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# New quinoxaline-based derivatives as PARP-1 inhibitors: design, synthesis, antiproliferative, and computational studies

Yasmin M. Syam[a], Manal M. Anwar[a], Somaia S. Abd El-Karim[a], Khaled M. Elokely[b], Sameh H. Abdelwahed[c,*]

[a] *Department of Therapeutic Chemistry, National Research Center, Dokki, Cairo, 12622, Egypt.*
[b] *Institute for Computational Molecular Science and Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, USA.*
[c] *Department of Chemistry, Prairie View A&M University, Prairie View, TX 77446, USA.*

**Corresponding author's e-mail address: shabdelwahed@pvamu.edu*

**Abstract**: Herein, the 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline[1] was used as a bio-isosteric scaffold to the phthalazinone motif of the standard drug Olaparib[2] to design and synthesize new derivatives of potential PARP-1[3] inhibitory activity using the 6-sulfonohydrazide analog **3** as the key intermediate. Although the new compounds represented PARP-1 suppression impact of $IC_{50}$ values in the nanomolar range, compounds **8a**, **5** were the most promising suppressors producing $IC_{50}$ values of 2.31 and 3.05 nM compared to Olaparib of $IC_{50}$: 4.40 nM. Compounds **4**, **10b**, and **11b** showed a mild decrease in the potency of the $IC_{50}$ range: 6.35-8.73 nM. Furthermore, compounds **4**, **5**, **8a**, **10b**, **11b** were evaluated as in vitro antiproliferative agents against the mutant BRCA1 (MDA-MB-436, breast cancer) compared to Olaparib as a positive control. Compound **5** exhibited the most significant potency of $IC_{50}$: 2.57 $\mu$M, whereas the $IC_{50}$ value of Olaparib[2] was 8.90 $\mu$M. In addition, the examined derivatives displayed a promising safety profile against the normal WI-38 cell line. Cell cycle, apoptosis, and autophagy analyses were carried out in the MDA-MB-436 cell line for compound **5** which exhibited cell growth arrest at the G2/M phase, in addition to induction of programmed apoptosis and an increase in the autophagic process. Molecular docking of the compounds **4**, **5**, **8a**, **10b**, **11b** into the active site of PARP-1 was carried out to find out their modes of interaction. In addition, in silico ADMET study was performed. The results evidenced that compound **5** could serve as a new framework for discovering new potent anticancer agents targeting the PARP-1 enzyme.

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# Chemo- and Regioselective Cross-dehydrogenative Coupling of 3-Hydroxycarbazoles Using a Heterogeneous Oxovanadium Catalyst

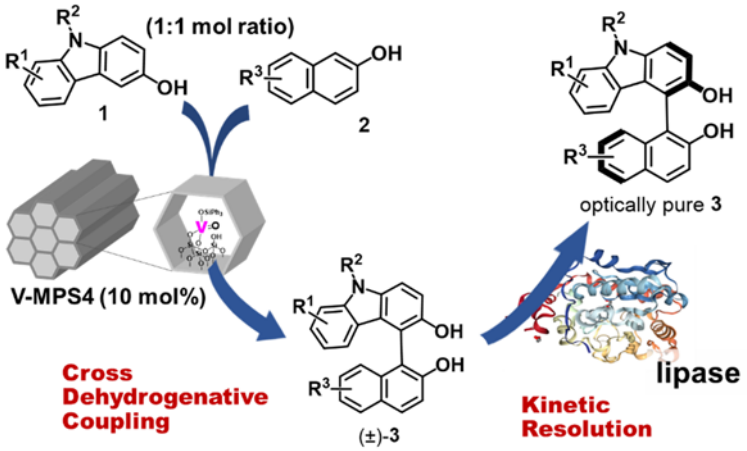
Shuji Akai,[a,*] Kengo Kasama,[a] Yuuya Hinami,[a] Karin Mizuno,[a] Kyohei Kanomata[a]

[a] *Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka, Japan*
**akai@phs.osaka-u.ac.jp*

**Background and objective**: The direct oxidative coupling of the C-H bonds of two aromatic compounds is a powerful and atom-economical method for biaryl formation without requiring pre-functionalization of the substrates. While various transition metal catalysts have been successfully used for homo-coupling reactions, oxidative cross-coupling of two different aromatic compounds, i.e., cross dehydrogenative coupling (CDC), still remains challenging because of the need to supress the homo-coupling and to control the reaction position precisely. We have invented a unique catalyst, V-MPS4, in which an oxovanadium(V) moiety is immobilized on the inner surface of mesoporous silica with a pore size of 4 nm, and used it as a racemization catalyst in lipase-catalyzed dynamic kinetic resolution of secondary alcohols.[1] In this study, we have aimed to develop a new CDC reaction using V-MPS4 to produce heterobiaryls having 3-hydroxycarbazole moieties and also to combine it with lipase-catalyzed kinetic resolution (KR) to obtain optically pure heterobiaryls (Figure).

**Results and discussion:** As a result of intensive studies, CDC of 3-hydroxycarbazole **1** and an equal amount of 2-naphthol **2** using 10 mol% V-MPS4 under ambient pressure of molecular oxygen was successfully established to obtain the desired cross-coupling product (±)-**3** in high yield and with excellent chemo- and regioselectivity. The reaction showed a wide substrate scope, including *N*-substituted 3-hydroxycarbazoles **1**. Particularly noteworthy is the fact that the heterogeneous V-MPS4 catalyst has a much higher activity than a homogeneous catalyst, $VO(OSiPh_3)_3$, even though the oxovanadium structures of both reagents are almost identical. Furthermore, V-MPS4 was reused three times without a significant decrease in product yield.[2] These results are noteworthy because homogeneous oxovanadium catalysts have been mainly investigated for the homo- and cross-coupling reactions of hydroxycarbazoles so far.

We also found that a commercially available *Pseudomonas* sp. lipase was suitable for KR of (±)-**3**. In particular, KR was highly efficient for (±)-**3** with substituents on the carbazole nitrogen atom producing (*R*)-**3** and (*S*)-**3** with high optical purity (98% *ee*).[3]

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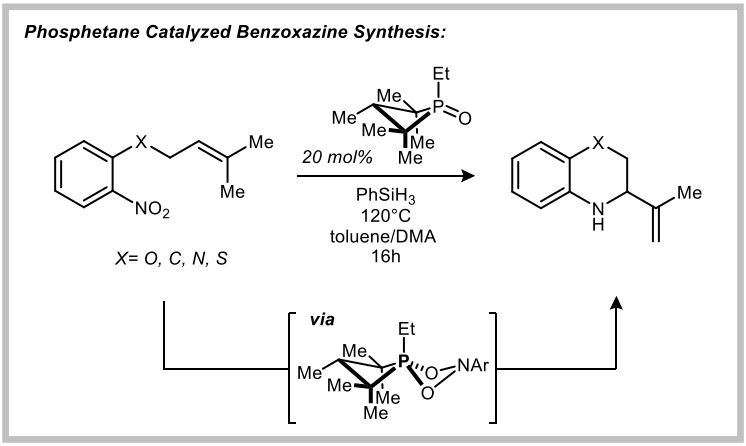
# Catalytic Benzoxazine Synthesis Enabled by $P^{III}/P^{V}$=O Cycling

John M. Andjaba,[a] Avipsa Ghosh[a] Alexander T. Radosevich[b,*]

[a,b] *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139*
** radosevich@mit.edu*

Nitrogen containing heterocycles are commonly displayed in a wide array of commercially attractive molecules, including, pharmaceuticals, dyes, conjugated polymers and polymer resins. An attractive method to access nitrogen containing heterocycles is through the generation of nitrene or nitrenoid equivalents to induce group transfer reactions, such as aziridination, or bond insertion strategies, such as C–H aminations. Recently, biphillic phosphorous catalysts have been identified towards accessing carbazole and indole derivatives via nitroarene deoxygenation followed by C–H bond insertion[1]. Here, we expand this work utilizing a $P^{III}/P^{V}$=O platform to catalytically access benzoxazine derivatives from nitro deoxygenation and subsequent nitroso-ene reactivity.

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# *In silico* generation of heterocycle-containing drug-like small molecules: towards tools for the many different needs of drug discovery projects.

B. R. Atwood,[a] V. B. R. da Silva,[b] R. Sabechkine, [b] M. Lhuillier-Akakpo,[b] B. Hoffmann,[b] K. Feher, [b] Y. Gasthon-Mathé,[b] N. D. Huu,[b] and Q. Perron[b,*]

*[a]Iktos Inc., San Diego, CA, United States of America; [b]Iktos, Paris, France, *quentin.perron@iktos.com*

Using heterocyclic scaffolds in drugs and drug-like small molecules is a fundamental pillar in small molecule drug discovery. There are many reasons for heterocycles appearing in so many small molecule drugs and the topic has been well discussed in the literature.[1-5] Our focus for this work is on heterocycles 1) utility as bioisosteres, 2) well-defined structure scaffolding and conformational properties, 3) tunable physiochemical and ADME properties, and 4) synthetic challenges and opportunities. These properties of heterocycles can be computed and encapsulated by computational representations and used in modern artificial intelligence (AI) and machine learning (ML) applications.[6-10]

Iktos is a chemistry AI company. We develop AI/ML tools to aid our drug discovery collaboration projects and to provide as a SaaS application to computational and medicinal chemists.[11] The primary tools from Iktos are Makya for *de novo* generative compound design and Spaya for data-driven retrosynthesis prediction. We have developed a variety of approaches generate virtual molecules within Makya and to direct these generations to converge towards an optimal *in silico* profile of properties.[12-13] The target profiles of virtually generated compounds can encompass a range of goals including QSAR-modellable properties, predicted binding with docking or free-energy perturbation, and synthesizability. We will discuss technology improvements directed towards use of heterocycle properties during molecule optimization, exploration of diverse heterocyclic scaffolds, and integration of heterocycle synthesis strategies to guide generations. We have implemented scaffold hopping algorithms, synthesis-based forward generation algorithms, and new molecular fingerprints and have made comparisons with some of the tools, techniques, and algorithms from the scientific literature. We have evaluated the performance of these newly implemented tools, techniques, and algorithms, in a virtual drug discovery project focused on identifying novel inhibitors of VEGFR2 with desirable physiochemical and predicted ADME properties and present the results through multiple rounds of design and evaluation with a discussion of improving the outcomes of the AI/ML tools for a practical drug discovery project.

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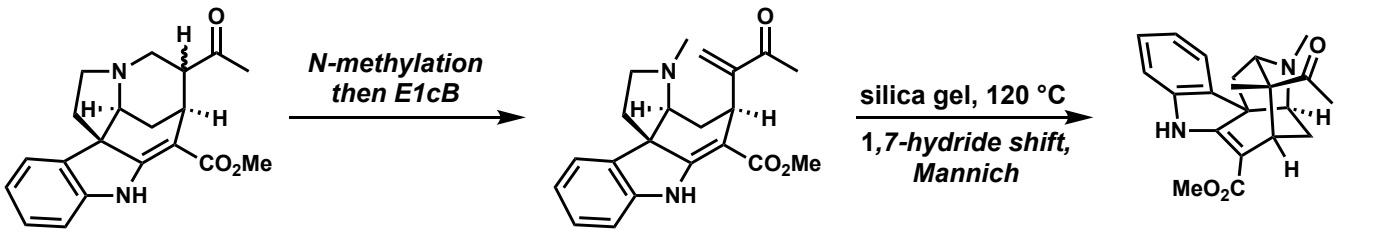
# Total Synthesis of (±)-Alstonlarsine A from (±)-Alstolucines B or F through a 1,7-Hydride Shift/Mannich Cascade

G. L. Barnes, A. Y. Hong, and C. D. Vanderwal*

*University of California, Irvine, Irvine, CA USA*
**cdv@uci.edu*




**1: (±)-alstolucine B, F**

***26% yield, 11 steps from PMB-tryptamine***

**2**

**3: (±)-alstonlarsine A**

A total synthesis of (±)-alstonlarsine A is described. *N*-Methylammonium derivatives of alstolucines B or F (**1**) were transformed to enone **2** through an E1cB reaction. This intermediate was converted to alstonlarsine A (**3**) after adsorption onto silica gel and heating. This sequence supports the chemical feasibility of an intramolecular hydride shift/Mannich cascade as the biosynthetic origin of alstonlarsine A. Both starting materials, alstolucine B and F, were previously synthesized in our lab as intermediates in a synthesis of alsmaphorazine B.[1]

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# Applications of Biocatalysis in the Synthesis of PCSK9 Inhibitors

Marc R. Becker, Paul Devine, Mark Huffman, Leo Joyce, Jeffrey Kuethe, Joshua Lee, Hongming Li, Michael Lo, Grant Murphy, Christopher Prier, and Nobuyoshi Yasuda

*Merck & Co., Inc, Rahway, NJ*

Inhibition of Proprotein Convertase Subtilisin/Kexin type-9 (PCSK9) improves cardiovascular outcomes in patients requiring additional low-density lipoprotein cholesterol reduction on top of statins, but there has been limited uptake of the two commercialized PCSK9 antibody inhibitors due in part to cost and route of administration. The protein-protein interaction between PCSK9 and the low-density lipoprotein receptor which is targeted by these therapies is a large, flat surface, which has made the discovery of orally bioavailable small molecule inhibitors highly challenging. This poster will introduce the use of macrocyclic peptides to interrupt such protein-protein interactions and describe the early chemistry development of such a PCSK9 inhibitor. These compounds feature several unnatural amino acids as well as a complex, multicyclic architecture, presenting challenges in their chemical synthesis. New biocatalytic tools are presented that rely on engineered enzyme to address the challenging synthesis of these unnatural amino acids.

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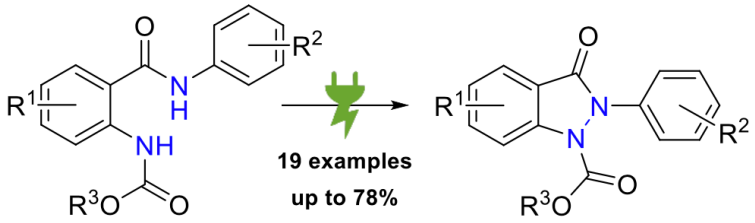
# Direct Electrochemical Synthesis of *N*,*N*'-Disubstituted Indazolin-3-ones under Sustainable and Metal-Free Conditions

J. C. Bieniek,[a] M. Grünewald,[a] J. Winter,[a] D. Schollmeyer[a] and S. R. Waldvogel[a,*]

[a]*Johannes Gutenberg University, Department of Chemistry, Duesbergweg 10–14, 55128 Mainz, Germany*
**waldvogel@uni-mainz.de*




Indazolin-3-ones represent an important class of N-heterocycles due to their broad range of biological activity.[1] Conventional indazolin-3-one syntheses often involve harsh reaction conditions, the use of toxic reagents in stoichiometric amounts or transition metal catalysts, leading to large amounts of reagent waste, high costs and safety hazards.[2] In contrast, electrochemical methods have proven to provide a sustainable and broadly applicable synthetic tool for the synthesis of various N-heterocycles. By applying current as a traceless oxidant, reagent waste can be diminished, work safety increased and costs can be lowered.[3]

Recently, we developed the first broadly applicable and sustainable electrochemical synthesis of *N*,*N*'-disubstituted inda- zolin-3-ones via an intramolecular anodic dehydrogenative N-N coupling reaction.[4] This method features mild reaction conditions, an easy experimental setup, sustainable and inexpensive electrode materials and a low supporting electrolyte concentration, providing access to various indazolin-3-one derivatives in very good yields up to 78%. Additionally, the excellent scalability of the reaction was demonstrated. Cyclic voltammetry experiments were conducted to get insights into the mechanism. Currently, selected indazolin-3-one derivatives are investigated regarding their antifungal properties.

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# Diazaborines: Phenolic Isosteres with Hydroxy Group Exchange Capability

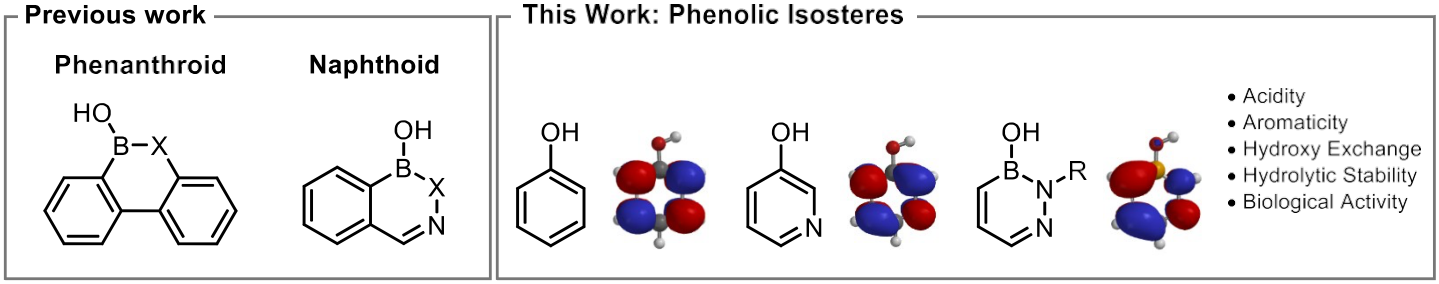
J. J. Blackner, W. O. Wong, and D. G. Hall*

[a]*Department of Chemistry, Centennial Center for Interdisciplinary Science, University of Alberta, Edmonton, Alberta, T6G 2G2, Canada*

**dennis.hall@ualberta.ca*

Heterocyclic organic molecules have a diverse range of applications, such as ligands in catalysis, integral components of functional materials, and as important substructures in medicinal chemistry.[1-3] The design and preparation of therapeutics that contain boronic acids and their derivatives has recently gained a significant amount of attention due to a large variety of possible molecular interactions and the relatively non-toxic nature of boron.[4] The potential of these heterocycles is exemplified by the success of the benzoxaborole ring system as a pharmacophore, which is present in the FDA approved pharmaceuticals Tavaborole (Kerydin®) and Crisaborole (Eucrisa®). As such, there exists an opportunity to design boron heterocycles as novel chemotypes that could provide solutions to previously unmet problems in medicine and human health.

Our laboratory has recently rectified some long-convoluted questions regarding the acidic and aromatic nature of boranol- containing (B-OH) naphthoid and phenanthroid isosteres.[5,6] Understanding these fundamental properties is essential for guiding the application of boroheterocyclic compounds in catalysis, materials, and medicinal chemistry. These previous studies on naphthoid and phenanthroid analogs motivated us to explore the parent benzenoid diazaborines, a novel class of boranol-containing phenolic isosteres that are free of influence from a fused aromatic ring. In order to gain a better understanding of this new chemotype, their acidic and aromatic properties have been interrogated through a combination of experimental, spectroscopic, and computational studies. The preparation of these compounds and the evaluation of their physical properties will allow for the synthesis of derivatives tailor-made for specific applications in catalysis, materials, and medicinal chemistry.

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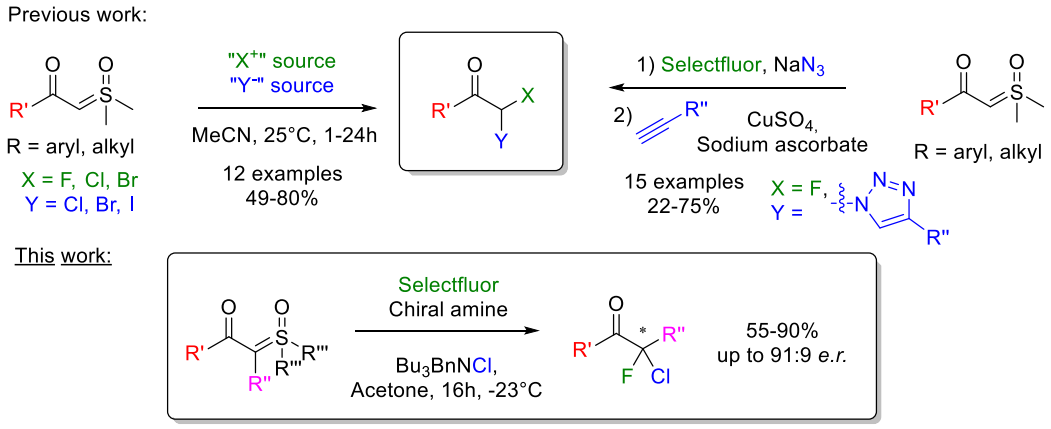
# Asymmetric dihalogenation of sulfoxonium ylides

Lucas G. Furniel [a] and Antonio C. B. Burtoloso [a,*]

[a]*São Carlos Institute of Chemistry, University of São Paulo, São Carlos, Brazil*
**antonio@iqsc.usp.br*

Introduction of fluorine substituents can alter the pKa of neighboring groups, dipole moments, and other molecular properties such as metabolic stability, lipophilicity and bioavailability, which makes organoflourine compounds ubiquitous in agrochemicals and medicinal compounds.[1-3] In contrast to the number of studies involving asymmetric α-mono-flourination[4] and asymmetric α-mono-chlorination of carbonyl compounds, there are only a few studies involving asymmetric formation of α,α-dihalogenated carbonyl compounds.[5-7] In every case, the halogens are installed in different steps, with the two C-X bonds being formed in subsequent reactions.

Utilizing the ability of sulfur ylides in promoting both nucleophilic and electrophilic reactions, our group recently reported methodologies allowing access to a variety of α,α-difunctionalized carbonyl compounds, in racemic fashion (Scheme 1).[8,9] Inspired by these contributions, we envisioned that using a chiral source of electrophilic halogen would enable access to enantioenriched α-chloro-α-fluor carbonyl compounds. Herein we report the first example of asymmetric dihalogenation in which both C-X are formed in the same reaction step. Up to this point we were able to prepare 5 examples of enantioenriched α-chloro-α-fluor carbonyl compounds in 55-90% yields and up to 91:9 *e.r.*




*Scheme 1. Difunctionalization of sulfoxonium ylides: previous racemic works and novel asymmetric methodology.*

Studies are underway to explore the scope and limitations of this methodology and to increase the enantioselectivity.

