A New Cationic, Chiral Catalyst For Highly Enantioselective Diels-Alder Reactions

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Supporting Information

Materials and Methods: For moisture-sensitive reactions, glassware was flame-dried under high vacuum, and cooled under positive nitrogen pressure. All solvents were distilled over appropriate drying agents under nitrogen. Thin-layer chromatography was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm). Flash chromatography was performed using Baker silica gel (40 μ m particle size). Gas chromatography (GC) analyses were performed on Hewlett-Packard 6850 Series GC equipped with flame-ionization detection. The J & W Cyclosil- β (30 m x 0.25 mm) column was used for enantiomeric resolutions. To boron tribromide was added octene until the yellow hue (Br_2) disappeared, after which it was distilled from CaH_2 , and stored neat at -20°C . Methacrolein, ethylacrolein, and 2,5-dimethylquinone were distilled from CaH_2 , and stored neat at -80°C . Angelic aldehyde (*Z*-2-methyl-2-butenal) was prepared via Swern oxidation¹¹ of angelic alcohol,¹² and distilled. Cyclopentene-1-carboxaldehyde was prepared and purified via literature precedent.¹³ 1,3-Cyclopentadiene was generated from the dimer at 170°C , redistilled, and stored neat at -80°C .

Illustrative Procedure for Catalyst Preparation and Diels-Alder Reaction. Ligand **1** was dried by azeotropic distillation from toluene or benzene and all volatiles were removed under vacuum (< 0.5 mm) for 2 h with magnetic stirring. Ligand **1** (21.2 mg, 0.059 mmol) was dissolved in CH_2Cl_2 (1.5 mL) under N_2 , cooled to 10°C , and 2,6-di-*tert*-butylpyridine (13.3 μL , 0.059 mmol) was added. Boron tribromide (59 μL , 0.059 mmol, as a 1.0M solution in CH_2Cl_2) was added slowly to the reaction mixture and a colorless precipitate formed. The cold bath was removed and the reaction mixture was allowed to warm to room temperature over 4-5 min during which time the precipitate had dissolved. Fifteen min after dissolution of the solid, the colorless, clear reaction mixture was cooled to -94°C (liq. N_2 , hexanes), and methacrolein (49 μL , 0.59 mmol) was added directly to the stirred reaction mixture. A precooled solution (-94°C) of 1,3-cyclopentadiene (247 μL , 2.95 mmol, in 494 μL CH_2Cl_2) was added by cannula along the cold flask wall to the reaction

¹¹ Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, 43, 2480.

¹² Zaidlewicz, M.; Uzarewicz, A.; Sarnowski, R. *Synthesis* **1979**, 62.

¹³ Kozikowski, A. P.; Tuckmantel, W. *J. Org. Chem.* **1991**, 56, 2826.

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mixture over a 10 minute period. The reaction was monitored by TLC, and quenched with Et₃N (*ca.* 100 μ L) upon completion. The reaction mixture was carefully concentrated (volatile product) under reduced pressure, and the slurry was subjected to flash chromatography on silica gel (Et₂O-pentane; for less volatile products, EtOAc-hexanes) to furnish (1*S*, 2*R*, 4*S*)-bicyclo[2.2.1]hept-5-ene-2-methyl-2-carboxaldehyde (77.2 mg, 96%) and ligand **1** (21.2 mg, >99%). Product R_f values were as follows (10:1 hexanes-EtOAc): 2,6-di-*tert*-butylpyridine, R_f = 0.78; (1*S*, 2*R*, 4*S*)-bicyclo[2.2.1]hept-5-ene-2-methyl-2-carboxaldehyde, R_f = 0.46; ligand **1**, R_f = 0.28.

