

Poster Presentations Abstract Booklet



Introducing ReSOLVE™: A Transformational Tool for Computer-Aided Drug Design

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Although it has long been appreciated that the exclusion of high-energy water from the surface of a protein is the thermodynamic driving force of ligand binding, the development of a robust tool that can computationally describe this solvation has been elusive. With ReSOLVE™, Ventus has developed a tool which is able to create a high-resolution solvation map of all the relevant conformational states of a protein, which we call a hydrocophore, providing us with a powerful tool to deploy across all stages of pre-clinical drug discovery. This poster will describe how we use the hydrocophore for target identification, lead identification and lead optimization.

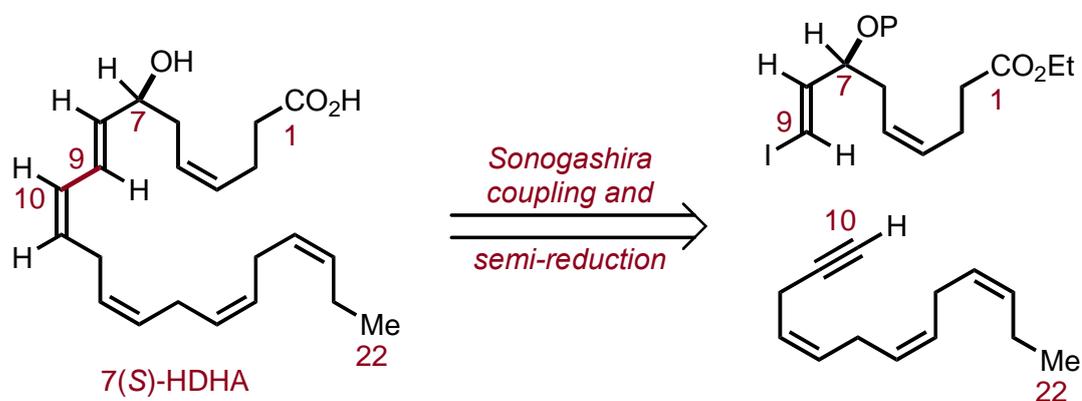
Enantioselective Synthesis of 7(S)-Hydroxydocosahexaenoic Acid

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The polyunsaturated fatty acid 7-hydroxydocosahexaenoic acid (7-HDHA) was recently identified as a possible endogenous ligand for peroxisome proliferator-activated receptor alpha (PPAR α) [1]. While this discovery presented an opportunity to gain further understanding of PPAR α 's mechanism of action and related diseases (Alzheimer's disease, cerebral ischemia, retina inflammation, etc.), the study of the interactions between 7-HDHA and PPAR α has been hampered by the high cost and limited supply of 7-HDHA. We report the first total synthesis 7-HDHA in the racemic form and the enantioselective synthesis of 7(S)-HDHA [2]. Both syntheses follow a convergent approach that unites the C1-C9 and C10-C22 fragments using Sonogashira coupling and Boland reduction as key steps. These syntheses enabled the unambiguous characterization of this natural product for the first time and helped establish 7(S)-HDHA as a high affinity ligand for PPAR α .



Scheme 1: Retrosynthetic Analysis of 7-HDHA

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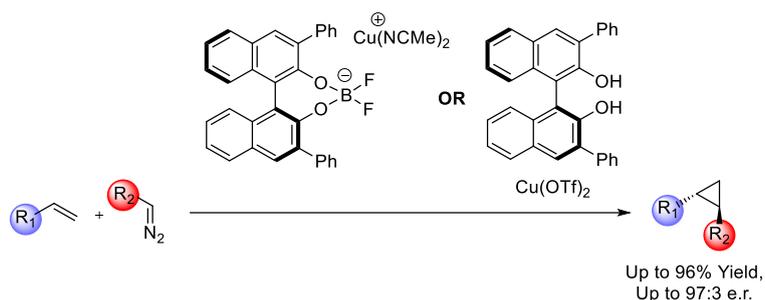
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Chiral Borate Counterions in Copper Catalysis: From Cautionary Tale to an Enantioselective Chiral Catalyst

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A new type of chiral counterion can be generated from (S)-Binol derivatives and a BF₄ source, mimicking chiral phosphoric acids while avoiding coordination to metal center and thus better insuring its role as a counterion. Initial attempts at cyclopropanation highlight the sensitive interaction between the counterion and the copper center. The structure of the catalyst appeared to completely change after the reaction and being exposed to traces of air. As a secondary finding, simple 3-3'-diphenyl-Binol can be used in asymmetric Cu(II) catalyzed cyclopropanation reaction.



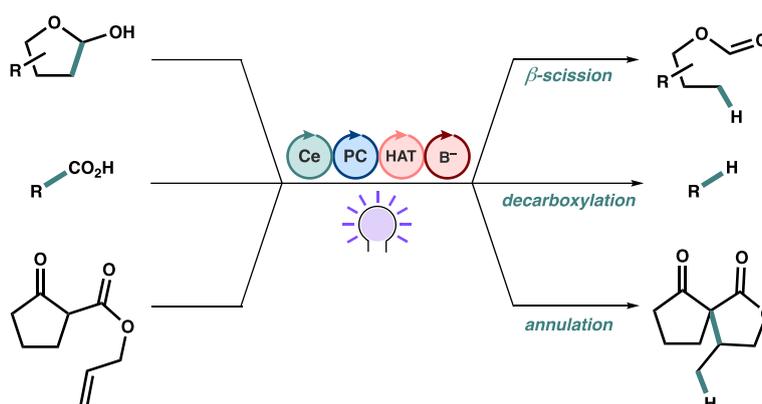
A Multicatalytic Cerium-Based Photoredox Platform for Redox Neutral Transformations

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New strategies for structural remodelling are highly sought after for the rapid construction of complex molecular scaffolds [1]. Recently, cerium-based photoredox platforms have shown the ability to generate high energy radical intermediates capable of delivering a wealth of reactivity [2–4]. A system comprised of cerium, a hydrogen atom transfer agent, base, and photocatalyst enables a variety of redox neutral transformations. Utilizing this system, we demonstrate fragmentations of lactols and cycloalkanols to the corresponding formate esters and ketones, decarboxylative hydrogenation, and both inter- and intramolecular hydroalkylation of alkenes from 1,3-dicarbonyls. The role of atomic chlorine in a proton-coupled electron transfer activation mode will be discussed.



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A concise and scalable synthesis of the natural product Koningic Acid

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The natural product koningic acid (KA) is a selective covalent inhibitor of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a critical node in the glycolysis pathway. While KA is available commercially, sources are limited and its cost becomes rapidly prohibitive beyond the milligram scale. The KA scaffold consists of an unsaturated ϵ -lactone system trans-fused to a 6-membered ring bearing an exocyclic epoxide. Prior work by Danishefsky and coworker described a multi-step synthesis of this natural product which permitted isolation of only milligram quantities of racemic material. As part of a research program probing the biological activity of KA and its derivatives, a practical and flexible synthetic route was desired. We have developed a new route that is operationally safer, scalable, and offers a five-step reduction in the previously reported longest linear sequence.

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Towards the synthesis of morphinan and *daphniphyllum* alkaloids

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The synthesis of 10-keto opiates is motivated by the pursuit of novel opioid κ -selective agonists [1] that offer comparable analgesic effects to their alkaloid precursors while limiting the risks of physical dependence [2]. While there have been multiple syntheses of oxycodone reported [3], there has been only one total synthesis of 10-keto-oxycodone to date [4]. Herein is an oxidative dearomatization approach to oxycodone and 10-keto-oxycodone, beginning from isovanillin.

There are over three dozen species of shrubs and trees within the *Daphniphyllum* genus from which over 320 alkaloids have been isolated, including daphenylline [5]. Unlike other alkaloids, daphenylline demonstrates little to no medicinal properties, having displayed IC₅₀ values >40 μ M against human tumor cell lines HL-60, SMMC-7721, A-549, SKBR-3 [6]. Thus, interest in this alkaloid is exclusively limited to the challenge-driven synthetic efforts. Progress towards the synthesis daphenylline invoking a key Ichikawa rearrangement will be presented.

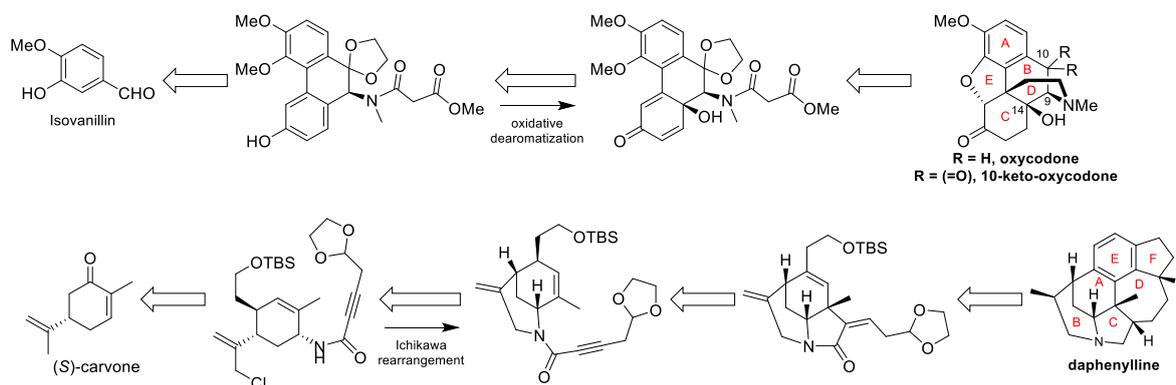


Figure: Retrosynthesis of oxycodone and 10-keto-oxycodone.

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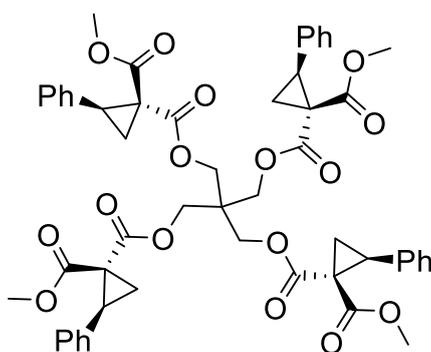
Donor-Acceptor Cyclopropane Based Dendrimer Synthesis

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Dendrimers have exploded in popularity due to their interesting properties such as biocompatibility, utilization for drug encapsulation, specific cellular targeting [1]. What has not been reported in the literature is a dendrimer with a donor-acceptor cyclopropane (DAC) motif. The reactions of DACs are well established and is still a developing field of inquiry. DACs have been shown to have increased reactivity toward soft nucleophiles and may undergo a variety of transformations such as ring expansion, rearrangements, and a multitude of cycloadditions [2]. These transformations only require a small amount of a Lewis acid. The utilization of these types of catalysts especially in pharmaceuticals, are advantageous due to their facile removal. Herein, we report the successful 4 step synthesis of a DAC based first generation dendrimer. The core of the dendrimer is pentaerythritol, and due to the very solubility of the substrate, tetra esterification was problematic which warranted a stepwise approach requiring protecting groups to increase solubility. The molecule was di-protected with chlorotriethylsilane yielding the desired species in a 20% yield. Di-esterification was achieved through Steglich esterification allowing for a 78% yield. De-protection was rapidly achieved though excess TBAF giving the desilylated product with a 93% yield. The Steglich esterification conditions were utilized once again to produce the desired molecular target in 95% yields. These conditions were effective at producing the dendrimer at the gram scale with an overall yield of 14%. With the synthesis of this novel dendrimer reported, it is now possible to probe the reactivity of these DACs utilizing well established and high yielding reactions to access unique synthetic targets.



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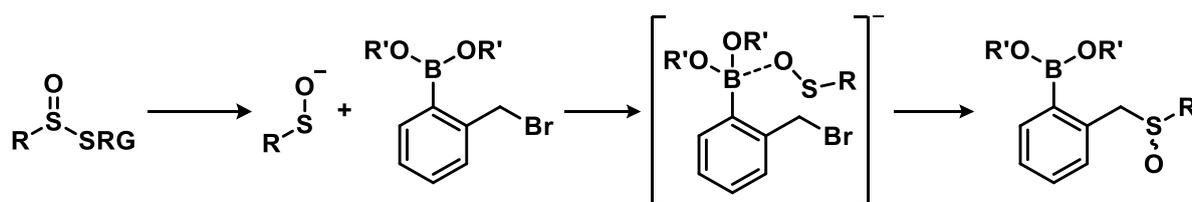
Examining the Role of Proximal Boron Functionalities in the S-Alkylation of Sulfenic Acid Anions

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The S-functionalization chemistry of sulfenic acid anions, also known as sulfenate anions, represents an emerging method for the preparation of sulfoxides. Nearby functional groups can often influence the S-functionalization chemistry of sulfenate anions through non-bonding interactions [1]. Recently, several reports have reported the combination of the Lewis acidity of trivalent boron and Lewis basicity of sulfinyl groups to perform interesting chemistry [2-4]. Among these reports is a study by Benkovic and coworkers who investigated the reversible complexation of the oxygen of a sulfenate anion with the boron atom of boronic acids and a benzoxaborole [2]. This report illustrated that a reversible R-S-O-B bond forms between the sulfenate anion and the boron atom indicating that a proximal boron functional group could potentially influence the S-functionalization chemistry of sulfenate anions [2]. We decided to investigate this R-S-O-B interaction in hopes that initial complexation of a sulfenate oxygen to boron could direct and accelerate the S-alkylation chemistry of sulfenate anions. Both computational investigations and competition based sulfenate S-alkylation reactions have been conducted to determine the role of a proximal boron functionality. To date, computation investigations have illustrated that there can be a significant energetic benefit to the inclusion of boron functionalities (~3.7 kcal/mol) and competition sulfenate anion S-alkylation experiments between benzyl bromide and *o*-bromomethyl boronic esters have shown up to a 97% selectivity for the boron containing electrophile. The full details on our investigations are presented in the poster.



