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Chiral selenide-catalyzed enantioselective synthesis of trifluoromethylthiolated 2,5-disubstituted oxazolines†

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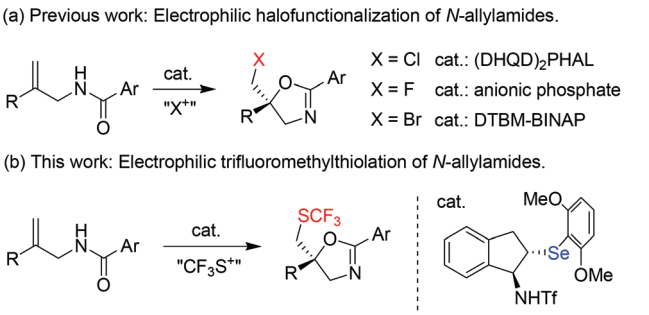
Chiral selenide-catalyzed enantioselective trifluoromethylthiolation of 1,1-disubstituted alkenes is disclosed. By this method, a variety of chiral trifluoromethylthiolated 2,5-disubstituted oxazolines were obtained in good yields with high enantioselectivities. This work not only provides a new pathway for the synthesis of chiral oxazolines, but also expands the library of chiral trifluoromethylthiolated molecules.

The oxazoline structural moiety is present in natural products, bioactive molecules, and several chiral ligands.[1,2] A number of methods have been documented for the synthesis of oxazolines.[3] Among the developed methods, electrophilic cyclization of alkenes is an efficient pathway to directly construct substituted oxazoline derivatives.[4–7] In particular, organocatalytic enantioselective electrophilic functionalization of alkenes has been applied to construct chiral substituted oxazolines (Scheme 1a).[5–7] For example, Borhan demonstrated $(DHQD)_2PHAL$-catalyzed electrophilic chlorocyclization of *N*-allylamides to synthesize chiral chloro-substituted oxazolines in 2011.[5] Toste reported an enantioselective electrophilic fluorination of *N*-allylamides to construct chiral fluorinated oxazolines using an anionic chiral phase-transfer catalyst in the same year.[6] Besides, Hamashima has developed DTBM-BINAP-catalyzed bromocyclization of *N*-allylamides to prepare chiral bromo-containing oxazolines.[7] Despite these great advances, developing new methods to construct chiral oxazolines bearing a privileged functional group is still in great demand.

The trifluoromethylthio (CF_3S) group is a privileged fluorine-containing functional group due to its strong electron-withdrawing effect and high lipophilicity (π = 1.44).[8] Incorporation of the CF_3S group into molecules can dramatically change the physical, chemical, and biological properties of these parent molecules.[9] In this scenario, numerous methods have been developed for the synthesis of various CF_3S-containing compounds by direct or indirect introduction of the CF_3S group.[10] However, in the field of direct trifluoromethylthiolation, synthesis of chiral CF_3S-containing compounds is relatively rare compared with the preparation of achiral CF_3S-containing molecules.[11–14] Historically, β-ketoesters and their analogues were utilized to construct chiral CF_3S compounds by organic small molecule- and transition metal-catalyzed enantioselective trifluoromethylthiolation in the beginning.[11] Recently, Wang developed metal-catalyzed trifluoromethylthiolation of diazo compounds *via* [2,3]-sigmatropic rearrangement of sulfonium ylides to form chiral CF_3S molecules bearing a quaternary stereogenic center.[12] More recently, Wang realized Cu-catalyzed tandem 1,4-addition/trifluoromethylthiolation of acyclic enones to prepare α-CF_3S-β-substituted ketones.[13] Furthermore, Cahard described the synthesis of chiral CF_3S molecules by substrate-controlled asymmetric induction.[14]

To expand the area for the synthesis of chiral CF_3S molecules, we have developed a new class of bifunctional chalcogenide catalysts for enantioselective trifluoromethylthiolation



Scheme 1 Catalytic construction of chiral substituted oxazolines with *N*-allylamides.

