Award Lecture Abstracts

Taylor Awardee Viresh Rawal

Katritzky Awardee Sarah Reisman

Industrial Awardee Rémy Angelaud

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Efficient Construction and Selective Functionalization of Heterocycles in the Manufacturing of Active Pharmaceutical Ingredients

R. Angelaud

Genentech, Inc., Department of Small Molecule Process Chemistry, South San Francisco, USA
angelaud.remy@gene.com

Heterocycles are present in more than 90% of active pharmaceutical ingredients (API) and come in a very wide variety of shapes and sizes. We will present the different synthesis strategies designed and developed to access some of these heterocyclic molecules towards the manufacture of marketed pharmaceutical drugs and APIs currently in clinical development.

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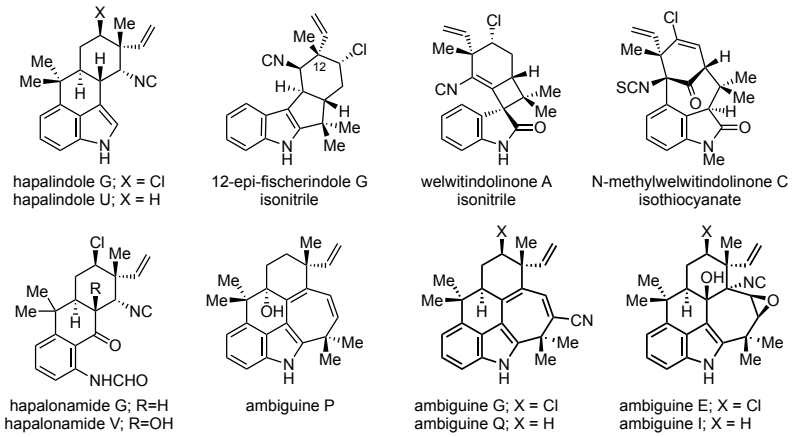
Progress toward members of the hapalindole family of alkaloids

V. H. Rawal,[a],*J. Xu,[a] and L. Hu[a]

[a]*Department of Chemistry, University of Chicago, Chicago, IL USA*
**vrawal@uchicago.edu*

Abstract: A chemical synthesis comprises a series of reactions that gradually increase the complexity of the starting material until it is finally transformed into the desired target. While the specific reactions—the tactics—chosen for each step are crucial, a successful total synthesis campaign must also be undergirded by an overall strategy that solves the crucial structural challenges inherent to a particular class of natural products. In this presentation, I will discuss the strategic and tactical considerations that went into our work on the synthesis of some cyanobacteria derived indole alkaloid metabolites, focusing in particular on the pentacyclic ambiguines group of compounds, which are a subset of the hapalindole family of alkaloids.[1-3]



Representative of Hapalindoles, Welwitindolinones, Hapalonamide, and Ambiguines

References:

1. Comprehensive review: Bhat, V., Dave, A., MacKay, J.A., Rawal, V.H. The Chemistry of Hapalindoles, Fischerindoles, Ambiguines, and Welwitindolinones, *The Alkaloids: Chemistry and Biology*, **2014**, *73*, 65-160.
2. Ambiguine P: (a) Johnson, R. E.; Ree, H.; Hartmann, M.; Lang, L.; Sawano, S.; Sarpong, R. *J. Am. Chem. Soc.* **2019**, *141*, 2233-2236. (b) Xu, J.; Rawal, V.H. Total Synthesis of (-)-Ambiguine P, *J. Am. Chem. Soc.*, **2019**, *141*, 4820-4823.
3. Ambiguine G: Hu, L. B.; Rawal, V. H. Total Synthesis of the Chlorinated Pentacyclic Indole Alkaloid (+)-Ambiguine G, *J. Am. Chem. Soc.* **2021**, *143*, 10872–10875.

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

Sarah E. Reisman[a,*]

[a]*California Institute of Technology, Pasadena, CA, USA*
**reisman@caltech.edu*

The chemical synthesis of natural products provides an exciting platform from which to conduct fundamental research in chemistry and biology. Our group is currently pursuing the synthesis of several structurally complex natural products, many of which contain heterocycles at their core. The densely packed arrays of heteroatoms and stereogenic centers that constitute these polycyclic targets challenge the limits of current technology and inspire the development of new synthetic strategies and tactics. This seminar will describe the latest progress in our target-directed synthesis endeavors.

Plenary Lecture Abstracts

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Innovation By Evolution: Bringing New Chemistry To Life

F. H. Arnold

California Institute of Technology, Pasadena, USA
frances@cheme.caltech.edu

Not satisfied with biology's vast catalyst repertoire, I want to create new enzyme catalysts and expand the chemistry of life. We use the most powerful biological design process, evolution, to optimize existing enzymes and invent new ones, thereby circumventing our profound ignorance of how sequence encodes function. Evolution can innovate by exploiting the promiscuous catalytic activities of extant proteins to mold new enzymes. We are using this insight to explore chemistries that become available to enzymes in a new environment. I will illustrate with a few examples how 'carbene transferase' and 'nitrene transferase' enzymes have been generated by directed evolution of Fe-heme proteins in the presence of abiological carbene and nitrene precursors. These new-to-nature biocatalysts can exhibit remarkable selectivity for their targeted reactions, arising from macromolecular active sites that are readily tuned by evolution.

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Changing the World, One Reaction at a Time

L.-C. Campeau[a]

[a]*Department of Process Research and Development, Merck Research Laboratories, Merck & Co. Inc., Rahway, New Jersey, 07065, USA*
**lc.campeau@merck.com*

Nucleoside analogues are ubiquitous in nature and are critical component of life-saving therapies used in the treatment of viral disease and cancer. Despite their widespread use and commercial value, the state-of-the-art methods for their preparation in drug discovery, drug development and eventual commercialization are lacking and remain a poorly solved problem in organic synthesis. In addition to posing synthetic challenges, custom nucleoside total synthesis presents several challenges with respect to green and sustainable chemistry, where current methods largely rely on chiral pool feedstocks and protecting group chemistry. We have developed a suite of novel methods for the synthesis and scale-up of nucleosides and cyclic dinucleotides. These efforts have culminated to an aspirational synthesis from commodity chemicals using a biocatalytic in-vitro cascade for construction of nucleosides.

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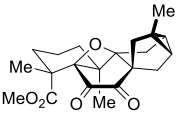
Recent Developments in Strategies and Tactics Towards Complex Secondary Metabolites

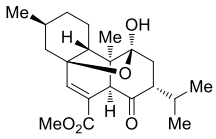
Erick M. Carreira

ETH-Zürich

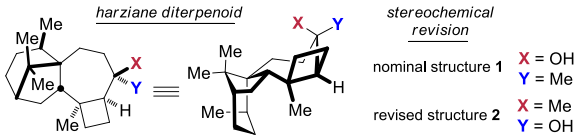
The talk will include discussion and analysis of recent natural product targets that have been synthesized in the group. It will focus on target oriented synthesis as an engine for the generation of novel methods and approaches to bioactive agents. The methods involve novel, unexpected reactivity and unusual building blocks that are fully integrated to lead to efficient routes.



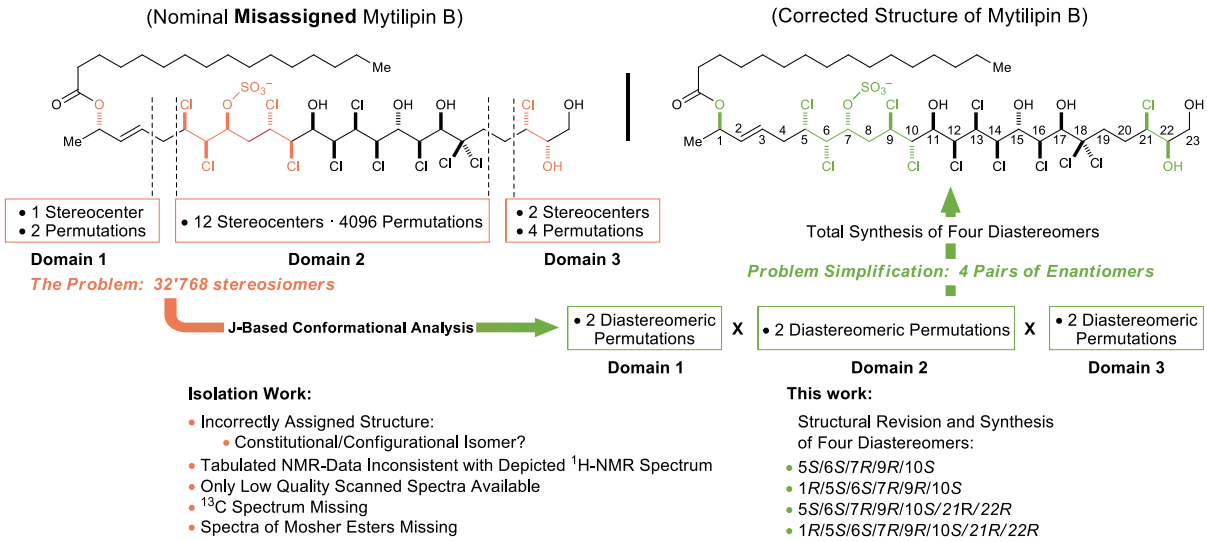
(–)-Mitrephorone A



(+)-Sarcophytin
reassigned absolute configuration



- unprecedented and highly caged 6–5–7–4 skeleton
- 6 contiguous stereocenters
- 3 quaternary carbon atoms



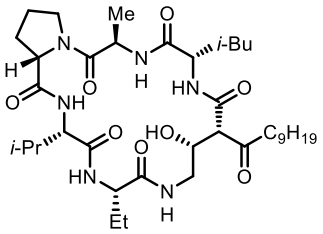
Isolation Work:

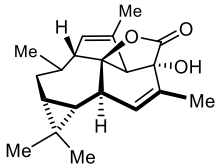
- Incorrectly Assigned Structure:
  - Constitutional/Configurational Isomer?
- Tabulated NMR-Data Inconsistent with Depicted ^{1}H-NMR Spectrum
- Only Low Quality Scanned Spectra Available
- ^{13}C Spectrum Missing
- Spectra of Mosher Esters Missing

This work:

Structural Revision and Synthesis of Four Diastereomers:

- 5*S*/6*S*/7*R*/9*R*/10*S*
- 1*R*/5*S*/6*S*/7*R*/9*R*/10*S*
- 5*S*/6*S*/7*R*/9*R*/10*S*/21*R*/22*R*
- 1*R*/5*S*/6*S*/7*R*/9*R*/10*S*/21*R*/22*R*





Euphorikanin A

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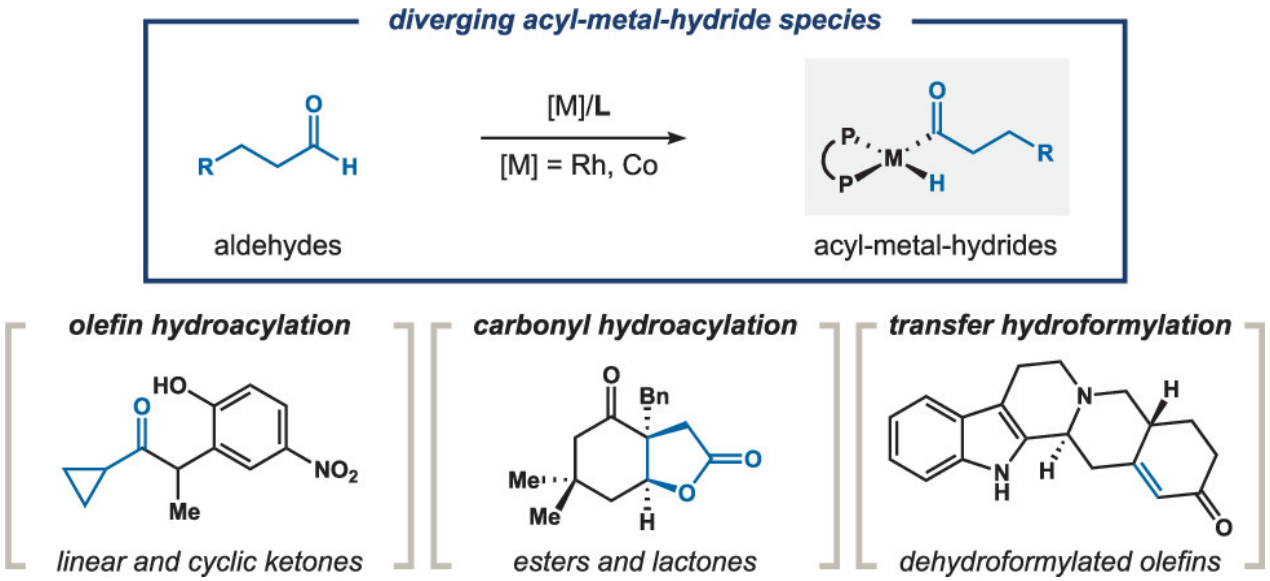
Choose Your Own Adventure in Metal-Hydride Catalysis

Vy M. Dong[a]

[a]*University of California at Irvine, Irvine, CA, United States*
dongv@uci.edu

Metal hydrides promote diverse organic transformations that include both C─C bond making and C─C bond breaking processes.[1,2] This lecture will highlight the development of Rh, Co, and Cu-catalysts for use in enantioselective hydrofunctionalizations (e.g., hydroacylation, hydroamination, and hydrothiolation). A unique transfer hydroformylation will be described that allows conversion of aldehydes or alcohols to olefins. The presentation emphasizes mechanistic studies that demonstrate the role of counter-ions in controlling selectivity. Lastly, we disclose applications of these catalysts for transforming feedstocks into more complex building blocks and targets for applications in biology and medicine.



References

1. Davison, R. T.; Kuker, E. L.; Dong, V. M. Teaching Aldehydes New Tricks Using Rhodium- and Cobalt-Hydride Catalysis. Acc. Chem. Res. 2021, 54 (5), 1236–1250.
2. Parker, P. D.; Hou, X.; Dong, V. M. Reducing Challenges in Organic Synthesis with Stereoselective Hydrogenation and Tandem Catalysis. J. Am. Chem. Soc. 2021, 143 (18), 6724–6745.

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Photocatalytically Inducible Tetrazine Ligation

A. Hillman,[a] Y. Fang,[a] A. Jemas,[a] C. Makara,[a] J. E. Pigga,[a] P. Ramaraj,[a] J. E. Rosenberger,[a] S. Scinto,[a] A. Tallon,[a] W. Trout,[a] S. Tsang,[a] C. Wang,[a] Y. Xie,[a] C. W. am Ende,[b] J. M. Fox[a,*]

[a]*University of Delaware, Department of Chemistry and Biochemistry, Newark, DE 19713, USA*
[b]*Pfizer Worldwide Research and Development, Eastern Point Road, Groton, Connecticut 06340, USA*
**jmfox@udel.edu*

This seminar will discuss recent advances in development of the tetrazine ligation– the fastest known bioorthogonal reaction.[1] Tetrazine ligation has been used broadly by the scientific community, and finds application across chemical biology, medicine, nuclear medicine, and material science. The talk will describe advances in photochemistry, flow chemistry, and cross-coupling chemistry that have enabled access to improved *trans*-cyclooctene and tetrazine reagents including a suite of tool molecules developed in collaboration between UD and Pfizer.[2–4] The talk will also discuss the catalytic activation of bioorthogonal chemistry with light, or CABL, a new method for 'turning on' rapid bioorthogonal chemistry *in vivo* and in cellular context through the photocatalyzed oxidation of dihydrotetrazines to tetrazines.[5–7] Discussed will be new tool molecules with high stability in the cellular environment in their 'off' state, and the fastest bioorthogonal reactions to date in their 'on' state. CABL photocatalysts are based on fluorescein or silarhodamine dyes with activation at 470 or 660 nm, respectively. CABL is rapid even at sub-micromolar concentrations, and CABL-photocatalysts are biocompatible due to their minimal singlet oxygen production. With single photon activation, CABL can be used to activate subcellular activation in the nucleus, mitochondria, actin, or cytoplasm and two-photon excitation promotes CABL at the suborganelle level to selectively pattern live cells under no-wash conditions. CABL can also applied to spatially resolved live-cell labeling of the low abundant protein target monoacylglycerol lipase at endogenous concentration. Kinetic studies have been used to develop a proposal explaining the fast and selective photocatalytic oxidation of dihydrotetrazines with molecular oxygen as the terminal oxidant and hydrogen peroxide as a reaction product.

References

1. Scinto, S. L.; Bilodeau, D. A.; Hincapie, R.; Lee, W.; Nguyen, S. S.; Xu, M.; am Ende, C. W.; Finn, M. G.; Lang, K.; Lin, Q.; Pezacki, J. P.; Prescher, J. A.; Robillard, M. S.; Fox, J. M. *Nature Reviews Methods Primers* **2021**, *1*, 30.
2. Pigga, J. E.; Rosenberger, J. E.; Jemas, A.; Boyd, S. J.; Dmitrenko, O.; Xie, Y.; Fox, J. M.. *Angew. Chem. Int. Edit.* **2021**, *60*, 14975-14980.
3. Xie, Y.; Fang, Y.; Huang, Z.; Tallon, A. M.; am Ende, C. W.; Fox, J. M. *Angew. Chem. Int. Edit.* **2020**, *59*, 16967-16973.
4. Lambert, W. D.; Fang, Y.; Mahapatra, S.; Huang, Z.; am Ende, C. W.; Fox, J. M. *J. Am. Chem. Soc.* **2019**, *141*, 17068-17074.
5. Jemas, A.; Xie, Y.; Pigga, J. E.; Caplan, J. L.; am Ende, C. W.; Fox, J. M. *J. Am. Chem. Soc.* **2022**, *144*, 1647-1662.
6. Wang, C.; Zhang, H.; Zhang, T.; Zou, X.; Wang, H.; Rosenberger, J. E.; Vannam, R.; Trout, W. S.; Grimm, J. B.; Lavis, L. D.; Thorpe, C.; Jia, X.; Li, Z.; Fox, J. M. *J. Am. Chem. Soc.* **2021**, *143*, 10793-10803.
7. Zhang, H.; Trout, W. S.; Liu, S.; Andrade, G. A.; Hudson, D. A.; Scinto, S. L.; Dicker, K. T.; Li, Y.; Lazouski, N.; Rosenthal, J.; Thorpe, C.; Jia, X.; Fox, J. M. *J Am Chem Soc* **2016**, *138*, 5978-5983.

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New synthetic chemistry to probe the biology of nucleic acids

Matthew J. Gaunt

[a]*Yusuf Hamied Department of Chemistry, University of Cambridge, Cambridge, United Kingdom. CB22 7GA*
**mjg32@cam.ac.uk*

The primary code stored within RNA is displayed through the linear sequence of four nucleobases (A, C, G, U). Beyond the core information stored in the sequence of RNA, a second layer of programming exists in the form of many chemical modifications to the canonical nucleobases. By comparison, the array of modifications to the canonical nucleobases in DNA–known as the epigenetic code–is relatively limited, albeit crucial to its regulation of the gene, with methylation at C being the prevalent chemical mark. In contrast, over 140 distinct chemical variations identified in RNA, to date. These post-transcriptionally modified ribonucleotides play integral roles in the cellular control of information that is encoded in the gene. The modifications are prevalent across all RNA types and are collectively referred to as the epitranscriptome. The sheer diversity of RNA modification means that a variety of tools are needed to fully explore the epitranscriptome. Currently, most of the methods for the detection of modified RNAs use an antibody that is selective for a particular modification. Beyond the oligomeric nucleic acids, small-molecule nucleosides and nucleotides also play a crucial role in the treatment and regulation of disease. These molecules also display a plethora of structural modification compared to the native monomeric components.

This lecture will focus on developing new synthetic chemistry, based primarily on visible-light photocatalysis, that selectively modifies nucleic acids – from small molecules to genetic material – and can potentially help to unlock new lines of research in drug discovery, probe design, topology and sequencing.

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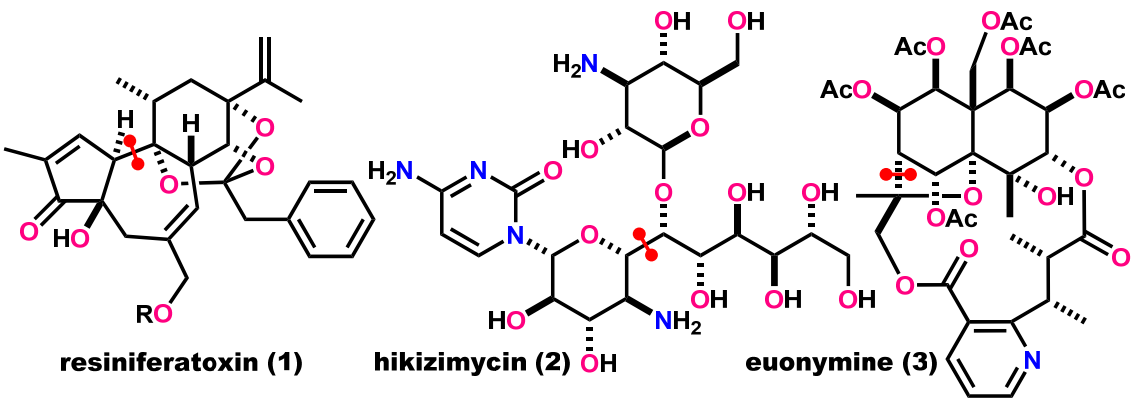
Radical-Based Approach for Synthesis of Complex Natural Products

Masayuki Inoue

Graduate School of Pharmaceutical Sciences, The University of Tokyo, JAPAN
inoue@mol.f.u-tokyo.ac.jp

Natural products with a high ratio of sp^3-hybridized atoms and oxygen-substituted stereogenic centers represent privileged structures for the development of pharmaceuticals and chemical probes. The multiple oxygen functionalities of these natural products endow their potent and selective biological activities, although they significantly heighten the challenge of their chemical assemblies.[1] We focused on developing efficient strategies for the total syntheses of this biologically and chemically important class of molecules. Specifically, we have designed and devised radical-based strategies for assembling highly oxygenated natural products.[2,3] In this lecture, we report the development of the radical coupling reactions and the synthetic routes to resiniferatoxin (**1**),[4,5] hikizimycin (**2**),[6] and euonymine (**3**)[7] by applying the radical chemistry.