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Diastereoselective Synthesis of Fluorinated Lactams Using Difluorocarbene

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The incorporation of fluorine into biologically active organic molecules can have drastic effects on their physicochemical properties. Fluorine's small atomic radius makes it a useful isostere of hydrogen, and its high electronegativity can affect the polarity, lipophilicity, and pharmacological properties of pharmaceuticals [1]. Recently, difluorocarbene reagents have found use as a way of introducing a carbon-fluorine unit into organic molecules through a variety of diverse transformations [2,3]. One important class of medicinally relevant molecules are γ -lactams [4], and while methods for the synthesis of various fluorinated lactams are known [5], monofluorinated γ -lactams are an underrepresented moiety, likely due to difficulties in their synthetic construction. Therefore, the development of reactions for the formation of this group of molecules would allow for the strategic and selective incorporation of fluorine into this scaffold during medicinal chemistry campaigns. A recent report from this year has shown the application of a difluorocarbene reagent towards the synthesis of fluorinated amides [6]. In a conceptually similar transformation, this work explores their cyclic analogues, using difluorocarbene towards the diastereoselective synthesis of fluorinated γ -lactams from readily-preparable starting materials and simple-to-handle reagents.

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Development of lipid nanoparticles for the targeted delivery of antibiotics

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Antimicrobial resistance (AMR) occurs when the frequent use of antibiotics creates a selective pressure that forces microbes to evolve over time and become resistant to the antibiotics. AMR is a growing public health threat which has made microbial infection more difficult to treat and results in an increased the risk of severe illness. Overcoming AMR is an urgent need and progress has been made in recent years. One of the methods being explored are nano- based drug delivery systems, which have been successful in the treatment of certain cancers, and more recently demonstrated as effective in the delivery of SARS-CoV-2 mRNA vaccines. The work herein explores the versatility of lipid nanoparticles (LNPs) for targeted antibiotic delivery. The functional LNPs have ligands which lead the LNP selectively to the bacteria surface, and the encapsulated antibiotics within will then kill the targeted bacteria. This approach may reduce the quantity of antibiotic needed to treat an infection (versus oral or intravenous delivery), avoid systematic toxicity, and provide a means to repurpose some previously abandoned antibiotics due to their toxicity. In this report, we will describe the construction of the NPLs, their binding to selected bacteria, their capability of drug encapsulation, as well as their bactericidal activities.

Exploring the Interactions of a Click-Functionalized Poly[Tetrazine-co-Fluorene]-Conjugated Polymer with SWNTs

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The electronic, chemical, and physical properties of conjugated polymers are dependent on the polymer backbone, however, alterations to their properties typically requires a *de novo* synthesis. [1-2] Thus, it is difficult to create directly comparable library of polymers without the interference of other macromolecule influences. [3] Post-polymerization modification of polymers through rapid and efficient “click” chemistry has been explored as a route for the preparation of conjugated polymers. [4] s-Tetrazines can rapidly undergo an inverse-electron-demand Diels-Alder (IEDDA) reaction with cyclooctenes, cyclooctynes, and norbornenes and are tolerant to Suzuki polymerization conditions. [5-6] Recently, alumnus Dr. Vlad Kardelis designed a poly(furyl tetrazine)-co-hexadecylfluorene conjugated polymer system able to click-functionalize with a series of trans-cyclooctene (TCO) derivatives within 30 minutes post-polymerization. [7] Though able to successfully demonstrate the rapid functionalization of the tetrazine-based polymer, many aspects and applications of this system that have yet to be investigated. Single-walled carbon nanotubes (SWNT) have unique optoelectronic and physical properties, such as high conductivity, tensile strength, and chemical stability. [1, 8] However, carbon nanotubes are plagued with difficulties in processing. Dispersing carbon nanotubes with conjugated polymers allows them to be solubilized, which can be altered through modifications to the backbone, sidechains, and molecular weight of the conjugated polymer. [9] Herein, we propose to utilize the previously made system of a tetrazine-based polymer to prepare new conductive materials and observe differences in interactions between the conjugated polymer and carbon nanotubes through modification of the backbone. The modified polymers will be used to disperse carbon nanotubes in solvent to study their impact on solubility, selectivity, and stability. Furthermore, click efficiency pre- and post-dispersion will be investigated using a poly(ethylene glycol) TCO derivative. These dispersions will be used to further study the effects on solubility and selectivity of functional groups on carbon nanotube dispersions.

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Accessing Heterocyclic Structures from Alkene Tethered Aryl Iodides via Palladium Domino Catalysis

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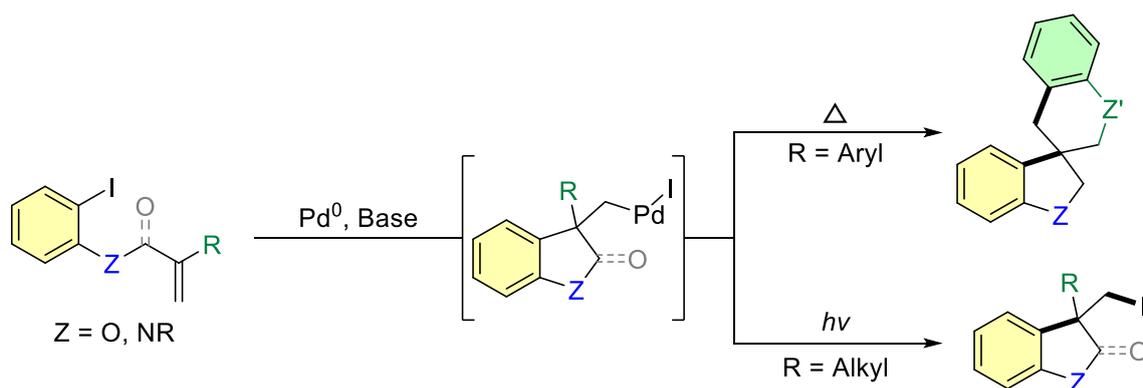
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Domino catalysis enabled by palladium has streamlined the synthesis of many polycyclic heterocyclic molecules. Typically an alkene tethered aryl iodide undergoes an oxidative addition-migratory insertion process to generate a heterocycle and a neopentyl palladium(II) species which has a variety of potential reactivity pathways. Our group has an interest in using the neopentyl palladium species arising from the cyclization in subsequent domino C-H activation in subsequent domino C-H activation pathways forming fused systems and carbocyclic spirocycles.^[1] We also discovered and developed carboiodination reactions arising from a C-I reductive elimination from a neopentyl palladium species.^[2]

We have reported a domino C-H activation with tethered aryl groups forming bis-heterocyclic spirocycles. This method generates a variety of [4.4] and [4.5] bis-heterocyclic spirocycles in up to excellent yields. The modularity of this approach is indicated by the variety of combinations of heterocycles that were amenable to this transformation.^[3]

Photocatalytic processes in combination with palladium^[4] have recently been applied to the carbohalogenation reaction, removing some of the existing limitations. Allowing for the inclusion of many diverse functionalities. In depth mechanistic studies have uncovered interesting information relating to the reversibility of C-I bond formation.



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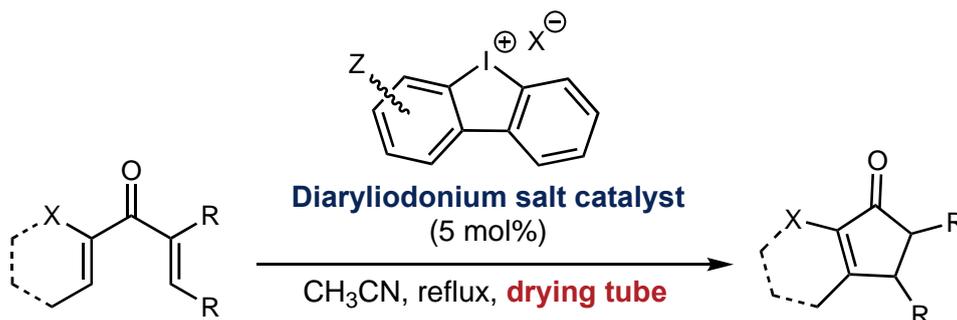
Simple diaryliodonium salt catalysis, right?

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Diaryliodonium salts are a subset of hypervalent iodine(III) compounds which contain a central cationic iodine connecting two aryl rings. Recently, the Lewis acidity of diaryliodonium salts, and their applicability in homogeneous halogen-bond catalysis has been studied [1-4]. To further develop the synthetic utility, and study the Lewis acidity of diaryliodonium salts, we sought to apply them as catalysts for the Nazarov cyclization. The Nazarov cyclization is a 4 π -electrocyclization commonly achieved with conventional Lewis or Brønsted acid activation and describes the conversion of a divinyl ketone into a cyclopentenone. This presentation will discuss the application of diaryliodonium catalysts in the Nazarov cyclization, and the control experiments that suggest a puzzling need for molecular oxygen in the reaction.



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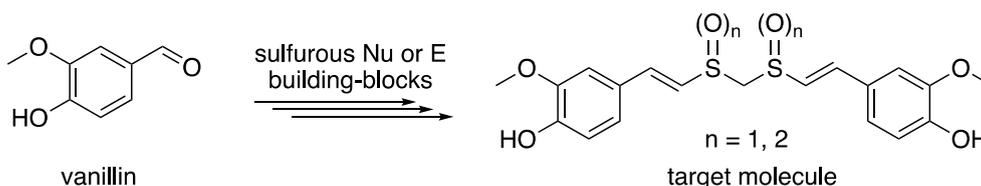
Towards the Synthesis of Sulfur-Containing Curcuminoids to Combat Alzheimer's Disease

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Alzheimer's disease (AD) is a neurodegenerative disease that affects memory, cognition, behaviour, and emotion. The disease is most prevalent in individuals aged 75 or older, with the clinical hallmarks of gradual memory impairment, eventually leading to overall cognitive decline [1]. The disease is the leading cause of dementia, which affects approximately 50 million individuals worldwide [1]. Curcumin, a natural product of the *Curcuma longa* plant and active ingredient in the common household spice turmeric, has been shown to exhibit anti-AD potential since the early to mid 2000's [2,3]. Early structure-activity relationship studies elucidated the main structural components responsible for curcumin's bioactivity; (i) two terminal aromatic groups, (ii) the presence of H-bond donors or acceptors on the aromatic termini, and (iii) a π -conjugated bridging region that connects the two aromatic termini [4]. As such, the past decade has seen the synthesis and bioactive investigation of several curcuminoid derivatives according to these criteria to unveil new families of potentially therapeutic compounds [5]. However, one general group of compounds that has been overlooked are curcuminoids containing sulfur functional groups (either sulfoxide or sulfone) in place of the native carbonyl moieties. The extent of these compounds in the literature is limited to one patent published in 2006 [6], and thus the present research aims to probe new methods for synthesizing these compounds with a focus on atom economy and methodologies for incorporating the sulfur into the scaffold. Building up the curcumin scaffold has started from the inexpensive starting material vanillin, and modifications to said starting material have allowed for the introduction of a sulfur source and further C-S bond forming steps in which the sulfurous precursor is nucleophilic or electrophilic in nature. Current strategies and obstacles, as well as future ideas for different aromatic starting materials and incorporating sulfurous heterocycles into the bridging region are to be discussed.



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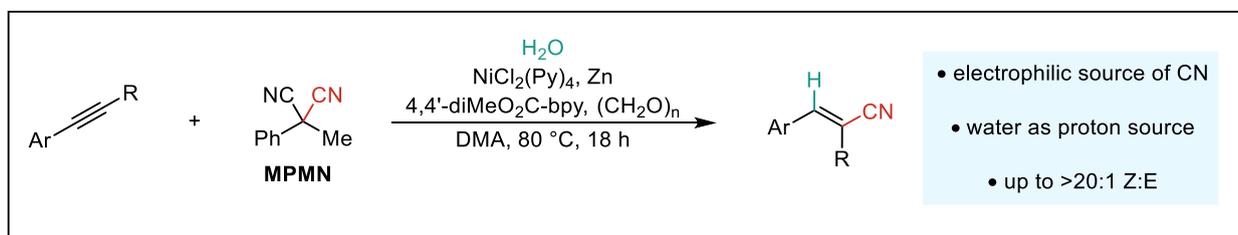
Ni-Catalyzed Reductive Hydrocyanation of Alkynes using H₂O and an Electrophilic CN Source

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Alkenyl nitriles are valuable functional groups that can serve as versatile synthetic handles, due to their ability to engage in a variety of chemoselective transformations at either the olefinic or nitrile sites [1]. Alkenyl nitriles are also found in a variety of pharmaceutical compounds where, in the context of covalent inhibition, the highly polarized conjugated motif can serve as a Michael acceptor for irreversible target binding [2]. Accessing alkenyl nitriles from alkynes requires a formal addition of HCN which is frequently achieved with Ni-catalysis by invoking H-Ni(II)-CN oxidative addition intermediates [3]. HCN surrogates, such as cyanohydrins, are commonly employed but toxicity risks and cyanide induced catalyst poisoning often limit the feasibility of such reactions [4]. Our group has demonstrated that 2-methyl-2-phenyl malononitrile (MPMN), a carbon-bound source of electrophilic CN, undergoes Ni-catalyzed transnitration to afford nitrile-containing products, while generating innocuous α -methylbenzyl cyanide as a by-product [5]. The use of MPMN, which is bench-stable and readily accessible from commercial reagents, can therefore help reduce the necessity for toxic HCN surrogates. Herein, we describe the ongoing development of a Ni-catalyzed reductive alkyne hydrocyanation methodology using H₂O and MPMN as the source of H and CN, respectively. The substrate scope, mechanistic experiments, and the elucidation of an intriguing additive effect of paraformaldehyde will be discussed.



