Communication

Chiral Selenide-Catalyzed Enantioselective Allylic Reaction and Intermolecular Difunctionalization of Alkenes: Efficient Construction of C–SCF3 Stereogenic Molecules

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Chiral Selenide-Catalyzed Enantioselective Allylic Reaction and Intermolecular Difunctionalization of Alkenes: Efficient Construction of C–SCF_3 Stereogenic Molecules

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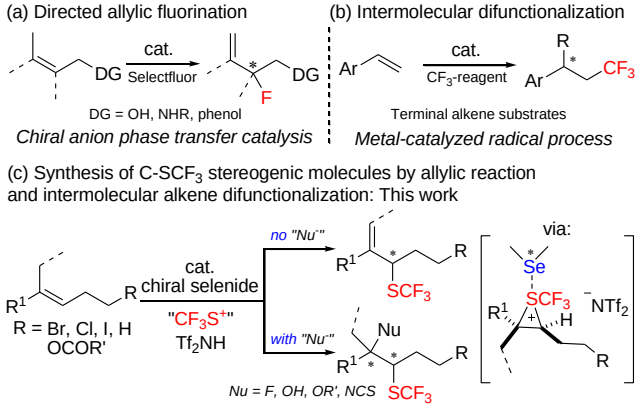
Supporting Information Placeholder

ABSTRACT: New approaches for the synthesis of enantiopure trifluoromethylthiolated molecules by chiral selenide catalyzed allylic trifluoromethylthiolation and intermolecular difunctionalization of unactivated alkenes are disclosed. In these transformations, functional groups were well tolerated, and the desired products were obtained in good yields with excellent chemo-, enantio- and diastereoselectivities. This work is nicely complementary to enantioselective trifluoromethylthiolation, allylic functionalization and intermolecular alkene difunctionalization.

Fluorine and fluorine-containing moieties can adjust the chemical, physical and biological properties of parent molecules.[1] Consequently, synthesis of fluorinated molecules is of great interest in the field of pharmaceuticals and agrochemicals.[2,3] Owing to the prevalence of alkene structural unit on molecules, much attention has been paid to the synthesis of fluorinated compounds by incorporation of a fluorine or fluorine-containing moiety into parent alkenes. However, construction of chiral fluorinated molecules from alkenes has been largely limited.[2b,d] In particular, utilizing very useful enantioselective allylic C–H functionalization and intermolecular difunctionalization of alkenes to synthesize fluorinated molecules remains a formidable challenge. Only recently, a few elegant approaches have been developed.[4-8] For example, Toste reported directed allylic fluorination via C–H bond cleavage by chiral anion phase transfer catalysis (Scheme 1a),[4] and Liu demonstrated Cu-catalyzed enantioselective intermolecular CF_3-functionalization of terminal alkenes via radical process (Scheme 1b).[7c,d] In comparison with fluoro and trifluoromethyl groups, trifluoromethylthio (CF_3S) group has higher lipophilicity value.[3a] Compounds bearing a CF_3S group may possess some unique properties. Herein, we report our discovery that C–SCF_3 stereogenic molecules could be efficiently produced by chiral selenide-catalyzed allylic functionalization via C–H bond cleavage and intermolecular difunctionalization of alkenes (Scheme 1c).

