Trifluoromethylthiolation

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Enantioselective Trifluoromethylthiolating Lactonization Catalyzed by an Indane-Based Chiral Sulfide

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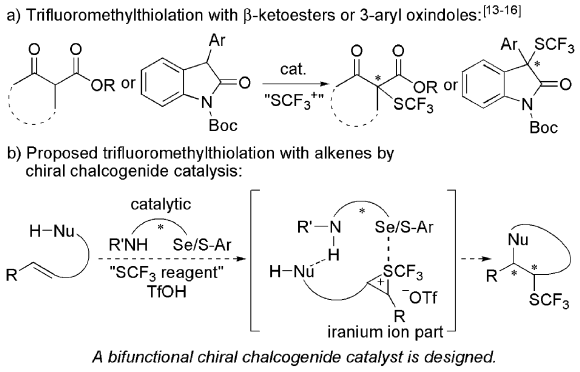
Abstract: *Enantioselective trifluoromethylthiolation, especially of alkenes, is a challenging task. In this work, we have developed an efficient approach for enantioselective trifluoromethylthiolating lactonization by designing an indane-based bifunctional chiral sulfide catalyst and a shelf-stable electrophilic SCF_3 reagent. The desired products were formed with diastereoselectivities of $>99:1$ and good to excellent enantioselectivities. The transformation represents the first enantioselective trifluoromethylthiolation of alkenes and the first enantioselective trifluoromethylthiolation that is enabled by a catalyst with a Lewis basic sulfur center.*

The incorporation of fluorine-containing moieties into organic molecules can improve the physical, chemical, and biological properties of both pharmaceutically and agrochemically relevant compounds.[1] The trifluoromethylthio group (SCF_3) is a particularly intriguing fluorinated moiety with high stability, electronegativity, and lipophilicity ($\pi_R = 1.44$). This property can greatly enhance the transmembrane permeability of drug candidates.[2] Much effort has been devoted to developing efficient methods for the synthesis of trifluoromethylthiolated molecules.[3–12] However, these achievements mainly focused on the preparation of achiral SCF_3-containing compounds. Although chiral SCF_3-containing molecules might lead to further advances in drug discovery, methods for the enantioselective introduction of the SCF_3 group remain rare. To date, only a few examples have been reported by the groups of Rueping,[13] Shen,[14] Gade,[15] and Tan.[16] These reactions were based on the use of electrophilic SCF_3 reagents in combination with nucleophilic β-ketoesters or 3-aryl oxindoles as the substrates and cinchona alkaloids or chiral copper complexes as the catalyst, and proposed to proceed through an S_N2 pathway (Scheme 1 a). Owing to the lack of an appropriate setup to achieve high enantioselectivity, no other catalytic processes for the formation of chiral SCF_3-containing compounds have been developed, specifically for enantioselective alkene trifluoromethylthiolation.[17]

The difunctionalization of alkenes to generate racemic SCF_3-containing compounds by simultaneously introducing SCF_3 and another group was reported by Billard and co-workers.[9b] This method provides a great opportunity to medicinal chemists to quickly synthesize multifunctional molecules. Recently, we reported the non-asymmetric aminotrifluoromethylthiolation of alkenes with an electrophilic SCF_3 reagent by diaryl chalcogenide catalysis.[18] Owing to the involvement of a chalcogenide in the catalytic cycle, we envisioned that chiral trifluoromethylated products could be formed through chiral chalcogenide catalysis (Scheme 1 b). Compared to the asymmetric incorporation of SCF_3 groups by S_N2 pathways,[13–16] the enantioselective trifluoromethylthiolation of alkenes is more challenging. According to studies of enantioselective alkene bromo- and chalcofunctionalizations by the groups of Denmark[19] and Yeung,[20] the enantioselectivities can be heavily affected by two issues: racemization of the iranium ion through olefin-to-olefin degeneration and the racemization derived from which nucleophilic partners may capture the thiiranium or seleniranium species. To overcome these possible racemization problems, we considered the use of a bifunctional catalyst that would stabilize the intermediary iranium ion. The proposed bifunctional catalyst possesses a chalcogenide group as the Lewis base and an NH moiety as the hydrogen-bond donor. Herein, we report an efficient approach for the asymmetric trifluoromethylthiolation of alkenes that is based on the use of such an indane-based chiral bifunctional sulfide catalyst and a new electrophilic SCF_3 reagent.



Scheme 1. Enantioselective trifluoromethylthiolation.

