Highly Efficient and Enantioselective Cyclization of Aromatic Imines via Directed C-H Activation

Reema K. Thalji, Jonathan A. Ellman,* Robert G. Bergman*

*Department of Chemistry, University of California and Division of Chemical Sciences
Lawrence Berkeley National Laboratory
Berkeley, CA 94720*

Supporting Information

Experimental:

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. THF and diethyl ether were distilled under N₂ from sodium benzophenone ketyl and methanol from magnesium methoxide immediately prior to use. Benzene, toluene, CH₂Cl₂, pyridine and NEt₃ were all distilled under nitrogen from CaH₂ immediately prior to use. All organic reactions were performed under an atmosphere of N₂ in flame-dried or oven-dried glassware unless otherwise stated. All C-H activation experiments were prepared in a N₂-filled Braun inert atmosphere box. The following compounds were prepared according to the referenced literature procedures: (PPh₃)₃RhCl,¹ [RhCl(coe)₂]₂,² and ligands **1-2**,³ **6**,⁴ **7-10**,⁵ and **11-16b**.⁶ Ligand **3** was purchased from Strem, and ligands **4** and **5** were purchased from Aldrich. Thin-layer chromatography was performed on Merck 60 F₂₅₄ 250-μm silica gel plates. Visualization of the developed chromatogram was performed by fluorescence quenching, KMnO₄ stain, *para*-anisaldehyde stain, or phosphomolybdic acid stain. Flash chromatography was carried out according to the general procedure of Still⁷ using Merck 60 230-240 mesh silica gel or activity I basic Al₂O₃ as noted. Organic extracts were dried over Na₂SO₄ and were concentrated using a Büchi rotary evaporator under high vacuum pressure. Melting points were determined on a Mel-Temp apparatus and are

uncorrected. IR spectra were recorded on a Mattson Galaxy 3000 Fourier Transform spectrometer using NaCl plates and only partial data are reported. Unless otherwise noted, ^1H , ^{13}C , and ^{19}F NMR spectra were obtained in CDCl_3 . NMR chemical shifts are reported in ppm and referenced to residual protonated solvent. Elemental analyses and mass spectra were performed by the University of California, Berkeley Micro-Mass Facility. Chiral HPLC analyses were performed on a Hewlett-Packard 1100 system with an HP 1100 Diode Array Detector (monitoring at 254 nm) using a Chiracel OD (250 mm x 4.6 mm) or AS (250 mm x 4.6 mm) column as noted using a flow rate of 1 mL/min. Chiral gas chromatography (GC) analyses were performed on a Hewlett-Packard 5890 gas chromatograph with an FID detector using a G-TA column. A Perkin-Elmer 241 polarimeter with a sodium lamp was used to determine specific rotations and concentrations are reported in g/dL. Specific rotations were determined for each product obtained by cyclization with the optimal chiral ligand. The sense of induction provided by the other ligands was then determined by comparison of GC or HPLC traces. The absolute configurations of two cyclization products (**33** and **40**) were determined by x-ray crystallography after derivatization; the absolute configurations of the remaining substrates were assigned by analogy to those results.

General procedure for imine formation. To a solution of ketone in benzene (0.5 M) was added benzylamine (1.1 equiv). The reaction mixture was stirred over 4Å molecular sieves (1.00 g sieves/1.00 mmol ketone) for 12 h, after which it was diluted with CH_2Cl_2 , filtered through Celite, and concentrated *in vacuo*. The imine was purified and immediately stored in an inert atmosphere glove box at $-35\text{ }^\circ\text{C}$.

General procedure for the cyclization of N-benzyl imine substrates with Wilkinson's catalyst. In a dry-box, to a medium-walled glass reaction vessel was added a solution of $(\text{PPh}_3)_3\text{RhCl}$ (5 mol %) and the imine derivative in toluene (0.1 M). The vessel was placed in an oil bath at 125 °C. After the noted reaction time, the vessel was removed and cooled to rt. The solution was concentrated, 1N HCl was added, and the resulting mixture vigorously stirred for 3 h. The mixture was extracted with EtOAc (3x), and the combined organic extracts were washed with brine, dried, filtered, and concentrated. The crude product was dry-loaded onto a silica gel chromatography column for purification.

