Enantioselective Nitroaldol Reaction of $\alpha$-Ketoesters Catalyzed by Cinchona Alkaloids

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Supporting Information

General Information. $^1$H and $^{13}$C NMR spectra were recorded on a Varian instrument (400 MHz and 100 MHz, respectively) and internally referenced to tetramethylsilane signal or residual protio solvent signals. Data for $^1$H NMR are recorded as follows: chemical shift ($\delta$, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration, coupling constant (Hz). Data for $^{13}$C NMR are reported in terms of chemical shift ($\delta$, ppm). Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrometer and are reported in frequency of absorption. Low resolution mass spectra for all the new compounds were performed by 70SE CI+, and were recorded and exact mass spectra on a 70-VSE-B high resolution mass spectrometer. Specific rotations were measured on a Jasco Digital Polarimeter.

High performance liquid chromatography (HPLC) analysis was performed on a Hewlett-Packard 1100 Series instrument equipped with a quaternary pump, using a Daicel Chiralcel OJ, OD Column (250 x 4.6 mm) or Chiralpak AD, AS Column (250 x 4.6 mm). UV absorption was monitored at 220 nm or at 280 nm.
Materials: (For structure of \( \alpha \)-ketoesters 2, see Table1, for structure of cinchona alkaloid catalysts, see Figure 1) \( \alpha \)-ketoesters 2a, 2b were prepared according to literature procedures.\(^1\) Other \( \alpha \)-ketoesters 2 were commercially available and purified by flash chromatography (silica gel 60, 0.040-0.063 mm, purchased from EM SCIENCE Inc.) before they were used for the nitroalcohol reaction. Catalysts QD, DHQD-PHN, (DHQD)\(_2\)AQN were purchased from Aldrich company and used without any further purification. C6'-OH catalysts Q-1a-c and QD-1a-c were prepared following procedures reported from these laboratories, \(^2\) and \( \beta \)-ICD was prepared according to literature procedures.\(^3\) Petroleum ether (36-60 °C) for chromatography was purchased from Fisher Company.

Preparation of catalyst Q-1d:

6'-OTIPS Quinine derivative Q-2:
A suspension of quinine (3.6 g, 11.46 mmol), NaSEt (90% purity, 5g, 5eq.) in anhydrous DMF (60 mL) was heated at 105 °C (oil bath temperature) under N₂ for 16 hours. The mixture was cooled to room temperature then poured into sat. NH₄Cl aq. (100 mL) and pH of the aqueous phase was around 7. The mixture was extracted with ethyl acetate (2 x 200 mL). The combined organic phase was washed with aqueous HCl (2N, 4 x 25 mL) and the combined aqueous phase was treated with ammonium hydroxide (20 mL) and the pH of the aqueous phase is 10-11. The mixture was exacted with ethyl acetate (2 x 250 mL), and the combined organic phase was washed with brine, dried over anhydrous Na₂SO₄. The solvent was removed in vacuo and the residue was dissolved in anhydrous DMF (50 mL). At room temperature, TIPSCl (4.6 mL, 2 eq.) was added to the solution, followed by addition of imidazole (1.5 g, 2 eq.). The resulting solution was stirred at room temperature for 4h, when TLC analysis indicated that the starting material was completely consumed. The reaction mixture was diluted with ethyl acetate (400 mL) and washed with sat. NaHCO₃ aq. (2 x 50 mL), brine and dried over anhydrous Na₂SO₄. The solvent was removed in vacuo and the crude product was purified by flash chromatography (ethyl acetate to ethyl acetate/MeOH/NH₄OH = 20/2/0.5) to give Q-2 (4.7g, 90% yield over 2 steps). [α]D²⁵ = -77.2 (c 0.43, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.71 (d, J = 4.0 Hz, 1H), 7.99 (d, J = 6.8 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.46 (s, 1H), 7.33 (dd, J = 2.4 Hz, 9.2 Hz, 1H), 5.81-5.72 (m, 1H), 5.43 (d, J = 4.8 Hz, 1H), 4.99-4.91 (m, 2H), 3.36-3.32 (m, 1H), 3.22-3.27 (m, 1H), 3.07 (dd, J = 10.0 Hz, 1H), 2.68-2.63 (m, 2H), 2.25 (br, 1H), 1.81-1.80 (m, 1H), 1.70-1.64 (m, 4H), 1.48 (br, 1H), 1.37-1.26 (m, 3H), 1.13 (d, J = 7.6 Hz, 18H); ¹³C NMR (100 MHz, DMSO-d6) δ 154.2, 147.65, 147.59, 144.1, 141.9, 131.4, 126.7, 124.9, 118.6, 114.2, 109.9, 72.6, 59.9, 57.0, 43.1, 40.0, 27.8, 27.7, 22.4, 17.9, 12.7; IR (CHCl₃) ν 3400-2400(br), 2943, 2866, 1616, 1506, 1457, 1258; HRMS (CI) m/z calcd. for (C₂₈H₄₂N₂O₂Si + H⁺): 467.3094, found: 467.3106.

Catalyst Q-Id:
At room temperature to a solution of Q-2 (3.3 g, 7 mmol) in anhydrous CH$_2$Cl$_2$ (40 mL) was added PhCOCl (0.91 mL, 1.1 eq.) and Et$_3$N (1.97 mL, 2 eq.). The resulting mixture was stirred at room temperature for 3 hours and TLC analysis indicated that the starting material was completely consumed. The reaction mixture was diluted with CH$_2$Cl$_2$ (250 mL) and washed with sat. NaHCO$_3$, brine and dried over anhydrous Na$_2$SO$_4$. The solvent was removed in vacuo and the residue was dissolved in CH$_3$CN (50 mL). To the resulting solution, HF (48% aqueous solution, 2.5 mL) was added dropwise through syringe. After 15 minutes, TLC analysis showed that the starting material was completely consumed and the reaction mixture was diluted with ethyl acetate (400 mL), washed with sat. NaHCO$_3$ aq. (2 x 50 mL) and brine and dried over anhydrous Na$_2$SO$_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography (ethyl acetate/MeOH = 20/1) to give Q-1d as a white powder (2.7 g, 73% yield over 2 steps).

m.p: 204-207 °C; [α]$_D^{25}$ = + 89.3 (c 0.45, CHCl$_3$); $^1$H NMR (400 MHz, DMSO-d$_6$) δ 10.16 (br, 1H), 8.62 (d, $J$ = 4.4 Hz, 1H), 8.07 (d, $J$ = 8.0 Hz, 2H), 7.90 (d, $J$ = 8.4 Hz, 1H), 7.70 (t, $J$ = 7.2 Hz, 1H), 7.59-7.51 (m, 4H), 7.32 (d, $J$ = 9.2 Hz, 1H), 6.44 (d, $J$ = 7.6 Hz, 1H), 5.99-5.91 (m, 1H), 5.03 (d, $J$ = 18.4 Hz, 1H), 4.98 (d, $J$ = 11.6 Hz, 1H), 3.50-3.48 (m, 1H), 3.09 (br, 1H), 2.92-2.86 (m, 1H), 2.54-2.43 (m, 2H), 2.24 (br, 1H), 1.96-1.93 (m, 1H), 1.79 (br, 1H), 1.72-1.68 (m, 1H), 1.59-1.49 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 165.7, 156.4, 147.3, 144.0, 143.9, 142.9, 134.4, 132.0, 130.0, 129.9, 129.6, 127.6, 122.3, 119.6, 115.1, 105.2, 79.8, 75.3, 59.9, 56.6, 42.4, 27.9, 27.8, 25.3; IR (CHCl$_3$) ν 3500-2300 (br), 2943, 1717, 1540, 1558, 1507, 1268; HRMS (CI) m/z calcd for (C$_{26}$H$_{26}$N$_2$O$_3$ + H$^+$): 415.2022, found:415.2027.

