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# Pd(II)-Catalyzed *ortho*-Trifluoromethylation of Arenes Using TFA as a Promoter

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Fluorinated compounds possess unique physical properties that make them indispensible for application as pharmaceuticals, agrochemicals, and organic materials.[1] In medicinal chemistry, for example, the incorporation of $CF_3$ groups into drug candidates often improves their binding selectivity, lipophilicity, and metabolic stability.[1b,2] Notably, many biologically active aromatics, including the commercially successful antidepressant Prozac and the herbicide Fusilade, contain $CF_3$ groups as the essential motif.[3] As a consequence, the development of new methods for the introduction of trifluoromethyl groups onto aromatic rings has received intensive attention.[4] Recent findings concerning the stoichiometric and catalytic coupling of ArI with in situ-generated $CuCF_3$[5] provides an alternative to the century-old Swarts reaction.[6] Moreover, a single example of Pd(0)-catalyzed coupling of ArI with $CF_3I$ using Zn power and a Pd(0) catalyst under ultrasonic irradiation has also been reported.[7] Generally speaking, the challenge of developing cross-coupling reactions to forge carbon−$CF_3$ bonds is largely rooted in the inert nature of the metal−$CF_3$ species.[8] Herein we report a Pd(II)-catalyzed arene trifluoromethylation reaction via C−H activation.

On the basis of the three distinct modes of reactivity of ArPd(II) species with nucleophiles,[7] electrophiles[9] and highly oxidizing reagents,[10] we envisioned three possible reaction pathways (A, B, and C, respectively) that could follow a C−H activation event to give the trifluoromethylated products, as outlined in Scheme 1.

Although oxidation of Pd(II) to higher oxidation states by $CF_3^+$ has not been observed to date, the electrophilic trifluoromethylating reagent **1a** is known to react with carbon nucleophiles.[11−13] Therefore, it is also possible that ArPd(II) species generated from C−H activation could react with **1a** as an electrophile to give $ArCF_3$ via path B. To minimize possible complications in our exploratory studies, we selected 2-phenylpyridine (**2a**), for which cyclopalladation is known to be robust, as the platform for screening the reaction conditions. Initially, we found that the reaction of **2a** with 10−20 mol % $Pd(OAc)_2$ and 1 equiv of **1a** under various conditions did not give observable amounts of desired product (Table 1, entry 1). However, we were pleased to find that the presence of 10 equiv of trifluoroacetic acid (TFA) in dichloroethane (DCE) promoted the trifluoromethylation reaction, giving the desired product **3a** in 50% yield (entry 2). Notably, the lack of reactivity with $Pd(OTFA)_2$ alone suggests that the presence of TFA is essential for the observed trifluoromethylation reaction (entries 3 and 4). Other acids such as AcOH, TsOH, and TfOH, on the other hand, were not effective (entries 5−7).

Although either pathway B or C would theoretically regenerate the catalytically active Pd(II) species, the concomitant release of a sulfur-containing compound (the sulfoxide formed from **1a** was detected by GC−MS) could be problematic in that this compound could occupy the vacant sites of Pd(II) or reduce Pd(II) to Pd(0). With these considerations in mind, we began to test additives that we hypothesized could act as both Lewis acids for sulfur and oxidants for Pd(0). We found that the presence of copper(II) acetate significantly improved the yield, while other oxidants proved ineffective (entries 11−14). A control experiment showed that no trifluoromethylation product was observed using $Cu(OAc)_2$ in the absence of $Pd(OAc)_2$ (entry 15). At this stage, the role of $Cu(OAc)_2$ remains to be elucidated.

To investigate effects of the counteranion in **1a**, we performed the trifluoromethylation of **2a** with 5-(trifluoromethyl)dibenzothiophenium tetrafluoroborate (**1b**) and found that the yield could be increased to 86% (entry 16). While the origin of this improvement remains to be