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# An Enantioselective Synthesis of Wickerol B

J. Chung,[a] M. Göhl,[a] J. S. Capani, Jr.,[a] P. C. Roosen,[a] and C. D. Vanderwal[a,*]
[a]*Department of Chemistry, University of California, Irvine, California 92697, United States*
**cdv@uci.edu*

We report the total synthesis of antiviral diterpenoid wickerol B. Our strategy relied upon early installation of a tertiary alcohol stereogenic center followed by sequential C–C bond forming events for construction of the planar 6-6-5 tricyclic core through stereochemical relay. Elaboration to the strained tetracyclic core was achieved through a late-stage Prins cyclization that could lead to several unusual and undesired products formed by strain-induced rearrangements. Throughout this campaign, desired stereoselectivity and reactivity outcomes proved challenging to attain. Consequently, numerous detours were taken while accessing key structural features, including enoate ester installation via a cerium-mediated 1,2 alkynylation/Meyer–Schuster rearrangement and formal aldehyde α-methylation via a Claisen rearrangement/deoxygenation sequence. Investigation of substrate-controlled C–C bond formation led to the development of conditions providing complementary stereochemical outcomes and diverse carbocyclic frameworks. Discoveries enabled by this endeavor may translate to the synthesis of other complex targets.

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# Syntheses of the *ortho*-polysubstituted azobenzenes

Marijo Čičak, Zlatko Janeba*

*Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Prague, Czech Republic*
** e-mail: zlatko.janeba@uochb.cas.cz*

Azobenzenes are a subclass of reversible light-switchable molecules due to their ability to undergo photoisomerization.[1] The basic structure of the azobenzenes is represented by two benzene rings connected by an azo bond. Reversible photoisomerization is observed as *trans-cis* isomerization around the azo bond. As the *trans* isomer is more stable in most of the cases, the thermal stability of the *cis* isomer is studied in order to investigate the physico-chemical properties of the azobenzene systems. The thermal stability (measured as half-life $t_{1/2}$) of *cis* isomer can be tuned by the character (electron-donor/acceptor, spatial demands) and position of substituents on benzene rings (e.g., fluoro substituents in *ortho* positions substantially extend the half-life of the *cis* isomer).[2,3]

The goal of this study was to develop a synthetic approach for the derivatization of 2,6-dichloroazobenzene as well as 2,6-dichloro-2',6'-difluoroazobenzene using the Suzuki reaction, and subsequently investigate the effect of the aryl and fluorine substituents on the photoisomerization and half-life of new *ortho*-polysubstituted azobenzenes.

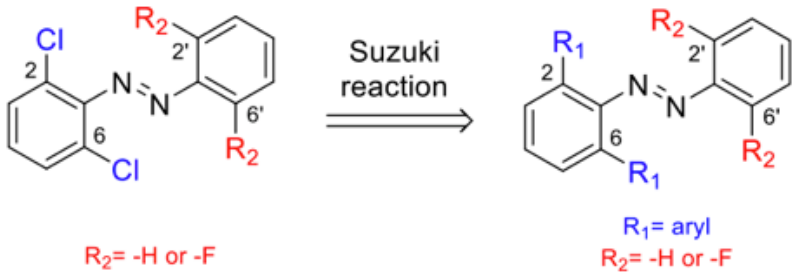


**Figure 1.** Unsymmetrically substituted azobenzenes

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# Synthesis and Reactivity of 5-Hydrazino-3-nitro-1,2,4-triazole (HNT): an Amphoteric Energetic Platform

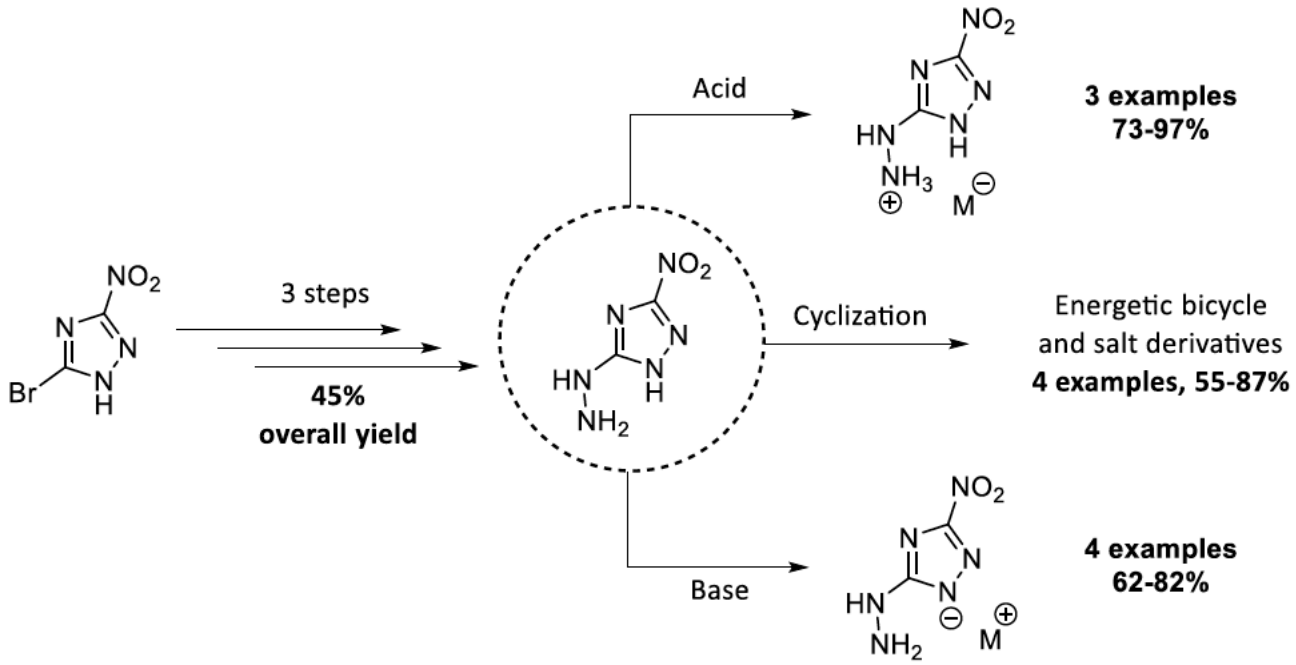
M. Daniel,* L. Habert, and E. Pasquinet

*CEA, DAM, Le Ripault, F-37260 Monts, France*
**matthieu.daniel@cea.fr*

Triazoles are a major class of heterocyclic compounds, widely used in pharmaceutical and energetic applications due to their high nitrogen content coupled with the presence of explosophoric groups like nitro, hydrazino or azido.

Although some hydrazino-1,2,4-triazoles have been described lately,[1] HNT is still surprisingly missing, making it doubtful as a free base, as only hydrochloride and sulfate salts were reported.[2,3]

Herein, the first synthesis of HNT is described from 5-bromo-3-nitro-1,2,4-triazole (BNT) in three steps, as well as other energetic compounds derived from it, including salts, thus demonstrating that HNT is not only a feasible, stable molecule, but also a valuable platform towards powerful and thermally stable energetic compounds.

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# Development of a [2+2] Photocycloaddition of 2-Pyridones using Organic Photocatalysis

A. Davis, C. Slough, E. Hardwick, and M. Daub*
*Furman University, Greenville, USA*
**marybeth.daub@furman.edu*

Pyridones are important heterocycles owing to their applications in medicinal chemistry and their use as building blocks in organic synthesis. In particular, photochemical reactions of pyridones provide access to diverse molecular scaffolds that would otherwise be challenging to make. We are developing a two-step synthesis of annulated 2-pyridones using visible light photocatalysis that features a [2+2] photocycloaddition followed by cyclobutane fragmentation. While [2+2] photocycloadditions of 2-pyridones have been well documented in the literature, these methods have relied on triplet sensitizers that absorb UV light. We have been investigating both transition metal and organic photosensitizers that absorb visible light to improve reaction efficiency and functional group compatibility. We have identified two photocatalysts capable of catalyzing the intramolecular [2+2] reaction of *N*-alkylated 2-pyridones, which will enable the development of an oxidative cyclobutane fragmentation toward annulated pyridones.

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# Organoboron-Catalyzed, Regioselective Alkylation of Azoles

S. P. Desai,[a] M. T. Zambri,[a] and M. S. Taylor[a,*]

[a]*University of Toronto, 80 St. George Street, Toronto, Ontario, M5S 3H6, Canada*

**marks.taylor@utoronto.ca*

Aromatic nitrogen heterocycles, or azoles, are found in around 59% of FDA-approved small molecule drugs.[1,2] These rings are a subset of molecular fragments that have the capacity to alter pharmacological profiles of drugs through key descriptors such as lipophilicity, polarity, molecular weight, and hydrogen bonding. Typically comprised of five- and six-membered aromatic rings, a common modification of azoles in druglike molecules is the incorporation of an N atom in place of a CH group which often improves molecular properties such as potency.[3] A route towards this modification is through substitution reactions of commercially available nitrogenous rings. The simplest of these reactions is N-alkylation which involves replacing a hydrogen atom with an alkyl species on the NH group of a ring.

*N*-alkylation of unsubstituted heterocycles such as triazoles, tetrazoles, indazoles and purines is of great interest due to their aforementioned medicinal applications. However, a challenge with using these species as nucleophiles is that they can react at two or more different nitrogen atoms, giving rise to mixtures of isomeric products. Organoboron catalysis provides a means of inducing *N*-selectivity in alkylations of azoles through epoxy alcohol ring-openings and conjugate additions of enones.[4] This work discusses two sets of electrophiles used in alkylating azoles in a regioselective manner (**Figure 1**).[5,6] With 2,3- and 3,4- epoxy alcohols, organoboron acids can coordinate to the primary alcohol tether and deliver the azole intramolecularly to provide high ring-opening- and *N*-selectivity. When using enones, an amine additive is required to activate the electrophile via an iminium intermediate. A range of diazoles, triazoles, and tetrazoles are explored in both studies, including the nucleobase purine.

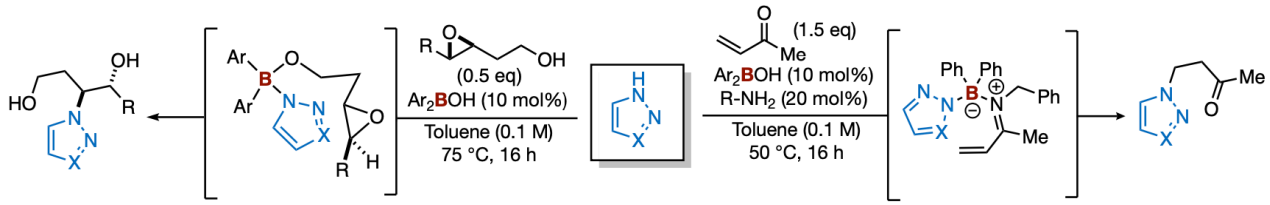


**Figure 1.** Organoboron-catalyzed, regioselective alkylation of azoles via epoxy alcohol ring-opening and *aza*-Michael additions.

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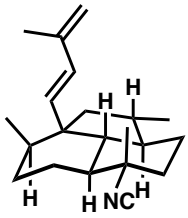
# The Total Synthesis of Isoneoamphilectane

Natalie C. Dwulet[a] and Christopher D. Vanderwal[a,*]

[a] *Department of Chemistry, University of California, Irvine, California 92697-2025, United States*
**cdv@uci.edu*

We report the first total synthesis of the rare isocyanoterpene natural product, isoneoamphilectane, in 23 steps from known materials. The core of the unique 6/6/5 ring system is generated in a concise sequence involving a Mukaiyama–Michael addition and sequential intramolecular alkylation reactions. The completion of the synthesis hinged on a challenging contrathermodynamic *cis*-to-*trans* decalone epimerization; we investigated multiple epimerization strategies and discovered a cyclic sulfite-based pinacol-like rearrangement to install the strained ring system. Additional key steps in our route include an intramolecular alkoxide-directed elimination and an HAT-mediated alkene hydroazidation.



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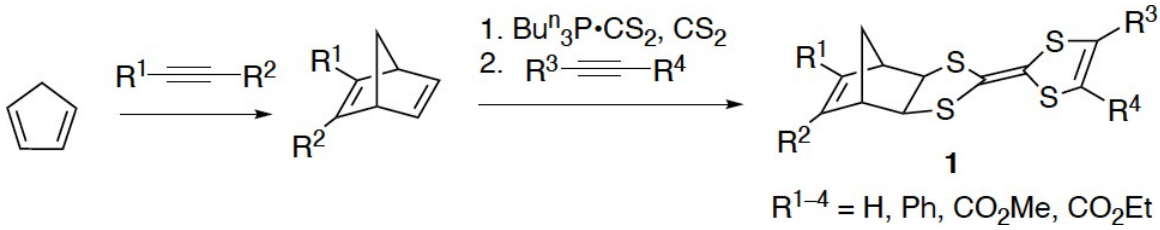
# Synthesis and Evaluation of New Dihydrotetrathiafulvalene Systems for Metal Surface Adsorption and Hydrogen Bonding

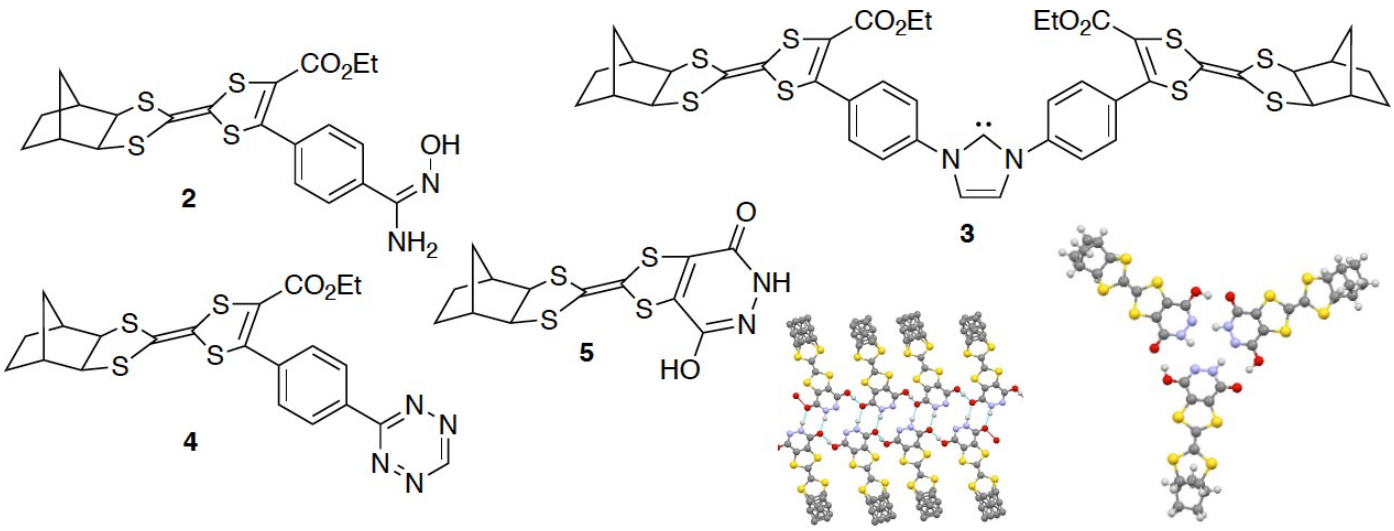
Fiona M. Fotherby and R. Alan Aitken*

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

Some years ago we described a new direct method to prepare norbornane-fused dihydro-TTF compounds **1**.[1,2] Although yields are only moderate, the method allows modular construction of a wide range of substituted examples and structural and electronic properties of a range of these will be presented.




We have already shown that a tetrakis(thiol-functionalised) analogue is efficiently adsorbed on a gold surface,[3] and current work towards new functionalised dihydro-TTFs capable of metal binding and self-association through hydrogen bonding will be described. In particular the amidoxime-compound **2** is designed to bind strongly to copper, the NHC **3** should show metal binding, the target tetrazine donor acceptor compound **4** is of interest.




The pyridazinedione compound **5** forms several different hydrogen bonded crystal forms including a cyclic trimer and a linear ribbon structure depending on the solvent of recrystallisation.

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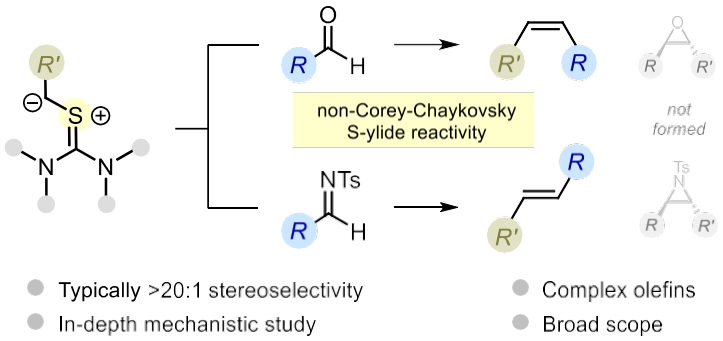
# Direct stereodivergent olefination of carbonyl compounds with sulfur ylides

Jérémy Merad[‡,a], Phillip S. Grant[‡,a], Tobias Stopka[‡,a], Juliette Sabbatani[a], Ricardo Meyrelles[a,b,c], Alexander Preinfalk[a], Ján Matyasovsky[a], Boris Maryasin[a,b], Leticia González[b] and Nuno Maulide[a,*]

[‡] *equal contribution*

[a]*Institute of Organic Chemistry, University of Vienna, Vienna, Austria*
[b]*Institute of Theoretical Chemistry, University of Vienna, Vienna, Austria*
[c]*Doctoral School in Chemistry, University of Vienna, Austria*

The reactivity of phosphorus and sulfur ylides toward carbonyl compounds constitutes a well-known dichotomy that is a common educational device in organic chemistry—the former gives olefins, while the latter gives epoxides.[1-3] Herein, we report a stereodivergent carbonyl olefination which challenges this dichotomy, showcasing thiouronium ylides as valuable olefination reagents. With this method, aldehydes are converted to *Z*-alkenes with high stereoselectivity and broad substrate scope, while N-tosylimines provide a similarly proficient entry to *E*-alkenes. In-depth computational and experimental studies clarified the mechanistic details of this unusual reactivity.




**Revisiting the dichotomy of sulfur and phosphorus ylide reactivity**

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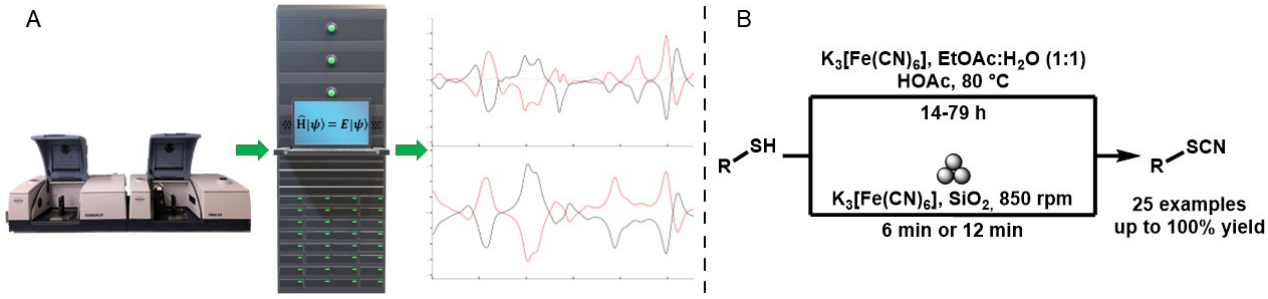
# Computer-Aided Natural Product Structure Elucidation and Mechanochemical Synthesis of Organic Thiocyanates

Jonathan Gross and Till Opatz*

*Johannes Gutenberg University, Department of Chemistry, 55128 Mainz, Germany.*
*Corresponding author: opatz@uni-mainz.de*

A well-established approach in drug discovery is the identification of pharmacologically active compounds from natural sources (plants, sponges, fungi, etc.), some of which have been known for their biological activity for centuries. An important part of this workflow is the elucidation of the correct structure of unknown secondary metabolites.

By combining spectroscopic methods with quantum mechanical calculations on the DFT-level, the capability to predict and confirm the exact chemical structure of several small molecules of such examples arose, using NMR- and CD-spectroscopy as well as polarimetry as standard working tools.[1,2]




Organic thiocyanates are a very versatile compound class not only with interesting biological activities but also as potential new drug motifs that could bypass increasing drug resistances.

In another project, a method development in the sense of the green chemistry principles is demonstrated by the preparation of thiocyanates using a biphasic reaction mixture or a ball-milling approach in combination with a non-toxic cyanide source. The optimized approach proofed to be widely applicable to a variety of commercially available thiols and disulfides.[3]

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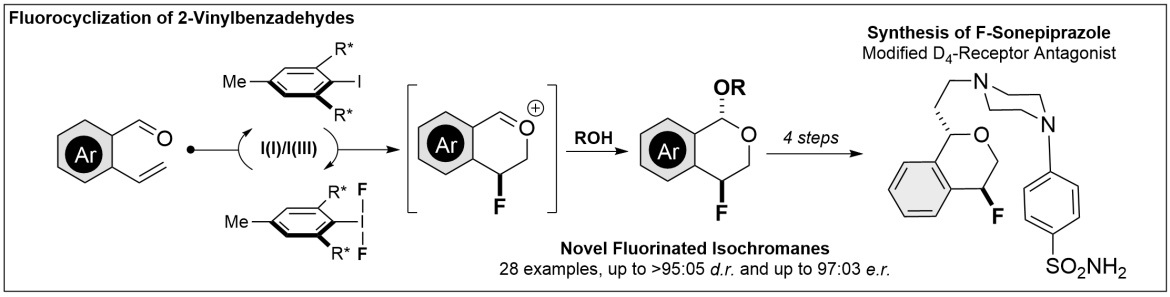
# Stereocontrolled Synthesis of Fluorinated Isochromans via I(I)/I(III) Catalysis[1]

J. Häfliger,[a] Olga O. Sokolova,[a] Madina Lenz,[a] Constantin G. Daniliuc,[a] and Ryan Gilmour,[a,*]

[a]*Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Münster, Germany.*
**ryan.gilmour@uni-muenster.de*

**Abstract:** Fluorinated, heterocyclic compounds play a highly important role in modern drug discovery.[2,3] Novel fluorinated isochromane building blocks were designed, enabling the expansion of the organofluorine chemical space from 2 to 3 dimensions.[4] For the synthesis of the desired products, a fluorocyclization/acetalization cascade was considered. It was found, that simple 2-vinylbenzaldehydes undergo a fluorocyclization mediated by an aryl iodide organocatalyst (20 mol%). Selectfluor® was used as a terminal oxidant and a HF•Pyridine mixture as a nucleophilic fluoride source in $CHCl_3$ as a solvent. In the presence of an additional alcohol to trap the intermediate oxocarbenium ion (see Scheme below), the desired 4-fluoro-1-alkoxyisochromanes were obtained with high stereoselectivities (up to 95:05 *d.r.* and up to 97:03 *e.r.*) and good yields. To show the synthetic utibility and possible applications of the obtained products, synthetic manipulations of the acetal functionality were demonstrated, including the multi-step synthesis of a fluorinated version of sonepiprazole, a highly potent $D_4$-receptor antagonist.[5] Structural analysis using single crystal X-Ray diffraction revealed stereoelectronic aspects such as $\pi \rightarrow \sigma^*_{C\text{-}F}$,[2b] suggesting the [$CH_2$-CHF] unit to act as a stereoelectronic mimic of the [O-CH(OR)] acetal motif.

