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Fluoroform-Derived $CuCF_3$ for Trifluoromethylation of Terminal and TMS-Protected Alkynes

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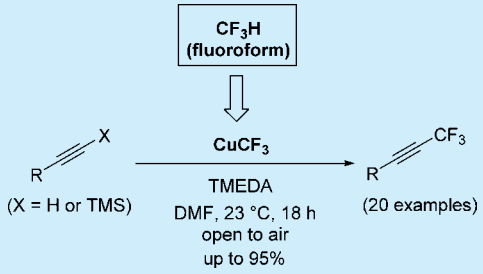
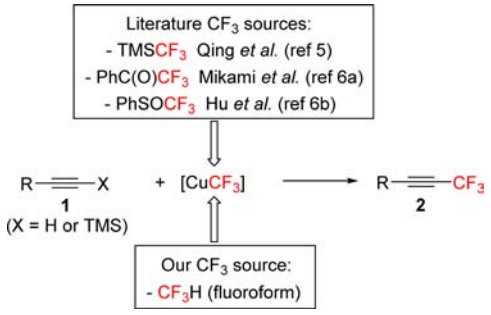
Supporting Information

ABSTRACT: An efficient trifluoromethylation reaction of alkynes using a fluoroform-derived $CuCF_3$ reagent is described. The CF_3 source is the inexpensive industrial waste fluoroform (CF_3H). The air-stable $CuCF_3$ reagent can be prepared in large quantities and is convenient to use. Synthetically useful trifluoromethylated alkynes containing a wide range of functional groups were successfully synthesized under mild conditions. Both terminal and TMS-protected alkynes gave the products in one step. The beneficial effect of a diamine ligand tetramethylethylenediamine (TMEDA) with the fluoroform-derived $CuCF_3$ reagent was also demonstrated.



The introduction of a trifluoromethyl (CF_3) group into organic molecules can profoundly change their physical and chemical properties.[1] A great number of important pharmaceutical compounds, including anti-HIV efavirenz (Sustiva), antidepressant fluoxetine (Prozac), and anti-inflammatory celecoxib (Celebrex), contain the trifluoromethyl group. Many drug properties, such as bioavailability, lipophilicity, receptor-binding selectivity, and metabolic stability, can be enhanced by the presence of the CF_3 group. It is therefore not surprising to witness the rapid development of new trifluoromethylation methods in the past decades.[2] Compared to the advances achieved in trifluoromethylation of arenes and heteroarenes, the formation of $C(sp)-CF_3$ bonds by trifluoromethylation of alkynes is still in its infancy, despite the widespread use of trifluoromethylated acetylenes in pharmaceutical, agrochemical and material science applications.[3] Previous preparation of trifluoromethylated alkynes used prefunctionalized alkynyl metals and electrophilic trifluoromethylating reagents, which often suffered from tedious procedures and precautionary preparation of sensitive organometallic reagents.[2c] The direct conversion of the C−H bond of a terminal alkyne into the $C-CF_3$ bond would be a much more attractive solution. Indeed, copper-mediated/catalyzed trifluoromethylation of terminal alkynes with electrophilic trifluoromethylating reagents have been developed,[4a−c] as well as photoredox catalytic trifluoromethylation of terminal alkynes with CF_3I.[4d] These methods circumvent the use of prefunctionalized alkynes but at the same time are limited by the prohibitively expensive trifluoromethylating reagents and photoredox catalysts in large-scale syntheses. In search of alternative low-cost CF_3 sources and convenient operations, Qing's copper-mediated/catalyzed oxidative trifluoromethylation of terminal alkynes using nucleophilic $TMSCF_3$ (Ruppert−Prakash reagent) emerged as a useful method.[5] Other CF_3 sources such as trifluoromethyl ketones[6a] and sulfoxides[6b] have been subsequently employed in analogous copper-mediated processes by Mikami and Hu's group, respectively. However, the use of fluoroform (CF_3H) as the ultimate CF_3 source would provide a highly atom-economical process and yet has not been reported. We herein describe an efficient method for synthesizing trifluoromethylated alkynes using a fluoroform-derived $CuCF_3$ reagent (Scheme 1).

