

C–H Activation

Exceedingly Fast Copper(II)-Promoted *ortho* C–H Trifluoromethylation of Arenes using TMSCF₃**

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Dedicated to Professor Li-Xin Dai on the occasion of his 90th birthday

Abstract: The direct *ortho*-trifluoromethylation of arenes, including heteroarenes, with TMSCF₃ has been accomplished by a copper(II)-promoted C–H activation reaction which completes within 30 minutes. Mechanistic investigations are consistent with the involvement of C–H activation, rather than a simple electrophilic aromatic substitution (*S_EAr*), as the key step.

The incorporation of the trifluoromethyl group into biologically active molecules has emerged as a widely employed strategy in medicinal chemistry to enhance the binding selectivity, increase lipophilicity, and improve the metabolic stability of a variety of pharmaceutically relevant compounds.^[1] To this end, a number of methods have been developed to install this integral functional group onto the aromatic scaffolds of these molecules, including palladium-catalyzed^[2] and palladium-mediated^[3] cross-coupling reactions of aryl halides, as well as copper-catalyzed cross-couplings of both aryl halides^[4] and arylboronic acids.^[5]

In recent years, the direct C–H trifluoromethylation of arenes has emerged as an attractive approach to generate C–CF₃ bonds for a few classes of substrates. As such, a number of new technologies have been developed to meet this end, including palladium-catalyzed *ortho* C–H trifluoromethylation by Pd^{II}/Pd^{IV} redox catalysis [Eq. (1); DG = directing

group],^[6–8] as well as methods which take advantage of CF₃ radical formation.^[9,10] Furthermore, protocols involving relatively inexpensive copper-catalyzed or copper-mediated systems have been reported, albeit generally limited to the functionalization of either electron-rich indolyl or weakly acidic C–H bonds.^[11,12] A single example of CuI-mediated trifluoromethylation of indole using a combination of chlorodifluoroacetate and potassium fluoride was also described in one of these studies.^[11f] Intrigued by the report from Chu and Qing on the direct copper-catalyzed trifluoromethylation of acidic C–H bonds in 1,3-azoles^[11d] using the Ruppert–Prakash reagent (TMSCF₃),^[13] we were curious as to whether this copper/CF₃[–] platform could be utilized to affect the direct *ortho* trifluoromethylation of inert aryl C–H bonds using a synthetically useful amide directing group. Recently, an elegant example of *ortho* trifluoromethylation using AgCF₃, by a radical pathway, has been reported [Eq. (2)].^[14] Although either the *para*-position or one of the *ortho*-positions needs to be substituted, the electronic effect of the triazene functional group favors the *ortho*-radical attack with synthetically useful selectivity. Herein we detail the first example of *ortho* C–H trifluoromethylation of benzamides with TMSCF₃ using a directed C–H cupuration approach [Eq. (3); TMS = trimethylsilyl].

We began our studies with the functionalization of the amide **1a**, which was prepared from the condensation of benzoic acid and 2-(2-oxazolyl)aniline (Table 1).^[15] Treating **1a** with 30 mol % Cu(OAc)₂, 5 equivalents of TMSCF₃ (**2**), 1 equivalent of Ag₂CO₃, and 4 equivalents KF in DMSO at 100 °C gave the desired trifluoromethylated benzamide **3a** in

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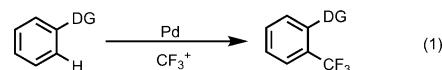
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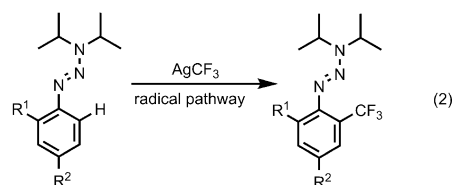
[**] We gratefully acknowledge the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, the CAS/SAFEA International Partnership Program for Creative Research Teams, and the Recruitment Program of Global Experts for financial support. We gratefully acknowledge The Scripps Research Institute, for financial support. This work was supported by NSF under the CCI Center for Selective C–H Functionalization, CHE-1205646. TMS = trimethylsilyl.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201404822>.

