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Copper-Catalyzed Oxidative Trifluoromethylation of Terminal Alkenes Using Nucleophilic CF_3SiMe_3: Efficient $C(sp^3)-CF_3$ Bond Formation

Lingling Chu[†] and Feng-Ling Qing[*,‡]

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China, and College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

flq@mail.sioc.ac.cn

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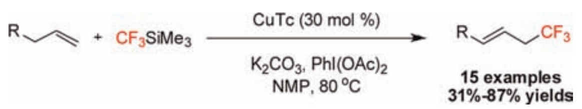
ABSTRACT



An efficient $C(sp^3)-CF_3$ bond-forming reaction via Cu-catalyzed oxidative trifluoromethylation of terminal alkenes has been developed, which proceeds under mild conditions using readily available, less expensive CF_3SiMe_3 as the source of the CF_3 group. This method allows access to a variety of trifluoromethylated allylic compounds.

Development of new methods for the incorporation of the trifluoromethyl group (CF_3) into diverse organic molecules is of great importance due to the useful properties that the trifluoromethyl group imparts on organic molecules such as excellent metabolic stability and high lipophilicity.[1,2] Accordingly, a variety of processes for the incorporation of the CF_3 group into diverse organic molecules has been developed.[2] Transition-metal-mediated carbon−CF_3 bond formation reactions have emerged as powerful synthetic tools in this area.[2−5] For example, Pd-[3] or Cu-based[4] protocols have been developed

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[†] Shanghai Institute of Organic Chemistry.

[‡] Donghua University.

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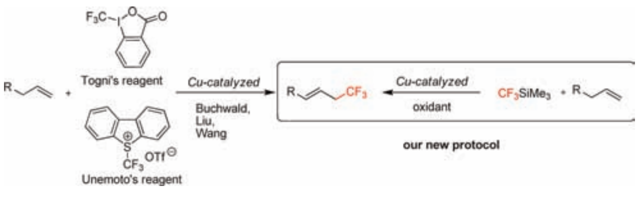
for the trifluoromethylation of halides,[3b,c,4a,4b,4e−4h,4l−4p] boronic acids,[4c,d,i−k] and sulfonates,[3c] allowing efficient access to a diverse array of trifluoromethylated analogues. Recent advances in direct C−H trifluoromethylation protocols are particularly attractive due to obviating the need for prefunctionalization of the substrates.[5] Using a nucleophilic, electrophilic, or radical-based trifluoromethylating reagent, it is now possible to install the trifluoromethyl group in place of C−H bonds of arenes and heteroarenes.[5] While construction of C(sp^2)−CF_3 bonds via direct trifluoromethylation of C(sp^2)−H bonds has been achieved with high efficiency, the analogous transformation to form C(sp)−CF_3 and C(sp^3)−CF_3 was less explored.

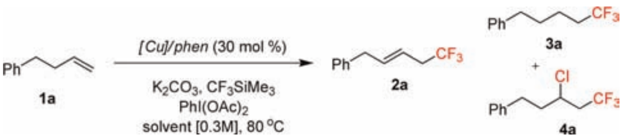
Very recently, the groups of Buchwald,[6a] Liu,[6b] and Wang[6c] have independently reported Cu-catalyzed trifluoromethylation of olefins to construct allylic C−CF_3 bonds using electrophilic trifluoromethylating reagents (Togni's reagent and Umemoto's reagent). These methods not only provide a straightforward and efficient route to allylic trifluoromethylated products that were previously prepared from Pd-catalyzed or Cu-mediated trifluoromethylation of 'prefunctionalized' starting materials such as allylstannanes or allylic halides[7] but also represent rare examples of C(sp^3)−CF_3 bond formation through C(sp^3)−H activation (Scheme 1). However, these methods are limited by the high cost of the electrophilic trifluoromethylating reagents.

