

Copper-catalyzed nucleophilic trifluoromethylation of propargylic halides†

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Cite this: *Chem. Commun.*, 2013, 49, 7809Received 13th June 2013,
Accepted 3rd July 2013

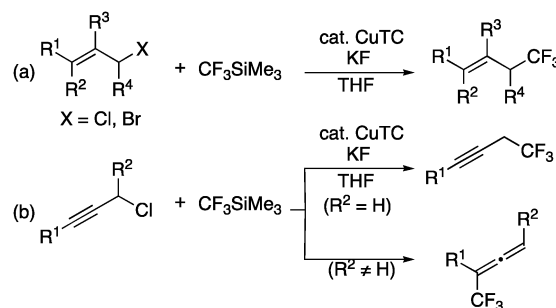
DOI: 10.1039/c3cc44434a

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Reactions of propargylic halides with trifluoromethyltrimethylsilane in the presence of a catalytic amount of copper(i) thiophene-2-carboxylate (CuTC) have been found to give the corresponding trifluoromethylated products in good to high yields with a high selectivity.

Trifluoromethylation of organic compounds is one of the most important methodologies in organic synthesis¹ because a wide range of organic molecules bearing a trifluoromethyl (CF₃) group have attracted considerable attention as highly promising skeletons in the field of pharmaceuticals and materials.² In this context, the development of methods for the formation of C(sp²)-¹ and C(sp³)-CF₃^{3–6} bonds has been expected and extensively studied for the last several years. Recently, we have also succeeded in the development of copper-catalyzed nucleophilic trifluoromethylation of allylic halides, where the introduction of a CF₃ group occurred at the α-position of the carbon-halogen bond with complete regioselectivity (Scheme 1a).^{7,8}

Transition metal-catalyzed propargylic substitution reactions of propargylic alcohol derivatives and halides are expected to be simple methods for constructing carbon-carbon and carbon-heteroatom bonds at the propargylic position.⁹ We have continuously studied ruthenium-¹⁰ and copper-catalyzed¹¹ propargylic substitution reactions of propargylic alcohols and derivatives with a variety of nucleophiles to give the corresponding propargylic substituted products in good to high yields with complete selectivity. In sharp contrast, successful examples of nucleophilic trifluoromethylation of propargylic halides using transition metal complexes are quite limited.^{8b,12} In these reactions, stoichiometric amounts of copper metal or copper salts are required to obtain the trifluoromethylated products in good yields.^{12b,c} To the best of our knowledge, there is no report on *catalytic* trifluoromethylation of propargylic halides.



Scheme 1 (a) Copper-catalyzed nucleophilic trifluoromethylation of allylic halides. (b) Copper-catalyzed nucleophilic trifluoromethylation of propargylic halides (this work).

As an extension of our study, we have now envisaged copper(i)-catalyzed nucleophilic trifluoromethylation of propargylic halides with trifluoromethyltrimethylsilane (Ruppert-Prakash reagent; CF₃SiMe₃).¹³ In fact, we have succeeded in the introduction of a CF₃ group at the *propargylic*- (R² = H) and *allenyl*- (R² ≠ H) positions from reactions of *primary* and *secondary* propargylic halides, respectively (Scheme 1b). Preliminary results are described herein.

Treatment of 3-phenylpropargyl chloride (**1a**) with 3.0 equiv. of CF₃SiMe₃ in the presence of a catalytic amount of copper(i) thiophene-2-carboxylate (CuTC) (5 mol%) and a stoichiometric amount of potassium fluoride (KF) (3.0 equiv.) in tetrahydrofuran (THF) at 60 °C for 20 h gave 1,1,1-trifluoro-4-phenylbut-3-yne (**2a**) in 72% yield with complete regioselectivity, where no formation of 1,1,1-trifluoro-2-phenylbuta-2,3-diene (**3a**) was observed at all (Table 1, entry 1). The choice of leaving groups is one of the most important factors to promote this trifluoromethylation effectively. In fact, when 3-phenylpropargyl bromide was used in place of **1a**, a mixture of **2a** and **3a** was obtained in 35% and 16% yields, respectively (Table 1, entry 2). Other substrates such as 3-phenylpropargyl iodide, mesylate (OMs = OSO₂Me), and alcohol were ineffective (Table 1, entries 3–5). Use of a smaller amount of CF₃SiMe₃ afforded **2a** effectively. In fact, the reaction of **1a** with 1.5 equiv. of CF₃SiMe₃ took place smoothly to give **2a** in 78% yield (Table 1, entry 6).

