Empowering Women in Organic Chemistry 2021

Poster Abstract Booklet

Abstracts listed alphabetically by last name

Poster Session 1: 4:00–5:00pm EDT, **June 24, 2021**
Poster Session 2: 5:00–6:00pm EDT, **June 24, 2021**

Information for Attendees

Each poster will have an assigned Zoom room by session. Session assignments are indicated at the top of each abstract page in this booklet.

Links to access the rooms will be provided to registrants via the conference landing page https://meetingtomorrow.com/event/ewoc2021/ or directly at https://meetingtomorrow.com/event/ewoc2021/poster-sessions. These pages are password-protected. The password will be provided to registered atteendees by email a few days in advance of the conference.

Select the room link(s) to visit the poster(s) of interest to you. You may come and go from the poster rooms as you please. In this virtual poster session format, we have encouraged presenters to use whatever format works best to present their work; in some cases, presenters may use several slides instead of the traditional static poster.

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ABRAHAM

Characterizing Release of Small Molecule Cargo from Phenylalanine-Derived Supramolecular Hydrogels

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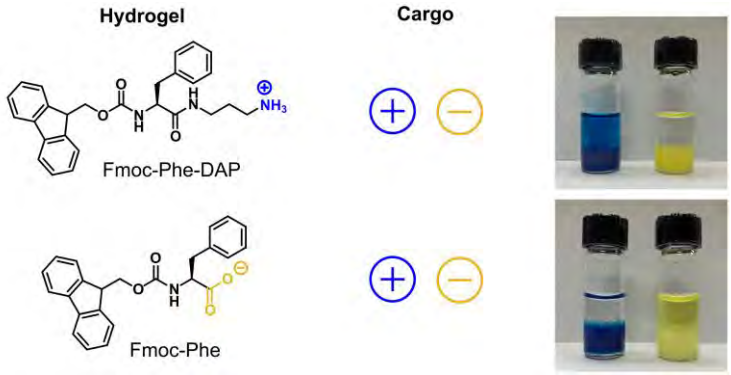
Supramolecular hydrogels, formed by the self-assembly of molecules into nanostructures that entangle in water to form a three-dimensional network, have shown promise as biomaterials for sustained drug delivery. Peptide-based hydrogels have attracted special interest because they are inherently biocompatible and are easily customized to impart desired functionality. However, bulk manufacturing of synthetic peptides is expensive, so low molecular weight (LMW) amino acid-derived gelators have been developed to address this problem while retaining some of the beneficial emergent properties of peptide-based materials. Recently, we demonstrated that modified fluorenylmethyloxycarbonyl-phenylalanine (Fmoc-Phe) derivatives form hydrogels suitable for *in vivo* sustained drug release.[1] The hydrogel, loaded with a nonsteroidal anti-inflammatory drug, acted as a reservoir for localized and sustained release in a mouse model to mitigate pain for nearly two weeks. To further understand the interactions between cargo and the hydrogel network, we characterized the release of cationic, neutral, and anionic small molecules from both cationic and anionic supramolecular hydrogels.[2] Cargo that was neutral or of the same charge as the gelator were released at similar rates, but cargo in hydrogels with complementary charge was highly retained. These results highlight the importance of considering electrostatic interactions between the cargo and LMW gelator when designing supramolecular hydrogel systems for drug delivery.



Acknowledgements: This work was supported by the National Science Foundation (DMR-1148836), the National Heart, Lung, and Blood Institute of the National Institutes of Health (R01HL138538), and a University of Rochester University Research Award. BLA was supported by a University of Rochester Robert L. and Mary L. Sproull Fellowship. We gratefully acknowledge Karen Bentley at the URMC Electron Microscope Shared Resource for her assistance in TEM imaging experiments.

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AHMED

Investigating The Mechanical and Photodynamic Behavior of Two Schiff Base Derivatives

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Organic crystals that absorb light, have potential use in various applications such as light emitting diodes[1], organic sensors[2,3] and solid lasers.[4] Furthermore, because many organic crystals also show mechanical flexibility, they can be used in applications such smart materials and actuators.[5]

Schiff bases are a class of organic materials that can display photochromism upon irradiation, through excited state intramolecular proton transfer (ESIPT). In more details, irradiation of Schiff bases with UV light, can switch their enol form, which is yellow in color, to their keto tautomer, which absorbs at longer wavelengths and displays reddish color. In here, we investigated the mechanical and the photodynamic behavior of two rod-like N-salicylideneanilines Schiff base crystals, one with halogen substitution, A, and the other without any halogens B. The halogen-halogen interactions on the crystal packing and the intermolecular interactions, affect the crystal response to mechanical stress or UV light irradiation. The two crystals showed elastic mechanical response to a different extent. Interestingly, crystal A moved away from the 365 nm UV source upon irradiation, whereas crystal B failed to show any photodynamic response. To explain their different behaviors, we used single crystal X-ray structure analysis, the crystal packing arrangement, and calculated total intermolecular interactions in the crystals using CrystalExplorer.17 software.

Acknowledgement: Support for this research is provided by the National Science Foundation CHE-1800140.

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AKANDE

Some Menispermaceae species have dual effects against *Mycobacteria sp* and *Caenorhabditis elegans*

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In tuberculosis (TB)/helminth coinfection, studies reveal that an indication of helminth infections in experimental conditions and human infection, can lead to increased immune responses (T helper (Th)2 and T regulatory cells)[1]. This in turn impairs Th1 cell development, and results in pathogenesis of TB. Some Menispermaceae plant species are used locally for tuberculosis and helminth infections[2]. The antibiofilm and antihelminthic effect of extracts of *Cissampelos owariensis*, *Cissampelos mucronata* and *Tinospora fragosa* was investigated. Based on previous preliminary investigation, the minimum inhibitory concentration, antibiofilm inhibition and dispersal effects of the acetone extracts of *C. owariensis*, *C. mucronata* and *T. fragosa* and hot water extract of *C. mucronata* against *Mycobacterium smegmatis* mc^2 155 was evaluated. The minimum inhibitory concentration was evaluated using a two-fold serial dilution method. The antibiofilm effect was evaluated using a modified crystal violet method. The anthelmintic effect was evaluated against *Caenorhabditis elegans* in a mortality assay. The extracts had good to poor antimycobacterial activity with minimum inhibitory concentration between 0.06 – 2.5 mg/ml. The extracts had strong antibiofilm inhibitory effect between 91.45 - 100% and potent dispersal effects between 13.30 - 46.59%. *Cissampelos mucronata* leaf (hot water extracts) exhibited the most potent antihelminthic effect at 1 and 2 mg/ml after 24 and 48 h. This study reveals that Menispermaceae species might be a good source of phytochemicals effective against agents of TB and parasites and potentially against their co-morbidities.

Acknowledgement: Support for this study is provided by Phytomedicine programme, University of Pretoria

ALAM

[1,3]-Claisen Rearrangement via Removable Functional Group Mediated Radical Stabilization

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A thermal O- to –C [1,3]-rearrangement of α-hydroxy acid derived enol ethers was achieved under mild conditions. The 2-aminothiophenol protection of carboxylic acids facilitates formation of the [1,3] precursor and its thermal rearrangement via stabilization of a radical intermediate. Experimental and theoretical evidence for dissociative radical pair formations, its captodative stability via aminothiophenol, and a unique solvent effect are presented. The aminothiophenol was deprotected from rearrangement products as well as after derivatization to useful synthons.

The thermal [1,3]-rearrangement of O-alkyl enolates was first described by Claisen in 1896 [i] well before the famous [3,3]]-Claisen sigmatropic rearrangement in 1912.[ii] The [1,3]-rearrangement is theoretically a similar waste-free transformation. Despite that only a handful literature reports with very high temperature requirements, narrow substrate scopes, and often poor yields. Thus far, formal [1,3]-rearrangement have generated much controversy over the year due to its lack of generality with radical, ionic, and concerted mechanistic possibilities.

In this context, we describe herein an inexpensive, stable, and naturally abundant α-hydroxy acids were converted to 2-aminothiophenol derived enol ether precursors for their thermal [1,3]-rearrangements under mild conditions. A highly electron rich enol ether led to a facile radical stabilization [1,3]-rearrangement. The transformation useful for both alkyl and aryl α-hydroxy acids and a large variety of migrating group with good and excellent yields. The reaction mechanism and its efficiency are supported by both experiments and computations. [iii]

Acknowledgements: This research was supported by the SERB (EMR/2015/000711 and CRG/2019/001065). Md.N.A. thanks UGC for a fellowship. The support from centralanalytical facility, NCL is greatly acknowledged. The support and the resources provided by "PARAM Brahma Facility" under the National SupercomputingMission, Government of India at the Indian Institute of Science Education and Research (IISER) Pune are gratefully acknowledged.

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ALEKTIAR

Thiol-Catalyzed Radical Chain Alkene Hydrocarboxylation

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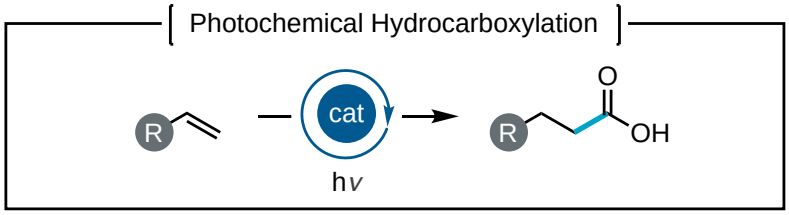
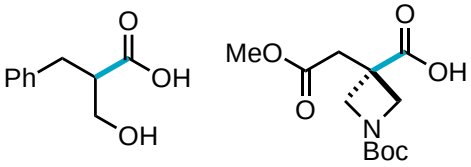
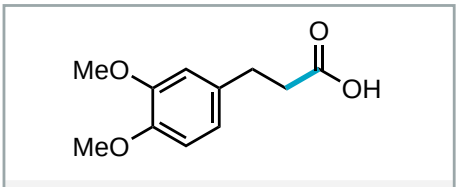
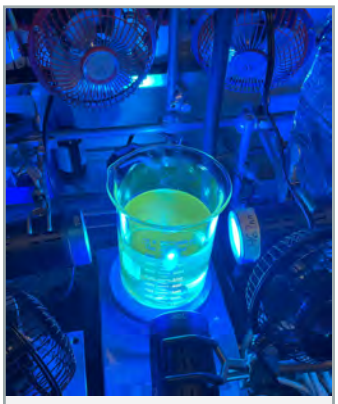
Linear carboxylic acids are widely represented in natural products, pharmaceuticals, and commodity chemicals and are basic building blocks for organic synthesis. However, despite major advances in other areas of alkene functionalization, selective synthesis of linear carboxylic acids remains a major challenge. Herein we disclose a new photocatalytic alkene hydrocarboxylation strategy that relies on a cheap and user-friendly C1 source. This transformation proceeds in high yield with exquisite selectivity for the linear, mono-carboxylation product, and is readily scalable (up to 50 mmol in batch).







Application towards drug synthesis



50 mmol scale

ARORA

N–Heteroaromatics with Thermally Generated Benzynes: Pathway and Product diversity

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Nitrogen heterocycles (*N*–heterocycles) are among the most significant structural components of today's pharmaceuticals. According to a report from the Journal of Medicinal Chemistry, 84% of the drugs available in the current market have at least one nitrogen atom present in them. [1] More significantly, 59% of the total FDA-approved drugs contain at least one nitrogen heterocycle. These data are compelling and motivate a chemist to creatively develop numerous synthetic strategies that can be used for (i) construction of new *N*-heterocycles from simple starting materials and (ii) functionalization of known *N*-heterocycles. My PhD thesis research has been guided by these two ideas. In my quest to achieve these goals, I have been using a reaction as a tool, which is called the hexadehydro-Diels–Alder (HDDA) reaction (**1** to **2**, Fig. **1**).[2] This reaction is a valuable new variant of the Diels–Alder reaction, which is found in every introductory organic chemistry textbook. The HDDA reaction operates in a purely thermal (and, therefore, milder) environment to generate benzynes, which are one of the most reactive intermediates in organic chemistry. Because of their highly reactive nature, benzynes have extremely high potential energy and, thus, can be used to trap (i.e., react) with a wide variety of reagents. In this session, I will present novel variations of the HDDA reaction with nitrogen containing trapping agents.[3] In addition to unfolding novel reaction mechanisms, this methodology can quickly assemble structurally complex and diverse heterocycles in relatively fewer steps.

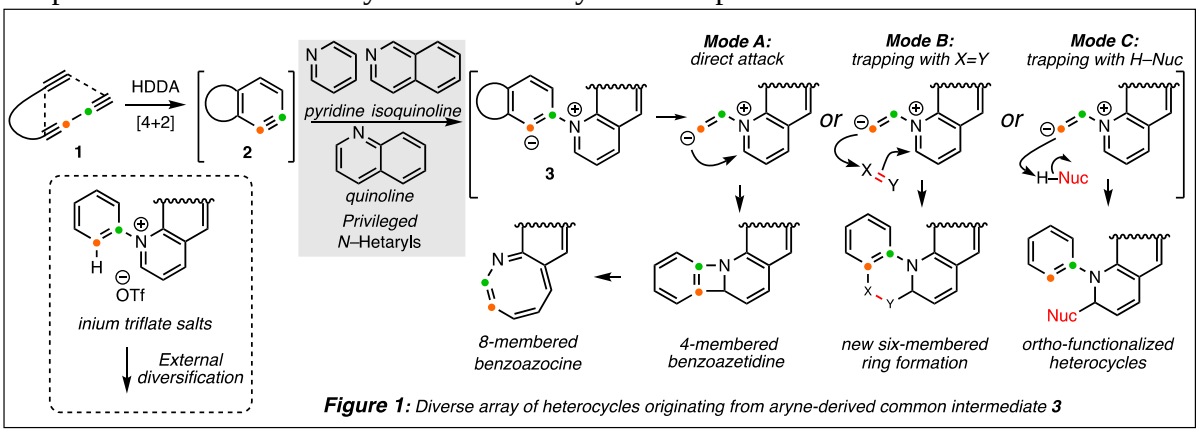

Figure 1: *Diverse array of heterocycles originating from aryne-derived common intermediate* ***3***

Acknowledgements: This work was supported by the National Institute of General Medical Sciences of the U.S. Department of Health and Human Services (R35 GM127097).

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BADMUS

Brønsted Acid-Catalyzed Syntheses of Highly Functionalized Tetrahydrobenzofurans, Tetrahydroindoles and Tetrahydrocyclopenta[b]pyrroles via Silyloxyallyl Cations

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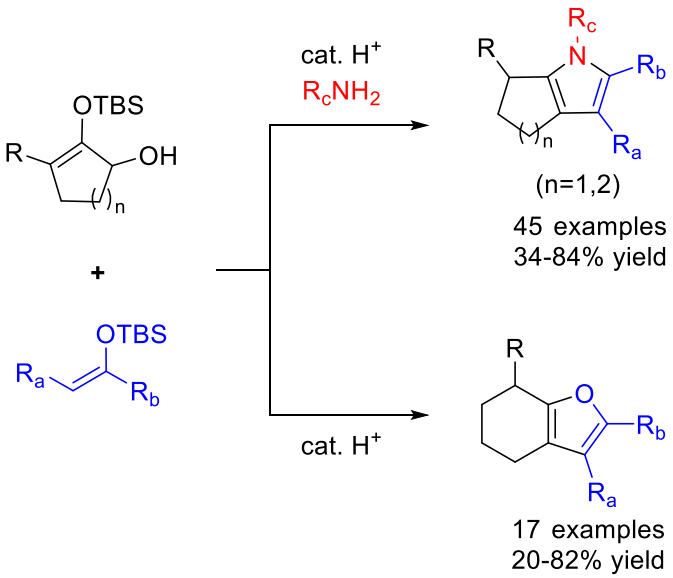
Tetrahydrobenzofurans, tetrahydroindoles and tetrahydrocyclopenta[b]pyrroles are classes of heterocycles which can be found as components in naturally occurring and synthetic compounds of great biological importance. As a result, the need to develop synthetic methods that readily construct these compounds remains an important research endeavor in the synthetic community. Established synthetic methods towards tetrahydroindoles and tetrahydrocyclopenta[b]pyrroles rely on linear preconstruction of the substrates prior to cyclization, consequently preventing the introduction of a vast array of functionalities to these rings. Also, previous approaches to tetrahydrobenzofuran centered on the assembly of the six-membered ring and require furan-derived substrates as one of the starting materials. To contribute to this cause, we have developed a unified strategy which focus on the assembly of the heterocyclic core and allow for the incorporation of broad range of functionalities to the heterocyclic rings. More specifically, our method highlights cascade cycloaddition reactions that are enabled by unsymmetrical silyloxyallyl cation intermediates that are generated under Brønsted acid catalysis, followed by Paal-Knorr cyclization. Our method is operationally simple, robust and is tolerated by a broad scope of substrates.



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BAGUE

Natural Product FR900098 Analogs as Small Molecule Inhibitors for the MEP Pathway

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In *Mycobacterium tuberculosis (Mtb)* and *Plasmodium falciparum (Pf),* the methylerythritol phosphate (MEP) pathway is responsible for isoprene synthesis. The process and its products are vital to bacterial/parasitic metabolism. This pathway represents an attractive set of drug targets due to its essentiality in these pathogens but non-essentiality in humans. The second step in the MEP pathway is the conversion of 1-deoxy-D-xylulose-5-phosphate (DXP) to MEP and is catalyzed by 1-deoxy-D-xylulose-5-phosphate reductoisomerase (Dxr). Natural products fosmidomycin and FR900098 inhibit Dxr, however they lack the required lipophilicity to reach the desired target inside the cell. Synthesized FR900098 analogs with lipophilic substitution in the position α to the phosphorous atom showed promise, resulting in increased activity against *Mtb* and *Pf*. An α substitution, consisting of a 3,4-dichlorophenyl substituent, in combination with various *O*-linked alkylaryl substituents on the hydroxamate moiety is strategically utilized in the synthesis of a novel series of FR900098 analogs. The purpose of the *O*-linked alkylaryl substituents is to further enhance Dxr inhibition by extending into the bi-substrate NADPH binding pocket, thus blocking the binding of NADPH. This series of FR900098 analogs includes diammonium salts and both diethyl and dipivaloyloxymethylene (POM) prodrug esters. Data from these compounds suggest that this combination of substituents is advantageous in designing a new generation of antimicrobials.

Acknowledgements: Support for this research is provided by the NIH AI123433 and The George Washington University Chemistry Department.

BAILEY

Cyclopentadienone–Norbornadiene Diels–Alder Adducts as Photo-protected Cyclopentadiene for On Demand, Spatially Controlled Click Chemistry

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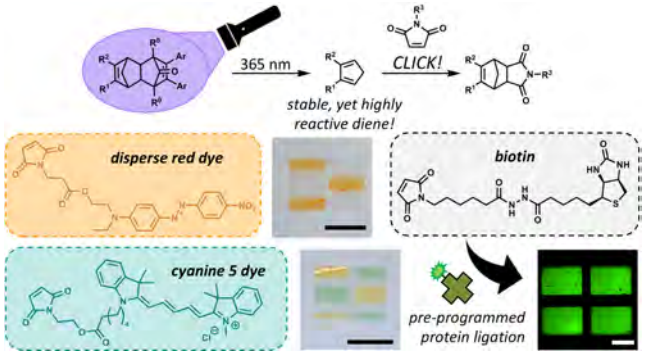
Diels–Alder (DA) cycloadditions are a distinguished click chemistry that have been extensively employed throughout organic synthesis, materials science and bioconjugation; however, the reactivity of the diene and dienophile is critical for utility in click conjugation platforms. For normal electron demand Diels-Alder reactions, cyclopentadiene (Cp) is one of the most reactive diene choices; however, its inherent instability has prevented its widespread use in click applications within polymers or biomaterials. Methods to harness the high reactivity of Cp – such as with steric groups or by chemical deprotection of norbornadiene precursors – have been developed to expand its utility. To add to this toolbox of Cp harnessing strategies, we present the of photo-induced unveiling of Cp to allow for subsequent, spatially controlled click DA reactions. The photo- and thermally induced loss of carbon monoxide from cyclopentadienone–alkene DA adducts is well-known[1] and has been used in the preparation of substituted benzenes[2] and, more recently, in CO-releasing drug molecules.[3] We demonstrate that by utilizing norbornadiene as the alkene, the photo-induced de-carbonylation event is followed by a retro-DA cleavage to afford Cp on demand, which can then be used in follow-up DA click reactions. A series of cyclopentadienone–norbornadiene adducts were prepared and exploited for selective, photo-patterned conjugation of maleimide-functionalized dyes and biomolecules within polymer networks.



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BENTZ

Design, Synthesis, and Characterization of Self-Assembling Nucleoside Phosphoramidate Hydrogels

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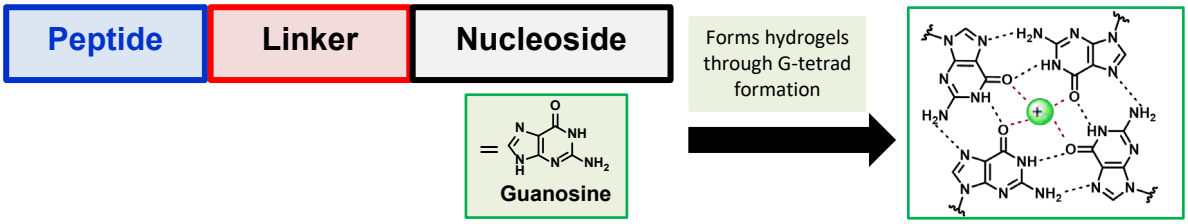
Self-assembling nucleoside phosphoramidates are low molecular weight molecules that incorporate a short self-assembling peptide conjugated to a nucleoside phoshoramidate moiety through a short PEG linker. In this work, we investigate their assembling properties and characterize how different regions of the molecule contribute to assembly. After synthesizing and characterizing a panel of self-assembling nucleoside phosphoramidates with varying nucleobases, our studies have revealed that the identity of the nucleobase plays a key role in defining gelation capability of self-assembling nucleoside phosphoramidate nanofibers. Specifically, we have discovered the unique ability of our guanosine self-assembling nucleoside phosphoramidate to form supramolecular hydrogels in PBS buffer, as a product of ionic screening in higher salt concentrations and G-tetrad formation resulting from Hoogsteen hydrogen bonding patterns. Further, we demonstrate the application of these novel biomaterials for controlled drug release.



BERCHER

Deaminative Reductive Methylation of Alkylpyridinium Salts

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Alkyl amines are highly versatile, widely abundant feedstock chemicals. The ease in which they can be carried throughout multistep syntheses make them a highly sought-after candidate for further functionalization. Recently, we have discovered a powerful transformation of alkyl amines via the carbon–nitrogen (C–N) bond mainly to form $C(sp^3)$–$C(sp^2)$ bonds. Due to the high degree of saturated carbon–carbon bonds in bioactive molecules, methods to form alkyl–alkyl bonds have become highly desirable. We recently developed a nickel-catalyzed cross-coupling of Katritzky's alkylpyridinium salts and alkylzinc halides to create new $C(sp^3)$–$C(sp^3)$ bonds. Notably, this method provides a method to transform a simple amine into a methyl group. However, the harsh conditions limited the functional group tolerance including radiolabeled ^{11}C. Inspired by overcoming these limitations, we have now developed a reductive cross-coupling utilizing alkylpyridinium salts and a simple methylating agent. By providing an accessible route to install methyl groups, this method enables our collaborator, Zibo Li at the University of North Carolina Chapel Hill, for the radiolabeling of bioactive compounds which are used to detect and measure molecular interactions through positron emission tomography (PET). The optimization, scope and mechanistic understanding of this transformation will be presented.

BERGER

Aliphatic Primary Amine "Deletion" using an Anomeric Amide Reagent

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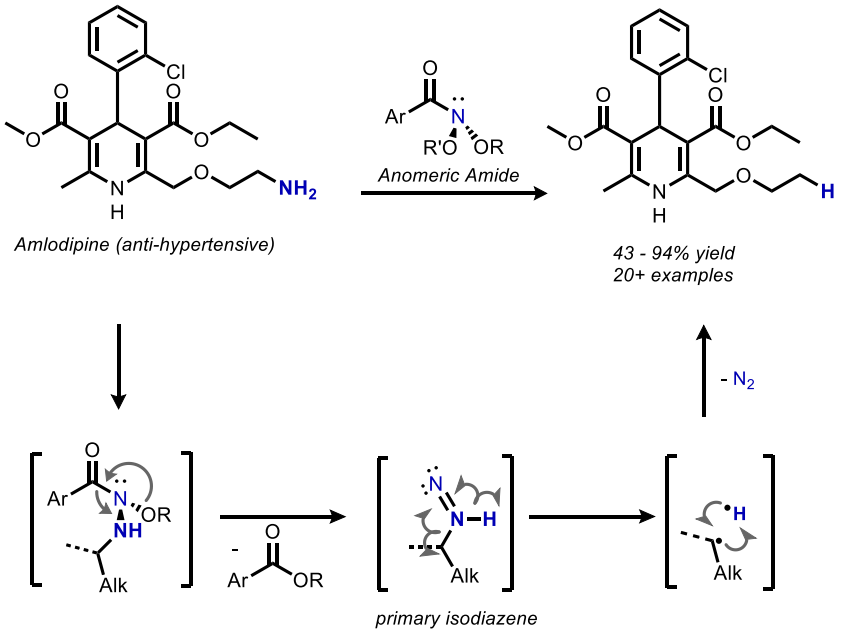
Primary aliphatic amines are prevalent in pharmaceuticals and natural products. However, their poor leaving group character renders diversification through C-N cleavage challenging. Accordingly, pre-functionalization by conversion to a Katritzky-type pyridinium salt is typically required in order to perform deaminative substitution chemistry.[1] Moreover, existing strategies for reductive deamination of amines to alkanes require forcing conditions and suffer from low yields and functional group tolerance. We report a facile method for direct aliphatic deamination (without pre-functionalization) which exhibits a remarkable substrate scope.

Our group has recently reported that anomeric amide reagents react with secondary amines to yield isodiazene intermediates, which rearrange to lose dinitrogen and produce two alkyl radicals that recombine, resulting in the net "deletion" of the amine.[2] Primary amines undergo an analogous reaction with anomeric amides, resulting in their "deletion" to alkanes by way of primary isodiazene intermediates, a previously unknown reactive intermediate. This reaction proceeds rapidly under mild conditions and can be utilized for late-stage deamination of a variety of bioactive molecules.



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BEZOLD

Potential novel small molecule inhibitors of mPGES-1

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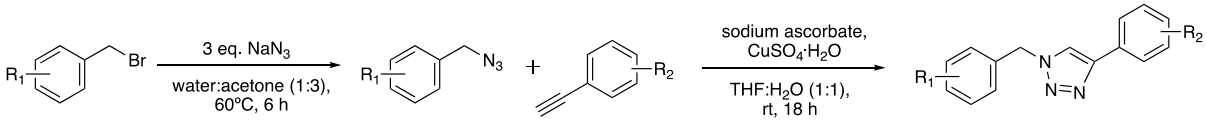
NSAIDs/coxibs are the most commonly used medications for the mitigation of pain and inflammation. NSAIDs provide relief through the inhibition of COX-1 and COX-2, while coxibs selectively inhibit COX-2. The long-term use of NSAIDs/coxibs is limited, as they have been shown to possess serious gastrointestinal and cardiovascular side effects; and the severity of the cardiovascular side effects forced several drugs to be pulled from the market. These severe cardiovascular events are now linked to the inhibition of COX-2-mediated PGI_2.[1] Thus, the inhibition of mPGES-1 has become a popular target as it selectively inhibits PGE_2 (a lipid mediator of inflammation) without inhibiting PGI_2. Despite the fact that highly potent and selective inhibitors have been developed, only a few have advanced to clinical trials.

We began to synthesize analogues that contain a 1,2,3-triazole functional group based on the hypothesis that these molecules would have a greater binding affinity in the mPGES-1 active site compared to previously synthesized molecules. The key synthetic step involves a copper-catalyzed modified Huisgen 1,3-dipolar cycloaddition between the appropriate alkyne and azide intermediates.[2] The copper-catalyzed cycloaddition is an example of "Click Chemistry" as it is a reaction that is high yielding, wide in scope, regiospecific, simple to perform, and conducted in aqueous conditions usually at room temperature.[3] In addition to the synthesis, we have performed molecular docking studies on the analogues, which show that the best docked molecules contained a shorter carbon linkage between the aryl groups as well as fluoro-substituents on the rings (Scheme 1). Lastly, we are currently testing the mPGES-1 inhibitory activity of our novel compounds using microsomes of A549 cells.[4] Correlation of docking scores and biological results will allow us to apply an iterative SAR-driven approach to develop and optimize lead compounds in order to obtain a selective and potent mPGES-1 inhibitor.



Scheme 1

Acknowledgements: Support for this research is provided by KY INBRE (Kentucky IDeA Networks of Biomedical Research Excellence) NIGMS grant # 8P20GM103436 and the College of Arts & Sciences at Northern Kentucky University.

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BHATTACHARJEE

Modular Synthesis Towards Designer Anion Binding Receptors

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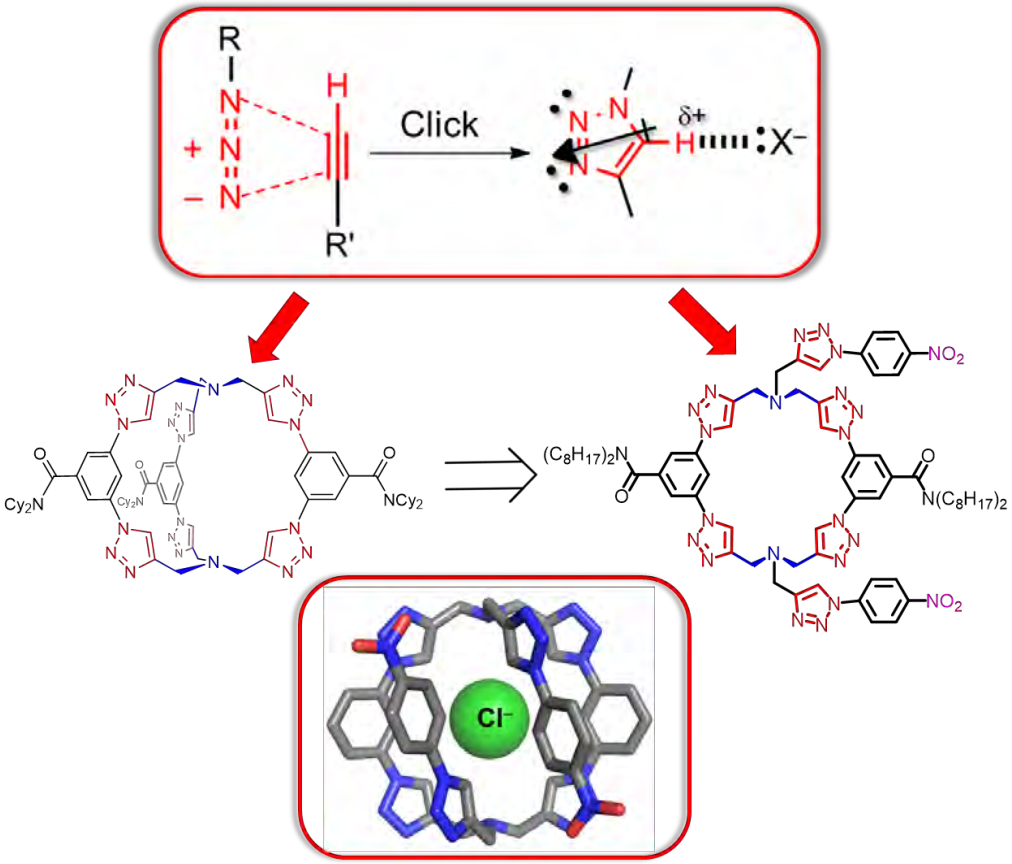
The creation of synthetic receptors with high affinity and selectivity is required for the effective management of anions in modern society. This need has attracted chemists to design and synthesize receptors and to learn the rules governing anion recognition. To this end, we demonstrate a new class of anion receptor developed using a modular synthetic strategy involving click chemistry. Inspired by the attomolar binding behavior of the CH hydrogen bonding triazolo cage[1] we outline a modular synthesis for the development of a structurally novel receptor that rely on a common structural motif. This work also establishes the anion recognition properties of selective and high affinity receptors named triazolo cones. The cones are designed by disconnecting one of the cage's three linkages leaving a flexible macrocycle bearing two triazole-based arms. The chloride binding strength is correlated with the degree of preorganization relative to more and less rigid analogs. Structurally, the cones lay the groundwork for the development of anion receptors that can be modified with a variety of functional units to achieve high affinity and novel functions.



Acknowledgements: Support for this research is provided by the US Department of Energy (DOE).

