A Direct Catalytic Asymmetric Mannich-Type Reaction to Syn-Amino Alcohols.

Barry M. Trost* and Lamont R. Terrell

Department of Chemistry, Stanford University, Stanford, California 94305-5080.

Experimental Procedure

General procedure for the imine aldol (Mannich-type) reaction of glyoxalates:

Preparation of the catalyst:

To a room temperature solution of ligand **1a** (5 mg, 0.0075 mmol) in THF (0.3 mL) was added dropwise a solution of diethylzinc (15 μ L, 0.015 mmol, 1.0 M hexanes) and continued to stir for 30 minutes.

Mannich-type (Imine Aldol) reaction:

To a -78°C suspension of imine **4b** (66 mg, 0.30 mmol), 2-hydroxyacetophenone (82 mg, 0.60 mmol) and crushed 4Å molecular sieves (60 mg) in THF (0.6 mL) was added the zinc catalyst from above. After stirring at -5°C for 6 – 12 hours, the reaction mixture was diluted with Et₂O (6 mL) and then a phosphate buffer (pH = 7) solution (3 mL). After stirring for 30 minutes, the phases were separated and the aqueous phase was extracted with Et₂O (1 mL x 2). The combined organics were washed with brine (1.5 mL), dried over MgSO₄, filtered and concentrated to give an oil. The crude residue was purified by flash chromatography on silica gel [PE / EtOAc 10 % $\rightarrow$ 15 %] to give 87 mg (81%) of imine aldol **5** as a yellow oil.

Syn diastereomer: t_r = 13.9 min (major enantiomer) and 21.1 min, (Chiralcel OD, λ = 254 nm, heptane:*i*-PrOH = 90:10, 0.9 mL/min); $[\alpha]_D^{25} +46.3^{\circ}$ (c 0.659, CHCl₃, 93.6% ee); ^1H NMR (300 MHz, CDCl₃) δ = 7.92 (d, J = 8.8 Hz, 2 H), 7.64 (t, J = 7.8 Hz, 1 H), 7.52 (t, J = 7.8 Hz, 2 H), 6.71 (d, J = 2.0 Hz, 1 H), 6.64 (dd, J = 2.0, 8.8 Hz, 1 H), 6.54 (d, J = 8.8 Hz, 1 H), 5.39 (s, 1 H), 4.49 (s, 1 H), 4.37 (br s, 1 H), 4.02 (m, 2 H), 3.72 (s, 3 H), 2.27 (s, 3 H), 1.11 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl₃) δ = 198.6, 169.6, 153.0, 138.1, 134.2, 134.1, 129.0, 128.3, 126.5, 116.9, 114.0, 111.6, 74.3, 61.8, 61.4, 55.5, 17.7, 13.9; IR (neat, 4 cm^{-1}): ν = 3282, 2933, 1678, 1657, 1598, 1505, 1449, 1275, 1221, 1157, 1047, 804, 693; HRMS (EI) m/z 357.1275 [M^+ ; calcd for C₂₀H₂₃NO₅, 357.1576].

diastereomeric mixture (dr = 2:1); Syn diastereomer: t_r = 44.7 min (major enantiomer) and 65.3 min, (Chiralcel AD, λ = 254 nm, heptane:*i*-PrOH = 90:10, 1 mL/min); $[\alpha]_D^{25} +15.3^{\circ}$ (c 0.647, CHCl₃, 84% ee);

^1H NMR (300 MHz, CDCl_3) $\square$ = (syn isomer) 7.93 (m, 2 H), 7.64 (m, 1 H), 7.52 (m, 2 H), 6.78 (d, J = 8.8 Hz, 2 H), 6.68 (d, J = 8.8 Hz, 2 H), 5.38 (d, J = 2.0 Hz, 1 H), 4.46 (d, J = 2.0 Hz, 1 H), 4.01 (m, 2 H), 3.72 (s, 3 H), 1.11 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) $\square$ = (syn isomer) 198.5, 169.5, 153.4, 140.0, 134.2, 134.1, 129.1, 129.0, 128.4, 128.3, 116.5, 114.8, 74.2, 61.9, 61.4, 55.6, 13.9; IR (neat, 4 cm^{-1}): $\square$ = 3457, 3373, 2983, 2935, 2834, 1747, 1687, 1598, 1514, 1464, 1450, 1408, 1370, 1241, 1183, 1102, 1034, 970, 824, 770, 694; HRMS (EI) m/z 343.1423 [M^+ ; calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5$, 343.1420].

