

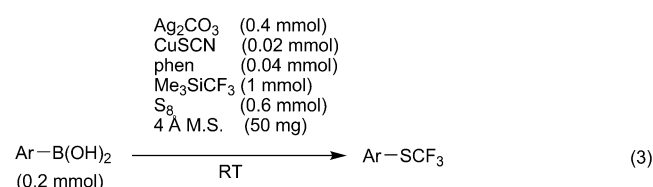
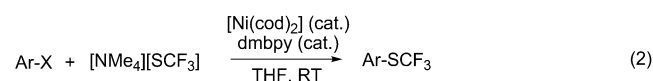
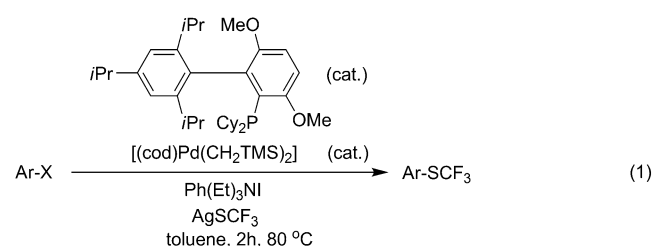
Oxidative Trifluoromethylthiolations of Aryl Boronic Acids Using a Copper/ O_2 -Based Protocol

Cheng-Pan Zhang and David A. Vici^{*[a]}

The development of new protocols to prepare perfluoroalkyl sulfides is of growing synthetic interest.^[1] Carbon–sulfur bonds are prevalent in medicinally and agriculturally relevant molecules,^[2] and fluorination provides additional functionality unique from the non-fluorinated forms.^[1a,3] One motivation for the synthesis of perfluoroalkyl sulfides is the high lipophilicities of these derivatives. The SCF_3 functional group, for instance, has one of the highest Hansch lipophilicity parameters for its size ($\pi=1.44$ ^[4]), which makes it an appealing functional group to incorporate into new library syntheses. Traditional methods to form perfluoroalkyl sulfides have involved, among other methods, substitution of perchloroalkyl sulfides with fluoride sources,^[5] UV irradiation of thiophenols or disulfides with perfluoroalkyl iodides in liquid ammonia,^[6] and perfluoroalkylation of thiols using hypervalent iodine sources.^[7]

It has recently been shown that, in addition to the aforementioned classical methods, Group 10 metals can mediate trifluoromethylthiolations by cross-coupling aryl halides under quite mild conditions.^[1b,c] Buchwald and co-workers found that a Brettphos-ligated palladium complex can convert aryl bromides and iodides into aryl trifluoromethyl sulfides at 80 °C using $AgSCF_3$ as the nucleophilic partner [Eq. (1); Cy = cyclohexyl, cod = 1,5-cyclooctadiene, TMS = trimethylsilyl].^[1b] Vici and co-workers found that the same substrates undergo trifluoromethylthiolations at room temperature using the less expensive and more conveniently prepared $[NMe_4][SCF_3]$ nucleophile in combination with an earth-abundant nickel bipyridine catalyst [Eq. (2); dmbpy = 4,4'-dimethyl-2,2'-bipyridine].^[1c] Both of these protocols represent significant advances to earlier known methods used to prepare aryl trifluoromethyl sulfides.^[1a] However, neither protocol was successful in the trifluoromethylthiolation of aryl chlorides. Since aryl chlorides can be catalytically converted to aryl boronic acids,^[8] we imagined that a copper-catalyzed oxidative trifluoromethylthiolation reaction might be an alternative approach to the formation of aryl trifluor-

omethyl sulfides from substrates that could ultimately originate from aryl chlorides. Indeed, in the course of preparing this manuscript, Qing and co-workers showed that $CuSCN$ mediates such a reaction [Eq. (3)].^[1d] Qing's method allows for the coupling of a variety of aryl boronic acids bearing additional functionality on the aryl groups, and proceeds under relatively mild conditions. Although the protocol outlined in Equation (3) employs the use of a catalytic amount (10%) of $CuSCN$, four mole equivalents of silver atoms are required relative to the boronic acid for high conversions. Additionally, a fivefold excess of the costly Me_3SiCF_3 was also employed. Here, we present our own efforts to develop copper-catalyzed oxidative trifluoromethylthiolations, and offer a complementary protocol to that shown in Equation (3) which does not require the use of silver salts or large excesses of Me_3SiCF_3 in the presence of the organic coupling substrate.

