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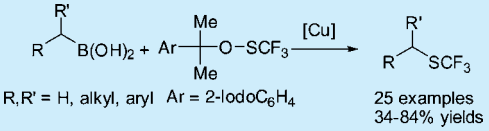
Copper-Catalyzed Trifluoromethylthiolation of Primary and Secondary Alkylboronic Acids

Xinxin Shao, Tianfei Liu, Long Lu,* and Qilong Shen*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China

Supporting Information

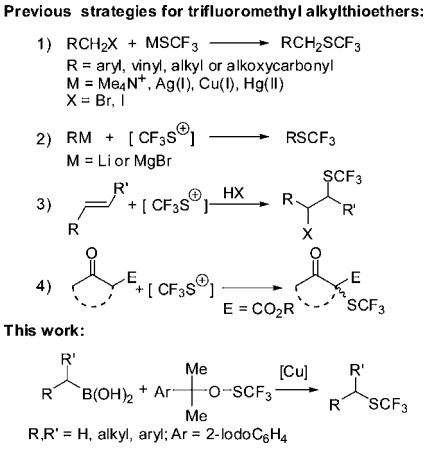
ABSTRACT: A Cu-catalyzed trifluoromethylthiolation of primary and secondary alkylboronic acids with an electrophilic trifluoromethylthiolating reagent is described. Tolerance for a variety of functional groups was observed.



Due to its high lipophilicity (π_R = 1.44) and strong electronegativity, the trifluoromethylthio group (CF_3S-) is generally considered a privileged structural motif that is frequently employed in new drug and agrochemical design and routinely evaluated for fine-tuning biological properties of leading compounds.[1] Consequently, development of methods for the introduction of the trifluoromethylthio group into small molecules is of great interest for both academic and industrial chemists.[2,3] In recent years, several elegant methods involving transition metal catalysis or metal-free conditions for trifluoromethylthiolation of aryl halides, boronic acids, and terminal alkynes employing a nucleophilic CF_3S reagent such as CF_3SAg, CF_3SCu, or CF_3SNMe_4 have been established by the research groups of Buchwald,[4] Vicic,[5] Qing,[6] and Weng.[7] Alternatively, direct trifluoromethylthiolation of indoles,[8] aryl boronic acids,[9] or alkynes[11] with an electrophilic trifluoromethylthiolating reagent[12] were reported by Billard, Shibata, Rueping, and us.[9a,10] More recently, Gooßen reported a Sandmeyer-type trifluoromethylthiolation of arenediazonium salts with NaSCN and $TMSCF_3$ under mild conditions.[13] These new methods or reagents allow the introduction of the trifluoromethylthio group at a late stage of the synthesis of the drug molecules.

In contrast to these significant achievements of trifluoromethylthiolation that typically involved the formation of $C(sp^2)-SCF_3$ or $C(sp)-SCF_3$ bonds, processes that facilitate the construction of $C(sp^3)-SCF_3$ bonds from unactivated alkyl substrates remain much less developed. Alkyltrifluoromethylthio-ethers can be accessed through classical halogen−fluorine exchange of polyhalogenomethyl thioethers or the trifluoromethylation of sulfur-containing compounds such as disulfides, thiocyanates, and thiols via radial pathways.[14] Alkyl trifluoromethylthio ethers could also be generated by the electrophilic trifluoromethylation of thiolates.[15] These indirect strategies are of interest but generally require preformed sulfur precursors. Direct nucleophilic trifluoromethylthiolation of alkyl halides are reported using $MSCF_3$ (M = Me_4N^+, Ag(I), Cu(I), or Hg(II)) reagents (Scheme 1).[16] However, these methods were mainly applied to activated alkyl halides such as benzyl, allyl, or propargyl halides or α-haloesters or ketones.[17] Few examples for the nucleophilic trifluoromethylthiolation of simple alkyl halides were reported previously.[16m] More recently, Billard et al. reported the preparation of the air and moisture stable trifluoromethanesulfanylamides that were capable of trifluoromethylthiolation of alkenes, Grignard or lithium reagents.[11a,18] Qing reported that the same reagent enabled trifluoromethylthiolation of allylsilane mediated by acid chloride.[12b,c] Meanwhile, several groups independently reported trifluoromethylthiolation of β-keto esters using different electrophilic trifluoromethylthiolating reagents in high yields.[8b,9a,12e−g] Hu, Wang, and Rueping independently reported trifluoromethylthiolation of α-diazoesters from the formation of α-trifluoromethylthiolated esters.[19] Despite these important advances, numerous challenges such as starting material availability, functional group tolerance, and operational simplicity remain. Herein, we report the first Cu-catalyzed trifluoromethylthiolation of primary (1°) and secondary (2°) alkylboronic acids with an electrophilic trifluoromethylthiolating reagent developed in our laboratory. The reaction is compatible with a variety of functional groups.

