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Copper-mediated oxidative difluoromethylation of terminal alkynes with $\text{TMSCF}_2\text{H}^\dagger$

Sheng-Qing Zhu,^a Xiu-Hua Xu^a and Feng-Ling Qing^{*a,b}

A copper-mediated oxidative difluoromethylation of terminal alkynes using nucleophilic TMSCF_2H in the presence of an oxidant 9,10-phenanthraquinone was developed. This reaction provided a direct and efficient method for preparation of difluoromethylated alkynes.

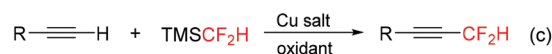
Fluorinated alkynes have become a type of useful building blocks taking advantage of the unique properties of fluorine atoms and fluorine-containing groups.¹ Among them, difluoromethylated alkynes ($\text{RC}\equiv\text{CCF}_2\text{H}$) are important intermediates for the preparation of valuable fluorinated compounds,² because the CF_2H group is considered isosteric and isopolar to a hydroxyl (OH)³ and it could act as a lipophilic hydrogen bond donor.⁴ Consequently, a number of methods have been developed for the synthesis of difluoromethylated alkynes. Fluorination of aldehydes with a nucleophilic fluorinating reagent is an orthodox route to difluoromethylated alkynes.⁵ However, this method suffers from harsh reaction conditions that are incompatible with many functional groups. These compounds could also be accessed through the transformation from other CF_2 -containing intermediates, such as gem-difluoromethylenated ketones,⁶ difluoromethylated vinyl iodides,⁷ and (phenylsulfonyl)difluoromethylated alkynes.⁸ Although these methods boast high levels of reactivity and site selectivity, the direct approaches to difluoromethylated alkynes are more attractive on account of the high atom and step economy.

While tremendous progress has been made recently in the direct synthesis of trifluoromethylated alkynes,⁹ the direct approaches to analogous difluoromethylated alkynes are less developed. The cross-coupling of 1-iodoalkynes with the thermally unstable reagent CuCF_2H was developed by Burton and Hartgraves (Scheme 1a).¹⁰ This protocol required prefunctionalized terminal alkynes. Kitazume^{11a} and Hu^{11b,c} reported the difluoromethylation of the *in situ* generated lithium acetylides with difluorocarbene precursors (Scheme 1b). However, some

Previous work



This work



Scheme 1 Direct approaches to difluoromethylated alkynes.

sensitive functional groups would not be compatible with the alkynyl-Li and/or :CF_2 used in these systems. Thus, it is highly desirable to develop new methods such as transition metal-mediated/catalyzed direct difluoromethylation of terminal alkynes for the preparation of difluoromethylated alkynes.

Recently, we have developed a new type of trifluoromethylation reaction, oxidative trifluoromethylation, for the synthesis of a wide range of trifluoromethylated compounds.¹² This protocol allows the direct installation of a trifluoromethyl group in place of C–H bonds of terminal alkynes with TMSCF_3 .^{9a–c} Inspired by these results, we anticipated that a similar copper-mediated oxidative C–H difluoromethylation of terminal alkynes with TMSCF_2H might be possible. However, this transformation is more challenging than trifluoromethylation of alkynes, because the Si– CF_2H bond is more inert than the Si– CF_3 bond¹³ and difluoromethyl copper complexes are less stable than trifluoromethyl copper complexes.¹⁴ Herein, we describe the copper-mediated oxidative difluoromethylation of terminal alkynes with TMSCF_2H (Scheme 1c) on the basis of recent developments in copper-mediated difluoromethylation of arenes.¹⁵ This protocol avoids the use of prefunctionalized alkynes or the generation of alkynyl-Li intermediates.

Optimization of the reaction conditions was explored using phenylacetylene **1a** as the model substrate (Table 1). Under the optimized conditions for copper mediated trifluoromethylation of terminal alkynes,^{9a} the reaction of **1a** with TMSCF_2H

^aKey Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China. E-mail: flq@mail.sioc.ac.cn

^bCollege of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

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Table 1 Optimization of reaction conditions^a

