Highly Enantioselective Conjugate Additions to α,β -Unsaturated Ketones Catalyzed by a (salen)Al Complex.

Mark S. Taylor, David N. Zalatan, Andreas M. Lerchner, and Eric N. Jacobsen*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Supporting Information

General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of nitrogen, unless otherwise noted. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.

Materials. Commercial reagents were purchased from Sigma Aldrich, Alfa Aesar, or Lancaster, and used as received with the following exceptions: toluene and tetrahydrofuran were distilled from sodium at 760 Torr, and acetonitrile and dichloromethane were distilled from calcium hydride at 760 Torr.

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Mercury-400 (400 MHz), Inova-500 (500 MHz), or an Inova-600 (600 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl_3 : δ 7.25). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl_3 : δ 77.0). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and assignment. Infrared (IR) spectra were obtained using a Mattson Galaxy Series FTIR 3000 spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak). Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 370 digital polarimeter. Melting points were measured on a Mel-Temp apparatus, and are uncorrected. The mass spectroscopic data were obtained at the Harvard University mass spectrometry facility. Chiral GC analysis was performed on a Hewlett-Packard 5890 gas chromatograph. Chiral HPLC analysis was performed on either a Hewlett-Packard 1050, or a Shimadzu VP-series instrument.

α,β -Unsaturated Ketone Substrates. 3-Hepten-2-one (97%) was purchased from Alfa Aesar. 4-Phenyl-3-buten-2-one (99+%), 4-(2-thienyl)-3-buten-2-one (98%), 5-methyl-3-hexen-2-one (75%), and chalcone (97%) were purchased from Sigma Aldrich. 1-Phenyl-1-hepten-3-one, 6-decen-5-one, and 2-methyl-4-octen-3-one were prepared from the corresponding α,β -unsaturated aldehyde by Grignard reaction followed by Swern oxidation, according to the procedure of Tietze.¹ 1-Phenyl-2-hexen-1-one was prepared by

Friedel-Crafts acylation of benzene with 2-hexenoyl chloride, following the procedure of Haynes.² 4-Methyl-1-phenyl-1-penten-3-one was prepared by aldol condensation of benzaldehyde and 3-methylbutanone, following the procedure of Brophy.³ 6-Benzyloxyhex-3-en-2-one, 4-(4-bromophenyl)-3-buten-2-one, 4-(4-tolyl)-3-buten-2-one, 4-(4-methoxyphenyl)-3-buten-2-one and 4,4-dimethyl-7-oxo-oct-5-enenitrile were prepared by Horner-Wadsworth-Emmons reaction of diethyl (2-oxopropyl)phosphonate (96%, Aldrich) and the corresponding aldehyde, using a modification of the method of Shabat⁴ (see general experimental procedure A for details). Characterization data for previously reported compounds were in good agreement with literature values.⁵

6-Decen-5-one: The product was obtained as a colorless oil in 78% yield over two steps from 2-hexenal, and purified by distillation (bp 50-55°C, 0.2 torr), followed by chromatography on silica (2% diethyl ether in hexanes). FTIR (cm⁻¹): 2961 (s), 2874 (m), 1676 (s), 1632 (m), 1464 (w), 1188 (*w), 1045 (w), 980 (m). ¹H NMR (500 MHz, CDCl₃): δ 6.81 (1H, dt, J = 16.0, 7.0 Hz, HC=CHCO), 6.08 (1H, d, J = 16.0 Hz, HC=CHCO), 2.52 (2H, t, J = 7.5 Hz, COCH₂), 2.18 (2H, dd, J = 14.5, 7.0 Hz, CH₂CH=C), 1.58 (tt, J = 7.5, 7.5 Hz, COCH₂CH₂), 1.49 (tq, J = 7.0, 7.0 Hz, HC=CHCH₂CH₂CH₃), 1.32 (tq, J = 7.5, 7.5 Hz, CH₂CH₂CH₂CH₃), 0.93 (3H, t, J = 7.0 Hz, COCH₂CH₂CH₃), 0.90 (3H, t, J = 7.0 Hz, CH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 201.2, 147.3, 130.7, 40.0, 34.7, 26.7, 22.6, 21.6, 14.1, 13.9. MS (CI) m/z: 153.9 (80%) [M]⁺.

(A) General procedure for the preparation of enones by Horner-Wadsworth-Emmons reaction.

4,4-Dimethyl-7-oxo-oct-5-enenitrile:

Diethyl (2-oxopropyl)phosphonate (4.04 mL, 20.1 mmol, 1.05 equiv.), then lithium hydroxide (497 mg, 20.0 mmol, 1.0 equiv.) were added sequentially to a solution of 4-cyano-2,2-dimethylbutanal⁶ (2.51 g, 20.0 mmol) in tetrahydrofuran (100 mL) at 0°C. The mixture was allowed to warm slowly to 23°C over 15 hours, then concentrated *in vacuo*. The residue was dissolved in diethyl ether, and washed twice with 1M aqueous hydrochloric acid, twice with saturated aqueous sodium bicarbonate solution, and once with brine, then dried (sodium sulfate) and concentrated. The resulting oil was purified by chromatography on silica (20% ethyl acetate in hexanes), yielding the title compound as a colorless oil (1.65 g, 50%).

Product: FTIR (cm⁻¹): 2967 (m), 2874 (w), 2247 (w), 1676 (s), 1626 (m), 1362 (m), 1258 (m), 988 (m). ¹H NMR (500 MHz, CDCl₃): δ 6.65 (1H, dt, J = 16.5 Hz, HC=CHCO), 6.02 (1H, d, J = 16.5 Hz, HC=CHCO), 2.27 (3H, s, COCH₃), 2.23 (2H, d, J = 8.0 Hz, CH₂CN), 1.18 (2H, d, J = 8.0 Hz, CH₂C(CH₃)₂), 1.12 (6H, s, C(CH₃)₂). ¹³C NMR (100 MHz, CDCl₃): δ 198.6, 153.9, 129.0, 119.9, 37.6, 36.8, 27.7, 26.2, 13.2. MS (CI) m/z: 165.9 (100%) [M+H]⁺.

4-(4-Bromophenyl)-3-buten-2-one:

mp = 81–83°C. FTIR (cm⁻¹): 3044 (w), 1657 (s), 1402 (m), 1362 (m), 1262 (m), 978 (s). ¹H NMR (500 MHz, CDCl₃): δ 7.53 (2H, d, J = 8.5 Hz, ArH), 7.44 (1H, d, J = 16.0 Hz, HC=CHCO), 7.40 (2H, d, J = 8.5 Hz, ArH), 6.70 (1H, d, J = 16.0 Hz, HC=CHCO), 2.38 (3H, s, COCH₃). ¹³C NMR (100 MHz, CDCl₃): δ 198.3, 142.1, 133.6, 132.5, 129.8, 127.8, 125.0. MS (CI) m/z: 224.8 (40%) [M+H]⁺, 227.1 (100%) [M+H]⁺.

(B) Preparation of catalyst **1a**:⁷

In a flame-dried round-bottomed flask equipped with a stir bar and reflux condenser, (*S,S*)-*N,N'*-bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediamine (1.79 g, 3.28 mmol) was suspended in acetonitrile (10 mL) and toluene (3.3 mL). Trimethylaluminum (1.64 mL, 2.0 M solution in toluene, 3.28 mmol, 1.00 equiv.) was added dropwise by syringe at 23°C. The mixture was stirred at 23°C for 30 minutes, then heated to reflux and stirred for 5 hours. After cooling to 23°C, water (59 μL, 3.28 mmol, 1.00 equiv.) was added by syringe. The resulting mixture was heated to reflux and stirred for 15 hours. After cooling to 23°C, acetonitrile (25 mL) was added and the mixture filtered through Celite and washed with acetonitrile (total volume 200 mL). The filtrate was discarded, and the Celite washed with dichloromethane (total volume 125 mL). The filtrate was concentrated *in vacuo*, yielding the aluminum complex **1a** as a pale yellow solid in 85% yield (1.61 g, 1.40 mmol).

Product: α²⁵_D = +715 (c = 1.0, toluene). FTIR (CHCl₃ film, cm⁻¹): 3054 (m), 2961 (s), 2867 (m), 1626 (s), 1555 (m), 1416 (m), 1265 (s), 1177 (m), 1015 (w), 601 (w). mp > 300°C. ¹H NMR (500 MHz, d₁₂-cyclohexane): δ 7.99 (2H, s, HC=N), 7.55 (2H, s, HC=N), 7.45 (2H, s, ArH), 7.21 (2H, s, ArH), 6.98 (2H, s, ArH), 6.75 (2H, s, ArH), 3.34–3.29 (2H, m, CHN=C), 2.68–2.64 (2H, m, CHN=C), 2.27–2.26 (2H, m, (CH₂)₄), 1.85–1.82 (2H, m, (CH₂)₄), 1.56–1.12 (18H, m, (CH₂)₄), 1.50 (18H, s, C(CH₃)₃), 1.31 (18H, s, C(CH₃)₃), 1.24 (18H, s, C(CH₃)₃), 1.12 (18H, s, C(CH₃)₃), 0.99–0.96 (2H, m, (CH₂)₄), 0.80–0.78 (2H, m, (CH₂)₄). ¹³C NMR (100 MHz, d₁₂-cyclohexane): δ 166.7, 166.0, 163.9, 160.1, 141.8, 141.5, 137.2, 136.3, 129.8, 129.1, 127.5, 126.7, 119.1, 119.1, 66.1, 62.5, 36.3, 35.9, 34.5, 34.3, 32.0, 30.3, 29.9, 29.0, 27.4, 27.0, 25.1, 24.3.

(C) General procedure for the conjugate addition of nitriles to enones.