In recent years, many efforts have been devoted to the synthesis of CF_3S-molecules.[3,9-11] But, the successful examples of enantioselective trifluoromethylthiolation are rare.[10,11] To expand this area, we have developed efficient approaches to construct chiral CF_3S-molecules through bifunctional chalcogenide-catalyzed intramolecular reactions of alkenes.[11b-e] In these transformations, an additional functional group had to be installed on substrates as a nucleophile group to promote the cyclizations and prevent the racemization of thiiranium ion. Due to this installation, the scopes are limited to the relatively specialized substrates, which led to specific stereogenic CF_3S-products. We questionated whether chiral CF_3S-molecules could be accessed not by the former intramolecular mode, but by allylic functionalization and intermolecular difunctionalization of alkenes. To achieve this goal, two challenging issues needed to be overcome: (i) The difficulty of enantiocontrol of reactions, especially without a binding group assistance.[4] (ii) The racemization of thiiranium ion intermediate through C–S bond cleavage to form a unstable carbocation and olefin-to-olefin degeneration of thiiranium ion.[12] On the basis of the previous studies,[11,12h] we envisioned that relatively stable thiiranium ion might not be easy to racemize. Furthermore, a proper chiral environment to control the enantioselectivity would be feasible to provide by tuning catalysts and additives. Thus, it is possible to gain chiral allylic and difunctionalization products in high enantioselectivities when allylic proton elimination and nucleophilic attack proceed smoothly after the formation of relatively stable thiiranium ion.

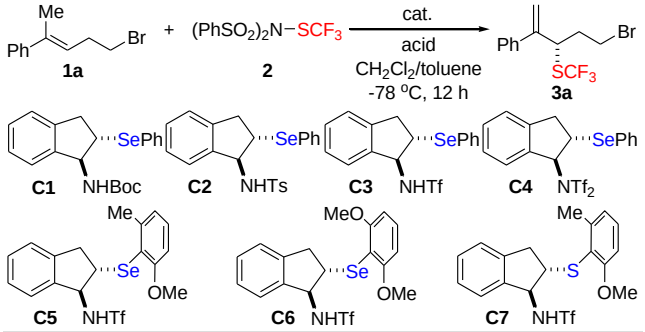
Scheme 1. Catalytic Enantioselective Construction of Fluorinated Molecules with Alkenes



Keeping the assumption in mind, we first investigated allylic trifluoromethylthiolation via C–H bond cleavage. Considering that the formed thiiranium ion from trisubstituted alkenes with an appropriate electronic property might be relatively stable, easily prepared (*E*)-(5-bromopent-2-en-2-yl)benzene (**1a**) was selected as the model substrate. Lewis basic selenium catalysis has exhibited great potentials[11-13] and different chiral selenide catalysts were examined for this reaction (Table 1). When **1a** was treated with electrophilic $(PhSO_2)_2NSCF_3$ (**2**) using Boc-protected selenide catalyst **C1**, it was found that allylic reaction occurred to give the desired product **3a** in 42% yield with 10% ee in the presence of TfOH (entry 1). Although the enantioselectivity was quite low, this indicated that enantioselective implementation was viable by chiral selenide catalysis. Ts-protected catalyst **C2** was further tested. Product **3a** was generated in trace amounts (entry 2).

When selenide catalyst **C3** with NHTf group was employed, **3a** was formed with 78% ee (entry 3). These results revealed that the NHTf group was crucial and might bind to the TfO^- anion to set up a proper steric hindrance for high enantiocontrol.[11e] To probe this spectulation, catalyst **C4** with nitrogen protected by two Tf groups was examined. The enantioselectivity decreased to 43% (entry 4). Next, effect of electron density and steric hindrance of aryl group on catalysts was studied (entries 5 and 6). It was found that methyl and methoxy groups installed at the *ortho* positions of the phenyl ring led to improved yield and ee (entry 5). Less sterically hindered **C6** resulted in the drop of yield (entry 6). In contrast, the sulfide catalyst was not effective for this transformation (entry 7). We realized that an appropriate anion from the corresponding acid could not only accelerate allylic proton elimination but also bind to catalyst to provide a proper chiral environment. So different acids combined with catalyst **C5** were screened. The reactivity and enantioselectivity were largely affected (entries 8-10). Finally, product **3a** was obtained in high yield with 91% ee using Tf_2NH as the acid (entry 10). Less loading of acid affected the yield slightly (entry 12).