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Development of a New Linchpin Reagent towards a Modular Synthesis of Amides

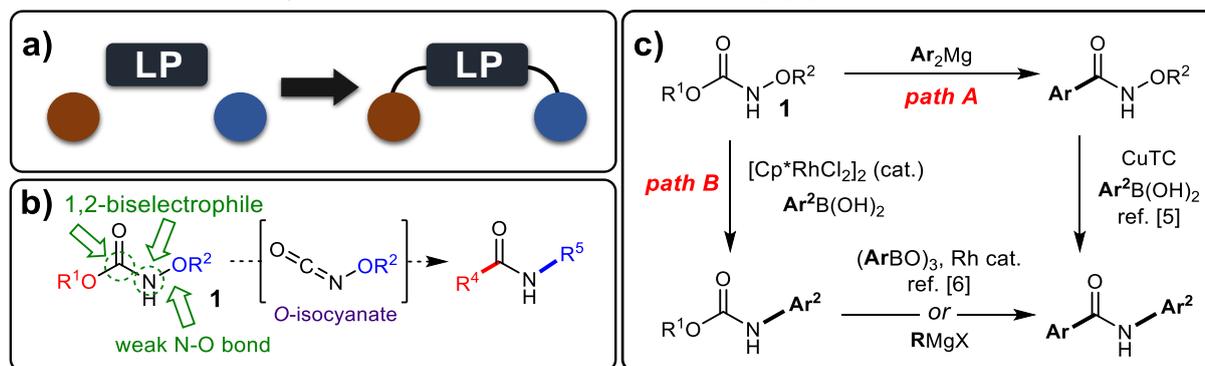
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Linchpins are small molecules designed to be chemoselectively functionalized via sequential reactions (**a**), enabling the modular syntheses of olefins [1], polyenes [2], and ketones [3]. To our knowledge, a linchpin reagent has not been reported for the synthesis of amides, despite the importance of this and other C(=O)N subunits in bioactive molecules, including pharmaceuticals and agrochemicals. Although many approaches exist for amide syntheses, there is an ongoing need for new synthetic methods [4]. To develop such an amide linchpin, we hypothesized that masked *O*-isocyanate **1** can serve as a viable starting point.

The biselectrophilicity of *O*-isocyanates is attractive, with the variation of the leaving groups (R¹, R²) potentially providing a balance between stability and reactivity (**b**). Our linchpin candidates release a highly electrophilic isocyanate *in situ*, while promoting metal-catalyzed electrophilic amination reactions through the cleavage of the weak N-O bond. Herein, we will present the evaluation of several linchpin contenders, and the assessment of two alternative pathways that can lead to secondary amide products: 1) **path A** employs electrophilic amination of hydroxamate intermediates (C-C, then C-N); 2) **path B** employs organometallic additions to complex masked isocyanate intermediates (C-N, then C-C) (**c**).



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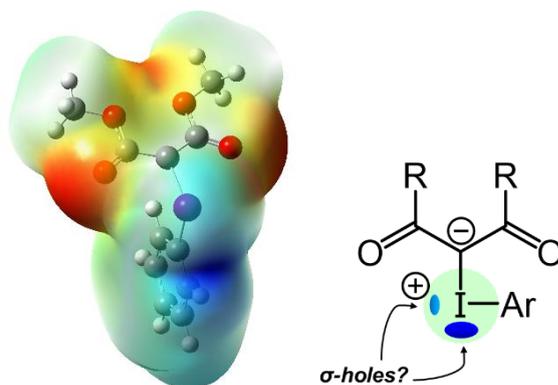
σ -Holes in Iodonium Ylides: Halogen-Bond Activation May Enable X–H Insertion Reactions

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Halogen bonding is an exciting phenomenon that describes the interaction between a Lewis base and an electropositive, sigma hole region of a halogen found along an extension of the C–X covalent bond axis. Iodine-containing species have the strongest of the sigma holes, as they are the most polarizable of all the halogens. To date, the electropositive character ($V_{s,max}$) of such sigma holes has been quantified computationally for several organoiodine and hypervalent organoiodine species [1]. In this work, the evaluation of electrostatic potential maps of iodonium ylides was conducted, and the strengths of their sigma holes was quantified for both cyclic and acyclic motifs. Iodonium ylides were found to exhibit two sigma holes, analogously to diaryliodonium salts [2,3], with the weaker hole found opposite the arene and the stronger sigma hole extending along the β -dicarbonyl dative bond axis. Little variability was observed between sigma hole strengths when comparing acyclic versus cyclic iodonium ylides; however, the strength of both sigma holes could be modified by use of electron-donating substituents on the aryl ring. These findings were used as a basis to explain the X–H insertion reactivity observed within iodonium ylides that does not occur within analogous β -distabilized diazo surrogates. The scope of this reactivity has been investigated, and carboxylic acids, phenols, and thiophenols were within the X–H bond acidity threshold required for viability.



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Novel Caffeine Analogues as PCSK9 Inhibitors

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In 2022, Prof. Richard Austin and colleagues discovered that caffeine reduces circulating PCSK9 levels and increased hepatic LDLR expression [1]. PCSK9 is a known therapeutic target for the regulation of cholesterol and treatment for cardiovascular diseases. Our medicinal chemistry program expanded on these findings and synthesized additional caffeine-derived analogs with increased potency for PCSK9 inhibition compared to caffeine itself. For example, many of our novel analogues are > 1000 times as potent as caffeine and effective in both cell and animal-based assays. These compounds contain aryl groups at the C-8 position, which are installed via various types of synthetic methods (Figure 1). This poster presentation will detail the synthetic methods being applied to generate our compounds, as well as promising caffeine analogues for improved reduction of PCSK9 levels.

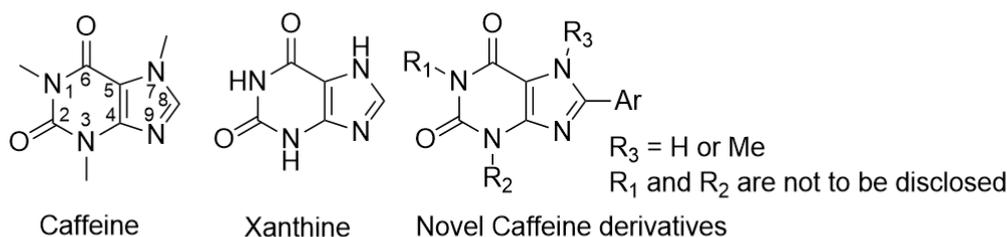


Figure 1: Structures of caffeine, xanthine, and caffeine derivatives

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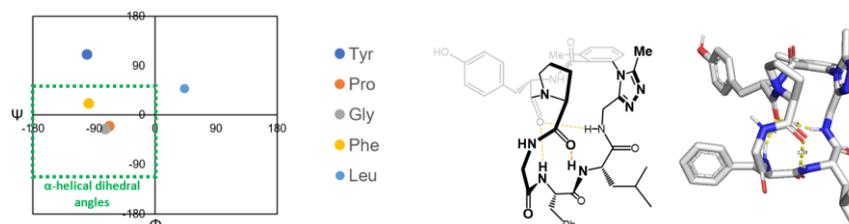
Synthesis of α -Helix-Containing Semi-Peptidic Macrocycles

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Over the last few decades, protein-protein interactions (PPIs) have received a great deal of attention from the pharmaceutical industry because of their involvement in the biological pathways of numerous diseases[1-3]. PPIs are hydrophilic and large yet shallow chemical surfaces, which display α -helical motifs (α -helix, 3_{10} -helix, or π -helix) >60% of the time, making it difficult to inhibit these targets using conventional small molecule drugs[1-4]. Peptidic macrocycles (PMs), however, are large, chemically diverse, and hydrophilic, which has brought more attention to this potential class of drug compounds as a means of inhibiting PPIs[1-4]. Several strategies have been reported that can be used to stabilize α -helical-like conformations in relatively small PMs (4-10 amino acids), theoretically enabling molecular recognition and inhibition of PPIs[3,5]. However, most of these α -helical-like PMs fall short of truly replicating an α -helix that would be found in a protein, and instead exhibit a similar backbone structure without any of the characteristic intramolecular hydrogen bonding (IMHB) [3]. Pre-helical structures which displayed two nestled β -turns (one β -turn within the frame of another, characteristic of a 3_{10} -helix) has been reported in linear and cyclic tetrapeptides[5-6]. However, these examples were too small to be considered true helices. In our lab we have discovered a semi-peptidic 22-membered macrocycle which displays IMHBs similar to that found within a 3_{10} -helix, and dihedral angles which correspond to an α -helical structure. This report will outline the discovery of these α -helical semi-PMs and their structural analysis.



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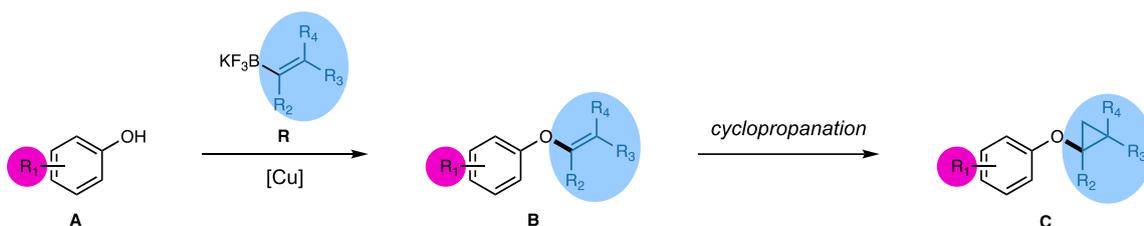
First Synthesis of 1-Methylcyclopropyl Aryl Ethers via Cyclopropanation of the Corresponding Methylvinyl Aryl Ethers

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The synthesis of 1-methylcyclopropyl aryl ethers represents an unsolved problem in organic chemistry. Access to such compounds could enable studies aimed at elucidating the metabolism of aryl cyclopropyl ethers by CYP450s. In this poster, we will show our results on the development of a method to prepare methylcyclopropyl aryl ethers **C** via the copper-promoted alkenylation of phenols **A** using potassium vinyltrifluoroborates **R** followed by the cyclopropanation of the aryl alkenyl ethers **B** [1]. The optimization of the reaction conditions and the scope for both steps will be presented. Studies comparing the chemical stability of aryl alkenyl ethers **B** vs cyclopropyl derivatives **C** will be shown.



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Synthesis of Fluorinated Thiogalactoside Analogues as Potential Galectin Inhibitors

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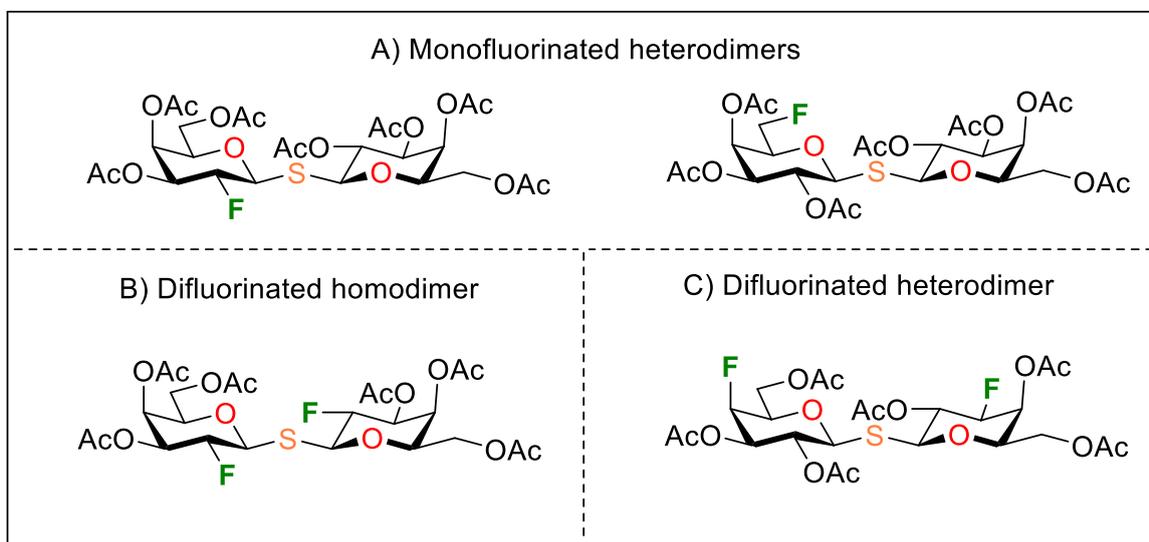
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Galectins are proteins that have the ability to bind to galactoside residue. They contain at least one carbohydrate recognition domain [1]. Galectins contribute to some physiological and biological processes like tumor cell survival, immune response, tumor metastasis, and many others [2-3]. Fluorinated carbohydrate are valuable chemical probes that are useful in molecular recognition studies. Moreover, carbon-fluorine bonds stabilize the glycosidic linkage when the fluorine atom is closer to the anomeric center. It also decreases the *in vivo* degradation of carbohydrates.

We report the synthesis of monofluorinated and polyfluorinated thiogalactoside analogues [4]. To achieve this goal, we synthesized two monofluorinated heterodimers, a difluorinated homodimer and a difluorinated heterodimer, as shown in Figure 1. We used the tri-isopropylsilyl thioglycosides as glycosyl thiol masked nucleophiles to form the S-linked glycosides and thus to form the different dimers. Moreover, we developed an alternative synthesis of 3-deoxy-3-fluorogalactose and 4-deoxy-4-fluorogalactose to further achieve the desired thiogalactosides [4].

Figure 1: Thiogalactoside analogues prepared in this study.



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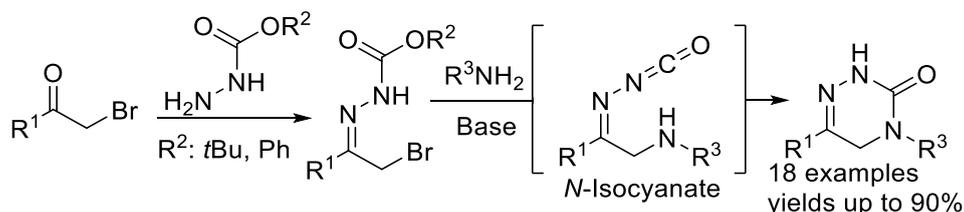
Synthesis of Triazinones by Cyclisation of N-Isocyanate Precursors

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Nitrogen-substituted isocyanates are a rare and seldom used reagents in organic synthesis due to their high propensity to undergo side reactions.[1] However, under appropriate conditions, N-isocyanates can be generated *in-situ* and enable new approaches to heterocyclic compounds. Triazinones are useful compounds in drug discovery, as radiotracers and in agrochemistry (e.g. pymetrozine). However, their synthesis can be challenging due to the difficulty in accessing α -aminoketones.[2] The discovery of a reaction sequence forming 1,2,4-triazin-3(2H)-ones from α -bromohydrazone and an amine or hydrazine derivative will be presented. This approach relies on nucleophilic substitution to yield an intermediate primed for cyclisation on the masked N-isocyanate. Varying the blocking group structure ($R^2 = \text{Ph}$) allows a cascade synthesis. Selected optimization efforts, the scope of the reaction and mechanistic insights will be presented.