We began our study with (*E*)-4-phenylbut-3-enoic acid (**1a**) as the model substrate. The bifunctional catalysts were synthesized from readily available, inexpensive sources, such as amino acids. The L-valine-derived, Ts-protected aminoselenide **C1** was prepared first. When the trifluoromethylthiolating lactonization was attempted with Shen's *N*-trifluoromethylthiosaccharin (**2a**) as the SCF_3 reagent and selenide **C1** as the catalyst in the presence of triflic acid, the *trans*-

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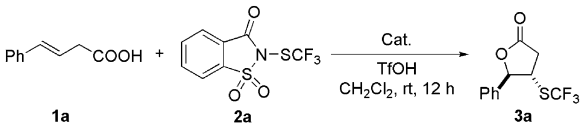
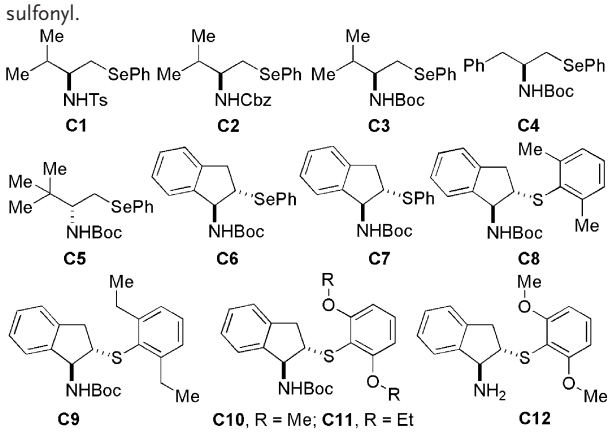
Table 1: Catalyst evaluation.[a]



1a 2a 3a

Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**C1**	44	−7
2	**C2**	78	11
3	**C3**	98	27
4	**C4**	98	32
5	**C5**	98	−38
6	**C6**	94	72
7	**C7**	94	79
8	**C8**	71	81
9	**C9**	76	83
10	**C10**, **C11** or **C12**	92	83

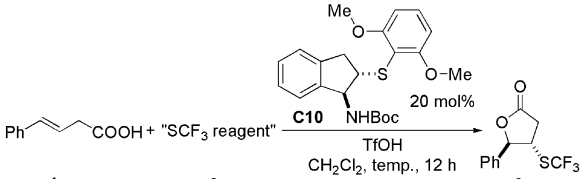
[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.075 mmol), TfOH (0.5 equiv), catalyst (20 mol%), CH_2Cl_2 (2 mL), RT, 12 h. [b] Determined by 400 MHz NMR spectroscopy with quinoline as the internal standard. All of the products were formed with >99:1 d.r. [c] Determined by HPLC analysis on a chiral stationary phase. Boc = *tert*-butoxycarbonyl, Cbz = carboxybenzyl, Tf = trifluoromethanesulfonyl, Ts = *para*-toluenesulfonyl.



configured product **3a** was generated in 44% yield with 7% *ee* and >99:1 d.r. (Table 1, entry 1). To adjust the hydrogen-bonding ability of the NH group, selenide **C2**, which bears a Cbz protecting group, was synthesized. When **C2** was used as the catalyst, the enantioselectivity slightly improved (entry 2). With Boc-protected aminoselenide **C3**, the *ee* value further increased to 27% (entry 3). Other substituents on the nitrogen atom, such as ethyl, diethyl, or acyl moieties, led to lower enantioselectivities. Based on these observations, the use of the Boc protecting group appeared to be promising. Next, the influence of steric hindrance in the backbone was studied. Increased steric hindrance resulted in higher enantioselectivity; for example, with L-*tert*-leucine-derived phenyl selenide **C5**, the desired product was obtained in 38% *ee* (entry 5). Notably, when indane-based phenyl selenide **C6** was synthesized from readily available *cis*-aminoindanol and utilized as the catalyst, the enantioselectivity increased to 72% *ee* (entry 6). Considering that the properties of sulfides are similar to those of the selenide analogues, phenyl sulfide **C7** was prepared and used as the catalyst instead of selenide **C6**. Interestingly, the enantioselectivity increased to 79% *ee* (entry 7). We surmise that the smaller size of the sulfur atom compared to selenium results in subtle changes in the configuration of the intermediate. The bulkier sulfides **C8** and **C9**, which feature 2,6-dimethyl and 2,6-diethyl substituents, respectively, delivered slightly higher enantioselectivities (entries 8 and 9), but led to lower yields. Based on our previous studies,[18] electron-rich catalysts could increase the reactivity. Methoxy and ethoxy groups were thus placed on the aryl ring. As expected, product **3a** was formed in higher yield (92%) with the same enantioselectivity when sulfides **C10** and **C11** were used as the catalysts (entry 10). It is well known that Boc groups can be removed under acidic conditions. To determine whether the Boc group on the catalyst was indeed cleaved during the reaction, the unprotected sulfide **C12** with a free NH_2 group was prepared. When **C12** was employed as the catalyst, the same yield and enantioselectivity were achieved as with catalysts **C10** and **C11** (entry 10).

