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# Organocatalytic Enantioselective Sulfur-Michael Addition of Thioacetic Acid to Arylmethylidenemalonates

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**Abstract:** An organocatalytic enantioselective sulfur-Michael addition of thioacetic acid to arylmethylidenemalonates was developed with high yields and up to 97% enantiomeric excess. Both enantiomers of the products were accessible with two different organocatalysts. The current method provides the first, practical, and convenient preparation of enantiomerically enriched acetylthiomethylmalonate derivatives.

**Keywords:** alkylidenemalonates; Michael addition; organocatalysis; thioacetic acid

## Introduction

Optically active chiral organic sulfur-containing compounds play an important role in biochemistry and pharmaceutical chemistry.[1] The asymmetric sulfur-Michael addition (SMA) represents a fundamental method for creating the carbon-sulfur bond in an asymmetric fashion.[2] Although various catalytic asymmetric SMAs employing alkyl or aryl thiols as sulfur nucleophiles have been developed over the past few decades,[3] reactions using thiocarboxylic acids have been less explored. The asymmetric additions of thiocarboxylic acids to α,β-unsaturated ketones catalyzed by *Cinchona* alkaloid, chiral amine thiourea or urea have been reported during the past few years with moderate enantioselectivities.[4] Wang and co-workers disclosed an efficient method for enantioselective SMA of thioacetic acid with β-nitrostyrenes with high yields and moderate enantioselectivities in 2006.[5] Ellman's group applied the *N*-sulfinylurea-catalyzed enantio- and diastereoselective SMA of thioacetic acid to nitroalkenes with high stereocontrol.[6] Chiral squaramides were also effective organocatalysts in the SMA of thioacetic acid to α,β-disubstituted nitroalkenes with good to excellent diastereo- and enantioselectivities.[7] Currently, the substrate scope of asymmetric SMAs using thiocarboxylic acids is limited to α,β-unsaturated ketones and nitroalkenes.

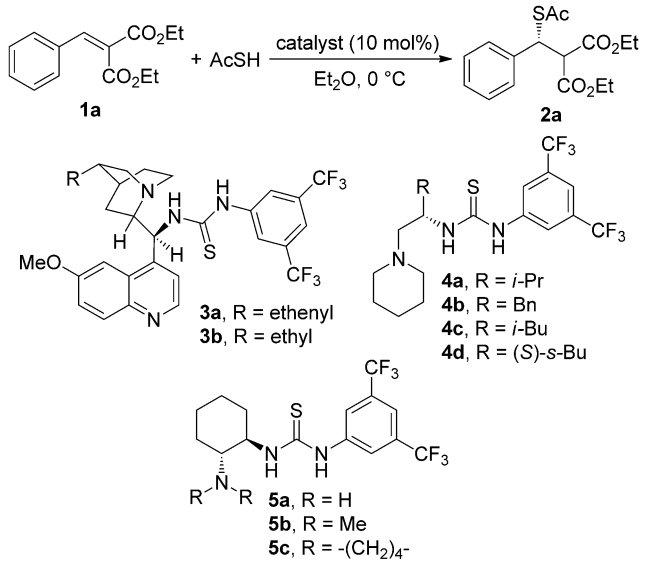
Arylmethylidenemalonates, as good Michael addition acceptors, have been involved in asymmetric reactions with several nucleophiles, such as ketones,[8] indoles,[9] and nitroalkanes[10] etc. However, the asymmetric SMA of thiocarboxylic acids to arylmethylidenemalonates has not been explored to date. Herein, we present the first and highly enantioselective SMA of thioacetic acid to arylmethylidenemalonates catalyzed by bifunctional amine thioureas with high yields and up to 97% *ee*.

## Results and Discussion

Bifunctional amine thioureas have proved to be powerful catalysts in asymmetric SMAs, thus three types of amine thiourea catalysts bearing different chiral skeletons were synthesized and tested in the enantioselective SMA of thioacetic acid to diethyl 2-benzylidenemalonate (**1a**). As the results in Table 1 show, organocatalysts **3–5** effectively catalyzed the reaction with high yields and good enantioselectivities. Catalyst **3a** based on quinine was found to be the best choice with 76% *ee* (Table 1, entry 1), while catalysts **4** derived from L-amino acids afforded slightly lower enantioselectivities than **3** (Table 1, entries 1–6). The opposite enantiomer was obtained with catalysts **5**, derived from (*R*,*R*)-cyclohexane-1,2-diamine (Table 1, entries 7–9), and good enantioselectivity is maintained with catalyst **5b** compared with catalyst **3a** (Table 1, entry 8). Thus, both enantiomers of products **2a** and *ent*-**2a** were accessible by using either catalyst **3a** or **5b**.

**Table 1.** Asymmetric Michael addition of thioacetic acid to diethyl 2-benzylidenemalonate (**1a**) catalyzed by different organocatalysts.[a]




| Entry | Catalyst | Yield[b] [%] | *ee*[c] [%] |
|---|---|---|---|
| 1 | **3a** | 98 | 76 |
| 2 | **3b** | 97 | 75 |
| 3 | **4a** | 95 | 66 |
| 4 | **4b** | 92 | 62 |
| 5 | **4c** | 96 | 64 |
| 6 | **4d** | 95 | 67 |
| 7 | **5a** | 90 | −34[d] |
| 8 | **5b** | 94 | −74[d] |
| 9 | **5c** | 93 | −68[d] |

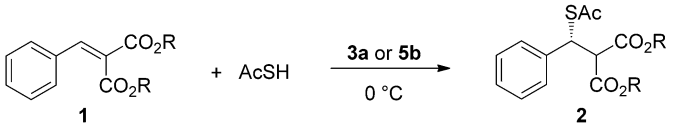
[a] Reactions were carried out with **1a** (24.8 mg, 0.10 mmol) and AcSH (14 μL, 15.2 mg, 0.2 mmol) in the presence of 10 mol% organocatalyst in $Et_2O$ (1 mL) at 0 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using an AS-H chiral column and hexane-2-propanol (90:10, *v*/*v*) as eluent.
[d] The product is *ent*-**2a**.

After identifying the catalysts **3a** and **5b** as the best catalysts for each of the enantiomers, we turned our attention to optimizing the reaction conditions and the results are shown in Table 2. The catalyst loading had little effect on enantioselectivity and 5 mol% catalyst loading provided the best result (Table 2, entries 1–5). To check the effect of the ester group on the reactivity and enantioselectivity in the asymmetric SMA reaction, substrates bearing different ester groups were probed (Table 2, entries 6–13). The reactivity of the substrate dropped significantly as the steric hindrance of the substrate increased, and the enantioselectivity varied to a certain extent. Among the five substrates bearing different ester groups, diethyl substrate **1a** gave the best result with both catalysts **3a** and **5b**, and diisopropyl 2-benzylidenemalonate (**1c**) gave slightly lower *ee* compared with **1a**. Substrate concentration had almost no influence on the reaction (Table 2, entries 14 and 15), and use of 4 Å molecule sieve had a negative effect on the enantioselectivity in the reaction. Next we undertook a screening of the solvent effect and found that the solvent has a great impact on the asymmetric SMA (Table 2, entries 17–23). The reaction became sluggish when performed in dichloromethane or chloroform, meanwhile *ee* values decreased. Toluene is a good reaction medium, and ether was found to be superior for the reaction. Diisopropyl ether was finally selected as the reaction solvent with the highest *ee* of 78%. Lowering the reaction temperature resulted in an improvement on the product *ee* although at the expense of longer reaction time, and the reaction at −40 °C afforded the desired product **2a** in 97% yield with 82% *ee* (Table 2, entries 24 and 25).

