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# Chiral Selenide-Catalyzed Enantioselective Construction of Saturated Trifluoromethylthiolated Azaheterocycles

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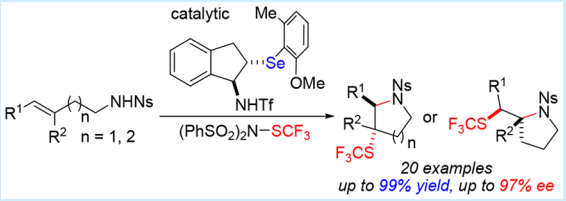
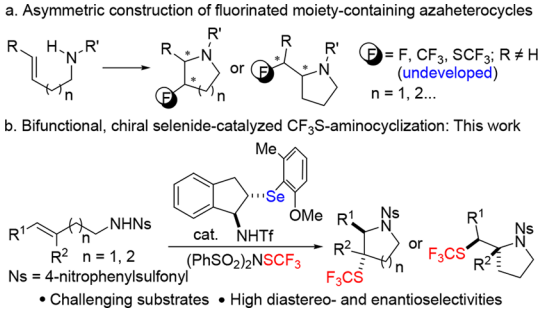
Supporting Information

**ABSTRACT:** An indane-based, bifunctional, chiral selenide catalyst has been developed. The new catalyst is efficient for the enantioselective synthesis of saturated azaheterocycles possessing a trifluoromethylthio group. The desired products were obtained in good yields with high diastereo- and enantioselectivities.




The synthesis of saturated azaheterocycles such as pyrrolidines and piperidines has been a long-standing endeavor of the synthetic community[1] because these structural motifs are present in many drugs and bioactive natural products.[2] Among the developed methods for their preparation, the electrophilic cyclization of alkenes represents an efficient strategy to construct these valuable molecular frameworks.[3] Normally, a nitrogen-containing ring is formed with the concomitant introduction of an additional functional group (−F, −Cl, −Br, −I, −SR) in the cyclization step. Because of the significant importance of fluorinated moieties,[4] many efforts have been devoted to generating fluorinated azaheterocycles in a similar way.[5,6] However, successful examples of enantioselective synthesis are very rare.[7] In particular, the enantioselective cyclization of internal alkenes with incorporation of a fluorinated moiety to produce saturated azaheterocycles has not been developed (Scheme 1a).

**Scheme 1. Synthesis of Saturated Azaheterocycles**




Lewis basic selenium catalysis has emerged as a powerful tool in organic synthesis.[3h,8−11] Its utilization in asymmetric transformations began several years ago. In 2011, Denmark demonstrated BINAM-derived selenophosphoramide catalysts for the asymmetric sulfenylation of olefins.[8c−h] In 2013, Yeung reported a new, sugar alcohol-derived monofunctional cyclic selenium catalyst for bromoaminocyclization of trisubstituted olefins.[9] Despite these advances, studies in this field are still in their infancy. Thus, developing new chiral selenium catalysts and using them for valuable organic transformations is highly desirable. Herein, we report a bifunctional selenide catalyst that is efficient for the enantioselective $CF_3S$ aminocyclization of internal alkenes to afford a series of saturated azaheterocycles (Scheme 1b).[12]

Owing to the importance of the $CF_3S$ group in bioactive molecules, methods for the preparation of achiral $CF_3S$ compounds have been rapidly developed.[13] In contrast, enantioselective strategies for generating $CF_3S$ stereocenters are scarce.[14] Recently, we have brought chalcogenide catalysis into the field of trifluoromethylthiolation.[11] With the participation of selenide/sulfide-captured $CF_3S^+$, the developed system offered a chance for asymmetric trifluoromethylthiolation. Accordingly, an indane-based chiral sulfide catalyst for the enantioselective $CF_3S$ lactonization of alkenoic acids was developed.[11c] It was efficient for 4-arylalkenoic acid substrates, but when 4-alkylalkenoic acids were used under similar conditions, the desired products were generated with moderate enantioselectivities. These facts suggested that indane could act as a privileged catalyst scaffold, and 4-alkyl-substituted substrates were challenging. With these points in mind, we initiated a series of $CF_3S$ aminocyclization reactions with the (*E*)-ethyl-substituted, Ns-protected olefinic sulfonamide **1a** as a model substrate (Table 1).[15] Sulfide **C1** with an NHBoc group was first examined in the cyclization of **1a**. Not surprisingly, product **2a** was generated with only 18% ee at 0 °C using $(PhSO_2)_2NSCF_3$ (Table 1, entry 1). To test the effect of a hydrogen bond donor, the amine group on the catalyst was protected by different groups such as Ts, Bz, and Tf (Table 1, entries 2−4). It was found that catalyst **C4**, with its strong hydrogen bond donor group, delivered a 39% ee for the formation of **2a**.

