

SUPPORTING INFORMATION I

Highly Versatile Enantioselective Conjugate Addition of Grignard Reagents to α,β -Unsaturated Thioesters

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General Procedures: All reactions were carried out under a nitrogen atmosphere using oven dried glassware. *t*-BuOMe was purchased as anhydrous grade, stored on 4Å MS and used without further purification. CuI was purchased from Aldrich and used without further purification. Grignard reagents were purchased from Aldrich (MeMgBr, EtMgBr, *i*-BuMgBr) or prepared from the corresponding alkyl bromides and magnesium turnings in Et₂O following standard procedures. Grignard reagents were titrated using *s*-BuOH and catalytic amounts of 1,10-phenanthroline.

Racemic 1,4-addition products **2** and **4** were synthesized by reaction of the thioesters **1** and **3** with the corresponding Grignard reagent at -78 °C in THF in the presence of CuI (2 mol%) and racemic BINAP (2 mol%).

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by staining with a solution of a mixture of KMnO₄ (10 g) and K₂CO₃ (10 g) in H₂O (500 mL). Progress and conversion of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on a AEI-MS-902 mass spectrometer. ¹H- and ¹³C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) using CDCl₃ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl₃: δ 7.26 for ¹H, δ 77.0 for ¹³C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). Enantioselectivities were determined by capillary GC analysis using a flame ionization detector (in comparison with racemic products). HPLC analysis was carried out on a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector.

1. Procedures for the synthesis of α,β -unsaturated thioesters

1.1. Procedure for the synthesis of α,β -unsaturated thioesters from carboxylic acids¹

Dicyclohexyl carbodiimide (DCC) (1.09 g, 5.3 mmol) was added at 0 °C to a solution of the corresponding α,β -unsaturated carboxylic acid (5.0 mmol), ethanethiol (481 µL, 6.5 mmol) and 4-(dimethylamino)pyridine (DMAP) (61 mg, 0.5 mmol) in CH₂Cl₂ (25 mL) and the resulting mixture was allowed to slowly warm to rt overnight. The mixture was then filtered through Celite® and the filter cake was washed with CH₂Cl₂. The filtrate was washed with a saturated aqueous NaHCO₃ solution,

¹ Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978**, 17, 522.

H_2O and brine, then dried over MgSO_4 , concentrated under reduced pressure and the crude product purified by flash chromatography to give the corresponding thioester.

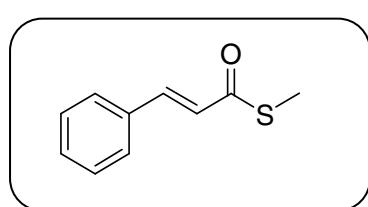
1.2. Procedure for the synthesis of α,β -unsaturated thioesters from esters²

To a solution of the ester (5.0 mmol) in THF (17 mL) at rt were added AlCl_3 (6.0 mmol) and $\text{Me}_3\text{Si-SEt}$ or $\text{Me}_3\text{Si-SMe}$ (10.0 mmol). The resulting mixture was stirred at reflux for 12 h and then quenched at rt by addition of a saturated aqueous NH_4Cl solution. After extraction with Et_2O , the combined organic phases were dried over MgSO_4 , concentrated under reduced pressure and the product purified by flash chromatography to afford the desired thioester.

1.3. Procedure for the synthesis of α,β -unsaturated thioesters from aldehydes through a Wittig reaction³

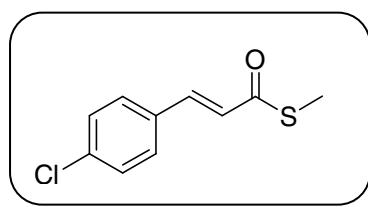
A solution of the aldehyde (2 mmol) and $\text{Ph}_3\text{PCHCOSEt}$ (2.6 mmol, 947.6 mg) in CHCl_3 or CH_2Cl_2 (20 mL) was heated at reflux for 1–3 h. The solution was concentrated under reduced pressure and purified by column flash chromatography to afford the desired α,β -unsaturated thioester.

1.4. Data for the α,β -unsaturated thioesters



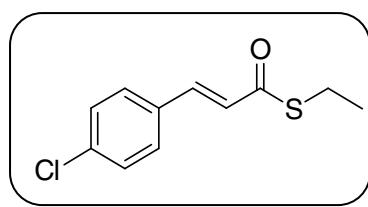
S-Methyl (2E)-3-phenylprop-2-enethioate (1a)⁴:

Thioester **1a** was obtained from *trans*-cinnamic acid following the general *Procedure 1.1* and had identical properties (NMR, MS) to the reported compound.