General procedure for the enantioselective cyclization of N-benyl imine substrates. In a dry-box, to a medium-walled glass reaction vessel was added a solution of $[\text{RhCl}(\text{coe})_2]_2$ (5 mol %), chiral phosphine (10 or 15 mol %), and the imine derivative in toluene (0.1 M). Critical to reaction conversion (but not enantioselectivity) is premixing the $[\text{RhCl}(\text{coe})_2]_2$ and chiral phosphine before addition of the imine derivative. Additionally, very pure imine starting material must be used. The mixture was then stirred at rt or placed in an oil bath at 50, 75, or 125 °C. After the noted reaction time, the mixture was concentrated and the product was hydrolyzed by adding 1N HCl (aq) (except for the indole substrate **23**; *vide infra*) and vigorously stirring for 3 h. After extraction with EtOAc (3x), the combined extracts were dried, filtered and concentrated. The residues were dry-loaded onto a silica gel chromatography column for purification.

Representative procedure for enantioselective ^1H -NMR experiments in Table 2. In a dry-box, to a medium-walled NMR tube was added a solution of $[\text{RhCl}(\text{coe})_2]_2$ (1.8 mg, 0.0025 mmol) and ligand **15** (3.1 mg, 0.0075 mmol) in 0.25 mL d_8 -toluene,

followed by a solution of imine **17** (12.6 mg, 0.050 mmol) and 2,6-dimethoxytoluene internal standard (1.5 mg, 0.010 mmol) in 0.25 mL *d*₈-toluene. The tube was fitted with a Cajon adapter and was vacuum sealed with a flame. The NMR tube was then placed in a 125 °C oil bath and the progress of the reaction was monitored periodically by ¹H-NMR spectroscopy. After 2 h, the reaction was complete and the yield was determined by ¹H-NMR to be 100%. The tube seal was broken, the mixture was concentrated, and the product was hydrolyzed by adding 1N HCl(aq) (2 mL) and vigorously stirring for 3 h. After extraction with EtOAc (3x), the combined extracts were dried, filtered, and concentrated. The residue was dry-loaded onto a silica gel plug (1 x 4 cm) and eluted with 10% EtOAc/Hex for chiral GC or chiral HPLC analysis.

Benzyl-{1-[3-(2-methyl-allyl)-phenyl]-ethylidene}-amine (17**)**. Prepared according to our previously reported procedure⁸ except here, the material was purified by Kugelrohr distillation (135 °C, 0.05 mm Hg) to a colorless oil. Spectral data agree with that previously reported.⁸

(±)-(1-(2-Methyl-indan-4-yl)-ethanone (29**))**. Prepared from **17** according to our previously reported procedure.⁸

(S)-(-)-(1-(2-Methyl-indan-4-yl)-ethanone (29). Reaction of **17**⁸ (150.0 mg, 0.597 mmol) using chiral ligand **16a** according to the general procedure for enantioselective cyclization (125 °C, 2.5 h) afforded **(S)-(-)-29** as a colorless oil (68 mg, 65% yield) after imine hydrolysis and silica gel chromatography (5% Et₂O/Hex). ¹H NMR (500 MHz): δ 7.65 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 3.45 (dd, *J* = 7.6, 17.4 Hz, 1H), 3.06 (dd, *J* = 10.3, 18.2 Hz, 1H), 2.85 (dd, *J* = 7.1, 17.4 Hz, 1H), 2.59 (s, 3H), 2.57-2.51 (m, 2H), (d, *J* = 6.4 Hz, 3H). ¹³C{H} NMR (125 MHz): δ 199.9, 145.8, 144.9, 133.9, 128.6, 127.4, 126.1, 42.3, 40.5, 34.0, 28.3, 20.8. Chiral HPLC (Chiralcel AS column, 1% *i*PrOH/Hex, 1 mL/min): major, 8.619 min; minor, 6.451 min; 88% ee. Chiral GC (Chiraldex G-TA column, 110 °C, 15 psi): major, 43.407 min; minor, 42.424 min; 88% ee. [α]_D²⁵ -12.86 (c 1.04, CHCl₃). Maximum [α]_D²⁵ -14.61 (c 1.04, CHCl₃).

