SUPPLEMENTARY MATERIAL

A New Ligand Scaffold for Catalytic Asymmetric Alkylzinc Additions to Aldehydes

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Experimental parts and spectral data for ligands **6** and **7**. ^1H and ^{13}C NMR spectra.

General: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_D^{25}$ (c g/100mL). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^1H NMR spectra were recorded in CDCl_3 unless otherwise noted on a Bruker Avance-300 (300 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuteriochloroform: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded in CDCl_3 unless otherwise noted on a Bruker Avance-300 (75 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuteriochloroform: δ 77.0 ppm). Mass spectra were obtained on a VG-7070 or Fisons Autospec high resolution magnetic sector mass spectrometer.

Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described on EM silica gel 60 (230-240 mesh).¹ Analytical gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 5890 Series II gas chromatograph with a flame ionization detector and split mode capillary injection system, using a Chiraldex G-TA column (20 m x 0.25 mm) (Advanced Separation Technologies Inc.). Helium was used as the carrier gas at the indicated pressures. Analytical high performance liquid chromatograph (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm), using a Daicel Chiralcel OD-H column (250 x 4.6 mm) (Daicel Inc.). HPLC grade isopropanol and hexanes were used as the eluting solvents.

All experiments were carried out under a nitrogen atmosphere in oven or flame-dried glassware using standard inert atmosphere techniques for introducing reagents and solvents. Dichloromethane (CH_2Cl_2), hexanes, toluene, and triethylamine (Et_3N) were distilled from CaH_2 under N_2 . All other commercially obtained reagents were used as received.

Scheme 1

(1*R*,6*R*)-6-Benzylloxycarbonylaminocyclohex-3-enecarboxylic acid methyl ester (3). To a solution of **2** (1.25 g, 4.94 mmol) in THF (78.0 mL) and H_2O (21.9 mL) was added 30% H_2O_2 (1.34 g, 39.5 mmol) followed by addition of $\text{LiOH}\cdot\text{H}_2\text{O}$ (259 mg, 6.17 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 19 h, cooled to 0 °C, and treated with a 1.35 N solution of Na_2SO_3 in H_2O (35.6 mL) followed by 0.5 N NaHCO_3 in H_2O (62.1 mL). The THF was evaporated in vacuo. The aqueous residue was diluted with water and extracted with CH_2Cl_2 (4x). The aqueous residue was acidified to pH 1-2 by 5 M HCl and extracted with EtOAc (4x). The combined organic layers were dried (MgSO_4) and concentrated. The residue was purified by chromatography on SiO_2 ($\text{MeOH}/\text{CH}_2\text{Cl}_2$, 5:95) to give acid monomethyl ester as a colorless oil (895 mg, 98%): $[\alpha]_{\text{D}} -177$ (c 1.14,

¹ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

CH₂Cl₂); IR (neat) 3300 (br), 3032, 2953, 2847, 1739, 1716, 1439, 1309, 1200, 1177, 661 cm⁻¹; ¹H NMR δ 11.35 (br-s, 1 H), 5.68 (s, 2 H), 3.69 (s, 3 H), 2.90-2.82 (m, 2 H), 2.50-2.39 (m, 2 H), 2.25-2.16 (m, 2 H); ¹³C NMR δ 181.1, 175.3, 125.0, 124.8, 52.1, 41.1, 40.9, 27.8 (2 C); MS (EI) *m/e* (relative intensity) 166 ([M]⁺, 11), 153 (9), 138 (29), 124 (24), 107 (8), 91 (6), 79 (100), 65 (6), 57 (8); HRMS (EI) *m/z* calculated for C₉H₁₀O₃ (M-H₂O) 166.0630, found 166.0630.

A solution of this acid (895 mg, 4.86 mmol) in toluene (14 mL) was treated with DPPA (1.34 g, 4.86 mmol) and Et₃N (492 mg, 4.86 mmol) at room temperature under nitrogen. The mixture was stirred for 3 h, quenched with cold water, extracted with Et₂O (3x), and dried (MgSO₄). After concentration, the residue was further dried in vacuo for 20 min and dissolved in toluene (14 mL). The crude acyl azide was heated at reflux for 1.5 h. Then, benzyl alcohol (499 mg, 4.62 mmol) was added at 85 °C. The reaction mixture was stirred at 85 °C overnight (13.5 h), cooled to room temperature, and the solvent was removed in vacuo. The residue was purified by chromatography on SiO₂ (EtOAc/hexanes, 20:80) to give **3** as a colorless oil (1.15 g, contaminated with a trace of benzyl alcohol) that was used directly for the next step.