S-Methyl (2E)-3-(4-chlorophenyl)prop-2-enethioate (1b)⁴:

Thioester **1b** was obtained from methyl 4-chlorocinnamate following the general *Procedure 1.2* and had identical properties (NMR, MS) to the reported compound.



S-Ethyl (2E)-3-(4-chlorophenyl)prop-2-enethioate (1c):

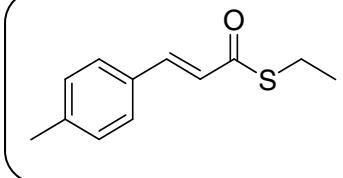
Thioester **1c** was obtained from methyl 4-chlorocinnamate following the general *Procedure 1.2*, after purification by flash chromatography (pentane/ Et_2O 60:1), as a waxy solid (83% yield). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.31 (t, J = 7.3 Hz, 3H), 3.01 (q, J = 7.3 Hz, 2H), 6.66 (d, J = 15.8 Hz, 1H), 7.35 (m, 2H), 7.46 (m, 2H), 7.53 (d, J = 15.8 Hz, 1H). $^{13}\text{C-NMR}$ (100.59 MHz, CDCl_3) δ 14.7, 23.4, 125.5, 129.2, 129.4, 132.6, 136.3, 138.6, 189.6. LRMS (CI) m/z : 228 (M^++2), 226 (M^+), 167, 165 (100), 139, 137, 102; HRMS calcd for $\text{C}_{11}\text{H}_{11}\text{ClOS}$ (M^+): 226.0219; found: 226.0211.

² Mukaiyama, T.; Takeda, T.; Atsumi, K. *Chem. Lett.* **1974**, 3, 189-192.

³ Keck, G. E.; Boden, E. P.; Mabury, S. A. *J. Org. Chem.* **1985**, 50, 709-710.

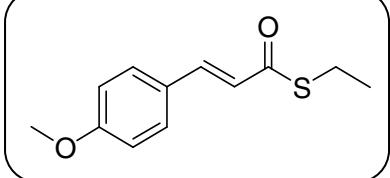
⁴ Howell, G. P.; Fletcher, S. P.; Geurts, K.; ter Horst, B.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, 128, 14977-14985.

S-Ethyl (2E)-3-(4-methylphenyl)prop-2-enethioate (1d):



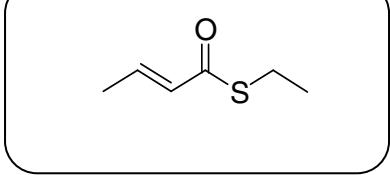
Thioester **1d** was obtained from 4-methyl benzaldehyde following the general *Procedure 1.3*, after purification by flash chromatography (pentane/Et₂O 50:1), as a waxy solid (86% yield). ¹H-NMR (400 MHz, CDCl₃) δ 1.32 (t, *J* = 7.3 Hz, 3H), 2.37 (s, 3H), 3.01 (q, *J* = 7.3 Hz, 2H), 6.67 (d, *J* = 15.8 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 15.8 Hz, 1H). ¹³C-NMR (100.59 MHz, CDCl₃) δ 15.1, 21.7, 23.6, 124.4, 128.6, 129.9, 131.6, 140.5, 141.2, 190.2. LRMS (CI) *m/z*: 206 (M⁺), 145 (100), 115, 91; HRMS calcd for C₁₂H₁₄OS (M⁺): 206.0765; found: 206.0774.

S-Ethyl (2E)-3-(4-methoxyphenyl)prop-2-enethioate (1e):



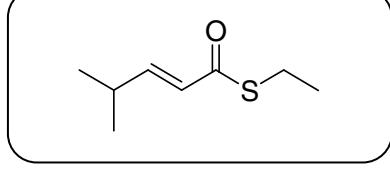
Thioester **1e** was obtained from 4-methoxy benzaldehyde following the general *Procedure 1.3*, after purification by flash chromatography (pentane/Et₂O 60:1), as a waxy solid (90% yield). ¹H-NMR (400 MHz, CDCl₃) δ 1.31 (t, *J* = 7.3 Hz, 3H), 3.00 (q, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.89 (m, 2H), 7.47 (m, 2H), 7.56 (d, *J* = 15.8 Hz, 1H). ¹³C-NMR (100.59 MHz, CDCl₃) δ 14.8, 23.2, 55.3, 114.3, 122.8, 126.7, 130.0, 139.9, 161.5, 189.8. LRMS (CI) *m/z*: 222 (M⁺), 161 (100), 133; HRMS calcd for C₁₂H₁₄O₂S (M⁺): 222.0715; found: 222.0704.