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Reversible C-C Bond Formation Under Palladium Catalysis

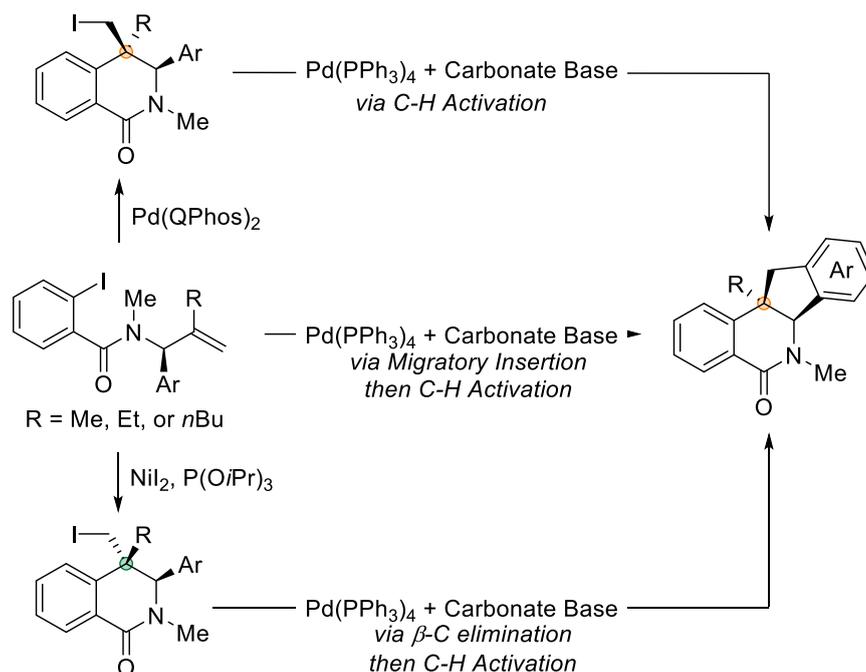
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Transition metal C–C bond forming reactions represent an important class of reactions in modern organic synthesis. Less well studied are the microscopic reverse, mainly C–C bond cleavage. There has been increasing interest in C–C bond activation to perform novel transformations, most successful results are in systems that are biased by ring- or steric strain [1], release of strong π -systems [2], or use of directing groups [3].

Herein, we will report our strategy to utilize less biased systems to observe reversible C–C bond formation under palladium catalysis [4]. Utilizing our previous work to access both diastereomers of neopentyl iodides, we were able to converge to a common product through a formal epimerization of a quaternary carbon via a β -C elimination under catalytic conditions. A thorough mechanistic analysis was performed to better understand factors which dictate β -C elimination and reversible C–C bond forming reactions.



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Drug Discovery: Towards the Synthesis of Novel CDK2-Spy1 Inhibitors

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As vital regulatory proteins in the cell cycle, cyclin-dependent kinases (CDKs) and cyclins ensure normal cell division and growth by monitoring check points in the cell cycle. [1] CDKs are inactive on their own, but when a cyclin binds to CDK the activated CDK-Cyclin complexes then carry out their role as cell cycle regulators. Unregulated CDK-Cyclin complexes cause cells to grow and divide at a premature stage, and that can lead to uncontrolled cell growth. Existing treatments such as CKI (cyclin-dependent kinase inhibitor) therapy have cytotoxicity issues because of their inability to differentiate cancer cells from healthy cells, resulting in unwanted side effects. [2]

Spy proteins are alternative activators to CDKs in cancer cells, but not in healthy cells, making them an ideal therapeutic target. Notably, the Spy1 gene is among the top 50 genes associated with carcinoma, yet the CDK2-Spy1 complex has never been selectively targeted before in terms of CKI therapy. We therefore aim to synthesize molecules that selectively target CDK2-Spy1 complexes to develop a chemotherapy that has minimal cytotoxicity issues.

In this poster presentation I will discuss our current progress towards small molecule inhibitors that show promising selectivity for CDK2-Spy1 complexes based on computational studies. Our synthetic routes and the analytical techniques employed to characterize these compounds will be described.

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Use of Hexafluoroisopropyl Sulfamate (HFIPS) for the Synthesis of Sulfamate- and Sulfamide Inhibitors of Metallo- β -Lactamases

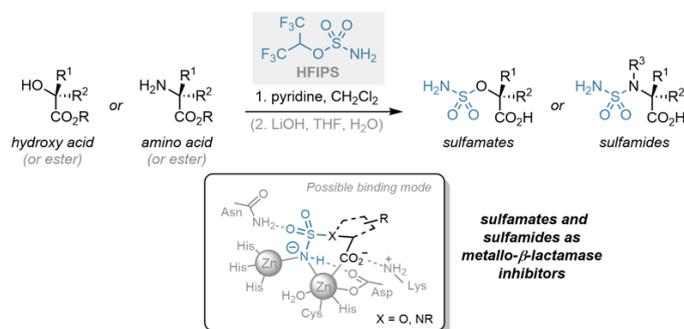
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Sulfamates and sulfamides are important functional groups in chemistry and biology and are most often synthesized from alcohols and amines with sulfamoyl chloride, a moisture-sensitive and unstable reagent. Recently, our group identified hexafluoroisopropyl sulfamate (HFIPS) as an alternative sulfamoylation reagent that is a bench-stable solid and reacts with alcohols and amines under mild conditions.^[1] Since hexafluoroisopropanol is released as a volatile byproduct, the sulfamate and sulfamide products can often be isolated in high purity after an aqueous workup and removal of the solvents by evaporation.

Sulfamates and sulfamides are known as zinc-binding functionalities and have been used for the inhibition of carbonic anhydrases and carboxypeptidases.^[2] Metallo- β -lactamases (MBLs) are zinc-dependent enzymes that cleave most classes of β -lactam antibiotics and confer resistance to penicillins, cephalosporins, and carbapenems. Since MBLs are often found in multidrug-resistant strains of Gram-negative bacteria, they remain a serious and growing clinical concern and MBL inhibitors are desperately needed.^[3] Here, we describe the design and synthesis of a series of sulfamate- and sulfamide inhibitors of MBLs and disclose our preliminary inhibitory data.



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1,5-Diaza-3,7-diphosphacyclooctanes as versatile ligands for palladium and nickel catalyzed Mizoroki-Heck reactions

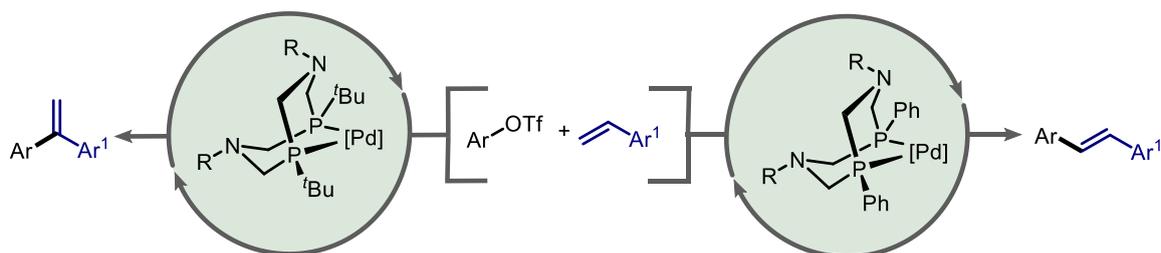
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1,5-Diaza-3,7-diphosphacyclooctanes (P₂N₂'s) are an underreported ligand class for C-C bond formation reactions, despite their prevalence in coordination chemistry and electrocatalytic reduction/oxidation processes. Recently, we disclosed the unique utility of P₂N₂ ligands in the reductive arylation of aldehydes and the related redox neutral α -arylation of primary alcohols [1]. A high-throughput experimentation (HTE) approach has uncovered the strength of P₂N₂ ligands in Mizoroki-Heck reactions compared to the "gold standard" ligands previously reported in the primary literature. Results from palladium and nickel catalysis will be highlighted. Of particular note, by varying the structural framework of the P₂N₂ ligand, a distinct change in regioselectivity can be observed between the linear *trans* and branched isomer in the coupling of aryl triflates with styrenes. Under optimized conditions, with novel P₂N₂Pd G3 precatalysts, >20:1 selectivity for the desired isomer can be achieved.



regioselectivity ■ high throughput experimentation ■ novel Pd precatalysts

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Photocontrol of β -lapachone Activity Against Cancer

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β -lapachone is an *ortho*-naphthoquinone natural product with significant antiproliferative activity but suffers from adverse systemic toxicity, namely methemoglobinemia and anemia. With such in mind, photoremovable protecting groups (“photocages”) can serve as an attractive prodrug approach to limit toxicity, controlling drug release with high spatial and temporal resolution. However, masking of electrophilic moieties such as the quinone group is an immense challenge in the development and use of photocages. In this work, we report the covalent inactivation of the β -lapachone quinone via a C_{sp^3} - C_{sp^3} bond to a photocage, such that it displays innocuous behavior. Upon light activation, the cage cleaves the carbon-based bond to release β -lapachone and restore its bioactivity. The efficiency of the prodrug approach was evaluated both *in vitro* and *in cellulo* against a panel of human cancer cell lines and whole human blood. The controllable drug release with light can widen the therapeutic window of β -lapachone for use against cancers and demonstrated the extension of photocage applications to quinone agents.

Aqueous Stability of Hydrosilanes

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Hydrosilanes are compounds possessing an Si-H bond. This bond is polarized such that the hydrogen is hydridic, and because of this, hydrosilanes are commonly used as reducing agents in organic synthesis.[1] However, the aqueous stability of this Si-H bond is not fully explored as there is inconsistent information about how hydrosilanes are stored/handled. The main concern is the hydrolysis of the hydrosilane (Si-H) to form the silanol (Si-OH). Perhaps because of this, there are few examples of hydrosilanes used for biological applications (e.g. as a silicon switch). By contrast, there are numerous reports using fully substituted organosilanes (without Si-H bonds) because of their established chemical and aqueous stability.[2] Interestingly, methods to prepare silanols from hydrosilanes typically use metal catalysts and an external oxidant,[3] suggesting that the Si-H bond might be more stable to hydrolysis than previously suggested. Investigating what structural aspects of the hydrosilane affect its stability in aqueous conditions will make it clearer what types of hydrosilanes can be used for biological applications. Thus, we collected/synthesized several hydrosilanes to test their aqueous stability. In particular, we sought to understand how 1) the number of Si-H bonds and 2) the identity (e.g. aryl, alkyl) of non-H substituents affected the aqueous stability of the Si-H bond.

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Progress Towards the Total Syntheses of Corallocin B and C and Hericerin A via Alumina-Templated *Ortho*-Allylation

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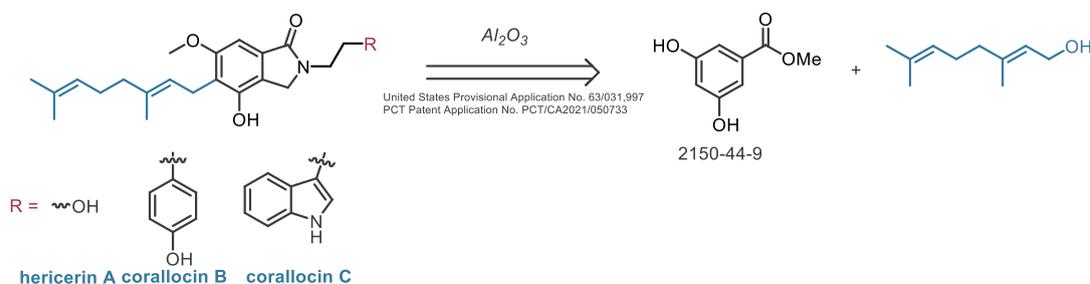
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Phenols constitute one of the largest classes of natural products in the fungi kingdom and demonstrate a multitude of biological effects. To better understand these reported bioactivities, the synthesis of phenolic natural products in the laboratory is an important endeavor. One of the key challenges in the synthesis of phenolic products is the addition of a prenyl, geranyl, or farnesyl chains to the ring. Utilizing a proprietary alumina-promoted *ortho*-alkylation strategy, the scaffolds of corallocin and hericerin natural products are accessed efficiently. Other key steps in the synthesis offer modular functionality to access these three natural products to further probe structure-activity relationships. The synthetic route employed minimizes issues of regioselectivity and the need for protecting groups, allowing access to these natural products in an atom-efficient and concise manner.