(*S*)-2-Cyano-5-oxo-3-phenyl-hexanoic acid methyl ester (**2a**):

Methyl cyanoacetate (529 μL , 6.0 mmol, 1.2 equiv.) was added to a solution of 4-phenyl-3-buten-2-one (731 mg, 5.0 mmol) and (*R,R*)-**1a** (57.7 mg, 0.05 mmol, 1.0 mol%) in cyclohexane (25.0 mL). The solution was stirred at 23°C for 16 hours, then the solvent removed *in vacuo* and the residue purified by chromatography on silica (20% ethyl acetate in hexanes). Residual methyl cyanoacetate after chromatography was removed by gentle heating *in vacuo*. The product was obtained as a colorless oil in 91% yield (1.23 g) and 93% enantiomeric excess, as determined by chiral HPLC ((*S,S*)-Whelk-01, 14% ethanol/hexanes, 1.4 mL/min, 220 nm, $t_r(\text{min}) = 9.6$ min, $t_r(\text{maj}) = 11.2$ min). $\alpha_D^{25} = -29^\circ$ ($c = 1.45$, CHCl_3). FTIR (cm^{-1}): 3034 (m), 2957 (m), 2250 (w), 1754 (s), 1436 (s), 1219 (s), 1015 (s), 704 (s). ^1H NMR (500 MHz, CDCl_3 , 1.7:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 7.35-7.26 (10H, m, ArH, ArH*), 4.24 (1H, d, $J = 6.0$ Hz, CH*(CN)CO₂CH₃), 3.98-3.91 (2H, m, CHAr, CH*Ar), 3.83 (1H, d, $J = 5.0$ Hz, CH(CN)CO₂CH₃), 3.75 (3H, s, CO₂CH₃), 3.63 (3H, s, CO₂CH*₃), 3.22-3.17 (2H, m, CH₂COCH₃, CH₂*COCH₃), 3.01 (1H, dd, $J = 7.5, 18.0$ Hz, CH₂COCH₃), 2.99 (1H, $J = 5.0, 18.0$ Hz, CH*₂COCH₃), 2.20 (3H, s, CH₂COCH*₃), 2.15 (3H, s, CH₂COCH₃). ^{13}C NMR (100 MHz, CDCl_3): δ 206.1, 205.5, 165.8, 165.6, 139.3, 138.2, 129.3, 129.1, 128.5, 128.4, 128.1, 127.8, 115.7, 115.6, 53.8, 53.5, 46.4, 45.4, 44.1, 43.3, 40.6, 40.0, 30.6. MS (CI): 243.7 (100%) [M-H]⁻.

(*S*)-2-Cyano-5-oxo-3-thiophen-2-yl-hexanoic acid methyl ester (2b):

The reaction was performed on 5.0 mmol scale. Using 1.0 mol% (*R,R*)-**1a** and after a reaction time of 36 hours, the product was obtained as a orange oil in 93% yield (1.17 g) and 90% enantiomeric excess, as determined by chiral HPLC ((*S,S*)-Whelk-01 (Pirkle), 14% ethanol/hexanes, 1.4 mL/min, 220 nm, $t_r(\text{min}) = 10.0$ min, $t_r(\text{maj}) = 11.6$ min). $\alpha_D^{25} = -19^\circ$ ($c = 1.14$, CHCl_3). FTIR (cm^{-1}): 3109 (w), 3007 (w), 2957 (m), 2917 (w), 2252 (w), 1741 (s), 1435 (s), 1362 (s), 1260 (s), 1216 (s), 1168 (s), 916 (w), 851 (m), 784 (w), 712 (s). ^1H NMR (500 MHz, CDCl_3 , 2.2:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 7.23-7.217 (m, 2H, ArH, ArH*), 7.04-7.02 (m, 2H, ArH, ArH*), 6.98-6.95 (m, 2H, ArH, ArH*), 4.28-4.25 (m, 3H, ArCH, ArCH*, CH*(CN)CO₂CH₃), 3.94 (d, 1H, $J = 5.0$ Hz, CH(CN)CO₂CH₃), 3.78 (s, 3H, CO₂CH₃), 3.72 (s, 3H, CO₂CH*₃), 3.22-3.05 (m, 4H, CH₂COCH₃, CH*₂COCH₃), 2.22 (s, 3H, CH₂COCH*₃), 2.18 (s, 3H, CH₂COCH₃). ^{13}C NMR (100 MHz, CDCl_3): δ 205.6, 205.1, 165.5, 165.4, 141.8, 140.2, 127.4, 127.3, 126.3, 126.1, 125.3, 125.2, 115.4, 115.2, 53.9, 53.7, 47.3, 46.6, 44.4, 44.0, 36.2, 35.7, 30.6, 30.5. MS (CI): 249.7 (100%) [M-H]⁻.

2-Cyano-5-oxo-3-propyl-hexanoic acid methyl ester (2c):

The reaction was performed on 5.0 mmol scale. Using 1.0 mol% (*R,R*)-**1a**, after a reaction time of 17 hours, the product was obtained as a colorless oil in 86% yield (906 mg) and 89% enantiomeric excess, determined by demethoxycarboxylation to 5-oxo-3-propyl-hexanenitrile (0.50 mmol scale: NaCl (33 mol%), 5:1 DMSO:H₂O, 200°C, 5 minutes⁸) and analysis by chiral GC (γ -TA, 120°C isothermal, $t_r(\text{min}) = 9.1$ min, $t_r(\text{maj}) = 10.3$ min). $\alpha_D^{25} = -25^\circ$ ($c = 1.04$, CHCl_3). FTIR (cm^{-1}): 2960 (s), 2876 (m), 2250 (w), 1746 (s), 1713 (s), 1454 (m), 1370 (m), 1257 (s), 1171 (s), 1018 (m), 917 (w). ^1H NMR (500 MHz, CDCl_3 , 1.01:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 3.99 (1H, d, $J = 4.0$ Hz, CH(CN)CO₂Me), 3.82 (3H, s,

CO₂CH^{*}₃), 3.78 (3H, s, CO₂CH^{*}₃), 3.72 (1H, d, J = 3.5 Hz, CH^{*}(CN)CO₂Me), 2.74-2.54 (6H, m, COCH₂, COCH^{*}₂, CH(C₃H₇), CH^{*}(C₃H₇), 2.19 (3H, s, COCH^{*}₃), 2.16 (3H, s, COCH₃), 1.48-1.24 (8H, m, CH₂CH₂CH₃, CH^{*}₂CH^{*}₂CH₃), 0.94 (3H, dd, J = 7.5, 7.5 Hz, CH₂CH^{*}₃), 0.91 (3H, dd, J = 7.0, 7.0 Hz, CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 207.1, 206.4, 166.7, 166.4, 115.6, 115.6, 53.7, 53.6, 45.2, 44.8, 41.8, 41.3, 35.1, 34.6, 34.0, 33.6, 30.6, 30.6, 20.3, 20.1, 14.1, 14.0. MS (CI): 179.7 (100%) [M-(OCH₃)]⁺, 211.8 (60%) [M+H]⁺.

3-(2-Benzyloxy-ethyl)-2-cyano-5-oxo-hexanoic acid methyl ester (2d):

The reaction was performed on 1.0 mmol scale. Using 1.0 mol% (*R,R*)-**1a** and after a reaction time of 16 hours, the product was obtained as a colorless oil in 90% yield (272 mg) and 83% enantiomeric excess, as determined by chiral HPLC (OD, t_r(maj) = 10.4 min, t_r(min) = 11.5 min). α²⁵_D = +13° (c = 0.68, CHCl₃). FTIR (cm⁻¹): 3412 (w), 3032 (w), 2955 (m), 2870 (m), 2338 (w), 2251 (w), 1746 (s), 1715 (s), 1454 (s), 1362 (s), 1211 (s), 1169 (s), 1101 (s), 1017 (s), 748 (s). ¹H NMR (500 MHz, CDCl₃, 1.1:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 7.35-7.25 (10H, m, ArH, ArH^{*}), 4.48-4.45 (4H, m, OCH₂Ph, OCH^{*}₂Ph), 4.01-4.00 (2H, m, CH(CN)CO₂CH₃, CH^{*}(CN)CO₂CH₃), 3.75 (3H, s, CO₂CH^{*}₃), 3.73 (3H, s, CO₂CH₃), 3.58-3.47 (m, 4H, PhCH₂COCH₂, PhCH₂COCH^{*}₂) 2.90-2.85 (2H, m, CHCH₂CH₂OBn, CH^{*}CH₂CH₂OBn), 2.75 (1H, dd, J = 4.5 Hz, 18.5 Hz, CH^{*}₂COCH₃), 2.67 (1H, dd, J = 5.0 Hz, 18.5 Hz, CH₂COCH₃), 2.61 (1H, dd, J = 7.0, 18.5 Hz, CH₂COCH₃), 2.58 (1H, dd, J = 9.0, 18.5 Hz, CH^{*}₂COCH₃), 2.10 (6H, m, CH₂COCH₃, CH₂COCH^{*}₃), 1.82-1.65 (m, 4H, CH₂CH₂OBn, CH^{*}₂CH₂OBn). ¹³C NMR (100 MHz, CDCl₃): δ 206.9, 206.3, 166.6, 166.3, 138.3, 138.2, 128.7, 128.6, 128.0, 127.9, 127.9, 115.8, 115.7, 73.2, 73.0, 68.2, 67.6, 53.6, 53.6, 45.3, 45.0, 41.7, 33.3, 32.5, 32.4, 31.2, 30.5, 30.5. MS (CI): 303.7 (100%) [M+H]⁺.

2-Cyano-5-oxo-3-phenyl-nonanoic acid methyl ester (2e):

The reaction was performed on 1.0 mmol scale. Using 1.0 mol% (*R,R*)-**1a** and after a reaction time of 20 hours, the product was obtained as a colorless oil in 91% yield (251 mg) and 82% enantiomeric excess, as determined by chiral HPLC ((*S,S*)-Whelk-01 (Pirkle), 10% ethanol/hexanes, 1.2 mL/min, 208 nm, t_r(min) = 8.7 min, t_r(maj) = 9.6 min). α²⁵_D = -28° (c = 1.06, CHCl₃). FTIR (cm⁻¹): 3034 (m), 2958 (s), 2874 (s), 2250 (w), 1747 (s), 1713 (s), 1605 (w), 1455 (s), 1262 (s), 1208 (s), 1127 (m), 1029 (m), 915 (w), 757 (m), 702 (s). ¹H NMR (500 MHz, CDCl₃, 1.7:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 7.36-7.27 (10H, m, ArH, ArH^{*}), 4.24 (1H, d, J = 6.0 Hz, CH^{*}(CN)CO₂CH₃), 3.99-3.92 (1H, m CHPh, CH^{*}Ph), 3.82 (1H, d, J = 5.0 Hz, CH^{*}(CN)CO₂CH₃), 3.74 (3H, s, CO₂CH₃), 3.62 (3H, s, CO₂CH^{*}₃), 3.17 (2H, m, CH^{*}₂COCH₃, CH₂COCH₃), 3.05 (1H, dd, J = 7.0, 17.5 Hz, CH₂COCH₃), 2.96 (1H, dd, J = 5.5, 17.5 Hz, CH^{*}₂COCH₃), 2.49-2.32 (4H, m, CH₂COCH₂C₃H₇, CH₂COCH^{*}₂C₃H₇), 1.58-1.47 (4H, m, CH₂COCH₂CH₂CH₂CH₃, CH₂COCH₂CH₂CH^{*}₂CH₃), 1.32-1.20 (4H, m, CH₂COCH₂CH₂CH₂CH₃, CH₂COCH₂CH₂CH^{*}₂CH₃), 0.89 (3H, dd, J = 7.0, 7.0 Hz, CH₂COCH₂CH₂CH₂CH^{*}₃), 0.86 (3H, dd, J = 7.0, 7.0 Hz, CH₂COCH₂CH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 208.7, 207.9, 165.9, 165.6, 139.5, 138.3, 129.2, 129.1, 128.5, 128.4, 128.1, 127.7, 115.7,

115.6, 53.8, 53.5, 45.5, 44.7, 44.1, 43.3, 43.2, 43.2, 40.6, 40.0, 26.0, 25.8, 22.4, 22.4, 14.0. MS (CI): 285.8 (100%) [M-H]⁻.