S-Ethyl (2E)-but-2-enethioate (3a)⁴:



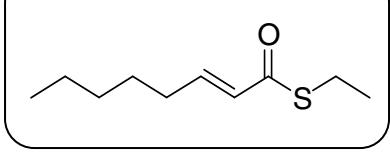
Thioester **3a** was obtained from (*E*)-but-2-enoic acid following the general *Procedure 1.1* and had identical properties (NMR, MS) to the reported compound.

S-Ethyl (2E)-4-methylpent-2-enethioate (3b):

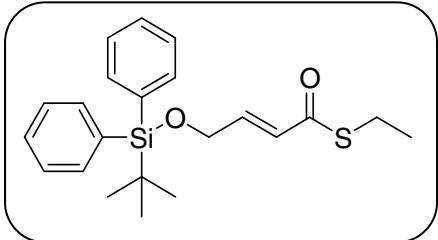


Thioester **3b** was obtained from 4-methylpent-2-enoic acid following the general *Procedure 1.1*, after purification by flash chromatography (pentane/Et₂O 60:1), as a colorless oil (90% yield). ¹H-NMR (300 MHz, CDCl₃) δ 1.04 (d, *J* = 6.9 Hz, 6H), 1.24 (t, *J* = 7.3 Hz, 3H), 2.39 (m, 1H), 2.90 (q, *J* = 7.3 Hz, 2H), 6.01 (d, *J* = 15.7 Hz, 1H), 6.83 (dd, *J* = 6.6 Hz, *J* = 15.7 Hz, 1H). ¹³C-NMR (100.59 MHz, CDCl₃) δ 14.7, 21.1, 22.9, 30.8, 125.9, 151.1, 190.3. LRMS (CI) *m/z*: 158 (M⁺), 97 (100), 41; HRMS calcd for C₈H₁₄OS (M⁺): 158.0765; found: 158.0767.

S-Ethyl (2E)-oct-2-enethioate (3c)⁴:



Thioester **3c** was obtained from ethyl (*E*)-oct-2-enoate following the general *Procedure 1.2* (Me₃Si-SEt) and had identical properties (NMR, MS) to the reported compound.



S-Ethyl (2E)-4-[[tert-butyl(diphenyl)silyl]oxy]but-2-enethioate (3d)⁴:

Thioester **3d** was obtained following the procedure in the literature⁴ and had identical properties (NMR, MS) to the reported compound.

2. General Procedure for the catalytic asymmetric conjugate addition of Grignard reagents to α,β -unsaturated thioesters

2.1. Using Josiphos

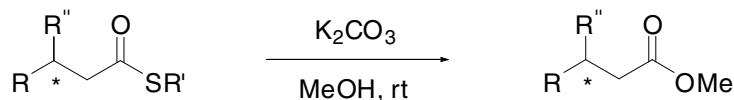
Dry *t*-BuOMe (2 mL) was added to a mixture of CuBr.SMe₂ (5.14 mg, 0.025 mmol) and (*R,S*)-Josiphos (17.84 mg, 0.03 mmol) under a nitrogen atmosphere at room temperature and the orange solution was stirred for 20 min before cooling to -75 °C. While ensuring that stirring continued, MeMgBr (3 M solution in Et₂O, 0.20 mL, 0.67 mmol) was added resulting in a yellow reaction mixture. After an additional 10 min the corresponding thioester (0.5 mmol) in dry *t*-BuOMe (3 mL) was added. Stirring at -75 °C was continued for 12 h and the reaction mixture was removed from the cooling bath. The reaction mixture was stirred for 1 h at room temperature before being quenched by the addition of MeOH (*ca.* 1 mL) at -75 °C. The mixture was allowed to reach room temperature and NH₄Cl (sat. aq. *ca.* 1 mL) was added. The mixture was partitioned between *t*-BuOMe and water (5 mL), and the aqueous layer extracted three times with Et₂O. The combined organic layers were dried (MgSO₄), filtered and the solvent evaporated. Flash chromatography of the dark orange residue over silica gel gave the corresponding 1,4-addition products.

2.2. Using Tol-BINAP

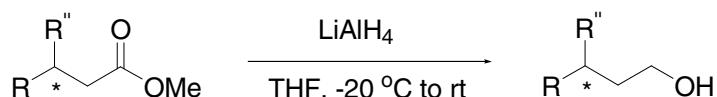
CuI (1 mol%, 0.47 mg) and (-)-(*S*)-Tol-BINAP (1.1 mol%, 1.87 mg) were dissolved in *t*-BuOMe (2 mL) and stirred at rt under nitrogen until a yellow suspension was observed. The mixture was cooled to -70 °C and the appropriate Grignard reagent (1 mmol, solution in Et₂O) was added dropwise. After stirring for 10 min, a solution of thioester **1** (0.25 mmol) in DCM (0.5 mL) was added slowly (5 min). The reaction mixture was stirred at -70 °C for 8 h (or for 16 h for the aromatic substrates). Subsequently, the reaction was quenched by the addition of MeOH and saturated aqueous NH₄Cl solution and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous layer extracted with Et₂O. The combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash column chromatography to afford the desired 1,4-addition products.

