Regio- and Stereoselective Cross Coupling of Substituted Olefins and Imines. A Convergent Stereoselective Synthesis of Saturated 1,5-Aminoalcohols and Substituted Piperidines

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SUPPORTING INFORMATION - 1

Experimental Procedures and Spectral Data
General. All reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents, unless otherwise noted. Dry diethyl ether (Et₂O) and dichloromethane (CH₂Cl₂) were obtained by passing HPLC grade solvents through activated alumina columns. Dry tetrahydrofuran (THF) was obtained by distillation over sodium metal and benzophenone. Carbon tetrachloride (CCl₄) and methanol (MeOH) were purchased in anhydrous form and used without further purification. Titanium tetraisopropoxide was purified by distillation at 150 millitorr. Commercially available alcohols 14, 18, 21, and 24 were distilled prior to use. Alcohols 33, 38, and ent-38² (>99% ee by Mosher’s ester) as well as imine 15³ were synthesized by known procedures. All other known imines 28 and ent-28⁴ (>99% ee by Mosher’s amide of the amine precursor) were prepared by stirring the aldehyde and amine (1:1 molar ratio) in THF (0.2 M) in the presence of anhydrous MgSO₄ for 16 h, followed by filtration and concentration. All other commercially available reagents were used as received. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 250 μm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of p-anisaldehyde or an aqueous solution of potassium permanganate with heat as developing agent. Silica gel for flash column chromatography was purchased from Silicycle (P60, particle size 40-63 μm). ¹H NMR data were recorded at 500 MHz using a Bruker AM-500 instrument. ¹H NMR chemical shifts are reported relative to residual CHCl₃ (7.26 ppm). ¹³C NMR chemical shifts were reported relative to the central line of CDCl₃ (77.23 ppm). Infrared spectra were recorded using a Thermo Electron Nicolet 6700 FT-IR spectrometer. Low resolution mass spectrometry was performed on a Waters Micromass® ZQᵀᴹ instrument using electrospray ionization. Optical rotations were measured on a Perkin Elmer Model 341 polarimeter using a 1 mL capacity micro cell with a 10 cm path length. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless indicated otherwise. Relative stereochemistry was defined using the R*/S* convention proposed by IUPAC.

Synthesis of (±)-5-(N-benzylamino)-5-phenylpentan-1-ol (16). To a solution of imine 15 (75 μL, 78.7 mg, 0.403 mmol) and Ti(Oi-Pr)₄ (180 μL, 173 mg, 0.609 mmol) in diethyl ether (1.2 mL) at −70 °C was added c-C₅H₅MgCl (2.15 M in diethyl ether, 1.20 mmol) in a drop wise manner. The mixture was warmed to −40 °C over 1 h and stirred for 1 h at this temperature. A
solution of lithium alkoxide 14a, prepared by the deprotonation of alcohol 14 (52 μL, 43.6 mg, 0.605 mmol) in diethyl ether (0.8 mL) at −78 °C with n-BuLi (2.6 M in hexanes, 0.650 mmol) followed by warming to 0 °C over 20 min, was added in a drop wise manner to the brown solution of imine−Ti complex at −40 °C via cannula. The mixture was warmed to −20 °C over 30 min and stirred at this temperature for 6 h. The reaction was quenched by addition of water (2 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous NaHCO₃ (15 mL) and extracted with ethyl acetate (4 × 15 mL). The organic extracts were combined, dried over MgSO₄ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (10→30% acetone/hexanes) to afford amino alcohol 16 as a pale yellow oil (82 mg, 76%).

Data for (±)-5-(N-benzylamino)-5-phenylpentan-1-ol (16): ¹H NMR (500 MHz, CDCl₃) δ 7.36-7.22 (m, 10H), 3.64 (d, J = 13.0 Hz, 1H), 3.60 (t, J = 7.0 Hz, 1H), 3.56 (t, J = 6.5 Hz, 2H), 3.52 (d, J = 13.0 Hz, 1H), 1.78-1.71 (m, 1H), 1.70-1.62 (m, 1H), 1.57-1.45 (m, 4H), 1.40-1.31 (m, 1H), 1.27-1.18 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 144.36, 140.84, 128.64, 128.64, 128.38, 127.52, 127.24, 127.06, 62.91, 62.77, 51.74, 38.26, 32.89, 22.71; IR (thin film, NaCl) νmax 3312 (br), 3084, 3061, 3026, 2934, 2859, 1493, 1453, 1361, 1066, 1028, 735, 700, 451 cm⁻¹; LRMS (EI, H) m/z calc’d for C₁₈H₂₄NO [M + H]⁺ 270.2, found 270.7; Rf 0.13 (silica gel, 1:1 EtOAc/hexanes).

Synthesis of (R*)-4-((R*)-(N-benzylamino)(phenyl)methyl)hexan-1-ol (19). To a solution of imine 15 (75 μL, 78.7 mg, 0.403 mmol) and Ti(Oi-Pr)₄ (180 μL, 173 mg, 0.609 mmol) in diethyl ether (1.2 mL) at −70 °C was added c-C₅H₉MgCl (2.15 M in diethyl ether, 1.20 mmol) in a drop wise manner. The mixture was warmed to −40 °C over 1 h and stirred for 1 h at this temperature. A solution of lithium alkoxide 18a, prepared by the deprotonation of alcohol 18 (74 μL, 60.5 mg, 0.604 mmol) in diethyl ether (0.8 mL) at −78 °C with n-BuLi (2.6 M in hexanes, 0.650 mmol) followed by warming to 0 °C over 20 min, was added in a drop wise manner to the brown solution of imine−Ti complex at −40 °C via cannula. The mixture was warmed to 0 °C over 1 h and stirred at this temperature for 6 h. The reaction was quenched by addition of water (2 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous NaHCO₃ (15 mL) and extracted with ethyl acetate (4 × 15 mL). The organic extracts were combined, dried over MgSO₄ then concentrated in vacuo. The crude
The product was purified by column chromatography on silica gel (10→20% acetone/hexanes) to afford amino alcohol 19 as a colorless oil (single diastereomer; 87 mg, 73%). See 19→20 for the determination of relative stereochemistry.

**Data for (R*)-4-((R*)-(N-benzylamino)(phenyl)methyl)hexan-1-ol (19):**

\[ ^1H \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 7.37-7.23 (m, 10H), 3.63 (d, J = 13.0 \text{ Hz, 1H}), 3.60-3.58 (m, 2H), 3.51 (d, J = 7.5 \text{ Hz, 1H}), 3.45 (d, J = 13.0 \text{ Hz, 1H}), 1.98 (br, 2H), 1.64-1.53 (m, 3H), 1.51-1.43 (m, 2H), 1.32-1.22 (m, 1H), 1.07 (ddq, J = 15.0, 7.5, 7.5 Hz, 1H), 0.78 (t, J = 7.5 \text{ Hz, 3H}); \]

\[ ^{13}C \text{ NMR (126 MHz, CDCl}_3) \delta 143.41, 140.63, 128.57, 128.55, 128.49, 128.00, 127.13, 127.07, 65.07, 62.87, 51.88, 45.56, 29.92, 25.10, 23.72, 11.68; \]

IR (thin film, NaCl) 3317 (br), 3083, 3061, 3025, 2932, 2872, 1493, 1453, 1378, 1069, 1028, 739, 700, 451 cm\(^{-1}\); LRMS (EI, H) \(m/z\) calc’d for C\(_{20}\)H\(_{28}\)NO \([M + H]^+\) 298.2, found 298.6; \(R_f\) 0.38 (silica gel, 1:1 EtOAc/hexanes).

**Synthesis of (4\(R^*\),5\(R^*\))-5-(benzylamino)-4-methyl-5-phenylpentan-1-ol (22).**

To a solution of imine 15 (75 \(\mu\)L, 78.7 mg, 0.403 mmol) and Ti(O-i-Pr\(_4\)) (180 \(\mu\)L, 173 mg, 0.609 mmol) in diethyl ether (1.2 mL) at \(-70 \text{ ^\circ C}\) was added \(c\)-C\(_5\)H\(_9\)MgCl (1.8 M in diethyl ether, 1.21 mmol) in a drop wise manner. The mixture was warmed to \(-40 \text{ ^\circ C}\) over 1 h and stirred for 1 h at this temperature. A solution of lithium alkoxide 21a, prepared by the deprotonation of alcohol 21 (61 \(\mu\)L, 51.8 mg, 0.601 mmol) in diethyl ether (0.8 mL) at \(-78 \text{ ^\circ C}\) with n-BuLi (2.5 M in hexanes, 0.650 mmol) followed by warming to 0 \text{ ^\circ C}\) over 20 min, was added in a drop wise manner to the brown solution of imine–Ti complex at \(-40 \text{ ^\circ C}\) via cannula. The mixture was warmed to 15 \text{ ^\circ C}\) over 3 h and stirred at ambient temperature for 1 h. The mixture was quenched with saturated aqueous NaHCO\(_3\) (30 mL) and extracted with ethyl acetate (4 \(\times\) 30 mL). The organic extracts were combined, dried over MgSO\(_4\) then concentrated \(in \text{ vacuo}\). The crude product was purified by column chromatography on silica gel (50→75% EtOAc/hexanes) to afford amino alcohol 22 as a colorless oil (single diastereomer; 72 mg, 63%). See 22→23 for the determination of relative stereochemistry.