**Preparation of catalyst QD-1d**

$6'$-OTIPS quinidine derivative QD-2:
Following same procedure as described for preparation of Q-2, QD-2 was obtained in 75\% yield from quinidine (QD). \([\alpha]_D^{25} = +137.8\) (c 1.0, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 8.71 (d, \(J = 5.2\) Hz, 1H), 7.87 (d, \(J = 9.2\) Hz, 1H), 7.65 (d, \(J = 4.4\) Hz, 1H), 7.37 (d, \(J = 2.8\) Hz, 1H), 7.20 (dd, \(J = 2.4\) Hz, 9.2 Hz, 1H), 6.50 (br, 1H), 6.02-5.93 (m, 1H), 5.22 (d, 3.6 Hz, 1H), 5.19 (d, \(J = 10.4\) Hz, 1H), 4.25 (br, 1H), 3.37-3.31 (m, 3H), 3.14-3.08 (m, 1H), 2.54-2.51 (m, 1H), 2.32 (t, \(J = 12.0\) Hz, 1H), 1.93-1.86 (m, 2H), 1.68-1.63 (m, 1H), 1.36 (hept. \(J = 7.2\) Hz, 3H), 1.13 (d, \(J = 7.2\) Hz, 9H), 1.11 (d, \(J = 7.2\) Hz, 9H); 1.00-0.90 (m, 2H); \(^{13}\)C NMR (100 MHz, DMSO-d₆) \(\delta\) 154.4, 147.8, 144.1, 143.7, 136.6, 131.3, 125.6, 124.7, 119.0, 117.3, 110.0, 67.3, 60.2, 49.2, 48.7, 37.6, 27.7, 23.6, 18.5, 18.05, 18.01, 12.8; IR (CHCl₃) \(\nu\) 3217 (br), 2943, 2867, 1617, 1589, 1504, 1456, 1259; HRMS (CI) m/z calcd. for (C₂₈H₄₂N₂O₂Si + H\(^+\)): 467.3094, found: 467.3103.

* Catalyst QD-1d:

Following the same procedure described above for the preparation of Q-1d, QD-1d was prepared in 87\% yield from QD-2. m.p.: 235-237 °C; \([\alpha]_D^{25} = -10\) (c 0.31, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 9.61 (br, 1H), 8.65 (d, \(J = 4.4\) Hz, 1H), 8.04 (d, \(J = 7.6\) Hz, 2H), 7.92 (d, \(J = 9.6\) Hz, 1H), 7.69 (s, 1H), 7.54 (t, \(J = 6.8\) Hz, 1H), 7.42-7.40 (m, 3H), 7.20 (d, \(J = 9.2\) Hz, 1H), 6.75 (d, \(J = 5.6\) Hz, 1H), 6.02-5.93 (m, 1H), 5.08 (d, \(J = 6.4\) Hz,
1H), 5.05 (d, J = 17.2 Hz, 1H), 3.39 (dd, J = 8.4 Hz, 6.4 Hz, 1H), 3.10-3.05 (m, 1H),
3.01-2.95 (m, 1H), 2.84-2.79 (m, 1H), 2.73-2.65 (m, 1H), 2.27 (dd, J = 7.6 Hz, 8.0 Hz, 1H),
2.01 (t, J = 9.6 Hz, 1H), 1.83 (s, 1H), 1.50-1.48 (m, 3H); ^{13}C NMR (100 MHz, CDCl_{3}) \delta
165.2, 156.4, 146.1, 143.6, 143.4, 139.8, 133.3, 131.0, 129.7, 129.6, 128.5, 127.3, 122.8,
118.6, 115.1, 105.8, 74.3, 58.8, 49.6, 49.1, 39.2, 27.5, 26.0, 23.0; IR (CHCl_{3}) ν 2500-
3500 (br), 3071, 2940, 1723, 1618, 1469, 1452, 1269, 1107; HRMS (ESI) m/z calcd for
(C_{26}H_{26}N_{2}O_{3} + H^{+}): 415.2022, found: 415.2026.
General procedure for enantioselective addition of nitromethane to α-ketoesters 2 catalyzed by QD-1d and Q-1d:

![Chemical structure](image)

Table 2  Enantioselective Nitroaldol Addition of Nitromethane to α-Ketoester 2 Catalyzed by QD-1d and Q-1d (in brackets).  

| Entry | R          | Time / h | yield / % | ee / % |
|-------|------------|----------|-----------|--------|
| 1     | 2a noise   | 14 (15)  | 92 (92)   | 96 (97)|
| 2     | 2b noise   | 24 (24)  | 98 (99)   | 94 (95)|
| 3     | 2c noise   | 35 (46)  | 96 (96)   | 95d (93)|
| 4     | 2d noise   | 96 (96)  | 86 (84)   | 94 (97)|
| 5     | 2e noise   | 72 (72)  | 86 (86)   | 96 (96)|
| 6     | 2f noise   | 12 (12)  | 98 (96)   | 97d (96)|
| 7     | 2g noise   | 9 (11)   | 96 (98)   | 94 (97)|
| 8     | 2h noise   | 11 (11)  | 91 (96)   | 95 (95)|
| 9     | 2i noise   | 60 (60)  | 96 (97)   | 94 (94)|
| 10    | 2j noise   | 12 (12)  | 89 (90)   | 95 (95)|
| 11    | 2k noise   | 17 (15)  | 90 (90)   | 93 (93)|
| 12    | 2l noise   | 14 (11)  | 88 (89)   | 95 (94)|
| 13    | 2m noise   | 15 (11)  | 87 (86)   | 94 (93)|

Unless noted, reactions were run with 0.5 mmol of 2, 5 mmol CH₃NO₂ in 0.5 mLCH₂Cl₂ with 5 mol% QD-1d, the results in parentheses were obtained with Q-1d to give opposite enantiomer, see Supporting Information for details. Isolated yield. Determined by HPLC analysis. The absolute configuration is determined to be S, see Supporting Information for details.

