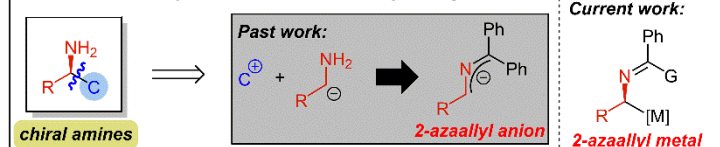


I. Introduction

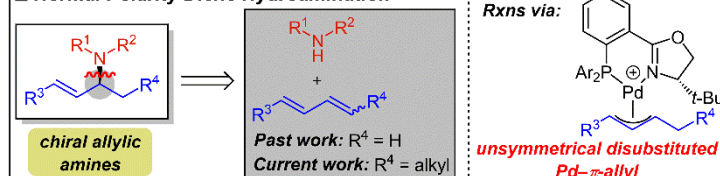
In the final year of this award, we have moved from preparing chiral amines by developing diastereoselective and stereospecific, purely stoichiometric additions of 2-azaallyl anions (imine umpolung reagents) to chiral electrophiles to achieving this goal by the development of catalytic enantio- and diastereoselective

Scheme 1. Concepts Explored in the Last Funding Period: Azaallyl Reagents & Diene Hydroamination

Reverse Polarity Reactions with Azaallyl Reagents



Normal Polarity Diene Hydroamination



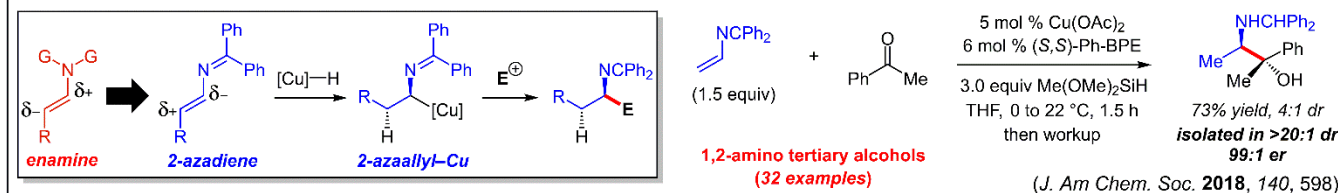
transformations of *in situ*-generated 2-azaallyl transition metals (Scheme 1). Preliminary work in this latter area was communicated in the last progress report. The 2-azaallyl transition metal reagents are catalytically generated in a new way, via migratory insertions or polar additions to 2-azadienes (enamine umpolung reagents), rarely utilized chemical building blocks. Additionally, besides the achieved reverse polarity transformations with 2-azadienes, attempts to utilize these reagents for normal polarity reactions were unsuccessful but did lead to the discovery of a Pd-catalyzed protocol for the enantioselective intermolecular hydroamination of internal acyclic 1,3-dienes via unsymmetrical Pd- π -allyls (Scheme 1).

II. Reactions of 2-Azaallyl-Metals Catalytically Generated from 2-Azadienes

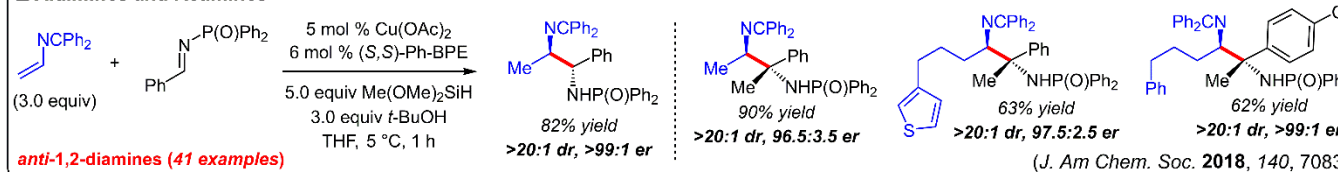
a. Cu-catalyzed reductive couplings with ketones and imines. We hypothesized that, compared to enamines, the polarity of the C–C double bond in a 2-azadiene should be reversed, allowing for migratory insertion to generate a stabilized and, depending on the metal, nucleophilic 2-azaallyl transition metal reagent (Scheme 2). Indeed, Cu-catalyzed reductive couplings with both ketones and imines have been developed. In the reactions, which proceed via a 2-azaallyl–Cu intermediate, Ph-BPE was found to be an essential ligand not only for stereoselectivity but especially for chemoselectivity (reductive coupling versus electrophile reduction). Enantioselectivities were excellent. Diastereoselectivity was better when ketones were sterically hindered (*ortho*-substituted aryl ketones). Diastereoselectivity was perfect with both aldimine and ketimine electrophiles. A range of alpha-alkyl amines are accessible within the sterically congested vicinal amino alcohol and diamine products.