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BRAY

Synthesis of Small Molecules for Protein Control

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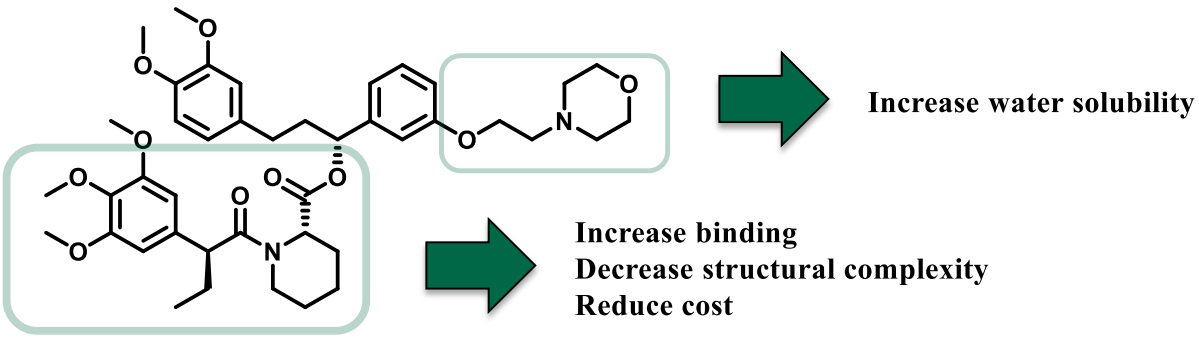
The treatment of infectious diseases is of the utmost importance in modern society. To treat infectious diseases, one must understand the way the disease functions. Toxoplasmosis is a disease caused by *Toxoplasmosis gondii*, a protozoan parasite that infects more than 60 million people in the world chronically and is listed by the CDC as one of five Neglected Parasitic Infections. Although symptoms commonly manifest as asymptomatic, immunocompromised people are at high risk for severe symptoms such as blindness, death, etc. The protozoan lifecycle goes through dormant and active phases controlled by specific genes in the parasite. Although treatment in the active phase can be done with current medicines, the dormant phase of the parasite is a lifelong infection with no treatment or cure. Shield-1 is a small molecule that has been used for protein control in biological systems. In this study, we have developed and synthesized novel analogs of Shield-1 to study transcription factors of the parasite designed to improve their pharmacokinetic properties with an eye toward in vivo utilization.



Acknowledgements: Support for this research is provided by the NIH under Grant No. R01AI124682.

BUCHHOLZ

Chemical Probe Development for BPTF Reader Domains Utilizing Biophysical Assays

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Abstract: In many disease states there is a dysregulation in gene expression, which can be driven by the aberrant levels or function of epigenetic protein complexes. One such epigenetic protein dysregulated in numerous cancers is the bromodomain and PHD-finger containing transcription factor (BPTF), which binds to chromatin via interactions with acetylated histone (H4K16ac) through its bromodomain and trimethylated histone (H3K4me3) through its C-terminal PHD finger to facilitate chromatin remodeling.[1] This is in part via protein-protein interaction with the oncoprotein c-MYC.[2] Together, this makes BPTF a promising anti-cancer therapeutic target. Although evidence supports the role of the BPTF protein in disease, the relevance of its individual domains is unclear. In order to study disease function of each BPTF reader domain it will be advantageous to design selective probes for each. Currently, there are several reported BPTF bromodomain inhibitors,[3] but there is a significant need for improved potency and selectivity to develop useful chemical probes. In our lab we have a promising new pyridazinone scaffold with improved potency for BPTF and selectivity over the BET family of bromodomains (>350-fold). We have utilized Protein-Observed Fluorine (PrOF) NMR, AlphaScreen, and x-ray crystallography to rationally design and expand the pyridazinone scaffold into a potent lead against the BPTF bromodomain (IC_{50} = 70 nM) that has shown preliminary on-target effects in synergistic cellular studies with chemotherapeutics. For the BPTF PHD finger, there are no reported small molecule binders. Recent progress in our lab towards assessing the ligandability of the PHD finger by computational analysis, as well as method development for future NMR-based fragment screening will also briefly be discussed.

Acknowledgements: Support for this research is provided by the National Institute of General Medical Sciences MIRA award R35 GM140837-01 and the National Institutes of Health Chemistry-Biology Interface Training Grant 5T32GM132029-02.

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BUTMAN

Design and Synthesis of Compounds to Inhibit CoA Biosynthesis as Novel Antimicrobials

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The increase in multidrug-resistant pathogens due to the overuse of antibiotics, as well as the lack of development of novel therapeutics, has presented an urgent need for the discovery of next-generation antibacterial agents. The biosynthesis of the enzyme cofactor coenzyme A (CoA) has long been known to be essential in both prokaryotes and eukaryotes due to its fundamental role in central metabolism. The lack of sequence similarities between microbial and mammalian CoA biosynthetic pathways makes microbial CoA biosynthesis an attractive set of targets for drug development. In bacteria, CoA precursor pantothenate (Pan) is synthesized by PanB, PanC, PanD, and PanE. In the second stage, Pan is converted to CoA in five enzymatic steps catalyzed by four proteins – PanK, CoaBC, CoaD, and CoaE. It was recently shown that, of all the enzymes in the CoA pathway, depletion only of CoaBC resulted in bactericidal activity, while depletion of the remaining enzymes was merely bacteriostatic. This leads to the hypothesis that inhibitors of CoaBC will disrupt CoA biosynthesis and kill bacterial cells. CoaBC is a bifunctional protein that harbors the enzymatic activities of both phosphopantothenoylcysteine synthetase (PPCS) and phosphopantothenoylcysteine decarboxylase (PPCDC), the second and third steps in the biosynthesis of CoA. Together, these activities catalyze the transformation of 4'-phosphopantothenic acid (P-Pan) into 4'-phosphopantetheine (P-PantSH), the precursor of CoA. This reaction proceeds through formation of the reactive intermediate, 4’-phosphopantothenoyl-CMP (Pan-CMP). Our work sets out to design, synthesize, and evaluate an array of Pan-CMP mimetics as inhibitors of CoaBC. These compounds have the potential to chemically validate CoaBC as a new antibacterial drug target and serve as lead compounds toward novel inhibitors.

CACIOLLA

Naturally inspired flavonoid-based inhibitors of aromatase

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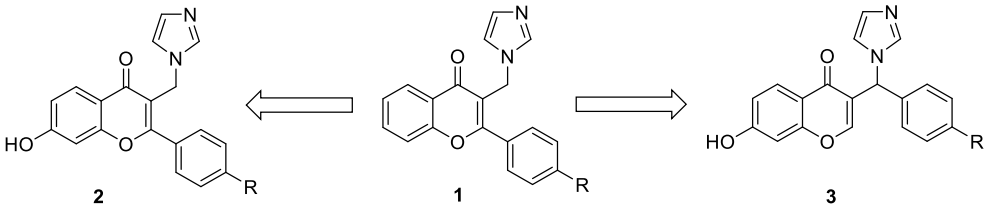
One of the current strategies to fight estrogen dependent breast cancer (BC) is based on estrogens deprivation obtained with the inhibition of cytochrome P450 aromatase (AR), key enzyme for their biosynthesis or by administration of selective estrogen receptor modulators (SERMs).[1] Despite the effectiveness of these targeted therapy, some issues regarding compliance with side effects and development of resistance to available drugs still need to be addressed. Recently the multitarget approach, i.e. the design of a single molecule able to interact with multiple targets involved in the same disease, has become one of the most investigated therapeutic strategies for the treatment of complex multifactorial pathologies, such as BC.[2] Our research group has been involved for years in the design and synthesis of AR inhibitors, and a series of imidazolyl-flavone derivatives proved to be very potent AR inhibitors (1, Figure 1).[3] The flavone scaffold is a well-recognized privileged structure, able to engage different targets when properly decorated.[4] A new series of properly substituted flavon- (2, Figure 1) and homoisoflavon-based derivatives (3, Figure 1) was then designed and synthetized, aiming to act both as AR inhibitors and SERMs. The compounds were prepared applying the Baker-Venkataraman rearrangement followed by an acid catalysed cyclodehydration and a Claisen condensation in selected reaction conditions in order to obtain the desired isomer, identified via an NMR study.



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CHEANG

New Methods for Stereocontrol in Hydrogen Borrowing Catalysed Enolate Alkylation

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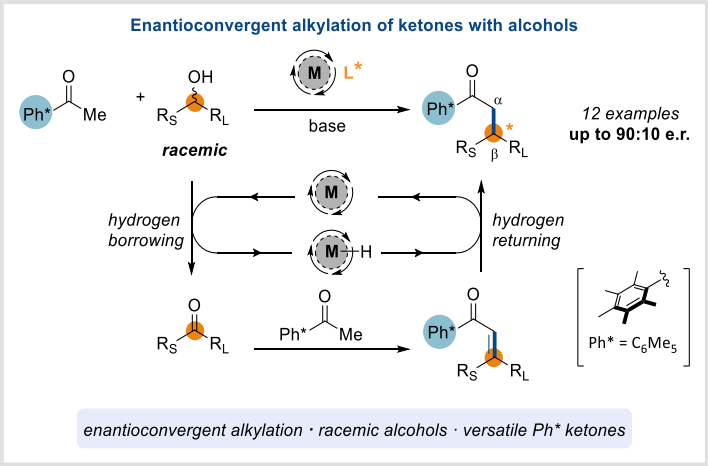
Hydrogen borrowing catalysis has recently emerged as a powerful strategy for C–C bond formation and represents a green alternative to typical alkylation methodologies,[1,2] One of the principal advantages of this methodology is that alcohols can be employed directly as electrophiles, negating the synthesis the corresponding halide (or pseudohalide), and therefore producing water as the sole byproduct.[3,4] However, despite numerous advances in this field, no general methods have been reported to control the absolute stereochemical outcome of the process.



We describe a solution to this challenge in the form of an iridium catalyzed enantioconvergent synthesis of β,β-disubstituted ketones.[5] Using commercially available [Ir(cod)acac] and (*R*)-DTBM SEGPHOS, this process is able to efficiently form sterically hindered C(sp^3)–C(sp^3) carbon bonds in excellent yields. The key step of this methodology involves asymmetric reduction of an isomerically pure acyclic enone, a process which proceeds in excellent yields and with high levels of enantioselectivity. Furthermore, the β-substituted ketone products were readily cleaved to a wide range of functional groups *via* retro-Friedel-Crafts acylation without any racemization of the newly installed stereogenic centre.

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CHEN (DORIS)

Intramolecular interrupted formal homo-Nazarov cyclization using tethered (hetero)arenes: Facile access to fused carbocycles and heterocycles

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The formal homo-Nazarov reaction (ring-opening cyclization of alkenyl cyclopropyl ketones) is recognized as a practical and versatile method for the construction of carbocyclic and heterocyclic scaffolds seen in a broad range of biologically active natural and synthetic compounds. Herein, we disclose the first example of an intramolecular interrupted formal homo-Nazarov cyclization involving alkenyl cyclopropyl ketones with tethered (hetero)arenes. Using catalytic $SnCl_4$, these alkenyl cyclopropyl ketones undergo ring-opening cyclization to form six-membered cyclic oxyallyl cations which are immediately trapped by the tethered (hetero)arenes in a Friedel-Crafts-type arylation to access fused polycyclic scaffolds, such as the naturally-occurring abietane skeleton. This highly amendable oxyallyl intramolecular trapping protocol provides facile access to natural product-based and medicinally-relevant polycyclic cores in a single step transformation while utilizing mild reaction conditions.

CHEN (TIFFANY)

Ligand-to-Copper Charge Transfer: A General Catalytic Solution to Aromatic Decarboxylative Functionalization

*Tiffany Q. Chen,[1] P. Scott Pedersen,[1] Nathan W. Dow,[1] Remi Fayad,[2] Cory E. Hauke,[2] Michael C. Rosko,[2] Evgeny O. Danilov,[2] David C. Blakemore,[3] Anne-Marie Dechert-Schmitt,[3] Thomas Knauber,[3] Felix N. Castellano,[2] David W. C. MacMillan[1]**

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Aryl carboxylic acids are versatile, bench-stable, and widely abundant functional handles in organic synthesis. Historically, their activation with established two-electron methods has required forcing conditions, rendering such protocols limited in scope. In contrast, we envisioned that copper's ability to generate open-shell species through ligand-to-metal charge transfer (LMCT), combined with its unique capacity to act as a potential aroyloxy and aryl radical reservoir, could mediate facile light- and copper-enabled aromatic decarboxylative functionalization by mitigating undesired reactivity of radical intermediates formed during aromatic decarboxylation. We report herein a general copper-LMCT open-shell activation platform for aromatic halodecarboxylation. Catalytic decarboxylative chlorination, bromination, and iodination of diverse (hetero)aryl carboxylic acids have been achieved to provide broadly used electrophilic cross-coupling handles from widely available aromatic acid precursors. Notably, decarboxylative fluorination of aryl carboxylic acids – a long-standing challenge in the field of organic synthesis – is readily accessible over a wide breadth of (hetero)aryl substrates. Ultrafast transient absorption (TA) spectroscopy experiments in combination with steady-state UV-vis spectroscopy studies are consistent with the proposed copper-LMCT mechanism, supporting the mechanistic basis of this activation platform.

Acknowledgements: The authors are grateful for financial support provided by the National Institute of General Medical Sciences (NIGMS), the NIH (under Award R35GM134897-01), the Princeton Catalysis Initiative, BioLec, an Energy Frontier Research Center (U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences, under Award DE-SC0019370), and kind gifts from Pfizer, Merck, Janssen, Bristol-Myers Squibb, Genentech, and Celgene.

CHIU

Photomodulation of Polymer Dispersity

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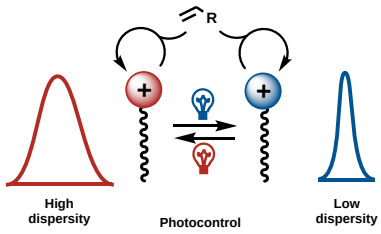
Departing from a historical focus on synthesizing polymers with low dispersity, access to broad dispersities and the ability to deliberately manipulate polymer dispersity are promising means of tailoring a polymer's material properties without changing its chemical structure. The dearth of methods for tuning polymer dispersity therefore poses a significant challenge in polymer chemistry, especially with respect to expanding these capabilities beyond radical polymerizations and enabling dynamic regulation of dispersity. To address these challenges, we developed photoswitchable Bronsted acid initiators for controlled cationic polymerization that enable regulation of polymer dispersity using light. The synthesis and characterization of the photochromic initiators, the monomer scope of the polymerization, and progress toward block copolymer synthesis and characterization of self-assembly kinetics will be described. These results provide new mechanistic insights to controlled cationic polymerizations and demonstrate proof of principle for dynamic modulation of polymer dispersity.



Acknowledgements: Support for this research is provided by the National Science Foundation CAREER Award under Grant No. CHE-1945271.

CHMIEL

Non-innocent radical ion intermediates in reductive photoredox catalysis

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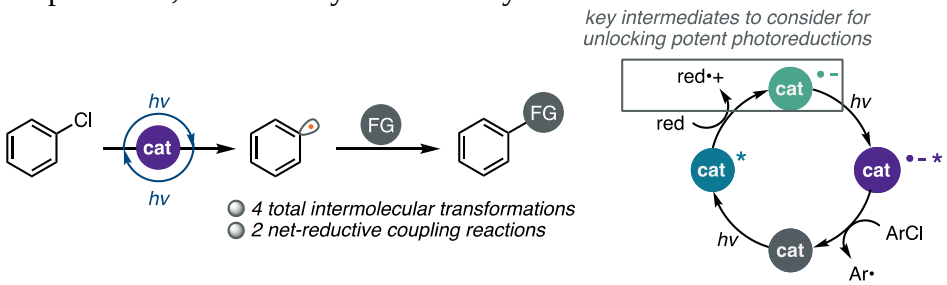
Reductive single electron transfer (SET) to small molecules is a fundamental elementary step that underpins diverse and powerful synthetic transformations. The power, mildness, and exquisite chemoselectivity of photoredox catalysis has rendered it an attractive strategy for promoting reductive SET. However, when considering classic photoredox catalyst parameters: (1) $E_{1/2}(PC^*/PC^{\bullet+})$ and (2) $E_{1/2}(PC^{\bullet-}/PC)$, many abundant substrates would remain inert. In particular, reductive SET to aryl halides is a desirable strategy to access aryl radicals which are known to act as diverse coupling partners.[1] However, aryl chlorides, which make up more than two-thirds of the commercially available aryl halides, have limited examples of reductive activation due to their deeply negative reduction potentials and high C(sp^2)-Cl BDE.[2] While there has been recent progress for aryl radical generation via SET to aryl chlorides,[3a-e] a general approach for intermolecular aryl radical coupling from these precursors remains elusive. Herein, we disclose that selection of an appropriate reductant to generate and maintain an active electron-primed photoredox catalyst in situ enables photoredox reduction potentials far beyond those expected considering conventional photoredox catalyst selection criteria. These new reduction conditions promote a diverse array of intermolecular coupling reactions, including net-reductive processes, from readily available aryl chloride substrates.



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COK

Synthesis of Skipped Dienes through Palladium-Catalyzed Cross-Couplings of Aryl Halides and Sulfonyl Hydrazones

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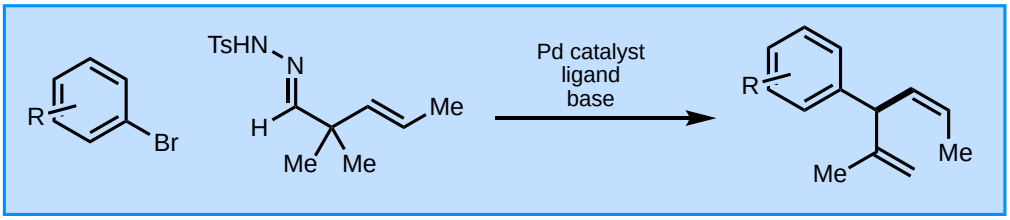
The synthesis of 1,4-dienes, “skipped dienes”, is a challenge that has received considerable attention due to the prevalence of this structural moiety in natural products derived from terpenoid, alkaloid, and fatty acid biosynthetic pathways. Current synthetic methods for the formation of skipped dienes utilize reductive cross-coupling reactions with alkynes or interception of metal π-allyl intermediates with nucleophiles, which primarily lead to linear skipped dienes. The formation of branched skipped dienes with diverse functionality at the C3 position remains challenging. Herein we report the development of a palladium-catalyzed cross-coupling reaction of aryl halides and sulfonyl hydrazones to produce branched skipped dienes with aryl incorporation at the C3 position. Mechanistic studies conducted in our lab suggest this transformation proceeds through an unprecedented 3-*exo*-trig cyclization of an *in situ* generated palladium π-benzyl intermediate to furnish a cyclopropyl carbinyl palladium species. Subsequent collapse of this species and β-hydride elimination leads to a diverse library of branched skipped dienes in up to 90% yield. We have synthesized a number of sulfonyl hydrazones that are bench-stable precursors to the palladium carbene formed *in situ*. The use of commercially abundant aryl halides as coupling partners provides opportunity for incorporation of numerous functional groups as well as late-stage functionalization of complex molecules.



Development of a Hiyama Cross-Coupling of Highly Substituted Vinylsilanes

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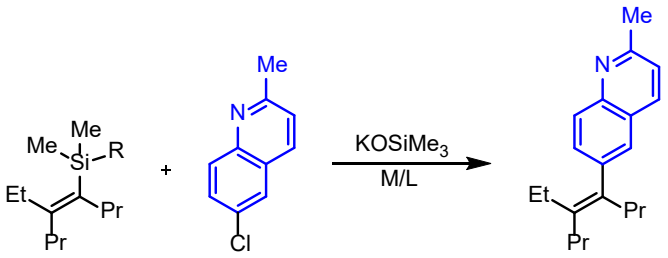
A method to synthesize geometrically defined tri- and tetrasubstituted alkenes through a Hiyama cross-coupling is reported. Easily prepared and handled tri- and tetrasubstituted vinylsilanes bearing four carbon substituents on the silicon center can be coupled with a variety of aryl halides, without the requirement of undesirable additives such as 18-crown-6 ether or fluoride salts, to achieve high-yields of highly substituted alkene products.



•No undesirable additives
•High yields
•Easily prepared starting materials

Acknowledgments: Support for this research is provided by the University of Delaware, the National Science Foundation under Award Nos. CAREER CHE-1254360 and CHE-1800011, and the National Institute of Health under Award No. T32GM133395.

COX

Stereoselective Synthesis of Azacycles *via* a Cation-Triggered Annulation

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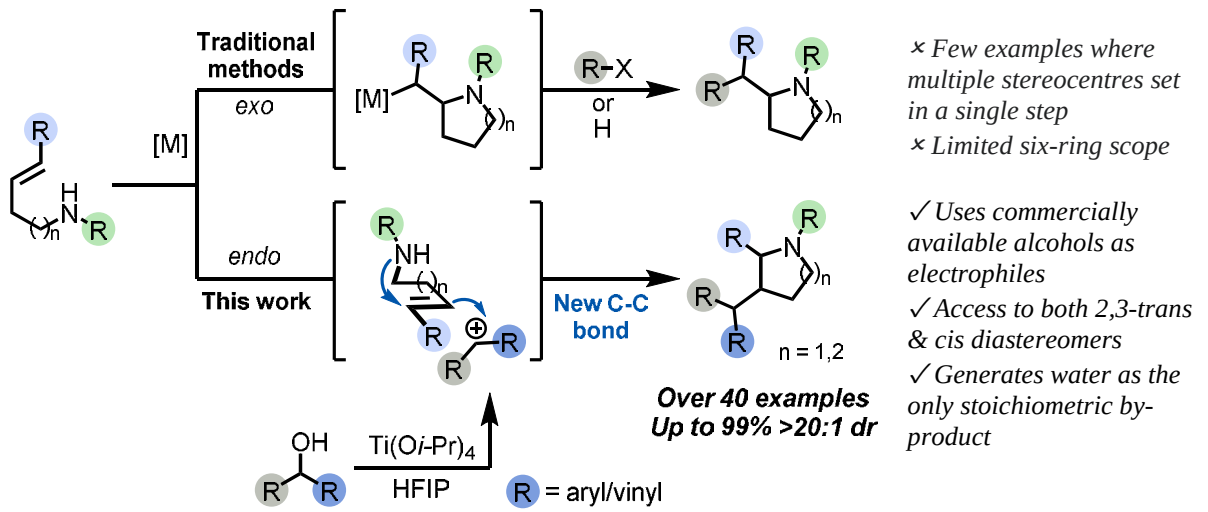
The stereoselective synthesis of highly functionalised azacycles has received significant attention due to their prevalence in natural products and biologically active molecules. Although several methods exist to access such structures, the carboamination of alkenes has emerged as a popular approach; the possibility of generating two new stereogenic centres in a single step making it an efficient and atom-economical route to complex scaffolds.[1] However limitations remain due to the reliance on expensive transition metals to activate the system and a poor atom economy due to use of activated electrophiles. The mode of reactivity also poses a problem, in many cases the alkene reacts in an *exo* fashion, generating one stereocentre in the ring, and methods to generate azacycles with greater substitution in the ring remain minimal.



The Donohoe group has established an alternative approach to preparing such molecules through the use of a secondary alcohol and an unsaturated amine in the presence of hexafluoroisopropanol (HFIP) as the solvent. HFIP has a crucial role in the transformation, enabling alcohols to act as alkylating agents *via* formation of a cation.[2,3] The aforementioned cationic electrophile then triggers an *endo*-trig cyclisation, forming a C-C bond in addition to a concomitant C-N bond in a single step. Along with the two new stereocentres in the ring, an additional exocyclic stereocentre can be set through use of non-symmetric secondary alcohols. This synthetic approach enables the rapid construction of key small azacycles and facilitates the preparation of a number of medicinally relevant pyrrolidines and piperidines.[4]

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CRANS

Essential and Non-Essential Metal Ions and Their Complexes as Therapeutic Agents

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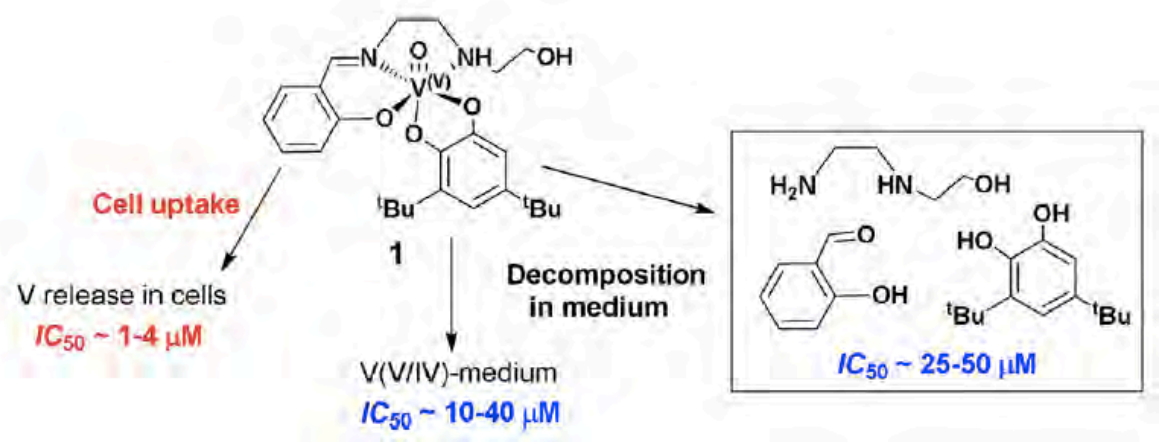
First-row transition metals play several roles in biological processes and in medicine, but can be toxic in high concentrations (1). The speciation of metal ions are critical to their activity. Despite these limitations, metal complexes such as cisplatin has had a profound effect on treatment of cancer and is still used 40-years after its discovery in the clinic. We are involved in developing metal based complexes such as ternary V^{V} complexes, 1 ([VOL1L2], where L1 is N-(salicylideneaminato)-N'-(2-hydroxyethyl)ethane-1,2-diamine and L2 is 3,5-di-tert-butylcatechol) (2-3), Scheme 1. We are currently working on a number of related systems (2-3). These complexes enter cells and induce high cytotoxicity in a range of human cancer cells. Including brain tumor T98g (glioma multiforme) and human bone cancer chondrosarcoma (SW1353) cells. We find that complex hydrophobicity and stability are important to the activity of these complexes.



Scheme 1. Complex **1** and its decomposition reactions in cell culture (2).

Acknowledgements: Support for this research is provided by CSU and as indicated in the publications listed below.

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CYR

Synthesis and Characterization of Ellagic Acid Derivatives to Explore their Optoelectronic Properties

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The development of organic-based functional materials is a continuous, yet fruitful endeavour for researchers in the pursuit of electronic devices that are smaller, lightweight, flexible, and more efficient in comparison to their conventional silicon-based counterparts.[1] Materials that possess a high degree of conjugation, good charge carrier mobility, and a low reorganization energy will typically demonstrate better semiconductive properties. In the past decades, researchers have been investigating new organic materials that can be produced in a sustainable manner without extensive synthetic methodologies and that can also act as efficient semiconductors. Ellagic acid (EA), a natural polyphenol found in a variety of plants and trees such as the North American white oak, meets these requirements and is an ideal candidate in the search for sustainable materials for use in organic electronics.[2] EA in its natural state consists of a planar molecule with a thermally stable electron-rich core. Its natural abundance and its underexplored performance as an organic semiconductor leave great room for future advancement in using this molecule as a core building block for organic electronic materials.

This presentation will focus on the functionalization of EA's peripheral hydroxyl groups with aryl moieties through S_NAr reactions, providing a facile two-step approach to tailor the properties of the material by extension of π-conjugation in two-dimensions. Initial density-functional theory (DFT) studies for the pyrazine, quinoxaline, and fluorinated aryl halide analogues have shown that these compounds are stable towards atmospheric oxidation (energy of the HOMO level **< -5.8 eV**). In addition, the synthesized pyrazine and quinoxaline derivatives have shown to have high thermal stability **(>330°C at 130 mTorr)** indicating a close packing arrangement, which will be beneficial for charge transport in electronic devices. Although this work is still ongoing, initial results obtained from the pyrazine and quinoxaline derivatives have shown promising data for the fine-tuning of their electrochemical properties. Device performance along with the synthesis and characterization of EA derivatives will be presented, as well as our recent efforts shifted towards synthesizing fluorinated derivatives.

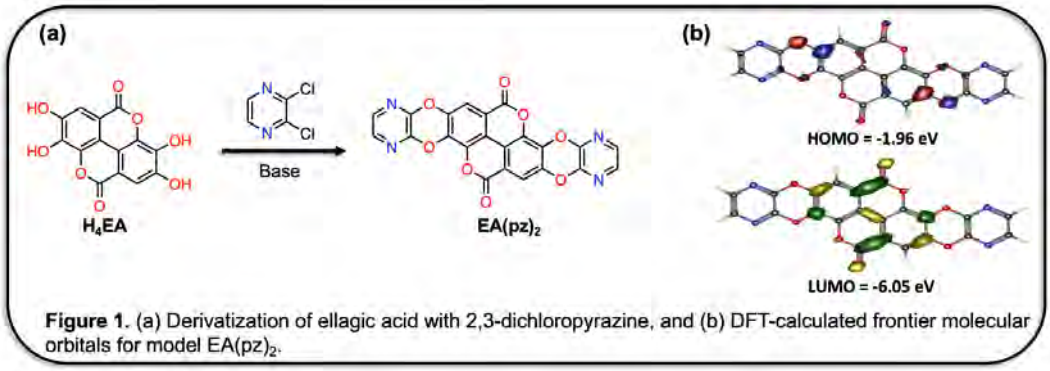

Figure 1. (a) Derivatization of ellagic acid with 2,3-dichloropyrazine, and (b) DFT-calculated frontier molecular orbitals for model $EA(pz)_2$.

Acknowledgements: Support for this research is provided by the uOttawa Department of Chemistry and Department of Chemical Engineering, and NSERC.

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DAMANI

Synthesis of Stimuli-Responsive and Conducting Polyelectrolyte Complexes

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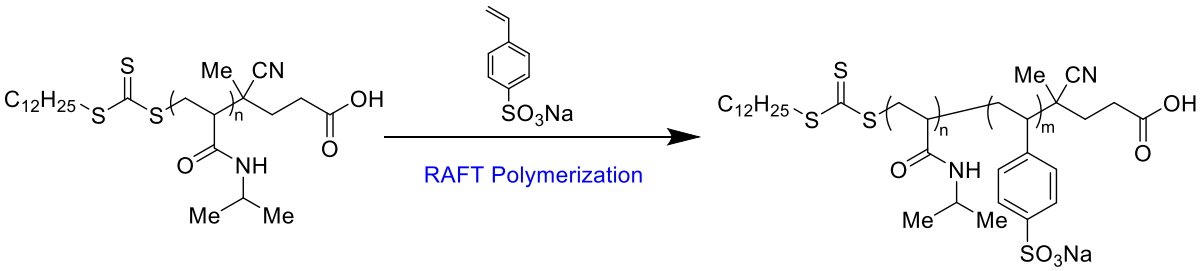
Stimuli-responsive block copolymers have been utilized in actuators, for drug delivery and as shape-memory materials. While they are commonly stimulated using light and temperature, these stimuli may prove to be impractical for integrating into devices for actuation (e.g., for soft robotics).[1] To overcome this, we are developing a conductive thermo-responsive material and plan to employ Joule heating to actuate it. By eliminating the need for a separate source of heating, this approach will enable easier integration in actuating devices. Additionally, properties such as flexibility and light weight of the material would facilitate a more portable device and solve a common problem faced in electronic actuators that use metals and alloys for actuation.[2] In this approach, we use a thermo-responsive block copolymer as a matrix for a conductive polymer. The thermo-responsive block copolymer poly(*N*-isopropylacrylamide)-*block*-poly(styrene sulfonate) or PNIPAM-*b*-PSS was synthesized using reversible addition-fragmentation chain transfer (RAFT) polymerization. PNIPAM was selected for demonstrating a thermal response close to body temperature—it exhibits a lower critical solution temperature transition in water above 32°C.[3] The addition of the PSS block in the copolymer is required as a stabilizer and matrix to disperse the doped conductive polymer, poly(3,4-ethylene dioxythiophene) (PEDOT), in water.[4] Together, PEDOT:PSS-*b*-PNIPAM is a polyelectrolyte complex that displays conductivity and thermo-response. In this presentation, the optimization process of the RAFT polymerization (initiators, RAFT agents and solvent systems) (Scheme 1) will be discussed. We are currently characterizing PEDOT:PSS-*b*-PNIPAM samples for properties such as electrical conductivity, self-assembly, thermal response and particle size. These conductive and thermo-responsive polyelectrolyte complexes could prove valuable as actuating materials in assistive robotics and stimuli-responsive mixed-ionic conductors for bioelectronics.



