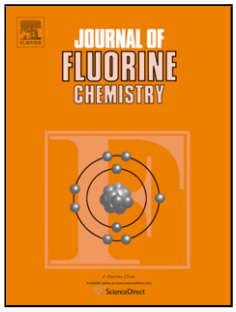

Title: Cu-Mediated Oxidative Trifluoromethylthiolation of Arylboronic Acids with (bpy)$CuSCF_3$

Author: <ce:author id="aut0005" author-id="S0022113916304833-b2f25a7498636c336534da0361705913"> Mingzhu Zhao<ce:author id="aut0010" author-id="S0022113916304833-05079f887e326f7ffe4caa17e36b5bdb"> Xiaoming Zhao<ce:author id="aut0015" author-id="S0022113916304833-6e002966fafb4921f9c90100809bd88f"> Purui Zheng<ce:author id="aut0020" author-id="S0022113916304833-951c2e121f7ae73df7a850d1fc495755"> Yawei Tian

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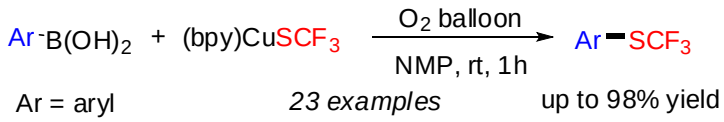
Cu-Mediated Oxidative Trifluoromethylthiolation of Arylboronic Acids with (bpy)CuSCF$_3$

Mingzhu Zhao, Xiaoming Zhao*, Purui Zheng, and Yawei Tian

Shanghai Key Lab of Chemical Assessment and Sustainability, Department of Chemistry, Tongji University, 1239 Siping Road, Shanghai 200092, China

Graphical abstract

Cu-mediated oxidative trifluoromethylthiolation of aryl boronic acids with (bpy)CuSCF$_3$ under mild conditions is presented, giving aryl trifluoromethylthioethers in good to excellent yield.



Highlights:

- Use of aryl boronic acids and (bpy)CuSCF$_3$.
- Tolerance a wide range of functional groups on the aryl ring.
- Under mild conditions.

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ABSTRACT

An efficient trifluoromethylthiolation reaction of arylboronic acids with (bpy)CuSCF$_3$ in the presence of oxygen at room temperature is described. This method produces a variety of aryl trifluoromethylthioether derivatives in good to high yield. The mechanism of this trifluoromethylthiolation is discussed as well.

1. Introduction

Trifluoromethylthiolated compounds have received incredible attention since SCF$_3$ with strong electron-withdrawing character makes organic compounds more lipophilic than that of trifluoromethyl group (the greatest Hansch constant π = 1.44 for SCF$_3$ *vs.* 0.88 for CF$_3$) [1]. These could enhance the drug molecule's cell membrane permeability and improve the pharmacokinetics and efficacy [2]. SCF$_3$-containing lead compounds have been increasing in medicinal chemistry during the recent decade [3]. Therefore, new practical method for the synthesis of trifluoromethylthiolated compounds is highly desirable. There are four representative examples such as the coccidiostatic Toltrazuril [4], the parenteral cephalosporin Cefazaflur [5], the Dopamine antagonists [6], and the inhibitor of ubiquitin-activating enzyme for the treatment of cell proliferation disorders TAK-243 [7] (**Fig. 1**).

Several methods for C-SCF$_3$ bond formation were reported [8]; for example, trifluoromethylthioethers were prepared through the radical reaction and electrophilic of CF$_3$SCl [9]. Indirect trifluoromethylthiolation strategies involved trifluoromethylation of sulfur-containing compounds including thiols, thiolates, and disulfides [10]. The substitution of halogen atoms by fluorine in aryl polyhalogenalkyl sulfides provided synthetic route toward aryl trifluoromethyl sulfides [11]. These methods required preformation of the thiolated precursors and suffer from either harsh conditions or limited substrate scope [12]. Recently, several shelf-stable and conveniently handled trifluoromethylthio reagents have been developed, which demonstrated potential in the electrophilic trifluoromethylthiolation of alkenes, alkynes, and aromatic compounds [13]. In recent decade, either metal-mediated or metal-catalyzed trifluoromethylthiolation has been withdrawing great attention [14]. Among these methods, trifluoromethylthiolations of arylboronic acids with trifluoromethylthio reagent such as hypervalent iodine [15], *N*-(trifluoromethylthio)-phthalimide [16], Me$_4$NSCF$_3$ [17], TMSCF$_3$ and S$_8$ have also been reported [18]. Although some trifluoromethylthiolation reactions proceed under mild conditions, they need either long reaction time or excessive trifluoromethylthio reagent. Recently, Weng reported an elegant air-stable (bpy)CuSCF$_3$ and its application in trifluoromethylthiolation with aryl halides [19] (eq 1 in Scheme 1), allylic bromides [20], and benzyl bromides [21]. Nevertheless, use of (bpy)CuSCF$_3$ in cross-coupling trifluoromethylthiolation has less reported. Herein, we report Cu-mediated oxidative cross-coupling trifluoromethylthiolation of arylboronic acids with (bpy)CuSCF$_3$, which provides trifluoromethylthiolated products (eq 2 in Scheme 1).