(1*R*,2*R*)-2-Methanesulfonylaminocyclohexanecarboxylic acid (4). A solution of **3** (325 mg, contaminated with a trace of benzyl alcohol) in EtOAc (11 mL) was treated with 10% Pd/C (35.9 mg, 0.0337 mmol) at room temperature. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 3 h, and passed through a pad of celite. The solvent was removed in vacuo. The residue was dried in vacuo, dissolved in CH₂Cl₂ (11 mL) and treated at 0 °C with Et₃N (227 mg, 2.25 mmol) and methanesulfonyl chloride (193 mg, 1.68 mmol). The resulting mixture was stirred at room temperature for 19 h, and the solvent was removed in vacuo. The residue was purified by chromatography on SiO₂

(EtOAc/hexanes, 30:70) to give the sulfonamide as a colorless oil (250 mg, contaminated with a trace of MsCl). A solution of this colorless oil (245 mg) in THF/H₂O (11 mL, 10:1) was treated with LiOH•H₂O (219 mg, 5.21 mmol) at room temperature. The reaction mixture was stirred at room temperature for 19 h, THF was removed in vacuo, and the residue was diluted with water, acidified to pH 1-2 by addition of 5.0 M HCl, and extracted with EtOAc (3x). The combined organic layers were dried (MgSO₄) and concentrated. The residue was purified by chromatography on SiO₂ (MeOH/CH₂Cl₂, 8:92) to give **4** as a white solid (183 mg, 76% over 3 steps): Mp 163.5-164.2 °C; [α]_D -74.3 (c 0.96, MeOH); IR (neat) 3295, 2936, 1725, 1294, 1218, 1148, 1120 cm⁻¹; ¹H NMR δ (MeOD) 3.51-3.42 (m, 1 H), 3.02 (s, 3 H), 2.38 (dt, 1 H, *J* = 3.7, 11.4 Hz), 2.24-2.21 (m, 1 H), 2.14-2.08 (m, 1 H), 1.89-1.81 (m, 2 H), 1.69-1.31 (m, 5 H); ¹³C NMR δ (MeOD) 178.0, 55.2, 51.0, 41.6, 35.5, 30.7, 25.9, 25.5.

(1*R*,2*R*)-*N*-[2-(4-Isopropyl-4,5-dihydrooxazol-2-

yl)cyclohexyl]methanesulfonamide (6). To a suspension of **4** (183.4 mg, 0.829 mmol) in CH₂Cl₂ (4.1 mL) was added dimethyl formamide (7.9 mg, 0.108 mmol) and oxalyl chloride (158 mg, 1.24 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 20 h. The solvent was removed in vacuo, and the crude acid chloride was redissolved in CH₂Cl₂ (3.1 mL). A solution of (*L*)-valinol (107 mg, 1.04 mmol) in CH₂Cl₂ (1.0 mL) was treated with Et₃N (252 mg, 2.49 mmol) and a solution of the acid chloride in CH₂Cl₂ (3.1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3.5 h and purified by chromatography on SiO₂ (Acetone/CH₂Cl₂, 40:60) to give **5** as a white solid (226 mg) (contaminated with a trace of (*L*)-valinol) that was used directly for the next step: ¹H NMR (MeOD) δ 3.78–3.76 (m, 1 H), 3.69-3.65 (m, 2 H), 3.55-3.51 (m, 1 H), 3.00 (s, 3 H), 2.34-2.25 (m, 2 H), 2.07-1.96 (m, 2 H), 1.89-1.82 (m, 2 H), 1.69-1.28 (m, 4 H), 1.09-

1.04 (m, 6 H); ^{13}C NMR (MeOD) δ 176.7, 63.0, 57.8, 54.9, 52.8, 41.9, 35.8, 31.6, 29.6, 26.3, 25.9, 20.0, 19.1; MS (EI) m/e (relative intensity) 288 ($[\text{M}-\text{H}_2\text{O}]^+$, 2.4), 275 (80), 245 (20), 227 (16), 204 (89), 176 (26), 150 (32), 140 (50), 127 (22), 109 (58), 81 (69), 72 (100), 56 (32); HRMS (EI) m/z calculated for $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$ (M-H₂O) 288.1508, found 288.1499.

