Supporting Information for

Direct Catalytic Asymmetric Aldol-Type Reaction of Aldehydes with Ethyl Diazoacetate

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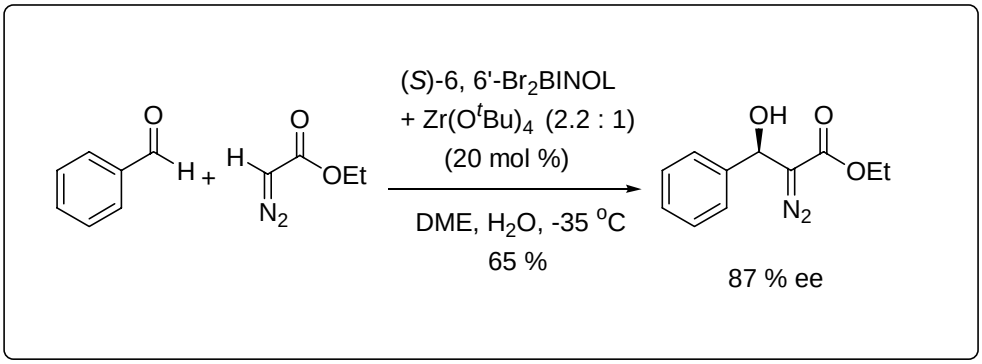


General. All reactions were performed under a nitrogen atmosphere in a flame-dried reaction flask, and the components were added via Syringe. All solvents were distilled prior to use. For chromatography, 100-200 mesh silica gel (Qindao, China) was employed. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz with Varian Mercury 300 spectrometer. Chemical shifts are reported in ppm using tetramethylsilane as internal standard. IR spectra were recorded with a Nicolet 5MX-S infrared spectrometer. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. $Zr(O^tBu)_4$ was purchased from Fluka. HPLC analysis was performed at HP 1100 apparatus with Chiralcel OJ column.

Typical procedure of the catalytic asymmetric condensation: Chiral ligand (0.056 mmol) was dissolved in 0.5 mL of anhydrous DME, and then was added $Zr(O^tBu)_4$ (97%, 10 mg, 0.025 mmol) to the solution under N_2 at r.t.. After stirred for 1 hour, N_2CHCO_2Et (43 mg, 0.375 mmol) was added to the solution, and then water (0.45 uL, 0.025 mmol) was added. After the solution was stirred for another 3 h, it was cooled by dry ice/CCl_4 bath (-23℃) or dry ice/$ClCH_2CH_2Cl$ bath (-35℃). Aldehyde (0.125 mmol) was added under N_2. The solution was stirred for 3 days. And the solvent and excess N_2CHCO_2Et were removed with rotvap. The crude residue was purified with silica gel column (petroleum ether/acetone = 8 : 1).

In entries 3, 4, 7 and 8 of Table 2, $MgBr_2$ (0.188 mmol) was added before the addition of the aldehyde.

In the cases of **3a** and the entries 2,3,4 of Table 2, the crude β–hydroxyl product was directly converted into β–acetoxy product by the following procedure: To the crude β–hydroxyl product was added CH_2Cl_2 (5 mL), triethylamine (3 mL), DMAP (5 mg) and acetic anhydride (1 mL). The solution was stirred overnight between 0 ^oC and room temp. Saturated aqueous $NaHCO_3$ (20 mL) was added, and the mixture was extracted with CH_2Cl_2 for 3 times. The combined extracts were dried over Na_2SO_4. The solvent was removed in vacuum, and the residue was purified with silica gel column (petroleum ether : acetone = 8 : 1).

*Ethyl 2-Diazo-3-phenyl-3-hydroxypropanoate **3a**.* 87 % ee. $[\alpha]_D^{20}$ = -9.5 (c 3.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 3.25 (s, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 5.91 (d, *J* = 3.0 Hz, 1H), 7.31-7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.41, 61.15, 68.64, 125.67, 128.26, 128.70, 138.81, 166.40. (For racemic **3a**, see: Pellicciari, R.; Natalini, B.; Cecchetti, S.; Fringuelli, R. *J. Chem. Soc. Perkin Trans. 1*, **1985**, 493; Jiang, N.; Wang, J. *Tetrahedron Lett.* **2002**, *43*, 1285.)

*Ethyl 2-Diazo-3-phenyl-3-acetoxypropanoate **8a**.* 72 % ee. $[\alpha]_D^{20}$ = -67.8 (c 0.95, CH_2Cl_2); IR 2981, 2101, 1751, 1701, 1372, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.09 (s, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 6.85 (s, 1H), 7.28-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.86, 20.26, 60.74, 69.78, 125.19, 128.08, 128.40, 136.04, 164.13, 168.88; MS *m/z* (EI) 234 [$(M-N_2)^+$, 0.1], 192 (70), 175 (3), 146 (25), 129 (17), 118 (100), 105 (60.5), 90 (45). Anal. calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.53; H, 5.44; N, 11.03.