Scheme 1. Previous Direct Trifluoromethylthiolation Strategies for Alkylthioethers



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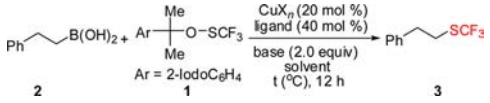
Alkyl boronic acids are valuable cross-coupling partners since they are crystalline compounds that can be easily prepared from alkenes or alkyl halides and are compatible with a variety of functional groups.[20] Direct trifluoromethylthiolation of alkyl boronic acids under mild conditions using abundant, cheap metal catalysts would provide a new strategy for the construction of Csp^3–SCF_3 bond. Cu catalysts would be an ideal choice since they have been extensively employed for a variety of functional group manipulations. Unlike numerous reported reactions of aryl and alkenyl boronic acids such as the Suzuki–Miyaura reaction[21] and Chan–Lam–Evans reaction,[22] few Cu-catalyzed cross-coupling reactions of alkyl boronic acids have been reported.[23]

We began the study by examining the reaction between phenethylboronic acid and the electrophilic reagent **1** as a model reaction to survey the reaction conditions. When the reaction was conducted at 35 °C using 20 mol % $Cu(MeCN)_4PF_6$ and 40 mol % 2,2′-bipyridine as the catalyst in diglyme, the conditions that were efficient to promote the Cu-catalyzed trifluoromethylthiolation of arylboronic acids, no desired product was detected by GC-MS or ^{19}F NMR spectroscopy (Table 1, entry 1).

To our delight, when the mixture was heated to 80 °C for 36 h, the trifluoromethylthiolated product was formed in 35% yield, along with side products such as alkyl iodide and alkane from proto-deboronation (Table 1, entry 2). When the amount of alkyl boronic acid was increased to 1.5 equiv, the yield was improved to 60% (Table 1, entry 3). Further screening of Cu salts showed that when $CuCl_2{\cdot}2H_2O$ was used as the catalyst, the product yield improved to 73% (Table 1, entry 5). The reaction time could be significantly shortened to 12 h with a slightly increased yield when the temperature was increased to 120 °C (Table 1, entries 6–7). The amount of the alkyl boronic acid was important for the yield of the desired product. When 1.3 or 2.0 equiv of alkyl boronic acid were used, the yield decreased to 71% and 60%, respectively (Table 1, entries 8–9). The effects of the ligands and bases were further studied. Reactions were less effective when 4,4′-dimethoxy-2,2′-bipyridine **L2**, 4,4′-*tert*-butyl-2,2′-bipyridyl **L3**, or 1,10-phenanthroline **L4** was used as the ligand (Table 1, entries 10–12). We further studied the influence of bases on the reaction. Reactions in the presence of KOAc, K_3PO_4, Na_3PO_4, or Na_2CO_3 gave the corresponding trifluoromethylthiolated product in lower yields than those in the presence of K_2CO_3 (Table 1, entries 13–16). Likewise, using other Cu salts such as copper(I) thiophene-2-carboxylate (CuTc), $Cu(OAc)_2$, and $CuBr{\cdot}SMe_2$ led to slightly lower yields (Scheme 2, entries 17, 19–20). Interestingly, using $CuBr_2$ as the catalyst was equally effective (Table 1, entry 18). The yield decreased significantly to 30% when the reaction was conducted in the absence of ligand (Table 1, entry 21). Likewise, no desired trifluoromethylthiolated product was observed in the absence of the Cu catalyst (Table 1, entry 22). The effects of the solvents were also evaluated. Reactions in toluene were slightly less effective, while reactions in polar solvents such as NMP, acetone, THF, or acetonitrile led to <35% yields (Table 1, entries 23–27).

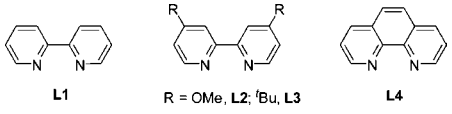
With the optimized conditions (Table 1, entry 7) in hand, we then studied the substrate scope of the Cu-catalyzed trifluoro-

Table 1. Optimization of Reaction Conditions[a]

