Empowering Women in Organic Chemistry Conference 2022

Poster Abstract Booklet

Thurs, June 23: VIRTUAL POSTER SESSION

4:30–5:00pm EDT Posters V1–V36
5:00–5:30pm EDT Posters V37–V72

Fri, June 24: IN-PERSON POSTER SESSION

5:00–5:45pm EDT Posters 1–20
5:45-6:30pm EDT Posters 21–40

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Information for Attendees

Virtual Poster Session: Each poster will have an assigned Zoom room. You will receive a list of the links to these Zoom rooms separately. Please visit the posters 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 multiple slides instead of the traditional static poster. Posters V1–V36 will be available from 4:30–5:00pm EDT. Posters V37–V72 will be available from 5:00–5:30pm EDT.

In-Person Poster Session: The posters will be displayed during the networking session. Posters 1–20 will be available from 5:00–5:45pm EDT. Posters 21–40 will be available from 5:45–6:30pm EDT.

On the poster abstracts pages that follow, the poster number can be found in the upper right corner. Virtual posters have a V proceeding their poster number. In-person posters just have a poster number.

Please do not photograph or record the poster presentations, unless you have the explicit permission of the presenter.

List of Posters for Quick Reference

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V5	Eleanor P. Bentley	Green Groebke-Blackburn-Bienaymé synthesis of 3-aminoimidazo[1,2-a]-heterocycles
V6	Nicole Berry	Synthesis of aryl-orthoesters: New building blocks for organic semiconductors
V7	Rebecca Bogart	Synthesis of PAC1R Small Molecule Antagonists
V8	Abigail Boon	Electrochemical versus chemical oxidation of 2,6-diphenylphenol
V9	Meredith Borden	LEVERAGING LATENT CATALYSIS TO DIVERSIFY MATERIALS' PROPERTIES IN ADDITIVE MANUFACTURING
V10	Jacob Bouchard	Structural and Functional Characterization of Conformationally Discrete Amyloid-Beta Oligomers for Probe Development
V11	Amy Brown	Design and Synthesis of Fused Acenedichalcogenophenes Based on Benzo[1,2-b:4,5-b']difuran in the Development of Novel Materials For Organic Electronics
V12	Caroline Buchholz	CHEMICAL PROBE DEVELOPMENT FOR BPTF READER DOMAINS UTILIZING BIOPHYSICAL ASSAYS
V13	Mary Cacace	Small Molecule Allosteric Inhibition of Cytosolic Sulfotransferases
V14	Amanda Canfield	Convergent Synthesis of Dihydrobenzofurans Via Urea Ligand-enabled Heteroannulation of 2-Bromophenols with 1,3-Dienes
V15	WITHDRAWN	
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V17	Ling Cheng	DESIGN AND DEVELOPMENT OF TRYPANOSOMA CRUZI. BENZOXABOROLE PRODRUGS
V18	Abigail Clapperton	Gram-scale synthesis of sequence-specific polypeptoids
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V20	Riley Cooper	Catalytic Radical-Polar Crossover Ritter Reaction
V21	Stephanie Corio	A Mechanistic Study of Arene C-H Amination Using Oxygen-Mediated Photoredox Catalysis
V22	Krystyna Demkiw	Hyperconjugative Interactions of the Carbon–Halogen Bond Control Stereoselectivity in Glycosylation Reactions and Contribute to the Geometry of the Products
V23	Serena DiLiberti	Total Synthesis of (+)–Eburnamonine via Asymmetric Alkene Cyanoamidation and C–CN Bond Activation
V24	Sun Dongbang	NI/PHOTOREDOX-CATALYZED C(SP3)−C(SP3) COUPLING BETWEEN AZIRIDINES AND ACETALS AS ALCOHOL-DERIVED ALKYL RADICAL PRECURSORS
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V39	Neha Rani Kumar	Synthesis of bent-shaped π-extended thienoacenes from 2,5-distannylated 3,4-dialkynethiophene
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V72	Yingchuan Zhu	Synthetic Studies Towards the Indole Diterpenoid Natural Products
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5	Julia Borowski	Investigation of phosphine ligand steric effects on ligation state and reactivity in Ni-catalyzed cross-coupling
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7	Tiffany Chen	A Unified Approach to Decarboxylative Halogenation of (Hetero)aryl Carboxylic Acids
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9	Mikaela DiBello	Studies Toward the Total Synthesis of (-)-lomaiviticin A
10	Sarah Dishman	C–H Insertion of Donor/Donor Carbenes into Stereogenic Centers and the Asymmetric Synthesis of Dihydrobenzoxanthones
11	Allison Domhoff	Innovative Automotive Paint B1:B2 Compact Paint Systems
12	Madeline Frischling	TOTAL SYNTHESIS OF NENESTATIN A AND ITS APPLICATION TOWARD ELUCIDATING ATYPICAL ANGUCYCLINE DIMERIZATION
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OVERCOMING THE CONSTRAINTS OF AROMATICITY IN 1,3-DIPOLAR CYCLOADDITION FOR SYNTHESIS OF COMPLEX HETEROCYCLES

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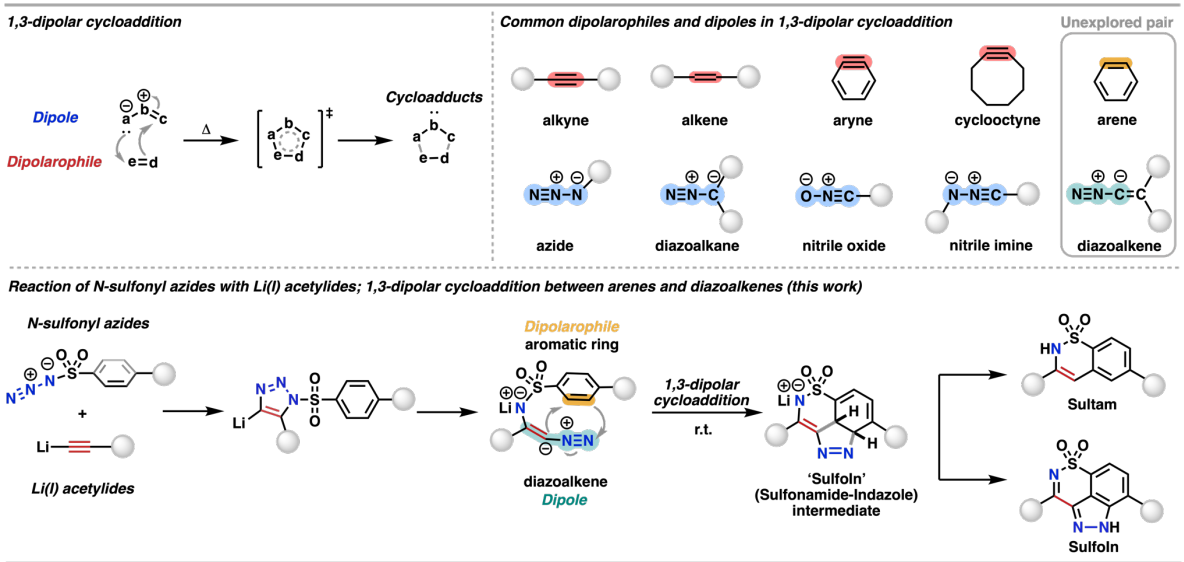
The venerable 1,3-dipolar cycloaddition has been widely used in organic synthesis for the construction various heterocycles with a broad range of carbon-heteroatom bonds from structurally diverse dipoles and dipolarophiles. However, in its over a century-long history, the simple and ubiquitous aromatic ring has evaded being engaged in the reaction as a dipolarophile. Since 2001, interest in this field was reinvigorated following the discovery of the copper-catalyzed azide-alkyne cycloaddition. The ensuing finding of 1,2,3-triazoles bearing electron-withdrawing groups at the *N1*-position has been of particular interest due to the unusual chemical reactivity demonstrated by this family of heterocycles. Reactivity of such molecules under transition-metal free conditions has been recently explored. During our investigations, we observed an intriguing reaction of lithium acetylides and *N*-sulfonyl azides. The reaction proceeds via unprecedented cascade of transformations involving *in situ* generation of a diazoalkene species that undergoes an intramolecular 1,3-dipolar cycloaddition with an aromatic group. The involvement of aromatic groups in the 1,3-dipolar cycloadditions broadens the utility of the diazoalkenes, a family of dipoles that have been barely explored and are otherwise difficult to access. The new process described here provides a route for the synthesis of broadly relevant heterocycles and can be extended to other arene-containing starting materials.



ASSEMBLY OF COMPLEX POLYCYCLIC SCAFFOLDS BY AN ENANTIOSELECTIVE DEAROMATIZATION STRATEGY

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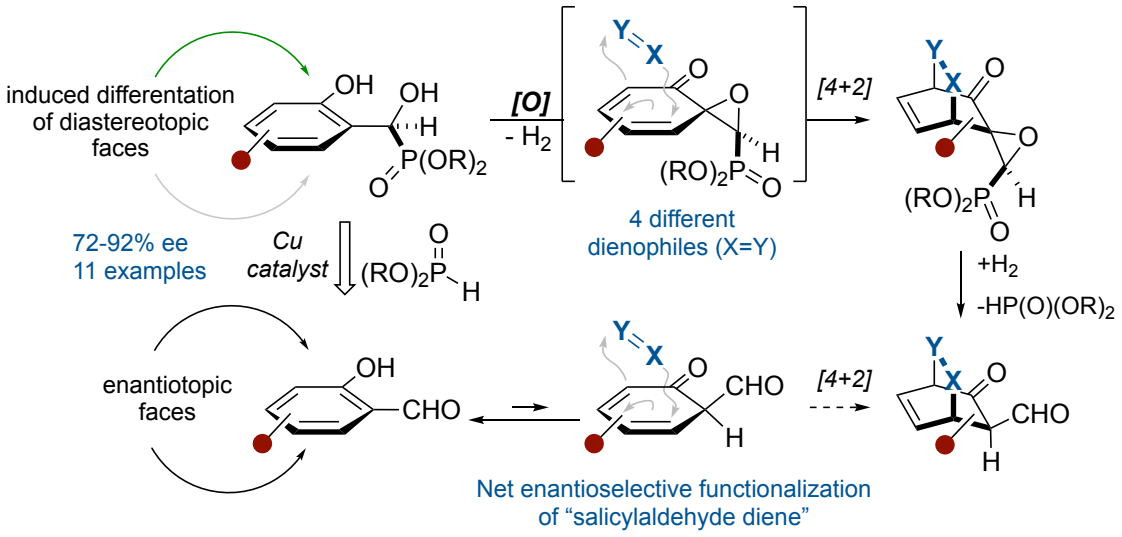
The oxidative dearomatization of phenols, particularly in an enantioselective fashion, is still a challenge despite its utility in complex molecule synthesis. We report an alternative platform for enantioselective salicylaldehyde dearomatization that employs the use of chiral nonracemic α-hydroxyphosphonates as a cleavable aldehyde oxidation state protecting group. We developed a copper bis(oxazoline)-catalyzed hydrophosphonylation of salicylaldehydes, allowing access to enantioenriched material in one step. The adducts were then used in a tandem phosphono-Adler-Becker oxidation/[4+2] cycloaddition to give bicyclo[2.2.2]-octanes bearing phosphonoepoxy ketone functionalities in nearly perfect regio- and diastereoselectivities for both the oxidative dearomatization and cycloaddition steps. The epoxyphosphonates can be reductively cleaved to reveal the parent aldehyde, giving enantioenriched complex polycyclic scaffolds in 3-4 steps from salicylaldehydes. We anticipate this platform for enantioselective salicylaldehyde dearomatization will be useful for the synthesis of densely functionalized oxygen-containing natural products.



DESIGN AND SYNTHESIS OF CHIRAL HETEROBIARYL ATROPISOMERS

Kristen M. Baker, Colby J. Agostino, Emily A. Orloff, Lorenzo D. Battistoni, Riley R. Hughes, Erin M. McHugh, Michael P. Shaw, Seann P. Mulcahy*

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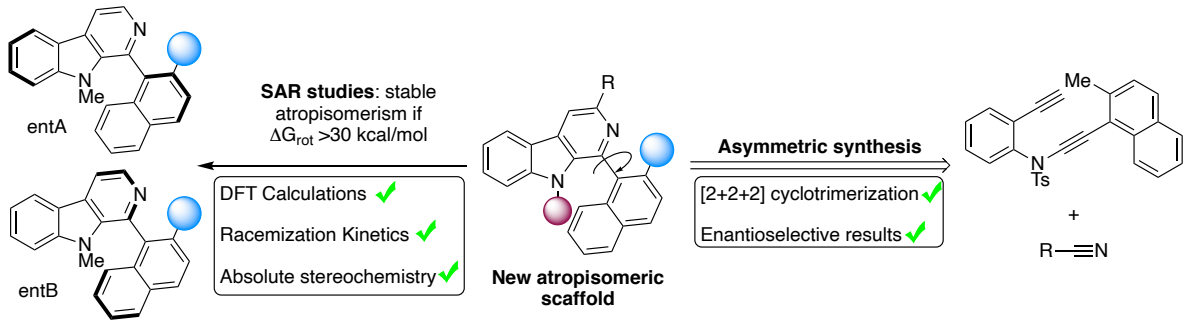
Atropisomers are a class of molecules that are axially chiral due to their high barriers to rotation about a single bond. Notably, if the barrier to rotation about the sigma bond in a biaryl system is high enough, these atropisomers can be isolated as non-interconverting enantiomers that may have stereospecific properties. Due to this, motifs that could form enantiopure atropisomers are increasingly desirable in drug discovery. In our initial work, we envisioned the formation of novel heterobiaryl atropisomers with a β-carboline scaffold, which have been shown to be useful bioactive molecules. Utilizing computational studies, we determined the barrier to rotation of an array of molecules, allowing us to identify the functional groups that impart stable atropisomerism. Synthesis of a few of the best candidates allowed us to determine their experimental barrier to rotations and determine the absolute stereochemistry of these stable enantiopure atropisomers. Excitingly, we observed a high barrier of rotation for these molecules, up to 39 kcal/mol. Investigations into the asymmetric synthesis of atropisomeric β-carbolines will also be presented, including our work towards the optimization of the key [2+2+2] cyclotrimerization step of our 5-step synthesis.



CHEMICAL SYNTHESIS OF FLUORINATED CARBOCYCLIC NUCLEOSIDE ANALOGUES: TOWARDS NEW PHARMACOPHORE SPACE

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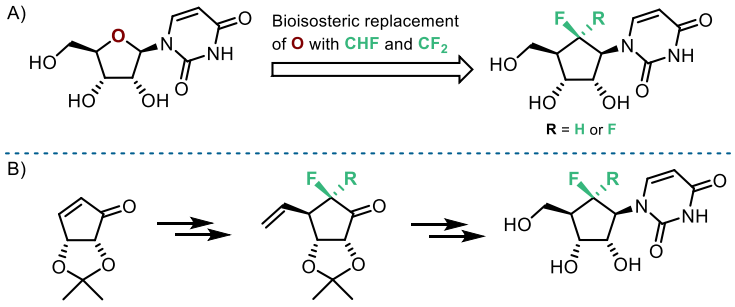
Nucleoside analogues (NAs) represent an important class of antiviral and antitumor agents. Currently, there are more than 25 NAs on the market, forming the backbone of chemotherapeutic treatment of cancers[1] and many viral infections.[2] However, they are not without their limitations, and often display adverse side effects and poor oral bioavailability. As such, the development of new NAs with improved bioavailability, selectivity and metabolic stability, as well as a lower toxicity, remains a topic of high interest.[3–5] Carbocyclic nucleosides, wherein the furanosyl oxygen is replaced with carbon, have increased chemical and metabolic stability due to the lack of a hemiaminal bond.[6] The inclusion of fluorine within nucleoside pharmacophores has also proven beneficial, conferring increased metabolic stability, lipophilicity, bioavailability and binding affinity.[7] With this in mind, a novel synthetic route to a largely unexplored class of NAs, incorporating the bioisosteric replacement of furanose oxygen with CHF and CF2, has been developed.



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2. E. De Clercq and G. Li, *Clin. Microbiol. Rev.*, 2016, **29**, 695–747.
3. G. J. Miller, *Science*, 2020, **369**, 623
4. M. Guinan, N. Huang, M. Smith and G. J. Miller, *Bioorg. Med. Chem. Lett*., 2022, **61**, 128605.
5. Mieke Guinan, Ningwu Huang, C. S. Hawes, M. A. Lima, Mark Smith and G. J. Miller, *Org. Biomol. Chem*., 2022, **20**, 1401–1406
6. K. L. Seley-Radtke and M. K. Yates, *Antiviral Res*., 2018, **154**, 66–86
7. A. D. Westwell, in *Fluorinated Pharmaceuticals: Advances in Medicinal Chemistry*, ed. A. D. Westwell, Future Science Ltd, London, UK, 2015, pp. 2–5.

GREEN GROEBKE-BLACKBURN-BIENAYMÉ SYNTHESIS OF 3-AMINOIMIDAZO[1,2-A]-HETEROCYCLES

Eleanor P. Bentley[†], Leepakshi Johar[‡], Hendrik Szurmant[‡], David A. Vosburg[†]*

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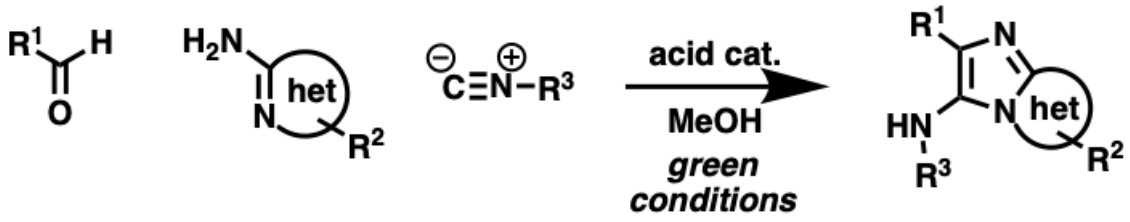
3-Aminoimidazo[1,2-a]pyridines and related structures have demonstrated a range of biological activities, including antimicrobial effects. We synthesized a series of 3-aminoimidazo[1,2-a]-heterocycles, some of which were novel, using a green, microwave-assisted Groebke-Blackburn-Bienaymé multicomponent reaction. Compounds with 4-chlorophenyl and tert-butyl substituents and varied core heterocyclic structures were found to exhibit antimicrobial activity against gram-positive bacteria.



SYNTHESIS OF ARYL-ORTHOESTERS: NEW BUILDING BLOCKS FOR ORGANIC SEMICONDUCTORS

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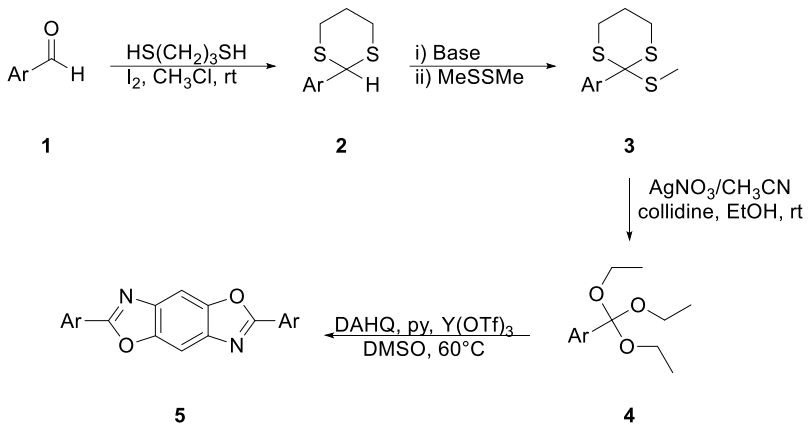
Condensation is the most ubiquitous method for synthesizing commodity polymers, conjugated polymers, oligomers, and the small molecules used as organic semiconductors in light-emitting diodes (OLEDs) and photovoltaic cells (PVCs). Tetraaryl-benzo[1,2-*d*:4,5-*d'*]bisoxazole (BBO) are generally synthesized using bis-*o*-aminophenols and aromatic dicarboxylic acid chlorides in mixtures containing trimethylsilyl polyphosphate/o-dichlorobenzene, polyphosphoric acid, or phosphorus pentoxide/methanesulfonic acid and heated to temperature above 200°C. These reaction conditions are both caustic and harsh limiting the scope of substituents that could be substituted on the BBO structural unit. Previously, our group reported that orthoesters can be used for the synthesis of functional BBO's under mild conditions. Unfortunately, the methods for the synthesis of the requisite orthoester are limited in scope and number. The goal for this project is twofold. First, I developed and employed a versatile synthetic method for making orthoesters that uses economically obtainable starting materials and has milder reactions conditions, Figure 1. Second, I utilized these synthons as building blocks for new BBO-based organic electronic materials.



SYNTHESIS OF PAC1R SMALL MOLECULE ANTAGONISTS

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Class B G protein-coupled receptors (GPCRs) are activated by the secretin/glucagon/VIP family of related peptides for physiological homeostasis including neuroendocrine hormone production and secretion, cardiovascular responses, glucose metabolism, gastrointestinal motility, micturition and germ cell development. Importantly, the family members pituitary adenylate cyclase activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP) are involved in many central effects such as feeding/satiety, autonomic responses, nociceptive sensitivity, cognition and learning/memory and stress-associated behaviors, through shared PAC1 and VPAC receptor subtypes. By targeting these receptors to regulate signaling, small molecule antagonists have therapeutic potential to mitigate maladaptive PACAP/PAC1 signaling that may be contributory to a number of disorders including chronic pain/migraine and post-traumatic stress disorder (PTSD). There are several PAC1 receptor variants and among several signaling cascades, PAC1 receptor downstream activation of the MEK/ERK pathway has been implicated in stress and chronic pain sensitivity. Recently, we have discovered a novel antagonist scaffold. This new scaffold is able to block PACAP/PAC1R-stimulated Ca^{+2} flux and ERK activation at low micromolar IC_{50} concentrations; concentrations to inhibit cAMP signaling were higher. Previous scaffolds synthesized from our lab appeared bias and not to impact the cAMP pathway. After identification of the scaffold, SAR studies were performed. We divided the compound into three regions and are currently modifying each of these areas systematically to enhance compound potency, efficacy and specificity. Concurrently, we are using molecular modeling approaches to identify other unique antagonist scaffolds for the PAC1 receptor system.

ELECTROCHEMICAL VERSUS CHEMICAL OXIDATION OF 2,6-DIPHENYLPHENOL

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Phenolic compounds are used in many industries including agriculture and biotechnology, yet inevitably end up in our environment. These compounds may serve as a phenolic precursor to produce raw materials for a wide range of applications. The selective electrochemical oxidation of bulky phenols was recently achieved [1]. Herein, the electrochemical oxidation of 2,6-diphenylphenol (DPP) was carried out and compared to traditional chemical oxidation. Contrasted with chemical oxidation, electrosynthesis resulted in a range of products based on the specific potential applied. The electrooxidation and chemical oxidation of DPP resulted in a solution colour change and the formation of new products monitored by UV-vis, nuclear magnetic spectroscopy (NMR), X-ray single crystal diffraction, and gas chromatography-mass spectrometry (GC-MS). Our data indicate that the synthetic outcomes are dependent on the synthetic methodology employed and that electrooxidation may yield products that are not always possible by chemical means.

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LEVERAGING LATENT CATALYSIS TO DIVERSIFY MATERIALS' PROPERTIES IN ADDITIVE MANUFACTURING

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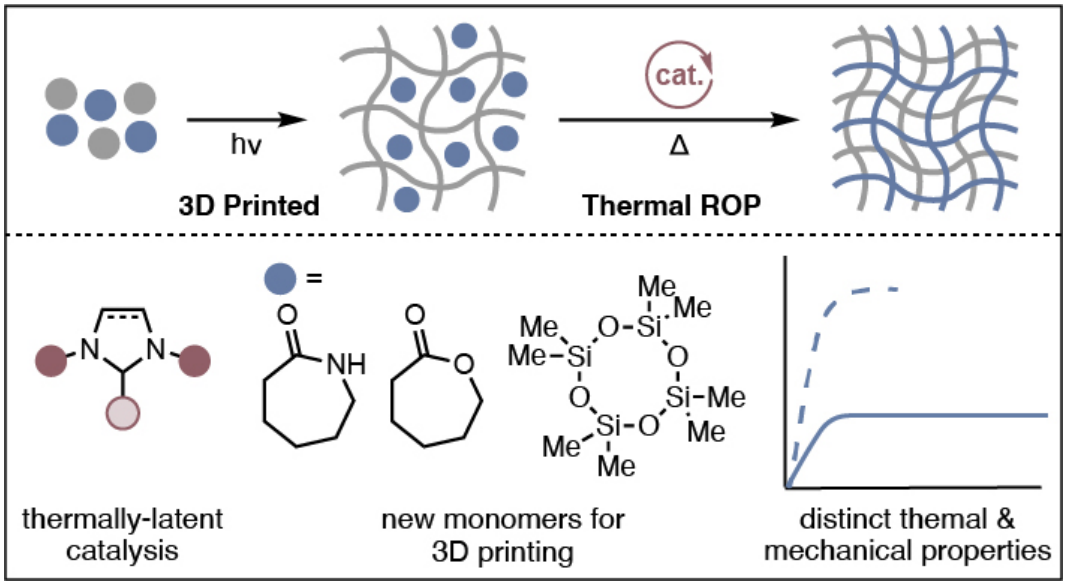
Additive manufacturing, also known as 3D printing, is an enabling technology for rapid prototyping and custom manufacturing. 3D printing technologies that proceed through VAT photopolymerization, such as digital light processing (DLP), typically rely on photo-initiated free radical polymerization of acrylates to enable rapid build times. However, reliance on acrylate monomers limits the thermal and mechanical properties that are accessible in parts fabricated via DLP. To diversify the composition of 3D-printed parts, we developed a dual-cure strategy to deliver a library of interpenetrating networks composed of an acrylate network with a secondary network composed of polyesters, siloxanes or nylons. Our approach capitalizes on an initial photo-promoted acrylate polymerization to deliver the shape of parts using a commercial DLP printer followed by a second thermal process in which a latent *N*-heterocyclic carbene catalyzes the ring-opening polymerization of a diverse array of monomers. Structure-reactivity relationships were examined to determine the optimal catalyst for representative lactone, siloxane and lactam monomers. Resultant dual-cure materials were evaluated using differential scanning calorimetry, uniaxial tensile testing, and rheology to identify materials with distinct thermal and mechanical properties relative to acrylate-only materials. These studies have demonstrated the potential of this dual-cure, catalytic approach for 3D printing to deliver materials with unique compositions and properties.



STRUCTURAL AND FUNCTIONAL CHARACTERIZATION OF CONFORMATIONALLY DISCRETE AMYLOID-BETA OLIGOMERS FOR PROBE DEVELOPMENT

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Alzheimer's disease (AD) is one of the most devastating neurodegenerative diseases and is currently the 6th leading cause of death in the United States.[1] While the exact cause of AD is unknown, soluble aggregates of the protein amyloid-beta (Ab), termed "oligomers", have been strongly implicated in disease pathology and increasing experimental evidence has demonstrated their toxic properties.[2] However; the study of these aggregates is difficult due to the inherent heterogeneity of oligomer formation and the tendency of Ab assemblies to dynamically interconvert. Consequently, previous studies have focused solely on understanding the disease properties of one or two aggregates or a heterogeneous mixture of oligomers. Therefore, efforts are needed to elucidate disease relevant structural isoforms.

We have developed methodology to generate stable, soluble oligomers of Ab from a recombinant protein expression system.[3,4] Through photo-crosslinking and size exclusion chromatography we were able to isolate discrete populations of oligomers for biophysical characterization and toxicity assessment.[4,5] Preliminary data show that SH-SY5Y cells treated with stable oligomers exhibit cellular dysfunction that resembles treatment with pooled oligomeric species, suggesting that these stabilized aggregates may possess similar attributes to that of disease state oligomers. Building off of these observations, a combinatorial library was designed and synthesized to screen stabilized oligomer species generated from a recombinant variant of Ab42. This screen identified hits that could serve as leads for the development of selective chemical probes.

Overall, this work highlights new tools for the study of Ab oligomers and their role in the pathophysiology of AD. These tools thus provide essential starting points for the development of diagnostics and potential therapeutics for this debilitating disease.

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DESIGN AND SYNTHESIS OF FUSED ACENEDICHALCOGENOPHENES BASED ON BENZO[1,2-*b*:4,5-*b'*]DIFURAN IN THE DEVELOPMENT OF NOVEL MATERIALS FOR ORGANIC ELECTRONICS

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With 300 million and growing consumers of electronic devices, there is a concurrent increasing demand for semiconducting materials. Organic semiconductors offer a diverse field of practical applications to meet this need and provide a better alternative to traditional inorganic based materials such as silicon. In fact, in recent years, there has been a flurry of activity in the field of organic electronic materials and as a result, the field mobilities, the standard measure of performance for these devices, has approached those of inorganic silicon components. Consequently, organic-based electronics are now an industrially viable alternative to inorganic circuits for applications in both large scale-arrays and low-end microelectronics. Small molecules and polymers are ideal for use in organic devices because these materials exhibit unique optical and semiconducting properties that are readily tuned as a function of structure.