Syn diastereomer: t_r = 14.4 min (major enantiomer) and 18.2 min, (Chiralcel AD, $\square$ = 254 nm, heptane:*i*-

PrOH = 80:20, 1 mL/min); ^1H NMR (300 MHz, CDCl_3) $\square$ = (syn isomer) 7.85 (dd, J = 1.9, 7.8 Hz, 1 H), 7.55 (dt, J = 1.9, 8.8 Hz, 1 H), 7.08 (t, J = 7.8 Hz, 1 H), 7.01 (d, J = 7.8 Hz, 1 H), 6.70 (d, J = 1.9 Hz, 1 H), 6.61 (dd, J = 2.9, 8.8 Hz, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 5.43 (d, J = 3.9 Hz, 1 H), 4.48 (s, 1 H), 4.36 (br s, 1 H), 4.10 – 3.92 (m, 2 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 2.26 (s, 3 H), 1.12 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) $\square$ = 199.5, 170.1, 158.4, 152.8, 138.6, 134.9, 131.8, 126.4, 124.4, 121.2, 116.7, 114.2, 111.6 (2), 78.4, 61.3, 55.6 (2), 17.7, 14.0; IR (neat, 4 cm^{-1}): $\square$ = 3426, 2977, 2940, 2831, 1996, 1745, 1667, 1598, 1512, 1486, 1465, 1438, 1291, 1245, 1224, 1184, 1163, 1097, 1052, 1021, 975, 866, 803, 760; HRMS (EI) m/z 387.1680 [M^+ ; calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_6$, 387.1682].

Syn diastereomer: t_r = 18.6 min and 27.3 min (major enantiomer), (Chiralcel OD, $\square$ = 254 nm, heptane:*i*-PrOH = 90:10, 0.9 mL/min); ^1H NMR (300 MHz, CDCl_3) $\square$ = (syn isomer) 7.45 (m, 3 H), 7.17 (dd, J = 2.9, 7.8 Hz, 1 H), 6.71 (d, J = 2.9 Hz, 1 H), 6.63 (dd, J = 2.9, 8.8 Hz, 1 H), 6.56 (d, J = 7.8 Hz, 1 H), 6.56 (d, J = 7.8 Hz, 1 H), 5.36 (d, J = 1.9 Hz, 1 H), 4.51 (d, J = 2.9 Hz, 1 H), 4.02 (m, 2 H), 3.85 (s, 3 H), 3.72 (s, 3 H), 2.27 (s, 3 H), 1.13 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) $\square$ = (syn isomer) 198.5, 169.6, 160.0, 153.0, 138.1, 135.5, 130.0, 126.5, 120.6, 120.4, 116.9, 114.1, 112.7, 111.6, 74.3, 61.9, 61.4, 55.5, 55.4, 17.7, 13.9; ^1H NMR (300 MHz, CDCl_3) $\square$ = minor diastereomer (non-overlapping peaks): 6.37 (dd, J = 2.9, 8.8 Hz, 1 H), 5.95 (d, J = 8.8 Hz, 1 H), 5.54 (s, 1 H), 4.24 (m, 2 H), 3.81 (s, 3 H), 3.64 (s, 3 H), 2.12 (s, 3 H), 1.29 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) $\square$ = 171.1, 120.8, 120.7, 120.0, 116.6, 113.7, 111.3, 17.5, 14.1; IR (neat, 4 cm^{-1}): $\square$ = 3426, 2938, 2833, 1996, 1746, 1687, 1593, 1582, 1511, 1483, 1448, 1432, 1273, 1223, 1192, 1157, 1098, 1047, 867, 790; HRMS (EI) m/z 387.1679 [M^+ ; calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_6$, 387.1682].

