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Pd(II)-Catalyzed *Ortho*-Trifluoromethylation of Benzylamines

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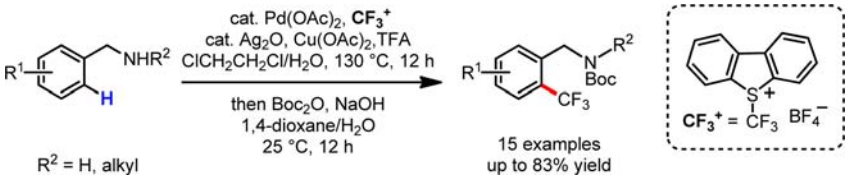
ABSTRACT



The Pd(II)-catalyzed *ortho*-C−H trifluoromethylation of benzylamines has been achieved utilizing an electrophilic CF_3 reagent. Additives, such as H_2O and Ag_2O, were found to be crucial for obtaining good yields. This protocol will be useful in medicinal chemistry for the preparation of *ortho*-trifluoromethyl-substituted benzylamines.

The incorporation of trifluoromethyl groups in pharmaceuticals and biologically active molecules is important to medicinal chemists because the addition of a trifluoromethyl group can improve the metabolic stability and lipophilicity of such compounds.[1] Given such utility, there has been interest in the development of new methods for the installation of trifluoromethyl groups onto the aromatic scaffolds of these important compounds.[2] One general approach toward arene trifluoromethylation is to use transition metals to forge arene C−CF_3 bonds from prefunctionalized arenes. Currently, arene trifluoromethylation can be accomplished via copper-catalyzed cross-coupling of both aryl halides[3] and arylboronic acids.[4] Palladium-catalyzed[5] and -mediated[6] cross-coupling reactions of aryl halides have also been used to access trifluoromethylated arenes.

Another approach for arene trifluoromethylation is centered on the direct conversion of the arene C−H bond to a new C−CF_3 bond. One method that has received recent attention is arene C−H trifluoromethylation via the generation of a CF_3 radical.[7,8] The other method for arene trifluoromethylation is via transition-metal-catalyzed C−H activation. However, there are inherent difficulties in the development of such a reaction, which stem from the

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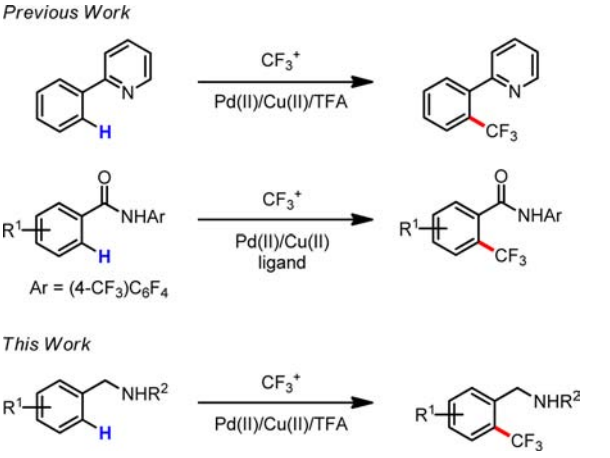
unfavorable reductive elimination of an Ar−Pd−CF_3 species[6] and the lack of appropriate ligands that can promote both reductive elimination and C−H activation. We have reported the first palladium-catalyzed *ortho*-trifluoromethylation of 2-phenylpyridines with Umemoto's trifluoromethylation reagent[9] and have recently expanded our protocol to include benzoic acid derived *N*-arylbenzamides (Scheme 1).[10] We found in these studies that Cu(II) salts were crucial for forming the aryl−CF_3 bonds. Recently, Shi has also reported a palladium-catalyzed C−H *ortho*-trifluoromethylation of acetanilides with the Umemoto's trifluoromethylation reagent.[11] Interestingly, Liu has reported a palladium-catalyzed C−H trifluoromethylation of indoles with the nucleophilic Ruppert−Prakash reagent ($TMSCF_3$).[12,13] However, despite these recent reports, the substrate scope of palladium-catalyzed C−H trifluoromethylation has yet to encompass the breadth and utility observed with other arene trifluoromethylation methods.