Of particular interest is the development of materials based on an benzo[1,2-*b*:4,5-*b'*]difuran (BDF) acene motif (Figure 1) as these species are particularly promising as their two-dimensional (2D) fused latter like structure reduces the conformational freedom between adjacent aryl groups increasing planarity, conjugation and π-π stacking interactions thereby improving charge carrier mobilities. Introducing heteroatoms into the acene core is one approach for improving overall stability as these systems can still exhibit high charge-carrier mobilities with better air-stability than acenes containing the same number of rings. Using readily available and cost effective starting materials, my work focuses on the synthesis and characterization of these acenedichalcogenophene species by exploiting benzannulation chemistry in the pursuit of making efficient organic materials.

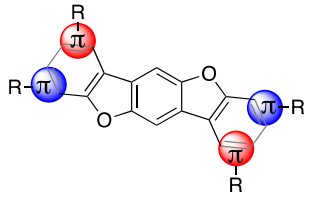

Figure 1. Generic representation of a BDF heteroacene.

CHEMICAL PROBE DEVELOPMENT FOR BPTF READER DOMAINS UTILIZING BIOPHYSICAL ASSAYS

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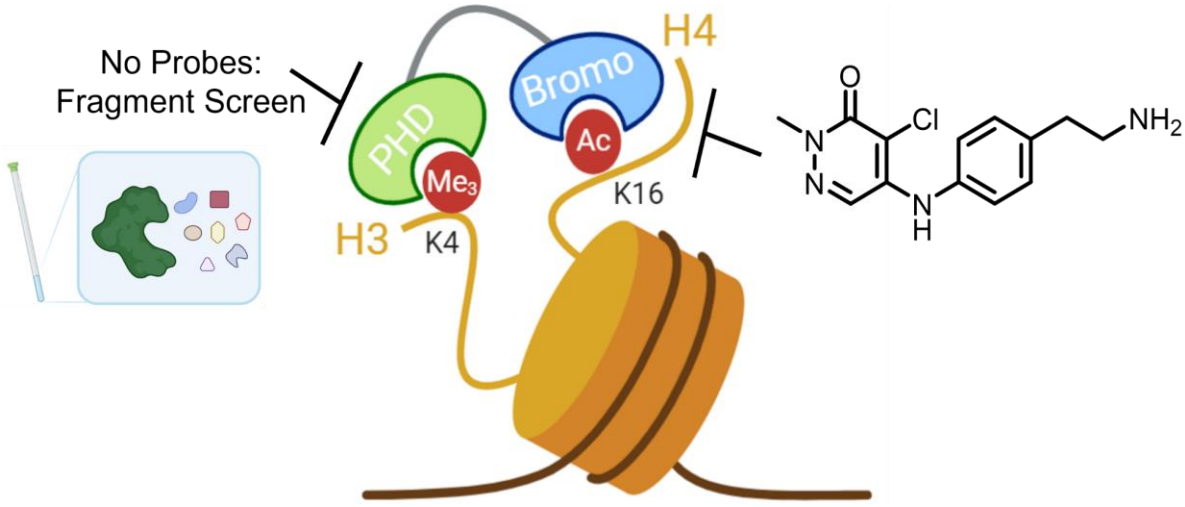
In many disease states there is a dysregulation in gene expression, which can be driven by the aberrant levels or function of epigenetic protein complexes. One such epigenetic protein dysregulated in numerous cancers is the bromodomain and PHD-finger containing transcription factor (BPTF), which binds to chromatin via interactions with acetylated histone through its bromodomain and trimethylated histone through its C-terminal PHD finger to facilitate chromatin remodeling.[1] Although evidence supports the role of the BPTF protein in disease, the relevance of its individual domains is unclear, making the design of selective probes advantageous. Currently, there are several reported BPTF bromodomain inhibitors, but there is a significant need for potency and selectivity gains. A promising new class of BPTF inhibitors based on a pyridazinone scaffold will be discussed. We have utilized Protein-Observed ^{19}F (PrOF) NMR, AlphaScreen, and x-ray crystallography to rationally design and expand the pyridazinone scaffold into a potent lead against the BPTF bromodomain (K_d = 6.3 nM).[2] 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 a NMR-based fragment screening will also briefly be discussed.



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SMALL MOLECULE ALLOSTERIC INHIBITION OF CYTOSOLIC SULFOTRANSFERASES

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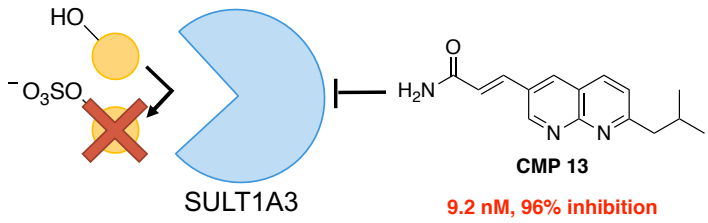
The human cytosolic sulfotransferase (SULT) enzymes are a class of thirteen metabolic enzymes that utilize an adenosine-based co-factor, 3'-phosphoadenosine-5'-phosphosulfate (PAPS) for sulfuryl group (SO_3^-) transfer to drugs, xenobiotics, hormones, and neurotransmitters. SULT activity has been linked to numerous diseases including depression, obesity, neurodegeneration, skin diseases, and cancers. Isoform-specific inhibition of SULTs is challenging due to the high degree of structural homology of the enzyme class, particularly of their active sites. Allosteric regulation, until now, has remained a largely unexplored area of SULT biology. We have developed the first synthetic, isoform specific allosteric inhibitors of SULT1A3, an isoform responsible for the metabolism of neurotransmitters, such as serotonin and dopamine.[1,2] Inhibitor specificities and affinities were validated through enzymatic assays with other cytosolic SULT isoforms. *In vitro* efficacies of lead compounds were confirmed in mammalian cells expressing comparable SULT1A3 levels to those found in neurons.[2] Current work is centered on establishing a preclinical profile of our top SULT1A3 inhibitor in mouse models as a novel treatment for major depression. Additional work is focused toward developing allosteric inhibitors of additional SULT isoforms to demonstrate SULT inhibition as a platform technology for novel small molecule therapeutics.



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V14

Convergent Synthesis of Dihydrobenzofurans Via Urea Ligand-enabled Heteroannulation of 2-Bromophenols with 1,3-Dienes

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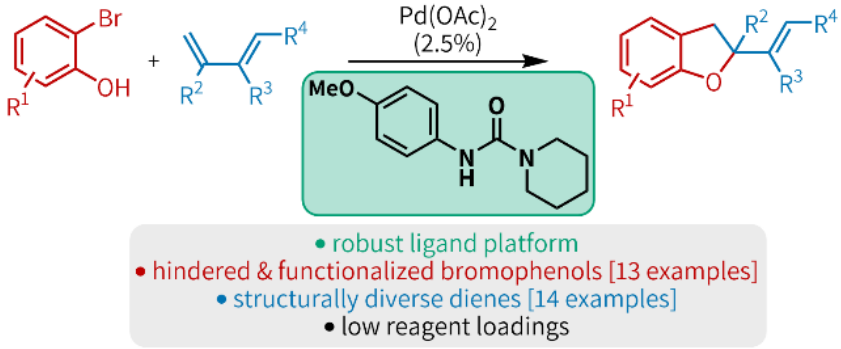
ABSTRACT: We disclose a versatile palladium and urea ligand-mediated heteroannulation of 2-bromophenols and 1,3-dienes. This method addresses practical synthetic challenges present in the palladium-catalyzed heteroannulation of bifunctional reagents and olefins by engaging a diverse scope of coupling partners under a unified set of reaction conditions. Our recently developed urea ligand platform outperforms conventional phosphine ligands to generate the dihydrobenzofuran motif in a convergent manner. Dihydrobenzofuran and other furan derivatives are prevalent core scaffolds in natural products (1) and as therapeutics (2), organic materials (3), and agrochemicals. (4) In contrast to previous transformations, I was able to successfully engage structurally diverse diene classes in our reaction under a single set of reactions conditions. This chemistry can be performed with low reagent loadings and is robust to ambient conditions, making this an attractive approach for the synthesis of these core structures.



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WITHDRAWN

Direct Synthesis and Applications of Solid Silylzinc Reagents

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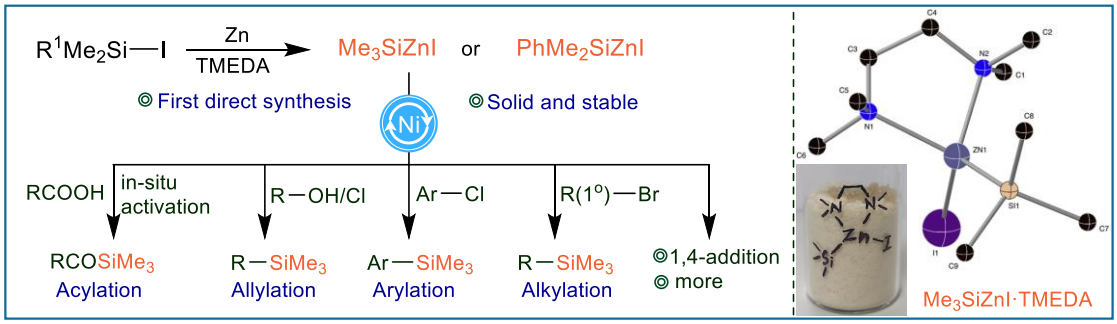
The milder and more practical method for the synthesis of organosilanes are imperative due to its diverse synthetic utility. Silylzinc reagents are typically the most functional group tolerant, and difficult to synthesize because they are obtained by a pyrophoric reaction of silyllithium, particularly Me_3SiLi which is itself prepared by the reaction of MeLi and disilane. Furthermore, the dissolved LiCl in silylzinc may have a detrimental effect. We describe for the first time, the direct synthesis of $PhMe_2SiZnI$ and Me_3SiZnI reagents by employing a coordinating TMEDA ligand. Importantly, they can be obtained as solid and stored for longer period at 4 ^oC. We also demonstrate their significance in cross-coupling of various free alkyl/aryl/alkenyl carboxylic acids with broader functional group tolerance and API derivatives. The general applicability and efficiency of solid Me_3SiZnI are shown in a wide variety of reactions including alkylation, arylation, allylation,1,4-addition, acylation and more.



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DESIGN AND DEVELOPMENT OF *TRYPANOSOMA CRUZI.* BENZOXABOROLE PRODRUGS

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Trypanosoma cruzi is a protozoan parasite that causes American trypanosomiasis, commonly referred to as Chagas disease. This disease induces congestive heart failure and is the leading cause of death among young-to-middle age adults in endemic areas of Latin American countries. Currently, there are neither vaccines nor chemotherapeutic regimens that are effective in preventing and curing *T. cruzi* infection. Compound **AN14667** belongs to the benzoxaborole class of compound that has successfully delivered a clinical treatment candidates for Chagas disease, and it was found to have a potent inhibitory on *T. cruizi* with an intramolecular EC_{50} of 6 μM. By conjugating a chromophore tag to **AN14667** through amidation reaction with a methylenedioxy bridge, we aim to illustrate the activation mechanism of the resultant prodrug candidates that is mediated by the serine carboxypeptidase present in *T. cruzi* parasite. Furthermore, we are exploring the potential role of the methylenedioxy bridge linker for increased permeability and selectivity against *T. cruzi*. These studies will expand our understanding in the inhibition mechanism on *T. cruzi* by the **AN14667** drug and the using of small-molecular fluorescent probe for parasite inhibitory characterization.

GRAM-SCALE SYNTHESIS OF SEQUENCE-SPECIFIC POLYPEPTOIDS

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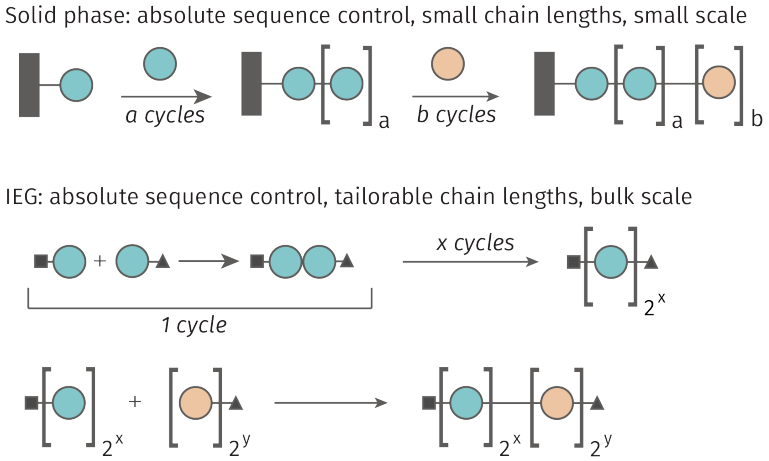
The precise structural organization and presentation of functional domains within sequence-defined biopolymers such as proteins allows for highly selective interactions with various ligands involved in signalling and recognition pathways. Peptoids, a class of peptidomimetic polymers, draw inspiration from these ordered protein scaffolds and can self-assemble into two-dimensional nanosheets with highly tunable surfaces for the display of molecular recognition elements relevant for biosensing. The stepwise solid-phase synthesis of peptoids offers unmatched sequence-control but is limited by the reaction scale (typically 100 milligrams) and attainable chain lengths (typically a maximum of 30 repeat units). Solution phase alternatives can be run on larger scales but sacrifice the sequence-control necessary for the precise ordering of recognition motifs for biosensing. To address the need for bulk samples in materials applications while maintaining sequence-control, we present the use of iterative exponential growth as a scalable method for the sequence-specific synthesis of peptoid polymers with chain lengths greater than the 30 repeat units typically obtained with solid-phase techniques.



ORGANOTRIFLUOROBORATES SUGAR DERIVATIVES: SYNTHESIS OF NEW POTENTIAL RADIOTRACERS FOR PET

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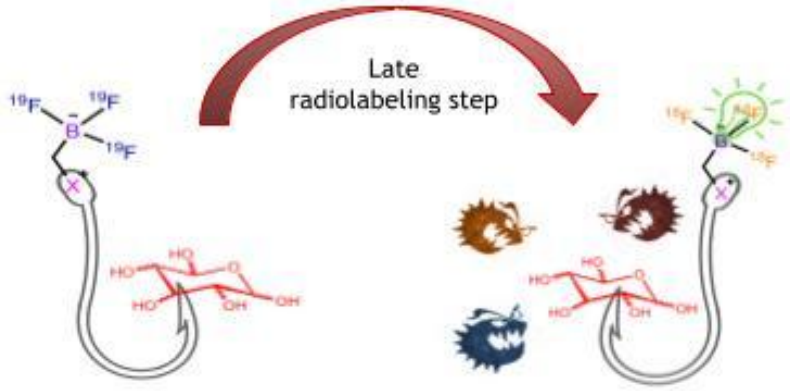
^{18}F is extensively used in Positron Emission Tomography (PET) thanks to its good nuclear properties. But, the poor nucleophilicity of F^- in aqueous media and ^{18}F short half-life results in challenging C-^{18}F bond formation[1]. Using boron instead of carbon could overcome these problems. The B-F couple can afford a rapid ^{18}F-^{19}F isotopic exchange in mild conditions, allowing the cold precursors' labeling at the very end of the synthesis. We aimed to synthesize some organotrifluoroborate sugar derivatives as new potential PET radiotracers. These products contain a carbohydrate moiety for cancer cell targeting and a stable trifluoroborate group (BF_3^-) as a tracer. The BF_3^- group is stabilized toward hydrolysis by an internal salt[2]. The synthesis began with a glycosylation reaction between the sugar and a mono-tosylated spacer, followed by nucleophilic substitution. Then, the heteroatom alkylation with iodomethylboronyl pinacolate and the treatment with potassium hydrogen fluoride yielded the trifluoroborate group. We obtained twelve new organotrifluoroborates sugars in quite good yields. All products showed good solubility in aqueous media and a half-life of up to 120 hours in pH 7.4 phosphate buffer. These molecules can be synthesized in large quantities and labeled when needed, allowing safer and simpler radiosynthesis.



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CATALYTIC RADICAL-POLAR CROSSOVER RITTER REACTION

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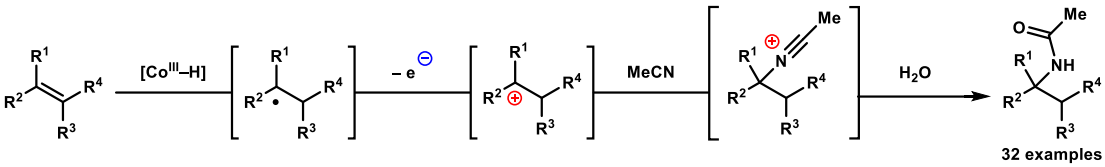
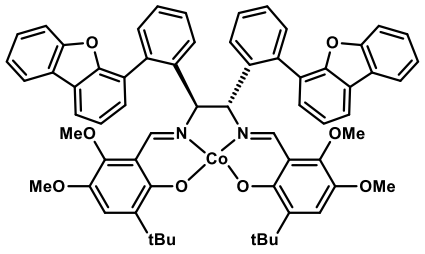
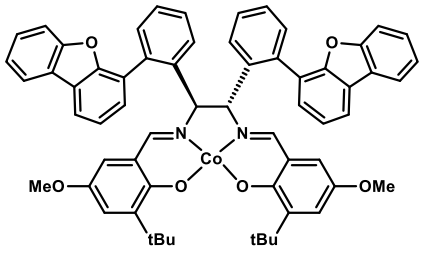
The chemoselectivity of metal hydride-mediated HAT **(**MHAT) processes permits Markovnikov selective radical hydrofunctionalizations of alkenes in the presence of other functionalities. The MHAT radical-polar crossover (RPC) reaction manifold offers identical chemoselectivity in alkene engagement while also permitting polar hydrofunctionalizations reminiscent of Brønsted-acid mediated transformations. Over the past decade, method development with Co(II)-salen catalysts has produced an array of cationic RPC transformations such as hydroalkoxylation, hydroamination, and hydroacylation. While these methods are often efficient and exhibit broad functional-group compatibility, their alkene-substitution tolerance remains largely restricted to mono- and 1,1-disubstituted alkenes. Through catalyst design, our lab has addressed some of these limitations regarding substitution pattern of the reactant alkene. This is shown in our development of a catalytic radical-polar crossover Ritter reaction which is compatible with tri- and tetra-substituted alkenes. We have also demonstrated that these prior limitations in alkene-substitution tolerance can be attributed to unproductive pathways that competitively consume silane and oxidant, including production of hydrogen gas. We have identified that the salen ligand scaffold influences the extent of hydrogen evolution activity which was evaluated by gas chromatography-thermal conductivity detection (GC-TCD).







A MECHANISTIC STUDY OF ARENE C-H AMINATION USING OXYGEN-MEDIATED PHOTOREDOX CATALYSIS

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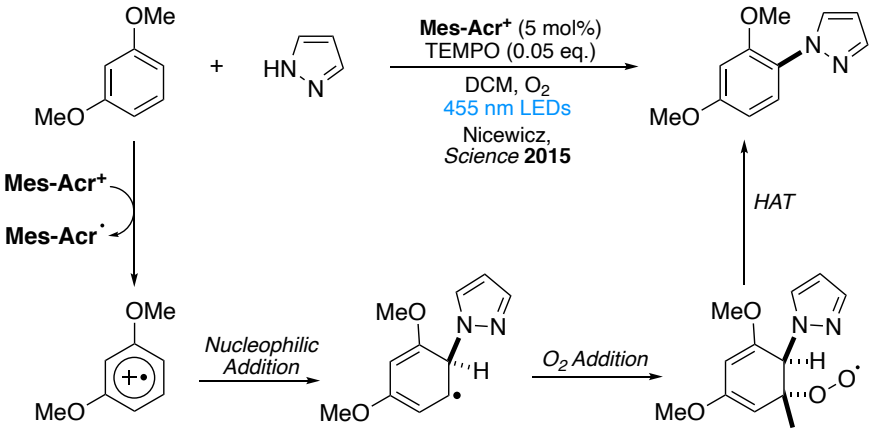
Site-selective C-H amination of aryl compounds reported by the Nicewicz laboratory offers an innovative methodology for aromatic C-H bond functionalization using photoredox catalysis.[1] Given the significant prevalence of aryl C-N bonds in pharmaceuticals, this methodology for direct, selective transformations of aryl C-H bonds offers a chemically benign, synthetically powerful approach to creating these important derivatives. Furthermore, it serves as a more practical alternative to traditional transition metal-catalyzed C-H activation strategies. Due to the rapid pace of reaction discovery in photocatalysis as well as its immense usage in synthetic and pharmaceutical chemistry, there is a significant need for mechanistic characterization of such photocatalytic methodologies. In this presentation, an evaluation into the mechanistic details of photocatalytic C-H arene amination will be discussed. Insight into the overall mechanism as well as its fine mechanistic details, such as the rate-determining step and the role of dioxygen, will be assessed via intramolecular ^{13}C kinetic isotope effects in conjunction with theoretical analysis.



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HYPERCONJUGATIVE INTERACTIONS OF THE CARBON–HALOGEN BOND CONTROL STEREOSELECTIVITY IN GLYCOSYLATION REACTIONS AND CONTRIBUTE TO THE GEOMETRY OF THE PRODUCTS

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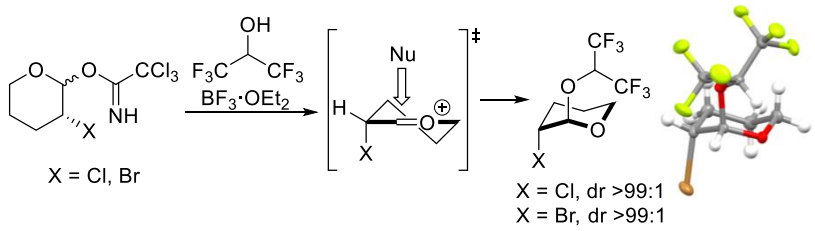
Glycosylation reactions of α-halogenated cyclic acetals are highly diastereoselective in the additions of *C*- and *O*-nucleophiles to both six- and five-membered-rings. An erosion of selectivity is observed as nucleophilicity increases, suggesting that an α-halogen stabilized oxocarbenium ion is the reactive intermediate, not a halonium ion intermediate. Greater selectivity is observed when going down the group of halogens, likely due to the increased electron-donating ability of the carbon–halogen bonding orbital that can more greatly stabilize the oxocarbenium ion intermediate though hyperconjugative interactions ($\sigma_{C–X} \rightarrow \pi^*_{C–O+}$). Analysis of the products of glycosylation by X-ray crystallography reveal changes in bond lengths and angles that correspond to hyperconjugative interactions of the carbon–halogen bond in the ground state. The extent of these interactions that contribute to the diaxial geometry of 1,2-disubstituted α-haloacetals were determined by natural bond orbital (NBO) analysis, and these interactions are largely dependent on the electron-donating and electron-accepting ability of the carbon–halogen bond. In both the transition state and the ground state, hyperconjugative interactions of the carbon–halogen bond appear to be more influential with bromine and chlorine, and less pronounced with fluorine.



DILIBERTI

Total Synthesis of (+)–Eburnamonine via Asymmetric Alkene Cyanoamidation and C–CN Bond Activation

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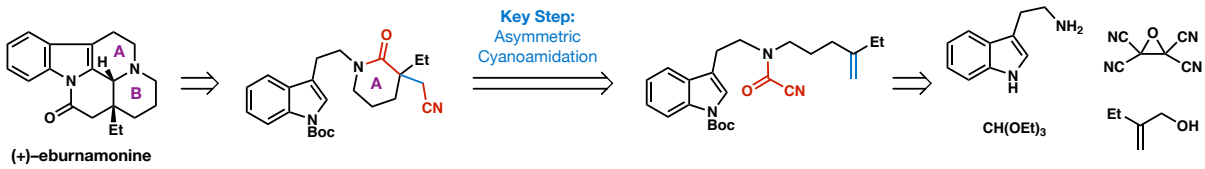
Alkaloid natural products are of great interest to the synthetic community due to their biological properties. Eburnamonine is an indole alkaloid that is part of the *Aspidosperma* family and has been shown to have antitumor activity. The key step to this approach is an asymmetric cyanoamidation of a pendant alkene to form the key A ring with high enantioselectivity. Palladium-catalyzed asymmetric cyanoamidation is a C–C bond activation method that intramolecularly adds a cyanoformamide C–CN across an alkene to form a new lactam ring. To prepare the cyanoformamide, a Johnson Claisen rearrangement and subsequent hydrolysis afforded a carboxylic acid primed for coupling with tryptamine. Reduction of the amide, indole protection, and installation of the cyanoformamide create the cyanoamidation precursor. Subsequently, the B ring was formed via a Bischler-Napieralski reaction followed by a diastereoselective reduction to afford (+)–eburnamonine.



NI/PHOTOREDOX-CATALYZED C(SP^3)−C(SP^3) COUPLING BETWEEN AZIRIDINES AND ACETALS AS ALCOHOL-DERIVED ALKYL RADICAL PRECURSORS

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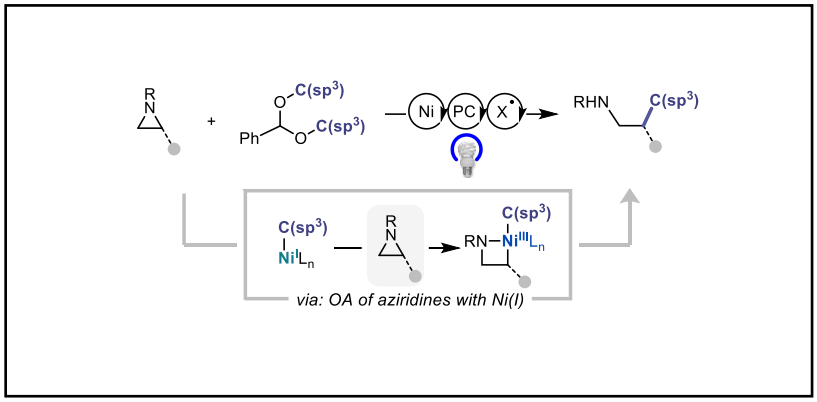
Aziridines are readily available C(sp^3) precursors that give facile access to β-functionalized amines. Although there have been recent developments of transition-metal catalyzed cross-coupling of aziridines with various organometallic reagents, C(sp^3)−C(sp^3) cross-electrophile coupling remains elusive due to the challenges in imparting cross-selectivity between each C(sp^3) component. Herein, we report a Ni/photoredox methodology for C(sp^3)−C(sp^3) coupling between aziridines and methyl/1º/2º alkyl radicals generated via C−H abstraction of alcohol-derived alkyl precursors, benzaldehyde dialkyl acetals. The orthogonal activation mode of each alkyl coupling partner provides the cross-selectivity between the two C(sp^3)−C(sp^3); while a bromide additive serves as hydrogen atom transfer (HAT) reagents to release an alkyl radical from acetals via β-scission, the aziridine is activated at the Ni center, enabling each coupling component to sequentially ligate at different oxidation states of Ni. We demonstrate that an azametallacycle Ni(II) species, conventionally proposed in aziridine cross-coupling, is not an intermediate in the productive pathway. Rather, stoichiometric studies and linear free energy relationships suggest the aziridine activation proceeds via oxidative addition of Ni(I), a previously unexplored elementary step.



COMPUTER ASSISTED RATIONALIZATION OF HIGH THROUGHPUT CATALYSIS: ADDING DEPTH TO THE DATA BY USING KINETIC INFORMATION

Rama El-khawaldeh[1], Bowen Wang [1], Connor Bourgonje [1] and Juan Scaiano*[1]

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Catalyst discovery is an inherently unpredictable and laborious process that relies on serendipitous discoveries, granting it the bottleneck for chemical innovation.[1] Fortunately, machine learning (ML) algorithms can accelerate the process of catalyst discovery by quickly exploring the space of chemical reactions and finding the optimal value with only a few iterations.[2] The pre-requisite of ML is the presence of a consistent, diverse, and unbiased dataset.[3] To satisfy these requirements, the use of high-throughput experimentation (HTE) becomes essential as they can execute an array of reactions under identical conditions. Despite the high-throughput catalysis synthesis, low-throughput data analysis remains a lingering problem in material science. Herein, we describe a novel framework that incorporates high-throughput catalysis kinetic data with a machine learning algorithm and visualization tools to discover new materials. We deployed a real-time high-throughput (HT) fluorescence assay, in which a nitro moiety is reduced to an amine fluorophore, that serves as a reporter for simultaneous absorbance and fluorescence detection. Unlike conventional HT methods that rely on endpoint analysis, the proposed fluorogenic HT system offers a method for monitoring reaction profiles and opens an avenue for mechanistic investigation (intermediate detection). A library of 105 materials was screened under identical conditions. After developing a system with data-rich experimental capabilities, a ML algorithm was utilized to process catalytic kinetic data faster than it can be performed manually. Visualization tool, graph theory,[4] was used to represent multivariate catalyst big data (kinetic information and catalyst properties) with networks that reveal complex relationships among the datasets. This led to the discovery of new and greener catalyst compositions for reduction reactions with low price, low toxicity, and high natural abundance properties. This work marks a step towards the machine-learning-assisted discovery of reductive catalysts and demonstrates the importance of visualization tools in data interpretation.

