Total Synthesis of Enantiopure (+)-γ-Lycorane Using Highly Efficient Pd-Catalyzed Asymmetric Allylic Alkylation

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SUPPORTING INFORMATION

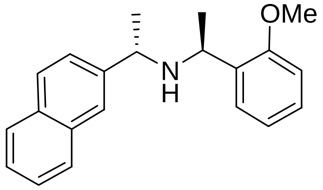
General Method and Material:

^{1}H and ^{13}C and ^{31}P NMR were measured on a Varian Inova-500 NMR (500 MHz ^{1}H, and 125 MHz ^{13}C), a Varian Inova-400 NMR (400 MHz ^{1}H; 100 MHz ^{13}C; 162 MHz ^{31}P) or a Varian Gemini-2300 (300 MHz ^{1}H; 75 MHz ^{13}C; 121.5 MHz ^{31}P) spectrometer in a deuterated solvent using residual protons ($CHCl_3$:^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm. C_6H_6: ^{1}H, 7.15 ppm) as the internal standard or phosphoric acid as the external reference (^{31}P 0.00 ppm). Analytical HPLC in reverse phase was carried out with a Shimadzu LC-2010A HPLC system using a Chiralpak AD-RH analytical column. Analytical HPLC in normal phase was carried out with a Waters M-45 system equipped with a Waters 484 UV detector using a Daicel Chiralpak AD column. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Helmer Model 241 polarimeter. Infrared spectra were recorded with Shimadzu FTIR-8400S spectrophotometer. TLC analyses were performed using Merck DC Alufolien $60F_{254}$ aluminum pre-coated silica gel plates. Flash chromatography was carried out using Silicyle Silia*Flash*P60® silica gel (particle size 40–63 μm). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratory, University of Illinois Urbana-Champaign, Urbana, IL. Unless otherwise noted all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques. Solvents were reagents grade and freshly distilled before use. Tetrahydrofuran (THF) and dichloromethane were dried and degassed using an Innovative Technology PureSolv^{TM} solvent purification system. Acetonitrile was distilled from calcium hydride. Anhydrous *N,N*-dimethylformamide

(DMF) was purchased from DrySolv® and used without further purification. Other solvents were used without purification. Chemicals and reagents were purchased from Aldrich or Fisher Scientific and used without further purification unless otherwise noted.

Enantiopure *N,N*-bis(1-arylethyl)amines were synthesized following the reported procedure and were in full agreement with the experimental data.[1,2] *N,N*-[(*S*)-(1-(Naphtalen-2-yl)ethyl][(*S*)-1-(2-methoxyphenyl)ethyl]amine was synthesized using the same method.[1,2] 1,4-*cis*-Dibenzoyloxycyclohex-2-ene (**1**) was prepared according to the literature method.[3] 2-Bromopiperonal was prepared according to the reported procedure.[4]

***N,N*-[(*S*)-1-(Naphtalen-2-yl)ethyl][(*S*)-1-(2-methoxyphenyl)ethyl]amine:**



The crude amine was purified by flash chromatography on silica gel (eluent hexanes/ethyl acetate = 10:1 then 8:1) leading to diastereoisomerically pure amine as a light yellow oil (69% yield). Rf = 0.33 (SiO_2, hexanes/ethyl acetate = 3/1); $[\alpha]_D^{22}$ - 187 (*c* 1.66, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.6 Hz, 3H), 1.36 (d, *J* = 6.6Hz, 3H), 1.92 (br.s., 1H), 3.70 (q, *J* = 6.6Hz, 1H), 3.74 (s, 3H), 3.79 (q, *J* = 6.6Hz, 1H), 6.88-6.98 (m, 2H), 7.15 (dd, *J* = 1.5, 7.2Hz, 1H), 7.14-7.27 (m, 1H), 7.43-7.49 (m, 3H), 7.62 (s, 1H), 7.78-7.85 (m, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 22.8, 25.07, 51.59, 55.10, 55.45, 110.69, 120.58, 125.22, 125.24, 125.50, 125.70, 127.52, 12761, 127.70, 127.92, 127.95, 132.79, 133.29, 133.47, 143.41, 157.53. HRMS (EI) calcd for $C_{21}H_{23}NO$ $[M]^+$ 305.1772; found 305.1779 (Δ = 2.2 ppm).

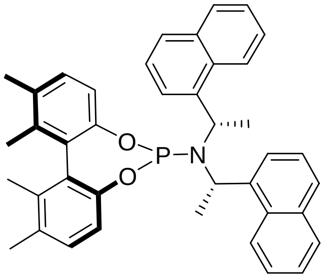
Ligand synthesis

General procedure for preparations of phosphoramidite ligands:

Phosphorous trichloride (87 μL, 1.0 mmol) was added dropwise to Et_3N (70 μL, 5 mmol) at 0 °C under N_2. To this mixture was added a solution of an amine (1.0 mmol) in THF

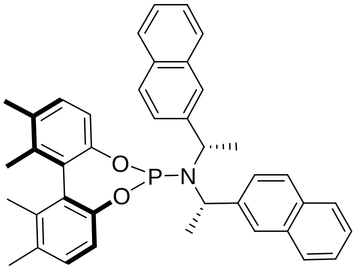
(2 mL). The mixture was stirred at room temperature and monitored by ^{31}P-NMR until the peak of the aminophosphorous dichloride was solely observed together with the disappearance of the peaks of PCl_3 in THF/Et_3N. The mixture was then cooled to 0 °C and a solution of 5,5',6,6'-tetramethylbiphenyl-2,2'-diol (1.0 mmol, 242 mg) in THF (3 mL) was added. The resulting mixture was stirred for 12 h at room temperature. After addition of ether (2 mL), the resulting solid was quickly filtered off on a short pad of silica gel and washed with ether. The combined solution was concentrated *in vacuo* to give a crude product. Purification of the crude product by flash chromatography on a short silica gel column using hexanes/EtOAc as eluent afforded the desired phosphoramidite ligand.

