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Practical Method for the Cu-Mediated Trifluoromethylation of Arylboronic Acids with CF_3 Radicals Derived from $NaSO_2CF_3$ and *tert*-Butyl Hydroperoxide (TBHP)

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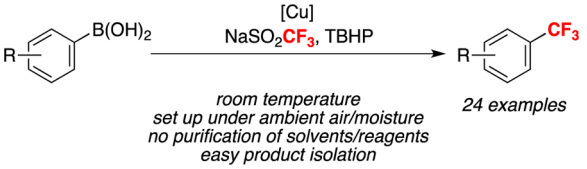
ABSTRACT



A mild and practical protocol for the copper-mediated trifluoromethylation of aryl and heteroaryl boronic acids using $NaSO_2CF_3$ (Langlois' reagent) and TBHP is described. The reaction proceeds at room temperature under ambient conditions, and the products can be readily purified by extraction or column chromatography.

Trifluoromethyl-substituted arenes and heteroarenes are increasingly important structural motifs in pharmaceuticals, agrochemicals, and organic materials.[1] As a result, the development of practical protocols to achieve aromatic trifluoromethylation efficiently, selectively, and cost effectively has been the subject of intense research effort.[2] Over the past 3 years, a variety of Cu-mediated and/or catalyzed methods have been reported for the trifluoromethylation of aryl and heteroaryl boronic acids using "CF_3^-" or "CF_3^+" reagents, including $TMSCF_3$,[3] $K[CF_3B(OMe)_3]$,[4] CF_3H,[5] *S*-(trifluoromethyl)diphenylsulfonium triflate,[6] Togni's reagent,[7] and Umemoto's reagent.[8,9] However, most of these procedures are limited by the requirement for an inert atmosphere and/or dry solvents. Further, the high cost and/or lack of bulk availability of many of these trifluoromethylating reagents limits their usage on a large scale. Finally, these methods commonly lead to competitive formation of protodeboronated byproducts, which are challenging to separate from the desired compounds.

We recently reported the Cu-catalyzed trifluoromethylation of aryl boronic acids with CF_3I in the presence of a

(1) (a) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (d) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (e) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) (a) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (c) Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V.-D. *Tetrahedron* **2011**, *67*, 2161. (d) Wu, X.-F.; Neumann, H.; Beller, M. *Chem.—Asian J.* **2012**, *7*, 1744. (e) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048. (f) Ye, Y.; Sanford, M. S. *Synlett* **2012**, *23*, 2005. (g) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950.

(3) (a) Chu, L.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 5060. (b) Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. *J. Org. Chem.* **2011**, *76*, 1174. (c) Jiang, X.; Chu, L.; Qing, F.-L. *J. Org. Chem.* **2012**, *77*, 1251. (d) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 536.

(4) Khan, B. A.; Buba, A. E.; Gooßen, L. J. *Chem.—Eur. J.* **2012**, *18*, 1577.

(5) Novák, P.; Lishchynskyi, A.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 7767.

(6) Zhang, C.-P.; Cai, J.; Zhou, C.-B.; Wang, X.-P.; Zheng, X.; Gu, Y.-C.; Xiao, J.-C. *Chem. Commun.* **2011**, *47*, 9516.

(7) (a) Liu, T.; Shen, Q. *Org. Lett.* **2011**, *13*, 2342. (b) Liu, T.; Shao, X.; Wu, Y.; Shen, Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 540.

(8) Xu, J.; Luo, D.-F.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Fu, Y.; Liu, L. *Chem. Commun.* **2011**, *47*, 4300.

(9) For an example of fluorobutylation of arylboronic acids with R_FI, see: Qi, Q.; Shen, Q.; Lu, L. *J. Am. Chem. Soc.* **2012**, *134*, 6548.

(10) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034.

(11) (a) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (b) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119. (c) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224.

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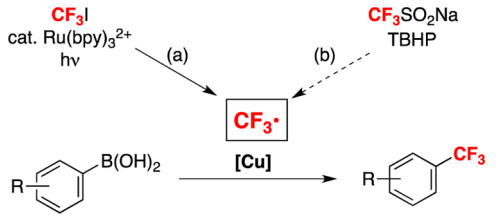
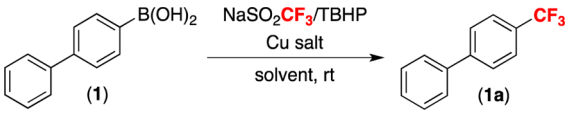
photocatalyst and visible light (Scheme 1a).[10] A key feature of this transformation is the merger of CF_3• (generated via a photocatalysis cycle)[11] with a Cu–aryl intermediate. The high selectivity and mild conditions associated with this process led us to consider more practical potential sources of CF_3• to use in Cu-mediated boronic acid trifluoromethylation. Several reports have shown that the combination of $NaSO_2CF_3$ (Langlois' reagent) and TBHP generates trifluoromethyl radicals at room temperature in the presence of ambient air and moisture.[12,13] This *in situ* generated CF_3• has been shown to react with electron-rich arenes and heterocycles to afford mixtures of isomeric C–H trifluoromethylation products.[12,13] We reasoned that in the presence of a Cu salt, the CF_3• generated from $NaSO_2CF_3$ and TBHP could instead be harnessed to achieve site selective trifluoromethylation of a boronic acid (Scheme 1b). We report herein the feasibility of this approach and the development of a general, mild, and practical protocol for Cu-mediated trifluoromethylation of aryl boronic acids with $NaSO_2CF_3$ and TBHP.

