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Silver-Mediated Oxidative Trifluoromethylation of Alcohols to Alkyl Trifluoromethyl Ethers

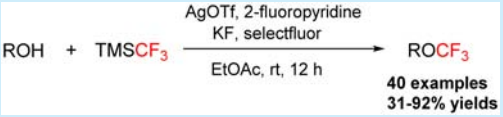
Jian-Bo Liu,[†] Xiu-Hua Xu,[†] and Feng-Ling Qing*[,†,‡]

[†]Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, 345 Lingling Lu, Shanghai 200032, China

[‡]College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

Supporting Information

ABSTRACT: The development of an efficient and practical method for the preparation of alkyl trifluoromethyl ethers is urgently demanding. The silver-mediated oxidative *O*-trifluoromethylation of primary, secondary, and tertiary alcohols with $TMSCF_3$ under mild reaction conditions is established to provide a novel approach to a broad range of alkyl trifluoromethyl ethers. Further, this method is applied to the late-stage *O*-trifluoromethylation of complex natural products and prescribed pharmaceutical agents.

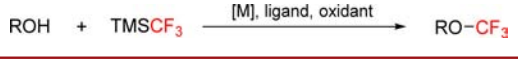


Extensive recent efforts have been devoted to the preparation of fluorinated compounds[1] because the introduction of fluorine atom and fluorine-containing group into organic compounds often changes the chemical, physical, and biological properties of parent compounds.[2] Among the fluorinated moieties, the trifluoromethoxy group (OCF_3) is strongly electron withdrawing and offers advantages such as increased lipophilicity over the popular F and CF_3 group.[3] Therefore, this group offers increasingly important functionality in materials, agricultural, and pharmaceutical research.[4] Significant progress has been made toward the incorporation of a fluorine atom, trifluoromethyl group, and trifluoromethylthio group onto aromatic and aliphatic systems.[1] However, methodologies for the general and efficient synthesis of alkyl trifluoromethyl ethers are extremely underdeveloped and limited.

There are mainly three types of methods for the preparation of alkyl trifluoromethyl ethers. The deoxyfluorination of alkyl fluoroformates[5] and oxidative desulfurization−fluorination of alkyl xanthates[6] are the most widely used procedures, but the harsh reaction conditions employed in these reactions are incompatible with many functional groups. The nucleophilic trifluoromethoxylation of alkyl triflates and bromides with trifluoromethoxide salts provides an alternative route to alkyl trifluoromethyl ethers.[7] However, the reversible degradation of trifluoromethoxide into carbonyl difluoride and fluoride in solution above room temperature hinders widespread adoption. Clearly, the direct trifluoromethylation of alcohols under mild reaction conditions would be an ideal route to alkyl trifluoromethyl ethers due to the abundance and accessibility of alcohols.[8] In fact, the formation of an $O-CF_3$ bond from alcohol with a trifluormethylating reagent is difficult because the oxygen atom, a hard nucleophile, is disfavored to react with the electrophilic trifluoromethlating reagents. Umemoto and co-workers reported that the direct electrophilic trifluoromethylation of 2-phenylethanol and *n*-decanol with *O*-(trifluoromethyl)-dibenzofuranium reagents gave the corresponding alkyl trifluoromethyl ethers.[8a] However, these highly active *O*-(trifluoromethyl)dibenzofuranium reagents need to be generated prior to use by photochemical decomposition of diazonium salts containing a trifluoromethoxy group at −100 to −90 °C. Togni and co-workers have developed the $Zn(NTf_2)_2$-mediated synthesis of alkyl trfluoromethyl ethers from alcohols and electrophilic hypervalent iodine trifluoromethylation reagent,[8b] but the use of alcohols as both the substrate and solvent was necessary to obtain good yields of alkyl trfluoromethyl ethers. Thus, the development of a practical and broadly applicable trifluoromethylation of alcohols for synthesis of alkyl trfluoromethyl ethers is still highly desirable.

