Metal-Free Direct Trifluoromethylthiolation of Aromatic Compounds Using Triptycenyl Sulfide Catalyst

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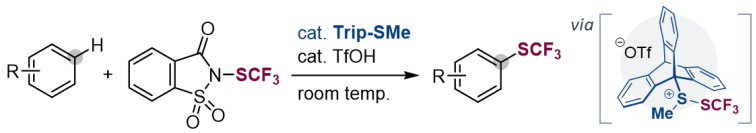
Supporting Information Placeholder

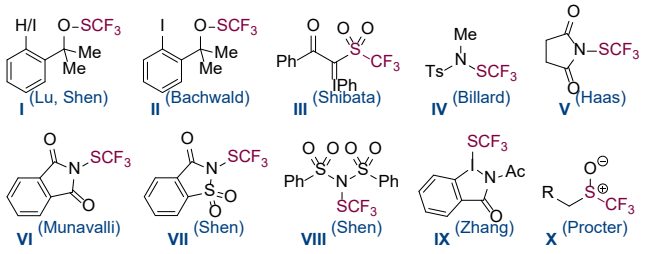


ABSTRACT: Herein we report an efficient synthetic method for the electrophilic trifluoromethylthiolation of aromatic compounds. The key is to use triptycenyl sulfide (Trip-SMe) and TfOH to enhance the electrophilicity of SCF_3 fragment through the formation of sulfonium intermediates. This method enables direct installation of an SCF_3 group onto unactivated aromatics at room temperature adopting a commercially available saccharin-based reagent. Preliminary DFT calculation was carried out to investigate the substitution effect on the catalytic activity.

Over the past few decades, the characteristic effect of incorporating fluorine and fluorinated substituents within the organic compounds has been highlighted in various research fields. In particular, strategic synthesis of functional molecules bearing trifluoromethylthio (SCF_3) group has recently attracted significant attention.[1] A notable feature of SCF_3 functionality is an extremely high lipophilicity parameter (Hansch constant 1.44, as being the highest among common functional groups),[2] which is valuable for the design and development of new medicines and agrochemicals. Indeed, several trifluoromethylthiolated compounds[3] with potent pharmacological activity have already been marketed, involving cefazaflur,[4] tiflorex,[5] toltrazuril,[6] etc.

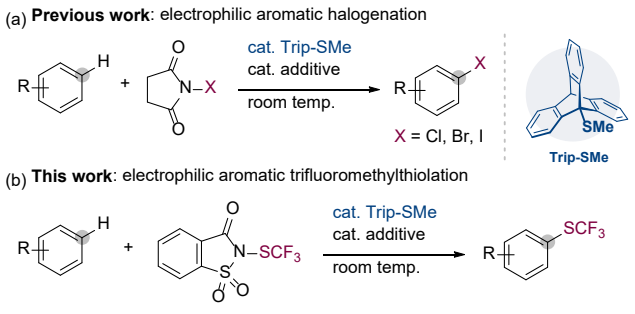
An attractive synthetic method for installing SCF_3 groups to the interested molecule is the direct functionalization of C–H bonds using electrophilic reagents (Scheme 1)[7].

Scheme 1. Representative Examples of Electrophilic SCF_3 Reagents



In the early stage of this approach, Cl-SCF_3 and CF_3CO_2-SCF_3 have been utilized as the SCF_3 source. [8] These classical reagents have been superseded by readily available, shelf-stable, and user-friendly alternatives because of their toxicity and handling difficulty. The rapid progress in this direction has been achieved in virtue of pioneering researchers and recent contributors such as Haas,[9] Munavalli,[10] Billard and Langlois,[11] Lu and Shen,[12] Shibata,[13] Buchwald,[14] Zhang,[15] Procter,[16] Iskra,[17] and others by introducing a series of new electrophilic SCF_3 transfer agents. These reagents are generally used in combination with Brønsted or Lewis acids to enhance the electrophilicity of SCF_3 fragment.[18] The direct substitution of aromatic compounds are, however, generally limited to highly nucleophilic (activated) aromatics like phenols, anilines, pyrroles, and indoles, whereas reactions involving unactivated substrates have been scarce.[16,17,18,19,20] In order to meet the growing demand for accomplishing late stage functionalization of complex molecules, development of an efficient trifluoromethylthiolation strategy is still a challenging and urgent task.