Previous work:

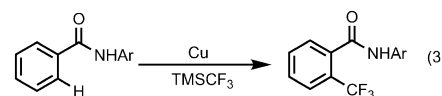


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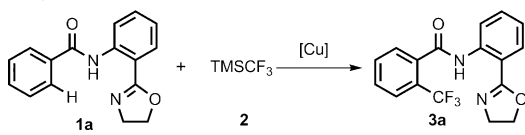
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(3)

Table 1: Optimization of reaction conditions.^[a,b]

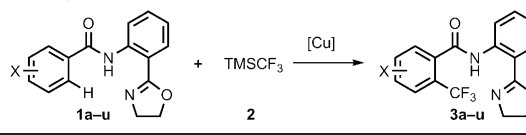
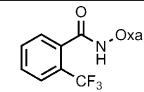
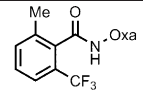
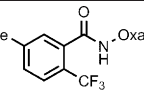
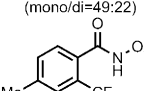
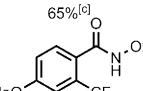
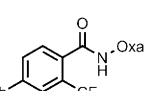
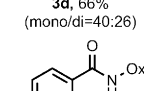
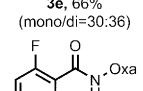
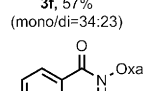
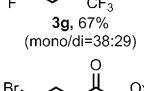
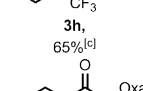
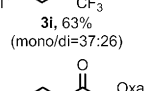
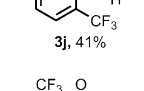
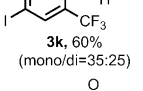
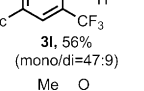
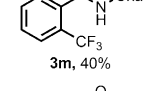
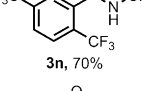
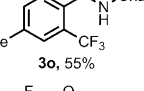
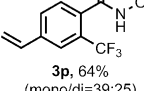
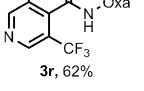
					
Entry	[Cu] (equiv)	Ag (equiv)	Base	t [h]	Yield [%]
1	Cu(OAc) ₂ (0.3)	Ag ₂ CO ₃ (1.0)	KF	5	37
2	Cu(OAc) ₂ (0.3)	Ag ₂ CO ₃ (1.0)	NaF	5	29
3	Cu(OAc) ₂ (0.3)	Ag ₂ CO ₃ (1.0)	CsF	5	36
4	Cu(OAc) ₂ (0.5)	Ag ₂ CO ₃ (1.0)	KF	5	44 + 8 (di)
5	Cu(OAc) ₂ (1.0)	Ag ₂ CO ₃ (1.0)	KF	5	55 + 13 (di)
6	Cu(OAc) ₂ (1.0)	Ag ₂ CO ₃ (1.5)	KF	5	54 + 26 (di)
7	Cu(OAc) ₂ (1.0)	Ag ₂ CO ₃ (2.0)	KF	5	18 + 17 (di)
8	Cu(OAc) ₂ (1.0)	AgF (1.5)	KF	5	24
9	Cu(OAc) ₂ (1.0)	Ag ₃ PO ₄ (1.5)	KF	5	20
10	Cu(OAc) ₂ (1.0)	AgBF ₄ (1.5)	KF	5	16
11	Cu(OAc) ₂ (1.0)	Ag ₂ O (1.5)	KF	5	27
12	Cu(OAc) ₂ (1.0)	Ag ₂ CO ₃ (1.5)	KF	0.5	65 + 17 (di)
13	CuI (1.0)	Ag ₂ CO ₃ (1.5)	KF	0.5	31
14	Cu(TFA) ₂ (1.0)	Ag ₂ CO ₃ (1.5)	KF	0.5	25
15	Cu(OTf) ₂ (1.0)	Ag ₂ CO ₃ (1.5)	KF	0.5	10
16	Cu(OAc) ₂ (0)	Ag ₂ CO ₃ (1.5)	KF	0.5	NR
17	Cu(OAc) ₂ (1.0)	Ag ₂ CO ₃ (0)	KF	0.5	19

