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Chiral squaramide-catalysed one-pot enantioselective sulfa-Michael addition/thioesterification of thiols with α,β-unsaturated *N*-acylated succinimides†

Bo-Liang Zhao and Da-Ming Du*

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A novel highly enantioselective one-pot dithiolation through sulfa-Michael addition/thioesterification of thiols with α,β-unsaturated *N*-acylated succinimides catalysed by squaramide has been developed. This organocatalysed reaction proceeded well in high to excellent yields (up to >99%) to afford useful bioactive β-sulfated thioester derivatives with high enantioselectivities (up to 96% ee).

Introduction

To develop a mild and efficient method for carbon–sulfur (C–S) bond formation without the use of transition metal catalysts is still a major challenge.[1] Optically active chiral thiols and sulfides seen as having broad prospects of application in biology are a class of compounds with potential pharmaceutical value.[2] Especially, the synthesis of enantiomerically pure β-sulfated carboxylic acid derivatives has become an important part of organic synthesis.[3] As substructures, they exist in pharmaceuticals and various biologically active compounds.[4] Therefore, the development of a simple and efficient catalytic asymmetric sulfa-Michael reaction has seen considerable research effort invested and is currently a hot topic. However, the development of effective catalysts for asymmetric sulfa-Michael reactions involving the less reactive but synthetically more useful simple alkyl thiols remains a significant challenge. Several effective chiral metallic[5] and organic catalysts[6] have been developed for conjugate additions of aryl thiols to various Michael acceptors. Therefore, the development of an efficient catalytic system suitable for sulfa-Michael additions of aryl and alkyl thiols to α,β-unsaturated acid derivatives becomes particularly important. In recent years, there have been a few examples of sulfa-Michael addition of both alkyl and aryl thiols to α,β-unsaturated *N*-acylated oxazolidinones and α,β-unsaturated *N*-acylated 3,5-dimethyl-1*H*-pyrazole. In contrast, as a Michael acceptor, the analogous compounds of α,β-unsaturated *N*-acylated succinimides have not yet been achieved.

In recent years, chiral squaramide catalysts have been used in various organic reactions.[7] Chen and coworkers have reported sulfa-Michael addition of various thiols to *trans*-chalcones and α,β-unsaturated *N*-acylated oxazolidinones using squaramide as a catalyst and the corresponding products were obtained in high yields with enantioselectivity.[6a,g] Herein, we report a novel highly enantioselective one-pot dithiolation through sulfa-Michael addition/thioesterification of thiols with α,β-unsaturated *N*-acylated succinimides catalysed by squaramide. This organocatalysed reaction proceeded well in high to excellent yields (up to >99%) to afford β-sulfated thioester derivatives with high enantioselectivities (up to 96% ee).

Results and discussion

Initially, we made a trial through the reaction (*E*)-1-(but-2-enoyl)-pyrrolidine-2,5-dione **1a** with thiophenol **2a** using catalyst **I**. The experimental results show that **1a** may undergo an activation process by the squaramide moiety through a double hydrogen-bonding interaction in a manner similar to α,β-unsaturated *N*-acylated oxazolidinones. At first, we obtained the single sulfa-Michael addition product. As the reaction proceeded, the product of single sulfa-Michael addition slowly disappeared and completely converted into the desired product **3aa**, which can be tracked by TLC. No matter how the ratio of the two reactants was adjusted, there was always some **3aa** product formed. This means that we can not obtain a high yield of the single sulfa-Michael addition compound. In order to increase the yield of this reaction and control the reaction, we choose to extend the reaction time and finally obtain the novel compound **3aa** having two sulfur functional groups and

School of Chemical Engineering and Environment, Beijing Institute of Technology, Beijing 100081, People's Republic of China. E-mail: dudm@bit.edu.cn; Tel: +86 10 68914985

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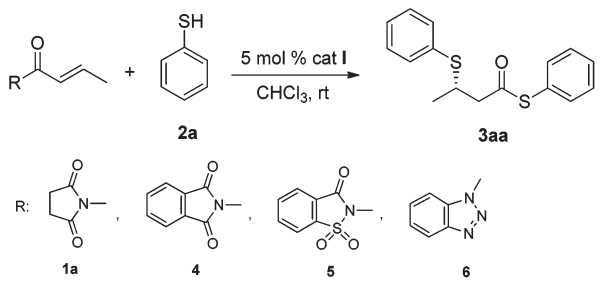
having broad prospect of application in biology. So far, there is no similar report about the synthesis of this type of chiral compound.[8]

We then compared the performance of α,β-unsaturated *N*-acylated succinimide **1a**, α,β-unsaturated *N*-acylated phthalimide **4**, α,β-unsaturated *N*-acylated saccharin **5** and α,β-unsaturated *N*-acylated benzotriazole **6** in this cascade Michael addition/thioesterification with thiophenol **2a** using squaramide **I** as catalyst. The results are listed in Table 1. From comprehensive consideration of the yield and enantioselectivity of product **3aa**, α,β-unsaturated *N*-acylated succinimide **1a** is the best Michael acceptor. Notably, we found that the course of this reaction can be divided into two steps as monitored by TLC, the first stage is the Michael addition of thiophenol to α,β-unsaturated amide, the second stage is the thioesterification reaction of excess thiophenol replacing the succinimide, phthalimide, saccharin or benzotriazole. We find the first step of the reaction which required a few hours for completion is much faster than the second step which required a few days to complete. In other words, the reaction rate is controlled by the second step.

Based on the above evaluation results, we choose the reaction of (*E*)-1-(but-2-enoyl)pyrrolidine-2,5-dione **1a** with thiophenol **2a** as the model reaction. The catalyst screening was firstly investigated. Some squaramide catalysts and one thiourea catalyst **I–X** incorporating cinchona alkaloid and (1*S*,2*S*)-(+)-1,2-diaminocyclohexane were screened (Fig. 1). From Table 2, we can find that all catalysts could smoothly promote the reaction in $CHCl_3$ in the presence of 5 mol% catalyst loading at room temperature for 48–72 h. The squaramide **I** derived from quinidine was identified as the best catalyst to afford the desired Michael adduct **3aa**. Both squaramides **I** and **IV** gave good yields, but the former exhibited better enantioselectivity (81% ee) (Table 2, entries 1 and 4).

Table 1 Screening of Michael acceptors



Entry[a]	Acceptor	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	**3aa**	48	99	81
2	**4**	**3aa**	120	31	91
3	**5**	**3aa**	96	20	92
4	**6**	**3aa**	24	90	79

[a] Reaction conditions: **1a**, **4a**, **5a** or **6a** (0.2 mmol) and thiophenol **2a** (0.48 mmol) in $CHCl_3$ (0.5 mL) with 5 mol% catalyst at room temperature. [b] Isolated yields. [c] Determined by HPLC on a Daicel Chiralpak OJ-H column.

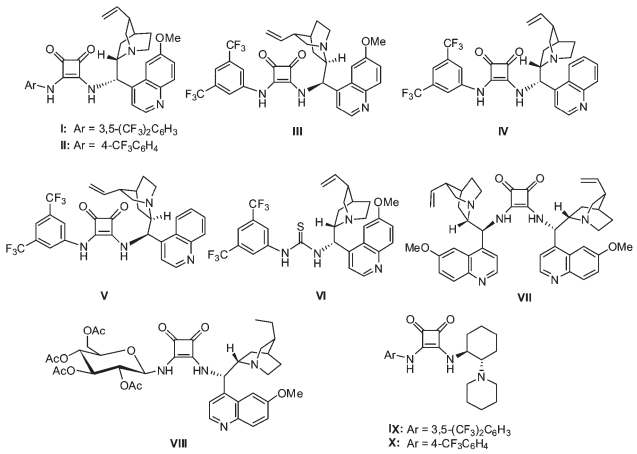
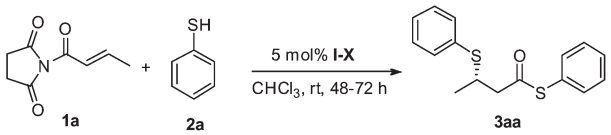


Fig. 1 Screened squaramide and thiourea catalysts.