1-{3-[2-(Dimethyl-phenyl-silanyl)-allyl]-phenyl}-ethanone (31). Magnesium turnings (0.396 g, 16.3 mmol) were crushed and flame-dried in a 100 mL round bottom flask equipped with a pressure equalizing addition funnel. THF (2 mL) was added to the turnings. At rt, approximately 30 drops of a solution of aryl bromide **30**⁹ (1.98 g, 8.14 mmol) in THF (6 mL) were added to the turnings, and the mixture was stirred until a

color change was observed (~5 min). The remaining solution was then added dropwise over 3 h, and the mixture was stirred for another hour. This Grignard solution was transferred dropwise over 30 min via cannula to a solution of (1-bromomethyl-vinyl)-dimethyl-phenyl-silane¹⁰ (2.50 g, 9.77 mmol) in THF (10 mL). After stirring overnight, the THF was removed *in vacuo* and the residue diluted with Et₂O, washed with H₂O, dried, filtered, and concentrated to a yellow oil. This oil was dissolved in MeOH (8 mL), and H₂O (1.6 mL), and then conc. aqueous HCl (0.50 mL) was added. After stirring for 1 h, the MeOH was removed *in vacuo* and the residue was dissolved in Et₂O and washed once with sat. NaHCO₃ (aq). The organic layer was dried, filtered and concentrated to give an orange oil. Chromatography on SiO₂ (10% EtOAc/Hex) afforded the desired ketone **31** contaminated with 5% acetophenone which was simply distilled away using a Kugelrohr (60 °C, 0.15 mm Hg) to provide pure ketone **31** (1.77 g, 74%) as a light yellow oil. IR: 3049, 2957, 1687, 1584, 1428, 1270, 933 cm⁻¹. ¹H NMR (400 MHz): δ 7.75 (m, 1H), 7.61 (m, 1H), 7.44 (m, 2H), 7.38-7.31 (m, 4H), 7.26 (m, 1H), 5.57 (m, 1H), 5.54 (m, 1H), 3.48 (s, 2H), 2.55 (s, 3H), 0.29 (s, 6H). ¹³C{H} NMR (100 MHz): δ 198.3, 149.2, 140.4, 137.7, 137.1, 134.2, 133.9, 129.2, 129.1, 128.3, 128.2, 127.8, 126.1, 42.5, 26.7, -3.0. Anal. Calcd. for C₁₉H₂₂OSi: C, 77.50; H, 7.53. Found: C, 77.38; H, 7.73.

Benzyl-(1-{3-[2-(dimethyl-phenyl-silanyl)-allyl]-phenyl}-ethylidene)-amine

(19). Prepared according to the general procedure for imine formation from **31** (300 mg, 1.02 mmol). Isolated as a yellow oil in 82% yield (319 mg) as a mixture of *E/Z* isomers

(13.3:1 by ^1H NMR) and used without purification. *E* isomer: ^1H NMR (500 MHz): δ 7.68-7.11 (m, 14H), 5.56 (m, 1H), 5.51 (m, 1H), 4.74 (s, 2H), 3.47 (s, 2H), 2.28 (s, 3H), 0.30 (s, 6H). *Z* isomer: ^1H NMR (500 MHz): δ 7.68-6.86 (m, 14H), 5.56 (m, 1H), 5.51 (m, 1H), 4.39 (s, 2H), 3.44 (s, 2H), 2.33 (s, 3H), 0.25 (s, 6H).