2. Results and discussion

Initially, we conducted a model reaction of (bpy)$CuSCF_3$ **1** with 4-biphenylboronic acid **2a** in DCM at room temperature for 1h under air atmosphere. To our delight, the formation of biphenyl-4-yl(trifluoromethyl)sulfane **3a** was observed in a 25% yield (entry 1). The subsequent examination of additives such as 4Å MS, triethylamine (TEA) and Cs_2CO_3 indicated that the improvement in yield was not achieved (entries 2-4). Interestingly, the reaction was carried out under oxygen atmosphere instead of air and the yield of **3a** was improved from 25 to 50% (entry 1 *vs.* entry 5). Under oxygen atmosphere, we further screened the solvents. For example, the halogenated solvents ($CHCl_3$ and DCE) gave **3a** in comparable yields (entries 6-7). However, THF, dioxane, EtOAc, toluene, and acetone gave acceptable to moderate yield (entries 8-12). Both diglyme and MeOH resulted in the similar yields (entries 13-14). Notably, the protic solvent (^{i}PrOH) was deleterious for this reaction (entry 15). More significantly, the aprotic polar solvents such as *N*-methyl-2-pyrrolidone (NMP), MeCN, DMSO, DMF were examined. NMP gave the best result (entry 16), whereas others led to good results (entries 17-19). We next tested the different reaction temperature (entries 20-21). When the reaction was conducted at 0 °C and it underwent slowly (entry 20). The reaction at 50 °C resulted in a slight lowering yield (entry 21) Furthermore, (bpy)$CuSCF_3$ (0.1 equiv) **1** was used and it gave a trace amount of **3a**.

With the optimized conditions shown in entry 16 of Table 1 in hand, the scope of various arylboronic acids **2** with (bpy)$CuSCF_3$ **1** were explored and the results were summarized in Table 2. The benzeneboronic acid **2b** and arylboronic acids **2b-2i** with either electron-rich (e.g., Ph, Me, *o*-OMe, *p*-OMe, *m*-OMe) or electron-poor (e.g., *p*-F, *p*-Cl and *p*-Br) group on the phenyl ring gave the corresponding products **3a-3i** in good to high yield, except for **2g**, in which an *ortho* effect (a 52% yield of **3g**) was observed (Table 2). Interestingly, the substrates with halogen (*e.g.*, *p*-F, *p*-Cl and *p*-Br) on the phenyl ring were still tolerated. Moreover, the trifluoromethylthiolation reaction of arylboronic acid **2j-2q** was also tolerant of the varying functional groups such as hydroxy, aldehyde, ketone, ester, cyano, nitro and sulfone (Table 2). It was noteworthy that 1-naphthylboronic acid **2r** performed well in spite of the *ortho*-effect (**3r** *vs.* **3s**). In addition, both 9-anthraceneboronic acid **2t** and 9-phenanthreneboronic acid **2u** were suitable for this trifluoromethylthiolation, giving more than 80% yields of **3t-3u**. Furthermore, the heterocyclic boronic acids **1v-1w** were compatible with the reaction conditions and showed good reactivity (Table 2).

