A Mechanistically Guided Design Leads to the Synthesis of an Efficient and Practical New Reagent for the Highly Enantioselective, Catalytic Dihydroxylation of Olefins

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Supplementary Material

General. Tetrahydrofuran, methylene chloride, toluene, N,N-dimethylformamide were dried using standard techniques and freshly distilled before use. When necessary, all reactions were carried out in oven (120 °C) or flame dried glassware under an atmosphere of nitrogen. Purification by flash column chromatography was performed on Baker 230-400 mesh silica gel. Melting points were determined using a Buchi hot oil bath apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. FTIR spectra were recorded as thin films on a Nicolet 5 ZDX FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury and Inova series instruments (400 MHz or 500 MHz) in CDCl_3 . Mass spectra analyses and high-resolution mass spectral analyses were measured on a JEOL model AX-505 or SX-102 spectrometer by means of electron ionization (EI), chemical ionization (CI), fast-atom bombardment (FAB) or electrospray (ESI). Chiralcel or Chiralpak HPLC columns were obtained from Daicel Chemical Industries, Ltd.

Coupling of Cbz-(R)-Proline with Dihydroindole. To the ice-cooled solution of N-carbonylbenzyloxy-(R)-proline (2.49 g, 10.0 mmol) and 5 drops of DMF in CH₂Cl₂ (30 mL) was slowly added oxalic chloride (1.50 mL, 17.1 mmol) by syringe in 20 min. Evolution of gas was observed. The mixture was warmed to room temperature and stirred for another 5 h. After concentration *in vacuo* CH₂Cl₂ (15 mL) was added to the semi-solid residue and the resultant solution was cooled in an ice-bath and was treated with a solution of indoline (1.20 g, 10.0 mmol) and pyridine (1.4 mL, 17.1 mmol) in CH₂Cl₂ (15 mL). The mixture was stirred for 4 h at room temperature. The solution was successively washed with water, saturated aqueous sodium bicarbonate, hydrochloric acid (1 N) and brine. The organic layer was dried on Na₂SO₄. Removal of solvent provided an off-white solid as two rotamers: 3.48 g (99%). $[\alpha]_D^{22} = +31.2^\circ$ ($c = 1.05$, CHCl₃); m.p. 137-138 °C. ¹H NMR (CDCl₃, 500 MHz): δ 8.25 (t, $J = 9$ Hz), 7.31-7.38 (m), 7.12-7.23 (m), 6.98-7.07 (m), 5.20 (d, $J = 12$ Hz), 5.08 (m), 4.96 (d, $J = 12$ Hz), 4.67 (m), 4.50 (m), 4.42 (m), 4.08 (m), 3.85-3.92 (m), 3.75 (m), 3.56-3.64 (m), 3.24 (m), 3.06 (m), 2.83 (m), 2.24 (m), 2.05 (m), 1.93 (m) ppm; ¹³C (CDCl₃, 400 Hz): δ 171.13, 170.77, 155.17, 154.32, 143.24, 143.13, 136.98, 136.43, 131.30, 128.68, 128.46, 128.24, 128.14, 128.08, 128.04, 127.84, 127.74, 124.67, 124.15, 124.11, 117.67, 117.57, 67.65, 67.26, 59.19, 58.64, 47.88 47.74, 47.50, 46.99, 30.83, 29.84, 28.42, 28.15, 24.60, 24.04 ppm. FTIR (cm⁻¹, film): 2969, 2883, 1687, 1667, 1655, 1478, 1415, 1360, 1337, 1301, 1128, 731. MS (CI) m/z : 351([M + H⁺]). HRMS calcd for [C₂₁H₂₂N₂O₃ + H⁺]: 351.1708, found: 351.1702.

Its enantiomer was synthesized from N-carbonylbenzyloxy-(S)-proline in the same manner and is physically identical except for $[\alpha]_D^{22} = -32.2^\circ$ ($c = 1.10$, CHCl₃).