Under the optimal reaction conditions, a series of arylmethylidenemalonates **1** was reacted with thioacetic acid as shown in Table 3. Firstly we were pleased to find that *ortho*-substitution on the aromatic ring resulted in a remarkable increase in the enantioselectivity (Table 3, entries 2–4). The benefit of *ortho*-substitution was further demonstrated *via* various *ortho*-substituted arylmethylidenemalonates with excellent stereocontrol compared with their *para*-substituted counterparts (Table 3, entries 5–12). Except for methoxy-substituted substrate **1m** with moderate enantioselectivity possibly due to the electronic effect and formation of hydrogen bonding between the catalyst and the methoxy group, the substrates with electron-withdrawing groups at the *ortho*-position afforded excellent *ee* values. Diethyl 2-(naphthalen-1-ylmethylene)malonate (**1q**) was also a suitable substrate for the reaction with 96% yield and 97% *ee* (Table 3, entry 13). However, 2,6-dichlorophenylmethylidenemalonate (**1r**), a double *ortho*-substituted substrate, gave rise to the desired adduct **2r** in excellent yield but poor enantioselectivity (Table 3, entry 14). Furthermore, the opposite enantiomers with high yields and moderate to excellent *ee* values were obtained as the major products with catalyst **5b** (Table 3, entries 15–21). Similar to the results obtained with catalyst **3a**, o*rtho*-substitution was also critical for obtaining high stereoselectivity with **5b** as a catalyst. To extend the substrate scope, an aliphatic substrate diethyl cyclohexylmethylidenemalonate (**1s**) was prepared and attempted. However, moderate yield and poor enantioselectivity were observed (Table 3, entry 22). The results reveal that our catalytic system shows good performance for *ortho*-substituted aromatic substrates with high yields and excellent enantioselectivity.

To determine the absolute configuration of the products **2**, **2a** was selected and converted to 3-mercapto-3-phenylpropanoic acid *via* acidic hydrolysis.

**Table 2.** Optimization of the reaction conditions for the asymmetric Michael addition of thioacetic acid to different arylmethylidenemalonates.[a]




| Entry | R | Catalyst (mol%) | Solvent | Time [h] | Product | Yield[b] [%] | *ee*[c] [%] |
|---|---|---|---|---|---|---|---|
| 1 | Et | **3a** (20) | $Et_2O$ | 0.5 | **2a** | 95 | 74 |
| 2 | Et | **3a** (10) | $Et_2O$ | 1 | **2a** | 96 | 76 |
| 3 | Et | **3a** (5) | $Et_2O$ | 1.5 | **2a** | 94 | 76 |
| 4 | Et | **3a** (2.5) | $Et_2O$ | 3 | **2a** | 93 | 74 |
| 5 | Et | **3a** (1.3) | $Et_2O$ | 4 | **2a** | 94 | 74 |
| 6 | Me | **3a** (5) | $Et_2O$ | 1 | **2b** | 98 | 56 |
| 7 | *i*-Pr | **3a** (5) | $Et_2O$ | 14 | **2c** | 94 | 75 |
| 8 | *t*-Bu | **3a** (5) | $Et_2O$ | 20 | **2d** | 55 | 67 |
| 9 | Bn | **3a** (5) | $Et_2O$ | 1.5 | **2e** | 94 | 53 |
| 10 | Me | **5b** (5) | $Et_2O$ | 1 | *ent*-**2b** | 96 | −68 |
| 11 | *i*-Pr | **5b** (5) | $Et_2O$ | 12 | *ent*-**2c** | 95 | −70 |
| 12 | *t*-Bu | **5b** (5) | $Et_2O$ | 24 | *ent*-**2d** | 70 | −60 |
| 13 | Bn | **5b** (5) | $Et_2O$ | 1.5 | *ent*-**2e** | 92 | −61 |
| 14[d] | Et | **3a** (5) | $Et_2O$ | 1 | **2a** | 98 | 76 |
| 15[e] | Et | **3a** (5) | $Et_2O$ | 3 | **2a** | 97 | 76 |
| 16[f] | Et | **3a** (5) | $Et_2O$ | 2 | **2a** | 99 | 67 |
| 17 | Et | **3a** (5) | $CH_2Cl_2$ | 5.5 | **2a** | 20 | 44 |
| 18 | Et | **3a** (5) | $CHCl_3$ | 5.5 | **2a** | 15 | 29 |
| 19 | Et | **3a** (5) | PhMe | 3.5 | **2a** | 93 | 73 |
| 20 | Et | **3a** (5) | THF | 5 | **2a** | 60 | 34 |
| 21 | Et | **3a** (5) | $(i\text{-Pr})_2O$ | 4 | **2a** | 99 | 78 |
| 22 | Et | **3a** (5) | *t*-BuOMe | 4 | **2a** | 96 | 75 |
| 23 | Et | **3a** (5) | PhOMe | 6 | **2a** | 89 | 29 |
| 24[g] | Et | **3a** (5) | $(i\text{-Pr})_2O$ | 7 | **2a** | 96 | 81 |
| 25[h] | Et | **3a** (5) | $(i\text{-Pr})_2O$ | 22 | **2a** | 97 | 82 |

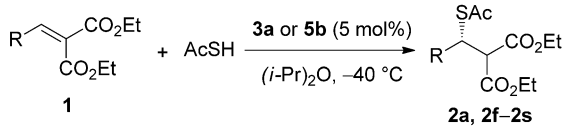
[a] Reactions were conducted with **1** (0.10 mmol) and AcSH (14 μL, 15.2 mg, 0.2 mmol) in the presence of organocatalyst **3a** or **5b** in solvent (1 mL).
[b] Isolated yield.
[c] Determined by HPLC analysis using an AS-H or AD-H chiral column.
[d] With $Et_2O$ (0.5 mL) as solvent.
[e] With $Et_2O$ (2 mL) as solvent.
[f] With 4 Å molecular sieve.
[g] Reaction was performed at −20 °C.
[h] Reaction was carried out at −40 °C.

The acid was further esterified to afford the corresponding known ester **6**,[11] which shows the opposite direction of optical rotation compared with the reported methyl (*S*)-3-mercapto-3-phenylpropanoate.[12] Thus, the absolute configuration of both esters **6** and **2a** should be *R* (Scheme 1). Certain decrease in the enantiomeric excess was observed in this transformation, which was possibly due to the enolization of the carboxylic acid group and the double bond rearrangement to the conjugated position with the phenyl group under reflux at high temperature.

To extend the application of products **2**, product **2a** was also subjected to selective hydrolysis. The free mercaptan, diethyl (*R*)-mercapto(phenyl)methylmalonate (**7**), was obtained in high yield and without loss of enantioselectivity in acidic ethanol solution (12 M HCl/EtOH) (Scheme 1).[13] The results indicate that both thioacetate and malonate were hydrolyzed in the relatively diluted hydrochloric acid (6 M HCl aqueous solution), while only acetyl was removed in the concentrated solution of hydrochloric acid in ethanol (12 M HCl/EtOH), revealing that the thioacetate group is less stable than the carboxylates in the acidic hydrolysis because deacetylation occurred in each of cases (Scheme 1). Here, diethyl (*R*)-acetylthio(phenyl)methylmalonate (**2a**) was successfully converted to diethyl (*R*)-mercapto(phenyl)methylmalonate (**7**), (*R*)-3-mercapto-3-phenylpropanoic acid, and methyl

