Supporting Information

Catalytic Asymmetric Addition of Dialkylzinc Reagents to α -Aldiminoesters

Sandeep Basra, Michael W. Fennie, and Marisa C. Kozlowski*

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA

General Considerations. Unless otherwise noted, all non-aqueous reactions were carried out under an atmosphere of dry N₂ in dried glassware. All manipulations involving Et₂Zn were carried out using standard Schlenk techniques. When necessary, solvents and reagents were dried prior to use. Toluene was distilled from Na. Ti(Oi-Pr)₄ was distilled and stored as a 1.0 M solution in hexanes. Et₂Zn was used as a freshly prepared 1.0 M solution in toluene. Bu₂Mg was used as a 1.0 M solution in toluene, purchased from Aldrich. Al(Oi-Pr)₃ was purchased from Aldrich. Salen ligands for metal complexes **1-5** were prepared as previously described (see references 11 and 15 in main text). (–)-MIB was provided by Professor Patrick Walsh, from the University of Pennsylvania. All additives (Table 2) were purchased and used without further purification (morpholine, Et₃N and benzyl alcohol were distilled prior to use). Substrate **6** was prepared according to literature procedure,¹ as were substrates used in entries 9-11¹ and entries 12-14² of Table 3.

Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica-gel 60-F plates. Visualization was accomplished with UV light. Chromatography on silica gel was performed using a forced flow of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh).³ Enantiomeric excesses were measured using an Agilent 1100 high performance liquid chromatograph (HPLC) with UV detection at 254 nm and Daicel Chiralpak OD column (0.46 cm x 25 cm). ¹H NMR spectra were recorded on Bruker AM-500 (500 MHz) spectrometers at ambient temperature. Chemical shifts are reported in ppm from the solvent resonance (CDCl₃ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Proton decoupled ¹³C NMR spectra were recorded on a Bruker AM-500 (125 MHz) spectrometer at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane (0 ppm) or from the solvent resonance (CDCl₃ 77.16 ppm). IR spectra were taken on a ASI ReactIR 1000 equipped Si-Comp probe. Optical rotations were measured on a Perkin-Elmer Polarimeter 341 with a sodium lamp and are reported as follows [α]_{T_λ} (c g/100 mL solvent). High resolution mass spectra were performed by Dr. Kohli at the Mass Spectrometry Laboratory at the University of Pennsylvania.

General Procedure for the Addition of Diethylzinc to α -Aldiminoesters

The salen (0.025 mmol) was introduced into a dry Schlenk flask, and the system purged with N₂. The salen was dissolved in dry toluene (1 mL) and Ti(O*i*-Pr)₄ (15 μ L, 1.0 M in toluene, 0.025 mmol) was added. After stirring at room temperature for 1 h, the catalyst solution was cooled to -40 °C and the additive (0.125 mL, 1.0 M in toluene, 0.125 mmol) was added and stirred for 1 min, followed by Et₂Zn (0.5 mL, 1.0 M in toluene, 0.5 mmol). After 5 min, the α -aldiminoester (0.25 mmol) in 0.2 mL of toluene was added and stirred at -40 °C. After 4 h the reaction was quenched with saturated NH₄Cl and extracted with CH₂Cl₂. The organic extracts were dried over Na₂SO₄, and concentrated. Purification by preparative TLC on SiO₂ (50% EtOAc/hexanes) or flash chromatography on SiO₂ (20% EtOAc/hexanes) afforded the 1,2-addition product and imidazolidines as yellow oils.

(*S*) [α]_D²⁰ -27.9 (*c* 0.8, 59% ee, CH₂Cl₂); (*R*) [α]_D²⁰ +32.1 (*c* 0.7, 67% ee, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.76 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.92 (t, *J* = 6.3 Hz, 1H), 3.73 (s, 3H), 1.89-1.76 (m, 2H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.4, 152.8, 141.2, 115.2, 115.0, 61.0, 59.1, 55.8, 26.3, 14.4, 10.1; IR (film) 3374 (br), 2972 (br), 1733, 1513, 1235 cm⁻¹; HRMS (ES) calcd for C₁₃H₁₉O₃N (M⁺) 237.1364, found 237.1350; HPLC (Chiralpak OD, 1.0 mL/min, 97:3 hexanes:*i*-PrOH): t_R(*S*) = 10.2 min, t_R(*R*) = 12.8 min.