A suspension of **5** (258 mg) and 4-(dimethylamino)pyridine (15.4 mg, 0.126 mmol) in CH_2Cl_2 (12 mL) was treated with Et_3N (213 mg, 2.10 mmol) and a solution of *p*-toluenesulfonyl chloride (192 mg, 1.01 mmol) in CH_2Cl_2 (5.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 41 h, and treated again with Et_3N (85 mg, 0.841 mmol), 4-(dimethylamino)pyridine (10.3 mg, 0.0841 mmol) and a solution of *p*-toluenesulfonyl chloride (80 mg, 0.421 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 47 h, quenched with a saturated aqueous solution of NH_4Cl , and extracted with EtOAc (3x). The combined organic layers were dried (MgSO_4) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 90:10) to give **6** as a white solid (198 mg, 73% over 2 steps): Mp 93.0-94.0 °C; $[\alpha]_{\text{D}} -77.4$ (c 0.90, CH_2Cl_2); IR (neat) 3282, 2934, 2866, 1664, 1320, 1149, 997, 895, 753 cm^{-1} ; ^1H NMR δ 5.72 (d, 1 H, $J = 8.0$ Hz), 4.34-4.26 (m, 1 H), 4.10-4.02 (m, 2 H), 3.51-3.44 (m, 1 H), 3.01 (s, 3 H), 2.49 (dt, 1 H, $J = 3.3, 11.5$ Hz), 2.40-2.30 (m, 1 H), 2.10-2.00 (m, 1 H), 1.86-1.64 (m, 4 H), 1.50-1.30 (m, 3 H), 1.04 (d, 3 H, $J = 6.7$ Hz), 0.97 (d, 3 H, $J = 6.8$ Hz); ^{13}C NMR δ 167.9, 71.3, 70.1, 54.6, 44.5, 41.5, 34.8, 32.6, 29.6, 25.0, 24.7, 18.7, 18.1; MS (EI) m/z (relative intensity) 288 ($[\text{M}]^+$, 1.8), 245 (14), 209 (47), 150 (28), 140 (33), 129 (22), 97 (22), 81 (48), 69 (100), 57 (95); HRMS (EI) m/z calculated for $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$ 288.1508, found 288.1498.

Scheme 2

(1*R*,2*R*)-*N*-[2-(4-Isopropyl-4,5-dihydrothiazol-2-

yl)cyclohexyl]methanesulfonamide (7). A solution of colorless **5** (61.7 mg, 0.201 mmol) in DMF (4.0 mL) was treated with imidazole (27.4 mg, 0.403 mmol) and a solution of TBDMS-Cl (45.5 mg, 0.302 mmol) in DMF (1.0 mL) at 0 °C. After stirring at 0 °C for 5 h, the reaction mixture was quenched with water and extracted with Et₂O. The ether layer was washed with water, dried (MgSO₄), and concentrated. The residue was purified by chromatography on SiO₂ (EtOAc/hexanes, 30:70) to give the silyl ether as a white solid (81.1 mg, 96%): M p 202.5-203.0 °C; [α]_D -73.5 (c 0.57, CH₂Cl₂); IR (neat) 3292, 2928, 2857, 1641, 1544, 1463, 1320, 1155, 1123, 1087, 837, 774 cm⁻¹; ¹H NMR δ 5.86 (d, 1 H, *J* = 9.0 Hz), 5.06 (d, 1 H, *J* = 8.9 Hz), 3.73-3.68 (m, 2 H), 3.57-3.46 (m, 2 H), 2.95 (s, 3 H), 2.30-2.25 (m, 1 H), 2.06 (dt, 1 H, *J* = 3.0, 11.3 Hz), 1.92-1.86 (m, 4 H), 1.60-1.45 (m, 1 H), 1.38-1.19 (m, 3 H), 0.99-0.90 (m, 15 H), 0.06 (s, 6 H); ¹³C NMR δ 173.5, 62.9, 55.7, 54.3, 51.9, 41.2, 35.0, 30.5, 28.6, 25.9, 25.0, 24.8, 19.6, 19.1, 18.3, -5.4; MS (EI) *m/z* (relative intensity) 405 ([M-CH₃]⁺, 3.8), 377 (11), 363 (100), 275 (30), 204 (21), 109 (16), 75 (50); HRMS (EI) *m/e* calculated for C₁₈H₃₇N₂O₄SiS (M-CH₃) 405.2243, found 405.2255.