2.3. Derivatization of the β -substituted thioesters for the determination of the enantiomeric excess.

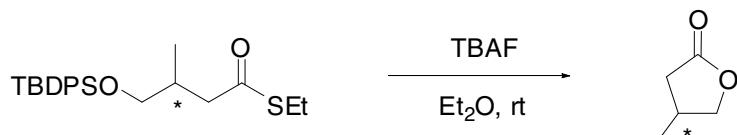
2.3.1. Preparation of the corresponding methyl esters: The thioester (0.1 mmol) was dissolved in MeOH (10 mL) and K₂CO₃ (1 g) was added before stirring at room temperature for 5 h. After addition of Et₂O and aqueous 1 M HCl (to pH ~ 1), the aqueous phase was separated and extracted with Et₂O (3 × 10 mL). The combined organic phases were washed (brine) and dried (MgSO₄), and the solvent was evaporated. The residue was purified by flash column chromatography (pentane/Et₂O 50:1) to give the corresponding ester in quantitative yield (>95%).



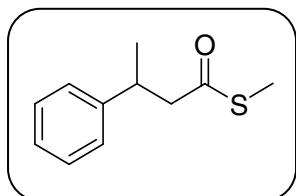
2.3.2. Preparation of the corresponding alcohols: The corresponding methyl ester (0.1 mmol) (prepared as described above) was added to a suspension of LiAlH₄ (0.5 mmol) in anhydrous THF (5 mL) at -20 °C. The mixture was stirred for 3 h, allowing the temperature to raise until room temperature. The reaction was quenched with 1 mL of H₂O and 0.5 mL of aqueous NaOH (2 M). After addition of Et₂O, the aqueous phase was separated and extracted with Et₂O (3 × 10 mL). The combined organic phases were dried over MgSO₄, concentrated under reduced pressure and the product was purified by flash column chromatography (pentane/Et₂O 25:1) to afford the desired alcohol in quantitative yield (>95%).



2.3.3. Preparation of the corresponding lactone: The thioester **4i** (0.1 mmol) was dissolved in Et₂O (1 mL) and treated with TBAF 1 M in THF (1 mL) at room temperature to yield a pure sample of 4-methyl-dihydrofuran-2(3H)-one.⁴

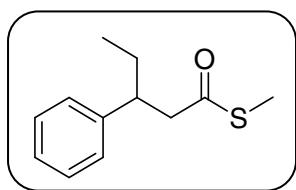


2.4. Data of the products 2 and 4



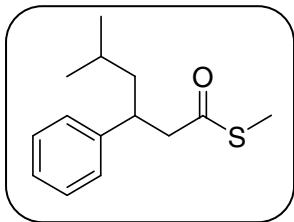
S-Methyl 3-phenylbutanethioate (2a):

Thioester **2a** was obtained from **1a** following the general procedure (MeMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [65% yield, 95% ee, $[\alpha]_D = +45.1$ (c = 0.3, CHCl₃) with (R,S)-Josiphos; 88% yield, 94% ee, $[\alpha]_D = -38.4$ (c = 0.3, CHCl₃) with (S)-Tol-BINAP]. *Ee* determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane/i-PrOH 99: 1, retention times: 10.7 (major enantiomer with (S)-Tol-BINAP) and 12.1 min (major enantiomer with (R,S)-Josiphos).



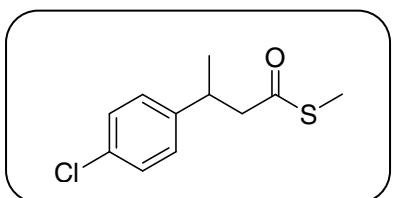
S-Methyl 3-phenylpentanethioate (2b):

Thioester **2b** was obtained from **1a** following the general procedure (EtMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [93% yield, 92% ee, $[\alpha]_D = -14.0$ (c = 1, CHCl₃) with (S)-Tol-BINAP]. ¹H-NMR (400 MHz, CDCl₃) δ 0.78 (t, *J* = 7.3 Hz, 3H), 1.60 (m, 1H), 1.72 (m, 1H), 2.23 (s, 3H), 2.86 (2dd, A and B of ABX, *J*_{AB} = 14.7 Hz, *J*_{AX} = 7.7 Hz, *J*_{BX} = 7.0 Hz, 2H), 3.09 (m, X of ABX, 1H), 7.19 (m, 3H), 7.31 (m, 2H). ¹³C-NMR (100.59 MHz, CDCl₃) δ 11.6, 11.8, 28.8, 44.2, 50.6, 126.4, 127.5, 128.3, 143.4, 198.6. LRMS (CI) *m/z*: 208 (M⁺), 161, 132, 119, 91 (100); HRMS calcd for C₁₂H₁₆OS (M⁺): 208.0922; found: 208.0929. *Ee* determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane/i-PrOH 99.5: 0.5, retention times: 11.9 (major enantiomer with (S)-Tol-BINAP) and 13.4 min.



