Published in final edited form as:
J Org Chem. 2011 February 18; 76(4): 1174–1176. doi:10.1021/jo1023377.

Room Temperature Aryl Trifluoromethylation via Copper-Mediated Oxidative Cross-Coupling

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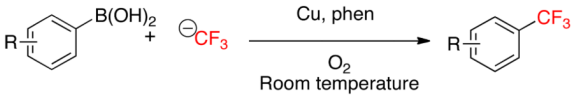
Abstract



A method for the room temperature copper-mediated trifluoromethylation of aryl and heteroaryl boronic acids has been developed. This protocol is amenable to normal benchtop setup and reactions typically require only 1–4 hours. Proceeding under mild conditions, the method tolerates a range of functional groups, allowing access to a variety of trifluoromethylarenes.

The development of methods for the construction of organofluorine compounds is of great importance due to the presence of fluorine in 20% of pharmaceuticals and 30% of agrochemicals that are currently on the market.1 In particular, the benzotrifluoride group is present in several top-selling pharmaceuticals, including Januvia® (Sitagliptin), Celebrex® (Celecoxib), Prozac® (Fluoxetine), and Avodart® (Dutasteride). While trifluoromethyl groups possess many desirable characteristics such as electron-withdrawing character, high lipophilicity, and excellent metabolic stability,2 their installation is often far from routine.

Traditionally, benzotrifluorides are formed through treatment of benzotrichlorides with HF and/or metal fluorides such as SbF_5 (Swarts reaction),3 conditions that are typically unsuitable for functionalized late-stage intermediates. Transition metal-mediated cross-coupling offers the potential for mild conditions. Nevertheless, progress has been hampered by the inherent instability of the trifluoromethyl anion4 and reluctance of the metal center to undergo reductive elimination to afford trifluoromethylarenes.5 Despite these challenges, recent reports from Grushin,6a Sanford,6b,c Yu,7 and our own group8 have demonstrated the use of Pd catalysts for the trifluoromethylation of aromatic substrates. While these represent important achievements in trifluoromethylarene synthesis, significant limitations of these Pd-based methods remain (e.g., generality, user friendliness, cost). Thus we decided to also investigate copper-mediated processes.

While there are few reports of palladium-mediated trifluoromethylation protocols, copper-mediated processes have been studied extensively. Pioneering investigations by Burton shed light on the instability and complexity of [Cu-CF_3].9 Matsui's use of trifluoroacetate salts10 and Chen's methyl fluorosulphonyldifluoroacetate11 have been shown to be attractive sources of trifluoromethyl anion for copper-mediated couplings with aryl iodides. Schlosser's trifluoromethylation of pyridine iodides proceeds at room temperature, but to

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Supporting Information Available: Detailed reaction protocols as well as spectral data of all products is available free of charge via http://pubs.acs.org.

date its substrate scope is narrow.12 Vicic illustrated the ability of ligands to stabilize [Cu-CF_3].13 This concept was further expanded upon in an important paper by Amii that disclosed the first copper-catalyzed trifluoromethylation process of aryl iodides.14 As is the case with many copper-based cross-coupling reactions, these techniques are applicable to aryl iodides or activated aryl bromides, providing complementary reactivity to palladium-based systems. While substantial progress has been made, the development of alternate copper-mediated trifluoromethylations remains an attractive goal.

Recently, Qing reported a method for the copper-mediated oxidative trifluoromethylation of alkynes.15 Analogous to this transformation, we postulated that a copper-mediated oxidative coupling could be used to access benzotrifluorides. One of the most notable copper-promoted oxidative couplings is the Chan-Lam reaction,16 where an aryl boronic acid is coupled with an amine or alcohol, typically at room temperature. The mild conditions of a Chan-Lam-type coupling would be an advantage relative to those employed in the methods currently available for benzotrifluoride synthesis. Due to its potential utility, we began investigating the development of a system for the room temperature oxidative trifluoromethylation of aryl boronic acids (Figure 1).

