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Pd(II)-Catalyzed Ortho Trifluoromethylation of Arenes and Insights into the Coordination Mode of Acidic Amide Directing Groups

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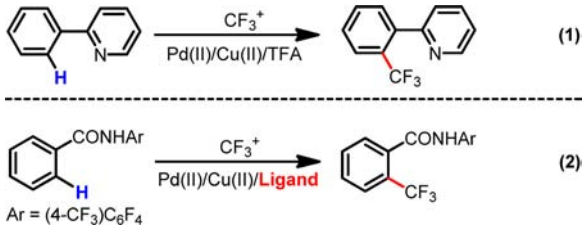
Supporting Information

ABSTRACT: A Pd(II)-catalyzed trifluoromethylation of ortho C−H bonds with an array of *N*-arylbenzamides derived from benzoic acids is reported. *N*-Methylformamide has been identified as a crucial promoter of C−CF_3 bond formation from the Pd center. X-ray characterization of the C−H insertion intermediate has revealed a rare coordination mode of acidic amides as directing groups and the origin of their capacity in directing C−H activation.

Trifluoromethylated arenes are essential structural motifs in a great number of pharmaceuticals, agrochemicals, and organic materials.[1,2] As a consequence, extensive efforts have been recently directed toward the development of methods for introducing trifluoromethyl groups onto arenes.[3] To date, Pd- or Cu-catalyzed/mediated cross-coupling reactions of aryl halides[4,5] or boronic acids[6] with trifluoromethylating reagents have been a major focus of study in this area. While direct trifluoromethylation of heteroarenes via electrophilic substitution, the Minisci reaction, and deprotonation reactions have been successfully developed,[7,8] transition-metal-catalyzed trifluoromethylation of aryl C−H bonds remains a largely unsolved problem, presumably because of the slowness of aryl/CF_3 reductive elimination and a lack of ligands that are mutually compatible for both the reductive elimination and C−H activation steps.[9,10]

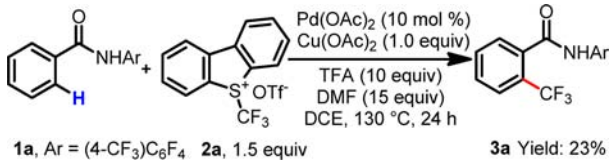
We recently reported the first example of Pd(II)-catalyzed ortho trifluoromethylation of 2-phenylpyridines (eq 1) using



trifluoroacetic acid (TFA) and $Cu(OAc)_2$ as crucial promoters.[11] In contrast to the broad substrate scope of other C−H activation transformations using weakly coordinating directing groups,[12] the trifluoromethylation of synthetically versatile arenes remains to be demonstrated. Herein we report the Pd(II)-catalyzed trifluoromethylation of benzamides using an *N*-alkylformamide as a crucial promoter. Moreover, the C−H insertion intermediate of the benzamide was characterized by X-ray crystallographic analysis, providing insights into the coordination mode of acidic amides as effective directing groups (eq 2).

In the ortho trifluoromethylation of 2-phenylpyridine substrates (eq 1),[11] the strongly coordinating pyridyl group is able to direct cyclopalladation in the presence of the trifluoromethylating reagent **2a**. However, dibenzo[*b*,*d*]-thiophene released from reagent **2a** can coordinate to the Pd catalyst and prevent C−H activation when weakly binding carboxyl and hydroxyl groups are used as directing groups. To overcome this problem, we turned to a recently developed acidic amide auxiliary with higher binding affinity than carboxyl, which has been highly versatile in directing a diverse range of sp^2 and sp^3 C−H activation reactions.[13,14] We therefore began to test whether *N*-arylbenzamide **1a** could perform as a viable substrate for the Pd-catalyzed ortho trifluoromethylation with **2a** under suitable conditions. Following the previous conditions for the trifluoromethylation of 2-phenylpyridines,[11] **1a** was treated with **2a** in the presence of 1 equiv of $Cu(OAc)_2$ and 10 equiv of TFA in 1,2-dichloroethane (DCE) at various temperatures. Unfortunately, the trifluoromethylation of **1a** did not proceed under these conditions, presumably because of the absence of a weak base, which was found to be essential for the C−H activation of acidic *N*-arylbenzamides[13,14] and carboxylic acids.[15] Noting that both inorganic and organic bases, including *N*,*N*-dimethylformamide (DMF), were previously found to be effective in promoting Pd-catalyzed C−H activation of benzoic acids,[15b] we tested various bases [see the Supporting Information (SI)] and found that the trifluoromethylation proceeded in the presence of 15 equiv of DMF, giving the desired product **3a** in 23% yield (Scheme 1).