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.5 mmol), [Cu], [Ag], NMO (0.2 mmol), base (0.4 mmol), DMSO (1.0 mL), 100 °C, air. [b] Yield determined by ¹⁹F NMR analysis of crude reaction mixture using fluorobenzene as an internal standard. DMSO = dimethylsulfoxide, NMO = *N*-methylmorpholine *N*-oxide, TFA = trifluoroacetate, Tf = trifluoromethanesulfonyl.

a promising 37% yield (entry 1). Alternative fluoride sources other than KF proved to be less efficient in promoting trifluoromethylation (entries 1–3). Higher loadings of Cu(OAc)₂ and Ag₂CO₃ led to a dramatic increase in yield, thus delivering **3a** in 80% yield as a 2:1 mixture of mono-trifluoromethylated to di-trifluoromethylated (mono/di) products (entries 4–7). After a brief survey of both copper and silver salts, Cu(OAc)₂ and Ag₂CO₃ remained the optimal choice (entries 8–11 and 13–15). Remarkably, the reaction time could be shortened to 30 minutes, and had the additional benefit of improving the mono/di selectivity (3.8:1; entry 12). It should also be noted that in the absence of copper no reactivity is observed. In contrast, the reaction still proceeds (albeit in low yield) in the absence of a silver promoter (entries 16 and 17). These results suggest that the C–H activation step is mediated by copper.

With these optimized reaction conditions in hand, we next sought to investigate the substrate scope. As shown in Table 2, a wide variety of benzamide derivatives undergo trifluoromethylation efficiently, thus including electron-rich methyl- and methoxy-substituted arenes (**3b–e**). Moreover, halogen and vinyl substituents were well tolerated (**3g–k** and **3p**). Of particular interest are the products derived from benzamides bearing bromine, iodine, and vinyl groups (**3j**, **3k**, **3p**), which leave intact synthetic handles for further functionalization. Electron-deficient arenes also underwent C–H activation smoothly, thus yielding the desired trifluoromethylated products in moderate to good yield (**3l–n**), as did trisubstituted substrates (**3o**). Gratifyingly, we also found this newly

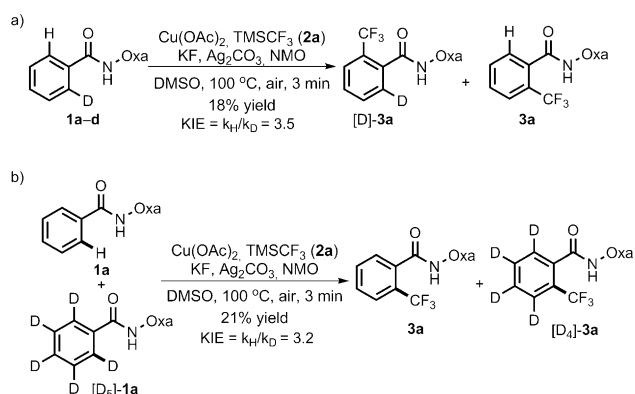
Table 2: Scope of substrates.^[a,b]

		
 3a , 71% (mono/di=49:22)	 3b , 65% ^[c]	 3c , 46%
 3d , 66% (mono/di=40:26)	 3e , 66% (mono/di=30:36)	 3f , 57% (mono/di=34:23)
 3g , 67% (mono/di=38:29)	 3h , 65% ^[c]	 3i , 63% (mono/di=37:26)
 3j , 41%	 3k , 60% (mono/di=35:25)	 3l , 56% (mono/di=47:9)
 3m , 40%	 3n , 70%	 3o , 55%
 3p , 64% (mono/di=39:25)	 3q , 52% (mono/di=27:25)	 3r , 62%
 3s , 80%	 3t , 61%	 3u , 40%

