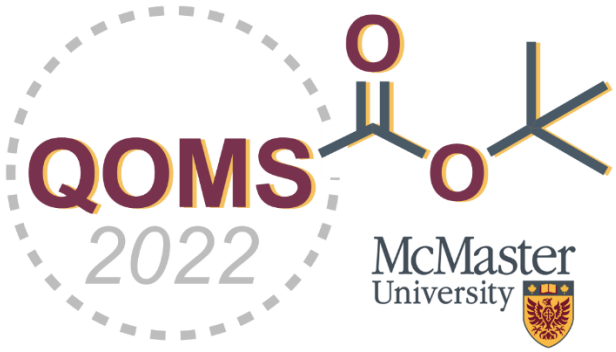
Oral Presentations
Abstract Booklet



Mining the Reactivity of Dearomatized 4-Alkylpyridines

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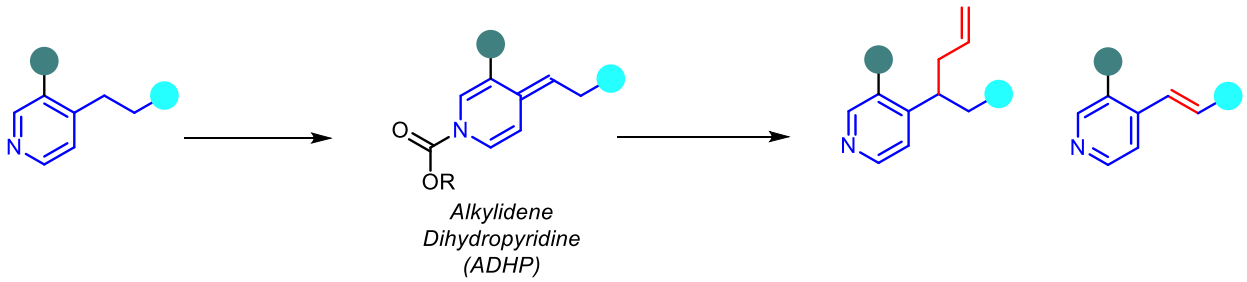
Pyridines and related heterocycles enjoy widespread occurrence in biologically relevant natural products and drug-like molecules. Therefore, new methods that facilitate their synthesis and incorporation into drug-like structures will likely have a significant impact on the drug development process. 4-Alkylpyridines can be dearomatized using a 'soft enolization' approach to generate alkylidene dihydropyridines (or ADHPs). These semi-stable intermediates present many opportunities for diversification of 4-alkylpyridines, providing access to attractive building blocks for discovery chemistry. Using ADHPs we have recently developed palladium catalyzed allylation and dehydrogenation of 4-alkylpyridines [1-2]. These reactions tolerate a broad range of sensitive functional groups and activated positions, and display pyridylic selectivity. In this presentation, I will provide a summary of our efforts towards the development of the two reactions.



Alkylidene Dihydropyridine (ADHP)

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Versatile Palladium-Catalyzed Approach to Acyl Fluorides and Carbonylations by Visible Light and Light-Driven Operations

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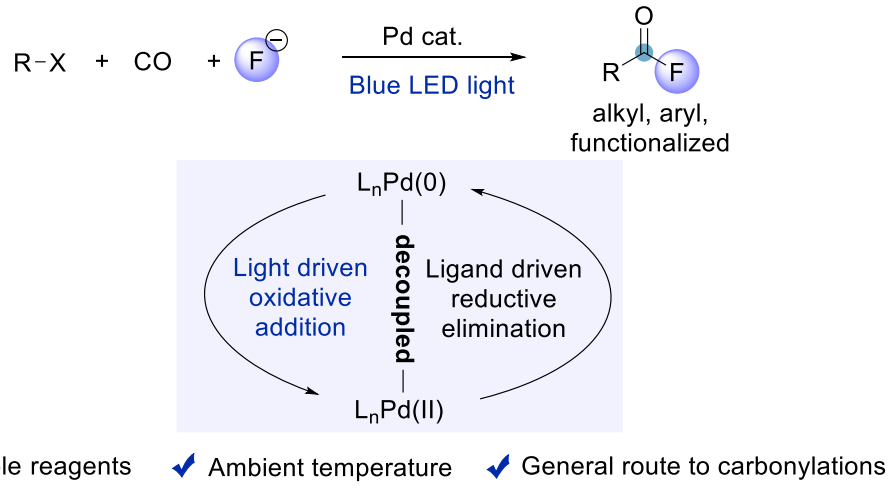
We develop a general palladium-catalyzed carbonylative method to synthesize acyl fluorides from aryl, heteroaryl, alkyl, and functionalized organic halides. The reaction is believed to proceed via the synergistic combination of visible light photoexcitation of Pd(0) catalyst to induce oxidative addition together with a ligand-favored reductive elimination. These together create a unidirectional catalytic cycle that is uninhibited by the classical effect of carbon monoxide (CO) coordination. Coupling the catalytic formation of more stable acyl fluorides with their subsequent nucleophilic reactions has opened a method to perform carbonylation reactions with wide breadth, including the assembly of highly functionalized carbonyl-containing products and drug-liked molecules.



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SPAAC Incorporation of Fluorine into FC131 Analogues Towards the Discovery of CXCR4 Radiopharmaceuticals

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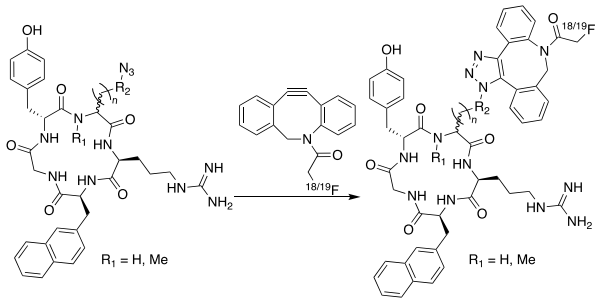
The cyclic pentapeptide FC131 binds the CXCR4 receptor with high affinity and can be used as a targeting entity in the development of ^{18}F-labelled PET imaging agents. Due to the time constraint of radiolabelling, click chemistry is an attractive class of reactions to introduce a ^{18}F-labelled prosthetic group to a targeting entity specific for a biological target. Strain-promoted alkyne-azide cycloaddition (SPAAC) allows for facile, bioorthogonal conjugation of an imaging moiety with a targeting peptide and thereby is an effective strategy for radiolabelling. We propose the incorporation of a fluorine-containing azadibenzocyclooctyne (F-ADIBO) imaging moiety to the cyclic peptide FC131, by attaching the F-ADIBO in a position known to be accepting of bulky substituents [1]. A focused library of F-ADIBO FC131 analogues were synthesized through modifications to D and L stereochemistry, *N*-methylation, side-chain length, and linker composition. The library of FC131-based peptides were synthesized using standard Fmoc solid-phase peptide synthesis, purified by preparative HPLC, and characterized by high-resolution mass spectrometry. An azide-containing unnatural amino acid was incorporated in the peptide sequence allowing for SPAAC conjugation to ^{19}F-ADIBO, which was produced following a seven-step synthetic scheme [2]. The peptides were evaluated for binding toward the CXCR4 receptor through a competitive radioligand displacement binding assay using a U87 cell line transfected to overexpress CXCR4 [3]. Successful high-affinity peptide binders are subsequently being translated into PET cancer imaging probes by substituting the non-radioactive ^{19}F-prosthetic group with its ^{18}F-analogue. This study demonstrates the straightforward incorporation of the small molecule imaging moiety F-ADIBO and its ability to functionalize the FC131 peptide core toward the discovery of PET radiopharmaceuticals.



