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An Improved Copper-Mediated Oxidative Trifluoromethylation of Terminal Alkynes

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An improved method for the efficient copper-mediated trifluoromethylation of terminal alkynes has been developed. This protocol highlights the convenient access to a variety of aryl-substituted trifluoromethylated alkynes by oxidative trifluoromethylation with two equivalents of $TMSCF_3$ at room temperature.

Introduction

Currently, organic chemists and medicinal chemists have been paying attention to the introduction of fluorine atom(s) or fluorine-containing groups into potentially biologically active molecules because their introduction could bring about remarkable and profound changes in physical, chemical, and biological properties of the compounds.[1] For example, over 100 fluorine-containing compounds have been approved by the FDA in the United States for the treatment of different diseases. In 2007, 9 of the top 20 best-selling drugs in the world were fluorine-containing compounds or mixtures of fluorine-containing compounds and other compounds. Of all the fluorine-containing compounds, trifluoromethylated compounds are widely used in pharmaceuticals and agrochemicals.[2] Thus, the introduction of the strongly electron-withdrawing trifluoromethyl group (CF_3) into organic molecules, which has been shown to greatly change the bioactivity, biostability, and lipophilicity[1,2] of these compounds, continues to be a hot topic in current organic chemistry.

Generally, several methods have been utilized for the incorporation of the trifluoromethyl group into organic molecules, including radical,[3] electrophilic,[4] and nucleophilic[5] reactions. The efficient generation of the trifluoromethyl radical is the key step in radical-mediated trifluoromethylation reactions. For example, MacMillan and co-workers[3c] recently reported the asymmetric α-trifluoromethylation of aldehydes by the successful merger of an enamine and an organometallic photoredox, whose mechanism relied on the propensity of the trifluoromethyl radical (derived from the reduction of trifluoromethyl iodide by a photoredox catalyst) to combine with facially biased enamine intermediates (derived from aldehydes and a chiral amine catalyst). Nucleophilic trifluoromethylation has involved the generation of CF_3^- or a trifluoromethyl metal complex. For example, Amii's group[6] and Buchwald's group[7] described the Cu-catalyzed and Pd-catalyzed trifluoromethylation of aryl halides, respectively. We[8] and Buchwald[9] reported the Cu-mediated oxidative trifluoromethylation of boronic acids with the nucleophilic trifluoromethylation agent $TMSCF_3$ (Ruppert–Prakash reagent). Liu,[10] Sheng,[11] and Xiao[12] documented the Cu^I-catalyzed trifluoromethylation of boronic acids with electrophilic trifluoromethylation agents (Umemoto reagent and Togni reagent). Noteworthy is that Hartwig[13] and Grushin[14] recently prepared the trifluoromethylation Cu reagent [(phen)$CuCF_3$] and [(phen)Cu(PPh_3)(CF_3)], respectively, both of which reacted with aryl iodides to afford trifluoromethylated arenes in high yields. Most of the aforementioned examples involved the preparation of CF_3-substituted aryl compounds. In view of the importance of trifluoromethylated olefins and alkynes, several groups have recently developed efficient methodologies for the direct trifluoromethylation of unactivated olefins and alkynes. Buchwald[15] followed by Wang[16] described the Cu-catalyzed trifluoromethylation of terminal olefins by using the Togni electrophilic trifluoromethylation reagent. Using Umemoto's reagent and catalyzed by (thiophene-2-carbonyloxy)copper in the presence of 2,4,6-collidine, Liu and co-workers[17] reported another method for the trifluoromethylation of terminal alkenes. In 2010, our group[18] described the first example of a Cu-mediated protocol for the C_{sp}–C_{sp^3} oxidative trifluoromethylation of terminal alkynes with $TMSCF_3$. This method represented a straightforward and functional group compatible approach to a broad range of trifluoromethylated acetylenes in moderate to high

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yields. However, reaction temperatures up to 100 °C and the requirement of 5.0 equivalents of $TMSCF_3$ rendered this methodology less than ideal (Figure 1). We assume that this oxidative trifluoromethylation reaction would be successful at room temperature by using fewer equivalents of $TMSCF_3$ if the (phen)$Cu(CF_3)$ generated in situ from $TMSCF_3$[13] was used (Figure 1).

