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Trifluoromethoxylation

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Silver-Promoted Oxidative Benzylic C-H Trifluoromethoxylation**

Haodong Yang,[+] Feng Wang,[+] Xiaohuan Jiang, Yu Zhou, Xiufang Xu and Pingping Tang**

Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday

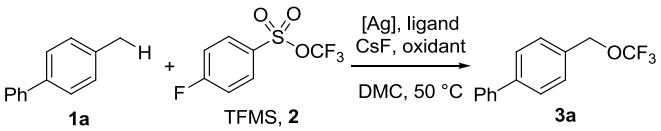
***Abstract**: A silver-catalyzed or silver-promoted oxidative benzylic C-H trifluoromethoxylation has been reported for the first time. With trifluoromethyl arylsulfonate (TFMS) as the trifluoromethoxylation reagent, various arenes with diverse functional groups undergo trifluoromethoxylation of their benzylic C-H bonds to form trifluoromethyl ethers under mild reaction conditions. In addition, the trifluoromethoxylation and the fluorination of methyl groups of electron-rich arenes have been achieved to prepare α-fluorobenzyl trifluoromethyl ethers in one step.*

Fluorinated molecules are of great interest in the fields of pharmaceutical, agrochemical, and material science.[1] In particular, the trifluoromethoxy group (OCF_3) has received much attention due to its strongly electron-withdrawing effect and high lipophilicity.[2] However, methods for the synthesis of trifluoromethyl ethers are limited because of the reversible decomposition of the trifluoromethoxide anion and the limited availability of trifluoromethoxylation reagents.[3] Recently, we reported that trifluoromethyl arylsulfonate (TFMS) could be used as a new trifluoromethoxylation reagent for the synthesis of trifluoromethyl ethers.[4] Herein, based on this new reagent, we reported the first example of a silver-catalyzed or silver-promoted oxidative benzylic C-H trifluoromethoxylation under mild reaction conditions.

The selective trifluoromethoxylation of C-H bonds has emerged as an efficient way to prepare trifluoromethyl ethers.[5] However, there are only a few reports of direct C-H trifluoromethoxylation reactions. In 2012, Navarrini reported a direct trifluoromethoxylation of aromatic C-H bonds using trifluoromethyl hypofluorite.[6] However, the toxicity of this reagent and the low trifluoromethoxylation yields are major drawbacks. Recently, Liu and co-workers reported a palladium-catalyzed trifluoromethoxylation of allylic C-H bonds with $CsOCF_3$ as the trifluoromethoxylation reagent.[7] A Pd^0/Pd^{II} catalytic cycle was proposed for the reaction. In 2018, Ngai group and Togni group reported a photolytic C-H trifluoromethoxylation of arenes and heteroarenes with new trifluoromethoxylation reagents, respectively.[8] Mechanistic studies revealed that an OCF_3 radical was generated in the reaction. To the best of our knowledge, no benzylic C-H trifluoromethoxylation reactions have been reported to date; thus, the development of a new method for direct benzylic C-H trifluoromethoxylation is highly desirable.

Previously, we reported a silver-catalyzed benzylic C-H activation to prepare difluoromethylated arenes.[9] The reaction was believed to proceed through a benzylic radical intermediate. This result inspired us to develop a direct trifluoromethoxylation of benzylic C-H bonds with our new trifluoromethoxylation reagent (TFMS). The initial investigation was focused on the reaction of 4-methyl-1,1'-biphenyl (**1a**) with trifluoromethyl 4-fluorobenzenesulfonate (TFMS, **2**) in the presence of CsF as a model system to optimize the reaction conditions. As briefly illustrated in Table 1 (See more details in the supporting information), a catalyst screen revealed that AgOTf was the best catalyst as it gave desired trifluoromethoxylated product **3a** in 67% yield along with the benzylic C-H fluorination byproduct, and no desired product was observed in the absence of a silver salt (Table 1, entry 1 to 6). In addition, the ligand was critical for this transformation, and 1,10-phenanthroline-5,6-dione gave the highest yield, and only 12% yield of product **3a** was observed without ligand (entries 7 to 9). Meanwhile, different oxidants were

Table 1. Optimization of the reaction conditions.[a]