Other solvents, such as 1,2-dichloroethane, chloroform, toluene, THF, and acetonitrile, were also tested but found to be less effective than dichloromethane for our transformation. We then turned our attention to examining SCF_3 reagents. Billard's *N*-trifluoromethanesulfenamide **2b** gave the desired product **3a** in a low yield of 44% with slightly higher enantioselectivity (84% *ee*; Table 2, entry 1). To obtain a more reactive SCF_3 reagent, we synthesized a new shelf-stable SCF_3 reagent, $(PhSO_2)_2N–SCF_3$ (**2c**), from the corresponding sulfimide. When it was used for our asymmetric lactonization, the yield improved to 98%, and the reaction proceeded with good enantioselectivity (84% *ee*; entry 2). The reaction is sensitive to the reaction temperature: When the reaction was run at 0°C, the desired product was isolated in 85% yield, and the enantioselectivity increased to 90% *ee* (entry 4). When the reaction was carried out at −20°C, the enantioselectivity increased even further (93% *ee*), but **3a**

Table 2: Evaluation of other parameters.[a]



1a 2 3a

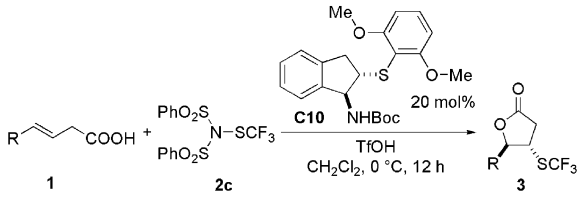
Entry	SCF_3 reagent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	$PhNH–SCF_3$ (**2b**)	RT	44	84
2	$(PhSO_2)_2N–SCF_3$ (**2c**)	RT	98	84
3	**2c**	10	87	87
4	**2c**	0	87 (85)	90
5	**2c**	−20	40	93

[a] Reaction conditions: **1a** (0.05 mmol), **2** (0.075 mmol), TfOH (0.5 equiv), **C10** (20 mol%), CH_2Cl_2 (2 mL), 12 h. [b] Determined by 400 MHz NMR spectroscopy with quinoline as the internal standard. Yields of isolated products given in parentheses. All of the products were formed with >99:1 d.r. [c] Determined by HPLC analysis on a chiral stationary phase.

was formed in only 40% yield (entry 5). The yield did not increase even when the reaction time was prolonged to 24 hours.

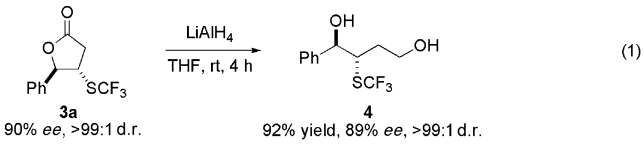
Next, the substrate scope was evaluated under the optimized reaction conditions (Table 3). Various *E*-configured 4-aryl-substituted but-3-enoic acids **1** underwent the trifluoromethylthiolating lactonization to give the desired products with >99:1 d.r. and 79–91% *ee*. When alkyl substituents were introduced at the *para* position of the aryl ring, the corresponding products were generated in excellent yields and enantioselectivities (**3b** and **3e**, 90% *ee* each; entries 1 and 4). The more hindered carboxylic acid **1d** gave product **3d** with slightly lower enantioselectivity than **1b** (entry 3). Electron-donating groups, such as a methoxy substituent at the *para* position of the aryl ring, led to lower enantioselectivities, but did not affect the reactivity (entries 5 and 6). When electron-withdrawing groups, such as Cl, Br, F, or CF_3, were introduced at the *para* position of the aryl ring, the reactions did not go to completion, resulting in moderate to good yields (entries 7–10). For example, product **3h** was formed in 51% yield, and the reaction to form product **3k** had to be carried out at room temperature to achieve reasonable conversion. Similarly, substrates with chloro or bromo substituents at the *meta* position of the aryl ring were not consumed completely, resulting in moderate yields (**3p**: 63%; **3r**: 55%), but the enantioselectivities were still high (entries 15 and 17). The aryl substituent could also be replaced by a benzyl group (**1s**), and the corresponding product **3s** was formed in moderate yield with 79% *ee* (entry 18). However, when thiophenyl- or long-chain-alkyl-substituted but-3-enoic acids were utilized as the substrates, the desired products were formed as mixtures of diastereomers with moderate enantioselectivities. A new catalyst might be required to improve these selectivities. The absolute configuration of the trifluoromethylthiolated lactones **3** was assigned to be (4*S*,5*R*) by X-ray crystallographic analysis of **3l**. Lactones **3** can be easily converted into multifunctional compounds. For example, when product **3a** was treated with $LiAlH_4$ in THF, the valuable trifluoromethylthiolated diol **4** was obtained in 92% yield and 89% *ee* [Eq. (1)].

