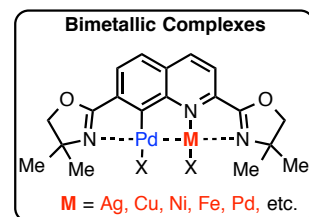


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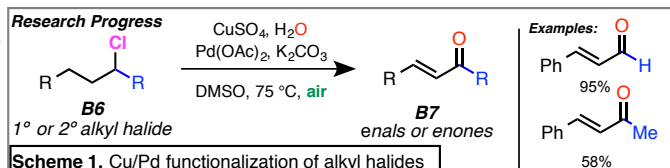
TITLE: **Development of Unique Functional Group Interconversions**PI: **Alejandro Bugarin**; Department of Chemistry and Biochemistry, University of Texas at Arlington**Progress of Research and Impact:**

Discovery of specialized compounds and new materials, together with our constant need for improved eco-friendly technologies, are dependent on parallel innovation of better strategies to generate the requisite key molecules from simple building blocks. In particular, there is a fundamental need to identify more effective routes to improve the overall efficiency, economics, and general applicability of many synthetic processes. Our research activities involve work centered on development of novel *bimetallic catalysts* to activate simple molecules (alkyl halides, alkynes, alkenes, allenes, etc.). It is, of course, widely recognized that metal-catalyzed carbon-carbon and carbon-heteroatom bond forming reactions play a central role in the synthesis of key organic materials and pharmaceutical targets. However, a long-standing problem afflicting organometallic chemistry is control of both selectivity and regulation of the transition metal catalysts. Very recently, we initiated studies to examine direct site selectivity and reactivity based on the idea that use of bi-metallic catalysts may provide both improved selectivity and reactivity. In contrast to the extensive literature involving monometallic transformations, or bimetallic cooperative catalysis, there are virtually no data involving the use of bimetallic catalysts wherein both transition metals interact significantly. Our current progress is extremely encouraging in that our bimetallic catalysts exhibit excellent reactivity towards many molecules (e.g., activation of alkynes), leading to facile functional group interconversion. Our current and future plans involve an interesting variety of bimetallic complexes, (e.g. Pd-Cu, Pd-Ag, etc.) and chiral ligands, to be employed as tunable catalysts.

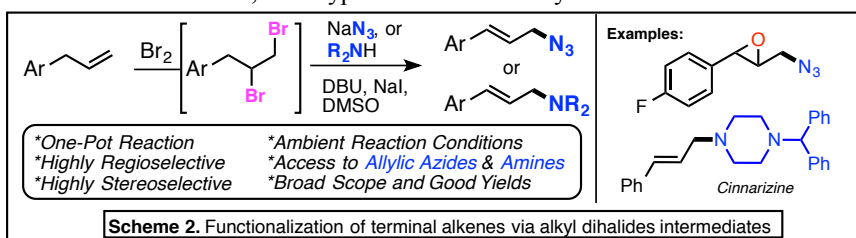


Our proposed plan was to carefully assess the overall utility, as well as possible limitations, involved in each of the following aims:

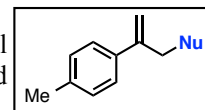
(1) A new catalytic strategy to functionalize alkyl halides into α,β -unsaturated carbonyls. Taking advantage of the properties of copper and palladium as catalysts, during this past year we have developed, for the first time, a direct strategy for the synthesis of α,β -unsaturated carbonyls with water and air, via hydration or hydrolysis of the alkyl halides, followed by oxidation of the resulting alcohols to create enals (from primary alkyl halides) and enones (from secondary alkyl halides), with yields up to 95% (Scheme 1). Despite the enormous potential synthetic utility of these transformations, surprisingly, we are the first research group working on this area. With our very recent, unpublished preliminary results to access α,β -unsaturated carbonyls, we are well-positioned to provide a definite advance in the field. Specifically, the 1st examples of enals from alkyl chlorides, achieved via use of a cooperative dual catalytic system involving copper and palladium, were recently produced in our group with good yield and excellent regioselectivity (Scheme 1, [manuscript in preparation](#)). Because alkyl halides proved to be excellent substrates, we hypothesized that alkyl dihalides will also work.



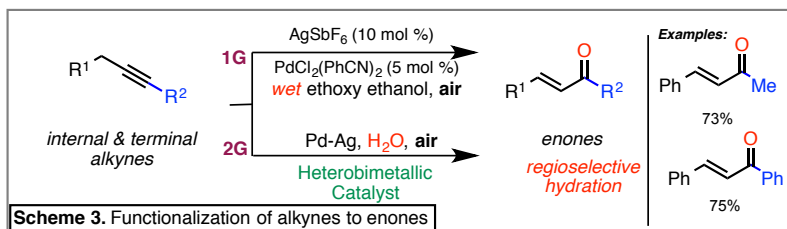
However, after performing our transformation under standard conditions, we observed the formation of an allylic system instead (Scheme 2). With this new result on hand, we decided to fully optimized the reaction conditions and investigate the substrate scope. To our delight, the need of transition metals was avoided and the substrate scope was excellent (more than 25 adducts), even the well-known calcium channel blocker *cinnarizine* was synthesized in one-pot reaction (Scheme 2). [The manuscript of this work is current under peer-review](#). Importantly, this work was performed mainly by undergraduate students. Students that benefited in many ways, for example; Octavio Miranda received the undergraduate student research award for his contribution to the project, in April 2018. A few weeks after that, he was recruited as a McNair scholar to continue his research work.