Table 2 Screening of squaramide catalysts

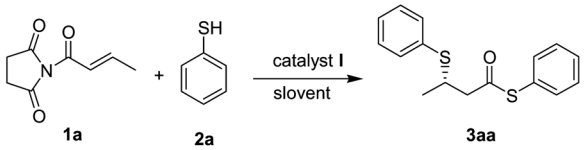


Entry[a]	Catalyst	Yield[b] (%)	ee[c] (%)
1	**I**	99	81
2	**II**	99	75
3	**III**	94	77[d]
4	**IV**	99	80
5	**V**	95	74[d]
6	**VI**	99	63
7	**VII**	88	70
8	**VIII**	86	20[d]
9	**IX**	94	59
10	**X**	95	33

[a] Reaction conditions: (*E*)-1-(but-2-enoyl)pyrrolidine-2,5-dione **1a** (0.2 mmol) and thiophenol **2a** (0.48 mmol) in $CHCl_3$ (0.5 mL) with 5 mol% catalyst for 48–72 h at room temperature. [b] Isolated yields. [c] Determined by HPLC on a Daicel Chiralpak OJ-H column. [d] The opposite enantiomer.

Subsequently, we carried out the screening of the reaction solvent. The results show that toluene is the optimal solvent and also confirm that nonpolar solvents without Lewis basic sites (such as toluene, xylene, dichloromethane, and chloroform) are better when used in conjunction with this type of hydrogen-bonding catalysts. With the optimal catalyst and solvent in hand, the other parameters, such as temperature and catalyst loading were further investigated to obtain the optimal reaction conditions. The results are summarized in Table 3. Notably, when the model reaction is first performed at lower temperature for several hours and then warmed to room temperature, that is to reduce the temperature of the first reaction stage, the enantioselectivity is greatly improved (Table 3, entries 13 and 14). When increasing the loading of the catalyst, the enantioselectivity or yield of the product **3aa** cannot be further improved. However, when reducing the loading of the

Table 3 Optimization of reaction conditions for the asymmetric Michael addition



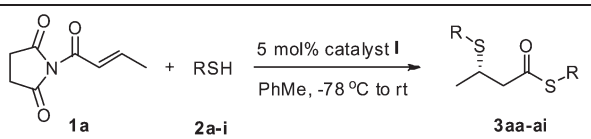
Entry[a]	Solvent	Loading	T (°C)	t/h	Yield[b] (%)	ee[c] (%)
1	$CHCl_3$	5	rt	36	99	81
2	CH_2Cl_2	5	rt	36	99	81
3	CH_2ClCH_2Cl	5	rt	36	98	80
4	CCl_4	5	rt	36	75	76
5	THF	5	rt	36	95	80
6	PhMe	5	rt	36	99	82
7	Xylene	5	rt	36	90	82
8	α,α,α-Trifluorotoluene	5	rt	36	99	78
9	CHCN	5	rt	36	95	63
10	Et_2O	5	rt	36	94	80
11	1,4-Dioxane	5	rt	36	71	81
12	H_2O	5	rt	36	90	58
13	PhMe	5	−20 to rt	1 + 36	99	86
14	PhMe	5	−78 to rt	2 + 36	96	96
15	PhMe	5	−78 to 60	2 + 18	90	86
16	PhMe	10	−78 to rt	2 + 36	96	94
17	PhMe	2.5	−78 to rt	3 + 48	72	95
18	PhMe	1	−78 to rt	6 + 60	57	95

[a] Reaction conditions: (*E*)-1-(but-2-enoyl)pyrrolidine-2,5-dione **1a** (0.2 mmol) and thiophenol **2a** (0.48 mmol) in solvent of 0.5 mL. [b] Isolated yields. [c] Determined by HPLC on a Daicel Chiralpak OJ-H column.

catalyst, the yield of product sharply decreased. This phenomenon may be due to the second thioesterification stage that needs a strong catalytic environment to react completely (Table 3, entries 17 and 18).

Having identified the optimized conditions for this reaction, a variety of thiols was then tested using **1a** as a Michael acceptor (Table 4). Good to high enantioselectivities (up to 96% ee) can be obtained when various aryl or alkyl thiols were used as the nucleophiles. It is noteworthy that the enantioselectivity will decrease with the increase of steric hindrance of the substituent on the aromatic ring of the thiol (Table 4, entry 3). The electronic nature of the 4-substituted group on the aromatic ring of thiols has little effect on the enantioselectivity (Table 4, entries 2, 4, 5 and 6). A longer reaction time was required for the completion of the reaction when less reactive benzyl mercaptan was employed as the nucleophile, and the corresponding enantioselectivity also decreased. We have tried to improve the enantioselectivities of products **3ah–3ai** by increasing the loading of catalyst or adjusting the temperature, but the outcome cannot be improved (Table 4, entries 8 and 9).

Table 4 sulfa-Michael addition/thioesterification of thiols to (*E*)-1-(but-2-enoyl)pyrrolidine-2,5-dione **1a**

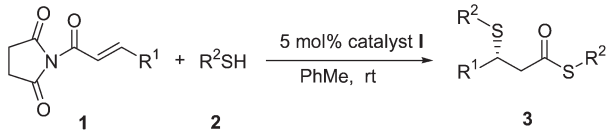


Entry[a]	R	Product	t/h	Yield[b] (%)	ee[c] (%)
1	C_6H_5	**3aa**	2 + 48	96	96
2	4-MeC_6H_4	**3ab**	2 + 48	95	95
3	2-MeOC_6H_4	**3ac**	2 + 48	94	71
4	4-ClC_6H_4	**3ad**	2 + 48	95	93
5	4-BrC_6H_4	**3ae**	2 + 48	95	91
6	4-FC_6H_4	**3af**	2 + 48	97	93
7	2-Naphthyl	**3ag**	2 + 48	94	94
8	Bn	**3ah**	6 + 72	89	48
9	4-ClBn	**3ai**	6 + 72	91	47

[a] Reaction conditions: (*E*)-1-(but-2-enoyl)pyrrolidine-2,5-dione **1a** (0.2 mmol) and thiophenol **2a** (0.48 mmol) in toluene (0.5 mL) with 5 mol% catalyst at −78 °C for a few hours, and then the reaction was allowed to warm to room temperature. [b] Isolated yields. [c] Determined by HPLC on a Daicel Chiralpak IB or OJ-H column.

To extend the scope of this reaction, sulfa-Michael addition/thioesterification with structurally different substituted *N*-acryl succinimides **1b–1m** were investigated. The results are summarized in Table 5. Good to high enantioselectivities were achieved for a wide variety of Michael donors and acceptors. We find that as the alkyl chain grows and the steric hindrance increases at the β-substituted position of **1**, the enantioselectivity and yield moderately decrease. When the β-substituted position of **1** was replaced by aryl substituents, the rate of sulfa-Michael addition reduces. But in contrast, the thioesterification reaction rate and the yields of product **3** has significantly increased (Table 5, entries 4–6). Next, we evaluated the reaction of benzyl mercaptan with the Michael acceptors **1** containing aryl substituents. We were pleased to find that similar results to those described above take place, and

Table 5 Substrate scope of sulfa-Michael addition/thioesterification of thiols to α,β-unsaturated *N*-acylated succinimides