(±)-1-[2-(Dimethyl-phenyl-silanyl)-indan-4-yl]-ethanone (27). Reaction of **19** (100 mg, 0.261 mmol) according to the general procedure for cyclization with Wilkinson's catalyst (125 °C, 1 h) afforded (±)-**27** as a viscous colorless oil (70 mg, 87% yield) after imine hydrolysis and silica gel chromatography (10% EtOAc/Hex). IR: 2952, 1679, 1582, 1428, 1258, 1114 cm^{-1} . ^1H NMR (500 MHz): δ 7.63 (d, $J = 7.7$ Hz, 1H), 7.57-7.55 (m, 2H), 7.38-7.35 (m, 4H), 7.21 (t, $J = 7.6$ Hz, 1H), 3.49 (dd, $J = 9.0, 17.7$ Hz, 1H), 3.08 (dd, $J = 11.0, 17.7$ Hz, 1H), 3.00 (dd, $J = 9.0, 15.8$ Hz, 1H), 2.81 (dd, $J = 11.1, 15.6$ Hz, 1H), 2.58 (s, 3H), 1.81 (m, 1H), 0.34 (s, 3H), 0.32 (s, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (125 MHz): δ 200.0, 146.9, 146.1, 138.2, 133.9, 133.7, 129.0, 128.3, 127.8, 127.4, 126.1, 35.9, 34.4, 28.3, 25.4, -4.3, -4.8. EI-HRMS Calcd. for $\text{C}_{19}\text{H}_{22}\text{OSi}$ $[\text{M}]^+$: 294.1440. Found: 294.1441.

(S)-(+)-1-[2-(Dimethyl-phenyl-silanyl)-indan-4-yl]-ethanone (27). Reaction of **19** (75.0 mg, 0.195 mmol) using chiral ligand **16b** according to the general procedure for

enantioselective cyclization (50 °C, 20 h) afforded (*S*)-(+)-**27** as a viscous colorless oil (50 mg, 87% yield) after imine hydrolysis and silica gel chromatography (5% EtOAc/Hex). ¹H NMR (400 MHz): δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.56-7.54 (m, 2H), 7.37-7.34 (m, 4H), 7.20 (t, *J* = 7.6 Hz, 1H), 3.49 (dd, *J* = 9.0, 17.7 Hz, 1H), 3.08 (dd, *J* = 11.0, 17.7 Hz, 1H), 3.00 (dd, *J* = 9.0, 15.8 Hz, 1H), 2.81 (dd, *J* = 11.1, 16.0 Hz, 1H), 2.57 (s, 3H), 1.81 (m, 1H), 0.33 (s, 3H), 0.32 (s, 3H). ¹³C{H} NMR (100 MHz): δ 200.0, 146.9, 146.2, 138.2, 133.9, 133.7, 129.0, 128.3, 127.8, 127.5, 126.2, 36.0, 34.5, 28.3, 25.4, -4.2, -4.7. Chiral HPLC (Chiralcel OD, 1% *i*PrOH/Hex, 1 mL/min): major, 7.552 min; minor, 9.246 min; 42% ee. $[\alpha]_D^{25} +5.53$ (c 1.03, CHCl₃). Maximum $[\alpha]_D^{25} +13.17$ (c 1.03, CHCl₃).

(S)-(+)-1-(2-Hydroxyindan-4-yl)ethanone (28). Reaction of **19** (700 mg, 1.82 mmol) using chiral ligand **15** according to the general procedure for enantioselective cyclization (125 °C, 1 h) afforded (*S*)-(+)-**27** (70% ee) contaminated with 10% of ketone **31** in 66% yield (355 mg) after imine hydrolysis and silica gel chromatography (5% EtOAc/Hex). This material was taken on without further purification since oxidation to **28** would allow easier separation from **31**. To an ice-cold solution of the 9:1 mixture of (*S*)-(+)-**27** and **31** (150 mg, 0.509 mmol) in dry CH₂Cl₂ (11 mL) was added HBF₄•Et₂O (0.76 mL, 10.2 mmol). After the reaction mixture was stirred at 25 °C for 2 h, the reaction was quenched with saturated aqueous NaHCO₃ (11 mL) under ice-cooling, and the resultant mixture was then extracted with Et₂O. The extracts were washed with brine, dried, filtered and