Scheme 1. Direct Trifluoromethylation of Alkenes



In 2010, our group demonstrated the first example of Cu-mediated oxidative trifluoromethylation of terminal alkynes using a nucleophilic trifluoromethylating reagent (CF_3SiMe_3).[8] This is the first example of C(sp)−CF_3 bond formation via transition-metal-mediated C−H oxidative trifluoromethylation. Later, the Cu-mediated oxidative trifluoromethylation protocol was successfully employed in the direct trifluoromethylation of boronic acids[4c] and even C−H bonds of heteroaromatics.[5i] Particularly, preliminary mechanistic studies have successfully enabled this oxidative transformation in a catalytic fashion.[5i,9] Herein, we describe Cu-catalyzed direct allylic C−H oxidative trifluoromethylation of terminal alkenes with nucleophilic CF_3SiMe_3 (Ruppert−Prakash reagent).[10] In comparison with the trifluoromethylation of olefins using electrophilic trifluoromethylating reagents,[6] our new method employed readily available and less expensive CF_3SiMe_3 as the trifluoromethylating reagent.[11]

Table 1. Optimization of Cu-Catalyzed Oxidative Trifluoromethylation of 4-Phenyl-1-butene **1a** with CF_3SiMe_3[a]



entry	copper (30 mol %)	ligand (30 mol %)	solvent [0.3 M]	yield of **2a** (%)[b]
1	CuCl	phen	DCE	24 + 24 (**4a**)[c]
2	CuCl	phen	DMF	52
3	CuCl	phen	DMSO	50
4	CuCl	phen	NMP	57
5	CuCl	phen	DME	complex
6	CuCl	phen	CH_3CN	58 + 11 (**4a**)[c]
7	CuOAc	phen	NMP	12
8	CuTc	phen	NMP	80
9	**CuTc**	/	**NMP**	**82**
10	/	/	NMP	12 + 51 (**3a**)[c]

[a] Reaction conditions: **1a** (0.3 mmol), copper catalyst (0.09 mmol), ligand (0.09 mmol), CF_3SiMe_3 (1.2 mmol), K_2CO_3 (1.2 mmol), PhI($OAc)_2$ (0.6 mmol), solvent (1 mL), 80 °C, 24 h, under N_2 atmosphere. [b] Yield was determined by ^{19}F NMR analysis using fluorobenzene as an internal standard. [c] Detected by GC-MS and ^{19}F NMR.

Based on the previous reports of Cu-based oxidative trifluoromethylations,[4c,5i,8,9] we first examined the ability of various oxidants to mediate the trifluoromethylation of 4-phenyl-1-butene **1a** using CF_3SiMe_3 in the presence of base and catalytic copper salts. After some initial experiments, we found PhI($OAc)_2$ to be a promising oxidant for the transformation, providing the desired linear allylic

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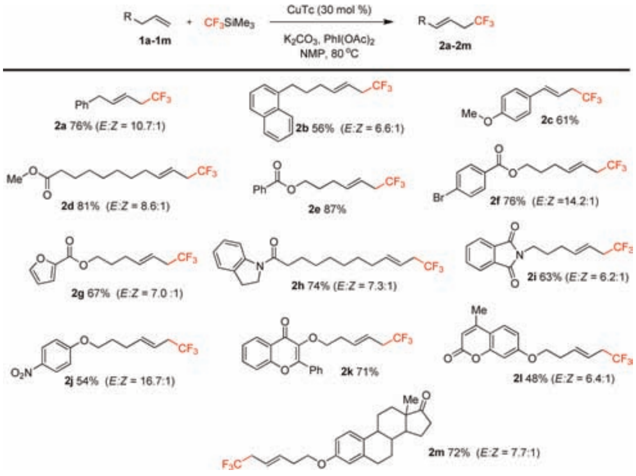
(11) Current prices for these reagents (Sigma-Aldrich in China) are $74,106.6/mol (Umemoto's reagent), $81,440.3/mol (Togni's reagent), and $3,535.9/mol ($CF_3SiMe_3$).