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Rhodium-Catalyzed Enantioselective Pauson-Khand Reaction of 1,6-Chloroenynes with 1,1-Disubstituted Olefins

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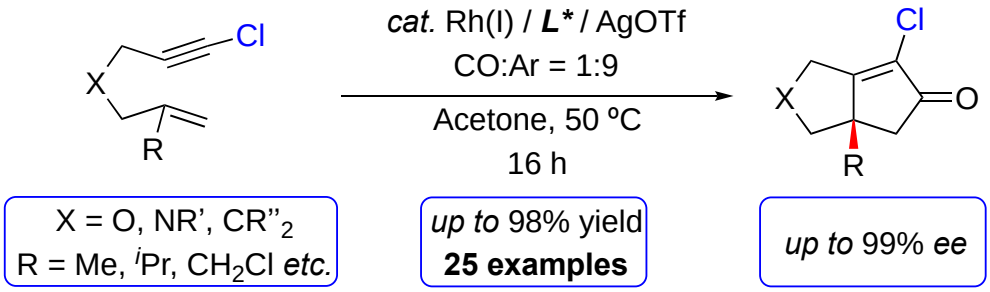
The transition metal-catalyzed Pauson-Khand Reaction (PKR) provides a convenient approach towards bicyclopentenones, which are a privileged motif present in bioactive targets [1,2]. Although the enantioselective variant of the PKR is dominated by simple 1,6-enynes with terminal olefins, substrates with substituted olefins are underdeveloped. Nevertheless, leveraging polysubstituted olefins offers potential to install multiple stereocenters with defined configuration, including quaternary stereogenic centers. This presentation will describe a new approach for the enantioselective rhodium-catalyzed PKR using 1,6-chloroenynes that permit deployment of a wide range of 1,1-disubstituted olefins. Importantly, DFT studies provide insight into the origin of excellent enantiocontrol, which is supported experimentally. Hence, this unique approach highlights the ability for a 1,6-chloroenyne to function as a "Universal Alkyne" to overcome the requirement for substrate activation via specific alkynyl substitution, thereby allowing the diversification on resulting PK scaffold to extend the synthetic utility.



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Synergistic Organoboron/Palladium Catalysis for Regioselective *N*-Allylations of Azoles with Allylic Alcohols

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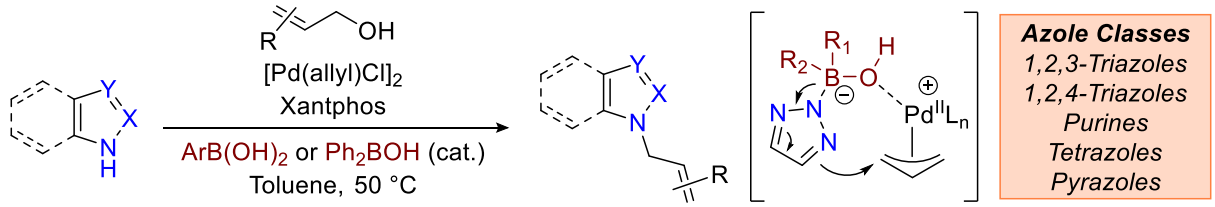
Regioselective *N*-functionalization of ambident nitrogen heterocycles is a significant topic, given the applications of such structures in medicinal and coordination chemistry [1,2]. This talk will describe a palladium-catalyzed allylic alkylation of azoles using simple allylic alcohols as electrophiles. Addition of an arylboronic or diarylborinic acid co-catalyst serves two purposes, promoting ionization of free allylic alcohols toward π-allylpalladium formation and subsequent delivery of an ambident heterocyclic nucleophile to this intermediate in a regioselective manner. The method was applied to a variety of substituted aromatic *N*-heterocycles including 1,2,3- and 1,2,4-triazoles, purines, tetrazoles, and pyrazoles for regioselective allylation, and was also suitable with substituted allylic alcohols as electrophiles. Examples of "contrasteric" allylation were also noted, in which the more hindered allylation product was formed in the presence of the organoboron catalyst. Regiochemical outcomes are proposed to arise by the mode of coordination of the heterocycle to the organoboron catalyst.



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Development of Small-Molecules TEAD Inhibitors Derived from Flufenamic Acid

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The Hippo pathway regulates organ size and tissue homeostasis by controlling cell proliferation and apoptosis via the YAP–TEAD transcriptional complex [1]. Dysregulation of the Hippo pathway in cancer cells results in the over expression of genes that regulate cancer cell growth and proliferation [2-3].

In 2015, flufenamic acid (FA) was reported to bind in the TEAD palmitic acid pocket, leading to reduction of the expression of associated oncogenes [4]. In this talk, I will present our investigations into the replacement of the trifluoromethyl group of FA by aromatic groups, leading to compounds with increased affinity for TEAD. The impact of these compounds on the activation and expression of TEAD-associated genes will be presented and a docking model will be proposed to explain the binding mode of these compounds.