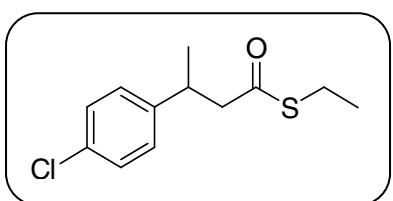
S-Methyl 5-methyl-3-phenylhexanethioate (2c):

Thioester **2c** was obtained from **1a** following the general procedure (*i*-BuMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [70% yield, 80% *ee*, $[\alpha]_D = -16.5$ (c = 2.3, CHCl₃) with (*S*)-Tol-BINAP]. ¹H-NMR (400 MHz, CDCl₃) δ 0.82 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 1.30 (m, 1H), 1.46 (m, 1H), 1.50 (m, 1H), 2.22 (s, 3H), 2.81 (d, *J* = 7.3 Hz, 2H), 3.27 (m, 1H), 7.18 (m, 3H), 7.28 (m, 2H). ¹³C-NMR (100.59 MHz, CDCl₃) δ 11.6, 21.5, 23.4, 25.2, 40.4, 45.0, 51.5, 126.4, 127.4, 128.4, 143.6, 198.5. LRMS (CI) *m/z*: 236 (M⁺), 189, 160, 147, 91 (100); HRMS calcd for C₁₄H₂₀OS (M⁺): 236.1235; found: 236.1246. *Ee* determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane/*i*-PrOH 99.5: 0.5, retention times: 10.6 (major enantiomer with (*S*)-Tol-BINAP) and 11.2 min.



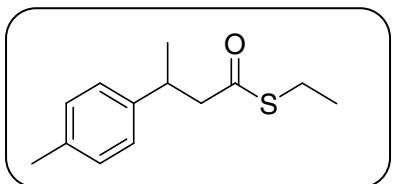
S-Methyl 3-(4-chlorophenyl)butanethioate (2d):

Thioester **2d** was obtained from **1b** following the general procedure (MeMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [60% yield, >99% *ee*, $[\alpha]_D = +59.3$ (c = 0.3, CHCl₃) with (*R,S*)-Josiphos]. *Ee* determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane/*i*-PrOH 99.5: 0.5, retention times: 10.9 and 12.3 min (major enantiomer with (*R,S*)-Josiphos).



S-Ethyl 3-(4-chlorophenyl)butanethioate (2e):

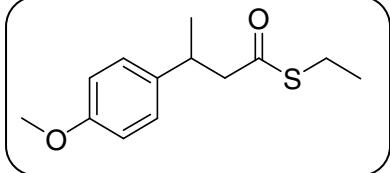
Thioester **2e** was obtained from **1e** following the general procedure (MeMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [93% yield, 99% *ee*, $[\alpha]_D = -36.2$ (c = 0.8, CHCl₃) with (*S*)-Tol-BINAP]. ¹H-NMR (400 MHz, CDCl₃) δ 1.19 (t, *J* = 7.3 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 2.73 (dd, *J*_{AB} = 8.1 Hz, *J*_{AX} = 15.0 Hz, 1H), 2.80 (dd, *J*_{AB} = 7.0 Hz, *J*_{AX} = 15.0 Hz, 1H), 2.82 (q, *J* = 7.3 Hz, 2H), 3.31 (m, 1H), 7.14 (m, 3H), 7.25 (m, 2H). ¹³C-NMR (100.59 MHz, CDCl₃) δ 14.7, 21.4, 23.3, 36.4, 52.0, 128.1, 128.5, 132.0, 143.7, 197.9. LRMS (CI) *m/z*: 244 (M⁺+2), 242 (M⁺), 152, 139 (100); HRMS calcd for C₁₂H₁₅ClOS (M⁺): 242.0532; found: 242.0542. *Ee* determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane/*i*-PrOH 99.5: 0.5, retention times: 10.8 (major enantiomer with (*S*)-Tol-BINAP) and 11.5 min.



