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Copper-Mediated Aerobic Oxidative Trifluoromethylation of Terminal Alkynes with Me_3SiCF_3

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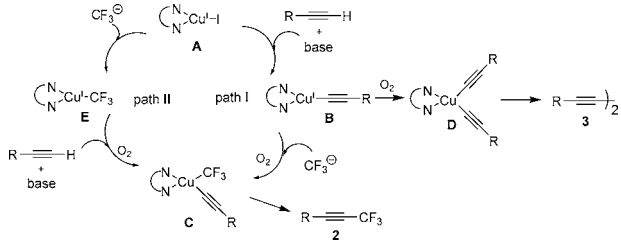
Trifluoromethylated compounds are of particular interest in the fields of polymers, agrochemicals, and pharmaceuticals due to the unique characteristics of the trifluoromethyl group ($-CF_3$), such as high electronegativity, electron density, steric hindrance, and hydrophobicity.[1] Hence, it has been of great synthetic interest to develop an efficient method for incorporation of CF_3 into organic structures.[2] The cross-coupling reactions between $CuCF_3$ and electrophiles, such as aromatic halides,[3] and nucleophilic additions of CF_3^- to carbonyls[4] or imines[5] provide a number of powerful methods to access these valuable compounds. However, to the best of our knowledge, no example relating direct cross-coupling of $CuCF_3$ with nucleophiles has ever been reported so far, albeit this alternative strategy may open up a new viewpoint to prepare trifluoromethylated compounds. Recently, metal-catalyzed oxidative coupling reactions via functionalization of C−H bonds have received a great deal of interest and attention due to their atom and step economy.[6] Among these impressive research, significant progress has also been made in the arena of metal-catalyzed oxidative cross-coupling of terminal alkynes with nucleophiles,[7] which inspired us to hypothesize that the direct cross-coupling of terminal alkynes with $CuCF_3$ may be possible (Scheme 1).

Scheme 1. Plausible Reaction Pathways for Trifluoromethylation



On the other hand, as versatile building blocks, trifluoromethylated acetylenes have found widespread use in medicinal, agrochemical, and material science.[8] Usually, they can be prepared by Pd(0) catalyzed cross-coupling reactions of trifluoro-propynyl metal reagents with aryl iodides or dehalogenation of trifluoromethylethenes.[9] Electrophilic trifluoromethylation of alkynyl metal reagents have also been reported.[10] However, this "prefunctionalization" process suffers from tedious procedures and great caution for preparation of alkynyl metal reagents or using toxic substrates, thus the formation of alkynyl−CF_3 bonds remains an elusive goal. Herein, we described the first example of a copper-mediated protocol for $C_{sp}-C_{sp^3}$ oxidative trifluoromethylation of terminal alkynes with nucleophilic (trifluoromethyl)trimethylsilane (Ruppert−Prakash reagent, Me_3SiCF_3) (eq 1).[11] This reaction represents a straightforward and functional group compatible approach to a broad range of trifluoromethylated acetylenes in moderate to good yields.

$$R{-}\equiv \;+\; Me_3SiCF_3 \xrightarrow[\text{air}]{[Cu]} R{-}\equiv{-}CF_3 \qquad (1)$$

To test our hypothesis, initially, phenylacetylene **1a** was chosen as a model substrate for direct trifluoromethylation. When a mixture of **1a**, Me_3SiCF_3 (1.5 equiv), KF (1.5 equiv), and CuI (1.0 equiv) in DMF was heated at 100 °C under air atmosphere, a diyne byproduct **3a** was formed in 98% yield instead of our desired product **2a** (Table 1, entry 1). We ascribed that this negative result is presumably because the formation of Cu(alkynyl)(trifluoromethyl) complex **C** via path **I** or path **II** was inhibited by the competitive formation of bis-alkynyl-Cu complex **D** which will produce the undesired diyne byproduct (Scheme 1). Thus, we assumed that using a pregenerated $CuCF_3$ to avoid the formation of complex **B** might be possible to drive the reaction via path **II** to furnish **2a**.

As expected, when **1a** was added by using a syringe pump over a period of 4 h to $CuCF_3$[3a−h] generated *in situ* by mixing Me_3SiCF_3, KF, and CuI in DMF under air atmosphere, the desired product **2a** was formed in 16% yield, but the diyne **3a** was still the major product (78% yield) (entry 2). With this preliminary result in hand, the improvement of the reaction efficiency was conducted by screening of the diamine ligands as additive. To our delight, the yield of **2a** was improved to 51% and the byproduct **3a** was reduced to 43% in the presence of 1,10-phenanthroline (phen) (entries 3−5). The beneficial effects of phen included stabilizing the reactive Cu−CF_3 by chelation[3h] and increasing the electron density on the copper center by coordination and thus promoting the formation of Cu(II)[12] or Cu(III)[13] complex **C**, which then undergoes reductive elimination to deliver **2a** (Scheme 1). However, the mechanism of the formation of Cu(II) (or Cu(III)) complex from **E** (Scheme 1) was not clear at the moment. The ^{19}F NMR of the reaction mixture showed that Me_3SiCF_3 was fully consumed, and it indicated the decomposition of Me_3SiCF_3 took place under these reaction conditions, so the amount of Me_3SiCF_3 was increased to 5 equiv and we were pleased to find that the yield of **2a** was enhanced to 93% (entry 6). Other Cu(I) salts were less effective than CuI (entries 7−9). The screening of solvents showed that DMF was the optimal solvent (entries 10−11). When the loading of CuI was reduced to 0.5 equiv, the yield of **2a** dramatically dropped to 43% (entry 12). Surprisingly, when air was replaced with O_2, the reaction was completely inhibited and only **3a** was generated (entry 13). We surmised that the reactive $CuCF_3$ was quenched by the high concentration of oxygen.[3a]

