Empowering Women in Organic Chemistry Conference 2023

Poster Abstract Booklet

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

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Poster Abstracts

Poster 1

Overview of Agricultural Discovery at FMC

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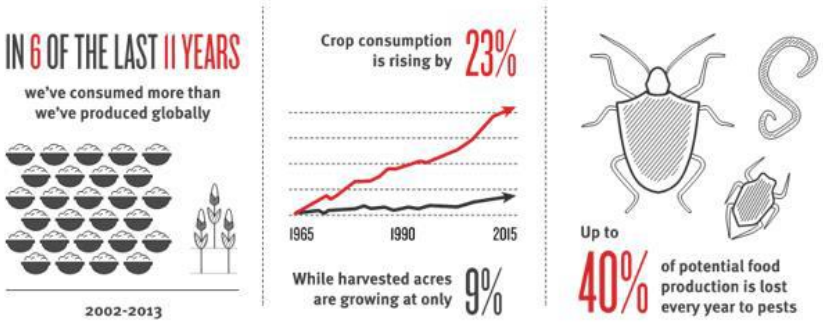
Plant diseases, harmful insects, and weeds can have a devastating impact on global food security, one of the greatest issues of the 21st century. Up to 40% of potential food production is lost every year to pests. These challenges can be managed using reliable and innovative crop protection solutions.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



Poster 2

ATROPOSELECTIVE METHODOLOGY FOR DEVELOPING PHARMACEUTICALLY RELEVANT PYRAZOLOPYRIMIDES

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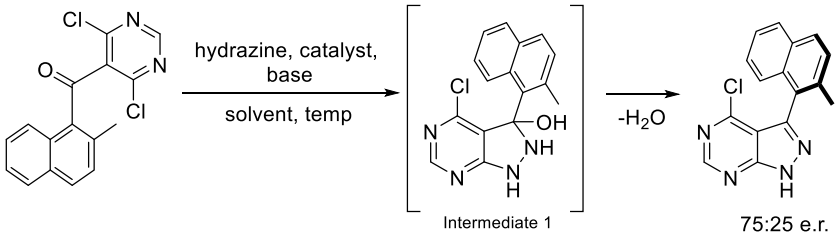
The goal of this research is to design a method for an atroposelective cyclodehydration to obtain atropisomerically stable 3-aryl pyrrolopyrimidines. We found that the S_NAr of hydrazine into a pyrimidine scaffold followed by a cyclodehydration with ketone yielded atropisomerically stable PPs. Privileged chiral catalysts such as quinine-based cinchona alkaloid derivatives that have basic tertiary quinuclidine nitrogen atom have demonstrated enantioselectivity over a wide range of reactions. Obtained preliminary data shows that chiral quaternary ammonium salts could render the reaction enantioselectivity, giving greater than 75:25 e.r. in good yields. Similar cyclization approach will be applicable to many relevant atropisomeric scaffolds.



Poster 3

DIVERGENT CATALYSIS: CATALYTIC ASYMMETRIC [4+2] CYCLOADDITION OF PALLADIUM ENOLATES

Kaylin N. Flesch[†], Peng-Jui Chen[†], Alexander Q. Cusumano[†], Christian Santiago Strong[†], Stephen R. Sardini[†], Yun E. Du[†], Michael D. Bartberger[‡], William A. Goddard III[ς]*, Brian M. Stoltz[†]*

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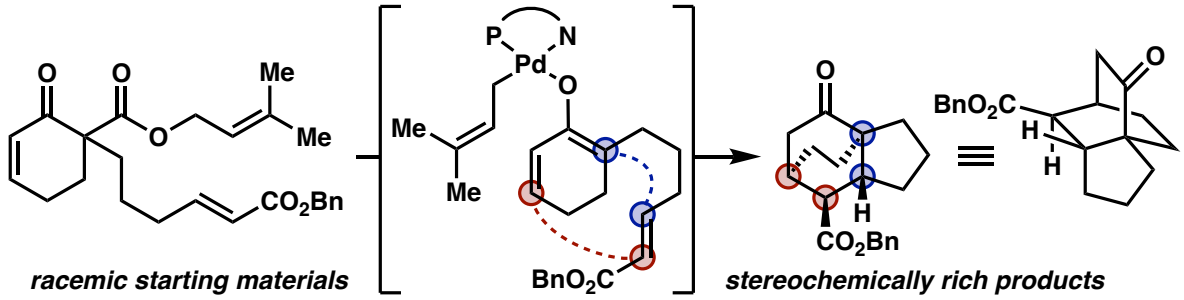
Abstract:

An asymmetric decarboxylative [4+2] cycloaddition from a catalytically-generated chiral Pd enolate was developed, forging four contiguous stereocenters in a single transformation. This was achieved through a strategy termed divergent catalysis, wherein departure from a known catalytic cycle enables novel reactivity of a targeted intermediate prior to re-entry into the original cycle. Mechanistic studies including quantum mechanics calculations, Eyring analysis, and KIE studies offer insight into the reaction mechanism.



- ***4-5 contiguous stereocenters and 1-2 quaternary centers***
- ***up to 92% yield and up to 97% ee***

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[1] Kaylin N. Flesch, Alexander Q. Cusumano, Peng-Jui Chen, Christian Santiago Strong, Stephen R. Sardini, Yun E. Du, Michael D. Bartberger, William A. Goddard III, Brian M. Stoltz. *Divergent Catalysis: Catalytic Asymmetric [4+2] Cycloaddition of Palladium Enolates. J. Am. Chem. Soc. In Press.*

Poster 4

Pyrrolic Small Molecule Chromophores for Applications in Electrochromic Materials

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Electrochromic materials (EC) provide functional solutions for a variety of applications, including smart windows and optical display technologies. The use of organic materials in electrochromic devices provides advantages over inorganic materials [1]. For example, the ability to readily tune structure in organic materials through synthetic methods affords precision in controlling redox, optoelectronic, mechanical, and processing properties. Additionally, as superior light-absorbing materials to inorganic materials, organic materials enable high optical contrast, allowing for the use of thinner films [2]. Finally, the solution-processability of organic materials and their relatively low cost allow the use of coating methods to form functional, reproducible thin films that can be layered on a substrate [3].

Although organic electroactive polymers are promising candidates in this realm [4], these materials have distinct drawbacks, including inherent structural disorder resulting in spectral diffusion [5], limited modularity in structure and bandgaps, depletion of absorption at long wavelengths, and diminished performance with material deformation [6]. In contrast, electrochromic small molecules with highly delocalized structures such as fused ring systems are promising chromophores that have received less attention in this field. Recent research in using small molecules has been motivated by their well-defined and rationally tunable structures, enhanced stability toward oxidative degradation, and batch-to-batch reproducibility [7]. We report the development of a new class of small molecule chromophores based on pyrrolic scaffolds to address current limitations in the field of electrochromic materials.

Acknowledgements: This research was supported by an appointment to the Intelligence Community Postdoctoral Research Fellowship Program at Massachusetts Institute of Technology administered by Oak Ridge Institute for Science and Education (ORISE) through an interagency agreement between the U. S. Department of Energy and the Office of the Director of National Intelligence (ODNI).

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Poster 5

CHEMICALLY TRIGGERED BIOORTHOGONAL PROBES TO TAG RNA STRUCTURES

Sharon Chen[1], Christopher D. Sibley[4], Kyle H. Cole[2], Andrej Lupták[1-3], John S. Schneekloth Jr.[4], and Jennifer A. Prescher[1-3]

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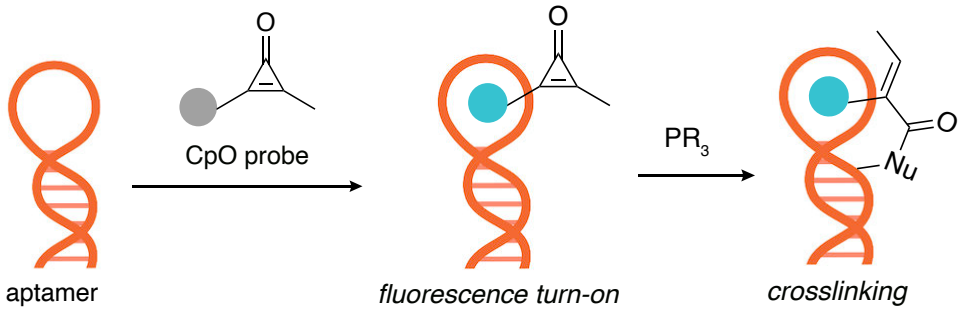
RNA is a structured biopolymer that regulates protein production and other critical cellular processes. Misfolded RNA can also potentiate disease, but a complete picture is lacking. Efforts to establish more comprehensive RNA structure-function relationships would benefit from methods to interrogate RNA and trap native conformations in live cells. Existing tools primarily rely on electrophiles that are constitutively "on" or triggered by harmful UV light, often resulting in high background reactivity. We developed an alternative, chemically triggered approach to crosslink RNAs using bioorthogonal cyclopropenones (CpOs) and phosphines. These reagents selectively react to provide ketenes—electrophiles that can trap neighboring nucleophiles to forge covalent crosslinks. As proof-of-concept, we synthesized a panel of CpOs and appended them to thiazole orange (TO-1). The TO-1 conjugates bound selectively to a model RNA aptamer (Mango) with nanomolar affinity. Fluorescence turn-on was also observed upon binding. After phosphine administration, covalent crosslinks were formed between the CpO probes and RNA. The degree of crosslinking was both time and dose-dependent. We applied the chemically triggered tools to studies of RNA structure and function in biologically relevant conditions. Collectively, this work expands the toolkit of probes for studying RNA and its native conformations in cellular environments.



Poster 6

DEVELOPMENT OF A BUCHWALD-HARTWIG AMINATION FOR AN ACCELERATED LIBRARY SYNTHESIS OF CEREBLON BINDERS

Natalie Holmberg-Douglas*, Anastasia Lejava, Giulianna A. Miseo, Thomas Phan and Hannah Powers

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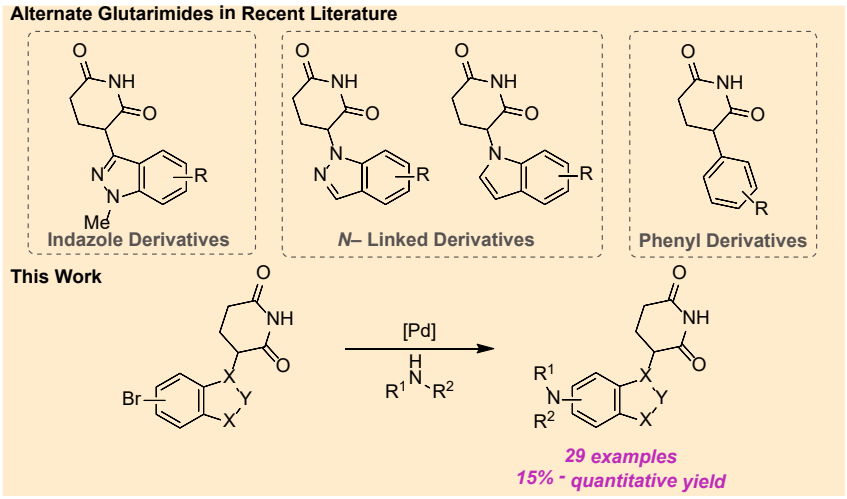
In recent years, targeted protein degradation has come to be a powerful therapeutic modality. Both heterobifunctional ligand directed degraders and molecular glues have been utilized to recruit E3 ligases to induce proteasomal degradation of a protein of interest. The immunomodulatory drugs lenalidomide and pomalidomide bind to cereblon (CRBN), a known substrate receptor of the CRL4A E3 ligase complex, to initiate protein ubiquitination and subsequent degradation. In the last decade, non-lenalidomide or pomalidomide type binders of CRBN, also referred to as alternate glutarimides, have been growing in popularity and offer an extended scope of potential degraders with varying physio-chemical properties. In particular, 3-substituted indazole derivatives have emerged as potent CRBN binders. These compounds are traditionally synthesized through the cross-coupling of the protected glutarimide and subsequent deprotection. However, there is little precedent of direct couplings with the unprotected alternate glutarimides, possibly due to the increased risk of ring opening via hydrolysis. To address this, we developed conditions for the cross-coupling of unprotected glutarimides with amines, which streamlines the synthesis of CRBN binders, avoids protecting group manipulations, and ultimately saves time and resources. A variety of secondary and primary amines were successful alongside a range of electronically diverse aryl halides, including *N*- linked glutarimides. This methodology offered a rapid synthesis for a library of 29 unique CRBN binders.



Poster 7

THE SYNTHESIS AND CHARACTERIZATION OF A RUTHENIUM PHOTOCATALYST FOR USE IN PHARMACEUTICALS

Camille Conte[1], Stephen DiLuzio[2], Hannah Sayre*[3]
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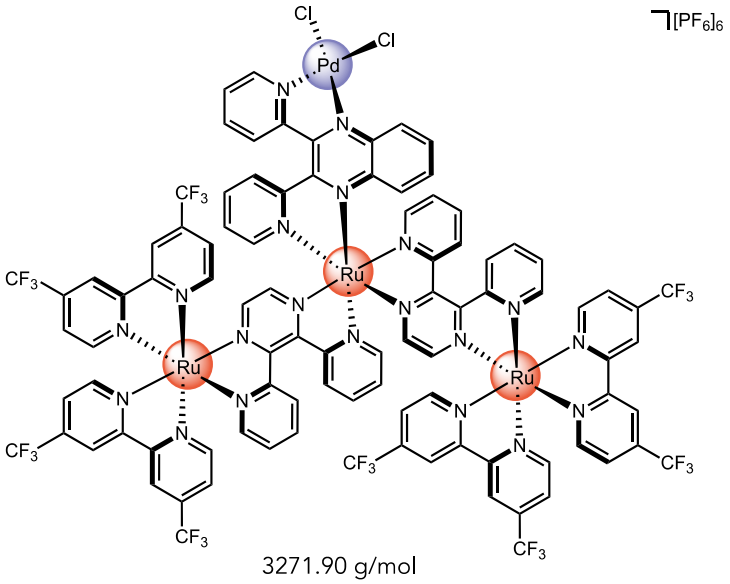
The development of broad-spectrum photocatalysts would enable light-powered chemical synthesis using a highly renewable and abundant resource – red light from the sun. Broad-spectrum ruthenium-based supramolecular photocatalysts are presented as an alternative to iridium photocatalysts that have limited light wavelength absorption. Powering reactions using the energy from sunlight via the photocatalyst's ability to convert light energy to chemical energy has applications in pharmaceutical synthesis and would increase the sustainability of these processes. Editing the functional groups on the photocatalyst such as the addition of trifluoromethyl groups(*1*) and the coordination of a palladium atom are potential strategies to electro- and photochemically tune these complexes for maximum photoexcitation efficiency. A trimetallic ruthenium-based photocatalyst with these groups was synthesized(*2*) and characterized for photocatalytic capabilities via various excitation and emission assays to determine efficiency.