Scheme 1. Trifluoromethylation of Alkynes with Different CF_3 Sources



Fluoroform (CF_3H, trifluoromethane, HFC-23) is a large-volume byproduct from Teflon manufacturing and a potent greenhouse gas. It is readily available at low cost, nontoxic, and ozone-friendly and, therefore, would be a very attractive CF_3 source in synthesizing trifluoromethylated compounds. However, the activation of fluoroform is challenging due to its chemical inertness, and only recently have synthetic methods utilizing fluoroform emerged.[7] In particular, the use of metals in the direct metalation of CF_3H to produce organometallic trifluoromethylating reagents showed promising synthetic applications.[8] The pioneering work from Grushin's group on the direct cupration of fluoroform to prepare a $CuCF_3$ reagent

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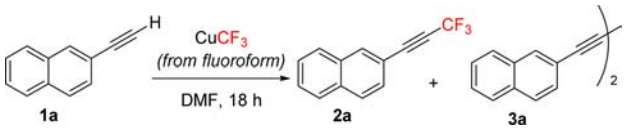
is one of the most useful and practical methods, which has been successfully demonstrated in the trifluoromethylation of aryl/vinyl halides, arenediazonium salts, α-haloketones and arylboronic acids.[8d−l] However, to the best of our knowledge, there are no examples of trifluoromethylation at the sp-hybridized carbon centers using a fluoroform-derived organometallic reagent.

We initially tested the trifluoromethylation of 2-ethynylnaphthalene **1a** with triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$)-stabilized $CuCF_3$ reagent in dimethylformamide (DMF), prepared by Grushin's protocol using CuCl/*t*-BuOK/fluoroform,[8d] under an air atomosphere.[8e] The trifluoromethylated product **2a** was obtained only in 12% yield, and the undesired byproduct diyne **3a** was obtained in 85% yield (Table 1, entry 1). Bubbling air through the reaction mixture increased the yield of **2a** significantly but still generated a large amount of **3a** (Table 1, entry 2). In the trifluoromethylation of aryl boronic acids with the same fluoroform-derived $CuCF_3$ reagent,[8e] air was proposed to oxidize the air-sensitive Cu(I)CF_3 to a much more electrophilic Cu(II)CF_3 species for the transmetalation process. In our case, the oxidation process is competing with the formation of diyne **3a**, which is known to occur at a Cu(I) center.[5a] We therefore decided to preform the Cu(II)CF_3 species by bubbling air through the initially prepared Cu(I)CF_3 solution for 1 h before adding the alkyne substrate[9] and let the reaction proceed in open air.[10] The result showed a drastic improvement in yield (Table 1, entry 3, cf. entry 1). At elevated temperatures, we observed a decrease in yield of **2a** accompanied by an increase in yield of **3a** (Table 1, entries 4 and 5). It has been shown that the use of ligand helped to stabilize the reactive Cu−CF_3 by chelation and increase the electron density on the Cu center.[5a,11] In contrast, the "ligandless" fluoroform-derived $CuCF_3$ reagent has often been more reactive in trifuoromethylation processes.[8d−l] Our results showed that adding phosphine ligands such as triphenylphosphine (PPh_3) and 1,2-bis(diphenylphosphino)ethane (dppe) caused a drop in yield of **2a** and increased the yield of **3a** (Table 1, entries 6 and 7, cf. entry 3). On the other hand, adding a diamine ligand such as 1,10-phenanthroline (phen) improved the yield of **2a** significantly (Table 1, entry 8). The highest yield (93%) was obtained with a cheap and commercially available tetramethylethylenediamine TMEDA (Table 1, entry 9).[12] To prove that TMEDA acted as a ligand instead of simply a base, we added Et_3N and observed no beneficial effects (Table 1, entry 10, cf. entry 3). We have also found that reducing the equivalents of $CuCF_3$/TMEDA and increasing the concentration of the reaction gave poorer yields. Finally, slowly oxidizing the Cu(I)CF_3 in air in the presence of TMEDA was not as efficient as using the preformed Cu(II)CF_3 and TMEDA (Table 1, entry 11, cf. entry 9)[13] albeit significantly more efficient than the ligand-free case (cf. Table 1, entry 1).