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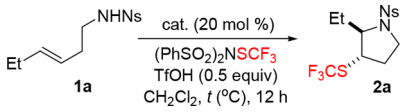
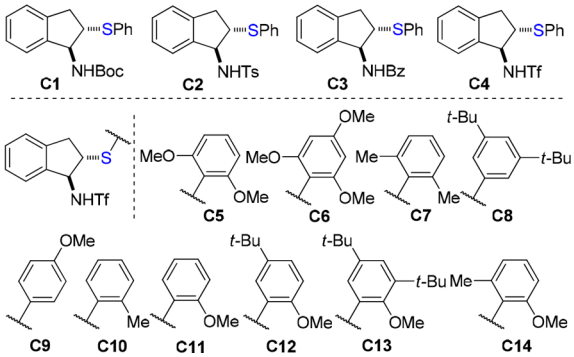
**Table 1. Condition Evaluation with Sulfide Catalysts**[a]




| entry | cat. | $t$ (°C) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | **C1** | 0 | 80 | 18 |
| 2 | **C2** | 0 | 79 | -10 |
| 3 | **C3** | 0 | 83 | -11 |
| 4 | **C4** | 0 | 87 | 39 |
| 5 | **C4** | -20 | 53 | 41 |
| 6 | **C4** | -45 | 7 | 44 |
| 7 | **C4** | -78 | 0 | --- |
| 8 | **C5** | -45 | 99 | 66 |
| 9 | **C6** | -45 | 92 | 61 |
| 10 | **C7** | -45 | 13 | 52 |
| 11 | **C8** | -45 | 61 | 51 |
| 12 | **C9** | -45 | 60 | 53 |
| 13 | **C10** | -45 | 38 | 54 |
| 14 | **C11** | -45 | 53 | 66 |
| 15 | **C12** | -45 | >99 | 69 |
| 16 | **C13** | -45 | 12 | 52 |
| 17 | **C14** | -45 | >99 | 70 |
| 18 | **C14** | -78 | 31 | 77 |
| 19 | **C5** | -78 | 37 | 77 |
| 20 | **C12** | -78 | 13 | 75 |



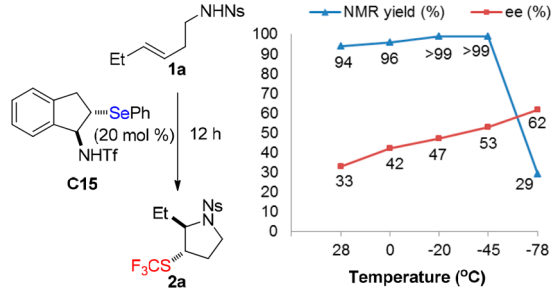

[a]Conditions: **1a** (0.05 mmol), $(PhSO_2)_2NSCF_3$ (1.5 equiv), catalyst (20 mol %), TfOH (0.5 equiv), $CH_2Cl_2$ in 0.025 M concentration for 12 h. Unless noted, diastereoselectivity is >99:1. [b]Refers to NMR yield using trifluoromethylbenzene as the internal standard. [c]Determined by HPLC analysis.

The reactivity of **1a** was heavily affected by the reaction temperature (Table 1, entries 5−7). When the reaction was carried out at −45 °C, the product was formed in only 7% yield with 44% ee (Table 1, entry 6). The reaction did not occur at −78 °C (Table 1, entry 7). To improve the reactivity and enantioselectivity, the steric hindrance and the effect of electron density within the catalyst were studied at −45 °C (Table 1, entries 8−17). The electron-rich and sterically hindered, *ortho*-disubstituted phenyl sulfides were tested in the cyclization of **1a**. As expected, 2,6-dimethoxy-substituted phenyl sulfide **C5** not only enhanced reactivity but also raised the enantioselectivity to 66% (Table 1, entry 8). More electron-rich groups on the phenyl ring did not help increase enantioselectivity and reactivity (Table 1, entry 9). In sharp contrast, replacement of the two methoxy groups with larger methyl groups led to a dramatic drop in yield and a decrease in enantioselectivity, which revealed that substituents at the *ortho* position heavily affected the reactivity (Table 1, entry 10).

