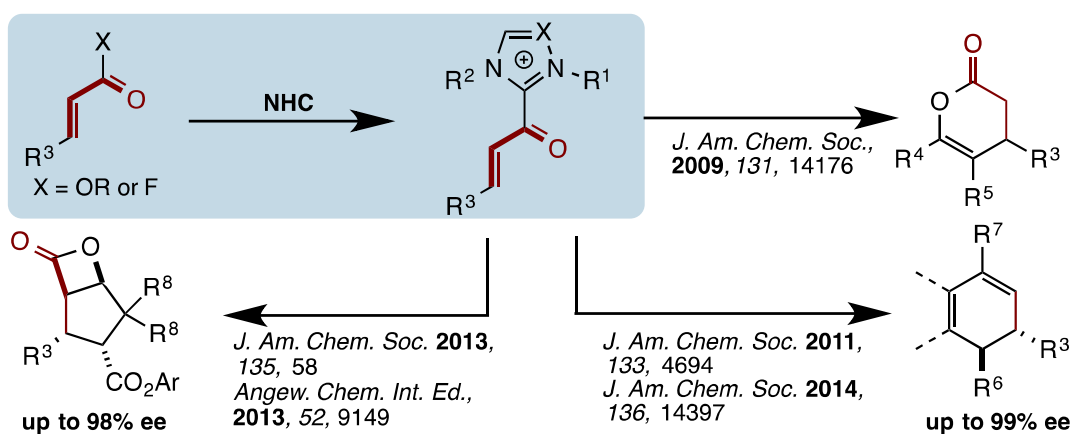


Enantioselective *N*-heterocyclic carbene catalysis with ester substrates.

David Lupton

Monash University, Melbourne, Victoria, Australia

N-Heterocyclic carbenes (NHCs) are powerful catalysts for some of the most diverse chemical transformations observed in organocatalysis.¹ Beyond acyl anion chemistry they are active in many reactions that are acyl anion free often exploiting normal polarity intermediates.² A number of our studies in the field of NHC catalysis are focused on reaction discovery using ester, and ester surrogate, substrates. In this presentation recent discoveries in enantioselective catalysis using Lewis basic, and nucleophilic, catalysts will be discussed



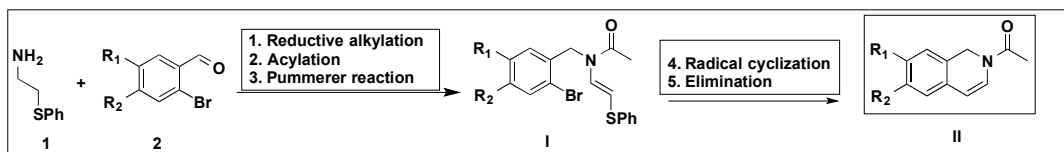
1. Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.
2. Ryan, S. J.; Candish, L. Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906.

Synthesis of 1,2-dihydroisoquinolines via radical cyclization and elimination of (*E*)-*N*-(2-bromobenzyl)-*N*-(2-(phenylthio)vinyl)acetamide

HOLBER ZULETA PRADA¹, BENITO REYES TREJO¹, LIUS GERMAN LOPEZ VALDEZ¹, DIANA GUERRA RAMIREZ¹, JULIO MEJIA GONZALEZ², CRISTABEL PAULINA RAMIREZ GARCIA²

¹UNIVERSIDAD AUTONOMA CHAPINGO, TEXCOCO DE MORA .ESTADO DE MEXICO, Mexico, ²UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO, MEXICO DF, Mexico

Isoquinoline and its derivatives are very important compounds due to their pharmacological and biological activities. The development of practically simple and efficient strategies for the synthesis of these compounds remains a very important challenge for modern organic synthesis. Several strategies have been reported for the construction of this class of heterocycles. Herein, we developed a methodology of synthesis using a Pummerer processes with the intention of assessing its viability as a general strategy for the preparation of (*E*)-*N*-(2-bromobenzyl)-*N*-(2-(phenylthio)vinyl)acetamide **I**. These compounds allowed the development of a methodology of synthesis focused on access to different alkaloids of type 1,2-dihydroisoquinoline **II**. The major achievement of this work, was the obtaining of the (*E*)-*N*-(2-bromobenzyl)-*N*-(2-(phenylthio)vinyl)acetamide, like as a precursor for a radical cyclization reaction followed by elimination reaction to generating 1,2 dihydroisoquinoline in acceptable yields (40-60%). We describe the results of the reactions involved in the preparation of three examples of this family of compounds, the process of elaboration of these compounds was carried out in 5 steps of synthesis, using raw materials from easy availability, such as 2-(phenylthio)ethan-1-amine **1** and 2-bromobenzaldehydes **2**. Scheme 1. In the poster, all the steps of the reaction and the mechanisms involved in the process will be discussed.

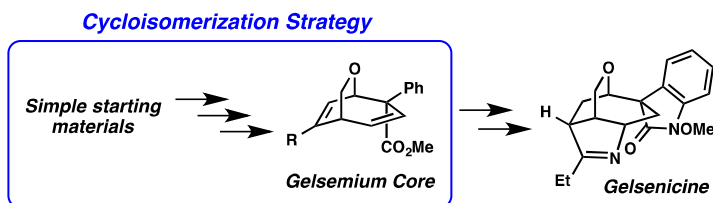


Scheme 1. Preparation of 1,2-dihydroisoquinolines

The Total Synthesis of Gelsenicine via Platinum-Catalyzed Cycloisomerization

Eric Newcomb, Phillip Knutson, Blaine Pedersen, [Eric Ferreira](#)

University of Georgia, Athens, GA, USA



The Gelsemium alkaloids constitute a significant family of natural products featuring a breadth of both structural and biological diversity. Our efforts toward a unified total synthesis of these molecules will be presented. A focal point of this endeavor is the application of a cascade platinum-catalyzed cycloisomerization/rearrangement to establish the core molecular architecture of these alkaloids. Our analysis of this specific transformation provided a fundamental understanding of this unique process and the facets that govern it. Our studies of this central process and subsequent direct manipulations have culminated in the successful total synthesis of gelsenicine, representing the shortest total synthesis to date of a Gelsemium alkaloid. We envision strategic diversifications will enable the syntheses of a broad array of members in the gelsemium family. Our overall efforts in this project will be presented.

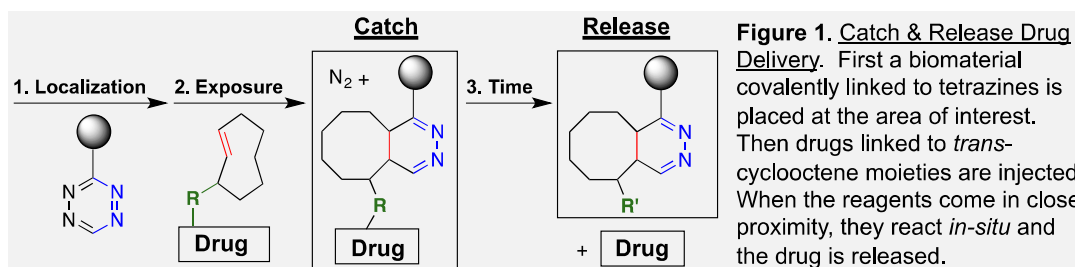
Catch & Release Drug Delivery System – Heterocycles, Bioorthogonal Chemistry and Implantable Biomaterials Optimize the Pharmacokinetics of Systemic Small Molecules

Jose Mejia Oneto¹, Munish Gupta¹, J. Kent Leach^{1,2}, LeAnn Lindsay², Jane Sykes², Maksym Royzen³

¹University of California, Davis, Sacramento, CA, USA, ²University of California, Davis, Davis, CA, USA, ³University at Albany, State University of New York, Albany, NY, USA

Purpose: We present a heterocyclic-based drug delivery platform that optimizes the concentration of a systemic drug at a location of interest. As a therapeutic proof of concept, we apply the system to the construction of an antibiotic agent based on vancomycin.

Background: Our prior studies have shown that an area of the body pre-implanted with a biomaterial containing a bioorthogonal reaction partner (*trans*-cyclooctene, TCO) can increase by ten times the local concentration of a heterocycle (tetrazine, Tz) carrying a radioactive payload *in-vivo*. Now we present a platform that localizes and releases small molecules at the desired location (Fig. 1).



Methods/Results: We modified fluorophores and vancomycin with TCO and as well as synthesized an alginate biomaterial modified with tetrazine (Tz-gel). We tested them through *in-vivo* and *in-vitro* models over multiple days. The results indicate that the “Catch & Release” method can deliver an increased payload to a local area pre-implanted with the biomaterial. The *in-vitro* therapeutic efficacy of the releasable vancomycin was comparable to vancomycin when tested in the presence of the Tz-gel against luminescent methicillin sensitive *Staph. aureus* (MSSA, Xen 29, Perkin Elmer, MA).

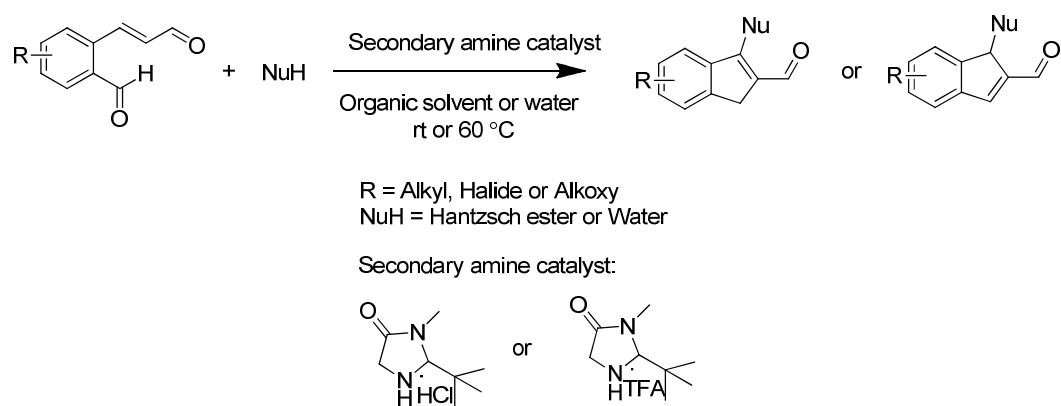
Conclusions: We present a drug delivery system that enables medical practitioners to direct drug to specific locations of the body by pre-implanting a biomaterial. This system could have major implications to improve the therapeutic index of new and old drugs.

Efficient Synthesis of Indene-Aldehyde Derivatives Catalyzed by Secondary Amine Catalysts

HUI MAO, Jung Woon YANG

Sungkyunkwan University, Suwon, Republic of Korea

Substituted indene derivatives are valuable synthetic targets in organic and medicinal chemistry because of their important biological activities and applications in functional materials. These indene-based materials have shown a wide range of biological activities such as antineoplastic, anti-inflammatory, aromatase inhibitory, and cytotoxic activities. A variety of effective approaches were already reported for indene synthesis. However, many of these existing methods suffer from shortcomings including low tolerance of functionality, the necessity of expensive transition metal catalysts and harsh reaction conditions. Herein, we describe a novel method for the synthesis of various substituted indene aldehydes using secondary amine catalysts under mild reaction conditions.



Scheme 1. Formation of indene aldehyde derivatives catalyzed by secondary amine catalysts

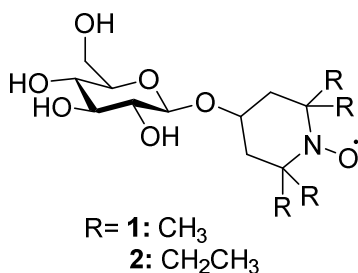
Synthesis and *in vitro* NMR and phantom MRI studies of TEMPO-Glc and TEEPO-Glc, potential contrast agents for MRI

Maiju Soikkeli, Jari Kavakka, Sami Heikkinen

University of Helsinki, Helsinki, Finland

Magnetic resonance imaging (MRI) is one of the most important medical imaging methods due to its non-invasiveness and superior image quality. Contrast agents are used in MRI to improve the contrast between different tissues. They are paramagnetic substances mainly based on gadolinium chelates.

We present two fully organic free radicals, TEMPO-Glc (1) and TEEPO-Glc (2), as potential contrast agents for MRI.¹ Due to their unpaired electrons, these compounds possess relaxation enhancing properties. Also, heterocyclic nitroxide radicals can be made very stable by synthetically modifying the structure to shelter the unpaired electron. These structures can be further developed to incorporate for example tumor targeting properties. In the poster, synthesis, stability assessment and relaxivity studies by *in vitro* MRI of these compounds will be discussed.



1. Soikkeli, M.; Sievänen, K.; Peltonen, J.; Kaasalainen, T.; Timonen, M.; Heinonen, P.; Rönkkö, S.; Lehto, V.-P.; Kavakka, J.; Heikkinen, S. *RSC Adv.* **2015**, *5*, 15507

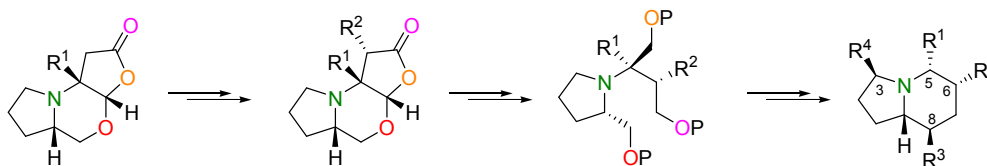
Asymmetric Synthesis of Poison Dart Frog Indolizidine Alkaloids

Yu-Jang Li, Chung-Chien Hou, Kuei-Chen Chang, Rou-Jie Huang, Yu-Fu Liang, Lee-Ya Wang

Department of Applied Chemistry, National Chiayi University, Chiayi City, Taiwan

5-Substituted, 3,5-disubstituted, 5,8-disubstituted and 5,6,8-trisubstituted indolizidines belong to a group of alkaloids separated from the skin of poison dart frogs which lived in the tropical rainforest of Central and South America. Some of these indolizidines have shown interesting AChEI activity which is important for the development of new drugs.

A series of substituted indolizidines, including 167B, 195G, 209B, 209D, 209I, 223A, 223AB, synthesized starting from tricyclic lactones will be discussed. Key steps involved : 1) [3,3]-sigmatropic rearrangement to form tricyclic compounds with needed R^1 substituent, 2) asymmetric alkylation/epimerization to obtain R^2 , 3) cyclization to form C7-C8 bond with R^3 in correct stereochemistry, 4) construction of R^4 (223AB case only), and 5) cleavage of the excess one carbon substituent on C5.



References:

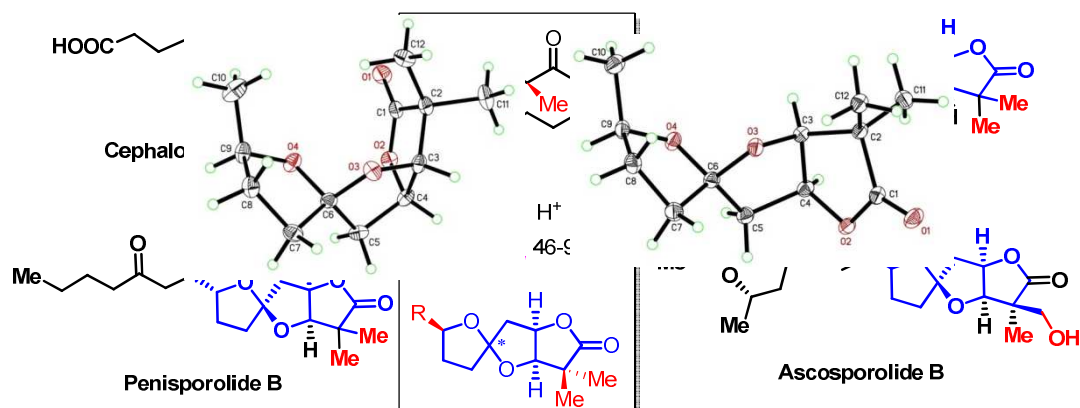
- [1] Li, Y.-J.; Chang, Y.-K.; Ho, G.-M.; Huang, H.-M. *Org. Lett.* **2009**, *11*, 4224.
- [2] Li, Y.-J.; Chuang, H.-Y.; Yeh, S.-M.; Huang, W.-S. *Eur. J. Org. Chem.* **2011**, 1932.
- [3] Li, Y.-J.; Hou, C.-C.; Chang, K.-C. *Eur. J. Org. Chem.* **2015**, 1659.

A Bioinspired Approach to Tricyclic Spiroacetal-fused γ -Lactones

Jian Wang, Rongbiao Tong

Hong Kong University of Science and Technology, Kowloon, Hong Kong

A bio-inspired approach involving ring-contraction rearrangement of decanolides was developed for the synthesis of spiroacetal-fused γ -lactones and applied to the total synthesis of reported structures of cephalosporolides H and I and penisporolide B and their diastereomers.

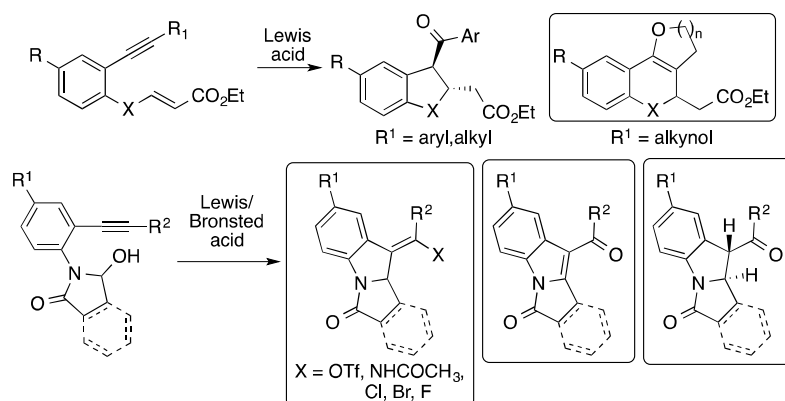


Stereoselective synthesis of oxa- and aza-cycles using reactions of alkynes

Santosh Gharpure

Indian Institute of Technology Bombay, Powai Mumbai Maharashtra, India

In recent years, metal catalysed transformations of alkynes have gain prominence for the synthesis of oxa- and aza-cycles. However, their utility under metal free conditions is still under explored. In a programme directed at the stereoselective synthesis of oxa- and aza-cycles using vinylogous carbonates and carbamates, we demonstrated that the oxonium and iminium ion intermediates generated from these functional groups in the presence of Lewis acids can be trapped with alkynes giving stereoselective access to functionalized 2,3-disubstituted dihydrobenzofurans and indoline derivatives. The regioselectivity of alkyne iminium ion cyclization can be reversed using a tethered hydroxy group as nucleophile. Further, we have also developed divergent synthesis of *N*-fused indolyldiene, indole, and indoline derivatives using alkyne-iminium ion cyclisation. Interestingly, trapping of vinyl cation intermediate generated after alkyne iminium ion cyclisation was found to be dependent on the Lewis/Bronsted acid and solvent used. This talk will highlight some details of these studies.



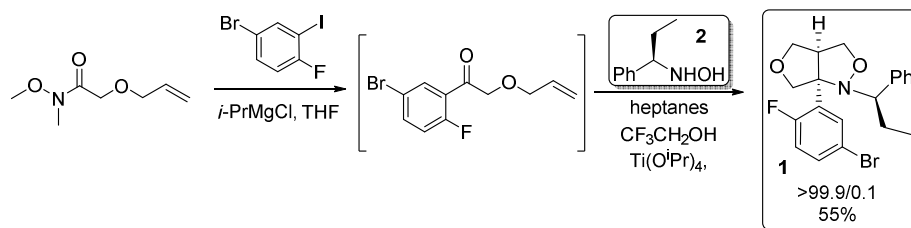
References: 1. Gharpure, S. J.; Prasath, V. *J. Chem. Sci.* **2011**, *123*, 943. 2. Gharpure, S. J.; Shelke, Y. G.; Kumar, D. P. *Org. Lett.* **2015**, *17*, 1926.

Synthetic Development and Pilot Plant Scale-up of a Heterocyclic Pharmaceutical Intermediate

Stanley Kolis

Eli Lilly and Company, Indianapolis, IN, USA

A scalable, asymmetric synthesis of (3*a*S,6*a*S)-6*a*-(5-bromo-2-fluorophenyl)-1-((*R*)-1-phenylpropyl)tetrahydro-1*H*,3*H*-furo[3,4-*c*]isoxazole (**1**), a key intermediate in the synthesis of **LY2886721** is reported. Highlights of the synthesis include: (1) The development of an asymmetric [3+2] intramolecular cycloaddition through a combined kinetic modeling and experimental approach; (2) The development of a new synthesis of (*R*)-*N*-(1-phenylpropyl)hydroxylamine tosylate (**2**) which proceeds through a *p*-anisaldehyde imine and avoids the formation of toxic hydrogen cyanide gas as a by-product. Results of a synthesis executed on the multi-100 kg scale (which proceeded in 36% overall yield) will be discussed.

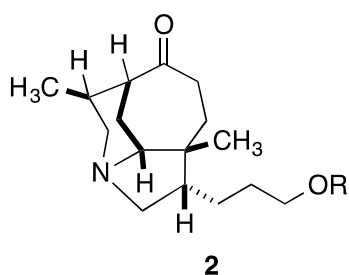
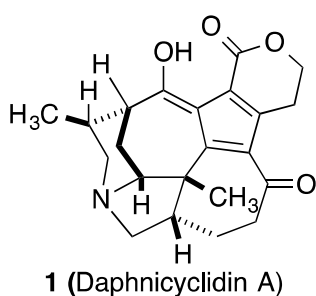


Studies Toward the Synthesis of Daphnicyclidin A

David R Williams

Indiana University, Bloomington, IN, USA

Daphniphyllum alkaloids are a family of complex, polycyclic natural products derived from evergreen shrubs in southern China. The daphnicyclidins represent a subset of these alkaloids as exemplified by daphnicyclidin A (**1**). A stereocontrolled synthesis of the tricyclic ABC ring system will describe the formation of the amine **2** via a novel nine-membered *Z*-enone. The discussion will present methodology for an efficient preparation of α -linked bis-enones as well as novel features of reactivity directly leading to functionalized heterocyclic systems. Applications of this methodology for synthesis of the condensed fulvene of **1** will be described.

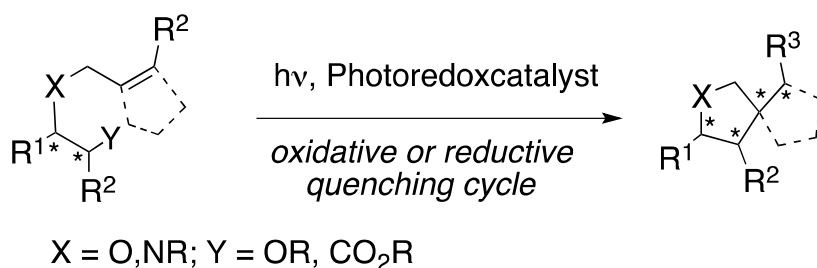


Visible light mediated deoxygenation and decarboxylation as key step for the synthesis of tetrahydrofurans and pyrrolidines.

Daniel Rackl, Viktor Kais, Christian Faderl, Eugen Lutsker, Georgiy Kachkovskiy, Oliver Reiser

University of Regensburg, Regensburg, Germany

Polyols, amino alcohols and amino acids are readily available from renewable resources in enantiomerically pure form. Using such compounds as a starting point, we have developed the synthesis of novel tetrahydrofurans and pyrrolidines utilizing visible light mediated photoredox catalyzed deoxygenations and decarboxylations as key step. The scope and limitation of this strategy in combination with the development of novel photoredoxcatalysts will be discussed.¹



(1) *Leading references:* (a) D. Rackl, V. Kais, P- Kreitmeier, O. Reiser, *Beilstein J. Org. Chem.* **2014**, *10*, 2157; (b) D. B. Bagal, G. Kachkovskiy, M. Knorn, T. Rawner, B. M. Bhanage, O. Reiser, *Angew. Chem. Int. Ed.* **2015**, *54*, Early View; (c) G. Kachkovskiy, C. Faderl, O. Reiser, *Adv. Synth. Catal.* **2013**, *355*, 2240.

Development of Aminooxazoline Xanthene-based β -Amyloid Cleaving Enzyme (BACE1) Inhibitors with Improved Selectivity Towards Cathepsin D (CatD)

Jonathan Low¹, Michael Bartberger¹, Jian Jeffery Chen¹, Alan Cheng², Robert Dunn II¹, Dean Hickman¹, Ana Minatti¹, Hugo Vargas¹, Paul Wen¹, Jonathan Werner¹, Douglas Whittington², Stephen Wood¹, Ryan White², Yuan Cheng¹

¹Amgen Inc., Thousand Oaks, CA, USA, ²Amgen Inc., Cambridge, MA, USA

Alzheimer's disease (AD) is a neurodegenerative disorder that currently affects 36 million people worldwide. It therefore represents one of the largest unmet medical needs in neuroscience today. The β -amyloid cleaving enzyme (BACE1) is considered a prime therapeutic target due to its genetically-verified, detrimental role in the initiation and progression of the disease. As part of an ongoing effort at Amgen to develop a disease-modifying therapy for AD, we have previously used the aminooxazoline xanthene (AOX) scaffold to generate potent and orally efficacious BACE1 inhibitors.¹ While AOX-based BACE1 inhibitors demonstrating robust reduction of CSF and brain A β levels, both in rat and non-human primates, were identified with acceptable cardiovascular safety margins, a retinal pathological finding in advanced rat toxicological studies demanded further investigation. It has been widely postulated that such retinal toxicity might be related to off-target inhibition of Cathepsin D (CatD), a closely related aspartyl protease.² Here we report the development of AOX-based BACE1 inhibitors with improved selectivity towards CatD utilizing a structure- and property-based approach to gain further insight into the observed ocular toxicity.

(1) (a) *J. Med. Chem.* **2014**, 57, 9811-9831. (b) *J. Med. Chem.* **2014**, 57, 9796-9810. (c) *ACS Med. Chem. Lett.* **2015**, 6, 210-215. (d) *J. Med. Chem.* **2012**, 55, 9156-9159. (e) *Bioorg. Med. Chem. Lett.* **2015**, 25, 767-774

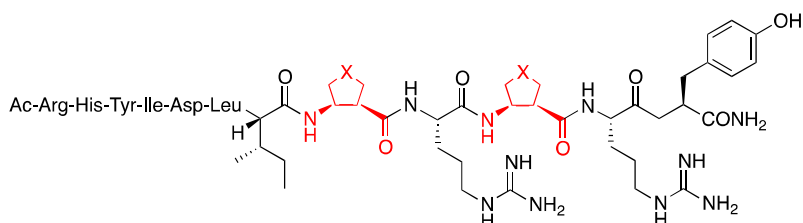
(2) *Toxicol. Pathol.* **2014**, 0192623314553804 (published on-line)

□/□-Peptides containing pyrrolidine-based □-residues as useful tools for neuropeptide Y receptor-subtype selectivity

Thomas Ertl¹, Chiara Cabrele², Armin Buschauer¹, Oliver Reiser¹

¹University of Regensburg, Regensburg, Germany, ²University of Salzburg, Salzburg, Austria

Pyrrolidine-based non-natural amino acids have been shown to be valuable building blocks for the design of pharmaceutically interesting peptides and peptidic foldamers. In this work we show the application of the □-amino acid (3R,4R)-4-amino-pyrrolidine-3-carboxylic acid (*cis*-APC) in the design and synthesis of novel □/□ analogs of neuropeptide Y (NPY). This is a 36-residue long, C-terminally amidated peptide hormone that is expressed in the brain and in the peripheral nervous system, and, upon binding to four NPY Y_n (n=1,2,4,5) receptors, it regulates food intake, the circadian rhythm and cardiorespiratory parameters. Moreover, the NPY/Y_n-receptor system is involved in several pathological disorders like obesity, depression, anxiety-related disorders and epilepsy. To control the Y_n-receptor-mediated function of NPY, it is important to develop NPY analogs with Y_n-receptor-subtype selectivity. For this purpose we have modified the NPY fragment 25-36 by introducing *cis*-APC and other cyclic □-amino acids at positions 32 and 34.¹ The synthesis of these NPY analogs and the ability of the investigated building blocks to modulate receptor-binding selectivity will be presented.



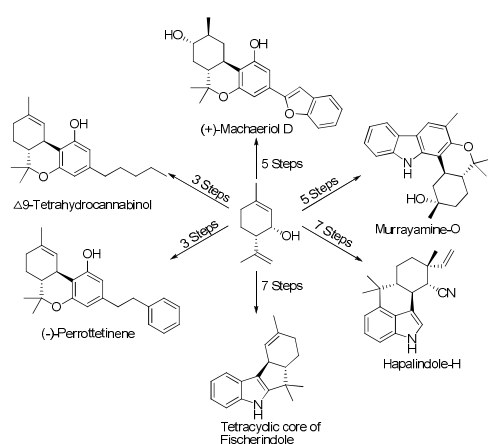
[1] *Leading references:* (a) Berlicki, Ł.; Kaske, M.; Gutiérrez-Abad, R.; Bernhardt, G.; Illa, O.; Ortuño, R. M.; Cabrele, C.; Buschauer, A.; Reiser, O. *J. Med. Chem.* **2013**, *56*, 8422. (b) Cabrele, C.; Martinek, T. A.; Reiser, O.; Berlicki, Ł. *J. Med. Chem.* **2014**, *57*, 9718. (c) Berlicki, Ł.; Pilsl, L.; Weber, E.; Mandity, I. M.; Cabrele, C.; Martinek, T. A.; Fülöp, F.; Reiser, O. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 2208.