trifluoromethylated product **2a** in 24% yield as well as other side products (Table 1, entry 1). No product was observed in the presence of other oxidants such as 1,4-benzoquinone (BQ), Ag(I) salts, $K_2S_2O_8$, Selectfluor, and even $PhI(OCOCF_3)$ (see Supporting Information, Table S1). To suppress the formation of the further chlorinated side product **4a** which might be derived from the solvent (1,2-dichloroethane), various solvents containing no chloro were subsequently evaluated. As summarized in Table 1, reactions in polar and aprotic solvents such as DMF, DMSO, or NMP occurred in moderate yields, while reaction in DME was found to be sluggish (entries 1–6). NMP was found to be optimal. Although a comparable yield of the desired product **2a** was obtained in the case of CH_3CN as the solvent, the formation of side product **4a** complicated the reaction (entry 6). This result further suggested that the formation of **4a** might be derived from the copper catalyst with a chloride counterion (CuCl). To improve the yield, we further screened the catalysts and found that (thiophene-2-carbonyloxy)copper (CuTc) dramatically increased the yield of the desired product **2a** to 80% (entry 8). It should be noted that the yield of **2a** was slightly increased without ligand 1,10-phenanthroline (phen) (entry 9). The oxidative trifluoromethylation of **1a** proceeded smoothly in the absence of a copper catalyst, but it was surprising that the major product was side product **3a** in 51% yield and the desired product **2a** was formed in only 12% yield (entry 10). Apparently, the copper catalyst plays a pivotal role in the formation of trifluoromethylated allylic compounds.

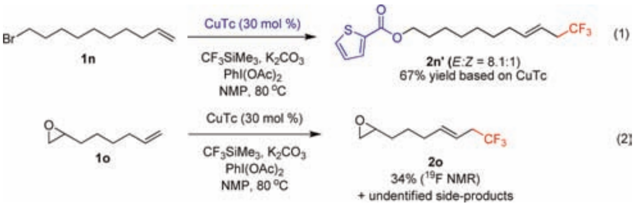
Scheme 2. Scope of Cu-Catalyzed Oxidative Trifluoromethylation of Terminal Alkenes with CF_3SiMe_3[a]



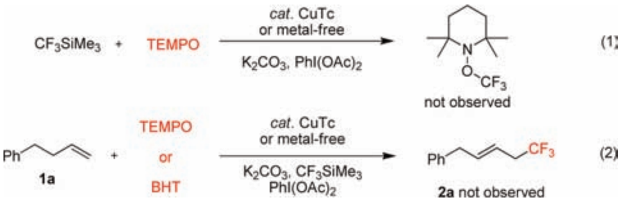
[a] Reaction conditions: **1a** (1.2 mmol), CuTc (0.36 mmol), CF_3SiMe_3 (4.8 mmol), K_2CO_3 (4.8 mmol), $PhI(OAc)_2$ (2.4 mmol), NMP (4 mL), 80 °C, 24 h, under N_2 atmosphere, isolated yield, the *E*/*Z* ratio in parentheses was determined by ^{19}F NMR spectroscopy.

With the optimized reaction conditions in hand, we next examined the scope of the Cu-catalyzed oxidative trifluoromethylation process and found that a variety of terminal alkenes can be transformed into the desired products in moderate to good yields (Scheme 2). Terminal alkenes such as those derived from 3-hydroxyflavone (**2k**), 4-methylumbelliferone (**2l**), and estrone (**2m**) also underwent the transformation, producing the corresponding allylic trifluoromethylation products in moderate to good yields. A range of functional groups, including esters (**2d**–**2g**, **2l**), amides (**2h**, **2i**), nitro (**2j**), ketone (**2k**, **2m**), and heteroaromatic rings (**2g**), were tolerated in this transformation. Bromo on the arene ring was tolerated in the reaction (**2f**), providing a platform for further functionalization, whereas an alkyl bromide was found to be an unsuitable substrate because of the competitive nucleophilic substitution of the alkyl bromide by (thiophene-2-carbonyloxy)-copper (CuTc) (Scheme 3, eq 1). Terminal peroxide was found to be unstable under the oxidative conditions (Scheme 3, eq 2), and the formation of a complex mixture of the desired product and other unidentified products was observed. In most cases, the *E*/*Z* selectivity was moderate, with a ratio range of 6:1–17:1 for the substrates evaluated (Scheme 2).

