Empowering Women in Organic Chemistry Conference 2025

Poster Abstract Booklet

Table of Contents

Information for Attendees

The poster session will be on Friday, June 13, 2025 from 4:45–6:15pm. Session 1 posters will be displayed from 4:45–5:30pm. Session 2 will be displayed from 5:35–6:15pm.

In the List of Posters for Quick Reference below, the location for each poster is given.

On the poster abstracts pages that follow, the session number and poster number can be found in the upper right corner.

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

List of Posters for Quick Reference

Poster Number	Presenting Author	Poster Title
SESSION 1: 4:45–5:30PM		
1	Sabrina Carneiro	Deaminative Fluorination of N-(Hetero)Aryl Sulfonamides Facilitated by Cyclopropenium Adducts
2	Vidya Nadar	Brocazine family of natural products: From total synthesis efforts to targeted chemical screening library construction
3	Allie Paton	CATNIP: Connecting chemical and protein sequence space to predict biocatalytic reactions
4	Isuri Wijesekera	Kinetic control and trapping in the supramolecular polymerization of m-terphenyl bis-urea macrocycles
5	Katie Jane Torma	Chemoenzymatic synthesis of reduced azaphilone natural products and their analogs
6	Reem Al-Ahmad	C–H Functionalization-Enabled 11-Step Semisynthesis of (−)-Veragranine A and Characterization of Synthetic Analogs in Osteoarthritis-related Pain Treatment
7	Dallas Dukes	Redox: A Strategic Guide to Alkaloid Synthesis
8	Carys Obertone	Accessing Sulfonamides via Formal SO2 Insertion into C-N Bonds
9	Young Ju Yun	Discovery of triplet sensitizers using selective photoreactions
10	Josephine Bernard	Total Synthesis of Conidiogenone B
11	Ellie Plachinski	A General Synthetic Strategy toward the Truxillate Natural Products via Solid-State Photocycloadditions
12	Alana Rose Meyer	COMBINED SYNTHETIC, SPECTROSCOPIC, AND COMPUTATIONAL INSIGHTS INTO A GENERAL METHOD FOR PHOTOSENSITIZED ALKENE AZIRIDINATION
13	Bhavana Uppalapati	Linchpin Reagents for the Synthesis of NCO- and NCS-Containing Molecules
14	Lauren Tran	Potent and Biased Peptide Agonists of the PTHR1, a Class B GPCR, from a Heterochiral Design Strategy
15	Jana Enns	SYNTHETIC ANTIMICROBIAL PEPTIDES ACTIVATE MRGPRX2 SIGNALING THROUGH DIFFERENT G PROTEIN SUBUNITS
16	Abby Bracken	Regiospecific Synthesis of Pyrroles from Isoxazoles
17	Brianna Jepsen	PHOTODYNAMIC APPLICATIONS OF ATOMICALLY PRECISE GRAPHENE QUANTUM DOTS
18	Diana Lomowska-Keehner	Engineering Bacterial Terpene Synthases to Produce High Value Pharmaceutical Diterpenoid Precursors
19	Ipshita Roy	CHIRAL PYRROLIDINES VIA AN ENANTIOSELECTIVE HOFMANN LÖFFLER-FREYTAG REACTION
20	Luana Cardinale	Non-Innocent Role of Sacrificial Anodes in Electrochemical Nickel-Catalyzed C(sp2)-C(sp3) Cross-Electrophile Coupling
21	Julianna Mouat	Translation of Nickel-Catalyzed C(sp2)-C(sp3) Cross-Electrophile Coupling to Non-Amide Solvents
22	Julia Pomeroy	Tetracyclic Quinazolinone Scaffold Optimization Leading to Structurally Novel Inhibitors of Highly Lethal, Neuropathogenic Naegleria fowleri Amoeba
23	Julia Dörner	SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIP STUDIES ON BENZYLTETRAHYDROISOQUINOLINES AS AGONISTS FOR G PROTEIN-COUPLED RECEPTORS
24	Reagan Carter	Prochiral Substrate Synthesis and Biocatalytic Oxidations to Access Acyloin Scaffolds and Natural Products

25	Serena DiLiberti	EXPLORING DEFLUORINATION REACTIONS USING POTASSIUM TERT-BUTOXIDE
26	Suha Yacoob	Chemoselective Electrocatalytic Manganese-Mediated Oxygen Atom Transfer to High Potential Organic Molecules
27	Nikki Keramati	Redox-Tunable Ring Expansion Enabled By A Single-Component Electrophilic Nitrogen Atom Synthon
28	Charity Ganskow	Optimization of PTBA analogs as therapeutics for kidney disease
29	Caitlin Vitro	AN ADENYLOSUCCINATE LYASE IN ANTIBIOTIC BIOSYNTHESIS AND BIOCATALYSIS
30	Carmen Magestro	USING A DYNAMIC COVALENT SCREENING METHOD TO EXPAND THE UNLIGANDABLE PROTEOME
31	Pei Hsuan Chen	ΔSulf: A Bioorthogonal pro-amino acid for Introducing Dehydroamino Acids into Peptides & Applications for Anti-Aggregation Therapies.
32	Ruohan Deng	Lewis acid-Promoted Electrocatalytic Turnover of Ti(IV)- oxo Complex for Reductive O-atom Transfer
33	Sagarika Taneja	RHODAMINE-DIPEPTIDE CONJUGATES FOR CELLULAR TRACKING AND DRUG DELIVERY
34	Jihyeon Yeo	Co(III) -Catalyzed Sequential C–H Bond Addition to Dienes and One-Carbon Electrophiles: Syntheses of α-Quaternary Aldehydes and Amides
35	Ningxi Song	Electrochemical Synthesis of C(sp3)Rich Amines by Aminative Carbofunctionalization of Carbonyl Compounds
36	Brittany Klootwyk	Design and Synthesis of Boryl Allyloxy Caged Linkers: Demonstration of Peroxide-mediated Release of a Latent Fluorophore from a FRET Pair
37	Noushin Zahedi	INHIBITION OF ERK/MAPK PATHWAY BY INTRACELLULAR EXPRESSION OF A CIRCULAR RNA INTRAMER
38	Alyssa Olszewski	Design and development of phenanthroline ligands for heteroaryl ketone synthesis via cross-electrophile coupling
39	Holly Hutchinson	N-Substituted 1,4-Dihydropyridines as Novel Scaffolds for 1º Amine Activation
40	Felicia Yu	Energy-Activated and Diversifiable Aryne Precursors from Carboxylic Acids
41	Jillian Hirano	Utilizing Rhodium-(III) Catalysis to Construct Peptide Macrocycles
42	Sophie Perruffel	Improving the efficiency of secondary metabolite extraction in microbes that may produce antibiosis
43	Sunipa Goswami	Cu-Promoted ipso-Hydroxylation of sp2 C-H Bonds with Concomitant Aromatic 1,2-Rearrangement Involving a Cu-oxyl-hydroxo Species
44	Brysa Alvarado	Conformational Tuning of Arylamide Foldamers Using Aromatic Substitution Pattern
SESSION 2: 5:35–6:15PM		
1	Zoe Wachtel	Exploring the Use of Redox for the Formation of Challenging Bonds from Nickel and Palladium Centers
2	Kristen Baker	Synthesis of Benzisothiazoles at a Primary Undergraduate Institution
3	Marla Gravino	Into the Unknown: Covalently Targeting RNA with Electrophilic Warheads
4	Alyssa Bright	SYNTHESIS OF NOVEL 3D CARBON ALLOTROPES: A BOTTOM UP APPROACH
5	Meemie Hwang	Photochemical Cyclization of a-Amino Esters to Access 3-Azetidinones
6	Rachel Shey	IRON-CATALYZED DECARBOXYLATIVE RADICAL ADDITION TOWARD BICYCLO[1.1.1]PENTANE
7	Alisha Doda	PROGRESS TOWARDS EVALUATING THE FUNCTIONAL SELECTIVITY OF ENDOGENOUS D-AMINO ACID-CONTAINING NEUROPEPTIDES
8	Liza Ryutov	Stereoinverted E2 Unlocks Z-selective C–H Functionalization of Terminal Alkenes
9	Meghan Rice	EFFORTS TOWARDS THE TOTAL SYNTHESIS OF BALGACYCLAMIDE C

10	Isabelle Petrucci	ALIPHATIC TRANSMUTATIONS VIA AN INTERRUPTED NITROGEN DELETION
11	Estefania Armendariz-Gonzalez	Cascade Grignard Addition – Propargyl Claisen Rearrangement for the Stereoselective Synthesis of α-Allene Quaternary Centers in Cyclohexanone
12	Gisela Gonzalez-Montiel	LARGE LANGUAGE MODELS (LLMs) FOR REACTION DATA EXTRACTION
13	Cassie Zaremba	Metal Mayhem: Synthetic Efforts Towards Teredinibactin A and Analogs
14	Samantha Barlock	Stereodivergent Assembly of a Common Decalin Intermediate in Complex Terpenoid Architectures
15	Darshika Singh	Rearrangements of oxy-substituted allyl silanes
16	Oluwaseun Adegbite	Design, Synthesis, and therapeutic exploration of novel derivatives of natural products
17	Hilary Kerchner	Sustainability in the Design of Automotive Coatings
18	Jacquelin Zak	LEVERAGING COMPUTATIONAL METHODS TO DEVELOP STEREOSELECTIVE SYNTHESES
19	Catherine Gazolla Santana	Enantioselective Isoprene-Mediated Carbonyl tert-Prenylation via Chiral-at-Ruthenium-SEGPHOS Catalyst
20	Emma Doukmak	Developing Photoaffinity Probes For Dopamine Receptor D2 To Determine Targets Of Parkinson's Disease Drugs
21	Nayani Aloka Amarasooriya Marasinghe Prins	FAVIPIRAVIR ANALOGUES AND COCRYSTALS: SYNTHESIS, PREDICTIONS, AND STRUCTURE-PROPERTY RELATIONSHIPS
22	Chen Mozes Ramrazker	SCREENING DERIVATIVES OF A MULTI-KINASE INHIBITOR REVEALS A SELECTIVE AURORA KINASE A STABILIZER
23	Hannah McFadden	PROGRESS TOWARDS USING ORGANOSILANOL LIGANDS FOR CATALYSIS WITH EARTH ABUNDANT AND TRANSITION METALS
25	Rana Abdu	Utilizing Rare Earth Metal Complexes to Solve Challenges in Organic Synthesis
26	Sydney Cobb	SAR EVALUATION OF HYDROXYQUINOLINONE COMPOUNDS AS 20S PROTEASOME ENHANCERS FOR TREATING ALZHEIMER'S DISEASE
27	Ruoyu Zoe Qian	Enantioselective [2π + 2σ] Photocycloaddition Enabled by Brønsted Acid Catalyzed Chromophore Activation
28	Elizabeth Adams	SYNTHESIS OF A PHOSPHOETHANOLAMINE CELLULOSE GLYCOMIMETIC AND INVESTIGATION OF ITS BIOFILM MODULATING PROPERTIES
29	Julia Viana Bento	C-H FUNCTIONALIZATION OF BENZENE ISOSTERES AT PALLADIUM: CUBANE AND CUNEANE
30	Elsa Hinds	Iron-Facilitated Bi(hetero)aryl formation via N-(2-picolyl)picolinamide complexes
31	Romualda Aquino	Synthesis of Nickel Complexes with para-Substituted Bidentate N-Heterocyclic Carbene Ligands for C–F Activation and NO Reduction
32	Supriya Gupta	RESONANT SOFT X-RAY SCATTERING TO PROBE MOLECULAR ORIENTATION IN POLYMER-GRAFTED NANOPARTICLES
33	Briana Krupinsky	Linear Free Energy Relationships of N-Heterocyclic Carbene-Carbodiimide (NHC-CDI) Adducts with Physical Descriptors
34	Roxane Jourdain	Improving Accessibility for Students with Blindness and Low Vision in the Organic Chemistry Teaching Laboratory
35	Sabrina Reich	Visible-Light Photocatalytic SNAr Pyridination of Aryl Halides and Triflates Utilizing Acridine–Lewis Acid Complexes
36	Maria Gonzalez Esguevillas	IBUZATRELVIR END-GAME JOURNEY: OPTIMIZATION AND SYNTHESIS. FROM DISCOVERY TO EARLY CAMPAIGNS

37	Caroline Roach	HIT IDENTIFICATION, SYNTHESIS, AND OPTIMIZATION OF QUINAZOLINONE-BASED CHIKUNGUNYA VIRUS INHIBITORS
38	Shannon Cartwright	EVALUATION OF SMALL MOLECULE 20S PROTEASOME ENHANCERS AS A THERAPEUTIC FOR HPV+ CERVICAL CANCER
39	Ila Castro De la Torre	SPECIATION OF COPPER (II) ACTIVATION OF CYCLOMETALATED DIRECTED COMPLEXES
40	Stephanie Johnson	ELECTRODES ARE TUNABLE LIGANDS: INVESTIGATING THE ELECTRO-INDUCTIVE EFFECT ON AN ANCHORED POLYMERIZATION CATALYST
41	Rashi Bhatnagar	REDUCTIVELY INDUCED ARYL TRANSMETALATION: A COMPETING MECHANISTIC PATHWAY IN NI-CATALYZED REDUCTIVE BIARYL COUPLING REACTIONS
42	Aina Antony	Enzyme Driven Reaction Discovery and Optimization - The In-Situ Enzymatic Screening (ISES) Approach
43	Jessica Sarmiento	Exploring the Bioactive Potential of Notoincisol A Derivatives Via Sonogashira Cross-Coupling Reaction

Poster Abstracts

DEAMINATIVE FLUORINATION OF N-(HETERO)ARYL SULFONAMIDES FACILITATED BY CYCLOPROPENIUM ADDUCTS

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Leaving groups are central to organic chemistry, facilitating a wide range of substitution reactions. Despite the many available options, the design of new leaving groups remains a dynamic area of research. By developing groups with enhanced selectivity and faster reaction rates, we can enable previously unattainable transformations and broaden the scope of organic synthesis. In this work, we demonstrate that attaching an electrophilic aminocyclopropenium adduct to nitrogen-containing groups enhances their nucleofugality, enabling efficient deamination. Using nucleophilic fluorination of various nitrogen-containing electrophiles as a model, the versatility of this approach was demonstrated.

Our target electrophile is the secondary sulfonamide, particularly N-(hetero)aryl sulfonamides which are prevalent in bioactive molecules and widely commercially available. Despite their ubiquity, breaking the S(VI)–N bond in sulfonamides remains challenging, especially for secondary sulfonamides.[1] We demonstrate that attaching an aminocyclopropenium group to the NH of a secondary sulfonamide creates an electrophilic SO_2^+ surrogate, which can undergo further functionalization to generate sulfonyl fluorides and cyclopropenimines. This method tolerates a wide range of N-alkyl and N-(hetero)aryl secondary sulfonamides, including drug-like compounds (Figure 1). Notably, the conditions developed for secondary sulfonamides also enable deamination of secondary amides, yielding acid fluorides. Overall, this work aims to provide a modular functional handle for the deaminative functionalization of nitrogen-containing molecules.

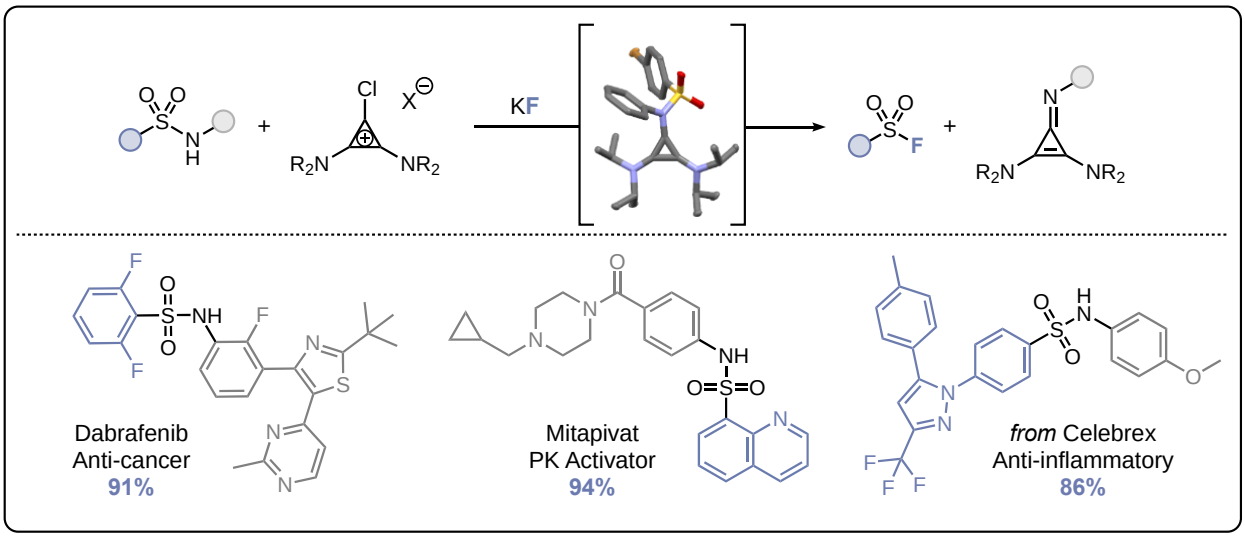

Figure 1. Deaminative Fluorination of Sulfonamide Drugs

[1] (a) *J. Am. Chem. Soc.* 2019, 141, 4, 1441–1445, (b) *J. Am. Chem. Soc.* 2019, 141, 46, 18416–18420 (c) *Angew. Chem. Int. Ed.* 2019, 58, 50, 18235-18239, (d) *Org. Lett.* 2025, 27, 9, 2268–2273

Brocazine family of natural products: From total synthesis efforts to targeted chemical screening library construction

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Natural products have been and continues to be one of the primary sources for discovery of pharmaceutically active compounds. Their total synthesis has given rise to multiple drugs that are primary treatment for numerous diseases. Our lab has been focusing on the brocazine family of natural products isolated from endophytic fungus derived from the marine mangrove plant *Avicennia marina* named *Penicillium brocae* MA-231by Wang and co-workers. Seven different brocazines (A-G) were isolated, and of those brocazine E showed the strongest activity against human pancreatic cancer cell line SW1990 (IC_{50} of 2.1 μM), whereas Brocazine F was shown to possess strongest activity against prostate cancer cell line DU145 (IC_{50} of 1.7 μM) and lung cancer cell line NCI-H460 (IC_{50} of 0.89 μM). Brocazine G showed strong activity against ovarian carcinoma cell line A2780 (IC_{50} of 0.664 μM), Cisplatin-resistant human ovarian cancer cells CisR A2780 (IC_{50} of 0.661 μM) and possesses strong and selective activity against human pathogen Staphylococcus aureus (MIC of 0.25 μg/mL). Other members possess different and interesting biological activity. All members of this family are composed of two unique, but structurally comparable units. Our lab has developed multiple routes to access each of the discrete units of the brocazine family. Coupling these units furnish the carbon framework of brocazine family members. We are currently in final stages to install the disulfide linkage to complete the first total synthesis of brocazine E, F and G. These synthetic efforts will be presented. Furthermore, the route developed allows accessing new targeted small molecule screening libraries. This can be achieved by derivatizing intermediates within the total synthesis route.

CATNIP: CONNECTING CHEMICAL AND PROTEIN SEQUENCE SPACE TO PREDICT BIOCATALYTIC REACTIONS

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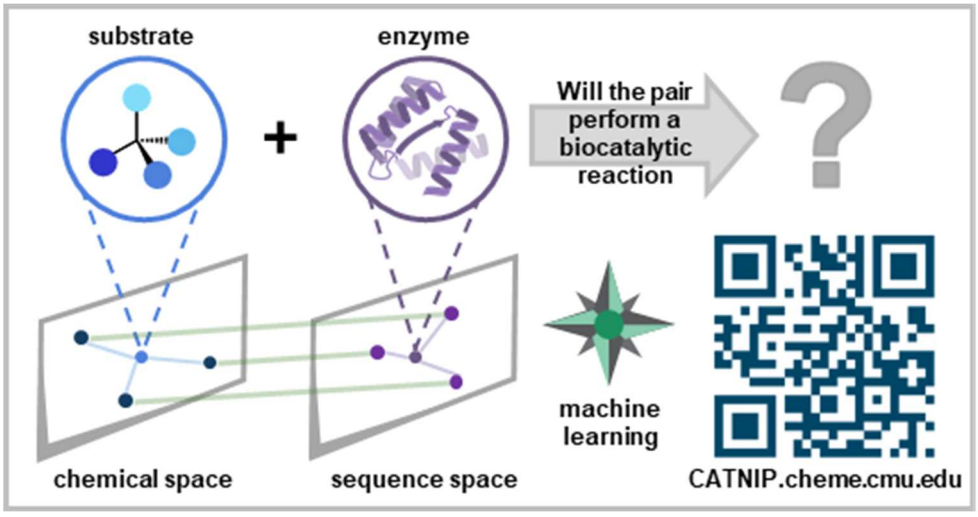
The application of machine learning with biocatalysis has the potential to offer advancements in organic chemistry and synthetic biology, through the development of streamlined target-oriented synthesis with improved sustainability profiles, and by offering insights into relevant small molecule-protein interactions. Despite these implications, biocatalytic strategies can be high risk to implement. Successful execution of this approach requires identifying an enzyme capable of performing chemistry on a specific substrate, which often calls for extensive screening of enzymes for initial reactivity and protein engineering. Strategies for predicting which enzyme is most likely to be compatible with a given small molecule have been hindered by the lack of well-studied biocatalytic reactions. The under exploration of connections between chemical and protein sequence spaces constrains navigation between these two landscapes. Herein, this challenge is addressed in a two-phase effort relying on high throughput experimentation to populate connections between substrate chemical space and biocatalyst sequence space, and the subsequent development of machine learning models that enable the navigation between these two landscapes. Using a curated library of α-ketoglutarate-dependent non-heme iron (NHI) enzymes, the BioCatSet1 dataset was generated to capture the reactivity of >300 biocatalysts with >100 substrates. In addition to the discovery of novel reactivity, BioCatSet1 was leveraged to develop a substrate-to-enzyme workflow, to identify a compatible enzyme for a substrate of interest, an enzyme-to-substrate workflow, to rank potential substrates for a given enzyme sequence, and a substrate-enzyme compatibility predictor, to quantify the likelihood of compatibility between a user input pair. To make these tools accessible to the community, we built CATNIP, an open access web interface to our predictive workflows. We anticipate our approach can be readily expanded to additional enzyme and transformation classes, and will derisk the investigation and application of biocatalytic methods.



KINETIC CONTROL AND TRAPPING IN THE SUPRAMOLECULAR POLYMERIZATION OF *M*-TERPHENYL BIS-UREA MACROCYCLES

Gamage Isuri P. Wijesekera, Isabella G. Rushton, Vaibhavi A. Samant, Fahidat A. Gbadamosi, Md Faizul Islam, Mark D. Smith, Shehani T. Wetthasinghe, Sophya Garashchuk, Linda S. Shimizu*

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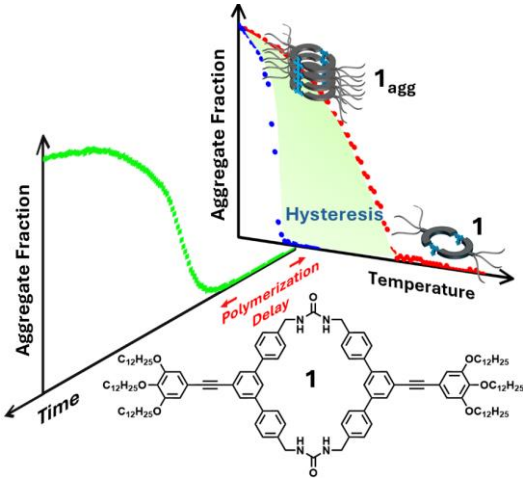
Supramolecular polymerization offers a powerful strategy for designing dynamic, responsive materials, yet controlling polymerization pathways to achieve desired structures remains a challenge. In this study, we investigated and controlled the supramolecular polymerization pathways of a novel m-terphenyl bis-urea macrocycle (**1**) by leveraging pathway complexity. Engineered to promote kinetically metastable states, its concentration-dependent aggregation was examined using ^{1}H NMR and FT-IR spectroscopy in THF and $CHCl_3$. Temperature-dependent UV-Vis spectroscopy in water/THF revealed a cooperative nucleation-growth mechanism, marked by a red shift in λmax upon cooling. Morphological analysis via DLS, AFM, and SEM confirmed fibrous aggregate formation. Thermal hysteresis observed in assembly-disassembly cycles pointed to kinetically trapped species, with cooling governed by kinetic barriers and heating dictated by thermodynamic equilibrium. Discrepancies in ΔH values during cooling, compared to van't Hoff analysis, contrasted with the alignment of heating ΔH values with thermodynamic expectations, further highlighting this distinction. Time-dependent UV-Vis studies also demonstrated polymerization delays due to spontaneous nucleation retardation, emphasizing kinetic control over assembly. Computational studies identified the parallel urea conformation as the more stable monomeric form, while the antiparallel arrangement was preferred in dimers. By exploring pathway complexity in this macrocycle, we highlight a unique ability to control and stabilize kinetically trapped states, expanding the potential for designing macrocyclic supramolecular polymers with customized properties. This study enhances the understanding of supramolecular dynamics, shedding light on ON-pathway mechanisms and advancing tunable supramolecular materials.



Wijesekera, G. I. P.; Rushton, I. G.; Samant, V. A.; Gbadamosi, F. A.; Islam, M. F.; Smith, M. D.; Wetthasinghe, S. T.; Garashchuk, S.; Shimizu, L. S. Kinetic Control and Trapping in the Supramolecular Polymerization of *m*-Terphenyl Bis-Urea Macrocycles. *Chem. Eur. J.* **2025**, e202404552. **VIP Paper** https://doi.org/10.1002/chem.202404552

CHEMOENZYMATIC SYNTHESIS OF REDUCED AZAPHILONE NATURAL PRODUCTS AND THEIR ANALOGS

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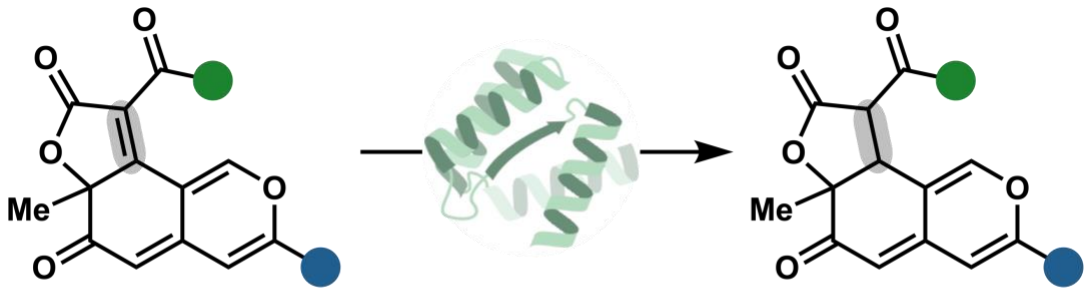
Azaphilones are a large class of fungal natural products of which over six hundred unique molecules have been isolated and characterized. These compounds have been demonstrated to possess a wide range of biological activities such as antifungal, anti-inflammatory, cytotoxic, and antioxidant properties. Therefore, the azaphilone scaffold holds promise for developing bioactive compounds, however, methods to efficiently access more complex azaphilones are underdeveloped. In particular, approaches which leverage late-stage functionalization strategies could be incredibly impactful by enabling the rapid diversification of these cores. A subclass that is prevalent in this natural product family are the reduced azaphilones, however this subclass is difficult to selectively access using traditional chemical methods. This work utilizes a biocatalytic method to selectively achieve reduced tricyclic azaphilone compounds. To obtain the selective reduction of azaphilones, a library of reductase enzymes was built using ancestral sequence reconstruction and sequence similarity networks. Several ancestral enzymes have shown excellent activity on angular and linear tricyclic azaphilones. This work includes the exploration of the substrate scope of these ancestral enzymes while also comparing to a panel of commercial ene-reductases for enzymes that exhibit activity on varying azaphilone cores.



C–H FUNCTIONALIZATION-ENABLED 11-STEP SEMISYNTHESIS OF (−)-VERAGRANINE A AND CHARACTERIZATION OF SYNTHETIC ANALOGS IN OSTEOARTHRITIS-RELATED PAIN TREATMENT

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

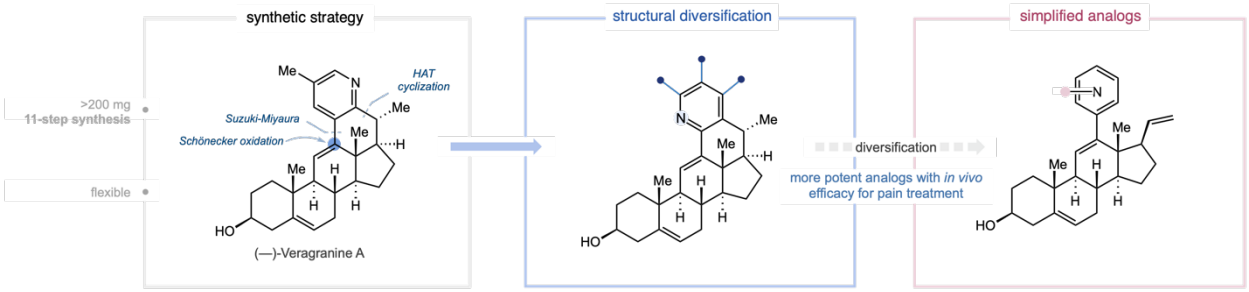

Figure 1. Overview of the synthetic strategy towards (−)-Veragranine A, highlighting the exploration of new chemical space and the development of analogs with enhanced potency compared to the natural product.