At -20 °C, to a solution of α-ketoester 2 (0.5 mmol), nitromethane (5 mmol) in CH₂Cl₂ (0.5 mL) was added catalyst QD-1d or Q-1d (5 mol%). The resulting mixture was kept
at the indicated temperature until 2 is completely consumed. The reaction mixture was directly subjected to silica gel flash chromatography using the eluent specified below to afford the desired product in the yields and enantiomeric excess summarized above. The catalyst is recovered in greater than 95% yield by washing the silica gel column with MeOH. The recovered catalyst was identical to that before the reaction by NMR analysis and can be reused without further treatment.

**Data for nitroaldol products 3:**

(+)–2-Hydroxy-2-nitromethyl-pent-3-enoic acid ethyl ester (3a) This product was obtained as a colorless oil in 92% yield after flash chromatography (elution gradient: ethyl acetate/hexane = 1/15) and 96% ee as determined by HPLC analysis [Daicel chiralpak AD, hexanes:IPA, 90:10, 0.8 ml/min, λ 215 nm, t (major) = 10.03 min, t (minor) = 10.91 min] from a reaction catalyzed by QD-1d (5 mol%) at -20°C for 14 hours. [α]D25 = +56.0 (c 0.93, CHCl3); 1H NMR (400 MHz, CDCl3) δ 6.13 (dq, J = 15.2 Hz, 6.8 Hz, 1H), 5.45 (dq, J = 15.2 Hz, 1.6 Hz, 1H), 4.86 (d, J = 14.0 Hz, 1H), 4.48 (d, J = 14.0 Hz, 1H), 4.42-4.28 (m, 2H), 3.77 (s, 1H), 1.75 (dd, J = 1.2 Hz, 14.0 Hz, 3H), 1.34 (t, J = 6.8 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 171.8, 130.6, 125.7, 79.9, 75.0, 63.2, 17.6, 13.9; these data is in agreement with those reported in literature.4

(-)-2-Hydroxy-2-nitromethyl-pent-3-enoic acid ethyl ester (3a) This product was obtained as a colorless oil in 92% yield and 97% ee from a reaction catalyzed by Q-1d (5.0 mol %) at -20°C for 15 hours.

(+)–5-Benzylxoy-2-hydroxy-2-nitromethyl-pent-3-enoic acid ethyl ester (3b) This product was obtained as a colorless oil in 98 % yield after flash chromatography (elution gradient: diethyl ether) and 94 % ee as determined by HPLC analysis [Daicel chiralpak AD, hexanes:IPA, 90:10, 0.8 ml/min, λ 215 nm, t (major) = 17.65 min, t (minor) = 19.99 min] from a
reaction catalyzed by QD-1d (5 mol%) at -20°C for 24 hours. \([\alpha]_D^{25} = +29.8\ (c\ 1.22, \text{CHCl}_3)\); \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \(\delta\ 7.36-7.32\ (m,\ 5H),\ 6.25\ (dt, J = 15.2\ Hz,\ 4.8\ Hz,\ 1H),\ 5.76\ (dt, J = 15.2\ Hz,\ 1.6\ Hz,\ 1H),\ 4.88\ (dd, J = 14.0\ Hz,\ 1.2\ Hz,\ 1H),\ 4.53\ (s,\ 2H),\ 4.48\ (d, J = 13.2\ Hz,\ 1H),\ 4.41-4.29\ (m,\ 2H),\ 4.08-4.06\ (m,\ 2H),\ 3.84\ (s,\ 1H),\ 1.34\ (t, J = 7.2\ Hz,\ 3H);\ ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \(\delta 171.4,\ 137.7,\ 131.5,\ 128.3,\ 127.7,\ 127.6,\ 125.8,\ 79.7,\ 75.1,\ 72.6,\ 68.9,\ 63.3,\ 13.9;\ IR (\text{CHCl}_3) \nu 3489\ (br),\ 3031,\ 2983,\ 2859,\ 1742,\ 1560,\ 1453,\ 1378,\ 1220;\ HRMS (ESI) m/z calcd for (C\(_{15}\)H\(_{19}\)NO\(_6\) + Na\(^+\)): 332.1110, found: 332.1102.

**(-)-5-Benzylxoy-2-hydroxy-2-nitromethyl-pent-3-enoi acid ethyl ester (3b)** This product was obtained as a colorless oil in 99% yield and 95% ee from a reaction catalyzed by Q-1d (5 mol %) at -20°C for 24 hours.

\[\text{(-)-5-Benzyloxy-2-hydroxy-2-nitromethyl-pent-3-enoi acid ethyl ester (3b)}\]

\[\text{IR (CHCl}_3) \nu 3489\ (br),\ 3031,\ 2983,\ 2859,\ 1742,\ 1560,\ 1453,\ 1378,\ 1220;\ HRMS (ESI) m/z calcd for (C}_{15}H_{19}NO_6 + Na^+: 332.1110, found: 332.1102.\]

**(+)-S-2-Hydroxy-3-nitro-2-phenyl-propionic acid ethyl ester (3c)** This product was obtained as a colorless oil in 96% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/19) and 95% ee as determined by HPLC analysis [Daicel chiralcel OD, hexanes/IPA, 80:20, 1.0 ml/min, \(\lambda\ 220\ nm,\ t\ (major) = 7.49\ min,\ t\ (minor) = 9.46\ min]\] from a reaction catalyzed by QD-1d (5 mol%) at -20°C for 35 hours. \([\alpha]_D^{25} = +28.4\ (c\ 1.05, \text{CHCl}_3)\); \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \(\delta 7.62-7.60\ (m,\ 2H),\ 7.43-7.40\ (m,\ 3H),\ 5.26\ (d, J = 14.0\ Hz,\ 1H),\ 4.68\ (d, J = 14.0\ Hz,\ 1H),\ 4.44-4.31\ (m ,2H),\ 4.22\ (s,\ 1H),\ 1.34\ (dt,\ J = 1.2Hz,\ 7.2\ Hz,\ 3H);\ ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \(\delta 171.6,\ 136.4,\ 129.0,\ 128.8,\ 125.2,\ 80.7,\ 75.9,\ 63.5,\ 13.8;\ these\ data\ are\ in\ agreement\ with\ those\ reported\ in\ literature.\]

The absolute configuration of (+)-3c was determined to be S by converting 3c into \(\beta\)-lactam 5c and comparing the value of the specific rotation of 5c with that reported in the literature. (for details see below preparation of \(\beta\)-lactam 5c part).
(-)-R-2-Hydroxy-3-nitro-2-phenyl-propionic acid ethyl ester (3c) This product was obtained as a colorless oil in 96% yield and 93% ee from a reaction catalyzed by Q-1d (5 mol %) at -20 °C for 46 hours.