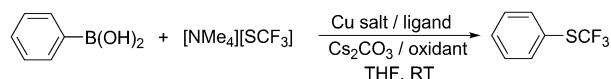


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Our initial search for conditions that could promote oxidative trifluoromethylthiolations is presented in Table 1. When excess copper(II) salts are used in the absence of any additional oxidant, high yields of cross-coupled product could be observed (Table 1, entry 1). However, low yields of

Table 1. Identifying optimal conditions for copper-mediated trifluoromethylthiolation of aryl boronic acids.^[a]



Entry	Cu salt ([Cu])	Ligand (L)	Oxidant	ArB(OH) ₂ : [SCF ₃]: [Cu]:L:Cs ₂ CO ₃	Yield [%] ^[b]
1	Cu(OTf) ₂	dtbpy	–	1:2.4:2:2:1.2	90
2 ^[c]	Cu(OTf) ₂	dtbpy	–	1:1:1:1:1.2	37
3	CuOTf	dtbpy	–	1:1:1:1:1.2	trace
4	Cu(OTf) ₂	dtbpy	air	1:1.3:1:1:1.2	91
5	Cu(OTf) ₂	dtbpy	air	1:1:0.5:0.5:1.2	49
6	Cu(OTf) ₂	dtbpy	air	1:1:0.3:0.3:1.2	trace
7	CuCl ₂	dtbpy	air	1:1:1:1:1.2	20
8	Cu(OAc) ₂	dtbpy	air	1:1:1:1:1.2	0
9	CuO	dtbpy	air	1:1:1:1:1.2	0
10	Cu(acac) ₂	dtbpy	air	1:1:1:1:1.2	0
11 ^[d]	Cu(OTf) ₂	dtbpy	BQ	1:1:1:1:1.2	59
12 ^[d]	Cu(OTf) ₂	dtbpy	DDQ	1:1:1:1:1.2	0
13 ^[d]	Cu(OTf) ₂	dtbpy	(<i>t</i> BuO) ₂	1:1:1:1:1.2	50
14	Cu(OTf) ₂	^{OMe} bpy	air	1:1:1:1:1.2	75
15	Cu(OTf) ₂	bpy	air	1:1:1:1:1.2	73
16	Cu(OTf) ₂	phen	air	1:1:1:1:1.2	34
17	Cu(OTf) ₂	terpy	air	1:1:1:1:1.2	0
18	Cu(OTf) ₂	dmbpy	air	1:1:1:1:1.2	68
19	Cu(OTf) ₂	^{6Me} bpy	air	1:1:1:1:1.2	60
20	Cu(OTf) ₂	^{6,6Me} bpy	air	1:1:1:1:1.2	18
21	Cu(OTf) ₂	dtbpy	O ₂	1:1:0.5:0.5:1.2	61
22	Cu(OTf) ₂	dtbpy	O ₂	1:1:0.4:0.4:1.2	47
23	Cu(OTf) ₂	dtbpy	O ₂	1:1:0.3:0.3:1.2	6
24	CuOTf	dtbpy	O ₂	1:1:1:1:1.2	43