Scheme 3. Trifluoromethylation of Substrates Containing Epoxide or Bromo



Scheme 4. Trapping Experiments



The direct oxidative trifluoromethylation of terminal alkenes with CF_3SiMe_3 in the presence of $PhI(OAc)_2$ was not expected to proceed through an equivalent of Togni's eletrophilic trifluoromethylating reagent, *in situ* generated $PhI(CF_3)(OAc)$ based on the following experimental results. All attempts to synthesize the acyclic trifluoromethyl hypervalent iodides failed due to the instability of the resulting trifluoromethylated compounds.[12] ^{19}F NMR analysis of the reaction mixture showed that no related peak of $PhI(CF_3)(OAc)$ (Togni's reagent resonates from $\delta = -30$ to -40 ppm) was observed under the reaction

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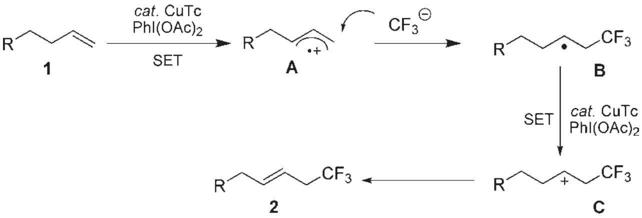
conditions of entries 1−10 of Table 1. Buchwald[6a] and Wang[6c] found that the Cu catalyst was necessary for the trifluoromethylation of olefins with Togni's reagent, whereas oxidation of terminal alkene **1a** using CF_3SiMe_3 and $PhI(OAc)_2$ in the absence of a Cu catalyst provided trifluoromethylated products **2a** in 12% yield and **4a** in 51% yield (Table 1, entry 10). Additionally, no detectable amounts of the TEMPO−CF_3 trapped product was observed in the reaction mixture of CF_3SiMe_3, $PhI(OAc)_2$, and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a well-known radical scavenger, in the presence or absence of CuTc (Scheme 4, eq 1). But the TEMPO−CF_3 trapped product was formed in 44% yield from treatment of TEMPO with Togni's reagent and stoichiometric CuCl.[6c]

Before mechanism consideration, inhibition experiments were conducted. Addition of 2,6-di-*tert*-butyl-4-methyl-phenol (BHT) or TEMPO to the reaction mixture led to a complete inhibition of the desired transformation under either the Cu-catalyzed or metal-free conditions (Scheme 4, eq 2). These experimental results showed that our present oxidative trifluoromethylation reaction involves radical intermediates. However, neither an allyl-TEMPO adduct nor a TEMPO−CF_3 adduct was detected, precluding the involvement of the allylic radical or the trifluoromethyl radical in this process (Scheme 4). These experimental results prompted us to consider that a single electron transfer mechanism was operating in these oxidative trifluoromethylation reactions (Scheme 5), as this mechanism was proposed for hypervalent iodine-induced functionalization of arenes.[13] In the presence of a Cu catalyst and $PhI(OAc)_2$, the terminal alkene **1** might be oxidized to a radical cation intermediate **A** via single electron transfer,[14] and subsequent nucleophilic attack of the radical cation **A** by the CF_3 anion would give rise to a radical intermediate **B**. Intermediate **B** could be then oxidized to form cation intermediate **C**. Finally, deprotonation of **C** would give the desired product **2**. This proposed mechanistic pathway was further supported by the formation of side products **3a** and **4a** under the specific reaction conditions (Table 1); compound **3a** might be formed by radical intermediate **B** via H-abstraction, and either chloro-abstraction by **B** or nucleophilic attack of cation **C** by a chloride anion would give compound **4a**. However, the exact role of the Cu catalyst in the reaction is still unclear. The 12% yield of the desired product and 51% yield of **3a** were observed under metal-free conditions using the $PhI(OAc)_2$ oxidant alone (Table 1, entry 10), indicating that the Cu catalyst might play an important role in the selectivity of the oxidative trifluoromethylation.

Scheme 5. Proposed Mechanism



In summary, an efficient copper-catalyzed oxidative trifluoromethylation of terminal alkenes using CF_3SiMe_3 as the trifluoromethylating reagent has been developed. This method allows a general, direct approach to construct allylic trifluoromethylated compounds containing numerous functional groups, providing a complementary method to the analogous allylic trifluoromethylations using Togni's reagent or Umemoto's reagent. Ongoing studies will focus on probing the mechanism and expanding the scope of this transformation.

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

The authors declare no competing financial interest.

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