Diastereomeric mixture (dr = 1:1); syn diastereomer: t_r = 22.1 min (major enantiomer) and 29.6 min, (Chiralcel OD, λ = 254 nm, heptane:*i*-PrOH = 90:10, 0.9 mL/min); ^1H NMR (300 MHz, CDCl_3) δ = 7.94 (t, J = 8.8 Hz, 4 H), 6.98 (dd, J = 3.9, 8.8 Hz, 4 H), 6.71 (d, J = 1.9 Hz, 1 H), 6.63 (dd, J = 1.9, 8.8 Hz, 1 H), 6.58 (d, J = 2.9 Hz, 1 H), 6.54 (d, J = 8.8 Hz, 1 H), 6.40 (dd, J = 1.9, 8.8 Hz, 1 H), 5.98 (d, J = 8.8 Hz, 1 H), 5.51 (s, 1 H), 5.35 (d, J = 5.9 Hz, 1 H), 4.47 (s, 2 H), 4.32 – 4.20 (m, 3 H), 4.11 – 3.94 (m, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.72 (s, 3 H), 3.64 (s, 3 H), 2.27 (s, 3 H), 2.12 (s, 3 H), 1.29 (t, J = 6.8 Hz, 3 H), 1.10 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ = 196.6, 196.2, 171.3, 169.7, 164.3 (2), 152.9, 152.6, 138.3, 138.2, 130.9, 130.7, 129.9, 126.9, 126.5, 126.0, 125.8, 116.9, 116.6, 114.3, 114.1, 113.9, 113.5, 111.5, 111.3, 76.6, 73.8, 73.7, 61.9, 61.8, 61.5, 61.3, 55.5, 55.4, 17.7, 17.6, 14.2, 13.9; HRMS (EI) m/z 387.1679 [M^+ ; calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_6$, 387.1682].

Anti diastereomer: t_r = 16.6 min (major enantiomer) and 19.7 min, (Chiralcel OD, λ = 254 nm, heptane:*i*-PrOH = 90:10, 0.9 mL/min) 55% ee.

Diastereomeric mixture (dr = 5:1); syn diastereomer: t_r = 47.5 min and 58.7 min (major enantiomer), (Chiralcel OD, λ = 254 nm, heptane:*i*-PrOH = 90:10, 1 mL/min); ^1H NMR (300 MHz, CDCl_3) δ = (syn isomer) 7.69 (d, J = 2.0 Hz, 1 H), 7.40 (d, J = 3.9 Hz, 1 H), 6.70 (m, 3 H), 6.63 (dd, J = 2.0, 3.9 Hz, 1 H), 5.15 (d, J = 3.9 Hz, 1 H), 4.74 (d, J = 3.9 Hz, 1 H), 4.04 (m, 2 H), 3.72 (s, 3 H), 2.26 (s, 3 H), 1.10 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ = (syn isomer) 186.7, 169.9, 152.8, 150.8, 147.1, 138.1, 126.1, 118.9, 117.0, 113.4, 112.9, 111.6, 74.4, 61.5, 61.3, 55.5, 17.7, 13.8; IR (neat, 4 cm^{-1}): ν = 3420, 3137, 2981, 1996, 1745, 1674, 1570, 1513, 1465, 1386, 1289, 1224, 1161, 1098, 1020, 883, 768; HRMS (EI) m/z 347.1369 [M^+ ; calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_6$, 347.1369].

General procedure for the imine aldol (Mannich-type) reaction of aldimines:

Preparation of the catalyst:

To a room temperature solution of ligand **1a** (10 mg, 0.015 mmol) in THF (0.3 mL) was added dropwise a solution of diethylzinc (30 μL , 0.030 mmol, 1.0 M hexanes) and continued to stir for 30 minutes.

Mannich-type (Imine Aldol) reaction:

To a $-78\text{ }^{\circ}\text{C}$ suspension of imine **6b** (64 mg, 0.30 mmol), 2-hydroxyacetophenone (82 mg, 0.60 mmol) and crushed 4Å molecular sieves (60 mg) in THF (0.6 mL) was added the zinc catalyst from above. After stirring at $-5\text{ }^{\circ}\text{C}$ for 18 – 24 hours, the reaction mixture was diluted with Et₂O (6 mL) and then a phosphate buffer (pH = 7) solution (3 mL). After stirring for 30 minutes, the phases were separated and the aqueous phase was extracted with Et₂O (1 mL x 2). The combined organics were

washed with brine (1.5 mL), dried over MgSO₄, filtered and concentrated to give an oil. The crude residue was purified by flash chromatography on silica gel [PE / EtOAc 10 %] to give 69 mg (66%) of imine aldol **7** as a yellow oil.