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc44434a

Table 1 Copper-catalyzed trifluoromethylation of 3-phenylpropargyl substrates with trifluoromethyltrimethylsilane^a

$\text{Ph}-\text{C}\equiv\text{C}-\text{X} + \text{CF}_3\text{SiMe}_3 \xrightarrow[\text{THF, 60 } ^\circ\text{C, 20 h}]{\text{CuTC (5 mol\%), KF}} \text{Ph}-\text{C}\equiv\text{C}-\text{CF}_3 \text{ (2a)} + \text{Ph}-\text{C}(\text{CF}_3)=\text{C} \text{ (3a)}$				
Entry	X	CF ₃ SiMe ₃ and KF (equiv.)	Yield of 2a ^b (%)	Yield of 3a ^b (%)
1	Cl (1a)	3.0	72	0
2	Br	3.0	35	16
3	I	3.0	48	8
4	OMs	3.0	47	2
5	OH	3.0	7	0
6	Cl (1a)	1.5	78 (73) ^c	1

^a All reactions of the phenylpropargyl substrate (0.50 mmol) with CF₃SiMe₃ were carried out in the presence of CuTC (0.025 mmol) and KF in THF (3 mL) at 60 °C for 20 h. ^b Determined by ¹H NMR. ^c Isolated yield.

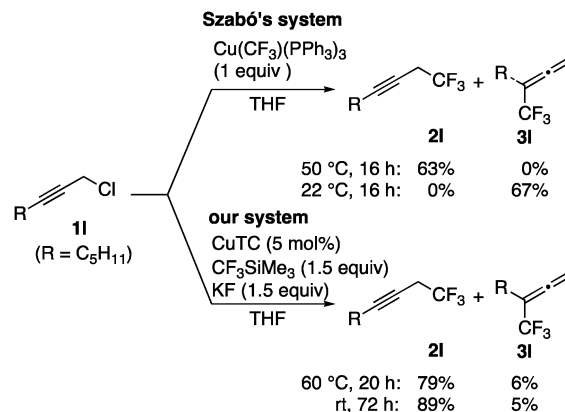
Unfortunately, when reactions of 3-phenylpropargyl acetate and trifluoroacetate were carried out, only a small amount of 2a was obtained in both cases (4% and 3%, respectively). Separately, we confirmed that no formation of 2a was observed in the absence of CuTC or KF.

Propargylic trifluoromethylation of a variety of 3-arylpropargyl chlorides in the presence of a catalytic amount of CuTC proceeded smoothly to give the corresponding propargylic trifluoromethylated products 2 in good to high yields. Typical results are shown in Table 2. The introduction of a substituent such as methyl, chloro, or methoxy at the *para*-position in the benzene ring of 1a did not affect the yields of 2 much (Table 2, entries 1–3). The reaction of *p*-trifluoromethylphenylpropargyl chloride (1e) for 48 h gave 2e in 75% yield although a larger amount (10 mol%) of CuTC was required (Table 2, entry 4). Reactions of 3-tolylpropargyl chlorides (1f and 1g) and 3-naphthylpropargyl chlorides (1h and 1i) also took place to give the corresponding propargylic trifluoromethylated products (2f–2i) in good to high yields (Table 2, entries 5–8). Propargylic chlorides bearing no conjugated aromatic rings

Table 2 Copper-catalyzed trifluoromethylation of primary propargylic chlorides (1) with trifluoromethyltrimethylsilane^a