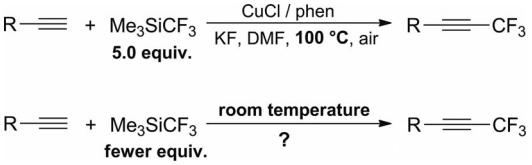


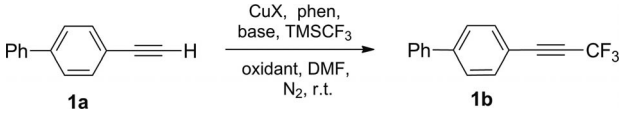
Figure 1. Cu-mediated trifluoromethylation of terminal alkynes.

Results and Discussion

To test our assumption, 4-ethynylbiphenyl was selected as a model substrate for direct trifluoromethylation; (phen)-$Cu(CF_3)$ was in situ prepared by using $TMSCF_3$ (2.0 equiv.), CuCl (2.0 equiv.), and *t*BuOK in DMF,[13] and then 4-ethynylbiphenyl was added to the mixture in air at room temperature. Analysis of the reaction mixture by ^{19}F NMR spectroscopy demonstrated that a trace amount of the trifluoromethylation product was formed. GC–MS of the reaction mixture showed that the major product was the diyne. On the basis of the above experimental result, we decided to replace the air with other oxidants. We were happy to find that substitution of $PhI(OAc)_2$ for air gave desired product **1b** in 53% yield (Table 1, Entry 2). The oxidant *t*BuOO*t*Bu gave almost the same yield (Table 1, Entry 3). In view of the successful trifluoromethylation of boronic acids by using Ag_2CO_3 as an oxidant,[8] Ag_2CO_3 was used instead of air for this oxidative trifluoromethylation. Excitingly, the yield of desired compound **1b** was improved to 90% yield (Table 1, Entry 4). Switching CuCl to other Cu salts, such as CuBr, CuI, and $Cu(OAc)_2$, significantly decreased the yield of **1b** (Table 1, Entries 5–7). It was found that compound **1b** was formed in low yield when KF was used as the base instead of *t*BuOK for the preparation of (phen)$Cu(CF_3)$ (Table 1, Entry 8). Thus, the optimal reaction conditions were established as follows: 2.0 equiv. of CuCl, 2.0 equiv. of phen, 2.0 equiv. of *t*BuOK, 2.0 equiv. of Ag_2CO_3, 2.0 equiv. of $TMSCF_3$, and 1.0 equiv. of terminal alkyne in DMF at room temperature.

With the optimal reaction conditions in hand, the scope of the oxidative trifluoromethylation of terminal alkynes was investigated (Table 2). Electron-rich terminal alkynes could be smoothly trifluoromethylated to give the corresponding products (i.e., **1b**, **6b**, **7b**–**10b**) in moderate to good yields. Trifluoromethylated aryl alkyne **3b** with a methoxycarbonyl substituent in the *ortho* position of the benzene ring was also obtained in 71% yield. Noteworthy is that ketone and ester groups were well tolerated (i.e., **3b**, **4b**, **11b**, **12b**) although substrates containing ketone groups were problematic because of the competitive 1,2-addition of the trifluoromethyl anion to the carbonyl group.[19]