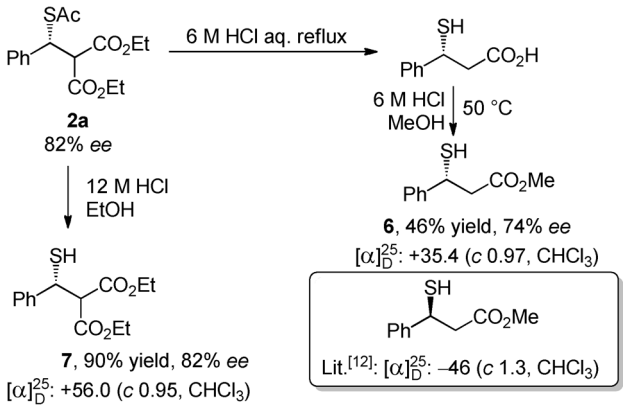
  

**Table 3.** Asymmetric Michael addition of thioacetic acid to arylmethylidenemalonates **1**.[a]



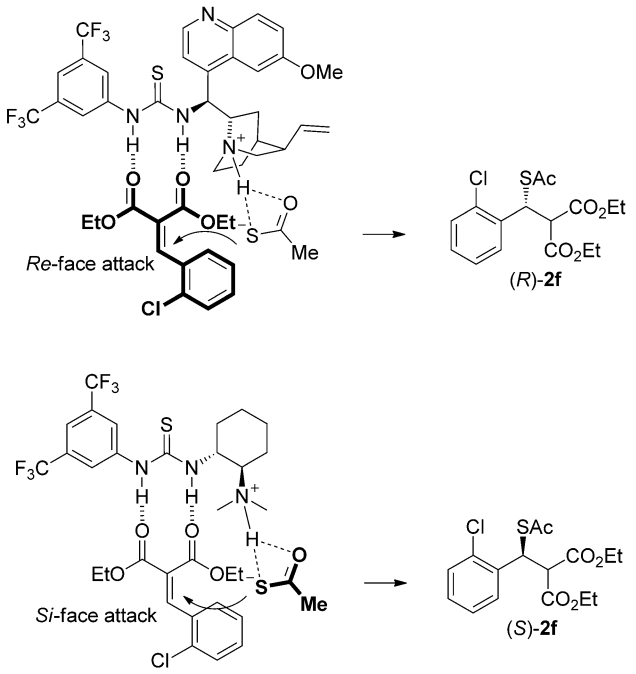

| Entry | R | Catalyst | Product | Yield[b] [%] | *ee*[c] [%] |
|---|---|---|---|---|---|
| 1 | Ph | **3a** | **2a** | 97 | 82 |
| 2 | 2-$ClC_6H_4$ | **3a** | **2f** | 95 | 97 |
| 3 | 3-$ClC_6H_4$ | **3a** | **2g** | 96 | 82 |
| 4 | 4-$ClC_6H_4$ | **3a** | **2h** | 98 | 81 |
| 5 | 2-$FC_6H_4$ | **3a** | **2i** | 99 | 91 |
| 6 | 2-$BrC_6H_4$ | **3a** | **2j** | 99 | 97 |
| 7 | 2-$F_3CC_6H_4$ | **3a** | **2k** | 94 | 97 |
| 8 | 2-$MeC_6H_4$ | **3a** | **2l** | 92 | 90 |
| 9 | 2-$MeOC_6H_4$ | **3a** | **2m** | 90 | 68 |
| 10 | 4-$FC_6H_4$ | **3a** | **2n** | 94 | 79 |
| 11 | 4-$BrC_6H_4$ | **3a** | **2o** | 97 | 79 |
| 12 | 4-$MeOC_6H_4$ | **3a** | **2p** | 99 | 60 |
| 13 | 1-naphthyl | **3a** | **2q** | 96 | 97 |
| 14 | 2,6-$Cl_2C_6H_3$ | **3a** | **3r** | 92 | 26 |
| 15 | 2-$ClC_6H_4$ | **5b** | *ent*-**2f** | 97 | −96 |
| 16 | 4-$ClC_6H_4$ | **5b** | *ent*-**2h** | 95 | −77 |
| 17 | 2-$MeC_6H_4$ | **5b** | *ent*-**2l** | 93 | −92 |
| 18 | 2-$MeOC_6H_4$ | **5b** | *ent*-**2m** | 94 | −72 |
| 19 | 4-$BrC_6H_4$ | **5b** | *ent*-**2o** | 95 | −79 |
| 20 | 4-$MeOC_6H_4$ | **5b** | *ent*-**2p** | 96 | −62 |
| 21 | 1-naphthyl | **5b** | *ent*-**2q** | 97 | −97 |
| 22 | cyclohexyl | **3a** | **2s** | 85 | 12 |

[a] Reactions were carried out with **1** (0.10 mmol) and AcSH (14 μL, 15.2 mg, 0.2 mmol) in the presence of 5 mol% catalyst in $(i\text{-Pr})_2O$ (1 mL) at −40 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using an AS-H or AD-H chiral column.




**Scheme 1.** Transformations of product **2a**.

(*R*)-3-mercapto-3-phenylpropanoate (**6**). Different optically active sulfur-containing compounds were obtained from our products **2** *via* simple conversion.




**Scheme 2.** Plausible transition state models.

Based on the experimental results, both plausible transition state models for the two complementary catalyst systems were proposed to account for the major products' absolute stereochemistry (Scheme 2).[14] Arylmethylidenemalonate **1f** interacts with the thiourea moiety of the catalyst **3a** *via* double H-bonds, while thioacetic acid is deprotonated by the tertiary amine group and attacks the pro-chiral carbon center of **1f** from its *Re* face, thus generating the desired product **2f** with *R* configuration. In addition, the *ortho*-substitution on the aromatic ring increases the steric hindrance near the pro-chiral center, inhibiting the free rotation of the C–C bond between the aryl group and the C=C bond, predominant formation of the π-stacking interaction between the aryl group and thioacetate. The π-stacking interaction is favorable to the proposed transition state, resulting in improvement of the enantioselectivity (Table 3, entries 1 and 16). Thioacetate is an electron-rich conjugative species. The electron-deficient *ortho*-substituted substrates **1f** and **1i–k** show stronger π-stacking interaction with it, resulting in higher *ee* values than the substrates **1l** and **1m** with electron-rich *ortho*-substituents. For aliphatic substrate **1s**, poor enantioselectivity was observed possibly due to the lack of π-stacking interaction. These results support the π-stacking interaction. Similar phenomena were also observed in other asymmetric catalytic reactions.[15] When catalyzed by **5b**, thioacetic acid attacks the *Si* face of the pro-chiral carbon center of **1f** due to the opposite configuration of the thiourea and ter-

tiary amine groups in the catalysts **5**, and (*S*)-**2f** was obtained as the major product.

## Conclusions

In summary, we have successfully developed the first organocatalytic and highly stereoselective sulfur Michael addition of thioacetic acid to arylmethylidenemalonates. High yields and moderate to excellent enantioselectivities are observed with a wide substrate scope, especially with *ortho*-substituted arylmethylidenemalonates, and both enantiomers of the products are accessible. This approach expands the scope of the asymmetric sulfur-Michael addition with thiocarboxylic acids and provides a practical method for the preparation of enantiomerically enriched sulfur-containing malonate derivatives.

## Experimental Section

### General Information

Melting points were measured on a Yanaco MP-500 melting point apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Bruker 400 MHz spectrometer. Chemical shifts are reported in ppm with TMS signal at 0.0 ppm as an internal standard. $^{13}$C NMR spectra were recorded at 100 MHz. The IR spectra (KBr pellets, $v$ [cm$^{-1}$]) were taken on a Nicolet 370 MCT FTIR spectrometer. The high resolution mass spectra were obtained with ESI ionization using a Waters Xevo G2 Q-Tof MS. Optical rotations were measured with an Anton Paar MCP 200 polarimeter at the indicated concentration with units g/100 mL. The enantiomeric excesses were determined by chiral HPLC analysis using an Agilent 1260 LC instrument with Daicel Chiralpak AS-H or AD-H column. Column chromatography was carried out with silica gel (200–300 mesh). Commercially available compounds were used as received without further purification, unless otherwise stated. Catalysts **3**,[16] **4**,[17] and **5**[18] and arylmethylidenemalonates[19] were prepared according to the literature procedures and their analytic data are identical as those reported.

