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PII: S0040-4020(19)30199-1

DOI: https://doi.org/10.1016/j.tet.2019.02.040

Reference: TET 30163

To appear in: *Tetrahedron*

Received Date: 21 December 2018

Revised Date: 4 February 2019

Accepted Date: 18 February 2019

Please cite this article as: Hu W-F, Zhao J-Q, Chen X-Z, Zhou M-Q, Zhang X-M, Xu X-Y, Yuan W-C, Organocatalytic enantioselective sulfa-Michael addition of thiocarboxylic acids to *β*-trifluoromethyl-*α,β*-unsaturated ketones for the construction of stereogenic carbon center bearing a sulfur atom and a trifluoromethyl group, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.02.040.

Graphical Abstract

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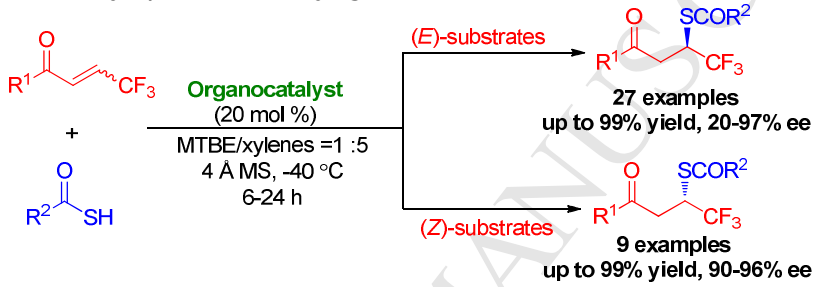

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Asymmetric sulfa-Michael addition
Organocatalysis
β-Trifluoromethyl-*α*,*β*-unsaturated ketones
Thiocarboxylic acids
Bifunctional catalysts

ABSTRACT

An organocatalyzed asymmetric sulfa-Michael addition of thiocarboxylic acids to *β*-trifluoromethyl-*α*,*β*-unsaturated ketones with a chiral bifunctional amine-squaramide as the catalyst is presented. A wide range of chiral ketone compounds bearing a sulfur atom and a trifluoromethyl group at the stereogenic carbon center could be obtained with excellent results (up to 99% yield, 97% ee) under mild conditions. The developed catalytic system is well-tolerated to both (*E*)-and (*Z*)-*β*-trifluoromethylated-*α*,*β*-unsaturated ketones.

1. Introduction

Chiral sulfur-containing motifs are widespread in a broad range of natural and unnatural biologically active products, as well as pharmaceutically important compounds.[1] On the other hand, incorporating a trifluoromethyl group into an organic molecular structure can greatly improve their physical, chemical, and biological properties, such as enhanced binding selectivity, higher lipophilicity, and increased metabolic stability.[2] With the objective to design potential new drugs, the development of efficient strategies for the enantioselective synthesis of new skeletons possessing a sulfur atom and a trifluoromethyl group together into a carbon atom is valuable. As expected, numerous biologically active compounds containing a sulfur atom and a trifluoromethyl group at the stereogenic carbon center exist in fact (Fig. 1).[3] For example, (R)-*γ*-trifluoromethyl *γ*-sulfone hydroxamate is the potent inhibitor of MNP-3.[3a] Therefore, development of simple and convenient strategies for the construction of chiral molecules bearing a sulfur atom and a trifluoromethyl group at the stereogenic carbon center is not only a necessity for biochemists and medicinal chemists, but also a challenge for organic synthetic chemists.

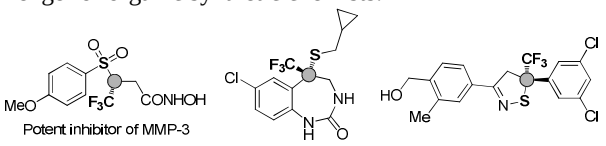

Fig. 1. Biologically active compounds bearing a sulfur atom and a trifluoromethyl group at the stereogenic carbon center.

Asymmetric sulfa-Michael addition of sulfur-centered nucleophiles to electron-deficient alkenes has received tremendous attention and has been recognized as the most efficient and straightforward method to create chiral C-S bonds.[4] Meanwhile, well-documented approaches to access optically active chiral trifluoromethylated compounds are booming in recent years.[5] Many approaches for the construction of chiral skeletons bearing a sulfur atom and a trifluoromethyl group at the stereogenic carbon center have been reported.[6] However, most of the developed methods were restricted to the sulfa-Michael addition of thiols to trifluoromethyl-*α*,*β*-unsaturated substrates. Furthermore, we found that thiocarboxylic acids,[7] a class of good sulfur-centered nucleophiles, have not been explored to react with trifluoromethyl-*α*,*β*-unsaturated substrates for the synthesis of such chiral skeletons. More recently, our group reported an efficient organocatalyzed enantioselective conjugated addition of sodium bisulfite to *β*-trifluoromethyl-*α*,*β*-unsaturated ketones to access a series of optically active sulfonic acids, bearing a tertiary stereocenter containing a trifluoromethyl group and a SO_3H group.[8] As part of our interest in asymmetric organocatalysis,[9] during our studies, we have found that *β*-trifluoromethyl-*α*,*β*-unsaturated ketones[10] are able to react with thiocarboxylic acids by using suitable chiral bifunctional organocatalysts for the direct construction of chiral molecules bearing a sulfur atom and a trifluoromethyl group at the stereogenic carbon center. It is noteworthy that the developed protocol is well-tolerated to both (*E*)-and (Z)-*β*-

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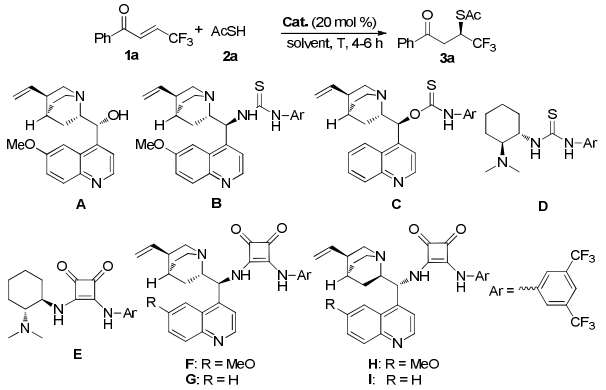
trifluoromethylated-*α*,*β*-unsaturated ketones. Herein we wish to report our research results on this subject.

2. Results and discussion

Table 1

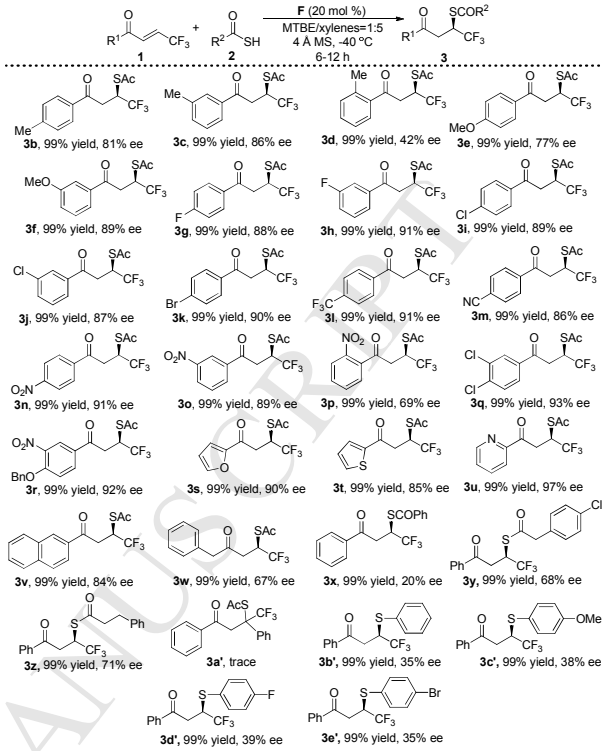
Optimization of reaction conditions[a]



