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Copper-catalyzed nucleophilic trifluoromethylation of benzylic chlorides

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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 (CF$_3$) group into organic molecules 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.

In this context, development of the methods for the formation of C(sp$^3$)-CF$_3$ bond at the allylic and propargylic positions has been extensively studied. Recently, we have succeeded in the development of the copper-catalyzed nucleophilic trifluoromethylation of allylic and propargylic halides, where the formation of C(sp$^3$)-CF$_3$ bond at the allylic and propargylic positions occurred efficiently.

Benzylic trifluoromethylation of benzylic halides using trifluoromethyl-copper species is expected to be a useful method for the formation of C(sp$^3$)-CF$_3$ bond at the benzylic position, but has been considerably less studied. Unfortunately, generality of applicable substrates is unexplored in most of these reactions. Particularly, Shibata and co-workers have recently reported the trifluoromethylation of various benzylic bromides with electrophilic CF$_3$ reagents using a copper metal, but applicable substrates are limited to only primary benzylic halides.

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. Previously, Chen and co-worker reported the copper-catalyzed trifluoromethylation of benzylic halides with methyl fluoro sulfonyldifluoroacetate (FO$_2$SCF$_2$CO$_2$Me), but applicable substrates are quite limited to benzylic chloride, bromide and iodide (C$_6$H$_5$CH$_2$X), unfortunately. To the best of our knowledge, there is no report for catalytic trifluoromethylation of benzylic halides by directly using trifluoromethyltrimethylsilane (Ruppert-Prakash reagent; CF$_3$SiMe$_3$) as a trifluoromethylating reagent. As an extension of our study, we have now envisaged copper(I)-catalyzed nucleophilic trifluoromethylation of benzylic chlorides with CF$_3$SiMe$_3$. 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 CF$_3$SiMe$_3$ 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)

<table>
<thead>
<tr>
<th>Entry</th>
<th>benzyl chloride (1)</th>
<th>Yield of 2 (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ar = p-MeOC6H4Cl (1a)</td>
<td>85 (2a)</td>
</tr>
<tr>
<td>2</td>
<td>Ar = p-ClC6H4Cl (1b)</td>
<td>0 (2b)</td>
</tr>
<tr>
<td>3</td>
<td>Ar = 3,4-methylenedioxyC6H4Cl (1c)</td>
<td>94 (2e)</td>
</tr>
<tr>
<td>4</td>
<td>Ar = 4-MeO-1-naphthyl (1d)</td>
<td>93 (2d)</td>
</tr>
<tr>
<td>5</td>
<td>Ar = 2-thienyl (1e)</td>
<td>82 (2e)</td>
</tr>
<tr>
<td>6</td>
<td>Ar = 1-tosyl-3-indolyl (1f)</td>
<td>86 (2f)</td>
</tr>
<tr>
<td>7</td>
<td>Ar = 5-bromo-1-tosyl-3-indolyl (1g)</td>
<td>90 (2g)</td>
</tr>
<tr>
<td>8</td>
<td>Ar = 5-MeO-1-tosyl-3-indolyl (1h)</td>
<td>89 (2h)</td>
</tr>
</tbody>
</table>

a All 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. b Isolated yield. c Determined 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 are 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 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)-1l (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 Sn2 (stereoinversion)13,14 or Sn2 (stereoretention)13,14 pathway but via the cationic benzyl-copper intermediate.15

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.

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