The scope with respect to terminal alkynes is presented in Table 2. Aromatic alkynes (**1a**−**1p**) as well as aliphatic alkynes (**1q**−**1r**) afforded the corresponding trifluoromethylated products in moderate to good yields. Both electron-rich (**1a**−**1b**, **1e**, **1j**, **1p**) and electron-

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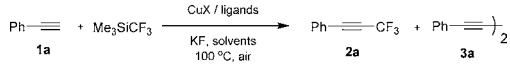
Table 1. Initial Studies for Copper-Mediated Trifluoromethylation of Terminal Alkynes[a]

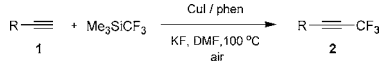


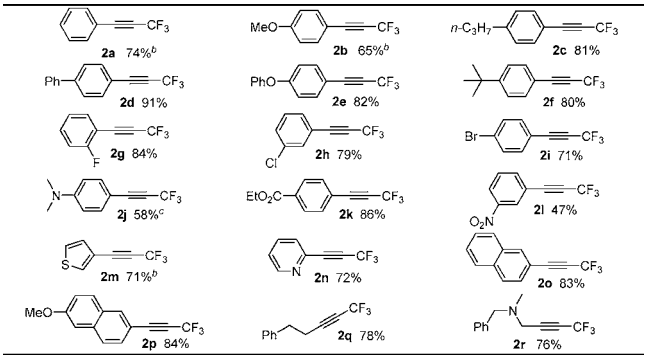
entry	CuX (equiv)	ligand (equiv)	solvent	% yield **2a** (**3a**)[b]
1[c,d]	CuI (1.0)	/	DMF	0 (98)
2[d]	CuI (1.0)	/	DMF	16 (78)
3[d]	CuI (1.0)	TMEDA (1.0)	DMF	8 (71)
4[d]	CuI (1.0)	Bipy (1.0)	DMF	25 (69)
5[d]	CuI (1.0)	phen (1.0)	DMF	51 (43)
6	**CuI (1.0)**	**phen (1.0)**	**DMF**	**93 (2)**
7	CuCl (1.0)	phen (1.0)	DMF	77 (16)
8	CuBr (1.0)	phen (1.0)	DMF	65 (23)
9	CuCN (1.0)	phen (1.0)	DMF	49 (44)
10	CuI (1.0)	phen (1.0)	Toluene	24 (54)
11	CuI (1.0)	phen (1.0)	CH_3CN	35 (49)
12	CuI (0.5)	phen (0.5)	DMF	43 (49)
13[e]	CuI (1.0)	phen (1.0)	DMF	<5 (92)

[a] Reaction conditions: **1a** (0.2 mmol), Me_3SiCF_3 (1.0 mmol), KF (1.0 mmol), air (1 atm), solvent (2 mL), 100 °C; **1a** was added to the reaction mixture over a 4 h period by using a syringe pump. [b] **2a**: yield was determined by ^{19}F NMR using benzotrifluoride as an internal standard. **3a**: yield was determined by GC. [c] **1a** was added in a single aliquot. [d] 1.5 equiv of Me_3SiCF_3. [e] Reaction was performed under O_2 atmosphere. phen = 1,10-phenanthroline, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, Bipy = 2,2′-bipyridine.

deficient aryl alkynes (**1g**−**1i**, **1k**−**1l**) were effective. A variety of functionalities, such as alkoxyl, amino, ester, and nitro groups were tolerated under the reaction conditions (**1b**, **1e**, **1j**−**1l**, **1p**, **1r**). Importantly, both chloro- and bromo-containing aryl alkynes were effective and further trifluoromethylated products were not observed while aryl chlorides and bromides are reactive coupling partners in Cu-mediated fluoro-*alkyl* cross-coupling reactions (**1h**−**1i**).[3a−h] The heterocyclic alkynes were also suitable in this reaction (**1m**−**1n**). It is particularly noteworthy that the reactions can be scaled up efficiently. **2a**, **2b**, and **2m** were successfully prepared on 10 mmol scales and the isolated yields after distillation were moderate, indicating the good reliability of the process.

Table 2. CuI-Mediated Trifluoromethylation of Terminal Alkynes[a]





[a] Reactions were conducted on 0.2 mmol scale under the reaction conditions of entry 6 in Table 1; Isolated yield. [b] Isolated yield after distillation on 10 mmol scale. [c] 27% of **1j** remained.

In conclusion, we have developed an efficient copper-mediated trifluoromethylation of terminal alkynes with a nucleophilic trifluoromethylating reagent (Me_3SiCF_3). This reaction provides a general, straightforward, and practically useful method to prepare trifluoromethylated acetylenes.

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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