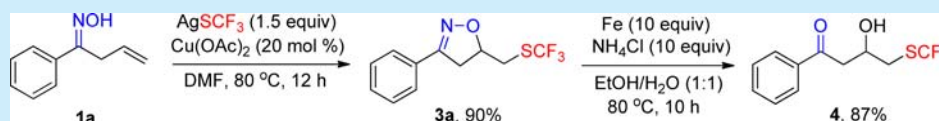# Copper-Catalyzed Intramolecular Oxytrifluoromethylthiolation of Unactivated Alkenes

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S *Supporting Information*

ABSTRACT: A mild, versatile, and convenient method for efficient intramolecular oxytrifluoromethylthiolation of unactivated alkenes catalyzed by $Cu(OAc)_2$ has been developed. The reactions were carried out under aerobic conditions and formed a variety of isoxazolines bearing a $-SCF_3$ substituent.

The modification of drug candidates by introduction of fluorine or fluorine-containing moieties has become an important strategy in drug discovery.[1] Among the fluorine-containing groups, the trifluoromethylthio group ($-SCF_3$) has attracted increasing interest for its strong electron-withdrawing effect and high lipophilicity property.[2] Accordingly, in the past several decades, numerous methods to introduce $-SCF_3$ onto organic compounds have been reported. Typical methods include a halogen−fluorine exchange reaction (often under harsh conditions)[3] or trifluoromethylation of sulfur-containing compounds.[4]

Recently, a few new synthetic approaches for construction of C−SCF_3 have been developed. For instance, transition-metal-mediated or -catalyzed trifluoromethylthiolation uses nucleophilic SCF_3 sources ($CuSCF_3$, $AgSCF_3$, or NMe_4SCF_3, etc.; Scheme 1, eq 1).[5] More recently, several new electrophilic SCF_3 reagents, such as hypervalent iodonium ylide (**I**),[6] trifluoromethylthiolated thioperoxy reagent (**II**),[7] N-(trifluoromethylthio)-phthalimide (**III**) and its analogues,[8] and trifluoromethanesulfenamide (**IV**) and its analogues,[9] were developed and employed in electrophilic trifluoromethylthiolation under transition-metal-catalytic or transition-metal-free conditions. However, the substrate scopes are mainly restricted in strong nucleophilic compounds, such as terminal alkynes, indoles, and oxindoles, or the α-position of carbonyl compounds (eq 2). Thus, developing a methodology for trifluoromethylthiolation of unactivated substrates, especially for construction of C_{sp3}−SCF_3 is highly desirable.

Transition-metal-catalyzed difunctionalization of unactivated alkenes attracts much attention, which represents a versatile and step economical strategy to furnish multiple C−C bond/C−heteroatom bonds in a single step.[10] In this area, one of the most synthetically important reactions is transition-metal-catalyzed radical addition to alkenes. Despite the successful employment of nucleophilic or electrophilic SCF_3 reagents in trifluoromethylthiolation, the radical-type reaction by using •SCF_3 has been very seldom studied.[11] Recently, Buchwald and Qing reported oxytrifluoromethylation of unactivated alkenes, respectively.[12] However, the oxytrifluoromethylthiolation for difunctionalization of unactivated alkenes is still unknown.

Isoxazoline motifs exhibit interesting biological activities[13] and serve as versatile organic synthesis intermediates.[14] The modification of isoxazoline by introduction of $-SCF_3$ is of great interest both for biology and organic synthesis research. We envisioned that by using alkene-substituted oxime as substrate[15] isoxazoline featuring an SCF_3 group can be easily synthesized. As part of our research interests on copper-catalyzed synthesis of heterocycles,[16] we disclose here the first example of Cu(II)-catalyzed intramolecular oxytrifluoromethylthiolation of unactivated alkenes for the synthesis of C_{sp3}−SCF_3. The mechanistic study indicated that a radical pathway was involved in this transformation. Notably, in the reaction, $AgSCF_3$ was directly