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Poster 8

MECHANISTIC INSIGHTS AND DEUTERATION SCOPE OF A PLP-DEPENDENT CYCLASE FROM A TOXIC CYANOBACTERIUM

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Pyridoxal-5'-phosphate (PLP) is a cofactor utilized by enzymes to catalyze a diverse range of chemical transformations, including transaminations, epimerizations, and aldolase reactions.[1] PLP-dependent enzymes can be used to produce noncanonical amino acids (ncAAs), that can be incorporated as late-stage intermediates into larger molecules.[2,3] Recently, our lab and collaborators elucidated the biosynthetic pathway for the cyanobacterial neurotoxin guanitoxin, which utilizes the PLP-dependent cyclase GntC.[4] This enzyme utilizes a divergent mechanism to convert (*S*)-γ-hydroxylated-L-arginine to L-enduracididine, a cyclic ncAA. Through the process of probing the GntC mechanism, we utilized deuterium labelling studies to assess the number of deprotonations that occurred through the process of the mechanism.[5] Using the native substrate, we determined up to three deuterium atoms are incorporated at the α- and β-positions of the product and the remainder of the unreacted substrate when the *in vitro* assay was assessed in D_2O, as opposed to the normal H_2O. Using this system, we assessed alternative substrates that lacked the γ-hydroxy group of the native substrate to determine the deuteration scope of GntC. We determined GntC has a preference to deuterate substrates that are linear and polar up to three times. Through this project, we aim to better understand the biocatalytic capability of GntC, and we will use the deuteration scope of GntC to gain insight into the cyclization substrate scope of GntC.

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Poster 9

PROGRESS TOWARDS THE TOTAL SYNTHESIS OF NOGALAMYCIN

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The anthracycline natural product family is known for their significant demonstrations of anticancer activity; the molecules of this family also possess stereochemical complexity and unique structural features. Representative examples from this family include daunorubicin, doxorubicin, menogaril, and nogalamycin (Figure 1a). Nogalamycin is an anthracycline natural product that has displayed potent inhibition against gram positive bacteria and prominent toxicity against cancer cell lines. Nogalamycin differs from other anthracyclines with the addition of a unique bicyclic aminosugar tethered to its D-ring. To our knowledge, all reported analogs of Nogalamycin are semisynthetic derivatives; as such, structural modifications are limited and do not effectively test the interplay of the A-ring and D-ring sugars nor substitution on the aglycone core. To this end, our development of a highly modular synthesis would mark not only the first NOG total synthesis, but also provide an opportunity to evaluate the structure-activity relationships of the NOG family toward the development of safer, more effective analogs. We hypothesized that the tetracyclic core **1** could be formed from a Weix cross-electrophile coupling between an aryl bromide **2** and an aryl aldehyde **3**, followed by intramolecular C–H carbonylation (Figure 1b). The current plan for accessing this core employs a boron-directed benzyne cycloaddition with iodo-triflate **4** and furan **5** to access the key oxabenzonorbornadiene (OBD) intermediate **6**. The synthetic challenges encountered during the exploration of published OBD opening reactions will be presented as well as the successful alternative ring-opening strategy and the current, improved synthetic route.

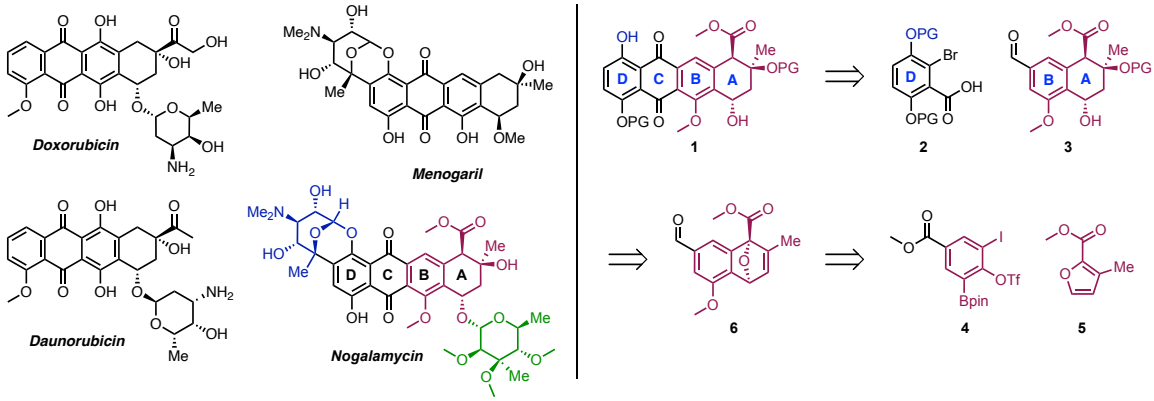

Figure 1. (a) Members of the anthracycline antibiotic natural product family. (b) Our devised retrosynthetic strategies toward accessing the tetracyclic anthracycline core *via* key Ni-catalyzed cross-electrophile coupling and benzyne cycloaddition steps.

Poster 10

Keep an eye on the experiment: a generalized computer-vision-based system for real-time automated monitoring and control of diverse chemical and non-chemical processes

Rama El-khawaldeh[1], Mason Guy[1], Nina Taherimakhsousi[1], Sebastien Monfette[2], Joel M. Hawkins[2], Kris N. Jones[2], and Jason E. Hein*[1]

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Chemists spend significant time performing menial tasks that rely on visual cues such as observing colour changes, monitoring liquid levels, detecting crystal formation, etc.[1] Digital cameras can be combined with computer vision (CV) algorithms to automatically capture, process, and analyse such visual inputs.[2] However, traditional CV systems are rigid in functionality when they are inherently designed to target specific tasks while exclusively relying on colour, grayscale, or edge identification for image analysis.[3] Previously, the Hein Lab has focused on building fully integrated automated monitoring and control systems using flexible hardware and CV for liquid-level monitoring.[4] Herein, we present a generalizable CV and machine learning model that was trained on images from a diverse array of chemical and non-chemical processes. Our newly developed system can be used for automated real-time monitoring and control of experiments and can be readily trained to adjust to the ever-changing needs of the experiments. Compared with conventional CV systems that rely on selective parameterization for data analysis,[5] our model simultaneously monitors multi-parameters (*e.g.,* liquid level, homogeneity, turbidity, solid, residue, and colour), offering a method for rapid data acquisition and deeper analysis from multiple visual clues. We demonstrated a single platform (consisting of CV, machine learning, and automated robotics) to monitor and control vision-based experimental techniques, including titration, solvent swap distillation, liquid-liquid extraction, solid-liquid mixing, crystallization, and solvent evaporation. Both qualitative (video capturing) and quantitative data (parameters measurement) were obtained which provided a method for data cross-validation. Our CV model's ease of use, generalizability, and non-invasiveness make it an appealing complementary option to *in situ* and real-time analytical monitoring tools. Additionally, our platform is integrated with Mettler-Toledo's iControl software, which acts as a centralized system for real-time data collection, visualization, and storage. With consistent data representation and infrastructure, we were able to efficiently transfer the technology and reproduce results between different labs. This ability to easily monitor and respond to the dynamic situational changes of the experiments is pivotal to enabling future flexible automation workflows.

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(4) Zepel, T.; Lai, V.; Yunker, L. P. E.; Hein, J. E. Automated Liquid-Level Monitoring and Control Using Computer Vision. **2020.** doi:10.26434/chemrxiv.12798143.v1
(5) Barrington, H.; Dickinson, A.; McGuire, J.; Yan, C.; Reid, M. Computer Vision for Kinetic Analysis of Lab- and Process-Scale Mixing Phenomena. *Org. Process Res. Dev.* **2022**, *26* (11), 3073–3088. https://doi.org/10.1021/acs.oprd.2c00216.

Poster 11

UTILIZING CONFORMATIONAL CONTROL AS A FILTER TO OBTAIN SELECTIVE 3-ARYL PYRIDONE KINASE INHIBITORS

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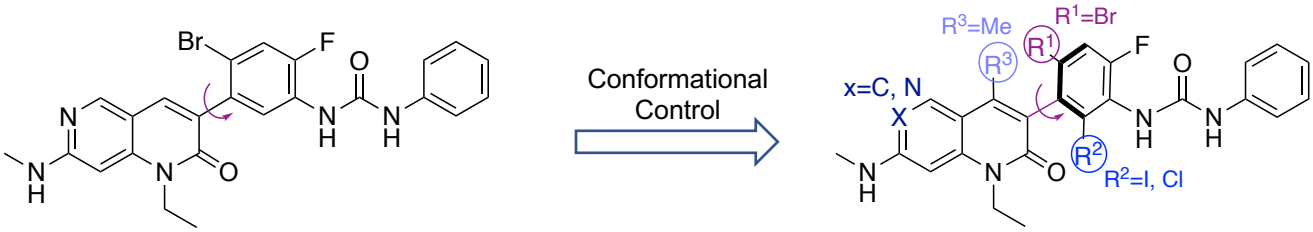
Atropisomerism is a form of axial chirality that arises from hindered rotation about a bond. Currently, over 85% of FDA approved kinase inhibitors (KIs) possess a rapidly interconverting atropisomeric axis. We hypothesize that while one atropisomer will bind the target active site, the other atropisomer can bind to off-target kinases, leading to undesired side effects seen in numerous FDA approved drugs. Furthermore, we predict that selectivity towards a particular kinase can be improved by tuning the dihedral angle about the atropisomeric axis in a low energy conformation that corresponds to the desired target.[1] We are employing this hypothesis to obtain a potent, and selective inhibitor of the receptor tyrosine kinases (RTKs) KIT and PDGFRA. Activating mutations and genetic alterations in these kinases have been identified in many cancers, including gastrointestinal stromal tumors, gliomas, and lung cancers.[2] Our conformational energy mapping of the 3-aryl pyridone scaffold revealed that the FDA approved KIT/PDGFRA inhibitor, Ripretinib, binds KIT in an orthogonal conformation about the aryl-heterocycle axis. While Ripretinib is somewhat selective because it has been found to target a broad range of oncogenic and drug resistant KIT/PDGFRA variants, it has also been shown to inhibit several other RTKs.[3] Thus, we hypothesize that Ripretinib's selectivity can be improved to target KIT/PDGFRA through tuning the dihedral angle about the sp^2-sp^2 axis in a near-orthogonal conformation, aligning with the low energy binding mode of this kinase. We plan to achieve this by incorporating steric bulk adjacent to the chiral axis in the Ripretinib scaffold to stabilize the dihedral angle in this conformation. In order to validate our hypothesis, we will obtain IC_{50} values to determine the selectivity and potency of our compounds, as well as evaluate our inhibitors in cellular models of KIT/PDGFRA driven cancers to study the effect of our inhibitors *in vitro*.



Ripretinib, Promiscuous KI

Class-3 Atropisomers: Increase in KI Selectivity

[1]Toenjes, S. T., et al. *ACS Chem. Biol.* **2019**, 14 (9), 1930-1939.
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Poster 12

PROCESS CHEMISTRY AT GSK

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Drug Substance Development, GSK
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Process chemistry at GSK is built on a highly collaborative team and industry-leading scientific innovation. Six areas of our department will be discussed including new route design, scale-up and pilot plant work, high throughput chemistry, predictive chemistry, academic collaborations, and discovery process chemistry. This poster will highlight the chemistry and the scientists at GSK. The projects that will be presented enabled our teams to synthesize active pharmaceutical ingredients (API) and discover new reaction paradigms.

Poster 13

METHYLATION OF (HETERO)ARYL ELECTROPHILES VIA NICKEL CATALYZED CROSS-COUPLING AND HYDRAZONE CHEMISTRY

Daliah Farajat and Léa Philippe,[†] Anastasiia Afanasenko,[†] Durbis Costello Pazos,[†] Juan Lasso,[†] Joaquín Barroso,[‡] Chao-Jun Li*[†]

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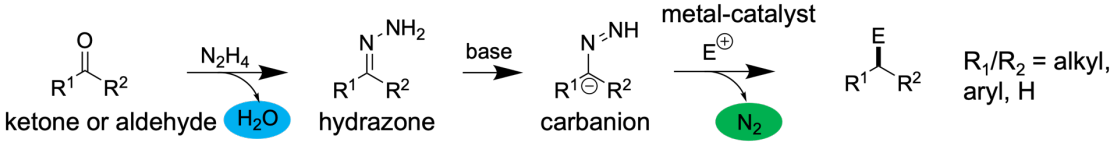
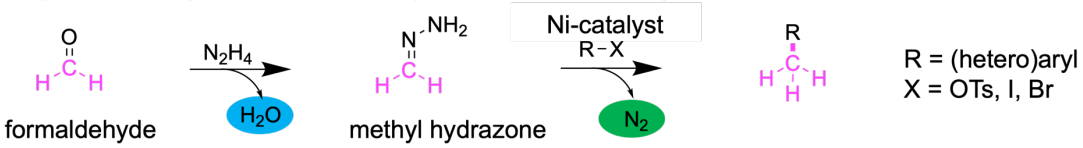
Methyl groups are known to play a vital role in pharmaceutical substrates, where they are often present on aryl and heteroaryl moieties. Notably, it has been demonstrated that the addition of methyl groups to drug molecules can drastically improve drug potency by enhancing drug-target interactions – a phenomenon which has been termed the "magic methyl effect". Development of new methylation strategies therefore has significant implications for organic and medical chemistry. In recent years, the use of hydrazones as latent carbanions for nucleophilic addition reactions or as coupling partners has shown robust reactivity and has been utilized under mild reaction conditions while extruding inert by-products such as nitrogen gas and water. The present research establishes a new methodology for methylation of (hetero)aryl phenol derivatives and (hetero)aryl halides via Ni-catalyzed cross-coupling and hydrazone chemistry. The reaction produces moderate to good yields on a wide variety of substrates with broad functional group tolerance. Late-stage functionalization of biologically active substrates including camptothecin and estrone are also reported. In combination with the diverse scope, experimental and computational investigations were used to support the proposed mechanism for this reaction.

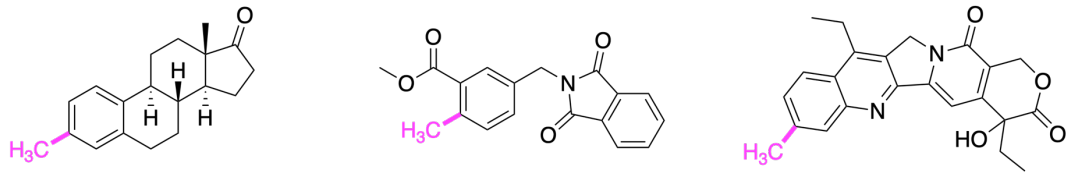
Hydrazone Chemistry



Methylation via Hydrazone Chemistry and Cross-Coupling



Late-Stage Methylation of Biologically Active Small Molecules



Poster 14

SYNTHESIS AND CHARACTERIZATION OF NOVEL CATIONIC SILYL LIPID NANOPARTICLES

Sydney Figueroa, Leah Thompson, David Coppage, and Annaliese K. Franz*

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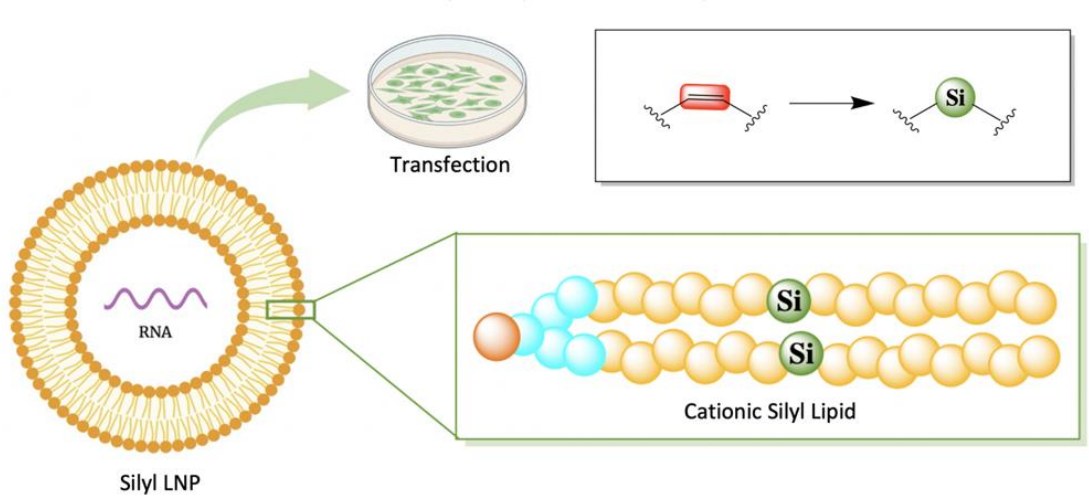
The rapid development of the COVID-19 mRNA vaccine was made possible with lipid nanoparticles (LNPs), molecular delivery vehicles that can transport fragile RNA therapeutics safely and selectively into cells. Current efforts focus on methods to enhance the transfection efficiency and stability of LNPs, both within the body and during storage. One way to do so is through LNP lipid tail optimization, which remains largely unexplored in commercially available formulations. Pre-existing cationic lipids, a crucial ingredient in LNP formulations, utilize cis alkene incorporations to crudely modulate LNP properties and enhance RNA delivery. However, the incorporation of a cis alkene leaves their lipid tails vulnerable to storage degradation, toxic oxidative metabolism, and decreased lipid tail packing, which can hinder LNP formation and potentially cause a premature release of RNA contents during biodistribution. The strategic replacement of this cis alkene with a branched silicon bioisostere is a promising avenue to optimize and fine-tune LNP properties while also minimizing toxicity and degradation. Branched silyl analogs offer enhanced lipophilicity to increase lipid packing and can be readily diversified using hydrosilylation as a modular synthetic tool. Cationic silyl lipids have the potential to improve LNP formulations by exploring the sweet spot between lipid packing for LNP stability and branching for enhanced RNA delivery. A diverse range of novel cationic silyl lipids can be generated through an easily accessible three to four-step synthesis. Various characterization techniques, such as dynamic and electrophoretic light scattering (DLS/ELS), were used to evaluate silyl LNP structures and elucidate a structure-activity relationship. Preliminary data reveals that LNP properties can be controlled through varying silyl position, tail length, and silyl substituents. Future work will explore the potential for silyl LNPs to increase transfection efficiency in cell lines with low transfection rates using currently available LNP products.