To gain insight into the trifluoromethylthiolation process, we carried out five control experiments. We found that the yields of trifluoromethylthioether **3a** decreased from 96% to 75% when the atmosphere was changed from O_2 to air (eq 1 in Scheme 2). Trace amount $ArSCF_3$ **3a** was observed when the reaction performed under argon (eq 2). Under the optimal conditions, TEMPO (1.0 equiv), a radical scavenger, was tested and 88 % of **3a** was obtained (eq 3); a trace amount of **3a** was observed under argon (eq 4). These results suggest that the formation of free radical intermediates is unlikely, and that oxygen instead of TEMPO works as an oxidizing agent for this trifluoromethylthiolation. 2-Phenylethylboronic acid **2w** failed to take place this reaction, which was in consistent with the oxidative coupling pathway supposition [22] (eq 5).

Given these observations, a cross coupling mechanism for this reaction is proposed (**Fig. 2.**). In the presence of O_2, an oxidative addition of (bpy)$CuSCF_3$ **1** to arylboronic acid **2** followed by a transmetallation gives ***Int A***, which is in the equilibrium with ***Int B*** oxidizing by O_2. Both ***Int A*** and ***Int B*** could undergo reductive elimination to afford the aryl trifluoromethylthioether **3**. The reductive elimination rate of ***Int B*** undergoes faster than that of ***Int A***. These give rational explanation on the effect of oxygen on this transformation [23].

To illustrate the synthetic value of the trifluoromethylthioethers **3** generated by this method, the preparative scale reaction was performed under the standard conditions. The (bpy)$CuSCF_3$ **1** (1.28 g, 4.0 mmol) reaction with (4-((methoxycarbonyl)amino)phenyl)boronic acid **4** (940 mg, 4.8 mmol) led to **5** (810 mg, in 81% isolated yield), the fungicide and herbicide (Scheme 3), which was synthesized by thiophenol and suffered from the harsh conditions [24].

3. Conclusion

In conclusion, we developed a trifluoromethylthiolation of arylboronic acids with (bpy)$CuSCF_3$ under the mild conditions, which gave the corresponding trifluoromethylthioethers in fair to high yield. This method allows the use of oxygen atmosphere, tolerates various functional groups, and provides a new way to aryl trifluoromethylthioethers.

4. Experimental

4.1. General

^{1}H NMR (TMS as the internal standard), ^{19}F NMR spectra and ^{13}C NMR was recorded on Bruker AM400 spectrometer. ^{1}H NMR spectra were obtained at 400 MHz and recorded relative to tetramethylsilane signal (0 ppm) or residual protic solvent. ^{13}C NMR spectra were obtained at 100 MHz and chemical shifts were recorded relative to the solvent resonance ($CDCl_3$, 77.0 ppm). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, coupling constant (s) in Hz, integration). ^{19}F NMR spectra were obtained at 376 MHz. IR spectra were measured on Thermo Nicolet spectrometer. GC-MS was conducted on Agilent 8453/5973N. Unless otherwise noted, all reagents and starting materials were purchased from commercial sources and used without further purification

4.2. General procedure for trifluoromethylthiolation of arylboronic acids

Arylboronic acid **2** (0.12 mmol) and (bpy)Cu(SCF_3) **1** (0.1 mmol) were added to a Schlenk flask fitted with magnetic stir bar and O_2 balloon. The flask was evacuated and back filled with O_2. The solvent NMP (2.0 mL) was added by syringe at room temperature and

the solution was stirred for 1h. For the products reported with isolated yields (**3a**, **3k**, **3l**, **3m**, **3n**, **3o**, **3p**, **3q**, **3r**, **3s**, **3t**, **3u** and **3w**), the reaction mixture was diluted with EtOAc, then washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate gradient) to afford the desired compounds. Gram-scale synthesis of compound **5** was prepared following the similar procedure. The relatively volatile products (**3b**, **3c**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j** and **3v**) were not isolated and their yields were determined by ^{19}F NMR measurement in $CDCl_3$ of the reaction mixture. For the products reported with ^{19}F NMR yields, $PhOCF_3$ (1.0 equiv) was added to the reaction mixture as internal standard added after the reaction completed. The reaction mixture was purified by flash chromatography on silica gel (pentane/diethyl ether gradient) to afford the desired compounds.

*4.2.1. 4-[(Trifluoromethyl)thio]biphenyl **(3a)***

Colorless solid (22.8 mg, 90%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.66 – 7.62 (m, 2H), 7.60 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.50 – 7.44 (m, 2H), 7.43 – 7.37 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (s), 139.7 (s), 136.8 (s), 129.7 (q, *J* = 308.2 Hz), 129.0 (s), 128.2 (s), 127.3 (s), 123.1 (q, *J* = 2.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.7 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 254 (M^+, 79), 185 (M^+-CF_3, 100), 152 (47), 139 (14), 115 (19), 69 (30). The data corroborate with the literature report [18].