Scheme 1. DMF-Promoted Trifluoromethylation of 1a



Initial screening of the reaction parameters failed to improve the yield. We surmised that the dibenzo[*b*,*d*]thiophene released from **2a** during the reaction could inhibit the C−H activation and result in poor turnovers, and we therefore decided to increase the amount of $Cu(OAc)_2$ to scavenge the free thiophene. We found that the reaction yield improved to

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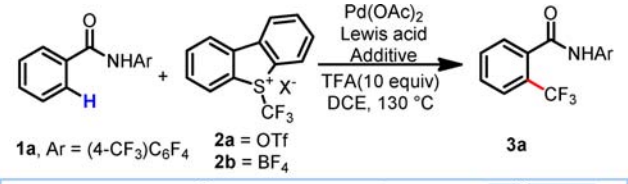
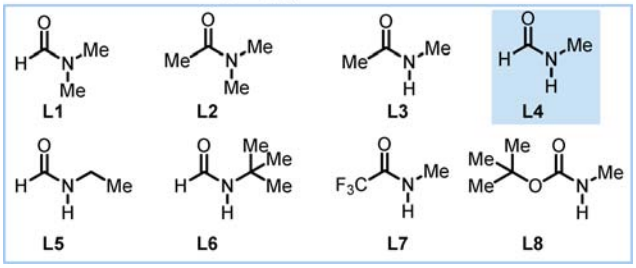
57% with 2.0 equiv of $Cu(OAc)_2$ (Table 1, entry 3). The coordination of $Cu(OAc)_2$ with **2a** could also generate more reactive CF_3^+ species and promote trifluoromethylation. To improve the yield further, various amide additives **L1**–**L8** were tested. The N-monoalkylated amides significantly improved the yield of the trifluoromethylation reaction (entries 5–7). When 15 equiv of *N*-methylformamide (**L4**) was used, the product **3a** was isolated in 79% yield (entry 6). Subsequent investigation of the formamides showed that the yield decreased when bulkier amides were used (entries 7 and 8). Additionally, trifluoroacetamide **L7** and carbamate **L8** were ineffective and did not provide the desired product (entries 9 and 10). The sensitive dependence of the reaction on the structure of the formamide additives is suggestive of their role as a ligand in addition to their action as a base. Consistent with this hypothesis, a catalytic amount of **L4** (0.2 equiv) was sufficient to promote the trifluoromethylation, albeit giving lower yields (entries 11–13).

Removing $Cu(OAc)_2$ or replacing it with the Lewis acid $Yb(OTf)_3$ resulted in loss of reactivity, indicating that $Cu(OAc)_2$ may play other roles in addition to being a scavenger for the thiophene (Table 1, entries 14–18; also see the SI). Although TFA was found to be essential for the trifluoromethylation of 2-phenylpyridines,[11] the absence of TFA did not have a deleterious effect on the yield of **3a** (entry 19). We also found that the counteranions in reagents **2b** or **2a** do not have a significant impact on this reaction (entry 20). It is worth noting that Togni's reagent and $TMSCF_3$ were ineffective.

With these optimized conditions in hand, we surveyed the substrate scope of the benzamides (Table 2). Arenes with *o*- and *m*-methyl substitution gave yields of 84 and 94%, respectively (**3b** and **3c**), whereas the *p*-methyl-substituted arene afforded a lower yield of 53% (**3d**). Similar results were obtained for MeO-substituted arenes (**3e** and **3f**). The reactions of *tert*-butyl- and phenyl-substituted arenes afforded the desired products in 77 and 67% yield, respectively (**3g** and **3h**). Trifluoromethylation of fluoro-, chloro- and bromoarenes proceeded smoothly to give their corresponding products in

Table 1. Reaction Optimizations with Other Ligands[a]