Entry[a]	R^1	R^2	Product	*t*/h	Yield[b] (%)	ee[c] (%)
1[d]	Et (**1b**)	C_6H_5 (**2a**)	**3ba**	60	97	90
2[d]	*n*-Pr (**1c**)	C_6H_5 (**2a**)	**3ca**	96	93	68
3[e]	i-Pr (**1d**)	C_6H_5 (**2a**)	**3da**	120	82	82
4	C_6H_5 (**1e**)	C_6H_5 (**2a**)	**3ea**	18	>99	73
5[f]	C_6H_5 (**1e**)	C_6H_5 (**2a**)	**3ea**	18	>99	70
6	C_6H_5 (**1e**)	4-MeC_6H_4 (**2b**)	**3eb**	18	>99	80
7	C_6H_5 (**1e**)	Bn (**2h**)	**3eh**	30	99	91
8[g]	C_6H_5 (**1e**)	Bn (**2h**)	**3eh**	30	95	89
9	C_6H_5 (**1e**)	4-ClBn (**2i**)	**3ei**	48	99	89
10	4-ClC_6H_4 (**1f**)	Bn (**2h**)	**3fh**	48	96	90
11	4-ClC_6H_4 (**1f**)	4-ClBn (**2i**)	**3fi**	48	94	90
12	2-ClC_6H_4 (**1g**)	Bn (**2h**)	**3gh**	48	99	82
13	2-ClC_6H_4 (**1g**)	4-ClBn (**2i**)	**3gi**	48	99	79
14	4-BrC_6H_4 (**1h**)	Bn (**2h**)	**3hh**	60	99	90
15	4-FC_6H_4 (**1i**)	Bn (**2h**)	**3ih**	60	98	88
16	4-MeOC_6H_4 (**1j**)	Bn (**2h**)	**3jh**	60	97	87
17	4-MeOC_6H_4 (**1j**)	4-ClBn (**2i**)	**3ji**	60	99	86
18	1-Naphthyl (**1k**)	Bn (**2h**)	**3kh**	48	98	90
19	1-Naphthyl (**1k**)	4-ClBn (**2i**)	**3ki**	48	94	92
20	4-O_2NC_6H_4 (**1l**)	Bn (**2h**)	**3lh**	48	99	89
21	4-MeC_6H_4 (**1m**)	Bn (**2h**)	**3mh**	48	>99	89

[a] Reaction conditions: **1** (0.2 mmol) and **2** (0.48 mmol) in 0.5 mL of toluene with 5 mol% catalyst **I** at room temperature. [b] Isolated yields. [c] Determined by HPLC. [d] The reaction firstly performed at −78 °C for 2 h, and then allowed to warm to room temperature. [e] The reaction firstly performed at −78 °C for 4 h, and then allowed to warm to room temperature. [f] The reaction firstly performed at −78 °C for 10 h, and then allowed to warm to room temperature. [g] The reaction firstly performed at −40 °C for 12 h, and then allowed to warm to room temperature.

the final corresponding enantioselectivities of products **3** have been significantly improved, which should be ascribed to the decrease of relative reactivity of benzyl mercaptans (Table 5, entries 7–9). This phenomenon may be ascribed to increasing probability of the good Michael addition control of the process by the chiral catalyst. However, the position of the substituent on the aromatic ring of Michael acceptor has an evident effect on enantioselectivity (Table 5, entries 10–13). The electronic nature of the substituent on the aromatic ring of the Michael acceptor or donor has little effect on enantioselectivity of the product (Table 4, entries 14–21).

The proposed transition state models to explain the generation of the final product **3aa** are shown in Fig. 2. Squaramide activates the (*E*)-1-(but-2-enoyl)pyrrolidine-2,5-dione through a double hydrogen-bonding interaction, while the thiophenol is activated by the tertiary nitrogen of the quinuclidine. Initially the thiophenol anion attack the (*E*)-1-(but-2-enoyl)pyrrolidine-2,5-dione from the *Si*-face *via* transition state **A** forming the corresponding Michael adduct anion, subsequently the generated anion abstract the proton from the quinuclidine nitrogen *via* transition state **B** leads to the formation of the major

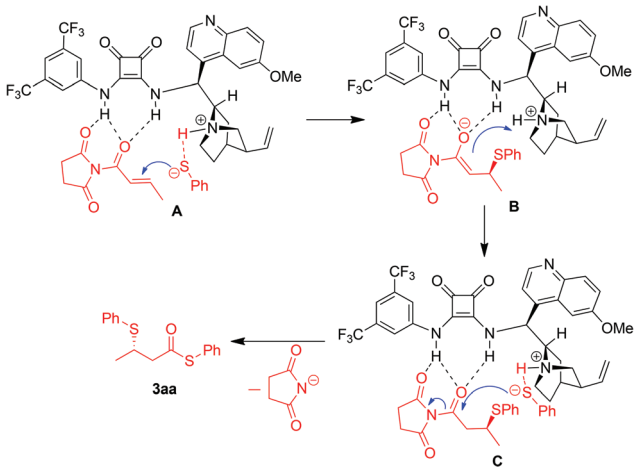


Fig. 2 Proposed reaction mechanism.

enantiomer. Then, the excess thiophenol continues to be activated by the tertiary nitrogen of the quinuclidine and formation of the new anion. The final step is thioesterification of transient ion pair **C** with the removal of the succinimide auxiliary giving bifunctional product **3aa**.

Conclusions

In conclusion, we have developed an effective one-pot enantioselective sulfa-Michael addition/thioesterification of thiols with α,β-unsaturated *N*-acylated succinimides using squaramide as catalyst, the corresponding disulfur products with good to excellent yields (up to >99%) and high enantioselectivities (up to 96% ee) were obtained. This reaction provides a facile and innovative access to β-sulfated thioester derivatives from α,β-unsaturated *N*-acylated succinimides. A broad scope of substrates and easily available raw materials make this approach very competitive in the synthesis of enantiomerically pure β-sulfated thioester derivatives. Further studies focusing on the development of new applications of squaramide catalysts in Michael additions are currently under way in our laboratory.

Experimental

General information

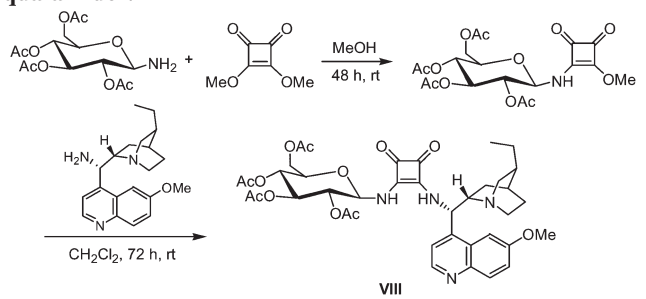
Unless otherwise stated, commercially available compounds were used without further purification. Column chromatography was carried out with silica gel (200–300 mesh). Melting points were measured with a melting point apparatus without correction. ^{1}H NMR spectra were recorded with a Varian Mercury-plus 400 MHz spectrometer. Chemical shifts were reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br s = broad singlet), coupling constant(s) in Hz, integration assignment. ^{13}C NMR spectra were recorded at 100 MHz. Infrared spectra were

obtained with a Perkin Elmer Spectrum One spectrometer. The high resolution MS spectra were obtained with ESI ionization using a Bruker APEX IV FTMS spectrometer. Optical rotations were measured with a WZZ-3 polarimeter at the indicated concentration with unit g per 100 mL. The enantiomeric excesses were determined by chiral HPLC using an Agilent 1200 LC instrument with Daicel Chiralpak column IA, IB, OJ-H or AD-H.

Synthesis of organocatalysts

Squaramide catalysts **I–V**,[7c] **IX** and **X**,[7d] **VII**,[9] thiourea **VI**[10] were prepared according to the reported procedures.

Squaramide VIII



VIII

In 25 mL round-bottomed flask, 1-amino-2,3,4,6-tetraacetyl-β-D-glucopyranose[11] (1.74 g, 5.0 mmol) was added to dimethyl squarate (0.71 g, 5.0 mmol) which was dissolved in 10 mL methanol at room temperature. The reaction mixture was stirred for 48 h at room temperature and a large white precipitate was obtained by filtration to afford the mono-squaramide as a white solid (1.65 g, 72% yield). To a solution of 9-amino-(9-deoxy)epihydroquinine[10] (325 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added mono-squaramide (457 mg, 1 mmol). After stirring for 72 h at room temperature, the squaramide catalyst **VIII** was obtained by filtration as a white solid (419 mg, 56% yield). M.p. 182–184 °C; $[\alpha]_D^{28}$ = −43.3 (*c* 0.30, DMSO). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1H, ArH), 8.03 (d, J = 9.2 Hz, 1H, ArH), 7.75 (s, 1H, ArH), 7.47 (d, J = 4.4 Hz, 1H, ArH), 7.41 (d, J = 9.2 Hz, 1H, ArH), 6.16 (br s, 1H, CH), 5.43 (d, J = 7.6 Hz, 1H, CH), 5.29 (t, J = 9.2 Hz, 1H, CH), 5.04 (t, J = 9.6 Hz, 1H, CH), 4.96 (s, 1H, CH), 4.28 (dd, J_1 = 12.0 Hz, J_2 = 4.4 Hz, 1H, CH), 4.03 (d, J = 6.0 Hz, 1H, CH_2), 3.98 (s, 3H, OCH_3), 3.90 (d, J = 9.6 Hz, 1H, CH_2), 3.47 (br s, 2H, CH_2), 3.27 (t, J = 10.4 Hz, 1H, CH), 2.78 (br s, 1H, CH), 2.50 (d, J = 10.4 Hz, 1H, CH), 2.05 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 2.00 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 1.68 (s, 2H, CH_2), 1.60–1.41 (m, 5H, CH_2), 1.34–1.24 (m, 3H, CH_2), 0.83 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.6, 182.6, 170.5, 169.7, 169.5, 168.4, 158.5, 147.5, 144.7, 131.8, 131.7, 122.4, 122.3, 119.3, 109.7, 101.5, 81.9, 77.2, 73.3, 73.0, 70.8, 67.9, 61.6, 60.0, 57.3, 55.9, 40.8, 36.7, 27.8, 27.2, 25.5, 24.8, 20.8, 20.6, 20.5, 11.9 ppm; IR (KBr): ν 3194, 3169, 3030, 2940, 2866, 1800, 1751, 1688, 1680, 1652, 1622, 1587, 1571, 1543, 1511, 1473, 1461, 1435, 1368, 1322, 1230, 1170, 1140, 1093, 1036, 976, 909, 850, 715, 694, 635, 601 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{38}H_{47}N_4O_{12}$ $[M + H]^+$ 751.31850, found 751.31967.

