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Pd(II)-Catalyzed Olefination of sp^3 C−H Bonds

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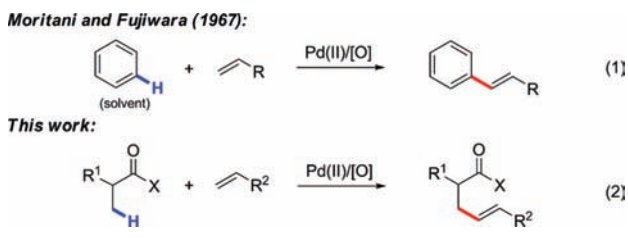
The Pd-catalyzed Mizoroki−Heck reaction, which couples olefins with aryl and vinyl halides and sulfonates, is a uniquely powerful transformation for forging C−C bonds and plays a pivotal role in modern organic synthesis.[1] Given its widespread use, the development of complementary methods to couple unactivated C−H bonds with olefins is highly attractive. Indeed, as early as 1967, Fujiwara and Moritani reported the first example of Pd-mediated C−H olefination of excess benzene (eq 1).[2] Since then, several research groups have sought to expand the synthetic utility of arene C−H olefination by improving the reactivity, controlling the positional selectivity, and using the arene as the limiting reagent; this has been achieved by exploiting electron-rich heterocycles,[3] proximate directing groups,[4] and ligand assistance.[3b,4d] At the same time, Pd(II)-mediated aryl C−H olefination has emerged as an efficient tool for constructing diverse carbon skeletons of natural products.[4d,5]

While aryl C−H olefination *via* either electrophilic palladation or other C−H activation pathways has been extensively explored in recent years, Pd-catalyzed olefination of unactivated sp^3 C−H bonds remains undeveloped, with no examples reported to date. Because sp^3 C−H olefination is mechanistically distinct from aryl C−H olefination, the conceptual and practical challenges in developing this technology are numerous.[6] First, Pd(II)-mediated sp^3 C−H cleavage is far less facile than sp^2 C−H cleavage, and as a consequence, devising reaction conditions that enable directed sp^3 C−H activation to occur in the presence of competitively coordinating olefins is a tremendous challenge. Additionally, following sp^3 C−H activation, carbopalladation of the resulting [Pd(II)−R] intermediate across a double bond is less well established.[7] For instance, undesired β-hydride elimination is often a competitive pathway, particularly in the case of intermolecular olefination. We were encouraged with respect to this latter potential barrier by the pioneering work of Fu concerning intramolecular olefination of unactivated, β-hydrogen-containing alkyl halides catalyzed by a Pd/*N*-heterocyclic carbene complex.[8] Moreover, based on our recent discovery of highly efficient Pd(II)-catalyzed sp^3 C−H activation using an *N*-arylamide (CONHAr) directing group,[9] we conjectured that the former problem could also be overcome.

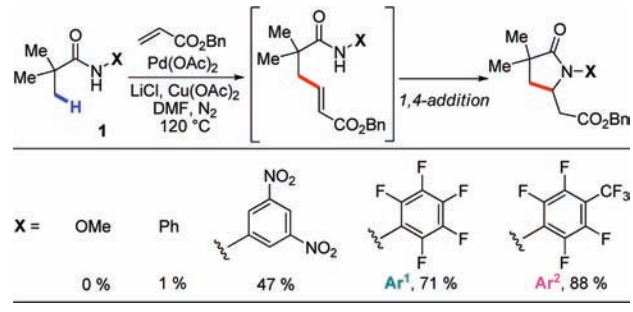
Scheme 1. Pd-Catalyzed C−H Olefination Reactions



With these considerations in mind, we initiated our study on β-olefination of *N*-arylpivalamides (**1**) by carrying out a systematic screening of reaction conditions (Table 1). Gratifyingly, we found that olefination of these substrates with benzyl acrylate occurred using $Pd(OAc)_2$ (10 mol %) as the catalyst and $Cu(OAc)_2$ (2 equiv) as the terminal oxidant in DMF. The products were isolated as the corresponding γ-lactams formed *via* a tandem intramolecular 1,4-addition of the amide to the newly installed acrylate. The yield with the CONHAr[1] directing group was increased from 45% to 71% by adding LiCl (2 equiv) to the reaction mixture. Two potential roles for LiCl are (1) serving as a source of Cl^- which can act as a ligand to prevent the deactivation of Pd(0) to Pd black[10] and (2) inducing the *in situ* formation of a chloro-bridging complex which is more prone to carbopalladation.[7a]

As established in our previous report, electron-withdrawing substituents (CF_3, F, and NO_2) on the *N*-aryl group dramatically enhance the reaction.[9] Indeed, the more electron-withdrawing CONHAr[2] group improved the yield further to 88% (Table 1). Notably, the directing groups for sp^3 C−H activation previously developed in our laboratory, such as carboxylic acid, hydroxamic acid, oxazoline, and pyridine,[11] were unreactive under these conditions. The choice of solvent was also critical, with polar and strongly coordinating amide solvents such as DMF, DMA, and NMP giving the best reactivity. Our preliminary screening was carried out using $Cu(OAc)_2$ (2 equiv) for reoxidation of Pd(0); however, further optimization revealed that a mixture of $Cu(OAc)_2$ and AgOAc (1.1 equiv each) gave the highest yield (90% by ^{1}H NMR) even when the less reactive CONHAr[1] directing group was used. We also found that using N_2 in place of air gave consistently higher yields.

