QOMSBOC 2024 Poster Presentation Abstracts

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Imidazopyrimidine-Based Ligand for the Selective Synthesis of Heteromultimetallic Catalysts

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Bimetallic catalysts are transition metal complexes in which rigid, binucleating ligands situate two metal atoms close together, giving rise to unique reactivity through metal-metal synergy.[1] In comparison to traditional monometallic catalysts that are tuned predominantly through ligand design, additional parameters are tunable such as the metal pairing, degree of metal-metal bonding, and metal-metal distance. As an emerging field, developing the scope of binucleating ligands and their resulting bimetallic complexes such that these parameters are easily tunable is crucial to developing bimetallic catalysis. Regarding metal pairings, there remains a dearth of reported heterobimetallic complexes due to the difficulty in selectively binding each metal atom to a given binding site.[2] Here, we report the selective synthesis of a heterobimetallic and heterotrimetallic nickel(II)/copper(II) complex, using our recently reported unsymmetrical imidazopyrimidine-based ligand 2,7-di(pyridin-2-yl)imidazo[1,2-*a*]pyrimidine (dpip).[3] The optimized synthesis of dpip is achieved a multi-gram scale in an overall yield of 54% starting from 2-acetylpyridine. The synthesis of the heterometallic complexes was achieved by spontaneous assembly simply by combining dpip with 1 equivalent of copper(II) trifluoroacetate and 1 or 2 equivalents of nickel(II) trifluoroacetate for the heterobimetallic or heterotrimetallic complex respectively (**Figure 1**). It was demonstrated through metal redistribution experiments that the heterometallic complexes were the thermodynamic product in the presence of both metals, as evidenced by the selective conversion when the opposing metal salt was added to either the homometallic copper or nickel complex.

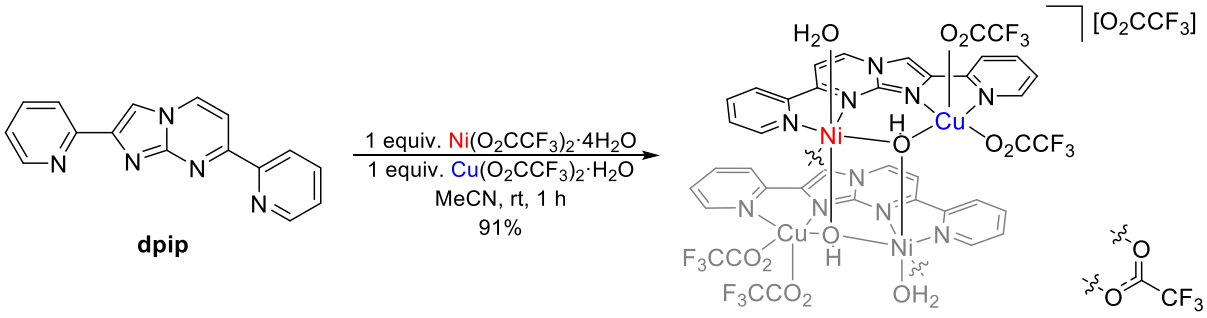

Figure 1. Synthesis of heterobimetallic nickel(II)/copper(II) complex.

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Understanding and Controlling the Mizoroki−Heck Reaction of Cyclic Enones

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Cyclic α,β-unsaturated carbonyls are versatile intermediates in the synthesis of active pharmaceutical compounds. One of the ways of functionalizing cyclic enones is through β-arylation using MizorokiHeck reaction.[1] However, Heck reaction of cyclic enones with aryl halides is a challenging transformation and remains underexplored in the literature.[2,3]

We report palladium-catalyzed Mizoroki-Heck reaction of cyclic enones with aryl bromides, including heteroaryl bromides.[4] Some challenges of the reaction include deactivation of the catalyst by heteroaryl bromides, homocoupling of aryl bromides, and reduction of β-arylated enone. Our method containing catalytic palladium with BippyPhos ligand promotes cross-coupling reactions of wide range of aryl bromides with cyclic enones in good to excellent yields under mild conditions.

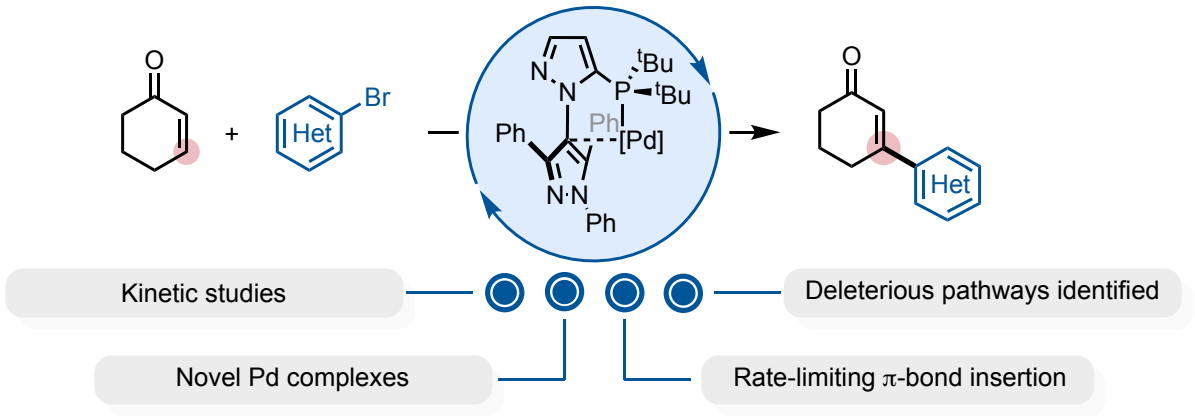

Figure 1. Pd-catalyzed β-arylation of cyclohexenone.

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C–H Functionalization-Enabled 11-Step Semisynthesis of (−)-Veragranine A and Characterization of Synthetic Analogs in Osteoarthritis-related Pain Treatment

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We report an efficient semisynthesis of the cholestane steroidal alkaloid (−)-veragranine A with a 6/6/6/5/6/6 hexacyclic ring system, eight stereocenters, and a unique C12–C23 linkage. Our synthesis features a Schönecker–Baran C–H oxidation at C12, a Suzuki–Miyaura cross-coupling to form the C12–C23 bond, and a hydrogen atom transfer (HAT)-initiated Minisci C–H cyclization to forge the C20–C22 bond with desired stereochemistry at C20. These enabling transformations significantly enhanced the overall synthetic efficiency and delivered (−)-veragranine A in 11 steps and over 200 mg from cheap and readily available dehydroepiandrosterone. In addition, this approach allowed flexible syntheses of novel synthetic analogs for biological evaluations in sensory neurons *in vitro* and in an *in vivo* model of arthritic pain, from which two novel lead compounds were identified for further development.

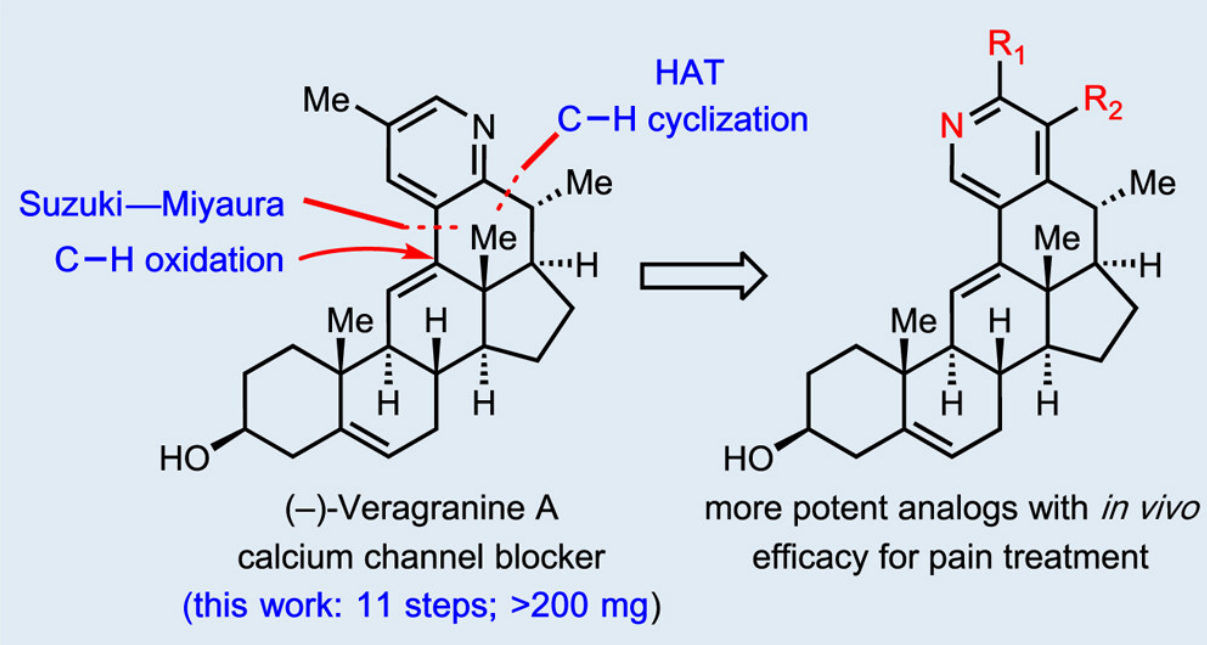

Figure 1. Overview of the synthetic strategy towards (–)-Veragranine A, highlighting the exploration of new chemical space and the development of analogs with enhanced potency compared to the natural product.

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P4

NMR Fragment-Based Drug Discovery: Pivotal tool for the Rapid Enablement of Hit-to-Lead Phase in Medicinal chemistry

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Because of its power to probe the intrinsically weak interactions (Kd) between protein targets and low-molecular weight fragments, NMR fragment-based drug discovery (FBDD) showcases a powerful biophysical method to exploit difficult target proteins. The NMR-FBDD process enables early guidance of the structure-activity relationship (SAR) with low molecular weight fragment compounds offering a better chance to fully match the interactions with small pockets within the target protein, otherwise inaccessible with drug-like compounds (MW > 350). However, due to the aggregation of some molecules, artifacts can be encountered, that can produce misleading SAR information during biochemical tests, among other tests. In addition to providing information on the effects of the compounds on the protein fingerprint, NMR is also critical for monitoring free state behavior of the compounds as the incorporation of binding data from only well-behaved compounds (soluble and non-aggregating) is key to generating reliable SAR information. Our group strategy is based on the structural optimization of the fragment molecules (hits), the early evaluation of their aqueous solubility and aggregation behaviour by NMR in addition to monitoring the effects of these molecules on the protein fingerprint. Through interdisciplinary work between medicinal chemists, biophysicists and biochemists, we used this NMR for SAR approach to guide medicinal chemistry efforts to improve the binding affinity (Kd from ~7-10 mM to low µM) of molecules allowing protein-protein interaction inhibition between HRAS and SOS and therefore selective inhibition of the proliferation of cancer cells. This strategy should allow a more rapid path from hit-to-lead in drug discovery.

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P5

Delivery of Vascular Progenitors via Hyaluronan-based hydrogels for Treating Myocardial Infarction

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Introduction: The transplantation of vascular progenitor (VP) cells holds great promise for treating myocardial infarctions (MI) by promoting vascular regeneration to damaged tissue [1]. Despite the benefits, cell transplantation still faces challenges such as cell survival, integration into heart tissue, and suboptimal delivery methods. Mimicking the niche microenvironment of cardiac tissue to enhance VP cell viability has opened new avenues to address these obstacles [2]. We hypothesized that the delivery of VP cells via hyaluronan-based hydrogels would improve the engraftment of vascular progenitors and promote neovascularization for treating MI.

Materials and Methods: We have engineered a hyaluronan (HA)-based hydrogel utilizing the inverse electron-demand Diels–Alder (IEDDA) “click” reaction between norbornene and methylphenyltetrazine as a crosslinking mechanism [3]. The mechanical properties and gelation time of this vehicle can be tuned by varying the ratio of HA-norbornene (HAN) and HA-methylphenyltetrazine (HAT) [3]. To better replicate the cardiac tissue environment and enhance the adhesion of VP cells, the collagen-derived peptide, KGHRGF, was synthesized and conjugated to HA-norbornene (HAN).

Results: The synthesized HA-based hydrogel significantly promoted neovascularization and enhanced the functionality of VP cells compared to commercial materials like Matrigel™. Alamar Blue, MTT, and LIVE/DEAD staining confirmed the ability of the hydrogel to promote angiogenesis, as evidenced by increases in junctions, meshes, and segments in vascular networks. Additionally, LEGENDplex detection of angiogenic factors secreted by VP cells further highlighted its potential as a platform for enhancing functional cellular survival in therapeutic applications.

Conclusions: This comprehensive approach allowed us to synthesize an HA-based hydrogel to encapsulate and deliver VP cells to enhance vascular regeneration. The platform’s unique advantage lies in its capacity to mimic the heart's microenvironment to significantly enhance cell survival while amplifying the angiogenic potential of VP cells in the treatment of MI. By offering a fully customizable and synergistic strategy for cardiac repair, this therapy paves the way for advanced controlled delivery systems designed to optimize vascular regeneration and improve therapeutic outcomes for MI.

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Oxidative Syntheses of *N,N*-Dialkylhydroxylamines

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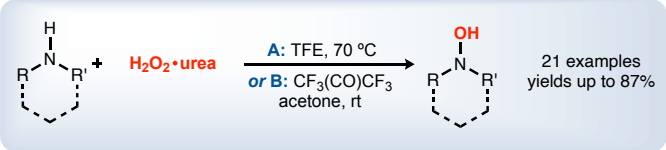
Hydroxylamines are widely used reagents in various organic transformations, such as amination reactions, metal catalyzed reactions and Cope-type hydroamination. Despite their usefulness, the broad use of hydroxylamines has been hindered by direct oxidation of amines that are low-yielding, inefficient, poorly selective and/or require the use of hazardous and unstable reagents.[1] The synthesis of unsymmetrical hydroxylamines is often even more challenging, requiring the alkylation of a primary hydroxylamine,[2] thus highlighting the attractiveness of a direct oxidation approach from the corresponding secondary amine. While several two-step sequences have been developed to circumvent these issues, there is a need and opportunity for development of efficient, one-step oxidation of amines to hydroxylamines.

Herein, we report two complementary methods to accomplish direct oxidation of secondary amines to hydroxylamines using UHP as oxidant.[3] The first method uses 2,2,2-trifluoroethanol (TFE) and a large excess of amine. Isolation of hydroxylamine products is enabled by selective salt formation, and the recovery of excess amine is demonstrated. The second method uses hexafluoroacetone as an additive and is highlighted by 1:1 stoichiometry between oxidant and amine. Mechanistic insight into the nature of the active oxidant will also be presented.



simple conditions / functional group tolerance / optimized isolation / scalable

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Nonenzymatic Hydration of Phosphoenolpyruvate: General Conditions for Hydration in Protometabolism by Searching Across Pathways

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Metabolic theories propose that life originated from a self-organized, nonenzymatic reaction network called protometabolism. This network likely involved a small set of recurring mechanisms, accumulating key metabolites and resembling the core of biological metabolism. Recent studies support this hypothesis by reproducing metabolic pathways nonenzymatically using inorganic catalysts. However, many focus on individual reactions or pathway segments, lacking unified conditions across different pathways.[1] Exploring metabolic pathways to find recurring chemical mechanisms could offer a complementary approach, helping to identify conditions relevant to the origins of metabolism. The reversible alkene hydration is one of the key biological transformations occurring in three steps of the reverse Krebs cycle (producing all of life's universal building blocks) and in the second step of gluconeogenesis (making sugars). Nonenzymatic hydration reactions have been reported, but they usually occur under harsh conditions (highly acidic pH and high temperatures, Fig. 1A).[2] Moreover, nonenzymatic hydration conditions for the conversion of phosphoenolpyruvate (PEP) to 2-phosphoglycerate (2-PGA) have not been found, and existing conditions are chemically incompatible with this reaction, due to competing hydrolysis of PEP to pyruvate. In this study, we identified mild conditions, promoted by Fe oxides such as green rust, which apply to all hydration reactions of the Krebs cycle and gluconeogenesis (Fig. 1B). They unify hydration reactions reported under different conditions and, more importantly, promote key metabolic reactions that failed in all previously explored nonenzymatic systems, namely the hydration of PEP to 2-PGA.

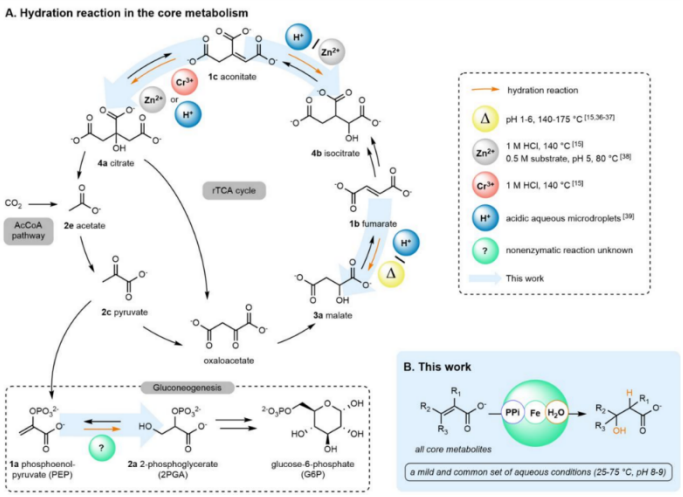

Figure 1. (A) Hydration reactions in core metabolism and the different reports of this nonenzymatic transformation. (B) This work, in which a common set of mild aqueous conditions is suitable for the hydration of all core metabolites in the figure.

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Efforts Towards Silane-Mediated Direct Amidation Using Porphyrin Silanes

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Amide bonds are prevalent in valuable products like pharmaceuticals. Amidation is a widely used reaction in pharmaceutical synthesis, constituting up to 16% of all reactions.[1] Lewis-acidic silanes have in recent years, been researched as coupling reagents for direct amidation. Silicon possesses advantages due to its low cost, ease of extraction and functionalization. Silane-mediated amidation involves the activation of the carboxylic acids with a silane, followed by an attack by the amine to form an amide product.[2] Porphyrins are aromatic compounds that have the unique ability to encapsulate metal ions to form metalloporphyrins, with silicon forming hexacoordinated species called porphyrin silanes. Our research is focused on these complexes, as they display unique electronic properties and stability. These compounds, have a robust aromatic structure for enhanced stability and uncomplicated modification through the periphery rings and silyl axial ligands.[3,4] For direct amidation, the presence of a porphyrin framework can enhance the activation of carboxylic acid by stabilizing the intermediate species. Moreover, the axial coordination sites would greatly affect amidation. Thus, we hypothesize that, these properties and their potential for amidation could exceed that of previously established silanes. This study explores the synthesis of porphyrin silanes by modifying the periphery rings by incorporating electron-poor/rich and sterically hindered substituents. The coupling capability of these silanes will be explored, focusing on reaction conditions such as the acid/amine substrate scope, reaction time, temperature, and solvent. Lastly, spectroscopic analyses will be employed mechanistic studies and identify key intermediates.

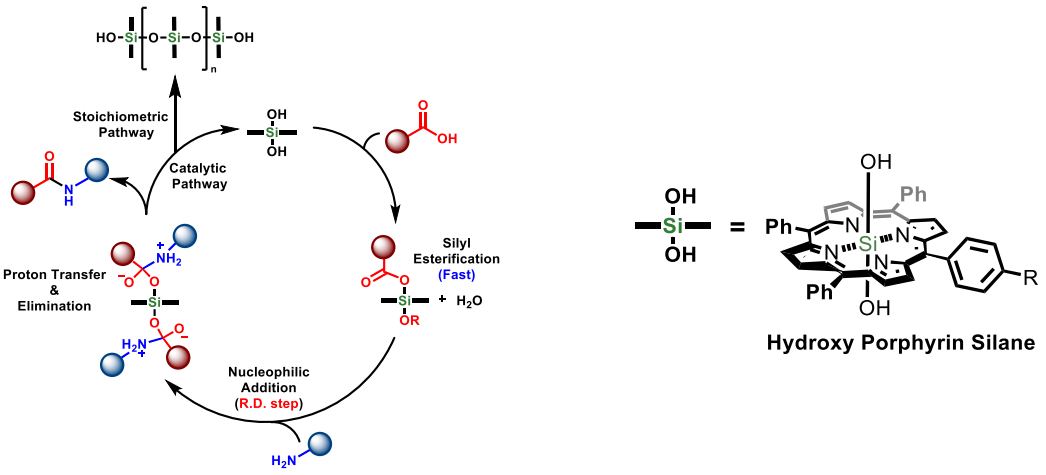

Figure 1. Mechanism(s) of dihydroxy porphyrin silane-mediated direct amidation of carboxylic acids.

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Nicholas Reactions in the Preparation of 3-Hydroxybenzo[b]oxepines; Application Towards Heliannuol C Analogues

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Allelochemicals are naturally occurring herbicides that are present in, and can be extracted from, the cultivated sunflower amidst other sources. Among these allelochemicals of interest are the heliannanes, which cover a more specialized subset of these natural phytotoxic compounds, more specifically, heliannuols. The synthesis of these heliannuols and their analogues proves to be advantaged in the exploration of related compounds of interest with greater potential allopathic properties.

We herein explore the applicability of intramolecular Nicholas reaction chemistry in the synthesis of 3-hydroxybenzo[b]oxepine species by way of seven-membered ring formation. We will discuss the viability of the reaction (**1**→**2**), with attention paid to its diastereoselectivity, and the required substitution patterns that is seemingly observed of the arenes. Lasty, investigation of the decomplexation reaction of the alkynedicobalt unit and conversion of the resulting compounds (**2**) to heliannuol C and its analogues will be addressed.

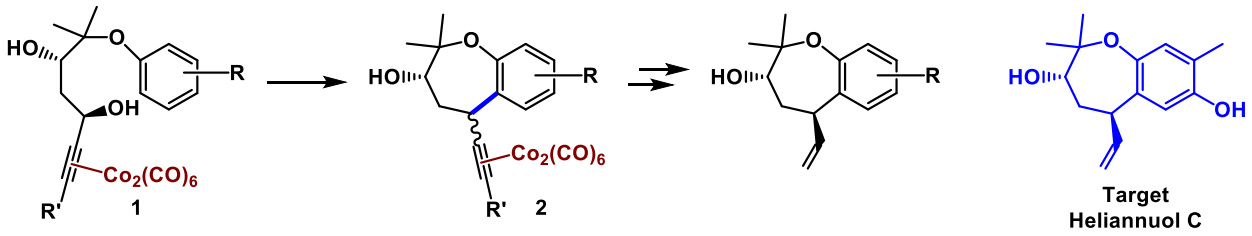

Figure 1. Nicholas Reaction Pathway

Synthesis and Lewis Base-Catalyzed Functionalization of Carbamoyl Fluorides

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Carbamoyl fluorides are an emerging class of electrophiles that have been applied in a handful of C-C bond forming reactions in recent years due to their unique reactivity and stability profile.[1,2] However, the majority of these reports require the use of strongly nucleophilic organometallic reagents or Ni(0) catalysts at elevated temperatures to achieve C-F bond cleavage. My research explores the synthesis and reactivity of carbamoyl fluorides under mild, metal-free conditions. This work includes a preparation of carbamoyl fluorides using a difluorophosgene surrogate derived from a stable difluorocarbene source and pyridine *N*-oxides,[3] as well a their fluoride-catalyzed cross coupling with alkynyl silanes.[4] Current work is focused on the cyanoalkylation of carbamoyl fluorides using silyl ketene imines (SKI).[5] This transformation provides access to α-cyanoamides bearing a quaternary carbon centre – a motif that can be transformed into various medicinally relevant amines, heterocycles, and unnatural β-amino acids. The method proceeds at room temperature and provides high yields of the desired products, with optimization of diastereo- and enantioselective reactions in progress.

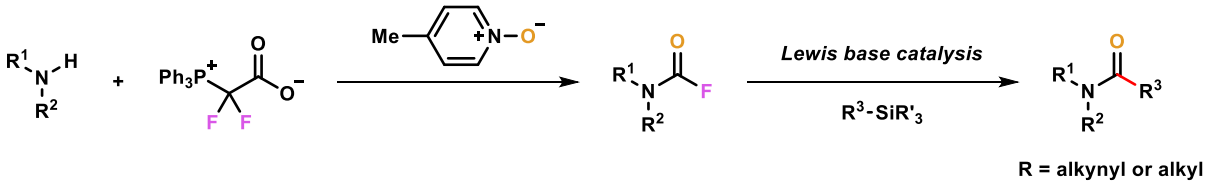

Figure 1. Preparation of carbamoyl fluorides and subsequent catalytic functionalization

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Exploring the Structure-Reactivity Relationship of Iodonium Ylides for Nucleophilic Fluorination Using *in-Silico* Methods

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Fluorine-18 labelled compounds are vital radiopharmaceuticals, playing a key role in clinical diagnosis and drug development. Forming C-F bonds, especially on aromatic rings, has historically posed synthetic challenges. Iodonium ylides, specifically spirocyclic iodonium ylides, have emerged as effective ^{18}F-labelled arene precursors.[1] Notably, the size of the spirocyclic ring or the introduction of an *ortho*-effect-inducing group significantly influences the reaction yield of the fluorinated arene.[2-4] It is proposed that the reaction proceeds by association between the iodonium ylide and fluorine, followed by a reductive elimination step.[4] Our recent computational studies showed two electropositive sigma-holes on iodonium ylides, which are suspected to play a critical role in facilitating a halogen bond-mediated initial association.[5,6] Further investigation of the structure-reactivity relationship could improve our ability to predict reactivity and improve yields, a process that can be expedited through *in-silico* methods.

The reaction coordinate diagram for a series of iodonium ylides of modified spirocyclic size is presented here, developed using benchmarked DFT *in-silico* methods. Applying this framework, energy barriers across the series are compared to rationalize deviations in reactivity. To further explain these differences, natural bonding orbital (NBO) analysis and natural energy decomposition analysis (NEDA) analyze bonding interactions within these iodonium ylides and their halogen bond complexes. This methodology emphasizes the utility of various computational tools for locating and optimizing stationary and saddle points along the reaction coordinate, while also providing a physical interpretation to unexplained reactivity.