General procedure for one-pot enantioselective sulfa-Michael addition/thioesterification

A mixture of α,β-unsaturated *N*-acylated succinimide **1** (0.2 mmol) and catalyst **VII** (6.3 mg, 0.01 mmol, 5 mol%) was stirred at room temperature or low temperature for 15 min, then thiol **2** (0.48 mmol) was added in one portion. After stirring at room temperature or first reacting under low temperature conditions for a few hours, and then allowing to warm to room temperature for 18–120 h, the reaction mixture was concentrated and directly purified by silica gel column chromatography to afford the desired product **3**.

(*S*)-3-Phenylsulfanylthiobutyric acid *S*-phenyl ester (3aa).[8] The title compound **3aa** was obtained according to the general procedure as yellow oil (55.4 mg, 96% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{major} = 16.9 min, t_{minor} = 49.9 min, 96% ee. $[\alpha]_D^{25}$ +45.9 (*c* 2.23, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.43 (m, 3H, ArH), 7.41–7.37 (m, 4H, ArH), 7.34–7.24 (m, 3H, ArH), 3.76–3.67 (m, 1H, CH), 2.98 (dd, J_1 = 15.2 Hz, J_2 = 5.2 Hz, 1H, CH_2), 2.75 (dd, J_1 = 15.2 Hz, J_2 = 8.8 Hz, 1H, CH_2), 1.36 (d, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 134.4, 133.6, 132.7, 129.5, 129.2, 129.0, 127.5, 127.4, 50.3, 39.6, 20.5 ppm.

(*S*)-3-*p*-Tolylsulfanylthiobutyric acid *S*-*p*-tolyl ester (3ab).[8] The title compound **3ab** was obtained according to the general procedure as yellow oil (61.4 mg, 95% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{major} = 10.5 min, t_{minor} = 25.1 min, 95% ee. $[\alpha]_D^{25}$ +45.6 (*c* 3.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 8.0 Hz, 2H, ArH), 7.26–7.19 (m, 4H, ArH), 7.12 (d, J = 8.0 Hz, 2H, ArH), 3.65–3.60 (m, 1H, CH), 2.93 (dd, J_1 = 15.2 Hz, J_2 = 5.6 Hz, 1H, CH_2), 2.71 (dd, J_1 = 15.4 Hz, J_2 = 9.2 Hz, 1H, CH_2), 2.36 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 1.33 (d, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 139.7, 137.8, 134.3, 133.5, 130.0, 129.7, 123.9, 50.2, 40.0, 21.3, 21.1, 20.5 ppm.

(*S*)-3-(2-Methoxyphenylsulfanyl)thiobutyric acid *S*-(2-methoxyphenyl)ester (3ac). The title compound **3ac** was obtained according to the general procedure as yellow oil (65.5 mg, 94% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{major} = 19.6 min, t_{minor} = 32.7 min, 71% ee. $[\alpha]_D^{25}$ +21.2 (*c* 3.28, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.24 (m, 4H, ArH), 6.99–6.87 (m, 4H, ArH), 3.88 (s, 3H, CH_3), 3.87–3.84 (m, 1H, CH), 3.81 (s, 3H, CH_3), 2.96 (dd, J_1 = 15.2 Hz, J_2 = 4.4 Hz, 1H, CH_2), 2.73 (dd, J_1 = 15.0 Hz, J_2 = 9.6 Hz, 1H, CH_2), 1.37 (d, J = 7.6 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9, 159.0, 158.7, 136.5, 133.4, 131.7, 128.9, 121.8, 121.0, 120.9, 115.7, 111.5, 110.8, 55.9, 55.7, 50.2, 37.7, 20.0 ppm; IR (KBr): ν 3004, 2963, 2935, 2836, 1699, 1582, 1477, 1462, 1432, 1273, 1260, 1245, 1178, 1161, 1105, 1091, 1070, 1041, 1023, 983, 798, 750, 686 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}NaO_3S_2$ $[M + Na]^+$ 371.07461, found 371.07538.

(*S*)-3-(4-Chlorophenylsulfanyl)thiobutyric acid *S*-(4-chlorophenyl)ester (3ad).[8] The title compound **3ad** was obtained

according to the general procedure as yellow oil (67.9 mg, 95% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{major} = 10.5 min, t_{minor} = 14.8 min, 93% ee. $[\alpha]_D^{25}$ +50.4 (*c* 3.40, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (dd, J_1 = 8.6 Hz, J_2 = 2.0 Hz, 4H, ArH), 7.29 (dd, J_1 = 8.6 Hz, J_2 = 2.4 Hz, 4H, ArH), 3.71–3.62 (m, 1H, CH), 2.93 (dd, J_1 = 7.6 Hz, J_2 = 5.6 Hz, 1H, CH_2), 2.76 (dd, J_1 = 15.4 Hz, J_2 = 8.4 Hz, 1H, CH_2), 1.35 (d, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.7, 136.0, 135.6, 134.2, 133.8, 132.0, 129.5, 129.2, 125.7, 109.7, 50.2, 40.0, 20.6 ppm.

(*S*)-3-(4-Bromophenylsulfanyl)thiobutyric acid *S*-(4-bromophenyl)ester (3ae). The title compound **3ae** was obtained according to the general procedure as yellow oil (87.5 mg, 95% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{major} = 12.2 min, t_{minor} = 16.1 min, 91% ee. $[\alpha]_D^{25}$ +50.5 (*c* 4.38, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 8.4 Hz, 2H, ArH), 7.44 (d, J = 8.4 Hz, 2H, ArH), 7.30 (d, J = 8.4 Hz, 2H, ArH), 7.22 (d, J = 8.4 Hz, 2H, ArH), 3.72–3.63 (m, 1H, CH), 2.93 (dd, J_1 = 15.4 Hz, J_2 = 6.0 Hz, 1H, CH_2), 2.76 (dd, J_1 = 15.6 Hz, J_2 = 8.0 Hz, 1H, CH_2), 1.35 (d, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.4, 135.8, 135.5, 134.2, 134.1, 132.7, 132.4, 132.1, 129.5, 129.2, 126.3, 124.2, 121.8, 50.2, 39.8, 20.6 ppm; IR (KBr): ν 3082, 3056, 2964, 2922, 1705, 1568, 1472, 1411, 1385, 1340, 1261, 1092, 1067, 1021, 1011, 865, 800, 766, 749, 732, 704 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}Br_2NaOS_2$ $[M + Na]^+$ 466.87450, found 466.87485.

