

### Copper-catalyzed nucleophilic trifluoromethylation of benzylic chlorides†

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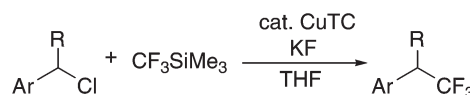
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Reactions of primary and secondary benzylic chlorides with trifluoromethyltrimethylsilane in the presence of a catalytic amount of copper(i) thiophene-2-carboxylate (CuTC) have been found to give the corresponding benzylic trifluoromethylated products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

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

Benzylic trifluoromethylation of benzylic halides using trifluoromethyl-copper species is expected to be a useful method for the formation of the C(sp<sup>3</sup>)-CF<sub>3</sub> bond at the benzylic position, but has been considerably less studied.<sup>8</sup> Unfortunately, generality of applicable substrates is unexplored in most of these reactions.<sup>8a-f</sup> Particularly, Shibata and co-workers have recently reported the trifluoromethylation of various benzylic bromides with electrophilic CF<sub>3</sub> reagents using a copper metal, but applicable substrates are limited to only primary benzylic halides.<sup>8g,10,11</sup> In most of the reported reactions, a stoichiometric amount of copper metals or copper salts is required to obtain the trifluoromethylated products in good yields.<sup>8</sup> Previously, Chen and co-workers reported the copper-catalyzed trifluoromethylation of benzyl halides with methyl fluorosulfonyldifluoroacetate (FO<sub>2</sub>SCF<sub>2</sub>CO<sub>2</sub>Me), but applicable



Scheme 1 Copper-catalyzed nucleophilic trifluoromethylation of benzylic chlorides.

substrates are quite limited to benzyl chloride, bromide and iodide (C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>X), unfortunately.<sup>11</sup> To the best of our knowledge, there is no report for catalytic trifluoromethylation of benzylic halides by directly using trifluoromethyltrimethylsilane (Ruppert-Prakash reagent; CF<sub>3</sub>SiMe<sub>3</sub>)<sup>12</sup> as a trifluoromethylating reagent.<sup>8,11</sup> As an extension of our study, we have now envisaged copper(i)-catalyzed nucleophilic trifluoromethylation of benzylic chlorides with CF<sub>3</sub>SiMe<sub>3</sub>. 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.

Treatment of *p*-methoxybenzyl chloride (**1a**) with 3.0 equiv. of CF<sub>3</sub>SiMe<sub>3</sub> 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). Also, 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 a methyl moiety was introduced on the benzene ring (Table 1, entry 2). Using benzyl chloride as a substrate, benzyl chloride was also recovered in 94% without the formation of the corresponding trifluoromethylated product. The corresponding trifluoromethylated products were obtained in the reactions of **1c** and **1d** (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 (**2e–2h**) being obtained in high yields (Table 1, entries 5–8).

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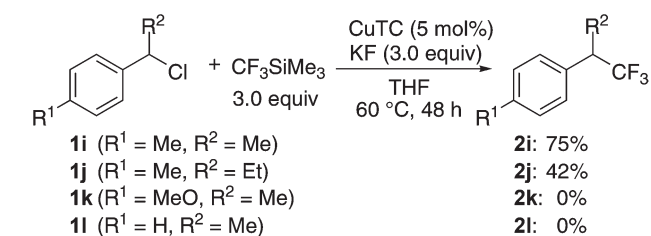
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ob00957f



**Table 1** Copper-catalyzed trifluoromethylation of primary benzylic chlorides (**1**)<sup>a</sup>

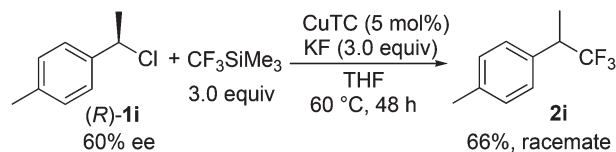
Entry	Benzylic chloride	Yield of <b>2</b> <sup>b</sup> (%)
1	Ar = <i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> ( <b>1a</b> )	85 ( <b>2a</b> )
2	Ar = <i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> ( <b>1b</b> )	0 ( <b>2b</b> )
3	Ar = 3,4-methylenedioxy-C <sub>6</sub> H <sub>3</sub> ( <b>1c</b> )	94 ( <b>2c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

<sup>a</sup> All reactions of **1** (0.50 mmol) with CF<sub>3</sub>SiMe<sub>3</sub> (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. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by <sup>1</sup>H NMR.

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

Interestingly, our catalytic system is applied for the trifluoromethylation of secondary benzylic chlorides (Scheme 2). Reactions of secondary benzylic chlorides (**1i** and **1j**) bearing the *p*-tolyl group with CF<sub>3</sub>SiMe<sub>3</sub> 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% yield. The results in Table 1 and Scheme 2 indicate that electron-donating groups such as the methoxy group raise the reactivities of both primary and secondary benzylic chlorides because of stabilization of the cationic intermediates. However, the use of **1k** accelerates side reactions and many of the by-products including 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.