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[2] Han, X.; et. al. *Nature Comm.* **2021**, 12, 7233

Poster 15

MACROCYCLIZATION AND LINEARIZATION OF DIVERSE MACROCYCLIC PEPTIDOMIMETIC LIBRARIES

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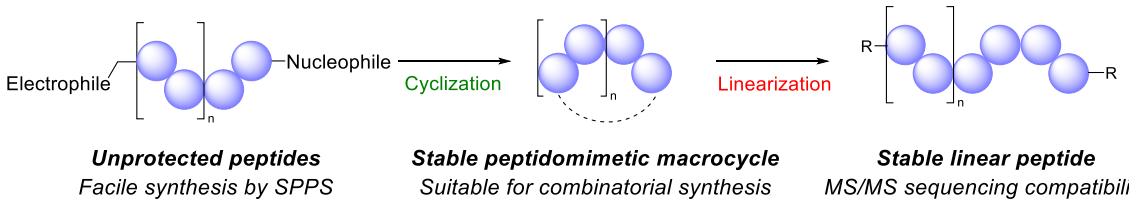
Macrocyclic peptides are valuable therapeutic modalities due to their high potency and biocompatibility. Limited methodology exists for the synthesis of small, stable macrocyclic peptides, particularly those that can be selectively linearized in response to stimuli. This key feature can be leveraged for many applications across chemical biology, including for tandem mass spectrometry sequencing of peptidic hits following combinatorial macrocycle library screenings. Herein, we detail novel methodology for the generation of head-to-tail cyclized peptidomimetics that can be chemically linearized in a chemoselective fashion. Our methodology is compatible with thiol-free, canonical and non-canonical unprotected peptides and can be used to generate a range of macrocycle ring sizes from 13–45+ atoms under mild, aqueous conditions. The resulting peptidomimetics closely resemble native cyclic peptides and are stable at pH 2.5–10, making them ideal therapeutic candidates. Importantly, the macrocycles can be chemically linearized under mild conditions in the presence of all canonical amino acids with no protecting groups necessary, making our macrocyclic peptidomimetic technology ideal for large, diverse library screening campaigns.



Unprotected peptides
Facile synthesis by SPPS

Stable peptidomimetic macrocycle
Suitable for combinatorial synthesis

Stable linear peptide
MS/MS sequencing compatibility

Poster 16

SYNTHESIS OF VICINAL CARBOCYCLES BY INTRAMOLECULAR NICKEL-CATALYZED CONJUNCTIVE CROSS-ELECTROPHILE COUPLING REACTION

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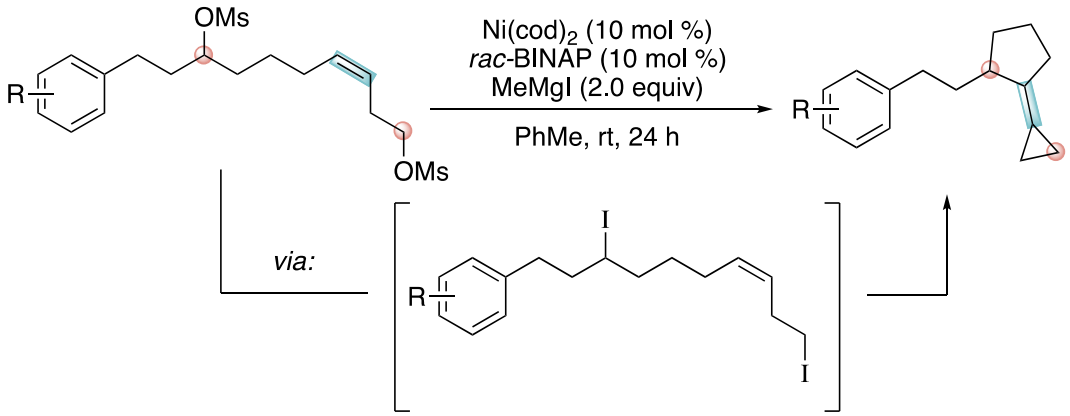
Nickel-catalyzed cross-electrophile coupling (XEC) reactions are a fundamental tool for C–C bond construction. Specifically, conjunctive XEC reactions, which couple two electrophiles with an olefin, allow for rapid access to complex scaffolds. The development of an intramolecular Ni-catalyzed conjuctive XEC reaction of alkyl dimesylates for the synthesis of 3,5-vicinal carbocycles will be presented. Mechanistic experiments demonstrate conversion of the alkyl dimesylates to alkyl iodides in situ and evidence of radical intermediates (1).



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Poster 17

UTILIZING DIHEDRAL ANGLE CONTROL AS A STRATEGY TO OBTAIN SELECTIVE DIARYLAMINE KINASE INHIBITORS

Beeta Heydari, Bahar Heydari, David Salazar, Elona Hasani, and Jeffrey L. Gustafson*

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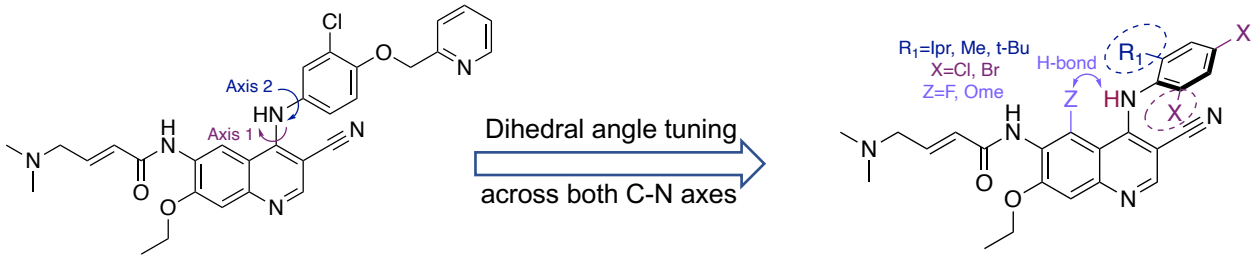
Atropisomerism is a type of conformational chirality that occurs when there is hindered rotation about a chiral bond. Our group has shown that Class-1 atropisomers bind to targets in a small subset of conformations, and that different targets can prefer different subsets of conformations about the atropisomeric axis[1]. Building on this hypothesis, we have shown that tuning the dihedral angle of the atropisomeric axis towards the target's preferred low-energy dihedral angle conformation can cause significant gains in the selectivity of kinase inhibitors[1]. Diarylamines, which possess two contiguous C-N axes, are one of the most privileged scaffolds in drug discovery. An analysis of the protein data bank revealed that out of 1600+ entries, approximately 100 ligands bind their target in conformations where one of the axes is planar and the other axis is near-orthogonal. We hypothesize that preorganizing diarylamines into these unique conformations will bias the selectivity towards targets that prefer these conformations. Conformational mapping of various diarylamine inhibitors reveals that Neratinib, a promiscuous irreversible tyrosine kinase inhibitor (TKI), binds HER2 in these conformations. HER2 is receptor tyrosine kinase that is significantly overexpressed and/or mutated in breast cancer, as well as gastric, bladder, and esophageal cancers[2,3]. We hypothesize that the selectivity of Neratinib can be significantly improved by preorganizing or 'tuning' its atropisomeric axes towards the preferred low energy binding conformations of HER2, thus reducing off-target side effects. We will achieve this by employing intramolecular H-bonding across the quinoline C-N axis, and adding steric bulk adjacent to the second chiral axis. To validate our hypothesis, we will obtain IC_{50} values to assess how selective our inhibitors are towards HER2 and evaluate their efficacy in cellular models of HER2 driven cancers.



Neratinib: Promiscuous Class-1 TKI

Class-3 Atropisomer: Selective TKI

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[1] Toenjes, S. T., et al. *ACS Chem. Biol*. **2019**, 14(9),1 930–1939.
[2] Collins, D. M., et al. *Cancers.* **2019**, 11(6), 1–27.
[3] Hanker, A. B., et al. *Cancer Cell*. **2021**, 39(8), 1099-1114.

Poster 18

Are small molecule efficiency metrics relevant for the design of molecular glues?

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Targeted protein degradation (TPD) can be mediated by small molecules that act as molecular glue between an E3 ligase and a degradation target. These molecular glues are catalytic in nature, distinguishing them from traditional stoichiometric inhibitors. In addition to potency, molecular glue compounds are characterized by the depth and kinetics of the protein degradation response. These key aspects introduce additional layers of complexity toward identifying drug candidates suitable for clinical assessment. Efficiency metrics such as ligand efficiency (LE) or lipophilic ligand efficiency (LipE) are well established parameters to support the design of stoichiometric protein inhibitors. However, applying efficiency metric to assess molecular glues has not been reported in the literature. Given the history of our organization to discover and develop molecular glue compounds such as immunomodulatory imide drugs (IMiDs) and cereblon E3 ligase binding modulators (CELMoDs), we evaluated whether traditional small molecule efficiency metrics would apply to these modalities. The application of these metrics may enable the identification of project lead molecules and thus accelerate TPD drug discovery programs.

Poster 19

TRANSITION METAL-CATALYZED HYDROFUNCTIONALIZATION OF ALKYNES AND CYCLOPROPENES

Xintong Hou, Brian S. Daniels, Ryan T. Davison, Stephanie A. Corio, Vy M. Dong*, Jennifer S. Hirschi*, Shaozhen Nie*

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Irvine, California, 92697.

Transition metal-catalyzed hydrofunctionalizaiton of unsaturated hydrocarbons is a powerful and atom-economical approach for the construction of complex molecules. By using Rh–H catalysis, we can access α,α-disubstituted α-amino acid precursors bearing two contiguous stereogenic centers. The methodology involves the enantio- and diastereoselective addition of α-nitroesters to alkynes. The Rh–H species promotes the isomerization of the alkyne into a Rh–π–allyl electrophile, which is then trapped by the α-nitroester nucleophile. The resultant allylic α-nitroester can then be readily reduced to the corresponding allylic α-amino esters in a chemoselective fashion (Figure 1a).[1] In addition, we also developed a copper-catalyzed addition of phosphines to cyclopropenes with high enantio- and diastereocontrol (Figure 1b).[2] With this hydrophosphination method, we can access various enantioenriched cyclopropyl phosphine motifs possessing different stereoelectronic properties. Mechanistic studies support the formation of a Cu(I)–phosphido species,[3] which then undergoes migratory insertion to form the key C–P bond.

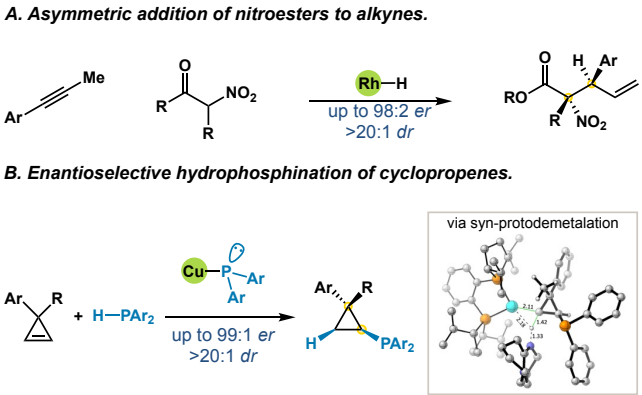

Figure 1. Hydrofunctionalization of unsaturated hydrocarbons.

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[2]Daniel, B.S.; Hou, X.; Corio, S. A.; Weissman, L. M; Dong, V. M.; Hirschi, J. S.; Nie, S.; ChemRxiv. Cambridge: Cambridge Open Engage; 2023; This content is a preprint and has not been peer-reviewed.

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Poster 20

COBALT-CATALYZED ENANTIOSELECTIVE RING-OPENING OF UNSTRAINED HETEROCYCLIC ALKENES

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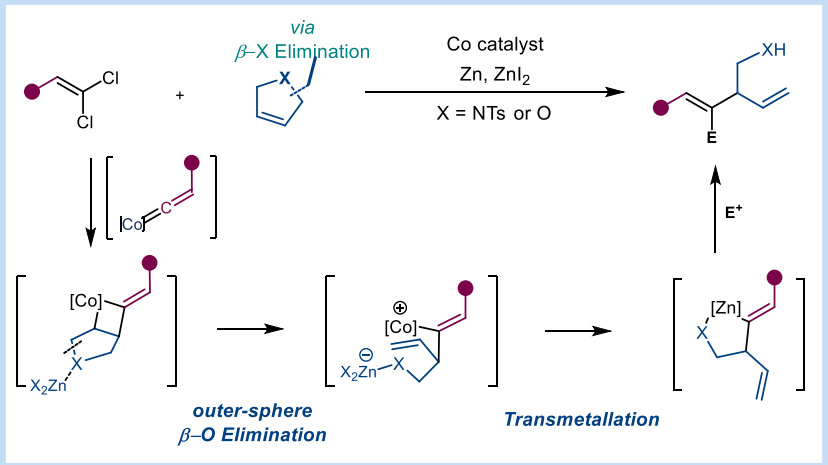
Ring strain is the driving force for numerous ring-opening reactions of three- and four-membered heterocycles. By comparison, five-membered heterocycles lack this thermodynamic driving force. As a result, only a few methods exist for the ring-opening of five-membered heterocycles using transition metal catalysts. For unstrained and unactivated 2,5-dihydrofurans this is achieved via a β-O elimination process, wherein, gaining selectivity over a competing β-H elimination is challenging. We report a novel strategy for the asymmetric ring-opening of 2,5-dihydrofurans with dichloroalkenes utilizing an earth-abundant cobalt catalyst. We propose that the dichloroalkenes form reactive vinylidene intermediates with the chiral ($^{i\text{Pr}}$Pybox)$CoBr_2$ catalyst, followed by a [2+2] cycloaddition with the heterocyclic alkene. This cobaltacyclobutane exclusively undergoes an outer-sphere β-O elimination assisted by zinc halide. Alternative inner-sphere β-O and β-H elimination pathways are inaccessible from this four-membered metallacycle. This is followed by a transmetallation step to form a zinc metallacycle, which subsequently gives rise to homoallylic alcohols, upon quenching, with high diastero- and enantioselectivity. Additionally, the organozinc intermediate can be trapped in situ by various electrophiles for further derivatizations. DFT model predicts the origin of the high diastereo- as well as enantioselectivity observed in the reaction.