_O,O'_-(_S_)-(5,5',6,6'-Tetramethyl-biphenyl-2,2'-diyl)-_N,N_-bis[(_S_)-1-(napthalen-1-yl)-ethyl]phosphoramidite (L7):



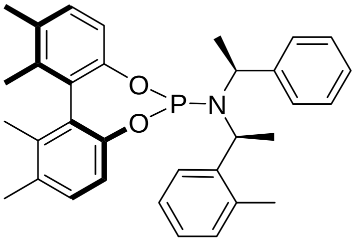
Purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 50/1 then 40/1); white solid; yield 60%; Rf = 0.35 (SiO_2, hexanes/EtOAc = 10/1); mp 222.5-224 °C; $[\alpha]_D^{22}$ +168.2 (c 1.32, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.65 (d, J = 6 Hz, 6H), 1.98 (s, 6H), 2.07 (s, 3H), 2.31 (s, 3H), 5.42 (m, 2H), 6.58 (q, J = 8.1 Hz, 2H), 7.00 (t, J = 7.8 Hz, 2H), 7.14-7.41 (m, 8H), 7.64-7.73 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 17.29, 17.46, 19.99, 20.29, 23.04, 23.21, 52.91, 53.07, 118.36, 118.91, 118.95, 123.23, 123.26, 124.44, 124.51, 124.83, 124.92, 125.30, 126.87, 128.46, 129.26, 129.29, 129.88, 130.65, 131.69, 133.24, 133.46, 136.33, 135.36, 139.63, 139.67, 149.41, 149.60, 149.71; ^{21}P-NMR (121.5 MHz, $CDCl_3$) : δ 151.03. HRMS (ESI) calcd for $C_{40}H_{39}NO_2P$ $[M+H]^+$ 596.2718; found 596.2706 (Δ = -2.1 ppm).

***O,O'*-(*S*)-(5,5',6,6'-Tetramethylbiphenyl-2,2'-diyl)-*N,N*-bis[(*S*)-1-(napthalen-2-yl)-ethyl]phosphoramidite (L8):**



Purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 40/1); white solid; yield 78%; Rf = 0.36 (SiO_2, hexanes/EtOAc = 10/1); mp 167-169.5 °C; $[\alpha]_D^{22}$ –415.3 (c 0.98, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.78 (d, J = 7 Hz, 6H), 1.97 (s, 3H), 2.02 (s, 3H), 2.19 (s, 3H), 2.30 (s, 3H), 4.56 (m, 2H), 6.84 (m, 2H), 7.11 (d, J = 8 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.33-7.42 (m, 5H), 7.46 (s, 2H), 7.54 (t, J = 9 Hz, 3H), 7.71 (d, J = 8 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 17.36, 17.62, 20.14, 20.26, 22.92, 23.08, 54.53, 54.67, 118.687, 118.93, 118.97, 125.49, 125.64, 126.42, 126.46, 126.94, 126.98, 127.08, 127.34, 127.87, 128.29, 129.28, 129.87, 129.89, 130.54, 131.73, 132.33, 132.97, 133.37, 133.39, 136.39, 137.27, 140.84, 149.31, 149.43, 149.67; ^{31}P-NMR (121.5 MHz, $CDCl_3$) δ 145.75; HRMS (ESI) calcd for $C_{40}H_{39}NO_2P$ $[M+H]^+$ 596.2718 found 596.2739 (Δ = 3.4 ppm).

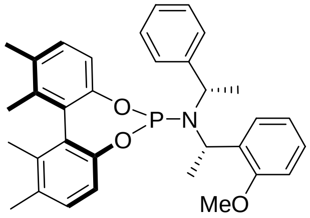
***O,O'*-(*S*)-(5,5',6,6'-tetramethylbiphenyl-2,2'-diyl) -*N,N*-[(*S*)-1-phenylethyl][(*S*)-1-*o*-tolylethyl]phosphoramidite (L9):**



Purified by flash chromatography on short silica gel column (hexanes/EtOAc = 40/1); white solid; yield 76%; Rf = 0.45 (SiO_2, hexanes/EtOAc = 20/1); mp 73-75 °C; $[\alpha]_D^{22}$ -126 (c 1.1, $CHCl_3$); ^{1}H-NMR (500 Hz, $CDCl_3$) δ 1.54 (d, J = 6.5Hz, 3H), 1.61 (d, J =