Compound 9. The above indoline amide (4.20 g, 12.0 mmol) was dissolved in acetic acid (50 mL) and added to a flask charged with Pd/C (10% wt, 1.3 g). The mixture was degassed and refilled with hydrogen via a balloon and this process was repeated five times. The mixture was stirred overnight under a hydrogen atmosphere. Removal of the catalyst and concentration gave **9** as a brown oil which was purified by flash chromatography (MeOH/CH₂Cl₂/NH₄OH = 5/95/0.5, R_f = 0.21): tan oil, 2.55 g (89%). $[\alpha]_D^{25} = +104.6^\circ$ ($c = 1.25$, CHCl₃). ¹H NMR (CDCl₃, 500 MHz): δ 8.22 (d, $J = 8.5$ Hz, 1 H), 7.21 (m, 2 H), 7.04 (t, $J = 7.0$ Hz, 1 H), 4.16 (m, 1 H), 4.09 (m, 1 H), 3.94 (m, 1 H), 3.24 (m, 3 H), 2.91 (m, 1 H), 2.72 (br, 1 H), 2.22 (m, 1 H), 1.78-1.87 (m, 3 H) ppm; ¹³C (CDCl₃, 400 Hz): δ 172.84, 143.20, 131.31, 127.85, 124.83, 124.22, 117.39, 60.57, 48.12, 47.58, 30.83, 28.41, 26.78 ppm. FTIR (cm⁻¹, film): 3296, 2951, 2861, 1649, 1598, 1480, 1461, 1392, 1289, 1263, 752. MS (CI) m/z : 216 ($[M + H]^+$). HRMS calcd for [C₁₃H₁₆N₂O + H⁺]: 216.1341, found: 216.1346.

Its enantiomer was synthesized in the same manner and is identical to **9** except for $[\alpha]_D^{23} = -107.8^\circ$ ($c = 1.0$, CHCl₃).

Compound 8. Sodium hydride (57-63% in mineral oil, 120 mg, 3.0 mmol) and dimethyl formamide (5 mL) were charged into a flame-dried flask under a nitrogen atmosphere at 10 °C. A solution of hydroquinidine (326 mg, 1.0 mmol) in dimethyl formamide (3 mL) was slowly added to the vigorously stirred suspension by syringe. The mixture was stirred at 23 °C for another 3 h followed by addition of solution of 3,6-dichloropyridazine (150 mg, 1.0 mmol) in dimethyl formamide (2 mL). The resultant mixture was stirred at 23 °C overnight. The solvent was removed by aspirator and the residue was extracted with diethyl ether (3x20 mL). The organic extracts were washed with brine and dried on Na₂SO₄. The solvent was removed and the

residue was purified by flash chromatography (2% triethyl amine in ethyl acetate, $R_f = 0.15$): colorless solid; 400 mg, 91%. $[\alpha]_D^{22} = -41.4^\circ$ ($c = 1.0$, CHCl_3). m.p.: 73-74 °C. ^1H NMR (CDCl_3 , 500 MHz): δ 8.68 (d, $J = 5$ Hz, 1 H), 8.00 (d, $J = 9$ Hz, 1 H), 7.52 (s, 1 H), 7.36 (m, 3 H), 7.05 (d, $J = 9.5$ Hz, 1 H), 3.98 (s, 3 H), 3.39 (d, $J = 7$ Hz, 1 H), 2.75-2.96 (m, 5 H), 1.95 (m, 1 H), 1.77 (m, 1 H), 1.49-1.63 (m, 6 H), 0.93 (t, $J = 6$ Hz, 3 H) ppm; ^{13}C (CDCl_3 , 400 Hz): δ 163.58, 158.14, 151.63, 147.55, 144.98, 131.98, 131.3, 127.42, 122.13, 120.12, 118.82, 101.86, 59.95, 55.92, 51.26, 50.33, 49.31, 45.98, 45.37, 44.63, 42.28, 38.74, 37.55, 34.79, 31.30, 30.91, 28.47, 27.44, 26.26, 25.71, 23.48, 12.24 ppm. FTIR (cm^{-1} , film): 2930, 2863, 1620, 1581, 1502, 1411, 1293, 1223, 1022, 983, 825, 719. MS (CI) m/z : 439 ($[\text{M} + \text{H}^+]$). HRMS calcd for $[\text{C}_{24}\text{H}_{27}\text{ClN}_4\text{O}_2 + \text{H}^+]$: 439.1901, found: 439.1911.

Compound 4. Compound **9** (207 mg, 0.96 mmol), Compound **8** (420 mg, 0.96 mmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (50 mg, 0.05 mmol), racemic-BINAP (62 mg, 0.10 mmol), Cs_2CO_3 (938 mg, 2.88 mmol) and dioxane (2 mL) were mixed in a flame-dried test tube. The mixture was degassed, refilled with nitrogen and stirred at 55-60 °C for 30 h. The mixture was cooled to room temperature and poured into ethyl acetate (50 mL). The organics were successively washed with water, brine and dried on sodium sulfate. The solvent was evaporated under vacuum and the residue was purified by flash (1-2% triethyl amine in ethyl acetate, $R_f = 0.1 - 0.15$) chromatography: colorless solid, 415 mg, 75%. $[\alpha]_D^{22} = +29.0^\circ$ ($c = 1.2$, CHCl_3). m.p.: 131-132 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 8.64 (d, $J = 4$ Hz, 1 H), 8.16 (d, $J = 8$ Hz, 1 H), 7.95 (d, $J = 9$ Hz, 1 H), 7.53 (s, 1 H), 7.40 (d, $J = 4$ Hz, 1 H), 7.32 (dd, $J = 9$ Hz, $J = 2$ Hz, 1 H), 7.20