$\text{R}^1-\text{C}\equiv\text{C}-\text{Cl} + \text{CF}_3\text{SiMe}_3 \xrightarrow[\text{THF, 60 } ^\circ\text{C, 20 h}]{\text{CuTC (5 mol\%), KF (1.5 equiv)}} \text{R}^1-\text{C}\equiv\text{C}-\text{CF}_3 \text{ (2)}$		
Entry	Propargylic chloride (1)	Yield of 2 ^b (%)
1	R ¹ = <i>p</i> -MeC ₆ H ₄ (1b)	83 (2b)
2	R ¹ = <i>p</i> -ClC ₆ H ₄ (1c)	71 (2c)
3	R ¹ = <i>p</i> -MeOC ₆ H ₄ (1d)	79 (2d)
4 ^{c,d}	R ¹ = <i>p</i> -CF ₃ C ₆ H ₄ (1e)	75 (2e)
5	R ¹ = <i>o</i> -MeC ₆ H ₄ (1f)	84 (2f)
6	R ¹ = <i>m</i> -MeC ₆ H ₄ (1g)	62 (2g)
7	R ¹ = 1-naphthyl (1h)	86 (2h)
8	R ¹ = 2-naphthyl (1i)	72 (2i)
9	R ¹ = PhCH ₂ (1j)	80 (2j)
10	R ¹ = PhCH ₂ CH ₂ (1k)	93 (2k)

^a All reactions of 1 (0.50 mmol) with CF₃SiMe₃ (0.75 mmol) were carried out in the presence of 5 mol% of CuTC (0.025 mmol) in THF (3 mL) at 60 °C for 20 h. ^b Isolated yield. ^c 10 mol% of CuTC was used. ^d For 48 h.

**Scheme 2** Copper-mediated and catalyzed propargylic trifluoromethylation of 1l.

(1j and 1k) were also applicable to this reaction system, giving the corresponding propargylic trifluoromethylated products (2j–2k) in high yields (Table 2, entries 9 and 10).

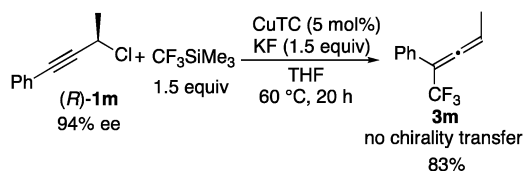
Recently, Szabó's group has reported the copper-mediated trifluoromethylation of propargylic halides.^{12c} In their reaction system, the reaction of 1l with a stoichiometric amount of Cu(CF₃)(PPh₃)₃ at room temperature gave the corresponding trifluoromethylated allene 3l in good yield, while the formation of the propargylic trifluoromethylated product 2l was observed when the reaction was carried out at 50 °C (Scheme 2; Szabó's system).^{12c} In sharp contrast to the result obtained by Szabó's group, only 2l was obtained from the reaction of 1l in the presence of 5 mol% of CuTC even at room temperature (Scheme 2; our system). These results indicate that our catalytic reaction proceeds *via* a different pathway from that of Szabó's system.

Next, nucleophilic trifluoromethylation of a variety of secondary propargylic chlorides in the presence of a catalytic amount of CuTC was investigated. Typical results are shown in Table 3. When we carried out the reaction of 2-chloro-4-phenylbut-3-yne (1m) with 1.5 equiv. of CF₃SiMe₃, the corresponding trifluoromethylated allene (3m) was obtained in 89% isolated yield (Table 3, entry 1). The introduction of a substituent such as methyl and chloro groups at the *para*-position in the benzene ring of 1m did not affect the yields of 3 much

Table 3 Copper-catalyzed trifluoromethylation of secondary propargylic chlorides (1) with trifluoromethyltrimethylsilane^a

$\text{R}^1-\text{C}\equiv\text{C}-\text{Cl} + \text{CF}_3\text{SiMe}_3 \xrightarrow[\text{THF, 60 } ^\circ\text{C, 20 h}]{\text{CuTC (5 mol\%), KF (1.5 equiv)}} \text{R}^1-\text{C}(\text{CF}_3)=\text{C} \text{ (3)}$		
Entry	Propargylic chloride (1)	Yield of 3 ^b (%)
1	R ¹ = Ph (1m)	89 (3m)
2	R ¹ = <i>p</i> -MeC ₆ H ₄ (1n)	79 (3n)
3	R ¹ = <i>p</i> -ClC ₆ H ₄ (1o)	81 (3o)
4 ^c	R ¹ = <i>p</i> -MeOC ₆ H ₄ (1p)	77 (3p)
5	R ¹ = PhCH ₂ CH ₂ (1q)	71 (3q)

^a All reactions of 1 (0.50 mmol) with CF₃SiMe₃ (0.75 mmol) were carried out in the presence of 5 mol% of CuTC (0.025 mmol) in THF (3 mL) at 60 °C for 20 h. ^b Isolated yield. ^c At 40 °C for 48 h.



