Synergistic Catalysis for the Umpolung Trifluoromethylthiolation of Tertiary Ethers

Wentao Xu, Junyang Ma, Xiang-Ai Yuan, Jie Dai, Jin Xie,* and Chengjian Zhu*

Abstract: The first transition-metal-free, site-specific umpolung trifluoromethylthiolation of tertiary alkyl ethers has been developed, achieving the challenging tertiary C(sp³)–SCF₃ coupling under redox-neutral conditions. The synergism of organophotocatalyst 4CzIPN and BINOL-based phosphorothioles can site-selectively cleave tertiary sp³ C(sp³)–O ether bonds in complex molecules initiated by a polarity-matching hydrogen-atom-transfer (HAT) event. The incorporation of several competing benzylic and methine C(sp³)–H bonds in alkyl ethers has little influence on the regioselectivity. Selective difluoromethylthiolation of C–O bonds has also been achieved. This represents not only an important step forward in trifluoromethylthiolation but also a promising means for site-selective C–O bond functionalization of unsymmetrical tertiary alkyl ethers.

Organofluorine compounds are used widely in all fields of science.¹ The strongly electron-withdrawing and highly lipophilic (τₛ = 1.44) trifluoromethylthio group (SCF₃) is a privileged biososoter, which can substantially improve the cell-membrane permeability and metabolic stability of parent drug molecules.² Besides metal-catalyzed C(sp³)– and C(sp)–SCF₃ coupling,³ the direct nucleophilic or electrophilic trifluoromethylthiolation of alkyl precursors, alkenes, and even directed C(sp³)–H bonds is currently of great interest to those seeking to construct primary and secondary C(sp³)–SCF₃ bonds (Scheme 1a).⁴ However, the efficient construction of a tertiary C(sp³)–SCF₃ bond from unreactive coupling partners remains a challenge.⁵ The major reason for this is the significant steric hindrance effect in the δ+δ− bonding regimes.

The radical C(sp³)–SCF₃ coupling was first reported in 1962 by Harris,⁶ but this strategy attracted little attention⁷ until 2014 when a Ag-catalyzed decarboxylative radical trifluoromethylthiolation reaction was disclosed.⁸ Subsequently, transition-metal-catalyzed, hydrogen atom transfer (HAT)-controlled C(sp³)–H radical trifluoromethylthiolation was successfully achieved based on the bond-dissociation energy (BDE) of benzylic or methine C–H bonds.⁹ Despite this important advance, site-specific tertiary C(sp³)–CF₃ coupling remains a major barrier to C(sp³)–H trifluoromethylthiolation when the substrates contain several competing C(sp³)–H bonds with comparable BDE or electronic properties. This again results in uncontrollable selectivity. The use of transition-metal catalysts⁸,⁹a–c and/or external strong oxidants⁸,⁹a–c also compromises the substrate’s utility in late-stage modification reactions. Ethers are readily available, non-toxic, and widely used electrophiles in the C–O activation scenario.¹⁰ To the best of our knowledge, selective C–O trifluoromethylthiolation of unsymmetrical aliphatic ethers has rarely been studied. Herein, we report a metal-free, site-specific umpolung (reversed polarity) trifluoromethylthiolation of activated tertiary alkyl ethers initiated by a polarity-matching HAT process (Scheme 1b).

In 2018, we reported the first inverse hydroborylation of imines with NHC-boranes via synergistic catalysis.¹¹ This was enabled by combining iridium-based photoredox catalysis with organocatalysis. As part of our ongoing interest in photoredox catalysis,¹² a new review of this promising combination revealed a site-selective umpolung trifluoromethylthiolation of tertiary ether C–O bonds. To achieve the site-selective C–O cleavage of unsymmetrical tertiary alkyl ethers, the polarity-matching strategy¹¹ is taken into account.
to initiate an exclusive HAT event of a C–H bond adjacent only to an oxygen atom. In this context, the electrophilic thyl radical would be liable to undergo homolytic cleavage of the hydridic α-C(sp³)–H bond of ethers (BDE ≈ 93 kcal mol⁻¹[14]) even in the presence of weaker neutral C–H bonds such as a benzylic C–H bond (BDE ≈ 90 kcal mol⁻¹[15]) (Scheme 1b). Since about half of the top-selling 200 pharmaceutical products contain a benzylic structural motif,[16] the compatibility of benzylic C–H bonds makes this protocol practical for the enhancement of bioisosteric lead screening.