During the preparation of this manuscript, Qing described the first oxidative trifluoromethylation of aryl and vinyl boronic acids to afford the C_{sp2}—CF_3 products in high yields.17 While a notable achievement, this method requires use of a nitrogen-filled glove box, highly air-sensitive $[Cu(OTf)]_2•C_6H_6$, 5 equivalents of trifluoromethyltrimethylsilane ($TMSCF_3$), the slow addition of the boronic acid substrate, and use of superstoichiometric quantities of Ag_2CO_3 as the reoxidant. Herein, we report a complementary method for the oxidative trifluoromethylation of aryl and heteroaryl boronic acids that ameliorates many of these limitations and provides a useful means to prepare benzotrifluorides.

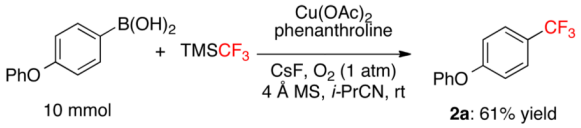
We commenced our studies by examining the trifluoromethylation of 4-phenoxyphenylboronic acid under typical Chan-Lam-type conditions. Using one equivalent of $Cu(OAc)_2$, 2.2 equivalents of NEt_3, and $TMSCF_3$ as the trifluoromethylating reagent in an atmosphere of air, 5% of benzotrifluoride product was observed (Table 1, entry 1). In accord with a bevy of literature precedent for copper-mediated aryl trifluoromethylation reactions,14،15،17 addition of 1,10-phenanthroline as a ligand substantially increased the yield of **2a** to 45% (Table 1, entry 2). In addition to the desired product, a significant amount of arene **1** (24%), via protodeboronation, was formed. Switching to an atmosphere of dry oxygen resulted in substantially less arene formation (1%) and increased the yield of the desired product to 71% (Table 1, entry 3). The use of oxygen as the stoichiometric reoxidant has obvious advantges in terms of efficiency and cost relative to the use of Ag_2CO_3. An examination of different copper sources revealed that the use of Cu halides resulted in the formation of significant quantities of aryl halide by-product **3** (Table 1, entry 4). Even when using a copper source without a halide counterion [*e.g.*, $Cu(OAc)_2$], a 5% yield of aryl chloride was still observed, presumably due to halide transfer from the dichloroethane solvent. As the separation of aryl chloride by-products from the desired trifluoromethylarenes was problematic, we explored the use of a variety of non-chlorinated solvents. Of these, isobutyronitrile (*i*-PrCN) proved best, providing a 67% yield of benzotrifluoride product with no observed products of protodeboronation or chlorination (Table 1, entry 10).18

With optimal conditions in hand, we investigated the scope of this transformation (Table 2). Electron-rich and -deficient aryl boronic acids can be trifluoromethylated in moderate to good yields on both 1 mmol (Table 2) and 10 mmol scales (eq 1). Arenes bearing substitution in the *ortho* position (**2d, 2e, 2l, 2n, 2o**) are typically difficult substrates from copper-mediated cross-coupling processes.19 Thus, we were pleased that these substrates

provided the corresponding trifluoromethyl arenes in good yield. We note that in some cases (**2e**), biaryl formation via oxidative homocoupling of the aryl boronic acids is seen as a by-product.

Five- and six-membered heteroaryl boronic acids can also be trifluoromethylated. Whereas unprotected indoles gave poor results20, both *N*-methyl (**2j**) and *N*-Boc (**2n**) indoles were competent substrates. It should be noted that since five-membered heteroaryl boronic acids substituted at the 2-position are more prone to protodeboronation,21 ~10–20% heteroarene is also observed.

