Supporting Information

Highly Enantioselective Deracemization of Linear and Vaulted Biaryl Ligands

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Experimental procedure and spectral data.

General: All the solvents were of ACS grade and used as purchased. BINOL, $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, CuCl and (-)-sparteine were purchased from Aldrich and used without further purification. Racemic VANOL (**2**) was prepared via a procedure that will be published separately. Racemic VAPOL (**3**) was synthesized by the published procedure¹. Melting points were determined on a Hoover Unimelet apparatus and are uncorrected. IR spectra were recorded on a Nicolet 20SX FTIR spectrophotometer. ¹H NMR spectra were recorded on a QE-300 MHz instrument, ¹³C NMR spectra were obtained on the QE-300 instrument at 75 MHz. Low-resolution mass spectra were performed at Michigan State University. High-resolution mass spectra were recorded on a VG 70-250 instrument in University of Chicago or obtained from the Midwest center for Mass Spectrometry in Lincoln, NE. Elemental analyses were done by Galbraith Laboratories, Knoxville, TN. Compounds were separated via flash chromatography using 230-400 mesh silica gel. Chiral HPLC chromatography was obtained on a Varian chromatograph using a Pirkle covalent D-phenylglycine column. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter at 589 nm (sodium D Line) using 1.0 dm cells. Specific rotations, $[\alpha]_D$ are reported in degrees per decimeter at 25°C, and the concentration (*c*) is given in grams per 100 mL.

Typical experimental procedure for deracemization of VANOL(**2**) using $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and (-)-sparteine:

To a 500 mL Schlenk flask was added 100 mL MeOH, 333 mg of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (1.95 mmol) and 942 mg of (-)-sparteine (4.01 mmol). A solution of VANOL (**2**) (620 mg, 1.42 mmol) in a 250 mL round bottom flask containing 60 mL of CH_2Cl_2 and 20 mL of MeOH was deoxygenated by purging with argon for 40 min and then this solution was transferred via cannula to the 500 mL Schlenk flask containing the

(1) Bao, J.; Wulff, W. D.; Dominy, J. D.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S.; Ostrander, R. L.; Rheingold, A., *J. Am. Chem. Soc.* **1996**, *118*, 3392

CuCl₂·2H₂O and sparteine. After the VANOL solution was transferred, the Schlenk flask was deoxygenated by the freeze-thaw method (2 cycles). The flask was then sealed under argon and stirred at room temperature for 50 hours. The reaction was quenched by adding 20 mL of concentrated HCl and then stirring for 10 minutes. Upon removal of most of the organic solvents, the mixture poured into a separatory funnel. The CH₂Cl₂ layer was collected and the upper MeOH/H₂O layer was washed with 2 × 30 mL of CH₂Cl₂. The CH₂Cl₂ solutions were combined and dried over MgSO₄. Upon removal of solvent, the crude reaction mixture was loaded onto a silica gel column and eluted with a 1:10 mixture of EtOAc/hexane to give 479 mg (1.09 mmol, 77% yield) of (S)-**2** as a white foam-like solid. The optical purity of (S)-**2** was determined to be of ≥ 99 % ee by HPLC on a Pirkle D-Phenylglycine column with a 98:2 mixture of hexane/isopropanol (254nm, flow rate: 1 mL/min to 2 mL/min over 30 min). Under these conditions, the retention time of (R)-**2** was 16.14 min and that of (S)-**2** was 17.32 min.

