1. **PRF#:** 54968-UR1
2. **Project Title:** Palladium Catalyzed alpha Heteroarylation of Ketones
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From September 1st, 2017 to August 31st, 2018, we continued our research on palladium-catalyzed direct alpha-heteroarylation of ketones with the support from ACS PRF. Specifically, we finished the substrate scope study for over 40 heteroaryl compounds and over 20 ketones using the method established in our group; we developed the one-pot synthesis of isocoumarin derivatives using palladium-catalyzed domino reactions and successfully synthesized about 20 isocoumarin products; we discovered a reaction route to 1,2-diketones using palladium catalysis and optimized the reaction conditions. We also established a collaboration with University of Texas Rio Grande Valley on the Density Functional Theory (DFT) study of palladium-catalysis mechanisms.

1. Methodology establishment for the palladium-catalyzed direct α-C(sp3) heteroarylation of ketones under microwave irradiation:

We established a highly efficient method for the palladium-catalyzed direct α-heteroarylation of ketones under microwave irradiation. The reaction time was greatly reduced from 10 - 24 hours under thermal heating to 10 – 20 minutes under microwave irradiation. The final optimized conditions were 1 mol % XPhos Pd G4, 2.2 equiv. ^{t}BuONa, toluene, microwave irradiation at 130 ^{o}C for 10 – 20 min. We tested over forty heteroaryl halides and over twenty ketones. Twenty-eight (**28**) heteroarylation compounds with various functional groups were successfully synthesized in good isolated yields and purity. The mechanistic investigation on this reaction using NMR techniques and DFT calculation are currently ongoing. The major findings from heteroaryl substrate scope study are as follows:

For heteroaryl substrate reactivity, the results are complicated yet interesting. First, heteroaryl halides with only one heteroatom generally gave good to excellent yields under the optimized reaction conditions established above. Though there were a few successful examples, heteroaryl halides with two heteroatoms such as 4-bromoisoxazole, 2-bromothiazole and 5-bromo-1-methyl-1H-imidazole tended to decompose and were not able to form the desired products. Second, better yields were achieved when the N atom is one or more carbon away from the halide, and low yields were observed when the N atom is adjacent to the carbon with the halide. When N atom is closer to the metal center, the catalyst poisoning chance is greatly increased. Third, the effect of different leaving groups (Cl, Br and I) on heteroaryl substrate reactivity was investigated in this catalytic system. Heteroaryl iodides demonstrated higher yields than heteroaryl bromides, which showed higher reactivity than heteroaryl halides. Additionally, some heteroarylation only happened when the corresponding iodides were used. Lastly, when the heteroaryl atoms are not on the ring directly attached to the ketone, the reactions went smoothly. As a matter of fact, this catalytic system was tested on aryl halides such as bromobenzene, and very high isolated yields were obtained for these compounds. These encouraging results broaden the applicable area of the catalytic system developed in this study.

For the ketone substrate reactivity, the palladium-catalyzed direct heteroarylation reaction went smoothly with a variety of ketones. First, aryl methyl ketones, represented by acetophenone, showed great compatibility with many substituents such as methyl, methoxy, hydroxyl and halides. Alkyl methyl ketones were also reactive in this reaction with expected regioselectivity – the less hindered methyl group ($-CH_3$) is much more reactive than the more hindered methylene ($-CH_2-$) or methane (-CH-) groups. Second, when a primary carbon ($-CH_3$) is not available on the α-position of the ketone, higher reaction temperature or longer reaction time was required to drive the reaction to completion due to the increased steric hindrance for secondary carbon. Third, it was exciting to find out that this catalytic system also worked well for heteroaryl ketones including 3-acetyl-2,5-dimethylfuran, 3-acetyl-2,5-dimethylthiophene, 2-acetylpyridine, 3-acetylpyridine and 4-acetylpyridine. Lastly, the ketones with active methylene groups (1-phenyl-1,3-butanedione, 1,3-cyclohexanedione, ethyl levulinate, etc) didn't give expected products, probably due to the strong basicity of ^{t}BuONa. For these reactions, the use of a weaker base such as NaOEt might give improved results. For ketones bearing cyano or nitro groups, no alpha-heteroarylation was observed possibly due to their reactions with strong bases and nucleophiles. Overall, most ketones went smoothly in the palladium-catalyzed direct heteroarylation reactions, demonstrating that the palladium-catalyzed direct heteroarylation of ketones is of great value to access pharmaceutically important molecules.