*4.2.2. 4-(Trifluoromethylthio)benzene **(3b)***

^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.4 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4 (s), 130.9 (s), 129.7 (q, *J* = 307.9 Hz), 129.5 (s), 124.5 (q, *J* = 1.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.8 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 178 (M^+, 44), 109 (M^+-CF_3, 100), 69 (39), 51 (21). The data corroborate with the literature report [10j].

*4.2.3. 1-Fluoro-4-[(trifluoromethyl)thio]benzene **(3c)***

^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.5, 5.3 Hz, 2H), 7.12 (t, *J* = 8.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6 (d, *J* = 252.6 Hz), 138.8 (d, *J* = 8.9 Hz,), 129.4 (q, *J* = 305.7 Hz), 119.70 (m), 116.8 (d, *J* = 22.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -43.4 (s, 3F), -108.6 (s, 1F). GC-MS (EI, 70eV): m/z (%) =196 (M^+, 49), 127 (M^+-CF_3, 100), 83 (72), 69 (39), 57 (42). The data corroborate with the literature report [25].

*4.2.4. 1-Chloro-4-[(trifluoromethyl)thio]benzene **(3d)***

^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7 (s), 137.6 (s), 129.8 (s), 129.4 (q, *J* = 308.2 Hz), 122.8 (q, *J* = 2.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.9 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 214 (21), 212 (M^+, 42), 145 (37), 143 (M^+-CF_3, 100), 108 (70), 69 (79), 63 (36), 50 (24). The data corroborate with the literature report [10j].

*4.2.5. 1-Bromo-4-[(trifluoromethyl)thio]benzene **(3e)***

^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (s), 132.8 (s), 129.3 (q, *J* = 308.3 Hz), 126.0 (s), 123.4 (q, *J* = 2.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.7 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 258 (M^+, 77), 256 (M^+, 70), 189 (M^+-CF_3, 59), 187 (M^+-CF_3, 50), 108 (100), 69 (70), 63 (33). The data corroborate with the literature report [18].

*4.2.6. 4-(Trifluoromethylthio)toluene **(3f)***

^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4 (s), 136.4 (s), 130.3 (s), 129.7 (q, *J* = 307.9 Hz), 120.92 (q, *J* = 1.7 Hz), 21.32 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -43.2 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 192 (M^+, 82), 123 (M^+-CF_3, 100), 91 (63), 77 (36), 69 (65). The data corroborate with the literature report [8].

*4.2.7. 1-(Methoxy)-2-[(trifluoromethyl)thio]benzene **(3g)***

^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.6 Hz, 1H), 7.46 (td, *J* = 8.2, 1.6 Hz, 1H), 7.01 – 6.96 (m, 2H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 160.6 (s), 138.6 (s), 132.9 (s), 129.6 (q, *J* = 308.8 Hz), 121.2 (s), 112.5 (q, *J* = 1.6 Hz), 111.76 (s), 56.05 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.4 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 208 (M^+, 100), 139 (M^+-CF_3, 21), 96 (55), 95 (40), 69 (93). The data corroborate with the literature report [13c].

*4.2.8. 1-(Methoxy)-3-[(trifluoromethyl)thio]benzene **(3h)***

^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.18 (s, 1H), 7.01 (dd, *J* = 8.2, 1.6 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.98 (s), 130.21 (s), 129.69 (q, *J* = 307.9 Hz), 128.43 (s), 125.25 (q, *J* = 1.9 Hz), 121.23 (s), 116.89 (s), 55.41 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.6 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 208 (M^+, 100), 139 (M^+-CF_3, 41), 124 (55), 96 (54), 95 (65), 69 (82)**.** The data corroborate with the literature report [13c].

*4.2.9. 1-(Methoxy)-4-[(trifluoromethyl)thio]benzene **(3i)***

^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9 (s), 138.3 (s), 129.7 (q, *J* = 308.0 Hz), 115.0 (s), 114.9 (d, *J* = 2.0 Hz), 55.40 (s).^{19}F NMR (376 MHz, CDCl3) δ -44.0 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 208 (M^+, 53), 139 (M^+-CF_3, 100), 124 (15), 95 (39), 69 (49). The data corroborate with the literature report [13c].

