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Pd-Catalyzed Dehydrogenative Cross-Coupling of Polyfluoroarenes with Heteroatom-Substituted Enones

Fei Chen,[†] Zhang Feng,[†] Chun-Yang He,[‡] Hao-Yang Wang,[†] Yin-long Guo,[†] and Xingang Zhang*,[†]

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China, and College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

xgzhang@mail.sioc.ac.cn

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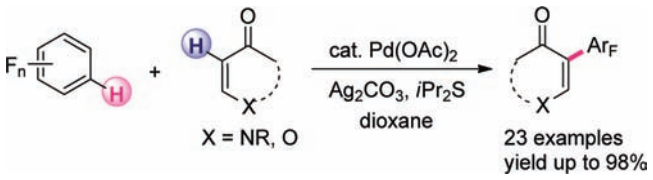
ABSTRACT



The first example of intermolecular regioselective α-arylation of heteroatom-substituted enones with polyfluoroarenes via twofold C−H bond functionalization using a palladium catalyst is reported. This approach provides rapid access to a wide range of α-fluoroarylated enones of interest in life science.

Heteroatom-substituted enones are an important structural motif found in a wide range of natural products and functional materials.[1] In particular, such α-substituted enones constitute a distinct class of biologically active compounds in medical applications, such as cancer chemotherapies, antiallergy treatments, and antimicrobial and antiviral therapies.[2] Hence, it is of great synthetic interest to develop an efficient reaction to access these valuable molecules. In the past few years, impressive progress has been made in the area of transition-metal-catalyzed dehydrogenative cross-couplings.[3−5] Since this tandem oxidation of C−H bonds avoids the prefunctionalization steps of both cross-coupling partners, it provides a far more efficient and straightforward

[†] Shanghai Institute of Organic Chemistry.
[‡] Donghua University.

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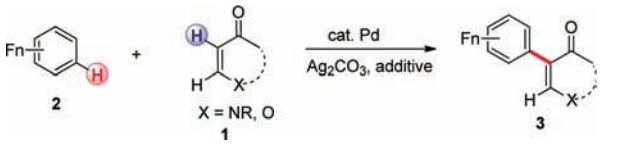
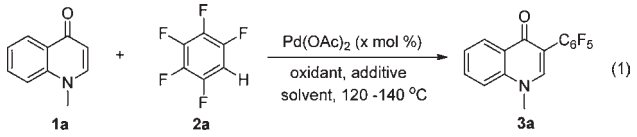
access to the target molecules. Thus, from the point of view of synthetic simplicity, the synthesis of α-substituted, heteroatom-substituted enones from simple arenes and readily available heteroatom-substituted enones via twofold C−H bond functionalization would be an ideal strategy. However, the transition-metal-catalyzed intermolecular dehydrogenative cross-coupling of heteroatom-substituted enones with simple arenes via this strategy has not been reported to date,[6] and to the best of our knowledge, only Pd-catalyzed direct α-C−H functionalization of such enones with arylmetals[7] or alkenes[8] has been developed. This strategy still faces intrinsic challenges, suppressing undesired homocouplings. Considering the nucleophilic character of heteroatom-substituted enones, we hypothesized that if electron-deficient polyfluoroarenes were chosen as the coupling partner, the difference between the reactivities of the heteroatom-substituted enones and polyfluoroarenes would facilitate the two metalation steps of the catalytic cycle, and thus the dehydrogenative cross-coupling of heteroatom-substituted enones with simple arenes would be possible (Scheme 1). Furthermore, polyfluoroarenes are a key structural motif found in various functional molecules, such as pharmaceuticals, agrochemicals, liquid crystals, and electronic devices.[9] Consequently, the development of transition-metal-catalyzed methods for introducing polyfluoroaryl groups into organic molecules has been the subject of intense research. Despite significant progress in the direct arylation of polyfluoroarenes,[10,5h−j] there are few examples for introducing vinyl substituents.[11]

Scheme 1. Pd-Catalyzed Dehydrogenative Cross-Coupling of Polyfluoroarenes with Heteroatom-Substituted Enones



Herein, we present the first example of intermolecular regioselective α-arylation of heteroatom-substituted enones with polyfluoroarenes via twofold C−H bond functionalization using a palladium catalyst. This reaction provides an efficient and straightforward protocol for the preparation of α-fluoroarylated enones of interest in life science.