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V26

[2]-Ladderane Building Blocks as *Meta*-Substituted Aromatic Ring Isosteres and Rigidified Cyclohexanes

Rachel Epplin,[1] Shashwati Paul,[1] Loic Herter,[2] Christophe Salome, [2] Erin Hancock,[1] Jay F. Larrow,[3] Erich W. Baum,[3] David Dunstan,[3] Thomas Fessard,[2] and M. Kevin Brown*[1]

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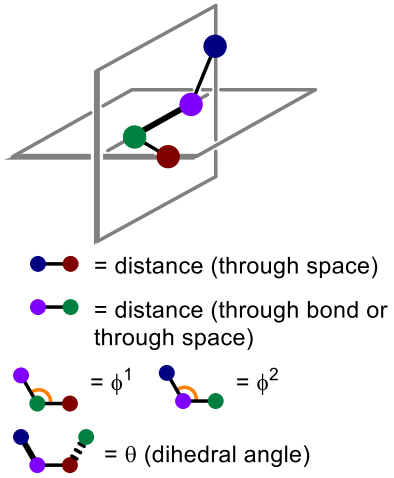
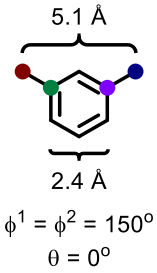
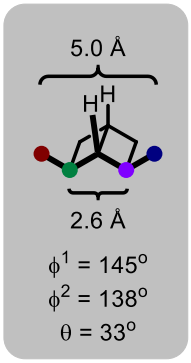
Medicinal chemists use isosteres in the form of atoms or functional groups to manipulate the physicochemical properties or metabolism of a drug lead. While there have been numerous examples of *para*-substituted aromatic ring isosteres, those for the *meta*-substitution are rare. Due to our group's interest in ladderane-containing natural product synthesis, we present a straightforward synthesis of bicyclo[2.2.0]hexane ([2]-ladderane) building blocks and representative derivatizations. Preliminary studies show that the [2]-ladderanes present similar pharmacokinetic properties as their aryl counterparts. We also show that this motif could be used as a potential rigidified cyclohexane.







- New class of isostere
- Novel IP
- New class of building block for med chem

PHOTOREDOX-CATALYZED ISOTOPIC LABELING OF COMPLEX PHARMACEUTICALS

Olivia L. Garry[†], Haifeng Yang[‡], Sumei Ren[‡], Neil Strotman[‡] and David W. C. MacMillan[†,*]

[†]Merck Center for Catalysis at Princeton University, Princeton, NJ 08544, USA.
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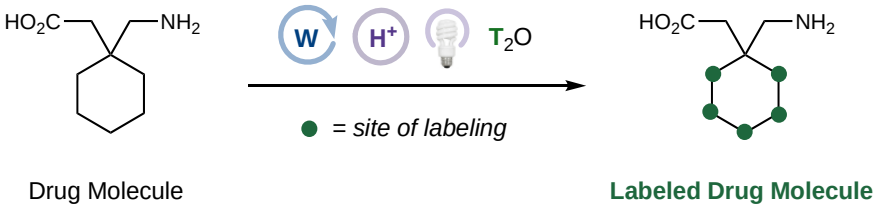
Isotopically labeled compound are critical in drug development for understanding the fate of a potential drug candidate in biological systems. Herein, we describe a novel one-step protocol for the labeling of complex pharmaceutical molecules which proceeds under mild conditions, has high functional group tolerance and greatly expands the scope of currently targetable sites for isotopic labeling.



IMPACT OF A REMOTE STEREOCENTER ON THE DYNAMIC KINETIC ASYMMETRIC ALLENIC PAUSON–KHAND REACTION

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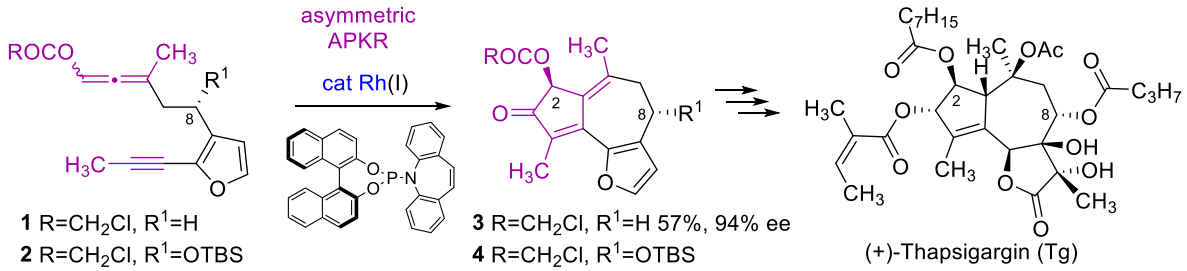
Thapsigargin (Tg) is a member of the guaianolide sesquiterpene family isolated from the Mediterranean plant *Thapsia garganica* in 1978. Tg is a highly selective and potent inhibitor of SERCA and recently shown to inhibit major human respiratory viruses including OC43, RSV and SARS-CoV-2. The Brummond group has designed an asymmetric allenic Pauson–Khand (APKR) approach to synthesize Tg and analogs starting from 3-furaldehyde. Building on our previous results showing that **1** affords **3** with high enantioselectivity, we are investigating the impact of the remote stereocenter at C8 of **2** on this stereoconvergent APKR.[1] I will report on our experimental findings and APKR mechanistic insight gained from this double stereodifferentiating reaction.



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AMINO-FUNCTIONALIZED EXTENDED NUCLEOBASES FOR TRIPLE HELIX FORMATION AND RECOGNITION OF THE A-U AND U-A BASE PAIRS IN DOUBLE-HELICAL RNA

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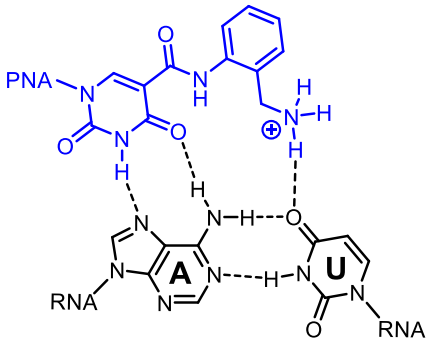
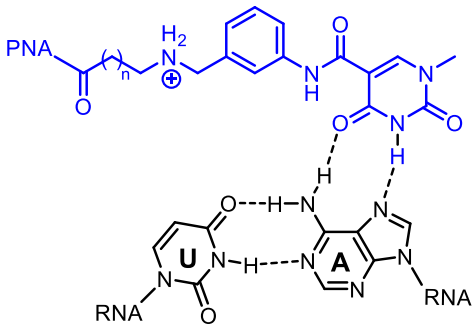
While non-coding RNAs serve various biological roles as enzymes, gene regulators, and post-transcriptional modifiers, undiscovered functions likely remain. To better understand non-coding RNA, we design triplex-forming peptide nucleic acids (PNAs) with modified nucleobases that bind sequence-specifically to double-helical, non-coding RNA. PNA contains a neutral amide backbone that has favorable binding to negatively charged double-helical RNA. Our modified nucleobases subsequently allow for sequence-specific molecular recognition of RNA.

Here we report two extended nucleobases derived from isoorotic acid containing cationic amino groups. The first extended nucleobase contains an amino group proposed to exhibit favorable hydrogen bonding to the outer face of the A-U base pair while also imparting cationic character on the PNA for increased binding affinity. The final product of a six-step synthesis was incorporated into a PNA strand and preliminary binding studies demonstrate excellent binding to the A-U base pair. The second nucleobase is designed to recognize the U-A base pair inversion, by reversing the attachment point of PNA to the monomer. Current studies involve improving pyrimidine recognition for sequence-selective recognition of any RNA double helix.

A-U Recognition



U-A Recognition



NICKEL-CATALYZED DOMINO CROSS-ELECTROPHILE COUPLING DICARBOFUNCTIONALIZATION REACTION FOR THE SYNTHESIS OF VINYLCYCLOPROPANES WITH A TETRASUBSTITUTED ALKENE

Nadia Hirbawi,[†] Kirsten A. Hewitt,[†] Pei-Pei Xie,[‡] Taylor A. Thane,[†] Shuo-Qing Zhang,[‡] Alissa C. Matus,[†] Erika L. Lucas,[†] Xin Hong,[‡]* Elizabeth R. Jarvo[†]*

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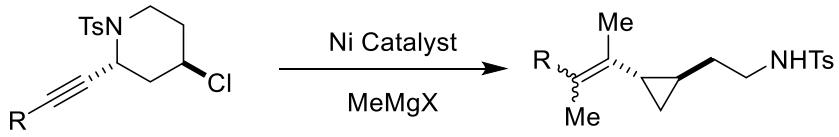
Prior work in the Jarvo lab has established that nickel catalysis can enable the activation of unstrained and neutral C–N bonds towards cross-electrophile coupling. This includes a method for the cross-electrophile coupling of 4-chloro-*N*-tosylpiperidines to form cyclopropanes.[1] Expansion of this reaction led to the development of a nickel-catalyzed domino cross-electrophile coupling dicarbofunctionalization reaction of alkynyl substituted *N*-tosylpiperidines to form vinylcyclopropanes with a tetrasubstituted alkene.[2] This method is a rare example of a domino reaction that involves a cross-electrophile coupling as a discrete step. Work discussed will include: the expansion of the scope of the reaction, a cross-over experiment, and the derivatization of the domino reaction products.



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CLICKABLE GIBBERELLIC ACID DERIVATIVE AND EARLY RECRUDESCENCE PHENOTYPE FROM ARTEMISININ-INDUCED DORMANCY

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Artemisinin (ART) is known to induce dormancy in the ring stage parasite, during which parasite growth is arrested, with growth resuming 7-10 days after drug exposure. ART induced dormancy is a stress response that allows parasites to withstand the cytotoxic effects of the drug. Recently, Gibberellic Acid (GA) exposure was found to promote early recrudescence from artemisinin induced dormancy 48 hours earlier than non-GA-treated dormant parasites. A limited structure-activity relationship study led to the identification GA derivatives that activated the dormant parasites and resulted in faster recovery from dormancy as compared to the control. Importantly, selected GA derivatives contain a functional group that is amenable to click chemistry reactions. Herein, we discuss the use of two clickable GA derivatives to (1) localize GA within *Plasmodium falciparum* and (2) to develop click chemistry mediated pull down methods in order to identify the interacting proteins, with the goal to perform mass spectrometry to eventually identify GA interacting partners. Furthermore, we attempt to expand the repertoire of click chemistry reactions by optimizing and using the sulfo-click reaction, an amination reaction between thioacids and sulfonyl azides. These studies will broaden our scope of understanding of the dormancy mechanism of *Plasmodium* and will elucidate the potential mechanism(s) for phytohormones modulating recovery from dormancy.

JANOSKO

Rapamycin-based optical on- and off-switches of protein function

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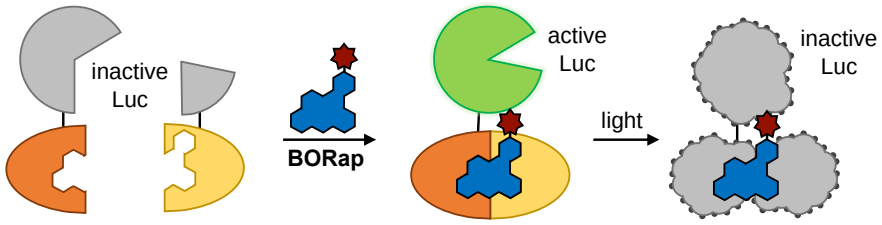
Rapamycin and its various analogs have been used extensively to induce dimerization of FKBP and FRB domains, as well as proteins fused to them. This has been used to control a wide range of biological processes, including activation of split-proteins, intracellular protein translocation, and protein stabilization. Small molecule induced dimerization of proteins, while an important tool in chemical biology, has previously been limited in its irreversible behavior. Gaining the ability to turn the FKBP-rapamycin-FRB ternary complex back off is significant to the study of the reversible nature of biological processes. In this work, two methods were developed toward this goal – photoswitchable rapamycin analogs were synthesized with the aim of inducing and breaking the ternary complex in response to a configurational change,[1] while ROS-generating rapamycin analogs were synthesized to oxidize and deactivate the ternary complex with singlet oxygen upon irradiation.[2] Though photoswitching did not provide the necessary structural changes required to break a rapamycin-induced ternary complex, we showed targeted protein oxidation via optically triggered singlet oxygen generation can be used as an off-switch for rapamycin-induced protein interactions.



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V33

MEXICAN CHEMICALS

Gabriel Jiménez Zerón

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As a university professor, I want to pay tribute to the Mexican scientists who have excelled in the study of chemistry, showing my students that there is a place for them in the study of science.

In addition, Esther Luque, the first certified Mexican chemist, is originally from the state of Hidalgo, where our university is located.

Download: https://drive.google.com/file/d/1vNsmHsaPd0QZdWf6dJlXcc8hmb2UKEDe/view?usp=sharing

[1] https://conecta.tec.mx/es/noticias/nacional/investigacion/25-mujeres-mexicanas-que-dedican-su-vida-la-ciencia-y-la-tecnologia

REDOX-SWITCHABLE POLYMERIZATION BY CHAIN TRANSFER

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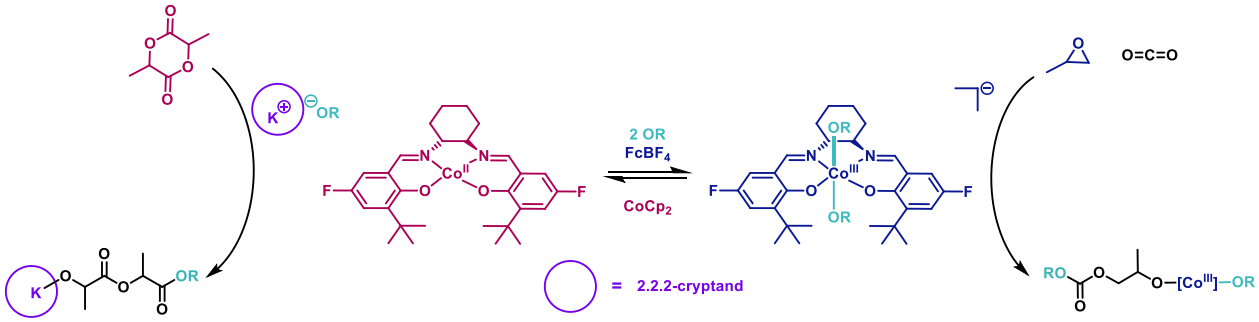
Switchable polymerizations typically make use of a single active catalyst that exhibits orthogonal reactivity upon application of an external stimulus. Herein, we report a new type of switchable polymerization in which a chain transfer agent moves the growing polymer chain between two separate catalysts, facilitating switchable copolymerization of lactide, propylene oxide (PO), and CO_2. The system consists of a potassium 2.2.2-cryptand alkoxide that performs lactide ring-opening polymerization and a cobalt(III) salen catalyst that performs alternating ring-opening copolymerization of PO and CO_2. Liberation or capture of the propagating alkoxide chain end enables switching between the two polymerizations. When the catalyst system is in the reduced state, it is inactive for PO-CO_2 copolymerization and active for lactide polymerization. Oxidation of the system results in coordination of two alkoxide chain ends to the cobalt salen complex, forming a six-coordinate cobalt(III) salen bisalkoide complex that is active for PO-CO_2 copolymerization but not lactide polymerization. Subsequent changes to the oxidation state allows synthesis of di- or triblock copolymers. When a mixture of cobalt(II) and cobalt(III) oxidation states is present, simultaneous copolymerization of lactide, PO, and CO_2 produces statistical copoly(ester-carbonates).This reactivity results in the synthesis of copolymers whose microstructures could be controlled by catalyst oxidation state.



COBALT-CATALYZED ASYMMETRIC RING-OPENING OF UNSTRAINED HETEROCYCLIC ALKENES

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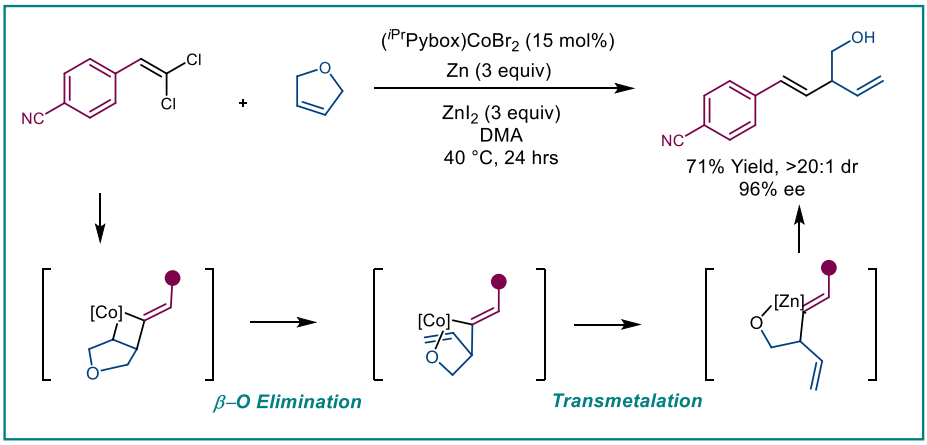
Ring strain is the driving force for numerous ring-opening reactions of 3- and 4-membered heterocycles.[1] By comparison, 5-membered heterocycles lack this thermodynamic driving force. As a result, only a few methods exist for the ring-opening of unactivated 5-membered heterocycles using transition metal catalysts.[2,3] Additionally, reductive strategies for such ring opening reactions remain underexplored. We report an asymmetric ring-opening of 2,5-dihydrofurans and *N*-protected 3-pyrrolines with aryl dichloroalkenes utilizing an earth-abundant cobalt catalyst. We propose that the dichloroalkenes form reactive vinylidene intermediates with the chiral ($^{i\text{Pr}}$Pybox)$CoBr_2$ catalyst, followed by a [2+2] cycloaddition with the heterocyclic alkene. This complex could potentially undergo a β-H elimination, form cyclopropanes via a direct reductive elimination, or undergo the desired β-O/β-N elimination. We optimized our catalytic system to overcome these challenges and selectively perform the β-O/β-N elimination. The resulting 5-membered metallacycle can transmetallate with Zn and subsequently give rise to homoallylic alcohols or amines, upon quenching, with high diasteroselectivity and enantioselectivity.



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2. *Tetrahedron.,* **1995** , *51,* 4383
3. *ACS Catal*, **2020,** *10***,** 2958

Unsaturated β,β-Disubstituted Carbonyl Synthesis Via Negishi Reaction

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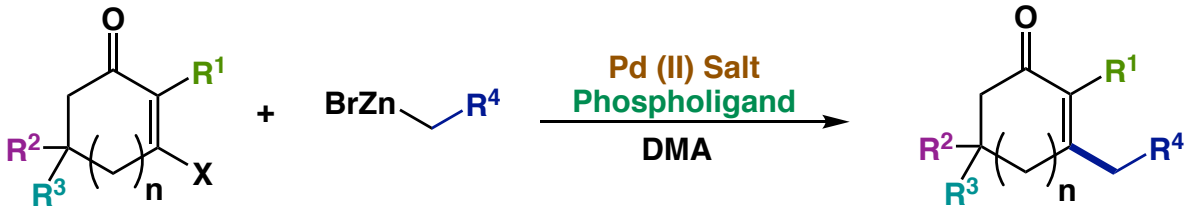
Unsaturated β,β-disubstituted carbonyls serve an integral role in synthetic chemistry as important substrates for direct addition[1], conjugate addition[2], and cycloadditions. Reactions involving these substrates have the potential to generate functionalized β-quaternary carbonyls and other desirable structures that are useful in complex molecule synthesis. Among cross-couplings, Negishi reactions leverage highly chemoselective organozinc nucleophiles. The mild reactivity and ready accessibility of alkyl organozincs facilitated the use of these reagents with β-haloenones in a Csp2 -Csp3 cross-coupling to synthesize β,β-unsaturated disubstituted carbonyls. We observed that various Pd(II) precatalysts with dialkylbiarylphosphine ligands promote an efficient coupling reaction with catalyst loadings at or below 2 mol% and reaction times generally less than 1 hour. Various functional groups are well tolerated, including cyclohexenone, cyclopentenone, lactone, and etc. providing over 25 reactions products in 55 to 95% yields.



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OPTIMIZING SMALL MOLECULE INHIBITORS FOR CHAGAS DISEASE

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Chagas disease is a neglected tropical disease caused by the kinetoplastid parasite *Trypanosoma cruzi* which infects an estimated 6-7 million people worldwide, and causes a loss of over 800,000 disability-adjusted life years. Current treatments are limited due to severe side effects and low efficacy; there is a lack of financial incentive for drug discovery efforts due to there being little potential to recoup research costs for the profit driven pharmaceutical industry. Hence, the responsibility for developing new therapies shifts to the academic sector.

This project focuses on optimizing small molecules for improved potency against the parasite, mammalian cell selectivity, and drug-like properties. These compounds originated from a high-throughput screen (HTS) conducted in collaboration with GlaxoSmithKline against another kinetoplastid parasite, *T. brucei*, which causes human African trypanosomiasis. Analogs of one of the HTS hits, a substituted purine (NEU-1106), were designed and synthesized, and their structure-activity relationships will be reported. The compounds described have increased potency and selectivity, with work to improve their drug-like properties is needed.

Synthesis of pyrrolopiperazinone scaffold using novel routes: Application to the total synthesis of bromopyrrole alkaloids

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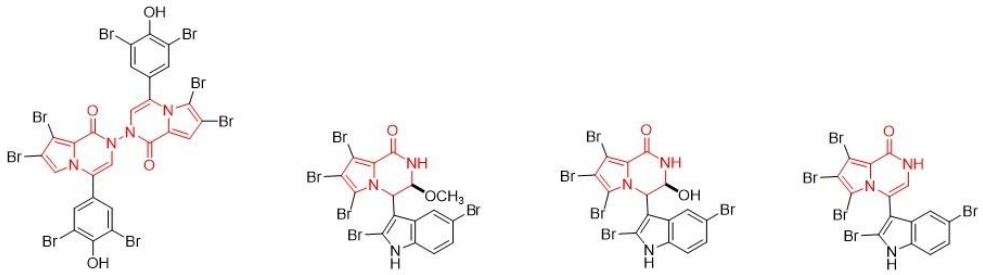
Pyrrolopiperazinone scaffold is one of the salient features of bromopyrrole alkaloids possessing various biological activities, including cytotoxic, antibiotic, antitumor, and growth inhibitory activities against various cell lines. Due to their potential applications as pharmaceuticals, synthesizing this scaffold has become an attractive research focus. Bromopyrrole alkaloids isolated from Patagonian Bryozoan *Aspidostoma giganteum* contain phenyl and indole analogues of pyrrolopiperazinone scaffold. Aspidazide A is a unique asymmetric acyl azide containing N-N linkage of two different phenylpyrrolopiperazinones. Aspidostomides D, E, and F contain indolopyrrolopiperazinone in their core structure. The challenging synthesis of these natural products is still unaddressed. This work describes a novel and concise route to synthesize these scaffolds and their derivatives using mild reagents. Both the phenyl as well as indole versions can be accessed using similar routes. α-amino nitriles are used as the starting materials, which can be easily synthesized via well known Strecker synthesis from commercially available aldehydes. The final key cyclization is accessed via Bischler-Napieralski type reaction. The construction of N-N linkage is acheived via electrochemical oxidation.

Figure 1. Bromopyrrole alkaloids containing pyrrolopiperazinone scaffold



SYNTHESIS OF BENT-SHAPED Π-EXTENDED THIENOACENES FROM 2,5-DISTANNYLATED 3,4-DIALKYNETHIOPHENE

Abhijeet R.Agrawal[a], Neha Rani Kumar[b], Aditya Choudhury[a] and Sanjio S. Zade[a]*

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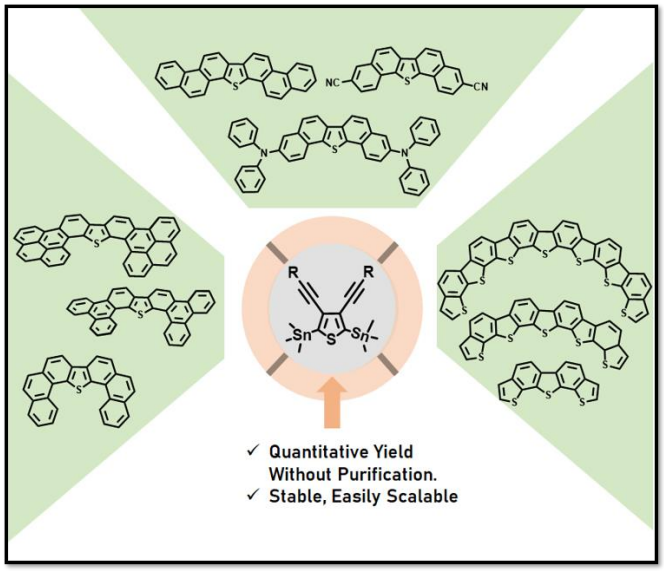
Bent-shaped thienoacenes show promise as next-generation organic semiconductors. Here we present the synthesis of an air-stable, pure and easily scalable thiophene precursor, 2,5-distannylated-3,4-dialkyne thiophene, starting from 3,4-dialkyne thiophene in quantitative yields. This precursor has been used for the synthesis of a versatile class of *syn*-thienoacenes comprising up to 13 fused rings, helical acenes and donor–acceptor acenes.



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CONTINUOUS PLATFORMS AND TECHNOLOGY FOR PROCESS DEVELOPMENT AND MANUFACTURING AT SNAPDRAGON CHEMISTRY

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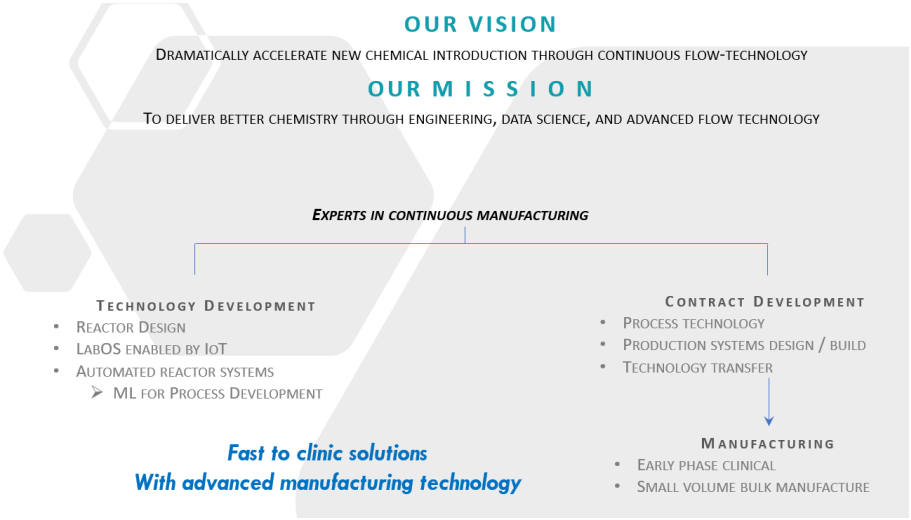
Snapdragon Chemistry, a process development and manufacturing company, specializes in finding innovative solutions to chemical challenges in the pharmaceutical and materials industries. Using advanced technologies, engineering techniques, and data-rich reaction optimization, we have been able to develop scalable synthetic processes for project goals ranging from experimental validation to GMP manufacturing. Expertise across a broad range of chemical disciplines – including flow chemistry, photochemistry, electrochemistry, crystallizations, catalysis, and polymer chemistry – allows for our technologies to be applied to numerous processes and unit operations. These technologies will be highlighted along with case studies demonstrating the employment of these systems. Through these tools, Snapdragon Chemistry can provide fast to clinic solutions to clients.



THEORETICAL STUDY OF THE DIELS-ALDER REACTIONS OF ALLENYLBORONIC ACID PINACOL ESTER AND RELATED DIENOPHILES

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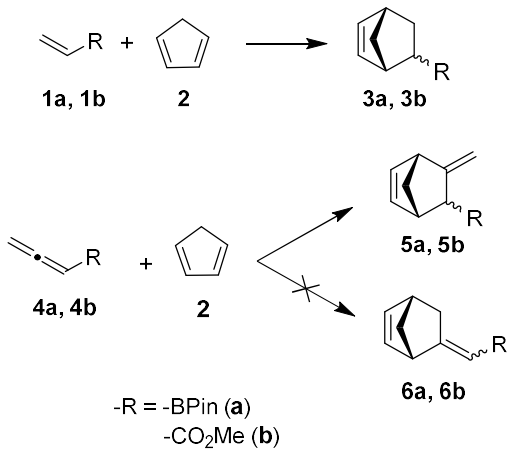
The high atom efficiency as well as the interesting mechanistic and stereochemical features render the Diels-Alder (DA) reaction one of the most useful ring-forming reactions in organic synthesis. Unsaturated organoboron compounds are attractive DA substrates due to their wide availability and high reactivity, selectivity and versatility for subsequent functional group transformations. The DA reactions of vinylboron dienophiles have been studied extensively by our group and we have recently developed the reaction of an allenylboron compound.[1]

In this work, we present the results of a comparative DFT study of the DA reactions of vinylboronic acid pinacol ester (**1a**), methyl acrylate (**1b**), allenylboronic acid pinacol ester (**4a**) and methyl 2,3-butadienoate (**4b**) with cyclopentadiene (**2**). In particular, the distortion/interaction model was used to gain insight into the reactivity and selectivity patterns observed experimentally. The higher reactivity of the carboxylic ester relative to the boron analogue originates from stronger interaction energies for the former. On the other hand, the higher reactivity of the vinyl dienophiles can be explained by the higher distortion energy involved in the DA reactions of allenyl compounds.



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V42

AN OVERVIEW OF PERFORMANCE MONOMERS R&D AT DOW

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Acrylates and other specialty monomers serve as important precursors towards various market segments such as paints, coatings, construction chemicals, home & personal care, adhesives, and oil & gas applications.