(*R*) [α]_D²⁰ -14.3 (*c* 0.68, 60% ee, CH₂Cl₂); (*S*) [α]_D²⁰ +15.8 (*c* 0.53, 71% ee, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.38 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.2 Hz, 2H), 5.62 (s, 1H), 4.25 (t, *J* = 5.2 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.12-2.04 (m, 2H), 1.16-1.12 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 171.1, 169.4, 158.4, 153.6, 139.9, 128.0, 125.3, 115.3, 114.6, 114.2, 78.2, 62.3, 62.1, 55.9, 55.6, 25.2, 14.0, 9.5; IR (film) 2937 (br), 1718, 1513, 1251 cm⁻¹; HRMS (ES) calcd for C₂₂H₂₆O₅N₂ (M⁺) 398.1841, found 398.1830; HPLC (Chiralpak OD, 1.0 mL/min, 95:5 hexanes:*i*-PrOH): t_R(*R,R*) = 50.9 min, t_R(*S,S*) = 69.1 min.

[α]_D²⁰ -32.5 (*c* 0.73, 73% ee, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.78 (d, *J* = 6.6 Hz, 2H), 6.60 (d, *J* = 6.6 Hz, 2H), 3.94 (t, *J* = 6.3 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 1.88-1.75 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.9, 152.7, 141.1, 115.1, 115.0, 59.0, 55.7, 52.0, 26.3, 10.1; IR (film) 3377 (br), 2973 (br), 1737, 1513, 1266 cm⁻¹; HRMS (ES) calcd for C₁₂H₁₇O₃N (M⁺) 223.1208, found 223.1214; HPLC (Chiralpak OD, 1.0 mL/min, 97:3 hexanes:*i*-PrOH): t_R(*S*) = 13.7 min, t_R(*R*) = 15.5 min.

$[\alpha]_D^{20}$ -10.4 (*c* 1.22, 63% ee, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.38 (d, *J* = 12 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.65 (s, 1H), 4.25 (t, *J* = 5.2 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.70 (s, 3H), 2.11-2.04 (m, 2H), 1.13 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.1, 169.9, 158.4, 153.6, 139.8, 127.9, 125.2, 115.3, 114.7, 114.2, 78.0, 62.4, 55.8, 55.5, 52.8, 25.3, 9.5; IR (film) 2926 (br), 1741, 1714, 1513, 1247 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{21}\text{H}_{24}\text{O}_5\text{N}_2$ (MNa^+) 407.1583, found 407.1594; HPLC (Chiralpak OD, 1.0 mL/min, 95:5 hexanes:*i*-PrOH): $t_R(R,R)$ = 61.6 min, $t_R(S,S)$ = 81.9 min.

$[\alpha]_D^{20}$ -13.4 (*c* 0.86, 74% ee, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.50-7.25 (m, 10H), 4.85 (s, 1H), 4.26-4.20 (m, 2H), 3.19 (t, *J* = 6.9 Hz, 1H), 2.13 (br.s, 1H), 1.77-1.68 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.02 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.7, 144.5, 143.0, 128.6, 128.5, 127.7, 127.4, 127.2, 65.6, 60.1, 60.0, 27.1, 14.5, 10.4; IR (film) cm^{-1} 3335 (br), 2976 (br), 1729, 1451, 1189, 1027; HRMS (ES) calcd for $\text{C}_{19}\text{H}_{23}\text{O}_2\text{N}_2$ (MH^+) 298.1807, found 298.1798;