We turned our attention to less sterically hindered catalysts. When catalysts **C8**−**C11** were utilized, the enantioselectivities did not increase (Table 1, entries 11−14). Other catalysts with one methoxy group (**C12**−**C14**) were tested for the reactions. Catalyst **C12** with a 3-*tert*-butyl substituent delivered a slightly higher ee compared to catalyst **C4**, and the reactivity remained (Table 1, entry 15). Interestingly, when another *tert*-butyl group was placed at the *ortho* position to the methoxy group (**C13**), the reaction almost shut down (Table 1, entry 16). Catalyst **C14** bearing both *o*-methyl and methoxy groups afforded **2a** in excellent yield with 70% ee (Table 1, entry 17). In comparison to the results from other catalysts, this improvement depended on the appropriate electron effect and steric hindrance of catalyst that affects the interaction between selenium and $CF_3S^+$ cation and the chiral environment of the reaction, respectively. Furthermore, the enantioselectivity could be improved when the reactions were performed at −78 °C, but the yields were low (Table 1, entries 18−20).

In our previous studies,[11a] selenium had a special ability to promote trifluoromethylthiolation compared with the other Lewis base atoms such as N, P, and S. This drove us to do further research to exploit the catalytic properties of selenium. Subsequently, chiral selenide **C15** was tested in the same reaction (Scheme 2). Product **2a** was formed in a higher yield

**Scheme 2. Selenide-Catalyzed $CF_3S$-aminocyclization**[a]




[a]Conditions: As described in Table 1.

with a higher ee compared to the use of catalyst **C4** when the reaction was performed at 0 °C. The reaction temperature was further studied. The lower the reaction temperature, the higher the enantioselectivity of the product. To our surprise, even at −78 °C, the selenide catalyst still resulted in the formation of **2a** with 62% ee.

From the above results, it was concluded that selenide catalysis was promising for the cyclization. In analogy to the studies of sulfide catalysis, steric hindrance and the effect of electron density in the selenium catalyst were studied at −78 °C to improve the enantioselectivity (Scheme 3). As expected, 2,6-dimethoxy-substituted phenyl selenide **C17** raised the enantioselectivity to 77%. In contrast, replacement of the two methoxy groups with larger ethoxy groups (**C18**) led to a dramatic drop in yield and a decrease in enantioselectivity. There was nearly no reaction using difluoro-substituted catalyst **C16** and dimethyl-substituted catalyst **C19**. When less sterically hindered catalysts were utilized, the product was formed in high yield, but with reduced ee. To our surprise, catalyst **C23** bearing an alkylseleno group did not afford any product. Next, we focused on *ortho*-monosubstituted catalysts. A methoxy group was better at the *ortho* position than a methyl group. Other catalysts with one methoxy group (**C26**-**C28**) were tested for the reactions. Gratifyingly, catalyst **C28** bearing both *o*-methyl and methoxy groups afforded **2a** with 81% ee. This discovery is similar to the observation in sulfide catalysis.

To further enhance the enantioselectivity, the reactions were optimized with different acids since acids affect the activation of electrophilic reagents and may change the chiral environment of transition states in Lewis base-catalyzed transformations.[8c−h,11] We were glad to discover that the reaction proceeded smoothly