Protecting Group Free Enantiospecific Total Syntheses of Structurally Diverse Natural Products of Four Different Classes

DATTATRAYA DETHE

INDIAN INSTITUTE OF TECHNOLOGY KANPUR, KANPUR, UTTAR PRADESH, India

A simple, highly diastereoselective, Lewis acid catalyzed coupling of cyclic allylic alcohol with carbazole, resorcinol and indole derivatives has been developed. The method was applied for the enantiospecific total syntheses of structurally diverse natural products such as murrayamine-O, machaeriol-D, Δ^8 -THC, Δ^9 -THC, *epi*-perrottetinene and tetracyclic core of fischerindole and hapalindoles, having wide range of biological activities. Synthesis of both natural products and their enantiomers has been achieved with high atom economy, protecting group free manner and in less than 5 steps longest linear sequence in very good overall yield starting from *R*-(+) and *S*-(-)-limonene.



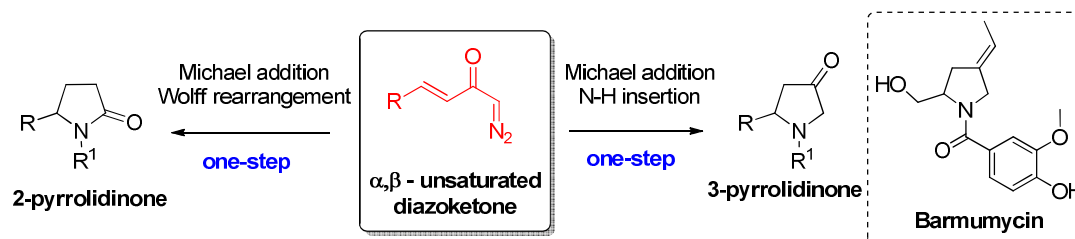
References: (a) Dattatraya H. Dethe,* Saikat Das, Balu D. Dherange and Samarpita Mahapatra, *Chem. Eur. J.*, **2015**, *Just Accepted*. (b) Dattatraya H. Dethe,* Rohan D. Erande, Samarpita Mahapatra, Saikat Das and Vijay Kumar B, *Chem. Commun.*, **2015**, *51*, 2871. (c) Dattatraya H. Dethe,* Ganesh Murhade, Saikat Das and Samarpita Mahapatra, *Manuscript under preparation*.

One-step syntheses of 2-pyrrolidinones and 3-pyrrolidinones from α,β -unsaturated diazoketones and amines

Rafael Dias, Antonio Burtoloso

University of São Paulo, São Carlos, São Paulo, Brazil

Pyrrolidine ring is an important type of nitrogen heterocycle due to its large occurrence in natural products, its significant biological activities and its application as intermediates in the synthesis of more complex molecules. Many methodologies have been described for these N-heterocycles to date. However, the use of common intermediates to obtain a large number of pyrrolidine analogs, in a direct fashion, is limited. In this context, α,β -unsaturated diazoketone (UDK) are versatile and multifunctional building blocks in synthesis and allow the rapid construction of different N-heterocycles and analogs from the same intermediate. Herein we wish to describe how we prepared several 2- and 3-pyrrolidinones from UDK in a single reaction vessel by a sequence of two transformations as described below. 1) For 2-pyrrolidinones: Aza-Michael addition followed by exposure to light (photochemical Wolff rearrangement). 2) For 3-pyrrolidinones: Aza-Michael addition, followed by addition of Cu or Rh salts (intramolecular N-H insertion reaction). All the pyrrolidinones could be prepared in good yields from the UDK. Finally, this one-step method was also applied in the synthesis of Barmumycin, a pyrrolidine alkaloid with antitumor activity.



An Efficient Process for the Synthesis of Perfluoroalkylated Benzazepines

Xuechun Sun¹, Jing Han¹, Jie Chen¹, Hui Zhang¹, Weiguo Cao^{1,2}

¹Shanghai University, Shanghai, China, ²Shanghai Institute of Organic Chemistry, Shanghai, China

Benzazepine moiety occurs frequently in both natural and synthetic drugs and is of highly biological interest. The usage of this class of compound is not merely confined to the management of stress related conditions and for their use as antibacterial agents¹. Besides, the quinoxaline core is present in many drugs with antitumor, anticancer, antiamoebic². Because of important applications of benzazepine and quinoxaline compounds, we proposed an efficient protocol for the synthesis of perfluoroalkylated compounds **3** consisted of benzazepine and quinoxaline structure with 3-(2-aminophenyl)quinoxalin-2(1H)-one derivatives **1** and methyl perfluoroalk-2-ynoate **2**.

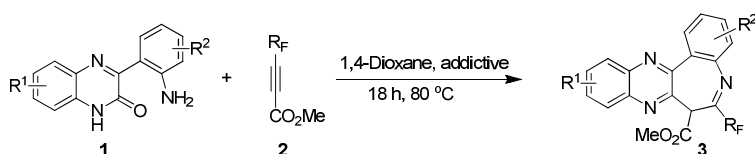


Table 1 Optimization of the reaction conditions for the synthesis of compound **3**^a

Entry	R ¹	R ²	R _F	Additive/ equiv	Yield (%) ^b
1	H	H	CF ₃	<i>p</i> -TSA/ 0.5	30
2	H	H	CF ₃	HOAc/ 0.5	71
3	H	H	CF ₃	PhCO ₂ H/ 0.5	70
4	H	H	CF ₃	-	71
5	H	H	CF ₃	NH ₄ Cl/ 0.5	69
6	H	H	CF ₃	Et ₃ N/ 0.5	trace
7	H	H	CF ₃	FeCl ₃ / 0.5	50
8	H	H	CF ₃	ZnCl ₂ / 0.5	31

^a Reaction condition: 3-(2-aminophenyl)quinoxalin-2(1H)-one (1 mmol), methyl perfluoroalk-2-ynoate (1.5 mmol), 80 °C, 18 h; ^b Isolated yield.

Supported by National Natural Science Foundation of China (Grant No. 21272152)

References

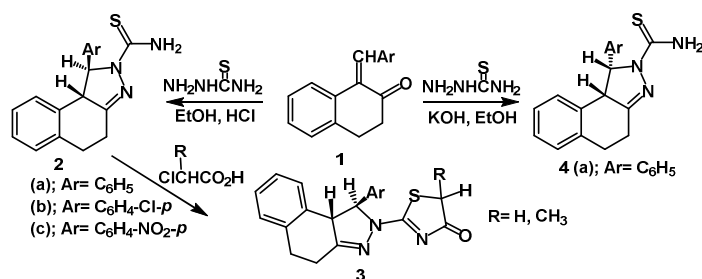
1. B. Krishan, O. Prakash, E. H. ElMossalmy, *Orient. J. Chem.* **2013**, *29*(1), 381-388.
2. A. Budakoti, A. R. Bhat, A. Azam, *Eur. J. Med. Chem.* **2009**, *44*(3), 1317-1325.

Regioselective Synthesis, X-ray and DFT studies of new Indazolyl-thiazole derivatives

Ram Pal Chaudhary, Deepika Gautam, Poonam Gautam

Sant Longowal Institute of Engineering and Technology, Longowal (Sangrur) Punjab, India

Fused tricyclic systems containing pyrazole moiety have shown enhanced inhibitory activity against a variety of protein kinases and been found useful in the treatment of several cell proliferative disorders. We report herein the regioselective synthesis and biological activities of some new derivatives in continuation to our work on synthesis¹⁻³ of antimicrobial agents. 1-Arylidene-2-tetralone, obtained from reaction of 2-tetralone and aromatic aldehydes, on condensation with thiosemicarbazide in acidic and alkaline medium afforded tetrahydro-2H-benzo[e]indazole-2-carbothioamide as *cis* and *trans* diastereoisomers of 1-*H* and 9b-*H* respectively. The synthesis of a new series of indazolyl-thiazol-4(5*H*)-ones from *cis* isomer and α -halo acids is reported. A DFT study along with single crystal X-ray diffraction data of a representative compound is presented. The reaction of indazole-2-carbothioamides with methyl iodide, DMAD and acetic anhydride are described. Newly synthesised indazolyl-thiazol-4(5*H*)-ones were screened for their antibacterial and antifungal activities. Some of the newly synthesised derivatives have shown promising antibacterial and antifungal activities.



References

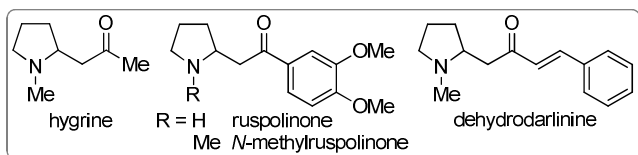
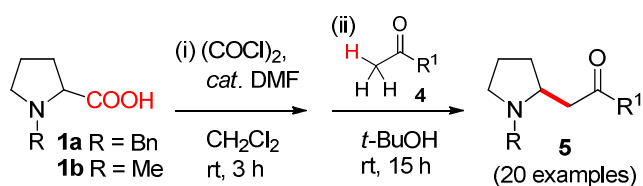
- (1) Gupta, R.; Chaudhary, R. P. *J. Mol. Struct.* **2013**, 1049, 189.
- (2) Gupta, R.; Chaudhary, R. P. *J. Heterocycl. Chem.* **2014**, DOI 10.1002/jhet.2098.
- (3) Gautam, D.; Chaudhary, R. P. *Spectrochim. Acta, Part A.* **2015**, 135, 219.

Biomimetic Approach toward the Total Synthesis of *rac*-2-(Acylmethylene)pyrrolidine Alkaloids

Tun-Cheng Chien

National Taiwan Normal University, Taipei, Taiwan

2-(Acylmethylene)pyrrolidine derivatives were synthesized via intermolecular decarbonylative Mannich reaction from various methyl ketones and 1-alkyl-1-pyrroliniums, generated *in situ* from 1-alkylprolines. 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. 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.



The title

“Elucidation of the Structure and Stereochemistry of the Metabolites of the HCV Protease Inhibitor Faldaprevir”

Carl Busacca

Boehringer-Ingelheim Pharmaceuticals, Ridgefield, CT 06877, USA

Faldaprevir is an HCV Protease Inhibitor for the treatment of Hepatitis C infection. The first small molecule treatment for HCV, the macrocycle BILN 2061, was the predecessor of Faldaprevir. Human clinical isolates following administration of Faldaprevir were found to contain four major human metabolites. Elucidation of the structure of each of these metabolites was achieved through a combination of isotopic labelling, LC-NMR, HPLC-MS, global esterification/chromatography and total synthesis. Implications for the molecular-level interactions of the drug in the Cyp-3A4 active site will also be discussed.

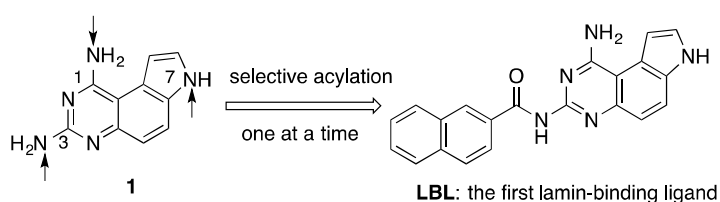
Some text

Teaching an old dog new tricks: chemical biology studies of pyrroloquinazolines

Bingbing Li, Jingjin Chen, Larry David, Xiangshu Xiao

Oregon Health & Science University, Portland, USA

7*H*-Pyrrolo[3,2-*f*]quinazoline-1,3-diamine (**1**) is a privileged chemical scaffold with significant biological activities. These include inhibition of dihydrofolate reductase (DHFR), protease-activated receptors (PAR) and protein tyrosine phosphatase 1B (PTP1B). However, the currently accessible chemical space derived from **1** is rather limited. In this presentation, we expanded the chemical space related to **1** by developing efficient methods for regioselective monoacylation at *N*¹, *N*³ and *N*⁷, respectively. With this novel methodology, a focused library of mono-*N*-acylated pyrroloquinazoline-1,3-diamines were prepared and screened for anti-breast cancer activity. The structure-activity relationship (SAR) results showed that *N*³-acylated compounds were in general more potent than *N*¹-acylated compounds while *N*⁷-acylation significantly reduced their solubility. Among the compounds evaluated, **LBL1** possessed significantly more potent activity than **1** in MDA-MB-468 cells. More importantly, **LBL1** was not toxic to normal human cells. Further chemical biology and mechanistic studies showed that **LBL1** targets nuclear lamins to inhibit repair of double-strand DNA breaks (DSB) in breast cancer cells. The discovery of **LBL1** as the first lamin-binding ligand from a focused novel library of **1** supports that **1** is a privileged scaffold. The availability of **LBL1** should enable us to address the poorly understood molecular mechanisms of lamins in DSB repair processes.



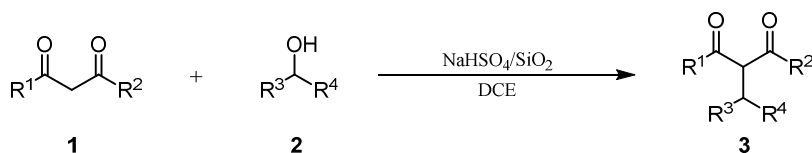
Simple and efficient alkylation of 1,3-dicarbonyl compounds and synthesis of 4*H*-chromenes using NaHSO₄/SiO₂

Tadashi Aoyama, Mamiko Hayakawa, Akihiko Ouchi

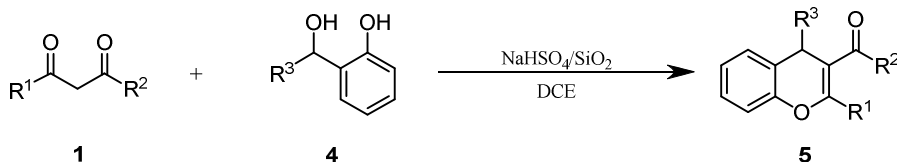
Nihon Univ., Tokyo, Japan

We have developed a simple and efficient procedure for the C-C bond formation between alcohols and active methylene containing compounds using silica-gel supported sodium hydrogen sulfate (NaHSO₄/SiO₂) under mild conditions. This method was applied to the synthesis of chromenes. NaHSO₄/SiO₂ can be reused for the alkylation without loss of catalytic activity at least 10 times.

Reaction of **1** with **2** was carried out in the presence of NaHSO₄/SiO₂ at 80 °C in dichloroethane (DCE) to give corresponding **3** in moderate to excellent yields; eg. acetyl acetone **1a** (R¹, R² = CH₃) and benzhydrol **2a** (R³, R⁴ = Ph) were reacted for 30 min to give **3a** in 98 % yield.



When *o*-hydroxy benzhydrol **4** was used in place of **2a**, consecutive alkylation and intramolecular cyclization occurred to give 1-(2-methyl-4-phenyl-4*H*-chromen-3-yl)ethanone **5** quantitatively. Similar reactions using *o*-hydroxy benzylic alcohols and 1,3-dicarbonyl compounds gave the corresponding chromens in moderate to good yields.



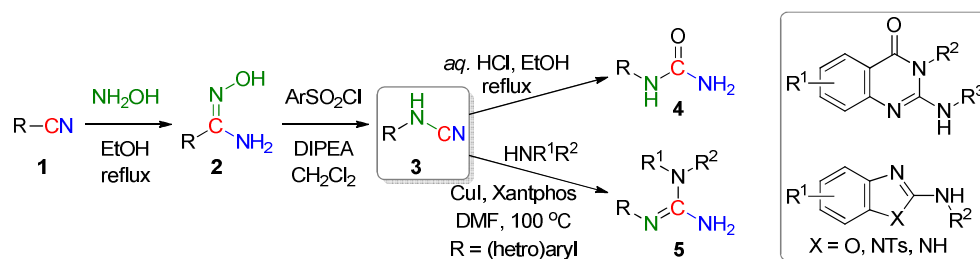
Some text

Practical Synthesis of *N*-Substituted Cyanamides as *N*-C-N Building Blocks for Heterocycle Synthesis

Tun-Cheng Chien

National Taiwan Normal University, Taipei, Taiwan

A variety of carboxamidoximes (**2**), prepared from carbonitriles with NH_2OH , could react with benzenesulfonyl chlorides (TsCl or *o*-NsCl) and DIPEA to form *N*-substituted cyanamides (**3**) in very good yields. The benzenesulfonyl chlorides promoted Tiemann rearrangement of carboxamidoximes (**2**) is readily amenable for the synthesis of a wide variety of cyanamide derivatives in multi-gram scales from carbonitriles.¹ Acidic hydrolysis of the *N*-substituted cyanamides (**3**) afforded the corresponding *N*-monosubstituted ureas (**4**) in good yields. The preparation of the *N*-monosubstituted ureas (**4**) could also be accomplished in a one-pot fashion effectively from carbonitriles (**2**) with comparable yields.² *N*-Alkyl-*N'*-arylguanidines (**5**) could be obtained from the reaction of *N*-arylcyanamides (**3**) with various primary and secondary alkylamines, under the catalysis of CuI and Xantphos in DMF. This methodology provides a direct access to versatile *N,N'*-disubstituted guanidine derivatives (**5**) from previously described *N*-arylcyanamides (**3**).³ The application of *N*-substituted cyanamides (**3**) toward the synthesis of various heterocycles, including benzimidazoles, benzoxazoles, and quinazolinones, has also been demonstrated.



References

1. Lin, C.-C.; Hsieh, T.-H.; Liao, P.-Y.; Liao, Z.-Y.; Chang, C.-W.; Shih, Y.-C.; Yeh, W.-H.; Chien, T.-C. *Org. Lett.* **2014**, *16*, 892.
2. Wang, C.-H.; Hsieh, T.-H.; Lin, C.-C.; Yeh, W.-H.; Lin, C.-A.; Chien, T.-C. *Synlett*, **2015**, in press.
3. Zeng, C.-J.; Chen, C.-J.; Chang, C.-W.; Chen, H.-T.; Chien, T.-C. *Aust. J. Chem.* **2014**, *67*, 1134.

The title: Formation of quinoline skeleton from chalcone: The effect of amino protective group to the reactivity of 2-aminochalcones

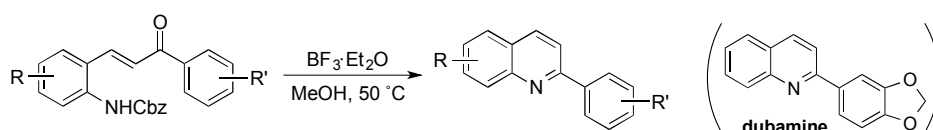
Tomohiro Maegawa, Akira Nakamura, Yasuyoshi Miki

Kinki University, Osaka, Japan

A number of natural products and drugs with quinoline skeleton have useful bioactivities such as antibacterial, anticancer and so on. Many synthetic methods for quinoline syntheses have been reported, and various substrates were employed for the precursor of quinolines. In the case of non-protected 2-aminochalcone as a starting material,^{1,2)} it is necessary to isomerize olefin geometry from *E* to *Z* for the reaction progress. The reaction conditions such as $h\nu$ ¹⁾ or NIS,²⁾ therefore, were required for isomerization of the olefin in situ in addition to cyclization.

During the study for the reactivity of 2-aminochalcones, we found that the protecting group on amino function significantly affected the reactivity of 2-aminochalcone and *N*-Cbz-2-aminochalcones were cyclized to give the corresponding quinoline by treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$. Other *N*-protected 2-aminochalcone was not suitable for this reaction, although *N*- COCF_3 2-aminochalcones were effective for the formation of indole ring via the rearrangement reaction by hypervalent iodine reagent.

The substrates bearing electron-donating or withdrawing substituents on aromatic ring successfully underwent the cyclization reaction to give the quinolines under the conditions. This method was applicable to the synthesis of dubamine, which was isolated from plant and has antibacterial activity.



1) T. Horaguchi *et al.* *J. Heterocyclic Chem.* **2002**, 39, 61.

2) K. Okuma *et al.* *Bull. Chem. Soc. Jpn.* **2007**, 80, 1824.

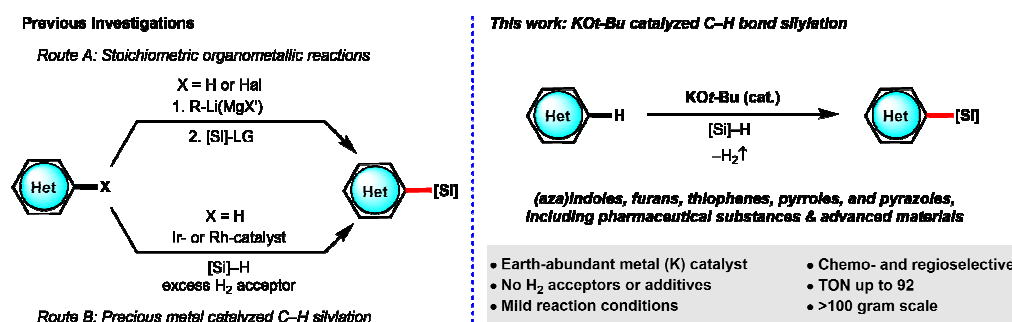
Cross-dehydrogenative C–H Bond Silylation of Aromatic Heterocycles by an Earth-abundant Metal Catalyst

Anton Toutov, Wen-Bo Liu, Kerry Betz, Alexey Fedorov, Brian Stoltz, Robert Grubbs

Caltech, Pasadena, CA., USA

Arylsilanes are of great interest in the fields of organic electronics and photonics, medicinal chemistry, and complex molecule synthesis due to the unique physicochemical features of the aromatic carbon-silicon (C–Si) bond.

We have recently discovered a mild and regioselective C–H bond functionalization of aromatic heterocycles catalysed by a plentiful and inexpensive Earth-abundant metal salt [1]. The method enables the direct silylation of heteroaryl C(sp²)–H bonds that both obviates the need for expensive precious metal catalysts and overcomes various limitations of previous methods. Applications to materials science and to the late-stage derivatization of pharmaceutical substances will be presented.



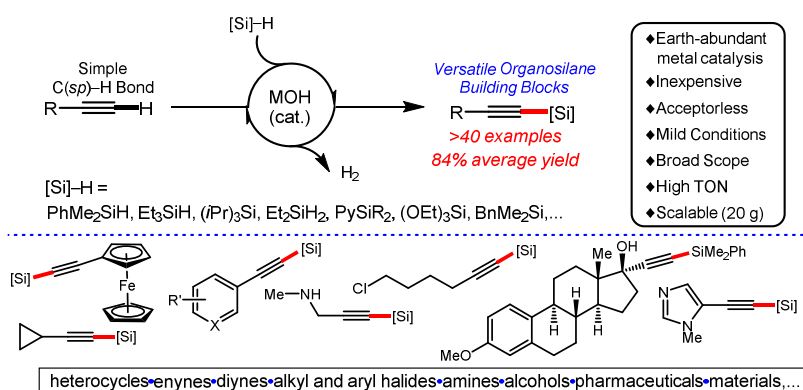
[1] Toutov et al. *Nature* **2015**, 518, 80.

Cross-dehydrogenative silylation of non-aromatic C–H bonds by an Earth-abundant metal catalyst

Anton Toutov, Kerry Betz, Wen-Bo Liu, Brian Stoltz, Robert Grubbs

California Institute of Technology, Pasadena, CA, USA

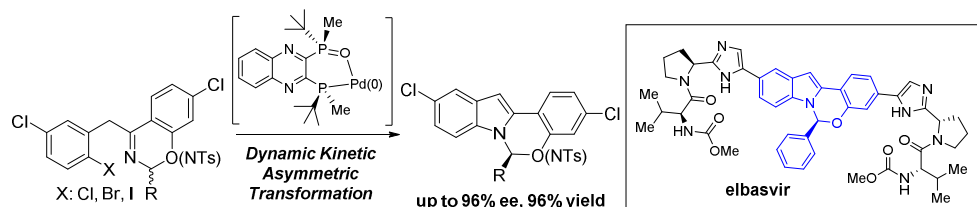
A cross-dehydrogenative C–H bond functionalization of non-aromatic systems employing readily available and inexpensive Earth-abundant metal catalysts is described. The method allows for the direct coupling of a C(sp)–H bond and silane Si–H bond to furnish the corresponding C–Si bond in a single step. The catalysis is scalable and proceeds under mild conditions, in the absence of hydrogen acceptors or other additives, and liberates dihydrogen as the byproduct. The scope of the method is broad, enabling the direct silylation of aromatic and aliphatic acetylenes in the presence of a wide array of crucial functional groups such as electron rich and electron deficient aromatic heterocycles, π -conjugated systems, various heteroatoms, alkyl- and aryl halides, alcohols and amines, strained rings, and organometallic scaffolds. Substrate classes that are challenging to activate by classical stoichiometric deprotonations or with state-of-the-art transition metal catalysis strategies are functionalized in good yields. Applications to pharmaceuticals and materials science, multi-component couplings, and directing group chemistries highlight the broad utility and remarkable scope of this catalytic C–H functionalization method across multiple disciplines.



Enantioselective Synthesis of Hemiaminals via Pd-Catalyzed C-N coupling with Chiral Bisphosphine Mono-Oxides

Hongming Li, Kevin Belyk, Jingjun Yin, Qinghao Chen, Alan Hyde, Matthew Tudge, Louis-Charles Campeau, Kevin Campos

Merck, Department of Process Chemistry, Rahway, NJ, USA



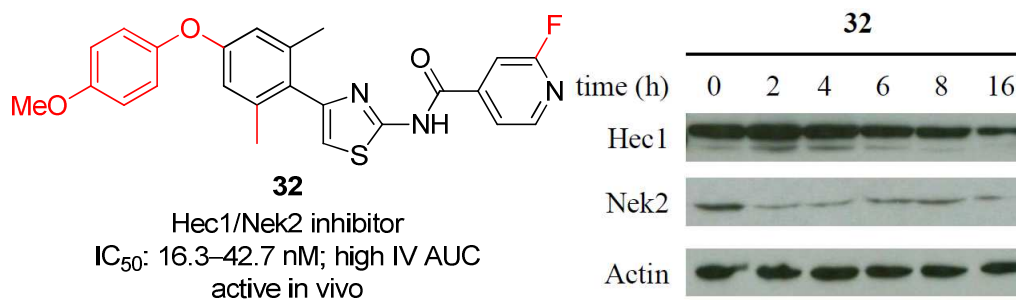
A novel asymmetric synthesis of fully functionalized chiral *N,O*- and *N,N*-acetals has been developed. The reaction tolerates a wide range of aromatic and aliphatic substituents at the stereochemically labile aminal position. Starting from racemic starting materials, the desired products are obtained in high yield and enantiomeric excess. Additionally, we will discuss our investigations towards understanding the mechanistic aspects of this reaction. With the implementation of high-throughput experimentation, the current method was quickly developed and implemented to provide a highly efficient synthesis of a late stage drug candidate.

Discovery of 4-Aryl-N-arylcarbonyl-2-aminothiazoles as Hec1/Nek2 Inhibitors. Part I: Optimization of In Vitro Potencies and Pharmacokinetic Properties

Jiann-Jyh Huang

Department of Applied Chemistry, National Chiayi University, Chiayi City, Taiwan

A series of 4-aryl-N-arylcarbonyl-2-aminothiazoles of scaffold **4** was designed and synthesized as Hec1/Nek2 inhibitors. Structural optimization of **4** led to compound **32** bearing C-4' 4-methoxyphenoxy and 4-(*o*-fluoropyridyl)carbonyl groups that showed low nanomolar in vitro antiproliferative activity (IC_{50} : 16.3–42.7 nM), high IV AUC (64.9 μ M·h, 2.0 mg/Kg) in SD rat, and significant in vivo antitumor activity (T/C = 32%, 20 mg/Kg, IV) in mice bearing human MDA-MB-231 xenografts. Cell responses due to Hec1/Nek2 inhibition were observed in cells treated with **32**, including a reduced level of Hec1 co-immunoprecipitated with Nek2, degradation of Nek2, mitotic abnormalities, and apoptosis. Compound **32** showed selectivity of cancer cells over normal phenotype cells and was shown to be inactive in a [3 H]astemizole competitive binding assay for hERG liability screening. Therefore, **32** served as a good lead in our discovery of a preclinical candidate targeting Hec1/Nek2 interaction.