(+)-2-Hydroxy-2-(4-methoxy-phenyl)-3-nitro-propionic acid ethyl ester (3d) This product was obtained as a white solid in 86% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/10) and 94% ee as determined by HPLC analysis [Daicel chiralpak AS, hexanes:IPA, 80:20, 1.0 ml/min, λ 220 nm, t (major) = 10.90 min, t (minor) = 13.49 min] from a reaction catalyzed by QD-1d (5 mol%) at -20 °C for 96 hours. M.p.: 70-73 °C; [α]_D^{25} = + 26.9 (c 1.25, CHCl_3), ^1H NMR (400 MHz, CDCl_3) δ 7.51 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.22 (d, J = 14.4 Hz, 1H), 4.41-4.31 (m, 2H), 4.65 (d, J = 14.4 Hz, 1H), 4.17 (s, 1H), 3.82 (s, 3H), 1.34 (t, J = 6.8 Hz, 3H); ^13C NMR (100 MHz, CDCl_3) δ 171.8, 160.1, 128.3, 126.3, 114.2, 80.8, 75.7, 63.5, 55.3, 13.9; these data are in agreement with those reported in lit. 4

(-)-2-Hydroxy-2-(4-methoxy-phenyl)-3-nitro-propionic acid ethyl ester (3d) This product was obtained as a colorless oil in 84% yield and 97% ee from a reaction catalyzed by Q-1d (5 mol %) at -20 °C for 96 hours.

(+) 2-Hydroxy-2-(4-methylsulfanyl-phenyl)-3-nitro-propionic acid ethyl ester (3e) This product was obtained as a white solid in 86% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/7) and 96% ee as determined by HPLC analysis [Daicel chiralcel OD, hexanes:IPA, 80:20, 1.0 ml/min, λ 220 nm, t (major) = 8.84 min, t (minor) = 12.15 min] from a reaction catalyzed by QD-1d (5.0 mol%) at -20 °C for 72 hours. M.p.: 84-86 °C; [α]_D^{25} = + 29.7 (c 1.1, CHCl_3), ^1H NMR (400 MHz, CDCl_3) δ 7.51 (dd, J = 2.0 Hz, 6.8 Hz, 2H), 7.25 (d, J = 6.8 Hz, 2H), 5.22 (d, J = 14.4 Hz, 1H), 4.65 (d, J = 14.4 Hz, 1H), 4.43-4.30 (m, 2H), 4.19 (s, 1H), 2.49 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^13C NMR (100 MHz, CDCl_3) δ 171.5, 140.2, 132.8, 126.2, 126.6,
80.6, 75.7, 63.6, 15.3, 13.9; IR (CHCl₃) ν 3484, 2984, 2924, 1736, 1559, 1493, 1378, 1226; HRMS (ESI) m/z calcd for (C₁₂H₁₅NO₅S + Na⁺): 308.0569, found: 308.0571.

**(-)-2-Hydroxy-2-(4-methylsulfanyl-phenyl)-3-nitro-propionic acid ethyl ester (3e)**
This product was obtained as a colorless oil in 86 % yield and 96 % ee from a reaction catalyzed by Q-1d (5 mol %) at -20°C for 72 hours.

![(-)-S-2-(4-Chloro-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3f)](image)

**(+)-S-2-(4-Chloro-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3f)** This product was obtained as a colorless oil in 98 % yield after flash chromatography (elution gradient: ethyl acetate/hexane =1/15) and 97 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexanes:IPA, 85:15, 1.0 ml/min, λ 220 nm, t (major) = 7.67 min, t (minor) = 9.17 min] from a reaction catalyzed by QD-1d (5 mol%) at -20°C for 12 hours. [α]D²⁵ = + 24.4 (c 1.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.56 (td, J = 2.4 Hz, 8.8 Hz, 2H), 7.39 (td, J = 2.4 Hz, 8.8 Hz, 2H), 5.22 (d, J = 14.0 Hz, 1H), 4.64 (d, J = 14.0 Hz, 1H), 4.44-4.31 (m, 2H), 4.24 (s, 1H), 1.34 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.2, 135.2, 134.9, 129.0, 126.7, 80.5, 75.6, 63.7, 13.8; these data are in agreement with those reported in lit.⁴

The absolute configuration of (+)-3f was determined to be S by comparing the specific rotation with that of literature data. [α]D²⁵ = + 21.7 (c 1.0, CH₂Cl₂) for 96% ee [lit.⁴ [α]D²³ = -17.5 (c 1.02, CH₂Cl₂) 88 % ee for R isomer ].

**(-)-R-2-(4-Chloro-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3f)** This product was obtained as a colorless oil in 96% yield and 96% ee from a reaction catalyzed by Q-1d (5 mol %) at -20°C for 12 hours.
(+)-2-(4-Cyano-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3g) This product was obtained as a white solid in 96% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/6) and 94% ee as determined by HPLC analysis [Daicel chiralpak AD, hexanes:IPA, 80:20, 0.9 ml/min, $\lambda$ 220 nm, t (major) = 15.44 min, t (minor) = 13.99 min] from a reaction catalyzed by QD-1d (5 mol%) at -20 $^\circ$C for 9 hours. M.p.: 97-100 $^\circ$C; $[\alpha]_D^{25} = + 24.9$ (c 1.05, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J$ = 8.4 Hz, 2H), 7.72 (d, $J$ = 8.4 Hz, 2H), 5.23 (d, $J$ = 14.0 Hz, 1H), 4.65 (d, $J$ = 14.0 Hz, 1H), 4.47-4.33 (m ,2H), 4.32 (s, 1H), 1.36 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.6, 141.3, 132.6, 126.3, 118.0, 113.3, 80.3, 75.7, 64.2, 13.9; IR (CHCl$_3$) $\nu$ 3475 (br), 2985, 2232, 1741, 1502, 1378, 1229; HRMS (CI) m/z calcd for (C$_{12}$H$_{12}$N$_2$O$_5$ + H$^+$): 265.0824, found: 265.0831.

(-)-2-(4-Cyano-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3g) This product was obtained as a colorless oil in 98% yield and 97% ee from a reaction catalyzed by Q-1d (5 mol %) at -20 $^\circ$C for 11 hours.

(+)-2-(3-Chloro-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3h) This product was obtained as a colorless oil in 91 % yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/15) and 95 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexanes:IPA, 85/15, 1.0 ml/min, $\lambda$ 220 nm, t (major) = 7.86 min, t (minor) = 10.15 min] from a reaction catalyzed by QD-1d (5 mol%) at -20 $^\circ$C for 11 hours. $[\alpha]_D^{25} = + 25.2$ (c 1.1, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.64 (d, $J$ = 1.6 Hz, 1H), 7.51-7.47 (m , 1H), 7.38-7.32 (m, 2H), 5.22 (d, $J$ = 14.8 Hz, 1H), 4.65 (d, $J$ = 14.8 Hz, 1H), 4.46-4.33 (m, 2H), 4.25 (s, 1H), 1.36 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.1, 138.3, 135.0, 130.1, 129.3, 125.7, 123.4, 80.5, 75.6, 63.9, 13.9; IR (CHCl$_3$) $\nu$ 3486 (br), 3073, 2984, 2926, 1739, 1562, 1475, 1416, 1377, 1227; HRMS (ESI) m/z calcd for (C$_{11}$H$_{12}$ClNO$_5$ + Na$^+$): 296.0302, found: 296.0300.
(-)-2-(3-Chloro-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3h) This product was obtained as a colorless oil in 96% yield and 95% ee from a reaction catalyzed by Q-1d (5 mol %) at -20°C for 11 hours.