References

J. Am. Chem. Soc. 2024, 146, 24, 16698-16705

REDOX: A STRATEGIC GUIDE TO ALKALOID SYNTHESIS

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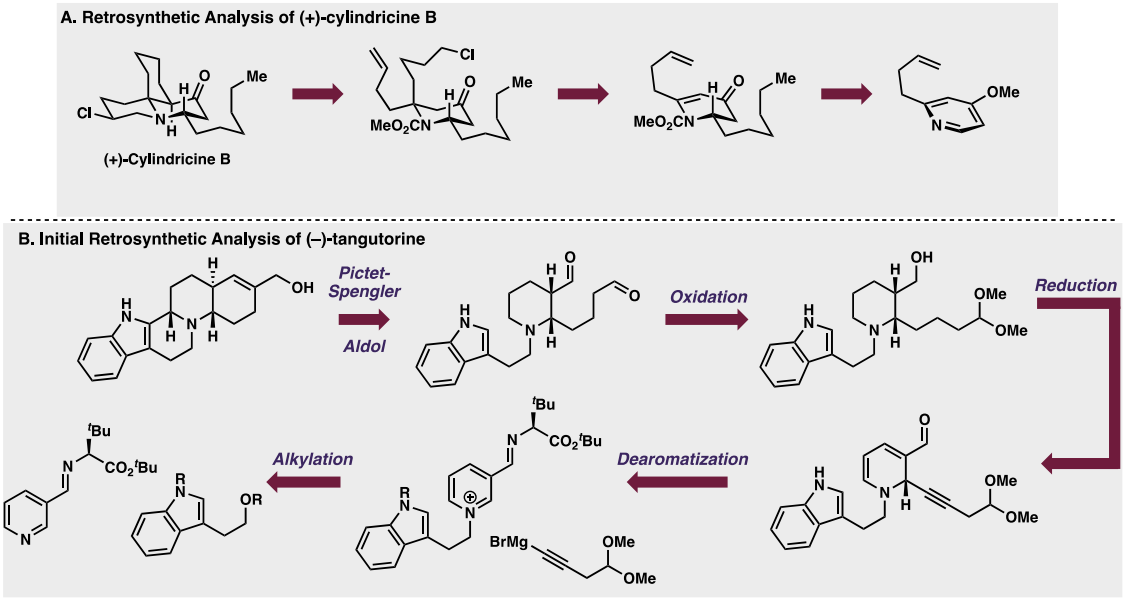
Alkaloid natural products and their derivatives have played a vital role in drug discovery and human health. Thus, their structures serve as a forcing function for the invention of novel synthetic strategies and tactics for molecular assembly. In practice, control of redox economy has been essential for the construction of targets containing basic nitrogen atoms, both in the areas of total synthesis and drug discovery. By utilizing a two-phase synthetic approach to alkaloid total synthesis, our research group has increased the synthetic efficiency by which alkaloids are constructed. Notably, this synthetic platform does not just apply to one biogenetic family of alkaloid natural products, but can be applied broadly, with an emphasis on (1) minimizing oxidative transformations and (2) the rapid assembly, cyclization, and reduction of intermediates that stem from higher oxidation starting materials. My doctoral work has concerned the redox economic synthesis natural products from the morphinan, cylindricine, and tangutorine families.
The presentation describes the first enantioselective synthesis of marine alkaloid (+)-cylindricine B and ongoing research toward a total synthesis of the terrestrial alkaloid tangutorine. Cylindricine B contains a tricyclic scaffold with four stereogenic centers and a polyfunctionalized piperidone core. Our group has leveraged a dearomative approach of high oxidation level starting material to concisely and controllably adorn the core heterocycle with the required functionality which includes a challenging alpha-tertiary amine. This key challenge was addressed through the realization of a rare a Cu-catalyzed 1,4 addition into a N-acyl-dihydropyridone to create the fully substituted center. The scope of this reaction was further explored using various organometallic nucleophiles enabling a novel tactical entry for these crowded moieties. Overall, our enantioselective synthesis of cyclindricine B requires only 5 steps from commercially available starting materials.[1] Additionally, progress towards the total synthesis of the anticancer natural product tangutorine will be presented. The synthesis utilizes glutarimide, as the starting material, and, following appropriate functionalization, leverages a strategic Dies-Alder cycloaddition to build the hexahydroquinoline core of the natural product. It is anticipated that tangutorine will be afforded following alkylation of this core with a protected tryptophol unit followed by a canonical reductive Bischler-Napieralski reaction to afford the unique natural product structure of Tangutorine.



[1]Dukes, D. M.; Atanossov, V. K.; Smith, J. M. *Chem. Sci.*, **2024**, 15, 16554–16558

ACCESSING SULFONAMIDES VIA FORMAL SO_2 INSERTION INTO C-N BONDS

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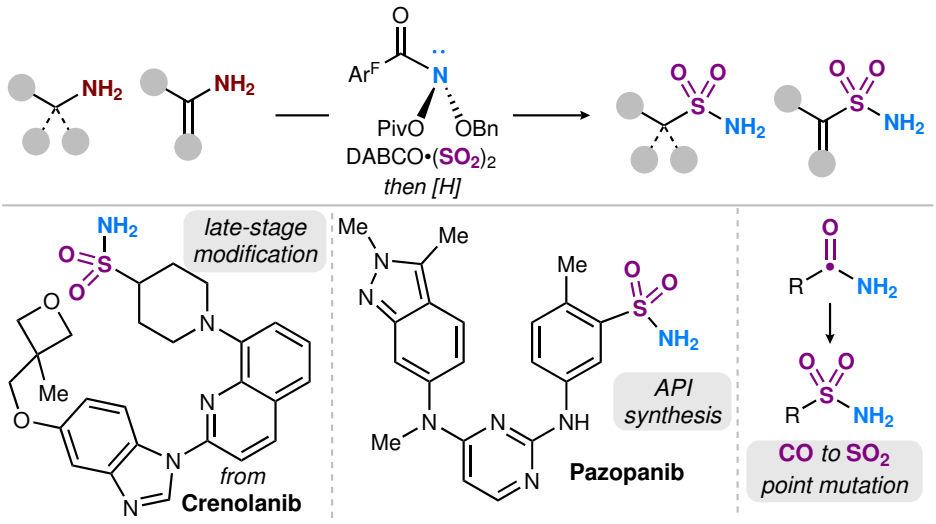
Functional group interconversions are particularly sought after by medicinal chemists as a means to enable both lead optimization and library diversification. Here, we report SO_2-insertion into the C–N bond of primary amines, enabling the direct synthesis of primary sulfonamides without pre-activation and effectively inverting the nitrogen's properties (acidity, hydrogen bonding, etc.). The key to this transformation is the implementation of an anomeric amide as a dual-function reagent which both serves to cleave the initial C–N bond and delivers a nitrogen atom to the product after SO_2 incorporation. The process tolerates a wide array of functionalities and can be run in an automated fashion thus allowing libraries of amines to be viable progenitors to highly desirable sulfonamides. Mechanistic studies support an isodiazene radical chain mechanism that generates an intermediate sulfinate which reacts with the anomeric amide to forge the S–N bond. Our protocol was used to conduct a high-throughput library diversification campaign, was applied to the synthesis and modification of approved active pharmaceutical ingredients and was used to enable a net CO-to-SO_2 "isosteric replacement" approach.



Discovery of triplet sensitizers using selective photoreactions

Young Ju Yun, Zamira K. Harris-Ryden, Jonathan Sklar, Guru P. Neupane, Eric J. Berns, Milan Mrksich, and Julia A. Kalow*

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Despite notable progress in automation and machine learning, traditional techniques for materials synthesis and testing continue to be inefficient, hindering the experimental validation and discovery process. Therefore, to effectively address these difficulties and meet the evolving requirements of society, there is a pressing need to explore and implement innovative approaches. Triplet sensitizers are essential to applications, including photocatalysts, triplet-triplet annihilation photon upconversion (TTA-PUC), and photodynamic therapy (PDT). However, their discovery still largely relies on one-at-a-time synthesis and testing. In this poster, I will discuss a new approach to discovering light-harvesting organic molecules with long-lived excited states that can participate in energy transfer and C–H activation. In our approach, selective photoreactions are used to “tag” triplet sensitizers from ketone libraries designed using cheminformatic analysis. In high-throughput experiments, we isolate and analyze the resulting products using self-assembled monolayer matrix-assisted desorption/ionization mass spectrometry (SAMDI-MS). This poster presentation will summarize our efforts in library design, selective photoreaction development, data analysis and characterization, and the application of the resulting photosensitizers to polymer upcycling.

Total Synthesis of Conidiogenone B

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Antibiotic resistance is a growing global health crisis, demanding the development of novel therapeutic agents. Conidiogenone B, a natural product with significant antibacterial activity, has emerged as a promising candidate. This compound exhibits potent inhibition at 8 µg/ml against drug-resistant pathogens such as MRSA, Pseudomonas, and Staphylococcus, demonstrating activity comparable to Ampicillin without relying on the traditional β-lactam pharmacophore[1]. However, the limited natural availability of Conidiogenone B has impeded extensive biological investigation and development of structural analogs.

Our research focuses on the innovative total synthesis of Conidiogenone B to enable further biological evaluation and modification for enhanced antibacterial properties. This synthetic strategy employs a Johnson-Claisen rearrangement to establish a key all-carbon quaternary center, a challenging feature in complex molecule synthesis. Following this, an intramolecular metal-hydride hydrogen atom transfer (MHAT) cyclization efficiently constructs the core skeletal framework of the natural product.

The synthesis is accomplished in a concise sequence, allowing access to Conidiogenone B in sufficient quantities for further study. Our approach not only provides access to this promising antibacterial agent but also opens the door to the generation of structurally diverse analogs that could exhibit improved therapeutic profiles. This work aims to advance the development of novel treatments for antibiotic-resistant infections by creating new opportunities for chemical innovation in drug design. Through our efforts, we hope to contribute to the growing need for effective and sustainable antibacterial agents.

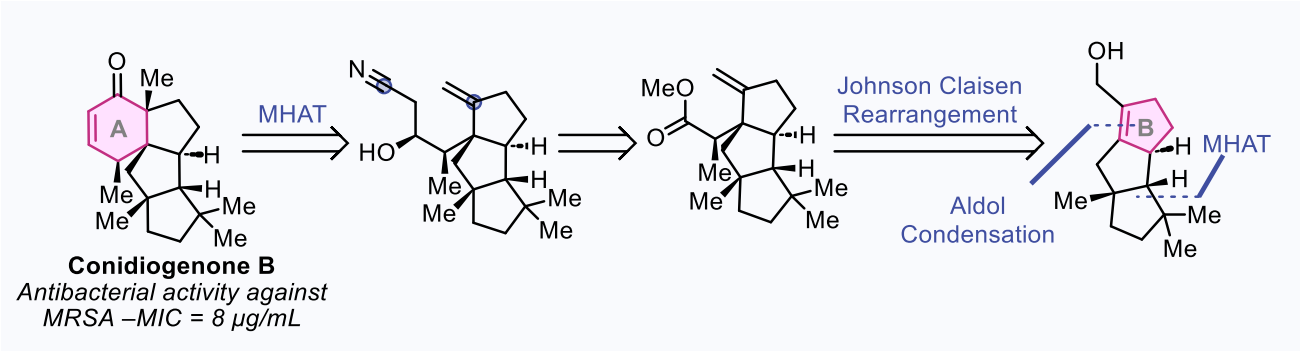

Figure 1. Retrosynthetic analysis of Conidiogenone B

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A GENERAL SYNTHETIC STRATEGY TOWARD THE TRUXILLATE NATURAL PRODUCTS VIA SOLID-STATE PHOTOCYCLOADDITIONS

Ellie F. Plachinski, Hyung Joo Kim, Matthew J. Genzink, Kyana M. Sanders, Riley M. Kelch, Ilia A. Guzei, Tehshik P. Yoon.*

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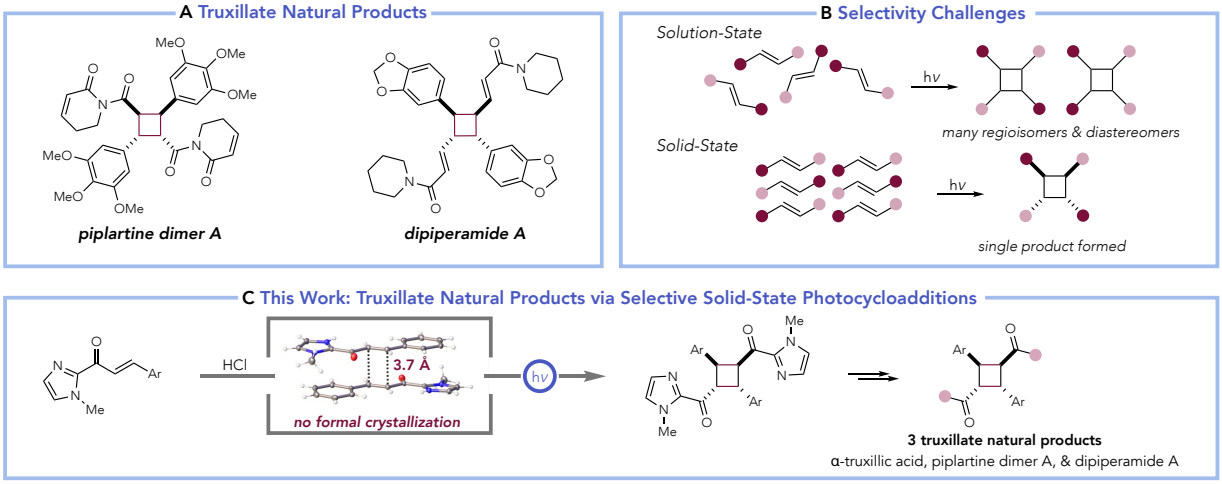
The truxillates constitute a large class of dimeric natural products featuring a central, highly substituted cyclobutane core. In principle, these structures could be efficiently synthesized via [2 + 2] photocycloadditions. However, the difficulty in controlling the high-energy electronically excited reactive intermediates in the solution state can lead to poor regio- and diastereocontrol. This has limited the use of photocycloaddition methodology toward the synthesis of this important class of natural products. We demonstrate that acid-controlled precipitation of *C*-acyl imidazoles promotes a highly selective solid-state photocycloaddition, and the products of this reaction can be quickly transformed into truxillate natural products.[1]



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COMBINED SYNTHETIC, SPECTROSCOPIC, AND COMPUTATIONAL INSIGHTS INTO A GENERAL METHOD FOR PHOTOSENSITIZED ALKENE AZIRIDINATION

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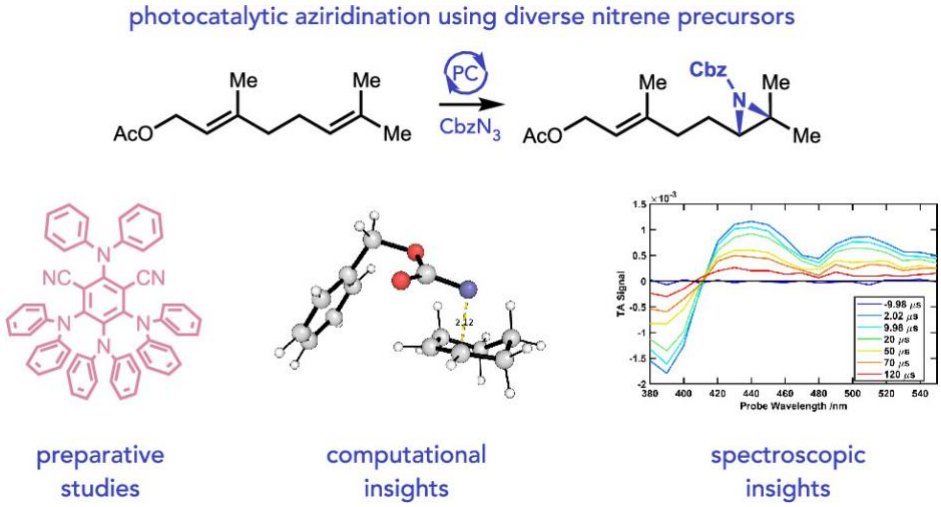
Aziridines are important targets for synthetic chemistry, and many methods involving the aziridination of alkenes by olefins with nitrenes have been reported. In general, however, nitrene transfer reactions are optimized for a limited range of nitrene precursors, and the synthesis of structurally diverse aziridines featuring a range of *N*-substituents requires the application of multiple methods with varying reaction conditions. Herein, we report a photocatalytic method for the aziridination of olefins that operates with a wide range of *N*-substituted nitrene precursors. A combination of synthetic, spectroscopic, and computational data is consistent with a mechanism involving the photocatalytic generation of triplet nitrene intermediates. The effectiveness of 4DPAIPN as a photocatalyst for this process can be rationalized as a consequence of its exceptionally long lifetime, rather than of its excited state energies or redox properties in isolation. We envision this insight will serve not only as a useful synthetic strategy, but also provide a roadmap for rationalizing the superiority photocatalysts in photocatalytic methods.



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LINCHPIN REAGENTS FOR THE SYNTHESIS OF NCO AND NCS-CONTAINING MOLECULES

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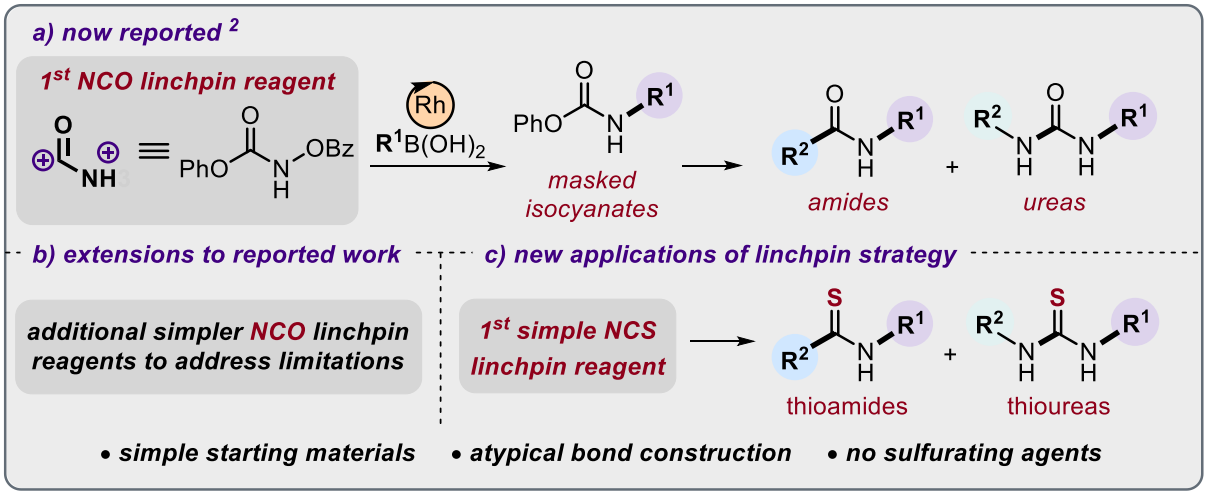
Linchpin reagents are small building blocks that can be chemoselectively functionalized to afford products with a common, useful functional group (ketones, alkenes, etc). Surprisingly, there have been no reports of an NCO linchpin reagent, despite the ubiquitous nature of this subunit in pharmaceuticals and natural products. Building on previous work on masked *O*-isocyanates,[1] we developed the first NCO linchpin reagent and demonstrated its use as a doubly electrophilic building block for the synthesis of various amides, including challenging classes (21 examples, 49-92% yields).[2] The overall transformation proceeded with high chemoselectivity, demonstrating the ability of this reagent to provide amides through an atypical bond construction. The extension to more NCO-containing products such as unsymmetrical ureas and lactams was also demonstrated.

Building on this work, we have developed additional, simpler linchpin reagents that address the limitations present within the previous methodology, specifically in constructing N-C(sp^3) bonds. These reagents expand the scope of products that can be accessed both intermolecularly (amides, unsymmetrical ureas) and intramolecularly (heterocycles, such as lactams). Separately, an NCS linchpin reagent has been validated, which, to our knowledge, has not been reported, notably providing thioamides and thioureas without the use of sulfurating agents. Overall, research on the development and application of four linchpin reagents for the synthesis of NCO and NCS-containing molecules will be discussed, including ongoing, unpublished work.



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POTENT AND BIASED PEPTIDE AGONISTS OF THE PTHR1, A CLASS B GPCR, FROM A HETEROCHIRAL DESIGN STRATEGY

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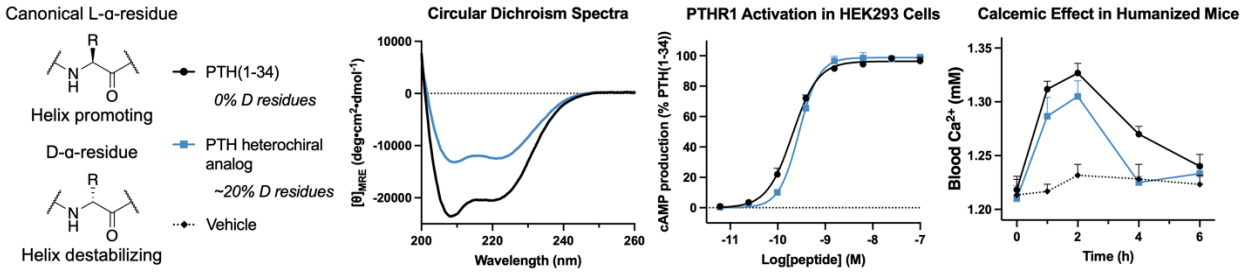
The role of dynamics in Class B GPCR activation is an increasing area of interest, and recent reports have highlighted the importance of peptide agonist flexibility in the glucagon family of receptors. We looked to explore agonist dynamics in an unrelated Class B GPCR, the parathyroid hormone receptor-1 (PTHR1). The PTHR1 regulates calcium homeostasis and bone remodeling and is a therapeutic target for treatment of osteoporosis. We designed agonists of the PTHR1 with multiple L-to-D residue substitutions, generating "heterochiral" peptides with a mixture of L- and D-amino acids. D-amino acids reduce the α-helical character of peptides, thereby increasing flexibility. This heterochiral strategy was unexpected to yield potent agonists given the defined α-helix present in existing static agonist-bound structures of Class B GPCRs. Yet heterochiral analogs of parathyroid hormone (PTH) exhibited high potency at the PTHR1 despite lower α-helical character. We discovered heterochiral PTH analogs that manifested bias away from β-arrestin recruitment and receptor internalization signaling outcomes. These functional biases may be beneficial in promoting bone formation over bone breakdown in osteoporosis treatment. Additionally, we demonstrated that our lead heterochiral peptide is active in vivo. This work challenges the existing paradigm in drug design to rigidify the ligand-bound structure, encourages the importance of dynamic structural information, and may serve as a potential framework for future therapeutic peptide applications.



SYNTHETIC ANTIMICROBIAL PEPTIDES ACTIVATE MRGPRX2 SIGNALING THROUGH DIFFERENT G PROTEIN SUBUNITS

Jana Enns[1], Ghazl Al Hamwi[2]*, Evi Kostenis[3]*, Christa E. Müller[2]*, Günther Weindl[1]*

[1]*University of Bonn, Pharmaceutical Institute, Pharmacology and Toxicology, Bonn, Germany*
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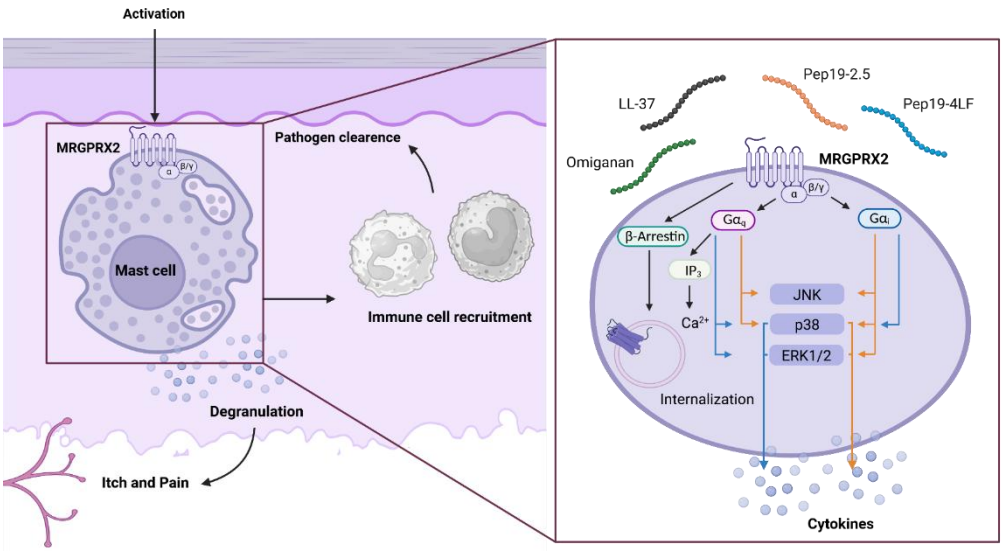
Mas-related G protein-coupled receptor X2 (MRGPRX2) is a mast cell receptor that plays a crucial role in neurogenic inflammation, pain and itch. Upon activation, MRGPRX2 activates G_i and G_q proteins, triggering mast cell degranulation and promoting cytokine and chemokine production via the mitogen-activated protein kinase (MAPK) pathway. MRGPRX2 ligands include cyclic neuropeptides like cortistatin-14, the small molecule ZINC-3573, the synthetic polymer C48/80, and antimicrobial peptides (AMPs) like the endogenous cathelicidin LL-37. The recognition of AMPs by MRGPRX2 is thought to be an important antimicrobial mechanism during infection, highlighting the immunomodulatory function of AMPs. However, whether endogenous and synthetic AMPs differentially regulate MRGPRX2 signaling remains unclear. In this study, we explored the effects of the cathelicidin derivative omiganan and synthetic lipopolysaccharide (LPS)-neutralizing peptides Pep19-4LF and Pep19-2.5, selected for their structural similarity to LL-37. The peptides were profiled in a broad panel of functional cell-based assays using pharmacological and genetic approaches. We report that omiganan, Pep19-4LF and Pep19-2.5 show distinct activation profiles for MRGPRX2, engaging different signaling pathways with varying potency. While the LPS-neutralizing peptides triggered Gq-mediated responses, Pep19-4LF also activated Gi signaling more effectively. Compared to this, omiganan primarily activates the Gi signaling while exhibiting minimal Gq-mediated signaling. The LPS-neutralizing peptides triggered MRGPRX2-dependent cytokine expression and release through distinct signaling pathways. Differences were observed in MAPK activation patterns, β-arrestin recruitment, and MRGPRX2 internalization, highlighting variations in their functional outcomes. Our findings contribute to a better understanding of how synthetic peptides modulate MRGPRX2 signaling, potentially shaping future therapeutic development of MRGPRX2 ligands.



REGIOSPECIFIC SYNTHESIS OF PYRROLES FROM ISOXAZOLES

Abigail J. Bracken, Alexa P. Lawrie, Isabella F. Romita, Mark D. Levin*

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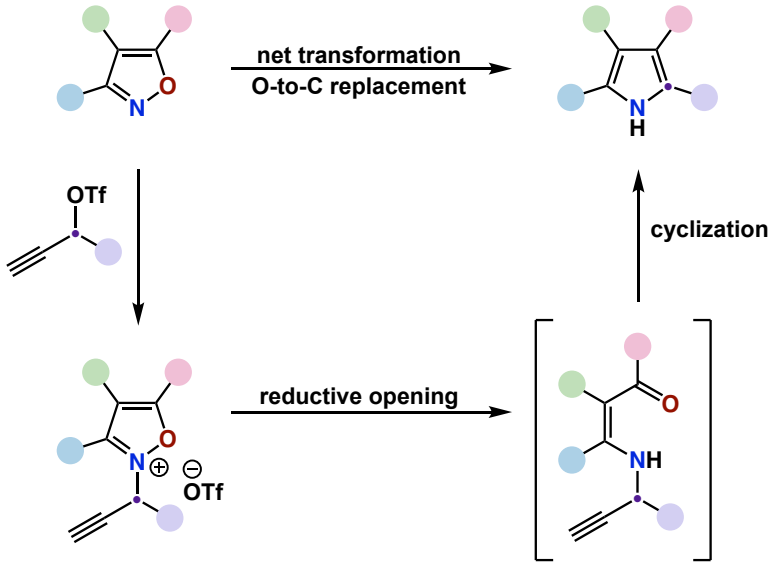
Carbon insertion generally requires highly active species as carbon-atom sources, such as diazo or diazirine compounds. While still useful, reactions with these compounds can be limited as they are often quite sensitive, prone to decomposition, and not industrially applicable on large scales due to their high reactivity. At the same time, drug development in the pharmaceutical industry greatly benefits from the ability to make slight changes to a molecule's core structure using skeletal editing. This underscores a need to develop other strategies for carbon insertion which use less reactive precursors. This work demonstrates the use of propargyl groups as carbon atom sources in a net O-to-C replacement reaction of isoxazoles, in which a rearrangement cascade incorporates the propargylic carbon atom into a pyrrole heterocycle. The transformation is accomplished via alkylation of the isoxazole to form an isoxazolium triflate species, which can be subjected to a one-pot reductive ring opening and cyclization sequence to form a pyrrole. The overall transformation converts an oxygen atom to a carbon while otherwise maintaining the substitution pattern of the heterocycle as a new approach to synthesizing pyrroles in a regiospecific fashion.



PHOTODYNAMIC APPLICATIONS OF ATOMICALLY PRECISE GRAPHENE QUANTUM DOTS

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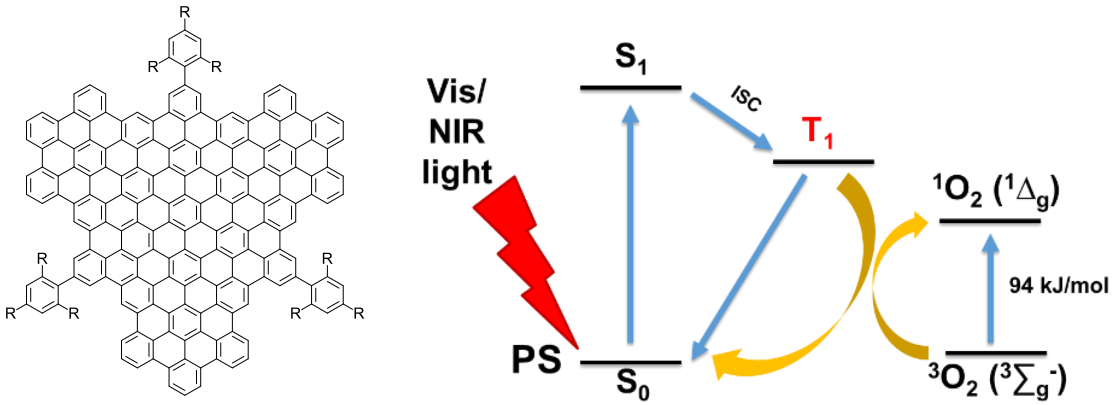
Graphene is an attractive material because of its extensive conjugation and size-dependent properties when confined to the nanometer-scale. Graphene quantum dots (GQDs) are near-planar, nanoscale sheets of graphene with varying edge structures and side chains. Atomically precise GQDs offer a unique opportunity to combine the structural tunability afforded small molecules with the attractive, size-dependent properties of graphene to generate structures with optimized optical and electronic properties. This tunability can be advantageous for a variety of applications, including as photosensitizers where the GQDs can be studied for their ability to generate singlet oxygen via the photodynamic effect. Singlet oxygen can induce targeted cell death in photodynamic therapy as an alternative cancer treatment or inhibit biological growth on surfaces for anti-microbial applications. Stepwise synthesis generates atomically precise structures and allows for molecular control that translates to precise insertion of specific atoms or functional groups and homogenous final structures. Synthesis of the GQDs, analysis of photo- and electrochemical properties, and future directions will be presented.