Entry	Cu salt	Ligand	Oxidant	Solvent	Temperature	Yield ^b (%)
1 ^c	CuI	Phen	Air	DMF	100 °C	0
2	CuI	Phen	DDQ	DMF	−15 °C to rt	32
3	CuI	Phen	Air	DMF	−15 °C to rt	Trace
4	CuI	Phen	PhI(OAc) ₂	DMF	−15 °C to rt	5
5	CuI	Phen	Ag ₂ CO ₃	DMF	−15 °C to rt	Trace
6	CuI	Phen	O-1	DMF	−15 °C to rt	34
7	CuI	Phen	O-2	DMF	−15 °C to rt	Trace
8	CuI	Phen	O-3	DMF	−15 °C to rt	16
9	CuI	Phen	O-4	DMF	−15 °C to rt	43
10	CuI	—	O-4	DMF	−15 °C to rt	66
11	CuI	—	O-4	DMSO	−15 °C to rt	Trace
12	CuI	—	O-4	MeCN	−15 °C to rt	4
13	CuBr	—	O-4	DMF	−15 °C to rt	60
14	CuCN	—	O-4	DMF	−15 °C to rt	34
15	CuSCN	—	O-4	DMF	−15 °C to rt	48
16	CuI	—	O-4	DMF	0 °C to rt	72
17 ^d	CuI	—	O-4	DMF	0 °C to rt	0
18 ^e	CuI	—	O-4	DMF	0 °C to rt	0

^a Reaction conditions: **1a** (0.2 mmol), TMSCF₂H (2.0 equiv.), Cu salt (1.0 equiv.), ligand (1.0 equiv.), oxidant (1.2 equiv.), *t*-BuOK (3.0 equiv.), DMF (2.0 mL), temperature, under Ar, 10 h. ^b Yields determined by ¹⁹F NMR spectroscopy using fluorobenzene as an internal standard. ^c KF was used as the initiator. ^d CuI (0.5 equiv.). ^e *t*-BuOK (2.0 equiv.).

(2.0 equiv.), CuI (1.0 equiv.), and 1,10-phenanthroline (phen, 1.0 equiv.) in the presence of KF (3.0 equiv.) under an air atmosphere in DMF at 100 °C provided dimer **3a** as the major product, and none of the desired product **2a** was observed (entry 1). Then, the reaction was investigated using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant and *t*-BuOK as the initiator based on our previous work of oxidative cross-coupling reaction of terminal alkynes with α -silyldifluoromethylphosphonates.¹⁶ To our delight, the desired product **2a** was formed in 32% yield (entry 2). Switching to other oxidants such as air, PhI(OAc)₂, and Ag₂CO₃ led to a dramatic decrease in the reaction yield (entries 3–5). Considering the effectiveness of DDQ as the oxidant, several quinones, including 2,3,5,6-tetrachloro-1,4-benzoquinone (**O-1**), naphthoquinone (**O-2**), 3,4,5,6-tetrachloro-1,2-benzoquinone (**O-3**), and 9,10-phenanthraquinone (**O-4**) were examined (entries 6–9). 9,10-Phenanthraquinone (**O-4**) proved to be better than other oxidants, giving **2a** in 43% yield (entry 9). Surprisingly, the yield of **2a** was increased up to 66% in the absence of any ligand (entry 10). In our opinion, the solvent DMF might also act as a ligand to stabilize Cu–CF₂H species.^{15b} In fact, **2a** was obtained in extremely low yields in other solvents such as DMSO or MeCN (entries 11 and 12).

Different Cu salts, including CuBr, CuCN, and CuSCN, could also mediate this transformation, but none of them showed higher reactivity than CuI (entries 13–15). Finally, the yield reached 72% when the reaction was performed from 0 °C to rt (entry 16). It was noteworthy that both the amounts of CuI and *t*-BuOK were crucial to this transformation. None of **2a** was produced when the amount of CuI was decreased from 1.0 equiv. to 0.5 equiv. (entry 17) or the amount of *t*-BuOK was decreased from 3.0 equiv. to 2.0 equiv. (entry 18).

