# QOMSBOC 2024 Oral Presentation Abstracts

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Plenary Lecture 1

## Aminoquinoline Synthesis and Process Development Enabled by Non-Aqueous Suzuki-Miyaura Cross-Coupling Reaction

*Dr. Rebecca Green, Bristol Myers Squibb*

This talk will present the strategic bond disconnections of an aminoquinoline NLRP3 Agonist to enable a convergent synthesis. In addition to the overall synthetic route design, the process development of several key steps will be presented with a focus on process robustness, simplicity, and sustainability to provide high quality drug substance to enable clinical studies.

**Biography**

Rebecca Green completed her B.Sc. at McGill University in 2011 in her hometown of Montréal, Canada. She then moved to California to pursue her Ph.D. at UC Berkeley. During her graduate studies, working in the lab of Professor John F. Hartwig, she focused on Ni (and some Pd) catalyzed C-N coupling reactions with a particular interest in mechanistic studies. After graduating in 2016, Rebecca moved to New Brunswick, NJ, and joined the process chemistry group at Bristol Myers Squibb, where she is currently an Associate Scientific Director. While at BMS, Rebecca continues to follow her passion for transition-metal catalysis and mechanistic studies in process chemistry. She currently leads project teams with a focus on safe, robust, and sustainable process development.

Plenary Lecture 2

## Combining Synthetic Chemistry and Biology for Streamlining Access to Complex Molecules

*Prof. Hans Renata, Rice University*

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

**Biography**

Hans Renata was born in Surabaya, Indonesia. After completing his high school education in Singapore, he moved to the US and received his B.A. degree from Columbia University in 2008, conducting research under the tutelage of Professor Tristan H. Lambert. He earned his Ph.D. from The Scripps Research Institute in 2013 under the guidance of Professor Phil S. Baran. After postdoctoral studies with Professor Frances H. Arnold at the California Institute of Technology, he started his independent career at The Scripps Research Institute in 2016. His research focuses on the development of new biocatalytic methods and chemoenzymatic strategies to prepare complex, bioactive molecules. For these efforts, he has received several notable awards, such as the NSF CAREER award, the Sloan fellowship, the Chemical and Engineering News “Talented 12” and the Arthur C. Cope Scholar award. In July 2022, he took a position at Rice University as a Cancer Prevention and Research Institute of Texas (CPRIT) scholar.

Plenary Lecture 3

## Leveraging One- and Two-Electron Mechanisms in Nickel-Catalyzed Cross-Coupling

*Prof. Tianning Diao, New York University*

While palladium-catalyzed cross-coupling reactions have revolutionized the construction of multi-aryl scaffolds in pharmaceutical synthesis, the reactivity of nickel in mediating radical pathways has expanded the scope of cross-coupling to include a variety of alkyl motifs. Through mechanistic investigations and understanding the ligand effects, we have established that strong s-donor and p-acceptor ligands exhibit redox-activity, facilitating nickel catalysts to initiate radical formation, capture radicals, and direct bond formation from open-shell intermediates. The orthogonal reactivity of radicals with polar functional groups in biomolecules has opened new avenues for synthesizing non-canonical peptides and carbohydrates, which are important for drug discovery. In contrast, two-electron pathways are crucial for nickel-catalyzed bi-aryl coupling. Building on this insight, we have developed a novel ligand that enhances the reactivity of nickel-catalyzed Suzuki-Miyaura couplings, paving the way for the application of nickel catalysts in pharmaceutical process synthesis.

**Biography**

Tianning Diao is a Professor of Chemistry at New York University (NYU). She received her Ph.D. in Chemistry from the University of Wisconsin–Madison in 2012, followed by postdoctoral research at Princeton University from 2012 to 2014. Since her appointment at NYU in 2014, Diao's research has been focused on understanding the mechanisms of nickel-catalyzed cross-coupling reactions and developing new methodologies to address challenges in organic synthesis and sustainable energy conversion. Her work has advanced understanding of radical initiation, propagation, and bond formation processes mediated by nickel catalysts. Furthermore, her insights into ligand effects have inspired the design of new ligands that facilitate nickel-catalyzed cross-coupling reactions. More recently, she has applied these methods to the modification of biomolecules. Diao is the recipient of multiple awards, including the NSF-CAREER award (2016), Sloan Research Fellowship (2018), Chinese-American Chemistry Professors Association Distinguished Junior Faculty Award (2018), Organometallics Distinguished Author Award (2018), Camille-Dreyfus Teacher-Scholar Award (2019), and the Cope Scholar Award (2023).

OR1

# Pd-Catalyzed Suzuki-Type Cross-Coupling of 2-Pyridyl Carbamoyl Fluorides

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Carbamoyl fluorides have recently been recognized as a promising class of electrophiles, providing an alternative method for amide synthesis via C–C bond formation instead of the conventional amidation methods via C–N bond formation. However, current methods are primarily limited to intramolecular reactions or rely on the use of activated *N*–$CF_3$ carbamoyl fluorides.[1,2] To broaden the scope to intermolecular cross-coupling reactions, it is essential to develop strategies that promote the cleavage of strong C–F bonds, while mitigating undesirable decarbonylation pathways. In this context, we demonstrate the distinctive fluoride-enabled reactivity of carbamoyl fluorides in a Suzuki-type cross-coupling reaction facilitated by a directing group strategy.[3] Our findings showcase the successful synthesis of medicinally significant 2-pyridyl amides and 2-pyridyl amines, which are key pharmacophores in various therapeutics. Through detailed control experiments and mechanistic studies, including the isolation of the first oxidative addition complex from carbamoyl fluorides, we highlight the importance of the directing group and the use of a fluoride electrophile in catalysis.

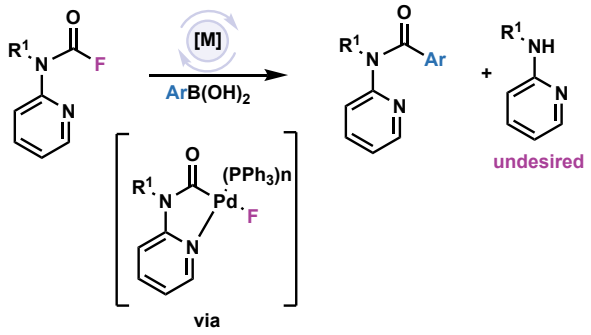


**Figure 1.** Suzuki-type cross-coupling of 2-Pyridyl Carbamoyl Fluorides enabled by Directing group strategy

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OR2

# From anilines to azo compounds vis photo dual catalysis

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Given the increasing significance of azo compounds across multiple disciplines, the development of innovative synthetic methods for their preparation remains a key priority. In this pursuit, there is a strong demand for technologies that incorporate the benefits of catalysis, sustainability, simplicity, broad applicability, and high yields for the synthesis of azo compounds. In this presentation, a novel dual-photocatalytic approach to synthesize azo compounds from commercially available or easily accessible amines will be covered. This synthetic strategy harnesses renewable light energy and mild reaction conditions to efficiently produce azo compounds. The utility of this photo-catalyzed method is demonstrated by its broad substrate compatibility, including the synthesis of privileged eight-membered diazocine and arylazopyrazole photoswitches. Finally, mechanistic insight into this reactivity will be discussed, shedding light on this powerful dual photocatalytic process.

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OR3

# Use of Computational modeling and Continuous-Flow Solid-Phase Peptide Synthesis for the design and synthesis of peptide ligands targeting HLA and Hsp90

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Most drug candidate molecules being developed focus on their ability to bind to a protein thus altering its function. Small organic molecules achieve this by binding to small cavities in desired targets, inhibiting catalytic centers or blocking the binding of the natural substrate in such pockets. However, these small molecules fail to inhibit protein-protein interactions, which have garnered significant attention in the pharmaceutical industry in recent years. Peptides possess attractive features, including high structural compatibility with the targeted proteins and their ability to disrupt the protein-protein interfaces. Efficient *in silico* design of high-affinity peptide ligands is an ever-growing field that still demands the synthesis of such ligands to confirm their desired activity.[1]

Batch-mode solid-phase peptide synthesis has been the standard for drug discovery; however, synthesizing a library of candidates can be time- and resource-consuming, as well as considered less “green” due to the significant amount of waste produced. Strategies such as the search for new environmentally friendly solvents or processes that reduce the use of materials during the synthesis and purification of potential candidates allow easier activity screening, complimenting the computational design.[2]

In this work, we present our efforts for the rational design of two libraries of peptides targeting HLA-DR (autoimmune diseases) and Hsp90 (cell cycle control), as well as the use of CF-SPPS for synthesizing potential candidates to evaluate both the design model and the synthetic feasibility of the peptide ligands.

