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Asymmetric hydrogenation of alkyl(vinyl)thioethers: a promising approach to α-chiral thioethers

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Abstract—This paper describes the enantioselective hydrogenation of vinylthioethers. We show that thioether derivatives of maleic esters can be hydrogenated with full conversion and up to 60% ee, and that α-thioether cinnamic acids can be hydrogenated in 51% ee with modest conversion.

1. Introduction

α-Chiral thioethers are of academic and industrial interest since they are a common structural element present in many pharmaceuticals, natural products, and synthetic intermediates.[1] Their importance to the pharmaceutical industry is illustrated by the dihydrobenzoxanthiins,[2] (selective estrogen receptor modulators), Diltiazem[3] (a calcium channel blocker used in the treatment of hypertension), and Singulair[4] (used in the treatment of chronic asthma) (Fig. 1).

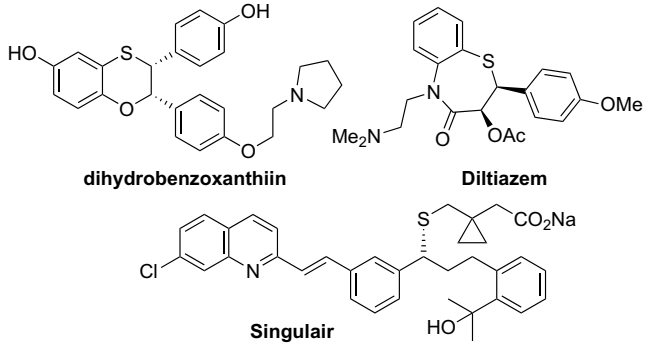

Figure 1. Important pharmaceuticals containing α-chiral thioethers.

Currently, the industrial scale synthesis of enantiopure α-chiral thioethers typically involves nucleophilic displacement of thiols onto enantiopure activated alcohols or epoxides.[5,6] This indirect approach requires several additional steps compared with the direct, catalytic asymmetric methodology. Moreover, when the stereocenter resides at an electron-rich benzylic position, this route introduces the danger of racemization with a competing S_N1 mechanism. In an academic context, α-chiral thioethers have been prepared by asymmetric conjugate addition to α,β-unsaturated carbonyl compounds, first reported with high ee by Wynberg, with mixed success.[5,7] Recently, the diastereoselective lithiation–alkylation of thiocarbamates was presented as an alternative approach.[8]

Hydrogenation of vinylthioethers[9] and asymmetric hydrogenation of sulfur containing olefins have been reported only sporadically.[10] However, no examples of the catalytic asymmetric hydrogenation of alkyl(vinyl)thioethers or alkyl(vinyl)thioesters are known.

The absence of asymmetric hydrogenation as a tool for preparing enantiopure thioethers seems surprising considering its widespread application, especially on an industrial scale.[11] It is likely that most researchers have avoided this approach in the preparation of α-chiral thioethers because of (at least in part) the conventional wisdom that sulfur in its lower oxidation states is a poison for transition metal catalysts. This potentially limiting stigma is highlighted by the paucity of examples of hydrogenations of

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alkyl(vinyl)thioethers reported in the literature,[9,12–17] none of which are asymmetric.

Herein, we report the first examples of the catalytic, asymmetric hydrogenation of alkyl(vinyl)thioethers, where rhodium catalyzed hydrogenation affords the α-chiral thioethers with enantioselectivities of up to 60%. We are convinced that this proof of principle demonstrates that the asymmetric hydrogenation of alkyl(vinyl)thioethers is a feasible and potentially practical route to this class of target molecules.

Additionally, we show that within the scope of the 12 ligands used in this study, bidentate phosphine ligands are the most promising since they lead to cleaner reactions, faster hydrogenations, and higher conversions. While phosphoramidites[18] sometimes gave comparable enantioselectivities, with some substrates, we observed a competing desulfurization side process under the conditions used for the reaction.

1.1. Substrate selection

Since the asymmetric hydrogenation of alkyl(vinyl)-thioethers was previously unknown, we decided to first investigate the catalytic asymmetric hydrogenation of compounds, which resemble benchmark substrates used in the preparation of amino acids[19] and dihydrocinnamic acid derivatives[20] (Fig. 2).

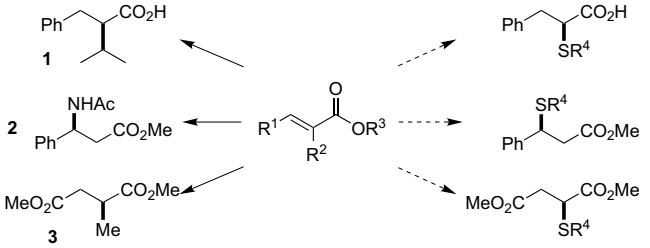


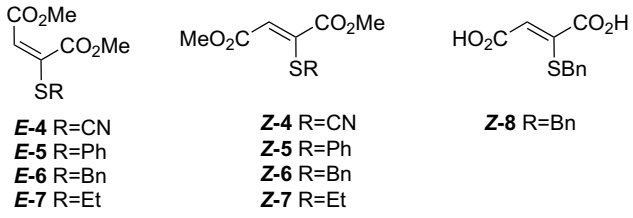
Figure 2. Benchmark substrates for hydrogenation (left), adapted to incorporate thioethers (right).

Acid **1** was prepared in 99% ee by asymmetric hydrogenation of the corresponding cinnamic acid derivative[20] using $Rh(COD)_2BF_4$ with a mixture of a phosphoramidite and an achiral phosphine. *N*-Acetyl β-phenyl alanine **2** and dimethyl 2-methyl succinate **3** have been prepared in excellent ee's by the asymmetric hydrogenation of the corresponding enamide and dimethyl itaconate, respectively.[21] We reasoned that structurally similar substrates possessing vinylthioethers could also be good candidates for hydrogenation (Fig. 2, right).