### General Procedure for the Organocatalytic Enantioselective Michael Addition of Thioacetic Acid to Arylmethylidenemalonates 1

To a stirred solution of arylmethylidenemalonate **1** (0.1 mmol), catalyst **3a** or **5b** (5 mol%) in (*i*-Pr)$_2$O (1 mL) at −40 °C was added thioacetic acid (14 μL, 15.2 mg, 0.2 mmol). The reaction mixture was stirred until the disappearance of the starting material as detected by TLC. The solution was directly subject to column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1 *v*/*v* as eluent) to afford the desired product **2**.

**Diethyl (*R*)-acetylthio(phenyl)methylmalonate (2a):** Colorless oil; yield: 31.4 mg (97%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, $J$ = 7.2 Hz, 3H), 1.25 (t, $J$ = 7.2 Hz, 3H), 2.28 (s, 3H), 4.02 (q, $J$ = 7.2 Hz, 2H), 4.01 (d, $J$ = 10.0 Hz, 1H), 4.20 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.21 (dq, $J$ = 10.8, 7.2 Hz, 1H), 5.34 (d, $J$ = 10.0 Hz, 1H), 7.21–7.30 (m, 3H), 7.35–7.38 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.7, 14.0, 30.3, 46.0, 57.3, 61.8, 61.9, 127.8, 128.1, 128.5, 139.4, 166.4, 166.8, 192.8; IR (KBr): $v$ = 2962, 2922, 1734, 1696, 1384, 1258, 1096, 1031, 801, 698, 629 cm$^{-1}$; HR-MS (ESI): $m/z$ = 325.1109, calcd. for $C_{16}H_{21}O_5S^+$ $[M+H]^+$: 325.1110. The *ee* was determined to be 82% by chiral HPLC analysis (AS-H column, hexane-2-propanol 90:10, 1.0 mL min$^{-1}$, λ = 220 nm): $t_R$ (major, *R*) = 7.4 min, $t_R$ (minor, *S*) = 6.7 min; $[\alpha]_D^{20}$: 104.4 (*c*, 1.08, $CHCl_3$).

**Dimethyl (*R*)-acetylthio(phenyl)methylmalonate (2b):** Colorless oil; yield of **2b**: 29.1 mg (98%); yield of *ent*-**2b**: 28.5 mg (96%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 3.57 (s, 3H), 3.74 (s, 3H), 4.05 (d, $J$ = 9.6 Hz, 1H), 5.33 (d, $J$ = 9.6 Hz, 1H), 7.21–7.32 (m, 3H), 7.34–7.37 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 30.3, 46.1, 52.7, 52.8, 57.1, 127.9, 128.0, 128.6, 139.1, 166.8, 167.2, 192.7; IR (KBr): $v$ = 2953, 2923, 1740, 1696, 1453, 1354, 1255, 1142, 1022, 952, 699, 624 cm$^{-1}$; HR-MS (ESI): $m/z$ = 297.0800, calcd. for $C_{14}H_{17}O_5S^+$ $[M+H]^+$: 297.0797. The *ee* was determined to be 56% with catalyst **3a** and −68% with catalyst **5b** by chiral HPLC analysis (AS-H column, hexane-2-propanol 90:10, 1.0 mL min$^{-1}$, λ = 220 nm): $t_R$ (*R*) = 8.2 min, $t_R$ (*S*) = 7.8 min; **2b:** $[\alpha]_D^{20}$: +65.8 (*c*, 0.96, $CHCl_3$); *ent*-**2b**: $[\alpha]_D^{20}$: −79.6 (*c*, 0.98, $CHCl_3$).

**Diisopropyl (*R*)-acetylthio(phenyl)methylmalonate (2c):** Colorless crystals; yield of **2c**: 33.0 mg (94%); yield of *ent*-**2c**: 33.6 mg (95%); mp 66–68 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, $J$ = 6.4 Hz, 3H), 1.07 (d, $J$ = 6.4 Hz, 3H), 1.22 (d, $J$ = 6.0 Hz, 3H), 1.23 (d, $J$ = 6.0 Hz, 3H), 2.28 (s, 3H), 3.96 (d, $J$ = 10.0 Hz, 1H), 4.85 (hept, $J$ = 6.4 Hz, 1H), 5.06 (hept, $J$ = 6.4 Hz, 1H), 5.33 (d, $J$ = 10.0 Hz, 1H), 7.19–7.24 (m, 1H), 7.25–7.30 (m, 2H), 7.35–7.38 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 21.3, 21.4, 21.6, 30.3, 45.9, 57.5, 69.5, 69.5, 127.7, 128.1, 128.4, 139.6, 165.9, 166.4, 192.8; IR (KBr): $v$ = 2981, 2933, 1732, 1699, 1454, 1375, 1261, 1102, 909, 698, 630 cm$^{-1}$; HR-MS (ESI): $m/z$ = 353.1426, calcd. for $C_{18}H_{25}O_5S^+$ $[M+H]^+$: 353.1423. The *ee* was determined to be 75% with catalyst **3a** and −70% with catalyst **5b** by chiral HPLC analysis (AS-H column, hexane-2-propanol 90:10, 1.0 mL min$^{-1}$, λ = 220 nm): $t_R$ (*R*) = 5.0 min, $t_R$ (*S*) = 4.5 min; **2c:** $[\alpha]_D^{20}$: +90.4 (*c*, 1.01, $CHCl_3$), *ent*-**2c:** $[\alpha]_D^{20}$: −83.4 (*c*, 1.06, $CHCl_3$).

**Di-*tert*-butyl (*R*)-acetylthio(phenyl)methylmalonate (2d):** Colorless crystals; yield of **2d**: 21.0 mg (55%), yield of *ent*-**2d**: 26.5 mg (70%); mp 98–99 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9H), 1.44 (s, 9H), 2.28 (s, 3H), 3.83 (d, $J$ = 10.0 Hz, 1H), 5.27 (d, $J$ = 9.6 Hz, 1H), 7.19–7.29 (m, 3H), 7.35–7.38 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 27.5, 27.8, 30.3, 46.0, 58.8, 82.2, 82.3, 127.5, 128.2, 128.3, 139.9, 165.6, 166.1, 193.0; IR (KBr): $v$ = 2978, 2932, 1733, 1699, 1393, 1369, 1290, 1256, 1139, 849, 747, 698, 631 cm$^{-1}$; HR-MS (ESI): $m/z$ = 381.1735, calcd. for $C_{20}H_{29}O_5S^+$ $[M+H]^+$: 381.1736. The *ee* was determined to be 67% with catalyst **3a** and −60% with catalyst **5b** by chiral HPLC analysis (AD-H column, hexane-2-propanol 90:10, 1.0 mL min$^{-1}$, λ = 220 nm): $t_R$ (*R*) = 5.3 min, $t_R$ (*S*) = 7.4 min; **2d:** $[\alpha]_D^{20}$: +75.2 (*c*, 1.01, $CHCl_3$), *ent*-**2d:** $[\alpha]_D^{20}$: −67.5 (*c*, 1.13, $CHCl_3$).