Table 1. Condition Optimization[a]

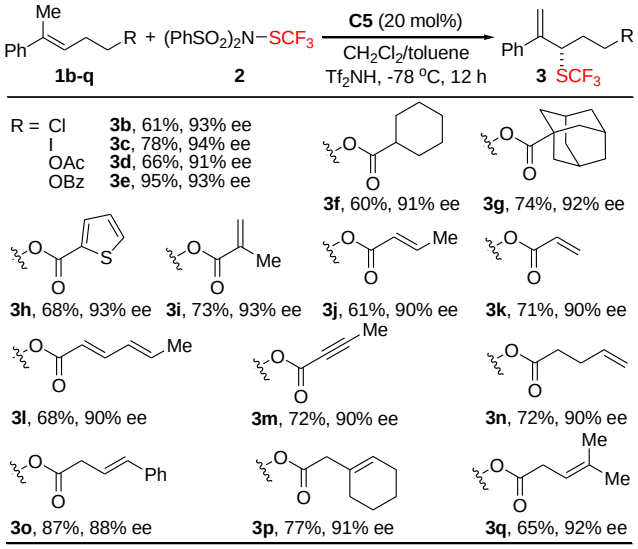


entry	cat.	acid	yield (%)[b]	ee (%)[c]
1	**C1**	TfOH	42	10
2	**C2**	TfOH	<5	--
3	**C3**	TfOH	45	78
4	**C4**	TfOH	14	43
5	**C5**	TfOH	50	90
6	**C6**	TfOH	42	87
7	**C7**	TfOH	12	67
8	**C5**	$BF_3{\cdot}OEt_2$	18	82
9	**C5**	TMSOTf	90	87
10	**C5**	Tf_2NH	99(95)	91
11[d]	**C5**	Tf_2NH	87	83
12[e]	**C5**	Tf_2NH	92	91

[a]Conditions: **1a** (0.05 mmol), **2** (1.5 equiv), acid (2.0 equiv), catalyst (20 mol%), CH_2Cl_2/toluene = 1 mL/1 mL, -78 °C, 12 h. [b]NMR yield using trifluoromethylbenzene as the internal standard. Isolated yield is in parentheses on 0.1 mmol scale. [c]Determined by chiral HPLC analysis. [d]At -40 °C. [e]Tf_2NH (0.5 equiv).

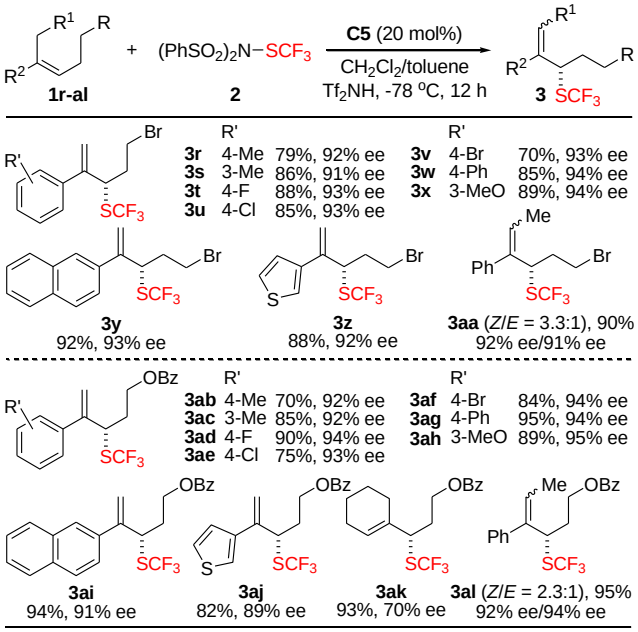
Then, we evaluated the substrate scope of reaction. Different functional groups on the long chain of alkenes **1** were first studied under the similar conditions (Scheme 2). When bromo group was replaced by chloro or iodo group, the corresponding products were generated in good yields with high enantioselectivities. The replacement by OAc, OBz or alkyl ester groups slightly affected the enantioselectivities of the transformation (**3d-g**, 91-93% ees). Functional groups containing double bond, triple bond, heterocycle and conjugated diene were well tolerated (**3h-q**). It is noteworthy that when the substrates having two allylic units were used, the allylic trifluoromethylthiolation always took place at the allylic side where three substituents including aryl group was attached to the double bond. For example, products **3n-q** were successfully obtained with 88-92% ees. No byproducts derived from the other allylic unit were observed, even using substrate **1o** with a phenylallylic moiety. The high selectivity of allylic unit might stem from the slight stabilization difference between the formed ion intermediates from the two double bonds. Based on these results, this method provides a good pathway for the selective trifluoromethylthiolation of alkenes with multiple double bonds.