Spectral data for **2**: white solid; mp = 231-232 °C; R_f=0.36 (1:9 EtOAc/hexane). ¹H NMR (CDCl₃, 300MHz) δ 5.83 (s, 2 H), 6.61 (d, 4 H, J = 7.2 Hz), 6.93 (t, 4 H, J = 7.7 Hz), 7.03 (t, 2 H, J = 7.3 Hz), 7.29 (s, 2 H), 7.50-7.54 (m, 4 H), 7.73-7.75 (m, 2 H), 8.30-8.32 (m, 2 H); ¹³C NMR (CDCl₃, 75 MHz) δ = 112.64, 122.00, 122.78, 122.86, 125.66, 126.59, 127.43, 127.51, 127.67, 128.86, 134.56, 140.12, 140.65, 150.33; IR (neat) 3508 s, 3054 m, 3030 w, 1948 w, 1630 w, 1502 m, 1569 m, 1493 s, 1439 w, 1383 s, 1285 m, 1233 m, 1221 m, 1192 m, 1140 m, 1062 m, 1020 w, 947 m, 908 s, 879 m, 853 w, 798 w, 759 s cm⁻¹; mass spectrum, m/z (% rel intensity), 438 M⁺ (100), 420 (6), 361 (9), 231 (11), 219 (23), 202 (14), 180 (20), 157(16); exact mass calculated for C₃₂H₂₂O₂: m/z 438.1620, exact m/z 438.1610. Anal. Calcd for C₃₂H₂₂O₂: C, 87.65; H, 5.06. Found: C, 87.89; H, 5.10. Specific rotation: [α]_D = -372.3 (THF, c = 1.0).

Typical experimental procedure for deracemization of VANOL (**2**) using CuCl and (-)-sparteine:

To a 500 mL round bottom flask was added 300 mL MeOH, 1.55 g of CuCl (15.66 mmol) and (-)-7.6 g of sparteine (32.4 mmol). The flask was sonicated in an ultrasonic water bath with air bubbled below the surface of solution. The temperature was maintained at or below 25 °C by the addition of ice to the water in the bath. The flask was sealed with a septum after 20 minutes and purged with argon for 60 minutes. The green Cu-sparteine solution was transferred via cannula to the solution of racemic **2** (5 g, 11.4 mmol) in 1200 mL CH₂Cl₂ in a 2L round bottom flask which had previously been purged with argon and sonicated for 60 minutes. The combined solution was sonicated for 15 more minutes and then the flask was removed from ultrasonic bath, covered with aluminum foil and the reaction mixture allowed to stir at room temperature for 105 minutes under a positive pressure of argon maintained by slow flow through the head space of the flask. The reaction was quenched by adding 100 mL of concentrated HCl and then stirring for 10 minutes. Approximately 1 L of the solvent was removed by rotavapor and then the solution was poured into a 500 mL separatory funnel. The lower CH₂Cl₂ layer was collected and the upper MeOH/H₂O layer was washed with 2 × 50 mL of CH₂Cl₂. The combined CH₂Cl₂ layers were dried over MgSO₄. Upon removal of solvent, the crude reaction mixture was loaded to a silica gel column and eluted with a 1:10

mixture of EtOAc/hexane to give 3.43 g (7.8 mmol, 69 % yield) of (S)-**2** as a white foam-like solid. The optical purity of (S)-**2** was determined to be ≥ 99 % ee by HPLC.

Enrichment of (S)-VANOL (2) by Precipitation of Racemate. (S)-**2** (4.0 g, 9.13mmol) with 90 % ee was introduced into a 250 mL round bottom flask. Ethyl acetate was added dropwise until all the solid had dissolved. Hexane (100 mL) was added and the flask was manually shaken for one or two minutes. A white solid appeared in the flask which was then allowed to stand still for 2 hours. The VANOL in the solution was checked by HPLC and it was found to be greater than 99.5% ee. Removal of the solid by filtration and removal of solvent afforded 3.5 g white foam-like (S)-**2** solid with > 99.5 % ee.

Typical experimental procedure for deracemization of VAPOL (3) using $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and (-)-sparteine:

To a light green solution of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (44 mg, 0.258 mmol) in degassed methanol (4 mL, purged with argon for 30 min) was added (-)-sparteine (122 mg, 0.516 mmol) in degassed methanol (8 mL, purged with argon for 30 min) *via* a cannula to give a lime green milky solution. After 30 min, a solution of racemic VAPOL (0.1 g, 0.186 mmol) in 10 mL of a degassed 1 : 1 mixture of methanol and methylene chloride (purged with argon for 30 min) was added *via* a cannula. The brownish black mixture was allowed to stir under nitrogen at 25 °C for 24 h. The reaction was quenched by the dropwise addition of concentrated HCl until the solution turned light green. Water was added and the volatiles removed to give a yellow precipitate which was filtered. The precipitate was purified by flash column chromatography (CH_2Cl_2 :hexane = 1:1) to give 64 mg of (S)-VAPOL with 98.8 % ee. The enantiomeric excess was determined by HPLC on a chiral Pirkle D-phenylglycine column.

