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In Situ Generation of Electrophilic Trifluoromethylthio Reagents for Enantioselective Trifluoromethylthiolation of Oxindoles

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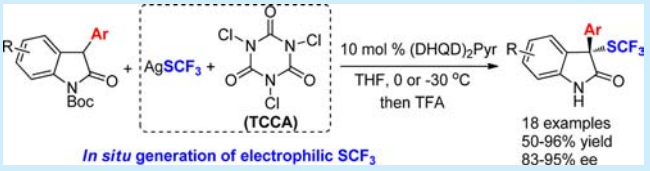
Supporting Information

ABSTRACT: An organocatalytic asymmetric trifluoromethylthiolation reaction via in situ generation of active electrophilic trifluoromethylthio species involving trichloroisocyanuric acid and $AgSCF_3$ as a practical and easily handled electrophilic SCF_3 source for $C_{SP}^3-SCF_3$ bond formation was developed. Reactions with this one-pot version strategy occurred in good yields and excellent stereoselectivities to access enantiopure oxindoles bearing a SCF_3-substituted quaternary chiral center. The straightforward process described here makes use of simple starting materials and proceeds under mild conditions, which will be useful in medicinal chemistry and diversity-oriented syntheses.



It is well-known that the extremely high lipophilicity and high electron-withdrawing character of the trifluoromethylthio (SCF_3) group may contribute to an increase in their transmembrane permeation, thus enhancing their bioavailability.[1] Therefore, the introduction of a SCF_3 group into small molecules is of considerable interest for the design and discovery of bioactive compounds,[2] such as JUK 0422, Tiflorex, and Toltrazuril (Figure 1).

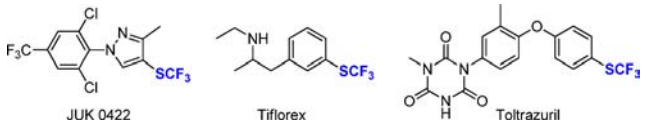
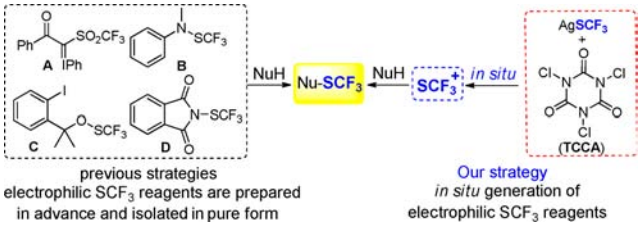


Figure 1. Bioactive compounds bearing an SCF_3 group.

Accordingly, the development of efficient methods for the incorporation of the SCF_3 group into organic compounds has drawn much attention from synthetic research groups.[1,2] Apart from earlier indirect strategies,[2c,3,4] a series of nucleophilic SCF_3-transfer reagents have been disclosed and employed for the direct construction of the trifluoromethylthio moiety into organic molecules.[5] Recently, several elegant transformations for $C_{sp3}-CF_3S$ bond formation have been reported involving newly developed electrophilic SCF_3 reagents (Scheme 1, left). Shibata and co-workers developed a hypervalent iodonium ylide reagent (**A**) via in situ reduction of the trifluoromethanesulfonyl group to afford SCF_3-substituted products.[6] However, atom economy is very low, and metal is necessary for SCF_3-transfer, indicating that organocatalytic transformation is difficult. Billard and co-workers reported that trifluoromethanesulfenamide (**B**) is an effective electrophilic SCF_3 source for the trifluoromethylthiolation of various substrates.[7] Inspired by Togni's reagent, the Shen group described a novel trifluoromethylthiolated thioperoxy reagent (**C**) with interesting reactivity.[8] However, the synthetic process

Scheme 1. General Synthetic Strategies for Direct Trifluoromethylthiolation Involving Electrophilic SCF_3 Reagents



appears to be not so easy to carry out, and its stability seems limited. *N*-(Trifluoromethylthio)phthalimide (**D**) appears to be the best reagent in terms of accessibility, reactivity, and enantioselective control.[9] Even though these direct trifluoromethylthiolation reagents are shelf-stable and safe, a more critical issue is the fact that these SCF_3 reagents must be prepared in advance. Because of these limitations and negative aspects, it is still highly desirable to develop a more practical and easily handled method for the generation of the SCF_3 source directly. Our strategy is to generate the electrophilic SCF_3 reagents in situ from simple and readily available starting materials, which would be trapped by nucleophile to access the desired SCF_3 product with good results (Scheme 1, right). If this approach is successful, this would be an excellent method without workup and isolation of SCF_3 reagents.