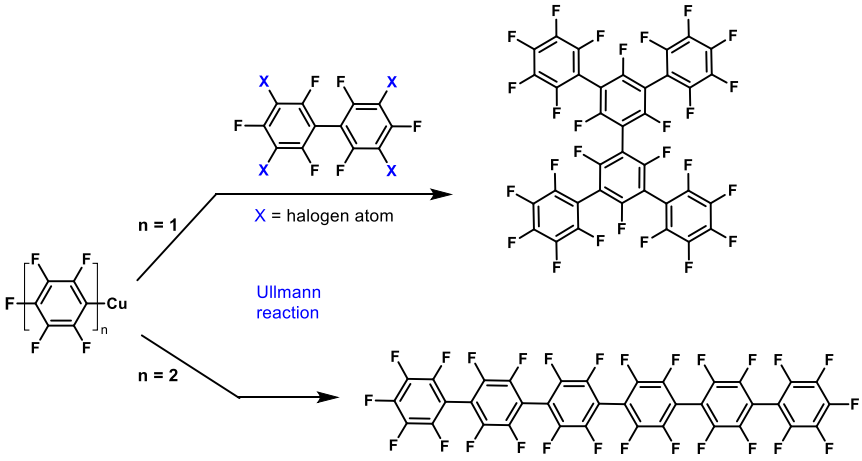
Poster 21

ONE-STEP SYNTHESIS OF PERFLUORINATED POLYPHENYLENES USING MODIFIED ULLMANN COUPLING CONDITIONS

Zheng Sonia Lin[a,b], Benoît H. Lessard[b,c], and Jaclyn Brusso[a*]

[a] *Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Canada;* [b] *Department of Chemical and Biological Engineering, University of Ottawa, Ottawa, Canada;* [c] *School of Electrical Engineering and Computer Science, University of Ottawa, Ottawa, Canada*
** Corresponding author E-mail addresses: jbrusso@uottawa.ca (J.L. Brusso)*

Fluorinated compounds have attracted attention in both the pharmaceutical industry and materials science due to the small size and strong electron-withdrawing property of the fluorine atom. In materials science, among the various fluorinated compounds, perfluorinated polyphenyl-based materials play an important role in acting as electron transport layers in organic electronics such as light-emitting diodes (OLED). While various strategies for the preparation of fluorinated arenes have been reported, the number of synthetic methods available for perfluorinated arenes remains limited, mainly due to the change in reactivity of reagents and substrates at the reaction site upon the introduction of additional fluorine atoms. Given the important applications of perfluorinated polyphenyl-based compounds, we report here the one-step synthesis of the dendrimer perfluoro-3,3'5,5'-tetrakisphenyldiphenyl-1,1', which to date no example of a targeted synthesis has been reported in literature, and the synthetic methodology for the direct preparation of linear perfluorinated para-sexiphenyl. Both strategies use starting materials that are either commercially available or can be easily accessed using standard literature methods. The mechanism for the formation of perfluorinated para-sexipenyl will also be discussed.



Poster 22

DEVELOPMENT OF NICKEL-CATALYZED CROSS-ELECTROPHILE COUPLING REACTION FOR THE SYNTHESIS OF VINYL FLUORIDE-SUBSTITUTED CYCLOPROPANES

Patricia C. Lin[†], Chetan Joshi[‡], Tristan McGinnis[†], Sharath Chandra Mallojjala[‡], Amberly B. Sanford[†], Jennifer S. Hirschi*[,‡], Elizabeth R. Jarvo*[,†]

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[‡]*Department of Chemistry, Binghamton University*
Department of Chemistry, University of California, Irvine California 92697, United States
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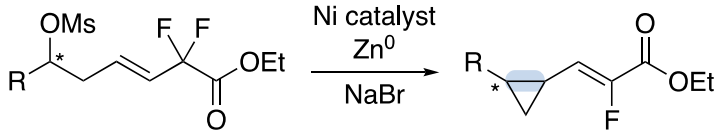
Nickel-catalyzed cross-electrophile coupling (XEC) reactions involving trifluoromethyl alkenes have been utilized for the synthesis of *gem*-difluoroalkenes present in many complex molecules. However, the use of allylic difluorides in XEC reactions employing nickel catalysts are less well developed. The development of a nickel-catalyzed XEC reaction between alkyl mesylates and allylic *gem*-difluorides for the synthesis of vinyl fluoride-substituted cyclopropanes will be discussed. Additionally, proposed mechanisms will be presented based on DFT calculations and experimental mechanistic studies.



Poster 23

ASYMMETRIC SYNTHESIS OF 3,5-SUBSTITUTED HYDANTOINS VIA AN AZA-HECK CYCLIZATION

Ellie A. Meck, Humair B. Omer, Anna K. Schroeder, Montana J. Edwards, Katerina M. Korch, and Donald A. Watson*.

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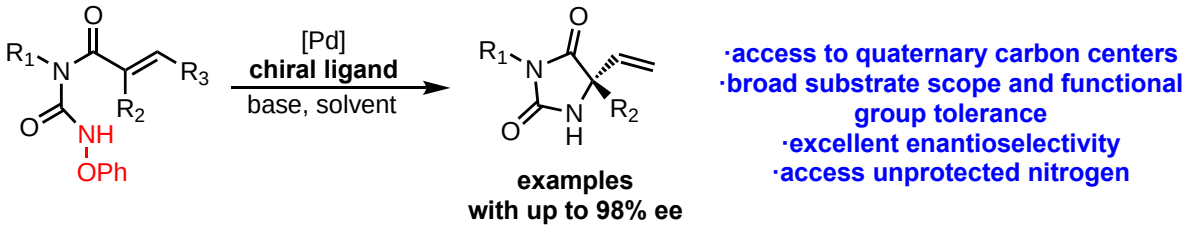
An enantioselective aza-Heck cross-coupling to form quaternary hydantoins has been developed. Chiral quaternary hydantoins are frequently found in pharmaceuticals and other bioactive compounds, but are most often prepared from chiral alpha,alpha substituted amino acids. In this work, we show that chiral hydantoins can be accessed via an aza-Heck cyclization that simultaneously establishes both the heterocycle and the quaternary center from simple acyclic precursors. These palladium-catalyzed conditions tolerate a range of functional groups and starting material topologies, allowing the formation of complex products under straightforward conditions. This methodology will allow expanded access to asymmetric hydantoins.



Poster 24

Discovery of CC-99282, a cereblon E3 ligase modulator (CELMoD™) for the treatment of relapsed or refractory non-Hodgkin lymphomas and chronic lymphocytic leukemia/small lymphocytic lymphoma

Hannah L. Powers, Timothy Kercher, Joshua D. Hansen, Matthew Alexander, Roy Harris, Mark Nagy, Matthew Correa, Dehua Huang, Véronique Plantevin Krenitsky, Preethi Janardhanan, Derek Mendy, Yang Tang, Sophie Peng, Leo Barnes, Rama Krishna Narla, Antonia Lopez-Girona, and Jennifer R. Riggs*

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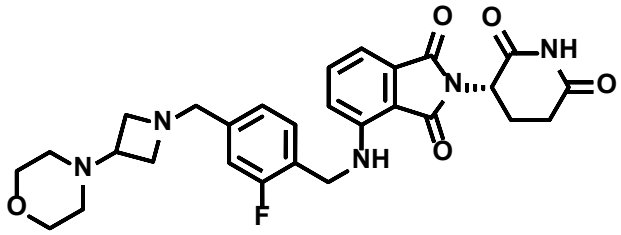
Induction of protein degradation as a therapeutic strategy has been clinically validated by the class of immunomodulatory drugs that includes lenalidomide and pomalidomide, which are known to target Ikaros and Aiolos for degradation. Herein, we report the discovery of CC-99282, a CELMoD™ agent designed to address the unmet needs of patients with relapsed or refractory (R/R) lymphomas. CC-99282 drives the formation of a protein–protein interaction between zinc finger protein neosubstrates such as IKZF1/3 (Ikaros/Aiolos) and ZFP91 with cereblon (CRBN). This interaction in turn induces targeted association of the respective neosubstrate to the $CRL4^{CRBN}$ E3 ubiquitin ligase complex, and subsequent proteasome-mediated neosubstrate degradation. A description of the structure–activity relationship, preclinical drug metabolism and pharmacokinetics, and antitumor efficacy data leading up to the discovery and selection of the novel protein degrader CC-99282 is shared.



CC-99282

Poster 25

Translating planar heterocycles into 3D analogs via photoinduced hydrocarboxylation

Myriam Mikhael,[1] Sara N. Alektiar,[2] Charles S. Yeung,*,[1] and Zachary K. Wickens*,[2]

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*Charles S. Yeung –email: charles.yeung@merck.com

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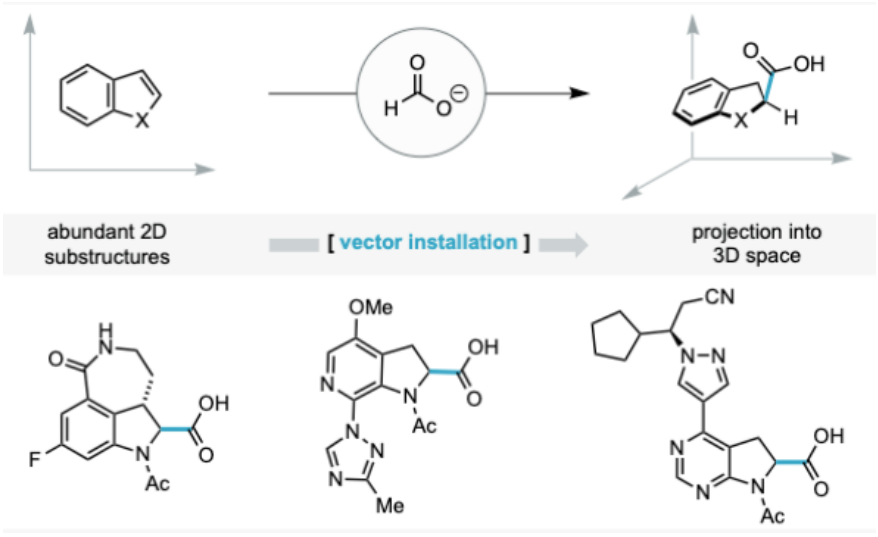
Presenting author: Myriam Mikhael; myriam.mikhael@merck.com; 102 Franklin Street, Apt 1, Brookline, MA 02445.

Abstract: The rapid preparation of complex three-dimensional (3D) heterocyclic scaffolds is a key challenge in modern medicinal chemistry. Despite the increased probability of clinical success for small molecule therapeutic candidates with increased 3D complexity, new drug targets remain dominated by flat molecules due to the abundance of coupling reactions available for their construction. In principle, heteroarene hydrofunctionalization reactions offer an opportunity to transform readily accessible planar molecules into more three-dimensionally complex analogs through the introduction of a single molecular vector. Unfortunately, dearomative hydrofunctionalization reactions remain limited. Herein, we report a new strategy to enable the dearomative hydrocarboxylation of indoles and related heterocycles. This reaction represents a rare example of a heteroarene hydrofunctionalization that meets the numerous requirements for broad implementation in drug discovery. The transformation is highly chemoselective, broad in scope, operationally simple, and readily amenable to high-throughput experimentation (HTE). Accordingly, this process will allow existing libraries of heteroaromatic compounds to be translated into diverse 3D analogs and enable exploration of new classes of medicinally relevant molecules



Poster 26

DEVELOPMENT OF A NICKEL-CATALYZED N–N COUPLING FOR THE SYNTHESIS OF HYDRAZIDES

Jay P. Barbor, Vaishnavi N. Nair‡, Kimberly R. Sharp‡, Trevor D. Lohrey, Sara E. Dibrell, Tejas K. Shah, Martin J. Walsh, Sarah E. Reisman*, and Brian M. Stoltz*

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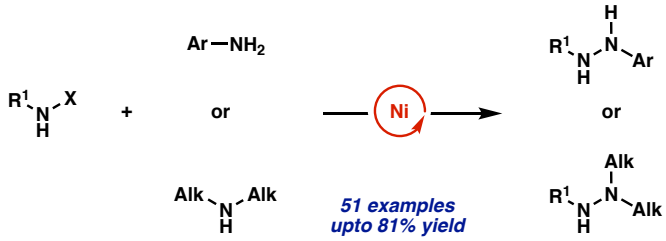
Molecules containing N–N bonds are prevalent among bioactive natural products and other pharmaceutical and agrochemical agents. Rapid access to highly functionalized N–N containing compounds is challenging as traditional approaches often rely on stepwise functionalization of hydrazine. Strategies to construct these molecules using direct N–N coupling have been of great interest to synthetic community, however, most approaches developed are limited to the synthesis of fully aromatic products.[1] In recent years, transition metal-catalyzed N–N coupling via nitrene intermediates has emerged as a useful method.[2] Our research describes the development of a Ni-catalyzed N–N coupling allowing easy access to hydrazides using both arylamines and dialkylamines as coupling partners. Mechanistic studies imply the intermediacy of a Ni-stabilized acyl nitrene in the transformation.



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2. a) Maestre, L.; Dorel, R.; Pablo, Ó.; Escofet, I.; Sameera, W. M. C.; Álvarez, E.; Maseras, F.; Díaz-Requejo, M. M.; Echavarren, A. M.; Pérez, P. J. J. *Am. Chem. Soc.* **2017**, *139*, 2216–2223. b) Kono, M.; Harada, S.; Nemoto, T. *Chem. Eur. J.* **2019**, *25*, 3119–3124. c) Wang, H.; Jung, H.; Song, F.; Zhu, S.; Bai, Z.; Chen, D.; He, G.; Chang, S.; Chen, G. *Nat. Chem.* **2021**, *13*, 378-385.

Poster 27

THE HUNT FOR NEW BIOACTIVE NATURAL PRODUCTS FORMED BY SITE-SPECIFIC VANADIUM DEPENDENT HALOPEROXIDASES IN ACTINOBACTERIA

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Vanadium-dependent haloperoxidases (VHPOs) are capable of site-specifically installing halogens onto certain organic scaffolds, as well as forming new carbon-carbon and carbon-oxygen bonds in the same step. Nonselective VHPOs from algae have been studied and used as biocatalysts, however few site-specific VHPOs have been studied. There is a lack of knowledge on the substrate scope and mechanism of halogen addition that has prevented site-specific VHPOs from widespread biocatalytic application. However, the majority of the site-specific VHPOs that have been characterized are involved in the biosynthesis of complex halogenated antibiotic meroterpenoid products from actinobacteria.