entry	Cat.	solvent	T (^{o}C)	yield (%)[b]	ee (%)[c]
1	**A**	CH_2Cl_2	0	99	10
2	**B**	CH_2Cl_2	0	99	53
3	**C**	CH_2Cl_2	0	99	-6
4	**D**	CH_2Cl_2	0	99	52
5	**E**	CH_2Cl_2	0	99	-45
6	**F**	CH_2Cl_2	0	99	73
7	**G**	CH_2Cl_2	0	99	61
8	**H**	CH_2Cl_2	0	99	-66
9	**I**	CH_2Cl_2	0	99	-68
10	**F**	toluene	0	99	75
11	**F**	xylenes	0	99	77
12	**F**	MTBE	0	99	77
13	**F**	CH_3CN	0	99	28
14	**F**	ethyl acetate	0	99	51
15	**F**	MTBE/xylenes= (1:5)	0	99	79
16	**F**	MTBE/xylenes= (1:5)	-40	99	80
17	**F**	MTBE/xylenes= (1:5)	-40	99	84[d]
18	**F**	MTBE/xylenes= (1:5)	-40	99	88[d,e]

[a]Unless noted, the reactions were carried out with **1a** (0.1 mmol), **2a** (0.12 mmol), and 20 mol % catalyst in 1.0 mL of solvent at specified temperature for 4-6 h. MTBE = Methyl *tert*-butyl ether
[b]Isolated yield.
[c]Enantiomeric excess was determined by chiral HPLC analysis.
[d]5 mL of solvent was used.
[e]50 mg 4 Å MS was used.

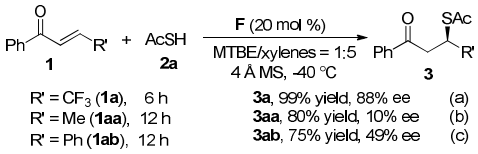
We initiated our investigation by examining the model reaction of (*E*)-*β*-trifluoromethylated-*α*,*β*-unsaturated ketone **1a** and thioacetic acid **2a** with different organocatalysts in CH_2Cl_2 at 0 ^{o}C. With 20 mol % commercial quinine **A** as catalyst, the reaction gave the desired product **3a** in 99% yield with only 10% ee (Table 1, entry 1). And then, using cinchonidine-derived thiourea bifunctional catalyst **B** for the reaction, **3a** was obtained in 99% yield with 53% ee (Table 1, entry 2). In the presence of catalyst **C**, **3a** was obtained in nearly racemate (Table 1, entry 3). Furthermore, **3a** could be obtained in 99% yield with 52% ee by employing Takemoto's catalyst **D** (Table 1, entry 4). Different squaramide catalysts, which had a longer distance between the two donor hydrogen atoms than that of thioureas,[11] were screened and quinine-derived squaramide catalyst **F** is better than other squaramide catalysts **E** and **G-H** in term of enantioselectivity, (Table 1, entry 6 *vs* entries 5 and 7-9). Afterwards, experiments were carried out with different single solvents including toluene, xylenes, MTBE, CH_3CN and ethyl acetate, and it revealed that xylenes and MTBE were better than other solvents (Table 1, entry 10-14). Despite all this, the enantioselectivity was still unsatisfactory. Therefore, we further screened different mixed solvents and found that the mixture solvent of MTBE/xylenes (*v*:*v*=1:5) gave **3a** in quantitative yield with 79% ee (Table 1, entry 15). Lowering the reaction temperature to -40 ^{o}C resulted in 80% ee (Table 1, entry 16). We were gratified to find that the ee could be elevated to 84% by reducing the substrates concentration (Table 1, entry 17). Ultimately, adding 50 mg 4 Å molecular sieves (MS) into the reaction mixture, the ee value could be further improved to 88% (Table 1, entry 18).



Scheme 1. Substrate scope of asymmetric sulfa-Michael addition of thiocarboxylic acids to (*E*)-*β*-trifluoromethylated-*α*,*β*-unsaturated ketones. Reaction conditions: the reactions were carried out with **1** (0.1 mmol), **2** (0.12 mmol), 50 mg 4 Å MS, and 20 mol % catalyst **F** in 5.0 mL of MTBE/xylenes (1:5) at -40 ^{o}C for 6-12 h. The ee values were determined by chiral HPLC.

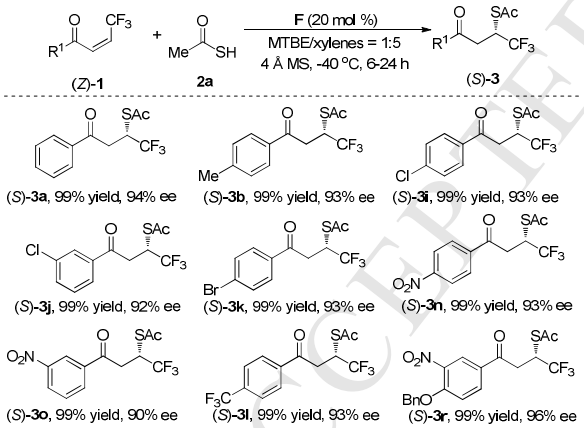
With the optimized reaction conditions in hand, the substrate scope of the enantioselective sulfa-Michael addition of thiocarboxylic acids to (*E*)-*β*-trifluoromethyl-*α*,*β*-unsaturated ketones was examined. As shown in Scheme 1, installing an electron-donating or electron-withdrawing group into the phenyl ring of (*E*)-*β*-trifluoromethyl-*α*,*β*-unsaturated ketones, regardless of their different positions, the (*E*)-*β*-trifluoromethyl-*α*,*β*-unsaturated ketones could react smoothly with thioacetic acid, delivering the corresponding products **3b-p** in quantitative yields with moderate to excellent ee values. It should be noted that the substituent at *ortho*-position of the phenyl ring of (*E*)-*β*-trifluoromethyl-*α*,*β*-unsaturated ketones gave poor enantioselectivity, possibly due to the steric hinderance effect (for products **3d** and **3p**). Moreover, products **3q** and **3r** bearing two substituent groups could be readily obtained in quantitative yields with 93% and 92% ee, respectively. Furthermore, heteroaromatic ring substituted substrates also proved to be amenable to this developed protocol, and the corresponding products **3s-u** could be obtained with satisfactory results. Introducing sterically hindered 2-naphthyl substituent group into the *α*,*β*-unsaturated ketone had no obvious effect on the reaction, yielding **3v** in 99% yield with 84% ee. Nevertheless, an aliphatic substrate could still proceed smoothly under the standard conditions and furnished product **3w** in 99% yield with 67% ee. On the other hand, a survey of thiocarboxylic acid substrates was also conducted. Thiobenzoic acid could react with **1a**, providing **3x** in 99% yield with only 20% ee. Some aliphatic substituted thiocarboxylic acids serving as nucleophiles addition to substrate **1a**, the reaction provided the products **3y-z** in quantitative yields

with moderate ee values. Unfortunately, the reaction with *β*-trifluoromethyl-*β*,*β*-disubstituted-*α*,*β*-unsaturated ketone **1a'** as substrate proceeded slowly under the standard conditions, giving **3a'** with only a trace amount, and maybe it was due to the highly steric hindrance at the *β*-position. Finally, we tried to use different thiophenols as nucleophiles to react with **1a** in the standard conditions, and the expected products **3b'-e'** were obtained with quantitative yields, but in low ee values.