Oxindole compounds bearing a quaternary stereogenic center at the 3-position are a prominent substructure in numerous pharmaceuticals and bioactive compounds.[10] In this context, various synthetic strategies have been devised in recent years for the asymmetric synthesis of 3,3-disubstituted oxindole

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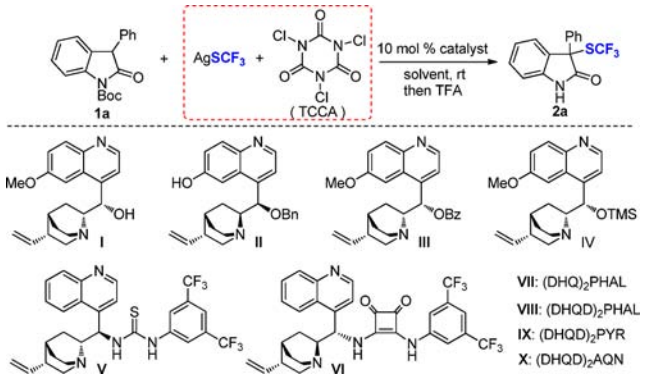
derivatives.[11] If SCF_3 group would be combined with oxindole, it might result in further advances in the pharmacological applications. Therefore, an effective approach for the installation of a SCF_3 group into 3-position of oxindoles bearing a quaternary stereogenic center attracts our attention. As for the enantioselective catalytic direct trifluoromethylthiolation reaction, only a few examples have been developed very recently by Gade, Shen, and Rueping.[12] During the preparation of this manuscript, Rueping and co-workers reported the first catalytic asymmetric trifluoromethylthiolation of oxindoles using cinchona alkaloid catalyst and electrophilic SCF_3 reagent **D**,[13] but the more practical approach is still desirable from the point of view of step-economy and potential industrial applications. Herein, we demonstrate an organocatalytic enantioselective trifluoromethylthiolation of oxindoles via in situ generation of electrophilic trifluoromethylthio reagents from trichloroisocyanuric acid (**TCCA**) and $AgSCF_3$ in the presence of cinchona alkaloids as organocatalysts.

We initiated our studies by mixing the commercially available reagent **TCCA** and $AgSCF_3$ (3.3 equiv) in dichloromethane. After the mixture was stirred at 30 °C for 30 min, **1a** and quinidine (**I**) were added (Table 1). To our delight, the reaction proceeded smoothly and afforded the desired product in 50% yield, albeit with poor enantioselectivity (8% ee), suggesting that the electrophilic trifluoromethylthio reagents were able to be in situ generated and trapped by 3-substituted oxindole (Table 1, entry 1). Considering the pioneering studies of Barbas[14]and others by using cinchona alkaloid[16,17] bifunctional catalysts efficiently in functionalization of 3-substituted oxindole substrates, we turned our attention to catalysts **II**, **V**, and **VI**. The disappointed results (Table 1, entries 2, 5, and 6) indicated that the bifunctional catalysts with a hydrogen bond donor part have a negative effect on this transformation. In great contrast, when the hydroxyl group of quinidine was protected by a benzoyl group, the enantioselectivity was improved to moderate (49% ee, entry 3) and the TMS-protected quinidine did not have any improvement (Table 1, entry 4). These results possibly demonstrated that the aromatic interaction plays a crucial role in the control of enantioselectivity. Based on these results and previous reports,[14−16] we postulated the commercially available Sharpless ligands (**VII**, **VIII**, **IX**, and **X**) may be suitable catalysts for this attractive transformation. Indeed, the yield and enantioselectivity of the reaction increased when catalyst $(DHQD)_2PYR$ **IX** (Table 1, entry 9) was used. Of the solvents tested, tetrahydrofuran (THF) proved optimal with respect to catalytic activity and selectivity (Table 1, entry 12). The best result (78% yield and 90% ee) in terms of selectivity and yield was obtained when the reaction was conducted at 0 °C (Table 1, entry 16).

