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COMMUNICATION

Copper-catalyzed nucleophilic trifluoromethylation of benzylic chlorides

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th May 2014,
Accepted 00th May 2014

DOI: 10.1039/x0xx00000x

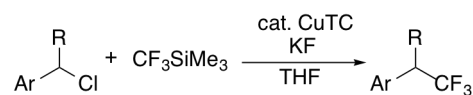
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Reactions of primary and secondary benzylic chlorides with trifluoromethyltrimethylsilane in the presence of a catalytic amount of copper(I) thiophene-2-carboxylate (CuTC) have been found to give the corresponding benzylic trifluoromethylated products in good to high yields.

Introduction of trifluoromethyl (CF₃) group into organic molecules¹ provides a promising method for the synthesis of trifluoromethylated compounds, which have attracted considerable attention as highly promising skeleton in the field of pharmaceuticals and materials.² In this context, development of the methods for the formation of C(sp³)-CF₃ bond at the allylic and propargylic positions has been extensively studied.^{1f,3-9} Recently, we have succeeded in the development of the copper-catalyzed nucleophilic trifluoromethylation of allylic and propargylic halides, where the formation of C(sp³)-CF₃ bond at the allylic and propargylic positions occurred efficiently.⁹

Benzylic trifluoromethylation of benzylic halides using trifluoromethyl-copper species is expected to be a useful method for the formation of C(sp³)-CF₃ bond at the benzylic position, but has been considerably less studied.⁸ Unfortunately, generality of applicable substrates is unexplored in most of these reactions.^{8a-1} Particularly, Shibata and co-workers have recently reported the trifluoromethylation of various benzylic bromides with electrophilic CF₃ reagents using a copper metal, but applicable substrates are limited to only primary benzylic halides.^{8g,10,11} In most of the reported reactions, a *stoichiometric amount* of copper metals or copper salts are required to obtain the trifluoromethylated products in good yields.⁸ Previously, Chen and co-worker reported the copper-catalyzed trifluoromethylation of benzyl halides with methyl fluorosulfonyldifluoroacetate (FO₂SCF₂CO₂Me), but applicable substrates are quite limited to benzyl chloride, bromide and iodide (C₆H₅CH₂X), unfortunately.¹¹ To the best of our knowledge, there is no report for catalytic

trifluoromethylation of benzylic halides by directly using trifluoromethyltrimethylsilane (Ruppert-Prakash reagent; CF₃SiMe₃)¹² as a trifluoromethylating reagent.^{8,11} As an extension of our study, we have now envisaged copper(I)-catalyzed nucleophilic trifluoromethylation of benzylic chlorides with CF₃SiMe₃. In fact, we have succeeded in the trifluoromethylation of primary and secondary benzylic chlorides to afford the trifluoromethylated products in good to high yields (Scheme 1). Preliminary results are described herein.



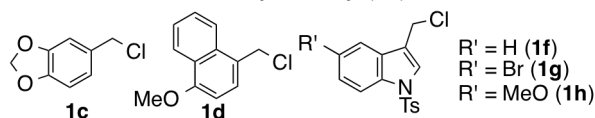
Scheme 1 Copper-catalyzed nucleophilic trifluoromethylation of benzylic chlorides.

Treatment of *p*-methoxybenzyl 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 48 h gave 1-methoxy-4-(2,2,2-trifluoroethyl)benzene (**2a**) in 85% yield (Table 1, entry 1). Separately, we confirmed that no formation of **2a** was observed in the absence of CuTC or KF. In contrast, no reaction occurred at all with the quantitative recovery of **1b** when a less electron-donating group such as methyl moiety was introduced on the benzene ring (Table 1, entry 2). In the use of benzyl chloride as a substrate, benzyl chloride was also recovered in 94% without the formation of the corresponding trifluoromethylated product. Similar results were obtained in the reactions of **1d** and **1e** (Table 1, entries 3-4). Benzylic chlorides bearing heteroaromatic moieties such as thiophene and indole rings were applicable to this reaction system, the

corresponding trifluoromethylated products (**2f-2h**) being obtained in high yields (Table 1, entries 5-8).