Entry	Silver salt	Ligand	Oxidant	Yield (%)[b]
1	none	1,10-phenanthroline-5,6-dione	$K_2S_2O_8$	0
2	AgOTf	1,10-phenanthroline-5,6-dione	$K_2S_2O_8$	67
3	$AgBF_4$	1,10-phenanthroline-5,6-dione	$K_2S_2O_8$	40
4	Ag_2CO_3	1,10-phenanthroline-5,6-dione	$K_2S_2O_8$	10
5	AgF	1,10-phenanthroline-5,6-dione	$K_2S_2O_8$	65
6	AgF_2	1,10-phenanthroline-5,6-dione	$K_2S_2O_8$	66
7	AgOTf	1,10-phenanthroline	$K_2S_2O_8$	38
8	AgOTf	4,4'-dimethoxy-2,2'-bipyridine	$K_2S_2O_8$	20
9	AgOTf	none	$K_2S_2O_8$	12
10	AgOTf	1,10-phenanthroline-5,6-dione	$Na_2S_2O_8$	17
11	AgOTf	1,10-phenanthroline-5,6-dione	Selectfluor	51
12	AgOTf	1,10-phenanthroline-5,6-dione	$PhI(OAc)_2$	0
13	AgOTf	1,10-phenanthroline-5,6-dione	none	0
14[b]	AgOTf	1,10-phenanthroline-5,6-dione	$K_2S_2O_8$	76
15[c]	AgOTf	1,10-phenanthroline-5,6-dione	$K_2S_2O_8$	80

[a] General conditions: **1a** (1.0 equiv), **2** (5.0 equiv), silver salt (30 mol%), ligand (5 mol%), oxidant (3.0 equiv), CsF (4.0 equiv), DMC, 50 °C, N_2. [b] 0.5 equiv of AgOTf was used. [c] 1.0 equiv of AgOTf was used. [d] Yields were determined by ^{19}F NMR with benzotrifluoride as a standard. DMC = dimethyl carbonate.

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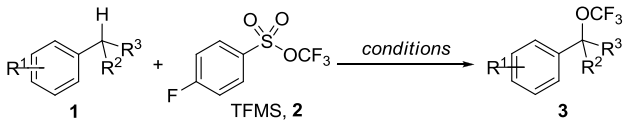
evaluated, and $K_2S_2O_8$ was found to be the best oxidant. The replacement of $K_2S_2O_8$ with $Na_2S_2O_8$, Selectfluor, and $PhI(OAc)_2$ afforded **3a** with lower yields (entries 10 to 12). A control reaction in the absence of oxidant showed none of the trifluoromethoxylated product (entry 13). Furthermore, the effect of the amount of AgOTf was investigated. Increasing the amount of AgOTf to 0.5 equiv improved the yield of product **3a** to 76%, and stoichiometric AgOTf afforded 80% yield (entry 14, 15). However, since the reaction was sensitive to the electronic properties of substrates, it's not always get higher yields using 1.0 equiv of AgOTf compared to 0.3 equiv of AgOTf, so 0.3 equiv of AgOTf was chosen for further studies.