With the optimized reaction conditions in hand (Table 1, entry 16), we next investigated the substrate scope of copper-mediated oxidative difluoromethylation of terminal alkynes. A variety of aromatic and aliphatic alkynes **1** could be transformed into the corresponding difluoromethylated products **2** in moderate to good yields (Table 2). Both electron-rich and -deficient aryl alkynes were compatible in this reaction. In general, the electron-rich aryl alkynes (**1b–1h**) afforded slightly higher yields compared to the electron-deficient substrates (**1i–1k**). Many functionalities, including alkoxy, amino, bromo, cyano, and ester groups were well-tolerated in the reaction. Importantly, substrate **1i** bearing a ketone group exhibited moderate reactivity in this transformation, despite the potential for ketones to undergo competing addition of the

Table 2 Copper-mediated oxidative difluoromethylation of terminal alkynes^{a,b}

$\text{R}-\text{C}\equiv\text{CH} + \text{TMSCF}_2\text{H} \xrightarrow[\text{DMF, 0}^\circ\text{C to rt}]{\text{CuI, } t\text{-BuOK, 9,10-phenanthraquinone}} \text{R}-\text{C}\equiv\text{CF}_2\text{H}$	
1	2

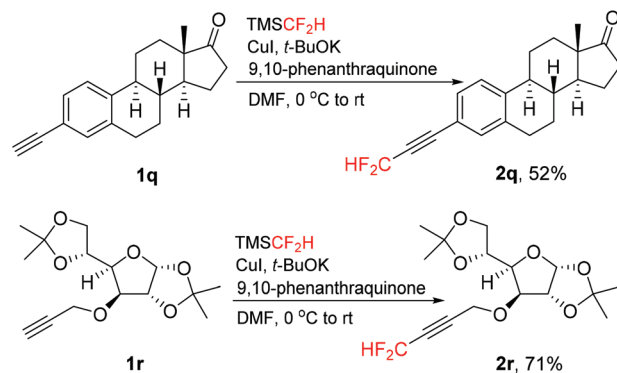
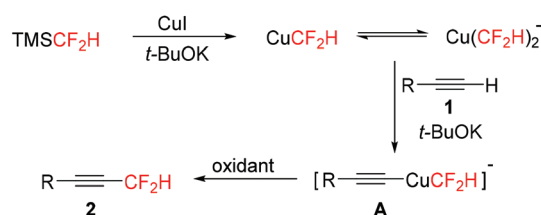
^a Reaction conditions: **1** (0.4 mmol), TMSCF₂H (2.0 equiv.), CuI (1.0 equiv.), *t*-BuOK (3.0 equiv.), 9,10-phenanthraquinone (1.2 equiv.) under argon in DMF (1.0 mL) at room temperature. ^b Isolated yield.

difluoromethyl group to the carbonyl unit.¹⁷ The aliphatic alkynes **1l–1n** were also effective to produce the desired products in moderate to good yields.

Notably, heteroaryl alkynes **1o** and **1p** derived from pyridine and thiophene proceeded smoothly to give products **2o** and **2p** respectively in moderate yields.

This direct difluoromethylation protocol could also be applied for complex molecules, such as estrone and glucofuranose derivatives **1q** and **1r** (Scheme 2). The corresponding difluoromethylated alkynes **2q** and **2r** were isolated in moderate to good yields. These results showed that this protocol can be applicable to “late-stage difluoromethylation” of medicinally relevant compounds.

To understand the reaction mechanism, ¹⁹F NMR spectroscopy was used to track the reaction (see the ESI†). When TMSCF₂H, CuI, and *t*-BuOK were combined, ¹⁹F NMR confirmed the generation of both CuCF₂H (resonates at δ = −110.8 ppm, d, *J* = 45.3 Hz) and Cu(CF₂H)₂[−] (resonates at δ = −116.9 ppm, d, *J* = 44.2 Hz).^{14,15a} After the alkyne was added, a

**Scheme 2** Direct difluoromethylation of estrone and glucofuranose derivatives.**Scheme 3** Proposed reaction mechanism.

new fluorine-containing intermediate was formed (resonates at δ = −115.9 ppm, d, *J* = 42.7 Hz). Finally, the desired difluoromethylated product was detected after the addition of oxidant **O-4**. On the basis of these experimental results, a plausible mechanism for copper-mediated difluoromethylation of terminal alkynes is shown in Scheme 3. The difluoromethylcopper species were firstly generated and then reacted with alkyne **1** to give intermediate **A**. Subsequently, intermediate **A** was oxidized to high-valent copper complexes, which finally underwent the reductive elimination to afford product **2**.

Conclusions

In conclusion, we have developed an efficient copper-mediated oxidative difluoromethylation of terminal alkynes with easily accessible TMSCF₂H. This protocol provides a direct route to the difluoromethylated alkynes from alkynes. As difluoromethylated alkynes are important intermediates for the preparation of other fluorine-containing compounds, this methodology will be potentially useful in pharmaceutical, agrochemical, and material fields.

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