Scheme 1. Trifluoromethylthiolation Using Nucleophilic or Electrophilic SCF_3 Reagents
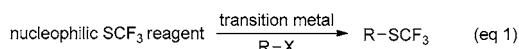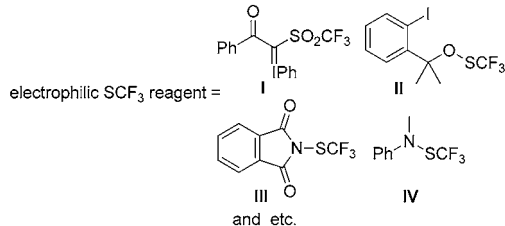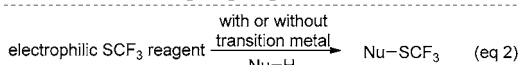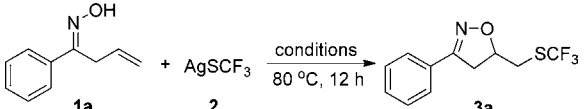
used as SCF$_3$ source without other oxidant's assistance or the preparation of trifluoromethylthiolated hypervalent iodine. Moreover, the radical addition product can be easily transferred to a synthetic useful building block, α-trifluoromethylthio alcohol derivatives in one step.

The investigation was initiated by using oxime **1a** as substrate, 1.5 equiv of AgSCF$_3$ (**2**) as trifluoromethylthio reagent, 20 mol % of Cu(OTf)$_2$ as catalyst, and DMF as solvent. The reaction was stirred at 80 °C for 12 h under aerobic conditions and gave the desired product **3a** in 38% yield (the same yield was obtained under argon atmosphere, Table 1, entry 1). We then tested other

Table 1. Optimization of Reaction Conditions

entry[a]	catalyst	solvent	yield[b] (%)
1	Cu(OTf)$_2$	DMF	38
2	CuCl$_2$	DMF	64
3	Cu(OAc)$_2$	DMF	93 (90)
4	CuCl	DMF	59
5	CuBr	DMF	67
6	CuI	DMF	65
7	FeCl$_3$	DMF	<5
8	In(OTf)$_3$	DMF	trace
9	La(OTf)$_3$	DMF	trace
10	Sc(OTf)$_3$	DMF	<5
11	Zn(OTf)$_2$	DMF	trace
12	Al(OTf)$_3$	DMF	trace
13	NiCl$_2$.6H$_2$O	DMF	trace
14[c]	Cu(OAc)$_2$	DMF	50
15[d]	Cu(OAc)$_2$	DMF	trace
16	Cu(OAc)$_2$	CH$_3$CN	52
17	Cu(OAc)$_2$	toluene	66
18	Cu(OAc)$_2$	1,4-dioxane	49
19	Cu(OAc)$_2$	DCE	89
20[e]	Cu(OAc)$_2$	DMF	85
21[f]	Cu(OAc)$_2$	DMF	67
22		DMF	trace

[a]All reactions were carried out by using **1** (0.2 mmol), **2** (1.5 equiv), catalyst (20 mol %), and solvent (2 mL), stirred at 80 °C for 12 h, except as noted. [b]Yields were determined by GC with internal standard; isolated yield was indicated in parentheses. [c]22 mol % of 1,10-phenanthroline was used. [d]22 mol % of 2,2′-bipyridine was used. [e]At 40 °C. [f]At 120 °C.

copper catalysts, such as CuCl$_2$, Cu(OAc)$_2$, CuCl, CuBr, and CuI (entries 2−6). The copper salts with different valencies were all effective for this reaction, and Cu(OAc)$_2$ gave the highest yield (93%, entry 3). Other transition-metal catalysts were also examined in the reaction: FeCl$_3$ and Sc(OTf)$_3$ only afforded less than 5% desired product; In(OTf)$_3$, La(OTf)$_3$, Zn(OTf)$_2$, Al(OTf)$_3$, and NiCl$_2$·6H$_2$O were completely ineffective for this reaction (entries 7−13). Using of ligands, namely 1,10-phenanthroline and 2,2′-bipyridine, led to poor yields (entries 14 and 15). The solvent screening indicated that DMF is the best choice for the reaction (entries 16−19). The attempts to increase the yields by variation of the reaction temperature were also failed (entries 20 and 21). It should be noted that the reaction did not occur in the absence of catalyst, which revealed that copper was crucial to this transformation (entry 22).