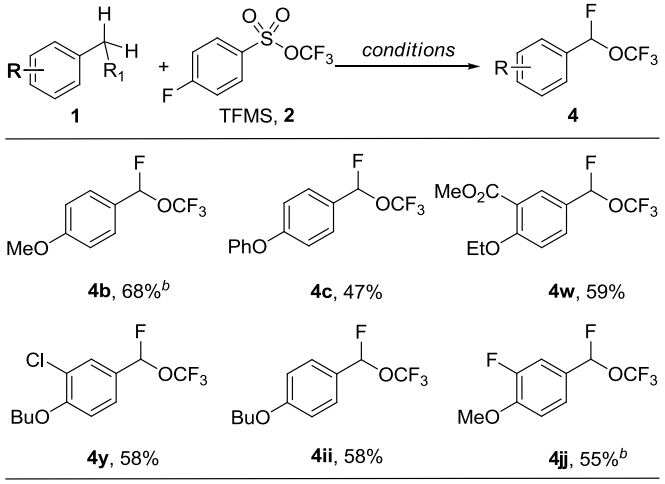
The scope of the reaction with respect to the arene derivatives is shown in Scheme 1. Various methylated arenes containing electron-donating groups and electron-withdrawing groups were suitable substrates and provided the corresponding trifluoromethoxylated products in 28% to 81% yield. The moderate yields were observed since the reaction was incomplete and also less than 10% monofluorinated byproducts were found in the reaction. The reaction conditions were varied based on the electronic properties of the substituents on the aromatic ring. For example, for compounds containing electron-withdrawing groups (**1i** to **1n**), stoichiometric AgF_2 as the oxidant and silver salt was found to be advantageous.[10] Fluoride, chloride, bromide, ether, ester, ketone, nitrile, nitro, and sulfonamide functionalities were tolerated. However, functional group with free hydrogens such as hydroxyl, amine, and acid was not tolerated and no desired product was observed. When toluene (**1g**) was used as the substrate, an ^{19}F NMR yield of only 28% of the product (**3g**) was observed because toluene reacted with F-TEDA-OTf to form 1-(chloromethyl)-4-(4-methyl-phenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} [11] as a major byproduct. Heterocyclic substrates (**1s** and **1t**) are also reactive. In addition to methyl groups, we found that methylene groups (**1dd** to **1ff**) can also be trifluoromethoxylated to give the corresponding trifluoromethoxylated products (**3dd** to **3ff**) in 45% to 58% yield, and yields less than 20% were observed with methine groups. Substrates **1o** and **1p** were used to investigate the selectivity of the reaction (See more details in the supporting information). For the substrate **1o**, trifluoromethoxylation was observed exclusively at the primary benzylic position over the tertiary benzylic position. When substrate **1p** was used, the ratio of trifluoromethoxylation at the primary versus secondary benzylic position was 4:5. These results indicated the selectivity favoring reaction at a secondary benzylic C-H > primary benzylic C-H > tertiary benzylic C-H. More importantly, more complex substrates were successfully trifluoromethoxylated to give the corresponding products (**3gg** and **3hh**) in moderate yields. Furthermore, the reaction is amenable to gram scale synthesis without a substantial decrease in the reaction yield. For example, product **3e** was prepared on a gram scale in 70% isolated yield, which demonstrates the scalability of this method.



3a[a] 67% (79%[e])
3b[a,f,g] 57% (36%[e])
3c[a] 65% (81%[e])
3d[b] 68% (77%[d])
3e[b] 69%
3f[b] 52%
3g[b,d,g] 28%
3h[b,g] 50%
3i[c,g] 46%
3j[c] 51%
3k[c] 48%
3l[c] 53%
3m[c,g] 50%
3n[c] 36%
3o[a] 50%
3p[a] **3p'**[a] 63% combined yield, **3p**/**3p'** = 4:5
3q[b,d] 50% (53%[e])
3r[b,d] 49% (51%[e])
3s[a] 61%
3t[b] 50%
3u[a] 65%
3v[a] 44%
3w[a] 50%
3x[a] 54%
3y[a] 67% (78%[d])
3z[b] 50%
3aa[b] 59%
3bb[a,g] 57% (74%[e])
3cc[b] 41% (36%[e])
3dd[a] 58%
3ee[a,d] 50%
3ff[a,d,g] 45%
3gg[b,d] 50%
3hh[b,d] 40%

