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Cu-Mediated Chemoselective Trifluoromethylation of Benzyl Bromides Using Shelf-Stable Electrophilic Trifluoromethylating Reagents

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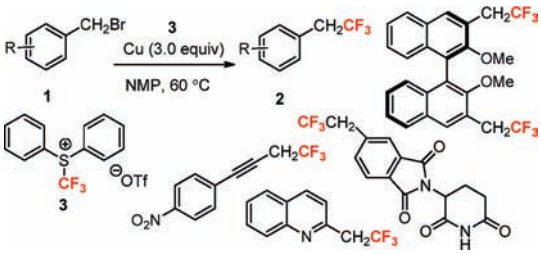
ABSTRACT



Copper-mediated chemoselective trifluoromethylation at the benzylic position by the use of shelf-stable electrophilic trifluoromethylating reagents 3 in good to high yields under mild conditions is described for the first time. The generality of this trifluoromethylation for a wide variety of benzyl bromides facilitates the rapid creation of structural diversity of medicinal candidates in drug discovery.

Direct introduction of a CF_3 group into organic molecules provides straight entrance to trifluoromethylated compounds that are important building blocks in the synthesis of drug and agrochemical candidates as well as other unique products in material sciences.[1] Among the many potential trifluoromethylated synthons for these purposes,[2] a considerable research effort has been focused on the synthesis of trifluoromethyl-containing aromatic compounds such as (trifluoromethyl)arenes,[3] (trifluoromethoxy)arenes,[4] and (trifluoromethylthio)arenes[5] (Figure 1). In contrast to the long-standing interest in these trifluoromethyl-containing arenes, (trifluoroethyl)arenes as well as their heteroaromatic variants remain remarkably uncommon synthetic targets despite their high potential utilities in various fields including medicinal, biological, agricultural, and material chemistry.[6]

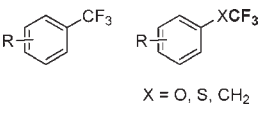


Figure 1. Trifluoromethyl-containing aromatic compounds.

Although tremendous progress has been achieved in this area, particularly for the trifluoromethylation of an aromatic ring,[3] the preparation of (trifluoroethyl)arenes by direct introduction of a trifluoromethyl group at the benzylic position has been considerably less studied.[7] Trifluoromethylation of benzyl bromide with [$CuCF_3$] generated from CF_3I and Cu powder was initially examined by Kobayashi and co-workers in 1979.[7a] This method requires a high reaction temperature in a stainless steel tube

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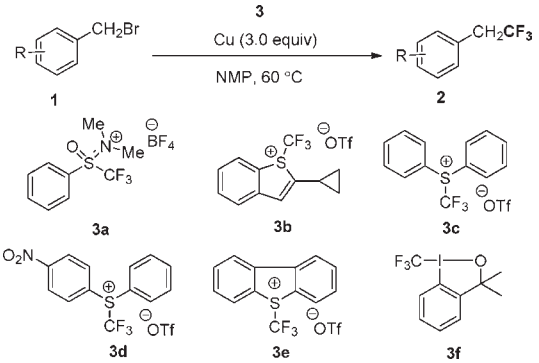
to prepare [$CuCF_3$] species and removal of excess amounts of copper in a glovebox. One year later, Yagupolskii's group achieved trifluoromethylation of benzyl bromide in moderate yield using [$CuCF_3$] generated from $(CF_3)_2Hg$.[7b] In order to avoid the vigorous conditions, toxic material or a troublesome procedure is necessary to promote the reaction. Fuchikami and Urata devised the conditions for the trifluoromethylation of benzyl bromide by the use of Et_3SiCF_3 in the presence of a stoichiometric amount of KF and CuI.[7c] The generation of reactive [$CuCF_3$] and related species were further examined by developing conditions such as Me_3SiCF_3/KF/CuI in ionic liquid,[7d] $FO_2SCF_2CF_2OCF_2CO_2Me$/CuI,[7e] CF_3Br/copper anode,[7f] and Me_3SiCF_3/*N*-heterocyclic carbene−Cu complexes.[7g,h] Although all the reported works describe the trifluoromethylation of benzyl halides, substrate generality is unexplored.[7] As part of our ongoing research programs directed toward the development of efficient electrophilic trifluoromethyl reagents,[8] and methodologies for the introduction of the trifluoromethyl group,[9] we hypothesized that benzyl bromides would reacted with [$CuCF_3$] generated in situ from the reduction of electrophilic trifluoromethylating reagents. We have started our work, during which time trifluoromethylations of aromatic ring (sp^2 carbon) using shelf-stable electrophilic trifluoromethylating reagents such as (trifluoromethyl)diphenylsulfonium salt were successively disclosed.[10] However, no example was reported for the trifluoromethyaltion at the benzylic position (sp^3 carbon). We herein report the copper-mediated chemoselective trifluoromethylation reaction of a series of benzyl bromides through in situ generated [$CuCF_3$] species from shelf-stable electrophilic trifluoromethylating reagents **3**[11] and copper (Scheme 1). Reactive functional groups such as ester, ketone, and imide are well retained under the condition, while they are reacted under the conventional nucleophic trifluoromethylation condition. To the best of our knowledge, this is the first example for trifluoromethylation of benzyl bromides using electrophilic trifluoromethylating reagents.