**Data for (4\(R^*\),5\(R^*\))-5-(benzylamino)-4-methyl-5-phenylpentan-1-ol (22):**

\[ ^1H \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 7.36-7.22 (m, 10H), 3.64-3.61 (m, 3H), 3.47 (d, J = 13.0 \text{ Hz, 1H}), 3.44 (d, J = 7.5 \text{ Hz, 1H}), 1.81-1.60 (m, 5H), 1.56-1.46 (m, 1H), 1.26-1.17 (m, 1H), 0.75 (d, J = 7.0 \text{ Hz, 3H}); \]

\[ ^{13}C \text{ NMR (126 MHz, CDCl}_3) \delta 142.81, 140.88, 128.52, 128.47, 128.35, 128.27, 127.11, 127.06, \]
Synthesis of (3S*,5R*)-5-(benzylamino)-3-methyl-5-phenylpentan-1-ol (25) and (3R*,5R*)-5-(benzylamino)-3-methyl-5-phenylpentan-1-ol (25a). To a solution of imine 15 (75 μL, 78.7 mg, 0.403 mmol) and Ti(Oi-Pr)₄ (180 μL, 173 mg, 0.609 mmol) in diethyl ether (1.2 mL) at −70 °C was added c-C₅H₉MgCl (2.15 M in diethyl ether, 1.20 mmol) in a drop wise manner. The mixture was warmed to −40 °C over 1 h and stirred for 1 h at this temperature. A solution of lithium alkoxide 24a, prepared by the deprotonation of alcohol 24 (61 μL, 52.0 mg, 0.604 mmol) in diethyl ether (0.8 mL) at −78 °C with n-BuLi (2.6 M in hexanes, 0.650 mmol) followed by warming to 0 °C over 20 min, was added in a drop wise manner to the brown solution of imine–Ti complex at −40 °C via cannula, then the mixture was warmed to 0 °C over 1 h and stirred at this temperature for 6 h. The reaction was quenched by addition of water (2 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous NaHCO₃ (15 mL) and extracted with ethyl acetate (4 × 15 mL). The organic extracts were combined, dried over MgSO₄ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (10→30% acetone/hexanes) to afford a diastereomeric mixture of amino alcohols (25:25a = 4:1; 76 mg, 67%). The mixture was subjected to further purification by column chromatography on silica gel (10→70% EtOAc/hexanes) to isolate pure 25 and 25a as colorless oils. See 25→26 and 25a→26a for the determination of relative stereochemistry.

Data for (3S*,5R*)-5-(benzylamino)-3-methyl-5-phenylpentan-1-ol (25): ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.22 (m, 10H), 3.74 (t, J = 7.3 Hz, 1H), 3.64-3.54 (m, 3H), 3.52 (d, J = 13.0 Hz, 1H), 1.69-1.57 (m, 4H), 1.55-1.48 (m, 2H), 1.40-1.32 (m, 1H), 0.91 (d, J = 6.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 144.34, 140.65, 128.74, 128.57, 128.45, 127.43, 127.32, 127.11, 11.21, 60.41, 51.61, 45.92, 39.98, 26.72, 20.71; IR (thin film, NaCl) 3313 (br), 3084, 3061, 3026, 2925, 2869, 1494, 1453, 1377, 1361, 1057, 1028, 754, 700, 501, 450 cm⁻¹; LRMS (EI, H) m/z calc’d for C₁₉H₂₆NO [M + H]⁺ 284.2, found 284.6; Rf 0.16 (silica gel, 1:1 EtOAc/hexanes).

Data for (3R*,5R*)-5-(benzylamino)-3-methyl-5-phenylpentan-1-ol (25a): ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.22 (m, 10H), 3.74 (t, J = 7.3 Hz, 1H), 3.64-3.54 (m, 3H), 3.52 (d, J = 13.0 Hz, 1H), 1.69-1.57 (m, 4H), 1.55-1.48 (m, 2H), 1.40-1.32 (m, 1H), 0.91 (d, J = 6.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 144.34, 140.65, 128.74, 128.57, 128.45, 127.43, 127.32, 127.11, 60.41, 51.61, 45.92, 39.98, 26.72, 20.71; IR (thin film, NaCl) 3313 (br), 3084, 3061, 3026, 2925, 2869, 1494, 1453, 1377, 1361, 1057, 1028, 754, 700, 501, 450 cm⁻¹; LRMS (EI, H) m/z calc’d for C₁₉H₂₆NO [M + H]⁺ 284.2, found 284.6; Rf 0.16 (silica gel, 1:1 EtOAc/hexanes).
MHz, CDCl$_3$) $\delta$ 7.38-7.22 (m, 10H), 3.71-3.58 (m, 4H), 3.50 (d, $J = 13.0$ Hz, 1H), 1.84 (br, 2H), 1.77-1.66 (m, 2H), 1.58-1.52 (m, 1H), 1.47-1.39 (m, 2H), 0.87 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 144.89, 140.60, 128.72, 128.55, 128.45, 127.25, 127.21, 127.11, 60.72, 60.50, 51.73, 45.90, 40.13, 26.97, 20.39; IR (thin film, NaCl) 3313 (br), 3084, 3062, 3026, 2924, 2869, 1494, 1453, 1377, 1363, 1057, 1028, 754, 699, 501, 450 cm$^{-1}$; LRMS (EI, H) $m/z$ calc’d for C$_{19}$H$_{26}$NO [M + H]$^+$ 284.2, found 284.6; $R_f$ 0.23 (silica gel, 1:1 EtOAc/hexanes).

Synthesis of (±)-1-benzyl-2-phenylpiperidine (17). A solution of amino alcohol 16 (68 mg, 0.252 mmol), PPh$_3$ (99 mg, 0.377 mmol) and imidazole (34 mg, 0.499 mmol) in carbon tetrachloride (5.0 mL) was heated at reflux for 15 h. The mixture was poured into water (20 mL) and extracted with dichloromethane (4 × 15 mL). The combined organic extracts were washed with brine (1 × 15 mL), dried over MgSO$_4$ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes, then 1→3% EtOAc/hexanes) to afford piperidine 17 as a white solid (54 mg, 85%).

Data for (±)-1-benzyl-2-phenylpiperidine (17): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.47 (d, $J = 7.0$ Hz, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.28-7.18 (m, 6H), 3.77 (d, $J = 13.5$ Hz, 1H), 3.12 (dd, $J = 11.0$, 2.8 Hz, 1H), 3.00-2.96 (m, 1H), 2.81 (d, $J = 14.0$ Hz, 1H), 1.94 (app td, $J = 11.5$, 3.5 Hz, 1H), 1.82-1.76 (m, 2H), 1.67-1.54 (m, 3H), 1.43-1.33 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 145.97, 140.08, 128.89, 128.69, 128.20, 127.66, 127.05, 126.71, 69.43, 60.02, 53.58, 37.25, 26.24, 25.48; IR (thin film, NaCl) 3083, 3062, 3025, 2932, 2854, 2789, 2750, 2725, 1725, 1602, 1494, 1452, 1441, 1381, 1370, 1310, 1291, 1272, 1255, 1130, 1104, 1067, 1047, 1028, 758, 732, 700, 499, 449 cm$^{-1}$; LRMS (EI, H) $m/z$ calc’d for C$_{18}$H$_{22}$N [M + H]$^+$ 252.2, found 252.6; $R_f$ 0.48 (silica gel, 1:9 EtOAc/hexanes).

Synthesis of (2$R^*$,3$R^*$)-1-benzyl-3-ethyl-2-phenylpiperidine (20). A solution of amino alcohol 19 (78 mg, 0.262 mmol), PPh$_3$ (103 mg, 0.393 mmol) and imidazole (36 mg, 0.529 mmol) in
carbon tetrachloride (5.2 mL) was heated at reflux for 15 h. The mixture was poured into water (20 mL) and extracted with dichloromethane (4 × 15 mL). The combined organic extracts were washed with brine (1 × 15 mL), dried over MgSO$_4$ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes, then 1→3% EtOAc/hexanes) to afford piperidine 20 as a white solid (59 mg, 81%). The relative stereochemistry was determined by $^1$H NMR.

Data for (2$R^*$,3$R^*$)-1-benzyl-3-ethyl-2-phenylpiperidine (20): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.43 (d, $J = 7.5$ Hz, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.27-7.17 (m, 6H), 3.66 (d, $J = 13.5$ Hz, 1H), 2.98-2.94 (m, 1H), 2.79 (d, $J = 9.5$ Hz, 1H), 2.75 (d, $J = 13.5$ Hz, 1H), 2.00-1.96 (m, 1H), 1.92 (app td, $J = 11.5$, 3.7 Hz, 1H), 1.69-1.52 (m, 3H), 1.13-1.00 (m, 2H), 0.94-0.85 (m, 1H), 0.73 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 144.13, 140.48, 128.91, 128.82, 128.41, 128.14, 127.12, 126.63, 74.78, 60.22, 53.50, 45.11, 30.07, 26.00, 25.73, 11.28; IR (thin film, NaCl) 3084, 3062, 2960, 2934, 2874, 2854, 2788, 2711, 1729, 1603, 1494, 1453, 1378, 1370, 1341, 1307, 1291, 1259, 1224, 1157, 1119, 1073, 1029, 925, 757, 737, 701 cm$^{-1}$; LRMS (EI, H) $m/z$ calc’d for C$_{20}$H$_{26}$N [M + H]$^+$ 280.2, found 280.6; $R_f$ 0.50 (silica gel, 1:9 EtOAc/hexanes).

Synthesis of (2$R^*$,3$R^*$)-1-benzyl-3-methyl-2-phenylpiperidine (23). A solution of amino alcohol 22 (29 mg, 0.102 mmol), PPh$_3$ (40 mg, 0.153 mmol) and imidazole (14 mg, 0.206 mmol) in carbon tetrachloride (2.0 mL) was heated at reflux for 18 h. The mixture was poured into water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried over MgSO$_4$ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes, then 1→3% EtOAc/hexanes) to afford piperidine 23 as a white solid (21 mg, 77%). The relative stereochemistry was determined by $^1$H NMR.

Data for (2$R^*$,3$R^*$)-1-benzyl-3-methyl-2-phenylpiperidine (23): $^1$H NMR (500 MHz, CDCl$_3$)
δ 7.42 (d, J = 6.0 Hz, 2H), 7.32 (t, J = 7.8 Hz, 2H), 7.27-7.16 (m, 6H), 3.68 (d, J = 13.5 Hz, 1H), 2.97-2.93 (m, 1H), 2.76 (d, J = 13.0 Hz, 1H), 2.69 (d, J = 9.5 Hz, 1H), 1.92 (app td, J = 11.8, 3.3 Hz, 1H), 1.83-1.79 (m, 1H), 1.74-1.58 (m, 3H), 1.12 (app qd, J = 12.5, 4.3 Hz, 1H), 0.61 (d, J = 6.5 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 144.10, 140.40, 128.84, 128.41, 128.15, 127.12, 126.65, 76.39, 60.14, 53.46, 39.09, 34.28, 25.84, 19.93; IR (thin film, NaCl) 3061, 3026, 2926, 2849, 2766, 2726, 1603, 1493, 1452, 1377, 1356, 1335, 1306, 1280, 1260, 1226, 1185, 1134, 1111, 1067, 1045, 1029, 977, 918, 758, 736, 700, 451 cm−1; LRMS (EI, H) m/z calc’d for C19H24N [M + H]+ 266.2, found 265.9; Rf 0.51 (silica gel, 1:9 EtOAc/hexanes).

