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Copper-Mediated Oxidative Trifluoromethylation of Boronic Acids

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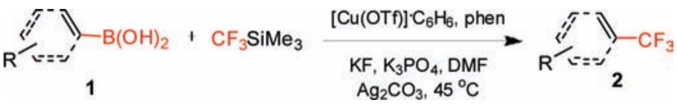
ABSTRACT



A copper-mediated oxidative cross-coupling of aryl- and alkenylboronic acids with (trifluoromethyl)trimethylsilane (Me$_3$SiCF$_3$) under mild conditions has been developed. This method allows a wide range of functional group tolerant trifluoromethylated arenes and alkenes to be easily prepared. This oxidative trifluoromethylation has the potential to introduce trifluoromethyl groups into advanced, highly functionalized organic molecules.

A large number of biologically active pharmaceuticals and agrochemicals contain trifluoromethylated aromatic groups, as the incorporation of a CF$_3$ group into aromatics often enhances their chemical and metabolic stability, lipophilicity, and binding selectivity.[1] The Swarts reaction (chlorine−fluorine exchange using reactive SbF$_5$)[2] and treatment of benzoic acid derivatives with SF$_4$[3] are the traditional methods for the construction of aryl carbon-CF$_3$ bonds; however, such harsh reaction conditions are not compatible with a large number of functional groups. The cross-couplings of aromatic halides with CuCF$_3$ generated in situ represent the most popular protocols for the synthesis of trifluoromethylated aromatics but are mainly limited to aryl iodides and activated aryl bromides as substrates.[4,5] The radical[6] and electrophilic[7] trifluoromethylation of arenes were also reported, but these methods were only applied to the trifluoromethylation of arenes bearing activating substituents such as hydroxy, methoxy, or amino groups, and in some cases, mixtures of regioisomers were observed. Recently, palladium-mediated reactions for the introduction of trifluoromethyl groups onto aromatic rings have been intensely sought.[8,9] Among this impressive research, the palladium-catalyzed trifluoromethylation of aryl chlorides developed by Buchwald's group is one of the most important breakthroughs in the arena of

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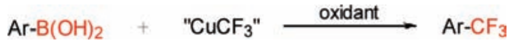
trifluoromethylation chemistry.[8a] The high reaction temperature (120−140 °C) and the unsuitability for substrates bearing aldehydes or ketones are current challenges of this method. Thus, the development of a method of mild reaction conditions and wide substrate scope for the incorporation of trifluoromethyl groups into aromatic rings remains a topic of great current interest. Herein, we report the first copper-mediated oxidative trifluoromethyaltion of aryl- and alkenylboronic acids with nucleophilic (trifluoromethyl)trimethylsilane (CF_3SiMe_3). Advantages of the reported trifluoromethylation include mild reaction conditions, high functional group tolerance, and ready availability of boronic acids.

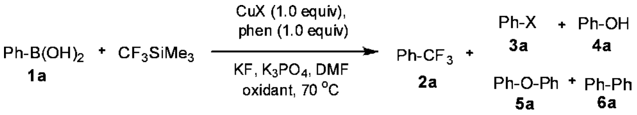
Arylboronic acid derivatives are compatible with a broad range of common functional groups, commercially available and stable to air and moisture.[10] Thus, arylboronic acid derivatives have been widely used in organic synthesis. Among a wide range of coupling reactions employing boronic acids as partners, one class with growing importance is the copper-mediated oxidative coupling of boronic acids and nucleophiles,[11] first developed by Chan and Evans and separately Evans in 1998.[12] A wide range of heteroatom nucleophiles, including amines, amides, nitrogen heterocycles, alcohols, and phenols, were used in the Chan−Evans−Lam coupling reactions. However, to the best of our knowledge, these protocols do not involve carbon (sp^3)-nucleophiles. It was noteworthy that the fluorination of arylboronic acids was reported,[13] but the trifluoromethylation of arylboronic acids has not been described in the literature. Very recently, we have successfully developed the first example of a copper-mediated protocol for Csp−Csp^3 aerobic oxidative trifluoromethylation of terminal alkynes with nucleophilic (trifluoromethyl)trimethylsilane (Me_3SiCF_3).[14] This reaction provides a general, straighforward, and practically useful method to prepare trifluoromethylated acetylenes. Inspired by this work, we envisioned that the oxidative cross-coupling of in situ generated $CuCF_3$ with arylboronic acid may be possible and would provide new type of trifluoromethylation protocols for preparation of aryl-CF_3 (Scheme 1).