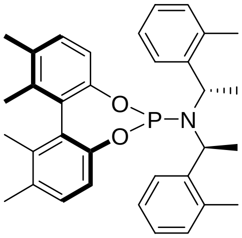
6.5Hz, 3H), 1.67 (s, 3H), 2.01 (d, J = 10.5 Hz, 6H), 2.04 (s, 3H), 2.31 (s, 3H), 4.33 (m, 1H), 4.52 (m, 1H), 6.81-6.87(m, 3H), 7.00-7.25 (m, 9H), 7.91 (d, J = 7.5 Hz, 1 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 17.36, 17.58, 18.53, 20.13, 20.20, 20.25, 25.31, 25.65, 52.11, 52.39, 54.66, 118.54, 118.92, 118.96, 126.01, 126.12, 126.30, 126.58, 126.76, 127.19, 128.20, 129.28, 129.60, 129.82, 130.57, 130.63, 131.64, 133.31, 133.34, 134.19, 136.31, 137.23, 137.25, 141.71, 144.07, 149.49, 149.61; ^{31}P-NMR (121.5 MHz, $CDCl_3$) δ 146.46. HRMS (ESI) calculated for $C_{33}H_{36}NO_2P$ $[M+H]^+$ 510.2559; found 510.2558 (Δ = -0.2 ppm).

***O,O'*-(*S*)-(5,5',6,6'-Tetramethylbiphenyl-2,2'-diyl) -*N,N*-[(*S*)-1-phenylethyl][(*S*)-1-(2-methoxyphenyl)ethyl]phosphoramidite (L10):**



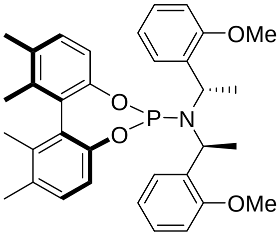
Purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 50/1); white solid; yield 65%; Rf = 0.33 (hexanes/EtOAc = 40/1); mp 77-78.5 °C; $[\alpha]_D^{22}$ -102.4 (c 1.25, $CHCl_3$); ^{1}H-NMR (400 MHz, C_6D_6) δ 1.58 (d, J = 6.8 Hz, 6H), 1.82 (s, 3H), 1.85 (dd, J = 2, 7.6 Hz, 3H), 1.87 (s, 3H), 1.91 (s, 3H), 2.02 (s, 3H), 3.06 (s, 3H), 5.04 (m, 2H), 6.31 (dd, J = 1.2, 7.6 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.90-7.04 (m, J = 6.8 Hz, 6H), 7.26 (t, J = 6.8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 8.06 (dt, J = 1.6, 7.6 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 17.36, 17.60, 20.15, 20.25, 20.46, 20.53, 24.63, 24.96, 48.80, 49.07, 54.52, 54.80, 109.55, 118.71, 189.94, 118.98, 120.13, 125.99, 126.84, 127.19, 127.74, 127.87, 128.30, 129.21, 129.77, 130.57, 130.68, 131.54, 133.20, 133.23, 134.11, 136.27, 137.20, 141.97, 149.55, 149.66, 149.72, 155.48; ^{21}P-NMR (121.5 MHz, $CDCl_3$) δ 147.32. HRMS (ESI) calcd for $C_{33}H_{37}NO_3P$ $[M+H]^+$ 526.2511; found 526.2506 (Δ = 1.0 ppm).

_O,O'_-(_S_)-(5,5',6,6'-Tetramethylbiphenyl-2,2'-diyl) -_N,N_-bis[(_S_)-1-_o_-tolylethyl]-phosphoramidite (L11):



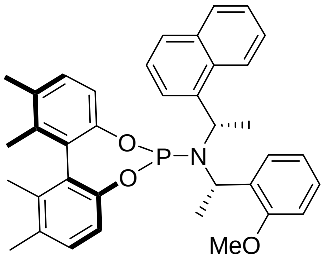
Purified by flash chromatography on short silica gel column (eluent; hexanes/EtOAc = 40/1); white solid; yield 60%; Rf = 0.35 (SiO_2, hexanes/EtOAc = 30/1); mp 75-77 °C; $[\alpha]_D^{22}$ +72 (c 1.05, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.33 (dd, J = 1.5, 6.9 Hz, 6H), 1.95 (s, 6H), 2.00 (s, 6H), 2.25 (s, 3H), 2.31 (s, 3H), 4.52 (m, 2H), 6.76 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 7.8 Hz, 3H), 7.05 (dt, J = 1.5, 7.5 Hz, 2H), 7.15-7.22 (m, 4H), 7.75 (d, J = 7.5 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 17.28, 17.43, 18.85, 20.09, 20.27, 22.55, 22.78, 55.05, 55.21, 118.24, 118.92, 118.96, 126.03, 126.23, 126.28, 126.35, 129.41, 129.87, 129.98, 131,50, 134.94, 143.26, 143.28, 149.64, 150.01, 150.12; ^{31}P-NMR (121.5 MHz, $CDCl_3$) δ 150.71. HRMS (ESI) calculated for $C_{34}H_{39}NO_2P$ $[M+H]^+$ 524.2718; found 524.2727 (Δ = 1.6 ppm).