Scheme 2. Functional Group Tolerance[a]



[a]Conditions: **1** (0.1 mmol), **2** (1.5 equiv), Tf_2NH (2.0 equiv), **C5** (20 mol%), CH_2Cl_2 (2 mL) + toluene (2 mL), -78 °C, 12 h. The yields refer to isolated yields. The ee value was determined by HPLC analysis.

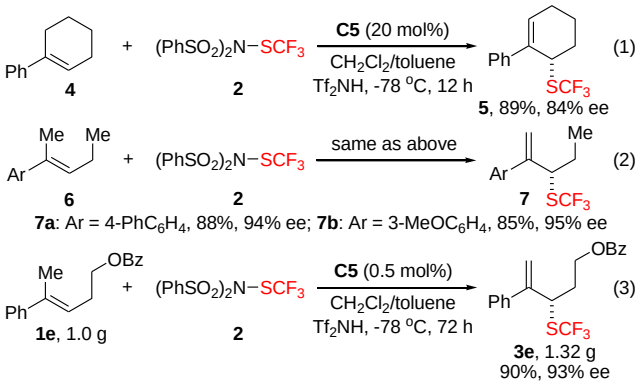
Scheme 3. Allylic Trifluoromethylthiolation of Different Alkenes[a]



[a]Conditions: As described in Scheme 2.

We turned our attention to the allylic trifluomethylthiolation of different aryl-substituted alkenes (Scheme 3). Bromo-substituted substrates bearing *para*- or *meta*-substitutent on the phenyl ring could efficiently undergo trifluoromethylthiolation to form the products in good yields with excellent enantioselectivities (e.g. **3r-x**, 70-89% yields and 91-94% ees). Electron-rich naphthyl and thiophen-3-yl alkenes also underwent the same conversion to give the corresponding products with excellent enantioselectivities (**3y**, 93% ee; **3z**, 92% ee). When 1,1-ethylphenyl-substituted alkene

was used as the substrate, the isomer products with acceptable isomer ratio *Z*/*E* = 3.3:1 were obtained. The enantioselectivities of the isomers were excellent. Similarly, the allylic trifluoromethylthiolation of ester-tethered alkenes proceeded efficiently to give the corresponding products in good yields (**3ab-al**, 70-95% yields). The enantioselectivities were excellent for most cases except for the formation of **3ak** (**3ak**, 70% ee). The decrease of enantioselectivity might ascribe the change of steric hindrance around the double bond on substrate.