Scheme 1. Copper-Mediated Trifluoromethylation of Benzyl Bromides with Electrophilic Trifluoromethylating Reagents



We started our investigation with the reaction of 4-nitrobenzylbromide (**1a**) with a series of electrophilic trifluoromethylating reagents **3** in the presence of copper in DMF at 60 °C (Table 1). First, the trifluoromethylation of **1a** with our trifluoromethylsulfoxinium salt **3a** was attempted; however, it gave a disappointing result, and only a trace amount of desired product **2a** was obtained (entry 1).

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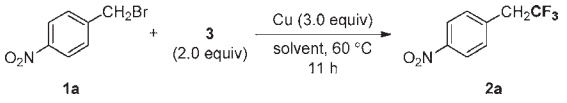
Next we attempted the same reaction using *S*-(trifluoromethyl)benzothiophenium salt **3b**, and desired product **2a** was obtained in 35% yield (entry 2), which was improved to 54% by the use of *S*-(trifluoromethyl)diphenylsulfonium salt **3c** (entry 3), although its analogue **3d** gave a slightly inferior result (entry 4, 42%). Umemoto's reagent, *S*-(trifluoromethy1)dibenzothiophenium salt **3e** proved to be equally effective, affording **2a** in 52% yield (entry 5). Hypervalent iodine(III)−CF_3 reagent **3f** provided no desired **2a** under the same reaction condition (entry 6). These results might provide one possibility that trifluoromethylation proceeds thorough the reaction of benzyl bromide and reductively generates [$CuCF_3$] species via single electron transfer from copper to the cationic sulfur in **3**, and a mechanism by the electrophilic trifluoromethylation of Cu-benzyl spices could be ruled out, although further work is necessary to substantiate a detailed mechanism. The solvent was next screened for further improvement of yields. While DMI, $CH_2(CH_2Cl)_2$, DMSO, and HMPA did not effectively improve yield, NMP proved to be a better solvent in the reaction to provide **2a** at 81% (entries 7−12).

Table 1. Optimization of CF_3^+ Reagents **3** and Solvents for Copper-Mediated Trifluoromethylation of Benzyl Bromides[a]



entry	CF_3^+ reagent	solvent	yield[b] (%)
1	**3a**	DMF	trace
2	**3b**	DMF	35
3	**3c**	DMF	54
4	**3d**	DMF	42
5	**3e**	DMF	52
6	**3f**	DMF	nr
7	**3c**	DMI	10
8	**3c**	$CH_2(CH_2Cl)_2$	nr
9	**3c**	DMSO	11
10	**3c**	HMPA	52
11	**3c**	DMF/NMP (1/1)	73
12	**3c**	NMP	81

[a] The reaction of **1a** with **3** (2.0 equiv) was carried out in the presence of Cu (3.0 equiv) at 60 °C. [b] Isolated yield.