concentrated *in vacuo* to give the resultant fluorosilane (120 mg) as a colorless oil which was used without purification. ^1H NMR (400 MHz): δ 7.73 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.28 (m, 1H), 4.72 (m, 1H), 3.56 (dd, J = 9.0, 17.8 Hz, 1H), 3.21-3.10 (m, 2H), 2.95 (dd, J = 10.8, 16.0 Hz, 1H), 2.64 (s, 3H), 1.79-1.73 (m, 1H), 0.33 (d, J = 7.6 Hz, 3H), 0.30 (d, J = 7.6 Hz, 3H). To a solution of the crude fluorosilane (120 mg, 0.508 mmol) in THF-MeOH (1:1, 21 mL) were added KF (88.5 mg, 1.52 mmol), KHCO_3 (153 mg, 1.52 mmol), and 31% H_2O_2 (aq) (0.13 mL, 4.65 mmol) under ice-cooling. After the reaction mixture was stirred for 10 h at 25 $^\circ\text{C}$, it was quenched with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (25 mL) under ice-cooling, and the resultant mixture was then extracted with ethyl acetate. The extracts were washed with brine, dried, filtered and concentrated *in vacuo*. Silica gel chromatography (50% EtOAc/hexanes) gave (*S,S*)-**28a** in 92% yield (74.5 mg) as a colorless oil. This product was confirmed to exist in 70% ee after derivatization to the corresponding Mosher's ester (see (*S,S*)-**28a** and (*R,S*)-**28b** below). IR: 3399, 2913, 2844, 1671, 1442, 1258 cm^{-1} . ^1H NMR (500 MHz): δ 7.70 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 7.0 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 4.72 (m, 1H), 3.49 (dd, J = 5.8, 18.3 Hz, 1H), 3.34 (d, J = 18.5 Hz, 1H), 3.19 (dd, J = 5.5, 16.5 Hz, 1H), 2.94 (dd, J = 16.5 Hz, 1H), 2.58 (s, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (125 MHz): δ 199.8, 143.1, 142.2, 134.1, 129.3, 128.1, 126.8, 72.5, 44.2, 41.9, 28.1. EI-HRMS Calcd. For $\text{C}_{11}\text{H}_{12}\text{O}_2$ $[\text{M}]^+$: 176.0837. Found: 176.0834. $[\alpha]_{\text{D}}^{25}$ +26.4 (c 1.01, CHCl_3). Maximum $[\alpha]_{\text{D}}^{25}$ +37.8 (c 1.01, CHCl_3).

3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-acetyl-indan-2-yl ester (28a and 28b). A solution of (*S*)-(+)-**28** (30 mg, 0.170 mmol) in dry CH₂Cl₂ (15 mL) was treated with (*S*)-(-)-MTPA (124 mg, 0.511 mmol), DCC (2.55 mL of a 1M solution in CH₂Cl₂, 2.55 mmol), and DMAP (125 mg, 1.02 mmol). This mixture was stirred overnight at room temperature after which time TLC (25% EtOAc/hexanes) indicated complete consumption of starting material. The solvent was removed *in vacuo* and the residue chromatographed on silica gel (25% EtOAc/hexanes) to give 47 mg (71% yield) of a mixture of diastereomers (*S*, *S*)-**28a** and (*R*, *S*)-**28b** (85:15 by ¹H NMR and ¹⁹F NMR). This corresponds to a 70% ee of (*S*)-(+)-**28**. ¹H NMR of mixture (500 MHz): δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.47 (m, 2H), 7.42-7.26 (m, 5H), 5.80 (m, 1H), 3.70 (dd, *J* = 7.0, 19.0 Hz, 1H), 3.56-3.48 (m, 1H), 3.50 (s, 3H), 3.38 (dd, *J* = 6.5, 17.5 Hz, 1H), **28b** 3.12 (br d, *J* = 17.0 Hz, 0.15H), **28a** 3.00 (br d, *J* = 17.0 Hz, 0.85H), **28a** 2.59 (s, 2.55H), **28b** 2.57 (s, 0.45H). ¹⁹F NMR of mixture (376 MHz): δ **28a** -70.8 (s, 2.55H), **28b** -70.9 (s, 0.45H).