ENGINEERING BACTERIAL TERPENE SYNTHASES TO PRODUCE HIGH VALUE PHARMACEUTICAL DITERPENOID PRECURSORS

Diana Łomowska-Keehner, Doireann Doherty, Jeffrey D. Rudolf*

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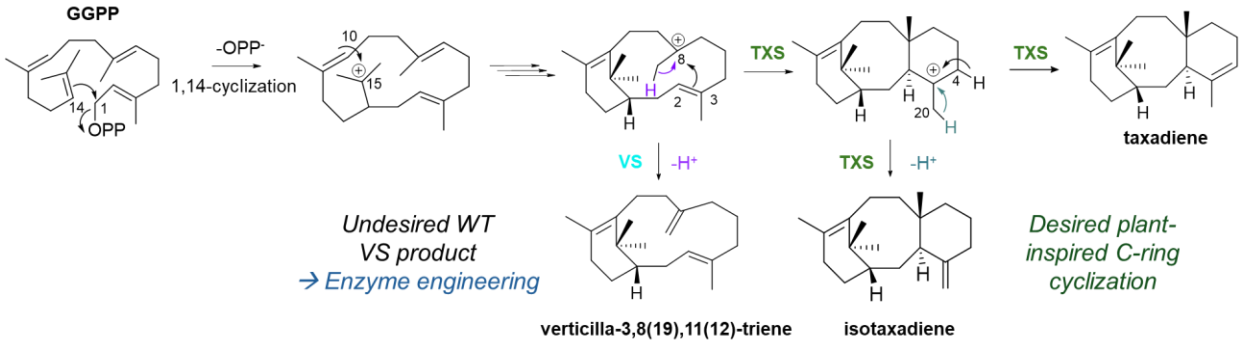
Terpenoids are the largest class of natural products (NPs), encompassing over 100,000 compounds with valuable bioactivities including antibacterial, cytotoxic, and anti-inflammatory properties. Taxol (paclitaxel) is a diterpenoid NP from the Pacific yew (*Taxus brevifolia*) that has been used to treat several cancers since 1993. Historically, plants have been known as the most prolific producers of bioactive terpenoids; however, genome mining revealed that bacteria also harbor terpene synthase (TS) enzymes. TSs produce the hydrocarbon scaffold precursors to bioactive diterpenoid NPs. Our group screened over 300 bacterial TSs for the production of novel diterpenes and conducted mechanistic studies of the carbocation chemistry and cyclization mechanisms controlled by key amino acids in TS active sites. The TS screen revealed two verticillene synthases of great interest for engineering as they share key intermediates with the biosynthesis of the Taxol diterpene precursor, taxadiene.[1] As enzymes adhere to many principles of green chemistry, their use in producing pharmaceutical compounds has grown more desirable. However, microbial factory development for Taxol production has been hampered by the *T. brevifolia* taxadiene synthase (TXS) as one of the rate limiting steps. Thus, the optimization of a selective, reliable, and highly productive taxadiene synthase of bacterial origin through enzyme engineering can significantly accelerate efforts toward production of the Taxol precursor at scale. Our studies of aromatic residues dictating active site chemistry driving product profiles and mechanistic insights into key residues will be presented. We hope this research lays the groundwork for improved biocatalysis efforts in sustainable taxadiene production by engineering new-to-nature enzyme functions capable of operating more efficiently in microbes than the plant TXS currently in use.



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CHIRAL PYRROLIDINES VIA AN ENANTIOSELECTIVE HOFMANN-LÖFFLER-FREYTAG REACTION

Ipshita Roy[†], Pavitra Laohapaisan[†], David A. Nagib*
[†]*These authors contributed equally*

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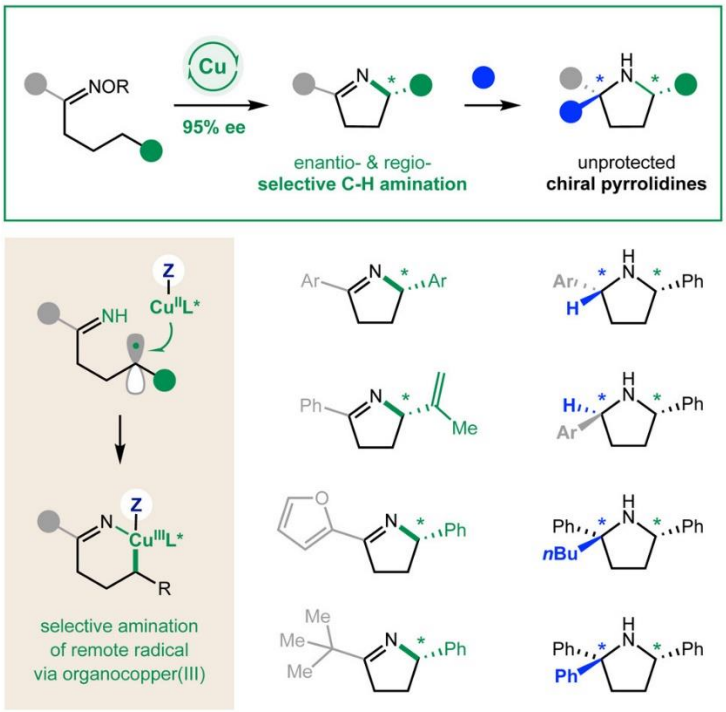
Radical C–H aminations enable rapid access to the most common heterocycles in medicines (e.g., pyrrolidines), yet stereocontrol of these powerful transformations remains a challenge. Here, the discovery of the first enantio- and regioselective C–H imination is reported, which readily converts ketones to enantioenriched pyrrolidines. This enantioselective Hofmann-Löffler-Freytag reaction mechanism entails iminyl radical generation from an oxime ester by a chiral Cu catalyst that facilitates 1,5-H-atom transfer (HAT) to form a remote C-radical regioselectively. The selective capture of this alkyl radical as an organocopper(III) complex then mediates highly stereoselective reductive elimination to unprotected chiral pyrrolines. The broad steric and electronic scope of this remote C–H amination has been probed systematically, along with key mechanistic aspects of enantiodetermination, radical intermediacy, and atypical Cu(III) ligands that enable this uniquely selective C–N coupling. Importantly, either (1) reductions or (2) nucleophilic additions to these enantioenriched pyrrolines provide the most rapid syntheses of chiral pyrrolidines to date.[1]



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[1] Laohapaisan, P.[†]; Roy, I.[†]; Nagib, D. A. Chiral pyrrolidines via an enantioselective Hofmann-Löffler-Freytag reaction. *Chem Catalysis*, **2024**, *4*, 101149-101158. ([†] - co-first author)

Non-Innocent Role of Sacrificial Anodes in Electrochemical Nickel-Catalyzed C(sp^2)-C(sp^3) Cross-Electrophile Coupling

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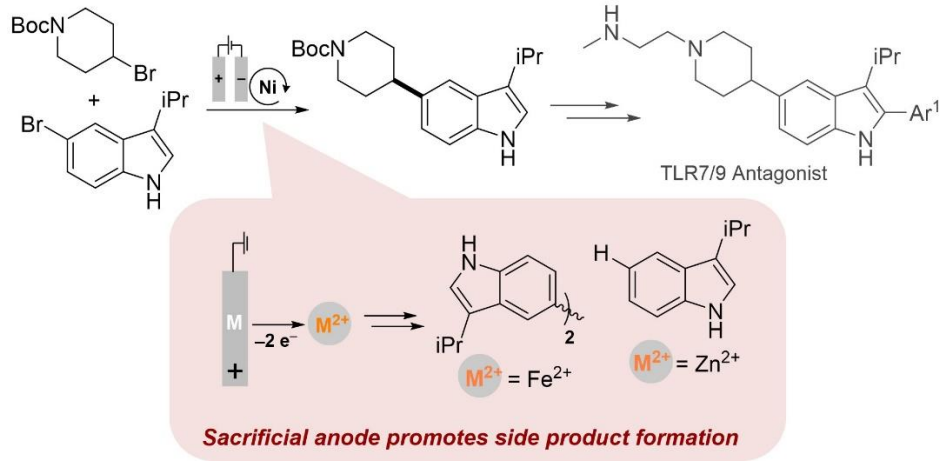
[b]*Bristol Myers Squibb, Chemical Process Development, 1 Squibb Drive, New Brunswick, NJ 08903, United States*

Sacrificial anodes composed of inexpensive metals such as Zn, Fe and Mg are widely used to support electrochemical nickel-catalyzed cross-electrophile coupling (XEC) reactions, in addition to other reductive electrochemical transformations. Such anodes are appealing because they provide a stable counter-electrode potential and typically avoid interference with the reductive chemistry. The present study[1] outlines the development of an electrochemical Ni-catalyzed XEC reaction that streamlines access to a key pharmaceutical intermediate. Metal ions derived from sacrificial anode oxidation, however, directly contribute to homocoupling and proto-dehalogenation side products that are commonly formed in chemical and electrochemical Ni-catalyzed XEC reactions. Use of a divided cell limits interference by the anode-derived metal ions and supports high product yield with negligible side product formation, introducing a strategy to overcome one of the main limitations of Ni-catalyzed XEC.



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[1] Cardinale, L.; Beutner, G. L.; Bemis, C. Y.; Weix, D.; Stahl, S. S. *J. Am. Chem. Soc.* **2024**, *146,* 47, 32249–32254.

TRANSLATION OF NICKEL-CATALYZED C(SP^2) -C(SP^3) CROSS ELECTROPHILE COUPLING TO NON-AMIDE SOLVENTS

Julianna Mouat†, Brett Akana-Schneider†, Sisi Zhang§, Michelle Akana, Bin Wu*§, Daniel J. Weix†*

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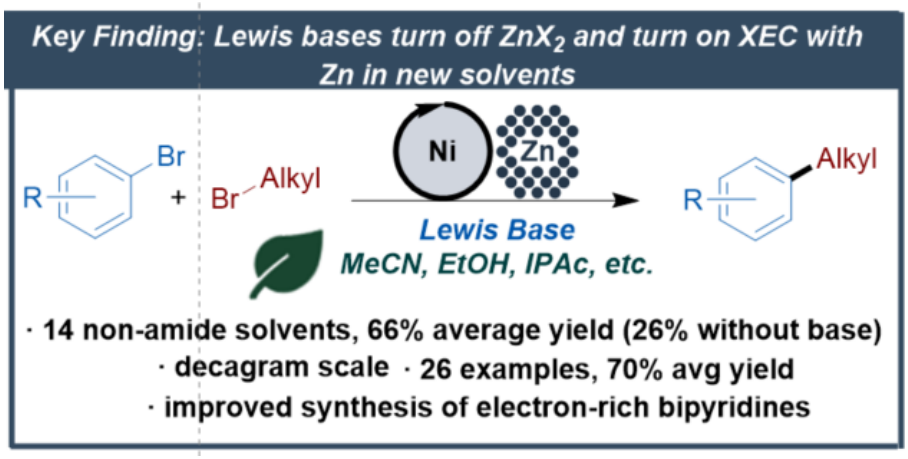
The cross-electrophile coupling (XEC) of organobromides is widely utilized in organic synthesis, but generally requires undesirable amide solvents (e.g. DMF, NMP) that can pose health and environmental concerns. Recent advances in XEC methodology have illustrated that organic reductants, electrochemical methods, or photochemical conditions can enable reactions in non-amide solvents. However, XEC conditions that both 1) utilize bench-stable, easily sourced metal reductants (Zn and Mn) and 2) offer broader solvent compatibility remain rare. We report that the combination of LiI and 4-picoline enables Ni-catalyzed C(sp^2)-C(sp^3) XEC of organobromides in 14 different industrially preferred solvents using metallic Zn as reductant.[1] Utilizing nickel catalysts with strongly donating bidentate nitrogenous ligands maintains high selectivity for the cross-product over dimeric byproducts, enabling coupling of electronically diverse bromoarenes with both primary and secondary alkyl bromides (21 examples). We demonstrate the scalability of these conditions up to decagram scale for different substrates across several industrially utilized reaction apparatuses. An improved and modular synthesis of the optimal 4,4'-bis(dimethylamino)-2,2-bipyridine ligand is also presented.



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[1] Akana-Schneider, B.D. †, Mouat, J.M. †, Zhang, S., Akana, M.E., Wu, B.,* Weix, D. J.* *Org. Lett*., ASAP., † denotes co-authorship

TETRACYCLIC QUINAZOLINONE SCAFFOLD OPTIMIZATION LEADING TO STRUCTURALLY NOVEL INHIBITORS OF HIGHLY LETHAL, NEUROPATHOGENIC *NAEGLERIA FOWLERI* AMOEBA

Julia M. Pomeroy[1], Seoyoung Kim[2], Matthew S. Lish[1], Jillian E. M. McKeon[2], Caroline M. Palmentiero[3], Colm P. Roster[3], James C. Morris[3], and Jennifer E. Golden[1,2]*

[1]*Department of Chemistry, University of Wisconsin-Madison*
[2]*School of Pharmacy, Division of Pharmaceutical Sciences, University of Wisconsin-Madison*
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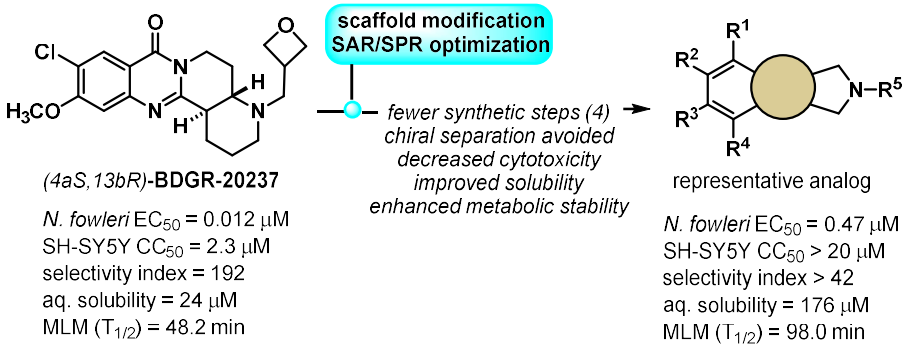
Naegleria fowleri is a thermophilic amoeba found in fresh water that can cause a highly lethal, human brain infection known as primary amoebic meningoencephalitis (PAM). Current treatment relies on repurposed drug combinations, such as amphotericin B and miltefosine, which have limited efficiency and significant toxicity. An internal compound screen identified several tetracyclic quinazolinone-based inhibitors of *N. fowleri* which resulted from a synthetic methodology involving the developmentof a Mannich-coupled domino quinazolinone-amidine rearrangement. A subsequent structure-activity optimization effort delivered a single enantiomer, (*4aS*,*13bR*)-**BDGR-20237**, which showed potent inhibition of *N. fowleri* (EC_{50} = 0.012 μM) but modest mouse liver microsomal (MLM) stability ($T_{1/2}$ ~ 50 min) and solubility (24 μM). Subsequent scaffold modifications afforded a new quinazolinone chemotype, reduced the number of synthetic steps from seven to four, enabled late-stage diversification, and avoided costly chiral purification procedures while also reducing cell toxicity and improving solubility and metabolic stability. Medicinal chemistry optimization continues; however, to date we have identified an active anti-amoebic analog (EC_{50} = 0.47 μM) that demonstrates improvements in MLM stability and solubility compared to the preceding generation of compounds. The identification and development strategy of the first and second generation chemotypes will be highlighted.



SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIP STUDIES ON BENZYLTETRAHYDROISOQUINOLINES AS AGONISTS FOR G PROTEIN-COUPLED RECEPTORS

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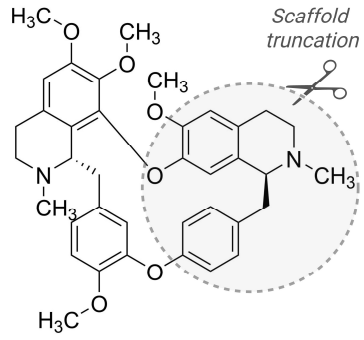
Benzyltetrahydroisoquinolines are highly abundant among natural products as well as in synthetic small molecule libraries, and a wide range of biological activities and molecular targets have been reported for compounds featuring a benzyltetrahydroisoquinoline scaffold. These targets include enzymes (e.g. human cholinesterases)[1], ion channels (e.g. two-pore channel 2 [TPC2])[2], the drug efflux transporter P-glycoprotein[3] and G protein-coupled receptors (e.g. D_2-like dopamine receptors, α_1-adrenoceptors and orexin OX_1 receptors)[4-6].

A screening campaign of more than 2,000 compounds performed in our research group identified tetrandrine, a natural bisbenzyltetrahydroisoquinoline alkaloid isolated from the plant *Stephania tetrandra,* as an agonist for a poorly investigated orphan G protein-coupled receptor (GPCR), whose endogenous ligand remains unknown.

Aiming at structural simplification, synthetic diversification and improved potency, we followed a scaffold truncation approach and set out to investigate monomeric benzyltetrahydroisoquinolines as ligands for the target GPCR. More than 60 compounds with systemic variations of the tetrahydroisoquinoline lead structure were synthesized and tested for receptor activation in *β*-arrestin recruitment and G protein-dependent assays to explore structure-activity relationships (SARs). Our results represent a promising starting point for the development of a novel class of tool compounds for the targeted orphan GPCR, which are required to gain deeper insights into the receptor's (patho)physiological roles and for its validation as a drug target.



Tetrandrine
EC_{50} = 1.16 ± 0.10 µM
E_{max} = 116 %
(*β*-arrestin assay)

[1] Xu *et al*., *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2368–2373.
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[4] Perrey *et al*., *J. Med. Chem*. **2013**, 56, 6901–6916.
[5] Iturriaga-Vásquez *et al*., *J. Nat. Prod*. **2003**, 66, 954–957.
[6] Silva *et al*., *J. Nat. Prod*. **2020**, 83, 127–133.

Prochiral Substrate Synthesis and Biocatalytic Oxidations to Access Acyloin Scaffolds and Natural Products

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The Baeyer-Villiger reaction commonly utilizes peroxyacids to oxidize ketone functional groups into esters. However, chemical methods have disadvantages such as using excess oxidant and halogenated solvents, which are not eco-friendly. A greener approach would be implementing a biocatalyst to selectively perform the desired oxidation. Enzymes are inherently biodegradable catalysts, and Baeyer-Villiger monooxygenases (BVMOs) utilize a flavin cofactor while leveraging molecular oxygen as the terminal oxidant. Notably, BVMOs have the potential to facilitate oxidations with regio-, chemo-, and stereoselectivity. Our results detailing the reactivity of prochiral diketone substrates will be shared. Oxidation outcomes will be compared between chemical methods and biocatalysts, and the requisite α-acyloxy ketone standards for the biocatalytic reactions were prepared through orthogonal routes when necessary. Additionally, current synthetic efforts toward the chemoenzymatic synthesis of acyloin natural products will be disclosed.

EXPLORING DEFLUORINATION REACTIONS USING POTASSIUM TERT-BUTOXIDE

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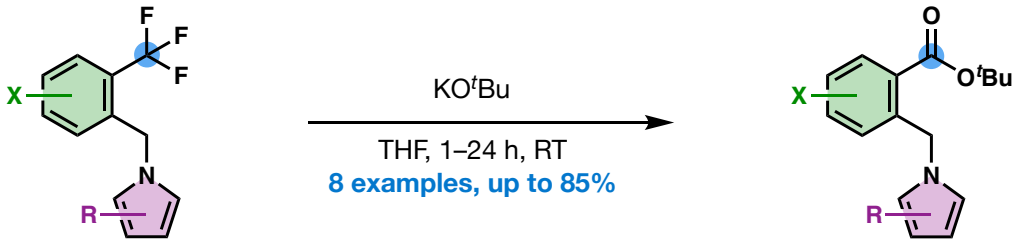
During an exploratory study, my former lab mate, Dr. Sangyun Kim, fortuitously discovered that ortho-substituted trifluoromethyl arenes could undergo complete defluorination upon treatment with KO^{t}Bu. However, there was an unknown major product formed that we could not easily identify, with conflicting NMR and MS data. Based on the ^{1}H and ^{13}C NMR spectra, we originally suspected that the -CF3 was being substituted by -O^{t}Bu. However, direct substitution of a trifluoromethyl group with a t-butyl ether was unknown in the literature. Upon reflection, a more likely product was the t-butyl ester, where fluoride is the leaving group and the carbon of the trifluoromethyl group was transformed into the carbon of the t-butyl ester. Based on this hypothesis, I synthesized the t-butyl ester via an alternative pathway, confirming that this was indeed the product from the defluorination reaction. We have pursued optimization studies and we are currently exploring the scope of this reaction. I have successfully synthesized and tested 8 successful substrates in this defluorination. I plan to pursue mechanistic studies, such as kinetics and rates of defluorination, as well as isolate an intermediate.



Chemoselective Electrocatalytic Manganese-Mediated Oxygen-Atom Transfer to High Potential Organic Molecules

Suha Yacoob,[†,a] Md Asmaul Hoque[†], Tianxiao Jiang[†], Matthew D. Graaf,[‡] and Shannon Stahl[†*]

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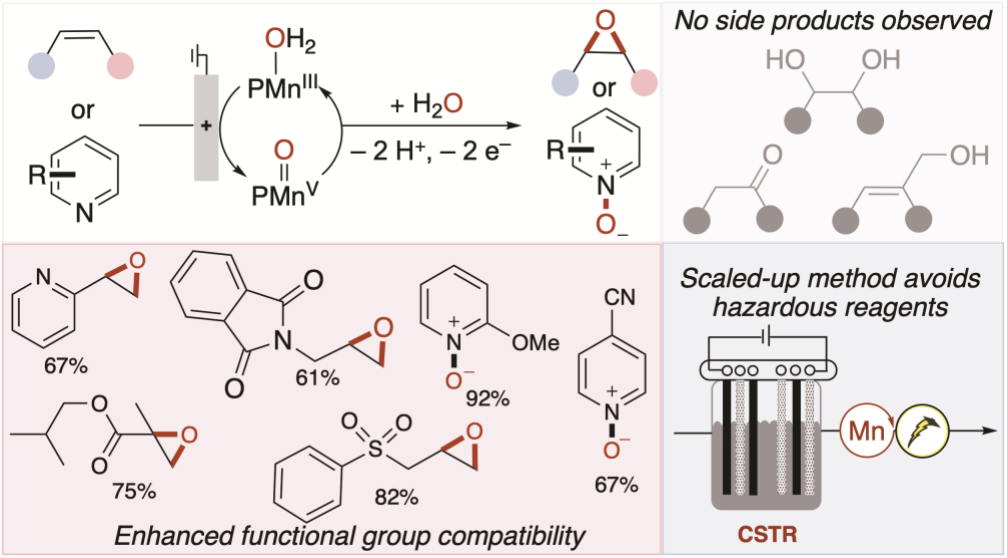
Oxygenation of organic compounds is an essential class of oxidation reactions that often require stoichiometric, high-energy oxygen donors. The reaction is an important strategy to introduce polarity to lipophilic compounds, increase metabolic performance, and convert simple hydrocarbon molecules to synthetically useful linchpins. Despite tremendous progress in developing oxygen-atom transfer reactions, chemoselective, atom economical, environmentally benign, and green approaches remain limited for challenging oxygenation reactions due to high thermodynamic and kinetic barriers. Using water as the oxygen source in these reactions offers a safer alternative, bypassing the need for hazardous reagents. In this study, we present an electrochemical method that activates water via proton-coupled oxidation of the manganese (Mn(III)-OH_2) complex to the reactive manganese-oxo (Mn(V)=O) species, using a manganese porphyrin electrocatalyst. This approach enables the oxygenation of challenging organic substrates, including the oxidation of unactivated alkenes to epoxides and pyridines to pyridine *N*-oxides. The methodology is compared against the chemical reactivity of commonly employed oxidant, *meta*-chloroperoxybenzoic acid as well as a chemically generated manganese-oxo complex via a hypervalent iodine reagent. The electrochemical method exhibits improved yields for terminal and electron-poor alkenes that have historically been challenging to oxidize with metal-oxo complexes. A broad epoxide scope is shown with high chemoselectivity towards product formation, avoiding potential side products from allylic oxidation, overoxidation, or hydrogen-atom transfer. Sterically encumbered and electron-poor pyridine *N*-oxides can also be accessed. This method has been applied for the gram scale synthesis of various pharmaceutically relevant epoxides using a continuous stir tank reactor (CSTR), proving the basis for the safer and greener access to oxygenated molecules.



REDOX-TUNABLE RING EXPANSION ENABLED BY A SINGLE-COMPONENT ELECTROPHILIC NITROGEN ATOM SYNTHON

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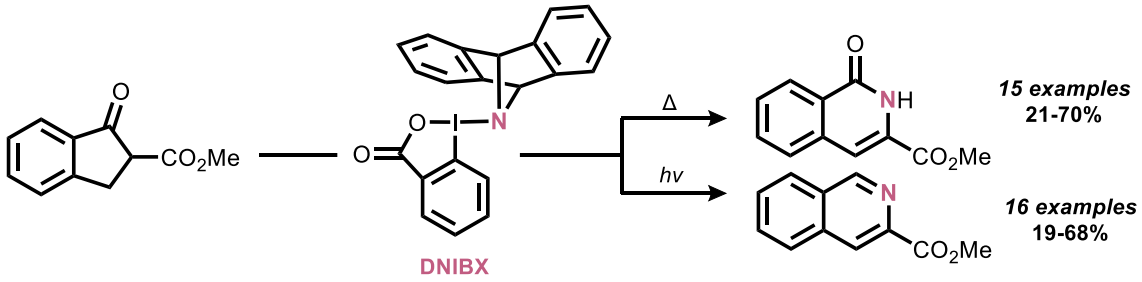
Skeletal editing has emerged as a new platform for streamlining molecular diversity. Development of novel atom transfer reagents allows for skeletal edits that do not require prefunctionalized atomic precursors for nitrenes, carbenes, or other suitable atomic equivalents. This work discloses DNIBX, an amino-hypervalent iodine reagent that enables electrophilic transfers of dbabh (dibenzoazabicycloheptadiene).[1] This species serves as a masked nitrogen atom synthon, such that upon amination of indanone β-ketoesters, dbabh-functionalized products can undergo divergent, condition-dependent ring expansions to isoquinolines (photochemical) or isoquinolones (thermal). The scope of the amination, as well as the mechanism and scope of each ring expansion is explored. Additionally, the reactivity of the indanone dbabh products is compared to other nitrogen atom precursors.



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[1] Kelly, P. Q.; Keramati, N. R.; Kaplin, K. R.; Lynch-Colameta, T.; Phelan, J.P.; Levin, M.D. *Angew. Chem. Int. Ed.* **2025**, *64*, e202420664.

OPTIMIZATION OF PTBA ANALOGS AS THERAPEUTICS FOR KIDNEY DISEASE

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[†]*Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, USA,* [‡]*Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, USA,* [⊥]*Department of Cell Biology, University of Pittsburgh, Pittsburgh, USA*
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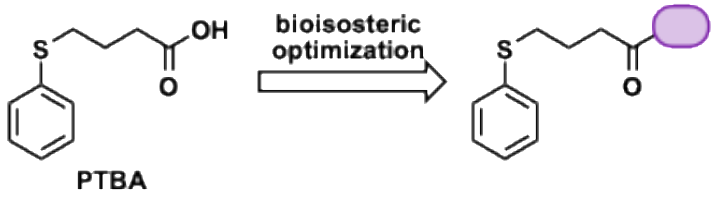
Acute kidney injury (AKI), the sudden loss of renal function, frequently occurs in patients in the intensive care units, particularly in those with critical illnesses, sepsis or post-surgical complications. Early detection and intervention are critical to mitigate the progression to chronic kidney disease or end-stage renal disease.[1] Despite advancements in diagnostic biomarkers and therapeutic strategies, a thorough understanding of the causes for AKI and reliable diagnostic biomarkers are limited. Additionally, a few pharmacological targets have been validated and treatment to address the underlying pathology are scarce



Previously, we reported that 4-phenylthiobutanoic acid (PTBA) demonstrated promising therapeutic effects in a zebrafish AKI model.[2] However, PTBA's carboxylic acid group significantly restricts its permeability and absorption, requiring a pro-drug approach in order to observe *in vivo* effects in mice.[3] To overcome this limitation, we designed novel PTBA analogs by bioisosterically replacing the carboxylic acid moiety. Isosteres have the potential to enhance drug permeability, potency, and stability, eliminating the need for a pro-drug. We will present our work in identifying bioisosteric replacements as well as further optimization, resulting in novel compounds with *in vivo* efficacy that do not require a pro-drug for delivery.

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[1] Siew, E. D. *et al.*, *American Journal of Kidney Diseases* **2020**, *75*, 204–213.

[2] De Groh, E. D. *et al.*, *Journal of the American Society of Nephrology* **2010**, *21*, 794–802.

[3] Skrypnyk, N. I. *et al.*, *American Journal of Physiology-Renal Physiology* **2016**, *310*, 705–716.