(d, $J = 7$ Hz, 1 H), 7.15 (t, $J = 7$ Hz, 1 H), 7.01 (t, $J = 7$ Hz, 1 H), 6.89 (d, $J = 9$ Hz, 1 H), 6.75 (m, 2 H), 4.86 (d, $J = 5$ Hz, 1 H), 4.44 (m, 1 H), 4.04 (m, 1 H), 3.87 (s, 3 H), 3.69 (m, 1 H), 3.43 (m, $J = 8$ Hz, 1 H), 3.17-3.30 (m, 3 H), 2.71-2.82 (m, 4 H), 2.28 (m, 2 H), 2.06 (m, 2 H), 1.94 (m, 1 H), 1.70 (m, 1 H), 1.44-1.51 (m, 5 H), 0.85 (t, $J = 7$ Hz, 3 H) ppm; ^{13}C (CDCl_3 , 400 Hz): δ 171.68, 158.35, 155.03, 147.69, 144.90, 143.55, 131.73, 131.38, 127.66, 124.72, 123.90, 121.80, 119.39, 119.01, 117.47, 117.36, 102.49, 60.46, 59.57, 55.86, 51.09, 50.26, 47.95, 47.78, 37.78, 30.08, 28.44, 27.72, 26.38, 25.55, 24.06, 23.58, 12.22 ppm. FTIR (cm^{-1} , film): 2936, 2865, 1666, 1456, 1427, 1288, 1213, 988, 831, 749. MS (CI) m/z : 619 ($[\text{M} + \text{H}^+]$). HRMS calcd for $[\text{C}_{37}\text{H}_{42}\text{N}_4\text{O}_3 + \text{H}^+]$: 619.3396, found: 619.3386.

The (S)-proline analogue of compound **4** (**5**) was synthesized in the same manner as described above: colorless solid, 62%; $[\alpha]_{\text{D}}^{22} = -4.2^\circ$ ($c = 0.95$, CHCl_3). m.p.: 144-145 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz): δ 8.64 (d, $J = 4$ Hz, 1 H), 8.09 (d, $J = 8$ Hz, 1 H), 7.93 (d, $J = 9$ Hz, 1 H), 7.47 (s, 1 H), 7.39 (d, $J = 4$ Hz, 1 H), 7.28 (dd, $J = 9$ Hz, $J = 2$ Hz, 1 H), 7.16 (d, $J = 7$ Hz, 1 H), 7.12 (t, $J = 7$ Hz, 1 H), 6.98 (t, $J = 7$ Hz, 1 H), 6.88 (m, 2 H), 6.72 (d, $J = 9$ Hz, 1 H), 4.89 (d, $J = 5$ Hz, 1 H), 4.50 (m, 1 H), 4.09 (m, 1 H), 3.84 (s, 3 H), 3.74 (m, 1 H), 3.50 (m, $J = 8$ Hz, 1 H), 3.36 (m, 1 H), 3.20 (m, 2 H), 2.75-2.85 (m, 4 H), 2.31 (m, 2 H), 2.06 (m, 3 H), 1.71 (m, 1 H), 1.25-1.50 (m, 5 H), 0.89 (t, $J = 7$ Hz, 3 H) ppm; ^{13}C (CDCl_3 , 400 Hz): δ 171.34, 158.66, 155.07, 147.72, 144.90, 143.40, 131.82, 131.20, 127.73, 124.72, 123.97, 121.78, 119.41, 119.06, 117.43, 102.39, 59.62, 55.86, 51.00, 50.26, 48.02, 47.76, 37.77, 30.25, 28.47, 27.63, 26.41, 25.56, 23.98, 22.88, 12.30 ppm. FTIR (cm^{-1} , film): 2926, 2867, 1659, 1616, 1451, 1411, 1286, 1223, 1022, 987, 821, 754. MS (CI) m/z : 619 ($[\text{M} + \text{H}^+]$). HRMS calcd for $[\text{C}_{37}\text{H}_{42}\text{N}_4\text{O}_3 + \text{H}^+]$: 619.3396, found: 619.3398.