Table 1. Optimization of Trifluoromethylation of 1a with Fluoroform-Derived $CuCF_3$[a]

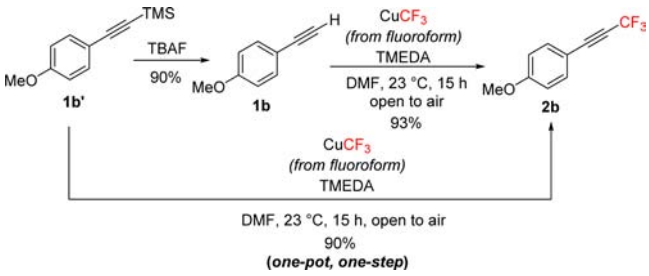


entry	preparation method of $CuCF_3$[b]	ligand	temp (°C)	yield of **2a** (%)
1[c]	A	none	23	12[e]
2[d]	A	none	23	52[e]
3[c]	B	none	23	65[e]
4[c]	B	none	45	46[e]
5[c]	B	none	65	18[e]
6[c]	B	PPh_3	23	18[e]
7[c]	B	dppe	23	28[e]
8[c]	B	phen	23	81[e]
9[c]	**B**	**TMEDA**	**23**	**95**[e] **(93**[f]**)**
10[c]	B	Et_3N	23	65[e]
11[c]	A	TMEDA	23	75[e]

[a]Conditions: $CuCF_3$ (in DMF solution, 3.0 equiv, stabilized by $Et_3N{\cdot}3HF$), ligand (3.0 equiv), **1a** (0.1 mmol in 1 mL of DMF). [b]The $CuCF_3$ solution was prepared from CuCl/*t*-BuOK/fluoroform by the procedure in ref 8d (method A). A modification of the procedure used air to bubble through the $CuCF_3$ solution for 1 h before addition of the alkyne substrate (method B). [c]The reaction vessel was open to air. [d]Air was bubbled through the reaction mixture for 2 h, and then the reaction vessel was open to air for the remaining time. [e]Yield was determined by ^{19}F NMR analysis using benzotrifluoride as the internal standard. [f]Isolated yield.

Terminal alkynes such as **1a** are often obtained from the TMS-protected alkynes by desilylation. The fluoroform-derived $CuCF_3$ reagent contains $Et_3N{\cdot}3HF$ and KF, which are also known for desilylation. Therefore, we envisioned that this reagent can perform both desilylation and trifluoromethylation of easily accessible and stable TMS-protected alkynes, saving the extra steps for preparing and handling terminal alkynes, especially for some volatile and unstable terminal alkynes. Indeed, the TMS-protected alkyne **1b′** was trifluoromethylated smoothly under the optimized conditions in 90% yield (Scheme 2). This one-pot/one-step protocol is more convenient and efficient than the separate desilylation and trifluoromethylation sequence. The study of shorter reaction time (1.5 h) under the one-pot condition revealed a mixture of **1b** (79%) and **2b** (21%) suggesting the actual intermediate toward the trifluoromethylated product is the terminal alkyne **1b**. We have also studied the nature of the silyl protecting group, including TMS, TES, TBS, TIPS, and DMPS groups, and the yield of the trifluoromethylated product parallels the ease of desilylation.[14] The TMS-protected alkynes gave the highest yields.