_O,O'_-(_S_)-(5,5',6,6'-Tetramethylbiphenyl-2,2'-diyl)-_N,N_-bis[(_S_)-1-(2-methoxyphenyl)-ethyl]phosphoramidite (L12):



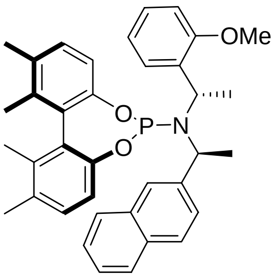
Purified by flash chromatography on a short silica gel column (eluent; hexanes/EtOAc = 30/1); white solid; yield 68%; Rf = 0.30 (SiO_2, hexanes/EtOAc = 30/1); mp 149-150.5 °C; $[\alpha]_D^{22}$ + 34.4 (c 0.64, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.46 (d, J = 7.5 Hz, 6H), 2.01 (d, J = 8 Hz, 6H), 2.24 (s, 3H), 2.31 (s, 3H), 3.63 (s, 6H), 4.89 (m, 2H), 6.51 (d, J = 8 Hz, 2H), 6.72 (d, J = 10 Hz, 1H), 6.81 (m, 3H), 7.05 (m, 3H), 7.18 (d, J = 8 Hz, 1H), 7.53 (d, J = 8 Hz, 2H);. ^{13}C-NMR (125 MHz, $CDCl_3$) δ 17.31, 17.49, 20.14, 20.23, 22.16, 22.26, 50.43, 50.53, 54.63, 110.14, 118.70, 119.00, 119.55, 127.17, 127.72, 127.76, 129.13, 129.69, 131.13, 132.84, 133.07, 136.03, 137.13, 149.67, 156.09; ^{31}P-NMR (121.5 MHz, $CDCl_3$) δ 151.20. HRMS (ESI) calcd for $C_{34}H_{39}NO_4P$ $[M+H]^+$ 556.2617; found 556.2607 (Δ = -1.7 ppm).

***O,O'*-(*S*)-(5,5',6,6'-Tetramethylbiphenyl-2,2'-diyl)-*N,N*-[(*S*)-1-(napthalen-2-yl)ethyl]-[(*S*)-1-(2-methoxy-phenyl)ethyl]phosphoramidite (L13):**



Purified by flash chromatography on silica gel (eluent, hexanes/ethyl acetate = 40:1), white solid, yield 53%. Rf = 0.32 (SiO_2, hexanes/ethyl acetate = 30/1); mp 92-94 °C; $[\alpha]_D^{22}$ + 96.7 (*c* 1.23, $CHCl_3$); ^{1}H-NMR (400 MHz, CD_2Cl_2) δ 1.4 (d, J = 7.2 Hz, 3H), 1.60 (d, J = 7.2 Hz, 3H), 1.98 (s, 6H), 2.12 (s, 3H), 2.32 (s, 3H), 3.58 (s, 3H), 3.75 (m, 1H), 5.37 (m, 1H), 6.49-6.67 (m, 4H), 6.89 (td, J = 0.8, 7.2 Hz, 1H), 7.10 (d, J = 8 Hz, 1H), 7.22 (d, J = 8 Hz, 1H), 7.29 (t, J = 8 Hz, 1H), 7.37 (m, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.71 (m, 1H), 7.81 (m, 1H); ^{13}C-NMR (100 MHz, CD_2Cl_2) δ 17.62, 17.79, 20.32, 20.57, 22.89, 22.99, 23.17, 23.32, 51.67, 50.70, 55.29, 109.90, 119.01, 119.40, 120.37, 124.09, 124.12, 124.72, 124.76, 125.40, 125.45, 125.83, 127.61, 127.70, 128.36, 128.42, 128.93, 129.80, 130.31, 131.66, 132.35, 133.08, 134.02, 134.20, 136.95, 137.98, 140.72, 140.76, 150.14, 150.32, 150.39, 156.41; ^{31}P-NMR (121.5 MHz, $CDCl_3$) δ 151.12. HRMS (ESI) calcd for $C_{37}H_{39}NO_3P$ $[M+H]^+$ 576.2668; found 576.2668 (Δ = 0.2 ppm).

_O,O'_-(_S_)-(5,5',6,6'-Tetramethylbiphenyl-2,2'-diyl) -_N,N_-[(_S_)-1-(napthalen-2-yl)ethyl]-[(_S_)-1-(2-methoxy-phenyl)ethyl]phosphoramidite (L14):

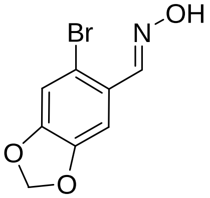


Purified by flash chromatography on silica gel (Hexanes/EtOAc = 40/1); white solid; yield 77%; Rf = 0.29 (SiO_2, hexanes/EtOAC= 30/1); mp 103-105 ° C; $[\alpha]_D^{22}$ -246 (c = 0.8, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.63 (dd, J = 7.5, 16 Hz, 6H), 2.01 (d, J = 13.5 Hz, 6H), 2.20 (s, 3H), 2.31 (s, 3H), 2.99 (s, 3H), 4.66 (m, 1H), 4.71 (m, 1H), 6.26 (d, J = 8 Hz, 1H), 6.85-6.91 (m, 3H), 7.00 (t, J = 8.5 Hz, 1H), 7.10 (d, J = 8 H, z 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.27 (m, 1H), 7.38 (m, 3H), 7.58 (s, 1H), 7.61-7.68 (m, 2H), 7.81 (d, J = 7.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 17.37, 17.61, 20.12, 20.24, 25.09, 25.29, 48.47, 48.64, 54.40, 109.29, 118.74, 118.96, 118.99, 120.13, 125.23, 125.78, 126.40, 127.15, 127.21, 127.51, 127.90, 127.98, 129.25, 129.82, 131.58, 132.13, 132.82, 133.25, 134.08, 136.33, 137.23, 139.63, 149.59, 149.72, 155.24; ^{31}P-NMR (121.5 MHz, $CDCl_3$) δ 146.32. HRMS (ESI) calcd for $C_{37}H_{39}NO_3P$ $[M+H]^+$ 576.2668; found 576.2659 (Δ = -1.4 ppm).

