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Copper-mediated trifluoromethylation of arylboronic acids by trifluoromethyl sulfonium salts†

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The ligand-free trifluoromethylation of arylboronic acids with a $[Ph_2SCF_3]^+[OTf]^-$/Cu(0) system has been carefully investigated. Aryl-, alkenyl- and heteroarylboronic acids with a variety of functional groups were suitable substrates for this reaction. It is suggested that a $CuCF_3$ species is formed under the reaction conditions.

Trifluoromethylated compounds have been widely used in the fields of biochemistry and materials science. Their unique physical and biological properties, the direct result of the fluorine substituents, have made them suitable as pharmaceuticals, agricultural chemicals, polymers and liquid crystals.[1] Trifluoromethylated compounds are often more difficult to synthesize than their non-fluorinated analogues. Although there are many approaches, the development of more efficient methodology to meet the increasing demands for fluorinated chemicals is a high priority.[2]

It is known that methods for the direct introduction of the trifluoromethyl group into common organic compounds are available through radical, nucleophilic or electrophilic approaches.[1] Recently, notable breakthroughs have been made in transition metal-catalyzed cross-coupling trifluoromethylation.[3] For example, Sanford *et al.* developed the Pd(II/IV)-catalyzed arene trifluoromethylation reaction, in which Ar–CF_3 species were formed by thermolysis of the palladium(IV) intermediate.[3a,b] Furthermore, Buchwald *et al.* found that the use of suitable ligands enabled the Pd(II)-catalyzed trifluoromethylation of a wide variety of aryl chlorides, allowing the transformation of a wide range of substrates in excellent yields.[3d] Although Pd-catalyzed coupling reactions have achieved remarkable results, Cu-mediated trifluoromethylation is still the main approach for the preparation of trifluoromethylated compounds.[4] However, Cu-mediated trifluoromethylation has, so far, been limited almost entirely to the reaction of aryl iodides and bromides with nucleophilic trifluoromethylating reagents [*e.g.* $TMSCF_3$, $FSO_2CF_2CO_2Me$, $CF_3CO_2Na(K)$].[1,4] Chu and Qing have recently developed a method to trifluoromethylate terminal alkynes using Me_3SiCF_3 as the reagent,[4c] and this is a significant advance in the Cu(I)-mediated trifluoromethylation field. In addition, Chu and Qing found that Cu(I)-mediated oxidative cross-coupling takes place between aryl- or alkenylboronic acids and Me_3SiCF_3.[4d] Soon afterwards, Buchwald *et al.* reported a Cu-mediated oxidative arene trifluoromethylation, in which aryl and heteroarylboronic acids are trifluoromethylated by Me_3SiCF_3 at room temperature.[4e] It is clear that copper-mediated trifluoromethylation using the available reagents under mild and environment-friendly conditions has drawn considerable attention from medicinal and materials chemists.

S-(Trifluoromethyl)diarylsulfonium salts, which were first prepared by Yagupolskii and then developed by Umemoto, Shreeve and Shibata, have been successfully used for the electrophilic trifluoromethylation of nucleophiles.[5] However, only a few applications over and above the electrophilic reactions of these reagents have been reported.[3c,4h,i,6] In fact, reactions using Cu(I) and electrophilic CF_3^+ as trifluoromethylating reagents can achieve the same goal as using nucleophilic CF_3^- reagents.[4,6] Although only catalytic amounts of Cu(I) salts were needed in these reactions, it was found necessary to use ligands.[6] Moreover, cuprous salts have been carefully investigated but the use of copper powder has never been reported. Therefore, it was important to examine the Cu(0)-mediated trifluoromethylation of arylboronic acids using an *S*-(trifluoromethyl)diphenylsulfonium salt without ligands, and this is what we have done. Herein, we report the details of this work.