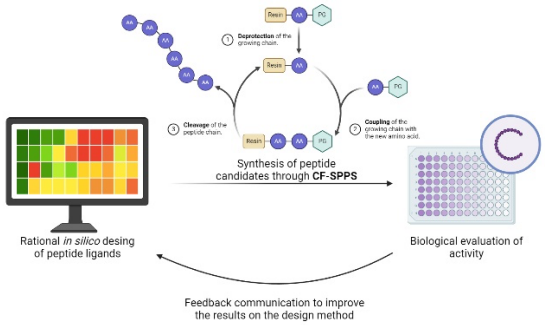


**Figure 1.** Workflow of computational modeling, synthesis and evaluation of peptide ligands.

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OR4

# Towards the concise total synthesis of 19-nor-clerodane diterpenoid natural products

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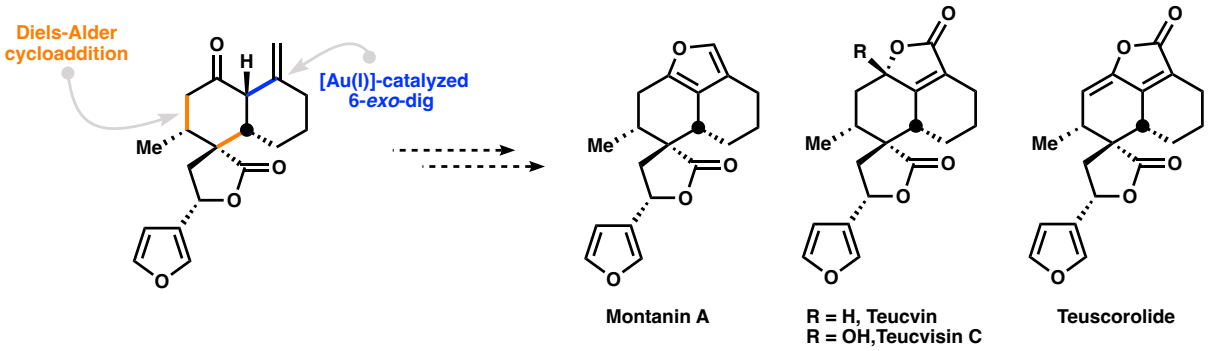
Clerodane diterpenoids, along with their 19-nor variants, represent a highly diverse class of natural products, with over 1,300 members identified to date.[1] These compounds exhibit a broad range of notable biological and pharmacological activities, including insect anti-feedant properties, selective *κ*-opioid receptor agonism, anti-cancer, anti-inflammatory, and antibiotic effects. Among these, 19-nor-clerodanes have emerged as particularly attractive synthetic targets due to their intricate structures, which include a densely functionalized decalin core, a spiro *γ*-lactone unit, and a fused *α,β*-unsaturated *γ*-lactone or a furan moiety. This distinctive polycyclic scaffold provides an excellent platform for the development of innovative synthetic strategies. Due to the complexity of the structure only a handful of publications have successfully described the synthesis of clerodanoids.[2] Herein, we describe our efforts toward the synthesis of 19-nor-clerodane diterpenoids, utilizing a dual key-step approach. This strategy involves a highly efficient Lewis-acid catalyzed Diels-Alder cycloaddition that stereoselectively forms the spirolactone, followed by a novel [Au(I)]-catalyzed 6-*exo*-dig carbocyclization to rapidly construct the decalin core. This approach enables the rapid formation of the core skeleton of 19-nor-clerodane diterpenoids, allowing for further diversification of the scaffold into various members of this family. Ongoing work toward the completion of this project, along with our end-game synthetic strategy, will also be discussed.

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OR5

# Synthesis of Oligonucleotide Conjugates Containing Selenium Modified Linkers

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Oligonucleotide conjugates are an important class of nucleic acid modifications that have shown significant therapeutic potential, including targeted delivery, cellular uptake, and improved stability. These conjugates can range from small, simple molecules like cholesterol to chemically complex, large molecules such as peptides, antibodies, and fluorescent dyes, offering numerous applications. However, the synthesis of such conjugates poses challenges given incompatibilities between the molecules to be ligated. Recently, our laboratory developed an approach to prepare DNA peptide conjugates employing reductive diselenide-selenoester ligation (rDSL). This process involves a 5'-diselenide cross-linked DNA dimer and a C-terminal selenoester peptide with efficient ligation observed between the two biomolecules.

In the present study, we explored the synthesis of alkylene linkers containing a terminal 2-cyanoethyl protected selenium functionality for coupling to the 5'-end of an oligonucleotide by solid phase synthesis (SPS). Upon deprotection and cleavage from the solid support, formation of 5'-diselenide cross-linked DNA dimers were evaluated. Linkers with alkylene chain lengths of 4 and 10 between the selenium atom and DNA were prepared, with efficient formation of the 5'-diselenide cross-linked DNA dimer observed for the longer alkylene chain, based on product characterization by denaturing polyacrylamide gel electrophoresis. Using this 5'-diselenide cross-linked DNA, strategies to functionalize the DNA with other molecules, as well as extending this process to RNA and chemically modified oligonucleotides will be explored. The development of more efficient synthesis strategies to prepare oligonucleotide conjugates will serve to advance the application of these molecules as therapeutic agents.

OR6

# Electrochemical transformation of triclosan as a greener alternative to chemical treatment

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Triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol), is a phenol commonly used in personal care products and industrially, but inevitably end up in our water and soil, thus becoming an environmental pollutant of public health concern [1,2]. The implementation of harsh chemical treatments and rigorous remediation methods can effectively remove such chemicals from the environment. Alternatively, milder, greener and more sustainable avenues like electrochemical methods can be beneficial for achieving the desired mitigation of contaminants [1,3]. The conversion rather than remediation of triclosan post end-of-use also allows for the reuse, repurposing and recycling of the phenolics into value-added chemicals of industrial interest. Herein, the conversion of triclosan *via* electrochemical methods was compared to a traditional chemical oxidation process [3]. The transformation of triclosan was monitored analytically by spectroscopy, chromatography and mass spectrometry. The degradation and oxidation of triclosan was achieved by electrochemical and organic synthesis methods. In comparison to the chemical oxidation process, the electrochemical methods achieved 6x greater overall transformation of triclosan with more selectivity. Overall, electrochemical methods such as electrosynthesis provide alternative, greener and more sustainable avenues for mitigation and transformation of common organic pollutants with applications in green chemistry and sustainable industrial processes towards value-added chemicals.

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OR7

# Cyclopropylamine derivatives from cyclopropanols via electrophilic homoenolate reactivity

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Cyclopropylamines are valuable small-ring motifs found in several biologically active compounds.[1] While unsubstituted cyclopropylamine is a commonly used commercially available material, access to substituted cyclopropylamines is significantly more challenging, particularly with control of stereochemistry. One method to access cyclopropylamines from cyclopropanols was recently developed by our group, taking advantage of the electrophilic nature of the carbonyl that is unmasked by cyclopropanol ring opening. This reaction gave high *trans* selectivity and tolerated a variety of primary and secondary amines.[2,3] Here a second generation of the reaction is presented, using sulfinamides as nucleophiles. These sulfinamide products can be cleaved to access the primary cyclopropylamine or oxidized to access sulfinamides or S(VI) functional groups. The use of commercially available enantiopure sulfinamide auxiliaries (e.g. Ellman's auxiliary) gives access to both enantiomers of the cyclopropylamine. This presentation will highlight the scope and applications of this reaction, as well as future directions for the area of electrophilic homoenolate chemistry.