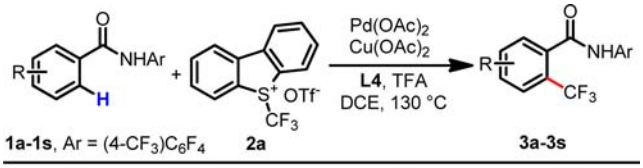


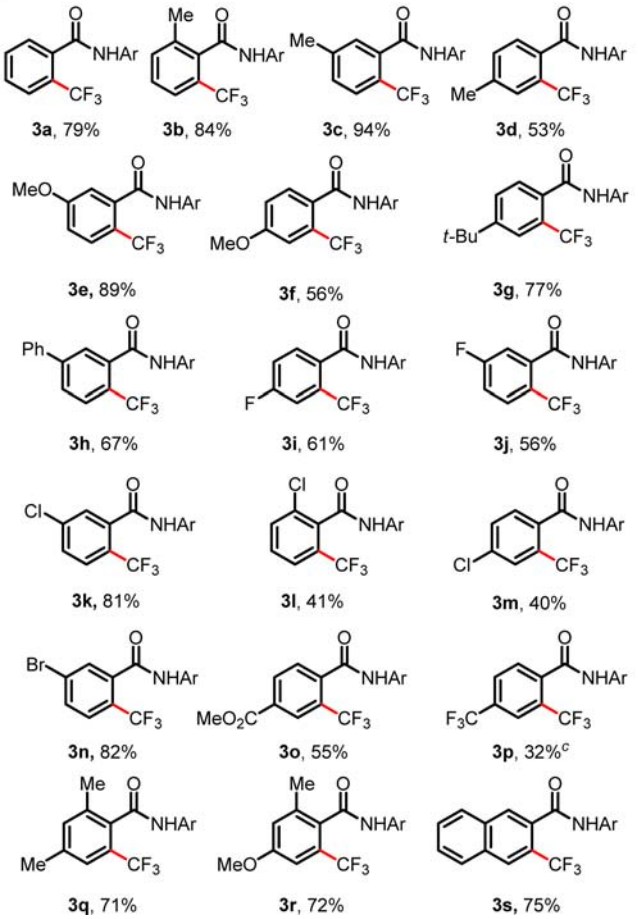


entry	additive (equiv)	Lewis acid (equiv)	yield (%)[b]
1	–	$Cu(OAc)_2$ (1)	NR
2	**L1** (15)	$Cu(OAc)_2$ (1)	23
3	**L1** (15)	$Cu(OAc)_2$ (2)	57
4	**L2** (15)	$Cu(OAc)_2$ (2)	61
5	**L3** (15)	$Cu(OAc)_2$ (2)	75
6	**L4 (15)**	**$Cu(OAc)_2$ (2)**	**79**
7	**L5** (15)	$Cu(OAc)_2$ (2)	72
8	**L6** (15)	$Cu(OAc)_2$ (2)	21
9	**L7** (15)	$Cu(OAc)_2$ (2)	trace
10	**L8** (15)	$Cu(OAc)_2$ (2)	NR
11	**L4** (10)	$Cu(OAc)_2$ (2)	64
12	**L4** (2)	$Cu(OAc)_2)_2$ (2)	22
13	**L4** (0.2)	$Cu(OAc)_2$ (2)	24
14	**L4**(15)	$Cu(OTf)_2$ (2)	28
15	**L4** (15)	$Cu(TFA)_2$ (2)	34
16	**L4** (15)	CuF_2 (2)	64
17	**L4** (15)	$Yb(OTf)_3$ (2)	NR
18	**L4** (15)	–	trace
19[c]	**L4** (15)	$Cu(OAc)_2$ (2)	57
20[d]	**L4** (15)	$Cu(OAc)_2$ (2)	65

[a]Conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), TFA (1 mmol), DCE (3 mL), 130 °C, 24 h. [b]Isolated yields. [c]Without TFA. [d]**2b** was used.

Table 2. Pd-Catalyzed Ortho Trifluoromethylation[a,b]





[a]Conditions: **1** (0.1 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (0.2 mmol), TFA (1 mmol), **L4** (1.5 mmol), DCE (3 mL), 130 °C, 24 h. [b]Isolated yields are shown. [c]**2a** (0.2 mmol) for 48 h.

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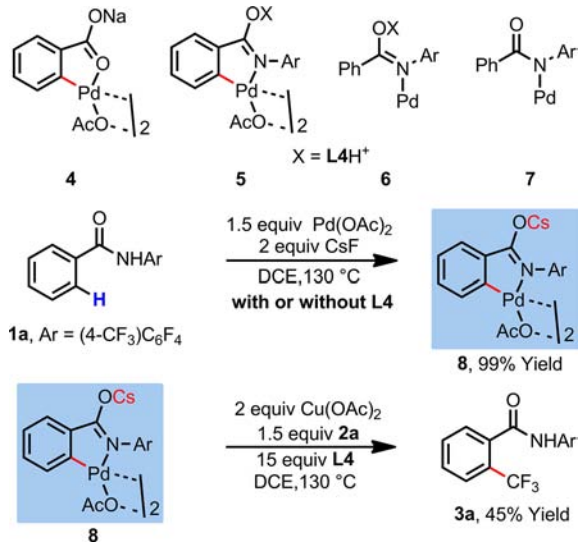
40−82% yields (**3i**−**n**). The presence of strongly electron-withdrawing CO_2Me and CF_3 groups at the para position reduced the yield to 55% (**3o**) and 32% (**3p**), respectively. Trifluoromethylation of trisubstituted arenes gave tetrasubstituted arenes in good yields (**3q** and **3r**). Highly selective β-trifluoromethylation of a naphthalene-based substrate gave the product in 75% yield (**3s**).