(*S*)-*S*-(4-Fluorophenyl)3-((4-fluorophenyl)thio)butanethioate (3af). The title compound **3af** was obtained according to the general procedure as yellow oil (63.0 mg, 97% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{major} = 11.5 min, t_{minor} = 21.3 min, 93% ee. $[\alpha]_D^{25}$ +45.4 (*c* 3.15, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.44 (m, 2H, ArH), 7.37–7.33 (m, 2H, ArH), 7.12–7.08 (m, 2H, ArH), 7.05–7.00 (m, 2H, ArH), 3.64–3.55 (m, 1H, CH), 2.91 (dd, J_1 = 15.4 Hz, J_2 = 5.8 Hz, 1H, CH_2), 2.74 (dd, J_1 = 15.4 Hz, J_2 = 8.2 Hz, 1H, CH_2), 1.33 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 163.5 (d, $^1J_{C-F}$ = −248.9 Hz), 162.7 (d, $^1J_{C-F}$ = −247.0 Hz), 136.4 (d, $^3J_{C-F}$ = 9.0 Hz), 135.8 (d, $^3J_{C-F}$ = 8.0 Hz), 128.2 (d, $^4J_{C-F}$ = 3.3 Hz), 122.5 d, $^4J_{C-F}$ = 3.2 Hz), 116.5 (d, $^2J_{C-F}$ = 22.0 Hz), 116.1 (d, $^2J_{C-F}$ = 21.5 Hz), 50.0, 40.5, 20.6 ppm; IR (KBr): ν 3096, 3069, 2965, 2926, 2869, 1891, 1706, 1590, 1491, 1455, 1398, 1377, 1341, 1291, 1261, 1227, 1157, 1110, 1091, 1026, 1014, 989, 897, 881, 829, 815, 793, 764, 659, 646, 636, 518 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}F_2NaOS_2$ $[M + Na]^+$ 347.03463, found 347.03529.

(*S*)-*S*-Naphthalen-2-yl 3-(naphthalen-2-ylthio)butanethioate (3ag). The title compound **3ag** was obtained according to the general procedure as a colorless solid (73.0 mg, 94% yield). HPLC (Daicel Chiralpak IB, *n*-hexane–2-propanol = 95 : 5, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 9.3 min, t_{major} = 16.0 min, 94% ee. M.p. 74–76 °C; $[\alpha]_D^{25}$ +103.8 (*c* 3.65, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.93–7.75 (m, 8H, ArH), 7.52–7.36 (m, 6H, ArH), 3.91–3.83 (m, 1H, CH), 3.05 (dd, J_1 = 15.4 Hz, J_2 = 5.4 Hz, 1H, CH_2), 2.83 (dd, J_1 = 15.4 Hz, J_2 = 8.6 Hz, 1H, CH_2), 1.42 (d, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 134.2, 133.6, 133.4, 133.3, 132.4, 131.3, 131.1, 130.7, 129.8, 128.8, 128.6, 127.9, 127.72, 127.66, 127.4, 127.1, 126.54, 126.52, 126.3, 124.6, 53.4, 50.4, 39.6, 20.6 ppm; IR (KBr): ν 3054, 2965, 2924, 2867, 1702, 1625, 1587, 1500, 1454, 1406, 1377, 1343, 1292, 1268, 1238, 1195, 1113, 1110, 1074, 1027, 987, 944, 893, 857, 813, 745, 665, 631, 473 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{20}NaOS_2$ $[M + Na]^+$ 411.08478, found 411.08475.

(*S*)-*S*-Benzyl 3-(benzylthio)butanethioate (3ah). The title compound **3ah** was obtained according to the general procedure as yellow oil (56.3 mg, 89% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 17.9 min, t_{major} = 20.8 min, 48% ee. $[\alpha]_D^{25}$ −5.8 (*c* 2.82, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.24 (m, 10H, ArH), 4.13 (s, 2H, CH_2), 3.74 (s, 2H, CH_2), 3.20–3.14 (m, 1H, CH), 2.85 (dd, J_1 = 15.2 Hz, J_2 = 10.0 Hz, 1H, CH_2), 2.66 (dd, J_1 = 15.2 Hz, J_2 = 8.4 Hz, 1H, CH_2), 1.27 (d, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 138.0, 137.3, 128.80, 128.77, 128.6, 128.5, 127.2, 127.0, 50.8, 36.3, 35.5, 33.3, 21.0 ppm; IR (KBr): ν 3086, 3065, 3026, 2964, 2922, 1683, 1602, 1495, 1453, 1411, 1377, 1261, 1096, 1071, 1025, 800, 701, 661, 564 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}NaOS_2$ $[M + Na]^+$ 339.08478, found 339.08506.

(*S*)-*S*-4-Chlorobenzyl 3-((4-chlorobenzyl)thio)butanethioate (3ai). The title compound **3ai** was obtained according to the general procedure as yellow oil (70.1 mg, 91% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 16.6 min, t_{major} = 17.9 min, 47% ee. $[\alpha]_D^{25}$ −6.8 (*c* 3.51, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.20 (m, 8H, ArH), 4.07 (s, 2H, CH_2), 3.68 (s, 2H, CH_2), 3.16–3.10 (m, 1H, CH), 2.82 (dd, J_1 = 15.2 Hz, J_2 = 6.0 Hz, 1H, CH_2), 2.66 (dd, J_1 = 15.2 Hz, J_2 = 8.0 Hz, 1H, CH_2), 1.26 (dd, J = 6.4 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 136.4, 136.0, 133.1, 132.8, 130.1, 128.7, 128.6, 50.7, 36.2, 34.7, 32.6, 21.0 ppm; IR (KBr): ν 3040, 3028, 2961, 2923, 2863, 1899, 1686, 1596, 1490, 1451, 1406, 1377, 1339, 1277, 1261, 1242, 1197, 1092, 1031, 1015, 992, 892, 876, 828, 822, 808, 747, 728, 696, 643, 506 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{18}Cl_2NaOS_2$ $[M + Na]^+$ 407.00683, found 407.00690.

(*S*)-*S*-Phenyl-3-(phenylthio)pentanethioate (3ba).[12] The title compound **3ba** was obtained according to the general procedure as yellow oil (58.7 mg, 97% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{major} = 13.0 min, t_{minor} = 33.6 min, 90% ee. $[\alpha]_D^{25}$ +34.2 (*c* 2.94, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.37 (m, 7H, ArH), 7.35–7.24 (m, 3H, ArH), 3.60–3.53 (m, 1H, CH), 2.94 (dd, J_1 = 15.6 Hz, J_2 = 6.4 Hz, 1H, CH_2), 2.86 (dd, J_1 = 15.6 Hz, J_2 = 7.6 Hz, 1H, CH_2), 1.76–1.71 (m, 1H, CH_2), 1.66–1.59 (m, 1H, CH_2), 1.07 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 134.4, 133.9, 132.6, 129.5, 129.2, 129.0, 127.4, 127.3, 48.5, 46.6, 27.2, 11.3 ppm.

(*S*)-*S*-Phenyl-3-(phenylthio)hexanethioate (3ca). The title compound **3ca** was obtained according to the general procedure as yellow oil (58.9 mg, 93% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{major} = 8.5 min, t_{minor} = 16.9 min, 68% ee. $[\alpha]_D^{25}$ +23.8 (*c* 2.94, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.36 (m, 7H, ArH), 7.33–7.23 (m, 3H, ArH), 3.64–3.58 (m, 1H, CH), 2.94 (dd, J_1 = 15.6 Hz, J_2 = 6.0 Hz, 1H, CH_2), 2.84 (dd, J_1 = 15.8 Hz, J_2 = 8.0 Hz, 1H, CH_2), 1.66–1.49 (m, 4H, CH_2), 0.92 (t, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 134.4, 133.9, 132.6, 129.4, 129.2, 129.0, 127.4, 127.3, 49.1, 44.8, 36.4, 20.1, 13.8 ppm; IR (KBr): ν 3078, 3059, 2961, 2931, 2872, 1704, 1583, 1478, 1465, 1440, 1410, 1380, 1329, 1300, 1261, 1178, 1091, 1068, 1024, 957, 799, 745, 704, 689, 661, 625 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}NaOS_2$ $[M + Na]^+$ 339.08478, found 339.08564.