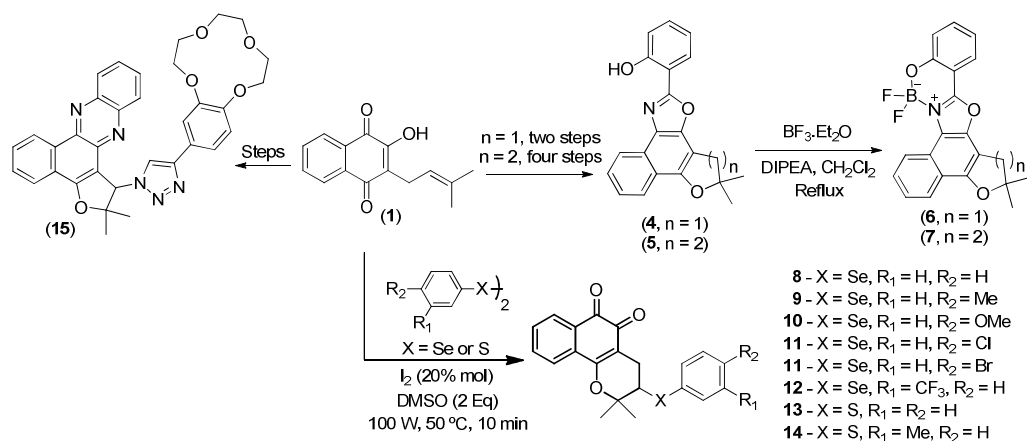


Structural Modifications of Quinoidal Molecules towards Bioactive and Fluorescent Heterocycles

Gleiston Dias¹, Brenno Neto², José Corrêa², Claudia Pessoa³, Bruno Cavalcanti³, Antonio Braga⁴, Solange de Castro⁵, Rubem Menna-Barreto⁵, Eufrânio da Silva Júnior¹

¹Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil, ²University of Brasilia, Brasília, Distrito Federal, Brazil, ³Federal University of Ceará, Fortaleza, Ceará, Brazil, ⁴Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil, ⁵Oswaldo Cruz Foundation, Rio de Janeiro, Rio de Janeiro, Brazil

Over the past five years, our group has employed in design, synthesis and optimization of new heterocyclic compounds with different biological applications.^{1,3} In this context, we revealed the synthesis and the biological evaluations (e.g. bioimaging, cellular uptake and dynamics in living cells) of some new fluorescent oxazoles and their boron complexes which have allowed for selectively visualizing the whole endocytic pathway. The target compounds were characterized by spectroscopic analyses, single crystal X-ray, photophysics and DFT calculations. In addition, a straightforward synthesis of chalcogen-containing β -lapachones with trypanocidal and antitumor activities and a new probe for alkaline metals are also described from lapachol, an affordable naturally occurring naphthoquinone.



References: 1. da Silva Júnior, E. N. et al.; *Bioorg. Med. Chem.* **2012**, *20*, 6482; 2. da Silva Júnior, E. N. et al.; *Eur. J. Med. Chem.* **2013**, *69*, 678; 3. da Silva Júnior, E. N. et al.; *Eur. J. Org. Chem.* **2015**, 703.

Domino Strategies for Syntheses of Natural Products and New Molecular Scaffolds

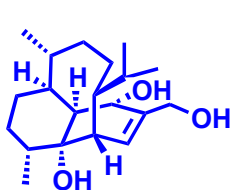
Krishna Kaliappan

Indian Institute of Technology Bombay, Mumbai, Maharashtra, India

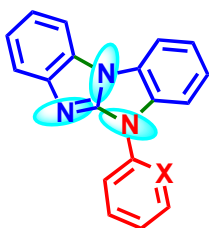
Our group has been engaged in designing simple and efficient domino strategies for the syntheses of natural products and natural product like molecules. In this lecture, our efforts leading to syntheses of vinigrol, cyclic guanidines and *N*-heterocyclic amides will be discussed in details.

Vinigrol, a unique diterpene, containing the decahydro-1,5-butanonaphthalene carbon skeleton has been shown to exhibit a broad spectrum of biological activity. Besides the multiple sites of oxygenation, vinigrol contains a tricyclic core having a *cis*-fused [4.4.0] system bridged by an eight-membered ring and eight contiguous stereocenters. We recently reported an enantioselective formal synthesis of vinigrol, involving a **1-2-3 strategy (one pot and 2-reactions with the formation of 3-rings)**, leading to the core structure of vinigrol from its stereochemically well-defined acyclic precursor.

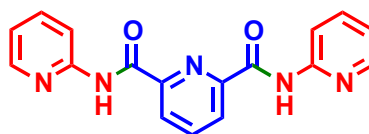
The cyclic guanidines and *N*-heterocyclic amides are important structural units present in biologically active drug molecules. However, the existing methods suffer from harsh conditions, narrow functional group tolerance, poor atom economy, low yielding and so; it warrants an efficient protocol for their syntheses. We have developed a one-pot Cu-catalyzed cascade routes to these unique cyclic guanidines and *N*-heterocyclic amides from readily available starting materials.



Vinigrol



Cyclic guanidines



N-Heterocyclic amides

Synthesis of azabicyclic natural product analogues aiming at biological activity

Christian Stevens, Thomas Heugebaert, Melissa Vanoverveldt, Iris Wauters

Ghent University, Gent, Belgium

Many natural products with interesting biological activity contain azabicyclic or bridged nitrogen containing scaffolds. These conformationally restricted compounds are characterised by a considerable ring strain which may complicate ringclosing reactions.

The lecture will discuss ringclosing methodology for the synthesis of several classes of azabicyclic and azamulticyclic derivatives designed towards agrochemical or medicinal applications.

A dynamic ring closure has been developed for the synthesis of 7-azabicyclo[2.2.1]heptanes. This skeleton is present in epibatidine, a very active analgesic compound isolated from the skin of the Ecuadorian frog *Epipedobates tricolor*. Its potency was proven to be 200-fold higher than morphine, however epibatidine cannot be used clinically because of its high toxicity. Different classes of epibatidine analogues have been prepared trying to minimize toxicity while maintaining the analgesic properties.

Gold catalysed ringclosing reactions have been developed for the synthesis of functionalised isoindoles, dehydrothiazoles and pyrroles. The ring closing involves a 5-exodig cyclization, followed by a [1,3]-alkyl shift and a [1,5]-H shift.

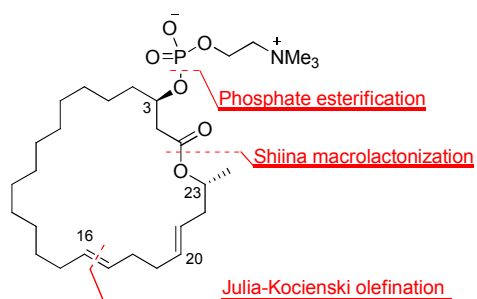
Diketopiperazines are well recognized as an important moiety in medicinal active secondary metabolites of plants. We developed a new cyclization for the straightforward synthesis of constrained diketopiperazine analogues of the brevianamide family. This new class of analogues with a 3,5-bridged structure and bearing an α -chloro amine function allows the synthesis of a library of compounds using a variety of nucleophiles. We also performed ab initio calculations to get insight on the mechanism of the DKP-tryptophane ring closure.

Total synthesis of (3*R*,16*E*,20*E*,23*R*)-eushearilide

Takayasu Yamauchi, Yuya Karino, Kaori Kumagai, Hironori Yoshizawa, Yuka Ebisawa, Minoru Kobayashi, Tatsuya Motegi, Shigeru Sasaki, Kimio Higashiyama

Hoshi University, Tokyo, Japan

Eushearilide is antifungal activity against various fungi and yeasts including the human pathogens *Aspergillus fumigatus*, *Trichophyton* sp. and *Candida* sp. The structure of **1** comprises a novel 24-membered macrolide with two chiral carbons of unknown configuration and non-conjugated double bonds and possesses phosphate diester attached to choline at C3 hydroxyl group. To determine the absolute configuration of two chiral carbon, we synthesized two diastereomers of **1** with different chirality at C23 and compared the spectroscopic properties of natural product with those of synthetic diastereomers. Those were not completely identical to the only chemical shifts of C14–C18 in ¹³C NMR spectrum. Therefore, we speculated the geometry of double bond at 16 position of the natural product was *trans*, *E*-form. The total synthesis of the third diastereomer having both dipolar ionic choline phosphate chain and lipophilic 24-membered macrolide skeleton was achieved. The *cis* selective coupling of two long chains by Julia-Kocienski olefination set C16 geometry. Macrolactonization of seco acid using Shiina reagent was performed the heterocycle in high yield. Finally, by installing choline phosphate in the C3 hydroxyl group was converted to the target molecule (3*R*,16*E*,20*E*,23*R*)-**1**.



(3*R*,16*E*,20*E*,23*R*)-Eushearilide (**1**)

Synthetic Studies on a Total Synthesis of Antitumor Renieramycin T

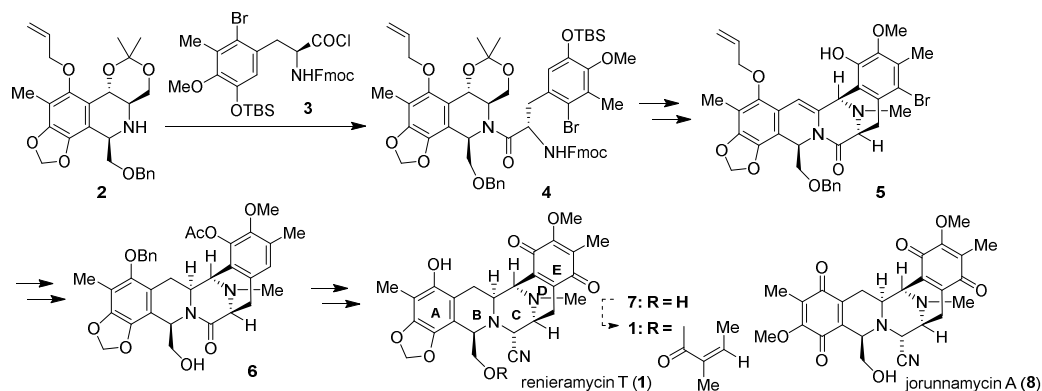
Masashi Yokoya¹, Ryoko Toyoshime¹, Naoki Saito¹, Vy Le², Robert M. Williams²

¹Department of Pharmaceutical Sciences, Meiji Pharmaceutical University, Kiyose, Japan,

²Department of Chemistry, Colorado State University, Colorado, USA

[Introduction] Renieramycin T (**1**) has been found from Thai blue sponge *Xestospongia* sp. as a very minute constituent in 2009. It is a first entry of antitumor bis-1,2,3,4-tetrahydroisoquinolinequinones that has a novel hybrid structure of ecteinascidins and renieramycins.¹ We studied a total synthesis of **1** from **2**, which was prepared using a radical cyclization reaction as crucial key steps.²

[Results and Discussion] Condensation of **2**² with an acyl chloride **3** (as an *E*-ring component) gave amide **4**. Double cyclization of **4** into the pentacyclic framework **5** has been succeeded in several steps. Regioselective oxidation of the benzyl protected phenol **5**, followed by converting an amide carbonyl of **6** into an aminonitrile by partial hydride reduction, and introduction a cyano group sequence produced the primary alcohol **7**. This structure was identified with the authentic sample prepared from jorunnamycin A (**8**) under our original photochemical transformation. We are now ongoing to transform **7** into **1**.



1) Daikuhara N.; Tada Y.; Yamaki S.; Charupant K.; Amnuoypol S.; Suwanborirux K.; Saito N. *Tetrahedron Lett.*, **50**, 4276-4278 (2009).

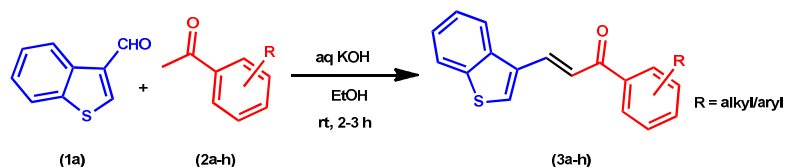
2) Fishlock, D.; Williams, R. M. *Org. Lett.*, **8**, 3299-3301 (2006).

Study on interaction of novel heteroaryl chalcones with calf thymus DNA using molecular docking and spectroscopic techniques

Paresh N Patel, Anju Chadha

Indian Institute of Technology Madras, Chennai, India

A series of new heteroaryl chalcone conjugates [Scheme 1, 3a-h] have been synthesized by Claisen–Schmidt condensation reactions of various substituted acetophenones (2a-h) with benzo[b]thiophene-3-carbaldehyde (1a). The heteroaryl chalcone conjugates thus obtained were characterized by IR, ^1H NMR, ^1H - ^1H COSY, ^{13}C NMR, mass spectral analyses and single crystal XRD data and were found to be thermally stable up to 300 °C. A large number of hybrid chalcones reportedly show anticancer activity [1,2]. In this study, automated docking was used to determine the orientation of the synthesised chalcones that bind to the CT-DNA [d(CGCGAATTCG CG)₂ dodecamer (PDB ID: 1BNA)] obtained from the Protein Data Bank. Binding of these chalcones was studied using computational methods and biophysical studies. The results obtained from the binding study of the prepared compounds with CT-DNA at physiological pH will be presented along with molecular docking.



Scheme 1

References:

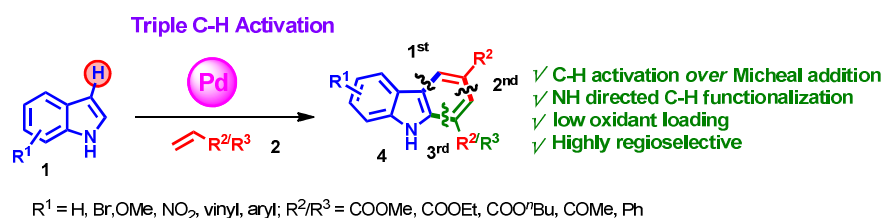
1. V Markovi, et al, *Eur J Med.Chem*; 89 (2015) 401.
2. C H Tseng, et al, *Eur J Med Chem*; 59 (2013) 274.

Indole Directed C-H Activation: Direct Synthesis of Functionalized Carbazoles from Indoles via Triple C-H Activation

Akhilesh Verma

Department School of Physical Sciences (SPS), Jawaharlal Nehru University, Delhi-119967, India, New Delhi, India

Synthesis of small heterocyclic molecules in terms of selectivity, operational simplicity, functional group tolerance and environmental sustainability are in constant demand as majority of drugs; drug-like compounds contain hetero atom at their core. Since the discovery of the first intermolecular alkenylation (discovery of first C-H activation) by Fujiwara and Moritani in 1967.¹ Literature revealed that second successive alkenylation on alkene obtained by the first oxidative Heck is still unknown. In continuation of our ongoing work on the coupling reactions using in-house developed ligands² in this presentation I would like to discuss about our recent success on the synthesis of highly functionalized carbazoles from NH-indoles via palladium-catalyzed triple successive C-H activation.



1. (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *12*, 1119. (b) Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Lett.* **1968**, *5*, 633

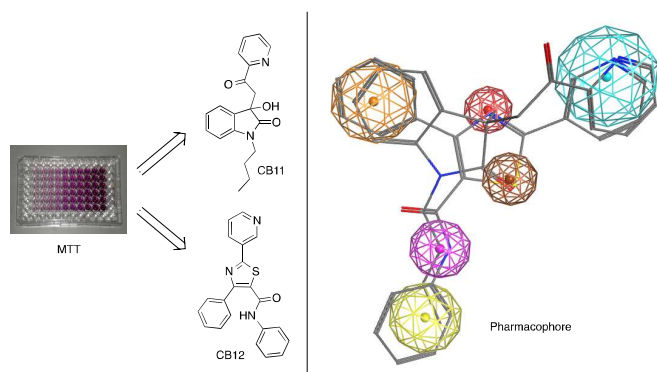
2. (a) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 1138. (b) Verma, A. K.; Jha, R. R.; Chaudhary, R.; Tiwari, R. K.; Reddy, K.S.K.; Danodia, A. *J. Org. Chem.* **2012**, *77*, 8191. (c) Verma, A. K.; Joshi, M.; Singh, V. P. *Org. Lett.* **2011**, *13*, 1630. (d) Joshi, M.; Patel, M.; Tiwari, R.; Verma, A. K. *J. Org. Chem.* **2012**, *77*, 5633. (e) Verma A. K.; Jha, R. R.; Chaudhary, R.; Tiwari R. K.; and Danodia, A. *Adv. Syn. Cat.* **2013**, *355*, 421-436. (f) Verma A. K.; Patel M.; Joshi M.; Likhar P. r.; Tiwari R. K.; Parang K. *J. Org. Chem.* **2014**, *78*, 6657-6669

Small Molecules for Treatment of Retinal Degenerative Diseases

Christopher Lindsey^{1,2}, Craig Beeson^{1,2}, Baerbel Rohrer^{1,2}, Yuri Peterson², Nathan Perron², Cecile Nasarre², Mausumi Bandyopadhyay², Richard Comer¹, Kimberly Casalvieri¹

¹MitoChem Therapeutics Inc., Charleston, SC, USA, ²Medical University of South Carolina, Charleston, SC, USA

Retinitis Pigmentosa (RP) is a family of progressive retinal degenerative diseases that effects small populations. The diseases are associated with many different genes hindering drug development – there are currently no treatments. We have hypothesized that metabolic stress is downstream to many of the gene mutations. Recently, a high throughput screen (HTS) was developed under conditions that mimic RP.¹ Hits from this primary screen were then subjected to a second assay that measures mitochondrial flux capacity, addressing the oxidative stress component affiliated with this neurodegenerative process. Two of these hits, CB11 and CB12, come together to form a pharmacophore from which novel chemical entities were synthesized. From these efforts, a small panel of analogs were developed and tested as a means to optimize protection of mitochondria from metabolic stress. Achieving cellular protection via the cell's "power house" offers a novel approach towards treating this disease and the potential for addressing other pathologies where mitochondria are part of the degenerative process.



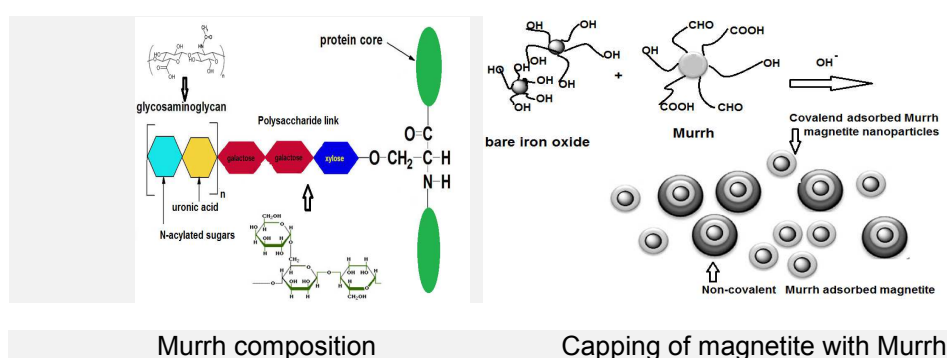
1) Beeson, Craig Cano; Rohrer, Baerbel; Perron, Nathan R. Compositions and methods for the treatment of degenerative diseases PCT Int. Appl. (2011), WO 2011119869 A1 20110929

Production of Antimicrobial Silver and Magnetite nanoparticles Using Natural Products based on Rosin And Murrh Gums^[1]

hamad al-lohedan

king saud university, riyadh, Saudi Arabia

In the present study, new silver and magnetic nanoparticles were prepared using modified cationic, nonionic surfactants and amino-amidoximes based on rosin as natural products^[2, 3]. The produced modified rosin surfactants and amino-amidoximes were used as capping agents for magnetite nanoparticles to prepare hydrophobic coated magnetic powders^[4-6]. Water soluble carbohydrates produced from Murrh natural gum were used to produce capped magnetite and silver nanoparticles as natural gums. A new class of monodisperse amphiphilic magnetite and silver nanoparticles were prepared by a simple and inexpensive green method.



The structure and morphology of magnetite and silver capped with modified rosin and Murrh gums were characterized by Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), transmission electron microscopy (TEM), zeta potential, thermogravimetric analysis (TGA) and dynamic light scattering (DLS). The magnetic properties were determined from vibrating sample magnetometer (VSM) analyses. These prepared silver and magnetite nanoparticles were tested as bioactive nanosystems and their antimicrobial effects were investigated.

¹ under preparation; ²A. M. Atta, H. A. Al-Lohedan, S. A. Al-Hussain, *Int. J. Mol. Sci.* **2015**, *16*(4), 6911-693; ³A. M. Atta, H. A. Al-Lohedan, S. A. Al-Hussain, *Molecules* **2014**, *19*(8), 11263-1127; ⁴A. M. Atta, G. A. El-Mahdy, H. A. Al-Lohedan, S. A. Al-Hussain, *Int. J. Mol. Sci.* **2014**, *15*(4), 6974-6989⁵G. A. El-Mahdy, A. M. Atta, H. A. Al-Lohedan, *J. Taiw. Instit. Chem. Eng.*, **2014**, *45*, 1947-1953; ⁶M. Ali, H. A. Al-Lohedan, A. M. Atta, A. O. Ezzat, S. A. Al-Hussain, *J. Mol.*, **2015**, *204*, 248-254.

The title A novel [3+2] cycloaddition reaction of allenolate and isoquinoline

Xueshun Jia, Zhiqiang Liu, Jian Li

Shanghai University, Shanghai, China

Allenolate has received significant interests in organic synthesis due to its facile preparation and versatile reactivity.¹ For instance, the nucleophilic addition and electrophilic addition reactions with a wide range of substances as well as rearrangements have been well documented. In particular, they were proven to be valuable building blocks in many types of cycloaddition reactions.² In this field, phosphine-catalyzed cycloaddition reaction is of great interest due to simple reagent and structural diversity of the adduct.

In 2011, we have reported a [2+2+1] cycloaddition involving allenolate by using isocyanide as nucleophile instead of phosphine.³ In such case, the allenolate and electron-deficient carbonyl-containing isatin in the presence of isocyanide gave a quick access to spirooxindole. As a continuation of our ongoing research, Herein we wish to report that the blending of isoquinoline and allenolate can give a quick access to polycyclic skeletons, which involves an unusual [3+2] cycloaddition.

Notably, flexibility of this method allows the rapid synthesis of polycyclic framework with high efficiency. The mechanistic proposal indicates that proton transfer take place to induce the unusual [3+2] cycloaddition in the presence of nitrogen-containing base. This method is also distinguished by its convenient experimental set-up and excellent atom-economy. As a result, the present protocol has potential to be applied in medicinal and synthetic chemistry.

Reference:

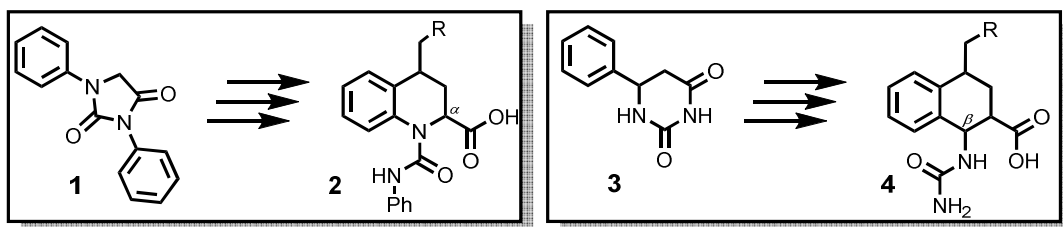
1. For reviews, see: (a) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590-3593. (b) López, F.; Mascareñas, J. L. *Chem. Soc. Rev.* **2014**, *43*, 2904-2915.
2. (a) Danis, J.-B.; Masson, G.; Retailleau, P.; Zhu, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5356-5360. Clavier, H.; Jeune, K. L.; de Riggi, I.; Tenaglia, A.; Buono, G. *Org. Lett.* **2011**, *13*, 308-311.
3. Li, J.; Liu, Y. J.; Li, C. J.; Jia, X. S. *Chem. Eur. J.* **2011**, *17*, 7409-7413.

DESIGN OF A FREE RADICALS PROCESS, BASED ON XANTHATES CHEMISTRY, TO PRODUCE NEW SYNTHETIC AND OPTICALLY ACTIVE (α and β) AMINO ACIDS

Luis Germán López-Valdez, Holber Zuleta-Prada, Benito Reyes-Trejo, Diana Guerra-Ramirez

Universidad Autónoma Chapingo, Texcoco, Estado de México, Mexico

The synthesis of β -amino acids optically active, is still a challenge in organic synthesis. In recent years, has been reported a series of different mechanisms of synthesis to obtain β -amino acids and derivatives efficiently. Nevertheless, few of them are based on using chemo-enzymatic process. Indeed, several methodologies have been developed to produce α and β amino acids optically active, among them are: kinetic resolutions with synthetic catalyst, biocatalytic process to isomerize α to β amino acids. Here in, we report a methodology to produce α and β amino acids, though reactions of allylation, radical addition cyclization-oxidation and the possible enzymatic hydrolysis using hydantoinases from legume. We used the Hydantione **1** and Dihydrouracil **3**, which after allylation, in the ($-\text{CH}_2-$) α -carbonyl position, followed by a radical cascade addition cyclization-oxidation, and submitted to enzymatic conditions, to obtain the hydrolysed products α and β amino acids precursors **2** and **4**, (Scheme. 1).



R= $\text{CH}_2\text{C}(\text{O})\text{OEt}$ or CH_2CN

Scheme 1. General scheme of the methodology

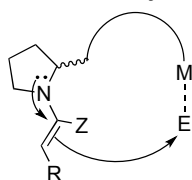
Merging Enamine Catalysis with Hard Metal Lewis Acid Catalysis for Asymmetric Organic Transformations

Hong Wang¹, Zhenghu Xu², Yongming Deng¹, Philius Daka¹

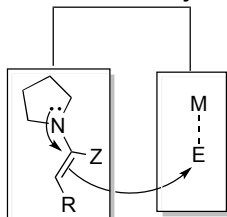
¹Miami University, Oxford, Ohio, USA, ²Shandong University, Jinan, China

The combination of organocatalysis with metal catalysis is an emerging field, aiming to achieve organic transformations that cannot be achieved through organocatalysis or metal catalysis alone. My research group has been engaged in developing new asymmetric reactions through combining enamine catalysis with hard metal Lewis acid catalysis. The biggest challenge in combining enamine catalysis with hard metal Lewis acid catalysis is the acid-base quenching reaction leading to catalyst inactivation. In this talk, I will present two strategies developed in our laboratory to synergistically incorporate enamine catalysis with hard metal Lewis acid catalysis. The first strategy is to use competition coordination to solve the critical acid-base quenching problem; the second strategy is to use the inversion of soft/hard approach to solve the acid-base quenching problem. Using these two strategies, we have developed a number of new asymmetric reactions including inverse-electron-demand asymmetric oxo-Diels-Alder reaction of ketones and multicomponent aza-Diels-Alder reaction of ketones.

Bifunctional enamine/metal Lewis acid catalysis



Synergistic enamine/metal Lewis acid catalysis

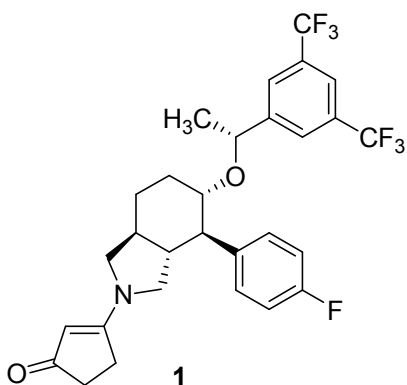


Synthesis of a Highly Functionalized Octahydro-Isoindole-Based NK1 Receptor Antagonist

Jeff Kuethe

Merck & Co., Inc., Rahway, New Jersey, United States Minor Outlying Islands

Primarily associated with sensory neurons and located within specific areas of the central nervous system (CNS), neurokinin-1 (NK-1) is a member of the seven-transmembrane G-protein-coupled receptor family. The tachykinin peptide Substance P is the natural ligand for NK-1 and has been implicated in the pathophysiology of a wide range of diseases including anxiety, asthma, cystitis, emesis, inflammatory bowel disease, migraine, movement disorders, pain, and psoriasis. Merck has identified an octahydro-isoindole-based compound **1** which has significant binding affinity (sub-nanomolar) for the hNK-1 receptor. Compound **1** contains five stereocenters: a central core possessing four contiguous all-*trans* stereocenters, a pendent bis(trifluoromethyl)benzylic ether, and a cyclopentenone moiety. In order to fully evaluate this compound, an efficient and practical synthesis was required which would allow for the preparation of multi-kilogram quantities to support both pre-clinical and clinical development. Key to the success of the preparation of **1** was control of the relative and absolute stereochemistry. This presentation will address the evolution of a highly efficient asymmetric synthesis of **1**.

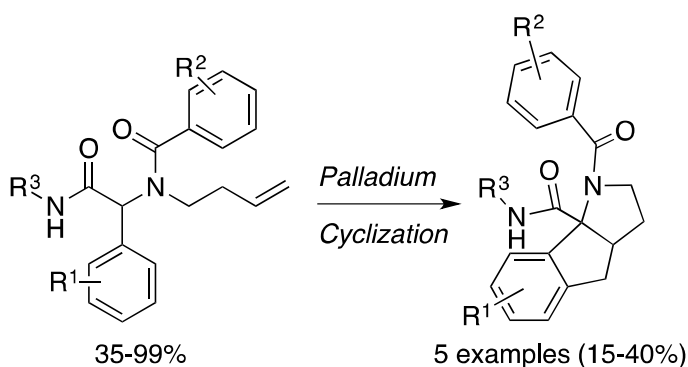


Sequential Ugi/Palladium-Catalyzed Aerobic Oxidative Cyclization: novel TetrahydroIndeno[1,2-b]Pyrrolidines Synthesis.