Ethyl 2-Diazo-3-(3-trifluoromethyl)phenyl-3-acetoxyproponate ***8b***. 65 % ee; $[\alpha]_D^{20}$ = -9.8 (c 0.7, CH_2Cl_2); IR 2987, 2104, 1752, 1700, 1331, 1222, 1174, 1126 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.18 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 6.87(s, 1H), 7.52-7.63 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.15, 20.64, 61.29, 69.62, 121.87, 122.47, 125.28, 129.06, 129.35, 130.48-131.77 (q, *J* = 129 Hz), 137.65, 164.28, 169.33; MS *m/z* (EI) 302 [$(M-N_2)^+$, 0.8], 260 (67), 215 (22), 186 (100), 173 (47), 158 (26), 145 (21). Anal. calcd for $C_{14}H_{13}F_3N_2O_4$: C, 50.91; H, 3.97; N, 8.48. Found: C, 50.69; H, 3.98; N, 8.71.

Ethyl 2-Diazo-3-chlorophenyl-3-acetoxyproponate ***8c***. 72 % ee; $[\alpha]_D^{20}$ = +57.8 (c 0.55, CH_2Cl_2); IR 2980, 2102, 1750, 1700, 1218, 1018, 756 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.15 (s, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 6.78 (s, 1H), 7.28-7.37 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.22, 20.72, 61.19, 69.57, 127.00, 128.91, 134.21, 134.89, 164.34, 169.25; MS *m/z* (EI) 268 [$(M-N_2)^+$, 0.7], 226 (34), 180 (17), 152 (63), 139 (31), 91 (51), 43 (100), 29 (72). Anal. calcd for $C_{13}H_{13}ClN_2O_4$: C, 52.62; H, 4.42; N, 9.44. Found: C, 52.66; H, 4.54; N, 9.37.

Ethyl 2-Diazo-3-bromophenyl-3-acetoxyproponate ***8d***. 78 % ee; $[\alpha]_D^{20}$ = -45.1 (c 0.75, CH_2Cl_2); IR 2983, 2102, 1750, 1699, 1374, 1221, 1018, 750 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.16 (3H, s), 4.26 (q, *J* = 7.2 Hz, 2H), 6.77 (s, 1H), 7.25-7.50 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.33, 20.85, 61.35, 69.45, 122.89, 124.30, 128.74, 130.40, 131.65, 138.76, 164.41, 169.31; MS *m/z* (EI): 312 [$(M-N_2)^+$, 0.1], 270 (66), 226 (25), 196 (100), 183 (52). Anal. calcd for $C_{13}H_{13}BrN_2O_4$ C, 45.77; H, 3.84; N, 8.21. Found: C, 46.34; H, 3.88; N, 7.88.

Ethyl 2-Diazo-5-phenyl-3-hydroxypent-4-enoate ***3e***. 79 % ee; $[\alpha]_D^{20}$ = -11 (c 0.4, CH_2Cl_2); IR 3435, 2983, 2098, 1683, 1378, 1336 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3H), 3.24 (s, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 5.42-5.46 (m, 1H), 6.25 (dd, *J* = 5.4, 15.9 Hz, 1H), 6.79 (d, *J* = 15.9 Hz, 1H), 7.23-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.39, 61.13, 66.97, 114.70, 125.66, 126.63, 128.06, 128.57, 132.05, 135.88, 166.15; MS *m/z* (EI) 218 [$(M-N_2)^+$, 11], 171 (30), 144 (33), 131 (71), 115 (64), 103 (48), 69 (76), 57 (100). Anal. calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.45; H, 5.77; N, 11.15.

Ethyl 2-Diazo-3-[2-(6-methylpyridyl)]-3-hydroxyproponate ***3f***. 53 % ee; $[\alpha]_D^{20}$ = -10 (c 0.3, CH_2Cl_2); IR 3413, 2982, 2098, 1691, 1588, 1459 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.55 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 5.40 (s, 1H), 5.77 (1H, s), 7.10 (d, *J* = 7.8, 1H), 7.23 (d, *J* = 7.8, 1H), 7.60-7.65 (t, *J* = 7.8,7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.22, 23.85, 60.71, 66.75, 117.65, 122.52, 117.65, 122.52, 137.45, 156.56, 157.00, 165.80; MS *m/z* (EI) 207 [$(M-N_2)^+$, 10], 178 (19), 146 (12), 135 (43), 120 (18), 93 (100), 84 (98). Anal. calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.30; H, 5.65; N, 17.43.

Ethyl 2-Diazo-3-(2-Furyl)-3-hydroxyproponate ***3g***. 86 % ee; $[\alpha]_D^{20}$ = -15 (c 0.4, CH_2Cl_2); IR 3415, 2986, 2104, 1682, 1380, 1291 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 3.98 (s, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 5.80 (s, 1H), 6.34-6.37 (m, 2H), 7.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.21, 61.12, 63.10,

107.19, 110.21, 142.56, 151.91, 165.88; MS *m/z* (EI) 210 (M^+, 2), 182 [$(M-N_2)^+$, 4], 154 (25), 136 (84), 108 (41), 95 (93); Anal. calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.83; H, 5.06; N, 12.97.