Typical experimental procedure for deracemization of VAPOL (3) using CuCl and (-)-sparteine:

To a 500 mL round bottom flask was added 300 mL of MeOH, 1.55 g of CuCl (15.66 mmol) and 7.6 g of (-)-sparteine (32.42 mmol). The flask was sonicated in an ultrasonic bath with air sparged into the solution. The temperature was maintained at or below 25 °C by the addition of ice to the water in the bath. The flask was sealed with a septum after 45 minutes and then purged with argon for 60 minutes in the ultrasonic bath. The green Cu(II)-sparteine solution was transferred *via* cannula to the solution of racemic **3** (5 g, 9.29 mmol) in 1.2 L of CH_2Cl_2 in a 2 L round bottom flask which was had previously been purged with argon and sonicated for 60 minutes. The combined solution was sonicated for 10 minutes and then the flask was removed from ultrasonic bath, covered with aluminum foil and stirred at room temperature for 6 hours under a positive pressure of argon maintained by slow flow through the head space of the flask. The reaction was quenched by adding 120 mL of concentrated HCl and then stirring for 10 minutes. Approximately 1 L of the solvent was removed by rotavapor and then the solution was poured into a 500 mL separatory funnel. The lower CH_2Cl_2 layer was collected, the upper MeOH/ H_2O layer was washed with 2×50 mL of CH_2Cl_2 . The combined CH_2Cl_2 layer was dried over MgSO_4 . Upon removal of solvent,

the crude reaction mixture was loaded to silica gel column and eluted with a 1:1 mixture of CH₂Cl₂/hexane to give 4.19 g (7.79 mmol, 84% yield) (S)-**3** as a white solid. The optical purity of (S)-**3** was found to be of $\geq 99\%$ by HPLC on a Pirkle D-Phenylglycine column with a 75:25 mixture of hexane/isopropanol (260 nm, flow rate: 2 mL/min). Under these conditions the retention time of (R)-**3** was 12.50 min and that of (S)-**3** was 18.54 min.

Spectral data for **3**: white solid; mp > 250 °C; R_f = 0.60 (1:1 CH₂Cl₂/hexane); ¹H NMR (CDCl₃) δ 6.59 (s, 2 H), 6.66 (d, 4 H, J = 7.7 Hz), 6.93 (t, 4 H, J = 7.5 Hz), 7.04 (t, 2 H, J = 7.4 Hz), 7.42 (s, 2 H), 7.61 (t, 2 H, J = 7.3 Hz), 7.64-7.67 (m, 4 H), 7.79 (d, 2 H, J = 8.8 Hz), 7.91 (d, 2 H, J = 7.7 Hz), 9.71 (d, 2 H, J = 8.4 Hz); ¹³C NMR (CDCl₃) δ 115.77, 118.09, 123.23, 126.36, 126.81, 126.99, 127.03, 127.53, 128.44, 128.82, 129.29, 130.28, 132.80, 135.27, 139.70, 141.56, 153.41 (one carbon not located); IR (neat) 3473 s, 3049 m, 1611 w, 1590 w, 1555 w, 1372 m, 1330 m, 1246 w, 1210 w, 1175 m, 1027 w, 816 w, 774 m, 731 m, 665 m cm⁻¹; mass spectrum, m/z (rel intensity), 538 (18) M⁺, 520 (5), 370 (3), 270 (100), 241 (30), 215 (7), 165 (10); exact mass calculated for C₄₀H₂₆O₂ m/z 538.1933, found m/z 538.1933. Anal. Calcd for C₄₀H₂₆O₂: C, 89.19; H, 4.87. Found: C, 88.43, H, 5.29. Specific rotation: $[\alpha]_D = 124.96$ (THF, c = 1.0).