Characterization Data for Diels-Alder Adducts

(1*S*, 2*R*, 4*S*)-bicyclo[2.2.1]hept-5-ene-2-methyl-2-carboxaldehyde. The physical and spectral data were identical to those previously reported for this compound:¹⁴ ¹H NMR (500 MHz, CDCl₃) δ 9.68 (s, 1H), 6.28 (dd, *J* = 5.6, 3.1 Hz, 1H), 6.09 (dd, *J* = 5.7, 3.1 Hz, 1H), 2.87 (bs, 1H), 2.80 (bs, 1H), 2.23 (dd, *J* = 12.0, 3.9 Hz, 1H), 1.38 (d, 2H), 1.00 (s, 3H), 0.75 (bd, *J* = 12.0 Hz, 1H). Diastereoselectivity (*exo-endo* ratio) was determined by ¹H-NMR analysis of the crude reaction mixture: 9.68 (s, *exo*), 9.38 (s, *endo*). Enantioselectivity was determined by reduction with NaBH₄, esterification to the (*R*)-MTPA ester and ¹H NMR integration (500 MHz): δ 4.34 (d, minor, 1H), 4.31 (d, major, 1H), 4.25 (d, major, 1H), 4.22 (d, minor, 1H) at 47:1 (96% ee). Absolute configuration was determined by comparison with an authentic sample and from optical rotation: $[\alpha]$ -16.6 (*c* = 1.22, CHCl₃, 96% ee, pure *exo*).

(1*S*, 2*R*, 4*S*)-bicyclo[2.2.1]hept-5-ene-2-ethyl-2-carboxaldehyde. The physical and spectral data were identical to those previously reported for this compound:¹⁵ ¹H NMR (500 MHz, CDCl₃) δ 9.70 (s, 1H), 6.26 (dd, *J* = 5.8, 3.2 Hz, 1H), 6.05 (dd, *J* = 5.8, 3.2 Hz, 1H), 2.95 (bs, 1H), 2.88 (bs, 1H), 2.15 (dd, *J* = 12.0, 3.8 Hz, 1H), 1.65-1.30 (m, 5H), 0.77 (t, *J* = 7.4 Hz, 3H); $[\alpha]$ ²² -24.4 (*c* 0.41, CHCl₃). Diastereoselectivity (*exo-endo* ratio) was determined by ¹H NMR analysis of the crude reaction mixture: 9.70 (s, *exo*), 9.42 (s, *endo*). Enantioselectivity was determined by ¹H NMR

¹⁴ Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, 124, 3808.

analysis after conversion to the chiral acetal with (2*R*,4*R*)-2,4-pentanediol and integration: ^1H NMR (500 MHz, CDCl_3) δ 4.85 (s, major, 1H) and 4.82 (s, minor, 1H) at 35:1 (94% ee).

(1*S*, 2*R*, 6*S*, 7*R*)-Tricyclo[5.2.1.0]dec-8-ene-2-carboxaldehyde. The physical and spectral data were identical to those previously reported for this compound:¹⁶ ^1H NMR (500 MHz, CDCl_3) δ 9.70 (s, 1H), 6.27 (dd, $J = 5.5, 3.0$ Hz, 1H), 6.17 (dd, $J = 5.3, 3.3$ Hz, 1H), 2.92 (bs, 1H), 2.84-2.81 (m, 1H), 2.81 (bs, 1H), 1.82-1.77 (m, 1H), 1.72-1.63 (m, 2H), 1.61 (d, $J = 8.5$ Hz, 1H), 1.57 (d, $J = 8.5$ Hz, 1H), 1.54-1.45 (m, 1H), 1.25-1.19 (m, 1H), 1.13-1.06 (m, 1H). Diastereoselectivity (*exo-endo* ratio) was determined by ^1H NMR analysis of the crude reaction mixture: 9.70 (s, *exo*), 9.42 (s, *endo*). Enantioselectivity was determined by integration from GC analysis: Retention times at 120 °C isotherm: (+/-) 13.25, 13.40 (*endo* enantiomers) 13.85, 14.58 (*exo* enantiomers). Reaction sample 13.85 (major): 14.58 (minor) at 20:1 (90% ee). Absolute configuration was determined by comparison with an authentic sample and from optical rotation: $[\alpha] +20.0$ (c 1.27, CHCl_3 , 96% ee, pure *exo*).

(1*S*, 2*R*, 3*R*, 4*S*)-bicyclo[2.2.1]hept-5-ene-2,3-dimethyl-2-carboxaldehyde. ^1H NMR (400 MHz, CDCl_3) δ 9.63 (s, 1H), 6.28 (dd, $J = 6.0, 2.8$ Hz, 1H), 6.19 (dd, $J = 5.6, 3.2$ Hz, 1H), 2.80 (bs, 1H), 2.75 (bs, 1H), 2.53 (dq, $J = 7.2, 3.2$ Hz, 1H), 1.42-1.34 (m, 2H), 0.85 (s, 3H), 0.74 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 205.92, 137.83, 135.10, 55.88, 50.18, 49.03, 46.31, 37.15, 15.28, 14.92; IR (thin film) 1716, 755, 731 cm^{-1} ; $[\alpha]^{22} + 74.6$ (c 0.70, CHCl_3). Enantioselectivity was determined by reduction with NaBH_4 , esterification to the (*R*)-MTPA ester and ^1H NMR integration (500 MHz, CDCl_3): δ 0.70 (d, major 3H), 0.66 (d, minor, 3H) at 12.9:1 (86% ee).