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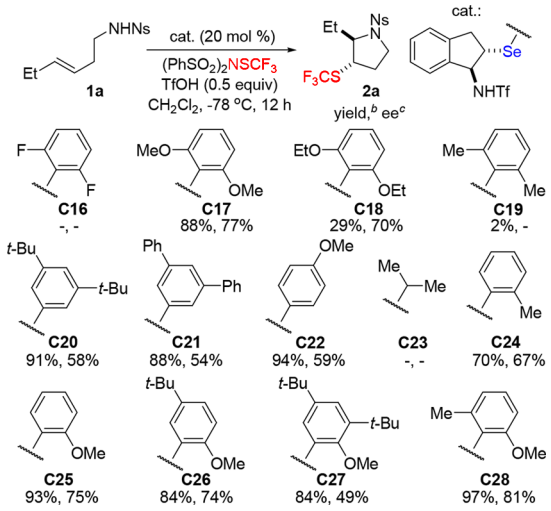
**Scheme 3. Screening of Selenide Catalysts**[a]



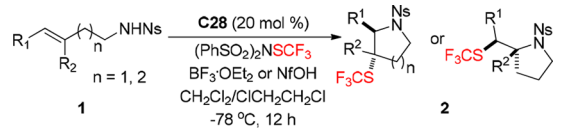

[a]Conditions: As described in Table 1. The reaction was performed at −78 °C. [b]Refers to NMR yield using trifluoromethylbenzene as the internal standard. [c]Determined by HPLC analysis.

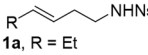
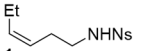
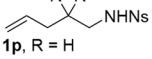
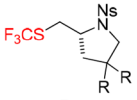
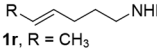
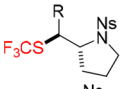
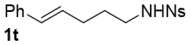
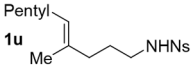
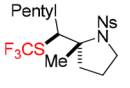
to afford product **2a** with 86% ee when $BF_3{\cdot}OEt_2$ was added to the reaction instead of protic acid. After a screening of mixed solvents and studies of different concentrations of **1a**, the desired product was formed in 89% ee in $CH_2Cl_2/ClCH_2CH_2Cl$ at 0.025 M concentration in the presence of 1 equiv of $BF_3{\cdot}OEt_2$ (see the Supporting Information for details).

With these optimal conditions in hand, we began to evaluate substrate scope (Table 2). When the ethyl group on the double bond was replaced by other alkyl groups, the corresponding products were still formed in high yields with excellent enantioselectivities (**1b**−**e**, 87−93% ees). To establish the robustness of the catalyst, a series of aryl-substituted olefinic sulfonamides were tested under similar conditions. All of them afforded the corresponding products in excellent yield with no less than 90% ee except sterically hindered 2-methylphenyl alkene **1g**. When an electron-withdrawing group such as −Cl and −Br was put on the phenyl ring of the substrates (**1j** and **1k**), the cyclization slowly proceeded to give the corresponding products at −78 °C. Moreover, when the reactions were carried out at −60 °C, they worked very efficiently to generate the desired products in high yield with excellent ee (**2j**, 94% ee; **2k**, 95% ee). Substrates with more electron-withdrawing groups, i.e., $-CF_3$, did not afford any products even at −60 °C. Pleasingly, alkene **1l** bearing a *p*-methoxy group on the phenyl ring still underwent aminocyclization to afford product **2l** in 85% yield with 93% ee. In the literature, the selenium-catalyzed electrophilic cyclization of the substrates bearinga *p*-methoxy group on the phenyl ring was not efficient, and even racemization occurred in the bromoaminocyclization.[9a,11c] The conditions were also suitable for an alkene bearing a 2-thienyl group which afforded the desired product **2n** in 83% yield with 90% ee. Similarly, studies of cyclizations of alkenes bearing a heterocycle are rare because their high reactivities easily lead to side reactions. This method proved to be efficient for the cyclization of (*E*)-alkenes. In contrast, when the (*Z*)-alkene **1o** was utilized, no desired product was formed, which was attributed to inherent reactivity of the alkene[16] or steric hindrance in the alkene.