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DAS_PRADIPTA

Nickel-catalyzed cross coupling promoted by substrate photoexcitation

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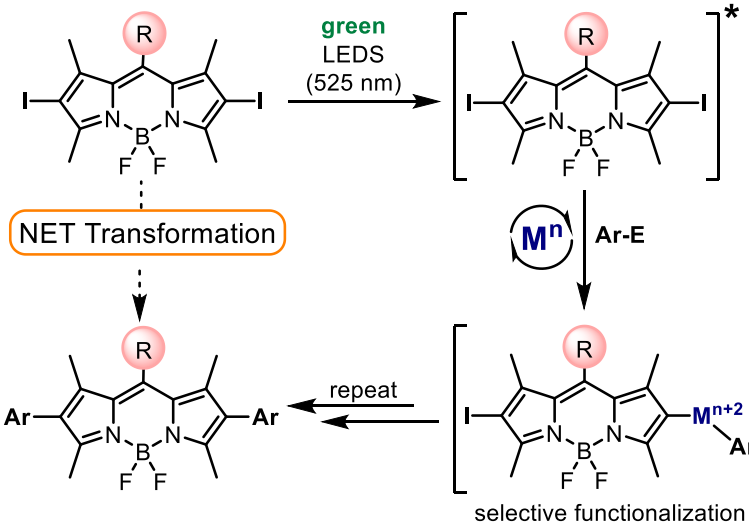
Over the past decade, photoredox catalysis has rapidly emerged as a powerful platform for synthetic methods development. Through photoinduced electron transfer (PET), this chemistry allows for the generation of highly reactive intermediates under operationally mild conditions, and typically uses low-energy visible light. The required photoredox catalysts are usually transition-metal complexes or organic dyes. Among them, halogenated organic dyes comprise an important class of photoredox catalysts due to the increased oxidizing and reducing ability of their long-lived excited states relative to the ground state. To date, the reactivity of these dye excited states has not been exploited to functionalize the dye itself. We have uncovered a visible-light-mediated cross-coupling method that selectively functionalizes halogenated dyes.

In this work, BODIPY dyes, a common class of tunable, bright, photostable fluorophores used in imaging, photocatalysis, triplet photosensitization and photouncaging, underwent photoinduced cross coupling reaction in the presence of nickel catalysts. Using a bis-iodo substituted BODIPY substrate, the selectivity for mono- vs. bis-arylation was found to be governed by the photophysics of the substrate. Preliminary photophysical measurements suggest that the selectivity arises from the difference in intersystem crossing efficiency between the starting material and the product. This efficient strategy is scalable and compatible with a variety of substituted BODIPY dyes and electrophilic partners, which are further elaborated into construction of new class of fluorophores containing both electron donor and acceptor moieties. We anticipate that this novel substrate photoexcitation strategy could open the door for other covalent modifications of dyes and fluorophores, thus improving their properties as colorants, photosensitizers, catalysts, and imaging agents.



Acknowledgements: Support for this research is provided by the American Chemical Society Petroleum Research Fund (58452-DNI4), Air Force Office of Scientific Research Young Investigator Program (FA9550-18-1-0159).

DIBRELL

SeO_2-Mediated Oxidative Transpositions of Pauson–Khand Products

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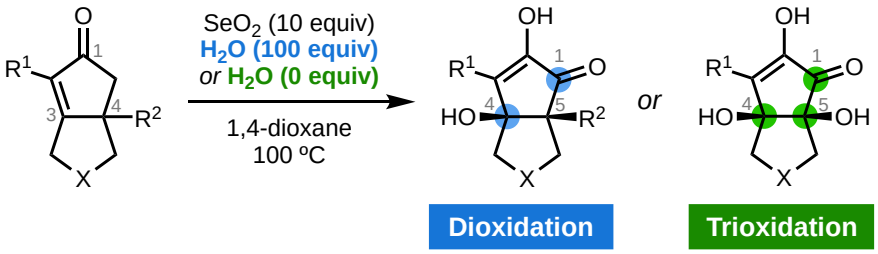

Bicyclic cyclopentenones found in many natural products are often prepared by the Pauson–Khand reaction (PKR).[1] While the well-developed intramolecular PKR affords 3,4-fused bicyclopentenones from tethered enynes, access to isomeric 4,5-fused bicyclopentenones requires the intermolecular PKR, which has severe limitations in scope. As part of the synthesis of (+)-ryanodol, selenium dioxide (SeO_2) was discovered to mediate unusual oxidative reactivity: treating intramolecular PKR products with SeO_2 under either aqueous or anhydrous conditions provided highly oxidized, transposed 4,5-fused cyclopentenones.[2] Herein, we describe our development of these peroxidations to construct oxidation patterns elusive via canonical PKRs and provide valuable synthetic building blocks.[3]

Treatment of readily available PKR products with SeO_2 in the presence of excess water leads to selective dioxidation, whereas the exclusion of water selects for trioxidation. We found the reactions to be general to 5/5-bicyclic systems and afford 4,5-fused bicyclopentenones as single diastereomers that can be readily elaborated via Pd-catalyzed cross-coupling.

Identification of fleeting intermediate species led us to propose two possible pathways for the formation of di-and trioxidation products. We present Hammett analyses and study of the enantiospecificity of reaction steps that implicate water concentration in the sequencing of SeO_2-mediated Riley oxidation and allylic C–H oxidation steps,[4] leading to product selectivity. Our mechanistic studies have also resulted in an improved reaction protocol and scope.

Acknowledgements: Fellowship support was provided by the NSF under Grant No. DGE-1144469.

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DING

Pedal Motion and Thermal Expansion in Mixed Cocrystals and Halogen-Bond Donors with Motion-Capable Bridges

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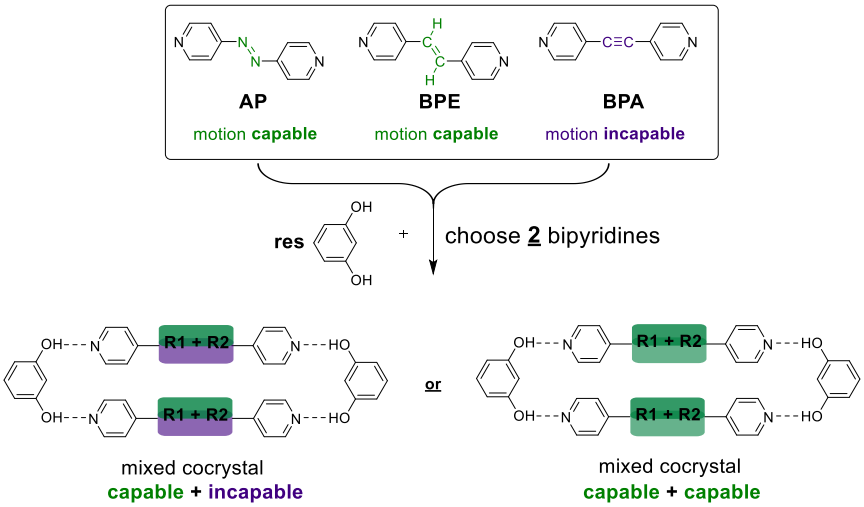
Thermal expansion (TE) is the response of a material to changes in temperature.[1] It is classified as positive, negative, or zero TE. Positive TE (PTE) involves an increase in size upon heating and is the most common behavior in materials. Negative TE (NTE) or zero TE (ZTE) are rarer behaviors, which refer to decrease or nearly no change in size upon heating, respectively.

Organic molecules are capable of motion in the crystalline state and the motion can be investigated using variable temperature crystallographic studies.[2] Our group has shown that dynamic pedal motion can lead to large PTE along the direction where motion happens. The most widely studied motion-capable moieties include olefin (C=C) and azo (N=N) groups. Imine (C=N) groups are also capable of pedal motion; however, the pedal motion in imines has not been well explored. We designed a series of halogen-bond donors with the three motion-capable groups to study pedal motion and TE behaviors in single-component crystals.

Cocrystals are solids that incorporate two or more unique molecules held together by intermolecular interactions, and most traditional cocrystals contain two components. We designed a series of three-component mixed cocrystals, which provides a strategy to tune TE in organic solids (Scheme 1).[3]



Scheme 1. Synthesis of mixed cocrystals.

Acknowledgements: Support for this research is provided by Texas Tech University.

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DISHMAN

Divergent Stereochemical Outcomes in the Insertion of Donor/Donor Carbenes into the C–H Bonds of Stereogenic Centers

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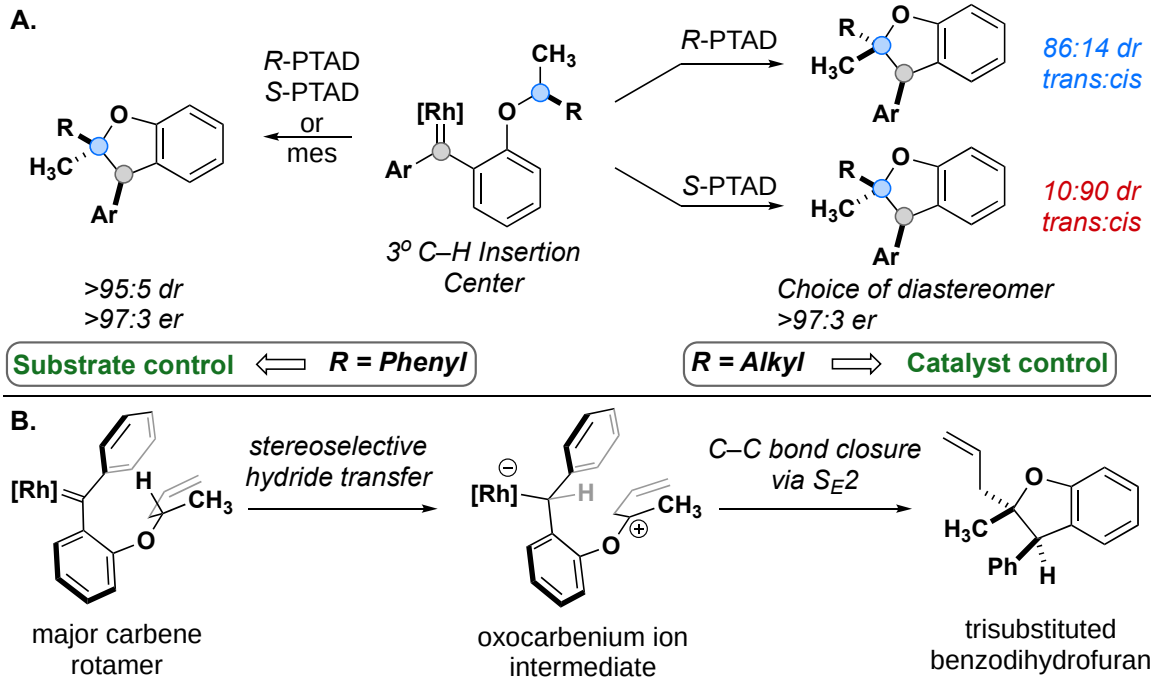
Intramolecular C–H insertions with donor/donor dirhodium carbenes provide a concise and highly stereoselective method to set two contiguous stereocenters in a single step. Here we report the expansion of this donor/donor system to stereogenic C–H insertion centers enabling the stereoselective synthesis of highly substituted benzodihydrofuran cores. Sterically bulky, highly activated C–H insertion centers exhibit high substrate control yielding a single diastereomer and a single enantiomer of product. Less bulky, less activated C–H insertion centers exhibit catalyst control over the dr wherein a single enantiomer of each diastereomer is observed (Scheme 1A). Donor/donor carbenes have been hypothesized to proceed through a stepwise mechanism and from a combination of experimental and DFT calculations we propose a novel stereochemical rationale for this donor/donor system (Scheme 1B). First, a major rotamer of metal carbene forms from diazo, followed by a hydride transfer resulting in an oxocarbenium ion intermediate. The hydride transfer occurs with high stereoselectivity determining the enantiomeric ratio (er) of the reaction. Next, isomerization of the oxocarbenium ion can occur to expose the other prochiral face of the oxocarbenium ion. Both conformers can then undergo C–C bond closure via an S_E2 mechanism, leading to separate diastereomers of product. Finally, the ratio of oxocarbenium ion conformers is dependent on the steric bulk and electronics at the C–H insertion center.



Acknowledgements: Support for this research is provided by the National Institutes of Health (R01/GM124234).

Poster Session 1

DORN

Advances in Cu/Pd-Catalyzed Alkenylboration: Enantioselectivity, Selective Access to Diastereomers, and Mechanistic Investigation

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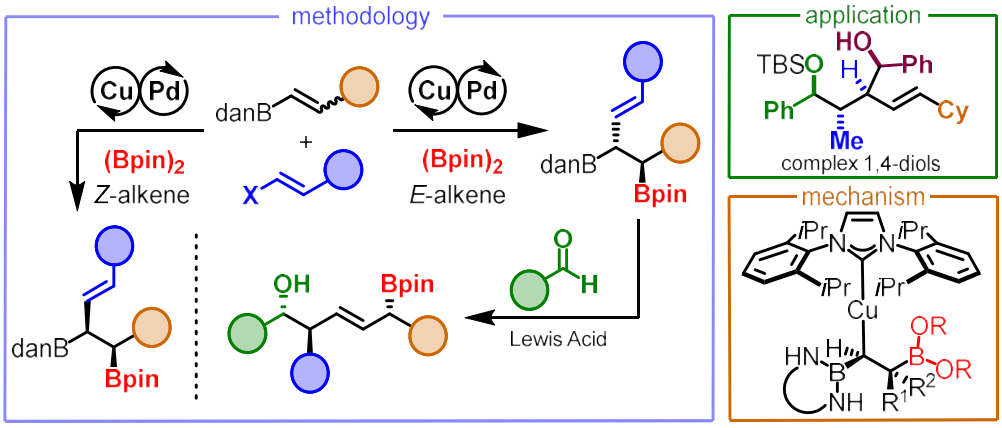

Alkenes are ubiquitous molecular motifs, and their functionalization presents opportunities for building molecular complexity in a rapid manner. Our research group has previously utilized Cu/Pd-catalyzed carboboration for the difunctionalization of 1,1- and 1,2-disubstituted styrene derivatives in a diastereoselective[1] and enantioselective[2] fashion. Recently, we have developed an efficient approach towards accessing Type III bifunctional allylation reagents *via* Cu/Pd-catalyzed alkenylboration of alkenylboronamide derivatives (dan = 1,8-diaminonaphthalene).[3] These types of double-allylation reagents allow for the rapid construction of highly complex diols in an expedient fashion through iterative allylation reactions.[4] Although parts of this work were presented at the last EWOC conference, significant advances have been made since then, including 1) access to both diastereomers of alkenylboration product; 2) rendering the reaction enantioselective for both diastereomers; 3) mechanistic investigation into the alkenylboration reaction; and 4) increased scope for the allylation reaction. Overall, the modularity and the ease in which complex structural motifs can be accessed in a rapid manner signify the importance and utility of this method.

Acknowledgements: Support for this research is provided by the NIH under Grant No. R35GM131755.

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EROLMEZ

Design and Synthesis of pH-Responsive Novel Activatable Photodynamic Therapy Agent

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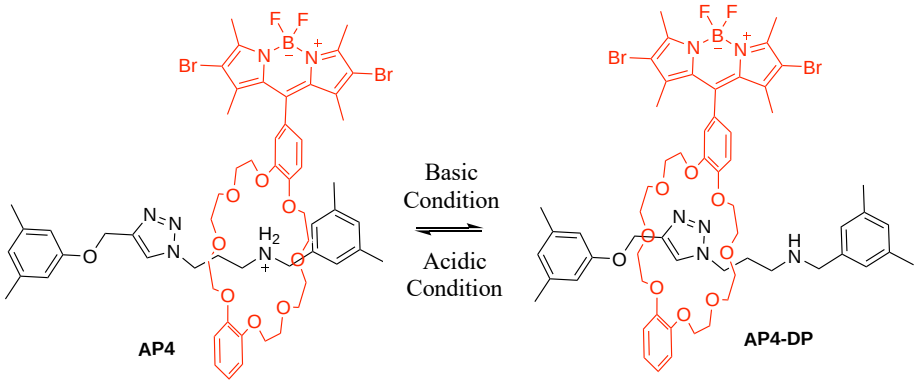
Photodynamic Therapy (PDT) is phototherapy method, widely used in cancer treatments, alternative to radiotherapy and chemotherapy. PDT requires excitation of photosensitizer agent by certain wavelength of light, result in generation of singlet oxygen ($^1O_2$) from triplet oxygen ($^3O_2$), causing apoptosis formation in the photo irradiated region.[1] Boron dipyrromethene (BODIPY) is used recently as photosensitizing agent in PDT, possessing high fluorescent properties, stable structure moiety, well-known chemistry and able to be functionalized from every position.[2] Switchable rotaxanes are molecular machines in which its macrocycle undergoes positional change in response to stimuli, have potential applications in organic chemistry. [3]

In this context, structure of AP4 molecule has designed as shown in the Figure, having both switchable rotaxane molecule and BODIPY molecule as photosensitizer. Once photosensitizer absorbs energy from light in a certain wavelength, its electrons are being excited, results in energy transfer to $^3O_2$ to generate $^1O_2$. PDT agent is pH-responsive, activating only in low pH and with the excitation of certain wavelength of light. In high pH, oxygens of the crown ether appended to the BODIPY, creating charge transfer system. However, in low pH, these oxygens interact with the ammonium group of the thread, ceasing the charge transfer, start to generate singlet oxygen which is highly toxic for cancer cells. Thus, controlling the position of the macrocycle in different pH condition upon excitation by light would suggests effective cancer therapy, because cancer cells are more acidic than healthy cells, while AP4 molecule can only generate singlet oxygen in low pH. All together, BODIPY dyes in PDT concept has not been applied in a rotaxane system, contributing uniqueness of the project.



Acknowledgements: Support for this research is provided by the Scientific and Technological Research Council of Turkey under Project No. 219Z126.

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FADLER

Within Chaos Is Opportunity: Entropy Rescues Order in Cyanostar [3]pseudorotaxanes

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Substituent-mediated recognition underpins critical processes in biology[1] and chemistry,[2] but the role of organic substituents is poorly understood.[3] Previous studies by supramolecular chemists have primarily focused on how the number of organic substituents effects the phosphate anion's overall charge and steric bulk. In this work, we highlight the power of organic substituents (Figure 1a) as novel design tools to regulate cyanostar recognition (Figure 1b) to form desired assemblies (Figure 1c). NMR solution studies and crystal structures show that the introduction of competitive hydrogen bond donors, i.e. hydroxyls -OH-, fold up phosphates to minimize pseudorotaxane formation. To recover the desired threaded architectures, we developed a new entropy-driven assembly strategy[4] that relies on increasing molecular chaos of building blocks. When the length of the phosphates substituents is increased, the competing OH•••O interactions are disabled such that the phosphates unfold and form threaded [3]pseudorotaxanes with cyanostar. The work of organophosphates continues with examining the role of sterically bulky substituents on threading kinetics and the effect of linker lengths on cyanostar cooperativity in sequence-specific oligomers.

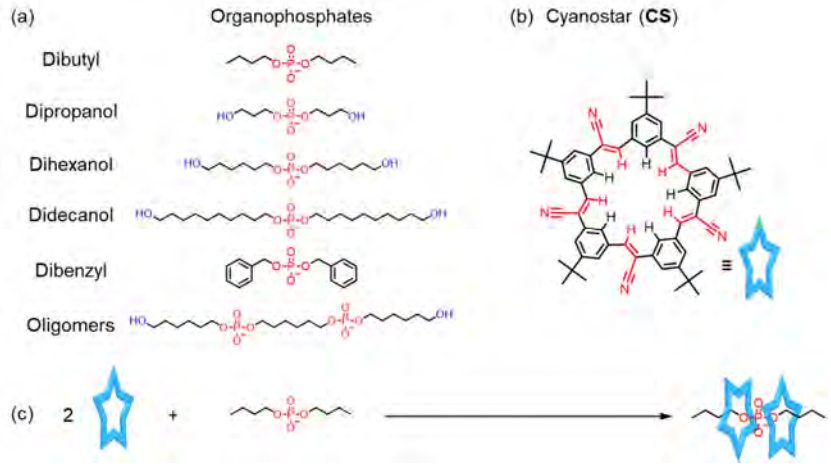

Figure 1. (a) Organophosphates and (b) cyanostar form (c) [3]pseudorotaxanes

Acknowledgements: Support for this research is provided by the National Science Foundation under Grant No. CHE-1709909. R.E.F. supported by Raymond Siedle Materials Fellowship and National Institutes of Health under Grant No. T32 GM109825 and T32 GM131994.

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GABBEY

Nickel-Catalyzed Reductive Arylation of α-Substituted NHP Esters

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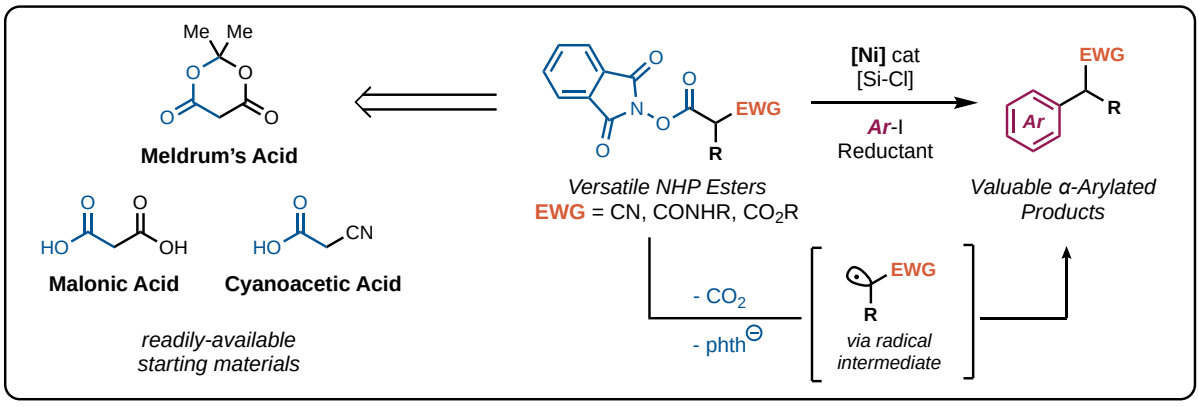
N-hydroxyphthalimide (NHP) esters have emerged as powerful and versatile substrates in nickel-catalyzed cross-coupling reactions.[1,2] Notably, NHP esters are redox-active and are capable of undergoing single-electron fragmentation to generate the corresponding carbon-centered radicals that can participate in a variety of synthetic transformations.[3] Transformations of this class are desirable not only for the orthogonal reactivity that they display in comparison to traditional two-electron cross-coupling, but also for the relatively low cost of nickel and the ease of preparation of NHP esters from commercially available materials.

We report the ongoing development of nickel-catalyzed reductive cross-couplings of aryl iodides with NHP esters that bear an electron-withdrawing group at the alpha position (**Scheme 1**). This methodology provides direct access to a variety of α-arylated products such as α-arylated esters, amides, and nitriles, each of which represent valuable motifs in modern pharmaceuticals. Notably, the reaction occurs under mild conditions; the addition of harsh reagents such as strong base, as is typical in α-arylation strategies, is avoided. This poster will present details of reaction optimization, scope, and mechanistic studies.



Scheme 1. A mild nickel-catalyzed α-arylation strategy from accessible NHP ester substrates.

Acknowledgements: Support for this research is provided by NSERC, the University of Toronto, Merck & Co., Canada Foundation for Innovation (CFI), and Ontario Research Fund.

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GANIU

Triphosgene Mediated Organic Synthetic Transformations

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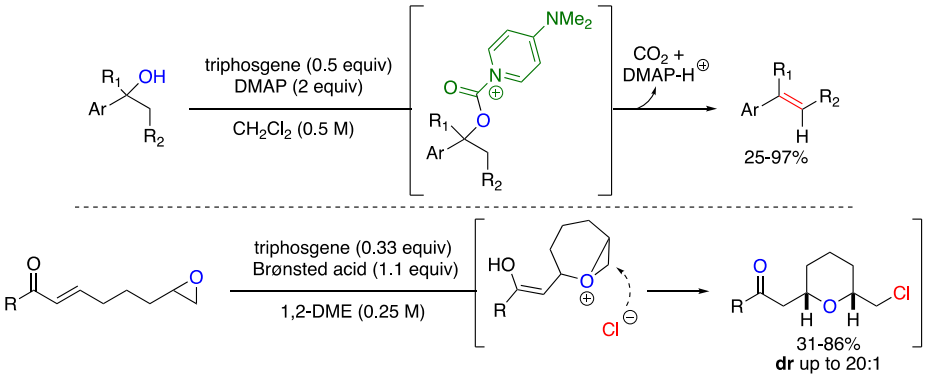
Triphosgene, also known as bis(trichloromethyl) carbonate or BTC is a crystalline solid that serves as a convenient substitute for phosgene gas. Due to its ease of handling as a solid, it is more desired for preparative laboratory scale reactions as exact amounts of materials can be weighed out effectively. By exploiting this unique quality of triphosgene, we have been able to develop simple strategies towards the synthesis of various molecules of synthetic relevance.

For example, we recently reported a triphosgene and DMAP enabled dehydration strategy via an E2 elimination. The devised method enabled the synthesis of trisubstituted alkenes from tertiary alcohols with excellent to moderate control over the resulting alkene selectivity. In addition to this, we are also interested in regioselective capture of epoxonium ions by chloride ions leading to chlorine-containing tetrahydropyran fragments.

A recent investigation from our lab examines the generation of epoxonium ions via intramolecular nucleophilic addition of an epoxide onto an α,β-unsaturated ketone in the presence of triphosgene and a Brønsted acid catalyst. The putative transient epoxonium species is directly captured by chloride ions in a regioselective manner, liberating exocyclic *syn*-2,6-disubstituted tetrahydropyrans with excellent diastereocontrol. Scope of substrate studied as well as mechanistic insights will be presented.



Acknowledgements: Support for this research is provided by the NSF under Grant No. CHE-1464788 and NIH under Grant No. RO1-GM127649.

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GAO

C-C Bond Formation of Phenolic Analogues using Electrochemical Oxidation

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The phenolic compounds are used as precursor to raw materials for a wide range of applications, including industrial, agricultural, and pharmaceutical. While chemical oxidation of phenolics may lead to high yields, the selectivity is limited, and reactions require harsh chemicals and produce waste. Hence, new green methodologies are needed to achieve selective oxidation of such compounds. The selective electrochemical oxidation of bulky phenols was recently achieved to produce new C-C bonds leading to compounds with extended conjugation.[1] Herein, 2,6-diphenylphenol (DPP) (Figure 1) was electrooxidized in an aprotic environment using cyclic voltammetry and chronoamperometry, and the reaction was monitored by spectroscopy. DPP was characterized with an irreversible oxidation. The electrooxidation of DPP resulted in a solution colour change (from clear to yellow) indicating the formation of new products. The product formation was monitored by UV-vis and fluorescence spectroscopy and products characterized by mass spectrometry and nuclear magnetic resonance. The data indicate that electrochemical oxidation is a viable strategy for the formation of new C-C bonds towards value-added chemicals in a green and sustainable alternative.

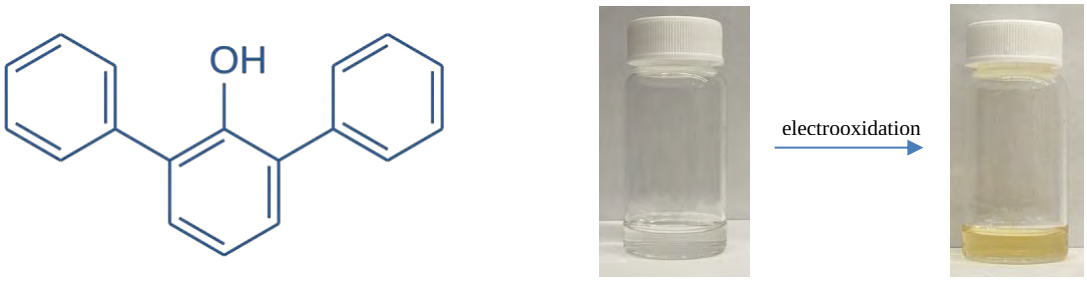

Figure 1. Chemical structure of DPP and electrochromic conversion during electrooxidation.

Acknowledgements: Support for this research is provided by NSERC.

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GERTHOFFER

Compression of π-π Stacked Co-Crystals *en route* to Sequence-Specific Nanothread Design

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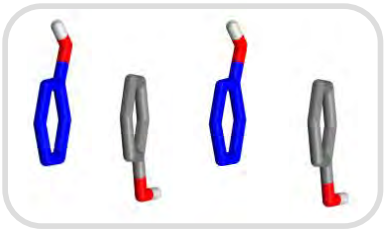
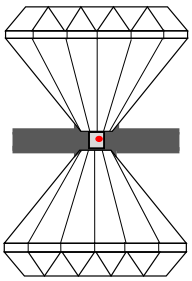
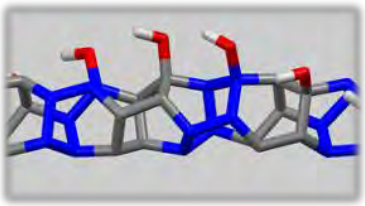
Unique one-dimensional diamondoid architectures known as nanothreads have recently been added to the library of attractive carbon-based materials.[1] Nanothreads are polymerized upon compression (to 10s of GPa) by a unidirectional cycloaddition of π-π stacked aromatic monomers in the solid-state.[1] A supramolecular approach has enabled the realization of sequence-defined sp^3-saturated copolymer nanothreads from the pressure-induced polymerization of closely eclipsed electronically alternating aromatic cores.[2] Here, we will discuss efforts to polymerize supramolecular monomers into one-dimensional sp^3 architectures using guided noncovalent interactions in solid-state co-crystal design. This effort explored preorganized monomer pair design using guided external functionalities, aryl:perfluoroaryl synthons, and intermolecular hydrogen bonding to determine nanothread output. Our approach lowered polymerization initiation pressures compared to the individual components and has provided insights into functional group tolerances under high pressure polymerization conditions. The polymerization of supramolecular monomers lends insight toward the further design of complex sequence-specific polymeric nanothreads, with potential toward donor-acceptor polymer applications.







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GULOTTY

Oxyphosphonium Enolate Equilibria in a (4+1)-Cycloaddition Approach toward Quaternary C3-Spirooxindole Assembly

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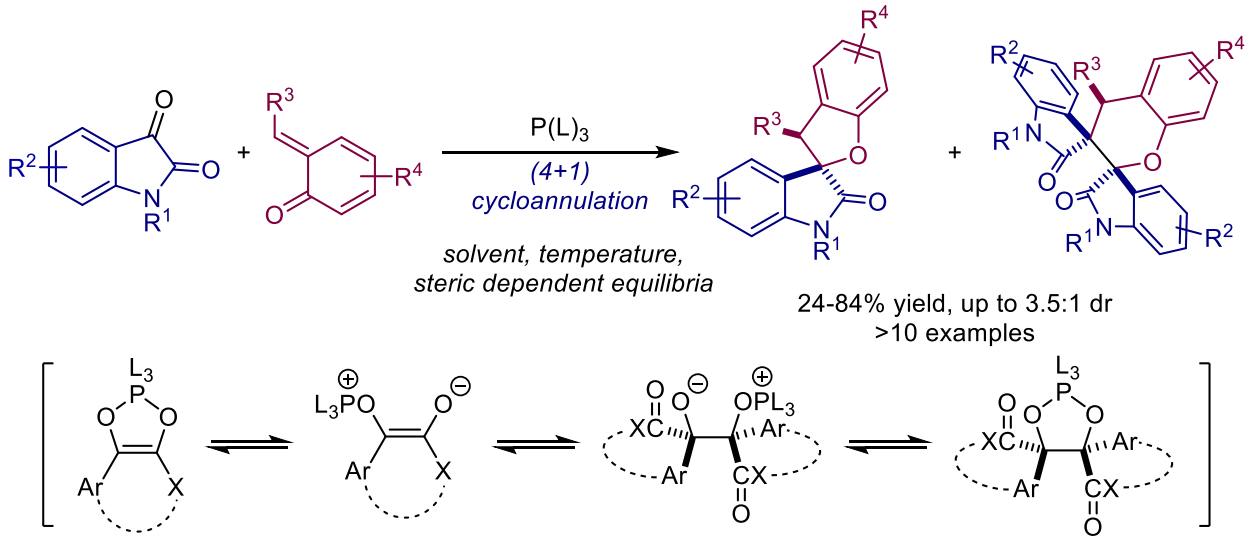
Recently published work on an efficient and convergent (4+1)-cycloaddition strategy toward the construction of spirooxindole benzofurans is presented along with mechanistic investigations employing *in situ* variable temperature NMR analysis to investigate isatin-derived oxyphosphonium enolate intermediates, which revealed a correlation between phosphonium enolate structure and product distribution that was heavily influenced by both solvent and reaction temperature.[1]

Targeting a metal-free method to access the pharmaceutically relevant spirooxindole scaffold and inspired by Rhodium catalyzed (4+1)-cycloaddition strategies and phosphorus mediated enolate cyclizations, we employed an *in situ* generated oxyphosphonium enolate to perform this formal (4+1) cycloannulation with *ortho*-quinone methides.[2] It quickly became clear that the choice of single atom component in these cyclizations was crucial to the reaction outcomes, and we were inspired to critically evaluate the influence of substrate structure, reaction temperature, and solvent as minor changes in each of these factors significantly influenced product distribution and yield.