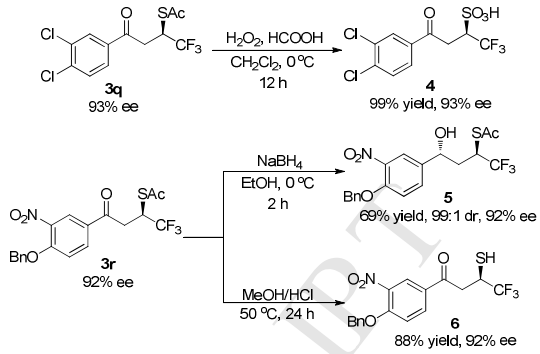
Scheme 2. Control experiments to evaluate the role of the CF_3 group in the sulfa-Michael addition reaction.

In order to evaluate the important role of the electron-withdrawing CF_3 group in the sulfa-Michael addition, some control experiments were carried out (Scheme 2). With the aforementioned standard conditions, the reaction of (*E*)-1-phenylbut-2-en-1-one (**1aa**) with **2a** became sluggish, and afforded the desired product **3aa** in 80% yield with only 10% ee along with prolonging reaction time to 12 h (Scheme 2 (b)). Similarly, changing the CF_3 group of *β*-trifluoromethyl-*α*,*β*-unsaturated ketone to phenyl group, the reaction also became sluggish, and the corresponding product **3ab** was formed in 75% yield with 49% ee after 12 h (Scheme 2 (c)). Comparing the results of the reactions of different *β*-trifluoromethyl-*α*,*β*-unsaturated ketones with **2a** (Scheme 2), we concluded that (1) carbon-carbon double bond in *α*,*β*-unsaturated ketone was better activated by the electron-withdrawing CF_3 group than methyl or phenyl group, and hence accelerated undergoing this sulfa-Michael addition;[6a-b,12] (2) it could be some extra H-bonding between the catalyst and trifluoromethyl group which maybe lead to higher stereoselectivity.[6g]



Scheme 3. Substrate scope of asymmetric sulfa-Michael addition of thioacetic acid to (*Z*)-*β*-trifluoromethylated-*α*,*β*-unsaturated ketones. Reaction conditions: the reactions were carried out with (*Z*)-**1** (0.1 mmol), **2a** (0.12 mmol), 50 mg 4 Å MS, and 20 mol % catalyst **F** in 5.0 mL of MTBE/xylenes (1:5) at -40 °C for 6-24 h. The ee values were determined by chiral HPLC.

Importantly, (*Z*)-*β*-trifluoromethylated-*α*,*β*-unsaturated ketone (*Z*)-**1a** could also react smoothly with thioacetic acid under the standard conditions, giving (*S*)-**3a** in 99% yield with 94% ee. Hence, in order to explore the effect of *cis*- and *trans*-isomers of *β*-trifluoromethylated-*α*,*β*-unsaturated ketones on the reaction, we further examined the scope of asymmetric addition of thioacetic acid to diverse (*Z*)-*β*-trifluoromethylated-*α*,*β*-unsaturated ketones under the standard conditions (Scheme 3). By incorporating various groups on the aromatic ring of (*Z*)-*β*-trifluoromethylated-*α*,*β*-unsaturated ketones, irrespective of the substitution pattern, the reaction could smoothly proceed to completion, affording the corresponding products in quantitative yields with 90-96% ee with *S*-configuration. It suggests that the catalytic system is compatible to both (*E*)-and (*Z*)-*β*-trifluoromethylated-*α*,*β*-unsaturated ketones.



Scheme 4. Different transformations of the product **3q** and **3r.**

In order to highlight the potential utility of this methodology, some transformations of the products into other compounds were performed. Product **3q** could be oxidized to sulfonic acid by using 30% H_2O_2 and formic acid, giving compound **4** in 99% yield without loss of the enantioselectivity. The reduction of the carbonyl moiety of **3r** into hydroxyl group with $NaBH_4$ delivered product **5** in 69% yield with 99:1 dr and 92% ee. The absolute configuration of **5** was assigned by comparing electronic circular dichroism (ECD) spectrum which was recorded in MeOH with the theoretically calculated results.[13] Treating **3r** with 12 M HCl in MeOH at 50 °C for 24 h, the unprotected thiol **6** could be obtained in 88% yield with 92% ee.

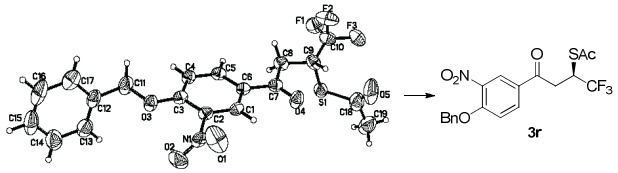


Fig. 2. X-ray crystal structure of **3r.**

The absolute configuration of product **3r** was determined to be *R*-configuration by single-crystal X-ray analysis (Fig. 2).[14] Assuming through a common reaction pathway, the absolute configuration of the other products was assigned by analogy.

3. Conclusion

In summary, we have developed an efficient organocatalyzed enantioselective sulfa-Michael addition of thiocarboxylic acids to *β*-trifluoromethyl-*α*,*β*-unsaturated ketones using the cinchona-derived squaramide bifunctional catalyst. With the developed protocol, a wide range of chiral ketone compounds bearing a sulfur atom and a trifluoromethyl group at the stereogenic carbon center could be obtained with excellent results (up to 99% yield, 97% ee). Importantly, this catalytic system was well-tolerated to both (*E*)- and (*Z*)-*β*-trifluoromethylated-*α*,*β*-unsaturated ketones. The usefulness of the protocol was also demonstrated by the conversions of the products into other compounds. Further investigations on the synthetic application of this methodology are ongoing in our laboratory.

4. Experimental section Conclusion

4.1. General

Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by TLC. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. ^{1}H NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the

solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.20 ppm, DMSO-d_6 at 39.51 ppm). Melting points were recorded on a Buchi Melting Point B-545.

4.2. General experimental procedures for asymmetric synthesis of compounds 3. In an ordinary vial equipped with a magnetic stirring bar, the compounds **1** (0.10 mmol), 50 mg dried 4 Å MS and catalyst **F** (20 mol %) were dissolved in 5.0 mL of MTBE/xylenes (1:5), stirred for 15 minutes at -40 °C and then the compounds **2** (0.12 mmol) was added. After completion of the reaction at -40 °C, the reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/ dichloromethane = 4:1~1:1) to give the desired product **3**.

4.2.1 (R)-S-(1,1,1-Trifluoro-4-oxo-4-phenylbutan-2-yl) ethanethioate (**3a**). Colorless oil; 27.4 mg; 99% yield; 88% ee; $[\alpha]_D^{20}$ = -104.1 (c 1.50, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 8.69 min (major), 7.81 min (minor); ^1H NMR (300 MHz, $CDCl_3$) δ 7.98–7.88 (m, 2H), 7.63–7.55 (m, 1H), 7.52–7.42 (m, 2H), 5.02–4.82 (m, 1H), 3.54–3.38 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 190.9, 135.8, 133.7, 128.7, 128.0, 125.9 (q, *J* = 276.0 Hz), 40.2 (q, *J* = 30.8 Hz), 36.9, 29.9; HRMS (ESI-TOF) Calcd. for $C_{12}H_{11}F_3O_2SNa$ $[M + Na]^+$: 299.0324; found: 299.0325.

(S)-S-(1,1,1-Trifluoro-4-oxo-4-phenylbutan-2-yl) ethanethioate (**3a**). Colorless oil; 27.5 mg; 99% yield; 94% ee; $[\alpha]_D^{20}$ = +107.2 (c 1.38, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 7.92 min (major), 8.93 min (minor).