With optimal conditions in hand, the scope of copper-mediated trifluoromethylation of benzyl bromides with **3c** was explored with a variety of substrates selected in order to establish the generality of the process (Figure 2). The results were almost independent of the position of the aromatic ring, as well as the nature and number of the substituents. For instance, *o*-, *m*-, and *p*-nitrobenzyl bromides **1a**−**c** and dinitro-substituted benzyl bromide **1d** were nicely converted into trifluoromethyl compounds **2a**−**d** in 56−81% yields. This method can tolerate the coexistence of both a fluorine atom and a nitro group on an aromatic ring. It is known that fluorine acts as a leaving group on the aromatic substitution reaction if a strong electron-withdrawing group is attached on the aromatics. Fortunately, 2-fluoro-6-nitrobenzyl bromide was converted into **2e** in 61% yield, and none of the aromatic trifluoromethylation was observed. Moreover, the reaction of benzyl bromides having electron-withdrawing cyano (**1f**), ester (**1g**), and acetyl (**1h**) and electron-donating *tert*-butyl (**1i**) and methoxy (**1j**) groups on the aromatic rings provided the desired products **2f**−**j** in 58—82% yield. It should be noted that *the benzyl position was chemoselectively trifluoromethylated, and carbonyl moieties in ester* ***2g*** *and ketone* ***2h*** *survived well under the reaction conditions, while the conventional nucleophilic trifluoromethylation using* Me_3SiCF_3 *generally occurs at carbonyl carbons.*[1f] Neutral and sterically demanding 2-(bromomethyl)naphthalene (**1k**) and 9-(bromomethyl)phenanthrene (**1l**) also afforded **2k**−**l** in 77% and 79% yield, respectively, under the same reaction conditions. Trifluoromethylation of methoxy BINOL derivative **1m**, which has a bromomethyl group at the 3-position, nicely proceeded to give

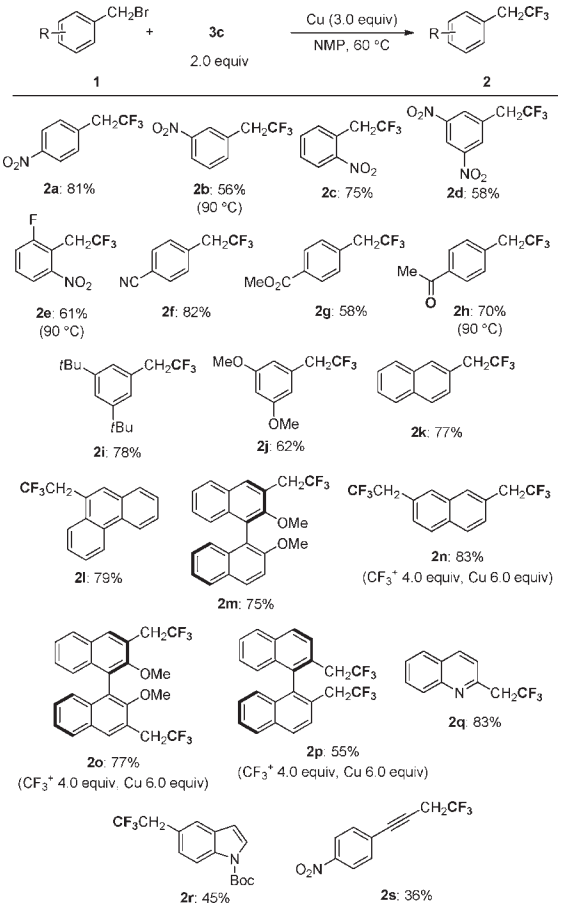


Figure 2. Copper-mediated trifluoromethylation of benzyl bromides **1** with **3c**.

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trifluoromethylated product **2m** in 75% yield. It should be noted that bis(bromomethyl)-substituted naphthalene **1n** was also a suitable substrate for the copper-mediated trifluoromethylation reaction with **3c** (4.0 equiv) in the presence of Cu (6.0 equiv), affording a double trifluoromethylated adduct **2n** in 83% yield. Methoxy-BINOL derivative **1o** with a bis(bromomethyl) group at the 3,3′-position and BINOL derivative **1p** having a bis(bromomethyl) group at the 2,2′-position also gave double trifluoromethylated adducts **2o** and **2p** in 77% and 55% yield, respectively. These chiral compounds, **2m**, **2o**, and **2p**, are attractive as chiral ligands for organic synthesis. 2-Bromomethylquinoline (**1q**) containing an exposed basic nitrogen was converted to the corresponding trifluoromethyl compound **2q** in 83% yield. Heteroaromatic, *N*-Boc-protected bromomethylindole (**1r**) afforded the desired adduct **2r** in moderate yield (45%). Trifluoromethylation of 1-(3-bromoprop-1-ynyl)-4-nitrobenzene **1s** proceeded under the same conditions to furnish **2s** in 36%, which is the first example of the trifluoromethylation of propargyl halides.