4.2.10. 4-((Trifluoromethyl)thio)phenol ***(3j)***

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.22 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9 (s), 138.6 (s), 129.6 (q, *J* = 308.0 Hz), 116.6 (s), 115.4 (q, *J* = 2.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -43.9 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 194 (M^+, 37), 125 (M^+-CF_3, 100), 97 (25), 81 (19), 69 (51), 53 (16). The data corroborate with the literature report [25].

4.2.11. 4-(Trifluoromethylthio)benzaldehyde ***(3k)***

Colorless oil (16.4 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2 (s), 137.4 (s), 135.9 (s), 131.7 (q, *J* = 2.0 Hz), 129.2 (q, *J* = 308.5 Hz), 130.3 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -41.5 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 206 (M^+, 100), 205 (87), 109 (56), 108 (50), 69 (87). The data corroborate with the literature report [26].

4.2.12. 1-(4-((Trifluoromethyl)thio)phenyl)ethanone ***(3l)***

Colorless oil (20.0 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 2.64 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1 (s), 138.5 (s), 135.8 (s), 130.0 (q, *J* = 2.1 Hz), 129.3 (q, *J* = 308.4 Hz), 129.1 (s), 26.76 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -41.8 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 220 (M^+, 42), 205 (M^+-CH_3, 100), 136 (27), 108 (45), 69 (78), 43 (72). The data corroborate with the literature report [14g].

4.2.13. Methyl 4-[(trifluoromethyl)thio]benzoate ***(3m)***

Colorless solid (16.7 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 1H), 3.95 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1 (s), 135.6 (s), 132.2 (s), 130.4 (s), 129.9 (q, *J* = 2.1 Hz), 129.3 (q, *J* = 308.4 Hz), 52.5 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -41.8 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 236 (M^+, 53), 205 (100), 177 (21), 108 (44), 69 (36). The data corroborate with the literature report [18].

4.2.14. 4-[(Trifluoromethyl)thio]benzonitrile ***(3n)***

Colorless oil (16.6 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0 (s), 133.0 (s), 130.6 (q, *J* = 2.3 Hz), 129.1 (q, *J* = 308.7 Hz), 117.6(s), 114.7 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -41.5 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 203 (M^+, 81), 134 (M^+-CF_3, 100), 107 (21), 90 (39), 69 (74). The data corroborate with the literature report [18].

4.2.15. (3-Nitrophenyl)(trifluoromethyl)sulfane ***(3o)***

Yellowish oil (16.7 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.38 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6 (s), 141.8 (s), 130.8 (s), 130.48 (s), 129.1 (q, *J* = 308.9 Hz), 126.7 (q, *J* = 2.2 Hz), 125.78 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.0 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 223 (M^+, 100), 177 (M^+-NO_2, 26), 127 (32), 108 (M^+-NO_2-CF_3, 83), 95 (40), 69 (70). The data corroborate with the literature report [14a].

4.2.16. 1-(Methylsulfonyl)-4-[(trifluoromethyl)thio]benzene ***(3p)***

Yellow solid (20.7 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.86 (d, *J* = 8.2 Hz, 2H), 3.10 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7 (s), 136.2 (s), 131.6 (q, *J* = 2.1 Hz), 129.1 (q, *J* = 308.7 Hz), 128.4 (s), 44.39 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -41.4 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 256 (M^+, 100), 241 (M^+-CH_3, 44), 193 (69), 108 (87), 95 (55), 69 (100). The data corroborate with the literature report [18].

4.2.17. tert-Butyl (4-((trifluoromethyl)thio)phenyl)carbamate ***(3q)***

White solid (27.2 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 6.68 (s, 1H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$), δ 152.3 (s), 141.2 (s), 137.6 (s), 129.6 (q, *J* = 308.1 Hz). 118.8 (s), 117.2 (q, *J* = 2.0 Hz), 81.3 (s), 28.3 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -43.6 (s, 3F). IR (KBr): ν_{max} (cm^{-1}) = 3334, 2988, 1701, 1587, 1515, 1400, 1369, 1312, 1156, 1211, 826, 775, 519. GC-MS (EI, 70eV): m/z (%) = 293 (M^+, 3), 237 (M^+-*t*Bu, 17), 193 (M^+-Boc, 41), 124 (M^+-Boc-CF_3, 100), 80 (35), 57 (48). HRMS (ESI-TOF) m/z calcd. for $C_{12}H_{14}F_3NNaO_2S$ $[M+Na]^+$: 316.0590; found: 316.0590. The data corroborate with the literature report [14b].