References

1. Urabe, D.; Asaba, T.; Inoue, M. *Chem. Rev.* **2015**, *115*, 9207.
2. Inoue, M. *Acc. Chem. Res.* **2017**, *50*, 460.
3. Nagatomo, M.; Inoue, M. *Acc. Chem. Res.* **2021**, *54*, 595.
4. Hirose, A.; Watanabe, A.; Ogino, K.; Nagatomo, M.; Inoue, M. *J. Am. Chem. Soc.* **2021**, *143*, 12387.
5. Hikone, Y.; Kato, T.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2022**, *24*, 929.
6. Fujino, H.; Fukuda, T.; Nagatomo, M.; Inoue, M. *J. Am. Chem. Soc.* **2020**, *142*, 13227.
7. Wang, Y.; Nagai, T.; Watanabe, I.; Hagiwara, K.; Inoue, M. *J. Am. Chem. Soc.* **2021**, *143*, 21037.

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Oxygen Driven Fragment Coupling for the Synthesis of Natural Products and Antibacterials

Marisa Kozlowski[a,*]

[a]*Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104-6323, USA*
**marisa@sas.upenn.edu*

Nature uses oxidative couplings to construct carbon-carbon, carbon-oxygen, and carbon-nitrogen bonds with a high degree of efficiency. Surprisingly, few laboratory equivalents are as selective or as efficient as the biological versions. The use of parallel microscale screening to discover selective and efficient catalysts for such processes using oxygen as the terminal oxidant will be discussed. The unexpected outcomes obtained highlight the value of interrogating large numbers of rationally selected variables under the umbrella of general hypothesis. The development of selective oxidative catalytic processes for phenol coupling, enol coupling, and alkyl C–H activation will be discussed. Applications in total synthesis of hypocrellin, honokiol, chaetoglobin, and pyrolaside B will be presented. Finally, studies on the mechanisms of these transformations will be described with the goal of understanding the governing principles and how they might be used to discover further new transformations.

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Heterocycles in the context of natural products synthesis

Armen Zakarian

Department of Chemistry and Biochemistry, University of California, Santa Barbara

Natural products are a rich source of heterocyclic structures. Varying from aromatic, often represented in classic medicinal chemistry, to more strereochemically complex saturated nitrogen, oxygen, and other heteroatom heterocycles, they present exciting challenges for synthesis. Saturated or partially saturated heterocyclic compounds are also an emerging class of privileged targets in medicinal chemistry. In many cases, construction of heterocyclic structures is a main problem in the synthesis design. Several contributions from our group focusing on the synthesis of cylindrospermopsins, xestospongins, and other select examples will be discussed.

Invited Lecture Abstracts

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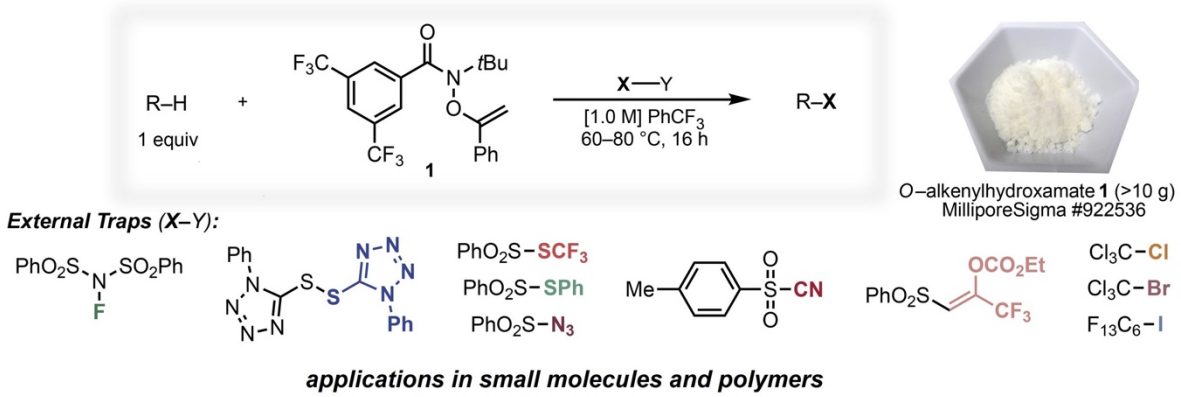
New Strategies for Hydrocarbon Functionalization

Erik J. Alexanian

Department of Chemistry, The University of North Carolina, Chapel Hill, NC (USA)
eja@email.unc.edu

Reactions that functionalize aliphatic C–H bonds site-selectively are valuable in a range of synthetic contexts, from the sustainable synthesis of small molecules to the upcycling of post-consumer plastic waste. Our recent efforts towards the development of a general platform for intermolecular aliphatic C–H functionalization of both small molecules and polymers using heteroatom-centered radicals will be presented. The strategy features easily-accessed radical precursors to enable a diverse set of practical C–H transformations with excellent site selectivities and chemoselectivities. Applications of the reaction platform to the decarboxylative functionalization of complex molecules will also be discussed.



References

1. Fazekas, T. J.; Alty, J. W.; Neidhart, E. K.; Miller, A. S.; Leibfarth, F. A.; Alexanian, E. J. *Science* **2022**, *375*, 545–550.
2. Na, C. G.; Ravelli, D.; Alexanian, E. J. *J. Am. Chem. Soc.* **2020**, *142*, 44–49.
3. Tierney, M. M.; Crespi, S.; Ravelli, D.; Alexanian, E. J. *J. Org. Chem.* **2019**, *84*, 12983–12991.

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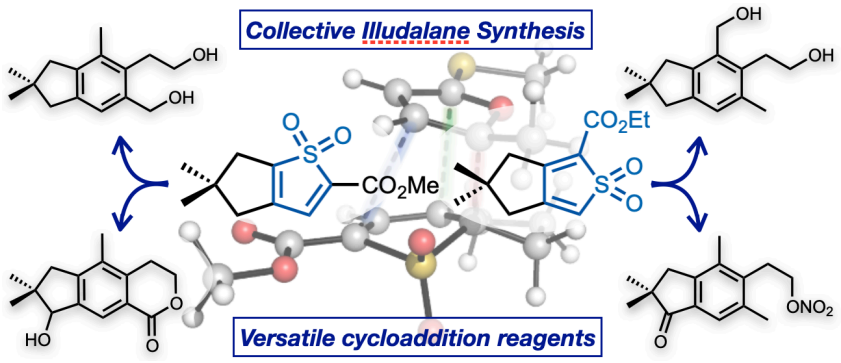
Thiophene *S*,*S*-dioxides: Versatile heterocycles for natural product synthesis

Edward A. Anderson,* Kun Ho (Kenny) Park, Nils Frank, Fernanda Duarte

Chemistry Research Laboratory, Department of Chemistry, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, U.K.
**edward.anderson@chem.ox.ac.uk*

The *de novo* synthesis of polysubstituted benzene rings is an attractive strategy that avoids the need for lengthy synthetic manipulations of pre-formed arenes. One approach to such structures involves cascade Diels-Alder / retro-Diels Alder chemistry, where the extrusion of small molecules such as N_2 (from pyridazines) or CO_2 (from pyrones) can drive the cascade. A class of diene that has been largely overlooked to date in such chemistry are thiophene *S*,*S*-dioxides, derivatives of thiophenes that are easily prepared by peracid oxidation.[1] This lecture will describe recent work from our group on the first applications of thiophene *S*,*S*-dioxides as substrates for intermolecular Diels-Alder cascades in natural product total synthesis, in the context of a collective synthesis of 9 members of the illudalane family of sesquiterpenes.[2] Calculations revealed that the particular cycloaddition used in this synthesis – reaction of the thiophene *S*,*S*-dioxide with a furan – proceeds via an ambimodal transition state rather than a pure pericyclic process, with subsequent bifurcation to different (4+2) cycloadducts.[3,4] The extent of asynchronicity in this transition state is unusual in the field. Finally, recent work involving the application of thiophene *S*,*S*-dioxide cascades towards other natural product families will be described.



References

1. Nakayama, J., *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1–17.
2. Park, K. H. (K.); Frank, N.; Duarte, F.; Anderson, E. A., *J. Am. Chem. Soc.* **2022**, *144*, 10017–10024.
3. Houk, K. N.; Xue, X.-S.; Liu, F.; Chen, Y.; Chen, X.; Jamieson, C., *Isr. J. Chem.* **2022**, *62*, e202100071.
4. Hare, S. R.; Tantillo, D. J., *Pure Appl. Chem.* **2017**, *89*, 679–698.

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Engineering Fe(II)/α-Ketoglutarate-Dependent Halogenases and Desaturases

R. Buller [a,*]

[a]*Competence Center for Biocatalysis, Zurich University of Applied Sciences, Wädenswil, Switzerland*

*rebecca.buller@zhaw.ch

Late-stage functionalization of complex molecular scaffolds offers an elegant route to create novel biologically active entities. In discovery chemistry, inactivated C-H bonds are regarded as particularly promising, if challenging, points of diversification as they allow to create new analogs without resorting to *de novo* synthesis. As a prerequisite for this approach, however, the reaction procedures must be compatible with already existing functional groups in the lead structural scaffold – a task still challenging most chemical methodologies. In this context, Fe(II)/α-ketoglutarate dependent dioxygenases, enzymes which are capable of halogenating and hydroxylating sp^3 carbons with high stereo- and regiocontrol under benign conditions, have attracted increasing attention. This enzyme family's reported substrate scope, however, is often limited to natural substrates and their close analogues. By employing a combination of smart library design and machine learning assisted directed evolution, we engineered several Fe(II)/α-ketoglutarate dependent dioxygenases for the late-stage functionalization of molecules of pharmaceutical interest, ranging from non-natural amino acids to bulky macrolides, hitherto not accepted substrates.[1-4] Notably, our enzyme engineering approach allowed us to rapidly identify more active enzyme variants increasing the apparent k_{cat} and the turnover number of the enzymes by orders of magnitude. In addition, in case of the engineered soraphen halogenases, we could predict and consequently modulate the regioselectivity of soraphen halogenation allowing the targeted analysis of the small molecule's structure-function activity in biological assays.

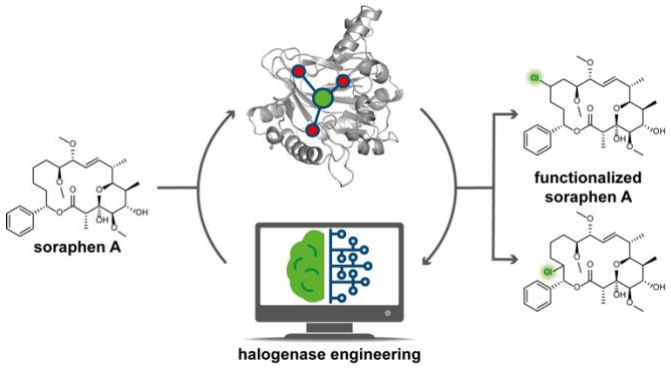

Figure: Engineering Fe(II)/α-ketoglutarate dependent halogenases for the late-stage modification of the natural product soraphen.

1. Büchler, J.; Malca, S. H.; Patsch, D.; Voss, M.; Turner, N. J.; Bornscheuer, U. T.; Allemann, O.; Le Chapelain, C.; Lumbroso, A.; Loiseleur, O.; Buller, R. *Nat Commun* **2022,** *13* (1), 371.
2. Meyer, F.; Frey, R.; Ligibel, M.; Sager, E.; Schroer, K.; Snajdrova, R.; Buller, R. *ACS Catal* **2021,** *11* (10), 6261-6269.
3. Papadopoulou, A.; Meierhofer, J.; Meyer, F.; Hayashi, T.; Schneider, S.; Sager, E.; Buller, R. *Chemcatchem* **2021,** *13* (18), 3914-3919.
4. Hayashi, T.; Ligibel, M.; Sager, E.; Voss, M.; Hunziker, J.; Schroer, K.; Snajdrova, R.; Buller, R. *Angew Chem Int Ed* **2019**, *58*, 18535 - 18539.

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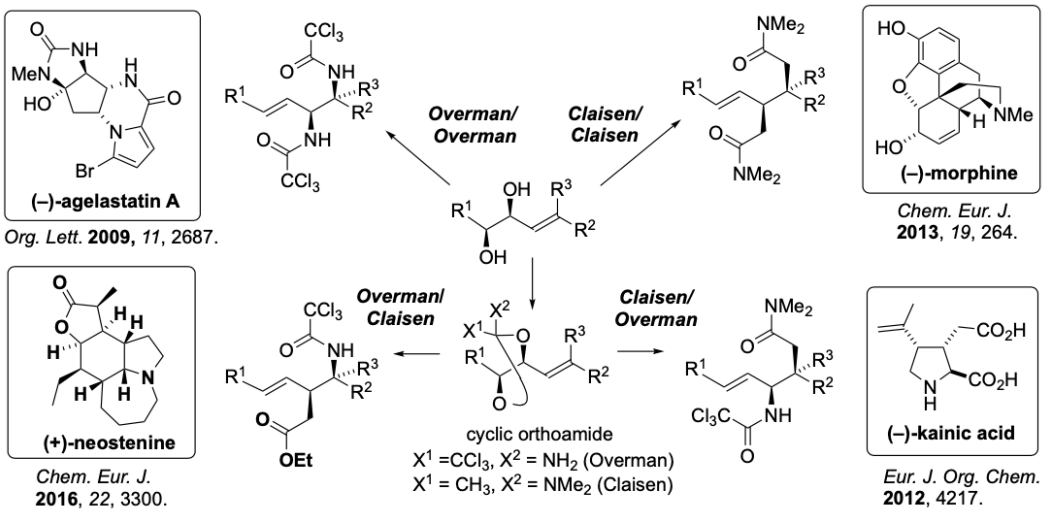
Synthesis of Biologically Active Alkaloids Based on the Sequential Sigmatropic Rearrangement

Noritaka Chida*

Keio University, Yokohama, Japan

**chida@applc.keio.ac.jp*

Sigmatropic rearrangement of chiral allylic alcohols is a powerful method for the chiral synthesis of natural products due to its effective chirality transfer. In this lecture, stereoselective syntheses of some biologically active alkaloids based on the methodology using the sequential sigmatropic rearrangement is presented. Treatment of a chiral allylic vicinal diol derived from sugars or tartrates with excess amount of Cl3CCN, followed by heating, afforded a product of sequential Overman/Overman rearrangement as a single diastereomer.[1] Likewise, thermal reaction of the diol in the presence of excess MeC(OEt)3 or MeC(OMe)2NMe caused the sequential Claisen/Claisen rearrangement.[2] On the other hand, reaction of the diol with stoichiometric amount of the reagent provided a cyclic orthoamide, which, upon heating, afforded the singly rearranged product. Applying the second sigmatropic rearrangement to the resulting allylic alcohol, Overman/Claisen[3] and Claisen/Overman[2b] products were obtained. By use of the sequential sigmatropic rearrangement, syntheses of several types of alkaloids have been completed.[4]



References

1. (a) Momose, T.; Hama, N.; Higashino, C.; Sato, H.; Chida, N. *Tetrahedron Lett*. **2008**, *49*, 1376-1379. (b) Hama, N.; Matsuda, T. Sato, T.; Chida, N. *Org*. *Lett*. **2009**, *11*, 2687-2690.
2. (a) Tanimoto, H.; Saito, R.; Chida, N. *Tetrahedron Lett*. **2008**, *49*, 358-362. (b) Kitamoto, K.: Nakayama, Y.; Sampei, M.; Ichiki, M.; Furuya N.; Sato, T.; Chida, N. *Eur*. *J*. *Org*. *Chem*. **2012**, 4217-4231.
3. Nakayama, Y.; Sekiya, R.; Oishi, H.; Hama, N.; Yamazaki, M.; Sato, T.; Chida, N. *Chem*. *Eur*. *J*. **2013**, *19*, 12052-12058.
4. Okuyama, Y.; Okamoto, R.; Mukai, S.; Kinoshita, K.; Sato, T.; Chida, N. *Org*. *Lett*. **2020**, *22*, 8697-8701. Okuyama, Y.; Kidena, M.; Kato, E.; Kawano, S.; Ishii, K.; Maie, K.; Miura, K.; Simizu, S.; Sato, T.; Chida, N. *Angew*. *Chem*. *Int*. *Ed*. **2021**, *60*, 5193- 5198, and references therein.

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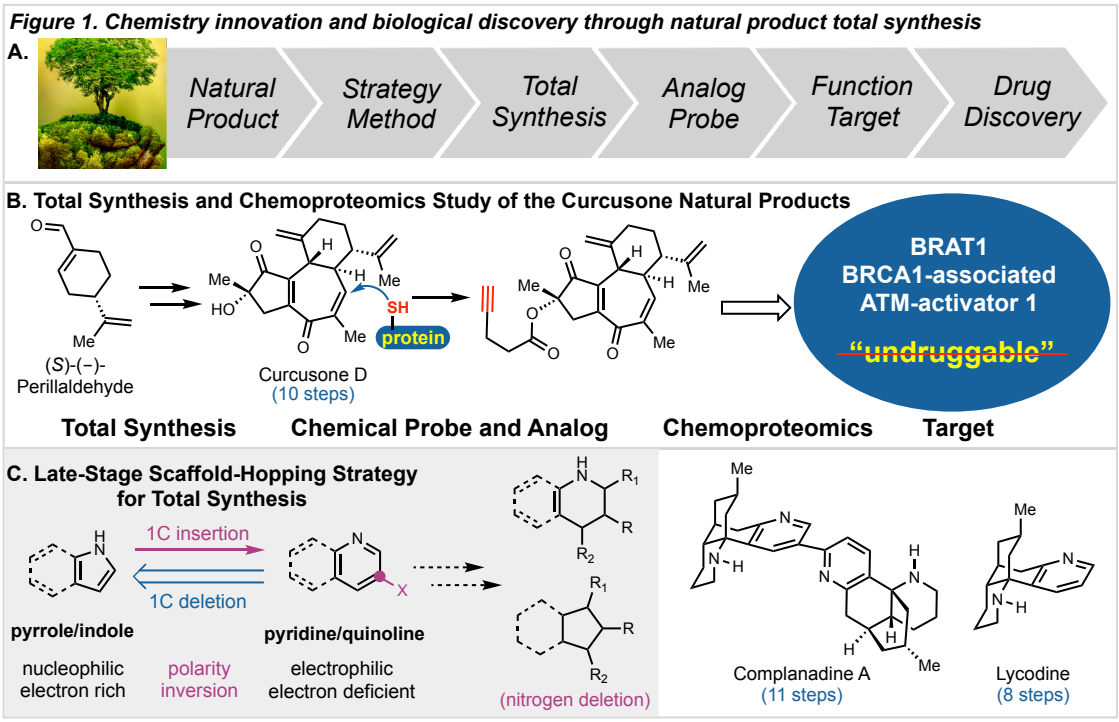
Chemistry Innovation and Biological Discovery through Total Synthesis

Mingji Dai[a,*]

[a]*Department of Chemistry, Emory University, Atlanta, GA 30322, United States of America*
**mingji.dai@emory.edu*

Our research focuses on innovating the strategy and methodology of organic synthesis to solve problems of biological and medicinal importance and ultimately impact human health (Figure 1A). We view the completion of a total synthesis as the beginning of a larger and deeper scholarly inquiry, which will enable us to profile the biology of the selected natural products, decipher their mode of actions, and optimize the lead compounds into novel therapeutics. This talk will highlight elements of our recent efforts in the total syntheses of the anticancer curcusone diterpenoids (Figure 1B)[1,2] and the neurotrophically active *Lycopodium* alkaloids (Figure 1C).[3] For the former, I will discuss our synthetic and chemoproteomics studies of the curcusone natural products, which culminated in the efficient total syntheses of curcusones A-D and dimericursone A for the first time and the identification and validation of BRCA1-associated ATM activator 1 (BRAT1), a master regulator of DNA damage response, as a cellular target of the curcusone natural products. For the latter, I will share how we use *Lycopodium* alkaloids complanadine A and lycodine as inspiration to develop a late-stage scaffold-hopping strategy for complex natural product total synthesis.