¹⁵ Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, 120, 6920.

¹⁶ Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, 124, 9992.

(1S, 2S, 7R, 8S)-2,5-Dimethyl-tricyclo[6.2.1.0]undeca-4,9-diene-3,6-dione. The physical and spectral data were identical to those previously reported for this compound:¹⁷ ¹H NMR (500 MHz, CDCl₃) δ 6.37 (d, J = 1.5 Hz, 1H), 6.03 (dd, J = 5.5, 3.0 Hz, 1H), 5.88 (dd, J = 5.5, 3.0 Hz, 1H), 3.33 (s, 1H), 2.98 (s, 1H), 2.75 (d, J = 4.0 Hz, 1H), 1.85 (d, J = 1.5 Hz, 1H), 1.60 (d, J = 9.5 Hz, 1H), 1.44 (d, J = 9.0 Hz, 1H), 1.37 (s, 3H). Enantioselectivity was determined by GC analysis of the saturated species at C-9,10, accomplished with Pd/C, H₂, and EtOH at 0 °C: Retention times at 155 °C isotherm: (+/–) 16.49, 17.23. Reaction sample 16.49 (minor): 17.23 (major) at 1:13.7 (86% ee). Absolute configuration was determined by comparison with an authentic sample and from optical rotation: $[\alpha]$ –10.1 (c = 1.06, CHCl₃, 86% ee).

Characterization Data for Compounds 1, 4-11.

(*E,E*)-1,6-Diphenylhexa-1,5-diene (4). Cinnamyl alcohol (175 ml, 1.36 mol) was dissolved in Et₂O (1.3 L) in a 5-L, two-necked round-bottom flask, and cooled to 0 °C. Phosphorus tribromide (47.4 mL, 0.5 mol) was added to the reaction mixture via syringe every 3 min in 5 ml portions. Upon full addition, the cloudy yellow solution was warmed to room temperature over 10 min and stirred for an additional 15 min. Complete conversion of cinnamyl alcohol (R_f = 0.10, 10:1 hexanes–EtOAc) to cinnamyl bromide was verified by thin layer chromatography (R_f = 0.65, 10:1 hexanes–EtOAc). Saturated aqueous NH₄Cl (50 mL) was slowly added, a colorless precipitate appeared, and the mixture was stirred for an additional 2 h. The ether layer was decanted into a 6" deep, 4" wide SiO₂ column, and was eluted directly into pre-dried, nitrogen filled 3-neck, 5-L flask. The reaction flask was rinsed with Et₂O (3 x 500 mL) and flashed through the column to assure full transfer of the cinnamyl bromide.

The 5-L, 3-necked flask containing the light yellow ethereal solution of cinnamyl bromide was kept under a nitrogen atmosphere and equipped with an overhead mechanical stirrer and an internal low-temperature thermometer. The solution was vigorously stirred and cooled to –40 °C internally (–45 °C external), and zinc powder (422 g, 6.45 mol) was added. Iodine (737 g, 2.9 mol) was added to the reaction mixture in 10-20 gram portions so as to not allow the internal temperature

