Summary of Research Experience and Doctoral Dissertation

I was a founding member of the Meek Lab where I developed carbodicarbene (CDC) ligated metal complexes for electrophilic alkene activation. My doctoral work demonstrated that CDC-Rh complexes catalyze a variety of atom-economical hydrofunctionalization reactions by activating unpoledared \( \pi \)-systems. Electrophilic activation of unpoledared \( \pi \)-systems (Scheme 1) has allowed for efficient hydroamination, hydroarylation, and hydroalkylation of dienes while introducing CDCs as a new class of catalytically active ligands with unique donor properties.

I. Introduction

Catalyst inhibition is an unsolved problem in many hydrofunctionalization reactions resulting in significant limitations to substrate scope. I theorized that strongly donating neutral ligands could stabilize a cationic metal catalyst to discourage inhibition while maintaining the electrophilic character necessary for alkene activation. CDCs were identified as an unexplored ligand class with desirable donor properties linked to their unique structure; the highest occupied molecular orbitals of a CDC manifest as two reactive lone pairs on the central carbon atom, implying that CDCs can donate two electrons, both as a \( \sigma \)-donor and as a \( \pi \)-donor (Scheme 2).

II. Developing CDC Ligands for Rh Catalyzed Hydroamination

A new class of CDC ligands was developed in which a cyclic diazepinium core was used to maintain planarity and conjugation of the \( \pi \)-orbitals (Scheme 3: Catalyst Design). A tridentate structure was included to prevent \( \beta \)-hydride elimination. The neutral CDC-Rh-Cl complex 1 was prepared in high yield by a simple three-step synthesis and shown to catalyze to efficiently catalyze the intermolecular hydroamination of dienes. The catalyst proved to be general for an unusually broad range of amine nucleophiles, demonstrating the value of the CDC ligand for preventing substrate inhibition (Scheme 3: Intermolecular Hydroamination). This research introduced CDC ligands as a method for solving challenges in alkene activation and marks the first publication of CDCs in catalysis.

III. Rh Catalyzed Hydroarylation of Dienes through Lewis Acid Activation of CDCs

A method for the hydroarylation of dienes with indoles was developed to extend the utility of CDC-Rh catalysts to C-C bond formations. Initial hydroarylations were promising, but encountered solubility problems from Ag precipitates. This was addressed by a second generation CDC-Rh complex 2 that replaced the X-type chloride ligand with styrene. However, catalyst 2 gave no reactivity without the addition of AgCl, which was previously assumed to be an insoluble spectator (Scheme 4: Discovery of Lewis Acid Activators). This serendipitous effect was caused by a beneficial interaction between AgCl and the lone pair of the CDC, which transiently increased the electrophilicity of the catalyst (Scheme 4: Mechanistic Rationale). Screening of the Lewis acid provided conditions for the efficient...
hydroarylation of a broad range of dienes with various N-heterocycles (Scheme 4: Intermolecular Hydroarylation). The reaction is tolerant of polar functional groups and can hydroarylate challenging internal diene substrates. This work provided a rationale for the novel efficiency of CDC ligands in alkene activation.

IV. CDC-Rh Catalyzed Hydroalkylation

In order to extend CDC-Rh catalysis to the formation of sp³ C-C bonds, enolvable oxazolones were employed as nucleophiles for the hydroalkylation of terminal dienes. Pairing 2 with a lithium activator catalyzed the formation of fully substituted N-quaternary stereocenters with high selectivity for the anti-addition products (Scheme 5: Diastereoselective Hydroalkylation). It was discovered that the addition of an alcohol additive significantly affected yield and diastereoselectivity, likely due to a favorable hydrogen bonding interaction between the alcohol and oxazoline that assists in enolization. The transformation tolerates aryl and alkyl dienes, polar functional groups, and various substituted oxazolones to produce allylic oxazolones in good yields and diastereoselectivities. The products can be epoxidized to relay diastereocenctrol from the stereocenters to the alkene (Scheme 5: Oxazoline Product Functionalizations). This methodology provides densely functionalized amino acid analogs diastereoselectively.

V. Ongoing and Future Efforts

Part A - Expanding the Scope of Hydroalkylation: The success of oxazoline nucleophiles for hydroalkylation prompted the exploration of alternative enolvable carbon nucleophiles (Scheme 6: Additions of Enolvable Nucleophiles). Preliminary results have shown that 1,3-diones, β-keto esters and malonate esters react efficiently with dienes. To extend this success, 2-(siloxy)furan derivatives were tested to introduce nucleophiles that do not require thermal enolization. Initial experiments show that CDC-Rh 2 can catalyze the addition of silylketene acetals to form γ-substituted 2-butanoles with modest conversions and diastereoselectivities (Scheme 6: Additions of Siloxyfurans). Work is ongoing to improve the diastereoselectivity and scope before publication.

Part B - Enantioselective CDC-Rh Catalysis:

Several chiral CDC ligands have been developed with the goal of generating a highly enantioselective catalyst for the above hydrofunctionalization reactions. Variants of the CDC ligands have been synthesized that incorporate chiral centers on the diazepinium core (eg: 3) or phosphorus substituents (eg: 4) (Scheme 7). Catalysts 3 and 4 have been successfully applied to the hydroarylation of phenylbutadiene to provide modest enantioselectivities.

VI. Doctoral Dissertation and Postdoctoral Work

My doctoral dissertation was completed in July 2016, after which I began a postdoctoral position at the University of Rochester in August 2016. The dissertation summarized the field of electrophilic alkene activation as a catalytic method and included detailed discussions of CDCs and their uses as ligands for transition metals. The dissertation included four chapters on the following topics: (i) Hydroamination and characterization of CDC-Rh complexes; (ii) Hydroarylation and the unique properties of CDC ligands in catalysis; (iii) Hydroalkylation and the development of diastereoselective synthetic methods; and (iv) Methods for stereoselective hydrofunctionalization and the exploration of chiral CDC ligands for stereoselective catalysis. My last year (Summer 2016 to Present) has been spent in the Weix lab where I have contributed to the field of cross-electrophile coupling through (i) the development of methods for the coupling of aryl psuedohalides with alkyl halides, and (ii) the invention of a Ni catalyzed intermolecular method for forming C-N bonds via a radical chain initiated by the decarboxylation of redox active esters. Most recently I was awarded an NIH Postdoctoral Fellowship to continue these studies and expand my interest to exploring Ni(I) and Ni(III) intermediates that have been widely postulated in cross-electrophile coupling mechanisms.