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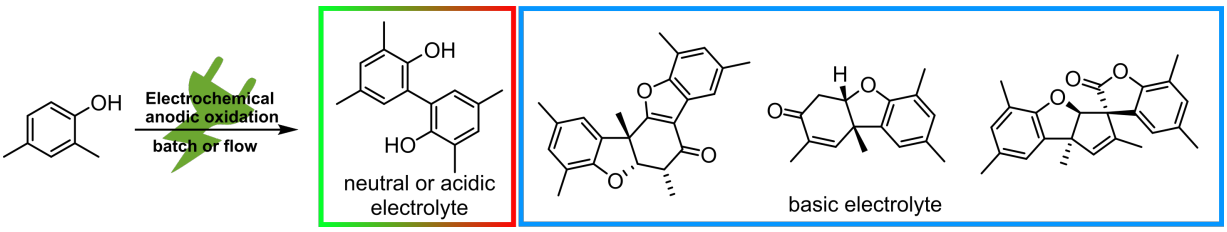
# The Anodic Phenol-Phenol Coupling – Optimizing Electrolysis Conditions is the Key to the Efficient Formation of Biphenols and Polycycles.

M. M. Hielscher, M. Selt, S. R. Waldvogel*
*Johannes Gutenberg University, Mainz, Germany*
* *waldvogel@uni-mainz.de*




The anodic C,C–coupling represents a sustainable and efficient synthetic pathway for the formation of symmetrical or non-symmetrical biaryls and for the construction of a series of polycyclic scaffolds. In contrast to established approaches such as reductive coupling reactions the generation of reagent waste can be completely avoided, since there is no need for leaving groups and transition-metal catalysts.[1] Recently, our group developed a wide range of synthesis protocols for various biaryl systems using neutral or acidic electrolytes,[2] and polycyclic scaffolds using basic electrolytes.[3] Nevertheless, the optimization of the numerous reaction parameters, such as current density, supporting electrolyte, choice of electrode material, poses a challenge, as these parameters usually correlate with each other. Classical optimization approaches such as the one-factor-at-a-time method (OFAT) often fail to quantify the relevant correlations between the individual parameters and fail to address the global optimum of yield or selectivity.[4] Using design of experiments (DoE), we optimized the protocol for the phenol arene cross-coupling, enabling high current densities and increased cell loadings of up to 5 mmol for *ortho* as well as *para* coupling reactions in 25 mL beaker-type cells.[5] When the reaction is transferred from the batch cell to an electrochemical flow cell, additional parameters such as the flow rate increase the complexity of the parameter space even further.[4–6] Using a fractional factorial design, we optimized multiple reaction parameters in a flow electrolyzer at once by means of 35 experiments, resulting in highly efficient reaction condition with an almost threefold increase in space-time yield in contrast to time-consuming linear OFAT optimization.[6]

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# Minimalist Tetrazine Carbohydrate Probe for Rapid Bioorthogonal No-Wash Live-Cell Labeling of Bacterial Peptidoglycan

Ashlyn S. Hillman,[a] Stephen N. Hyland,[a] Kimberly A. Wodzanowski[a], Sushanta Ratna[a], Catherine L. Grimes[a] and Joseph M. Fox[a,*]

[a]*Department of Chemistry and Biochemistry, University of Delaware, Newark, DE, United States; * jmfox@udel.edu*

Bacterial peptidoglycans (PG) are recognized by immune cells and broken down into fragments that are used as signaling molecules for further immune system activation.[1] Misrecognition of different bacterial fragments has been implicated in different inflammatory and autoimmune conditions.[2] As a result, bioorthogonal carbohydrate probes have been utilized as important tools for monitoring PG biosynthesis and breakdown. PG is composed of two carbohydrate subunits, *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM). Commonly used bioorthogonal NAM probes typically contain alkyne or azide groups, due to their small size and increased incorporation into bacterial PG.[3] However, copper-catalyzed alkyne-azide cycloaddition reactions are not compatible with live cells, and strain promoted alkyne-azide cycloaddition reaction rates are modest and therefore not as desirable for live-cell labeling. Alternatively, the tetrazine-transcyclooctene ligation, which is the fastest known bioorthogonal reaction and not cytotoxic, allows for rapid live-cell labeling of PG at biologically relevant concentrations.[4] Previous work to increase reaction kinetics by using tetrazines probes was limited due to low incorporation of the probe because of its size.[5] In this work, we have utilized new synthetic approaches to making asymmetric tetrazines to construct a tetrazine NAM probe with a minimized linker. This minimalist tetrazine carbohydrate probe has been successfully incorporated into Gram-negative and Gram-positive bacterial PG. Fixed and rapid live-cell, no-wash labeling was successful in both free bacteria and bacteria that had invaded macrophages. Overall, this probe allows for rapid, efficient, no-wash labeling of bacterial PG which will prove to be an exceptional tool for monitoring PG biosynthesis and investigating fragment production and subsequent immune signaling cascades.

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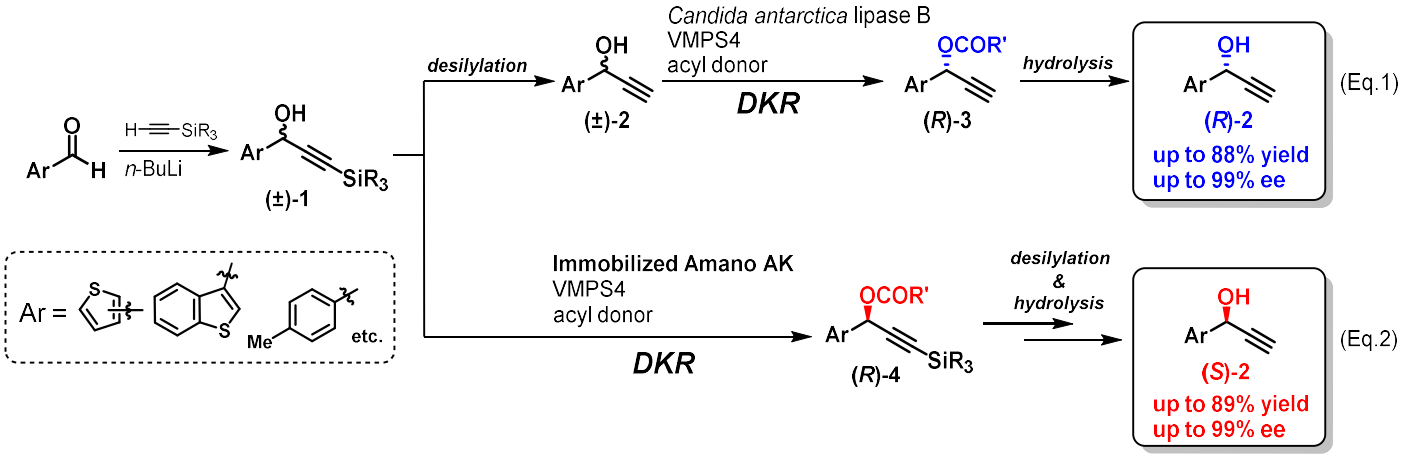
# Enantiodivergent synthesis of both enantiomers by dynamic kinetic resolution with *R*-selective lipases

Satoshi Horino[a], Tomoya Nishio[a], Shinji Kawanishi[a], Shinya Oki[a], Takashi Ikawa[b], Kyohei Kanomata[a] and Shuji Akai[a,*]

[a]*Grad. Sch. Pharm. Sci., Osaka Univ., Osaka, Japan*
[b]*Gifu Pharm. Univ., Gifu, Japan*
**akai@phs.osaka-u.ac.jp*

**Background and Purpose:** Natural lipases tend to recognize the size differences of substituents near the carbinol moiety and selectively esterify (*R*)-alcohols. Although kinetic resolution utilizing this property has been widely reported, each enantiomer are obtained in a maximum 50% yield. Recently, we have developed a dynamic kinetic resolution (DKR) method for the quantitative conversion of racemic alcohols to optically active compounds by the combined use of our original racemization catalyst, VMPS4, in which oxovanadium species are immobilized within mesoporous silica (MPS) pores, and commercial lipases[1]. Furthermore, we reported that secondary propargylic alcohol (±)-**2** can be converted to (*R*)-**3** in excellent yield and optical purity using this method (Eq. 1)[2]. On the other hand, (*S*)-selective hydrolase has been rarely used for DKR due to their low catalytic activity and stability[3]. Therefore, we investigated another DKR method for the synthesis of (*S*)-alcohols (*S*)-**2** to using (*R*)-selective lipases by introducing a bulky trialkylsilyl group on ethynyl terminal carbon of **2** to temporarily invert the size relationship of the substituents near the carbinol moiety.

**Results:** After screening of lipases applicable to the substrate (±)-**1**, *Pseudomonas fluorescence* lipase (commercial name, Amano AK) was found to be optimal. Then, by combining lipase AK immobilized on Celite and VMPS4, DKR of (±)-**1** afforded (*R*)-**4** in high yield and high optical purity (Eq. 2). Thus, the choice of either (±)-**1** or **2** has achieved the enantiodivergent synthesis of both enantiomers of propargylic alcohols **2**.

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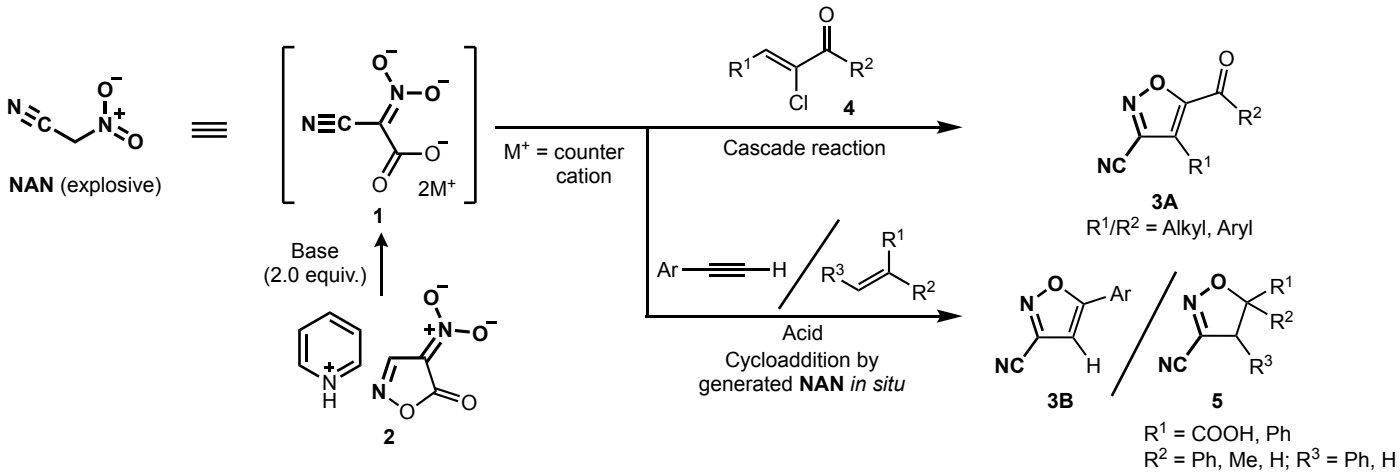
# A Safe Synthetic Equivalent of Nitroacetonitrile and Its Synthetic Uses toward 3-Cyanoisoxazoles

K. Iwai, and N. Nishiwaki*

*Kochi University of Technology, Kami, Kochi 782-8502, Japan*
**nishiwaki.nagatoshi@kochi-tech.ac.jp*

The active methylene compounds are essential building block in organic synthesis. Among them, nitroacetnitrile (**NAN**) has fascinating cyano and nitro groups which facilitate further chemical conversion. However, **NAN** should be handled as an explosive compound, thus, its synthetic uses have been limited. Based on these background, cyano-*aci*-nitroacetate **1**, safe synthetic equivalent of **NAN**, has been investigated in our group.[1] Dianion **1** can be generated from pyridinium salt of 4-nitrooxazol-5-one **2** upon treatment with two equivalents of base. Reagents **1** and **2** were easy to handle, and soluble in common organic solvents when organic amine was used as a base. Besides, the safety of **1** and **2** was confirmed by differential scanning calorimetry (DSC) measurement. In this poster, we will introduce two synthetic pathways towards 3-cyanoisoxazoles **3** using **2**. The first method is a cascade reaction with α-chloro-α,β-unsaturated ketones **4**, in which Michael addition of **1** to **4**, subsequent intramolecular substitution and dehydrative aromatization furnishes 5-acyl-3-cyanoisoxazoles **3A**. Acyl and cyano groups of **3A** exhibited high electrophilicity due to their electron-withdrawing effect through the isoxazole ring, thus, **3A** readily underwent the click reaction with organic azide and annulation between 5-acyl and 4-aryl units. The second synthetic method was performed by cycloaddition with alkynes or alkenes to afford corresponding isoxazoles **3B** and isoxazolines **5**, respectively, in which protonated **NAN** serves as a 1,3-dipole. Thus, **NAN** can be used as a synthetic equivalent of the cyanonitrile oxide which requires several limitations in the generation and handling. Since synthetic routes for 3-cyanoisoxazoles **3** and 3-cyanoisoxazolines **5** were limited to date despite high chemical convertibility of the cyano group, these synthetic methods are valuable to construct a library of isoxazoles and isooxazolines.

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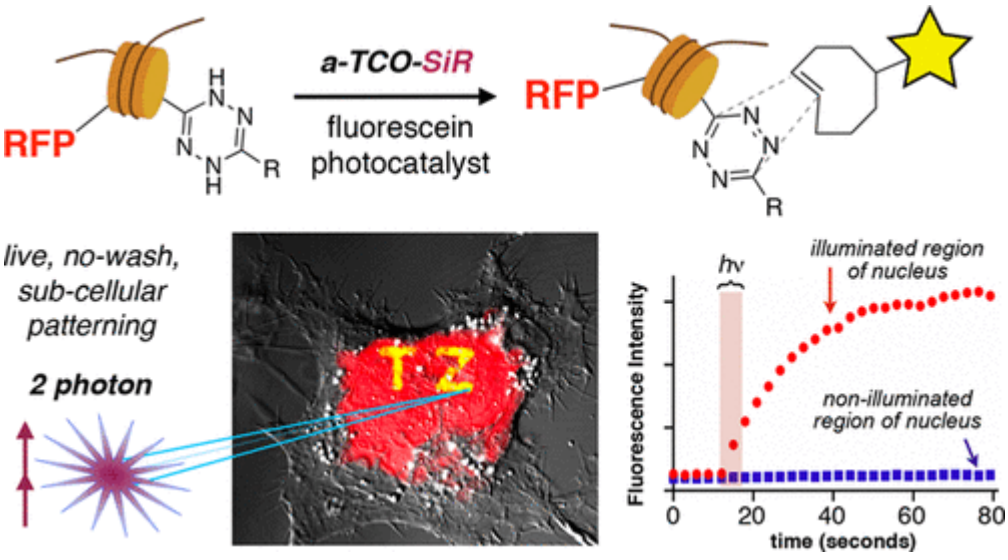
# Catalytic Activation of Bioorthogonal Chemistry with Light (CABL) Enables Rapid, Spatiotemporally Controlled Labeling and No-Wash, Subcellular 3D-Patterning in Live Cells Using Long Wavelength Light

[a]A. Jemas*, [a]Y. Xie, [a]JE. Pigga, [b]JL. Caplan, [c]CW. Am Ende, [a]JM. Fox

*[a]Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware, United States*
*[b]Department of Plant and Soil Sciences and Delaware Biotechnology Institute, University of Delaware, Newark, Delaware 19716, United States*
*[c]Pfizer Worldwide Research and Development, Eastern Point Road, Groton, Connecticut 06340, United States*
**jemasa@udel.edu*

Described is the spatiotemporally controlled labeling and patterning of biomolecules in live cells through the catalytic activation of bioorthogonal chemistry with light, referred to as "CABL". Here, an unreactive dihydrotetrazine (DHTz) is photocatalytically oxidized in the intracellular environment by ambient O2 to produce a tetrazine that immediately reacts with a trans-cyclooctene (TCO) dienophile. 6-(2-Pyridyl)- dihydrotetrazine-3-carboxamides were developed as stable, cell permeable DHTz reagents that upon oxidation produce the most reactive tetrazines ever used in live cells with Diels−Alder kinetics exceeding $k^2$ of $10^6$ $M^{-1}$ $s^{-1}$ . CABL photocatalysts are based on fluorescein or silarhodamine dyes with activation at 470 or 660 nm. Strategies for limiting extracellular production of singlet oxygen are described that increase the cytocompatibility of photocatalysis. The HaloTag self-labeling platform was used to introduce DHTz tags to proteins localized in the nucleus, mitochondria, actin, or cytoplasm, and high-yielding subcellular activation and labeling with a TCO-fluorophore were demonstrated. CABL is light-dose dependent, and two-photon excitation promotes CABL at the suborganelle level to selectively pattern live cells under no-wash conditions. CABL was also applied to spatially resolved live-cell labeling of an endogenous protein target by using TIRF microscopy to selectively activate intracellular monoacylglycerol lipase tagged with DHTz-labeled small molecule covalent inhibitor. Beyond spatiotemporally controlled labeling, CABL also improves the efficiency of "ordinary" tetrazine ligations by rescuing the reactivity of commonly used 3-aryl-6-methyltetrazine reporters that become partially reduced to DHTzs inside cells. The spatiotemporal control and fast rates of photoactivation and labeling of CABL should enable a range of biomolecular labeling applications in living systems.



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# Enantiospecific Heteroatom-Tethered 1,6-Enyne Cycloisomerizations and Their Utilization in Natural Product Total Synthesis

*Haofan Ji,*[a] *Phil C. Kuntson,*[b] *Eric M. Ferreira*[a,]*

[a]*Univeristy of Georgia, Athens, GA, USA;* [b]*Milliken & Company, Spartanbug, SC, USA*

**emferr@uga.edu*

Cycloisomerizations of 1,n-enynes catalyzed by electrophilic π-acid metal complexes provide a powerful method of carbon–carbon bond formation, and a unique platform for studying reactivity and mechanism.[1] Our previous report on the total synthesis of (±)-gelsenicine took advantage of a cycloisomerization/rearrangement strategy to access the central bridging bicyclic structure of the compound (Figure 1).[2] Continuing our interest in the gelsenicine total synthesis and enyne cycloisomerization, we began to formulate our own strategy toward an asymmetric variant of our route.

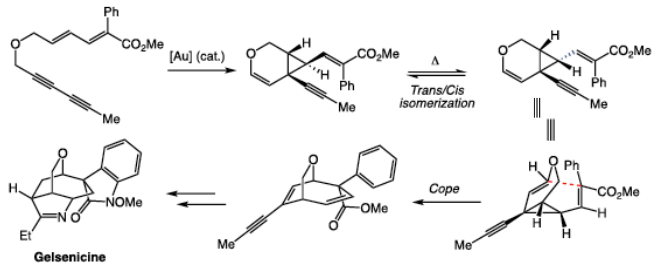



**Figure 1. Our cycloisomerization/Cope rearrangement approach to gelsenicine.**

In developing our asymmetric synthetic strategy based on chirality transfer, we had demonstrated enantiospecific cycloisomerizations of chiral ethereal 1,6-enynes (Figure 2).[3] This process requires a propargylic stereocenter in the substrates; although this stereocenter is destroyed in the transformation, its stereogenicity transfers in the cycloisomerization process. The substituent that dictates enantiospecificity ends up incorporated at the bridgehead position after the Cope rearrangement (Figure 2B). Therefore, we would need a removable group after the cycloisomerization/rearrangement process. Select entries from our investigation of the cycloisomerization under several Au- and Pt-catalyzed conditions are illustrated in Table 1.

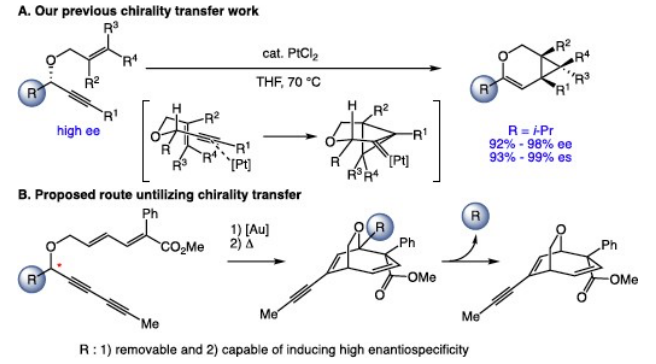
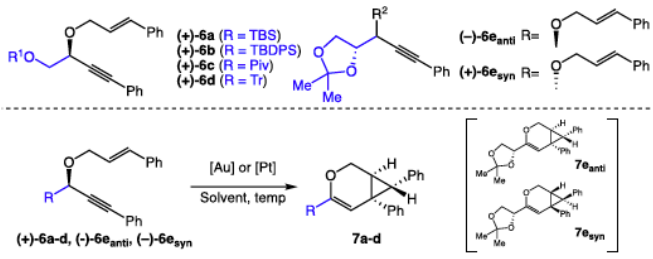



**Figure 2. Chirality transfer – application to gelsenicine synthesis.**

**Table 1. Chirality transfer cycloisomerization with oxygenated substituents.**




| Entry | Substrate | Catalyst[a] | Solvent, temp (°C) | Yield (%) | ee(%) | dr[b] |
|---|---|---|---|---|---|---|
| 1 | (+)-6a | Pt-1 | PhMe, 23 | 35 | ~74 | |
| 2 | (+)-6a | Au | $CH_2Cl_2$, 23 | 66 | 82 | |
| 3 | (+)-6b | Au | PhMe, 23 | 77 | 86 | |
| 4 | (+)-6b | Pt-2 | THF, 70 | 15 | ND[c] | |
| 5 | (+)-6c | Au | $CH_2Cl_2$, 23 | 71 | 86 | |
| 6 | (+)-6d | Pt-1 | THF, 23 | 75 | 79 | |
| 7 | (+)-6d | Au | PhMe, 23 | <5 | ND[c] | |
| 8 | (–)-6eanti | Au | $CH_2Cl_2$, 23 | 35 | | 87 : 13 |
| 9 | (+)-6esyn | Au | $CH_2Cl_2$, 23 | 26 | | 18 : 82 |

[a] Catalyst: Au: JohnPhosAu(MeCN)$SbF_6$, Pt-1: $[(C_2H_4)PtCl_2]_2$, Pt-2: $PtCl_2$. [b] Anti/syn ratio, determined by $^1H$ NMR. [c] ND: Not determined.