Figure 1. Chemistry innovation and biological discovery through natural product total synthesis



References

1. Li, Y.; Dai, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 11624-11627.
2. Cui, C.; Dwyer, B. G.; Liu, C.; Abegg, D.; Cai, Z.; Hoch, D.; Yin, X.; Qiu, N.; Liu, J.; Adibekian, A.; Dai, M. *J. Am. Chem. Soc.* **2021**, *143*, 4379-4386.
3. Ma, D.; Martin, B. S.; Gallagher, S. K.; Saito, T.; Dai, M. *J. Am. Chem. Soc.* **2021**, *143*, 16383-16387.

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Stereoselective Construction of Challenging C-C Bonds *via* Allylic Anions: Tetrasubstituted Alkenes and β-Stereocenters Centers

P. Andrew Evans
Department of Chemistry, Queen's University, 90 Bader Lane, Kingston, Ontario K7L 3N6, Canada
E-mail: Andrew.Evans@chem.queensu.ca

Carbonyl olefination provides an important strategy for constructing stereodefined alkenes that are ubiquitous in important functional molecules and synthetic intermediates. Nevertheless, the difficulty associated with the stereoselective construction of alkenes tracks with the degree of substitution, in which tetrasubstituted alkenes are regarded as the most challenging and the planar equivalents of quaternary stereogenic centers. Moreover, the specific alkene geometry is often critical for conferring a specific biological or physical property, as exemplified in important pharmaceuticals and optoelectronic materials. The first part of the seminar will describe a novel dynamic kinetic resolution of polysubstituted α,β-unsaturated cyanohydrins.[1]

Polarity reversal of a conventional functional group often provides a practical advantage in synthesis, which can avoid the inherent limitations associated with a more conventional bond-forming strategy. For example, heteroatom-stabilized allylic anions constitute useful synthons for the construction of β-substituted carbonyl compounds. Nevertheless, the application of these masked homoenolate equivalents can be problematic, which can be ascribed to their ambident reactivity that often leads to the formation of regioisomeric products. Furthermore, despite the longstanding utility of allylic anions as homoenolate synthons, the *catalytic* enantioselective variant of this transformation has not been forthcoming. The seminar will also describe the catalytic enantioselective allylation of a homoenolate equivalent to provide a novel method for the construction of β-stereogenic carbonyl derivatives.[2]

References:

1. Majhi, J.; Turnbull, B. W. H.; Ryu, H.; Park, J.; Baik, M.-H.; Evans, P. A. *J. Am Chem. Soc.* **2019**, *141*, 11770.
2. Wright, T. B.; Turnbull, B. W. H.; Evans, P. A. *Angew. Chem. Int. Ed.* **2019**, *58*, 9886.

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Applications of enzyme cascades in heterocycle synthesis

Sabine L. Flitsch

School of Chemistry &MIB, The University of Manchester, UK
Sabine.Flitsch@manchester.ac.uk

Biocatalysis has become an important aspect of modern organic synthesis, both in academia and across the chemical and pharmaceutical sciences.[1,2] Its success has been largely due to a rapid expansion of the range of chemical reactions accessible, made possible by advanced tools for enzyme discovery and protein engineering. As the enzyme toolbox for biocatalysis has expanded, so has the potential for the construction of powerful enzyme cascades for efficient and selective synthesis of target molecules. The dramatic increase of biocatalysts that are now available can make design of enzyme cascades highly challenging, in particular to the non-expert.

In this talk, I will present the application of RetroBioCat,[3] a collection of tools for automated biocatalytic cascade design, that is freely available to the scientific community (https://retrobiocat.com/). I will describe its implementation in a number of *de novo* multistep biosynthetic sequences towards chiral amines, amino-polyols and heterocycles.[4]

References :

1. Bell, E.L.; Finnigan, W.; France, S.P.; Green, A.P.; Hayes, M.A.; Hepworth, L.J.; Lovelock, S.L.; Niikura, H.; Osuna, S.; Romero, E.; Ryan, K.S.; Turner, N.J.; Flitsch, S.L. *Nature Reviews Methods Primers* **2021**, *1*, 46
2. Romero, E.; Jones, B.S.; Hogg, B.N.; Casamajo, A.R.; Hayes, M.A.; Flitsch, S.L.; Turner, N.J.; Schnepel, C.; *Angew. Chem. Int. Ed.* **2021**, *60(31),* 16824
3. Finnigan, W.; Hepworth, L.J.; Flitsch, S.L.; Turner, N.J.; *Nature Catalysis* **2021**, *4*, 98
4. Mattey, A.P.; Ford, G.J.; Citoler, J.; Baldwin, C.; Marshall, J.R.; Palmer, R.B.; Thompson, M.; Turner, N.J.; Cosgrove, S.C.; Flitsch, S.L. *Angew. Chem. Int. Ed.* **2021**, *60(34),* 18660. Hepworth, L.; France, S.; Hussain, S.; Both, P.; Turner, N.; Flitsch, S. L. *ACS Catalysis*, **2017**, *7*, 2920; France, S. P; Hepworth, L. J; Turner, N. J.; Flitsch, S. L *ACS Catalysis*, **2017**, *7(1),* 710. Ford, G.J.; Baldwin, C.R; Bradshaw Allen, R.T.; Marshall, J.R.; Mattey, A.P.; Turner, N.J.; Clapes, P.; Flitsch, S.L. **2022** *preprint ChemRxiv (*10.26434/chemrxiv-2022-61fhr); Schnepel, C.; Rodriguez-Perez, L.; Yu, Y.; Angelastro, A.; Heath, R.S.; Lubberink, M.; Falcioni, F.; Mulholland, K.; Hayes, M.; Turner, N.J.; Flitsch, S.L. **2022** *preprint ChemRxiv (*10.26434/chemrxiv-2022-sqnl1); Swanson, C.; Ford, G.; Mattey, A.; Gourbeyre, L.; Flitsch, S.L. **2022** *preprintChemRxiv* 10.26434/chemrxiv-2022-4zzq4

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Development of Strong and Tough Polymers from Renewable Resources

Brett P. Fors[a]

[a]*Cornell University, Ithaca, NY*

The development of sustainable plastics is arguably one of the most important societal challenges that need to be addressed. The current production of plastics is energy intensive, uses a significant portion of the world's petroleum supply, and leads to materials that are accumulating in our landfills and oceans.[1] On this basis, we have been focusing on making materials from dihydrofuran (DHF). DHF can be made sustainably and economically in a single step from 1,4-butanediol, which is already manufactured on a large scale from biobased resources.[2] We have developed a new cationic polymerization to yield high molar mass polyDHF, which gives a thermoplastic with high tensile strength and stiffness. This new material has properties better than, or comparable to, commercial polycarbonates and polystyrenes, enabling the use of polyDHF as a biorenewable alternative to these materials. Significantly, we have developed a new electrochemical depolymerization of polyDHF to enable chemical recycling and a circular life-cycle of this polymer.

References

1) Ellen MacArthur Foundation, *The new plastics economy: Rethinking the future of plastics and catalysing action,* 2017.
2) Stonkus, V.; Edolfa, K.;Leite, L.; Sobczak, J. W.; Plyasova, L.; Petrova, P. *Appl. Catal., A* **2009**, *362*, 147.

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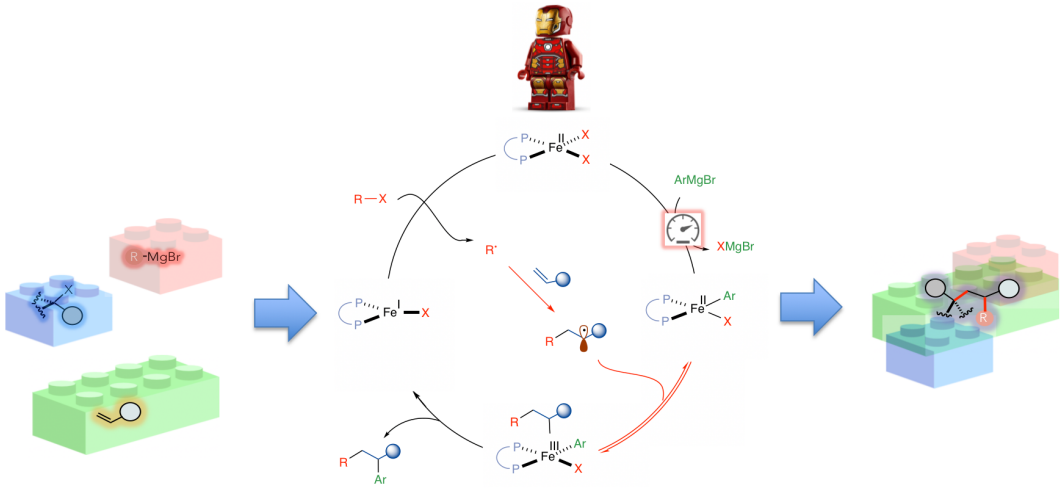
Recent Advances in Fe-Catalyzed Multicomponent Cross-Couplings

Osvaldo Gutierrez
Department of Chemistry, Texas A&M University, College Station, Texas 77843, United States
og.labs@tamu.edu

Despite advances in high-throughput screening methods leading to a surge in the discovery of catalytic reactions, our knowledge of the molecular-level interactions in the rate- and selectivity-determining steps of catalytic reactions, especially those involving highly unstable and reactive open-shell intermediates, is rudimentary. These knowledge gaps prevent control, suppression or enhancement, of competing reaction channels that can drive development of unprecedented catalytic reactions. In this talk, I will focus on our use of high-level quantum mechanical calculations, rigorously calibrated against experimental data, to interrogate the mechanisms of asymmetric iron-catalyzed C(sp2)-C(sp3) cross-coupling reactions. Then, I will focus on how our group used this combined experimental and computational approach to quickly develop a vast array of multicomponent Fe-catalyzed cross-coupling reactions.[1]



References :

1. a) Liu, L.; Aguilera, M. C.; Lee, W.; Youshaw, C. R.; Neidig, M. L.; Gutierrez, O. *Science* **2021**, *374*, 432-439. (b) Rotella, M. E.; Sar, D.; Liu, L.; Gutierrez, O. *Chem. Commun.* **2021**, *57*, 12508-12511. (c) Liu, L.; Lee, W.; Youshaw, C. R.; Yuan, M.; Geherty, M. B.; Zavalij, P. Y.; Gutierrez, O. *Chem. Sci.* **2020**, *11*, 8301-8305. (d) Liu, L.; Lee, W.; Yuan, M.; Acha, C.; Geherty, M. B.; Williams, B. Gutierrez, O. *Chem. Sci.* **2020**, *11*, 3146-3151. (e) Lee, W.; Zhou, J.; Gutierrez, O. *J. Am. Chem. Soc.* **2017**, *139*, 16126-16133

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Sabine Hadida

Vertex Pharmaceuticals, San Diego, CA

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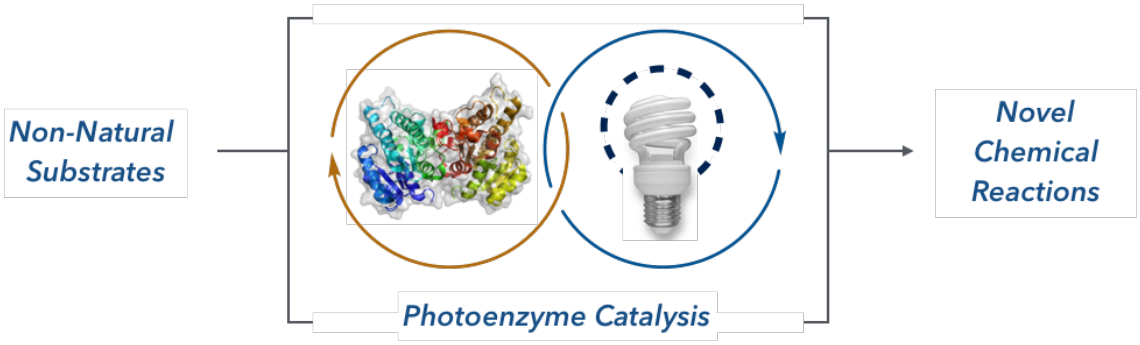
Photoenzymatic Catalysis – Using Light to Reveal New Enzyme Functions

Todd K. Hyster*

[a]*Department of Chemistry and Chemical Biology, Cornell University, Ithaca, Ny 14850*
**thyster@cornell.edu*

Enzymes are exquisite catalysts for chemical synthesis, capable of providing unparalleled levels of chemo-, regio-, diastereo- and enantioselectivity. Unfortunately, biocatalysts are often limited to the reactivity patterns found in nature. In this talk, I will share my groups efforts to use light to expand the reactivity profile of enzymes. In our studies, we have exploited the photoexcited state of common biological cofactors, such as NADH and FMN to facilitate electron transfer to substrates bound within enzyme active sites. In other studies, we found that enzymes will electronically activate bound substrates for electron transfer. In the presence of common photoredox catalysts, this activation can be used to direct radical formation to enzyme active sites. Using these approaches, we can develop biocatalysts to solve long-standing selectivity challenges in chemical synthesis.



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Design, Synthesis and Biological Evaluation of Sphaerimicin Analogues

S. Ichikawa[a,*]

[a]*Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan*
[b]*Global Station for Biosurfaces and Drug Discovery, Global Institution for Collaborative Research and Education (GI-CoRE), Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Sapporo, Japan*
**ichikawa@pharm.hokudai.ac.jp*

The abstract Drug-resistant bacterial infections have claimed the lives of millions of people worldwide in the current status, therefore, the development of antibacterial agents with novel mechanisms of action is urgently necessary. MraY is an integral membrane enzyme, which is responsible for peptidoglycan biosynthesis. MraY is an essential enzyme for bacterial replication and an attractive target for drug-resistant bacterial drugs. Sphaerimicins are nucleoside natural products isolated from *Sphaerisporangium sp.* SANK60911.[1] Sphaerimicin A exhibits strong MraY inhibitory activity (IC_{50} 13.5 ng/mL for MraY) and promising antibacterial activity against gram-positive bacteria (MIC 1-16 μg/mL). Sphaerimicins consist of a 5'-glycyluridine, an aminoribose, a highly substituted piperidine, and a highly methyl-branched fatty acid, resulting in a complex chemical structure. The most intriguing structural feature of sphaerimicins is a macrocyclic structure fused with the aminoribose and the piperidine ring. Here I will describe the design, synthesis and biological evaluation of simplified sphaerimicin analogues.

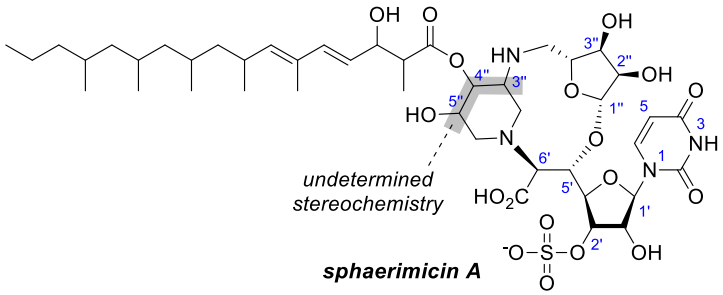

Figure 1. Structures sphaerimicin A

References :

1. Funabashi, M.; Baba, S.; Takatsu, T.; Kizuka, M.; Ohata, Y.; Tanaka, M.; Nonaka, K.; Spork, A. P.; Ducho, C.; Chen, W.-C. L.; Lanen, S. G. V. Structure-based gene targeting discovery of sphaerimicin, a bacterial translocase I inhibitor. *Angew. Chem. Int. Ed.* **2013**, *52*, 11607-11611.

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Lewis base catalyzed polarity inversion of Michael acceptors

D. W. Lupton[a]*

[a]*Monash University, Melbourne, Australia*
**david.lupton@monash.edu*

In 1962 Price reported the hexamerization of acrylonitrile when it was exposed to phosphine catalysts in the presence of alcohols.[1] In contrast to transformations such as the Morita-Baylis-Hillman reaction it was observed that the enolate from 1,4-addition of the phosphine undergoes tautomerization to invert the polarity of the β–carbon. The related polarity inversion of Michael acceptors under NHC catalysis was observed by Fu in 2006.[2] In a series of studies from our group we have discovered and developed the polarity inversion of Michael acceptors as a valuable approach to reaction discovery.[3] In this presentation recent studies on this topic focused on enantioselectivity and reaction cascades will be discussed.[4]

References

1. Takashina, N.; Price, C. C. *J. Am. Chem. Soc.* **1962**, *84*, 489.

2. Fischer, C.; Smith S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472.

3. For a short reviews covering our work on NHC organocatalysis by Michael acceptor polarity inversion see: Nguyen, X. B.; Nakano, Y.; Lupton, D. W. *Aust. J. Chem.* **2020**, *73*, 1.

4. a) Nakano, Y.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2016**, *55*, 3135. b) Scott, L.; Nakano, Y.; Zhang, C.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2018**, *57*, 10299 c) Nguyen, X. B.; Nakano, Y.; Duggan, N. Scott, L.; Breugst, M.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2019**, *131*, 11607 d) Bae, S.; Zhang, C.; Gillard, R. M.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2019**, 58, 13370 e) Cromwell, S.; Sutio, R. Zhang, C. Such, G.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2022**, e202206647.

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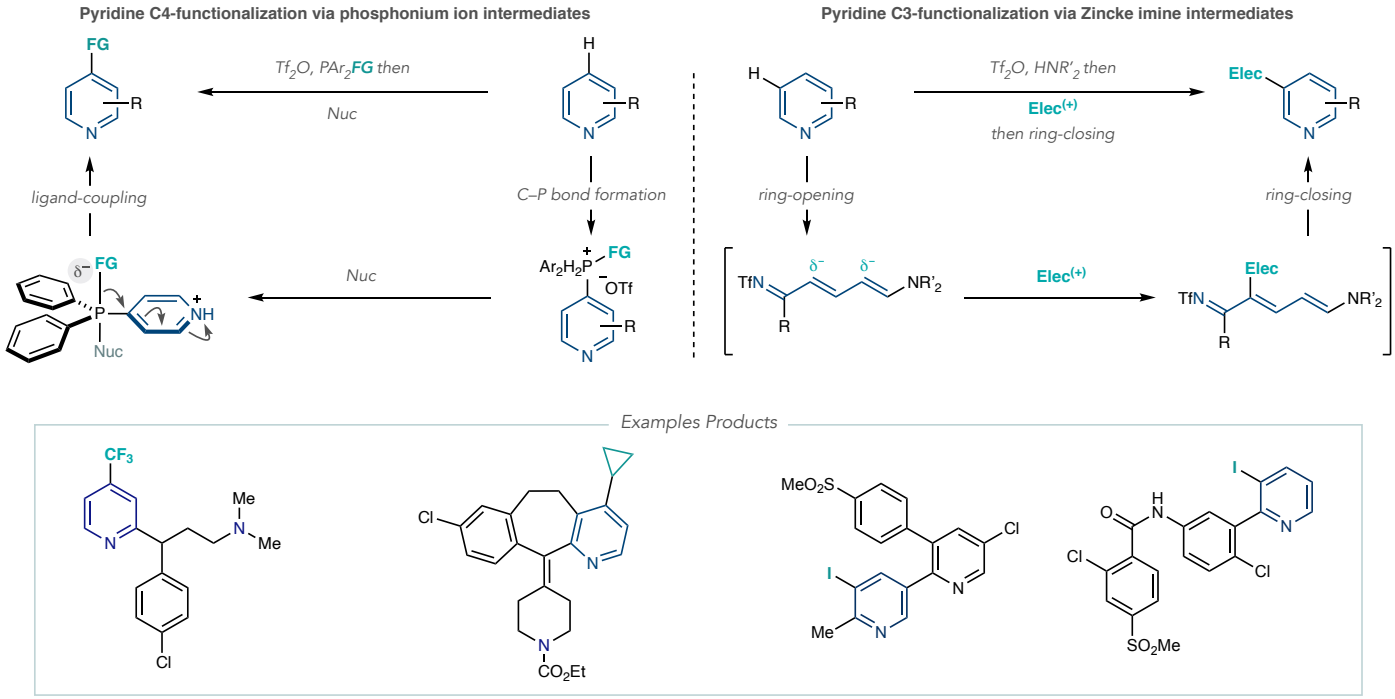
Selective Functionalization of Pyridines, Diazines and Pharmaceuticals via Unconventional Intermediates

Andy McNally*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States.
**andy.mcnally@colostate.edy*

Pyridines and diazines are ubiquitous in pharmaceuticals and agrochemicals, yet there are limits in synthetic methods that can directly functionalize the C–H bonds in these structures. We will show two distinct approaches, using phosphorus and ring-opened intermediates, that enable selective functionalization of these heterocycles into a range of valuable derivatives. A range of C–C and C–Heteroatom bond formations are viable, and the chemistry functions on structures typically encountered in drug discovery programs. Our lab has also performed mechanistic and computational studies of the regioselectivity of these reactions and the phosphorus ligand-coupling processes involved.



References

1. X. Zhang*, K. G. Nottingham*, C. Patel, J. V. Alegre-Requena, J. N. Levy, R. S. Paton, A. McNally, *Nature*, **2021**, *594*, 217.
2. B. T. Boyle*, J. N. Levy*, L. D. Lescure, R. S. Paton, A. McNally. *ChemRxiv*., **2022**. https://doi.org/10.26434/chemrxiv-2022-88802-v3

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Strongly Reducing Organic Photoredox Catalysts

G. M. Miyake[a]*

[a]*Colorado State University, Fort Collins, Colorado, USA*
**garret.miyake@colostate.edu*

Photoredox catalysis uses light to access electron or energy transfer pathways that can be exploited for catalysis. This presentation will focus on the design and employment of strongly reducing visible-light absorbing organic photoredox catalysts. These photoredox catalysts have been used in organocatalyzed atom transfer radical polymerization and small molecule synthesis. The developing catalyst design principles and the implications in the catalytic mechanisms will be discussed.