Recently, we have developed the transition-metal-mediated oxidative trifluoromethylation of various nucleophiles with nucleophilic $TMSCF_3$ in the presence of oxidants, and these methods allow novel and efficient construction of $C(sp,sp^2,sp^3)-CF_3$, $P-CF_3$, and $S-CF_3$ bonds.[9] We wondered if it was possible to achieve the analogous reaction of alcohols with $TMSCF_3$ to form an $O-CF_3$ bond (Scheme 1). This transformation is more challenging than other oxidative trifluoromethylation reactions because alkanols are sensitive toward the oxidation conditions[10] and metal alkoxide intermediates might undergo competitive *β*-hydride elimination.[11] We assumed that these competitive reactions could be eliminated or reduced by choosing the appropriate metal salt, ligand, and oxidant. Herein, we disclose

Scheme 1. Synthesis of Alkyl Trifluoromethyl Ethers via Oxidative Trifluoromethylation of alcohols



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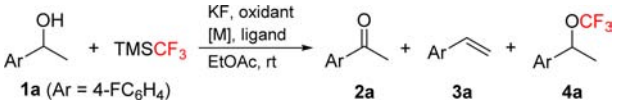
the AgOTf-mediated oxidative trifluoromethylation of alcohols with $TMSCF_3$ at room temperature to alkyl trifluoromethyl ethers. Not only primary alcohols but also secondary and tertiary alcohols were compatible in this protocol. The late-stage *O*-trifluoromethylation of complex natural products and prescribed pharmaceutical agents is also exhibited.

Initially, we chose 1-(4-fluorophenyl)ethan-1-ol (**1a**) as the model substrate to optimize the reaction conditions (Table 1).

Table 1. Optimization of Oxidative Trifluoromethylation of Alcohol 1a with $TMSCF_3$[a]



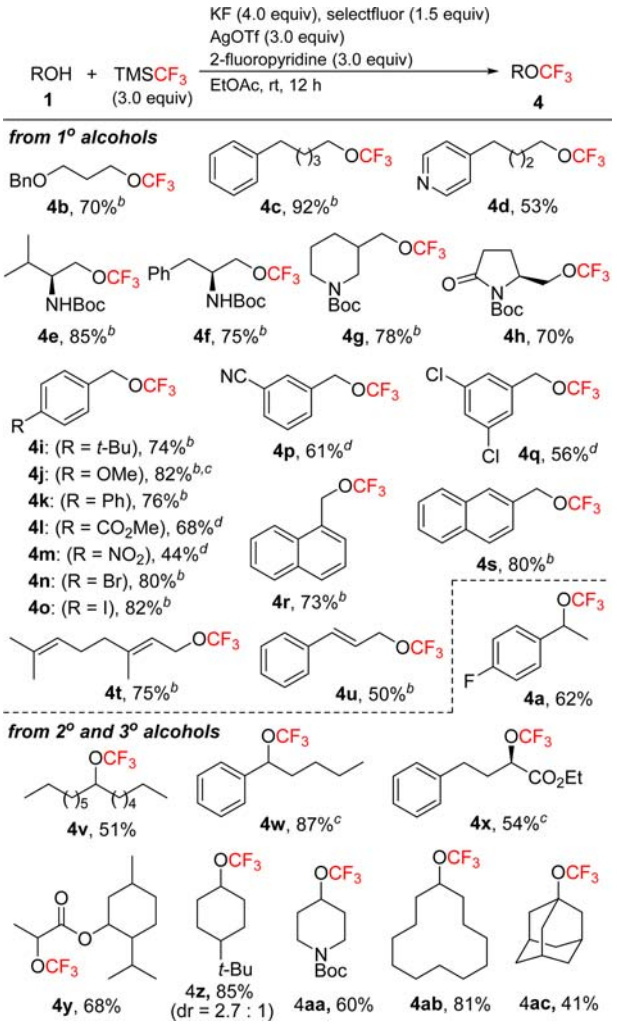
entry	[M]	ligand	oxidant	conv[b] (%)	yield[b] (%) 2a/3a/4a
1	$AgNO_3$	pyridine	Selectfluor	55	55/−/trace
2	$Cu(OTf)_2$	pyridine	Selectfluor	35	35/−/−
3	$Pd(OAc)_2$	pyridine	Selectfluor	91	83/−/−
4	$Ni(OTf)_2$	pyridine	Selectfluor	9	9/−/−
5	AgOTf	pyridine	Selectfluor	47	42/−/5
6	Ag_2CO_3	pyridine	Selectfluor		−/−/−
7	AgOTf	PPh_3	Selectfluor	20	20/−/−
8	AgOTf	Phen	Selectfluor	50	50/−/trace
9	AgOTf	2-fluoropyridine	Selectfluor	49	23/−/26
10	AgOTf	3-fluoropyridine	Selectfluor	44	24/−/20
11	AgOTf	2-fluoropyridine	air	24	18/6/−
12	AgOTf	2-fluoropyridine	BzOO-*t*-Bu	33	18/8/−
13	AgOTf	2-fluoropyridine	NFSI	> 99	>99/−/−
14[c]	AgOTf	2-fluoropyridine	Selectfluor	54	13/−/41
15[c,d]	AgOTf	2-fluoropyridine	Selectfluor	80	22/−/58
16[d,e]	AgOTf	2-fluoropyridine	Selectfluor	96	12/−/81