We initiated our investigation using a genomic approach to identify multiple actinobacterial strains with homologs to known site-selective VHPO, NapH1 in the napyradiomycin biosynthetic gene cluster. Candidate strains were obtained from microbial repositories, cultured, and organically extracted and fractionated. To analyze our samples, liquid chromatography-tandem mass spectrometry has been applied to identify compounds within our anticipated mass ranges and containing diagnostic halogen isotope labeling patterns. Further analyses using the Global Natural Product Social Molecular Networking platform has suggested chemical novelty within our organic fractions. We have also tested fractions for antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and Group A *Streptococcus* bacterial pathogens, and assessed cytotoxicity against non-small cell lung cancer (NSCLC) cell lines. From these lines of inquiry, we are actively working to further purify and characterize compounds of interest.

Through this project to discover novel VHPO-catalyzed natural products, we aim to provide insight into the biosynthetic role of site-specific VHPOs. Once a novel VHPO product has been identified, future directions involve genomic and biochemical approaches in order to characterize the VHPO itself. This research will identify new organic molecules and broaden the breadth of known VHPOs.

Poster 28

CATALYTIC CYCLOPROPANATION *VIA* UNSTABILIZED CARBENES

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David Nagib*: nagib.1@osu.edu

The cyclopropane ring is key to numerous compounds that possess interesting bioactivity and is increasingly incorporated into drug molecules. However, current methods are often limited by the use of explosive diazo reagents or unstable gem-dihalides as a precursor for the Simmons-Smith cyclopropanation. Herein, we report a mild and novel strategy to access multi-substituted cyclopropanes from α-acyloxy halides or directly from alkyl aldehydes. Iron catalysts were employed to generate unstabilized carbene *in situ* and afford cyclopropanation with an olefin partner. Through this approach, a variety of electron-rich and electron-poor alkenes were surveyed to achieve diversely functionalized cyclopropanes in one step. Examination of different catalyst-Li salt combinations provide more insights into the mechanism of carbene formation. Furthermore, a series of additives were investigated to showcase high functional group tolerance, along with the robustness of this method.

Poster 29

DEVELOPMENT OF CHIRAL HEMIBORONIC ACID CATALYSTS FOR DIRECT DIOL FUNCTIONALIZATION

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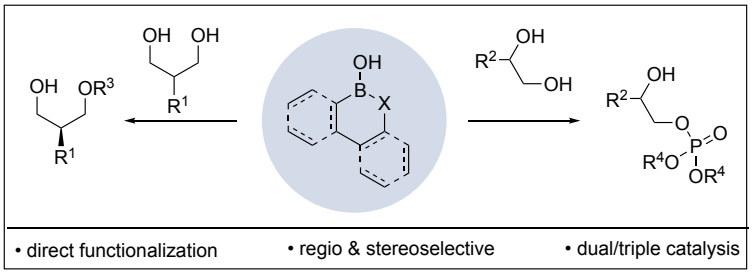
The hydroxy group (–OH) is ubiquitous in organic chemistry, with an estimated 37% of marketed drugs containing at least one.[1] The addition, removal, or modification of a hydroxy group can drastically alter the efficacy of a bioactive molecule by several orders of magnitude.[1] However, due to the relatively inert reactivity of the –OH group, alcohol functionalization is often reliant on stoichiometric activating agents generating significant amounts of waste, or harsh reaction conditions to achieve energetically demanding transformations. Furthermore, these challenges are amplified when multiple hydroxy groups are present on a substrate. For this reason, there is high demand in both the pharmaceutical and agrochemical industries for reactions that allow for the selective, direct, and catalytic transformation of hydroxy groups.

Due to their ability to reversibly form covalent bonds with –OH groups, boronic and hemiboronic acids present the unique capacity to catalytically activate alcohols in either a nucleophilic or electrophilic manner.[2] Diols can undergo nucleophilic activation under basic conditions via the formation of a tetravalent anionic complex, which transiently increases the electron density on the diol oxygen atoms. Moreover, by altering the catalyst structure, regio- and enantioselective transformations can be achieved. This concept has been exemplified in recent reports on the enantioselective desymmetrization of diols via boroxarophenanthrene catalyzed benzylation, and the benzoxazaborine catalyzed regioselective phosphorylation of 1,2-diols.[3,4] Despite new innovations in this field, there remains an opportunity for the development of easily accessed chiral catalysts that enable access to a wider scope of substrates and catalytic applications.



[1] Cramer, J.; Sager, C. P.; Ernst, B. *J. Med. Chem.* **2019**, *62*, 8915–8930
[2] Hall, D. G. *Chem. Soc. Rev.* **2019**, *48*, 3475–3496
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Poster 30

COBALT-CATALYZED ELECTROREDUCTIVE FUNCTIONALIZATION OF UNACTIVATED ALKYL CHLORIDES

Immaculata O. Onuigbo, Samir Al-Zubaydi, Blaise L. Truesdell, Christo S. Sevov*

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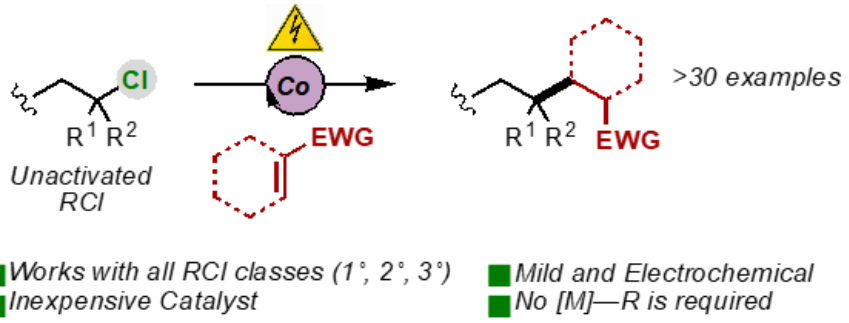
This seminar details a cobalt-catalyzed electrochemically mediated strategy for the formation of C(sp3)-C(sp3) bonds from unactivated alkyl chlorides and electrophilic olefins. The utility of this methodology is exemplified by its scalability, good functional-group tolerance, and its ability to functionalize primary, secondary, and the more challenging tertiary alkyl chlorides. Mechanistic studies, including stoichiometric, radical clock, and competition experiments support a pathway involving halogen atom abstraction by the Co(I), followed by the release of a carbon-centered radical. Deuterium labeling experiments revealed that the addition of a proton source is crucial for capturing transient enolates produced via a reductive Giese-type addition during the reaction. This work represents a rare example of alkyl chloride activation and is promoted by electrocatalysis in place of high-energy chemical reductants. Finally, the methodology enables the coupling of different classes of alkyl chlorides with diverse conjugated alkenes, including α-β unsaturated ketohydes.



Poster 31

DESIGN AND SYNTHESIS OF NON-TRADITIONAL CEREBLON BINDERS: MOVING BEYOND THALIDOMIDE, LENALIDOMIDE AND POMALIDOMIDE

Jayce Rhodes, Stephen Norris, Xiaochu Ba, Dehua Huang, Gody Khambatta, Jennifer Buenviaje, Brandon Whitefield, Matt Alexander, Patrick Papa, and Deborah S. Mortensen.

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Since the molecular target of thalidomide, lenalidomide and related analogs was identified as cereblon (CRBN) mediated targeted protein degradation, the discovery process leveraging the modality has moved beyond serendipitously observed effects to intentionally design small molecules. One key aspect of the discovery process for efficient and selective E3 mediated degraders is the modification of CRBN binders. Adaptations to the cereblon binding moiety for use in molecular glues as well as heterobifunctional molecules, modulates cereblon binding efficiency, selectivity over neosubstrates, and optimized drug-like properties. This work details the design and synthesis of novel CRBN binders by evaluation of CRBN binding of non-traditional binders as well as degradation profiles for common neosubstrates such as Aiolos and GSPT1.

Poster 32

PRACTICAL NI-CATALYZED SYNTHESES OF ALLYLIC BORONATES

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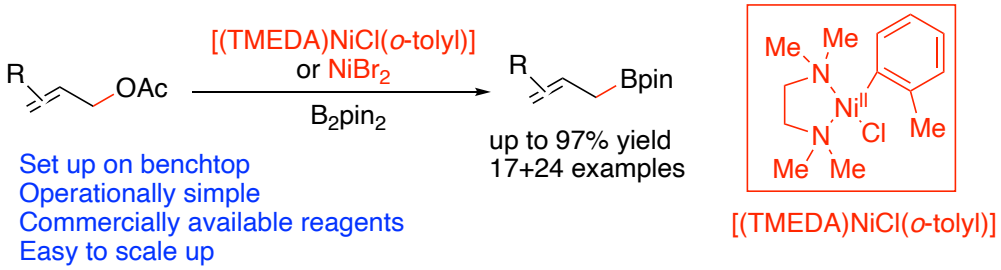
Allylic boronates are versatile intermediates for constructing C-C bonds via Suzuki-Miyaura cross-coupling reactions and accessing both homoallylic alcohols and amines with high stereose-lectivities via a *Zimmerman-Traxler* type transition state.[1,2] Due to the importance of allylic boronates in modern organic chemistry, two Ni-catalyzed borylations of allylic acetates to access allylic boronates in the presence of B_2pin_2 have been developed in an efficient and practical manner. The borylations can be set up on benchtop using commercially available and inexpensive nickel catalysts and reagents. The protocol worked well for a wide range of substrates (17+ 24 examples) with up to 97% isolated yield. The practicality of this process is further demonstrated with multigram-scale reactions without any erosion of reactivities.



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Poster 33

NI-CATALYZED ENANTIOSELECTIVE INTRAMOLECULAR MIZOROKI-HECK REACTION FOR THE SYNTHESIS OF PHENANTHRIDINONE DERIVATIVES

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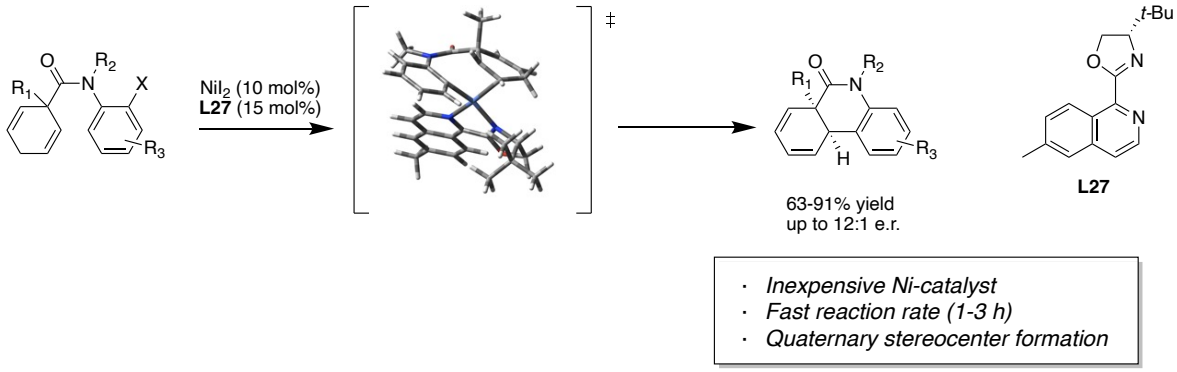
A Ni-catalyzed enantioselective intramolecular Mizoroki-Heck reaction has been developed to transform symmetrical 1,4-cyclohexadienes with attached aryl halides to phenanthridinone analogs containing quaternary stereocenters. Herein we report important advances in reaction optimization enabling control of unwanted proto-dehalogenation and alkene reduction side products. Moreover, this approach provides direct access to six-member ring heterocyclic systems bearing all-carbon quaternary stereocenters, which have been much more challenging to form enantioselectively with nickel-catalyzed Heck reactions. A wide range of substrates were demonstrated to work in good to excellent yields. Good enantioselectivity was demonstrated using a new synthesized chiral iQuinox-type bidentate ligand (**L27**). The sustainability, low price of nickel catalysts, and the significantly faster reaction rate versus a recently reported palladium-catalyzed reaction (1 h vs 20 h) make this work a very attractive alternative.



Poster 34

DEVELOPING NEW DRUG SCAFFOLDS WITH BORON: PROPERTIES, CHEMISTRY, AND PHARMACEUTICAL POTENTIAL OF HEMIBORONIC NAPHTHOIDS

Olivia M. Schneider,* M. H. Zain Kazmi, and Dennis G. Hall

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In pharmaceutical development, chemists tend to design molecules from a limited repertoire of functional groups, as they must meet strict pharmacokinetic and pharmacodynamic requirements. For this reason, the incorporation of new chemotypes is a significant occurrence, as it improves chemical diversity, which is key to addressing relevant diseases. The goal of this work is to develop new classes of boron-based heterocycles for drug design inspired by benzoxaborole, the core scaffold of tavaborole (antifungal) and crisaborole (atopic eczema treatment). Though boron is relatively new in drug design, it has already been proven to engage in unique and versatile molecular interactions with various targets due to its moderate Lewis acidity, leading to significant diversity in applications.[1] However, practical applications are currently limited due to poor pharmacokinetics and limited synthetic chemistry. This work aims to generate new boron-based scaffolds and the associated synthetic chemistry, with strong biological activity and improved pharmacokinetics for practical and diverse drug applications.

To this end, we investigated a variety of underexplored heterocyclic hemiboronic acids. Boron-containing naphthoids provided exemplary physical properties, pK_a, stability, and ease of access.[2] With the support of compatible and selective synthetic methods, an initial library of derivatives was generated and screened for antimicrobial activity, where several compounds were identified as having biological activity against *C. albicans* and methicillin-resistant *S. aureus* comparable to or better than current drugs. Promising scaffolds were then advanced to preliminary drug metabolism and pharmacokinetic testing. Many scaffolds displayed drug-like properties, including high intestinal uptake and high metabolic stability, demonstrating their potential suitability for oral administration and a wider range of drug targets than currently accessible to known boron compounds. Lead compounds are currently undergoing structure optimization.

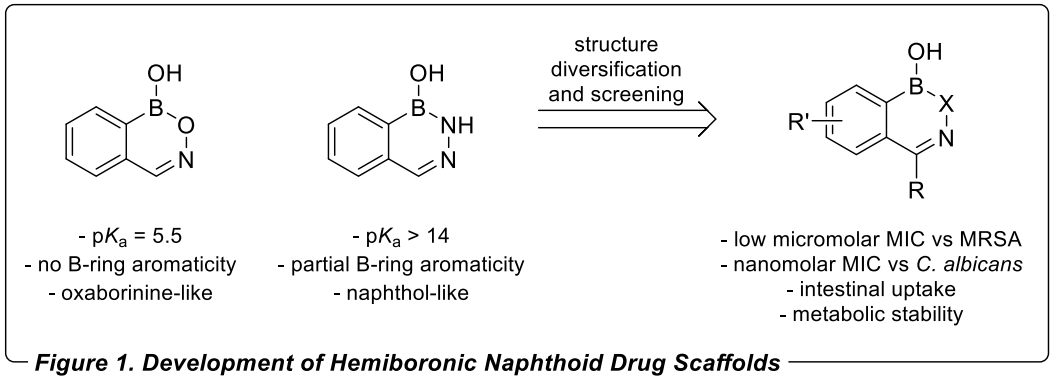

Figure 1. Development of Hemiboronic Naphthoid Drug Scaffolds

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Poster 35

REACTIVITY OF COINAGE METAL COMPLEXES SUPPORTED BY TETRAMETHYLGUANIDINYL TRIPHENYL STIBINE AND BISMUTHINE LIGANDS TOWARDS NITRENE TRANSFER CHEMISTRY

Meenakshi Sharma, Reece M. Fritz, Amitava Choudhury, Pericles Stavropoulos*

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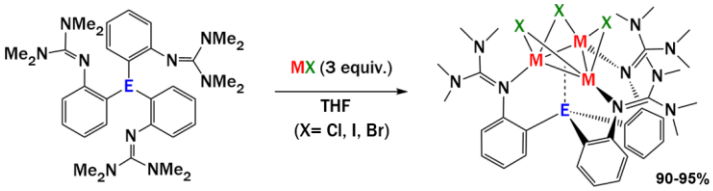
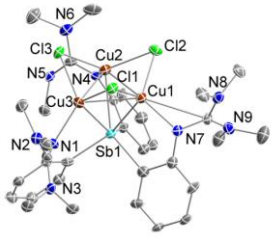
Transition-metal catalyst frameworks supported by tripodal [TMG_3trphen] ligands mediate nitrene transfer from nitrogen sources such as PhI=NR (PhI=NTs or PhINTces) to a diverse group of aliphatic and aromatic hydrocarbons and olefins. These reactions are categorized as amination and aziridination reactions. Novel tripodal ligands and their complexes with late first- and second-row transition metals (Cu, Ag, Au) with different axial atoms such as CH, Sb and Bi and benzene platform have been designed to impart weaker axial ligand field, which, in turn, enhances the electrophilicity of nitrene, potentially affording more reactive and site-selective aminated products.