(*R*)-*S*-Phenyl-4-methyl-3-(phenylthio)pentanethioate (3da). The title compound **3da** was obtained according to the general procedure as yellow oil (51.9 mg, 82% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{major} = 8.9 min, t_{minor} = 23.3 min, 82% ee. $[\alpha]_D^{25}$ +2.4 (*c* 2.60, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.38 (m, 7H, ArH), 7.30–7.20 (m, 3H, ArH), 3.67–3.62 (m, 1H, CH), 2.98 (dd, J_1 = 15.8 Hz, J_2 = 6.4 Hz, 1H, CH_2), 2.89 (dd, J_1 = 15.8 Hz, J_2 = 7.2 Hz, 1H, CH_2), 2.06–2.00 (m, 1H, CH), 1.07 (d, J = 6.8 Hz, 3H, CH_3), 1.03 (d, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 135.3, 134.4, 131.7, 129.4, 129.1, 129.0, 127.4, 126.9, 52.2, 46.5, 31.7, 19.8, 18.8 ppm; IR (KBr): ν 3073, 3059, 2960, 2931, 2872, 1703, 1583, 1478, 1463, 1440, 1409, 1380, 1328, 1301, 1262, 1178, 1091, 1068, 1024, 959, 797, 745, 704, 689, 661, 626 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}NaOS_2$ $[M + Na]^+$ 339.08478, found 339.08539.

(*R*)-*S*-Phenyl-3-phenyl-3-(phenylthio)propanethioate (3ea).[8] The title compound **3ea** was obtained according to the general procedure as a colorless solid (69.4 mg, >99% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 30.4 min, t_{major} = 46.6 min, 73% ee. M.p. 75–77 °C; $[\alpha]_D^{25}$ +43.5 (*c* 3.47, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.30 (m, 6H, ArH), 7.27–7.23 (m, 9H, ArH), 4.73 (t, J = 8.0 Hz, 1H, CH), 3.25 (d, J = 7.6 Hz, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.6, 139.8, 134.3, 133.5, 133.1, 129.4, 129.1, 128.9, 128.5, 127.8, 127.7, 127.6, 127.2, 49.3, 49.1 ppm.

(*R*)-*S*-*p*-Tolyl-3-phenyl-3-(*p*-tolylthio)propanethioate (3eb).[8] The title compound **3eb** was obtained according to the general procedure as a colorless solid (75.0 mg, >99% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 17.9 min, t_{major} = 22.2 min, 80% ee. M.p. 85–87 °C; $[\alpha]_D^{25}$ +52.4 (*c* 3.75, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.20 (m, 7H, ArH), 7.17–7.12 (m, 4H, ArH), 7.04 (d, J = 7.6 Hz, 2H, ArH), 4.65 (t, J = 7.6 Hz, 1H, CH), 3.22 (d, J = 7.6 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.30 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 140.0, 139.7, 138.1, 134.3, 133.7, 129.9, 129.6, 128.4, 127.8, 127.5, 49.5, 49.1, 21.3, 21.1 ppm.

(*R*)-*S*-Benzyl-3-(benzylthio)-3-phenylpropanethioate (3eh). The title compound **3eh** was obtained according to the general procedure as colorless oil (74.9 mg, 99% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 19.4 min, t_{major} = 46.7 min, 91% ee. $[\alpha]_D^{25}$ +115.1 (*c* 3.74, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.13 (m, 15H, ArH), 4.26–4.21 (m, 1H, CH), 4.03 (s, 2H, CH_2), 3.49 (ABq, J = 13.2 Hz, 2H, CH_2), 3.06 (d, J = 8.0 Hz, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 140.4, 137.5, 137.1, 128.9, 128.7, 128.54, 128.49, 128.41, 127.9, 127.5, 127.2, 127.0, 49.8, 45.1, 35.7, 33.2 ppm; IR (KBr): ν 3084, 3061, 3028, 2920, 2851, 1687, 1615, 1602, 1584, 1494, 1453, 1412, 1320, 1240, 1198, 1181, 1072, 1048, 1029, 1003, 984, 768, 699, 565 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{22}NaOS_2$ $[M + Na]^+$ 401.10043, found 401.10036.

(*R*)-*S*-4-Chlorobenzyl-3-((4-chlorobenzyl)thio)-3-phenylpropanethioate (3ei). The title compound **3ei** was obtained according to the general procedure as yellow oil (88.6 mg, 99% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 21.3 min, t_{major} = 29.2 min, 89% ee. $[\alpha]_D^{25}$ +115.4 (*c* 4.43, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.19 (m, 9H, ArH), 7.09 (d, J = 8.4 Hz, 2H, ArH), 7.06 (d, J = 8.4 Hz, 2H, ArH), 4.17 (t, J = 7.6 Hz, 1H, CH), 3.98 (ABq, J = 14.4 Hz, 2H, CH_2), 3.44 (ABq, J = 13.6 Hz, 2H, CH_2), 3.04 (d, J = 7.6 Hz, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 140.0, 136.0, 135.8, 133.0, 132.8, 130.2, 130.0, 128.6, 128.5, 127.8, 127.7, 49.8, 45.2, 35.0, 32.5 ppm; IR (KBr): ν 3077, 3056, 3028, 2922, 2847, 1687, 1597, 1490, 1453, 1406, 1317, 1277, 1258, 1240, 1197, 1178, 1092, 1047, 1028, 1015, 1005, 984, 938, 876, 830, 824, 806, 763, 749, 699, 642, 506 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{202}Cl_2NaOS_2$ $[M + Na]^+$ 469.02248, found 469.02213.

(*R*)-*S*-Benzyl-3-(benzylthio)-3-(4-chlorophenyl)propanethioate (3fh). The title compound **3fh** was obtained according to the general procedure as yellow oil (79.3 mg, 96% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane–2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 6.8 min, t_{major} = 7.6 min, 90% ee. $[\alpha]_D^{25}$ +117.7 (*c* 3.96, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.22 (m, 7H, ArH), 7.20–7.16 (m, 5H, ArH), 7.11 (d, J = 7.6 Hz, 2H, ArH), 4.17 (dd, J_1 = 6.6 Hz, J_2 = 8.6 Hz, 1H, CH), 4.02 (ABq, J = 14.0 Hz, 2H, CH_2), 3.48 (ABq, J = 13.6 Hz, 2H, CH_2), 3.07–2.96 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 138.9, 137.2, 137.0, 133.1, 129.3, 128.8, 128.7, 128.6, 128.50, 128.47, 127.2, 127.1, 49.6, 44.4, 35.7, 33.2 ppm; IR (KBr): ν 3085, 3062, 3029, 2960, 2918, 1688, 1615, 1601, 1492, 1453, 1409, 1310, 1291, 1261, 1240, 1197, 1179, 1091, 1072, 1049, 1028, 1014, 988, 942, 814, 765, 701, 529 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{21}ClNaOS_2$ $[M + Na]^+$ 435.06146, found 435.06082.

(*R*)-*S*-4-Chlorobenzyl-3-((4-chlorobenzyl)thio)-3-(4-chlorophenyl)-propanethioate (3fi). The title compound **3fi** was obtained according to the general procedure as yellow oil (90.6 mg, 94% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane–2-propanol =

90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 10.1 min, t_{major} = 11.0 min, 90% ee. $[\alpha]_D^{25}$ +104.0 (*c* 4.53, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.27–7.15 (m, 8H, ArH), 7.10–7.04 (m, 4H, ArH), 4.11 (dd, J_1 = 7.0 Hz, J_2 = 8.6 Hz, 1H, CH), 3.97 (ABq, *J* = 14.0 Hz, 2H, CH_2), 3.49 (d, *J* = 13.6 Hz, 1H, CH_2), 3.38 (d, *J* = 13.6 Hz, 1H, CH_2), 3.06–2.94 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9, 138.5, 135.7, 135.7, 133.3, 133.0, 132.9, 130.1, 130.0, 129.2, 128.7, 128.6, 49.6, 44.4, 35.0, 32.5 ppm; IR (KBr): ν 3060, 3043, 3028, 2920, 2851, 1689, 1596, 1490, 1408, 1309, 1242, 1197, 1178, 1093, 1049, 1015, 986, 942, 880, 827, 748, 700, 643, 507 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}Cl_3NaOS_2$ $[M + Na]^+$ 502.98351, found 502.98350.

