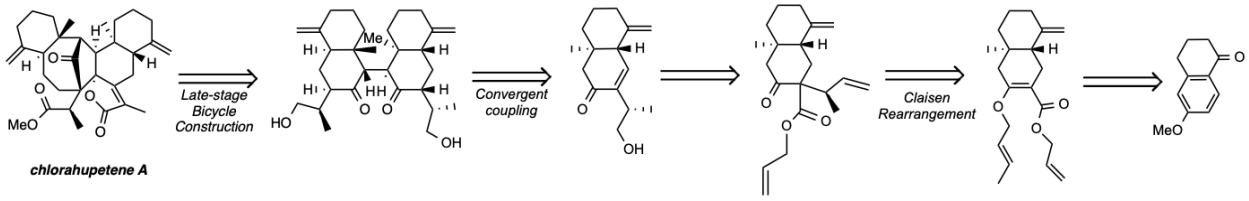
Caltech
Student-Faculty Programs

Session E Abstracts

Radical-based deoxygenation of alcohols via visible-light irradiation of a titanium-porphyrin complex
Sophia Razavi
Mentors: Brian M. Stoltz and Benjamin Gross

The deoxygenation of alcohols is a fundamental transformation in organic synthesis that enables the selective removal of oxygen groups to yield hydrocarbons. Inspired by the oxygen transport and activating functions of iron-containing porphyrins such as heme, we are developing a titanium-porphyrin complex that performs the reverse process: radical-mediated deoxygenation. Our method centers around radical-based deoxygenation of alcohols and homolytic cleavage, initiated by visible light irradiation of a Ti(IV)-porphyrin complex. Upon photoexcitation with purple LEDs in the presence of an electron and proton donor, the reduced Ti(III) complex serves as the active species for substrate activation, and the alcohols coordinate with the Ti(III)-porphyrin complex enabling homolytic cleavage of the C-O bond.

Preparation of the enolate coupling partner towards the total synthesis of sesquiterpenoid dimer natural products
Raquel G. Lample
Mentors: Brian M. Stoltz and Chloe Cerione



Sesquiterpenoid dimers are a medicinally relevant class of natural products. Recently, four new enantiomeric pairs of eudesmane-type sesquiterpenoid dimers were isolated. Among these compounds, the unique 6/6/5/6/6 pentacyclic carbon skeleton of chlorahupetene A inspired an effort towards its first total synthesis. Our strategy leverages a convergent oxidative enolate coupling to construct a key C_2-symmetric scaffold which can undergo a late-stage aldol reaction to form the highly strained [3.2.1]-bicycle. To stereoselectively install the β-methyl group on the enone, a chiral guanidinium-catalyzed Claisen rearrangement will be employed. We predict that the *N,N'*-diphenylguanidinium ion associated with the noncoordinating BArF counterion will afford enantioselectivity through key hydrogen-bonding interactions between the catalyst and substrate.

Asymmetric reverse prenylation of 3-substituted indoles
Tommaso Colombo
Mentors: Brian M. Stoltz and Jonathan Farhi

The enantioselective construction of all-carbon quaternary centers is longstanding challenge in synthetic organic chemistry. Even more challenging is the formation of vicinal all-carbon quaternary centers. To this end, we have developed a protocol to install a "reverse-prenyl" group at the C3 position of C3 propargyl indole enantioselectively via an iridium-catalyzed allylic alkylation. The reaction will be optimized with a variety of solvents, reactant concentrations and bases to afford the C3 reverse-prenylated propargyl indole in high yields.

Selectivity in palladium-catalyzed CDC of substituted pyrroles for (+)-cyanocycline A synthesis
Neiman C. Sneed
Mentors: Brian M. Stoltz and Bryce E. Gaskins

Cyanocycline A is a complex natural product with notable anticancer and antitumor activity. Its total synthesis presents multiple challenges due to its densely substituted ring system. A key step in the synthetic plan involves forming a Carbon–Carbon bond between a pyrrole and a pyridine N-oxide via a palladium-catalyzed cross-dehydrogenative coupling (CDC) which enables direct C–H activation without pre-functionalization. This project examined how changes in reaction order and catalytic conditions influence the regioselectivity of the CDC step. Reactions were carried out under inert atmosphere using various oxidant ligand combinations, and products were monitored and analyzed by TLC, flash chromatography, and ^{1}H NMR. These efforts aim to identify conditions that favor selective arylation at the desired position on the pyrrole, contributing to broader advances in C–H functionalization and highlighting the impact of electronic and steric effects on catalyst-controlled site selectivity.