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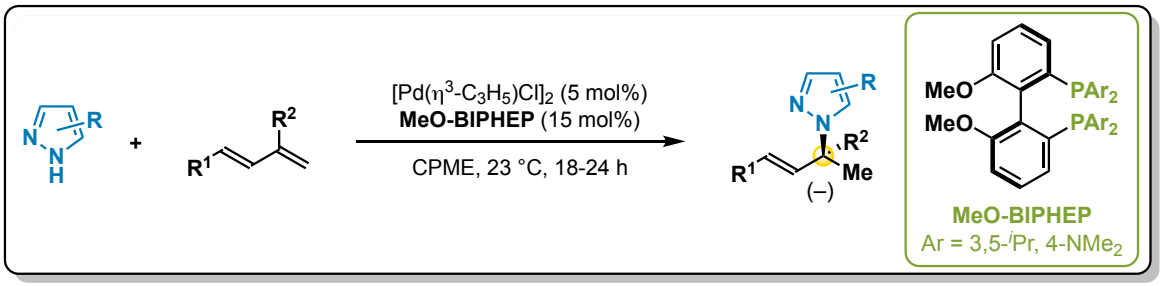
# Enantioselective Addition of Pyrazoles to Dienes

Alexander Y. Jiu, Hannah S. Slocumb, Charles S. Yeung, Xiao-Hui Yang and Vy M. Dong

[a] *Department of Chemistry, University of California, Irvine, Irvine, California 92697, United States*
*dongv@uci.edu*




Nitrogen-containing heterocycles, such as pyrazoles, represent valuable scaffolds for drug discovery and thus remain an inspiration for synthetic methods. The direct addition of a pyrazole to an olefin represents an attractive and atom-economical approach for forging C–N bonds. We report the first enantioselective addition of pyrazoles to 1,3-dienes. Secondary and tertiary allylic pyrazoles can be generated with excellent regioselectivity. Mechanistic studies support a Pd(0)-catalyzed ligand-to-ligand hydrogen transfer (LLHT), distinct from previous hydroaminations. This transformation tolerates a wide range of functional groups and advances the hydrofunctionalization of dienes.

Jiu, A. Y.; Slocumb, H. S.; Yeung, C. S.; Yang, X.-H.; Dong, V. M. *Angew. Chem. Int. Ed.* **2021**, 60, 19660–19664.

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# Cobalt-Catalyzed Annulation via Hydrogen Atom Transfer: Expedient Access to Arene-Fused Cycloalkanes

L. K. Johnson,[a,§] G. L. Barnes[a,§] and C. D. Vanderwal[a,*]

[a]*Department of Chemistry, University of California, Irvine, USA*
[§]*L.K.J. and G.L.B. contributed equally.*
**cdv@uci.edu*

An annulation between allyl-substituted arenes and electron-deficient alkenes is described. Cobalt-catalyzed hydrogen atom transfer (HAT) facilitates tandem radical C–C bond formation and generates six-membered benzocyclic products that contain useful functional handles for downstream derivatization. The fate of the nascent alkyl radical depends on catalyst structure. The reaction proceeds under mild conditions, tolerates various functional groups, and provides interesting diastereoselectivity in some cases.

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# Designing New Strategy For C-H Functionalization using a Hypervalent Iodine Reagent

Milanpreet Kaur[a], Julian Colton Cooper[b] and Jeffrey Van Humbeck[a]*

[a] *Department of Chemistry, University of Calgary, Alberta, Canada*
[b]*Department of Chemistry, University of Illinois, Urbana-Champaign, IL, United States*
**jeffrey.vanhumbec1@ucalgary.ca*

Research in the field of C–H functionalization has modified the way chemists approach the synthesis of natural products and medicinally relevant molecules, leading to rapid and efficient derivatization. In particular, the transformation of the C-H bond into a C-X bond (where X= carbon, oxygen, or nitrogen) in heterocycles has gained interest due to their presence in medicinal chemistry.[1-3] However, despite recent advancements, various approaches for the hydroxylation of C–H bonds are carried in the presence of a transition metal.[4-6] Our research group is working on addressing this challenge by developing a novel C-H Hydroxylation strategy using a metal free reaction. We focus on using a hypervalent iodine reagent that should possess the ability to not only selectively break the benzylic C-H bond adjacent to azaheterocycle but can also favor C-H functionalization in heterocyclic substrates with multiple reactive positions. The current research efforts that will be presented focus on exploring substrate scope under this strategy.

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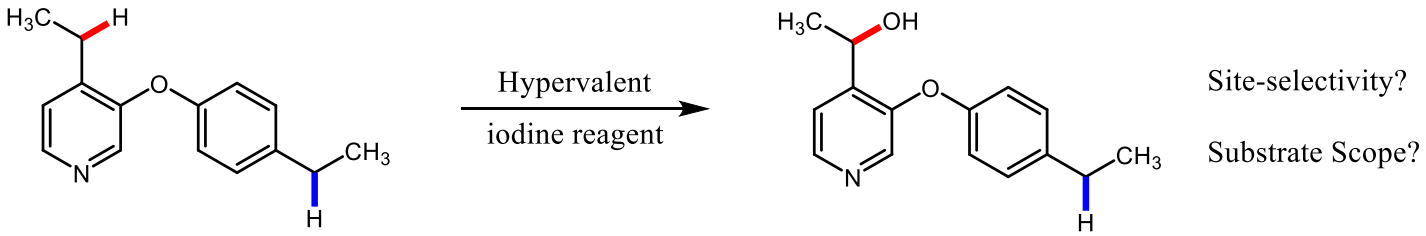

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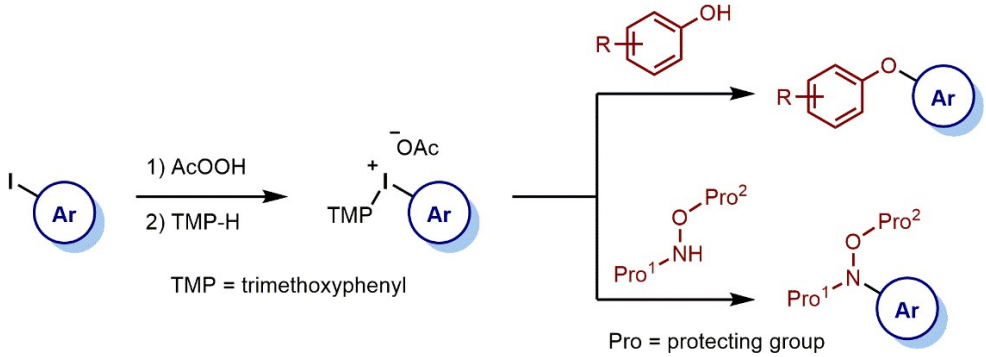
# Transition-Metal-Free Functionalization of (Hetero)arenes via Highly Reactive TMP-iodonium(III) Acetates

K. Kikushikma,[a] N. Miyamoto,[a] K. Yamada,[a] A. Morita,[a] E. E. Elboray,[a,b] Y. Kita[c,*] and T. Dohi[a,c,*]

[a]*College of Pharmaceutical Sciences, Ritsumeikan University, Kusatsu, Japan*
[b]*Department of Chemistry, Faculty of Science, South Valley University, Qena, Egypt*
[c]*Research Organization of Science and Technology, Ritsumeikan University, Kusatsu, Japan*
**td1203@ph.ritsumei.ac.jp (T.D.), kita@ph.ritsumei.ac.jp (Y.K.)*

Diaryliodonium salts ($Ar^1Ar^2I^+X^-$) are hypervalent iodine(III) compounds, which are generally stable salts that serve as versatile arylating agents.[1] Various aryl-heteroatom and aryl-carbon bonds can be constructed under transition-metal- free conditions using the combination of diaryliodonium salts with the corresponding nucleophiles, such as alcohols, carboxylic acids, amines, amides, fluoride, and various carbon nucleophiles. Trimethoxyphenyl (TMP)- iodonium(III) salts, which contain a TMP group as one aryl group, lead to unified selective bond formation with another aryl group.[2] Our group recently established the efficient synthesis of TMP-iodonium acetates ($Ar(TMP)I^+AcO^-$) involving the generation of aryliodine diacetate using peracetic acid followed by condensation with 1,3,5-trimethoxybenzene.[3] Various phenol derivatives underwent arylation in the presence of TMP-iodonium acetate to afford the corresponding diaryl ethers in high yields.[4] Protected amines, such as *N*-methoxy sulfonamide derivatives, were also successfully arylated by using TMP-iodonium acetate with high reactivity. The present aryl- heteroatom bond formations were highly compatible with a wide variety of functional groups and would offer practical functionalization of (hetero)arenes.

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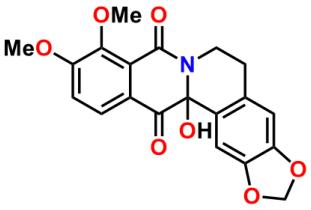
# Strategies Towards the Synthesis of Heterocyclic Natural Products

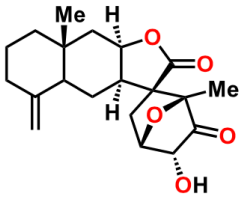
K. G. M. Kou,* Y. Cao, A. Trinh, J. M. Larach, J. Debow, S. Abraham, X. Kou

*University of California, Riverside, USA*
** kevin.kou@ucr.edu*

The strategic use of electron-rich substrates, such as silyl enol ethers and furans, to streamline the synthesis of isoquinoline and lycopodium alkaloids, as well as terpenoid lactones is presented. Electron-rich alkenes such as silyl enol ethers have tremendously impacted synthetic organic chemistry through the Mukaiyama aldol, Rubottom, Saegusa–Ito, and metal- catalyzed α-arylation reactions. Their use in C–H bond functionalization, however, is underexplored. Through oxidative Rh(III)/(IV)/(II)-catalysis, we implement silyl enol ethers in C–H functionalization, applying it to the concise syntheses of bioactive isoquinoline natural products. Our approaches to strained ring systems within sesquiterpene lactones and lycopodium alkaloids will also be described.



*prechilenine*



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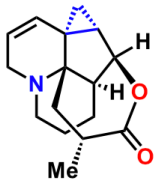
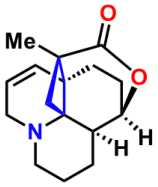


*annotinolide A*



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# Modulators of Human and Bacterial Adenylate Cyclases Based on 7-Substituted 7- Deazapurine Analogues of Adefovir

Pavel Kraina,[a] Michal Česnek,[a] Eva Tloušťová,[a] Helena Mertlíková-Kaiserová,[a] Val J. Watts,[b]* Zlatko Janeba[a]*

[a]*Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, 16610, Prague 6, Czech Republic*
[b]*Department of Medicinal Chemistry and Molecular Pharmacology, College of Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN-47907, USA*
** e-mail: wattsv@purdue.edu (V.J.W.), janeba@uochb.cas.cz (Z.J.)*

Acyclic nucleoside phosphonates (ANPs) possess a large spectrum of biological activities, however the most pronounced are their antiviral properties[1,2]. It was found, that bisamidate prodrugs of 7-halogenated 7-deazapurine analogues of adefovir exhibit a sub-micromolar activity against *Bordetella pertussis* adenylate cyclase toxin (ACT) in macrophage cell-based assays, and are able to selectively modulate some human adenylate cyclases (ACs)[3].

A number of over twenty new 7-substituted 7-deazapurine analogues of adefovir as bisamidate prodrugs were synthesised, and evaluated for their biological properties, as a continuation of an ongoing SAR study (Fig. 1). Moreover, two other types of prodrugs of the most potent derivative were prepared, to compare the prodrug masking group effects on the activity. Also, for evaluation on enzymatic assays, three most active compounds were prepared in their active metabolite form as phosphonodiphosphates.

Biological evaluation in macrophage cell-based assays revealed fourteen single-digit micromolar inhibitors of *B. pertussis* ACT. Many compounds also possessed low micromolar cytotoxic effects on some human carcinoma cells while being non-toxic for normal dermal fibroblasts. Tests on human adenylate cyclases revealed some selective modulators of AC1 and AC5 or of AC2.

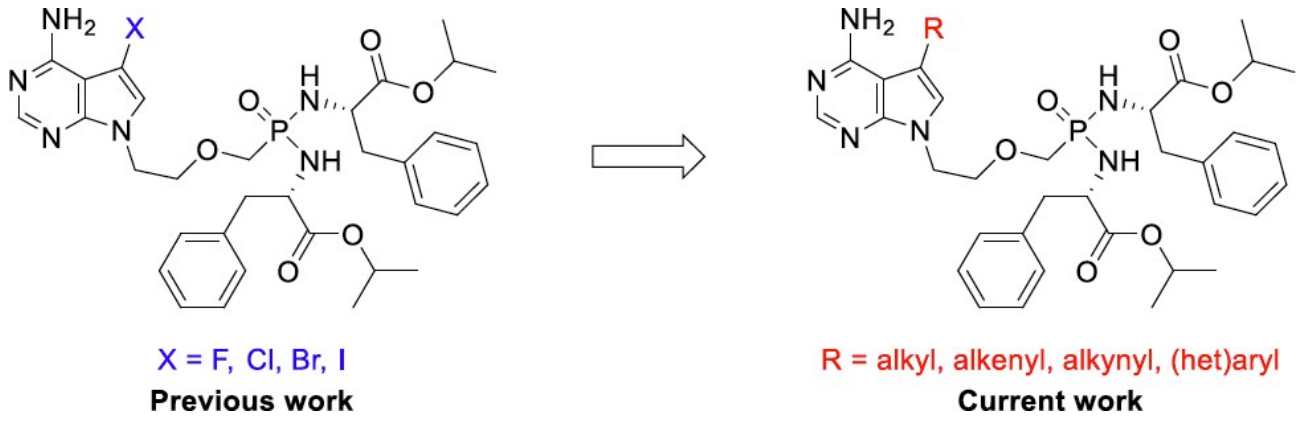


**Figure 1.** Overview of this work.

*Acknowledgment: This work was supported by the Ministry of Education, Youth and Sports (MŠMT in Czech) in the program INTER-EXCELLENCE (project LTAUSA18086).*

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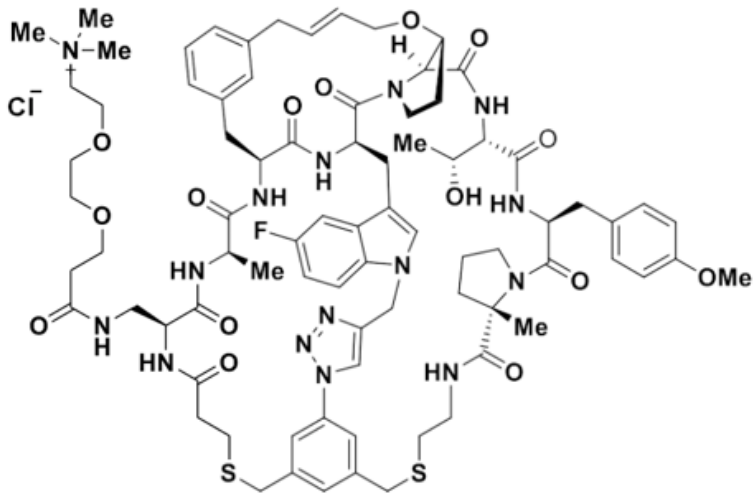
# Total Synthesis of a Macrocyclic PCSK9 Inhibitor

Kuethe, J.T.,* Lee, J., Thaisrivongs, D., Pollack, S., Yasuda, N., Leone, J.

*Department of Process Research and Development, Merck & Co., Inc. Rahway, NJ 07065, USA*

*Jeffrey_Kuethe@Merck.com*

The discovery of the extremely potent, orally bioavailable proprotein convertase subtilisin-like type 9 (PCSK9) inhibitor **1** for the regulation of plasm LDL-chloesterol necessitated the need for further scaleup of this highly complex molecule. The initial synthesis involved solid phase peptide synthesis (SPPS) followed by cleavage and subsequent solution-based steps to arrive at milligram quantities of compound **1**. Recognizing that this approach would not deliver multiple gram quantities, a fully solution-based approach was required. Key aspects of these synthetic efforts leading to the gram-scale synthesis of compound **1** will be highlighted.



**MW 1612**
**Ki 2.39 pM**

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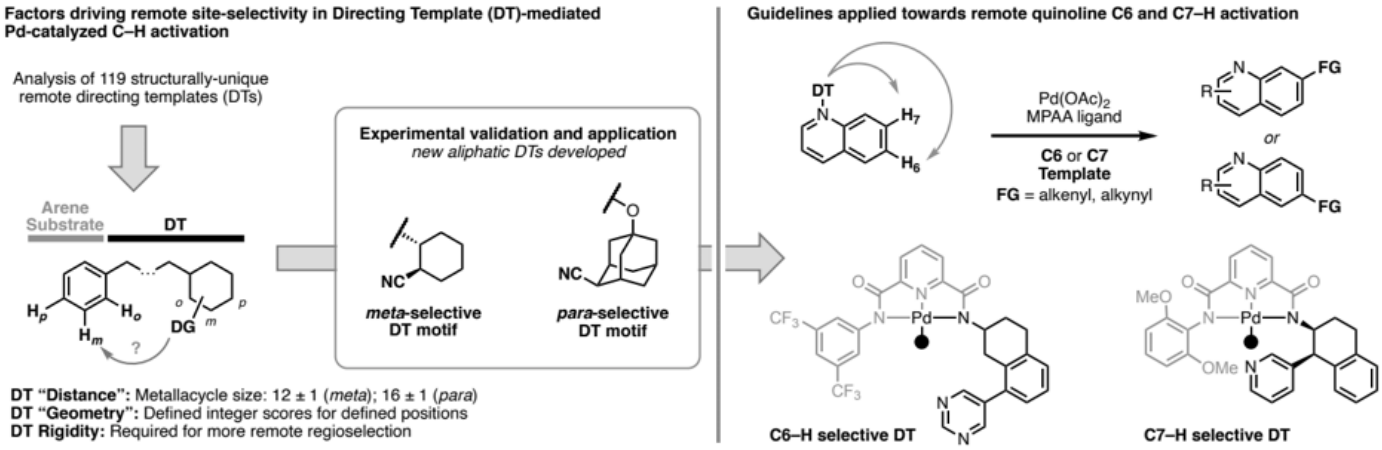
# Guidelines for Predictable Remote Directed C(sp$^2$)–H Activation and their Application Towards Site-Selective Remote C–H Activation of Quinolines

Nelson Y. S. Lam, Zhoulong Fan, Kevin Wu, Keita Tanaka, Han Seul Park, Su Yong Shim, Daniel A. Strassfeld, Jin-Quan Yu*
*Scripps Research, 10550 North Torrey Pines Road, La Jolla, CA, USA 92037*
**yu200@scripps.edu*

The ability to differentiate and selectively activate remote C–H bonds represents a perennial challenge in the field of Pd- catalyzed C–H activation. To this end, a "directing template" (DT) strategy has proven particularly promising, where selectivity is thought to be determined by the optimal spatial positioning of a reactive catalyst to a target C–H bond *via* a macrocyclophane-like transition state.[1] Despite its seemingly algorithmic origins, however, a systematic study on its requisite factors remain unelucidated. Here, we present an in-depth analysis of 119 structurally unique published DTs, revealing DT "distance", "geometry" and rigidity as key variables that determine selectivity at defined aryl positions. These findings are experimentally corroborated through the development of new aliphatic *meta* and *para*-selective DTs for electronically unbiased arenes.[2] Through judicious consideration of DT "distance", "geometry" and rigidity, further applications of these guidelines also facilitated the development of site-selective C–H activation and diverse functionalization at previously inaccessible C6 and C7 positions on quinolines and related heteroarenes. In doing so, this method now fully establishes a unified late-stage "molecular C–H editing" strategy to modify these pharmaceutically- relevant heterocycles at any given site and order.[3]

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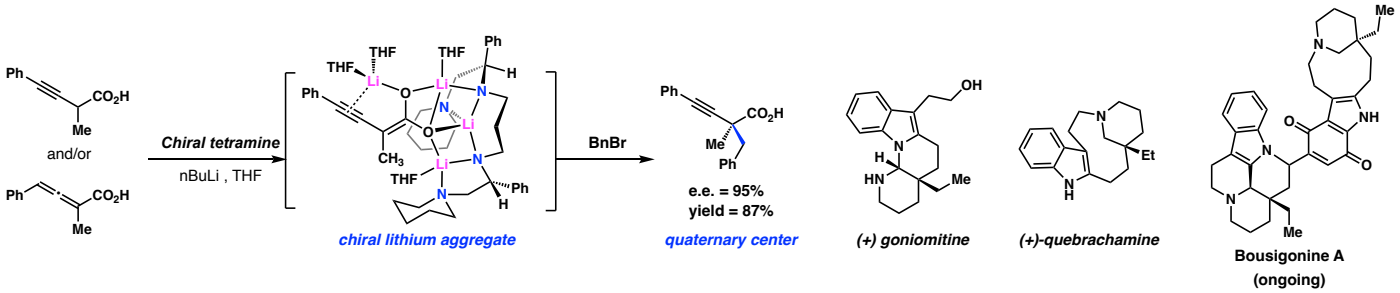
# Lithium Enolate with a Lithium-Alkyne Interaction in the Enantioselective Construction of Quaternary Carbon Centers: Efficient Synthesis of Indole Alkaloids (+)-Goniomitine and (+)-Quebrachamine

Y. Li,[a] E. Paola,[a] Z. Wang[a] and A. Zakarian[a]*

[a]*Department of Chemistry and Biochemistry, University of California Santa Barbara, Santa Barbara, CA 93106 (USA)*
**zakarian@chem.ucsb.edu*

All-carbon quaternary stereocenters, a structural feature that can impart significant chemical and biological impact to a molecule, are critical to many synthetic and medicinal application. Consequently, catalytic and enantioselective approaches for constructing all-carbon quaternary centers, especially functionalized stereocenters, are highly desirable. On the other hand, the alkynyl group is an important building block in organic synthesis. Construction of alkyne substituted quaternary carbon stereocenters, coupled with subsequent functionalization of the alkyne group, would enable access to various functionalized quaternary stereocenters. A highly enantioselective, practical, and scalable technique for the assembly of alkyne-substituted quaternary centers from easy starting materials are highly desirable.