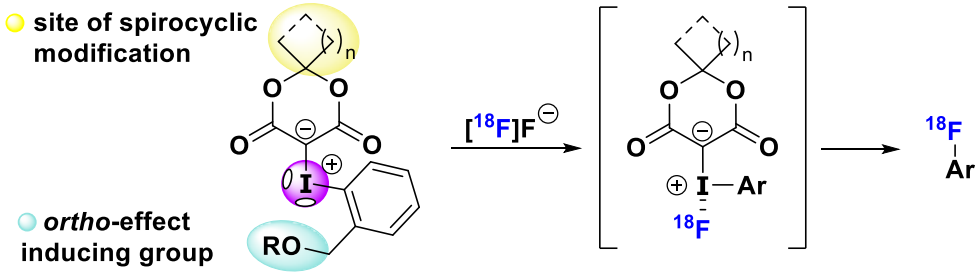

Figure 1. Proposed pathway for nucleophilic fluorination of iodonium ylides.

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THE SYNTHESIS OF INDOLES VIA A GOLD (I) CATALYZED REDOX NEUTRAL REACTION

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Due to their ease of functionalization and significant biological activity, indoles are very attractive structural motifs for the chemical industry, especially for the pharmaceutical and agrochemical sectors. While a variety of methods exist to access indoles; the use of harsh reaction conditions and limited functional group tolerance are significant drawbacks. Our group has previously demonstrated the ability of electrophilic gold species to catalyze the formation of functionalized indoles *via* a cascade reaction involving a hydride shift from the α-position of a tertiary amine to an intermediately formed gold(I)-carbene. Following this seminal result, it was considered that a similar reactivity could be attained using ethers as hydride donors instead of amines. After optimization of the catalytic conditions, it was found that benzyl ether derivatives could be employed as substrates in such a transformation. The reaction proceeds under mild reaction conditions, is tolerant of diverse functional groups, and rapidly delivers a variety of functionalized indoles in moderate to excellent yields. By slightly modifying the structure of the substrates, it was demonstrated that the transfer of nucleophilic groups other than a simple hydride could be achieved thus extended the interest of the strategy to access unique indole-based structures.

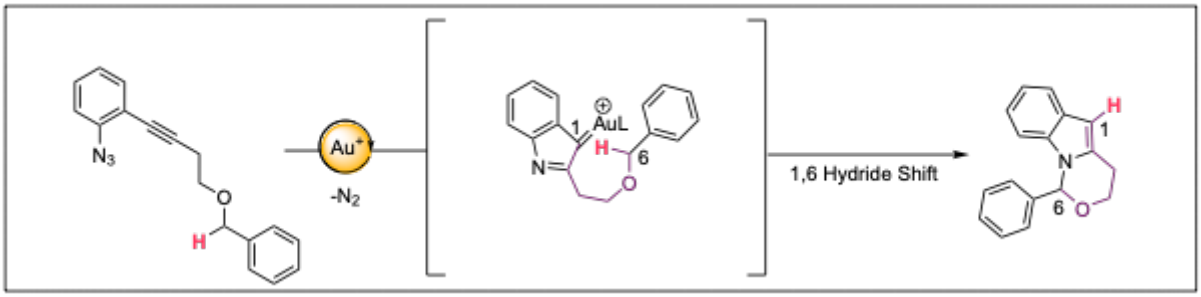

Figure 1. General approach to the formation of indoles via a gold (I) catalyzed intramolecular cascade reaction.

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Synthesis of α-Quaternary Aldehydes via a Dual Ni/Rh-Catalyzed Tandem Isomerization–Propargylation Reaction

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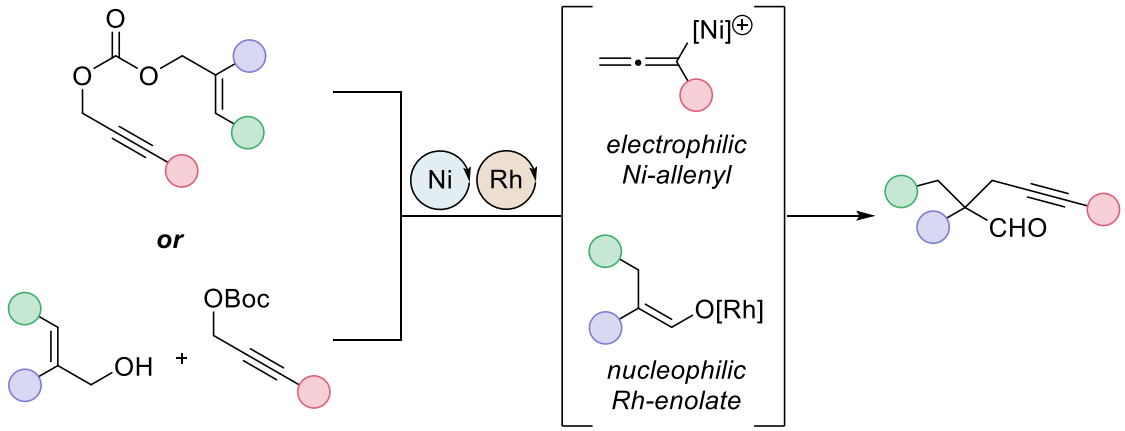
Domino catalysis, wherein each metal in a multi–catalyst system promotes a single reaction in a defined sequence, is an emerging strategy and one that has been adapted to address the important problem of stereoselective construction of all–carbon quaternary centers. The transition metal–catalyzed decarboxylative asymmetric alkylation reaction has been an attractive strategy to afford enantioenriched carbonyl compounds with α–quaternary centers through an intramolecular transformation, proceeding through an *in situ* generated enolate and metal–electrophile.[1] Our group has recently reported the use of allylic alcohols as enolate surrogates for the intramolecular decarboxylative allylic alkylation reaction. Unsymmetrical diallyl carbonates were used in a rhodium catalyzed tandem isomerization–allylation procedure to generate α–allylated aldehydes, and a follow up report involved a dual palladium/rhodium catalyzed tandem isomerization–allylation system to access α–allylated ketones.[2],[3] Herein, we describe a nickel/rhodium dual catalytic system to generate α–propargylated aldehydes intramolecularly starting from allyl propargyl carbonates, and intermolecularly from allylic alcohols and propargyl carbonates.[4] Oxidative addition from nickel generates the electrophilic nickel–allenyl species while the nucleophilic rhodium–enolate is obtained *via* isomerization of the allylic alcohol. Recombination of both partners then affords the desired α–propargylated aldehydes. Mechanistic insights into the development of a multi–metal, multi–ligand procedure for an enantioselective variant will also be discussed.



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Reductive Alkyne Hydrocyanation Enabled by Nickel-Catalyzed Coupling of Nitriles with Aldehydes

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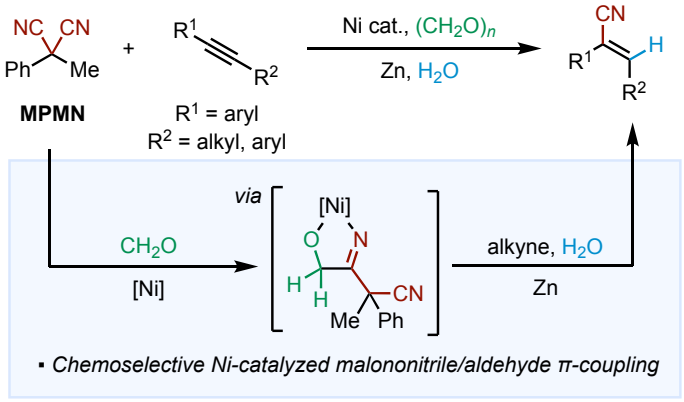
Ni-catalyzed reductive couplings of π-type electrophiles are efficient methods to synthesize complex molecular structures.[1,2] The alkyne group is commonly used as a π-electrophile for couplings with nitriles or aldehydes, generating functionalized products such as substituted pyridines or allylic alcohols.[3,4] These couplings typically proceed via mechanisms involving an oxidative cyclization between alkyne and either nitrile *or* aldehyde catalyzed by a low-valent Ni species.[5,6] However, selective Ni-catalyzed couplings between nitriles and aldehydes have not been reported. We present our discovery of a Ni-catalyzed reductive coupling between 2-methyl-2-phenyl-malononitrile (MPMN) and formaldehyde, which enabled the development of a Ni-catalyzed reductive alkyne hydrocyanation methodology to access alkenyl nitrile products.[7] This work demonstrates a novel mode of reactivity for malononitriles, which is distinct from prior reports by our group using MPMN as an electrophilic CN source for Ni-catalyzed aryl halide cyanation.[8] The discovery of the effect of formaldehyde and mechanistic studies to probe its role in enabling hydrocyanation will be discussed, together with current efforts to extend the chemistry of malononitriles under Ni-catalysis towards other nitrile-containing products.



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Design of ^{13}C-Labeled Thioalkyl Phosphonium Salts as Tools for Isotopic Enrichment of Biological Building Blocks

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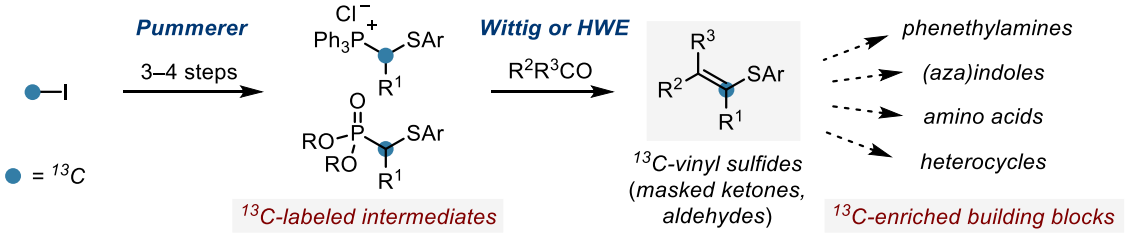
Thioalkyl phosphonium salts are versatile intermediates for the synthesis of vinyl sulfides with diverse substituents.[1] Since vinyl sulfides can be hydrolyzed under mild conditions, they can be considered as masked carbonyl compounds,[2] and potentially used as precursors to a variety of biologically relevant building blocks, such as amino acids and heterocycles. Here, we disclose our synthetic efforts toward the preparation of vinyl sulfide intermediates from methyl iodide.



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Efforts Towards the Use of the Beckmann Rearrangement to Obtain Oxazole-Embedded Peptides

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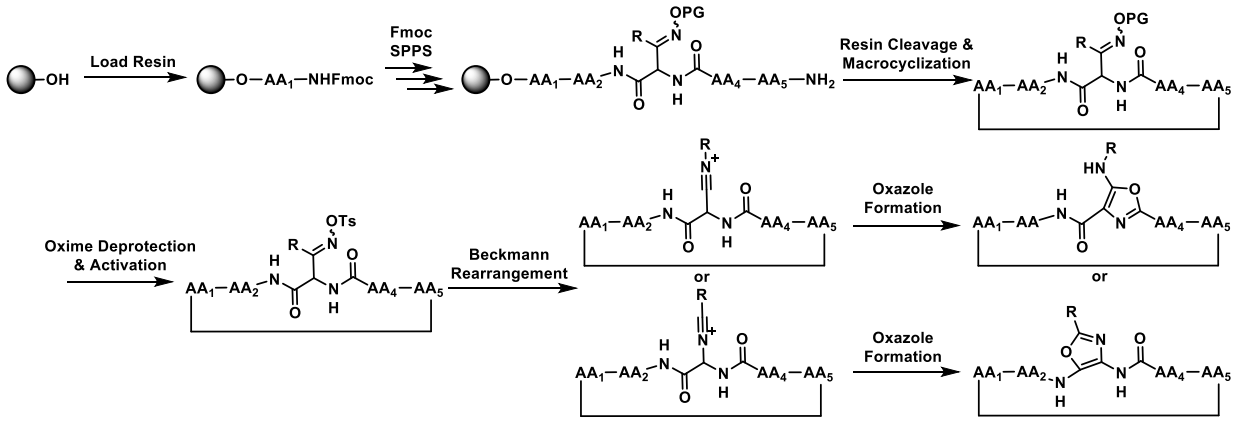
Development of new chemical transformations is central to all areas of chemistry and often involves production of charged intermediates that are relatively high in energy. One promising research direction is the idea of intercepting these intermediates by readily available exogenous reagents. Recently, oxazole-fused macrocyclic peptides have been of interest for the Yudin group because their heterocyclic units can arise from the Cornforth rearrangement, a mechanistically interesting process that offers an opportunity to intercept nitrilium ions.[1] Accordingly, there is continuing interest in installing the fused oxazole at a late stage to see if molecules with novel conformational attributes could be designed. The key step of the Cornforth rearrangement is the attack of the amide at the nitrilium ion to give the final oxazole.[1] To intercept this process, an orthogonal synthesis of the nitrilium would be needed. A well-known reaction that generates a nitrilium intermediate is the Beckmann rearrangement, commonly used to make large ring lactams.[2] To extend this reaction to a peptidic backbone, a beta-oximo-amino acid derivative will be synthesized and utilized in solid phase peptide synthesis. After cleavage from the resin and macrocyclization, the oxime would be unprotected and activated for Beckmann rearrangement. As the reaction is stereospecific, this should lead to two different regioisomers of the oxazole-fused macrocyclic peptide (Scheme 1). To enable the synthesis of the required protected beta-oximo-alpha-amino acid building block, a systematic investigation into the Fmoc SPPS compatibility of varying oxime protecting group is also underway.



Scheme 1: Proposed synthesis of fused-oxazole macrocyclic peptides by Beckmann rearrangement. AA = Amino Acid, Fmoc = fluorenylmethyloxycarbonyl, SPPS = Solid Phase Peptide Synthesis, PG = Protecting Group.

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Elucidating the Redox Chemistry of Metal-Free Phthalocyanines for Their Low-Temperature Synthesis and Access to AB_3 Hybrids

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Metal-free phthalocyanines (**MF Pcs**) are aromatic macrocycles with unique photophysical profiles and high extinction coefficients, making them excellent photosensitizers in photodynamic therapies.[1, 2] Although **MF Pcs** can be synthesized in good yield from 1,3-diiminoisoindoline **(DI3)** or 1,2-dicyanobenzenes for such applications, an under-explored redox process during macrocycle formation forces the need for harsh heating in standard syntheses. Therefore, we wish to present the findings of our low-temperature (50 °C) synthesis of **MF Pc**, leveraging a reduced precursor **(AI3)** that correctly adjusts the oxidation state of the reagents. A full investigation into our synthesis of the reduced **AI3** precursor on the multi-gram scale will be presented, along with electrochemical analysis for the reduction reaction and computational modelling of the tautomers. Lastly, the optimization of the low-temperature synthesis of **MF Pc** in the presence of common bases will be presented, outlining control experiments and a kinetic study. Using various 1,2-dicyanobenzenes and the **AI3** precursor, phthalocyanine AB_3 hybrids with selective placement of chemical handles are outlined as current targets to rationally tune the solubility and photophysical properties of phthalocyanines. Ultimately, placement of functional groups for cross-coupling or *click* chemistry to append chemotherapeutics to the phthalocyanine for dual chemo/photodynamic therapy is envisioned.

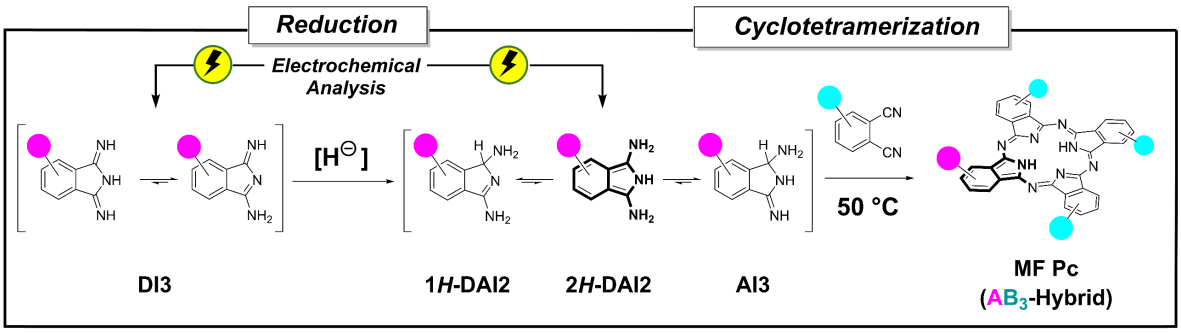

Figure 1. Synthetic route for low-temperature metal-free phthalocyanine (MF Pc) formation

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Design and Synthesis of PROTACs for HRAS G12V

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Harvey-RAS (HRAS) has long been considered an undruggable target (proteins that are too challenging to bind with conventional molecules) and associated with many cancers. In our laboratories, we implemented an innovative strategy aimed at developing promising compounds with pronounced affinities for HRAS. We employed NMR spectroscopy techniques to screen NMX's library of compounds to first identify binders (hits) then to explore the hit-to-lead phases of drug discovery. Key to this process was our "NMR for SAR" approach which effectively allowed for the rank-ordering of compound binding affinities and enable chemists to establish structure-activity relationships (SAR). Furthermore, we were able to also monitor the free-state solution behavior of compounds to flag self-aggregators that result in false positives. Having identified binders to HRAS, our poster will describe how we then extended our studies to design chimeric compounds called PROteolysis TArgeting Chimeras (PROTACs). PROTACs are hetero-bimolecular entities, featuring a ligand for the protein of interest (POI) and a ligand for an E3 ligase, whereas both are chemically connected by a linker. The main goal of our PROTAC compounds will be to formulate a drug that functions by first forming a ternary complex involving HRAS (the POI), the PROTAC and a E3 ligase which then promotes the in cellular degradation of the POI through a ubiquitination-proteasome system. This poster presents the modeling studies and synthetic pathway for the first PROTACs developed in our lab.

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Functionalization of SWNTs with Conjugated Graft Copolymers

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A series of graft copolymers having increasing molecular weight within the grafted chains were used to determine their effect on the stability of SWNT (single-walled carbon nanotube) dispersions. The aim was to investigate the behaviour of SWNTs as the steric barrier is gradually increased. This was accomplished by synthesizing three graft copolymers by strain promoted azide-alkyne cycloaddition chemistry (SPAAC) using an azide-decorated polyfluorene backbone (PF-N_3) and a series of methoxy-polyethylene glycol-amine (mPEG-amine) chains with differing molecular weights (1000, 2000, 5000 g/mol) and end-functionalized with dibenzocyclooctyne (DBCO) groups. These polymers were used for SWNT dispersions and characterized by UV-Vis Spectroscopy, Atomic Force Microscopy (AFM) and Raman Spectroscopy. Based on these results, further studies will be conducted to study backbone extension of the main chain polymer and the consequent effect on SWNT dispersions. Synthesis of a more densely grafted polymer with three differing molecular weights (10,000, 20,000, 40,000 g/mol) of main chain polymer as well as three differing molecular weights (5,000, 10,000, 20,000 g/mol) of the grafted chains will allow for this examination.

Hypervalent Iodine-Mediated Synthesis of Fluorinated PAHs

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Phenacenes are a class of polycyclic aromatic hydrocarbons (PAHs) which have potential use in organic electronics due to their extended π-systems. A practical limit to potential applications of PAHs is their lack of solubility within organic solvents as the ring systems become more extensive; however, mono-fluorination of phenacenes has been shown to improve solubility. Our group previously established that hypervalent iodine (HVI) reagents could react with *ortho*-vinylbiaryl precursors (**1**) to produce phenacenes (e.g. **3**) via a mechanistically unique cross-coupling involving (**2**). Our current work seeks to expand on the previous study and produce mono-fluorinated phenacenes (**5**) from *ortho*-acetylenylbiaryl precursors (**4**) using fluorinated HVI reagents. This poster will present recent efforts towards developing this reaction.

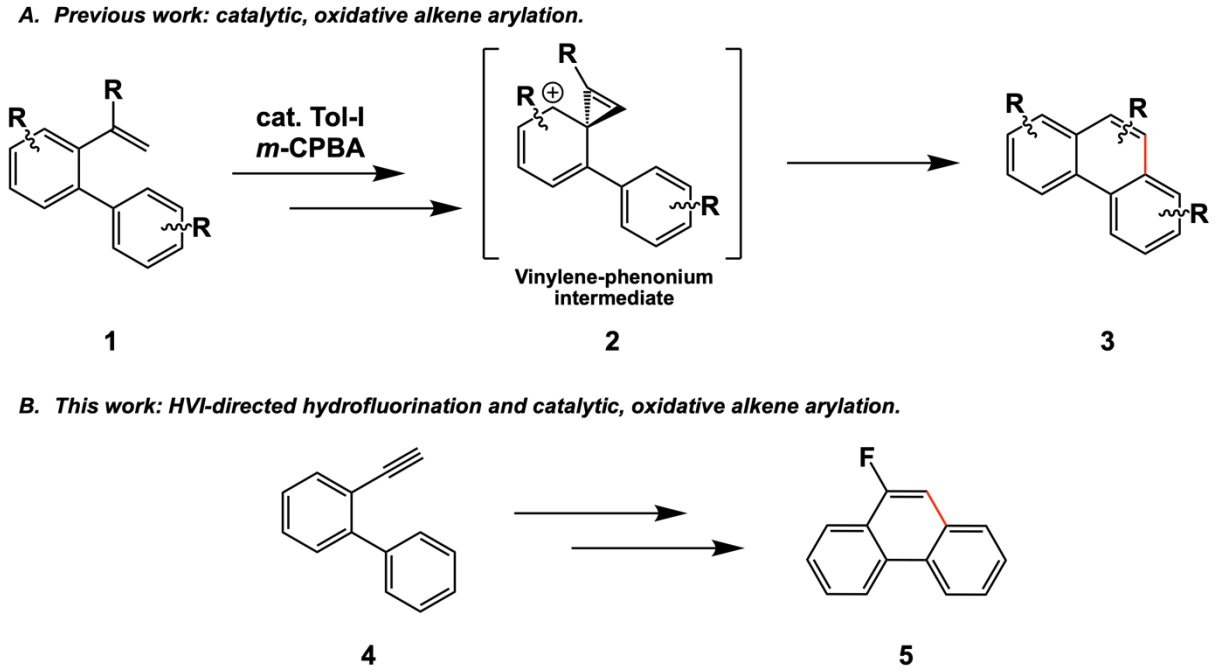

Figure 1. A. Previous work: catalytic, oxidative alkene arylation. B. This work: HVI-directed hydrofluorination and catalytic, oxidative alkene arylation.

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Safety considerations for the scale-up of the Schmidt reaction of ketones in a flow system

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High energy reagents play a pivotal role in organic synthetic chemistry. For example, the Schmidt reaction features hydrazoic acid, a highly reactive, unstable species, that transforms ketones into amides.[1] Reactions that employ high energy reagents are important for the synthesis of industrially-relevant compounds and therefore large-scale reactions must be performed. Unfortunately, they can be highly toxic and explosive, and with an increase in scale comes an inevitable increase in risk.[2] Therefore, extra safety considerations must be implemented. We aim to develop a continuous flow system to aid in controlling the hazards associated with hydrazoic acid. The Schmidt reaction was chosen as representative. Flow reactors can be run under pressure, helping to keep hydrazoic acid in solution and minimizing the amount present in the vapour headspace, where its explosion risks are often greatest. Additionally, the continuous nature of flow chemistry can enable relatively small reactors to produce relatively large amounts of product. This keeps the scale of the reaction and thus the hazard relatively low while still accessing large quantities of product. We will present current data of representative Schmidt reactions on small scale flow setups and future concepts for the reactor design for a large-scale system.

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Synthesis of Enantioenriched Polysubstituted Cyclopropanes via β-Boryl Acyl Silane Photocyclization

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Cyclopropanes are important motifs in natural products and pharmaceuticals, finding increasing presence in food and drug administration (FDA) approved drugs.[1] Strategic implementation of polysubstituted cyclopropanes in bioactive molecules can alter drug lipophilicity, metabolic stability, and potency.[2] Strategies to access structurally diverse polysubstituted cyclopropanes contribute significantly to drug discovery campaigns.[3] General approaches to functionalized enantioenriched cyclopropanes by olefin cyclopropanations using Simmons-Smith or diazo-derived carbenoids have been particularly effective in accessing enantioenriched cyclopropanes.[4] However these approaches are limited in variety of synthetic handles, and substitution patterns.

To address this need, we sought to develop synthetic methods for the enantioselective formation of cyclopropanes containing versatile, and orthogonal synthetic handles for diverse functionalization. Herein, we report the stereospecific synthesis of α-siloxy cyclopropylboronic esters from enantioenriched β-boryl acyl silanes (Figure 1). This approach uses an intramolecular strain-increase 1,2-boronate rearrangement triggered by photochemically generated α-siloxycarbenes. Additionally, synthesis of enantioenriched boronic ester acyl silane starting materials offers a modular approach to access diverse cyclopropane cores.[5]

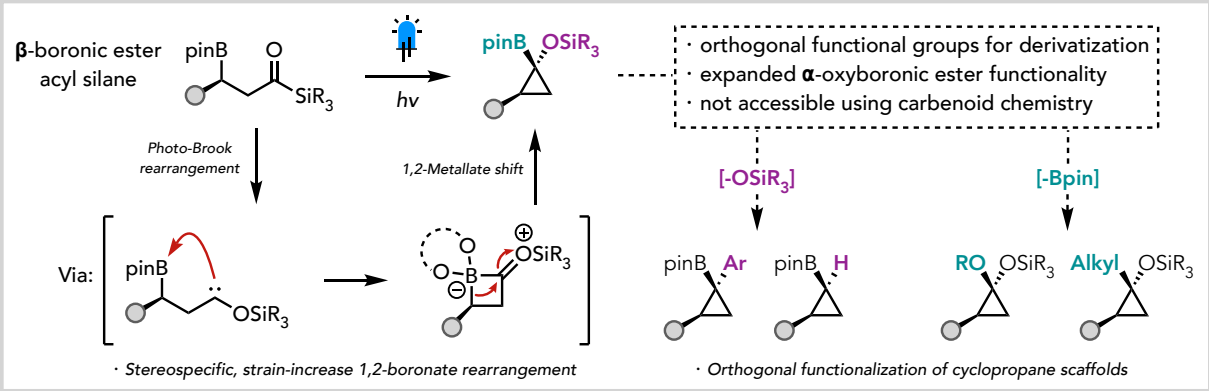

Figure 1. Photochemical cyclization of β-boronic ester acyl silanes.