4.2.2 (R)-S-(1,1,1-Trifluoro-4-oxo-4-(p-tolyl)butan-2-yl) ethanethioate (**3b**). Colorless oil; 29.1 mg; 99% yield;81% ee; $[\alpha]_D^{20}$ = -118.3 (c 1.48, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 9.24 min (major), 8.72 min (minor); ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.01–4.81 (m, 1H), 3.45 (d, *J* = 6.3 Hz, 2H), 2.41 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 190.9, 144.7, 133.5, 129.4, 128.2, 126.0 (d, *J* = 276.2 Hz), 40.4 (q, *J* = 30.9 Hz), 36.8, 30.0, 21.6; HRMS (ESI-TOF) Calcd. for $C_{13}H_{13}F_3O_2SNa$ $[M+Na]^+$: 313.0481, found: 313.0489.

(S)-S-(1,1,1-Trifluoro-4-oxo-4-(p-tolyl)butan-2-yl) ethanethioate (**3b**). Colorless oil; 29.0 mg; 99% yield; 93% ee; $[\alpha]_D^{20}$ = +124.5 (c 1.46, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 7.86 min (major), 9.70 min (minor).

4.2.3 (R)-S-(1,1,1-Trifluoro-4-oxo-4-(m-tolyl)butan-2-yl) ethanethioate (**3c**). Colorless oil; 28.7 mg; 99% yield; 86% ee; $[\alpha]_D^{20}$ = -111.2 (c 1.43, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 6.98 min (major), 6.44 min (minor); ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.46–7.32 (m, 2H), 5.01–4.84 (m, 1H), 3.47 (d, *J* = 6.3 Hz, 2H), 2.41 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 190.9, 138.7, 135.9, 134.5, 128.6, 128.6, 125.9 (d, *J* = 276.2 Hz), 125.3, 40.5 (q, *J* = 30.8 Hz), 36.9, 30.0, 21.2; HRMS (ESI-TOF) Calcd. for $C_{13}H_{13}F_3O_2SNa$ $[M+Na]^+$: 313.0481, found: 313.0485.

4.2.4 (R)-S-(1,1,1-Trifluoro-4-oxo-4-(o-tolyl)butan-2-yl) ethanethioate (**3d**). Colorless oil; 28.9 mg; 99% yield; 42% ee; $[\alpha]_D^{20}$ = -45.2 (c 1.49, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 3/97; flow rate = 0.7 mL/min; UV detection at 254 nm; t_R = 10.84 min (major), 9.59 min (minor); ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.44–7.35 (m, 1H), 7.32–7.22 (m, 2H), 4.97–4.79 (m, 1H), 3.51–3.26 (m, 2H), 2.48 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 190.9, 138.8, 136.4, 132.2, 132.0, 128.4, 125.9 (q, *J* = 276.3 Hz), 125.8, 40.6 (q, *J* = 30.8 Hz), 39.5, 30.0, 21.2; HRMS (ESI-TOF) Calcd. for $C_{13}H_{13}F_3O_2SNa$ $[M+Na]^+$: 313.0481; found: 313.0482.

4.2.5 (R)-S-(1,1,1-Trifluoro-4-(4-methoxyphenyl)-4-oxobutan-2-yl) ethanethioate (**3e**). Colorless oil; 30.4 mg; 99% yield; 77% ee; $[\alpha]_D^{20}$ = -117.2 (c 1.56, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 18.71 min (major), 13.40 min (minor); ^1H NMR (300 MHz, $CDCl_3$) δ 7.97–7.82 (m, 2H), 7.01–6.88 (m, 2H), 5.01–4.82 (m, 1H), 3.86 (s, 3H), 3.42 (d, *J* = 6.7 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 191.1, 164.0, 130.4, 129.0, 126.0 (d, *J* = 276.2 Hz), 114, 55.5, 40.4 (q, *J* = 30.8 Hz), 36.4, 30.1; HRMS (ESI-TOF) Calcd. for $C_{13}H_{13}F_3O_3SNa$ $[M+Na]^+$: 329.0430, found: 329.0431.

4.2.6 (R)-S-(1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-oxobutan-2-yl) ethanethioate (**3f**). Colorless oil; 30.1 mg; 99% yield; 89% ee; $[\alpha]_D^{20}$ = +94.3 (c 1.39, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 7.89 min (major), 9.43 min (minor); ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.43 (m, 2H), 7.42–7.33 (m, 1H), 7.17–7.06 (m, 1H), 5.01–4.81 (m, 1H), 3.84 (s, 3H), 3.54–3.37 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5, 190.9, 160.0, 137.2, 129.8, 125.9 (q, *J* = 276.3 Hz), 120.6, 120.3, 112.3, 55.4, 40.3 (q, *J* = 30.8 Hz), 37.1, 30.0; HRMS (ESI-TOF) Calcd. for $C_{13}H_{13}F_3O_3SNa$ $[M+Na]^+$: 329.0430; found: 329.0433.

4.2.7 (R)-S-(1,1,1-Trifluoro-4-(4-fluorophenyl)-4-oxobutan-2-yl) ethanethioate (**3g**). Colorless oil; 29.1 mg; 99% yield; 88% ee; $[\alpha]_D^{20}$ = -100.6 (c 1.50, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 9.75 min (major), 7.73 min (minor); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06–7.88 (m, 2H), 7.21–7.05 (m, 2H), 4.99–4.81 (m, 1H), 3.55–3.36 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 190.8, 166.1 (d, *J* = 254.6 Hz), 132.4 (d, *J* = 3.0 Hz), 130.8 (d, *J* = 9.4 Hz), 125.9 (q, *J* = 276.3 Hz), 116.0 (d, *J* = 22.0 Hz), 40.3 (q, *J* = 30.9 Hz), 36.9, 30.0; HRMS (ESI-TOF) Calcd. for $C_{12}H_{10}F_4O_2SNa$ $[M+Na]^+$: 317.0230, found: 317.0231.

4.2.8 (R)-S-(1,1,1-Trifluoro-4-(3-fluorophenyl)-4-oxobutan-2-yl) ethanethioate (**3h**). Colorless oil; 29.2 mg; 99% yield; 91% ee; $[\alpha]_D^{20}$ = -104.1 (c 1.52, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 7.55 min (major), 6.61 min (minor); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74–7.67 (m, 1H), 7.65–7.57 (m, 1H), 7.52–7.42 (m, 1H), 7.34–7.25 (m, 1H), 4.99–4.81 (m, 1H), 3.58–3.31 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5 (d, *J* = 2.2 Hz), 190.8, 162.9 (d, *J* = 247.2 Hz), 138.0 (d, *J* = 6.2 Hz), 130.5 (d, *J* = 7.7 Hz), 125.8 (q, *J* = 276.3 Hz), 123.8 (d, *J* = 3.1 Hz), 120.8 (d, *J* = 21.4 Hz), 114.9 (d, *J* = 22.4 Hz), 40.3 (q, *J* = 31.1 Hz), 37.3,

30.0; HRMS (ESI-TOF) Calcd. for $C_{12}H_{10}F_4O_2SNa$ $[M+Na]^+$: 317.0230, found: 317.0226.

4.2.9 (R)-S-(4-(4-Chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl) ethanethioate (**3i**). Colorless oil; 31.4 mg; 99% yield; 89% ee; $[\alpha]_D^{20}$ = -125.3 (c 1.55, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 11.03 min (major), 8.94 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 5.01–4.77 (m, 1H), 3.55–3.34 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 190.9, 140.4, 134.2, 129.5, 129.2, 125.8 (q, *J* = 276.3 Hz), 40.2 (q, *J* = 31.0 Hz), 37.0, 30.1; HRMS (ESI-TOF) Calcd. for $C_{12}H_{10}ClF_3O_2SNa$ $[M+Na]^+$: 332.9934; found: 332.9941.

