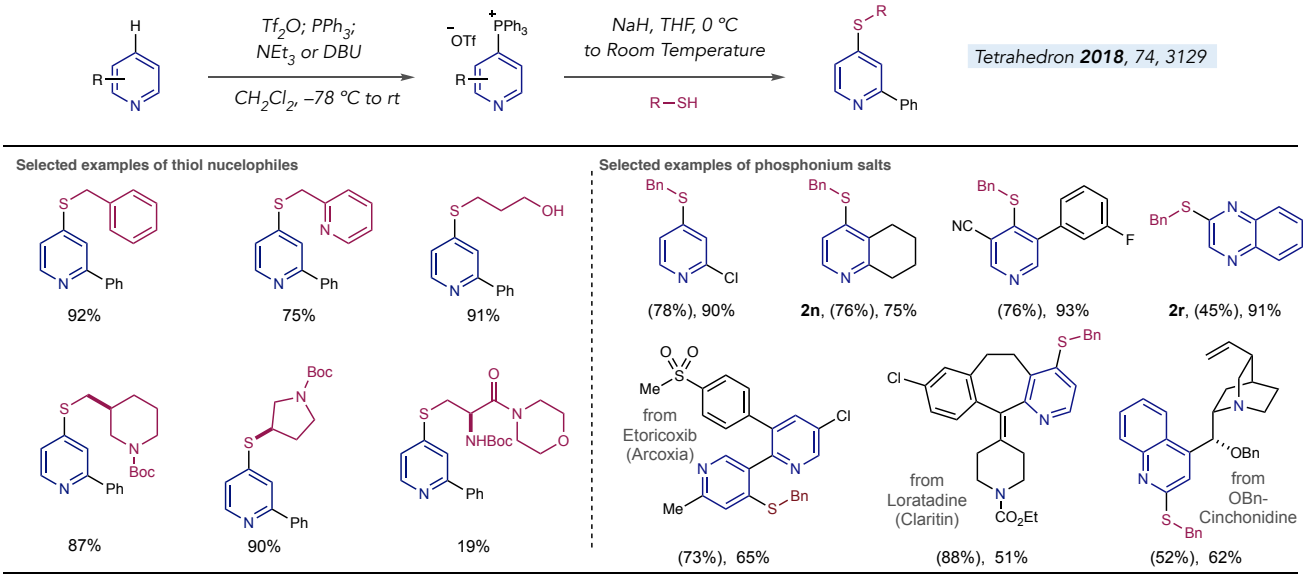
1. PRF Number: 56878-DNI1
2. Project Title: A New Class of Reagents for Heterocycle Coupling Reactions
3. Prof. Andrew McNally, Colorado State University

Narrative Progress Repor 2017-2018t.

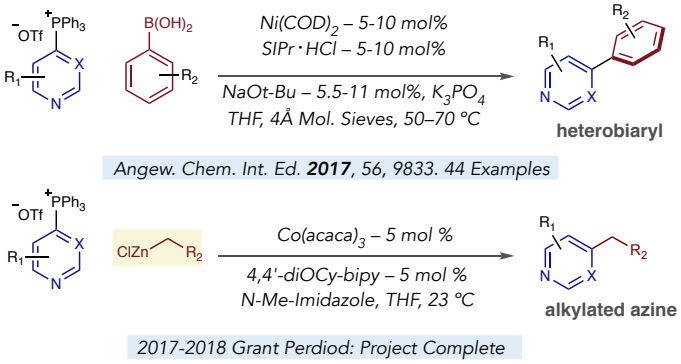
Reaction of Heterocyclic Phosphonium with Thiols to Form Heteroarylthioethers.
Our initial publication (outside of the grant period) involved adding alkoxide nucleophiles to heterocyclic phosphonium salts as a new strategy to make heteroaryl ethers. Our goal during this period was to establish that thiols were also viable nucleophiles to construct heteroarylthioethers. We completed this study and the result were disseminated in 2018 (*Tetrahedron* **2018**, *74*, 3129-3136). Brianna Jett, an undergraduate student worked with a graduate student during this project and made a significant contribution to the final output. We found that the reaction has a good level of generality in both the heterocyclic phosphonium salt and thiol nucleophile. The reaction protocol is simple and involved deprotonating the thiol and adding the phosphonium salt to the reaction mixture at room temperature. Primary, secondary and tertiary thiols were all competent nucleophiles as well as complex thiols containing saturated amine heterocycles and amino acids (Scheme 1). During this study, we found that pKa effects can be exploited so that chemoselective transformations are possible. In particular, thiols will react preferentially over alcohols and Boc-protected amines. The heterocyclic phosphonium scope was equally broad; a range of substituted pyridine and diazine salts were effective that were distinct in their steric and electronic properties. Thiol addition to the phosphonium ion also outcompetes outcompetes SNAr reactions of 2-halopyridines. Finally, we demonstrated that phosphonium salts derived from complex pharmaceuticals could be coupled to petroleum-derived thiol nucleophiles (Scheme 1).