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HANDS

p-NO_2-Cbz Derivatization of Primary Chiral Amines Enables Superior Resolution by Supercritical Fluid Chromatography

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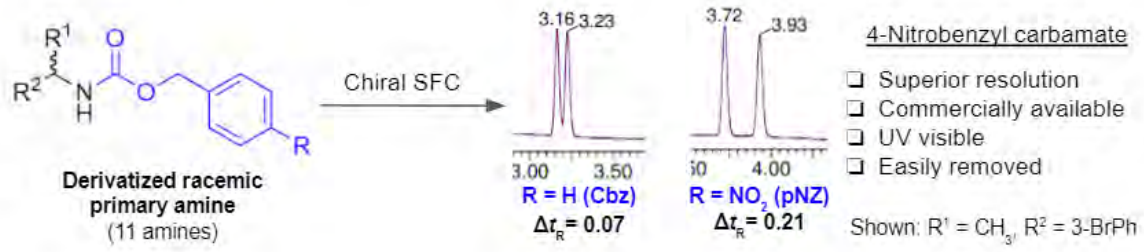
Enantioenriched chiral primary amines are a challenging family of compounds to isolate by chiral chromatography and often require derivatization to facilitate separation. Recently, it was shown that derivatization as the 4-nitrobenzyl carbamate (*p*-NO_2-Cbz, pNZ) enabled an otherwise challenging preparative scale resolution of BRD4780, *rac*-3-*exo*-isopropylbicyclo[2.2.1]heptan-2-*endo*-amine, with supercritical fluid chromatography (SFC) on chiral stationary phase (CSF). In this study, we investigated whether protection with pNZ is a general method to improve separation of chiral primary amines relative to Cbz. pNZ is an achiral, UV visible protecting group that is commercially available and easily removed under mild conditions. Eleven primary amines were synthesized as the pNZ and Cbz protected compounds and profiled using SFC. Both gradient and isocratic methods were run on a suite of nine Daicel CHIRALPAK columns (IA-3 - IH-3, IJ-3) across four mobile phases: supercritical CO_2 modified with MeOH, EtOH, iPrOH and MeCN. We found superior resolution was consistently achieved with pNZ for all compounds compared to Cbz. Thus, we establish derivatization of primary amines as the 4-nitrobenzyl carbamate as a valuable strategy for improving separation efficiency on CSF.



HENDY

Radical Chain Reduction via Carbon Dioxide Radical Anion

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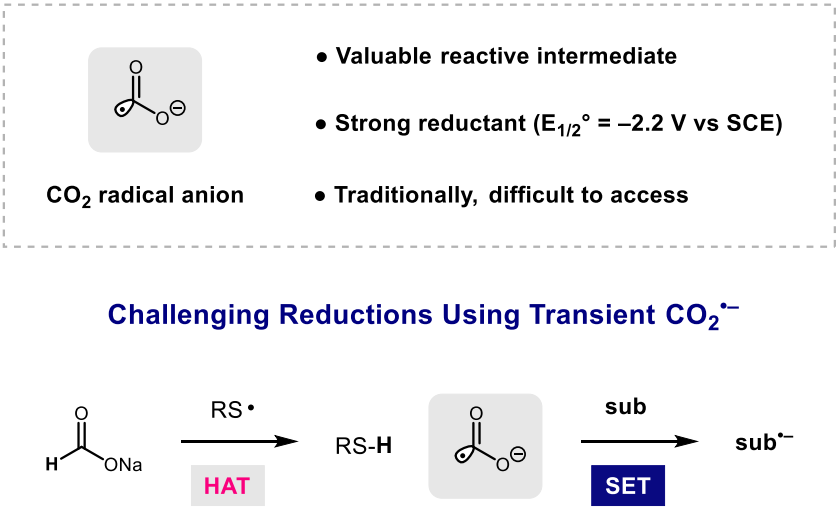
Single electron reduction of organic molecules allows access to valuable radical intermediates that display unique reactivity when compared to their ionic counterparts. In this context, we have developed a novel reductive radical chain system that utilizes the reducing power of carbon dioxide radical anion ($CO_2^{\bullet-}$; $E_{p/2}$ = –2.2 V vs SCE)[1] to accomplish difficult reduction events. Through a polarity matched hydrogen atom transfer (HAT) between a thiyl radical and a formate salt, $CO_2^{\bullet-}$ formation is achieved under benign conditions (no metals required). Several initiation pathways feed into the chain mechanism via both photochemical and thermal means. We illustrate the ability of this approach to accomplish reductive activation of a range of substrate classes. Specifically, we have employed this strategy for the intermolecular hydroarylation of unactivated alkenes with (hetero)aryl chlorides/bromides, radical deamination of arylammonium salts, aliphatic ketyl radical formation, and sulfonamide cleavage. Additionally, we show that in the presence of electron deficient alkenes dual reactivity is observed; alkenes with a less negative potential than that of $CO_2^{\bullet-}$ undergo single electron transfer and alkenes with a more negative potential undergo Giese type conjugate addition to yield hydrocarboxylated products.



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HERBERT

Nickel-Catalyzed Kumada Cross-Coupling Reactions of Benzylic Sulfonamides

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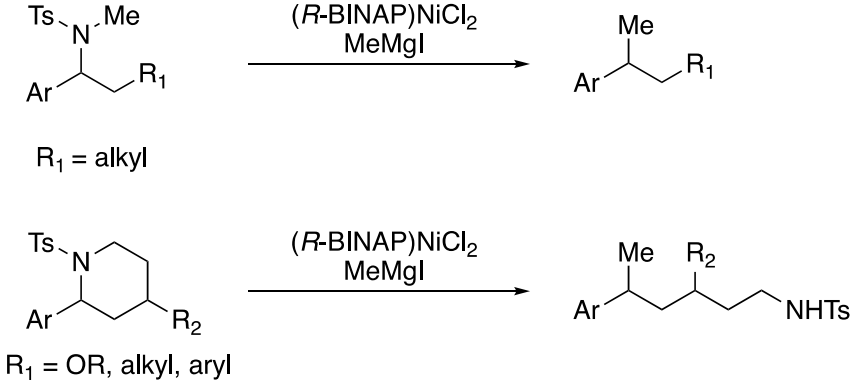
The C-N bond of benzylic amines is challenging to activate towards cross-coupling absent the use of high energy synthetic intermediates. We report the development of a nickel-catalyzed Kumada cross-coupling reaction of unactivated benzylic amines. In this reaction, both cyclic and acyclic sulfonamides are employed to form new tertiary carbon centers.



HEWITT

Nickel-Catalyzed Cross-Electrophile Coupling Reactions of Sulfonamides: Expansion to Domino Reactions

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Nickel-catalyzed domino reactions are essential transformations that allow for rapid synthesis of complex chemical targets that minimize the amount of waste produced and increase the atom economy.[1] Recently we have developed cross-electrophile coupling reactions of aryl and vinyl sulfonamides.[2] Utilizing mechanistic insights of this transformation, a domino reaction was envisioned utilizing propargyl sulfonamides.[3] This reaction allows for the formation of three new carbon-carbon bonds, a strained ring, and three new stereocenters in a single transformation. The broad scope and mechanistic details will be discussed.

Acknowledgements: Support for this research is provided by the National Science Foundation CHE-1464980

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HOCHBERG

Measurement of Hammett Sigma Values for Common Boryl Substituents

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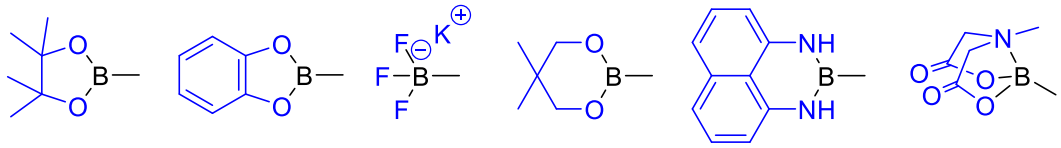
In 1937, Hammett's seminal work demonstrated a linear relationship between reaction rates or equilibrium constants and Hammett sigma values.[1] Still today the Hammett plot is a valuable tool that reveals useful inferences about the transition states. It is not surprising then that sigma values for myriads of substituents have been measured.[2] Interestingly, despite the utility and development of boron containing material,[3] physical values, such as the Hammett sigma value, for common boryl substituents have yet to be measured. Sigma values of boryl substituents, such as those shown in Scheme 1, can be readily calculated by the difference in pK_a of the substituted benzoic acid and that of benzoic acid. In this study, the desired benzoic acids will be synthesized followed by measurement of ionization constants. A UV-vis spectrophotometric method developed by Leito, Koppel and co-workers,[4,5] as well as a potentiometric method, will be employed in order to precisely measure these pK_a values.

Common Boryl Subsituents with Unknown Sigma Values



Acknowledgements: Generous support for this research is provided by the Welch Foundation and The Nancy Cain and Jeffrey A. Marcus Science Endowment.

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HOLMAN

Synthetic Studies Toward Falcatin A

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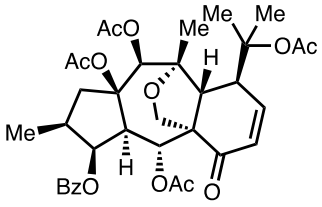
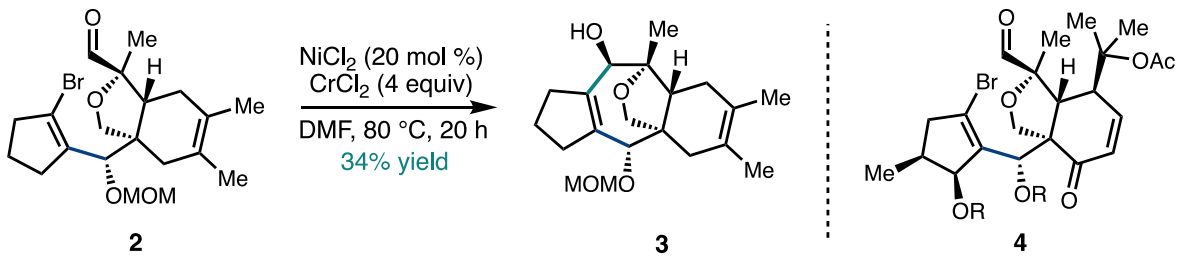
Falcatin A (**1**) is a myrsinane diterpene isolated from *Euphorbia falcata*.[1] Falcatin A was found to block G protein-activated inwardly rectifying potassium ion (GIRK) channels, abnormalities in which are implicated in the pathophysiology of cardiac arrhythmias.[2] In addition to its potential anti-arrhythmic activity, **1** is also an attractive synthetic target due to its structural complexity. No total syntheses of **1** have been disclosed to date.



1

We describe herein our efforts toward the synthesis of falcatin A via a convergent fragment coupling/scaffold tailoring approach. Our initial work was directed toward the construction of model substrate **2** to test our key bond-forming transformations. Upon synthesis of **2**, we were pleased to find that we could form the challenging 7-membered ring of falcatin A using a Nozaki–Hiyama–Kishi reaction, affording **3** in 34% yield. We are currently developing a route to fully elaborated substrate **4**, which we anticipate will be advanced to the natural product in a short series of functional group manipulations following 7-membered ring formation.



2 **3** **4**

Acknowledgements: K. R. H. is supported by a National Defense Science and Engineering Graduate Fellowship. S. E. R. is a Heritage Medical Research Institute Investigator and acknowledges financial support from the NSF (CHE-1800536).

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HORAN

Synthesis of pyridylsulfonium salts and their application in sulfur-mediated bis-heteroaryl synthesis

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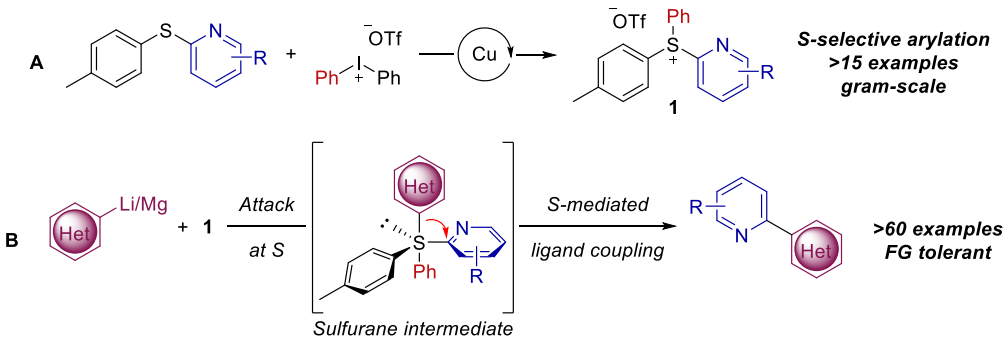
Sulfonium salts have been shown to be highly versatile synthetic reagents.[1] Synthetic routes to pyridylsulfonium salts are rare and their utility as functional handles remains underexplored. Bipyridines are used abundantly as ligands in transition metal catalysis.[2] Transition metal-catalysed routes to bipyridines have significant limitations.[3] Recently, alternative transition metal-free syntheses of heterobiaryls using phosphorus- and sulfur-mediated ligand coupling strategies have been reported.[4,5] We disclose a complementary sulfur-mediated bipyridine synthesis using novel pyridylsulfonium salts, addressing previous limitations such as 2,3-bipyridine synthesis.[6]

Presented herein is the development of an S-selective arylation methodology of pyridylsulfides (**A**). Novel, bench-stable pyridylsulfonium salts (**1**) are produced on gram scale and have been applied in transition metal-free bis-heteroaryl synthesis (**B**). The addition of lithiated pyridines to **1** is proposed to proceed *via* a sulfurane intermediate, with subsequent ligand coupling yielding the desired bipyridine product. Symmetrical and unsymmetrical 2,2'- and 2,3'-bipyridines have been synthesized, and extensive functional group tolerance is demonstrated.[6] Recent advances in this project have shown magnesiated pyridines to be advantageous coupling partners in addressing previous limitations.[7]



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HUBBELL

Progress in the novel total syntheses of the ugibohlin natural products

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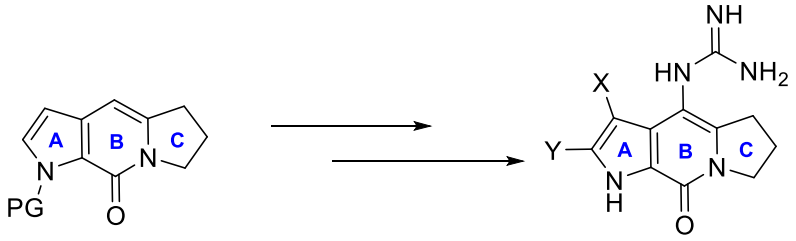
The pyrrole-imidazole alkaloid family of natural products contain an immense number of biological activities including anticancer and immunosuppressive activities. Among this group are the ugibohlin natural products including ugibohlin[1], 4-debromougibohlin and 5-debromougibohlin. These compact marine sponge metabolites contain a 1,5,6,7-tetrahydro-9H-pyrrolo[2,3-f]indolizin-9-one tricyclic ABC core common to many biologically active bromopyrrole alkaloids. The ugibohlins contain a guanidyl moiety at the 4-position of the central pyridone ring and differ only in the substitution and number of bromine atoms located within their pyrrole rings. The synthesis of ugibohlin was previously reported by the Lindel group in 2009 and was achieved from conversion of presynthesized *rac*-dibromoisophakellin under acidic conditions.[2] However, the recently discovered debromougibohlins[3] have yet to undergo total synthesis. Previous reports have focused upon synthesis of the tricyclic ABC ugibohlin core, as it is a central feature to other complex bromopyrrole alkaloids including the yet-to-be-synthesized styloguanidines.[4,5] Key challenges associated with synthesis and transformation of the core include regioselective functionalization[4] and introduction of a suitable amino group at the C-4 position of the pyridone ring. The latter approach is especially challenging, as C-4 aminated species undergo facile auto-oxidation to afford α-hydroxy ketones.[5] With these challenges in mind, we have sought to explore a novel synthetic approach towards the ugibohlins utilizing a late-stage regioselective guanidylation of the pyridone core. We describe herein progress in a novel approach to the tricycle and subsequent studies in its functionalization.



ugibohlin (X,Y= Br)
4-debromougibohlin (X=H, Y=Br)
5-debromougibohlin (X=Br, Y=H)

Acknowledgements: Support for this research is provided by National Institutes of Health R01 AG066223-01A1.

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HWANG

Chirality-Matched Catalyst-Controlled Macrocyclizations

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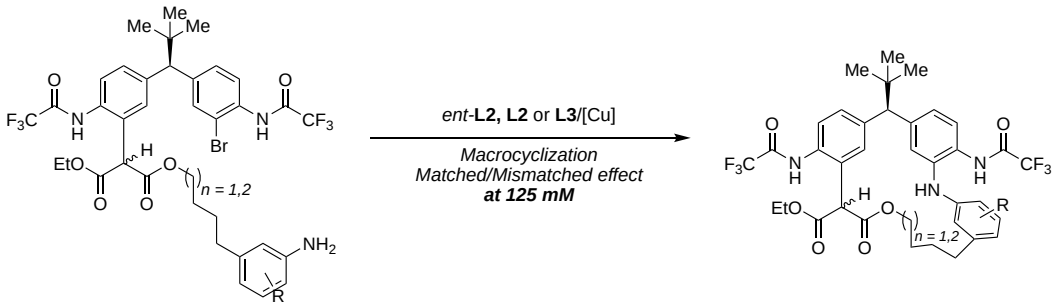
Macrocycles, formally defined as compounds that contain a ring with 12 or more atoms, continue to attract great interest due to their important applications in physical, pharmacological and environmental sciences. In syntheses of macrocyclic compounds, the ring closing step is often considered the most challenging step, as competing di- and oligomerization pathways must be overcome to favor intramolecular reaction. Furthermore, syntheses of macrocycles with stereogenic elements confer an additional challenge, while access to such macrocycles are of great interest. Herein, we have reported the remarkable effect peptide-based catalysts can have in promoting macrocyclization reactions. We show that the chirality of the catalyst is essential for promoting favorable, matched transition state relationships that favor macrocyclization of substrates with pre-existing stereogenic elements; curiously, the chirality of the catalyst is essential for successful reactions, even though no new stereogenic elements are created (Scheme 1). Control experiments involving either achiral variants of the catalyst, or the enantiomeric form of the catalyst, fail to deliver the macrocycles in significant quantity in head-to-head comparisons. The generality of the phenomenon, demonstrated here with a number of substrates with varying substituents and two ring sizes, stimulates analogies to enzymatic catalysts that produce naturally occurring macrocycles, presumably through related, catalyst-defined outer-sphere interactions with their acyclic substrates.[1]



*for R = o-Me, n = 1

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[1] *Manuscript submitted.*

Cyclic Amphipathic Peptides for Improved siRNA Delivery

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Oligonucleotide therapeutics present advantages for treating a variety of genetic diseases; however, their application in clinical settings has been limited by significant challenges in their delivery.[1] To address this issue, we are currently investigating utilization of disulfide-constrained cyclic amphipathic cell-penetrating peptides (CAPs) for the delivery of siRNA (**Fig. 1**) towards developing therapeutics to treat acute respiratory distress syndrome (ARDS), a pathology resulting from conditions including sepsis, severe trauma, and bacterial/viral pneumonia, including SARS-Cov-2[2,3].

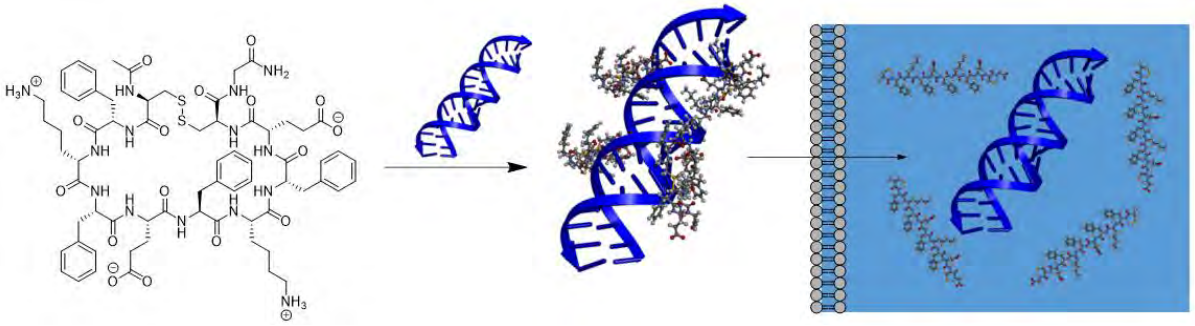

Figure 1. Schematic representation of CAP-siRNA delivery system.

We have demonstrated that our CAPs can facilitate significant knockdown *in vitro* and *in vivo* in lung epithelium.[4] Cyclic Ac-C(FKFE)$_2$CG-NH$_2$ and Ac-C(WR)$_4$CG-NH$_2$ peptides complexed with rhodium-labeled siRNA to form CAP-siRNA nanoparticles were tested in human A549 lung cancer cells, with (WR)$_4$ demonstrating significantly enhanced cytosolic delivery.[4] *In vivo* studies utilized our CAPs complexed with thyroid transcription factor-1 (TTF-1) siRNA, resulting in approximately 80% gene knockdown. Additionally, we are interested in investigating the importance of peptide sequence on (1) siRNA binding efficiency, (2) cellular delivery and (3) endocytic uptake mechanism. Specifically, we are probing the effect of tryptophan on siRNA binding, the role of the guanidinium ion of arginine when compared to the ammonium ion of lysine both with and without tryptophan present, and the possible role of CH-π hydrogen-bonding[5] with aromatic amino acids and the carbohydrate backbone.

Acknowledgements: Support for this research is provided by the the National Institutes of Health (EB9903 and HLI20521) and by the National Science Foundation (DMR-1148836, CHE-0840410, and CHE-0946653).

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JAIME

Synthesis of Bifunctional Chiral Amide Catalysts and H-bonding with Silanediols

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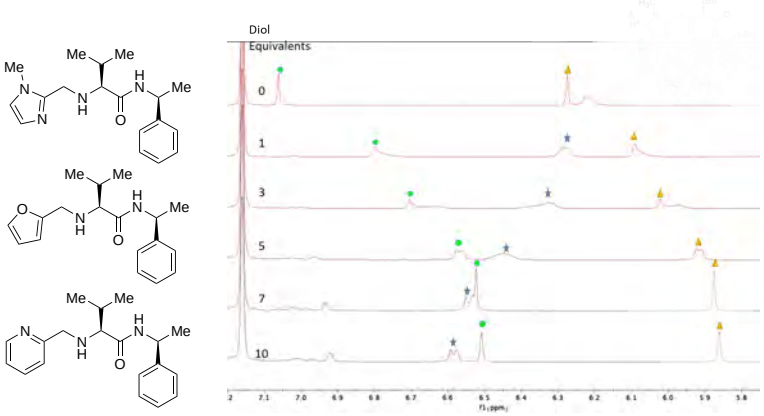
Silicon can be found in many organic compounds such as in everyday products ranging from agricultural chemicals to personal care products[1,2,3,4]. Previous work in the Franz group has demonstrated that silanol-containing organic catalysts possess unique hydrogen-bonding and anion-recognition properties[3]; however, reactions to selectively produce chiral-at-silicon center remain limited[5,6,7]. In order to develop new methods for the selective synthesis of molecules with stereogenic silicon centers, we have investigated molecular recognition of silanediols with bifunctional chiral amide catalysts. This work describes a four-step procedure for the synthesis of several bifunctional chiral amide catalysts related to an imidazole catalyst first reported by Hoveyda and Snapper[8]. After synthesizing these catalyst analogs, we will use ^{1}H NMR spectroscopy to compare the binding interactions of the modified catalysts and the Hoveyda-Snapper catalyst by measuring the silanediol peaks shifts after saturation.



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JONES

Biomimetic Macrolactonizations in Pursuit of Marine Natural Products

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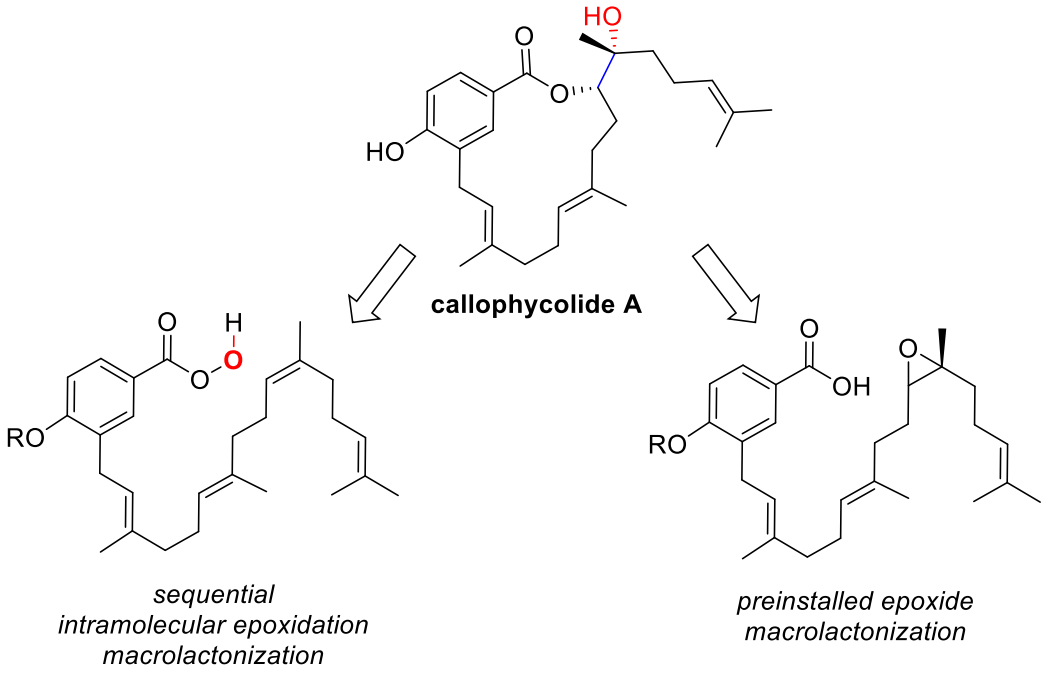
Natural products continue to play a vital role in the development and inspiration of drug discovery programs. While terrestrial natural products have been the most prevalent in this context, their marine counterparts are of increasing interest to the medicinal community given their high degree of chemical diversity. With a rise in marine natural product discovery and subsequent biological evaluations yielding promising results, there is a need to access these unique and complex scaffolds in step-efficient manner. Currently, we are exploring the potential of a two-step intramolecular reaction to access a novel macrolide in a biologically promising marine natural product family.



Acknowledgements: LJ is supported through Presidential and Specic Fellowships through Georgia Institute of Technology.

KAUR

Building EDI Connections at the University of Calgary

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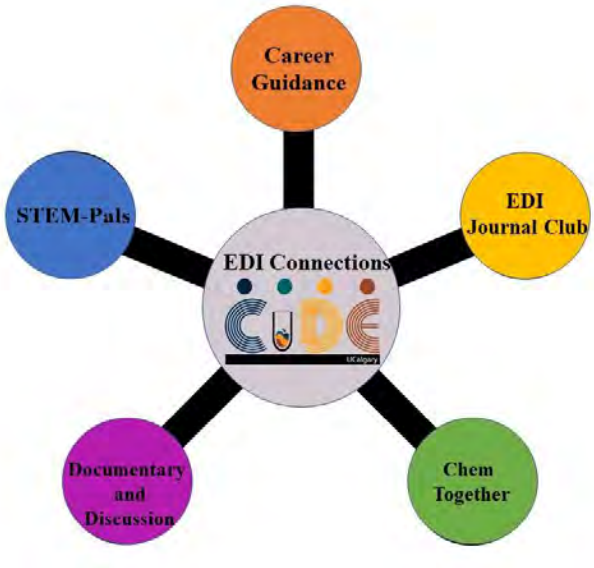
Founded in July 2020, UCalgary Chemists for Inclusion, Diversity and Equity (UCalgary CIDE) is a Chapter of the Canadians Working for Inclusivity in Chemical Sciences, Engineering, and Technology (CWIC) network. The team members are working towards promoting inclusivity, diversity and equity in the chemical sciences and engineering by connecting their members (including students, postdoctoral researchers, staff, and faculty), as well as by connecting with other CWIC Chapters across Canada. Over the last couple of months, CIDE has regularly organized various thought-provoking, diverse networking events such as EDI Journal club, Picture A Scientist - Documentary and Discussion, CHEM Together, STEM-Pals, Black History Month, IUPAC-GWB event, and a Career Guidance Panel Discussion, focusing on bringing diverse audiences together with the goals of leading to lifelong connections and strengthen the community. Through this talk we will show our strategies to support diverse communities through various collaborations and personal experiences in the pandemic context. We believe that building such connections in the world of science can contribute towards innovation and creativity that can help both in tackling global problems and benefiting humanity.



KAUR

New Radical Strategy for Site Selective C-H Functionalization in Azaheterocycles

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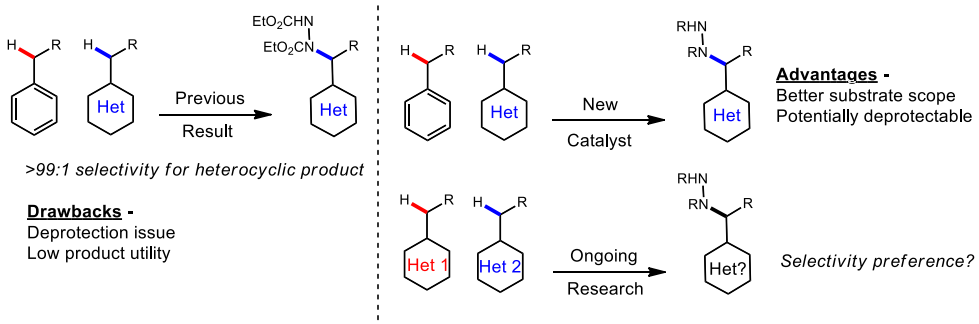
Research in the field of C-H functionalization has modified the way chemists approach the synthesis of natural products and medicinally relevant synthetic molecules. However, there has been a noticeable challenge in 1) Carrying competitive C-H functionalization when several sites of comparable reactivity are present. 2) Accessing many possible reactive sites within such a substrate. Our research group is working on addressing these challenges by developing a novel C-H amination strategy for heterocyclic substrate using a dual catalytic system - consisting of transition metal Lewis acid and an organic hydrogen atom transfer (HAT) catalyst.[1,2] Our current work is working towards a more challenging problem: Can we develop a catalytic system that 1) can synthesize complex substrates under mild conditions; 2) can selectively activate one heterocycle in the presence of a second heterocycle. Ideally, we aim to create complementary catalysts systems that allow for selective functionalization of *either* heterocycle in the pair. Our preliminary results reveal that our new catalytic system 1) offers a lot of advantages over previously used aminating reagent; 2) can lead to activation of C-H bonds in different heterocyclic substrates and is impacted by the specific catalyst combination (copper source, ligand and HAT), and that in the case of particular heterocycle pairs (*e.g.* heterocycles with vs. without metal chelating groups) selectivity for either component of the pair can be achieved.



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KENNELLY

Investigating Ligands to Disrupt the Binding Interaction of SARS-CoV-2 Receptor-Binding Domain Using Bio-Layer Interferometry

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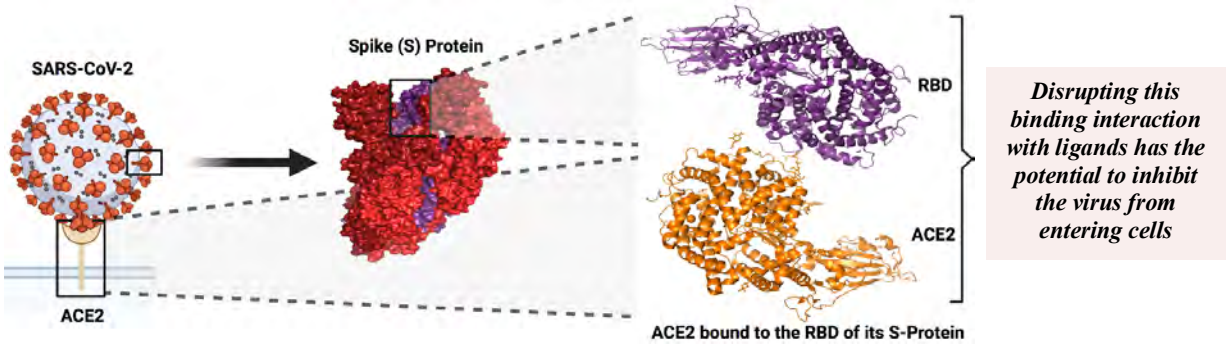
With the outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) leaving an immeasurable toll on the human population, there lies a significant need for foundational studies of virus-host receptor interactions and new therapeutics. We are investigating the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein using bio-layer interferometry (BLI). Using this biophysical technique, we are examining the RBD of SARS-CoV-2 interactions with the host cell receptor, angiotensin-converting enzyme 2 (ACE2), as well as RBD-binding peptides and DNA aptamers against the RBDs of both SARS-CoV-2 and SARS-CoV. The poster will detail our assay optimizations and set-up, as well as report compounds screened in our assay along with their binding affinities. We hope to utilize our optimized assay for evaluating compounds that are undergoing development as new therapeutics for SARS-CoV-2.