2. Results and discussion

2.1. Synthesis of the substrates

2-(Alkylthio)succinic acids, esters, and derivatives (Fig. 3) are an attractive class of structures to prepare in an enantioselective way because their racemates have been found



***E*-4** R=CN
***E*-5** R=Ph
***E*-6** R=Bn
***E*-7** R=Et

***Z*-4** R=CN
***Z*-5** R=Ph
***Z*-6** R=Bn
***Z*-7** R=Et

***Z*-8** R=Bn

Figure 3. Substituted maleic and fumaric acid derivatives made by conjugate addition to DMAD.

to be promising inhibitors of glutathione (*S*)-transferases.[22] Moreover, substrates for their preparation by asymmetric hydrogenation can be conveniently obtained by the conjugate addition of a thiol onto dimethyl acetylenedicarboxylate (DMAD). In this way, substrates *E*-**4**, *Z*-**4**,[23] *E*-**5**, and *Z*-**5**[24] were prepared by the literature procedures. Similarly, diesters *E*-**6**, *Z*-**6**, *E*-**7**, and *Z*-**7** were prepared by the conjugate addition of benzyl mercaptan and ethanethiol to DMAD in 75% (3:2, *E*:*Z*) and 88% (8:1, *E*:*Z*) yield, respectively, and their stereochemistry was verified by NOESY experiments. Since cinnamic acid derivatives are sometimes better substrates for asymmetric hydrogenation than their corresponding esters,[20] acid *Z*-**8** was also prepared by saponification of *Z*-**6**.

α- and β-Thioether dihydrocinnamic acids and esters are also a pharmaceutically relevant class of compounds as is illustrated by the major effort dedicated to the asymmetric synthesis of these products.[5] To investigate their preparation by asymmetric hydrogenation, we needed to have access to the corresponding vinyl ethers as substrates. Substrates *Z*-**9**, *E*-**9**, *Z*-**10**, and *E*-**10** were prepared by the triethylamine-catalyzed conjugate addition of the corresponding thiol on ethyl phenylpropiolate in good yields (Fig. 4).

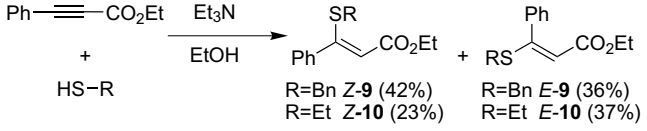


Figure 4. Conjugate addition of thiols to ethyl phenylpropiolate.

The preparation of 2-(alkylthio)cinnamic acids and esters proved to be more challenging. Initially we pursued the Knoevenagel condensation of ethyl thioglycolates with aromatic aldehydes, reported by Paranjpe and Bagavant.[25] Unfortunately, this route failed in our hands, despite attempts to change the base and solvent. This difficulty has been corroborated by Larrson.[26]

We then explored an alternative approach to prepare these derivatives. Wadsworth and Detty reported[27] the synthesis of (*Z*)-2-(phenylthio)cinnamic acid by refluxing ethyl phenylpropiolate with thiophenol in the presence of air, which likely proceeds through a radical addition. When aliphatic thiols were employed in this procedure, mixtures of β- and α-adducts were formed as the major and minor products, respectively. However, we found that the addition of

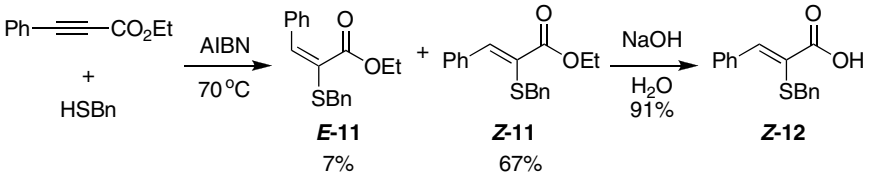
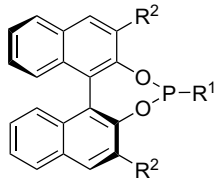


Figure 5. Radical addition of benzyl mercaptan to ethyl phenylpropiolate, followed by saponification.

0.2 equiv of AIBN allowed the reaction to be performed cleanly at lower temperature (70 °C) to give the α-substituted product **11** as a mixture of *Z* and *E* isomers in 67% and 7% yields, respectively (Fig. 5). Acid *Z*-**12** was also prepared by saponification of *Z*-**11**.

2.2. Asymmetric hydrogenation[28]

Initially we pursued the hydrogenation of thiocyanate *E*-**4** under the assumption that the electron-withdrawing cyano function might diminish the electron density on sulfur, making it less likely to coordinate to the rhodium. Unfortunately, conditions, which have been used successfully to hydrogenate similar substrates (without the thiocyanate function) including Rh(I) and PipPhos (Fig. 6) in CH_2Cl_2, failed to give any conversion to the desired product **13** (Fig. 7). Competitive hydrogenation of benchmark substrate **14** in the presence of *E*-**4** gave no conversion of either substrate, thus confirming that the thiocyanate was most probably a catalyst poison.



L1 R^1 = piperidine, R^2 = H (PipPhos)
L2 R^1 = NMe_2, R^2 = H
L3 R^1 = N[(*R*)-α-MeBn]$_2$, R^2 = H
L4 R^1 = NMe_2, R^2 = Me
L5 R^1 = N(*i*-Pr)$_2$, R^2 = H

Figure 6. Phosphoramidites used in this study.

The attempted hydrogenation of *E*-**5** (Fig. 8) using rhodium(I) and PipPhos **L1** in CH_2Cl_2 gave dimethyl fumarate **15** and dimethyl succinate **16** in approximately 5% overall yield, and the remaining starting material left unreacted. Longer reaction times did not change the conversion. The 1:1 stoichiometry between rhodium used (5%) and total eliminated thiol (5%) strongly supports catalyst poisoning by thiophenol.

In contrast, rhodium(I) with 2 equiv of PipPhos and 25 bar of H_2 in CH_2Cl_2 hydrogenated *E*-**6** gave **17** with 25% conversion and with minimal desulfurized product. This change in reactivity may be related to the poorer leaving group ability of the benzylthiolate when compared to thiophenolate. Unfortunately, this reaction gave racemic product. When preliminary optimization of these conditions showed minimal improvements in conversion with no enantioselectivity, we chose to investigate bidentate ligands,[29] which we reasoned might be less likely to be influenced by competitive coordination by thioethers.

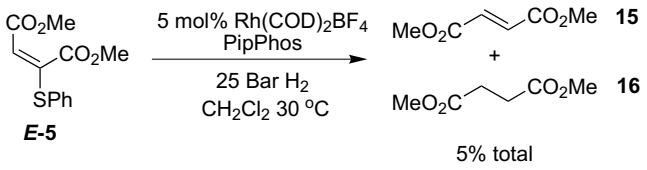
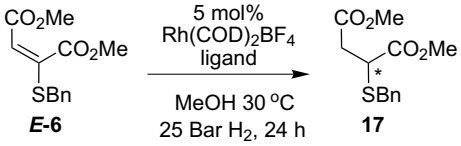


Figure 8. Hydrogenation of substrate *E*-**5** gives desulfurized products **15** and **16**.