**Dibenzyl (*R*)-acetylthio(phenyl)methylmalonate (2e):** Colorless crystals; yield of **2e**: 42.3 mg (94%), yield of *ent*-

**2e**: 41.3 mg (92%); mp 119–121 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 3H), 4.14 (d, $J$ = 10.0 Hz, 1H), 4.95 (s, 2H), 5.12 (d, $J$ = 12.4 Hz, 1H), 5.16 (d, $J$ = 12.4 Hz, 1H), 5.36 (d, $J$ = 9.6 Hz, 1H), 7.07–7.10 (m, 2H), 7.21–7.32 (m, 13H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 30.2, 46.0, 57.2, 67.4, 67.5, 127.8, 128.0, 128.2, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 134.8, 135.0, 139.1, 166.1, 166.5, 192.6; IR (KBr): $\nu$ = 3064, 3033, 2958, 1737, 1698, 1455, 1377, 1258, 1215, 1133, 1029, 951, 750, 698, 626. HRMS (ESI) calcd for $C_{26}H_{25}O_5S^+$ $[M+H]^+ = m/z$: 449.1423; found: 449.1423 cm$^{-1}$. The *ee* was determined to be 53% with catalyst **3a** and −61% with catalyst **5b** by chiral HPLC analysis (AS-H column, hexane-2-propanol 90:10, 1.0 mL min$^{-1}$, λ = 220 nm): $t_R$ (*R*) = 10.9 min, $t_R$ (*S*) = 12.6 min; **2e:** $[\alpha]_D^{20}$: +41.9 (*c*, 1.09, $CHCl_3$), *ent*-**2e**: $[\alpha]_D^{20}$: −47.9 (*c*, 1.00, $CHCl_3$).

**Diethyl (*R*)-acetylthio(2-chlorophenyl)methylmalonate (2f):** Yellowish oil; yield of **2f**: 34.0 mg (95%), yield of *ent*-**2f**: 34.9 mg (97%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.09 (t, $J$ = 7.2 Hz, 3H), 1.24 (t, $J$ = 7.2 Hz, 3H), 2.29 (s, 3H), 4.06 (q, $J$ = 7.2 Hz, 2H), 4.17 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.20 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.32 (d, $J$ = 9.2 Hz, 1H), 5.70 (d, $J$ = 9.2 Hz, 1H), 7.18–7.21 (m, 2H), 7.34–7.36 (m, 1H), 7.48–7.51 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.8, 13.9, 30.1, 44.0, 55.5, 61.8, 126.8, 129.1, 130.0, 131.0, 133.6, 136.3, 166.5, 166.8, 192.8; IR (KBr): $\nu$ = 2980, 2928, 1733, 1699, 1475, 1391, 1245, 1132, 1038, 954, 755, 630 cm$^{-1}$; HR-MS (ESI): $m/z$ = 359.0719, calcd. for $C_{16}H_{20}ClO_5S^+$ $[M+H]^+$: 359.0720. The *ee* was determined to be 97% with catalyst **3a** and −96% with catalyst **5b** by chiral HPLC analysis (AS-H column, hexane-2-propanol 90:10, 1.0 mL min$^{-1}$, λ = 220 nm): $t_R$ (*R*) = 6.6 min, $t_R$ (*S*) = 6.2 min. **2f:** $[\alpha]_D^{20}$: 68.5 (*c*, 1.06, $CHCl_3$), *ent*-**2f:** $[\alpha]_D^{20}$: −65.8 (*c*, 1.01, $CHCl_3$).

**Diethyl (*R*)-acetylthio(3-chlorophenyl)methylmalonate (2g):** Yellowish oil; yield: 34.4 mg (96%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.10 (t, $J$ = 7.2 Hz, 3H), 1.26 (t, $J$ = 7.2 Hz, 3H), 2.30 (s, 3H), 3.97 (d, $J$ = 9.6 Hz, 1H), 4.05 (q, $J$ = 7.2 Hz, 2H), 4.20 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.22 (dq, $J$ = 10.8, 7.2 Hz, 1H), 5.29 (d, $J$ = 9.6 Hz, 1H), 7.20–7.23 (m, 2H), 7.25–7.27 (m, 1H), 7.36–7.37 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.8, 13.9, 30.3, 45.5, 56.9, 61.9, 62.0, 126.4, 128.0, 128.4, 129.7, 134.2, 141.4, 166.2, 166.6, 192.5; IR (KBr): $\nu$ = 2982, 1735, 1700, 1476, 1369, 1301, 1249, 1131, 1098, 953, 692, 626 cm$^{-1}$; HR-MS (ESI): $m/z$ = 359.0716, calcd. for $C_{16}H_{20}ClO_5S^+$ $[M+H]^+$: 359.0720. The *ee* was determined to be 82% by chiral HPLC analysis (AD-H column, hexane-2-propanol 99:1, 1.0 mL min$^{-1}$, λ = 220 nm): $t_R$ (major, *R*) = 32.8 min, $t_R$ (minor, *S*) = 30.3 min. $[\alpha]_D^{20}$: 84.7 (*c*, 0.94, $CHCl_3$).

**Diethyl (*R*)-acetylthio(4-chlorophenyl)methylmalonate (2h):** Yellowish oil; yield of **2h**: 35.3 mg (98%), yield of *ent*-**2h**: 34.0 mg (95%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.09 (t, $J$ = 7.2 Hz, 3H), 1.26 (t, $J$ = 7.2 Hz, 3H), 2.29 (s, 3H), 3.97 (d, $J$ = 10.0 Hz, 1H), 4.04 (q, $J$ = 7.2 Hz, 2H), 4.19 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.22 (dq, $J$ = 10.8, 7.2 Hz, 1H), 5.29 (d, $J$ = 9.6 Hz, 1H), 7.25 (d, $J$ = 8.4 Hz, 2H), 7.32 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.8, 14.0, 30.3, 45.4, 57.0, 61.9, 62.0, 128.6, 129.6, 133,6, 138.0, 166.2, 166.6, 192.6; IR (KBr): $\nu$ = 2962, 2920, 1733, 1699, 1490, 1384, 1259, 1127, 1015, 799, 625 cm$^{-1}$; HR-MS (ESI): $m/z$ = 381.0539, calcd. for $C_{16}H_{19}ClO_5SNa^+$ $[M+Na]^+$: 381.0539. The *ee* was determined to be 81% with catalyst **3a** and −77% with catalyst **5b** by chiral HPLC analysis (AS-H column, hexane-2-propanol 98:2, 1.0 mL min$^{-1}$, λ = 220 nm): $t_R$ (*R*) = 16.1 min, $t_R$ (*S*) = 15.1 min. **2h**: $[\alpha]_D^{20}$: 64.4 (*c*, 1.02, $CHCl_3$), *ent*-**2h**: $[\alpha]_D^{20}$: −61.5 (*c*, 0.98, $CHCl_3$).