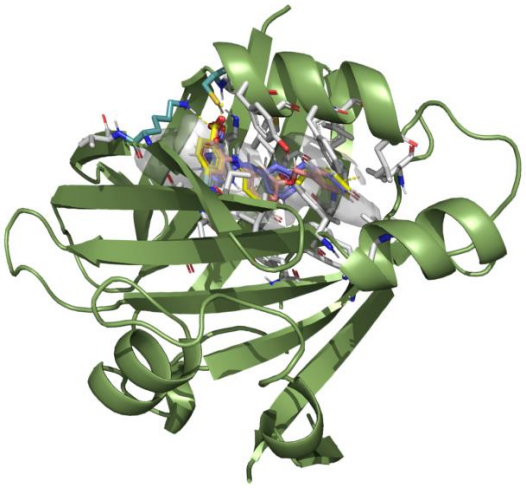

Figure: Docking of Small Molecules Inhibitors in the Hydrophobic Pocket of TEAD Protein

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Towards Depeptidized Aminoboronic Acid Derivatives Through the Use of Borylated Iminium Ions

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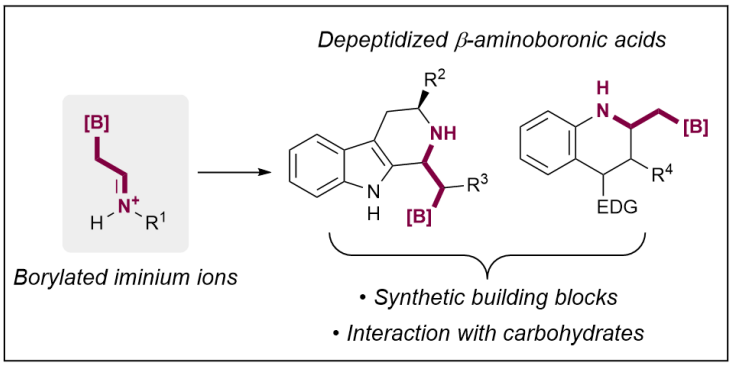
Aminoboronic acids are analogues of amino acids with applications in biomedical sciences, synthesis, and catalysis. Research efforts on this class of compounds have mostly focused on α-aminoboronic acids, especially for their use as serine protease inhibitors. β-Aminoboronic acids have been relatively less studied despite some promising applications. Current methods for the synthesis of β-aminoboronic acids are limited either by narrow substrate scope or by the necessity for substrates pre-functionalization. Our group has developed several methyliminodiacetate (MIDA)-protected borylated building blocks that can be used to synthesize aminoboronic acids from modular multicomponent reactions. While we have previously focused on accessing peptidomimetic aminoboronic acids, this presentation will focus on using α-boryl iminium ions to access nonpeptidic branched β-aminoboronic acids functionalized with biologically relevant heterocycles. We investigated the interaction of these new compounds with carbohydrates under physiological conditions and demonstrate their potential as synthetic intermediates to polycyclic scaffolds [1].



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Dual-Metal Catalysis to Permit the Use of Unprotected Alcohols in Suzuki-Miyaura Reactions

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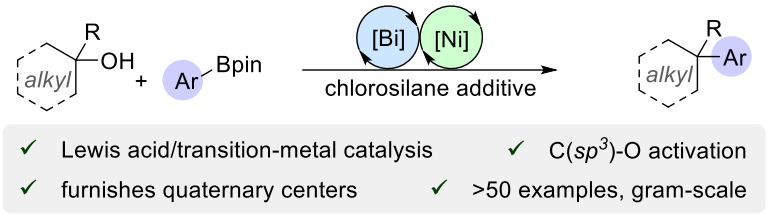
Suzuki-Miyaura cross-coupling has emerged as a valuable tool for modern chemists who aim to rapidly generate molecular complexity [1]. Most often, these reactions are performed with aryl-sp^2 hybridized organohalides/pseudohalides – although reliable, the necessity for these species to be prepared synthetically along with concerns regarding their environmental and metabolic consequences has prompted chemists to search for alternative electrophiles for use in their place [2]. The field of C-O activation has emerged to propose a solution to this problem, as C-O bonds are naturally abundant and their activation often leads to environmentally benign byproducts.

While remarkable strides have allowed for the employment of a diverse range of activated C-O bond-bearing species in cross-coupling reactions, the use of unprotected alkyl-sp^3 hybridized alcohols – often viewed as the ideal electrophilic coupling partner – has remained limited [3]. Recent research in the Newman lab has seen the development of a Lewis-acid/transition metal catalyst system to approach this problem, successfully allowing for the use of cyclic tertiary alcohols as electrophiles in nickel-catalyzed Suzuki cross-coupling reactions. A range of alcohols have been demonstrated to undergo this transformation, while mechanistic investigations have revealed the synergistic importance of both a Lewis acid and silane additive, suggesting that electrophilic activation of the alcohol group facilitates activation by the Ni catalyst.



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Cerium-HAT Photoredox Catalyzed Hydroalkylation

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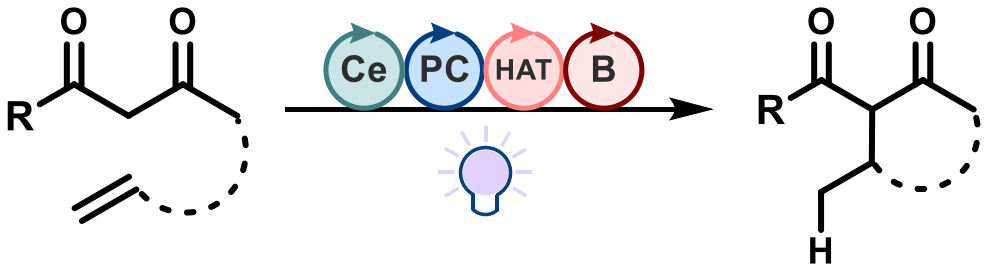
A photoredox system utilizing cerium/hydrogen atom transfer catalysis enables radical hydroalkylation of 1,3–dicarbonyls onto electron rich and unactivated alkenes. An equivalent oxidative transformation is known using manganese triacetate that requires stoichiometric metal reagents and harsh conditions [1]. Modern photocatalysis allows access to the requisite high energy radical intermediates in a milder manner using catalytic amounts of earth–abundant cerium and organic dyes. To date, moderate to excellent yields have been achieved for intramolecular cyclizations and intermolecular additions. Evidence for the role of catalytically generated atomic chlorine in substrate activation will be discussed.