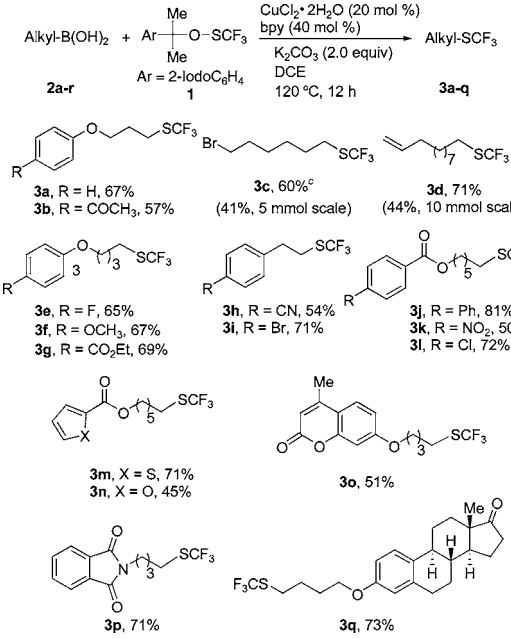


entry	CuX_n	ligand	base	solvent	temp (°C)	yield (%)[b]
1	$Cu(MeCN)_4PF_6$	**L1**	K_2CO_3	Diglyme	35	-[c]
2	$Cu(MeCN)_4PF_6$	**L1**	K_2CO_3	Diglyme	80	35[b]
3	$Cu(MeCN)_4PF_6$	**L1**	K_2CO_3	DCE	80	60[c]
4	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	DCE	80	58[c]
5	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	DCE	90	73[c]
6	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	DCE	100	73[c]
7	**$CuCl_2{\cdot}2H_2O$**	**L1**	**K_2CO_3**	**DCE**	**120**	**80**
8	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	DCE	120	71[d]
9	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	DCE	120	60[e]
10	$CuCl_2{\cdot}2H_2O$	**L2**	K_2CO_3	DCE	120	59
11	$CuCl_2{\cdot}2H_2O$	**L3**	K_2CO_3	DCE	120	66
12	$CuCl_2{\cdot}2H_2O$	**L4**	K_2CO_3	DCE	120	54
13	$CuCl_2{\cdot}2H_2O$	**L1**	KOAc	DCE	120	39
14	$CuCl_2{\cdot}2H_2O$	**L1**	K_3PO_4	DCE	120	45
15	$CuCl_2{\cdot}2H_2O$	**L1**	Na_3PO_4	DCE	120	69
16	$CuCl_2{\cdot}2H_2O$	**L1**	Na_2CO_3	DCE	120	35
17	$Cu(OAc)_2$	**L1**	K_2CO_3	DCE	120	49
18	$CuBr_2$	**L1**	K_2CO_3	DCE	120	79
19	$CuBr{\cdot}SMe_2$	**L1**	K_2CO_3	DCE	120	72
20	CuTc	**L1**	K_2CO_3	DCE	120	74
21	$CuCl_2\ 2H_2O$	-	K_2CO_3	DCE	120	30
22	-	**L1**	K_2CO_3	DCE	120	-
23	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	Toluene	120	72
24	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	NMP	120	trace
25	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	Acetone	120	trace
26	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	CH_3CN	120	31
27	$CuCl_2{\cdot}2H_2O$	**L1**	K_2CO_3	THF	120	25

[a]Reaction conditions: alkyl boronic acid (0.15 mmol), reagent **1** (0.1 mmol), CuX (20 mol %), ligand (40 mol %), and base (2.0 equiv) in solvent (0.5 mL) at temperatures indicated in Table 1 for 12 h; yields were determined by ^{19}F NMR analysis of the crude reaction mixture with an internal standard. [b]1.0 equiv of alkylboronic acid was used. [c]Reaction was conducted at corresponding temperature for 36 h. DCE = 1,2-dichloroethane. [d]Alkyl boronic acid (1.3 equiv) was used. [e]Alkyl boronic acid (2.0 equiv) was used.



Scheme 2. Scope of Cu-Catalyzed Trifluoromethylthiolation of 1° Alkyl Boronic Acids[a,b]



[a]Reaction conditions: alkylboronic acid (0.75 mmol), reagent **1** (0.5 mmol), $CuCl_2{\cdot}2H_2O$ (20 mol %), bpy (40 mol %), and K_2CO_3 (2.0 equiv) in 1,2-dichloroethane (2.5 mL) at 120 °C for 12 h. [b] Isolated yield. [c] CuTc was used as the catalyst and ((2-phenylpropan-2-yl)oxy)(trifluoromethyl)sulfane was used as the electrophilic trifluoromethylthiolating reagent in toluene.