**Diethyl (*R*)-acetylthio(2-fluorophenyl)methylmalonate (2i):** Colorless oil; yield: 34.0 mg (99%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, $J$ = 7.2 Hz, 3H), 1.25 (t, $J$ = 7.2 Hz, 3H), 2.29 (s, 3H), 4.01 (q, $J$ = 7.2 Hz, 2H), 4.16 (d, $J$ = 10.4 Hz, 1H), 4.19 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.22 (dq, $J$ = 10.8, 7.2 Hz, 1H), 5.49 (d, $J$ = 10.8 Hz, 1H), 7.00–7.08 (m, 2H), 7.21–7.27 (m, 1H), 7.42–7.46 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.7, 13.9, 30.2, 41.3, 55.7 (d, $^3J_{C,F}$ = 3 Hz), 61.8, 61.9, 115.7 (d, $^2J_{C,F}$ = 22 Hz), 124.0 (d, $^4J_{C,F}$ = 3 Hz), 126.2 (d, $^2J_{CF}$ = 13 Hz), 129.7 (d, $^3J_{C,F}$ = 8 Hz), 130.7 (d, $^3J_{C,F}$ = 4 Hz), 160.5 (d, $^1J_{C,F}$ = 247 Hz), 166.3, 166.6, 192.5; IR (KBr): $\nu$ = 2984, 2925, 1735, 1696, 1492, 1369, 1309, 1236, 1142, 1106, 954, 757, 625 cm$^{-1}$; HR-MS (ESI): m/z = 343.1012, calcd. for $C_{16}H_{20}FO_5S^+$ $[M+H]^+$: 343.1015. The *ee* was determined to be 91% by chiral HPLC analysis (AS-H column, hexane-2-propanol 90:10, 1.0 mL min$^{-1}$, λ = 220 nm): $t_R$ (major, *R*) = 7.8 min, $t_R$ (minor, *S*) = 6.9 min. $[\alpha]_D^{20}$: 100.0 (*c*, 0.99, $CHCl_3$).

**Diethyl (*R*)-acetylthio(2-bromophenyl)methylmalonate (2j):** Yellowish oil; yield: 40.0 mg (99%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, $J$ = 7.2 Hz, 3H), 1.23 (t, $J$ = 7.2 Hz, 3H), 2.30 (s, 3H), 4.07 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.09 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.16 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.19 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.33 (d, $J$ = 8.4 Hz, 1H), 5.71 (d, $J$ = 8.4 Hz, 1H), 7.11 (ddd, $J$ = 1.2, 7.6, 7.6 Hz, 1H), 7.24 (ddd, $J$ = 1.2, 7.6 7.6 Hz, 1H), 7.51 (dd, $J$ = 1.2, 7.6 Hz, 1H), 7.55 (dd, $J$ = 1.2, 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.8, 13.9, 30.1, 46.0, 55.6, 61.8, 61.8, 123.8, 127.4, 129.3, 131.0, 133.3, 137.9, 166.5, 166.8, 192.9; IR (KBr): $\nu$ = 2980, 2928, 1732, 1699, 1469, 1369, 1259, 1097, 953, 752, 626 cm$^{-1}$; HR-MS (ESI): $m/z$ = 403.0219, calcd. for $C_{16}H_{20}BrO_5S^+$ $[M+H]^+$: 403.0215. The *ee* was determined to be 97% by chiral HPLC analysis (AS-H column, hexane-2-propanol 96:4, 1.0 mL min$^{-1}$, λ = 220 nm): $t_R$ (major, *R*) = 11.9 min, $t_R$ (minor, *S*) = 11.0 min. $[\alpha]_D^{20}$: 40.2 (*c*, 1.06, $CHCl_3$).

**Diethyl (*R*)-acetylthio(2-trifluorophenyl)methylmalonate (2k):** Colorless oil; yield: 37.0 mg (94%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, $J$ = 7.2 Hz, 3H), 1.22 (t, $J$ = 7.2 Hz, 3H), 2.28 (s, 3H), 4.09 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.12 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.16 (d, $J$ = 6.8 Hz, 1H), 4.16 (dq, $J$ = 10.8, 7.2 Hz, 1H), 4.19 (dq, $J$ = 10.8, 7.2 Hz, 1H), 5.76 (d, $J$ = 6.8 Hz, 1H), 7.34–7.39 (m, 1H), 7.47–7.51 (m, 1H), 7.65–7.67 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.7, 13.9, 30.0, 42.1, 57.3, 61.8, 61.9, 124.1 (q, $J_{C,F}$ = 272.6 Hz), 126.6 (q, $J_{C,F}$ = 5.8 Hz), 127.8 (q, $J_{C,F}$ = 29.8 Hz), 127.9, 130.6, 132.0, 137.9, 166.4, 167.0, 192.4; IR (KBr): $\nu$ = 2982, 1737, 1704, 1312, 1156, 1127, 1037 cm$^{-1}$; HR-MS (ESI): $m/z$ = 393.0988, calcd. for $C_{17}H_{20}F_3O_5S^+$ $[M+H]^+$: 393.0984. The *ee* was determined to be 97% by chiral HPLC analysis (AD-H column, hexane-2-propanol 90:10, 1.0 mL min$^{-1}$, λ = 220 nm): $t_R$ (major, *R*) = 7.3 min, $t_R$ (minor, *S*) = 7.7 min. $[\alpha]_D^{20}$: 84.9 (*c*, 1.0, $CHCl_3$).

**Diethyl (*R*)-acetylthio(2-methylphenyl)methylmalonate (2l):** Colorless oil; yield of **2l**: 31.3 (92%), yield of *ent*-**2l**: 31.6 mg (93%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, $J$ = 7.2 Hz, 3H), 1.26 (t, $J$ = 7.2 Hz, 3H), 2.27 (s, 3H), 2.53 (s, 3H), 3.98 (q, $J$ = 7.2 Hz, 2H), 4.03 (d, $J$ = 10.0 Hz, 1H), 4.19 (dq, $J$ = 9.2, 7.2 Hz, 1H), 4.21 (dq, $J$ = 9.2, 7.2 Hz, 1H), 5.59

(d, $J=10.4$ Hz, 1H), 7.12–7.15 (m, 3H), 7.25–7.28 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ=13.7, 13.9, 19.6, 30.1, 42.4, 57.3, 61.7, 61.8, 126.2, 127.7, 127.9, 130.7, 136.2, 137.5, 166.5, 166.9, 192.9; IR (KBr): $\nu$=2974, 2929, 1735, 1696, 1464, 1369, 1306, 1253, 1128, 1094, 1049, 626 cm$^{-1}$; HR-MS (ESI): $m/z$=339.1265, calcd. for $C_{17}H_{23}O_5S^+$ $[M+H]^+$: 339.1266. The *ee* was determined to be 90% with catalyst **3a** and −92% with catalyst **5b** by chiral HPLC analysis (AS-H column, hexane-2-propanol 94:6, 1.0 mL min$^{-1}$, λ=220 nm): $t_R$ (*R*)=6.8 min, $t_R$ (*S*)=6.2 min. **2l**: $[\alpha]_D^{20}$: 107.5 (*c*, 1.00, $CHCl_3$), *ent*-**2l**: $[\alpha]_D^{20}$: −112.1 (*c*, 1.06, $CHCl_3$).

**Diethyl (*R*)-acetylthio(2-methoxyphenyl)methylmalonate (2m):** Colorless oil; yield of **2m**: 32.0 mg (90%), yield of *ent*-**2m**: 33.4 mg (94%). $^1$H NMR (400 MHz, $CDCl_3$): δ=1.01 (t, $J=7.2$ Hz, 3H), 1.24 (t, $J=7.2$ Hz, 3H), 2.27 (s, 3H), 3.89 (s, 3H), 3.96 (q, $J=7.2$ Hz, 2H), 4.17 (dq, $J=10.8$, 7.2 Hz, 1H), 4.21 (dq, $J=10.8$, 7.2 Hz, 1H), 4.36 (d, $J=10.4$ Hz, 1H), 5.48 (d, $J=10.8$ Hz, 1H), 6.83–6.89 (m, 2H), 7.20–7.25 (m, 1H), 7.36–7.39 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ= 13.7, 14.0, 30.2, 43.2, 55.4, 55.5, 61.4, 61.6, 110.9, 120.4, 126.8, 129.2, 130.5, 157.1, 166.8, 167.2, 193.4; IR (KBr): $\nu$=2924, 1734, 1696, 1251, 1118, 1026 cm$^{-1}$; HR-MS (ESI): $m/z$= 355.1212, calcd. for $C_{17}H_{23}O_6S^+$ $[M+H]^+$: 355.1215. The *ee* was determined to be 68% with catalyst **3a** and −72% with catalyst **5b** by chiral HPLC analysis (AS-H column, hexane-2-propanol 90:10, 1.0 mL min$^{-1}$, λ=220 nm): $t_R$ (*R*)= 7.4 min, $t_R$ (*S*)=6.6 min. **2m**: $[\alpha]_D^{20}$: 90.8 (*c*, 0.98, $CHCl_3$), *ent*-**2m**: $[\alpha]_D^{20}$: −98.0 (*c*, 1.02, $CHCl_3$).