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Mechanistic Insights of a Stereoselective Oxidative Cyclization for POP Inhibitors, Discovery of Pathways by Computational Modelling

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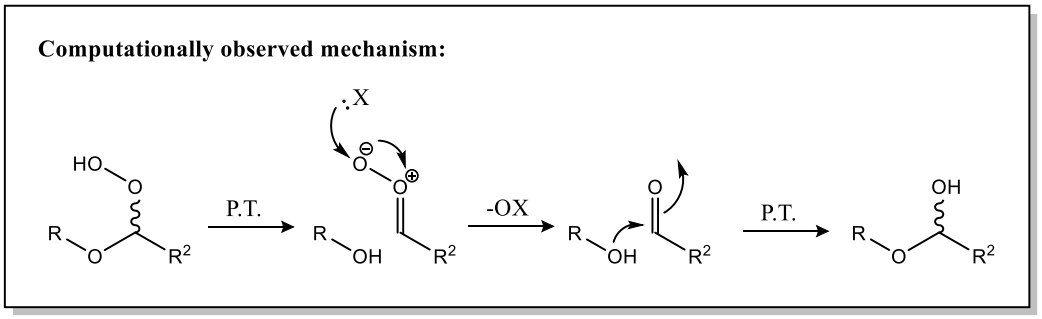
Stereoselective reactions are among the most important and fundamental tools available to synthetic chemists. Chiral centers appear in a wide variety of organic molecules including pharmaceuticals, building blocks, natural products, and industrially or commercially relevant molecules to name a few. As such, the ability to perform stereoselective transformations is highly valuable. One drawback is often the lack of supporting information and evidence for a mechanism which hinders further development and optimization of the chemical systems. Developed by our group is a bicycle scaffold that has applications for prolyl oligopeptidase (POP) inhibition, a protein has which been linked to several neurodegenerative diseases. A key step of the synthesis for the bicycle is a stereoselective oxidative acid catalyzed cyclization. This features a partial ozonolysis and is proposed to be followed by an intramolecular nucleophilic attack resulting in cyclization. Intriguingly, the reaction is stereoselective depending on what reducing agent is used and notably, the achiral reducing agents dimethyl sulphide and triphenylphosphine afford different diastereomers. DFT calculations were used to gain a better understanding of the chemical system and reason for the selectivity observed. The proposed mechanism and preliminary computational modelling with molecular dynamics suggested a steric preference for one of the intermediates formed. However, observations from further modelling of the reaction refute this possibility and additional computational studies suggested a new pathway which to the best of our knowledge, has not been reported in the past (Figure 1). Spontaneous ring opening followed by rapid concerted reduction of the regenerated Criegee Intermediate (CI) proceeds through a surprisingly low energy barrier. Additionally, cyclization is not observed to proceed through an oxonium intermediate but rather through an S_N2 like behaviour. Reported is the use of computational modelling to determine the mechanism of a stereoselective reaction that proceeds through an unexpected pathway.

Figure 1.



Invoking Palladium-Vinylidenes for the Modular Synthesis of Photoluminescent Bis-Heterocycles

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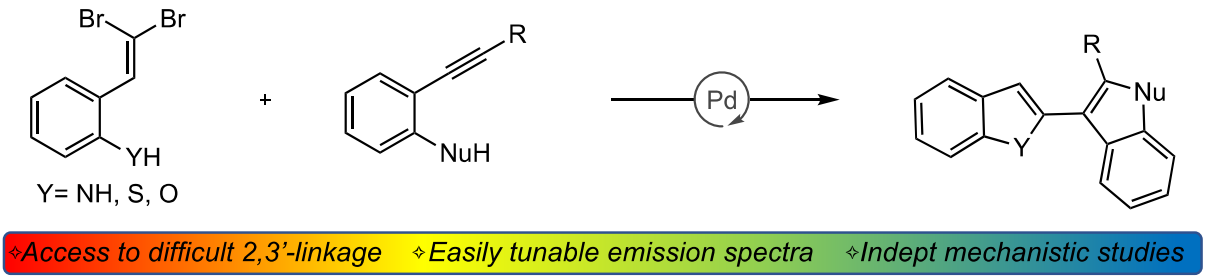
Palladium domino catalysis has existed at the forefront of synthetic methodologies to forge an array of heterocycles. The development of new coupling reactions to link heterocycles represents an important goal in order to assemble core scaffolds that are found as pharmaceutical agents and novel materials. We report a palladium-catalyzed strategy to access unsymmetrically linked bis-heterocycles through coupling an indole reaction developed in our lab, with a palladium (II) cycloisomerization reaction, to generate 2,3'-linked bisheterocycles. Through this methodology, we have synthesized 45 bis-heterocycles in up to 98% yield. We have also explored the fluorescent properties of these compounds to formulate a computationally driven synthetic strategy to access a wide array of emission wavelengths and quantum yields up to 0.59. Mechanistic studies, along with DFT analysis suggest the intermediacy of a palladium vinylidene that undergoes a 1,1-insertion. This transformation provides an efficient route to industrially relevant molecules, thereby making this a valuable asset in the toolbox of synthetic chemists.



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Synthesis of Chemo-ID Enabling Compounds - A Method for Determining Drug-Protein Interactions

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We propose a novel method called Chemo-ID for determining in vivo drug-protein interactions, thereby predicting drug side reactions and informing on mechanisms of action. Chemo-ID is based on the well-established method of Bio-ID in which a protein of interest (the bait protein) is fused to a biotin ligase enzyme called BirA. In a Bio-ID experiment, the protein interactome of the bait is identified through the proximity-dependent biotinylation catalyzed by the pendant BirA. In Chemo-ID, the bait protein is replaced with a bait small molecule (drug). In a live cell, this construct catalyzes the biotinylation of proteins that closely associate with the bait drug. We envision assembling the bait drug-BirA construct within a live cell *via* either genetic code expansion or halo-tag conjugation. In the genetic code expansion approach, the BirA protein is expressed bearing a strained alkyne click partner, and the bait drug, modified with an azide group, is then covalently appended *via* bioorthogonal strain-promoted azide-alkyne cycloaddition. In the halo-tag approach, the BirA protein is expressed as a fusion with a protein called halo-tag, which selectively forms a covalent linkage with the bait drug, modified with a chlorohexyl group. The realization of Chemo-ID requires the chemical synthesis of unnatural amino acids bearing a strained alkyne side chain for incorporation into BirA, as well as the modification of a bait drug with an appropriate tether to an azide or chlorohexyl group. To validate this method, early experiments employ bait drugs with well-studied protein interactions. Future work on this project will entail the exploration of a wider variety of bait drugs and click partners.