Tannya R. Ibarra-Rivera¹, Ma. Rocio Gamez-Montano², Eugenio Hernandez-Fernandez¹, Veronica M. Rivas-Galindo¹, Manuel A. Renteria-Gomez², Orlando Escalon Campos¹, Noemi Herminia Waksman de Torres¹

¹Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, Mexico, ²Universidad de Guanajuato, Guanajuato, Guanajuato, Mexico

The general strategy of combining multicomponent reaction with post-condensation reactions has been successfully used to prepare a wide variety of drug-like heterocycles. This communication discloses a novel synthesis of TetrahydroIndeno[1,2-b]Pyrrolidines by a two step Ugi multicomponent reaction/Palladium oxidative cyclization sequence. As usual Ugi adducts were obtained in good to high yields and palladium oxidative conditions afforded the cyclized products in moderate yield. Five new TetrahydroIndeno[1,2-b]Pyrrolidines were synthesized using two powerful reactions in which 6 new chemical bonds were formed.



R¹= H, *p*-Cl, *p*-NO₂
R²= *o*-NO₂, *p*-NO₂, *o*-F
R³= *tert*-Butyl, Cyclohexyl

Structure-Activity Relationship of Matrine Type Alkaloids Part 24; Synthesis and Antinociception of 3-Arylpiperidine Derivatives.

Hiroyoshi Teramoto, Jun-ichi Koizumi, Toshiyuki Shimekake, Hiroataka Minomata, Shigeru Sasaki, Takayasu Yamauchi, Kimio Higashiyama

Hoshi university, Shinagawa-ku, Tokyo-to, Japan

We previously reported that (+)-matrine (**1**) and (+)-allomatrine (**2**), a typical matrine type lupine alkaloid isolated from some *Sophora* plants (Leguminosae), has the antinociceptive properties identical to those of pentazocine. The effects of **1** are mediated mainly through activation of μ -opioid receptors and partially through κ -opioid receptors, and these of **2** are mediated only through activation μ -opioid receptors. Because the skeleton of matrine type alkaloid differ from those of conventional μ -opioid receptor agonists, the structure-activity relationship of this antinociceptive effects are very interesting.

4-Dimethylamino-1-pentanoylpiperidine (**3**) was determined as a lead compound by identifying

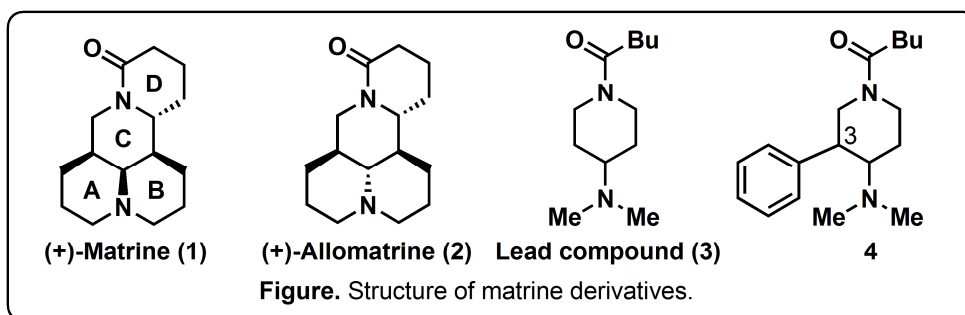


Figure. Structure of matrine derivatives.

we synthesized some derivatives of lead compound **3** and evaluated for these antinociceptive effects. This research gave important information that compound **4**, which had phenyl group on 3 position of piperidine ring, exert high antinociceptive effects compared to **3**. Taking this result, we attempted to synthesize the derivatives converted phenyl moiety of **4** and evaluate for these antinociception to find higher active compound. As a result, several derivatives of **4** having high antinociceptive effects were revealed.

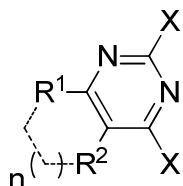
the
partial
struct
ure of
1 for
expre
ssing
the
effect
s.
Then

Can Ketones Be Productive Dienophiles For IEDDA Reactions?

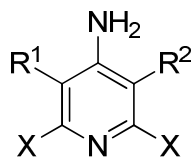
Kai Yang, Qun Dang, Xu Bai

Jilin University, Changchun, Jilin, China

The development of the inverse electron demand Diels-Alder (IEDDA) reactions of 1,3,5-triazines has led to the total syntheses of a series of pyrimidine-containing natural products and the preparation of highly functionalized pyrimidine heterocycles.¹ The dienophiles of these IEDDA reactions have been limited to electron-rich alkenes and alkynes, such as enamines, ynamines and amidines. Recently, we have discovered that ketones could be employed directly as productive dienophiles in the 1,3,5-triazine IEDDA reactions under conditions, such as using catalytic amount of hydrazine and trifluoroacetic acid. For examples, pyrimidine fused heterocycle **1** and functionalized pyridine-4-amine **2** may be prepared in moderate to excellent yields by applications of the new methods. The details of these investigations will be discussed.



1



2

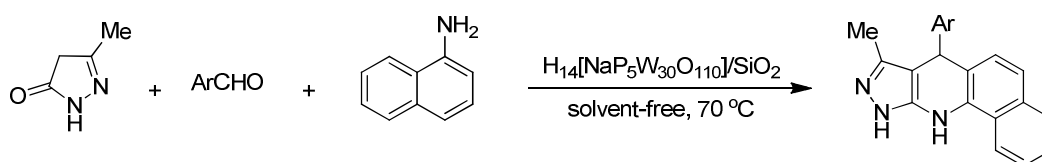
(1) (a) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (b) Foster, R. A. A.; Willis, M. C. *Chem. Soc. Rev.* **2013**, *42*, 63.

A Green and Efficient Protocol for the Synthesis of Novel Pyrazolo[3,4-*b*]quinolines *via* a One-pot, Three-component Reaction Under Solvent-free Conditions

Majid heravi, Behnoosh Alimadai, Niusha Nazari

Alzahra University, Tehran, Iran

Novel pyrazolo[3,4-*b*]quinoline derivatives are synthesized *via* a one-pot, three-component reaction involving 3-methyl-5-pyrazolone, aromatic aldehydes and 1-naphthylamine catalyzed by nano silica-supported Preyssler heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$ under solvent-free conditions at 70 °C. Pure desired compounds are obtained in high to excellent yields over short reaction times with an easy work-up procedure.

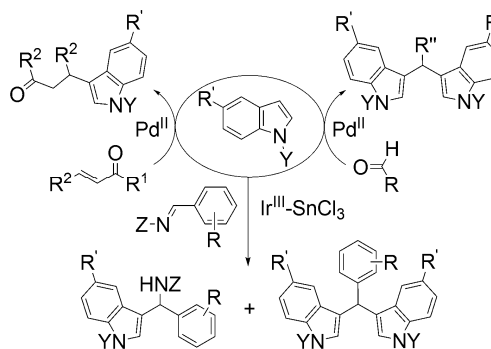


Efficient C-3 Selective Functionalization of Indoles: Mono/Bimetallic Catalysis Approach

Swapna Sarita Mohapatra, Sujit Roy

Organometallics & Catalysis Laboratory, School of Basic Sciences, Indian Institute of Technology, Bhubaneswar, Odisha – 751013, India

Functionalization of indoles has been widely investigated since structural motifs bearing the 'indole core' are frequently found in pharmaceuticals, natural products, and other functional synthetics [1]. In this regard, metal-catalyzed or organocatalytic routes have assumed distinct significance. Within the broader realm of multimetallic catalysis, we have been working into transition metal/tin based motif and delivered a number of selective, atom-economic and bench-friendly strategies [2]. In the present work, we report the functionalization of indoles using bimetallic Ir^{III}-SnCl₃ and monometallic Pd^{II} catalyst. The bimetallic catalyst [Ir(COD)(SnCl₃)Cl(μ-Cl)]₂ promoted the reaction of electron-rich indoles with aldimines giving rise to functionalized amines and triheteroarylmethanes [2]. On the other hand, facile C-3 alkylation of indoles with electrophiles like carbonyls and enones was achieved using the monometallic catalyst [PdCl₂(MeCN)₂]. The major advantage of such a reaction is that it does not require any co-catalyst, acid, base, additive, or external ligand and is totally insensitive to air and moisture.



Reference:

1. Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.*, **2009**, *48*, 9608.
2. Das, D.; Mohapatra, S. S.; Roy, S. *Chem. Soc. Rev.* **2015** (ASAP article).
3. Chatterjee, P. N.; Maity, A. K.; Mohapatra, S. S.; Roy, S. *Tetrahedron.* **2013**, *69*, 2816.

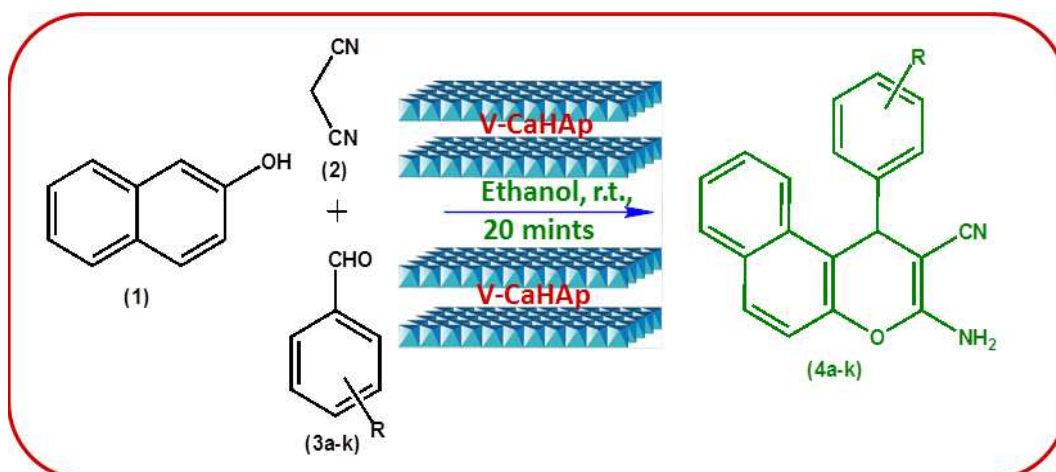
V-CaHAp as a recyclable catalyst for the green multicomponent synthesis of benzochromenes

MADDILA SURESH, MADDILA SURYANARAYANA, JONNALAGADDA SREEKANTH BABU

SCHOOL OF CHEMISTRY & PHYSICS, UNIVERSITY OF KWAZULU NATAL, WESTVILLE CAMPUS, DURBAN, KWAZULU NATAL, South Africa

A simple, efficient one-pot synthesis has been developed for the synthesis of benzochromenes (4a-k) using V-CaHAp as a heterogeneous catalyst by the condensation of aldehydes, β -naphthol and malononitrile in ethanol as solvent at R.T. for 20 mints. The reaction, with these catalysts was carried out under mild reaction conditions with very good to excellent yields (89-98%). The catalyst material can be recycled very easily and reused at least for 6 runs devoid of substantial loss in activity, which makes this methodology environmentally benign. We achieve that the cost-effective, minimal catalyst, non-toxic materials, easy handling and feasibility.

Keywords: Green synthesis, V-CaHAp catalyst, One-pot reaction, Recyclability, Benzochromenes.

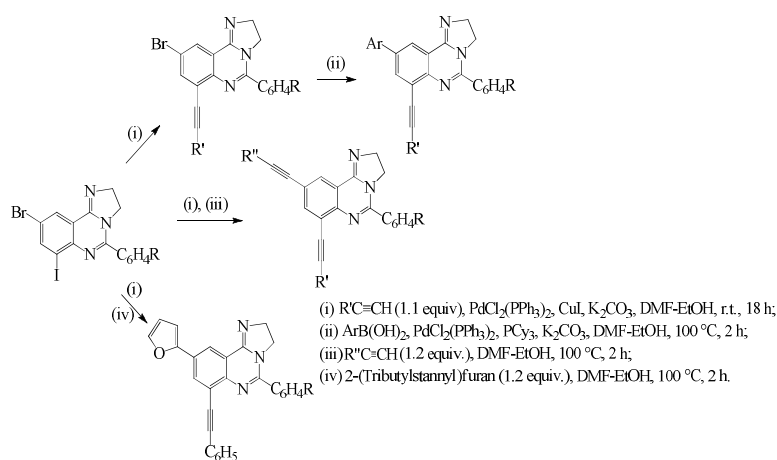


One-pot two-step cross-coupling approach towards the synthesis of novel unsymmetrical polycarbo-substituted imidazo[1,2-c]quinazolines

Malose Mphahlele, Tebogo Khoza

Unisa, Pretoria, South Africa

We are currently interested in the synthesis of polycarbo-substituted imidazo[1,2-c]quinazolines because compounds bearing this heterocyclic moiety exhibit a wide range of biological and photophysical properties. These compounds are accessible via the condensation of 4-chloroquinazolines with aminoalkanols or imidazole derivatives with aromatic aldehyde. Despite their efficiency, these methods cannot be adapted for the synthesis of imidazo[1,2-c]quinazolines bearing carbon-based substituents on the fused benzo ring. Herein we describe the results of sequential (Sonogashira/ Suzuki-Miyaura) and one-pot two-step (bis-Sonogashira; Sonogashira/ Stille) cross-coupling of the 5-aryl-9-bromo-7-iodo-2,3-dihydroimidazo[1,2-c]quinazolines to afford novel unsymmetrical polycarbo-substituted derivatives.



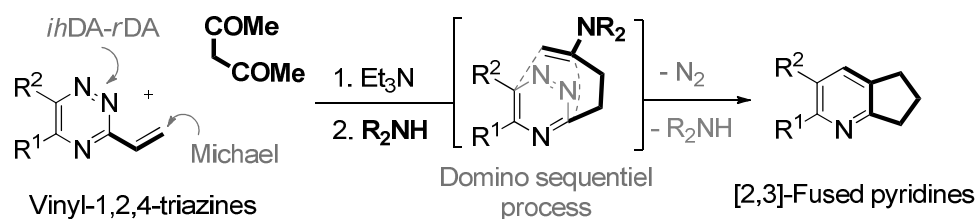
Sequential Michael Addition and Enamine-Promoted Inverse Electron Demanding Diels-Alder Reaction upon 3-Vinyl-1,2,4-Triazine Platforms

Magali Lorion¹, Gérald Guillaumet¹, Jean-François Brière², Franck Suzenet¹

¹University of Orléans, ICOA, UMR CNRS 7311, 45067 Orléans, France, ²Université de Normandie/INSA Rouen, COBRA UMR CNRS 6014, 76821 Mont Saint Aignan, France

1,2,4-Triazine derivatives belong to an important class of heterocycles encompassing applications in medicine and agrochemistry, but also as useful building blocks in organic synthesis.¹ The π -electron-deficient triazine, flanked by a suitable leaving group, is well known to undergo aromatic nucleophilic substitution (S_NAr) reactions to give functionalized products. Furthermore, these heterocyclic platform are capable to undergo domino inverse-electron-demand hetero-Diels-Alder (*ihDA*)/retro-Diels-Alder (*rDA*) reactions with various dienophiles that allow for a straightforward access to substituted pyridine derivatives, which are ubiquitous derivatives in pharmaceutical ingredients.²

In this project, we aim to study a new reactivity of 1,2,4-triazines as Michael acceptor and capitalize on a subsequent intramolecular cycloaddition reaction. Thus, an original one-pot Michael addition-*ihDA*/*rDA* sequence was achieved from 3-vinyl-1,2,4-triazine platforms. This sequence provides a novel access to functionalized [2,3]-fused pyridine derivatives *via* a unique enamine promoted intramolecular *ihDA* reaction of 1,2,4-triazine intermediates to access saturated-unsaturated heterocycles.



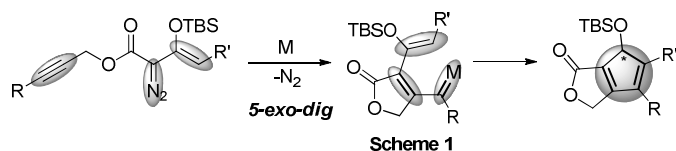
(1) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 6, p 507. (b) Lindsley, C. W.; Layton, M. E. In *Science of Synthesis*; Weinreb, S. M., Eds.; Thieme: Stuttgart, 2003; Vol. 17, p 357. (2) (a) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (b) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (d) Raw, S.A.; Taylor, R. J. K. In *Advances in Heterocyclic Chemistry*; 2010, 100, 76. (c) Fosterand, R. A. A.; Willis, M. C. *Chem. Soc. Rev.* **2013**, *42*, 63.

A Straightforward Access to the Chiral Cyclopentadienes via Intramolecular Metal Carbene/Carbenoid Cascade Transformations

Xinfang Xu

Soochow University, Suzhou, Jiangsu, China

Intramolecular metal carbene cascade reactions are effective and convenient access to construct functionalized cyclic frameworks. In this context, pioneering work was reported by Padwa,¹ and multi-substituted furane derivatives synthesis is the focus via the carbonyl ylide intermediate at that age.² Meanwhile, detailed mechanism study was carried out by Hoyer and co-workers.³ Recently, this strategy has been applied to the synthesis of various cyclic frameworks via ending with two kinds of traditional metal carbene reactions:⁴ X-H insertion⁵ and cyclopropanation.⁶ Moreover, Doyle and co-workers have found that cycloaddition reactions could occur with cyclopropene intermediate in the presence of a compatible metal catalyst.⁷ Inspired by these works, we designed a intramolecular metal carbene cascade reactions, which is initiated from a metal carbene species generated from the corresponding diazo group, and terminated with an electronic rich alkenyl unite to form a cyclopentadiene derivatives with high to excellent enantioselectivity and high yields via cyclopropene intermediate (Scheme 1). To our best knowledge, although there are types of catalytic asymmetric metal carbene reactions disclosed, there is no asymmetric version reported in the metal carbene cascade reactions.



Reference:

1. Padwa, A.; Kennedy, G. D. *J. Org. Chem.* 1984, 49, 4344-4352.
2. Padwa, A.; Dean, D. C.; Fairfax, D. J.; Xu, S. L. *J. Org. Chem.* 1993, 58, 4646-4655.
3. Hoyer, T. R.; Dinsmore, C. J. *J. Am. Chem. Soc.* 1991, 113, 4343-4345.
4. Archambeau, A.; Miege, F.; Meyer, C.; Cossy, J. *Acc. Chem. Res.* 2015, 48, 1021-1031.
5. Jansone-Popova, S.; May, J. A. *J. Am. Chem. Soc.* 2012, 134, 17877-17880.
6. Miege, F.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* 2011, 50, 5932-5937.
7. Xu, X.; Zavalij, P. Y.; Doyle, M. P. *J. Am. Chem. Soc.* 2013, 135, 12439-12447.

Synthesis of functionalized indoles under continuous flow conditions

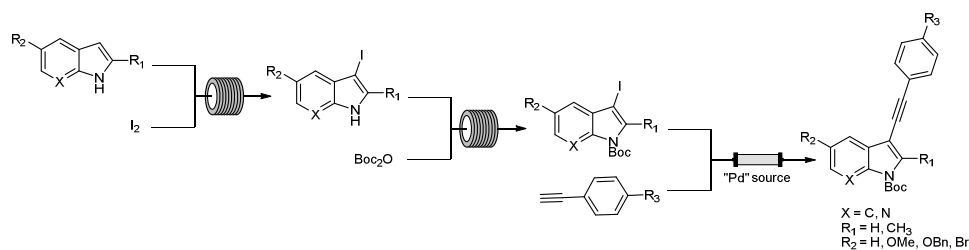
Frédéric Buron¹, Joseph D'Attoma¹, Grégoire Cozien¹, Stéphane Bostyn², Sylvain Routier¹

¹Institut de Chimie Organique et Analytique (ICOA), Université d'Orléans, UMR CNRS 7311, Orléans, France, ²Institut de Combustion, Aérodynamique, Réactivité, et Environnement, Orléans, France

Indole is an aromatic heterocycle present in many structures of natural alkaloids and in a multitude of biologically and pharmacologically active compounds.^a For example, it is found as the structural scaffold of signaling mediators or hormones such as melatonin.^b Given the interest generated by this heterocyclic compound, it is not surprising that fast and efficient access to these derivatives remains of interest to the chemical community.

To functionalize indole and its derivatives, we were interested in the development of an innovative technology in organic chemistry, continuous flow synthesis. This eco-efficient system offers a variety of advantages like faster and cleaner reactions with less solvent^c as well as the possible manipulation of short-lived and highly reactive species. Benefits also include diminished chemical exposure and easy scale-up to furnish larger amounts of product necessary for *in-vivo* studies.

The aim of this project is to transfer usual reactions of indole chemistry to continuous flow process. Thus, this communication will present this transposition for C-3 iodination and NH protection with BOC group. Moreover, we investigated an original copper-free Sonogashira reaction in C-3 position using supported Pd catalyst.



Bibliographic references:

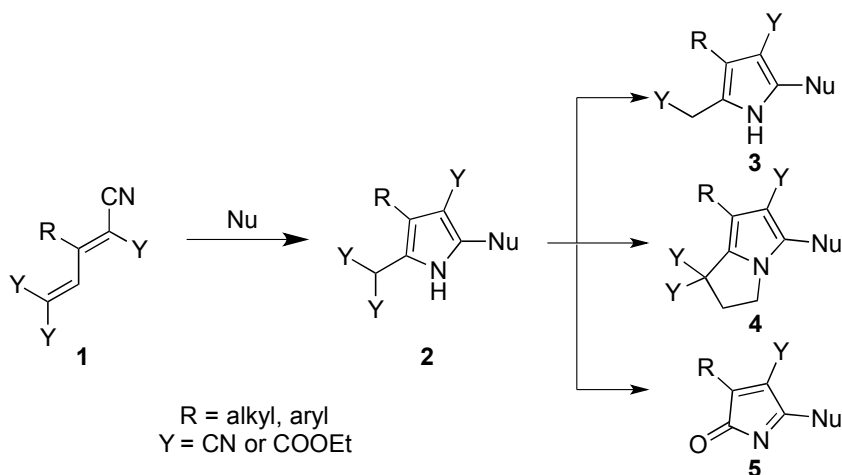
a) D.F. Taber, P.K. Tirunahari. *Tetrahedron* **2011**, *67*, 7195. b) E. Merkul, F. Klukas, D. Dorsch, U. Grädler, H.E. Greinerb and T.J.J. Müller. *Org. Biomol. Chem.* **2011**, *9*, 5129-5136. c) B.P. Mason, K.E. Price, J.L. Steinbacher, A.R. Bogdan and D.T. McQuade. *Chem. Rev.* **2007**, *107*, 2300-2318.

The simple and versatile synthesis of tetrasubstituted pyrroles and subsequent functionalization

Tristan Reekie^{1,2}, Giorgio Manenti², François Diederich²

¹University of Sydney, Sydney, Australia, ²ETH Zurich, Zurich, Switzerland

The cycloaddition–retroelectrocyclization reaction is a useful reaction for the conversion of electron-rich alkynes and electron-poor alkenes into buta-1,3-dienes.¹ We have recently shown that this reaction is more widely applicable to ester-substituted alkenes to afford compounds of type **1**.² In this presentation we will describe how compounds of type **1** can be efficiently and rapidly converted into highly substituted pyrroles **2**. Further one-step functionalization allows isolation of substituted pyrroles of type **3** and **4** and 2*H*-pyrrol-2-ones **5**, the latter of which exhibit strong chromophoric behaviour and a bathochromic shift upon protonation.



1. T. Michinobu, J. C. May, J. H. Lim, C. Boudon, J.-P. Gisselbrecht, P. Seiler, M. Gross, I. Biaggio, F. Diederich, *Chem. Commun.* **2005**, 737–739.

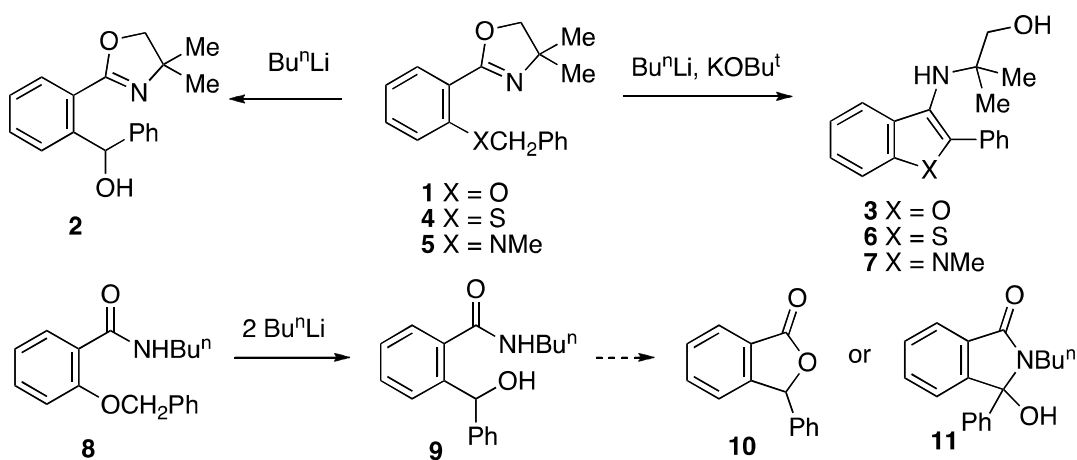
2. T. A. Reekie, E. J. Donckele, L. Ruhlmann, C. Boudon, N. Trapp, F. Diederich, manuscript submitted.

A new synthesis of heterocycles from *o*-substituted aryl benzyl ethers

R. Alan Aitken, Andrew D. Harper

EaStCHEM School of Chemistry, University of St Andrews, St Andrews, Fife, UK

The [1,2]-Wittig rearrangement has not been widely exploited synthetically. Treatment of the oxazoline-containing benzyl ether **1** with Bu^nLi does give the rearrangement product **2** in low yield. However simply adding KOBU^t to the reaction mixture changes the outcome completely and gives a high yield of 3-aminobenzofuran **3**. This method has been extended to the benzyl sulfide **4** and amine **5** which give respectively the 3-aminobenzothiophene **6** and indole **7**.



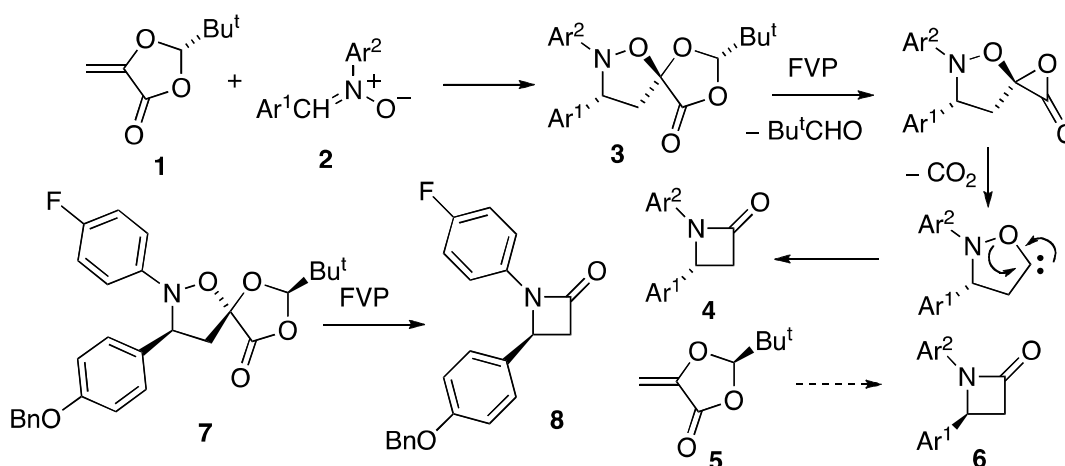
By moving to the secondary amide **8**, [1,2]-Wittig rearrangement is achieved in high yield with Bu^nLi , and the initial product **9** is readily converted into either the phthalide **10** or the hydroxyisoindolone **11**.

Asymmetric synthesis of β -lactams by gas phase pyrolysis

R. Alan Aitken, Anna Meehan, Lynn A. Power, Léa Ward

EaStCHEM School of Chemistry, University of St Andrews, St Andrews, Fife, UK

The chiral methylenedioxyloxanone **1** is readily available from (*S*)-lactic acid but it has not been used as a dipolarophile for 1,3-dipolar cycloaddition before. Diarylnitrones **2** add stereoselectively to give spiro adducts **3**, and when these are subjected to flash vacuum pyrolysis at 440 °C, they eliminate Bu^tCHO and CO_2 as shown to give β -lactams **4** via an oxacarbene rearrangement.



The enantiomeric methylenedioxyloxanone **5**, conveniently available from (*R*)-alanine,¹ gives products **6** of the opposite enantiomeric series. Synthesis and FVP of the example **7** affords the advanced Ezetimibe precursor **8**, thus completing a formal total synthesis of this important cholesterol-lowering drug.