Synthesis of (2R*,4R*)-1-benzyl-4-methyl-2-phenylpiperidine (26). A solution of amino alcohol 25 (70 mg, 0.247 mmol), PPh3 (97 mg, 0.370 mmol) and imidazole (34 mg, 0.499 mmol) in carbon tetrachloride (4.9 mL) was heated at reflux for 15 h. The mixture was poured into water (20 mL) and extracted with dichloromethane (4 × 15 mL). The combined organic extracts were washed with brine (1 × 15 mL), dried over MgSO4 then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes, then 1→3% EtOAc/hexanes) to afford piperidine 26 as a white solid (50 mg, 76%). The relative stereochemistry was determined by 1H NMR.

Data for (2R*,4R*)-1-benzyl-4-methyl-2-phenylpiperidine (26): 1H NMR (500 MHz, CDCl3) δ 7.47 (d, J = 7.0 Hz, 2H), 7.33 (t, J = 7.8 Hz, 2H), 7.29-7.19 (m, 6H), 3.79 (d, J = 13.5 Hz, 1H), 3.43 (dd, J = 11.3, 3.3 Hz, 1H), 2.91 (d, J = 13.5 Hz, 1H), 2.73 (app dt, J = 11.8, 3.9 Hz, 1H), 2.26 (app td, J = 12.3, 3.0 Hz, 1H), 2.08-2.01 (m, 1H), 1.93-1.84 (m, 2H), 1.59 (app dq, J = 13.5, 2.7 Hz, 1H) 1.43-1.38 (m, 1H), 1.10 (d, J = 7.5 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 145.94, 140.19, 128.84, 128.64, 128.22, 127.74, 126.93, 126.71, 63.17, 59.94, 47.20, 42.40, 31.50, 26.48, 17.91; IR (thin film, NaCl) 3083, 3061, 3026, 2955, 2924, 2844, 2795, 2757, 1494, 1452 cm−1; LRMS (EI, H) m/z calc’d for C19H24N [M + H]+ 266.2, found 266.7; Rf 0.50 (silica gel, 1:9 EtOAc/hexanes).
Synthesis of (2R*,4S*)-1-benzyl-4-methyl-2-phenylpiperidine (26a). A solution of amino alcohol 25a (47 mg, 0.166 mmol), PPh₃ (65 mg, 0.248 mmol) and imidazole (23 mg, 0.338 mmol) in carbon tetrachloride (3.3 mL) was heated at reflux for 15 h. The mixture was poured into water (20 mL) and extracted with dichloromethane (4 × 15 mL). The combined organic extracts were washed with brine (1 × 15 mL), dried over MgSO₄ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes, then 1→3% EtOAc/hexanes) to afford piperidine 26a as a white solid (35 mg, 79%). The relative stereochemistry was determined by ¹H NMR.

Data for (2R*,4S*)-1-benzyl-4-methyl-2-phenylpiperidine (26a): ¹H NMR (500 MHz, CDCl₃) δ 7.47 (d, J = 7.0 Hz, 2H), 7.34 (t, J = 7.8 Hz, 2H), 7.28-7.19 (m, 6H), 3.80 (d, J = 13.5 Hz, 1H), 3.16 (dd, J = 11.3, 2.8 Hz, 1H), 2.98 (app dt, J = 11.5, 3.5 Hz, 1H), 2.81 (d, J = 13.5 Hz, 1H), 1.98 (app td, J = 12.0, 2.5 Hz, 1H), 1.78 (app dq, J = 13.0, 3.0 Hz, 1H), 1.63-1.51 (m, 2H), 1.37-1.24 (m, 2H), 0.92 (d, J = 6.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 145.84, 140.12, 128.87, 128.71, 128.21, 127.05, 126.72, 69.11, 59.76, 53.25, 45.85, 34.62, 31.91, 22.18; IR (thin film, NaCl) 3084, 3061, 3026, 2948, 2923, 2869, 2843, 2789, 2750, 2713, 1494, 1452 cm⁻¹; LRMS (El, H) m/z calc’d for C₁₉H₂₄N [M + H]⁺ 266.2, found 266.7; Rf 0.53 (silica gel, 1:9 EtOAc/hexanes).

Synthesis of (R)-5-((R)-2-methoxy-1-phenylethylamino)-5-phenylpentan-1-ol (29). To a solution of imine 28 (50 μL, 53.5 mg, 0.224 mmol) and Ti(Oi-Pr)₄ (100 μL, 96.0 mg, 0.338 mmol) in diethyl ether (1.0 mL) at −60 °C was added c-C₅H₉MgCl (2.0 M in diethyl ether, 0.680 mmol) in a drop wise manner. The mixture was warmed to −30 °C over 30 min and stirred for 2 h
at this temperature. A solution of lithium alkoxide 14a, prepared by the deprotonation of alcohol 14 (29 μL, 24.3 mg, 0.337 mmol) in diethyl ether (0.5 mL) at −78 °C with n-BuLi (2.5 M in hexanes, 0.363 mmol) followed by warming to 0 °C over 20 min, was added in a drop wise manner to the brown solution of imine–Ti complex at −30 °C via cannula. The mixture was warmed to ambient temperature over 30 min and stirred at this temperature for 6 h. The reaction was quenched by addition of water (0.5 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous NaHCO₃ (15 mL) and extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined, dried over MgSO₄ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (20→60% EtOAc/hexanes) to afford a diastereomeric mixture of amino alcohols as a pale yellow oil (29:29a = 24:1; 58 mg, 83%). The mixture was subjected to further purification by column chromatography on silica gel (10→60% EtOAc/hexanes) to isolate pure 29 as a colorless oil. The diastereomeric ratio was determined from the integration of methoxy signals (singlet) at 3.34 ppm (29) and 3.26 ppm (29a). The absolute stereochemistry was assigned by analogy based on previously reported stereoselective coupling of imine 28 with alkynes.⁴,⁵

Data for (R)-5-((R)-2-methoxy-1-phenylethylamino)-5-phenylpentan-1-ol (29): ¹H NMR (500 MHz, CDCl₃) δ 7.25-7.16 (m, 10H), 3.91 (dd, J = 7.0, 4.5 Hz, 1H), 3.62 (dd, J = 8.0, 5.5 Hz, 1H), 3.56 (t, J = 6.5 Hz, 2H), 3.53-3.47 (m, 2H), 3.34 (s, 3H), 1.86-1.79 (m, 1H), 1.71-1.64 (m, 1H), 1.56-1.46 (m, 2H), 1.30-1.16 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 144.72, 141.90, 128.38, 127.80, 127.46, 127.31, 126.89, 77.28, 62.91, 60.95, 60.42, 59.14, 36.70, 32.90, 22.38; IR (thin film, NaCl) 3330 (br), 3026, 2931, 2860, 1602, 1493, 1453, 1353, 1194, 1107, 1029, 969, 759, 700, 495, 451 cm⁻¹; LRMS (EI, H) m/z calc’d for C₂₀H₂₈NO₂ [M + H]⁺ 314.2, found 314.3; [α]D₂₀ −22.8 (c 1.00, CHCl₃); Rf 0.23 (silica gel, 1:1 EtOAc/hexanes).

Synthesis of (R)-4-[(R)-2-methoxy-1-phenylethylamino]phenyl)methyl]hexan-1-ol (31). To a solution of imine 28 (50 μL, 53.5 mg, 0.224 mmol) and Ti(Oi-Pr)₄ (100 μL, 96.0 mg, 0.338 mmol) in diethyl ether (1.0 mL) at −60 °C was added c-C₃H₇MgCl (2.0 M in diethyl ether, 0.680 mmol) in a drop wise manner. The mixture was warmed to −30 °C over 30 min and stirred for 2 h at this temperature. A solution of lithium alkoxide 27a, prepared by the deprotonation of alcohol 27 (40 μL, 33.9 mg, 0.338 mmol) in diethyl ether (0.5 mL) at −78 °C with n-BuLi (2.5 M in...
hexanes, 0.363 mmol) followed by warming to 0 °C over 20 min, was added in a drop wise manner to the brown solution of imine−Ti complex at −30 °C via cannula. The mixture was warmed to 0 °C over 40 min and stirred at this temperature for 6 h. The reaction was quenched by addition of water (0.5 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous NaHCO₃ (15 mL) and extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined, dried over MgSO₄ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (10→30% EtOAc/hexanes) to afford a diastereomeric mixture of amino alcohols as a pale yellow oil (31:31a = 20:1; 57 mg, 75%). The mixture was subjected to further purification by column chromatography on silica gel (5→30% EtOAc/hexanes) to isolate pure 31 as a colorless oil. The diastereomeric ratio was determined from the integration of methyl signals (triplet) at 0.84 ppm (31) and 0.67 ppm (31a). See 31→32 for the determination of absolute stereochemistry.

Data for [(R)-4-[(R)-(R)-2-methoxy-1-phenylethlamino](phenyl)methyl]hexan-1-ol (31): ¹H NMR (500 MHz, CDCl₃) δ 7.23-7.14 (m, 10H), 3.74 (t, J = 5.7 Hz, 1H), 3.67 (d, J = 6.7 Hz, 1H), 3.64-3.59 (m, 2H), 3.55 (dd, J = 5.7, 2.0 Hz, 2H), 3.33 (s, 3H), 2.14 (br, 2H), 1.67-1.46 (m, 5H), 1.36-1.28 (m, 1H), 1.06 (ddq, J = 14.3, 7.2, 7.2 Hz, 1H), 0.84 (t, J = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 143.83, 142.23, 128.36, 128.10, 128.08, 127.68, 127.27, 126.71, 76.74, 64.06, 62.79, 60.59, 59.18, 45.49, 29.99, 25.09, 23.55, 11.81; IR (thin film, NaCl) 3349 (br), 3061, 3026, 2931, 2874, 1602, 1493, 1453, 1379, 1194, 1105, 1028, 969, 759, 700, 451 cm⁻¹; LRMS (EI, H) m/z calc’d for C₂₂H₃₂NO₂ [M + H]⁺ 342.2, found 342.4; [α]D²⁰ −2.9 (c 1.00, CHCl₃); Rf 0.53 (silica gel, 1:1 EtOAc/hexanes).