As shown in Scheme 2, the photosexcited photocatalyst PC*, an oxidant, undergoes single-electron transfer (SET) with thiolate anion to give thyl radical 4 via a reductive quenching pathway. The resulting highly electrophilic thyl radical 4 rapidly undergoes a HAT event with the most hydridic α-C–H group of the ether to generate alkoxyl radical 5. This then cleaves the C–O bond[17] homolytically to form a tertiary alkyl radical 6. There are two plausible pathways, paths A and B (Scheme 2) for tertiary alkyl radical trifluoromethylthiolation. In path A, the resulting Phth-SCF³ radical anion 7 undergoes radical–radical coupling[18] with the tertiary alkyl radical 6 to afford the desired product 3, releasing Phth anion. In path B, the tertiary alkyl radical addition to the electrophilic Phth-SCF³ reagent occurs first and is followed by SET reduction of the phthalimide radical, producing a Phth anion. In both cases, the resulting Phth⁺ ion can abstract one proton from the thiol organocatalyst to yield phthalimide and thiolate anion and so restart the catalytic cycle.

The presence of a suitable thiol organocatalyst in the catalytic combination should be a factor crucial to the umpolung trifluoromethylthiolation. The reason for this is that the resulting thyl radical 4 should be capable of achieving a site-selective HAT event with a hydridic C–H bond to initiate the C–O homolytic cleavage. Aside from the kinetic polarity-matching effect, the thyl radical reactivity would, to a certain extent, control the H-atom abstraction efficiency. Accordingly, the singly occupied molecular orbital (SOMO) energies of several kinds of thyl radicals were computed. Different thyl radicals have significantly different SOMO energies, indicative of variable reactivity towards the HAT process (Scheme 3a). According to our DFT calculations, the BINOL-based phosphorothyl radical 2g has the highest electrophilic reactivity amongst the thyl radicals examined. Combining organocatalyst 2g with an organo-photocatalyst (4CzIPN), several unsymmetrical tertiary alkyl ethers were investigated (Scheme 3b). The optimized reaction conditions require 2 mol% 4CzIPN, 2 mol% 2g, 0.1 equiv K₂CO₃ as base, and DCM as solvent at room temperature under irradiation from blue LEDs (see the Supporting Information for optimization details).

We found that shelf-stable and easily available methoxy-methyl (MOM)-type tertiary alkyl ethers[19] 1d, 1e could undergo the expected reaction to afford the desired product 3a in 76% and 57% yields, respectively. Other substrates (1a–c) gave little or no trifluoromethylthiolation product (Scheme 3b). Control experiments revealed that 4CzIPN, thiol, and light were crucial to a successful transformation. Benzylic C–H bonds are entirely compatible with the reaction, although it remains highly challenging for HAT-controlled C(sp³)-H functionalization precedents.[20] We rationalized that the stronger hydridic C–H bond in MOM-type ethers could facilitate the site-selective C(sp³)-H abstraction steered by a polarity-matching effect.

The scope of the tertiary ether substrates was examined (Scheme 4). The protocol has a broad substrate scope and can achieve the site-specific C–O bond trifluoromethylthiolation of tertiary alkyl ethers even when the substrate has several competing electronically similar C–H bonds. For example, a wide array of tertiary alkyl ethers bearing weak benzylic C–H bonds were found to be competent coupling partners. These included the derivatives of oxaprozin, ibuprofen, and flurbiprofen (3o–q, Scheme 4). Electron-withdrawing and donating substituents in the ortho, meta- and para-positions of phenyl rings were tolerated and substrates bearing -Me (3j), -Et (3k), and -CH₂TMS (3l) at the tertiary carbon center performed well. Heteroaromatic rings were also compatible (3n) and the bistrifluoromethylthiolation product (3m) was successfully obtained in 70% yield.

Subsequently, we examined substrates containing competing hydridic C–H bonds. The reaction showed satisfactory tolerance of a wide range of versatile functional groups, such as ketone (3r), ester (3s, 3t, 3w), amide (3v), heteroaromatic ether (3u), and halogen (3w). Notably, most HAT-controlled

![Scheme 2. Mechanistic hypothesis.](image)

![Scheme 3. Reaction development.](image)
aliphatic C–H trifluoromethylthiolation reactions usually occurred at the methine C–H bonds.\textsuperscript{[9]} In our case, the polarity-matching principle enabled these methine (sp\textsuperscript{3})–H bonds to survive (3x–aa) and offered an effective route for the site-specific construction of a tertiary C(sp\textsuperscript{3})–SCF\textsubscript{3} bond from C–O bonds under redox-neutral reaction conditions. In addition, other kinds of cyclic, linear, and branched alkyl ethers can undergo this useful transformation to afford the corresponding products (3bb–hh) in 47–75% yields. Interestingly, when the substrate contains both secondary and tertiary MOM ether units, the tertiary MOM ether moiety was preferentially trifluoromethylthiolated (3i).