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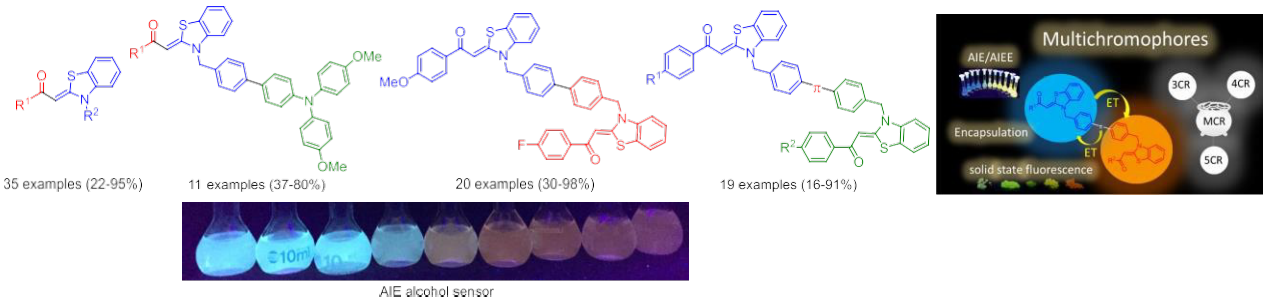
S,N-Ketene Acetal Merocyanines – Switchable AIEgens

T. J. J. Müller,[a,*] L. Biesen,[a] J. Krenzer,[a] N. Nirmalananthan-Budau [b] and U. Resch-Genger [b]

[a]*Institut für Organische Chemie und Makromolekulare Chemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstraße 1, D-40225 Düsseldorf, Germany*
[b]*Division Biophotonics, Bundesanstalt fü r Materialforschung und -prü fung (BAM), Department 1, Richard-Willstä tter-Straße 11, D-12489 Berlin, Germany*
**E-mail: ThomasJJ.Mueller@hhu.de*

We are developing concise, efficient one-pot syntheses of functional chromophores by multi-component reactions.[1] Amongst diversity-oriented syntheses and properties of fluorophores,[2] AIE (aggregation induced emission) chromophores are particularly interesting.[3] Just recently, a modular synthesis of solid-state emissive aroyl-*S*,*N*-ketene acetals with tunable AIE characteristics could be disclosed.[4] Further expansion of the methodology gave access to aroyl-*S*,*N*-ketene acetal merocyanine based bichromophores as multifunctional AIE sensors by consecutive three-component condensation-Suzuki sequence and one-pot Masuda-Suzuki sequence,[5] and even unimolecular multichromophores with tunable AIE.[6] Bi- and multichromophore arrays are affected by the AIE of the merocyanine moieties which govern the emission readout, resulting in emission color change. The synthetic concept and AIE studies shall be discussed.



References

1. a) Levi, L.; Müller, T. J. J. *Chem. Soc. Rev.* **2016**, *45*, 2825–2846. b) Müller, T. J. J.; D'Souza, D. M. *Pure Appl. Chem.* **2008**, *80*, 609–620.
2. a) Levi, L.; Müller, T. J. J. *Eur. J. Org. Chem.* **2016**, 2907–2918. b) Müller, T. J. J. *Drug Discov. Today Technol.* **2018**, *29*, 19– 26.
3. a) Merkt, F. K.; Müller, T. J. J. *Isr. J. Chem.* **2018**, *58*, 889–900. b) Müller, T. J. J. In *Aggregation Induced Emission: Materials and Applications*, Fujiki, M.; Tang, B. Z.; Liu, B., Eds., ACS Symposium Series e-book, **2016**, Chapter 6, pp 85.
4. Biesen, L.; Nirmalananthan-Budau, N.; Hoffmann, K.; Resch-Genger, U.; Müller, T. J. J. *Angew. Chem. Int. Ed.* **2020**, *59*, 10037–10041.
5. a) Biesen, L.; May, L.; Nirmalananthan-Budau, N.; Hoffmann, K.; Resch-Genger, U.; Müller, T. J. J. *Chem. Eur. J.* **2021**, *27*, 13426–13434. b) Biesen, L.; Müller, T. J. J. *Aggregate* **2021**, *2*, e105.
6. Biesen, L.; Krenzer, J.; Nirmalananthan-Budau, N.; Resch-Genger, U.; Müller, T. J. J. *Chem. Sci.* **2022**, *13*, 5374–5381.

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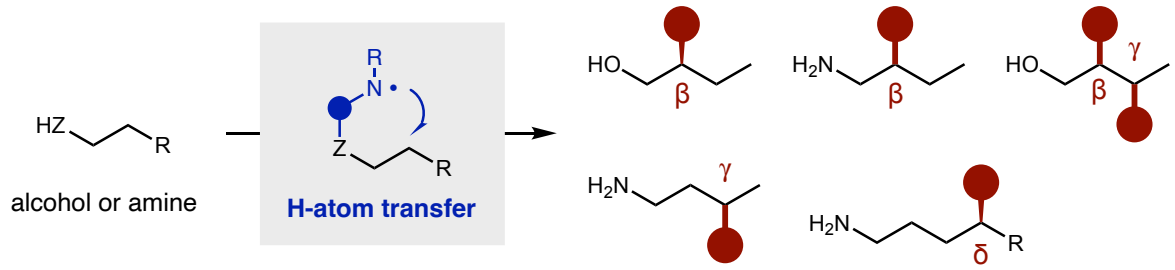
Remote, Double, and Enantioselective C-H Functionalizations via Radical Chaperones

David A. Nagib

The Ohio State University, Columbus, Ohio, United States

nagib.1@osu.edu

Our research is focused on developing radical chaperone strategies to harness intramolecular (1,5- or 1,6-) H-atom transfer (HAT) mechanisms to enable new modes of chemo-, regio-, and stereo- selectivity for remote, single and double C-H functionalizations of alcohols and amines. These radical chaperone tools are continually being developed to streamline the synthesis of medicinally relevant molecules and heterocycles. Key examples include: (1) enantioselective C-H amination of imidates[1] to access chiral β amino alcohols, (2) vicinal, double β,γ C-H functionalization[2] via radical-polar-crossover, (3) remote δ C-H desaturation of amines[3] for the synthesis of five- and six-membered aza-heterocycles, and (4) γ C-H functionalization of amines[4] via a triple HAT cascade. Collectively, these mechanisms merge: (*i*) either thermal or photocatalysis to generate N-centered radicals, and (*ii*) Cu or Co catalysis to selectively trap the distal radicals upon intramolecular HAT.



References

(1) †Nakafuku, K. M.; †Zhang, Z.; †Wappes, E. A.; Stateman, L. M.; Chen, A. D.; Nagib, D. A. Enantioselective Radical C-H Amination for the Synthesis of β-Amino Alcohols. *Nat. Chem.*, **2020**, *12*, 697 – 704.

(2) Prusinowski, A. F.; Twumasi, R. K.; Wappes, E. A.; Nagib, D. A. *Vicinal*, Double C-H Functionalization of Alcohols via an Imidate Radical-Polar Crossover Cascade. *J. Am. Chem. Soc.*, **2020**, *142*, 5429 – 5438.

(3) †Stateman, L. M., †Dare, R. M., Paneque, A. N., Nagib, D. A. Aza-heterocycles via copper-catalyzed, remote C–H desaturation of amines. *Chem*, **2022**, *8*, 210 – 224.

(4) †Herbort, J. H.; †Bednar, T. N.; Chen, A. D.; RajanBabu, T.V.; Nagib, D. A. γ C-H Functionalization of Amines via Triple H-Atom Transfer of a Vinyl Sulfonyl Radical Chaperone. *J. Am. Chem. Soc.*, **2020**, *in press*.

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Biocatalysis and Complex Molecule Synthesis

Alison Narayan

Department of Chemistry and the Life Sciences Institute, University of Michigan, Ann Arbor, MI

Natural sources, such as plants, fungi and microbes, have historically provided compounds with potent pharmaceutical properties. While it can be challenging to build complex natural products in a lab using existing chemistry methods, Nature has perfected these biosynthetic pathways. The work described leverages the power of Nature's tools for building complex molecules to synthesize novel molecules with therapeutic potential. The reactivity and selectivity of enzymes from natural product pathways are often unparalleled in existing chemical methods. Enzymes with potential synthetic utility are used as a starting point for engineering biocatalysts with (1) broad substrate scope, (2) high catalytic efficiency, and (3) exquisite site- and stereoselectivity. These biocatalytic methods are employed to efficiently synthesize biologically active complex molecules.

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New Avenues in Synthesis via Organic Photoredox Catalysis

David A. Nicewicz*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-3290
**nicewicz@unc.edu*

Single electron pathways are common in the biological realm and are integral to photosynthesis and physiological processes in humans. As synthetic chemists, we seek to harness the power of single electron mediated pathways to more efficiently make the pharmaceuticals, agrochemicals and materials that the modern world requires. My group seeks to use organic salts as excited state catalysts to mediate single electron processes in the development of new chemical transformations. This lecture will give a brief background to organic photoredox catalysis and cover some of the reactivity from my group including C-H functionalization chemistry and applications to radiolabeling technology. Lastly, this lecture will describe how acridinium photooxidants can be transformed to excited state super reductants via two-photon absorption.

References

1. Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. "Site-Selective Arene C–H Amination via Photoredox Catalysis." *Science*, **2015**, *349*, 1326-1330.
2. Tay, N. E.; Nicewicz, D. A. "Cation Radical-Accelerated Nucleophilic Aromatic Substitution via Organic Photoredox Catalysis." *J. Am. Chem. Soc.* **2017**, *139*, 16100-16104.
3. Chen, W.; Huang, Z.; Tay, N. E. S.; Giglio, B.; Wang, M.; Wu, Z.; Nicewicz, D. A.; Li, Z. "Arene C-H Fluorination with $^{18}F^-$ via Organic Photoredox Catalysis." *Science* **2019**, *364*, 1170-1174.
4. MacKenzie, I. A.; Wang, L.; Onuska, N. P. R.; Williams, O. F.; Begam, K.; Moran, A. M.; Dunietz, B. D.; Nicewicz, D. A. "Discovery and Characterization of Acridine Radical Photoreductants." *Nature*, **2020**, *580,* 76-80.

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Combining Synthetic Chemistry and Biology for Streamlining Access to Complex Molecules

Hans Renata

Rice University, Houston, TX, USA
**hr28@rice.edu*

By virtue of their unrivaled selectivity profiles, enzymes possess remarkable potential to address unsolved challenges in chemical synthesis. The realization of this potential, however, has only recently gained traction. Recent advances in enzyme engineering and genome mining have provided a powerful platform for identifying and optimizing enzymatic transformations for synthetic applications and allowed us to begin formulating novel synthetic strategies and disconnections. This talk will describe our recent efforts in developing a new design language in chemical synthesis that centers on the incorporation of biocatalytic approaches in contemporary synthetic logic. Case studies will focus on the use of this platform in the chemoenzymatic syntheses of complex natural products and also highlight how this platform could serve as a starting point to enable further biological and medicinal chemistry discoveries.

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Molecular glues co-opting cereblon: Discovery of CC-99282 and future opportunities to target the undruggable proteome

Jennifer R. Riggs

Small Molecule Drug Discovery, Bristol Myers Squibb, San Diego, USA
**jennifer.riggs@bms.com*

Considerable advances in the protein degradation field have opened further opportunities to target the "undruggable" proteome. Molecular glue molecules co-opting cereblon and leading to cellular protein degradation of transcriptional regulators are clinically approved. A number of next-generation cereblon E3 ligase modulators, CELMoDs®, are currently advancing to the clinic or are already undergoing clinical assessment. CC-99282 was specifically designed to address the unmet needs of patients with relapsed or refractory (R/R) lymphomas, who tend to have a poor prognosis and life expectancy. The medicinal chemistry optimization campaign culminating in strong in vivo xenograft efficacy and clinical responses will be described. Additionally, historical learnings and applications from molecular glue protein degradation programs and key scientific aspects from ongoing drug discovery programs will be discussed.

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Synthesis and Structure Assignment of Natural Products

Scott Rychnovsky

Department of Chemistry, University of California, Irvine
**srychnov@uci.edu*

Natural product synthesis forces us to develop strategies and methods to overcome synthetic challenges, and it can be used to establish structure and to provide material for testing. I will present recent syntheses of a sesquiterpene, illisimonin A, and a macrolide, strasseriolide B, that illustrate challenges we encountered and how they were overcome. Strasseriolide B shows anti-malarial activity, which is unusual for a macrolide natural product. The structure of illisimonin A was revised through synthesis, and the new method developed during the structure assignment will be discussed.

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Azetidines, Azetines, and Oxetanes: New Cycloadditions of Imines and Carbonyls

Corinna S. Schindler

University of Michigan, Willard-Henry-Dow Laboratory, 930 North University Avenue, 48109 Ann Arbor, MI
**corinnas@umich.edu*

Four-membered nitrogen heterocycles such as azetidines possess unique properties that make them desirable for drug discovery and synthesis applications. However, synthesis of these compounds is challenging, limiting their applicability. While oxetanes and cyclobutanes are commonly synthesized by highly atom-economical light-mediated [2+2] reactions, this powerful methodology remains limited for the synthesis of azetidines via the aza Paternò-Büchi reaction. Herein we report the development of visible-light mediated intermolecular aza Paternò-Buchi reactions,[1,2,3] harnessing the triplet state of unique cyclic oximes, specifically 2-isoxazoline-3-carboxylates, as imine equivalents for the synthesis of unique azetidine and azetine products. Following energy transfer from an iridium photocatalyst, these cyclic oximes initiate [2+2] reactions with unactivated alkenes and alkynes, allowing access to a broad range of azetidines and azetines with excellent yield. This method is mild, operationally simple, and broadly applicable. Importantly, these products can be easily converted to free monocyclic azetidines, offering a new approach to these desirable targets.

References

1. Wearing, E.R.; Blackmun, D.E.; Becker, M.R.; Schindler, C.S. *J. Am. Chem. Soc.* **2021**, *143*, 16235-16242.
2. Becker, M.R.; Wearing, E.R.; Schindler, C.S. *Nat. Chem.* **2020**, *12*, 898–905.
3. Becker, M.R.; Richardson, A.D.; Schindler, C.S. *Nat. Commun.* **2019**, DOI: 10.1038/s41467-019-13072-x.

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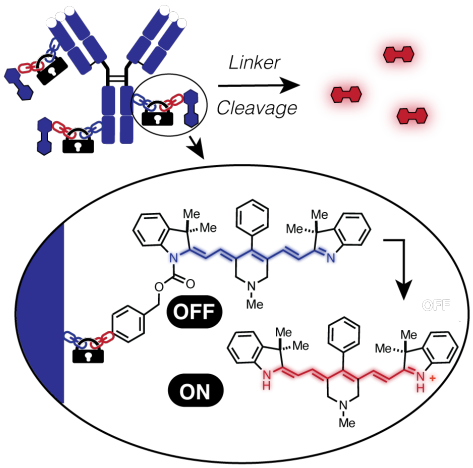
Harnessing Cyanine Chemistry to Learn the Rules of Antibody-Drug Conjugate Targeting

Martin Schnermann[a,*]

[a]*Chemical Biology Laboratory, National Cancer Institute, Frederick, MD*
**martin.schnermann@nih.gov*



Recent progress in the translation of antibody-drug conjugates (ADCs) has validated the potential of ligand-targeted drug delivery strategies. However, the clinical application of these strategies has encountered significant, often unanticipated, toxicity. Critically, many of these toxicities do not result from monoclonal antibody (mAb) binding to its cognate target, but rather from deleterious effects of the hydrophobic small molecule/linker combination on *in vivo* targeting of the mAb. Novel experimental approaches are needed to assess targeting early in the design, synthesis, and testing process. We hypothesize that *in vivo* optical imaging is uniquely poised to assess the role of payloads and linkers on ADC properties. This is because optical probes are small molecules of similar molecular weight and physical properties to drug payloads. We first set out to address the role of payload properties. By developing synthetic methods that enable the rapid synthesis of chemically varied heptamethine cyanines, we have assembled and quantitatively compared the targeting of a series of substituted variants.[1,2] These efforts suggest that highly polar, and specifically zwitterionic, substituents dramatically improve the *in vivo* properties of mAb conjugates. To examine the role of ADC linkers, conventional always-ON probes are not suitable to study the site and extent of bond cleavage. To address this, we have created a new class of fluorogenic probes in the near-infrared (NIR) range that result from modification of heptamethine norcyanines with stimuli-responsive carbamate linkers. These nor*cy*anine car*bam*ates (CyBams) exhibit exceptional turn-ON ratios and can be activated by a range of enzymatic and chemical triggers. [3,4] By optimizing the cellular uptake and retention of these probes, we have created mAb-targeted variants that allow us to quantitatively study linker chemistry in animal models. Overall, our goal is to develop and ultimately apply an "imaging-first" workflow for the design and testing of well-tolerated targeted drug delivery agents.

References

1. Luciano, M. P.; Crooke, S. N.; Nourian, S.; Dingle, I.; Nani, R. R.; Kline, G.; Patel, N. L.; Robinson, C. M.; Difilippantonio, S.; Kalen, J. D.; Finn, M. G.; Schnermann, M. J. A Nonaggregating Heptamethine Cyanine for Building Brighter Labeled Biomolecules. *ACS Chem Biol* **2019**, *14*, 934.
2. Thapaliya, E. R.; Usama, S. M.; Patel, N. L.; Feng, Y.; Kalen, J. D.; St Croix, B.; Schnermann, M. J. Cyanine Masking: A Strategy to Test Functional Group Effects on Antibody Conjugate Targeting. *Bioconjug Chem* **2022**, *33*, 718.
3. Usama, S. M.; Inagaki, F.; Kobayashi, H.; Schnermann, M. J. Norcyanine-Carbamates Are Versatile Near-Infrared Fluorogenic Probes. *J Am Chem Soc* **2021**, *143*, 5674.
4. Usama, S. M.; Marker, S. C.; Caldwell, D. R.; Patel, N. L.; Feng, Y.; Kalen, J. D.; St Croix, B.; Schnermann, M. J. Targeted Fluorogenic Cyanine Carbamates Enable In Vivo Analysis of Antibody-Drug Conjugate Linker Chemistry. *J Am Chem Soc* **2021**, *143*, 21667.

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Chromenylium fluorophores for *in vivo* imaging

Ellen M. Sletten

University of California, Los Angeles, USA

**sletten@chem.ucla.edu*

Fluorescence imaging is a central tool for visualizing complex biological systems, yet the contrast and resolution attainable *in vivo* is limited due to autofluorescence and light scattering at visible and near infrared (NIR) wavelengths. Recently, the shortwave infrared region of the electromagnetic spectrum (SWIR, 1000 – 2000 nm) has emerged as an optimal region for *in vivo* fluorescence imaging due to few endogenous SWIR chromophores and minimized scattering of light by tissue. While the SWIR demonstrates great promise, suitable materials are needed with emission at these low energies for the development of optical contrast agents. Namely, non-toxic organic small molecules with bright emission > 1000 nm are necessary to expand both the basic science and clinical applications of fluorescence imaging. Our group has developed biocompatible polymethine fluorophores with shortwave infrared emission. We discovered that chromenylium heterocycles condensed with a polymethine linker yield bright SWIR-emissive fluorophores. Heterocycle modification has provided a suite of fluorophores that can be used in concert with each other for multiplexed imaging.

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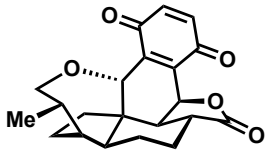
Pleurotin: highlights of its history and synthesis

Erik J. Sorensen* and John F. Hoskin

Department of Chemistry, Princeton University, Princeton, New Jersey, USA

ejs@princeton.edu

Abstract: Over a period spanning 75 years, research on pleurotin has revealed its antibiotic properties, intricate molecular structure, and potential as an anticancer agent. The discovery that pleurotin inhibits the thioredoxin-thioredoxin reductase system and transcription of cancer-related genes triggered improvements to its production by fermentation methods. Thirty-four years ago, the Hart laboratory demonstrated that this metabolite is also accessible by the concepts and methods of organic synthesis.



Pleurotin

This lecture will address these achievements and give an emphasis to our recently described 8-step formal synthesis of pleurotin.[1] This project challenged our assumptions about Diels-Alder chemistry and ultimately gave us an opportunity to probe a unique strategy for inverting the configuration of an unactivated hydrogen-bearing stereocenter.