Scheme 2. One-Pot Trifluoromethylation of a TMS-Protected Alkyne with Fluoroform-Derived $CuCF_3$



The scope of the reaction was subsequently explored using both terminal and TMS-protected alkynes (Scheme 3). All reactions were conveniently run in air and at room temperature. The fluoroform-derived $CuCF_3$ reagent was easy to handle, prepared on a large scale (15 mmol), and stable in air for days.[14] Under the optimized conditions, trifluoromethylated alkyne products **2** were obtained in moderate to excellent yields with good functional group compatibilities. In general, electron-

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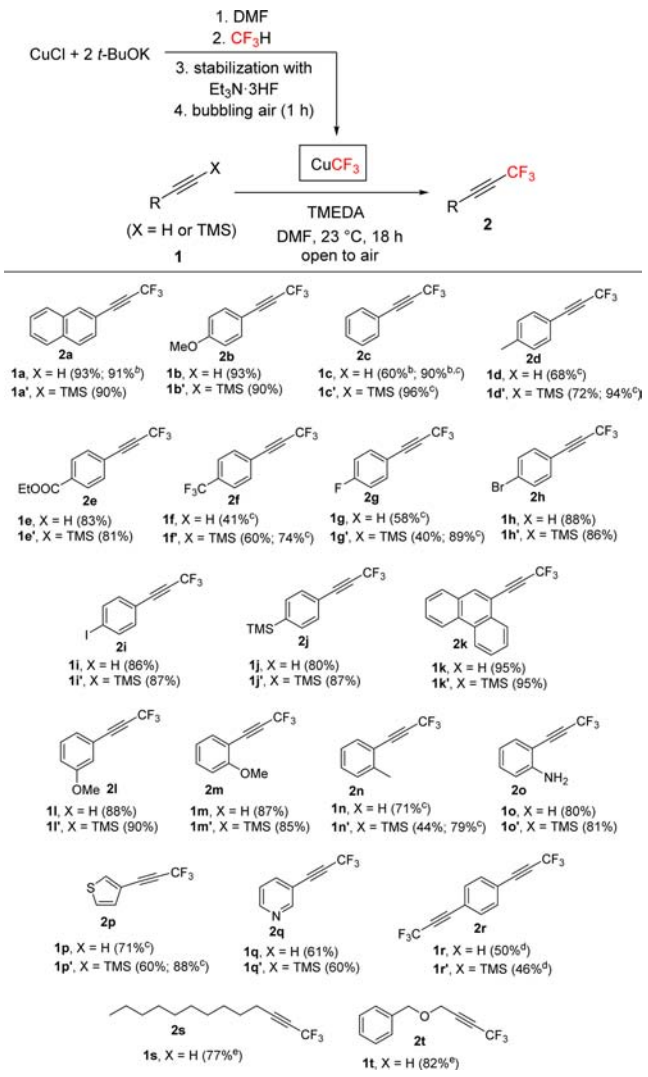
Scheme 3. Scope of Terminal and TMS-Protected Alkynes in Trifluoromethylation with Fluoroform-Derived $CuCF_3$[a]

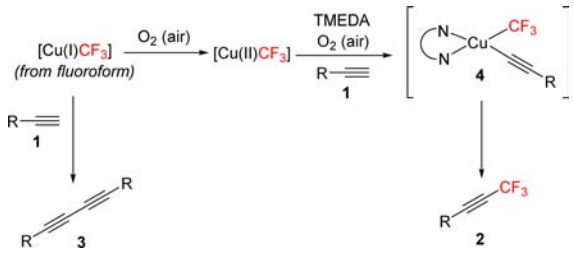


[a]Conditions: $CuCF_3$ (0.5 M in DMF, 1.2 mL, 3.0 equiv, stabilized by $Et_3N{\cdot}3HF$), TMEDA (3.0 equiv), alkyne **1** (0.2 mmol in 2 mL of DMF), isolated yields. [b]2.0 mmol scale. [c]Yield was determined by ^{19}F NMR analysis using benzotrifluoride as the internal standard. [d]6.0 equiv of $CuCF_3$ and TMEDA. [e]36 h reaction time.