S-Ethyl 3-(4-methylphenyl)butanethioate (2f):

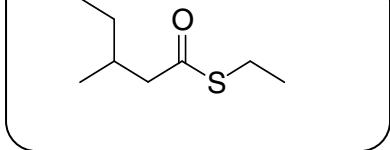
Thioester **2f** was obtained from **1d** following the general procedure (MeMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [33% yield, >99% *ee*, $[\alpha]_D = +48.5$ (c = 0.1, CHCl₃) with (*R,S*)-Josiphos; 34% yield, 99% *ee*, $[\alpha]_D = -73.0$ (c = 1, CHCl₃) with (*S*)-Tol-BINAP]. ¹H-NMR (400 MHz, CDCl₃) δ 1.22 (t, *J* = 7.3 Hz, 3H), 1.29 (d, *J* = 7.0 Hz, 3H), 2.32 (s, 3H), 2.75 (dd, *J*_{AB} = 8.4 Hz, *J*_{AX} = 14.7 Hz, 1H), 2.82 (dd, *J*_{AB} = 6.6 Hz, *J*_{AX} = 14.7 Hz, 1H), 2.85 (q, *J* = 7.3 Hz, 2H), 3.32 (m, 1H), 7.11 (s, 4H). ¹³C-NMR (100.59 MHz, CDCl₃) δ 14.7, 21.0, 21.5, 23.3, 36.5, 52.3, 126.6, 129.1, 135.8, 142.4, 198.3. LRMS (CI) *m/z*: 193 (M⁺-29), 192, 132, 119 (100), 91; HRMS calcd for C₁₃H₁₈OS (M⁺): 222.1078; found: 222.1068. *Ee* determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane/*i*-PrOH 99.5: 0.5, retention times: 12.7 (major enantiomer with (*S*)-Tol-BINAP) and 14.9 min (major enantiomer with (*R,S*)-Josiphos).

S-Ethyl 3-(4-methoxyphenyl)butanethioate (2g):



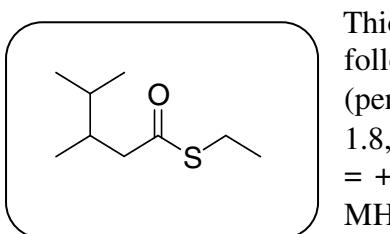
Thioester **2g** was obtained from **1e** following the general procedure (MeMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [24% yield, 93% *ee*, $[\alpha]_D = +52.0$ (c = 0.2, CHCl₃) with (R,S)-Josiphos; 15% yield, 96% *ee*, $[\alpha]_D = -44.0$ (c = 0.5, CHCl₃) with (S)-Tol-BINAP]. ¹H-NMR (400 MHz, CDCl₃) δ 1.20 (t, *J* = 7.3 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 2.72 (dd, *J*_{AB} = 8.1 Hz, *J*_{AX} = 14.7 Hz, 1H), 2.80 (dd, *J*_{AB} = 6.6 Hz, *J*_{AX} = 14.7 Hz, 1H), 2.83 (q, *J* = 7.3 Hz, 2H), 3.29 (m, 1H), 3.78 (s, 3H), 6.83 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H). ¹³C-NMR (100.59 MHz, CDCl₃) δ 14.7, 21.6, 23.3, 36.2, 52.5, 55.2, 113.8, 127.7, 137.5, 158.1, 198.4. LRMS (CI) *m/z*: 193 (M⁺-29), 192, 132, 119 (100), 91; HRMS calcd for C₁₃H₁₈O₂S (M⁺): 238.1028; found: 238.1025. *Ee* determination by chiral HPLC analysis, Chiralcel OJ-H column, Heptane/i-PrOH 98: 2, retention times: 20.7 (major enantiomer with (S)-Tol-BINAP) and 22.1 min (major enantiomer with (R,S)-Josiphos).

S-Ethyl 3-methylpentanethioate (4a)⁵:



Thioester **4a** was obtained from **3a** following the general procedure (EtMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [53% yield, 80% *ee*], $[\alpha]_D = -4.5$ (c = 1.1, CHCl₃). *Ee* determination of the corresponding methyl ester [methyl 3-methylpentanoate]⁶ by GC Chiraldex G-TA (30 m × 0.25 mm × 0.125 μ m), split ratio 153, initial temp. 50 °C for 20 min, then 10 °C/min to 120 °C (final temp), retention times: 11.8 (major enantiomer with (S)-Tol-BINAP) and 12.8 min.