*Ethyl 2-Diazo-3-hydroxyhexanoate **3h***. 57 % ee; $[\alpha]_D^{20}$ = +9.3 (c 0.3, CH_2Cl_2); IR 3410, 2967, 2095, 1688, 1379, 1296 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 6.9 Hz, 3H), 1.33-1.73 (m, 4H), 3.55 (s, 1H), 4.20-4.27 (q, *J* = 7.2 Hz, 2H), 4.64-4.70(m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.49, 14.22, 18.66, 35.97, 60.79, 65.84, 166.58; MS *m/z* (EI) 186 (M^+, 3.5), 158 [$(M-N_2)^+$, 4], 143 (66), 115 (27), 87 (60), 71(44), 55(95); Anal. calcd for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.32; H, 7.44; N, 15.15.

*Determination of the absolute configuration of **3a***. The absolute configuration of **3a** was determined to be *R* by converting it to a known compound through hydrogenation. The hydrogenation of **3a** (87 % ee) following the literature procedure (Pellicciari, R.; Natalini, B.; Cecchetti, S.; Fringuelli, R. *J. Chem. Soc. Perkin Trans. 1*, **1985**, 493) resulted in partial racemization, but it was possible to determine the absolute configuration by comparing the sign of optical rotation with a known compound.

3a (35 mg, 0.16 mmol, 87 % ee) was dissolved MeOH (2 mL), and 10 % Pd/C (15 mg) was added. The mixture was hydrogenated under 1 atm H_2 for 1 h, and then the mixture was filtered. The filtrate was removed with rotvap, and the residue was purified by silica gel column (petroleum ether : acetone = 4 : 1) to give 3-hydroxy-3-phenylpropionate (20 mg, 64 %). $[\alpha]_D^{20}$ = -2.3 (c 0.3, $CHCl_3$), literature data for (*S*)-3-hydroxy-3-phenylpropionate: $[\alpha]_D^{20}$ = -44.8 (c 1.6, $CHCl_3$) (Cabon, O.; Buisson, D.; Larcheveque, M.; Azerad, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2199-2210).

*Oxidation of Ethyl 2-Diazo-3-phenyl-3-acetoxypropanoate **8a**.* $NaHCO_3$ (332 mg, 4 mmol) was added to the solution of H_2O (1.5 mL) and acetone (1 mL) and the mixture was cooled by ice-bath. Oxone® (625 mg 1.0 mmol) was then added. To this mixture, **8a** (52 mg, 0.2 mmol, 72 % ee) in CH_2Cl_2 (1.5 mL) was added dropwise in 15 min under nitrogen atmosphere. Ice-bath was then removed and the temperature was raised to room temperature. The yellow color was disappeared after about 1.5 h, and TLC check indicated that the starting material had disappeared. The mixture was extracted by CH_2Cl_2 twice. The combined extracts were dried over anhydrous Na_2SO_4. The solvent was removed by rotvap, and the residue was purified by silica gel column (petroleum ether : acetone = 4 : 1) to give ethyl 2-Oxo-3-phenyl-3-acetoxypropanoate **9** (45 mg, 90 %, 73 % ee). $[\alpha]_D^{20}$ = +145 (c 0.65, CH_2Cl_2); IR 3477, 2987, 1739, 1373, 1230, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.19 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 6.66 (s, 1H), 7.38-7.48 (m, 5H); ^{13}C NMR ($CDCl_3$): 13.79, 20.46, 62.75, 77.76, 128.90, 129.05, 129.74, 130.83, 159.25, 170.20, 186.66; MS *m/z* (EI) 250 (M^+, 0.1), 208 (0.8), 149 (48), 107 (98), 105 (10), 90 (5), 79 (16), 43 (100).

*Reduction of ethyl 2-Oxo-3-phenyl-3-acetoxypropanoate **9***. **9** (20 mg, 0.08 mmol**)** was dissolved in EtOH (2 mL) and the solution was cooled by dry ice-$ClCH_2CH_2Cl$ bath (-35 ^oC). $NaBH_4$ (3 mg, 0.08 mmol) was added and the solution was stirred for 1 h. Saturated aqueous NH_4Cl was then added and the

mixture was extracted with CH_2Cl_2 for three times. The combined extracts were dried over anhydrous Na_2SO_4. Solvent was removed and the residue was purified by silica gel column (petroleum ether : acetone = 4 : 1) to give an oil (20 mg, 99 %). Inspection of the product suggested that it was a diastereomeric mixture of *syn*- and *anti*- ethyl 2-hydroxy-3-phenyl-3-acetoxyproponates with a ratio of 12 : 1. The major isomer was confirmed to be *anti* by converting it to diol **11** and by comparison with the ^{1}H NMR spectra of a known compound (*vide infra*). ^{1}H NMR ($CDCl_3$) for major *anti* isomer **10**: δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.15 (s, 3H), 2.88 (d, *J* = 7.2 Hz, 1H), 4.22 (t, *J* = 7.2 Hz, 2H), 4.61 (dd, *J* = 3.6, 7.2 Hz, 1H), 6.07 (d, *J* = 3.9 Hz, 1H), 7.33-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) for major *anti* isomer **10**: δ 14.07, 21.05, 62.21, 72.90, 76.02, 127.32, 128.28, 128.66, 134.84, 169.92, 171.38.