1-[3-(2-Phenyl-allyl)-phenyl]-ethanone (32). Magnesium turnings (0.600 g, 24.7 mmol) were crushed and flame-dried in a 100 mL round bottom flask equipped with a pressure equalizing addition funnel. THF (3 mL) was added to the turnings. At rt, approximately 30 drops of a solution of aryl bromide **30**⁹ (3.00 g, 12.3 mmol) in THF (9.3 mL) were added to the turnings, and the mixture was stirred until a color change was observed (~5 min). The remaining solution was then added dropwise over 3 h, and the

mixture was stirred for another hour. This Grignard solution was transferred dropwise over 30 min via cannula to a solution of 3-bromo-2-phenyl-propene (3.65 g, 18.5 mmol) in THF (18.5 mL). After stirring overnight, the THF was removed *in vacuo* and the residue diluted with Et₂O, washed with H₂O, dried, filtered, and concentrated to a yellow oil. This oil was dissolved in MeOH (12 mL), and then H₂O (2.4 mL) and conc. aqueous HCl (0.75 mL) was added. After stirring for 1 h, the MeOH was removed *in vacuo* and the residue was dissolved in Et₂O and washed once with sat. NaHCO₃ (aq). The organic layer was dried, filtered and concentrated to give an orange oil, which was purified using SiO₂ chromatography (10% EtOAc/Hex) to a light yellow oil (1.78 g, 61%). IR: 3056, 2917, 1681, 1438, 1357, 1270, 1183, 904 cm⁻¹. ¹H NMR (400 MHz): δ 7.85 (s, 1H), 7.78 (m, 1H), 7.46-7.23 (m, 7H), 5.53 (m, 1H), 5.05 (m, 1H), 3.91 (s, 2H), 2.58 (s, 3H). ¹³C{H} NMR (100 MHz): δ 198.3, 146.5, 140.4, 140.1, 137.3, 133.7, 128.8, 128.6, 128.4, 127.7, 126.4, 126.2, 115.1, 41.5, 26.7. Anal. Calcd. for C₁₇H₁₆O: C, 86.40; H, 6.82. Found: C, 86.15; H, 6.95.

Benzyl-{1-[3-(2-phenyl-allyl)-phenyl]-ethylidene}-amine (21). Prepared according to the general procedure for imine formation from **32** (500 mg, 2.12 mmol). Isolated as a light yellow solid after recrystallization from pentane/Et₂O in 76% yield (520 mg) as a mixture of *E/Z* isomers (by ¹H NMR). *E* isomer: ¹H NMR (400 MHz): δ 7.75-7.23 (m, 14H), 5.52 (s, 1H), 5.04 (s, 1H), 4.76 (s, 2H), 3.90 (s, 2H), 2.32 (s, 3H). *Z*

isomer: ^1H NMR (400 MHz): δ 7.75-7.03 (m, 14H), 5.50 (m, 1H), 5.07 (m, 1H), 4.35 (s, 2H), 3.88 (s, 2H), 2.40 (s, 3H).