4.2.18. 1-[(Trifluoromethyl)thio]naphthalene ***(3r)***

Colorless oil (19.3 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.5 Hz, 1H), 8.00 (dd, *J* = 17.3, 7.7 Hz, 2H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.66 (m, 1H), 7.58 (m, 1H), 7.51 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9 (s), 135.4 (s), 134.3 (s), 132.4 (s), 129.7 (q, *J* = 309.4 Hz), 128.6 (s), 127.7 (s), 126.8 (s), 125.9 (s), 125.6 (s), 121.66 (q, *J* = 1.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -41.4 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 228 (M^+, 100), 159 (M^+-CF_3, 77), 115 (97), 69 (39). The data corroborate with the literature report [19a].

4.2.19. 2-[(Trifluoromethyl)thio]naphthalene ***(3s)***

Colorless oil (20.9 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 3H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.61 – 7.51 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.1 (s), 133.9 (s), 133.4 (s), 131.8 (s), 129.7 (q, *J* = 309.4 Hz), 129.3 (s), 128.2 (s), 128.0 (s), 127.8 (s), 127.0 (s), 121.5 (q, *J* = 1.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.5 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 228 (M^+, 52), 159 (M^+-CF_3, 44), 115 (100), 69 (29). The data corroborate with the literature report [10j].

4.2.20. 9-[(Trifluoromethyl)thio]anthracene ***(3t)***

Yellow solid (22.5 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 8.8 Hz, 2H), 8.66 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.69 – 7.65 (m, 2H), 7.57 – 7.53 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.17 (s), 132.53 (s), 131.78 (s), 129.78 (q, *J* = 311.4 Hz), 128.92 (s), 127.87 (s), 126.53 (s), 125.69 (s), 117.2 (q, *J* = 2.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -41.2 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 278 (M^+, 89), 209 (M^+-CF_3, 55), 165 (100), 69 (59). The data corroborate with the literature report [14g].

*4.2.21. .9-[(Trifluoromethyl)thio]phenanthrene **(3u)***

White solid (23.0 mg, 83%). mp: 98.3 – 99.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 – 8.61 (m, 3H), 8.30 (s, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.76 – 7.69 (m, 3H), 7.63 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 132.5, 131.8, 131.2, 131.1, 129.8 (q, *J* = 309.4 Hz), 129.3, 128.9, 127.5, 127.5, 127.3, 126.9, 123.0, 122.7, 120.6 (q, *J* = 1.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.0 (s, 3F). IR (KBr): ν_{max} (cm^{-1})= 3073, 3056, 2925, 1610, 1449, 1244, 1140, 1109, 895, 763, 750, 721. GC-MS (EI, 70eV): m/z (%) = 278 (M^+, 65), 209 (M^+-CF_3, 100), 208 (30), 165 (58), 69 (58). HRMS (ESI-TOF) m/z calcd. for C15H8F3S $[M-H]^-$: 277.0304; found: 277.0344.

*4.2.22. 4-(Trifluoromethylthio)pyridine **(3v)***

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 5.7 Hz, 2H), 7.51 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6 (s), 135.8 (q, *J* = 2.1 Hz), 129.0 (q, *J* = 308.7 Hz), 127.8 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -40.6 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 179 (M^+, 100), 110 (M^+-CF_3, 45), 83 (27), 78 (33), 69 (81), 57 (24), 51(37). The data corroborate with the literature report [25].

*4.2.23. 3-((Trifluoromethyl)thio)quinolone **(3w)***

Colorless solid (19.7 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, *J* = 1.5 Hz, 1H), 8.54 (d, *J* = 1.1 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.90 – 7.82 (m, 2H), 7.67 – 7.63 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (s), 148.4 (s), 144.8 (s), 131.7 (s), 129.6 (s), 129.2 (q, *J* = 308.8 Hz), 128.2 (s), 127.9 (s), 118.3 (q, *J* = 1.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.3 (s, 3F). GC-MS (EI, 70eV): m/z (%) = 229 (M^+, 100), 160 (M^+-CF_3, 96), 133 (19), 116 (25), 89 (76), 69 (61). The data corroborate with the literature report [25]

