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# Copper-mediated trifluoromethylation of potassium alkynyltrifluoroborates with Langlois' reagent

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ABSTRACT

Synthesis of trifluoromethylated acetylenes by copper-mediated trifluoromethylation of potassium alkynyltrifluoroborates with $CF_3$ radicals generated from $NaSO_2CF_3$ and *tert*-butyl hydroperoxide (TBHP) is communicated. The trifluoromethylated acetylenes were obtained in good to moderate yields. The presented method tolerates a wide range of aromatic, heteroaromatic, and aliphatic potassium alkynyltrifluoroborates.



## 1. Introduction

Trifluoromethyl-substituted compounds are increasingly important structural motifs in pharmaceuticals, agrochemicals, and organic materials due to their unique properties imparted by the trifluoromethyl group, such as high electron density, steric hindrance, and solubility.[1] The importance of incorporation of a trifluoromethyl group into aryl, alkenyl-, alkynyl motifs is evident from their elaborate use in material and medicinal chemistry.[2] The development of efficient methods for preparing trifluoromethylated arenes, alkenes, and acetylenes has been a topic of increasing importance in organic synthesis.[3] The trifluoromethyl group is incorporated into organic molecules by several methods, including nucleophilic,[4] electrophilic,[5] or radical reactions.[6]

Copper in catalytic/stoichiometric amounts is widely used in nucleophilic, electrophilic, and radical reactions. A trifluoromethyl group is installed by the reaction between a nucleophilic $CF_3^-$ source (Ruppert reagent ($CF_3SiMe_3$),[7] $K[CF_3B(OMe)_3]$,[8] $CF_3H$,[9] ($FSO_2CF_2SO_2Me$, $ClCF_2CO_2Me$, $CF_3CO_2Na$, etc.)[3e]), and aryl halides/triflates. A trifluoromethyl group is also incorporated via electrophilic $CF_3^+$ sources (Umemoto's reagent,[10] and Togni's reagent[11]) with aryl/heteroaryl boronic acids. Besides, oxidative coupling reactions also have been applied.[12] Langlois reported of the use of $CF_3SO_2Na$ to generate $CF_3$ radicals by the reaction with *tert*-butyl hydroperoxide (TBHP), and its subsequent incorporation into aryl and heteroaryl motifs.[13] The latter method is further elaborated into Cu-catalyzed/mediated reactions with boronic acids.[14,15]

Recently, groups of Buchwald,[16] Wang,[17] and others[18] developed Cu-catalyzed trifluoromethylation of unactivated olefins by using Togni's reagent. Pd-catalyzed cross-coupling is typically employed in the synthesis of trifluoromethylated acetylenes.[19,20] Direct C–H bond trifluoromethylation of terminal alkynes provides trifluoromethylated acetylenes in a straightforward fashion.[21–23] Research groups of Qing, Weng, and Fu made use of Cu in catalytic/stoichiometric amounts in the trifluoromethylation of terminal alkynes using Ruppert, Togni or Umemoto reagents. While these methods deliver an equitable protocol to trifluoromethyl alkynes, they still require excess amounts of reagents and/or base and high reaction temperatures, leaving behind a forcing need for further development of methods towards competent formation of such molecules. Recently, Huang and Weng reported copper-catalyzed trifluoromethylation of potassium

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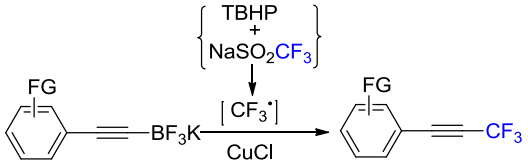
alkynyltrifluoroborates with Togni's reagent.[24] However, Langlois' reagent ($NaSO_2CF_3$) has not been explored as a trifluoromethylating agent with potassium alkynyltrifluoroborates. Very recently, we reported copper-mediated trifluoromethylation of potassium aryl- and alkenyltrifluoroborates with Langlois' reagent.[25]

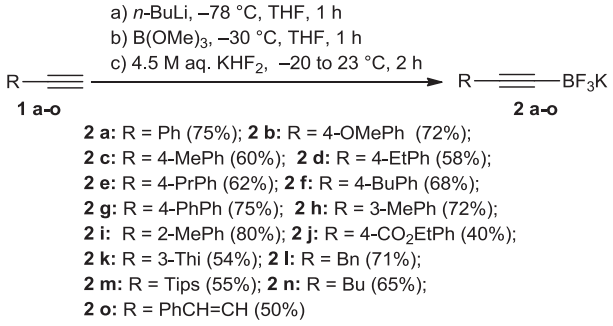
Herein we report the synthesis of trifluoromethylated acetylenes by the reaction of potassium alkynyltrifluoroborates with Langlois' reagent and TBHP in a copper-mediated trifluoromethylation (Scheme 1).