(+)-γ -Lycorane Synthesis

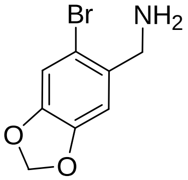
Synthesis of nucleophile 6

2-Bromo-4,5-(methylenedioxy)benzaldehyde oxime (4):



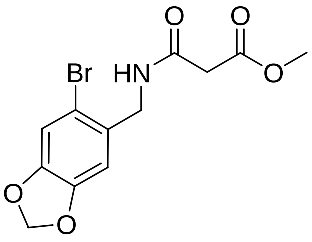
Hydroxylamine hydrochloride (1.55 g, 22.3 mmol) was added in portions to a solution of $NaHCO_3$ (1.83 g, 21.8 mmol) in 50 mL of water at room temperature. The solution was added to a vigorously stirred suspension of 2-bromopiperonal (**3**) (5.0 g, 21.8 mmol) in ethanol (45 mL). The resulting mixture was stirred for 5 h and then left at –20 °C overnight. The suspension was filtered, washed with a few mL of cold ethanol and dried under vacuum to give **4** as a pure white solid (4.9 g, 93%): Rf: = 0.39 (eluant: hexanes:EtOAc = 2:1); mp 153-155 °C; IR (KBr) 3463, 3325, 3101, 1500, 1473, 1249, 1041 cm^{-1}; ^{1}H-NMR (400 MHz, d_6-DMSO) δ 6.11 (s, 2H) 7.24 (s, 1H), 7.27 (s, 1H), 8.22 (s, 1H), 11.48 (s, 1H); ^{13}C-NMR (100 MHz, d_6-DMSO) δ 102.38, 105.39, 112.45, 114.27, 125.12, 146.64, 147.60, 149.45. HRMS (ESI) calcd for $C_8H_7BrNO_3$ $[M+H]^+$ 243.9609; found 243.9612 (Δ = 1.2 ppm).

1-Bromo-6-aminomethyl-3,4-(methylenedioxy)benzene (5):



To a solution of **4** (4.0 g, 16.3 mmol) in THF (200 mL) was added a 2*N* HCl solution (80 mL), followed by zinc (10.4 g, 160 mmol). The mixture was vigorously stirred under reflux for 2.5 h until the reaction completed. The reaction mixture was cooled to room temperature, filtered on a celite pad to remove the excess zinc and condensed under reduced pressure to about 90 mL. The aqueous layer was extracted with EtOAc (50 mL) and then its pH adjusted to >10 by addition of saturated ammonia solution. The resulting precipitate was filtered off through a celite pad and washed with EtOAc (50 mL). The two layers were separated and the water layer was washed with EtOAc (4x75 mL). The combined organic layers were dried over anhydrous K_2CO_3, filtered and evaporated *in vacuo* to give crude **9** as an oil. The oil was purified by passing through a short silica gel column (eluent: EtOAc/2% Et_3N). The combined fractions were concentrated *in vacuo* to afford amine **9** as a clear oil (3.4 g, 91% yield): Rf = 0.4 (SiO_2, EtOAc/10% Et_3N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.62 (br. s, 2H), 3.79 (s, 2H), 5.95 (s, 2H), 6.87 (s, 1H), 6.98 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 46.76, 101.62, 109.08, 112.78, 113.54, 135.46, 147.18, 147.46. HRMS (ESI) calcd for $C_8H_9BrNO_2$ $[M+H]^+$ 229.9817; found 229.9822 (Δ = 2.2 ppm).

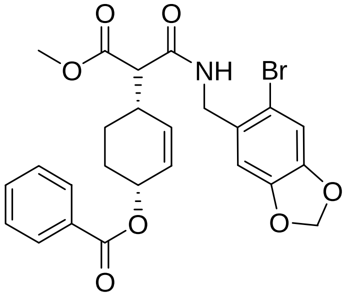
Methyl *N*-[6-bromo-3,4-(methylenedioxy)benzyl]carbamoylacetate (6):



To a solution of amine **9** (615 mg, 2.67 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (0.93 mL, 680 mg, 6.7 mmol) at 0 °C under N_2. Then, methyl malonyl chloride (0.35 mL, 440 mg, 3.2 mmol) in CH_2Cl_2 (5 mL) was slowly added. The mixture was stirred at room temperature for 12 h. Saturated $NaHCO_3$ solution (10 mL) was added to quench the reaction. The resulting two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x15 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give the crude product as yellow oil. The crude product was purified by flash chromatography on silica gel (eluent; hexanes:EtOAc = 2:1 then 1:1) to afford pure **2** as a white solid (756 mg, 86% yield): mp 118-119 °C; IR (KBr) 3273, 3071, 1738, 1630, 1550, 1503, 1479, 1205, 1034 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 2H), 3.75 (s, 3H), 4.44 (d, 2H, J = 6Hz), 5.96 (s, 2H), 6.85 (s, 1H), 7.00 (s, 1H), 7.54 (br. s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 40.76, 43.70, 52.44, 101.78, 110.25, 112.72, 114.20, 130.19, 147.45, 147.89, 164.68, 169.84. HRMS (ESI) calcd for $C_{12}H_{13}BrNO_5$ $[M+H]^+$ 329.9977; found 329.9977 (Δ = -0.2 ppm).