In view of the prevalence of the difluoromethylthio group in pharmaceuticals and agrochemicals, we successfully applied this synergistic catalysis for the site-exclusive difluoromethylthiolation of C–O bonds (Scheme 5). Among the tertiary alkyl ethers examined, only the MOM-type ethers underwent this difluoromethylthiolation smoothly (see the Supporting Information). Although the direct nucleophilic substitution of primary and secondary alcohols with AgSCF\textsubscript{3} can occur smoothly, Qing et al. reported that tertiary alcohols fail to undergo this transformation.\textsuperscript{[4b]}

To further demonstrate the practicality of this protocol, a complementary trifluoromethylthiolation of complex tertiary alcohols was achieved (Scheme 6). The MOM-type ether was obtained by treatment of complex tertiary alcohols 8 and 9 with chloromethyl methyl ether (MOMCl), and was used directly in the subsequent trifluoromethylthiolation procedure without purification. The consecutive synthetic route provides an important access to trifluoromethylated alkylthioethers from unreactive tertiary alcohols in acceptable yields.

Further experiments were carried out to gain insight into the mechanism of this reaction (see the Supporting Information). Stern–Volmer quenching studies showed that photoexcited 4CzIPN\textsuperscript{*} was quenched by thiolate anions. Significantly, the postulated tertiary alkyl radical could be successfully trapped by TEMPO and BHT.

Analysis of the \textsuperscript{1}H NMR spectrum of the model reaction mixture clearly revealed the generation of methyl formate along with product 3a. Comparison of the potential of the

\begin{table}
\centering
\begin{tabular}{|c|c|}
\hline
Scheme 4. The ether scope: yields of isolated products are given. [a] 1 mmol scale. [b] 6 mmol scale (gram scale). [c] PhthSCF\textsubscript{3} (2 equiv). [d] \textsuperscript{19}F NMR yield.\hline
\end{tabular}
\end{table}
Three kinds of known tertiary alkyl radical precursors were used to investigate the radical C(sp³)–SCF₃ coupling by photoredox catalysis. As shown in Scheme 7, under photoredox radical C–H trifluoromethylthiolation conditions,[9d] the benzylic and methine C–H bonds in isobutylbenzene appeared to be trifluoromethylthiolated simultaneously (3a/3a' = 45:55). Neither reactive tertiary alkyl oxalates[22] nor carboxylic acids,[23] however, undergo this transformation [Eqs. (4), (5)]. These investigations further underscore the synthetic advantages of our protocol.

In conclusion, we have developed a synergistic organophotoredox catalysis and organocatalysis for the first site-selective trifluoromethylthiolation and difluoromethylthiolation of tertiary C(sp³)–O ether bonds under mild reaction conditions. The polarity-matching principle enables competing benzylic, methine, and hydridic C(sp³)–H bonds to survive during the HAT-initiated C–O bond-functionalization event, and this highlights the excellent regioselectivity and functional group compatibility of this protocol. Furthermore, the implementation of challenging tertiary C(sp³)–SCF₃ coupling in complex molecules represents a significant advance in future lead screening. Exploration of this new alkyl radical source for the construction of chiral quaternary carbon stereocenters by means of visible-light photoredox catalysis is in progress in our laboratory.

Acknowledgements

We gratefully acknowledge National Natural Science Foundation of China (21702098, 21732003, 21672099, and 21703118), “1000-Youth Talents Plan”, the Fundamental Research Funds for the Central Universities (Nos. 020514380158, 020514380131), Shandong Provincial Natural Science Foundation (No. ZR2017MB008), and the open training program of undergraduate organic experiment course for financial support. We are grateful to Professor Qilong Shen at Shanghai Institute of Organic Chemistry for generously providing PhthSCF₃-H.

Conflict of interest

We declare that one Chinese patent has been applied.

Keywords: C–O bond activation · cooperative catalysis · polarity-matching effect · trifluoromethylthiolation · umpolung

How to cite: Angew. Chem. Int. Ed. 2018, 57, 10357–10361
Angew. Chem. 2018, 130, 10514–10518


Conflict of interest

We declare that one Chinese patent has been applied.

Keywords: C–O bond activation · cooperative catalysis · polarity-matching effect · trifluoromethylthiolation · umpolung

How to cite: Angew. Chem. Int. Ed. 2018, 57, 10357–10361
Angew. Chem. 2018, 130, 10514–10518


[19] In one seminal work, radical-chain deoxygenation of an alkyl ether was achieved at high temperature. However, the rapid H-atom abstraction of alkyl radical from thiols seriously limited its synthetnic application for the construction of new C-C and C-X bonds in organic synthesis. See: H.-S. Dang, P. Franchi, B. P. Roberts, Chem. Commun. 2000, 499.


Manuscript received: May 23, 2018
Accepted manuscript online: June 28, 2018
Version of record online: July 12, 2018