S-Ethyl 3,4-dimethylpentanethioate (4b):



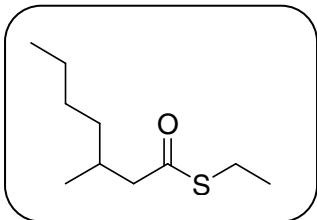
Thioester **4b** was obtained from **3a** (*i*-PrMgBr) or from **3b** (MeMgBr), following the general procedure, after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [70% yield, 66% *ee*, $[\alpha]_D = -8.8$ (c = 1.8, CHCl₃) for the addition of *i*-PrMgBr to **1a** and 82% yield, 99% *ee*, $[\alpha]_D = +1$ (c = 0.2, CHCl₃) for the addition of MeMgBr to **1c**]. ¹H-NMR (400 MHz, CDCl₃) δ 0.83 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 1.23 (t, *J* = 7.5 Hz, 3H), 1.57 (m, 1H), 1.94 (m, X of ABX, 1H), 2.30 (dd, A of ABX, *J*_{AB} = 14.3 Hz, *J*_{AX} = 9.2 Hz, 1H), 2.55 (dd, B of ABX, *J*_{AB} = 14.3 Hz, *J*_{BX} = 5.1 Hz, 1H), 2.86 (q, *J* = 7.5 Hz, 2H). ¹³C-NMR (100.59 MHz, CDCl₃) δ 15.0, 15.7, 18.4, 20.0, 23.5, 32.2, 36.8, 49.0, 199.9. LRMS (CI) *m/z*: 175 (M⁺+1), 145, 113, 43 (100); HRMS calcd for C₇H₁₃OS (M⁺-C₂H₅): 145.0687; found: 145.0696. *Ee* determination of the corresponding methyl ester [methyl 3,4-dimethylpentanoate]⁷ by GC Chiraldex G-TA (30 m × 0.25 mm × 0.125 μ m), split ratio 153, initial temp. 50 °C for 20 min, then 10 °C/min to 120 °C (final temp), retention times: 19.0 (major enantiomer with (S)-Tol-BINAP) and 20.1 min.

⁵ Des Mazery, R.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, 127, 9966-9967.

⁶ Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorre, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, 128, 9103-9118.

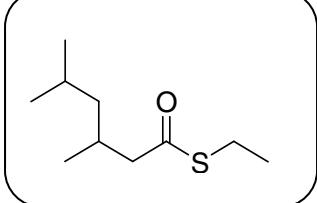
⁷ Enders, D.; Rendenbach, B. E. M. *Tetrahedron* **1986**, 42, 2235-2242.

S-Ethyl 3-methylheptanethioate (4c)⁵:



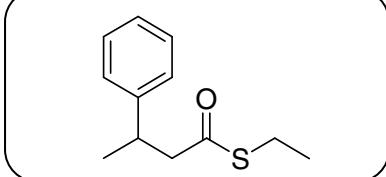
Thioester **4c** was obtained from **3a** following the general procedure (*n*-BuMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [94% yield, 74% *ee*], $[\alpha]_D = 0.1$ (*c* = 0.7, CHCl₃]. *Ee* determination of the corresponding methyl ester [methyl 3-methylheptanoate]⁸ by GC Chiraldex G-TA (30 m × 0.25 mm × 0.125 μm), split ratio 154, initial temp. 40 °C for 30 min, then 0.1 °C/min to 48 °C, then 10 °C/min to 120 °C (final temp), retention times: 73.0 and 76.0 min.

S-Ethyl 3,5-dimethylhexanethioate (4d):



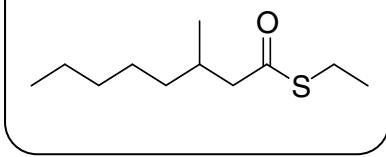
Thioester **4d** was obtained from **3a** following the general procedure (*i*-BuMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [88% yield, 82% *ee*], $[\alpha]_D = +10.0$ (*c* = 0.3, CHCl₃]. ¹H-NMR (400 MHz, CDCl₃) δ 0.85 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 1.10 (m, 2H), 1.23 (t, *J* = 7.4 Hz, 3H), 1.61 (m, 1H), 2.10 (m, X of ABX, 1H), 2.30 (dd, A of ABX, *J*_{AB} = 14.3 Hz, *J*_{AX} = 8.4 Hz, 1H), 2.49 (dd, B of ABX, *J*_{AB} = 14.3 Hz, *J*_{BX} = 5.7 Hz, 1H), 2.85 (q, *J* = 7.4 Hz, 2H). ¹³C-NMR (100.59 MHz, CDCl₃) δ 14.8, 19.6, 22.1, 23.1, 23.2, 25.1, 28.8, 46.1, 51.6, 199.2. LRMS (CI) *m/z*: 189 (M⁺+1), 159, 127, 109 (100); HRMS calcd for C₈H₁₅O (M⁺-SC₂H₅): 127.1123; found: 127.1126. *Ee* determination by GC Chiraldex G-TA (30 m × 0.25 mm × 0.125 μm), split ratio 154, initial temp. 70 °C for 30 min, then 10 °C/min to 180 °C (final temp), retention times: 33.1 and 33.4 min (major enantiomer with (S)-Tol-BINAP).