KENNEMUR

The Development of Strong Chiral Brønsted Acids for Asymmetric Functionalizations of Simple Olefins

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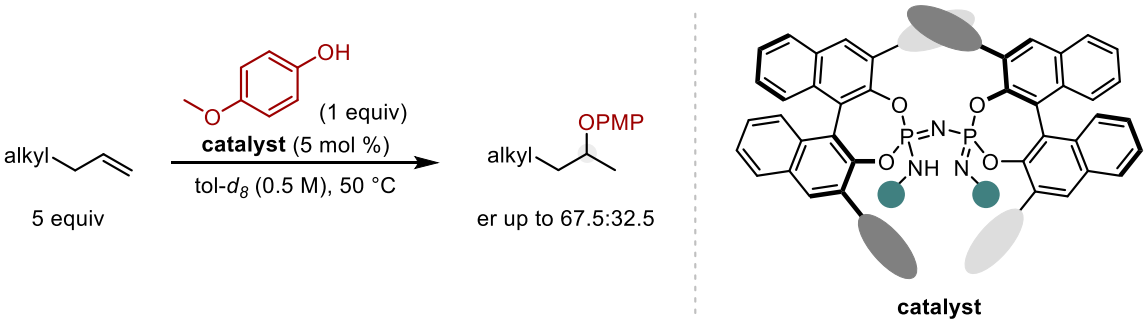
While a number of transition-metal catalyzed approaches toward asymmetric hydrofunctionalization reactions of olefins have been developed, enantioselective hydroalkoxylations remain relatively elusive.[1] It is hypothesized that asymmetric hydroalkoxylations will be particularly challenging for transition-metal systems due to so-called *hidden acid catalysis*, i.e. the propensity of such complexes to release competent Brønsted acids, inducing non-asymmetric background reactivity.[2] Alternatively, enzymes exhibit an extraordinary capacity to activate simple olefins[3]; however, an efficient and general enzymatic approach to asymmetric hydroalkoxylations of simple olefins is yet to be disclosed.[4] As part of our program on asymmetric counteranion-directed catalysis, we aim to design and synthesize strong chiral Brønsted acids that can engage weakly basic olefin moieties within a highly-confined, enzyme-like microenvironment. We have previously reported the early fruition of these goals with an intermolecular hydroalkoxylation reaction of styrene with benzyl alcohol to afford the corresponding ether in 95% yield with a very promising enantioselectivity (er = 76.5:23.5).[5] Herein, we show the expansion of this methodology to structurally-simple, yet chemically challenging olefins and report efficient hydroalkoxylations of alkyl-substituted olefins with moderate levels of enantioselectivity (er up to 67.5:32.5). In an effort to improve upon the enantioselectivity of this reaction, we recently designed and synthesized a new class of chiral catalysts with dramatically increased acidity and two additional chiral handles within the catalyst pocket. With this new catalyst motif in hand, our current investigations are aimed at further establishing organocatalysis as a proficient strategy to activate simple olefins for a myriad of asymmetric chemical transformations.



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KLEIN

Synthetic Routes towards an Azatitanacyclohexadiene

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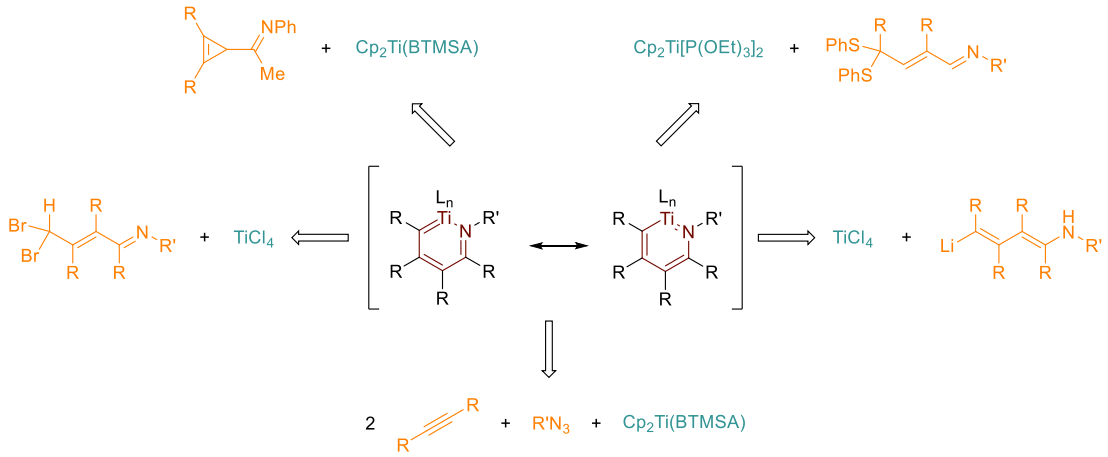
Pyrroles are a very common motif in industrial fine chemicals, including pharmaceuticals and herbicides.[1] Despite their ubiquity, many highly-decorated pyrroles are still difficult to access synthetically.[2] Tonks and co-workers reported in 2016 an atom-economical and sustainable route to pyrroles via Ti-catalyzed [2+2+1] coupling of alkynes and diazenes.[3] Subsequent mechanistic studies showed that pyrrole formation occurred via Ti^{IV}-Ti^{II} reductive elimination, which is rare in the literature. However, this step was never characterized experimentally as it occurs after the rate-determining second alkyne insertion.[4] Therefore, the primary aim of this project was independent synthesis of an azatitanacyclohexadiene, as it was envisioned that the reactivity of this complex might inform further Ti redox chemistry.

Multiple approaches to azatitanacyclohexadiene synthesis were attempted, including carbene, cyclopropenyl imine, and alkyne precursors (Scheme 1). The synthesis of an azatitanacyclohexadiene has yet to be accomplished; however, the multicomponent approach led to the synthesis and characterization of two novel Ti complexes, a Ti imido dimer and an azatitanacyclobutene. This exploration of a relatively underexplored chemical space has revealed new reactivities of Ti and may guide further attempts at synthesis of this elusive complex.



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KORCH

Total Synthesis of Impatien A: Utilizing a Novel Cyclization

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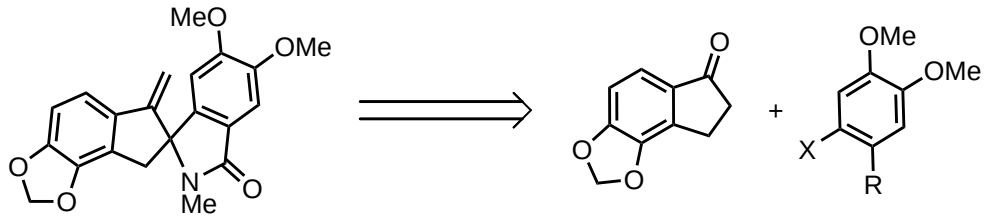
Impatien A, an isoindolone natural product isolated from *Corydalis impatiens* possess a scaffold featuring a spirocyclic stereogenic center and an adjacent exocyclic methylene. While the closely related natural product ochotensimine has been shown to inhibit TNF-α production and it exists as a single enantiomer, much less is known about the related impatien A. Construction of the key spirocyclic center and exocyclic methylene of impatien A poses a challenge in both racemic and enantioenriched forms. We envisioned a metal-catalysed approach to the creation of these adjacent functionalities which would be amenable to asymmetric induction. From readily available starting material, the substituted indanone and an arene tagged with a cross-coupling handle can be synthesized with minimal chromatographic steps. Key palladium-catalysed arylation couples these two fragments and a subsequent palladium-catalysed 5-*exo* cyclization allows for the construction of the spirocyclic framework. Introduction of the methyl group furnishes impatien A.



Impatien A

Acknowledgements: Support for this research is provided by University of Delaware.

KOSTENKOVA

Conformation of Truncated Ubiquinone in the Respiratory Complex

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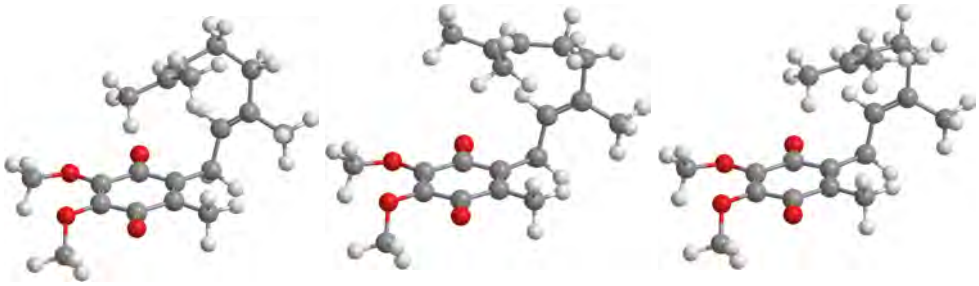
Ubiquinone is an essential component of the electron transport chain in mammals and most bacteria and participates in aerobic cellular respiration. Despite the importance of ubiquinone to life, little is understood about the conformation of the isoprenyl side-chain with respect to the quinone moiety within the cellular membrane. Lipoquinones, such as ubiquinone, are generally depicted in extended conformations in primary literature. Very few studies explored conformations of the side chain in the cellular membrane, and the reported computational studies focused on the location of the headgroup rather than the location of the isoprene tail. The assumptions about extended conformations are still widespread even though model studies have been reported suggesting that the ubiquinone structures may not be the all-trans extended conformation. In this context, we describe herein a series of ^{1}H-^{1}H 2D NMR (NOESY and ROESY) spectroscopic studies of a simple analog, ubiquinone-2 (UQ-2), that demonstrated that UQ-2 adopts a folded conformation in polar and non-polar organic solvents (Scheme 1). These conformational studies are important, as the conformations of a simple UQ-2 analog can be compared to ubiquinone-10, a cofactor in the eukaryotic electron transport chain. The differences in conformation within the cellular membrane likely impact reactivity of UQ-10 in vital cellular redox processes.

Scheme 1. UQ-2 conformations elucidated by the 2D NMR spectroscopic studies in a) DMSO-d_6, b) benzene-d_6 and c) model membrane interface system



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KUMAR

Effect of connectivity variation in Azulene-BODIPY triads and their optoelectronic properties

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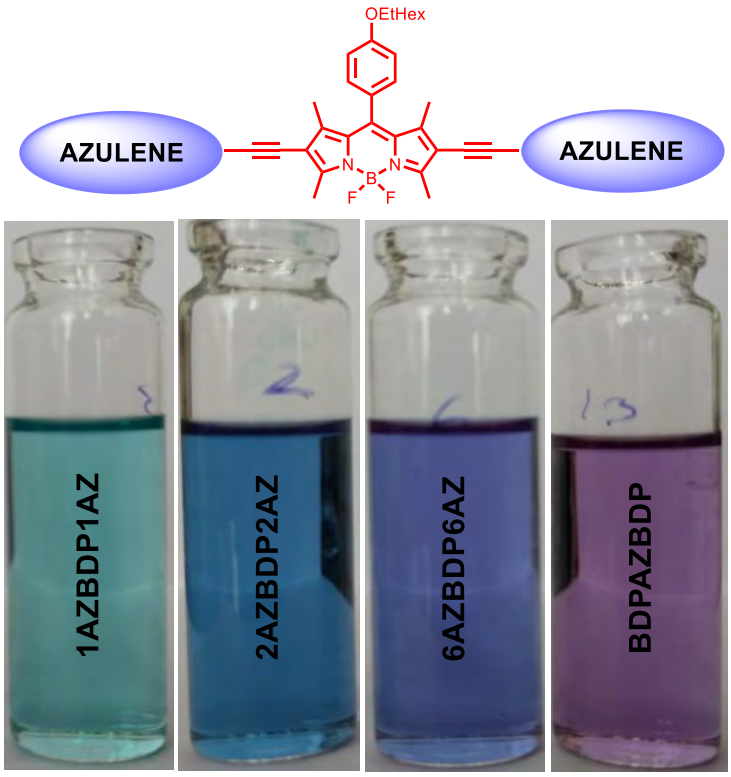
Here we discuss the synthesis of a series of Azulene-BODIPY triads with acetylene spacer by varying the linking position of azulene. In solution phase the introduction of 1-azulenyl moieties onto the BODIPY core results in more red-shifted absorption band and the shift is lowest for the triad consisting of single azulene unit linked to BODIPY chromophore via 1,3-position. All the molecules are highly stable making them promising candidates for application in organic electronic devices. The results indicate that the polarity change of organic FETs based on the four isomeric triads could be controlled by the molecular orbital distributions through the connection position between the azulene unit and BODIPY.



Acknowledgements: Support for this research is provided by the SERB, India, (CRG/2018/002784).

LABADIE

Studies on the Diels-Alder Reactions of Allenylboronic Acid Pinacol Ester

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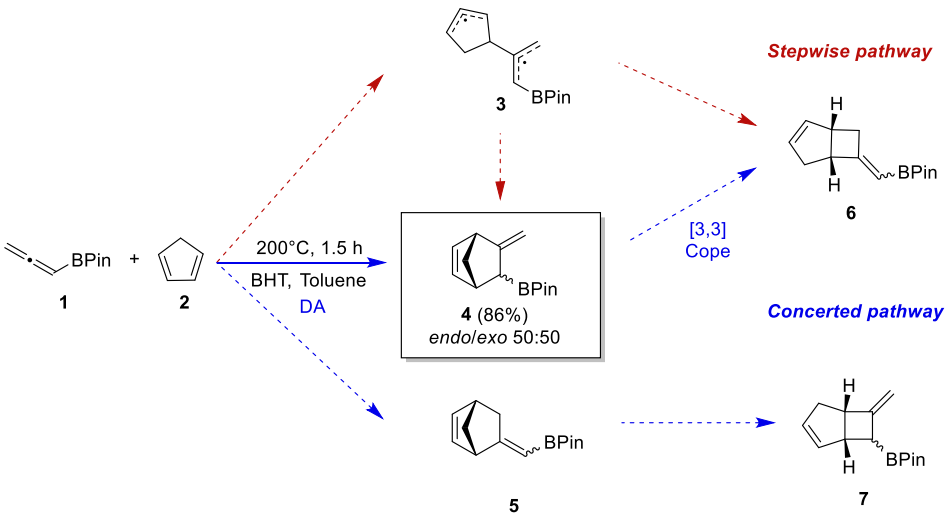
Allenes are compounds with two contiguous double bonds that react in a particular manner due to their structural features.[1] They participate in [4+2], [3+2] and [2+2] cycloadditions, both under thermal and photochemical conditions. Allenylboron compounds, in particular, have been used in a variety of organic reactions[2] but, curiously, their potential in cycloaddition reactions has not been addressed yet. Our group has been advocated to the study of the reactivity of varied boron-substituted alkenes and alkynes as Diels-Alder (DA) dienophiles, so we aimed to explore the reactivity in allenylboron compounds in DA reactions. Initially, the DA reaction between allenylboronic acid pinacol ester (**1**) and cyclopentadiene (**2**) was developed.[3] In this work, we present the results of a computational study of the competing concerted and stepwise mechanisms for the formation of all possible cycloadducts. Furthermore, the catalytic version of the DA reaction, as well as the reactivity of **1** with different dienes have been explored. Also, we have investigated further functionalizations of cycloadducts **4** to demonstrate the synthetic potential of the studied transformation.



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3 Manuscript submitted for publication.

LADD

Evaluation of *ortho*-Phenylenediamine (*o*PD) as an Additive for Glacial Acrylic Acid (GAA) Production

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Dow is one of the leading global manufacturers of Glacial Acrylic Acid (GAA), a key monomer used in the manufacture of superabsorbent polymers (SAPs) commonly found in various consumer-end products including disposable diapers, construction, oil field and other industrial chemical applications.

Acrylic acid is primarily manufactured via a heterogeneous two-stage propylene oxidation process using mixed metal oxide (MMO) catalysts. Such MMO catalysts are not 100% selective and generate minor carbonyl-containing impurities that are undesirable in SAP manufacturing processes. Consequently, global GAA manufacturers have developed various technological approaches to eliminate unwanted carbonyl impurities. One strategy involves chemically treating crude acrylic acid with a carbonyl sequestration additive via reactive distillation.

Dow Performance Monomers recently evaluated *ortho*-Phenylenediamine (*o*PD) as a potential, cost-effective additive for GAA production. Relative reaction rates, byproduct composition, fouling risks, process safety, product quality, environmental impact and financial benefit were the key criteria studied prior to scale-up and commercialization. This poster will outline process and economic considerations, will summarize the experimental program conducted to assess the performance of *o*PD as a novel additive for this application, and will provide insights regarding key considerations influencing the technical team's scale-up recommendations.

LEUNG

Development of a Scalable Synthesis of *trans*-4-Fluorocyclohexylamine via Directed Hydrogenation

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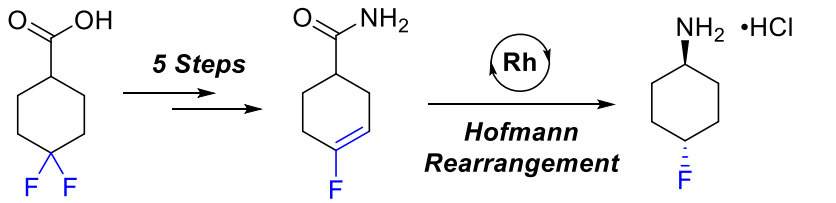
Herein, a scalable and practical process to prepare *trans*-4-fluorocyclohexylamine hydrochloride is presented. By exploiting the embedded *gem*-difluoride motif in the commercially available 4,4-difluorocyclohexanecarboxylic acid, a derived orthoester-masked acid underwent dehydrofluorination to provide the requisite vinyl fluoride for a directed hydrogenation event, enabling selective access to the *trans*-configuration of 4-fluorocyclohexylamine hydrochloride.



53.5% overall yield, 7 steps

LI

Exploring Anion Binding and Self-Assembly with Lower Symmetry Macrocycles

Yan Li,[†] James R. Dobscha,[†] Henry Castillo,[†] Steven L. Tait[†] and Amar H. Flood*,[†]
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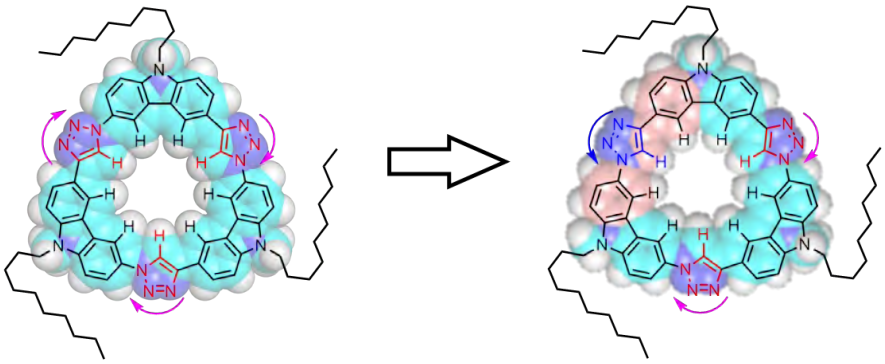
C$_3$ Symmetric tricarbazole trizazolophanes (tricarb) are shape-persistent macrocycles that are able to bind anions in the inner cavity and to display self-assembly in both solution phases and on the graphite surfaces.[1] Here, we synthesized a tricarb derivative with the orientation of one triazole moiety flipped using the modified version of the previously reported stepwise synthetic strategy.[2] The change of the orientation of one triazole broke the *C*$_3$ symmetry of the tricarb skeleton, leading to a disruption of the alignment of the alternating local dipoles on the tricarb skeleton, which is hypothesized to weaken the dipole-enhanced π-stacking and hence to impact the macrocycle's self-association in solution phases and the cooperativity of the 2:1 complexation with anions. The breaking of the *C*$_3$ symmetry on the macrocyclic skeleton also influenced the lateral hydrogen bonding arrays in between adjacent tricarb macrocycles, which led to changes in relative energies of self-assembly polymorphs of tricarb macrocycles on the graphite surfaces. This work highlighted our ability to control the build-up and the symmetry of macrocyclic skeleton by synthetic design, and will contribute to the understandings of the dipole-enhanced π-stacking and the roles of symmetries in macrocyclic functions.



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LIN (PATRICIA)

Mechanistic Studies of Nickel-Catalyzed Cross-Electrophile Coupling Reaction

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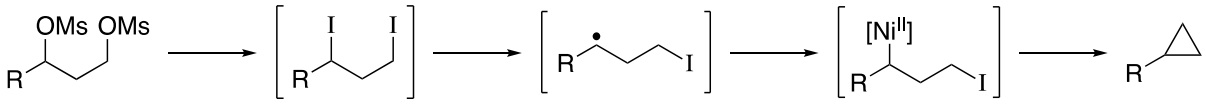
We have recently developed the nickel-catalyzed intramolecular cross-electrophile coupling (XEC) reaction of 1,3-dimesylates to synthesize cyclopropanes. Through initial mechanistic studies, it was determined that the dimesylates are converted into diiodides in situ. Then, halogen atom abstraction by the nickel catalyst at the secondary center forms a secondary alkyl radical species, which recombines with the nickel(I) species to yield an organonickel(II) intermediate. The lifetime of the secondary alkyl radical intermediate in the nickel-catalyzed XEC reaction of 1,3-dimesylates was investigated through the use of radical clock experiments.



LIN (ZHENG SONIA)

Reaction of 3-Cl/OMe Substituted 5-Nitrobenzisothiazoles with Hydrazine: Structural and Computational Evidence for Rearrangement Pathways Involving Intramolecular Formation of Pivotal Meisenheimer Complexes

Zheng Sonia Lin,[1] Xing Tong, [2,3] Brian Patrick,[2] Pierre Kennepohl,[2,3] and David Grierson*,[1]
[1]*Faculty of Pharmaceutical Sciences, University of British Columbia, 2405 Wesbrook Mall, Vancouver, BC V6T 1Z3,* [2]*Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC, V6T 1Z1,* [3]*Department of Chemistry, University of Calgary, 2500 University Drive NW, Calgary AB T2N 1N4*
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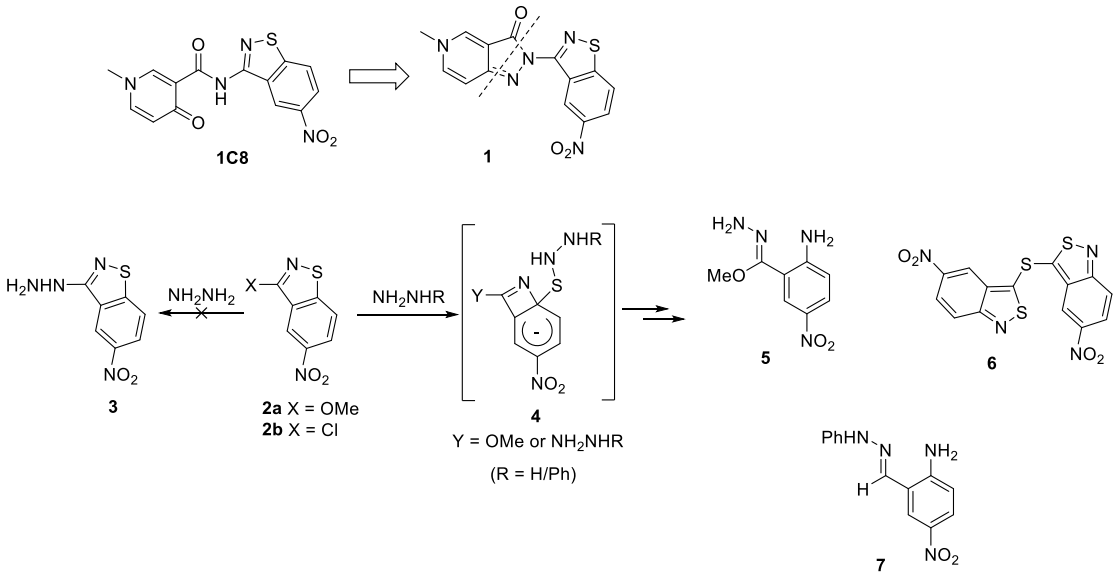
In projected SAR studies on the novel diheteroarylamide-based anti-HIV agent (1C8), one objective was to evaluate the influence of incorporating the central amide motif into a 5-membered pyrazolone ring (**1**). It was envisaged that the key 3-hydrazino-5-nitrobenzisothiazole intermediate (**3**) for the synthesis of pyrazolone analogue **1** could be prepared through reaction of the reaction of 3-methoxy / 3-chloro-5-nitrobenzisothiazole (**2a** and **2b**) with hydrazine. Surprisingly, the compounds isolated in these reactions corresponded to ring-opened hydrazonate **5** and S-bridged-2,1-benzisothiazole dimer **6**.[1] In a further study where **2b** was reacted with phenylhydrazine, a different rearranged product **7** was isolated. Meisenheimer complex (**4**) formation, favored by the presence of the 5-nitro substituent on the benzisothiazole ring, was postulated to be a key feature in the formation of these deep-seated rearranged products. Mechanisms leading to the formation of the rearranged products, supported by Density Function Theory calculations, will be presented.



Acknowledgements: This work was generously supported by grants from the Canadian Institutes of Health Research (CIHR) and NSERC (Discovery). NSERC Discovery grant number: 2016-05453. CIHR Doctoral Scholarship number: 293029.

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Enhancing Cooperativity in Double Helical Photofoldamers by Modular Sequence Control

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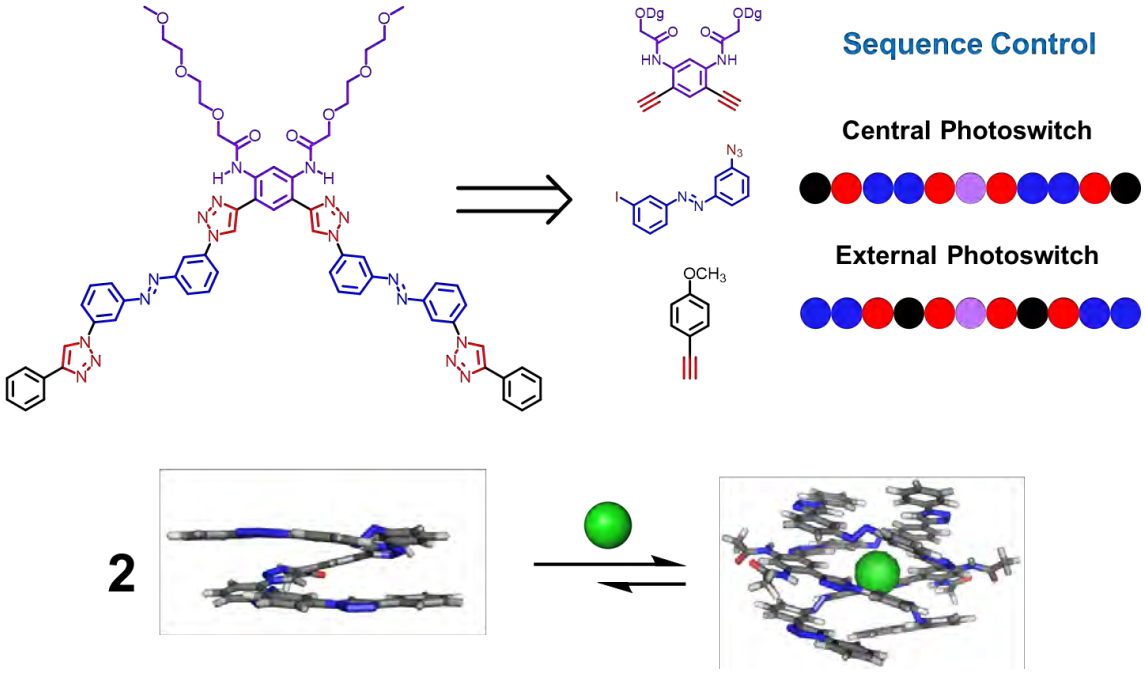
The regulation and control of anions is critical for human health, clean water, nuclear waste remediation, and more recently anion recognition has been used in catalysis. Anion concentration in solution can be regulated using switchable receptors, where binding affinity can be modulated by an external stimulus. Photofoldamers, containing azobenzene photoswitches, are readily synthesized using copper(I) catalyzed azide-alkyne cycloaddition of modular, small organic building blocks. While the photoswitchable motif within an anion recognition photofoldamer is known to create an observable affinity swing (K_{ON} / K_{OFF}),[1] the influence it has on guest recognition of any sort remains underexplored. Exploring knowledge from previous work in the Flood lab using sequence specific control to drive double helical formation,[2] we designed and synthesized two photofoldamers containing an external azobenzene and an internal azobenzene to study the structure-function properties of the photoswitch. We find that placement of the isosteric azo groups can either enhance or lower cooperativity. Isomerization with UV light is expected to break apart the stronger binding double helix into a weaker binding single helix. We expect this noninvasive method to capture and release anions can be exploited in liquid-liquid extractions to improve extraction efficiency.



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LYNCH-COLAMETA

Synthesis of Aza-Quaternary Centers via Pictet–Spengler Reactions of Ketonitrones

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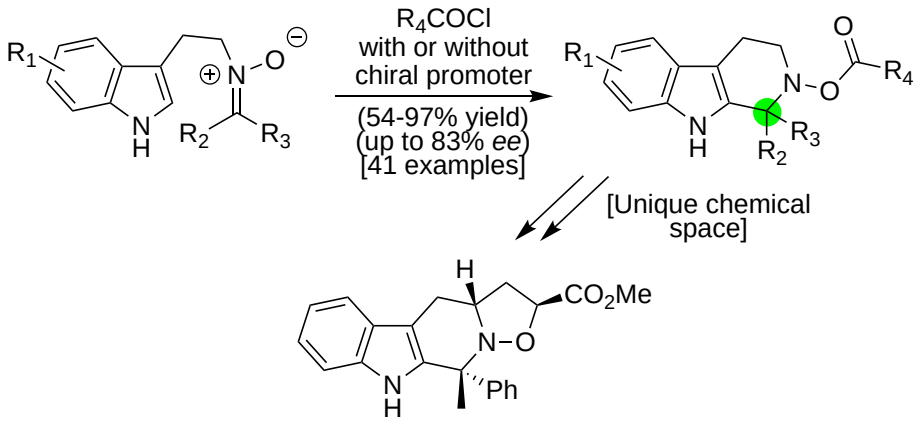
Despite the array of advances that have been made in Pictet–Spengler chemistry, particularly as it relates to the synthesis of β-carboline derivatives of both natural and designed origin, the ability to use such reactions to generate aza-quaternary centers remains limited.[1] Herein, we report a simple procedure that enables the synthesis of a variety of such products by harnessing the distinct reactivity profiles of ketonitrones as activated by commercially available acyl chlorides.[2] Notably, the reaction process is mild, fast, and high-yielding (54–97%) for a diverse collection of substrates, including some typically challenging ones, such as indole cores with electron-deficient substituents. In addition, by deploying an acyl bromide in combination with a thiourea promoter, a catalytic, asymmetric version has been established, leading to good levels of enantioselectivity (up to 83% *ee*) for several ketonitrones. Finally, the resultant N–O bonds within the products can also be functionalized in several unique ways, affording valuable complementarity to existing Pictet–Spengler variants based on the use of imines.



Acknowledgements: We thank Dr. Alexander Filatov, Dr. Andrew McNeece, and Ms. Kate Jesse for X-ray analysis, and Dr. Josh Kurutz, Dr. Antoni Jurkiewicz, and Dr. C. Jin Qin for assistance with NMR and mass spectrometry. We also wish to thank colleagues at Merck for donating several ureas and thioureas, as well as the Rawal group for several squaramide and thiosquaramide precursors. Financial support for this work came from the University of Chicago and the Jeff Metcalf Summer Internship Program (Fellowship to S.G.).

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MARTIC

Selective electrooxidation of substituted phenols towards new C-C bond formation

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Electrocatalytic transformations giving rise to new C-C bond formation and new products is of value. We have recently discovered that phenolic compounds undergo selective electrochemical oxidation giving rise to reactive radicals which combine to produce product with new C-C bond formed [1]. Five phenolic compounds including butylated hydroxytoluene (BHT), 4-*tert*-butylphenol (4TBP), 2-*tert*-butylphenol (2TBP), 2,4,6-tri-*tert*-butylphenol (TTBP), and 2,6,-di-*tert*-butylphenol (DTBP) were systematically evaluated by electrochemical methods to determine their oxidation/reduction potentials as a function of concentration. At identical experimental conditions, only DTBP exhibited electrochromic behavior which was dependent on concentration and electrochemical cycling. The electrocatalytic oxidation of DTBP resulted in a formation of a new compounds due to C-C coupling. The reaction was monitored by electrochemical methods, UV-vis spectroscopy and final product characterized by X-ray diffraction. Current efforts in expanding the electrocatalysis to include diverse phenolics will also be described.