***Scheme 1.*** Plausible Reaction Pathways for Trifluoromethylation

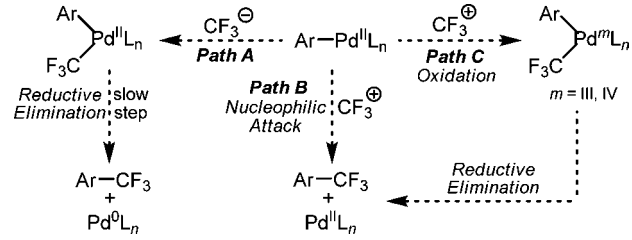
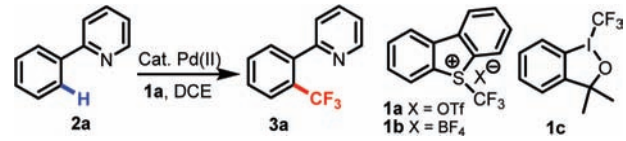



***Table 1.*** Pd(II)-Catalyzed C−H Trifluoromethylation[a]




| entry | catalyst | additive (equiv) | oxidant (equiv) | yield (%)[b] |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | | | 0 |
| **2** | **$Pd(OAc)_2$** | **TFA (10)** | | **50** |
| 3 | $Pd(OTFA)_2$ | | | 0 |
| **4** | **$Pd(OTFA)_2$** | **TFA (10)** | | **52** |
| 5 | $Pd(OAc)_2$ | AcOH (10) | | 5 |
| 6 | $Pd(OAc)_2$ | TsOH (10) | | 0 |
| 7 | $Pd(OAc)_2$ | TfOH (10) | | 0 |
| 8 | $Pd(OAc)_2$ | TFA (10) | $Cu(OAc)_2$ (1) | 70 |
| 9 | $Pd(OAc)_2$ | TFA (10) | $Cu(OTFA)_2$ (1) | 71 |
| 10 | $Pd(OAc)_2$ | TFA (10) | $Cu(OTf)_2$ (1) | 47 |
| 11 | $Pd(OAc)_2$ | TFA (10) | AgOAc (2) | 43 |
| 12 | $Pd(OAc)_2$ | TFA (10) | $Ag_2CO_3$ (1) | 45 |
| 13 | $Pd(OAc)_2$ | TFA (10) | $Ag_2O$ (1) | 44 |
| 14 | $Pd(OAc)_2$ | TFA (10) | BQ (1) | 30 |
| 15[c] | $Pd(OAc)_2$ | TFA (10) | $Cu(OAc)_2$ (1) | 0 |
| **16**[d] | **$Pd(OAc)_2$** | **TFA (10)** | **$Cu(OAc)_2$ (1)** | **86** |
| 17[e] | $Pd(OAc)_2$ | TFA (10) | $Cu(OAc)_2$ (1) | 11 |

[a] Unless otherwise noted, the reaction conditions were as follows: **2a** (0.2 mmol), Pd(II) catalyst (0.02 mmol, 10 mol %), **1a** (0.3 mmol, 1.5 equiv), DCE (1 mL), 110 °C, 48 h. [b] Isolated yield. [c] No $Pd(OAc)_2$ was added. [d] **1b** was used instead of **1a**. [e] **1c** was used instead of **1a**.

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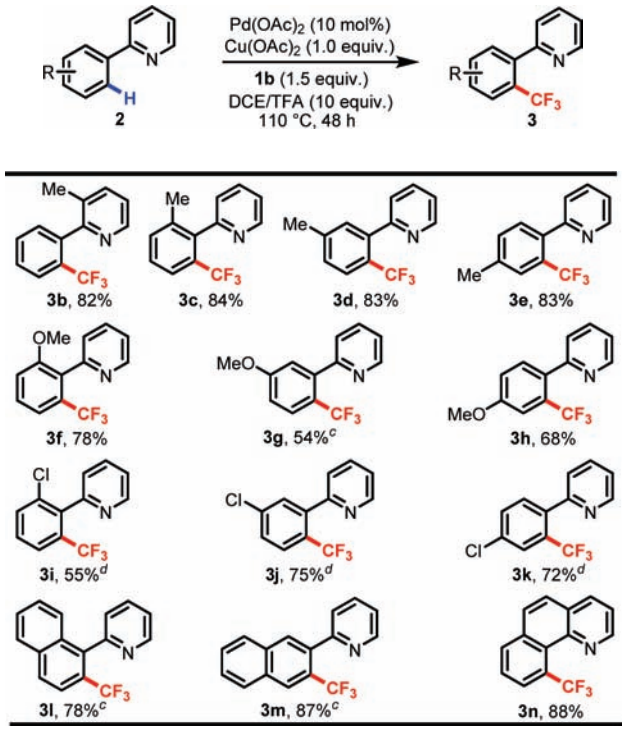
***Table 2.*** C−H Trifluoromethylation of Pyridine Derivatives[a,b]