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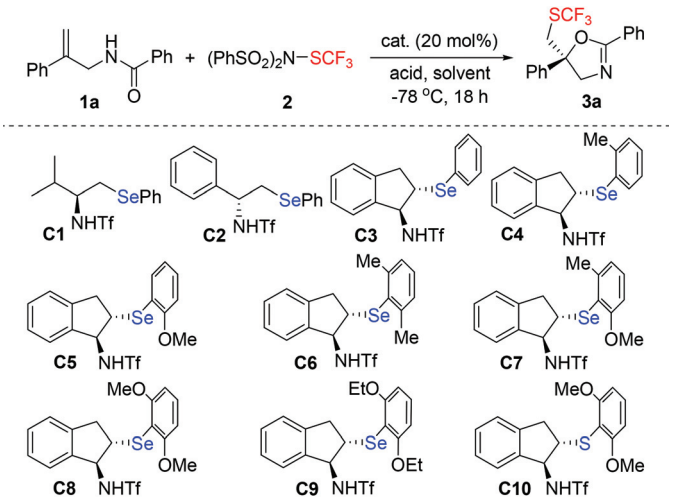
of alkenes.[15] As a result, 1,2-disubstituted and trisubstituted alkenes could be efficiently converted to the corresponding chiral CF_3S products in an intramolecular or intermolecular way. In these transformations, the racemization of the thiiranium ion intermediate through olefin-to-olefin degradation and the formation of an unstable carbocation could be overcome because of the bifunctional binding or the relative stability of the thiiranium ion intermediate. As a continuation of our interest in the synthesis of chiral CF_3S molecules, we questioned whether 1,1-disubstituted alkenes could undergo a similar enantioselective trifluoromethylthiolation to give chiral CF_3S compounds in high enantioselectivity. Specifically, if substituted *N*-allylamides are used as substrates, valuable chiral CF_3S-functionalized oxazolines would be generated. This will provide a new pathway for the synthesis of chiral functionalized oxazolines. Herein, we demonstrate that *N*-allylamides can be efficiently trifluoromethylthiolated to afford chiral CF_3S oxazolines by chiral selenide catalysis (Scheme 1b).

We commenced enantioselective trifluoromethylthiolation with *N*-(2-phenylallyl)benzamide (**1a**) as a model substrate (Table 1). Different chiral selenide catalysts were first tested in the presence of electrophilic CF_3S reagent **2** and $BF_3{\cdot}Et_2O$. To our delight, amino acid-derived selenide catalysts were effective for electrophilic cyclization of **1a** to generate the desired product **3a** with up to 50% enantioselectivity (entries 1 and 2). On the basis of our previous findings,[15] amino indanol-derived selenide catalysts were superior to those amino acid-derived for enantioselective trifluoromethylthiolation of common alkenes. Consequently, several indane scaffold-based selenide catalysts were screened (entries 3–10). It was found that **C8** with two methoxy groups on the phenyl group delivered the highest enantioselectivity for this transformation (entry 8). Next, different acids such as TMSOTf, Tf_2NH, and TfOH were examined (entries 11–13). None of them gave better results than $BF_3{\cdot}Et_2O$. Other solvents such as toluene led to the reaction being sluggish (entry 14). However, a mixed solvent consisting of CH_2Cl_2 and toluene gave the product in 93% ee (entry 15). In contrast, other electrophilic CF_3S reagents such as N-CF_3S-saccharin, prolonging reaction time, or increasing the amount of acid did not result in better results (entries 16–18).

With the optimal conditions in hand, we evaluated the substrate scope (Table 2). It was found that various *N*-allylamides could be efficiently transformed to the corresponding CF_3S oxazolines under the standard conditions. When electron-withdrawing and -neutral groups such as F–, Cl–, Br–, and Me– were placed at the *para* position of the phenyl ring attached to the double bond, the reactions proceeded well to form the products in high enantioselectivities (**3b–3e**, 83–90% ee). The functional groups such as the electron-withdrawing group (*e.g.* Cl–) and electron-donating group (*e.g.* MeO–) at the *meta* position of the phenyl group had a positive impact on this trifluoromethylthiolation (**3g**, 94% ee; **3h**, 91% ee). In general, *meta*-substituted substrates gave the products in a little higher enantioselectivity than those *para*-substituted. When electron-rich *N*-allylamide bearing a naphthyl substituent was utilized for the reaction, the desired product **3j** could still be obtained in high enantioselectivity. It is worth noting that when the naphthyl group was replaced by an alkyl group such as the pentyl or heteroaryl group such as 3-thienyl, the desired products were obtained only in low and moderate enantioselectivities. Then, we turned our attention to the effect of different aroyl groups on the nitrogen. It was found that electron-withdrawing, -neutral, and -donating groups such as Cl–, Br–, Me–, MeO–, and CF_3O– at the *para* position of the phenyl ring of the aroyl group had a slight effect on this transformation (**3k–3p**, 88–92% ee). In contrast, *meta*-substitution of the aroyl group led to slightly lower enantioselectivities (**3q**, 87% ee; **3r**, 85% ee). To determine the absolute configuration of chiral products, **3a** was converted to salt **4** under acidic conditions