Scheme 1. Oxidative Trifluoromethylation of Arylboronic Acids



To test our hypothesis, initially, the oxidation trifluoromethylation of phenylboronic acid under the optimal reaction conditions of the oxidative trifluoromethylation of terminal alkynes was investigated.[14] When phenylboronic acid was added by using a syringe pump to $CuCF_3$ generated in situ by combination of KF (5.0 equiv), Me_3SiCF_3 (5.0 equiv), and CuI (1.0 equiv) in the presence of 1,10-phenanthroline (phen, 1.0 equiv) in DMF at 70 °C under air atmosphere, the products (including the desired product and byproducts) formed from phenylboronic acid were not observed (Table 1, entry 1). Fortunately, when K_3PO_4 (3.0 equiv) was added to the reaction mixture, the desired product $PhCF_3$ was formed in 37% yield along with byproducts PhI (43% yield),

Table 1. Evaluation of Reaction Conditions for the Copper-Mediated Trifluoromethylation of Benzeneboronic Acid[a]



entry	CuX	oxidant (equiv)	yield of **2a** (%) (**3a/4a/5a/6a**)[b]
1[c]	CuI	air (no K_3PO_4)	none
2[c]	CuI	air	37 (43/5/11/2)[d]
3[c]	CuBr	air	17 (15/12/34/4)[e]
4[c]	CuCl	air	8 (6/8/31/12)[f]
5[c]	CuCN	air	6 (4/43/14/3)[g]
6[c]	$[Cu(OTf)]_2{\cdot}C_6H_6$	air	63 (−/10/21/3)
7	$[Cu(OTf)]_2{\cdot}C_6H_6$	DDQ (1.0)	61 (2/−/−/6)[f]
8	$[Cu(OTf)]_2{\cdot}C_6H_6$	BQ (1.0)	73 (−/−/−/3)
9	$[Cu(OTf)]_2{\cdot}C_6H_6$	Chloranil (1.0)	46 (2/−/−/5)[f]
10	$[Cu(OTf)]_2{\cdot}C_6H_6$	$CuCl_2$ (1.0)	56 (4/−/−/4)[f]
11	$[Cu(OTf)]_2{\cdot}C_6H_6$	TEMPO (1.0)	43 (−/−/−/12)
12	$[Cu(OTf)]_2{\cdot}C_6H_6$	1,2-Dibromo-ethane (1.0)	71 (26/−/−/−)[e]
13	$[Cu(OTf)]_2{\cdot}C_6H_6$	1,2-Dichloro-isobutane (1.0)	63 (7/−/−/3)[f]
14	$[Cu(OTf)]_2{\cdot}C_6H_6$	Ag_2CO_3 (1.0)	85 (−/−/−/3)
15	$[Cu(OTf)]_2{\cdot}C_6H_6$	AgOTf (1.0)	61 (−/−/−/2)
16[h]	$[Cu(OTf)]_2{\cdot}C_6H_6$	Ag_2CO_3 (1.0)	87 (−/−/−/4)
17[h,i]	**$[Cu(OTf)]_2{\cdot}C_6H_6$**	**Ag_2CO_3 (1.0)**	**93 (−/−/−/2)**

[a] Reaction conditions: **1a** (0.2 mmol), $[Cu(OTf)]_2{\cdot}C_6H_6$ (0.1 mmol), phen (0.2 mmol), Me_3SiCF_3 (1.0 mmol), KF (1.0 mmol), K_3PO_4 (0.6 mmol), DMF (4 mL), 70 °C, under nitrogen atmosphere. [b] Yield was determined by GC using dodecane as an internal standard. [c] The reaction was conducted under air atmosphere. CuX (X = I, Br, Cl, CN, 0.2 mmol). [d] **3a** was PhI. [e] **3a** was PhBr. [f] **3a** was PhCl. [g] **3a** was PhCN. [h] $[Cu(OTf)]_2.C_6H_6$ (0.12 mmol), phen (0.24 mmol). [i] The reaction was conducted at 45 °C.