Hydrolysis of ethyl 2-hydroxy-3-phenyl-3-acetoxyproponate with catalytic K_2CO_3. A literature procedure (Desai, S. B.; Argade, N. P.; Ganesh, K. N. *J. Org. Chem.* **1996**, *61*, 6730.) was followed. The mixture of *syn*- and *anti*- ethyl 2-hydroxy-3-phenyl-3-acetoxyproponates (30 mg, 0.12 mmol) was dissolved in anhydrous EtOH (2 mL), and then K_2CO_3 (1 mg) was added. The solution was stirred for 4 h at room temp. under N_2. The solution was filtered and the filtrate was evaporated in vacuum. The residue was purified with silica gel column (petroleum ether : acetone = 4 : 1) to give of **11** (20 mg, 84 %). ^{1}H NMR ($CDCl_3$) δ 1.16 (t, *J* = 7.2 Hz, 3H), 2.94 (d, *J* = 6.0 Hz, 1H), 3.00 (d, *J* = 6.6 Hz, 1H), 4.10-4.17 (t, *J* = 7.2 Hz, 2H), 4.49 (dd, *J* = 4.2, 6Hz, 1H), 5.01-5.04 (m, 1H), 7.30-7.43 (m, 5H).

This product was different from the sample of *syn*- ethyl 2,3-dihydroxy-3-phenylproponate, which was prepared from the dihydroxylation of *trans*- ethyl cinnamate with $KMnO_4$. ^{1}H NMR ($CDCl_3$) δ 1.27 (t, *J* = 6.9 Hz, 3H), 2.77 (d, *J* = 7.2 Hz, 1H), 3.13 (d, *J* = 5.7 Hz, 1H), 4.26 (t, *J* = 7.2 Hz, 2H), 4.37 (dd, *J* = 3.0, 5.4 Hz, 1H), 5.00 (s, 1H), 7.29-7.47 (m, 5H).

Chiralcel OJ; Flow = 0.8 mL/min; hexane/*iso*-propanol = 96 : 4

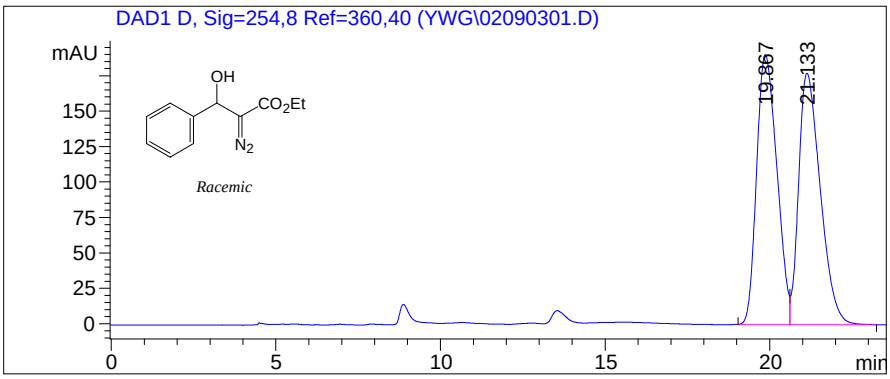


Table 1, entry 7

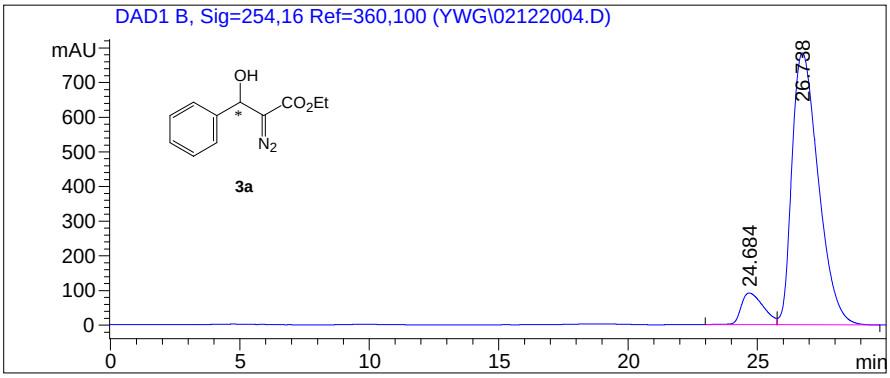
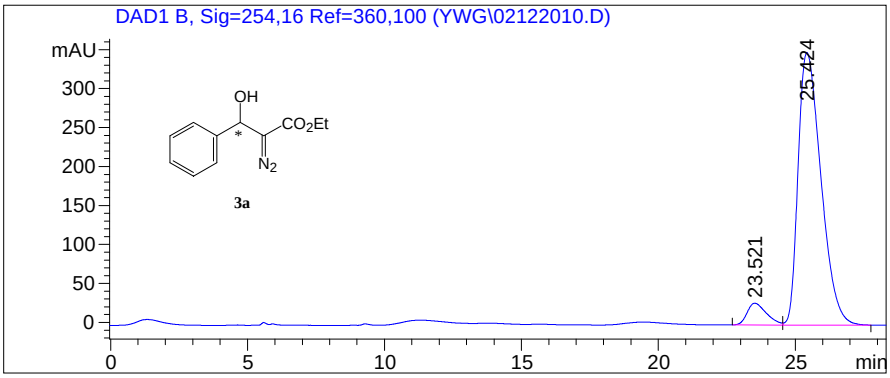