Syn diastereomer: t_r = 21.1 min and 40.0 min (major), (Chiralcel OD, λ = 254 nm, heptane:*i*-PrOH = 90:10, 0.9 mL/min); $[\alpha]_D^{25}$ -44.8° (c 0.862, CHCl₃, >99% ee); ¹H NMR (300 MHz, CDCl₃) δ = 7.91 (d, J = 7.8 Hz, 2 H), 7.67 (t, J = 7.8 Hz, 1 H), 7.54 (t, J = 7.8 Hz, 2 H), 7.16 (m, 3 H), 6.96 (m, 2 H), 6.77 (dd, J = 1.9, 6.8 Hz, 1 H), 6.63 (m, 2 H), 6.31 (m, 1 H), 5.64 (s, 1 H), 4.95 (s, 1 H), 3.91 (s, 3 H), 3.70 (br s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ = 198.7, 147.1, 136.4, 136.0, 134.2, 129.1, 128.6, 128.0, 127.8, 127.4, 120.9, 117.1, 111.2, 109.5, 76.3, 60.2, 55.4;

Diastereomeric mixture (dr = 5:1); $[\alpha]_D^{25}$ -9.58° (c 0.748, CHCl₃, 99% ee); syn diastereomer: t_r = 18.1 min (major enantiomer) and 20.9 min, (Chiralcel OD, λ = 254 nm, heptane:*i*-PrOH = 90:10, 0.9 mL/min); ¹H NMR (300 MHz, CDCl₃) δ = 7.88 (m, 3 H), 7.52 (t, J = 7.8 Hz, 3 H), 7.14 (m, 2 H), 6.90 (m, 2 H), 6.66 (d, J = 8.8 Hz, 2 H), 6.54 (d, J = 8.8 Hz, 2 H), 5.58 (br s, 1 H), 4.82 (dd, J = 1.9, 6.8 Hz, 1 H), 3.66 (s, 3 H); minor diastereomer (non-overlapping peaks): 7.64 (m, 4 H), 7.37 (d, J = 7.8 Hz, 2 H), 7.31 (t, J = 7.8 Hz, 2 H), 6.31 (d, J = 8.8 Hz, 2 H), 5.32 (d, J = 2.9 Hz, 1 H), 3.61 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ = (both diastereomers) 200.0, 198.7, 152.3, 152.2, 140.2, 140.1, 136.4, 134.2, 134.1, 133.9, 133.8, 129.1, 128.9, 128.6, 128.5, 128.4, 128.0, 127.8, 127.6, 127.5, 127.4, 126.9, 115.4, 115.3, 114.7, 114.5, 76.0, 61.3, 60.7, 55.5; IR (neat, 4 cm⁻¹): ν = 3390, 3062, 3029, 2932, 2833, 1683, 1619, 1598, 1580, 1513, 1451, 1407, 1241, 1180, 1103, 1075, 1036, 1002, 988, 821, 790, 759, 699, 668; HRMS (EI) m/z 347.1529 [M⁺; calcd for C₂₂H₂₁NO₃, 347.1521].

Anti diastereomer: t_r = 27.2 min and 34.9 min (major enantiomer), (Chiralcel OD, λ = 254 nm, heptane:*i*-PrOH = 90:10, 0.9 mL/min), 95% ee.

Syn diastereomer: t_r = 27.1 min and 47.9 min (major enantiomer), (Chiralcel OD, λ = 254 nm, heptane:*i*-PrOH = 90:10, 0.9 mL/min); $[\alpha]_D^{25}$ -104.5° (c 0.633, CHCl₃, >99% ee); ¹H NMR (300 MHz, CDCl₃) δ = 7.90 (dd, J = 1.9, 8.8 Hz, 2 H), 7.68 (t, J = 7.8 Hz, 1 H), 7.54 (t, J = 7.8 Hz, 2 H), 7.10 (d, J = 8.8 Hz, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 6.76 (m, 1 H), 6.62 (m, 2 H), 6.23 (m, 1 H), 5.60 (d, J = 3.9 Hz, 1 H), 5.50 (br s, 1 H), 4.88 (d, J = 2.9 Hz, 1 H), 3.90 (s, 3 H), 3.68 (d, J = 7.8 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ = 198.5, 147.2, 135.7, 135.1, 134.5, 134.0, 133.6, 129.3, 128.8, 128.6, 128.3, 120.8, 117.4, 111.3, 109.6, 76.1, 59.8, 55.5; IR (neat, 4 cm⁻¹): ν = 3429, 3064, 2936, 2835, 1684, 1600, 1579, 1512, 1490, 1456, 1430, 1409, 1343, 1270, 1244, 1225, 1178, 1134, 1108, 1093, 1050, 1028, 1014, 990, 952, 880, 825, 789, 740, 695, 670.