¹⁷ Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003** ASAP

reach above $-30\text{ }^{\circ}\text{C}$ (Note 1). Once the I_2 was consumed, (Note 2) the reaction was allowed to recool ($-35\text{ }^{\circ}\text{C}$) before another dose of I_2 was added. Once all of the I_2 was consumed, the reaction was quenched slowly with isopropanol (150 mL). The reaction mixture was allowed to reach room temperature and stirring was ceased. The ethereal solution was decanted from the solid portion and filtered through a large Büchner funnel. The reaction flask was rinsed, decanted and filtered with Et_2O (3 X 400 mL) to assure full transfer of the product. The ethereal solution was washed in a separatory funnel with water (2 x 1 L) and brine (1 x 500 mL). The collected water layers were re-extracted from with ether (2 x 500 mL), the organic layers were combined, dried over MgSO_4 and filtered. The mixture was concentrated under reduced pressure to yield a yellow slurry, which was dissolved in hot MeOH (3 L), and placed in a freezer ($-20\text{ }^{\circ}\text{C}$) where by colorless crystalline needles emerged. The precipitate was collected via vacuum filtration. The recovered MeOH solution was concentrated under reduced pressure and the remaining slurry was resubjected to crystallization conditions. The combined crystallizations furnished (*E,E*)-1,6-diphenylhexa-1,5-diene (61.2 g, 39%, after 3 crystallizations) as colorless crystals. mp = $78\text{--}80\text{ }^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 500 MHz) δ 7.42 (d, $J = 7.5\text{ Hz}$, 4H), 7.35 (t, $J = 7.5\text{ Hz}$, 4H), 7.25 (t, $J = 7.5\text{ Hz}$, 2H), 6.50 (d, $J = 16.0\text{ Hz}$, 2H), 6.34 (dt, $J = 15.5, 6.5\text{ Hz}$, 2H), 2.46-2.45 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 138.00, 130.66, 130.27, 128.80, 127.23, 126.29, 33.21; IR (thin film) $1450, 1442, 967\text{ cm}^{-1}$.

Note 1: Optimum formation of the desired product occurs at lowest possible reaction temperature. If the internal temperature increases due to heavy exotherm, the ratio of desired product to undesired coupling product significantly decreases.

Note 2: Addition of I_2 causes a color change to reddish brown. The iodine is consumed when the reaction color returns to milky grayish-white.

(1*R*,2*R*,5*R*,6*R*)-1,6-Diphenylhexan-1,2,5,6-tetra-ol (5). H_2O (400 mL) and *t*-BuOH (400 mL) were added to a securely-clamped 5-L, 2-necked flask equipped with a mechanical stirrer, and cooled to $+4\text{ }^{\circ}\text{C}$. $(\text{DHQD})_2\text{PHAL}$ (1.33 g, 1.71 mmol), K_2CO_3 (70.8 g, 513 mmol), $\text{K}_2\text{OsO}_4\cdot 2\text{H}_2\text{O}$ (63 mg, 0.171 mmol), $\text{K}_3\text{Fe}(\text{CN})_6$ (168.9 g, 513 mmol), and methanesulfonamide (8.12 g, 85.5 mmol) were added, and the heterogeneous orange mixture was stirred vigorously at $+4^{\circ}\text{C}$ for 20 min. (*E,E*)-1,6-diphenylhexa-1,5-diene (**4**, 20.0 g, 85.5 mmol) was partially dissolved in warm hexanes (240 mL) in a 1-L Erlenmeyer flask, and the warm hexane–hexadiene mixture was quickly

added to the vigorously stirred reaction mixture. The Erlenmeyer flask was washed with hexane (20 mL) to assure complete transfer of the hexadiene (Note 3). The reaction was monitored by TLC (disappearance of starting diene, $R_f = 0.75$, 10:1 hexanes-EtOAc, Note 4). Saturated aqueous Na_2SO_3 (200 mL) was added, the reaction mixture was allowed to stir for 10 min, then was transferred to a separatory funnel and partitioned between water (200 mL) and EtOAc (750 mL). The layers were separated, and the water layer was re-extracted with EtOAc (2 x 200 mL). The organic layers were combined, dried over Na_2SO_4 , filtered, then concentrated under reduced pressure to yield a white solid. Recrystallization with hot EtOAc-hexanes yielded (1*R*,2*R*,5*R*,6*R*)-1,6-diphenyl-hexane-1,2,5,6-tetraol (25.1 g, 97%) as a single isomer (Note 5). mp = 123-125 °C; ^1H NMR (CD_3COCD_3 , 400 MHz) δ 7.35-7.20 (m, 10H), 4.37-4.35 (m, 2H), 4.30 (m, 2H), 3.95 (m, 2H), 3.58-3.48 (m, 2H), 1.53-1.43 (m, 2H), 1.38-1.28 (m, 2H); ^{13}C NMR (CD_3COCD_3 , 100 MHz) δ 143.04, 128.04, 127.34, 127.29, 77.72, 75.93, 29.47; IR (thin film) 3537 (broad), 1643, 1047 cm^{-1} ; HRMS ($\text{M} + \text{NH}_4^+$) calcd for $[\text{C}_{18}\text{H}_{26}\text{NO}_4]$ 320.1862, found 320.1871; $[\alpha]^{22} -12.97$ (c 0.73, acetone).