(+)-2-Hydroxy-2-naphthalen-2-yl-3-nitro-propionic acid ethyl ester (3i) This product was obtained as a white solid in 96% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/19) and 94% ee as determined by HPLC analysis [Daicel chiralcel OD, hexanes:IPA, 60:40, 1.0 ml/min, λ 280 nm, t(major) = 7.60 min, t(minor) = 19.91 min] from a reaction catalyzed by QD-1d (5 mol%) at -20°C for 60 hours. M.p.: 75-77 °C; [α]D25 = + 47.6 (c 1.1, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.12 (s, 1H), 7.89-7.84 (m, 3H), 7.67 (dd, J = 2.0 Hz, 8.8 Hz, 1H), 7.56-7.52 (m, 2H), 5.39 (d, J = 14.0 Hz, 1H), 4.76 (d, J = 14.0Hz, 1H), 4.46-4.33 (m, 2H), 4.34 (s, 1H), 1.36 (t, J = 7.2 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 171.6, 133.6, 133.2, 132.9, 128.7, 128.4, 127.5, 127.0, 126.7, 125.0, 122.3, 80.7, 76.2, 63.6, 13.9; IR (CHCl3) v 3487 (br), 3059, 2983, 1738, 1560, 1415, 1377, 1270, 1224, 1133; HRMS (CI) m/z calcd for (C15H15NO5)+: 289.0950, found: 289.0942.

(-)-2-Hydroxy-2-naphthalen-2-yl-3-nitro-propionic acid ethyl ester (3i) This product was obtained as a colorless oil in 97% yield and 94% ee from a reaction catalyzed by Q-1d (5.0 mol %) at -20°C for 60 hours.

(-)-2-Hydroxy-2-methyl-3-nitro-propionic acid ethyl ester (3j) This product was obtained as a colorless oil in 89% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/6) and 95% ee as determined by HPLC analysis [Daicel chiralpak AS, hexanes:IPA, 95:5, 1.0 ml/min, λ 215 nm, t (major) = 16.90 min, t (minor) = 19.93 min] from a reaction catalyzed by QD-1d (5 mol%) at -20°C for 12 hours. [α]D25 = - 5.1 (c 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 4.84 (d, J = 14.0 Hz, 1H), 4.56 (d, J = 14.0 Hz, 1H), 4.40-
4.28 (m, 2H), 3.73 (s, 1H), 1.46 (s, 3H), 1.34 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$173.5, 80.9, 72.4, 63.0, 23.8, 13.9; these data are in agreement with those reported in lit.$^4$

(+) -2-Hydroxy-2-methyl-3-nitro-propionic acid ethyl ester (3j) This product was obtained as a colorless oil in 90% yield and 95% ee from a reaction catalyzed by Q-1d (5.0 mol %) at -20 °C for 12 hours.

(-)-2-Hydroxy-2-nitromethyl-pentanoic acid ethyl ester (3k) This product was obtained as a colorless oil in 90% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/15) and 93% ee as determined by HPLC analysis [Daicel chiralpak AS, hexanes:IPA, 90:10, 1.0 ml/min, $\lambda$ 215 nm, t (major) = 8.75 min, t (minor) = 10.84 min] from a reaction catalyzed by QD-1d (5.0 mol%) at -20 °C for 17 hours. $[\alpha]_D^{25} = -14.0$ (c 1.15, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.82 (d, $J = 13.2$ Hz, 1H), 4.56 (d, $J = 13.2$ Hz, 1H), 4.41-4.29 (m, 2H), 3.70 (s, 1H), 1.72-1.59 (m, 2H), 1.57-1.45 (m, 1H), 1.34 (t, $J = 7.2$ Hz, 3H), 1.26-1.14 (m, 1H), 0.93 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.9, 80.8, 75.2, 62.9, 38.6, 16.0, 14.0, 13.8; IR (CHCl$_3$) $\nu$ 3505 (br), 2967, 2937, 1739, 1561, 1467, 1380, 1234, 1162; HRMS (CI) m/z calcd for (C$_8$H$_{12}$NO$_5$ + H$^+$): 206.1028, found: 206.1023.

(-)-2-Hydroxy-2-nitromethyl-pentanoic acid ethyl ester (3k) This product was obtained as a colorless oil in 90% yield and 93% ee from a reaction catalyzed by Q-1d (5.0 mol %) at -20 °C for 15 hours.

(-)-2-Hydroxy-2-nitromethyl-4-phenyl-butyric acid ethyl ester (3l) This product was obtained as a colorless oil in 88% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/15) and 95% ee as determined by HPLC analysis [Daicel chiralpak AS, hexanes:IPA, 90:10, 1.0 ml/min, $\lambda$ 220 nm, t (major) = 10.75 min, t (minor) = 14.79 min] from a reaction catalyzed by QD-1d (5 mol%) at -20 °C for 14 hours.
[α]_D^{25} = -18.8 (c 1.5, CHCl₃); ^1H NMR (400 MHz, CDCl₃) δ 7.31-7.14 (m, 5H), 4.83 (d, J = 13.2 Hz, 1H), 4.58 (d, J = 13.2 Hz, 1H), 4.39-4.25 (m, 2H), 3.82 (s, 1H), 2.86-2.79 (m, 1H), 2.53-2.45 (m, 1H), 2.06-1.92 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^13C NMR (100 MHz, CDCl₃) δ 172.6, 140.1, 128.5, 128.2, 126.2, 80.7, 74.9, 63.0, 38.1, 28.9, 14.0; these data are in agreement with those reported in lit. ⁴

(+)-2-Hydroxy-2-nitromethyl-4-phenyl-butyric acid ethyl ester (3l) This product was obtained as a colorless oil in 89% yield and 94% ee from a reaction catalyzed by Q-1d (5.0 mol %) at -20 °C for 11 hours.

(-)-2-Hydroxy-2-nitromethyl-hexanedioic acid diethyl ester (3m) This product was obtained as a colorless oil in 87% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/5) and 94% ee as determined by HPLC analysis [Daicel chiralcel OJ, hexanes:IPA, 70:30, 1.0 ml/min, λ 215 nm, t (major) = 17.23 min, t (minor) = 12.00 min] from a reaction catalyzed by QD-1d (5 mol%) at -20 °C for 15 hours. [α]_D^{25} = -5.3 (c 1.15, CHCl₃); ^1H NMR (400 MHz, CDCl₃) δ 4.82 (d, J = 14.0 Hz, 1H), 4.57 (d, J = 14.0 Hz, 1H), 4.43-4.30 (m, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.75 (s, 1H), 2.37-2.26 (m, 2H), 1.86-1.73 (m, 2H), 1.70-1.64 (m, 1H), 1.59-1.49 (m, 1H), 1.35 (t, J = 6.8 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^13C NMR (100 MHz, CDCl₃) δ 172.7, 172.6, 80.7, 75.0, 63.1, 60.4, 35.6, 33.5, 18.2, 14.1, 14.0; IR (CHCl₃) ν 3492 (br), 2983, 2939, 1733, 1560, 1419, 1379, 1224; HRMS (ESI) m/z calcd for (C₁₁H₁₉NO₇ + Na⁺): 300.1059, found: 300.1053.

