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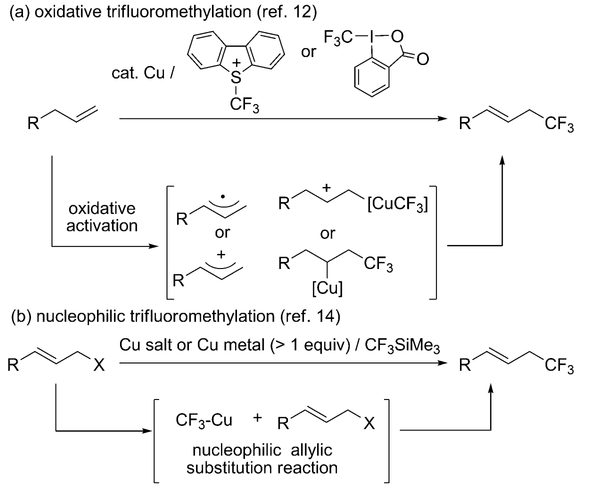
Copper-Catalyzed Nucleophilic Trifluoromethylation of Allylic Halides: A Simple Approach to Allylic Trifluoromethylation

Yoshihiro Miyake, Shin-ichi Ota, and Yoshiaki Nishibayashi*[a]

Considerable attention has been paid to the development of efficient methods for the introduction of a trifluoromethyl (CF_3) group into diverse molecular skeletons[1] because a wide range of organic molecules bearing trifluoromethyl groups has been applied in the field of pharmaceuticals and materials.[2] In fact, the introduction of a trifluoromethyl group into aromatic rings (the formation of C_{sp^2}–CF_3 bonds) through, for example, trifluoromethylation of aryl C–H bonds,[3,4] aryl halides,[5–7] and aryl boronic acids[8] has been extensively developed.

In sharp contrast to methods for the formation of C_{sp^2}–CF_3 bonds, methods for the formation of C_{sp^3}–CF_3 bonds are still limited.[1f] The development of allylic trifluoromethylation methods is important because compounds containing allylic trifluoromethyl groups are versatile building blocks for the preparation of CF_3-containing compounds.[9] Recently, there have been some reports on copper-catalyzed electrophilic allylic trifluoromethylation reactions of terminal alkenes using Umemoto's[10] and Togni's reagents[11] (Scheme 1 a).[12,13] Although the precise reaction mechanism has not been reported, the oxidation of allyl groups to give either allylic cations or radicals and the reaction of electrophilic CF_3–copper species with alkenes have been proposed as key steps for these trifluoromethylation reactions. The nucleophilic allylic trifluoromethylation of allylic halides using transition-metal complexes is also a promising method for the synthesis of compounds containing allylic trifluoromethyl groups, but has been considerably less studied.[6b,14–16] Most of the reported reactions are copper-mediated trifluoromethylation reactions of allylic halides, where stoichiometric amounts of either copper metal or a copper salt is required to obtain the products in good yields (Scheme 1 b).[14] Previously, Kitazume and Ishikawa reported the palladium-catalyzed trifluoromethylation of allylic halides in the presence of a mixture of CF_3I and Zn under ultrasonic irradiation.[6b] However, examples of catalytic nucleophilic substitution reactions are quite limited.[15,16] Moreover, in these reports, the generality of the reactions was not explored. Herein, we report on the development of an efficient catalytic allylic trifluoromethylation reaction, specifically, a copper(I)-catalyzed allylic nucleophilic trifluoromethylation of allylic halides in the presence of trifluoromethyltrimethylsilane (Ruppert–Prakash reagent; CF_3SiMe_3).[17] In this reaction, the CF_3 group was incorporated into the α position of the carbon–halogen bond with complete regioselectivity. Herein, the scope and limitations of the catalytic allylic nucleophilic substitution reaction with CF_3SiMe_3 are described.



Scheme 1. Copper-catalyzed and copper-mediated allylic trifluoromethylation reactions.