To elucidate the origin of the reactivity of the amide auxiliary for C−H activation under the trifluoromethylation conditions, we decided to investigate how the amide substrate coordinates to the Pd(II) center. Following our previous study of the coordination mode of sodium carboxylate **4**,[15] we anticipated that we would be able to identify an analogous C−H insertion intermediate **5** that could be formed directly from precursor **6**. It is reasonable to postulate that precursor **6** is more reactive than **7**, as the former could achieve a minimum dihedral angle between the C−H and Pd−OAc bonds with less entropic cost because of the geometry of the imine moiety. Although we could not observe the formation of **5**, we were able to obtain the analogous alkali amidate **8** in the presence of counter-cations. Thus, treatment of benzamide **1a** with 1.5 equiv of $Pd(OAc)_2$ and 2 equiv of CsF in DCE at 130 °C with or without **L4** afforded arylpalladium complex **8** as a yellow powder in 99% yield (Scheme 2). The X-ray structure of

Scheme 2. Coordination Mode of Acidic Amides



complex **8** showed that the acidic amide forms a cesium amidate that coordinates to the Pd(II) center via the imine moiety (Figure 1). The structure of **8** is consistent with our hypothesis that the sp^2-nitrogen atom in **6** instead of sp^3 nitrogen atom in **7** is involved in directing C−H activation, which could account for the superior reactivity of acidic amide substrates compared to simple amides.

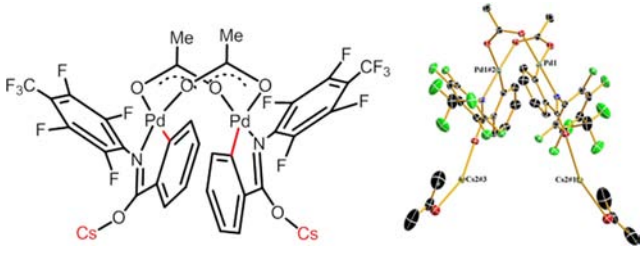
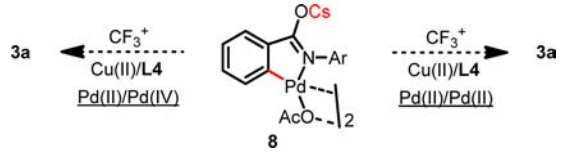


Figure 1. ORTEP diagram of Pd(II) complex **8**. Thermal ellipsoids are drawn at 50% probability, and H atoms have been omitted for clarity.

To test the viability of complex **8** to undergo trifluoromethylation, we conducted a series of experiments that shed light to the importance of $Cu(OAc)_2$ and **L4** in this reaction. The reaction of **8** with **2a** in the absence of **L4** or $Cu(OAc)_2$ was sluggish and gave less than 5% yield of the desired product **3a**. In contrast, trifluoromethylation of **8** with **2a** in the presence of **L4** and $Cu(OAc)_2$ gave the desired product in 45% yield (Scheme 2), suggesting that both **L4** and $Cu(OAc)_2$ are crucial for the C−CF_3 bond-forming step. The moderate yield is not surprising considering that the preformed dimer is perhaps not as reactive as the monomer generated in situ in the presence of **L4**.

The detailed redox chemistry involved in the C−CF_3 bond-forming step remains to be investigated. On the basis of the observed stoichiometric oxidation of $[(bzq)Pd(OAc)]_2$ (bzq = benzo[*h*]quinoline) to the corresponding Pd(IV) species by CF_3^+,[16] the reaction of **8** with CF_3^+ could proceed through a Pd(II)/Pd(IV) pathway with **L4** as the enabling ligand (Scheme 3). However, an electrophilic cleavage pathway that

Scheme 3. Redox Chemistry for C−CF_3 Bond Formation



proceeds on a Pd(II) center cannot be ruled out, in view of the fact that the oxidation of Pd(II) to Pd(IV) is less facile with weakly coordinating substrates.

In summary, we have developed a Pd(II)-catalyzed trifluoromethylation of *N*-arylbenzamides derived from readily available benzoic acids. *N*-Methylformamide has been identified as a crucial promoter of C−CF_3 bond formation from the Pd center. A rare X-ray structure of the C−H insertion intermediate has provided valuable insight into the coordination mode of acidic amides and the possible origin of their power in directing C−H activation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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