Scheme 1. Cu-Mediated Trifluoromethylation of Aryl Boronic Acids Using *in Situ* Generated CF_3 Radical



Our initial studies focused on the CuOAc-mediated reaction of [1,1′-biphenyl]-4-ylboronic acid (**1**) with $NaSO_2CF_3$ and TBHP at room temperature in DCM/H_2O. With 0.2 equiv of CuOAc, the desired trifluoromethylated product (**1a**) was formed in 18% yield.[14] The yield increased to 47% in the presence of 1 equiv of CuOAc. Optimization of the solvent (to a 5:5:4 mixture of MeOH, DCM and H_2O) resulted in a further increase in yield to 71%.[15] Finally, an extensive evaluation of copper salts revealed that CuCl provides an 80% yield of **1a** on a 0.05 mmol scale.[16] There are several important features of this protocol that highlight its practicality. First, the reactions are all set up on the benchtop, without any purification of commercial solvents and reagents. Second, protodeboronation is not observed under these conditions, and the only detectable byproduct is 4-hydroxybiphenyl. Third, the reaction scales well, proceeding in 85% isolated yield on a 0.5 mmol scale.

Table 1. Optimization of the Trifluoromethylation of **1**[a]

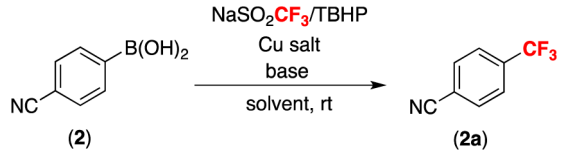


entry	copper salt	solvent	yield[b]
1[c,d]	CuOAc	DCM/H_2O	18%
2[d]	CuOAc	DCM/H_2O	47%
3[d]	CuOAc	MeOH/H_2O	60%
4[e]	CuOAc	MeOH/DCM/H_2O	71%
5[e]	CuCl	MeOH/DCM/H_2O	80%
6[e]	–	MeOH/DCM/H_2O	<1%

[a] General conditions: substrate **1** (1 equiv, 0.05 mmol), [Cu] (1 equiv), $NaSO_2CF_3$ (3 equiv), TBHP (5 equiv) at 23 °C for 12 h. [b] Yields determined by ^{19}F NMR analysis. [c] 0.2 equiv of CuOAc. [d] Solvent ratio = 5:2. [e] Solvent ratio = 5:5:4.

While electron-neutral and -rich boronic acids underwent trifluoromethylation in excellent yields under the optimal conditions from Table 1 (*vide infra*), several electron-deficient derivatives did not. For example, (4-cyanophenyl)-boronic acid (**2**) reacted to afford **2a** in only 36% yield (Table 2). We reasoned that the lower yield might be due to slower transmetalation of the electron-deficient boronic acid. Consistent with this proposal, the addition of 1 equiv of $NaHCO_3$ (which is expected to accelerate transmetalation) led to an increase in yield to 46%. Further evaluation of different Cu sources showed that the substitution of CuCl with $(MeCN)_4CuPF_6$ resulted in the best yield of **2a** (59%).

Table 2. Optimization for Electron-Poor Boronic Acids[a]



entry	copper salt	base	yield[b]
1[c]	CuCl	–	36%
2[c]	CuCl	$NaHCO_3$	46%
3[d]	$(MeCN)_4CuPF_6$	–	42%
4[d,e]	$(MeCN)_4CuPF_6$	–	38%
5[d]	$(MeCN)_4CuPF_6$	$NaHCO_3$	49%
6[d,e]	$(MeCN)_4CuPF_6$	$NaHCO_3$	59%

[a] General conditions: substrate **2** (1 equiv, 0.05 mmol), [Cu] (1 equiv), base (1 equiv), $NaSO_2CF_3$ (3 equiv), TBHP (5 equiv) at 23 °C for 12 h. [b] Yields determined by ^{19}F NMR analysis. [c] Solvent = MeOH/DCM/H_2O (5:5:4 ratio). [d] Solvent = MeOH. [e] 4 equiv of TBHP.