Enrichment of (S)-VAPOL (**3**) using Soxhlet extraction.

To a Soxhlet thimble (33 x 94 mm) was added (4.0 g, 7.43 mmol) **3** of 97% ee. The thimble was placed in the extractor and 250 mL of pentane was added to a 500 mL round bottom flask attached to the bottom of the extractor. The pentane solution was heated at 55 °C in an oil bath and allowed to reflux. Off-white VAPOL precipitate appeared in the flask within 12 hours. After 24 hours, removal of the solvent from the pentane solution afforded 3.0 g (5.57 mmol) **3** which was determined by HPLC to be $\geq 99.5\%$ ee.

Oxidation of VAPOL with Ceric Ammonium Nitrate to give Quinone **5**.

A solution of 0.300 g (0.56 mmol) VAPOL in 10 mL ether was treated with 12 mL of 0.5 M aqueous ceric ammonium nitrate at room temperature and then was allowed to stir for 2 days. The reaction was monitored by TLC. When all of the VAPOL was consumed 10 mL of dichloromethane was added. The aqueous layer was separated and washed with an additional 10 mL of dichloromethane. The combined organic layers were then dried with MgSO₄. After removal of solvent, the crude product was purified by flash column chromatography with a 1:1 mixture of hexane and CH₂Cl₂ (R_f =0.30) as eluent to afford 0.134 g (0.24 mmol, 42 %) of quinone **5** as an orange solid. No other silica gel mobile compound was produced in this reaction. The yield of this reaction varied from 27 to 42 % over three runs. Spectral data for **5**: ¹H NMR (300 MHz, CDCl₃): δ 6.79 (d, 4 H, J = 8.2 Hz), 7.16 (t, 4 H, J = 7.7 Hz), 7.25 (t, 2 H, J = 7.7 Hz), 7.66 (t, 2 H, J = 7.1 Hz), 7.74 (t, 2 H, J = 7.1 Hz), 7.94 (d, 2 H, J = 7.1 Hz), 8.17 (d, 2 H, J = 8.8 Hz), 8.19 (d, 2 H, J = 8.8 Hz), 9.52 (d, 2 H, J = 8.8 Hz); ¹³C NMR (300 MHz, CDCl₃): δ 122.2, 127.6, 127.7, 128.2, 128.76, 128.82, 129.0, 129.4, 129.9, 130.2, 131.6, 132.2, 135.3, 136.5, 143.7, 143.8, 184.3, 187.9; IR (neat) 1658s, 1588s, 1458m, 1445m, 1287s, 1248s, 1089s cm⁻¹; mass spectrum, m/z (rel intensity), 567 (11), 566 M⁺ (27), 522 (67), 521 (38), 461 (18), 376 (4), 283 (4), 154 (10), 126 (100), 44 (48).

Preparation of (-)-sparteine-copper complex:

To a 50 mL round bottom flask was added 20 mL of MeOH followed by CuCl (200 mg, 2 mmol) and (-)-sparteine (469 mg, 2 mmol). The mixture was sonicated open to air for 20 min. The solid CuCl dissolved within 15 min. The resulting green solution was filtered to remove any insoluble solid and concentrated in vacuo to give a green solid. This solid was dissolved in 12 mL CH₂Cl₂ and then 250 mL of hexane was added to cause precipitation. Filtration and drying of the precipitate afforded a lime-green solid (440 mg, 1.26 mmol, 63 % yield) which, based on literature precedent,³ was expected to be Cu(-sparteine)Cl(OH): mp 148-151°C.