Table 3: Substrate scope.[a]



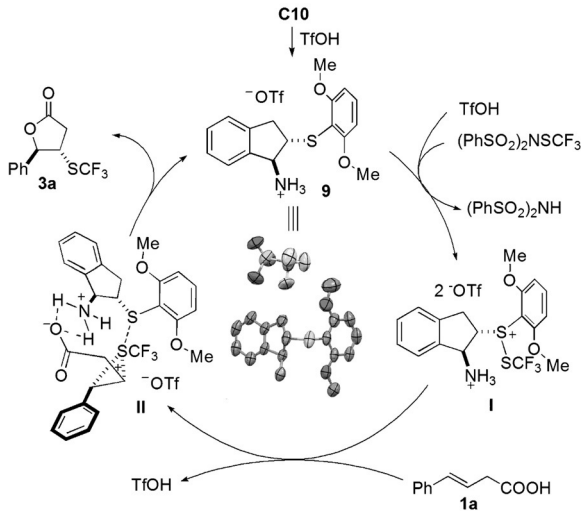
Entry	1	R	Product	Yield [%][b]	*ee* [%][c]
1	**1b**	4-MeC_6H_4	**3b**	90	90
2	**1c**	3-MeC_6H_4	**3c**	80	89
3	**1d**	2-MeC_6H_4	**3d**	90	83
4	**1e**	4-*i*PrC_6H_4	**3e**	88	90
5	**1f**	4-$MeOC_6H_4$	**3f**	75	79
6	**1g**	2-$MeOC_6H_4$	**3g**	89	81
7	**1h**	4-ClC_6H_4	**3h**	51	91
8	**1i**	4-BrC_6H_4	**3i**	65	90
9	**1j**	4-FC_6H_4	**3j**	72	88
10[d]	**1k**	4-$CF_3C_6H_4$	**3k**	61	90
11	**1l**	4-PhC_6H_4	**3l**	87	87
12	**1m**	2-naphthyl	**3m**	88	90
13	**1n**	3,4-$Me_2C_6H_3$	**3n**	93	84
14	**1o**	3-F-4-MeC_6H_3	**3o**	79	89
15	**1p**	3-Br-4-MeC_6H_3	**3p**	63	87
16	**1q**	2-Br-4-MeC_6H_3	**3q**	83	84
17[d]	**1r**	3,4-$Cl_2C_6H_3$	**3r**	55	89
18	**1s**	$PhCH_2$	**3s**	55	79

[a] Reaction conditions: **1** (0.10 mmol), **2c** (0.15 mmol), TfOH (0.5 equiv), **C10** (20 mol%), CH_2Cl_2 (4 mL), 0°C, 12 h. [b] Yields of isolated products are given. All of the products were obtained with >99:1 d.r. [c] Determined by HPLC analysis on a chiral stationary phase. [d] At room temperature.



(1)

As shown in Table 1, product **3a** was formed with the same yield and enantioselectivity regardless of whether catalyst **C10** or **C12** was used. Furthermore, when catalyst **C10** was treated with TfOH, removal of the Boc group was observed by NMR spectroscopy. Based on these observations, a possible reaction mechanism is proposed in Scheme 2. Boc-protected **C10** is first transformed into salt **5** in the presence of TfOH. The SCF_3 reagent **2c** is activated by **5** and TfOH to give $(PhSO_2)_2NH$, which is accompanied by the formation of species **I**. When the olefinic carboxylic acid **1a** is present in the reaction mixture, intermediate **II** can be generated by the formation of a trifluoromethylthiiranium ion and hydrogen bonding. Then, the oxygen of the carbonyl group attacks the iranium ion to give the desired product **3a** along with compound **5**. In this transformation, the strong acid TfOH



Scheme 2. Proposed reaction mechanism.

might interact with the SCF_3 reagent **2c** to diminish its acidity, which renders the conversion of intermediate **I** into **II** feasible.[18,19c]

In conclusion, we have reported an enantioselective trifluoromethylthiolating lactonization reaction that affords the desired products with good to excellent enantio- and diastereoselectivities. This report constitutes the first successful enantioselective trifluoromethylthiolation of alkenes and might enable the development of other asymmetric trifluoromethylthiolation reactions. Furthermore, a highly reactive, shelf-stable electrophilic SCF_3 reagent was developed and should find applications in other trifluoromethylthiolation processes. A new chiral bifunctional sulfide catalyst was also designed and delivered excellent enantioselectivities for this transformation, which should inspire the design of other Lewis basic catalysts based on this scaffold. We are currently investigating the application of this catalyst in other asymmetric olefin trifluoromethylthiolation reactions.

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Keywords: alkenes · asymmetric catalysis · chiral sulfides · organocatalysis · trifluoromethylthiolation

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