Synthesis of [(R)-4-[(R)-(R)-2-methoxy-1-phenylethlamino](phenyl)methyl]hexan-1-ol (31). To a solution of imine 28 (50 μL, 53.5 mg, 0.224 mmol) and Ti(O-i-Pr)₄ (100 μL, 96.0 mg, 0.338 mmol) in diethyl ether (1.0 mL) at −60 °C was added c-C₅H₉MgCl (2.0 M in diethyl ether, 0.680 mmol) in a drop wise manner. The mixture was warmed to −30 °C over 30 min and stirred for 2 h at this temperature. A solution of lithium alkoxide 18a, prepared by the deprotonation of alcohol 18 (41 μL, 33.5 mg, 0.334 mmol) in diethyl ether (0.5 mL) at −78 °C with n-BuLi (2.5 M in hexanes, 0.363 mmol) followed by warming to 0 °C over 20 min, was added in a drop wise manner to the brown solution of imine−Ti complex at −30 °C via cannula. The mixture was
warmed to 0 °C over 40 min and stirred at this temperature for 6 h. The reaction was quenched by addition of water (0.5 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous NaHCO₃ (15 mL) and extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined, dried over MgSO₄ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (5→30% EtOAc/hexanes) to afford a diastereomeric mixture of amino alcohols as a pale yellow oil (31:31b:31a = 25:4:1; 47 mg, 61%). The diastereomeric ratio was determined from the integration of methyl signals (triplet) at 0.88 ppm (31b), 0.84 ppm (31) and 0.67 ppm (31a).

**Synthesis of (R)-1-((R)-2-methoxy-1-phenylethyl)-2-phenylpiperidine (30).** To a solution of amino alcohol 29 (54 mg, 0.172 mmol), triethylamine (48 μl, 34.8 mg, 0.344 mmol) and 4-(dimethylamino)pyridine (2 mg, 0.016 mmol) in dichloromethane (0.6 mL), a solution of 2-nitrobenzenesulfonyl chloride (40 mg, 0.180 mmol) in dichloromethane (0.3 mL) was added in a drop wise manner. The mixture was stirred for 5 h at ambient temperature, then poured into saturated aqueous NaHCO₃ (15 mL) and extracted with dichloromethane (3 × 15 mL). The organic extracts were combined, dried over MgSO₄ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (5% EtOAc/hexanes) to afford piperidine 30 as a colorless oil (39 mg, 77%).

**Data for (R)-1-((R)-2-methoxy-1-phenylethyl)-2-phenylpiperidine (30):** ¹H NMR (500 MHz, CDCl₃) δ 7.47-7.44 (m, 4H), 7.34-7.29 (m, 4H), 7.25-7.20 (m, 2H), 3.94-3.89 (m, 2H), 3.85 (dd, J = 10.8, 2.7 Hz, 1H), 3.82-3.77 (m, 2H), 3.31 (s, 3H), 2.89-2.85 (m, 1H), 2.41 (app td, J = 11.5, 2.5 Hz, 1H), 1.82-1.76 (m, 2H), 1.70-1.59 (m, 2H), 1.51 (app qt, J = 12.3, 3.5 Hz, 1H), 1.40 (app qt, J = 12.8, 3.5 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 145.40, 141.93, 128.69, 128.08, 127.97, 127.94, 127.14, 126.45, 70.35, 66.34, 59.14, 58.99, 46.86, 37.69, 26.79, 25.73; IR (thin film, NaCl) 3028, 2930, 2853, 2805, 1601, 1491, 1451, 1374, 1329, 1312, 1267, 1257, 1220, 1192, 1116, 1099, 1068, 1045, 1031, 1007, 980, 962, 759, 738, 700, 496, 452 cm⁻¹; LRMS (EI, H) m/z calc’d for C₂₀H₂₆NO [M + H]⁺ 296.2, found 296.3; [α]D²⁰ = -20.0 (c 1.50, CHCl₃); Rf 0.52 (silica gel, 1:9 EtOAc/hexanes).
Synthesis of (2R,3R)-3-ethyl-1-((R)-2-methoxy-1-phenylethyl)-2-phenylpiperidine (32). To a solution of amino alcohol 31 (57 mg, 0.167 mmol) and triethylamine (47 μl, 34.1 mg, 0.337 mmol) in dichloromethane (1.0 mL), methanesulfonyl chloride (14.5 μl, 21.4 mg, 0.187 mmol) was added in a drop wise manner. The mixture was stirred for 2 h at ambient temperature, then poured into water (15 mL) and extracted with dichloromethane (3 × 15 mL). The organic extracts were combined, dried over MgSO₄ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (5% EtOAc/hexanes) to afford piperidine 32 as a colorless oil (47 mg, 87%). The relative stereochemistry (Ph, Et) was determined by ¹H NMR. The absolute stereochemistry was assigned by analogy based on previously reported stereoselective coupling of imine 28 with alkynes.⁴,⁵

Data for (2R,3R)-3-ethyl-1-((R)-2-methoxy-1-phenylethyl)-2-phenylpiperidine (32): ¹H NMR (500 MHz, CDCl₃) δ 7.45-7.41 (m, 4H), 7.34-7.27 (m, 4H), 7.25-7.17 (m, 2H), 3.89 (dd, J = 8.7, 4.1 Hz, 1H), 3.83-3.78 (m, 2H), 3.48 (d, J = 9.5 Hz, 1H), 3.31 (s, 3H), 2.85-2.83 (m, 1H), 2.35 (app td, J = 11.7, 2.5 Hz, 1H), 2.01-1.98 (m, 1H), 1.66-1.62 (m, 1H), 1.60-1.48 (m, 2H), 1.08-1.00 (m, 2H), 0.94-0.85 (m, 1H), 0.73 (t, J = 7.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 143.53, 142.22, 129.03, 128.49, 127.99, 127.95, 127.21, 126.37, 71.62, 69.90, 59.11, 59.02, 46.78, 45.76, 30.43, 26.39, 26.09, 11.37; IR (thin film, NaCl) 3028, 2929, 2873, 2805, 1601, 1492, 1452, 1375, 1342, 1308, 1258, 1185, 1155, 1114, 1069, 1047, 1031, 973, 952, 758, 740, 700, 495, 452 cm⁻¹; LRMS (EI, H) m/z calc’d for C₂₂H₃₀NO [M + H]⁺ 324.2, found 324.4; [α]D²⁰ −49.9 (c 1.50, CHCl₃); Rf 0.54 (silica gel, 1:9 EtOAc/hexanes).
Synthesis of (3R,6S,7S)-7-((S)-2-methoxy-1-phenylethylamino)-6-methyl-1,7-diphenylheptan-3-ol (34). To a solution of imine ent-28 (40 μL, 42.8 mg, 0.179 mmol) and Ti(Oi-Pr)₄ (80 μL, 76.8 mg, 0.270 mmol) in diethyl ether (0.8 mL) at −60 °C was added c-C₅H₉MgCl (2.0 M in diethyl ether, 0.540 mmol) in a drop wise manner. The mixture was warmed to −30 °C over 30 min and stirred for 2 h at this temperature. A solution of lithium alkoxide 33a, prepared by the deprotonation of alcohol 33 (>99% ee; 52 μL, 51.0 mg, 0.268 mmol) in diethyl ether (0.5 mL) at −78 °C with n-BuLi (2.5 M in hexanes, 0.288 mmol) followed by warming to 0 °C over 20 min, was added in a drop wise manner to the brown solution of imine−Ti complex at −30 °C via cannula. The mixture was warmed to 0 °C over 30 min then stirred at ambient temperature for 6 h. The reaction was quenched by addition of water (0.5 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous NaHCO₃ (15 mL) and extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined, dried over MgSO₄ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (10→30% EtOAc/hexanes) to afford a diastereomeric mixture of amino alcohols as a colorless oil (34:34a = 26:1; 66 mg, 85%). The mixture was subjected to multiple purifications by column chromatography on silica gel (5→25% EtOAc/hexanes) to isolate pure 34. The diastereomeric ratio was determined from the integration of methyl signals (doublet) at 0.76 ppm (34) and 0.60 ppm (34a). See 34→41→42→35 for the stereochemical assignment.

Data for (3R,6S,7S)-7-((S)-2-methoxy-1-phenylethylamino)-6-methyl-1,7-diphenylheptan-3-ol (34): ¹H NMR (500 MHz, CDCl₃) δ 7.31-7.28 (m, 2H), 7.22-7.16 (m, 11H), 7.14-7.12 (m, 2H), 3.78 (t, J = 5.8 Hz, 1H), 3.64-3.60 (m, 1H), 3.56 (d, J = 6.5 Hz, 1H), 3.52 (d, J = 5.5 Hz, 2H), 3.32 (s, 3H), 2.81 (ddd, J = 15.5, 9.5, 6.0 Hz, 1H), 2.67 (ddd, J = 16.5, 9.5, 7.0 Hz, 1H), 2.00 (br, 2H), 1.83-1.73 (m, 3H), 1.69-1.58 (m, 2H), 1.44-1.38 (m, 1H), 1.27-1.21 (m, 1H), 0.76 (d, J = 7.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 143.13, 142.47, 142.13, 128.64, 128.58, 128.34, 128.29, 127.98, 127.74, 127.25, 126.76, 125.97, 76.91, 71.67, 65.77, 60.46, 59.19, 39.16, 38.87, 34.80, 32.32, 29.25, 16.29; IR (thin film, NaCl) 3354 (br), 3026, 2929, 1602, 1494, 1453, 1379, 1194, 1107, 1029, 968, 758, 699, 499, 450 cm⁻¹; LRMS (EI, H) m/z calc'd for C₂₉H₃₈NO₂ [M + H]⁺ 432.3, found 432.5; [α]D²⁰ +4.9 (c 1.00, CHCl₃); Rf 0.27 (silica gel, 1:3 EtOAc/hexanes).
Synthesis of (3\textit{R},6\textit{R},7\textit{R})-7-((\textit{R})-2-methoxy-1-phenylethylamino)-6-methyl-1,7-diphenylheptan-3-ol (36) and (3\textit{R},6\textit{S},7\textit{S})-7-((\textit{R})-2-methoxy-1-phenylethylamino)-6-methyl-1,7-diphenylheptan-3-ol (36a). To a solution of imine 28 (40 μL, 42.8 mg, 0.179 mmol) and Ti(Oi-Pr)$_4$ (80 μL, 76.8 mg, 0.270 mmol) in diethyl ether (0.8 mL) at $-60$ °C was added c-C$_5$H$_9$MgCl (2.0 M in diethyl ether, 0.540 mmol) in a drop wise manner. The mixture was warmed to $-30$ °C over 30 min and stirred for 2 h at this temperature. A solution of lithium alkoxide 33a, prepared by the deprotonation of alcohol 33 (>99% ee; 52 μL, 51.0 mg, 0.268 mmol) in diethyl ether (0.5 mL) at $-78$ °C with n-BuLi (2.5 M in hexanes, 0.288 mmol) followed by warming to 0 °C over 20 min, was added in a drop wise manner to the brown solution of imine–Ti complex at $-30$ °C via cannula. The mixture was warmed to 0 °C over 30 min then stirred at ambient temperature for 6 h. The reaction was quenched by addition of water (0.5 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous NaHCO$_3$ (15 mL) and extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined, dried over MgSO$_4$ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (10→30% EtOAc/hexanes) to afford a diastereomeric mixture of amino alcohols as a colorless oil (36:36a:36b = 6:3:1; 66 mg, 85%). The mixture was subjected to multiple purifications by column chromatography on silica gel (5→25% EtOAc/hexanes) to isolate pure diastereomers 36 and 36a. The diastereomeric ratio was determined from the integration of methyl signals (doublet) at 0.76 ppm (36b), 0.73 ppm (36) and 0.64 ppm (36a). See 36→43→44→37 and 36a→41→42→35 for the stereochemical assignment.