2-Cyano-5-oxo-3,5-diphenyl-pentanoic acid methyl ester (2f):

The reaction was performed on 5.0 mmol scale. Using diethyl ether (25.0 mL) as solvent and 5.0 mol% (*R,R*)-**1a**, after a reaction time of 40 hours, the product was obtained as a viscous oil in 91% yield (1.37 g) and 87% enantiomeric excess, as determined by chiral HPLC ((*S,S*)-Whelk-01, 10% ethanol/hexanes, 1.2 mL/min, *t_r*(min) = 15.7 min, *t_r*(maj) = 17.0 min). $\alpha_D^{25} = +3.6^\circ$ (*c* = 0.96, CHCl₃). FTIR (cm⁻¹): 3063 (m), 3033 (m), 2955 (m), 2250 (w), 1754 (s), 1688 (s), 1597 (s), 1498 (m), 1449 (s), 1372 (s), 1264 (s), 1211 (s), 1002 (s), 912 (m), 754 (s), 702 (s). ¹H NMR (500 MHz, CDCl₃, 1.7:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 7.99-7.95 (4H, m, ArH, ArH*), 7.62-7.57 (2H, m, ArH, ArH*), 7.50-7.45 (4H, m, ArH, ArH*), 7.41-7.28 (10H, m, ArH, ArH*), 4.39 (1H, d, *J* = 5.0 Hz, CH*(CN)CO₂CH₃), 4.21-4.12 (2H, m, CHAr, CH*Ar), 3.93 (1H, d, *J* = 4.5 Hz, CH(CN)CO₂CH₃), 3.76-3.65 (m, 3H, CH₂COCH₃, CH*₂COCH₃), 3.75 (3H, s, CO₂CH₃), 3.68 (3H, s, CO₂CH*₃), 3.53 (1H, dd, *J* = 5.0, 18.0 Hz, CH*₂COCH₃). ¹³C NMR (100 MHz, CDCl₃): δ 197.4, 196.9, 165.9, 165.7, 139.5, 138.5, 136.6, 136.5, 134.0, 133.8, 129.3, 129.2, 129.0, 129.0, 128.5, 128.4, 128.3, 128.2, 127.8, 115.8, 115.7, 53.8, 53.5, 44.3, 43.5, 41.7, 40.9, 40.7, 40.3. MS (CI): 307.5 [M+H]⁺.

2-Cyano-6-methyl-5-oxo-3-phenyl-heptanoic acid methyl ester (2g):

The reaction was performed on 1.0 mmol scale. Using 5.0 mol% (*R,R*)-**1a** and after a reaction time of 20 hours, the product was obtained as a colorless oil in 85% yield (231 mg) and 75% enantiomeric excess, as determined by chiral HPLC ((*S,S*)-Whelk-01 (Pirkle), 14% ethanol/hexanes, 1.4 mL/min, 208 nm, *t_r*(min) = 6.1 min, *t_r*(maj) = 6.8 min). $\alpha_D^{25} = -22^\circ$ (*c* = 1.31, CHCl₃). FTIR (cm⁻¹): 3034 (m), 2971 (s), 2250 (w), 1746 (s), 1712 (s), 1604 (m), 1497 (m), 1435 (s), 1369 (m), 1261 (s), 1207 (s), 1095 (m), 1026 (s), 764 (m), 703 (s). ¹H NMR (500 MHz, CDCl₃, 1.6:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 7.34-7.25 (10H, m, ArH, ArH*), 4.23 (1H, d, *J* = 5.5 Hz, CH*(CN)CO₂CH₃), 3.98-3.90 (2H, m, CHAr, CH*Ar), 3.83 (1H, d, *J* = 5.0 Hz, CH(CN)CO₂CH₃), 3.72 (3H, s, CO₂CH₃), 3.60 (3H, s, CO₂CH*₃), 3.21-3.16 (2H, m, CH₂CO*i*-Pr, CH*₂CO*i*-Pr), 3.09 (1H, dd, *J* = 7.0, 17.5 Hz, CH₂OCH(CH₃)₂), 2.99 (1H, dd, *J* = 5.0, 17.5 Hz, CH₂OCH(CH₃)₂), 2.63-2.53 (2H, m, CH₂COCH(CH₃)₂, CH₂COCH*(CH₃)₂), 1.11 (3H, d, *J* = 6.5 Hz, CH₂COCH(CH₃)₂), 1.06 (3H, d, *J* = 7.0 Hz, CH₂COCH(CH₃)₂), 1.06 (3H, d, *J* = 7.0 Hz, CH₂COCH(CH₃*)₂), 1.00 (3H, d, *J* = 7.0 Hz, CH₂COCH(CH₃)₂). ¹³C NMR (100 MHz, CDCl₃): δ 212.3, 211.4, 165.9, 165.4, 139.6, 138.4, 131.3, 129.5, 129.2, 129.1, 128.5, 128.3, 128.1, 127.8, 115.8, 115.6, 53.7, 53.4, 44.0, 43.4, 43.2, 42.6, 41.4, 41.4, 40.6, 40.0, 18.4, 18.3, 18.2, 18.2. MS (CI) *m/z*: 271.8 (100%) [M-H]⁻.

2-(3-Oxo-1-propyl-butyl)-malononitrile (2h):

The reaction was performed on a 5.0 mmol scale. Using 0.25 mol% (*R,R*)-**1a** and after a reaction time of 24 hours, the product was obtained as a colorless oil in 76% yield (681 mg) and 94% enantiomeric excess, as determined by derivatization to the corresponding

1,3-dioxolane (see below for procedure) and analysis by chiral GC (γ -TA, 135°C isothermal, $t_r(\text{min}) = 11.4$ min, $t_r(\text{maj}) = 12.4$ min). $\alpha_D^{25} = +45^\circ$ ($c = 0.98$, CHCl_3). FTIR (cm^{-1}): 2964 (m), 2930 (m), 2865 (m), 2255 (w), 1716 (s), 1467 (m), 1420 (m), 1371 (m), 1170 (m), 974 (w). ^1H NMR (500 MHz, CDCl_3): δ 4.31 (1H, d, $J = 4.5$ Hz, $\text{CH}(\text{CN})_2$), 2.78 (1H, dd, $J = 4.5, 19.0$ Hz, CH_2COCH_3), 2.64 (1H, dd, $J = 7.5, 19.0$ Hz, CH_2COCH_3), 2.56-2.50 (m, 1H, CHC_3H_7), 2.20 (3H, s, CH_2COCH_3), 1.71-1.64 (m, 1H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.58-1.50 (m, 1H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.49-1.40 (m, 1H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.39-1.31 (m, 1H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.98 (3H, dd, $J = 7.5, 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3): δ 206.5, 112.6, 112.2, 43.7, 35.3, 33.5, 30.5, 27.0, 20.0, 13.9. MS (CI): 176.8 (95%) $[\text{M}-\text{H}]^-$.

Derivatization of **2h** for GC analysis:

2-(3-Oxo-1-propyl-butyl)-malononitrile (89 mg, 0.50 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 10 mol%) were dissolved in 2-ethyl-2-methyl-1,3-dioxolane (2.0 mL, excess). The mixture was heated to reflux for 18 hours, then loaded directly onto a silica gel column and purified by chromatography on silica, yielding the product as a colorless oil, which was analyzed by GC as described above.

2-Benzenesulfonyl-5-oxo-3-propyl-hexanenitrile (**2i**):

The reaction was performed using benzenesulfonylacetonitrile as the limiting reagent (906 mg, 5.0 mmol). Using 1.0 mol% (*R,R*)-**1a** and 1.2 equivalents of 3-hepten-2-one (795 μL , 6.0 mmol), after a reaction time of 23 hours, the product was obtained as a white solid in 91% yield (1.34 g) and 96% enantiomeric excess, as determined by chiral HPLC (Chiralpak AS, 15% isopropanol/hexanes, 1.2 mL/min, $t_r(\text{min}) = 13.8$ min, $t_r(\text{maj}) = 16.9$ min). mp = 119-121°C. $\alpha_D^{25} = +1^\circ$ ($c = 1.0$, CHCl_3). FTIR (cm^{-1}): 3058 (m), 2964 (m), 2877 (m), 2307 (w), 1719 (s), 1488 (m), 1334 (s), 1269 (s), 1160 (s), 1086 (m), 722 (m). ^1H NMR (500 MHz, CDCl_3 , 3.0:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 8.03-7.98 (4H, m, ArH^* , ArH), 7.79-7.74 (2H, m, ArH^* , ArH), 7.67-7.63 (4H, m, ArH^* , ArH), 4.50 (1H, d, $J = 4.0$ Hz, $\text{CH}(\text{CN})\text{SO}_2\text{Ph}$), 4.06 (1H, d, $J = 3.0$ Hz, $\text{CH}^*(\text{CN})\text{SO}_2\text{Ph}$), 3.14 (1H, dd, $J = 3.5, 18.0$ Hz, COCH_2^*), 3.02-2.98 (1H, m, $\text{CH}^*(\text{CH}_2\text{CH}_2\text{CH}_3)$), 2.92 (1H, dd, $J = 3.5, 19.0$ Hz, COCH_2), 2.86-2.82 (1H, m, $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)$), 2.63 (1H, dd, $J = 8.0, 18.0$ Hz, COCH_2^*), 2.58 (1H, dd, $J = 9.0, 19.0$ Hz, COCH_2), 2.19 (3H, s, COCH_3^*), 2.17 (3H, s, COCH_3), 1.99-1.93 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.60-1.51 (2H, m, $\text{CH}_2^*\text{CH}_2\text{CH}_3$), 1.49-1.42 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.34-1.26 (2H, m, $\text{CH}_2\text{CH}_2^*\text{CH}_3$), 0.96 (3H, dd, $J = 7.5, 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.89 (3H, dd, $J = 7.5, 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3^*$). ^{13}C NMR (100 MHz, CDCl_3): δ 207.2, 205.7, 137.7, 137.0, 125.5, 135.3, 130.0, 129.9, 129.5, 129.3, 113.3, 113.2, 60.0, 59.6, 45.1, 43.9, 35.5, 32.8, 32.5, 32.3, 30.6, 20.2, 20.1, 14.0, 13.7. MS (CI) m/z : 293.7 (100%) $[\text{M}^+]$.

Recrystallization of **2i** from diethyl ether yielded crystals suitable for X-ray crystallography, which permitted assignment of the absolute configuration as 3*S*.