Performance Monomers R&D has a broad research portfolio that relies on process & discovery chemistry skills to provide plant support, to design new monomers, and to develop new technologies. Chemists work as part of an interdisciplinary team and use their chemistry knowledge to solve challenging problems with high financial value to the business while addressing global sustainability issues on a large-scale.

This poster will provide a high-level overview of our R&D group, capabilities, and a snapshot into what chemical research looks like from a Dow perspective through case study examples.

ELECTROCHEMICAL MODIFICATIONS OF TRICLOSAN

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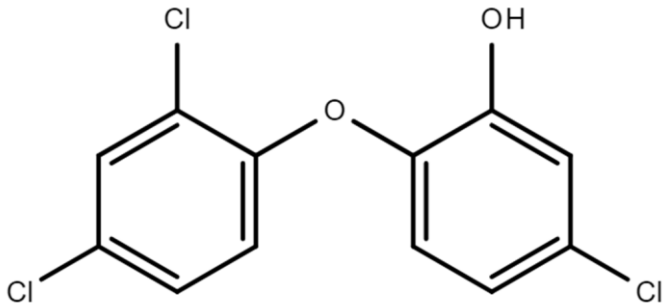
Phenolic compounds are generally known for their benefits toward human health. Triclosan (5-chloro-2-(2,4-dichlorophenoxy) phenol) plays a role as an antibacterial agent and is often found in personal care products such as toothpaste, disinfecting products, and cosmetics amongst others.[1] However, despite the named health benefits, several concerns have arisen due to the compound's potential environmental toxicity, as a result of its transportation to wastewater treatment plants from consumer products.[1-2] Thus, implementing methods for removal of triclosan from such pathways is important for maintaining environmental health. Previously, a variety of methods including adsorption, photolysis, and biodegradation processes have been studied, with the aim of removing the wastewater contaminant. However, these techniques require highly trained technicians and extensive sample preparation periods. Herein, we utilize electrochemical methods for selective electrochemical oxidation/reduction of triclosan toward dichlorination and oxidation products.[3] The electrochemical reactions were monitored by UV-Vis spectroscopy and GC-MS. Electrochemical oxidation of triclosan was also compared to the traditional chemical oxidation, and data suggest that the electrochemical process is faster. Hence, electrosynthesis provides an alternative way of bond breaking and bond making.



Triclosan

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ACRIDINE RADICAL CATALYZED KETONE-OLEFIN COUPLING

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Ketone-olefin coupling reactions are common methods for the formation of carbon-carbon bonds. This reaction class typically requires stoichiometric or super stoichiometric quantities of metal reductants, and catalytic variations are limited in application. Photoredox catalysis has offered an alternative method towards ketone-olefin coupling reactions, although most methods are limited in scope to easily reducible aromatic carbonyl compounds. We describe a mild, metal-free ketone-olefin coupling reaction using an excited state acridine radical super reductant as a photoredox catalyst. We demonstrate both intra and intermolecular ketone-olefin couplings of aliphatic and aromatic ketones and aldehydes.

TUNING REACTION SELECTIVITY DURING CARBON-CARBON BOND FORMATION OF SUBSTITUTED PHENOLS

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The electrochemical synthesis offers advantageous over traditional organic synthesis. The reactivity of reagents can be selectively tuned by using various electrode materials, electrolytes, and applied potentials. The irreversible electrooxidation of phenol is a viable route towards new phenol-based products. Often oxidation of phenol and formation of quinones takes place, however, other reactivities such as carbon-carbon bond formation are also possible. We have previously reported on the selective carbon-carbon dimerization of bulky phenols via electrochemical synthesis (1). The electrooxidation was further explored towards dimerization of substituted phenols with extended conjugation. The formation of dimer was highly dependent on the electrode materials, and potential used. The electrooxidation was compared to chemical oxidation. The products formed were characterized by UV-Vis spectroscopy, NMR, GC-MS and X-ray diffraction. Current efforts in expanding the electrocatalysis to include diverse phenolics will also be described.

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Semi-synthesis of CoQ_{10} probes to investigate protein binding interactions

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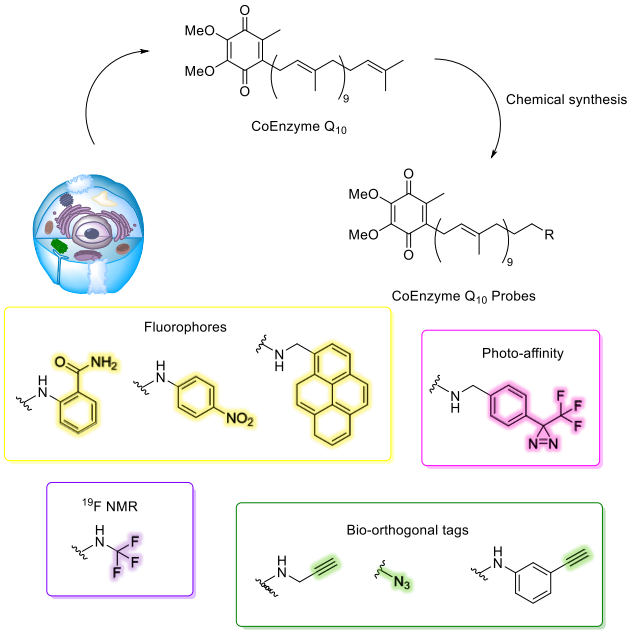
Ubiquinone or Coenzyme Q_{10} (CoQ_{10}) is a redox active isoprenoid molecule necessary to human electron mitochondrial energy production.[1] CoQ_{10} is present in almost every cell in our body and is thought to have crucial roles in many diseases and aging.[2] CoQ_{10}-derived probes could be applied to a number of biological experiments that could give insight into CoQ_{10} interactions with binding proteins and CoQ_{10} processing enzymes. A semi-synthesis strategy to achieve this library of ubiquinone probes is hence extremely valuable. Herein we report the successful synthesis of ubiquinone probes, achieved utilising ω-modification chemistry. These probes have a wide range of applications; from ^{19}F NMR studies to click chemistry. We have also synthesised a portion of a known CoQ_{10} binding protein and work is currently ongoing to establish a viable FRET assay, and ^{19}F NMR studies to demonstrate the viability and wide applications of CoQ_{10} probes.



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DESIGN AND SYNTHESIS OF GUAIANOLIDE ANALOGS

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Structure activity relationship (SAR) information for sesquiterpene lactones (SLs) are largely absent from drug discovery due to the toxicity concerns stemming from the highly reactive α-methylene-γ-butyrolactone moiety. Guaianolides are a subclass of SLs possessing rich biological activity, such as antiviral, antibacterial, and antitumor. We have designed a convergent synthesis featuring the Crabbé homologation, a borylation, and an allenic Pauson–Khand reaction (APKR) to access the guaianolide analogs in which the α-methylene-γ-butyrolactone is replaced with an α-methylene-γ-lactam as γ-lactams are a privileged scaffold. Varying substituents on the lactam nitrogen distal from the α-methylene modulates the thiol reactivity of the α-methylenyl group affording natural product analogs with reduced toxicity, while maintaining biological activity. Late-stage functionalization of the guaianolide analogs and its effect on thiol reactivity and bioactivity will be studied to determine SAR data.

Cetylpyridinium Trichlorostannate: Synthesis, Antimicrobial Properties, and Controlled-Release Properties via Electrical Resistance Tomography

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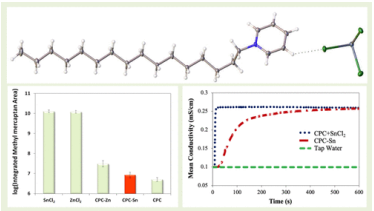
Cetylpyridinium trichlorostannate (CPC-Sn), comprising cetylpyridinium chloride (CPC) and stannous chloride, was synthesized and characterized via single crystal X-ray diffraction (SC-XRD) measurements indicating a stoichiometry of $C_{21}H_{38}NSnCl_3$ where the molecules are arranged in a 1:1 ratio with a cetylpyridinium cation and a $[SnCl_3]^-$ anion. CPC-Sn has shown potential for application as a broad-spectrum antimicrobial agent, to reduce bacteria-generated volatile sulfur compounds (VSCs) and to produce advanced functional materials. In order to investigate its controlled-release properties, Electrical Resistance Tomography (ERT) was implemented. The results demonstrate that CPC-Sn exhibits extended-release properties in an aqueous environment as opposed to the CPC counterpart.



ALPHA METHYL PROLINATE SALT AS AN EFFECTIVE CATALYST FOR THE ANTI-SELECTIVE MANNICH REACTION

Madison Neukirch, Anuradha Dagar, Mathew Vetticatt*

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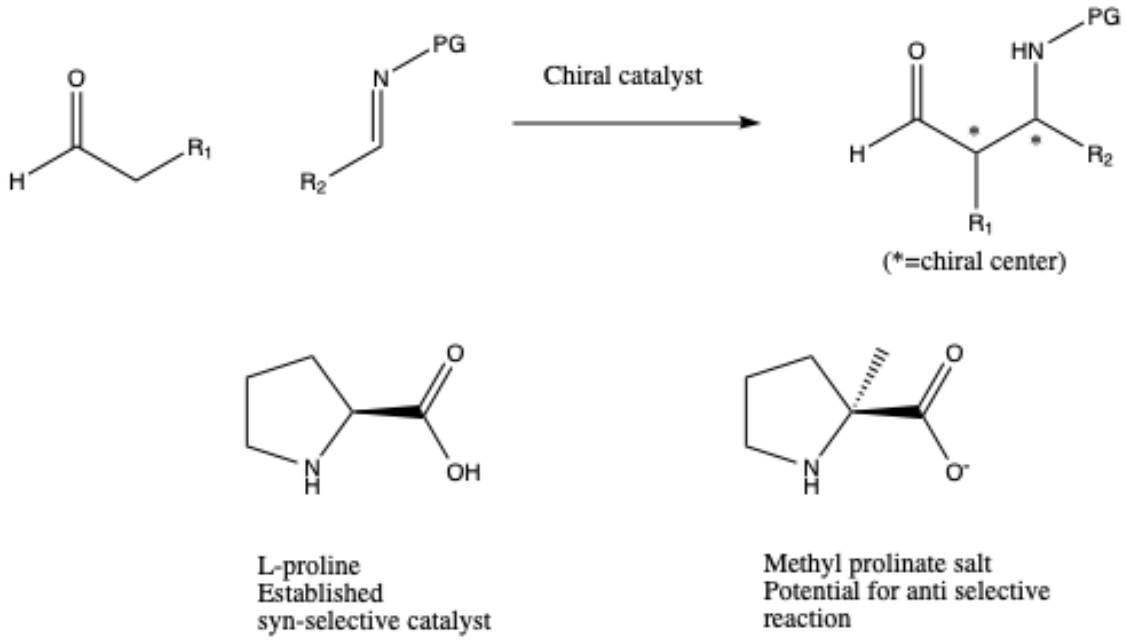
The Mannich reaction is a well-known example of an asymmetric organocatalyzed C-C bond forming reaction with the potential to create two chiral centers. Forming the anti-diastereomer of a Mannich base with high enantioselectivity has been done in the past with secondary amine catalysts that are formed via multiple step syntheses; However, syn selective reactions are much more accessible when considering readily available or easily synthesized chiral catalysts. A study on L-proline derived catalysts shows that an alpha-methyl L-prolinate salt is a catalyst closely related to L-proline that may catalyze the Mannich reaction in an anti-selective, enantioselective manner with acceptable yield. Methyl prolinate may act in this manner with a wide range of Mannich donors and is active in a wide range of solvents. A methyl prolinate salt offers a potential alternative to other chiral catalysts with the same convenience as L-proline, but with opposite diastereoselectivity.



Copper-Catalyzed Three-Component Carboamination of Electron-Deficient Olefins

Andrei G. Popov[‡], Aja M. Nicely[‡], Hannah C. Wendlandt[‡], Grace L. Trammel, Daniel Kohler, Kami L. Hull*

[‡]A.G.P., A.M.N., and H.C.W. contributed equally.

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Grace L. Trammel -*Department of Chemistry, University of Illinois at Urbana–Champaign, 600 South Mathews Avenue, Urbana, Illinois 61801, United States email: gneathe@iu.edu*
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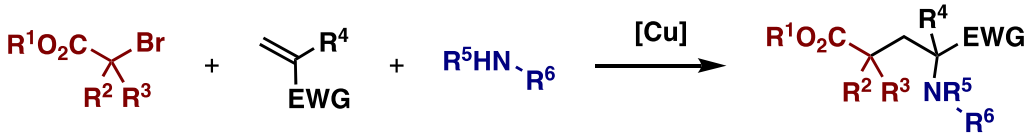
The prevalence of nitrogen in drug molecule candidates is ever-increasing, as nearly 75% of drug molecules contain nitrogen. Traditional amination methods can be laborious and time-intensive, creating a need for regio- and chemoselective technology that accesses these nitrogen-containing scaffolds with atom-economic and fiscal considerations. This has led to our group's use of copper-catalyzed three-component carboamination reactions to accomplish a modular approach to molecular construction. Currently we have explored this field using alkyl boronic acids and α-haloesters as carbon sources, as well as styrene and 1,3-butadiene as olefin sources. To expand the scope of these reactions, this work utilizes 1,1-substituted electron-deficient olefins, e.g. acrylate derivatives. Incorporating electron-withdrawing substitutions on olefins is mechanistically interesting due to the destabilized intermediates and is also synthetically crucial as it will provide an accessible pathway to unnatural amino acids. Using acrylate derivatives, α-haloesters, and amines complex molecules are achieved, and mechanistic insight is elucidated.



ORGANOCATALYTIC ASYMMETRIC SYNTHESIS OF α-AMINOPHOSPHINATES

Cáoimhe J. Niland[1,2], Joseph J. Ruddy[1], Martin P. Ó Fearraigh[1] and Eoghan M. McGarrigle*[1,2]

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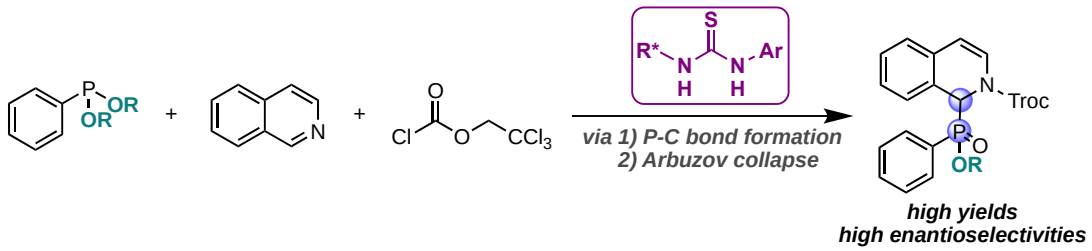
P-Stereogenic organophosphorus compounds have found widespread use as chiral ligands and are important molecules in medicinal and synthetic chemistry. It would be desirable to access *P*-stereogenic aminophosphinates since α-aminophosphinate derivatives are used as surrogates for α-amino acids. Jacobsen and co-workers showed that the enantioselective addition to acyl-activated isoquinolines could be achieved through anion-binding catalysis.[1,2] The Mukherjee group successfully applied this method to the synthesis of α-aminophosphonates by using silyl phosphites as nucleophiles in the enantioselective dearomatisation of isoquinolines catalysed by a chiral thiourea. They achieved high enantioselectivities for the *C*-stereogenic products.[3] Here, we report the organocatalytic reactions of prochiral phosphonites with acyl-activated isoquinolines, giving access to α-aminophosphinates which bear both *C*- and *P*-stereogenic centres. An enantiopure chiral thiourea catalyst gave phosphinate products in moderate-to-excellent yields and enantioselectivities. The reactions are suggested to proceed *via* P-C bond formation followed by Arbuzov-type collapse at phosphorus. Our efforts to develop and understand this new route to enantioenriched α-aminophosphinates will be described.



Scheme 1. Organocatalytic synthesis of α-aminophosphinates containing *P,C*-stereogenic centres.

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INTRODUCTION OF (3-HYDROXYNAPHTH-2-YL)METHYL PHOTOLABILE LINKER INTO POLYESTER BACKBONE: TOWARDS UVA-DEGRADABLE PLASTICS

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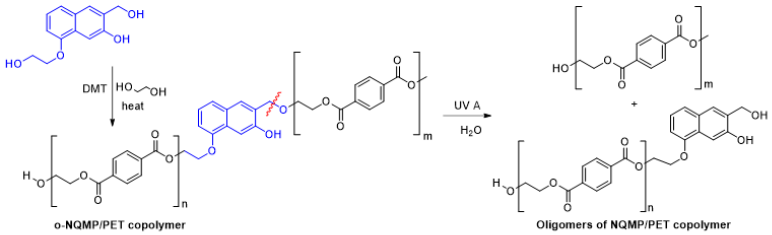
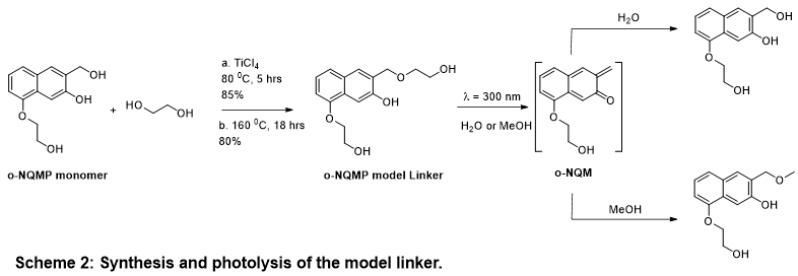
UVA irradiation of (3-hydroxynaphth-2-yl)methanol (o-NQMP) or its ethers results in the efficient C–O bond cleavage with the formation o-naphthoquinone methide (o-NQM). This reaction has been employed in various applications.

In our drive to explore the practical feasibility of photo-depolymerizable plastics, we have developed a novel o-NQMP-based PET-compatible monomer. It is expected to undergo co-polymerization with dimethyl terephthalate (DMT) and ethylene glycol to form o-NQMP/polyethylene terephthalate (PET) copolymer (scheme 1). The importance of our design is that the polymer is expected to cleave under UVA light when exposed to sunlight. Thus, our approach will be a novel solution to make biodegradable polymers.

Initially, we designed an o-NQMP model linker that resembles bis(hydroxyethyl terephthalate), the smallest oligomer of PET. Then, we used the linker to test the photophysical properties and prove the formation of o-naphthoquinone methide (o-NQM). Irradiation of the o-NQMP model linker using 300 nm UV lamps in a fully aqueous medium or methanol resulted in the formation of o-NQMP monomer or methylated o-NQMP monomer, respectively. In both cases, 50% conversion of the model linker was achieved in 5 minutes (scheme 2). Furthermore, the monomer's quantum efficiency (37%) supports that o-NQMP linker is suitable for the design of biodegradable polymer.



Scheme 1: Design, synthesis and photocleavage of the novel o-NQMP/PET copolymer.



Scheme 2: Synthesis and photolysis of the model linker.

DISCOVERY PROCESS RESEARCH AT JANSSEN PHARMACEUTICA

Carla Obradors*, Ferdinand H. Lutter, Matthieu Jouffroy, Shane Plunkett, Lindsey G. DeRatt, Scott D. Kuduk, Jaume Balsells, Nicole E. Behnke, Zachary S. Sales, Minyan Li and Aaron T. Hermann

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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. In this poster a selection of recent chemistry highlights from our group will be presented (references below).

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.

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[1] *Chemistry – European Journal* **2021**, *27*, 14816–14820

[2] *Organic Letters* **2020**, *22*, 7662–7666

[3] *Journal of Organic Chemistry* **2021**, *86*, 12945–12955

HARNESSING HYDROXYLATING ENZYMES FOR THE SYNTHESIS OF NATURAL PRODUCTS AND THEIR ANALOGUES WITH RELEVANCE TO DEMENTIA

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Total syntheses of the natural product, clausenamide, a potential anti-dementia candidate, and its analogues, are described. Work elsewhere is still establishing the SAR profile of clausenamide isomers; the current study will add to this profile by evaluating rigidified clausenamide analogues which will provide information about the contribution of the phenyl groups and their relative spatial distribution to the observed activity. Separate skeleton-building and functionalisation steps are introduced, whereby the functional groups are introduced at the end of the synthesis. Enzymatic late-stage oxidation of lactam cores allows synthetic strategies to focus on skeleton-building without the need for protecting groups. An initial synthetic route involved as key steps: [2+2] cycloaddition, reductive dechlorination, ring-expansion to the lactam, and late-stage hydroxylation, the latter to be facilitated by $P450_{BM3}$ variants. A more efficient two-step route to the lactams was then developed using enolate alkylation followed by reductive amination with cyclisation *in situ*; current research is focused on optimising this short route. With access to all lactam variants completes, enzyme-screening will be conducted using subsets of $P45O_{BM3}$ variants that have demonstrated high activity with lactams, and the clausenamide analogues thus obtained will be assayed for cytotoxicity and for their ability to induce long-term potentiation of the dentate gyrus by electrophysiological assay.

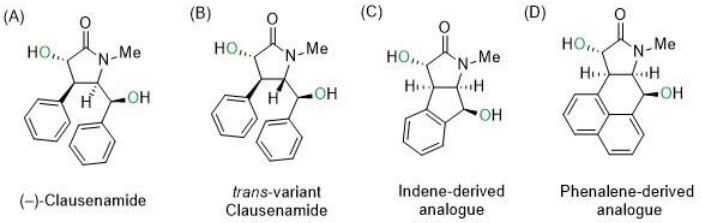
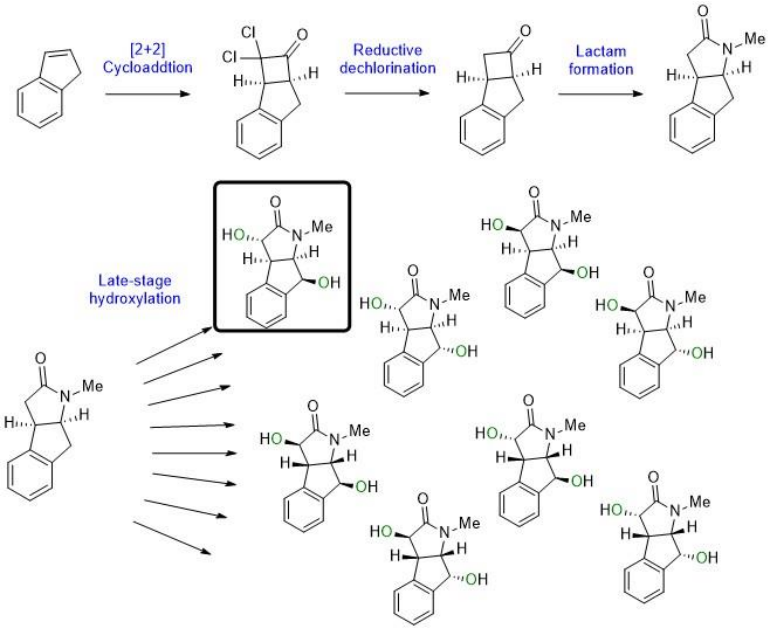
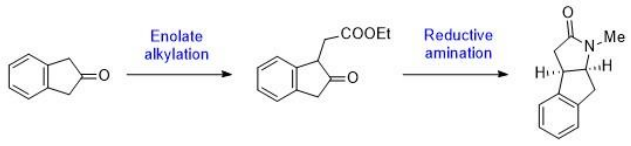


Figure 1. The chemical structures of (–)-clausenamide and proposed analogues.



Scheme 1. The initial synthetic route for indene-derived analogue C.



Scheme 2. The two-step approach to the indene-derived lactam.

CHIRAL PROTON-CATALYZED ENANTIOSELECTIVE REDUCTION OF VINYLOGOUS NITROAMINES

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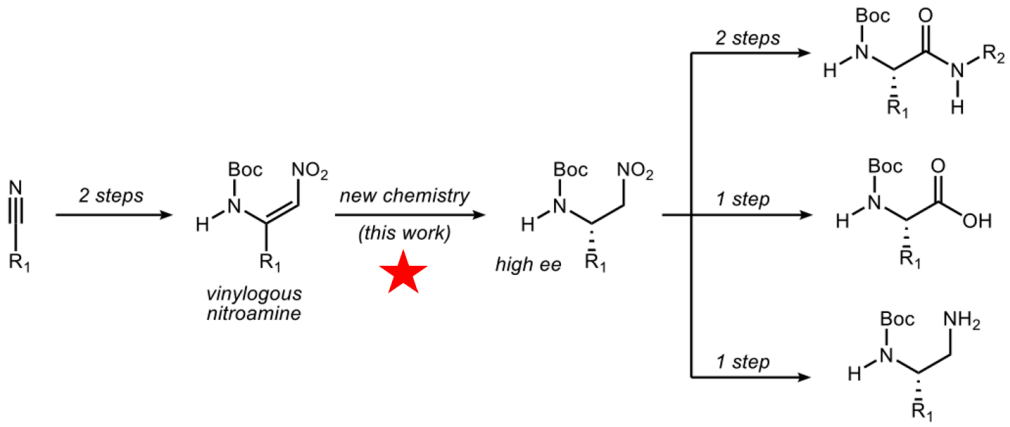
β-Amino nitroalkanes are important precursors to a vast array of organic scaffolds such as α-amino amides, α-amino acids, and 1,2-diamines. While BAM-catalyzed enantioselective aza-Henry reactions can yield these nitroalkanes, this methodology is not amenable to all substrates, especially those that produce alkyl-substituted amines. We envisioned that the reduction of vinylogous nitroamines could be a viable alternative to circumvent these challenges.

Traditionally, the enantioselective reduction of vinylogous nitroamines required harsh conditions (hydrogen under pressure) and expensive metal catalysts such as iridium and rhodium. In recent years, there has been much focus on applying organocatalytic transfer hydrogenation to effect this transformation. We have developed a MonoAMidinium (MAM) chiral proton catalyst that can accelerate this reduction in good yield and excellent enantiomeric excess (ee). We have optimized this reduction and illustrate how the resulting β-amino nitroalkanes can be converted into a variety of useful products, particularly unnatural amino acids (UAAs), in enantiopure form. This method is used for an efficient and cost-effective approach to an experimental therapeutic. Overall, this work harnesses the power of enantioselective organocatalysis to access key enantioenriched scaffolds while expanding our tools for sustainable synthesis.



Synthesis of disubstituted bicyclo[2.1.1]hexane building block.

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Conformational restriction of molecules is an established strategy in medicinal chemistry. It not only can make binding more favorable by adopting a preferred conformation, but also decreases the side effects by eliminating other bioactive conformers[1]. Although this strategy tends to improve the physicochemical property of drug molecules, the process requires an effective synthetic route. For decades medicinal chemists have used cyclobutane and cyclopropane for their rigid structure and defined spatial orientation of the substituent attached to it[2]. However, cyclohexane and cyclopentane are flexible, yet do not have established rigidified analogs.

We hypothesized the disubstituted bicyclo[2.1.1]hexane moiety can be used as a rigid variant of these rings. Although the synthesis of 1,2-disubstituted bicyclo[2.1.1]hexane are known[3], other substitution patterns on bicyclo[2.1.1]hexane are underexplored. We have developed scalable route to bicyclo[2.1.1]hexane with functional handles, that can be manipulated easily to access libraries of novel bicyclo[2.1.1]hexanes. Exit vector measurement of these building blocks can be useful for their strategic application for mimicking medium ring.

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3. a. Mykhailiuk, P. K. *et al*. *Angew*. *Chem*. *Int*. *Ed*. **2020**, *59*, 20515. b. Glorius, F., *et al*. Nature. **2022**. DOI: 10.1038/s41586-022-04636. c. Brown, M. K., *et al*. *J*. *Am*. *Chem*. *Soc*. **2022**, ASAP. d. Procter D. ChemRxiv. **2022**.

LEWIS BASE PROMOTED PHOTOREDOX CATALYZED ADDITION OF ALLYLIC RADICALS TO MICHAEL ACCEPTORS

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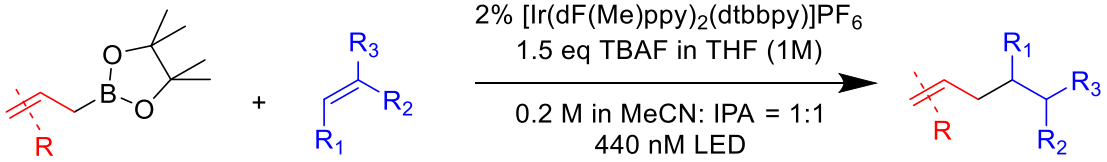
Upon activation, allylic boronic esters can generate allylic radicals under photoredox reaction conditions. The formed allylic radicals react readily with Michael acceptors. The functionalized alkene products formed through this reaction can then be further transformed to other synthetically useful structures. As an example of this, we synthesized lipid-like structures that could be utilized for nucleic acid delivery. The robustness of these organoboronic reactions will allow for derivatization of these branched lipid structures where amino groups and aliphatic tails may be tuned to optimize and assess potency of these ionizable excipients.