Deracemization of VAPOL (3) using (-)-sparteine-copper complex:

To a 250 mL round bottom flask filled with argon was added 12 mL of MeOH and 48 mL of CH₂Cl₂ and the resulting mixture was sparged with argon for 1 h. To this solvent mixture was added racemic VAPOL (3) (200 mg, 0.37 mmol) and (-)-sparteine copper complex (155 mg, 0.44 mmol) which afforded a light green solution. This solution turned black upon addition of (-)-sparteine (103 mg, 0.44 mmol). The dark solution was stirred under argon and at room temperature for 6 hours. The reaction was quenched by adding 10 mL of concentrated HCl and then stirred for 10 minutes. The contents of the flask was transferred to separatory funnel. The lower CH₂Cl₂ layer was collected and the upper MeOH/H₂O layer was washed with 2 × 50 mL of CH₂Cl₂. The combined CH₂Cl₂ layer was dried over MgSO₄. Upon removal of solvent, the crude reaction mixture was loaded onto a silica gel column and eluted with a 1:1 mixture of CH₂Cl₂/hexane to give 114 mg (0.21 mmol, 57 % yield) (S)-**3** as a white solid. The optical purity of (S)-**3** was found to be of 97% ee as described in the VAPOL deracemization procedure above.

Deracemization of 6,6'-dibromo-VAPOL (4) using CuCl₂·2H₂O and (-)-sparteine.

To a 100 mL round bottom flask was added 6.7 mL of argon sparged MeOH and then CuCl₂·2H₂O (73 mg, 0.428 mmol) was added. A solution of (-)-sparteine (200 mg, 0.853 mmol) in 13 mL of deoxygenated MeOH was added to the 100 mL flask by cannula, which turned the solution a murky lime green. The solution was stirred for 0.5 hr at room temperature. In a separate flask, racemic **4** (213 mg, 0.31 mmol) was partially dissolved in 10 mL of deoxygenated CH₂Cl₂ and then transferred into the reaction mixture via cannula with concurrent addition of 10 mL of deoxygenated MeOH. The remaining undissolved starting material was dissolved in 6.5 mL of deoxygenated CH₂Cl₂ and this was transferred into the reaction flask with concurrent addition of 6.5 mL of deoxygenated MeOH. The mixture turned black and was stirred for 24 h. The reaction was quenched with 1 mL conc. HCl and then partitioned between 50 mL of H₂O and 50 mL of CH₂Cl₂. The organic layer was dried over MgSO₄, filtered and then adsorbed onto a small amount of SiO₂. Purification by silica gel chromatography (5:1 hexane /EtOAc) afforded 108 mg of a white/pale yellow solid (50 % yield). *R_f* = 0.38 (4:1 hexane/EtOAc). The optical purity of **4** was determined as > 98 % ee by chiral HPLC on Pirkle D-Phenylglycine column, (70:30

mixture of hexane/isopropanol, 260nm, flow rate: 2 mL/min), Chiral HPLC retention time of S-isomer was 16.9 min. X-ray quality crystals were grown by dissolving sample in a minimum amount of hot EtOAc, allowing this to cool to room temperature, and then layering with hexane, which produced clear, faintly pale green crystals. Crystallography as well as ^1H NMR indicated the crystal contained two equivalents of EtOAc. Absolute configuration is assigned to the (S)-isomer by analogy with the parent molecule VAPOL (**3**) which upon deracemization with (-)-sparteine/CuCl affords (S)-(+)-VAPOL.

Spectral data for **4**: ^1H NMR: (500 MHz, CDCl_3) δ 6.60 (s, 2H), 6.64 (d, 4H, $J = 7.5$ Hz), 6.94 (t, 4H, $J = 7.6$ Hz), 7.05 (t, 2H, $J = 7.3$ Hz), 7.40 (s, 2H), 7.65 (d, 2H, $J = 8.7$ Hz), 7.69 (d, 2H, $J = 8.3$ Hz), 7.75 (t, 4H, $J = 9.5$ Hz), 9.91 (s, 2H). ^{13}C NMR: (75MHz, CDCl_3) δ 116.0, 117.1, 121.3, 123.2, 126.9, 127.4, 127.6, 128.6, 128.8, 129.4, 129.6, 131.27, 131.35, 131.42, 135.3, 139.5, 142.2, 153.3 IR (neat film, NaCl), cm^{-1} : 3482(s), 3139(w), 3052(w), 3027(w). MS (EI) m/z (intensity): 699(23, $(\text{M}+1)^+$, $^{81}\text{Br}_2$), 698(65, M^+ , $^{81}\text{Br}_2$), 697(48, $(\text{M}+1)^+$, $^{81}\text{Br}^{79}\text{Br}$), 696(100, M^+ , $^{81}\text{Br}^{79}\text{Br}$), 695(26, $(\text{M}+1)^+$, $^{79}\text{Br}_2$), 694(41, M^+ , $^{79}\text{Br}_2$), 618(22), 616(18), 536(5), 268(72), 239(27), 149(42). Anal. Calcd. for $\text{C}_{40}\text{H}_{24}\text{O}_2\text{Br}_2 \cdot 2(\text{C}_4\text{H}_8\text{O}_2)$: %C: 6.07 %H: 4.62. Found %C: 66.16 %H: 4.57. Specific rotation: $[\alpha]_D = +445^\circ$ ($c = 1$, THF).