In contrast to other methods for benzotrifluoride synthesis, the mild conditions of this method provide a high level of functional group tolerance. While aromatic iodides are not compatible with the method, boronic acids bearing chloro (**2c**) or bromo (**2d**) groups are acceptable substrates, providing convenient handles for subsequent functionalization processes. Substrates containing aldehydes or ketones are problematic for many trifluoromethylation methods. This is due to their tendency to undergo competitive 1,2-addition of the trifluoromethyl anion to yield α-trifluoromethyl alcohols.22 While substrates bearing aldehyde moieties were not viable for our method, a boronic acid bearing a methyl ketone chemoselectively provided the trifluoromethylarene (**2f**). Although silyl protecting groups are ubiquitous in organic synthesis, high reaction temperatures in conjunction with fluoride activators have prevented their use in trifluoromethylation chemistry. The mild conditions of our method allows for the efficient trifluoromethylation of boronic acids containing a *tert*-butyldimethylsilyl-protected phenol (**2g**) and an *N*-triisopropylsilyl-protected pyrrole (**2k**).



(1)

In summary, we have developed a room temperature method for the oxidative trifluoromethylation of aryl and heteroaryl boronic acids. The mild reaction conditions allow for high functional group compatibility previously unseen in trifluoromethylation chemistry. Moreover, the ability to conduct the reaction under typical benchtop conditions and the use of oxygen as the stoichiometric reoxidant will make this method of use to medicinal and academic chemists.

Experimental Section

General procedure for the oxidative trifluoromethylation of aryl boronic acids

To a test tube equipped with a magnetic stir bar was added 250 mg 4Å powdered molecular sieves and cesium fluoride (304 mg, 2.0 mmol, 2.0 equiv). The vessel was sealed with a Teflon-lined septum, evacuated, and flame dried under vacuum until the sieves were fully activated. The test tube was allowed to cool to room temperature, after which it was backfilled with argon. To a separate vial was added 1,10-phenanthroline (198 mg, 1.1 mmol, 1.1 equiv), copper(II) acetate (181 mg, 1.0 mmol, 1.0 equiv), and aryl boronic acid (1.0 mmol, 1.0 equiv). The vessel was fitted with a Teflon-lined septum and subsequently purged with argon. The contents of the vial containing the copper(II) acetate, 1,10-phenanthroline, and aryl boronic were quickly added to the test tube containing the sieves and cesium fluoride. The test tube containing all solid reagents was then evacuated and backfilled with

oxygen gas (via balloon fitted with a syringe and needle)--this sequence was repeated a total of three times. Solvent (5 mL) and $TMSCF_3$ (0.3 mL, 2.0 mmol, 2.0 equiv) were then added to the reaction tube via syringe, which was then placed under a balloon of O_2 and was stirred vigorously for the specified time. After the reaction was complete, the reaction was filtered through a plug of celite on silica and eluted with diethyl ether (50 mL). 4-Fluorotoluene (330 μL, 3 mmol) was added as an internal standard, and the yield of the crude reaction was measured via ^{19}F NMR. The solution was then pre-adsorbed onto silica, dried *in vacuo*, and purified via silica gel column chromatography to yield the benzotrifluoride product. A representative example is as follows.

1-Phenoxy-4-(trifluoromethyl)benzene (2a)

Following the general procedure with 214 mg of 4-phenoxyphenylboronic acid and isobutyronitrile as the solvent. The reaction was complete after stirring for 1 h and the product was purified by column chromatography (silica gel, hexanes, visualized with UV and $KMnO_4$) to yield 1-phenoxy-4-(trifluoromethyl)benzene as a colorless oil. (161 mg, 68%). **^{1}H NMR (300 MHz, $CDCl_3$)**: δ 7.66 – 7.55 (m, 2H), 7.48 – 7.36 (m, 2H), 7.25 – 7.17 (m, 1H), 7.12 – 7.02 (m, 4H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 160.7 (q, *J* = 1.4 Hz), 155.9, 130.3, 127.3 (q, *J* = 3.7 Hz), 125.0 (q, *J* = 32.7 Hz), 124.7 (s), 124.4 (q, *J* = 269.8 Hz), 120.2, 118.1. Complexity of ^{1}H and ^{13}C NMR spectra is due to ^{19}F coupling. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ −62.22. **IR (neat, cm^{-1})**: 3066, 3043, 1618, 1591, 1514, 1491, 1247, 1168, 1123, 1066.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health for financial support of this project (Grant GM-46059). T. S. thanks EMD Serono and the Martin Family Society of Fellows for Sustainability for graduate fellowships. A.P. is a Ruth L. Kirschstein Postdoctoral Fellow of the National Institutes of Health (Grant 1F32GM093532) for which he is grateful. The 300 MHz NMR instrument used was supported by the National Science Foundation (NSF, Grants CHE-9808061 and DBI-9729592).