We adapted the reaction conditions to those previously used in asymmetric hydrogenation with high enantioselectivity using bidentate ligands.[30] As might be expected, 1 equiv of the bidentate ligands with respect to $Rh(COD)_2BF_4$ gave the highest conversions. After subjecting *E*-**6** to asymmetric hydrogenation with Rh(I) and a series of bidentate ligands in MeOH at 25 bar at 30 °C, we found several ligands including BINAP, Josiphos, and SL-J002-1 induced promising enantioselectivities (Table 1, Figs. 9–11).

Table 1. Optimization of the ligand for the hydrogenation of *E*-**6**



Ligand (5 mol %)	Conversion (%)	ee (%)
rev-Josiphos	12	22
BINAP	12	41
Josiphos	45	52
Taniaphos	27	17
SL-J005	0	0
SL-J011-1	11	26
SL-J002-1	36	46

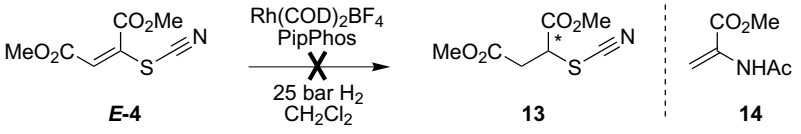


Figure 7. Attempted hydrogenation of *E*-**4** with and without methyl 2-acetamidoacrylate.

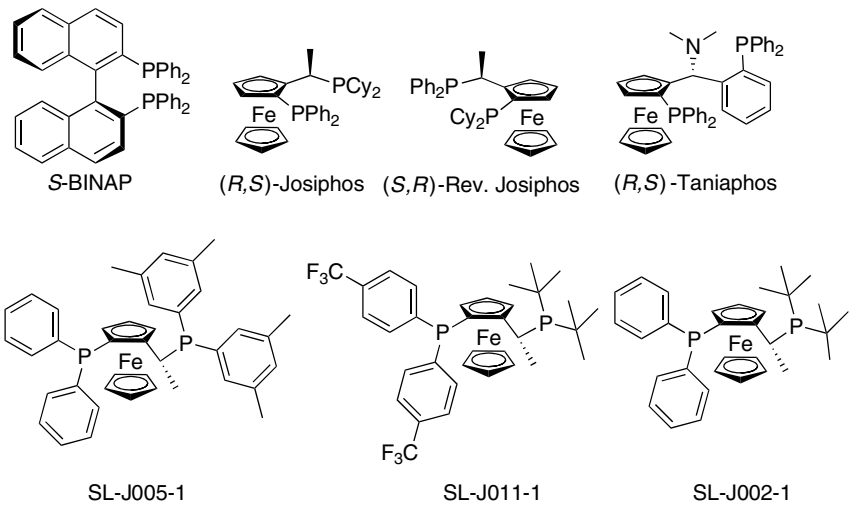


Figure 9. Structures of the bidentate ligands used in this study.

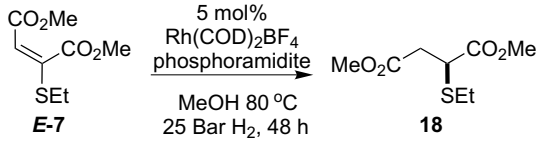


Figure 10. Hydrogenation of *E*-**7**.

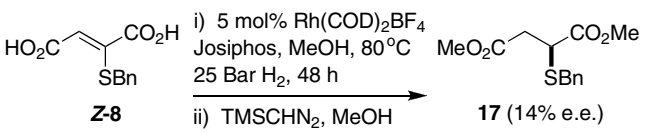


Figure 11. Hydrogenation of diacid **8**.

Josiphos induced the highest conversion (45%) and ee (52%). Interestingly, both isomers, *E*-**6** and *Z*-**6**, of the remaining starting material were recovered, indicating that the substrate isomerizes to some extent (typically 5%) under the reaction conditions. Importantly, these conditions minimized the desulfurization side reaction to ~10%.[31]

Several solvents were screened to further optimize the conversion and ee. Out of the solvents tested (THF, CH_2Cl_2, EtOAc, MeOH, and *i*PrOH) the only ones which allowed even modest conversion were alcohols. We focused our attention on MeOH since it gave the best conversion and because the substrate contains methyl esters.

Increasing the temperature from 30 °C to 80 °C, as well as extending the reaction time to 48 h resulted in full conversion of *E*-**6** to **17** with a small increase in the enantioselectivity.[32] Hydrogenation of *Z*-**6** under these optimized conditions gave comparable enantioselectivities (59% ee), but lower conversion (59%) and with a more desulfurized product (24% with respect to **17**).

Since the amount of water in the solvent has been shown to have a significant effect on the conversion and ee, this avenue was explored (Table 2).[20] In this case, the use of water as co-solvent at proportions up to 60% does not significantly influence the conversion or ee. The use of larger amounts of water leads to a significant drop in the enantioselectivity.

Table 2. Influence of water on the ee and conversion in the hydrogenation of *E*-**6**

Water/MeOH	Conversion (%)	ee (%)
10:90	95	51
30:70	91	54
50:50	Full	54
60:40	97	52
90:10	83	14

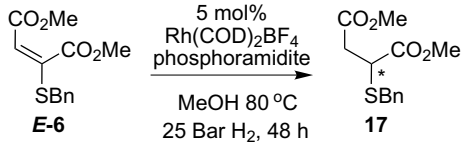
Conditions: 5% $Rh(COD)_2BF_4$, Josiphos, 80 °C, 25 bar H_2, 48 h.

Modest changes in the structure of the substrate had minimal influence on the enantioselectivity, suggesting that this method could be quite general. As observed with *E*-**6**, hydrogenation of the related substrate *E*-**7** gave complete conversion and similar enantioselectivity (56% ee) to provide product **18**. Compound *Z*-**7** gave lower enantioselectivities (36%) with considerably lower conversion (72%) and more desulfurized product (30%).

After having pursued several approaches to optimize the enantioselectivity of this hydrogenation it became clear that significant improvements in ee would likely necessitate screening for alternative ligands. We focused on using phosphoramidite ligands, which offer the possibility of significant structural diversity, and are often prepared in a one-pot procedure.