SYNTHESIS OF A NOVEL PORPHYRIN–ROSAMINE CONJUGATE AND SPECTROSCOPIC STUDIES TOWARDS CU(II)

Carla Queirós[‡], Nuno M. M. Moura[¥], Ana F. R. Cerqueira[¥], A. Leite[‡], Maria G. P. M. S. Neves[¥], Augusto C. Tomé[¥], Ana M. G. Silva[‡,*]

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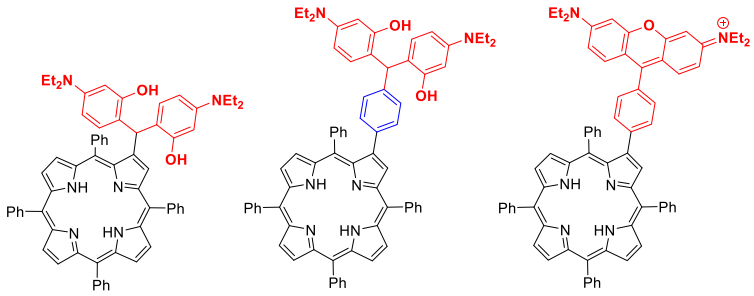
The design of novel dyes with improved photophysical properties and sensitivity towards selected analytes is an important research field for several applications such as optoelectronics, sensing and bioimaging [1]. Porphyrin and rhodamine derivatives are among some of the most studied and important dyes for chemosensing applications due to their attractive photophysical properties, that include high absorption coefficients and high fluorescence quantum yields. Several studies report porphyrin–rhodamine conjugates with interesting spectroscopic properties and sensing ability [2].

Considering our experience with porphyrin and xanthene derivatives, herein we report the synthesis of the novel porphyrin–rosamine conjugate **3** (Figure 1). To synthesize it, condensation of 3-(diethylamino)phenol with 2-(4-formylphenyl)-5,10,15,20-tetraphenyl-porphyrin was carried out to give **2**, followed by oxidative cyclization using *p*-chloranil. Derivative **1** was also prepared, but in this case the cyclized compound was not obtained, probably due to steric hindrance. All derivatives were characterized by NMR and mass spectrometry, and their spectroscopic properties (UV-Vis, fluorescence and EPR) were studied in several solvents and in the presence of Cu(II).



1 2 3

Figure 1. Porphyrin derivatives **1**, **2** and **3**.

[1] A. Shinohar, G. Shao, T. Nakanishi, H. Shinmori, *Front. Chem.* **2021**, *9*, 777041.
[2] a) S. M. G. Pires, C. Núñez, V. V. Serra, A. Sánchez-Coronilla, M. A. F. Faustino, M. M. Q. Simões, A. M. S. Silva, M. G. P. M. S. Neves, J. L. Capelo, C. Lodeiro, *Dyes Pigm.* **2016**, *135*, 113; b) T. Mani, D. M. Niedzwiedzki, S. A. Vinogradov, *J. Phys. Chem. A* **2012**, *116*, 3598; c) X. Sun, D. Li, G. Chen, J. Zhang, *Dyes Pigm.* **2006**, *71*, 118.

Acknowledgments: This work received financial support from National Funds (FCT/MCTES), under the Partnership Agreement PT2020 through projects NORTE-07-0162-FEDER-000048, LAQV-REQUIMTE (UIDB /50006/2020), and the projects PTDC/QUI-QIN/28142/2017, PTDC/QUI-QOR/29426/2017 and EXPL/QUI-OUT/1554/2021. A.F.R. Cerqueira thanks FCT for her doctoral grant (SFRH/BD/135597/2018) and N.M.M. Moura for his research contract (REF. 048-88-ARH/2018).

NICKEL-CATALYZED ENANTIOSELECTIVE SYNTHESIS OF NEW PHENANTHRIDINONE ANALOGS WITH QUATERNARY CARBON STEREOCENTERS USING THE BIRCH-HECK REACTION SEQUENCE

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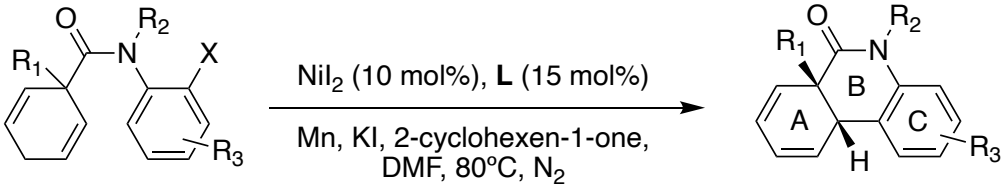
The Birch reduction-alkylation coupled to the desymmetrizing Mizoroki-Heck reaction is a novel synthetic tool to form fused 6-6-6 tricyclic ring systems with a quaternary stereocenter from inexpensive and easily available starting materials. The method was used to create phenanthridinone analogs using 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.



76-99% yield, up to 10:1 e.r.

Divergent Reactivity of Cyclopropyl Carbinyl Species: Mechanistic Insights and Discovery of New Modes of Selectivity

Nina F.C. Ritchie, Hengye Xiang[†], Adam J. Zahara, Peng Liu[*†], and Sidney M. Wilkerson-Hill[*]

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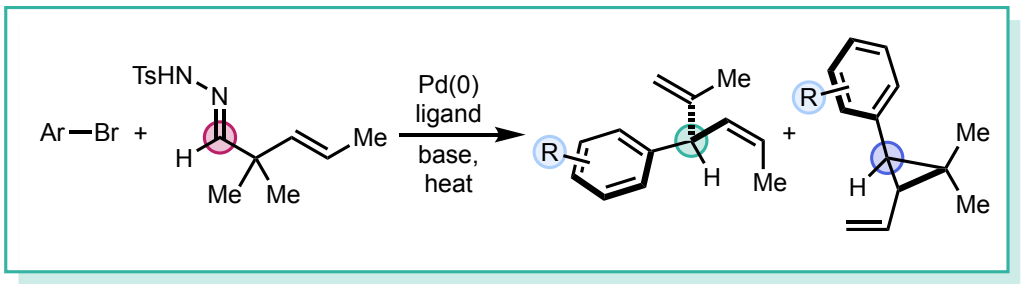
Gem-disubstituted cyclopropanes are a ubiquitous motif found in biologically active compounds such as the pyrethroids, an important class of compounds in the agrochemical industry. Our interest in developing cyclopropanation methods inspired by the biosynthetic pathways of terpenoid natural products led us to develop a library of sulfonyl hydrazones that serve as bench-stable cyclopropyl carbinyl equivalents. Herein we showcase the divergent reactivity of these species to furnish 1,4-dienes, "skipped dienes," through collapse of the cyclopropyl intermediate, or vinyl cyclopropanes through a β-hydride elimination. The selectivity between the two products can be controlled through judicious choice of substrate. Sterically encumbered aryl bromides selectively lead to vinyl cyclopropane products in up to 69% isolated yield. Hammett data reveals a linear free energy relationship between the ratio of skipped diene to cyclopropane and arene σ_{para} parameters. Additionally, we present preliminary results of selectivity between the two products via reagent and ligand control. A deeper mechanistic understanding of the reactivity of cyclopropyl carbinyl intermediates will facilitate accessing new modes of reactivity, leading to novel cyclopropanes that are inaccessible by current methods.



FLOW CHEMISTRY AS A NOVEL APPROACH FOR THE SYNTHESIS OF SPIROEPOXYDIENONES

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†*CBIOS—Universidade Lusófona's Research Center for Biosciences & Health Technologies, Campo Grande, 376, 1749-024 Lisbon, Portugal.*

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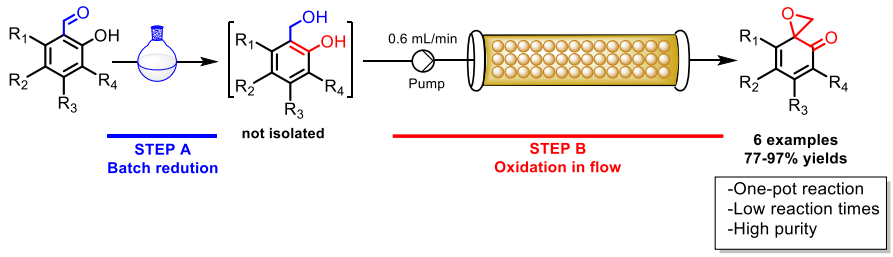
First reported in 1971, the Becker-Adler reaction is the periodate-mediated oxidative dearomatization of salicyl alcohols to spiroepoxydienones.[1,2] Spiroepoxides have a diverse chemical reactivity that allows the synthesis of a diverse array of compounds with different chemical structures. These compounds are useful as intermediates in synthetic routes of several natural compounds such as tropolones and (−)-4-Hydroxyzinowol.[3,4] Nowadays, flow reactions are gaining adepts due to their numerous advantages, such as higher safety, better mixing, more efficient heat transfer, and easy scale-up.[5] In a way to improve the Becker Adler efficiency, we have developed a continuous flow methodology where the reaction promotor is immobilized in the solid phase, and the substrate is passed through in the mobile phase. The continuous flow method allows us to obtain higher yields when compared with batch reactions, and it was possible to recycle the reaction promotor (**Scheme 1**).[6]



Scheme 1. Becker-Adler reaction in flow conditions.

Acknowledgements: We thank Fundação para a Ciência e Tecnologia (FCT) (Ref. PTDC/QUI-QOR/32008/2017, PTDC/CTM-CTM/29869/2017, UIDB/04138/2020, UIDP/04138/2020, UIDB/04567/2020 and UIDP/04567/2020) for financial support. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996.

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Asymmetric Synthesis of Diazaspirocycles for MRCK Inhibitors as Cancer Therapeutics

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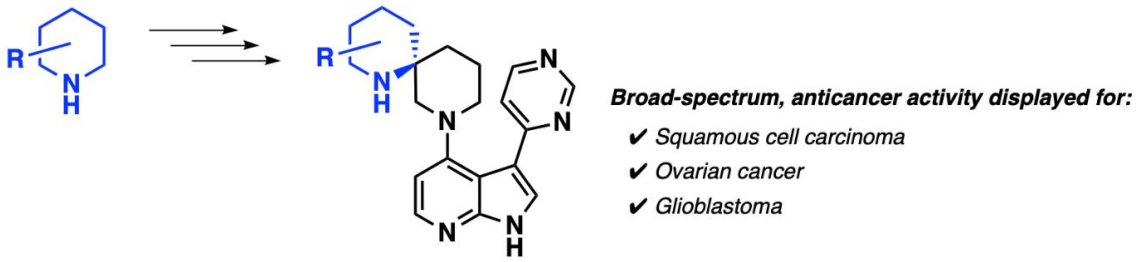
In the pursuit of new therapeutics that target the metastatic spread of cancer, the synthesis of novel inhibitors for underexplored kinases is at the forefront. Recently, potent and selective inhibitors for a new target in the myotonic dystrophy-related Cdc42-binding kinases (MRCK) have been discovered for the treatment of aggressive cancers, including high grade serous ovarian cancer and glioblastoma. The inhibitors feature a diazaspirocycle that largely influences the potency. Spirocycles are privileged structural motifs in medicinal chemistry, yet synthetic methods for their construction are limited, and asymmetric methods are needed to access single enantiomers for biological applications. This work highlights the design and synthesis of diazaspirocycles for MRCK inhibition, while focusing on developing efficient asymmetric methods. Functionalized alpha-amino nitriles were employed as building blocks to expand into the desired bicyclic structure through haloalkylation and reductive cyclization. Chiral directing groups, including naturally occurring menthol and amino alcohols, were assessed for their ability to promote stereochemical control. This synthetic pathway was designed with versatility in mind to enable further medicinal chemistry on various substrates. As a result, the asymmetric construction of innovative spirocycles for MRCK inhibition opens the door for the discovery of modern therapeutics that target the spread of aggressive cancers.



Toward Robust Protein-Mimetic Nanomaterials for Sensing and Catalysis

Mica Schenkelberg, Kyle E. Murphy, Kyle T. McKay, Jianing Li,*

And Severin T. Schneebeli

University of Vermont, Department of Chemistry, Burlington, VT 05405

Our research focuses on next-generation sequence-defined materials inspired by proteins. We integrate new synthetic chemistry with computer-aided design to achieve novel three-dimensional nanostructures able to mimic the functions of protein cavities. In this poster presentation, I am going to discuss the basic design philosophy and provide examples for the scalable synthesis of some of the first molecular springs with tunable spring constants, which do not unfold. The synthesis is adaptable to helices with different pitch and diameter, which allowed us to investigate, for the first time, how molecular flexibility in solution depends on the exact geometry of freeform ladder polymers. We show with molecular simulations and by measuring the longitudinal ^{1}H-NMR relaxation times T_1 for our polymers at five different Larmor frequencies, that increasing the helix diameter leads to increased flexibility.

ASYMMETRIC SYNTHESIS OF (+)- AND (–)-COLLYBOLIDE ENABLE REEVALUATION OF *KAPPA*-OPIOID RECEPTOR AGONISM

Sophia Shevick[1], Stephan Freeman[1], Guanghu Tong, Robin Russo[2], Laura Bohn[2], Ryan Shenvi[1]*

1 Department of Chemistry, Scripps Research, 10550 North Torrey Pines Road, La Jolla, California 92037, United States.
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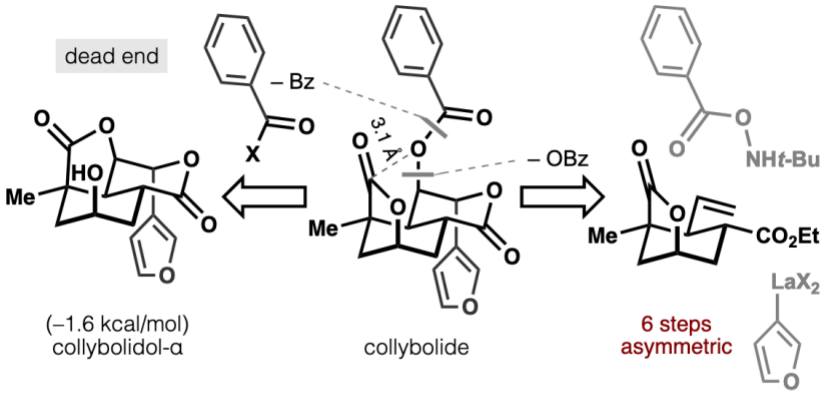
The fungal metabolite collybolide attracted attention as a non-nitrogenous, potent and biased agonist of the kappa-opioid receptor (KOR). We report a 10-step asymmetric synthesis of this complex sesquiterpene that enables facile access to either enantiomer. The synthesis relies on a diastereoselective α-benzoyloxylation to install the buried C6 benzoate and avoid irreversible translactonization of the congested, functionally dense core. Neither enantiomer, however, exhibited KOR agonism, indicating that collybolide has been mischaracterized as a KOR agonist. Given the pharmaceutical, medical and societal interest in collybolide as a next-generation antipruritic and analgesic, this refutation of KOR activity has important ramifications for ongoing studies. Excitement over identification of a new non-nitrogenous, KOR-selective, potent agonist with the same clinical potential as salvinorin A seems to have been misplaced.



Synthesis of both enantiomers and biological assay

OHMIC HEATING SYNTHESIS AND FLUORESCENCE PROPERTIES OF ROSAMINE DYES

Ana M. G. Silva*, Fábio Martins, Carla Queirós

LAQV/REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências da Universidade do Porto, 4169-007 Porto
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The development of new sustainable transformations is a mandatory goal in modern synthetic chemistry that aims to improve efficiency and reduce the environmental impact of chemical reactions, thus providing the necessary tools for the green transition. This objective stimulated the use of ohmic heating (ΩH), an advanced heating process where an AC electrical current is passed into the reaction mixture (aqueous media), which serves as an electrical resistor, thus resulting in a uniform and rapid heating, with the possibility of an efficient reaction scale-up [1].

Belonging to the family of xanthenes [2], rosamines are highly versatile and fluorescent dyes, that offer different degrees of functionalization at different positions of the xanthene (Figure 1). Herein we describe the synthesis of a series of 9-(hetero)aryl substituted rosamines [3], aiming to achieve fluorophores with photophysical properties suitable for sensing applications. The synthetic strategy involved the acid catalyzed condensation of the appropriate aldehyde with 3-(diethylamino)phenol, followed by oxidative cyclization. Results obtained using ohmic heating will be present, as well as the most relevant photophysical properties of fluorophores prepared.

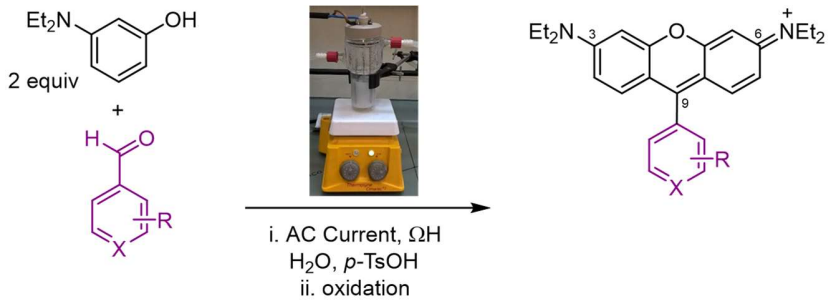

Figure 1. Ohmic heating assisted synthesis of rosamines

Acknowledgments: This work received financial support from National Funds (FCT/MCTES, Fundação para a Ciência e Tecnologia and Ministério da Ciência), under the Partnership Agreement PT2020 through projects NORTE-07-0162-FEDER-000048, UIDB /50006/2020, UIDP/50006/2020, and also the projects PTDC/QUI-QOR/29426/2017 and EXPL/QUI-OUT/1554/2021. A.M.G.S. thanks FCT for funding through program DL 57/2016 – Norma transitória.

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SYNTHESIS OF INDAZOLES VIA INTRAMOLECULAR INVERSE ELECTRON DEMAND DIELS−ALDER REACTION OF YNE-PYRIDINES

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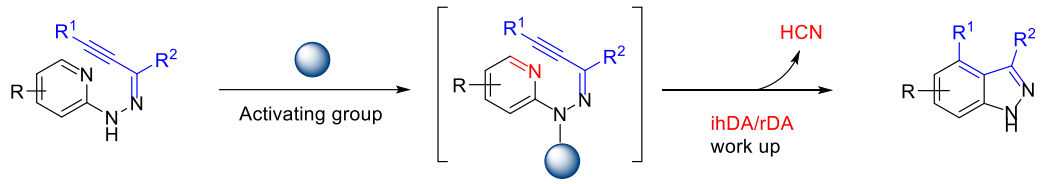
Pyridines are a versatile class of building blocks in synthetic chemistry owing to their unique reactivity, commercial availability, and low cost. Despite these advantages, the use of pyridines in Diels-Alder reactions their synthetic application is scarce due to their inherent aromatic stabilization and low reactivity. It has been found that the harsh reaction conditions (1-3) are required to make pyridine undergo Diels−Alder cycloadditions with alkenes. To address the lack of reactivity of pyridines towards Diels-Alder reactions, we came with a hypothesis whereby using an activating group can make pyridine electron-poor and lower down the energy of its LUMO and hence making it more reactive towards inverse electron demand Diels-Alder reaction. We have developed a method for the activation of pyridines and synthesis of nitrogen-containing heterocycles via inverse-electron-demand Diels-Alder reaction by using a suitable activating agent for the cycloaddition reaction of pyridines. We intend to test the versatility of the transformation by screening a variety of substrates under optimized reaction conditions. Further we want to test the application of the method in the synthesis of bioactive molecules.



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SYNTHESIS AND PROPERTIES OF MULTI-TURN HELICENES

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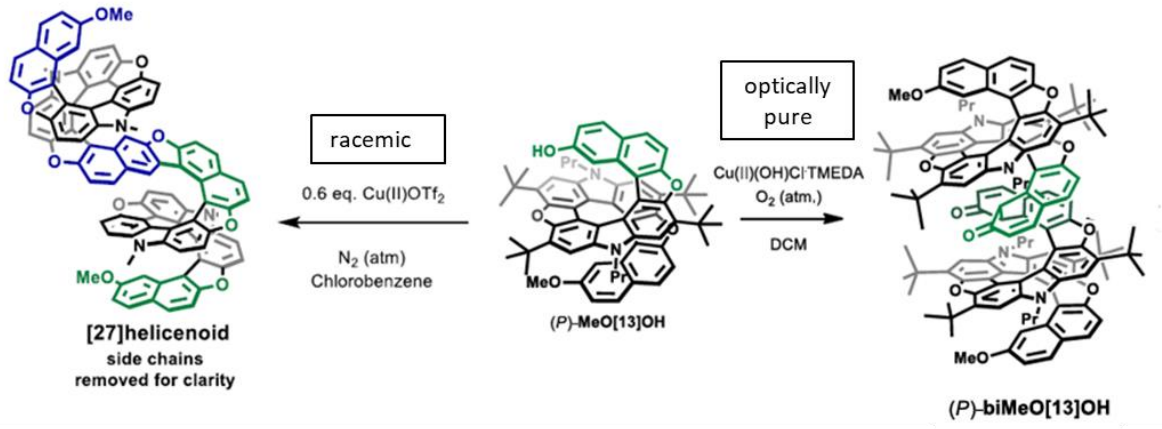
In the recent developments of the organic electronic devices, helicenes—ortho-fused polycyclic aromatic hydrocarbons (PAHs)—have received considerable attention from the organic chemistry and material science communities due to their unique optical properties[1].

In our previous studies we described the synthesis of a series of azaoxa[n]helicenes, which is based on iterative oxidative furan formation between 3,6-dihydroxycarbazoles and/or 2-naphthols[2]. The flexibility of this method allows the convenient and scalable synthesis of symmetric, unsymmetrical, and asymmetric homo-chiral structures.

By further modifying these reaction conditions, we were able to access new highly strained structures of elongated helicenes from diazaoxa[7]helicene core. Namely, we have carried out the studies concerning the oxidative homo-coupling i.e., dimerization of two [n]helicenes, to access a helicene of [2n+1] length (Scheme 1). This synthetic strategy is appealing for accessing helicenes of extraordinary length. The compounds were characterized using NMR and optical spectroscopy (UV/Vis, fluorescence, and CD) along with single-crystal X-ray crystallography.



Scheme 1. Dimerization of enantiomerically pure HO[13]OMe (right) and a racemic HO[13]OMe (left)

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MODULATING POLYMERIZATION THERMODYNAMICS OF THIOLACTONES THROUGH SUBSTITUENT AND HETEROATOM INCORPORATION

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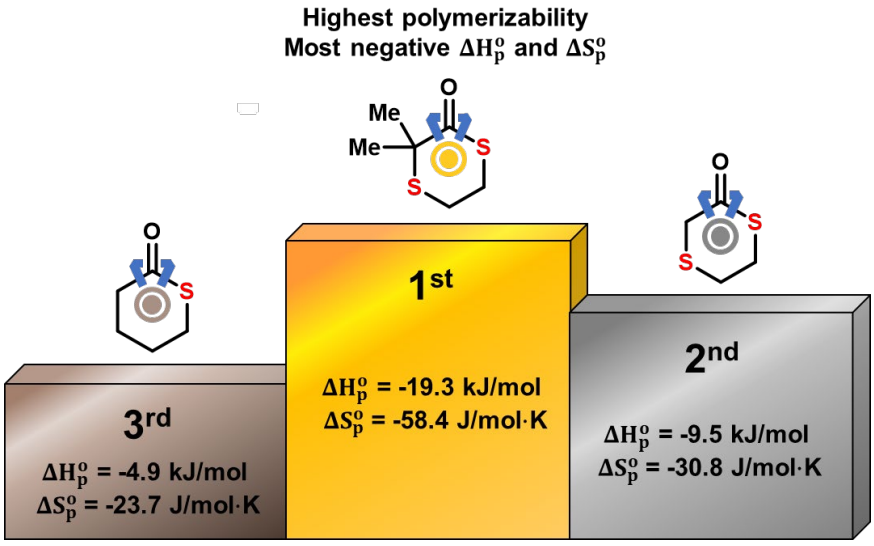
A central challenge in the development of next-generation sustainable materials is to design polymers that can easily revert back to their monomeric starting material through chemical recycling to monomer (CRM). An emerging monomer class that displays efficient CRM are thiolactones, which exhibit rapid rates of polymerization and depolymerization. This report details the polymerization thermodynamics for a series of thiolactone monomers through systematic changes to substitution patterns and sulfur heteroatom incorporation. Additionally, computational studies highlight the importance of conformation in modulating the enthalpy of polymerization, leading to monomers that display high conversions to polymer at near-ambient temperatures, while maintaining low ceiling temperatures (T_c). Specifically, the combination of a highly negative enthalpy (-19.3 kJ/mol) and entropy (-58.4 J/(mol·K)) of polymerization allows for a monomer whose equilibrium polymerization conversion is very sensitive to temperature.



SYNTHESIS AND EVALUATION OF ANTAGONIST ACTIVITY OF TETRAPEPTIDE LIGANDS ON THE MELANOCORTIN-4 RECEPTOR (MC4R)

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The melanocortin pathway has been shown to regulate various physiological functions, including energy balance, sexual function, and eating behavior. Melanocortin receptors are members of the G protein-coupled receptor (GPCRs) family, have five receptor subtypes (MC1R, MC2R, MC3R, MC4R, and MC5R), with the melanocortin-4 receptor (MC4R) contributing to energy homeostasis. As a result, the MC4R is a pharmacological target for treating obesity and states of negative energy balance including cachexia. To explore the specific pharmacological features of the MC4R and to uncover new medicinal treatments, finding novel MC4R antagonists is important. A mixture-based positional scanning approach utilized by our laboratory identified a nanomolar potent MC4R antagonist scaffold with the structure of Ac-DPhe(pI)-Arg-Nal(2')-Arg-NH_2 (pA_2 = 9.0 ± 0.2, antagonist K_i = 1.0 nM).(1) This tetrapeptide possesses equipotent antagonism as the MC4R endogenous AgRP(86-132) antagonist. The research presented here focused on continued structure-activity relationship studies on the identified tetrapeptides to boost the scaffold's potency. These ligands were synthesized by standard solid phase peptide synthesis and pharmacologically investigated by the AlphaScreen™ assay on mouse melanocortin receptors (mMCRs) to evaluate their antagonist potency. Our findings revealed the first tetrapeptides with antagonist activity at all assayed mouse melanocortin receptors (mMC1R, mMC3R, mMC4R, and mMC5R).

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V70

IDENTIFICATION OF *PLASMODIUM FALCIPARUM* FORMATE NITRITE TRANSPORTER (*PF*FNT) INHIBITORS VIA VIRTUAL SCREEN

Alicia Wagner[1], Roger Trombley[1], Maris Podgurski[1], Meng Cui[1], Adriana A. Marin[2], Steven P. Maher[2], Dennis E. Kyle[2], Roman Manetsch[1,3,*]

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The recent rise in antimicrobial resistance against current malaria treatment options necessitates the identification of alternative malaria targets and new antimalarial drugs. *Plasmodium falciparum* formate-nitrite transporter (*Pf*FNT) has been identified as one such druggable target, though current inhibitors are not drug-like. Through a virtual high-throughput screen of the ZINC drug-like library against *Pf*FNT, cheminformatics-driven down selection, and whole cell phenotypic assays, we have identified two active scaffolds. We are currently conducting structure-activity relationship studies on 1,2,4-triazole carboxamide derivatives to further investigate and optimize this class of compounds.

TUNING HYDROGEL MECHANICS WITH DYNAMIC COVALENT CHEMISTRY

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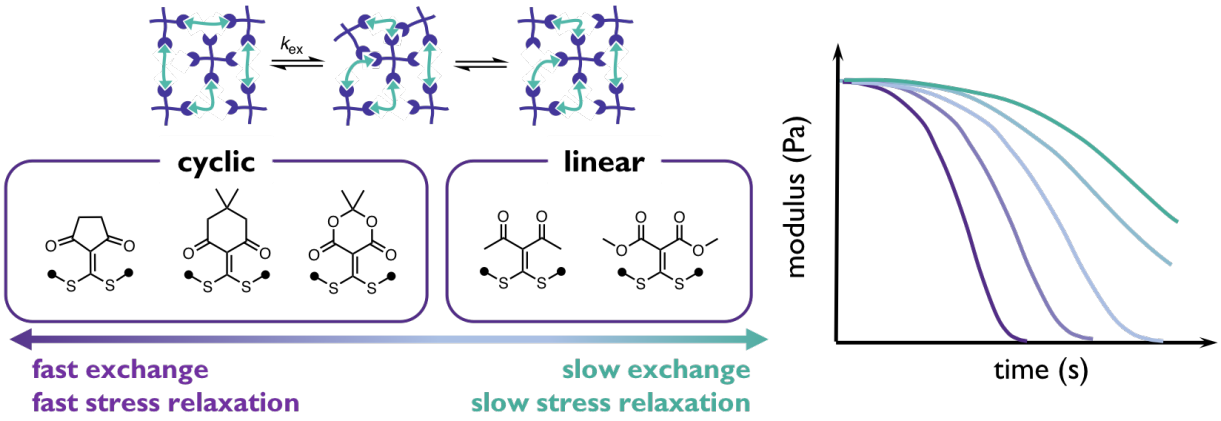
The incorporation of dynamic covalent chemistries into polymer networks enables capabilities such as self-healing, responsiveness, and adaptability. Hydrogels, a subset of polymer networks that are water-swollen and biocompatible, recapitulate viscoelastic features of natural tissues like stress relaxation when dynamic crosslinks are incorporated. Unlike their permanently covalently-crosslinked counterparts, which are mechanically static, these biomaterials can mimic changes to mechanical properties that occur over space and time. Most dynamic hydrogels exchange through dissociative reaction mechanisms, but in these materials, the mechanical properties of stiffness and stress relaxation are challenging to decouple. Here, we report on two efforts to 1) develop a hydrogel with independently tunable mechanical properties using dithiolalkylidene-based crosslinkers that exchange associatively and 2) apply a visible-light-responsive boronic ester-based hydrogel with reversible mechanics to interrogate cell behavior in response to mechanical changes.[2] The former illustrates how structure-reactivity relationships gleaned from kinetics of crosslinker exchange directly allows us to control the mechanical properties of hydrogels. The latter demonstrates how incorporating a photoswitchable azobenzene proximal to a dynamic crosslink provides a handle to interrogate cell mechanobiology with spatiotemporal control. We envision that these hydrogels contribute a means to study unexplored biomechanical mechanisms underlying physiology and disease.