[a]Reaction conditions: **1a** (0.1 mmol), $TMSCF_3$ (0.2 mmol), KF (0.3 mmol), oxidant (0.1 mmol), [M] (0.1 mmol), ligand (0.1 mmol), EtOAc (0.5 mL), rt, 12 h. [b]Determined by ^{19}F NMR spectroscopy using trifluoromethylbenzene as an internal standard. [c]AgOTf (0.2 mmol), 2-fluoropyridine (0.2 mmol). [d]Selectfluor (0.15 mmol). [e]$TMSCF_3$ (0.3 mmol), KF (0.4 mmol), AgOTf (0.3 mmol), 2-fluoropyridine (0.3 mmol).

This substrate contains an aryl fluorine moiety, which is beneficial for tracing the reaction by ^{19}F NMR spectroscopy. Inspired by our very recent work on silver-mediated oxidative trifluoromethylation of phenols for synthesis of aryl trifluoromethyl ethers,[12] we attempted the trifluoromethylation of **1a** with $TMSCF_3$ in the presence of silver salt ($AgNO_3$), ligand (pyridine), and oxidant (Selectfluor) (entry 1). Unfortunately, only a trace amount of the desired product **4a** was observed, and ketone **2a** was formed as the major product. Other metal salts including $Cu(OTf)_2$, $Pd(OAc)_2$, and $Ni(OTf)_2$ also led to the formation of **2a** (entries 2−4). To our delight, compound **4a** was produced in 5% yield in the presence of AgOTf (entry 5), while there was no reaction when Ag_2CO_3 was used instead of AgOTf (entry 6). Then, different ligands were investigated. Neither PPh_3 nor 1,10-phenanthroline (phen) gave better results (entries 7 and 8). Both 2-fluoropyridine and 3-fluoropyridine were superior to pyridine (entries 9 and 10), and 2-fluoropyridine was the optimal choice probably because of its comparatively lower basicity.[13] Switching to other oxidants such as air, BzOO-*t*-Bu, and *N*-fluorobenzenesulfonimide (NFSI) could not produce **4a** (entries 11−13). To further improve the yield of **4a**, we decided to increase the amounts of AgOTf, 2-fluoropyridine, Selecfluor, $TMSCF_3$, and KF. The high selective formation of **4a** was achieved when 2.0 equiv of AgOTf and 2-fluoropyridine were used (entry 14), while the use of 1.5 equiv of Selectfluor resulted in higher conversion of **1a** (entry 15). Finally, the conversion of **1a** reached up to 96%, and the yield of **4a** was improved to 81% (entry 16) in the presence of AgOTf (3.0 equiv), 2-fluoropyridine (3.0 equiv), Selectfluor (1.5 equiv), $TMSCF_3$ (3.0 equiv), and KF (4.0 equiv).

With the optimized reaction conditions in hand, we next investigated the substrate scope of this silver-mediated oxidative trifluoromethylation of alcohols (Scheme 2). Various primary, secondary, and tertiary alcohols were converted to the corresponding trifluoromethyl ethers in moderate to excellent

Scheme 2. Substrate Scope of Silver-Mediated Trifluoromethylation of Alkanols[a]



[a]Isolated yields. [b]$TMSCF_3$ (2.0 equiv), KF (3.0 equiv), AgOTf (2.0 equiv), 2-fluoropyridine (2.0 equiv). [c]2,6-Di-*tert*-butylphenol (0.5 equiv) was added. [d]Selectfluor (1.0 equiv).