[a] All the reactions were run on 0.1 mmol scale in 4 mL of dry THF for 15 h. Abbreviations: OTf = CF₃SO₃, OAc = acetate, acac = acetylacetonate, dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine, ^{OMe}bpy = 4,4'-dimethoxy-2,2'-bipyridine, bpy = 2,2'-bipyridine, phen = 1,10-phenanthroline, terpy = 2',2':6,2''-terpyridine, dmbpy = 4,4'-dimethyl-2,2'-bipyridine, ^{6Me}bpy = 6-methyl-2,2'-bipyridine, ^{6,6Me}bpy = 6,6'-dimethyl-2,2'-bipyridine, BQ = 1,4-benzoquinone, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. [b] The yields were determined by ¹⁹F NMR spectroscopy using PhCF₃ as internal standard. [c] The same yields were obtained in DMF and THF. [d] Two equivalents of the oxidants were employed.

product are obtained when the amount of copper(II) salt is scaled back to stoichiometric amounts (Table 1, entry 2), suggesting that in entry 1 the copper is serving as both a catalyst and as an oxidant. Upon optimizing the reaction for amounts of reagents, ligand type, and oxidant type, the optimal conditions ultimately proved to be those in Table 1, entry 4. We note that simple ambient air was gratifyingly observed to be the best oxidant for the coupling reaction. Interestingly, the phenanthroline ligand, which was effective in the oxidative trifluoromethylthiolations involving silver oxidants,^[1d] was less effective than bipyridine ligands for the reactions carried out under aerobic conditions (Table 1, entries 4 versus 16).

With the optimized conditions in hand, we then set out to explore the scope of the copper-mediated aerobic trifluoromethylthiolations. Table 2 describes the effectiveness of the protocol with a variety of aryl and heteroaryl boronic acids. Both electron-poor and electron-donating aryl boronic acids gave high yields of products (Table 2, entries 1–6, 9), with the electron-withdrawing arenes slightly outperforming the electron-donating ones. This reactivity contrasts the nickel-mediated cross-coupling chemistry, in which electron-rich aryl halides provided the highest yields of cross-coupled pro-

duct.^[1c] Sulfur- and oxygen-containing heterocycles were also reactive towards the oxidative couplings (Table 2, entries 7 and 8). As was observed in our screening conditions, the coupling reactions will indeed take place under a nitrogen atmosphere, as long as excess oxidant is present (Table 2, entry 9),

Finally, we set out to explore if the conditions could also be used to couple vinyl boronic acids. Table 3 describes the preliminary results of this study. Both alkyl- and aryl-substituted vinyl boronic acids could be converted to trifluoromethylthioethers, however the vinyl substrate bearing the chlorine-substituted aryl group (Table 3, entries 4 and 5) gave poor yields. Substitution of air with dioxygen (Table 3, entry 3) improved the yield of the biphenyl-substituted vinyl trifluoromethylthioether substantially. Of all the vinyl groups tested, the cyclohexyl-substituted one afforded the best yields with the standard protocol. To our knowledge, the data shown in Table 3 represents the first time that successful trifluoromethylthiolation of vinyl boronic acids has been reported.

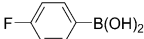
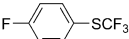

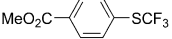
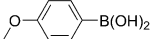
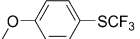
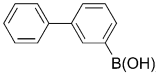
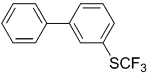

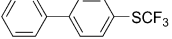
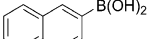
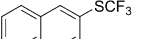
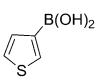

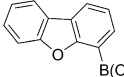
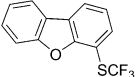

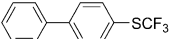
In conclusion, we present here a new protocol which could oxidatively couple [NMe₄][SCF₃] with boronic acids to afford aryl- and vinyl-SCF₃ products. There is a significant advantage of the current conditions over those previously reported in that no silver oxidants are required and simple air can be used as the oxidant. With the absence of any known procedure to form aryl trifluoromethyl sulfides directly from aryl chlorides, this method provides a work-around to obtain the desired SCF₃ products from intermediate aryl boronic acids.