Given that C3 substituted 4-quinolones not only are used for the antimicrobial and anticancer therapies but also display significant antimalarial activity,[12] we began this study by choosing 1-methyl-4(1*H*)-quinolone **1a** and pentafluorobenzene **2a** as model substrates (eq 1).



Initially, the reaction was carried out with **1a** (1.0 equiv), **2a** (3.0 equiv), Ag_2CO_3 (1.5 equiv), and $Pd(OAc)_2$ (10 mol %) in DMF + DMSO (5 equiv) at 120 °C, providing no desired product **3a** (see Table S1 in the Supporting Information). Further switching of the solvent to DMSO also failed to give **3a**. After screening a series of reaction mediums, we found that DMSO and dioxane are critical for the reaction efficiency. The absence of DMSO or the use of a mixed DMSO in other solvents was totally ineffective. Different Pd-catalysts and oxidants were also examined (see Table S2 in the Supporting Information), and $Pd(OAc)_2$ and Ag_2CO_3 were found to be the best choice, although only a reasonable yield was obtained. Inspired by the importance of DMSO in the reaction, a series of sulfides previously demonstrated to have a beneficial effect on the dehydrogenative cross-coupling of two simple arenes[5j] were tested to further improve the reaction efficiency (see Table S1 in the Supporting Information). To our delight, a 56% isolated yield of **3a** was obtained when 5.0 equiv of iPr_2S[13] and 3.0 equiv of Ag_2CO_3 were employed. Increasing the reaction concentration or the Pd-catalyst loading gave no further improvements in yield due to the difficulty in suppressing the homocouplings of both coupling partners. To improve the reaction efficiency further, we found the optimal isolated yield (68%) and homocouplings of **1a** and **2a** (14%, based on **1a**;11%, based on **2a**) were afforded by three consecutive additions of $Pd(OAc)_2$ (5 mol %) and Ag_2CO_3 (1.0 equiv) over a period of 5 h.

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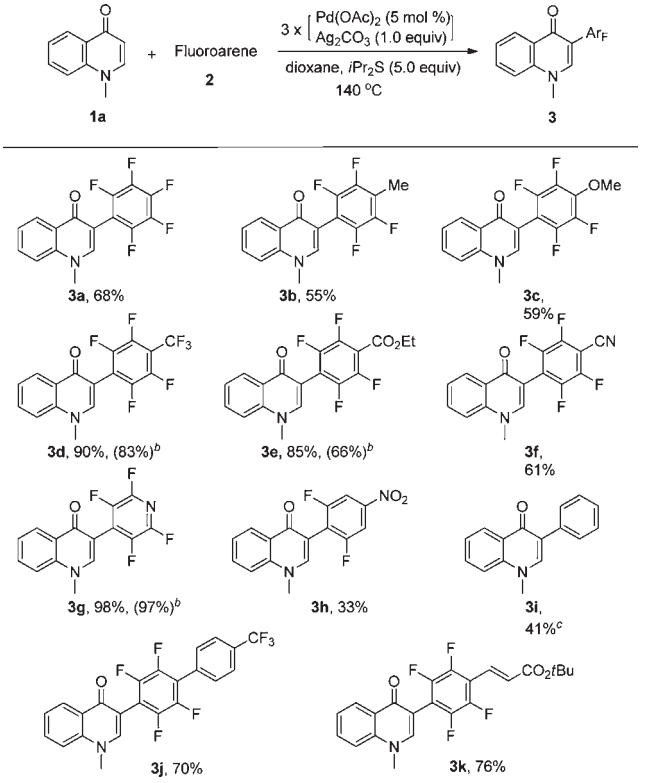
(13) The amount of iPr_2S is important for the reaction efficiency. Using less than 5.0 equiv of iPr_2S led to a lower yield; see Table S2 in the Supporting Information.