**Data for (3\textit{R},6\textit{R},7\textit{R})-7-((\textit{R})-2-methoxy-1-phenylethylamino)-6-methyl-1,7-diphenylheptan-3-ol (36):** $^1$H NMR (500 MHz, CDCl$_3$) δ 7.30-7.27 (m, 2H), 7.22-7.16 (m, 11H), 7.13-7.11 (m, 2H), 3.77 (t, $J$ = 6.0 Hz, 1H), 3.63-3.58 (m, 1H), 3.54 (d, $J$ = 6.0 Hz, 2H), 3.51 (d, $J$ = 7.5 Hz, 1H), 3.33 (s, 3H), 2.82 (ddd, $J$ = 13.5, 8.0, 7.5 Hz, 1H), 2.69 (ddd, $J$ = 14.0, 8.5, 8.0 Hz, 1H), 2.12 (br, 2H), 1.80-1.74 (m, 3H), 1.68-1.61 (m, 1H), 1.52-1.47 (m, 2H), 1.41-1.34 (m, 1H), 0.73 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 143.34, 142.54, 142.10, 128.65, 128.56,
128.35, 128.18, 127.73, 127.27, 126.78, 125.94, 76.86, 70.94, 66.16, 60.66, 59.21, 39.52, 38.59, 34.67, 32.37, 29.52, 16.87; IR (thin film, NaCl) 3410 (br), 3061, 3026, 2926, 2873, 1602, 1583, 1494, 1453, 1378, 1194, 1106, 1029, 967, 910, 758, 699, 500, 450 cm⁻¹; LRMS (EI, H) m/z calc’d for C_{29}H_{38}NO_{2} [M + H]^+ 432.3, found 432.5; [α]_D^{20} −16.1 (c 1.00, CHCl₃); RF 0.29 (silica gel, 1:3 EtOAc/hexanes).

Data for (3R,6S,7S)-7-((R)-2-methoxy-1-phenylethylamino)-6-methyl-1,7-diphenylheptan-3-ol (36a): ^1H NMR (500 MHz, CDCl₃) δ 7.33-7.19 (m, 13H), 7.09-7.07 (m, 2H), 3.62 (ddd, J = 12.0, 4.1, 4.1 Hz, 1H), 3.58 (dd, J = 9.6, 3.6 Hz 1H), 3.42 (t, J = 9.7 Hz, 1H), 3.25 (dd, J = 9.5, 4.0 Hz, 1H), 3.24 (s, 3H), 3.07 (d, J = 8.0 Hz, 1H), 2.82 (ddd, J = 14.0, 10.0, 5.5 Hz, 1H), 2.68 (ddd, J = 13.7, 9.8, 6.7 Hz, 1H), 2.06 (br, 2H), 1.88-1.67 (m, 4H), 1.55-1.48 (m, 1H), 1.38-1.31 (m, 1H), 1.27-1.20 (m, 1H), 0.63 (d, J = 7.0 Hz, 3H); ^13C NMR (126 MHz, CDCl₃) δ 143.35, 142.57, 141.00, 128.67, 128.60, 128.49, 128.35, 128.30, 127.95, 127.61, 126.87, 125.98, 77.95, 71.97, 64.40, 59.02, 58.72, 39.82, 39.28, 34.85, 32.30, 29.32, 17.27; IR (thin film, NaCl) 3334 (br), 3025, 2882, 2857, 1602, 1493, 1454, 1379, 1358, 1309, 1195, 1105, 1049, 1029, 762, 668, 495, 449 cm⁻¹; LRMS (EI, H) m/z calc’d for C_{29}H_{38}NO_{2} [M + H]^+ 432.3, found 432.5; [α]_D^{20} −83.4 (c 1.00, CHCl₃); RF 0.24 (silica gel, 1:3 EtOAc/hexanes).

Synthesis of (3R,6R,7R)-7-((R)-2-methoxy-1-phenylethylamino)-6-methyl-1,7-diphenylheptan-3-ol (36). To a solution of imine 28 (40 μL, 42.8 mg, 0.179 mmol) and Ti(Oi-Pr)₄ (80 μL, 76.8 mg, 0.270 mmol) in diethyl ether (0.8 mL) at −60 °C was added c-C₅H₉MgCl (2.0 M in diethyl ether, 0.540 mmol) in a drop wise manner. The mixture was warmed to −30 °C over 30 min and stirred for 2 h at this temperature. A solution of lithium alkoxide 38a, prepared by the deprotonation of alcohol 38 (>99% ee; 52 μL, 51.0 mg, 0.268 mmol) in diethyl ether (0.5 mL) at −78 °C with n-BuLi (2.5 M in hexanes, 0.288 mmol) followed by warming to 0 °C over 20 min, was added in a drop wise manner to the brown solution of imine–Ti complex at −30 °C via cannula. The mixture was warmed to 0 °C over 30 min then stirred at ambient temperature for 6 h. The reaction was quenched by addition of water (0.5 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous NaHCO₃ (15 mL) and extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined, dried over MgSO₄ then concentrated in vacuo. The crude product was purified by column
chromatography on silica gel (10→30% EtOAc/hexanes) to afford a diastereomeric mixture of amino alcohols as a colorless oil (36:36c:36d = 35:4:1; 68 mg, 88%). The diastereomeric ratio was determined from the integration of methyl signals (doublet) at 0.80 ppm (36c), 0.74 ppm (36) and 0.67 ppm (36d). Analysis and structure determination of the major diastereomer (36) were conducted using its enantiomer ent-36, prepared by coupling of ent-28 and ent-38 according to the procedure described above. The diastereomeric mixture obtained was subjected to multiple purifications by column chromatography on silica gel (5→25% EtOAc/hexanes) to isolate pure ent-36. See ent-36→ent-43→ent-44→ent-37 for the stereochemical assignment.

Data for (3S,6S,7S)-7-((S)-2-methoxy-1-phenylethylamino)-6-methyl-1,7-diphenylheptan-3-ol (ent-36): 1H NMR (500 MHz, CDCl3) δ 7.31-7.28 (m, 2H), 7.23-7.16 (m, 11H), 7.14-7.12 (m, 2H), 3.78 (t, J = 5.8 Hz, 1H), 3.64-3.59 (m, 1H), 3.55 (d, J = 6.0 Hz, 2H), 3.51 (d, J = 7.5 Hz, 1H), 3.34 (s, 3H), 2.82 (ddd, J = 13.5, 8.0, 8.0 Hz, 1H), 2.70 (ddd, J = 13.8, 8.1, 8.1 Hz, 1H), 2.13 (br, 2H), 1.80-1.75 (m, 3H), 1.69-1.62 (m, 1H), 1.56-1.45 (m, 2H), 1.42-1.35 (m, 1H), 0.74 (d, J = 6.5 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 143.33, 142.54, 142.09, 128.64, 128.55, 128.35, 128.17, 128.03, 127.72, 127.26, 126.77, 125.93, 76.85, 70.93, 66.15, 60.65, 59.20, 39.51, 38.58, 34.66, 32.36, 29.51, 16.85; IR (thin film, NaCl) 3413 (br), 3026, 2926, 2875, 1602, 1494, 1453, 1379, 1311, 1194, 1104, 1029, 758, 699, 497, 450 cm⁻¹; LRMS (EI, H) m/z calc’d for C29H38NO2 [M + H]⁺ 432.3, found 432.5; [α]D²⁰ +15.7 (c 1.50, CHCl3); Rf 0.29 (silica gel, 1:3 EtOAc/hexanes).

Synthesis of (3R)-7-((S)-2-methoxy-1-phenylethylamino)-6-methyl-1,7-diphenylheptan-3-ol (39). To a solution of imine ent-28 (40 μL, 42.8 mg, 0.179 mmol) and Ti(Oi-Pr)₄ (80 μL, 76.8 mg, 0.270 mmol) in diethyl ether (0.8 mL) at −60 °C was added c-C₆H₅MgCl (2.0 M in diethyl ether, 0.540 mmol) in a drop wise manner. The mixture was warmed to −30 °C over 30 min and stirred for 2 h at this temperature. A solution of lithium alkoxide 38a, prepared by the deprotonation of alcohol 38 (>99% ee; 52 μL, 51.0 mg, 0.268 mmol) in diethyl ether (0.5 mL) at −78 °C with n-BuLi (2.5 M in hexanes, 0.288 mmol) followed by warming to 0 °C over 20 min, was added in a drop wise manner to the brown solution of imine–Ti complex at −30 °C via cannula. The mixture was warmed to 0 °C over 30 min then stirred at ambient temperature for 6 h. The reaction was quenched by addition of water (0.5 mL) followed by rapid stirring until the...
precipitate became white in color. The mixture was diluted with saturated aqueous NaHCO₃ (15 mL) and extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined, dried over MgSO₄ then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (10→30% EtOAc/hexanes) to afford amino alcohol 39 as an inseparable mixture of four diastereomers (39a:39b:39c:39d = 19:12:4:1; 59 mg, 76%). The diastereomeric ratio was determined from the integration of methyl signals (doublet) at 0.90 ppm (39a), 0.76 ppm (39c), 0.73 ppm (39d) and 0.60 ppm (36b).