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MELDRUM'S ACID BASED CONJUGATIONS

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Click chemistry offers a versatile approach for linking modular units via simple chemical reactions under mild conditions, often in benign solvents.[1] Our research explores the conjugation of biomolecules using Meldrum's acid derivatives as linkers. We aim to investigate the potential of these conjugates for controlled release using biologically available decoupling agents. Additionally, we explored structurally related compounds, such as barbituric acid,[2] as conjugate acceptor, which demonstrated enhanced stability. Our ongoing work seeks to optimize the functionalization and release mechanisms, with the goal of developing a highly tunable and sustainable drug delivery platform.

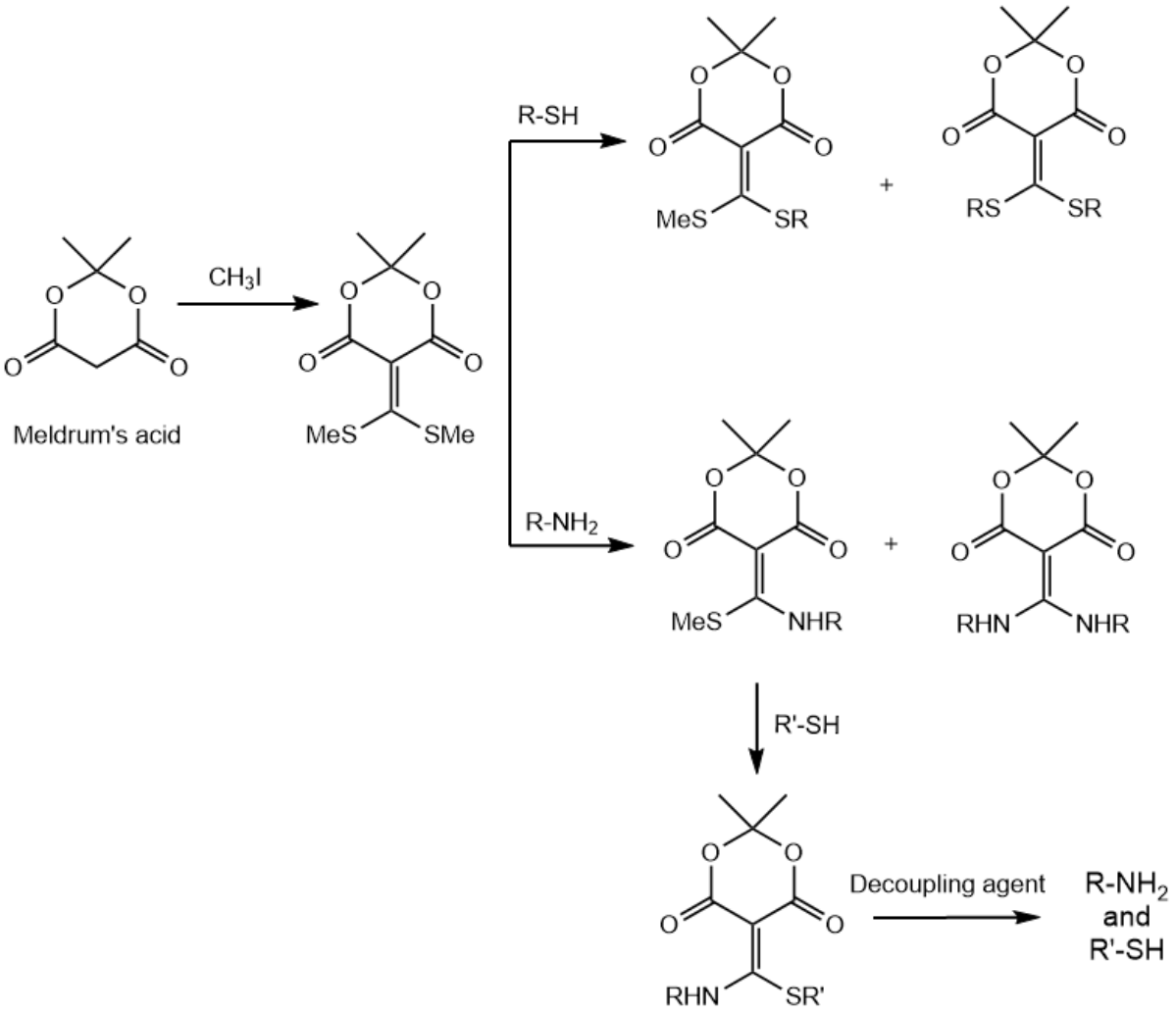

Figure 1. General synthetic pathway for Meldrum's acid conjugations.

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Development of a Generalized Nickel-Catalyzed Reductive Cross-Coupling between *N*-Hydroxyphthalimide Esters and (Hetero)Aryl Halides

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The formation of C(sp^2)-C(sp^3) bonds is an important challenge for the pharmaceutical and agrochemical industries in order to increase the proportion of sp^3-hybridized carbons to sp^2-hybridized carbons in molecules. In recent years, cross-electrophile coupling has become a popular method to form these bonds. In particular, nickel-catalyzed reductive cross-couplings using *N*-hydroxyphthalimide (NHP) esters and (hetero)aryl halides has been established to be a powerful method to generate these C(sp^2)-C(sp^3) bonds with excellent yields, under mild conditions, and with exceptional functional group tolerance.[1-4] These NHP esters are attractive starting materials due to their facile one step synthesis from carboxylic acids which are readily available and encompass a diverse chemical space. However, with previously developed methods, the conditions are often tailored to a specific substrate class and the potential breadth of reactivity is not fully demonstrated.[2-4] In order to address this, we have taken a variety of substrates and subjected them to three generalized methods to determine which set of conditions is best for representative substrate groups. Here, we present how the couplings of a wide variety of NHP esters and (hetero)aryl halide substrates perform in these different conditions, and how the addition of a trimethylsilyl chloride (TMSCl) additive is instrumental in enabling reactivity.

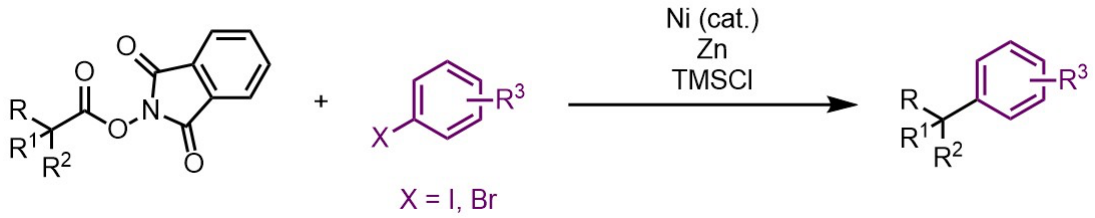

Figure 1. Generalized reaction conditions for the nickel-catalyzed reductive coupling between an NHP ester and an aryl halide.

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Examining structures and dynamics of DNA in simulated cytoplasmic fluids

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Biological structures have historically been studied outside of their native environments. While scientists have often studied these structures in dilute buffers, the cytoplasm of a cell is a highly crowded and viscous environment in which the movement of materials is restricted. This phenomenon is known as macromolecular crowding.[1] This study aimed to examine the structures and dynamics of DNA in simulated cytoplasmic fluids which closely mimics the cytoplasmic fluid of E. *coli*.[2] The structures of DNA duplexes were examined at near biological concentrations in simulated cytoplasmic fluids using synchrotron radiation circular dichroism (SRCD). The results of these studies demonstrated that DNA is destabilized in the presence of sucrose and is stabilized in the presence of polyethylene glycol (PEG) 10,000. Results of these studies were verified through UV/*vis* spectroscopy and thermal melt UV/*vis* spectroscopy. The dynamics of DNA in simulated cytoplasmic fluids were examined using fluorescence. DNA duplexes may undergo scrambling at temperatures below their melting temperatures. Complementary DNA strands were prepared with fluorescein on one strand and black hole quencher on another in the presence of excess unlabelled complementary DNA duplexes in simulated cytoplasmic fluids. Samples were incubated at 37 °C and fluorescence intensity increased over time as strand scrambling proceeded. DNA duplexes were found to undergo rapid scrambling in viscous solutions and slower scrambling in less viscous solutions.[3]

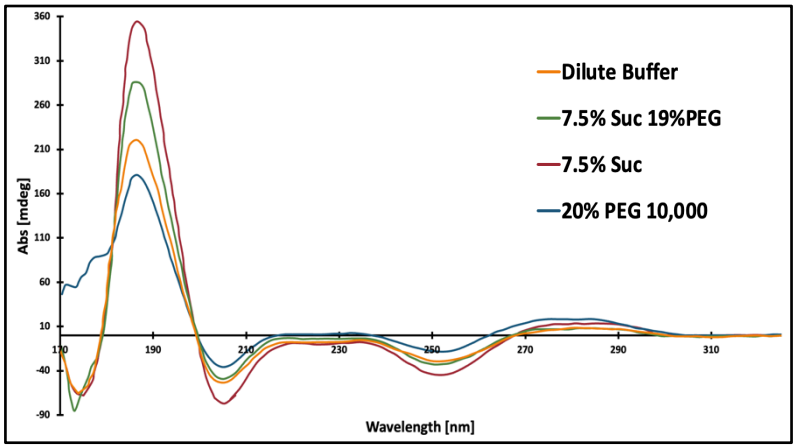

Figure 1. Synchrotron radiation circular dichroism (SRCD) spectra of DNA oligonucleotides at near biological concentrations in the presence on simulated cytoplasmic fluids.

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Ligand-directed covalent labelling electrophiles are differentially stabilized by proximity effects

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Small molecules that form irreversible covalent bonds to proteins are widely used as chemical probes and targeted inhibitors.[1] Selective labelling is a sought-after trait for covalent probes, and "latent" electrophiles that only become sufficiently reactive upon binding target protein are highly desirable. We envisioned that the selectivity and "turn-on" reactivity of latent electrophiles could be quantitatively characterized by applying the concept of kinetic effective molarity (kEM). kEM is the ratio of selective (intramolecular) to off-target (intermolecular) reaction rate constants. We synthesized a range of sulfonylating, acylating, and alkylating probes, linked to a hapten affinity handle, that target lysine, serine, and tyrosine residues in the binding pocket of a monoclonal antibody. We also synthesized complementary probes lacking an affinity handle to measure off-target labelling. Using this library of probes, we calculated kEMs for each electrophile. Interestingly, we observed that probes with mechanistically distinct electrophiles are associated with significantly different kEM values, despite equal binding affinities and comparable distance between electrophile and affinity handle. Within the series of electrophiles evaluated, we identified sulfonyl fluorides as uniquely latent.[2] To better understand the relationship between kEM and electrophile mechanism, we measured the transition state parameters associated with intra- and intermolecular reaction kinetics. We find that kEM depends on transition state stabilization through electrophile pre-organization in the binding pocket, and this enzyme-like transition state stabilization is sensitive to electrophile labeling mechanism. These results will aid in the development of highly selective covalent probes and inhibitors capable of latent, "turn-on" reactivity.

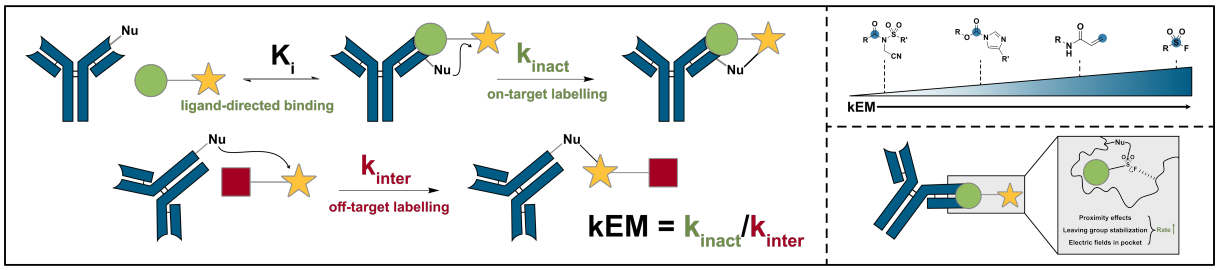

Figure 1. Assessing the selectivity of covalent electrophiles using kinetic effective molarity.

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A New Take on an Old Synthesis: Resynthesizing and Characterizing an Old Generation of Tn Antigen

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Thomsen-nouveu (Tn) antigen is often expressed on the surface of various cancer cells but is not found in healthy tissue; it is therefore an intriguing target for the development of cancer vaccines. Tn antigen is comprised of an N-acetylgalactosamine appended to the side chain of a serine or threonine; thus a suitably protected Tn antigen could be linked to an immunogenic peptide using solid-phase peptide synthesis (SPPS).

During our work towards **A** we had some difficulties reconciling our data with that of the related compound **8**, previously described by Danishefsky.[1] In the process, we found that several steps lacked experimental procedures, and that characterization data is incomplete. We thus embarked on a resynthesis of **8**, for confirmation extant data and a side-by-side comparison of two generations of synthesis.

In this presentation I will describe our synthesis of Danishefsky's protected Tn antigen, highlighting any unreported steps and the reproducibility of the procedures. These will then be contrasted with our own approach towards the preparation of a Tn antigen that can be used in SPPS.

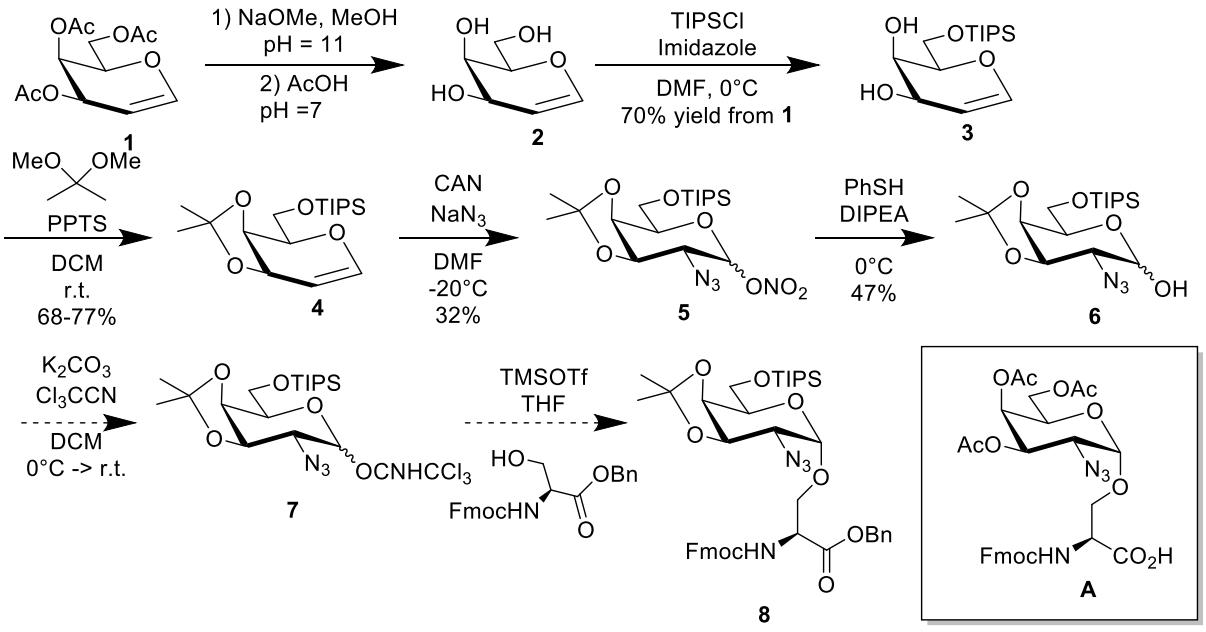

Figure 1. Reaction scheme produced for the synthesis of the acetonide and TIPS-protected Tn antigen azide precursor.

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Asymmetric Allylboration of Diosphenol Ethers : An Expedient Access to Tertiary α-Hydroxy Ketones

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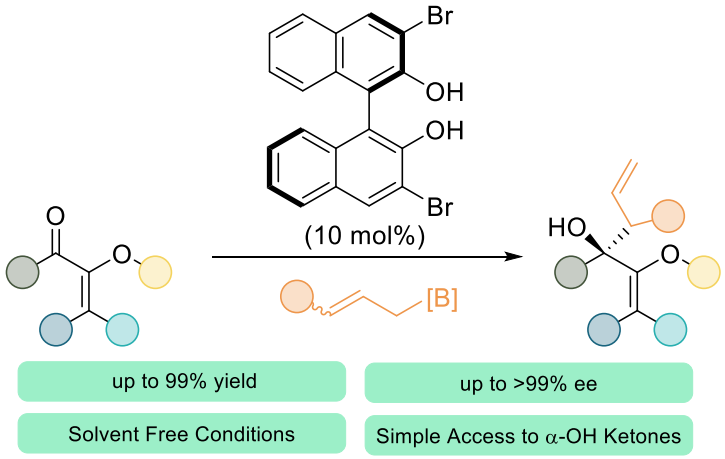
Enantioenriched α-hydroxyketones represent an important scaffold within drug molecules, natural products, and as useful synthetic intermediates. Due to their synthetic versatility significant efforts have been made to access these valuable compounds. Herein we report an organocatalyzed asymmetric allylboration of diosphenol ethers to access α-hydroxy enol ethers in yields up to 98%, and up to 99% ee. These products can be subsequently transformed into a wide range of highly oxygenated products such as α-hydroxy ketones, α-hydroxy enones and γ-hydroxy vinylogous esters. This methodology is also applicable to other α-heteroatom containing ketones in up to 99% yield and 98% ee.

Figure 1.



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Synthesis of Non-Lipophilic Prosthetic Groups for the Chemoselective ^{18}F-Labeling of Cysteine Residues of Peptide-Based Radiopharmaceuticals

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Prosthetic groups (PGs) provide a simple and efficient handle for in-direct ^{18}F-radiolabelling of sensitive peptide and protein-based targeting vectors. This ^{18}F-labelling strategy allows for the development of a diverse range of diagnostic and theragnostic radiopharmaceuticals. However, the lipophilic nature of current PGs results in significant hepatobiliary clearance of the final radiopharmaceutical, limiting their diagnostic potential.[1] To overcome this challenge, we envisioned the use of novel N-alkylated pyridinium salt-based PGs that incorporate a cationic or zwitterionic charge to increase the hydrophilicity, hoping to mitigate this biodistribution pattern (Figure 1). Further, these PGs possess reactivity to facilitate highly selective cysteine bioconjugation producing upwards of 97% conversion to the protein-bound product in a matter of minutes or seconds at the fluorine or sulfone-activated 2-position of these pyridinium salts.[2]

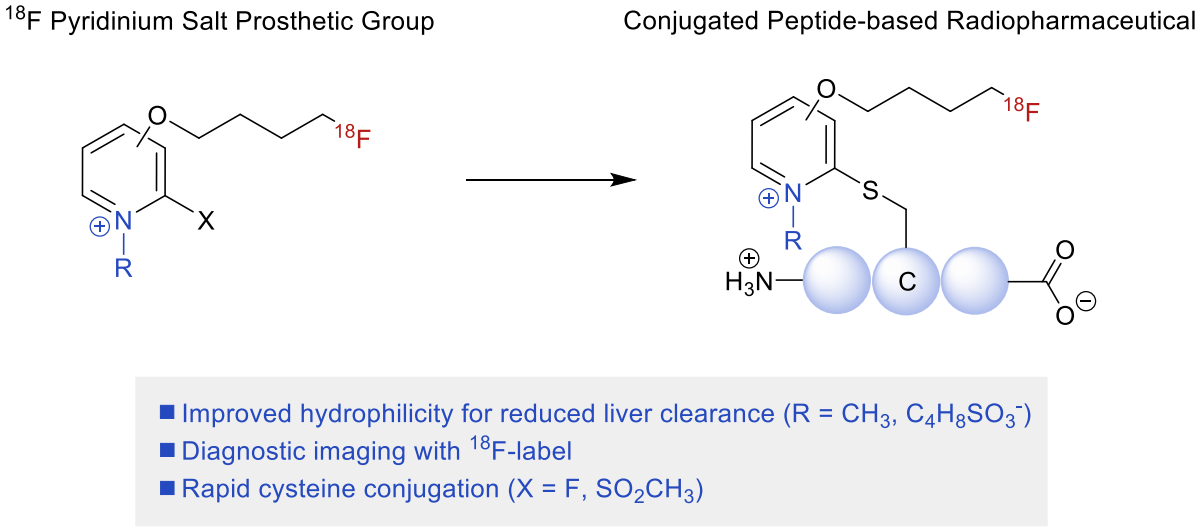

Figure 1. Non-lipophilic pyridinium salt-based prosthetic groups for in-direct ^{18}F-labeling of sensitive biological probes.

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Site-selective O-arylation of carbohydrate derivatives through nickel–photoredox catalysis

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Non-natural carbohydrate-derived aryl ethers comprise an interesting class of molecules with broad utility, including as chiral ligands, biological probes, pharmacophores, and as protected building blocks for oligosaccharide synthesis. Nickel-photoredox co-catalysis represents a promising strategy for selective O-arylation with mild reaction conditions. Selective arylations of less substituted OH groups over more substituted OH groups has been demonstrated with this approach, but differentiation between secondary OH groups has not been reported.[1,2,3] In this presentation, I will show the site-selective O-arylation of carbohydrate diols by couplings with electron-deficient bromoarenes in the presence of an iridium photoredox catalyst and nickel complex upon irradiation with blue LEDs. Arylation took place at the less sterically hindered OH group, which was dependent on the substitution pattern and configuration of the specific glycoside substrate. The use of percent buried volume calculations to quantify steric hinderance and rationalize the observed site-selectivity will also be discussed.

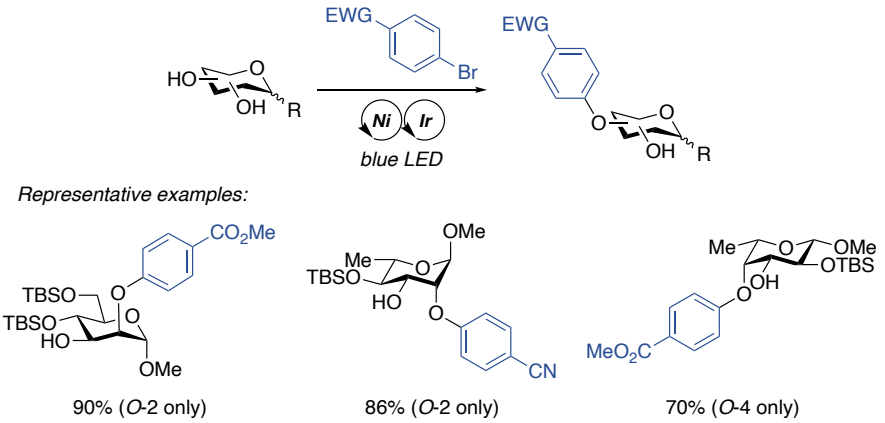

Figure 1. O-arylation reaction scheme and representative examples with corresponding yields and selectivity.

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Synthesis of deuterated nucleosides

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This project aims at the synthesis of *C*-5 or *C*-2' deuterated nucleosides and their incorporation into oligonucleotides, as probes for the study of nucleic acid conformations. Toward this goal, 5,6-bisdeutero-2'-deoxycytidine **1** was generated by the treatment of 5-iodo-2'-deoxycytidine in D_2O in the presence of appropriate palladium catalysts and a base. Under similar conditions, 5-iodo-2'-deoxyuridine was converted to 5-deutero-2'-deoxyuridine **2**. Current efforts focus on the incorporation of deuterium at the 2'-position of nucleosides (as in **3**) through a modified Barton-McCombie deoxygenation chemistry.

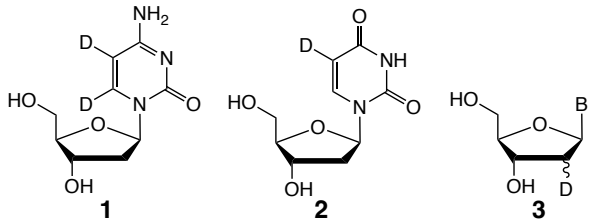

Figure 1: Modified nucleosides 5,6-bisdeutero-2'-deoxycytidine **1**, 5-deutero-2'-deoxyuridine **2**, and incorporation of deuterium at the 2'-position of ribose in nucleosides **3**.

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P32

Examining structures and dynamics of biological molecules in simulated cytoplasmic fluids

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Biological structures have historically been studied in dilute buffers which do not reflect the physiochemical properties of the cellular environment. The cytoplasm of a cell is a highly crowded and viscous environment in which the movement of materials is restricted.[1] This study aimed to examine the structures and dynamics of DNA and proteins in simulated cytoplasmic fluids, which closely mimics the cytoplasmic fluid of bacteria E. *coli*.[2] The structures of DNA duplexes were examined at near biological concentrations in simulated cytoplasmic fluids using synchrotron radiation circular dichroism (SRCD). These results showed that duplexes are destabilized by sucrose, but stabilized by polyethylene glycol (PEG) 10,000. The dynamics of DNA in simulated cytoplasmic fluids were examined using fluorescence resonance energy transfer.[3] DNA duplexes were found to undergo scrambling in viscous solutions more rapidly than in less viscous solutions. Enzyme kinetics were also measured in simulated cytoplasmic fluids and a buffered system using *p*-nitrophenyl phosphate and alkaline phosphatase as a model system. The results of these experiments showed a greater V_{max} and lower K_m in PEG 10,000 and a higher V_{max} but higher K_m in sucrose.