Scheme 3 Copper-catalyzed trifluoromethylation of (R)-**1m** with trifluoromethyltrimethylsilane.

(Table 3, entries 2 and 3). The reactions of 2-chloro-4-(4-methoxyphenyl)but-3-yne (**1p**) at lower temperature (40 °C) gave the good result (Table 3, entry 4). Secondary propargylic chloride bearing no conjugated aromatic ring (**1q**) was also applicable to this reaction system, giving the corresponding trifluoromethylated allene (**3q**) in 71% yield (Table 3, entry 5). Only a small amount (8%) of the corresponding trifluoromethylated allene was obtained from the reaction of 1-chloro-1-phenylprop-2-yne under the same reaction conditions.

In order to obtain information on the reaction pathway, we investigated the reaction of an optically active secondary propargylic chloride. Treatment of (R)-**1m** (94% ee) with 1.5 equiv. of CF_3SiMe_3 under the same reaction conditions afforded **3m** in 83% yield with a complete loss of optical purity (Scheme 3). This result indicates that our catalytic reaction proceeds not *via* an anti- $\text{S}_{\text{N}}2'$ pathway¹⁴ but *via* other pathways involving cationic propargyl/allenyl-copper complexes as reactive intermediates.^{7,9c}

In summary, we have found the copper-catalyzed nucleophilic trifluoromethylation of propargylic chlorides with trifluoromethyltrimethylsilane. In our system, reactions of *primary* propargylic chlorides (**1**) afford the corresponding propargylic trifluoromethylated products (**2**), while the trifluoromethylated allenes (**3**) can be obtained from reactions of *secondary* propargylic chlorides. This is the first successful example of *catalytic* trifluoromethylation of propargylic halides. We believe that the method described here provides an efficient strategy for the synthesis of CF_3 -containing compounds at the propargylic and allenyl positions, which are useful building blocks in pharmaceuticals.^{12c,15} Further work is currently in progress to apply this strategy to the enantioselective reactions and to clarify the precise reaction mechanism.

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalyst" from the Ministry of Education, Culture, Sports, Science and Technology, Japan and the Funding Program for Next Generation World-Leading Researchers (GR025). We thank Dr Shingo Ito and Prof. Dr Kyoko Nozaki at The University of Tokyo for measurement of ^{19}F NMR.

Notes and references

- For recent reviews on trifluoromethylation, see: (a) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1; (b) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (c) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470; (d) T. Besset, C. Schneider and