1 Aitken, R. A.; Meehan, A.; Power, L. A. *Synthesis* **2015**, 47, 1557–1559.

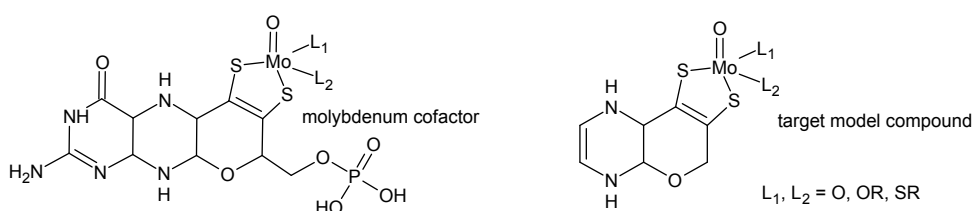
Synthesis of pyrazine-pyrane-dithiolene complexes mimicing specific features of the molybdenum cofactor (MoCo)

Claudia Schindler, Carola Schulzke

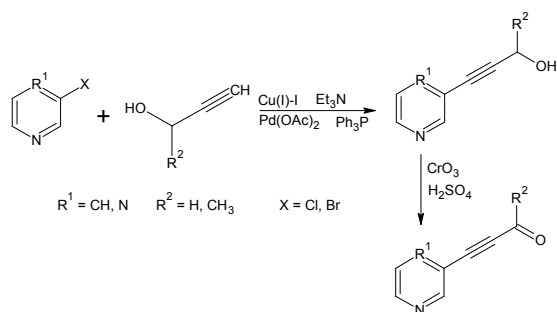
Institut für Biochemie, Universität Greifswald, Greifswald, Germany

Molybdopterin (MPT) dependent enzymes are part of nearly any known organism on earth ranging from ancient archaea over plants to modern human beings.

The aim of the project is the synthesis of model compounds for the molybdopterin depending cofactor, which are able to catalyse oxygen atom transfer reactions and which can be incorporated into the apoenzyme. The focus of our research are the development of ligand precursors addressing the dithiolene function, the pyrane ring and the adjacent pyrazine ring and their coordination with molybdenum to understand the influence of various structural units on the stability, the catalytic properties or the redox potential.



N-heterocyclic substituted alkynes serve as intermediates in reaction series for such model compounds. None of the investigated compounds was stable for long. Because of their substantial reactivity and their N-heterocyclic functions they do have great potential for synthetic developments in different fields of research.



References

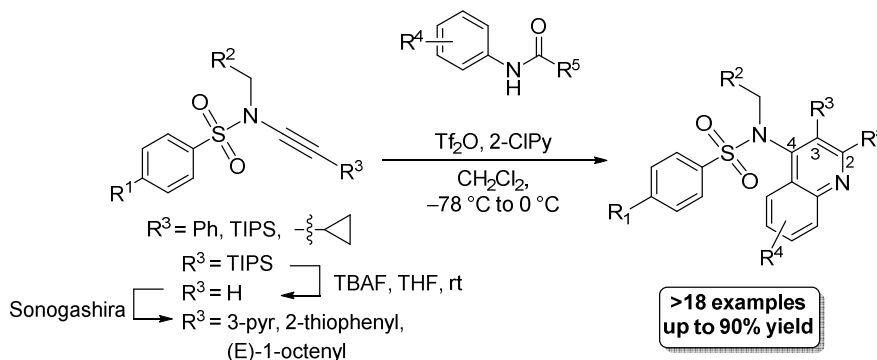
1. Ben Bradshaw, Andrew Dinsmore, David Collison, C. David Garner, John A. Joule, J. Chem. Soc., Perkin Trans. 1, 2001, 3232-3238.
2. Edward C. Taylor, Reinhard Dötzer, J. Org. Chem., No. 5, 1991.
3. Ulf Ryde, Carola Schulzke, Kerstin Starke, J. Biol. Inorg. Chem., 2009, 1053-1064.

Synthesis of Highly Functionalized 4-Aminoquinolines

Tim Wezeman, Sabilla Zhong, Stefan Bräse

Institute of Organic Chemistry, Karlsruhe Institute of Technology, Karlsruhe, Germany

A method for the synthesis of highly functionalized 4-aminoquinolines from sulphynamides and amides is presented. The amides are activated by triflic anhydride (Tf₂O) and 2-chloropyridine (2-ClPy) and, as Movassaghi *et al.* have shown, can be used to prepare a wide range of heterocyclic structures.^[1] Sulphynamides can be prepared using copper catalysis and alkyl bromides^[2] and further derivatized by using Sonogashira chemistry.^[3] The main challenge in existing quinoline syntheses is the functionalization at the C-2 and C-3 positions. By combining the Sonogashira approach with the ynamide/amide methodology a wide range of substitutions at C-3 is possible and the C-2 and C-5 to C-8 positions are also accessible. In order to show the broad applicability of the methodology, it was found that the ynamides also readily react with paracyclophane-based amides, creating very interesting planar chiral compounds.



[1] a) M. Movassaghi, M. D. Hill, O. K. Ahmad, *JACS* **2007**, *129*, 10096-10097; b) M. Movassaghi, M. D. Hill, *Org. Lett.* **2008**, *10*, 3485-3488; c) M. Movassaghi, M. D. Hill, *JACS* **2006**, *128*, 14254-14255; d) M. Radi, S. Schenone, M. Botta, *Org. Biomol. Chem.* **2009**, *7*, 2841-2847.

[2] Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett.* **2004**, *6*, 1151-1154

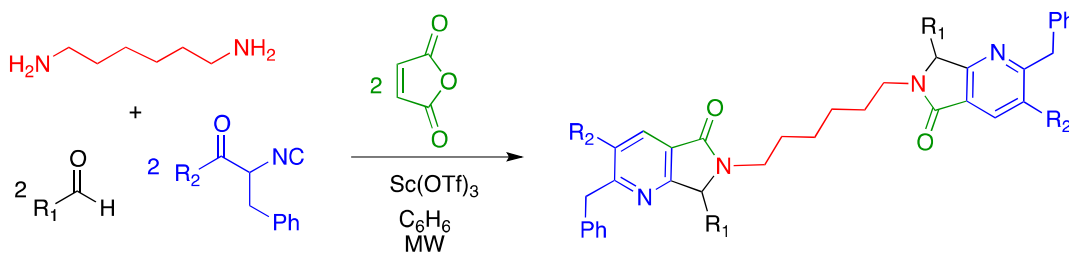
[3] M. R. Tracey, Y. Zhang, M. O. Frederick, J. A. Mulder, R. P. Hsung, *Org. Lett.* **2004**, *6*, 2209-2212.

One-pot Synthesis of cyclic analogues of hexamethylenebis(3-pyridine)amide (HMBPA)

Eduardo González-Zamora, Angel Zamudio-Medina, Ma. Carmen García-González, Atilano Gutierrez-Carrillo

Universidad Autónoma Metropolitana, México, D.F., Mexico

A series of cyclic analogues of hexamethylenebis(3-pyridine)amide was prepared based upon a Ugi-3CR and aza-Diels-Alder reaction as a post-functionalization in a one-pot process. A simple condensations of commercially available diamine and aldehydes followed by isonitrile α -addition provides the oxazoles intermediates, finally an aza-Diels-Alder cycloaddition and ring-opening using maleic anhydride provides the desired compounds in modest overall yield (12 examples, 6-69%) in approximately 40 min using microwaves as the heat source and scandium (III) triflate as a catalyst. The lecture will describe our efforts in achieving the construction of final compounds in a "one-pot" process.

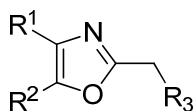


Preparation and Reactions of 2-Functionalized-4, 5-diaryloxazoles: Synthesis of Extended Diaryloxazole Scaffolds

Frederick Luzzio, Pravin Patil

University of Louisville, Louisville, Kentucky, USA

As a heterocyclic class, oxazole derivatives have become increasingly important due to their use as starting points and intermediates for the preparation of new biologically-relevant compounds. 2-(Halomethyl)-4, 5-diaryloxazoles, prepared by cyclization of benzoin haloacetates or free-radical halogenation of 2-methyl-4, 5-diaryloxazoles, are effective, reactive scaffolds which can be utilized for synthetic elaboration at the 2-position. Through substitution reactions, these electrophilic intermediates were used to prepare a number of 2-alkylamino-, 2-alkylthio- and 2-alkoxy(methyl) oxazoles which are valuable synthetic intermediates. Another product of the halomethyloxazole intermediates are the corresponding 2-(hydroxymethyl)-4,5-diaryloxazoles, which in turn on exposure to oxidants such as the Dess-Martin (DM) periodinane, provide efficient



R₁, R₂=Ar, R₃=Heteroatom

access to the corresponding 2-formyl-4,5-diaryloxazoles. When the formyl compounds are reacted with diamines, the Schiff-base products offer a number of unique scaffolds for which to build ligands and other diverse structures. The 2-(methylene) position of the diaryloxazole framework was also found to be amenable to anion formation when conjoined with suitable activating groups. In turn, the 2-(methyl) oxazole anions were found to enable numerous carbon-carbon bond reactions which allows for greatly expanded synthetic latitude. The diverse reactions, utility and potential applications of the title compounds and their products will be presented.

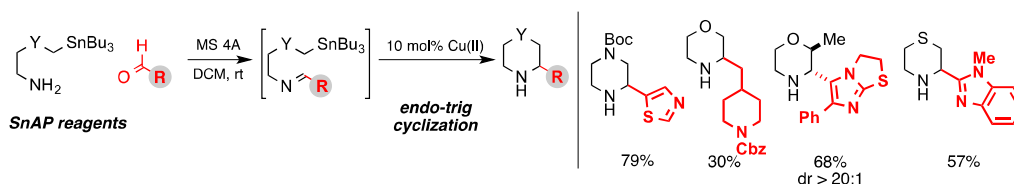
Catalytic One-Step Synthesis of Unprotected Piperazines, Morpholines and Thiomorpholines using SnAP Reagents

Michael U. Luescher, Jeffrey W. Bode

ETH Zurich, Zurich, Switzerland

Saturated N-heterocycles have long been considered as privileged elements for the preparation of bioactive small molecules. Increasing recognition of problems associated with aromatic pharmacophores, such as poor solubility, bioavailability, or pharmacokinetics have further enhanced their importance in drug development.^[1] Despite this, their synthesis often have considerable limitations, including harsh reaction conditions, restricted substrate scope, long synthetic routes, and intractable protecting groups. To directly access a variety of saturated N-heterocycles in a single synthetic operation, we have recently introduced SnAP (Stannyl Amine Protocol) reagents, which convert aldehydes and ketones into (thio)morpholines, piperazines, diazepanes, spiro- and other N-heterocycles.^[2–6]

The major limitation using the SnAP reagents is the need for stoichiometric copper reagents. We have now identified new ligands and conditions that render the reaction catalytic in copper and expanded the substrate scope including α -bis(substituted) SnAP reagents. These studies, including approaches towards an enantioselective process and insights into the unique reaction mechanism, will be discussed.



References:

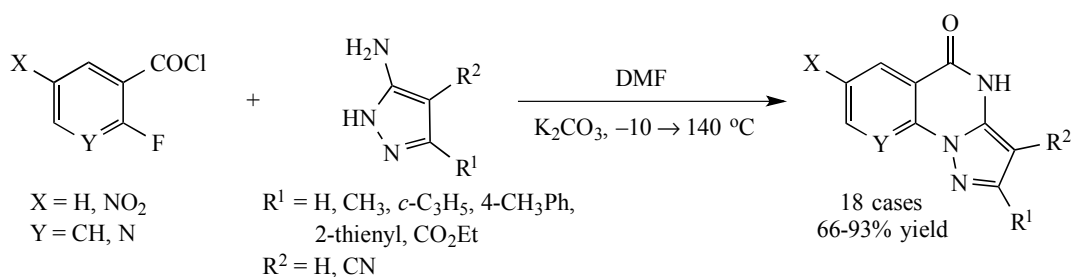
1. N. A. Meanwell, *Chem. Res. Toxicol.* **2011**, *24*, 1420–1456.
2. C.-V. T. Vo, G. Mikutis, J. W. Bode, *Angew. Chem. Int. Ed.* **2013**, *52*, 1705–1708.
3. M. U. Luescher, C.-V. T. Vo, J. W. Bode, *Org. Lett.* **2014**, *16*, 1236–1239.
4. C.-V. T. Vo, M. U. Luescher, J. W. Bode, *Nat. Chem.* **2014**, *6*, 310–314.
5. W.-J. Siau, J. W. Bode, *J. Am. Chem. Soc.* **2015**, *136*, 17726–17729.
6. K. Geoghegan, J. W. Bode, *Org. Lett.* **2015**, *17*, 1934–1937.

Pyrazoloquinazolinones and benzimidazoquinazolinones via a 3 + 3 S_NAr strategy

Richard A. Bunce, Krishna Kumar Gnanasekaran, Nagendra Prasad Muddala

Oklahoma State University, Stillwater, OK, USA

An efficient synthesis of pyrazolo[1,5-*a*]quinazolin-5(4*H*)-ones and pyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidin-5(4*H*)-ones is reported from the reaction of 2-haloaroyl chlorides with 5-amino-1*H*-pyrazoles. A similar preparation of benzo[4,5]imidazo[1,2-*a*]quinazolin-5(6*H*)-ones and benzo[4,5]imidazo[1,2-*a*]pyrido[3,2-*e*]pyrimidin-5(6*H*)-ones results from the reaction of 2-haloaroyl chlorides with 2-aminobenzimidazoles. These syntheses take advantage of the 1,3-disposition of electrophilic centers in the acid chloride and a similar arrangement of nucleophilic sites in 5-amino-1*H*-pyrazole and 2-aminobenzimidazole to form the central six-membered ring by a 3 + 3 strategy. Initial acylation of the amino group of the pyrazole or benzimidazole occurs in DMF containing carbonate base at $-10\text{ }^{\circ}\text{C}$. Subsequent heating, in the same reaction vessel, completes the synthesis via an S_NAr ring closure between N1 of the pyrazole or benzimidazole and the 2-haloarylamide. The reaction gives 66–93% yields for the two-step sequence. These compounds are known to intercalate into DNA, and thus, may be useful as antiproliferative agents for cancer treatment. Mechanistic and spectral aspects of the project will also be presented.

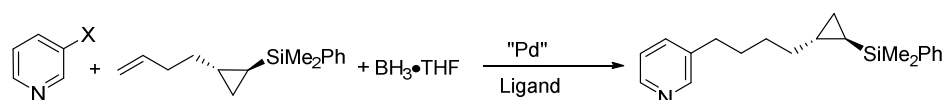


A Concise and Atom-Economical Suzuki-Miyaura Coupling Reaction Using Unactivated Trialkyl- and Triarylboranes with Aryl Halides

Yong-Li Zhong, Hongmei Li, Cheng-yi Chen, Ashley E. Ferraro, Dengjin Wang

Process Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA

A concise and atom-economical Suzuki-Miyaura coupling of trialkyl- and triarylboranes with aryl halides is described.



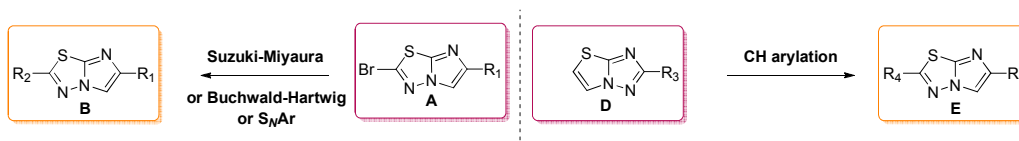
Regioselective functionalizations of thiazolotriazoles and imidazothiadiazoles

Sylvain Routier, Gérald Guillaumet, Frédéric Buron, Chloé Copin, Mikaël Le Meur

Institut de Chimie Organique et Analytique (ICOA), Université d'Orléans, UMR CNRS 7311, Orléans, France

The interest in the [5,5]-fused bicyclic as thiazolotriazoles and imidazothiadiazoles for use in pharmaceutical products makes these scaffolds a highly useful building block for organic chemistry. Such derivatives have found applications in oncology,¹ infectiology² or neurodegenerative diseases.³

However, the synthetic tools for accessing of highly functionalized thiazolotriazoles or imidazothiadiazoles are very limited and only few functionalization methods are described.⁴⁻⁶ In order to access to new families of imidazo[1,2-*b*][1,3,4]thiadiazoles **B** or thiazolo[3,2-*b*][1,2,4]triazoles **D**, there is consequently tremendous interest in developing efficient synthetic methodologies. In order to introduce a wide range of functional groups, a promising solution is to find an efficient alternative to selectively functionalize imidazo[2,1-*b*][1,3,4]thiadiazoles or thiazolo[3,2-*b*][1,2,4]triazoles at the C-2 position. Consequently, we report the efficient functionalization of these scaffolds with various reactions as classical S_NAr or selective palladium-catalyzed reactions like Suzuki-Miyaura and Buchwald-Hartwig cross couplings or CH arylations.^{7,8} These methodologies will have a major impact on the synthesis of new bioactive compounds containing thiazolotriazoles and imidazothiadiazoles as central skeleton.



1) Terzioglu, N. *et al. Eur. J. Med. Chem.* **2003**, *38*, 781-786. 2) Kolavi, G. *et al. Bioorg. Med. Chem.* **2006**, *14*, 3069-3080. 3) Jaquith, J. B. *et al. W02003/051809A1*. 4) Khazi, I. A. M. *et al. Tetrahedron* **2011**, *67*, 3289-3316. 5) Seok, K. *et al. Org. Lett.* **2010**, *12*, 1868-1871. 6) Ferrari, S. *et al. J. Med. Chem.* **2011**, *54*, 211-221. 7) Copin, C. *et al. Eur. J. Org. Chem.* **2012**, 3079-3083. 7) Le Meur, M. *et al. Eur. J. Org. Chem.* **2014**, 3704-3714.

Synthesis of cotinine and iso-cotinine analogs using an Ugi-4CR approach

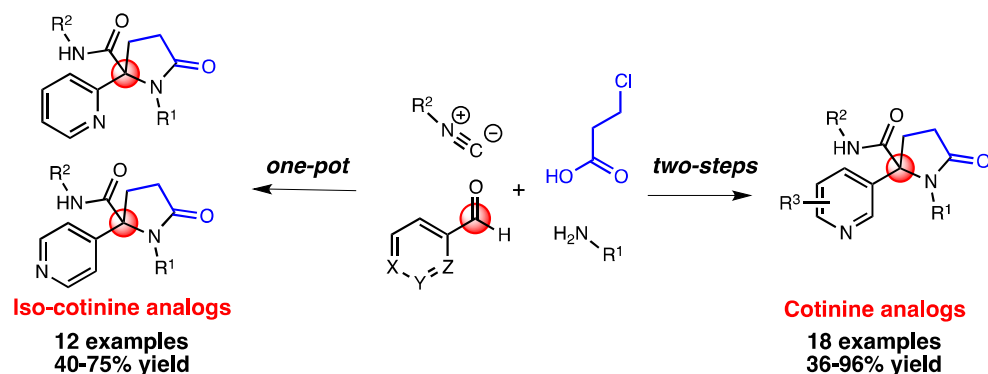
L. Angel Polindara-Garcia, Dario Montesinos-Miguel, Alfredo Vazquez

National Autonomous University of Mexico, Mexico, Mexico

The nocive side effects that tobacco consumption has on human health continue to be the subject of numerous studies to better understand the relation between nicotine and its secondary metabolites with the central nervous system (CNS). Cotinine, the main metabolite of nicotine has proved to be less toxic than nicotine itself, apart from not having addictive or cardiovascular effects on humans, despite the structural similarity between both molecules. Pre-clinical studies have shown that cotinine facilitates the elimination of fear memories and improve attention and working memory in a model for Alzheimer disease (AD), reduce fear and anxiety of post-traumatic stress disorder (PTSD), as well as antipsychotic drug-like properties.

Despite the outstanding biological profile of cotinine, there is a lack of efficient synthetic methods that allow the preparation of this molecule and its derivatives, and the known procedures for their construction rely mainly on the C-H oxidation at C-2 from the corresponding nicotine analogs using highly toxic oxidants.

We present a convenient base-mediated two-step synthesis of cotinine analogs and a one-pot base-free synthesis of iso-cotinine derivatives featuring an Ugi-4CR/cyclization protocol.



Synthesis of Heterocycles By Cyclizations and Functionalizations

Janine Cossy

ESPCI ParisTech, PARIS, France

In general, the synthesis of complex biologically active molecules are problematic but the problems, encountered during the syntheses, can be a good source of inspiration to develop methods. One major challenge is the design of concise strategies as well as chemoselective and efficient methods that rapidly lead to the skeleton framework of natural and/or biologically active heterocyclic compounds.

In this context, we have explored the construction of heterocycles using catalytic reactions involving transition metal catalysts and heat. Metal catalysts and heat can induce rearrangements, cyclizations, functionalizations which can be highly diastereoselective and enantioselective if a chiral ligand is added in the reaction media. These reactions and their applications to the synthesis of heterocyclic natural and non-natural products will be presented.

Enantioselective aza-Henry Reaction of Arylnitromethane using Homogeneous Brønsted Acid-Base Catalyst under Intermittent-Flow Conditions with a Recycle

Sergey Tsukanov^{1,2}, Martin Johnson¹, Scott May¹, Jeffrey Johnston², Matthew Yates¹

¹*Eli Lilly, Indianapolis, IN, USA*, ²*Vanderbilt University, Nashville, TN, USA*

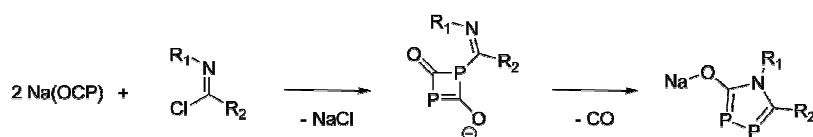
Growing knowledge in the area of continuous processing has established that flow methods could serve as an effective substitute to the majority of batch techniques providing unique advantages and straightforward solutions to the challenging chemical reactions. We have transformed a standard enantioselective batch aza-Henry reaction into intermittent-flow process. This novel platform produces valuable synthetic building blocks on a multigram scale with an increased overall intensity while addressing the common safety concerns associated with utilization of nitroalkanes. Organocatalyst was separated and continuously recycled providing reduced catalyst loadings. This project showcases successful synergy between efficiency of organocatalysis and transformative power of continuous processing. It also allows to effectively integrate green chemistry (reduced production footprint), atom economy (minimized reactor size, solvent volumes and application of catalyst recycle) and higher safety margins (decreased safety risks, defined operating space for nitroalkanes); overall these advantages lead to a significant cost benefit. The designed process could be utilized for a large scale synthesis of differentially protected diamines which are useful building blocks with a broad scope of applications.

1-Aza-3,4-diphospholides – Synthesis, Structure and Reactivity

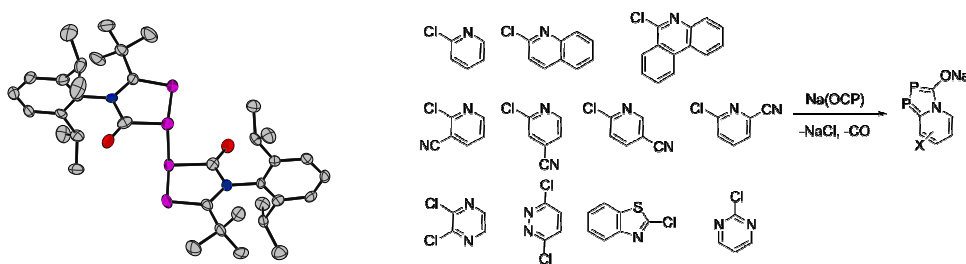
Riccardo Suter¹, Zoltan Benkő², Hansjörg Grützmacher¹

¹ETH Zürich, Laboratory of Inorganic Chemistry, Zurich, Switzerland, ²Budapest University of Technology and Economics, Budapest, Hungary

Na(OCP) has been shown to be a versatile precursor for a variety of compounds.^[1,2] The versatility and the easy synthesis make this salt a powerful building block. The anion can act as a P⁻ transfer agent^[3] and the unsaturated C≡P bond can undergo cyclo-addition reactions^[4]. Two equivalents of Na(OCP) react with imidoyl chlorides to form 1-aza-3,4-diphospholides in good yields up to 80%. These electron rich diphospholides were oxidized with hexachloroethane to form the phosphorus coupled dimers.



The reactivity of Na(OCP) towards imidoyl chlorides was transferred to 2-chloro-pyridines and its derivatives. The result is a variety of new products with outstanding properties. The light absorption and emission are easily tuned by the substituents in the backbone. Further studies on the use of those ring systems as building blocks for chelating ligands, and electronic materials will be presented.



[1] Puschmann, F. F. *et al.*, *Angew. Chem. Int. Ed.*, **2011**, *50*, 8420.

[2] Jupp, A. R., Goicoechea, J. M., *J. Am. Chem. Soc.*, **2013**, *135*, 19131.

[3] Tondreau, A., Benkő, Z., Harmer, J., Grützmacher, H., *Chem. Sci.*, **2014**, *5*, 1545.

[4] Benkő, Z., Grützmacher, H., *et al.*, *Angew. Chem. Int. Ed.*, **2014**, *53*, 1641.

Acyclic Nucleoside Phosphonates Containing A Second Phosphonate Group As Potent Inhibitors Of 6-Oxopurine Phosphoribosyltransferases With Antimalarial Activity

Petr Spacek¹, Dianne T. Keough², Zlatko Janeba¹, Michael D. Edstein³, Marina Chavchichd³, Tzu-Hsuan Wang², Luke W. Guddat², Dana Hockova¹

¹Institute of Organic Chemistry and Biochemistry, AS CR, v.v.i. Flemingovo nám. 2, Prague, Czech Republic, ²The School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Australia, ³Australian Army Malaria Institute, Enoggera, Brisbane, Australia

Hypoxanthine-guanine-(xanthine) phosphoribosyltransferase (HG(X)PRT) is a key enzyme of the purine salvage pathway. This enzyme is a validated target for anti-malarial chemotherapy because parasites of the genus *Plasmodium* are unable to synthesise purine bases *de novo* and depend on the transport of preformed bases from the host cell. HG(X)PRT then catalyses the conversion of these 6-oxopurine bases to the corresponding nucleoside monophosphates which are required for DNA/RNA production. Specific structural analogues of nucleotides - acyclic nucleoside phosphonates (ANPs) - have been recognized as potent inhibitors of HG(X)PRT.

Crystal structures of HG(X)PRT in complex with known inhibitors suggested that attachment of an additional functional group which could occupy the pyrophosphate binding site may lead to the increased affinity of these ANP-based inhibitors. These new compounds were prepared by multistep synthesis and are referred to as acyclic nucleoside bisphosphonates (ANbPs)¹. Their prodrugs have promising antimalarial activity in erythrocyte cultures.

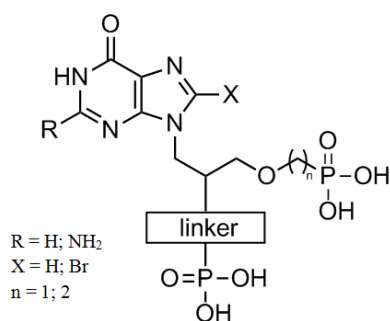


FIG. Examples of ANbPs structures.

- 1) Keough D.T. et al. *J. Med. Chem.* **2013**, 56, 2513.

Application of C-H Functionalization Reactions to the Synthesis of Novel Heterocycles

Andre Charette

Universite de Montreal, Montreal, QC, Canada

In the first part of the lecture, a two-step synthesis of structurally diverse 3-aminoindazoles from readily available starting materials will be presented. This sequence includes a one-pot chemoselective electrophilic activation of tertiary amides and nucleophilic addition of hydrazides to form aminohydrazone. These precursors then participate in an intramolecular ligand-free Pd-catalyzed C-H amination. The azaheterocycles synthesized via this approach were further diversified by subsequent deprotection/functionalization and transition Ru-catalyzed C-H arylation.

In the second part of the presentation, the preparation of tailored novel fluorescent derivatives that features an intramolecular C-H functionalization will be presented. The fluorescent properties can easily be finely tuned by modifying the basic molecular scaffold.

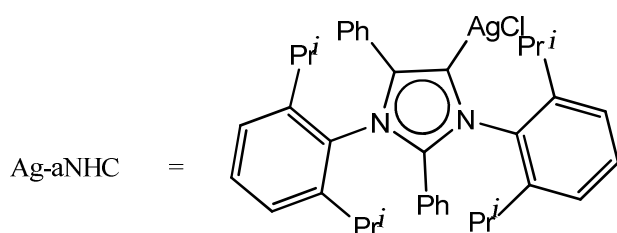
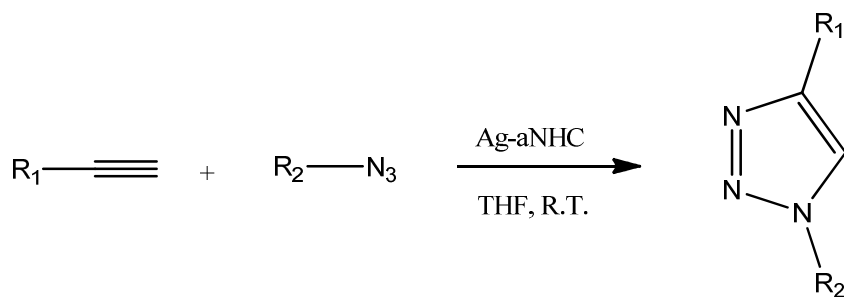
Triazole synthesis by alkyne-azide cycloaddition using silver catalysis

EUGENIA JOSEFINA ALDECO-PEREZ¹, ERICK CUEVAS-YAÑEZ², ALDO IVAN ORTEGA-ARIZMENDI²

¹Facultad de Química, Universidad Autónoma de Querétaro, Querétaro, Mexico, ²Centro Conjunto de Investigación en Química Sustentable UAEM-UNAM, Toluca, Mexico

1,2,3-Triazoles were synthesized from a variety of alkyne and azides using silver compounds. Additionally to common silver salts (nitrate, sulphate, oxide and chloride), we also tried an N-heterocyclic “abnormal” complex, a derivative of a mesoionic carbene, that proved to be a better catalytic system. Good yields of the 1,2,3-triazoles were obtained, by means of an alternative methodology, avoiding side reactions, the use of additives and facilitating the purification of final products. A plausible mechanism were proposed, according to the literature.