Table 1, entry 8 (Table 2, entry 1)



Chiralcel OJ, Flow = 1.0 mL/min, hexane/*iso*-propanol = 99.7 : 0.3

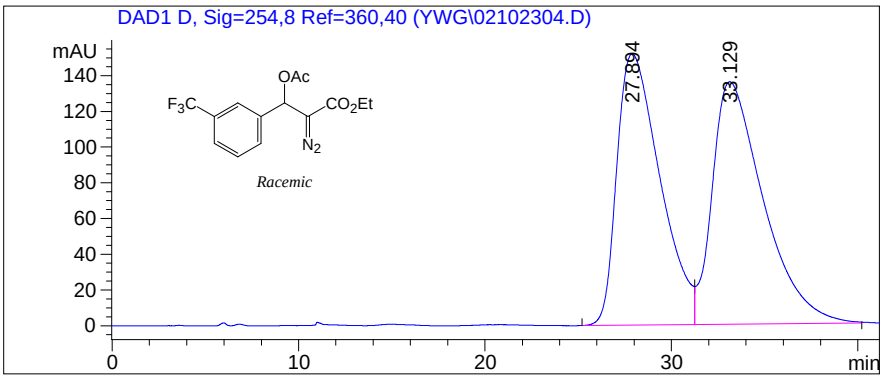
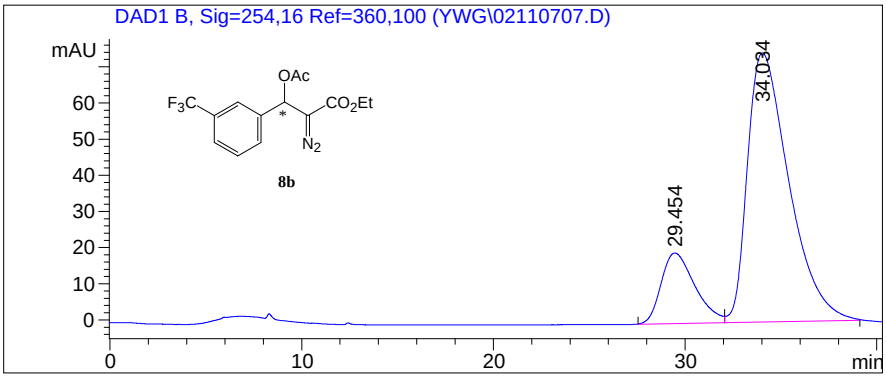


Table 2, entry 2.



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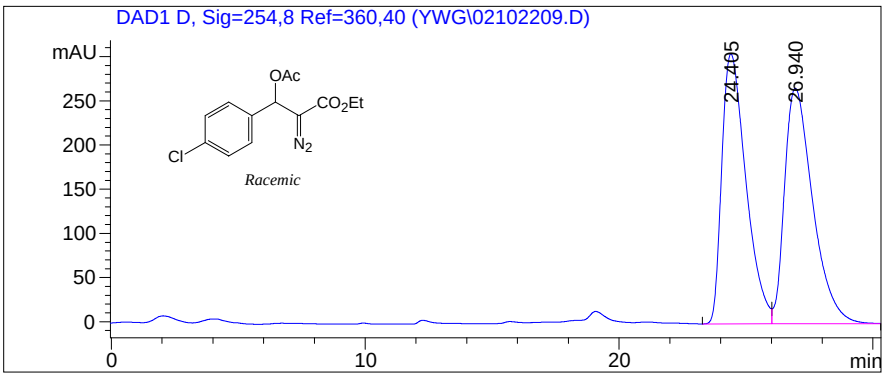