Given the prevalence of the *ortho*-trifluoromethyl benzylamine moiety in medicinally relevant compounds (Figure 1),[14] it would be desirable to develop a palladium-catalyzed *ortho*-C−H trifluoromethylation protocol for benzylamine substrates. Although there have been several reports on the palladium-catalyzed *ortho*-C−H carbonylation and olefination of benzyl- and phenethyl amines,[15] the *ortho*-trifluoromethylation of benzylamines via palladium-catalyzed C−H activation is still unknown to the best of our knowledge. Furthermore, palladium-catalyzed *ortho*-functionalization of N−H-containing benzylamines has been met with limited success. The only known example is the palladium(II)-catalyzed C−H arylation of both *N*-unsubstituted and *N*-methyl-substituted benzylamines in TFA reported by Daugulis.[16] Herein, we report the palladium-catalyzed *ortho*-trifluoromethylation of *N*-unsubstituted benzylamine derivatives that has a moderate substrate scope.

Scheme 1. Pd-Catalyzed C−H *Ortho*-Trifluoromethylation



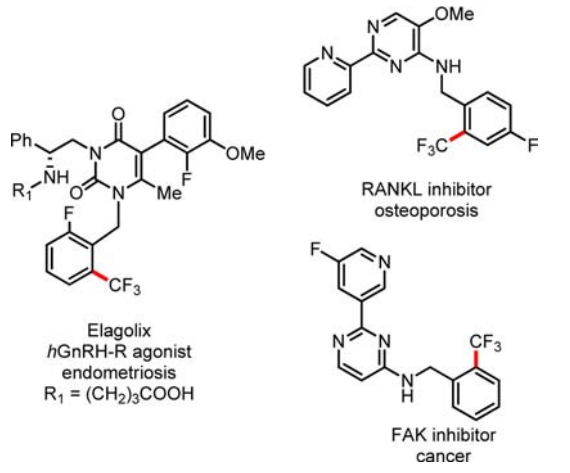


Figure 1. Biologically active *ortho*-trifluoromethylated benzylamines.

We initiated our studies into the palladium-catalyzed C−H *ortho*-trifluoromethylation of benzylamines by using conditions adapted from our previous methods.[10] To our delight, subjection of benzylamine **1a** with catalytic palladium acetate, 1 equiv of copper acetate, 10 equiv of trifluoroacetic acid, and electrophilic fluorination reagent **3** yielded the *ortho*-CF_3 adduct in 20% yield after subsequent Boc protection (Table 1, entry 1). Increasing the amount of $Cu(OAc)_2$ to 2 equiv resulted in a beneficial boost in yield (Table 1, entry 2). This is unsurprising, as we believe that the copper acetate can scavenge the free dibenzothiophene released over the course of the reaction, which can hamper C−H activation. Decreasing the equivalents of TFA also improved the yield,[17] which suggests that the equilibrium ratio between the free amine and the amine

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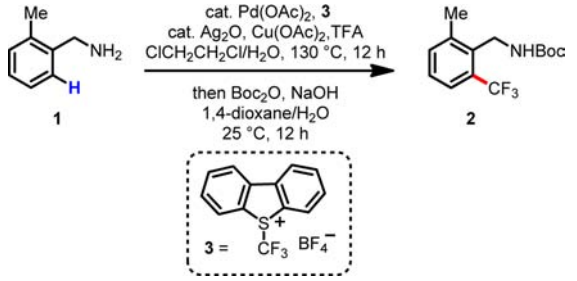
(17) Other acids, such as AcOH, MsOH, TfOH, and CCl_3CO_2H, were also examined, yielding no observed *ortho*-trifluoromethylated product.