**Scheme 1.** Cu-mediated trifluoromethylation of potassium alkynyltrifluoroborates with Langlois' reagent.

## 2. Results and discussion

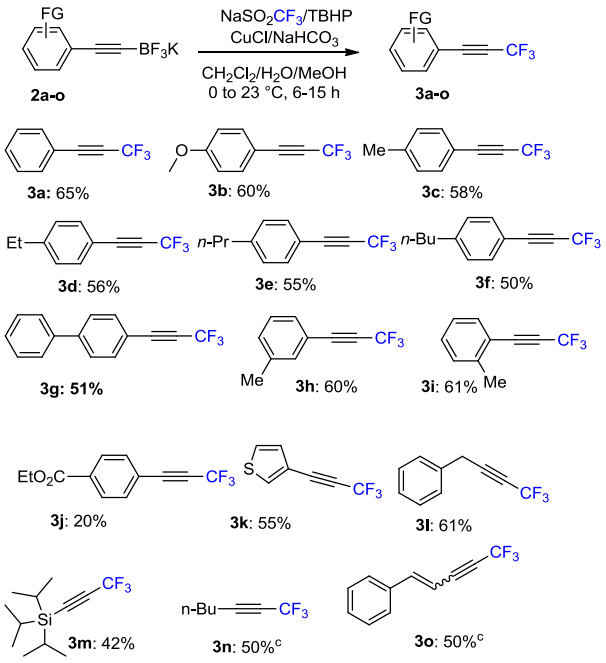
The potassium alkynyltrifluoroborates **2a**–**o** used in this study were prepared from the corresponding acetylenes **1a**–**o** (Scheme 2). The acetylenes were deprotonated with *n*-BuLi in THF at −78 °C. After 60 min, addition of trimethoxyborane (1.5 equiv, −30 °C, 60 min), followed by $KHF_2$ (6.0 equiv) in $H_2O$ resulted in the formation of alkynyltrifluoroborates **2a**–**o** in good yields (Scheme 2) and their structures were confirmed by $^1H$, and $^{19}F$ NMR analyses.[26] Interestingly, the triisopropylsilyl group was not removed by $KHF_2$ and compound **2m** was obtained in 55% yield. Furthermore, we prepared enyne trifluoroborate **2o** in 50% yield.




**Scheme 2.** Preparation of alkynyltrifluoroborates **2a**–**o**; for structures, see Table 1.

In this study of preparing trifluoromethylated alkynes from potassium alkynyltrifluoroborates, we directly applied the previously optimized conditions for the preparation of trifluoromethylated arenes and alkenes, i.e., (trifluoroborate (1.0 equiv, 0.25 mmol), CuCl (1.0 equiv), $NaHCO_3$ (1.0 equiv), $NaSO_2CF_3$ (3.0 equiv), TBHP (5.0 equiv) in $CH_2Cl_2$/MeOH/$H_2O$ at 0–23 °C). Subsequently we explored the substrate scope of this method. Aromatic, heteroaromatic, and aliphatic potassium alkynyltrifluoroborates were selected for the trifluoromethylation reaction. We found that electron-rich substrates gave good yields in most of the cases whereas electron-withdrawing substrates gave only poor yield (Table 1). Ethynylarenetrifluoroborates bearing electron-donating substituents (methoxy, methyl, ethyl, propyl, butyl, and phenyl) underwent trifluoromethylation in good yields (Table 1, **3b**, 60%; **3c**, 58%; **3d**, 56%; **3e**, 55%; **3f**, 50%; **3g**, 51%). Trifluoromethylation of an electron-deficient substrate produced the desired trifluoromethylated product in poor yield (Table 1, **3j**, 20%). Our protocol also accommodates *meta* and *ortho*-substituted aryl ethynyltrifluoroborate (**2h**, **2i**) affording acceptable yields (Table 1, **3h**, 60%; **3i**, 61%). We also employed a heterocycle, 3-ethynyl thiophenetrifluoroborate **2k** that gave moderate yield (Table 1, **3k**, 55%). Additionally, we tested aliphatic alkynyltrifluoroborates under our reaction conditions to give the corresponding trifluoromethylated products in good yield (Table 1, **3l**, 61%; **3m**, 42%; **3n**, 50%). Under our reaction conditions, we could engage enyne trifluoroborate (**2m**) for trifluoromethylation, whereby, **3m** was obtained in 50%. Usually, trifluoromethylated enynes are considered as quite valuable synthetic intermediates.[27]