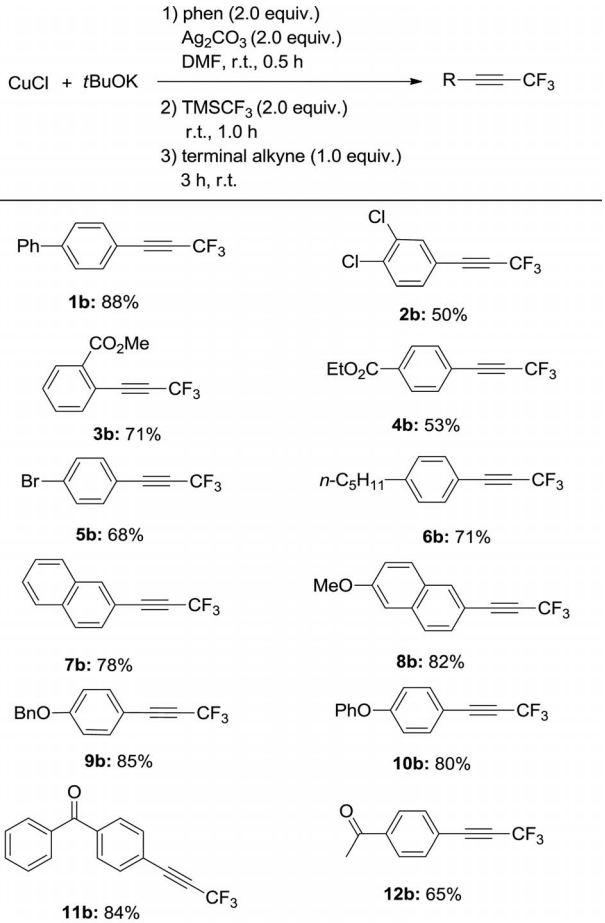
Table 1. Optimization of the oxidative trifluoromethylation of 4-ethynylbiphenyl (**1a**) at room temperature.[a]



Entry	Cu	Base (equiv.)	Oxidant	Yield [%][b]
1	CuCl	*t*BuOK (2.0)	air	2
2	CuCl	*t*BuOK (2.0)	$PhI(OAc)_2$	53
3	CuCl	*t*BuOK (2.0)	*t*BuOO*t*Bu	50
4	CuCl	*t*BuOK (2.0)	Ag_2CO_3	90
5	CuI	*t*BuOK (2.0)	Ag_2CO_3	30
6	CuBr	*t*BuOK (2.0)	Ag_2CO_3	37
7	$Cu(OAc)_2$	*t*BuOK (2.0)	Ag_2CO_3	13
8	CuCl	KF (2.0)	Ag_2CO_3	31

[a] Reaction conditions: **1a** (0.5 mmol), $TMSCF_3$ (1.0 mmol), [Cu] (1.0 mmol), phen (1.0 mmol), oxidant (1.0 mmol), and base(1.0 mmol) in DMF (4 mL) at room temperature under N_2. [b] Yield was determined by ^{19}F NMR spectroscopy with benzotrifluoride as an internal standard.

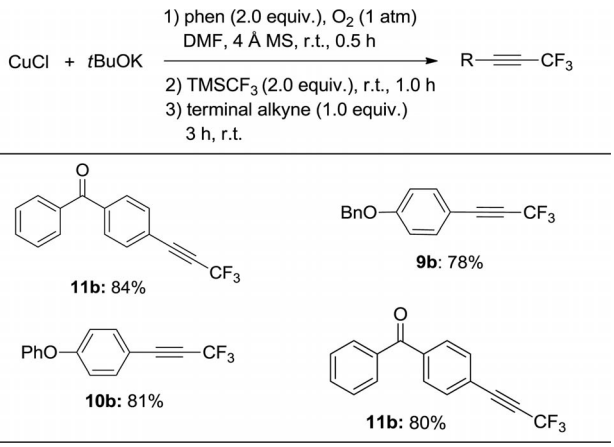
Table 2. Oxidative trifluoromethylation of terminal alkynes.[a,b]



[a] Reactions were conducted with 0.5 mmol of the terminal alkyne under the optimal conditions. [b] Isolated yields are given.

Although Ag_2CO_3 was a suitable oxidant in this protocol, this method was limited by its high price. We turned our attention to the development of an alternative oxidant. Recently, Buchwald and co-workers described the oxidative trifluoromethylation of aryl boronic acids by using oxygen as an oxidant.[9] Accordingly, oxygen was used for the oxidative trifluoromethylation of alkynes instead of expensive Ag_2CO_3 (Table 3). The isolated yields of the trifluoromethylated alkynes with the use of oxygen in the presence of 4 Å powdered molecular sieves were similar to those obtained with Ag_2CO_3.