References

1. Hoskin, J. F.; Sorensen, E. J. *J. Am. Chem. Soc.* **2022**, https://doi.org/10.1021/jacs.2c06504.

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Stereoselective Reactions with Feedstock Chemicals

Uttam K. Tambar[a,*]

[a] *Department of Biochemistry, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9038, USA*
* *Uttam.Tambar@utsouthwestern.edu*

For several decades, chemists have developed new approaches to valuable materials that are economically efficient and environmentally benign. To this end, synthetic chemists have developed new synthetic strategies to access complex molecules from simple, inexpensive, and abundant feedstock chemicals. Our research group is motivated to develop new methods in this area. We present recent examples from our laboratory of stereoselective reactions with feedstock chemicals as starting materials. First, we discuss our approach to the stereoselective functionalization of unsaturated hydrocarbons through catalytic pericyclic reactions with chalcogen-based reagents. For example, we have developed enantioselective allylic functionalizations of terminal and internal alkenes. Second, we describe our approach to the enantioselective α-alkylation of aldehydes with amino acid derived alkylating reagents. We have devised a strategy for the activation of pyridinium salts derived from amino acids through the formation of light-activated charge transfer complexes with catalytically generated electron rich chiral enamines derived from aldehyde substrates and a chiral amine catalyst.

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Natural Products in the Atmosphere

Regan J. Thomson

Department of Chemistry, Northwestern University, Evanston, IL 60208
**r-thomson@northwestern.edu*

Volatile terpenes emitted from the world's forests play a significant role in the formation of atmospheric aerosol particles, which in turn influence climate, air quality, and human health through a variety of direct and indirect mechanisms. Despite the importance of these aerosol particles, they remain poorly understood and continue to contribute the largest uncertainty to estimates of total radiative forcing. This lecture will describe efforts within my lab towards the synthesis of putative biogenic terpene-derived constituents of atmospheric aerosol particles, including isoprene-derived epoxides, in order to investigate their climate relevant physical properties. Recent advances in the synthesis of isotopically-labeled pinene derivatives that are driving collaborative investigations into the complex oxidation pathways of terpenes in the atmosphere will also be presented.

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Driving Efficiencies in Drug Discovery via the Tactical Application of High-throughput Chemistry Solutions

Matthew Tudge

Medicinal Chemistry, Glaxo SmithKline, King of Prussia, PA

High-throughput chemistry platforms are increasingly becoming a part of modern Medicinal Chemistry departments due to the strategic advantages they offer in terms of improving drug discovery efficiencies. Herein, we will introduce our recent work on merging synthetic chemistry experiments and biological assays - a concept that we term direct-to-biology (D2B) - through the disclosure of several case studies that highlight the effectiveness of this approach in the rapid discovery of novel Proteolysis Targeting Chimeras (PROTACSs) and other small molecule modalities.

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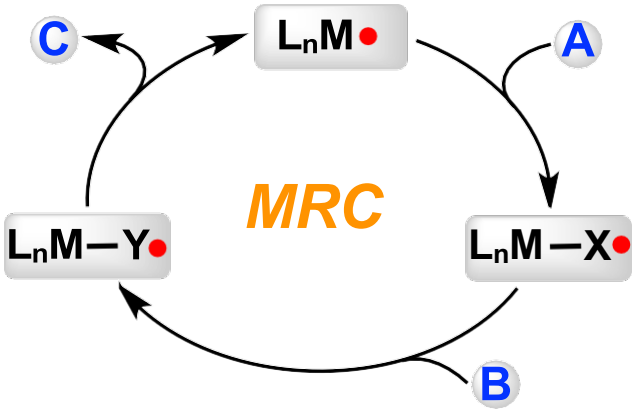
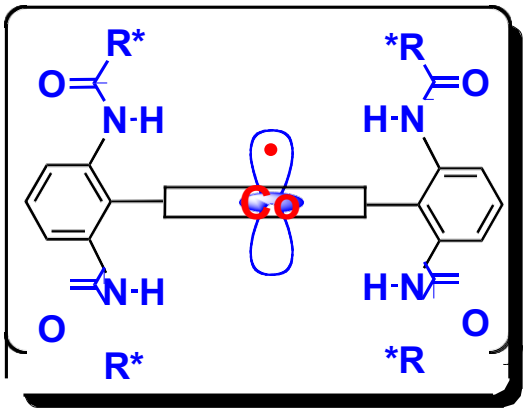
Metalloradical Catalysis for Stereoselective Radical Reactions

X. Peter Zhang[a,*]

[a]*Department of Chemistry, Boston College, Chestnut Hill, MA 02467, USA*
**peter.zhang@bc.edu*

Organic synthesis has been dominated by the development of chemical reactions that are based on two-electron heterolytic ionic processes, either stoichiometrically or in catalytic fashion. While one-electron homolytic radical chemistry is equally rich and has been demonstrated with a number of unique features, its application for practical synthesis of organic molecules has been hampered by several enduring challenges. Over the past two decades, my laboratory has been in the process of formulating metalloradical catalysis (MRC) as a general concept to guide the development of fundamentally new approaches for controlling both reactivity and stereoselectivity of radical reactions. In essence, metalloradical catalysis aims for the development of metalloradical-based systems for catalytic generation of carbon- and nitrogen-centered radicals from common organic compounds without the need of radical initiators or the use of light. The subsequent reactions of the resulting organic radical intermediates, which remain covalently bonded or closely associated with the metal center, can be effectively controlled by the catalyst. For achieving enantioselective radical reactions via MRC, we have developed a family of unique chiral metalloradical catalysts based on structurally well-defined Co(II) complexes of D_2-symmetric chiral porphyrins with tunable electronic, steric, and chiral environments. These Co(II)-based metalloradical catalysts have been shown to be highly effective for a wide range of stereoselective organic reactions, including C=C cyclopropanation, C=C aziridination, C–H alkylation, and C–H amination. Due to their distinctive stepwise radical mechanisms that involve unprecedented α-metalloalkyl and α-metalloaminyl radical intermediates, the Co(II)-based metalloradical systems enable addressing some long-standing problems in these important organic transformations while offering ample opportunity for invention of new synthetic tools.





Short Talk Abstracts

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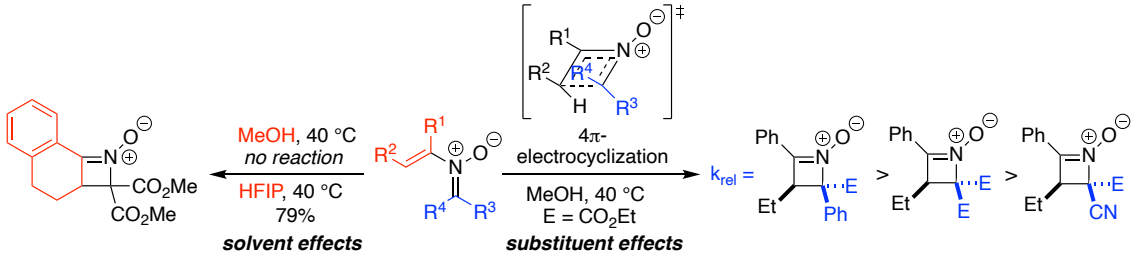
Substituent and Solvent Effects on 4π-Electrocyclizations of *N*-Alkenylnitrones

Laura L. Anderson,[a]* Laura Alonso,[a] Michael Shevlin[a,b]

[a]*Department of Chemistry, University of Illinois at Chicago, Chicago, IL, USA*
[b]*Department of Process Research and Development, Merck & Co. Inc. City, USA*
**lauralin@uic.edu*

The role of substituent and solvent effects in promoting the 4π-electrocyclization of *N*-alkenylnitrones to give azetidine nitrones have been investigated by experimental examination of relative rates, reversibility, and alternative reaction pathways. These transformations favor formation of a strained heterocyclic ring and can be combined with a Chan-Lam-Evans reaction to provide modular access to *N*-alkenylnitrones from simple starting materials.[1] In-depth analysis of these reactions was undertaken to facilitate the development of azetidine nitrones as versatile precursors for the synthesis of densely-substituted azetidines.[1] Mechanistic investigations, including solvent-dependent Hammett and Eyring studies, provide insight into the stereoelectronic effects that control these electrocyclizations and identify trends that can be used to expand the synthetic utility of the method for the rapid and facile synthesis of stereodefined azetidines.



References

1. Reidl, T. W.; Son, J.; Wink, D. J.; Anderson, L. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 11579-11583.

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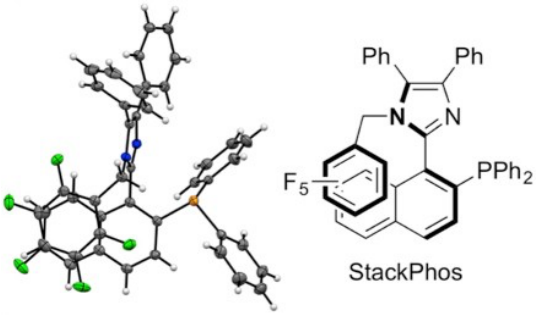
Making Chiral Heterocycles Using Chiral Heterocycles as Ligands

Aaron Aponick*

Florida Center for Heterocyclic Compounds & Department of Chemistry, University of Florida, Gainesville, Florida 32611, USA
**aponick@ufl.edu*

Enantioselective catalysis has been a mainstay of contemporary organic chemistry and, as such, the development of new ligands for transition metal catalysis is an important and active area of research. Finding new ligand archetypes enables the development of new reactions and new synthetic strategies. In this vein, we introduced imidazole-based chiral biaryl *P*,*N*-ligands[1,2] where the axial chirality is enabled by stabilizing pi-pi interactions. These ligands have proven to be excellent promoters for Cu- and Pd-catalyzed reactions and recent results in this area from our laboratory will be presented.[3-5]



References

1. Cardoso, F. S. P.; Abboud, K. A.; Aponick, A. *J. Am. Chem. Soc.* **2013**,*135*, 14548.
2. Paioti, P.H.S.; Abboud, K. A.; Aponick, A. *ACS Catal.,* **2017**, *7*, 2133.
3. Mangadan, A. R. K.; Liu, J. Aponick, A. *Angew. Chem., Int. Ed.* **2021**, *60,* 22224.
4. Dahiya, G.; Pappoppula, M.; Aponick, A. *Angew. Chem., Int. Ed.* **2021**, *60,* 19604.
5. Dahiya, G.; Abboud, K.; Aponick, A. *Synthesis*, **2022**, *54*, 2157.

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Pro-Aromaticity Induced Triplet Photochemistry in Acene-quinodimethyl Thioamides: Synthesis, Mechanism, and Photophysics

A. Jean-Luc Ayitou*

Department of Chemistry, University of Illinois Chicago, Chicago, IL, 60607 USA
**aayitou@uic.edu*

Molecular systems containing pro-aromatic units such as *ortho*– or *para*–quinodimethyl ring are often presented to exist as a mixture of resonant species *viz.* closed– and open–shell structures. Recently, a number of strategies have been employed to isolate/stabilize either one of the resonant species/forms of quinodimethyl based molecules. Yet, there are still queries regarding the ground and excited states aromaticity of these exotic systems. To this end, our group developed a new reaction that allowed to synthesize novel acene-quinodimethyl thioamides starting from readily available acene diimides.[1,2] Expectedly, upon photo-excitation ($S_0 \rightarrow S_1 \rightarrow T_1$), the acene-quinodimethyl thioamides of our interest will undergo aromaticity reversal in their lowest triplet excited state following the Baird rule of aromaticity. To afford the acene-quinodimethyl thioamides, we established a novel [2 + 4] cycloaddition reaction followed by reductive desulfurization. Furthermore, we employed computational tools to map out the reaction trajectory as well as evaluate discrete aromaticity and global/total aromaticity of the quinoidal based systems.[3]

The presentation will describe a rationale design and execution of the new quinodization reaction involving acene diimides. I will also discuss the mechanistic rationale which is based on computational modelings of the reaction trajectory and reactive intermediates. The discussion will also cover the aromaticity and photophysical properties of the new quinoidal chromophores.

References :

1. S. Shokri, J. Li, G. P. Wiederrecht, D. J. Gosztola, A. Ugrinov, S. Jockush, A. Yu Rogachev and A. J.-L. Ayitou*, A Naphtho-*p*-quinodimethane Exhibiting Baird's Anti-Aromaticity, Broken Symmetry and Attractive Photoluminescence. *J. Org. Chem.*, **2017**, *82*, 10167–10173. (**link**)

2. Nareshbabu Kamatham, Jingbai Li, Siamak Shokri, Guang Yang, Andrey Yu. Rogachev and A. Jean-Luc Ayitou*, Quinoidization of Polyacene Diimides: Photophysics, Aromaticity, and Stability of the Novel Quinoidal Acenes, *Eur. J. Org. Chem.*, **2020**, 917–922. (**link**)

3. Guang Yang, Abed Jamhawi, Nareshbabu Kamatham, Gonzalo Jiménez-Osés and A. Jean-Luc Ayitou*, Pro-Aromaticity Induced Triplet Photochemistry in π–Extended Quinoidal Acenes, *Manuscript in Preparation*.

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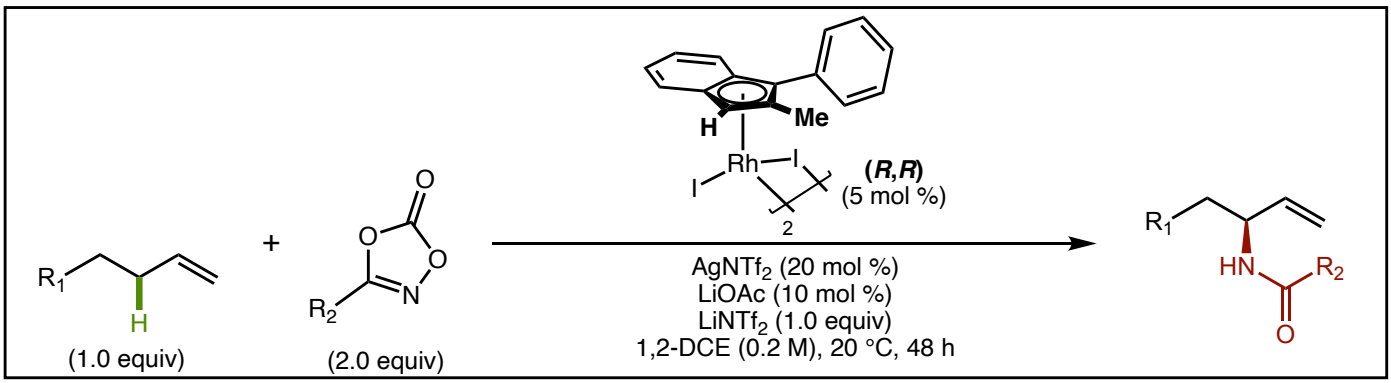
Planar Chiral Rhodium Complexes for Enantioselective Catalysis

Simon B. Blakey

Emory University, Atlanta, U.S.A.

The development of new reactions and catalysts for the oxidative cross-coupling of C-H bonds with C-H, N-H and O-H bonds will be discussed. Strategically, these reactions allow for the synthesis of complex molecules from their constituent components, minimizing the need for functional group activation and manipulation. A novel planar chiral catalyst platform for enantioselective reactions will be presented. Illustrative examples of emergent applications will be provided.



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Cyclic Amines: from Production to Application

Ida (Xue) Chen

Dow Industrial Solutions R&D, The Dow Chemical Company, Lake Jackson, TX, 77566
chen2c7ab2@dow.com

Cyclic amines are either secondary or tertiary amines. Examples of cyclic amines include aziridine, piperidine, piperazine etc. In this talk, commercial process to produce cyclic amines will be discussed and new application of these amines will also be included. In addition, challenges in the cyclic amine area will also be proposed.

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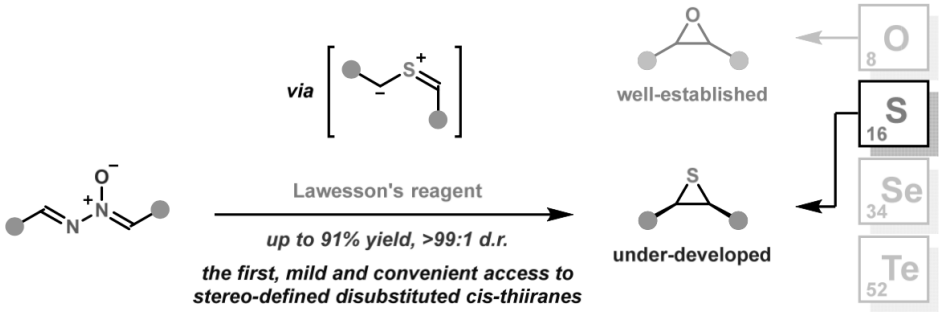
Synthesis of *cis*-Thiiranes as Diastereoselective Access to Epoxide Congeners via 4π-Electrocyclization of Thiocarbonyl Ylides

S.-m. Song, J. Jin, J.-H. Choi,* and W.-j. Chung*

Department of Chemistry, Gwangju Institute of Science and Technology, Gwangju, Republic of Korea [b]Autho
** junhochoi@gist.ac.kr; wjchung@gist.ac.kr*

Organochalcogen heterocycles are ubiquitously present and widely utilized in various fields. Among them, oxirane has been extensively studied, and all of the stereoisomeric forms are readily available. In contrast, synthetic studies on thiirane were rarely reported, and thus the useful sulfur-congener of oxirane has been difficult to access in a stereodefined form.[1] In this research, a general stereoselective synthesis of *cis*-thiiranes is accomplished by taking advantage of stereospecific electrocyclization of *trans*-thiocarbonyl ylides, which are generated in situ from readily available *E*,*E*-aldazine *N*-oxides upon treatment with Lawesson's reagent.[2] This newly developed practical method provides a variety of *cis*-1,2-diarylthiiranes as essentially single diastereomers in high yields under mild reaction conditions. The intermediacy of *trans*- thiocarbonyl yilde is confirmed by mechanistic experiments, and the excellent stereocontrol is rationalized by DFT calculation.



References

1. (a) Liao, S.; Leutzsch, M.; Monaco, M. R.; List, B. *J. Am. Chem. Soc.* **2016**, *138*, 5230–5233. (b) Duan, M.; Díaz-Oviedo, C. D.; Zhou, Y.; Chen, X.; Yu, P.; List, B.; Houk, K. N.; Lan, Y. *Angew. Chem. Int. Ed.* **2022**, *61*, e202113204. (c) Lin, X.; Pu, M.; Sang, X.; Li, S.; Liu, X.; Wu, Y.-D.; Feng, X. *Angew. Chem. Int. Ed.* **2022**, *61*, e202201151. (d) Schmidt, T. A.; Sparr, C. *Angew. Chem. Int. Ed.* **2021**, *60*, 23911–23916. (e) Cano, I.; Gómez-Bengoa, E.; Landa, A.; Maestro, M.; Mielgo, A.; Olaizola, I.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2012**, *51*, 10856–10860. (f) Zhou, C.; Fu, C.; Ma, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 4379–4381.
2. Song, S.-m.; Jin, J.; Choi, J.-H.; Chung, W.-j. *Nat. Commun.* **2022**, *13*, *Accepted*.

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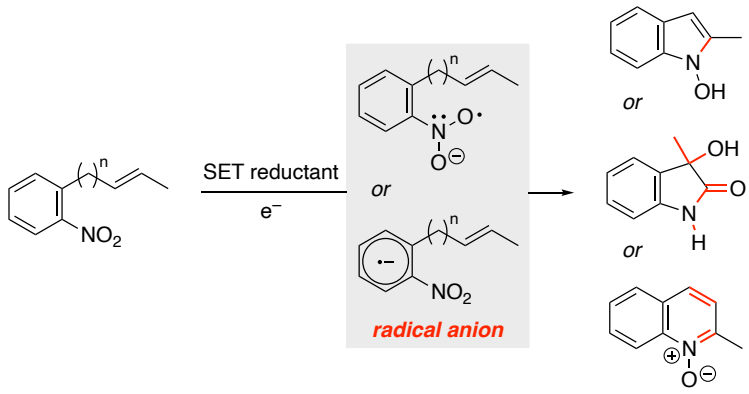
The Development of Single Electron Transfer Reductive Processes to Construct *N*-Heterocycles from Nitroarenes via Radical Anion Intermediates

H. Zhu[a] and T. G. Driver[a,*]

[a]*Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois, USA, 60607*
**tgd@uic.edu*



Our research program is centered on the development of new methods to construct *N*-heterocycles by leveraging the reactivity embedded in aryl azides, nitroarenes, or aryl amines. While our previous efforts have focused on generating electrophilic *N*-aryl nitrogen reactive species using transition metal catalysts, we were curious if we could access radical intermediates through the single electron reduction of nitroarenes. We found that these species could be accessed at room temperature using *tert*-butoxide as the reductant and that the resulting radical anions exhibit unique reactivity to enable the formation of C–NAr and/or C–O and C–C bonds in the construction of five- or six-membered *N*-heterocycles.[1]

References

1. Zhao, Y.; Zhu, H.; Sung, S.; Wink, D. J.; Zadrozny, J. M.; Driver, T. G. *Angew. Chem. Int. Ed.* **2021**, *60*, 19207–19213.

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Alkene Dicarbofunctionalization with C(sp^3) Carbon Sources

R. Giri*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802.
**rkg5374@psu.edu*

Alkenes are important feedstock for organic synthesis with two vicinal sites for bond formation. Simultaneous construction of two carbon-carbon bonds across these vicinal positions is a most powerful strategy to generate complex products from simple starting materials. This process is highly significant from a synthetic perspective due to its ability to reduce a multistep process to a one-step endeavor. However, developing such a process is a challenging feat due to the intrinsic nature of unactivated alkenes to undergo migratory insertion with kinetics slower than cross-coupling, and alkylmetal intermediates to undergo β-H elimination with kinetics faster than transmetalation/reductive elimination, both of which are detrimental to alkene difunctionalization. This process is even more challenging when C(sp^3) (alkyl) coupling partners are used as carbon sources. In this talk, we will discuss and present our strategies to difunctionalize unactivated and mildly activated alkenes with two carbon sources with particular focus on the use of C(sp^3) (alkyl) coupling partners.[1] Mechanistic pathways pertaining to these new reactions devised based on radical probes, competition experiments and quantitative kinetic studies will also be discussed.