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MASON

Scalable On-Demand Production of Purified Diazomethane Suitable for Sensitive Catalytic Reactions

Sara Mason, Jillian W. Sheeran, Kiersten Campbell, Christopher P. Breen, Gerald Hummel, Changfeng Huang, Anamika Datta, Serge H. Boyer, Scott J. Hecker, Matthew M. Bio, Yuan-Qing Fang, David D. Ford*, and M. Grace Russell *.
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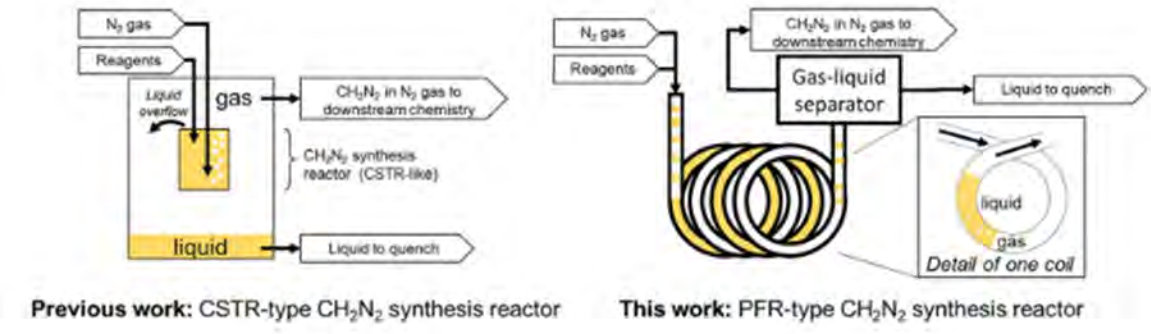
We have developed a convenient development-scale reactor (0.44 mol/h) to prepare diazomethane from N-methyl-N-nitroso-p-toluenesulfonamide (MNTS) in~80% yield. Building off previous work using a CSTR-type reactor we have moved forward to a continuous PFR-type reactor. Diazomethane (CH_2N_2) made with this reactor is extracted into nitrogen gas from the liquid reaction mixture, effectively removing it from reagents and byproducts that may interfere in subsequent reactions. The CH_2N_2/N_2 gas mixture is then available to use in subsequent reactions. Vertically oriented tubular reactors were used to produce and consume diazomethane in situ. Key features of this reactor include high productivity and correspondingly low reactor and a commercially available gas/liquid separator equipped with a selectively permeating hydrophilic membrane. The design of the reactor keeps the inventory below 53 mg of CH_2N_2 during normal operation. The reactor was demonstrated by generating CH_2N_2 that was used in a connected continuous reactor. We evaluated esterification reactions and a continuous Pd-catalyzed cyclopropanation reaction with the reactor and achieved high conversion.



Acknowledgements: This project was funded in part with Federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority (BARDA), under OTA number HHSO100201600026C.

Reference: Org. Process Res. Dev. 2021, 25, 3, 522–528.

MCKNIGHT

Avidity Optimization of Anti-EGFR Fibronectin Bispecific Chemically Self-Assembled Nanorings (CSANs)

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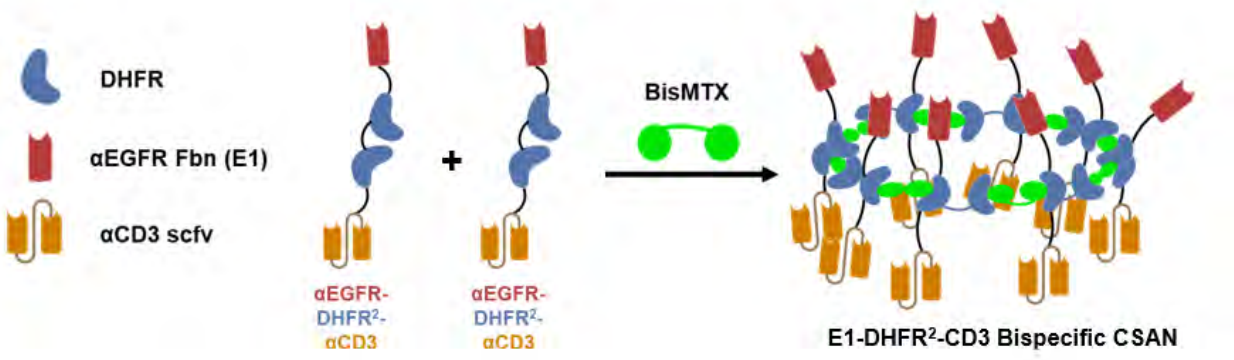
Department of Medicinal Chemistry, The University of Minnesota-Twin Cities, Minneapolis, Minnesota

Our laboratory has developed an approach to non-genetically modify T cells using Chemically Self-assembled Nanorings (CSANs) as prosthetic antigen receptors (PARs). Bispecific PARs have been developed to selectively target the human CD3 receptor and a known Cancer antigen. In recent work, we demonstrated that the distribution of each monomer in a bispecific CSAN could be quantitatively tuned by mixing different equivalences of each monomer during ring formation. Although the monomer distribution could be modified, bispecific αCD3/αEGFR rings either predominantly displayed the αCD3 single-chain variable fragment (scFv) or αEGFR fibronectin (FN3). Current work focuses on the development of bispecific CSANs in which the valency of the αEGFR FN3 could be tuned without simultaneously decreasing the valency of the αCD3 scFv and *vice versa*. We hypothesize that higher αCD3 valency of the rings would enhance cytotoxicity due to preferred binding to T cells and modified valency for αEGFR would allow for discrimination between tissues displaying different amounts of EGFR. Consequently, we developed an αEGFR/αCD3 fusion protein which consisted of two targeting ligands fused to our dihydrofolate reductase molecules ($DHFR^2$). As with our current CSANs, the αCD3 scFv is fused to the C-terminus of our $DHFR^2$-based scaffold while αEGFR is fused to the N-terminus of the $DHFR^2$-αCD3 scaffold. The αEGFR/αCD3 fusion has been developed; characterization of the protein is currently underway.



MICHAUD

Next generation disinfectants to combat resistance in the post-COVID era

Kyle J. Sommers,[†] Marina E. Michaud,[‡] Cody E. Hogue,[†] Amber M. Scharnow,[‡] Lauren E. Amoo,[†] Ashley A. Petersen,[†] Robert G. Carden,[†] Prof. William M. Wuest,*[‡] Prof. Kevin P. C. Minbiole*[†]

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The introduction and growing use of disinfectants and antiseptics over the past century has concomitantly led to the emergence of resistance to these antimicrobials, specifically quaternary ammonium compounds (QACs). The extensive use of disinfectants and antiseptics during the COVID-19 pandemic has subsequently risen concerns regarding the acceleration of resistance to these antimicrobials. To address this growing resistance, we have envisioned expanding beyond mono-cationic nitrogen-based antimicrobial amphiphiles into other multi-cationic and heteroatom-centered compounds. Accordingly, we have synthesized compound libraries spanning various structural classes of cationic amphiphiles and further probed their structure-activity relationships against Gram-positive, Gram-negative, and clinically isolated multidrug resistant bacteria. The results of our screening coupled with bioinformatic analysis revealed improved activity against these pathogens, as well as insight into genotypic resistance against commercial QACs. As a whole, these investigations demonstrate the need and promise of next-generation disinfectant and antiseptic compounds.

Acknowledgements: This work was funded by the National Institute of General Medical Sciences (R35 GM119426 to W.M.W.) and Major Research Instrumentation grants from the National Science Foundation (CHE-1827930 and CHE-2018399 to K.P.C.M.).

MILLER

Rigid cyclophanes as hosts for perfluorinated aromatic guests

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Host-guest chemistry has become a useful tool in many applications in both chemistry and biology including contaminant removal, drug delivery, and sensing. Finding inspiration in nature's high affinity "host-guest" pair, biotin/(strept)avidin, synthetic chemists have sought to emulate this selective and strong association behavior. As we consider new applications of synthetic molecular recognition, we are most interested in non-covalent interactions that have been underexplored in the field of host-guest chemistry and which are orthogonal to non-covalent interactions commonly found in biological systems. We have designed and synthesized preorganized electron-rich cyclophanes as host molecules which preferentially bind abiotic perfluoroaromatic small molecules. By determining specific design rules for this arene-perfluoroarene host-guest system, we hope to access high affinity synthetic hosts for perfluorinated aromatic guests and apply this system to cell-surface labeling applications.

Acknowledgements: This work was supported by a NIGMS grant to E.M.S. (1DP2GM13268) and the Chemical-Biology Interface Training Program to M.A.M. (5T32GM008496).

MONDAL

Thiamin Biosynthesis in Yeast-THI5, a Remarkable Suicide Enzyme

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Department of Chemistry, Texas A&M University, College Station, Texas
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[Abstract: Thiamin pyrophosphate (TPP) is an essential co-factor in all living systems.[1] TPP biosynthesis in yeast involves thiamin pyrimidine synthase THI5 that forms the pyrimidine core of thiamin. THI5 is a PLP-dependent single turn-over or 'suicide' enzyme that uses its own active site His66 in presence of Fe (II) and oxygen to form the product pyrimidine moiety (HMP-P). Through mechanistic investigation in the THI5 enzyme catalysis, we have identified a new form of oxidatively dearomatized PLP (Ox-PLP) as the key intermediate of this complex transformation.]

Thiamin pyrophosphate biosynthesis in yeast contains some of the most complex organic rearrangements catalyzed by enzymatic reactions. Thiamin pyrimidine synthase, THI5 catalyzes the transformation (Figure 1) of its own active site His66 and PLP in presence of Fe (II) and O_2 to form 4-amino-2-methyl-5-hydroxymethyl pyrimidine phosphate (HMP-P,**4**).[2] After only one catalytic cycle the enzyme becomes inactive as it's active site His66 gets modified in the form of a keto-acid (**5**). We have carried out chemical rescue experiment with H66G mutant of this enzyme and discovered the key intermediate in the form of an oxidatively dearomatized PLP (Ox-PLP, **3**). Ox-PLP acts as a suitable diene that carries out a formal Diels-Alder type of reaction with the imidazole part of properly positioned His66 (Figure 1). Parts of PLP and the active site His66 are incorporated into the product HMP-P making the enzyme a co-substrate of the reaction (Figure 1). In the reaction, oxygen is activated by the active site bound Fe (II) to initiate the PLP oxidation. This type of oxidative dearomatization of PLP is unprecedented in any other PLP-dependent enzyme chemistry. The suicidal nature of THI5 may also imply that this enzyme might have some yet unidentified role in yeast physiology.

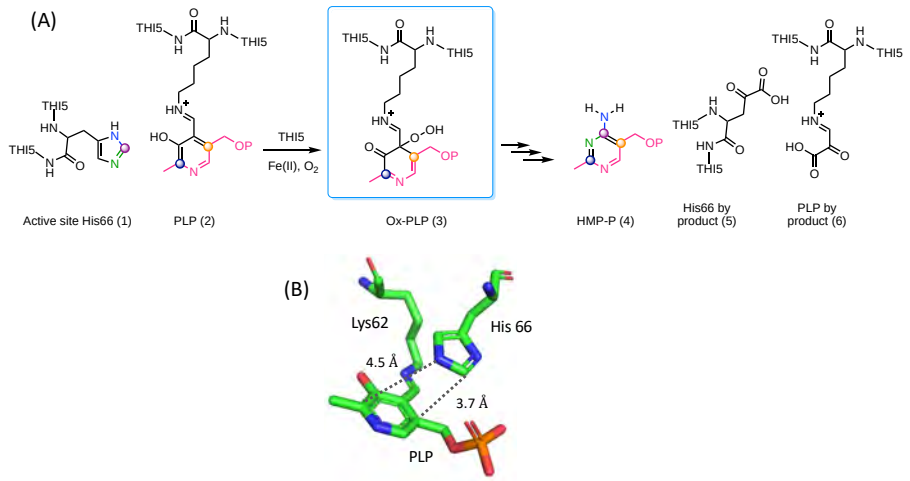

Figure 1. A) THI5 catalyzed reaction and B) active site of THI5.

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MOOR

Advances in Multifunctional Urethanes for Information Storage

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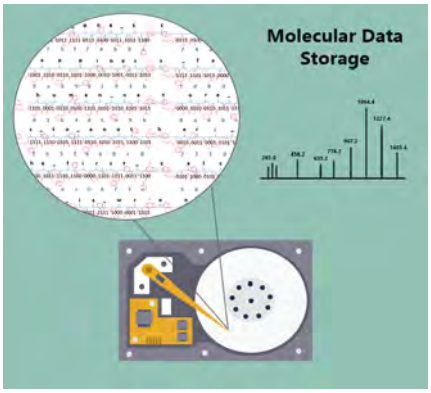
Dense and cost-effective means for storing information for future use is needed as society continues to produce data exponentially. Abiotic polymers (plastics) are an exceptional platform for information storage because of their accessibility and limitless structural modifications.[1] However, efficient, high-throughput means for ‘‘writing’’ and ‘‘reading’’ with them are still needed. Herein, we report the high-throughput synthesis (writing) and sequencing (reading) of urethanes. As a proof of principle, a text passage from Jane Austen’s Mansfield Park was encoded in sequence-defined oligourethanes and reconstructed via self-immolative sequencing.[2,3] We develop Mol.E-coder, a software tool that uses a Huffman encoding scheme to convert the character table to hexadecimal. The oligourethanes are then generated by a high-throughput parallel synthesis. Sequencing of the oligourethanes by self-immolation is done concurrently in a parallel fashion, and the liquid chromatography-mass spectrometry(LC-MS) information decoded by our Mol.E-decoder software. The passage is capable of being reproduced wholly intact by a third-party, without any purifications or the use of tandem MS (MS/MS), despite multiple rounds of compression, encoding, and synthesis. We hope to further develop this technology to allow multiple oligourethanes to be read concomitantly along with automating the synthesis and deconvolution of information.



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MORALES-COLÓN

Tetramethylammonium Fluoride Alcohol Adducts for S_NAr Fluorination

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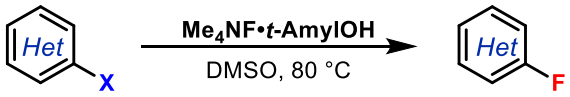
Nucleophilic aromatic fluorination (S_NAr) is among the most common methods for the formation of C(sp^2)–F bonds.[1] Despite many recent advances, a longstanding limitation of these transformations is the requirement for rigorously dry, aprotic conditions to maintain the nucleophilicity of fluoride. This work addresses this challenge by leveraging tetramethylammonium fluoride alcohol adducts (Me_4NF•ROH) as fluoride sources for S_NAr fluorination. Systematic variation of R enabled the identification of the optimal reagent, which is effective for the S_NAr fluorination of more than 50 (hetero)aryl halides and nitroarene electrophiles. Overall, we anticipate that this method will find widespread application in the construction of C(sp^2)–F bonds.



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NAIR

Catalyst-controlled regiodivergence in rearrangements of indole-based onium-ylides

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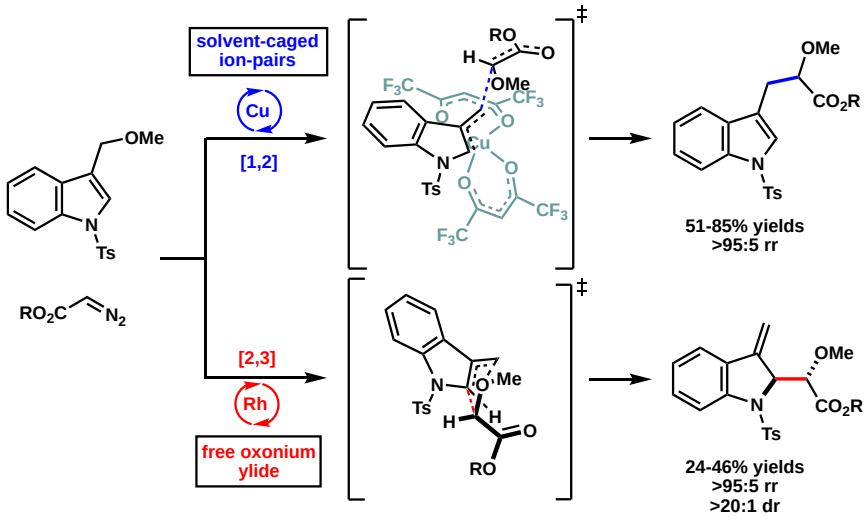
Sigmatropic rearrangements belong to a powerful class of transformations enabling the synthesis of valuable organic molecules with complex architectures. Recent advances in catalytic onium-ylide rearrangements enable catalyst-control of these traditionally unselective rearrangements. Despite their utility, most of this class of rearrangements involving a variety of ylides are limited to the functionalization of aliphatic systems.

We have developed the catalyst-controlled regio-divergent rearrangements of indole-based oxonium-ylides. Oxonium ylides formed *in situ* from substituted indoles selectively undergo [2,3]- and [1,2]-rearrangements in the presence of a rhodium and copper catalyst, respectively. The combined experimental and density functional theory (DFT) computational studies indicate divergent mechanistic pathways involving a metal-free ylide in the rhodium catalyzed reaction favoring [2,3]-rearrangement, and a metal-coordinated ion-pair in the copper catalyzed [1,2]-rearrangement that recombines in the solvent-cage. The applications of our methodology were demonstrated in the first total synthesis of the indole alkaloid (±)-sorazolon B enabling the stereochemical reassignment of the molecule.



NÉMETHOVÁ

Four-step access to the sesquiterpene natural product presilphiperfolan-1β-ol and unnatural derivatives via supramolecular catalysis

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Dario Schmid[a] and Konrad Tiefenbacher [a,b]

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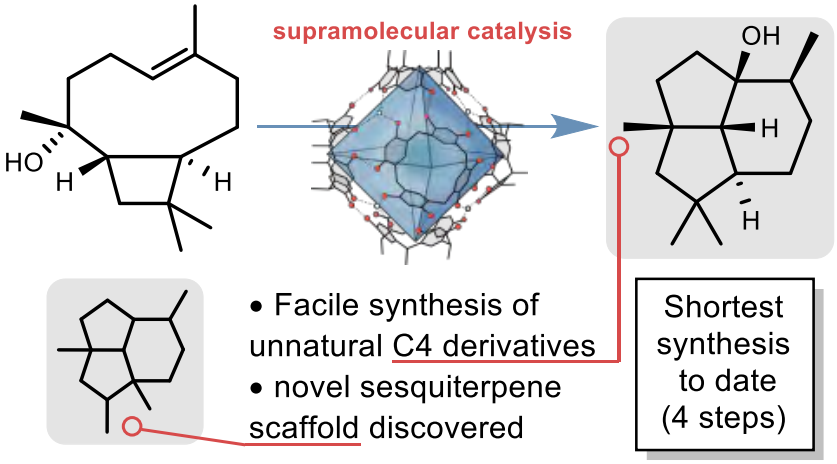
Terpenes constitute one of the most structurally varied classes of natural products.[1] A wide range of these structures are produced in nature by type I terpene cyclase enzymes from one single substrate.[2] However, such reactivity has proven difficult to reproduce in solution with man-made systems.[3]

Herein we report the shortest synthesis of the tricyclic sesquiterpene presilphiperfolan-1β-ol to date, utilizing the supramolecular resorcinarene capsule as catalyst for the key step. This synthetic approach also allows access to unnatural derivatives of the natural product, which would not be accessible through the biosynthetic machinery. Additionally, this study provides useful insight into the biosynthesis of the presilphiperfolanol natural products, including the first experimental evidence consistent with the proposed biosynthetic connection between caryophyllene and the presilphiperfolanols.



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NUNZIATA

Structure-Activity Relationship of STING Compounds

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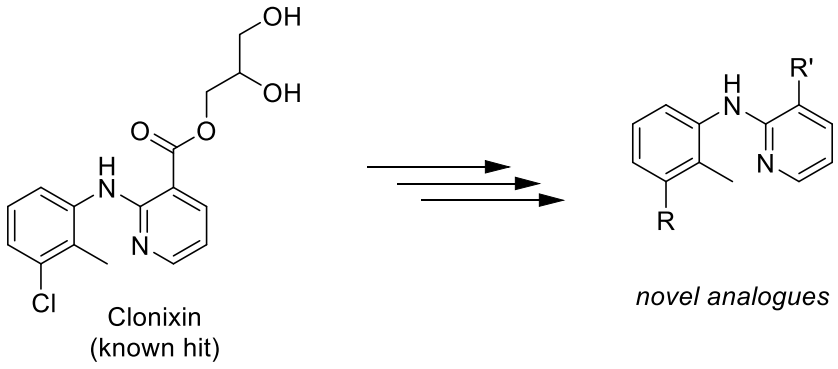
Stimulator of Interferon Genes (STING) is an important transmembrane protein involved in innate immune response to foreign or damaged DNA or RNA in a cell's cytosol. When a cell is infected with an intracellular pathogen, STING acts as a sensor that triggers the production of type I interferon, which then promotes an anti-inflammatory response. Enhancers of STING can increase the immune response to the abnormal DNA of tumor cells and inhibitors of STING can help treat autoimmune disorders where there may be an overly aggressive immune response to self-DNA. Through molecular modeling studies performed by the Guida group at USF, we have been able to identify several compounds that have been active toward the STING pathway. Our goal for this project is to assess the structure-activity relationship of molecules that have had a positive response toward STING along with the synthesis of new analogs to test their enhancing or inhibiting activity.



Acknowledgements: Support for this research is provided by the National Institute of Health under Grant No. R21AI149450.

PELLEGRINET

Reactivity, Selectivity and Scope of Diels-Alder Reactions of Boron-substituted Furans

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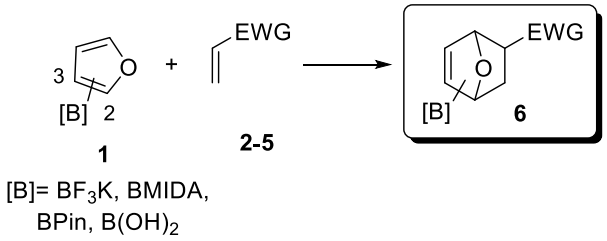
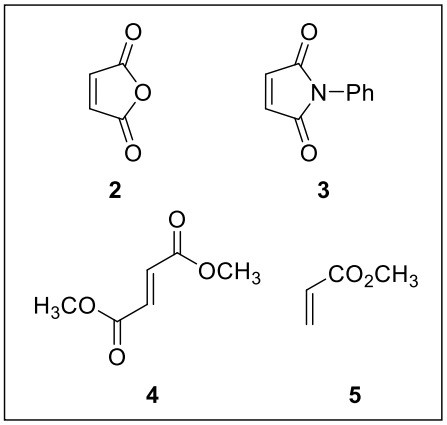
The Diels-Alder reactions of unsaturated organoboron compounds have been known for many decades.[1] However, new variants continue to appear in the literature. The first examples with simple alkynyl-[2] and alkenylboronic esters[3] progressively evolved into a wide range of reactions.[4] In 2019, we reported an experimental and theoretical study of the Diels-Alder reactions of boron-substituted furans (**1**) with maleic anhydride (**2**).[5] Within the analogues with boron substituents at C-3, the potassium trifluoroborate emerged as a highly reactive and *exo* selective diene. On the other hand, the reactions for the C-2 derivatives were unsuccessful. Herein, we describe the results of the [4+2] cycloadditions with other electron deficient dienophiles. The reactions of *N*-phenylmaleimide (**3**) with the boron-substituted furans at C-3 occurred very efficiently and showed variable *endo/exo* selectivities. Gratifyingly, when the potassium furan-2-trifluoroborate was reacted with **3** the *exo* cycloadduct was obtained exclusively with high yield. Other dienophiles such as dimethyl fumarate (**4**) and methyl acrylate (**5**) were evaluated but the reactions were less favorable. In addition, we have explored different alternatives to convert the 7-oxabicyclo[2.2.l]hept-2-ene products **6** into a variety more functionalized and diverse compounds. Theoretical calculations to rationalize the experimental results are underway.





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PETTI

Go with the eFlow: Electrifying Synthesis of Ureas, Carbamates and Thiocarbamates

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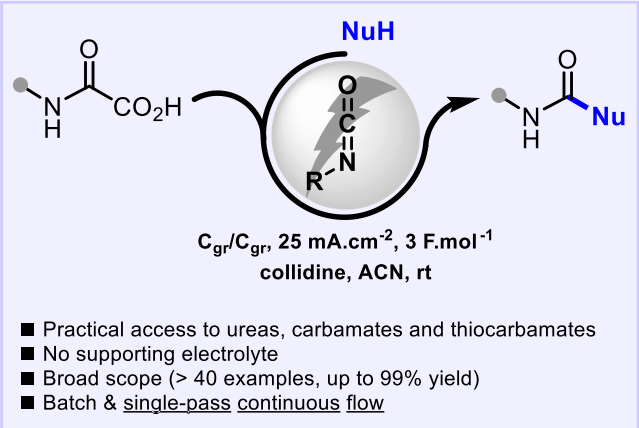
In the last decades, innovative synthetic approaches, able to reduce the ecological footprint, gained considerable attention within academia and industry.[1] Organic electrochemistry is well placed in this context. Indeed, using electricity to drive chemical transformations allows us to overcome significant drawbacks, commonly encountered in synthetic practices, such as the reliance on expensive and hazardous reagents or harsh reaction conditions.

In this poster, a new and phosgene-free electrochemical method to access ureas, carbamates, and thiocarbamates from anodic oxidation of oxamic acids will be disclosed.[2] This practical and straightforward approach proceeds via the *in situ* generation of reactive isocyanates, which are then trapped in the presence of a suitable nucleophile. Single-pass continuous electrochemical flow conditions were also applied to the newly discovered reaction. As a result, the desired products were afforded in high yields within 6 min, unlocking substrates that were inaccessible under batch conditions while being easily scalable. This provides the synthetic community with an efficient way to access pharmaceutical targets under mild and oxidant free conditions, without using any toxic reagent or isolating harmful intermediates. Attention to the environment, rapid and cost-efficient procedures, innovative reaction pathways represent the future of organic chemistry, and electrosynthesis has the potential to be part of it!



Acknowledgements: Support for this research is provided by EPSRC (Grant EP/S017907/1 to KL) and the University of Greenwich (Vice Chancellor's PhD Scholarship to AP).

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PIA

Exploring the Electrophilicity of Metal Homoenolates: Synthesis of 1- and 1,2-Disubstituted Cyclopropylamines

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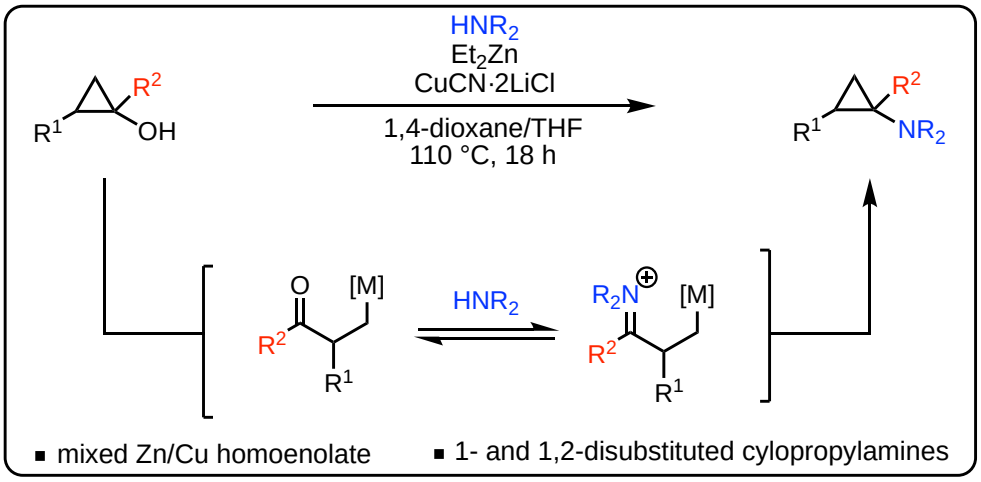
Cyclopropylamines are prevalent structures in pharmacologically active compounds.[1] They are found in a range of drugs, including inhibitors for cancer therapy and antidepressants.[1,2] Previously, our group has synthesized *trans*-2-substituted cyclopropylamines via the formation of an aldehyde-containing metal homoenolate intermediate (**Scheme 1**, R^2 = H).[2] Alternatively, the production of 1-substituted cyclopropylamines has shown limited success under these reaction conditions.[3] This is hypothesized to be due to the lower electrophilicity of the resulting ketone-containing homoenolate intermediate (**Scheme 1**, R^2 = alkyl group), which could hinder both condensation and subsequent ring closure.

In further exploration of the electrophilic nature of homoenolates, we have identified the use of a mixed zinc/copper homoenolate to produce 1- and 1,2-disubstituted cyclopropylamines in moderate to high yields (**Scheme 1**). The copper additive is hypothesized to enhance the nucleophilicity of the carbon–metal bond, allowing for enhanced ring closure on the iminium. This methodology will provide access to new routes to these pharmaceutically relevant structural motifs. The reaction optimization, scope, and future work will be discussed.



Scheme 1: Accessing 1- and 1,2-cyclopropylamines via Zn/Cu homoenolate.

Acknowledgements: Support for this research is provided by NSERC and the University of Toronto.

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PINTER

N-Directed Fluorination of Unactivated Csp^3–H Bonds

Emily N. Pinter, Jenna E. Bingham, Deyaa I. AbuSalim, and Silas P. Cook*,
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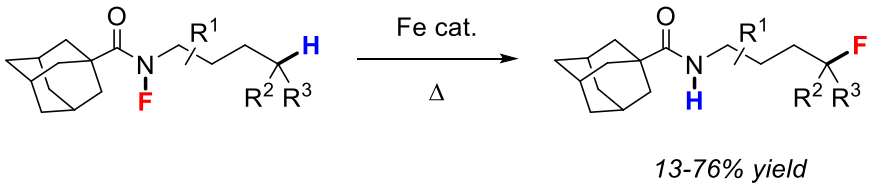
Introducing fluorine atoms into pharmaceutical and agrochemical candidates is a critical step in the discovery process. The unique properties imparted by fluorine atoms can affect conformation, acidity, and metabolic stability of drug candidates. Consequently, these unique properties also make site-selective Csp^3–F bond installation a challenge. While directed C–H fluorination has emerged as a promising approach, the limited work conducted to date has enabled few functional groups as the arbiters of direction.

We have developed an iron-catalyzed, N-fluoroamide directed system for the fluorination of unactivated Csp^3–H bonds.[1] Leveraging insights gained from both computations and experimentation, we found that adamantoyl-based N-fluoroamides were optimal for directed Csp^3–H fluorination. The reaction proceeds with complete site-selectivity in all substrates in only 20 minutes. Furthermore, computational studies revealed a unique reaction coordinate for the catalytic process which offers an explanation for the high site-selectivity observed.



13-76% yield

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POMFRET

Shape Shifting Polymers from Bullvalene

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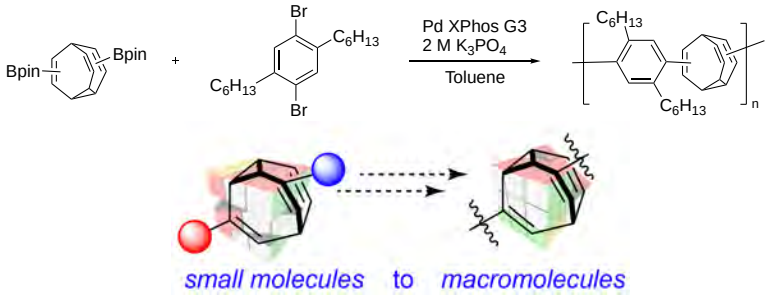
Rigid-rod polymers are a class of high-performance lightweight materials that are made up of a highly conjugated heteroaromatic backbone.[1] We hypothesize that by incorporating stimuli responsive small molecules into the rigid-rod backbone we can achieve control over chain stiffness in these materials. Bullvalene is the ideal fluxional molecule for this application because it can undergo rapid room temperature Cope rearrangements to form 1.2 million possible degenerate isomers.[2,3] We anticipate that bullvalene in a main chain polymer can act as a thermally responsive 'molecular Rubik's cube' and induce macromolecular chain movement as a result of a small molecule Cope rearrangement.

In this work, we incorporate bullvalene into the rigid-rod backbone by copolymerizing a bis-boronate ester bullvalene[4] with 1,4-dibromo-2,5-dihexyl-benzene using a Suzuki polycondensation resulting in a molar mass (M_n) of up to 27 kDa and dispersities (M_w/M_n) of ~1.2. In order to create a static analog to our fluxional polymer we also established appropriate diimide reduction conditions to reduce the double bonds of bullvalene without opening the vinyl cyclopropane ring. Based on our success using a small molecule bullvalene model compound, we anticipate that the diimide reduction on our polymers will halt the Cope rearrangement and create the desired static analog without disrupting the rigid, cage-like structure in the polymer backbone. Once our static polymer is synthesized, we can observe how small molecule Cope rearrangements can affect the thermal and mechanical properties of a rigid rod polymer.



Acknowledgements: Support for this research is provided by the University of Washington and the American Chemical Society Petroleum Research Fund (PRF#62163-DNI7).