General Procedure for Catalytic Asymmetric Dihydroxylation. A mixture of ligand **4** (5 mg, 0.0081 mmol), $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (1.0 mg, 0.0027 mmol), $\text{K}_3\text{Fe}(\text{CN})_6$ (1.18 g, 3.57 mmol), K_2CO_3 (0.493 g, 3.57 mmol) and MeSO_2NH_2 (113 mg, 1.19 mmol, only when 1,2-disubstituted or tri-

substituted olefins were used as substrates) in 12 mL of 1:1 *t*-BuOH–H₂O was stirred at 0 °C for 0.5 h. The olefin (1.19 mmol) was added to the suspension and the resulting mixture was stirred vigorously at 0 °C for 8-24 h. The reaction was monitored by TLC (20-50% EtOAc/hexane). After completion of the reaction as indicated by TLC, the mixture was quenched with Na₂SO₃ (1.5 g) at 0 °C, and was then warmed to room temperature and stirred for 45 min. The reaction mixture was extracted three times with ethyl acetate (3 x 25 mL). The organic extract was washed with 1 N KOH (to remove methyl sulfonamide when necessary) and 15 mL of brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the diol (10-70% EtOAc in hexane) as colorless solid or colorless oil and the recovered ligand **4** (5% TEA/EtOAc). The enantiomeric excess (ee) of the diols was determined either by chiral-column HPLC analysis or ¹H NMR analysis of the corresponding MTPA esters.

Characterization of Diols.

Rotation: $[\alpha]^{23}_D$ [*c* = 1.1, 95% EtOH] –36.7. The enantiomeric purity was determined by ¹H NMR integration of the corresponding bis-MTPA ester derivative (CDCl₃, 500 MHz): δ 6.28 ppm (dd, 1 H, (R, major)), 6.18 ppm (dd, 1 H, (S, minor)).¹

Rotation: $[\alpha]^{23}_D$ [$c = 1.1$, 95% EtOH] -31.3 . The enantiomeric purity was determined by ^1H NMR integration of the corresponding bis-MTPA ester derivative (CDCl_3 , 500 MHz): δ 5.97 ppm (d, 1 H, (R, major)), 6.03 ppm (d, 1 H, (S, minor)).²

Rotation: $[\alpha]^{23}_D$ [$c = 1.1$, 95% EtOH] -4.55 . The enantiomeric purity was determined by ^1H NMR integration of the corresponding bis-MTPA ester derivative (CDCl_3 , 500 MHz): δ 5.51 ppm (d, 1 H, (1R,2S major)), 5.46 ppm (d, 1 H, (1S,2R, minor)).³

Rotation: $[\alpha]^{23}_D$ [$c = 1.0$, 95% EtOH] $+92.6$. The enantiomeric purity was determined by ^1H NMR integration of the corresponding bis-MTPA ester derivative (CDCl_3 , 500 MHz): δ 6.21 ppm (s, 1 H, (R,R, major)), 6.32 ppm (s, 1 H, (S,S minor)).⁴

Rotation: $[\alpha]^{24}_D$ [$c = 1.1$, 95% EtOH] $+30.5$. The enantiomeric purity was determined by ^1H NMR integration of the corresponding bis-MTPA ester derivative (CDCl_3 , 400 MHz): δ 5.22 ppm (t, $J = 6.4$ Hz, 1 H, (R,R, major)), 5.13 ppm (t, $J = 6.4$ Hz, 1 H, (S,S minor)).⁵

Rotation: $[\alpha]^{23}_{\text{D}}$ [$c = 1.0$, 95% EtOH] -3.6. The enantiomeric purity was determined by ^1H NMR integration of the corresponding bis-MTPA ester derivative (CDCl_3 , 500 MHz): δ 5.70 ppm (qd, $J = 6.0$ Hz, $J = 2.0$ Hz, 1 H, (2S,3R, major)), 5.62 ppm (qd, $J = 6.0$ Hz, $J = 2.0$ Hz, 1 H, (2R,3S minor)).⁶

Rotation: $[\alpha]^{23}_{\text{D}}$ [$c = 1.4$, CHCl_3] -8.0. The enantiomeric purity was determined by ^1H NMR integration of the corresponding mono-MTPA ester derivative (CDCl_3 , 500 MHz): δ 6.02 ppm (s, 1 H, (2S,3R, major)), 6.05 ppm (s, 1 H, (2R,3S, minor)).⁷