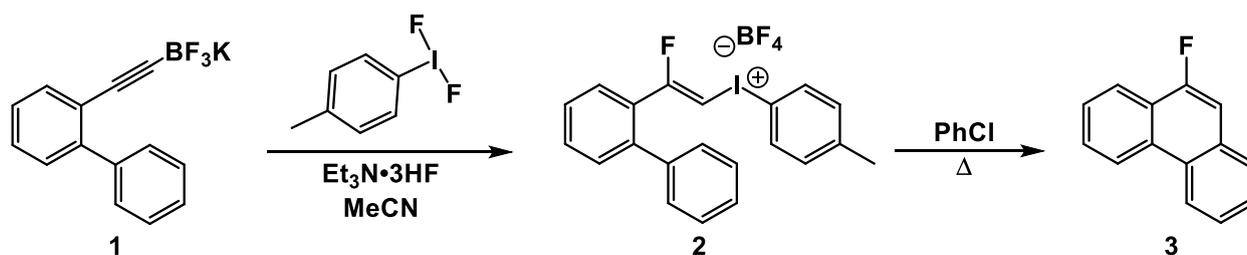


Umpolung Cyclizations of Alkynes in the Synthesis of Fluorinated Polycyclic Aromatic Hydrocarbons

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Numerous industries employ fluorine and fluorinated motifs in their small-molecule design strategies to engineer and modulate their molecule's physical properties.[1, 2] In recent years there has been increased interest in fluorinated polycyclic aromatic hydrocarbons (PAHs) and conjugated polymers due to their applications in organic-based electronics. This research exploits the reactivity of hypervalent iodine reagents to develop a fluorination/tandem cyclization strategy for the synthesis of novel fluorine-substituted PAHs. (Difluoriodo)toluene (TollF₂) is a versatile hypervalent iodine-based fluorinating agent that can be made on large scale using 48% aqueous HF.[3] Ethynyl trifluoroborates have been shown in the literature to undergo ligand exchange with hypervalent iodine reagents to displace suitable apical nucleofuges (e.g. OTs, OAc, Cl).[4] Using TollF₂, these ethynyl trifluoroborates (**1**) can be converted to isolatable fluorovinylaryl iodoniums (**2**) through conjugate addition of HF. Biarylfluorovinylaryl iodoniums synthesized this way can cyclize to give 9-fluorophenanthrenes (**3**) through a suspected vinylic S_N2 process. This research seeks to address a critical scientific need, by developing novel reactivity to incorporate fluorine into valuable PAHs directly, using inexpensive feedstock metal or hydrogen fluorides. Bypassing the multistep preparation of fluorinating agents, it could be an invaluable tool for researchers who use site-specific fluorination as a tool in molecular engineering.



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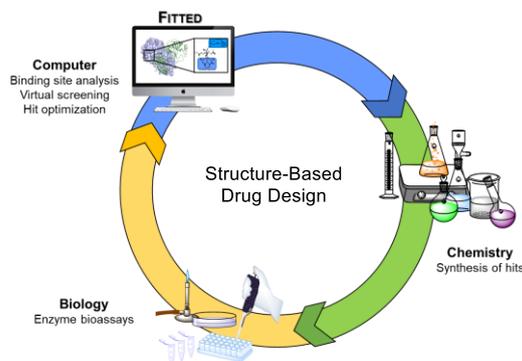
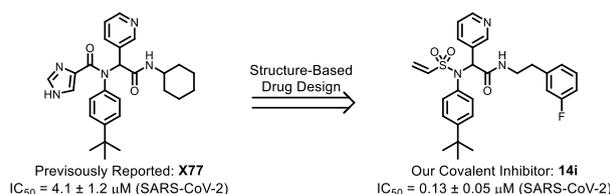
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Design, synthesis and in vitro evaluation of novel SARS-CoV-2 3CL^{pro} covalent inhibitors

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Severe diseases such as the ongoing COVID-19 pandemic, as well as the previous SARS and MERS outbreaks, are the result of coronavirus infections and have demonstrated the urgent need for antiviral drugs to combat these deadly viruses. Coronaviruses express 3-chymotrypsin-like cysteine proteases (3CL^{pro}), also referred to as the main proteases (M^{pro}), which feature a Cys-His catalytic dyad (Cys145, His41) and are required for viral replication and infection. 3CL^{pro} enzymes were identified early on as attractive targets for antiviral development[1]. Previously reported SARS-CoV 3CL^{pro} non-covalent inhibitors, **X77** (IC₅₀ with SARS-CoV-2 3CL^{pro}: 4.1 ± 1.2 μM), was used as a starting point for the development of covalent inhibitors of SARS-CoV-2 3CL^{pro}[2]. We were able to convert the non-covalent inhibitor to covalent inhibitors with an improvement of IC₅₀ up to 20-fold. We herein report our efforts in the design and synthesis of submicromolar covalent inhibitors when the enzymatic activity of the viral protease was used as a screening platform.



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Progress Towards the Total Synthesis of Hericene A, B, and C via an Alumina Directed *Ortho*-Allylation Strategy

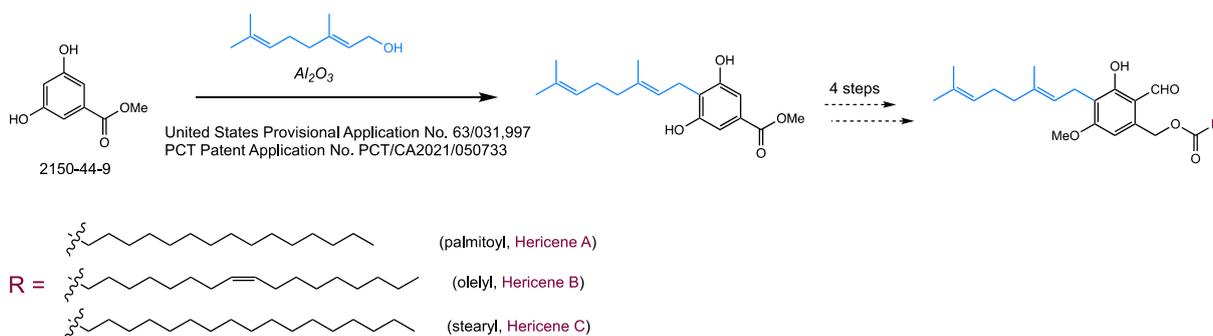
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Hericene A, B, C are a family of phenolic natural products isolated from mushroom *Hericium erinaceus*. These compounds have known bioactivity to induce axon outgrowth. A concise synthesis total synthesis of these compounds is sought to explore their biological activity. The 5-step synthesis features a facile and proprietary installation of geranyl chain using an alumina directed ortho-allylation reaction. Such modular synthesis will further allow for scalable access to hericene analogues with efficiency.



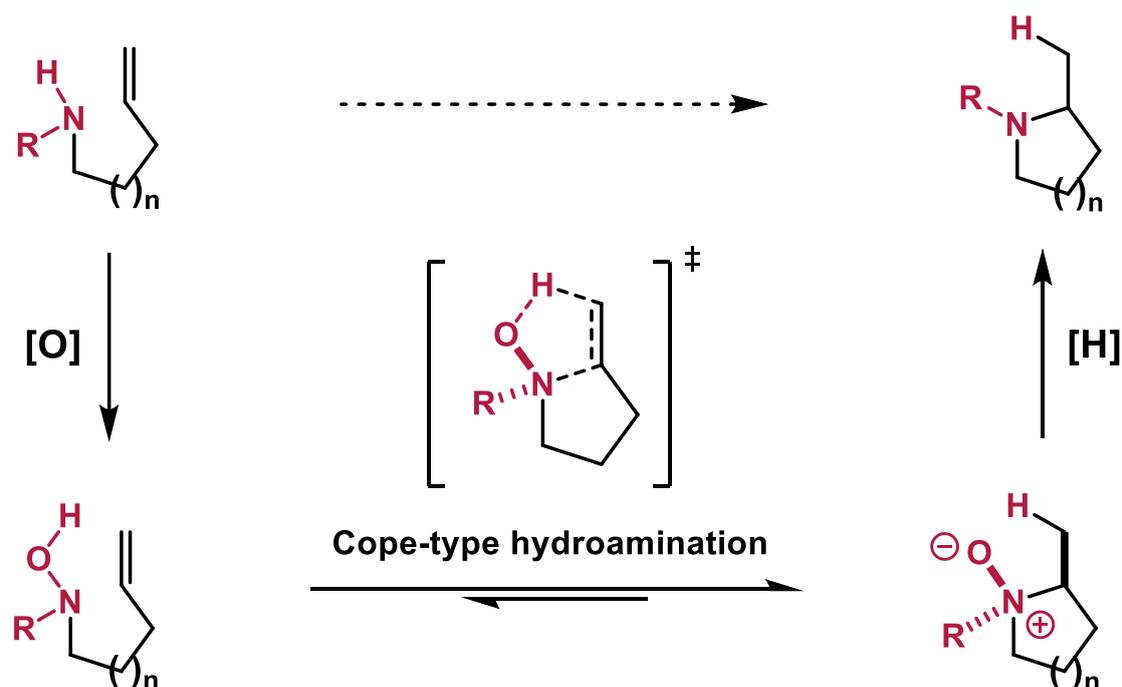
Cope-type hydroamination via an oxygen transfer strategy

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Intramolecular hydroamination of alkenes is a well-known method for the synthesis of pyrrolidines and piperidines, which are common moieties in numerous natural compounds and commercially available medications. Hydroamination reactions in the presence of transition metal catalysts have been utilized efficiently for decades for this purpose. However, specific requirements on substrates' structures, such as Thorpe-Ingold bias, and often harsh conditions have limited the applicability of this approach.[1] Recently, a redox-enabled strategy for hydroamination has been reported, exploiting the ability of hydroxylamines to cyclize under mild reaction conditions.[2] While efficient stoichiometric reagents can be used, the use of catalysts may result in a more efficient process. In this poster, the development of a chemoselective catalyst will be presented, along with results for intramolecular and intermolecular hydroaminations.



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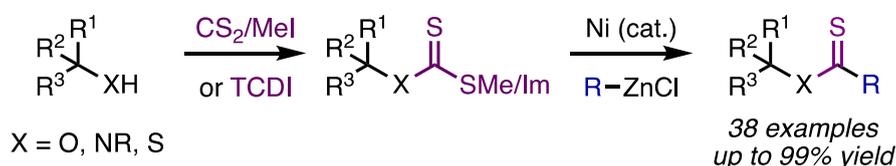
Ni-Catalyzed Synthesis of Thiocarboxylic Acid Derivatives

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Thiocarboxylic acid derivatives have found applications in many total synthesis efforts, in the synthesis of a large array of sulfur-containing heterocycles, and as a convenient precursor for the CF₂ functional group, which can impart desirable effects on pharmaceuticals and agrochemicals. From a biological perspective, thiocarboxylic acid derivatives have recently shown promise as a novel class of chemical agents that can slowly release hydrogen sulfide (H₂S), an important signaling molecule, under physiological conditions. Despite the use of thiocarboxylic acid derivatives in organic and biological chemistry, accessing these products can be particularly challenging. We have developed a Ni-catalyzed cross-coupling of readily accessible O-alkyl xanthate esters or thiocarbonyl imidazolides and organozinc reagents for the synthesis of thiocarboxylic acid derivatives. This method employs an underexplored retrosynthetic disconnection relative to conventional methodologies and benefits from a fast reaction time, low catalyst loadings and mild reaction conditions. We show that a diverse array of thiocarboxylic acid derivatives can be synthesized in moderate to excellent yields following the simple activation of the corresponding alcohol, amine, or thiol precursors using commercially available thiocarbonyl sources. Efforts pertaining to reaction optimization and scope for this complementary approach toward thiocarboxylic acid derivatives will be presented.



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Protecting-group free synthesis of clevidine (L-FMAU), an Oral Treatment of Hepatitis B Virus

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Hepatitis B is a viral infection attacking the liver, that can lead to cirrhosis and hepatocellular carcinoma. According to the World Health Organization, 296 million people were living with chronic hepatitis B infection in 2019, with 1.5 million new infections and approximately 1 million deaths each year [1]. Many of the actual treatment for this illness require long-term therapy or continuous dosing to maintain their efficacy [2]. Thus, there is still a need for more efficient drugs in the treatment of hepatitis B.

Clevidine (**L-FMAU**) is an unnatural nucleoside analog showing antiviral activity against the Hepatitis B virus. It has no effect on mitochondrial structure or DNA content or function and its posttreatment antiviral activities are sustained for as long as 24 weeks after discontinuation of treatment [2].

Many paths suggested for the synthesis of this arabinosyl nucleoside either start with expensive materials such as L-ribose and L-xylose [3] or require too many steps (up to 14) [4]. We developed a protecting-group-free synthesis of clevidine using only 6 steps from commercially available 2-deoxy-2-fluoro-galactopyranose. The key step involves the preparation of fluorinated galactofuranoside from the corresponding pyranoside [5].

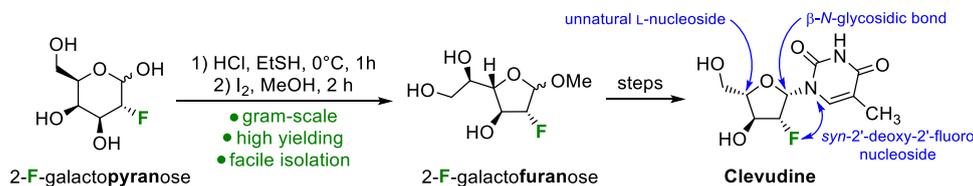


Figure 1: Protecting-group free synthesis of clevidine

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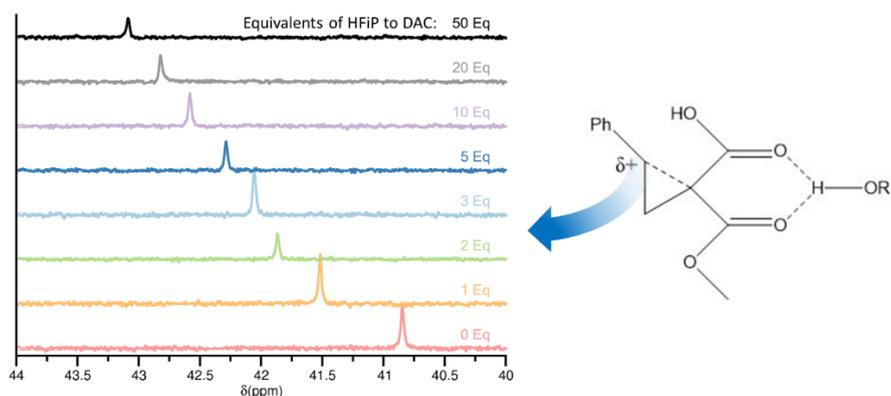
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The Activation of Donor Acceptor Cyclopropanes by a Hydrogen Bond Donor

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Donor acceptor cyclopropanes (DACs) are versatile organic building blocks that are able to undergo a variety of ring opening and cycloaddition reactions¹. DAC reactivity is attributed to a combination of two effects; a strained 3-member ring, and adjacent electron donating and withdrawing groups. This ultimately leads to pseudo zwitterionic characteristics that can be further enhanced through coordination to a Lewis acid. Shown in previous work by the Kerr group, DACs can be activated using a hydrogen bond donor solvent in place of a Lewis acid². This mechanism eliminates the need for more expensive and toxic metal catalysts commonly used and therefore is of great interest to expand to a greater range of reagents. This work expands on previous success of the Kerr group utilizing hexafluoroisopropanol (HFIP) to activate DACs for ring opening reactions with thiol reagents under mild conditions (70-91% yield). To further investigate and compare the mechanism with traditional Lewis acid methods ¹³C NMR spectroscopy titrations were used³. The chemical shift of the DACs electrophilic carbon was recorded at varying equivalents of HFIP or mol % scandium triflate (Sc(OTf)₃). This data demonstrated that the conditions used in the Kerr groups method (25 equivalents HFIP) exceeded the effect on the chemical shift with 10 mol % Sc(OTf)₃, a commonly reported amount for similar reactions with DACs.