AN ADENYLOSUCCINATE LYASE IN ANTIBIOTIC BIOSYNTHESIS AND BIOCATALYSIS

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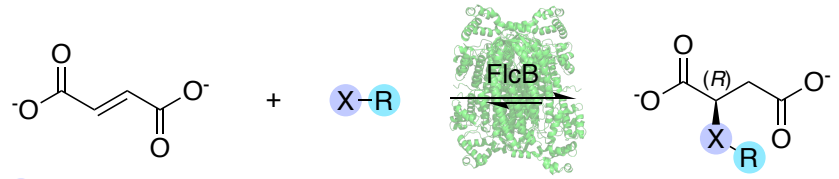
The aspartase/fumarase superfamily of enzymes catalyze C–N or C–O bond cleavage from succinate containing compounds, releasing fumarate as the common product.[1] Adenylosuccinate lyases are members of this superfamily that typically catalyze C–N bond cleavage of adenylosuccinate leading to formation of adenosine monophosphate (AMP) in purine biosynthesis.[2] Our lab identified FlcB, an adenylosuccinate lyase in the biosynthesis of a copper-containing antibiotic, fluopsin C, from the bacterium *Pseudomonas aeruginosa*. In the first step of fluopsin C biosynthesis, FlcB catalyzes the formation of a C–S bond between cysteine and fumarate, generating an (*R*)-stereocenter.[3] The enantioselectivity of FlcB differs from other adenylosuccinate lyases and therefore makes it an intriguing subject for future study. We showed that FlcB is permissive toward various thiol- and amine-containing substrates. Kinetic parameters of FlcB were measured and essential catalytic residues were identified. Together, these findings shed light on the mechanism of FlcB. The enantioselective C–S bond formation catalyzed by FlcB has potential applications in biocatalysis for generating C(sp^3)–S stereocenters.



X = S or N

R = carboxylic acids with straight and branched alkyl chains of varying length, amino acids, cyclohexyl, propyl, and isobutyl groups

[1]V.P Veetil; G. Fibriansah; H. Raj; A.W.H. Thunnissen; G.J. Poelarends, *Biochemistry* **2012**, *51* (21), 4237-4243.
[2]E.A. Toth; T.O. Yeates, *Structure* **2000**, *8* (2), 163-174.
[3]J.B. Patteson; A.T. Putz; L. Tao; W.C. Simke; L.H. Bryant III; R.D. Britt; B. Li, *Science* **2021**, *374* (6570), 1005-1009.

USING A DYNAMIC COVALENT SCREENING METHOD TO EXPAND THE UNLIGANDABLE PROTEOME

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About 60-80% of the human proteome is considered unligandable with traditional non-covalent small molecules. Among the currently untargetable proteome are dynamic and/or disordered proteins that have health implications when misregulated. One successful ligand discovery strategy for these proteins has been *covalent* small molecule targeting, albeit the strategy is not widely adopted as commercially available covalent ligands are neither structurally diverse nor selective in screens. To address this gap, we are developing a novel covalent screening method to facilitate the expansion of covalent ligand libraries. This innovative technology uses a thermodynamically-controlled and high-throughput combinatorial chemistry approach combined with irreversible warheads. We have also built a computational pipeline that allows us to rationally select commercially available building blocks for screening, increasing the efficiency of the screening method. Future work will focus on applying the dynamic covalent screening strategy to unligandable classes of proteins to create diverse and selective small molecules. For example, this method will be used to observe differential targeting between conserved cysteines within protein families or to target dynamic and/or disordered proteins that lack classical binding pockets. We expect this method will advance the covalent chemistry field, revolutionizing ligand discovery for dynamic and/or disordered proteins by increasing the diversity and selectivity of covalent ligand libraries.

ΔSulf: A Bioorthogonal *pro*-amino acid for Introducing Dehydroamino Acids into Peptides & Applications for Anti-Aggregation Therapies.

Pei-Hsuan. Chen, S. Bloom*
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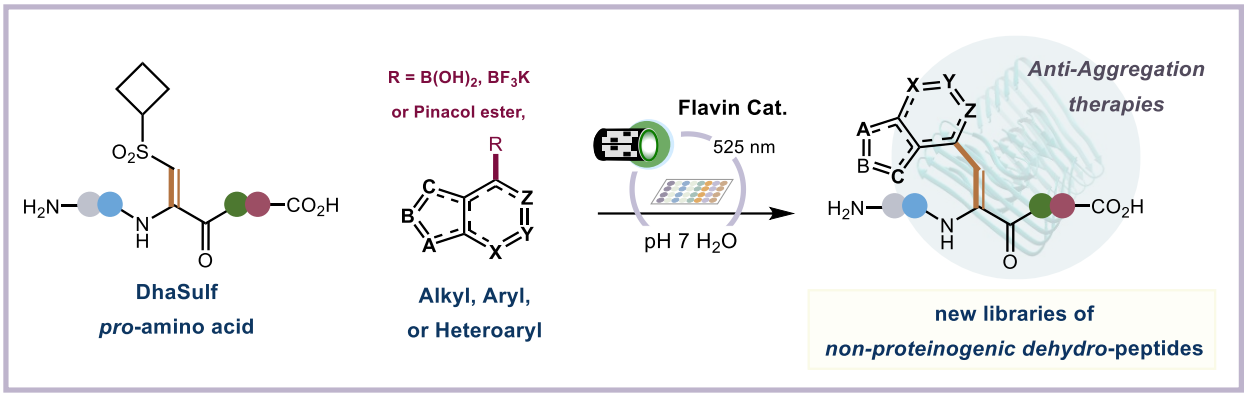
α, β-Dehydroamino acids (**ΔAAs**), characterized by a double bond between their Cα- and Cβ-carbons, are integral to many bioactive peptides and biomedical materials. The rigid olefin locks the amino acid into one of two possible configurations, (E)- or (Z), each affecting key physicochemical properties such as molecular topology, hydrophobicity, and cellular permeability. But deducing which **Δ**AA chemotype (aliphatic, aromatic, heteroaromatic) to use and which orientation (E or Z) to place it requires exhaustive medicinal chemistry, each dhAA variant being separately made and then incorporated into the nascent polypeptide through a long tedious chemical synthesis. To streamline the discovery of optimal **Δ**AA variants, we developed a novel AA, **ΔSulf**—essentially a dehydroalanine residue with a sulfonyl group appended to Cβ—, that can be incorporated into peptides and then transformed into one of several **Δ**AAs through reaction with a boronic acid and a flavin photocatalyst; the exact wavelength of light controlling the geometry and substitution pattern of the final **Δ**AA. In this way, one **Δ**Sulf peptide can become many **Δ**AA analogs that can be tested for biological activity. Applying this methodology, we prepared a series of **Δ**AA peptides, namely, AcNH-Gly-Pro-**ΔAA**-Phe-NH_2, that mimic the aggregation prone region of the Aβ42 peptide in Alzheimer's Disease (**AD**). We found that peptides with aliphatic **Δ**AAs inhibited Aβ42 aggregation into mature amyloid plaques, establishing a set of lead structures for the development of new anti-aggregation therapies for AD.



Lewis acid-Promoted Electrocatalytic Turnover of Ti(IV)-oxo Complex for Reductive O-atom Transfer

Ruohan Deng,[1#] Tianxiao Jiang,[1#] and Shannon S. Stahl[1*]

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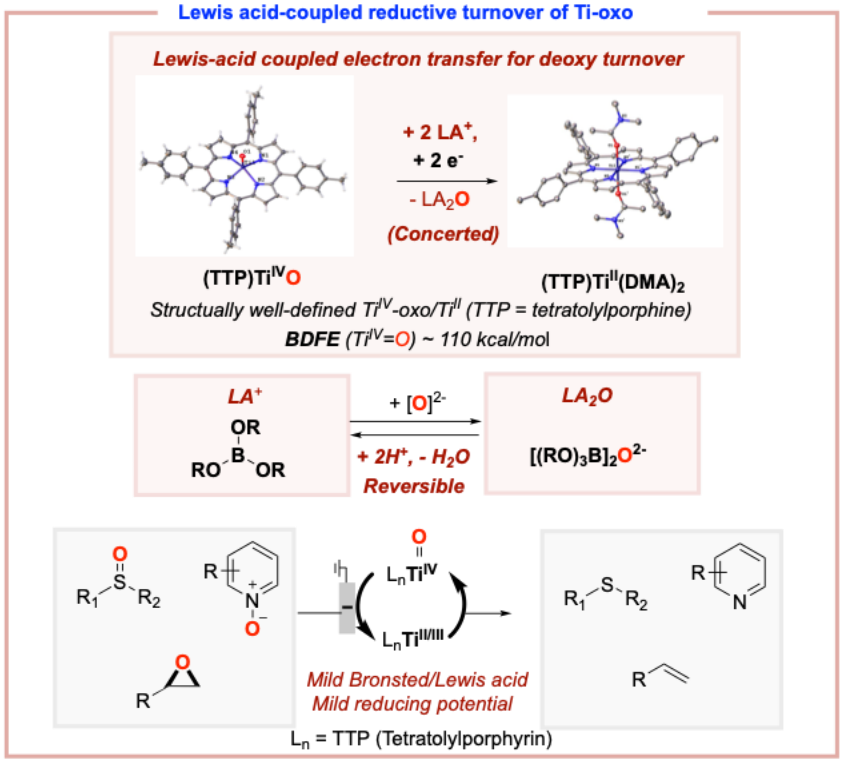
Deoxygenation reactions represent one of the most important class of transformations in organic chemistry from oxygen-containing surrogates that are most abundant as starting materials. However, in most of these reactions potent electrophiles have been used as “oxygen sink” to drive the reactions forward, such as silyl-chloride, sulfonyl chloride and phosphines. In addition, the formation of stoichiometric byproducts either cause isolation problems or cannot be recycled due to unfavorable thermodynamics. Therefore, it would be highly desirable to consider an “ideal oxygen scavenger” for reductive deoxygenation processes. In this context, the use of a mild Lewis acid which can be easily restored after reaction would be appealing to consider. On the other hand, titanium is known to have abundant redox property (II,III,IV) and well-known deoxygenation reactivity at it low-valent oxidation state with formation of Ti(IV)-oxo species. Despite its “oxophilicity” as a formidable challenge for active species regeneration as a catalyst, here we show that it can be achieved electrochemically with boronic ester as the mild Lewis acid as turnover reagents. Using diphenyl sulfoxide deoxygenation as a benchmark reaction for catalyst turnover of Ti-oxo, B(OPh)3 gave quantitative yields of sulfide with >90% Faradaic efficiency. Furthermore, we obtained solid evidence of generation of Ti^{II} and Ti^{III} with coulometry, ^{1}HNMR and EPR studies, both of which are responsible for substrate deoxygenation. Instead of stepwise Ti-oxo deoxygenation using potent electrophiles like silyl-chloride, we proved that these deoxygenation goes through a Lewis-acid electron-coupled transfer, allowing for the reaction to run at mild reduction potential. This work lays foundation to more synthetically impactful deoxygenation reactions.



RHODAMINE-DIPEPTIDE CONJUGATES FOR CELLULAR TRACKING AND DRUG DELIVERY

Sagarika Taneja, Bingxun Li, Ziyuan Meng, Jon R. Parquette*

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The importance of peptide-based nanomaterials is rapidly expanding due to their biocompatibility, tendency to self-assemble, structural diversity and design flexibility, ease of cellular uptake, and ability to function as a drug delivery carrier[1]. Previously, we synthesized rhodamine B-dipeptide conjugates, **RhB-KK/RhB-KE** (RhB: Rhodamine B, K: Lysine, E: Glutamic acid), that form stable nanotubes at physiological pH (λ_{max} 460 nm) but dissociate into highly fluorescent monomers (λ_{max} 580 nm) within the acidified interior of endosomal/lysosomal cellular compartments[2]. In this work, we have expanded the utility of our rhodamine-peptide nanotubes into a drug delivery carrier by (1) chemically conjugating 5-fluorouracil (5-FU) to RhB-KK/RhB-KE via a succinic acid linker using solid-phase peptide synthesis (SPPS) and (2) co-assembling them with CPT-KK nanotubes (CPT: Camptothecin). pH-Dependence studies have been carried out using UV-Vis, circular dichroism (CD), and fluorescence spectroscopy. **RhB-KK-5-FU** self-assembled into nanospheres with a diameter of ~ 16 nm, as characterized by transmission electron microscopy (TEM) and atomic force microscopy (AFM). The succinic acid linker is cleaved by intracellular enzymes through hydrolysis, releasing the free drug within the cells[3]. Co-assembly of **CPTKK** and **RhB-KE** nanotubes resulted in helical wrapping of CPTKK around RhB-KE nanotubes. The cellular uptake would be quantified using flow cytometry, and the movement of the drug inside different cancer cell lines would be visualized in real time using confocal laser scanning microscopy (CLSM). The cellular uptake pathway(s) employed will be investigated. We are also screening the structural changes that will enhance endosomal escape and increase the bioavailability of the drug. The cytotoxicity of the system will be measured using the MTS assay. In summary, our developed system would self-report the nanotubular assembly before it gets endocytosed. Once uptaken by the cells, it would emit 580 nm (from the lysosomes), indicating the monomeric state while simultaneously releasing the free drug inside the cells.

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Co^{III}-CATALYZED SEQUENTIAL C–H BOND ADDITION TO DIENES AND ONE-CARBON ELECTROPHILES: SYNTHESES OF α-QUATERNARY ALDEHYDES AND AMIDES

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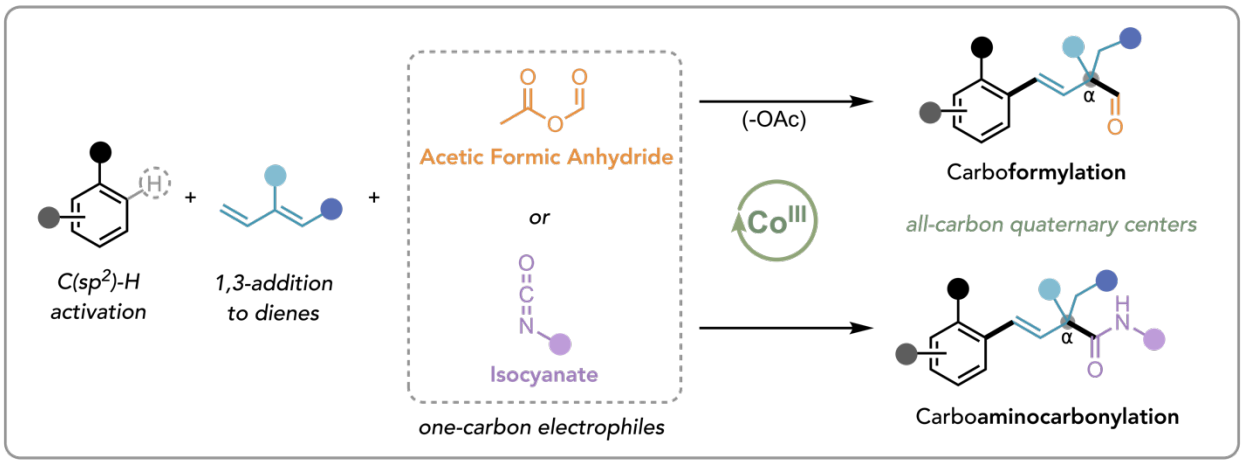
All-carbon α-quaternary aldehydes and amides were synthesized via Co(III)-catalyzed sequential C–H bond addition to 1,3-dienes and one-carbon electrophiles.[1] First, hydroformylation is an extensively studied reaction but faces challenges in synthesizing α-quaternary aldehydes, accessible by this new approach. This rare example of intermolecular carboformylation employed acetic formic anhydride as a formyl source with Proton Sponge® additive while circumventing the use of high-pressure toxic CO gas. The resulting aldehydes served as versatile intermediates, demonstrated by proline-catalyzed asymmetric aldol addition, olefination, reductive amination, and asymmetric amine synthesis using tert-butanesulfinamide technology. Mechanistic investigations suggested the potential roles of acetic formic anhydride and Proton Sponge® in a catalytic cycle.

Next, given the ubiquity of amides in industrially and biologically relevant products, a Co(III)-catalyzed carboaminocarbonylation method was developed.[2] Isocyanates, commercially available and scalable reagents, were used for C–C bond formation with 1,3-dienes to afford α-tertiary and quaternary amides. *N*-substitutions of secondary amides were modulated by incorporating different isocyanate inputs. The amide products could transform into other useful functional groups, such as carboxylic acids, γ-lactones, and amines. NMR studies of the reaction mixture also provided insights into the isocyanate activity in the reaction.



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Electrochemical Synthesis of C(sp^3)-Rich Amines by Aminative Carbofunctionalization of Carbonyl Compounds

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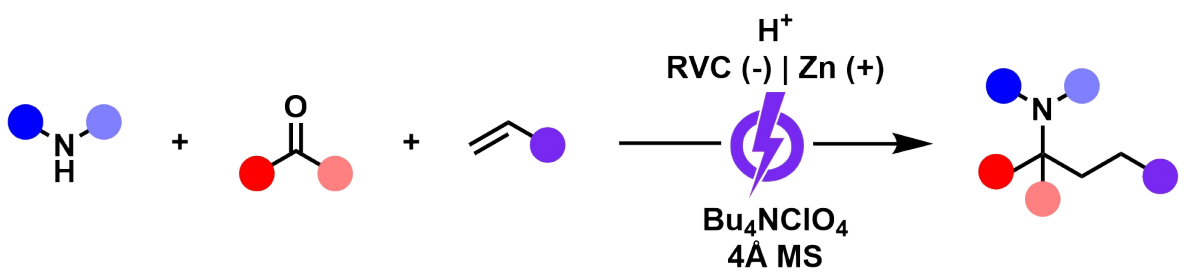
[B] - Department of Chemistry, Scripps Research, San Diego, California, USA

Amines are one of the most important classes of organic compounds and have a wide variety of applications including as building blocks for organic synthesis, and as bioactive molecules. Among amines, α-tertiary amines in particular have proven to be one of the most challenging synthetic targets. Existing synthetic methods to access α-tertiary amines often employ harsh conditions and suffer from high process mass intensity from the use of stoichiometric or superstoichiometric reagents. In recent years, electro-organic synthesis has emerged as a promising alternative to traditional organic synthesis, enabling novel, efficient, mild, and selective synthetic transformations. In this report, a new methodology for the synthesis of α-tertiary amines using electro-organic synthesis is described, efficiently assembling cheap and abundant building blocks into α-tertiary amines under mild conditions, with applications to the synthesis of fine chemicals and pharmaceuticals. Mechanistic studies reveal that the reaction proceeds via an ECEC mechanism involving cathodic reduction of an in situ-generated iminium to an α-amino radical intermediate; which undergoes radical addition to an olefin; followed by a second cathodic reduction and protonation. The optimization and scope of this reaction will also be presented.



No pyrophoric reagents | No PGM catalysts | Air- and water-tolerant | One-pot reaction | Undivided cell

Liu, W.-Q.; Lee, B. C.; Song, N.; He, Z.; Shen, Z.-A.; Lu, Y.; Koh, M. J. Electrochemical Synthesis of C(sp^3)-Rich Amines by Aminative Carbofunctionalization of Carbonyl Compounds. Angew. Chem. Int. Ed. 2024, 63 (26), e202402140. https://doi.org/10.1002/anie.202402140.

DESIGN AND SYNTHESIS OF BORYL ALLYLOXY CAGED LINKERS: DEMONSTRATION OF PEROXIDE-MEDIATED RELEASE OF A LATENT FLUOROPHORE FROM A FRET PAIR

Brittany Klootwyk, Grace Fleury, Savannah Albright, Alexander Deiters, and Paul E. Floreancig*

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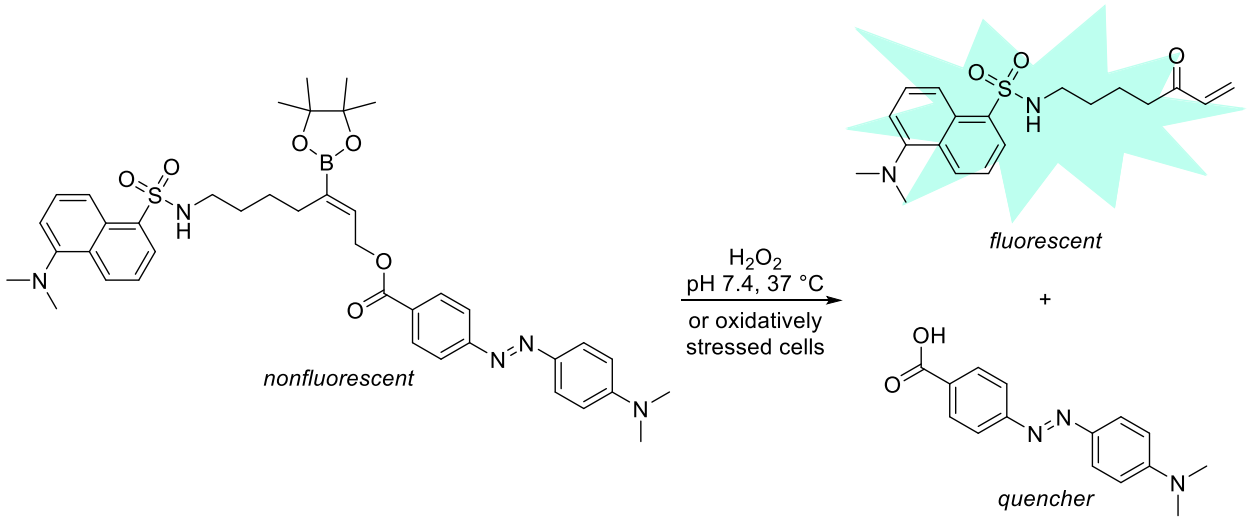
Boronic esters and acids undergo efficient oxidation in the presence of hydrogen peroxide to afford alcohols, ketones, and aldehydes. Several disease states, including cancer and viral infections, are characterized by oxidative stress. The increase of hydrogen peroxide concentration in diseased cells prompts the exploration into harnessing this small molecule in targeted prodrug strategies. This poster describes the synthesis of two boryl allyloxy (BAO)-caged linkers with a fluorophore-quencher pair, Dansyl and Dabcyl, installed for fluorescence monitoring. Peroxide-mediated release was demonstrated for both linkers using ^{1}H-NMR and fluorescence assays. Cellular assays revealed successful breakdown of the BAO-caged linker in the presence of both exogenous and endogenous hydrogen peroxide with selectivity of release observed in cancerous cell lines.[1]



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[1] Klootwyk, B. M.; Fleury, G. F.; Albright, S.; Deiters, A.; Floreancig, P. E. *Chem*. *Commun*. **2025**, *61*, 3375-3378.

INHIBITION OF ERK/MAPK PATHWAY BY INTRACELLULAR EXPRESSION OF A CIRCULAR RNA INTRAMER

Noushin Zahedi, David-Marian Otte, Maren Elisabeth Wojke and Günter Mayer *

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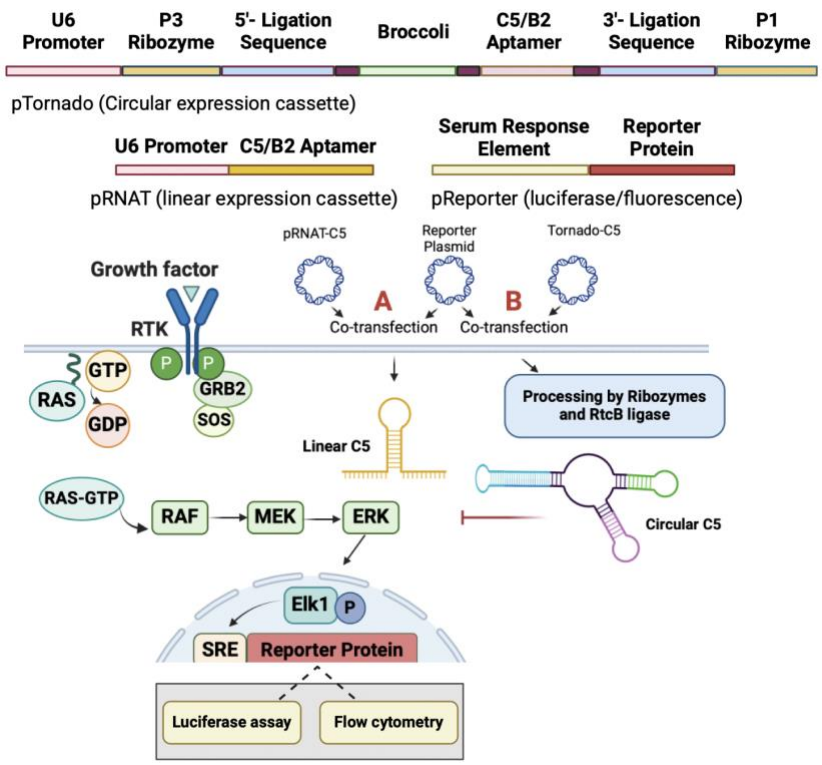
Effective protein targeting and disruption of molecular signaling complexes are essential for comprehensive analysis of signaling pathways and biological systems. Among the versatile approaches developed for this purpose, aptamers—nucleic acid sequences with high target specificity—have emerged as powerful tools for modulating protein interactions. Despite encouraging advances, the intracellular application of aptamers remains challenging mainly due to limitations in RNA stability. In this study, we employed the Tornado system (Twister-optimized RNA for durable overexpression) to enable the expression of an intracellular aptamer, termed the C5 intramer, which specifically binds to and inhibits extracellular signal-regulated kinases 1 and 2 (ERK1/2). Using luminescence and fluorescence reporter assays, we demonstrated significant inhibition of the mitogen-activated protein kinase (MAPK) pathway by C5 intramer expression in HEK293T cells. These findings underscore the potential of intramers as powerful tools for modulating protein activity and probing intracellular signaling cascades with high efficiency. A comparison of intracellular C5 expression via the Tornado system versus an alternative expression system, with respect to MAPK pathway inhibition, will be presented in our poster.



DESIGN AND DEVELOPMENT OF PHENANTHROLINE LIGANDS FOR HETEROARYL KETONE SYNTHESIS VIA CROSS-ELECTROPHILE COUPLING

Alyssa K. Olszewski, Paul Onnuch, Michael M. Gilbert, Jiang Wang, Daniel J. Weix*

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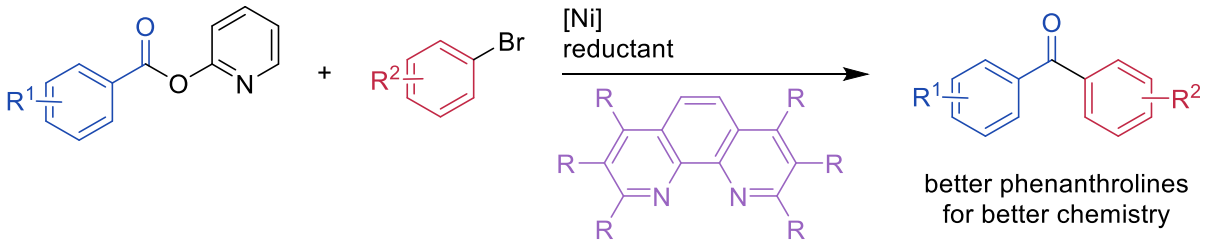
Mono- and bis-heteroaryl ketones are common structural motifs that appear in pharmaceuticals and natural products. While the Grignard addition to Weinreb amides is still a common synthetic route, methods that utilize commercially available and abundant substrates are still underdeveloped. We report a nickel-catalyzed cross-electrophile coupling (XEC) of (hetero)aryl bromides and 2-pyridyl esters synthesized from commercially abundant carboxylic acids. This coupling method and others that invoke acyl fragments often utilize 1,10-phenanthroline ligands, a class of ligands underexplored in XEC compared to 2,2'-bipyridine ligands. A library of structurally and electronically diverse 1,10-phenanthroline ligands was synthesized and screened in our model heteroaryl ketone synthesis. Through experimental screening data and DFT calculations of key (phen)[Ni] intermediates, insight into productive electronic and structural properties of 1,10-phenanthrolines in acyl-aryl XEC reactions is shown.



N-Substituted 1,4-Dihydropyridines as Novel Scaffolds for 1° Amine Activation

Holly Hutchinson,[†] Samantha L. Goldschmid,[†] Trevor C. Sherwood,[‡] Candice L. Joe,[§] Eric R. Welin,[#] Tomislav Rovis*,[†]

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[‡]*Discovery and Development Sciences, Bristol Myers Squibb, Princeton, NJ, USA*
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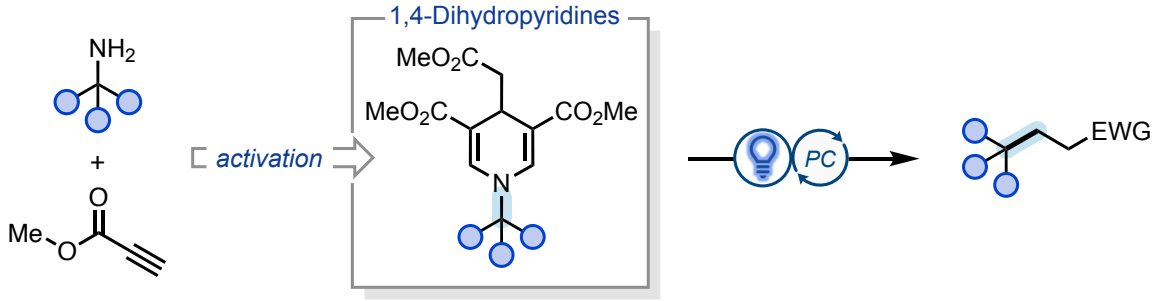
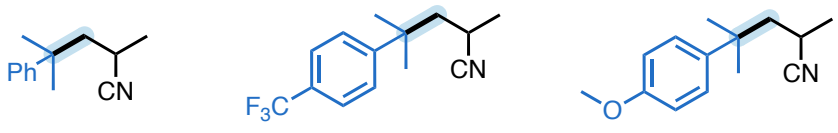
Primary amines are widely found in natural products, synthetic building blocks, and therapeutics. Accordingly, their structural diversity, low cost, and compatibility with late-stage functionalization render them highly attractive building blocks in organic synthesis. Recent advancements in deaminative functionalization methodologies, particularly those that leverage redox-active Katritzky salts and Redox Active Imines (RAIs), have revitalized interest in C–N bond activation. While these methods have been highly enabling for constructing valuable bond forming reactions, methods that liberate tertiary benzylic radicals in a controlled and selective fashion remain elusive. Specifically, the synthesis of an existing substrate class that liberates these radicals is inherently challenging, and the high stability of the resulting radicals can lead exclusively to radical dimerization. Nonetheless, controlled access to tertiary benzylic radicals represents a valuable strategy for constructing quaternary carbon centers, structural motifs known to enhance the pharmacological properties of therapeutics. Herein, we report a photoredox-catalyzed Giese reaction to achieve a novel C–N bond cleavage of 1,4-dihydropyridines, a substrate class readily synthesized from primary amines, to generate tertiary benzylic radicals for selective radical addition. Scope studies reveal broad tolerance of electron neutral, electron rich, and electron withdrawing substituents. Finally, mechanistic investigations support the cleavage of the C–N bond via single-electron oxidation of the 1,4-dihydropyridine.