A solution of the colorless silyl ether (81.1 mg, 0.193 mmol) in CH₂Cl₂ (19 mL) was treated with Lawesson's reagent (117 mg, 0.289 mmol) at room temperature. The reaction mixture was stirred at room temperature for 23 h. The solvent was removed in vacuo. The residue was purified by chromatography on SiO₂

(EtOAc/hexanes, 25:75) to give thioamide as a colorless gum (54.4 mg, 65%): IR (neat) 3315, 2931, 2858, 1531, 1432, 1301, 1143, 1109, 1061, 987, 837, 778, 727, 675 cm^{-1} ; ^1H NMR δ 7.84 (d, 1 H, $J = 8.8$ Hz), 5.16 (br-s, 1 H), 4.58-4.53 (m, 1 H), 3.98-3.77 (m, 3 H), 3.07 (s, 3 H), 2.52-2.45 (m, 2 H), 2.22-2.15 (m, 1 H), 1.98-1.86 (m, 4 H), 1.50-1.32 (m, 3 H), 1.10-1.00 (m, 15 H), 0.15 (d, 6 H, $J = 4.6$ Hz); ^{13}C NMR δ 206.1, 61.5, 61.3, 60.2, 56.8, 41.8, 35.0, 33.7, 28.3, 25.9, 25.0, 24.8, 19.5, 19.3, 18.3, -5.5; MS (EI) m/z (relative intensity) 421 ($[\text{M}-\text{CH}_3]^+$, 3.3), 379 (30), 357 (24), 289 (25), 237 (13), 143 (100), 98 (77), 75 (79); HRMS (EI) m/z calculated for $\text{C}_{18}\text{H}_{37}\text{N}_2\text{O}_3\text{SiS}_2$ (M- CH_3) 421.2015, found 421.2009.

A solution of the colorless thioamide (49.3 mg, 0.113 mmol) in THF (1.2 mL) and H_2O (1.2 mL) was treated with acetic acid (3.6 mL) at room temperature and stirred for 11 h. The solvents were removed in vacuo. The residue was dried under vacuum, dissolved in CH_2Cl_2 (6 mL) and treated with Deoxo-Fluor (200 mg, 0.903 mmol) at -20°C . After 30 min, the reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 , extracted with EtOAc (3x), dried (MgSO_4), and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 40:60) to give **7** as an off-white solid (33.3 mg, 97% over 2 steps): Mp $80.0\text{--}81.0^\circ\text{C}$; $[\alpha]_{\text{D}} -53.8$ (c 0.48, CH_2Cl_2); IR (neat) 3281, 2932, 2858, 1622, 1450, 1320, 1148, 1075, 980, 898, 754 cm^{-1} ; ^1H NMR δ 5.28 (d, 1 H, $J = 5.9$ Hz), 4.34 (dt, 1 H, $J = 6.2, 9.0$ Hz), 3.50-3.40 (m, 1 H), 3.35 (dd, 1H, $J = 9.0, 11.0$ Hz), 3.13 (dd, 1 H, $J = 9.0, 11.0$ Hz), 3.06 (s, 3 H), 2.67 (dt, 1 H, $J = 3.7, 11.4$ Hz), 2.50-2.40 (m, 1 H), 2.20-2.05 (m, 2 H), 1.90-1.80 (m, 2 H), 1.65-1.35 (m, 4 H), 1.14 (d, 3 H, $J = 6.8$ Hz), 1.06 (d, 3 H, $J = 6.8$ Hz); ^{13}C NMR δ 172.5, 82.9, 55.8, 48.5, 41.9, 34.8, 34.7, 33.1, 31.2, 24.8, 24.6, 19.7, 18.8; MS (EI) m/z (relative intensity) 304 ($[\text{M}]^+$, 14), 289 (6), 261 (16), 225 (100), 166 (39), 156 (43), 122 (17), 68 (37), 55 (24); HRMS (EI) m/z calculated for $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_2\text{S}_2$ 304.1279, found 304.1283.

General procedure for Et₂Zn addition to aldehydes: A solution of aldehyde (0.50 mmol) and ligand (0.010 mmol) in hexanes (1.2 mL) was treated with a 1.0 M solution of diethylzinc in hexanes (1.10 mL, 1.10 mmol) at 0 °C. The mixture was stirred at 0 °C for 20-40 h, quenched with a 1.0 M solution of HCl in H₂O, and extracted with CH₂Cl₂ (3x). The combined organic layers were dried (MgSO₄) and concentrated. The residue was purified by chromatography on SiO₂ to give product.

1-Phenylpropan-1-ol. ¹H NMR δ 7.37-7.27 (m, 5 H), 4.62 (t, 1 H, *J* = 6.6 Hz), 1.90-1.70 (m, 3 H), 0.93 (t, 3 H, *J* = 7.4 Hz). Analysis of the enantiomers by chiral HPLC (Daicel Chiracel OD-H column, flow rate 1.0 mL/min, 2% *i*-PrOH, 98% hexane, T_r 14.6 and 17.0 min) was used to determine the enantiomeric excess.

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