(+)-2-Hydroxy-2-nitromethyl-hexanedioic acid diethyl ester (3m) This product was obtained as a colorless oil in 86% yield and 93% ee from a reaction catalyzed by Q-1d (5 mol %) at -20 °C for 11 hours.
Concise Asymmetric Syntheses of β-lactam 5, aziridines 7 and α-methylcysteine derivative 8 from nitroaldol products 3:

**Synthesis of 3-phenyl-3-hydroxyazetidin-2-one (5c).**

At -20 °C, to a solution of α-ketoester 2c (1.136g, 6.38 mmol), nitromethane (3.4 mL) in CH₂Cl₂ (6.4 mL) was added catalyst QD-1d (132 mg, 5.0 mol%) The resulting mixture was kept at -20 °C for 40 hours when TLC showed 2c was completely consumed. The reaction mixture was directly subjected to silica gel flash chromatography (EA/Hexanes = 1/15) to furnish 3c as a clear oil (1.503g, 98% yield) and in 95% ee. The column was washed with MeOH and the catalyst 1d was recovered almost quantitatively (> 131 mg). The recovered catalyst was shown to be identical to that before the reaction by NMR analysis.

To a solution of 3c (1.04g, 4.35mmol) obtained from reactions using QD-1d in EtOH (25 mL) was added Raney nickel (1.0 g in 10 mL). The resulting reaction mixture was stirred under H₂ at atmospheric pressure for 4 h at room temperature. After the starting material
was completely consumed (monitored by TLC), the reaction mixture was passed through a short pad of celite and the celite was then washed with EtOH (2 x 10 mL). The filtrate was concentrated in vacuo and the residue 4c was used in next step without further purification (864 mg, 95% yield).

At 0 °C, to a solution of 4c (113 mg, 0.54 mmol) in anhydrous THF (2.0 mL) was added 1PrMgCl (2.0 M in THF, 1.35 mL, 2.7 mmol) dropwisely via a syringe. The resulting reaction mixture was stirred at room temperature for 19 hours. The reaction was quenched with NH₄Cl aq. (sat. 10.0 mL) and extracted with ethyl acetate (50 mL). The organic phase was washed with brine and dried over anhydrous Na₂SO₄. The solvent was removed in vacuo and the residue was purified by flash chromatography (ethyl acetate:hexanes = 1.5:1) to give 5c as a white powder (36 mg, 37% yield over 3 steps from 2c). The ee of 5c was determined to be 95% by HPLC analysis (chiralcel OD, IPA/Hexane = 95/5, 1.0 ml/min, 220 nm, t(major) = 32.27 min, t(minor) = 28.73 min). M.p.: 127-130 °C; [α]D²⁵ = -107° (c: 0.27 in CHCl₃) {lit.⁵ [α]D²³ = -57.4°, (c: 0.25 in CHCl₃) for 80% ee, S isomer}. The absolute configuration of 5c is therefore determined to be S, which indicate that the absolute configuration of 3c obtained with QD-1d is S.

1H NMR (400 MHz, CDCl₃) δ 7.48-7.45 (m, 2H), 7.36-7.26 (m, 3H), 6.89 (br, 1H), 3.56 (d, J = 5.6 Hz, 1H), 3.47 (d, J = 5.6 Hz, 1H); 13C NMR (100 MHz, CDCl₃) δ 171.9, 138.0, 128.6, 128.4, 125.3, 86.9, 54.1. The data is consistent with those reported in the literature.⁵

**Synthesis of Propionic acid 2-azido-1-hydroxy-1-phenyl-ethyl ester (6c):**⁶

\[
\begin{align*}
\text{Ph} & \quad \text{CO₂Et} \\
\text{NH₂} & \quad \text{TfN₃} \quad \text{CuSO₄} \\
\text{4c} & \quad \text{H₃} \quad \text{CO₂Et} \\
\text{Ph} & \quad \text{N₃} \\
\text{6c}
\end{align*}
\]

A mixture of NaN₃ (1.76g, 27 mmol), water (4 mL) and CH₂Cl₂ (2 mL) was cooled to 0 °C in an ice-water bath. To this mixture under vigorous stirring, Tf₂O (0.75 mL, 4.5
mmol) was added dropwise via a syringe. The resulting mixture was stirred at 0 °C for 3 h and 1 mL of water was added to the reaction mixture, after which the aqueous and organic phase was separated. The organic phase was collected, and the aqueous phase was extracted with CH₂Cl₂ (2 mL). The combined organic phase was washed with sat. aqueous NaHCO₃ (5 mL), after which it was used for the reaction with 4c.

At room temperature, to a solution of crude 4c (341 mg, 1.6 mmol, derived from hydrogenation of 3c as described above) in CH₂Cl₂ (1.5 mL) was added Et₃N (0.63 mL, 4.8 mmol) and an aqueous solution of CuSO₄ (12 mg in 0.25 mL of water) consecutively. To the resulting mixture, a solution of TfN₃ in CH₂Cl₂ freshly prepared as described above was added. This is followed by the addition of MeOH (around 1 mL), and the reaction mixture became homogenous. The reaction mixture was stirred at room temperature for 2.5 hours, after which it was poured into sat. NaHCO₃ aq. (20 mL). The resulting mixture was extracted with CH₂Cl₂ (2 x 40 mL). The combined organic phase was washed with brine and dried over anhydrous Na₂SO₄. The solvent was removed in vacuo and the residue was purified by chromatography (silica gel, ethyl acetate/hexanes = 1/20) to give 6c as a clear oil (339 mg, 88% yield, 84% yield over 2 steps from 3c). The ee of 6c was determined to be 96% by HPLC analysis (chiracel OJ, IPA/Hexanes = 90/10, 1.0 mL/min, 220nm, t(minor)=10.03 min, t(major)=13.17 min). [α]D²⁵⁻=30° (c: 1.1 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, J = 6.8 Hz, 2H), 7.40-7.32 (m, 3H), 4.39-4.25 (m, 2H), 4.01 (s, 1H), 3.84 (d, J = 12.4 Hz, 1H), 3.62 (d, J = 12.4 Hz, 1H), 1.33 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.8, 138.3, 128.5, 125.3, 79.3, 63.1, 58.4, 14.0; IR (CHCl₃) ν 3496, 3063, 2984, 2102, 1732, 1448, 1250; HRMS (ESI) m/z calcd for (C₁₁H₁₅N₃O₃ + Na⁺): 258.0855, found: 258.0860.