Table 1. Reaction Optimization

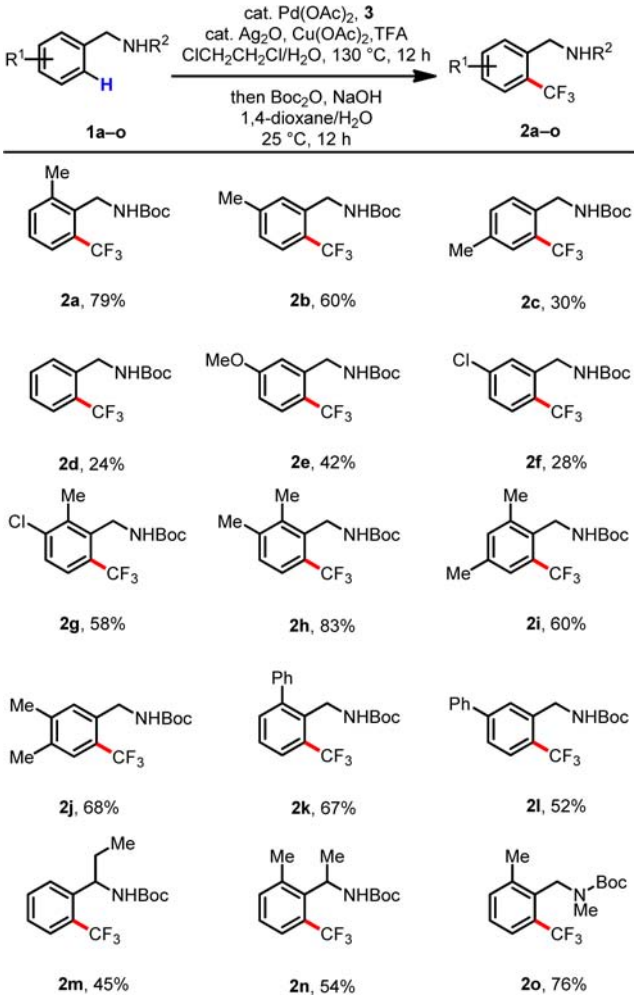


entity	$Cu(OAc)_2$ (equiv)	TFA (equiv)	H_2O (equiv)	Ag_2O (equiv)	yield (%)[a,b]
1[c]	1	10	0	0	20
2	2	5	0	0	44
3[c]	2	5	20	0	63
4[d]	2	5	20	0.15	69
5[d,e]	2	5	20	0.15	0
6[d]	0	5	20	0.15	0
7[d]	2	0	20	0.15	4
8[f]	2 × 2	5	56	0.15 × 2	87 (79)[g]

[a] Conditions (unless otherwise specified): Substrate (0.1 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (0.20 mmol), **3** (0.15 mmol), TFA (0.5 mmol), H_2O (2.0 mmol), Ag_2O (15 mol %), $ClCH_2CH_2Cl$ (0.5 mL), 130 °C, 24 h, then Boc_2O (0.5 mmol), sat. aq Na_2CO_3 (2.0 mL), EtOAc (1.0 mL), 25 °C, 12 h. [b] The yields were determined by ^1H NMR analysis of the crude products using CH_2Br_2 as an internal standard. [c] Reaction was performed at 110 °C for 48 h. [d] Reaction was run at 130 °C for 8 h. [e] Reaction was performed without $Pd(OAc)_2$. [f] Conditions for batchwise addition: (first batch) Substrate **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (0.20 mmol), **3** (0.15 mmol), TFA (0.5 mmol), H_2O (5.6 mmol, 0.1 mL), Ag_2O (15 mol %), $ClCH_2CH_2Cl$ (1.0 mL), 130 °C, 6 h; (second batch) $Cu(OAc)_2$, **3** (0.15 mmol), Ag_2O (15 mol %), 130 °C, 6 h; then Boc_2O (0.3 mmol), NaOH (5.0 mmol), 1,4-dioxane (1.0 mL), H_2O (1.0 mL), 25 °C, 12 h. [g] The isolated yield is given in parentheses.

salt is important for the reaction. The previously used formamide additives[10] as promoters were not effective for this substrate. Our optimization studies also revealed that the addition of H_2O improves both the reaction yield and total mass balance (Table 1, entry 3). Further intensive screening for additives revealed that a catalytic amount of Ag_2O gave the product in 69% yield (Table 1, entry 4).[18] It is possible that Ag_2O reoxidizes Pd(0) generated from side pathways. In the absence of $Pd(OAc)_2$, $Cu(OAc)_2$, or TFA, little or no *ortho*-trifluoromethylation product was observed, indicating that these three reagents are crucial for reactivity (Table 1, entries 5−7). Monitoring the reaction by ^1H NMR revealed that the electrophilic fluorination reagent **3**[19] was completely consumed while starting material remained after 8 h; thus, the reaction was performed via batchwise addition of **3**, $Cu(OAc)_2$, and Ag_2O, yielding

Scheme 2. Substrate Scope of Pd-Catalyzed *Ortho*-Trifluoromethylation of Benzylamines[a,b]



[a] Conditions: (first batch) Substrate **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$(0.20 mmol), **3** (0.15 mmol), H_2O (5.6 mmol, 0.1 mL), TFA (0.5 mmol), Ag_2O (15 mol %), $ClCH_2CH_2Cl$ (1.0 mL), 130 °C, 6 h; (second batch) $Cu(OAc)_2$, **3** (0.15 mmol), Ag_2O (15 mol %), 130 °C, 6 h; then Boc_2O (0.3 mmol), NaOH (5.0 mmol), 1,4-dioxane (1.0 mL), H_2O (1.0 mL), 25 °C, 12 h. [b] The isolated yields are given.