Table 3. Oxidative trifluoromethylation of terminal alkynes by using oxygen as an oxidant.[a,b]



[a] CuCl (2.0 mmol), phen (2.0 mmol), *t*BuOK (2.0 mmol), $TMSCF_3$ (2.0 mmol), O_2 (1 atm), and 4 Å MS (200 mg) in DMF(2 mL) at room temperature; terminal alkyne/DMF (2.0 mL) solution was slowly added to the mixture over 3 h by using a syringe pump. [b] Isolated yields are given.

Conclusions

An improved procedure for the Cu-mediated oxidative trifluoromethylation of terminal alkynes has been developed. By using (phen)Cu(CF_3) generated in situ from $TMSCF_3$, this oxidative trifluoromethylation proceeded smoothly at room temperature with a smaller amount of $TMSCF_3$. We believe that the milder and more efficient reaction conditions described herein will be widely used for oxidative trifluoromethylation.

Experimental Section

General Procedure for the Oxidative Trifluoromethylation of Terminal Alkynes Outside of the Glove Box with Ag_2CO_3 as the Oxidant: To a 25-mL three-necked round-bottomed flask equipped with a magnetic stir bar was added CuCl (99 mg, 1.0 mmol, 2.0 equiv.). Then, air in the flask was evacuated and dry nitrogen was refilled (once). *t*BuOK (112 mg, 1.0 mmol, 2.0 equiv.), Ag_2CO_3 (275 mg, 1.0 mmol, 2.0 equiv.), and 1,10-phenanthroline (180 mg, 1.0 mmol, 2.0 equiv.) were added. Then, air in the flask was evacuated and dry nitrogen was refilled (twice). After that, DMF (2.0 mL) was added to the mixture, and the resultant dark red mixture was stirred at room temperature for 30 min under a nitrogen atmosphere. $TMSCF_3$ (0.148 mL, 1.0 mmol, 2.0 equiv.) was slowly added. The resulting mixture was further stirred at room temperature for 1 h. A solution of the terminal alkyne (0.5 mmol) in DMF (2.0 mL) was slowly added to the reaction mixture over 3 h by using a syringe pump under an atmosphere of N_2. The reaction mixture was kept for another 3 h at room temperature. The reaction mixture was filtered through a plug of Celite on silica and eluted with diethyl ether (50 mL). The combined solution was washed with water. The water was extracted with ethyl ether. The combined organic phase was washed with brine and then dried with magnesium sulfate. After filtration and removal of solvent, the residue was purified by silica gel column chromatography to give the trifluoromethylated product.

General Procedure for the Oxidative Trifluoromethylation of Terminal Alkynes Outside of the Glove Box with Oxygen as the Oxidant: To a 25-mL three-necked round-bottomed flask equipped with a magnetic stir bar was added 4 Å molecular sieves (250 mg). The molecular sieves were activated by flame under vacuum. After the molecular sieves were fully activated, the flask was allowed to cool to room temperature under an atmosphere of N_2. After it was backfilled with dry oxygen (once), CuCl (99 mg, 1.0 mmol, 2.0 equiv.), *t*BuOK (112 mg, 1.0 mmol, 2.0 equiv.), and 1,10-phenanthroline (180 mg, 1.0 mmol, 2.0 equiv.) were added. Then, the air in the flask was evacuated and dry oxygen was refilled (twice). After that, DMF (2.0 mL) was added to the mixture, and the resultant mixture was stirred at room temperature for 30 min under an atmosphere of oxygen. $TMSCF_3$ (0.148 mL, 1.0 mmol, 2.0 equiv.) was slowly added. The resulting mixture was further stirred at room temperature for 1 h. A solution of the terminal alkyne (0.5 mmol) in DMF (2.0 mL) was slowly added to the reaction mixture over 3 h by using a syringe pump under an atmosphere of dry oxygen. The reaction mixture was kept for another 3 h at room temperature. The reaction mixture was filtered through a plug of Celite on silica and eluted with diethyl ether (50 mL). The combined solution was washed with water. The aqueous phase was extracted with ethyl ether. The combined organic phase was washed with brine and then dried with magnesium sulfate. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography to give the trifluoromethylated product.

Supporting Information (see footnote on the first page of this article): General methods, experimental procedures, and characterization data for all new compounds.

Acknowledgments

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