We report a method for direct enantioselective alkylation of 3-alkynoic and 2,3-alkendioic acids that form quaternary stereogenic centers using chiral lithium amide as noncovalent stereodirecting auxiliaries. The methods were effective in the alkylation of both 3-alkynoic acids, 2,3-alkendioic acids substrates with a broad range of heterocyclic and functionalized alkyl group substituents. Accompanying crystallographic studies provide mechanistic insight into the structure of well-defined chiral aggregates, highlighting cation-pi interactions between lithium and alkyne groups. The synthetic utility of this method was further demonstrated in the enantioselective total synthesis of (+)-goniomitine and formal synthesis of (+)-quebrachamine. Further application of this methodology in the context of bisindole alkaloid total synthesis (bousigonine A) is under investigation.



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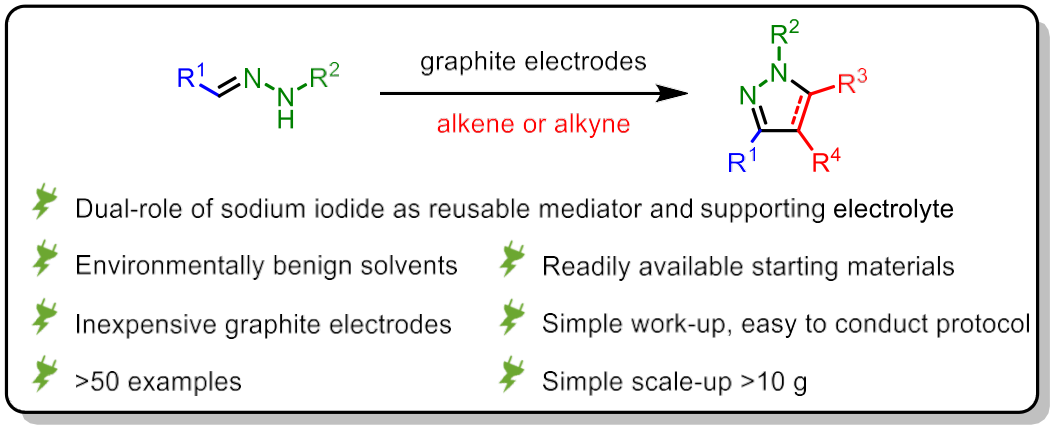
# Electrochemical Synthesis of Pyrazoles and Pyrazolines via Iodine-mediated [3+2] Dipolar Cycloaddition

M. Linden, S. Hofmann, S. R. Waldvogel*

*Johannes Gutenberg University, Department of Chemistry, Duesbergweg 10–14, 55128 Mainz, Germany*

waldvogel@uni-mainz.de




Highly biologically active pyrazole and pyrazoline derivatives are widely featured in pharmaceuticals as well as agricultural chemistry as pesticides, anti-cancerogenics or anti-microbiotics.[1] Conventionally, pyrazoles and pyrazolines can be accessed via [3+2] dipolar cycloaddition of nitril imines and dipolarophiles, requiring hydrazonoyl halo-genides as starting material, which are synthesized from hydrazones using hazardous chemicals like hypochlorite or NCS.[2] The electrochemical generation of 1,3-dipoles was established in our group for oxidation of aldoximes to the corresponding nitrile oxides, recently even for highly lipophilic betulin aldoxime.[3,4] We now developed a sustainable protocol for the electro-organic synthesis of 1,3,5-substituted pyrazoles and pyrazolines from readily available hydrazones and alkenes or alkynes. The reaction employs inexpensive sodium iodide as electrolyte as well as mediator, allowing for in situ formation of nitrile imines. Operating the reaction in a biphasic system using environmentally benign solvents allows for application of even highly sensitive alkenes such as styrene as dipolarophiles that would usually undergo side reactions or polymerization under electrolytic conditions. Thus, we herein present a protocol allowing for synthesis of pyrazolines from lab scale to 15-fold scale-up >10 g without any loss in yield.

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# A Stereoselective Enzymatic Mannich Reaction

Shaonan Liu,[a] Yang Hai[a,*]

[a]*Department of Chemistry and Biochemistry*
*University of California, Santa Barbara, Santa Barbara, United States*
**Corresponding author's e-mail address hai@chem.ucsb.edu*

## Abstract

The Mannich reaction is widely used to construct C-C bonds in organic chemistry, but enzymatic Mannich reactions are rarely reported and there is no PLP-dependent enzyme known to catalyze Mannich reactions. Here, we report the discovery of the first example of a PLP-dependent Mannichase, LolT, catalyzing intramolecular Mannich reaction. LolT's cyclization and annulation activities allow us to access a variety of heterocyclic α,α-disubstituted α-amino acids, including pyrrolidine, piperidine, pyrrolizidine, indolizidine, quinolizidine, and azepane.

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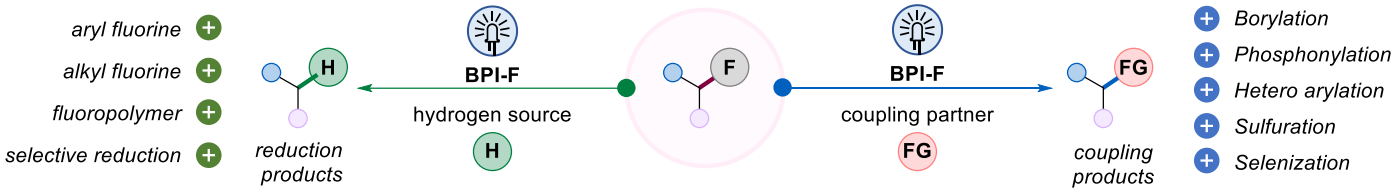
# Diversification of C−F bonds in organofluorides and fluoropolymers by visible-light organic photoredox catalysis

Xin Liu, Alex Green, Yingzi Li, Yucheng Zhao, Robert S. Paton, and Garret M. Miyake*

*Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523*
*garret.miyake@colostate.edu*

Organohalides are among the most fundamental and important building blocks in chemical synthesis because the halide serves as a versatile functional group for elimination, substitution and cross-coupling reactions. However, although organofluorides are the most commercially abundant organohalides, they are largely underutilized in chemical synthesis because the strong C−F bond severely limits reactivity. Here, we demonstrate that a strongly reducing visible-light absorbing organic photoredox catalyst can efficiently reduce C−F bonds to generate carbon centered radicals that can be intercepted for hydro-defluoronation and cross-coupling reactions. This system now enables use of organofluorides in chemical synthesis under mild reaction conditions through low loading of an organic photoredox catalyst.

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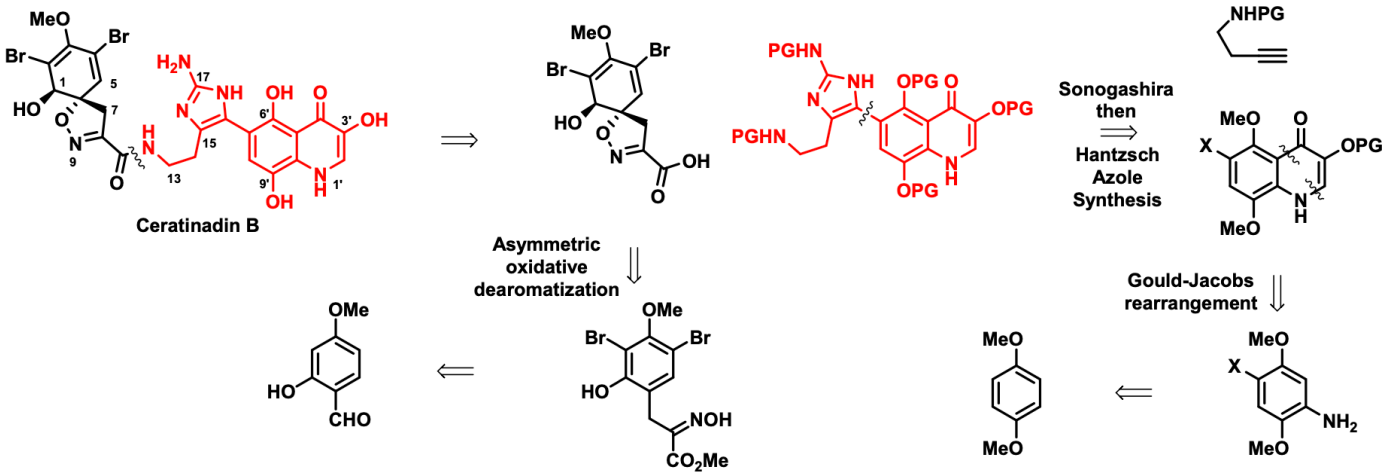
# Progress Towards a Total Synthesis of Ceratinadin B

Carl J. Lovely,[a]* Xiaofeng Meng,[a] Lesley R. Schmid[a] and Anasuya Ghoraia

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

Ceratinadin B is tyrosine derived secondary metabolite isolated from marine invertebrates initially by the Bewley lab (*Oceanapia sp*. in an NIH sample repository)[1] and subsequently the enantiopode was reported by Kobayashi and co-workers (*Pseudoceratina sp*. (SS-214)).[2] This natural product is intriguing from two different perspectives. Structurally, it contains three different heterocyclic domains, including the spiro isooxazoline common to the tyrosine natural products and the unusual imidazolyl quinolone framework in an apparent fusion of two different marine alkaloids. The (1S,6R) natural product enantiomer has been demonstrated to possess potent activity as an inhibitor of mycothiol amidase, an enzyme found in mycobacteria, including the causative agent of tuberculosis. Mycothiol is used to detoxify cells very much in the same type of vein as glutathione is used in eukaryotes and is recycled through the action of mycothiol amidase. As a result, this molecule then may be potentially useful as adjuvant in the treatment of tuberculosis. The enantiomeric congener was shown to possess anti-fungal activity.




Our initial synthetic approach involved cross-coupling chemistry to construct the bis heterocycle but this was largely unsuccessful and so our approach evolved into one utilizing a Hantzsch-like synthesis of the aminoimidazole via the α-haloketone. The quinolone moiety is derived from the Gould-Jacobs rearrangement of the Meldrum's acid derivative. Disconnecting back to a haloarene and the corresponding known alkyne concludes the formation of the imidazolyl-quinolone. The spiro isooxaline is known and can be constructed via dearomatization processes which ultimately afford this fragment as a racemic mixture. While this moiety can be obtained as a single enantiomer, to date no catalytic process exists for its synthesis. Preliminary studies in our lab directed to a transition metal catalyzed asymmetric dearomatization suggest that this may provide a solution. This poster will describe the evolution of our approach to this molecule and the synthesis of advanced intermediates.

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# Nucleoside Antibiotic Support Studies: Synthesis of 4'-(2-oxazolyl) Uridine Scaffolds

Frederick A. Luzzio[a]* and Paige J. Monsen[a]

[a]*Department of Chemistry, University of Louisville, 2320 South Brook Street, Louisville, Kentucky USA*
**faluzz01@louisville.edu*

The synthesis of new nucleoside-based antibiotics should benefit from the design of scaffolds which can bear the critical active components, but possess simpler molecular architecture as compared to that of the natural product. In efforts directed toward the synthesis of simplified analogues of phosphoglycosyl transferases (PGT's), a series of uridine-based compounds homologated at C-4' with an aryl-substituted oxazole ring were prepared. Conversion of 2', 3'-cyclopentylidene uridine to the corresponding 4'-carboxylate followed by Steglich ester coupling with a series of azidoalcohols gave the corresponding 4'-uridyl-derived azidoesters. The azido esters were cyclized to the substituted oxazolines using the Staudinger/aza-Wittig reaction and were directly carried on to the trisubstituted C-4'-uridyl oxazoles by treatment with DDQ or freshly-prepared nickel peroxide. The cyclopentylidine protecting group was easily removed in all cases by treatment with aqueous trifluoroacetic acid.

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# An Oxidation Study of Phthalimide-Derived Hydroxylactams and Lactams

Frederick A. Luzzio[a]* and Bernard L. Adjei[a]

[a]*Department of Chemistry, University of Louisville, 2320 South Brook Street, Louisville, Kentucky USA*

**faluzz01@louisville.edu*

The oxidation of both *N*-substituted hydroxylactams and isoindolinones (phthalimidines) to the corresponding phthalimides using a catalytic iron/*tert*-butylhydroperoxide (TBHP) reagent system is detailed. The 2-substituted-3-hydroxyisoindolin-1-one (hydroxylactam) oxidation constitutes a rather straightforward hydroxyl→carbonyl group conversion while the latter process is a methylene→carbonyl transformation. The iron oxidant, prepared by the treatment of iron (III) chloride with trifluoroacetic acid, is used catalytically (10 mol%) in conjunction with TBHP which is the stoichiometric oxidant. For the hydroxylactam substrates, the oxidation system was effective in providing the corresponding phthalimides in isolated yields ranging from 41 to 88% within a reaction time of 24h. For the N-substituted isoindolinone to phthalimide conversions, the imide products were obtained in 76 to 96% isolated yield using the same catalyst/oxidant system. Comparisons were made with a recently-reported hydroxylactam oxidation system using nickel peroxide ($NiO_2$).[1] Substrates are included in the discussion which will demonstrate selectivity and protecting group tolerance.

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# Development of a High Throughput Photochemical Flow Method for the Large-Scale Synthesis of *trans*-Cyclooctenes

Colette Makara,[a] Jessica Pigga, PhD,[a] Joseph M. Fox, PhD[a]

*University of Delaware, Newark, DE, United States*
*cmakara@udel.edu*

The synthesis of functionalized *trans*-cyclooctenes has been a major area of interest since the introduction of tetrazine ligation with *trans*-cyclooctenes in 2008.[1] *trans*-Cyclooctenes have become prominent in the field of biorthogonal chemistry due to their exceptional reaction kinetics with tetrazines.[2] Due to their widespread application in the fields of chemical biology, nuclear medicine, and material science[3], there has been a major drive to improve the throughput of the synthesis of *trans*-cyclooctenes. This work describes the photochemical isomerization of *trans*-cyclooctenes from *cis*-cyclooctenes using a high throughput photochemical flow method employing a custom reactor for the large-scale synthesis *trans*-cyclooctenes derivatives, as well as improved workup protocols. The custom flow reactor implements fluorinated ethylene propylene (FEP) tubing as an irradiation vessel in place of the previously utilized quartz flask, as well as an improved photocatalyst for Z-to-E isomerization. The ability to produce various *trans*-cyclooctenes faster, more efficiently, and on larger scale will greatly improve the efficiency and accessibility of these compounds.

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# Strategic Use of Gold(I)-Catalysis for the Concise Synthesis of Polycyclic Indole Motifs

A. Mansour, D. F. León Rayo and F. Gagosz*

*Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Canada*
**fgagosz@uottawa.ca*

Catalysis by electrophilic gold complexes represents an increasingly specific and powerful tool for the generation of molecular complexity and diversity.[1] The Lewis acidic and electron donating properties of electrophilic gold complexes provide an excellent opportunity for the efficient functionalization of carbon π-systems, particularly for alkynes and allenes by π-acid catalysis.[1-3] This reactivity mode is highlighted in the formal transfer of nitrene species onto gold(I)-activated carbon π-systems, where a key α-imino gold carbene intermediate is generated. Owing to the high reactivity of the α-imino gold carbene, the addition of nucleophiles to trap this species has been thoroughly studied.[4] We leverage this unique mode of reactivity by demonstrating the efficient and rapid access to polycyclic indole motifs that can be derived into structures relevant to natural products by the intermediate α-imino gold carbene (Figure 1). In this presentation, the total synthesis of brevianamide A and an approach to the synthesis of mitragynine pseudoindoxyl will be discussed.

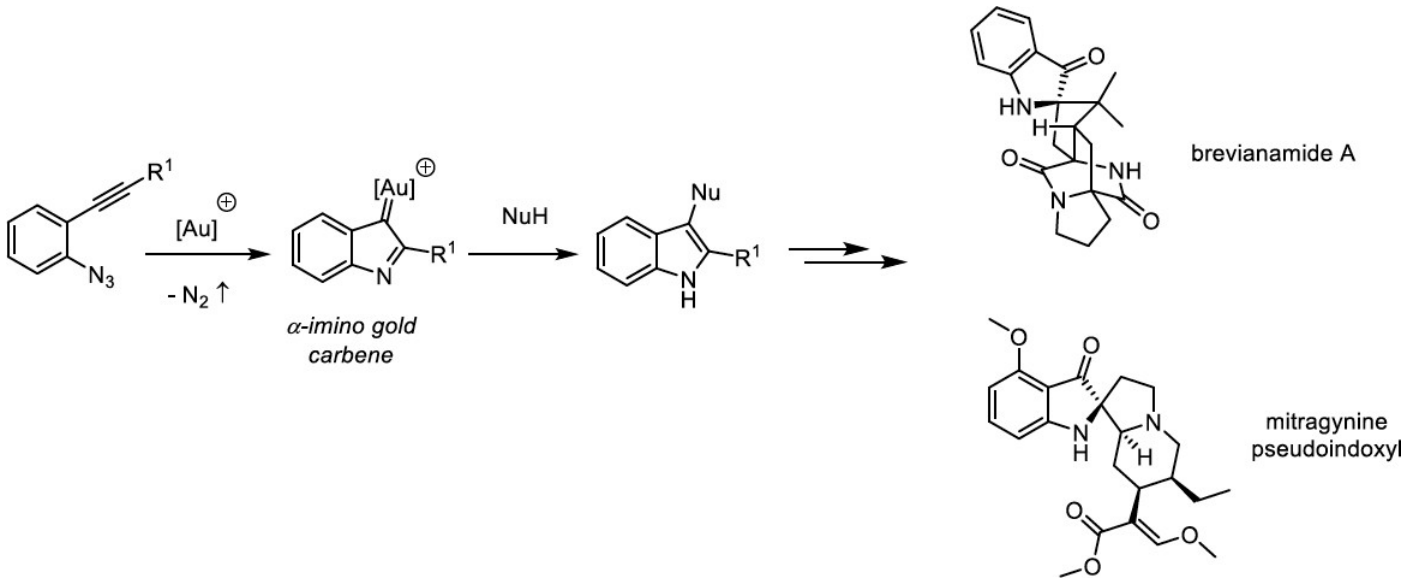


Figure 1. Synthesis of indole scaffolds utilizing gold(I)-catalysis

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# Cyanine Phototruncation: From Mechanistic Analysis to Applications in Super Resolution Microscopy and Cell Tracking

S. S. Matikonda,[a,*] and M. Schnermann[a]

[a] *Chemical Biology Laboratory, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Frederick, Maryland 21702, United States*
**Corresponding author's e-mail address: siddharth.matikonda@nih.gov*

Certain fluorophores undergo photoconversion to a blue-shifted fluorescent molecule – a phenomenon known as photobluing. While broadly used cyanine dyes had been reported to provide photoblued products during certain microscopy experiments, the underlying chemical basis was not well understood. We examined the chemistry of cyanine photobluing and found that a product of pentamethine cyanine irradiation was the corresponding trimethine cyanine.[1] This is cyanine phototruncation reaction had little chemical precedent and involves the net excision of ethene diradical from the cyanine polymethine.

We first addressed the mechanistic question: are these products derived from intermolecular derivatization of previously reported photooxidative cleavage reactions or an unprecedented intramolecular rearrangement reaction? Our deuterium-labeling studies conclusively demonstrate that cyanine phototruncation is a fully intramolecular process. We also developed a detailed mechanistic framework to understand the multi-step sequence which was strongly supported by DFT calculations. Taking note of the critical role of electrophilic trapping in our mechanism, we conducted an extensive screen of over 300 conditions. These efforts identified a nucleophilic additive that improves the yield of conversion by 15-fold. We then applied phototruncation for in vitro DNA-PAINT (DNA-based points accumulation for imaging nanoscale topography) experiments that benefit from increased imager-strand concentration and, consequently, reduced acquisition time.[2]

Our recent efforts are aimed at optimizing the cyanine structure to improve phototruncation yield and enhance its utility under physiological conditions. An extensive screen of different cyanines has identified a substrate (3'-OMe-substitution on the polymethine chain) that dramatically improved the phototruncation yield by over 8-fold. Enabled by efforts that significantly improve the yield of cyanine phototruncation, we apply this chemistry to cell-tracking applications and employ it to examine immune cell migration from the tumor to the tumor draining lymph nodes (TDLNs). These studies provide a quantitative means for the temporal characterization of the tumor-derived immune-cell population in the TDLN.[3] Further efforts are currently underway to develop antibody-targeted variants of the 3'-OMe-substituted probes to characterize other dynamic migration processes in an antigen-specific manner.

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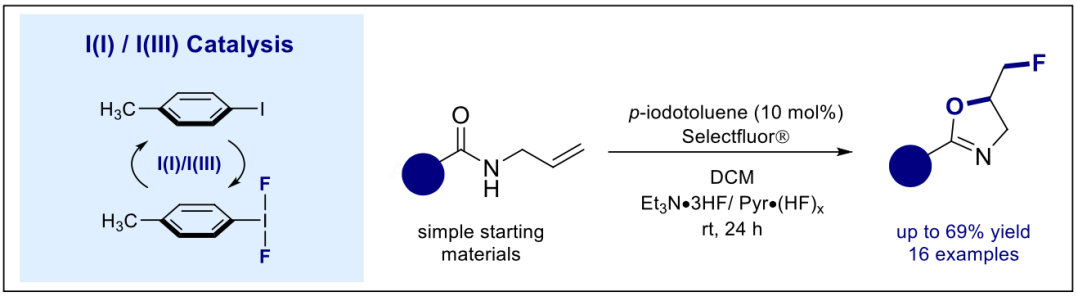
# Fluorocyclization via I(I)/I(III) catalysis: a concise route to fluorinated oxazolines[1]

F. Scheidt,[a] C. Thiehoff,[a] G. Yilmaz,[a] S. Meyer,[a] C. G. Daniliuc,[a] G. Kehr[a] and R. Gilmour[a,*]

[a]*Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstrasse 36, 48149 Münster, Germany*

* *ryan.gilmour@uni-muenster.de*




Given the importance of heterocycles in drug design,[2] efficient routes to access fluorinated scaffolds would be strategically advantageous to provide a rapid entry into important bioisostere classes and benefit from the unique physicochemical properties induced by fluorine incorporation.[3] This study reports the fluorocyclization of readily accessible *N*- allylcarboxamides enabled by iodine (I)/(III) catalysis to construct 2-oxazolines, a heterocycle prevalent within natural products[4] augmented with a fluoromethyl group. This serves to expand the current portfolio of fluorinated drug modules for drug discovery through the application of a catalytic system that offers mild conditions and features a broad substrate tolerance. The incorporation of several aryl groups containing electron rich, disubstituted or aliphatic motifs is presented, as well as the hydrolysis of the oxazolines products to the corresponding fluorohydrin. Crystallographic analysis reveals a highly preorganised structure with a *synclinal* relationship between the C($sp^3$)–F bond and the C($sp^3$)–O bond of the ring, demonstrating the presence of the stereoelectronic fluorine *gauche* effect.