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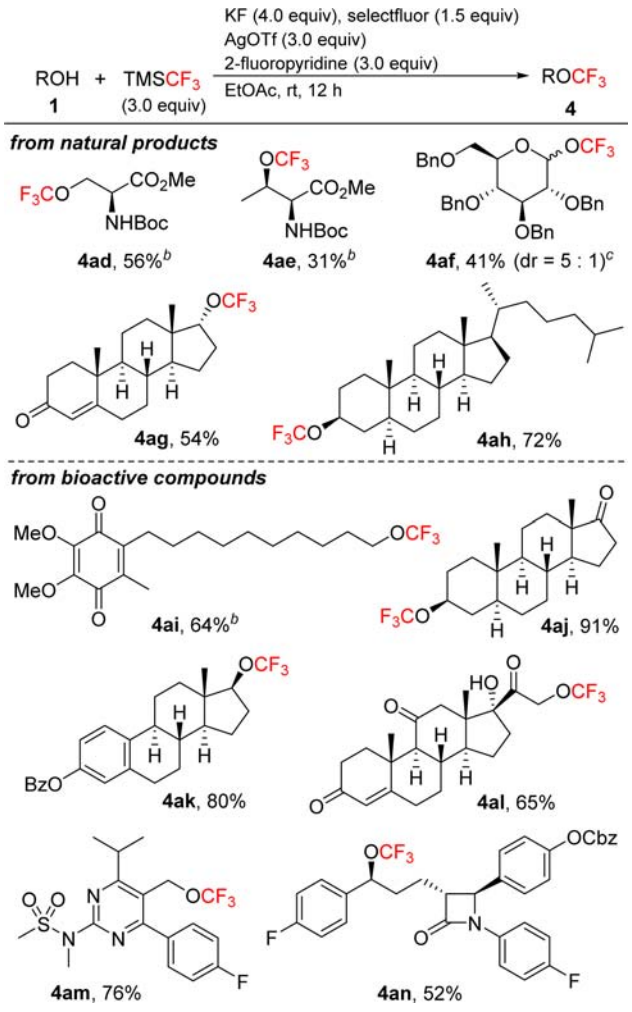
yields. For primary alcohols, lower amounts of $TMSCF_3$ (2.0 equiv), KF (3.0 equiv), AgOTf (2.0 equiv), and 2-fluoropyridine (2.0 equiv) could achieve high yields. A variety of functional groups, including benzyloxy, carbonyl, ester, amide, cyano, nitro, chloro, bromo, and iodo, are well tolerated under this mild reaction conditions. The reaction efficiency of alcohols containing the electron-rich aryl group (such as **1j**) was diminished by the competitive *C*-trifluoromethyaltion of electron-rich phenyl ring with eletrophilic CF_3 radical, because CF_3 radical was easily generated from the combination of $TMSCF_3$/KF/AgOTf.[14] To our delight, the *C*-competitive trifluoromethylation was sharply reduced by the addition of 2,6-di-*tert*-butylphenol. In the case of benzyl alcohols (**1l**, **1m**, **1p**, and **1q**) bearing the electron-withdrawing group on the phenyl ring, the corresponding benzaldehydes were formed as the major products under the standard reaction conditions (1.5 equiv of selecfluor). Fortunately, the desired trifluoromethyl ethers were obtained in moderate yields when 1.0 equiv of Selecfluor was used. It is noteworthy that the dr value of product **4z** (2.7:1) was almost the same as that of compound **1z** (2.6:1). This result showed that the configuration of alcohols was fully retained in this oxidative trifluoromethylation reaction.

To further extend the application of this protocol, a series of natural product derivatives and bioactive compounds was also investigated (Scheme 3). The protected L-serine (**1ad**), L-theronine (**1ae**), and D-glucopyranose (**1af**) were compatible with the reaction conditions to afford the corresponding trifluoromethyl ethers in moderate yields. This protocol allowed the direct trifluoromethylation of steroids epitestosterone (**1ag**) and dihydrocholesterol (**1ah**). Importantly, the reaction of idebenone (**1ai**), a drug for the treatment of Alzheimer's disease, gave product **4ai** in 64% yield. Several hormones including epiandrosterone (**1aj**), estradiol benzoate (**1ak**), and cortisone (**1al**) proceeded well to give the corresponding trifluoromethyl ethers (**4aj–al**) in good to excellent yields. Moreover, the alcohols derived from rosuvastatin (a member of the drug class of statins) and ezetimibe (a drug that lowers plasma cholesterol levels), respectively, were converted to the trifluoromethylated products **4am** and **4an**. These results showed that this protocol was applicable to the late-stage trifluoromethylation of medicinally relevant compounds.