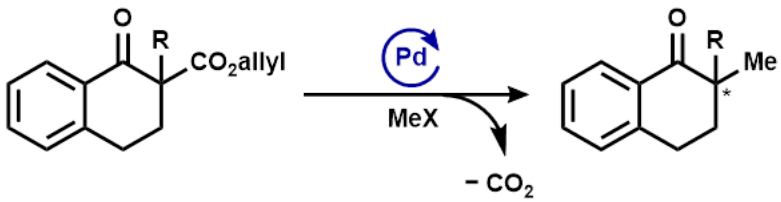
Preparation of cyclopentane fragment en route to Hypatulone A
Aniya M. Buckland
Mentors: Brian M. Stoltz and Kim R. Sharp

Hypatulone A, a natural product isolated from the *Hypericum patulum* plant known for its use in traditional Chinese medicine, is an appealing target for chemical synthesis due to its potential bioactivity and complex caged core. The highly functionalized molecule provides a number of synthetic challenges that can be approached through the development of novel methodology, and careful attention to both stereochemistry and selective incorporation of functional groups. Current investigation into the synthesis of Hypatulone A has been approached through combining a fully functionalized [3.3.1]bicyclononane intermediate and cyclopentane fragment, followed by a novel palladium-catalyzed carbonylation to form the caged core. As part of our investigation into the synthesis of the required cyclopentane fragment, we have achieved the formation of the core structure of the compound and are currently focusing on installing the necessary oxidation of substituents required for the target molecule. These results represent a promising advance in building the framework of Hypatulone A.

Enantioselective palladium-catalysed methylation of alpha-tetralones
Andrew S. Marriott
Mentors: Brian M. Stoltz and Sara Siddiqui

The construction of enantioenriched all-carbon quaternary stereocentres is a major challenge in synthetic chemistry; the steric bulk of these sites hinders reactivity, leading to very poor yields and limiting available synthetic pathways to complex targets. Successful development of enantioselective alkylation chemistry at tertiary sites would allow for straightforward late-stage modification of synthetic targets, simplifying synthetic routes to a range of natural products and pharmaceuticals.

The Tsuji-Trost allylation has been adapted by the Stoltz Group to give access to enantioenriched protonation and intramolecular alkylation products, but limited success has been had so far with intermolecular reactivity. We present an extension of this work to simple external electrophiles, exploring the methylation of alpha-tetralone derivatives in the presence of a chiral palladium catalyst.



Biocatalytic synthesis of chiral phosphonamides using engineered heme enzymes
Ethan N. Lin
Mentors: Frances H. Arnold and Hayden Carder

Abstract withheld from publication at mentor's request.

Engineering hemoproteins for regiodivergent C-H amination towards pyrrolidines and piperidines synthesis
Orna Mukhopadhyay
Mentors: Frances H. Arnold and Ziqi Li

Abstract withheld from publication at mentor's request.

Sulfoxonium ylides as a carbene precursor in biocatalysis
Chaoyi T. Zhang
Mentors: Frances H. Arnold, Chenghao Liu, and Theophile Lambert

Abstract withheld from publication at mentor's request.

Function conditioned enzyme generation with masked diffusion language models
Kerui Yang
Mentors: Frances H. Arnold and Jason Yang

Enzymes, proteins that catayze chemical reactions, are difficult to engineer due to their complex relationships between their sequence, structure and function. To generate enzymes with prespecified functions, we developed an approach using Masked Diffusion Language Models (MDLM) which have emerged as a new paradigm for data-efficient, scalable and steerable text generation. We adapted these models to condition amino acid sequence generation on enzymatic function, using classifier-free guidance. To enhance controllability and diversity, we further evaluated the effect of guidance techniques, as well as improved sampling strategies. *In silico*, we found that the proposed method can generate enzyme candidates that are diverse, realistic and designable, offering a promising direction for steerable enzyme generation with potential applications in biotechnology and synthetic biology.

Optimizing the gas diffusion electrode for lithium mediated nitrogen reduction
Anupama Subramanian
Mentors: Karthish Manthiram and Gangsan Lee

The current industry standard for producing ammonia, an essential component of fertilizers, is the Haber Bosch process. This reaction operates at extremely high temperatures (400-500 ºC) and pressures (150-250 bar). This results in heavy costs and high carbon emissions, consuming 1% of global energy. The electrochemical synthesis of ammonia through lithium mediated nitrogen reduction (LiNRR) provides a promising alternative that allows for production at near-ambient conditions. This project utilizes a gas diffusion electrode (GDE) which greatly improves nitrogen gas availability for lithium plated at the electrode. This project evaluates the implications of modulating pressure gradients and electrode surface areas to optimize ammonia production. By electrochemically plating porous copper onto stainless steel electrodes, the pore size and mesh surface area can be manipulated. The goal is to build a platform for modulating pressure to facilitate nitrogen reduction while gaining a fundamental understanding of electrode surface architecture. A greater understanding of the diffusion pathway and surface chemistry is integral for improving the Faradaic Efficiency of this system.