In contrast to the lack of reactivity, which we observed during previous attempts to hydrogenate *E*-**6** catalyzed by Rh(I) with phoshoramidite ligands in CH_2Cl_2, in MeOH this catalysis system gave moderate to good conversion (Table 3). Slightly lower ee's (30–46%) were obtained in comparison to Josiphos (51–60%) (Table 4). Disappoint-

Table 3. Monodentate ligands in the hydrogenation of *E*-**6**



Ligand (10 mol %)	Conversion (%)	Desulfurized[a] (%)	Temp (°C)
L2	Full	60	50
L2	Full	34	80
L2:PPh_3, 2:1[b]	Full	36	80
L3	69	22	80
L4	60	35	80

[a] Calculated as a percentage of desulfurization product relative to the amount of hydrogenated product.
[b] 15 mol % of ligand.

Table 4. Sensitivity of the desulfurization of *E*-**6** to ligand

Ligand (10 mol %)	Conversion (%)	Desulfurization[a] (%)	ee (%)
L3	72	47	46
L2	31	38	40
L4/PPh_3[b]	85	34	30
Josiphos[c]	Full	9	60

Conditions: 5% $Rh(COD)_2BF_4$, 80 °C, 25 bar H_2, 48 h, in MeOH.
[a] Calculated as the percentage of desulfurization product relative to the amount of hydrogenated product.
[b] 15 mol %.
[c] 5 mol %.

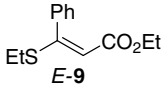
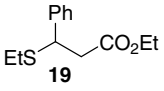
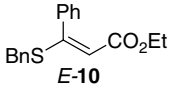
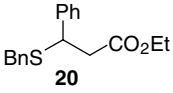
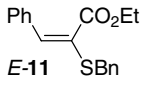
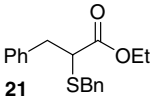
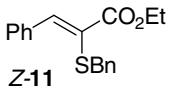
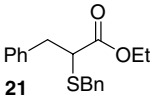
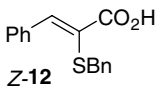
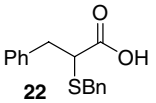
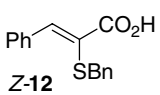
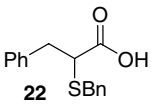
ingly, the proportion of the desulfurized product was larger than that observed with the bidentate ligands.

Since cinnamic acid derivatives were reported to be hydrogenated with improved conversion and enantioselectiv;ity when compared with their corresponding esters, we saponified substrate *E*-**6** in the hope that it would also show a similar improvement. Unfortunately hydrogenation of acid **8** only resulted in a slightly lower conversion (95%), much lower enantioselectivity (14%) with 10% desulfurized product (Fig. 11).

After having shown that asymmetric hydrogenation can be successfully achieved on maleic esters containing the vinyl-ether functionality, we wanted to explore this approach to prepare α- and β-thioether dihydrocinnamic acids and esters.

Asymmetric hydrogenation of *Z*-**9** and *Z*-**10** gave complex mixtures containing some of the desired products **19** and **20**, respectively, along with multiple unidentified side products, making analysis difficult. In contrast, *E*-**9** and *E*-**10** both gave excellent conversion, albeit with 0% and 28% ees, respectively (Table 5). Hydrogenation of both cinnamic esters *E*-**11** and *Z*-**11** with the sulfur at the α-position cleanly gave racemic **21** with moderate conversion. Interestingly, however, hydrogenation of acid *Z*-**12** to **22** gave promising enantioselectivities with Josiphos (42%) and with the 'mixed ligand' approach[20] with 5 mol % PPh_3 and 10 mol % **L3** (51% ee).

Table 5. Hydrogenation of cinnamic acid derivatives

Substrate	Product	Ligand (5 mol %)	Conversion (desulfurized product) (%)	ee (%)
		Josiphos	Full (11)	0
		Josiphos	Full (0)	28
		Josiphos	36 (0)	0
		Josiphos	50 (0)	0
		Josiphos	62 (0)	42
		**L4**:PPh_3 10:5 mol %	24 (0)	51

Conditions: 5% $Rh(COD)_2BF_4$, ligand, 80 °C, 25 bar H_2, 48 h.

2.3. On the mechanism of desulfurization

The desulfurization side reaction is problematic because it reduces yield, conversion, and likely poisons the catalyst. This desulfurization reaction was also observed by Ricci and co-workers.[9] Herein we report some preliminary observations that may give insight into the possible mechanism of desulfurization.

Using *E*-**6** as an example, we suggest that three of the more plausible mechanisms, which lead to this desulfurization process, include simple elimination of the thiol (path A, Fig. 12), insertion of the rhodium into the carbon–sulfur bond (path B), or a *syn*-elimination of a rhodium sulfide following the addition of the rhodium hydride to the olefin (path C).

We believe that the simple elimination mechanism (path A) is unlikely because (1) treatment of the purified product thioether **17** with the conditions used for the hydrogenation does not lead to the formation of desulfurized product (Fig. 13) and (2) asymmetric hydrogenation of diacid **8** also leads to the formation of eliminated product. The base mediated elimination is less likely in the presence of the carboxyl groups, which are more acidic and more likely to be deprotonated. Taken together, these data suggest that an alternative mechanism is operating.

We also found that when using the Josiphos ligand, the addition of 1 equiv of thiol relative to substrate (hence 20 times that of the Rh(I)) led to only a small drop in conversion.

3. Conclusions

This work offers a proof of principle that asymmetric hydrogenation can be used to prepare α-chiral thioethers from alkyl(vinyl)thioethers. This is highlighted by the hydrogenation of substrate *E*-**6** in quantitative yield and 60% ee using 5 mol % of $Rh(COD)_2BF_4$/Josiphos, and 25 bar of H_2 in methanol for 48 h at 80 °C. The use of monodentate phosphoramidite ligands leads to modest enantioselectivities, though also results in lower rates of hydrogenation, as well as reduced yields because of competing desulfurization. We find that this competing side reaction complicates the asymmetric hydrogenation of substrates possessing the thiol moiety in the β-position relative to acids and esters.

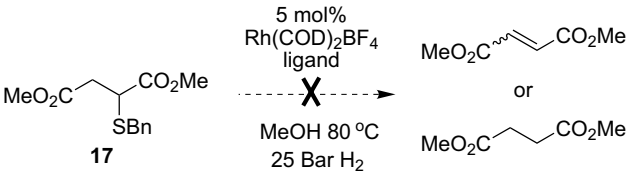


Figure 13. Stability of product **9** to the conditions optimized for hydrogenation.

Moreover, we also determined that α-thioether–cinnamic acid derivatives can be hydrogenated with 51% ee with no apparent desulfurization, albeit with incomplete conversion. As a result of this, and their ease of preparation, this substrate class is particularly promising for future study.