Several mechanism experiments were carried out to gain insight of the reaction mechanism (see the Supporting Information for details). All of the reactions outlined in Scheme 4 were monitored by ^{19}F NMR spectroscopy. No reaction was observed when **1a** was treated with AgOTf, KF, and 2-fluoropyridine (Scheme 4a). On the other hand, the reaction of $TMSCF_3$ and AgOTf, KF, and 2-fluoropyridine gave $Ag(I)CF_3$[15] in 50% yield along with Ag(III) complex $[Ag(CF_3)_4]^-$[16] in 6% yield (Scheme 4b). These results showed clearly that the oxidative trifluoromethylation proceeded through trifluoromethyl silver complex, not alkoxy silver complex. Interestingly, $Ag(I)CF_3$ could be converted into $[Ag(CF_3)_4]^-$ and only $[Ag(CF_3)_4]^-$ could be detected after 2 h (Scheme 4c). However, the reaction of $[Ag(CF_3)_4]^-$ with Selectfluor and **1a** did not give any trifluoromethyl ether **4a**. In contrast, the addition of **1a** and Selectfluor to the mixture of $Ag(I)CF_3$ and $[Ag(CF_3)_4]^-$ afforded **4a** in 12% yield (Scheme 4d). These results demonstrated that $Ag(I)CF_3$ was the really active intermediate for the oxidative trifluoromethylation of alcohols.

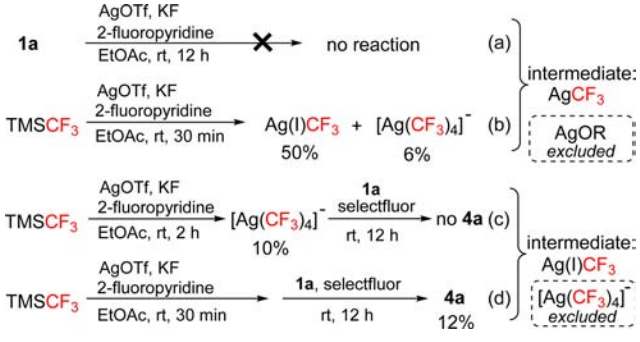
On the basis of the above experimental results and the silver-mediated oxidative cross-coupling reactions,[12,17] a plausible reaction mechanism was proposed in Scheme 5. First, $TMSCF_3$

Scheme 3. Late-Stage *O*-Trifluoromethylation of Natural Product Derivatives and Bioactive Compounds[a]

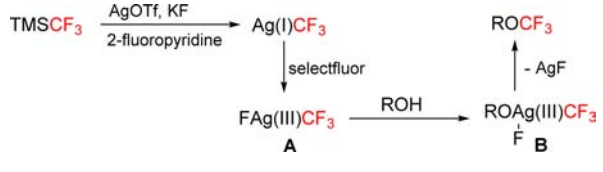


[a]Isolated yields. [b]$TMSCF_3$ (2.0 equiv), KF (3.0 equiv), AgOTf (2.0 equiv), 2-fluoropyridine (2.0 equiv). [c]2,6-Di-*tert*-butylphenol (0.5 equiv) was added.

Scheme 4. Mechanism Experiments



Scheme 5. Proposed Mechanism



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was converted into Ag(I)CF_3 in the presence of AgOTf, KF, and 2-fluoropyridine. Then, Ag(I)CF_3 was oxidized by Selectfluor to form Ag(III) complex **A**, which subsequently underwent ligand exchange with alkoxide to give intermediate **B**. Finally, reductive elimination of intermediate **B** afforded the desired alkyl trifluomethyl ether ($ROCF_3$).

In conclusion, we have developed an efficient and practical method for the preparation of alkyl trifluoromethyl ethers using silver-mediated oxidative trifluoromethylation of alcohols with $TMSCF_3$ at room temperature. Various primary, secondary, and tertiary alcohols, especially a series of highly complex medicinal molecules, proceeded efficiently under these mild reaction conditions. Due to the potential utility of the resulting alkyl trifluoromethyl ethers and the mild conditions employed, we expect this method to be of broad utility in the pharmaceutical and agrochemical fields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02522.

Preliminary investigation of reaction mechanism, experimental procedures, characterization data, and copies of ^1H, ^{19}F, and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: flq@mail.sioc.ac.cn.

Notes

The authors declare no competing financial interest.

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