(S)-S-(4-(4-Chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl) ethanethioate (**3i**). White solid; 31.5 mg; 99% yield; 93% ee; $[\alpha]_D^{20}$ = +86.7 (c 1.92, $CHCl_3$); m.p. = 54.9-55.7 °C; the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 8.31 min (major), 10.89 min (minor).

4.2.10 (R)-S-(4-(3-Chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl) ethanethioate (**3j**). Colorless oil; 30.6 mg; 99% yield; 87% ee; $[\alpha]_D^{20}$ = -106.8 (c 1.58, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak AD-H column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 8.61 min (major), 7.50 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.86 (m, 1H), 7.85–7.76 (m, 1H), 7.62–7.52 (m, 1H), 7.49–7.38 (m, 1H), 5.00–4.81 (m, 1H), 3.57–3.34 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 190.8, 137.4, 135.2, 133.7, 130.1, 128.2, 126.2, 125.8 (d, *J* = 276.3 Hz), 40.2 (q, *J* = 31.0 Hz), 37.2, 30.0; HRMS (ESI-TOF) Calcd. for $C_{12}H_{10}ClF_3O_2SNa$ $[M+Na]^+$: 332.9934, found: 332.9947.

(S)-S-(4-(3-Chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl) ethanethioate (**3j**). Colorless oil; 31.4 mg; 99% yield; 92% ee; $[\alpha]_D^{20}$ = +109.7 (c 1.57, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak AD-H column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 6.95 min (major), 8.30 min (minor).

4.2.11 (R)-S-(4-(4-Bromophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl) ethanethioate (**3k**). White solid; 35.0 mg; 99% yield; 90% ee; $[\alpha]_D^{20}$ = -108.1 (c 1.85, $CHCl_3$); m.p. = 69.1-70.1 °C; the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 11.93 min (major), 9.12 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.73 (m, 2H), 7.67–7.56 (m, 2H), 5.08–4.71 (m, 1H), 3.57–3.27 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 190.8, 134.6, 132.1, 129.5, 129.1, 125.8 (q, *J* = 276.3 Hz), 40.3 (q, *J* = 30.9 Hz), 37.0, 30.0; HRMS (ESI-TOF) Calcd. for $C_{12}H_{10}BrF_3O_2SNa$ $[M+Na]^+$: 376.9429, found: 376.9440.

(S)-S-(4-(4-Bromophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl) ethanethioate (**3k**). White solid; 35.1 mg; 99% yield; 93% ee; $[\alpha]_D^{20}$ = +98.1 (c 2.34, $CHCl_3$); m.p. = 71.2-71.7 °C; the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 8.84 min (major), 11.73 min (minor)。

4.2.12 (R)-S-(1,1,1-Trifluoro-4-oxo-4-(4-(trifluoromethyl)phenyl)butan-2-yl) ethanethioate (**3l**). Colorless oil; 34.1 mg; 99% yield; 91% ee; $[\alpha]_D^{20}$ = -84.6 (c 1.77, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 10.24 min (major), 7.95 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 5.03–4.79 (m, 1H), 3.61–3.40 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 190.8, 138.6, 135.1 (q, *J* = 32.9 Hz), 128.5, 125.9 (q, *J* = 3.8 Hz), 125.8 (q, *J* = 276.2 Hz), 123.4 (q, *J* = 271.1 Hz), 40.3 (q, *J* = 31.3 Hz), 37.4, 30.0 (d, *J* = 2.6 Hz); HRMS (ESI-TOF) Calcd. for $C_{13}H_{10}F_6O_2SNa$ $[M+Na]^+$: 367.0198; found: 367.0194.

(S)-S-(1,1,1-Trifluoro-4-oxo-4-(4-(trifluoromethyl)phenyl)butan-2-yl) ethanethioate (**3l**). Colorless oil; 34.2 mg; 99% yield; 93% ee; $[\alpha]_D^{20}$ = +86.1 (c 1.71, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 7.63 min (major), 9.92 min (minor).

4.2.13 (R)-S-(4-(4-Cyanophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl) ethanethioate (**3m**). Colorless oil; 29.7 mg; 99% yield; 86% ee; $[\alpha]_D^{20}$ = -97.9 (c 1.49, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 25.60 min (major), 23.51 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08–7.96 (m, 2H), 7.85–7.71 (m, 2H), 4.99–4.77 (m, 1H), 3.61–3.34 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6, 190.7, 138.7, 132.6, 128.5, 125.7 (q, *J* = 276.3 Hz), 117.6, 117.1, 40.2 (q, *J* = 31.1 Hz), 37.5, 30.0; HRMS (ESI-TOF) Calcd. for $C_{13}H_{10}F_3NO_2SNa$ $[M+Na]^+$: 324.0277, found: 324.0283.

4.2.14 (R)-S-(1,1,1-Trifluoro-4-(4-nitrophenyl)-4-oxobutan-2-yl) ethanethioate (**3n**). White solid; 31.8 mg; 99% yield; 91% ee; $[\alpha]_D^{20}$ = -121.1 (c 1.49, $CHCl_3$); m.p. = 109.2-110.1 °C; the enantiomeric excess was determined by HPLC on Chiralpak IC column: *dichloromethane*/*n*-hexane = 30/70; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 22.07 min (major), 19.69 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41–8.27 (m, 2H), 8.17–8.02 (m, 2H), 5.06–4.57 (m, 1H), 3.82–3.32 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 190.7, 150.8, 140.2, 129.2,125.7 (q, *J* = 276.5), 124.1, 40.2 (q, *J* = 31.1 Hz), 37.8, 30.1; HRMS (ESI-TOF) Calcd. for $C_{12}H_{10}F_3NO_4SNa$ $[M+Na]^+$: 344.0175, found: 344.0166.

(S)-S-(1,1,1-Trifluoro-4-(4-nitrophenyl)-4-oxobutan-2-yl) ethanethioate (**3n**). White solid; 31.8 mg; 99% yield; 93% ee; $[\alpha]_D^{20}$ = +132.9 (c 0.92, $CHCl_3$); m.p. = 108.5-108.9 °C; the enantiomeric excess was determined by HPLC on Chiralpak IC column: *dichloromethane*/*n*-hexane = 30/70; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 19.16 min (major), 23.43 min (minor).

4.2.15 (R)-S-(1,1,1-Trifluoro-4-(3-nitrophenyl)-4-oxobutan-2-yl) ethanethioate (**3o**). Colorless oil; 31.9 mg; 99% yield; 89% ee; $[\alpha]_D^{20}$ = -108.6 (c 1.61, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 17.57 min (major), 15.64 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82–8.67 (m, 1H), 8.55–8.37 (m, 1H), 8.34–8.21 (m, 1H), 7.80–7.64 (m, 1H), 5.00–4.83 (m, 1H), 3.65–3.43 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 190.7, 148.5, 137.1, 133.6, 130.2, 128.0, 125.7 (d, *J* = 276.5 Hz), 123.0, 40.2 (q, *J* = 31.1 Hz), 37.5, 30.1; HRMS (ESI-TOF) Calcd. for $C_{12}H_{10}F_3NO_4SNa$ $[M+Na]^+$: 344.0175, found: 344.0177.

(S)-S-(1,1,1-Trifluoro-4-(3-nitrophenyl)-4-oxobutan-2-yl) ethanethioate (**3o**). Colorless oil; 31.8 mg; 99% yield; 90% ee; $[\alpha]_D^{20}$ = +105.7 (c 1.61, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 15.59 min (major), 17.69 min (minor).