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# Innovations on the Process Development of a Tri-Sugar siRNA Ligand

S. Michalak (presenter),[a*] J. Tom,[a] M. Achmatowicz [a] and C. Borths[b]

[a] *Amgen, Inc., One Amgen Center Drive, Thousand Oaks, California 91320, United States*
[b] *Amgen Inc., 360 Binney Street, Cambridge, Massachusetts 02141, United States*
**smicha01@amgen.com*

Olpasiran is a small interfering RNA (siRNA) in Amgen's hybrid modality portfolio that lowers lipoprotein(a), also known as Lp(a). It is being investigated for the treatment of atherosclerotic cardiovascular disease currently under Phase 2 clinical trials. The drug substance is an siRNA duplex (~15 kDa) conjugated to a small molecule targeting ligand, the ligand is a tri-antennary N-acetylgalactosamine molecule (tri-GalNac, ~2 kDA). The synthetic strategy and process development of intermediates in this challenging tri-GalNAc synthesis is the topic of this poster abstract.

An efficient three-step synthesis of a key intermediate in the tri-GalNac route will be presented, along with challenges associated with a triple glycosylation reaction and early investigations into leveraging biocatalysis for triple aminolysis. Additionally, the process development of an amide coupling reaction to install a C8-PEG-fragment will be detailed. Kinetics analysis was performed to characterize the mechanism for a key impurity formation which led to the engineering design of a controlled continuous-pumped slurry addition. A highly optimized aqueous extraction protocol was developed, taking advantage of this late-stage intermediate's orthogonal aqueous solubility, to purge a critical impurity.

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# Tunable photochemical properties in 5-phenylazopyrimidines: From solution to solid state

Lucie Mužíková Čechová[1,2], Juraj Filo[3], Martin Dračínský[1], Zlatko Janeba[1], Marek Cigáň[3], Eliška Procházková[1]

[1] *Institute of Organic Chemistry and Biochemistry, the Czech Academy of Sciences, Flemingovo nám. 2, 166 10 Prague, Czech Republic*

[2] *University of Chemistry and Technology Prague, Czech Republic, Technická 5, 16628 Prague, Czech Republic*

[3] *Comenius University, Faculty of Natural Sciences, Ilkovičova 6, 842 15 Bratislava, Slovakia*

cechoval@uochb.cas.cz

Heteroaryl azo compounds consist of heteroaromatic and benzene moieties connected with the azo group. Benzothiazoles, pyrazoles, pyridines or pyrimidines can serve as the heterocyclic part of the azo molecule. Such derivatives undergo reversible *trans-cis* isomerization upon illumination by light. The formed metastable *cis* isomer is characterized by nonplanar structure and different physicochemical properties (e.g. dipole moment), compared to the *trans* isomer. Stability of the *cis* isomer is significantly dependent on ambient conditions. Moreover, big structural change can make more difficult photoisomerization in the solid state, due to lack of free space between arranged molecules.

We prepared three classes of novel 5-phenylazopyrimidines, differing in a number of hydrogen bond donors in the neighbouring position to the azo moiety, which leads to a formation of strong intramolecular hydrogen bonds (IMHBs). We used a unique combination of advanced experimental and theoretical methods to study their photochemical and physicochemical behavior, namely 1) NMR with *in situ* irradiation, 2) optical spectroscopy, 3) scanning electron microscopy, and 4) DFT calculations. We were able to tune thermal relaxation rate and irradiation wavelength by an introduction of suitable substituents, where IMHBs as well as "push-pull" character destabilize the *cis* isomer significantly (**Fig. 1**)[1,2]. In compounds with two different hydrogen bond donors, unique photoswitchable IMHBs were discovered[3]. Such derivatives can form two stable rotamers (A/B, both as *trans* photoisomers). Furthermore, we were able to prove that 5-phenylazopyrimidines undergo photoisomerization in the solid state[4].

5-Phenylazopyrimidines represent versatile photoswitches with a wide range of tunability of their photochemical properties, which makes them eligible candidates for application in many fields, e.g. as smart materials, as a storage of data or as a tool in photobiology.

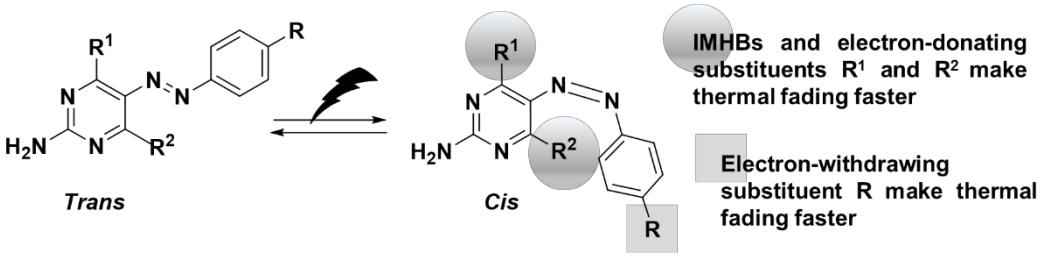


**Fig. 1**

This work was supported by the IOCB CAS (RVO 61388963).

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# Catalytic Activation of Biorthogonal Chemistry Using Thermal Catalysis

S. Neglia,[a*] C. Wang,[a] J. Rosenberger,[a] A. Jemas[a], J. Fox[a]

[a]*University of Delaware, Newark, DE, USA*
**sneglia@udel.edu*

Rapid bioorthogonal reactions are a useful tool for drug delivery and assembly. Previously our group has established small molecule photocatalysts that can be used to promote the oxidation of dihydrotetrazines to tetrazines which subsequently participate in rapid bioorthogonal chemistry. In the absence of light, peroxidase enzymes can also be used to catalyze oxidation. This work explores the first small molecule thermal catalyst that can activate a bioorthogonal reaction with temporal control. The catalyst is able to oxidize an unreactive dihydrotetrazine to a reactive tetrazine which can conjugate to an electron rich dienophile in an inverse electron demand Diels Alder mechanism. These reactions are successful in conjugation for a protein substrate in vitro. Further, the thermal catalytic activation of dihydrotetrazine can label on the cell surface of mammalian cells. The stepwise assembly is advantageous for cell permeability and has the potential to create multivalent molecules with spatial control at the organism level.

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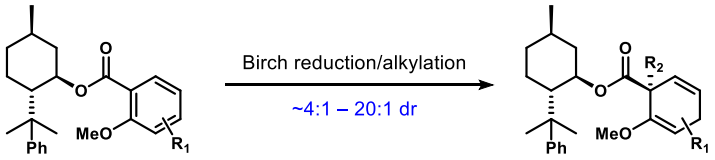
# Stereocontrolled Access to Quaternary Centers by Birch Reduction/Alkylation of Chiral Esters of Salicylic Acids

Hanh T. Nguyen,[a] Ryan A. Kozlowski,[a] Micheal E. Lehman,[a] and Christopher D. Vanderwal[a,b,*]

[a] *Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, CA 92697-2025, USA.*
[b] *Department of Pharmaceutical Sciences, 101 Theory #100, University of California, Irvine, CA 92617, USA.*
**cdv@uci.edu*




Herein is described a diastereoselective Birch reduction/alkylation using (–)-8-phenylmenthol as a chiral auxiliary to establish quaternary centers on salicylic acid derivatives. The method is compatible with a variety of alkyl electrophiles and provides synthetically useful chiral cyclohexadienes. Investigation of sterically and electronically demanding substrates provided an insight into the scope of this transformation. The chiral auxiliary can be removed via reduction with $LiAlH_4$ and recycled in subsequent reactions. The resulting products contain multiple functional handles which allow further derivations to synthetically challenging targets.

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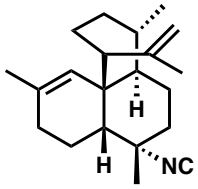
# Efforts Towards the Synthesis of Neoamphilectane

Scott W. Niman[a] and Christopher D. Vanderwal[a,*]

[a]*Department of Chemistry, University of California, Irvine, California 92697-2025, United States*
**cdv@uci.edu*

Our efforts towards the synthesis of neoamphilectane, a rare isocyanoterpene natural product, involve a concise synthesis of the spirocyclic core using a Robinson annulation and an acyl radical cyclization. Other key reactions in our sequence include a reductive deoxygenation of an oxalate and an enolate mediated epoxide-opening cyclization. Additionally, we have observed numerous counterproductive bicyclization reactions whose products lend themselves to interesting isocyanide containing analogs. Current work is focused on a key carbon–carbon bond fragmentation which will serve as a platform for the exploration of a late-stage isocyanation to complete a synthesis of neoamphilectane.



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# Direct Nucleophilic Substitution of Alcohols Using an Immobilized Oxovanadium Catalyst

T. Nishio, S. Yoshioka, K. Hasegawa, K. Yahata, K. Kanomata, S. Akai*

*Graduate School of Pharmaceutical Sciences, Osaka University, Japan*

**akai@phs.osaka-u.ac.jp*

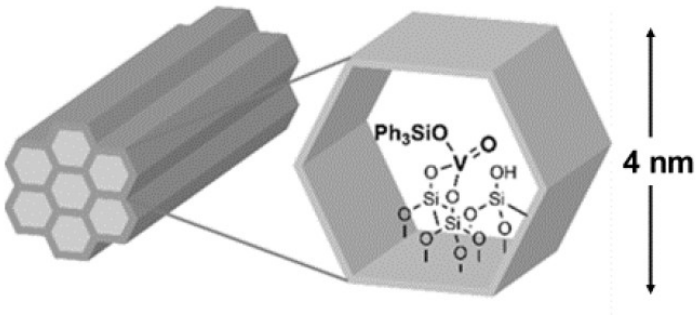
[Background & Aim]

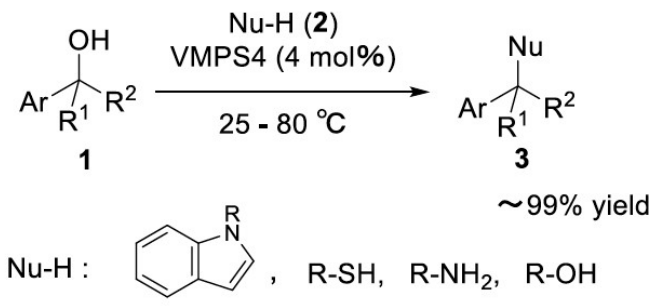
Direct substitution of alcohols is considered as one of the most important challenges for the development of green engineering in pharmaceutical and chemical industries and has been mainly studied using Brønsted acids, Lewis acids, and transition metal catalysts. However, the strong Lewis acidity of these catalysts often results in poor functional group tolerance. We recently reported a mesoporous silica-supported oxovanadium catalyst (VMPS4) in which oxovanadium was covalently bound on the surface of the mesoporous silica pore of 4-nm inner diameter (Figure 1).[1] VMPS4 catalyzes racemization via a cationic intermediate generated by the C−O bond cleavage in the substrate alcohols. Considering this, we have applied VMPS4 to the direct nucleophilic substitution of alcohols .

[Results]

The reaction of alcohols **1** and nucleophiles **2** effectively proceeded in the presence of 4 mol% VMPS4 under an argon atmosphere at room temperature to 80 ºC to give the desired compounds **3** in up to 99% yield (Scheme 1). Under the optimal conditions, VMPS4 exhibited highly chemoselective activation of alcohol **1** in the presence of an acetoxy group, which has been hardly attained by the known catalysts for the direct substitution of alcohols. Also, VMPS4 was recovered by simple centrifugation and reused over six cycles with maintaining its catalytic activity. [2]

**Figure 1**, The structure of VMPS4




**Shceme1**, Direct nucleophilic substitution of alcohols.

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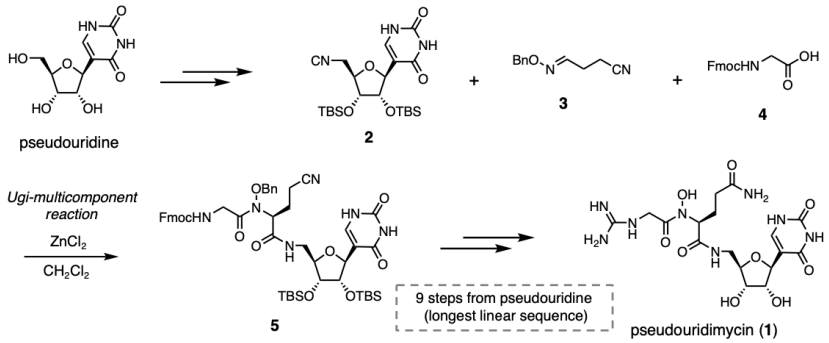
# Total synthesis of pseudouridimycin

R. Okawa,[a] C. C. Aldrich,[b,c] and S. Ichikawa[a,b,d,*]

[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, Japan*
[c]*Department of Medicinal Chemistry, Minnesota University, 8-123 Weaver-Densford Hall 308 Harvard St. SE, Minneapolis, MN 55455, USA*
[d]*Center for Research and Education on Drug Discovery, Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan*
**ichikawa@pharm.hokudai.ac.jp*

Pseudouridimycin (**1**), which is a nucleoside antibiotic isolated from *Streptomyces* species[1], possesses potent antibacterial activity against both gram-positive and gram-negative bacteria including drug-resistant strains. Biochemical and structural analysis showed that **1** selectively inhibits bacterial RNAP and binds within the active site of the polymerase, which is distinct from the rifamycin allosteric site. In addition, it exhibits no cross-resistance with the rifamycins and displays no cytotoxicity. Collectively, these properties indicate that **1** is a promising lead for antibacterial drug development.

We have accomplished the total synthesis of **1** featuring an unusual oxime Ugi-type multicomponent condensation[2] to simultaneously construct the dipeptide moiety of **1**. This key multicomponent reaction with **2**, which was easily prepared from pseudouridine in five steps, **3**, and **4** was successfully achieved in the presence of ZnCl2 in CH2Cl2. This strategy produces the non-proteinogenic *N*-hydroxyamino acid residue *in situ* from simple building blocks with simultaneous linking to substituents at the *C*- and *N*-termini in a single step. The application of this key reaction allowed us to synthesize **1** in the longest linear sequence of nine synthetic steps from pseudouridine. It is the shortest synthesis compared to the previous reports[3,4]. Additional two steps to modify the dipeptide moiety in the late stage enable us to facilitate the derivatization of **1**, followed by the global deprotection process. This short-step strategy can be applied to prepare a variety of pseudouridimycin analogs.

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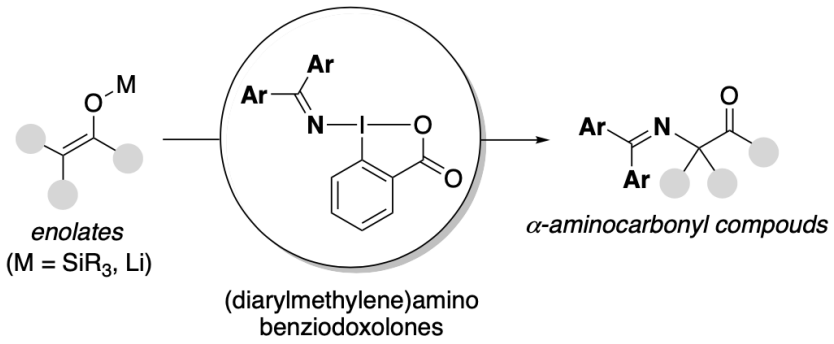
# Oxidative Amination of Enolates Utilizing (Diarylmethylene)amino Benziodoxolones

Daichi Okumatsu, Kazuki Kawanaka, Kensuke Kiyokawa* and Satoshi Minakata*

*Department of Applied Chemistry, Graduate School of Engineering, Osaka University*
*Yamadaoka 2-1, Suita, Osaka 565-0871, Japan*
**minakata@chem.eng.osaka-u.ac.jp*

α-Amino carbonyl compounds are ubiquitous in natural products, pharmaceuticals, and agrochemicals. α-Amination of carbonyl compounds is one of the most straightforward approaches for the synthesis of such valuable molecules, and commonly used methods involve the electrophilic amination of enolates and enamines with azodicarboxylates, nitrosoarenes, and iminoiodanes, etc. as an aminating reagent. Despite great advances in this type of reaction, a general problem is that the deprotection process for accessing the target α-amino carbonyl compounds requires multistep reactions and relatively harsh conditions.

Benzophenone imine derivatives are attractive compounds in organic synthesis because they undergo facile hydrolysis and hydride reduction, providing primary amines and diarylmethylamines. On the basis of this background, we envisioned that hypervalent iodine reagents containing (diarylmethylene)amino groups would offer a promising tool for oxidative amination to deliver modifiable amine products. Herein, we report the syntheis of (diarylmethylene)amino benziodoxolones, and their use in the oxidative amination of enolates such as silyl ketene acetals[1] and lithium enolates. This new protocol can provide various easily modifiable α-amino carbonyl compounds from esters, amides, and ketones. Mechanistic investigations indicate that the oxidative amination proceeds in a radical pathway through the formation of a nitrogen-centered radical generated through a single-electron transfer between an enolate and the hypervalent iodine reagent. The developed amination reaction features transition-metal-free conditions and simple operation.

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# Syntheses of Lissoclimide Analogues and the Investigation of Novel Halogen–π Interactions

Pak, B. S.[1]; Supantanapong, N.[1]; Nguyen, S.[1]; Terrosu, S.[2]; Kolosova, O.[2]; Zgadzay, Y.[2]; Wu, C.[3]; Lin, M.[4]; Nguyen, B.[1]; Blanchard,
S. C.[5]; Horne, D. A.[4]; Sachs, M.[3]; Yusupov, M.[2]; Furche, F.[1]; Vanderwal, C. D.*[1]

[1] *Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025, United States*
**cdv@uci.edu*

[2] *Department of Integrated Structural Biology, Institute of Genetics and Molecular and Cellular Biology, University of Strasbourg, 67404, Illkirch, France*

[3] *Department of Biology, Texas A&M University, College Station, Texas 77843-3258, United States*

[4] *Department of Molecular Medicine, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, California 91010, United States*

[5] *Department of Structural Biology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105-3678, United States*

Lissoclimides are succinimide-bearing labdane diterpenoids that exhibit potent cytotoxic activity against several cancer cell lines, which are attributed to their ability to inhibit translation. Herein, we report our successful efforts towards the semi-syntheses of lissoclimide analogues to gain a deeper understanding of the structural basis for their translation inhibition via interaction with the ribosome. The analogues are designed to probe a novel halogen–π interaction that was discovered through collaborative structural biology studies of chlorolissoclimide. Featuring a highly selective C–H functionalization of sclareolide and Evans-aldol-based succinimide introduction, we generated multiple lissoclimide analogues for collaborative studies, including X-ray co-crystallography with the 80s eukaryotic ribosome. Through this work, we anticipate learning more about the novel halogen–π interaction with neighboring guanine residues in the ribosome E-site, in the hope of finding other applications for this attractive force.

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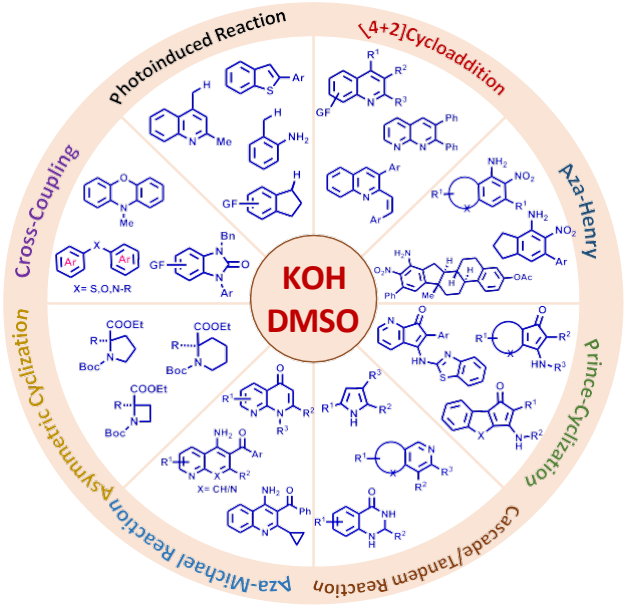
# Versatile Chemistry of KOH-DMSO

Monika Patel and Akhilesh K. Verma*

*Department of Chemistry, University of Delhi, Delhi -110007, India*

**averma@acbr.du.ac.in*




Hetero-atom containing small organic molecules have gained significant attention because of their presence in natural products, drug molecules, pharmaceuticals, agricultural chemicals, pesticides, organic materials, and solar cells. The KOH-DMSO mediated organic transformations[1] are the paradigm of contemporary, sustainable, green chemistry as it is an inexpensive, economical, non-toxic, waste-free, and environmentally benign process of fundamental simplicity. As an exemplar of green solvents along with the combination of alkali base, KOH-DMSO amalgamation revealed extraordinary basicity of about *pKa* 30–32 that was suggested to result from a synergism of two bases. This distinct property of the reagent makes it superior to the other available methods that involve the use of transition-metal catalysts. The KOH/DMSO permutation is a robust catalytic system that has witnessed significant progress in achieving nucleophilic addition/substitution, Diels Alder, [4+2] cycloaddition,[2] Aza-Henry,[3] prince cyclization,[4] cascade/tandem, aza-Michael, asymmetric cyclizations; coupling, and photoinduced reactions. This extraordinary chemistry is expected to find a versatile application in organic synthesis [5-7] and can fulfill an important role in the assembly of a useful class of interesting organic compounds.