General procedure for the Pd-catalyzed asymmetric allylic alkylation – desymmetrization reaction of dibenzoyloxycyclohexene (1) with nucleophile 6.

(1'*S,4'*R**)-2-(4'-Benzoyloxy-2'-cyclohexen-1'-yl)-2-*N*-[6"-bromo-3",4"-(methylenedioxy)benzyl]carbamoylacetate (7a):**

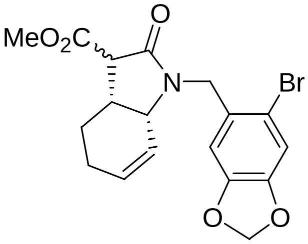


To a solution of **6** (122 mg, 0.37 mmol) in THF (3 mL) was added LDA (2N in THF, 0.186 mL, 0.37 mmol) at -78° C under N_2. Separately, a solution of $[Pd(allyl)Cl]_2$ (2.24mg, 0.006 mmol) and a ligand (0.024 mmol) in THF (3 mL) was stirred at room temperature for 10 min. Dibenzoate **1** (100mg, 0.31 mmol) was added at once to this catalyst solution and the resulting mixture was cooled to –78 ^{o}C. The nucleophile (i.e, **6** + LDA) solution was then slowly cannulated into the substrate-catalyst solution. The mixture was stirred at the given temperature until TLC showed completion of the reaction or no more progress in the reaction. A saturated NH_4Cl solution was added (2 mL) to quench the reaction. The two layers were separated and the water layer was further extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography on silica gel (eluent: hexanes:EtOAc = 3:1 then 2:1) to give **7a** as a white foamy solid. Product **7a** was obtained as a mixture of two diastereoisomers (dr = 54:46 by NMR). Rf = 0.4 (SiO_2, hexanes:EtOAc = 1:1): mp 57-61 ° C for a diastereoisomer mixture; IR (KBr): 3294, 3070, 1743, 1708, 1654, 1481, 1272, 1238 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.55-2.06 (m, 4H), 2.87 (m, 1H), 3.20 (d, J = 10 Hz, 0.54H), 3.26 (d, J = 9.2 Hz, 0.46 H), 3.73 (s, 1.6H), 3.75 (s, 1.7H), 4.42 (m, 2H), 5.41 (m, 1H), 5.81-5.89 (m, 1H), 5.90-6.00 (m, 1H), 5.94 (s, 2H), 6.86 (s, 1H), 6.94 (m, NH, 0.51H), 6.99 (d, J = 2.8 Hz, 1H), 7.12 (m, NH, 0.47H), 7.42 (m, 2H), 7.54 (m, 1H), 8.00

(m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.23, 22.41, 27.01, 37.41, 37.55, 43.96, 44.07, 52.47, 52.55, 57.44, 57.76, 66.59, 66.84, 101.83, 101.86, 110.29, 110.448, 112.75, 114.22, 127.07, 127.26, 128.28, 129.57, 129.99, 130.03, 130.50, 132.86, 133.17, 133.36, 147.47, 148.01, 165.99, 166.71, 171.81, 171.48. HRMS (ESI) calcd for $C_{18}H_{19}BrNO_5$ $[M\text{-}PhCO_2H]^+$ 408.0447; found 408.0438 (Δ = -2.0 ppm).

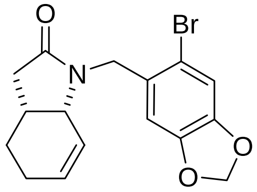
Conversion of 7 to 9 for the determination of enantioselectivity

(3aR*,7aS*)-1-[6'-Bromo-3,4-(methylenedioxy)-benzyl]-3-(methoxycarbonyl)-3a,4,5,7a-tetrahydroindolin-2-one (7c):



A solution of $[Pd(allyl)Cl]_2$ (2.65 mg, 7.24 μmol) and dppb (6.2 mg, 15 μmol) was stirred in CH_3CN (2 mL) under N_2 for 1h. Separately, a solution of **7a** (156 mg, 0.294 mmol) in THF (2 mL) was cooled to –50 °C under N_2. LDA (0.154 mL, 2M soln.) was added to this solution and the mixture was stirred for 5 min and warmed to room temperature. The Pd-dppb catalyst solution was then quickly added to the substrate solution and the mixture was stirred at rt for 2.5h. TLC analysis showed that the reaction was complete. To the reaction mixture, saturated NH_4Cl solution was added (3 mL) to quench the reaction and the reaction mixture was extracted with CH_2Cl_2. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography using hexanes-EtOAc (3:1) as the eluent to give **7c** as a colorless oil (85 mg, 71% yield): Rf = 0.36 (SiO_2, hexanes:EtOAc = 1:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.62 (m, 1H), 1.76 (m, 1H), 2.06 (m, 3H), 2.80 (m, 1H), 3.32 (d, 1H, J = 6.8Hz), 3.79 (s, 3H), 3.99 (m, 1H), 4.27 (d, 1H, J = 16Hz), 4.80 (d, 1H, J = 16Hz), 5.70 (m, 1H), 5.93-5.97 (m, 1H), 5.95 (s, 2H), 6.82 (s, 1H), 6.97 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.81, 23.24, 35.83, 44.14, 52.35, 52.55, 53.40, 101.80, 109.21, 112.50, 113.54, 122.86, 128.49, 131.64, 147.85, 169.38, 170.12. HRMS (ESI) calcd for $C_{18}H_{19}BrNO_5$ $[M+H]^+$ 408.0447; found 408.0460 (Δ = 3.3 ppm).