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Synthetic Studies Towards the Indole Diterpenoid Natural Products

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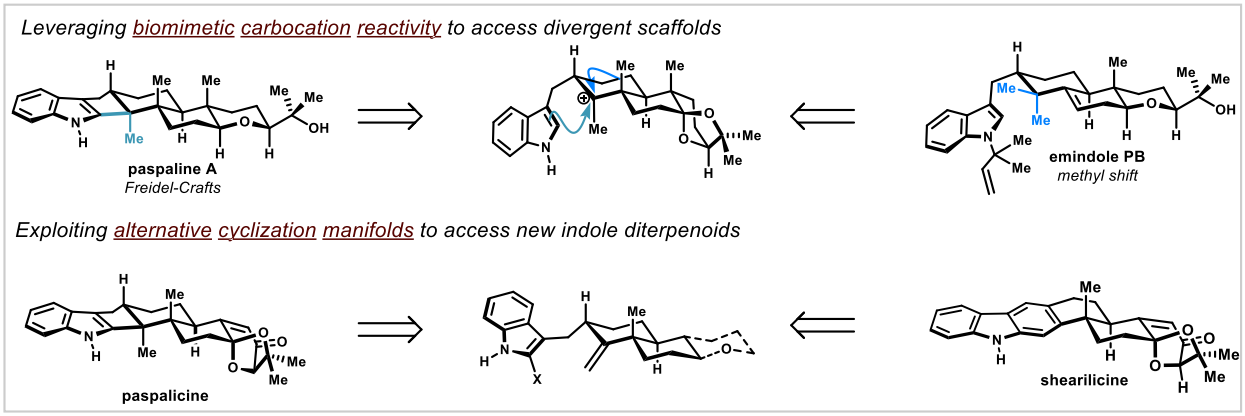
BK channels (big potassium) are voltage-gated/calcium-dependent potassium channels that participate in many crucial physiological processes.[1] Two tumor-associated BK channel variants (gBK and BK(L)) have been identified[2]. It has been revealed that inhibition of BK channels causes apoptosis and decrease of tumor size in glioma and breast cancers.[3] The indole diterpenoid family members are known to be potent and selective BK channel inhibitors.[4] An efficient and modular synthetic route to these indole diterpenoids will facilitate the investigation of the SAR of this family, providing access to analogs that are potential variant-selective BK channel inhibitors.

As previously described by our laboratory in the synthesis of paspaline A[5], the formation of the five–membered ring via the engagement of indole C–2 was highly enabling. We seek to realize this same disconnection by identifying other mechanistic manifolds in the context of synthesizing paspalicine and accessing the carbazole moiety observed in shearilicine. Here we report the completed and optimized total synthesis of shearilicine and the progress towards paspalicine.



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A MOLECULAR UNDERSTANDING OF MUCUS USING SYNTHETIC GLYCOPOLYMERS

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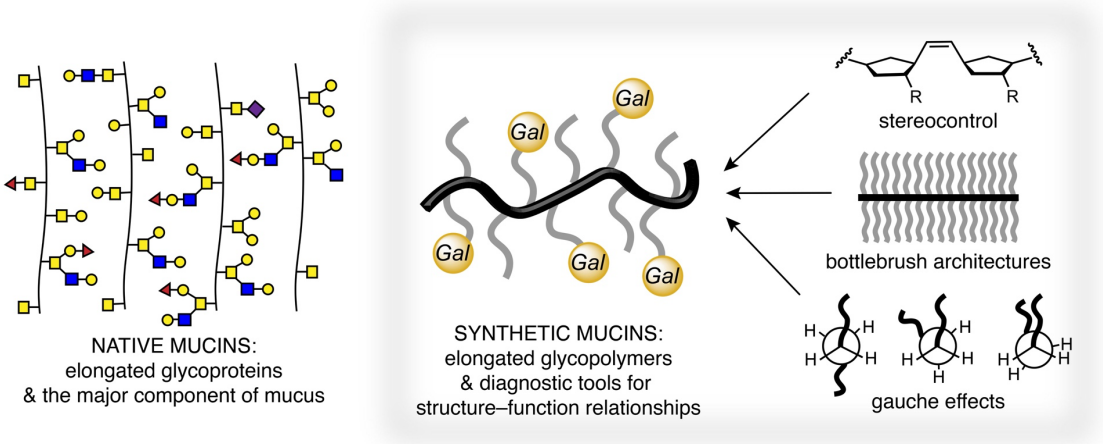
Though it is well-understood that slight variations in stereochemistry and connectivity determine the efficacy of therapeutics and plastics, similar insights into the structure of mucus, a complex biological hydrogel, are still lacking. Establishing these fundamental structure–property relationships can only be achieved if the chemical composition of the material can be manipulated. Synthetic mucus would illuminate this area of study; however, scientists have struggled to simultaneously recapitulate the high glycan density of mucus while maintaining the mechanical, biological, and structural properties that nature easily manufactures. Towards this goal, we synthetically mimicked mucins, the major constituent of mucus, by densely glycosylating polymers. Prior work revealed that stereocontrol of the polymerization dictated mechanical properties of the mucin mimics, which thereby differentiated the biological properties.[1] We sought to further evaluate other chemical structures within the polymer backbone, requiring other avenues of polymerization to be explored. Beyond stereocontrol, we have discovered that gauche effects and bottlebrush architectures also influence the polymers' mechanical properties and mucin-like function with respect to toxin inhibition and lectin binding. Direct comparison of polymers that are distinctly different in polymer backbone but bear the same glycan array will elucidate the molecular underpinnings of how mucosal structure influences function.



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DESIGN AND DEVELOPMENT OF ANTIMALARIAL 1,2,3,4-TETRAHYDROACRIN-9(10*H*)-ONES (THAS) AND THE DEVELOMENT OF QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR) MODELS

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Malaria is a fatal mosquito-borne parasitic disease. The World Health Organization reported that in 2020, there was an estimate of 241 million malaria cases, with approximately 602,000 deaths. Malaria transmission is caused by the genus, *Plasmodium*, where the two most prevalent species responsible for this disease in human are *P. vivax* and *P. falciparum*.[1] Due to the ever-increasing rate of resistance, a novel drug class is in urgent need to treat all stages of infection.

Historically, 4(1*H*)-quinolones have been identified as potent, antimalarial agents. Specifically, THAs has been identified to exhibit antimalarial activity since the 1940s.[2,3] Unfortunately, these molecules failed prior to clinical development as they possessed poor solubility and rapid induction of parasite resistance. Here, several series of THAs were synthesized and tested examining each compound for antimalarial activity against multiple strains of *Plasmodium spp.*, cytotoxicity, and its potential for cross resistance.

Concurrently, the development of QSAR models for THAs has been ongoing to generate predictive models for SAR studies. The current models demonstrated reliable predictive capabilities through standard statistical parameters R^2 and Q^2.[4] The QSAR models developed here will be useful to develop novel potent, orally bioavailable antimalarial THAs and provide immense guidance in our ongoing SAR study.

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NATURAL PRODUCT FR900098 ANALOGS AS INHIBITORS OF 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. This process is vital to bacterial/parasitic survival and represents an attractive set of drug targets due to its essentiality in these pathogens but absence 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 are too polar reach the intracellular target. FR900098 analogs with lipophilic substitution α to the phosphorus atom showed promise, displaying increased activity against *Mtb* and *Pf*. An α 3,4-dichlorophenyl substituent, in combination with various *O*-linked alkylaryl substituents on the hydroxamate moiety is utilized in the design of a novel series of analogs. The *O*-linked substituents further enhance Dxr inhibition by extending the structure into the adjacent NADPH binding pocket, normally occupied DXP and NADPH. Of these analogs, compound **7a** showed impressive activity against *Pf*. Utilizing a Topliss approach for aromatic substituents, additional compounds were synthesized. To increase lipophilicity, analogs were also made as the diPOM prodrugs. Data from the compounds suggest that this combination of substituents is advantageous for a new generation of antimicrobials.

DESIGN, SYNTHESIS, AND EVALUATION OF BRAIN-PENETRANT LIGANDS TO INVESTIGATE THE ROLE OF ALOX5AP IN NEUROINFLAMMATION

Nicole D. Bartolo, Hema S. Krishnan and other authors (give first and family name for all authors. Please star* the corresponding author.)

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Widespread neuroinflammation is observed in many neurodegenerative disorders, such as Alzheimer's disease (AD). Neuroinflammation in the central nervous system requires the activation of macrophage-like cells known as microglia, the resident immune cells of the brain. Recent single-cell transcriptomics studies have led to the identification of genes associated with AD-risk, such as ALOX5AP, whose expression in the brain is restricted to microglial cells. Novel ligands for ALOX5AP were designed from SAR analysis of non-brain penetrant ALOX5AP inhibitors, such as MK-591, and from novel chemical scaffolds identified through a DNA-encoded library screen. The resulting compounds were synthesized and evaluated for biological activity.

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[1] You may include references at the end of the abstract if you wish.

INVESTIGATION OF PHOSPHINE LIGAND STERIC EFFECTS ON LIGATION STATE AND REACTIVITY IN NI-CATALYZED CROSS-COUPLING

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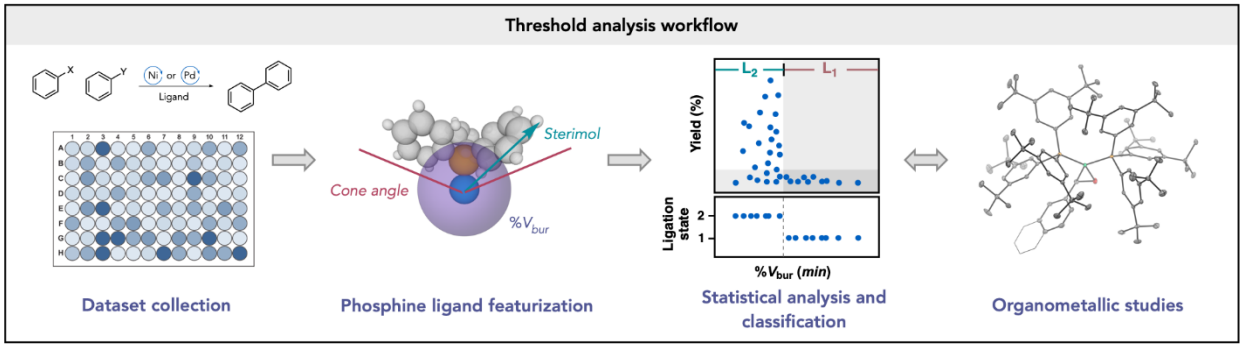
Recent efforts to develop Ni-catalyzed cross-coupling methodologies have been limited by an incomplete understanding of how ancillary ligand structure and catalyst speciation promote productive chemistry at the Ni center, in stark contrast with the extensive mechanistic studies and ligand development performed for Pd that have advanced Pd-catalyzed cross-coupling technology. Having previously developed a series of monodentate phosphines possessing remote steric bulk that were uniquely successful in a Ni-catalyzed Suzuki-Miyaura cross-coupling (SMC) of benzylic acetals, we were interested in mechanistically probing this steric profile and gaining a broader understanding of ligand requirements for Ni. Through a combination of high-throughput experimentation and ligand featurization, we developed a univariate analysis tool that revealed reactivity thresholds corresponding to the percent buried volume of the smallest ligand conformer. This reactivity threshold bifurcates ligands into active and inactive regions of chemical space across several cross-coupling datasets. Organometallic studies revealed that this buried volume threshold corresponds with the boundary between monodentate phosphines that form bis- or monoligated Ni complexes, with bisligated Ni complexes shown to be active in catalysis. This study provides insights into ligand structural requirements for Ni, while providing a new tool for mechanistic analysis.



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NOVEL APPROACHES TOWARDS INHIBITION OF BACTERIAL COA BIOSYNTHESIS

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Drug-resistant pathogens presents an urgent need for next-generation antibacterial agents. Coenzyme A (CoA) is an essential cofactor in all living organisms due to its fundamental role in metabolism. A recent study investigating the effect that depletion of the Pan and CoA biosynthetic enzymes has on bacterial cell viability provides convincing genetic validation of CoaBC as a bactericidal drug target. This leads to the hypothesis that inhibitors of CoaBC will disrupt CoA biosynthesis and kill bacterial cells. CoaBC is a bifunctional enzyme bearing both phosphopantothenoylcysteine synthetase (PPCS) and phosphopantothenoylcysteine decarboxylase (PPCDC), the second and third enzymes of the CoA biosynthetic pathway. A range of inhibitors have been designed and synthesized to target the PPCS activity of CoaBC. The compounds are analogs of pantothenic acid, the natural substrate of PanK, which catalyzes the first step of the CoA pathway. By employing a metabolic activation strategy, cell-permeable inhibitors will be substrates for the organism's PanK enzyme, undergoing phosphorylation and subsequent cytidylation to form the active PPCS inhibitor *in situ*. In a parallel strategy, a series of phosphorylated prodrugs have been prepared, bypassing metabolic activation. A third series of compounds (P-Pan-CMP mimetics) deliver the intact inhibitor. Thus, using various strategies, these compounds have the potential to chemically validate CoaBC as a new antibacterial drug target and serve as lead compounds toward novel therapeutics.

A UNIFIED APPROACH TO DECARBOXYLATIVE HALOGENATION OF (HETERO)ARYL CARBOXYLIC ACIDS

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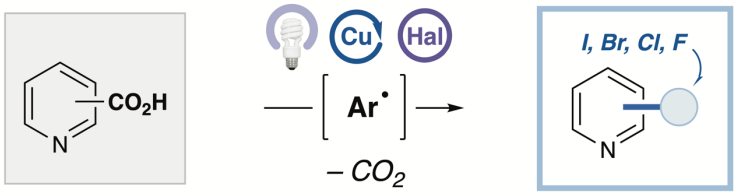
Aryl halides are a fundamental motif in synthetic chemistry, playing a critical role in metal-mediated cross-coupling reactions and serving as important scaffolds in drug discovery. Although thermal decarboxylative functionalization of aryl carboxylic acids has been extensively explored, the scope of existing halodecarboxylation methods remains limited, and there currently exists no unified strategy that provides access to any type of aryl halide from an aryl carboxylic acid precursor. We report a general catalytic method for direct decarboxylative halogenation of (hetero)aryl carboxylic acids via ligand-to-metal charge transfer. This strategy accommodates an exceptionally broad scope of substrates. We leverage an aryl radical intermediate toward divergent functionalization pathways: (1) atom transfer to access bromo- or iodo(hetero)arenes or (2) radical capture by copper and subsequent reductive elimination to generate chloro- or fluoro(hetero)arenes. The proposed ligand-to-metal charge transfer mechanism is supported through an array of spectroscopic studies.

unified approach to decarboxylative halogenation



direct use of (hetero)aryl carboxylic acids

via *atom transfer* or *Cu-mediated bond formation*

[1] Chen, T. Q.; Pedersen, S. P.; Dow, N. W.; Fayad, R.; Hauke, C. E.; Rosko, M. C.; Danilov, E. O.; Blakemore, D. C.; Dechert-Schmitt, A.-M.; Knauber, T.; Castellano, F. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, **2022**, doi:10.1021/jacs.2c02392.

PROGRESS TOWARDS THE TOTAL SYNTHESIS OF NOGALAMYCIN AND OTHER ANTHRACYCLINE GLYCOSIDES

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The anthracycline natural product family is known for their significant demonstrations of anticancer activity; the molecules of this family also possess stereochemical complexity and unique structural features. Representative examples from this family include daunorubicin, doxorubicin, menogaril, and nogalamycin (Figure 1a). Typically, the aglycone cores have been accessed through some sort of anionic cyclization, such as a Hauser annulation, or by intermolecular Diels−Alder reactions to establish the B or C ring. Here, we describe highly modular routes toward readily synthesizing the tetracyclic anthraquinone cores of these molecules (Figure 1b). The culmination of our syntheses is achieved by a Ni-catalyzed cross-electrophile coupling of an aryl bromide D ring with an aryl aldehyde AB-ring fragment, followed by intramolecular C–H carbonylation to execute closure of the C ring, effectively providing us with the respective tetracyclic aglycone cores. The aryl aldehyde AB-ring fragments can be traced back to simple synthetic modifications to key benzyne cycloaddition intermediates.

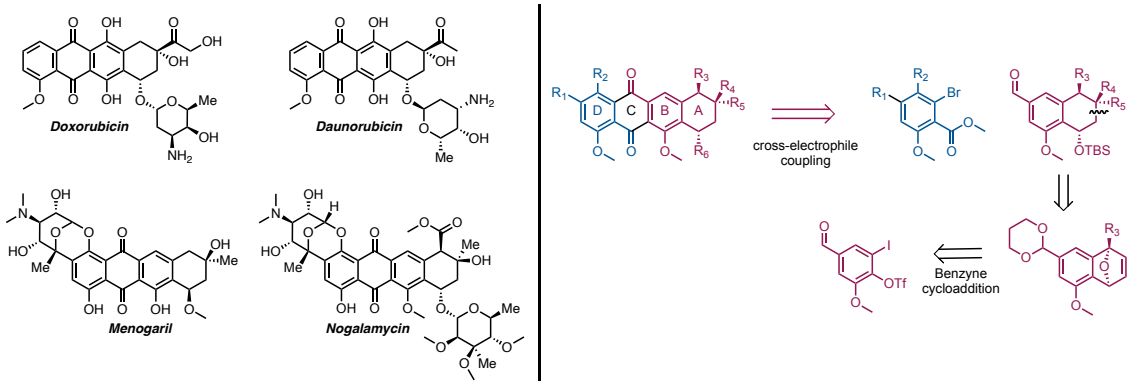

Figure 1. (a) Members of the anthracycline antibiotic natural product family. (b) Our devised retrosynthetic strategies toward accessing the tetracyclic anthracycline core *via* key Ni-catalyzed cross-electrophile coupling and benzyne cycloaddition steps.

STUDIES TOWARD THE TOTAL SYNTHESIS OF (-)-LOMAIVITICIN A

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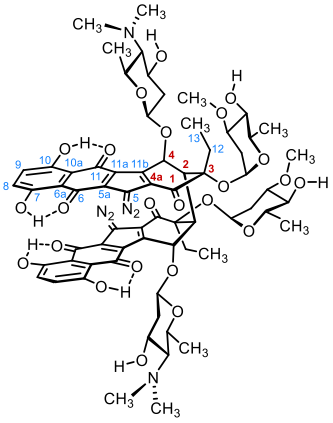
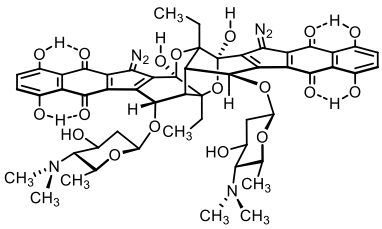
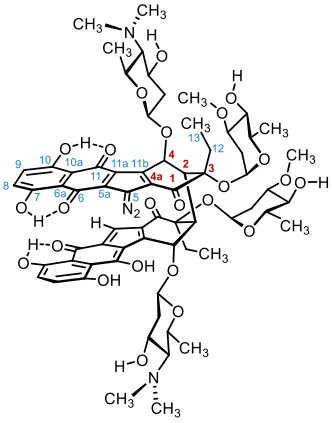
The lomaiviticins are a class of dimeric genotoxic metabolites containing a unique diazotetrahydro[*b*]benzofluorene core. Since the discovery of the first members of this class in 2001, these natural products have been of particular interest to the synthetic community.[1] Specifically, lomaiviticin A rose as a popular synthetic target due to its potent biological activity and interesting structural complexity. Despite immense efforts, this natural product, or any other member of its family, has never been synthesized. In addition, no lomaiviticin has ever been successfully analyzed by X-ray crystallography, leaving the structures of lomaiviticins A, B and C unconfirmed for nearly two decades. Recently, our lab, in collaboration with the Nelson lab, utilized microED studies, high field NMR data, and computational analysis to reassign the structures of lomaiviticins A, B and C.[2] Our group is developing a new and efficient synthesis to access the revised structure of lomaiviticin A. With this project, we hope to report the first synthesis of a member of the lomaiviticin class and fully confirm the structures of these natural products. We report here our current progress towards lomaiviticin A.



(–)-lomaiviticin A
(revised structure assignment)



(–)-lomaiviticin B
(revised structure assignment)



(–)-lomaiviticin C
(revised structure assignment)

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C–H INSERTION OF DONOR/DONOR CARBENES INTO STEREOGENIC CENTERS AND THE ASYMMETRIC SYNTHESIS OF DIHYDROBENZOXANTHONES

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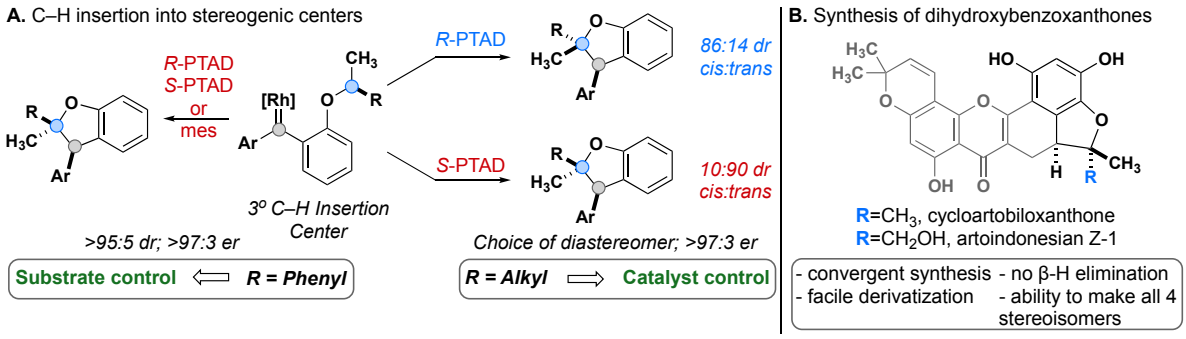
Intramolecular C–H insertions with donor/donor dirhodium carbenes provide a concise and highly stereoselective method to set two contiguous stereocenters in a single step.[1] Herein, we report the insertion of donor/donor carbenes into stereogenic carbon centers allowing access to trisubstituted benzodihydrofurans in a single step. This study illuminates, for the first time, the stereochemical impact on the carbene center and delineates the structural factors that enable control over both stereogenic centers.[2] Sterically bulky, highly activated C–H insertion centers exhibit high substrate control yielding a single diastereomer and a single enantiomer of product regardless of the catalyst used. Less bulky, less activated C–H insertion centers exhibit catalyst control over the diastereomeric ratio (dr), where a single enantiomer of each diastereomer is observed with high stereoselectivity. A combination of experimental studies and DFT calculations elucidate the origin of these results and demonstrate that donor/donor carbenes undergo uniquely stereoselective reactions that originate from a stepwise reaction mechanism. This methodology is currently being applied as the key step in the targeted synthesis of a subclass of xanthone natural products known as dihydrobenzoxanthones.[3]



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INNOVATIVE AUTOMOTIVE PAINT B1:B2 COMPACT PAINT SYSTEMS

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In automotive original equipment manufacturing (OEM) plants, traditional paint application lines require several baking steps to cure each layer of paint. Innovations from PPG have enabled both time and energy savings by reducing the number of ovens along the production line; this is known as PPG's B1:B2 Compact Paint System. Unique resin synthesis and formulation design fuels this technology, bringing customers immense cost savings and increase in production.

TOTAL SYNTHESIS OF NENESTATIN A AND ITS APPLICATION TOWARD ELUCIDATING ATYPICAL ANGUCYCLINE DIMERIZATION

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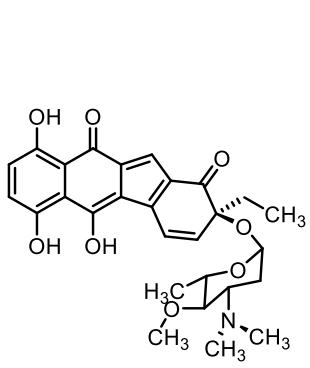
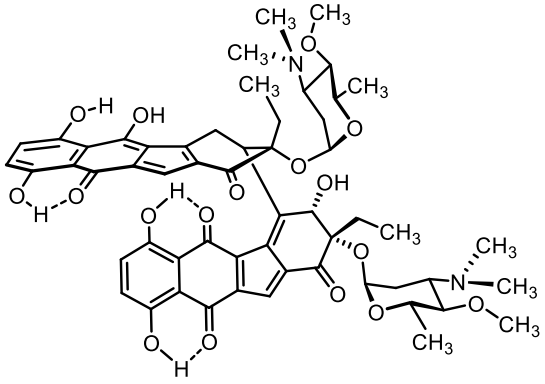
Nenestatin A, a new member of the atypical angucycline family, was isolated from a *Micromonospora* strain in 2017, followed by its heterodimeric counterpart, nenestatin B, in 2021.[1,2] Both contain a benzofluorene core and rare 4-*O*-methyl-angolosamine moieties. The nenestatins are homologous biosynthetically, and thereby structurally, to the closely related lomaiviticins. In accessing the nenestatins, we aim to explore the unknown biosynthetic pathway of carbon-carbon dimeric bond construction for these benzofluorene-containing natural products. Literature precedent suggests this may occur via a spontaneous nucleophilic event rather than enzymatically driven.[3] Our scalable, synthetic route yields nenestatin A for elaboration to nenestatin B, in order to probe this hypothesis.



nenestatin A



nenestatin B

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DESIGN AND CHARACTERIZATION OF CIRCULARLY PERMUTED CASPASE-2 MUTANTS AND THEIR USE IN EVALUATION OF NOVEL CASPASE-2 INHIBITORS

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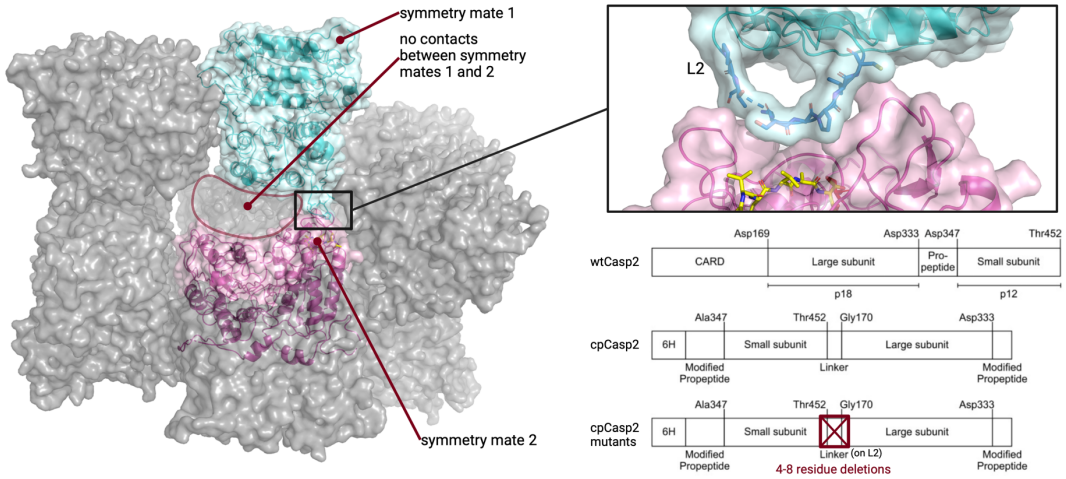
The exact cause of Alzheimer's disease (AD) has yet to be completely described despite the disease being defined over 100 years ago. A potential approach to better understand the pathogenesis of AD could be the development of selective caspase-2 (Casp2) probes, as we have shown that a Casp2-mediated cleavage product of tau (Δtau314) reversibly impairs cognitive and synaptic function in animal models of tauopathies. We have taken a multi-pronged approach to studying this target and are currently developing peptide inhibitors as well as characterizing both electrophilic and non-covalent fragments. Due to limitations with Casp2 protein production, we have expressed and characterized a recently published circularly permuted Casp2 (cpCasp2) to use as a surrogate for the wild type protein. cpCasp2 is both enzymatically and structurally similar to Casp2, but cpCasp2 does not appear to be conducive to the crystallographic studies needed to support our medicinal chemistry endeavors. The design of cpCasp2 involves linking loop 2 (L2) and L2', the N- and C-terminus, of Casp2 with a GS moiety, creating L2 of cpCasp2. This loop is not well ordered and appears to create challenges for crystal growth, stability, and data resolution. We have therefore designed six L2 mutants of cpCasp2 with the goal of eliminating structural clashes we have observed in its crystal packing. We expect that these mutations will stabilize crystal growth while preserving the enzymatic activity profile. Work from our recent publications and a closer look at the structural biology data generated to date on this project will be presented.