*4.2.24. tert-Butyl(4-((trifluoromethyl)thio)phenyl)carbamate **(5)***

White solid (810 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 6.89 (s, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 140.6, 137.6, 129.6 (q, *J* = 308.1 Hz), 119.0, 117.8 (q, *J* = 1.8 Hz), 52.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -43.5 (s, 3F). IR (KBr): ν_{max} (cm^{-1})= 3333, 1708, 1598, 1540, 1402, 1314, 1239, 1151, 1110, 836, 769, 678, 520. GC-MS (EI, 70eV): m/z (%) = 251 (M^+, 100), 219 (30), 182 (M^+-CF_3, 56), 150 (M^+-SCF_3, 48), 138 (33), 96 (34), 69 (47), 59 (55). HRMS (ESI-TOF) m/z calcd. for $C_9H_8F_3NNaO_2S$ $[M+Na]^+$: 274.0120; found: 274.0123. The data corroborate with the literature report [24].

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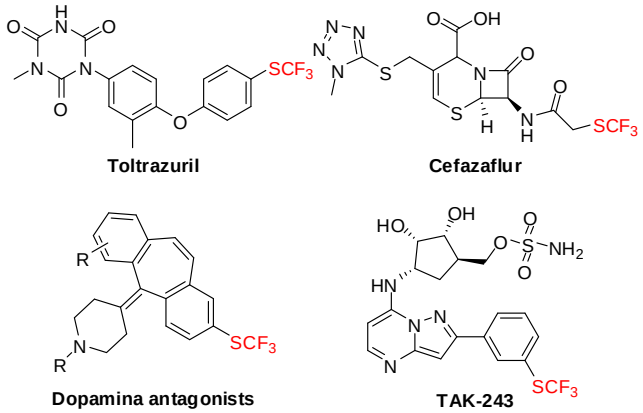


Fig. 1. Four representative CF_3S-containing compounds.

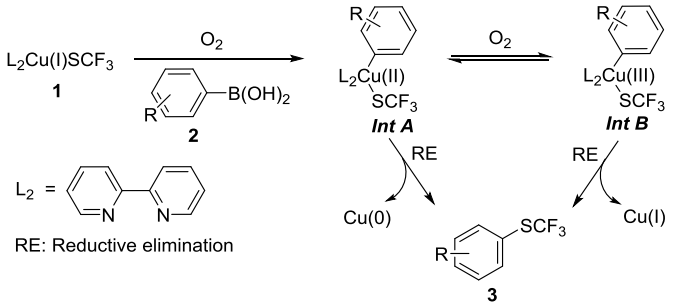
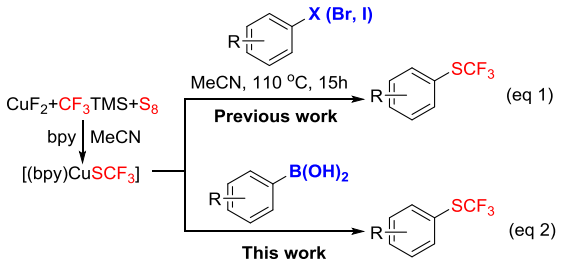
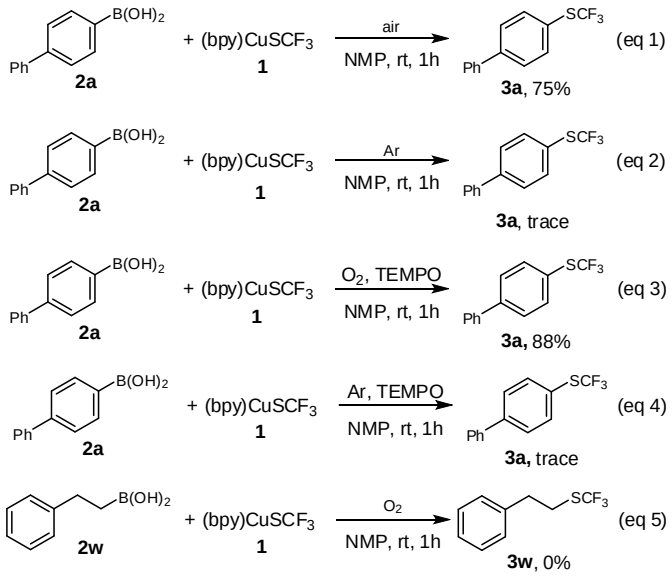


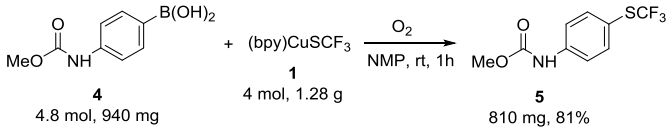
Fig. 2. Plausible mechanism.