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PONGENER

One Pot Beta-Mannosylations of Glycosyl Hemiacetals Mediated by LiI

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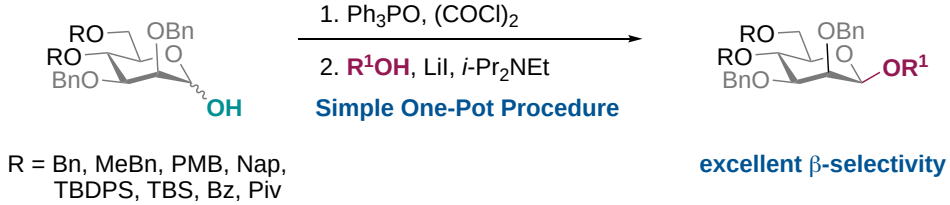
Despite the tremendous work in the area of chemical glycosylation, the synthesis of 1,2-*cis*-glycosides, in particular beta-mannosides and beta-rhamnosides, still remains challenging. Herein, a highly selective synthesis of beta-mannosides from glycosyl hemi-acetals is reported, following a one-pot chlorination, iodination, glycosylation sequence employing cheap oxalyl chloride, phosphine oxide and lithium iodide (1,2). The present protocol works excellently with a wide range of glycosyl acceptors and with glycosyl donors bearing a range of ethereal protecting groups. The method doesn't require conformationally restricted donors or directing groups to achieve the high beta-selectivities.



- Directing groups or restrained donor conformations not required
- Broad donor and acceptor scope
- 16 examples
- Cryogenic conditions not required

Acknowledgements: EMM, IP and DAP thank SFI (CDA/15/3625 and 18/RI/5702) and JJR thanks IRC (GOIPG/2019/2747) for funding.

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POST

Promysalin analogs reveal new binding cleft in succinate dehydrogenase

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Promysalin is a natural product produced by *Pseudomonas putida* that selectively inhibits growth of the Gram-negative ESKAPE pathogen, *Pseudomonas aeruginosa*. Our group completed the first total synthesis, in 8 longest linear steps and an overall yield of 35%. Subsequently, we used diverted-total synthesis to access 16 synthetic analogs and carried out structure-activity relationship testing on this library. Based on this information, we appended a minimalist probe to the amide, for use in affinity-based protein profiling. Proteomic analysis identified succinate dehydrogenase (Sdh) as the target of promysalin in *P. aeruginosa*. We also selected for a promysalin-resistant mutant and whole-genome sequencing revealed a mutation on Sdh, supporting our previous finding. Upon computational docking of promysalin in Sdh, we rationally designed a new series of analogs in which the alkyl chain was modified to probe binding interactions. Synthesis and biological investigation of these analogs indicated that this portion of the molecule is required for biological activity. Furthermore, computational docking revealed that analogs with a longer alkyl chain undergo a conformational change into a new binding cleft. This binding cleft contains a tryptophan residue, which has inspired a new analog series in which various aromatic groups will be appended to the alkyl chain in an attempt to induce pi-stacking and enhance binding. The synthesis of these compounds is in progress. Together this work has provided insight into the novel mechanism of action of a natural product that exhibits species-specific inhibition of *P. aeruginosa*. This unique activity inspired investigation into promysalin's clinical relevance through analysis of synergistic effects with antibiotics and other relevant small molecules, as well as activity against clinical isolates.

Acknowledgements: We are grateful to the NIH (Grants GM119426 and GM123336) and NSF (Grant CHE1755698) for financial support. Partial instrumentation support was provided by the NSF (Grant CHE1531620). S.J.P and A.R.K. acknowledge National Science Foundation Pre-Doctoral Fellowships (Grant DGE1937971). We thank Umicore for olefin metathesis catalysts and Profs. Buttaro (Temple University) and Goldberg (Emory University) for the generous donation of the strains. This work used the Extreme Science and Engineering Discovery Environment (XSEDE) Allocation MCB130049, which is supported by National Science Foundation Grant Number ACI-1548562. This research was also funded in part through the NIH/NCI Cancer Center Support Grant P30 CA006927.

RACHII

Nickel-Catalyzed Enantioselective Synthesis of New Phenanthridinone Analogs with Quaternary Carbon Stereocenters using the Birch-Heck Reaction Sequence

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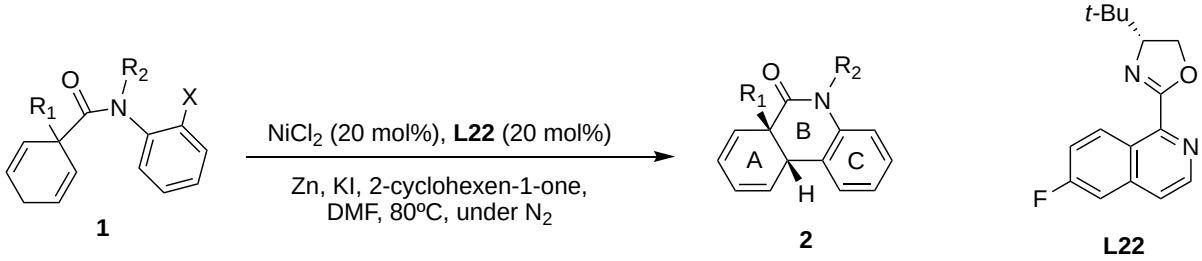
The Birch reduction-alkylation coupled to the desymmetrizing Mizoroki-Heck reaction is a novel synthetic tool to form fused 6-6-6 tricyclic ring systems with a quaternary stereocenter from inexpensive and easily available starting materials.[1-3] The method was used to create phenanthridinone analogs using an enantioselective intramolecular Ni-catalyzed Mizoroki-Heck reaction of symmetrical 1,4-diene systems tethered to aryl halides in good to excellent yields. We made important advances in reaction optimization and the development of a more enantioselective process. The sustainability, high efficiency and low price of nickel catalysts make this work a very attractive alternative to the palladium-version.[4]



76-91% yield, up to 10.2:1 e.r.

Acknowledgements: Support for this research is provided by the National Institutes of Health (National Institute of General Medical Sciences, 1-R15-GM123475-01A1).

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RITZ

Bisoxazoline-Pincer Ligated Cobalt-Catalyzed Hydrogenation of Alkenes

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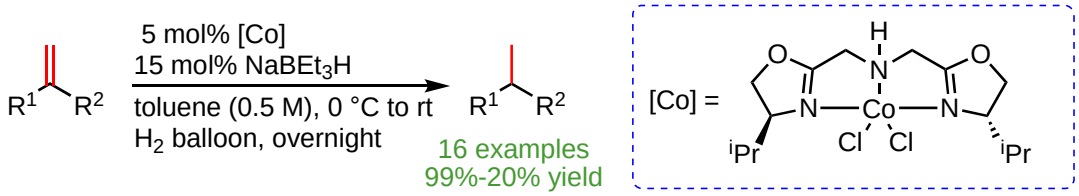
Catalytic hydrogenation reactions have garnered interest as they allow for the efficient formation of synthetic intermediates and bulk products in an atom economic fashion. While there are already multiple different systems for the hydrogenation of alkenes, most require the use of heavy metals such as: iridium, rhodium, ruthenium, and palladium. More recently, the use of early transition metals has been explored for this transformation due to their abundance, non-toxicity, and overall cost. However, first-row transition metal complexes can often undergo one electron pathways making their reactivity difficult to predict and/or control. Despite these challenges, there have been many recent advances in this field specifically involving cobalt; in particular, pincer ligated cobalt complexes have shown high reactivity for the hydrogenation of alkenes. However, most of these systems involve multi-step syntheses to afford ligands and/or are moisture- and air-sensitive, adding an additional amount of rigor to the hydrogenation reactions. Wanting to mediate these problems, we sought to synthesize a ligand from cheap and readily available starting materials. Herein, we report the synthesis of a bench stable, novel, bisoxazoline-pincer ligated cobalt(II) dichloride complex that was found to undergo efficient and atom-economical hydrogenation of a variety of alkenes (**Scheme 1**). Additionally, further investigations were performed to better understand overall catalytic reactivity.[1]

Scheme 1. Standard Hydrogenation Conditions



Acknowledgements: The authors gratefully acknowledge funding from the U.S. Department of Energy (Grant. No. DE-SC0020230) for instrument usage and chemicals. A.M.P. acknowledges funding from an NSF GRFP award (DGE-1419118). M.D.R. was supported by an NSF grant (CHE-1762350). The NSF program is acknowledged for the purchase of an X-ray diffractometer (CHE-1725028).

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RYKACZEWSKI

Visible-Light-Enabled Paternò–Büchi Reaction via Triplet Energy Transfer for the Synthesis of Oxetanes

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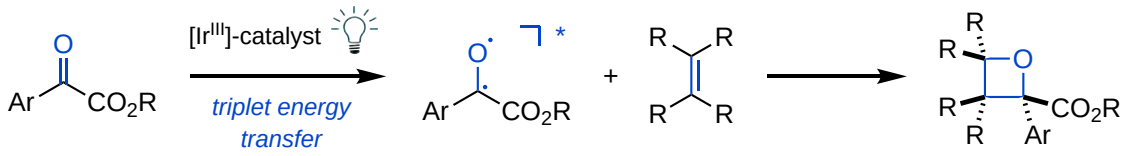
One of the most efficient ways to synthesize oxetanes is the light-enabled [2+2] cycloaddition reaction of carbonyls and alkenes, referred to as the Paternò-Büchi reaction. The reaction conditions for this transformation typically require the use of high energy UV light to excite the carbonyl, limiting the applications, safety, and scalability. We herein report the development of a visible light-mediated Paternò-Büchi reaction protocol that relies on triplet energy transfer from an iridium-based photocatalyst to the carbonyl substrates. This mode of activation is demonstrated for a variety of aryl glyoxylates and negates the need for both visible light-absorbing carbonyl starting materials or UV light to enable access to a variety of functionalized oxetanes in up to 99% yield.



activation via visible light • **important pharmaceutical scaffold** • **up to 99% yield**

Acknowledgements: Support for this research is provided by the National Science Foundation Graduate Research Fellowship.

SCHARNOW

Simplified tool compound enables investigation into the unique activity of natural product, carolacton against *Streptococcus mutans* biofilm

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Dental caries, or cavities, impose detrimental health risks and financial burdens on society. A subset of bacterial species that includes *Streptococcus mutans* are responsible for the acid production and biofilm formation that cause cavities and promote the establishment of a pathogenic niche. Novel approaches to prevent and treat this invasive disease, in addition to other gram-positive and biofilm-dependent infections, are drastically needed. Natural products are rich starting points for the development of novel therapeutics and chemical tools to elucidate unknown bacterial processes. Carolacton is one such 14-membered polyketide natural product that has garnered interest for its unique, acid-dependent mechanism against *S. mutans* and has been tied to cell wall homeostasis, acid tolerance response, and biofilm formation. However, its specific mechanism of action and molecular target remain elusive. Toward that end, we have developed a structurally related, simplified tool compound that requires fewer synthetic steps, maintains carolacton's acid-dependent mechanism, and exhibits improved activity that has proven more amenable to chemical biological investigation. This work has begun to provide insight into the specific mechanism of the tool compound and natural product within *S. mutans*.

SCHNEIDER

Design, Synthesis and Properties of Novel Hemiboronic Acids as Potential Pharmacophores

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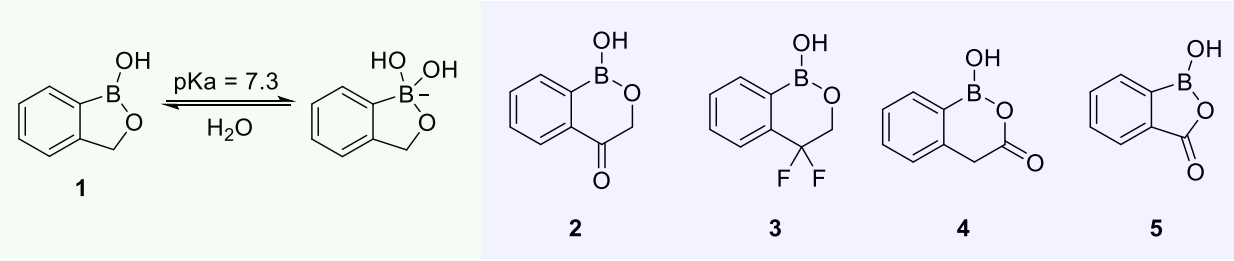
In drug design, the development of new pharmacophores improves chemical diversity, which is key to addressing diseases with insufficient treatment options, as well as providing expanded patent space. The goal of this project is to identify and characterize novel boron-based pharmacophores inspired by the hemiboronic acid benzoxaborole, the core structure of tavaborole (antifungal) and crisaborole (atopic eczema treatment). Benzoxaboroles (**1**) are of particular interest as pharmacophores because they have a lower pKa than typical boronic acids, improving their aqueous solubility and allowing them to permeate membranes at physiological pH (~7.4)[1]. Benzoxaboroles are more acidic because the change in hybridization upon ionization causes a favorable release of ring strain. As an alternative approach, this work aims to increase the acidity of the boron center by adjusting the electronic factors of the scaffold, for example: benzoketoborole **2**, the difluoromethylene analog (**3**), the constitutional isomer (**4**), and the lower homologue (**5**).



This presentation will cover the synthesis of each potential drug scaffold and related derivatives. The compounds will then be compared based on medicinally relevant properties, such as pKa, logP, solubility, and stability. Compounds **2** and **3** were both found to have potential drug-like properties similar to benzoxaborole. In contrast compounds **4** and **5** remain ionized at all pH values, limiting their solubility to polar protic solvents and reducing the pKa and logP below desirable levels.

Acknowledgements: Support for this research is provided by the Natural Sciences and Engineering Research Council of Canada in the form of a Postgraduate Scholarship – Doctoral (O.S.) and a Discovery Grant (RGPIN-2017-05086, D.G.H.).

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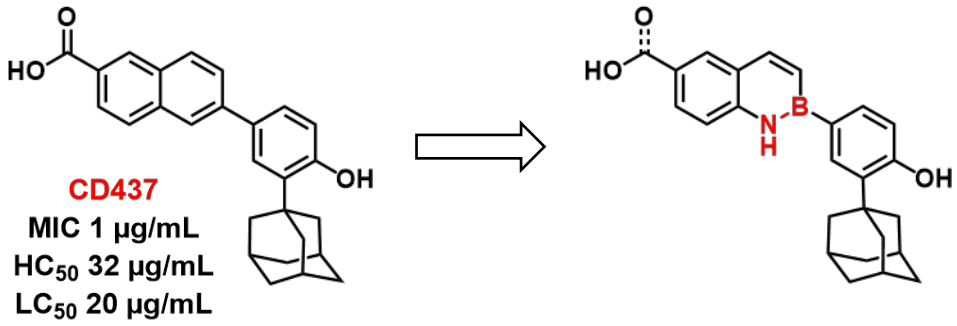
SCHRANK

Improving the Therapeutic Window: Synthetic Investigations into Azaborine Analogs of the Synthetic Retinoid, CD437

Cassandra L. Schrank, Brittney A. Haney, and William M. Wuest

In collaboration with the Mylonakis lab at Brown University, we have demonstrated the activity of the synthetic retinoid, CD437, against methicillin-resistant *Staphylococcus aureus* (MRSA) as well as their membrane-targeting mechanism of action. Although CD437 and subsequent analogs have shown promising activity against gram-positive pathogens, their broad-spectrum applicability and therapeutic viability remained unexplored. Specifically, through preliminary analysis, our best performing analog, Analog 2, displayed low solubility within serum as well as high affinity for retinoid binding proteins with a concentration dependent relationship. To improve the solubility and decrease binding affinity, we have proposed a class of analogs containing an azaborine substitution for the naphthalene ring. Azaborines have a nitrogen-boron bond substituting a carbon-carbon double bond that alters the electronics of the parent scaffold. This motif has been explored successfully in both cancer and agricultural research but has yet to be applied to antibiotics. We hypothesize that this isosteric substitution may be efficient in reducing the affinity to retinoid binding proteins as well as increase its solubility thereby improving its therapeutic index.



SCULIMBRENE

Desymmetrization of Diols by Phosphorylation with a Titanium BINOLate Catalyst

Bianca R. Sculimbrene, Erik T. Ouellette, Marshall G. Lougee, Andrea R. Bucknam, Paul J. Endres, John Y. Kim, Emma J. Lynch, Elizabeth J. Sisko,
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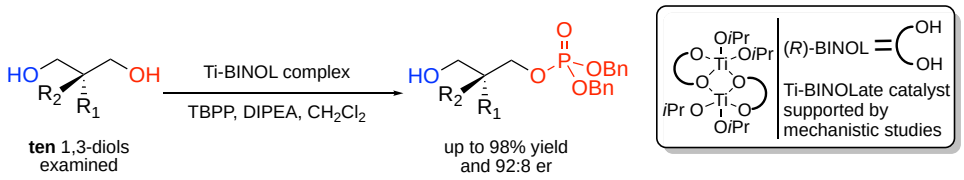
The selective functionalization of pro-chiral molecules with chiral catalysts is a valuable approach to the synthesis of optically active compounds. In this strategy, stereogenic attributes can be unveiled distant from the reacting functional group. Diols are a popular synthon in desymmetrization reactions though few reports exist for selective phosphoryl transfer to diols.

We will discuss the desymmetrization of pro-chiral diols by phosphoryl transfer with a titanium-BINOLate complex.[1] The phosphorylation of ten 1,3-propane diols is obtained in yields up to 98%. Enantiomeric ratios as high as 92:8 are achieved with diols containing a quaternary C-2 center incorporating a protected amine. The chiral ligand, base, solvent and stoichiometry are evaluated along with a nonlinear effect study to support an active catalyst species that is oligomeric in chiral ligand. The use of pyrophosphates as the phosphorylating agent in the desymmetrization facilitates a user-friendly method for enantioselective phosphorylation with desirable protecting groups (benzyl, *o*-nitrobenzyl) on the phosphate product.



Acknowledgements: Support for this research is provided by the College of the Holy Cross and the Camille and Henry Dreyfus Foundation.

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SEGHETTI

Dual D3R/GSK-3β modulation as innovative multitarget strategy for bipolar disorder treatment

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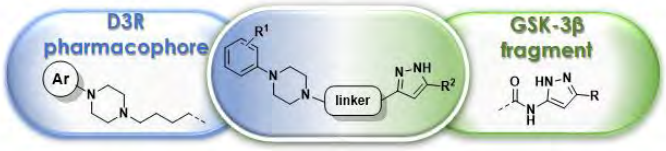
Among the psychiatric diseases, bipolar disorder (BD) is the sixth leading cause of disability with a prevalence up to 4 % worldwide. BD is a severe neuropsychiatric condition which alternates episodes of mania with symptoms of depression. Although the neurobiological pathways are not completely clarified, the dopamine (DA) hypothesis has been recognized the leading theory able to explain the pathophysiology of the malady. In detail, faulty homeostatic regulation of dopaminergic circuits is likely to play a role in cyclical and marked changes of DA neurotransmission, which are at the basis of the bipolar nature of the disorder. In this scenario, modulation of D2 and D3 receptors (D2/3R) through partial agonists represents the first-line therapeutic strategy for psychiatric diseases[1]. Moreover, a deregulation of the enzyme glycogen synthase kinase-3β (GSK-3β) has been reported as peculiar feature of BD[2]. In this scenario, the concomitant modulation of D3R and GSK-3β, by employing multifunctional compounds, could offer promises to achieve an effective cure of this illness. In the light of these findings, we rationally envisaged the pharmacophoric model at the basis of the design of several D3R partial agonists, suitable to be exploited for the dual D3R/GSK-3β ligand design. Thus, synthetic efforts were addressed to develop a first set of hybrid molecules able to concurrently modulate the selected targets. For a chemical structure point of view, we employed different spacers to combine a substituted aryl-piperazine moiety, reported in previously discovered D3R modulators[3], with a pyrazole-based fragment, already identified in GSK-3β inhibitors[4]. Fluorescent and cellular functional assays were carried out to assess the activity of all synthetized compounds against GSK-3β and on D3R, respectively. Most of the derivatives proved to effectively modulate both GSK-3β and D3R with potencies in the low-μM and low-nM range, respectively. The consistent biological data obtained allowed us to identify some lead candidates worth to be further modified with the aim to optimize their biological profile and to perform a structure-activity relationship (SAR) study[5].



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SHARMA

Development and Application of Novel Transition-Metal Reagents for C–N Bond Formation

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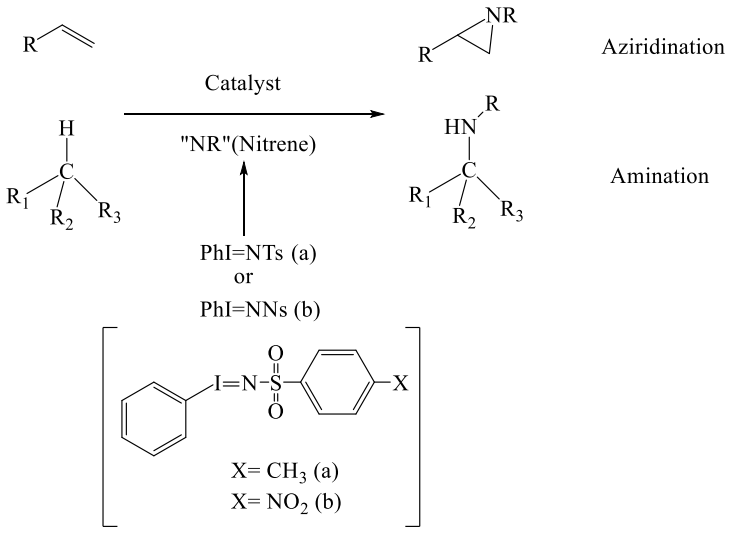
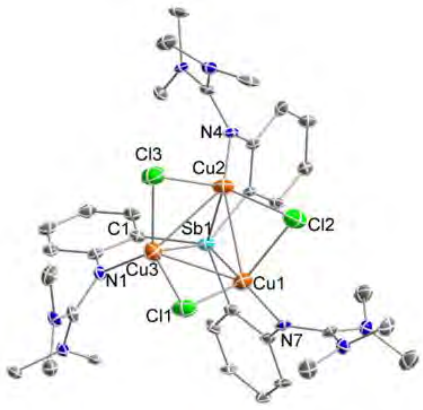
Transition-metal catalyst frameworks supported by tripodal [TMG$_3$trphen] ligands mediate nitrene transfer from nitrogen sources such as PhI=NR to a diverse group of aliphatic and aromatic hydrocarbons and olefins. These reactions are categorized as amination and aziridination reactions. Novel tripodal ligands and their complexes with late first- and second-row transition metals (Cu, Ag) with different axial atoms such as CH, Sb and Bi have been designed to impart weaker axial ligand field, which, in turn, enhances the electrophilicity of nitrene, potentially affording more reactive and site-selective aminated products.

The trinuclear copper catalysts [TMG$_3$trphenSb]Cu$_3$Cl$_3$ and [TMG$_3$trphenBi]Cu$_3$Cl$_3$ have shown promising results towards aziridination of styrenes with excellent yields. The complexes are also reactive for the amination of various hydrocarbons at benzylic and tertiary C–H sites, though more work has to be done to determine and explore their reactivity and selectivity for C–H amination reactions.





[TMG$_3$trphenSb]Cu$_3$Cl$_3$

Acknowledgements: Support for this research has been provided by NIH/NIGMS under R15GM117508 and R15GM139071

SOKOLOVA

Optimized iminium-catalysed 1,4-reductions inside the resorcinarene capsule: Achieving >90% *ee* with proline as catalyst

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The self-assembled resorcinarene hexamer **I** (Fig. 1a), first reported by Atwood[1] in the solid state in 1997, assembles from six resorcinarene units **1** and eight water molecules. Capsule **I** can entrap guest molecules temporally inside its cavity due to the dynamic nature and is used in catalysis.[1–3] In 2016, our group reported that iminium-catalysed 1,4-reduction of α,β-unsaturated aldehydes can be performed inside capsule **I** (Fig. 1b).[4,5]

Our understanding of capsule **I**-catalysis improved substantially over the last years. For instance, the importance of HCl as a co-catalyst for a selection of reactions inside **I** was elucidated.[6] However, the influence of HCl on iminium-catalysed reactions inside **I** remained unknown. We here report the results of (1) elucidating the role of HCl for the iminium catalysis inside **I**; (2) reducing the amount of capsule catalyst required; (3) optimizing the reaction conditions to improve the enantioselectivity.

As a highlight of these studies, unprecedented enantioselectivity (up to 92% *ee*) was achieved for the 1,4-reduction of α,β-unsaturated aldehydes[7–9] inside capsule **I** using simple L-proline as the sole source of chiral information. This is of high interest as proline in a regular solution setting is unable to deliver high enantioselectivity for 1,4-reductions.[9]

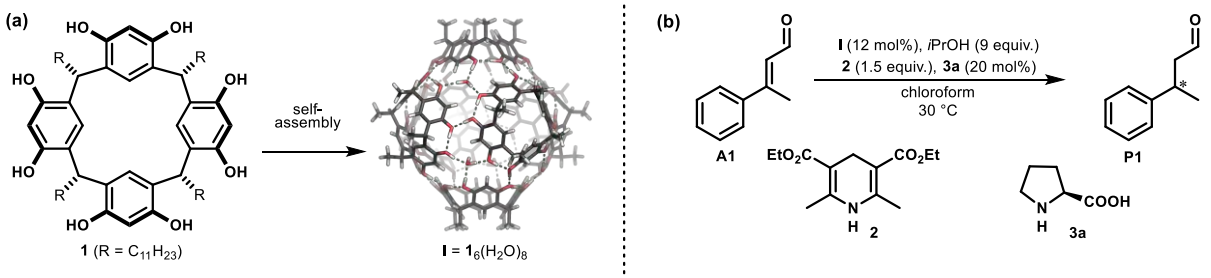

Figure 1. (a) Self-assembly of monomer **1** into hexameric capsule **I**. (b) General scheme of iminium-catalysed 1,4-reduction inside capsule **I**.

Acknowledgments: Support for this research is provided by funding from the European Research Council Horizon 2020 Programme [ERC Starting Grant 714620-TERPENECAT].

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STAERZ

Increased degradation of A53T mutant alpha-synuclein mediated by small molecule activated 20S proteasome.

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Currently, the treatment option for patients with neurodegenerative diseases is to lessen the severity of their symptoms. There is not therapeutic available to halt or slow the progression of these neurodegenerative diseases. A key histopathological feature of diseases like Parkinson's and Alzheimer's, are aggregates of intrinsically disordered proteins (IDPs).[1] It has been observed that the human 20S proteasome can degrade these IDPs with limited degradation of folded proteins. Furthermore, the enhancement of the proteolytic activity of the 20S proteasome can increase the degradation of the monomers and lower the concentration of the oligomers.[2] In a high throughput screen, a class of FDA approved phenothiazines were identified as 20S proteasome activators.[3] Further phenothiazine small molecules were designed and synthesized. Several of these novel phenothiazine small molecules proved to be potent and efficient 20S proteasome activators. A nanoMolar 20S proteasome activator was observed to increase the rate of degradation of the disease relevant IDP, Alpha-synuclein, in vitro and the A53T mutant Alpha-synuclein in a human cell line.

Acknowledgements: Support for this work was in part provided by the National Institute of Health (IR61NS111347-01A1, IR21AG061306-01) and National Institute of General Medical Science (T32GM097215).

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TAIMOORY

The bimetallic Ni complex mediates the C(sp^2)–C(sp^2) homo-dimerization of a pincer scaffold

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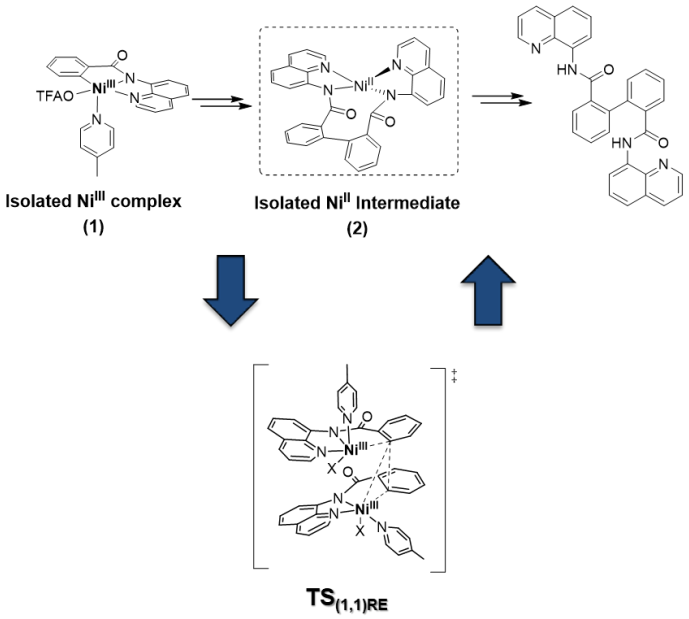
Abstract

Chemical transformations promoted by bimetallic systems are abundant in nature and catalytic processes.[1] In transition metal mediated organic reactions, the involvement of multinuclear complexes have been sparsely invoked for carbon−carbon, carbon−heteroatom and heteroatom−heteroatom bond-forming, reductive elimination processes.[2] However, the fundamental characterization of bimolecular systems as catalytic active sites is a significant challenge owing to the limited supporting experimental evidence in accurately tracing multinuclear reaction paths, and their complex nature that involve numerous intermediates and mechanistic possibilities.

This presentation will highlight our ongoing studies on of the key role of bimetallic Ni complexes in mediating the C(sp^2)−C(sp^2) reductive elimination on a catalytically relevant, quinoline-benzamide scaffold. Our mechanistic investigations support the conversion of Ni^{III} complex **1** to the Ni^{II} coupling product **2** via a bimetallic process involving novel synchronous (1,1)- or (1,2)-transition state binding modes.



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TAYLOR

A Chemoenzymatic Synthesis of the Mycobacterial Galactan

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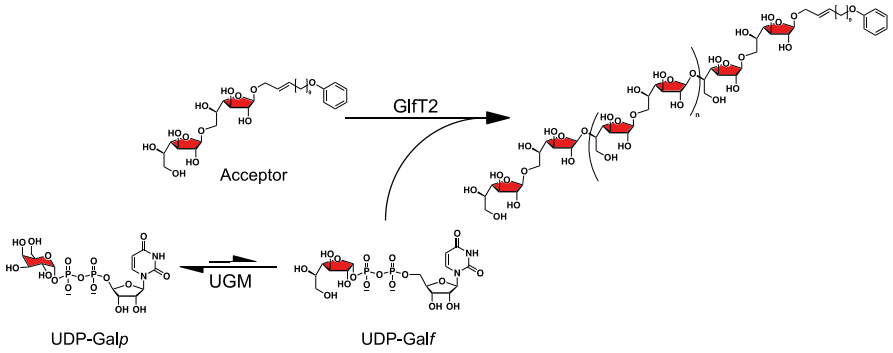
Macromolecular interactions between cell surface polysaccharides (glycans) and other biomacromolecules govern myriad biochemical processes. Still, little is known about the biogenesis and biological roles of extracellular glycans, particularly in microbial systems. For example, mycobacteria have an intricate carbohydrate coat, with a thick, hydrophobic outer mycolic acid layer covalently linked to the peptidoglycan via an extensive branched polysaccharide called arabinogalactan. The arabinogalactan is essential, yet its function is poorlyunderstood. This lack of knowledge is in part due to a dearth of methods for the facile synthesis of this biologically important polysaccharide. While traditional synthetic methods provide superb control over polysaccharide structure, they can be tedious and low yielding. Likewise, isolation of native polysaccharides from living cells can yield grams of material, but offers little control in tuning the structural properties of the desired polymers. Chemoenzymatic methods have been extensively studied, but have not, to date, been used to create large quantities of full length biologically relevant polysaccharides. I leveraged chemoenzymatic synthesis to produce milligram quantities of the galactan. My novel one pot synthesis affords milligrams of material and combines the strengths of chemical and biological synthesis. This chemoenzymatic route employs a commercially available sugar donor and an easily accessible synthetic acceptor, making our strategy broadly accessible. We anticipate that this chemoenzymatic approach will advance our understanding of mycobacterial glycan structure and recognition, and ultimately help address a number of unmet challenges in human health.



Acknowledgements: Support for this research is provided by the National Science Foundation Graduate Research Fellowship under Grant No. 2019281534 and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award number 5R01AI126592-06.