Scheme 1. Coupling of thiols to heterocyclic phosphonium salts



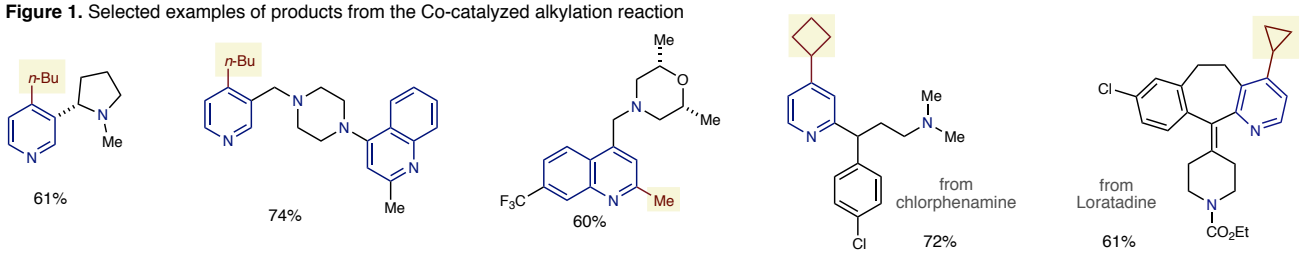
Metal-Catalyzed Cross-Coupling Reactions.
During the 2016-2017 period, we completed a study showing that phosphonium ions could serve as pseudohalides in a Nickel-catalyzed Suzuki type reaction (*Angewandte Chem. Int. Ed.* **2017**, *56*, 9833). Our aim in this period was to build from this sp2-sp2 coupling reaction into sp2-sp3 couplings. However, the previous Ni-catalyzed system was ineffective in coupling heterocyclic phosphonium salts with alkyl zinc reagents with mixtures of heterocycle and unwanted phenyl transfer observed. The same outcome was observed upon varying ligands at the Ni-center as well as resorting to a range of Pd-catalyst systems. A screening endeavor revealed that cobalt catalysts in conjunction with bipyridine ligands were optimal for this transformation with heterocycle coupling obtained as the exclusive outcome in these cases (Scheme 2). An optimization study indicated that electron-donating groups on the bipyridine scaffold improved the efficiency of this reaction with cyclohexyloxy groups proving the most effective. During this period, Dr. Xuan Zhang worked to fully exploit the scope of this transformation. The room temperature process is remarkably broad for a diverse set of pyridine-derived phosphonium salts; complex structures including other polar functional groups such as aliphatic amines and other nitrogen heterocycles (Figure 1). Quinolines and diazines are also competent coupling partners. Alkyl zinc reagents are conveniently derived from simple alkyl halides that are a major set of derivatives from petrochemicals. The scope of alkyl zinc reagents is also good with valuable fragments such as methyl groups, cyclobutane and cyclopropane rings amenable to coupling via the phosphonium ion.