2-Cyano-5-oxo-2-phenyl-3-propyl-hexanoic acid methyl ester (**2j**):

The reaction was performed on 5.0 mmol scale, in methylcyclohexane at 0°C. Using 2.5 mol% (*S,S*)-**1a** and 1.05 equivalents of methyl phenylcyanoacetate (919 mg, 5.25 mmol), after a reaction time of 24 hours, the product was obtained as a white solid in 87% yield (1.24 g), >30:1 d.r., as determined by ¹H NMR,⁹ and 89% enantiomeric excess, as determined by chiral HPLC (Chiralpak AD, 2% isopropanol/hexanes, 1.0 mL/min, *t_r*(min) = 9.5 min, *t_r*(maj) = 10.7 min). $\alpha_D^{25} = -53^\circ$ (*c* = 0.86, CHCl₃). mp = 42-43°C. FTIR (cm⁻¹): 2960 (m), 2875 (w) 2246 (w), 1746 (s), 1495 (w), 1450(m), 1364 (w) 1293 (w), 1239 (s), 1168 (m), 1025 (w), 932 (w), 734 (m). ¹H NMR (500 MHz, CDCl₃): δ 7.61-7.60 (2H, m, ArH), 7.44-7.37 (3H, m, ArH), 3.74 (3H, s, CO₂CH₃), 3.30-3.25 (1H, m, CH(C₃H₇)), 2.71 (1H, dd, *J* = 7.0, 17.5 Hz, CH₂COCH₃), 2.62 (1H, dd, *J* = 1.5, 17.5 Hz, CH₂COCH₃), 2.20 (3H, s, CH₂COCH₃) 1.20-1.12 (3H, m, CH₃CH₂CH₂), 1.03-0.96 (1H, m, CH₃CH₂CH₂), 0.71 (3H, dd, *J* = 7.0, 7.0 Hz, CH₃CH₂CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 205.6, 168.2, 133.4, 129.4, 129.3, 126.9, 117.6, 60.1, 54.1, 47.0, 40.0, 33.7, 30.4, 20.4, 14.2. MS (CI): 309.5 (80%) [M+Na]⁺, 228.0 (100%) [M-(CO₂CH₃)]⁺.

Recrystallization of **2j** from ethyl acetate/hexanes yielded crystals suitable for X-ray crystallography, permitting assignment of the relative configuration.

(D) Determination of absolute configuration of 2a by nitrile methanolysis.

Hydrogen chloride (10 mL, 1.0M in diethyl ether, 20 equiv.) was added to a solution of **2a** (123 mg, 0.50 mmol) in methanol (5.0 mL). The mixture was heated to 50°C in a sealed tube, and stirred for 3 days. An additional portion of hydrogen chloride (5 mL, 1.0M in diethyl ether) was added, and the mixture stirred at 50°C for 1 day. The resulting suspension was cooled to 23°C, and diluted with diethyl ether. The mixture was washed three times with saturated aqueous sodium bicarbonate, then once with brine. After drying (sodium sulfate), the solution was concentrated and the residue purified by chromatography on silica (20% → 33% ethyl acetate in hexanes), yielding the product as a colorless oil (106 mg, 76%). $\alpha_D = +12.5$ (*c* = 1.34, CHCl₃). Lit: -7.9° (*R* enantiomer, 73% *ee*, *c* = 1.00, CHCl₃).¹⁰ Characterization data were in agreement with those reported.¹⁰

(E) General procedure for conjugate additions of nitroalkanes catalyzed by 1a.

5-Nitro-4-phenyl-pentan-2-one (3a):

In a 10-mL Schlenk tube, 73 mg (500 μ mol, 1.00 eq) of 4-phenylbuten-2-one, 43.4 mg (375 μ mol, 7.50 mol%) (*R,R*)-**1a**, 100 mg (1.35 mmol, 2.70 eq) of *t*-butanol, 54 μ L (1.00 mmol, 2.00 eq) of nitromethane, and 0.50 mL of cyclohexane were stirred until a completely homogeneous reaction solution resulted. Then triethylamine (20 μ L, 145

μmol , 0.29 eq) was added by syringe, and the reaction stirred for 40 hours at 23°C. The reaction mixture was then diluted with ethyl acetate (1 mL) and purified by column chromatography on silica, eluting with hexanes/ethyl acetate, to yield 5-nitro-4-phenylpentan-2-one as a white crystalline solid in 90% yield (93 mg) and 95% enantiomeric excess, as determined by chiral HPLC (AS, 20% isopropanol/hexanes, 1.0 mL/min, 208 nm, $t_r(\text{min}) = 13.0$ min, $t_r(\text{maj}) = 16.4$ min), mp = 84°C. Characterization data were in agreement with those previously reported.¹¹

5-Nitro-4-(4-methoxyphenyl)-pentan-2-one (3b):

The reaction was performed on a 0.5 mmol scale. Using 7.5 mol% (*R,R*)-**1a** and after a reaction time of 72 hours, the product was obtained as a colorless oil in 80% yield (95 mg) and 93% enantiomeric excess, as determined by chiral HPLC (AS, 40% isopropanol/hexanes, 1.0 mL/min, 208 nm, $t_r(\text{min}) = 14.5$ min, $t_r(\text{maj}) = 26.5$ min). mp = 94 °C. $\alpha_D = +1.3$ ($c = 1.35$, CHCl_3). FTIR (cm^{-1}): 2960 (w), 2839 (w), 1715 (s), 1551 (s), 1514 (s), 1379 (m), 1252 (s), 1181 (m), 1032 (m). ^1H NMR (400 MHz, CDCl_3): δ 7.13 (2H, d, $J = 9.4$ Hz, ArH), 6.84 (2H, d, $J = 9.4$ Hz, ArH), 4.65 (1H, dd, $J = 12.1$ Hz, 7.0 Hz, CH_2NO_2), 4.55 (1H, dd, $J = 12.1$ Hz, 8.0 Hz, CH_2NO_2), 3.95 (1H, m, $\text{CHArCH}_2\text{NO}_2$), 3.77 (3H, s, OCH_3), 2.88 (2H, d, $J = 6.9$ Hz, CHArCH_2CO), 2.10 (3H, s, COCH_3). ^{13}C NMR (100 MHz, CDCl_3): 205.9, 159.3, 130.9, 128.7, 114.6, 79.9, 55.5, 46.5, 38.6, 30.7. HRMS (ESI) m/z : 255.1344 ($\text{M} + \text{NH}_4^+$), calcd for $\text{C}_{12}\text{H}_{19}\text{N}_2\text{O}_4^+$ 255.1345.

5-Nitro-4-(4-toluoyl)-pentan-2-one (3c):

The reaction was performed on a 0.25 mmol scale. Using 5 mol% (*R,R*)-**1a** and after a reaction time of 48 hours, the product was obtained as a white crystals in 70% yield (39 mg) and 93% enantiomeric excess, as determined by chiral HPLC (AS, 20% isopropanol/hexanes, 1.0 mL/min, 208 nm, $t_r(\text{min}) = 13.0$ min, $t_r(\text{maj}) = 16.2$ min). mp = 64 °C. $\alpha_D = +1.6$ ($c = 1.34$, CHCl_3). FTIR (cm^{-1}): 3025 (w), 2922 (w), 1719 (s), 1551 (s), 1516 (m), 1431 (m), 1379 (s), 1163 (m). ^1H NMR (400 MHz, CDCl_3): δ 7.14-7.08 (4H, m, ArH), 4.66 (1H, dd, $J = 12.4$ Hz, 7.0 Hz, CH_2NO_2), 4.56 (1H, dd, $J = 12.4$ Hz, 7.7 Hz, CH_2NO_2), 3.96 (1H, m, $\text{CHArCH}_2\text{NO}_2$), 2.89 (2H, d, $J = 7.0$ Hz, CHArCH_2CO), 2.31 (3H, s, ArCH₃), 2.11 (3H, s, COCH_3). ^{13}C NMR (100 MHz, CDCl_3): 205.8, 137.8, 136.0, 130.0, 127.5, 79.8, 46.4, 39.0, 30.6, 21.3. HRMS (ESI) m/z : 239.1402 ($\text{M} + \text{NH}_4^+$), calcd for $\text{C}_{12}\text{H}_{19}\text{N}_2\text{O}_3^+$ 239.1396.

5-Nitro-4-(4-bromophenyl)-pentan-2-one (3d):

The reaction was performed on a 0.5 mmol scale. Using 7.5 mol% (*R,R*)-**1a** and after a reaction time of 40 hours, the product was obtained as white crystals in 85% yield (122 mg) and 92% enantiomeric excess, as determined by chiral HPLC (AS, 30% isopropanol/hexane, 1.0 mL/min, 208 nm, $t_r(\text{min}) = 12.5$ min, $t_r(\text{maj}) = 16.4$ min). mp = 103 °C. $\alpha_D = +1.3$ ($c = 1.35$, CHCl_3). FTIR (cm^{-1}): 2918 (w), 1717 (s), 1551 (s), 1491 (m), 1377 (m), 1165 (m), 1076 (m), 1011 (m). ^1H NMR (400 MHz, CDCl_3): δ 7.44 (2H,

dd, $J = 6.6$ Hz, 1.8 Hz, ArH), 7.09 (2H, dd, $J = 6.6$ Hz, 1.8 Hz, ArH), 4.67 (1H, dd, $J = 12.4$ Hz, 6.8 Hz, CH_2NO_2), 4.56 (1H, dd, $J = 12.4$ Hz, 8.0 Hz, CH_2NO_2), 3.98 (1H, m, $\text{CHArCH}_2\text{NO}_2$), 2.88 (2H, d, $J = 7.0$ Hz, CHArCH_2CO), 2.11 (3H, s, COCH_3). ^{13}C NMR (100 MHz, CDCl_3): 205.3 , 138.1 , 132.4 , 129.4 , 122.1 , 79.3 , 46.1 , 38.7 , 30.6 . HRMS (ESI) m/z : 303.0338 ($M + \text{NH}_4^+$), calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{BrO}_3^+$ 303.0344 .

1-Nitro-2-phenyloctan-3-one (3e):

The reaction was performed on a 0.5 mmol scale. Using 7.5 mol% (*R,R*)-**1** and after a reaction time of 72 hours, the product was obtained as a white crystalline solid in 72% yield (90 mg) and 92% enantiomeric excess, as determined by chiral HPLC (AS, 20% isopropanol/hexane, 1.0 mL/min, 208 nm, $t_r(\text{min}) = 7.3$ min, $t_r(\text{maj}) = 9.2$ min). mp = 35°C . $\alpha_D = -4.8$ ($c = 1.02$, CHCl_3). FTIR (cm^{-1}): 3032 (w), 2959 (s), 2874 (m), 1713 (s), 1553 (s), 1379 (s), 700 (s). ^1H NMR (400 MHz, CDCl_3): δ 7.34 - 7.20 (5H, m, ArH), 4.69 (1H, dd, $J = 12.4$ Hz, 7.0 Hz, CH_2NO_2), 4.60 (1H, dd, $J = 12.4$ Hz, 7.6 Hz, CH_2NO_2), 4.02 (1H, m, $\text{CHArCH}_2\text{NO}_2$), 2.87 (2H, d, $J = 7.0$ Hz, CHArCH_2CO), 2.39 - 2.31 (2H, m, COCH_2CH_2), 1.52 - 1.45 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.28 - 1.20 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.852 (3H, t, $J = 7.3$ Hz, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3): 208.2 , 139.2 , 129.3 , 128.1 , 127.6 , 79.7 , 45.5 , 43.3 , 39.3 , 25.9 , 22.4 , 14.0 . HRMS (ESI) m/z : 250.1439 ($M + \text{H}^+$), calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_3^+$ 250.1443 .