(*R*)-*S*-Benzyl-3-(benzylthio)-3-(2-chlorophenyl)propanethioate (3gh). The title compound **3gh** was obtained according to the general procedure as yellow oil (81.9 mg, >99% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane–2-propanol = 98 : 2, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 11.2 min, t_{major} = 12.2 min, 82% ee. $[\alpha]_D^{25}$ +22.7 (*c* 4.10, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.6 Hz, 1H, ArH), 7.32 (d, *J* = 8.0 Hz, 1H, ArH), 7.25–7.14 (m, 12H, ArH), 4.83 (t, *J* = 7.6 Hz, 1H, CH), 4.07 (s, 2H, CH_2), 3.61 (s, 2H, CH_2), 3.12–3.01 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 138.0, 137.2, 137.1, 133.5, 129.7, 128.9, 128.7, 128.5, 128.4, 127.2, 127.0, 49.1, 41.8, 36.3, 33.2 ppm; IR (KBr): ν 3086, 3060, 3026, 2961, 1682, 1602, 1495, 1473, 1452, 1408, 1261, 1093, 1069, 1031, 800, 751, 725, 696, 594, 562 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{21}ClNaOS_2$ $[M + Na]^+$ 435.06146, found 435.06073.

(*S*)-*S*-4-Chlorobenzyl-3-((4-chlorobenzyl)thio)-3-(2-chlorophenyl)-propanethioate (3gi). The title compound **3gi** was obtained according to the general procedure as yellow oil (95.8 mg, >99% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 16.0 min, t_{major} = 25.1 min, 79% ee. $[\alpha]_D^{25}$ +29.2 (*c* 4.79, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.6 Hz, 1H, ArH), 7.31 (d, *J* = 7.6 Hz, 1H, ArH), 7.25–7.15 (m, 6H, ArH), 7.10 (t, *J* = 8.4 Hz, 4H, ArH), 4.79 (t, *J* = 7.6 Hz, 1H, CH), 4.02 (ABq, *J* = 14.0 Hz, 2H, CH_2), 3.55 (s, 2H, CH_2), 3.09–2.98 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 137.7, 135.83, 135.77, 135.75, 133.5, 133.0, 132.8, 130.2, 130.1, 129.7, 128.9, 128.6, 128.5, 127.2, 49.0, 41.8, 35.6, 32.5 ppm; IR (KBr): ν 3064, 3030, 2922, 2850, 1899, 1689, 1596, 1490, 1474, 1441, 1407, 1344, 1306, 1277, 1241, 1196, 1179, 1128, 1093, 1046, 1035, 1016, 988, 941, 877, 832, 809, 754, 730, 697, 681, 642, 594, 507 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}Cl_3NaOS_2$ $[M + Na]^+$ 502.98351, found 502.98274.

(*R*)-*S*-Benzyl-3-(benzylthio)-3-(4-bromophenyl)propanethioate (3hh). The title compound **3hh** was obtained according to the general procedure as yellow oil (90.6 mg, 99% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane–2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 7.1 min, t_{major} = 8.0 min, 90% ee. $[\alpha]_D^{25}$ +132.2 (*c* 4.53, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.4 Hz, 1H, ArH), 7.29–7.21 (m, 6H, ArH), 7.18–7.10 (m, 6H, ArH), 4.15 (dd, J_1 = 6.8 Hz, J_2 = 8.4 Hz, 1H, CH), 4.01 (ABq, *J* = 14.0 Hz, 2H, CH_2), 3.53 (d, *J* = 13.2 Hz, 1H, CH_2), 3.43 (d, *J* = 13.6 Hz, 1H, CH_2), 3.07–2.95 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 139.4, 137.2, 137.0, 131.6, 129.6, 128.8, 128.6, 128.5, 128.5, 127.2, 127.1, 121.3, 49.6, 44.4, 35.7, 33.2 ppm; IR (KBr): ν 3085, 3062, 3028, 2918, 2845, 1687, 1615, 1602, 1588, 1495, 1488, 1453, 1405, 1310, 1291, 1240, 1195, 1181, 1103, 1072, 1049, 1030, 1010, 986, 937, 822, 814, 768, 717, 702, 621, 565, 526 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{21}BrNaOS_2$ $[M + Na]^+$ 479.01094, found 479.01182.

(*R*)-*S*-Benzyl-3-(benzylthio)-3-(4-fluorophenyl)propanethioate (3ih). The title compound **3ih** was obtained according to the general procedure as a colorless solid (77.7 mg, 98% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane–2-propanol = 95 : 5, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 8.2 min, t_{major} = 8.8 min, 88% ee. M.p. 39–40 °C; $[\alpha]_D^{25}$ +75.7 (*c* 3.88, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.11 (m, 12H, ArH), 6.99–6.94 (m, 2H, ArH), 4.19 (dd, J_1 = 6.4 Hz, J_2 = 8.8 Hz, 1H, CH), 4.02 (ABq, *J* = 14.0 Hz, 2H, CH_2), 3.54 (d, *J* = 13.2 Hz, 1H, CH_2), 3.44 (d, *J* = 13.2 Hz, 1H, CH_2), 3.08–2.96 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 161.9 (d, $^1J_{C-F}$ = −244.9 Hz), 137.3, 137.1, 136.0, 129.5 (d, $^3J_{C-F}$ = 8.1 Hz), 128.8, 128.6, 128.5, 128.5, 127.2, 127.1, 115.4 (d, $^2J_{C-F}$ = 21.4 Hz), 49.9, 44.4, 35.7, 33.2 ppm; IR (KBr): ν 3086, 3063, 3030, 2957, 2921, 2849, 1949, 1887, 1688, 1682, 1602, 1506, 1497, 1454, 1416, 1311, 1296, 1260, 1224, 1196, 1181, 1158, 1129, 1097, 1072, 1049, 1028, 1015, 987, 940, 917, 835, 805, 768, 701, 631, 566, 537, 474 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{21}FNaOS_2$ $[M + Na]^+$ 419.09101, found 419.09080.

(*R*)-*S*-Benzyl-3-(benzylthio)-3-(4-methoxyphenyl)propanethioate (3jh). The title compound **3jh** was obtained according to the general procedure as yellow oil (79.2 mg, 97% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane–2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 8.5 min, t_{major} = 9.3 min, 87% ee. $[\alpha]_D^{25}$ +88.6 (*c* 3.96, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.12 (m, 12H, ArH), 6.83 (d, *J* = 8.4 Hz, 2H, ArH), 4.19 (t, *J* = 8.0 Hz, 1H, CH), 4.03 (ABq, *J* = 14.0 Hz, 2H, CH_2), 3.79 (s, 3H, CH_3), 3.53 (d, *J* = 13.2 Hz, 1H, CH_2), 3.44 (d, *J* = 13.2 Hz, 1H, CH_2), 3.07–3.01 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 158.8, 137.6, 137.2, 132.2, 129.0, 128.9, 128.7, 128.5, 128.4, 127.1, 127.0, 113.8, 55.2, 50.0, 44.5, 35.6, 33.1 ppm; IR (KBr): ν 3061, 3029, 3003, 2955, 2932, 2909, 2835, 1688, 1609, 1584, 1511, 1495, 1453, 1421, 1304, 1283, 1250, 1176, 1110, 1071, 1050, 1035, 987, 831, 807, 768, 703, 542 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{24}NaO_2S_2$ $[M + Na]^+$ 431.11099, found 431.11080.

(*R*)-*S*-4-Chlorobenzyl-3-((4-chlorobenzyl)thio)-3-(4-methoxyphenyl)propanethioate (3ji). The title compound **3ji** was obtained according to the general procedure as yellow oil (94.5 mg, 99% yield). HPLC (Daicel Chiralpak OJ-H, *n*-hexane–2-propanol = 70 : 30, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 39.5 min, t_{major} = 55.7 min, 86% ee. $[\alpha]_D^{25}$ +124.0 (*c* 4.73, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.14 (m, 6H, ArH), 7.09 (d, *J* = 8.4 Hz, 2H, ArH), 7.05 (d, *J* = 8.4 Hz, 2H, ArH), 6.81 (d, *J* = 8.8 Hz, 2H, ArH), 4.14 (t, *J* = 7.6 Hz, 1H, CH), 3.97 (ABq, *J* = 14.4 Hz, 2H, CH_2), 3.80

(s, 3H, CH_3), 3.47 (d, J = 13.6 Hz, 1H, CH_2), 3.38 (d, J = 13.6 Hz, 1H, CH_2), 3.04–2.98 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 158.9, 136.2, 135.9, 132.9, 132.7, 131.7, 130.2, 130.0, 129.0, 128.54, 128.49, 113.8, 55.2, 49.9, 44.6, 34.9, 32.4 ppm; IR (KBr): ν 3031, 3001, 2955, 2933, 2909, 2836, 1689, 1610, 1584, 1511, 1490, 1463, 1441, 1407, 1304, 1282, 1250, 1176, 1110, 1092, 1048, 1036, 1015, 987, 832, 809, 792, 730, 697, 643 cm^{-1}; HRMS (ESI): m/z calcd for $C_{24}H_{22}Cl_2NaO_2S_2$ $[M + Na]^+$ 499.03305, found 499.03363.