Typical experimental procedure for deracemization of BINOL (**1**) using CuCl and (-)-sparteine:

To a 50 mL round bottom flask was added 6.5 mL MeOH, 97 mg of CuCl (0.98 mmol) and 464 mg of (-)-sparteine (1.96 mmol). The flask was sonicated in an ultrasonic bath open to air. The temperature was maintained at or below 25°C by the addition of ice to the water in the bath. The flask was sealed with a septum after 25 minutes and the solution purged with argon for 60 minutes in the ultrasonic bath. The green Cu(II)-sparteine solution was transferred via cannula to the solution of racemic **1** (200 mg, 0.70 mmol) in 16.5 mL CH_2Cl_2 in a 50 mL round bottom flask which had been previously purged with argon and sonicated for 60 minutes. Upon transferring, the flask was sonicated for 10 more minutes. The flask was removed from the ultrasonic bath, covered with aluminum foil and the reaction mixture allowed to stir at room temperature for 8 hours and then at -20°C for 16 hours. The reaction was quenched by slow addition of 10 mL of a pre-cooled concentrated HCl at -20°C and then the mixture was stirred for 5 minutes. The solution was poured into a separatory funnel, the lower CH_2Cl_2 layer was collected and the upper MeOH/ H_2O layer was washed with 2×30 mL of CH_2Cl_2 . The combined CH_2Cl_2 layers were washed with 30 mL water and dried over MgSO_4 . Upon removal of solvent, the crude reaction mixture was loaded onto a silica gel column and eluted with a 15:1 mixture of CH_2Cl_2 /hexane to give 194 mg (0.68 mmol, 97 % yield) of (S)-**1** as a white solid. The material obtained was identical to that commercially available from Aldrich. The optical purity of (S)-**1** was found to be of 92 % ee by HPLC on a Chirapak AS column with a 90:10 mixture of hexane/isopropanol (260 nm, flow rate: 1 mL/min)². Under these conditions, the retention time of (S)-**1** was 10.3 min and that of (R)-**1** was 16.2 min.

(2) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, 3, 1137.

(3) Funahashi, Y.; Nakaya, K.; Hirota, S.; Yamauchi, O.; *Chem. Lett.*, **2000**, 1172.

PMS(tm) Calculations on ((-)-sparteine)copper complexes of S-VANOL and R-VANOL

R-VANOL-Cu(II) Complex

S-VANOL-Cu(II) Complex

Angles	R-VANOL-Cu Complex:	S-VANOL-Cu Complex:
N(1)-Cu-N(2)	94.1	93.8
N(1)-Cu-O(1)	112.7	89.4
O(1)-Cu-O(2)	96.7	98.4
N(2)-Cu-O(2)	92.0	93.5
N(1)-Cu-O(2)	101.8	157.8
N(2)-Cu-O(1)	149.2	139.8
Distortion dihedral angle	85.5	40.6

Note:

1) PM3(tm) semiempirical calculations with SPARTAN SGI v 5.1.3 (Wavefunction, Inc.: 18401 Von Karman Avenue, Suite 370; Irvine, CA 92612)

2) ΔH_f° for the (S)-VANOL complex is -14.781 Kcal/mol and ΔH_f° for the (R)-VANOL complex is -10.867 Kcal/mol.