Note 3: The reaction appeared biphasic, with a bright yellow upper layer, and an orange lower layer. Upon reaction completion, the mixture had turned to a homogenous-colored mustard-yellow mixture.

Note 4: The starting material was consumed after 40 h; the reaction was allowed to stir an additional 24 h.

Note 5: Diastereomeric excess was determined by ^1H NMR analysis. Enantiomeric excess was determined using Chiracel AD HPLC at 254 nm using 1% *i*-PrOH–Hexanes. (+/–) 16.7 min, 18.3 min; crystallized product, 16.7 min only detectable peak.

(1*R*,2*R*,5*R*,6*R*)-1,6-Diphenyl hexane-(1,2)-(5,6)-bis-carbonate (6). (1*R*,2*R*,5*R*,6*R*)-1,6-diphenyl-hexane-1,2,5,6-tetraol (**5**, 22.0 g, 73.0 mmol) was dissolved in CH_2Cl_2 (1.5 L) and Et_3N (81.3 mL, 584 mmol) and was cooled to -50°C . A room temperature solution of triphosgene (16.6 g, 56.0

mmol) in CH_2Cl_2 (200 mL) was added to the stirred reaction mixture via cannula over a 20 minute period, and the salty slurry was allowed to warm to room temperature over 30 min. After 1 hour at room temperature, satd. NaHCO_3 (150 mL) was added, and the reaction mixture was concentrated under reduced pressure in order to remove most of the CH_2Cl_2 . The slurry was taken up in Et_2O (1.5 L) and satd NaHCO_3 (750 mL) and transferred to a 4-L separatory funnel. The layers were separated, and the water layer was re-extracted with Et_2O (2 x 500 mL). The organic portions were combined, washed with brine (300 mL), and dried over MgSO_4 . The ethereal solution was decanted directly onto a 3"-deep, 4"-wide SiO_2 column and eluted into a round bottom flask. Additional Et_2O (750 mL) was used to flush any remaining product. The solvent was removed under reduced pressure to afford (1*R*,2*R*,5*R*,6*R*)-1,6-diphenylhexane-(1,2)-(5,6)-bis-carbonate (28.2 g, quantitative) as a flakey white solid at approximately 95% purity (^1H NMR). The crude material can be carried on to the next step as is, or be further purified via recrystallization (EtOAc -hexanes) or flash chromatography (3:1 hexanes- EtOAc to 1:1 hexanes- EtOAc , R_f = 0.63, 1:1 EtOAc -hexanes); mp = 131-133 °C; ^1H NMR (CDCl_3 , 500 MHz) δ 7.43-7.42 (m, 6H), 7.34-7.32 (m, 4H), 5.20 (d, J = 7.8 Hz, 2H), 4.52-4.49 (m, 2H), 2.14-2.07 (m, 2H), 1.99-1.93 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 153.80, 134.77, 129.93, 129.27, 83.08, 82.84, 28.23; IR (thin film) 1800 cm^{-1} ; $[\alpha]^{22} +8.37$ (c 10.27, CHCl_3).

(2*R*,5*R*)-1,6-Diphenylhexane-2,5-diol (6a). Crude (1*R*,2*R*,5*R*,6*R*)-1,6-Diphenylhexane-(1,2)-(5,6)-bis-carbonate (**6**, 73.0 mmol) was dissolved in EtOH (750 mL) and acetone (400 mL) in a 3-L, 2-neck flask equipped with an overhead mechanical stirrer. Raney Ni (*ca.* 75 g) was added as a slurry in acetone (50 mL), and the vigorously stirred reaction mixture was exposed to 1 atm H_2 (Note 5). The reaction was monitored by TLC (Note 6); once complete, the reaction flask was flushed with N_2 gas, the reaction mixture was allowed to settle, and the solution was decanted into a large Erlenmeyer flask equipped with a large magnetic stir bar (Note 7). The reaction flask was rinsed with additional acetone (3 x 200 mL) to assure complete product transfer. The grayish mixture was decanted through a cotton plug into a larger round-bottom flask. All except approximately 400 mL of the volatiles were removed under reduced pressure, and the resulting milky gray slurry was pushed through a 3"-deep, 4"-wide SiO_2 column and the colorless, clear eluent was collected in a large round bottom flask. Additional EtOAc (50 mL) was used to assure complete product transfer. The volatiles were removed under reduced pressure, and the resulting