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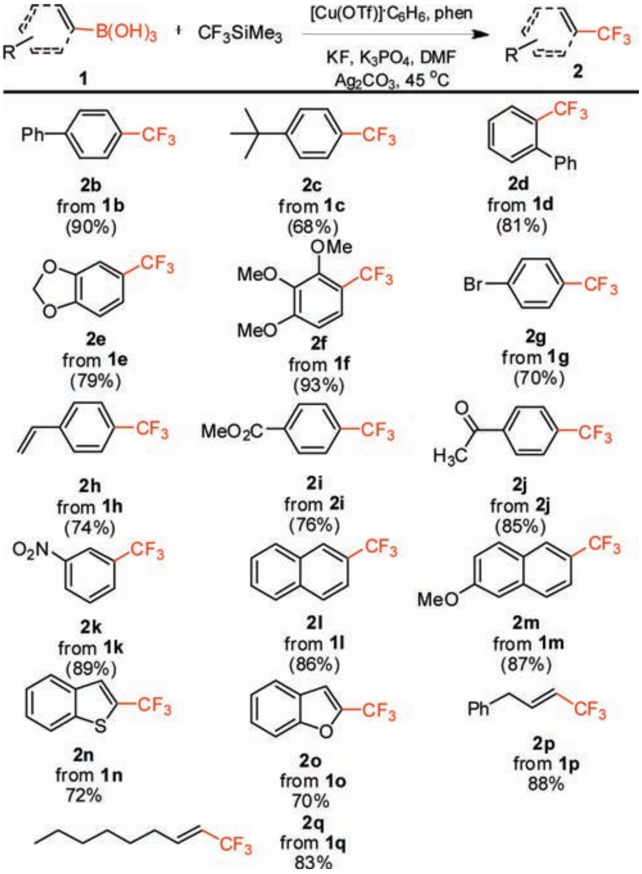
phenol (5% yield), diphenyl ether (11% yield), and biphenyl (2%) (entry 2). To improve the yield of $PhCF_3$, different Cu sources were further screened. Switching CuX (X = I, Br, Cl, CN) salt to nucleophilic ligand free $[Cu(OTf)]_2{\cdot}C_6H_6$, the desired product **2a** was enhanced to 63% yield and the byproduct Ph-X (**3a**) formed in the cases of CuX (X = I, Br, Cl, CN) was not detected, while byproducts phenol (**4a**), PhOPh (**5a**), and PhPh (**6a**) were observed (entries 2−6).[15] We surmised that the byproducts PhOH and PhOPh arose from trace water in the air that was used as the oxidant.[16] To overcome this hurdle, a suitable oxidizing agent instead of air, which enables the late oxidation and followed by reductive elimination and does not inhibit the generation of $CuCF_3$, was chosen. A series of oxidants were screened (entries 7−15), and to our delight, silver carbonate (Ag_2CO_3) displayed the best result for the Cu-mediated oxidative trifluoromethylation (entry 14). A higher yield of **2a** was obtained when the $[Cu(OTf)]_2{\cdot}C_6H_6$ loading was increased to 0.6 equiv (entry 16). Interestingly, further investigations revealed that the reaction was conducted at a lower temperature (45 °C) with the highest yield of **2a** (entry 17). Utimately, optimal reaction conditions were found to be as follows: 0.6 equiv of $[Cu(OTf)]_2.C_6H_5$, 1.2 equiv of phen, 5.0 equiv of CF_3SiMe_3, 5.0 equiv of KF, 3.0 equiv of K_3PO_4, and 1.0 equiv of Ag_2CO_3 in DMF at 45 °C. This afforded a 93% yield of **2a** (entry 17).

The substrate scope of the copper-mediated oxidative coupling reactions of arylboronic acids with in situ generated $CuCF_3$ was examined, and the results are summarized in Scheme 2. The oxidative trifluoromethylation of arylboronic aicds has substantial scope. Both electron-donating (**1b**−**f**,**m**) and electron-withdrawing groups (**1g**−**k**) were tolerated. In contrast to traditional cross-coupling reactions with aryl halides, electron-rich arylboronic acids afforded slightly higher yields compared to electron-deficient substrates. Functional groups such as bromo, alkenyl, ester, and carbonyl groups are compatible (**1g**−**j**). It is particularly noteworthy that the tolerance of a bromo substituent (**1d**) provided a complementary platform for further transformations via conventional copper mediated cross-coupling reactions. The heterocyclic arylboronic acids also served as suitable coupling partners (**1n**−**o**). Importantly, the copper-mediated oxidative trifluoromethylations presented herein has also been easily extended to alkenylboronic acids (**1p**−**q**).

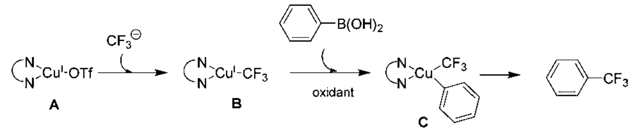
Scheme 2. Oxidative Trifluoromethylation of Aryl- and Alkenylboronic Acids[a]



[a] Reaction was conducted in 0.3 mmol of boronic acid under the optimal condition of entry 17 in Table 1. Isolated yield.

The detailed mechanism remains to be elucidated. On the basis of the previous work of trifluoromethylation of terminal alkynes, it was reasonable to assume that the reaction proceeds by the generation of reactive $CuCF_3$ **B** and followed by transmetalation with arylboronic acid (Scheme 3). The existence of the diamine ligand would stabilize the reactive Cu−CF_3 by chelation and increase electron density on the copper center by coordination to promote the oxidation of complex **C** to Cu(II) or Cu(III) complex,[17] which then undergoes facile reductive elimination to deliver the desired product. However, the mechanism of the formation of Cu(II) or Cu(III) complex from **B** is not clear at the moment.

Scheme 3. Plausible Reaction Pathways for Trifluoromethylation



In summary, we have demonstrated the first copper-mediated oxidative trifluoromethylation of aryl- and alkenylboronic acids with Me_3SiCF_3. The functional group

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tolerance, substrate scope, and mild reaction conditions are the advantages of this process. We expect this method to allow the introduction of trifluoromethyl groups into advanced, highly functionalized organic molecules at the late stage of synthetic chemistry.

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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