(3a*R,7a*S**)-1-[6'-Bromo-3,4-(methylenedioxy)benzyl]-3a,4,5,7a-tetrahydroindolin-2-one (9):**

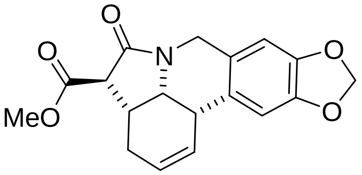


To a solution of **7c** (37 mg, 0.09 mmol) in DMSO (1 mL) were added water (0.3 mL) and NaCl (15 mg). The resulting solution was stirred at 175 °C for 2.5 h. TLC analysis showed the completion of the reaction. Water (2 mL) was added and the reaction mixture was extracted with Et_2O-CH_2Cl_2 (1:1) (4 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting oil was chromatographed on a silica gel column (eluent: hexanes:EtOAc = 5:3) to give **9** as a white crystalline solid (29 mg, 91% yield): Rf = 0.25 (SiO_2, hexanes:EtOAc = 1:1); mp 85-86 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.50-1.80 (m, 3H), 1.92-2.20 (m, 2H), 2.28 (m, 1H), 2.40-2.60 (m, 2H), 3.86 (m, 1H), 4.27 (d, 1H, J = 15.6 Hz), 4.74 (d, 1H, J = 15.6 Hz), 5.75 (m, 1H), 5.93-5.99 (m, 1H), 5.96 (s, 2H), 6.76 (s, 1H), 6.98 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.2, 24.11, 31.02, 35.72, 43.98, 54.76, 101.78, 109.26, 112.58, 113.50, 123.22, 129.30, 131.82, 147.74, 174.44. HRMS (ESI) calcd for $C_{16}H_{17}NO_3Br$ $[M+H]^+$ 350.0392; found 350.0383 (Δ = -2.4 ppm).

The determination of the enantiopurity of **9** was performed on a Shimadzu LC-2010A HPLC system using a Chiralpak AD-RH column (eluent CH_3CN/H_2O = 60/40; flow rate 0.5 mL/min).

Synthesis of (+)-γ-lycorane

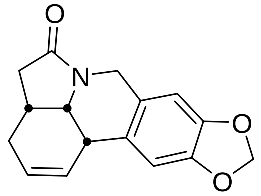
(3a*R*,12b*S*,12c*S*)-1,2-Dehydro-4-(methoxy-carbonyl)-5-oxo-γ-lycorane (8):



A solution of **7a** (70 mg, 0.132 mmol) in degassed dry DMF (0.5 mL) was slowly added to a suspension of NaH (60% oil, 5.8 mg, 0.145 mmol) in DMF (1 mL) under N_2 at –78° C. The solution was slowly warmed to 0 ° C. A stirred solution of $Pd(OAc)_2$ (1.7 mg, 7.5 μmol) and dppb (6.5mg, 15μmol) in DMF (0.5 mL) was prepared separately and cannulated to the reaction mixture of **7a** and NaH in DMF at 0 ° C. The temperature was raised to 50 ° C and the reaction monitored until the disappearance of **7a** and the clean formation of the allylic amination product **7c** was confirmed (3 h). Then, diisopropylethylamine (55 μL, 0.3 mmol) was added to the reaction mixture and the temperature was raised to 110 ° C. The reaction mixturre was stirred for 7 h and cooled to room temperature. Water (3 mL) was added to quench the reaction and the reaction mixture was extracted with ethyl acetate (5 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduce pressure to give crude Heck reaction product **8** as a brown oil. The crude oily product was purified by flash chromatography on silica gel (eluant: hexanes:EtOAc = 2:1) to yield pure **8** as a colorless oil (26 mg, 61% yield): Rf = 0.27 (SiO_2, hexanes:EtOAc = 2:3); $[\alpha]_D^{22}$ -19.6 (c 0.51, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.26 (m, 2H), 3.20 (d, J = 5 Hz, 1H) 3.28 (m, 2H), 3.80 (s, 3H), 4.16 (d, J = 17.5 Hz, 1H), 4.22 (dd, J = 4.5, 8 Hz, 1H), 4.85 (d, J = 17.5 Hz, 1H), 5.71 (d, J = 9.5 Hz, 1H), 5.92-5.95 (m, 1H), 5.96 (s, 2H), 6.58 (s, 1H), 6.66 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.71, 34.34, 38.29, 42.41, 52.74, 55.52, 55.71, 101.11, 105.96, 108.80, 124.02, 126.75, 129.25, 133.77, 146.93, 147.00, 168.61, 170.67.

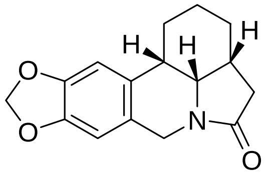
HRMS (ESI) calculated for $C_{18}H_{18}NO_5$ $[M+H]^+$ 328.1185; found 328.1185.(Δ = 0.1 ppm).

