C–H Activation

DOI: 10.1002/ange.201404822

Exceedingly Fast Copper(II)-Promoted *ortho* C–H Trifluoromethylation of Arenes using $TMSCF_3$**

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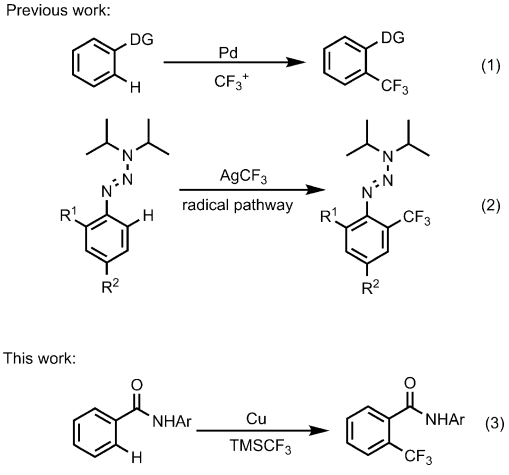
Dedicated to Professor Li-Xin Dai on the occasion of his 90th birthday

Abstract: *The direct ortho-trifluoromethylation of arenes, including heteroarenes, with $TMSCF_3$ 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–CF_3 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 CF_3 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 ($TMSCF_3$),[13] we were curious as to whether this copper/CF_3^- 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 $AgCF_3$, 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 $TMSCF_3$ 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 $TMSCF_3$ (**2**), 1 equivalent of Ag_2CO_3, and 4 equivalents KF in DMSO at 100 °C gave the desired trifluoromethylated benzamide **3a** in



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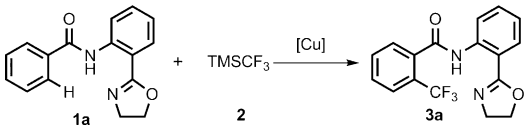
[**] We gratefully acknowledge the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, the CAS/SAFEA International Partnership Program for Creative Research Teams, and the Recruitment Program of Global Experts for financial support. We gratefully acknowledge The Scripps Research Institute, 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.

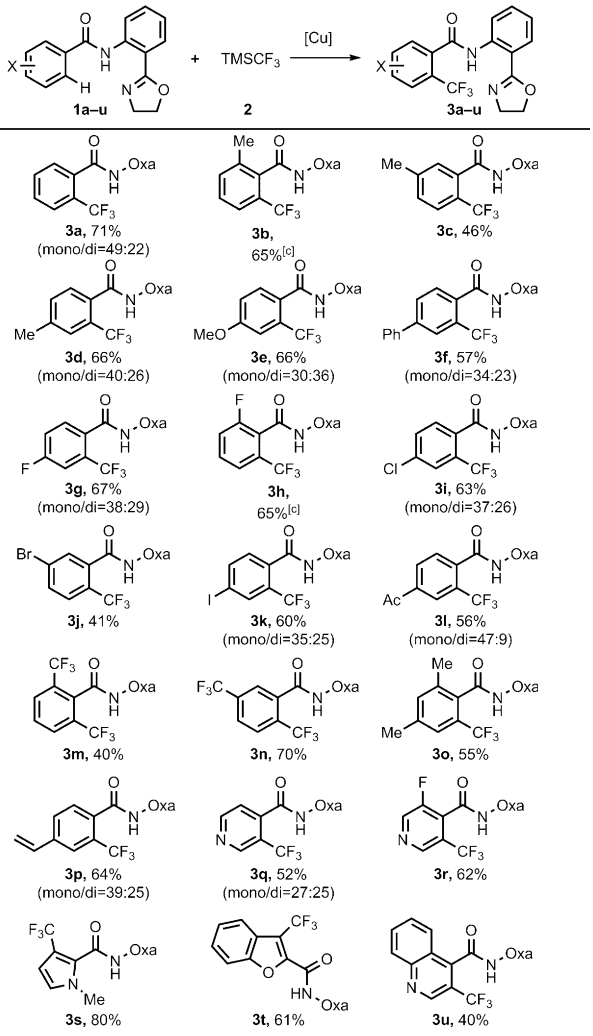
Table 1: Optimization of reaction conditions.[a,b]