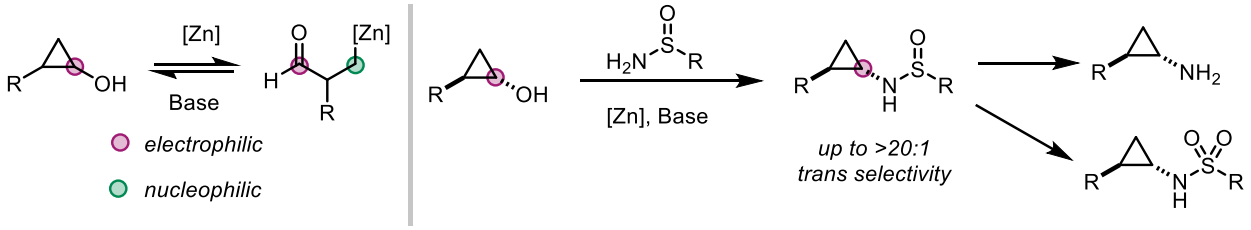


***Figure 1.*** *Reaction scheme showing the reactivity of cyclopropanols with sulfinamides.*

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OR8

# Two-Step Formation of Substituted Pyridines From Iodo-Enones

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A new access to substituted pyridines was developed from iodo-enones. This two-step procedure involves a Sonogashira coupling[1] with a free alkyne containing a nosylamide followed by a thiophenol treatment in basic conditions that triggers a nosyl deprotection, a Michael-retro-Michael process, a condensation and isomerization in cascade to yield the heterocycle. This method enables the introduction of different substituents at several pyridine positions. This approach offers new synthetic opportunities to produce heterocycles present in many bioactive compounds.[2]

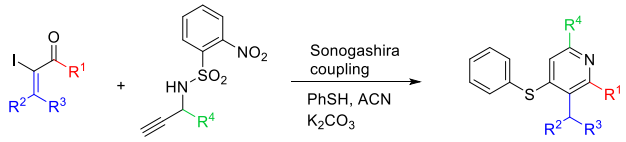


**Figure 1.** Two-Step Formation of pyridines via iodo-enones and enals

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OR9

# A Chemical Method to Generate Mono- and Dual- Antigen Specific Antibody Therapeutics

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Antibodies (IgG) target foreign substances for immune-mediated clearance primarily through Fc receptor interactions, including Antibody Dependent Cellular Phagocytosis (ADCP). Antibodies high specificity make them excellent substrates for bioconjugation protocols to generate novel therapeutics (e.g. Antibody Drug Conjugates). For example, covalent antibody recruiting molecules (cARMs) utilize a unique in situ bioconjugation strategy to equip IgG with novel targeting capabilities for immune-oncology. cARMs contain an electrophile, an antibody-binding domain (ABD) and a target-binding domain (TBD) to bridge a stabilized “ternary complex” at tumor cell surfaces. The ABD typically targets low-concentration anti-hapten antibodies in serum. Problematically, low concentrations of antibodies in serum may limit the efficacy of cARMs. We hypothesized it would be strategic to redirect total serum IgG against metastatic cancer cells to address this. Towards this end, we developed a covalent peptide based “proximity-induction” strategy that incorporates a pan-IgG binding peptide into a cARM scaffold to redirect serum IgG against cancer cells. This approach can also generate multi-antigen specific antibodies, circumventing complex protein engineering.

We have synthesized and validated a first-in-class covalent immune recruiter (CIR) that consists of an IgG binding peptide equipped with an electrophile and a TBD that targets urokinase-type plasminogen activator receptor (uPAR) on metastatic cancer. Validation of anti-tumor function in ADCP assays has demonstrated the ability of site-specifically reprogrammed IgG to induce phagocytosis against uPAR+ cancer cell lines. We have also demonstrated dual-antigen targeting capabilities via our CIR. Using our CIR technology, we demonstrate a broadly applicable technique to covalently reprogram antibodies for targeted tumor immunology.

# Nickel-Catalyzed Deoxygenative Suzuki-Miyaura Cross-Coupling of Ketones

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The Suzuki-Miyaura cross-coupling is among the most frequently used methods to forge new C–C bonds.[1] Organohalides and pseudohalides are recognized as the classical electrophilic coupling partner in Suzuki-Miyaura cross-coupling. However, given the abundance of C–O bonds in common feedstock molecules like phenols, carboxylic acids, and alcohols, these have emerged as attractive alternatives.[2] Ketones are particularly common precursors in cross-coupling chemistry, which are commonly converted to vinyl triflates first to enable activation by Pd or Ni catalysis.[3] While there has been a strong push in the recent literature to enable oxygen-containing substrates to undergo direct Suzuki-Miyaura cross coupling, eliminating isolation of an activated 'pseudohalide' intermediate,[4-5] such chemistry has not yet been identified for ketone activation.

Aiming to fill this void, we sought to identify mild and inexpensive activating agents that could enable in situ activation of the C–O bond of ketones for Suzuki-Miyaura cross-coupling. This requires compatibility between base, activating agent, and low valent metal catalyst. A high throughput screening campaign led us to a Ni-catalyzed, pivalic anhydride-mediated set of reaction conditions that enables the direct transformation of ketones into vinyl arenes. The discovery, development, and application of this new reaction will be described.

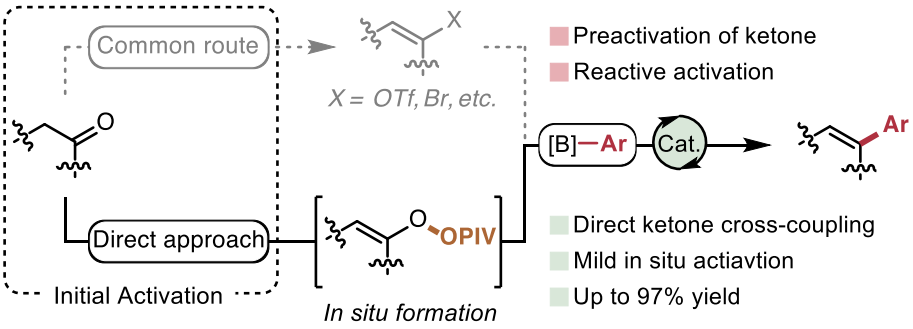


**Figure 1.** Direct Suzuki-Miyaura cross-coupling of ketones, via in situ formation of alkenyl pivalate.

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OR11

# The Nature and Chemical Utility of Proximal Boron Functionalities on the S-Alkylation of Sulfenic Acid Anions

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The S-functionalization chemistry of sulfenic acid anions, also known as sulfenate anions, represents an emerging method for the preparation of sulfoxides.[1] Nearby functional groups can often influence the S-functionalization chemistry of sulfenate anions through non-bonding interactions.[2] Recently, several reports have illustrated the combination of the Lewis acidity of trivalent boron and Lewis basicity of sulfinyl groups to perform interesting chemistry.[3-5] Among these reports is a study by Benkovic and coworkers who investigated the reversible complexation of the oxygen of a sulfenate anion with the boron atom of boronic acids and a benzoxaborole.[3] This report illustrated that a reversible R-S-O-B bond forms between the sulfenate anion and the boron atom indicating that a proximal boron functional group could potentially influence the S-functionalization chemistry of sulfenate anions.[3] We decided to investigate this R-S-O-B interaction in hopes that initial complexation of a sulfenate oxygen to boron could direct and accelerate the S-alkylation chemistry of sulfenate anions. To date, 22 competition sulfenate alkylations have been performed between borylated and non-borylated electrophiles with the reactions being up to 100% selective for the boron containing electrophile. In the case of the aryl sulfenate anions, the selectivity of the reaction was directly dependent on the electronic effects on the sulfenate anion and thus Hammett analysis was performed to ascertain the origin of this selectivity. Applications of this work in the stereoselective S-alkylation of sulfenate anions have also been investigated.