Table 1. Directing Group Optimization[a,b]



[a] Conditions: 0.2 mmol of substrate, 0.1 mL of benzyl acrylate, 10 mol % $Pd(OAc)_2$, 2.0 equiv of LiCl, 2.0 equiv of $Cu(OAc)_2$, 1 mL of DMF, 120 °C, N_2, 12 h. [b] The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard.

With the optimized conditions in hand, we converted a wide variety of commercial carboxylic acids into the corresponding CONHAr[1] amides to examine the scope of the olefination protocol. Products containing ether (**3a**, **6a**, **6b**, **12a**, and **14a**) and ester (**4a** and **13a**) groups could be obtained in good yields. Remarkably, this method was also found to be effective in activating methylene C−H bonds in cyclopropane substrates (**5a**, **6a**, and **7a**). For substrates **5** and **6**, *ortho*-olefination of the aryl groups also took

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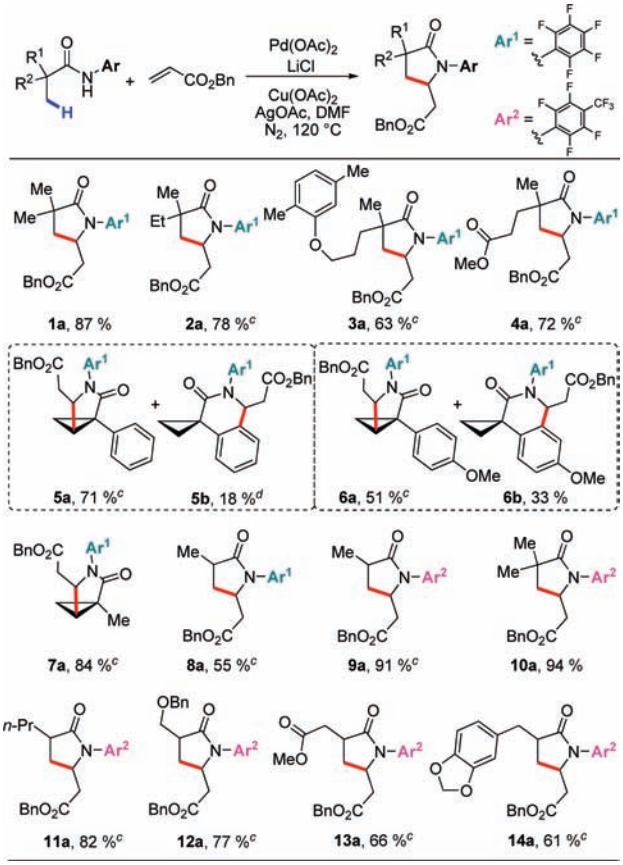
place, affording δ-lactam side products (**5b** and **6b)** in 18% and 33% yields, respectively. For substrate **7**, the cyclopropyl C−H bond was selectively olefinated in the presence of an α-methyl group to give **7a** as the only product in 84% yield. Lowering the temperature to 90 °C, we found that the cyclopropane substrates could still be olefinated effectively without a major decline in yield (**7a**, 77%).

In our previous reports concerning sp^3 C−H activation reactions using carboxylic acids and their derivatives,[11] substrates that contained α-hydrogen atoms were unreactive. Thus, the substrate scope was limited to compounds with quaternary α-carbon atoms. Nevertheless, we recently established that the facile conversion of the carboxylic acids to the corresponding CONHAr[1] amides provides a remedy to this problem, allowing access to a broad range of substrates containing α-hydrogen atoms.[9] We thus subjected substrate **8** to the olefination conditions described above; however, **8a** was obtained in only 55% yield. More complex substrates with α-hydrogen atoms gave virtually no product. In an effort to overcome this issue, we hypothesized that the reactivity could be improved by exploiting the CONHAr[2] directing group. Hence, we attempted C−H olefination of substrate **9**, and to our delight we observed a considerable increase in the product yield, of **9a** to 91% yield. Using the CONHAr[2] group, we successfully olefinated an array of α-hydrogen-containing substrates (**9**, **11**, **12**, **13**, and **14**) in good to excellent yields.

Table 2. Amide-Directed Olefination of sp^3 C−H Bonds[a,b]



[a] Conditions: 0.2 mmol of substrate, 0.1 mL of benzyl acrylate, 10 mol % $Pd(OAc)_2$, 2.0 equiv of LiCl, 1.1 equiv of $Cu(OAc)_2$, 1.1 equiv of AgOAc, 1 mL of DMF, 120 °C, N_2, 12 h. [b] Isolated yield. [c] Obtained as a mixture of inseparable *cis*/*trans* diastereomers (see Supporting Information). Optically inactive starting materials were used. [d] Yield determined by ^{1}H NMR.

A plausible mechanism for this process involves initial amide-directed C−H insertion by Pd(II) to generate an alkylpalladium intermediate which reacts with the olefin via carbopalladation, followed by β-hydride elimination to give the olefination product. Pd(0) is reoxidized to Pd(II) by Ag(I)/Cu(II) to close the catalytic cycle.

In summary, we have developed a Pd(II)-catalyzed reaction protocol for the direct olefination of sp^3 C−H bonds. After β-C−H olefination, the amide products underwent 1,4-conjugate addition to give the corresponding lactam compounds. The reaction conditions could also be applied to effect olefination of cyclopropyl methylene C−H bonds and substrates containing α-hydrogen atoms. Studies to expand the scope to simple carboxylic acid substrates and to develop enantioselective sp^3 C−H olefination reactions of *gem*-dimethyl- and cyclopropyl groups are currently underway in our laboratory.

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Supporting Information Available: Experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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