2-Methyl-6-nitro-5-phenylhexan-3-one (3f):

The reaction was performed on a 0.5 mmol scale. Using 7.5 mol% (*R,R*)-**1a**, 50 mg (675 μmol , 1.35 equiv.) of *t*-butanol, 54 μL (1.00 mmol, 2.00 eq) of nitromethane, 0.40 mL of cyclohexane and after 72 hours at 40°C , the product was obtained as a colorless oil in 76% yield (89 mg) and 88% enantiomeric excess, as determined by chiral HPLC (AS, 20% isopropanol/hexane, 1.0 mL/min, 208 nm, $t_r(\text{min}) = 6.9$ min, $t_r(\text{maj}) = 8.8$ min). $\alpha_D = -12.6$ ($c = 2.85$, CHCl_3). FTIR (cm^{-1}): 3032 (w), 2972 (s), 2876 (w), 1711 (s), 1551 (s), 1379 (s), 764 (m), 702 (s). ^1H NMR (400 MHz, CDCl_3): δ 7.33 - 7.19 (5H, m, ArH), 4.70 (1H, dd, $J = 12.2$ Hz, 6.8 Hz, CH_2NO_2), 4.62 (1H, dd, $J = 12.2$ Hz, 7.8 Hz, CH_2NO_2), 4.02 (1H, m, $\text{CHArCH}_2\text{NO}_2$), 2.96 - 2.87 (2H, m, $\text{CHArCH}_2\text{NO}_2$), 2.54 - 2.49 (1H, m, $\text{CH}(\text{CH}_3)_2$), 2.39 - 2.31 (2H, m, COCH_2CH_2), 1.06 - 0.97 (6H, m, $\text{CH}(\text{CH}_3)_2$). ^{13}C NMR (100 MHz, CDCl_3): 211.7 , 139.3 , 129.2 , 128.1 , 127.6 , 79.7 , 43.3 , 41.4 , 39.3 , 18.1 . HRMS (ESI) m/z : 236.1290 ($M + \text{H}^+$), calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_3^+$ 236.1286 .

5-Nitro-4-phenylhexan-2-one (3g):

The reaction was performed on a 0.25 mmol scale. Using 10 mol% (*S,S*)-**1a**, 19 mg (256 μmol , 1.02 eq) of *t*-BuOH, 90 μL of nitroethane, 0.40 mL of hexane, 35 μL (0.25 mmol, 1.00 eq) of NEt_3 , and after a reaction time of 72 hours, the less polar diastereoisomer was obtained as a colorless oil in 47% yield (29 mg) and 92% enantiomeric excess, as determined by chiral GC (γ -TA, 145°C isothermal, $t_r(\text{maj}) = 13.8$ min, $t_r(\text{min}) = 14.8$ min), and the more polar diastereoisomer was obtained in 43% yield (23 mg) and 91%

enantiomeric excess, as determined by chiral GC (γ -TA, 145 °C isothermal, $t_r(\text{maj}) = 12.4$ min, $t_r(\text{min}) = 14.0$ min). Characterization data were in agreement with those previously reported.¹¹

5-Nitro-4-(4-bromophenyl)-hexan-2-one (3h):

The reaction was performed on a 0.5 mmol scale. Using 7.5 mol% (*R,R*)-**1a**, 100 mg (1.35 mmol, 2.70 eq) of *t*-butanol, 180 μ L of nitroethane, 0.80 mL of cyclohexane and after a reaction time of 72 hours, the products were obtained as colorless oils in 54 mg yield (36% yield) and 92% enantiomeric excess for the more polar diastereoisomer as determined by chiral HPLC (AS, 10% isopropanol/hexane, 1.0 mL/min, 208 nm, $t_r(\text{min}) = 14.3$ min, $t_r(\text{maj}) = 17.6$ min). $\alpha_D = -7.0$ ($c = 0.70$, CHCl_3). FTIR (cm^{-1}): 2994 (w), 1721 (s), 1549 (s), 1491 (m), 1360 (s), 1165 (m), 1076 (m), 1011 (m), 827 (m). ^1H NMR (400 MHz, CDCl_3): δ 7.42 (2H, d, $J = 8.4$ Hz, ArH), 7.02 (2H, d, $J = 8.4$ Hz, ArH), 4.84 (1H, dq, $J = 6.6$ Hz, 6.6 Hz, CHCH_3NO_2), 3.68 (1H, ddd, $J = 7.6$ Hz, 6.6 Hz, 6.6 Hz, $\text{CHArCHCH}_3\text{NO}_2$), 3.01 (1H, dd, $J = 17.9$ Hz, 6.6 Hz, CH_2CO), 2.85 (1H, dd, $J = 17.9$ Hz, 7.6 Hz, CH_2CO), 2.11 (3H, s, COCH_3), 1.50 (3H, d, $J = 6.6$ Hz, CHCH_3NO_2). ^{13}C NMR (100 MHz, CDCl_3): 205.6, 137.2, 132.1, 130.1, 122.2, 85.9, 44.9, 44.2, 30.8, 17.1. HRMS (ESI) m/z : 317.0511 ($\text{M} + \text{NH}_4^+$), calcd for $\text{C}_{12}\text{H}_{18}\text{BrN}_2\text{O}_3^+$ 317.0501. and 58 mg (39% yield) and 93% enantiomeric excess for the less polar diastereoisomer as determined by chiral HPLC (AS, 10% isopropanol/hexane, 1.0 mL/min, 208 nm, $t_r(\text{min}) = 14.8$ min, $t_r(\text{maj}) = 16.7$ min). $\alpha_D = -3.9$ ($c = 1.10$, CHCl_3). FTIR (cm^{-1}): 2996 (w), 1721 (s), 1549 (s), 1489 (m), 1360 (s), 1165 (m), 1074 (m), 1011 (m), 829 (m). ^1H NMR (400 MHz, CDCl_3): δ 7.46 (2H, d, $J = 8.3$ Hz, ArH), 7.08 (2H, d, $J = 8.3$ Hz, ArH), 4.73 (1H, dq, $J = 9.7$ Hz, 6.9 Hz, CHCH_3NO_2), 3.69 (1H, ddd, $J = 9.7$ Hz, 9.7 Hz, 3.9 Hz, $\text{CHArCHCH}_3\text{NO}_2$), 2.93 (1H, dd, $J = 17.6$ Hz, 9.7 Hz, CH_2CO), 2.73 (1H, dd, $J = 17.6$ Hz, 3.9 Hz, CH_2CO), 2.02 (3H, s, COCH_3), 1.32 (3H, d, $J = 6.9$ Hz, CHCH_3NO_2). ^{13}C NMR (100 MHz, CDCl_3): 204.9, 137.6, 132.4, 130.1, 122.1, 86.8, 46.2, 44.9, 30.6, 17.9. HRMS (ESI) m/z : 317.0505 ($\text{M} + \text{NH}_4^+$), calcd for $\text{C}_{12}\text{H}_{18}\text{BrN}_2\text{O}_3^+$ 317.0501.

(F) Demethoxycarbonylation of methyl cyanoacetate adducts. (*R*)-5-oxo-3-phenyl-hexanenitrile (4):

The conjugate addition of methyl cyanoacetate to 4-phenyl-3-buten-2-one was performed on 5.0 mmol scale (731 mg) using (*R,R*)-**1a** as described in the general experimental procedure. The solvent was removed *in vacuo* and the residue passed through a short silica plug (eluting with 33% ethyl acetate in hexanes) to remove catalyst. The solvent was removed *in vacuo*, and the resulting oil was dissolved in 5:1 dimethylsulfoxide/water (30 mL), and heated to 130°C for 40 hours. After cooling to 23°C, 20% aqueous lithium bromide solution (75 mL) was added, and the mixture extracted five times with

dichloromethane (total volume 250 mL). The combined organic extracts were washed twice with 20% lithium bromide solution (60 mL total), dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica (33% ethyl acetate in hexanes), yielding the product as a colorless oil in 85% yield from 4-phenyl-3-buten-2-one (792 mg), and 93% enantiomeric excess, as determined by chiral HPLC ((*S,S*)-Whelk-01 (Pirkle), 14% ethanol/hexanes, 1.4 mL/min, 208 nm, $t_r(\text{min}) = 8.8$ min, $t_r(\text{maj}) = 10.8$ min). $\alpha_D^{25} = +43^\circ$ ($c = 1.07$, CHCl_3). FTIR (cm^{-1}): 3032 (w), 2928 (w), 2245 (w), 1714 (s), 1497 (m), 1424 (m), 1360 (m), 1163 (m), 764 (m), 702 (m). ^1H NMR (500 MHz, CDCl_3): δ 7.35 (2H, t, $J = 7.0$ Hz, ArH), 7.30-7.26 (3H, m, ArH), 3.57-3.51 (1H, m, CHPh), 3.02 (1H, dd, $J = 8.5, 18.0$ Hz, CH_2CN), 2.93 (1H, dd, $J = 6.0, 18.0$ Hz, CH_2CN), 2.76 (1H, dd, $J = 6.5, 17.0$ Hz, COCH_2), 2.69 (1H, dd, $J = 5.5, 17.0$ Hz, COCH_2), 2.15 (3H, s, COCH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 206.1, 141.2, 129.3, 128.0, 127.3, 118.3, 47.7, 36.7, 30.7, 24.5. MS (CI) m/z : 146.8 (100%) [$\text{M}-(\text{CHOCH}_3)$] $^+$, 188.0 (20%) [$\text{M}+\text{H}$] $^+$.

(G) Preparation of 2,6-disubstituted piperidines by reductive amination.