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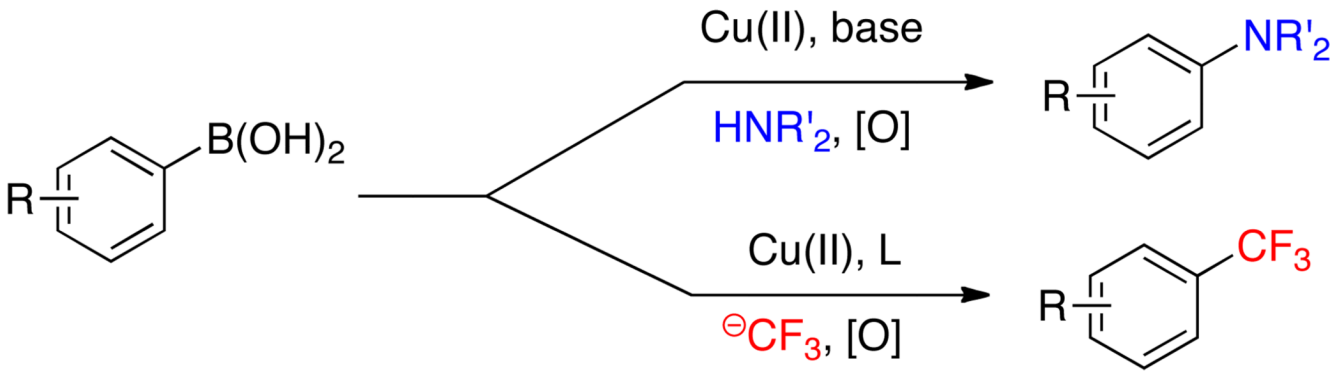
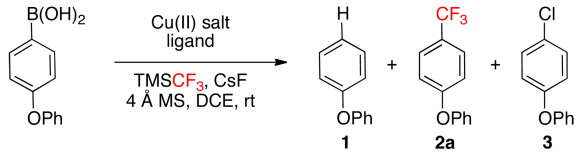


Figure 1.
Chan-Lam coupling (top) and proposed oxidative aryl trifluoromethylation (bottom).

Table 1

Optimization of the Copper-Mediated Oxidative Trifluoromethylation of Aryl Boronic Acids[a,b]



Entry	Cu Source	Ligand	Atmosphere	1	2a	3
1	$Cu(OAc)_2$	NEt_3[c]	air	42%	5%	0%
2	$Cu(OAc)_2$	1,10-phen	air	24%	45%	0%
3	$Cu(OAc)_2$	1,10-phen	O_2	1%	71%	5%
4	$CuCl_2$	1,10-phen	O_2	1%	24%	32%
5[d]	$Cu(OAc)_2$	1,10-phen	O_2	58%	21%	0%
6	$Cu(OAc)_2$	1,10-phen	N_2	30%	20%	0%
7	None	1,10-phen	O_2	5%	0%	0%
8[e]	$Cu(OAc)_2$	1,10-phen	O_2	7%	60%	4%
9[f]	$Cu(OAc)_2$	1,10-phen	O_2	34%	11%	2%
10[g]	$Cu(OAc)_2$	1,10-phen	O_2	0%	67%[h]	0%

[a] Reactions conditions: $ArB(OH)_2$ (1 mmol), $Cu(OAc)_2$ (1 mmol), ligand (1.1 mmol), $TMSCF_3$ (2 mmol), CsF (2 mmol), 4 Å mol sieves (250 mg), 5 mL 1,2-dichloroethane (DCE), 1 atm air, O_2 or N_2.