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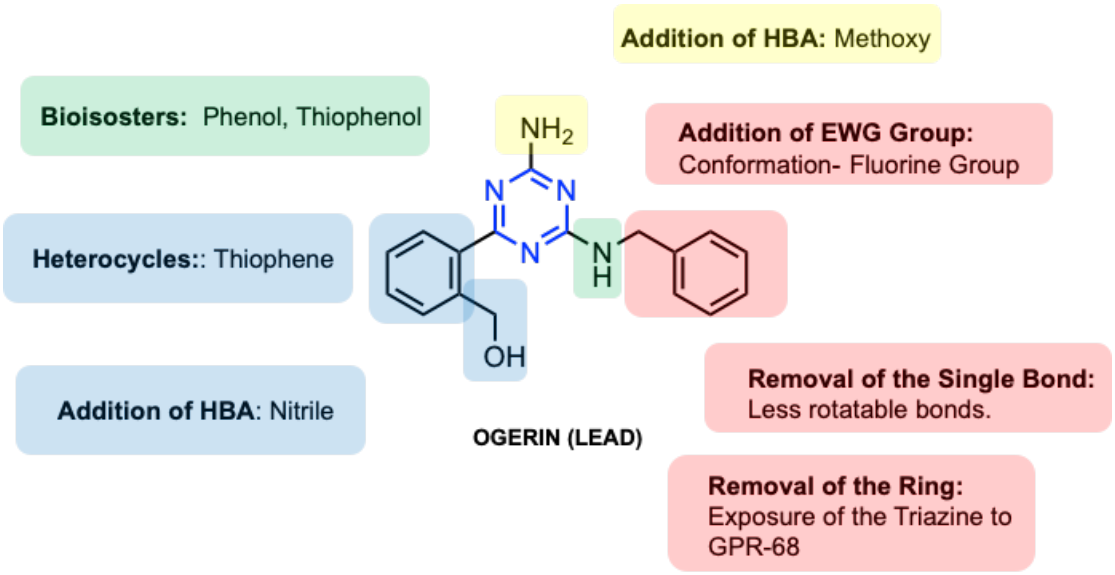
Drug Design, Synthesis and Structure-Activity-Relationship Studies of 1,3,5-Triazine Derivatives as Positive Allosteric Modulators for G-Protein-Coupled Receptor 68 (GPR-68)

Helena Braga and Pat Forgione

G-protein-coupled receptors are the largest family of proteins encoded in the genome, which transduce signals for the most diverse ligands of any receptor family. Among these, many GPRs are understudied or “dark receptors”, whose physiological roles are unknown. One of these is GPR-68, a transmembrane receptor that can induce physiological effects when activated by protons. One of these known effects is to induce the release of calcium, which may promote stem cell differentiation, making GPR-68 an attractive target for drug development.
Molecular Modelling studies proposed that 1,3,5-triazine scaffold have strong affinity for the GPR-68, being therefore considered the pharmacophore group. Among many candidates tested against this receptor, Ogerin, a trisubstituted form of this molecule, showed a promising biological activity, behaving as Positive Allosteric Modulator (PAM).
In this work, different Drug-Design strategies were employed for the synthesis of new 1,3,5-triazine derivatives, and the resulting calcium release was assessed.
The resulting Structure-Activity-Relationship (SAR) studies may be used to assess possible other pharmacophores for GPR-68. Different synthetic routes were developed to produce new 1,3,5-triazines derivatives as novel modulators of G-protein-coupled receptor 68.



Exploring the Role of Fluorinated Dienophiles in Diels-Alder Reactions

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Since the first reported Diels-Alder cycloaddition by Otto Diels and Kurt Alder in 1928, this pericyclic reaction has proven to be a powerful strategy for rapidly assembling ring systems. The Diels-Alder reaction has garnered interest across various fields owing to its advantageous properties, encompassing atomic conservation, precise stereochemical control, and the rapid assembly of structures from economical building blocks.[1] Fluorinated molecular scaffolds and synthetic strategies for expanding 3D-organofluorine chemical space are likewise impactful and gaining traction. Notably, fluorinated molecules are core to contemporary drug discovery programs for enabling breakthrough therapeutics and, more broadly, critical for advancing innovation in pharmaceutical chemistry, pesticides, catalysts, and functional materials.[2] In merging these important chemical themes, fluorinated Diels-Alder cycloaddition products are a particularly attractive subset of compounds with vast potential. This poster presentation explores an in-depth computational study of fluorine substitution effects on dienophile partners in Diels-Alder cycloadditions. Of particular focus to this study is understanding the origin of reaction rate de-acceleration as an artifact of employing fluorinated dienophiles and the factors controlling *endo*- vs. *exo*-selectivity. In unlocking insight into this unique reactivity, density function theory calculations, distortion/interaction-activation strain models, energy decomposition analysis and natural bond orbital analysis, among other computational methods, are applied. In addition, the influence of oriented external-electric-field-effects (OEEFs) and local electric field effects is explored. Collectively, this work offers a novel understanding of accelerating and shifting selectivity in Diels-Alder cycloadditions of fluorinated dienophiles as an avenue to important fluorinated scaffolds.

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Crystallization driven self-assembly of peptoid nanosheets

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Creating accurate, biocompatible sensors for detecting biological targets is crucial for improving medical diagnoses and treatments. Biosensor materials must have specific binding sites complementary to a target's surface molecules and generate a signal when binding occurs. Peptoids (N-substituted glycine polymers) are promising for biosensing applications due to their biocompatibility, enhanced protease stability, and wide range of possible side chains.[4] Peptoids are synthesized sequence-specifically via solid phase synthesis (Fig. 1 a)), using rink amide resin as a substrate, the reaction proceeds by acylation with bromoacetic acid and nucleophilic substitution with a primary amine.[3] This is repeated until the desired chain length is achieved and allows for the insertion of biomolecules or sensing moieties at specific locations (since almost any primary amine can be used), thus providing biosensing functionality. Nanosheets are prepared with peptoids containing a hydrophobic and a hydrophilic block through self-assembly but they are often polydisperse in size, which hinders their use in devices requiring specific dimensions.[4] Crystallization-driven self-assembly (CDSA) offers control over the self-assembly of semi-crystalline block copolymers.[5] This research focuses on optimizing CDSA for peptoids (Fig. 1 b)), using Ac-Ndc$_9$-Nte$_9$ (Fig. 1 c)) as a model to generate monodisperse nanosheets. This work aims to overcome limitations of peptoids for biosensing applications caused by polydisperse nanosheet sizes via the optimization of CDSA techniques to create monodisperse peptoid nanosheets.

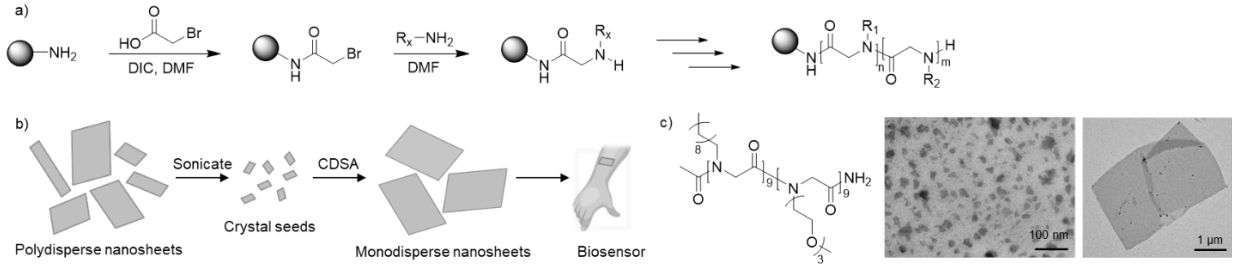

Figure 1. a) Solid phase synthesis of peptoids b) Preparation of monodisperse peptoid nanosheets via CDSA c) Ac-Ndc$_9$-Nte$_9$ structure, TEM micrographs of Ac-Ndc$_9$-Nte$_9$ crystal seeds(left) and a nanosheet (right).

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Synthesis and supramolecular encapsulation of psychotherapeutics for enhanced delivery to the brain

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Many drug candidates that show efficacy in *in vitro* and *in vivo* animal models never reach a stage where they are clinically administered.[1] This is often attributable to off target effects, poor bioavailability, and/or inconsistent dosing from patient to patient; however, these unfavourable attributes have the potential to be remedied using supramolecular drug-delivery systems that utilize nanoformulation (NF) technology.[2] NFs have shown strong efficacy in enhancing the bioavailability and targeting of a variety of drugs, and is a key technology for the COVID-19 mRNA vaccines which encapsulate the nucleic acid active pharmaceutical ingredient (API) in solid lipid nanoparticles.[3]

Our work investigates the synthesis and formulation of a class of APIs known as tryptamine-based psychotherapeutics that are in dire need of formulation due to the only routes of administration being vapor inhalation, and injection.[4] Tryptamines such as 5-MeO-DMT[5] and N,N-DMT[8] are potent 5-HT_{2A} agonists[9] that are being investigated in clinical trials for their use in the treatment of major depressive disorder and treatment resistant depression. These APIs are orally unavailable due to first-pass metabolism, oxidative degradation, enzymatic degradation *via* monoamine oxidase, and little to no blood-brain barrier penetration.[10, 11] These reasons necessitate creating formulations that bypass these barriers, which can be accomplished through utilizing the interactions at the oil-water interface. Our work displays a vignette of supramolecular drug delivery systems that uses surfactants and high-energy processing to mediate these interactions between the oil-water interface thus creating robust NFs that enhances the uptake of tryptamine-based APIs to the CNS.

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Catching COVID: Developing a nanoparticle-peptide conjugate to target SARS-CoV-2.

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COVID-19, caused by the SARS-CoV-2 virus is a respiratory disease that has a large global impact, claiming nearly 7 million lives worldwide. Despite the creation and development of vaccines, there remain relatively few treatments for active COVID infections. There is therefore a need for research into and development of new and alternative treatment approaches to mitigate the impact of the disease in affected individuals.

The SARS-CoV-2 virus has a protein (Spike) on its surface that plays a crucial role in infecting and hijacking cells. This spike protein targets a receptor on cells that will allow the virus to enter. A competitive peptide can be created to mimic the structure of the receptor to bind the virus particles before they infect a cell. Using a nanoparticle-peptide complex can further enhance the impact by using magnetic heating that can denature the virus. Together, the binding and denaturing elements functions to reduce viral load, minimize the impact the virus has on its host's cells, offering a promising antiviral therapy.

This presentation will discuss our work towards the synthesis of this nanoparticle-peptide complex, the proposed mechanism of action and biological and the further testing of its therapeutic impact against COVID-19.

Optimizing Peptoids for Stable Therapeutic Drug Delivery

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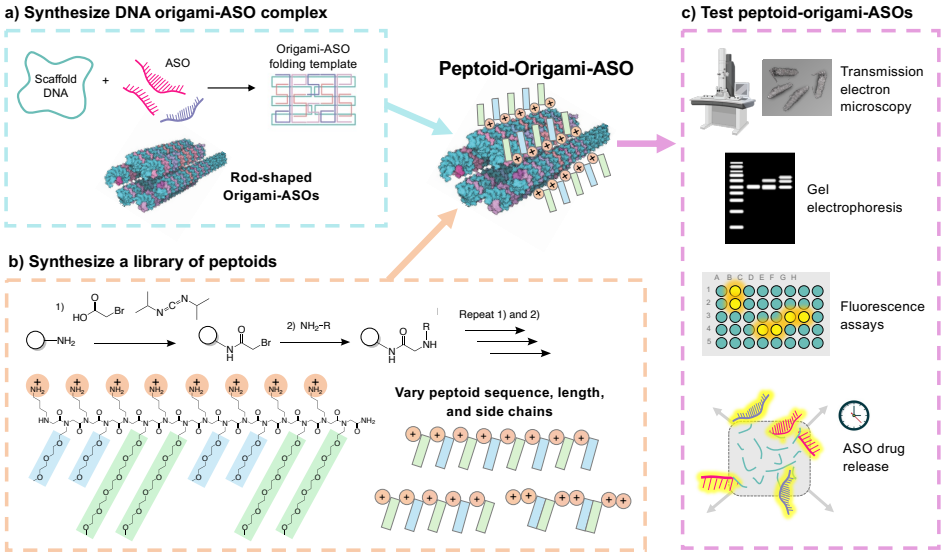
Antisense oligonucleotide (ASO) drug therapies are a promising new treatment for genetic disorders but are inefficient on their own.[1] ASOs lack stability in biological conditions due to rapid degradation by nuclease enzymes, and they require additional functionalizations to reach target cells. Deoxyribonucleic acid (DNA) origami nanostructures are a recent innovation that has helped deliver ASOs to target cells, but enzymatic degradation of origami-ASOs is still a problem.[2] In this project, peptoids (ie, N-substituted glycines) were synthesized to coat and stabilize origami-ASOs. Peptoids are peptidomimetic sequence-specific polymers, whose structure evades enzymatic degradation and can accommodate specific orders of side chain motifs.[3] In this project, different sequences of ethylene glycol (EG) and cationic side chains were investigated on peptoids because of these motifs' demonstrated benefits protecting pharmaceutical nanostructures and electrostatically binding to DNA. First, primary amine side chains were synthesized by Gabriel synthesis to add the desired motifs onto the peptoid. Then, solid-phase peptoid synthesis was performed through repeated iterations of bromoacetylation of the peptoid's N-terminus, followed by bromine displacement with the primary amine of the desired side chain. Mass spectrometry and high-performance liquid chromatography were performed to characterize and purify the peptoids. Peptoid-origami-ASO formulation is ongoing, with the complexes expected to demonstrate longer retention time and slower drug release than uncoated origami-ASOs in biological solutions, measured using fluorescence assays. By systematically tuning peptoids for origami-ASO coatings, this work will uncover key chemical components for stably delivering ASO therapies to a multitude of genetic disorders.

Figure 1. Experimental approach to creating peptoid-origami-ASO complexes.



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Nickel Catalyzed Photochemical Carbonylation Reactions

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Acyl electrophiles are essential reagents in the synthesis of carbonyl-containing functionalities such as amides and esters. Traditionally, acyl electrophiles are prepared by adding high energy electrophilic halogenating reagents such as thionyl chloride to carboxylic acids. An alternative approach is to "insert" carbon monoxide into alkyl/aryl halide bonds through transition-metal catalysis. Due to the challenge of breaking strong carbon-halogen bonds in oxidative addition in the presence of carbon monoxide, metal-catalyzed carbonylation reactions are traditionally limited to reactions with aryl halides as starting materials, and even here require high temperature and high-pressure conditions.[1] Our group has reported that acyl fluorides, the mildest acyl electrophiles among all acyl halides, can be prepared from alkyl/aryl halides and carbon monoxide by light-driven palladium catalysis at ambient conditions.[2] More recently, we reported the synthesis of acyl chlorides from alkyl iodides through photocatalyzed nickel carbonylation reactions.[3] Herein, we disclose our latest advances in the carbonylative synthesis of acyl fluorides from alkyl bromides, catalyzed by nickel complexes under photochemical conditions, featuring all commercially available and relatively inexpensive starting materials, an earth-abundant metal as catalyst, and proceeds room temperature and low-pressure conditions, with excellent functional group compatibilities. Preliminary mechanistic studies suggest the photon-driven radical oxidative addition as the rate-limiting step.

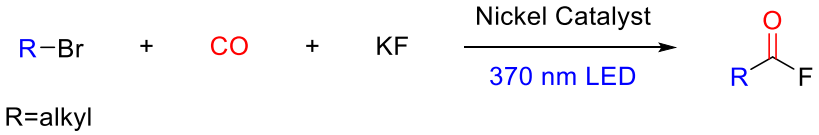

Figure 1. Carbonylative synthesis of acyl fluorides from alkyl bromides.

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Studies on Divergent Heterocycle Synthesis from High Oxidation State Building Blocks

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Heterocyclic frameworks serve as important structural cores across a wide range of applications including pharmaceuticals, polymers, and agrochemicals. Analysis of the CAS registry revealed that 10% of heterocyclic frameworks accounted for more than 80% of the organic compounds synthesized, emphasizing the lack of structural diversity in organic chemistry.[1] Synthetic efforts to develop methods towards novel heterocyclic scaffolds with structural and functional diversity are important for therapeutics and materials discovery processes. Structurally diverse heterocyclic frameworks can be prepared using divergent annulation reactions from different reagents. The Yudin group has explored a wide range of highly oxidized small building blocks as annulation reagents. Here we analyze their reactivity based on the oxidation state of carbon atoms.[2,3,4] Investigation of the involvement of carbon atoms in the construction of heterocycles from smaller modules allows for better understanding of synthetic disconnections and can be applied towards unexplored heterocyclic systems. This is exemplified in the 2-amino-3-cyanopyrrole (ACP) system which serves as a versatile, easily accessible, and sustainable scaffold for subsequent derivatization towards diverse heterobicycles. Through reactivity profile matching, the combination of different annulation reagents with ACPs allows divergent synthesis of heterobicyclic scaffolds with potentially important applications in medicinal chemistry, fluorescence imaging and materials chemistry.

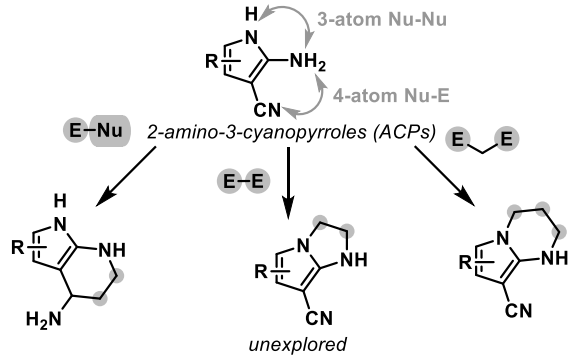

Figure 1. Reactivity profile matching of ACPs with highly oxidized annulation reagents gives access to divergent heterobicyclic scaffolds

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Unexpected Remote Asymmetric Induction via a Chiral Acetylene Equivalent

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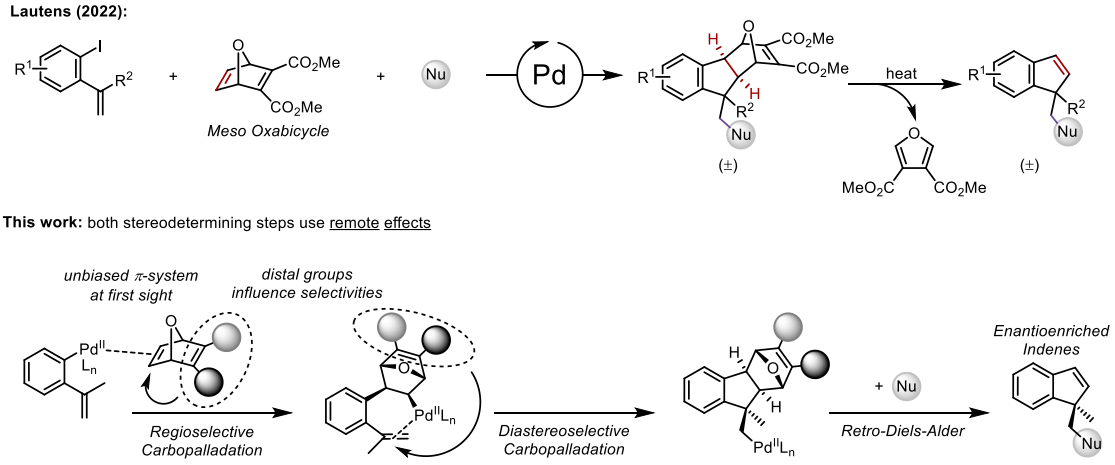
Asymmetric transformations have to date typically relied on proximal steric biasing to favour the formation of one enantiomer over the other during the enantiodetermining step.[1],[2] Our group has reported the racemic synthesis of indenes via a palladium-catalyzed multicomponent reaction using an ortho-iodostyrene, a meso-oxabicycle and a terminating reagent.[3] By introducing chirality on the oxabicycle substrate itself, we set out to study how remote effects can affect enantioselectivity. We report the use of an enantioenriched oxabicycle that serves as a chiral auxiliary following two selective palladium-catalyzed carbopalladations. Following a post-catalytic retro-Diels-Alder step, the oxabicycle acts as a formal chiral acetylene surrogate. Varying the functional groups, that are remote from the reactive alkene, direct the regio- and diastereoselectivity of the reaction with the ortho-iodostyrene in a domino fashion providing enantioenriched indenes. Mechanistic studies were conducted to better understand the selectivity observed and how remote functional groups affect the carbopalladation steps. The choice of achiral phosphine ligand has a sizable influence on the enantioselectivity, providing access to enantiomeric final indene products.

Figure 1. Synthesis of indenes using a chiral oxabicycle as an acetylene surrogate.



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A nitrilium ion-trapping strategy to access complex unsymmetrical thiadiazoles and triazolopyridines without cross-coupling

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Approximately 85% of all bioactive compounds contain at least one heterocycle and form a significant proportion of targets in medicinal chemistry campaigns.[1] Transition metal-mediated processes (*i.e.*, cross-coupling) dominate retrosynthesis strategies to obtain heterobiaryl scaffolds; however, this can become problematic in practice due to the availability of halide/boron reagents or competitive processes such as protodeboronation, protodehalogenation, and homocoupling.[2] The Yudin lab has previously used nitrilium ions as a versatile reactive intermediate that can be used to assemble heterobiaryl-containing peptides in a transition metal-free manner.[3] In this work, we trap the nitrilium intermediate, generated from a traditional Huisgen rearrangement,[4] with a C=X donor and *N*-nucleophiles in a multiple component reaction to rapidly assemble unsymmetrical, disubstituted, thiadiazoles, in air. This strategy formally bypasses two cross-couplings (Csp^2–Csp^2 or Csp^3–Csp^2, and Csp^2–N) in a single, operationally simple, workflow that addresses a practical challenge of accessing complex disubstituted thiadiazoles, a privileged yet underrepresented core in medicinal chemistry. The elevated reactivity profile exhibited by morpholine as a coupling partner was also investigated by density functional theory studies, and the trapping strategy could be further elaborated to 2-pyridyl-3-tetrazoles to furnish complex triazolopyridines.

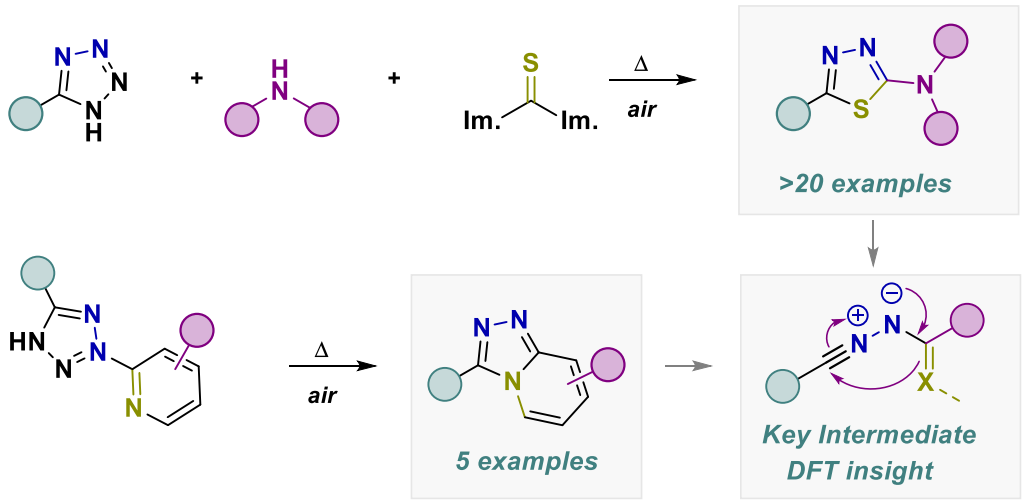

Figure 1. Facile access to unsymmetrical amino thiadiazoles and triazolopyridines *via* the interception of the Huisgen rearrangement. Im. = imidazole; Δ = heat.

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Palladium-Catalyzed Kumada-Corriu Coupling of Silyl Ketene Acetals

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Transition metal-catalyzed cross-coupling reactions are commonly used to synthesize new carbon-carbon bonds.[1] Traditionally, aryl halides are used as electrophilic reaction partners in many cross-coupling reactions. However, extensive research has been dedicated to increasing the scope of electrophiles, with esters being one substrate of interest.[2-4] Although there has been some success cross-coupling more activated esters, converting simple aliphatic esters into ketones and related species remains an ongoing challenge.

As a result, we aimed to develop a catalytic strategy to transform aliphatic esters into ketones. Our protocol involves the conversion of simple esters into their respective silyl ketene acetals. This conversion acts as both an activation strategy and to circumvent chemoselectivity issues that occur when using strong nucleophilic reagents with carbonyl substrates. With this unique silyl ketene acetal electrophile, we discovered a palladium-catalyzed Kumada-Corriu-type coupling reaction that enables the formation of ketones after hydrolysis of the intermediate methoxy-substituted vinyl arene. We hope that this method will ultimately become an alternative and reliable method for the synthesis of diverse ketones.

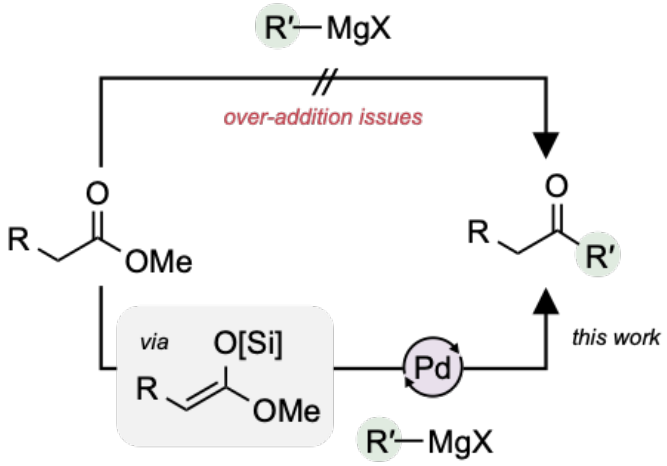

Figure 1. Reaction scheme for the palladium-catalyzed Kumada-Corriu-type coupling of silyl ketene acetals to form ketones.

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Amino acid-derived monomers for the synthesis of self-immolative polymers (SIPs)

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Self-immolative polymers (SIPs) are materials that undergo depolymerization with cleavage being initiated through a triggering event such as light, acid, base, heat, or reduction (Figure 1). SIPs have been used in self-destructing devices, sensors and smart coatings, but have limited use in biological systems because of limited biocompatibility; most extant SIPs often have toxic degradation products.

