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Direct Difunctionalization of Alkynes by Radical Oxidative Coupling Reaction

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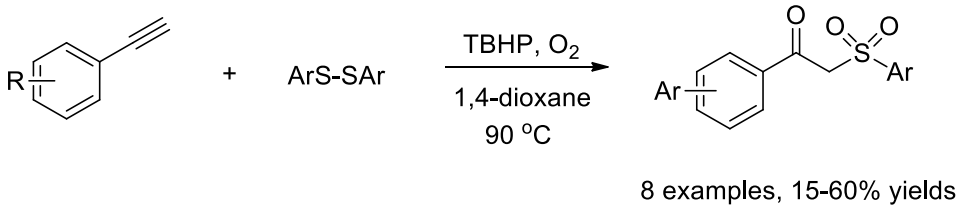
Research Progress

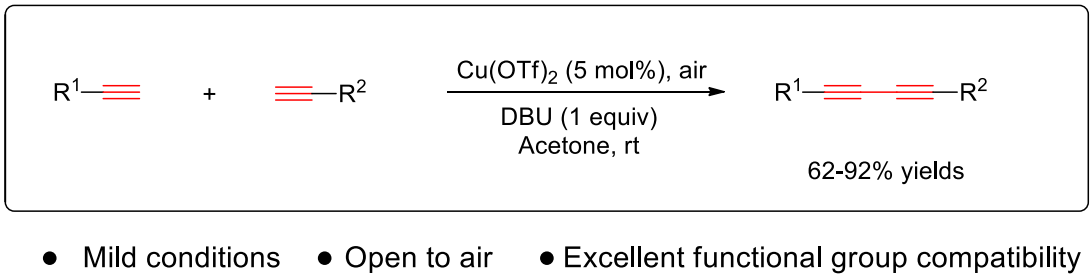
The goal of our research is to invent next generation synthetic methodologies which display improved efficiencies and highlight atom economy, green catalysis, and energy sustainability. Our approach to these challenges is to develop novel alkyne di-functionalization for the carbon-carbon and carbon-heteroatom bonds formation. We plan to advance an alkyne difunctionalization strategy by radical oxidative coupling to directly couple alkynes with un-activated unactivated C-H bonds. We aim to gain a deep understanding of the mechanism of the radical oxidative coupling reaction, the reactivity and stability of the reactive vinyl radical intermediate, and the regioselectvity and functional group compatibility of these reactions.

Since being funded by PRF, we first started the investigation on the oxidative coupling of alkynes and disulfides (Scheme 1). It was found that terminal aromatic alkynes can couple with disulfides in the presence of *t*-BuOOH (TBHP), molecular oxygen (oxygen balloon), and 1,4 dioxane (solvent) at 90 ^{o}C. α-Sulfonyl ketones were generated as oxidative coupling products. So far, we have prepared eight α-sulfonyl ketones in 15-60 % yields using this method. Currently, we are working on the expansion of the substrate scope and further improvement of the reaction yields. This method successfully constructs carbon-sulfur bond and carbon-oxygen double bond in one pot operation.



Scheme 1. Oxidative coupling of alkynes and disulfides

During the study of alkyne fuctionalizations, we have discovered a new method for alkyne homo- and hetero-coupling under ambient temperature and mild reaction conditions (Scheme 2). It was found that $Cu(OTf)_2$ can catalyze homo– and hetero-coupling of aromatic and aliphatic terminal alkynes. Symmetric and unsymmetric 1,3-diynes have been synthesized in good yields under an aerobic condition in the presence of an organic base DBU. This reaction features mild conditions, a wide substrate scope, and excellent functional group compatibility. We have published this work on *Tetrahedron Letters* early this year with five undergraduate co-authors.[i]



Scheme 2. Cu(II) catalyzed alkyne homo- and hetero-coupling

Impact on Undergraduates

For the last 12 month, seven undergraduate students directly involved in this project. Undergraduate students are engaged in every stage of the study. They learn how to read and interpret information from literature searches; we work closely together to design and conduct experiments for optimization of the reaction conditions, investigation of the substrate scope and limitation, elucidation of the mechanism, and multistep synthesis; they also operate instruments, obtain GC-MS, NMR, IR data, analyze the results, and communicate results orally and in writing to their peers, mentor, and members of the scientific community. Among the seven undergraduate students, two are currently enrolled in medical school, one is in dental school, and one is enrolled in our chemistry graduate program at WPU. This grant along with other internal grants from campus was able to support the student research during the academic year and summer. Five students co-authored a peer-reviewed publication on *Tetrahedron Letters*. Four students presented poster presentations at the GS-LSAMP/NNJ-B2B STEM Research Conference at Rutgers University on October 2018 and two students won the best presentation award. In addition, five students presented the research at Undergraduate Research Symposium at WPU (April 2019) and two students won best poster award. In May 2019, one student presented an oral presentation at the ACS Middle Atlantic Regional Meeting at Baltimore, MD.

Impact on PI

This grant greatly helped the PI sustain a strong research program involving undergraduate students at WPU. During the last 12 months, this grant and other small internal grants allowed the PI to purchase lab supplies and chemicals for the research as well as compensate the student researchers and support the conference travel. With the support from this grant, the PI attended *Gordon Research Conference: Organic Reaction and Process* in July 2019 and presented a poster presentation. The PI also presented an oral presentation at the Fall ACS meeting at San Diego in August 2019. The PI's research group has made a significant progress in the area of proposed research and obtained exciting preliminary results that helped the PI submit additional grant proposals to NSF in the summer of 2019.

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[i] M. K. Holganza, L. Trigoura, S. Elfarra, Y. Seo, J. Oiler, Y. Xing*. "Copper (II) catalyzed homocoupling and heterocoupling of terminal alkynes" *Tetrahedron Lett*. **2019**, *60*, 1179-1181.