**Diethyl (*R*)-acetylthio(4-fluorophenyl)methylmalonate (2n):** Colorless oil; yield: 32.3 mg (94%). $^1$H NMR (400 MHz, $CDCl_3$): δ=1.08 (t, $J=7.2$ Hz, 3H), 1.25 (t, $J=$ 7.2 Hz, 3H), 2.29 (s, 3H), 3.97 (d, $J=9.6$ Hz, 1H), 4.04 (q, $J=7.2$ Hz, 2H), 4.19 (dq, $J=10.8$, 7.2 Hz, 1H), 4.22 (dq, $J=$ 10.8, 7.2 Hz, 1H), 5.30 (d, $J=10.0$ Hz, 1H), 6.97 (dd, $J=8.4$, 8.8 Hz, 2H), 7.36 (dd, $J=5.2$, 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ=13.8, 13.9, 30.3, 45.4, 57.2, 61.9, 61.9, 115.3 (d, $^2J_{C,F}=22$ Hz), 129.9 (d, $^3J_{C,F}=8$ Hz), 135.2 (d, $^4J_{C,F}=3$ Hz), 162.1 (d, $^1J_{C,F}=246$ Hz), 166.3, 166.7, 192.7; IR (KBr): $\nu$=2961, 2923, 1735, 1696, 1509, 1368, 1098, 1023, 956, 799, 624 cm$^{-1}$; HR-MS (ESI): $m/z$=365.0834, calcd. for $C_{16}H_{19}FO_5SNa^+$ $[M+Na]^+$: 365.0835. The *ee* was determined to be 79% by chiral HPLC analysis (AS-H column, hexane-2-propanol 90:10, 1.0 mL min$^{-1}$, λ=220 nm): $t_R$ (major, *R*)= 8.2 min, $t_R$ (minor, *S*)=7.6 min. $[\alpha]_D^{20}$: 82.8 (*c*, 1.21, $CHCl_3$).

**Diethyl (*R*)-acetylthio(4-bromophenyl)methylmalonate (2o):** Yellowish oil; yield of **2o**: 39.0 mg (97%), yield of *ent*-**2o**: 37.8 mg (95%). $^1$H NMR (400 MHz, $CDCl_3$): δ=1.10 (t, $J=7.2$ Hz, 3H), 1.26 (t, $J=7.2$ Hz, 3H), 2.28 (s, 3H), 3.97 (d, $J=10.0$ Hz, 1H), 4.04 (q, $J=7.2$ Hz, 2H), 4.19 (dq, $J=$ 10.8, 7.2 Hz, 1H), 4.22 (dq, $J=10.8$, 7.2 Hz, 1H), 5.27 (d, $J=$ 10.0 Hz, 1H), 7.26 (d, $J=8.0$ Hz, 2H), 7.41 (d, $J=8.0$ Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ=13.8, 14.0, 30.3, 45.5, 56.9, 62.0, 62.0, 121.8, 129.9,131.6, 138.5, 166.2, 166.6, 192.6; IR (KBr): $\nu$=2980, 1736, 1698, 1488, 1369, 1309, 1249, 1132, 1029, 1011, 624 cm$^{-1}$; HR-MS (ESI): $m/z$=403.0214, calcd. for $C_{16}H_{20}BrO_5S^+$ $[M+H]^+$: 403.0215. The *ee* was determined to be 79% with catalyst **3a** and −79% with catalyst **5b** by chiral HPLC analysis (AD-H column, hexane-2-propanol 80:20, 1.0 mL min$^{-1}$, λ=220 nm): $t_R$ (*R*)=7.5 min, $t_R$ (*S*)=8.9 min. **2o**: $[\alpha]_D^{20}$: 83.4 (*c*, 1.05, $CHCl_3$), *ent*-**2o**: $[\alpha]_D^{20}$: −81.0 (*c*, 0.96, $CHCl_3$).

**Diethyl (*R*)-acetylthio(4-methoxyphenyl)methylmalonate (2p):** Colorless oil; yield of **2p**: 35.0 mg (99%), yield of *ent*-**2p**: 34.0 mg (96%). $^1$H NMR (400 MHz, $CDCl_3$): δ=1.08 (t, $J=7.2$ Hz, 3H), 1.26 (t, $J=7.2$ Hz, 3H), 2.28 (s, 3H), 3.77 (s, 3H), 3.98 (d, $J=9.6$ Hz, 1H), 4.03 (q, $J=7.2$ Hz, 2H), 4.19 (dq, $J=10.8$, 7.2 Hz, 1H), 4.22 (dq, $J=10.8$, 7.2 Hz, 1H), 5.30 (d, $J=10.0$ Hz, 1H), 6.81 (d, $J=8.8$ Hz, 2H), 7.29 (d, $J=8.8$ Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ=13.8, 14.0, 30.4, 45.6, 55.2, 57.4, 61.8, 61.8, 113.8, 129.3, 131.4, 159.0, 166.4, 166.9, 192.9; IR (KBr): $\nu$=2961, 2924, 1735, 1696, 1513, 1463, 1368, 1259, 1141, 1028, 799, 626 cm$^{-1}$); HR-MS (ESI): $m/z$=355.1211, calcd. for $C_{17}H_{23}O_6S^+$ $[M+H]^+$: 355.1215. The *ee* was determined to be 60% with catalyst **3a** and −62% with catalyst **5b** by chiral HPLC analysis (AD-H column, hexane-2-propanol 80:20, 1.0 mL min$^{-1}$, λ= 220 nm): $t_R$ (*R*)=9.3 min, $t_R$ (*S*)=10.6 min. **2p**: $[\alpha]_D^{20}$: 31.8 (*c*, 1.00, $CHCl_3$), *ent*-**2p**: $[\alpha]_D^{20}$: −30.3 (*c*, 1.01, $CHCl_3$).

**Diethyl (*R*)-acetylthio(naphthalen-1-yl)methylmalonate (2q):** Colorless oil; yield of **2q**: 36.0 mg (96%); yield of *ent*-**2q**: 36.4 mg (97%). $^1$H NMR (400 MHz, $CDCl_3$): δ=0.90 (t, $J=7.2$ Hz, 3H), 1.25 (t, $J=7.2$ Hz, 3H), 2.28 (s, 3H), 3.93 (q, $J=7.2$ Hz, 2H), 4.19 (dq, $J=10.8$, 7.2 Hz, 1H), 4.21 (dq, $J=10.8$, 7.2 Hz, 1H), 4.30 (d, $J=9.6$ Hz, 1H), 6.21 (d, $J=$ 9.2 Hz, 1H), 7.39 (dd, $J=7.6$, 7.6 Hz, 1H), 7.50 (dd, $J=7.2$, 7.6 Hz, 1H), 7.56 (d, $J=7.2$ Hz, 1H), 7.60 (dd, $J=8.0$, 7.2 Hz, 1H), 7.75 (d, $J=8.0$ Hz, 1H), 7.84 (d, $J=8.4$ Hz, 1H), 8.32 (d, $J=7.6$ Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ=13.6, 13.9, 30.1, 57.5, 61.7, 61.9, 123.4, 125.1, 125.9, 126.7, 128.6, 128.9, 130.5, 133.9, 135.2, 166.5, 167.0, 193.0; IR (KBr): $\nu$=2960, 2930, 1731, 1693, 1259, 1111, 1031, 797 cm$^{-1}$; HR-MS (ESI): $m/z$=375.1260, calcd. for $C_{20}H_{23}O_5S^+$ $[M+H]^+$: 375.1266. The *ee* was determined to be 97% with catalyst **3a** and −97% with catalyst **5b** by chiral HPLC analysis (AS-H column, hexane-2-propanol 94:6, 1.0 mL min$^{-1}$, λ=220 nm): $t_R$ (*R*)=9.9 min, $t_R$ (*S*)= 9.2 min. **2q**: $[\alpha]_D^{20}$: 67.8 (*c*, 1.11, $CHCl_3$), *ent*-**2q**: $[\alpha]_D^{20}$: −61.7 (*c*, 1.01, $CHCl_3$).