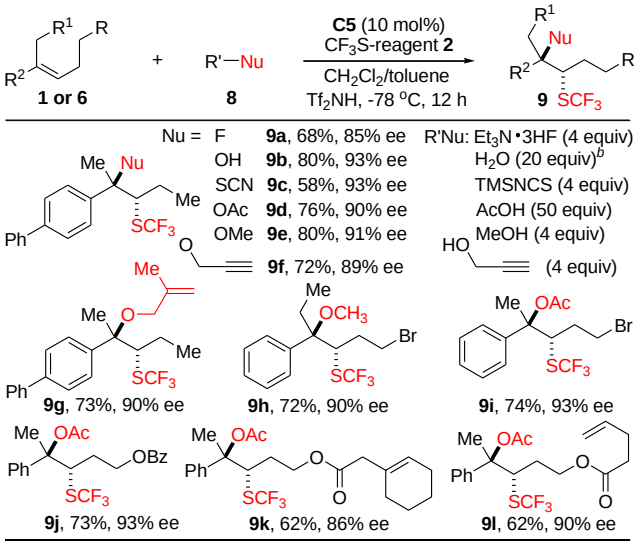


This method was extended to the trifluoromethylthiolation of pure hydrocarbons. When commerically available alkene **4** was treated with **2** under the similar conditions, product **5** was obtained in good yield with good ee (eq. 1). When alkene **6a**, **3ag**'s analogue, and **6b**, **3ah**'s analogue, were tested under the conditions, the corresponding products were obtained in high yields with almost unchanged ees in comparision to **3ag** and **3ah**, respectively (eq. 2). To evaluate reaction efficiency, the reaction was scaled up using gram-scale **1e** as the substrate in the presence of 0.5 mol% catalyst **C5** (eq. 3). The desired product was still obtained in excellent yield with the same ee, which indicates that this method has great potential for practical synthetic application.

It is rationalized that difunctionalization products could be generated in the presence of a nucleophile in reactions. Satisfactorily, when nucleophilic reagents such as Et_3N 3HF, H_2O, TMSNCS, AcOH, MeOH, propargyl alcohol and methallyl alcohol were added into reactions, the corresponding difunctionalization products were obtained in moderate to good yields with excellent enantio- and stereoselectivities (Scheme 4). Functional groups, i.e. Br–, double bond and triple bond, were well tolerated under the conditions. Selectivity for different double bond on substrates was excellent as what was observed in aforementioned allylic reaction (i.e. **9k**). It is noteworthy that this method provides a intriguing route for the synthesis of chiral fluorinated compounds with alkenes. For instance, **9a** was obtained with 85% ee. Its absolute configuration was determined by X-ray crystallagraphic analysis.

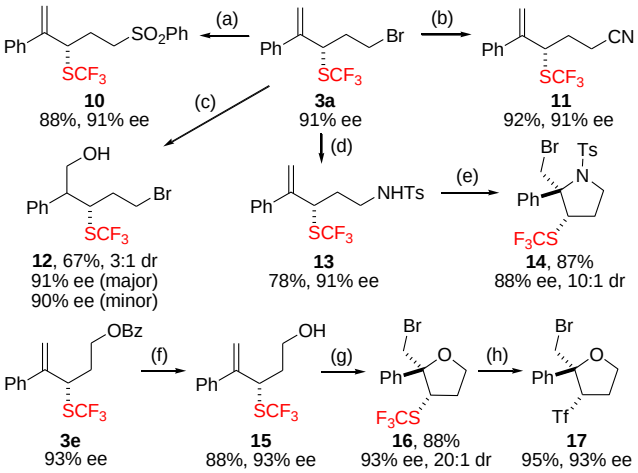
Allylic products are versatile synthetic intermediates and could be further converted to various compounds (Scheme 5). For example, **3a** bearing a removable bromo group could be efficiently transformed to sulfone **10** and nitrile **11** in high yields by substitution reactions. It also underwent hydroboration-oxidation reaction to give primary alcohol **12** in good yield with 3:1 *dr* by an *anti*-Markovnikov fashion. The bromo group on **3a** was easily replaced by TsNH group. The formed product **13** could undergo bromo-aminocyclization to give a quaternary-containing product **14** with the slight erosion of enantioselectivity. Furthermore, **3e** having a ester group could be easily deprotected to form alcohol **15** under basic conditions, then followed by selenide-catalyzed cyclization to generate cyclic ether **16** in high yield. The CF_3S group could be oxidized to Tf group, another type of useful fluorinated group. These results indicate that a series of CF_3S-compounds including important cyclic amines and ethers with a quaternary center can be easily accessed by the developed method.