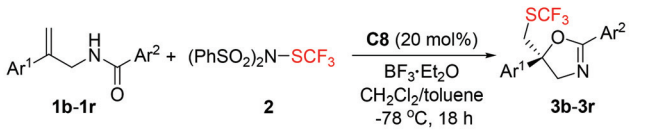
Table 1 Optimization of reaction conditions[a]

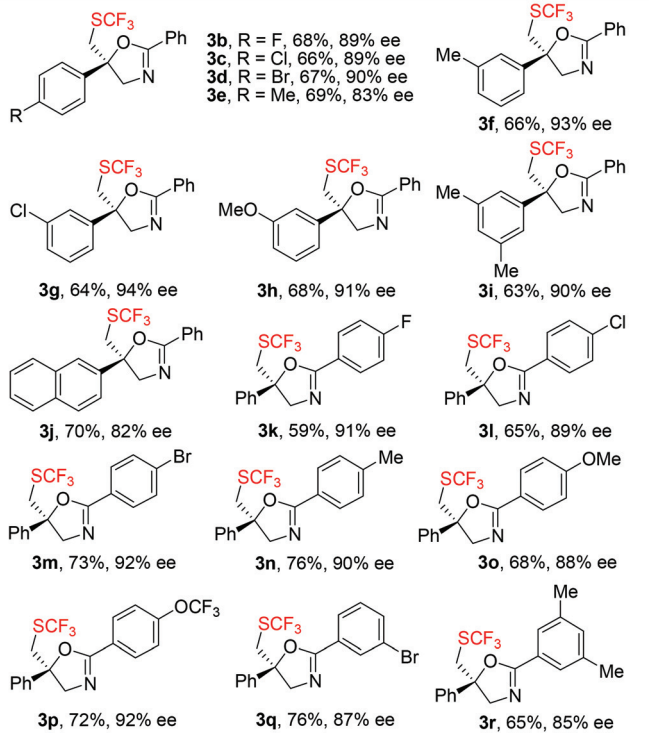


Entry	Catalyst	Solvent	Acid	Yield[b] (%)	ee[c] (%)
1	**C1**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	83	32
2	**C2**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	85	−50
3	**C3**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	42	54
4	**C4**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	58	53
5	**C5**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	86	80
6	**C6**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	35	47
7	**C7**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	88	86
8	**C8**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	89	87
9	**C9**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	91	85
10	**C10**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	37	84
11	**C8**	CH_2Cl_2	TMSOTf	52	75
12	**C8**	CH_2Cl_2	Tf_2NH	34	81
13	**C8**	CH_2Cl_2	TfOH	74	78
14	**C8**	toluene	$BF_3{\cdot}OEt_2$	<10	—
15	**C8**	CH_2Cl_2/toluene (1 : 1)	$BF_3{\cdot}OEt_2$	73 (70)	93
16[d]	**C8**	CH_2Cl_2/toluene (1 : 1)	$BF_3{\cdot}OEt_2$	18	91
17[e]	**C8**	CH_2Cl_2/toluene (1 : 1)	$BF_3{\cdot}OEt_2$	71	92
18[f]	**C8**	CH_2Cl_2/toluene (1 : 1)	$BF_3{\cdot}OEt_2$	93	88

[a] Conditions: **1a** (0.04 mmol), **2** (1.5 equiv.), catalyst (20 mol%), acid (1.5 equiv.), solvent (2.0 mL), −78 °C, 18 h. [b] Determined by ^{19}F NMR with trifluoromethylbenzene as the internal standard. The isolated yield is in the parenthesis in 0.1 mmol scale. [c] Determined by HPLC analysis. [d] *N*-CF_3S-saccharin instead of $(PhSO_2)_2N$-SCF_3. [e] 36 h. [f] $BF_3{\cdot}Et_2O$ (3.0 equiv.).