Synthesis of (3R,6S,7S)-7-amino-6-methyl-1,7-diphenylheptan-3-ol (41). A mixture of amino alcohol 34 (60 mg, 0.139 mmol) and Pd(OH)₂ (20% Pd dry weight basis on activated carbon, 50% water; 15 mg, 0.014 mmol) in 1:10 acetic acid/methanol (1.5 mL) was stirred under hydrogen atmosphere (1 atm) for 6 h at ambient temperature. The catalyst was removed by filtration through celite, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (1:9:90 NH₄OH/MeOH/CH₂Cl₂) to afford amino alcohol 41 as a white solid (38 mg, 92%).

Data for (3R,6S,7S)-7-amino-6-methyl-1,7-diphenylheptan-3-ol (41): ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.17 (m, 10H), 3.67 (d, J = 7.5 Hz, 1H), 3.63 (ddd, J = 8.0, 8.0, 4.0 Hz, 1H), 2.81 (ddd, J = 14.0, 9.5, 6.0 Hz, 1H), 2.67 (ddd, J = 13.7, 9.6, 6.8 Hz, 1H), 1.82-1.62 (m, 8H), 1.45-1.39 (m, 1H), 1.34-1.27 (m, 1H), 0.75 (d, J = 7.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 144.38, 142.51, 128.61, 128.59, 128.51, 127.37, 127.30, 125.88, 71.50, 61.38, 40.08, 39.27, 34.75, 32.36, 28.87, 16.83; IR (thin film, NaCl) 3277 (br), 3060, 3026, 2929, 2861, 1659, 1602, 1538, 1495, 1453, 1378, 1115, 1030, 1002, 939, 910, 764, 748, 700, 495, 448 cm⁻¹; LRMS (EI, H) m/z calc’d for C₂₀H₂₈N⁺O [M + H]⁺ 298.2, found 298.4; [α]D⁻²⁰ −28.6 (c 1.00, CHCl₃); Rf 0.33 (silica gel, 1:9:90 NH₄OH/MeOH/CH₂Cl₂).

Synthesis of (3S,6S,7S)-7-amino-6-methyl-1,7-diphenylheptan-3-ol (ent-43). A mixture of
amino alcohol *ent*-36 (64 mg, 0.148 mmol) and Pd(OH)$_2$ (20% Pd dry weight basis on activated carbon, 50% water; 16 mg, 0.015 mmol) in 1:10 acetic acid/methanol (1.6 mL) was stirred under hydrogen atmosphere (1 atm) for 6 h at ambient temperature. The catalyst was removed by filtration through celite, and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (1:9:90 NH$_4$OH/MeOH/CH$_2$Cl$_2$) to afford amino alcohol *ent*-43 as a colorless oil (40 mg, 91%).

**Data for (3S,6S,7S)-7-amino-6-methyl-1,7-diphenylheptan-3-ol (ent-43):**

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.33-7.17 (m, 10H), 3.66-3.61 (m, 2H), 2.81 (ddd, $J = 14.0, 8.0, 8.0$ Hz, 1H), 2.68 (ddd, $J = 13.7, 8.1, 8.1$ Hz, 1H), 1.87 (br, 2H), 1.79-1.66 (m, 5H), 1.57-1.38 (m, 3H), 0.73 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 144.39, 142.56, 128.64, 128.61, 128.51, 127.40, 127.24, 125.87, 70.78, 60.98, 39.61, 39.19, 33.75, 32.43, 28.73, 16.96; IR (thin film, NaCl) 3277 (br), 3061, 3026, 2930, 2861, 1602, 1495, 1454, 1378, 1334, 1030, 964, 764, 748, 700, 496, 448 cm$^{-1}$; LRMS (EI, H) $m/z$ calc’d for C$_{20}$H$_{28}$NO [M + H]$^+$ 298.2, found 298.4; $[\alpha]_D^{20} -26.8$ (c 1.00, CHCl$_3$); R$_f$ 0.33 (silica gel, 1:9:90 NH$_4$OH/MeOH/CHCl$_3$).

Synthesis of (3R,6S,7S)-7-amino-6-methyl-1,7-diphenylheptan-3-ol (41). A mixture of amino alcohol 36a (44 mg, 0.102 mmol) and Pd(OH)$_2$ (20% Pd dry weight basis on activated carbon, 50% water; 11 mg, 0.010 mmol) in 1:10 acetic acid/methanol (1.1 mL) was stirred under hydrogen atmosphere (1 atm) for 6 h at ambient temperature. The catalyst was removed by filtration through celite, and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (1:9:90 NH$_4$OH/MeOH/CH$_2$Cl$_2$) to afford amino alcohol 41 as a white solid (26 mg, 86%).

**Data for (3R,6S,7S)-7-amino-6-methyl-1,7-diphenylheptan-3-ol (41):**

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.33-7.17 (m, 10H), 3.66 (d, $J = 7.5$ Hz, 1H), 3.63 (dddd, $J = 8.0, 8.0, 4.0, 4.0$ Hz, 1H), 2.80 (ddd, $J = 14.0, 9.5, 6.0$ Hz, 1H), 2.66 (ddd, $J = 14.0, 9.5, 6.8$ Hz, 1H), 2.10 (br, 3H), 1.80-1.70 (m, 4H), 1.68-1.61 (m, 1H), 1.45-1.38 (m, 1H), 1.33-1.26 (m, 1H), 0.74 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 145.46, 142.50, 128.65, 128.64, 128.52, 127.17, 127.16, 125.96, 71.66, 61.36, 40.43, 39.31, 34.81, 32.37, 28.69, 16.93; IR (thin film, NaCl) 3277 (br), 3060, 3026, 2926, 2860, 1602, 1536, 1495, 1454, 1379, 1336, 1115, 1030, 968, 912, 764, 749, 700, 496, 448 cm$^{-1}$; LRMS (EI, H) $m/z$ calc’d for C$_{20}$H$_{28}$NO [M + H]$^+$ 298.2, found 298.4; $[\alpha]_D^{20} -26.4$ (c 1.00, CHCl$_3$); R$_f$ 0.33 (silica gel, 1:9:90 NH$_4$OH/MeOH/CHCl$_3$).
Synthesis of \((3R,6R,7R)-7\text{-amino-6-methyl-1,7-diphenylheptan-3-ol}\) (43). A mixture of amino alcohol 36 (60 mg, 0.139 mmol) and \(\text{Pd(OH)}_2\) (20% Pd dry weight basis on activated carbon, 50% water; 15 mg, 0.014 mmol) in 1:10 acetic acid/methanol (1.5 mL) was stirred under hydrogen atmosphere (1 atm) for 6 h at ambient temperature. The catalyst was removed by filtration through celite, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (1:9:90 \(\text{NH}_4\text{OH}/\text{MeOH}/\text{CH}_2\text{Cl}_2\)) to afford amino alcohol 43 as a colorless oil (37 mg, 89%).

**Data for \((3R,6R,7R)-7\text{-amino-6-methyl-1,7-diphenylheptan-3-ol}\) (43):** \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.33-7.17 (m, 10H), 3.64 (d, \(J = 8.5\) Hz, 1H), 3.62-3.58 (m, 1H), 3.08 (br, 3H), 2.79 (ddd, \(J = 14.0, 9.0, 6.5\) Hz, 1H), 2.65 (ddd, \(J = 14.0, 9.0, 6.5\) Hz, 1H), 1.87-1.80 (m, 1H), 1.77-1.71 (m, 3H), 1.57-1.39 (m, 3H), 0.71 (d, \(J = 6.5\) Hz, 3H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 144.53, 142.57, 128.66, 128.64, 128.55, 127.41, 127.26, 125.92, 70.95, 61.10, 39.58, 39.34, 33.94, 32.44, 28.82, 17.03; IR (thin film, NaCl) 3269 (br), 3061, 3026, 2931, 2860, 1602, 1544, 1495, 1454, 1378, 1334, 1030, 964, 910, 764, 748, 700, 503 cm\(^{-1}\); LRMS (El, H) \(m/z\) calc’d for C\(_{20}\)H\(_{28}\)NO \([\text{M} + \text{H}]^+\) 298.2, found 298.2; \([\alpha]_D^{20}\) +12.0 (c 1.00, CHCl\(_3\)); \(R_f\) 0.33 (silica gel, 1:9:90 \(\text{NH}_4\text{OH}/\text{MeOH}/\text{CHCl}_3\)).

Synthesis of \(N\)-(\((1S,2S,5R)-5\text{-hydroxy-2-methyl-1,7-diphenylheptyl})\)-2-nitrobenzenesulfonamide) (42). To a solution of amino alcohol 41 (from 34; 29 mg, 0.098 mmol), triethylamine (27 \(\mu\)L, 19.6 mg, 0.194 mmol) and 4-(dimethylamino)pyridine (1.2 mg, 0.010 mmol) in dichloromethane (0.7 mL) at 0 °C, a solution of 2-nitrobenzenesulfonyl chloride (22 mg, 0.099 mmol) in dichloromethane (0.7 mL) was added in a drop wise manner over 10 min. The reaction was warmed to ambient temperature over 15 min then stirred for 2 h. The mixture was diluted with ethyl acetate (20 mL) and washed successively with 1 N HCl, saturated aqueous NaHCO\(_3\), then brine (1 \(\times\) 15 mL each). The organic phase was dried over MgSO\(_4\) and concentrated in vacuo.
The crude product was purified by column chromatography on silica gel (30% EtOAc/hexanes) to afford sulfonamide 42 as a colorless oil (43 mg, 91%).

**Data for N-((1S,2S,5R)-5-hydroxy-2-methyl-1,7-diphenylheptyl)-2-nitrobenzenesulfonamide (42):**

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.63 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.59 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.45 (app td, $J = 7.8, 1.3$ Hz, 1H), 7.34-7.28 (m, 3H), 7.23-7.18 (m, 3H), 7.00-6.97 (m, 5H), 5.99 (d, $J = 9.5$ Hz, 1H), 4.26 (app t, $J = 9.0$ Hz, 1H), 3.67-3.62 (m, 1H), 2.81 (ddd, $J = 15.5, 10.0, 6.0$ Hz, 1H), 2.69 (ddd, $J = 13.8, 9.5, 6.7$ Hz, 1H), 1.95-1.63 (m, 5H), 1.52 (br, 1H), 1.46-1.39 (m, 1H), 1.30-1.22 (m, 1H), 0.71 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 147.35, 142.26, 139.10, 134.89, 132.81, 132.53, 130.90, 128.66, 128.33, 127.66, 127.29, 126.07, 124.95, 71.98, 64.46, 39.39, 39.31, 34.56, 32.24, 29.32, 16.69; IR (thin film, NaCl) 3348 (br), 3026, 2926, 2857, 1595, 1538, 1495, 1455, 1441, 1416, 1361, 1167, 1124, 1059, 1029, 917, 854, 741, 730, 701, 656, 590, 495, 451 cm$^{-1}$; LRMS (EI, H) $m/z$ calc’d for C$_{26}$H$_{31}$N$_2$O$_5$S [M + H]$^+$ 483.2, found 483.4; $[\alpha]_D^{20}$ $-172.8$ (c 1.00, CHCl$_3$); $R_f$ 0.59 (silica gel, 1:1 EtOAc/hexanes).