We seek to rectify this issue by developing novel SIPs with amino acid backbones, which will therefore degrade into biocompatible by-products upon depolymerization. The development of biocompatible SIPs expands the applications towards selective, triggerable drug delivery systems and providing novel matrices for 3D bioprinting.

In this presentation I will discuss our design of biocompatible SIPs, our synthetic strategy towards these useful materials, and our methodology for the introduction of thioester linkages into the framework of these SIPs.

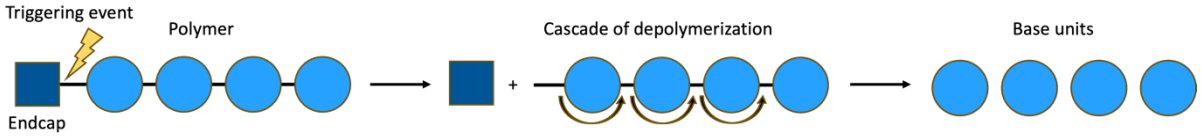

***Figure 1**. Self-immolative cascade of depolymerization following triggering event.*

Polymer-Supported Strong Lewis Acid Phosphonium Cation Catalysis Applied to Sydnone Synthesis

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Organochlorophosphonium P(V) species have considerable Lewis acid character allowing for the rapid development of redox-neutral P(V) catalytic cycles. This has led to notable improvements for synthetically useful reactions such as Mitsunobu[1], Appel[2], and Wittig[3] chemistries. Building upon this utility we have developed a novel polymer-supported P(V) Lewis acid catalyst applied to the one-pot synthesis of sydnone heterocycles. This protocol is easy to apply, selective, and benefits from mild conditions with short reaction times. Experimental and computational findings are also offered providing insight into the mechanistic role of the phosphonium cation catalyst in these reactions.

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Vinyl Sulfides as Versatile Intermediates for the Synthesis of Substituted Indoles and Azaindoles

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Previous work in the Magolan group has shown that thioalkyl phosphonium salts can be synthesized from sulfoxides via Pummerer reactions and used as versatile substrates in Wittig olefinations.[1] The vinyl sulfide products can be hydrolyzed or used as masked aldehydes and ketones in Fischer indole reactions.[2] Here, we describe alternative cyclization reactions with vinyl sulfides to form 2-substituted and 2,3-disubstituted indoles and aza-indoles.

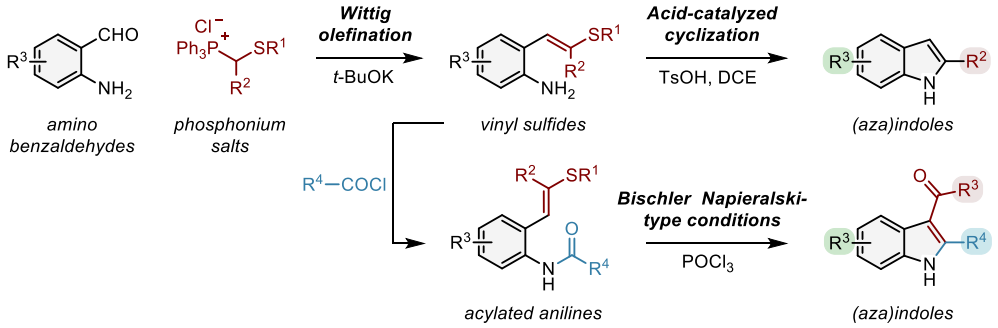

Figure 1. Use of vinyl sulfides in the synthesis of 2-substituted and 2,3-disubstituted indoles and azaindoles.

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Interactions and Click Functionalization of a Poly(Thiophenyl-Tetrazine-co-Fluorene) Conjugated Polymer with Single-Walled Carbon Nanotubes

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A highly soluble thiophene-based poly(tetrazine) polymer was prepared that can undergo inverse-electron-demand Diels-Alder (IEDDA) click reactions efficiently with different types of trans-cyclooctene (TCO) derivatives resulting in post-polymerization functionalization. The resulting pyridazines post-oxidation exhibited strong interactions with single-walled carbon nanotubes (SWNTs) and showed selectivity toward metallic SWNTs. The resulting dispersions were used to prepare thin films, whose sheet resistivity was measured. It was found that TEG functionalized pyridazine dispersion film resulted in a lower sheet resistance by several orders of magnitude compared to the non-clicked tetrazine dispersion indicating better conductivity post-IEDDA. Furthermore, modification of the polymer backbone while bound to the SWNT was performed successfully, preserving the properties of the nanotubes.

Suzuki Cross-Coupling of Carbamoyl Fluorides via C–F Bond Activation

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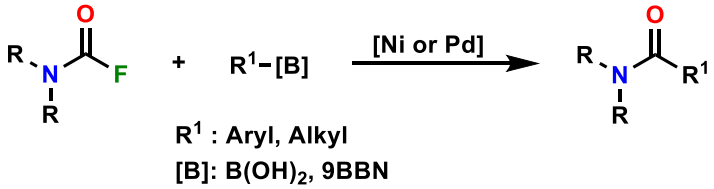
Carbamoyl fluorides have been applied as electrophiles in transition metal cross-coupling reactions to access amide-containing molecules.[1] However, recent examples are limited to intramolecular reactions or require the use of activated N-CF_3 carbamoyl fluorides.[1,2] To achieve an intermolecular cross-coupling reaction of carbamoyl fluorides with a broad substrate scope, strategies to promote C-F bond activation while minimizing undesired decarbonylation must be considered. Recently we reported the Pd-catalyzed Suzuki cross-coupling of carbamoyl fluorides with aryl-boronic acids enabled by a pyridyl directing group.[3] Herein, we report the intermolecular Suzuki-Miyaura cross-coupling reaction of carbamoyl fluorides with aryl-boronic acids and alkyl boranes under Ni catalysis, further expanding the utility of carbamoyl fluorides in metal-catalyzed cross-coupling reactions.



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Development of Novel Small Molecule Therapeutics for Alzheimer's Disease through Targeting Arginine Metabolism

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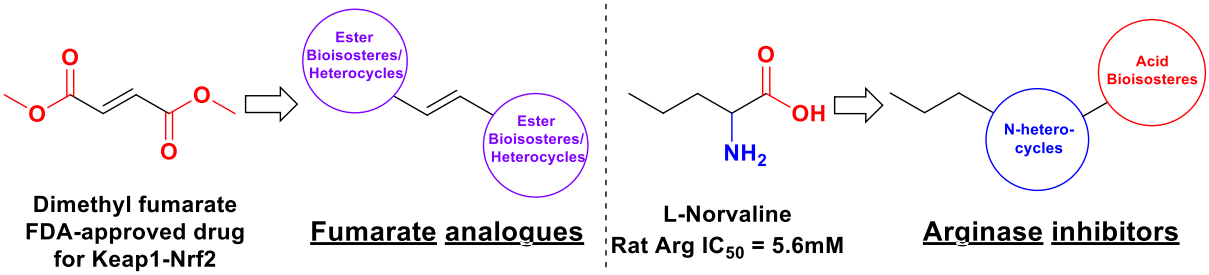
Hypothesis: More than 500,000 Canadians over the age of 65 suffer from cognitive decline due to Alzheimer's Disease (AD). Unfortunately, due to the complex mechanism of AD, limited medications are available, and available drugs only ease the symptoms without curing AD. The build-up of toxic amyloid-beta (Aβ) proteins in the brain has been a major hypothesis and treatment target for AD.[1] However, various therapies that target Aβ failed to improve AD. Recently, inflammation of brain cells (neuroinflammation) is proposed as a new direction for developing AD treatments.[2] Inflammation can be targeted through the arginine metabolic pathway by either inhibition of an enzyme (arginase) or mimicking a metabolic by-product (fumarate).[3,4]

Methods: Proposed arginase inhibitors and fumarate analogues are synthesized through synthetic protocols. Subsequently, we have identified active fumarate analogues and arginase inhibitors by monitoring their inhibition activities on respective targets (Keap1/arginase), using chemicals that produce light signals when bound to targets. Computational software (MOE) is used to understand the interactions between the compounds and the targets. Computational and biological analysis (*in vitro* and *in vivo*) are performed to analyze the compounds' physicochemical and pharmacokinetic properties. Lastly, we have administered the top compounds to an AD mouse model to determine their therapeutic potentials, through measuring the levels of neuroinflammation markers.

Results: 85 fumarate analogues and 55 potential arginase inhibitors have been synthesized. Biological testing is in progress.

Conclusions: This study will help understand the role of arginine metabolism in AD and open new directions for future AD drug research.



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INFLUENCE OF FLUORINE ON STERICALLY CONTROLLED RHENIUM-CATALYZED HYDROXYL TRANSPOSITION TO ACCESS ENANTIOENRICHED QUATERNARY CENTERS.

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The *p*-Menthylaldehyde[1,2,3] **1**, developed by Prof. Spino's group, is a chiral auxiliary allowing efficient access to enantioenriched tertiary centers. However, when aiming at quaternary centers, this auxiliary leads to a problematic formation of an allylic carbocation during the rhenium(VII) rearrangement of allylic alcohol 4a (Figure 1), destroying its precious stereogenic information[1]. We hypothesized that a source of fluorine, either on the chiral auxiliary or on the substrate (R^1), would prevent the formation of the allylic carbocation during the rearrangement, allowing access to enantioenriched quaternary centers. After delivering alcohol **8**, we successfully reached the quaternary center precursor **10** through a trans-methylboration followed by its proto-demetalation (Figure 2). We are currently optimizing the reaction conditions as well as testing out our research hypothesis for quaternary centers.

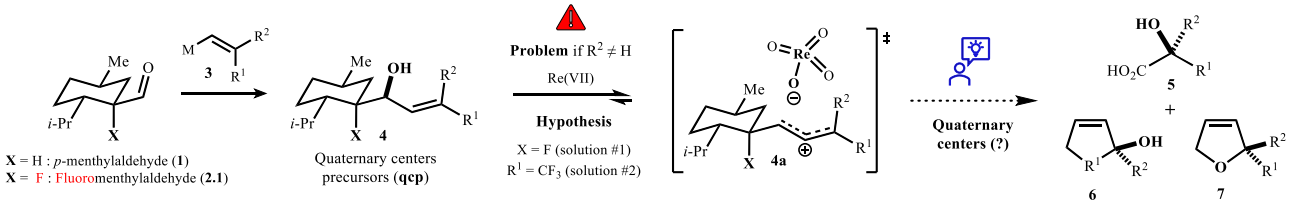

Figure 1. Influence of fluorine on the formation of an allylic carbocation during rearrangement

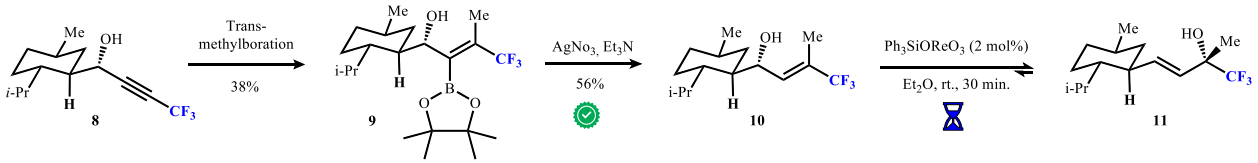

Figure 2. Synthesis of quaternary center precursor through a trans-methylboration

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Geminal Substitution Effects on Lewis Acidic Iodolium Salts for Catalysis

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Hypervalent iodine (HVI)-based cyclic iodolium salts are promising candidates as Lewis acid (LA) catalysts. These polarized iodine atoms possess sigma holes that can activate a substrate by accepting electrons from Lewis basic functional groups such as carbonyl oxygen atoms.[1] Previously, these catalysts exhibited promising activity in various Nazarov cyclizations, giving products in 29-70% yield.[2] Building upon these findings, we aim to leverage gem-substitution effects to search for higher catalytic efficiencies. By increasing the inner ring size, it increases the structural flexibility and allows us to investigate the effect of different substituents (R = H, Me, F, O) on the catalytic activity. The results of these investigations will be presented.

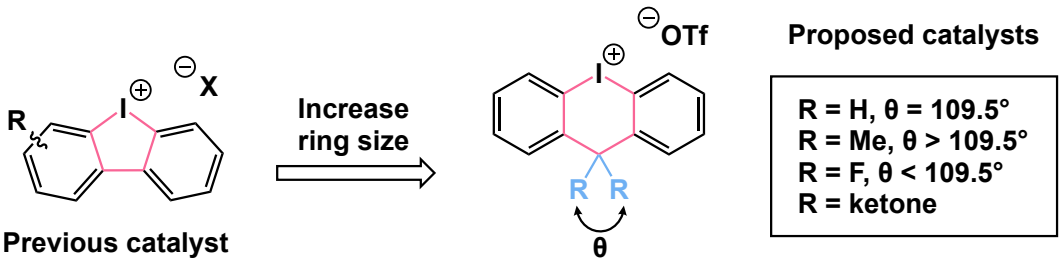

Figure 1. Proposed *changes* and new catalyst structures with bond angles between R groups

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Synthesis and Characterization of Fluorescent Non-Canonical Amino Acids for Detection of tRNA Aminoacylation

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Synthetic biology endows proteins with chemical properties that are otherwise not found in nature. To this end, noncanonical amino acids are used which possess different side chains than the 20 canonical amino acids which make up proteins in humans. By adding fluorescent moieties to the side chain, fluorescent noncanonical amino acids can act as probes to study protein localization, protein folding, and enzyme activity (1, 2). Fluorescent amino acids which display solvatochromism – a change in fluorescence intensity or wavelength in response to solvent properties – are highly valuable due to their ability to detect changes in their environment within the living cell.

In our experiments, we used electrochemistry as well as traditional organic chemistry to synthesize 5 fluorescent noncanonical amino acids with varying side chains based on coumarin, phenanthrene, pyrene, dansyl, and 6-acetylnaphthalen-2-ylamino We then characterized their fluorescent properties in a gradient of 12 solvents of varying polarity to mimic the shifting free and protein-bound environments. Three amino acids containing the dansyl, pyrene, and phenanthrene side chains were synthesized in high purity and yields of 41%, 18%, and 1% respectively. Fluorescence of the dansyl amino acid was redshifted as solvent polarity increased, whereas pyrene fluorescence was redshifted in some nonpolar solvents. Meanwhile, phenanthrene fluorescence remained constant. Further characterization in biochemical assays is currently ongoing with the aim to use these fluorescent amino acids as reporters of enzyme activity in live mammalian cells.

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Synthesis of Thioalkyl Phosphonates as Improved Precursors to Vinyl Sulfides via HWE Olefinations

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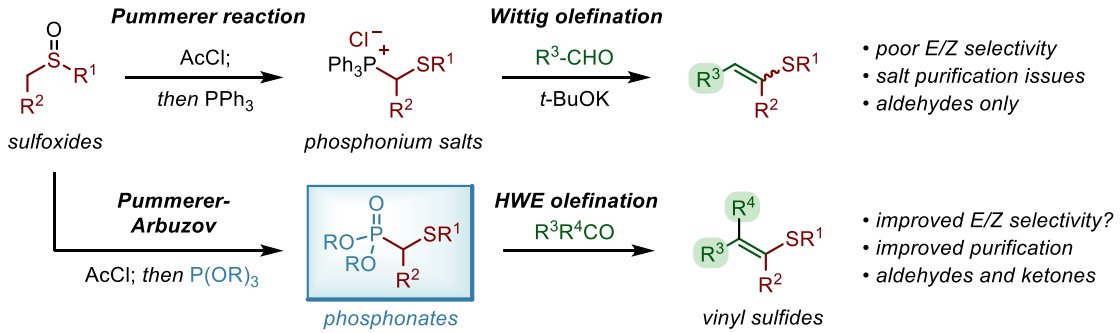
Our lab has previously developed an efficient method for the synthesis of vinyl sulfides from sulfoxides through Pummerer reactions and subsequent Wittig olefinations.[1] The thioalkyl phosphonium salts are versatile intermediates[2] but purification of certain salts can be challenging and Wittig olefinations show poor *E*/*Z* selectivity. Here, we describe the synthesis of thioalkyl phosphonates that (a) are easier to purify, (b) show improved *E*/*Z* selectivity in olefinations, and (c) show enhanced reactivity with ketones compared to the phosphonium salts.



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Synthesis of Prenylated Carbazole Natural Products via Alumina-Directed *Ortho*-Allylation

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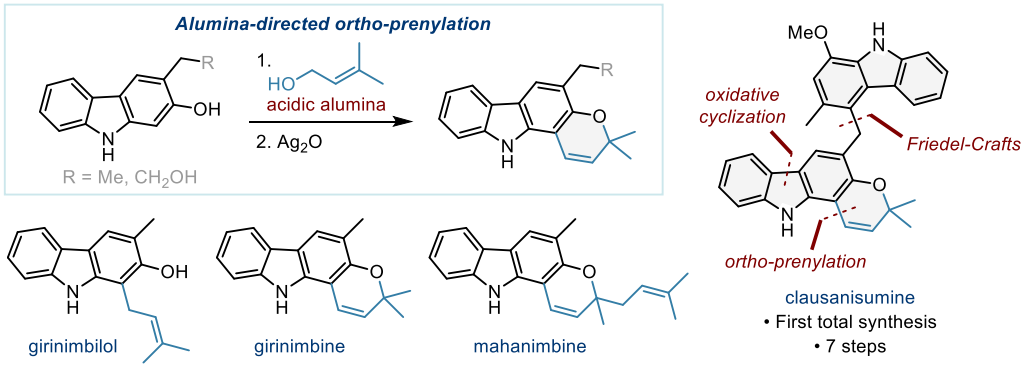
Prenylated carbazole alkaloids represent a prominent class of natural products that show anticancer, antiviral, and anti-HIV activities. The Magolan lab is currently developing methodology for highly *ortho*-selective prenylation of phenols using acidic alumina. Here, we use alumina-directed *ortho*-prenylation to access a series of prenylated carbazole natural products, including girinimbilol, girinimbine, and mahanimbine. We have also achieved the first total synthesis of clausanisumine, an anti-HIV alkaloid isolated from the fruits of *Clausena anisum-olens*.[1]



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Exploiting Cytochrome P450 Promiscuity through the Chemoenzymatic Synthesis of Bicyclic Seongsanamide B

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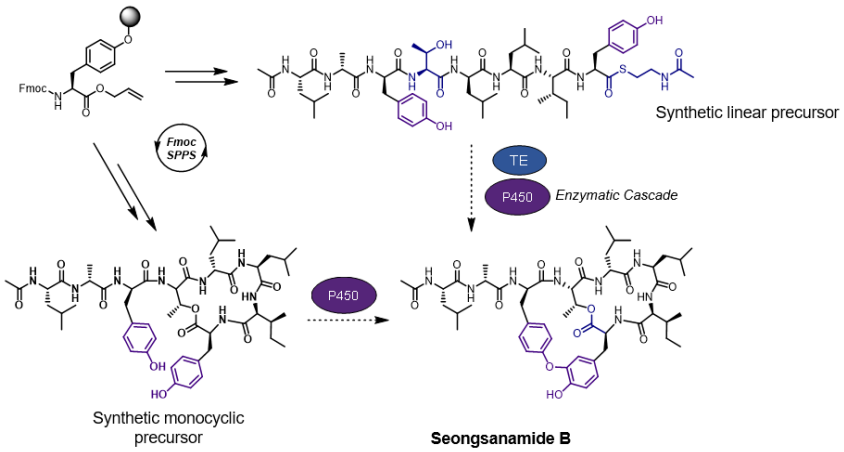

Figure 1. Chemoenzymatic synthesis of bicyclic Seongsanamide B

Non-ribosomal peptides are a diverse class of natural products with useful bioactivities, often used in developing pharmaceuticals such as antibiotics or immunosuppressants. Their extensive bioactivity is due to their vast structural diversity, arising from their unique biosyntheses.

However, often the biosynthetic assembly involves complex enzymatic reactions that are difficult to replicate synthetically.[1] Instead, a chemoenzymatic approach retains the synthetic flexibility of traditional organic synthesis and accomplishes difficult transformations through enzyme catalysis, ensuring excellent regio-, stereo-, and chemoselectivity.

In this study, we are investigating the promiscuity of a p450-catalyzed biaryl ether cyclization through the chemoenzymatic synthesis and derivatization of the bicyclic depsipeptide, seongsanamide B. This bacteria-derived antiallergenic contains a thioesterase-driven macrolactone ring, along with a p450-catalyzed biaryl ether cyclization.[2] While most reported p450-catalyzed transformations occur during biosynthetic assembly on enzyme-linked substrates, seongsanamide B uniquely has its transformation post-assembly, on the carrier protein-free substrate.[4,5] This suggests that this p450 has potential to be a versatile biocatalyst capable of catalyzing substrates beyond seongsanamide B.

We have previously established that treating the linear intermediate with its native thioesterase produces the monocyclic precursor, seongsanamide E.[3] We now attempt the subsequent transformation of the monocycle with the native p450 to catalyze the oxidative phenolic coupling to form the biaryl ether-containing bicyclic seongsanamide B. We are also interested in an enzymatic cascade, transforming the linear intermediate to the final bicyclic product with a one-pot incubation of its native thioesterase and p450. The promiscuity of this enzymatic transformation will be probed using synthetic analogs of its precursors.

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Light-catalyzed synthesis of multivalent glycopolymers

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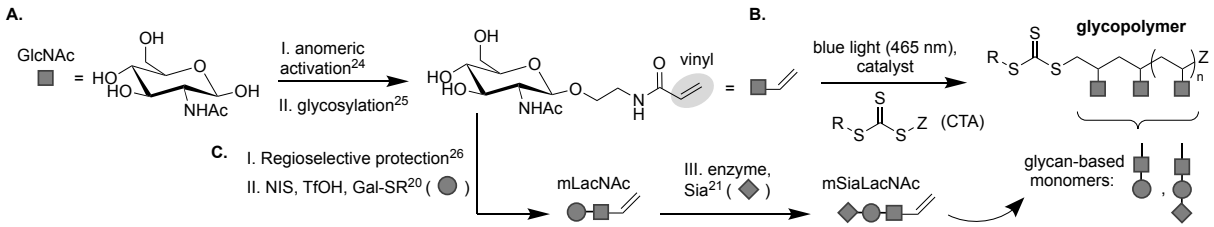
Glycans are carbohydrates that densely coat cell-surface proteins and lipids, acting as the first point of contact between cells and their microenvironment.[1,2] Over 700 enzymes, 10 monosaccharides, and architectural complexity give rise to diverse glycan structures with biological functions. Cell-surface proteins act as receptors for glycans, initiating binding events to influence processes within the cell. Receptor-glycan binding occurs with weak affinity, necessitating high copy numbers of glycans to realize meaningful biological outcomes. Structurally defined glycan material is required to study these pathways. However, glycans are not encoded in DNA and cannot be produced using genetic strategies. As such, there is a need for chemical approaches to access analogous macromolecules.[3,4] Polymers with pendant glycans (glycopolymers) are ideal analogs as the length and side-chain density can be tailored to ensure high valency, thus mimicking natural displays of glycan.[4] Synthetic advances offer opportunities to polymerize molecules on the cell surface. Pioneering work on cell-surface polymerizations using PEG-based monomers achieved excellent control of polymer distribution and density while maintaining cell viability.[5] These strategies have not been applied to access glycan analogs despite their potential impact on understanding glycan structure-function relationships in biology. This work aims to extend cell-surface polymerization approaches to glycopolymers and profile biological outcomes. We developed a synthesis to modify glycans and obtain appropriate monomers. Subsequent light-initiated polymerization yielded glycopolymers of varying length and side-chain density. We will apply this technology to grow glycopolymers on the surface of cells and advance understanding of the roles of glycans in health and disease.

Fig 1A. *Synthesis of glycomonomer with vinyl-functional group.* ***B.*** *Controlled synthesis of glycopolymers via PET-RAFT.* ***C****. Synthesis of complex glycomonomers from Gal (Galactose) and Sia (Sialic acid).*



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Mild Arylboration of Cyclic Enones via Cooperative Copper-Palladium Catalysis

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Cyclic enones are abundant chemicals that are commonly used as building blocks for the synthesis of pharmaceuticals and natural products. While a variety of catalytic methods for the mono-functionalization of cyclic enones have been reported,[1] direct catalytic difunctionalization to install two new functional groups remains underexplored. Arylboration is a particularly powerful method of direct alkene difunctionalization,[2,3] however, application to cyclic enones is surprisingly absent in the literature. This may be due to competing background conjugate borylation reactivity,[4] or kinetic difficulties in the trapping of transient enolate intermediates. The current work describes the development of a mild, catalytic synthetic method for the arylboration of cyclic enones to rapidly access complex trisubstituted building blocks. High-throughput screening identified a cooperative copper-palladium catalytic manifold allowing for the formation of the desired β-boryl, α-aryl cyclic ketone products in moderate yield (36 to 65%) and high *anti*-diastereoselectivity (5:1 to >20:1). Aryl bromides and triflates are compatible with this reaction, and a broad scope of aryl and heteroaryl substrates with varying steric and electronic profiles are tolerated. The resulting trisubstituted products can be modified further through diverse transformations at both the boron and ketone groups, providing access to polysubstituted cycloalkane scaffolds.

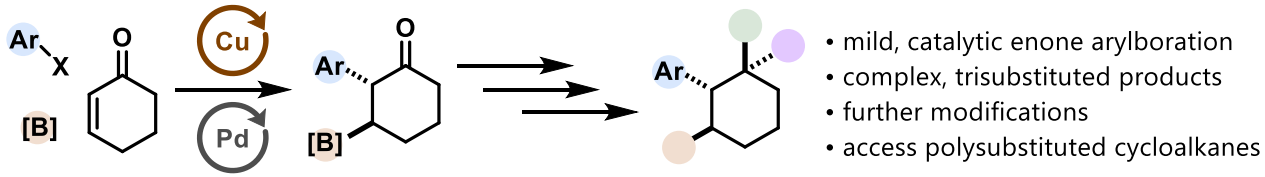

Figure 1. Cu/Pd-catalysed arylboration of cyclic enones to access complex trisubstituted building blocks with opportunities for further functionalization.