Syn diastereomer: t_r = 14.4 min (major enantiomer) and 17.8 min, (Chiralcel OD, λ = 254 nm, heptane:*i*-PrOH = 90:10, 0.9 mL/min); $[\alpha]_D^{25}$ +170.6° (c 0.942, CHCl₃, 98.6% ee); ¹H NMR (300 MHz, CDCl₃) δ = 7.66 (d, J = 7.8 Hz, 1 H), 7.59 (dt, J = 1.9, 8.8 Hz, 1 H), 7.09 (d, J = 7.8 Hz, 2 H), 7.04 (m, 2 H), 6.90 (d, J = 7.8 Hz, 2 H), 6.75 (dd, J = 1.9, 7.8 Hz, 1 H), 6.61 (dt, J = 1.9, 6.8 Hz, 2 H), 6.27 (dd, J = 1.9, 7.8 Hz, 1 H), 5.71 (dd, J = 2.9, 6.8 Hz, 1 H), 5.54 (br s, 1 H), 4.84 (br s, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ = 199.1, 159.0, 147.1, 136.2, 135.9, 135.4, 133.2, 131.8, 129.2, 128.5, 128.2, 127.9, 124.2, 121.3, 120.8, 116.9, 111.9, 111.1, 109.5, 79.7, 58.7, 55.7, 55.4; IR (neat, 4 cm⁻¹): ν = 3432, 3068, 3006, 2942, 2839, 1666, 1598, 1513, 1486, 1456, 1435, 1408, 1344, 1293, 1245, 1223, 1178, 1164, 1120, 1092, 1052, 1023, 978, 881, 825, 805, 781, 760, 739, 653;

Anti diastereomer: t_r = 13.0 min (major enantiomer) and 28.7 min, (Chiralcel OD, λ = 254 nm, heptane:*i*-PrOH = 90:10, 0.9 mL/min).

Syn diastereomer: t_r = 31.0 min and 49.1 min (major enantiomer), (Chiralcel OD, λ = 254 nm, heptane:*i*-PrOH = 90:10, 0.9 mL/min); $[\alpha]_D^{25}$ -125.19° (c 1.0, CHCl₃, 97.4% ee); ¹H NMR (300 MHz, CDCl₃) δ = 7.68

(s, 1 H), 7.30 (d, $J = 3.9$ Hz, 1 H), 7.14 (d, $J = 7.8$ Hz, 2 H), 6.99 (d, $J = 7.8$ Hz, 2 H), 6.77 (dd, $J = 1.9, 6.8$ Hz, 1 H), 6.70 – 6.60 (m, 3 H), 6.37 (dd, $J = 1.9, 6.8$ Hz, 1 H), 5.57 (br s, 1 H), 5.35 (s, 1 H), 5.05 (d, $J = 2.9$ Hz, 1 H), 3.89 (s, 3 H), 3.59 (br d, $J = 5.9$ Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ = 186.7, 150.5, 147.5, 147.1, 135.7, 135.6, 133.5, 128.7, 128.4, 120.8, 119.4, 117.3, 113.0, 111.1, 109.5, 76.1, 59.5, 55.4; IR (neat, 4 cm^{-1}): ν = 3422, 3133, 2936, 2836, 1671, 1602, 1570, 1512, 1490, 1458, 1430, 1385, 1344, 1286, 1247, 1225, 1176, 1134, 1110, 1090, 1050, 1023, 909, 883, 859, 794, 769, 739;

Preparation of oxazolidinone (8):