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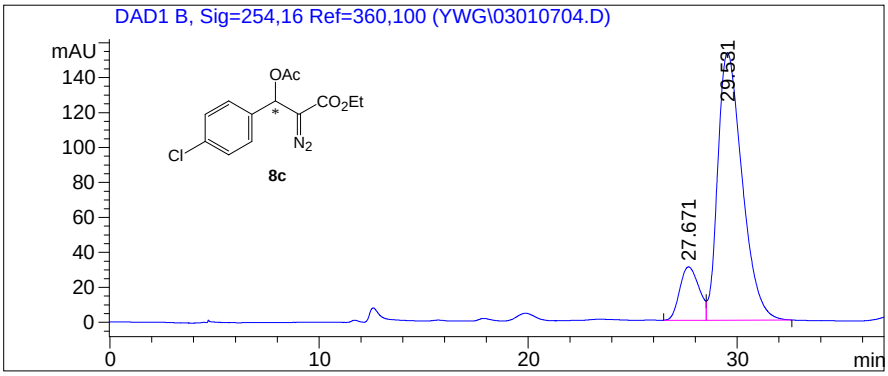
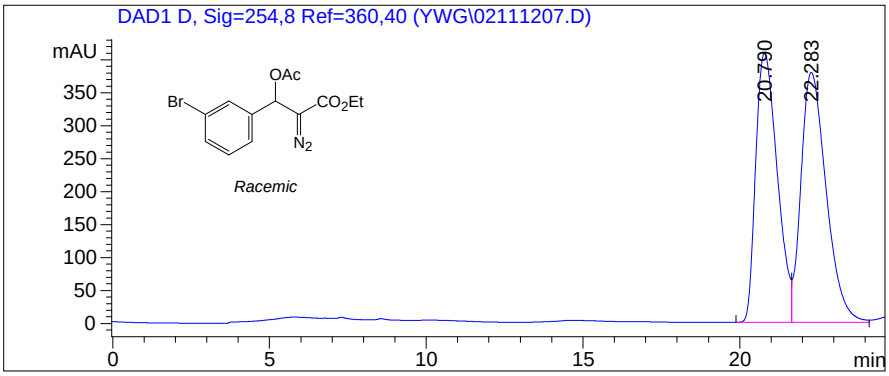


Chiralcel OJ, Flow = 0.5 mL/min, hexane/*iso*-propanol = 95 : 5



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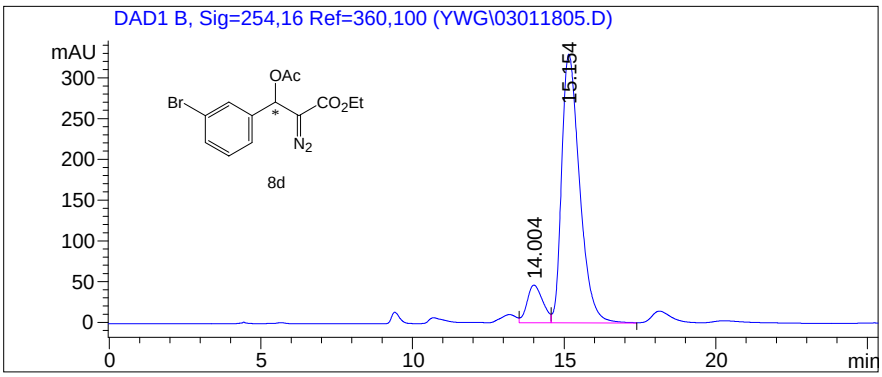
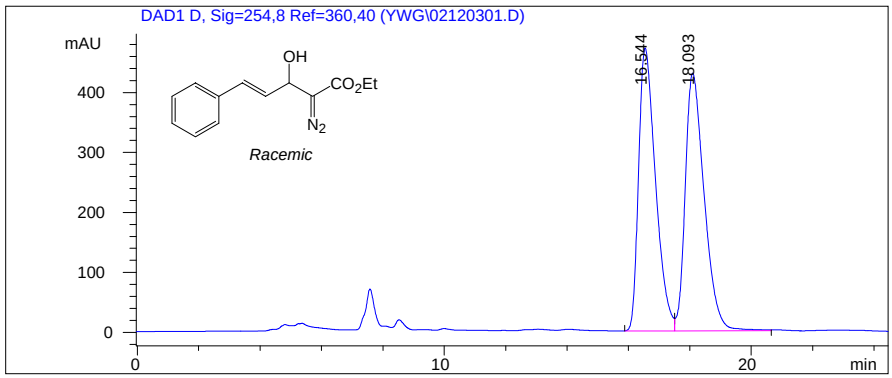