Treatment of (*E*)-cinnamyl bromide (**1a**) with 1.5 equivalents of CF_3SiMe_3 in the presence of a catalytic amount of copper(I) iodide (CuI, 5 mol%) and a stoichiometric amount of potassium fluoride (KF, 1.5 equiv) in tetrahydrofuran (THF) at 60 °C for 20 hours gave (*E*)-4,4,4-trifluoro-1-phenylbut-1-ene (**2a**) in 67% yield with complete regioselectivity for trifluoromethylation at the α position, that is, the product derived from γ trifluoromethylation (**3**) was not observed (Table 1, entry 1). The choice of solvent is one of the most important factors that affects the trifluoromethylation reaction. In fact, when *N*,*N*-dimethylformamide (DMF) was used in place of THF, in the presence of 5 mol% of CuI, **2a** was obtained in 29% yield; even when using 1.5 equivalents of CuI in DMF, **2a** was only obtained in 18% yield (Table 1, entries 2 and 3). These results indicate

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[a] Dr. Y. Miyake, S.-i. Ota, Prof. Dr. Y. Nishibayashi
Institute of Engineering Innovation
School of Engineering, The University of Tokyo
Yayoi, Bunkyo-ku, Tokyo, 113-8656 (Japan)
Fax: (+81) 3-5841-1175
E-mail: ynishiba@sogo.t.u-tokyo.ac.jp

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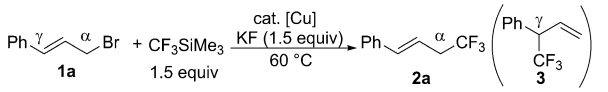
Table 1. Cu-catalyzed trifluoromethylation of cinnamyl bromide (**1a**).[a]



Entry	[Cu] [mol%]	Solvent	t [h]	Recovery of **1a** [%][b]	Yield of **2a** [%][b]
1	CuI (5)	THF	20	0	67
2	CuI (5)	DMF	20	0	29
3	CuI (150)	DMF	20	0	18
4	CuI (5)	NMP	20	0	16
5	CuI (5)	DCE	20	36	20
6	CuI (5)	toluene	20	52	7
7	CuI (5)	hexane	20	82	0
8	CuTC (5)	THF	48	0	83
9	CuTC (5)	THF	20	36	57
10	CuCl (5)	THF	48	0	75
11	CuOTf·0.5 C_6H_6 (5)	THF	48	27	46
12	CuTC (2)	THF	48	0	75
13[c]	CuTC (2)	THF	20	0	79 (75)[d]
14[c,e]	CuTC (2)	THF	20	0	79

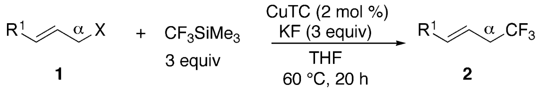
[a] All reactions of **1a** (0.50 mmol) with CF_3SiMe_3 (0.75 mmol) were carried out in the presence of a catalytic amount of copper complex in solvent (3 mL) at 60 °C. [b] Determined by ^{1}H NMR spectroscopy. [c] CF_3SiMe_3 (1.5 mmol, 3 equiv) and KF (1.5 mmol, 3 equiv) were used. [d] Yield of isolated product. [e] (E)-cinnamyl chloride (**1a′**) was used in place of **1a**. DCE = 1,2-dichloroethane.

that the use of CuI in combination with DMF as a solvent is not effective. The use of other solvents, such as N-methylpyrrolidone (NMP), 1,2-dichloroethane, toluene, and hexane, did not give better results (Table 1, entries 4–7). Previously, when aprotic polar solvents, such as DMF, NMP, hexamethylphosphoric triamide, and ionic liquids, were used for copper-mediated allylic nucleophilic trifluoromethylation reactions, the use of a stoichiometric amount of a copper(I) salt was essential.[14] In sharp contrast to these previously reported reactions, we found that less polar solvents, such as THF, are more effective for the Cu-catalyzed allylic nucleophilic trifluoromethylation reaction described herein.

The use of copper(I) thiophene-2-carboxylate (CuTC) led to an increase in the yield of **2a**, although a longer reaction time was necessary (Table 1, entries 8 and 9). When CuCl and CuOTf·0.5 C_6H_6 were used, **2a** was obtained in 75% and 46% yields, respectively (Table 1, entries 10 and 11). Interestingly, the use of only 2 mol% of CuTC was sufficient for an efficient reaction (Table 1, entry 12); the use of 3 equivalents of CF_3SiMe_3, 2 mol% of CuTC, and 3 equivalents of KF, together with a reaction time of 20 hours gave **2a** in 79% yield (75% yield upon isolation; Table 1, entry 13). In addition, the reaction of (E)-cinnamyl chloride (**1a′**) also took place smoothly to give **2a** in 79% yield (Table 1, entry 14). When either cinnamyl acetate, cinnamyl methyl ether, or cinnamyl tosylate were used as substrates, no reaction occurred at all. In another experiment, we confirmed that **2a** did not form in the absence of either CuTC or KF.