the *ortho*-trifluoromethylated product in 87% NMR yield and 79% isolated yield (Table 1, entry 8).[20]

With these optimized conditions in hand, we surveyed the substrate scope of this trifluoromethylation reaction (Scheme 2). Although *m*-methyl substituted benzylamine **1b** yielded *ortho*-trifluoromethylated product **2b** with a moderate 60% yield, the *p*-methyl (**1c**) and unsubstituted benzylamines (**1d**) were less reactive, affording their corresponding *ortho*-trifluoromethylated products in poor yields (30% and 24%, respectively).[21] An electron-donating group at the *meta*-position, such as the methoxy

(18) Increasing the amount of Ag_2O had no further effect on the reaction yield. Other Ag(I) reagents, such as AgOAc, Ag_2CO_3, and Ag(TFA), did not improve the yield.

(19) Other electrophilic trifluoromethylation reagents, such as 5-(trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate, 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (Togni's Reagent), and 1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one, were also examined with no improvement in yield.

(20) Without Boc protection, the corresponding free amine was isolated in 39% yield. Presumably, the excess amount of Cu might be coordinated with the product, resulting in complications in extraction during workup and lower overall yield.

(21) The corresponding di-*ortho*-CF_3 adducts were also obtained in about 3% yield.

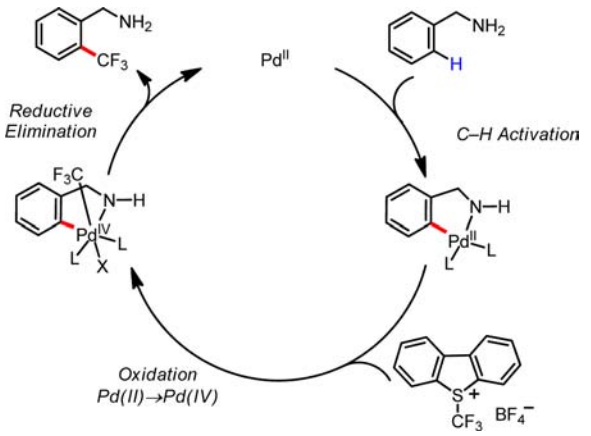


Figure 2. Proposed catalytic cycle.

substituent in **2e**, afforded the corresponding product in 42% yield while an electron-withdrawing group, such as a chloride substituent in **2f**, yielded the corresponding product in 28% yield. However, the introduction of a methyl group at the *ortho*-position was found to restore the reactivity on a *meta*-chloro substituted benzylamine (**1g**), producing the *ortho*-trifluoromethylated product **2g** in 58% yield. Dimethyl- and phenyl-substituted compounds were also well tolerated, and the corresponding trifluoromethylated products were obtained with moderate to good yields (Scheme 2, **2h**−**2l**). α-Substituted benzylamine derivatives, such as **1m** and **1n**, were also compatible substrates for this reaction, providing trifluoromethylated compounds with acceptable yields (45% and 54% yields, respectively). Notably, *N*-methyl substituted benzylamine (**1o**) also underwent *ortho*-trifluoromethylation in 76% yield.

Based on our previous studies, we tentatively propose a catalytic cycle of our palladium(II)-catalyzed *ortho*-trifluoromethylation of benzylamines (Figure 2). We believe that the first step is palladium(II)-mediated C−H cleavage to generate the [Ar−Pd^{II}] species, which can then react with the electrophilic trifluoromethylation reagent to form an octahedral Pd^{IV} intermediate.[22] This palladium(IV) species can then undergo reductive elimination to afford the *ortho*-trifluoromethylation product. It is worth mentioning that the possibility of a redox neutral, electrophilic cleavage pathway that proceeds via Pd(II) cannot be excluded.

In summary, we report a versatile Pd(II)-catalyzed *ortho*-C−H trifluoromethylation of *N*-unsubstituted benzylamines. The addition of H_2O and Ag_2O proved to be crucial for this transformation, and *ortho*-trifluoromethylated benzylamines were obtained with good yields. We anticipate that this reaction will have widespread applications in medicinal chemistry to functionalize benzylamines.

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

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The authors declare no competing financial interest.