DESIGN OF SEQUENTIALLY TARGETED POLYMERS THROUGH SUPRAMOLECULAR ASSEMBLY

Margaret C. Gerthoffer,[a] Stephen J. Koehler,[a] Sikai Wu,[a] Bohan Xu,[b] Bo Chen,[cd] Jordan Cox,[e] Tao Wang,[b] Steven Huss,[a] Shalisa M. Oburn,[a] Morgan B. Murphy,[a] Morgan Dierolf,[a] Hannah Venturini,[a] Tanner Wolf,[a] Steven A. Lopez,[e] Vincent H. Crespi,[abfg] John V. Badding,[abfg] and Elizabeth Elacqua[af]*

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[b]*Department of Physics, The Pennsylvania State University, University Park PA*
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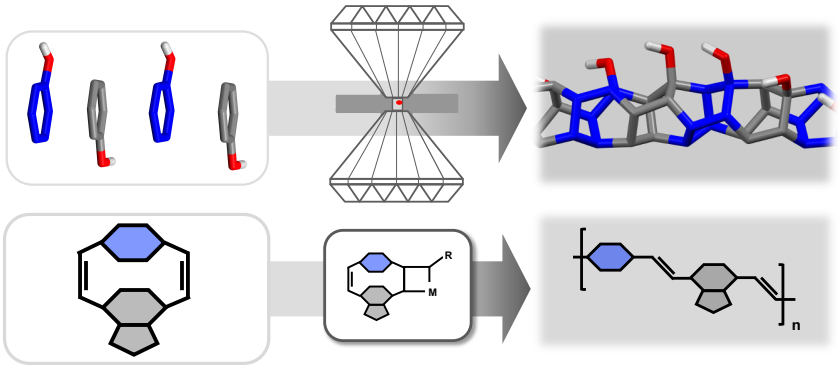
Targeted design of sequence-controlled polymers enables the strategic implementation of desired material properties, such as charge transfer, foldability, and information storage capabilities. However, current methods of obtaining discrete sequence control have generated a limited number of available synthetic polymer backbones. Intuitive monomer design that unionizes the selected sequence of the polymer through supramolecular assembly can achieve previously unattainable polymer architectures possessing sequence definition. Herein, two distinct methods of monomer design to achieve controlled sequence in structurally diverse polymers will be discussed: 1) the design of steric and electronically-governed cyclophanes capable of ring-opening metathesis polymerization[1] and 2) the solid-state engineering of co-crystalline solids capable of collapse through pressure-induced polymerization into sp^3-hybridized structures.[2,3] Both monomer design options provide distinct avenues of reactivity to form alternating copolymers.



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[3] *Chem. Sci.* **2020**, *11*, 11419-11424.

DETERMINATION OF ENDOCYCLIC CHIRALITY EFFECTS ON CONCAVE SCAFFOLDS FOR PROTEIN SURFACE RECOGNITION

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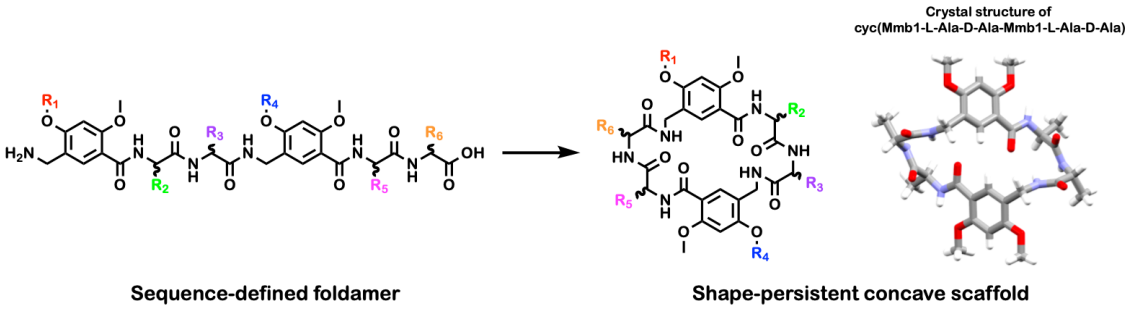
Medicinal chemists use small, drug-like molecules to target proteins that contain a deep binding pocket. However, it is estimated that only ~22% of the human proteome is "druggable",[1] leaving many proteins without a pocket to be understudied and undrugged. We have designed conformationally tunable, concave macrocycles with functionalization opportunities to be used to target convex protein surfaces. A series of cyclic foldamers with varying chirality and the general structure cyc(Mmb-Xaa-Xaa-Mmb-Xaa-Xaa), where Xaa is any alpha amino acid and Mmb, 2,4-dialkoxy-*meta*-aminomethylbenzoic acid is a previously reported peptidomimetic,[2] was synthesized. Solid-phase peptide synthesis yielded linear oligoamide chains, followed by solution-phase cyclization. Nuclear Magnetic Resonance and Circular Dichroism were used to assess macrocycle conformation in solution, and X-ray crystallography allowed for solid-state structural analysis. A comparison of six stereoisomers of cyc(Mmb-Ala-Ala-Mmb-Ala-Ala) revealed drastic conformational changes due to the endocyclic stereocenter sequence. Structural data revealed that macrocycle conformation is unperturbed by functionalization of the Mmb residue at the exocyclic 4-position and to amino acid substitution. The introduction of lysine also conferred the cyclic scaffold water solubility. The determination of how endocyclic chirality and functionalization affect macrocycle folding is crucial towards the rational design of shape-persistent, concave scaffolds to target undruggable proteins.



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DEAROMATIVE SYNTHESIS OF ALTEMICIDIN

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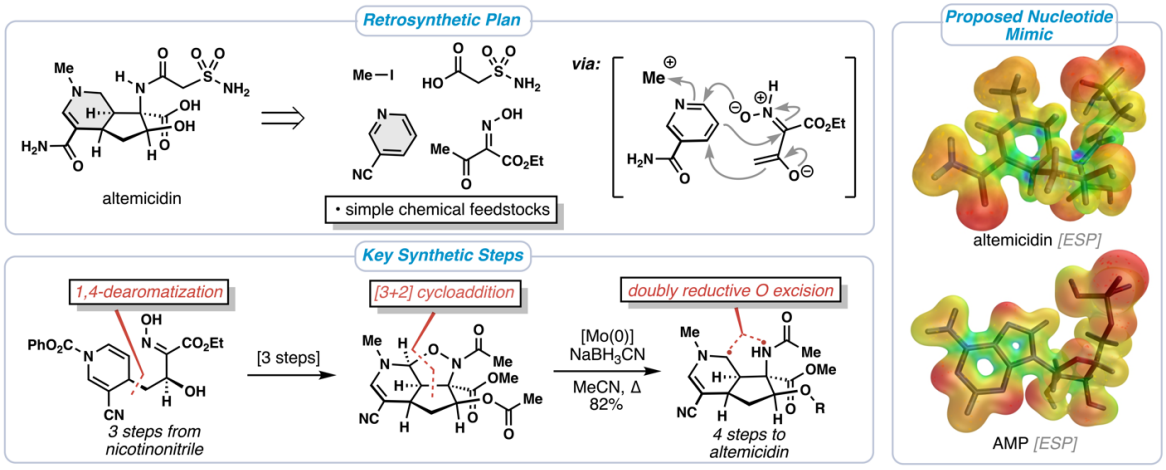
Altemicidin and related *Streptomyces*-derived monoterpene alkaloids are potent cytotoxins and demonstrate tRNA synthetase inhibitory properties. The highly-polar, dense azaindane core of altemicidin displays a congested α-amino acid motif and positions several polar atoms to mimic the electrostatic potential landscape of adenosine monophosphate (AMP). The amino stereocenter is further capped with a sulfonamide side chain which we suspect imitates the AMP phosphate. This work relates the synthetic process which culminated in a distinct and concise synthesis of altemicidin from simple chemical feedstocks. Key chemical findings include the exploitation of a dearomative pyridinium addition and dipolar cycloaddition sequence to stereospecifically install an α-tertiary amine stereocenter, and a chemoselective molybdenum-mediated double reduction to establish the fully functionalized azaindane structure with minimal redox manipulations.[1]



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Overview of Agricultural Discovery at FMC

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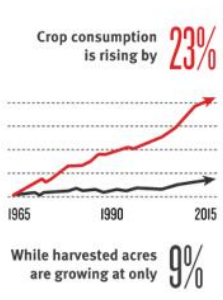
Rachel.slack@fmc.com

Plant diseases, harmful insects, and weeds can have a devastating impact on global food security, one of the greatest issues of the 21st century. Up to 40% of potential food production is lost every year to pests. These challenges can be managed using reliable and innovative crop protection solutions. This presentation will provide an overview of how modern crop protection discovery contributes new solutions to growers around the world to help them to raise production levels and improve the quality and sustainability of food.



Cyclic Amphipathic Peptides for Improved siRNA Delivery

Melissa L. Jagrosse,[†] Uday Baliga,[‡] Jade J. Welch,[†] David A. Dean*[‡] and Bradley L. Nilsson*,[†]

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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 previously demonstrated utilization of disulfide-constrained cyclic amphipathic cell-penetrating peptides (CAPs) for the delivery of siRNA[4] (**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].

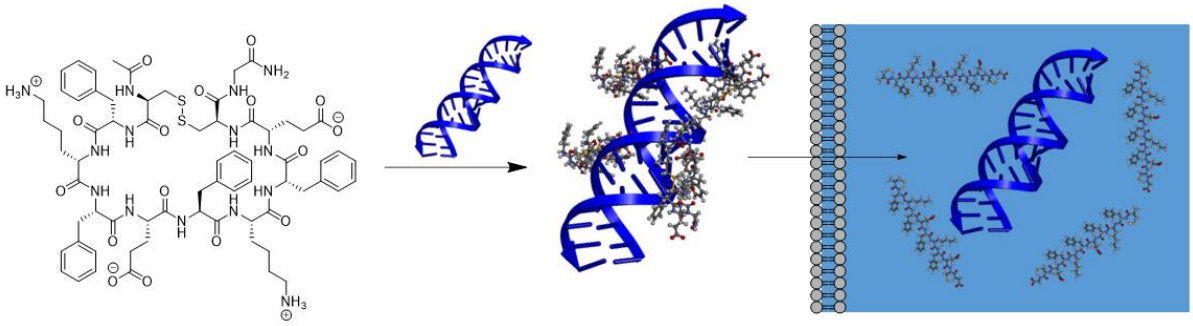

Figure 1. Schematic representation of CAP-siRNA delivery system.

In our current work, we synthesized an additional 8 peptide sequences for complexation with siRNA for determination of CAP-siRNA binding affinity, characterization of endocytic uptake mechanisms of these complexes, and determination of *in vitro* knockdown efficiency of occludin. Binding kinetics indicate that (1) cationic charge is essential for efficient binding with anionic oligonucleotides and (2) binding increases in the following trend for hydrophobic residues: His < Phe < Tyr < Trp. Complexation of our CAPs with FITC- siRNA allowed us to observe differences in siRNA translocation across the cell membrane and occludin knockdown *in vitro*, which can be correlated to CAP sequence and CAP-siRNA binding affinity. Utilization of small molecule inhibitors and targeted knockdown of essential endocytic pathway proteins allowed us to conclude that all of our CAP-siRNA nanoparticles are utilizing clathrin-mediated endocytosis, caveolin-mediated endocytosis, or a combination of both.

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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A STRATEGY TO REDUCE PYRIDINES TO PIPERIDINES IN COMPLEX, DRUG-LIKE MOLECULES

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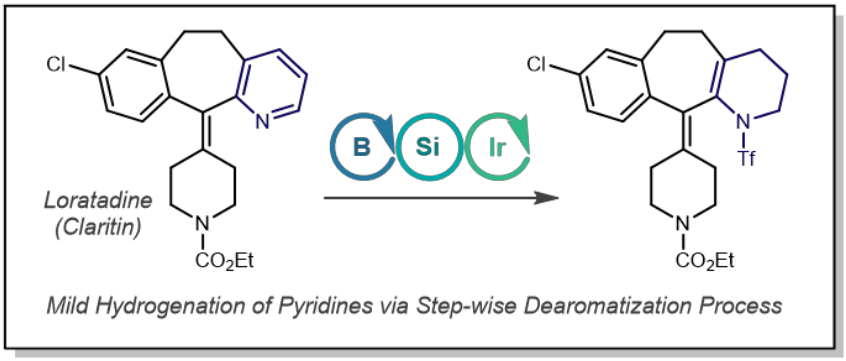
Dihydropyridines, tetrahydropyridines, and piperidines are valuable synthetic motifs found in pharmaceuticals, agrochemicals, and biologically active alkaloids. Considerable progress has been made to produce these heterocycles from pyridine precursors; however, despite this progress, current develop methods are limited to simple pyridines that may be mono-substituted or lack complex functionalities often found in medicinal chemistry drug libraries. Here, we report a general hydrogenation of complex pyridines to its piperidine counterpart. Our approach utilizes a combination of boron and iridium catalysis to achieve selective dearomatization and subsequent hydrogenation to chemoselectively hydrogenate complex, drug-like molecules. To showcase the versatility of the reaction, a variety of pharmaceuticals and drug-like fragments are shown.



Mild Hydrogenation of Pyridines via Step-wise Dearomatization Process

SYNTHESIS AND DESIGN OF BROAD-SPECTRUM ANTIVIRAL NUCLEOSIDES

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Nucleoside-based drugs are widely used as therapeutic agents for viral infections, having over twenty nucleoside-based therapeutics in the clinic and many undergoing evaluation in clinical trials. However, most nucleosides are not bioactive until they are metabolized to their 5'-triphosphate form through the activity of host cell enzymes. Despite the success of many nucleoside analogues, some compounds suffer from poor cellular permeability and metabolic activation. One strategy to address this issue is the utilization of 5'-phosphoramidate pronucleotide (or ProTide) that deliver the first 5'-monophosphate in masked form. This methodology has been successfully utilized in the blockbuster drug sofosbuvir, which is used for treatment of a hepatitis C. Our laboratory has utilized a similar strategy to afford the metabolic activation of 3′,4′-didehydro-cytidine (ddhC) to 3′,4′-didehydro-cytidine-5′-triphosphate (ddhCTP), which is a broad-spectrum antiviral nucleotide.[1] Our work to develop additional ddhC ProTides will be presented. In related work in response to the COVID-19 pandemic, the antiviral ProTide remdesivir has received emergency approval to treat SARS-CoV-2. This poster will highlight our efforts to synthesize RNA containing this antiviral nucleotide for mechanistic biochemical studies.[2] Collectivity, this work contributes to our understanding of the structure-activity relationship in nucleoside-based compounds, thus aiding the development of potent and effective antiviral agents.

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2 Moorthy, R., Kennelly, S. A., Rodriguez, D. J., Harki, D. A. *RSC Adv.* **2021**, *11*, 31373.

DESIGN, SYNTHESIS, AND EVALUATION OF NOVEL MEK4 CHEMICAL PROBES

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Ubiquitous across most organisms, the mitogen-activated protein kinase (MAPK) pathways are responsible for essential cellular processes such as growth, differentiation, and apoptosis. Because of their central role, dysregulation can lead to a myriad of debilitating diseases. Key to the MAPK signaling pathways is the MEK family of seven kinases. Of these, MEK1/2 were the first to be discovered and thoroughly studied, giving rise to four FDA-approved MEK1/2 inhibitors. However, there has been little investigation into the rest of the MEK family, despite the high clinical relevance.[1] In particular, high levels of MEK4 have been observed in conjunction with high mortality cancers.[2] While the involvement of MEK4 in cancer progression is now more heavily studied, many of the molecular mechanisms remain unknown. To date, a handful of MEK4 inhibitors have been reported in the literature, with our preliminary report showcasing one of the most potent and selective inhibitors.[3] We believe further refinement of our MEK4 inhibitors will allow us to better interrogate the role of MEK4 within the context of cancers. Herein, we describe progress towards the development of novel probe compounds to provide insights into the roles of MEK4.

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Reductively Generated Cobalt Hydride Enabled Alkene Hydrofunctionalization

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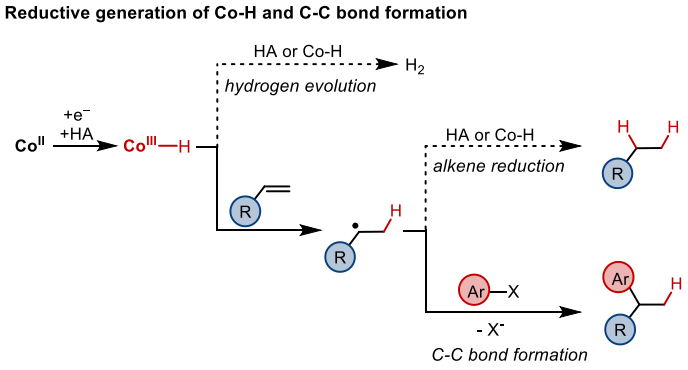
Transition metal hydride (M-H) can engage in hydrogen atom transfer (HAT) and hydrogen evolution reaction (HER).[1] The previous reactivity has found applications in the functionalization of unsaturated C-C, C-O and C-N bonds.[2] In particular, Co-H species are extensively studied in the hydrofunctionalization of alkenes through HAT.[3] Existing methods to generate Co-H relies on the use of superstoichiometric amount of oxidant as well as hydride source such as silanes. This inevitably leads to a limited substrate scope and poor atom economy. Here we report a reductive method to generate Co(salen)-H species, which is further harnessed in a cathodically coupled electrolysis to enable the hydroarylation of alkenes. This method significantly simplifies the traditional reaction system. Spectroscopic evidence supports the reductive generation of Co-H. Furthermore, electroanalytical studies provide kinetic and thermodynamic evidence of Co-H generation and insights into its reactivity.



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Optimization of a cinnoline scaffold against *Plasmodium falciparum*

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Malaria is a prevalent and dangerous infectious disease, affecting millions every year. The current recommended therapeutic treatment of Artemisinin Combination Therapy (ACT) consists of artemisinin paired with other antimalarial drugs like lumefantrine or piperaquine. However, ACT has shown increased instances of resistance to *Plasmodium falciparum* necessitating the need for continued drug discovery efforts. The target product profile for malaria calls for the development of a single dose, orally efficacious drug, with an excellent selectivity profile.

Sequencing the *Plasmodium falciparum* parasite genome has revealed that kinases are expressed throughout every stage of the life cycle. Given this, a lead repurposing strategy starting with the clinically approved drug, Lapatinib, will be utilized. A scaffold hop led to the identification of the 4-aminocinnolines which were potent against *P. falciparum*. Previous work focused on the optimization of this chemotype for *Trypanosoma brucei*, the causative agent of human African trypanosomiasis. Building on this, the main goals of this scaffold are displaying potent activity with improved physicochemical and ADME parameters. Further, we will describe our efforts to understand the molecular mechanism of action of this series.

PHOTOCHEMICALLY-MEDIATED POLYMERIZATION OF AROMATICS TOWARD NANOTHREAD FORMATION

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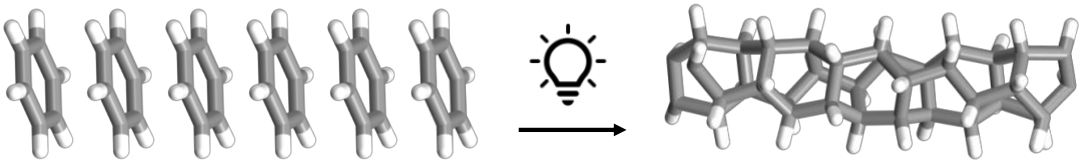
The pressure-induced polymerization of aromatic monomers can form crystalline sp^3-hybridized polymers known as nanothreads. Nanothread formation is guided through the collapse of molecules in sequential solid-state [4+2] cycloadditions observed at high pressures (23+ GPa), limiting the scalability and processibility for industrial synthesis. Recent work has shown that upon the addition of heat, monomers can react at lower pressures. Similar to providing a reduced threshold for a thermodynamically driven pathway, broadband UV exposure to monomers in the solid-state would facilitate a reduced photochemical barrier to cycloadditions forbidden by thermodynamically driven orbital symmetry (ex: [4+4] and [2+2]). Herein, the formation of nanothreads from monomers both enabling and circumventing photochemically-driven cycloadditions will be discussed as compared to their thermodynamically driven polymer products. Polymers derived from monomers that favor [4+4] and [2+2] pathways have illustrated similar spectroscopic characteristics and crystallinity as their thermodynamically driven products.



Aromatic monomer Resulting polymer

DEPOLYMERIZATION OF HYDROXYLATED POLYMERS VIA LIGHT-DRIVEN C–C BOND CLEAVAGE

Suong Nguyen[1], James Cox[1], Elizabeth McLoughlin[1], Lydia Fries[1], Brett Fors[2], Robert Knowles[1]*

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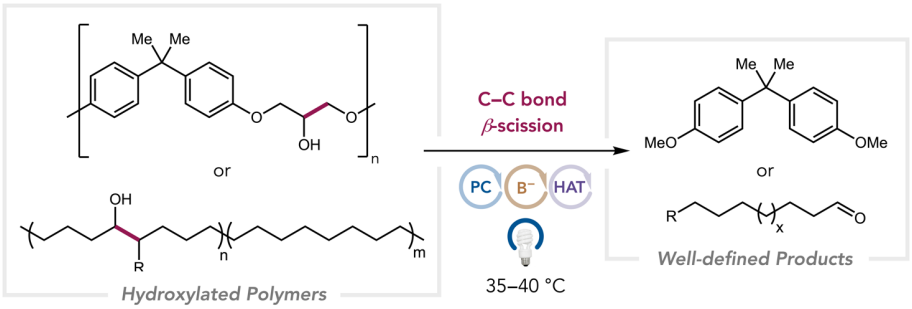
We present a new photocatalytic method to cleave unactivated aliphatic C−C bonds in macromolecules. This redox-neutral method, which operates near ambient temperature and consumes only visible photons, successfully mediated substantial to complete degradation of lignin biomass, commercial phenoxy resin, novel degradable-by-design hydroxylated polyolefin derivatives, and epoxy thermosets. Proton-coupled electron transfer (PCET) activation of hydroxyl groups periodically spaced along the polymer backbone furnishes reactive alkoxy radicals that promote chain fragmentation through C–C bond β-scission. Depolymerization produces well-defined and isolable product mixtures that are readily diversified to polycondensation monomers. In addition to controlling depolymerization, the hydroxyl group modulates the thermomechanical properties of the polyethylene derivatives, yielding myriad materials for diverse consumer applications. This new approach to polymer recycling has the potential to establish new links within a circular polymer economy and influence the development of next-generation polymers that are degradable by design, thereby helping to address global concerns about plastic pollution and sustainability.



Depolymerization of hydroxylated polymers enabled by light-driven O–H PCET

• compatible with insoluble polymers • no stoichiometric reagents

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STRUCTURE-ACTIVITY RELATIONSHIP OF STING COMPOUNDS

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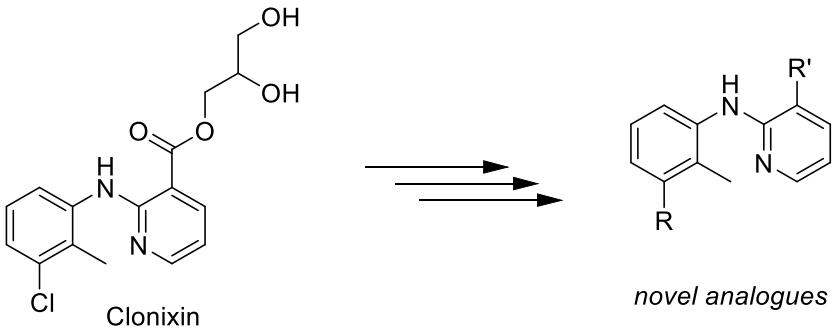
Stimulator of Interferon Genes (STING) is an important transmembrane protein involved in innate immune response to foreign or damaged DNA or RNA in a cell's cytosol. When a cell is infected with an intracellular pathogen, STING acts as a sensor that triggers the production of type I interferon, which 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.



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

CARBENE REACTIVITY FROM ALKYL AND ARYL ALDEHYDES

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In organic synthesis, several important classes of chemical reactivity are uniquely mediated by carbenes and carbenoids, including metathesis, rearrangement, small ring formation, and insertion into strong σ-bonds. However, reagents with high entropic or enthalpic driving forces, including explosive (diazo) or unstable (gem-dihalo) compounds, are often employed to access carbene intermediates. This poster illustrates how common aldehydes are readily converted to carbenes via their stable a-acyloxy halides. This strategy enables safe and novel reactivity of non-stabilized carbenes from alkyl, aryl, and formyl aldehydes via zinc carbenoids through >10 reaction classes. Notably, varying the metal catalyst ($FeCl_2$, $CoCl_2$, CuCl), allowed for the chemoselective carbene additions to σ- and π-bonds

TOTAL SYNTHESIS OF STRASSERIOLIDES A AND B, ANTIMALARIAL NATURAL PRODUCTS

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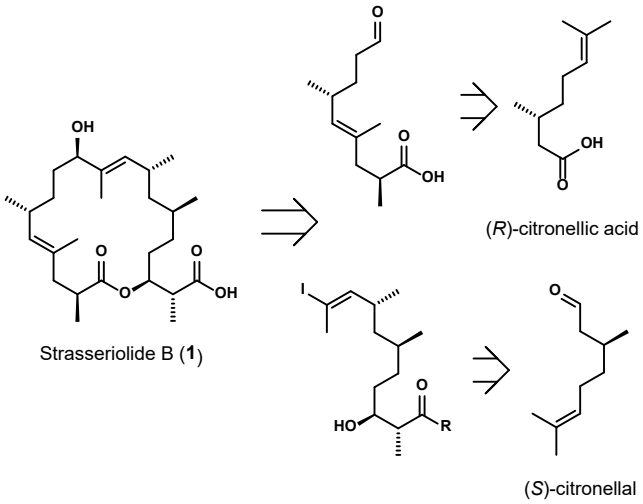
Strasseriolide B, a recently isolated macrolide natural product, demonstrates potent inhibitory activity towards the *P. falciparum* parasite, effectively reducing the effects of human malaria.[2] We have recently completed the total synthesis of this natural product and the related strasseriolide A using a convergent synthesis.[1] A brief summary of the synthesis of the western fragment and a detailed summary of the synthesis of the eastern fragment will be presented. Key steps include an enantioselective 1,4-conjugate addition to set the *anti* 1,3-dimethyl array and an intramolecular NHK macrocyclization event to forge the final carbon-carbon bond of the natural product skeleton. A completed total synthesis was achieved in 15 steps longest linear sequence.



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LAGUNAMIDE FAMILY: TOTAL SYNTHESIS EFFORTS, FINAL STRUCTURAL DETERMINATION, BIOLOGICAL EVALUATION, AND NEW FAMILY IDENTIFICATION.

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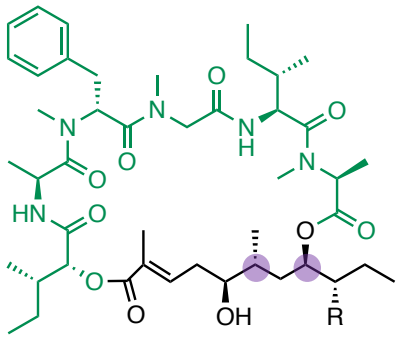
In 2011 Tan and co-workers isolated lagunamide C (LagC), a depsipeptide from the cyanobacterium *Lyngbya majsucle* from the western lagoon of Pulau Hantu Besar, Singapore. It was shown to possess potent cytotoxicity against a panel of cancer cell lines: lymphoma (P388, IC_{50} 24.4 nM), lung (A549, IC_{50} 2.4 nM), prostate (PC3, IC_{50} 2.6 nM), colon (HCT8, IC_{50} 2.1 nM), and ovarian (SK-OV3, IC_{50} 4.5 nM). In addition to its low nanomolar cytotoxicity, lagunamide C was also shown to display significant antimalarial activity with an IC_{50} of 0.29 μM towards Plasmodium falciparum and also possess weak anti-swarming activity towards Pseudomonas aeruginosa PA01 when screened at 100 ppm. To date, no total synthesis of this potent bioactive agent has been reported, while the total synthesis of A and B have. The polyketide unit within LagC possess an extra methylene unit, which prevents the use of the routes to the polyketide units of LagA/B. Furthermore, there is structural ambiguity about two of the four stereocenters within the polyketide of LagC, limiting the possible applications of this potent bioactive agent. As such, any total synthesis campaign of LagC must also allow for structural modification of these stereocenters for final determination of its stereochemistry. Our laboratory has developed a modular route to access the assumed possible diastereomers of the polyketide unit, this approach will allow for the structural determination and also give rise to invaluable SAR analysis for mode of action studies. The synthetic studies gaining access to the polyketide, as well as the polypeptide backbone of LagC will be discussed, and potentially the first total synthesis and final structural elucidation of LagC. Biological evaluation of key intermediates of the polyketide construction will be disclosed and their unexpected cytotoxicity, which has led to a new proposed mode of action for LagC and its family of natural products. Furthermore, based upon the recent discovery of LagD, a methyl truncate variant of LagA, we have undergone a synthesis of what we propose to be the natural product LagE based on the same methyl truncation. Synthetic efforts and biological identification of this proposed natural product will also be presented.