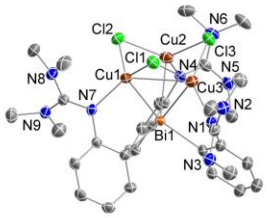
The trinuclear copper catalysts [TMG_3trphenSb$Cu_3(\mu_2\text{-}Cl)_3$] and [TMG_3trphenBi$Cu_3(\mu_2\text{-}Cl)_3$] have shown promising results towards aziridination of substituted styrenes with excellent yields while the reactivity of the silver catalyst [TMG_3trphenSb] Ag_3Cl_3 is comparatively low. The copper complexes are also reactive for the selective amination of various hydrocarbons at benzylic and tertiary C–H sites. The congener of [TMG_3trphenSb$Cu_3(\mu_2\text{-}Cl)_3$], [TMG_3trphenSb$Cu_3(\mu_2\text{-}Br)_3$] [TMG_3trphenSb$Cu_3(\mu_2\text{-}I)_3$] have also been synthesized to obtain comparative data for the catalytic reactions mediated by nitrene generated *in situ*.



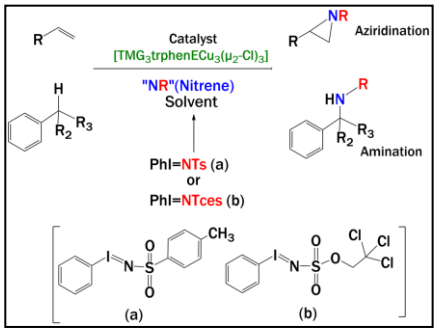
Scheme1. Synthesis of [TMG_3trphen$EM_3(\mu_2\text{-}X)_3$].



[TMG_3trphenSb$Cu_3(\mu_2\text{-}Cl)_3$]



[TMG_3trphenBi$Cu_3(\mu_2\text{-}Cl)_3$]



Scheme2. General scheme of aziridination and amination.

[1] Sharma, M., Choudhury, A., Stavropoulos, P., *Manuscript under preparation.*

Poster 36

Cationic Cobalt (I) Catalyzed Ligand controlled Chemo-,Regio-, and Enantioselective Cycloaddition Reactions between 1,3 Dienes and Alkynes.

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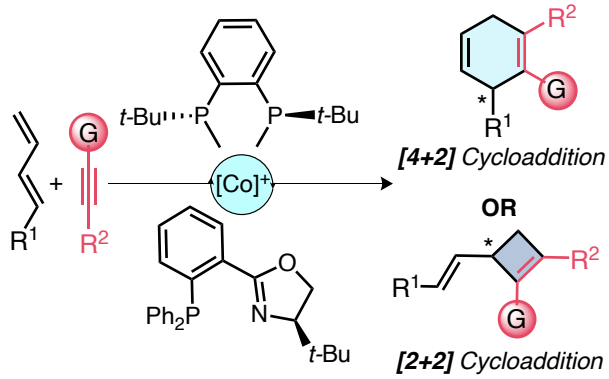
Asymmetric synthesis of valuable organic intermediates such as cyclobutenes and cyclohexadienes has garnered significant attention in recent years. This can be attributed to the capability of these intermediates to be tailored for synthesis of complex organic molecules relevant to medicinal, agricultural, and material applications. Strategies such as base metal catalyzed chemo-, regio- and especially enantioselective union of readily available starting materials such as dienes, and alkynes can provide quick access to these intermediates. Two very powerful reaction that can be envisioned between 1,3-dienes and alkynes, are [2+2] and [4+2] cycloaddition ,both of which have attracted significant attention because of their ability to forge multiple carbon-carbon bonds in a highly selective fashion. However, in the realm of alkyne chemistry the full potential of neither of these cycloaddition reactions have been realized. With no reports of a 1,3-diene reacting chemoselectively as a 2π-component with an alkyne. As for a diene reacting as 4π-component, chemoselective [4+2]-cycloaddition to yield chiral 1,4 cyclohexadienes, the scope is highly limited with prohibitively expensive Rh-based catalyst. To achieve divergent reactivity in cycloaddition reactions between 1,3- dienes and alkynes, we devised a cationic Co(I) catalytic system by finely tuning the electronics as well as sterics of the ligand employed on the metal center, to access both these cyclic motif in highest form of selectivity from same starting material. We found that smaller bite angle bis-phosphine ligands <93° favor [4+2] cycloaddition reaction, whereas large bite angle bis-phosphine ligands favor never known before [2+2] cycloaddition reaction. This excellent selectivity complimented with moderate to good yields provided us with broadly applicable protocol for synthesis of diversely substituted enantiopure cyclic motifs with ee upto 99%. The scope of this method has been expanded over a variety of simple aliphatic, aromatic, heteroaromatic 1,3-dienes and alkynes bearing a whole range of functional groups.



>40 examples with *er* up to 99.5:0.5 for [4+2] and 98:2 for [2+2]

Wide functional group tolerance: R^1 = Alkyl, aryl, R^2 = Alkyl, aryl, CO_2Me, G = CO_2R, C(O)R, $C(O)NR_2$

Poster 37

VISION-GUIDED, HIGH-THROUGHPUT LIQUID-LIQUID EXTRACTION SCREENING

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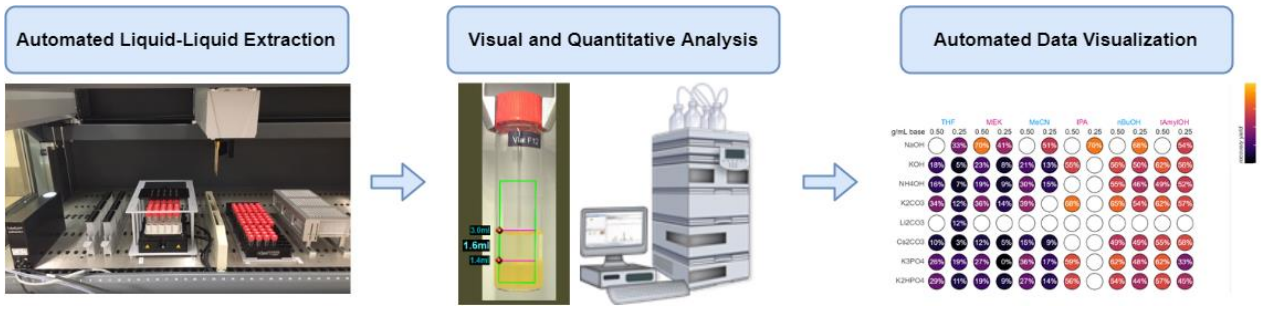
In a small molecule manufacturing process, optimization of workup parameters is critical for reducing plant operational costs, cycle time, and process mass intensity (PMI). However, identifying appropriate conditions for workup procedures, such as liquid-liquid extractions (LLE), can often be both time and operationally intensive. To address these challenges, we have developed a novel automated platform to enable rapid optimization of LLE conditions. This presentation will highlight a data-rich approach to screening workup conditions by leveraging high-throughput experimentation and automation. Direct application of this platform in recent pipeline projects will also be discussed. Notably, application of this automation platform has enabled access to workup conditions that provide access to greener solvent conditions, reduced PMI, and enhanced robustness across the overall process.



Poster 38

REGIODIVERGENT HYDROSELENATION OF ALKENES

Hannah S. Slocumb,[†] Gabriel S. Phun,[†] Shaozhen Nie,[‡] Cheyenne A. Antonio,[†] Dima A. Fishman,[†] Filipp Furche,[†]* Vy M. Dong,[†]* Xiao-Hui Yang[§]*

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Despite selenium's interesting chemical properties, it has from far fewer synthetic methods than its chalcogen cousins, oxygen and sulfur. To widen the scope of selenide synthesis, we envisioned a regiodivergent hydroselenation of styrenes and simple alkenes to afford the Markovnikov and *anti*-Markovnikov addition products (Fig. 2). Interestingly, we found that a Rh-precatalyst and MeO-BIPHEP ligand could afford the enantioenriched Markovnikov adduct,[1] while simply shining blue light on the starting materials with catalytic diselenide gave the *anti*-Markovnikov adduct.[2] The Rh-catalyzed reaction mostly requires styrenyl alkenes, however does show tolerance for a number of functional groups including halides and heterocyclic styrenes. The light-promoted reaction can also be undergone by simple alkenes and dienes in addition to styrenes, and can even tolerate functional groups such as carboxylic and boronic acids. Both reactions require the use of aryl selenols. The Rh-catalyzed pathway is shown to involve a Rh–H intermediate generated from oxidative addition into the Se–H bond. Using UV-visible spectroscopy, we identified the photoactive agent in the light-promoted reaction as diselenide, which contaminates commercial selenol samples in 3-10 mol% due to spontaneous dimerization from light or oxygen. Based on this, we theorized a homolytic cleavage event of the diselenide and subsequent addition to the alkene. Interestingly, the reaction shows high selectivity for the *anti* addition product, showing that the aryl selenide imparts high diastereoselectivity on the reaction.

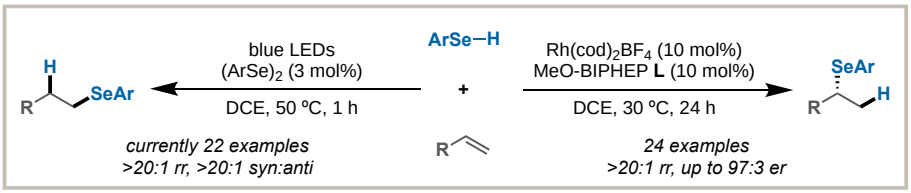

Figure 2. Both the enantio- and regioselective Markovnikov hydroselenation of styrenes and the regioselective *anti*-Markovnikov hydroselenation of alkenes.

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Poster 39

ENANTIOSELECTIVE NICKEL-CATALYZED α-SPIROCYCLIZATION OF LACTONES

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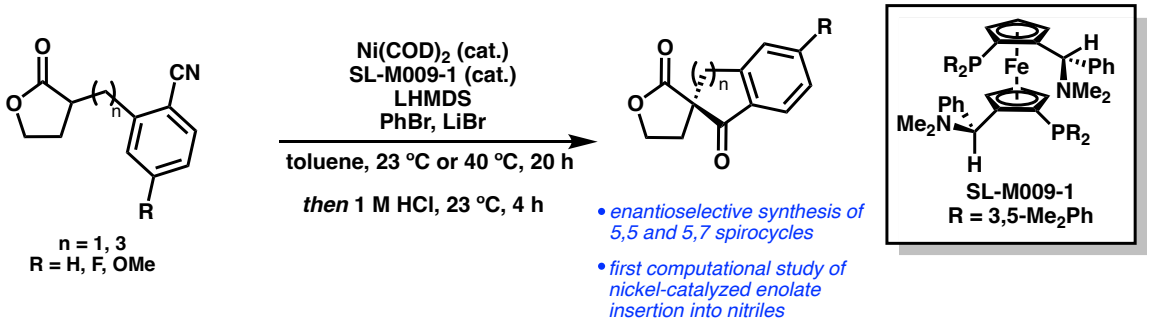
Spirocycles are omnipresent structural motifs in natural products, chiral ligands, and drug compounds.[1] Despite their relevance, methods for the enantioselective synthesis of these ring systems are limited, necessitating costly chiral separations and limiting the accessibility of spirocyclic scaffolds for medicinal chemistry.[2] Moreover, spirocycles containing chiral quaternary carbons as the spiro center are particularly challenging to synthesize, owing to the difficulty of installing all-carbon quaternary centers enantioselectively.[3] Herein we disclose an enantioselective nickel-catalyzed α-spirocyclization of lactones. The method provides access to spirocycles bearing all-carbon quaternary centers, forming 5 and 7-membered rings in good yields and enantioselectivities. Mechanistically, it is proposed that C–C bond formation occurs via insertion of a nickel enolate into a nitrile, giving rise to *N*-aryl imine products. Hydrolysis of the *N*-aryl imine upon workup affords spirocyclic β-keto lactones. The spirocyclization method described herein represents a rare example of nickel-catalyzed enolate insertion into a nitrile, prompting us to study the mechanism of this transformation computationally. Combining the power of computational analysis with organometallic studies, we aim elucidate the mechanism of nickel-catalyzed C–N insertion and understand the origin of enantioselectivity. Additionally, these mechanistic insights will inform the reaction optimization process and serve to improve the generality of the method, providing access to diverse spirocyclic scaffolds.



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Poster 40

A CROSS-ELECTROPHILE COUPLING APPROACH TOWARDS A CONVERGENT SYNTHESIS OF ISODOCARPIN

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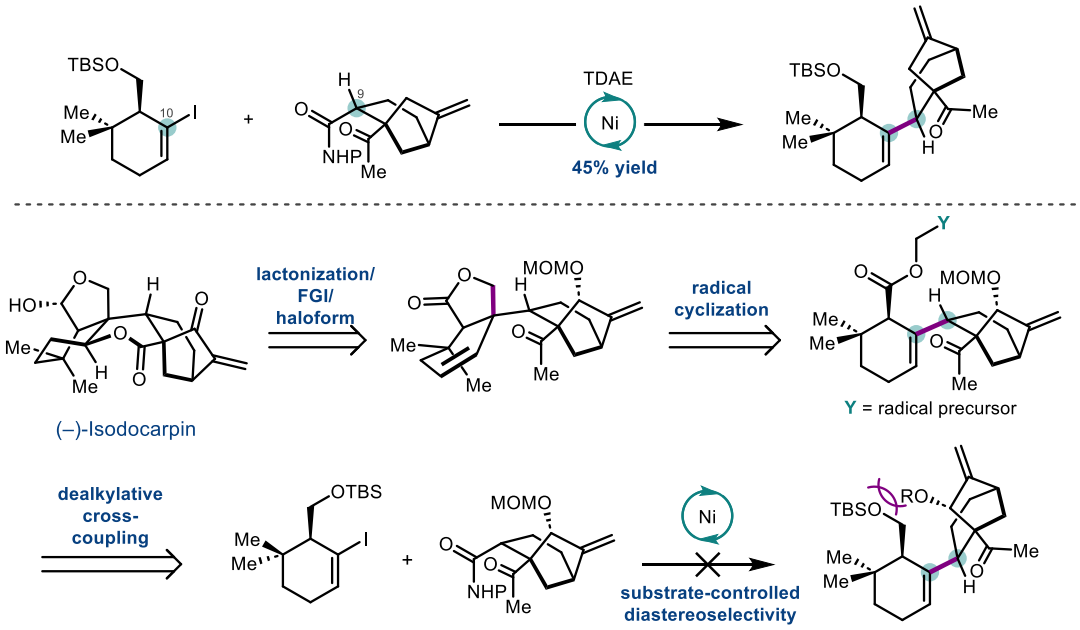
Ent-kaurene diterpenoids exhibit rich biological activities and intriguing structural complexity and have been popular targets for biological and synthetic studies.[1] Despite progress in the synthesis of *ent*-kauranoids, successful syntheses of compounds in the highly oxidized enmein-type subclass are very limited.[2,3] We herein report our progress towards the synthesis of the enmein-type *ent*-kauranoid isodocarpin. Retrosynthetically, the molecule is dissected through the central C ring to give equal sized fragments that can be joined via C9/C10 bond formation. A mechanism-driven optimization of a Ni-catalyzed reductive cross-electrophile coupling enabled formation of the sterically congested key C-C bond. Current work focuses on the optimization of the diastereoselectivity via a computation-guided substrate engineering approach that utilizes the oxidation pattern of isodocarpin to disfavor the undesired diastereomer and Design of Experiment (DOE) studies to optimize the ligand for the reaction.