[b] Yields determined by gas chromatography using dodecane as an internal standard.

[c] 2.2 equiv

[d] T = 60 °C.

[e] No 4 Å mol sieves.

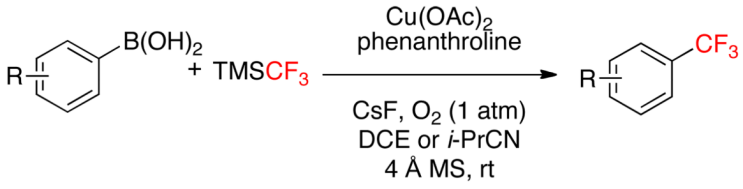
[f] No 4 Å mol sieves, 5 equiv H_2O.

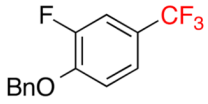
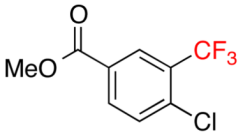
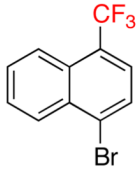
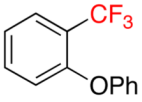
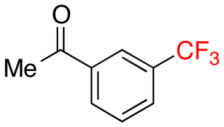
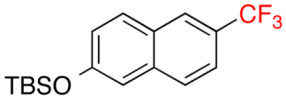
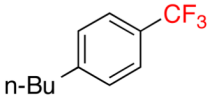
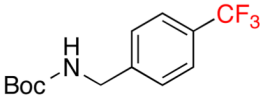
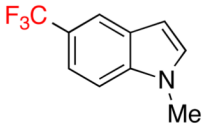
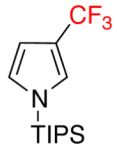
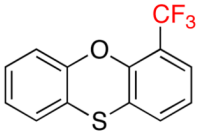
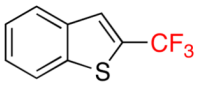
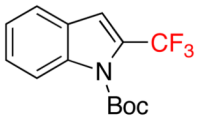
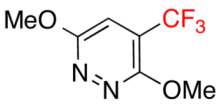
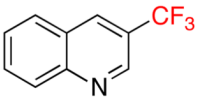
[g] Solvent = *i*-PrCN.

[h] Benchtop setup, isolated yield, average of 2 runs.

Table 2

Oxidative Trifluoromethylation of Aryl and Heteroaryl Boronic Acids[a,b]



 *i*-PrCN, 3 h **2b**: 68%	 *i*-PrCN, 3 h **2c**: 67%	 *i*-PrCN, 2 h **2d**: 60%
 *i*-PrCN, 1 h **2e**: 46%	 *i*-PrCN, 3 h **2f**: 58%	 *i*-PrCN, 3 h **2g**: 55%
 *i*-PrCN, 3 h **2h**: 54%	 *i*-PrCN, 3 h **2i**: 34%	 *i*-PrCN, 4 h **2j**: 44% (68%)[c]
 DCE, 3 h **2k**: 48%	 DCE, 1 h **2l**: 64%	 DCE, 1 h **2m**: 45%
 DCE, 1 h **2n**: 61%	 DCE, 4 h **2o**: 53%	 *i*-PrCN, 3 h **2p**: 38% (61%)[c]

[a] Reaction conditions: $ArB(OH)_2$ (1 mmol), $Cu(OAc)_2$ (1 mmol), 1,10-phenanthroline (1.1 mmol), $TMSCF_3$ (2 mmol), CsF (2 mmol), 4 Å mol sieves (250 mg/mmol $ArB(OH)_2$), solvent (5 mL/mmol $ArB(OH)_2$).

[b] Isolated yields; average of 2 runs.

[c] ^{19}F NMR yield, average of 2 runs using DCE as the solvent; chromatographically inseperable from 5–10% aryl chloride byproduct.