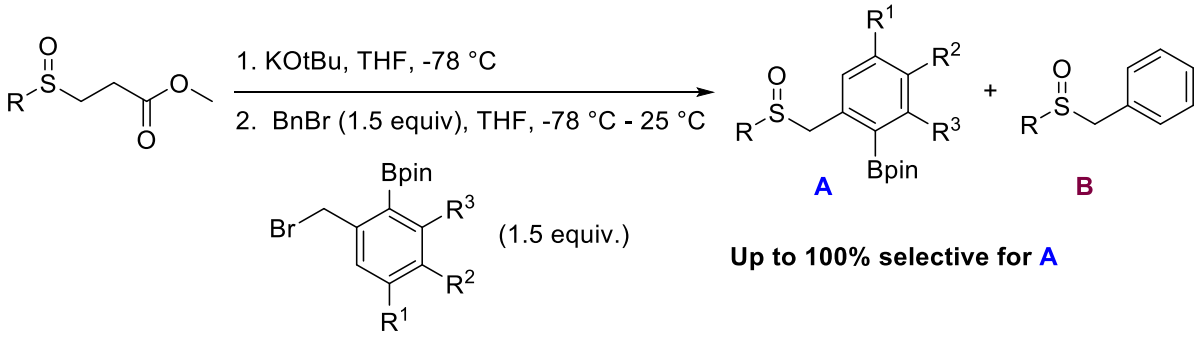


**Figure 1.** General competition experiment investigating the effect of a proximal boron functionality on the S-alkylation chemistry of sulfenate anions.

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OR12

# Synthetic Studies Towards $C_6$-Oxygenated $C_{19}$-Diterpenoid Alkaloids

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The $C_{19}$-diterpenoid alkaloids represent a class of natural products renowned for their bioactivity and structural complexity[1]. Despite their hexacyclic cage-like architecture, a few of these natural products have been synthesized[2]; however, limited success has been achieved when considering the more highly oxidized variants. To this end, synthetic strategies to address key challenges such as the installation of C3-, C6-, and C13 oxygenation have yet to be achieved[1]. With these key challenges at mind, we have sought to develop a unifying synthesis to achieve the synthesis of C6 oxygenated natural products.

In this presentation, a brief overview of our previous efforts towards aconitine, and our current strategy towards this class of natural products will be presented. Key to our current synthesis is use of a Mg-templated Diels-Alder[3] to synthesize a highly functionalized the AF-ring fragment. Additionally, this presentation will demonstrate some of our successes along this campaign, as well as some important lessons learned from the challenges of this synthesis.

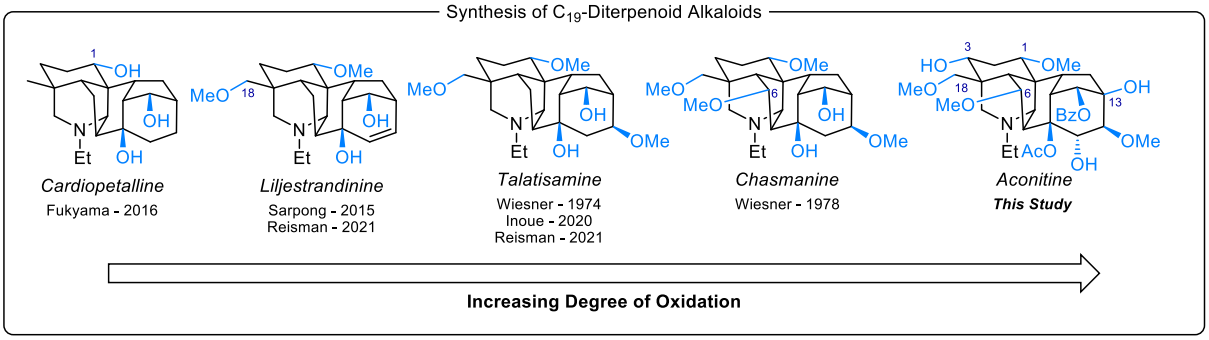


**Figure 1.** Synthesis of $C_{19}$-diterpenoid alkaloid natural products and labelling of carbons.

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OR13

# Conjugated Polymers with Self-Immolative Sidechain Linkers for Carbon Nanotube Dispersion

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Single-walled carbon nanotubes (SWNTs) are promising materials for generating high-performance electronic devices. However, these applications are greatly restricted by their lack of purity and solubility. Commercially available SWNTs are a mixture of semi-conducting (sc-) and metallic (m-) SWNTs and are insoluble in common solvents. Conjugated polymers can selectively disperse either sc- or m-SWNTs and increase their solubility; however, the conductivity of conjugated polymer-wrapped SWNTs is largely affected by the polymer side chains. This talk reports a poly(fluorene-*co*-phenylene) polymer containing a self-immolative linker as part of its sidechains.[1] The self-immolative linker is stabilized with a *tert*-butyldimethylsilyl ether group that, upon treatment with tetra-n-butylammonium fluoride (TBAF), undergoes a 1,6-elimination reaction to release the sidechain. Sonication of this polymer with SWNTs in tetrahydrofuran (THF) results in concentrated dispersions that are used to prepare polymer-SWNT thin films. Treatment with TBAF caused side-chain cleavage into carbon dioxide and the corresponding diol, which can be easily removed by washing with solvent. This process is characterized by a combination of absorption and Raman spectroscopy, as well as four-point probe measurements. The conductance of the SWNT thin films increased ≈60-fold upon simple TBAF treatment, opening new possibilities for producing high-conductivity SWNT materials for applications such as transparent electrodes[2] and pressure sensors.

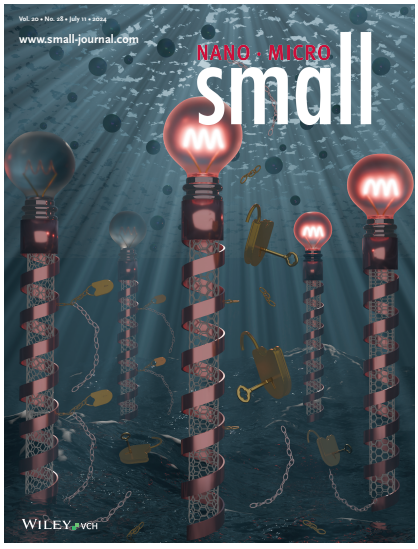


**Figure 1.** The sidechains are stabilized with an end-cap (“lock”) that is easily “unlocked” with an appropriate “key”. The polymer disperses SWNTs, and treatment with the “key” enhances the conductivity of polymer-SWNT thin films by nearly 60-fold, allowing current to flow.

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OR14

# Leveraging *N*-nitrenes for Targeted Chemistry: Tetrazenes and *N*-iminophosphoranes as Functional Tools in Bioorthogonal Chemistry