• *Novel C–N bond cleavage* • *Access to 3° benzylic radicals* • *Quaternary centers*



66%
electron neutral

39%
electron deficient

48%
electron rich

Energy-Activated and Diversifiable Aryne Precursors from Carboxylic Acids

Felicia Yu†, Chris M. Seong†, Sallu S. Kargbo†, Daniel Gibney, Jan-Niklas Boyn*, Courtney C. Roberts*

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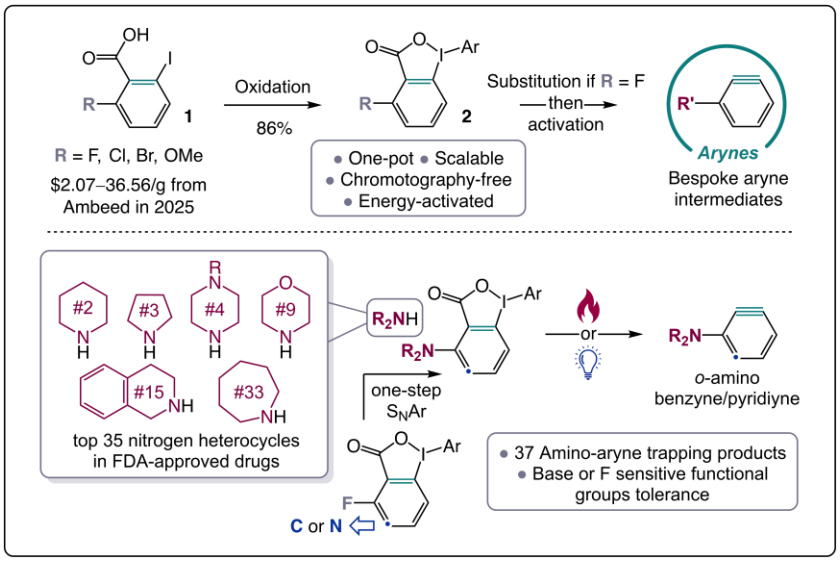
Densely substituted arene rings are ubiquitous in pharmaceuticals and agrochemicals which support human health and wellbeing. Arynes–a triple bond in a benzene ring–are an intriguing solution to the problem of generating decorated arenes. State-of-the-art aryne precursors are plagued by two issues: 1) the additives required for activation are incompatible with many desirable functional groups, and 2) derivatization of the precursors requires lengthy linear sequences rendering them impractical for discovery chemists. Here, we show the design of an aryne precursor made in a single step from a commercially available carboxylic acid and then derivatized in a single S_NAr step.[1] Unprecedented aryne activation proceeds using blue light or mild heat, avoiding the use of additives. The model system for this precursor incorporates an *ortho*-amino group in the final stage because anilines are found in 40% of medicinal chemistry patents and are highly underrepresented in aryne methodology. This approach has also contributed to pyridiyne due to pyridines as the most common scaffold among FDA-approved nitrogen-containing drugs. These precursors have the potential to supersede existing precursors and enable broad access to this desirable synthon.



[1]Under revision in Science; ChemRxiv. **2024**. DOI:10.26434/chemrxiv-2024-t6pcq

UTILIZING RHODIUM(III) CATALYSIS TO CONSTRUCT PEPTIDE MACROCYCLES

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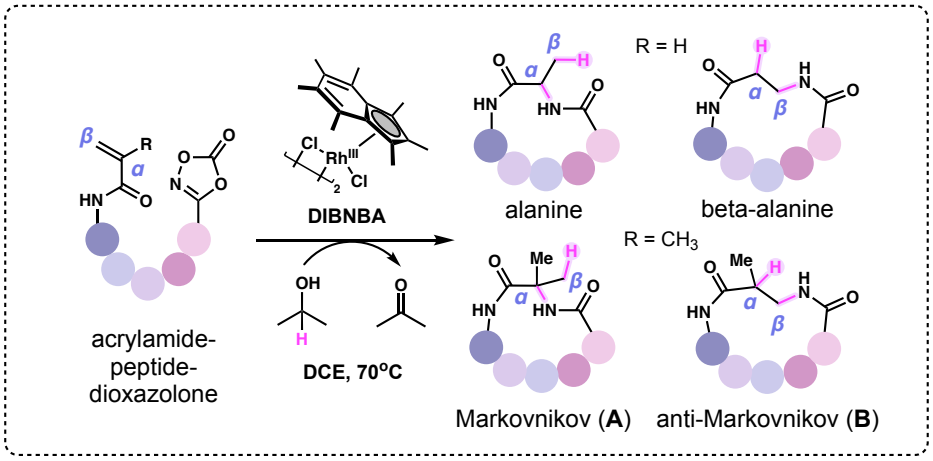
Peptide macrocycles have attracted significant attention in past decades for their unique ability to modulate both intracellular and extracellular protein-protein interactions. This capability is largely attributed to their function as a "smart molecule" allowing them to adopt to various environments. Thus, expanding the toolbox of synthetic peptide methodologies remains a critical focus to advancing modern drug design. While Rhodium-(III) has been extensively explored for C-N bond forming strategies, its application in peptide ligation has been underrepresented. In our work, we have successfully leveraged aryl carbons nucleophiles to form unnatural amino acid linkers derived from tyrosine, phenylalanine, and tryptophan[1]. More recently, we have harnessed hydride nucleophiles to obtain an alanine linker and other unnatural amino acid linkers including the elusive β[2]-homo-amino acids. Furthermore, we have demonstrated efficient synthesis of smaller peptide macrocycles such as tetramers and pentamers – structures that are traditionally more difficult to construct due to the inhert strain on medium sized rings. This presentation will highlight details of the reaction optimization and a preliminary scope of the macrocyclic peptides generated through hydride-based nucleophiles.



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[1] Lamartina, C.W.; Chartier, C.A.; Hirano, J.M.; Shah, N.H.; Rovis, T. *J. Am. Chem. Soc.* **2024**, 146, 30, 20868–20877.

IMPROVING THE EFFICIENCY OF SECONDARY METABOLITE EXTRACTION IN MICROBES THAT MAY PRODUCE ANTIBIOSIS

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This project is aimed at discovering secondary metabolites from microbes that produce antibiosis. This work is becoming increasingly essential as antibiotic-resistant bacteria continue to multiply and develop traits that are resistant to our current antibiotics. Discovering these metabolites will help improve the ability to fend off antibiotic-resistant bacteria. Thus, the goal is to find what makes these microbes active by identifying the metabolites they produce using methods such as the GC-MS. The research design involves isolating the strain producers present in the potentially antibiotic-resistant bacteria with more efficiency. Soil samples were collected primarily along the North Branch of the Chicago River. Dilution plates were used to find a countable number of colonies and look for unique colonies. A patch plate functioned as a clean library assay for the unique colonies. Streak plating was used to isolate the unique colonies. Antibiosis testing was conducted to identify which unique colonies can create antibiosis. The original samples of the potentially resistant microbes are from 2020. The secondary metabolites extraction methodology was explored via an ethyl acetate and water extraction, a methanol extraction, and a combination of the two, beginning with the ethyl acetate and water extraction. 10% TSA plates, 10% TSA broths, and cooked rice were compared as media to extract secondary metabolites. A Kirby-Bauer Disc diffusion assay was conducted for each extract. So far, none of the extracts from the tested isolated microbes have antimicrobial activity. Lastly, the GC-MS was used to identify metabolites with potential antimicrobial activity. Although initial disc-diffusion assays showed no significant zones of inhibition, GC-MS analysis revealed the presence of potentially antimicrobial metabolites, including pyrazine, ergot alkaloid, and coumarin derivatives. Additionally, the broth yielded more unique compounds and higher concentrations compared to agar plates and rice.

Cu-Promoted *ipso*-Hydroxylation of sp^2 C-H Bonds with Concomitant Aromatic 1,2-Rearrangement Involving a Cu-oxyl-hydroxo Species

Sunipa Goswami[a], Karan Gill[a], Xinyi Yin[a], Marcel Swart[b]*, Isaac Garcia-Bosch[a]*

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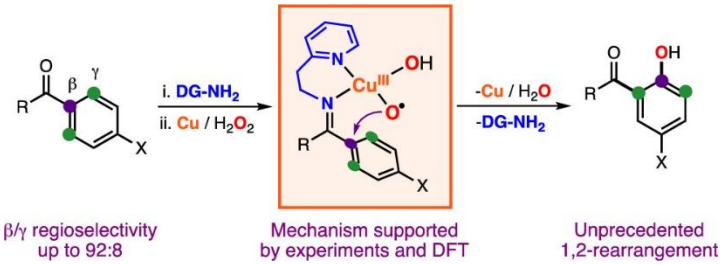
Cu-dependent metalloenzymes catalyze a wide array of oxidative transformations using O_2 as an oxidant under mild conditions. These include the hydroxylation of challenging organic substrates (e.g., oxidation of methane to methanol in particulate methane monooxygenase) and the regio- and enantioselective hydroxylation of complex molecules (e.g. benzylic hydroxylation of dopamine to noradrenaline in dopamine-b-monooxygenase). Lytic polysaccharide monooxygenases enzymes (LPMOs) promote the C-H hydroxylation and subsequent cleavage of the polysaccharide chains found in natural materials such as cellulose or chitin. Recent reports on the reactivity of LPMOs suggest that, instead of O_2, these Cu-dependent metalloenzymes utilize H_2O_2 as an oxidant. Due to the increasing demand for efficient and sustainable selective oxidation methods, extensive research in recent years has focused on copper-mediated hydroxylation of aromatic and aliphatic C-H bonds using oxidants like O_2 and H_2O_2. In this work, we showed that the utilization of copper, H_2O_2, and 2-(2-aminoethyl)pyridine as the directing group leads to β *ipso*-hydroxylation of substituted benzophenones. The *ipso*-oxidation induces a very unusual 1,2-rearrangement of the iminyl group to the vicinal γ position, an unprecedented transformation in metal-directed functionalization reactions[1]. The regioselectivity of this transformation was highly dependent on the directing group utilized (i.e., 2-picolylamine as DG led to γ C-H hydroxylation) and on the substituents of the benzophenone substrate (highly favored with 4-MeO substituents, up to 89:11 for the MeO-substituted arene ring and up to 92:8 for β *ipso*- vs. γ C-H hydroxylation). Oxidation products were characterized using NMR and GC-MS. Mechanistic studies (which include spectroscopic characterization (UV-vis) of reaction intermediates, kinetics, and calculations) suggested the formation of a mononuclear $Cu^{II}OOH$ species before the rate-determining step (rds) of the reaction. DFT calculations indicated that the γ C-H hydroxylation pathway involves a one-step concerted O-O bond cleavage and electrophilic aromatic attack. Conversely, β *ipso*-hydroxylation occurs in a stepwise fashion, in which O-O bond cleavage produces a Cu^{III}-oxyl-hydroxo species before electrophilic aromatic attack. Calculations also shed light on the mechanism of the 1,2-rearrangement step, which involves strain release from a spiro 5-membered to a 6-membered copper chelate.



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[1] Goswami, S.; Gill, K.; Yin, X.; Swart, M.; Garcia-Bosch, I., Cu-promoted *ipso*-hydroxylation of sp^2 bonds with concomitant aromatic 1,2-rearrangement involving a Cu-oxyl-hydroxo species, *Inorg. Chem.*, **2024**, *63*, 43, 20675–20688.

CONFORMATIONAL TUNING OF ARYLAMIDE FOLDAMERS USING AROMATIC SUBSTITUTION PATTERN

Brysa Alvarado, Haley Bolton, Joseph Meisel*

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Targeting deep hydrophobic pockets in disease-associated proteins with small molecules is a strategy commonly used in drug discovery. However, in the human proteome there remains an undruggable portion of proteins that small molecules fail to target. Many of these proteins lack targetable pockets and instead engage in protein-protein interactions (PPIs) that encompass large flat surface areas much larger than a small molecule. Arylamide foldamers are a class of short-chain oligomers that fold into well-defined conformations in solution and can be designed to present side chains to mimic protein surfaces and disrupt PPIs. To rationally design foldamer scaffolds that can mimic binding features, there remains a need to develop structural elements that control the conformational preference of foldamers in solution. We reason that the conformation of oligomers can be controlled by tuning the geometry around the arylamide bond that couples adjacent monomers. Here we describe the design and synthesis of arylamide foldamers comprising two to three monomers and investigate how the aromatic substitution pattern influences the conformation in solution and solid-state. Variable temperature and one-dimensional nuclear magnetic resonance (NMR) techniques and single crystal x-ray diffraction data suggest the main conformational determinants are hydrogen bonding and dipolar repulsion. We demonstrate that the foldamer conformation can be modulated by tuning the substitution pattern on the aryl ring. This study provides evidence for conformational control of arylamide foldamers to serve as valuable tools to mimic proteins and target PPIs of biomedical importance.

EXPLORING THE USE OF REDOX FOR THE FORMATION OF CHALLENGING BONDS FROM NICKEL AND PALLADIUM CENTERS

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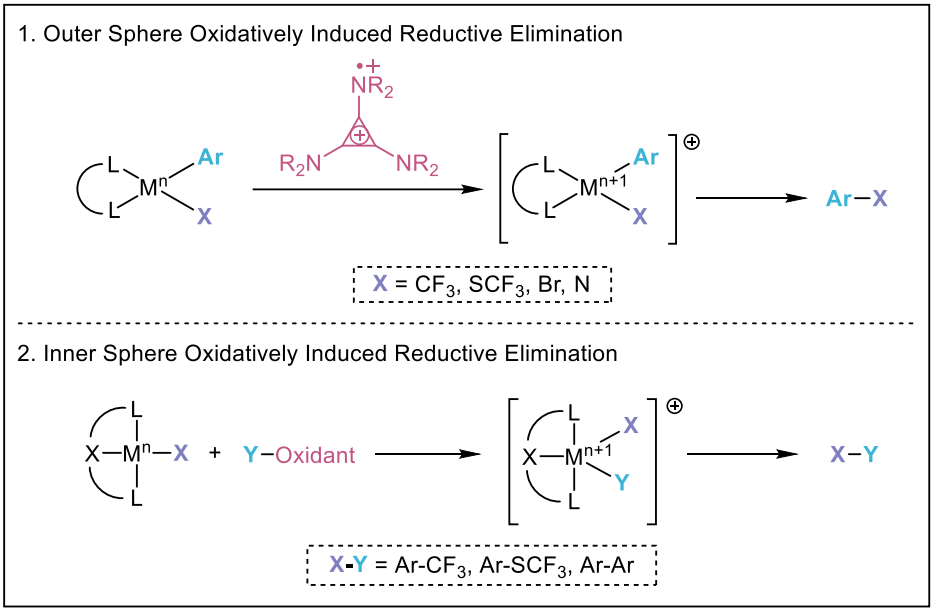
Oxidation of organometallic complexes can lead to changes in reactivity, allowing for new bond formations to occur. For instance, an inert organometallic complex bearing two R groups can be oxidized by *x* electrons, leading to facile reductive elimination to form carbon-carbon or carbon-heteroatom bonds.[1-2] Both outer-sphere and inner-sphere oxidants can be used to accomplish this same reactivity. Cyclopropenium molecules have been studied extensively for their use in catalysis as redox mediators, electrophotocatalysts, phase transfer catalysts, and as Brϕnsted bases.[3] Cyclopropenium radical dications are prime candidates for use as outer-sphere oxidants due to their high redox potentials, modularity, and stability. This work utilizes redox properties of metals to achieve the formation of difficult to form Aryl-X bonds, where X = Ar, CF_3, N, Br, F, SCF_3. Using the cyclopropenium radical dication as an outer-sphere oxidant, and inner-sphere oxidants such as arene diazoniums, diaryliodonium salts, and Umemoto's reagent, metal-mediated bond formation is explored from nickel and palladium centers.



[1] Bour, J. R.; Roy, P.; Canty, A. J.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2019**, *39* (1), 3–7. [2] Lanci, M. P.; Remy, M. S.; Kaminsky, W.; Mayer, J. M.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131* (43), 15618–15620. [3] Wilson, R. M.; Lambert, T. H. *Acc. Chem. Res.* **2022**, 55, 20, 3057–3069.

SYNTHESIS OF BENZISOTHIAZOLES AT A PRIMARY UNDERGRADUATE INSTITUTION

Kristen M. Baker*†, Amber S. Nickey†, Stefano E. Astudillo†, Bethany G. Dravk†, Nicholas T. Allen†, Olivia R. Terrazas†, Ariana Marshall† and Sophia N. Nightingale‡

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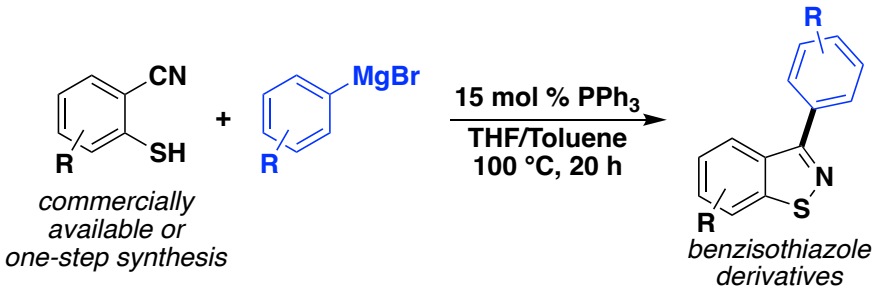
Benzisothiazoles are a privileged class of heteroaromatic compounds that have been shown to have a wide variety of insecticidal, antifungal, and antipsychotic activities. Despite their clear medicinal and agrochemical value, methods to synthesize benzisothiazoles still remain limited, with the most common methods utilizing substrates that require an expensive, multi-step synthesis. A more efficient method for synthesizing these compounds would potentially allow for further investigations into their biological activity. We have thus developed a cost-effective, one-step synthesis of benzisothiazoles from mercaptobenzonitriles. The current optimization and functional group tolerance of this reaction will be presented. This work was conducted entirely by undergraduate and high school researchers at a Primary Undergraduate Institution (PUI). In addition to our current chemical findings, the broader aspects and unique opportunities of conducting meaningful research at a PUI, including mentorship, student engagement, and the development of independent research skills, will also be discussed.



INTO THE UNKNOWN: COVALENTLY TARGETING RNA WITH ELECTROPHILIC WARHEADS

Marla Gravino, Adam Wier, Adam Albritton, Brittany S. Morgan*

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RNA is widely recognized for its role as a messenger in the central dogma. However, most RNA is non-coding and is largely understudied as structural, functional, and therapeutic characterization remains challenging. Though small molecules are useful tools to probe these properties, RNA is particularly challenging to target with traditional non-covalent ligands due to its dynamic nature. To overcome challenges with RNA dynamics, covalent chemistry can be utilized as RNA nucleotides contain nucleophilic positions that can react with electrophilic warheads, such as the 2'-hydroxyls that react with SHAPE reagents. Reacting RNA nucleotides with electrophiles will allow for a better understanding of reactivity with RNA. However, canonical and commercially available RNA nucleotides (NMPs) do not mimic RNA due to differences in the phosphate charges and the presence of a 3'-hydroxyl group. To address this gap, I designed RNA nucleotide mimetics that model the electronic environment of RNA; they contain ethylated phosphates with a -1 charge on both the 3'- and 5'-positions to mimic the charge state of an oligonucleotide while the ethyl groups mimic the "turn" of an additional nucleotide. Once synthesized, I will react these molecules *in vitro* with a library of diverse electrophiles and measure covalent bond formation by LC/MS. I will then utilize HPLC to quantify percent covalent bond formation of each reaction and NMR to identify where covalent bond formation occurred. I expect this screen to provide insights into RNA nucleotide reactivity, opening the door to capturing RNA selectively and elucidating the functions of this biological enigma.

SYNTHESIS OF NOVEL 3D CARBON ALLOTROPES: A BOTTOM UP APPROACH

Alyssa Bright and Christopher Douglas*

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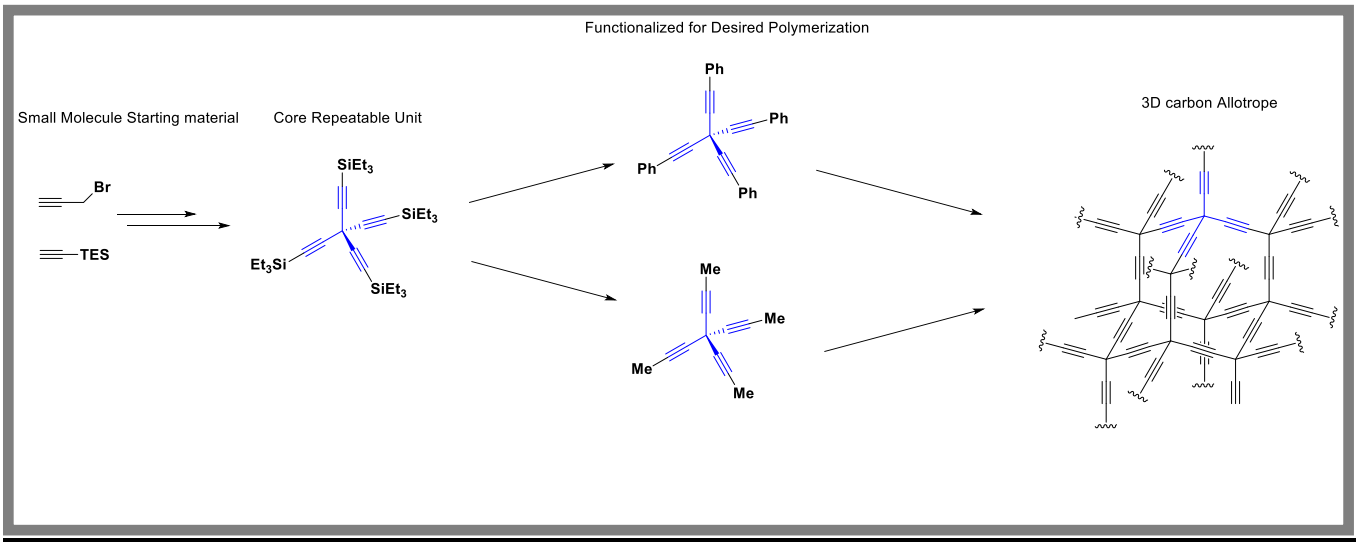
As the number of proposed 3D carbon network allotropes increases, synthetic chemistry has been challenged to develop comparable syntheses. A common strategy to making these theorized allotropes begins with the synthesis of a monomer precursor that sets a core repeatable unit with the desired geometry followed by further functionalization of the substituents to promote the polymerization of these monomers. My current work has focused on the initial steps of allotrope synthesis. A functionalization protocol of tetraethynyl methanes was developed based on previous work that provides a reliable route to the desired tetraethynyl core. We are also developing chemistry to prepare related ethynyl-substituted cyclooctatetraenes.



Photochemical Cyclization of α-Amino Esters to Access 3-Azetidinones

Meemie U. Hwang,[1] Achyut Gogoi,[2] Osvaldo Gutierrez,[2,*] and Prof. Karl A. Scheidt[1*]

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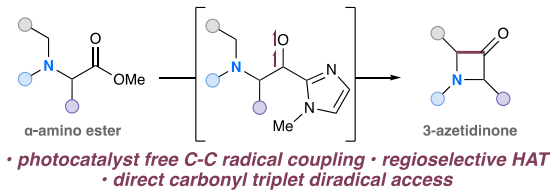
A light-driven cyclization of readily available α-amino esters to 3-azetidinones has been developed. This method leverages chromophore activation with the acyl imidazole to generate the triplet diradical species under mild conditions without the need for photosensitizers or transition metals. A selective hydrogen atom transfer event, followed by intramolecular Norrish-Yang radical coupling occurs to yield the *N*-heterocycle, with facile elimination of the imidazole group to access the 3-azetidinone. Computational calculations rationalize the selectivity of the Norrish Type I, Type II, and Norrish-Yang reaction pathways.



IRON-CATALYZED DECARBOXYLATIVE RADICAL ADDITION TOWARD BICYCLO[1.1.1]PENTANE

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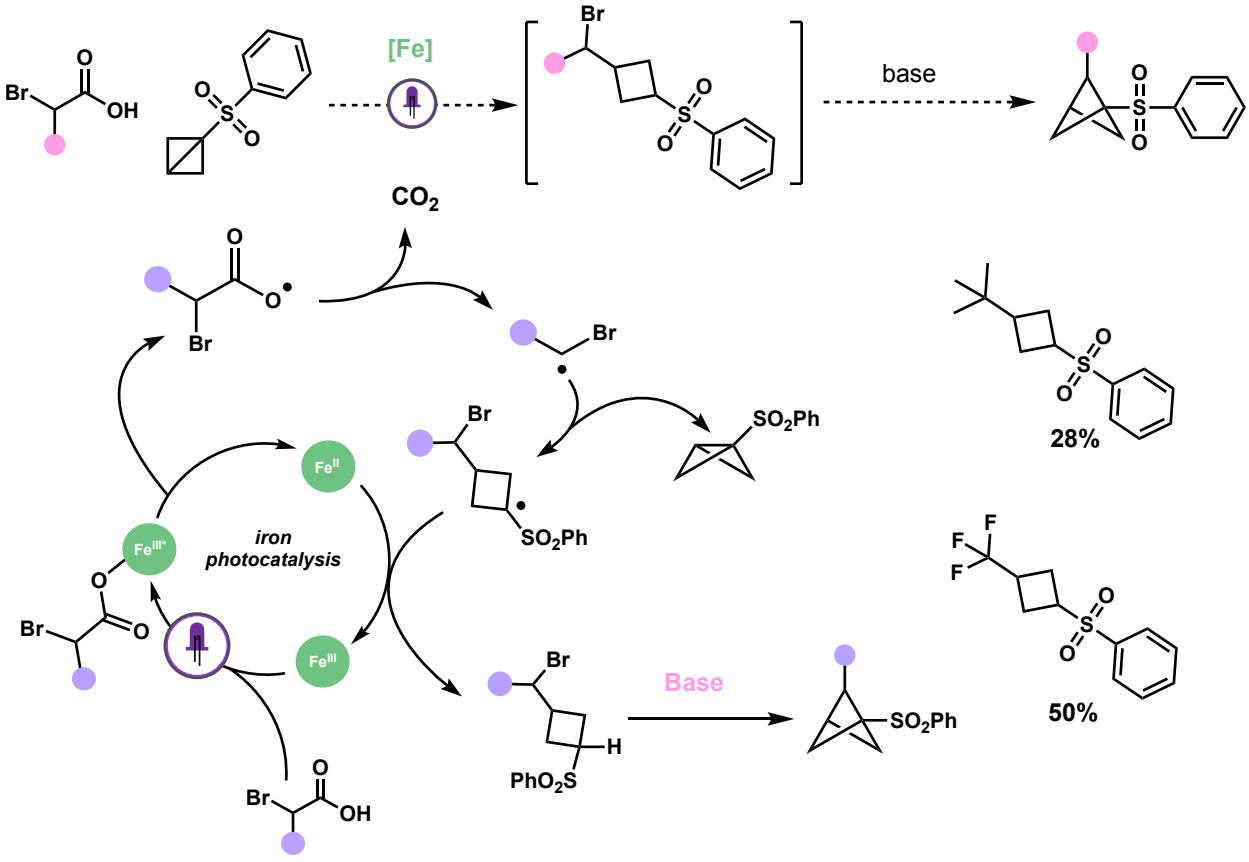
Bicyclo[1.1.1]pentanes are bioisosteric functional groups which can replace 1,4 substituted phenyl rings[1,2], enhancing drug lipophilicity and access to three-dimensional space.[3] Bridge-substituted bicyclo[1.1.1]pentane rings present a potential bioisostere for 1,2 substituted phenyl rings[4]; however, access to these bridge-substituted bicyclo[1.1.1]pentanes is difficult.[5] Iron-catalyzed decarboxylative radical addition work pioneered in our group[6] presents a potential method for accessing bicyclo[1.1.1]pentanes from bicyclo[1.1.0]butanes in a modular fashion. Surprising preliminary results and new research directions will be presented in this poster.



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PROGRESS TOWARDS EVALUATING THE FUNCTIONAL SELECTIVITY OF ENDOGENOUS D-AMINO ACID-CONTAINING NEUROPEPTIDES

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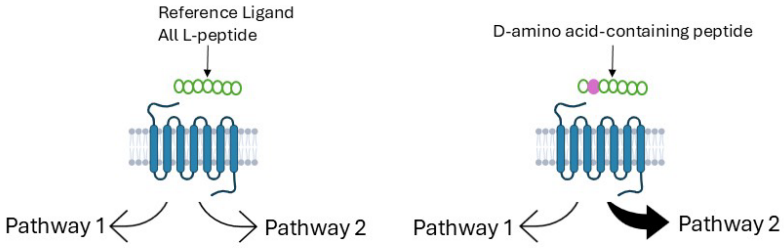
One of the understudied post-translational modifications that neuropeptides undergo is the conversion of L-amino acid residue to its corresponding D-amino acid residue. D-amino acid-containing peptides (DAACPs) have been shown to play significant biological roles, though these functions remain underexplored due to the lack of identified receptors for DAACPs. Currently, only two receptor classes for DAACPs are known: the achatin receptor, found in both *Aplysia californica* and *Platynereis dumerilli*, and two allatotropin-related peptide (ATRP) receptors (*ap*ATRPR1 and *ap*ATRPR2) in *Aplysia californica*. Only the D-amino acid-containing analog of achatin activates the achatin receptor in both *Aplysia* and *Platynereis*, while both the all-L-analog of ATRP (all-L-ATRP) and its corresponding D-amino acid-containing analog (D2-ATRP) activate the *Aplysia* ATRP receptors. We hypothesize that one diastereomer may differentially activate intracellular signaling pathways relative to all L-ATRP. In IP1 and cAMP assays performed with transiently transfected CHO-K1 cells, all-L-ATRP is a more potent activator of *ap*ATRPR1, whereas D2-ATRP activates *ap*ATRPR2 more effectively. However, *ap*ATRPR2 is more sensitive to D2-ATRP when signaling through $G_{\alpha s}$ pathway as compared to $G_{\alpha q}$ pathway. Similarly, *ap*ATRPR1 is more sensitive for all-L-ATRP when signaling through $G_{\alpha s}$ pathway as compared to $G_{\alpha q}$ pathway. These results suggest that the isomerization of L-amino acid residue to D-amino acid residue leads to preferential activation of one signaling pathway over another. To further investigate this hypothesis, we are conducting IP1, cAMP, β-arrestin, and pERK assays for both *ap*ATRPR1 and *ap*ATRPR2. Ligand bias will be assessed by calculating the bias factors using an operational model of agonism. This research will help us better understand the role of L- to D-residue isomerization in cellular signaling. Moreover, the presence of DAACPs across phyla suggests that cellular signaling involving DAACPs is not restricted to *Aplysia* or *Platynereis* and the knowledge of functional selectivity could be relevant to other systems.