Synthesis of 2-Phenyl-aziridine-2-carboxylic acid ethyl ester (7c): 🅃
To a solution of 6c (300 mg, 1.27 mmol) in anhydrous CH$_3$CN (8.0 mL) was added PPh$_3$ (501 mg, 1.9 mmol) at room temperature. The mixture was stirred at room temperature for 1.0 h and then refluxed for 14 h under Ar atmosphere. The solvent was removed in vacuo and the residue was purified by chromatography (ethyl acetate/hexanes = 1/15) to give 7c as a clear oil (196 mg, 80% yield). The ee of 7c was determined to be 91% ee by HPLC (chiralpak AS plus $R,R$-Whelko, IPA/Hexanes = 90/10, 1.0 ml/min, 220 nm, t(major)= 11.20 min, t(minor)=12.59 min). [$\alpha$]$_D^{25} = -7.4$ $^\circ$ (c: 1.0 in CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49-7.44 (m, 2H), 7.35-7.27 (m, 3H), 4.26-4.12 (m, 2H), 2.51 (dd, $J$ = 2.0 Hz, 10.4 Hz, 1H), 2.00-1.91 (m, 2H), 1.22 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.0, 136.3, 129.1, 127.9, 127.6, 62.2, 41.2, 35.2, 13.9; 3290, 2984, 1717, 1306, 1195; HRMS (CI) m/z calcld for (C$_{11}$H$_{13}$NO$_2$ + H$^+$): 192.1024, found: 192.1018.

Synthesis of azide 3-Azido-2-hydroxy-2-methyl-propionic acid ethyl ester (6j):$^4,6$

At -20 $^\circ$C, to a solution of $\alpha$-ketoester 2j (580 mg, 5 mmol), nitromethane (2.7 mL) in CH$_2$Cl$_2$ (5 mL) was added catalyst QD-1d (104 mg, 5 mol%). The resulting mixture was kept at -20 $^\circ$C for 13 hours and TLC showed 2j is completely consumed. The reaction mixture was directly subjected to silica gel flash chromatography (EA/Hexanes = 1/15) to give 3j as a clear oil (830 mg, 94% yield). The ee of 3j was determined to be 95%. The
To a solution of 3j (800 mg, obtained with QD-1d in 95% ee) in EtOH (20 mL) was added Raney nickel (1.5 g in 10 mL). The reaction mixture was stirred under H\textsubscript{2} at atmospheric pressure for 4 h at room temperature. After the starting material was completely consumed (monitored by TLC), the reaction mixture was passed through a short pad of celite and celite was washed with EtOH (2 x 10 mL). The filtrate was concentrated in vacuo and the residue 4j was used directly in next step (600 mg, 90% crude yield).

A solution of NaN\textsubscript{3} (3.5 g, 54 mmol) in water (8 mL) and CH\textsubscript{2}Cl\textsubscript{2} (3 mL) was cooled to 0 °C in an ice-water bath. To this solution under vigorous stirring, Tf\textsubscript{2}O (1.51 mL, 9 mmol) was added dropwise via a syringe. The reaction mixture was stirred at 0 °C for 3 h, after which the mixture was diluted with water (2 mL). The aqueous and organic phases were separated. The organic phase was collected and the aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 mL). The combined organic phase was washed with sat. NaHCO\textsubscript{3} aq. (10 mL). This solution was used for the next step.

At room temperature, to a solution of 4j (475 mg, crude from 3j as described before) in CH\textsubscript{2}Cl\textsubscript{2} (3 mL) was added Et\textsubscript{3}N (1.25 mL) and a solution of CuSO\textsubscript{4} (24 mg in 0.5 mL H\textsubscript{2}O) consecutively. To the resulting mixture, a freshly prepared solution of TfN\textsubscript{3} in CH\textsubscript{2}Cl\textsubscript{2} as described above was added. This is followed by the addition of MeOH (around 2.0 mL) after which the solution became homogenous. The resulting mixture was stirred at room temperature for 2.5 hours. The reaction mixture was poured into sat. NaHCO\textsubscript{3} aq. (30 mL). The resulting mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 x 50 mL). The combined organic phase was washed with brine and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed in vacuo and the residue was purified by chromatography (silica gel, petroleum ether/ether = 9/1) to give 6j as a clear oil (390 mg, 70% yield, 59% yield over 3 steps from 2j). The ee of 6j was determined to be 95% by HPLC analysis: Daicel
chiralpak AS, Hexane:IPA, 97:3, 1.0 mL/min, λ 215 nm t(major)= 8.40 min, t(minor)= 9.52 min); $[\alpha]_D^{25} = -83.3 \degree$ (c: 1.0 in CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.31-4.25 (m, 2H), 3.51 (s, 1H), 3.47-3.40 (m, 2H), 1.41 (s, 3H), 1.32 (t, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.7, 75.1, 62.5, 58.4, 23.3, 14.0; IR (CHCl$_3$) ν 3503, 2985, 2939, 2105, 1733, 1456, 1258.

(Cautious: the product is very volatile, be careful when remove solvent in vacuo)

**Synthesis of aziridine 2-Methyl-aziridine-2-carboxylic acid ethyl ester (7j):**

![Synthesis of aziridine 2-Methyl-aziridine-2-carboxylic acid ethyl ester (7j):](image)

To a solution of 6j (188 mg, 1.09 mmol) in anhydrous CH$_3$CN (4 mL) was added PPh$_3$ (427 mg, 1.6 mmol) at room temperature. The mixture was stirred at r.t. for 1 h and then refluxed for 9 h under Ar atmosphere. The solvent was removed in vacuo and the residue was purified by chromatography (silica gel, petroleum ether/ether = 5/1) to give 7j as a clear oil (99 mg, 71% yield). $[\alpha]_D^{25} = -28 \degree$ (c: 0.5 in CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.20 (dq, $J = 1.6$ Hz, 7.2 Hz, 2H), 2.17 (d, $J = 10.4$ Hz, 1H), 1.64 (d, $J = 4.8$ Hz, 1H), 1.42 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.2, 53.4, 34.7, 34.1, 17.9, 14.0; IR (CHCl$_3$) ν 3294, 3070, 2983, 2940, 1724, 1325, 1199; HRMS (CI) m/z calcd for (C$_6$H$_{11}$NO$_2$ + H$^+$): 130.0868, found: 130.0867.