Scheme 1. Cu-mediated trifluoromethylthiolation with (bpy)$CuSCF_3$.

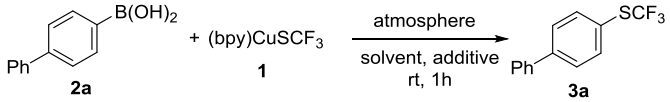


Scheme 2. Control experiments.



Scheme 3. Gram-scale reaction.

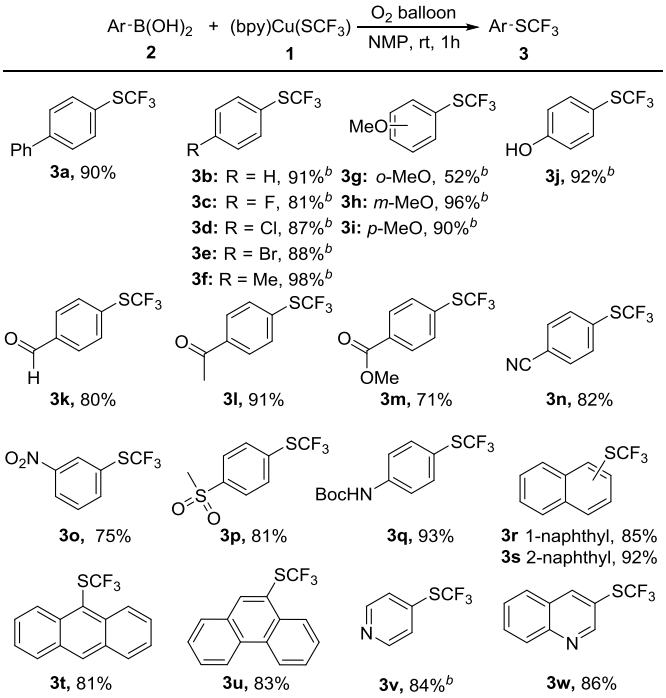
Table 1
Optimization reaction conditions for a trifluoromethylthiolation of 4-biphenylboronic acid **2a** with (bpy)$CuSCF_3$ **1**[a].



Entry	Solvent	Additive	Atmosphere	Yield of **3a** (%)[b]
1	DCM	-	air	25
2	DCM	4Å MS	air	18
3	DCM	TEA	air	15
4	DCM	Cs_2CO_3	air	10
5	DCM	-	O_2	50
6	$CHCl_3$	-	O_2	50
7	DCE	-	O_2	65
8	THF	-	O_2	65
9	Dioxane	-	O_2	56
10	EtOAc	-	O_2	68
11	Toluene	-	O_2	40
12	Aceton	-	O_2	66
13	Diglyme	-	O_2	53
14	MeOH	-	O_2	45
15	^{i}PrOH	-	O_2	Trace
16	NMP	-	O_2	96 (90)[c]
17	MeCN	-	O_2	67
18	DMSO	-	O_2	68
19	DMF	-	O_2	70
20[d]	NMP	-	O_2	90
21[e]	NMP	-	O_2	93

[a]Reaction conditions: **1** (0.1 mmol) and **2a** (0.12 mmol) in solvent (2.0 mL) at a range of zero to 50 °C for 1h.
[b]Determined by ^{19}F NMR using 1.0 equiv of $PhOCF_3$ as internal standard added after the reaction.
[c]Isolated yield in bracket.
[d]At 0 °C.
[e]At 50 °C.

Table 2
Scope of the trifluoromethylthiolation of arylboronic acid **2** with (bpy)CuSCF$_3$ **1**[a].



[a]Reaction conditions: **1** (0.1 mmol) and **2** (0.12 mmol) in NMP (2.0 mL) at room temperature under O_2 for 1h. Yields of isolated products are shown.
[b]Yields were determined by ^{19}F NMR using 1.0 equiv of $PhOCF_3$ as internal standard added after the reaction.