4. Experimental

4.1. General remarks

All chemicals were purchased from Aldrich unless otherwise stated, and used without purification. THF was dried over sodium.[33] All reactions were performed under a nitrogen atmosphere in oven dried glassware. Compounds **4**[23] and **5**[24] as well as phosphoramidites **L1**,[34] **L2**,[35] **L3** and **L4**,[36] and **L5**[37] were prepared according to the literature procedures. The $Rh(COD)_2(BF_4)$ and the Josiphos family ligands were purchased from Strem. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). NMR spectra were obtained using a Varian

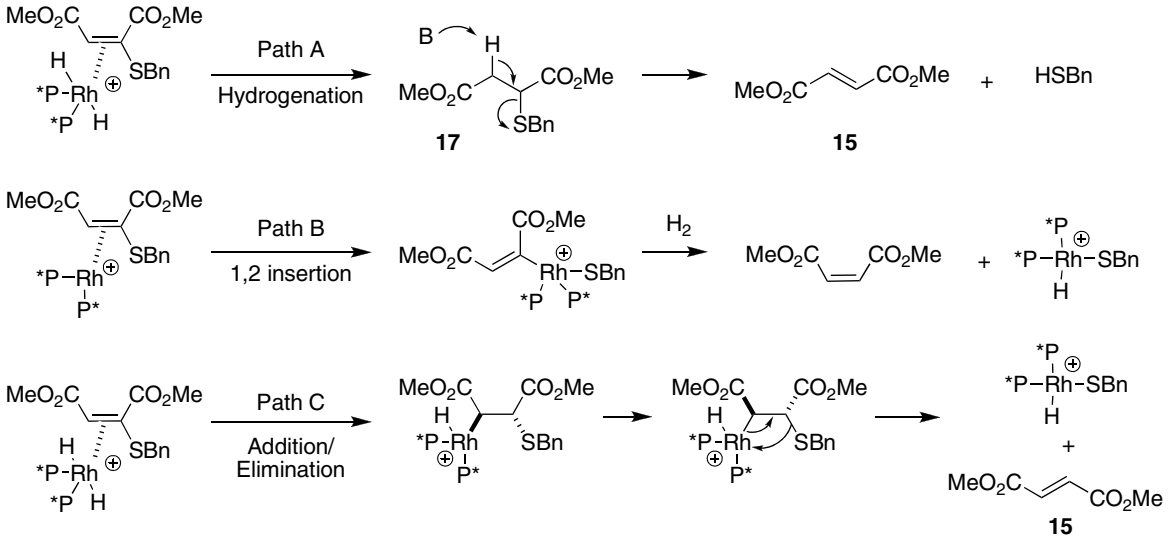


Figure 12. Possible pathways leading to desulfurization of *E*-**6**.

Gemini-200, a Varian 300, or a Varian Mercury Plus operating at 201.2, 301.8, or 399.93 MHz for the ^{1}H nucleus or at 50.32, 75.48, or 100.57 MHz, respectively, for the ^{13}C nucleus. ^{13}C NMR spectra were referenced to residual chloroform (^{1}H: 7.24 ppm, ^{13}C: 77.1 ppm) or residual DMSO (^{1}H: 2.49 ppm, ^{13}C: 49.5 ppm).

4.1.1. Standard operating procedure for hydrogenation

4.1.1.1. General procedure. The standard operating procedure for hydrogenation using the Endeavor™ semi-automated autoclave was as follows: To a glass reaction vessel was added 0.10 mmol of substrate, bidentate ligand (0.0050 mmol) or monodentate ligand (0.010 mmol), $Rh(COD)_2BF_4$ (0.0050 mmol), and 4.0 mL of solvent. The reaction vessel was placed in the autoclave and purged four times with nitrogen, heated to 30 °C and then pressurized to 15 bar of hydrogen. The reaction vessel was then heated to the desired temperature and pressurized to 25 bar of hydrogen. The sample was stirred at 700 rpm for 48 h, after which the stirrer was stopped and the hydrogen input to the reaction vessel was closed. The sample was filtered over a silica plug (1:1, EtOAc/heptane) after which the conversion and ee were determined by ^{1}H NMR and chiral HPLC, respectively. The ee and conversion of substrates containing carboxylic acids were determined after methylation by TMS–diazomethane in methanol (titrated until the yellow color persisted) to give the corresponding methyl esters.

4.1.2. Dimethyl-2-(benzylthio)maleate *E*-6 and dimethyl-2-(benzylthio)fumarate *Z*-6. To a solution of benzyl mercaptan (2.3 mL, 20 mmol, 1.0 equiv) in methanol (75 mL) was added dimethyl acetylenedicarboxylate (2.5 mL, 20 mmol, 1.0 equiv). The mixture was heated to reflux for 1.5 h, cooled, and the solvent was removed in vacuo. Purification by column chromatography (SiO_2, 9:1, heptane/EtOAc) gave the *Z*-isomer (2.4 g, 45%) as a yellow oil and the *E*-isomer (1.6 g, 30%) as a white solid. *E*-**6**: mp 69–70 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 5.77 (s, 1H), 4.03 (s, 2H), 3.84 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (C), 164.1 (C), 149.9 (C), 134.1 (C), 128.9 (CH), 128.0 (CH), 113.2 (CH), 53.1 (CH), 51.9 (CH_3), 36.5 (CH_2). HRMS (EI) calcd for $C_{13}H_{14}O_4S$: 266.0613; found, 266.0600. *Z*-**6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.24 (m, 5H), 6.32 (s, 1H), 4.09 (s, 2H), 3.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (C), 164.6 (C), 148.3 (C), 136.2 (C), 129.2 (CH), 128.6 (CH), 127.5 (CH), 119.7 (CH), 53.0 (CH_3), 51.8 (CH_3), 36.9 (CH_2); HRMS (EI) calcd for $C_{13}H_{14}O_4S$: 266.0613; found, 226.0601.

4.1.3. Dimethyl-2-(benzylthio)succinate 17

4.1.3.1. Enantioselective hydrogenation. The hydrogenation was performed with 0.1 mmol of *E*-**6** using standard conditions with MeOH as the solvent. Purification by column chromatography (SiO_2, 9:1, heptane/EtOAc) gave 28 mg (97%) of the diester as a colorless oil contaminated with 9% of desulfurization product. The ee was determined on an OB-H column eluted with *n*-heptane/*iso*-propanol (99:01, flow rate, 0.5 mL/min). Enantiomer 1 eluted at 88 min, enantiomer 2 at 96 min.