The trifluoromethylation of phenylboronic acid (**1a**) with $[Ph_2SCF_3]^+[OTf]^-$ (**3**) was selected as a model reaction. As shown in Table 1, copper and base had a major influence on this trifluoromethylation process. For example, treatment of **1a** with **3** in the absence of Cu and base at 50 °C for 14 h gave almost no conversion to **2a** (entry 1). Furthermore, the reaction of **1a**, **3** and K_2CO_3 in the absence of Cu under the same conditions did not produce the desired product **2a** either (entry 2). $[Ph_2SCF_3]^+[OTf]^-$ was consumed by K_2CO_3 in this reaction and 60% yield of CF_3H byproduct was formed (entry 2).[7a] This was determined by ^{19}F NMR

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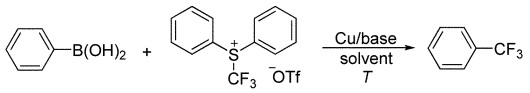
Table 1 Trifluoromethylation of phenylboronic acid by $[Ph_2SCF_3]^+$-$[OTf]^-$ without a ligand



1a 3 2a

Entry	1a:3:Cu:Base [a]	Base	Solvent	Conditions	Yield (2a, CF_3H, %) [b]
1	1 : 1 : 0 : 0	-	DMF	50 °C, 14 h	**0**, 0 (2 [c])
2	1 : 1 : 0 : 1	K_2CO_3	DMF	50 °C, 14 h	**0**, 60 (100 [c])
3	1 : 1 : 2 : 0	-	DMF	50 °C, 14 h	**22**, 0 (100 [c])
4	1 : 1 : 1 : 1	K_2CO_3	DMF	50 °C, 7 h	**46**, 19 (100 [c])
5	1 : 2 : 2 : 1	K_2CO_3	DMF	50 °C, 8 h	**28**, 62 (100 [c])
6	1 : 1 : 0.5 : 0.5	K_2CO_3	DMF	50 °C, 7 h	**24**, 26 (100 [c])
7	1 : 1 : 1 : 1	K_2CO_3	DMF	50 °C, 14 h	**48**, 20 (100 [c])
8	1 : 1 : 2 : 1	K_2CO_3	DMF	50 °C, 14 h	**61**, 19 (100 [c])
9	1 : 1 : 1 : 1	K_2CO_3	DMF	r.t., 14 h	**1**, 33 (99 [c])
10	1 : 1 : 1 : 1	K_2CO_3	CH_3CN	50 °C, 14 h	**4**, 24 (80 [c])
11	1 : 1 : 1 : 1	K_2CO_3	DCM	50 °C, 14 h	**0**, 0 (0 [c])
12	1 : 1 : 1 : 1	K_2CO_3	DMSO	50 °C, 14 h	**8**, 65 (100 [c])
13	1 : 1 : 1 : 1	K_2CO_3	THF	50 °C, 14 h	**0**, 40 (80 [c])
14	1 : 1 : 1 : 1	KF	DMF	50 °C, 14 h	**6**, 20 (100 [c])
15	1 : 1 : 2 : 1	Cs_2CO_3	DMF	50 °C, 14 h	**5**, 61 (100 [c])
16	1 : 1 : 1 : 1	NaOAc	DMF	50 °C, 18 h	**8**, 30 (100 [c])
17	1 : 1 : 2 : 1	2,2'-bipyridine	DMF	50 °C, 14 h	**10**, 0 (100 [c])
18	1 : 1 : 2 : 1	$NaHCO_3$	DMF	50 °C, 11 h	**38**, trace (100 [c])
19	1 : 2 : 2 : 1	$NaHCO_3$	DMF	50 °C, 11 h	**84**, trace (100 [c])
20	1 : 1 : 1 : 1	$NaHCO_3$	DMF	50 °C, 0.5 h	**36**, 3 (89 [c])

[a] Molar ratios. [a] Determined by ^{19}F NMR analysis of the reaction mixture, using $[OTf]^-$ as the internal standard. [a] The conversion of **3**, determined by ^{19}F NMR.

spectra (see ESI†). When our previous trifluoromethylation conditions were employed to conduct the reaction, **2a** was obtained as expected,[4h] but the yield was very low (entry 3). Further investigation indicated that the addition of the base could improve the yield of **2a** (entries 4–8). Byproducts such as benzene, phenol and biphenyl were also generated in this reaction, according to the GC-MS analysis of the reaction mixture. This was the same case as reported in the literature.[4d,e,6]

Moreover, the reaction time and the reactant ratio also influenced the reaction. Prolonging the reaction time from 7 h to 14 h, little difference was found in the yield of **2a** and CF_3H (entries 4 and 7). Increasing the amount of both **3** and Cu to 2 equiv. surprisingly suppressed the required reaction and led to higher yield of CF_3H (entry 5). Reducing the amount of Cu and K_2CO_3 to 0.5 equiv. also discouraged the trifluoromethylation (entry 6). The yield of **2a** was increased (61%) when 2 equiv. of Cu was used (entry 8). The temperature also has influence on this reaction. Running the reaction at room temperature resulted in the formation of only a trace of **2a** (entry 9).