THARP

Enantioselective Enzymatic Reduction of Acrylic Acids

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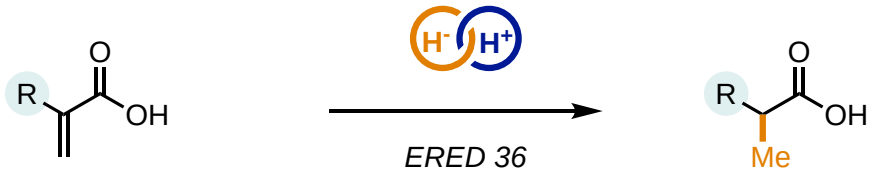
Over the past few years, the field of biocatalysis has come to the forefront of organic chemistry due to its wide range of capabilities to generate mild, green, and highly enantio- and chemoselective syntheses of chiral compounds. Prior to our report, there was no general method for the enzymatic reduction of α,β-unsaturated carboxylic acids towards the synthesis of enantioenriched α-substituted carboxylic acids. Unsaturated acids have traditionally been challenging substrates for ene-reductases (EREDs), due to their poor electronegativity. It has been well established that EREDs reduce activated alkenes, but the reduction of less activated alkenes was previously unprecedented. In this report, we identified an ERED capable of reducing α,β-unsaturated carboxylic acids in up to >99% ee. ERED 36 catalyzes a broad range of aromatic and aliphatic acrylic acids, including both acylic and cyclic unsaturated carboxylic acids. Future studies, which will focus on the reactivity of ERED 36, will give a deeper understanding of this enzyme's capabilities and enable future design of EREDs to reduce an even broader range of substrates with high selectivity.[1]



R = alphatic, aryl, benzyl

17 examples
>99% ee

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TONA

Discovery Process Research at Janssen Pharmaceutica

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Janssen Research & Development seeks to bring treatments in six therapeutic areas of unmet medical needs. Our Discovery Process Research team focuses on developing syntheses for innovative small molecule therapeutics to treat diseases among which Alzheimer's disease, various types of cancers, and infectious diseases like Hepatitis B.

Our main goal as DPR is to facilitate and accelerate medicinal chemistry research by finding new solutions to synthetic bottlenecks, enabling access to novel chemical space, and translating chemistry innovations to the development of efficient routes for the synthesis of small molecule drug candidates advancing into development. As such we deliver the first clinical volumes of active compounds using fast, reliable, scalable, and cost-effective synthesis methods. To achieve this, we both take advantage of state-of-the-art synthetic organic chemistry literature and seek to discover new approaches.

Being at the interface between discovery and process development, we build and maintain collaborations with colleagues in medicinal chemistry, chemical and pharmaceutical development as well as other adjacent functional areas of drug discovery and development.

TRAMMEL

Nickel-Catalyzed Regiodivergent Dearomative Arylboration of Indoles

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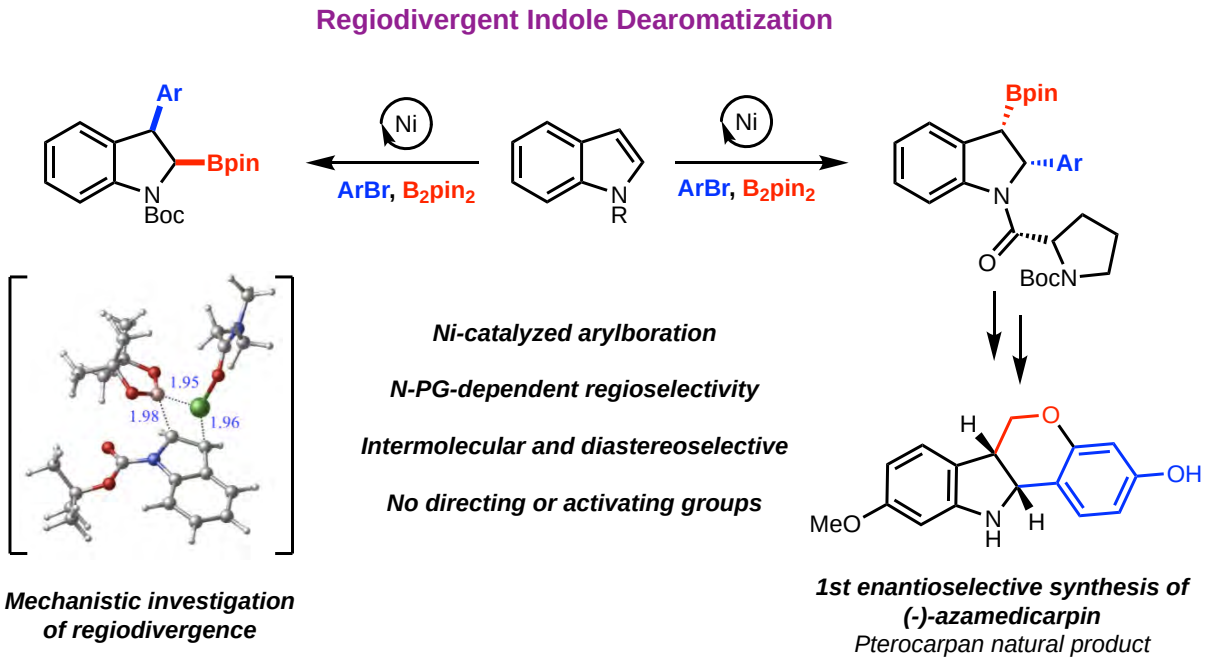
Indole dearomatization is an important strategy to access indolines, a motif present in a variety of natural products and pharmaceuticals. A method for transition-metal catalyzed regiodivergent dearomative arylboration of indoles to generate diverse indolines is presented. The method accomplishes intermolecular dearomatization of simple indoles through a migratory insertion pathway on substrates that lack activating or directing groups on the C2- or C3-positions. Synthetically useful C2- and C3-borylated indolines can be accessed through a simple change in *N*-protecting group in high regio- and diastereoselectivities (up to >50:1 rr and >20:1 dr) from readily available starting materials. Additionally, the origin of regiodivergence was explored experimentally and computationally to uncover the remarkable interplay between carbonyl orientation of the *N*-protecting group on indole, electronics of the C2-C3 π-bond, and sterics. The method enabled the first enantioselective synthesis of (-)-azamedicarpin.



Acknowledgements: Support for this research is provided by Indiana University and the NIH under Grant No. R35GM131755.

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TRENTADUE

Total Synthesis of Putative Biosynthetic Intermediate Ambruticin J

Kathryn Trentadue,[†] Chia-Fu Chang,[‡] and Richard Taylor*,[†]
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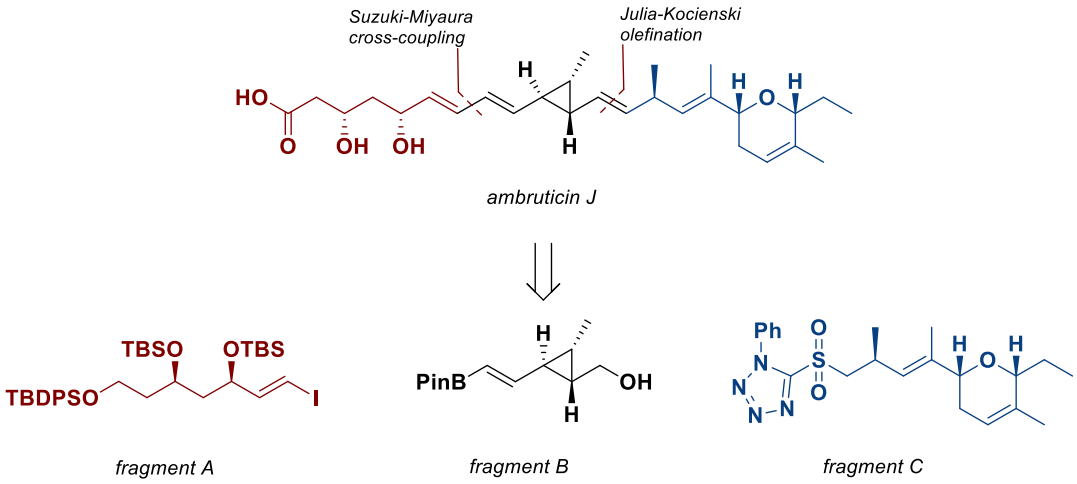
The ambruticin family of polyketide natural products, originally isolated in 1977, consists of several natural products with two pyran rings adorning a tri-substituted cyclopropane core. Previous biosynthetic studies by Reeves *et. al.* sequenced the gene cluster responsible for the synthesis of these compounds and identified the intermediate species released from the polyketide synthase (PKS) as ambruticin J, a diol in which two of the three rings have been formed.[1] The third ring is formed through post-PKS modification by the enzyme AmbJ, which appears to be responsible for the selective epoxidation of ambruticin J. The resulting highly strained intermediate then undergoes epoxide opening and cyclization to create the final ring found in the isolated ambruticins. Studies of this transformation have been hindered by lack of ambruticin J to serve as a substrate.

Here we report the first total synthesis of ambruticin J *via* a triply convergent synthetic route relying on a Suzuki-Miyaura cross-coupling and a Julia-Kocienski olefination for fragment coupling (Scheme 1).[2] The key central fragment is constructed through a highly stereoselective cyclopropanation reaction previously developed in our lab. This work sets the stage for future investigation of the role of AmbJ in the epoxidation and cyclization steps of the biosynthesis of the ambruticins.



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TURLIK

Mechanism and Origins of Stereoselectivity of the Aldol-Tishchenko Reaction of Sulfinimines

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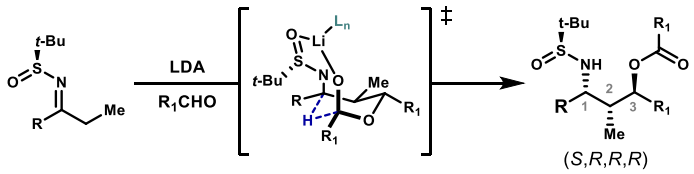

- DFT calculations reveal factors controlling selectivity
- Hydride transfer is the rate- and stereochemistry-determining step

1,3-Amino alcohols are synthetically useful moieties that are present in many biologically active molecules. In 2015, McGlacken and coworkers reported the stereoselective synthesis of 1,3-amino alcohols through an aldol-Tishchenko process.[1] Diastereoselectivity was imparted through the use of *t*-butylsulfinimines, the Ellman auxiliaries. After an initial aldol reaction of a *t*-butylsulfinimine with an aldehyde, the resulting alkoxide reacts with another equivalent of the aldehyde, followed by an intramolecular hydride transfer to produce the reduced amine. These reactions lead to the formation of 1,3-amino alcohols with high stereoselectivity, and double aldol-Tishchenko reactions can form 3-amino-1,5-diols with up to five contiguous stereocenters.

Curiously, divergent stereochemical outcomes were observed based on the identity of the sulfinimine starting materials. Density functional theory (DFT) calculations were performed in order to rationalize the source of stereoselectivity in these reactions.[2] Experimental investigations revealed an initial non-selective aldol step, and our computational studies thus focused on the irreversible and selectivity-determining intramolecular hydride transfer. Our study explains the origin of stereoselectivity for the aldol-Tishchenko reaction, and provides a guide to the selectivities expected for related reactions. In addition, we demonstrate the power of the interplay between computational and syn-thetic chemistry for predictions of stereochemical outcome and structure determination.

Acknowledgements: This work is supported by the National Science Foundation (grant CHE-1764328) and the National Institutes of Health under Ruth L. Kirschstein National Research Service Award F32GM134709. Calculations were performed on the Hoffman2 cluster at the University of California, Los Angeles, and the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by the National Science Foundation (grant OCI-1053575).

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ULIASSI

Phenothiazine-tacrine heterodimers as novel disease-modifying agents for Alzheimer's disease

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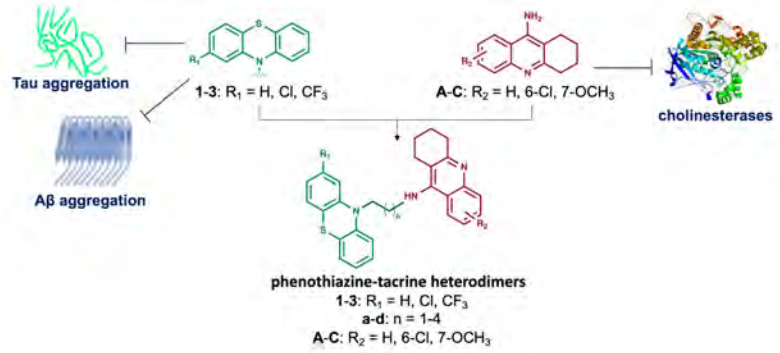
Alzheimer's disease (AD) has grown as a top 21st century's challenge for its socio-economical and scientific impact. AD has no cure and the lack of effective drugs is likely due to its complexity. The multi-target-directed ligand approach has been proposed as particularly suitable to combat the heterogeneity and the multifactorial nature of AD.[1] Motivated by these considerations and as a result of our medicinal chemistry interest in exploring original framework combinations, we propose herein a novel series of tacrine-phenothiazine heterodimers.[2] Particularly, such heterodimers have been rationally designed by linking differently substituted phenothiazines (**1-3**), which possess antiaggregating and neuroprotective effects, to the anticholinesterase activity of tacrine derivatives (**A-C**) via a methylene spacer of varying length (n = 1-4). A facile strategy allowed obtaining a 36-membered library through convergent synthesis. Next, we evaluated the in vitro anticholinesterase inhibitory profile. Compound **1dC** emerged as a potent and selective acetylcholinesterase inhibitor (IC_{50} = 8 nM) and **1aA** as a potent butyrylcholinesterase inhibitor (IC_{50} = 15 nM). **1dC** and **2dC** displayed a significant inhibitory activity toward τ(306–336) peptide aggregation and self-induced $A\beta_{1-42}$ aggregation. In vivo studies of **1dC** showed an acceptable safety and good pharmacokinetic properties.



Acknowledgements: Support is provided by the Ministry of Education, Youth and Sports of Czech Republic (project ERDF no. CZ.02.1.01/0.0/0.0/18_069/0010054); and by the Grant from the Czech Science Foundation (20-29633J). We also acknowledged the University of Bologna and the Italian Ministry for Education, Universities and Research.

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VERSAW

Designing Naphthopyran Mechanophores with Tunable Mechanochromic Behavior

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Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125,
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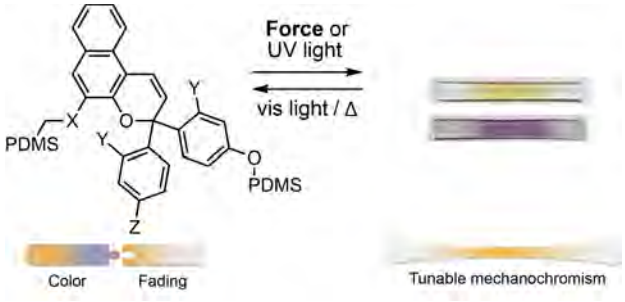
Polymeric materials that report applied stress or strain through a change in color are a developing area of interest for stress sensing applications. This force-reporting behavior can be accomplished through the incorporation of force-responsive small molecules termed mechanophores.

Here, we introduce a series of naphthopyran mechanophores that generate merocyanine dyes with highly tunable visible absorption properties and thermal reversion kinetics.[1] Diversification of a common naphthopyran scaffold using straightforward synthetic strategies affords a library of mechanophores that are incorporated into crosslinked polydimethylsiloxane (PDMS) networks. The resulting materials produce color in tension that varies from orange-yellow to purple and fades at rates controlled over three orders of magnitude. Beyond developing key structure-mechanochemical activity relationships, we also demonstrate the capacity of this platform to access complex force-reporting and multimodal stimuli-responsive functions.



Acknowledgements: Support for this research was provided by Caltech and the Dow Next Generation Educator Fund. B. A. V. and M. E. M. are supported by National Science Foundation Graduate Research Fellowships (DGE-1745301).

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WANG (DIANA)

Aziridines from coupling primary amines and α-olefins via an electrogenerated dicationic intermediate

Diana J. Wang,[†] Dylan E. Holst,[†] Min Ji Kim, [†] Ilia A. Guzei, [†] and Zachary K. Wickens*,[†]
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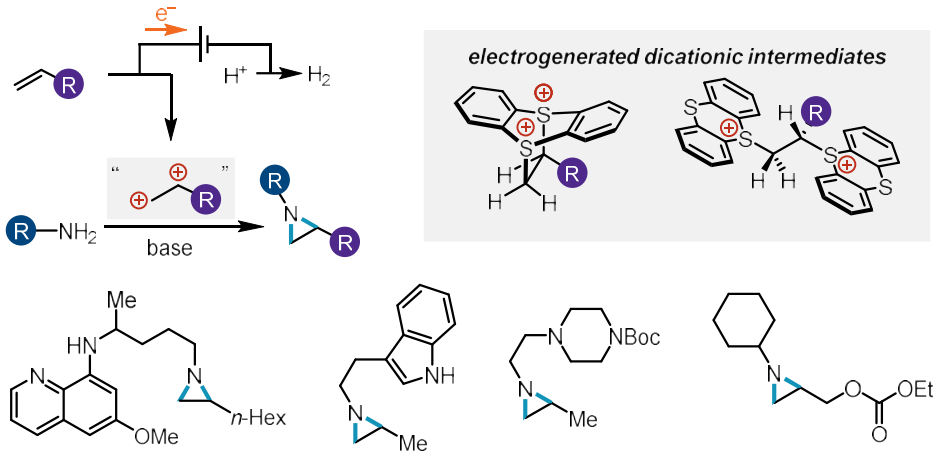
Aziridines are versatile synthetic intermediates used to access a variety of amine products due to their ring strain and regioselective ring opening reactivity.[1a] While aziridination of abundant, ubiquitous alkenes enables rapid formation of these cyclic synthons, limitations remain as most methods install electron-withdrawing *N*-substituents through requisite use of high-energy electrophilic nitrogen reagents or nitrene precursors.[1b] Recent work has made substantial progress on diversification to *N*-alkyl aziridines[2a-c], but these methods are still limited to a small subset of electrophilic nitrogen reagents, many of which require multistep synthesis.

In this context, we describe herein a novel, electrochemical approach to aziridination that couples commercial, primary amines and unactivated alkenes. Anodic oxidation of cheap, non-toxic thianthrene in the presence of alkene generates metastable, dicationic intermediates (Figure 1). This alkene activation then leverages the innate nucleophilicity of amines to greatly expand the scope of readily accessible *N*-alkyl aziridines. Substrates as simple as feedstock propene and as complex as primaquine are amenable. Using electrochemistry, this method expends only electricity and protons, generating minimal waste even when scaled to multigram quantities. Finally, we can expand beyond aziridination and show versatility of the dicationic intermediates themselves by probing with different nucleophiles, demonstrating the generality of this platform for alkene difunctionalization.



Acknowledgements: Support for this research is provided by the Office of the Vice Chancellor for Research and Graduate Education at the University of Wisconsin—Madison with funding from the Wisconsin Alumni Research Foundation.

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WANG (XIAOXU)

Asymmetric Radical Process for General Synthesis of Chiral Heteroaryl Cyclopropanes

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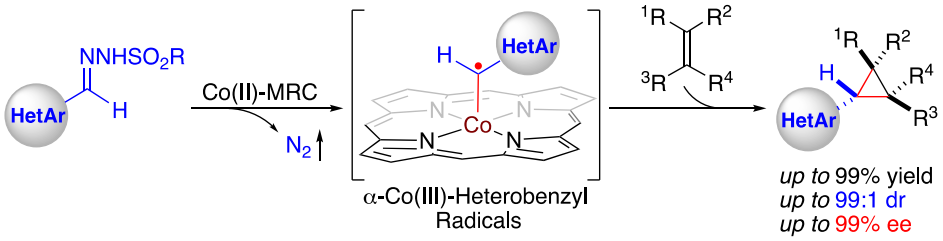
Chiral heteroaryl cyclopropanes are ubiquitous structural motifs found in pharmaceuticals and biologically active compounds.[1] Nevertheless, the methods for their stereoselective synthesis remain to be developed.[2] While metal-catalyzed asymmetric cyclopropanation of alkenes with heteroaryldiazomethanes offers a potentially attractive approach, there is no effective catalytic system that is capable of achieving high reactivity and stereoselectivity. Besides inherent instability of heteroaryldiazomethanes, the underlying challenge may be attributed to potential coordination of heteroaryl moieties to metal center in the existing catalytic systems. In pursuit of developing a general method to access this important class of molecules, we have developed a Co(II)-based metalloradical system that is highly effective for asymmetric radical cyclopropanation of alkenes with in situ-generated α-heteroaryldiazomethanes.

Supported by a newly-synthesized D_2-symmetric chiral amidoporphyrin ligand, the optimized Co(II)-based metalloradical system is broadly applicable to pyridyl and other heteroaryldiazomethanes for asymmetric cyclopropanation of a diverse range of alkenes, enabling the direct synthesis of various chiral heteroaryl cyclopropanes in high yields with excellent diastereoselectivities and enantioselectivities. In addition to high degree of functional group tolerance, the catalytic system is highlighted by the utilization of several classes of challenging olefin substrates, further showcasing the synthetic utility of this methodology. We also present detailed experimental and computational studies that shed light on the underlying stepwise radical mechanism of this Co(II)-catalyzed asymmetric cyclopropanation.



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WARNICA

Cation-π interactions in the stabilization of the asymmetric iminium catalyzed (*E*)-polyene cyclization

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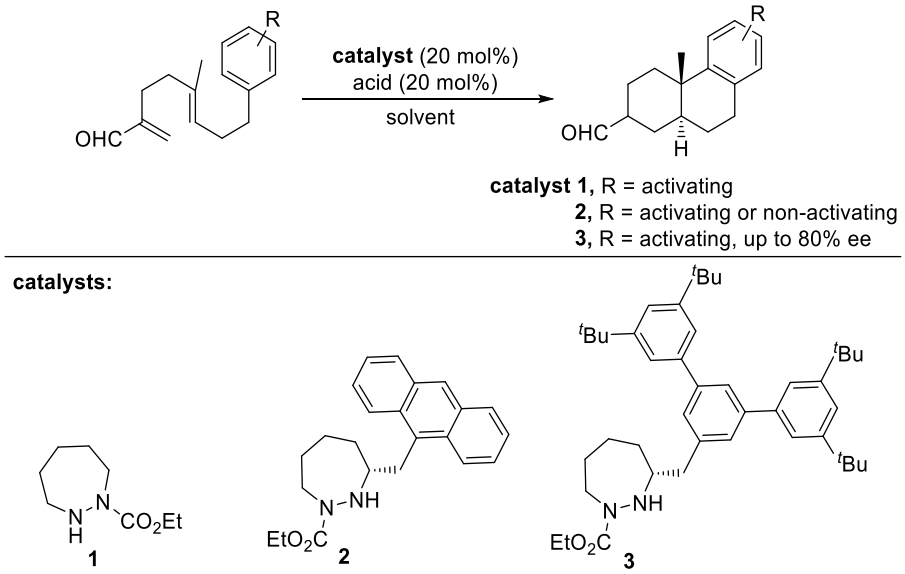
During the biosynthesis of steroids and other terpenoid natural products, cyclase enzymes catalyze the cationic cyclization of polyolefins into chains of fused carbon rings with complete chemo-, regio-, and stereocontrol. Positively charged intermediates are stabilized within the binding pockets of these enzymes through cation-π interactions with the side chains of aromatic amino acids.[1] The ability of the polyene cyclization to rapidly build molecular complexity from a simple achiral starting material has brought considerable interest from synthetic chemists. We have investigated iminium catalysis as a method to initiate the polyene cyclization and have reported the racemic iminium catalyzed (*E*)-polyene cyclization with the use of cyclic hydrazide catalyst **1** on substrates with terminating aromatic rings of strong nucleophilicity.[2] Through investigation into catalysts with aromatic substitution, we have been able to expand the scope of the reaction with catalyst **2**, to include non-activated terminating groups. Computational analysis of the reaction profile has shown stabilization of intermediates and transition states with the addition of the extended aromatic. Further combination of computational analysis with experimental investigation has led us to catalyst **3** which has resulted in polyene cyclization products of up to 80% ee.



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WILT

Synthetic exploration of phenolic bisabolanes and their antimicrobial activity

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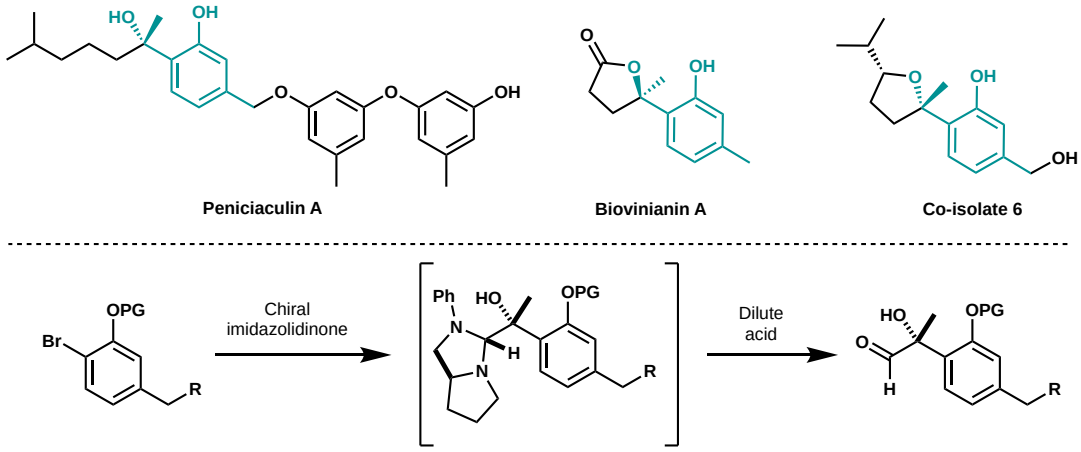
Phenolic bisabolane sesquiterpenoids isolated from marine sediment display potent activity towards numerous pathogens.[1] Despite structural similarities, these natural products are reported to have narrow spectrum activity suggesting minor changes in structure can result in unique mechanisms of action. Identification of a key common enantio-enriched intermediate allowed for rapid generation of several natural products and derivates. Investigation of the unique reported bioactivity is underway to illuminate potential trends and mechanisms of action of these marine isolates.



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ZEITLER

Mechanoredox Aryl "-onium" Salt Initiated Free Radical Polymerizations

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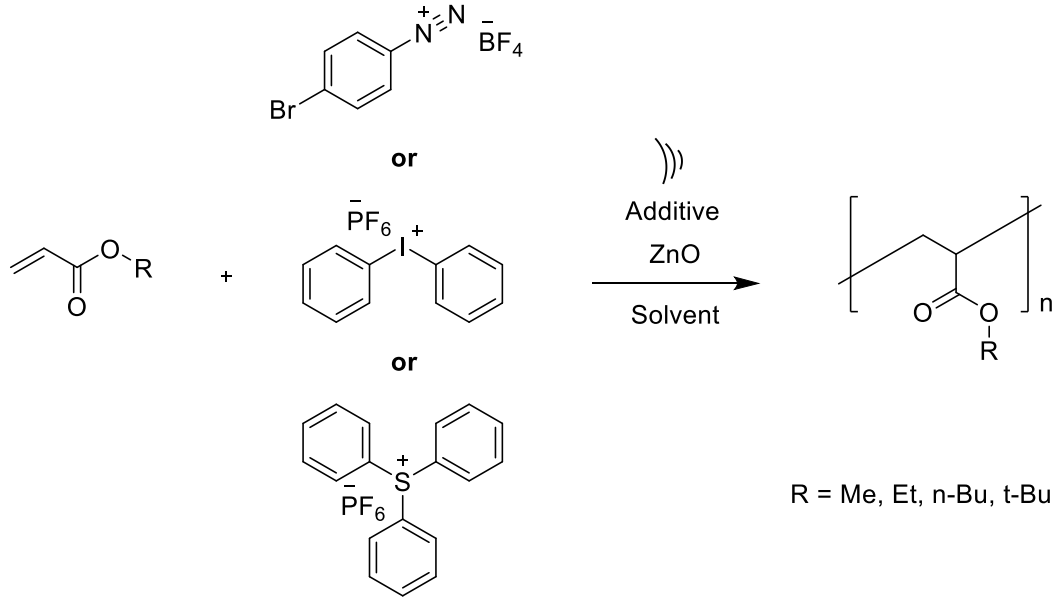
Stimuli-induced polymerizations continue to gain interest as synthetic polymers become more desirable for materials, industrial, and medical applications. While traditional stimuli such as heat, light, and electrochemistry have been extensively studied, they still have shortcomings such as unwanted side reactions, lack of consistent penetrability, and irregular and irreproducible equipment setups. Many of these shortcomings can be overcome by using force as a stimulus for polymerization. In particular, the use of piezoelectric nanoparticles enables force to initiate redox reactions, thus making force an even more useful and accessible stimulus.

Herein, we show various "-onium" salts can initiate free radical polymerizations of acrylates upon the introduction of ultrasonic force in the presence of piezoelectric nanoparticles. These salts have different redox potentials and properties making them valuable in a multitude of applications and have been shown to be reactive with piezoelectric nanoparticles.[1] Additionally, we have increased the initiator efficiency of the limited previous mechanoredox polymerizations reported, making our reactions more efficient than such findings.[2–4] In particular, iodonium salts have given high control and high conversions for polymerization. Finally, initial results of successful piezo polymerizations conducted with alternate sources of force are discussed. These initial "-onium" initiated mechanoredox polymerizations unlock the possibility to better utilize force in synthesizing polymers and creating useful adaptable materials.



Acknowledgements: Support for this research is provided by the University of Washington and seed funding from UW MRSEC MEM-C (NSF DMR-1719797).

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ZHANG

Controlling Enantioselectivity and Diastereoselectivity in Radical Cascade Cyclization for Construction of Bicyclic Structures

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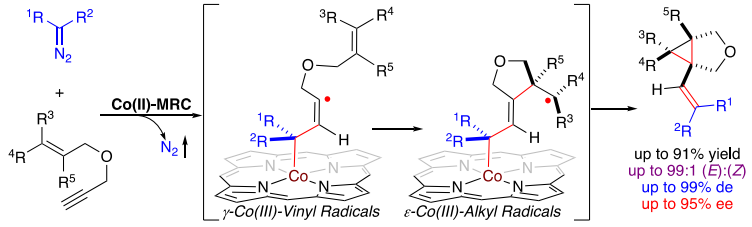
Radical cascade cyclization reactions are highly attractive synthetic tools for the construction of polycyclic molecules in organic synthesis.[1] While diastereoselective radical cascade has been successfully applied in many important transformations, control of enantioselectivity remains a formidable challenge in the field.[2] As the first application of metalloradical catalysis for controlling enantioselectivity as well as diastereoselectivity in radical cascade cyclization, we herein report the development of a Co(II)-based catalytic system for asymmetric radical bicyclization of 1,6-enynes with diazo compounds. Through the fine-tuning of D_2-symmetric chiral amidoporphyrins as the supporting ligands, the Co(II)-catalyzed radical cascade process, which proceeds in a single operation under mild conditions, enables asymmetric construction of multisubstituted cyclopropane-fused tetrahydrofurans bearing three contiguous stereogenic centers, including two all-carbon quaternary centers, in high yields with excellent stereoselectivities. Combined computational and experimental studies have shed light on the underlying stepwise radical mechanism for this new Co(II)-based cascade bicyclization that involves the relay of several Co-supported carbon-centered radical intermediates, including α-, β-, γ- and ε-metalloalkyl radicals. The resulting enantioenriched cyclopropane-fused tetrahydrofurans that contain a trisubstituted vinyl group at the bridgehead, as showcased in several stereospecific transformations, may serve as useful intermediates for stereoselective organic synthesis. The successful demonstration of this new asymmetric radical process via Co(II)-MRC points out a potentially general approach for controlling enantioselectivity as well as diastereoselectivity in synthetically attractive radical cascade reactions.



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ZHOU

Design and Syntheses of New Bifunctional Boronic Acids for Direct Dehydrative Amidation of Challenging Substrates

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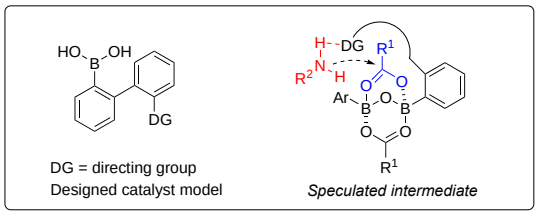
Amide synthesis has been of great interest to chemists as the amide moiety presents widely in agrochemicals, pharmaceutical agents, and biologically active molecules.[1a] Traditionally, amide bond formation requires the use of activated carboxylic acid derivatives or stochiometric amounts of coupling agents, which are generally toxic, expensive, and result in large amount of undesired by-products that complicate product purification.[1b] To develop more environmentally friendly methodologies and to enhance atom-economy, chemists have been exploring organoboron-catalyzed dehydrative amidation reactions in the past few decades.[1c]

A series of bifunctional boronic acid catalysts proposed by Whiting and co-workers exhibited good catalytic activity in the direct amide condensation, however they require elevated temperature to afford good yields.[2] Our laboratory reported 5-methoxy-2-iodophenylboronic acid (MIBA) as an efficient catalyst giving high yields at temperatures ranging from ambient to 50 °C.[3a,b] Unfortunately, the substrate scope of MIBA remained limited, especially with aniline derivatives, acyclic secondary amines, and heteroaromatic acids.

In 2018, Whiting's mechanistic study highlighted the existence of an active catalytic intermediate featuring a dimeric B–X–B motif (X = O, NR) that is capable of an intramolecular carbonyl activation as well as an amine delivery through B-N interactions.[4] Inspired by the dimeric motif, we designed a bifunctional boronic acid model aimed at activating the carboxylic acid with the B-O-B motif and direct the amine with a proper coordinating group. With balanced structural flexibility and rigidity, a series of new bifunctional boronic acids were synthesized and evaluated for amidation between challenging substrates, such as benzoic acid and aniline.



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