Encouraged by these results, we expanded the substrate scope of the reaction by using a variety of substituted oxindoles with the in situ generated electrophilic SCF_3 reagent under the optimized reaction conditions. It was discovered that most of the reactions were performed with good enantioselectivities and yields (Scheme 2). It was shown that the position and the electronic property of the substituents for aromatic rings have a very limited effect on the stereoselectivity of the process. For example, various 3-aromatic oxindoles, bearing electron-donating groups (X = OMe, Me) or electron-withdrawing groups (X = F, Cl, Br, CF_3) on the aryl ring, reacted efficiently with electrophilic SCF_3 reagents to afford the corresponding products **2a−j** in 61−95% yields with 83−95% ee. It is noteworthy that the substrates containing electron-withdrawing groups (**2f−j**) should be carried out at a temperature of −30 °C for better results.

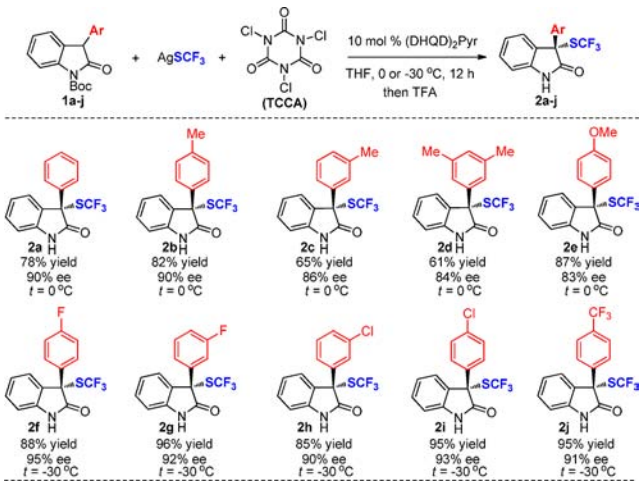
Table 1. Screening Results of Reaction Conditions[a]



entry	cat.	solvent	temp (°C)	yield[b] (%)	ee[c] (%)
1	**I**	DCM	30	50	8
2	**II**	DCM	30	33	−17
3	**III**	DCM	30	44	49
4	**IV**	DCM	30	41	6
5	**V**	DCM	30	27	8
6	**VI**	DCM	30	40	−7
7	**VII**	DCM	30	48	−66
8	**VIII**	DCM	30	38	58
9	**IX**	DCM	30	66	70
10	**X**	DCM	30	39	46
11	**IX**	toluene	30	67	83
12	**IX**	**THF**	**30**	**67**	**85**
13	**IX**	Et_2O	30	59	76
14	**IX**	CH_3CN	30	76	40
15	**IX**	THF	10	76	90
16	**IX**	**THF**	**0**	**78**	**90**

[a]Reaction conditions: **TCCA** (0.06 mmol) and $AgSCF_3$ (0.2 mmol) were mixed in solvent (1.0 mL) and stirred for 30 min at 30 °C, and then a solution of **1a** (0.1 mmol) and catalyst (0.01 mmol, 10 mol %) in solvent (1.0 mL) was added. After 12 h, the mixture was treated with trifluoroacetic acid (TFA). [b]Isolated yield. [c]Determined by chiral HPLC analysis.

Scheme 2. Scope of Trifluoromethylthiolation of Different Aryl Oxindoles



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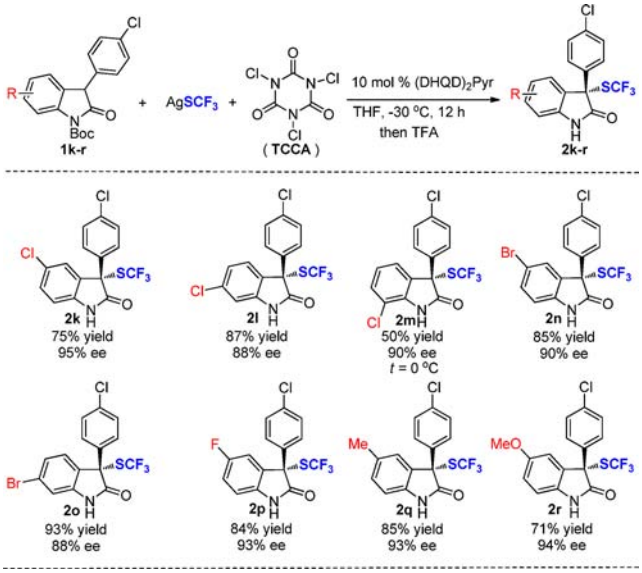
Further exploration of the substrate scope was focused on the indolinone moiety (Scheme 3). Various substituents bearing