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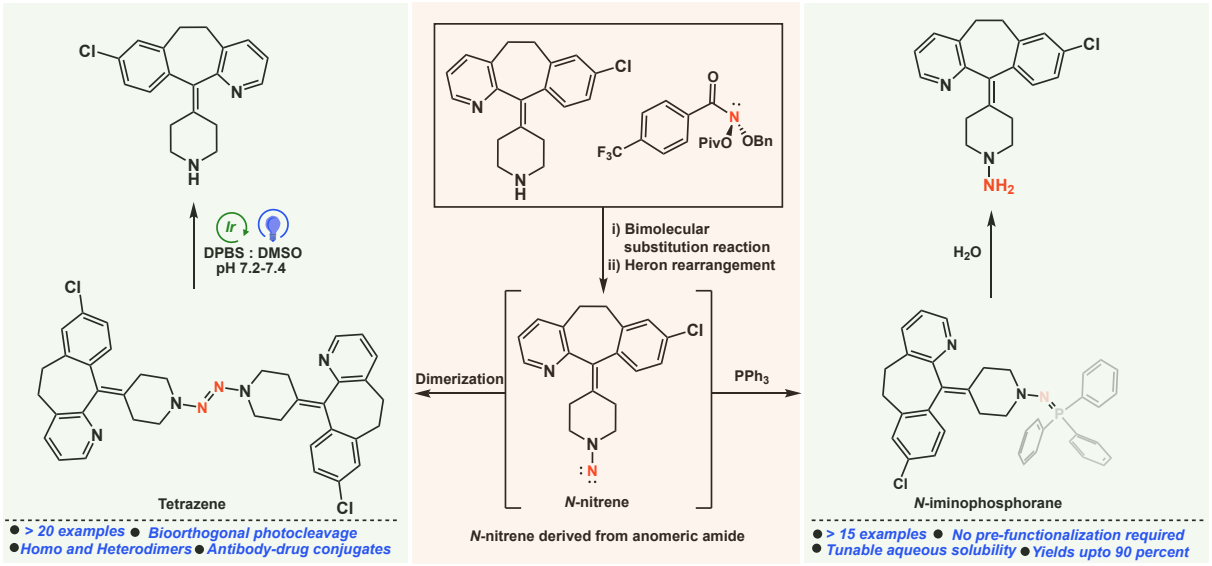
The chemistry of *N*-nitrenes (isodiazene or diazanylidene) has remained relatively underexplored in the literature compared to its structural analogs, such as carbenes and *C*-nitrenes. Due to their strong electrophilic nature, *N*-nitrenes exhibit high reactivity and a short lifespan, making them challenging to harness and control. Herein, we use anomeric amide as an electrophilic nitrogen transfer reagent to generate isodiazene from a target amine. Electron-deficient isodiazenes can either be dimerized to construct Tetrazenes or trapped with polarity-matching phosphine to synthesize *N*-iminophosphoranes. Tetrazenes, seemingly fragile nitrogen-enriched molecules, can hold structural integrity under physiological conditions and can be bioorthogonally cleaved using visible-light mediated energy transfer catalysis, making them well-suited for applications as photolabile linkers and light-controlled antibody-drug conjugates. *N*-iminophosphoranes can be hydrolyzed rapidly to furnish high-value hydrazines, and the electronics of these phosphorous ylides can be tuned to access corresponding stable phosphoniums with extended aqueous stability. We anticipate the positive charge will enable *N*-iminophosphoranes in mitochondrial localization, facilitate targeted mitochondrial delivery of hydrazines, and open avenues for mitochondrial profiling.




*Manuscript in preparation*

OR15

# Constructing the proaporhine skeletons through a radical-polar crossover dearomatization strategy

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Proaporphine skeleton is an important structure which can be found in many alkaloid families, such as proaporphines, tryptamine-proaporphine dimers, liriogerphines, etc. However, all the current strategies towards proaporphine skeleton are lack of selectivity, hard to diversify and problematic in functional group compatibility. In order to solve these problems, we designed a synthetic strategy defined by a radical dearomatization step that include a radical-polar crossover process. In this step, a racial can be generated on the side chain of a biaryl compound and go through a 5-exo cyclization to form a new radical. The resulting radical will then get oxidized and trapped by a nucleophile intermolecularly or intramolecularly. As such, simple, flat, and $sp^2$ rich starting material can be converted into $sp^3$ rich cyclic system in one step to drastically increase the stereochemical complexity. Now, we have finished the asymmetric syntheses of several proaporphine alkaloids.[1] Notably, our synthesis towards (-)-misramine has a longest linear sequence of 9 steps. It compares favorably to previous synthesis of this natural product by Takao and Zhou, which in 24 and 21 steps, respectively. This talk will describe our experimental efforts, as well as our more general interest in dearomatization by radical-polar crossover strategy, which we see as an enabling tool in complex molecule synthesis.

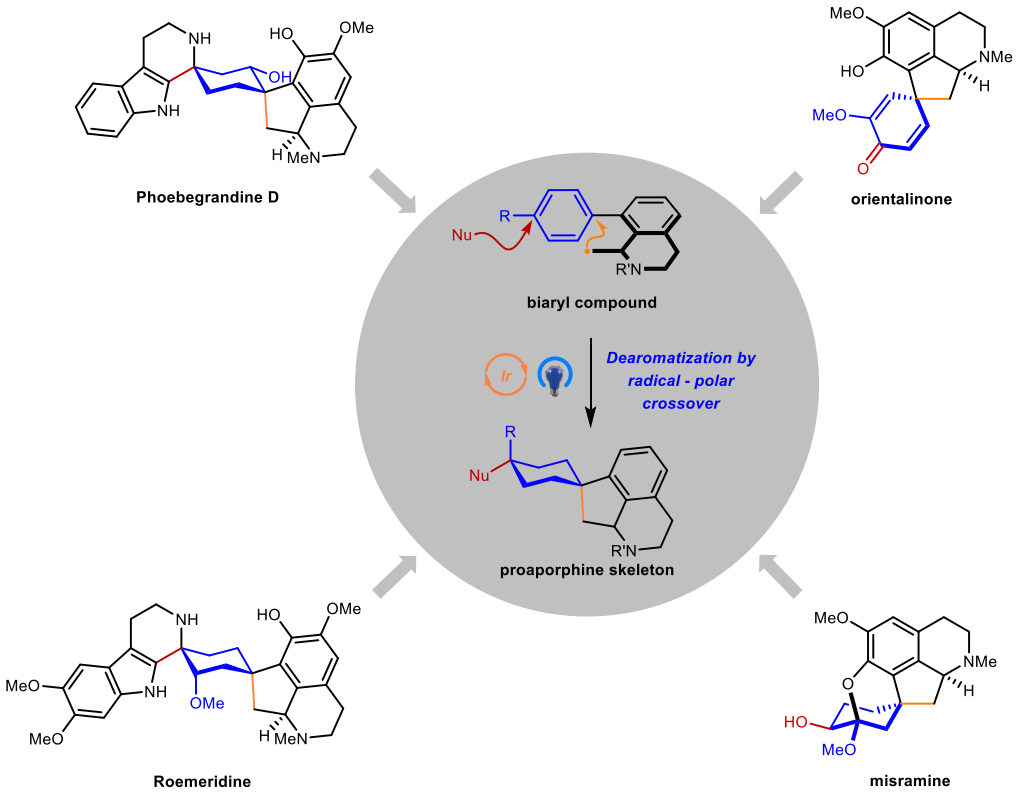


**Figure 1.** General strategy for constructing proaporphine skeletons

## References

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OR16

# Molecular Cryptids in Phenol Dearomatization Reactions Using Hypervalent Iodine

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Hypervalent iodine compounds are widely used in organic synthesis as strong, yet selective oxidation reagents. Their use in phenol dearomatization have unlocked a new method to add nucleophiles on aromatic moiety using a greener and cheaper alternative to heavy metals. This reaction is well known and has been used in several total synthesis[1] and synthetic methodologies[2, 3], but the mechanism behind this umpolung reactivity of phenols remains uncertain. Some researchers postulated an associative mechanism between the hypervalent iodine and the phenol, making a strong electrophilic complex. Others have postulated a peculiar and under-documented reactive intermediate: the phenoxenium cation. This molecular cryptid, stabilized by fluorinated polar solvent like 1,1,1,3,3,3-hexafluoroisopropanol, helps explain several observed reactivity leading to dearomatized phenols. This phenoxenium is not a trivial intermediate and two mechanistic pathways have been proposed to explain its generation using hypervalent iodine: two subsequent outer-shell single electron transfer or a heterolytic cleavage of a phenol-iodine bond complex. Using a combined theoretical, kinetic, and spectroscopic approach, we present direct evidence for the existence of the titular molecular cryptid and evidence for its generation mechanism.[4]