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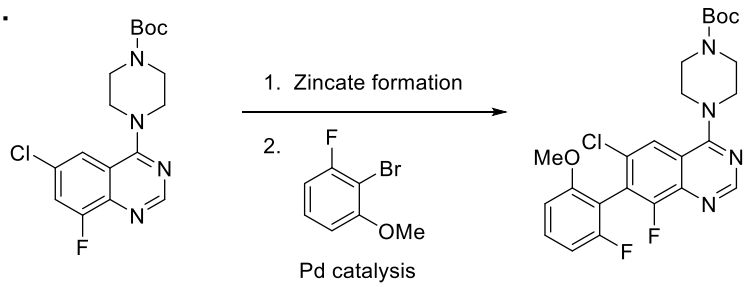
# New Methods for Heterocycle Functionalization in the Context of Drug Discovery Programs at Janssen La Jolla

Daniel J. Pippel[a,*]

[a]*Janssen Research & Development L.L.C., 3210 Merryfield Row, San Diego, CA, 92121*
**dpippel@its.jnj.com*

Janssen's "Discovery Process Research" team exists at the interface between Medicinal Chemistry and Process Chemistry. In addition to traditional roles of route development and API delivery to support early-stage toxicological profiling, the group is also charged with developing new synthetic approaches in the lead-optimization space to accelerate the design-make-test cycle. The selective functionalization of heterocyclic molecules in the presence of other potentially reactive moieties has been a recurring area of interest. Three recently developed methods will be presented: (**a**) selective metalation of functionalized quinazolines, (**b**) radical alkylation of heteroaryl halides, and (**c**) diastereoselective radical addition to heteroaryl sulfinimines.

**a.**

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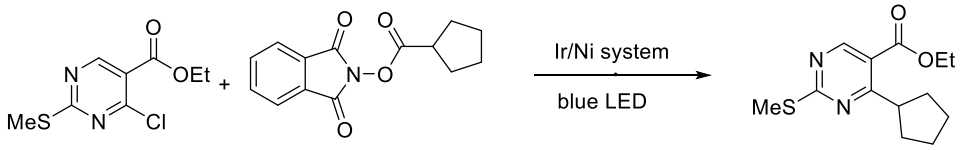


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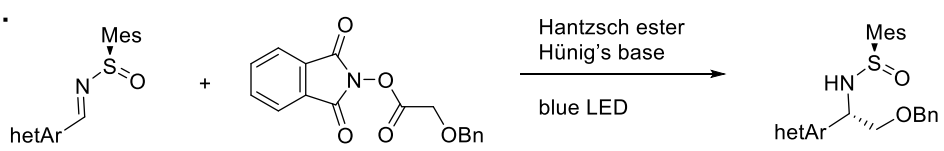

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# Intramolecular C(sp$^3$)–H Amination to Construct Chiral *N*-Heterocycles Enabled by Engineered Cytochrome P450 Enzymes

Ziyang Qin,[†,a] Shilong Gao,[†,a] Yike Zou,[b] Zhen Liu,[a] James B. Wang,[a] K. N. Houk,[*,b] Frances H. Arnold[*,a]

[a]*Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, USA.*
[b]*Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, USA.*
** houk@chem.ucla.edu; frances@cheme.caltech.edu*

Novel biocatalytic transformations are ideal for re-inventing traditional synthetic routes due to their high efficiency, selectivity, and sustainability. The rapid development of biotechnology in the past decades has led to the blooming of biocatalysis where enzymes are engineered for various useful and facile biocatalytic reactions. However, natural functions of enzyme are merely the tip of the iceberg. Due to demand for versatile transformations in chemical industry, one long-standing goal in biocatalysis is to develop new-to-nature enzymatic functions.

*N*-heterocycles are among the most significant structural components of pharmaceuticals reflecting their vital role in modern drug discovery and design. One attractive method to prepare *N*-heterocycles is intramolecular nitrene C(sp3)–H insertion. However, achieving these reactions with good regio- and enantioselective control has proven to be challenging. Herein, we report an enzymatic platform for enantioselective intramolecular C(sp3)–H amination with access to chiral pyrrolidines and indolines using alkyl and aryl azides as nitrene precursors. This biocatalytic process can aminate both benzylic and aliphatic C(sp3)–H bonds affording *N*-heterocycles with good activity and selectivity (up to 2280 total turnover number (TTN) and 97:3 *e.r.*) and can be performed on preparative scale. Enzymatic cascade reactions based on *N*-heterocyclic products is also identified demonstrating enzymes' outstanding capability to construct molecules in high complexity.

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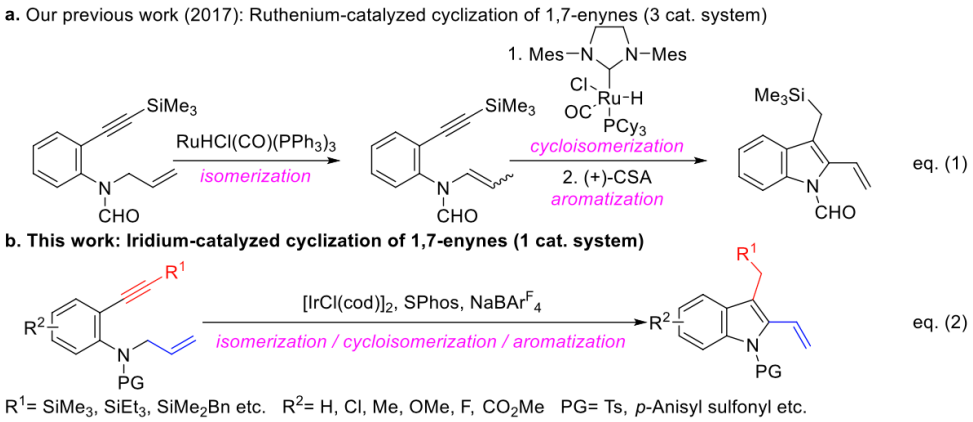
# Iridium-Catalyzed Isomerization/Cycloisomerization/Aromatization of *N*-Allyl-*N*-sulfonyl-*o*-($\lambda^1$-silylethynyl)aniline Derivatives to Give Substituted Indole Derivatives

J. Qiu,[a] M. Sako,[a] T. Tanaka,[a] T. Matsuzaki,[b] T. Takehara,[b] T. Suzuki,[b] S. Ohno,[a] K. Murai[a] and M. Arisawa[a,*]

[a]*Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka, Japan*
[b]*SANKEN, Osaka University, Ibaraki, Osaka, Japan*
**arisaw@phs.osaka-u.ac.jp*

The substituted indole structure is a widespread heterocyclic skeleton in natural products, optoelectronic materials, and pharmaceutical agents. Recently we have reported Ru-catalyzed cyclization of 1,7-enynes involving an enamide and a silyl alkyne **[eq. (1)]**.[1] Although it is an atom-economical and efficient method to yield 2-vinyl-3-(silylmethyl)indoles, which have chemical transferability, two kinds of Ru catalysts and one more extra camphorsulfonic acid for aromatization are necessary. To solve these problems, we developed a one-iridium-catalyst system that transforms *N*-allyl-*N*-sulfonyl-*o*-($\lambda^1$-silylethynyl)aniline derivatives to the corresponding substituted indole derivatives via isomerization/cycloisomerization/aromatization. This strategy provides a straightforward synthetic approach to a series of valuable indoles having vinyl and silylmethyl groups at the 2- and 3-positions **[eq. (2)]**.[2]

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# Origins of *Endo* Selectivity in Diels–Alder Reactions of Cyclic Allene Dienophiles

M. Ramirez,[a] D. Svatunek,[a] F. Liu,[b] N. K. Garg,[a] K. N. Houk[a,*]

[a]*University of California, Los Angeles, United States*
[b]*Nanjing Agricultural University, Nanjing, China*
**houk@chem.ucla.edu*

Strained cyclic allenes, first discovered in 1966 by Wittig and co-workers,[1] have recently emerged as valuable synthetic building blocks.[2] A diverse range of stereochemically-rich, heteroatom-containing products can be accessed via highly *endo* selective Diels–Alder cycloadditions to strained cyclic allenes. Previous experimental investigations, and computations reported here, demonstrate that the Diels–Alder reactions of furans and pyrroles with 1,2-cyclohexadiene and oxa- and azaheterocyclic analogs proceed with *endo* selectivity. This *endo* selectivity gives the adduct with the allylic saturated carbon of the cyclic allene *endo* to the diene carbons. The selectivity is very general and useful in synthetic applications. Our computational study establishes the origins of this *endo* selectivity.[3] We analyze the helical frontier molecular orbitals of strained cyclic allenes and show how secondary orbital and electrostatic effects influence stereoselectivity. The LUMO of carbon-3 of the allene (C-3 is not involved in primary orbital interactions) interacts in a stabilizing fashion with the HOMO of the diene in such a way that the carbon of the cyclic allene attached to C-1 favors the *endo* position in the transition state. The furan LUMO, allene HOMO interaction reinforces this preference. These mechanistic studies are expected to prompt the further use of long-avoided strained cyclic allenes in chemical synthesis.

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# Subcellularly-Localized Photocatalysts and Far-Red Light Enable Catalytic Bioorthogonal Uncaging in Live Cells

J. Rosenberger, Y. Xie, Y. Fang, and J. M. Fox*

*University of Delaware, Newark, DE, United States*

Bioorthogonal catalysis is an emerging field with applications in drug delivery and protein target identification. Most systems involve the expression of a non-native enzyme for the catalytic generation of biologically relevant compounds. However, targeted small molecule bioorthogonal catalysts would avoid the need for non-native expression. Furthermore, far-red photocatalysts allow for the use of long wavelength light as an external trigger. This work describes the localization of small molecule far-red photocatalysts for targeted uncaging of a biologically active compound. A dihydrotetrazine (DHTz) conjugated to a vinyl ether was used as a stable photocage for the tubulin disrupting compound nCA4. Once oxidized to tetrazine via far-red photocatalysis, an intramolecular Diels- Alder reaction occurs leading to uncaging of nCA4. In cellular studies, photocatalysts were localized to the nucleus or tubulin to observe uncaging. Cells treated with the DHTz photocage without photocatalyst or light demonstrated organized and elongated tubulin structures similar to the vehicle, whereas in the presence of both photocatalyst and light, cells exhibited disorganized tubulin structures similar to the free nCA4 control. Localized uncaging was further confirmed using ascorbate as a tool to quench extracellular photocatalysis. Overall, this work demonstrates the first photocatalytic reaction for directed uncaging at the organelle level in cells.

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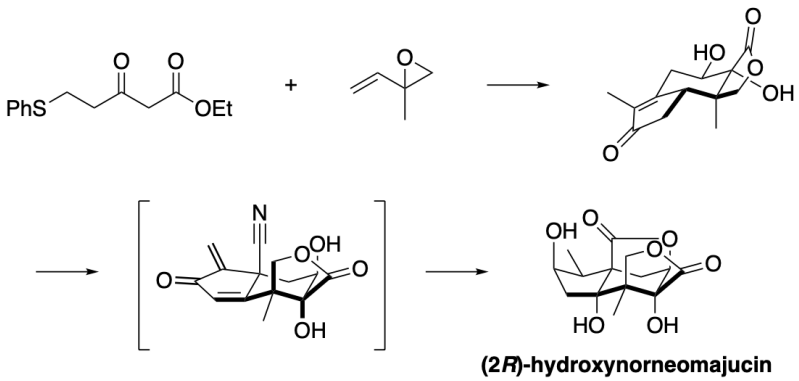
# Total Synthesis of (2*R*)-Hydroxynorneomajucin, a Norsesquiterpene from *Illicium Jiadifengpi*

Scott D. Rychnovsky and Charles J. Dooley III
*Department of Chemistry, University of California at Irvine, Irvine, California 92697, United States*

*Illicium* sesquiterpenes have garnered significant interest from synthetic chemists owing to their highly oxidized structures and intriguing biological activity. We will discuss the total synthesis of (2*R*)- hydroxynorneomajucin (HNNM), a norsesquiterpene derived from the *Illicium Jiadifengpi* plant.[1] This natural product displays neurotrophic activity. Small molecule neurotrophins are of interest because they have potential as therapeutic agents in neurodegenerative diseases. Key steps of our synthesis include a Tsuji–Trost asymmetric allylic alkylation, a Pauson–Khand cyclization, a Nagata hydrocyanation, and an unusual palladium-promoted oxidation. A simple sequence of reductions and a Mukaiyama hydration introduce the A-ring substituents with the correct configurations. The chemical synthesis we will present provides access to this unusual norsesquiterpene natural product.

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# A [2+2] Photocycloaddition–Cyclobutane Fragmentation Approach to Annulated Pyridones

C. Slough,[a] A. Davis,[a] E. Hardwick,[a] and M. Daub[a,]*

[a]*Furman University, Greenville, USA*
**marybeth.daub@furman.edu*

Pyridones compose the core of several biologically active nature products and pharmaceuticals. Annulated pyridones have been underexplored in medicinal chemistry as the direct functionalization of pyridones remains a synthetic challenge. We have been developing an oxidative cyclobutane fragmentation initiated by *N*-acyliminium formation as a new strategy toward annulated pyridones. The requisite cyclobutanes are easily accessible in two steps from 2-hydroxypyridine *via N*-alkylation and triplet sensitized [2+2] cycloaddition using visible light. We have validated our approach with the successful generation of *N*-acyliminium ions using an organic photocatalyst along with an oxidant. Progress towards the cyclobutane fragmentation will be discussed.

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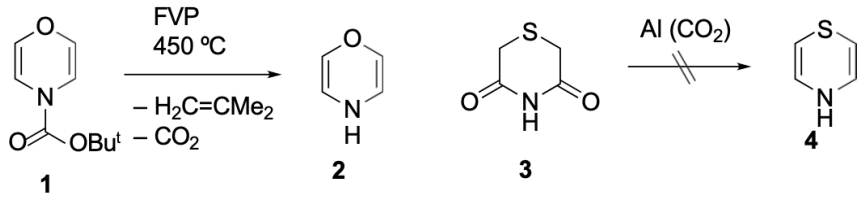
# Gas-phase Approaches to Generation of 1,4-Thiazine

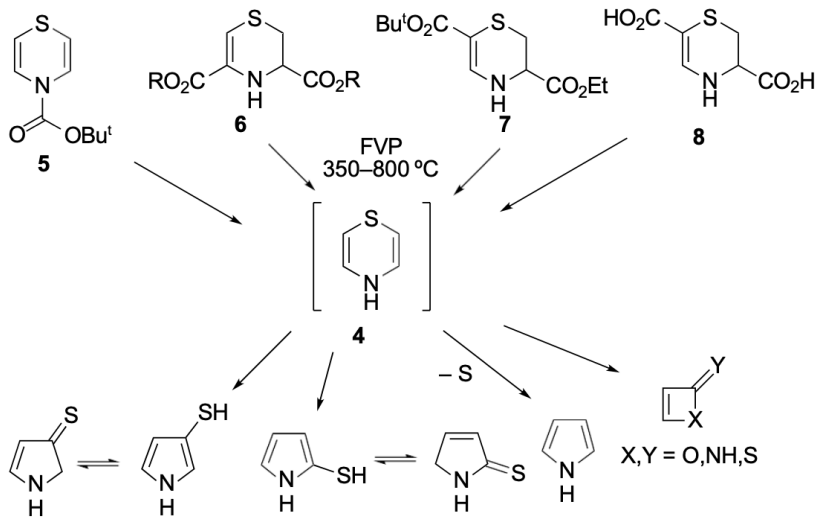
Dheirya K. Sonecha and R. Alan Aitken*

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

Some years ago we described formation and spectroscopic characterisation of the parent 1,4-oxazine **2** by flash vacuum pyrolysis (FVP) of precursor **1** at 450 °C.[1] Among all the possible isomeric parent 6-membered ring fully unsaturated heterocycles with one group 15 and one group 16 atom, this is so far the only example. An early report[2] of generation of 1,4-thiazine **4** by gas-phase deoxygenation of imide **3** over aluminium powder in a flow of $CO_2$ has never been reproduced and we believe it to be erroneous.




We now describe new attempts to generate **4** from FVP of a range of precursors including **5**, **6**, **7** and **8**. The latest evidence for the formation of **4** will be presented as well as identification of other heterocyclic products thought to be formed by its isomerisation or fragmentation.

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# Dihydrotetrazine oxidation by a genetically encodable catalyst for rapid turn-on of bioorthogonal chemistry intracellularly

A. Tallon,[a] J. M. Fox,[a]

[a]*University of Delaware, Department of Chemistry and Biochemistry, Newark, DE, USA*
**atallon@udel.edu*

The tetrazine-*trans*-cyclooctene ligation is the fastest bioorthogonal reaction to date with a second order rate constant up to $k_2 = 10^6\ M^{-1}s^{-1}$ with strained *trans*-cyclooctene (s-TCO) derivatives, far surpassing other biorthogonal reaction kinetics[1]. While electron-deficient tetrazines increase the rate of the tetrazine-TCO ligation, they are only suitable as chemical probes instead of reporters. DHT is a stable precursor to tetrazine with a longer half-life in aqueous conditions. The Fox group developed a system to induce the catalytic oxidation of DHT to tetrazine in situ, enzymatically by horseradish peroxidase (HRP) or by photooxidation in the presence of a photocatalyst and light for subsequent biorthogonal chemistry with TCO[2]. While HRP can enzymatically activate tetrazines, HRP is inactive when expressed in the reducing, calcium scarce mammalian cytosol which limits applications of this enzymatic system to mammalian endoplasmic reticulum and in vitro environments. APEX2 is an engineered ascorbate peroxidase that is active in reducing environments such as the mammalian cytosol and can oxidize a variety of aromatic molecules when $H_2O_2$ is present[3].We have developed a new enzymatic system that oxidizes DHT to tetrazine by utilizing an engineered ascorbate peroxidase (APEX2). We have shown that APEX2 can oxidize a wide range of DHT substrates, have elucidated the hydrogen peroxide independent enzymatic mechanism, and have conducted site-directed mutagenesis to afford an APEX2 variant that is more active towards DHT oxidation. We have also shown that APEX2 can oxidize a series of DHT prodrug scaffolds where upon oxidation, an intramolecular inverse-electron demand Diels-Alder (IEDDA) reaction occurs to release a cytotoxic drug. This prodrug scaffold has been adapted to develop a fluorogenic DHT where upon oxidation by APEX2, a free fluorophore is released resulting in the turn-on of fluorescence. We plan to utilize APEX2 to catalytically induce spatially controlled biorthogonal chemistry for imaging of proteins and cellular compartments and decaging of prodrugs for drug delivery in different areas of the mammalian cell.

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# Synthetic Strategies Toward the Total Synthesis of (–)-Enterocin

Y. Tao, S. Reisman

*California Institute of Technology, Pasadena, CA, USA*

With the increasing emergence of drug-resistant bacteria, new antibiotics are in urgent demand. As part of a broader program aimed at the synthesis of antibiotic natural products, we initiated a chemical synthesis of the natural polyketide (–)-enterocin, which is bacteriostatic against both gram-positive and gram-negative bacteria. A strategy featuring a radical-polar crossover reaction as an annulation step to quickly construct the [3.2.1] bicyclic core of enterocin is detailed. Initial studies have validated the feasibility of the two key C–C bond forming steps in a sequential fashion, and will guide the future development of the radical-polar crossover cyclization. The development of an efficient and general approach will allow a comprehensive evaluation of the potential for caged polyketides to serve as potent antibiotics.

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# Mechanistic Study of the Activation of Rapid Bioorthogonal Chemistry via Photocatalytic Oxidation of Dihydrotetrazines to Tetrazines

S. Tsang,* J. M. Fox

*Department of Chemistry and Biochemistry, University of Delaware, Newark, DE, United States*
**tsangste@udel.edu*

Bioorthogonal reactions are rapid and selective chemical reactions that can occur efficiently without interfering with endogenous biological activity. The fastest known bioorthogonal reaction is the tetrazine ligation, an inverse electron demand Diels-Alder reaction between the electron-poor tetrazine and electron-rich dienophile trans- cyclooctenes (TCO). A series of photocatalysts have been shown to promote the oxidation of dihydrotetrazine (DHTz) to tetrazine products, providing a biologically compatible method for activation of the tetrazine (Tz) ligation with spatiotemporal control. This photocatalytically inducible version of tetrazine ligation has been carried out in live mice and in live cells with suborganelle level spatial control. While several dyes have been developed as photocatalyts, the mechanism of photocatalysis is not well understood. This work examines the mechanism of DHTz oxidation using Silicon-rhodamine (SiR) and fluorescein dyes, which have been repurposed for photocatalysis from their traditional role as biological fluorophores. Computational and kinetic studies reveal that SiR and fluorescein dyes are able to form a ground state complexes with DHTz substrates, and the kinetic studies show that photocatalytic DHTz oxidation follows saturation kinetics. The elucidation of the mechanism is contributing to the design of more efficient photocatalysts.

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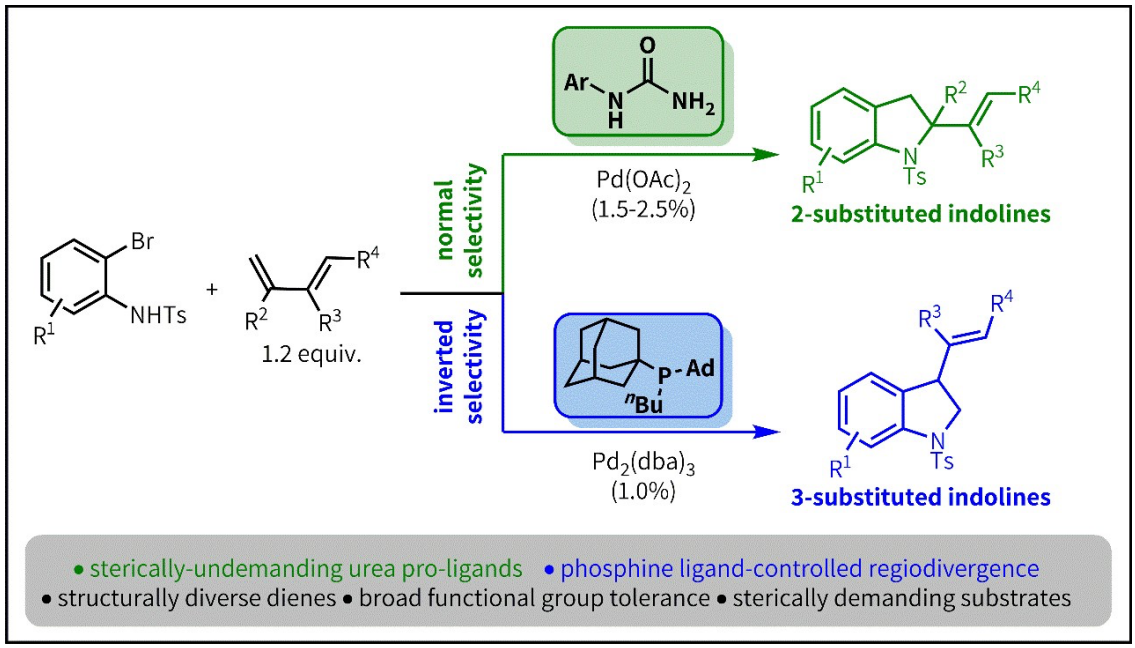
# Regiodivergent Synthesis of 2- and 3-Substituted Indolines and Pyrrolidines through Pd-Catalyzed Heteroannulation of 1,3-Dienes with Bifunctional Reagents

J. Vaith, D. Rodina, S. T. O'Neil, S. M. Paradine*

*Department of Chemistry, University of Rochester, Rochester, New York 14627, United States*
*jvaith4@ur.rochester.edu, sparadin@ur.rochester.edu*

The development of two atypical ligand platforms that enable palladium-mediated regiodivergent heteroannulation of 1,3- dienes with *o*-haloanilines and related bifunctional reagents will be presented. While this class of reactions represents a convergent approach to synthesis of five-membered and larger stereocentre-containing azaheterocycles, its scope has remained limited to iodoanilines and primarily mono-substituted linear 1,3-dienes for the last four decades.[1] Our hypothesis is that this arises from the incompatibility of established ligands with the steric congestion of the Pd complexes in this transformation. We have found that ureates are an effective sterically undemanding ligand platform for palladium catalysis able to overcome the limitations of traditional ligands for late transition metals in this transformation.[2] While the ureate ligand-enabled method provides access to 2-substituted indolines and pyrrolidines, we have found that the synthesis of the complementary 3-substituted azaheterocycles can be achieved by using sterically atypical phosphine ligands that invert the selectivity of the 1,3-diene migratory insertion step. The preliminary parametrization of the phosphine ligands that induce this unusual regiodivergence will be presented.