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Poster 41

HARNESSING MACHINE LEARNING TO STREAMLINE REACTION OPTIMIZATION

Olivia Taylor and Brennan McManus, Lang Cheng Hung, Kyle Arriola, Robert Bradley, Ana Bahamonde*.

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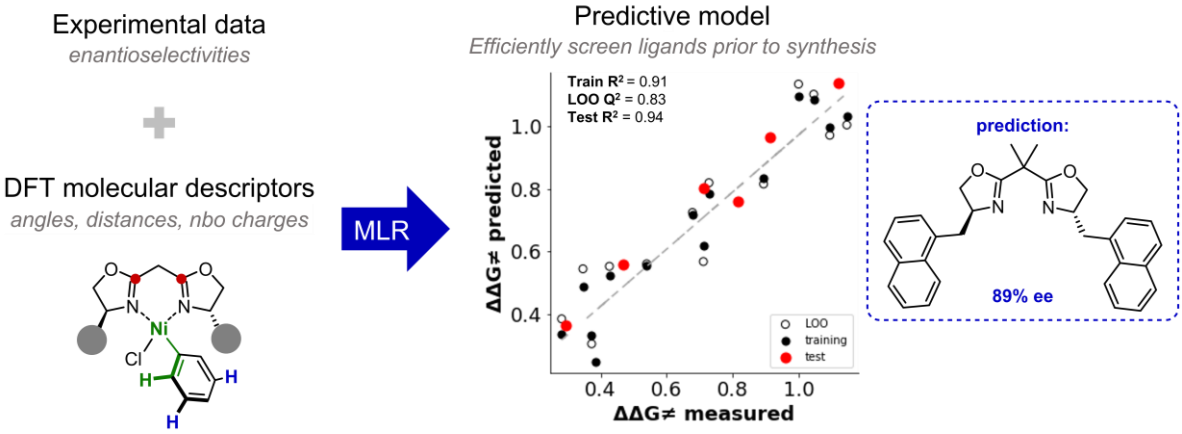
We are working to render the Ni/photoredox-catalyzed α-arylation of oxygen heterocycles enantioselective by identifying an optimal chiral ligand through a machine-learning based approach.[1] This is being accomplished through the use of a multivariate linear regression analysis strategy pioneered by the Sigman lab, which merges experimentally determined enantioselectivities and DFT-derived numerical descriptors to generate a predictive model.[2] The model we developed has been used to screen a vast array of Ni(II)PhCl complexes bearing a variety of bis-oxazoline (BOX) ligands prior to embarking on their synthesis. The current model indicates that the dihedral angles relating the phenyl ligand to the Ni center as well as NMR parameters of the phenyl hydrogen atoms and sp^2 hybridized carbon atoms on the ligand are important for determining the enantioselectivity of the reaction. This information provides useful insight into the enantioselectivity determining step of the reaction and guides the design of ligands to be screened *in-silico*. Based on the model, a BOX ligand bearing naphthyl substituents is predicted to facilitate a reaction with 89% ee. This ligand will be tested experimentally, and the outcome will be used to validate the model.



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Poster 42

RECENT ADVANCES IN HETEROCYCLE SYNTHESIS AND FUNCTIONALIZATION IN THE DISCOVERY PROCESS RESEARCH GROUP AT JANSSEN

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Within the Discovery Process Research (DPR) group at Janssen, efficient heterocycle syntheses and functionalizations are key to achieving success. In general, chemistry problem-solving forms the foundation to deliver against our goals, which include: contribute to Medicinal Chemistry program strategy and execution, enable and inspire broad structure–activity relationship studies, deliver bulk intermediates, and define the synthetic route for transition to preclinical development. This poster will present recent Janssen DPR group publications aimed at establishing novel heterocyclic chemistry and demonstrate the impact of these advances on the drug discovery process.

Poster 43

ZINC MEDIATED ONE-POT REDUCTIVE ACYLATION AND SILYLATION OF VARIOUS ELECTRON RICH *P*-QUINONES

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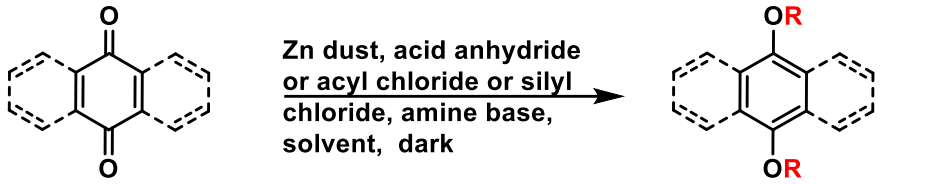
Quinone reduction is a commonly utilized reaction in nature for the formation of biologically active molecules. Hydroquinone variants are typically challenging to isolate and characterize when reduced from the parent *p*-quinone due to rapid oxidation, especially for electron rich systems. It can also lead to the formation of often complex undesired products. Methods for reducing and trapping the parent *p*-quinone derivatives provide an effective way to obtain protected hydroquinone species that may be suitable for use as a prodrug. Currently, research has shown successful one-pot reductive acylation and silylation on simple quinones but has yet to work on large electron rich acenes[i]. Research has also shown that ester protected reduced phylloquinone (vitamin K_1) and menaquinone (vitamin K_2) derivatives are capable of prodrug delivery as antitumor agents or skin therapy[ii,iii]. We report here a zinc-mediated one-pot reductive silylation and acylation of various *p*-quinones to obtain photosensitive protected hydroquinone derivatives in high yields. Characterization of these O-protected reduced hydroquinones will allow for further investigation into the development and future design of photosensitive protected hydroquinone prodrug molecules in pharmaceutical applications.



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Poster 44

Green Synthesized and Antimicrobial activity of Substituted Benzoxazole-Chromenes containing Arylsulfonamide Derivatives

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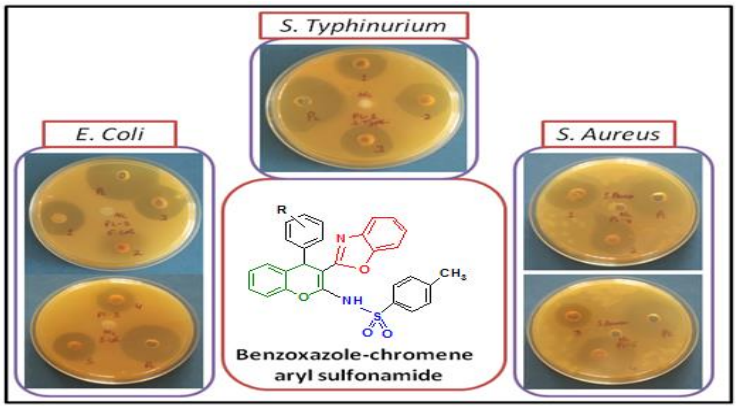
Corresponding Author: ajay.tiwari1591@gmail.com

Abstract: A group of arylsulfonamide derivatives were synthesized by three steps process using chemical catalyst in less solvent at ambient temperature. One of the reactions in whole process having multi-component reaction (MCR) which proceeds green synthesis, through Knoevenagel condensation followed by Michael addition of versatile reactants (1mmol) react in presence of L-Proline up to 6-8 hrs at pH 7.2±0.2 and 60±1°C to formed substituted heterocyclic products**.** Amino containing heterocyclic compound (1mmol) react with tosyl-Cl (1mmol) in presence of K_2CO_3 at 0°C to be prepared Benzoxazole-chromene containing aryl sulfonamide (BCS) and its derivatives structural characterized through TLC, UVvis, FTIR and ^{1}H-NMR. These synthesized compounds were evaluated against photogenic bacterial strains (Gram positive and Gram negative) to obtained promising antibacterial results. Perusal of tables clearly indicates that BCS_2, BCS_5, BCS_6 and BCS_{10} derivatives exhibited very good activity at different concentration are statistically significant. BCS derivatives exhibited better activity against *E. coli* as compared to *S. aureus* and *S. typhinurium.*

Keywords: Multi-component reaction (MCR), green synthesis, heterocyclic, Benzoxazole-chromene containing aryl sulfonamide (BCS), antibacterial, significant.



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Poster 45

STRUCTURE-BASED DESIGN OF BPTF BROMODOMAIN INHIBITORS AS A NOVEL APPROACH FOR ANTI-CANCER THERAPY

Chun-Ju Tsou and William Pomerantz*

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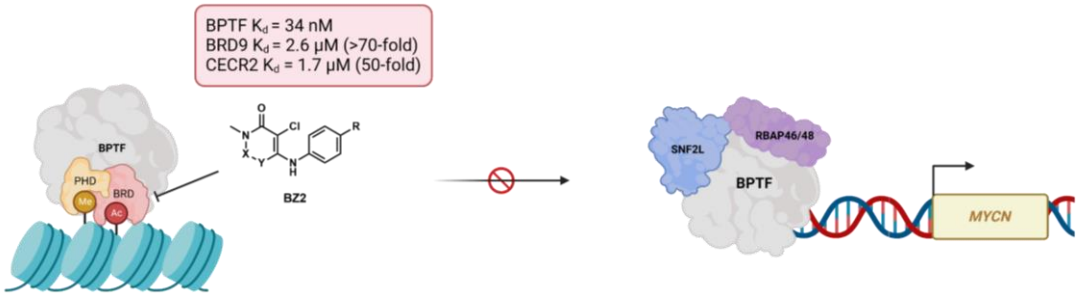
Post-translational histone modification is one of the most common epigenetic regulatory mechanisms that modifies chromatin structure and affects gene expression. BPTF (Bromodomain PHD Finger Transcription Factor), the largest subunit of NURF (Nucleosome remodeling complex), is an epigenetic reader protein that recognizes histone acetylation on H4K16ac through its bromodomain. Overexpression of BPTF is associated with several human cancers and has been correlated with poor patient prognosis. While mechanisms vary based on cancer type, many involve protein-protein interactions (PPI) transcription factors such as c-MYC, and MITF.[1,2] In the pediatric cancer, neuroblastoma, we found that knockdown of the BPTF protein also affects c-MYC and MYCN expression. To study its biological functions and molecular mechanisms within protein complexes, several BPTF bromodomain inhibitors have been developed in the Pomerantz lab,[3] including our newest inhibitor BZ2. BZ2 is a selective molecule with high affinity towards BPTF (K_d = 34 nM) and >10-fold selectivity over other class I bromodomain-containing proteins, CECR2, GCN5, and PCAF, and found to impact the growth of the neuroblastoma cell line via inhibiting MYCN protein levels. In addition to small molecules, BPTF bromodomain inhibitor-based degraders will be synthesized and optimized to evaluate the effect of BPTF modulation in various disease models.[4]



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Poster 46

TARGET IDENTIFICATION EFFORTS TO UNDERSTAND SMALL MOLECULE MEDIATED UNSILENCING OF PATERNAL *UBE3A*

Anna Welton-Arndt[1], Hanna Vihma[2], Ben Philpot[2,*], and Jeffrey Aubé[1,3,*]

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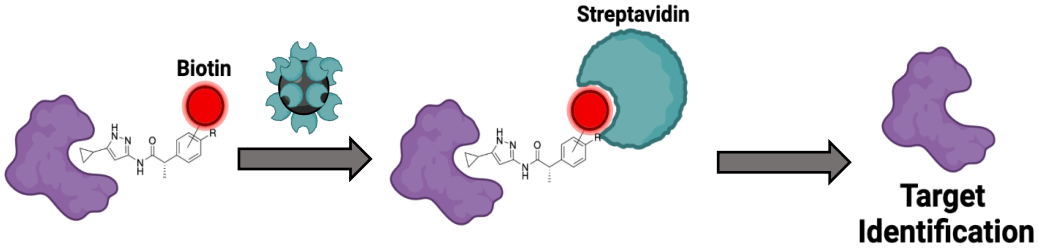
Angelman syndrome (AS) is a rare and severe neurodevelopmental disorder that occurs when the maternal copy of *UBE3A (UBE3A^m)* is deleted or deleteriously mutated. AS patients have a functional copy of paternal *UBE3A (UBE3A^p)*, although cell-type specific imprinting silences this copy of the gene in neurons.[1,2] Without functional *UBE3A,* the downstream E3A ubiquitin ligase (E6AP) is not functionally expressed in the brain, leading to symptoms including seizures, ataxia, and limited speech development.[2] *UBE3A-ATS* antisense oligonucleotides (ASOs) and several topoisomerase inhibitors have been reported as *UBE3A^p* unsilencers, although poor blood brain barrier penetrance and neurotoxicity pose significant obstacles to their further development as therapeutics. We report the identification of a small molecule that unsilences *UBE3A^p* without inhibiting any topoisomerases, as well as efforts to fully profile its protein interactions in model neurons. We seek to determine how these protein targets are implicated in AS biology with the goal of informing development of a small molecule therapy for AS.



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Poster 47

UNLOCKING ELUSIVE SITE-SELECTIVITY WITH NI/TI DUAL CATALYSIS: BRANCHED-SELECTIVE CROSS-COUPLING OF ALKYL AZIRIDINES AND ARYL IODIDES

Wendy L. Williams[†,‡], Neyci E. Gutiérrez-Valencia[†,‡], Abigail G. Doyle*[†]

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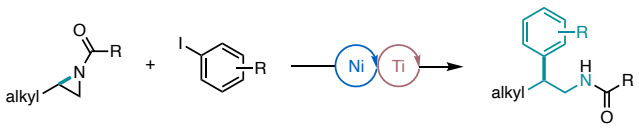
Aziridines are valuable building blocks in organic synthesis due to their ability to undergo ring opening to form β-substituted amines. In particular, arylation of 2-alkyl aziridines by nucleophilic ring opening or transition metal catalyzed cross-coupling enables facile access to biologically relevant β-phenethylamine derivatives. However, both approaches favor C–C bond formation at the less substituted carbon on the aziridine, only allowing access to linear products. This inherent reactivity has rendered the formation of branched arylated products an unsolved problem in alkyl aziridine functionalization. Herein, we address this long-standing challenge and report the first example of a branched-selective cross-coupling of alkyl aziridines with aryl iodides which was enabled by a unique and highly versatile Ni/Ti dual catalytic system. Following the development and optimization of this cross-coupling approach we conducted a comprehensive survey of its functional group tolerance via additive screening. Insights gleaned from this evaluation ultimately guided substrate scope selection, and notably, a variety of alkyl aziridines, were found to be amenable to this branched-selective coupling strategy. Next, we explored the reaction performance on a diverse and succinct aryl iodide scope covering chemical space defined by DFT featurization, dimensionality reduction, and hierarchal clustering. Overall, these studies showcase a highly enabling and robust approach to unlock elusive branched-selective cross-coupling selectivity and demonstrate the power of implementing data science techniques to expedite and guide scope selection.