R = Me; LagC
R = H; proposed LagE
● = Ambiguous stereocenters

UREATES AND STERICALLY ATYPICAL PHOSPHINES AS LIGAND PLATFORMS FOR REGIODIVERGENT SYNTHESIS OF 2- AND 3-SUBSTITUTED INDOLINES

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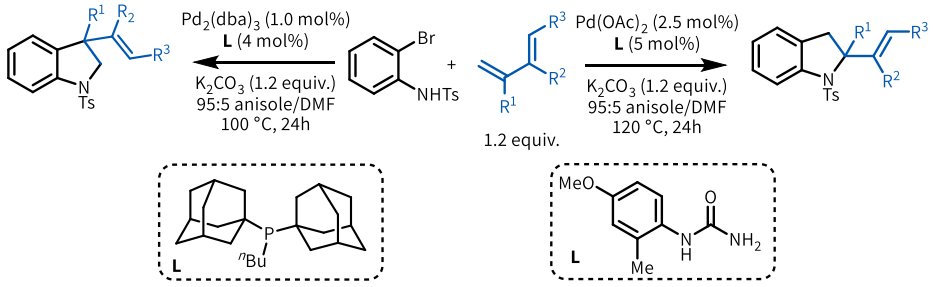
Palladium catalyzed heteroannulation is a versatile method which allows access to a variety of heterocycles. Nitrogen containing heterocycles, particularly, indolines are present in many biologically relevant and naturally occurring molecules such as vitamins, nucleic acids, antibiotics, and other essential molecules. Majority of previously reported methodologies focus on the synthesis of 2-substituted indolines and often require expensive, air or light sensitive starting materials. In addition, these methodologies offer a limited scope sensitive to steric bulk and functional groups. We report the first example of ligand-controlled site selectivity to generate 2 and 3-substituted indolines from of *N*-tosyl-*o*-bromoanilines with 1,3-dienes. Our approach addresses previous shortcomings by using bench stable and relatively cheap bromoanilines. Furthermore, we have expanded the scope of this chemistry to engage sensitive and sterically demanding substrates while reducing both catalyst and ligand loading as well as equivalents of the π-coupling partner.



Site Selective Phosphorylation with a Pyrophosphate Reagent

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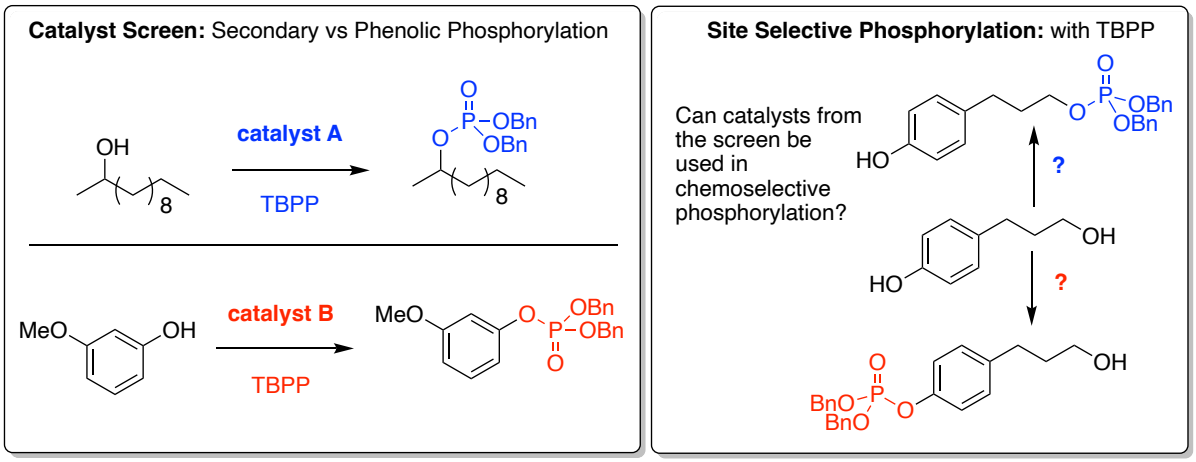
The selective functionalization of alcohols is a valuable approach in targeted oriented synthesis, often resulting in a more efficient process. Due to the prevalence and unique chemistry of phosphates, the site selective phosphorylation of alcohols allows access to molecules that are natural products, pro-drugs or novel materials. Synthetic strategies that enable the rapid discovery of catalysts that activate a particular alcohol are desirable. We will discuss a screen for catalysts that phosphorylate 2-dodecanol (model secondary alcohol) versus a 3-methoxyphenol (model phenol) with tetrabenzylpyrophosphate (TBPP). Catalysts identified as selective for either type of alcohol were further optimized for the chemoselective phosphorylation of a diol.



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

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

Meenakshi Sharma[†], Reece M. Fritz[†], Amitava Choudhury[†], Pericles Stavropoulos[*,†]
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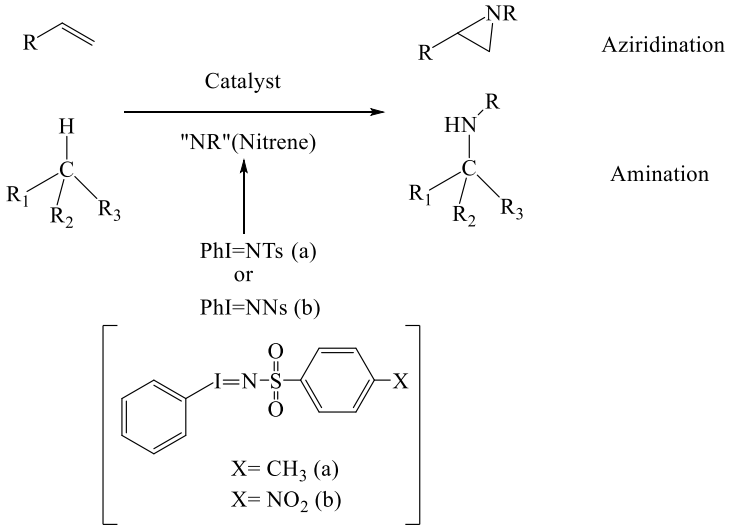
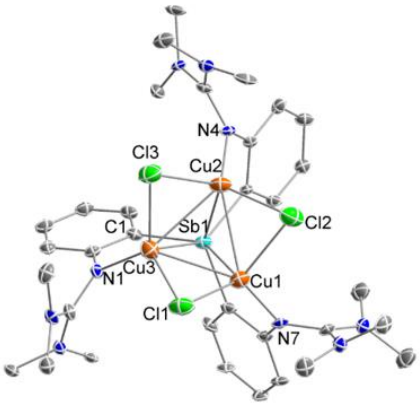
Transition-metal catalyst frameworks supported by tripodal [TMG_3trphen] ligands mediate nitrene transfer from nitrogen sources such as PhI=NR to a diverse group of aliphatic and aromatic hydrocarbons and olefins. These reactions are categorized as amination and aziridination reactions. Novel tripodal 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_3trphenSb]Cu_3Cl_3 and [TMG_3trphenBi]Cu_3Cl_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_3trphenSb]Cu_3Cl_3

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

Enantioselective Protio-Semipinacol Rearrangement Reactions Enabled by Dual-Hydrogen-Bond Donor and Brønsted Acid Co-Catalysis

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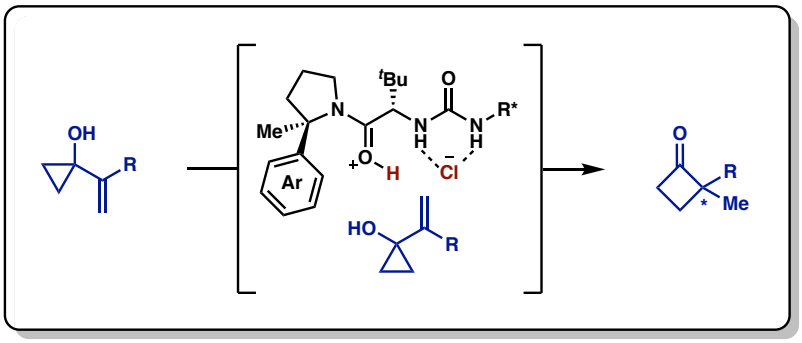
Synthetic methods employing chiral Brønsted acids have enabled access to a variety of enantioenriched products. Despite significant advances in design and preparation of chiral acids with increased acidity, activation of less basic substrate classes – such as those containing carbonyl groups and olefins – remains a challenge. To overcome some of the current limitations, our group has identified an alternative approach to asymmetric catalysis with Brønsted acids using achiral Brønsted acids in combination with chiral dual-hydrogen-bond donors (HBDs). We have identified that catalytic quantities of hydrochloric acid in the presence of an HBD facilitate an enantioselective semipinacol rearrangement reaction of tertiary cyclopropanols. The co-catalytic strategy delivers cyclobutanone products with alpha-quaternary stereocenters in high levels of enantioenrichment. This research marks a rare example of a protio-semipinacol ring-expansion process and provides enantioenriched cyclobutanone adducts valuable as end products or synthetic building blocks.



Exploiting thioether reactivity for labeling mycobacterial glycans

Stephanie R. Smelyansky[†,‡], Victoria M. Marando[†], Laura L. Kiessling[†*]

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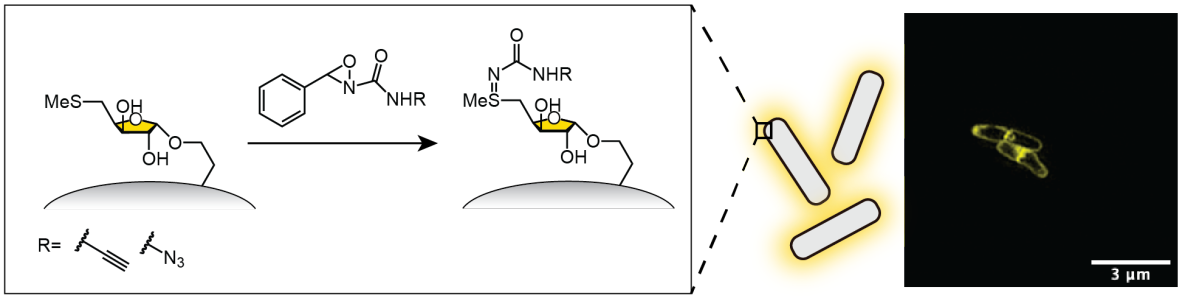
Many bacterial cell wall glycans are potent virulence factors and drivers of infectious disease. For example, in *Mycobacterium tuberculosis* (*Mtb*), the etiological agent of tuberculosis, cell wall glycans play key roles in mediating infection of host tissues and modulating the host immune response. However, glycans often lack reactive functional group diversity, precluding the use of standard bioconjugation strategies. This has limited our ability to study the structure and function of biologically relevant glycans. Methylthioxylofuranose (MTX) is a monosaccharide appended to an antigenic glycolipid in the *Mtb* cell wall that contains a unique thioether moiety, which can be exploited for selective bioconjugation. Previously, oxaziridine reagents have been used to label methionine thioethers in proteins, but this chemistry has yet to be applied to glycans. We expanded the use of oxaziridine bioconjugation to glycans by labeling the MTX monosaccharide in *Mtb*. We have demonstrated that oxaziridines can be used to label MTX containing glycans *in vitro*, as well as to label and visualize the *Mtb* cell wall *in vivo*. These studies will enable future work investigating the role of key *Mtb* cell wall glycans in pathogenesis and by leveraging the selective reactivity of thioethers have expanded the repertoire of glycan bioconjugation strategies.



Kinetic Probes of the Origin of Activity in MOF-Based C–H Oxidation Catalysis

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Metal-organic framework (MOF)-based catalysts have garnered increasing attention as platforms for C–H oxidation[1]. While several experimental strategies have been advanced for synthetic catalyst modification, few in operando methods are available to evaluate the origin of catalytic activity in these reactions.[2] Here, we performed benzylic oxidation and olefin epoxidation of organic small molecules and evaluated the role of MOFs in these reactions using kinetic experiments.[3] We provided evidence for an Fe-based MOF ($Fe_2(dotpdc^F)\cdot 2CH_3CN$) that is intimately involved in the C–H activation step and a Cu_2-based MOF (MIL-125-Cu_2O_2) that functions only as an initiator for solution-phase aldehyde autoxidation (**Figure 1**). For iron catalyzed oxidation with *2-tert*-butylsulfonyl iodosylbenzene, the disparity between the inter- and intramolecular kinetic isotope effects (KIEs) obtained for Fe-MOFs and $Fe(OTf)_2$ indicates that the structure of the catalyst is involved in the C–H cleavage transition state. However, the identical KIEs and diastereoselectivities obtained using Cu-MOF, $CoCl_2$, and $CuCl_2$ suggest that these additives only initiate autoxidation and are not involved in the turnover limiting transition state. We anticipate that the experimental strategy developed here will be helpful in clarifying the role of MOFs in C–H oxidation reactions.

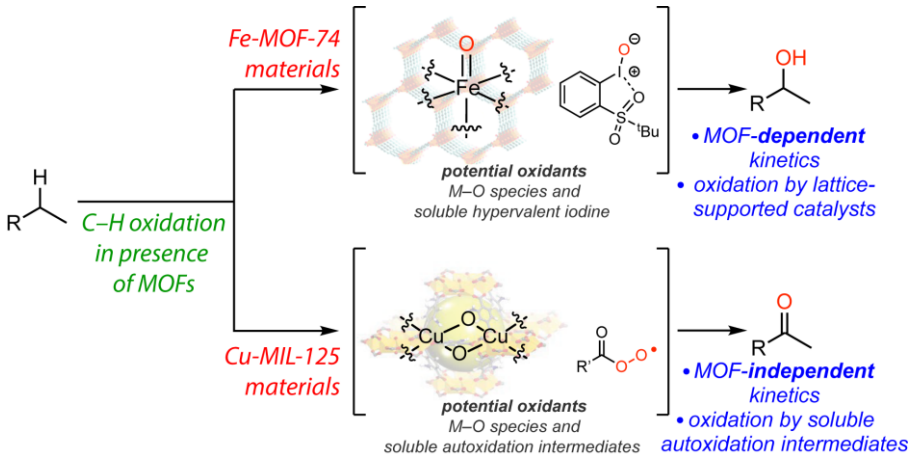

Figure 1. Analysis of deuterium kinetic isotope effects (KIEs) and olefin epoxidation diastereoselectivity as kinetic probes to differentiate lattice-confined and solution-phase oxidation activity identify lattice-supported Fe sites as the source of C–H oxidation in Fe-MOF-74-based materials and soluble autoxidation intermediates, not Cu sites, as the source of oxidation in MIL-125 based Cu materials.

[1]Liu, M.; Wu, J.; Hou, H. *Chem. Eur. J.* **2019,** *25*, 2935–2948.
[2]Gao, W.-Y.; Cardenal, A. D.; Wang, C.-H.; Powers, D. C. *Chem. Eur. J.* **2019,** *25*, 3465–3476.
[3]Sur, A.; Jernigan, N. B.; Powers, D. C. *ACS Catal.* **2022,** *12*, 3858-3867.

A COMPUTATIONAL AND EXPERIMENTAL APPROACH TO DESIGNING NOVEL BLUE ORGANIC LIGHT EMITTING DIODES BASED ON THE BISBENZOXAZOLE CORE

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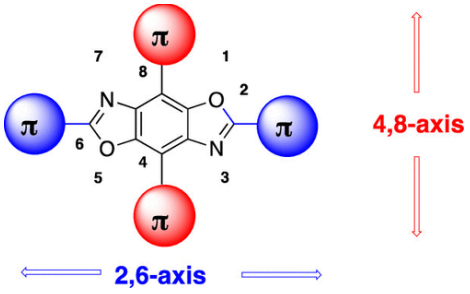
Organic light emitting diodes (OLEDs) are attractive alternatives to LEDs due to their tunability, flexibility and lower processing costs. There are several examples of known stable red and green OLEDs. However, blue OLEDs suffer from low stability and degrade at a much faster rate due to higher heats generated by blue fluorescence and large S0-S1 energy gaps (~ 3.0 eV). Bisbenzoxazole (BBO) cores have been shown to be highly stable and have four sites, along the 2,6 and 4,8 axes, that are readily available for addition of functional groups which can be exploited to tune their opto-electronic properties. We have designed a series of blue emitting BBO cruciforms, consisting of a BBO core and aromatic functional groups along the 2,6 and 4,8 axes. The aromatic groups have been functionalized with alkyl chains to improve their solubility. The resulting cruciform molecules have shown deep blue emission (< 452 nm) in solution as well as in solution-processed devices. The molecules have also been studied computationally at the mpw3PBE/sv level which has predicted their ground and excited state properties including their structures, HOMO levels, HOMO-LUMO gaps, and absorption profiles.



(1) Wheeler, D. L.; Tannir, S.; Smith, E.; Tomlinson, A. L.; Jeffries-EL, M. A Computational and Experimental Investigation of Deep-Blue Light-Emitting Tetraaryl-Benzobis[1,2-d:4,5-d']Oxazoles. *Mater. Adv.* **2022**.

SYNTHESIS OF 3,4,5-TRISUBSTITUTED 1,2,4 TRIAZOLES AS G-PROTEIN BIASED KAPPA OPIOID RECEPTOR AGONISTS

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Opioid addiction presents a major public health crisis in the US. The crisis is caused by a variety of factors including over-prescription of pain-relieving drugs, which are often addictive, and insufficient methods of treating opioid use disorder. One method to address this problem is to develop new pharmaceuticals that untangle the pain-relieving properties of small molecule analgesics from undesirable side-effects. The kappa opioid receptor (KOR) is a promising target for the development of new pain-relieving therapeutics due to its strong pain-killing potential along with a non-addictive side effect profile. In particular, G-protein biased agonists, in which an agonist selectively activates the G-protein signaling pathway over the alternative β-arrestin signaling pathway, may provide desired pain relief without undesirable effects such as sedation and dysphoria.[1] Triazole 1.1 was identified as a lead KOR selective, G-protein biased agonist through high throughput screening and structure-activity relationship (SAR) studies performed in our lab, but maintains metabolic liabilities.[2] This presentation will focus on novel 3,4,5-trisubsituted 1,2,4 triazoles that maintain the desired biased agonist characteristics and address issues with metabolic stability.

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[1] Brust, T. B.; Morgenwekc, J.; Kim, S. A.; Rose, J. H.; Locke, J. L.; Schmid, C. L.; Zhou, L.; Stahl, E. L.; Cameron, M. D.; Scarry, S. M.; Aubé, J.; Jones, S. R.; Martin, T. J.; Bohn, L. M., Biased Agonists of the Kappa Opioid Receptor Suppress Pain and Itch Without Causing Sedation and Dysphoria. *Sci. Signal* **2019**, *9*. (456), ra117-ra117.

[2] Frankowski, K. J.; Hedrick, M. P.; Gosalia, P.; Li, K.; Shi, S.; Whipple, D.; Ghosh, P.; Prisinzano, T. E.; Schoenen, F. J.; Su, Y.; Vasile, S.; Sergienko, E.; Gray, W.; Hariharan, S.; Milan, L.; Heynen-Genel, S.; Mangravita-Novo, A.; Vicchiarelli, M.; Smith, L. H.; Streicher, J. M.; Caron, M. G.; Barak, L. S.; Bohn, L. M.; Chung, T. D.; Aubé, J., Discovery of Small Molecule Kappa Opioid Receptor Agonist and Antagonist Chemotypes through a HTS and Hit Refinement Strategy. *ACS Chem. Neurosci*. **2012**, *3*, 221-236.

WICKRAMA-ARACHCHI

Asymmetric Synthesis of γ-Borylated Amines via Rh-Catalyzed Hydroboration of Allylamine Derivatives

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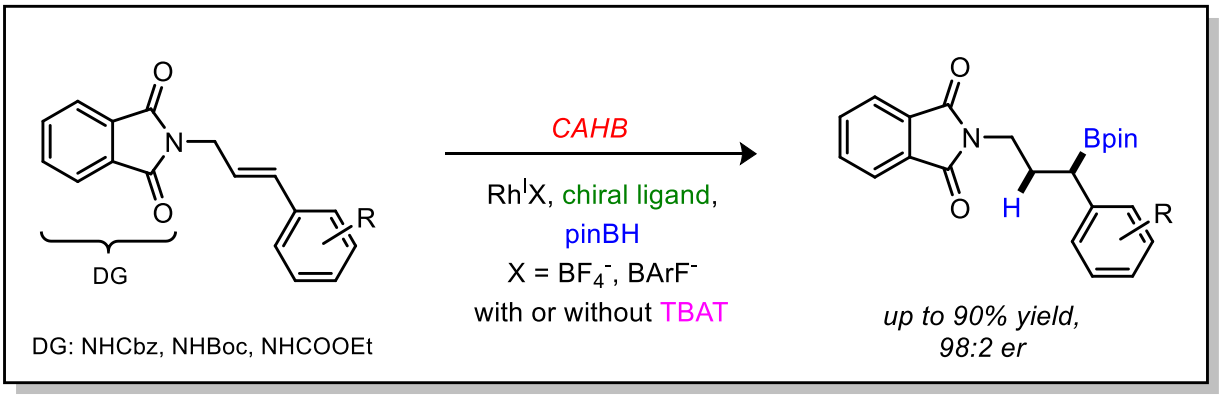
The Takacs group has explored different dimensions of Catalytic Asymmetric Hydroboration (CAHB) reaction mainly focusing on variety of amide, oxime ether and phosphonate directing groups. Inspired by the results obtained with BINOL- and TADDOL- derived chiral catalysts along with pinacolborane, we explored the potential of acyclic *N*-acyl allylamines as substrates for direct-hydroboration to prepare chiral amine derivatives bearing γ-boronic ester functionality, yields up to 90% with 98:2 enantioselectivity (Scheme 1). The major enantiomer obtained is independent of starting alkene geometry, revealing that rhodium-catalyzed *cis/trans*-alkene isomerization occurs prior to hydroboration. In this poster, we will discuss the generation of active catalysts starting from different pre-catalysts. We find that the counterion (e.g., BF_4^-, $BArF^-$) plays an important role in the reaction. Furthermore, we find that addition of an external fluoride source (e.g., tetrabutylammonium difluorotriphenylsilicate (TBAT)) significantly impacts the reaction rate. These and other observations lead us to consider a novel catalytic cycle initiated by a rhodium(I)-hydride complex. Finally, the stereospecific transformations of the newly generated C–B bond to access drug candidates will be highlighted to demonstrate the utility of these chiral synthons.



Scheme 1: General CAHB reaction conditions with different directing groups, and different methods to access CAHB major product.

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BIOORGANIC INVESTIGATION OF AMINO SUGAR TIGOGENYL SAPONINS

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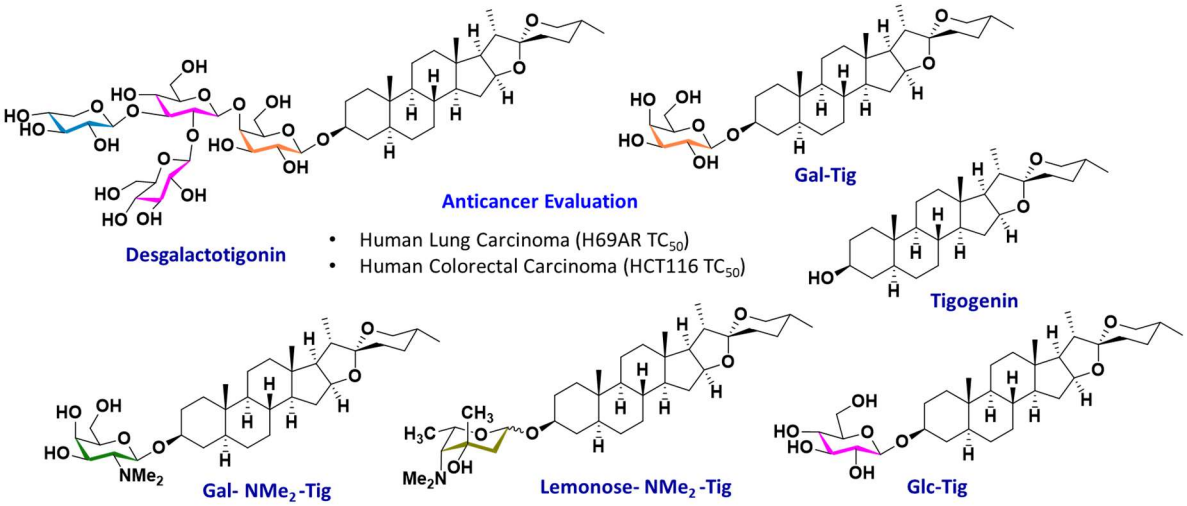
Patients treated with anthracycline chemotherapeutics are limited by dose-dependent cardiotoxicity on the cumulative amount of anthracyclines administered. The quinoline aglycone can generate reactive oxygen species (ROS) that are detrimental to cardiomyocytes, inducing cardiotoxicity side effects. Therefore, novel chemotherapeutics are needed that are not only potent anticancer agents, but also lack cardiotoxicity. Saponins, such as Desgalactotigonin (DGT), are known to exhibit cytotoxicity against various cancer cell lines. DGT is a glycosteroid composed of aglycone Tigogenin and lycotetraose (O-β-D-glucopyranosyl-(1→2)-O-[β-D-xylopyranosyl-(1→3)]-O-β-D-glucopyranosyl-(1→4)-D-galactose). Since the Codée group has shown that *N, N* dimethylated anthracycline derivatives exhibited reduced cardiotoxicity compared to the parent anthracyclines, we proposed to synthesize the *N,N* dimethylated aminosugar saponins. Additionally, we hypothesized that an anthracycline derived glycan and Tigogenin hybrid saponin would embody an effective chemotherapeutic can eradicate anthracycline resistant cell lines, while lacking the cardiotoxic anthracycline aglycone. We propose to synthesize truncated tigogenyl saponins, an anthracycline-saponin hybrid and a simplified aminosugar saponin. To further elucidate the structure-activity relationship between DGT, tigogenin, truncated congeners, aminosugar saponin, and anthracycline-saponin hybrid will be synthesized and assessed for the minimum anticancer pharmacophore.



SITE-SELECTIVE BENZYLIC C–H THIOLATION AS AN ENABLING TOOL FOR LATE-STAGE DIVERSIFICATION

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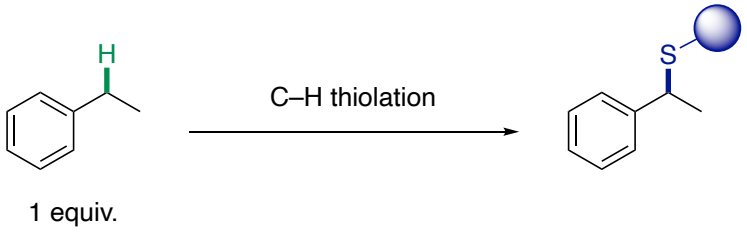
The direct, site-selective functionalization of C–H bonds that are ubiquitous in organic molecules is an ideal strategy for late-stage diversification. Benzylic C–H bonds are prevalent in complex molecules, however it can be challenging to functionalize these sites efficiently and chemoselectively with substrate as limiting reagent. In this poster, we report a method for site-selective benzylic C–H thiolation using a simple catalytic system under mild conditions. Notably, the reaction proceeds efficiently with substrate as limiting reagent in all cases. The reaction exhibits a broad substrate scope with high functional group tolerance, ideal for the late-stage functionalization of medicinally relevant molecules. The benzylic thioether is also easily elaborated through diverse substitution and cross-coupling reactions.



HIGH THROUGHPUT EXPERIMENTATION ENABLING DRUG DISCOVERY AT JANSSEN

Jordan Compton, Iulia Strambeanu*, Justin Diccianni, Bo Hao, Wei Liu, Zhicai Shi

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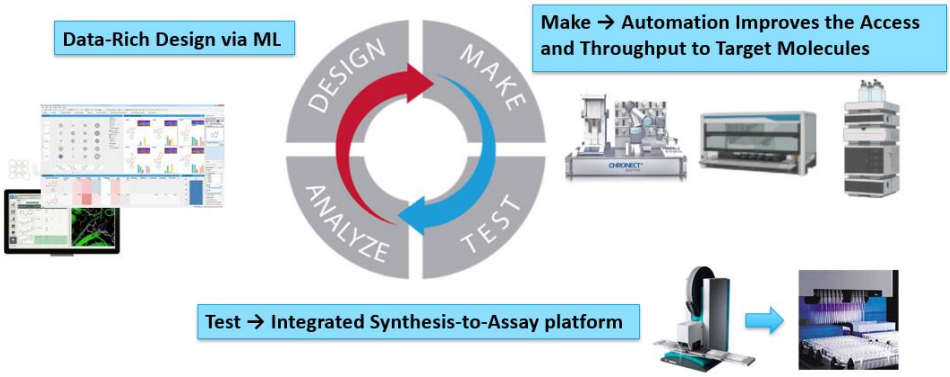

High Throughput Experimentation (HTE) has been established as a very effective technology in increasing productivity and cost-effectiveness in Pharma R&D over the past decade by enabling efficient access to complex molecular scaffolds. A combination of manual tools and automation are used to set up and run parallel reactions that use less material and generate more data on a rapid timescale relative to traditional reaction optimization. Overall, HTE technologies impact early discovery and process chemistry to accelerate drug development. Though HTE is not new to the pharmaceutical industry, in just the past two years Janssen has built a state-of-the-art, highly competitive laboratory and team to champion the identification, evaluation, implementation, and application of HTE capabilities to accelerate the portfolio across all Janssen Discovery Chemistry sites. Herein, we describe how this technology can enable more efficient Design-Make-Test-Analyze (DMTA) cycles in medicinal chemistry and how we approached building a state-of-the-art HTE group and laboratory at Janssen over the past 2 years. Our tactic in democratizing HTE within our Discovery Chemistry department and HTE impact examples will also be described.