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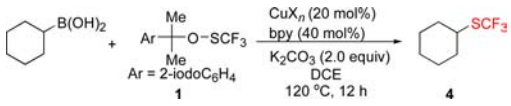
methylthiolation of 1° alkylboronic acids, as summarized in Scheme 2. A variety of alkyl boronic acids reacted with electrophilic trifluoromethylthiolating reagent **1** to give the corresponding trifluoromethylthiolated alkanes in good to excellent yields. Challenging functionalized alkyl boronic acids were compatible with the reaction conditions. Reactions of alkyl boronic acids with functional groups such as enolizable ketone, ester, alkene, nitro, amide, cyano, fluoride, chloride, and bromide occurred in good yields (Scheme 2, **3b**−**q**). Moreover, a structurally complicated biologically active estrone derivative also reacted with trifluoromethylthiolated reagent **1** to give the corresponding trifluoromethylthiolated product in good isolated yield (Scheme 2, **3q**). Notably, the yield for the reaction of 6-bromohexylboronic acid and undec-10-enylboronic acid with reagent **1** on a 5 or 10 mmol scale dropped significantly to give the corresponding product in 41% and 44% yield, respectively. The main side products observed for the reaction with undec-10-enylboronic acid were alkyl chloride (22%) and iodide (34%) as determined by ^{1}H NMR spectroscopy and GC/MS of the crude mixture. In contrast, the same reaction in a 1.0 mmol scale gave the desired product and two side products in 71%, 15%, and 28% yield, respectively (Scheme 2, **3d**).

Encouraged by these excellent results, we next turned our attention to 2° alkylboronic acids that are more challenging substrates in organic synthesis. The reaction conditions were slightly modified, and we found the highest yields were obtained when CuTc was used as the catalyst. Other Cu salts such as $CuBr_2$, CuSCN, CuI, CuBr, $Cu(OAc)_2$, CuCN, $CuBr{\cdot}SMe_2$, or $CuCl_2{\cdot}2H_2O$ were slightly less effective. However, much less side products were observed when CuTc was used as the catalyst (Table 2). Under these conditions, several cyclic and acyclic 2° alkyl boronic acids could be successfully trifluoromethylthiolated in good yields, as shown in Scheme 3. More importantly, ketones, esters, and *N*-protected piperidines were well tolerated with the reaction conditions (Scheme 3, **4f**−**h**). In addition, the reaction was not significantly affected by the ring size of the cyclic 2° alkyl boronic acids. Five-, six-, seven-, and twelve-membered cyclic alkyl boronic acids all reacted with reagent **1** to give the corresponding trifluoromethylthiolated products in good isolated yields (Scheme 3, **4a**−**b**, **4d**−**e**).

In conclusion, we report the first Cu-catalyzed trifluoromethylthiolation of 1° and 2° alkylboronic acids with an electrophilic trifluoromethylating reagent.[23] The advantage of the current method compared to the previous method using a Grignard or lithium reagent is its tolerance for a variety of functional groups. Thus, potentially, it will provide a general method for the construction of any desired trifluoromethylthio-substituted alkyl building blocks. Further investigation of the more challenging stereospecific trifluoromethylthiolation of 2° alkyl boronic acids and mechanistic studies of the reaction are underway in our laboratory.

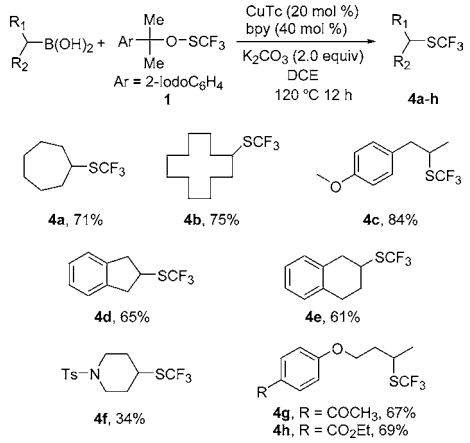
Table 2. Optimization of Reaction Conditions for Trifluoromethylthiolation of 2° Alkyl Boronic Acids[a,b]



Entry	CuX_n	Yield (%)
1	$Cu(MeCN)_4PF_6$	70
2	$CuBr_2$	70
3	CuSCN	60
4	CuI	72
5	CuBr	74
6	$Cu(OAc)_2$	73
7	CuTc	77
8	CuCN	72
9	$CuBr{\cdot}Me_2S$	60
10	$CuCl_2{\cdot}2H_2O$	74

[a]Reaction conditions: alkylboronic acid (0.15 mmol), reagent 1 (0.1 mmol), Cu catalyst (20 mol %), bpy (40 mol %), and K_2CO_3 (2.0 equiv) in 1,2-dichloroethane (2.5 mL) at 120 °C for 12 h. [b]Yields were determined by ^{19}F NMR with an internal standard.

Scheme 3. Scope of Cu-catalyzed Trifluoromethyl-thiolation of 2° Alkyl Boronic Acids[a,b]



[a]Reaction conditions: alkylboronic acid (0.75 mmol), reagent **1** (0.5 mmol), CuTc (20 mol %), bpy (40 mol %), and K_2CO_3 (2.0 equiv) in 1,2-dichloroethane (2.5 mL) at 120 °C for 12 h. [b] Isolated yield.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: shenql@sioc.ac.cn.
*E-mail: lulong@sioc.ac.cn.

Notes

The authors declare no competing financial interest.

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