The observed results represent a new source of potential catalysis using silver as the reactive center on the route to 1,2,3-triazoles, important heterocycles with many applications.

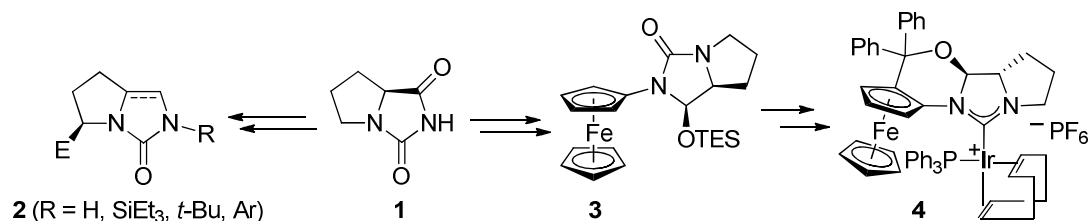


Development of Chiral Auxiliaries and Catalysts from Proline Hydantoin

Costa Metallinos

Brock University, St Catharines, Ontario, Canada

Our research program is focused on designing chiral reagents and catalysts for applications in asymmetric synthesis based on structural frameworks that have been under-exploited for lack of practical syntheses. Recent work has focused on the use of L-proline hydantoin (**1**) as a common starting material for the preparation of variously substituted imidazolone precursors (**2**) to *N*-heterocyclic carbenes (NHCs), including *N*-ferrocenyl imidazolones (**3**). Stereoselective induction of planar chirality in the latter molecules has enabled synthesis of iridium complexes bearing unusual NHCs (e.g., **4**) that catalyze asymmetric hydrogenation of quinolines at low hydrogen pressures (1-5 atm). A survey of recent results in this area will be presented.¹⁻⁵



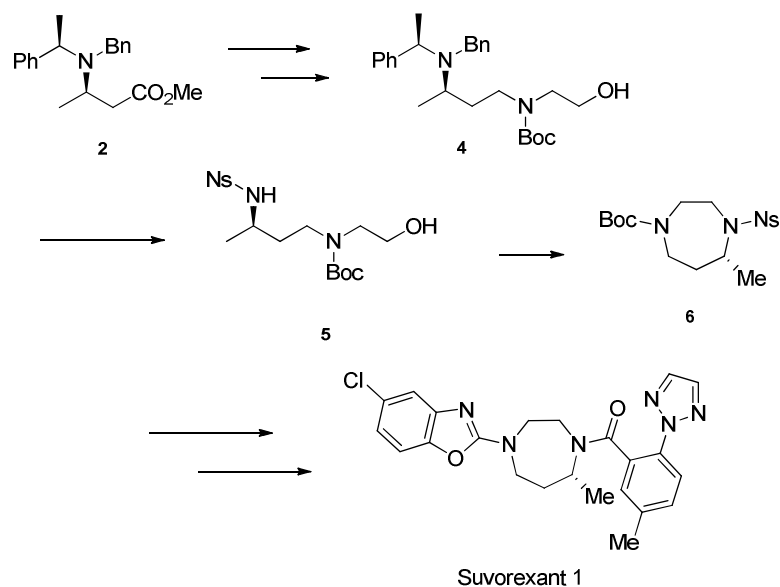
1. John, J.; Wilson-Konderka, C.; Metallinos, C. *Adv. Synth. Catal.* **2015**, 357, in press.
2. Metallinos, C.; Sadraei, S. E.; Zhukovskaya, N., *Heterocycles* **2014**, 88, 347.
3. Metallinos, C.; John, J.; Nelson, J.; Dudding, T.; Belding, L. *Adv. Synth. Catal.* **2013**, 355, 1211.
4. Metallinos, C.; John, J.; Zaifman, J.; Emberson, K. *Adv. Synth. Catal.* **2012**, 354, 602.
5. Metallinos, C.; Xu, S. *Org. Lett.* **2010**, 12, 76.

Laboratory and practical synthesis of Suvorexant, a selective dual orexin receptor antagonist

Satoyuki Takahara, Daisuke Minehira, Isao Adachi, Naoki Toyooka

University of Toyama, Toyamaken, Japan

The development of a laboratory and practical synthesis of Suvorexant 1, using intramolecular Mitsunobu cyclization reaction of intermediate 5 as the key reaction, has been reported. Compound 5 was obtained from known chiral ester 2 in three steps, and the key cyclization proceeded smoothly to provide the core seven-membered ring compound 6, which was transformed into 1 by an additional four-step sequence.



The procedure described here needs no chiral-HPLC separation, no classical resolution, and no unique enzyme reactions, and offers an alternative practical synthesis of 1.

Tetrahedron Lett. **2014**, *55*, 5778–5780

The second generation strategy of oligosaccharide synthesis via asymmetric intermolecular hydroalkoxylation of alkoxyallene

Soyeong Kang, Young Ho Rhee

Pohang University of Science and Technology, Pohang, Kyungbuk, Republic of Korea

We reported a new synthetic strategy toward various cyclic acetals using Pd-catalyzed asymmetric hydroalkoxylation of alkoxyallene.¹ This method can be used for de novo carbohydrate synthesis. Currently, we are interested in developing an alternative strategy that can expand the utility of this methodology. Herein our recent progress in these efforts will be presented.

References

1. Lim, W.; Kim, J.; Rhee, Y. H.; *J. Am. Chem. Soc.* **2014**, *136*, 13618.

Stereodivergent Synthesis of Decahydroquinoline-Type Poison Frog Alkaloids -Part 1-

Takuya Okada¹, Katsuki Takashima¹, Jungo Ishimura¹, Yuki Nakagawa¹, Naoki Wada¹, Masashi Kawasaki², Naoki Toyooka¹

¹University of Toyama, Toyama, Japan, ²Toyama Prefectural University, Toyama, Japan

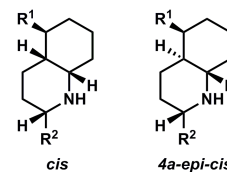
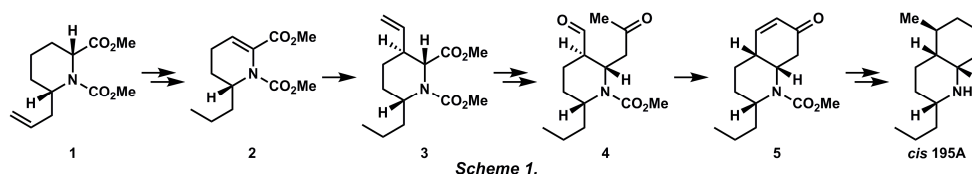


Figure 1.

Neotropical poisonous frogs are a rich source of a structurally diverse array of alkaloids. Among them, the 2,5-disubstituted decahydroquinolines are one of the major classes of these amphibian alkaloids. In addition, these alkaloids contain both *cis*- and *trans*-fused decahydroquinoline nuclei having the diastereomeric centers at C-2 and C-5 positions (Figure 1). However, no methodology for the stereodivergent synthesis of the *cis*- and *trans*-fused ring systems has been reported to date. We herein describe the stereoselective and stereodivergent route to the *cis*- and *trans*-fused decahydroquinoline ring core.

The synthesis began with known allyl derivative **1**, which was converted to enaminoester **2**. The key Michael-type of conjugate addition reaction of **2** proceeded smoothly to give rise to the trisubstituted piperidine **3** as a single isomer, which was converted to Weinreb's amide. The Weinreb's amide was transformed into the keto aldehyde **4**, which was subjected to an intermolecular aldol type of cyclization to afford the enone **5** as a single isomer. The methyl group was introduced on the C-5 position of **5** with highly stereoselective manner. Barton's deoxygenation of the resulting ketone followed by deprotection of methoxycarbonyl group provided **cis-195A** (Scheme 1).



On the other hand, the *trans*-fused compound **6** was also synthesized starting from the common Weinreb's amide. The conversion of **6** to **4a-epi-cis 195A** is now in progress and will be reported.

Stereodivergent Synthesis of Decahydroquinoline-Type Poison Frog Alkaloids -Part 2-

Takuya Okada¹, Katsuki Takashima¹, Jungo Ishimura¹, Yuki Nakagawa¹, Naoki Wada¹, Masashi Kawasaki², Naoki Toyooka¹

¹University of Toyama, Toyama, Japan, ²Toyama Prefectural University, Toyama, Japan

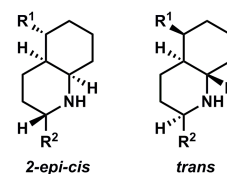
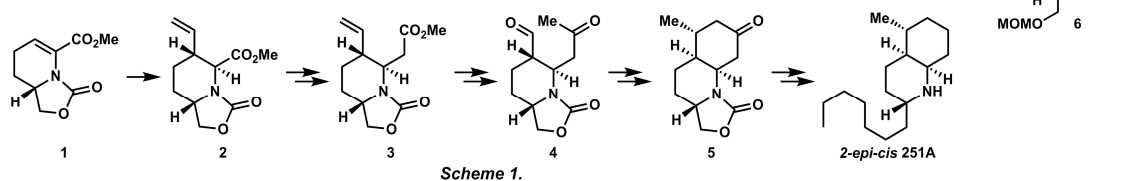


Figure 1.

Neotropical poisonous frogs are a rich source of a structurally diverse array of alkaloids. Among them, the 2,5-disubstituted decahydroquinolines are one of the major classes of these amphibian alkaloids. In addition, these alkaloids contain both *cis*- and *trans*-fused decahydroquinoline nuclei having the diastereomeric centers at C-2 and C-5 positions (Figure 1). However, no methodology for the stereodivergent synthesis of the *cis*- and *trans*-fused ring systems has been reported to date. We herein describe the stereoselective and stereodivergent route to the *cis*- and *trans*-fused decahydroquinoline ring core.

The synthesis began with known enaminoester **1**, which was converted to the adduct **2** using the key Michael-type of conjugate addition reaction as a single isomer. The adduct **2** was transformed into the homologated ester **3**, which was converted to keto aldehyde **4**. The second key step was an intermolecular aldol type of cyclization of **4** to afford the enone as a single isomer, which was introduced the methyl group on the C-5 position to afford the quinoline **5** with highly stereoselective manner. Barton's deoxygenation of the resulting ketone followed by hydrolysis of oxazolidinone ring provided amino alcohol, which was converted to **2-epi-cis 251A** in 4 steps (Scheme 1).



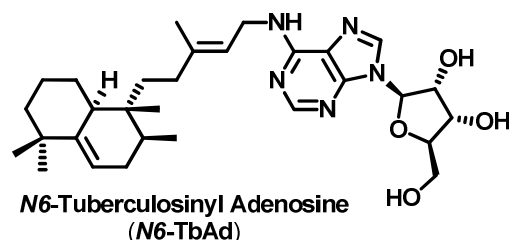
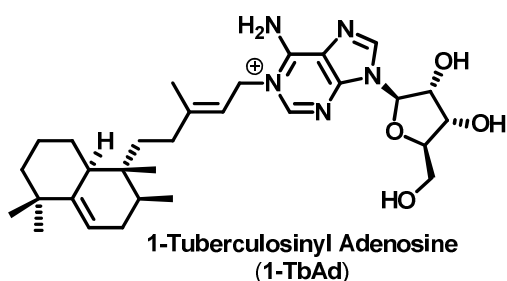
On the other hand, the *trans*-fused compound **6** was also synthesized starting from the common homologated ester **3**. The conversion of **6** to *trans* **195A** is now in progress and will be reported.

Tuberculosinyl Adenosines: Novel Terpene Nucleosides from *Mycobacterium Tuberculosis*

Jeffrey Buter¹, David Young², Emilie Layre², Branch Moody², Adriaan J. Minnaard¹

¹University of Groningen, Groningen, The Netherlands, ²Harvard Medical School, Boston, MA, USA

Tuberculosis (TB) remains a leading cause of death worldwide, resulting in 1.5 million deaths annually and yet no rapid, sensitive, and specific diagnostic test exists. Recently two novel terpene nucleosides were isolated from *Mycobacterium tuberculosis* (MTb) which were identified as 1-tuberculosinyl adenosine (1-TbAd) and N6-tuberculosinyl adenosines (N6-TbAd). In this presentation the first asymmetric total synthesis of the TbAd molecules will be discussed together with the development of specific diagnostic tests for MTb.

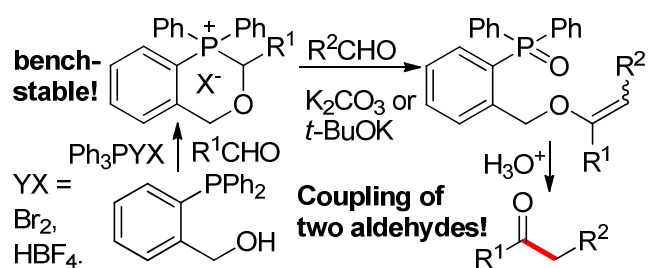


Synthesis and application of 2-substituted 1,1-diphenyl-2,4-dihydro-1H-benzo[d][1,3]oxaphosphinin-1-ium

Wenhua Huang, Hong-Ying Rong, Jie Xu

Tianjin University, Tianjin, China

In the presence of Ph_3PBr_2 or Ph_3PHBF_4 , 2-substituted 1,1-diphenyl-2,4-dihydro-1H-benzo[d][1,3]oxaphosphinin-1-ium can be synthesized from (2-(diphenylphosphino)phenyl)methanol and an aldehyde in 36-89% yields. These phosphonium salts are bench-stable solids and undergo Wittig olefination with another aldehyde under basic condition (K_2CO_3 or $t\text{-BuOK}$) to form benzylic vinyl ethers, which are readily hydrolyzed to 1,2-disubstituted ethanones under acidic condition. Therefore, the overall reaction provides a facile route to couple two aldehydes to form 1,2-disubstituted ethanones.

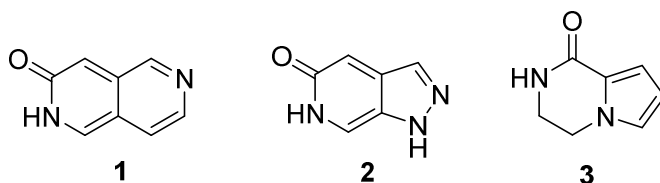


Synthesis of promising understudied heteroaromatic scaffolds for the drug discovery process

Paulo Eliandro da Silva Junior¹, Vinícius Maltarollo³, Arasu Ganesan², Gustavo Henrique Goulart Trossini³, Flavio da Silva Emery¹

¹Faculty of Pharmaceutical Sciences of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto/SP, Brazil, ²School of Pharmacy, University of East Anglia, Norwich, UK, ³Faculty of Pharmaceutical Sciences, University of Sao Paulo, Sao Paulo/SP, Brazil

The chemical space is quite vast, it is estimated that there are more than 10^{62} compounds with molecular weight below 500 Da. However only a small fraction of this area is exploited for drug discovery, usually by high throughput screening (HTS) approaches. Inevitably, HTS libraries generally present a large number of non drug-like compounds which generates constantly false positive results. Therefore in the present work we had selected three heteroaromatic systems for study (2,6-naphthyridin-3(2H)-one **1**, 1,6-dihydro-5H-pyrazolo[3,4-c]pyridin-5-one **2**, 3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one **3**) to conduce a synthetic and computational study to provide new drug-like compounds and innovation to drug discovery libraries. We have developed three novel and efficient synthetic routes for the promising heterocyclic scaffolds **1**, **2** and **3**, which are still underexploited by medicinal chemistry. First, the unpublished heterocyclic **1** had a robust synthetic route described based on pyridine substitution methodologies. The heterocycle **2** was achieved through *N*-acyl-*N*-nitroso intermediate cyclization in a few steps and low cost synthetic route. Finally, the structure **3** was synthesized by substitution methods of pyrrole ring. In addition, we proposed the synthesis of **1**, **2** and **3** derivatives and also a computational analysis, in order to ascertain their use as building blocks and also their potential for drug discovery processes. The three heteroaromatic scaffolds showed interesting medicinal chemical properties related to their structure, thus their application for libraries development is a promising “innovation tool” to drug discovery processes.

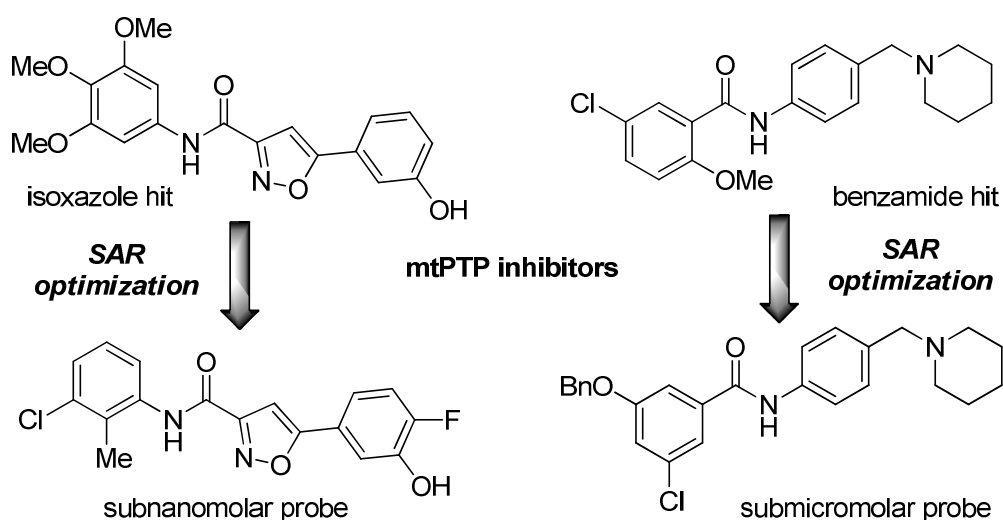


Discovery and Optimization of Novel Inhibitors of the Mitochondrial Permeability Transition Pore

Sudeshna Roy^{1,5}, Justina Šileikyte², Marco Schiavone², Benjamin Neuenswander¹, Michael Hedrick³, Thomas Chung³, Jeffrey Aubé^{1,5}, Michael Forte⁴, Paolo Bernardi², Frank Schoenen¹

¹University of Kansas, Lawrence, Kansas, USA, ²University of Padova, Padova, Italy, ³Sanford-Burnham Medical Research Institute, La Jolla, California, USA, ⁴Oregon Health & Science University, Portland, Oregon, USA, ⁵University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

The mitochondrial permeability transition pore (mtPTP) is a Ca^{2+} -requiring megachannel that permanently opens under pathological conditions and leads to deregulated release of Ca^{2+} and mitochondrial dysfunction. For the past couple of decades the mtPTP has been implicitly recognized as a therapeutic target for several deadly diseases such as Alzheimer's disease, muscular dystrophies, myocardial infarction, stroke, and diabetes. Herein we report the results of a high-throughput screening/chemical optimization approach that led to the discovery of two new chemotypes: (a) diarylisoxazole-3-carboxamides and (b) *N*-phenylbenzamides, which are first subnanomolar inhibitors of the mtPTP. The therapeutic potential and *in vivo* efficacy of the most potent analogues were validated in a biologically relevant zebrafish model of collagen VI congenital muscular dystrophies.



Mimicking the Molybdenum Cofactor by Synthesis of Molybdenum-Pterin Complexes.

Ivan Trentin, Carola Schulzke

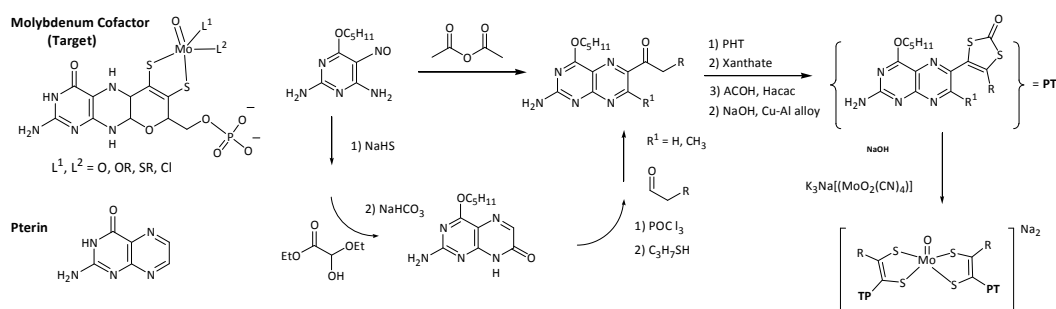
Institute of Biochemistry, Greifswald, Vorpommern, Germany

Pterins fulfil a variety of roles in biology including being pigments, toxins, redox cofactors and C1 transfer cofactors. The pterin structure is also present in a rather complicated molecule called molybdopterin, which, by coordinating to molybdenum, forms the molybdenum cofactor (Fig.)

The main purpose of this project is the study of differently substituted pterin-dithiolene moieties bound to molybdenum (fig.) in order to obtain a better understanding of structure-function relationships and the high instability of this very important part of all molybdenum dependent oxidoreductases. One example of a synthetic pathway is shown below.

Despite having shown that the third ring of mpt does not electronically influence the active site metal strongly if at all¹, we are not convinced that it is actually negligible. Bearing a keto, two amine and one amide group, it is potentially reactive and more importantly it is able to take part in a substantial number of hydrogen bonds.

Input from experts in the field of heterocyclic chemistry during the poster session will be highly appreciated.



References 1.U. Ryde, C. Schulzke, K. Starke, J Biol. Inorg. Chem. 2009, 14, 1053- 1064

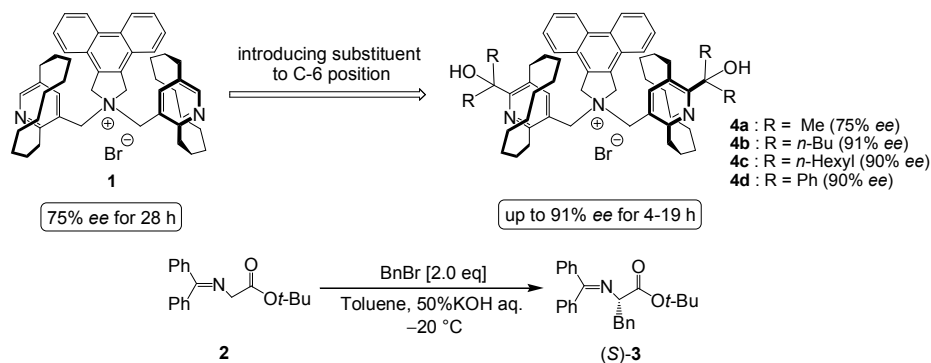
Synthesis of planar-chiral phase-transfer catalysts incorporating hydroxyl methyl pyridinophane moieties and their use for catalytic asymmetric reactions

Seiju Komaki, Megumi Imada, Nobuhiro Kanomata

Department of Chemistry and Biochemistry, Waseda University, Shinjuku-Ku, Tokyo 169-8555, Japan

Various phase-transfer catalysts (PTCs) have been reported useful for asymmetric reaction, however planar-chiral PTCs have not been reported yet in literature.

We have been studying planar-chiral PTCs having [10]parapyridinophanes as planar chiral moieties and have already revealed that bispyridinophane catalyst **1** having a dibenz[e,g]isoindoline unit has moderate enantioselectivity for asymmetric benzylation of glycine derivatives **2** (up to 75% ee). For exploring further effective catalysts, we have synthesized novel planar-chiral PTCs **4a-d** having tertiary hydroxyl groups on their pyridine rings. With these catalysts **4a-d**, asymmetric benzylation reaction afforded phenylalanine derivatives **3** with up to 91% ee. Significant improvement of enantioselectivity was observed according to remote steric effect¹⁾ by introduction of sterically demanding substituents pushing oligo-methylene bridge out to the reaction site around a quaternary ammonium nitrogen. Reactions were also accelerated when using catalyst **4a-d** as compared to our previous ones due to increase of hydrophilicity around hydroxyl groups.



References

- 1) Mugishima, N.; Kanomata, N.; Akutsu, N.; Kubota, H. *Tetrahedron. Lett.* **2015**, *56*, 1898-1903.

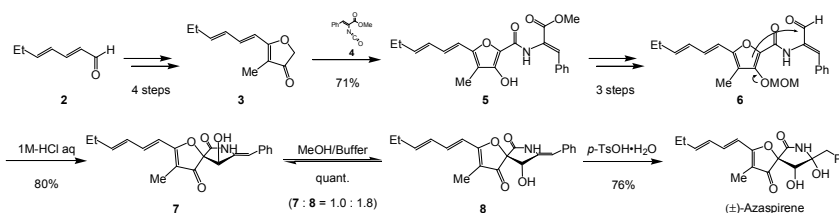
Total synthesis of (±)-azaspirene and racemization in aqueous media.

Takahiro Hasegawa¹, Katuhito Nakazono¹, Kazunori Souma², Shun Hirasawa¹, Nobuhiro Kanomata^{1,2}

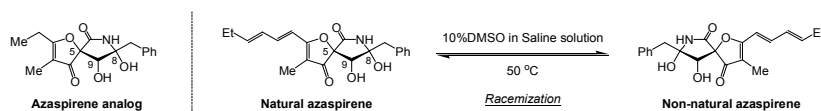
¹Department of Chemistry and Biochemistry, Waseda University, Shinjuku-Ku, Tokyo, 169-8555, Japan, ²Department of Applied Chemistry, Meiji University, Tama-Ku, Kawasaki, 214-8571, Japan

(-)-Azaspirene, isolated from the fungus *Neosartorya* sp., is an angiogenesis inhibitor having a characteristic spiro skeleton. Its asymmetric total synthesis was reported independently by two groups.¹ We have been studying synthesis of its natural and non-natural analogs and their in vitro assay.² During course of our research we found that the analog readily undergoes racemization of itself in water. Racemization of natural azaspirene, however, has not been announced yet. In this study, we synthesized (±)-azaspirene according to the following scheme and investigated its racemization.

Our synthesis started from commercially available aldehyde **2**. Condensation of furanone **3** and isocyanate **4** followed by transformation of substituents afforded MOM aldehyde **6**. Removing the MOM group induced intramolecular aldol reaction and spiro compound **7** was obtained as a single isomer. Compound **7** was isomerized to **8** in basic conditions and the following hydration afforded racemic azaspirene in good yield.



Racemization of optically active azaspirene, obtained by HPLC separation, was monitored in water. Racemization occurred more slowly than that of the analogous compound. This is probably because hydrogen bond between a hydroxyl group at C-8 and a carbonyl group of dihydrofuranone moiety is stronger in natural azaspirene due to longer conjugation with a hexadienyl side chain.



1 (a) Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, H.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 12078-12079. (b) Aoki, S.; Oi, T.; Shimizu, K.; Shiraki, R.; Takao, K.; Tadano, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1703-1716.

2 Emoto, M.; Yano, K.; Chojiamts, B.; Sakai, S.; Hirasawa, S.; Wakamori, S.; Aizawa, M.; Nabeshima, K.; Tachibana, K.; Kanomata, N. *Anticancer Res.* **2015**, *35*, 2739-2746.

N-acyl transfers in peptide elongation

JING SHANG, Craig Hutton

The university of Melbourne, Melbourne, Australia

We have recently developed the method for the synthesis of peptides using a silver-promoted coupling of thioamides with amino acids. This method was shown to generate peptide imides which can be selectively hydrolysed to give peptides. During this investigation, acyl migration of the imides was observed to occur.

We are exploring the acyl migration reactions of peptide imides towards the insertion of amino acid residues into peptide thioamides. In particular, application in the ring expansion of cyclic peptides through this peptide imide formation-acyl migration process will be described.