**Table 1**
Copper-mediated trifluoromethylation of aryl and aliphatic alkynyltrifluoroborates[a,b]




[a] Reaction conditions: Trifluoroborate (1.0 equiv, 0.25 mmol), CuCl (1.0 equiv), $NaHCO_3$ (1.0 equiv), $NaSO_2CF_3$ (3.0 equiv), TBHP (5.0 equiv) in $CH_2Cl_2$/MeOH/$H_2O$ at 0 to 23 °C for 6-12 h. [b] Isolated yield. [c] For volatile products, yields were determined by $^{19}F$ NMR with 4-fluorobenzonitrile as an internal standard added after the reaction.

Based on the above observations, we envisioned that the $CF_3$ radical generated from the reaction of TBHP with $NaSO_2CF_3$ oxidizes Cu(I) to a Cu(II)- or Cu(III)-complex. The Cu(II)- or Cu(III)-complex then undergoes transmetallation with the alkynyltrifluoroborate to form an alkynyl–Cu(II) or –Cu(III) intermediate. Reductive elimination then follows to produce the trifluoromethylated product.[28] Electron-withdrawing group results in a slower transmetallation of potassium alkynyltrifluoroborate, which might account for their poorer yields.[14,15,25]

## 3. Conclusions

In summary, we report a convenient Cu-mediated trifluoromethylation of aryl-, heteroaryl, alkenyl, and aliphatic alkynyltrifluoroborates,[29] using less expensive and stable $CF_3SO_2Na$ as the $CF_3$ source by in situ generation of $CF_3^{\bullet}$ as the active trifluoromethylating agent. The protocol is quite robust and the reactions work in water and $CH_2Cl_2$/MeOH at room temperature.

## 4. Experimental

### 4.1. General information

$^1$H NMR spectra, $^{19}$F NMR, and $^{13}$C NMR were recorded on Bruker 400 MHz or 300 MHz instruments in the solvents indicated; chemical shifts are reported in units (parts per million) by assigning $CHCl_3$ resonance in the $^1$H spectrum as 7.26 ppm and $CDCl_3$ resonance in the $^{13}$C spectrum as 77.0 ppm. $^{19}$F NMR chemical shifts were determined relative to $CFCl_3$ as internal standard and are measured proton decoupled. All coupling constants (*J* values) were reported in Hertz (Hz). GC and GC–MS spectra were measured on Shimadzu. Column chromatography was performed on silica gel 200–300 mesh on Combiflash. If not specially mentioned, all the solvents and reagents were used as purchased and without further purification.

### 4.2. General procedure for preparation of potassium alkynyltrifluoroborates (Scheme 2)

*n*-BuLi (4.70 mL, 1.6 M in hexane, 7.57 mmol, 1.0 equiv) was added dropwise to a solution of acetylene (7.57 mmol, 1.0 equiv) in 7.6 mL of dry THF at −78 °C under a nitrogen atmosphere. After 60 min at this temperature, trimethylborate (1.10 g, 11.3 mmol, 1.5 equiv) was added dropwise at −30 °C. The mixture was stirred at this temperature for 60 min and slowly allowed to warm to room temperature within another 60 min. A saturated 4.5 M aqueous solution of potassium hydrogen difluoride ($KHF_2$) (10.1 mL, 45.3 mmol, 6.0 equiv) was added at −20 °C to the vigorously stirred solution. The resulting mixture was continued to stir for 60 min at −20 °C after which it was allowed to warm to room temperature for 60 min. The solvent was removed under reduced pressure, and the resulting white solid was dried under high vacuum to remove water. The solid was washed first with acetone and then with hot acetone. The solution was concentrated to afford a white solid. The solid was dissolved in minimum amount of hot acetone, precipitated by adding methyl *tert*-butyl ether (MTBE), after which the solution was cooled to −20 °C to complete precipitation of the solid. The product was collected as an off white solid **2a**–**o** in 40–80% yield.