[a] Unless otherwise noted, the reaction conditions were as follows: substrate (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol %), $Cu(OAc)_2$ (0.2 mmol, 1.0 equiv), **1b** (0.3 mmol, 1.5 equiv), TFA (2.0 mmol, 10 equiv), DCE (1 mL), 110 °C, 48 h. [b] Isolated yield. [c] $Pd(OAc)_2$ (15 mol %) was used. [d] $Pd(OAc)_2$ (20 mol %) was used.

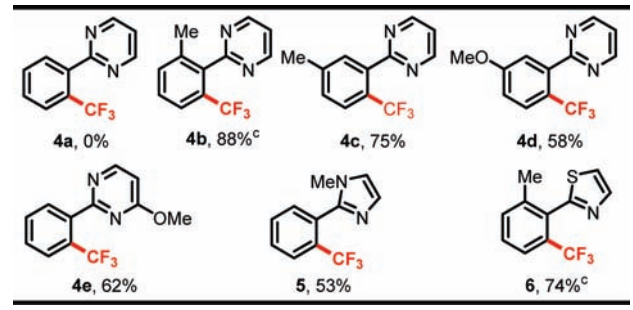
investigated, it appears that **1b** exhibits stronger electrophilicity and is thus more reactive with the ArPd(II) species. Trifluoromethylation with Togni's reagent (**1c**) under these optimized reaction conditions gave only 11% yield (entry 17).

With this newly established C−H trifluoromethylation protocol in hand, we examined the substrate scope (Table 2). Electron-donating groups [Me (**3c**−**e**) and OMe (**3f**−**h**)] are well-tolerated, although the OMe group is less effective. Moderately electron-withdrawing groups such as Cl are also compatible with this protocol (**3i**−**k**). Notably, the presence of Cl in the products is very useful for further synthetic manipulations. The use of substrates containing strong electron-withdrawing groups, such as keto, ester, and nitro groups, was found to give the desired products in less than 20% yield. The exclusive monoselectivity with all of the substrates is a practical advantage of this reaction. Naphthalene substrates were also successfully trifluoromethylated in good yields and with excellent regioselectivity (**3l** and **3m**).

To expand the potential utility of this reaction for medicinal chemistry, other heterocycles were also subjected to this reaction protocol (Table 3). The lack of reactivity when unsubstituted 2-phenylpyrimidine was used as a substrate (to form the presumed product **4a**) is likely due to the electron-withdrawing nature of the pyrimidine group. Indeed, introduction of an electron-donating methyl or methoxy group onto the biphenyl system allowed trifluoromethylation to proceed effectively, giving the desired products in 58−88% yield (**4b**−**e**). Furthermore, we were pleased to find that both imidazole (**5**) and thiazole (**6**), two commonly encountered motifs in medicinal chemistry, could also be used as directing groups for this C−H activation/trifluoromethylation reaction.

In summary, we have developed a new Pd(II)-catalyzed trifluoromethylation reaction of arenes through C−H functionalization.

***Table 3.*** C−H Trifluoromethylation Using Diverse Heterocyclic Directing Groups[a,b]




[a] Unless otherwise noted, the reaction conditions were as follows: substrate (0.2 mmol), $Pd(OAc)_2$ (0.04 mmol, 20 mol %), $Cu(OAc)_2$ (0.2 mmol, 1.0 equiv), **1b** (0.3 mmol, 1.5 equiv), TFA (2.0 mmol, 10 equiv), DCE (1 mL), 110 °C, 48 h. [b] Isolated yield. [c] $Pd(OAc)_2$ (10 mol %) was used.

The use of TFA was found to be crucial for the success of this $Ar-CF_3$ bond-forming protocol, and $Cu(OAc)_2$ was found to be effective for enhancing the catalytic turnover. Subsequent studies to apply this catalytic transformation to other broadly useful classes of substrates are currently underway in our laboratory.

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

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