colorless solid was recrystallized from EtOAc-hexanes to afford (2*R*,5*R*)-1,6-diphenylhexane-2,5-diol (17.68 g, 90%, two steps) as a flakey colorless solid. mp = 66-68 °C; ¹H NMR (CDCl₃, 500 MHz) δ 7.31 (t, *J* = 7.0 Hz, 4H), 7.24-7.22 (m, 2H), 7.20 (d, *J* = 6.5 Hz, 4H), 3.85-3.81 (m, 2H), 2.82 (bs, 1H), 2.78 (dd, *J* = 13.5, 5.5 Hz, 2H), 2.72 (dd, *J* = 13.5, 8.0 Hz, 2H), 1.76-1.70 (m, 2H), 1.61-1.55 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 138.51, 129.36, 128.45, 126.35, 72.93, 44.21, 33.36; IR (thin film) 3356 (broad), 1495, 1454, 1080, 1031, 744, 700 cm⁻¹; [α]²² -12.5 (*c* 2.42, CHCl₃).

Note 5: The reduction of the *bis*-carbonate was most efficient when it was a quicker reaction process. If the reaction occurred over several h, an unidentified biproduct forms (*R*_f = 0.9, 1:1 EtOAc-hexanes). For this reason, vigorous stirring and a heavy excess of Raney-Ni is used.

Note 6: The *R*_f values of the three compounds are as follows: *bis*-carbonate (*R*_f = 0.63, 1:1 EtOAc-hexanes), mono-carbonate-mono-alcohol (*R*_f = 0.52, 1:1 EtOAc-hexanes), diol (*R*_f = 0.42, 1:1 EtOAc-hexanes).

Note 7: The magnetic stir bar is used to capture any remaining Raney-Ni.

(2*R*,5*R*)-1,6-Diphenylhexane-2,5-*bis*-methanesulfonate (7). (2*R*,5*R*)-1,6-diphenylhexane-2,5-diol (**6a**, 757 mg, 2.80 mmol) was dissolved in CH₂Cl₂ (25 mL) and Et₃N (1.12 mL, 8.02 mmol) and was cooled to -30 °C. Methanesulfonyl chloride (475 μL, 6.17 mmol) was added dropwise, and the reaction was allowed to warm to room temperature over a 20-minute period. H₂O (*ca.* 5 mL) was added, the mixture was diluted with EtOAc (75 mL), and the layers were separated. The water layer was re-extracted with EtOAc (2 x 15 mL), the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated. The slurry was subjected to flash chromatography (4:1 hexanes-EtOAc to 2:1 hexanes-EtOAc) to afford (2*R*,5*R*)-1,6-diphenylhexane-2,5-*bis*-methanesulfonate (1.15 g, 97%) as a colorless solid. mp = 99-101 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.34-7.23 (m, 10H), 5.01-4.97 (m, 2H), 3.02 (dd, *J* = 14.3, 4.4 Hz, 2H), 2.90 (dd, *J* = 14.3, 9.1 Hz, 2H), 2.29 (s, 6H), 2.04-1.85 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ 137.29, 130.03, 128.97, 127.43, 84.57, 41.60, 37.86, 30.76; IR (thin film) 1347, 1172, 903 cm⁻¹; [α]²² +17.0 (*c* 0.70, CHCl₃).

(2*S*,5*S*)-*N*-2,5-Tribenzylpyrrolidine (7a). (2*R*,5*R*)-1,6-diphenylhexane-2,5-*bis*-methanesulfonate (**7**, 248 mg, 0.58 mmol) and benzylamine (317 μ L, 2.9 mmol) were heated to 80° C for 10 h. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (5 mL) and satd. NaHCO₃ (5 mL) and the layers were separated. The water layer was re-extracted with EtOAc (2 x 5 mL). The organic layers were combined, concentrated and subjected to flash chromatography (10:1 hexanes–EtOAc) to afford (2*S*,5*S*)-*N*-2,5-tribenzylpyrrolidine (162 mg, 92%) as a light yellow oil (ca. 5% *meso*-isomer). ¹H NMR (CDCl₃, 400 MHz) δ 7.53 (d, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.2 Hz, 4H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.09 (d, *J* = 7.2 Hz, 4H), 4.18 (d, *J* = 13.6 Hz, 1H), 3.91 (d, *J* = 13.8 Hz, 1H), 3.29-3.25 (m, 2H), 3.07 (dd, *J* = 13.6, 3.6 Hz, 2H), 2.41 (dd, *J* = 13.2, 10.0 Hz, 2H), 1.83-1.78 (m, 2H), 1.60-1.52 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 140.72, 140.55, 129.50, 128.89, 128.54, 128.47, 127.06, 126.00, 62.60, 52.40, 37.54, 27.57.