To a $-78\text{ }^\circ\text{C}$ solution of amino alcohol **5** (220 mg, 0.615 mmol) in CH_2Cl_2 (6 mL) were added *i*- Pr_2NEt (0.32 mL, 1.85 mmol) and a solution of triphosgene (270 mg, 0.923 mmol) in CH_2Cl_2 (1 mL) dropwise. The reaction was slowly allowed to warm to room temperature (overnight) and then quenched with NH_4OH (30 %, 1 mL) and water (1 mL). Et_2O (15 mL) was added, and the phases were separated. The organic phase was washed with brine (1 mL), dried over MgSO_4 , filtered and concentrated to give 0.46 g of a yellow oil. The residue was purified by flash chromatography on silica gel [PE / EtOAc 15 % δ 25 %] to give 230 mg (60 %) of oxazolidinone **8** as a yellow oil. $[\alpha]_D^{25} -33.9^\circ$ (c 0.923, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ = 8.11 (dd, $J = 1.0, 8.3$ Hz, 2 H), 7.66 (t, $J = 7.3$ Hz, 1 H), 7.53 (t, $J = 7.8$ Hz, 2 H), 7.29 (d, $J = 8.3$ Hz, 1 H), 6.74 (m, 2 H), 5.77 (d, $J = 3.9$ Hz, 1 H), 5.20 (d, $J = 3.4$ Hz, 1 H), 4.21 (q, $J = 6.8$ Hz, 2 H), 3.77 (s, 3 H), 2.25 (s, 3 H), 1.21 (t, $J = 6.8$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ = 191.0, 169.2, 159.5, 154.6, 138.0, 134.7, 133.1, 129.7, 129.4, 129.0, 126.8, 116.2, 112.1, 75.7, 62.5, 60.2, 55.3, 18.0, 13.9; IR (neat, 4 cm^{-1}): ν = 3065, 2978, 2936, 2850, 1775, 1694, 1608, 1598, 1581, 1506, 1450, 1421, 1395, 1285, 1230, 1163, 1142, 1103, 1021, 984, 960, 850, 817, 754, 729, 690, 657, 633; ; HRMS (EI) m/z 383.1357 [M^+ ; calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_6$, 383.1369].

CAN promoted nitrogen dearylation to give oxazolidinone (9):

To a cold ($0\text{ }^\circ\text{C}$) solution of aryl carbamate **8** (420 mg, 1.05 mmol) in CH_3CN (10 mL) was added dropwise a solution of ceric ammonium nitrate (CAN) (2.3 g, 4.20 mmol) in water (13 mL) over 5 minutes. The ice bath was removed and stirred at room temperature for 60 minutes. The reaction was quenched with saturated aqueous solutions of $\text{Na}_2\text{S}_2\text{O}_3$ (13 mL) and NaHCO_3 (10 mL). The reaction mixture was extracted with EtOAc (25 mL x 3). The combined organics were washed with brine (5 mL x 2), dried over MgSO_4 , filtered and concentrated to give a yellow oil. Purification by flash chromatography on silica gel [PE / EtOAc 25 %] afforded 125 mg (44 %) of the dearylated oxazolidinone **9** as a yellow oil. $[\alpha]_D^{25} -39.5^\circ$

(c 0.88, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 8.07 (d, *J* = 8.8 Hz, 2 H), 7.64 (t, *J* = 7.8 Hz, 1 H), 7.50 (m, 2 H), 5.86 (d, *J* = 3.9 Hz, 1 H), 5.79 (br s, 1 H), 4.92 (d, *J* = 3.9 Hz, 1 H), 4.29 (q, *J* = 6.8 Hz, 2 H), 1.31 (t, *J* = 6.8 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ = 190.8, 169.5, 156.3, 134.7, 133.2, 129.6, 128.9, 77.8, 62.8, 54.2, 14.1; IR (neat, 4 cm⁻¹): ν = 3355, 2986, 2926, 2850, 1778, 1698, 1597, 1450, 1374, 1228, 1109, 1021, 975, 758, 690; ; HRMS (EI) *m/z* 263.0786 [M⁺; calcd for C₁₃H₁₃NO₅, 263.0794].

Baeyer-Villiger oxidation of (9) to give phenyl ester (10):