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OR17

# Total Synthesis of Conidiogenone B

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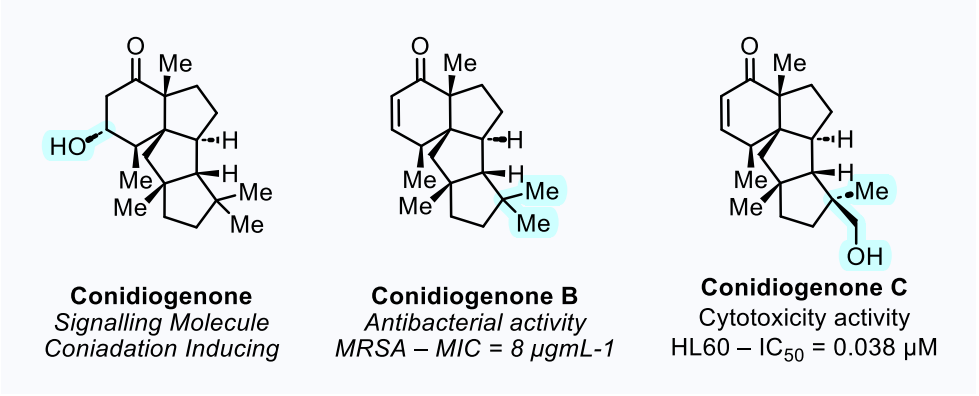
Antibiotic resistance is a growing global health crisis, demanding the development of novel therapeutic agents. Conidiogenone B, a natural product with significant antibacterial activity, has emerged as a promising candidate. This compound exhibits potent inhibition at 8 µg/ml against drug-resistant pathogens such as MRSA, Pseudomonas, and Staphylococcus, demonstrating activity comparable to Ampicillin without relying on the traditional β-lactam pharmacophore[2]. However, the limited natural availability of Conidiogenone B has impeded extensive biological investigation and development of structural analogs.

Our research focuses on the innovative total synthesis of Conidiogenone B to enable further biological evaluation and modification for enhanced antibacterial properties. This synthetic strategy employs a Johnson-Claisen rearrangement to establish a key all-carbon quaternary center, a challenging feature in complex molecule synthesis. Following this, an intramolecular metal-hydride hydrogen atom transfer (MHAT) cyclization efficiently constructs the core skeletal framework of the natural product.

The synthesis is accomplished in a concise sequence, allowing access to Conidiogenone B in sufficient quantities for further study. Our approach not only provides access to this promising antibacterial agent but also opens the door to the generation of structurally diverse analogs that could exhibit improved therapeutic profiles. This work aims to advance the development of novel treatments for antibiotic-resistant infections by creating new opportunities for chemical innovation in drug design. Through our efforts, we hope to contribute to the growing need for effective and sustainable antibacterial agents.




**Conidiogenone**
*Signalling Molecule*
*Coniadation Inducing*

**Conidiogenone B**
*Antibacterial activity*
*MRSA – MIC = 8 µgmL-1*

**Conidiogenone C**
Cytotoxicity activity
HL60 – $IC_{50}$ = 0.038 µM

**Figure 1.** Isolation and Biological Activity[1,2]

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OR18

# Development of well-defined, bench-stable Ni-NHC precatalysts and their applications in challenging C-N bond formation reactions

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The development of metal-catalyzed carbon-nitrogen (C−N) bond-forming reactions has significantly influenced the synthesis of pharmaceuticals, agrochemicals, and fine chemicals.[1] Therefore, developing sustainable catalysts is crucial for industrial applications. Over the past two decades, nickel catalysis has gained prominence due to its cost-effectiveness and unique properties compared to its precious metal sibling palladium.[2] Nickel is three times less expensive and offers greater electropositivity and versatility in oxidation states, facilitating more efficient cross-coupling reactions.[3]

This study aims to design a universal air-stable $Ni^{II}$-NHC precatalyst with high modularity and effectiveness in challenging C−N bond formations. We honor to report the successful synthesis of two generations of these air-stable precatalysts ($Ni^{II}$-NHC-IPr and $Ni^{II}$-NHC-$IPr^{Cl}$), characterized by proton and carbon NMR spectroscopy, mass spectrometry, and X-ray diffraction. Our investigations reveal several key characteristics of these precatalysts: 1) they exhibit high stability on the bench before running reactions, as well as high stability under reaction conditions without any decomposition; 2) they activate easily under mild condition to initiate the reaction; and 3) they demonstrate high catalytic activity in challenging C−N bond formation reactions, particularly with electron-rich electrophiles and electron-poor nucleophiles, achieving significant yields. Focusing on the selective monoarylation of primary amines—a challenging industrial C−N bond formation reaction—we found that utilizing bulkier NHC ligands enhances selectivity for mono-aryl products over di-aryl counterparts. Future work will involve synthesizing Ni-NHC-$IPent^{Cl}$ and Ni-NHC-$IHept^{Cl}$ to further optimize selectivity in this nickel-catalyzed amination reaction.

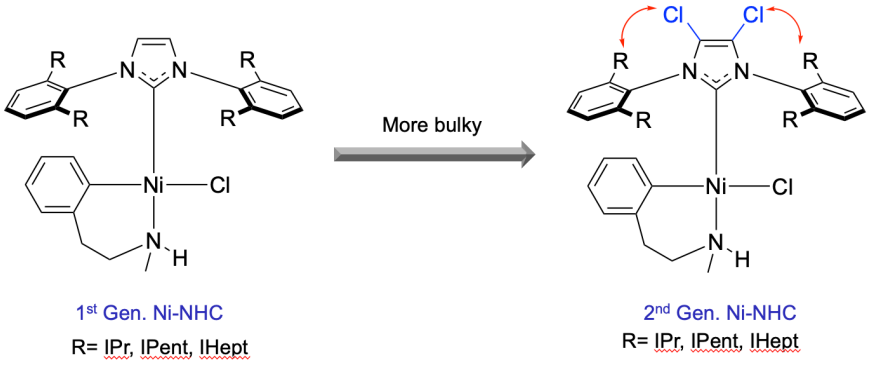


**Figure 1.** First and second generations of air-stable Ni-NHC precatalysts

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OR19

# Hydroamination enabled by selective osmium-catalyzed reduction

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Intramolecular hydroamination of alkenes is a widely recognized technique for creating C-N bonds, particularly useful in synthesizing pyrrolidines and piperidines. For many years, hydroamination reactions using transition metal catalysts have been utilized for this purpose. Despite significant advances in this area to address the high kinetic barrier (e.g. using catalysis), the types of accessible motifs remain limited. For example, reactions are often restricted to terminal alkenes, to amines with specific substitution patterns, or to the formation of 5-membered rings.[1,2]

Procedures featuring more stable alkenes and complex ring system formation remain rare. Herein, a redox-enabled process featuring oxidation of an amine to a hydroxylamine, a concerted intramolecular alkene hydroamination step, followed by catalytic reduction of the *N*-oxide is reported, and shown to be broadly applicable. Catalyst screening indicated that $K_2OsO_2(OH)_4$ displayed a unique ability to rapidly reduce the *N*-oxide cycloadduct in the presence of the hydroxylamine and DMSO, while also minimizing the formation of side products. This chemoselectivity was further improved by the use of ligands for Os, such as pinacol. The high selectivity for the reduction of the *N*-oxide product over the hydroxylamine precursor was exploited to drive the equilibria toward complex products that have not been previously accessible via hydroamination strategies. Additional experiments showed that the catalyst does not influence the kinetic profile of the hydroamination step, thus supporting the importance of the chemoselective N-O bond reduction event.