Scheme 4. Intermolecular Difunctionalization of Alkenes[a]



[a]Conditions: **1** or **6** (0.1 mmol), **2** (1.5 equiv), **8** (4 equiv) unless noted, Tf_2NH (2.0 equiv), **C5** (10 mol%), AcOH (50 equiv) or MeOH (4 equiv), CH_2Cl_2 (1 mL) + toluene (1 mL), -78 °C, 12 h. The yields refer to isolated yields. The ee value was determined by HPLC analysis. All the diastereoselectivities are >99:1. [b]TMSOTf (1 equiv) instead of Tf_2NH.

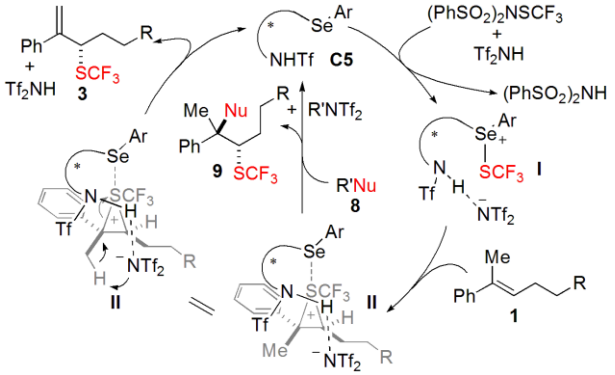
Scheme 5. Further Transformations of Products



Conditions: (a) $PhSO_2Na$, DMF, 80 °C, 12 h. (b) TMSCN, K_2CO_3, MeCN, 80 °C, 12 h. (c) BH_3, THF, rt, 12 h; then NaOH, H_2O_2, rt, 2 h. (d) $TsNH_2$, K_2CO_3, acetone, reflux, 12 h. (e) NBS, MsOH, CH_2Cl_2, rt, 12 h. (f) KOH, MeOH, rt, 12 h. (g) NBS, PhSePh, CH_2Cl_2, rt, 12 h. (h) $RuCl_3$, $NaIO_4$, MeCN/H_2O/CCl_4, rt, 14 h.

A plausible mechanism is proposed in Scheme 6.[11] Ion pair **I** is first formed after the reaction of catalyst **C5** with **2** in the presence of Tf_2NH. It interacts with alkene **1** to give thiiranium ion **II**. Intermediate **II** is relatively stable and undergoes deprotonation to generate allylic product **3** with the aid of anion as the base. When this intermediate is attacked by nucleophilic group, difunctionalization product **9** is formed. In these transformations, trisubstituted alkenes as the substrates are important to more favor the formation of thiiranium ion intermediate[14] than disubstituted alkenes.[15]

Scheme 6. Proposed Mechanism



In summary, we have developed efficient approaches toward enantioselective allylic C–H trifluoromethylthiolation and intermolecular difunctionalization of alkenes by chiral selenide catalysis. Notably, these transformations proceeded without an additional binding group assistance. As practical applications, the products were further converted into various valuable compounds and the reaction was scaled up to gram-scale with low catalyst loading (0.5 mol%). This work provides a new pathway for the synthesis of C–SCF_3 stereogenic compounds and implicates the possibility of successful enantiocontrol in other types of alkene functionalizations without a directing group assistance.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, NMR spectra of new compounds, and HPLC traces. 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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(14) When electrophilic *N*-(4-MeC_6H_4S)succinimide was used instead of $(PhSO_2)_2NSCF_3$ under the similar conditions, no C–S(4-MeC_6H_4) stereogenic product was observed (see Supporting Information). So the special property of trifluoromethylthiiranium ion might lead to the occurrence of reactions.

(15) Common 1,2-disubstituted alkenes such as 1-phenylpropene and 1-phenylbutene did not work under the similar conditions (see Supporting

Information). Furthermore, tetrasubstituted alkenes such as (*E*)-2,3-diphenyl-2-butene did not work under the standard conditions either.

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