To a flame dried flask with crushed molecular sieves 4Å (300 mg) were added trans-N,N-bis(*p*-toluenesulfonyl)-1,2-cyclohexanediamine (128 mg, 0.304 mmol) and CH₂Cl₂ (2 mL). The suspension was lowered to -20 °C and then a solution of SnCl₄ (0.30 mL, 1.0 M CH₂Cl₂, 0.30 mmol) and bis(trimethylsilyl) peroxide (BTSP) (0.26 mL, 1.22 mmol) were added. After stirring for 5 minutes, a solution of aryl ketone **9** (80 mg, 0.304 mmol) in CH₂Cl₂ (3 mL) was added. After stirring for an additional 2 hours between -20 °C and -10 °C, the reaction was quenched with a saturated aqueous solution of Na₂S₂O₃ (2 mL) and NaHCO₃ (2 mL). EtOAc (15 mL) was added and the phases were separated. The organics were washed with water (2 mL) and brine (2 mL), dried over Na₂SO₄, filtered and concentrated to give a yellow solid. EtOAc was added to the solid residue and decanted. Concentration of the solvent and purification by flash chromatography on silica gel [PE / EtOAc 25%] afforded 55 mg (65 %) of the desired Bayer-Villager adduct **10** as an oil. $[\alpha]_D^{25}$ -18.1° (c 0.40, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 7.40 (t, *J* = 7.8 Hz, 2 H), 7.29 (dd, *J* = 3.9, 7.8 Hz, 1 H), 7.14 (d, *J* = 7.8 Hz, 2 H), 5.81 (s, 1 H), 5.38 (d, *J* = 3.9 Hz, 1 H), 4.66 (d, *J* = 3.9 Hz, 1 H), 4.33 (q, *J* = 6.8 Hz, 2 H), 1.34 (t, *J* = 6.8 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ = 168.5, 166.1, 149.9, 129.6, 127.2, 126.6, 120.9, 74.8, 63.0, 56.5, 14.0; IR (neat, 4 cm⁻¹): ν = 3334, 2925, 2854, 1784, 1493, 1375, 1214, 1189, 1094, 1023, 932, 756, 689.

Determination of absolute stereochemistry:

Preparation of TBS-silyl ether (11):

To a cold (0 °C) solution of amino alcohol **7** (0.45 g, 1.20 mmol) in CH₂Cl₂ (5 mL) were added 2,6-lutidine (0.29 mL, 2.5 mmol) and TBSOTf (0.54 mL, 2.4 mmol). After stirring for 60 minutes at 0 °C, the reaction was quenched with water (1 mL) and a saturated aqueous NH₄Cl solution (1 mL). Et₂O (10 mL) was added and the phases separated. The organic phase was washed with brine (1 mL), dried over MgSO₄, filtered and concentrated to give 0.9 g of a yellow oil. Purification by flash chromatography on

silica gel [PE / EtOAc 5%] afforded 0.46 g (79%) of TBS-protected alcohol **11** as an oil. $[\alpha]_D^{25}$ -55.40° (c 0.740, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 7.82 (d, *J* = 7.8 Hz, 2 H), 7.52 (t, *J* = 7.8 Hz, 1 H), 7.38 (t, *J* = 7.8 Hz, 2 H), 7.17 (s, 4 H), 6.71 (dd, *J* = 1.9, 7.8 Hz, 1 H), 6.60 (m, 2 H), 6.27 (dd, *J* = 1.9, 7.8 Hz, 1 H), 5.30 (d, *J* = 8.8 Hz, 1 H), 5.09 (d, *J* = 4.9 Hz, 1 H), 4.86 (dd, *J* = 5.9, 8.8 Hz, 1 H), 3.84 (s, 3 H), 0.88 (s, 9 H), -0.10 (s, 3 H), -0.17 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ = 199.9, 147.1, 137.3, 135.5, 133.4, 133.1, 130.9, 129.4, 129.3, 129.0, 128.4, 128.2, 120.9, 117.1, 111.3, 109.5, 80.8, 60.0, 55.4, 25.7, 18.2, -4.9, -5.8; IR (neat, 4 cm⁻¹): ν = 3412, 3066, 2955, 2930, 2857, 1704, 1673, 1602, 1513, 1491, 1456, 1430, 1254, 1224, 1179, 1133, 1092, 1029, 980, 878, 836, 781, 736, 692.