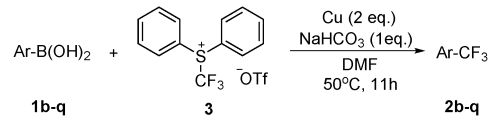
The effect of solvents was also investigated. Treatment of **1a** with **3** in CH_3CN gave **2a** in only 4% yield and CF_3H in 24% yield (entry 10). Unreacted compound **3** still remained in this reaction. When DCM was used instead of CH_3CN, no reaction took place (entry 11). Substantial amounts of CF_3H were formed when the reaction was conducted in DMSO (entry 12), and similar results were also found when THF was used as solvent (entry 13).

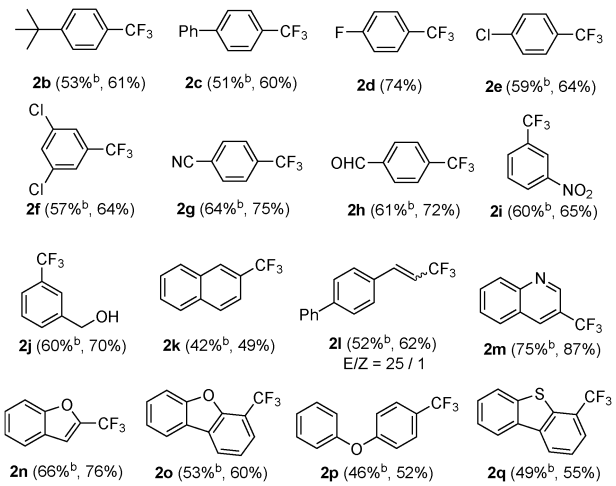
Various bases were employed to improve the trifluoromethylation of phenylboronic acid. It was found that the trifluoromethylation reaction is very sensitive to the choice of base. Using KF, Cs_2CO_3, and NaOAc as bases, **2a** was obtained in lower yield (entries 14–16), and CF_3H was generated in large amounts. Even 2 equiv. of Cu could not inhibit the formation of CF_3H and promote the trifluoromethylation. 2,2′-Bipyridine is a useful reagent and can be used not only as a base but also as a ligand. With 2,2′-bipyridine, no CF_3H was formed in this reaction, but the yield of **2a** was still very low (entry 17). Employing $NaHCO_3$ as base, **2a** was obtained in moderate yield (entry 18), and only a trace of CF_3H was observed. Increasing the molar ratio of **3** and Cu to 2 equiv., **2a** was obtained in a very satisfactory 84% yield (entry 19), and only small quantities of CF_3H were formed. This was very different from the case using K_2CO_3 and Cs_2CO_3 as the base (entries 5, 15 and 19). It seems that bases which are weak or sterically hindered favor the trifluoromethylation process and suppress the hydrogenation of *S*-(trifluoromethyl)diphenylsulfonium salts (entries 2 and 17). Sulfonium salts that are more reactive than fluoroalkyl halides would be easily hydrogenated by a strong base.[7b] On the other hand, the strength or the nucleophilicity of the base was important for the reaction. When its nucleophilicity is not strong enough, the $[CF_3]^-$ intermediate decomposes and generates a fluoride ion which then activates the phenylboronic acid, leading to the formation of fluorine-containing byproducts with signals around $\delta = -149$ ppm in the ^{19}F NMR spectrum (see ESI†). Under these conditions, trifluoromethylation is suppressed, leading only to a low yield of the desired product. Similar results were also obtained in the absence of a base (entry 3). Due to the stability of the B–F bond, reaction between the boron atom in **1a** and the fluoride ion is favourable, which leads to the decomposition of $[CF_3]^-$ species. On the basis of these arguments, we believe that $NaHCO_3$ has the best balance of properties and is the optimal choice of base for this reaction.