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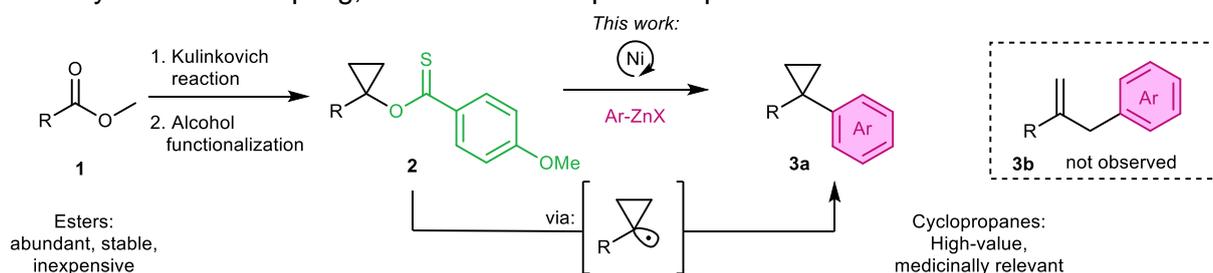
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New Redox Active Leaving Groups for the Deoxygenative Cross-Coupling of Cyclopropanols

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The addition of cyclopropane rings to drugs is an attractive strategy to increase sp^3 character of a potential drug without dramatically increasing molecular weight, which can improve the pharmacokinetic/dynamic properties of a drug molecule.¹ One interesting way to generate cyclopropanes is the Kulinkovich reaction, which forms cyclopropanols from esters and alkyl Grignards.² While alcohols can usually be activated for cross-coupling by transformation into an appropriate leaving group (-OMs, -OTs, etc.), cyclopropanols are not compatible with traditional cross-coupling strategies. When leaving groups typically associated with 2-electron (or polar) reactivity are used, only the ring-opened product (**3b**) is obtained. To access the ring-retained product, it is necessary to generate a cyclopropyl radical intermediate via C–O bond scission. The Rousseaux lab has recently been active in the development of thiocarbonyl-containing leaving groups which achieve the deoxygenative cross-coupling of alcohols via 1-electron (or radical) reactivity.^{3,4} Thionoester **2** has been discovered as a uniquely active leaving group for this chemistry, and an effective method allowing the coupling of alkyl cyclopropanols to a variety of aryl zinc coupling partners has been developed. This poster will highlight our discoveries in this area, focusing on the synthesis of thionoesters, reaction optimization for the Ni-catalyzed cross-coupling, and selected scope examples.



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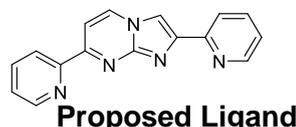
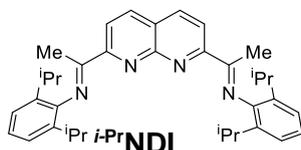
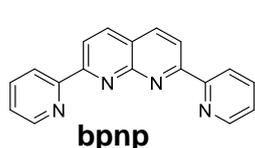
Synthesis of Novel Tetradentate Ligand for Bimetallic Catalysis

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Bimetallic catalysis, broadly stated, is simply catalysis utilizing two metals, particularly transition metals. Of particular interest to our group is the investigation of homogeneous, bimetallic catalysts that are synthesized from chelation of metals to specially designed heterocyclic ligands. In this space of homogeneous bimetallic catalysis, tetradentate, nitrogen-based heterocycles dominate, particularly derivatives of 1,8-naphthyridine. Such derivatives of 1,8-naphthyridine used to prepare bimetallic complexes range from compounds such as **bpnp**, which was the first reported ligand used in the preparation of this class of bimetallic catalysts¹ to the more recent *i*-Pr**NDI** developed by the Uyeda group.² Currently two major downsides to the development and widespread use of bimetallic catalysis exist: firstly the difficulty of synthesizing functionalized 1,8-naphthyridine ligands and secondly the inherent symmetry of these ligands. Regarding the former, the synthesis is complicated by requiring several steps and the use of harsher reagents. Regarding the latter and perhaps more important, is the incredible lack of asymmetric bimetallic ligands, with very few examples present in the literature. This is a problem as the selective binding of two different metals is not possible currently with the reported ligands due to the inherent symmetry of the ligands. Therefore, bimetallic complexes studied thus far in this bimetallic catalysis space have largely focused on homonuclear bimetallic complexes, such as dinickel complexes, etc. However, being able to synthesize a heteronuclear bimetallic catalyst would open the door for more unique and engineered catalysis. In order to expand the field, we propose the synthesis of a novel tetradentate ligand that only requires 4 steps to synthesize, uses convenient starting materials, and is inherently asymmetric allowing for the proposed binding of two different metals. In fact, synthesis of the ligand has already been successfully achieved and currently homonuclear bimetallic complexes are being characterized and explored, including dipalladium, dinickel, and dicopper complexes. Work on the heteronuclear bimetallic complexes is undergoing.



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Conjugate Addition of Alkylidene Dihydropyridine to α,β -Unsaturated Ketones

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With the importance of pyridines in drug discovery [1], it becomes of interest to develop new methods that facilitate their synthesis which will likely bring significant impact on drug development process. There is also a demand for mild and selective functionalization to accomplish functional group tolerance as well as selectivity. In terms of conjugate addition involving 4-alkylpyridines, previous method requires the use of cuprate reagents along with strong bases, which compromises functional group tolerance [2]. The second approach is to install an activating group at the pyridylic position or on the pyridine ring, which requires additional step to remove these groups [3]. We herein present our latest work on conjugate addition to α,β -unsaturated ketones, activated by silyl Lewis acid, with alkylidene dihydropyridines that can be readily prepared under mild condition (Figure 1). This method tolerates a wide array of functional groups and demonstrates regioselectivity towards 4-pyridylic position. The incorporation of the silyl Lewis acid allows the conjugate product with silyl enol ether moiety, using mild workup procedure, to be used for further chemical transformations.

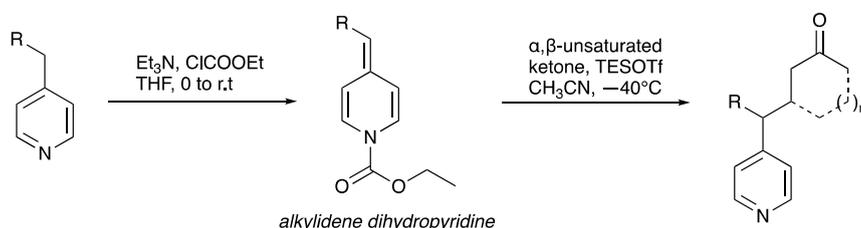


Figure 1: Conjugate Addition of Alkylidene Dihydropyridine to α,β -Unsaturated Ketone

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Photoactivated [3+2] and [4+2] Cycloaddition reactions

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An operationally simple light-mediated cycloaddition reaction of *N*-aryl cyclopropyl and cyclobutyl amines with α,β -unsaturated carbonyl system to afford *N*-arylaminoalkyl compounds. This simple method proceeding through a Single Electron Transfer (SET) offers a wide scope for the synthesis of amino-cyclopentanes in good to excellent yields^[1]. New forays into the use of diverse *N*-aryl cyclobutylamine derivatives, including mechanistic investigations, are underway.



^[1] Barriault, L.; Zidan, M. *ChemRxiv* **2022**. This content is a preprint and has not been peer-reviewed.

Finding and treating cancer: improving the synthesis of cyanine dyes and the Tn antigen

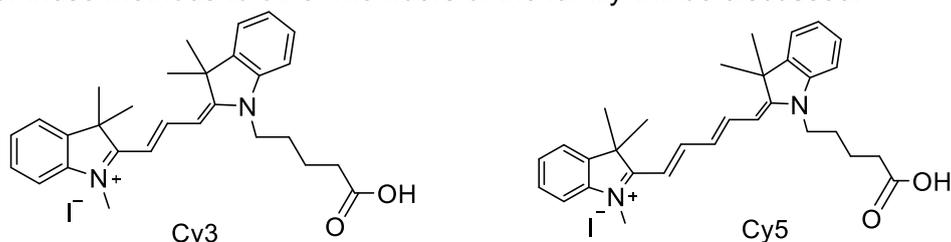
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Cyanine dyes are fluorescent compounds commonly used in biosensors because of their great compatibility *in vivo* and high extinction coefficient, which has made it the perfect choice for our previous studies investigations into prostate cancer. Although cyanine dyes are commercially available, they are very expensive with only few suppliers and problematic synthesis. To facilitate our cancer research projects, we have sought to develop improved synthetic routes to these useful compounds.

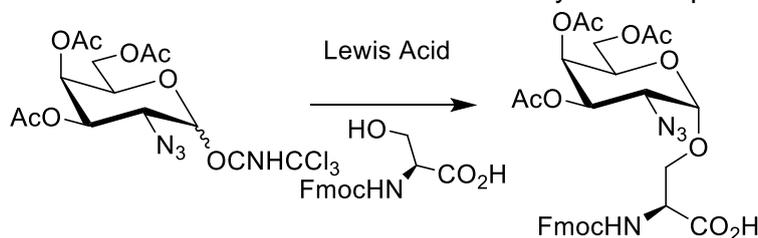
In this part I will describe our work towards the improved synthesis of some of the cyanine dyes, Cy3 and Cy5. The difficulties (and successes) of the synthesis will be analysed and extension of these methods to other members of the family will be discussed.



The Tn antigen is a member of the Tumour-Associated Carbohydrate Antigen (TACA) family, a series of compounds that are over-expressed in cancer cells, which makes them an ideal marker for cancer. Our group has published a concise total synthesis of the Tn Antigen[1].

However, an expensive catalyst was needed to catalyse the glycosylation step and even that gave the product in an unsatisfying yield. To further improve this synthesis, we are screening a series of Lewis acids and have found a few potential hits.

In this part I will present our work on Lewis acids screening, the ideas on how we chose the Lewis acids and the method we use to better obtain and analyse our experimental results.



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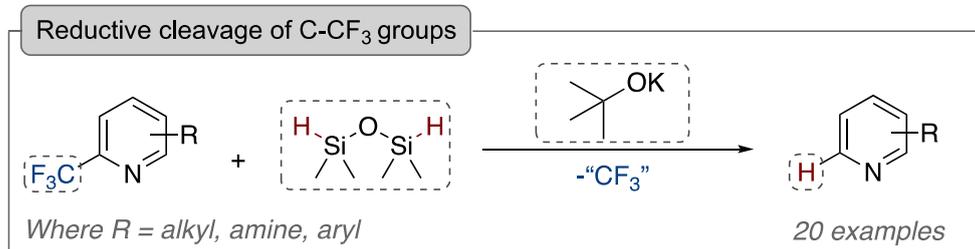
Reductive C–C Bond Cleavage of Trifluoromethyl Pyridines

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The installation of trifluoromethyl groups have seen extensive research owing to their place in pharmaceutical drug molecules.^[1] They've also proven to be a powerful synthetic handle in accessing difluoromethylarene type species.^[2] As such, various new methods to introduce these groups into molecules have emerged in the past decade, such as transition metal catalyzed^[3] and designer-reagent mediated^[4] methods. In contrast, examples of their removal are uncommon, due to the inert nature of C–CF₃ bonds, but have been published in the literature. For instance, Qiao and co-workers happened upon C–CF₃ bond cleavage of trifluoromethyl-substituted hydrobenzoxazoles using cesium carbonate and high temperatures,^[5] while Wang and co-workers recently disclosed a method to cleave aliphatic C–CF₃ groups of trifluoropropanamides.^[6] No examples, however, utilize the combination of siloxane and alkoxide base for the activation of the C(sp²)–CF₃ bond. In this work, the combination of a siloxane reductant and an alkoxide base allow for the efficient reductive de-trifluoromethylation of 2-trifluoromethylpyridines. Mechanistic studies suggest the reaction may proceed via single electron transfer (SET) from a powerful reducing agent, derived from KO^tBu and TMSO, to the trifluoromethylpyridine ring.



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Pd/Rh Dual Catalysis: Tandem Isomerization–Allylation to Access α -Quaternary Carbonyl Compounds

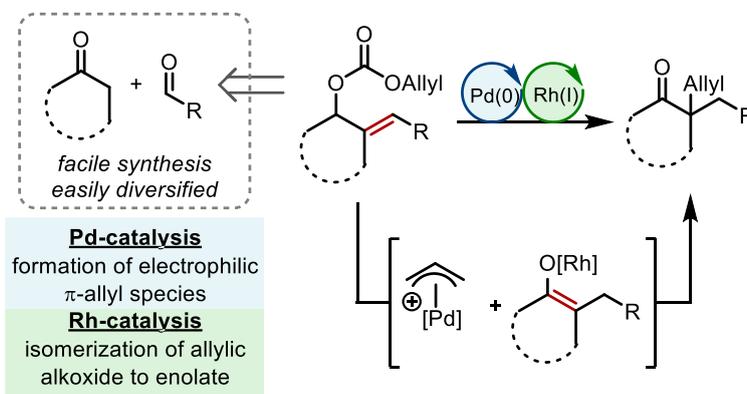
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Development of new methods for the stereoselective construction of all-carbon quaternary centers represents an active and important theme in organic chemistry.^[1] The Pd-catalyzed decarboxylative asymmetric allylic alkylation (Pd-AAA) has been an attractive strategy to afford enantioenriched carbonyl compounds with α -quaternary centers.^{[2],[3]} Our group has recently reported a rhodium-catalyzed tandem isomerization–allylation procedure to afford α -allylated aldehydes, with evidence of a rate-limiting step involving two rhodium species.^[4] Taking advantage of the bimetallic nature, herein, we describe a tandem Pd/Rh dual catalytic system to access α -quaternary allylated carbonyl compounds from unsymmetrical diallyl carbonates. The palladium catalyst forms the Pd π -allyl species while the rhodium catalyst isomerizes the allylic alkoxide into a Rh-enolate species. Recombination of both partners then affords the desired α -allylated carbonyl compound. The scope of this reaction was extended to cyclic and acyclic substrates, including both aldehydes and ketones. Preliminary enantioselective results were also demonstrated using a dual-metal, dual-ligand system. This method enables the use of highly modular and easily diversifiable substrates for the long-established Pd-AAA reaction.