4.2.16 (R)-S-(1,1,1-Trifluoro-4-(2-nitrophenyl)-4-oxobutan-2-yl) ethanethioate (**3p**). Colorless oil; 31.9 mg; 99% yield; 69% ee; $[\alpha]_D^{20}$ = -42.7 (c 1.65, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IC column: ethanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 18.05 min (major), 13.30 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.80–7.71 (m, 1H), 7.69–7.60 (m, 1H), 7.40 (dd, *J* = 7.5, 1.3 Hz, 1H), 4.96–4.72 (m, 1H), 3.43 (dd, *J* = 18.5, 4.1 Hz, 1H), 3.24 (dd, *J* = 18.5, 9.2 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 190.9, 145.6, 136.5, 134.4, 131.1, 127.5, 125.6 (q, *J* = 276.4 Hz), 124.6, 41.0 (d, *J* = 1.6 Hz), 39.9 (q, *J* = 31.1 Hz), 30.0; HRMS (ESI-TOF) Calcd. for $C_{12}H_{10}F_3NO_4SNa$ $[M+Na]^+$: 344.0175, found: 344.0174.

4.2.17 (R)-S-(4-(3,4-Dichlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl) ethanethioate (**3q**). White solid; 34.2 mg; 99% yield; 93% ee; $[\alpha]_D^{20}$ = -119.8 (c 1.58, $CHCl_3$); m.p.= 89.1-90.2 °C ; the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 8.71 min (major), 7.91 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.0 Hz, 1H), 7.75 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 4.98–4.79 (m, 1H), 3.53–3.30 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6, 190.8, 138.5, 135.3, 133.6, 131.0, 130.1, 127.0, 125.7 (d, *J* = 276.3 Hz), 40.2 (q, *J* = 31.1 Hz), 37.1, 30.1; HRMS (ESI-TOF) Calcd. for $C_{12}H_9Cl_2F_3O_2SNa$ $[M+Na]^+$: 366.9545, found: 366.9557.

4.2.18 (R)-S-(4-(4-(benzyloxy)-3-nitrophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl) ethanethioate (**3r**). White solid; 42.1 mg; 99% yield; 92% ee; $[\alpha]_D^{20}$ = -104.9 (c 2.07, $CHCl_3$); m.p.= 95.8-96.4 °C ; the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 54.80 min (major), 60.00 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.2 Hz, 1H), 8.09 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.51–7.30 (m, 5H), 7.22 (d, *J* = 8.9 Hz, 1H), 5.32 (s, 2H), 4.99–4.80 (m, 1H), 3.53–3.34 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 190.7, 155.6, 139.8, 134.5, 133.6, 128.8, 128.5, 128.4, 126.9, 125.8, 125.8 (q, *J* = 276.3 Hz), 114.89, 71.5, 40.2 (q, *J* = 31.0 Hz), 36.9, 30.0; HRMS (ESI-TOF) Calcd. for $C_{19}H_{16}F_3NO_5SNa$ $[M+Na]^+$: 450.0593; found: 450.0575.

(S)-S-(4-(4-(benzyloxy)-3-nitrophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl) ethanethioate (**3r**). White solid; 42.3 mg; 99% yield; 96% ee; $[\alpha]_D^{20}$ = +98.6 (c 2.12, $CHCl_3$); m.p.= 95.8-96.7 °C ; the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 59.83 min (major), 56.47 min (minor).

4.2.19 (R)-S-(1,1,1-Trifluoro-4-(furan-2-yl)-4-oxobutan-2-yl) ethanethioate (**3s**). Colorless oil; 26.4 mg; 99% yield; 90% ee; $[\alpha]_D^{20}$ = -115.3 (c 1.38, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 11.77 min (major), 9.38 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.55 (m, 1H), 7.24 (d, *J* = 3.6 Hz, 1H), 6.60–6.51 (m, 1H), 4.95–4.76 (m, 1H), 3.43–3.20 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 182.8, 151.9, 146.9, 125.8 (q, *J* = 276.4 Hz), 117.8, 112.6, 40.0 (q, *J* = 31.1 Hz), 36.7, 30.0; HRMS (ESI-TOF) Calcd. for $C_{10}H_9F_3O_3SNa$ $[M+Na]^+$: 289.0117, found: 289.0112.

4.2.20 (R)-S-(1,1,1-Trifluoro-4-oxo-4-(thiophen-2-yl)butan-2-yl) ethanethioate (**3t**). Colorless oil; mg; 99% yield; 85% ee; $[\alpha]_D^{20}$ = -103.2 (c 1.44, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 10.91 min (major), 9.27 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.69 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.15 (dd, *J* = 4.9, 3.9 Hz, 1H), 4.99–4.75 (m, 1H), 3.51–3.31 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 186.5, 143.0, 134.6, 132.4, 128.3, 125.8 (d, *J* = 276.5 Hz), 40.41 (q, *J* = 31.0 Hz), 37.5, 30.0; HRMS (ESI-TOF) Calcd. for $C_{10}H_9F_3O_2S_2Na$ $[M+Na]^+$: 304.9888; found: 304.9893.

4.2.21 (R)-S-(1,1,1-Trifluoro-4-oxo-4-(pyridin-2-yl)butan-2-yl) ethanethioate (**3u**). Colorless oil; 27.5 mg; 99% yield; 97% ee; $[\alpha]_D^{20}$ = -115.9 (c 1.33, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 8.21 min (major), 6.97 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71–8.63 (m, 1H), 8.06–7.98 (m, 1H), 7.89–7.77 (m, 1H), 7.55–7.45 (m, 1H), 5.07–4.80 (m, 1H), 3.82 (dd, *J* = 18.6, 9.4 Hz, 1H), 3.69 (dd, *J* = 18.6, 4.4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7, 191.2, 152.2, 149.0, 137.0, 127.7, 125.9 (d, *J* = 276.3 Hz), 122.0, 40.2 (q, *J* = 31.0 Hz), 36.46 (d, *J* = 1.2 Hz), 30.0; HRMS (ESI-TOF) Calcd. for $C_{11}H_{10}F_3NO_2SNa$ $[M+Na]^+$: 300.0277; found: 300.0271.

4.2.22 (R)-S-(1,1,1-Trifluoro-4-(naphthalen-2-yl)-4-oxobutan-2-yl) ethanethioate (**3v**). Colorless oil; 32.4 mg; 99% yield; 84% ee; $[\alpha]_D^{20}$ = -184.2 (c 1.57, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 11.60 min (major), 9.58 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.05–7.93 (m, 2H), 7.94–7.83 (m, 2H), 7.68–7.51 (m, 2H), 5.09–4.93 (m, 1H), 3.71–3.56 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 190.9, 135.8, 133.3, 132.4, 129.9, 129.6, 128.9, 128.7, 127.8, 127.0, 126.0 (q, *J* = 276.3 Hz), 123.52, 40.5 (q, *J* = 30.9 Hz), 37.0, 30.0; HRMS (ESI-TOF) Calcd. for $C_{16}H_{13}F_3O_2SNa$ $[M+Na]^+$: 349.0481; found: 349.0482.

4.2.23 (R)-S-(1,1,1-Trifluoro-4-oxo-5-phenylpentan-2-yl) ethanethioate (**3w**). Colorless oil; 28.7 mg; 99% yield; 67% ee; $[\alpha]_D^{20}$ = -51.6 (c 1.40, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 7.02 min (major), 6.42 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.25 (m, 3H), 7.23–7.14 (m, 2H), 4.78–4.60 (m, 1H), 3.72 (s, 2H), 3.00 (dd, *J* = 18.1, 4.4 Hz, 1H), 2.86 (dd, *J* = 18.1, 9.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 190.8, 132.9, 129.4, 128.9, 127.4, 125.6 (q, *J* = 276.3 Hz), 50.0, 39.9 (q, *J* = 31.0 Hz), 39.8, 30.0; HRMS (ESI-TOF) Calcd. for $C_{13}H_{13}F_3O_2SNa$ $[M+Na]^+$: 313.0481, found: 313.0476.