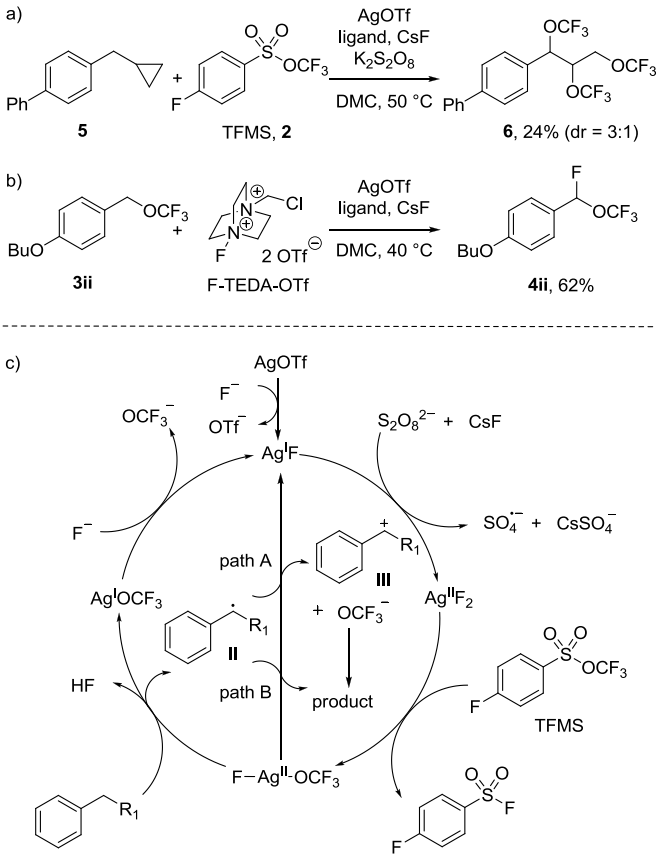
Scheme 1. Substrate scope of the benzylic C-H trifluoromethoxylation. [a] Reaction conditions: **1** (1.0 equiv), TFMS (**2**, 5.0 equiv), $K_2S_2O_8$ (3.0 equiv), AgOTf (30 mol%), 1,10-phenanthroline-5,6-dione (5 mol%), CsF (4.0 equiv), 50 °C, DMC, N_2. [b] Reaction conditions: **1** (1.0 equiv), TFMS (**2**, 3.0 equiv), F-TEDA-OTf (3.0 equiv), AgOTf (30 mol%), 1,10-phenanthroline-5,6-dione (5 mol%), 4,7-diphenyl-1,10-phenanthroline (5 mol%), CsF (4.0 equiv), 25 °C, DMC, N_2. [c] Reaction conditions: **1** (1.0 equiv), TFMS (**2**, 4.0 equiv), AgF_2 (6.0 equiv), 4,4'-dimethoxy-2,2'-bipyridine (10 mol%), di(2-pyridinyl)-methanone (10 mol%), 25 °C, MeCN, N_2. [d] 0.5 equiv of AgOTf was used. [e] 1.0 equiv of AgOTf was used. [f] The reaction was conducted at 40 °C. [g] Yields were determined by integration of the ^{19}F NMR spectrum using trifluoromethylthiobenzene or benzotrifluoride as internal standards. F-TEDA-OTf = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(trifluoromethanesulfonate).

Encouraged by our success with benzylic C-H trifluoromethoxylations, we turned our attention to the ditrifluoromethoxylation of benzylic C-H bonds. To our surprise, α-fluorobenzyl trifluoromethyl ether product **4** was a major product when F-TEDA-OTf was used as the oxidant, and no ditrifluoromethoxylated product was observed after the reaction. Methods for the introduction of a fluorine atom and a trifluoromethoxyl group at the same site are particularly rare.[12] Currently, there are no reports of this transformation using C-H functionalization; thus, we were very interested to investigate this reaction. After optimization of the reaction conditions, product **4b** could be obtained in 68% yield when the reaction of **1b** was conducted with 40 mol% AgOTf, 10 mol% diphenyl-1,10-phenanthroline, 4.0 equiv of TFMS (**2**), 3.0 equiv of F-TEDA-OTf, 4.0 equiv of CsF in DMC under a N_2 atmosphere at 40 °C for 15 h. Methylated arenes containing electron-donating groups are suitable substrates and provide the corresponding α-fluorobenzyl trifluoromethyl ethers in moderate yields (Scheme 2). When substrates containing electron-withdrawing and electron-neutral groups were used, no desired products were observed, and more than 80% of the starting materials were recovered. It is worth mentioning that during the preparation of α-fluorobenzyl trifluoromethyl ethers, we found that product **4** easily decomposed to give the corresponding aldehydes during the purification using silica gel or alumina.



Scheme 2. Substrate scope of the benzylic C-H trifluoromethoxylation and fluorination. [a] Reaction conditions: **1** (1.0 equiv), F-TEDA-OTf (3.0 equiv), TFMS (**2**, 5.0 equiv), AgOTf (40 mol%), CsF (4.0 equiv), 4,7-diphenyl-1,10-phenanthroline (10 mol%), 40 °C, DMC, N_2. b) Yields were determined by integration of the ^{19}F NMR spectrum using benzotrifluoride as an internal standard.