An Organocatalytic Oxy-Cope/Michael Cascade Reaction

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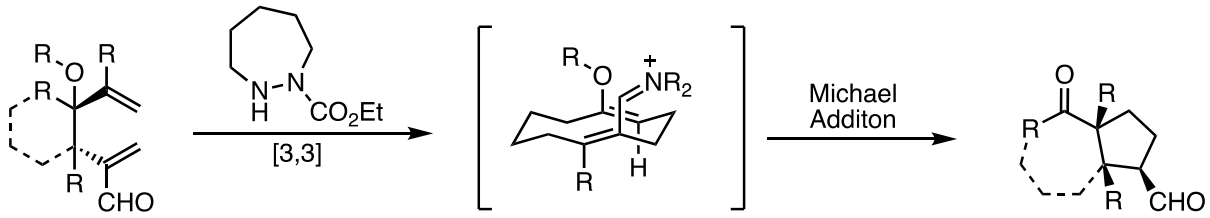
Our group has discovered a diazepane carboxylate catalyst to accelerate the all carbon cope rearrangement via LUMO-lowering catalysis[1]. In an effort to extend this rearrangement towards more synthetically valuable targets, our group pursued the oxy-Cope variant, which possess a thermodynamic driving force and sees significantly more use in synthesis. It was envisioned that the final product of the oxy-Cope would not be of that of a simple rearrangement, but one where the resulting enol/enol ether intermediate would further react via a Michael addition to furnish cyclopentane-containing products. The reaction proceeds with a range of 3 - hydroxy and 3–alkoxy-1,5-hexadiene-2-carboxaldehydes substrates, including both cyclic and acyclic substrates, and tolerates substitution on the vinyl substituent in good yield, at ambient temperature with a co acid present. Substrates fused on a cycloalkane framework undergo net ring-expansion/cyclopentannulation with a high degree of stereocontrol via chairlike transition states. This methodology allows quick access into natural products such as isodaucene that contains a 5-7 bicyclic framework and the fusicoccin/ophiobolin families that encompasses 5-8-5 tricyclic skeletons.



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Mechanochemical Synthesis of 3,5-Isoxazoles and Their application in the Desymmetrization of Unbiased Poly(alkynes)

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The synthesis of heterocycles has constituted a proliferate and growing area in organic chemistry. Specifically, isoxazole motifs are among the most frequently encountered heterocycle in many drug candidates and a versatile intermediate in synthesizing natural products [1]. Among the possible di-substitution patterns of isoxazoles, 3,5-isoxazoles (**1**) have been regularly encountered because of their synthetic accessibility [2]. However, significant drawbacks are commonly encountered for the solution-based protocols, such as the long reaction times, low atom economy, and low energy efficiency. Alternatively, mechanochemical synthesis has been utilized in synthesizing complex organic molecules, demonstrating unprecedented modes of reactivity and selectivity with a lower environmental impact [3]. Although the 3,5-isoxazole motif (**1**) has found application in diverse areas, only a limited number of reports have applied mechanochemistry, and have shown the impact of isoxazole in the synthesis of more intricate molecules [3]. Herein, we would like to discuss the impact of mechanochemistry in synthesizing 3,5-isoxazoles (**1**) from terminal alkynes (**2**) and hydroxyimidoyl chlorides (**3**) *via* a 1,3-dipolar cycloaddition catalyzed by a recyclable Cu(II) nanocomposite (**Figure 1a**). Additionally, we would like to deliberate further the impact of mechanochemistry in cycloaddition type reactions in the desymmetrization of unbiased poly(alkynes) (**4**) to selectively access unprecedented 3,5-isoxazoles-alkyne adducts, which allows for the modular synthesis of unsymmetrical bis(3,5-isoxazoles) systems (**6**) (**Figure 1b**).

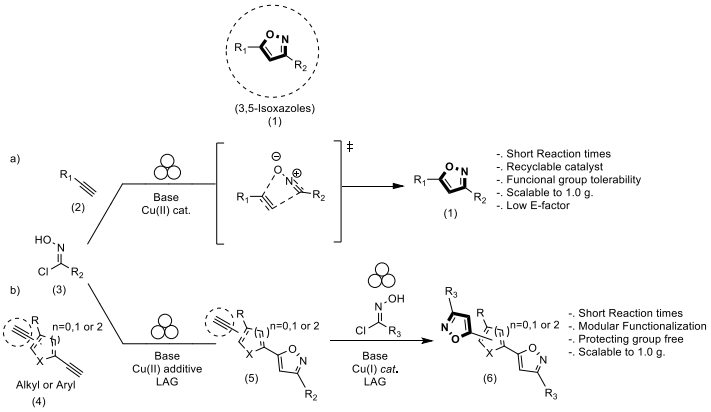

Figure 1: Schematic representation of (**a**) the mechanochemical synthesis of 3,5-isoxazole (**1**) and (**b**) mechanochemical desymmetrization of unbiased symmetrical poly(alkynes) (**4**).

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Do Antarafacial Cycloadditions Occur? Cycloaddition of Heptafulvalene with Tetracyanoethylene

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The cycloaddition of heptafulvalene (**1**) with tetracyanoethylene (TCNE) was previously described as an example of an antarafacial cycloaddition, a [$14_{\pi a}$+$2_{\pi s}$] process that afforded only the *trans*-cycloadduct [1] by virtue of an edge-to-face approach of TCNE and facilitated by the S-shape of **1**. The reaction has been investigated in depth and found not to be a concerted antarafacial process. At low temperature, the reaction is observed to give a mixture of *cis*-and *trans*-cycloadducts as well as a [4+2] adduct. The mixture of products is converted to the *trans*-cycloadduct by equilibration upon warming to room temperature. Studies with diethyl 2,3-dicyanofumarate and -maleate confirmed the formation of *cis*-cycloadducts, which were stable at room temperature. DFT studies (M06-2X/6-311+G(2d,p)//M06-2X/6-311+G(d), SCRF=acetone level of theory) show that the originally proposed edge-to-face approach of TCNE to **1** is highly disfavoured, while a stepwise mechanism involving addition of TCNE at C2 to form a zwitterion followed by collapse at either C2'or C7' forms the [14+2] cycloadducts. The Diels-Alder adduct is also formed in a stepwise reaction by competitive addition of TCNE at C4 of **1** [2].