Scheme 2. Trip-SMe Catalyst for Aromatic Electrophilic Substitution Reactions

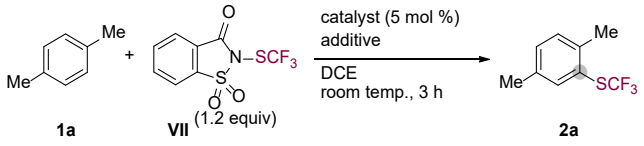


Recently, we developed a triptycene-based Lewis base catalyst Trip-SMe for electrophilic aromatic halogenation using *N*-halosuccinimides under mild reaction conditions (Scheme 2a).[21] Trip-SMe forms a relevant sulfonium complex [Trip-S(Me)Br]$^+$ as an active species, whose charge-separated character contributes the significantly high catalytic activity. As part of our continuous research interest in this field, we envisioned utilizing

this catalytic system for the activation of electrophilic SCF_3 reagents.[22] Herein, we report a Trip-SMe-catalyzed direct electrophilic trifluoromethylthiolation of unactivated aromatic compounds adopting commercially available starting materials (Scheme 2b). Preliminary DFT calculations suggested that the inductive effect of the triptycene moiety considerably increases the electrophilicity of SCF_3 fragment within the sulfonium intermediate.

At first, we conducted an optimization study adopting *p*-xylene (**1a**) as a model substrate for the catalytic trifluoromethylthiolation with SCF_3-saccharin **VII** (Table 1). This reagent is commercially available as a stable crystalline solid.

Table 1. Optimization Study [a]

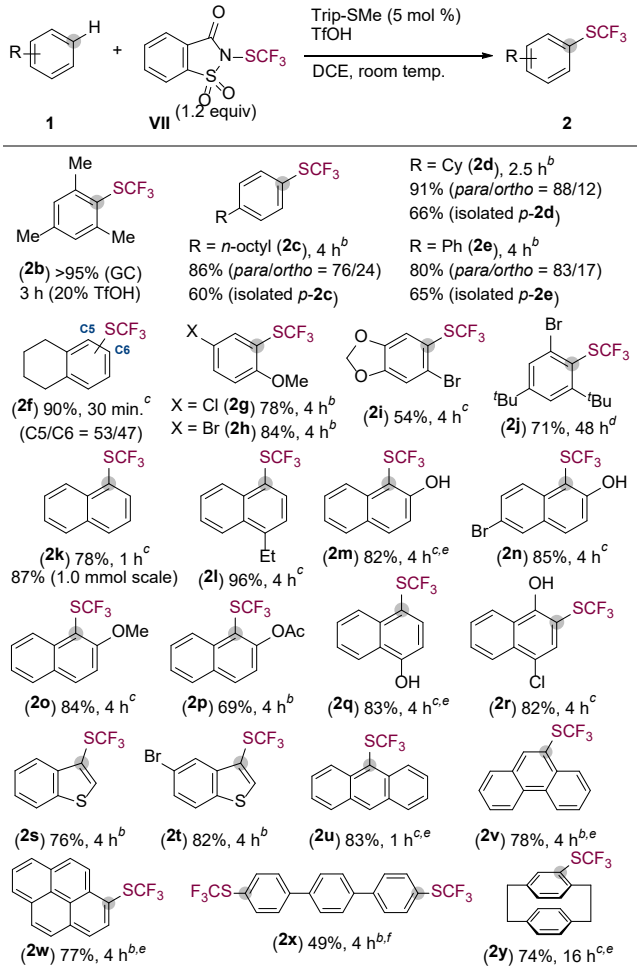


entry	catalyst	additive	yield [b]
1	Trip-SMe	TfOH (10 mol %)	21%
2	Trip-SMe	TfOH (50 mol %)	>95%
3	--	TfOH (50 mol %)	n.d.
4	Trip-SMe	--	n.d.
5 [c]	Trip-SMe	TfOH (50 mol %)	n.d.
6	*n*-Oct-SMe	TfOH (50 mol %)	n.d.
7	1-Ad-SMe	TfOH (50 mol %)	n.d.
8	S=PPh_3	TfOH (50 mol %)	n.d.
9	(4-OMe-C_6H_4)$_2$Se	TfOH (50 mol %)	trace
10 [d]	Trip-SeMe	TfOH (50 mol %)	trace

[a] Standard conditions: **1a** (0.2 mmol), **VII** (0.24 mmol), catalyst (5.0 mol %), additive, DCE (1.0 mL), RT, 3 h. [b] Determined by GC analysis. [c] SCF_3-phthalimide **VI** (see Scheme 1) was used as the SCF_3 source. [d] Conducted at 0.1 mmol scale. n.d. = not detected.