(±)-1-(2-Phenyl-indan-4-yl)-ethanone (33). Reaction of **21** (100 mg, 0.307 mmol) according to the general procedure for cyclization with Wilkinson's catalyst (125 °C, 5 h) afforded (±)-**33** as a white solid (60 mg, 82% yield) after imine hydrolysis and silica gel chromatography (5% EtOAc/Hex). Mp: 61-63 °C. IR: 1668, 1582, 1357, 1263 cm^{-1} . ^1H NMR (400 MHz): δ 7.71 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.34-7.28 (m, 5H), 7.22 (m, 1H), 3.81 (dd, J = 8.3, 17.3 Hz, 1H), 3.68 (m, 1H), 3.36 (m, 2H), 3.10 (dd, J = 8.7, 15.9 Hz, 1H), 2.60 (s, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz): δ 199.8, 145.3, 145.1, 144.2, 133.9, 128.5, 128.5, 127.9, 127.1, 126.7, 126.2, 45.1, 42.0, 40.3, 28.3. Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{O}$: C, 86.40; H, 6.82. Found: C, 86.43; H, 6.89.

(S)-(+)-1-(2-Phenyl-indan-4-yl)-ethanone (33). Reaction of **21** (225 mg, 0.691 mmol) according to the general procedure for enantioselective cyclization (75 °C, 3 h) using ligand **16a** afforded (S)-(+)-**33** as a white solid (130 mg, 80% yield) after imine hydrolysis and silica gel chromatography (5% EtOAc/Hex). ^1H NMR (500 MHz): δ 7.72 (d, J = 7.7 Hz, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.34-7.28 (m, 5H), 7.22 (m, 1H), 3.81 (dd, J = 8.3, 17.4 Hz, 1H), 3.68 (m, 1H), 3.36 (m, 2H), 3.09 (dd, J = 8.7, 15.9 Hz, 1H), 2.61 (s,

3H). $^{13}\text{C}\{\text{H}\}$ NMR (125 MHz): δ 199.7, 145.2, 145.0, 144.1, 133.8, 128.5, 128.4, 127.8, 127.0, 126.6, 126.2, 45.0, 41.9, 40.2, 28.3. Chiral HPLC (Chiralcel OD column, 5% *i*PrOH/Hex, 1 mL/min): major, 11.436 min; minor, 16.270 min; 90% ee. $[\alpha]_{\text{D}}^{25} +36.76$ (c 1.02, CHCl_3). Maximum $[\alpha]_{\text{D}}^{25} +40.84$ (c 1.02, CHCl_3).

(S_S, S)-4-Methyl-benzenesulfinic acid [1-(2-phenyl-indan-4-yl)-ethylidene]-amide (34**).** To a dry glass reaction vessel was added ketone **21** (90% ee, 30.0 mg, 0.127 mmol), (S)-(+)-*p*-toluenesulfinamide¹¹ (21.7 mg, 0.140 mmol), THF (0.25 mL), and $\text{Ti}(\text{OEt})_4$ (0.062 mL of an 85% solution in isopropanol, 0.254 mmol). This mixture was refluxed overnight (15h), cooled to rt, and poured onto rapidly stirring brine (0.50 mL). It was then filtered through a plug of celite and rinsed with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated, and eluted on a silica gel column (50% Hexanes/EtOAc) to give 35 mg (75% yield) of a light yellow oil which solidified upon standing. Recrystallization by vapor diffusion (ether/pentane) yielded x-ray quality crystals. The crystal structure of **34** identified the absolute configuration of (S)-(+)-**33**. IR: 1555, 1432, 1269, 1100 cm^{-1} . ^1H NMR (500 MHz): δ 7.69 (m, 2H), 7.41 (m, 1H), 7.32-7.23 (m, 9H), 3.59-3.50 (m, 2H), 3.32 (dd, $J = 7.5, 15.0$ Hz, 1H), 3.23 (dd, $J = 9.0, 17.0$ Hz, 1H), 3.05 (dd, $J = 9.0, 15.5$ Hz, 1H), 2.78 (s, 3H), 2.39 (s, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (125 MHz): δ 176.0, 144.9, 144.7, 143.3, 142.6, 141.8, 135.6, 129.7, 128.4, 127.0, 126.9,

126.7, 126.2, 125.9, 125.1, 45.1, 41.9, 40.3, 22.3, 21.4. EI-HRMS Calcd. for C₂₄H₂₃NOS
[M]⁺: 373.1500. Found: 373.1502.