Allylic trifluoromethylation of a variety of cinnamyl halides in the presence of a catalytic amount of CuTC proceeded smoothly to give the corresponding α-trifluoromethylation products in good yields (Table 2). The use of cinnamyl substrates bearing either a methyl or a chloro group, at the *para* position of the aromatic ring gave good yields of the corresponding product **2** (Table 2, entries 1 and 2). Although the yields of **2d** and **2e** were low when formed under similar reaction conditions, the reactions of **1d**, **1d′**, and **1e** at lower temperatures (room temperature or 40 °C) led to better yields (Table 2, entries 3–5). 3-Tolylallyl bromides (**1f** and **1g**) and 3-naphthylallyl bromides (**1h** and **1i**) were also good substrates for this reaction, the corresponding products (**2f**–**2i**) being obtained in good yields (Table 2, entries 6–9).

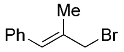
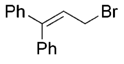
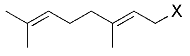
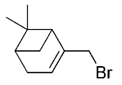
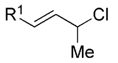
Table 2. Cu-catalyzed trifluoromethylation of cinnamyl halides (**1**).[a]



Entry	Allylic halide **1**	Yield of **2** [%][b]
1	R^1 = p-MeC_6H_4, X = Br (**1b**)	82 (**2b**)
2	R^1 = p-ClC_6H_4, X = Br (**1c**)	74 (**2c**)
3[c]	R^1 = p-MeOC_6H_4, X = Br (**1d**)	46 (**2d**)
4[c]	R^1 = p-MeOC_6H_4, X = Cl (**1d′**)	58 (**2d**)
5[d]	R^1 = p-MeO(CO)C_6H_4, X = Br (**1e**)	68 (**2e**)
6	R^1 = o-MeC_6H_4, X = Br (**1f**)	79 (**2f**)
7	R^1 = m-MeC_6H_4, X = Br (**1g**)	78 (**2g**)
8	R^1 = 1-naphthyl, X = Br (**1h**)	68 (**2h**)
9	R^1 = 2-naphthyl, X = Br (**1i**)	65 (**2i**)

[a] All reactions of **1** (0.50 mmol) with CF_3SiMe_3 (1.5 mmol) were carried out in the presence of 2 mol% of CuTc (0.010 mmol) in THF (3 mL) at 60 °C for 20 h. [b] Yield of isolated product. [c] At room temperature for 48 h. [d] At 40 °C.

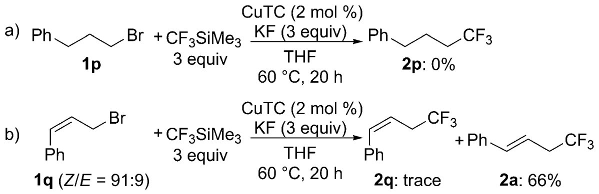
Table 3. Cu-catalyzed trifluoromethylation of allylic halides **1**.[a]

Entry	Allylic halide (**1**)		Yield of **2** [%][b]
1		(**1j**; E/Z = 20:1)	73 (**2j**)
2		(**1k**)	60 (**2k**)
3[c]		X = Br (**1l**)	45 (**2l**)
4[c]		X = Cl (**1l’**)	59 (**2l**)
5[d]		(**1m**)	81 (**2m**)
6[e]		R^1 = Ph (**1n′**)	44 (**2n**)
7[e]		R^1 = p-MeC_6H_4 (**1o’**)	45 (**2o**)

[a] All reactions of **1** (0.50 mmol) with CF_3SiMe_3 (1.5 mmol) were carried out in the presence of 2 mol% of CuTC (0.010 mmol) in THF (3 mL) at 60 °C for 20 h. [b] Yield of isolated product. [c] At room temperature for 48 h. [d] For 48 h. [e] In the presence of 10 mol% of CuTC (0.050 mmol) at 40 °C.

Other primary and secondary allylic halides were investigated as substrates (Table 3). The reactions of β-substituted and γ,γ-disubstituted bromides (**1j** and **1k**) proceeded smoothly to give the corresponding α-trifluoromethylation products (**2j** and **2k**) in good yields (Table 3, entries 1 and 2). Allylic halides containing no conjugated aromatic rings (**1l**, **1l′**, and **1m**) were also good substrates for this reaction, the corresponding products (**2l**–**2m**) being isolated in good yields (Table 3, entries 3–5). Interestingly, the reactions of secondary allylic chlorides **1n′** and **1o′** gave **2n** and **2o** in 44 and 45 % yield, respectively; however, the use of 10 mol % of CuTC was necessary to obtain the products in these moderate yields (Table 3, entries 6 and 7).