Entry	[Cu] (equiv)	Ag (equiv)	Base	*t* [h]	Yield [%]
1	$Cu(OAc)_2$ (0.3)	Ag_2CO_3 (1.0)	KF	5	37
2	$Cu(OAc)_2$ (0.3)	Ag_2CO_3 (1.0)	NaF	5	29
3	$Cu(OAc)_2$ (0.3)	Ag_2CO_3 (1.0)	CsF	5	36
4	$Cu(OAc)_2$ (0.5)	Ag_2CO_3 (1.0)	KF	5	44 + 8 (di)
5	$Cu(OAc)_2$ (1.0)	Ag_2CO_3 (1.0)	KF	5	55 + 13 (di)
6	$Cu(OAc)_2$ (1.0)	Ag_2CO_3 (1.5)	KF	5	54 + 26 (di)
7	$Cu(OAc)_2$ (1.0)	Ag_2CO_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_3PO_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_2O (1.5)	KF	5	27
12	$Cu(OAc)_2$ (1.0)	Ag_2CO_3 (1.5)	KF	0.5	65 + 17 (di)
13	CuI (1.0)	Ag_2CO_3 (1.5)	KF	0.5	31
14	$Cu(TFA)_2$ (1.0)	Ag_2CO_3 (1.5)	KF	0.5	25
15	$Cu(OTf)_2$ (1.0)	Ag_2CO_3 (1.5)	KF	0.5	10
16	$Cu(OAc)_2$ (0)	Ag_2CO_3 (1.5)	KF	0.5	NR
17	$Cu(OAc)_2$ (1.0)	Ag_2CO_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 ^{19}F NMR analysis of crude reaction mixture using fluorobenzene as an internal standard. DMSO = dimethylsulfoxide, NMO = *N*-methylmorpholine *N*-oxide, TFA = trifluoroacetate, Tf = trifluoromethanesulfonyl.

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

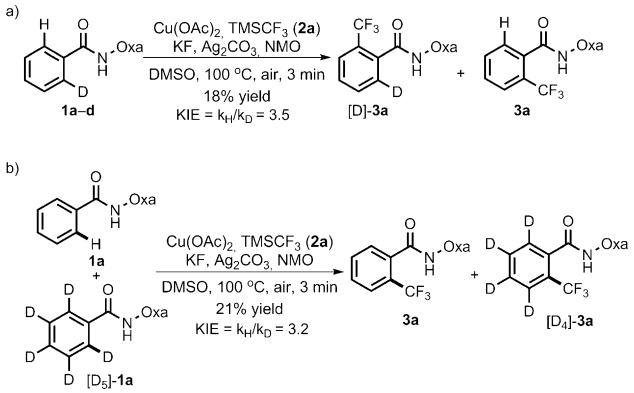


[a] **1a–u** (0.1 mmol), **2** (0.5 mmol), $Cu(OAc)_2$ (0.1 mmol), KF (0.4 mmol), Ag_2CO_3 (0.15 mmol), NMO (0.2 mmol), DMSO (1.0 mL), 100 °C, air, 30 min. [b] Yield of isolated product. [c] $Cu(OAc)_2$ (0.13 mmol), Ag_2CO_3 (0.18 mmol).

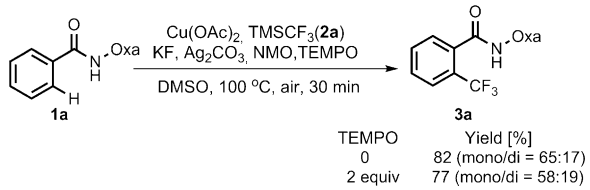
a promising 37 % yield (entry 1). Alternative fluoride sources other than KF proved to be less efficient in promoting trifuoromethylation (entries 1–3). Higher loadings of $Cu(OAc)_2$ and Ag_2CO_3 led to a dramatic increase in yield, thus delivering **3a** in 80 % yield as a 2:1 mixture of mono-trifluoromethylated to di-trifluoromethylated (mono/di) products (entries 4–7). After a brief survey of both copper and silver salts, $Cu(OAc)_2$ and Ag_2CO_3 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 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]

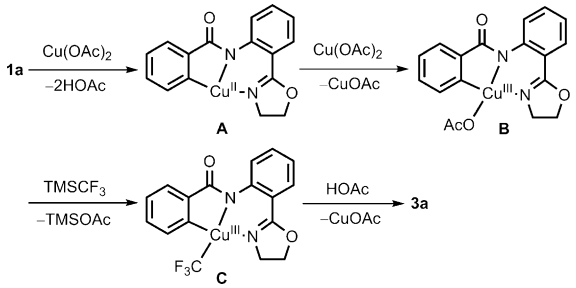
To probe the reaction mechanism, we measured intra- and intermolecular kinetic isotope effects. Significant isotope effects were observed in both cases (Scheme 1). In addition, the commonly used radical quencher 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was found to have negligible effect on the 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 transmetallation of this organocopper species with $TMSCF_3$ yields the Cu^{III}–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), $Cu(OAc)_2$ (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 $NH_3{\cdot}H_2O$ 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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