Nitrogen dearylation to give primary amine (**12**):

To a cold (0 °C) solution of amine **11** (360 mg, 0.726 mmol) in CH₃CN (7 mL) was added dropwise a solution of ceric ammonium nitrate (CAN) (1.6 g, 2.90 mmol) in water (9 mL) over 5 minutes. After stirring for 10 minutes at 0 °C, the reaction was quenched with a saturated aqueous Na₂S₂O₃ solution (8 mL). The reaction mixture was extracted with EtOAc (20 mL x 4). The combined organics were washed with a saturated aqueous NaHCO₃ solution (5 mL x 2) and brine (5 mL x 2), dried over MgSO₄, filtered and concentrated to give a yellow oil. Purification by flash chromatography on silica gel [PE / EtOAc 25 %] afforded 200 mg (71%) of primary amine **12** as an oil. $[\alpha]_D^{25}$ -59.8° (c 0.50, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 7.97 (d, *J* = 7.8 Hz, 2 H), 7.53 (t, *J* = 7.8 Hz, 1 H), 7.40 (t, *J* = 7.8 Hz, 2 H), 7.23 (s, 4 H), 4.74 (d, *J* = 6.8 Hz, 1 H), 4.31 (d, *J* = 6.8 Hz, 1 H), 1.80 (br s, 2 H), 0.75 (s, 9 H), -0.21 (s, 3 H), -0.24 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ = 200.1, 140.8, 135.4, 133.3, 133.2, 129.2, 128.9, 128.4, 128.2, 100.3, 82.3, 59.3, 25.6, 18.0, -5.0, -5.6; IR (neat, 4 cm⁻¹): ν = 3394, 3341, 2930, 2857, 1680, 1597, 1492, 1471, 1448, 1411, 1254, 1114, 1094, 1015, 837, 779, 691.

General procedure for the preparation of the O-methyl mandelate amides:

To a solution of amine **12** (25 mg, 0.064 mmol), (S)-O-methyl mandelic acid (11 mg, 0.067 mmol) and HOBT (9 mg, 0.067 mmol) in CH₂Cl₂ (0.6 mL) were added i-Pr₂NEt (0.012 mL, 0.070 mmol) and EDCI•HCl (13 mg, 0.067 mmol). After stirring for 20 minutes at room temperature, the reaction was diluted with EtOAc (2 mL) and then washed with 1 M HCl (0.2 mL x 2), NaHCO₃ (aq. sat.) (0.2 mL x 2), water (0.2 mL) and brine (0.4 mL). The organics were dried over MgSO₄, filtered and concentrated to give an oil. Purification by flash chromatography on silica gel [PE / EtOAc 5%] afforded 30 mg (90%) of the mandelate amide derived from the (S)-acid.

$[\alpha]_D^{25} +41.5^\circ$ (c 0.925, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ = 7.88 (d, J = 6.8 Hz, 2 H), 7.65 (d, J = 8.8 Hz, 1 H), 7.53 (t, J = 7.8 Hz, 1 H), 7.41 (d, J = 7.8 Hz, 2 H), 7.29 (s, 4 H), 7.15 (d, J = 8.8 Hz, 2 H), 7.03 (d, J = 7.8 Hz, 2 H), 5.45 (d, J = 4.9 Hz, 1 H), 5.39 (dd, J = 3.9, 7.8 Hz, 1 H), 4.62 (s, 1 H), 3.35 (s, 3 H), 0.95 (s, 9 H), 0.0 (s, 6 H); ^{13}C NMR (75 MHz, CDCl_3) δ = 198.0, 169.9, 136.5, 135.1, 135.0, 134.0, 133.5, 129.4, 128.8, 128.6, 128.4, 127.1, 124.7, 83.6, 77.8, 57.0, 55.5, 25.7, 18.4, -4.7, -5.7; IR (neat, 4 cm^{-1}): ν = 3424, 2930, 2857, 1682, 1598, 1493, 1471, 1448, 1255, 1197, 1141, 1095, 1016, 982, 837, 781, 697.

$[\alpha]_D^{25} -37.0^\circ$ (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ = 7.79 (d, J = 7.8 Hz, 2 H), 7.71 (d, J = 7.8 Hz, 1 H), 7.51 (t, J = 7.8 Hz, 1 H), 7.36 (m, 4 H), 7.19 (d, J = 8.8 Hz, 2 H), 7.10 (d, J = 8.8 Hz, 2 H), 5.33 (dd, J = 4.9, 7.8 Hz, 1 H), 5.24 (d, J = 4.9 Hz, 1 H), 4.56 (s, 1 H), 3.34 (s, 3 H), 0.92 (s, 9 H), -0.05 (s, 3 H), -0.08 (s, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ = 198.1, 169.8, 136.5, 135.9, 135.0, 133.9, 133.5, 129.4, 128.7, 128.6, 128.5, 128.4, 127.0, 83.5, 78.5, 57.2, 55.4, 25.7, 18.3, -4.7, -5.6.