2. one-pot synthesis of isocoumarin derivatives using palladium-catalyzed domino reactions and its mechanistic investigation:

Isocoumarin derivatives are an important class of secondary metabolites and they exhibit diverse biological activities such as antifungal, antimicrobial, antitumor, antioxidant and antiallergic effects. Normally isocoumarin are synthesized in 2-4 steps in reported literature. Last year we discovered a palladium-catalyzed domino approach to synthesize isocoumarin derivatives. This year we investigated this reaction in detail in terms of substrate scope and reaction mechanism.

First, we tested substrate scope of this reaction. A variety of ketones from aromatic to aliphatic were used in this reaction. Due to its commercial availability, only 8 heteroaryl substrates were able to obtain and they were tested in this reaction. Our results showed that 17 out of 23 ketones and 4 out of 8 heteroaryl substrates were successful and 21 isocoumarin derivatives were successfully synthesized in good yields and purity.

Second, we started to investigate the reaction mechanism by using ^{18}O-labelled acetophenone starting materials. Two mechanisms were proposed for this reaction. In Mechanism A, the palladium displaces the methyl group on the heteroaryl ester group after forming the heteroarylation product. The Metal-oxide group then acts as a nucleophile and attacks the carbonyl on the ketone substrate. The dehydrated product is thought to be more prevalent than the hydrated product, because the alkene allows for conjugation between the two arene groups, thus increasing the stability of the compound. Mechanism B proposes that after the initial heteroarylation between the ketone and the heteroaryl substrates, an enolate is formed. The now negatively charged oxygen atom attacks the carbonyl carbon of the heteroaryl ester. The ester is reformed, and the methoxide group is forced to leave. The alkene formation is thought to be promoted by ^{t}BuONa, a base necessary for all heteroaryl reactions. A major difference between the two mechanisms is the source of the carbonyl oxygen in the isocoumarin. In Mechanism A, the oxygen comes from the heteroaryl substrate. In Mechanism B, the oxygen comes from the ketone substrate. Thus using ^{18}O-labelled acetophenone as the substrate would let us distinguish mechanism A and mechanism B. Undergraduate students converted regular acetophenone to ^{18}O-labelled acetophenone using $H_2{}^{18}O$. Then the ^{18}O-labelled acetophenone was subject to the palladium-catalyzed domino reaction conditions. The HRMS results indicated that no ^{18}O was incorporated in the domino products, so mechanism B is ruled out. Further experiments to test mechanism A is ongoing.

3. Palladium-catalyzed 1,2-diketones formation

This is a reaction discovered in our previous research and we continued to explore and optimize the reaction conditions. In summer 2018, we tested a variety of oxidizing agents such as air, I_2, CuO, $CuSO_4$ and $AuCl_3$ to facilitate the oxidation of heteroarylated ketone to 1,2-diketone. Finally, we succeeded to synthesize 1,2-diketone via a palladium-catalyzed direct α-heteroarylation of ketones/CuO oxidation process. Specifically, the α-heteroarylation of ketones were carried out and the crude products were obtained. These products were subject to I_2 and CuO in DMSO under microwave irradiation. The 1,2-diketone products were isolated in 40-80% yields after flash chromatography. In future work, we will further optimized the conditions and hopefully to develop a one-pot process for diketone formation.

4. Impact on PI and undergraduate students

One manuscript based on the research findings of palladium-catalyzed direct α-heteroarylation of ketones under microwave irradiation is completed. It will be submitted to peer-reviewed journals (e.g., JOC) once I receive the DFT study results from our collaborator. An NSF RUI grant was awarded to the PI to investigate the unusual reactions discovered during our study on the palladium-catalyzed direct heteroarylation. The research findings were presented by PI at Organometallic Chemistry Gordon Research Conferences in 2017 and 2018.

The study on palladium-catalyzed alpha-heteroarylation of ketones also provides excellent research opportunities for NKU undergraduate students, especially women, minorities and other underrepresented groups. In the third year of our research supported by ACS PRF, there were 12 undergraduate students involved in this project, including two UR STEM students. Three full-time undergraduate researchers were paid through this ACS PRF grant in summer 2018. Two students received the competitive NKU internal research award in 2018: Swarts Milburn Undergraduate Research Award and Dorothy Westerman Herrmann Undergraduate Research Award. The rest of the students volunteered to work during the summer. Among these students, six of them are first-generation college students (50%), seven (58%) were female research students, and two (17%) were African American and/or Latino research students. Four students presented their research findings at the 255th ACS National Meeting in New Orleans, LA in March 2018. Five students are planning to present their research findings at the Kentucky Academy of Science Annual meeting in November 2018.