(*R,R*)-2-Methyl-4-phenyl-piperidine hydrochloride (5):

Raney nickel (60 mg, 2800 mesh) was added to a solution of 5-oxo-3-phenylhexanenitrile (206 mg, 1.10 mmol) in 4:1 toluene/methanol (5.5 mL). The mixture was subjected to 650 PSI hydrogen pressure in a stainless steel autoclave, heated to 75°C , and stirred for 15 hours. The mixture was cooled to 23°C , vented, and filtered through Celite, eluting with methanol. The solution was concentrated, yielding 2-methyl-4-phenylpiperidine as a colorless oil (189 mg, >99% yield), which was immediately dissolved in toluene (5.5 mL). 37% Hydrochloric acid (135 μL , 1.65 mmol, 1.5 equiv.) was added dropwise by syringe while the mixture was stirred vigorously at 23°C . Stirring was continued for 30 minutes at 23°C , and the resulting suspension was then cooled to 4°C and allowed to stand for 4 hours. The mixture was filtered, and the solids washed with cold toluene, yielding the product as a white solid in 72% yield (178 mg) and 90% enantiomeric excess, as determined by derivatization to the trifluoroacetamide (see below for procedure) and analysis by chiral HPLC ((*S,S*)-Whelk-01 (Pirkle), 2.5% ethanol/hexanes, 1.0 mL/min, $t_r(\text{min}) = 7.3$ min, $t_r(\text{maj}) = 8.0$ min). mp = $206\text{--}211^\circ\text{C}$ (decomp.) $\alpha_D^{25} = +5.0^\circ$ ($c = 1.02$, CH_3OH). FTIR (of free amine, thin film) (cm^{-1}): 3266 (w), 3028 (m), 2928 (s), 2089 (m), 1603 (w), 1495 (m), 1452 (m), 1377 (m), 1321 (m), 1071 (m), 762 (w). ^1H NMR (500 MHz, CD_3OD): δ 7.36-7.33 (2H, m, ArH), 7.29 (2H, d, $J = 7.0$ Hz, ArH), 7.26-7.23 (1H, m, ArH), 3.54-3.49 (1H, m, CH_2NH), 3.41-3.36 (1H, m, $(\text{CH}_3)\text{CHNH}$), 3.19 (1H, td, $J = 3.5, 13.0$ Hz, CH_2NH), 2.96 (1H, tt, $J = 3.5, 12.5$ Hz, CHPh), 2.13-2.06 (2H, m, $\text{PhCHCH}_2\text{CH}(\text{CH}_3)$, $\text{CH}_2\text{CH}_2\text{NH}$), 1.94-1.85 (1H, m, $\text{CH}_2\text{CH}_2\text{NH}$), 1.70 (1H, ddd, $J = 1.5, 12.5, 26.0$ Hz, $\text{PhCHCH}_2\text{CH}(\text{CH}_3)$), 1.40 (3H, d, $J = 6.5$ Hz, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 144.1, 128.6, 126.8, 126.5, 53.1, 44.5, 40.3, 38.0, 29.5, 18.4. MS (CI) m/z : 175.8 (100%) [$\text{M}-\text{Cl}$] $^+$.

Recrystallization of **5** from hot isopropanol yielded crystals (as the isopropanol solvate) suitable for X-ray crystallography, demonstrating that the relative configuration is *cis*, as shown.

Derivatization of **5** for HPLC analysis:

(*R,R*)-2-Methyl-4-phenyl-piperidine hydrochloride (45 mg, 0.20 mmol) was dissolved in trifluoroacetic anhydride (1.0 mL, excess) and stirred at 23°C for 4 hours. Excess trifluoroacetic anhydride was removed *in vacuo*, and the residue was purified by passage through a short silica plug (20% ethyl acetate in hexanes), yielding the product as a colorless oil which solidified upon standing; the enantiomeric excess was determined by chiral HPLC, as described above.

(H) Preparation of 5-phenylcyclohex-2-enone (**6**) by nitrile reduction and aldol condensation.

Step 1. (*R*)-5,5-Dimethoxy-3-phenyl-hexanenitrile:

p-Toluenesulfonic acid (29 mg, 0.15 mmol, 3 mol%) was added to a solution of (*R*)-5-oxo-3-phenyl-hexanenitrile (936 mg, 5.0 mmol) in a mixture of methanol (5 mL) and trimethyl orthoformate (5 mL, excess). The solution was heated to 70°C and allowed to stir for 4 hours. The reaction mixture was then allowed to cool to 23°C and was diluted with diethyl ether (10 mL). The solution was washed twice with a mixture of brine and 1M aqueous sodium hydroxide (1:1 v/v, 10 mL total volume), dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (33% ethyl acetate in hexanes) to provide the title compound as a colorless oil (1.05 g, 4.5 mmol, 90% yield).

¹H NMR (400 MHz, CDCl₃): 7.36–7.25 (5H, m, ArH), 3.20 (3H, s, OCH₃), 3.10 (3H, s, OCH₃), 3.15–3.09 (1H, m, CHAr), 2.74 (1H, dd, *J* = 5.6, 16.8 Hz, CH₂CN), 2.64 (1H, dd, *J* = 7.6, 16.8 Hz, CH₂CN), 2.23 (1H, dd, *J* = 6.4, 14 Hz, CH₂C(OMe)₂), 2.00 (1H, dd, *J* = 6.8, 14 Hz, CH₂C(OMe)₂), 1.15 (3H, s, CH₃C(OMe)₂). ¹³C NMR (100 MHz, CDCl₃): 143.1, 129.2, 127.6, 127.5, 119.0, 101.3, 48.6, 48.3, 41.6, 38.4, 26.0, 21.8. FTIR (cm⁻¹): 2953 (s), 2832 (m), 2245 (w), 1454 (m), 1381 (m), 1229 (s), 1175 (s), 1132 (s), 1047 (s), 839 (m), 762 (m), 702. LRMS (CI): 187.6 (100%) [M-C₂H₆O]⁺, 201.4 (40%) [M-CH₃OH]⁺, 233.5 (5%) [M]⁺.

Steps 2–4. (*R*)-5-Phenyl-cyclohex-2-enone (**6**):

Diisobutylaluminum hydride (0.90 mL, 1.0 M in hexane, 0.90 mmol, 1.2 equiv.) was added dropwise by syringe to a solution of (*R*)-5,5-dimethoxy-3-phenyl-hexanenitrile (174 mg, 0.75 mmol) in diethyl ether (3.75 mL) at -78°C. The reaction mixture was

stirred at -78°C for 4 hours. Water (7.5 mL) was added and the reaction was allowed to warm to 23°C . Tartaric acid (7.5 mL, 1M aqueous solution) was added and the reaction was allowed to stir for 30 minutes until all of the aluminum salts were dissolved. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate and concentrated. The crude product was then purified by passing through a plug of silica gel, eluting with 50% ethyl acetate in hexanes. The resulting keto aldehyde was then dissolved in toluene (15 mL) and to this solution was added (*R*)-camphorsulfonic acid (30 mg, 0.15 mmol, 20 mol%). The reaction mixture was heated to 110°C for 36 hours and then allowed to cool to 23°C . It was then washed three times with saturated aqueous sodium bicarbonate (15 mL total volume), then brine (5 mL), dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (20% ethyl acetate in hexanes) to yield the title compound as a colorless oil that solidified upon standing (65 mg, 0.46 mmol, 61% yield). ^1H NMR (500 MHz, CDCl_3): 7.37–7.34 (2H, m, ArH), 7.28–7.25 (3H, m, ArH), 7.08–7.04 (1H, m, CHCH₂), 6.13 (1H, dd, $J = 3.0, 10$ Hz, CHCOCH₂), 3.39–3.33 (1H, m, CHAr), 2.74–2.51 (4H, m, CH₂CO, CH₂CH). ^{13}C NMR (100 MHz, CDCl_3): 199.4, 149.8, 143.4, 130.0, 129.0, 127.2, 126.9, 45.1, 41.2, 33.9. FTIR (cm^{-1}): 3030 (m), 2892 (m), 1678 (s), 1497 (m), 1454 (m), 1385 (m), 1250 (m), 1165 (w), 878 (w). $\alpha_{\text{D}} = -38.5^{\circ}$ ($c = 1.1$, CHCl_3). Lit = -37.9° (89% *ee*, $c = 1.97$, CHCl_3).¹²

(I) General procedure for the conjugate addition of hydrazoic acid to enones.

(*R*)-4-Azido-heptan-2-one (7a):

CAUTION! Hydrazoic acid is a highly toxic and potentially explosive compound, and should be handled with extreme care in a well-ventilated fume hood.

Hydrochloric acid (164 μL , 37% aqueous, 2.0 mmol, 2.0 equiv.) was added dropwise to a suspension of sodium azide (130 mg, 2.0 mmol, 2.0 equiv.) in methylcyclohexane (5.0 mL) at 0°C . The resulting mixture was stirred at 0°C for 10 minutes, then warmed to 23°C and stirred 1.5 hours. The resulting orange heterogeneous mixture was cooled to -78°C , and 3-hepten-2-one (132 mL, 1.0 mmol), then catalyst (*S,S*)-**1a** (28.8 mg, 0.025 mmol, 2.5 mol%) were added sequentially. The mixture was warmed to -40°C and stirred for 24 hours. After warming to 23°C , ether (15 mL) was added. The solution was washed twice with 1M aqueous sodium hydroxide (10 mL each), then passed through a short silica plug, eluting with 1:1 hexanes:ether. The solution was concentrated carefully *in vacuo*, yielding the product as a colorless oil, in 88% yield (136 mg) and 94% enantiomeric excess, as determined by chiral GC (γ -TA, 100°C isothermal, $t_{\text{r}}(\text{min}) = 9.7$ min, $t_{\text{r}}(\text{maj}) = 13.0$ min). The product was found to racemize slowly upon standing at 23°C : to minimize racemization, all hydrazoic acid adducts were stored at -78°C . $\alpha_{\text{D}}^{25} = -28^{\circ}$ ($c = 1.31$, CHCl_3). FTIR (cm^{-1}): 2961 (s), 2513 (w), 2102 (s), 1721 (s), 1366 (s), 1260 (s), 1168 (m), 744 (w). ^1H NMR (500 MHz, CDCl_3): δ 3.87–3.84 (1H, m, CHN₃), 2.67 (1H, dd, $J = 8.0, 17.0$ Hz, COCH₂), 2.54 (1H, dd, $J = 4.0, 17.0$ Hz, COCH₂), 2.19 (3H, s, COCH₃), 1.53–1.39 (4H, m, CH₂CH₂CH₃), 0.94 (3H, dd, $J = 7.5, 7.5$ Hz,

CH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 206.1, 58.1, 48.2, 36.8, 30.8, 19.4, 14.0. MS (CI) m/z: 127.9 (100%) [M–N₂+H]⁺.