rich aromatic alkynes **2b** gave higher yields than electron-poor ones **2e**,**f**. Substituent groups were tolerated at the *ortho* **2m**−**o**, *meta* **2l**, and *para* **2b**−**j** positions on the aromatic ring. Aryl halides including bromide and even iodide gave high yields of the monotrifluoromethylated alkynes **2h**,**i**. This chemoselectivity is remarkable since aryl iodides are very reactive toward the fluoroform-derived $Cu(I)CF_3$ reagent in aromatic trifluoromethylations.[8d,h] It is also noteworthy that chemoselective desilylation/trifluoromethylation took place only at the alkyne terminus of the bis-silylated substrate **1j′** leaving the aryl TMS group intact in the product **2j**. The unprotected amino group was compatible, and alkyne **2o** was obtained in good yield. However, a hydroxyl group at the *para* or *ortho* position was not tolerated, and a complicated mixture of products was obtained. Heteroaromatic alkynes containing thienyl **2p** and pyridyl **2q** groups were also tolerated. TMS-protected alkynes generally gave comparable yields as terminal alkynes, except when the substrates are volatile **1d**,**f**,**g**, in which case using TMS-protected alkynes in the one-pot desilylation/trifluoromethylation was advantageous. The volatility of some products made the isolation difficult; therefore, NMR yields were given in these cases to describe more accurate yields of the reaction. The bis-trifluoromethylated product **2r** was successfully obtained using a larger excess of the reagent. The reaction was not only limited to aromatic alkynes; alkyl-substituted products **2s**,**t** were also formed in good yields albeit in longer reaction times.

Although the mechanism of copper-mediated oxidative trifluoromethylation is not fully understood,[5a,8e,15] particularly with the fluoroform-derived $CuCF_3$ reagent, we have proposed a plausible reaction pathway as the following (Scheme 4): the

Scheme 4. Proposed Mechanism



$[Cu(I)CF_3]$ reagent generated from fluoroform is air-sensitive and most likely is oxidized by air to a $[Cu(II)CF_3]$ species.[8d,e] Our NMR studies clearly showed the disappearance of $[Cu(I)CF_3]$ peak after bubbling air through it for 1 h.[14] The diamine TMEDA acts as a ligand to stabilize the Cu-CF_3 by chelation and increase the electron density on the copper center.[5a,11] In the presence of alkyne **1** and air, the Cu(II)/Cu(III) complex **4** is possibly formed,[16] which undergoes reductive elimination to deliver product **2**. However, the mechanism for the formation of **4** and its nature is not clear at the moment. In contrast, the $[Cu(I)CF_3]$ reagent facilitated the formation of the diyne product **3** via an oxidative homocoupling pathway.[5]

In conclusion, we have discovered a new application of fluoroform-derived $CuCF_3$ reagent in the oxidative trifluoromethylation of terminal and TMS-protected alkynes. A wide array of trifluoromethylated alkynes containing diverse functional groups was successfully synthesized from easily accessible substrates. By modifying the literature procedure, we were able to prepare a "$Cu(II)CF_3$" reagent from fluoroform in large quantities which is air-stable and convenient to use. The compatibility and utility of this reagent in the presence of a diamine ligand TMEDA was also demonstrated. Currently, we are investigating the potential of this reagent in other efficient C−CF_3 bond forming processes and their mechanisms.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00999.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(9) Preparation of $CuCF_3$ (method B) and reaction with **1a**:

(10) For the preparation of the $Cu(II)CF_3$ solution, bubbling oxygen gave similar results as bubbling air.

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(12) For other examples of using TMEDA as a key ligand in copper-mediated trifluoromethylation of terminal alkynes, see ref 6.

(13) Bubbling air through $Cu(I)CF_3$ in the presence of TMEDA or slow addition of alkyne **1a** to $Cu(I)CF_3$ and TMEDA in air for 2 h only slightly improved the yield of **2a** (80−83%).

(14) See the Supporting Information for details.

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