Chiralcel OJ, Flow = 0.8 mL/min, hexane/*iso*-propanol = 90 : 10



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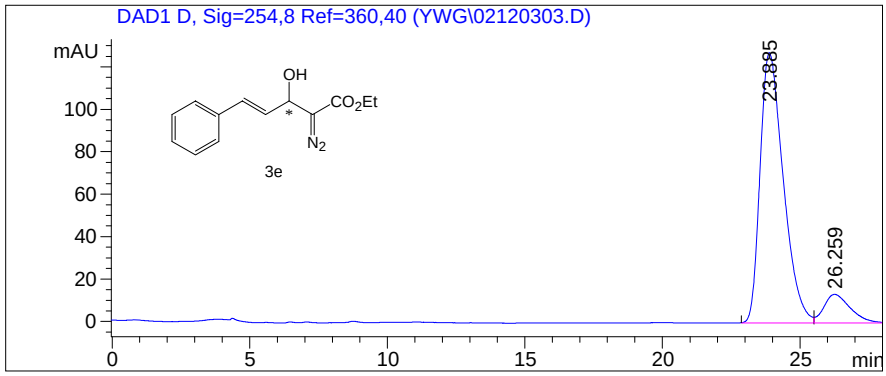
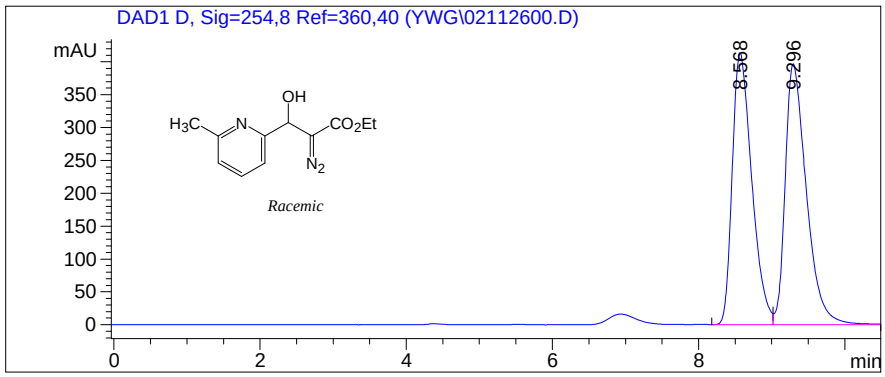


Chiralcel OJ, Flow = 0.8 mL/min, hexane/*iso*-propanol = 90 : 10



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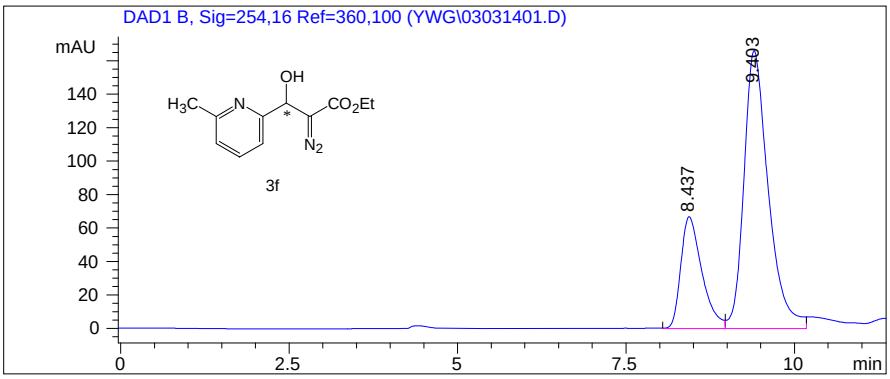

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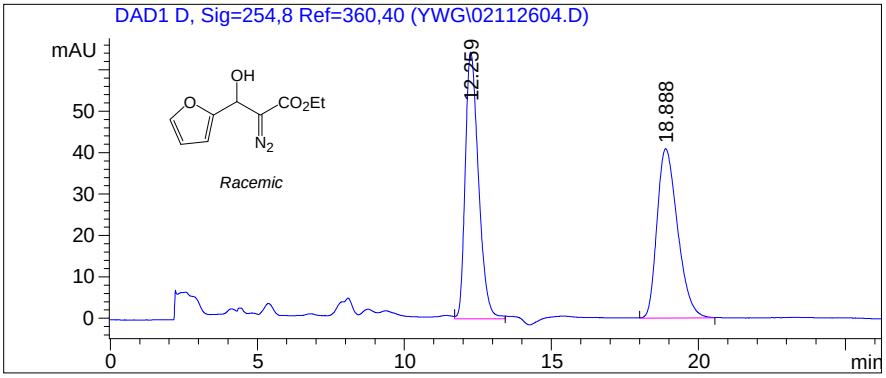

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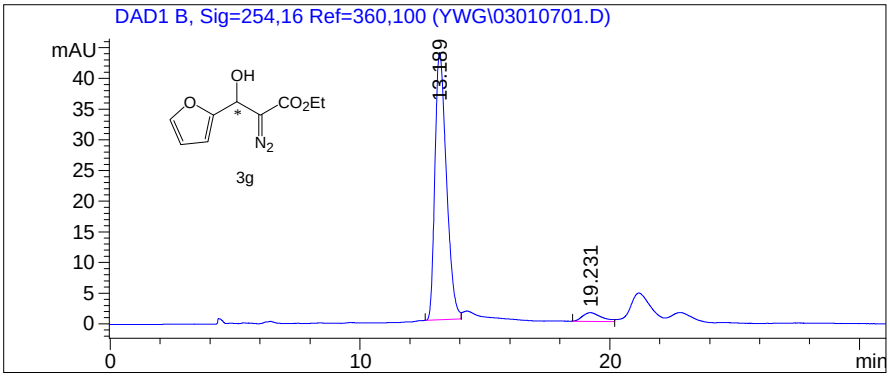