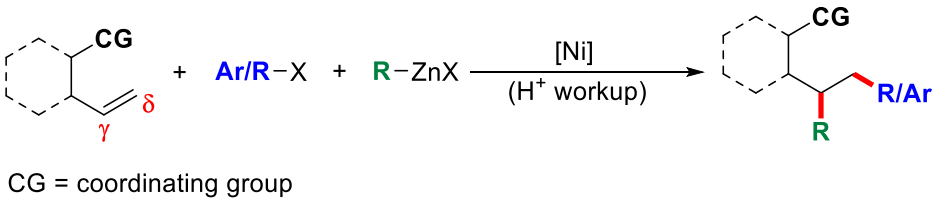

Figure 1. Alkene dicarbofunctionalization with C(sp^3) carbon sources.

References

(1) (a) Dhungana, R. K.; Sapkota, R. R.; Wickham, L. M.; Niroula, D.; Giri, R. *J. Am. Chem. Soc.* **2020**, *142*, 20930-20936; (b) Dhungana, R. K.; Sapkota, R. R.; Wickham, L. M.; Niroula, D.; Shrestha, B.; Giri, R. *Angew. Chem. Int. Ed.* **2021**, *60*, 22977-22982; (c) Aryal, V.; Chesley, L. J.; Niroula, D.; Sapkota, R. R.; Dhungana, R. K.; Giri, R. *ACS Catal.* **2022**, *12*, 7262-7268.

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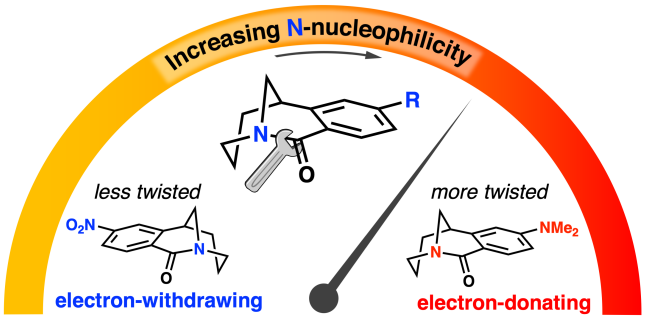
New Opportunities in Polymer Synthesis Using Twisted Amides

W. Gutekunst[a]* and M. Xu[b]

[a]*School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, United States*
[b]*Materials Research Laboratory, University of California, Santa Barbara, United States*
**willgute@gatech.edu*

While most amide bonds are regarded as robust linkages in chemical environments due to significant resonance stabilization from the nitrogen atom, twisted amides are at odds with this paradigm due to their unique geometric constraints. Removal or weakening of this key stabilizing interaction results in heightened reactivity that provides an opportunity for the development of new directions in polymer science. This presentation will highlight how twisted amides have been leveraged to produce a new class of living polymerization that is promoted through a halide-rebound cascade process.[1] Through remote functionalization, the rates of polymerization can be tuned over multiple orders of magnitude and change the rate limiting step of propagation.[2] During the presentation, the effect of geometric distortion on polymerization behavior will be highlighted to provide a rational framework for the development of future twisted amide systems.



References (sample format)

1. Fu, L.; Xu, M.; Yu, J.; Gutekunst, W. R. *J. Am. Chem. Soc.* **2019**, *141*, 2906–2910.
2. Xu, M.; Paul, M. K.; Bullard, K. K.; DuPre, C.; Gutekunst, W.R. *J. Am. Chem. Soc.* **2021**, *143*, 14657–14666.

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From Drug Discovery to Catalysis:

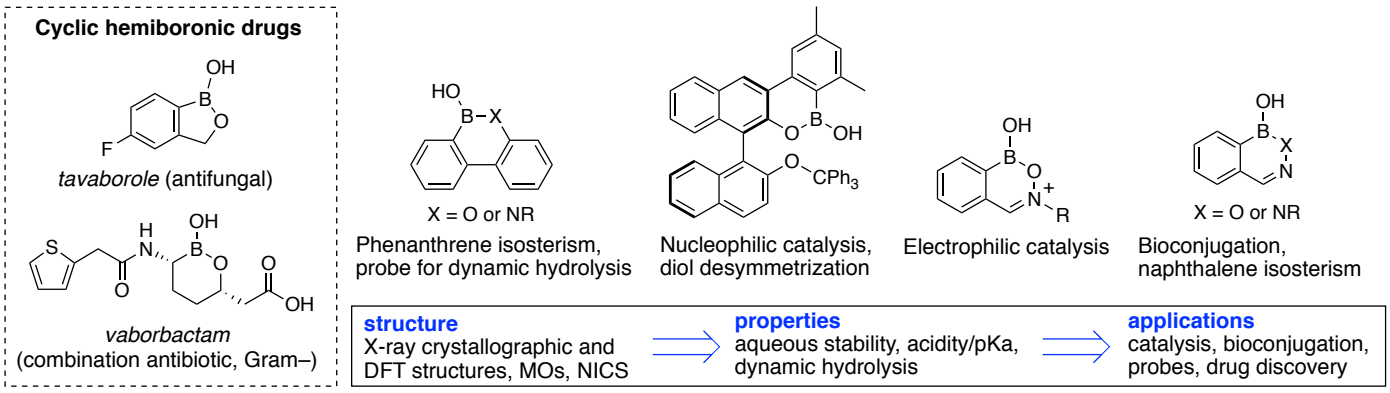
Design, Properties, and Application of Hemiboronic Heterocycles

D. G. Hall,[a,*] J. P. G. Rygus[a]

[a]*University of Alberta, Department of Chemistry, Edmonton, AB, T6G 2G2, Canada*
**dennis.hall@ualberta.ca*

The successful development and commercialization of the benzoxaborole drugs tavaborole and crisaborole has initiated a renaissance surrounding heterocycles derived from boronic acids in organic and medicinal chemistry. These new drugs, along with other cyclic hemiboronic acids, demonstrate a wide range of biological properties such as antifungal, antibacterial, and anti-inflammatory activity. Despite the success of these boroheterocycles, many questions remain unanswered regarding the desirable physical properties and the dynamic behavior of boranol (BOH)-containing heterocycles in aqueous media. Likewise, a precise knowledge of the acidic nature (Lewis *vs* Brønsted) of the boranol unit of these hemiboronic heterocycles is crucial toward tailoring their uses.

In the past few years, this laboratory has investigated several classes of hemiboronic heterocycles providing a comprehensive evaluation of their structure, stability, chemical and physical properties.[1-2] To resolve decades of conflicting views on the acidic and aromatic characteristics of pseudoaromatic hemiboronic acids, a multipronged experimental and computational approach was employed. These fundamental studies can help guide a systematic application of select boroheterocycles as enantioselective reaction catalysts,[3] in bioconjugation, and as new drug chemotypes and bioisosteres of pharmaceutically important classes of heterocycles. In recent work, hemiboronic heterocycles were identified as modular scaffolds enabling both nucleophilic and electrophilic activation of alcohols, which was exemplified in the monophosphorylation of diols, and the reduction of pi-activated alcohols and ketones with silanes under ambient conditions, respectively.



References

1. Kazmi, M. Z. H.; Rygus, J. P. G.; Ang, H. T.; Paladino, M.; Johnson, M. A.; Ferguson, M.; Hall, D. G. *J. Am. Chem. Soc.* **2021**, *143*, 10143–10156.
2. Ang, H. T.; Ponich, A. A.; Paladino, M.; Miskolzie, M.; Hall, D. G. *J. Am. Chem. Soc.* **2022**, *144*, 10570–10581.
3. Estrada, C. D.; Ang, H. T.; Vetter, K.-M.; Ponich, A. A.; Hall, D. G. *J. Am. Chem. Soc.* **2021**, *143*, 4162–4167.

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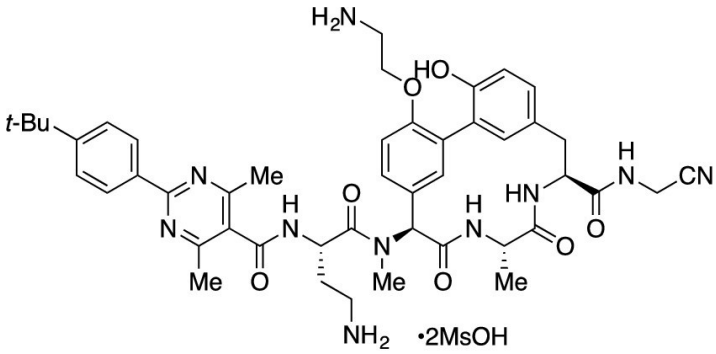
Stereocontrolled synthesis of arylomycin-based gram-negative antibiotic GDC-5338

A. Y. Hong,[a*] N. Wong,[a] F. Petronijević,[a] X. Linghu,[a] S. M. Kelly,[a] H. Hou,[a] N.-K. Lim,[a] S. J. Robinson,[a] C. Han,[a] C. Molinaro,[a] C. G. Sowell,[a] and F. Gosselin[a].

[a]*Department of Small Molecule Process Chemistry, Genentech, Inc., South San Francisco, California 94080, United States*
**hong.allen@gene.com*

We report an efficient, stereocontrolled, and chromatography-free synthesis of the novel broad spectrum antibiotic GDC-5338.[1] The route features the construction of a functionalized tripeptide backbone, a high-yielding macrocyclization via a Pd-catalyzed Suzuki–Miyaura reaction, and the late-stage elaboration of key amide bonds with minimal stereochemical erosion.



GDC-5338 (1)

- 17 steps longest linear sequence, 15% overall yield
- High yielding Suzuki-Miyaura macrocyclization in 88% yield
- High stereochemical integrity (>99:1 dr)
- High overall purity >99 A % HPLC

References

1. Wong, N.; * Petronijević, F.; * Hong, A. Y.; * Linghu X.; Kelly, S. M.; Hou, H.; Cravillion, T.; Lim, N.-K.; Robinson, S. J.; Han, C.; Molinaro, C.; Sowell, C. G.; Gosselin, F. *Org. Lett.* **2019**, *21*, 9099–9103.

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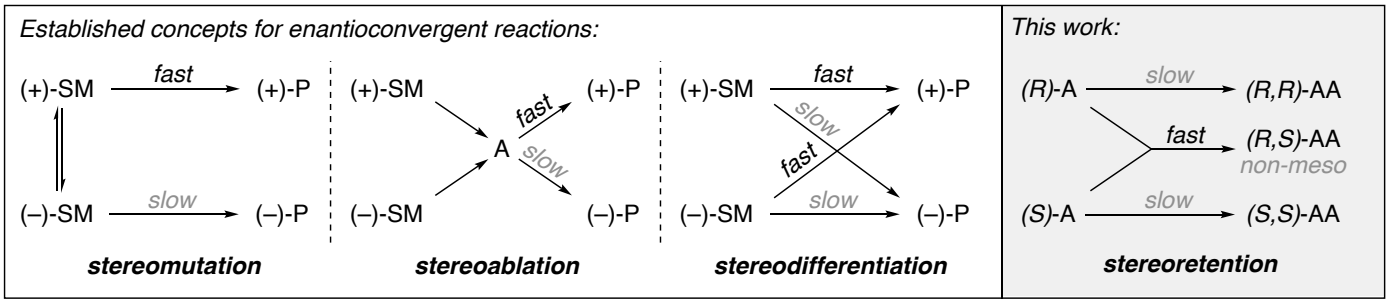
Exploring New Strategies in Asymmetric Synthesis

A. L. Lawrence*

School of Chemistry, University of Edinburgh, Joseph Black Building, David Brewster Road, Edinburgh, EH9 3FJ, UK.
**a.lawrence@ed.ac.uk*

The ability to synthesise chiral molecules in enantioenriched form is vitally important; it underpins many fields of pure and applied science. [1] The utilisation of racemic substrates in asymmetric synthesis is relatively challenging and complex. Resolution reactions give a maximum yield of 50% and necessitate the separation of remaining starting material from product. Enantioconvergent reactions, on the other hand, can convert 100% of a racemic starting material into a single enantioenriched product.[2] Three conceptual approaches have been exploited in the literature to achieve enantioconvergent reactions; *stereomutation*, *stereoablation*, and *stereodifferentiation*. These three established concepts all suffer from common limitations in their potential substrate scope. First, the stereogenic element of the starting material needs to be labile, towards mutation, ablation, or inversion. Second, substrates containing multiple stereogenic elements are not readily amenable. In this presentation, a fundamentally different approach to enantioconvergent reactions will be presented, which proceeds with retention of configuration. This *stereoretention* approach has the potential to enable the design of enantioconvergent reactions that utilize racemic substrates with robust and/or multiple stereogenic elements.



References

1. For reviews on the importance of asymmetric synthesis in medicine and materials science, see; a) Brooks, W. H.; Guida, W. C.; Daniel, K. G. The significance of chirality in drug design and development. *Curr. Top. Med. Chem.* **2011**, *11*, 760–770; b) Brandt, J.; Salerno, F.; Fuchter, M; The added value of small-molecule chirality in technological applications. *Nat. Rev. Chem.* **2017**, *1*, 45.

2. For reviews on enantioconvergent reactions, see; a) Steinreiber, J.; Faber, K.; Griengl, H. De-racemization of Enantiomers versus De-epimerization of Diastereomers—Classification of Dynamic Kinetic Asymmetric Transformations (DYKAT). *Chem. Eur. J.* **2008**, *14*, 8060–8072; b) Mohr, J. T.; Moore, J. T.; Stoltz, B. M. Enantioconvergent catalysis. *Beilstein J. Org. Chem.* **2016,** *12,* 2038–2045.

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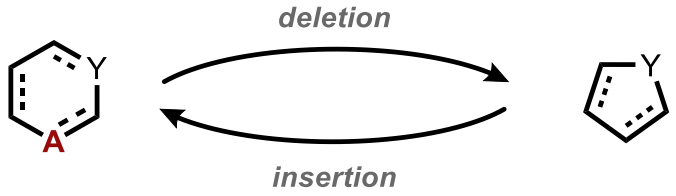
Single Atom Logic for Skeletal Editing

Mark D. Levin[a,*]

[a] *University of Chicago, Chicago, IL, USA*
*mark.levin@uchicago.edu

Reactions which can manipulate the connectivity of the molecular skeleton are underexplored as tools for late-stage functionalization, in part because their implementation has been hindered by their often nonintuitive retrosynthetic logic. This presentation will cover transformations discovered in our laboratory which address this challenge by enabling single-atom changes to aliphatic and aromatic systems through the insertion and deletion of single heavy atoms (C,N,O, etc.), as well as more complex manipulations leveraging combinations of these elementary transformations.[1] Our approach to this problem is modality-agnostic, drawing from a wide range of reactive species and synthetic disciplines (organometallic chemistry[2], reagent design[3-5] photochemistry[6]). Applications to late-stage functionalization and diversification of complex pharmaceutically relevant compounds as well as unique opportunities for synthesis will be presented alongside mechanistic findings.



References

1. Jurczyk, J.; Woo, J.; Kim, S.; Dherange, B.D.; Sarpong, R.; Levin, M.D. Single Atom Logic for Heterocycle Editing. *Nature Synthesis* **2022**, *1*, 352-364.
2. Kelly, P.Q.; Filatov, A.S.; Levin, M.D. A Synthetic Cycle for Heteroarene Synthesis by Nitride Insertion. *Chem RXiv*, **2022.** doi: 10.26434/chemrxiv-2022-1x9rq
3. Kennedy, S.N.; Berger, K.J.; Dherange, B.D.; Levin, M.D. Skeletal Editing Through Direct Nitrogen Deletion of Secondary Amines. *Nature*, **2021**, *593*, 223-227.
4. Dherange, B.D.; Kelly, P.Q.; Liles, J.P.; Sigman, M.S.; Levin, M.D. Carbon Atom Insertion into Pyrroles and Indoles Promoted by Chlorodiazirine Reagents. *J. Am. Chem. Soc.* **2021**, *143*(30), 11337-11344.
5. Berger, K.J.; Driscoll, J.L.; Yuan, M.; Dherange, B.D.; Gutierrez, O.; Levin, M.D. Direct Deaminaton of Primary Amines via Isodiazene Intermediates. *J. Am. Chem. Soc.* **2021**, *143*(42), 17366–17373.
6. Woo, J.; Christian, A.; Burgess, S. Jiang, Y.; Mansoor, U.F.; Levin, M.D. Scaffold Hopping by Net Photochemical Carbon Deletion of Azaarenes. *Science*, **2022**, *376*(6592), 527-532.

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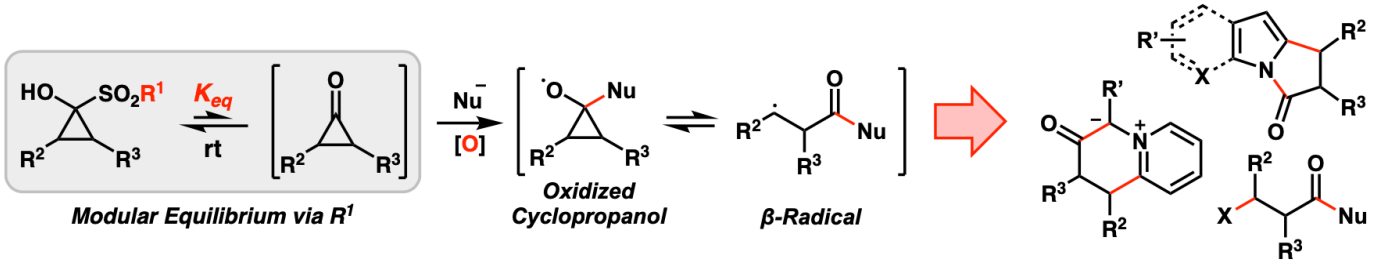
Reactivity of Sulfonylcyclopropanols as Precursors of Amide Homoenolates for the Synthesis of Fused Heterocycles

V. N. G. Lindsay*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695, United States

Our research group recently reported on the use of readily accessible 1-sulfonylcyclopropanols as versatile cyclopropanone equivalents in a range of new synthetic disconnections.[1] When these same species are treated with nitrogen nucleophiles such as *N*-heterocycles, the resulting transient hemiaminal adducts are reported here to act as effective amide β-radical equivalents in the presence of silver or iron catalysts, leading to fused heterocycles or β-halogenated amides difficult to access otherwise. The strategy was also extended to the use of pyridinium ylides as initial nucleophiles in the presence of manganese salts, affording fused dihydropyridine motifs highly relevant to medicinal chemistry and to the total synthesis of alkaloids.



References

1. (a) Poteat, C. M.; Jang, Y.; Jung, M.; Johnson, J. D.; Williams, R. G.; Lindsay, V. N. G. *Angew. Chem., Int. Ed.* **2020**, *59*, 18655-18661. (b) Machín Rivera, R.; Jang, Y.; Poteat, C. M.; Lindsay, V. N. G. *Org. Lett.* **2020**, *22*, 6510-6515. (c) Jang, Y.; Lindsay, V. N. G. *Org. Lett.* **2020**, *22*, 8872-8876. (d) Poteat, C. M.; Lindsay, V. N. G. *Org. Lett.* **2021**, *23*, 6482-6487.

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Chelate Forming Antimicrobial Conjugates for the Control of Biofilm-Forming Bacteria

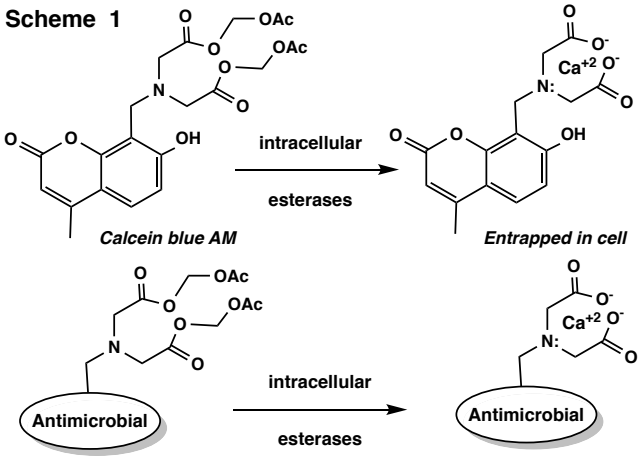
T. Livinghouse,[a]* D. Walsh,[a] H. Koenig[a] and P. Stewart[b]

[a]*Department of Chemistry and Biochemistry, Montana State University, Bozeman, MT, USA*
[b]*Center for Biofilm Engineering, Montana State University, Bozeman, MT, USA*
**livinghouse@chemistry.montana.edu*

Abstract: The discovery of new, highly potent antimicrobial agents for the control of biofilm-forming bacteria remains an enduring objective of the chemical and biological sciences. Over the years, the attainment of this goal has remained relatively elusive due to the pronounced ability of colonized bacteria to resist antibiotics by a variety of mechanisms, including efficient cellular efflux clearing. Since most pathogenic bacteria can exist as biofilm communities, the discovery of novel antimicrobial conjugates capable of eradicating established biofilms has the potential to markedly enhance the efficacy of antibiotics that are otherwise ineffective. Such therapeutic entities should have a significant impact on human medicine. Importantly, bacterial biofilms also underlie the persistent colonization of hospital facilities, both driving and sustaining nosocomial infections.