Scheme 2. 2-Azadienes, New Enamine Umpolung Reagents: Cu-Catalyzed Enantioselective Reductive Couplings with Ketones and Imines

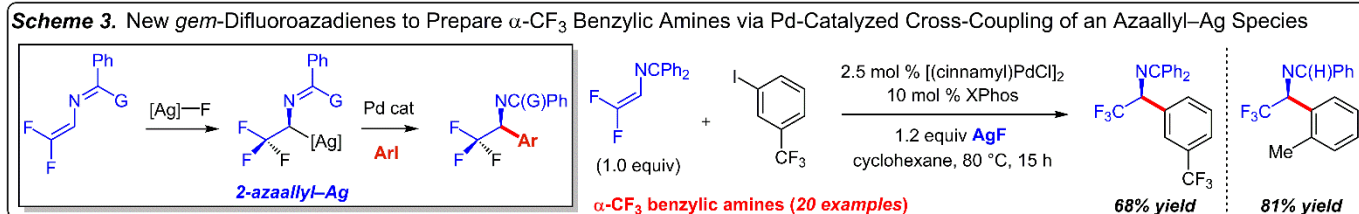
Ketones



Aldimines and Ketimines

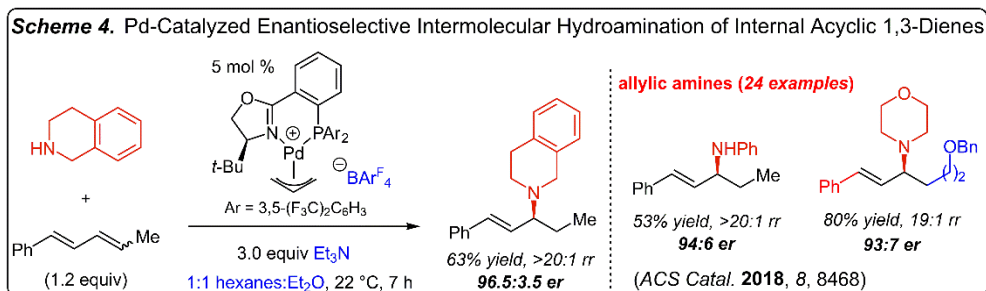


b. Pd-catalyzed fluoroarylation of gem-difluoro-2-azadienes. We have recently developed a Pd-catalyzed reaction that converts *gem*-difluoro-2-azadienes to alpha-trifluoromethyl benzylic amines via reaction with AgF and aryl iodides (Scheme 3). Silver fluoride stoichiometrically adds to the azadiene in a process catalyzed by XPhos to afford an azaallyl–Ag intermediate, which undergoes transmetalation with Pd (after aryl iodide insertion) to deliver the products. XPhos is the only ligand that promotes the reaction. Steric modification of the “imine” portion of the azadiene facilitates difficult cross-couplings such as reactions of *ortho*-substituted aryl iodides. A manuscript describing this work is currently being prepared.



III. Pd-Catalyzed Intermolecular Hydroaminations of 1,4-Disubstituted 1,3-Dienes

Stemming from some of our studies in the atom economical Pd-catalyzed hydroalkylation of normal 1,3-dienes with activated pronucleophiles (*JACS* **2018**, *140*, 2761), we initially attempted similar reactions with azadienes but with no success. However, the postdoc working on this project did discover that several allylic amines could be garnered through the Pd-catalyzed hydroamination of internal dienes (Scheme 4). Several factors, including catalyst counterion, addition of Et₃N, and solvent polarity were essential for the reaction to take place with this challenging class of substituted hydrocarbons. In this way, several Lewis basic alkyl amines and anilines take part in the hydroamination to afford myriad allylic amines with a variety of alpha-alkyl and olefin substituents.



IV. Impact of This Research

a. On science. Enantioselective synthesis of chiral amines is a critical objective owing to their presence in a plethora of diverse, biologically active molecules. Finding new methods that are more efficient, particularly C–C bond-forming and/or atom economical ones, to achieve this aim is important. The research developments we have achieved that were supported by this PRF grant have enabled us to form highly challenging bonds, affording stereochemically dense and sterically congested products, often in highly atom economic ways. In several instances, new chemical space has been accessed for the first time (e.g., diamines in Scheme 2).

b. On my career. The opportunities afforded by this grant have had an enormous impact on my career. The research conducted under the auspices of this award during the last year has already resulted in three publications (two in *JACS* and one in *ACS Catalysis*) and soon a fourth (fluoroazadiene work, Scheme 3). In total, six publications will have resulted from the support of this grant. My research group's efforts, as supported by the PRF award has laid the foundation for two independent projects in my lab, providing the data needed to secure both an NIH R01 grant (GM124286) and an NSF grant (CHE-1800012).

c. On student training. Students and postdocs have received training in organic synthesis, catalysis, method development, and analytical techniques (NMR spectroscopy, glovebox procedures, HPLC, LC-MS, *et al.*). Additionally, they have received training in scientific writing through group progress reports and in assisting me in composing papers and grants. All the while, they have been trained to think strategically and mechanistically about chemical science, preparing them for planned careers in academia and industry.

V. Publications This Funding Period

- 1) Li, K.;* Shao, X.;* Tseng, L.; Malcolmson, S. J. "2-Azadienes as Reagents for Preparing Chiral Amines: Synthesis of 1,2-Amino Tertiary Alcohols by Cu-Catalyzed Enantioselective Reductive Couplings with Ketones," *J. Am. Chem. Soc.* **2018**, *140*, 598–601. *Equal contribution.
- 2) Shao, X.; Li, K.; Malcolmson, S. J. "Enantioselective Synthesis of *anti*-1,2-Diamines by Cu-Catalyzed Reductive Couplings of Azadienes with Aldimines and Ketimines," *J. Am. Chem. Soc.* **2018**, *140*, 7083–7087.
- 3) Park, S.; Malcolmson, S. J. "Development and Mechanistic Investigations of Enantioselective Pd-Catalyzed Intermolecular Hydroaminations of Internal Dienes," *ACS Catal.* **2018**, *8*, 8468–8476.