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

of CF<sub>3</sub>SiMe<sub>3</sub> under similar conditions afforded **2i** in 66% yield with the complete loss of optical purity (Scheme 3). This result indicates that our catalytic reaction proceeds not *via* the S<sub>N</sub>2 (stereoinversion)<sup>13</sup> or S<sub>N</sub>*i* (stereoretention)<sup>13,14</sup> pathway but *via* the cationic benzylic-copper intermediate.<sup>9,10</sup>

## 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 CF<sub>3</sub>SiMe<sub>3</sub> as a trifluoromethylating reagent. We believe that the methodology described here provides an efficient strategy for the synthesis of CF<sub>3</sub>-containing compounds at the benzylic position, which are used as useful building blocks in pharmaceuticals.<sup>15</sup> Further work is currently in progress to investigate other types of *catalytic* trifluoromethylation and application to a larger scale synthesis.

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## Notes and references

- For reviews on trifluoromethylation, see: (a) M. Schlosser, *Angew. Chem., Int. Ed.*, 2006, **45**, 5432; (b) K. Uneyama, T. Katagiri and H. Amii, *Acc. Chem. Res.*, 2008, **41**, 817; (c) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1; (d) K. Sato, A. Tarui, M. Omote, A. Ando and I. Kumadaki, *Synthesis*, 2010, 1865; (e) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (f) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470;



- (g) T. Besset, C. Schneider and D. Cahard, *Angew. Chem., Int. Ed.*, 2012, **51**, 5048; (h) A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8950; (i) P. Chen and G. Liu, *Synthesis*, 2013, 2919; (j) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214.
- 2 (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.
- 3 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.
- 4 For examples on enantioselective  $\alpha$ -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.
- 5 For recent examples of allylic C–H trifluoromethylation, see: (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.
- 6 For recent examples of addition to alkenes, see: (a) P. G. Janson, I. Ghoneim, N. O. Iichenko 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.
- 7 For examples of nucleophilic trifluoromethylation using a stoichiometric amount of copper salts, see: (a) D. J. Burton, G. A. Hartgraves and J. Hsu, *Tetrahedron Lett.*, 1990, **31**, 3699; (b) J.-P. Bouillon, C. Maliverney, R. Merényi and H. G. Viehe, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2147; (c) D.-B. Su, J.-X. Duan and Q.-Y. Chen, *Tetrahedron Lett.*, 1991, **32**, 7689; (d) T. S. N. Zhao and K. J. Szabó, *Org. Lett.*, 2012, **14**, 3966; (e) J. M. Larsson, S. R. Pathipati and K. J. Szabó, *J. Org. Chem.*, 2013, **78**, 7330.
- 8 For examples of trifluoromethylation of benzylic halides using a stoichiometric amount of copper metals or salts, see: (a) Y. Kobayashi, K. Yamamoto and I. Kumadaki, *Tetrahedron Lett.*, 1979, **20**, 4071; (b) N. V. Kondratenko, E. P. Vechirko and L. M. Yagupolskii, *Synthesis*, 1980, 932; (c) H. Urata and T. Fuchikami, *Tetrahedron Lett.*, 1991, **32**, 91; (d) Q.-Y. Chen and J.-X. Duan, *J. Chem. Soc., Chem. Commun.*, 1993, 1389; (e) J. Kim and J. M. Shreeve, *Org. Biomol. Chem.*, 2004, **2**, 2728; (f) G. G. Dubinina, H. Furutachi and D. A. Vivic, *J. Am. Chem. Soc.*, 2008, **130**, 8600; (g) H. Kawai, T. Furukawa, Y. Nomura, E. Tokunaga and N. Shibata, *Org. Lett.*, 2011, **13**, 3596.
- 9 (a) Y. Miyake, S. Ota and Y. Nishibayashi, *Chem. – Eur. J.*, 2012, **18**, 13255; (b) Y. Miyake, S. Ota, M. Shibata, K. Nakajima and Y. Nishibayashi, *Chem. Commun.*, 2013, **49**, 7809.
- 10 Very recently, Altman's group has independently reported copper-mediated trifluoromethylation of benzylic xanthates including secondary benzylic xanthates, see: L. Zhu, S. Liu, J. T. Douglas and R. A. Altman, *Chem. – Eur. J.*, 2013, **19**, 12800.
- 11 Q.-Y. Chen and S.-W. Wu, *J. Chem. Soc., Chem. Commun.*, 1989, 705.
- 12 (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.
- 13 J. D. Weaver, A. Recio III, A. J. Grenning and J. A. Tunge, *Chem. Rev.*, 2011, **111**, 1846.
- 14 (a) J.-Y. Legros, M. Toffano and J.-C. Fiaud, *Tetrahedron*, 1995, **51**, 3235; (b) D. Imao, B. W. Glasspoole, V. S. Laberge and C. M. Crudden, *J. Am. Chem. Soc.*, 2009, **131**, 5024.
- 15 (a) R. C. Desai, E. Metzger, C. Santini, P. T. Meike, J. V. Heck, J. P. Berger, K. L. MacNaul, T. Cai, S. D. Wright, A. Agrawal, D. E. Moller and S. P. Sahoo, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1673; (b) Y. Shishido, H. Wakabayashi, H. Koike, N. Ueno, S. Nukui, T. Yamagishi, Y. Murata, F. Naganeo, M. Mizutani, K. Shimada, Y. Fujiwara, A. Sakakibara, O. Suga, R. Kusano, S. Ueda, Y. Kanai, M. Tsuchiya and K. Satake, *Bioorg. Med. Chem.*, 2008, **16**, 7193.