Synthesis of **N-((1S,2S,5S)-5-hydroxy-2-methyl-1,7-diphenylheptyl)-2-nitrobenzenesulfonamide (ent-44).** To a solution of amino alcohol ent-43 (29 mg, 0.098 mmol), triethylamine (27 μL, 19.6 mg, 0.194 mmol) and 4-(dimethylamino)pyridine (1.2 mg, 0.010 mmol) in dichloromethane (0.7 mL) at 0 °C, a solution of 2-nitrobenzenesulfonyl chloride (22 mg, 0.099 mmol) in dichloromethane (0.7 mL) was added in a drop wise manner over 10 min. The reaction was warmed to ambient temperature over 15 min then stirred for 2 h. The mixture was diluted with ethyl acetate (20 mL) and washed successively with 1 N HCl, saturated aqueous NaHCO$_3$, then brine (1 × 15 mL each). The organic phase was dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (30% EtOAc/hexanes) to afford sulfonamide ent-44 as a colorless oil (43 mg, 91%).

**Data for N-((1S,2S,5S)-5-hydroxy-2-methyl-1,7-diphenylheptyl)-2-nitrobenzenesulfonamide (ent-44):**

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.63 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.59 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.45 (app td, $J = 7.8, 1.3$ Hz, 1H), 7.34-7.28 (m, 3H), 7.23-7.18 (m, 3H), 7.00-6.97 (m, 5H), 5.99 (d, $J = 9.5$ Hz, 1H), 4.26 (app t, $J = 9.0$ Hz, 1H), 3.67-3.62 (m, 1H), 2.81 (ddd, $J = 15.5, 10.0, 6.0$ Hz, 1H), 2.69 (ddd, $J = 13.8, 9.5, 6.7$ Hz, 1H), 1.95-1.63 (m, 5H), 1.52 (br, 1H), 1.46-1.39 (m, 1H), 1.30-1.22 (m, 1H), 0.72 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 147.36, 142.26, 139.14, 134.87, 132.84, 132.54, 130.91, 128.65, 128.35, 127.66,
127.27, 126.06, 124.97, 71.45, 39.38, 39.18, 34.61, 32.31, 29.07, 16.63; IR (thin film, NaCl) 3343 (br), 3026, 2926, 2857, 1595, 1538, 1495, 1455, 1441, 1416, 1361, 1336, 1304, 1167, 1124, 1059, 1028, 854, 741, 731, 701, 656, 590, 552, 494, 449 cm$^{-1}$; LRMS (EI, H) $m/z$ calc’d for C$_{26}$H$_{31}$N$_2$O$_5$S $[M + H]^+$ 483.2, found 483.4; [$\alpha$]$_{D}^{20}$ −177.0 (c 1.00, CHCl$_3$); R$_f$ 0.59 (silica gel, 1:1 EtOAc/hexanes).

**Synthesis of N-((1S,2S,5R)-5-hydroxy-2-methyl-1,7-diphenyloctyl)-2-nitrobenzenesulfonamide (42).** To a solution of amino alcohol 41 (from 36a; 21 mg, 0.071 mmol), triethylamine (20 μL, 14.5 mg, 0.143 mmol) and 4-(dimethylaminomethyl)pyridine (0.9 mg, 0.007 mmol) in dichloromethane (0.5 mL) at 0 °C, a solution of 2-nitrobenzenesulfonyl chloride (16 mg, 0.072 mmol) in dichloromethane (0.5 mL) was added in a drop wise manner over 10 min. The reaction was warmed to ambient temperature over 15 min then stirred for 2 h. The mixture was diluted with ethyl acetate (20 mL) and washed successively with 1 N HCl, saturated aqueous NaHCO$_3$, then brine (1 × 15 mL each). The organic phase was dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (30% EtOAc/hexanes) to afford sulfonamide 42 as a colorless oil (31 mg, 90%).

**Data for N-((1S,2S,5R)-5-hydroxy-2-methyl-1,7-diphenyloctyl)-2-nitrobenzenesulfonamide (42):** $^1$H NMR (500 MHz, CDCl$_3$) δ 7.63 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.58 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.45 (app td, $J = 7.8, 1.5, 1$ Hz, 1H), 7.34-7.28 (m, 3H), 7.23-7.18 (m, 3H), 7.00-6.97 (m, 5H), 6.02 (d, $J = 9.5$ Hz, 1H), 4.25 (t, $J = 9.0$ Hz, 1H), 3.64 (ddd, $J = 8.0, 8.0, 4.0$ Hz, 1H, 2.81 (dd, $J = 14.0, 10.0, 6.0$ Hz, 1H), 2.69 (dd, $J = 13.5, 9.5, 6.8$ Hz, 1H, 1.97-1.63 (m, 5H), 1.61 (br, 1H), 1.46-1.39 (m, 1H), 1.29-1.22 (m, 1H), 0.71 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 147.27, 142.27, 139.05, 134.77, 132.82, 132.54, 130.88, 128.66, 128.63, 128.31, 127.64, 127.26, 126.03, 124.93, 71.94, 64.46, 39.30, 34.54, 32.22, 29.31, 16.67; IR (thin film, NaCl) 3350 (br), 3026, 2932, 2862, 1653, 1595, 1539, 1496, 1455, 1442, 1417, 1361, 1337, 1304, 1218, 1168, 1125, 1059, 1029, 913, 854, 781, 741, 731, 701, 657, 591, 553, 498, 452 cm$^{-1}$; LRMS (EI, H) $m/z$ calc’d for C$_{26}$H$_{36}$N$_2$NaO$_5$S $[M + Na]^+$ 505.2, found 505.3; [$\alpha$]$_{D}^{20}$ −161.3 (c 0.93, CHCl$_3$); R$_f$ 0.59 (silica gel, 1:1 EtOAc/hexanes).
Synthesis of N-((1R,2R,5R)-5-hydroxy-2-methyl-1,7-diphenylheptyl)-2-nitrobenzenesulfonamide (44). To a solution of amino alcohol 43 (29 mg, 0.098 mmol), triethylamine (27 μL, 19.6 mg, 0.194 mmol) and 4-(dimethylamino)pyridine (1.2 mg, 0.010 mmol) in dichloromethane (0.7 mL) at 0 °C, a solution of 2-nitrobenzenesulfonyl chloride (22 mg, 0.099 mmol) in dichloromethane (0.7 mL) was added in a drop wise manner over 10 min. The reaction was warmed to ambient temperature over 15 min then stirred for 2 h. The mixture was diluted with ethyl acetate (20 mL) and washed successively with 1 N HCl, saturated aqueous NaHCO₃, then brine (1 × 15 mL each). The organic phase was dried over MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (30% EtOAc/hexanes) to afford sulfonamide 44 as a colorless oil (44 mg, 93%).

Data for N-((1R,2R,5R)-5-hydroxy-2-methyl-1,7-diphenylheptyl)-2-nitrobenzenesulfonamide (44): ¹H NMR (500 MHz, CDCl₃) δ 7.63 (dd, J = 8.0, 1.0 Hz, 1H), 7.60 (dd, J = 8.0, 1.5 Hz, 1H), 7.46 (app td, J = 7.8, 1.3 Hz, 1H), 7.33 (app td, J = 7.8, 1.0 Hz, 1H), 7.31-7.28 (m, 2H), 7.23-7.18 (m, 3H), 7.01-6.97 (m, 5H), 6.02 (d, J = 9.5 Hz, 1H), 4.25 (app t, J = 9.0 Hz, 1H), 3.65 (br, 1H), 2.84-2.78 (m, 1H), 2.72-2.66 (m, 1H), 1.90-1.76 (m, 4H), 1.70 (br, 1H), 1.64-1.57 (m, 1H), 1.51-1.36 (m, 2H), 0.71 (d, J = 7.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 147.26, 142.29, 139.11, 134.73, 132.85, 132.54, 130.89, 128.64, 128.61, 128.32, 127.62, 127.23, 126.00, 124.92, 71.39, 64.59, 39.34, 39.09, 34.54, 32.30, 29.03, 16.60; IR (neat, NaCl) 3342 (br), 3027, 2932, 2863, 1595, 1539, 1496, 1455, 1442, 1418, 1361, 1337, 1304, 1218, 1167, 1124, 1059, 1029, 914, 854, 781, 741, 731, 702, 657, 591, 553, 497, 452 cm⁻¹; LRMS (EI, H) m/z calc’d for C₂₆H₃₀N₂NaO₅S [M + Na]⁺ 505.2, found 505.3; [α]D²⁰⁺158.8 (c 1.00, CHCl₃); Rf 0.59 (silica gel, 1:1 EtOAc/hexanes).

Synthesis of (2S,3S,6S)-3-methyl-1-(2-nitrobenzenesulfonyl)-6-phenethyl-2-phenylpiperidine (35). To a solution of sulfonamide 42 (from 34→41; 31 mg, 0.064 mmol) and PPh₃
(25 mg, 0.095 mmol) in tetrahydrofuran (1.3 mL), diisopropyl azodicarboxylate (19 μL, 19.5 mg, 0.096 mmol) was added in a drop wise manner. The reaction was stirred for 20 h at ambient temperature. The solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel (hexanes, then 5→15% EtOAc/hexanes; loading with 1:1 CH₂Cl₂/hexanes) to afford piperidine **35** as a white solid (28 mg, 94%). The absolute stereochemistry was determined by \(^1\)H NMR.