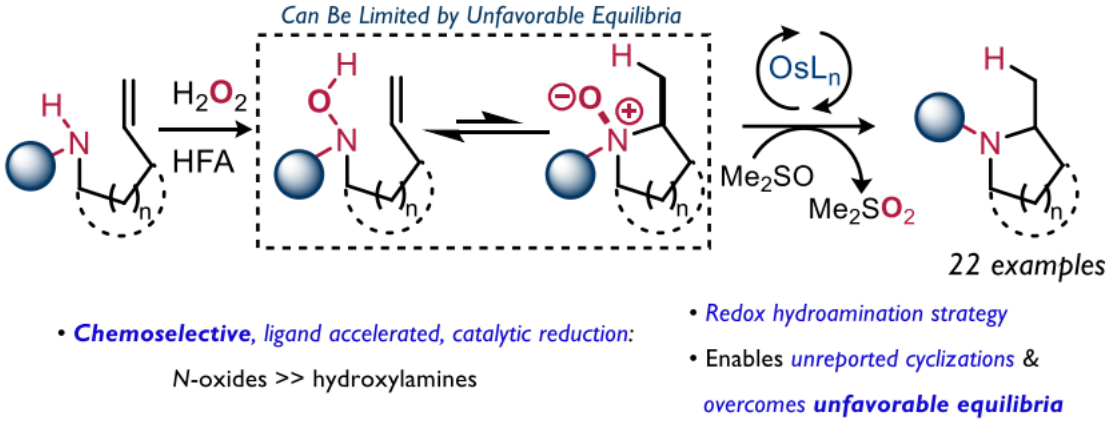


**Figure 1.** Cope-type hydroamination enabled by selective osmium-catalyzed reduction.

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OR20

# Diastereomeric and Dynamic Thermodynamic Resolution of Alkenyl Cyanohydrins: Stereoselective Access to *Z*-Tetrasubstituted Alkenes

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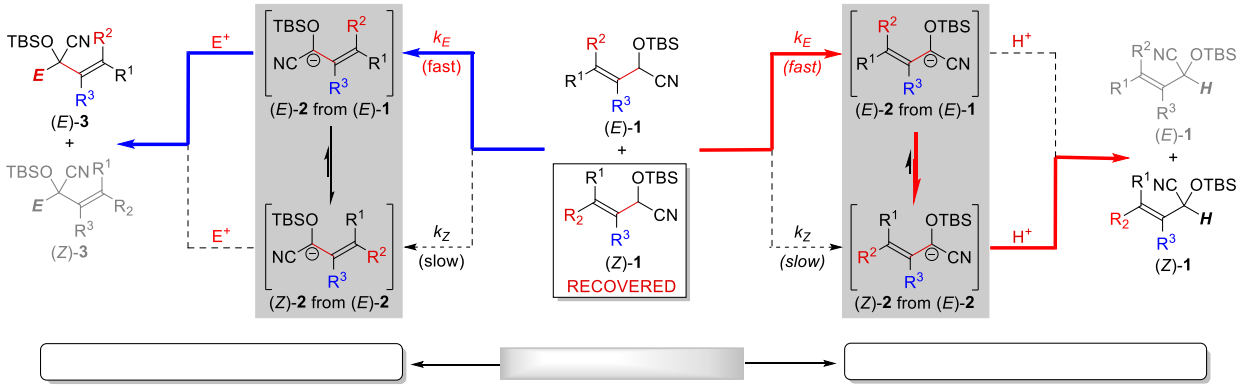
Stereodefined alkenes are ubiquitous motives in many important functional molecules and synthetic intermediates. The geometry of the alkene is often critical for eliciting a specific biological response or imbuing a physical property. However, the difficulty associated with the stereoselective construction of achiral diastereomeric alkenes tracks with the degree of substitution, in which tetrasubstituted alkenes are the most challenging to prepare in a stereoselective manner. The presentation will describe new processes for the diastereomeric and dynamic thermodynamic resolution of a mixture of *E*- and *Z*-tetrasubstituted alkenyl cyanohydrins with exquisite selectivity and excellent yields, providing a convenient approach to *Z*-tetrasubstituted alkenes for applications in target-directed synthesis. In addition, we present a detailed computational investigation that provides a conceptual understanding of the mechanism.



OR21

# SYNTHESIS OF FUNCTIONALIZED CYCLIC AZOBENZENE WITH PHOTO SWITCHING CAPABILITIES FOR SPATIOTEMPORAL CONTROL OF DNA AND CELL MEMBRANES

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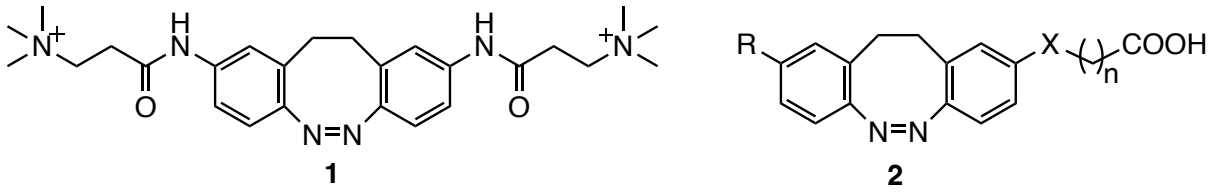
Cationic compounds called polyamines have been found to play a role in the natural condensation of DNA via non-covalent interactions. In recent years, cyclic azobenzene derivatives have been studied with special interest for their ability to isomerize to the lesser thermodynamically stable *trans* isomeric state under specific visible light. It has been previously shown that aromatic azobenzene derivatives can be utilized to condense DNA[1] and to regulate the membrane permeability in a reversible manner upon photoisomerization.[2] This study aims to investigate the utility of cyclic azobenzene in these two areas of application. Toward this goal, cyclic azobenzene containing suitable functional groups will be synthesized. On one hand, a cyclic azobenzene derivative containing bisammonium **1** will be examined for its ability to condense DNA, while a cyclic azobenzene-modified fatty acid **2** will be incorporated into membranes to regulate permeability.




**1** **2**

**Figure 1.** cis-cAb bisammonium (1) and cyclic azobenzene-modified fatty acid (2)

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OR22

# Regioselective ring opening of aziridyl alcohols with azoles using Boron catalysis

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Ring openings of aziridines can enable the preparation of important functional group pairs such as 1,2-diamines or 1,2-amino alcohols, which are frameworks critical for material, and polymer production and pharmaceutical development.[1,2] Azoles are a unique class of nucleophiles which are present in a variety of medicines ranging from cancer treatments to antimicrobial applications.[3,4] As such, methods for the incorporation of these moieties into molecules via aziridine ring openings have the potential to provide access to novel amino acid and nucleic acid derivatives. A major challenge in the preparation of these compounds lies in the simultaneous regioselective control of the nucleophilic azole nitrogen and of the electrophilic aziridine carbon. Prior works have used the tethering effect of an adjacent alcohol to activate epoxides or aziridines for regioselective ring opening with various nucleophiles including alcohols, thiols, and aromatic amines.[5–7] Within this work, regioselective ring openings of 2,3 tosyl-aziridyl alcohols with azoles was accomplished using diphenyl borinic acid or boron trifluoride. The ring openings gave moderate-excellent N and C regioselectivities using a variety of indazoles and pyrazoles. Furthermore, the reaction was also demonstrated to give good yields and selectivities for the ring opening of various aziridyl alcohol derivatives with azoles. This work reports a novel catalytic method of regioselectively functionalizing aziridyl alcohols with azoles providing facile access to novel drug-like compounds.

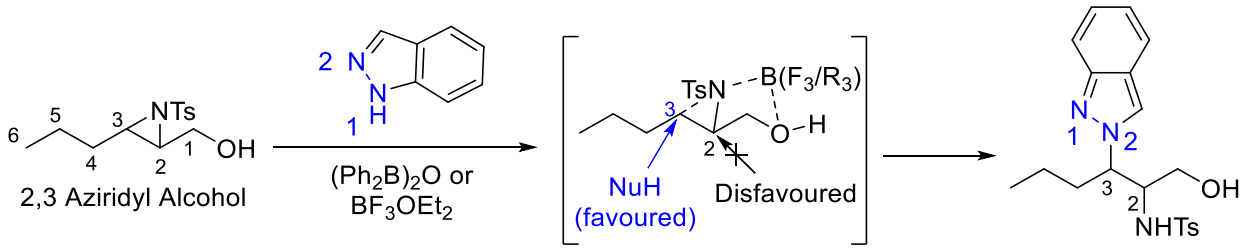


**Figure 1.** Representative scheme for ring opening of an aziridyl-alcohol with indazole.

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# TOWARDS THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF A NOVEL FUNGAL NRPS—PKS SECONDARY METABOLITE.

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Fungi represent an important resource for secondary metabolites with complex molecular architectures and bioactive properties[1]. In collaboration with Ariculture Agri-Foods Canada (AAFC), our investigations in the biosynthetic gene clusters of *Fusarium avenaceum* strains have revealed a novel macrocyclic hybrid polyketide synthase-nonribosomal peptide synthetases (PKS-NRPS) hybrid secondary metabolite. This novel metabolite has shown intriguing biological activity by modulating the plant immune response and holding potential as an agro-protective agent.