To extend this method to more challenging substrates, terminal alkene **1p** was examined. Product **2p** was formed in acceptable yield with good enantioselectivity (75% ee). In order

**Table 2. Substrate Scope**[a]




| substrate | product | yield (%)[b] | ee (%)[c] |
|---|---|---|---|
|  **1a**, R = Et | **2a**[d] | 93 | 89 |
| **1b**, R = Hexyl | **2b** | 99 | 87 |
| **1c**, R = $PhCH_2$ | **2c**[e] | 89 | 90 |
| **1d**, R = $PhCH_2CH_2$ | **2d** | 91 | 93 |
| **1e**, R = *i*-Bu | **2e** | 80 | 92 |
| **1f**, R = $C_6H_5$ | **2f**[f] | 94 | 95 |
| **1g**, R = 2-$MeC_6H_4$ | **2g**[f] | 97 | 74 |
| **1h**, R = 3-$MeC_6H_4$ | **2h**[f] | 86 | 92 |
| **1i**, R = 4-$MeC_6H_4$ | **2i**[f] | 83 | 94 |
| **1j**, R = 4-$ClC_6H_4$ | **2j**[f,g] | 99 | 94 |
| **1k**, R = 4-$BrC_6H_4$ | **2k**[f,g] | 88 | 95 |
| **1l**, R = 4-$MeOC_6H_4$ | **2l**[f] | 85 | 93 |
| **1m**, R = 2-Naphthyl | **2m**[f] | 87 | 93 |
| **1n**, R = 2-Thienyl | **2n**[f] | 83 | 90 |
|  **1o** |  **2o** | --- | --- |
|  **1p**, R = H |  **2p**[e] | 48 | 75 |
| **1q**, R = Me | **2q**[e] | 93 | 86 |
|  **1r**, R = $CH_3$ |  **2r**[h] | 77 | 97 |
| **1s**, R = $PhCH_2CH_2$ | **2s**[h] | 90 | 94 |
|  **1t** |  **2t**[f] | 61 | 89 |
|  **1u** |  **2u** | 96 | 71 |

[a]Conditions: **1** (0.1 mmol), $(PhSO_2)_2NSCF_3$ (1.5 equiv), $BF_3{\cdot}OEt_2$ (1.0 equiv), $CH_2Cl_2/ClCH_2CH_2Cl$ = 1:1 (v/v), in 0.025 M concentration, −78 °C, 12 h. [b]Isolated yield. All the products were obtained with >99:1 diastereoselectivities. [c]Determined by HPLC analysis. [d]1 mmol scale with 10 mol % of **C28**, 36 h. [e]$BF_3{\cdot}OEt_2$ (2.0 equiv), 24 h. [f]NfOH (0.75 equiv) instead of $BF_3{\cdot}OEt_2$, 24 h. [g]Reaction was carried out at −60 °C for 24 h. [h]$BF_3{\cdot}OEt_2$ (5.0 equiv), 24 h.

to evaluate what contribution would be made by the Thorpe−Ingold effect, substrate **1q** with two methyl groups on the alkyl chain was synthesized. As expected, the cyclization of **1q** proceeded more efficiently to give the desired product **2q** in 93% yield with 86% ee. In order to test the selectivity of *endo*/*exo* cyclization, alkyl-substituted olefinic sulfonamides **1r** and **1s** were examined. Their cyclizations gave rise to two constitutional isomers of the *exo*/*endo* products. For example, the reaction of **1r** produced the ca. 2:1 *exo*/*endo* products under the standard conditions. Interestingly, when the amount of $BF_3{\cdot}OEt_2$ was increased to 5.0 equiv, the molar ratio of the *exo*/*endo* products increased to 5:1, and the *exo* product **2r** was obtained as the major product in 77% yield with 97% ee. When a phenyl group replaced the alkyl group on the double bond, the *endo* cyclization took place as the main pathway to form the six-membered piperidine **2t** in 61% yield with 89% ee. It is noteworthy that trisubstituted alkene **1u** could still efficiently undergo $CF_3S$-aminocyclization to give the *exo* product **2u** with good enantioselectivity. The absolute configuration of **2** was determined through the X-ray crystallographic studies of **2f** and **2r**.

In summary, we have developed an indane-based, bifunctional chiral selenide catalyst that is efficient for the enantioselective



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$CF_3S$ aminocyclization of alkenes with construction of saturated pyrrolidines and piperidines. The method provides a new pathway for the synthesis of chiral azaheterocycles and is complementary for chiral selenium catalysis.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01392.

Experimental details, characterization data, NMR spectra of new compounds, HPLC traces, and X-ray data (PDF)
X-ray crystallgraphic data for **2f** (CIF)
X-ray crystallgraphic data for **2r** (CIF)

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### Notes

The authors declare no competing financial interest.

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