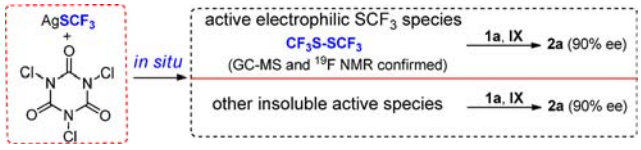
Scheme 3. Trifluoromethylthiolation of Oxindole with a Variety of Substituents on Indolinones



different electronic properties were tolerable, giving the corresponding products with high yields ranging from 50% to 93% and stereoselectivities (88−95% ee). The presence of Cl, Br, or F at the indolinone moiety is very important for drug discovery because halides are very reactive in many transition metal-catalyzed reactions,[17] which offer opportunities for further modifications at these positions.

Although we are sure the electrophilic SCF_3 reagents were involved in this transformation, the SCF_3 intermediate needs to be further investigated for a better understanding of this reaction. To gain some insights into the real SCF_3 reagents in current reaction, a series of control experiments were conducted. Initially, monitoring the reaction of **TCCA** (0.1 mmol) with $AgSCF_3$ (3.3 equiv) in CD_3CN (1 mL) at room temperature after 30 min by ^{19}F NMR spectroscopy and GC−MS revealed the formation of $F_3CS-SCF_3$ as the only active species during this process (characterized by the $F_3CS-SCF_3$ resonance at δ = −45.7 ppm[9a,18]). In order to further confirm $F_3CS-SCF_3$ as the active SCF_3 reagent, the in situ generated $F_3CS-SCF_3$[19] was bubbled with the help of argon gas into another solution of **1a** and catalyst **IX** in THF at 0 °C. The desired product was isolated with consistent enantioselectivity (90% ee), further suggesting $F_3CS-SCF_3$ should be one of the reactive species. To the best of our knowledge, it is the first time that $F_3CS-SCF_3$ has acted as an electrophilic SCF_3 source for $C_{sp^3}-SCF_3$ bond formation.[20] However, after removal of the $F_3CS-SCF_3$ active reagent and then the treatment of the resulting residue with **1a** and catalyst **IX**, to our surprise, the expected product was also obtained with 90% ee, indicating the existence of other electrophilic SCF_3 species under the current system. The resulting residue was difficult to characterize because of its insolubility in some organic solvents. Although we were not able to confirm the active SCF_3 intermediate at the present stage (Scheme 4), this in situ process provides a more convenient and practical approach for the synthesis of enantiopure SCF_3 substituted compounds. The absolute configuration of **2a** was determined to be (*S*) by X-ray

Scheme 4. Investigation for Reactive Electrophilic SCF_3 Species



crystallographic analysis (Figure 2), and those of other trifluoromethylthio-containing compounds were assigned on the assumption of the same mechanism.

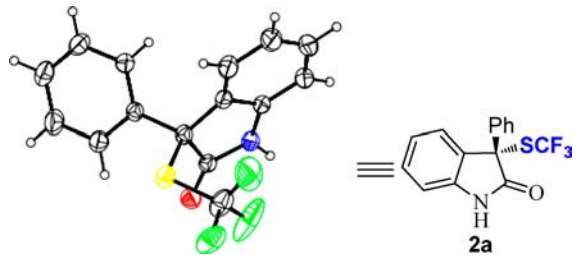


Figure 2. X-ray crystal structure of product **2a**.

In conclusion, we have developed an asymmetric trifluoromethylthiolation reaction via in situ generation of active electrophilic trifluoromethylthio species involving TCCA and $AgSCF_3$ as a practical and easily handled electrophilic SCF_3 source for $C_{sp^3}-SCF_3$ bond formation through organocatalysis. This practical protocol provided a highly efficient method for the rapid synthesis of oxindoles bearing a SCF_3-substituted quaternary chiral center with excellent enantioselectivity from simple and cheap starting materials without workup and isolation of SCF_3 reagents, which provide a particularly advantageous alternative to the current useful SCF_3 reagents. This convenient and practical strategy should facilitate the development of a wide range of trifluoromethylthiolation reactions catalyzed by organic and metal catalysts.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures, analytic date for products, crystal data for **2a** (CIF), and copies of ^1H, ^{13}C, and ^{19}F NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) The boiling point of $F_3CS-SCF_3$ is only 34 °C; it is very easy to bubble it into another solution of **1a** and catalyst in THF. Although this reagent is commercially available, it is very expensive and difficult to handle. Furthermore, in China, a special license is needed to purchase it from a chemical company.

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