The desired product **2a** was obtained in 21% yield in the presence of Trip-SMe catalyst (5.0 mol %) and TfOH additive (10 mol %) at room temperature in DCE solvent (entry 1). This reaction was significantly accelerated with an increased amount of TfOH (50 mol %) to afford **2a** quantitatively (entry 2). Both Trip-SMe and TfOH were essential to trigger the reaction, indicating the occurrence of a sulfonium salt consists of Trip-S(Me)SCF_3 and OTf counter anion as an active species (entries 3,4). In contrast, SCF_3-phthalimide **VI** was not a suitable reagent for this transformation (entry 5). Other Brønsted acids (CF_3CO_2H, $MeSO_3H$, $TfNH_2$, and HBF_4·OEt_2), Lewis acids (TMSOTf, Zn(OTf)$_2$, Sc(OTf)$_3$, and In(OTf)$_3$), and $AgSbF_6$ were not effective activators (see the Supporting Information). Interestingly, replacement of the triptycenyl group with an alkyl group (*n*-octyl or 1-adamantyl) resulted in the loss of its catalytic activity (entries 6 and 7). Triphenylphosphine sulfide was also not an active catalyst (entry 8). A selenide catalyst, which was adopted for aromatic sulfenylation by Gustafson,[20] yielded a negligible amount of the product (entry 9). Moreover, Trip-SeMe failed to trigger the reaction under the identical conditions (entry 1). These results clearly highlight the exceptional activity of the Trip-SMe catalyst for the electrophilic trifluoromethylthiolation.

Scheme 3. Substrate Scope [a]



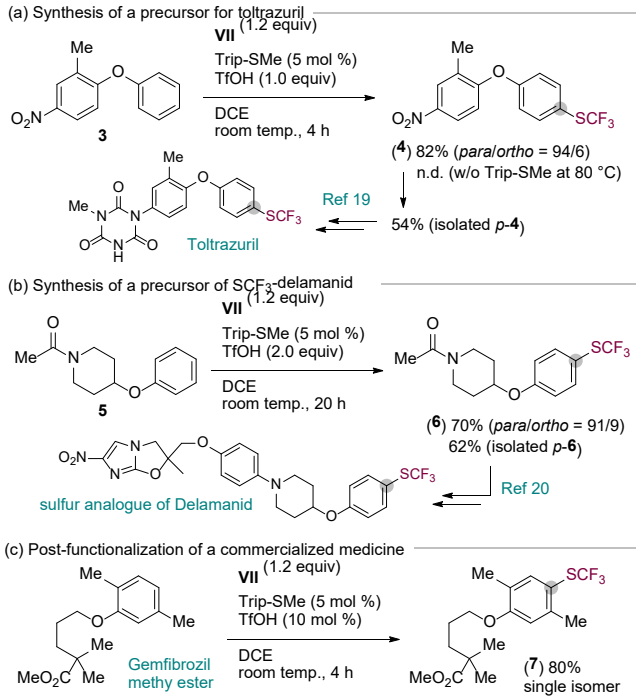
[a] Reaction conditions: **1** (0.2 mmol), **VII** (0.24 mmol), Trip-SMe (5.0 mol %), TfOH, DCE (1.0 mL). Isolated yields are shown, excepting **2a** and **2b** due to the volatility. [b] TfOH (100 mol %). [c] TfOH (10 mol %). [d] TfOH (200 mol %). [e] 1.0 equiv of **VII** was used. [f] 2.0 equiv of **VII** was used.

With the optimized combination of Trip-SMe and TfOH in hand, we examined the scope of aromatic substrates (Scheme 3). The reaction of mesitylene gave **2b** quantitatively. Less reactive mono-alkylbenzenes **1c** and **1d** were also smoothly converted to the corresponding products with high para-selectivity. The reaction of biphenyl (**1e**) preferentially produced a monosubstituted compound **2e**, and double substitution was not observed even with an excess amount of the reagent **VII**. This is probably because of the strong negative inductive effect of SCF_3 group. In contrast, tetralin (**1f**) afforded a mixture of isomers in almost 1:1 ratio. For the reaction of di- and tri-substituted haloarenes (**1g**–**1j**), the corresponding products were obtained as single isomers in 54–84% yield, respectively. Naphthalene and naphthol derivatives (**1k**–**1r**) underwent selective mono-substitution at the most nucleophilic position. The reaction of **1k** could be conducted in 1.0 mmol scale to afford **2k** in 87% yield. Benzo[*b*]thiophene (**1s**) and 5-bromobenzo[*b*]thiophene (**1t**) were also applicable to this protocol. Similarly, the reaction of anthracene (**1u**), phenanthrene (**1v**), and pyrene (**1w**) resulted in the formation of single regioisomers in high yield. Double substitution was possible for *p*-terphenyl to give the