We were next interested in the trifluoromethylation of phthalimide derivatives. Phthalimides are one of the key structural motifs frequently encountered in biologically active molecules and pharmaceuticals on the market, despite their rare occurrence in nature.[12] Our group has been engaged in the design and development of thalidomide derivatives for more than a decade[13] since we required trifluoroethyl analogues of thalidomide for anticancer research, particularly focusing on multiple myeloma since methyl analogues of thalidomide indicate the interesting biological activity (Figure 3).[14] To begin with, we examined the trifluoromethylation of *N*-phenylphthalimide derivative **1t**. Under the same reaction conditions using **3c**, Cu in NMP, the desired trifluoromethylated compound **2t** was obtained in 86%, chemoselectively. The two electrophilic carbonyl groups attached to the nitrogen atom, imide moiety, in **1t** were retained without suffering from nucleophilic addition.[15] In contrast, a complex mixture was obtained including only 13% of **2t** under previously reported conditions developed by Fuchikami[7c] using Et_3SiCF_3/KF/CuI. Encouraged by these results, our target trifluoroethyl thalidomide was nicely synthesized using our chemoselective trifluoromethylation method at the benzylic position of **3c** to provide thalidomide derivative **6** in 71% yield (Scheme 2).

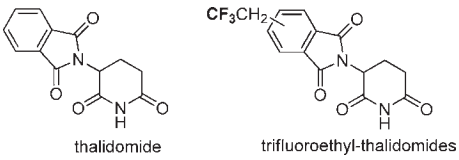
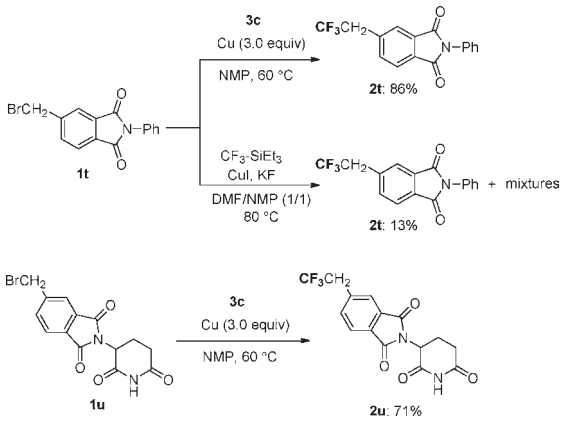


Figure 3. Thalidomide and (trifluoroethyl)thalidomides.

Scheme 2. Trifluoromethylations of Phtalimide Derivatives



In summary, we developed copper-mediated chemoselective trifluoromethylation at the benzylic position through the use of shelf-stable electrophilic trifluoromethylating reagents **3b**−**e** in good to high yields under mild conditions for the first time. Reactive carbonyl carbons including ester, ketone as well as imide are well retained under our chemoselective benzylic trifluoromethylation conditions. The method can be applicable to the trifluoromethylation of heteroarene derivatives as well as double-trifluoromethylation reactions of chiral BINOL derivatives. The generality of this trifluoromethylation for a wide variety of benzyl bromides facilitates the rapid creation of structural diversity of medicinal candidates in drug discovery represented by thalidomide drugs. This methodology remains a limitation in the trifluoromethylation of primary benzyl bromides and requires essentially a stoichiometric amount of copper metal. Hence, we are now focusing on developing the trifluoromethylation of secondary benzyl bromides and catalytic variants of this trifluoromethylation reaction.

Acknowledgment. This study was financially supported in part by Grants-in-Aid for Scientific Research (B21390030, 22106515) and the Asahi Glass Foundation.

Supporting Information Available. Experimental procedures and spectra data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Nucleophilic trifluoromethylation of imides easily proceeds with Me_3SiCF_3. See ref 9a, for example.