With the optimal conditions (Table 1, entry 3) in hand, we then studied the substrate scope for the oxytrifluoromethylthiolation reaction (Scheme 2). The aromatic oximes with

**Scheme 2. Investigation of Substrate Scope[a]**
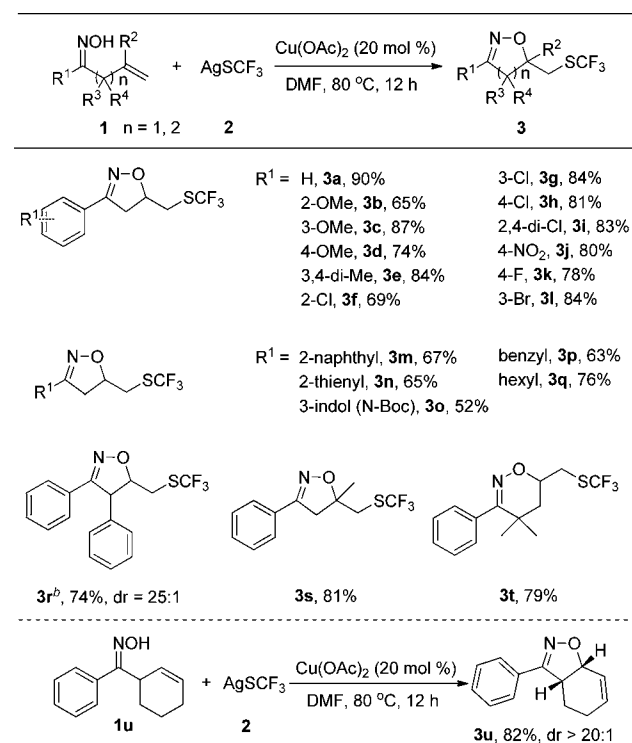
[a]All reactions were carried out by using 0.2 mmol of **1**, 1.5 equiv of **2**, 0.04 mmol of Cu(OAc)$_2$, and 2 mL of DMF. Yields refer to isolated yields. [b]Relative configuration was not assigned.

electron-donating or electron-withdrawing group at the o-, m-, or p- position were all worked well under standard conditions (**3b−i**). Other substituted aryl, naphthyl, and benzyl oximes also reacted smoothly (**3j−m,p**). The oxytrifluoromethylthiolation of oximes with heteroarene substituents gave the bihetero products **3n** and **3o** with acceptable yields (65% and 52%). We were pleased to find that the catalytic system worked well with aliphatic substrate, providing the corresponding product **3q** in 76% yield. The α-phenyl oxime was cyclized with excellent diastereoselectivity (dr = 25:1, **3r**).[17] Then, the current methodology was successfully employed to build a quaternary carbon center with −SCF$_3$ (**3s**). To further investigate the substrate scope, the oxytrifluoromethylthiolation reaction was employed for the synthesis of a six-membered ring. To our satisfaction, under the stated conditions, the desired product was obtained in good yield (**3t**). Interestingly, when **1u** was used, the alkene migration product **3u** was formed instead of the trifluoromethylthiolation.

To further illustrate the synthetic utility of oxytrifluoromethylthiolation product, isoxazoline **3a** was applied to a reductive ring-opening reaction (Scheme 3). The reaction proceeded smoothly and gave the highly functional SCF$_3$-containing building block, 3-hydroxy-1-phenyl-4-trifluoromethylthio-1-butanone **4** in 87% yield.

To understand the mechanism, some reactions were carried out (Scheme 4, see the Supporting Information for details). When 2,6-di-tert-butyl-4-methylphenol (BHT, 1.5 equiv) was added to the reaction under standard conditions, no desired

Scheme 3. Synthetic Utility of Current Method
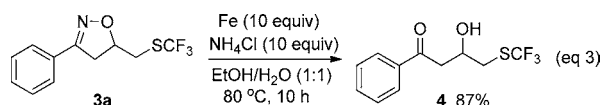
Scheme 4. Mechanistic Study for Oxime Radical Formation
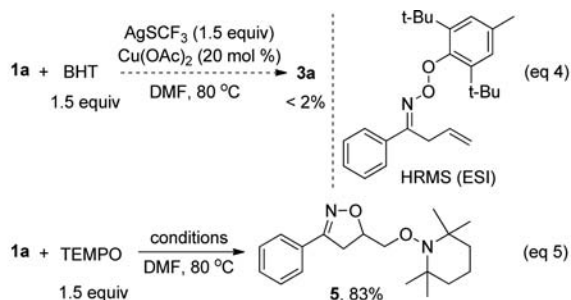
| entry	additives	reaction time	yield of 5[b]
1[a]	AgSCF$_3$ (1.5 equiv) Cu(OAc)$_2$ (20 mol %)	0.5 h	83%[c]
2		2 h	27%
		12 h	63%
3	Cu(OAc)$_2$ (20 mol %)	0.5 h	98%
4	AgSCF$_3$ (1.5 equiv)	2 h	54%
		5 h	91%
5	CuSCF$_3$ (1.5 equiv)	0.5 h	98%