Rotation: $[\alpha]^{23}_{\text{D}}$ [$c = 1.2$, 95% EtOH] -7.1 or [$c = 1.0$, benzene] +17.6. The enantiomeric purity was determined by chiral HPLC analysis (2% 2-propanol in hexane, Chiralcel OJ column, 1 mL/min flow rate, $\lambda = 254$ nm, retention times: 37.6 min (R,R, major), 26.7 min (S,S, minor)).⁸

Rotation: $[\alpha]^{24}_D$ [$c = 1.1$, 95% EtOH] +2.5. ^1H NMR (CDCl_3 , 400 MHz): δ .81 (m, 1 H), 3.80 (s, 3 H), 1.67-1.85 (m, 4 H), 1.48-1.56 (m, 3 H), 1.32 (m, 1 H) ppm. ^{13}C (CDCl_3 , 400 Hz): δ 176.92, 77.02, 72.47, 53.28, 34.59, 30.52, 24.27, 20.09 ppm. FTIR (cm^{-1} , film): 3465, 2933, 2852, 1728, 1438, 1238, 1148, 1066, 1029, 997. MS (CI): 192 ($\text{M} + \text{NH}_4^+$). Calculated for ($\text{C}_8\text{H}_{14}\text{O}_4 + \text{NH}_4^+$): 192.1236; Found: 192.1240. The enantiomeric purity was determined by ^1H NMR integration of the corresponding mono-MTPA ester derivative (CDCl_3 , 500 MHz): δ 3.47 ppm (s, 1 H, (1R,2R, major)), 3.51 ppm (s, 1 H, (1S,2S minor)).

Rotation: $[\alpha]^{24}_D$ [$c = 1.0$, CHCl_3] +3.2. ^1H NMR (CDCl_3 , 400 MHz): δ 3.45 (m, 1 H), 1.76-1.29 (m, 14 H), 0.91 (t, $J = 6.4$ Hz, 3 H) ppm. ^{13}C (CDCl_3 , 400 Hz): δ 73.61, 73.58, 38.71, 33.78, 30.58, 25.63, 23.59, 23.31, 21.50, 14.34 ppm. FTIR (cm^{-1} , film): 3322, 2937, 2854, 1447, 1073, 975. m.p. 84-86 °C. MS (EI): 172. Calculated for $\text{C}_{10}\text{H}_{20}\text{O}_2$: 172.1463; Found: 172.1468. The enantiomeric purity was determined by ^1H NMR integration of the corresponding mono-MTPA ester derivative (CDCl_3 , 500 MHz): δ 3.49 ppm (s, 1 H, (1S,2R, major)), 3.55 ppm (s, 1 H, (1R,2S, minor)).⁹

Rotation: $[\alpha]^{23}_D$ [$c = 1.3$, CHCl_3] +4.7. The enantiomeric purity was determined by chiral HPLC analysis (10% 2-propanol in hexane, Chiralcel OD column, 1 mL/min flow rate, $\lambda = 254$ nm, retention times: 43.7 min (1S,2R, major), 33.4 min (1R,2S, minor)).¹⁰

Rotation: $[\alpha]_D^{23}$ [c = 2.0, 95% EtOH] +15.7. ^1H NMR (CDCl_3 , 500 MHz): δ 5.41 (dt, 1 H, $J = 1.5, 7.2$ Hz), 4.25 (dd, 2 H, $J = 1.0, 6.5$ Hz), 3.87 (dd, 1 H, $J = 5.5, 2$ Hz), 2.28 (m, 1 H), 2.10 (m, 1 H), 1.80 (br, 2 H), 1.64 (s, 3 H), 1.60 (m, 1 H), 1.45 (m, 1 H), 1.21 (s, 3 H), 1.16 (s, 3 H), 1.05-1.10 (m, 21 H) ppm. ^{13}C (CDCl_3 , 400 Hz): δ 136.60, 125.54, 78.42, 73.25, 60.55, 36.82, 29.74, 26.70, 23.47, 18.25, 16.62, 12.26 ppm. FTIR (cm^{-1} , film): IR: 3393, 2942, 2865, 1463, 1381, 1060, 1012. MS (EI): 367 ($\text{M} + \text{Na}^+$). Calculated for $\text{C}_{19}\text{H}_{40}\text{O}_3\text{Si} + \text{Na}^+$: 367.2644; Found: 367.2635. The enantiomeric purity was determined by ^1H NMR integration of the corresponding mono-MTPA ester derivative (CDCl_3 , 500 MHz): δ 5.24 ppm (t, 1 H, (R, major)), 5.30 ppm (t, 1 H, (S, minor)).

References for Experimental

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