### 4.3. General procedure for copper-catalyzed trifluoromethylation of potassium alkynyltrifluoroborates with Langlois' reagent (Table 1)

A mixture of the potassium alkynyltrifluoroborate (0.25 mmol, 1.0 equiv), CuCl (24.8 mg, 0.25 mmol, 1.0 equiv), $NaSO_2CF_3$ (117 mg, 0.75 mmol, 3.0 equiv), $NaHCO_3$ (21.0 mg, 0.25 mmol, 3.0 equiv) in $CH_2Cl_2$ (1.5 mL), MeOH (1.5 mL), and $H_2O$ (1.2 mL) was cooled to 0 °C, and TBHP (70% solution in water, 172 μl, 5.0 equiv, 1.25 mmol) was added under vigorous stirring. The resulted reaction mixture was stirred for 6–12 h at room temperature. The organic phase was separated, the aqueous phase was extracted with $CH_2Cl_2$ (3×10 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$, the solvent was removed at 1 atm and the residue was purified by column chromatography on Combiflash with hexanes to afford desired compound.

The volatile products were not isolated (**3n** and **3o**) and their yields were determined only by $^{19}$F NMR of the reaction mixture. For the compounds reported with $^{19}$F NMR yields, 4-fluorobenzonitrile (0.25 mmol) was added as reference to the reaction mixture, stirred for 5 min, an aliquot of the organic phase was withdrawn for the $^{19}$F NMR measurement in $CDCl_3$.

Analytical data of isolated products **3a**,[21a] **3b**,[21a] **3c**,[22] **3d**,[22] **3e**,[22] **3f**,[24] **3g**,[21c] **3h**,[22] **3i**,[22] **3j**,[21] **3k**,[21a] **3l**,[22] and **3m**[23] are identical to those given in literature. The purity of isolated products was determined by GC and was >96%.

*4.3.1. (3,3,3-Trifluoroprop-1-ynyl)benzene (**3a**).*[21a] $^1$H NMR (400 MHz, DMSO-$d_6$): δ ppm 7.32–7.19 (m, 5H); $^{19}$F NMR (400 MHz, DMSO-$d_6$): δ ppm −50.00 (s, 3F); GC–MS *m*/*z* 170 ($M^+$).

*4.3.2. 1-Methoxy-4-(3,3,3-trifluoroprop-1-ynyl)benzene (**3b**).*[21a] $^1$H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J*=8.7 Hz, 2H), 6.89 (d, *J*=9.0 Hz, 2H), 3.84 (s, 3H); $^{19}$F NMR ($CDCl_3$, 282 MHz): δ −49.41 (s, 3F); GC–MS *m*/*z* 200 ($M^+$).

*4.3.3. 1-Methyl-4-(3,3,3-trifluoroprop-1-ynyl)benzene (**3c**).*[22] $^1$H NMR (400 MHz, $CDCl_3$): δ ppm 7.43 (d, *J*=7.9 Hz, 2H), 7.20 (d, *J*=7.9 Hz, 2H), 2.39 (s, 3H); $^{19}$F NMR (377 MHz, $CDCl_3$): δ ppm −50.40 (s, 3F); GC–MS *m*/*z* 184 ($M^+$).

*4.3.4. 1-Ethyl-4-(3,3,3-trifluoroprop-1-ynyl)benzene (**3d**).*[22] $^1$H NMR (400 MHz, $CDCl_3$): δ ppm 7.47 (d, *J*=8.3 Hz, 2H), 7.22 (d, *J*=8.2 Hz, 2H), 2.69 (q, *J*=7.7 Hz, 2H), 1.24 (t, *J*=7.8 Hz, 3H); $^{19}$F NMR (377 MHz, $CDCl_3$): δ ppm −49.57 (s, 3F); GC–MS *m*/*z* 198 ($M^+$).

*4.3.5. 1-Propyl-4-(3,3,3-trifluoroprop-1-ynyl)benzene (**3e**).*[22] $^1$H NMR (400 MHz, $CDCl_3$): δ ppm 7.46 (d, *J*=7.9 Hz, 2H), 7.20 (d, *J*=7.9 Hz, 2H), 2.61 (t, *J*=7.5 Hz, 2H), 1.66–1.61 (m, 2H), 0.95 (t, *J*=7.5 Hz, 3H); $^{19}$F NMR (377 MHz, $CDCl_3$): δ ppm −50.58 (s, 3F); GC–MS *m*/*z* 212 ($M^+$).

*4.3.6. 1-Butyl-4-(3,3,3-trifluoroprop-1-ynyl)benzene (**3f**).*[24] $^1$H NMR (400 MHz, $CDCl_3$): δ ppm 7.45 (d, *J*=7.9 Hz, 2H), 7.21 (d, *J*=7.9 Hz, 2H), 2.73–2.53 (m, 2H), 1.61–1.58 (m, 2H), 1.35–1.31 (m, 2H), 0.95 (t, *J*=7.5 Hz, 3H); $^{19}$F NMR (377 MHz, $CDCl_3$): δ ppm −50.77 (s, 3F). GC–MS *m*/*z* 226 ($M^+$).