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Lewis Acid-Catalyzed Carbofluorination Reactions of Alkynes

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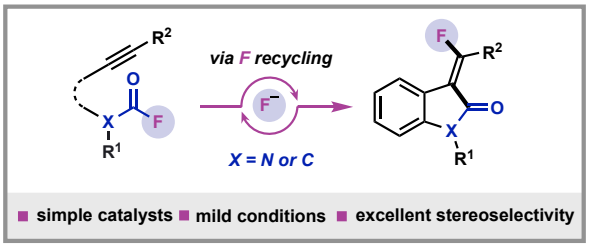
The introduction of C–F bonds into molecules can modulate the metabolic stability, bioavailability, and lipophilicity of the parent molecule, making organofluorine compounds of particular interest to agrochemical and pharmaceutical industries. One way to access complex fluorinated molecules is through atom-economical carbofluorination reactions, which involves the (formal) addition of a C–F bond across an unsaturated functionality, such as an alkene or alkyne. These reactions are generally hard to achieve, as the catalyst needs to be capable of both breaking and making C–F bonds. Recent reports have demonstrated that acyl, benzyl and propargyl fluorides can be applied in carbofluorination reactions, which typically proceed via fluoride abstraction to generate a carbocation intermediate. The work presented here shows that two simple Lewis acids, $BF_3{\cdot}OEt_2$ and $TrBF_4$, can catalyze the atom-economical carbofluorination of alkyne-tethered carbamoyl fluorides and acyl fluorides, respectively. Both methods provide access to previously inaccessible alkenyl fluorides with excellent stereoselectivities. Additionally, experimental and computational studies support a mechanistically distinct reaction pathway involving fluoride recycling that avoids the high barrier typically associated with cleaving strong C–F bonds.



Designing inhibitors of the CDK2-Spy1 complex – a new target for cancer treatment.

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The Speedy/RINGO family of proteins are often-overlooked cell cycle regulators that bind cyclin-dependent kinases (CDKs) instead of the cyclin, activating them while overriding standard cellular controls such as the need for phosphorylation and blocking the binding of tumor suppressor proteins.[1] The kinase enters a perpetually active state, leading to uncontrolled cell division and cancer. Upregulation of the human homolog Spy1 has been implicated in the development of multi-drug resistant breast cancers and other aggressive and treatment resistant cancers.
CDKs have long been targets for the treatment of cancer, and there have been many attempts to design small molecule CDK2/Cyclin A inhibitors (CKIs) to shut down cell division, yet all have failed in the clinic – which, we hypothesise, is because of the agency of Spy1 which induces changes in the shape of the binding site. We therefore require novel inhibitors designed to target the covert action of Spy1-activated CDK2.

In this presentation I will discuss our studies on the CDK2-Spy1 complex. We used docking and molecular dynamics simulations to investigate how inhibitor binding differs from the CDK2-CycA complex; a change in the CDK2 active site orientation results in reduced binding affinity of inhibitors. We then designed selective inhibitors for this altered binding site using HTVS, structure-based design, and machine learning based approaches. Our synthetic campaign towards these new molecules will also be discussed.

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SYNTHESIS OF *α*-L-FUCOSE-CONTAINING LUPANE-TYPE SAPONINS AS POTENTIAL ANTIVIRAL AGENTS

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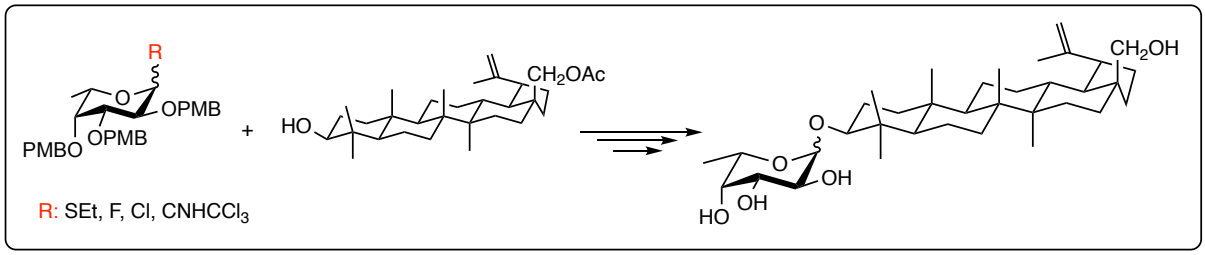
Human immunodeficiency virus type 1 (HIV-1), and other high-mutation-rate viruses, including Ebola and herpes simplex viruses, exploit the dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) receptor to infect immune cells. Preventing viral attachment to the carbohydrate recognition domain (CRD) of DC-SIGN is a promising antiviral strategy. Our group previously developed Lewis-X-containing saponins that inhibit DC-SIGN-mediated HIV-1 *trans*-infection *in vitro*. Since *α*-L-fucose is crucial for Lewis-X trisaccharide binding to DC-SIGN, we hypothesized that *α*-L-fucose-containing saponins could serve as simpler antiviral alternatives. Our present study aimed to establish a general *α*-L-fucosylation methodology for synthesizing *α*-L-fucose-containing saponins using betulin as aglycone, a naturally occurring non-toxic triterpenoid with inherent antiviral activity. Key challenges included forming the thermodynamically unfavorable and acid-sensitive 1,2-*cis*-*α*-L-fucopyranosyl linkage and avoiding Wagner-Meerwein rearrangement of the lupane core. As a proof of concept, we investigated stereoselective glycosylation between betulin-28-*O*-acetate and diverse fucosyl donors (thioglycosides, imidates, chlorides, and fluorides) bearing non-participating *para*-methoxybenzyl (PMB) groups. Optimizing reaction conditions (promoter, coupling partner equivalents, solvent, and temperature) yielded a favorable *α*:*β* anomeric ratio. The $CuBr_2$/Bu_4NBr-promoted thiofucoside glycosylation emerged as the most robust and effective approach. Cleavage of the protecting groups (PMB and Ac) afforded the target saponin as a 3:1 *α*:*β* diastereoisomeric mixture. Comparative antiviral assay with Lewis-X containing saponins are currently underway.

Figure 1. Synthetic Pathway Overview



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Prebiotic emergence of the Pyridoxal-5-Phosphate

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To understand and recreate the origin of life, our lab is searching for conditions under which geochemistry might organize itself into dynamic reaction networks that pre-patterned metabolism and its bioenergetics.[1] In order for the network to change over time, an important feature would be its ability to produce small molecules that could catalyse existing reactions within the network or turn on new ones, allowing the network to be expanded and pruned in the absence of genetic control. We have recently shown that several coenzymes, including pyridoxal-5-phosphate (PLP), are able to promote their associated reactions in the core of metabolism nonenzymatically.[2] However, it is yet to be demonstrated whether the biosynthetic pathways leading to the formation of these coenzymes can occur nonenzymatically. Here, we show a nonenzymatic analog of PLP biosynthesis. Dihydroxyacetone phosphate (DHAP), ribose and ammonia react in water to give PLP, supporting the feasibility of catalytic feedback effects within protometabolic networks.

The observation that ribose leads to PLP, whereas the biological substrate ribose-5-phosphate does not, provides insight into the environment needed to establish protometabolic networks that pre-pattern biological metabolism.

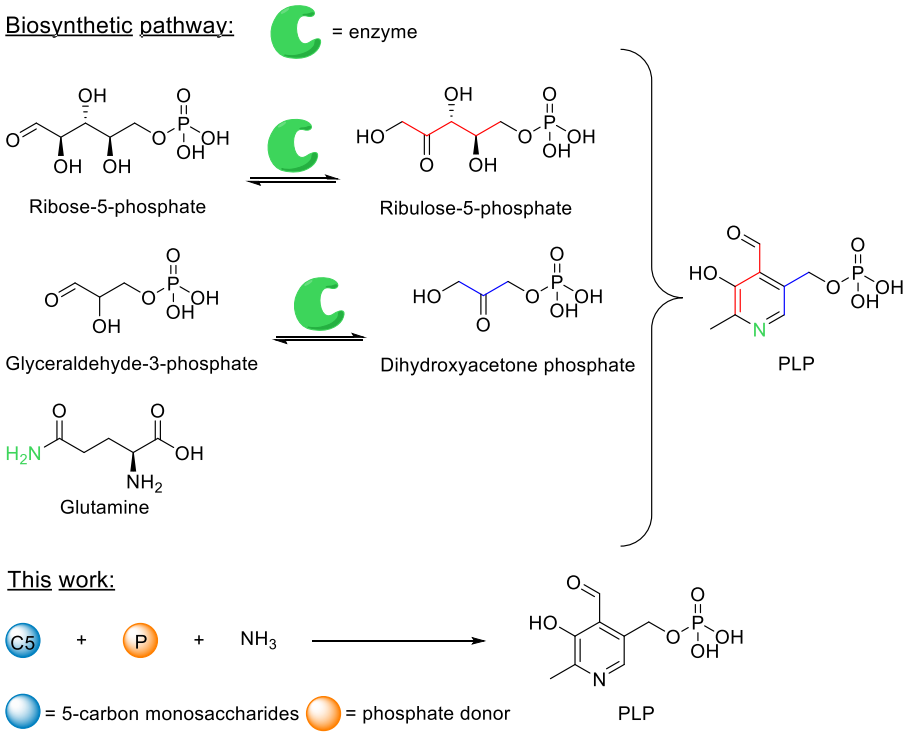

Figure 1. Biosynthetic pathway and possible non-enzymatic route for PLP synthesis.

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Towards the Total Synthesis of (+)-Havellockate and Related Cembranoid Natural Products

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Many marine natural products of the cembranoid family have been reported through isolation but scarcely synthesized due to their highly complex structures, with only a handful members synthesized so far.[1] Our initial target, (+)-Havellockate, possesses a densely decorated [5,5,6,5] tetracyclic system featuring a spirolactone moiety attached to a fused all-syn tricyclic core.[2] A meticulous retrosynthetic analysis has identified that the carbon scaffolding of (+)-Havellockate could be accessed from a spectacular reaction cascade that correctly generates 3 carbocycles and 3 stereocenters of the natural product in a stereo- and regiospecific manner.

Further studies led us to understand that the stereochemical outcome of this well-orchestrated sequence of events can be controlled. Thus, we intend to exploit this methodology to pave a synthetic pathway to access multiple members of this class of natural products, which have remained elusive from the synthetic community to this day

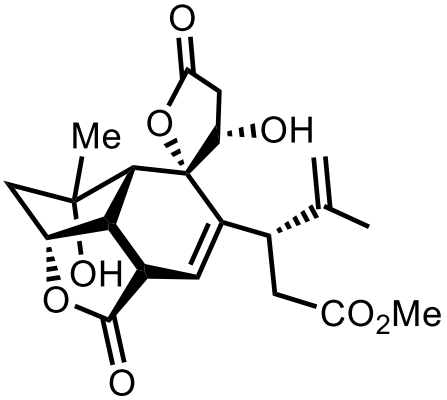

Figure 1. Structure of (+)-Havellockate

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[2] Tet. Lett. 1998, 39, 139-142

TMDSO and KO^{t}Bu enabled cross-electrophilic coupling of benzyl chlorides and alkyl halides

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The combination of alkoxide base and silicon hydride species are reported to conduct a range of unusual transformations, including C–O and C–N cleavage, reductive decyanation, and C–H silylation.[1] While triethylsilane is particularly common, our group recently reported that the use of 1,1,3,3-tetramethyldisiloxane (TMDSO), when used alongside KO^{t}Bu, performs transition metal-free hydroalkylation of styrenes with alkyl halides.[2] Mechanistically, this reagent pair is thought to be a powerful single electron reductant that can make carbanions in situ. In this study, this concept is applied towards the cross-electrophilic coupling (XEC) of organohalides for the formation of C(sp^3)-C(sp^3) bonds – a highly coveted goal in medicinal chemistry.[3,4] The reaction exploits the differing preference of certain organohalides to react as electron acceptors via SET vs their ability to react as S_N2 electrophiles. With widely accessible and relatively cheap starting materials, cross electrophilic coupling in transition metal, photochemistry, and electrochemistry free conditions can be achieved.

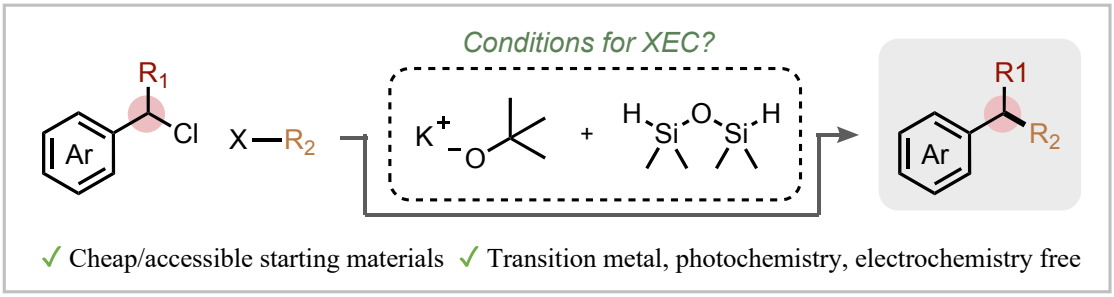

Figure 1. Cross-electrophilic coupling of benzyl chlorides and alkyl halides with KO^{t}Bu and TMDSO

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Investigation of saturated bioisosteres in conformational modulation of macrocycles

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Cyclic peptides are increasingly recognized for their valuable properties in drug discovery due to their unique structural and functional attributes.[1] These compounds are characterized by their ability to interact with protein targets due to their cyclic nature, fewer conformational degrees of freedom, which facilitates binding interactions.[2] Rigidifying the backbone of cyclic peptides is a key strategy for improving their binding efficiency to protein target sites. Our lab recently developed innovative methods for incorporating hetero-biaryl linkages into the backbone of cyclic peptides.[3–6] As part of this study, we have demonstrated that by using N-(isocyamino)triphenylphosphorane (PINC) reagent, through a nitrilium ion intermediate, one can access heterocycle biaryl linkages (***Fig 1a***).[7] The strained biaryl moiety significantly restricts the conformational landscape and reduces the overall flexibility of the cyclic peptide. Saturated bioisosteres, such as cubane, when substituted for the phenyl group, serve as potent structural rigidifying elements due to its unique molecular geometry and highly strained bond angle.[8–11] We are keen on exploring the unknown conformational landscape of a cubane amino acid embedded into the backbone of peptide macrocycles and the relationship between the conformation and properties of the macrocycles (***Fig 1c***). We propose the incorporation of the cubane moiety into cyclic peptides backbone structure significantly narrows and changes their conformational landscape due to its rigidity. This unique structural constraint results in properties, such as significant variations in the cell membrane permeability.

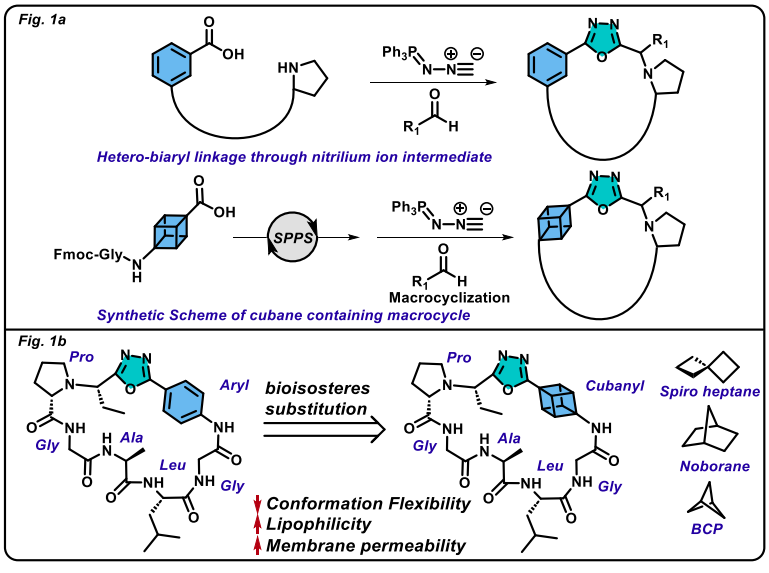

Figure 1. (*a. Use PINC as reagent for macrocyclization to synthesize hetero-biaryl containing macrocycle. b. Saturated bioisostere substitution for peptide macrocycle*)

Investigating fungal biosynthesis of 2,3-diaminopropionate

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L-2,3-diaminopropionate (Dap) is a non-proteinogenic amino acid building block found in some siderophores and nonribosomal peptide natural products. Its biosynthesis in the bacteria Staphylococcus aureus has recently been biochemically characterized. A handful of fungal strains are also known to produce DAP containing non-ribosomal peptides. Bioinformatic analysis of the genomes of known fungal Dap producers identified a two gene cassette that was hypothesized to lead to the formation of Dap. The first gene encoded a PLP-dependent enzyme, which we discovered catalyzes the condensation of either L-alanine to L-serine's side chain to yield *N*-(1-amino-1-carboxyl-2- ethyl)-alanine (ACE-A). The second gene encodes a Flavin-containing monooxygenase, likely responsible for oxidative removal of pyruvate to generate Dap. In this study, the PLP-dependent enzyme, Fda4, was recombinantly expressed and purified. Biochemical assays using this recombinant protein and different substrates were tested to determine the enzyme's function and substrate preference. Also, the Flavin-containing monooxygenase Fda3 was recombinantly expressed and purified to demonstrate its ability to produce Dap. This work provides the first characterization of Dap biosynthesis in fungi.

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RAPID ACCESS TO CYCLOPROPANE SCAFFOLDS VIA PHOTOCHEMICALLY INDUCED RING CONTRACTION

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Small ring systems are privilege structural motifs in the pharmaceutical industry mainly due to their capacity to act as bioisosteres. One of their most common representatives, cyclopropane, is found in the structure of several drugs and natural products. The three carbon atoms ring system is generally employed to improve potency, metabolic stability, brain permeability and binding of an active drug to the desired active site. [1,2] Its rigid three-dimensional structure can be a key aspect in the selectivity and potency of the drug. Over the years, various methods to access cyclopropane rings have been explored, most of which rely on ring closure or cycloaddition. Despite their popularity, these methods sometimes suffer from poor atom economy, low yields, or difficulties with scalability.[3] In this context, we aimed to develop a modular approach to access a wide range of cyclopropanes using a less common strategy based on a ring contraction event. The method involves the extrusion of sulfur dioxide from 2,3-disubstituted thietane dioxides under photochemical conditions, to produce the cyclopropane motif.[4] The easy, rapid and modular synthesis of the substrates is a key feature of the approach. The transformation was found compatible with a variety of O, N, Cand P-based functional groups and amenable to large-scale synthesis.

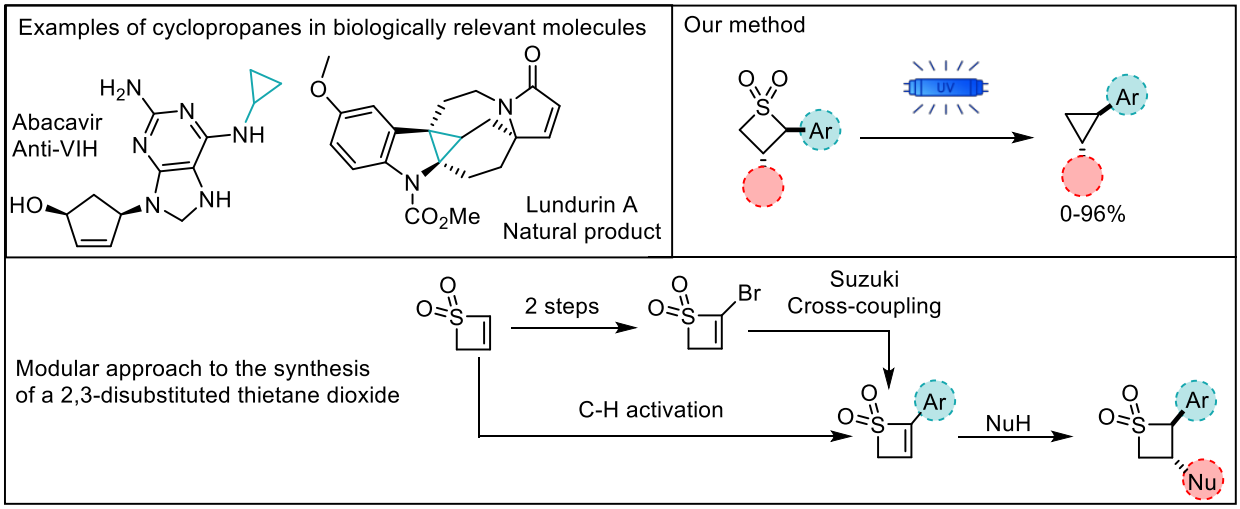

Figure 1. Photochemical synthesis of cyclopropanes from 1,1 thietane dioxides.

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Synthesis of α-Methylated Heteroarylalanine Amino Acids via Negishi Coupling

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Since the introduction of insulin into clinical use in the 1920s, peptides have been considered a promising class of potential therapeutics. Development of peptide therapeutics has been impeded by the rapid hydrolysis of peptides by proteases, resulting in many peptides having poor *in vivo* stability.[1] Of the structural modifications utilized to extend peptide half-lives, α-methylated amino acids were identified as being the most effective at reducing the rate of hydrolysis.[2] Presently, the implementation of these amino acids is limited by the lack of commercially available α-methylamino acids, particularly those with non-natural side chains. Building on our previously reported general strategy for the synthesis of a wide variety of non-natural α-methylamino acids,[3] development of new amino acids via Negishi coupling was achieved using an α-methylated iodoalanine building block. After the enantiopure building block was synthesized in three steps, it was converted to the corresponding organozinc and cross-coupled to various heteroaryl halides. A set of fourteen amino esters was produced, incorporating eleven different heterocycles including nitrogen-, sulfur-, and oxygen-containing aromatic rings. A representative amino acid was scaled up (>1 gram) and suitably protected for Fmoc-solid phase peptide synthesis, demonstrating how a range of α-methylated heteroarylalanine amino acids could be incorporated into peptides, further expanding the diversity of peptides accessible in drug discovery.

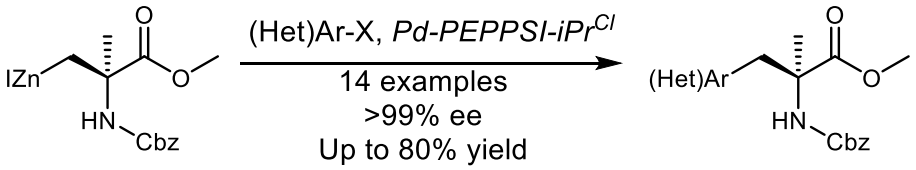

Figure 1. General transformation used in the synthesis of α-methylated heteroarylalanine amino esters.

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Efficient Cu(I)-Catalyzed Synthesis of Carbamates via a Three-Component Reaction

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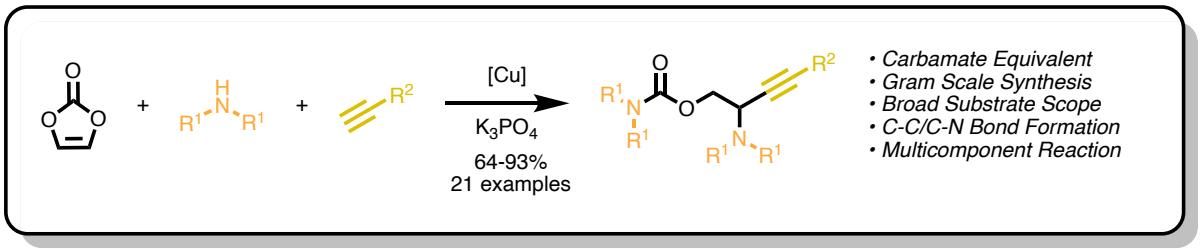
We report a copper-catalyzed three-component coupling reaction involving secondary amines, terminal acetylenes, and vinylene carbonate (VC) for the synthesis of carbamates. Utilizing vinylene carbonate as the carbamate source, twenty-one examples of carbamates were successfully produced. This novel methodology employs minimal catalyst loading, C–C and C–N bond formation, scalability to gram-scale synthesis, good to excellent yields and a broad substrate scope.

Figure1.



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Microwave-assisted synthesis of pomalidomide building blocks for rapid PROTAC and molecular glue development

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Targeted protein degradation (TPD) is an evolving therapeutic field with the potential to revolutionize drug discovery. While immunomodulatory imide IMiD-based molecular glues offer classical drug-like characteristics, proteolysis-targeting chimeras (PROTACs) are often outside the rule-of-5 molecular space, and require more intensive multi-step syntheses. Crucially, the chemoselective nucleophilic aromatic subsitution (S_NAr) of 4-fluorothalidomide, a widely-utilized reaction for linker installation, requires overnight reactions times at high temperatures to achieve efficient yields. Synthetic routes that facilitate high-yielding molecular glue or PROTAC intermediates would be extremely valuable. Herein, we disclose the development and optimization of a microwave-assisted synthesis (MAS) of pomalidomide building blocks for rapid and facile development of potential degrader molecules. The method affords high yields of spectroscopically pure pomalidomide conjugates within 15 min with a 24% or greater increase in yield, at gram-scale, without intermediate purification steps. Prior methods relied upon oil bath heating, overnight reaction times, and the need to perform flash chromatography. The utility of the methodology was demonstrated via the synthesis of clinical candidate, ARV-110. Overall, MAS was employed as a powerful tool to facilitate the rapid generation of libraries required for PROTAC and molecular glue development programs.