4,4”-substituted isomer **2x** as a major product. [2.2]Paracyclophane was converted to **2y** in 74% yield. Unfortunately, the present method was not readily applicable to aromatic compounds bearing strong electron withdrawing (ester, nitrile, pyridine ring, etc.) and acid-sensitive (terminal epoxide, Boc, furan derivatives, etc.) functional groups (not shown).

The developed catalytic system was highly useful for the trifluoromethylthiolation of aryl ethers. Particular examples are showcased in Scheme 4.

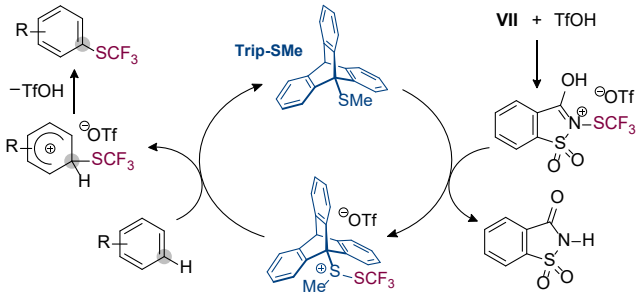
Scheme 4. Synthetic Application



A diaryl ether **3** was successfully converted to the corresponding product **4** in 82% yield with high para-selectivity. This compound is a synthetic precursor of toltrazuril,[23] a potent anticoccidial agent (Scheme 4a). Noteworthy, this reaction did not proceed in the absence of Trip-SMe catalyst even at 80 °C and resulted in ca. 30% decomposition of **3**. A phenoxypiperidine derivative **5** was also applicable to the reaction, giving **6** in 70% yield. The para isomer can be used for the synthesis of a sulfur analogue of delamanid,[24] which is a medicine for tuberculosis (Scheme 4b). In addition, the direct trifluoromethylthiolation gemfibrozil methyl ester produced **7** in 80% yield as a single isomer (Scheme 4c). These examples highlight a potential application of this protocol for the efficient screening of new SCF_3-containig drug candidates.

According to the literature,[21,25,26] we propose a reaction mechanism as shown in Scheme 5. Initial protonation of the reagent **VII** with TfOH reinforces its electrophilicity, thus facilitating the formation of a catalytically active sulfonium complex. Controlled NMR experiments support this SCF_3 group transfer event (for detail, see the Supporting Information). ^{1}H NMR spectra showed no obvious change when Trip-SMe was mixed with an equimolar amount of **VII** in DCM-d_2 solvent. Addition of TfOH to this mixture resulted in immediate disappearance of a peak at 2.5 ppm (SMe), and broad signals at around 3.0 ppm appeared. A similar trend was observed in our previous study on sulfonium intermediates.[17] Notably, in case the reagent **VI** is used instead of **VII**, such a spectral change was not observed upon treatment with TfOH. This is consistent with the result in Table 1 (entry 2 vs. 5). The reaction sequence then proceeds to an arenium ion intermediate via electrophilic addition of the SCF_3 fragment. Subsequent deprotonation liberates the corresponding product and regenerates TfOH.

Scheme 5. A Proposed Reaction Mechanism



In order to elucidate the electrophilicity of SCF_3 fragment of key intermediates, we conducted a computational study to acquire a trifluoromethylthio cation donating ability (Tt^+DA). This parameter has been introduced by Xue and Cheng as a quantitative descriptor for the reactivity of SCF_3 transfer reagents.[27] This is a relative free energy value (ΔG) to that of a reference molecule $CF_3CO_2SCF_3$ and, accordingly, lower Tt^+DA values correspond to higher electrophilicity of reagents (Figure 1, top) (for detail, see the Supporting Information). The Tt^+DA value of SCF_3-saccharin **VII** was 17.0 kcal/mol in DCE solvent, whereas considerably lower value of -2.3 kcal/mol was obtained for its TfOH adduct.[28] The proposed “active species” derived from Trip-SMe is suggested to be much more electrophilic considering the value of -7.0 kcal/mol. In sharp contrast, replacement of the sulfur atom with selenium considerably reduced the donating ability to -1.1 kcal/mol. This is consistent with the result in Table 1 (entry 2 vs. 19).