(2*S*,5*S*)-2,5-Dibenzylpyrrolidine ((2*S*,5*S*)-2,5-Dibenzylpyrrolidinium Hydrochloride) (8). (2*S*,5*S*)-*N*-2,5-tribenzylpyrrolidine (**7a**, 372 mg, 1.22 mmol) was dissolved in EtOH (10 mL) and 10% Pd–C (100 mg) was added. The reaction mixture was subjected to 1 atm of H₂ gas for 3 h. The flask was flushed with N₂ gas, the reaction mixture was vacuum filtered through Celite and concentrated to afford (2*S*,5*S*)-2,5-dibenzylpyrrolidine (301 mg, 98%) as a light yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ 7.30-7.26 (m, 4H), 7.22-7.16 (m, 6H), 3.53-3.46 (m, 2H), 2.75 (dd, *J* = 13.6, 7.6 Hz, 2H), 2.66 (dd, *J* = 13.2, 6.8 Hz, 2H), 1.98-1.90 (m, 2H), 1.78 (bs, 1H), 1.52-1.43 (m, 2H); ¹³C NMR (CDCl₃, 400 MHz) δ 140.23, 129.21, 128.62, 126.29, 59.10, 43.29, 31.52; HRMS [*M* + *H*] calcd for [C₁₈H₂₂N] 252.1752, found 252.1741; IR (thin film) 3062, 3027, 1603, 1496, 1453, 1406 cm⁻¹; [α]_D²² +49.1 (*c* 2.01, CHCl₃).

The hydrochloride salt was prepared via flushing a solution of (2*S*, 5*S*)-2,5-dibenzylpyrrolidine in EtOAc with HCl gas. The salt was recrystallized from hot EtOAc. mp = 188-190 °C; ¹H NMR (CDCl₃, 300 MHz) δ 7.30-7.19 (m, 10H), 4.04-3.91 (m, 2H), 3.48 (dd, *J* = 13.2, 4.8 Hz, 2H), 2.99 (dd, *J* = 13.2, 10.2 Hz, 2H), 2.08-1.96 (m, 2H), 1.80-1.66 (m, 2H); [α]_D²² +28.4 (*c* 0.73, CHCl₃).

(2*S*,5*S*)-*N*-2-Hydroxybenzyl-2,5-Dibenzylpyrrolidine (1). (2*S*,5*S*)-2,5-dibenzylpyrrolidine (**8**, 112 mg, 0.46 mmol) was dissolved in toluene (1.5 mL) and 2-hydroxybenzyl benzoate (115 mg, 0.50 mmol) was added. The mixture was heated to reflux for 1 h, allowed to cool to room temperature, and partitioned between satd. NaHCO₃ (15 mL) and EtOAc (15 mL). The water layer was re-extracted with EtOAc (2 x 5 mL), the organic portions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography furnished (2*S*,5*S*)-*N*-2-hydroxybenzyl-2,5-dibenzylpyrrolidine (163 mg, 99%) as a colorless oil. ¹H NMR (CDCl₃, 400 MHz) δ 7.30-7.19 (m, 6H), 7.12 (d, *J* = 6.4 Hz, 2H), 7.06 (d, *J* = 7.2 Hz, 4H), 6.90 (dd, *J* = 8.0, 0.4 Hz, 1H), 6.87 (dt, *J* = 7.2, 1.2 Hz, 1H), 4.35 (d, *J* = 14.0 Hz, 1H), 3.96 (d, *J* = 14.0 Hz, 1H), 3.31-3.25 (m, 2H), 3.16 (dd, *J* = 12.8, 3.6 Hz, 2H), 2.45 (dd, *J* = 12.8, 10.4 Hz, 2H), 1.93-1.84 (m, 2H), 1.66-1.59 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 158.51, 139.47, 129.34, 129.03, 128.72, 128.30, 126.45, 122.37, 119.48, 116.23, 62.73, 51.42, 27.56; IR (thin film) 2926 (bs), 1253, 741, 699 cm⁻¹. HRMS [*M* + *H*] calcd for [C₂₅H₂₈NO] 358.2171, found 358.2182; [α]_D²² -68.3 (*c* 1.08, CHCl₃).