Under the optimum reaction conditions, the substrate scope of direct α-fluoroarylation of 1-methyl-4(1*H*)-quinolone **1a** was tested (Scheme 2).

Scheme 2. Pd-Catalyzed Direct Cross-Coupling of Pentafluorobenzene with Various Heteroaromatic Tosylates[a]



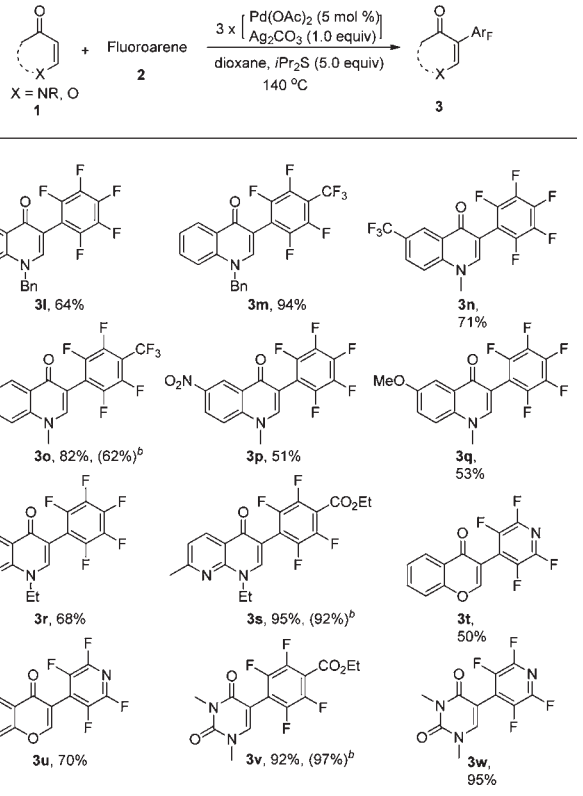
[a] Reaction conditions (unless otherwise specified): **1a** (0.3 mmol), **2** (3.0 equiv), 3 × [$Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (1.0 equiv), 5 h], iPr_2S (5.0 equiv), dioxane (1.0 mL), 140 °C. All reported reaction yields are isolated yields. [b] **1a** (0.3 mmol), **2** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (3.0 equiv), iPr_2S (5.0 equiv), dioxane (1.0 mL), 10 h, 140 °C. [c] Benzene (2.0 mL) instead of **2** was used.

The present method allowed the polyfluoroarylation of **1a** with a variety of fluoroarenes. Even for relatively unreactive 1,3-difluoro-5-nitrobenzene **2h** and benzene, reasonable yields still could be obtained (**3h**−**i**). Functional groups, such as ester, nitrile, nitro, and polyfluoropyridine were tolerated by the reaction conditions (**3e**−**f**, **3g**−**h**). Importantly, an α,β-unsaturated ester was compatible with the catalytic system with no formation of a Heck type reaction byproduct, thus demonstrating the utility of this protocol in the synthesis of highly functionalized α-fluoroarylated quinolones (**3k**). Furthermore, for substrates **3d**−**e** and **3g**, good yields were still obtained when 10 mol % of $Pd(OAc)_2$ was used.

In addition to the demonstrated the scope of this method, a variety of quinolones were tested, and moderate to good yields were provided (Scheme 3, **3l**−**q**).

Importantly, 1-ethyl-7-methyl-1,8-naphthyridin-4(1*H*)-one **1r**, a pharmacore in antibiotics, is a good substrate for the reaction (**3r**−**s**), thus providing opportunities for further discovery of new bioactive molecules. The substrates are not limited to quinolones, as chromones and pyrimidone also

Scheme 3. Pd-Catalyzed Direct Cross-Coupling of Fluoroarenes with Various Heteroaromatic Tosylates[a]



[a] Reaction conditions (unless otherwise specified): **1a** (0.3 mmol), **2** (3.0 equiv), 3 × [$Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (1.0 equiv), 5 h], iPr_2S (5.0 equiv), dioxane (1.0 mL), 140 °C. All reported reaction yields are isolated yields. [b] **1a** (0.3 mmol), **2** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (3.0 equiv), iPr_2S (5.0 equiv), dioxane (1.0 mL), 10 h, 140 °C.

underwent the reaction smoothly (**3t**−**w**). It should be pointed out that incorporation of a polyfluoroaryl group into DNA or RNA to study the hydrophobic, aromatic pairs that are orthogonal to the natural base pair in their recognition properties are an intense topic in life science.[14] Hence, rapid access to C-5 fluoroarylated pyrimidones via the present strategy (**3v**−**w**) would be helpful in this area.