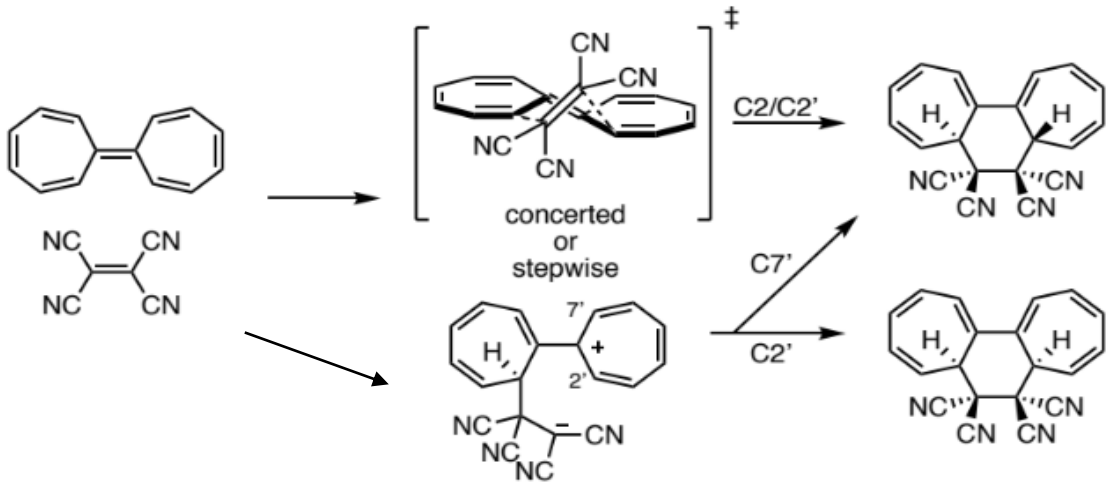

Figure:

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Making Venom on Demand: A Surprising Medical Need for Conotoxins and Our Efforts to Increase Supply

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Conotoxins, contained in the venom of cone snails, can be used to study pain pathways to create new drugs for pain relief and management, neuromuscular paralysis to optimize surgical conditions, and treat convulsive disorders and neurological conditions. [1] However, only minute amounts can be obtained by traditional venom extraction, limiting the availability to conduct clinical trials. This results in a vital need for a practical way to produce these and other similar cysteine-rich toxins, especially when unintended disulfide bonds pairing can easily occur to give unwanted protein conformations while folding. Orthogonal protecting groups on the cysteine sidechains are used to prevent such things during peptide synthesis. However, current protecting group strategies in literature are costly and low yield, requiring multiple steps and purification. [2]

The Team Trant investigates thermal-liable protecting groups to assist in the selective release of cysteine pairs in a single pot using a singular temperature trigger and bypassing the need for multiple steps. This talk will highlight the team's recent development around S to N shift complication from original designs into modified models and incorporating them into peptide synthesis.

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Palladium-Catalyzed Electrochemically Driven Carbonylation: Oxidation State Shuffling as a Catalyst Design Tool

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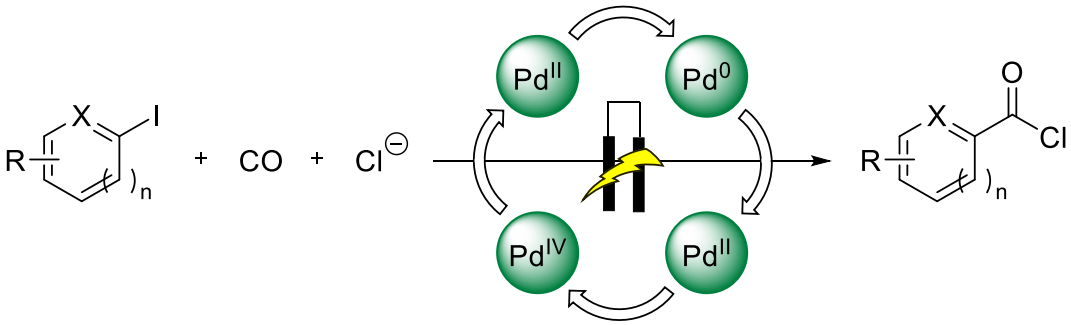
Carbonyl-containing products are perhaps the most common structural motif found in pharmaceuticals and other synthetic materials. Metal catalyzed carbonylation reactions offer an efficient method to access these structures but are usually limited to high temperatures and pressures and the use of relatively reactive substrates.[1-3] In addition, catalysts must be carefully designed to allow for distinct steps in the catalytic cycle, namely oxidative addition and reductive elimination, to proceed as features favoring one step inevitably hampers its mechanistic reverse. We describe herein a conceptually distinct approach to catalyst design where the nature of the metal center is altered over the course of the catalytic cycle by continuously cycling through its oxidation states. Application of this methodology allows for the catalytic synthesis of reactive acyl chlorides under exceptionally mild conditions, paving way to an array of carbonyl-containing products from simple organic building blocks.



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Merging Palladium Catalyzed Domino Reactions & Sulfur Dioxide: Synthesis of Sulfonylated Heterocycles

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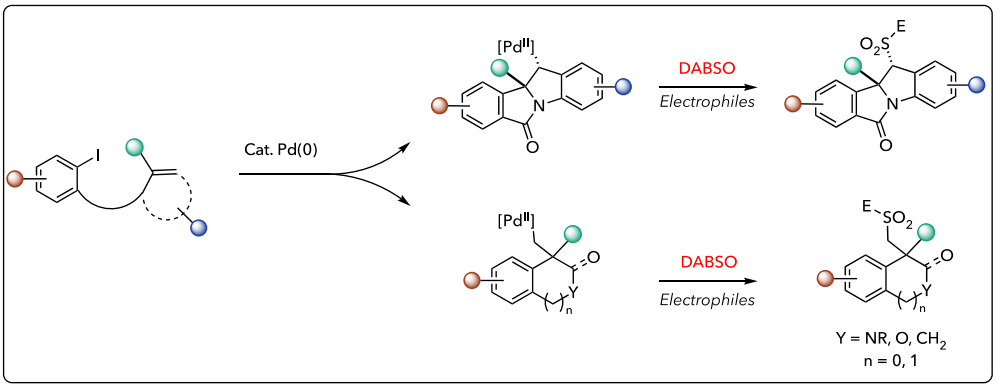
Sulfonyl groups are important motifs commonly found within a multitude of agrochemicals and pharmaceuticals. However, synthesizing sulfur-containing molecules from SO_2 gas, a readily available, inexpensive reagent comes with significant challenges. SO_2 gas is highly toxic, and its handling poses serious safety concerns which has driven the development of novel, safer and easier-to-handle alternatives to SO_2 gas such as DABCO-*Bis*(sulfur dioxide) (DABSO) [1].
DABSO has proven to be a powerful reagent within the field of palladium catalysis, allowing for the synthesis of a variety of sulfonyl-containing functional groups, as well as sulfinate salts themselves, directly from (hetero)aryl halides [2-3]. We have recently investigated the efficacy of DABSO in palladium catalyzed domino reactions, furnishing highly functionalized sulfonylated carbo- and heterocycles [4-5]. The sulfinate intermediates act as versatile nucleophiles, generating sulfones, sulfonamides and sulfonyl fluorides in good yields (up to 88%) in a one-pot, two-step fashion. Additionally, dearomative processes are amenable to this palladium-catalyzed approach and the resulting indoline products are obtained in high diastereoselectivity (>20:1 dr).