4.2.24 (R)-S-(1,1,1-Trifluoro-4-oxo-4-phenylbutan-2-yl) benzothioate (**3x**). Colorless oil; 33.6 mg; 99% yield; 20% ee; $[\alpha]_D^{20}$ = -8.0 (c 1.83, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 17.14 min (major), 15.88 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06–7.88 (m, 4H), 7.66–7.54 (m, 2H), 7.53–7.39 (m, 4H), 5.31–5.15 (m, 1H), 3.61 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 187.2, 136.0, 135.7, 134.1, 133.7, 128.8, 128.8, 128.1, 127.6, 126.1 (q, *J* = 276.5 Hz), 40.0 (t, *J* = 30.8 Hz), 37.4; HRMS (ESI-TOF) Calcd. for $C_{17}H_{13}F_3O_2SNa$ $[M+Na]^+$: 361.0481, found: 361.0464.

4.2.25 (R)-S-(1,1,1-Trifluoro-4-oxo-4-phenylbutan-2-yl) 2-(4-chlorophenyl)ethanethioate (**3y**). colorless oil; 38.4 mg; 99% yield; 68% ee; $[\alpha]_D^{20}$ = -38.3 (c 2.03, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-

propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 15.60 min (major), 10.05 min (minor); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 7.5 Hz, 2H), 7.65–7.56 (m, 1H), 7.52–7.44 (m, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 5.02–4.86 (m, 1H), 3.84 (s, 2H), 3.55–3.38 (m, 2H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 193.5, 192.5, 135.8, 133.8, 133.7, 131.0, 130.8, 128.9, 128.8, 128.0, 125.8 (q, *J* = 278.2 Hz), 49.0, 40.3 (q, *J* = 31.0 Hz), 36.9; HRMS (ESI-TOF) Calcd. for $C_{18}H_{14}ClF_3O_2SNa$ $[M+Na]^+$:409.0253, found:409.0266.

4.2.26 (R)-S-(1,1,1-Trifluoro-4-oxo-4-phenylbutan-2-yl) 3-phenylpropanethioate (**3z**). colorless oil; 36.4 mg; 99% yield; 71% ee; $[\alpha]_D^{20}$ = -45.8 (c 2.11, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 10.48 min (major), 8.10 min (minor); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.99–7.91 (m, 2H), 7.67–7.58 (m, 1H), 7.55–7.46 (m, 2H), 7.33–7.25 (m, 2H), 7.24–7.15 (m, 3H), 5.07–4.91 (m, 1H), 3.59–3.37 (m, 2H), 3.07–2.97 (m, 2H), 2.96–2.86 (m, 2H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 193.8, 193.6, 139.5, 135.9, 133.8, 128.8, 128.5, 128.3, 128.1, 126.4, 125.9 (q, *J* = 278.1 Hz), 45.2, 40.0 (q, *J* = 31.1 Hz), 37.0, 31.1; HRMS (ESI-TOF) Calcd. for $C_{19}H_{17}F_3O_2SNa$ $[M+Na]^+$:389.0799, found:389.0815.

4.2.27 (R)-4,4,4-trifluoro-1-phenyl-3-(phenylthio)butan-1-one (**3b'**). colorless oil; 30.8 mg; 99% yield; 35% ee; $[\alpha]_D^{20}$ = -17.3 (c 0.78, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak AD-H column: ethanol/*n*-hexane = 1/99; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 8.43 min (major), 10.19 min (minor); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.05–7.91 (m, 2H), 7.70–7.57 (m, 3H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.38–7.29 (m, 3H), 4.41– 4.25 (m, 1H), 3.50 (dd, *J* = 18.0, 9.8 Hz, 1H), 3.34 (dd, *J* = 18.0, 3.4 Hz, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 194.4, 136.3, 134.0, 133.7, 132.5, 129.2, 128.8, 128.8, 128.1, 126.8 (q, *J* = 276.7 Hz), 47.1 (q, *J* = 29.4 Hz), 37.7; HRMS (ESI-TOF) Calcd. for $C_{16}H_{13}F_3OSNa$ $[M+Na]^+$: 333.0531, found: 333.0521.

4.2.28 (R)-4,4,4-Trifluoro-3-((4-methoxyphenyl)thio)-1-phenylbutan-1-one (**3c'**). colorless oil; 33.9 mg; 99% yield; 38% ee; $[\alpha]_D^{20}$ = -26.1 (c 1.60, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak AD-H column: ethanol/*n*-hexane = 1/99; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 16.05 min (major), 19.97 min (minor); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04–7.95 (m, 2H), 7.68–7.47 (m, 5H), 6.93–6.82 (m, 2H), 4.25–4.10 (m, 1H), 3.83 (s, 3H), 3.48 (dd, *J* = 17.9, 10.0 Hz, 1H), 3.30 (dd, *J* = 17.9, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 194.6, 160.6, 137.0, 136.4, 133.8, 128.9, 128.2, 127.0 (q, *J* = 278.4 Hz), 122.6, 114.7, 55.4, 47.6 (q, *J* = 29.2 Hz), 37.5; HRMS (ESI-TOF) Calcd. for $C_{17}H_{15}F_3O_2SNa$ $[M+Na]^+$: 363.0637, found: 363.0631.

4.2.29 (R)-4,4,4-Trifluoro-3-((4-fluorophenyl)thio)-1-phenylbutan-1-one (**3d'**). colorless oil; 32,6 mg; 99% yield; 39% ee; $[\alpha]_D^{20}$ = -32.8 (c 1.60, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak AD-H column: ethanol/*n*-hexane = 1/99; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 8.10 min (major), 12.12 min (minor); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03–7.97 (m, 2H), 7.70–7.61 (m, 3H), 7.59–7.47 (m, 2H), 7.10–6.99 (m, 2H), 4.31–4.16 (m, 1H), 3.50 (dd, *J* = 18.0, 10.2 Hz, 1H), 3.35 (dd, *J* = 18.0, 3.0 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 194.4, 163.4 (d, *J* = 249.7 Hz), 136.8 (d, *J* = 8.5 Hz), 136.2, 133.9, 128.9, 128.2, 127.6 (d, *J* = 3.5 Hz), 126.9 (q, *J* = 276 Hz), 116.3 (d, *J* = 22.0 Hz), 47.8 (q, *J* = 30.3 Hz), 37.5; HRMS (ESI-TOF) Calcd. for $C_{16}H_{12}F_4OSNa$ $[M+Na]^+$: 351.0437, found: 351.0439.

4.2.30 (R)-3-((4-Bromophenyl)thio)-4,4,4-trifluoro-1-phenylbutan-1-one (**3e'**). colorless oil; 38.7 mg; 99% yield; 35% ee; $[\alpha]_D^{20}$ = -31.3 (c 1.80, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: ethanol/*n*-hexane = 1/99; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 9.69 min (major), 14.39 min (minor); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06–7.93 (m, 2H), 7.69–7.62 (m, 1H), 7.58–7.45 (m, 6H), 4.37–4.22 (m, 1H), 3.52 (dd, *J* = 18.0, 10.1 Hz, 1H), 3.37 (dd, *J* = 18.0, 3.1 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 194.3, 136.2, 135.6, 133.9, 132.4, 131.8, 128.9, 128.2, 126.8 (q, *J* = 277 Hz), 123.4, 47.4 (q, *J* = 29.8 Hz), 37.6; HRMS (ESI-TOF) Calcd. for $C_{16}H_{12}BrF_3OSNa$ $[M+Na]^+$: 410.9637, found: 410.9650.