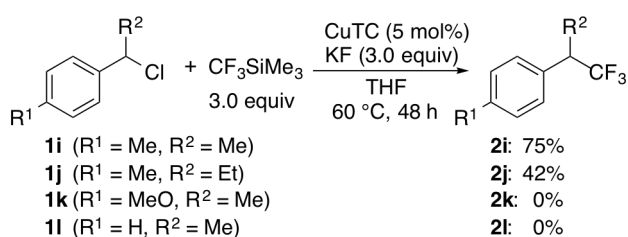
Table 1 Copper-catalyzed trifluoromethylation of primary benzylic chlorides (**1**)^a

Entry	benzylic chloride (1)	Yield of 2 (%) ^b
1	Ar = <i>p</i> -MeO-C ₆ H ₄ (1a)	85 (2a)
2	Ar = <i>p</i> -Me-C ₆ H ₄ (1b)	0 (2b)
3	Ar = 3,4-methylenedioxy-C ₆ H ₃ (1c)	94 (2c)
4	Ar = 4-MeO-1-naphthyl (1d)	93 (2d)
5	Ar = 2-thienyl (1e)	82 (2e) ^c
6	Ar = 1-tosyl-3-indolyl (1f)	86 (2f)
7	Ar = 5-bromo-1-tosyl-3-indolyl (1g)	90 (2g)
8	Ar = 5-MeO-1-tosyl-3-indolyl (1h)	89 (2h)

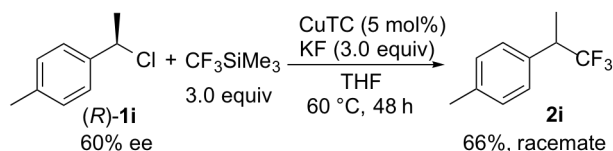


^aAll reactions of **1** (0.50 mmol) with CF₃SiMe₃ (1.5 mmol) were carried out in the presence of CuTC (0.025 mmol) and KF (1.5 mmol) in THF (3 mL) at 60 °C for 48 h. ^bIsolated yield. ^cDetermined by ¹H NMR.

Interestingly, our catalytic system is applied for the trifluoromethylation of secondary benzylic chlorides (Scheme 2). Reactions of secondary benzylic chlorides (**1i** and **1j**) bearing *p*-tolyl group with CF₃SiMe₃ in the presence of a catalytic amount of CuTC proceeded smoothly to give the corresponding trifluoromethylated products (**2i** and **2j**) in moderate to good yields. Unfortunately, when the reaction of **1k** was carried out, no formation of **2k** was observed with no recovery of **1k**. On the other hand, no reaction of **1l** under similar conditions occurred at all and **1l** was recovered in 86%. These results in Table 1 and Scheme 2 indicate that electron-donating groups such as methoxy group raise the reactivities of both primary and secondary benzylic chlorides because of stabilizing the cationic intermediates. However, the use of **1k** accelerates side reactions and many of by-products including



Scheme 2 Copper-catalyzed trifluoromethylation of secondary benzylic chlorides (**1**).



Scheme 3 Copper-catalyzed trifluoromethylation of (*R*)-**1i**.

styrene derivatives, which were generated from the elimination reaction of **1k**, were observed without the formation of **2k**.

In order to obtain information on the reaction pathway, we investigated the reaction of an optically active secondary benzylic chloride. Treatment of (*R*)-**1i** (60% *ee*) with 3.0 equiv of CF₃SiMe₃ under similar conditions afforded **2i** in 66% yield with complete loss of optical purity (Scheme 3). This result indicates that our catalytic reaction proceeds not via S_N2 (stereoinversion)¹³ or S_Ni (stereoretention)^{13,14} pathway but via the cationic benzyl-copper intermediate.^{9,10}

Conclusions

In summary, we have found the copper-catalyzed nucleophilic trifluoromethylation of benzylic chlorides (**1**). In this reaction system, not only primary benzylic chlorides but also secondary benzylic chlorides can be transformed into the corresponding trifluoromethylated products in good yields although applicable substrates were limited to benzylic chlorides bearing electron-donating groups. This is the first successful example of *catalytic* trifluoromethylation of benzylic halides by directly using CF₃SiMe₃ as a trifluoromethylating reagent. We believe that this methodology described here provides an efficient strategy for the synthesis of CF₃-containing compounds at the benzylic position, which are used as useful building blocks in pharmaceuticals.¹⁵ Further work is currently in progress to investigate other types of *catalytic* trifluoromethylation and application to a larger scale synthesis.

Acknowledgement

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 to Dr. Shingo Ito and Prof. Dr. Kyoko Nozaki at The University of Tokyo for measurement of ¹⁹F-NMR.

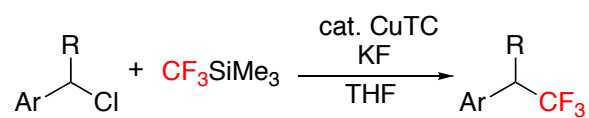
Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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CuTC: copper(I) thiophene-2-carboxylate

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