**Data for (2S,3S,6S)-3-methyl-1-(2-nitrobenzenesulfonyl)-6-phenethyl-2-phenylpiperidine (35):** \(^1\)H NMR (500 MHz, CDCl₃) δ 7.53 (dd, \(J = 8.0, 1.5\) Hz, 1H), 7.41 (td, \(J = 7.6, 1.3\) Hz, 1H), 7.34-7.29 (m, 4H), 7.24-7.20 (m, 1H), 7.09-7.06 (m, 3H), 6.95-6.92 (m, 1H), 6.89 (dd, \(J = 8.0, 1.0\) Hz, 1H), 6.83-6.80 (m, 2H), 4.36 (dddd, \(J = 10.5, 3.6, 3.4, 3.4\) Hz, 1H), 4.00 (d, \(J = 11.0\) Hz, 1H), 2.80 (ddd, \(J = 13.3, 11.5, 5.4\) Hz, 1H), 2.67-2.61 (m, 1H), 2.40-2.31 (m, 1H), 2.21-2.15 (m, 1H), 2.08-1.97 (m, 3H), 1.74 (dd, \(J = 14.0, 7.5, 3.8\) Hz, 1H), 1.53 (ddd, \(J = 25.7, 12.1, 5.2\) Hz, 1H), 0.57 (d, \(J = 6.5\) Hz, 3H); \(^13\)C NMR (126 MHz, CDCl₃) δ 147.16, 141.87, 137.06, 135.78, 132.16, 131.48, 129.75, 128.65, 128.64, 127.87, 127.24, 126.17, 124.02, 65.29, 56.89, 37.14, 33.41, 32.77, 27.30, 26.57, 19.12; IR (thin film, NaCl) 3029, 2934, 2869, 1603, 1593, 1539, 1495, 1455, 1366, 1331, 1266, 1240, 1210, 1159, 1126, 1099, 1059, 1028, 998, 908, 852, 838, 786, 740, 701, 658, 618, 589, 552, 450 cm\(^{-1}\); LRMS (EI, H) \(m/z\) calc’d for C\(_{26}\)H\(_{29}\)N\(_2\)O\(_4\)S [M + H]+ 465.2, found 465.4; \([\alpha]_D^{20}\) +54.1 (c 1.00, CHCl₃); \(R_f\) 0.52 (silica gel, 1:3 EtOAc/hexanes).

**Synthesis of (2S,3S,6R)-3-methyl-1-(2-nitrobenzenesulfonyl)-6-phenethyl-2-phenylpiperidine (ent-37).** To a solution of sulphonamide **ent-44** (31 mg, 0.064 mmol) and PPh\(_3\) (25 mg, 0.095 mmol) in tetrahydrofuran (1.3 mL), diisopropyl azodicarboxylate (19 μL, 19.5 mg, 0.096 mmol) was added in a drop wise manner. The reaction was stirred for 20 h at ambient temperature. The solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel (hexanes, then 5→20% EtOAc/hexanes; loading with 1:1 CH₂Cl₂/hexanes) to afford piperidine **ent-37** as a white solid (28 mg, 94%). The absolute stereochemistry was determined by \(^1\)H NMR.
Data for (2S,3S,6R)-3-methyl-1-(2-nitrobenzenesulfonyl)-6-phenethyl-2-phenylpiperidine (ent-37): ¹H NMR (500 MHz, CDCl₃) δ 7.88 (dd, J = 8.0, 1.5 Hz, 1H), 7.70-7.67 (m, 2H), 7.65 (dd, J = 7.8, 1.3 Hz, 1H), 7.59 (app td, J = 7.6, 1.3 Hz, 1H), 7.55 (dd, J = 8.0, 1.5 Hz, 1H), 7.38-7.35 (m, 2H), 7.31-7.28 (m, 1H), 7.20-7.17 (m, 2H), 7.14-7.11 (m, 1H), 6.86-6.85 (m, 2H), 4.87 (d, J = 4.5 Hz, 1H), 4.31-4.26 (m, 1H), 2.58-2.49 (m, 3H), 2.12-2.05 (m, 1H), 1.95 (ddd, J = 19.0, 9.6, 4.7 Hz, 1H), 1.89-1.81 (m, 1H), 1.53-1.44 (m, 2H), 1.22 (ddd, J = 13.5, 12.0, 6.0 Hz, 1H), 0.79 (d, J = 7.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 148.29, 141.90, 141.42, 134.56, 133.47, 131.41, 131.32, 128.63, 128.47, 128.36, 128.32, 127.56, 125.84, 123.89, 61.60, 54.44, 38.26, 33.44, 29.92, 24.28, 23.27, 19.48; IR (thin film, NaCl) 3026, 2938, 2870, 1602, 1589, 1544, 1496, 1454, 1373, 1342, 1294, 1266, 1209, 1165, 1128, 1079, 1062, 1030, 993, 962, 935, 914, 889, 852, 835, 777, 742, 728, 699, 655, 632, 573, 450 cm⁻¹; LRMS (EI, H) m/z calc’d for C₂₆H₂₉N₂O₄S [M + H]⁺ 465.2, found 465.5; [α]D₂₀ −18.5 (c 1.00, CHCl₃); Rf 0.40 (silica gel, 1:3 EtOAc/hexanes).

Synthesis of (2S,3S,6S)-3-methyl-1-(2-nitrobenzenesulfonyl)-6-phenethyl-2-phenylpiperidine (35). To a solution of sulfonamide 42 (from 36a→41; 21 mg, 0.044 mmol) and PPh₃ (17 mg, 0.065 mmol) in tetrahydrofuran (0.9 mL), diisopropyl azodicarboxylate (13 μL, 13.4 mg, 0.066 mmol) was added in a drop wise manner. The reaction was stirred for 20 h at ambient temperature. The solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel (hexanes, then 5→15% EtOAc/hexanes; loading with 1:1 CH₂Cl₂/hexanes) to afford piperidine 35 as a white solid (19 mg, 93%). The absolute stereochemistry was determined by ¹H NMR.
Data for \((2S,3S,6S)-3\)-methyl-1-(2-nitrobenzenesulfonyl)-6-phenethyl-2-phenylpiperidine (35): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.53 (dd, \(J = 8.0, 1.0\) Hz, 1H), 7.41 (app td, \(J = 7.8, 1.3\) Hz, 1H), 7.34-7.29 (m, 4H), 7.24-7.20 (m, 1H), 7.10-7.06 (m, 3H), 6.95-6.91 (m, 1H), 6.89 (dd, \(J = 8.0, 1.5\) Hz, 1H), 6.83-6.80 (m, 2H), 4.36 (dddd, \(J = 10.5, 3.5, 3.4, 3.4\) Hz, 1H), 3.99 (d, \(J = 11.0\) Hz, 1H), 2.80 (ddd, \(J = 13.3, 11.6, 5.4\) Hz, 1H), 2.67-2.61 (m, 1H), 2.39-2.31 (m, 1H), 2.21-2.14 (m, 1H), 2.07-1.95 (m, 3H), 1.73 (dddd, \(J = 11.2, 3.6, 3.6, 3.6\) Hz, 1H), 1.53 (ddd, \(J = 25.5, 12.3, 5.4\) Hz, 1H), 0.57 (d, \(J = 6.5\) Hz, 3H); \(^1\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 147.17, 141.88, 137.07, 135.80, 132.16, 131.49, 129.77, 128.66, 128.65, 127.88, 127.24, 126.18, 124.03, 65.30, 56.90, 37.14, 33.42, 32.78, 27.31, 26.57, 19.13; IR (thin film, NaCl) 3029, 2932, 2869, 1603, 1593, 1539, 1495, 1455, 1441, 1365, 1331, 1158, 1126, 1059, 1041, 1028, 998, 852, 785, 741, 701, 658, 618, 588, 497, 451 cm\(^{-1}\); LRMS (EI, H) \(m/z\) calc’d for C\(_{26}\)H\(_{29}\)N\(_2\)O\(_4\)S [M + H]\(^+\) 465.2, found 465.0; \([\alpha]\)\(_D\)\(^{20}\) +50.5 (c 1.00, CHCl\(_3\)); R\(_f\) 0.52 (silica gel, 1:3 EtOAc/hexanes).

Synthesis of \((2R,3R,6S)-3\)-methyl-1-(2-nitrobenzenesulfonyl)-6-phenethyl-2-phenylpiperidine (37). To a solution of sulfonamide 44 (33 mg, 0.068 mmol) and PPh\(_3\) (27 mg, 0.103 mmol) in tetrahydrofuran (1.4 mL), diisopropyl azodicarboxylate (20 \(\mu\)L, 10.5 mg, 0.102 mmol) was added in a drop wise manner. The reaction was stirred for 20 h at ambient temperature. The solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel (hexanes, then 5–20% EtOAc/hexanes; loading with 1:1 CH\(_2\)Cl\(_2\)/hexanes) to afford piperidine 37 as a white solid (28 mg, 89%). The absolute stereochemistry was determined by \(^1\)H NMR.
Data for (2R,3R,6S)-3-methyl-1-(2-nitrobenzenesulfonyl)-6-phenethyl-2-phenylpiperidine (37): $^1$H NMR (500 MHz, CDCl$_3$) δ 7.87 (dd, J = 7.9, 1.3 Hz, 1H), 7.69-7.68 (m, 2H), 7.65 (dd, J = 7.5, 1.5 Hz, 1H), 7.59 (app td, J = 7.8, 1.5 Hz, 1H), 7.55 (dd, J = 8.0, 1.0 Hz, 1H), 7.37-7.34 (m, 2H), 7.31-7.28 (m, 1H), 7.20-7.17 (m, 2H), 7.14-7.11 (m, 1H), 6.86-6.84 (m, 2H), 4.87 (d, J = 4.5 Hz, 1H), 4.31-4.26 (m, 1H), 2.57-2.49 (m, 3H), 2.12-2.05 (m, 1H), 1.94 (ddd, J = 18.9, 9.6, 4.6 Hz, 1H), 1.88-1.80 (m, 1H), 1.52-1.44 (m, 2H), 1.27-1.19 (m, 1H), 0.78 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 148.31, 141.91, 141.41, 134.60, 133.46, 131.41, 131.34, 128.64, 128.48, 128.37, 128.33, 127.58, 125.85, 123.90, 61.60, 54.45, 38.27, 33.44, 29.93, 24.28, 23.28, 19.49; IR (thin film, NaCl) 3026, 2940, 2871, 1602, 1590, 1544, 1496, 1455, 1439, 1373, 1342, 1295, 1266, 1211, 1165, 1128, 1079, 1062, 1030, 993, 962, 935, 916, 889, 852, 835, 753, 727, 700, 655, 632, 618, 573, 548, 453 cm$^{-1}$; LRMS (EI, H) m/z calc’d for C$_{26}$H$_{29}$N$_2$O$_4$S [M + H]$^+$ 465.2, found 465.2; [$\alpha$]$^\circ_{20} +17.4$ (c 1.00, CHCl$_3$); R$_f$ 0.40 (silica gel, 1:3 EtOAc/hexanes).


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