(S)-4-Azido-5-methyl-hexan-2-one (7b): Using 2.5 mol% (*S,S*)–**1a**, after a reaction time of 24 hours, the product was obtained as a colorless oil in 81% yield (125 mg) and 94% enantiomeric excess, as determined by chiral GC (γ-TA, 100°C isothermal, t_r(min) = 9.6 min, t_r(maj) = 13.5 min). α²⁵_D = –41° (c = 1.02, CHCl₃). FTIR (cm^{–1}): 2967 (s), 2878 (s), 2521 (w), 2111 (s), 1720 (s), 1387 (s), 1266 (s), 1166 (m), 942 (m). ¹H NMR (500 MHz, CDCl₃): δ 3.78–3.74 (1H, m, CHN₃), 2.63 (1H, dd, J = 9.5, 17.0 Hz, COCH₂), 2.53 (1H, dd, J = 3.5, 17.0 Hz, COCH₂), 2.20 (3H, s, COCH₃), 1.81–1.78 (1H, m, CH(CH₃)₂), 0.97 (3H, t, J = 7.0 Hz, CH(CH₃)₂), 0.94 (3H, t, J = 6.5 Hz, CH(CH₃)₂). ¹³C NMR (100 MHz, CDCl₃): δ 206.4, 63.9, 45.6, 32.7, 30.9, 19.4, 18.1. MS (CI) m/z: 153.9 (80%) [M–H]⁺, 127.9 (40%) [M–N₂+H]⁺.

(R)-4-Azido-6-benzyloxy-hexan-2-one (7c): Using 2.5 mol% (*S,S*)–**1a**, after a reaction time of 30 hours, the product was obtained as a colorless oil in 96% yield (237 mg) and 85% enantiomeric excess, as determined by chiral HPLC (Chiralpak AD, 5% ethanol/hexanes, 1.0 mL/min, t_r(min) = 9.6 min, t_r(maj) = 10.4 min). α²⁵_D = +7° (c = 1.04, CHCl₃). FTIR (cm^{–1}): 3030 (w), 2865 (m), 2112 (s), 1719 (s), 1364 (m), 1267 (m), 1115 (m). ¹H NMR (500 MHz, CDCl₃): δ 7.37–7.30 (5H, m, ArH), 4.53–4.48 (2H, m, OCH₂Ph), 4.14–4.10 (1H, m, CHN₃), 3.62–3.56 (2H, m, OCH₂Bn), 2.67 (1H, dd, J = 8.0, 17.5 Hz, COCH₂), 2.60 (1H, dd, J = 4.5, 17.5 Hz, COCH₂), 2.16 (3H, s, COCH₃), 1.87–1.81 (1H, m, CH₂CH₂OBn), 1.78–1.72 (1H, m, CH₂CH₂OBn). ¹³C NMR (100 MHz, CDCl₃): δ 205.9, 138.3, 128.7, 128.0, 128.0, 73.4, 66.6, 55.8, 48.3, 34.7, 30.7. MS (CI) m/z: 219.7 (100%) [M–N₂+H]⁺.

(S)-5-Azido-4,4-dimethyl-7-oxo-octanenitrile (7d): The reaction was performed at –30°C. Using 2.5 mol% (*S,S*)–**1a**, after a reaction time of 40 hours, the product was obtained as a colorless oil in 72% yield (150 mg) and 84% enantiomeric excess, as determined by chiral GC (γ-TA, 140°C isothermal, t_r(min) = 29.1 min, t_r(maj) = 30.1 min). α²⁵_D = –52° (c = 1.03, CHCl₃). FTIR (cm^{–1}): 2971 (m), 2880 (m), 2521 (w), 2247 (m), 2112 (s), 1721 (s), 1473 (m), 1371 (m), 1271 (m), 1165 (m), 1045 (m), 923 (w). ¹H NMR (500 MHz, CDCl₃): δ 3.74 (1H, dd, J = 4.0, 8.5 Hz, CHN₃), 2.67–2.59 (2H, m, COCH₂), 2.41–2.28 (2H, m, CH₂CH₂CN), 2.24 (3H, s, COCH₃), 1.81–1.75 (1H, m, CH₂CH₂CN), 1.65–1.59 (1H, m, CH₂CH₂CN), 0.95 (3H, s, C(CH₃)₂), 0.93 (3H, s, C(CH₃)₂). ¹³C NMR (100 MHz, CDCl₃): δ 205.8, 120.1, 65.9, 43.6, 37.5, 34.5, 30.8, 23.5, 23.4, 12.6. MS (CI) m/z: 208.8 (100%) [M+H]⁺.

(R)-7-Azido-decan-5-one (7e): Using 5.0 mol% (*S,S*)–**1a**, after a reaction time of 24 hours, the product was obtained as a colorless oil in 88% yield (173 mg) and 89% enantiomeric excess, as determined by chiral HPLC of the Huisgen cycloadduct with dimethyl acetylenedicarboxylate (prepared on 0.20 mmol scale according to general procedure K) ((*S,S*)-Whelk-01, 7% isopropanol/hexanes, 1.2 mL/min, t_r(min) = 43.4 min, t_r(maj) = 46.3 min). α²⁵_D = –14° (c = 1.25, CHCl₃). FTIR (cm^{–1}): 2961 (s), 2874 (m), 2116 (s), 1715 (s), 1466 (w), 1379 (w), 1260 (m), 758 (m). ¹H NMR (600 MHz, CDCl₃):

3.86-3.83 (1H, m, CHN₃), 2.62 (1H, dd, J = 7.8, 16.8 Hz, COCH₂), 2.48 (1H, dd, J = 4.8, 16.8 Hz, COCH₂), 2.40 (2H, t, J = 7.2 Hz, COCH₂CH₂), 1.55 (2H, tt, J = 7.2, 7.2 Hz, COCH₂CH₂), 1.49-1.36 (4H, m, CH₂CH₂CH₃), 1.29 (2H, qt, J = 7.8, 7.8 Hz, COCH₂CH₂CH₂CH₃), 0.92 (3H, dd, J = 6.6, 6.6 Hz, CH₂CH₂CH₃), 0.88 (3H, t, J = 7.8 Hz, COCH₂CH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 208.5, 58.2, 47.3, 43.5, 36.8, 25.9, 22.5, 19.4, 14.0, 13.9. MS (CI) m/z: 170.0 (100%) [M-N₂+H]⁺.

(R)-3-Azido-1-phenyl-hexan-1-one (7f): Using 2.5 mol% (*S,S*)-**1a**, after a reaction time of 24 hours, the product was obtained as a colorless oil in 93% yield (201 mg) and 77% enantiomeric excess, as determined by chiral HPLC ((*S,S*)-Whelk-01, 0.5% ethanol/hexanes, 1.0 mL/min, 220 nm, t_r(min) = 7.1 min, t_r(maj) = 8.4 min). α_D²⁵ = +15° (c = 1.08, CHCl₃). FTIR (cm⁻¹): 3027 (m), 2960 (s), 2874 (m), 2101 (s), 1688 (s), 1598 (m), 1460 (m), 1212 (m), 980 (m). ¹H NMR (500 MHz, CDCl₃): δ 7.96 (2H, d, J = 7.0 Hz, ArH), 7.59 (1H, t, J = 7.0 Hz, ArH), 7.48 (2H, t, J = 8.5 Hz, ArH), 4.10-4.07 (1H, m, CHN₃), 3.26 (1H, dd, J = 8.0, 17.5 Hz, COCH₂), 3.05 (1H, dd, J = 4.5, 17.5 Hz, COCH₂), 2.20 (3H, s, COCH₃), 1.63-1.45 (4H, m, CH₂CH₂CH₃), 0.97 (3H, t, J = 7.5 Hz, CH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 197.6, 136.9, 133.7, 128.9, 128.3, 58.6, 43.5, 37.1, 19.6, 14.0. MS (CI) m/z: 189.8 (100%) [M-N₂+H]⁺.

(R)-5-Azido-2-methyl-octan-3-one (7g): Using 5.0 mol% (*S,S*)-**1a**, after a reaction time of 24 hours, the product was obtained as a colorless oil in 97% yield (178 mg) and 61% enantiomeric excess, as determined by chiral HPLC of the Huisgen cycloadduct with dimethyl acetylenedicarboxylate (prepared on 0.20 mmol scale according to general procedure K) ((*S,S*)-Whelk-01, 10% ethanol/hexanes, 1.2 mL/min, 220 nm, t_r(min) = 13.1 min, t_r(maj) = 14.2 min). α_D²⁵ = -10° (c = 1.14, CHCl₃). FTIR (cm⁻¹): 2967 (s), 2876 (m), 2118 (s), 1713 (s), 1466 (m), 1273 (m), 914 (w), 735 (m). ¹H NMR (500 MHz, CDCl₃): δ 3.89-3.86 (1H, m, CHN₃), 2.70 (1H, dd, J = 8.5, 17.0 Hz, COCH₂), 2.58 (1H, qq, J = 7.0, 7.0 Hz, CH(CH₃)₂), 2.52 (1H, dd, J = 5.0, 17.0 Hz, COCH₂), 1.51-1.38 (4H, m, CH₂CH₂CH₃), 1.11 (3H, d, J = 7.0 Hz, CH(CH₃)₂), 1.10 (3H, d, J = 7.0 Hz, CH(CH₃)₂), 0.93 (3H, dd, J = 6.5, 6.5 Hz, CH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 212.1, 58.3, 45.1, 41.6, 36.9, 19.5, 18.2, 18.2, 14.0. MS (CI) m/z: 155.7 (100%) [M-N₂+H]⁺.

(J) Reduction and in situ protection of enantiomerically enriched azide.

(S)-(3-Oxo-1-propyl-butyl)-carbamic acid *tert*-butyl ester (**8**):

The general procedure for the conjugate addition of hydrazoic acid to 3-hepten-2-one catalyzed by (*R,R*)-**1a** was followed as described above, using ethyl acetate (15 mL) as the workup solvent instead of diethyl ether. After washing twice with 1M aqueous sodium hydroxide, the solution was passed through a short silica plug, eluting with ethyl acetate (10 mL). Di-*tert*-butyl dicarbonate (Boc₂O, 546 mg, 2.5 mmol, 2.5 equiv.) was added to the resulting solution.

10% Pd/C (15 mg) was suspended in ethyl acetate (1.0 mL) and stirred under 1 atm. H₂ for 30 minutes. The solution of azide and Boc₂O was added by syringe (flask rinsed with 1 mL ethyl acetate), and the resulting suspension stirred at 23°C for 15 hours. After filtering through Celite and washing with ethyl acetate, the filtrate was concentrated *in vacuo*, and the residue purified by chromatography on silica (25% ethyl acetate in hexanes). The product was obtained as a white solid in 79% yield (181 mg) and 94% enantiomeric excess, as determined by derivatization to 2,2,2-trifluoro-*N*-(3-oxo-1-propyl-butyl)-acetamide (CF₃CO₂H, CH₂Cl₂, 0°C; (CF₃CO)₂O, neat, 0°C, see below for details), and analysis by chiral GC (γ -TA, 90°C isothermal, *t_r*(min) = 38.2 min, *t_r*(maj) = 40.4 min). mp = 46-48°C. α_D^{25} -32° (c = 1.06, CHCl₃). FTIR (thin film from CH₂Cl₂, cm⁻¹): 3435 (w), 3055 (w), 2965 (m), 1711 (s), 1503 (s), 1368 (m), 1269 (m), 1169 (s), 721 (m). ¹H NMR (600 MHz, CDCl₃): δ 4.84 (1H, br d, *J* = 7.8 Hz, NHBoc), 3.90-3.89 (1H, m, CHNHBoc), 2.63-2.62 (2H, m, COCH₂), 2.15 (3H, s, COCH₃), 1.50-1.30 (4H, m, CH₂CH₂CH₃), 1.42 (9H, s, C(CH₃)₃), 0.91 (3H, t, *J* = 7.2 Hz, CH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 208.2, 155.7, 79.4, 48.4, 47.5, 37.1, 30.7, 28.6, 19.7, 14.0. MS (CI) *m/z*: 251.8 (100%) [M+Na]⁺.