4.1.3.2. Racemic product. To a solution of benzyl mercaptan (0.25 mL, 2.1 mmol, 1.0 equiv), triethylamine (0.29 mL, 2.1 mmol, 1.0 equiv) in ethanol (50 mL) was added dimethyl fumarate (0.30 g, 2.1 mmol, 1.0 equiv). The solution was heated to 40 °C and stirred overnight. Solvent was removed in vacuo. Purification by column chromatography (SiO_2, 9:1, heptane/EtOAc) gave **17** (0.35 g, 62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.25 (m, 5H), 3.84 (ABX, $J_{app} = 13.2$, 22.0 Hz, 2H), 3.72 (s, 3H), 3.63 (s, 3H), 3.58 (ABX, $J_{app} = 5.4$, 9.9 Hz, 1H), 2.94 (ABX, $J_{app} = 10.2$, 16.8 Hz, 1H), 2.78 (ABX, $J_{app} = 5.4$, 17.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.3 (C), 171.2 (C), 137.3 (C), 129.3 (CH), 128.8 (CH), 127.6 (CH), 52.7 (CH_3), 52.2 (CH_3), 41.1 (CH), 36.2 (CH_2); HRMS (EI) calcd for $C_{13}H_{16}O_4S$: 268.0769; found, 268.0756.

4.1.4. Dimethyl-2-(ethylthio)maleate *E*-7 and dimethyl-2-(ethylthio)fumarate *Z*-7.[38] To a solution of dimethyl acetylenedicarboxylate (1.70 mL, 14.0 mmol, 1.00 equiv) in MeOH (50 mL) was added ethanethiol (1.10 mL, 14.0 mmol, 1.0 equiv). The solution was stirred for 1 h, and the solvent removed in vacuo. Purification by column chromatography (SiO_2, 9:1, heptane/EtOAc) gave 2.22 g (78%) of the *Z*-isomer as a yellow oil and 0.27 g (9.5%) of the *E*-isomer as a colorless oil. *E*-**7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (s, 1H), 3.86 (s, 3H), 3.68 (s, 3H), 2.81 (q, $J = 7.2$ Hz, 2H), 1.33 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.3 (C), 164.3 (C), 150.8 (C), 112.5 (CH), 53.3 (CH_3), 52.0 (CH_3), 26.2 (CH_2) 13.4 (CH_3); HRMS (EI) calcd for $C_8H_{12}O_4S$: 204.0456; found, 204.0458. Z-**7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (s, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 2.84 (q, $J = 7.2$ Hz, 2H), 1.24 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.9 (C), 165.1 (C), 149.5 (C), 119.0 (CH), 53.3 (CH_3), 52.0 (CH_3) 27.1 (CH_2) 14.8 (CH_3). HRMS (EI) calcd for $C_8H_{12}O_4S$: 204.0456; found, 204.0455.

4.1.5. (*Z*)-Ethyl-3-(ethylthio)-3-phenylacrylate *Z*-9 and (*E*)-ethyl-3-(ethylthio)-3-phenylacrylate *E*-9. To a solution of ethyl phenylpropiolate (1.5 mL, 9.0 mmol, 1.0 equiv) in ethanol (10 mL) were added ethanethiol (0.68 mL, 9.0 mmol, 1.0 equiv) and triethylamine (1.5 mL, 9.0 mmol, 1.0 equiv). The mixture was stirred overnight, after which the solvent was removed in vacuo. Purification by column chromatography (SiO_2, 9.7:0.3, heptane/EtOAc) gave the *Z*-isomer (0.76 g, 36%) and the *E*-isomer (0.90 g, 42%) both as colorless oils. *Z*-**9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 5.73 (s, 1H), 3.76 (q, $J = 7.2$ Hz, 2H), 2.79 (q, $J = 7.6$ Hz, 2H), 1.32 (t, $J = 7.6$ Hz, 3H), 1.05 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (C), 159.8 (C), 137.5 (C), 128.7 (CH), 128.1 (CH), 127.8 (CH), 110.5 (CH), 59.6 (CH_2) 26.7 (CH_2), 14.0 (CH_3), 12.9 (CH_3); HRMS (EI) calcd for $C_{13}H_{16}O_2S$: 236.0871; found, 236.0879. *E*-**9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 5H), 5.84 (s, 1H), 4.16 (q, $J = 7.2$ Hz, 2H), 2.33 (q, $J = 7.6$ Hz, 2H), 1.23 (t, $J = 7.0$ Hz, 3H), 0.98 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 (C), 160.4 (C), 138.5 (C), 128.6 (CH), 128.3 (CH), 127.8 (CH), 115.8 (CH), 59.8 (CH_2), 26.7 (CH_2), 14.3 (CH_3), 14.2 (CH_3); HRMS (EI) calcd for $C_{13}H_{16}O_2S$: 236.0871; found, 236.0879.

4.1.6. (*E*)-Ethyl-3-(benzylthio)-3-phenylacrylate *E*-10 and (*Z*)-ethyl-3-(benzylthio)-3-phenylacrylate *Z*-10. To a solution of ethyl phenylpropiolate (1.0 mL, 6.0 mmol, 1.0 equiv) in EtOH (30 mL) were added benzyl mercaptan (0.70 mL, 6.0 mmol, 1.0 equiv) and triethylamine (0.84 mL, 6.0 mmol, 1.0 equiv). The solution was stirred overnight, after which the solvent was removed in vacuo. Purification by column chromatography (SiO_2, 9.5:0.5, heptane/EtOAc) gave the *E*-isomer (0.65 g, 37%) and the *Z*-isomer 0.42 g (23%) both as colorless oils. *E*-**10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–6.97 (m, 10H), 5.90 (s, 1H), 4.22 (q, $J = 7.0$ Hz, 2H), 3.63 (s, 2H), 1.29 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C), 159.6 (C), 138.2 (C), 136.6 (C), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 126.8 (CH), 115.9 (CH), 59.7 (CH_2), 37.0 (CH_2), 14.1 (CH_3); HRMS (EI) calcd for $C_{18}H_{18}O_2S$: 298.1027; found, 298.1013. *Z*-**10**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.28 (m, 10H), 5.84 (s, 1H), 4.00 (s, 2H), 3.98 (q, $J = 7.0$ Hz, 2H), 1.06 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100.32 MHz, $CDCl_3$) δ 164.3 (C), 159.4 (C), 137.0 (C), 135.0 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.0 (CH), 111.3 (CH), 59.8 (CH_2), 37.3 (CH_2), 14.0 (CH_3); HRMS (EI) calcd for $C_{18}H_{18}O_2S$: 298.1027; found, 298.1016.