*4.3.7. 4-(3,3,3-Trifluoroprop-1-yn-1-yl)-1,1′-biphenyl (**3g**).*[21c] $^1$H NMR (400 MHz, $CDCl_3$): δ ppm 7.68–7.55 (m, 6H), 7.48–7.43 (m, 2H), 7.41–7.38 (m, 1H); $^{19}$F NMR (377 MHz, $CDCl_3$): δ ppm −49.69 (s, 3F); GC–MS *m*/*z* 246 ($M^+$).

*4.3.8. 1-Methyl-3-(3,3,3-trifluoroprop-1-ynyl)benzene (**3h**).*[22] $^1$H NMR (400 MHz, $CDCl_3$): δ ppm 7.37–7.35 (m, 2H), 7.30–7.29 (m, 2H), 2.37 (s, 3H); $^{19}$F NMR (377 MHz, $CDCl_3$): δ ppm −49.73 (s, 3F); GC–MS *m*/*z* 184 ($M^+$).

*4.3.9. 1-Methyl-2-(3,3,3-trifluoroprop-1-ynyl)benzene (**3i**).*[22] $^1$H NMR (400 MHz, $CDCl_3$): δ ppm 7.50 (d, *J*=6.8 Hz, 1H), 7.50 (d, *J*=7.7 Hz, 1H), 7.32–7.19 (m, 1H), 7.17–7.12 (m, 1H), 2.49 (s, 3H); $^{19}$F NMR (377 MHz, $CDCl_3$): δ ppm −49.70 (s, 3F); GC–MS *m*/*z* 184 ($M^+$).

*4.3.10. Ethyl 4-(3,3,3-trifluoroprop-1-yn-1-yl)benzoate (**3j**).*[21a] $^1$H NMR (400 MHz, $CDCl_3$): δ ppm 8.12 (d, *J*=7.9 Hz, 2H), 7.65 (d, *J*=7.9 Hz, 2H), 4.42 (q, *J*=6.3 Hz, 2H), 1.45 (t, *J*=6.3 Hz, 3H); $^{19}$F NMR (377 MHz, $CDCl_3$): δ ppm −49.71 (s, 3F). GC–MS *m*/*z* 242 ($M^+$).

*4.3.11. 3-(3,3,3-Trifluoroprop-1-yn-1-yl)thiophene (**3k**).*[21a] $^1$H NMR (300 MHz, $CDCl_3$): δ ppm 7.58 (dd, *J*=3.1, 1.5 Hz, 1H), 7.28 (dd, *J*=5.3, 3.0 Hz, 1H), 7.17 (dd, *J*=5.0 Hz, 1.1 Hz, 1H); $^{19}$F NMR (377 MHz, $CDCl_3$): δ ppm −49.41 (s, 3F); GC–MS: 176 ($M^+$).

*4.3.12. (4,4,4-Trifluorobut-2-yn-1-yl)benzene (**3l**).*[22] $^1$H NMR (300 MHz, $CDCl_3$): δ ppm 7.38–7.31 (m, 2H), 7.32–7.27 (m, 3H), 3.73 (d, *J*=3.6 Hz, 1H), 3.71 (d, *J*=3.6 Hz, 1H); $^{19}$F NMR (377 MHz, $CDCl_3$): δ ppm −49.7 (s, 3F); GC–MS: 184 ($M^+$).

*4.3.13. Triisopropyl(3,3,3-trifluoroprop-1-yn-1-yl)silane (**3m**).*[23] $^1$H NMR (400 MHz, $CDCl_3$): δ ppm 1.25–1.05 (m, 3H), 1.10 (d, *J*=6.0 Hz,

18H); $^{19}$F NMR (377 MHz, $CDCl_3$): $\delta$ ppm −50.48 (s, 3F); GC–MS: 207 ($M^+$–43 ($CH(CH_3)_2$)).

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28. There might other unforeseen reaction mechanisms exist.
29. We attempted to generate phenylethynylboronic acid (**4a**) from potassium phenylethynyltrifluoroborate (**2a**) under basic reaction condition ($Cs_2CO_3$[30] in THF/$H_2O$ or $NaHCO_3$ in MeOH/$H_2O$) at 60 °C for 15–24 h. However, there was no conversion from **2a** to boronic acid **4a** and when the reaction was kept for longer time; protodeboronated phenylacetylene (**1a**) was observed.
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