STEREOINVERTED E2 UNLOCKS *Z*-SELECTIVE C–H FUNCTIONALIZATION OF TERMINAL ALKENES

Authors: Elizabeth A. Ryutov[1], Peter J. Verardi[1], Poulami Mukherjee[2], Remy Lalisse[2], Karina Targos[1], Tetsuya Inagaki[3], Megan Kelly[4], Ilia A. Guzei[1], Marcel Schreier[4*], Osvaldo Gutierrez[2*], and Zachary K. Wickens[1*]

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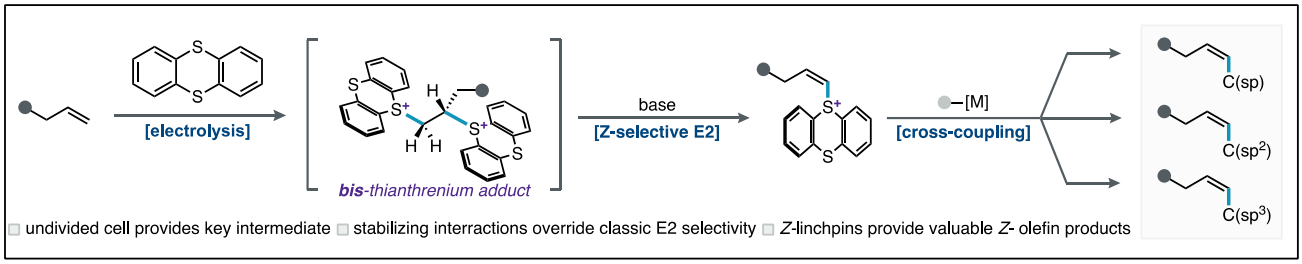
The stereoselective functionalization of C–H bonds represents a central challenge in modern organic synthesis. Despite decades of innovation in C–H activation chemistry, methods for *Z*-selective functionalization of alkenes have so far eluded synthetic practitioners. Terminal alkenes present the most vexing challenge for *Z*-selectivity, as they require selective cleavage of the more hindered of two otherwise virtually identical C–H bonds. Herein, we describe a fundamentally new strategy for *Z*-selective C–H functionalization. Our approach hinges on the transformation of alkenes into transient 1,2-*bis*-sulfonium intermediates found to undergo *Z*-selective elimination, overturning a textbook E2 stereoselectivity rule. We identify paired electrolysis as a uniquely enabling strategy to both selectively generate the requisite *bis*-sulfonium intermediate and drive its rapid elimination *in situ*. The resultant *Z*-alkenyl sulfonium linchpins provide access to a wide array of *Z*-alkene targets from inexpensive feedstocks through robust cross-coupling reactions. Beyond providing a practical approach to *Z*-alkene synthesis, this work illustrates how stabilizing interactions can override intrinsic steric preferences in elimination reactions.



EFFORTS TOWARDS THE TOTAL SYNTHESIS OF BALGACYCLAMIDE C

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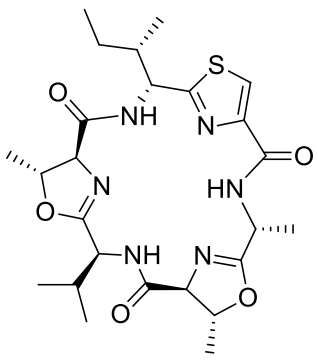
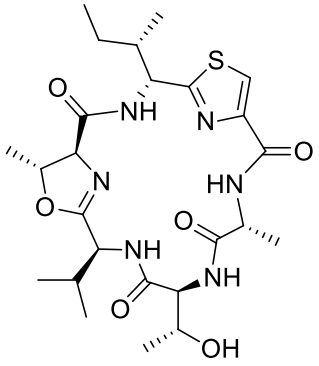
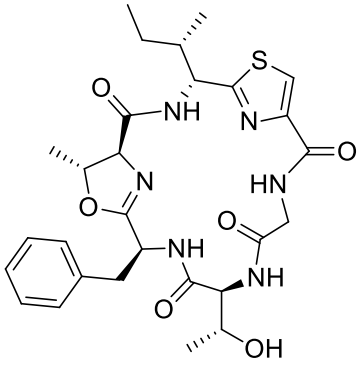
The balgacyclamide family consists of three heterocyclic and macrocyclic peptides, balgacyclamide A-C. These natural products were isolated from Microcystis aeruginosa, a phototropic cyanobacteria, which is found in eutrophic water bodies worldwide. Balgacyclamide A and B have been reported to have antiparasitic activity toward P. falciparum; however, there has been no biological activity reported for balgacyclamide C. Structurally, balgacyclamide A-C all contain three main components in the macrocyclic peptide: an oxazoline ring, a thiazole ring, and a dipeptide unit (linear or cyclized). There are two main differences between the structures of A/B and C that could impact the biological activity of these natural products. Balgacyclamide A and B both have valine in the oxazoline component, whereas C has phenylalanine. Another structural difference is that A and B have alanine incorporated in the dipeptide component, whereas C has glycine. The incorporation of alanine in the dipeptide component creates an additional chiral center that glycine does not. The result of one less chiral center, could be an explanation of the limited biological activity of balgacyclamide C. In this research, current efforts have been made toward the first total synthesis of balgacylamide C, as well as an analogue with the incorporation of alanine instead of glycine, to test the hypothesis that the additional chiral center from alanine is required for biological activity. Two possible routes have been explored in the synthesis: one route through single amino acid coupling and the other through a tetrapeptide intermediate with the incorporation of a pseudo-proline to favor macrocyclization.



Balgacyclamide A



Balgacyclamide B



Balgacyclamide C

ALIPHATIC TRANSMUTATIONS VIA AN INTERRUPTED NITROGEN DELETION

Isabelle E. Petrucci, Jeanne Masson-Makdissi, Zisheng Xue, Mark D. Levin*

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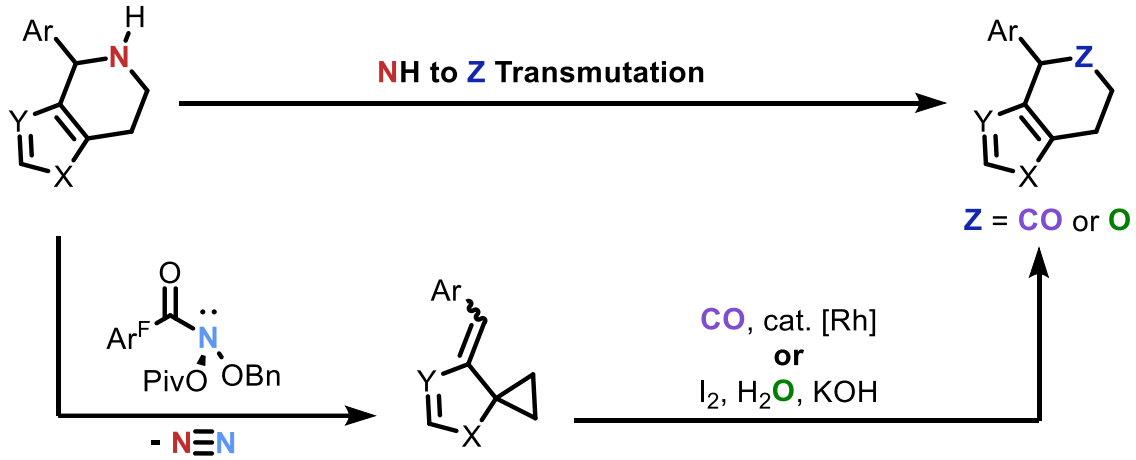
Single atom transmutations, wherein one constituent atom of a ring or chain is replaced with another atom, are a powerful strategy in synthetic chemistry to modify the skeleton of a molecule in a rapid and precise manner. While there are numerous examples of single atom transmutations on aromatic systems, the analogous transmutations on aliphatic systems are not as well studied, in part because of the difficulty of activating C(sp^3)-C(sp^3) bonds. Here, we demonstrate that heteroaromatic-fused piperidines undergo a nitrogen deletion in the presence of the anomeric amide to give dearomatized vinyl cyclopropanes. These interrupted N-deletion products can then undergo further transformations to give formal aliphatic transmutations, including a rhodium-catalyzed [5+1] cycloaddition with carbon monoxide to give NH-to-CO ketone products and an iodine-promoted oxidative ring opening to afford NH-to-O ether products.



Cascade Grignard Addition – Propargyl Claisen Rearrangement for the Stereoselective Synthesis of α-Allene Quaternary Centers in Cyclohexanone

Estefania Armendariz-Gonzalez,‡ Adi Saputra,‡ Edward W. Mureka, Cale M. Locicero, Gabrielle L. Womble, Abigail A. Watson, Frank R. Fronczek, and Rendy Kartika*

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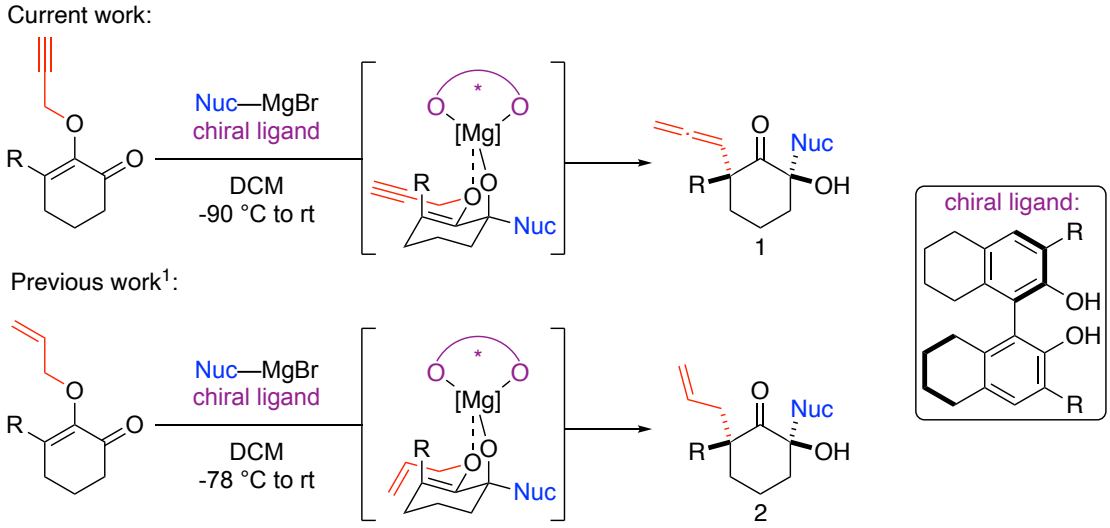
The Claisen rearrangement, discovered in 1912, is a widely used strategy for constructing carbon-carbon bonds. The feasibility of this mechanism is attributed to the generally accepted concerted chair-like conformation of the transition state, which facilitates the formation of sterically congested carbon centers. The stereoselectivity of the resulting compounds can then be controlled via preexisting internal or external effects. This presentation will discuss recent work that uses a novel synthetic approach that employs a chiral magnesium-chelated chair enolate complex generated in situ to produce stereo-enriched products 1 and 2. Our method is then showcased in a more complex molecule setting, in up-scaled conditions, and with further synthetic transformations.



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LARGE LANGUAGE MODELS (LLMs) FOR REACTION DATA EXTRACTION

Gisela A. Gonzalez-Montiel,[†] Mihir Surve,[†] Thierry Kogej,[‡] Samuel Genheden,[‡] Felix Faber,[‡] Per-Ola Norrby,[‡] Olaf Wiest*[†]

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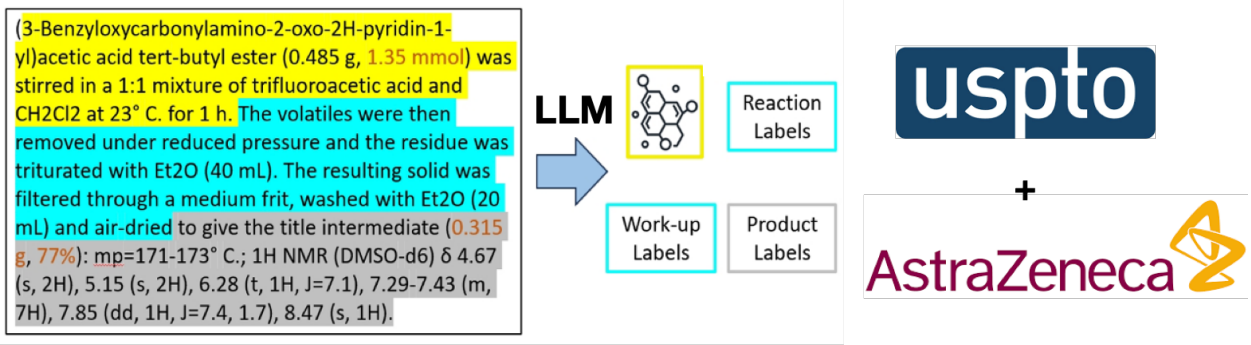
Large Language Models (LLMs) have demonstrated significant advancements across various scientific domains, assisting with tasks such as molecule design, property prediction, and literature analysis.[1] Despite these successes, their proficiency to extract chemical reaction information from diverse sources such as industry databases and academic publications is not well understood.[2] This study evaluates the performance and accuracy of LLMs in extracting and converting chemical information from text into structured output schemas. We assess LLMs using techniques like Pydantic models, prompt engineering (PE), and in-context learning (ICL) to enhance their potential in scientific applications. A proof of concept with OpenAI *gpt-4o* (nonlocal API) focuses on its ability to extract and structure the information from AstraZeneca Buchwald-Hartwig electronic lab notebooks (BH-ELNs) and US Patent database (USPTO).[3] Instruction tasks include identifying reaction components, reaction conditions, workup procedures, order of action, and characterizations. Verification is achieved through cross-validations, benchmarking, ground truth comparisons, and manual spot-checks to address errors like hallucinations. Additionally, a parallel, collaborative study is underway with Llama 3.2 *Ollama* (local API) on internal datasets from AstraZeneca (local ELNs and CRO reports). Preliminary results suggest promising performance for both types of LLMs. We envision that these studies will link LLMs to the integration of retrosynthesis programs and optimization protocols, such as Open Reaction Database (ORD)[4], thereby enhancing research efficacy through structured data templates.



[†] *Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556, USA. E-mail: owiest@nd.edu*
[‡] *AstraZeneca, Gothenburg, SE-431 83 Mölndal, Sweden.*

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METAL MAYHEM: SYNTHETIC EFFORTS TOWARDS TEREDINIBACTIN A AND ANALOGS

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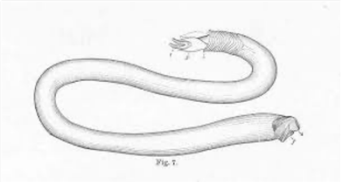
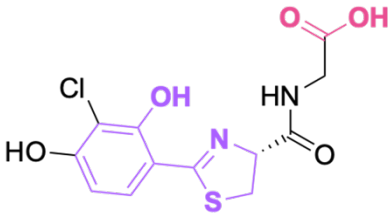
Antibiotic resistance represents a growing global health emergency, with projections indicating it could become the leading cause of death by 2050 and incur trillions in healthcare expenditures. A major obstacle in combating resistance is the limited pipeline of antibiotics with novel mechanisms of action. Recent strategies have shifted toward targeting bacterial virulence through disruption of metal homeostasis, which may work to minimize selective pressure for resistance. Siderophore natural products are of particular interest due to their metal-chelating capabilities—especially with biologically relevant ions such as Fe(III), Cu(II), and Mo(VI). Teredinibactin A (**1**), a structurally unique natural product, exhibits binding affinity for all three metals, yet its biological activity remains uncharacterized. Here, we report a streamlined four-step longest linear sequence for the total synthesis of Teredinibactin A, enabling access to sufficient material for biological studies. Additionally, we describe the design and synthesis of structurally guided analogs to probe structure-activity relationships and assess metal-binding preferences. This work lays the foundation for future investigations into the therapeutic relevance of Teredinibactin A and related scaffolds.





Teredinibactin (**1**)

STEREODIVERGENT ASSEMBLY OF A COMMON DECALIN INTERMEDIATE IN COMPLEX TERPENOID ARCHITECTURES

Samantha L. Barlock, Alexander S. Shved, Kayla D. Landers, Shogo Fujiki, Binh Khanh Mai, Peter C. Ryffel, Andrew Lo, Viet D. Nguyen†*, David A. Petrone†*, Scott E. Denmark*, and David Sarlah‡*

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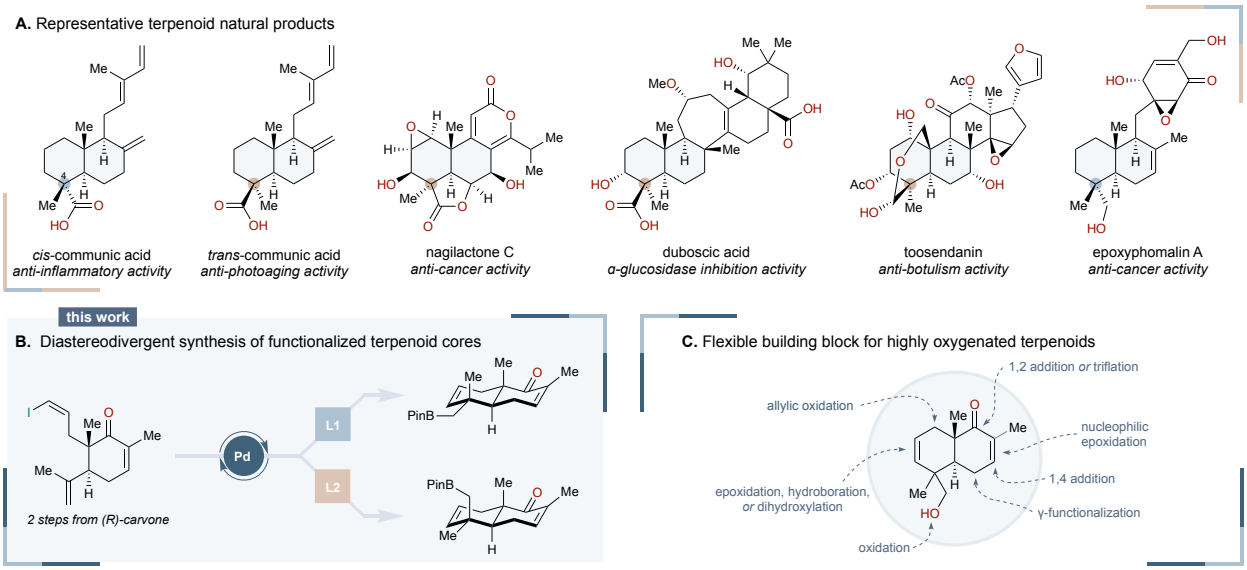
Thousands of highly oxygenated terpenoid natural products contain a common *trans*-decalin core bearing either axial or equatorial functionalization at the C(4) quaternary center. We report an expedient route to a versatile terpenoid building block primed for elaboration into numerous complex natural products. This intermediate is provided from (*R*)-carvone, a cheap and abundant chiral pool material, in three steps through a diastereodivergent borylative Heck reaction. Notably, this method uniquely provides either equatorial or axial functionalization products from a single, common precursor. Identification of optimal ligands required extensive screening efforts facilitated in part by high-throughput experimentation (HTE). Ultimately, incorporation of ligands identified by a large combinatorial *in silico* approach into an evolving HTE strategy facilitated discovery of an optimal phosphoramidite ligand. Key interactions responsible for the observed high diastereoselectivity were examined with density functional theory (DFT), distortion-interaction analysis (DIA), and energy decomposition analysis (EDA) studies. The synthetic utility of this diastereodivergent strategy towards accessing terpenoids possessing stereochemically diverse oxidation patterns was demonstrated in the total synthesis of several abietane and labdane diterpenoids.



Rearrangements of oxy-substituted allyl silanes

Darshika Singh, Emmanuel W. Maloba, Luis M. Mori-Quiroz, Robert E. Maleczka, Jr.*

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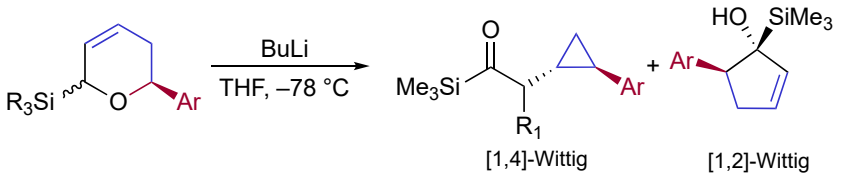
Our research on the Wittig rearrangements led us to explore the chemistry of other different oxy-substituted allyl silanes. The Wittig rearrangement has proven to be an essential tool in organic synthesis for C—C bond formation. Such rearrangements can be initiated either by silicon-lithium exchange or deprotonation α to the silane. The regioselective ring contraction of 2-silyl-pyrans via [1,2] or [1,4] pathways depend on both electronics of aryl substituents on the pyran and sterics of silyl groups.[1] Furthermore, 4-silyl-5,6-dihydropyrans undergo highly selective [1,4]-Wittig rearrangements to give silyl cyclopropane acetaldehydes in good yields. Generally, the substrates with migrating groups with electron-rich or electron-neutral characters provide high selectivity. Notably, the silyl and alkyl groups end up in a cis relationship.[2] Additionally, an acid-catalyzed [1,2]-carbon-to-carbon silyl migration of α-hydroxy allyl silanes for synthesizing α-silyl aldehydes will be presented.

(A) Regioselective Wittig rearrangement

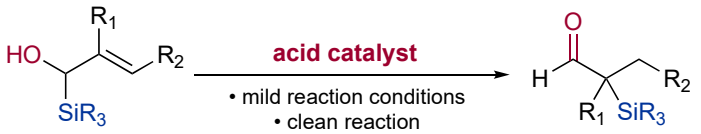


For trans: *n*-BuLi (1.2 equiv.), 10-30 min
For cis: *sec*-BuLi (3.0 equiv.), 3 h

larger SiR_3 groups
electron–rich Ar

smaller SiR_3 groups
electron–deficient Ar

(B) An acid-catalyzed [1,2]- carbon to carbon silyl migration



- mild reaction conditions
- clean reaction
- no purification required

up to 97%, 12 examples

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DESIGN, SYNTHESIS, AND THERAPEUTIC EXPLORATION OF NOVEL DERIVATIVES OF NATURAL PRODUCTS

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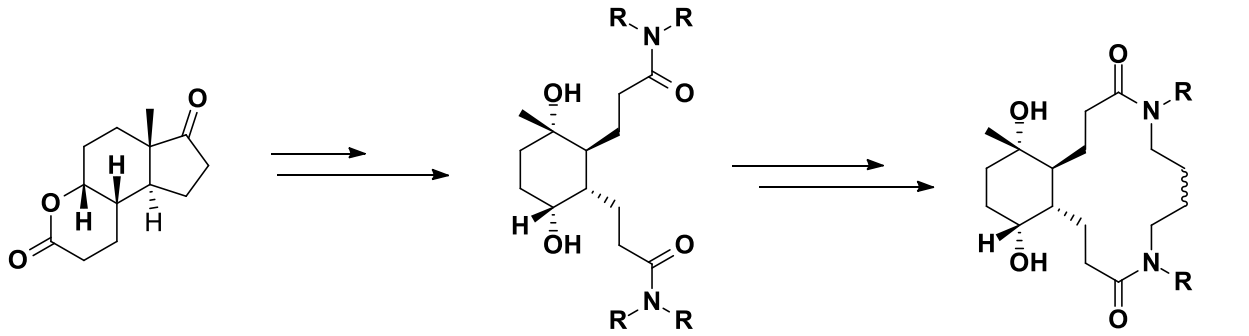
Natural products play a significant role in drug discovery, primarily in infectious diseases and cancer. They provide a bank of rich and complex chemical structures that have evolved to acquire specific ligand-protein binding motifs over the years. These have been utilized as leads in generating compounds with increased potency and activity while retaining the parent scaffolds.

Employing natural products as starting materials to generate new scaffolds for novel biological activities is an underexplored strategy that provides structurally complex molecules with physicochemical properties analogous to those of natural products. These derivatives can be accessed as rapidly as synthetic compounds because natural products offer excellent frameworks for site-selective and stereoselective transformations. In using natural products as the starting points for complex molecule synthesis, diversity can be added to the complexity already installed by nature.

This study focuses on designing and synthesizing novel scaffolds from natural products to create libraries of small molecules for their potential therapeutic ability. In this study, δ-lactone, a steroidal natural product with no reported biological activity, and stevioside, a diterpene glycoside, are synthetically modified by incorporating amide functionalities and macrocyclic frameworks to generate a library of compounds that are screened for their therapeutic potential.



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Sustainability in the Design of Automotive Coatings

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Coatings are an essential part of vehicle and infrastructure maintenance and sustainment. They provide both protection from the environment for a longer lifetime and a desired functional and aesthetic value. Many coatings used by various industries rely on liquid applied thermoset coating technologies that utilize a liquid carrier to enable application followed by thermal curing to develop desired properties. Both of these key enablers to current technologies are under regulatory and societal pressures to have a reduced impact on workers and the environment all while maintaining or improving manufacturing productivity. New features and technologies for industrial coatings can deliver significant benefits via reduced Environmental, Health, And Safety (EHS) risks while improving maintainability and sustainability. The need for coatings solutions that have decreased Volatile Organic Compounds (VOC) but can maintain or improve performance and productivity is a constant commercial need. For example, in the manufacture and repair of automobiles significant effort and cost goes into managing throughput, productivity, energy usage, and VOC output of a coating process. In industry, these efforts must stay in compliance with regulations while maintaining profitability. Further, in the repair and maintenance of vehicles, coatings are needed that can perform similarly to the original finish but often with different application and curing conditions. In this case, coatings with improved sustainability via a reduced EHS risk, lower energy cure requirements, and/or reduced VOC content may be more critical to allow for improved worker safety while also enabling efficient repair processes and regulatory compliance.

LEVERAGING COMPUTATIONAL METHODS TO DEVELOP STEREOSELECTIVE SYNTHESES

Jacquelin Zak, Elizabeth Reinbold, Laura Andreola, Paul Helquist*, Olaf Wiest*

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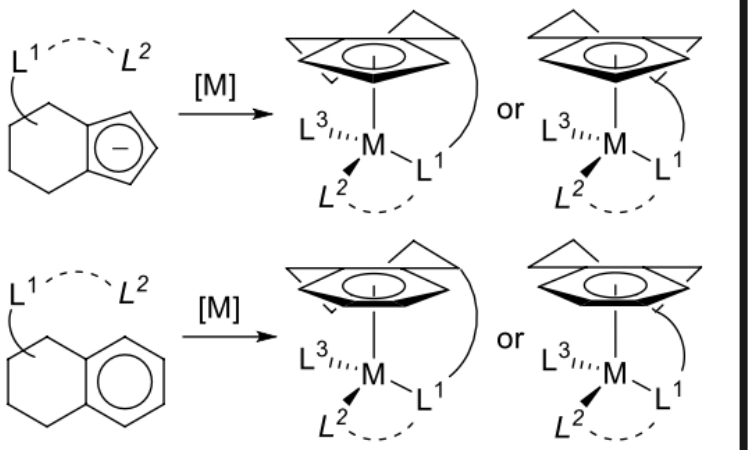
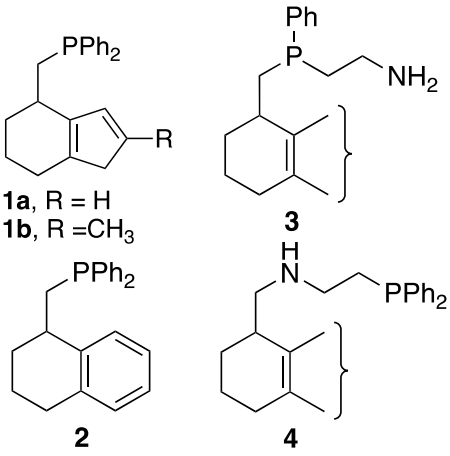
Quantum guided molecular mechanics (Q2MM) accelerates the ligand selection and the design of enantioselective catalysts using transition state force fields for stereoselective reactions which predict enantiomeric excess for known ligands and reactions (i.e. reductions of enamides and ketones) with accuracies better than <0.5 kcal/mol.[1] This project widens the application of Q2MM by developing a predictive forcefield for novel ligand types with novel synthetic utility. We describe the computational design of "piano stool" ligands where the fused ring system limits conformational space which could increase selectivity for asymmetric hydrogenation reactions. This project includes testing the feasibility of complexation of ligands to the metals and other features that influence enantioselectivity. We anticipate that the predictions of stereoselectivity and ability to complex of the half sandwich ruthenium transition states will enable highly stereoselective synthetic routes for the preparation of alcohols with high enantiomeric excess.



Fused Ring Ligands of Choice



1a, R = H
1b, R =CH_3

2 **3** **4**

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[1] Rosales, A. R.; Quinn, T. R.; Wahlers, J.; Tomberg, A.; Zhang, X.; Helquist, P.; Wiest, O.; Norrby, P.-O. Application of Q2MM to Predictions in Stereoselective Synthesis. Chem. Commun. 2018, 54 (60), 8294–8311.