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Synthesis of a Photocleavable Bolalipid for the Study of Phospholipid Transfer Proteins and Phospholipid Kinases

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Phosphatidylinositol transfer proteins (PITPs) are ubiquitous in eukaryotes. These nonenzymatic proteins are involved in the regulation of phospholipid metabolism, membrane trafficking, and signal transduction. Sec14 is a yeast PITP that has been shown to transfer phosphatidylinositol (PI) or phosphatidylcholine (PC) from the endoplasmic reticulum to the Golgi. Initially, it was believed that Sec14's role was that of a simple lipid transfer protein. However, it is believed that Sec14 may play a greater role than just shuttling PI and PC throughout the cell. There is genetic evidence to suggest that Sec14 may bind to membrane bound PI and present it to the phosphatidylinositol 4-kinase, Pik1. Pik1 then phosphorylates PI to generate phosphatidylinositol-4-phosphate (PI(4)P). This function of Sec14 can be verified by synthesizing a photocleavable bola-PI analogue that can be placed in a lipid membrane. This photocleavable bola-PI is designed to span the entire membrane, having one polar head group on each leaflet, and is connected by a photocleavable diacid esterified to glycerol. It is believed that Sec14 will not be able to present this bola-PI to Pik1 for phosphorylation when it is in the un-cleaved state as the head group will be difficult to lift from the bilayer. Once cleaved, it is believed that Sec14 will resume normal activity and phosphorylation by Pik1 would resume. We report here the synthesis of a photocleavable bola-PC, a precursor to the desired bola-PI. The synthesized bola-PC has been shown to undergo efficient photocleavage in under two minutes.

Asymmetric Synthesis of Diazaspirocycles for MRCK Inhibitors as Cancer Therapeutics

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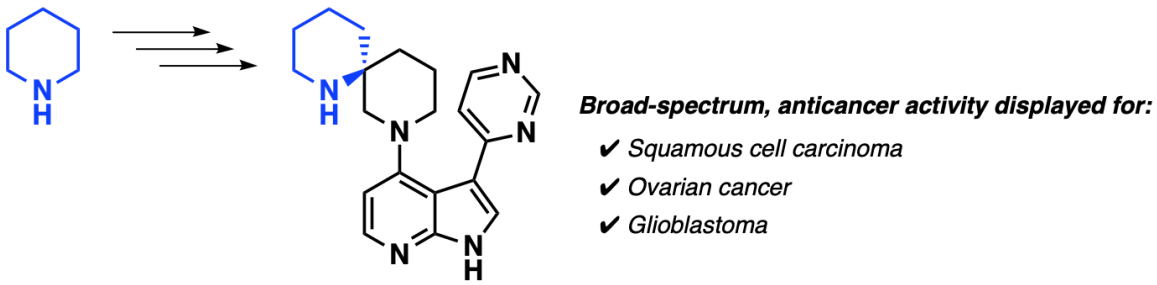
In the quest for new therapeutics that target the metastatic spread of cancer, the synthesis of novel inhibitors for underexplored kinases is at the forefront. Recently, potent and selective inhibitors for a new cancer therapy target in the myotonic dystrophy-related Cdc42-binding kinases (MRCK) have been discovered for the treatment of aggressive cancers. The incorporation of intricate three-dimensional spirocyclic ligands heightens the potency of the inhibitors. Although spirocycles are privileged structural motifs in medicinal chemistry, synthetic methods for their construction are limited, and asymmetric methods are in demand to access single enantiomers for biological applications. This work highlights the design and synthesis of diazaspirocycles for MRCK inhibition, with a focus on the development of efficient asymmetric methods. Substituted α-amino nitriles are employed as key building blocks to expand the parent heterocycle into the desired bicyclic structure through alkylation and direct reductive amination. Chiral directing groups, such as menthol and amino alcohols, are assessed on their ability to access the desired enantiomer necessary for MRCK inhibition. The methodology developed can be applied to a wide range of substrates to create an array of novel spirocyclic MRCK inhibitors. As a result, the asymmetric construction of innovative spirocycles for MRCK inhibition opens the door for the discovery of modern therapeutics that target the spread of aggressive cancers.

Figure:



Synthesis of Carbamoyl Fluorides with a Difluorophosgene Surrogate

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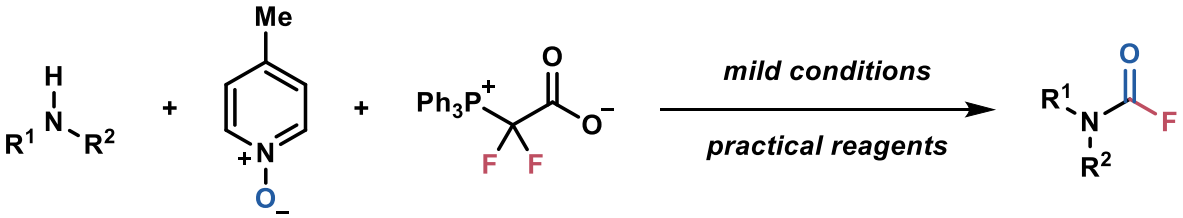
The use of carbamoyl fluorides has recently re-emerged as a tool for building amide-containing molecules [1]. Three recent reports have demonstrated that carbamoyl fluorides are competent electrophiles in transition metal-catalyzed cross coupling reactions and offer unique reactivity compared to their carbamoyl chloride counterparts [2-4]. The scarce appearance of carbamoyl fluorides in the literature is likely due to limitations in their preparation. Typically, such molecules have been synthesized from the respective carbamoyl chloride, but recent advances allow their preparation directly from secondary amines using a variety of difluorophosgene (COF_2) surrogates [5,6]. This presentation will describe the synthesis of carbamoyl fluorides from amines with a novel COF_2 surrogate comprised of a non-hygroscopic, air-stable source of difluorocarbene (DFC) and commercially available pyridine *N*-oxides [7]. This practical method offers a broad substrate scope, mild conditions, and short reaction times. Mechanistic studies support the generation of COF_2 only upon heating of all the reaction components, allowing for a relatively safe and well-controlled reaction compared to other commercial phosgenating reagents.