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Ni-Catalyzed Reductive 1,2-alkylarylation of Alkenes for the Synthesis of Spirocyclic γ-Lactams

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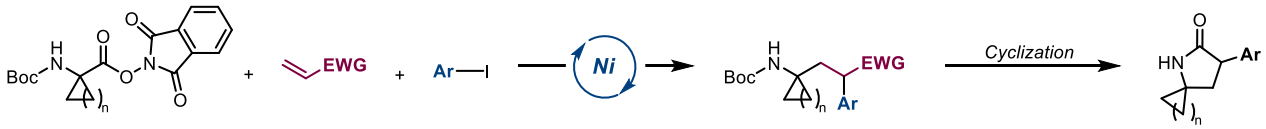
Ni-catalyzed reductive alkyarylations of alkenes has recently emerged as a powerful strategy to rapidly assemble complex aliphatic structures by enabling the addition of alky- and aryl- electrophiles across the π system in a single step. Despite the success of this approach, most reported alkylarylations rely on alkyl halides as a coupling partner, which can hinder wider application due to the limited availability of these aliphatic components. For example, the preparation of pharmaceutically relevant 1-subsituted cyclopropylamine scaffolds could benefit from this method, however, 1-halocyclopropylamines are not commercially available or accessible by existing methods. To this end, more abundant aliphatic carboxylic acids have emerged as attractive coupling partners in Ni-catalyzed cross-coupling reactions but remain underemployed in three-component transformations. In this presentation, a Ni-catalyzed reductive alkylarylation of acrylates with NHP esters, derived from their corresponding commercially available carboxylic acids in a single step, and aryl iodides will be described. Optimized on a cyclopropylamine scaffold, this operationally simple protocol provides direct access to >20 1-substituted cyclopropylamines. Notably, our optimized conditions are also compatible with four membered α-amino strained rings and acyclic coupling partners. To demonstrate the ability of this method to rapidly access complex scaffolds, we show that products obtained from this transformation can be subsequently derivatized to access α-arylated spirocyclic γ-lactams, a common motif found in several pharmaceuticals.



one step from commercially available carboxylic acid

n = 1, 2
EWG = CO_2R, CN
>20 Examples

Streamlining Hydrogenation: A Chemoselectivity Guide for Synthetic Chemists

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Hydrogenation reactions appear in over 40% of articles in the Journal of Medicinal Chemistry as one of the steps towards bioactive molecule synthesis.[1] It is an intuitive approach to transform sp^2-hybridized atoms into sp^3, allowing the molecule to "escape from flatland" and improve chances of clinical success.[2]

Noble metals on various support surfaces can effectively hydrogenate many functional groups at room temperature and low hydrogen pressure. For complex molecules, this creates challenges in chemoselectivity, which is usually addressed by a broad screening of often inaccessible catalyst panels.[4] As organic synthesis remains a rate-limiting factor in drug discovery,[5] we aim to provide chemists with a user-friendly guide for chemoselective hydrogenation, offering a more informed starting point when hydrogenation of one functional group in the presence of others is desired.

Commercial flow chemistry hydrogenation platforms like the H-Cube® have emerged to minimize the safety risks of autoclave-based catalytic hydrogenation while offering better control over reaction parameters, reproducibility, heat, and mass transfer.[3] We speculated that this would make an ideal platform for broadly assessing a range of catalysts, conditions, and substrates to design a data-rich user guide.

The reactions were conducted under progressively harsher conditions, with pressure, residence time, and temperature continuously increased. The yields of hydrogenation for each substrate and catalyst were plotted against these conditions, allowing us to tabulate the selectivity of each catalyst for different functional groups and apply our guidelines to the hydrogenation of challenging substrates.

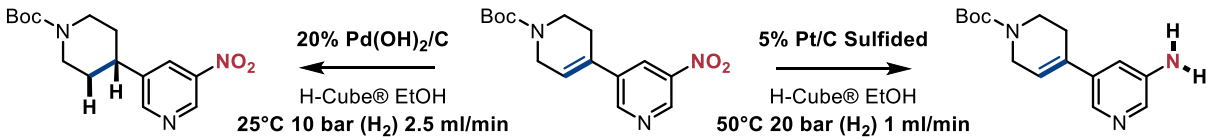

Figure 1. Chemoselective hydrogenation of alkene and nitro group in medicinal chemistry relevant molecule using conditions from our dataset.

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SAR Studies On PZM21 Analogues

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Pain relief is a very important therapeutic area that has an acute demand for safe analgesics displaying minimal side effects. Opioid-based analgesics (which act by targeting Mu-opioid receptor) have severe side effects including respiratory depression, constipation, drug tolerance and addiction. The global opioid market is estimated to be valued at 4.4 billion dollars a year, yet due to over-prescription and abuse, an opioid crisis was declared in Canada in 2018. There is a clear need and opportunity for development of new and safer analgesics.

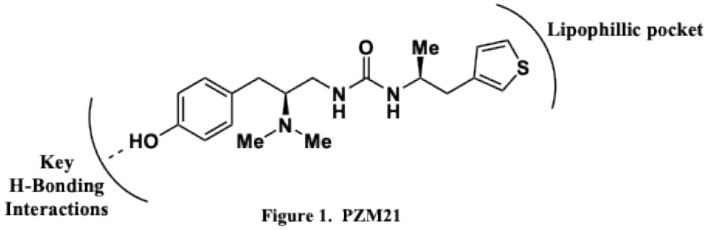

Figure 1. PZM21

PZM21 is a promising biased partial agonist that has high selectivity for Mu-OR.[1] Herein, we present SAR studies focusing on derivatives of PZM 21 with substituents occupying the lipophilic pocket of Mu-OR, for which relatively little is reported in the literature. Two key conclusions obtained from testing over 50 analogues of PZM21 will be discussed.

[1]A. Manglik, H. Lin, D.K. Aryl, J.D. McCovy, D. Dengler, G. Corder, A. Levit, R.C. Kling, V. Bernat, H. Hübner, X. Huang, M.F. Sassano, P.M. Giguère, S. Löber, D. Duan, G. Scherrer, B.K. Kobilka, P. Gmeiner, B.L. Roth & B.K. Shoichet, *Nature* **2016***, 537*, 185

Discovery and characterization of a novel amidase for the biocatalytic degradation of polyurethane foams

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Of the 300 million tons of plastic produced annually, only 10% is recycled.[1] Due to the inertness and durability of plastic, recycling techniques employ combustion and melting, exacerbating the climate crisis. Enzymatic degradation of plastic provides a promising alternative to traditional recycling approaches since enzymes function under milder conditions. Despite harboring hydrolytically sensitive functional groups, only a fraction of polyurethanes are recycled, often through mechanical processes.[3] Recently, three urethanases were identified that catalyze the hydrolysis of small-molecule dicarbamates produced from the glycolysis of polyether-polyurethane foam.[4] Despite the utility of this discovery, the necessary chemical glycolysis step produces undesirable byproducts, and the most promising urethanase lost significant activity after incubation at 30 °C for 12 hours.

In this work, we used sequence similarity networks to mine thermophilic microorganism genomes for novel urethanases with moderate similarity to those reported. Fifteen genes encoding putative urethanases were identified and synthesized into an overexpression construct. One promising candidate, PUase1, has been identified following heterologous protein expression, purification, and activity screening. PUase1 harbors a Ser-*cis*Ser-Lys catalytic triad conserved among members of the amidase family, which could be implicated in preliminary hydrolytic activities observed on model substrates containing carbamate, ester, and amide linkages. Excitingly, Impranil® DLN W50 polyester-polyurethane dispersions are cleared by treatment with PUase 1, suggesting that the enzyme can function on authentic polymeric substrates. Ongoing efforts include studying the catalytic mechanism of the enzyme via site-directed mutagenesis, molecular docking, and the differential kinetics of the PUase1-catalyzed hydrolysis of various model substrates and polyether-polyurethane thermoplastics.

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Novel Cesium Reagent as a Nucleophilic Trifluoromethylation Source

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A novel nucleophilic trifluoromethylation reagent, $CsCF_3B(OMe)_3$ was developed. Advantages of this reagent are that no additional activator is required and it reacts well in ethereal solvents as compared to the well-studied Ruppert-Prakash reagent and its potassium analogue, respectively. Good reactivity was shown with the addition towards carbonyl compounds. Further studies towards exploring other novel reagent variations and new reactivity are underway.

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A Novel Fluorinated Group via Hydroetherification-type Reactivity Expanding Brønsted acid Catalysis

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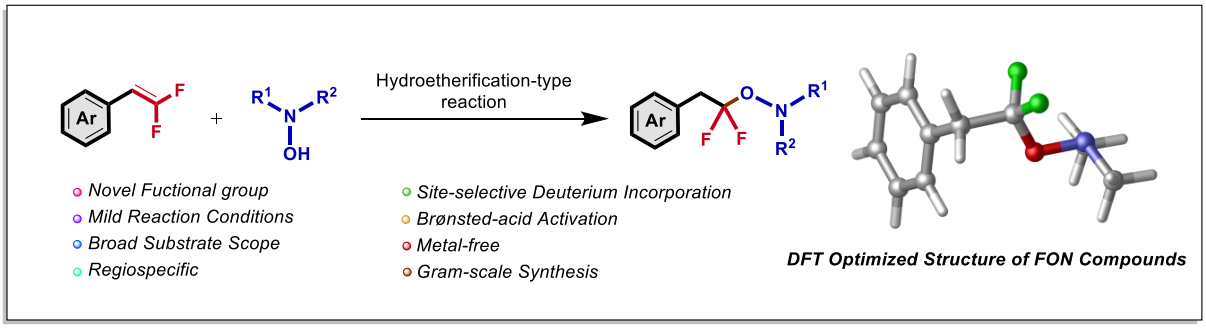
Fluorinated functional groups are prized for their ability to bestow unique chemical and physical properties to molecules including oxidative stability, high lipophilicity, and improved bioavailability. In expanding organofluorine chemical space, a straightforward and efficient strategy for synthesizing a novel fluorinated functional group CF_2-O-NR_2 coined FON is reported. This group in one-step unites *gem*-difluoro and N−O moieties via metal-free *O*-hydroxylamine additions to fluorinated alkenes with exclusive chemo- and regioselectivity for a diverse substrate scope. This protocol proceeds under mild conditions and is amenable to gram scale synthesis and site-selective deuterium incorporation. Lastly, this innovative reactivity was applied to Brønsted acid catalysis.



Functionalized Conjugated Polymer-SWNT Complexes as Sensors

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Single walled carbon nanotubes (SWNTs) show great potential as a material in device applications due to their electronic, optical, and mechanical properties. Unfortunately, SWNTs are insoluble in all solvents, and methods of solubilizing them on an industrial scale are inefficient. One potential solution which has garnered attention recently is conjugated polymer functionalization.[1] This process involves conjugated polymers selectively interacting with SWNTs through non-covalent π-π stacking to solubilize them without negatively impacting the inherent electronic properties of the SWNTs. Aside from solubilizing SWNTs, this process also imparts the properties of the polymer onto them, allowing for tuning toward desired applications, such as chemical analyte sensing. By synthesizing sensing moieties that can be attached onto the polymer side chains, we can develop polymer-SWNT based sensors.[2] In this work we synthesized a CO_2 responsive amidine and a cyclohexanone responsive thiourea compound. We utilized a copper catalyzed alkyne-azide cycloaddition (CuAAC) to attach the amidine group and a strain promoted azide-alkyne cycloaddition to attach the thiourea group to the polymer side chain. These polymers were used to disperse SWNTs, resulting in polymer-SWNT complexes that exhibit sensory function. We observed reversible response to CO_2 through a change in solubility. The amidine containing polymer-SWNT complex was used to produce thin film transistors, which demonstrated a reversible change in threshold voltage upon exposure to CO_2.[3] The cyclohexanone responsive polymer showed reversible interactions wth the analyte via changes in NMR signals, and the polymer-SWNT complex demonstrated reversible sensing by a change in sheet resistance.

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Enabling Medicinal Chemistry Focused on Hit-to-Lead for FBLD

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Abstract

Fragment-Based Lead Discovery (FBLD) has emerged as a valuable technique in drug discovery, aiming to identify fragment hits with low molecular weight. The main challenge lies in transforming the resultant low-affinity (K_D in the μM–mM range) fragment hits into higher-affinity (nM) lead compounds en route to potential drugs. Additionally, the solubility and potential aggregation of the compounds must be considered and evaluated by biophysical and bioassay methods. This poster emphasizes the crucial role of medicinal chemistry in enabling the hit-to-lead phase of drug discovery and surmounting obstacles encountered in the FBLD process. Biophysical and bioassay methods were consequently developed to monitor solubility and false-positives due to self-aggregate tendencies of compounds. We illustrate this with an example from our research group's work on HRAS, which has historically been considered an "undruggable" target due to its challenging nature. Our research team employs a combination of NMR biophysical experiments and medicinal chemistry to monitor compound behavior and binding affinity as a means to generate robust structure-activity relationships (SAR). This combination can serve as a general and pragmatic strategy for evolving weak hits to lead-like compounds.

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Exploring biocatalytic breakdown of nylon for sustainable plastic management

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Plastics have revolutionized modern life, with nylon production surpassing 8.9 million tons annually[1]. However, discarded nylons, such as "ghost nets," contribute significantly to ocean pollution, and fast fashion fuels demand for nylon and polyester. Inefficient recycling highlights the need for better waste management strategies. Promisingly, microorganisms capable of polyamide biodegradation offer potential for novel nylon recycling biotechnologies. To this end, sequence homology searches of the proteomes of a microbial library of communities enriched with various plastics as the sole source of carbon were performed to identify enzymes involved in nylon degradation. A putative 6-aminohexanoate-dimer hydrolase (LeuB) was identified in the proteome of an isolate belonging to the genus Leucobacter. Although this bacterium grows optimally at 28 °C, LeuB is stable up to ~54 °C, indicating that this protein should remain soluble and well-folded at elevated temperatures that will facilitate degradation of both nylon-6 and nylon-6,6. We also confirmed that LeuB is a catalytically active amidase using the dimer of nylon-6 as a substrate. In one hour, LeuB completely converted a solution of nylon-6 dimer into 6-aminohexanoate. Preliminary results also indicate that LeuB catalyzes the release of several degradants from nylon-6 films, including the monomeric building block of nylon-6.

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Diamino Variants of Piperazine-Based Transglutaminase Inhibitors

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Tissue transglutaminases (TG2) is a multifunctional protein that can catalyze the cross-linking between proteins, and function as a G-protein. TG2's unregulated behaviour has been associated with fibrosis, celiac disease and cancer metastasis. Recent focus has been on small molecule irreversible inhibitors bearing an electrophilic warhead that can react with the catalytic cysteine, abolishing TG2's catalytic and G-protein capabilities. Several research groups have converged on inhibitors comprising piperazine scaffolds, but no structure-activity relationships (SAR) of the piperazine core have been reported. In this study we synthesize a series of inhibitors with various diamino linkers, to understand what structural requirements are necessary for the core to help align the terminal acrylamide warhead in the optimal position. Kinetic evaluation using an *in vitro* biochemical assay provided the kinetic parameters k_{inact} and K_I for each inhibitor. This study revealed that adding a methyl group to the piperazine core can improve inhibitor efficiency.

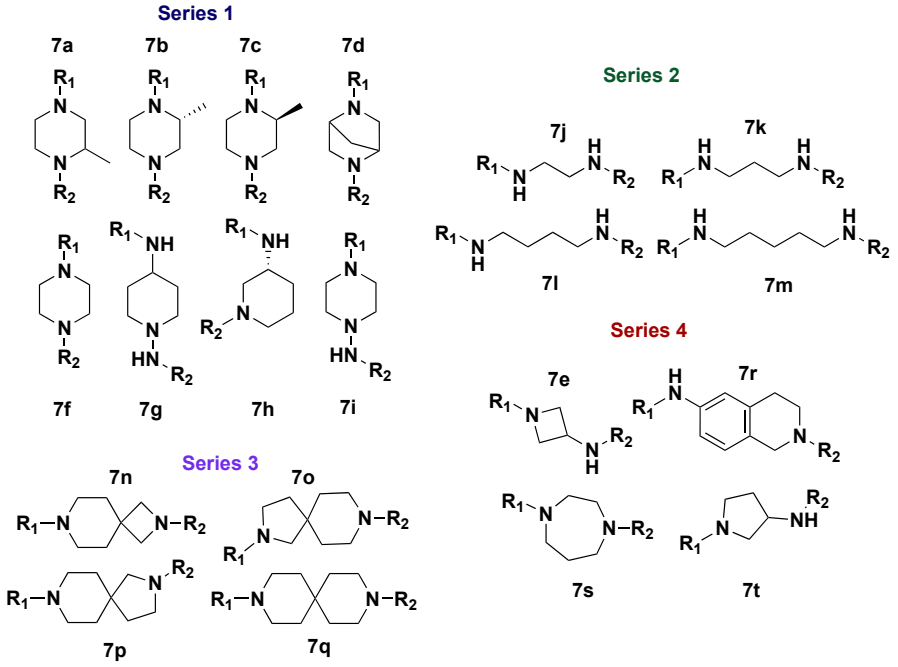

Figure 1. Diamino linkers used herein. (R_1 = adamantane carbonyl, R_2 = *N*-acryloylglycine.)

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Cross-couplings of transiently stable organolithium compounds

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Organolithium compounds are amongst the most important organometallic reagents and frequently used in difficult metalation reactions. Despite their importance, their direct use as nucleophiles in cross-coupling reactions to form C—C bonds is less common. Over the past decade, Feringa and co-workers have made significant advancements in the field of organolithium cross-couplings, primarily using commercial or stable organolithiums.[1–3] However, the use of transiently stable organolithium compounds as cross-coupling partners remains largely unexplored. This project aims to combine the concepts of flash chemistry to generate these transiently stable organolithium species in continuous-flow systems and use them in rapid Murahashi-couplings (Figure 1). High throughput experimentation has identified the optimal catalyst-ligand systems for these fast Murahashi-couplings. Then an array of organolithiums have been categorized based on stability, from medium to low. Different methods have been employed to generate these organolithiums, which are then used to cross-couple with aryl halides using the best catalyst-ligand system identified. Employing these organolithiums as nucleophiles offers a viable alternative to organoboron and organozinc reagents, whose synthesis often involves organolithiums. This project, thus, effectively demonstrates a method to cross-couple these transiently stable organolithiums generated in continuous-flow systems using the flash chemistry concept.

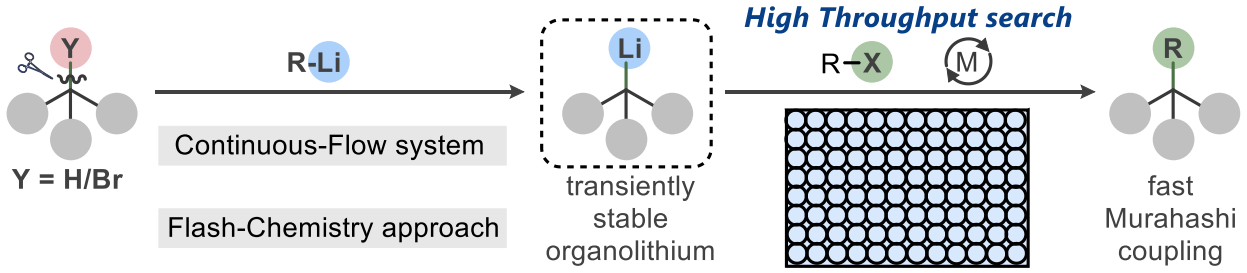

Figure 1. Cross-couplings of transiently stable organolithium compounds

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Design and Synthesis of a Clickable pH Sensitive Probe for Monitoring Viral Entry Through Endocytosis

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Fluorescent dyes are useful for visualizing the localization of viral components; however, pH dependent fluorophores would offer a superior approach for answering key mechanistic questions surrounding viral entry. Many advances have been made towards developing pH sensitive fluorophores, highlighting them as a tool for visualizing and investigating processes with varying environmental pHs.[1,2] Endocytosis is a viral entry mechanism that is commonly hijacked by exploiting pH changes in the maturation of the endosome to trigger a conformational change (in the viral particle's structural proteins) allowing for membrane fusion to occur, exposing the virus to the cytoplasm of the host cell. Herein, we aim to establish the importance of pH changes in a spatiotemporal fashion during the acidification of the early endosome by designing and applying a pH sensitive fluorescent probe that can be conjugated to biomolecules, through biorthogonal click chemistry. A control (static fluorescence) and pH sensitive probe have been designed using substituted BODIPY dye scaffolds along with a strained alkyne handle. Specifically, the addition of a bioorthgonal handle allows the probe to be conjugated to biomolecules by utilizing genetic code expansion technology to site-specifically incorporate an unnatural amino acid, such as azido-phenylalanine, enabling strain-promoted azide-alkyne cycloadditions (SPAAC).[3] We have successfully synthesized, purified and isolated these probes. Preliminary data suggests the ability of the clickable pH sensitive probe to modulate its fluorescence depending on changes in environmental pH.

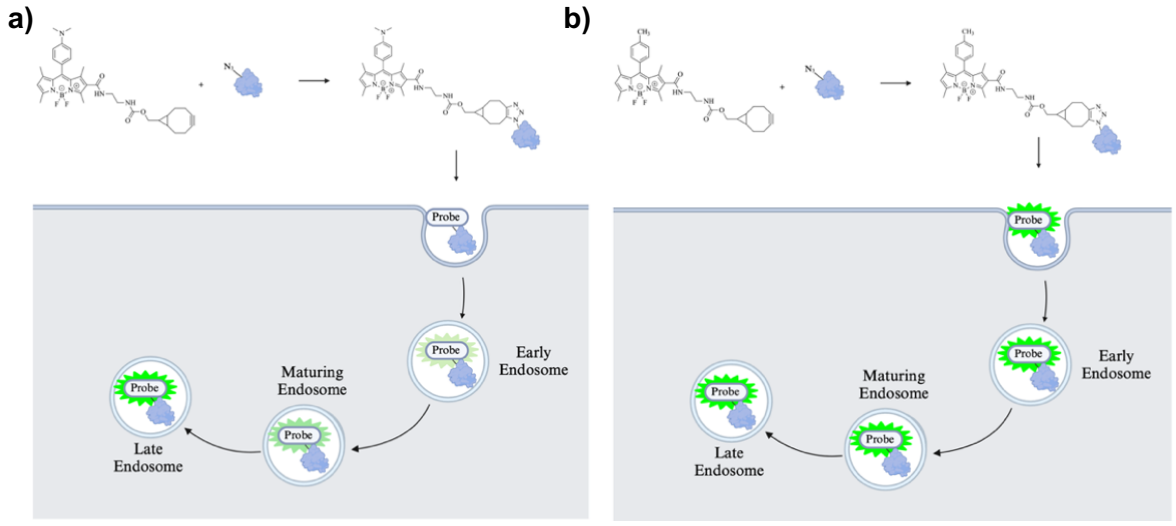

Figure 1. SPAAC reaction between **a)** pH sensitive or **b)** control probe with a protein of interest, followed by internalization of the probe-protein complex through endocytosis and fluorescent responses to acidification.

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The Design and Synthesis of Imidazopyrimidine Based Ligands for use in Heterobimetallic Catalysis

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Bimetallic catalysis is an expanding area in coordination chemistry, predominantly characterized by homobimetallic binding rather than heterobimetallic.[1,2,3] However, heteronuclear bimetallic catalyst systems have demonstrated greater reactivity and selectivity compared to their monometallic counterparts.[1,3] The challenge in developing non-symmetric bimetallic catalysts arises from the symmetric nature of many ligands.[1,4] Our previous research has tackled this issue by introducing a central imidazopyrimidine ring system as a non-symmetric backbone for bimetallic binding.[3] Starting from acetyl bromopyridine, a readily available and inexpensive compound, we can synthesize **Br-dpip** with a yield of 59% through a three-step, chromatography free process.[4] **Br-dpip** provides two differentiable binding sites and allows for a synthetic handle for further manipulation. Further functionalization has been demonstrated using 2-tributylstannyl pyridine through Stille coupling conditions, and 4-methylpyrazole using Buchwald-Hartwig amination conditions. Additionally, **Br-dpip** was shown to undergo substitution under S_NAr conditions, resulting in ligands with phosphine, carbene, and nitrogen binding sites with varying geometry. This work aims to broaden the scope of heterobimetallic catalysis by developing a series of ligands with tunable electronic, geometric, and steric properties.

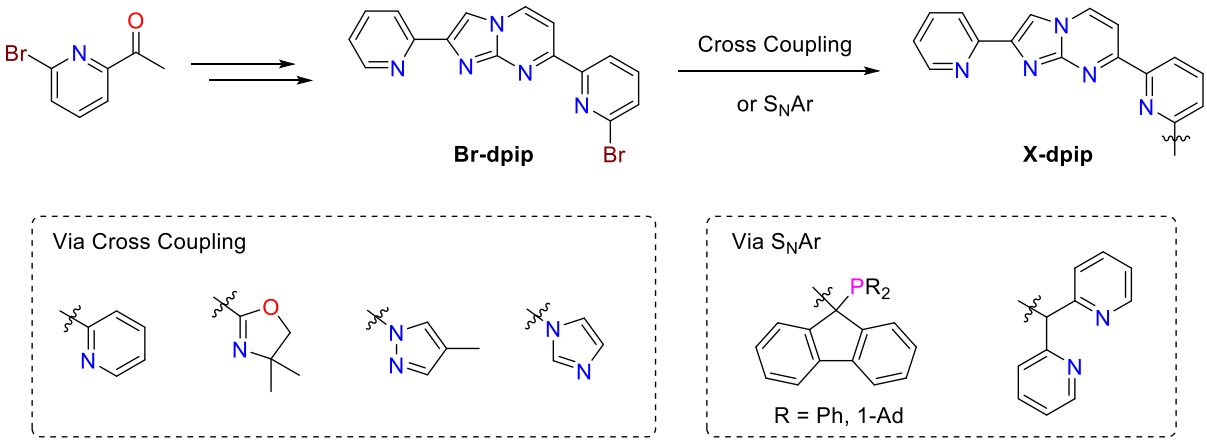

Figure 1. The late stage functionalization of **Br-dpip** through Stille coupling, nucleophilic aromatic substitution or Buchwald-Hartwig amination conditions.