- D. Cahard, *Angew. Chem., Int. Ed.*, 2012, **51**, 5048; (e) A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8950.
- (a) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (b) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
- For reviews on trifluoromethylation of carbonyl compounds, see: (a) G. K. S. Prakash and F. Wang, in *Organic Chemistry – Breakthroughs and Perspectives*, ed. K. Ding and L.-X. Dai, Wiley-VCH, Weinheim, 2012, ch. 12, pp. 413–476; (b) N. Shibata, S. Mizuta and H. Kawai, *Tetrahedron: Asymmetry*, 2008, **19**, 2633.
- For examples of enantioselective α -trifluoromethylation of aldehydes, see: (a) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 10875; (b) A. E. Allen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 4986.
- (a) A. T. Parsons and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 9120; (b) J. Xu, Y. Fu, D.-F. Luo, Y.-Y. Jiang, B. Xiao, Z.-J. Liu, T.-J. Gong and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 15300; (c) X. Wang, Y. Ye, S. Zhang, J. Feng, Y. Xu, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 16410; (d) R. Shimizu, H. Egami, Y. Hamashima and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2012, **51**, 4577; (e) L. Chu and F.-L. Qing, *Org. Lett.*, 2012, **14**, 2106.
- For recent examples, see: (a) P. G. Janson, I. Ghoneim, N. O. Ichenko and K. J. Szabó, *Org. Lett.*, 2012, **14**, 2882; (b) R. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2012, **134**, 12462; (c) Y. Li and A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8221; (d) Y. Yasu, T. Koike and M. Akita, *Angew. Chem., Int. Ed.*, 2012, **51**, 9567.
- Y. Miyake, S. Ota and Y. Nishibayashi, *Chem.-Eur. J.*, 2012, **18**, 13255.
- For examples of nucleophilic trifluoromethylation of allylic halides using a stoichiometric amount of copper salts, see: (a) Y. Kobayashi, K. Yamamoto and I. Kumadaki, *Tetrahedron Lett.*, 1979, **20**, 4071; (b) J.-P. Bouillon, C. Malverney, R. Merényi and H. G. Viehe, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2147; (c) H. Urata and T. Fuchikami, *Tetrahedron Lett.*, 1991, **32**, 91; (d) D.-B. Su, J.-X. Duan and Q.-Y. Chen, *Tetrahedron Lett.*, 1991, **32**, 7689; (e) Q.-Y. Chen and J.-X. Duan, *J. Chem. Soc., Chem. Commun.*, 1993, 1389; (f) J. Kim and J. M. Shreeve, *Org. Biomol. Chem.*, 2004, **2**, 2728.
- For recent reviews on propargylic substitution reactions, see: (a) G. W. Kabalka and M. L. Yao, *Curr. Org. Synth.*, 2008, **5**, 28; (b) N. Ljungdahl and N. Kann, *Angew. Chem., Int. Ed.*, 2009, **48**, 642; (c) Y. Miyake, S. Uemura and Y. Nishibayashi, *ChemCatChem*, 2009, **1**, 342; (d) R. J. Detz, H. Hiemstra and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2009, 6263; (e) C.-H. Ding and X.-L. Hou, *Chem. Rev.*, 2011, **111**, 1914; (f) Y. Nishibayashi, *Synthesis*, 2012, 489.
- For examples of ruthenium-catalyzed reactions, see: (a) K. Fukamizu, Y. Miyake and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2008, **130**, 10498; (b) M. Ikeda, Y. Miyake and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2010, **49**, 7289; (c) M. Ikeda, Y. Miyake and Y. Nishibayashi, *Chem.-Eur. J.*, 2012, **18**, 3321 and references therein.
- For examples of copper-catalyzed reactions, see: (a) G. Hattori, H. Matsuzawa, Y. Miyake and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2008, **47**, 3781; (b) G. Hattori, K. Sakata, H. Matsuzawa, Y. Tanabe, Y. Miyake and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2010, **132**, 10592; (c) A. Yoshida, G. Hattori, Y. Miyake and Y. Nishibayashi, *Org. Lett.*, 2011, **13**, 2460 and references therein.
- (a) D. J. Burton, G. A. Hartgraves and J. Hsu, *Tetrahedron Lett.*, 1990, **31**, 3699; (b) H. Kawai, T. Furukawa, Y. Nomura, E. Tokunaga and N. Shibata, *Org. Lett.*, 2011, **13**, 3596; (c) T. S. N. Zhao and K. J. Szabó, *Org. Lett.*, 2012, **14**, 3966.
- (a) G. K. S. Prakash and A. K. Yudin, *Chem. Rev.*, 1997, **97**, 757; (b) R. P. Singh and J. M. Shreeve, *Tetrahedron*, 2000, **56**, 7613.
- For recent examples of copper-catalyzed reactions, see: (a) C. Zhong, Y. Sasaki, H. Ito and M. Sawamura, *Chem. Commun.*, 2009, 5850; (b) H. Ohmiya, U. Yokobori, Y. Makida and M. Sawamura, *Org. Lett.*, 2011, **13**, 6312; (c) M. Yang, N. Yokokawa, H. Ohmiya and M. Sawamura, *Org. Lett.*, 2012, **14**, 816.
- Y. Matsuya, D. Ihara, M. Fukuchi, D. Honma, K. Itoh, A. Tabuchi, H. Nemoto and M. Tsuda, *Bioorg. Med. Chem.*, 2012, **20**, 2564.