ENANTIOSELECTIVE ISOPRENE-MEDIATED CARBONYL *TERT*-PRENYLATION *VIA* CHIRAL-AT-RUTHENIUM-SEGPHOS CATALYST

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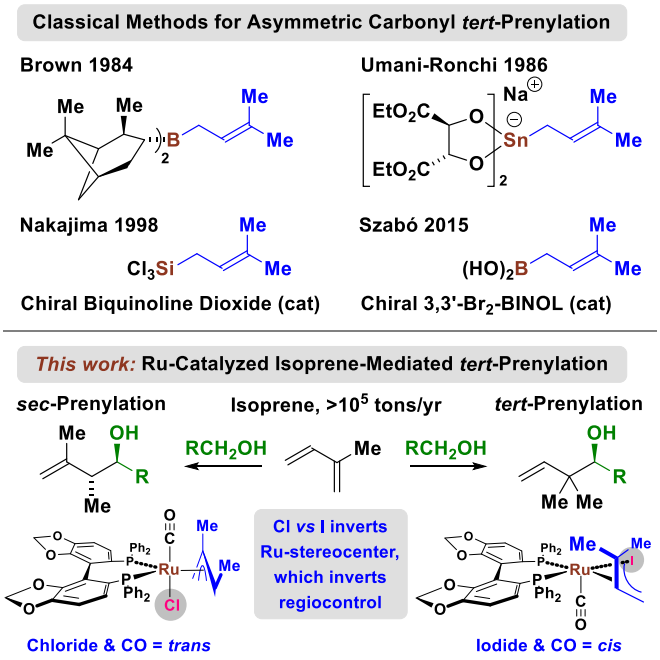
Chiral secondary alcohols are present in numerous natural terpenoids and polyketides, exhibiting diverse pharmaceutical activities. Classical asymmetric carbonyl addition methods rely on stoichiometric pre-metalated reagents. In contrast, hydrogen auto-transfer allows C-C bond formation from alcohol proelectrophiles to π-unsaturated pronucleophiles, generating transient carbonyl-organometal intermediates, that undergo carbonyl addition *in situ*. This approach bypasses preformed organometallic nucleophiles, avoiding stoichiometric metallic byproducts.

This work showcases the coupling of isoprene (>10^5 tons/year) as a pronucleophile to primary alcohols, being the *first* catalytically enantioselective isoprene-mediated carbonyl *tert*-prenylation, a common motif in natural products. This study also delineates the *first correlation* between metal-centered stereogenicity and regioselectivity in a catalytic process. We explored pseudo-diastereomeric chiral-at-ruthenium complexes of the type RuX(CO)[η^3-prenyl][(S)-SEGPHOS], where X = Cl and I, which exhibit halide-dependent formation and divergent regioselectivity in catalytic C–C couplings. Specifically, the chloride-bound ruthenium-SEGPHOS complex favors the formation of *sec*-prenylation products, whereas the iodide-bound ruthenium-SEGPHOS yields *tert*-prenylation products.[1]



[1] Shezaf, J. S.;‡ Santana, C. G.;‡ Saludares, C.; Briceno, E. S.; Sakata, K.; Krische, M. J. *J. Am. Chem. Soc.* **2023**, *145*, 18676–18683.

DEVELOPING PHOTOAFFINITY PROBES FOR DOPAMINE RECEPTOR D2 TO DETERMINE TARGETS OF PARKINSON'S DISEASE DRUGS

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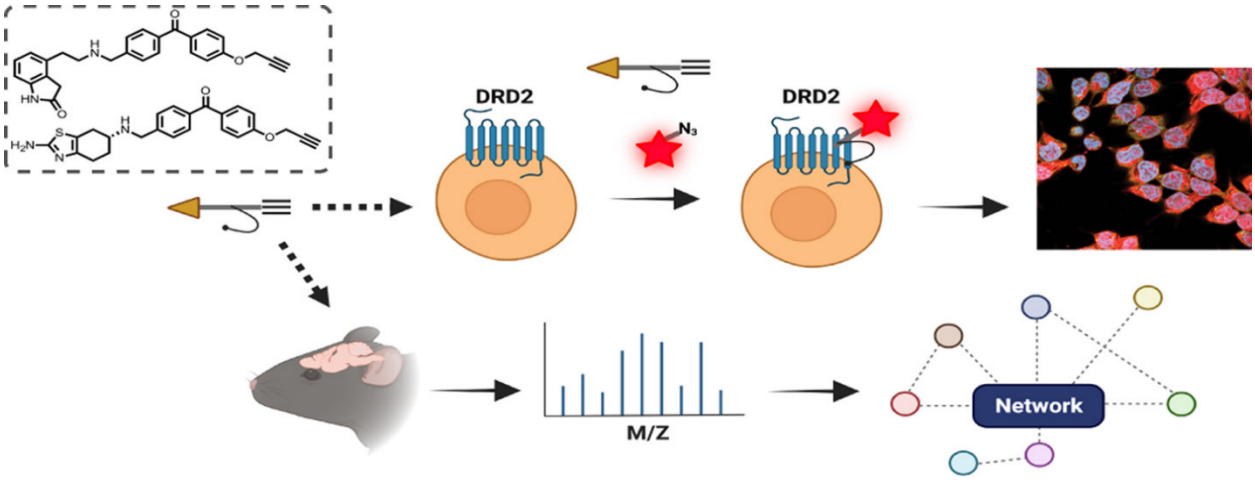
Dopaminergic pathways control crucial aspects of physiology and behavior. One of the most therapeutically important and best-studied receptors in these pathways is dopamine receptor D2 (D2R). Unfortunately, D2R is difficult to study by traditional techniques, and most drugs designed to target D2R are not specific to this receptor subtype. Here, we developed probes able to both covalently bind to D2R using photoaffinity labeling and provide a chemical handle for detection or affinity purification. These probes behaved well as D2R agonists in traditional biochemical assays and performed proficiently in chemical−biological assays of cell and receptor labeling. Rat whole brain labeling using these probes allowed for proteomic analysis of interacting proteins. Bioinformatic study of the hits revealed that the probes bound noncanonically targeted proteins in multiple physiological and disease pathways, including the dopamine receptor D1 (D1R) signaling network. Follow-up analysis may yield insights into how this dopaminergic signaling relates to Parkinson's disease or provide new targets for treatments. Our results demonstrate that the combination of chemical biology and omics-based approaches provides a broad picture of a molecule's "interactome", giving insight into a drug's efficacy and side effects or even indicating new applications.



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[1] Kim, S.T.; Doukmak, E.J.; Flax, R.G.; Gray, D.J.; Zirimu, V.N.; de Jong, E.; Steinhardt, R.C. Developing Photoaffinity Probes for Dopamine Receptor D2 to Determine Targets of Parkinson's Disease Drugs. ACS Chem. Neurosci., 2022, 13(20), 3008-3022.

FAVIPIRAVIR ANALOGUES AND COCRYSTALS: SYNTHESIS, PREDICTIONS, AND STRUCTURE-PROPERTY RELATIONSHIPS

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Favipiravir is an RNA polymerase inhibitor which was approved in 2004 in Japan for influenza treatment and received additional interest during the 2019 coronavirus outbreak as a potential COVID-19 therapeutic agent. Despite its broad-spectrum antiviral activity, Favipiravir faces some pharmaceutical challenges due to its moderate solubility and poor tabletability. Therefore, a few recent studies have been conducted to improve its physical properties by forming Favipiravir cocrystals. Organic cocrystals have attracted tremendous attention and emerged as promising solid-state functional materials to enhance the physicochemical properties of active pharmaceutical ingredients. Cocrystals are typically synthesized through structure-directing non-covalent interactions such as hydrogen bonds, halogen bonds, chalcogen bonds, and charge-transfer interactions. Cocrystals have already been employed as a way of improving properties such as stability, solubility, bioavailability, *etc*.

In this study, we synthesized and characterized an iodo analogue of Favipiravir and its cocrystals using coformers that were previously utilized in Favipiravir cocrystallization. Our primary objectives were to investigate how iodo substitution affects the solubility and stability issues they had with the Favipiravir drug and to explore the structure-property relationships between the cocrystals of the iodo analogue and the Favipiravir cocrystals.

Additionally, we used theoretical tools to predict the cocrystal formation of these materials, including hydrogen bond propensity calculations (HBP), hydrogen bond energy calculations (HBE), hydrogen bond coordination (HBC) calculations, and molecular complementarity (MC) calculations. We then compared these predictions with experimental outcomes to validate their ability to predict cocrystal formations, potentially reducing the need for extensive experimental screening.

Our findings allowed us to add valuable insights into understanding how structure-property relationships between the Favipiravir drug, its iodo analogue, and their cocrystals. Furthermore, this study also examines how the advancement of computational tools contributes to predicting cocrystal formation outcomes, establishing a method that may be applied broadly across pharmaceutical cocrystal studies.

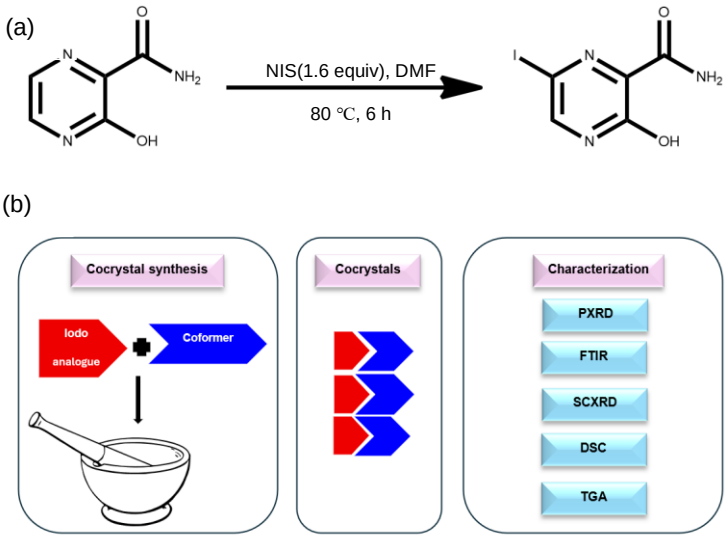

Figure:
(a) Synthesis of iodo analogue,
(b) Schematic diagram of cocrystal synthesis and characterization.

SCREENING DERIVATIVES OF A MULTI-KINASE INHIBITOR REVEALS A SELECTIVE AURORA KINASE A STABILIZER

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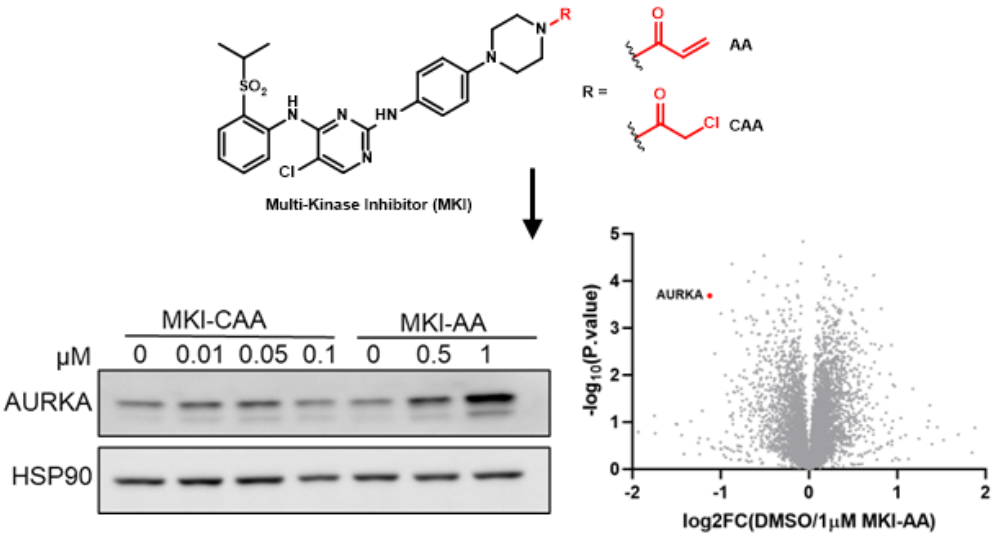
Molecular glues are emerging as powerful tools for therapeutic discovery by modulating protein stability and function in novel ways. To explore this modality, we synthesized a series of derivatives based on a multi-kinase inhibitor scaffold, each featuring a different electrophilic warhead. Screening these compounds revealed a lead molecule with an acrylamide warhead that selectively stabilizes Aurora kinase A (AURKA)- a serine/threonine kinase essential for mitotic spindle assembly and chromosome segregation. This effect was validated by western blotting and quantitative global proteomics, which consistently showed increased AURKA protein levels following treatment. Although AURKA is typically upregulated in tumors, a stabilizer could serve as a tool compound to probe its non-mitoti roles, particularly in contexts where AURKA regulation is critical, or potentially contribute to novel therapeutic strategies that exploit protein stabilization as a means of modulating cellular function.



PROGRESS TOWARDS USING ORGANOSILANOL LIGANDS FOR CATALYSIS WITH EARTH ABUNDANT AND TRANSITION METALS

Hannah E. McFadden, James I. Vesto, Yun-Pu Chang, Kevin Blanco-Herrero, and Annaliese K. Franz*

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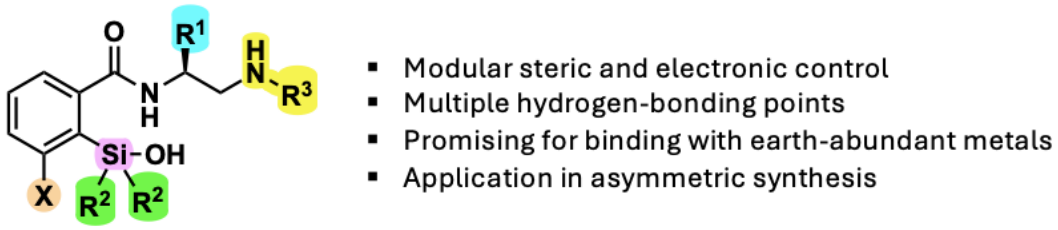
hmcfadden@ucdavis.edu

Silanol-containing ligands offer unique opportunities to design and study new ligands for coordinating with earth-abundant metals (e.g. calcium, magnesium, and titanium), with potential applications in a wide range of geo-inspired catalysis. Silanol and siloxide binding to metals can enhance Lewis acidity while hydrogen bonding can contribute to additional secondary structure elements, which can help create a well-defined metal-ligand complex structure. This work explores the design and synthesis of silanol-based metal-chelating ligands, guided by in-situ IR and NMR binding studies, and evaluated using polymerization and enantioselective catalysis. Our preliminary work has demonstrated that a chiral aminoamide silanol scaffold is an effective ligand for high enantioselectivity in a copper-catalyzed N-H insertion reaction, and a titanium siloxide complex can catalyze the ring-opening polymerization of lactide to poly-lactic acid. These initial results motivate further exploration of silanol ligands for catalysis with earth abundant metals in further enantioselective transformations, such as dipolar cycloadditions.



UTILIZING RARE EARTH METAL COMPLEXES TO SOLVE CHALLENGES IN ORGANIC SYNTHESIS

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Department of Chemistry, University of Minnesota, Minneapolis, Minnesota, USA
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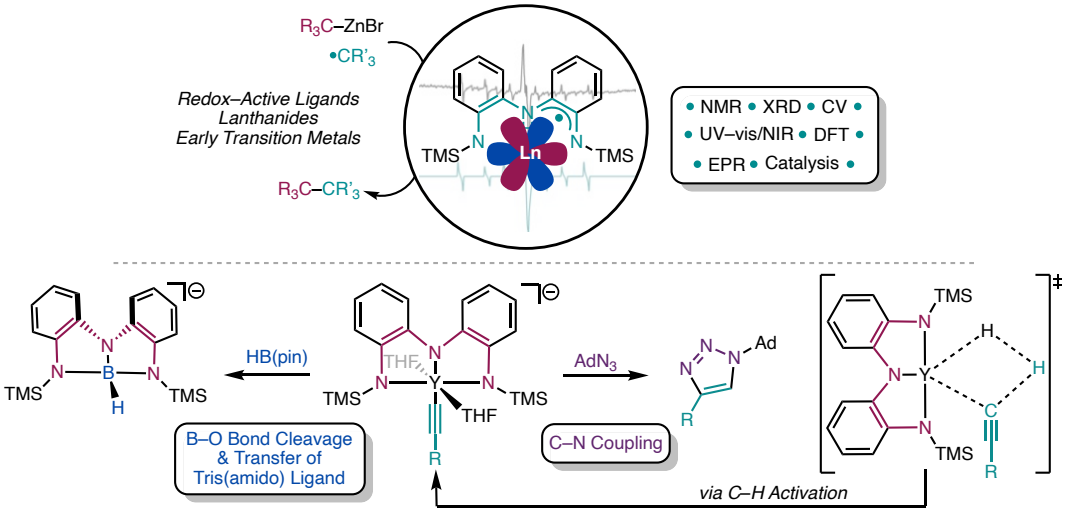
Rare earth metal complexes have been underutilized in organic synthesis as they lack the d electrons necessary for various traditional organometallic steps. The Roberts group addresses this challenge by employing a redox–active tris(amido) ligand which can act as an electron reservoir to provide the necessary electrons for organometallic transformations, i.e. oxidative addition. Improving our understanding of how these complexes react provides complimentary reactivity to late transition metal chemistry. For instance, our group previously reported an early transition metal catalyzed alkyl–alkyl cross–coupling reaction.[1,2] This filled a crucial gap in the literature of catalytic alkyl–alkyl cross–coupling reactions as late transition metal complexes (such as Pd) yielded low cross–coupled product. Therefore, further exploration of the complexes' structures as well as their reactivity provides ways to overcome these challenges.

In this work, the synthesis and full characterization of early transition metal (Sc, Y) and lanthanide (La, Tb–Lu) complexes bearing a tris(amido) redox–active ligand will be discussed.[3] In addition to the complexes' ability to catalyze alkyl–alkyl cross–coupling, their ability to form new C–C and C–heteroatom bonds *via* C–H activation of alkynes through σ–bond metathesis will also be described. These new reactions, as well as the complexes' unique reactivity with HB(pin), demonstrate the broad utility of these complexes in solving challenges in organic synthesis.[4]



[1]Belli, R.G.; Tafuri, V.C.; Joannou, M.V.; Roberts, C.C. *ACS Catal.* **2022,** 12, 5, 3094–3099. [2]Belli, R.G.; Tafuri, V.C.; *ACS Catal.* **2022**, 12, 15, 9430–9436. [3]Garcia, N.A.; Tafuri, V.C.; Abdu, R.B.; Roberts, C.C. *Inorg. Chem.* **2024**, 63, 33, 15283–15293. [4]Abdu, R.B.; Roberts, C.C. *Organometallics* **2025**, ASAPs.

SAR EVALUATION OF HYDROXYQUINOLINONE COMPOUNDS AS 20S PROTEASOME ENHANCERS FOR TREATING ALZHEIMER'S DISEASE

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Neurodegenerative diseases, such as Alzheimer's disease (AD) and its related dementias, impact the lives of millions worldwide and have high rates of mortality. Though the pathogenesis and progression of AD remains complex, one hallmark of the disease is the aberrant accumulation and aggregation of intrinsically disordered proteins (IDPs), such as tau, into larger toxic protein species. This rampant IDP accumulation and aggregation impacts a host of cellular pathways and systems, including protein degradation pathways. One such pathway involves the 20S proteasome, an enzyme primarily responsible for degrading IDPs and other unfolded proteins. An abundance of IDP aggregates can inhibit the proteolytic degradation activity of the 20S proteasome, thus perpetuating the toxicity. For these reasons, reducing the levels of accumulated IDP species by overcoming 20S proteasome inhibition remains a highly attractive therapeutic strategy for treating AD and its related dementias. Here, it is hypothesized that small molecules may be used to restore 20S proteasome activity, and this work focuses on expanding the structure-relationship activity (SAR) studies of a hit hydroxyquinolinone compound (MSU-8) for use as a 20S proteasome enhancer to influence cellular tau levels.

Enantioselective [2π + 2σ] Photocycloaddition Enabled by Brønsted Acid Catalyzed Chromophore Activation

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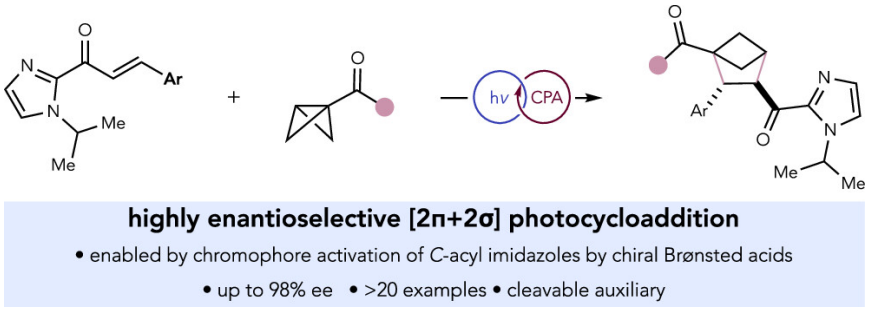
[2]Molecular Modalities Capabilities, GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, U.K.
[3]Crop Health R&D, Corteva Agriscience, 9330 Zionsville Rd, Indianapolis, Indiana 46268, United States
**Corresponding Author*
rqian25@wisc.edu

Saturated bicyclic scaffolds have recently emerged as bioisosteres for substituted benzene moieties in the pharmaceutical industry. Photochemical cycloadditions are especially advantageous to obtain these strained structures, as they can afford the bicycle backbone in a singular step with mild conditions. There have been many literature reports to generate bicyclo[2.1.1]hexanes (BCHs), but enantioselectivity remains a challenge. Herein we report an enantioselective method to construct BCHs from [2π + 2σ] cycloadditions between easily obtainable cinnamates and bicyclobutanes, utilizing a chiral Brønsted acid catalyzed chromophore activation strategy. Distinct from other methods, this cycloaddition is achieved by direct excitation of the activated *C*-acyl imidazole substrate. This method displays high functional group tolerance and excellent enantioselectivity, giving an array of decorated BCHs.



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[1] Plachinski, E. F.; Qian, R. Z.; Villanueva, R.; Poole, D. L.; Rosenthal, T.; Yoon, T. P. *J. Am. Chem. Soc.* **2024**, 146, 46, 31400–31404.

SYNTHESIS OF A PHOSPHOETHANOLAMINE CELLULOSE GLYCOMIMETIC AND INVESTIGATION OF ITS BIOFILM MODULATING PROPERTIES

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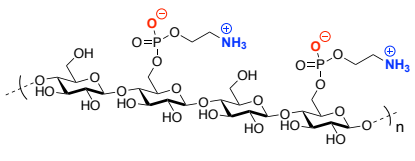
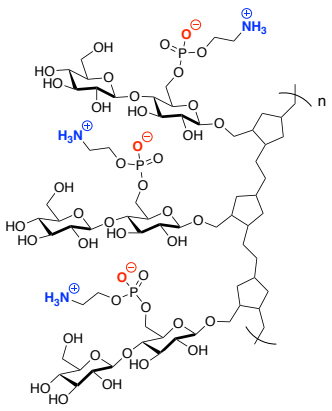
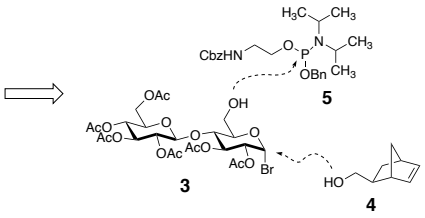
Zwitterionic polysaccharides (ZPSs) are a class of polysaccharides found on the extracellular surface of select pathogenic bacteria. These macromolecules play an important role in bacterial survival and host-microbe interactions during infection. However, the structural complexity of this class of biomolecules has obscured well-defined structure-function relationships. Uropathogenic *Escherichia coli* (UPEC), the causative agent of urinary tract infections, secrete a chemically modified cellulose called phosphoethanolamine cellulose (pEtN cellulose) that plays a vital role in biofilm assembly, however limited chemical tools exist to further examine its role in pathogenesis. To address this critical need, we designed and synthesized a library of chemically-defined glycopolymers to mimic the structure of pEtN cellulose leveraging ring-opening metathesis polymerization.[1] Synthetic studies including monomer design and synthesis, polymerization and global deprotection will be presented in addition to biofilm modulation and mechanism of action studies.



Representation of pEtN Cellulose **(1)**



Target pEtN Cellulose Mimetic **(2)**



[1] Adams, C. E.; Spicer, S. K.; Gaddy, J. A.; Townsend, S. D. *ACS Infect. Dis.* **2024**, *10(9),* 3245–3255.

C-H FUNCTIONALIZATION OF BENZENE ISOSTERES AT PALLADIUM: CUBANE AND CUNEANE

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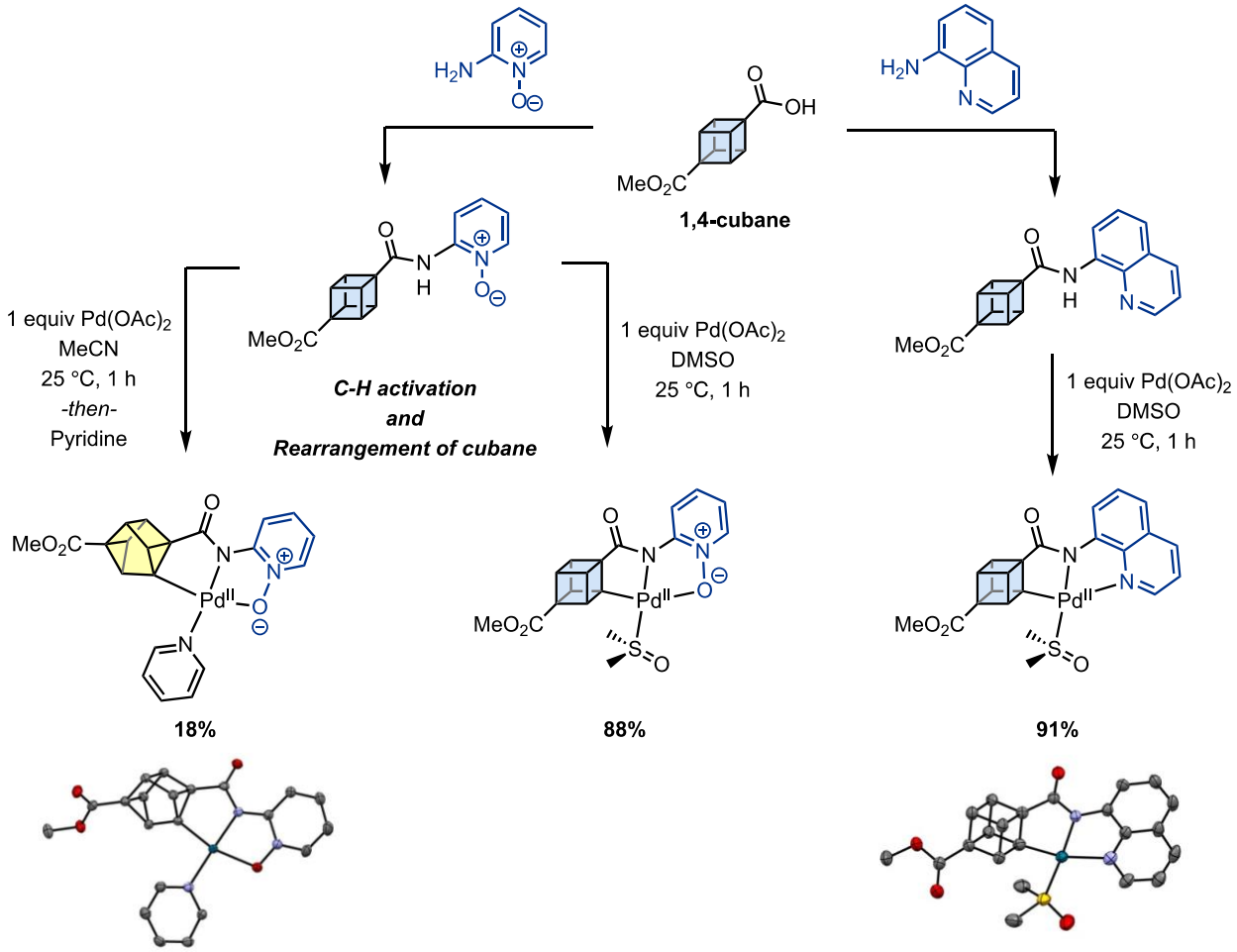
Cubane has emerged as a promising benzene bioisostere due to its similarity in size and potential to enhance the physicochemical properties of drug candidates. However, metal-catalyzed valence isomerization renders the effective functionalization of the cubane core through traditional protocols a synthetic challenge. This research focuses on the palladium-mediated C-H functionalization of cubane. Cyclometallated intermediates in Pd-mediated C–H activation of cubane have been isolated. Variables such as directing group and palladium source have been identified as being essential for the C-H activation and isomerization of the cubane motif.



IRON-FACILITATED BI(HETERO)ARYL FORMATION VIA *N*-(2-PICOLYL)PICOLINAMIDE COMPLEXES

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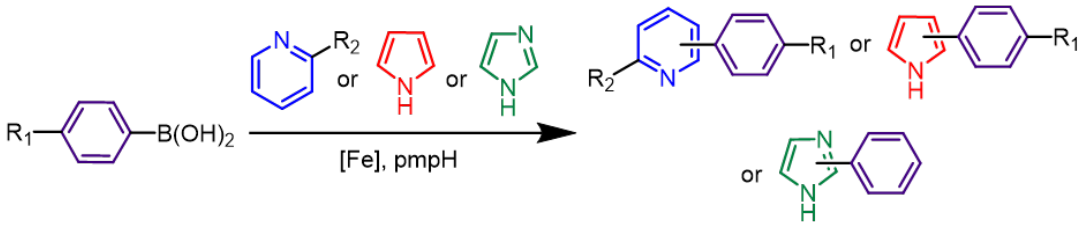
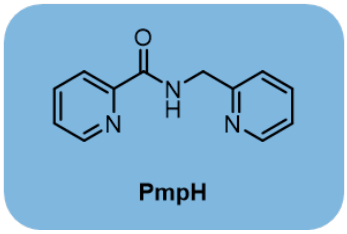
Biaryl compounds are an essential structural feature amongst pharmaceuticals, natural products, agrochemicals, and other materials. One of the most common methods to synthetically access these compounds is through metal-catalyzed cross coupling reactions, specifically the Suzuki-Miyaura reaction. Despite its widespread use, this approach requires the use of premodified molecules, which can limit its overall efficiency by adding additional steps to a synthesis. In addition, the use of expensive palladium catalysts is often needed. As a result, alternatives to access biaryl compounds are being studied extensively. In this work, we propose an iron-mediated direct C-H arylation of N-heterocyclic compounds, specifically pyridine, pyrrole, and imidazole, using an underutilized ligand in catalysis, *N*-(2-picolyl)picolinamide (pmpH). The synthesis of pmpH and preliminary scope of heteroatom functionalizations will be presented.