**Diethyl (*R*)-acetylthio(2,6-dichlorophenyl)methylmalonate (2r):** Colorless oil; yield: 36.3 mg (92%). $^1$H NMR (400 MHz, $CDCl_3$): δ=1.02 (t, $J=7.2$ Hz, 3H), 1.28 (t, $J=$ 7.2 Hz, 3H), 2.31 (s, 3H), 3.92–4.00 (m, 2H), 4.19–4.28 (m, 2H), 4.61 (d, $J=11.6$ Hz, 1H), 6.38 (d, $J=11.6$ Hz, 1H), 7.10–7.14 (m, 1H), 7.26–7.28 (m, 1H), 7.31–7.33 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ=13.6, 13.9, 29.8, 41.3, 55.0, 61.7, 61.9, 128.8, 129.3, 129.3, 134.8, 135.7, 136.2, 166.1, 166.4, 191.9; IR (KBr): $\nu$=2980, 2928, 1733, 1699, 1475, 1391, 1245, 1132, 1038, 954, 755, 630 cm$^{-1}$; HR-MS (ESI): $m/z$=392.0253, calcd. for $C_{16}H_{18}Cl_2O_5S^+$ $[M+H]^+$: 392.0252. The *ee* was determined to be 26% by chiral HPLC analysis (AS-H column, hexane-2-propanol 90:10, 1.0 mL min$^{-1}$, λ= 220 nm): $t_R$ (major, *R*)=7.5 min, $t_R$ (minor, *S*)=6.7 min. $[\alpha]_D^{20}$: 18.8 (*c*, 1.03, $CHCl_3$)

**Diethyl (*S*)-acetylthio(cyclohexyl)methylmalonate (2s):** Colorless oil; yield: 28.0 mg (85%). $^1$H NMR (400 MHz, $CDCl_3$): δ=0.95–1.20 (m, 5H), 1.24 (t, $J=7.2$ Hz, 3H), 1.27 (t, $J=7.2$ Hz, 3H), 1.55–1.75 (m, 5H), 1.80–1.85 (m, 1H), 2.32 (s, 3H), 3.86 (d, $J=6.8$ Hz, 1H), 4.10–4.26 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ=13.9, 14.0, 26.0, 26.0, 29.4, 30.3, 30.7, 40.4, 47.7, 54.0, 61.5, 61.7, 167.6, 167.8, 194.5; IR (KBr): $\nu$=2927, 2853, 1736, 1692, 1384, 1180, 1142, 1075, 629 cm$^{-1}$;. HR-MS (ESI): $m/z$=331.1582, calcd. for $C_{16}H_{27}O_5S^+$ $[M+H]^+$: 331.1579. The *ee* was determined to

be 12% by chiral HPLC analysis (AD-H column, hexane-2-propanol 90:10, 1.0 mL min$^{-1}$, $\lambda = 220$ nm): $t_R$ (major, *S*) = 5.0 min, $t_R$ (minor, *R*) = 4.8 min. $[\alpha]_D^{20}$: −7.19 (*c*, 1.21, $CHCl_3$).

### Transformation of Product 2a to Methyl (*R*)-3-Mercapto-3-phenylpropanoate (6)

Under an $N_2$ atmosphere a mixture of **2a** (130 mg, 0.4 mmol) and 6 M aqueous HCl (2 mL) was refluxed for 6 h and then cooled to room temperature. To the solution was added MeOH (8 mL) and the mixture was stirred at 50 °C for 24 h. After cooling to room temperature the reaction mixture was extracted with dichloromethane (20 mL × 3), and the combined organic phase was washed with brine, and dried over $Na_2SO_4$. After concentration under reduced pressure the crude product was purified by column chromatography (petroleum ether/EtOAc = 100/1) to give the desired product methyl (*R*)-3-mercapto-3-phenylpropanoate (**6**) as a colorless oil:[12]; yield: 36 mg (46%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.24 (d, *J* = 6.0 Hz, 1 H), 3.00 (d, *J* = 7.6 Hz, 1 H), 3.68 (s, 3 H), 4.49 (dt, *J* = 6.0, 7.6 Hz, 1 H), 7.30–7.36 (m, 5 H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 39.5, 44.4, 51.9, 126.7, 127.6, 128.8, 142.8, 171.2. The *ee* was determined to be 74% by chiral HPLC analysis (AD-H column, hexane-2-propanol 99:1, 1.0 mL min$^{-1}$, $\lambda = 220$ nm): $t_R$ (major, *R*) = 7.7 min, $t_R$ (minor, *S*) = 7.4 min. $[\alpha]_D^{25}$: +35.4 (*c*, 0.97, $CHCl_3$).

### Transformation of Product 2a to Diethyl (*R*)-Mercapto(phenyl)methylmalonate (7)

Under an $N_2$ atmosphere **2a** (97 mg, 0.3 mmol) was dissolved in EtOH (2 mL) at room temperature. To the solution was added 12 M aqueous HCl (0.3 mL). The reaction mixture was stirred at room temperature until the disappearance of the starting material was detected by TLC. After the solvent was evaporated the residue was dissolved in dichloromethane. The solution was washed with brine and dried over $Na_2SO_4$. After concentration under reduced pressure the crude product was purified by column chromatography (petroleum ether/EtOAc = 30/1, v/v) to afford the desired product diethyl (*R*)-2-[mercapto(phenyl)methyl]malonate (**7**) as a colorless oil; yield: 76 mg (90%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.2 Hz, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 2.42 (d, *J* = 6.8 Hz, 1 H), 3.92 (q, *J* = 7.2 Hz, 2 H), 4.02 (d, *J* = 11.2 Hz, 1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 4.63 (dd, *J* = 6.8, 11.2 Hz, 1 H), 7.27–7.34 (m, 5 H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 13.6, 14.1, 42.5, 61.3, 61.5, 62.0, 127.3, 127.9, 128.7, 140.3, 166.4, 167.4. $[\alpha]_D^{25}$: 56.0 (*c*, 0.95, $CHCl_3$). The *ee* of **7** could not be determined by HPLC analysis using available chiral columns after many attempts. After conversion of **7** to **2a** by acetylation with acetic anhydride,[13] the *ee* of **7** was determined to be 82%.

**Conversion of 7 to 2a:** To a stirred solution of **7** (10 mg, 0.035 mmol) in DCM (1 mL) at 0 °C was added acetic anhydride (17 μL, 18 mg, 0.18 mmol). The reaction mixture was stirred overnight at room temperature. Then the solution was washed with water and dried with anhydrous $MgSO_4$. After column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1 *v/v* as eluent) the desired product **2a** was obtained; yield: 8 mg (70%) and the *ee* was determined to be 82%.

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