Drug-conjugate strategies have been effectively used to modify a wide array of structurally diverse pharmaceuticals to improve their physicochemical, pharmacokinetic, solubility and biopharmaceutical properties. This can be achieved through the incorporation of bio-reversible functional groups, which will be cleaved enzymatically upon delivery of the drug to the desired site. *To target a biofilm, an ideal drug-conjugate would partition from the bulk aqueous phase into the biofilm, where it would be concentrated and retained*. A chemical strategy that illustrates this principle involves the concentration of fluorescent dyes within living cells. This mechanism should allow a small amount of antimicrobial agent to be added to the bulk medium and effectively deploy to biofilm-impacted surfaces *and undergo intracellular concentration therein*. Reactive esters have been employed to enhance membrane permeability and are used in fluorogenic cell viability stains (e.g., Calcein blue AM). This labile (acetoxy)methyl coumarin derivative passively crosses the cell membrane of viable cells where it is then converted into Calcein blue by esterase cleavage, which is retained within the cell as its Ca^{+2} chelate, without compromising the cell membrane (Scheme 1). *Importantly, the intensity of intracellular fluorescence* ***increases*** *over time as the cleaved dye becomes concentrated within cells of the biofilm*. We have recently shown the validity of this mechanism for the delivery and retention of antimicrobial cargos into *S. epidermidis and P. aeruginosa* biofilms.[1] Significant enhancements of antibacterial activities were observed in both the planktonic (MIC) and biofilm (MBEC) states.

Scheme 1



1. Walsh, D. J., Livinghouse,* T., Durling, G., Arnold, A., Braiser, W., Berry, L., Goeres, D. M., Stewart, P. S. *Chemical Biology and Drug Design* **2021**, *97(1)*, 134-147.

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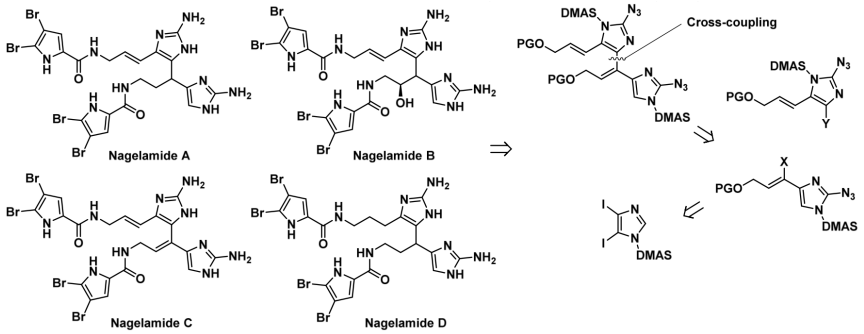
Total Synthesis of the Nagelamides

Carl J. Lovely,[a]* Olatunji Ojo,[a] Apsara Herath[a] and Manoj Bhandaria[a]

[a] *Department of Chemistry and Biochemistry, University of Texas at Arlington, Arlington, TX 76019, USA*

The nagelamides are small group, ca. 30 members, of pyrrole-aminoimidazole alkaloids belonging to the larger oroidin family of marine natural products. These compounds, first reported by the Kobayashi lab in 2004,[1] are considered to be acyclic oroidin dimers and may serve biosynthetically as precursors to other family members.[2] While the biological activities of these molecules have been reported to include antibiotic and anti-proliferative activity, their broadscale investigation remains to be accomplished. As part of a broader effort towards the oroidin alkaloids, we have been interested in developing approaches to the nagelamides as they not only serve as interesting targets themselves but they also may function as intermediates to other, more complex, family members. Initial studies have been directed towards family members with a C10-C15' link between the two oroidin fragments, specifically nagelamides A-D.



Our approach is predicated on a disconnection between the two imidazole containing fragments, specifically through the use of a cross-coupling reaction. Late-stage introduction of the imidazole 2-amino moieties via metalation and electrophilic trapping and incorporation of the pyrrole carboxamides through a novel application of the Mitsunobu reaction. The cross-coupling fragments would emerge from the derivatization of diiodoimidazole via sequential functionalization. This approach resulted in a total synthesis of the reported structure of nagelamide D.[3] Recent efforts have focused on nagelamide A and nagelamide C for which the core frameworks were readily constructed,[4,5] however, use of the same Mitsunobu strategy to incorporate the pyrrole carboxamides was thwarted by allylic transposition. Finding conditions to mitigate allylic transposition was challenging until it was discovered that azide could be incorporated; this gave tetra azides as late-stage intermediates. Once accomplished, our attention turned to incorporation of the pyrrole carboxamides and it was realized that opportunities existed for telescoping the sequence if the azides could be elaborated chemoselectively and a direct method for the incorporation of the amides could be developed. This presentation will report the construction of the cross-coupling building blocks and application to assembly of the nagelamide frameworks, in addition the discovery of pyrrole thio carboxylic acids as a means to convert azides into the corresponding amides will be discussed. Unexpected issues with thio acid oxidative coupling to form bisulfides will be described along with methods for mitigation. Applications of these new thio acids to the synthesis of oroidin analogs and as a means to complete the total synthesis of nagelamides A and C will be presented.

References (sample format)

1 Endo, T.; Tsuda, M.; Okada, T.; Mitsuhashi, S.; Shima, H.; Kikuchi, K.; Mikami, Y.; Fromont, J.; Kobayashi, J., Nagelamides A-H, new dimeric bromopyrrole alkaloids from marine sponge Agelas species. *J. Nat. Prod.* **2004,** *67*, 1262- 1267.

2 Das, J.; Bhandari, M. R.; Lovely, C. J., Isolation, Bioactivity and Synthesis of Nagelamides. In *Studies Nat. Prod. Chem.*, Att-ur-Rahman, Ed. Elsevier B.V.: Amsterdam, 2016; Vol. 50, pp 341-371.

3 Bhandari, M. R.; Sivappa, R.; Lovely, C. J., Total Synthesis of the Putative Structure of Nagelamide D. *Org. Lett.* **2009,** *11*, 1535-1538.

4 Bhandari, M. R.; Herath, A. K.; Rasapalli, S.; Yousufuddin, M.; Lovely, C. J., Total Synthesis of the Nagelamides – Synthetic Studies toward the Reported Structure of Nagelamide D and Nagelamide E Framework. *J. Org, Chem.* **2020,** *85*, 12971-12987.

5 Mukherjee, S.; Sivappa, R.; Yousufuddin, M.; Lovely, C. J., An Approach to the Oxazoline-Containing Fragments of the Oroidin Dimers Nagelamide R and T. *Synlett* **2010**, 817-821.

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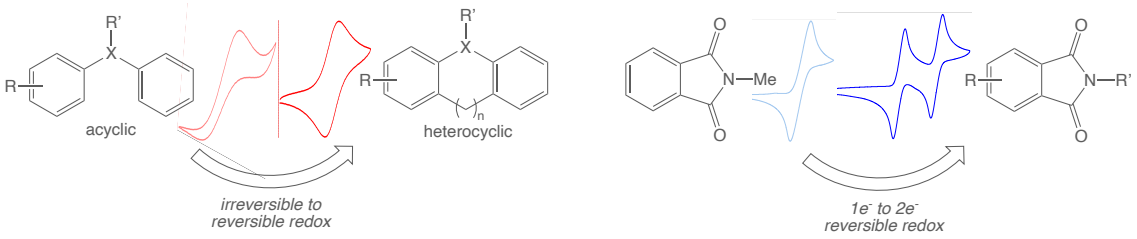
Development of *P*- and *N*-heterocycles as high-energy anolytes for organic-based redox flow batteries

C. A. Malapit*, A. Kitamura, and E. Mahoney,

Department of Chemistry, Northwestern University, Evanston, Il USA
**christian.malapit@northwestern.edu*



Redox flow batteries (RFBs) integrate renewable energy sources into grid-scale electricity production because their configuration enables decoupling of power and capacity. Non-aqueous RFBs offer the possibility of accessing higher energy densities than their aqueous analogues due to the larger electrochemical potential windows of organic solvents where the redox active molecules operate.[1] However, to fill in this chemical space, redox-active organic molecules as energy storage materials (anolytes and catholytes) are needed with a unique combination of properties, including highly reversible extreme redox potentials and/or multi-redox processes, high solubility in nonaqueous media, and stability to prolonged electrochemical charge–discharge cycling.[2,3] In this presentation, we report the discovery and development of two types of organic-based (phosphorous and nitrogen-containing heterocycles) redox active molecules that possess extreme redox potentials and their ability for multi-redox process. The design and synthesis of a library of target heterocyclic compounds, and the investigation of their electrochemical properties as anolytes in RFBs will be discussed.

References

1. Wei, X.; Pan, W.; Duan, W.; Hollas, A.; Yang, Z.; Li, B.; Nie, Z.; Liu, J.; Reed, D.; Wang, W.; Sprenkle, V. *ACS Energy Lett*. **2017**, *2*, 2187–2204.
2. Kwon, G. et al. *Joule* **2018**, *2*, 1771–1782.
3. Yan, Y.; Vogt, D. B.; Vaid, T. P.; Sigman, M. S.; Sanford, M. S. *Angew. Chem. Int. Ed*. **2021**, *60*, 27039–27045.

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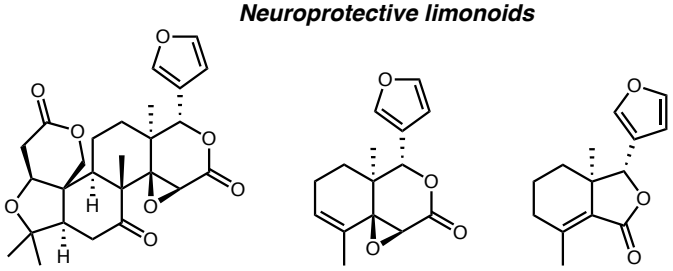
Synthesis of Neuroprotective Limonoid Natural Products

D.B.C. Martin,[a]* M. Raeisi,[a] C. Ludwig,[a] I. Jacobsen,[a] and C. Peiris[a]

[a]*University of Iowa, Iowa City, USA*
**david-martin@uiowa.edu*

Limonoids are polycyclic terpenes with diverse structures and myriad biological activity that have attracted the attention of synthetic chemists since their discovery in the 1960s.[1] A subset of the limonoids has been reported to have neuroprotective properties against glutamate toxicity, but details about their mechanism of action and structure-activity relationship studies are lacking.[2] We have developed an asymmetric synthesis of one class of degraded limonoids and investigated their neuroprotective effects in cell culture studies. Our results on the synthesis of analogs and probe molecules for the investigation of neuroprotective properties will be discussed.

Neuroprotective limonoids



References

1. Heasley, B. *Eur. J. Org. Chem.* **2011**, 19–46.
2. Yoon, J. S.; Sung, S. H.; Kim, Y. C. *J. Nat. Prod.* **2008**, *71*, 208–211.

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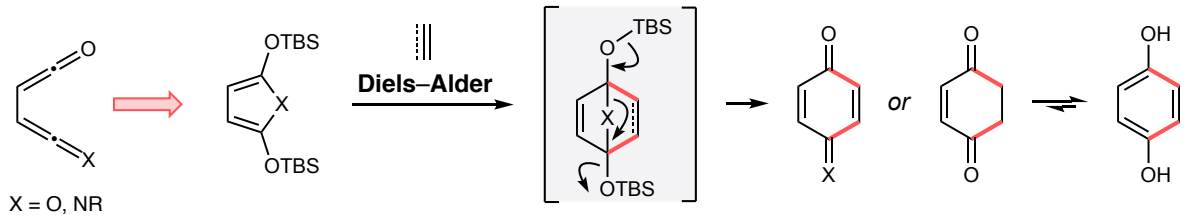
Bisketene Equivalents as Diels–Alder Dienes in Complex Natural Product Synthesis

Jacob Hart,[a] Jay Lawrence,[b] Jessica Budwitz,[b] Natarajan Kannan,[b] Steven Wheeler,[b] Jonathan George,[a] and Christopher Newton[b,*]

[a]*University of Adelaide, Adelaide, Australia*
[b]*University of Georgia, Athens, USA*

**chris.newton@uga.edu*

The *para*-(hydro)quinone motif features within a large number of biologically active natural products. Complex derivatives can often only be prepared in small quantities via lengthy multi-step sequences, impeding efforts to leverage targets in applied settings. We have recently developed a one-pot Diels–Alder methodology for accessing highly substituted *para*-quinones in a highly convergent manner. Central to realizing the transformation was the development of a bisketene equivalent that is sufficiently stable to be handled without specialized techniques, while also remaining primed for a facile ring-opening event. The generality of the approach was demonstrated through the preparation of several *para*-hydro-, benzo-, and imino-quinones, including a gram-scale synthesis of a neuroprotective para-hydroquinone-containing natural product. Ongoing studies concerning the application of this chemistry in the collective synthesis of several complex meroterpenoid natural products will also be discussed.



References

1. Dissanayake, I.; Hart, J.D.; Becroft, E. C.; Sumby, C. J.; Newton, C. G. *J. Am. Chem. Soc.* **2020**, *142*, 13328–13333.
2. Budwitz, J. E.; Newton, C. G. *Synlett* **2022**, DOI: 10.1055/s-0041-1737966.

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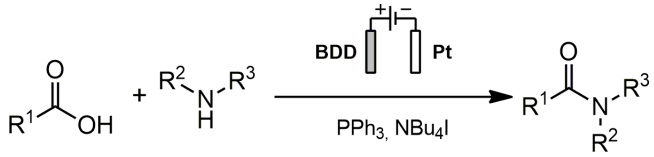
Electrochemical Amide Coupling and Photochemical Bond Activations

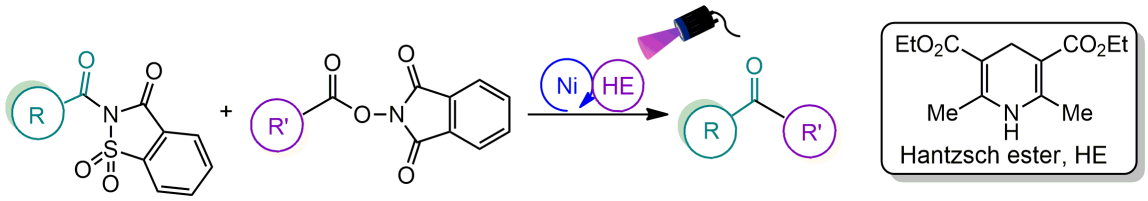
T. Opatz[a,*]

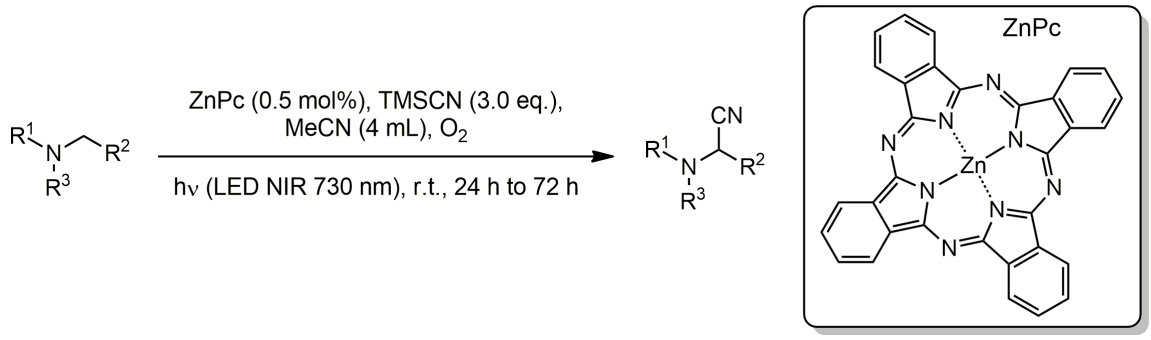
[a]*Johannes Gutenberg University, Mainz, Germany*

The formation of amides from amines and carboxylic acids is a key process employed in many areas of chemistry. While redox coupling approaches using stoichiometric amounts of oxidants and reductants are well established, electrochemical strategies are still scarce. Here, we present an anodic amide coupling protocol using PPh_3 and iodide which has a broad substrate scope. The stoichiometric co-product Ph_3PO can be recycled using known strategies. Even challenging couplings can be achieved in moderate to high yields while reagents posing safety risks are entirely avoided.[1]



A second topic of the presentation will be new bond formations using photochemical activation. Here, a dual nickel photoredox-catalytic synthesis of ketones and photoredox-catalytic transformations using infrared light will be presented.[2,3]





References

1. Großmann, L. M.; Beier, V.; Duttenhofer, L.; Lennartz, L.; Opatz, T. *ChemRxiv* **2022**, https://doi.org/10.26434/ chemrxiv-2022-rbcm3.
2. Brauer, J.; Quraishi, E.; Kammer, L. M.; Opatz, T. *Chem. Eur. J.*, **2021**, *27*, 18168-18174.
3. Grundke, C.; Silva, R.; Kitzmann, W.; Heinze, K.; de Oliveira, K.; Opatz, T. *J. Org. Chem.*, **2022**, *in press*. https://doi.org/10.1021/acs.joc.1c03101

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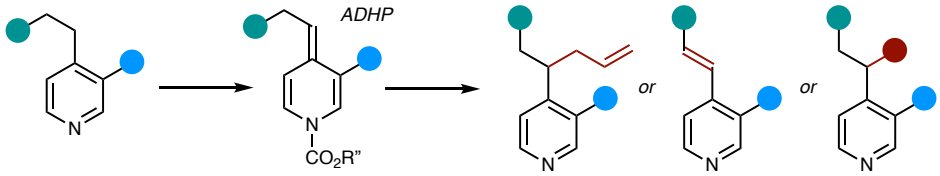
Mining the Reactivity of Dearomatized 4-Alkylpyridines

F. Rasheed[a], N. Wasfy[a], J. Shi[a], I. Hunter[a], B. Doan[a], A. Sayyad, D. Fishlock[b], A. Orellana[a]*

[a]*Department of Chemistry, York University, Toronto, Canada*
[b]*Roche Innovation Center, F. Hoffmann – La Roche, Basel, Switzerland*
**aorellan@yorku.ca*

4-Alkylpyridines can be dearomatized using a 'soft enolization' approach to generate alkylidene dihydropyridines (or ADHPs). These semi-stable intermediates present many opportunities for diversification of 4-alkylpyridines, providing access to attractive building blocks for discovery chemistry. Using ADHPs we have recently developed palladium-catalyzed allylation[1] and dehydrogenation[2] of 4-alkylpyridines. Through this work we also learned that ADHPs can behave as soft nucleophiles that undergo conjugate addition[3] to unsaturated ketones. These reactions tolerate a broad range of sensitive functional groups and activated positions, and display pyridylic selectivity. In this presentation I will provide an overview of our recent progress in this area.



References

1. Wasfy, N.; Rasheed, F.; Robidas, R.; Hunter, I.; Shi, J.; Doan, B.; Legault, C. Y.; Fishlock, D.; Orellana, A. Pyridylic Anions Are Soft Nucleophiles in the Palladium-Catalyzed C(Sp^3)-H Allylation of 4-Alkylpyridines. *Chem. Sci.* **2021**, *12*, 1503
2. Wasfy, N.; Doan, B.; Rasheed, F.; Fishlock, D.; Orellana, A. Palladium-Catalyzed, Mild Dehydrogenation of 4-Alkylpyridines. *ACS Catal.* **2021**, *11*, 3251
3. Shi, J.; Sayyad, A.; Fishlock, D.; Orellana, A. Alkylidene Dihydropyridines Are Surrogates for Pyridylic Anions in the Conjugate Addition to α,β-Unsaturated Ketones. *Org. Lett.* **2022**, *24*, 48.