Poster 48

MEDICINAL CHEMISTRY AT GSK

Tessa Lynch-Colameta

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Medicinal Chemistry at GSK is an interdisciplinary group of chemists whose main objective is to utilize a myriad of data to design new medicines for the advancement to clinical evaluation. We leverage advances in synthetic innovation and technology to deliver molecules that ultimately will have high impact for patients. This poster will highlight the four areas of the medicinal chemistry department, complemented by case studies where impacts have been made through diverse and creative chemistry solutions.

Poster 49

CU- AND RH-CATALYZED ENANTIOSELECTIVE HYDROFUNCTIONALIZATIONS TO FORM CHIRAL KETONES AND PYRAZOLES

Mengfei Xu, Josie M. Warnica, Minghao Wang, Vy M. Dong*

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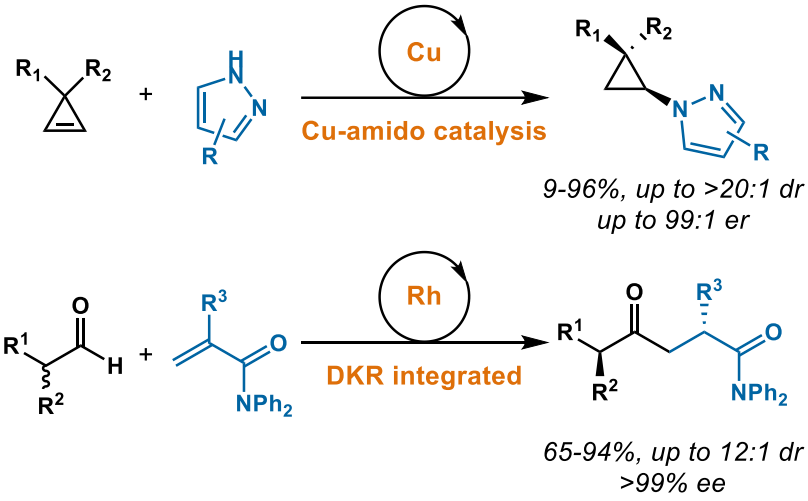
Transition-metal catalyzed hydrofunctionalization of alkene represents one of the most powerful and efficient strategies to construct a new C-H bond with a new C-Y (Y = H, C, B, O, N, Si, P, etc.) bond.[1] Starting with achiral or racemic materials, asymmetric hydrofunctionalizations allow synthesis of highly enantioenriched molecules. Herein, we report two enantioselective hydrofunctionalizations: 1) a Cu-catalyzed hydroamination of cyclopropenes with pyrazole motifs, and 2) a Rh-catalyzed hydroacylation of acrylamides with unfunctionalized aldehydes. The hydroamination features underexplored Cu-amido catalysis that leads to moderate to high enantioselectivity. The reaction also shows a unique regioselectivity, as the more hindered N is favored upon addition. The intermolecular hydroacylation integrates dynamic kinetic resolution (DKR) through rapid racemization of alpha-substituted aldehydes, therefore, giving access to 1,4-dicarbonyl compounds while setting two stereocenters in one step.



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Poster 50

Accelerated Discovery of Block Copolymers through Automated Chromatography

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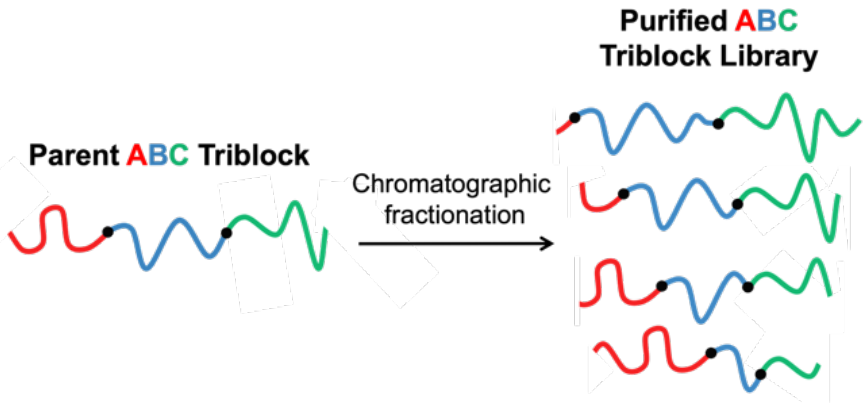
Block copolymers are an important class of materials that self-assemble into a variety of nanoscale morphologies with widespread applications. Block sequence and monomer design play key roles in their self-assembly, but the vast design space complicates the exploration of structure– property relationships. Here, we report a versatile and scalable strategy based on a combination of controlled radical polymerization and automated chromatography to accelerate the discovery of block copolymer phase behavior on multigram scales with excellent mass recovery. Fractionation of a small number of as-synthesized samples gives rise to large polymer libraries spanning a wide range of compositions. Small angle X-ray scattering reveals fractionation significantly enhances long-range order compared to as-synthesized materials and enables the preparation of detailed phase diagrams. This user-friendly and scalable automated separation strategy coupled with controlled polymerization significantly increases the availability of well-defined diblock and higher order multiblock copolymer libraries which are designed to tune the structures and properties of soft materials.[1]



[1]**Murphy, E.A.**; Chen, Y-Q.; Albanese, K.; Blankenship, J.R.; Abdilla, A.; Bates, M.W.; Zhang, C.; Bates, C.M.; Hawker, C.J. *Macromolecules* **2022**, *55 (19)*, 8875–8882.

Poster 51

PROGRESS TOWARDS THE TOTAL SYNTHESIS OF STRASSERIOLIDE D

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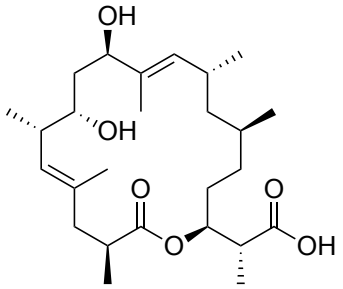
We describe the progress towards the total synthesis of strasseriolide D via a convergent synthesis. Strasseriolides A–D were isolated in 2020 from the fungal strain *Strasseria geniculate*.[1] We recently reported the first total syntheses of A and B with LLSs of 16 and 17 steps, respectively.[2] Strasseriolides B and D showed potent antimalarial activity against drug-sensitive and drug-resistant *P. falciparum* parasites. Later in vivo studies evaluated the treatment of strasseriolides A, B, and D in mice and found strasseriolide B to be acutely toxic while strasseriolide D displayed no cytotoxicity and significant inhibitory activity.[3] We are now investigating a synthetic strategy to provide material for further investigation of strasseriolide D's antimalarial activity. A summary of the synthesis of the eastern fragment and a thorough description of the western fragment will be presented. The eastern and western fragments are envisioned to coupled through a Yamaguchi esterification and the synthesis will be completed via an NHK macrocyclization.



Strasseriolide D

1. Annang, F.; Pérez-Moreno, G.; González-Menéndez, V.; Lacret, R.; Pérez-Victoria, I.; Martín, J.; Cantizani, J.; de Pedro, N.; Choquesillo-Lazarte, D.; Ruiz-Pérez, L. M.; González-Pacanowska, D.; Genilloud, O.; Vicente, F.; Reyes, F. *Org. Lett.* **2020**, *22*, 17, 6709–6713.
2. Annang, F.; Pérez-Moreno, G.; Díaz, C.; González-Menéndez, V.; de Pedro Montejo, N.; del Palacio, J. P.; Sánchez, P.; Tanghe, S.; Rodriguez, A.; Pérez-Victoria, I.; Cantizani, J.; Ruiz-Pérez, L. M.; Genilloud, O.; Reyes, F.; Vicente, F.; González-Pacanowska, D. *Malar. J.* **2021**, *20*, 1, 457.
3. Salituro, L. J.; Pazienza, J. E.; Rychnovsky, S. D. *Org. Lett.* **2022**, *24*, 5, 1190-1194.

Poster 52

Identification and optimization of a series of novel ERK/NLK inhibitors with potent antitumor efficacy in vitro and in vivo

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We sought to identify compounds that in combination with an mTOR kinase inhibitor (TORKi), would convert the growth inhibitory effect of mTOR pathway inhibition into an apoptotic effect. Towards this goal, we undertook an HTS screen using a NSCLC derived cell line in the presence of the TORKi CC-223. This cell-based screen and subsequent structure activity relationship (SAR) campaign identified a series of potent and selective ERK/NLK kinase inhibitors. Compounds in this series demonstrate potent antiproliferative efficacy, both in vitro and in vivo and were found to be targeting three tumor cell survival pathways: MAPK, Wnt, and Hippo. Compound synthesis, SAR optimization, in vitro and in vivo efficacy data will be reported.

Poster 53

PCET-ENABLED INTERMOLECULAR HYDROAMINATION OF ALKENES WITH SULFONAMIDES, SULFAMIDES, AND SULFAMATES

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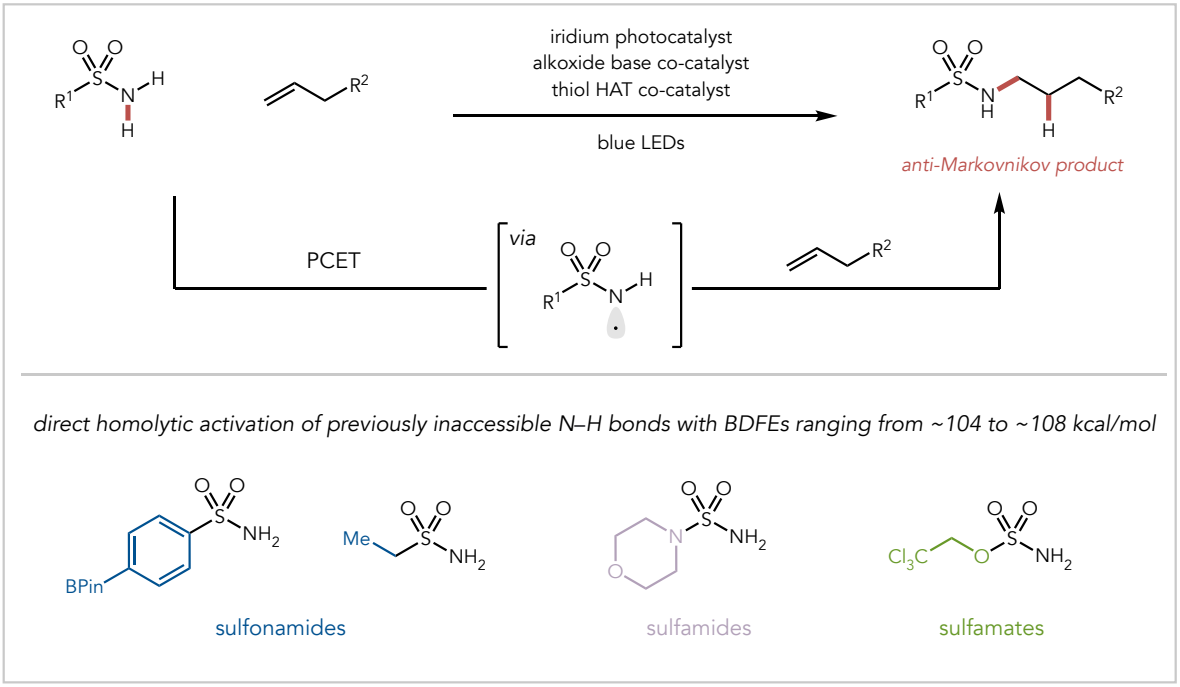
Sulfonamides and their sulfur(VI) analogues, such as sulfamides and sulfamates, are important motifs in a variety of agrochemicals and pharmaceuticals. However, current methods for obtaining secondary sulfonamide scaffolds from primary sulfonamides often rely on pre-functionalized coupling partners, thereby limiting their synthetic utility. In this report, we present a complementary and mild approach for accessing a wide range of desirable secondary sulfonamide derivatives through a light-driven, radical-mediated catalytic intermolecular hydroamination. Reactive sulfonamidyl radicals are proposed as key intermediates, generated through direct homolytic activation of strong sulfonamide N–H bonds through a proton-coupled electron transfer (PCET) mechanism. Notably, this reaction demonstrates a broad substrate scope and successfully couples aryl and alkyl sulfonamides, sulfamides, and sulfamates with alkenes bearing diverse substitution patterns.



Poster 54

STEREODIVERGENT, KINETICALLY CONTROLLED ISOMERIZATION OF TERMINAL ALKENES VIA NICKEL CATALYSIS

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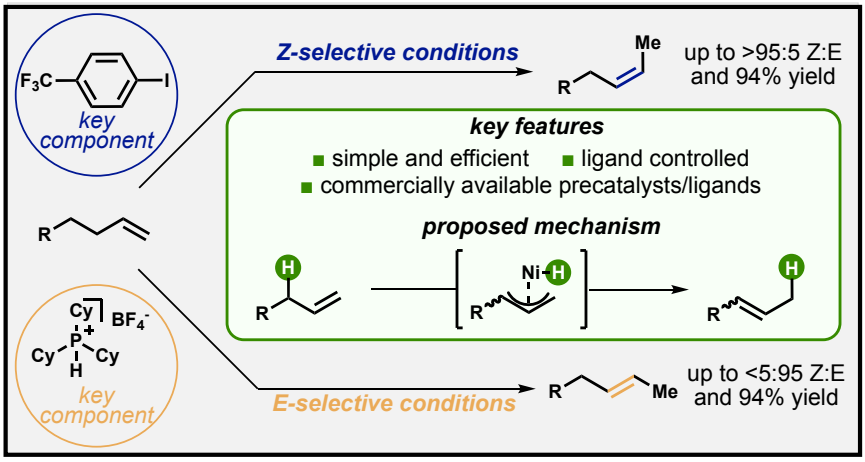
Terminal alkenes are commercial or relatively simple to access, in contrast, internal alkenes are synthetically challenging targets. Metal-catalyzed olefin transposition (i.e., positional isomerization) approaches have emerged to afford valuable *E*- or *Z*- internal alkenes from their complementary terminal alkene feedstocks. However, these methods are often limited in generality of substrate classes and use specialized catalysts or reagents, restricting their applicability. This work presents a nickel-catalyzed platform for the kinetically controlled, stereodivergent *E*- or *Z*-selective synthesis of internal alkenes at room temperature. Conjugated and non-conjugated products containing sensitive functional groups are obtained in high yield and isomeric purity using commercially available catalysts and reagents. Notable mechanistic discoveries include the substoichiometric addition of an aryl iodide to enhance reactivity and selectivity for the synthesis of the *Z*-isomers, and an unusual phosphonium ligand to enhance *E*-selectivity.



Poster 55

AMGEN GREEN CHEMISTRY – INNOVATION AND COMMITMENT FOR ENVIRONMENTAL STABILITY

Sharon Michalak and Lara Zetzsche

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Amgen is committed to increasing the energy efficiency of our chemical processes within the pipeline and to reduce human and environmental hazards. Our cross-functional Green Chemistry Team works to embed the principles and values of green chemistry across the Process Development organization and equip departments with innovative tools to drive sustainability goals. The outcome of these efforts can be seen across Amgen's pipeline. One example of this can be seen with the permeation of biocatalysis into the synthetic pipeline, with a special focus on biocatalytic nitro reduction. In another case study, both the efficiency and sustainability of the commercial synthesis of sotorasib is improved, allowing for dramatic reductions in DCM waste.