S-Ethyl 3-phenylbutanethioate (4e)⁵:



Thioester **4e** was obtained from **3a** following the general procedure (PhMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [85% yield, 0% *ee*]. *Ee* determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane/*i*-PrOH 99.5: 0.5, retention times: 12.0 and 14.9 min.

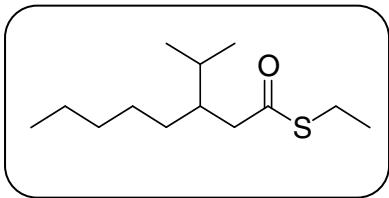
S-Ethyl 3-methyloctanethioate (4f)⁵:



Thioester **4f** was obtained from **3c** following the general procedure (MeMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [90% yield, 93% *ee*], $[\alpha]_D = -4.2$ (*c* = 0.7, CHCl₃]. *Ee* determination of the corresponding methyl ester [methyl 3-methyloctanoate]⁹ by GC Chiraldex G-TA (30 m × 0.25 mm × 0.125 μm), split ratio 150, initial temp. 60 °C for 50 min, then 1 °C/min to 80 °C, then 10 °C/min to 180 °C (final temp), retention times: 43.8 and 45.4 min (major enantiomer with (S)-Tol-BINAP).

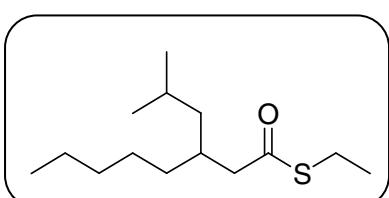
⁸ López, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 2752-2756.

⁹ Kitahara, T.; Hyun, K. S.; Tamogami, S.; Kaiser, R. *Nat Prod. Lett.* **1994**, *5*, 157-164.



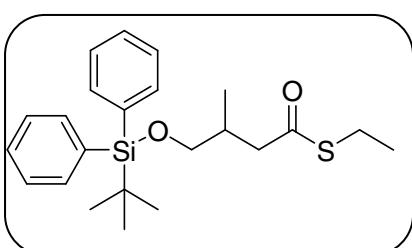
S-Ethyl 3-isopropyl octanethioate (4g)⁵:

Thioester **4g** was obtained from **3c** following the general procedure (*i*-PrMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [89% yield, 65% *ee*], $[\alpha]_D = -5.0$ ($c = 0.6$, CHCl₃]. *Ee* determination by GC CP Chiralsil Dex CB (25 m \times 0.25 mm \times 0.25 μ m), split ratio 75, initial temp. 95 °C for 50 min, then 10 °C/min to 180 °C (final temp), retention times: 56.7 (major enantiomer with (S)-Tol-BINAP) and 56.9 min.



S-Ethyl 3-isobutyl octanethioate (4h)⁵:

Thioester **4h** was obtained from **3c** following the general procedure (*i*-BuMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [70% yield, 80% *ee*], $[\alpha]_D = -1.4$ ($c = 0.7$, CHCl₃]. *Ee* determination of the corresponding alcohol [3-isobutyl octan-1-ol] by GC CP Chiralsil Dex CB (25 m \times 0.25 mm \times 0.25 μ m), split ratio 150, initial temp. 105 °C for 80 min, then 10 °C/min to 180 °C (final temp), retention times: 55.6 and 59.1 min (major enantiomer with (S)-Tol-BINAP).



S-Ethyl 4-{{[tert-butyl(diphenyl)silyl]oxy}-3-methylbutanethioate (4i)⁴:

Thioester **4i** was obtained from **3d** following the general procedure (MeMgBr), after purification by flash chromatography (pentane/Et₂O 50:1), as a colorless oil [95% yield, 83% *ee*], $[\alpha]_D = -7.0$ ($c = 1.0$, CHCl₃]. *Ee* determination of the corresponding lactone [4-methyl-dihydrofuran-2(3H)-one]⁴ by GC CP Chiralsil Dex CB (25 m \times 0.25 mm \times 0.25 μ m), split ratio 50, initial temp. 50 °C, then 1 °C/min to 90 °C, 5 min at 90 °C and then 1 °C/min to 100 °C, 5 min at 100 °C and the 1 °C/min to 110 °C, 5 min at 110 °C and then 1 °C/min to 120 °C and 5 °C/min to 140 (final temp), retention times: 85.6 (major enantiomer with (S)-Tol-BINAP) and 85.8 min.