Cyclic sulfate (10). (2*R*,5*R*)-1,6-diphenylhexane-2,5-diol (**6a**, 7.27 g, 26.9 mmol) was dissolved in CH₂Cl₂ (200 mL) and Et₃N (12.4 mL, 89.1 mmol) and was cooled to 0° C. A solution of thionyl chloride (2.55 mL, 35.0 mmol) in CH₂Cl₂ (8 mL) was added dropwise, and the reaction mixture was warmed to room temperature over a 10 minute period and was allowed to stir for an additional 90 min. The dark reaction mixture was quenched with H₂O, diluted with Et₂O (300 mL), and the layers were separated. The water layer was re-extracted with Et₂O (2 x 75 mL), the organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated. To the resulting slurry was added CH₃CN (60 mL), CCl₄ (60 mL) and H₂O (90 mL). NaIO₄ (11.5 g, 53.8 mmol) was added in one portion, followed by a catalytic amount of RuCl₃ (15 mg). The mixture was stirred at room temperature for 60 min, was vacuum filtered, and rinsed with EtOAc (2 x 20 mL) to assure complete product transfer. H₂O (20 mL) was added, the layers were separated, and the inorganic layer was re-extracted with EtOAc (2 x 20 mL). The organic portions were washed with brine, dried over Na₂SO₄, filtered and concentrated. Crystallization from minimal EtOAc and

hexanes afforded the cyclic sulfate (7.51 g, 84 %) as a colorless solid. Mp = 125-128 °C (dec.); ¹H NMR (CDCl₃, 400 MHz) δ 7.34-7.25 (m, 6H), 7.20 (d, *J* = 6.8 Hz, 4H), 4.88-4.82 (m, 2H), 3.10 (dd, *J* = 14.4, 6.4 Hz, 2H), 2.89 (dd, *J* = 14.0, 6.8 Hz, 2H), 1.93-1.81 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ 135.26, 129.44, 128.62, 127.12, 84.72, 41.51, 31.62; IR (thin film) 3088, 1381, 1185, 894, 694 cm⁻¹; HRMS [*M* + *H*] calcd for [C₁₈H₂₁O₄S] 333.1161, found 333.1155; [*α*]²² +11.4 (*c* 2.42, CHCl₃).

2'*S*,5'*S*-2-[2',5'-Dibenzylpyrrolidino]-Phenol (11). Cyclic sulfate **10** (1.1 g, 3.3 mmol) was dissolved in toluene (4 mL) in an uncapped 25 mL recovery flask equipped with a magnetic stir bar. *O*-aminophenol (1.8 g, 16.6 mmol) was added and the flask was dipped into a 140 °C oil bath. The toluene was allowed to boil off, and the resulting slurry was exposed to the 140 °C heat for an additional 30 min. The mixture was dissolved in EtOAc and NaHCO₃, and transferred to a separatory funnel. The layers were separated, and additional EtOAc (2 x 15 mL) was used to re-extract from the aqueous layer. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude oil was subjected to flash chromatography (hexanes to 10:1 hexanes–EtOAc) to yield 2-[(2*S*,5*S*)-2,5-dibenzylpyrrolidine]-phenol (882 mg, 78%) as a viscous colorless oil. ¹H NMR (CDCl₃, 400 MHz) δ 7.29-6.94 (m, 14H), 3.95 (bs, 1H), 3.78 (bs, 1H), 2.89 (d, *J* = 12.0 Hz, 1H), 2.63 (d, *J* = 10.8 Hz, 1H), 2.47 (dd, *J* = 10.8, 10.8 Hz, 1H), 2.29 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.05-2.00 (m, 1H), 1.85-1.80 (m, 1H), 1.80-1.60 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 153.56, 139.46, 139.26, 132.61, 129.50, 129.29, 128.54, 126.39, 126.21, 124.97, 120.05, 114.74, 63.41, 61.59, 41.10, 37.92, 29.10, 28.81; IR (thin film) 3400 (bs), 1491, 1453, cm⁻¹. HRMS [*M* + *H*] calcd for [C₂₄H₂₅NO] 343.1936, found 343.1933; [*α*]²² +43.1 (*c* 1.53, CHCl₃).