4.2.31 (S)-S-(4-Oxo-4-phenylbutan-2-yl) ethanethioate (**3aa**). Colorless oil; 17.8 mg; 80% yield; 10% ee; $[\alpha]_D^{20}$ = -5.9 (c 1.20, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IC column: ethanol /*n*-hexane = 2/98; flow rate = 0.7 mL/min; UV detection at 254 nm; t_R = 13.07 min (major), 11.87 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02–7.91 (m, 2H), 7.61–7.51 (m, 1H), 7.50–7.41 (m, 2H), 4.17–4.00 (m, 1H), 3.43 (dd, *J* = 16.7, 5.0 Hz, 1H), 3.12 (dd, *J* = 16.7, 8.3 Hz, 1H), 2.29 (s, 3H), 1.39 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 195.7, 136.5, 133.3, 128.6, 128.1, 45.0, 35.2, 30.6, 20.3; HRMS (ESI-TOF) Calcd. for $C_{12}H_{14}O_2SNa$ $[M+Na]^+$: 245.0607, found: 245.0608.

4.2.32 (R)-S-(3-Oxo-1,3-diphenylpropyl) ethanethioate (**3ab**). White solid; 21.4 mg; 75% yield; 49% ee; $[\alpha]_D^{20}$ = -83.3 (c 1.28, $CHCl_3$); m.p.= 90.4-91.3 °C ; the enantiomeric excess was determined by HPLC on Chiralpak IC column: *i*-propanol/*n*-hexane = 1/99; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 44.48 min (major), 31.36 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99–7.89 (m, 2H), 7.60–7.51 (m, 1H), 7.48–7.41 (m, 2H), 7.41–7.34 (m, 2H), 7.33–7.17 (m, 3H), 5.28 (dd, *J* = 7.9, 6.5 Hz, 1H), 3.77–3.58 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 194.4, 140.5, 136.4, 133.2, 128.6, 128.0, 127.7, 127.5, 44.5, 43.5, 30.3; HRMS (ESI-TOF) Calcd. for $C_{17}H_{16}O_2SNa$ $[M+Na]^+$: 307.0763, found: 307.0765.

4.3 Procedure for the oxidation of 3q. A mixture of formic acid (98%, 1 mL) and hydrogen peroxide (30%, 0.4 mL) was stirred at 0 °C for 30 min (peroxyformic acid solution was prepared in situ), then a solution of **3q** (89.7 mg, 0.26 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred at room temperature for 12 h until completion (monitored by TLC) and water (5 mL) was added. The mixture was washed with dichloromethane (5×3 mL). The aqueous solution was dried first under reduced pressure and finally in high vacuum. Finally, the crude product was chromatographed on silica gel eluting with DCM/MeOH = 20:1 ~ 10:1 to afford the desired sulfonic acid **4**.

4.3.1 (R)-4-(3,4-Dichlorophenyl)-1,1,1-trifluoro-4-oxobutane-2-sulfonic acid (**4**). Pale brown oil; 90.4 mg; 99% yield; 93% ee; $[\alpha]_D^{20}$ = +1.2 (c 1.96, EtOH); the enantiomeric excess was determined by HPLC on Chiralpak IA column after esterification with $CH_3C(OCH_3)_3$: *i*-propanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 11.20 min (major), 11.94 min (minor); ^{1}H NMR (300 MHz, D_2O) δ 7.77 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 4.54–4.39 (m, 1H), 3.67 (dd, *J* = 18.6, 4.8 Hz, 1H), 3.42 (dd, *J* = 18.6, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 137.8, 134.8, 132.6, 130.6, 129.60 127.3, 123.9 (q, *J* = 279.5 Hz), 57.0 (q, *J* = 27.7 Hz), 34.9; HRMS (ESI-TOF) Calcd. for $C_{10}H_6Cl_2F_3O_4S$ $[M-H]^-$: 348.9321, found: 348.9330.

4.4 Procedure for the reduction of 3r. 3r (85.7 mg, 0.20 mmol) was dissolved in 1 mL of ethanol and cooled to 0 °C on an ice

bath. $NaBH_4$ (4.7 mg, 0.12 mmol) was added portion wise. The reaction mixture was stirred for 2 h at the same temperature. After completion of the reaction, ethanol was evaporated off and brine (3 ml) was added to the residue. The mixture was extracted with ethyl acetate (2×5 ml) and concentrated. The crude products were purified by column chromatography with petroleum ether/ethyl acetate = 20:1~10:1 to afford the desired product **5**.

4.4.1 S-((2R,4R)-4-(4-(benzyloxy)-3-nitrophenyl)-1,1,1-trifluoro-4-hydroxybutan-2-yl) ethanethioate (**5**). Light yellow green oil; 59.5 mg; 69% yield; 92% ee; 99:1 dr; $[\alpha]_D^{20}$ = -10.2 (c 0.94, $CHCl_3$); the enantiomeric excess was determined by HPLC on Chiralpak IA column: ethanol/*n*-hexane = 5/95; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 26.48 min (major), 19.70 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 2.2 Hz, 1H), 7.55 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.47–7.33 (m, 5H), 7.14 (d, *J* = 8.7 Hz, 1H), 6.00 (dd, *J* = 8.5, 6.5 Hz, 1H), 5.24 (s, 2H), 2.99–2.83 (m, 1H), 2.47–2.34 (m, 1H), 2.26–2.14 (m, 1H), 2.07 (s, 3H), 1.93 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 152.1, 140.2, 135.2, 132.7, 130.9, 128.7, 128.3, 126.9, 125.7 (q, *J* = 277.6 Hz), 124.1, 115.4, 72.0, 71.3, 38.9 (q, *J* = 31.5 Hz), 36.8, 21.0; HRMS (ESI-TOF) Calcd. for $C_{19}H_{18}F_3NO_5SNa$ $[M+Na]^+$: 452.0750, found: 452.0745.

4.5 Procedure for the deacetylation of 3r. 3r (69.3 mg, 0.16 mmol) was dissolved in 2 mL of methanol/DCM (v/v=1/1) at room temperature. To the solution was added 12M aqueous HCl (0.5 mL). The reaction mixture was stirred at 50 °C for 24 h until the disappearance of the starting material was detected by TLC. After the solvent was evaporated the residue was dissolved in dichloromethane and dried over Na_2SO_4. After concentration under reduced pressure the crude product was purified by column chromatography (petroleum ether/DCM=2/1~1/1, v/v) to afford the desired product **6**.

4.5.1 *(R)-1-(4-(benzyloxy)-3-nitrophenyl)-4,4,4-trifluoro-3-mercaptobutan-1-one* (**6**). Off white solid; 54.6 mg; 88% yield; 92% ee; $[\alpha]_D^{20}$ = +7.3 (c 2.73, $CHCl_3$); m.p.= 138.6-139.4 °C; the enantiomeric excess was determined by HPLC on Chiralpak IC column: *dichloromethane*/*n*-hexane = 30/70; flow rate = 1.0 mL/min; UV detection at 254 nm; t_R = 28.43 min (major), 25.62 min (minor); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 2.0 Hz, 1H), 8.12 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.49–7.34 (m, 5H), 7.22 (d, *J* = 8.9 Hz, 1H), 4.16–3.98 (m, 1H), 3.42 (qd, *J* = 17.8, 6.3 Hz, 2H), 2.15 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 191.3, 155.7, 139.8, 134.5, 133.7, 128.9, 128.6, 126.9, 126.0 (q, *J* = 277.3 Hz), 125.9, 114.9, 71.5, 40.6, 36.7 (q, *J* = 31.7 Hz); HRMS (ESI-TOF) Calcd. for $C_{17}H_{14}F_3NO_4SNa$ $[M+Na]^+$: 408.0493, found: 408.0484.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (No. 21572223, 21572224, 21602217, 21871252), Sichuan Youth Science and Technology Foundation (2016JQ0024).

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13 See Supporting Information for more details.

14 CCDC-1882017 (**3r**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.