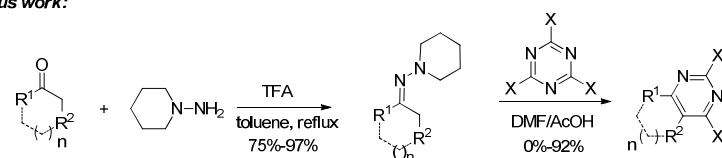
Hydrazine-Catalyzed Direct Inverse Electron Demand Diels-Alder Reactions of 1,3,5-triazines with Ketones

Kai Yang, Qun Dang, Xu Bai

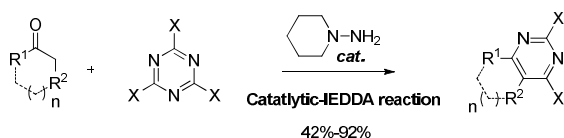
The Center for Combinatorial Chemistry and Drug Discovery of Jilin University, The College of Chemistry and The School of Pharmaceutical Sciences, Jilin University, Changchun, Jilin, China

Recently, we disclosed the successful development of hydrazones as productive dienophiles in the inverse electron demand Diels-Alder (IEDDA) reactions of 1,3,5-triazines.¹ To further expand the scope of IEDDA reactions of 1,3,5-triazines, we envisioned that ketones could participate in IEDDA reaction under hydrazine-catalysis conditions (**this work**). This catalytic IEDDA reaction with a broad substrate scope affords a succinct, economical and green approach to the synthesis of pyridimine fused heterocycles from readily available ketones, further expanding the scope for 1,3,5-triazine IEDDA reactions. Meanwhile, the applications of hydrazine-type organocatalyst have been expanded by these studies. The details of these investigations will be presented.

previous work:



this work:



Reference

(1) Yang, K.; Yang, Z.; Dang, Q.; Bai, X. *Eur. J. Org. Chem.* **2015**, DOI: 10.1002/ejoc.201500499

Mylyated Protein Isolates of some underutilized oil seeds and their Functional Properties

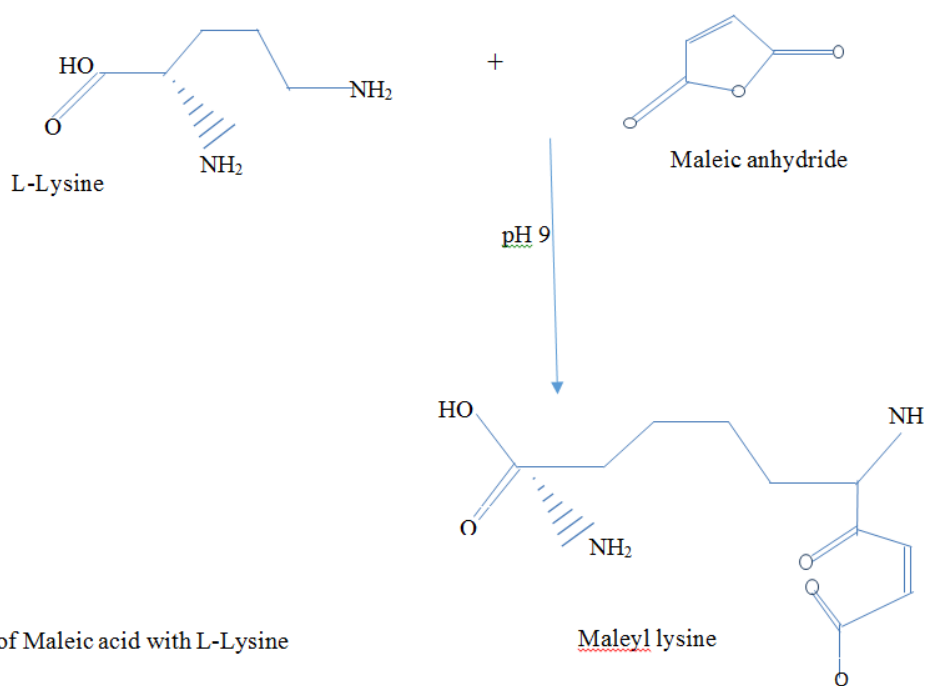
Joan Ogundele^{1,2}, Aladesanmi Oshodi², Toibudeen Sanni³, Isiaka Amoo⁰

¹Industrial Chemistry Department, Federal University Oye Ekiti, Oye Ekit, Ekiti State, Nigeria,

²Chemistry Department, Federal University of Technology, Akure, Akure, Ondo State, Nigeria,

³Food Science and Technology Department, Federal University Oye Ekiti, Oye Ekiti, Ekiti State, Nigeria

Protein isolates of some oil seeds were extracted using alkali extraction and precipitation at the isoelectric point. Maleic anhydride was used to modify the protein at pH 9 under ice, to produce Maleyl lysine. The functional properties of the mylyated proteins were determined using standard methods. The protein solubility of the products were very high at pH 11, with values ranging from 77.20 to 95.00 % soluble protein. They have low jelling ability with list jelling concentration ranging from 2 to 8 (%w/v). They are slightly hydrophobic with oil absorption capacity ranging from 1.94±0.26 to 2.84±0.26 (g/g) and water absorption capacity ranging from 3.50±0.50 to 3.00±0.00 (g/g).

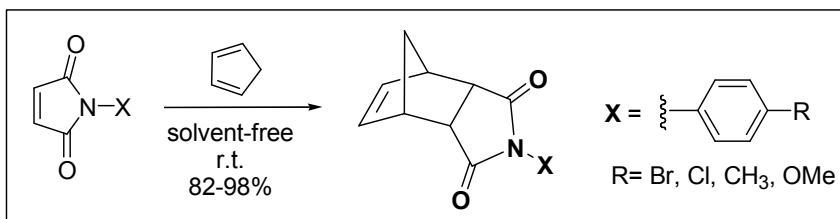


New Solvent-free Synthesis of Norbornenes Derived from Maleimides

Ingridhy O. M. F da Silveira¹, Cristiane Winck¹, Dênis Pires de Lima¹, Adilson Beatriz¹, Roberto da Silva Gomes²

¹Federal University of Mato Grosso do Sul, Campo Grande/MS, Brazil, ²Federal University of Grande Dourados, Dourados/MS, Brazil

In 2006, Kas'yan et al. reported the reactions of several bicycle [2.2.1] hept-5-ene-endo, endo-2, 3- dicarboxilic anhydride with cyclic non-aromatic amines to obtain the correspondent norbornene N-alkylamides and then N-alkyl norbornene dicarboximides. It is known that these compounds were used as components of repellent compositions and as agents endowed with sedative activity. To prepare the carboximides is required two steps: formation of a derivative norbornene acid in benzene, and closure of imidic ring using several days with yields of 86% and 74%, respectively. In this work, we describe an alternative, shorter, and efficient method for the synthesis of the N-aryl norbornene dicarboximides using a solvent-free Diels–Alder reaction between cyclopentadiene and N-aryl-4-substituted maleimides, at room temperature, affording excellent yields (82-98%). The required N-aryl maleimides were prepared from reaction of substituted anilines with maleic anhydride, using ethyl ether as solvent, leading to moderate to good yields (60-80%).

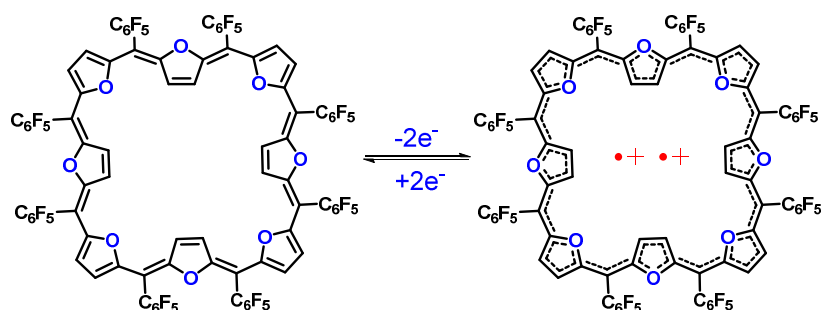


Reversible Oxidation of 40 π Antiaromatic Expanded Isophlorins into a Polaron Pair

Neelam Shivran, Venkataramanarao G. Anand, Kiran Reddy Baddigam

Indian Institute of Science Education and Research, Pune, India

30 π and 40 π isophlorins are higher analogues of 20 π isophlorins;^[1] and are the simplest example of expanded isophlorins having planar and ring inverted structures.^[2] The expanded derivatives of isophlorins provide number of examples for Huckel's (4n+2) π aromatic and 4n π anti-aromatic systems. In contrast to the aromatic expanded isophlorins, the 4n π antiaromatic systems differ in their optical and electrochemical properties. The large and planar expanded isophlorins exhibit reversible two-electron oxidation in comparison to their smaller analogues. A 40 π conjugated macrocycle with eight furan rings was yielded by acid-catalyzed condensation of furan and pentafluorobenzaldehyde;^[3] and oxidized with trifluoroacetic acid or [Et₃O+SbCl₆] or NOBF₄.^[4] The oxidized product was identified as polaron pair. Single-crystal X-ray diffraction analysis confirmed a planar structure of the oxidized product and the free base.



References:

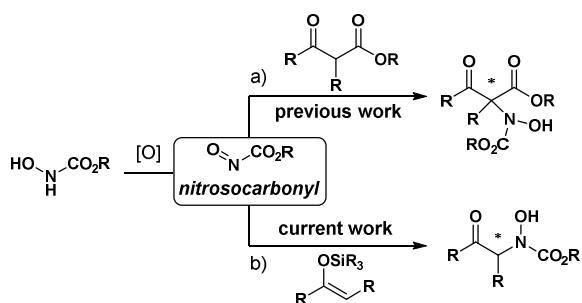
1. Reddy, J. S.; Anand, V. G., *J. Am. Chem. Soc.* **2008**, *130*, 3718-3719.
2. Reddy, J. S.; Anand, V. G., *J. Am. Chem. Soc.* **2009**, *131*, 15433-15439.
3. Reddy, J. S.; Mandal, S.; Anand, V.G., *Org. Lett.* **2006**, *8*, 5541.
4. Gopalakrishna, T. Y.; Anand, V. G., *Angew. Chem. Int. Ed.* **2014**, *53*, 6678.

Practical Asymmetric Electrophilic Amination of Silyl Enol Ether Derivatives via the Nitrosocarbonyl Ene Reaction

David Sandoval, [Andrey Samoshin](#), Javier Read de Alaniz

UCSB, Santa Barbara, CA, USA

Presented is an account of the first example of a general asymmetric nitrosocarbonyl ene reaction with silyl enol ether derivatives. The procedure is operationally simple and utilizes an easily accessible chiral nitrosocarbonyl precursor (EleNO_r), catalytic copper, and air as a benign oxidant. The transformation is both high yielding and highly diastereoselective for a variety of silyl enol ether derivatives including aromatic heterocyclic ketones. A range of non-exclusive post-functionalizations showcases the variety and scope of this method's potential synthetic applications.

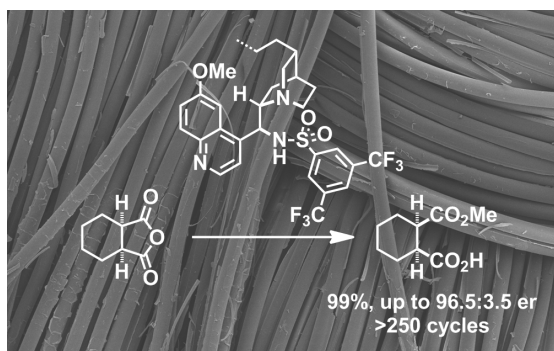


Organotextile Catalysis

JIWOONG LEE^{1,2}, THOMAS MAYER-GALL³, KALUS OPWIS³, CHOONG EUI SONG⁴, JOCHEN STEFAN GUTMANN^{3,5}, BENJAMIN LIST²

¹University of California, Berkeley, Berkeley, USA, ²Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, Germany, ³Deutsches Textilforschungszentrum, Krefeld, Germany, ⁴Sungkyunkwan University, Suwon, Republic of Korea, ⁵University Duisburg-Essen, Essen, Germany

Throughout human history, textiles have been integral to daily life, but their exploration in catalysis has been neglected. We demonstrated a facile and permanent immobilization of organocatalysts on the textile nylon using ultraviolet light, which doesn't require chemical modification for the immobilization. A Lewis basic, a Brønsted acidic, and a chiral organocatalyst immobilized on textile display excellent stability, activity, and recyclability for various reactions. High enantioselectivity (>95:5 er) can be maintained for more than 250 cycles of asymmetric catalysis. Practical and straightforward applications of textile organocatalysis may be beneficial for various fields by providing inexpensive and accessible functionalized catalytic materials.

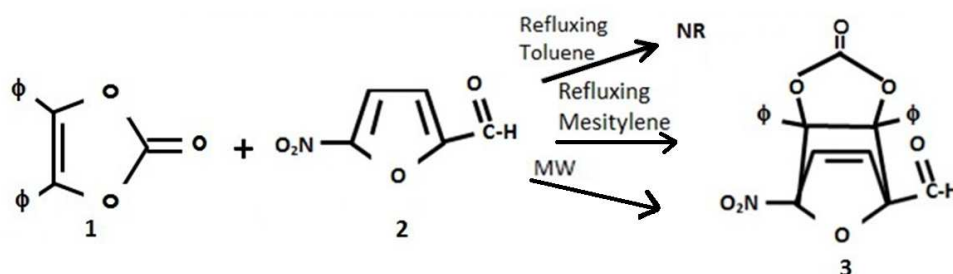


Progress Toward the Synthesis of Novel Heterocyclic Compounds Via Diels-Alder Reactions, Including Microwave Promotion

Douglas Armstrong, Kristen Richey

Olivet Nazarene University, Bourbonnais, Illinois, USA

This project involves “inverse-electron-demand” (IED) Diels-Alder (DA) reactions, microwave promotion (versus conventional heating), and retro-Diels-Alder (RDA) reactions. Concerning IED, we tried to figure out how electron-poor a diene would need to be, in order to require an electron-rich dienophile. Just a few examples of the many reactions done by ONU Honors Program undergraduate research student, Kristen Richey, are summarized below. MW refers to the use of our Biotage microwave instrument, “Initiator” model. **By the time this abstract was written, none of the product structures had been rigorously proven.** 4,5-diphenyl-1,3-dioxol-2-one **1** was reacted with 5-nitro-2-furaldehyde **2**. The nitro and formyl groups should provide enough IED electron deficiency, and **1** should be electron-rich enough. No reaction was observed in toluene, but in mesitylene, TLC analysis showed a single product, expectedly **3**, but both reactants were present, suggesting an incomplete reaction and/or RDA.



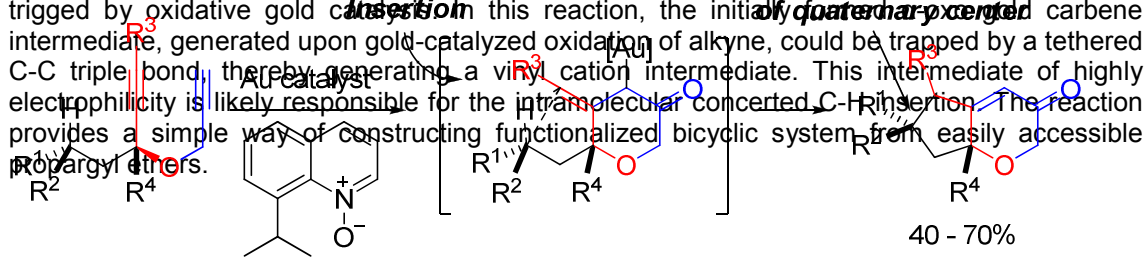
Several other combination of reactants were tried, in refluxing solvents of various boiling points, but with similar results. Therefore, microwave heating was tried, including several combinations of reactants, including **1** and **2**, and with several different sets of MW conditions, but all such attempts also resulted in both reactants being present (along with products). More research is needed.

C-H insertions in oxidative gold catalysis: Synthesis of bicyclic dihydropyran-3-ones from in situ generated α -oxo gold carbenes through the relay of vinyl cation intermediates

Zhitong Zheng, Liming Zhang

University of California, Santa Barbara, Santa Barbara, CA, USA

An expedient synthesis of bicyclic dihydropyran-3-one compounds is realized in a cascade triggered by oxidative gold catalysis. In this reaction, the initially generated α -oxo gold carbene intermediate, generated upon gold-catalyzed oxidation of alkyne, could be trapped by a tethered C-C triple bond, thereby generating a vinyl cation intermediate. This intermediate of high electrophilicity is likely responsible for the intramolecular concerted C-H insertion. The reaction provides a simple way of constructing functionalized bicyclic system from easily accessible propargyl ethers.



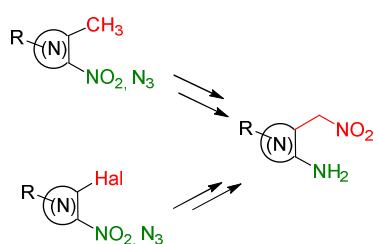
New access to bicyclic heterocyclic structures bearing a fused nitropyrazole

Thibaud Alaïme^{1,2}, Eric Pasquinet¹, Franck Suzenet², Gérald Guillaumet²

¹CEA Le Ripault, Monts, France, ²Institut de Chimie Organique et Analytique, Orléans, France

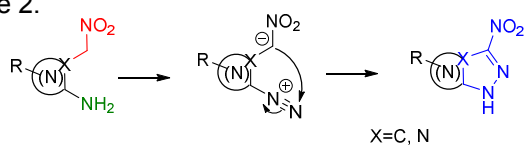
The strategy described in this work provides new access to bicyclic structures, with a 3-nitropyrazole fused with a six or a five-membered ring. The point is that cyclization occurs during the last sequence of the synthesis, so that reactivity relies mostly on the main ring.

The key point of the strategy was the introduction of the nitromethylene moiety, as few techniques exist to synthesize this kind of fragments, as well as its handling. Indeed this fragment makes compounds hard to purify and very sensitive to many reaction conditions (acidic protons, ease of oxidation and reduction...). This work also describes a new, practical and scalable method for isolation and purification of nitromethyl(het)arenes (scheme 1).



Scheme 1 – The route to 1-amino-2-(nitromethyl)arenes

The last reaction implies a condensation of a nitromethylene fragment on a diazonium placed in the ortho position on the main cycle. After re-aromatization, the newly formed heterocyclic compound presents a higher nitrogen content with a 3-nitropyrazole moiety. The reaction is summarized in scheme 2.



Scheme 2 – Intramolecular cyclization to fused 3-nitropyrazoles

New Methods for Amide Bond formation and Oxazole Synthesis

Aysa Pourvali, Craig Hutton

University of Melbourne, Melbourne, Australia

Synthesis of amide bonds is one the most important issues in organic chemistry. The reaction between thioamides and silver carboxylates, initially,¹ has been investigated for development into a general method for amide bond formation. A range of carboxylic acids and thioamides were reacted in the presence of silver (I) carbonate to generate imides. This system was shown to be effective for different N-protected amino acids and thioamides, including the preparation of dipeptide imides. Investigations of the cleavage of the imide products suggest this may be a viable general method for amide bond formation.²

Furthermore, dipeptide thioamides were shown to be useful precursors to 2-amino oxazoles.

References:

[1] Avalos, M.; Babiano, R.; Cintas, P.; Duran, C. J.; Higes, F. J.; Jimenez, J. L.; Lopez, I.; Palacios, J. C., *Tetrahedron* 1997, 53, 14463.

[2] A, Pourvali.; J. R. Cochrane.; C. A. Hutton., *Chem. Comm.* 2014, 50, 15963.

Developing a Library of Heterocycles to Fight Neglected Diseases

Flavio Emery

School of Pharmaceutical Sciences at Ribeirao Preto/University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil

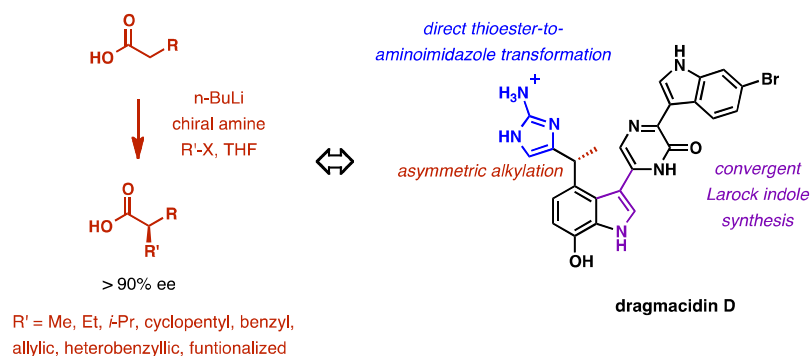
The available drug space for treating neglected diseases are limited and do not cover desirable drug-like properties. The most recent trends in neglected diseases drug discovery aim to change this picture. In order to succeed advancing medicinal chemistry in the area, a good library of structurally diverse compounds covering the property-space for drug-likeness plays a central role. This talk will present our work on building library of heterocycles, based on five main strategies: innovative scaffolds, heterocyclic reactivity, heterocyclic fragment embedment, diversity oriented synthesis and total synthesis.

Total Synthesis and Stereochemistry of (+)-Dragmacidin D

Jeffrey Jackson, Hiroyuki Kobayashi, Armen Zakarian

UC Santa Barbara, Santa Barbara, USA

Dragmacidin D is a complex deep-sea marine heterocyclic natural product whose stereochemical identity has remained unclear since its isolation. This bis(indole) pyrazinone alkaloid contains a single stereocenter, whose configuration was proposed based on stereochemistry of another congener, dragmacidin F. Recently, Capon and Jia revised the assignment to 6''*R* based on total synthesis, the first enantioselective preparation of dragmacidin D in 26 steps. We developed an effective direct asymmetric alkylation of arylacetic acids, which enabled the synthesis of (+)-dragmacidin D in 10 steps. Curiously, our own effort confirmed the originally proposed assignment as 6''*S*. We also determined that dragmacidin D undergoes a slow racemization in aqueous solution at pH 6.8, essentially complete within 16 days at room temperature.

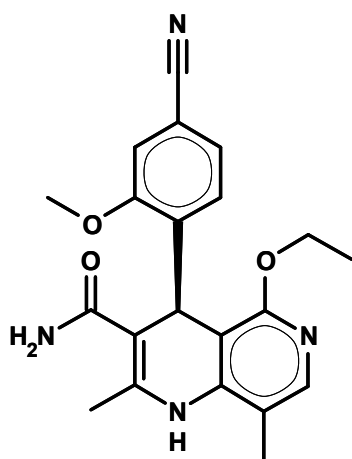


Synthesis and Up-Scaling of Finerenone, a Novel Potent and Selective Oral Non-Steroidal Mineralo-Corticoid Receptor (MR) Antagonist

Johannes Platzek

BAYER PHARMA AG, Wuppertal, Nordrhein Westfalen, Germany

Finerenone (BAY 94-8862) is a novel potent and selective oral non-steroidal mineralo-corticoid receptor (MR) antagonist blocking deleterious effects of aldosterone. Increased activation of the MR leads to pathological changes in the heart and kidneys, which can be prevented by effective MR antagonism. Finerenone has demonstrated a promising efficacy and safety profile in preclinical studies as well as in Phase IIa. The MR antagonist is currently in clinical Phase IIb development for the treatment of worsening chronic heart failure and diabetic nephropathy and is expected to enter clinical Phase III end of 2015. Synthesis and up-scaling of the novel optical active Dihydropyridine derivative to commercial scale, as well as challenges during process development will be discussed. Application of SMB technique for separation of enantiomers on large scale will be demonstrated. Additionally, the synthesis and characterization of metabolites will be presented.



Finerenone
BAY 94-8862

Toward a nature-inspired, dual-catalytic method to dehydrogenate organic compounds

Erik Sorensen, Julian West

Princeton University, Princeton, NJ, USA

This lecture will describe our development of a light-induced, dual-catalytic method for converting saturated hydrocarbons to alkenes with the simultaneous formation of hydrogen gas. This 'dehydrogenation' process uses two mutually compatible, base metal catalysts to generate alkenes and molecular hydrogen by sequential carbon–hydrogen bond cleavages. The sequential, catalyst-mediated hydrogen atom transfers occur at room temperature and call to mind the mechanism of nature's desaturase enzymes. In the wake of the alkene synthesis, the 'hydrido' forms of the catalysts undergo a reaction that liberates hydrogen gas and returns the catalysts to the reaction. Our ongoing efforts to achieve diverse chemical reactions that are attended by dehydrogenations will also be addressed.

Old Methods to New Targets: Accessing Highly Functionalized Heterocycles for Drug Development

Christopher Borths

Amgen, Thousand Oaks, CA, USA

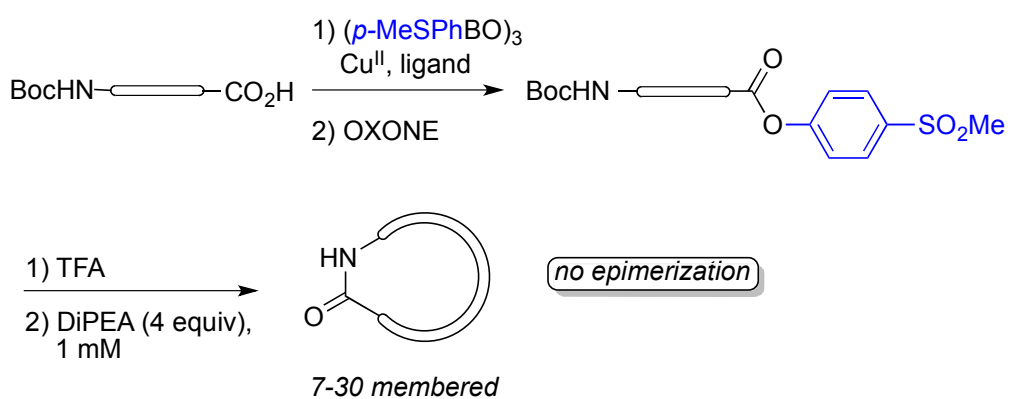
The development of a practical and efficient synthesis of an investigational drug candidate will be described. A Vilsmeier-Haak quinolinone synthesis was first developed to support the initial multi-kilo manufactures. Alternative chemistry based on a highly selective Friedlander cyclization was later discovered to provide efficient access to the key quinolinone intermediate. Development of subsequent transformations to access the target molecule including development of a challenging Negishi coupling and selective oxime hydrogenation will also be described. The process development ultimately provided access to the non-racemic drug candidate in 5-step chiral process with a 47% overall yield.

Epimerization-free Cu-catalyzed peptide activation and cyclization

Jan van Maarseveen, Stanimir Popovic, Linda Wijsman, Henk Hiemstra

University of Amsterdam, Amsterdam, The Netherlands

For peptide cyclization C-terminal carboxyl activation is mandatory. In general, peptide C-terminal activation is accompanied by partial epimerization. By replacing the traditional coupling reagents by the Cu-catalyzed Chan-Lam reaction mildly activated peptide aryl-esters were obtained that were cyclized with complete stereocontrol.

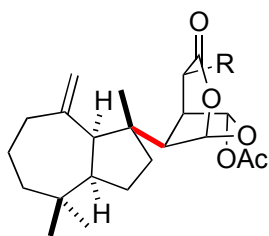


Fragment Coupling Using Bimolecular Free-Radical Reactions

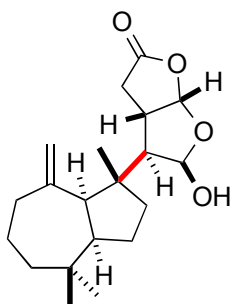
Larry Overman

University of California, Irvine, Irvine, CA, USA

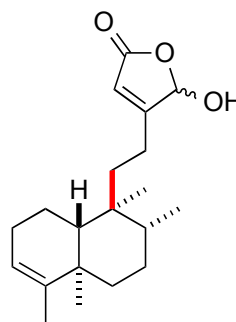
Convergent synthesis strategies are fundamental to the efficient preparation of complex organic molecules. As a result, reactions that achieve the high-yielding union of polyfunctional fragments have particular importance in the preparation of structurally intricate organic molecules. Especially demanding are fragment coupling reactions that form sp^3 - sp^3 sigma bonds and two stereocenters. When the two stereocenters reside in different rings and at least one of these stereocenters is quaternary, the challenge is enhanced substantially. This lecture will discuss the previously under appreciated utility of bimolecular reactions of free radicals to couple structurally intricate fragments.



macfarlandin E (R = OAc)
alyviolene (R = H)



chelviolene A



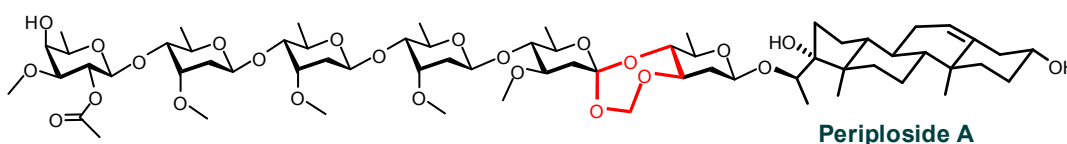
PL3

Total Synthesis of Periploside A, a Unique Pregnane Hexasaccharide with Potent Immunosuppressive Effects

Xiaheng Zhang, [Biao Yu](#)

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China

Periploside A is a pregnane hexasaccharide identified from the Chinese medicinal plant *Periploca sepium*, which features a unique seven-membered formyl acetal bridged orthoester (FABO) motif and shows potent immunosuppressive activities. The total synthesis of this natural product is achieved in a total of 76 steps with the longest linear sequence of 29 steps and 9.2% overall yield.^[1] The FABO motif is constructed via a combination of Sinaÿ's and Crich's protocol for the formation of orthoester and acetal glycosides, respectively. The 2-deoxy- β -glycosidic linkages are assembled stereoselectively with judicious choice of the glycosylation methods.^[2,3] The epimer at the spiro-quaternary carbon in the FABO motif has also been elaborated in a stereo-controlled manner. This epimer, as well as the synthetic analogs bearing FABO motif, retain largely the inhibitory activities of periploside A against the proliferation of T-lymphocyte, indicating the importance of the chemical connection of the FABO motif to their immunosuppressive activities.