(*R*)-*S*-Benzyl-3-(benzylthio)-3-(naphthalen-1-yl)propanethioate (3kh). The title compound **3kh** was obtained according to the general procedure as yellow oil (84.0 mg, 98% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane–2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{major} = 7.3 min, t_{minor} = 9.7 min, 90% ee. $[\alpha]_D^{25}$ +10.6 (c 4.19, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 7.6 Hz, 2H, ArH), 7.75 (d, J = 8.4 Hz, 1H, ArH), 7.63 (br s, 1H, ArH), 7.48–7.40 (m, 4H, ArH), 7.24–7.11 (m, 9H, ArH), 5.09 (br s, 1H, CH), 4.03 (s, 2H, CH_2), 3.57 (ABq, J = 13.2 Hz, 2H, CH_2), 3.27 (d, J = 7.2 Hz, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 137.5, 137.1, 135.8, 133.9, 130.8, 129.0, 128.9, 128.7, 128.5, 128.4, 128.2, 127.2, 127.0, 126.2, 125.7, 125.2, 122.9, 49.5, 36.2, 33.2 ppm; IR (KBr): ν 3082, 3061, 3029, 2957, 2919, 1686, 1600, 1510, 1495, 1453, 1412, 1396, 1334, 1277, 1240, 1199, 1183, 1158, 1071, 1048, 1028, 1013, 977, 936, 916, 796, 776, 701, 606, 565 cm^{-1}; HRMS (ESI): m/z calcd for $C_{27}H_{24}NaOS_2$ $[M + Na]^+$ 4451.11608, found 451.11690.

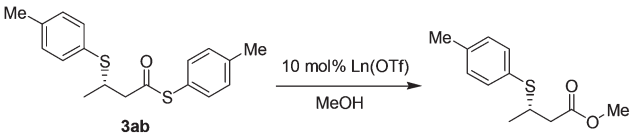
(*R*)-*S*-4-Chlorobenzyl-3-((4-chlorobenzyl)thio)-3-(naphthalen-1-yl)propanethioate (3ki). The title compound **3ki** was obtained according to the general procedure as yellow oil (93.5 mg, 94% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane–2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{major} = 11.8 min, t_{minor} = 9.6 min, 92% ee. $[\alpha]_D^{25}$ +16.0 (c 4.67, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (dd, J_1 = 36.4 Hz, J_2 = 7.6 Hz, 3H, ArH), 7.62 (s, 1H, ArH), 7.50–7.40 (m, 3H, ArH), 7.24–7.14 (m, 4H, ArH), 7.01 (d, J = 8.4 Hz, 4H, ArH), 5.05 (s, 1H, CH), 3.97 (ABq, J = 14.0 Hz, 2H, CH_2), 3.54 (d, J = 13.2 Hz, 1H, CH_2), 3.45 (d, J = 13.6 Hz, 1H, CH_2), 3.23 (d, J = 7.2 Hz, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 136.0, 135.7, 135.5, 133.9, 132.9, 132.7, 130.7, 130.2, 130.0, 128.9, 128.6, 128.5, 128.3, 126.3, 125.8, 125.2, 125.1, 125.0, 125.0, 122.7, 122.7, 122.6, 49.9, 35.4, 32.5, 28.3 ppm; IR (KBr): ν 3047, 2964, 2927, 1804, 1688, 1613, 1598, 1510, 1490, 1405, 1261, 1166, 1092, 1054, 1015, 979, 861, 797, 776, 734, 704, 641, 605, 507 cm^{-1}; HRMS (ESI): m/z calcd for $C_{27}H_{22}Cl_2NaOS_2$ $[M + Na]^+$ 519.03813, found 519.03989.

(*R*)-*S*-Benzyl-3-(benzylthio)-3-(4-nitrophenyl)propanethioate (3lh). The title compound **3lh** was obtained according to the general procedure as a colorless solid (83.8 mg, 99% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane–2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 13.0 min, t_{major} = 17.1 min, 89%. M.p. 61–63 °C; $[\alpha]_D^{25}$ +137.2 (c 4.19, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$):δ 8.10 (d, J = 8.8 Hz, 2H, ArH), 7.41–7.10 (m, 12H, ArH), 4.28–4.23 (m, 1H, CH), 4.00 (ABq, J = 14.0 Hz, 2H, CH_2), 3.58 (d, J = 13.6 Hz, 1H, CH_2), 3.45 (d, J = 13.6 Hz, 1H, CH_2), 3.13–2.99 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 148.1, 147.0, 136.9, 136.8, 129.0, 128.8, 128.6, 128.6, 128.5, 127.4, 127.3, 124.1, 123.7, 49.2, 44.4, 35.9, 33.2 ppm; IR (KBr): ν 3108, 3062, 3029, 2923, 2854, 1684, 1599, 1520, 1495, 1454, 1413, 1346, 1319, 1242, 1180, 1111, 1072, 1050, 1030, 1014, 986, 856, 769, 749, 703, 623, 565, 474 cm^{-1}; HRMS (ESI): m/z calcd for $C_{23}H_{21}NNaO_3S_2$ $[M + Na]^+$ 446.08551, found 446.08483.

(*R*)-*S*-Benzyl-3-(benzylthio)-3-(*p*-tolyl)propanethioate (3mh). The title compound **3mh** was obtained according to the general procedure as yellow oil (77.8 mg, >99% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane–2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, detection at 254 nm): retention time: t_{minor} = 6.2 min, t_{major} = 6.7 min, 89% ee. $[\alpha]_D^{25}$ +110.0 (c 3.88, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.29–7.09 (m, 14H, ArH), 4.25–4.18 (m, 1H, CH), 4.02 (m, 2H, CH_2), 3.49 (ABq, J = 13.6 Hz, 2H, CH_2), 3.04 (t, J = 1.6 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 137.6, 137.2, 137.2, 137.1, 129.2, 128.9, 128.7, 128.6, 128.4, 128.4, 127.7, 127.1, 127.0, 109.6, 49.9, 44.8, 35.6, 33.1, 21.1 ppm; IR (KBr): ν 3085, 3061, 3028, 2920, 2862, 1688, 1602, 1512, 1495, 1453, 1415, 1317, 1240, 1198, 1182, 1112, 1071, 1050, 1030, 985, 817, 807, 767, 702, 637, 566, 535, 473 cm^{-1}; HRMS (ESI): m/z calcd for $C_{24}H_{24}NaOS_2$ $[M + Na]^+$ 415.11608, found 415.11632.

Determination of the absolute configuration of product 3ab

(*S*)-Methyl-3-(*p*-tolylthio)butanoate.[13]



The title compound was obtained through the reaction of compound **3ab** with MeOH under 10 mol% lanthanum(III) trifluoromethanesulfonate as yellow oil (41.3 mg, 92% yield). $[\alpha]_D^{25}$ +26.9 (c 0.72, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.26 (d, J = 8.0 Hz, 2H, ArH), 7.04 (d, J = 8.0 Hz, 2H, ArH), 3.58 (s, 3H, OCH_3), 3.49–3.42 (m, 1H, CH), 2.54 (dd, J_1 = 15.6 Hz, J_2 = 6.0 Hz, 1H, CH_2), 2.33 (dd, J_1 = 15.8 Hz, J_2 = 8.8 Hz, 1H, CH_2), 2.25 (s, 3H, CH_3), 1.22 (d, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 137.7, 133.6, 129.6, 51.6, 41.5, 39.7, 21.0, 20.7 ppm.

The configurations of other products were assigned by analogy.

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