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# Novel *N*-Branched Acyclic Nucleoside Phosphonates as Inhibitors of *Plasmodium* 6-Oxopurine Phosphoribosyltransferases

Karolína Vaňková[a], Dianne T. Keought[b], Luke W. Guddat[b], Dana Hocková[a], Zlatko Janeba[a]*

[a]*Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Prague, Czech Republic*
[b]*School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane, Australia*
** e-mail: zlatko.janeba@uochb.cas.cz*

The production of nucleoside monophosphates is essential for the synthesis of DNA/RNA in all living organisms. Purine nucleotides can be provided *via* two metabolic pathways: *de novo* synthesis or less energetically demanding purine salvage pathway. Human cells utilize both pathways. However, some protozoan parasites, such as *Plasmodium* spp., rely on the synthesis of nucleotides only through the purine salvage pathway. The key enzyme in this pathway is hypoxanthine-guanine-(xanthine) phosphoribosyltransferase (HG(X)PRT), responsible for ribophosphorylation of 6-oxopurine nucleobases (**Fig.1A**). Thus, inhibition of the enzyme activity should result in the cessation of *Plasmodium* growth and reproduction.[1] In the last decade, acyclic nucleoside phosphonates (ANPs) and bisphosphonates were revealed as potent inhibitors of HG(X)PRT.[2-4] The present goal is to design even more potent inhibitors with a view to the development of effective chemotherapeutics against such infectious diseases. Using the chemical structure of the substrates/products of the enzymatic reaction and previously discovered inhibitors as the platform, a series of novel *N*-branched ANPs (**Fig.1B**) were designed and synthesized.

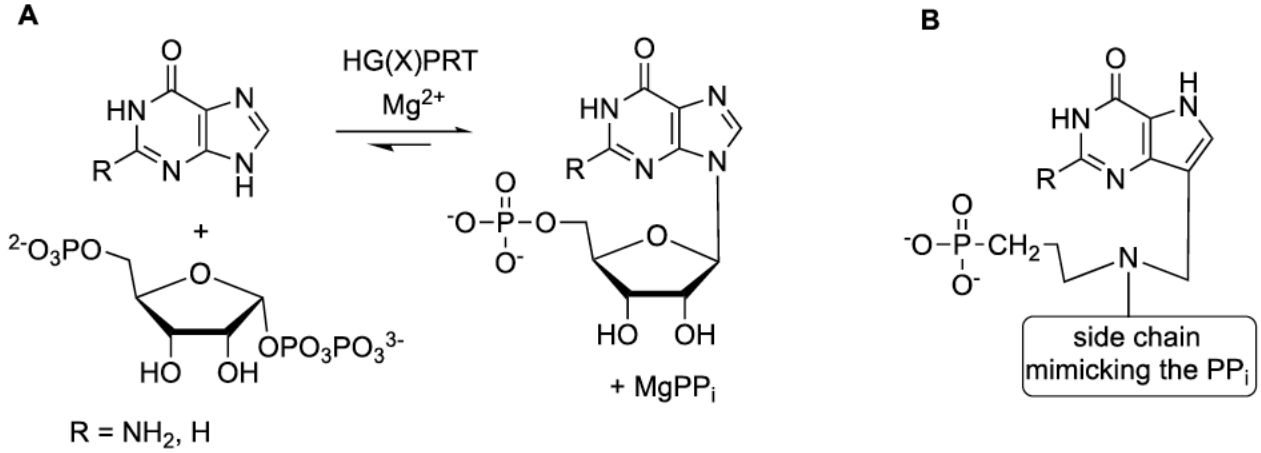


**Fig.1** (A) The reaction catalyzed by HG(X)PRT. (B) Design of novel ANPs

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# Carbon-Carbon Bond Formation between 1,4-Naphthoquinone and Ru-Carbene Complex with *N*-Heterocyclic Carbene (NHC) Ligand *via* Carbon(sp$^3$)-Hydrogen Bond Activation

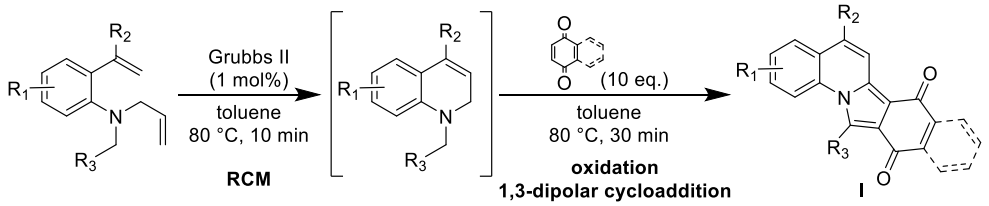
Y. Wada,[a] T. Takehara,[b] T. Suzuki,[b] K. Murai,[a] M. Sako,[a] and M. Arisawa[a,*]

[a] *Graduation School of Pharmaceutical Sciences, Osaka University, Osaka, Japan*
[b] *The Institute of Scientific and Industrial Research, Osaka University, Osaka, Japan*
**arisaw@phs.osaka-u.ac.jp*

*N*-heterocyclic carbenes (NHC) are widely used as metal-catalysts' ligands or ionic liquids. It is well known that metathesis catalysts with NHC ligands are one of the most powerful catalysts in many fields of synthetic chemistry. The ruthenium carbene catalyst has an NHC ligand, which is known as Grubbs catalyst 2$^{nd}$ generation, and is widely used as an olefin metathesis catalyst, and nowadays, there are a lot of publications for other reactivities of this catalyst other than metathesis reactions.

Near Infrared (NIR) dyes, which have their maximum absorption wavelengths in the NIR region, are commonly applied in CD-R, organic Els, bioimaging, and even in photodynamic therapy. The basic structures of these dyes, however, have been limited.

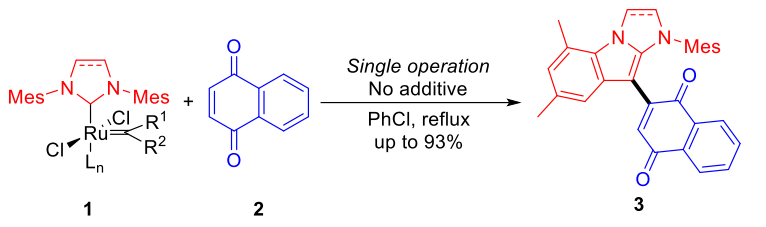
We previously developed a one-pot ring-closing metathesis (RCM)/oxidation/1,3-dipolar cycloaddition protocol[1], and we established a new skeleton, isoindolo[2,1-*a*]quinoline (**I**) (**Scheme 1**)[2]. In this project, we found a novel reaction between the NHC ligands on ruthenium carbene complexes (**1**) and 1,4-naphthoquinone (**2**), and synthesized new NIR dyes (**3**), which have blue color (λmax = 700.5 nm) (**Scheme 2**)[3]. In this poster session, we are going to show the optimization of this reaction with Box-Behnken design, substrate scope, and optical features of compounds **3**.




**Ia** ($R_1$ = 3-Me, $R_2$ = Me, $R_3$ = Ph, $\lambda_{max}$ = 736 nm)
**Ib** ($R_1$ = H, $R_2$ = Ph, $R_3$ = H, $\sigma_{978}$ = 50 GM)

$R_1$= Cl, Br, Me, OMe
$R_2$= Ph, Me
$R_3$= Ar ($C_6H_4$-4-$NO_2$, $C_6H_4$-4-F, $C_6H_4$-4-OMe), H

**Scheme 1**. One-pot RCM/oxidation/1,3-dipolar cycloaddition and photoproperties of compounds **I**




$\lambda_{max}$ = 700.5 nm

**Scheme 2**. Tandem C-H activation/C-C bonds formation between NHCs and 1,4-naphthoquinone

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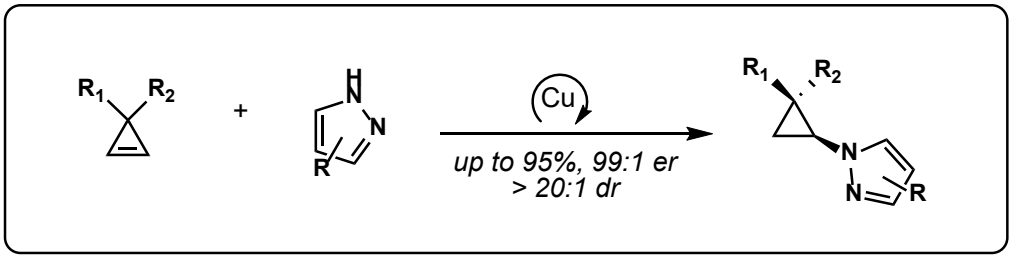
# Enantioselective Coupling of Cyclopropenes with Pyrazoles via Copper(I) Catalysis

M. Wang, J. C. Simon and V. M. Dong[a,*]

[a] *Department of Chemistry, University of California, Irvine, Irvine, California 92697, United States*
** dongv@uci.edu*

Cyclopropene hydrofunctionlization provides an efficient approach to construct molecular complexity[1]. With the increased interest in methods that incorporate nitrogen- containing heterocycles[2], we're investigating an asymmetric coupling of pyrazoles and cyclopropenes using copper catalysis. Our approach is the first enantioselective "copper-amido" hydroamination, affording high enantio- and diastereoselectivity, with wide functional group tolerance. Preliminary findings indicate the necessity of using bulky bisphosphine ligands to increase reactivity and inhibit the potential ring-opening pathway.

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# Electric Field Influence on Hydrocarbon Autoxidation and Amine Acylation

Xiye Wang,[a#] Boyuan Zhang,[b#] Tomislav Rovis,[a]* and Latha Venkataraman[ab]*

[a]*Department of Chemistry, Columbia University, New York, NY, USA.* [b]*Department of Applied Physics and Applied Mathematics, Columbia University, New York, NY, USA.*

**Email: tr2504@columbia.edu*

**Email: lv2117@columbia.edu*

*#X.W. and B.Z. contributed equally*

An external electric field, generated by the scanning tunneling microscopy-break junction (STM-BJ) technique, activates hydrocarbon autoxidation products to acylate amines. This novel mode of alkyl peroxide activation to generate acyl equivalents, and the subsequent intermolecular coupling can be monitored *in situ* by the conductance measurement in the STM-BJ and quantitatively characterized *ex situ* by mass spectrometry. The acylation is found to be influenced by the magnitude of the applied bias, indicating an electric field influence on thermodynamic parameters of this bulk reaction.

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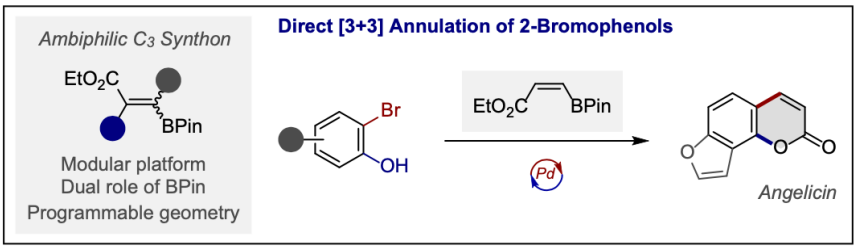
# Coumarin Synthesis by Direct Annulation: β-Borylacrylates as Ambiphilic $C_3$-Synthons[1]

M. Wienhold, J. J. Molloy, C.G. Daniliuc and R. Gilmour*

*Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstrasse 36, 48149 Münster, Germany*
** ryan.gilmour@uni-muenster.de*




The long-standing importance of the coumarin scaffold in pharmaceuticals, natural products and functional materials is evident from the early works of Perkin[2] and Pechmann.[3] Since these benchmark reports, synthetic methods for the generation of this bicyclic framework have been complemented by transition metal,[4] photochemical[5] and modified Knoevenagel condensation approaches.[6] To further extend the synthesis repertoire, a direct [3+3] annulation approach was envisaged. In this study, modular β-borylacrylates have been utilized as small molecule synthons in the Pd-catalysed annulation reaction with 2-bromophenols to generate coumarin scaffolds. Key to the success of this methodology is the bifunctional BPin moiety: It enables the C($sp^2$)-C($sp^2$) Suzuki-Miyaura cross coupling between the respective 2-bromophenol and β-borylacrylate that starts the reaction cascade leading to the formation of the coumarin core. Additionally, the BPin unit extends the chromophore of the synthon, enabling selective energy transfer catalysed alkene isomerisation, leading to the critical *Z*-geometry required for cyclisation. The synthetic utility of the protocol was demonstrated through the synthesis of several coumarins differing in electronic and steric properties, such as the natural product *angelicin*. It was also possible to extend the π-system of several bioactive molecules to modulate their photophysical properties. As these compounds exhibit characteristic absorption in UV/vis-analysis, the application of this simple annulation strategy could also lead to the development of new tools for molecular imaging.

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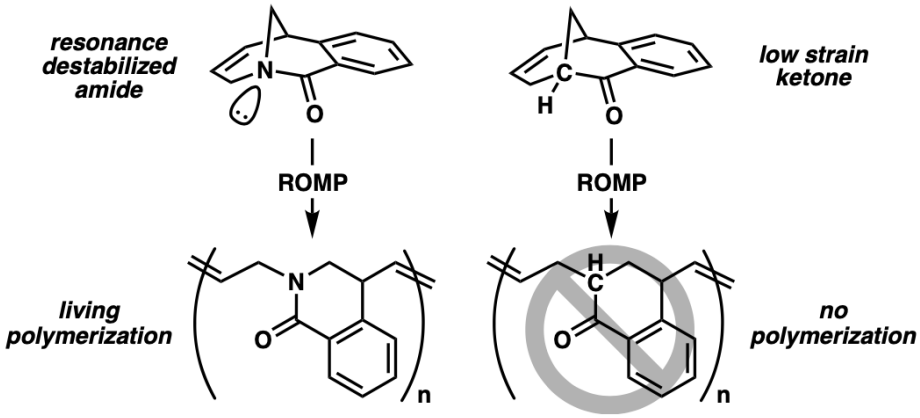
# Resonance Promoted Ring-Opening Metathesis Polymerization of Twisted Amides

M. Xu,[a,b] K. K. Bullard,[b] A. M. Nicely[b] and Will R. Gutekunst[b,*]

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

The living ring-opening metathesis polymerization (ROMP)[1,2] of an unsaturated twisted amide using the third generation Grubbs initiator is described.[3] Unlike prior examples of ROMP monomers that rely on angular or steric strain for propagation, this system is driven by resonance destabilization of the amide that arises from geometric constraints of the bicyclic framework. Upon ring-opening, the amide can rotate and rehybridize to give a stabilized and planar conjugated system that promotes living propagation. The absence of other strain elements in the twisted amide is supported by the inability of a carbon analogue of the monomer to polymerize and computational studies that find resonance destabilization accounts for 11.3 kcal•mol$^{-1}$ of the overall 12.0 kcal•mol$^{-1}$ ring strain. The twisted amide polymerization is capable of preparing high molecular weight polymers rapidly at room temperature, and post-polymerization modification combined with 2D NMR spectroscopy confirms a regioirregular polymer microstructure.

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# Olefination of Hydrazones and Oximes Mediated by Ruthenium Alkylidenes

T. E. Zehnder,[a] D. J. Nasrallah,[b] J. R, Ludwig,[a] D. C. Stiegerwald,[a] J. J. Kiernicki,[c] N. K. Szymczak,[a] and C. S. Schindler[a]*

[a]*Department of Chemistry ,University of Michigan, Ann Arbor, MI, USA*
[b]*Department of Chemistry and Biochemistry, University of California Los Angeles, Los Angeles, CA, USA*
[c]*Department of Chemistry and Physics, Drury University, Springfield, MO, USA*
**Corresponding author's e-mail address: corinnas@umich.edu*

Access to highly functionalized alkenes found in chemical feedstocks, pharmaceuticals, and natural products provides a desirable focus for the development of new carbon-carbon bond forming reactions. Previous approaches to imine-olefin metathesis have shown great potential for functionalized alkene synthesis but remain limited by stochiometric formation of catalytically inert metal imide products. We hypothesized that tuning the polarity of the C=N π-bond with electron withdrawing groups ($NR_2$, OR) would facilitate olefination reactivity with weakly electrophilic ruthenium alkylidenes to unlock a new olefination reaction. Herein, we report the use of air-stable commercially available ruthenium alkylidenes for oxime/hydrazone olefination[1], progress towards understanding the mechanism of this transformation, and potential for catalysis through a reducible ruthenium nitride intermediate.

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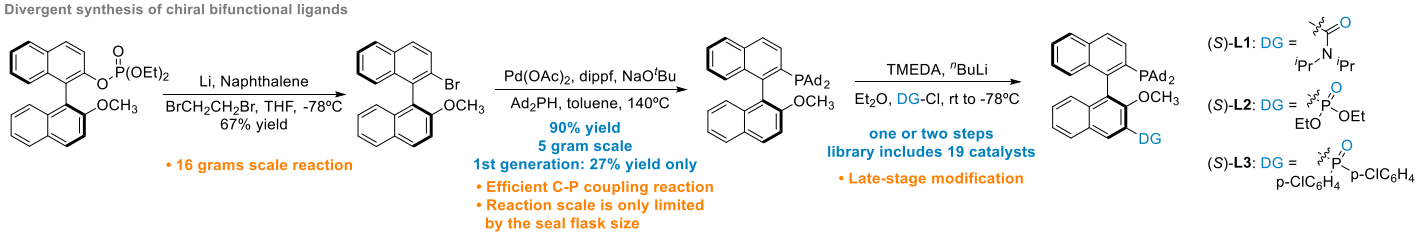
# Rational Design on Bifunctional Ligand in Asymmetric Gold Catalysis

K. Zhao,[a] Z. Yang,[a] and L. Zhang[a,*]

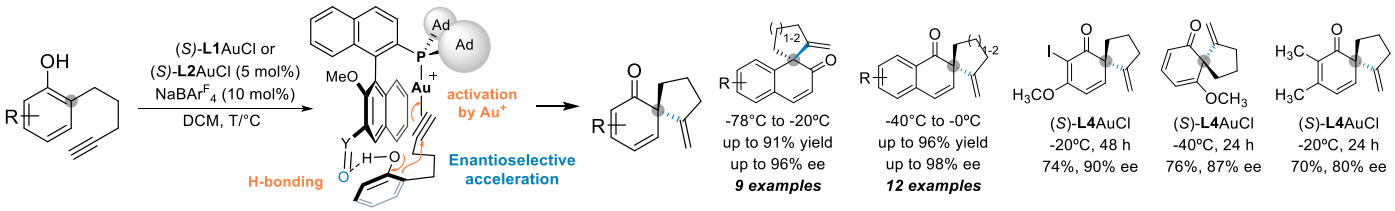
[a] *University of California Santa Barbara, Santa Barbara, US*
**zhang@chem.ucsb.edu*

In past one decade, the cooperative asymmetric gold catalysis has attracted organic chemists' attention and was applied into various types of reaction, including isomerization of alkynes[1] and asymmetrical cyclization of allenols[2]. Herein, we reported a late-stage divergent synthesis of chiral bifunctional ligands (Scheme 1).



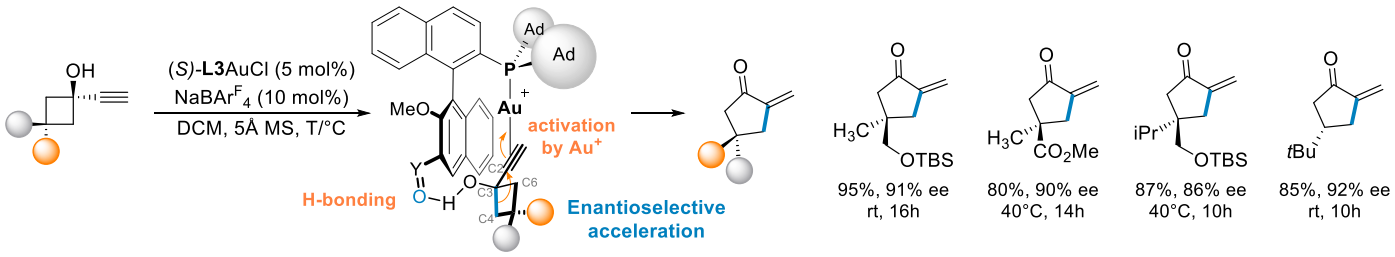

Scheme 1. Late-stage divergent synthesis of chiral bifunctional ligands.

With our new chiral bifunctional ligands, we realized a highly enantioselective dearomative cyclization, which is enabled by gold-ligand cooperative catalysis (Scheme 2). The alkyne moiety is activated by cationic gold coordination. At the same time, the basic directing group on ligand forms a hydrogen bond with hydroxy group on phenol, which accelerates one of spirocyclic enantiomers formation. The later scope study indicated that 2-naphthol, 1-naphthol and even phenol substrates can give dearomatization products in good to excellent enantioselectivity.




Scheme 2. Asymmetrical dearomatization enabled by cooperative gold catalysis

Later, we applied our chiral bifunctional ligands into desymmetrization of alkynylcyclobutanol to synthesis chiral β'-substituted cyclopentenones via conformation control (Scheme 3). The scope study indicates that chiral quaternary center and chiral tertiary center can be stablished in good enantioselectivity.

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