(3a*R*,12b*S*,12c*S*)-1,2-dehydro-5-oxo-γ-lycorane (8a):



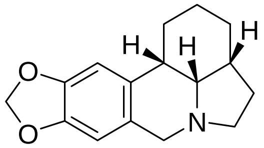
To a solution of **8** (23 mg, 0.07 mmol) in DMSO (1.5 mL) was added water (0.5 mL) and NaCl (13 mg). The mixture was stirred at 175 °C for 15 h. The reaction mixture was cooled to room temperature and water 2 mL was added. The reaction mixture was extracted with ethyl acetate (5x5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude product. Purification of the crude product by flash chromatography on silica gel (eluant: hexanes/EtOAc = 1/1.5) afforded pure **8a** as a white solid (18 mg, 93% yield): mp 174-177 °C (decomp.); Rf = 0.21 (SiO_2, hexanes:EtOAc = 1:5); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.10-2.21 (m, 3H), 2.66 (dd, J = 9.5, 17 Hz, 1H), 2.88 (m, 1H), 3.28 (m, 1H), 4.05 (m, 1H), 4.11 (d, J = 17 Hz, 1H), 4.79 (d, J = 17 Hz, 1H), 5.65 (d, J = 9.5 Hz, 1H), 5.88 (m, 1H), 5.94 (d, J = 2.5 Hz, 2H), 6.58 (s, 1H), 6.70 (s, 1H). HRMS (ESI) calculated for $C_{16}H_{16}NO_3P$ $[M+H]^+$ 270.1130; found 270.1118 (Δ = - 1.3 ppm).

(3a*R*,12b*S*,12c*S*)-5-oxo-γ-lycorane (8b):



5-Oxo-dihydrolycorane **8a** (11 mg, 0.037 mmol) was dissolved in methanol (1.5 mL) and 5% Pd/C (10 mg) was added at once. The solution was stirred under ambient pressure of H_2 at room temperature for 1.5 h (TLC analysis showed the reaction completed). The catalyst was filtered off on a short celite pad and the filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by flash chromatography on silica gel (eluent: hexane/EtOAc = 1/1.5) to afford 5-oxo-lycorane **8b** (10.7 mg, 95% yield) as colorless crystals: mp 169-170 °C; Rf = 0.31 (SiO_2, hexanes:EtOAc = 1:5); $[\alpha]_D^{22}$ +83.8 (c 0.74, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.13-1.38 (m, 3H), 1.67-1.76 (m, 3H), 2.09 (d, 1H, J = 26.5 Hz), 2.41 (m, 1H), 2.57 (dd, 1H, J = 11.5, 27 Hz), 2.75 (td, 1H, J = 7.5, 14 Hz), 3.77 (t, 1H, J = 7.5 Hz), 4.32 (d, AB, J = 29 Hz), 4.54 (d, 1H, J = 29 Hz), 5.93 (dd, AB, 2H, J = 2, 7.5 Hz), 6.60 (d, 2H, J = 9.5 Hz); ^{13}C-NMR (125 MHz,$CDCl_3$) δ 23.64, 27.89, 30.27, 32.98, 39.85, 40.32, 42.71, 55.73, 101.03, 106.69, 108.49, 123.33, 131.61, 146.64, 146.72, 175.67. HRMS (ESI) calculated for $C_{16}H_{16}NO_3P$ $[M+H]^+$ 272.1287; found 272.1281 (Δ = -1.9 ppm).

(+)-γ-Lycorane:



To a suspension of $LiAlH_4$ (10 mg, 0.28 mmol) in THF (1 mL) was added a solution of 5-oxo-lycorane **8b** (15 mg, 0.055 mmol) in THF (2 mL) at 0 °C under N_2. The solution was refluxed for 1.5 h (TLC showed the reaction completed). A saturated Na_2SO_4 solution (1 mL) was carefully added at 0 °C and the reaction mixture was stirred for 2 h. After addition of 1*N* NaOH (2 mL), the two layers were separated and the aqueous layer washed with EtOAc (4x5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product as a yellow oil. Purification of the crude product through silica gel chromatography (eluant: hexanes/EtOAc = 1/2 then 1/4) afforded pure (+)-γ-lycorane as a colorless oil (13 mg, 92% yield): Rf = 0.37 (SiO_2, hexanes:EtOAc = 1:6); $[\alpha]_D^{22}$ +18.1 (c 1.1, EtOH); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.27-1.35 (m, 3H), 1.43-1.52 (m, 3H), 1.62-1.64 (m, 1H), 1.69-1.71 (m, 1H), 1.74-1.77 (m, 1H), 2.00-2.03 (m, 1H), 2.13-2.20 (m, 1H), 2.38 (m, 1H), 2.74 (m, 1H), 3.21 (d, J = 14.5 Hz, 1H), 3.38 (m, 1H), 4.02 (d, J = 14.5 Hz, 1H), 5.89 (dd, J = 3.5, 5 Hz, 2H), 6.49 (s, 1H), 6.61 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.19, 29.28, 30.38, 31.69, 37.36, 39.46, 53.73, 57.11, 62.90, 100.65, 106.24, 108.33, 127.1, 133.16, 145.64, 146.04. HRMS (ESI) calculated for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1494; found 258.1487 (Δ = -2.7 ppm).

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