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Synthesis of Metergoline Antibiotics with Improved Permeability

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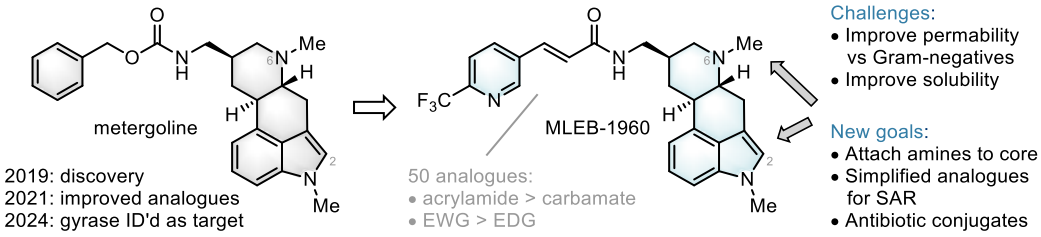
Since the recent discovery of metergoline's antibiotic activity against *Salmonella* Typhimurium, our lab has synthesized more than 50 analogues and, with the improved potency against MRSA, we were able to identify DNA gyrase as the antibiotic target.[1–3] MLEB-1960 shows good activity against Gram-positive bacteria and hyperpermeable strains of Gram-negative bacteria, but not wild-type strains of Gram-negatives. Here, we disclose our synthetic efforts toward analogues with pendant amines that could improve permeability through the Gram-negative outer membrane[4] and therefore unlock their potential as broad-spectrum antibiotics.



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Sulfonimidoyl Bromides As Precursors to Sulfur(VI) Radical Intermediates

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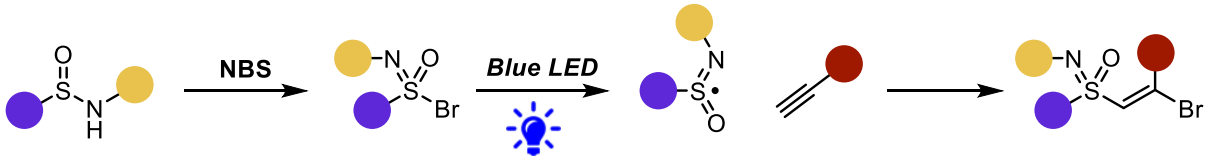
The sulfoximine group is an important pharmacophore in medicinal chemistry, which can increase the pharmacokinetic properties of molecules compared to corresponding sulfones[1]. To this day, the synthesis of various sulfoximines remains a challenge, often requiring organometallic reagents or harsh oxidants. Some of the recent strategies involve sulfonimidoyl radicals, generated from sulfinamides[2], sulfonimidoyl fluorides[3], and sulfonimidoyl chlorides[4], however, the use of sulfonimidoyl bromides and iodides remains underexplored.

We present *in situ* generation of sulfonimidoyl bromides from sulfinamides and their application in the difunctionalization of alkynes and allenes, yielding (*E*)-β-bromovinyl sulfoximines with excellent diastereoselectivity and good yields. We suggest that the process involves homolytic cleavage of the S–Br bond under blue light, producing a sulfur-centered radical that adds to the alkyne or allene. Preliminary mechanistic studies confirm the radical nature of this reaction and support the existence of a sulfur-bromine bond. We explored the scope of *N*-substituents, and investigation of radical acceptors scope is currently ongoing. This metal-free procedure offers mild conditions and a high atom economy, as well as compatibility with various functional groups.

Figure 1. Generation of Sulfonimidoyl Bromides and their Reaction with Alkynes.



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Characterization of the Gacamide (GacA) enzyme TE1 domain in de novo depsipeptide macrolactonization

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Depsipeptides are renowned for their bioactivity and structural diversity, with a key feature being their macrocyclic function. However, forming macrocycles synthetically presents significant challenges. To achieve macrocyclization, nature has given us quite a useful tool, thioesterases. These thioesterase domains (TE), are found at the C-terminus of NRPS's (Non-Ribosomal Peptide synthetase) and catalyze hydrolysis, but more commonly cyclization. With this knowledge, researchers have made a push to explore the potential of TE domains as catalysts for macrocyclization, which bore fruit to the chemoenzymatic creation of many macrocycles. Macrocyclization allows peptides to become more stable and have increased membrane permeability. In addition, macrocyclization is a more common method to improve the pharmacological properties as well as the bioactivity of said peptides. The specific TE enzyme discussed in this thesis is GacA TE1, which is responsible for macrolactonization of the natural product Gacamide A. Previous work in this lab has shown that GacA TE1 can macrocyclize synthetic, linear N-acetylcysteamine activated peptides that resemble the native substrate. In this research, the robustness and promiscuity of GacA TE1 are assessed to determine if it can be applied to a broader range of peptides with structures significantly different from its native substrates. Three linear de novo peptides sequences containing a nucleophilic threonine residue at positions 5, 6, or 7 were synthesized and purified, and the ability of GacA TE1 to macrocyclize was evaluated. This study demonstrates for the first time the ability of TEs to macrocyclize de novo designed non-native substrates with varying ring sizes. To gain further insight into the mechanism of GacA TE1, mutations were introduced via site directed mutagenesis within the active site of the GacA TE1 and the activity of the mutants was biochemically characterized.

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TMDSO and KO^{t}Bu as an Unconventional Reducing Agent for the Hydroalkylation of Styrenes

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In the past decade, the combination of potassium alkoxide bases and silicon hydride species has been reinvestigated, not for their hydridic properties but rather the unique myriad of transformations they promote which are thought to occur through exotic silicon-based intermediates proposed in the literature.[1] These transformations range from defunctionalization reactions, complex rearrangements, and silylations.[2,3,4] Recently our group disclosed that TMDSO and KO^{t}Bu can mediate an unusual de-trifluoromethylation of 2-trifluoromethylpyridines.[5] Since this initial report, we have found the powerful reducing capacity of this reagent combination can enable the transition metal-free hydroalkylation of styrenes and related molecules.[6] These reductive hydrofunctionalization reactions represent a new paradigm of reactivity for the alkoxide/silane reagent pair. The applications, mechanistic underpinnings, and future directions of this chemistry will be discussed.

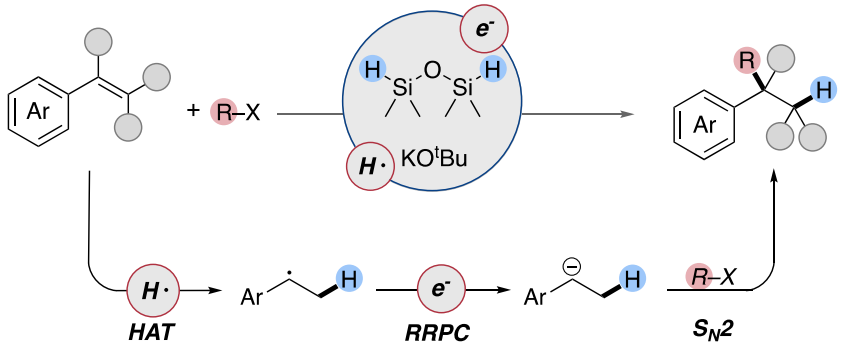

Figure 1: TMDSO and KOtBu mediated hydroalkylation of vinyl arenes thought to proceed through HAT, RRPC, and S_N2

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The Development of Anillin-Specific Inhibitors for Treatment Against Hepatocellular Carcinoma

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Cancer is defined by an overexpression of cell-growth regulators. Cytokinesis is a well conserved process which occurs at the final stage of mitosis. Understanding the intricate relationship between cytokinesis and cancer is essential for developing targeted therapeutic strategies in order to mitigate uncontrolled cancer cell proliferation[1]. Anillin, a key actin-binding protein, is considered to be one of the crucial regulators in cytokinesis[2,3,4]. Considering the amino acids in Anillin involved in the cytoskeletal dynamics, specific inhibitors can be designed to disrupt its functions[5]. As Anillin is upregulated in cancer cells, developing an Anillin-specific inhibitor provides exceptional therapeutic potential for the treatment of cancer. The objective of this project is to develop inhibitors that specifically block Anillin function. The RBD-RhoA and RBD-C2 interfaces in Anillin were identified as having key amino acids facing outward from two alpha helices[5]. Helical motifs are known to project residues i, i+4 and i+7 on the same face of the alpha-helix. Previous research on alpha-helical mimetic compounds suggest terphenyl compounds can mimic the i, i+4 and i+7 side chains[6,7]. Considering this, a library of five-membered sulfur-based terphenyl scaffolds with functional groups that can bind to the respective residues on Anillin was synthesized. The compounds were synthesized by optimizing cross-coupling techniques previously employed, as well as various derivatization reactions to ultimately expand the library of compounds. Structure-activity-relationship studies were employed following *in vitro* testing by the collaborator, providing further insight into the key functional groups required to disrupt the activity of Anillin.

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Developing chemical Tools for the study of tRNA Aminoacylation

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Aminoacylation of transfer RNAs (tRNAs) is the process where enzymes known as aminoacyl-tRNA synthetases (AARS) catalyze the covalent linkage formation between an amino acid and its cognate tRNA. Messenger RNAs (mRNAs) and ribosomes are actively transported to specific regions in the cell depending on the protein being expressed, and we therefore expect that tRNA aminoacylation is similarly localized. However, the actual localization where aminoacylation occurs in the cell is unknown and there is a lack of suitable tools to study the process.

Our goal is to develop a new chemical tool to study aminoacylation using genetic code expansion. With genetic code expansion, unnatural or noncanonical amino acids (ncAA), such as fluorescent amino acids, can be incorporated into proteins through an engineered aminoacyl-tRNA synthetase. We synthesized different fluorescent ncAA candidates with recently reported electrochemical methods to develop a highly environmentally sensitive fluorescent probe. We expect that the amino acid fluorescence will change as it is activated and bound to tRNA (aminoacylation) or used in mRNA translation and incorporated into a protein. We characterized these ncAA candidates with UV-VIS spectroscopy to determine their sensitivity to polarity as a proxy for different biological processes. We further developed different in vitro biochemical assays to assess the compatibility of these ncAA with cell-based protein synthesis. Our goal is to integrate our tools with different mammalian cell models to analyze how aminoacylation reactions colocalize with other components in the mRNA translation machinery and how their subcellular localization changes depending on the biological context.

Synthesis of Xanthine Derivatives as Inhibitors of PCSK9

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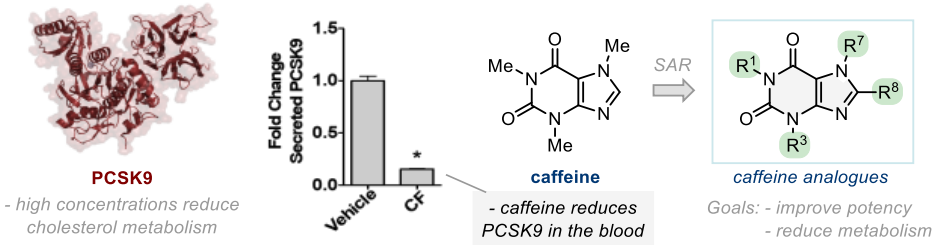
Increased levels of circulating cholesterol in the blood as low-density lipoprotein cholesterol (LDLc) are a significant risk factor for cardiovascular disease (CVD).[1] LDL receptors (LDLR) bind to circulating LDLc and induce cholesterol metabolism, but PCSK9 binding to the LDL receptors induces receptor degradation. Our laboratories have demonstrated recently that caffeine, which is known to reduce CVD risk, reduces PCSK9 concentrations in the blood in a dose-dependent manner. We have synthesized a large series of analogues in order to improve potency, metabolic stability, and reduce undesired neuro-stimulatory effects.



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Development and Applications of an Amide Linchpin Reagent

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Linchpin reagents are small building blocks that can be chemoselectively functionalized to afford products with a common, useful functional group (ketones, alkenes, alkynes, etc).[1] Surprisingly, there have been no reports of an amide linchpin reagent, despite the ubiquitous nature of this functional group in pharmaceuticals and natural products. While the synthesis of amides often involves construction of the N-(C=O) amide bond, an efficient alternative synthetic route involves the use of isocyanates. Previous work in the Beauchemin group enabled the development of bench-stable masked (blocked) *O*-isocyanates, which allow for the slow release of free *O*-isocyanates *in situ*, thereby controlling their concentration and reactivity.[2] In this work, we describe the development and validation of the *first amide linchpin reagent* (**1**) and demonstrate its use as a doubly electrophilic building block for the synthesis of a variety of products, including sterically hindered amides and enamides. Rhodium-catalyzed electrophilic amination of **1** provided masked *C*-isocyanates, which were further derivatized with Grignard reagents to produce secondary amides, or tertiary amides if an alkylating agent was added to quench the metal amidate intermediate. The success of this sequence relies on fully controlled reactivity at each electrophilic site: exploitation of the weak N-O bond, and then, formation of the free isocyanate intermediate *in situ*. The overall transformation proceeds with high chemoselectivity, demonstrating the ability of this new linchpin reagent to form amides through atypical bond construction. Finally, the potential of this reagent as a more broadly applicable NCO linchpin will be disclosed.

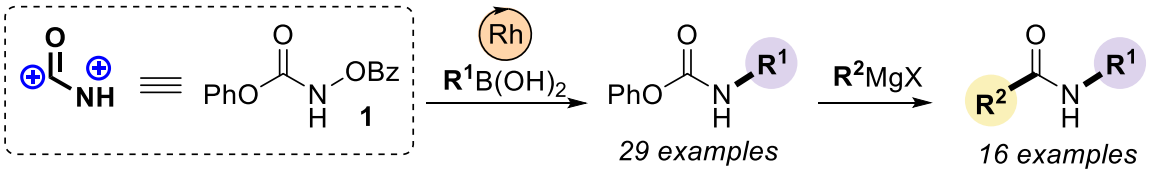

Figure 1. Synthesis of amides using the first amide linchpin reagent.

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Towards new NCO heterocyclic syntheses enabled by a highly reactive intermediate

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NCO heterocycles are common in pharmaceuticals and agrochemicals. More specifically, among aromatic heterocycles, over 50 drugs or agrochemicals possess an NNCO subunit[1] and pyrazolones account for an important fraction of these useful products. Consequently, there is much interest in commercially available heterocyclic building blocks, and in syntheses that allow rapid assembly of heterocyclic cores from simple, readily available reagents. Isocyanates are excellent building blocks to form a variety of heterocycles containing NCO subunits but can suffer from poor functional group compatibility associated with using free isocyanates. Unfortunately, the high reactivity of several classes of isocyanates has limited their use in heterocyclic synthesis. For example, O/N-isocyanates are too reactive to be isolated and show a propensity to oligomerize. However, masked isocyanates solve this issue by allowing the formation of these elusive reactive intermediates *in situ*. Herein, we disclose a new pyrazolone synthesis based on a rare amphoteric reactive intermediate. This allows formation of pyrazolones from simple hydrazones, via an *in situ* metallation, isocyanate formation, and cyclization sequence. Optimization and scope of three different sets of conditions will be presented. Preliminary results to further expand the approach to form other NCO heterocycles will also be presented.

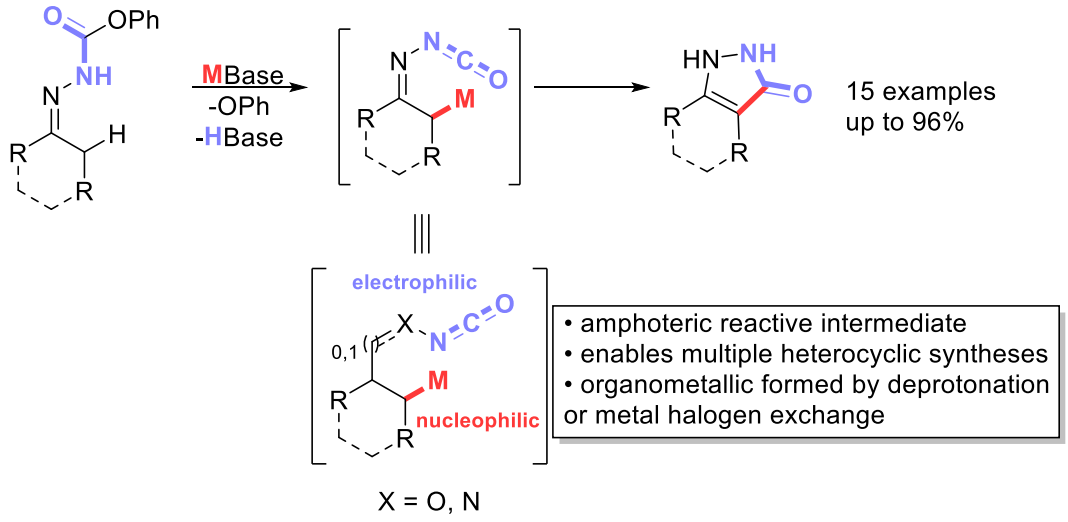

Figure 1. Approach towards pyrazolones and other heterocycles through an amphoteric reactive intermediate

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Synthesis of Prenylated Isoflavone Natural Products and Synthetic Efforts Toward Prenylated Flavones

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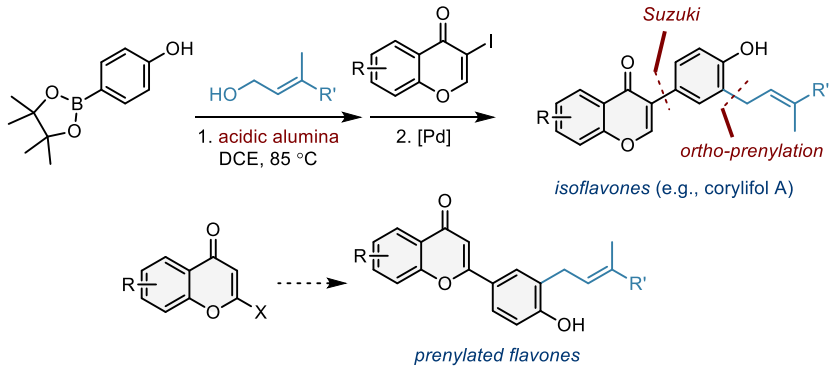
Flavonoid natural products have long been known to show antimicrobial and anti-inflammatory activities. Our laboratory is currently developing a highly *ortho*-selective method for the prenylation of phenols that involves coordination with acidic alumina. Here, we disclose the application of this methodology to the synthesis of a series of prenylated isoflavone natural products, which involves *ortho*-prenylation followed by Suzuki coupling. We also describe efforts in developing a concise convergent synthetic route to prenylated flavones.



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Covalent Bifunctional Molecules (CBMs) to engage Macrophage Lectin Receptors for Cancer Immunotherapy

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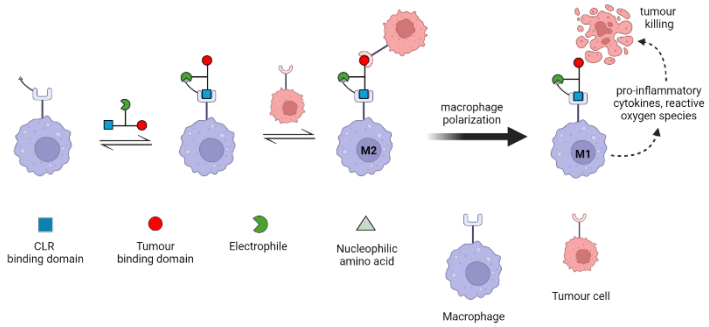
Innate immunity uses a wide variety of carbohydrate receptors to mediate inflammation, pathogen destruction and adaptive immune responses. Bifunctional molecules (BMs) containing carbohydrate ligands have been introduced as a new paradigm to target these receptors in immunotherapy applications. Previously in Rullo lab, we demonstrated the utility of rhamnose containing covalent bifunctional molecules (CBMs) for proximity induced covalent labeling of anti-rhamnose antibodies. Antibodies covalently modified with tumour ligands were successfully redirected towards the cancer cells and covalency played a profound effect on stabilizing the tumour-immune complex leading to an enhanced macrophage phagocytosis and tumoricidal function.[1]

Relying on the supremacy of covalency to overcome the typically low binding affinity (mM-μM) observed in carbohydrate-receptor interactions, we have proposed to synthesize a CBM that can directly modify macrophages and redirect them towards tumours. The current approach has eliminated the use of an intermediary antibody in forming the tumour-immune complex thus simplifying and stabilizing it improving the immune function. Targeting M2 like tumour associated macrophages (TAMs) via C-type lectin receptors (CLRs) is known to be a potential therapeutic approach in tumour immunotherapy.[2] The proposed CBM with CLR ligands target CLRs on macrophages and expected to polarize them to the M1 state which possesses anti-tumour characteristics. CBMs containing validation handles (i.e. fluorophores or biotin) complemented with strategic electrophiles will be used for biophysical assays while scaffolds appended with tumour ligands will be used for functional assays. The generated immune complexes will be investigated for their efficiency in comparison to their non-covalent analogs in future studies.

Abstract Figure : CBM containing CLR and tumour binding domain covalently interacting with the macrophage leading to its polarization and eventual tumour destruction



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Design and Synthesis of an Imidazopyrimidine-based Trinucleating Ligand

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Transition metal catalysis has revolutionized chemical synthesis, enabling powerful cross-coupling methodologies that facilitate C-C and C-Heteroatom bond formation to asymmetric hydrogenations that benefit the construction of secondary stereocenters. With this however, modern catalysts rely mainly on mono-metallic complexes of precious metals with a strong bias for 2-electron processes, limiting their scope and posing sustainability issues.[1] Ligand design and the study of poly-metallic complexes based on earth-abundant elements (EAE) has thus become a prominent field.[2] Our group has recently established a new ligand platform based on imidazopyrimidine (**dpip)** that allows the facile construction of bimetallic species.[3] With this, there is much interest in developing a trinucleating platform, as trimetallic transition metal-catalyzed processes are much less studied.[4]

In this work, a trinucleating ligand based on the imidazopyrimidine backbone of **dpip** was designed and developed. The ligand, comprised of one tridentate and two bidentate binding sites, was synthesized in 3 steps with an overall yield of 55%, starting from relatively affordable reagents. The synthesis is straightforward, avoids extensive and costly purification methods, and produces the target ligand on a gram scale. The ligand is currently being studied in metalation reactions and has been shown to form tri-nickel(II) complexes. The ability to form tri-metallic complexes with other EAEs such as cobalt and copper is also being evaluated. Extensions of the work involve determining the ability of the ligand to form hetero-trimetallic complexes and the study of these in catalytic systems.

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Cancer Vaccines: a total synthesis of the Tn Antigen

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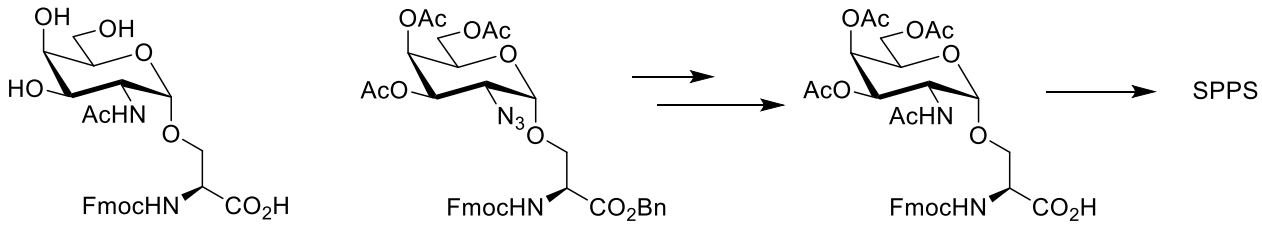
The Tn antigen is a member of the Tumour-Associated Carbohydrate Antigen (TACA) family, a series of compounds that are over-expressed in cancer cells, which makes them an ideal marker for cancer and hence target for vaccine development. The Tn antigen comprises an N-acetylgalactosamine unit appended to the side chain oxygen of a serine or threonine; it can therefore be readily incorporated onto an immunogenic peptide using solid-phase peptide synthesis (SPSS).

Our group has been developing a scalable synthesis of a suitably protected Tn antigen for SPSS. During scale up we identified some concerns regarding our earlier work that were propagated from earlier literature; this has caused us to both reinvestigate the literature compounds and revise our earlier route.

In this presentation I will describe our approach to the total synthesis of this Tn antigen: our initial approach and the modifications that provided the desired compound. I will also describe the key points in our characterization: the misinterpretations and how they occurred in the first place, and how we were able confirm the correct structure.[1,2]



Tn Antigen

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Mechanistic Analysis of Palladium/Organoboron-Catalyzed *N*-Allylation Resulting in an Improved Protocol

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Mechanistic analysis of chemical reactions can be a practical tool for greater understanding and/or improvement of known reactivities.[1] Our group recently reported a regioselective allylation of azole nucleophiles using a dual catalytic system of palladium and organoboron. Several azole nucleophiles including triazoles, purines, and tetrazoles were allylated efficiently with an arylboronic or diarylborinic acid catalyst activating both the nucleophile and electrophile toward the reaction.[2] In this presentation, a series of mechanistic tools used to gain insight into the details of this reaction will be discussed. Experimentally obtained kinetic reaction orders as well as computational analysis points to a more complex mechanistic picture hidden behind a seemingly simple reactivity. The resulting data yielded an unexpected finding; the reaction is autocatalytic. This motivated a study to assess how additives influence the rate of reaction, ultimately leading to an improved protocol that can employ significantly lower loadings of the palladium catalyst with addition of catalytic amounts of an inexpensive additive.[3]

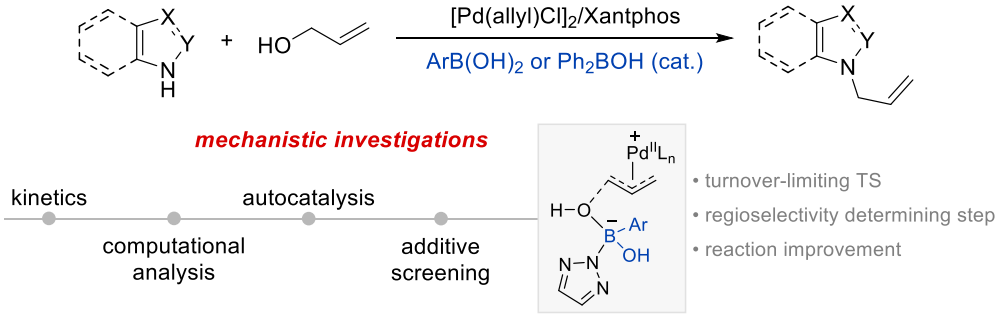

Figure 1. Mechanistic studies for regioselective *N*-allylation

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