- Easily accessible ligand
- Bench-stable ligand
- Underexplored pincer ligand

SYNTHESIS OF NICKEL COMPLEXES WITH PARA-SUBSTITUTED BIDENTATE *N*-HETEROCYCLIC CARBENE LIGANDS FOR C-F ACTIVATION AND NO REDUCTION

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N-heterocyclic carbenes (NHC) are widely used in organic synthesis and catalysis due to their high structural modularity, which enables fine tuning of catalyst electronic and steric properties. In this work, bidentate bis-NHC ($^{R}NHC_2Me$; R=aryl) nickel complexes were synthesized towards investigating their application in Ni-catalyzed NO reduction and C–F bond activation. To access the bis-NHC ligands, commercially available 1-benzylimidazole derivatives were combined with dibromomethane to generate the corresponding bis(imidazolium) salts varying in wingtip substitution. Arene substitution varied at the *para* position with the introduction of a –Br, –CN, or –OMe group. These bis(imidazolium) salts were then transferred to an inert-atmosphere glovebox for deprotonation with KHMDS and introduction of $Ni(COD)_2$, resulting in the desired bis-NHC Ni(0) complexes. These complexes were characterized by ^{1}H NMR spectroscopy, ^{1}H-^{1}H Correlation Spectroscopy (COSY), and infrared spectroscopy. Preliminary experiments demonstrate the ability of two of the bis-NHC Ni(0) complexes to activate a C-F bond and to form a Ni(I) complex upon reaction with NO.

RESONANT SOFT X-RAY SCATTERING TO PROBE MOLECULAR ORIENTATION IN POLYMER-GRAFTED NANOPARTICLES

Supriya Gupta[a], Ting Xu[b], Dean M DeLongchamp[c], Gregory Su[a]*

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[b]*University of California, Berkeley, CA, USA*
[c]*National Institute of Standards and Technology, Gaithersburg, MD, USA*

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Polymer chains anchored to surfaces are of significant interest in diverse industrial and scientific realms, particularly in the development of advanced materials with adjustable properties, renewable nanocomposites, solar device fabrication, and drug delivery systems. In the present study, polarized resonant soft X-ray scattering (P-RSoXS) was employed to investigate the spatially-resolved molecular orientation of the grafted polymer chains close to surfaces. The samples studied are monolayer thin films consisting of polystyrene chains tethered to nanoparticle surfaces. The RSoXS measurements were acquired across the carbon K-edge for different degrees of polarization revealing scattering anisotropy and evidence of polymer chain orientation. Furthermore, through scattering simulations, the degree of chain alignment is quantitatively assessed in the proximity of the nanoparticle surfaces. Overall, this study highlights that P-RSoXS is a powerful technique for elucidating and quantifying the orientational characteristics of nanostructures at the nanoscale.

LINEAR FREE ENERGY RELATIONSHIPS OF *N*-HETEREOCYCLIC CARBENE-CARBBODIIMIDE (NHC-CDI) ADDUCTS WITH PHYSICAL DESCRIPTORS

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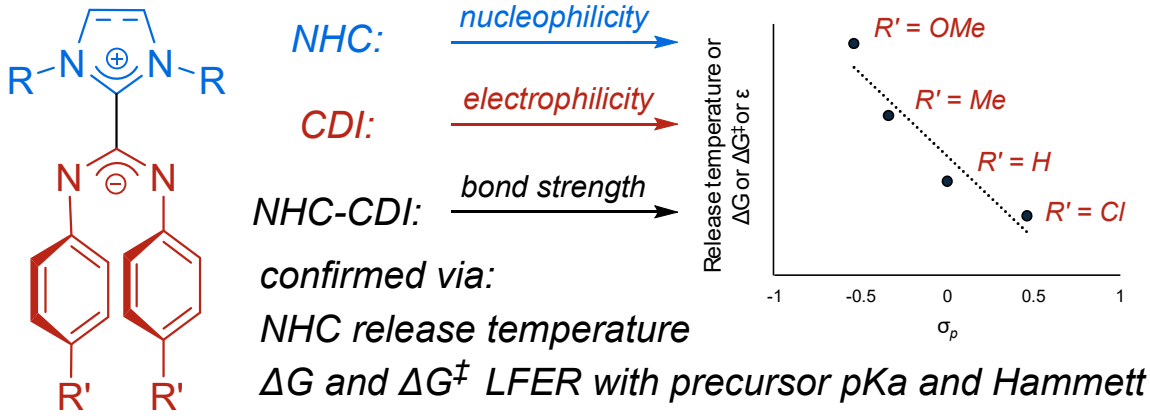
N-Heterocyclic carbenes (NHCs) are powerful organocatalysts with diverse applications in synthetic chemistry, including Umpolung reactivity and ring-opening polymerizations. However, a major challenge for NHCs is their inherent air sensitivity, which can be mitigated by "masking" the NHC reactivity with reversible adducts. NHC betaine adducts with carbodiimides (NHC-CDI) are one such example, and we have demonstrated these adducts as heat initiated NHC catalyst precursors. In our first study, we observed the ideal NHC-CDI precatalyst release temperature could be qualitatively correlated to the CDI electronic character. This principle was observed for three different NHC catalyzed reactions highlighting the trend holds for different NHC mechanisms. To follow up this work, we quantified this observation by determining the precatalyst kinetic and thermodynamic properties via in situ carbene trapping and variable temperature nuclear magnetic resonance spectroscopy, respectively. Even simple synthetic adjustments on NHC-CDI adducts can greatly change the physical descriptors. We developed several linear free energy relationships (LFERs) using common physical parameters for NHCs and CDIs, as well as spectroscopy measurements. Within these LFERs, we observed that facile synthetic changes via the CDI altered the physical properties in a similar magnitude as changing the more synthetically demanding NHC.



confirmed via:
NHC release temperature
ΔG and ΔG‡ LFER with precursor pKa and Hammett

Improving Accessibility for Students with Blindness and Low Vision in the Organic Chemistry Teaching Laboratory

Roxane Jourdain*, Levi Garza, Bryan Shaw. Baylor University, Department of Chemistry and Biochemistry, Waco TX

As of 2017, over 7 million people worldwide were blind or visually impaired. While accessibility in education for students with blindness or low vision (BLV) has improved, Organic Chemistry still presents a major obstacle for these students. Over the 2023 Fall semester, the Organic Chemistry laboratory at Baylor University hosted our first student with BLV. Thanks to help from Prof. Bryan Shaw and his BLV Chemistry incentive, we were able to use accessibility tools such as alt text, Braille labels and tactile images. These measures aimed to ensure a smooth and positive experience for the student, and future students with BLV after them. We further propose 3D printed aides to help students with BLV independently engage with the preparation of their experiments.

VISIBLE-LIGHT PHOTOCATALYTIC SNAR PYRIDINATION OF ARYL HALIDES AND TRIFLATES UTILIZING ACRIDINE–LEWIS ACID COMPLEXES

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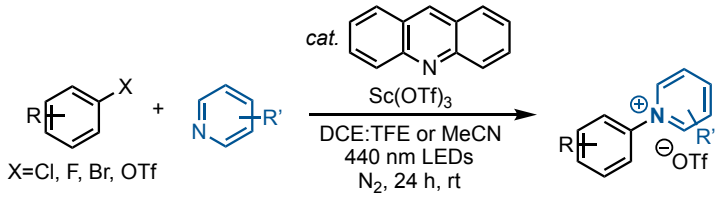
Aromatic carbon–nitrogen bonds are ubiquitous in natural products, agrochemicals, and pharmaceuticals. As such, there has been a notable focus on developing synthetic approaches to form aryl amines. This work describes the development of a visible-light (440 nm) photocatalytic method for the cation radical accelerated (CRA) S_NAr pyridination of aryl halides and triflates utilizing potent acridine-Lewis acid photocatalysts[1] that are assembled in situ from commercially available starting materials. A variety of electronically diverse aryl (pseudo)halides are effective electrophiles for this transformation in the presence of various substituted pyridine nucleophiles. Leveraging the simplicity and modularity of our developed in situ-generated photocatalysts allows promotion of the photocatalytic CRA-S_NAr pyridination of unactivated aryl halides (e.g chloro/bromobenzene) as the limiting reagent.



This work

• easily tunable photocatalysts • UV-Vis experimentation •
• broad scope are aryl halides and aryl triflates •
• visible (440 nm) light • photocatalytic and EDA pathways •

[1] Lasky, M. R.; Liu, E.; Remy, M. S.; Sanford, M. S. Visible-Light Photocatalytic C–H Amination of Arenes Utilizing Acridine–Lewis Acid Complexes. J. *Am. Chem. Soc.* **2024**, 146, 14799−14806.

IBUZATRELVIR END-GAME JOURNEY: OPTIMIZATION AND SYNTHESIS. FROM DISCOVERY TO EARLY CAMPAIGNS

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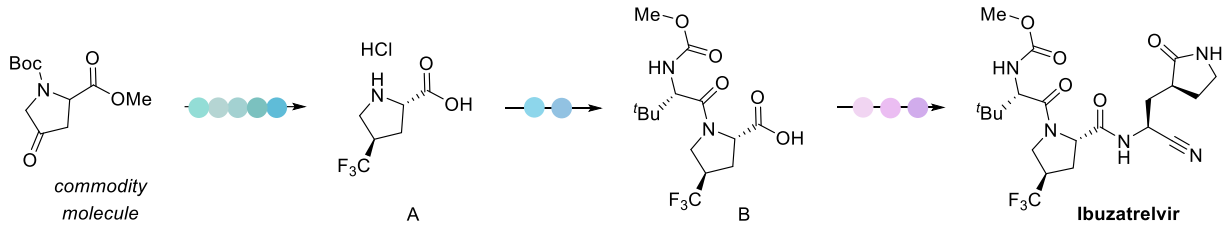
Ibuzatrelvir is a clinical candidate being developed as a potential second-generation oral treatment for patients with COVID-19 infection. Herein we describe the process development for ibuzatrelvir, focusing on rapid optimization for the synthesis of both the regulatory and starting material routes, identification of process related impurities, mapping of the intermediate crystalline form landscape, and final API isolation process. Treatment with aqueous ammonium hydroxide and a solvent swap with CPME were identified as key parameters to obtain the first metastable crystalline CPME solvate of ibuzatrelvir. Further optimization in subsequent campaigns established a greener/more sustainable approach via isolation of an IPAc solvate, enabling manufacture of more than 130 kg of ibuzatrelvir for phase 1 and phase 2 clinical studies in less than one year.



- *Work with CDMOs to obtain >235 Kg of A*
- *Route optimization to A, B and Ibuzatrelvir towards commercial process nomination*
- *5 campaigns with >130Kg for clinical studies in less than 1 year*

References

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[2] Algera, R. F.; Allais, C.; Cabrera, P. J.; González-Esguevillas, M.; Guan, Y.; James, C.; Lee, J. W.; Massicott, J. M.; McInturff, E. L.; Pearson, R. J.; Risley, H.; Watson, R. B. *Org. Process Res. & Dev.* **2024**, *28, 10*, 3827-3836.

HIT IDENTIFICATION, SYNTHESIS, AND OPTIMIZATION OF QUINAZOLINONE-BASED CHIKUNGUNYA VIRUS INHIBITORS

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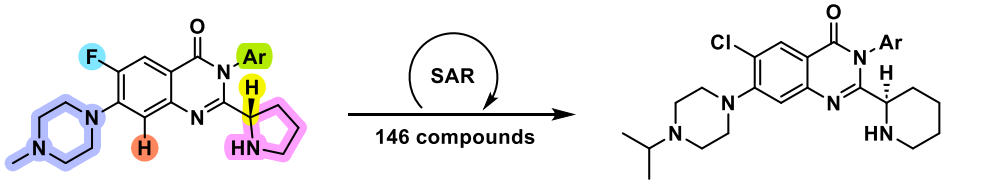
Chikungunya virus (CHIKV) is a mosquito-borne alphavirus that, in the last 10 years, has been responsible for millions of human infections globally. Acute infection is characterized by fever, nausea, myalgia, and arthralgia, but chronic symptoms occur in nearly half of patients and may last months to years, resulting in a significant health burden for which no small molecule-based antivirals are available. Using a structurally diverse subset of 200 compounds from the internal Golden lab compound library, a screening campaign was done (Streblow lab) which assessed CHIKV titer reduction *in vitro* as well as cytotoxicity in normal human dermal fibroblast (NHDF) cells. The hit compound, quinazolinone (*S*)-**1**, emerged with a modest 0.3 log reduction of CHIKV titer at 10 μM and no significant cytotoxicity (CC_{50} > 40 μM). An optimization effort was undertaken with the goal of improving potency and establishing a working pharmacophore from which advanced analogs could be designed and tested for solubility and microsomal stability in anticipation of future *in vivo* evaluations. A structural survey of six regions on the scaffold (highlighted below) was conducted, resulting in the synthesis of 146 analogs and the identification of (*R*)-**56** which reduced CHIKV titer by 4.1 log. The optimization efforts leading to analog (*R*)-**56** will be highlighted which included improving potency, minimizing cytotoxicity, avoiding racemization of 2-(piperidin-2-yl)quinazolin-4(3*H*)-one derivatives during synthesis, and enhancing solubility and microsomal stability.



(*S*) - 1, hit compound

CHIKV titer reduction at 10 µM : 0.3 log
CC_{50}, NHDF : >40 µM

(*R*) - 56

CHIKV titer reduction at 10 µM : 4.1 log
IC_{90} : 1.9 µM
$CC_{50,}$ NHDF : 18.6 µM
Kinetic solubility, PBS : 183 µM
Mouse microsomal stability : $T_{1/2}$ > 145 min

EVALUATION OF SMALL MOLECULE 20S PROTEASOME ENHANCERS AS A THERAPEUTIC FOR HPV+ CERVICAL CANCER

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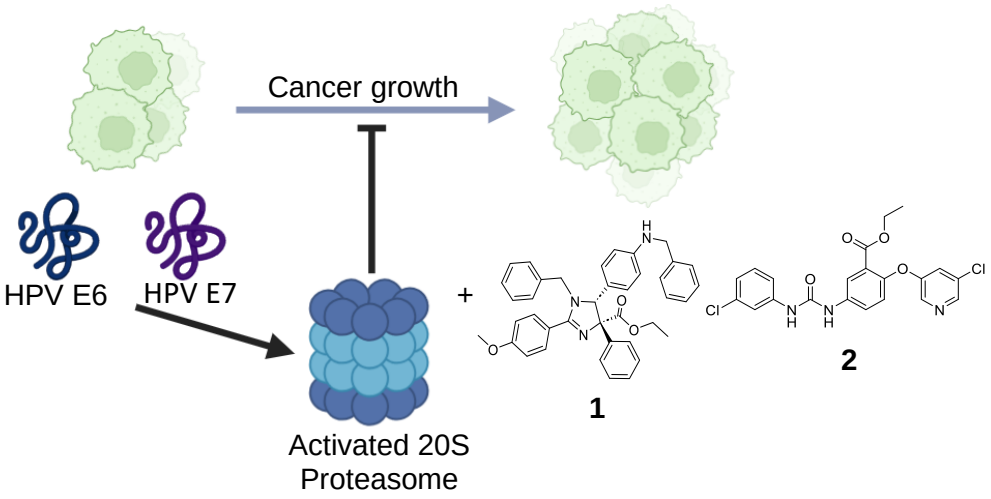
Approximately 5% of cancer cases in the world are due to persistent high-risk human papillomavirus (HPV) infection. The HPV vaccine can successfully prevent the infection of most high-risk HPVs; however, vaccination rates are low, and HPV is one of the most common sexually transmitted infections (STIs). There is no treatment for an HPV infection once it has occurred. While low-risk HPVs are often cleared by the host's immune system, high-risk strains are better at evading it and are more likely to cause cancer. In these high-risk HPVs, two viral oncoproteins, HPV E6 and E7, help drive the conversion of an HPV infected cell to a cancerous one. This is through their manipulation of multiple cell processes, such as cell cycle regulation. Both oncoproteins are partially intrinsically disordered proteins (IDPs), which allows them to interact with multiple targets in cells. Due to their lack of a stable binding pocket for drug targeting, proteins like these two are often deemed "undruggable." However, cells already have a natural process used to remove unwanted IDPs – the 20S proteasome. The 20S proteasome is a barrel shaped enzyme which removes disordered proteins in an ubiquitin-independent manner. The Tepe lab has developed several small molecules that enhance its protein degradation activity. We hypothesize that HPV E6 and E7 proteins might be substrates of the 20S proteasome and have discovered that two of our compounds (**1** and **2**) decrease E6 and E7 levels in high-risk HPV+ cervical cancer. This project is working to determine if their mechanism of action is through 20S proteasome activation. Additionally, we are investigating if this decrease is enough to reinstate cell cycle regulation and inhibit the out-of-control cell growth caused by HPV E6 and E7. This project explores whether 20S proteasome enhancement is a viable strategy for combatting HPV+ cervical cancer.



SPECIATION OF COPPER (II) ACTIVATION OF CYCLOMETALATED DIRECTED COMPLEXES

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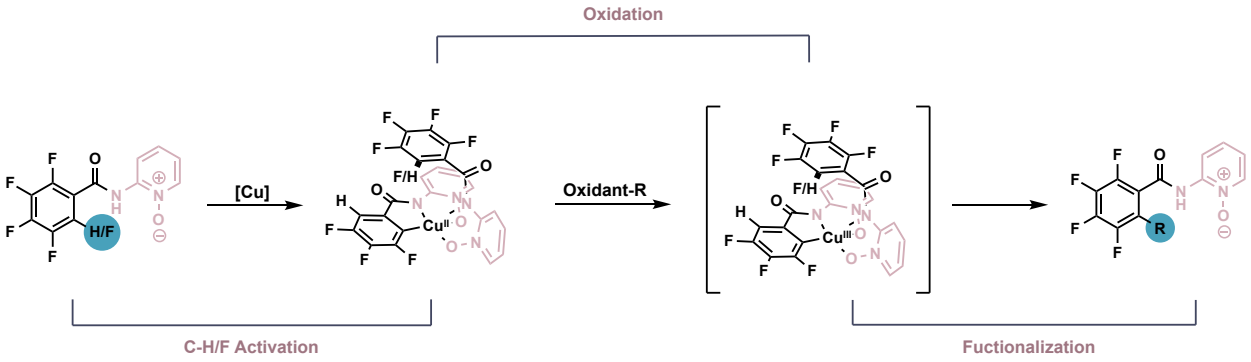
Traditionally, C–C or C–X bonds are formed via functional group interconversions. An alternative is the use of transition metal-catalyzed reactions that directly convert a C–H substrate of interest to a C–R functionalized product. Using base-metal catalysts, such as copper, has been found to functionalize inert C(sp2)–H bonds in aminoquinoline-directed systems[1]. Here we aim to understand Cu complexes that are C–H functionalization intermediates. These include cyclometalated Cu(II) and high-valent copper (Cu(III)) intermediates in copper-catalyzed directed C-H functionalization reactions. In this work, we describe directing group effect from aminoquinoline to pyridine N-oxide system to understand speciation of C–H and C–F activation to get discrete cyclometalated directed Cu(II) complexes. Furthermore, we explored systems to isolate Cu(III) intermediate and further functionalizations.



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ELECTRODES ARE TUNABLE LIGANDS: INVESTIGATING THE ELECTRO-INDUCTIVE EFFECT ON AN ANCHORED POLYMERIZATION CATALYST

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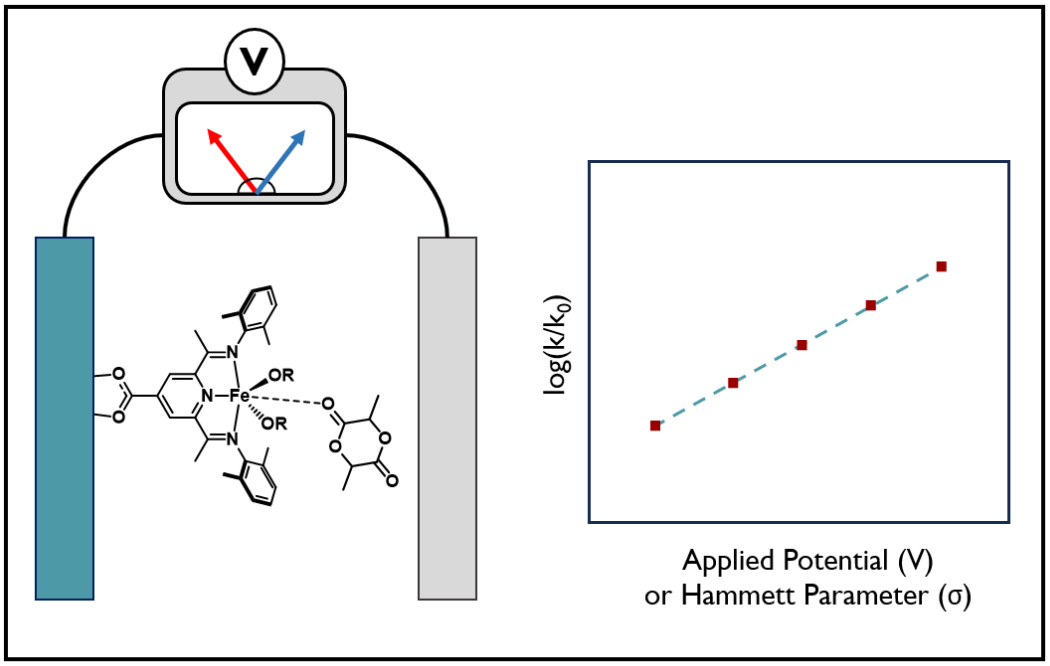
Since its discovery in 1937, the inductive effect has been used to tune the electronic properties of molecules. In particular, catalyst design has been advanced by logical ligand design, though the selection of different functional group substitutions to control the electronics of active sites. A major limitation of this approach is that electronics can only be changed in discrete amounts based on the identity of the functional group. Functional group selection is further restricted by the synthetic limitations for a desired electron donating or withdrawing substituent. Moreover, the effect a functional group imparts on a molecule is static—electronics cannot be tuned throughout a reaction to modulate reactivity. The recently disclosed electro-inductive effect provides an alternative solution to this problem. Instead of relying on the inherent electronics of a functional group, electron density may be supplied or removed through the use of applied potentials. Seminal work by both the Dawalty and Baik groups has focused on the development of electrochemical methods to control reactivity and to probe reaction mechanisms when a substrate is tethered to an electrode. Herein, we anchor a redox-switchable Fe polymerization catalyst in conjugation with an electrode and demonstrate that application of different potentials controls the reactivity of the catalyst without requiring changes to the catalyst structure.



REDUCTIVELY INDUCED ARYL TRANSMETALATION: A COMPETING MECHANISTIC PATHWAY IN NI-CATALYZED REDUCTIVE BIARYL COUPLING REACTIONS

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Biaryl motifs serve as crucial scaffolds in the synthesis of ligands, catalysts and drug molecules. Traditionally accessed via palladium or nickel catalyzed cross coupling of (hetero)aryl nucleophiles and electrophiles, biaryl motifs are now increasingly being synthesized through nickel catalyzed reductive cross-electrophile coupling (XEC) reactions. Several different mechanisms have been proposed for Ni-catalyzed homocoupling and cross-coupling of aryl electrophiles. The most widely invoked pathway involves sequential oxidative addition of the aryl electrophiles to Ni. This mechanism is proposed to begin with formation of Ni^0 from $Ni^{II}X_2$, followed by oxidative addition of Ar–X to form $Ni^{II}(Ar)X$. Reduction of $Ni^{II}(Ar)X$ to $Ni^{I}(Ar)$ precedes a second oxidative addition step to afford $Ni^{III}(Ar)_2X$, which undergoes rapid reductive elimination to furnish the biaryl product (**Figure 1a**). Here, we will provide evidence for a previously unrecognized pathway in which the $Ni^{I}(Ar)$ intermediate can engage in a competing pathway that involves transmetalation between $Ni^{I}(Ar)$ and $Ni^{II}(Ar)X$ affording $Ni^{II}(Ar)_2$ (which can furnish the biaryl product) and $Ni^{I}Br$ (**Figure 1b**).[1] The results of this study provide a new rationale for previously reported results in the literature and introduce an alternative pathway to consider in the development of Ni-catalyzed biaryl coupling reactions. We will also briefly explore the impact different reaction parameters (for example, steric and electronics of the aryl electrophile) can have on the dominant mechanistic pathway. Understanding the factors that favor different biaryl coupling mechanisms has important implications for Ni-catalyzed reactions that promote cross-coupling of aryl electrophiles over the undesired homocoupling.

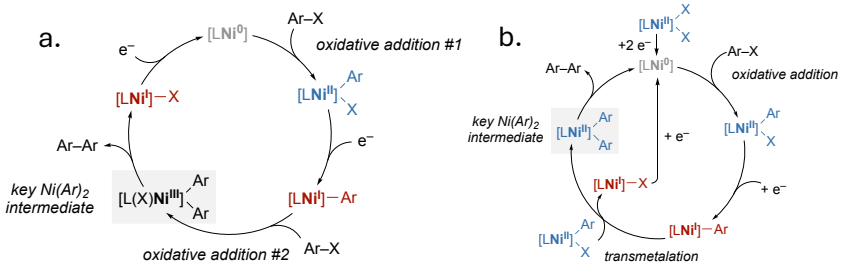

Figure 1. a) Sequential Oxidative Addition Pathway b) Ni^{I} to Ni^{II} Transmetalation Pathway

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Enzyme Driven Reaction Discovery and Optimization - The In-Situ Enzymatic Screening (ISES) Approach

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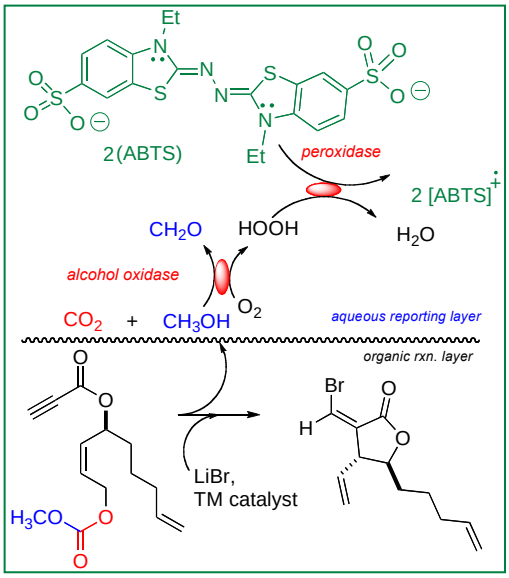
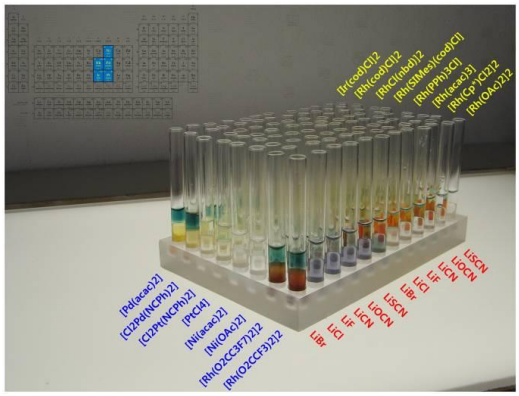
The Berkowitz group investigates the intersection of enzymatic and organometallic chemistry, employing enzymes as analytical tools to accelerate high-throughput reaction discovery. One such innovation is the In-Situ Enzymatic Screening (ISES) method, developed in our lab. In this biphasic system, organic reactions proceed in one layer, while a tailored set of 'reporting enzymes' in an adjacent aqueous buffer layer detect reaction progress. Successful transformations release products or byproducts into the enzyme layer, where enzyme-catalyzed reactions generate chromophores detectable by UV-visible or, more recently, fluorescence spectroscopy—providing real-time insights into reaction kinetics and, in some cases, stereoselectivity. The ISES platform has enabled the discovery of a novel bromorhodiation/carbocyclization reaction, thiocyanopalladation/carbocyclization reaction, and the development of chiral salen ligands based on β-pinene and D-carbafructopyranose scaffolds, which have shown excellent performance in Jacobsen's hydrolytic kinetic resolution (HKR) protocol.[1,2] This work introduces 'Phosphate ISES,' an advanced iteration of the ISES method with enhanced detection, elevated temperature tolerance, and expanded enzymatic capability. As a case study, we highlight the first catalytic, enantioselective synthesis of L- and D-α-(1'-fluoro)vinylglycine—mechanism-based inhibitors of tryptophan synthase that incorporate the classic "Abeles trigger."





Example of visual, colorimetric-ISES, leading to the discovery of the bromorhodiation /carbocyclization reaction.

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EXPLORING THE BIOACTIVE POTENTIAL OF NOTOINCISOL A DERIVATIVES VIA SONOGASHIRA CROSS-COUPLING REACTION

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Notoincisol A, a natural product derived from polyacetylenes compounds, has shown potential anti-inflammatory properties by targeting the PPARγ receptor, a key regulator of inflammation. Similarly, falcarinol, a related polyacetylene natural compound found in carrot extracts, has demonstrated antifungal properties by inhibiting the germination of fungal spores. This research focuses on synthesizing derivatives of Notoincisol A through a short synthesis using a sp^2-sp Sonogashira cross-coupling reaction, followed by the nucleophilic addition of a trans-2-decanal. The synthesized analogs were characterized using NMR spectroscopy and Gas Chromatography-Mass Spectrometry. This approach will synthesize analogs of Notoincisol A, allowing us to explore the structure-activity relationship between chemical modifications and biological activity. Additionally, Falcarindiol extract will be used as a reference to compare the bioactivity of the synthesized analogs by performing a disk diffusion assay to test for antifungal activity. These findings suggest that the synthesized derivatives of Notoincisol A could be promising candidates for further development as anti-inflammatory agents. Future studies will focus on optimizing the synthesis process, evaluating the efficacy of the derivatives in biological screening, and investigating their antifungal properties.