Scheme 2. Building on Ni-catalyzed arylation towards Co-catalyzed alkylation



We believe that this room temperature coupling process will be valuable to practitioners in several disciplines of the chemical sciences. The project has been completed and the manuscript is about to be sent out for publication.

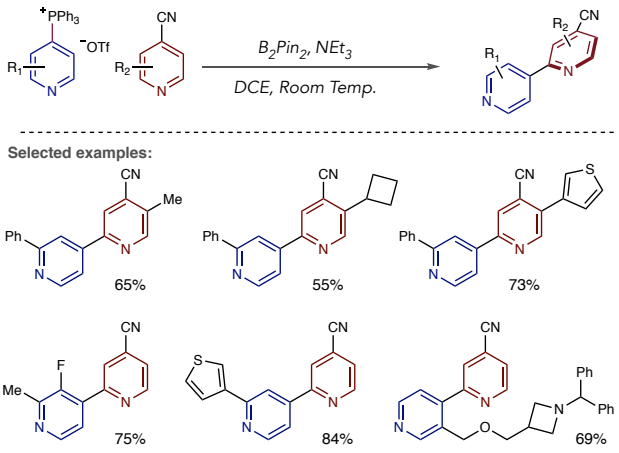
Figure 1. Selected examples of products from the Co-catalyzed alkylation reaction



Radical Coupling Reactions.

In the 2016-2017 period, we obtained a breakthrough results that indicated pyridine phosphonium salts could be coupled to cyanopyridines resulting in useful bipyridine products. In this period, we have extensively investigated this process and made a number of key advances. First, the reaction can be conducted without visible light photoredox catalysis and simply requires B_2pin_2 as a reagent and NEt_3 as a base. Mechanistic investigations indicate that combining the boron reagent with a cyanopyridine forms a stabilized radical that serves as a reducing agent to cleave the C–P bond via single-electron transfer. The resulting pyridyl radical then adds to a boron-activated cyanopyridine in an unusual Minisci type process. This new reaction is distinct from typical Minisci reactions as successful couplings require matching electron rich and electron poor substrates as coupling partners. In this case, both partners are electron deficient leading us to believe that charge transfer complexes are formed during the reaction process. Second, the scope of this process has been investigated and shows that a variety of heterocyclic phosphonium salts and cyanopyridines are effective as coupling partners (Scheme 3). It is also important to note that substituting the phoshphonium ion for other radical precursors such as halides, triflates or ammonium salts result in no formation of the bipyridine product. Currently, we are finalizing the scope of this process and performing further studies to elucidate the mechanism of this unique reaction. Publication is expected in six to eight weeks.

Scheme 3. Radical-mediated bis-azine biaryl formation



Impact

Impact on the PI's career. The PRF grant has been instrumental in launching the research program in my laboratory. As described in this report, a number of projects have emerged during the 2016-2018. The projects have resulted in highly visible publications and have allowed us to pursue other direction of the phosphonium ion chemistry. Because of these further studies, my laboratory has been awarded with an NSF Career grant and an R01 grant for the NIH. It has enabled me to deliver several lectures (ACS San Francisco & Philadelphia, Heterocycles GRC, Canadian Society of Chemistry 100th Anniversary Conference and given several talks at schools across the US as well as pharmaceutical companies). I am deeply indebted to the support from the PRF fund for providing a platform to establishing a highly visible program and the opportunity to engage and train with excellent students.

Impact on Students. One postdoctoral researcher, Xuan Zhang and has been supported on this grant. Dr. Zhang has gained one publication and will shortly receive another. He is currently applying for the 'Thousand Talents Program' where he intends to start his own academic career in China. Brianna Jet, an undergraduate researcher in my laboratory has developed into a highly skilled researcher and plans to continue into graduate school. She is currently applying for top graduate programs across the US and will be in a very strong position due to the activities during the period of the PRF grant.