Derivatization of **8** for GC analysis:

Trifluoroacetic acid (250 μ L, excess) was added to a solution of **8** (46 mg, 0.20 mmol) in dichloromethane (1.0 mL) at 0°C. The solution was stirred at 0°C for 45 minutes, then concentrated *in vacuo* at 0°C, and the residue dissolved in trifluoroacetic anhydride (1.0 mL, excess). After stirring at 0°C for 3 hours, the solution was concentrated *in vacuo*. The residue, a white solid, was analyzed by GC as described above.

(K) Thermal [3+2] cycloaddition of enantiomerically enriched azide.

(*R*)-1-(3-Oxo-1-propyl-butyl)-1*H*-[1,2,3]triazole-4,5-dicarboxylic acid dimethyl ester (**9a**):

4-Azido-heptan-2-one was prepared as described above on 1.0 mmol scale, then dissolved in toluene (10 mL). Dimethyl acetylenedicarboxylate (369 μ L, 3.0 mmol, 3.0 equiv.) was added by syringe, and the solution heated to 110°C for 2 hours. The resulting mixture was cooled to 23°C, loaded directly onto a column and purified by chromatography on silica (50% ethyl acetate/hexanes). The product was obtained as a colorless oil in 77% yield over two steps (229 mg) and 94% enantiomeric excess, as determined by chiral HPLC ((*S,S*)-Whelk-01, 10% ethanol/hexanes, 1.2 mL/min, 220 nm, *t_r*(min) = 24.0 min, *t_r*(maj) = 25.9 min). α_D^{25} = +89° (c = 1.07, CHCl₃). FTIR (cm⁻¹): 2959 (m), 2876 (w), 1738 (s), 1555 (w), 1460 (m), 1287 (m), 1179 (m), 1065 (w), 829 (w). ¹H

NMR (600 MHz, CDCl₃): δ 5.34-5.29 (1H, m, CHN), 4.02 (3H, s, CO₂CH₃), 3.93 (3H, s, CO₂CH₃), 3.43 (1H, dd, J = 9.5, 19.0 Hz, COCH₂), 2.96 (1H, dd, J = 4.0, 19.0 Hz, COCH₂), 2.13-2.05 (1H, m, CH₂CH₂CH₃), 2.06 (3H, s, COCH₃), 1.85-1.78 (1H, m, CH₂CH₂CH₃) 1.31-1.22 (1H, m, CH₂CH₂CH₃), 1.13-1.08 (1H, m, CH₂CH₂CH₃), 0.88 (3H, t, J = 7.5 Hz, CH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 205.1, 160.8, 159.7, 139.0, 132.1, 56.5, 53.7, 52.8, 48.2, 37.3, 30.2, 19.0, 13.7. MS (CI) m/z: 185.7 (100%) [M-(C₇H₁₂O)]⁺, 297.6 (30%) [M+H]⁺.

(L) Copper-catalyzed [3+2] cycloaddition of enantiomerically enriched azide.

(R)-4-(4-Phenyl-[1,2,3]triazol-1-yl)-heptan-2-one (9b):

To a solution of (R)-4-azido-heptan-2-one (78 mg, 0.50 mmol) in 1:1 ethanol/water (2.0 mL) in a 2-dram vial were sequentially added phenylacetylene (110 μ L, 1.0 mmol, 2.0 equiv.), sodium ascorbate (50 μ L, 1.0M aqueous solution, 10 mol%), and copper(I) sulfate pentahydrate (17 μ L, 0.3M aqueous solution 1.0 mol%). The resulting solution was stirred at 23°C for 36 hours, then water (15 mL) was added. The mixture was extracted three times with dichloromethane (40 mL total volume), and the combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. The product was obtained as a white solid in 89% yield (114 mg) and 93% enantiomeric excess, as determined by chiral HPLC ((S,S)-Whelk-01, 14% ethanol/hexanes, 1.4. mL/min, 254 nm, t_r (min) = 14.5 min, t_r (maj) = 28.8 min). mp = 101-103°C. $\alpha_D^{25} = +5^\circ$ (c = 1.04, CHCl₃). FTIR (cm⁻¹): 3146 (w), 3055 (m), 2965 (m), 2876 (m), 1721 (s), 1460 (m), 1366 (m), 1269 (m), 1167 (m), 1078 (m), 766 (s). ¹H NMR (500 MHz, CDCl₃): δ 7.83 (2H, dd, J = 1.5, 7.5 Hz, ArH), 7.80 (1H, s, ArH), 7.42 (2H, dt, J = 1.5, 6.5 Hz, ArH), 7.32 (1H, dt, J = 1.5, 7.5 Hz, ArH), 4.98-4.92 (1H, m, CHN), 3.45 (1H, dd, J = 8.5, 17.5 Hz, COCH₂), 2.96 (1H, dd, J = 5.0, 17.5 Hz, COCH₂), 2.14-2.04 (1H, m, CH₂CH₂CH₃), 2.13 (3H, s, COCH₃), 1.87-1.79 (1H, m, CH₂CH₂CH₃) 1.28-1.16 (2H, m, CH₂CH₂CH₃), 0.91 (3H, t, J = 7.5 Hz, CH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 205.5, 147.1, 130.9, 129.0, 128.3, 125.9, 120.8, 57.1, 48.5, 37.4, 30.7, 19.4, 13.7. MS (CI) m/z: 257.7 (100%) [M+H]⁺.

(M) Intramolecular [3+2] cycloaddition of enantiomerically enriched azide.

(S)-1-(6,6-Dimethyl-5,6,7,8-tetrahydro-tetrazolo[1,5-a]pyridin-5-yl)-propan-2-one (10):

A solution of (S)-5-azido-4,4-dimethyl-7-oxooctanenitrile (**7d**) (103 mg, 0.50 mmol) in toluene (5 mL) was heated to 130°C and stirred for 7 days. The resulting solution was

cooled to 23°C, concentrated *in vacuo*, and the residue purified by column chromatography on silica (33% hexanes in ethyl acetate) to yield the product as a white solid in 73% yield (75 mg) and 83% enantiomeric excess, as determined by chiral HPLC ((S,S)-Whelk-01, 14% ethanol/hexanes, 1.4 mL/min, 208 nm, $t_r(\text{min}) = 45.1$ min, $t_r(\text{maj}) = 48.6$ min). mp = 125–129°C. $\alpha_D = -5^\circ$ ($c=0.975$, CHCl_3). FTIR (thin film in CH_2Cl_2 , cm^{-1}): 3059 (w), 2971 (m), 1723 (s), 1526 (m), 1425 (m), 1356 (m), 1275 (m), 1169 (m), 733 (m). ^1H NMR (500 MHz, CDCl_3): δ 4.74 (1H, dd, $J = 8.5, 2.5$ Hz, CHN), 3.16 (1H, dt, $J = 18.0, 4.0$ Hz, ArCH_2CH_2), 3.03 (1H, dd, $J = 17.0, 8.5$ Hz, COCH_2), 2.97 (1H, dt, $J = 18.0, 9.0$ Hz, ArCH_2CH_2), 2.74 (1H, dd, $J = 17.0, 2.5$ Hz, COCH_2), 2.40 (3H, s, COCH_3), 1.92–1.89 (1H, m, ArCH_2CH_2), 1.16 (1H, s, $\text{C}(\text{CH}_3)_2$), 0.86 (1H, s, $\text{C}(\text{CH}_3)_2$). ^{13}C NMR (100 MHz, CDCl_3): δ 204.9, 151.3, 61.4, 42.7, 34.2, 33.8, 31.0, 26.6, 19.7, 17.8. MS (CI) m/z : 208.7 (100%) $[\text{M}+\text{H}]^+$, 206.7 (100%) $[\text{M}-\text{H}]^-$.

-
- (1) Tietze, L. F.; Henrich, M.; Niklaus, A.; Buback, M. *Chem. Eur. J.* **1999**, *5*, 297–304.
 - (2) Haynes, R. K.; Jackson, W. R.; Stragalinou, A. *Aust. J. Chem.* **1980**, *33*, 1537–1544.
 - (3) Brophy, P. M.; Campbell, A. M.; van Eldik, A. J.; Teesdale-Spittle, P. H.; Liebau, E.; Wang, M.F. *Bioorg. Med. Chem. Lett.* **2000**, *9*, 979–982.
 - (4) Shabat, D.; List, B.; Lerner, R. A.; Barbas III, C. F. *Tetrahedron Lett.* **1999**, *8*, 1437–1440.
 - (5) a) 1-Phenyl-1-hepten-3-one: Kim, S.; Lee, J. I. *J. Org. Chem.* **1983**, *15*, 2608–2610.
 b) 2-Methyl-4-octen-3-one: Bonadies, F.; Scarpatti, M. L.; Savagnone, F. *Gazz. Chim. Ital.* **1982**, *112*, 1.
 c) 1-Phenyl-2-hexen-1-one: See Ref. 2.
 d) 4-Methyl-1-phenyl-1-penten-3-one: K. Takahashi, A. Honma, K. Ogura, H. Iida, *Chem. Lett.* **1982**, 1263–1266.
 e) 6-Benzyloxy-hex-3-en-2-one: Hon, Y.-S.; Lu, L.; Chang, R.-C.; Lin, S.-W.; Sun, P.-P.; Lee, C.-F.; *Tetrahedron* **2000**, *56*, 9269–9280.
 f) 4-(4-Tolyl)-3-buten-2-one: Cacchi, S.; Palmieri, G. *Synthesis* **1984**, 575–577.
 g) 4-(4-Methoxyphenyl)-3-buten-2-one: See Ref. 5f.
 - (6) Brown, R. F.; Schmid, G. H. *J. Org. Chem.* **1962**, *27*, 1288–1294.
 - (7) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *124*, 11204–11205.
 - (8) The decarboxylation reaction was performed using a microwave reactor generously provided by Personal Chemistry, Inc.
 - (9) The diastereoselectivity of the reaction is 12:1; complete separation of diastereomers is effected by column chromatography on silica (10% → 20% ethyl acetate in hexanes).
 - (10) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 661–665.
 - (11) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331–8338.
 - (12) Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2001**, *40*, 927–930.
 - (13) Rostovtsev, V. V. Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599.