With these two sets of conditions in hand, we next explored the full substrate scope of Cu-mediated

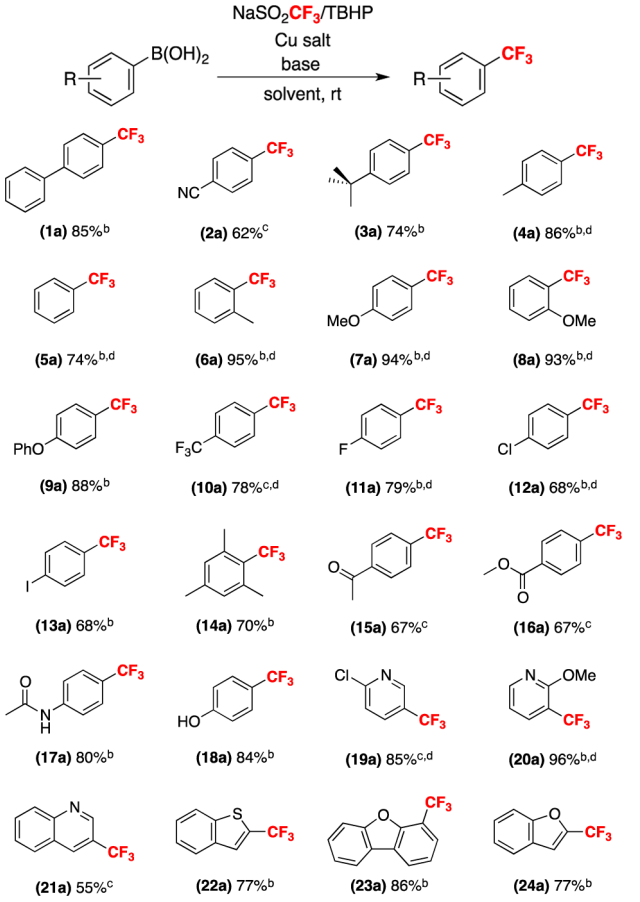
(12) Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1991**, *32*, 7525.
(13) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411.
(14) When substoichiometric Cu was used under these conditions, the major side product was the corresponding phenol (derived from substitution of the C–B bond with a C–OH bond).
(15) See Supporting Information for full optimization details.
(16) Notably, less than 1% of the trifluoromethylated product **1a** was observed when CuOAc was excluded from the optimal conditions.

trifluoromethylation with $NaSO_2CF_3$ and TBHP. As shown in Scheme 2, arenes bearing electron-donating alkyl, alkoxy, or phenoxy substituents reacted in excellent yield under the CuCl-mediated conditions (conditions a). Trifluoromethylation of electron-deficient substrates (eg, cyano, trifluoromethyl, and carbonyl-substituted aryl boronic acids) afforded the desired trifluoromethylated products in good to excellent yield in the presence of $(MeCN)_4CuPF_6$ and $NaHCO_3$ (conditions b).[17] Interestingly, the reaction of (4-iodophenyl)boronic acid resulted in exclusive trifluoromethylation of the C−B bond, leaving the C−I linkage intact. Sterically hindered boronic acid derivatives, which are generally challenging substrates for Cu-mediated cross-couplings,[18] afforded good to excellent yields in this transformation (cf., products **6a**, **8a**, **14a**, **20a**, and **23a**). Moreover, the reaction is compatible with diverse functional groups, including enolizable ketones, esters, amides, and phenols. Finally, heteroaryl boronic acids based on pyridine, quinoline, thiophene, and furan afforded moderate to excellent yields. Notably, trifluoromethylation of the C−B bond outcompeted free radical C−H trifluoromethylation in all of these substrates.

As noted above, most previously reported boronic acid trifluoromethylation protocols employ inert atmosphere conditions and dry solvents. Even under these controlled conditions, significant quantities (2−10%) of protodeboronated products are commonly observed and are very challenging to separate and purify from the desired Aryl−CF_3 products. In contrast, all of the trifluoromethylation reactions in Scheme 2 were insensitive to ambient air and moisture and were set up on the benchtop without purification of commercial reagents or solvents. Despite the presence of water, protodeboronation of the boronic acid was not detected under these conditions. This makes product isolation extremely straightforward, as the major side product (the corresponding hydroxylated arene) is readily removable by extraction or column chromatography.

In conclusion, this paper describes a practical copper-mediated trifluoromethylation of a variety of aryl and heteroaryl boronic acids using readily available $NaSO_2CF_3$ and TBHP. These reagents are believed to react *in situ* to generate CF_3• as the active trifluoromethylating reagent. The reactions are easy to set up under ambient conditions, and product purification is similarly straightforward. As a result, this protocol represents a significant synthetic advance for the selective preparation of trifluoromethylated compounds.

Scheme 2. Substrate Scope of Copper-Mediated Trifluoromethylation of Aryl Boronic Acids[a]



[a] Isolated yield. [b] Reaction conditions: substrate (1 equiv, 0.5 mmol), CuCl (1 equiv), $NaSO_2CF_3$ (3 equiv), TBHP (5 equiv) in DCM/MeOH/H_2O (5:5:4 ratio) at 23 °C for 12 h. [c] Reaction conditions: substrate (1 equiv), $(MeCN)_4CuPF_6$ (1 equiv), $NaSO_2CF_3$ (3 equiv), $NaHCO_3$ (1 equiv), TBHP (4 equiv) in MeOH at 23 °C for 12 h. [d] Yields determined by ^{19}F NMR analysis.

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Supporting Information Available. Experimental and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(17) For products **15a** and **16a**, the isolated material contained ~4% of the corresponding chloroarene as an inseparable byproduct. Elemental analysis of all of the reagents showed that the chlorine is an impurity in the $NaSO_2CF_3$. See Supporting Information for complete details.

(18) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.