[a]Standard conditions. [b]GC yield with internal standard. [c]Isolated yield.

product formed. However, the ESI-HRMS analysis of reaction mixture indicated the formation of BHT-oxime adduct (eq 4). Using 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, 1.5 equiv) as additive, the TEMPO addition product 5 was obtained in 83% yield (eq 5, entry 1). Although no •SCF$_3$ radical trapping product was detected in the experiments, these results indicated that oxime radical might generate in the system. We then set up a series of reactions to clarify the most active species which catalyzed the generation of oxime radical in the reaction mixture. Without any metal additives, 5 formed very slowly (after 2 h, 27% yield; after 12 h, 63% yield. entry 2). However, when 20 mol % of Cu(OAc)$_2$ was used, after only 0.5 h the radical addition product was obtained in 98% yield (entry 3). In the case of 1.5 equiv of AgSCF$_3$, a moderate reaction rate was observed (entry 4). It is interesting that CuSCF$_3$ showed similar catalytic activity to Cu(OAc)$_2$ (entry 5). These results indicated that, compared with AgSCF$_3$, a catalytic amount of copper additive was more efficient to promote this rapid TEMPO-trapping reaction and possibly also serve as the catalyst/promoter for the oxime radical formation in oxytrifluoromethylthiolation reaction.

Recently, Rueping and co-workers reported an example in which AgSCF$_3$ decomposes to give •SCF$_3$.[8c] In fact, we noticed a silver mirror in each case of Scheme 2, which might form in the •SCF$_3$-producing process. To further investigate the •SCF$_3$ formation step, F$_3$CSSCF$_3$ was in situ prepared using the known procedure, which was proven to release trifluorome-thylthio radical in the presence of Ag$^+$.[11a] The oxytrifluorome-thylthiolation product 3a was obtained in almost the same yield regardless the presence of Cu(OAc)$_2$ catalyst (Scheme 5, eq 6, see the Supporting Information for details). These results indicated that Cu(OAc)$_2$ is not essential for the formation of

Scheme 5. Mechanistic Study for •SCF$_3$ Formation
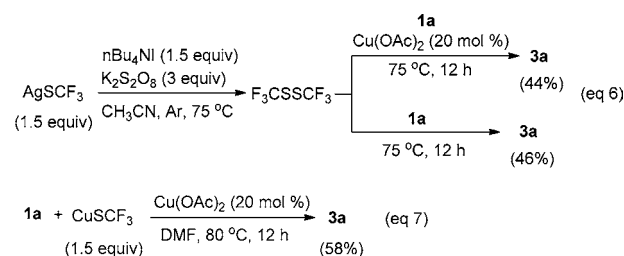
•SCF$_3$, and it may only act as the promoter for the oxime radical generation. CuSCF$_3$ is able to decompose to release •SCF$_3$.[18] When it was applied in the reaction instead of AgSCF$_3$, 3a was observed in 58% yield (eq 7).

Although the mechanism of oxytrifluoromethylthiolation is not completely clear yet, on the basis of previous reports and the above experimental results, the catalytic cycle could including the following components (see the Supporting Information for details):[19] (i) Cu(OAc)$_2$ catalyzes the formation of oxime radical; (ii) AgSCF$_3$ serves as the precursor to generate •SCF$_3$ and gives Ag^0 as by product;[20] (iii) the oxime radical adds to C=C bond via an intramolecular way and the result alkyl radical is trapped by •SCF$_3$, by which the difunctionalization of alkene is realized through an oxytrifluoromethylthiolation fashion.

In conclusion, we have developed a novel and convenient method for the intramolecular oxytrifluoromethylthiolation of alkenes for the first time. All of the reactions were carried out under aerobic conditions, directly utilizing the air stable and easily prepared AgSCF$_3$ as SCF$_3$ source, and without assistance of other oxidants. This methodology allows rapid access to a variety of isoxazolines bearing a −SCF$_3$ substituent. Moreover, the synthetic utility of product was demonstrated by one step synthesis of highly functional C$_{sp3}$−SCF$_3$-containing building block 4 in 87% yield.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(19) Another reaction pathway that trifluoromethylthio radical added to alkenes first followed by formation of isoxazoline cannot be ruled out.

(20) Since no SCF$_3$ radical trapping product was observed in the study, the generation of SCF$_3$ radical in the catalytic cycle was not fully supported.