Chiralcel OJ, Flow = 0.8 mL/min, hexane/*iso*-propanol = 99.5 : 0.5

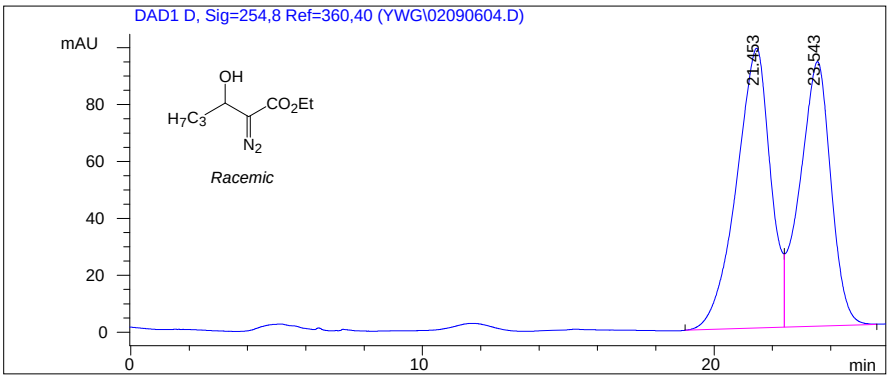
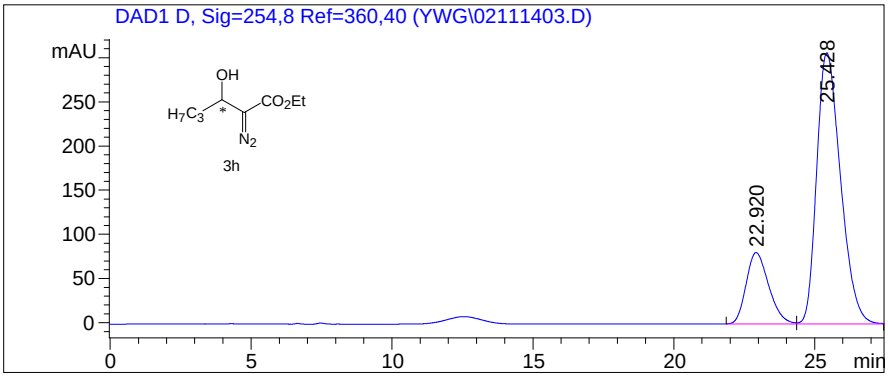
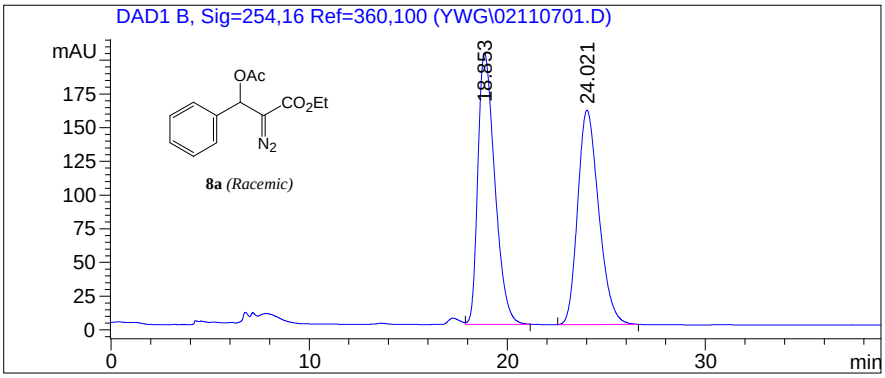
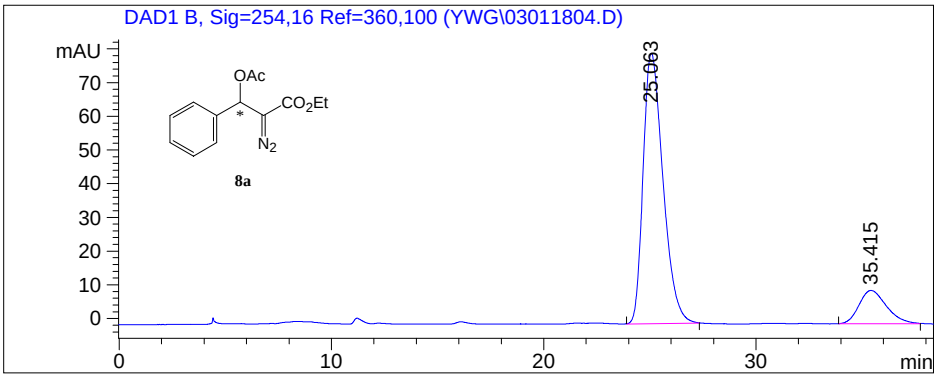


Table 2, entry 8



Chiralcel OJ, Flow = 0.8 mL/min, hexane/*iso*-propanol = 95 : 5

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N2
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35.415
0
10
20
30
min