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A Borindolizine Platform for the Design of Fluorophores with Tunable Emissions

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The development of functional, accessible boron-containing building blocks allows for the generation of heteroatom-rich boron-containing molecules in a facile manner. Boron-containing heterocycles were targeted using this methodology as they represent a unique class of molecules with desirable properties for a broad range of applications while simultaneously being challenging to access.[1] A new boron-containing heterocyclic scaffold – borindolizine – is reported with broadly tunable fluorescence and a high Stokes shift.[2] Two classes of emitters were synthesized through rational scaffold changes resulting in blue-emitting carboxyborindolizines ($\lambda_{max,em}$ = 431 – 459 nm) and green-emitting aryl borindolizines ($\lambda_{max,em}$ = 488 – 519 nm). Experimental structure-emission trends were used to validate a computational spectral prediction model and subsequently used to design a red-emissive fluorophoric scaffold. A red-emissive ($\lambda_{max,abs}$ = 370 nm, $\lambda_{max,em}$ = 635 nm) isoquinolyl borinidolizine was synthesized in excellent agreement with the theoretical emission ($\lambda_{max,em}$ = 621 nm). These results establish borindolizine as a highly attractive class of fluorescent heterocycle with a highly tunable emission, allowing for custom fluorophore synthesis.

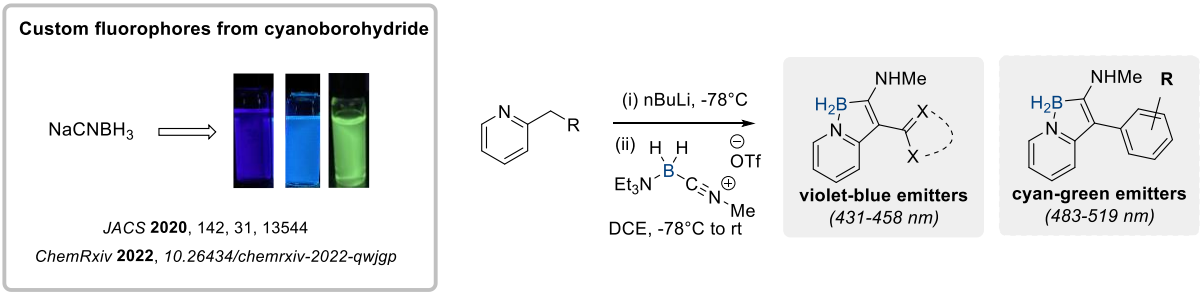

Figure: Sodium cyanoborohydride derived fluorescent boron heterocycles from substituted 2-methylpyridines

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The Synthesis of Novel MRCK Inhibitors Using an Azaindole Structural Motif

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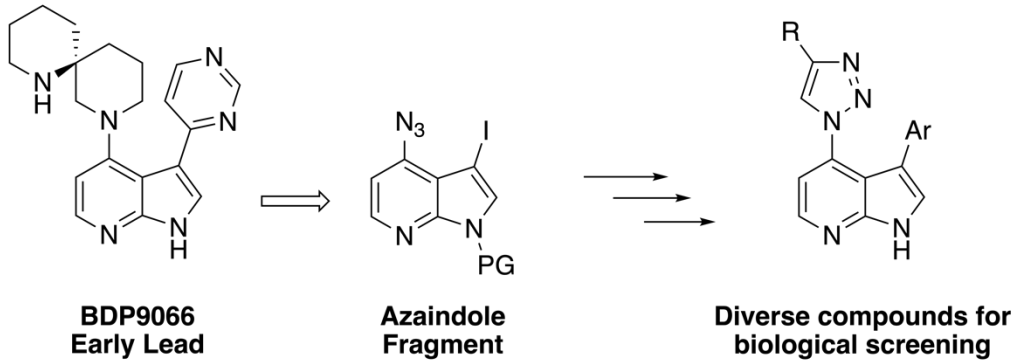
Targeted therapies are one of many treatments for cancer. Such treatment approaches could be directed towards many target proteins that subsequently modulate a variety of cancer-related processes, including, importantly, metastasis. Myotonic dystrophy kinase-related CDC42-binding kinases (MRCK) are important central regulators of the actin-myosin cytoskeleton that contributes to tumour cell invasiveness and is a powerful driver of metastasis. MRCK inhibitors display in vivo therapeutic effects that limit the invasive character of aggressive cancers like glioblastoma. There are only a small number of inhibitors that show good selectivity against MRCK. Consequently, the synthesis of novel MRCK inhibitors is crucial to understand the function of the kinase and the development of new therapeutics. BDP9066 is currently the most potent and selective MRCK inhibitor. Given this lead, we hypothesized that derivatized triazole inhibitors could have similar potency to BDP9066 allowing for a diverse range of new inhibitors to be synthesized. A simple synthetic route allowed for the rapid diversification of an azaindole scaffold, enabling these inhibitors to be realized.

Figure:



Synthesis of Borylated Cyclobutanols from Epihalohydrins or Epoxy Alcohol Derivatives

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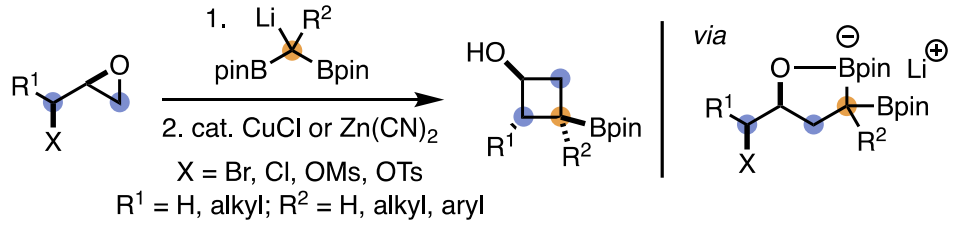
Within the synthetic chemistry community, interest in cyclobutanes has been growing due to their interesting biological and chemical properties [1]. Notably, their rigid and well-defined 3-dimensional backbone provides researchers an opportunity to “escape flatland”, enabling new opportunities in drug discovery and development [2,3]. Despite this interest, the synthesis of cyclobutanes still remains a challenge and therefore the development of new and efficient methods to make them is needed. In this presentation, the synthesis of borylated cyclobutanols from readily accessible epihalohydrins and epoxy alcohol derivatives will be discussed. The use of 1,1-bisnucleophilic reagents as C_1 sources will be presented, as will their preparation and reactivity with 1,3-biselectrophiles. Finally, derivatization studies demonstrating the utility of the alcohol and boronic ester functional handles will be presented.



rapid access to 3-borylated cyclobutanols | *polysubstituted cyclobutane core*

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