4.1.7. 2-(Benzylthio)fumaric acid *Z*-8. To dimethyl-2-(benzylthio)fumarate *Z*-**6** (5.70 g, 21.4 mmol, 1.0 equiv) in ethanol (30 mL) was added 2 M (aq) NaOH (50 mL, 0.10 mol, 4.7 equiv). This solution was heated to 80 °C for 3 h, cooled and washed three times with EtOAc (40 mL). The aqueous layer was acidified with concd HCl (aq) and extracted three times with EtOAc (40 mL). The organic layers were dried with Na_2SO_4 and the solvent removed in vacuo. Purification via recrystallization from methanol gave 3.8 g (74%) of the product as a yellow solid, mp 162–164.5 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.34–7.26 (m, 5H), 6.23 (s, 1H), 4.10 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ 166.4 (C), 165.6 (C), 149.4 (C), 137.0 (C), 129.4 (CH), 128.9 (CH), 127.7 (CH), 118.8 (CH), 36.2 (CH_2); Mass (EI) 238.9; Anal. Calcd for $C_{11}H_{10}O_4S$: C, 55.46; H, 4.23; S, 13.46. Found: C, 55.54; H, 4.34; S, 14.17. HRMS (EI) calcd for $C_{11}H_{10}O_4S$: 238.0330; found, 238.0297.

4.1.8. (*Z*)-Ethyl 2-(benzylthio)-3-phenylacrylate *Z*-11 and (*E*)-ethyl 2-(benzylthio)-3-phenylacrylate *E*-11. To stirred neat ethyl phenylpropiolate (1.0 mL, 6.0 mmol, 1.0 equiv) and benzyl mercaptan (0.70 mL, 6.0 mmol, 1.0 equiv) was added AIBN (0.20 g, 1.2 mmol, 0.2 equiv). This mixture was heated to 70 °C for 1.5 h, cooled to rt diluted with water (20 mL) and extracted with EtOAc (3 × 30 mL). The organic layers were dried over Na_2SO_4 and the solvent removed in vacuo to give a colorless oil. Purification via column chromatography (SiO_2, 99:1 heptane/EtOAc) gave the *Z*-isomer as a colorless oil (1.2 g, 67%) contaminated with 20% of the *E*-isomer and 0.12 g (7%) of *E*-isomer contaminated with ~20% of *Z*-isomer. Both compounds were obtained as colorless oils *Z*-**11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.67–7.65 (m, 2H), 7.35–7.18 (m, 8H), 4.33 (q, $J = 7.2$ Hz, 2H), 4.02 (s, 2H), 1.39 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C), 144.6 (CH), 137.6 (C), 134.9 (C), 130.9 (CH), 129.6 (CH), 129.2 (CH), 128.6 (CH), 128.3 (CH), 127.4 (CH), 126.8 (C), 62.0 (CH_2), 38.7 (CH_2), 14.6 (CH_3); HRMS (EI) calcd for $C_{18}H_{18}SO_2$: 298.1027; found, 298.1040. *E*-**11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.18 (m, 10H), 6.86 (s, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 3.99 (s, 2H), 1.18 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4 (C), 144.6 (CH), 137.6 (C), 137.2 (C), 130.6 (CH), 129.6 (CH), 129.3 (CH), 128.7 (CH), 128.7 (CH), 127.9 (C), 127.5 (CH), 61.5 (CH_2), 38.3 (CH_2), 14.1 (CH_3). HRMS (EI) calcd for $C_{18}H_{18}O_2S$: 298.1027; found, 298.1040.

4.1.9. (*Z*)-2-(Benzylthio)-3-phenylacrylic acid *Z*-12. To (*Z*)-ethyl 2-(benzylthio)-3-phenylacrylate *Z*-**11** (0.20 g, 0.67 mmol, 1.0 equiv) was added 5.0 mL of 4 M aqueous NaOH (7.5 equiv), and the mixture was stirred overnight. The aqueous layer was acidified with concd HCl (aq) to pH 1 and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried with Na_2SO_4, filtered, and the solvent removed in vacuo. Recrystallization from heptane/EtOAc gave 0.13 g (74%) of *Z*-**12** as yellow needles, mp 120.5–121.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.75–7.73 (m, 2H), 7.39–7.36 (m, 4H), 7.26–7.18 (m, 4H), 4.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (C), 148,1 (CH), 137.4 (C), 134,5 (C), 131.3 (CH), 130.3 (CH), 129.3 (CH), 128.7 (CH), 128.5 (CH), 127.5 (CH), 125.1 (CH), 39.0 (CH_2); HRMS (EI) calcd for $C_{16}H_{14}SO_2$: 270.0714; found, 270.0702; Anal. Calcd for $C_{16}H_{14}SO_2$: C, 71.11; H, 5.19; S, 11.95. Found: C, 71.09; H, 5.25; S, 11.97.

4.1.10. Ethyl-3-(benzylthio)-3-phenylpropanoate 20

4.1.10.1. Enantioselective. Hydrogenation and purification was performed using standard conditions with ethanol as the solvent. The ee determination was performed on an OD-H column eluted with *n*-heptane/*iso*-propanol (99:01, flow rate, 0.5 mL/min). Enantiomer 1 eluted at 21.6 min, enantiomer 2 at 24.4 min.

4.1.10.2. Racemic. To a solution of benzyl mercaptan (0.33 mL, 2.8 mmol, 1.2 equiv), triethylamine (0.40 mL, 2.8 mmol, 1.2 equiv) in ethanol was added *trans*-ethyl cinnamate (0.40 mL, 2.4 mmol). The solution was heated to 40 °C and stirred overnight. Solvent was removed in vacuo. Purification by column chromatography (SiO_2, 9.7:0.3, heptane/EtOAc) gave **10** (0.41 g, 51%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.18 (m, 10H), 4.15 (t, $J = 8.0$ Hz, 1H), 4.02–3.99 (m, 2H), 3.49 (ABX, $J_{app} = 13.2$, 36.0 Hz, 2H), 2.81 (ABX, $J_{app} = 15.6$, 7.2 Hz, 2H), 1.10 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C), 141.1 (C), 137.8 (C), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.5 (CH), 127.0 (CH), 60.6 (CH_2), 45.0 (CH), 41.5 (CH_2), 35.7 (CH_2), 14.1 (CH_3); HRMS (EI) calcd for $C_{18}H_{20}O_2S$: 300.1184; found, 300.1171.