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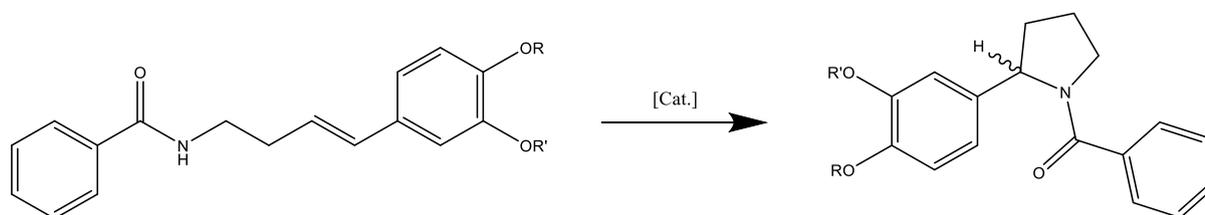
Developing Novel Catalysts For The Activation Of Non-Activated Olefins

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Electrophilic π -activation and addition reactions of olefins is a process of fundamental importance in organic chemistry and includes classics, such as Bronsted acid and Hg (II) promoted additions, to later processes that include hydroboration and Pd(II) promoted reactions such as Wacker oxidation. Efforts in our group have focused on the development of sequentially milder methods for π -activation, in particular those relevant to unactivated olefins, involving metals and TM-complexes in the d^{10} series (Zn⁺⁺, Ag⁺, Au⁺, Pd etc.), chiral phosphoric acids (CPAs) and a new organocatalytic series, the subject of the present investigation. Herein we report our research on the discovery of novel organocatalysts that effect π -activation and cycloaddition reactions under extremely mild conditions. Our novel catalysts follow traditional gold(I)-based chemistry, but without the need for expensive transition metals [1]. These catalysts polarize unactivated olefins such that even poor nucleophiles engage in intramolecular cyclization reactions leading to useful heterocycles. Present research is engaged in optimizing the reaction conditions required for the cyclization, and future research will include developing chiral versions of the catalysts to affect asymmetric versions of this new organocatalytic process.



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Palladium Catalyzed Electrochemical Amination of Aryl Halides

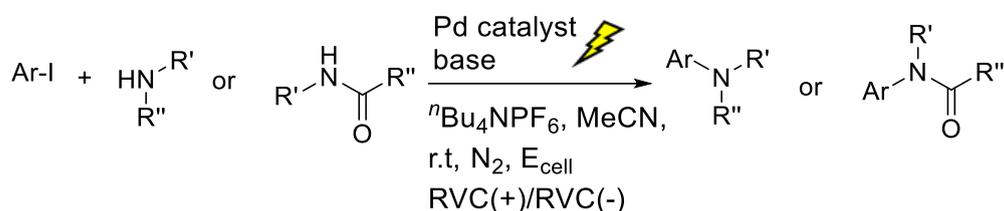
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Buchwald-Hartwig type aminations have become one of the most utilized reactions for carbon-nitrogen (C-N) bond formation. Nevertheless, similar to many variants of cross coupling reactions, these can require pressing conditions and/or specific ligand combinations when performed with challenging reagents [1-2]. Recently, we initiated a project on using electrochemical potential to drive palladium catalyzed C-N coupling. This exploits in situ anodic oxidation of palladium to Pd(III or IV) to drive reductive elimination, while substrate activation through oxidative addition is facilitated by reduction of Pd(II) to Pd(0). Together, this can offer an alternative to the ligand design typically employed in these systems. Preliminary results show that electrochemistry can allow the ambient temperature C-N coupling with pyrrolidone and aryl iodides: a reaction that typically requires more pressing conditions without current. The scope and mechanism of these transformations will be discussed.



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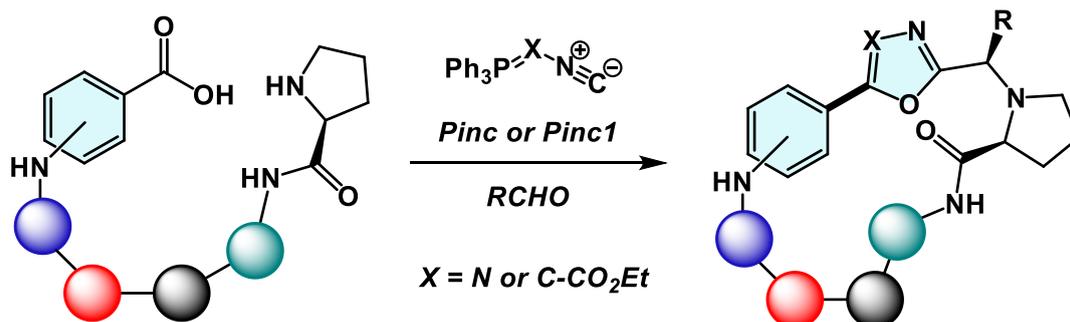
Forging Structurally Diverse Heterobiaryl-containing Peptide Macrocycles *via* a Highly-efficient Cyclization Strategy

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Biaryl and heterobiaryl-containing cyclic peptides represent promising scaffolds in the development of novel bio-active compounds as a result of their target selectivity, binding affinity, and low toxicity.^{1–3} In this work, we report a new macrocyclization strategy to install both oxadiazole- and oxazole-biaryl units in macrocyclic peptide targets. The method can be conducted at low dilutions on C-terminal 2-amino, 3-amino and 4-aminobenzoic-bearing linear peptide sequences to afford unique heterobiaryl-containing cyclic peptides. Further, NMR analysis and molecular dynamics simulations reveal a unique structural turn motif common to each member of these heterobiaryl containing peptides. This structural control element was used to mimic medically relevant secondary structure motifs and generate potentially new peptide-based antagonists of the $\alpha_4\beta_7$ integrin receptor.⁴



✓ *High-yielding* ✓ *Low-dilution*

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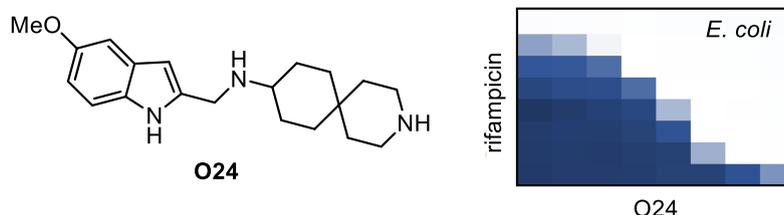
Discovery of a potentiator of Gram-positive antibiotics against Gram-negative bacteria: Synthesis and structure-activity relationships

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Antimicrobial resistance to antibiotics has been described by the World Health Organization as one of the biggest threats to global health, food security, and development today. The World Health Organization has identified Gram-negative bacteria to be one of the largest threats, with most of the pathogens included in the priority pathogen list falling under this class.¹ The difficulty in treating Gram-negative bacterial infections is a result of their highly impermeable outer membrane, which prevents most chemical matter from penetrating the cell and hinders antibiotics with intracellular targets.² Outer-membrane permeabilizing compounds chemically perturb and disrupt the outer membrane and can lower minimum inhibitory concentrations (MICs) of Gram-positive antibiotics to a clinically relevant range by enabling them to reach their targets.³ A large screen of a chemical library identified O24 as a hit that showed synergy with rifampicin, a Gram-positive antibiotic, against Gram-negative bacteria *Escherichia coli*. This poster will describe the synthesis of analogues and synergistic structure-activity relationships with antibiotics against Gram-negative bacteria.



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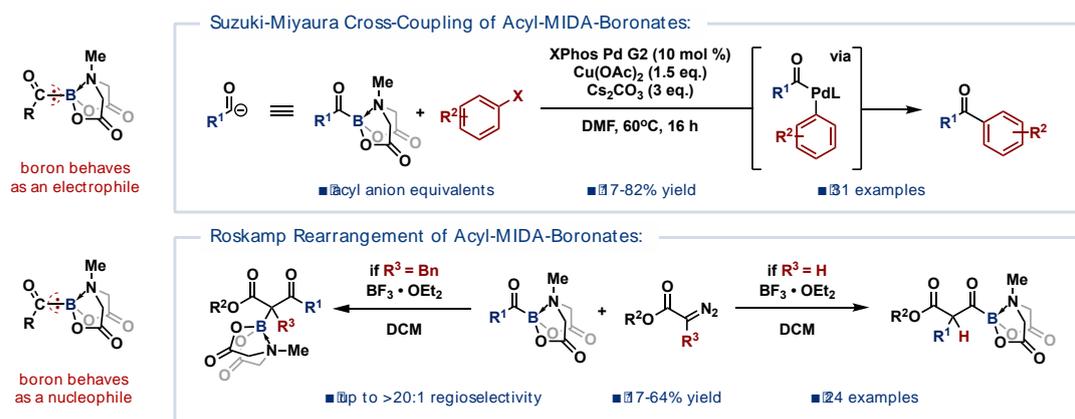
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Acylboronates: Mechanistic Dichotomy Enables Synthesis of Borylated Building Blocks and Ketones

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Organoboron compounds are widely used in modern organic synthesis, medicinal chemistry, and materials science [1]. Acylboronates are a class of boron-containing molecules with the R-C(O)-B motif [2]. We demonstrate that these compounds exhibit amphoteric behaviour depending on reaction conditions. A reported catalytic cross-coupling process between aryl (pseudo)halides and boron-based acyl anion equivalents represents polarity reversal (umpolung), which is supported by the observation of tetracoordinated boronate and acyl palladium(II) species by ¹¹B, ³¹P NMR, and mass spectrometry [3]. A broad scope of aliphatic and aromatic acylboronates has been examined, as well as a variety of aryl (pseudo)halides. The Roskamp rearrangement of acyl-MIDA-boronates and diazoacetates provides boron and alkyl migration products selectively depending on the steric bulk of the substituents and presents an electrophilic behaviour of acylboronates [4]. The mechanism of the reaction is explored computationally, and the scope includes both mono- and di-substituted α -boryl β -ketoesters and acylboronate β -ketoesters. The synthesized borylated compounds have been shown to undergo condensation and Suzuki-Miyaura reactions and could be converted to acyl trifluoroboronates in good yields. Enabled by acylboronates' chameleonic behaviour synthesis of building blocks might find application in drug discovery.



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Synthesis of a hexasaccharide epitope towards a vaccine against Group B Streptococcus

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Streptococcus agalactiae is a Gram-positive bacteria known as Group B Streptococcus (GBS). Type III of GBS bacteria is dangerous because pregnant women can infect new-born during childbirth. The WHO and the London School of Hygiene and Tropical Medicine urging the development of a vaccine as a matter of urgency after conducting a new study published in November 2021. According to the report, 91,000 deaths from newborn, 46,000 stillbirths and 40,000 infants with neurological disorders are due to GBS worldwide in 2020 [1]. The surface of the bacteria is made of a thick layer of poly-sialylated capsular (PSC). Moreover, the PSC is a key for immune response because of its virulence factor [2]. The capsular is a saccharide polymer consisting of a sequence of five sugars. Glycovaccine admits generally weak immune response, so adjuvant like Toll-Like Receptor (TLR) is combined at the proteinic platform to enhance this response. The recent identification of a hexasaccharide that binds to specific monoclonal antibodies convince us that compound **1** could be an interesting target. [3].

The synthesis of target **1** requires five glycosylations and four building blocks. All glycosylations need orthogonally protected sugars to ensure desired glycosylation regioselectivity. Also, specific conditions are necessary to form the proper anomers. The first glycosylation links a thioglycoside with a galactose residue promoted by *N*-iodosuccinimide under acidic conditions to form building block **2**. The second glycosylation binds the latter building block to *N*-phtalimido-glucose **3** with trimethylsilane triflate (TMSOTf) as promoter. The third glycosylation is achieved using silver triflate between the trisaccharide and lactose **4** to provide a pentasaccharide. Finally, glycosylation is operated with TMSOTf with donor **5** to generate target **1**.