Experimental Section

General Procedure for the Oxidative Trifluoromethylthiolations

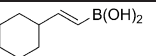
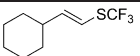
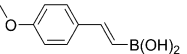
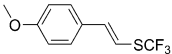
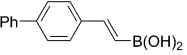
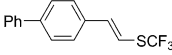
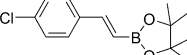
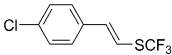
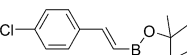
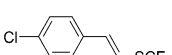
Example for Table 2, entry 4: Biphenyl-3-ylboronic acid (40 mg, 0.2 mmol), [NMe₄][SCF₃] (48 mg, 0.26 mmol), Cu(OTf)₂ (72 mg, 0.2 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (55 mg, 0.2 mmol), and Cs₂CO₃ (80 mg, 0.25 mmol) were added into THF (6 mL) and taken out from a glovebox. Dry air was introduced. The mixture was stirred at room temperature overnight. Then Et₂O (50 mL) and H₂O (50 mL) were added. The ether layer was separated, washed with H₂O (3 × 30 mL), dried over anhydrous Na₂SO₄, and evaporated under reduced pressure.

Table 2. Copper-mediated trifluoromethylthiolation of aryl boronic acids at room temperature.^[a]

Entry	ArB(OH) ₂	ArSCF ₃	Yield [%] ^[b]
1			91
2			93 (91)
3			75 (73)
4			89 (81)
5			88 (85)
6			80 (70)
7			73
8			71 (67)
9 ^[c]			91 (83)

[a] Reactions were run on 0.2 mmol scale in 6 mL THF, except entries 1, 7, and 9 (0.1 mmol scale in 4 mL THF). 1.3 equivalents [NMe₄][SCF₃] relative to ArB(OH)₂ was employed except entry 9. [b] The yields were determined by ¹⁹F NMR spectra using PhCF₃ as internal standard. Yields of isolated product are given in parentheses. [c] 2.4 equivalents [NMe₄][SCF₃], 1.2 equivalent Cs₂CO₃, and two equivalents Cu(OTf)₂ and dtbpy were employed in this reaction. The reaction was conducted at room temperature overnight in N₂ atmosphere. The excessive Cu(OTf)₂ itself was used as the oxidant.

Table 3. Copper-mediated trifluoromethylthiolation of vinyl boronic acids at room temperature.^[a]

Entry	ArB(OH) ₂	ArSCF ₃	Yield [%] ^[b]
1			70
2			57
3			52, 74 ^[c]
4			16
5 ^[d]			33

[a] All the reactions were run on 0.2 mmol scale in 6 mL THF. 1.3 equivalents [NMe₄][SCF₃] relative to ArB(OH)₂ was employed. [b] The yields were determined by ¹⁹F NMR spectra using PhCF₃ as internal standard. Yields of isolated products are given in parentheses. [c] Oxygen was employed instead of air. [d] The reaction was run at 50 °C.

The crude product was purified by flash chromatography column to give 41 mg of the desired product (0.16 mmol, 81 %).

Acknowledgements

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Keywords: copper • cross-coupling • fluorine • sulfur

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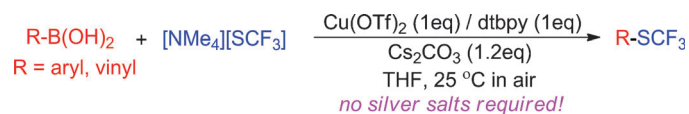
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COMMUNICATION

Cross-Coupling

Cheng-Pan Zhang,
David A. Vicic* ————— ■■■■—■■■■

Oxidative Trifluoromethylthiolations of Aryl Boronic Acids Using a Copper/O₂-Based Protocol



All you need is air: A new protocol has been developed which can mediate the coupling of aryl and vinyl boronic acids at room temperature in high yields (see scheme, dtbpy = 4,4'-di-*tert*-

butyl-2,2'-bipyridine). The reactions take place using simple copper(II) salts under aerobic conditions and do not require the use of expensive silver oxidants.