Table 2 Substrate scope[a]



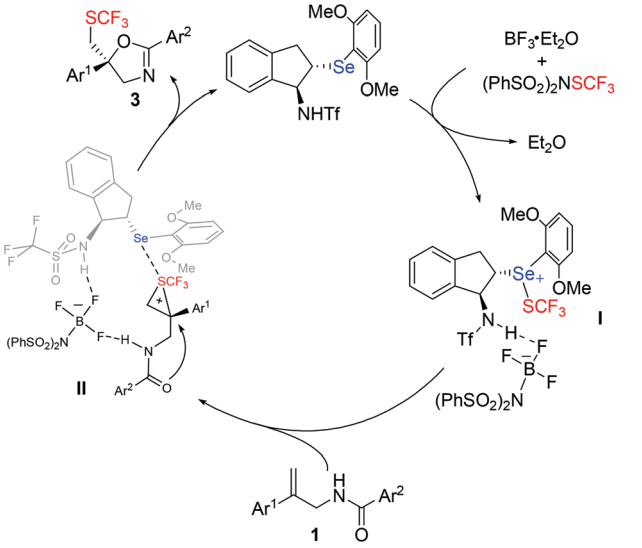


[a] Conditions: **1** (0.1 mmol), **2** (1.5 equiv.), **C8** (20 mol%), $BF_3{\cdot}Et_2O$ (1.5 equiv.), CH_2Cl_2 (2.0 mL) + toluene (2.0 mL), −78 °C, 18 h. The yield refers to the isolated yield. The ee value was determined by HPLC analysis.

(eqn (1)).[16] Compound **4** was determined to be (*R*)-configuration by X-ray crystallographic analysis.

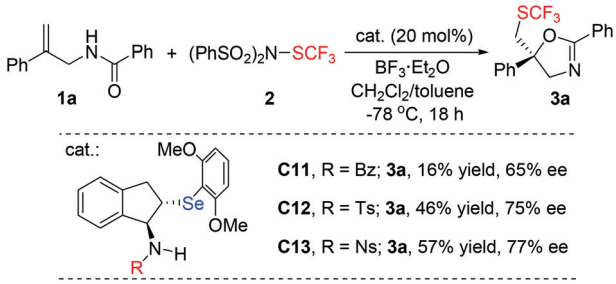
(1)

A plausible mechanism is proposed as shown in Scheme 2. In the presence of $BF_3{\cdot}Et_2O$, a cationic complex **I** is first formed by the reaction of the selenide catalyst with the electrophilic CF_3S reagent based on our former studies.[15] It then reacts with substrate **1** to generate intermediate **II**, followed by nucleophilic attack by the oxygen atom of the amide group to form product **3**. It is noted that acid $BF_3{\cdot}Et_2O$ not only helps the selenide catalyst to activate the CF_3S reagent, but also serves as a hydrogen bond acceptor that links the catalyst and the substrate.[15d] An anion bridge is proposed to set a suitable chiral environment. In the entire cycle, H-bonding interaction is essential for achieving high enantioselectivity of reaction. When catalysts with a weaker H-bonding donor were utilized,



Scheme 2 Proposed mechanism.

the enantioselectivity and reactivity of the reaction decreased evidently compared with the optimal result (eqn (2)). For example, using benzoyl-protected catalyst **C11**, the product was formed only in 16% yield with 65% ee. Moreover, catalysts with a stronger H-bonding donor such as sulfoamide (**C12** and **C13**) gave higher yields (46% and 57%) and better enantioselectivities (75% ee and 77% ee, respectively).



(2)

In summary, we have developed chiral selenide-catalyzed enantioselective trifluoromethylthiolation of *N*-allylamides. The optically active 2,5-disubstituted oxazolines bearing a CF_3S group were obtained in good yields with high enantioselectivities. This work enables enantioselective trifluoromethylthiolation of 1,1-disubstitued alkenes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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