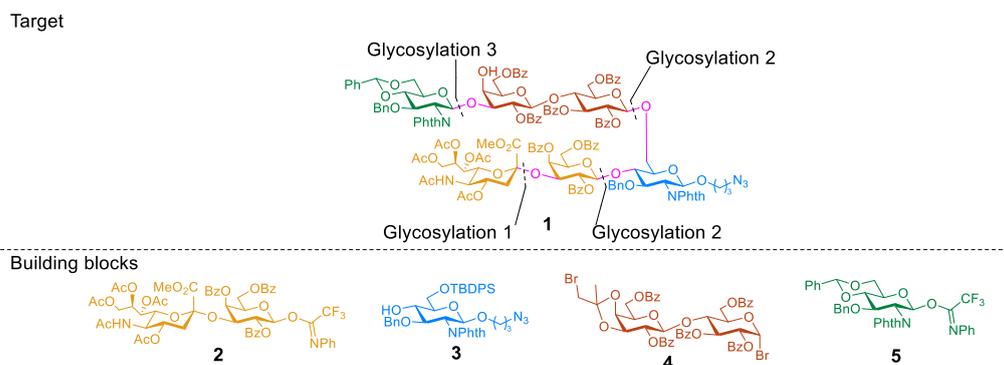


Figure 1. Top: Hexasaccharidic antigen; Bottom: Building blocks

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Mechanistic Insight into Iminium Catalyzed Diels-Alder Cycloaddition

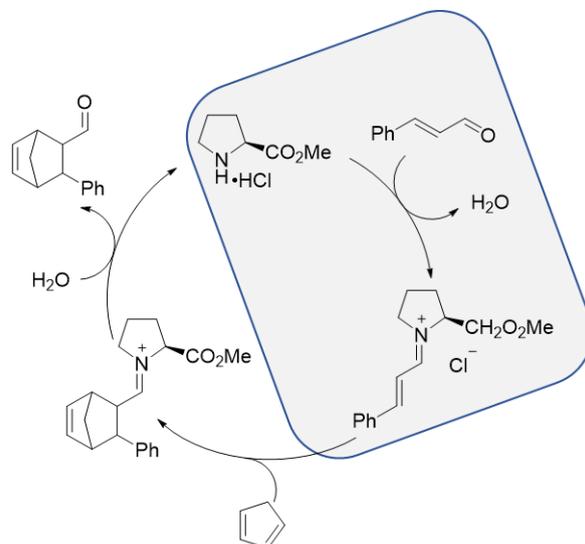
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Asymmetric organocatalysis has gained significant momentum in the past years and has been applied to reactions such as aldol reactions and Diels-Alder cycloadditions. Secondary amines have been used in LUMO lowering-type activation in many reactions, including the Diels-Alder cycloaddition. They activate the electrophile (aldehyde) by forming a reactive iminium intermediate, which then proceeds to react with the nucleophile (diene). When the secondary amine used is chiral, the iminium formed is also chiral, and can therefore induce stereoselectivity in the product formation. Interested in the computer-aided design and development of effective asymmetric organocatalysts, we noted that some details of the mechanisms were missing, in particular in the formation of the activated intermediates. We therefore embarked on an investigation, looking into the atomistic details of the iminium formation. In our study, we combine our group's expertise in both computational and experimental chemistry, and aim to provide a more detailed mechanism for the formation of the iminium, supported by experimental and computational data. [1, 2]



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pK_a Scale for Cyclopropenium Ions with Applications in CO₂ Capture

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Molecular acid–base properties are essential for predicting reactivity and understanding chemical systems. This concept holds for cyclopropenium ions and their broad use as (organo)catalysts, ligands, redox-flow batteries, and applications in materials sciences. In view of this significant status, and with it, the critical importance of acidity, we present a comprehensive computational study of the pK_a values of cyclopropenium ions employing a subset of 70 structurally diverse cyclopropenium derivatives. Capitalizing upon these computed findings, and with an eye toward greenhouse gas trapping, we further document the timely use of a cyclopropenium-cyclopropenylydene coupled platform for CO₂ capture and light-triggered release.¹

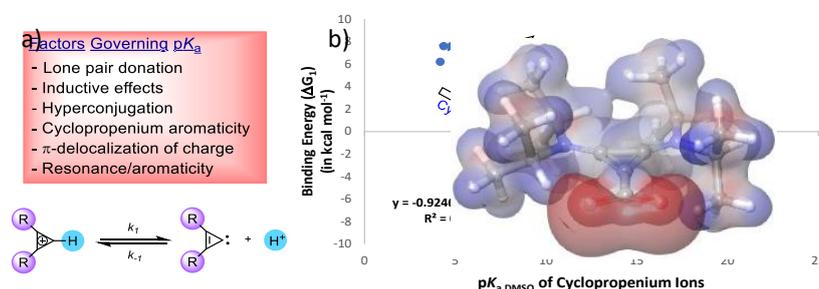


Figure. a) Cyclopropenium acidities and factors governing pK_a. b) Relationship between cyclopropenium-CO₂ binding energy versus pK_a(DMSO) of cyclopropenium ions.¹

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The Effect Of Sterol On Vesicular Nanovector Formation Of Amphiphilic Ionic Liquids In Water

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The impact of cholesterol (Cho) on vesicles formation of 1-hexadecyl-3-vinylimidazolium bromide (C₁₆VnImBr), 1-hexadecyl-3-methylimidazolium bromide (C₁₆MeImBr) and hexadecyltrimethyl ammonium bromide (C₁₆Me₃ABr) were studied in aqueous medium at 298.15 K. UV-Vis spectroscopy was employed to study the transition of spherical micelles to unilamellar vesicles. Methyl orange (MO) and Sudan-III dyes, which are sensitive to medium of polarity, were used as spectroscopic probe. At the same concentration of Cho, hypsochromic shift in absorbance maxima of dyes are more for Cho/C₁₆VnImBr mixtures compared to Cho/C₁₆MeImBr and Cho/C₁₆Me₃ABr mixtures, indicated bilayer of vesicles for Cho/C₁₆VnImBr mixtures provides more hydrophobic environment. Hydrodynamics diameter obtained from DLS revealed that Cho/C₁₆VnImBr mixtures in aqueous solution provided large unilamellar vesicles as compared to Cho/C₁₆MeImBr and Cho/C₁₆Me₃ABr mixtures. Size distributions obtained are monomodal with low PDI shows formation of uniform vesicular architectures. TEM measurements confirmed shape and size of the obtained unilamellar vesicles. Stability of the vesicles on dilution with water was investigated by methyl orange dye. The associations of vesicles are mainly due to interaction between the head groups of amphiphiles with hydroxyl group of cholesterol along with strong hydrophobic- hydrophobic interactions.

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Exploration of Organosilanes as Agents for Catalytic Amide Synthesis

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Amides, both natural and synthetic, are the backbone of many important biologically active molecules, polymers, and commercial products. Thus, amide synthesis is a fundamental reaction in synthetic organic chemistry. The most common method to make amides uses coupling reagents to activate the carboxylic acid making the hydroxy a better leaving group. Amongst these, carbodiimides, uronium and phosphonium salts, and benzotriazoles are widely used.[1] These routes to amides are often limited by poor atom economy and/or toxic and expensive reagents. Accordingly, the ACS Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) listed sustainable direct amide bond formation as one of their ten key green chemistry research areas in 2018.[2] Organosilanes have recently been reported as greener, efficient alternative amide coupling reagents. These methodologies present a significant advancement towards direct amide bond formation using silicon-based coupling reagents, however, current work in this field requires a stoichiometric (or more) amount of the silane.[3] While stoichiometric amide coupling reactions are still the methods of choice for their effectiveness and practicality, catalytic amide coupling reactions lead to greener methodologies with superior efficiency. The MJA Lab is currently investigating novel organosilane catalysts for direct amide bond formation and the development of a silicon catalyst for this transformation presents an advancement on existing catalytic methodologies. The silane catalysts are designed to have enhanced reactivity by incorporating a hydrogen bond donor to facilitate the formation of a silyl ester intermediate and nucleophilic attack at the carbonyl by the amine. Different organosilanes have been synthesized through various methods and are being tested as catalysts for the synthesis of amides from unactivated carboxylic acids and amines.

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Investigation of Masked *N*-Acyl-*N*-Isocyanates: Support for Oxadiazolones as Masked *N*-Isocyanate Precursors

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While carbon-substituted isocyanates are common building blocks, the use of *nitrogen*-substituted isocyanates is rare and their chemistry is underdeveloped. Reports of their *N*-acyl derivatives (i.e. amido-isocyanates) are exceedingly rare. [1] Herein, amido-isocyanates were investigated in the context of syntheses of *aza*-tripeptide and hydantoin subunits starting from simple bench-stable precursors. [2-3] A key finding is that the amido-isocyanate formed *in-situ* cyclizes to yield an oxadiazolone, and that under suitable reaction conditions, this heterocycle is a traceless blocked (masked) *N*-isocyanate. Using organic bases as catalysts and upon heating with various nucleophiles, oxadiazolone formation is observed to provide the desired azadipeptides or hydantoins in yields ranging from 51% to 91%. Further support for an amido-isocyanate intermediate was obtained using carboxylic acids as nucleophiles, affording *N*-acylhydrazide products.

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Synthesis and Physical and Biochemical Analysis of Analogues of PS-3114, a non-Nucleoside Inhibitor of DNMT3A

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DNA methylation is a stable epigenetic modification that leads to the installation of a methyl group at position 5 of cytosine [1]. Dysregulation of DNA methylation processes has been observed in several types of cancer leading to silencing of promoter regions of tumor suppressor genes [2]. It has been found that this change can be reversed and genes reactivated by inhibiting DNMTs [3]. Currently, the only approved drugs that target DNMTs are Vidaza and Dacogen for the treatment of myelodysplastic syndrome. However, these drugs, which have a nucleosidic structure, have poor PK profiles, are non-selective and are cytotoxic since they rely on a mechanism involving incorporation into the genome [4]. Thus, there is an urgent need to develop new powerful non-nucleoside inhibitors of DNMTs which have good biophysical properties and exhibit minimal toxicity. Our group recently identified by ¹H-NMR fragment screening PS-3114, a small molecule with an average IC₅₀ of 78.5 μM against DNMT3A. In this work, the synthesis of derivatives of PS-3114 will be presented to demonstrate the presence of SAR. The preparation of derivatives was guided by molecular docking studies and their behavior in solution and binding to DNMT3A was determined by ¹H-NMR analysis. The inhibitory activity of the compounds against DNMT3A was measured by a fluorescence and a radioactivity test.

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Spectroscopic and Photophysical Properties of Cytosine-based Fluorophores and G-Quadruplex Disruptors

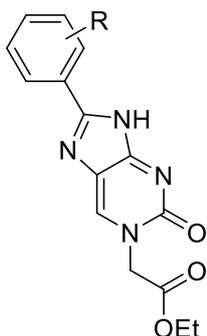
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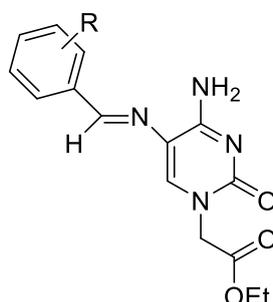
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Cytosine-based fluorophores are useful as probes for studying the structure and properties of nucleic acid-based materials. We have prepared a series of phenyl-imidazolocytosine compounds that remain complementary to guanosines and have examined their fluorescence properties.[1] These blue and yellow fluorophores were highly emissive (quantum yield > 0.3). In addition, our synthesis also produced non-fluorescent 5-phenyl-imino-cytosines that are soluble in non-protic NMR solvents and analyzed their binding affinity to guanosine via NMR titration. The association constants were observed to be high ($K_a > 10^4 \text{ M}^{-1}$). These compounds are also being investigated as potential disruptors of G-quadruplexes [2].

Figure:



**Phenyl-Imidazolo-Cytosine
Fluorophores**



**5-Phenyl-Imino-Cytosine
Non-Fluorescent G-Quadruplex Disruptors**

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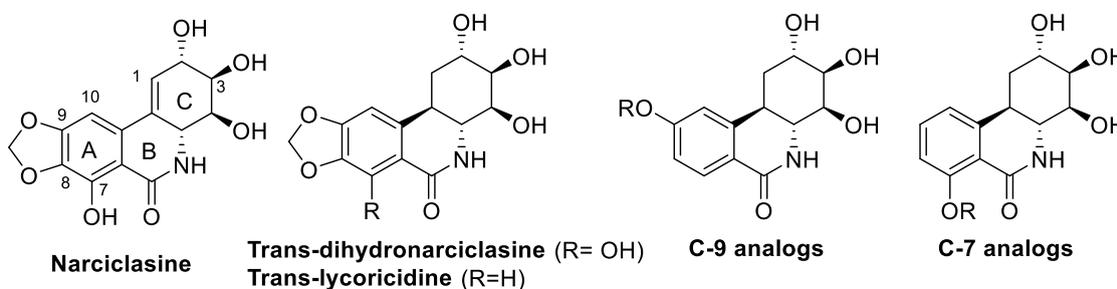
Synthesis of Amaryllidaceae alkaloid analogs discovers a potent antiviral activity to HSV-1 and SARS-CoV-2.

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The antiviral activity of Narciclasine and alkaloids of the lycorane sub-class was reported three decades ago. The potent antiviral activity of *trans*-dihydronarciclasine and *trans*-dihydrolycoricidine to DNA viruses such as Herpes (HSV-1, VZV) and RNA viruses, including Zika (ZIKV) has been described [1-3]. The overall RNA-virus activity of these alkaloids for developing novel anti-coronavirus drugs has recently been stated. The present work involved the iminium-ion mediated asymmetric organocatalytic stepwise [3+3] Michael-aldol sequence and epoxidation and Banwell-modified Bischler-Napieralski cyclization reactions as key steps [3-4]. The current development of synthesizing C-9 and C-7 analogs in the McNulty group will be presented.

Figure:



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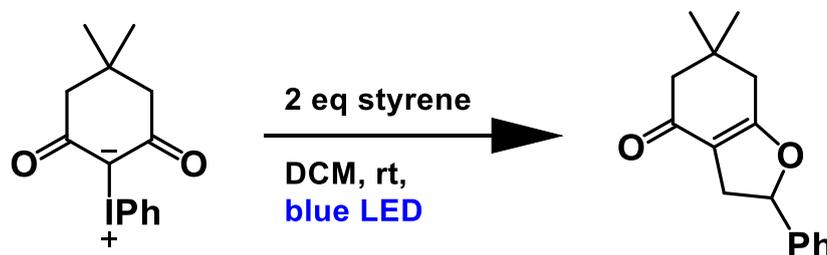
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Green Chemistry from Blue Light: Dihydrofurans from Blue LED Irradiation of Iodonium Ylides with Alkenes

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Hypervalent iodine has been in recent advancement in organic chemistry for its unique synthetic reactivity and mild reaction conditions. Here, iodonium ylides are irradiated using blue LED for formation of a dihydrofuran product which is an important precursor for natural product synthesis and synthetic chemistry. Previous dihydrofuran products have been made using high energy light sources and metals as well as through isomerization from the cyclopropane. Thus, a more environmentally friendly method using blue light is obtained. The mechanism and selectivity of the dihydrofuran product was investigated along with an optimized and developed reaction scope. Both meta and para electron withdrawing and electron donating styrene substituents with iodonium ylides under blue LED produced the dihydrofuran product in yields of 75-99%.



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