With the optimized conditions in hand (entry 19 in Table 1), we further investigated the scope of the ligand-free copper-mediated trifluoromethylation of arylboronic acids. As shown in Table 2, electron-rich and electron-poor arylboronic acids could be successfully trifluoromethylated (**2b–f**). Arylboronic acids with functional groups such as CN, CHO, NO_2, and OH were all suitable substrates for this reaction (**2g–j**). 2-Naphthylboronic acid was also converted into the trifluoromethyl-substituted product in a reasonable yield (**2k**). An alkenylboronic acid reacted with **3** and Cu under the same conditions, giving **2l** in a good yield. Heteroarylboronic acids could also be trifluoromethylated and some pharmaceutically important trifluoromethyl-substituted aromatic and heteroaromatic compounds were synthesized (**2m–q**).

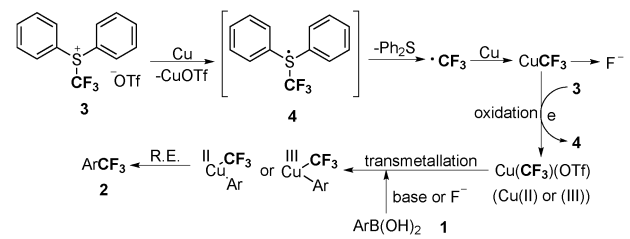
A mechanism for this reaction is proposed in Scheme 1.[4h,i,8] We suggest that the $CuCF_3$ intermediate is formed *via* a single electron transfer process and is then oxidated to a Cu(II)- or Cu(III)-complex by **3**. The Cu(II)- or Cu(III)-complex then undergoes transmetallation with the arylboronic acid to form an aryl-Cu(II) or -Cu(III) intermediate, which goes on to produce the trifluoromethylated product by facile reductive elimination. This was different in the process proposed by Liu.[6] Evidence for this mechanism was obtained by the analysis of the ^{19}F NMR and MS spectra of the reaction mixtures (see entries 10, 12, 14 and 20 of Table 1 and ESI†). ^{19}F NMR detection of the reaction mixture (entry 20 of Table 1) showed that $CuCF_3$ is generated in this reaction

Table 2 Trifluoromethylation of aryl-, heteroaryl and alkenylboronic acids by $[Ph_2SCF_3]^+[OTf]^-$[a]





[a] The molar ratio of **1b–q** : **3** : Cu : $NaHCO_3$ was 1 : 2 : 2 : 1. The yield was determined by ^{19}F NMR. [b] Isolated yield.



Scheme 1 Proposed mechanism for the trifluoromethylation of arylboronic acids with **3**.

(δ = −33.0 ppm). ESI-MS analysis further suggested that $CuCF_3$, $Cu(CF_3)(OTf)$, $Cu(CF_3)(C_6H_5)$, and $Cu(CF_3)(OTf)(C_6H_5)$ were formed in the reaction (m/z = 131.9, 280.9, 209.0 and 357.9, see ESI†).

In conclusion, the ligand-free trifluoromethylation of a variety of boronic acids with *S*-(trifluoromethyl)diphenylsulfonium triflate and copper powder has been carefully investigated. Aryl-, alkenyl- and heteroarylboronic acids incorporating a variety of functional groups are all suitable substrates for this reaction. The choice of base has an important influence on the trifluoromethylation process. We assume that a $CuCF_3$ species takes part in the reaction, and suggest that the mechanism involves a Cu(II)- or Cu(III)-complex undergoing transmetallation and reductive elimination.

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6 During the preparation of this manuscript, Liu *et al.* reported the Cu(I)-catalyzed trifluoromethylation of arylboronic acids using Umemoto's reagent and a suitable ligand (*Chem. Commun.*, 2011, **47**, 4300), and Shen *et al.* reported the Cu(I)-catalyzed trifluoromethylation of aryl and vinylboronic acids with Togni's reagent (*Org. Lett.* 2011, **13**, 2342).

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