4.1.11. Ethyl-3-(ethylthio)-3-phenylpropanoate 19

4.1.11.1. Enantioselective. Hydrogenation and purification was performed using standard conditions with ethanol as the solvent. The ee was determinated on an OD-H column eluted with *n*-heptane/*iso*-propanol (99:01, flow

rate, 0.5 mL/min). Enantiomer 1 eluted at 13 min, enantiomer 2 at 22 min.

4.1.11.2. Racemic. To a solution of ethanethiol (0.36 mL, 4.7 mmol, 2.0 equiv) and triethylamine (0.40 mL, 2.8 mmol, 1.2 equiv) in ethanol was added 10 mL *trans*-ethyl cinnamate (0.40 mL, 2.4 mmol, 1.0 equiv). This solution was stirred overnight at 40 °C. The solvent was removed in vacuo and then purified by column chromatography (SiO_2, 1:1, heptane/EtOAc) to give **19** (0.30 g, 46%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.16 (m, 5H), 4.28 (t, $J = 10.4$ Hz, 1H), 4.03 (q, $J = 9.6$ Hz, 2H), 2.83 (ABX, $J_{app} = 15.3$, 7.8 Hz, 2H), 2.29 (q, $J = 7.2$ Hz, 2H), 1.12 (t, $J = 7.5$ Hz, 3H), 1.11 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C), 141.3 (C), 128.3 (CH), 127.5 (CH), 127.1 (CH), 60.3 (CH_2) 44.7 (CH), 41.3 (CH_2), 24.9 (CH_2), 14.1 (CH_3), 13.9 (CH_3); HRMS (EI) calcd for $C_{13}H_{18}O_2S$: 238.1027; found, 238.1026.

4.1.12. Dimethyl-2-(ethylthio)succinate 18

4.1.12.1. Enantioselective. Hydrogenation and purification was performed using standard conditions with methanol as the solvent. The ee determination was performed on an OD-H column eluted with *n*-heptane/*iso*-propanol (97:03, flow rate, 0.5 mL/min). Enantiomer 1 eluted at 13 min, enantiomer 2 at 30 min.

4.1.12.2. Racemic. To a solution of ethanethiol (0.30 mL, 4.2 mmol, 2.0 equiv) and triethylamine (0.35 mL, 2.5 mmol, 1.2 equiv) in methanol (10 mL) was added dimethyl fumarate (0.30 g, 2.1 mmol, 1.0 equiv). The solution was stirred overnight, the solvent was removed in vacuo, and the residue purified by column chromatography (SiO_2, 9:1, heptane/EtOAc) to give **18** (0.40 g, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.69–3.65 (m, 4H), 2.99 (ABX, $J_{app} = 10.0$, 17.2 Hz, 1H), 2.69–2.62 (m, 3H), 1.24 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (C), 170.8 (C), 52.1 (CH_3), 51.6 (CH_3), 40.8 (CH), 35.9 (CH_2) 25.3 (CH_2) 14.0 (CH_3); HRMS (EI) calcd for $C_8H_{14}O_4S$: 206.0613; found, 206.0608.

4.1.13. Ethyl 2-(benzylthio)-3-phenylpropanoate 21

4.1.13.1. Enantioselective. Hydrogenation and purification was performed using standard conditions with methanol as the solvent. The ee determination was performed on an OB-H column eluting with *n*-heptane/isopropanol (98:02, flow rate, 0.5 mL/min). Enantiomer 1 eluted at 20.1 min, enantiomer 2 at 22.3 min.

4.1.13.2. Racemic. To a solution of benzyl mercaptan (0.33 mL, 4.2 mmol, 2.0 equiv) and triethylamine (0.40 mL, 2.8 mmol, 1.2 equiv) in methanol (10 mL) was added *trans*-ethyl cinnamate (0.40 g, 2.4 mmol, 1.0 equiv). The solution was stirred overnight, the solvent removed in vacuo, and the crude residue purified by column chromatography (SiO_2, 9:1, heptane/EtOAc) to give **21** (0.40 g, 51%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.09 (s, 1H), 7.09 (d, $J = 6.8$ Hz, 2H), 4.14–4.13 (m, 2H), 3.81 (ABX, $J_{app} = 22.0$, 8.8 Hz, 2H), 3.42 (ABX, $J_{app} = 9.2$, 2.0 Hz, 1H), 3.15 (ABX, $J_{app} = 14.0$, 4.8 Hz, 1H), 2.89 (ABX, $J_{app} = 13.6$, 7.6 Hz, 1H), 1.21 (t, $J = 24.0$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.3 (C), 138.1 (C), 137.5 (C), 129.3 (CH), 129.2 (CH), 128.7 (CH), 128.6 (CH), 127.4 (CH), 126.9 (CH), 61.3 (CH_2), 47.6 (CH), 37.7 (CH_2), 36.4 (CH_2), 14.4 (CH_3); HRMS (EI) calcd for $C_{18}H_{20}O_2S$: 300.1184; found, 300.1171.

4.1.14. Ethyl 2-(benzylthio)-3-phenylpropanoate 22

4.1.14.1. Enantioselective. Hydrogenation and purification was performed using standard conditions with methanol as the solvent. The ee determination was performed on an OD-H column eluting with *n*-heptane/*iso*-propanol (99:01, flow rate, 0.5 mL/min). Enantiomer 1 eluted at 25.7 min, enantiomer 2 at 27.5 min.

4.1.14.2. Racemic. *Z*-**12** was hydrogenated using Pd on carbon (10% paladium) (0.050 g, 0.005 mmol, 0.05 equiv) using standard conditions with methanol as the solvent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.22 (m, 8H), 7.07 (d, $J = 6.4$ Hz, 2H), 3.80 (ABX $J_{app} = 19.2$, 5.6 Hz, 2H) 3.64 (s, 3H), 3.43 (t, $J = 8.8$ Hz, 1H), 3.16 (ABX $J_{app} = 15.0$, 4.8 Hz, 1H), 2.89 (ABX $J_{app} = 13.6$, 7.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.5 (C), 137.8 (C), 137.2 (C), 129.0 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 127.2 (CH), 126.7 (CH), 52.2 (CH), 47.3 (CH), 37.5 (CH_2), 36.2 (CH_2); HRMS (EI) calcd for $C_{17}H_{18}O_2S$: 286.1027; found, 286.1035.

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