To investigate the working mode of the present catalytic system, kinetic isotope effect (KIE) experiments for both coupling partners were conducted, showing primary KIEs of 1.13 and 1.66 for pentafluorobenzene **2a** (eq 2 of Scheme 4) and 1-methyl-4(1*H*)-quinolone **1a** (eq 3 of Scheme 4), respectively. These results imply that the C−H bond cleavage of polyfluoroarenes and enones **1** is not involved in the rate-determining step in the overall catalytic process.

Further experiments by comparison of the homocoupling reactions of **1a** and **2a** revealed that both the 4-quinolone and fluoroarene could furnish homocouplings (Scheme 5). The structure of compound **4** was further

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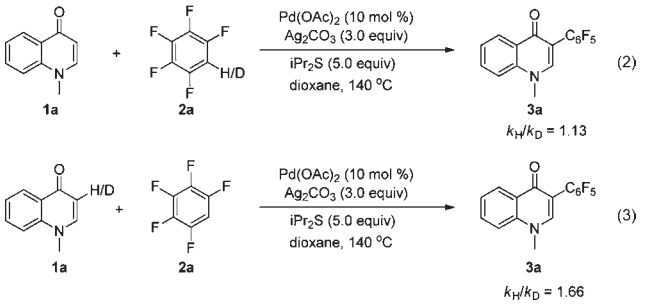
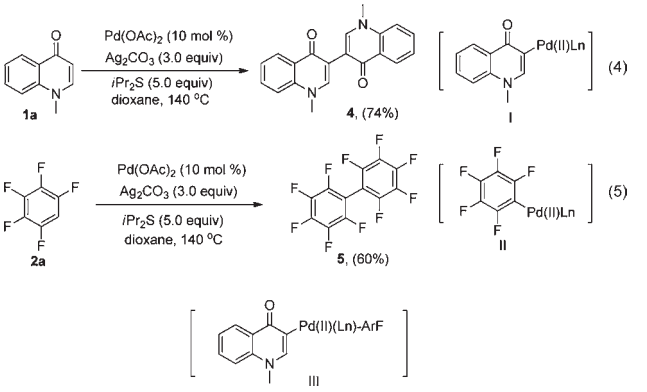
(15) For X-ray crystallographic analysis of **4**, see Supporting Information. CCDC 849643 also contains the supplementary crystallographic data for **4**.

Scheme 4. Kinetic Isotope Effect Studies



Scheme 5. Homocoupling Reactions of **1a** and **2a**



confirmed by X-ray crystallographic analysis.[15] These findings indicate that the palladated **I** and **II** are involved in the reaction, and avoiding the undesired homocouplings of both coupling partners is a significant challenge in the present reaction.

Although the aforementioned results do not reveal the detailed mechanism, they are informative. Consequently, we proposed that the dehydrogenative cross-coupling of polyfluoroarenes with enones **1** may begin with the formation of palladated **I** and **II**, which then react with fluoroarene **2** and enone **1**, respectively, in the presence of base to afford key intermediate Pd-complex **III**. Finally, reductive elimination and reoxidation by Ag(I) regenerates Pd(II).

In conclusion, we have demonstrated the first Pd-catalyzed intermolecular regioselective α-arylation of heteroatom-substituted enones. This reaction makes direct use of simple polyfluoroarenes and readily available heteroatom-substituted enones via twofold C−H activation without the multiple steps normally required to prepare cross-coupling partners. Hence, it is a straightforward method for the preparation of α-fluoroarylated enones of interest in life science. Further studies to uncover the detailed mechanism as well as expand the substrate scope and their applications are now in progress.

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Supporting Information Available. Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.