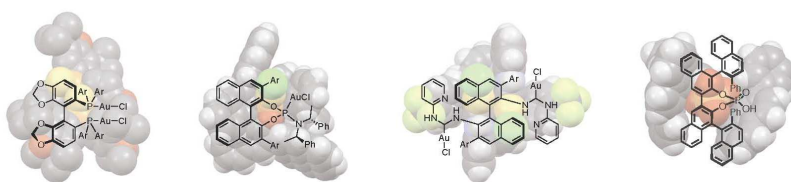
- [1] X. Zhang, Y. Zhou, J. Zuo, B. Yu, *Nature Commun.* 2015, 6:5879. doi: 10.1038/ncomms6879. [2] B. Yu, J. Sun, X. Yang, *Acc. Chem. Res.* 2012, 45, 1227–1236. [3] Y. Tang, J. Li, Y. Zhu, Y. Li, B. Yu, *J. Am. Chem. Soc.* 2013, 135, 18396–18405.

Enantioselective Synthesis of Heterocycles from Carbon-Carbon Multiple Bonds

F. Dean Toste

University of California, Berkeley, Berkeley, CA, USA

This lecture will emphasize a reactivity driven approach to development of electrophilic catalysts for addition, rearrangement, cycloaddition and coupling reactions of C-C multiple bonds. More specifically, the application of cationic gold(I) complexes, chiral counterions and chiral acids in enantioselective transformations initiated by π -activation will be discussed. Particular attention will be devoted to the mechanistic hypotheses that form the basis for catalyst discovery and the development of new reactions.



Complex Natural Products as a Driving Force for Discovery in Organic Chemistry

Brian Stoltz

Caltech, Pasadena, CA, USA

Our laboratory is deeply interested in the discovery and development of new reaction methodology *en route* to the chemical synthesis of complex bioactive molecules. Research in our group at the California Institute of Technology is centered in the general area of synthetic chemistry, with a focus on the development of new strategies for the preparation of complex molecules, including natural products that possess interesting structural, biological, and physical properties. Concurrent to this program of target driven synthesis is a strong effort directed toward the development of new techniques and reaction methods, which will be useful for a range of applications. Typically, the complex target structure is used as an inspiration for the discovery of new reactions and technologies that may eventually be regarded as general synthetic methodology. Consequently, this approach provides access to a) novel, medically relevant structures, b) a general method for their synthesis, and c) new synthetic methods that will be beneficial for a host of applications.

The catalytic asymmetric synthesis of all-carbon quaternary stereocenters stands as a significant challenge in synthetic chemistry and we have encountered this problem many times in the course of natural product total syntheses. As a result of such endeavors, we have been developing mild, catalytic methods that allow for efficient and stereoselective construction of these challenging centers. Our recent results and applications of these new methods will be discussed in the lecture.

Development of New Higher-Order Carbocyclization Reactions: Emulating Terpene Biosynthesis

P. Andrew Evans

Queen's University, Kingston, ON K7L 3N6, Canada

Transition metal-catalyzed higher-order carbocyclization reactions provide powerful methods for the stereoselective construction of complex polycyclic systems that are generally not accessible *via* classical pericyclic reactions.^[1] We have demonstrated the merit of the rhodium-catalyzed [m+n+n] carbocyclization reactions of carbon and heteroatom tethered 1,6-enynes with carbon monoxide, alkynes and dienes. More recently we have explored the development of a stereoselective rhodium-catalyzed [3+2+2] carbocyclization of 1,6-alkenylidenecyclopropanes with activated alkynes for the construction of *cis*-fused bicycloheptadienes,^[2] which prompted the isolation of the key metallacycle intermediate^[3] and the expansion of the scope of □-fragments to carbon monoxide and allenes.^[4,5] The seminar will outline some of these developments and their application to challenging bioactive natural products.

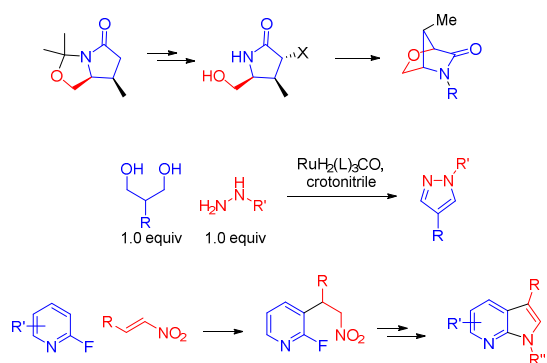
References

1. Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791.
2. (a) Evans, P. A.; Inglesby, P. A. *J. Am. Chem. Soc.* **2008**, *130*, 12838. (b) Evans, P. A.; Inglesby, P. A.; Kilbride, K. *Org. Lett.* **2013**, *15*, 1798. (c) Evans, P. A.; Negru, D. E.; Shang, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 4768.
3. Inglesby, P. A.; Bacsa, J.; Negru, D. E.; Evans, P. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 3952.
4. Mazumder, S.; Shang, D.; Negru, D. E.; Baik, M.-H.; Evans, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 20569.

Novel Strategies for the Preparation of Functionalizable Heterocyclic Motifs

Andrew Flick, Chulho (Charlie) Choi, Dan Schmitt, Alexandria Taylor, James Mousseau, Alpay Dermenci, Ming Chen, Niyi Fadeyi, Christophe Allais, Jotham Coe, Jessica Williams, Brian Gerstenberger, Stephen Wright, Xiaojing (Helen) Yang, Yvette Fobian, Bobby Kyne

Pfizer Global R & D, Groton, CT, USA



The preparation of heterocyclic motifs provides an exciting platform from which to conduct fundamental research, particularly that which supports the study of the interaction of small molecules with therapeutically-relevant biological targets. Densely packed arrangements of heteroatoms and stereogenic centers constituting these polycyclic subunit challenge the limits of current technology, prompting the need for new strategies for the synthesis of these systems. Novel approaches which have demonstrated our access to these challenging molecular architectures will be presented-- a ruthenium-catalyzed hydrogen transfer of 1,3-diols in the presence of alkyl hydrazines to furnish 1,4-disubstituted pyrazoles and an intramolecular displacement of an α -carbonyl fluoride by a tethered alkoxide to furnish [2.2.1] azabicyclics with excellent stereocontrol will be disseminated. Furthermore, a versatile approach to 5,6-fused heteroaromatics will be described which involves the conjugate addition of a metallated 2-fluoropyridine to substituted nitroolefins followed by a tractable 3-step sequence capable of furnishing these highly important bicyclic arrays.

Transcriptional Control of Cancer with Small Molecules: Towards Novel Therapeutics

Matthew Shair

Harvard University, Cambridge, USA

My lecture will describe our use of small molecules to discover a new mechanism to control aberrant transcription of key genetic programs in cancer. I will also describe our progress towards initiating first-in-class clinical trials based on our discoveries. Synthesis and development of precision targeting small molecules has played a key role in this project.

Nitrogen Dense Heterocycles as Antibiotic Adjuvants

Christian Melander

North Carolina State University, Raleigh, NC, USA

The emergence of resistance to multiple antimicrobial agents in pathogenic bacteria has become a significant global public health threat. Drug resistant bacterial infections cause considerable patient mortality and morbidity, and rising antibiotic resistance is seriously threatening the vast medical advancements made possible by antibiotics over the past 70 years. The Centers for Disease Control and Prevention (CDC) estimates that over two million people acquire antibiotic resistant bacterial infections each year in the United States, and more than 23,000 people die as a result.

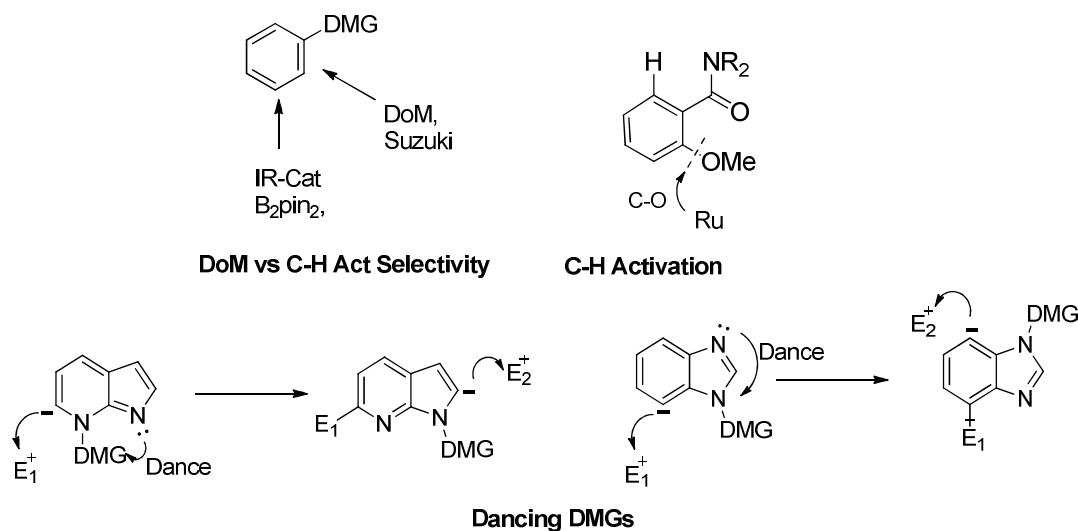
While the development of new antibiotics is one approach for the treatment of multi drug resistant pathogens, the fact remains that bacteria invariably develop resistance to any introduced therapy that relies solely upon a single bacteriostatic/bactericidal mechanism. For example, daptomycin was introduced into the clinic in 2003, and less than a year later the emergence of resistance was observed. As a result, alternative approaches to controlling bacterial infections are sorely needed and underexploited. One such approach is the identification of genes and pathways that play an important role in bacterial resistance to currently approved antibiotics, and the identification of small molecule adjuvants that target and block these pathways, thereby repotentiating the activity of the antibiotic when administered as a combination therapy. Efforts in our lab towards the development of such adjuvants based upon functionalized 2-aminoimidazoles will be presented, focusing on examples of breaking antibiotic resistance in multidrug resistant Gram-negative pathogens.

"Life is Heterocyclic" (Metalation)

Victor Snieckus

Queen's University, Kingston, Ontario, Canada

The common theme in our laboratories is the invention and development of new DoM aromatic chemistry, separate and linked to transition metal catalyzed processes, and their demonstration in bioactive molecule, natural product, and materials construction. In honour of Alan Katritzky, a selection of these themes bearing on heterocyclic chemistry, including new departures into DMG Dancing and Ir and Ru catalyzed DoM-enhancing Connections, will be described.



Board, J., Cosman, J., Singh, S. Rantanen, T., Snieckus, V., *Platinum Metals Rev.*, 2013, **57**, (4), 234–258.

Molecular Gymnastics: bond formation with rearrangements

Nuno Maulide

University of Vienna, Institute of Organic Chemistry, Vienna, Austria

The turn of the century brought about a pressing need for new, efficient and clean strategies for the chemical synthesis of biorelevant compounds. Our group has studied the use of various molecular rearrangements and atom-economical transformations as particularly appealing means towards the streamlined synthesis of complex small molecule targets.^{1,2,3}

In this lecture, we will present an overview of our research in these areas and how they provide efficient solutions for total synthesis as well as platforms for the discovery of unusual reactivity.

References

[1] (a) Luparia, M.; Oliveira, M.T.; Audisio, D.; Frébault, F.; Maulide, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 12631. (b) Audisio, D.; Luparia, M.; Oliveira, M.T.; Frébault, F.; Klütt, D.; Maulide, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 7314. (c) Misale, A. ; Niyomchon, S. ; Luparia, M. ; Maulide, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 7068.

[2] Huang, X.; Maulide, N. *J. Am. Chem. Soc.* **2013**, *135*, 7312.

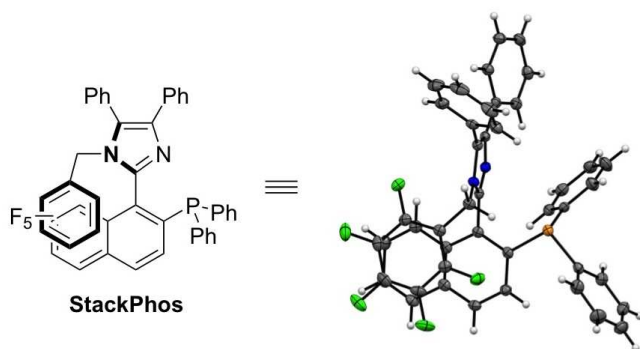
[3] Jurberg, I.D.; Peng, B.; Wöstefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 1950.

Development and Application of StackPhos, A New Chiral Biaryl Heterocyclic Ligand for Enantioselective Catalysis

Aaron Aponick

University of Florida, Gainesville, FL, USA

The development of new chiral ligands for enantioselective catalysis continues to be an important research area as the products impact a broad range of disciplines driven by organic synthesis. Our group has been involved in designing chiral biaryl P,N-ligands that incorporate a heterocycle into the biaryl backbone. This lecture will cover the developments in my laboratory that lead to the design and implementation of StackPhos, an imidazole-based P,N-ligand with unique ligation properties and catalytic activity.



Brønsted Acid Catalysis - Concepts and Applications in the Synthesis of Heterocycles

Magnus Rueping

RWTH Aachen University, Aachen, Germany

The development and application of metal-free catalysts has become an important topic in organic synthesis and catalysis. Recently, chiral Brønsted acids have been shown to be vital alternatives to metal catalysts and examples of highly enantioselective transformations have been reported. These reactions, similar to several enzymatic processes, proceed through ion-pair and hydrogen-bond activation. In this presentation our introduction to enantioselective Brønsted acid catalysis will be shown and new and valuable transformations will be highlighted. Additionally, efforts to delineate the general requirements for performing Brønsted acid as well as synergistic catalysis with the use of visible light or metals will be outlined and the applicability of these catalytic processes to the synthesis of natural product cores and heterocycles will be presented.

Recent Progress In The Total Synthesis of Natural Products

John Wood

Baylor University, Waco, TX, USA

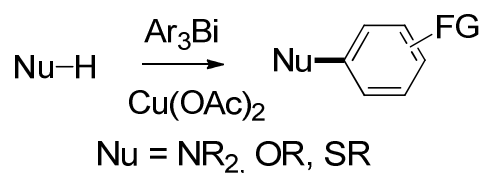
Efforts in our laboratories focus on the synthesis of complex natural products. Recent efforts directed toward syntheses of phomoidride D and hippolachnin A will be described.

Towards Chemoselective Arylation Reactions of Peptides Using Triarylbismuthanes

Martin Hébert^{1,2}, Adrien Le Roch^{1,2}, Marie-Jeanne Archambault^{1,2}, Alexandre Gagnon^{1,2}

¹Université du Québec à Montréal, Montréal, Canada, ²Pharmaqam, Montréal, Canada

There is a need for general methods that lead to post-synthetic modification of peptides. Currently, few methods exist for the chemoselective arylation on specific amino acid residues. Organobismuth reagents have recently gained interest due to their versatility in bond formation, functional group tolerance, low cost and low toxicity related to the inorganic bismuth salt. Recently, our group has developed efficient arylation methods using highly functionalized trivalent arylbismuth reagents to form C-C, C-O and C-N bonds.¹ In particular, indoles, phenols and aminoalcohols have been successfully arylated in good to excellent yields via substoichiometric copper catalysis in mild conditions. As a result, this method will be further employed as a mean of selective arylation of polypeptides. In this poster, we will present our progress in the development of arylation methods of peptides using triarylbismuthanes.



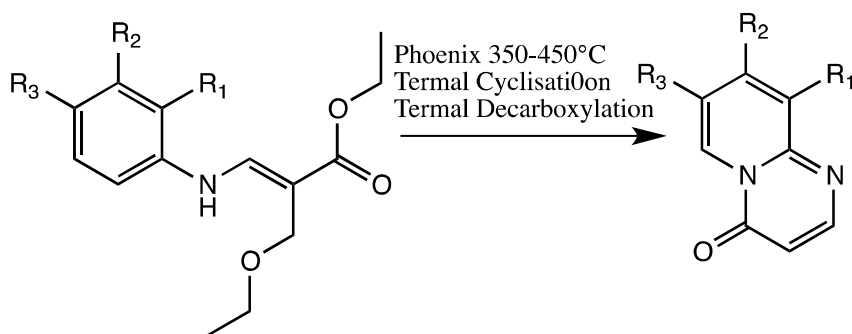
¹ a) Petiot, P.; Gagnon, A. *Eur. J. Org. Chem.*, **2013**, 5282; b) Crifar, C.; Petiot, P.; Ahmad, T.; Gagnon, A. *Chem. Eur. J.*, **2014**, *20*, 2755; c) Petiot, P.; Dansereau, J.; Gagnon, A. *RSC Adv.*, **2014**, *4*, 22255; d) Petiot, P.; Dansereau, J.; Hébert, M.; Khene, I.; Ahmad, T.; Samaali, S.; Leroy, M.; Pinsonneault, F.; Legault, C. Y.; Gagnon, A. *Org. Biomol. Chem.*, **2015**, *13*, 1322.

Investigation of the regioselectivity of thermal cyclization reactions in gas and liquid phase high temperature flow reactors

Richard Jones, Gellert Sipos, Laszlo Lengyel, Gyorgy Dorman, Laszlo Kcosis, Heather Graehl, Ferenc Darvas

Thalesnano, Budapest, Hungary

Gould-Jacobs type intramolecular thermal cyclisations were previously reported in a continuous flow reactor at high temperatures (300-360C) and pressure (100-160bar) in liquid phase. The regioselectivity of the ring closure depends on the nature and position of the substituents often leading to a mixture of products. We investigated the regiochemical outcome of substituted amino-pyridine substructures cyclisation under various conditions in liquid and gas phase as well, applying a flow pyrolysis apparatus under high vacuum between solvent-free conditions. Flash vacuum pyrolysis (FVP) allows a rapid exposure to high temperature (200 – 900C), which often favour the formation of one regioisomer. Here we compare the outcome of the thermal cyclisation of various unsaturated diesters or analogue substructures (derived from condensation with ethoxymethylenomalonate) performed in both systems.

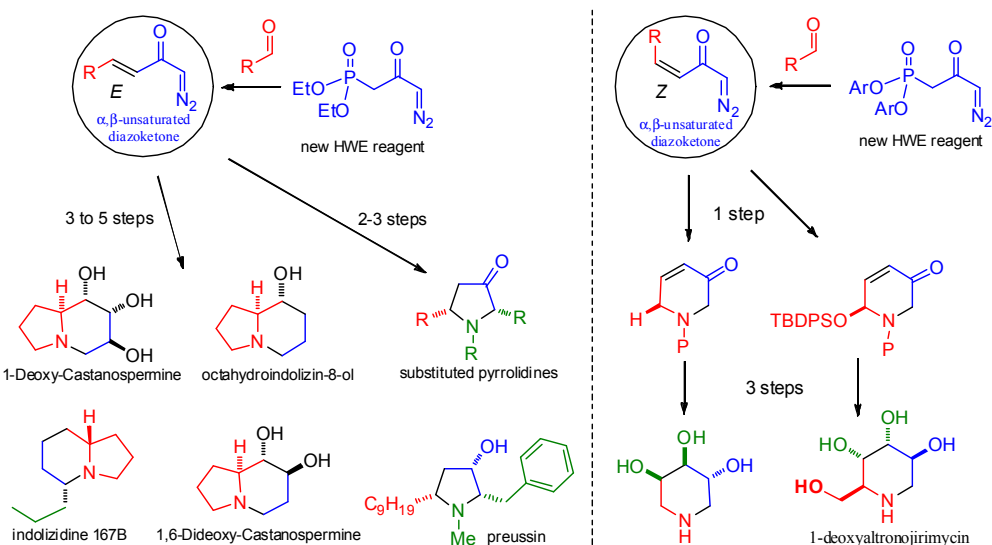


α,β -Unsaturated Diazoketones as Useful Platforms in the Synthesis of Nitrogen Heterocycles

Antonio Burtoloso

University of São Paulo, São Carlos, Brazil

Diazocompounds are a very interesting class of compounds that can promote a wide range of reactions, such as cyclopropanations, insertion reactions, ylide formation, dimerization and elimination reactions and formation of ketenes by the Wolff rearrangement, among others. An interesting class of these diazocompounds is the α,β -unsaturated diazoketones, which has received little attention when compared to the saturated ones due to the difficulty of its preparation by the usual existing methods. Herein, we would like to describe two methodologies for the preparation of α,β -unsaturated diazoketones with E and Z geometry employing new Horner-Wadsworth-Emmons reagents and their use as efficient platforms in the synthesis of pyrrolidines, indolizidines and piperidines.



The Functionalization of C—H Bonds

M. Christina White

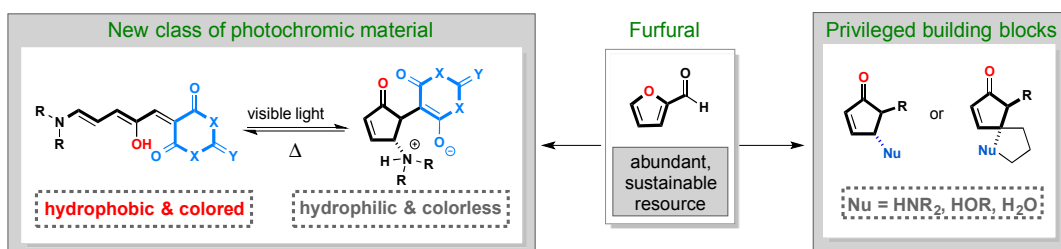
University of Illinois, University of Illinois, USA

Among the frontier challenges in chemistry in the 21st century are the interconnected goals of increasing control of chemical reactivity while synthesizing and diversifying complex molecules with higher efficiency. Traditional organic methods for installing oxidized functionality rely heavily on acid-base reactions that require extensive functional group manipulations (FGMs). In contrast, nature routinely uses allylic and aliphatic C—H oxidation methods, generally mediated by heme and non-heme iron monooxygenase enzymes, to directly install oxidized functionality into the preformed hydrocarbon framework of complex molecules. Due to their ubiquity in complex molecules and inertness to most organic transformations, C—H bonds have typically been ignored in the context of methods development for total synthesis. The exceptions to this rely on substrate directing groups to facilitate site-selectivity and reactivity. The discovery and development of highly selective oxidation methods for the direct installation of oxygen, nitrogen and carbon into allylic and aliphatic C—H bonds of complex molecules and their intermediates are discussed. Unlike Nature which uses elaborate shape or functional group recognition active sites, this chemistry harnesses the subtle electronic, steric, and stereoelectronic interactions between C—H bonds and small molecule transition metal complexes to achieve high regio-, chemo-, stereo- and site-selectivities with high substrate generality- and without the requirement for directing groups. Our current understanding of these interactions gained through empirical and mechanistic studies will be discussed. A user-friendly catalyst reactivity model that calculates and *even predicts* the major site of oxidation as well as the magnitude and direction of the site-selectivity in complex substrates as a function of catalyst will be delineated. Novel strategies for streamlining the process of complex molecule synthesis and diversification enabled by these methods will be presented.

Molecular Rearrangements of Furan Heterocycles

Javier Read de Alaniz

University of California Santa Barbara, Santa Barbara, CA, USA



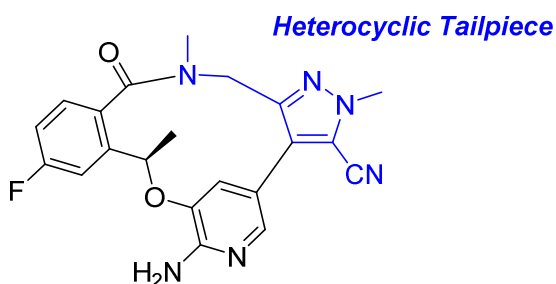
Materials derived from non-edible renewable resources, ideally by-products in food production processes, are valuable starting materials for chemistry. One such raw material, furfural, is produced from hemicellulose derived from agricultural waste products like bagasse, oat hulls and corncobs. Environmentally benign stock-chemicals are important to sustainable development by ensuring a future supply of raw materials. Our group has studied the molecular rearrangement of furfural and its derivatives to streamline the synthesis of molecular building blocks, including a novel class of photochromic material. In this lecture, we will present the development of this chemistry and highlight recent applications of the photochromic material as sensors and their use in light-controlled cargo delivery.

Synthesis and Conformational Studies of Small Molecule Macrocyclic Inhibitors of ALK/ROS1 – Discovery of PF-06463922

Paul Richardson, Ted Johnson, Jacqui Hoffman, Neal Sach, Simon Bailey, Mingying He, Michael Collins, Phuong Le, Bryan Li, Graham Smith, Jeff Elleraas

Pfizer WWMC, La Jolla, CA, USA

This talk will focus on the synthesis of the chemical properties of the macrocyclic inhibitors developed for the EML4 ALK program for the treatment of NSCLC leading to the discovery of the clinical candidate PF-06463922. The work disclosed will feature (i) variations of the heterocyclic tailpiece of the molecule, and the synthetic chemistry to incorporate these into the macrocyclic ring through either macrolactamization or direct arylation, (ii) conformational studies and atropisomerism of specific macrocyclic ring systems, and (iii) optimization and scale-up of the clinical candidate including the evolution of the synthesis of the pyrazole tailpiece.



PF-06463922

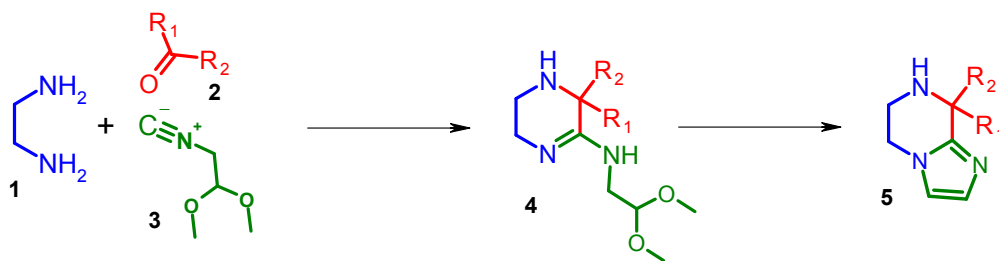
An Efficient Synthesis of Tetrahydroimidazo[1,2-a]pyrazines via Tandem Multicomponent Reaction

Volodymyr Kysil¹, Haiji Xia¹, Vasiliy Stolyarenko², Alan Tsavloev², Alexandre Ivachtchenko¹

¹ChemDiv, Inc., San Diego, CA, USA, ²Chemical Diversity Research Institute, Khimki, Moscow Reg., Russia

Isocyanide based multicomponent reactions (IMCRs) followed by cyclization have become a valuable tools of drug discovery oriented synthetic heterocyclic chemistry since they allow synthesizing diverse nature-like heterocyclic small molecules in simple one-pot procedures. Recently we have developed IMCR of various primary diamines and carbonyl compounds that leads to a wide variety of heterocyclic scaffolds with pyrazine, quinaxoline, hetarenopyrazine, 1,4-diazepine, 1,4-benzodiazepine, and other pharmaceutically relevant cores [1].

Here we report post-condensation modification of the discovered IMCR by involving of dimethyl isocyanoacetal as a bifunctional isocyanide component. This enables further cyclization of intermediate pyrazine-2-amines **4** into target imidazopyrazines **5** under acidic conditions. Since no purification is required for intermediates **4**, the entire synthesis can be performed in one-pot mode.



Notably, imidazopyrazine core of general formula **5** is a key structural feature of orexin receptor antagonists (2012), kappa receptor agonists, mGluR5 modulators, and TrkA inhibitors.

Scope of the developed tandem reaction including its expansion for the synthesis of spiro-imidazopyrazines and tetrahydroimidazo[1,2-a][1,4]diazepines as well as its application for small molecule libraries synthesis will be discussed.

[1] Kysil, V. et al. *Eur. J. Org. Chem.* **2010**, 1525–1543.

Gold catalysis in the synthesis of heterocycles

Liming Zhang

UCSB, Santa Barbara, CA, USA

Heterocycles are important structural motifs found in various natural products and functional materials. Their syntheses under mild reaction conditions and in highly efficient manners are still much in demand. On the other hand, Au catalysis has lately emerged as a powerful platform for the development of versatile synthetic methods.

In this presentation, two general strategies for the synthesis of *N/O*-heterocycles in the context of gold-catalyzed transformations of alkynes will be discussed. In the first strategy, oxidative catalysis using tethered or external nucleophilic oxidants provide rapid access to azetidion-3-ones, tetrahydrobenzazepinones, piperidin-4-ones, azepin-4-ones and other ring systems. In the second strategy, gold catalysis is employed as the 'spring board' to provide access to versatile intermediates otherwise difficult to obtain, and their further transformations/rearrangements enable the preparation of heterocycles. Among the various implementations of these strategies to be presented, three selected cases are outlined in the Scheme. Applications of these methods in natural product synthesis will also be discussed.

Scheme. Gold-Catalyzed Synthesis of Heterocycles