To obtain some information on the reaction pathway, we investigated the reactions of **1p** and **1q** under similar reaction conditions (Scheme 2). When the reaction of 3-phenyl-1-bromopropane (**1p**) was carried out, no formation of the corresponding trifluoromethylated product **2p** was observed at all (Scheme 2 a). This result clearly indicates that the presence of the double bond β to the halide group is necessary for the copper-catalyzed trifluoromethylation reaction. Furthermore, in the reaction of (*Z*)-cinnamyl bromide (**1q**), the *E*-configured product **2a** was obtained in 66 % yield without the formation of *Z*-configured product **2q** (Scheme 2 b). We monitored reactions of **1q** in [D$_8$]-THF at 60 °C both in the presence and in the absence of CuTC.[18] The use of 2 mol % of CuTC promoted the isomerization of the alkene moiety of substrate **1q**, thus converting it into **1a**; following reaction times of 2 hours and 20 hours, the ratio of **1q**/**1a** was 25:75 and 1:99, respectively. On the other hand, the isomerization was very slow in the absence of CuTC, the ratio of **1q**/**1a** being 83:17 even after a reaction time of 20 hours. In another experiment, we confirmed that no isomerization of **2q** into **2a** occurred at all under similar reaction conditions.[18] These results indicate that CuTC mediates the isomerization of **1q** into **1a**, which then undergoes trifluoromethylation to give the product **2a** (Scheme 2 b); an allylcopper species derived from complexation of copper with **1** is probably a key intermediate.



Scheme 2. Trifluoromethylation reactions of **1p** and **1q**.

Although a detailed reaction mechanism is not clear, a plausible pathway can be proposed. Copper-catalyzed allylic substitution reactions have been extensively studied,[19–21] and we believe that this allylic trifluoromethylation reaction may proceed in a similar way. The initial step is the formation of CF_3Cu^I through a transmetalation reaction of CuY and CF_3SiMe_3, as activated by fluoride anion.[5a,d,e] Oxidative addition of CF_3Cu^I to allylic halide **1** results in the formation of an allylcopper(III) species.[20] Finally, the reductive elimination reaction of an allylcopper(III) species gives the corresponding trifluoromethylated product **2** and regenerates CuY. As described above, DMF was an ineffective solvent for our reaction; we propose that the coordination of DMF to the allylcopper(III) species inhibits the regeneration of CuY.[18]

In summary, we have developed a copper-catalyzed trifluoromethylation reaction of allylic halides **1** that gives the corresponding allylic trifluoromethylation products **2** in good to high yields and with complete regioselectivity. We believe that this methodology, which is an efficient way to introduce C_{sp^3}–CF_3 bonds, can form part of useful strategies for accessing CF_3-containing compounds. The development of an asymmetric variant of this reaction and clarification of the precise reaction mechanism is currently in progress.

Experimental Section

Representative experimental procedure: CuTC (1.9 mg, 0.010 mmol) and KF (87.2 mg, 1.5 mmol) were placed in a 20 mL Schlenk flask. Anhydrous and degassed THF (3.0 mL) was added, and then the mixture was magnetically stirred at room temperature. After the addition of **1a** (98.5 mg, 0.50 mmol) and CF_3SiMe_3 (220 mL, 1.5 mmol), the reaction flask was kept at 60 °C for 20 h. The solution was poured into water (5 mL) and the resulting mixture was extracted with diethyl ether (30 mL × 3). The combined extracts were washed with brine, and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the resulting residue was purified by column chromatography (SiO_2, eluent: hexane) to give (*E*)-4,4,4-trifluoro-1-phenylbut-1-ene (**2a**) as a colorless oil (69.5 mg, 0.373 mmol, 75 % yield).

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Keywords: allylic compounds · copper · fluorine · homogeneous catalysis · trifluoromethylation

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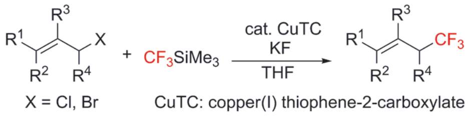

Trifluoromethylation: The treatment of allylic halides with trifluoromethyltrimethylsilane in the presence of a catalytic amount of copper(I) thiophene-2-carboxylate (CuTC) gives the corresponding allylic trifluoromethylation products in good to high yields and with complete regioselectivity (see scheme). The use of THF as a solvent is crucial for obtaining good yields of product.

Trifluoromethylation

Y. Miyake, S.-i. Ota,
*Y. Nishibayashi** .... ▮▮▮▮–▮▮▮▮

Copper-Catalyzed Nucleophilic Trifluoromethylation of Allylic Halides: A Simple Approach to Allylic Trifluoromethylation