[a] **1a–u** (0.1 mmol), **2** (0.5 mmol), Cu(OAc)₂ (0.1 mmol), KF (0.4 mmol), Ag₂CO₃ (0.15 mmol), NMO (0.2 mmol), DMSO (1.0 mL), 100 °C, air, 30 min. [b] Yield of isolated product. [c] Cu(OAc)₂ (0.13 mmol), Ag₂CO₃ (0.18 mmol).

developed copper-mediated C–H activation protocol to be compatible with a wide variety of heterocycles, including pyridines, pyrroles, benzofurans, and quinoline-derived substrates (**3q–u**). The *ortho* trifluoromethylation of these heterocycles have not been reported using either a palladium catalyst^[6] or radical pathway.^[14]

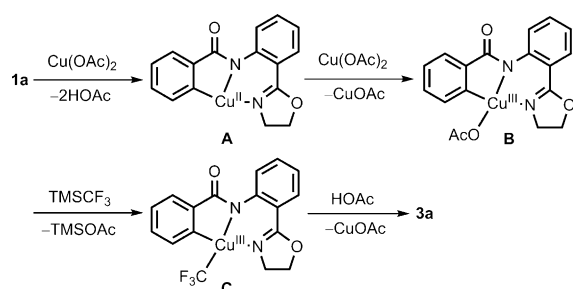
To probe the reaction mechanism, we measured intra- and intermolecular kinetic isotope effects. Significant isotope effects were observed in both cases (Scheme 1). In addition, the commonly used radical quencher 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was found to have negligible effect on the yield, thus rendering a radical pathway unlikely (Scheme 2). These combined data supports a mechanism which involves a copper-mediated C–H cleavage step rather than an electrophilic aromatic substitution (S_EAr) or radical pathway. Therefore, we propose a copper(II)-mediated C–H functionalization pathway (Scheme 3). Oxazoline-directed C–H activation of **1a** with subsequent disproportionation of



Scheme 1. a) Intramolecular kinetic isotope effect (KIE.) b) Intermolecular KIE.



Scheme 2. The effect of TEMPO.



Scheme 3. Plausible pathway.

copper(II) yields a chelated organocopper(III) complex (**B**).^[16] Subsequent transmetalation of this organocopper species with TMSCF_3 yields the $\text{Cu}^{\text{III}}\text{-CF}_3$ intermediate **C**. Reductive elimination would then afford the desired *ortho*-trifluoromethylated arene **3a**.

In summary, we have developed the first copper(II)-mediated *ortho* trifluoromethylation of arenes, including heteroarenes, with TMSCF_3 . This finding opens possibilities for further development of copper-catalyzed trifluoromethylation of *ortho* C–H bonds using a practical reagent, TMSCF_3 .

Experimental Section

The substrates **1** (0.1 mmol, 1 equiv), $\text{Cu}(\text{OAc})_2$ (0.1 mmol), Ag_2CO_3 (0.15 mmol), KF (0.4 mmol), NMO (0.2 mmol), DMSO (1 mL), and TMSCF_3 (0.5 mmol) were added to a 15 mL sealed tube. The reaction mixture was stirred at RT for 15 min under air. The tube was then placed into a preheated oil bath (100 °C) and stirred for 30 min. Upon completion, EtOAc was added to dilute the mixture and then washed

with $\text{NH}_3\cdot\text{H}_2\text{O}$ and saturated NaCl(aq). The organic fraction was dried over Na_2SO_4 , evaporated, and purified by flash column chromatography on silica gel with a gradient eluent of hexanes and ethyl acetate. The yield of the isolated product was the average of two paralleled reactions.

Received: April 30, 2014

Published online: August 5, 2014

Keywords: arenes · C–H activation · copper · fluorine · reaction mechanisms

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