To elucidate the mechanism, some preliminary studies were carried out (see more details in the supporting information). First, kinetic isotopic effect (KIE) experiments were conducted by subjecting compound **1a** and its deuterated analogue **1a'** to the standard reaction conditions. A k_H/k_D value of 1.4 was obtained in parallel reactions on the basis of ^{19}F nuclear magnetic resonance (NMR) analysis, which suggested that the cleavage of the C-H bond cannot be the rate-determining step of the reaction.[13] Second, no trifluoromethoxylated product was observed when 1.0 equiv of the radical inhibitors butylated hydroxytoluene (BHT) or 1,1-diphenylethylene was added, and the starting material was recovered. Furthermore, ring-opening product **6** was observed in 24% yield with substrate **5** as a radical probe (Scheme 3a). These results indicated that a free radical was involved in the reaction. Finally, monitoring of the benzylic C-H trifluoromethoxylation and fluorination reaction by ^{19}F NMR spectroscopy revealed that trifluoromethoxylation of benzylic C-H bonds was found to generate the monotrifluoromethoxylated intermediate **3gg**, which subsequently formed the desired product **4gg**. Furthermore, the monotrifluoromethoxylated intermediate (**3gg**) was isolated and reacted with F-TEDA-OTf to form product **4gg** in 62% yield in the absence of TFMS, which confirmed that product **4gg** was generated from monotrifluoromethoxylated intermediate **3gg** (Scheme 3b). In addition, benzylic C-H ditrifluoromethoxylated intermediates were observed by ^{19}F NMR spectroscopy, which was not stable in the reaction conditions and decomposed to the corresponding aldehydes.



Scheme 3. Mechanistic studies and proposed mechanism.

Based on these mechanistic studies and associated DFT calculations (see the supporting information for details), we proposed the mechanism shown in Scheme 3c. Ag(I)F is formed from

AgOTf and fluoride ion in situ, and it is subsequent oxidized to $Ag(II)F_2$ in the presence of an oxidant. Next, $Ag(II)F_2$ react with TFMS to generate $FAg(II)OCF_3$, which oxidizes the benzylic C-H bond to benzylic radical **II**. We also considered the formation of benzylic radical from oxidization of **1** by $SO4^{\bullet-}$, and our calculation result indicates that this pathway is disfavored.[14] Finally, benzylic radical **II** reacts with $FAg(II)OCF_3$ to form the desired product (path B). In addition, the results of our calculations indicate that generation of benzyl carbocation **III** from the oxidization of benzylic radical **II** by $FAg(II)OCF_3$ is exothermic by 1.8 kcal/mol (path A). This result suggests that the benzyl carbocation should be involved in the reaction and be in thermodynamic equilibrium with the benzylic radical, and the carbocation should ultimately be trapped by the OCF_3 anion to form the desired product.

In conclusion, we have developed the first silver catalyzed or silver-promoted benzylic C-H trifluoromethoxylation reaction. Trifluoromethyl arylsulfonate (TFMS) was chosen as the trifluoromethoxylation reagent. The reaction tolerates a range of functional groups and is applicable to gram-scale synthesis. Furthermore, the first example of direct benzylic C-H trifluoromethoxylation and fluorination reactions to prepare α-fluorobenzyl trifluoromethyl ethers was reported and occurs in one step. Mechanistic studies revealed that a monotrifluoromethoxylated intermediate was generated, and subsequent benzylic C-H fluorination was involved in the reaction. The development of new trifluoromethoxylation reactions with TFMS are currently underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: trifluoromethoxylation · trifluoromethyl arylsulfonate · C-H functionalization · silver · synthetic methods

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[10] The DFT calculation (see the supporting information for details) suggests that AgF_2 is necessary for the formation of the desired product in the reaction, and AgF_2 can catalyse the reaction without additional oxidant, which is consistent with the experiment. The formation of AgF_2 is the rate-determining step for reactions with AgOTf acting as the precatalyst because this step has the highest energy barrier among all of the key steps.

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Trifluoromethoxylation

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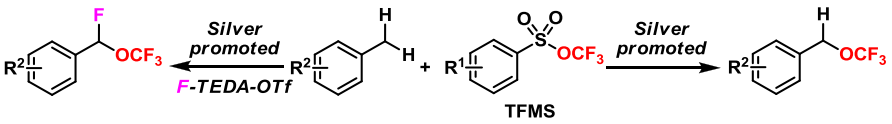
Silver-Promoted Oxidative Benzylic C-H Trifluoromethoxylation



With trifluoromethyl arylsulfonate (TFMS) as the trifluoromethoxylation reagent, a silver-catalyzed or silver-promoted oxidative benzylic C-H trifluoromethoxylation has been reported for the first time. In addition, the first example of direct benzylic C-H trifluoromethoxylation and fluorination reactions to prepare α-fluorobenzyl trifluoromethyl ethers was reported. Preliminary mechanistic studies and DFT calculations suggest that the single-electron transfer was involved in the reaction.