To determine the enantiomeric excess, **7c** was converted to **S1**: To **7c** (15 mg, 0.05 mmol) in MeOH (5 mL) was added 10 % Pd/C (10 mg, 0.01 mmol). The suspension was placed under an atmosphere of H_2 and stirred for 10 h. The mixture was filtered through a plug of celite. The MeOH was removed in vacuo to leave a yellow oil which was dissolved in CH_2Cl_2 (0.5 mL). To this solution Et_3N (14 μL , 0.1 mmol) was added followed by benzoyl chloride (11.6 μL , 0.1 mmol). After stirring for 1 h, the resulting mixture was purified by preparative TLC to yield **S1**. ^1H NMR (500 MHz, CDCl_3) δ 7.81-7.80 (m, 2H), 7.51-7.41 (m, 3H), 7.25 (d, *J* = 6.7 Hz, 1H), 4.78 (m, 1H), 4.24 (m, 2H), 2.02 (m, 1H), 1.84 (m, 1H), 1.29 (t, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H); HPLC (Chiralpak OD, 1.0 mL/min, 97:3 hexanes:*i*-PrOH): $t_R(R)$ = 13.3 min, $t_R(S)$ = 16.7 min.

To determine absolute configuration, **S1** was correlated to commercially available (*R*)-aminobutyric acid **S2**: A solution of **S2** (10 mg, 0.1 mmol) in absolute EtOH (1 mL) was cooled to 0 $^\circ\text{C}$. Neat SOCl_2 (51 μL , 0.7 mmol) was added dropwise and the solution allowed to warm to rt before heating to reflux for 10 h. The mixture was cooled and the solvents removed in vacuo to give a white crystalline solid, which was dissolved in CH_2Cl_2 (0.5 mL). To this solution Et_3N (28

μL , 0.2 mmol) was added followed by benzoyl chloride (11.6 μL , 0.1 mmol). After stirring for 1 h, the resulting mixture was purified by preparative TLC to yield (*R*)-**S1**. HPLC (Chiralpak OD, 1.0 mL/min, 97:3 hexanes:*i*-PrOH): $t_{\text{R}}(R) = 13.3$ min. From this, **7c** was assigned as the (*S*) enantiomer. The stereochemistry of compounds **7a-b** were then assigned by analogy.

Figure 1: 500 MHz ¹H NMR of compound **6** in CDCl₃

Figure 2: 500 MHz ^1H NMR of substrate used in Table 3, entries 9-11 in CDCl_3

Figure 3: 500 MHz ^1H NMR of substrate used in Table 3, entries 12-14 in CDCl_3

Figure 4: 500 MHz ¹H NMR of compound **7a** in CDCl₃

Figure 5: 125 MHz ^{13}C NMR of compound **7a** in CDCl_3

Figure 6: 500 MHz ¹H NMR of compound **8a** in CDCl₃

Figure 7: 125 MHz ^{13}C NMR of compound **8a** in CDCl_3

Figure 8: 500 MHz ^1H NMR of compound **7b** in CDCl_3

Figure 9: 125 MHz ^{13}C NMR of compound **7b** in CDCl_3

Figure 10: 500 MHz ¹H NMR of compound **8b** in CDCl₃

Figure 11: 125 MHz ^{13}C NMR of compound **8b** in CDCl_3

Figure 12: 500 MHz ¹H NMR of compound **7c** in CDCl₃

Figure 13: 125 MHz ¹³C NMR of compound **7c** in CDCl₃

Figure 14: 500 MHz ¹H NMR of compound **S1** in CDCl₃

- (1) Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575-580. Both esters were distilled: ethyl ester (**6**) at 0.7 Torr, 135-140 °C to give yellow oil (3.7g, 74% yield); methyl ester (Table 3, entries 9-11) at 0.5 Torr, 125-135 °C to give yellow oil (6.2g, 70% yield)
- (2) Lautens, M.; Tayama, E.; Nguyen, D. *Org. Lett.* **2004**, *6*, 345-347
- (3) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.