In this study, we explore a total synthesis of this natural product aimed at unambiguously elucidating its structure. While we have excellent 1D and 2D NMR data confirming the connectivity of the backbone, the absolute and relative stereochemistry is yet to be determined. Our initial model study examined routes to formation of the macrocyclic core and identified a diastereoselective macrolactamization between the amino acids residues that constitute the dipeptide backbone of the NRPS fragment as the optimal strategy for macrocyclization. Currently we are exploring a modular enantioselective approach to the construction of the PKS fragment, enabling us to access all the potential diastereomers. The completion of our synthesis will be described herein, with emphasis on how the flexibility of our strategy will enable practical on-route manipulations to characterize the stereochemistry of our target natural product.

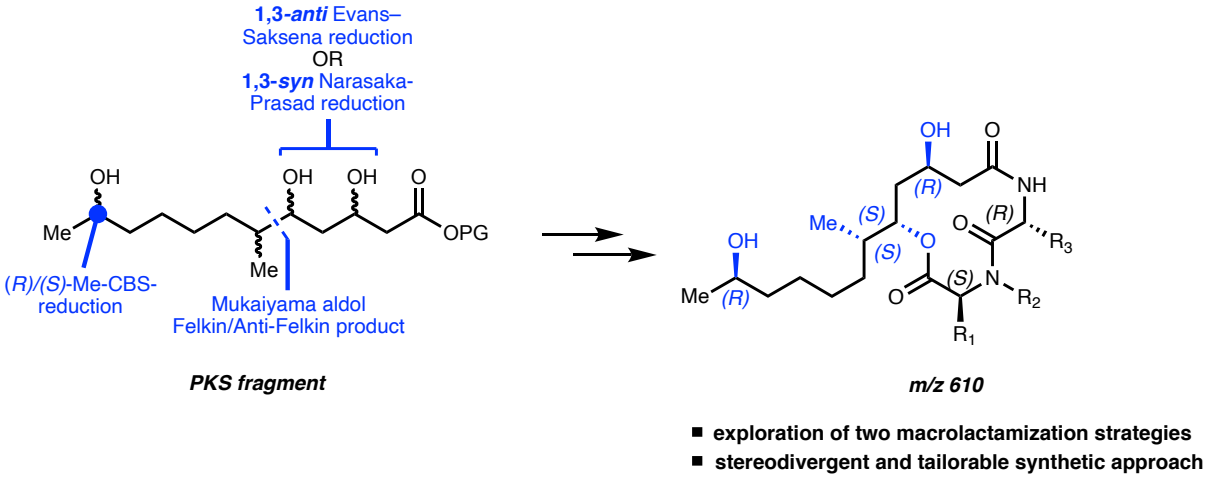


**Figure 1.** Synthetic strategy for a stereodivergent approach.

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# Multiple Targeting Ligands with Potent Anti-Parasitic Activity

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Neglected tropical diseases which are caused by trypanosomatid parasites present a major public healthcare issue [1]. Causing long-term disability and death, trypanosomatids infect over 20 million people globally each year [1]. Without effective vaccines, current treatments rely on chemotherapy [2]. Obstacles however, such as emerging drug-resistant parasites and host toxicity, undermine current therapy underscoring the exigency of new safe effective inexpensive medications [3].
Multiple targeting ligands represent a modern means to enhance therapeutic efficacy [4]. In a program targeting *Leishmania infantum* (*Ldi*)*, Trypanosoma (T.) brucei* and *T. cruzi* parasites, we are exploring conjugates of ribosomal and glycosomal inhibitors [5, 6]. Our dual targeting conjugates have exhibited potent activity, rivalling that of the parent ribosomal inhibitor especially against resistant strains. Moreover, our conjugates demonstrate superior antiparasitic efficacy compared to traditional drugs such as antimony, miltefosine, and pentamidine. Inhibition of parasite ribosomal and glycosomal function was indicated using thermal proteomic profiling. Moreover, the conjugate-ribosome complex has been elucidated using cryo-electron microscopy. Our findings have uncovered important structure-activity relationships for anti-parasite activity paving the way for novel therapy against trypanosomatid infections.

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# ENTHALPIC ANALYSIS TO IDENTIFY PREVIOUSLY UNKNOWN SMILES REARRANGEMENT VARIANTS

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This presentation will introduce a novel methodology for analyzing known reactions and predicting new ones, focusing on the concept of *enthalpic coupling*.[1] This approach simplifies reaction discovery by examining the energy changes associated with elementary bond-breaking and bond-making steps. By mapping the enthalpic profile of an elementary step, we propose that new reactions can be predicted through strategic modifications to enthalpically coupled components, allowing for targeted manipulation of reactions.

An application to show the utility of enthalpic coupling is explored in the context of the Smiles Rearrangement, an SNAr-type reaction that breaks and reforms C−X or C−C bonds in aromatic rings through ipso substitution. This rearrangement is highly versatile, enabling the functionalization of aromatic systems with a wide range of nucleophiles, leaving groups, and transition states. Despite its extensive use, there remains considerable potential for innovation and the discovery of novel reactivity patterns.[2]

In this work, we compile a comprehensive dataset of Smiles-type rearrangements, aiming to identify trends and patterns in current methodologies. Using a combinatorial computational approach, we explore enthalpic couplings between different nucleophiles and leaving groups, as well as varying aromatic groups and linkers. The goal is to predict favourable reaction pathways and decrease the trial-and-error approach to synthetically screening candidates. These predictions have then been experimentally validated to access new and innovative reactivity.

This talk will offer an overview of the enthalpic coupling concept, its application to the Smiles rearrangement, and how this strategy can lead to the discovery of new reactions, ultimately simplifying and streamlining the process of reaction discovery.

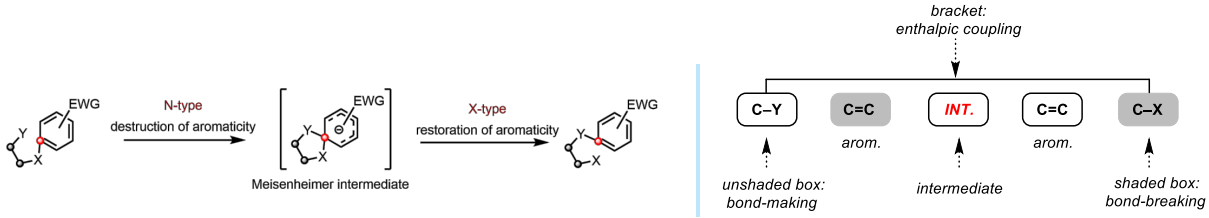


**Figure 1.** Enthalpic map of the Smiles rearrangement.

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# Hydrosilafluorenes as recyclable coupling reagents for direct amidation of carboxylic acids with amines

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Amides are responsible for the structural integrity of proteins, are an important component of synthetic polymers, and are present in half of the top 200 small molecule drugs sold in 2023.[1] For these reasons, amidation reactions are one of the most frequently performed reactions in chemistry. Current state-of-the-art routes to access amides are efficient, however, improvements can be made to the safety of reagents and atom economy to make the reaction more sustainable. In this regard, organosilanes are emerging as alternative amide coupling reagents because of their ease-of-handling and/or low toxicity of reagents/by-product.[2] With this in mind, we envisioned constraining an organosilane into a small-membered ring silacycle to make use of “strain-release Lewis acidity”. Silafluorenes 9-methyl-9H-9-silafluorene and 9-phenyl-9H-9-silafluorene were selected because the hydrosilanes are easier to handle (e.g., stable in open air) than the chlorosilane derivatives.[3] In this work, we have discovered both 9-methyl-9H-9-silafluorene and 9-phenyl-9H-9-silafluorene as effective reagents for direct amidation of carboxylic acids with amines. The protocol is performed under open-air conditions without rigorous exclusion of moisture, producing amides in high yields with only $H_2$ and disiloxane as by-products. The disiloxane by-product can be reduced in a separate step to recycle the silafluorenes.

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