(Cautious: the product is very volatile, be extremely careful when remove solvent in vacuo)

**Synthesis of 2-Amino-3-(4-methoxy-benzylsulfanyl)-2-methyl-propionic acid ethyl ester (8j):**

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S21
At 0 °C, to the solution of 7j (65 mg, 0.5 mmol) in CH2Cl2 (1.5 mL) was added p-methoxybenzyl mercaptan (0.21 mL, 1.5 mmol) and boron trifluoride diethyl etherate (0.11 mL). The resulting mixture was stirred at 0 °C for 12 h followed by stirring at room temperature for 24 h. The reaction mixture was poured into sat. NaHCO3 aq. (20 mL) and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na2SO4. The solvent was removed and the residue was purified by chromatography (silica gel, petroleum ether/ethyl acetate = 2/1) to give 8j as a clear oil (80 mg, 56% yield) in 94% ee (determined by HPLC: Daicel chiralcel OD, Hexane:IPA, 80:20, 0.5 mL/min, λ 254 nm, t (minor) = 14.56 min, t (major) = 15.22 min). α]D25 = - 12 ° (c: 1.05 in CHCl3); 1H NMR (400 MHz, CDCl3) δ 7.23 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.20-4.14 (m, 2H), 3.79 (s, 3H), 3.70 (s, 2H), 2.92 (d, J = 13.2 Hz, 1H), 2.59 (d, J = 13.2 Hz, 1H), 1.85 (br, 2H), 1.34 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 176.3, 158.6, 130.1, 129.9, 113.8, 61.2, 58.6, 55.2, 42.0, 37.1, 26.3, 14.1; IR (CHCl3) v 3373, 2978, 2933, 1731, 1610, 1512, 1249; HRMS (ESI) m/z calcd for (C14H21NO3S + H+): 284.1320, found: 284.1315.

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HPLC Conditions: Daicel chiralpak AD, Hexane:IPA, 90:10, 0.80 mL/min, λ 215 nm

Product obtained with QD-1d

(-)-3a 97% ee

Product obtained with QD-1d

(+)3a 96% ee

racemic 3a

CO2Et

OH

NO2

S

24
HPLC Conditions: Daicel chiralpak AD, Hexane:IPA, 90:10, 0.80 mL/min, λ 215 nm

(+) 3b - 95% ee
Product obtained with QD-1d

(+) 3b - 94% ee
Product obtained with QD-1d
HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 80:20, 1.00 mL/min, λ 220 nm

racemic 3c

(+) -S-3c 95% ee
Product obtained with QD-1d

(-) -R-3c 93% ee
Product obtained with Q-1d
HPLC Conditions: Daicel chiralpak AS, Hexane:IPA, 85:15, 1.00 mL/min, λ 220 nm

racemic 3d

(+)-3d 94% ee
Product obtained with QD-1d

(-)-3d 97% ee
Product obtained with Q-1d
HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 80:20, 1.00 mL/min, λ 220 nm

(+)-3e 96% ee
Product obtained with QD-1d

(-)-3e 96% ee
Product obtained with Q-1d
HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 85:15, 1.00 mL/min, λ 220 nm

(+)-S-3f 97% ee
Product obtained with QD-1d

(-)-R-3f 96% ee
Product obtained with Q-1d
HPLC Conditions: Daicel chiralpak AD, Hexane:IPA, 80:20, 0.90 mL/min, λ 220 nm

(+)-3g 94% ee
Product obtained with QD-1d

(-)-3g 97% ee
Product obtained with Q-1d
HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 85:15, 1.00 mL/min, λ 220 nm

racemic 3h

(+)-3h 95% ee
Product obtained with QD-1d

(-)-3h 95% ee
Product obtained with Q-1d
HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 60:40, 1.00 mL/min, λ 280 nm

Product obtained with QD-1d

(-)-3i 94% ee

Product obtained with Q-1d

(+)-3i 94% ee

racemic 3i
HPLC Conditions: Daicel chiralpak AS, Hexane:IPA, 95:5, 1.00 mL/min, λ 215 nm

(-)-3j 95% ee
Product obtained with QD-1d

(+)-3j 95% ee
Product obtained with Q-1d
HPLC Conditions: Daicel chiralpak AS, Hexane:IPA, 90:10, 1.00 mL/min, λ 215 nm

(-)-3k 93% ee
Product obtained with QD-1d

(+)-3k 93% ee
Product obtained with QD-1d

S34
HPLC Conditions: Daicel chiralpak AS, Hexane:IPA, 90:10, 1.00 mL/min, λ 220 nm

(-)-3l 95% ee
Product obtained with QD-1d

(+)-3l 94% ee
Product obtained with Q-1d
HPLC Conditions: Daicel chiralcel OJ, Hexane:IPA, 70:30, 1.0 mL/min, λ 215 nm

(-)-3m 94% ee
Product obtained with QD-1d

(+)-3m 93% ee
Product obtained with Q-1d
HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 95:5, 1.00 mL/min, λ 220 nm

racemic 5c

(-)-S-5c 95% ee
HPLC Conditions: Daicel chiralcel OJ, Hexane:IPA, 90:10, 1.0 mL/min, λ 220 nm

**racemic 6c**

![HPLC chromatogram of racemic 6c](image1)

**(-)-S-6c 96% ee**

![HPLC chromatogram of (-)-S-6c](image2)
HPLC Conditions: Daicel chiralpak AS plus (R, R)-whelk-O 1, Hexane:IPA, 90:10, 1.0 mL/min, $\lambda$ 220 nm

racemic 7c

(-)-$R$-7c 91% ee
HPLC Conditions: Daicel chiralpak AS, Hexane:IPA, 97:3, 1.0 mL/min, $\lambda$ 215 nm

racemic 6j

(-)-6j 95% ee
HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 80:20, 0.5 mL/min, λ 254 nm

racemic 8j

(-)-8j 94% ee
li-14-109-dmo-h

Pulse Sequence: s2pul

Solvent: DMO

Ambient temperature

File: li-14-109-dmo-h

INOVA-500 "gamble"

Pulse 45.1 degrees

Acq. time 1.638 sec

Wait 5000.0 ms

20 repetitions

OBSERVE NL. 199.55170 MHz

DATA PROCESSING

PT aise 15384

Total time 0 min, 26 sec
Pulse Sequence: z2pul

Solvent: DMSO

Ambient temperature

Field: 514.16-07-05-a-hor-kz

INOFX-500 "quadruple"

Pulse 53.1 degrees

Acq. time 1.599 sec

Width 2550.0 Hz

14773 repetitions

INOFX CI3, 100.5184566 MHz

DROPCOCUS II, 399.7571411 MHz

Lower 37 dm on during acquisition

off during delay

GRAP-3 modulated

DATA PROCESSING

Time broadbanding 1.0 Hz

FT size 61456

Total time 33 hr, 37 min, 0 sec

ppm
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: 11-14-103-1
Spectra-300 "quinte"

Pulse 46.1 degrees
Acq. time 1.636 sec
Width 5030.6 Hz
16 repetitions
FOREPA M1. 395.1532145 MHz
DATA PROCESSING
PT size 11384
Total time 0 min, 26 sec
Pulse sequence: e2pa1
Solvent: CDCl3
Ambient temperature
file: 11-14-11-b
MDVA-300 "Pulse"

Pulse 46.1 degrees
Acq. time 1.650 sec
M022 50±0.0 Hz
60 repetitions

RESERVE M: 399.7532±49 kHz
DATA PROCESSING
FT size 1024
Total time 1 min, 45 sec