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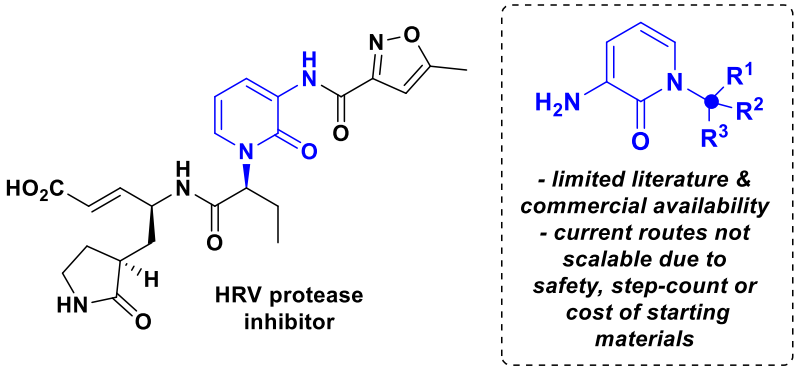
Efficient synthesis of *N*-substituted 3-amino-2-pyridones

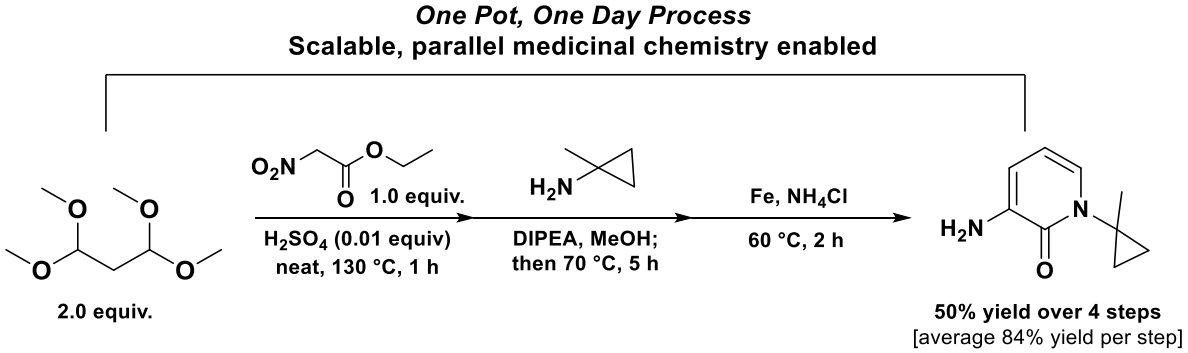
Magnus Pfaffenbach, Philippe N. Bolduc,* Vanna D. Blasczak,
Steven R. Mathieu, Emily A. Peterson

Biogen, 225 Binney Street, Cambridge, MA 02142, United States
Philippe.Bolduc@biogen.com

Pyridones have found extensive applications as versatile building blocks in organic synthesis and as privileged scaffold in drug discovery. This heterocycle is frequently applied in medicinal chemistry projects because it can serve both as a hydrogen bond acceptor and/or donor, act as a bioisostere for amides, phenyls, and pyridines, and impact a target drug molecule's lipophilicity, aqueous solubility and metabolic stability.[1,2] The *N*-substituted 3-amino-2-pyridone motif is precedented in a variety of compounds which exhibit interesting biological activities such as Jarin-1 inhibitor, interleukin-1B inhibitor and human leukocyte elastase inhibitor.



Multiple synthetic strategies have been developed to access this scaffold. However, 3-amino-2-pyridones bearing a quaternary carbon, cyclopropyl or heterocycle off the pyridone nitrogen atom remain challenging to prepare since they cannot be accessed via nucleophilic substitution reaction. Herein, we describe the efficient one-pot synthesis of a large variety of *N*-substituted 3-amino-2-pyridones from ethyl nitroacetate which is scalable and parallel medicinal chemistry (PMC) enabled.



References

1. Zhang, Y.; Pike, A., Pyridones in drug discovery: Recent advances. *Bioorg. & Med. Chem.* **2021**, 38, 127849.

2. Subbaiah, M. A. M.; Meanwell, N. A., Bioisosteres of the Phenyl Ring: Recent Strategic Applications in Lead Optimization and Drug Design. *J. Med. Chem.* **2021**, 64 (19), 14046-14128.

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Adventures in the Synthesis of Bioactive Natural Products

Joshua G. Pierce*

NC State University, Raleigh, North Carolina, United States
**jgpierce@ncsu.edu*

Marine natural products often have complex structures and potent biological activities; however, little is understood regarding how their molecular structure correlates with function or what biological targets or pathways are involved. Through rapid and efficient chemical syntheses of bioactive marine natural products we are able prepare ample quantities of material to explore both structure-activity relationships as well as target identification studies. In all our efforts, a key focus is the development of short, scalable and selective synthetic approaches, accomplished by new reaction development and strategic synthetic planning. This talk will focus on our efforts to develop novel approaches to prepare heterocycles in the context of marine natural products, particularly our efforts toward the bipolamine, curvulamine and related polypyrrole families of natural products.

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Quantitative Modeling Tools for Prediction in Synthesis and Catalysis

Jolene P. Reid[a,*]

[a] *Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia, V6T 1Z1, Canada*

**jreid@chem.ubc.ca*

When faced with unfamiliar reaction space, synthetic chemists typically apply the reported conditions (reagents, catalyst, solvent, and additives) of a successful reaction to a desired, closely related reaction using a new substrate type. Unfortunately, this approach often fails owing to subtle differences in reaction requirements. Consequently, an important goal in synthetic chemistry is the ability to transfer chemical observations from one reaction to another. Therefore, we have aimed to develop a program that assists the rapid analysis of the general interactions that impart asymmetric induction allowing the quantitative transfer of this stereochemical information to new reaction components and mechanisms. This talk will describe our recent efforts in developing this quantitative modeling workflow to assist in synthesis planning,[1] reaction optimization,[2,3] and selectivity prediction.[4]

References

1. Betinol, I. O.; Kuang, Y.; Reid, J. P. Guiding Target Synthesis with Statistical Modeling Tools: A Case Study in Organocatalysis. *Org. Lett.* **2022**, 24, 7, 1429–1433
2. Kuang, Y.; Reid, J. P. Transferable Selectivity Profiles Enable Prediction in Synergistic Catalyst Space. *ChemRxiv* **2021**, DOI: 10.26434/chemrxiv-2021-q5n18
3. Shoja, A.; Zhai, J.; Reid, J. P. Comprehensive Stereochemical Models for Selectivity Prediction in Diverse Chiral Phosphate-Catalyzed Reaction Space. *ACS Catal.* **2021**, *11*, 11897–11905.
4. Shoja, A.; Reid, J. P. Computational Insights into Privileged Stereocontrolling Interactions Involving Chiral Phosphates and Iminium Intermediates. *J. Am. Chem. Soc.* **2021**, *143* (18), 7209–7215.

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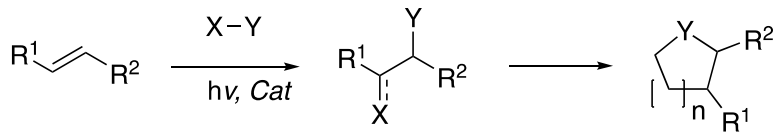
Photocatalyzed ATRA reactions as key step towards the synthesis of heterocycles

Oliver Reiser

University of Regensburg, Universitätsstr. 31, 93055 Regensburg, Germany
**oliver.reiser@chemie.uni-regensburg.de*

Photocatalyzed ATRA reactions provide a powerful tool for the difunctionalization of alkenes, which can be subsequently exploited for the synthesis of heterocyclic scaffolds. Representative examples from our group to illustrate this approach will be presented.



X = Hal, O; Y = SO_2R, NHR, CH_2NO_2, CHNHR

Leading References:

Krolo, T.; Bhattacharyya, A.; Reiser, O. *Org. Lett.* **2021**, *23*, 6283-6287; Engl, S., Reiser, O. *Org. Lett.* **2021**, *23*, 5581-5586.

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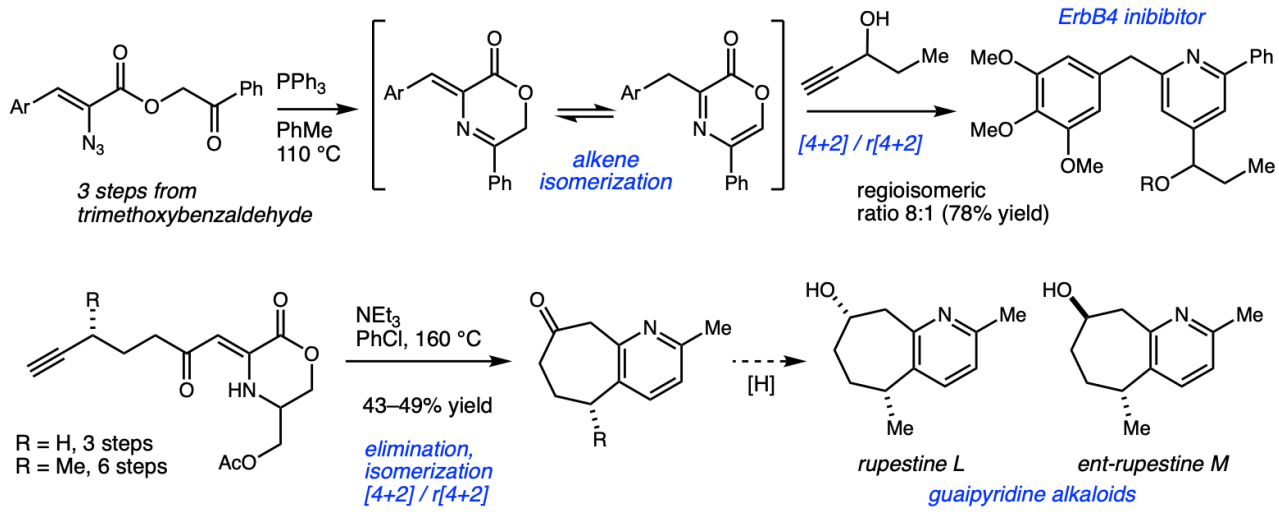
Preparation and Application of 1,4-Oxazinone Precursors in the Construction of Pyridine Derivatives

Jonathan R. Scheerer,* Nicole A. Carillo Vallejo, Jennifer A. Sprow, Ella B. Leeth

William & Mary, Department of Chemistry, Williamsburg, Virginia 23187
**jrscheerer@wm.edu*

1,4-Oxazinones are the most reactive precursors for cycloaddition / cycloreversion sequences leading to the formation of pyridines. Our recent efforts have revealed new methods for the preparation of oxazinones. Application of oxazinones in tandem cycloaddition / cycloreversion sequences has enhanced our understanding of the reactivity and selectivity of this reaction sequence. Several case studies in the preparation of polysubstituted pyridine structures of interest will be described, including the synthesis of (1) a bioactive trisubstituted pyridine[1] that shows ErbB4 enzyme inhibition and (2) studies directed toward rupestine L and *ent*-M, representative guaipyridine alkaloid natural products.[2]



References

1. Carrillo Vallejo, N. A.; Scheerer, J. R. Application of 1,4-oxazinone precursors to the construction of pyridine derivatives by tandem intermolecular cycloaddition/cycloreversion. *J. Org. Chem.* **2021**, *86*, 5863–5869.
2. He, F.; Nugroho, A. E.; Wong, C. P.; Hirasawa, Y.; Shirota, O.; Morita, H.; Aisa, H. A. Rupestines F–M, New Guaipyridine Sesquiterpene Alkaloids from *Artemisia rupestris*. *Chem. Pharm. Bull.* **2012**, *60*, 213–218.

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Accessing 4-Membered Heterocycles Through Metal-Ligand Cooperation Strategies

V. A. Schmidt[a]*

[a]*University of California San Diego, Department of Chemistry and Biochemistry, La Jolla, CA 92071, USA*
**vschmidt@ucsd.edu*

Recent developments for the construction of 4-memebered heterocycles via 2+2 carbonyl-olefin and imine-olefin photocycloadditions will be presented. Advancing these fundamental processes has been enabled by selective activation of non-conjugated, cyclic alkenes through a coordination-metal-ligand cooperation. Efforts in methods development will be presented alongside mechanistic investigations through a combination of experimental spectroscopes and computational studies.

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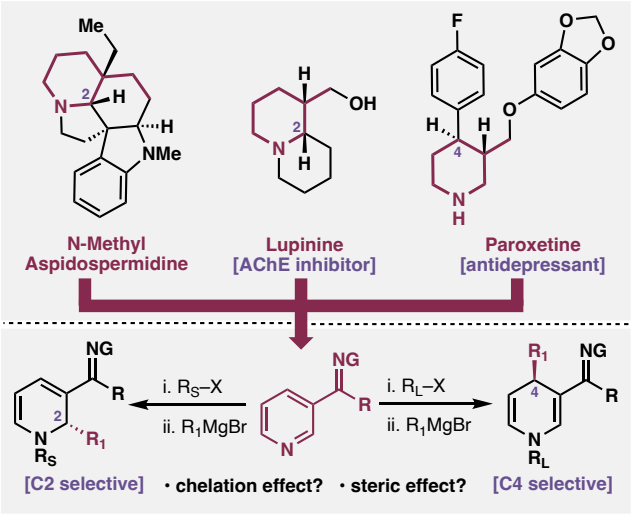
Dearomative Alkaloid Synthesis

T. A. Grigolo,[a] and J. M. Smith[a,*]

[a]*Florida State University, Tallahassee, Florida, United States*
**smith@chem.fsu.edu*

Alkaloid natural products are structurally diverse secondary metabolites that have served both as pharmaceutical leads and inspiration for the invention of novel chemical transformations. Substituted piperidine rings, a common motif found both in pharmaceutical ingredients and alkaloids alike, have continued to demand concise syntheses to allow for facile access to varied substitution patterns and privileged biologically active scaffolds. Our work has concerned the redox-economic construction of these alkaloids starting from readily available pyridine starting materials.[1] This discussion will first concern the innate regiochemical preference of organometallic nucleophiles to substituted pyridiniums,[2] followed by investigations into their controlled regioselective and stereoselective dearomatization as a platform for concise total synthesis.[3] Importantly, controlled regiodivergent asymmetric additions to pyridiniums have been achieved, enabling synthetic divergence to structurally distal targets that are natural and/or pharmaceutically relevant.[4] Discussion of mechanism and translational synthetic applications will also be highlighted.



References

1. Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. Redox Economy in Organic Synthesis. *Angew. Chemie Int. Ed.* **2009**, *48* (16), 2854–2867. https://doi.org/https://doi.org/10.1002/anie.200806086.
2. Knight, B. J.; Tolchin, Z. A.; Smith, J. M. A Predictive Model for Additions to: N -Alkyl Pyridiniums. *Chem. Commun.* **2021**, *57* (21), 2693–2696. https://doi.org/10.1039/d1cc00056j.
3. Grigolo, T.; Subhit, A.; Smith, J. Regioselective Asymmetric Alkynylation of <italic Toggle="yes">N</Italic>-Alkyl Pyridiniums. *Org. Lett.* *23* (17), 6703–6708. https://doi.org/10.1021/acs.orglett.1c02276.
4. Unpublished results.

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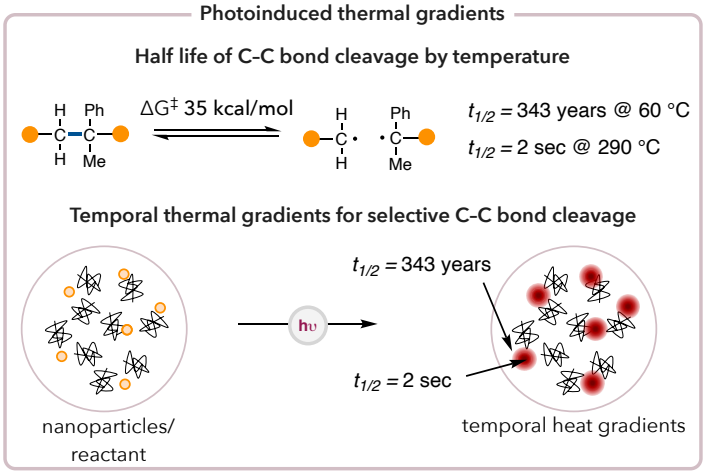
Photon-driven strategies for challenging bond activations

E. E. Stache*

Cornell University, Ithaca, New York, USA
**ees234@cornell.edu*

Photon-driven processes have emerged as a powerful tool for achieving challenging bond cleavages and bond formations.[1] Photocatalysis offers the benefit of temporal and spatial control with low energy light, which has been widely advantageous in polymers and materials to access sequence control or 3D structure. The judicious choice of photocatalyst enables a precision of reactivity not amenable to other strategies. We will demonstrate how photocatalyst identification can be leveraged for selective C–H abstraction for tunable product distributions, and applied in a scalable photo-flow process.[2] Additionally, I will discuss using visible light irradiation to enable temporal heating for generating and confining highly reactive intermediates for selective C–C bond cleavages.



References

[1] Corrigan, N.; Shanmugam, S.; Xu, J.; Boyer, C. Photocatalysis in Organic and Polymer Synthesis. *Chem. Soc. Rev.* **2016**, *45* (22), 6165–6212.
[2] Oh, S.; Stache, E. E. Chemical Upcycling of Commercial Polystyrene via Catalyst-Controlled Photooxidation. *J. Am. Chem. Soc.* **2022**, *144*, 5745-5749.

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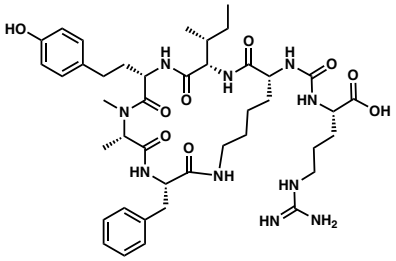
Synthesis of heterocyclic peptide secondary metabolites from cyanobacteria harmful algal blooms (cHABs)

J. L. Stockdill,[a]* J. A. Westrick,[a] R. M. I. Morsy,[a] B. S. Ramakrishna,[a] Z. Harris,[a] S. Kasmer,[a] D. C. Szlag[b]

[a]*Wayne State University, Detroit, MI, USA*
[b]*Oakland University, Rochester, MI, USA*
**stockdill@wayne.edu*

Cyanobacteria harmful algal blooms occur in freshwater, estuaries, and marine waters across the world and are a direct and increasing threat to human health via contamination of drinking water, recreational water, and freshwater and coastal seafood. Cyanobacteria thrive in warm, high-nutrient waters and produce heterocyclic peptide secondary metabolites that cause liver, neurological, dermal, gastrointestinal, and kidney diseases and cancer as well as antimicrobial and antiproliferative activities. This seminar will present synthetic approaches to selected heterocyclic cyanopeptides.



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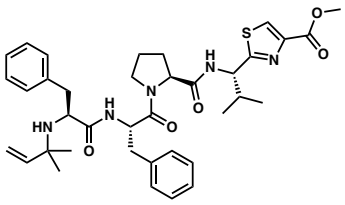

Aeruginosamide C

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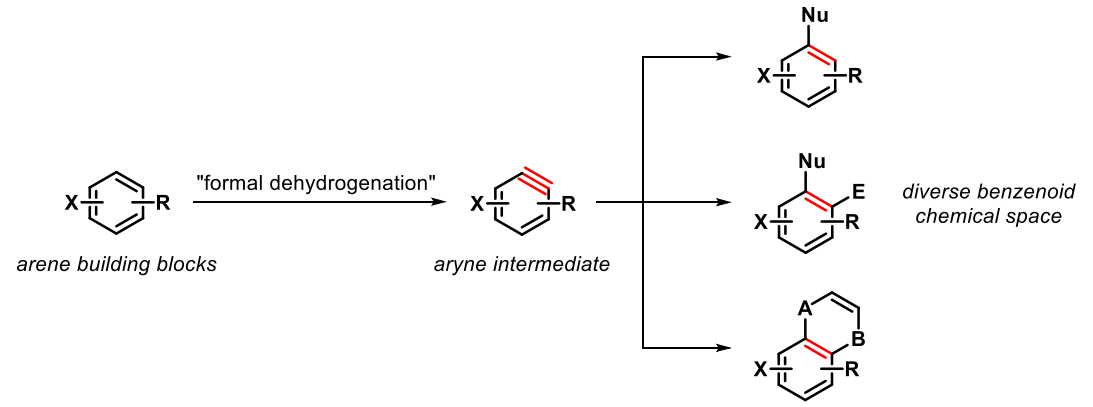
Aryne formation via formal dehydrogenation of simple arenes

D. R. Stuart,[a,*]

[a]*Portland State University, Portland, United States*
**dstuart@pdx.edu*

Arynes are novel intermediates for organic synthesis as they engage a diverse set of coupling partners. Consequently arynes are capable of generating a wide range of benzenoid chemical space. Despite a wide reactivity profile, major hurdles to using aryne chemistry are lengthy synthesis of the aryne precursor or harsh conditions to generate aryne intermediates themselves. Here, we describe a method to generate arynes that is both efficient and mild via a formal dehydrogenation of simple arenes. The method is so mild that all other halides are tolerated and therefore is a way to derivatize highly valuable aryl halide building blocks. Moreover, the method may be used for late-stage derivatization of advanced intermediates.



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New-to-Nature Metalloredox Biocatalysis for Stereoselective Radical Transformations

Yang Yang*

[a]*Department of Chemistry and Biochemistry, University of California Santa Barbara*
**yang@chem.ucsb.edu*

Abstract: Bringing new catalytic functions to naturally occurring enzymes can dramatically expand the repertoire of enzymology and generate novel biocatalysts. Inspired by the innate redox properties of first-row transition-metal cofactor, our group has recently begun to repurpose metalloproteins to catalyze stereoselective radical reactions triggered by single electron transfer. Due to the lack of exploitable stereocontrol elements in synthetic systems, steering the absolute and relative stereochemistry of these free radical processes is notoriously difficult in asymmetric catalysis. We engineered a set of metalloenzymes to impose excellent stereocontrol over the bond forming events in these unnatural processes, allowing stereodivergent radical catalysis to be easily carried out. These metalloenzymes are fully genetically encoded and function in bacterial cells, displaying excellent activities at room temperature. Collectively, this evolvable metalloenzyme platform represents a promising solution to tame fleeting radical intermediates for asymmetric catalysis.

References

1. Yue Fu, Heyu Chen, Wenzhen Fu, Marc Garcia-Borras, Yang Yang* and Peng Liu*, *J. Am. Chem. Soc.* **2022**, *144*, 13344–13355.
2. Qi Zhou, Michael Chin, Yue Fu, Peng Liu, and Yang Yang*, *Science* **2021**, *374*, 1612–1616.

Poster Abstracts