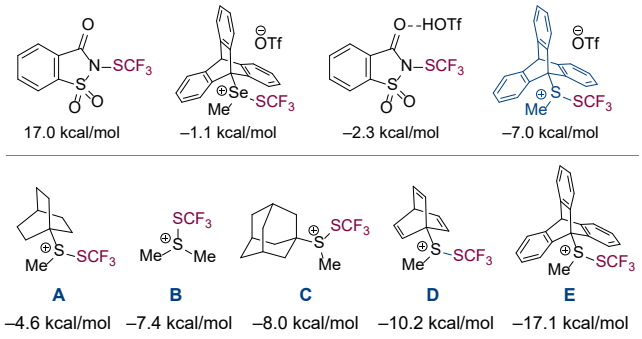


Figure 1. Tt^+DA values of electrophilic SCF_3 species calculated at the M06-2X/6-311++G(2df,2p)/PCM(DCE) level.

Subsequently, we have examined the donating ability of several sulfonium complexes **A**~**E** to elucidate the effect of substituents on the sulfur atom (Figure 1, bottom). Here the OTf anion is omitted to clarify the effect.[29] In accordance with the exceptionally high activity of the Trip-SMe catalyst, the lowest Tt^+DA value was given to **E** (-17.1 kcal/mol). Additionally, NPA charges on the sulfur atom of SCF_3 groups, which would directly reflect their electrophilic nature, considerably correlate to the Tt^+DA values (see the Supporting Information). It is notable that a barrelene-based complex **D** exhibited a relatively lower value (-10.2 kcal/mol) than alkyl-substituted sulfonium salts **A**~**C**; however, no obvious spatial interaction was found between the sulfonium moiety and π bonds within **D** by an NBO

analysis. We thus focused on the inductive effect of these substituents.

Considering the change in NPA charge distribution before and after the formation of sulfonium complexes **A**~**E**, the positive charge on the central sulfur atom is somewhat delocalized over the three substituents (for detail, see the Supporting Information). Accordingly, three minor contributors can be considered as shown in Figure 2.

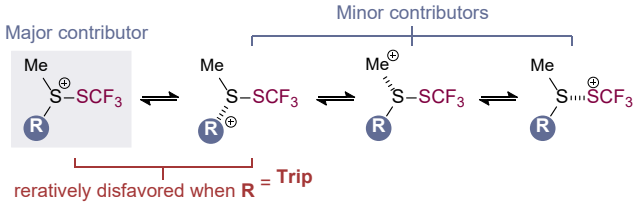


Figure 2. Schematic representation of possible contributors within the sulfonium complexes.

If the substituent R is a 9-triptycenyl (Trip) group, high s-character of the bridgehead carbon atom as well as the inductive effect of three benzene rings will relatively decrease the contribution of the left two structures.[30] Indeed, only Trip-SMe showed an elongation of the S–Me bond upon complexation with SCF_3 cation, and the longest S–SCF_3 bond length was given to **E** among the calculated structures. As a result, the cationic nature of the SCF_3 fragment is considerably reinforced. In the actual reaction system, the triptycene substituent may inhibit side reactions which lead to the deactivation of the catalyst. The Trip–S bond is inherently inert toward substitution and elimination reactions. Additionally, the steric bulk of triptycene moiety would kinetically stabilize the central cationic sulfur within **E**, preventing nucleophilic attack on the sulfur atom.

In summary, we have introduced a Trip-SMe/TfOH system for the electrophilic trifluoromethylthiolation of aromatic compounds. This method enables direct installation of an SCF_3 group onto unactivated aromatics such as alkylbenzenes, haloanisoles, etc. at room temperature adopting commercially available reagents. Preliminary DFT calculations suggested that the inductive effect of the triptycene moiety considerably increased the electrophilicity of SCF_3 fragment within the sulfonium complex.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

• Detail experimental procedures, computational method, products identification data, and copy of NMR spectra (PDF)

• Atomic coordinates of all calculated molecules (XYZ)

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Notes

The authors declare no competing financial interests.

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