By carefully selecting the reactions conditions and substrates, we discovered that terminal alkenes can be direct converted into styrene derivatives. These adducts are easily functionalized with nitrogen, oxygen, carbon, and sulfur nucleophiles, [manuscript under preparation](#).

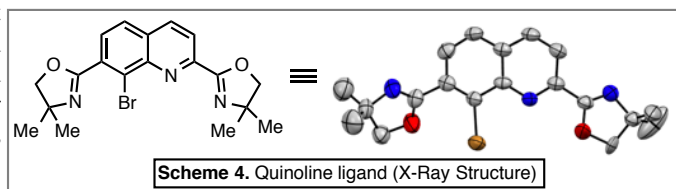


(2) Functionalization of simple alkynes to α,β -unsaturated carbonyls (enones). The catalytic functionalization of simple alkyne hydrocarbons, by reaction them with water and air and employing transition metals, are in progress. The synthetic advantage of this method is construction of new C–O, C=O, and C–H bonds in one synthetic step, under mild reaction conditions, and rapid conversion to C=C bonds with high regioselectivity. Furthermore, we seek to leverage our current results in order to develop an efficient strategy to convert several different alkynes into α,β -unsaturated ketones (enones) in a single operation using both the first



generation tandem catalytic system (ligandless: Scheme 3, top) and the second generation using our heterobimetallic catalysts (e.g., pincer Pd-Ag complex: Scheme 3, bottom). Our current results are encouraging for the first generation, where good yields and excellent regioselective hydration were observed, manuscript under preparation. However, we are yet to try the second-generation catalytic system. It is worth noting that traditional syntheses of internal alkynes involve Sonogashira couplings of terminal alkynes and aryl halides. In turn, the terminal alkynes are produced by deprotection of TMS-alkynes, using TBAF. While following those standard transformations, we discovered that TMS-alkynes can be indeed deprotected using TBAF. However, under special conditions the pi-bonds can migrate. Based on our observation, we developed a metal-free synthesis of allenols, from TMS-alkynes and aldehydes (now a name reaction, *Chem. Eur. J.* **2016**, 12696). We are currently working on the expansion to ketones and imines. Preliminary data is promising and we are planning to investigate its scope and limitations, together with a one-pot synthesis of carbazoles employing PtCl₂ as the transition metal catalyst.

(3) Development of new heterobimetallic catalysts: We are currently working on the combination of two transition metals, within a single ligand, to better tune the catalyst reactivity and selectivity of several tandem reactions. We are very optimistic about our current progress. In this regard, we have synthesized several quinoline-based ligands, both achiral and chiral, using aminoacids as the chiral source. For example, the quinoline ligand in Scheme 4 was synthesized and fully characterized, even with X-ray analysis. My undergraduate students and a graduate student are very excited to have obtained X-ray structures for 3 different ligands, some bearing bromo substituents and others iodo substituents. Presently, we are synthesizing and characterizing metal-complex with copper, silver, and/or palladium. Thus far, we can see them by ¹H NMR, but X-ray structures are still to be obtained. A manuscript will be submitted for publication as soon as we obtain those X-ray structures. We believe that the new bimetallic complexes are advantageous and should increase the turn over number (TON) of several transformations, by increasing stability and rigidity of the system, leading to a lower catalyst loading. Finally, and to further expand the power of this α,β -unsaturated carbonyl adducts, we are currently working on a couple of chemical transformations that take make use of *water and air as the environmental friendly reagents*.



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Summation:

It is well known that petroleum products, as used in manufacturing a wide variety of compounds, involves world-wide consumption of several million barrels each day. In light of the growing threat of environmental pollution from petrochemical use, development of synthetic alternatives that are more energy efficient and, at the same time, more economical and waste byproduct reduction would obviously be a very welcome advance. Herein, we have accomplished a couple of straightforward and new synthetic transformation that are superior to known strategies in terms of economic, environmental, and sustainability perspectives. The importance of our strategy lies on the potential utilization of those masked α,β -unsaturated carbonyl compounds that can be incorporated early in long-steps syntheses and carried through several synthetic steps to be revealed at a later stage, while **developing unprecedented functional group interconversions** and new catalytic systems that encompasses atom-economic transformations.

Overall, the ACS PRF ND grant provided economical support and a research platform, which offered a high-quality research training for graduate and undergraduate students, while allowing the PI to develop several research projects and to finish others. In addition, the students learned or improved necessary synthetic skills and handling of scientific instrumentation required for compounds' analysis and characterization.