1-[1-(2-Methyl-allyl)-1H-indol-3-yl]-ethanone (35). To a 250 mL round bottom flask fitted with a reflux condenser and stir bar was added 3-acetylimidazole (1.50 g, 9.42 mmol), 90 mL dry acetone, K₂CO₃ (2.61 g, 18.8 mmol), and 3-bromo-2-methylpropene (1.05 mL, 10.4 mmol). The solution was refluxed overnight in a 60 °C oil bath, and then cooled to rt. The acetone was removed *in vacuo* and the residue was taken up in distilled H₂O (80 mL) and extracted with Et₂O (3 x 100 mL). The combined organic extracts were dried, filtered and concentrated to give a thick oil which was purified using flash chromatography on SiO₂ (5% EtOAc/CH₂Cl₂) to give **35** in 71% yield (1.43 g) as a beige solid. Mp 71-73 °C. IR: 3088, 3030, 1640, 1531, 1389, 1197, 903 cm⁻¹. ¹H NMR (400 MHz): δ 8.40 (m, 1H), 7.72 (s, 1H), 7.33-7.25 (m, 3H), 4.98 (s, 1H), 4.76 (s, 1H), 4.66 (s, 2H), 2.52 (s, 3H), 1.70 (s, 3H). ¹³C{H} NMR (100 MHz): δ 193.1, 139.8, 137.1, 135.1, 126.3, 123.3, 122.6, 122.6, 117.3, 113.9, 110.2, 53.1, 27.7, 19.9. Anal. Calcd. for C₁₄H₁₅NO: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.99; H, 7.28; N, 6.53.

Benzyl-{1-[1-(2-methyl-allyl)-1H-indol-3-yl]-ethylidene}-amine (23). Prepared according to the general procedure for imine formation from **35** (500 mg, 2.34 mmol). Crude material was obtained as an orange viscous oil that solidified upon addition of pentane. Recrystallization by vapor diffusion using pentane/Et₂O gave **23** as large clear crystals in 78% yield (550 mg). ¹H NMR (500 MHz): δ 8.64 (m, 1H), 7.56-7.10 (m, 9H), 4.95 (s, 1H), 4.84 (s, 2H), 4.80 (s, 1H), 4.66 (s, 1H), 2.35 (s, 3H), 1.71 (s, 3H).

(±)-1-(2-Methyl-2,3-dihydro-1H-3a-aza-cyclopenta[a]inden-8-yl)-ethanone (36). Reaction of **23** (100 mg, 0.331 mmol) according to the general procedure for cyclization with Wilkinson's catalyst (125 °C, 30 min) afforded the desired product as the N-benzyl imine **24**. After removal of the toluene solvent, hydrolysis and purification were accomplished by eluting the residue on two silica gel chromatography columns (first using 33% EtOAc/Hex and second using 10% EtOAc/CH₂Cl₂). Ketone (±)-**36** was thus obtained as a white solid in 75% yield (52 mg). Mp 151-154 °C. IR: 2963, 1627, 1525, 1424 cm⁻¹. ¹H NMR (500 MHz): δ 8.27 (d, *J* = 7.7 Hz, 1H), 7.26-7.21 (m, 3H), 4.24 (dd, *J* = 8.0, 10.1 Hz, 1H), 3.65 (dd, *J* = 6.6, 10.2, 1H), 3.45 (dd, *J* = 8.2, 17.0 Hz, 1H), 3.19-3.12 (m, 1H), 2.86 (dd, *J* = 6.6, 17.0 Hz, 1H), 2.48 (s, 3H), 1.33 (d, *J* = 6.9 Hz, 3H). ¹³C{H} NMR (125 MHz): δ 192.8, 151.8, 132.8, 130.3, 122.2, 122.2, 122.1, 110.3, 109.6, 51.3, 36.0, 35.6, 29.4, 19.8. Anal. Calcd. for C₁₄H₁₅NO: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.41; H, 7.20; N, 6.72.

(R)-(-)-1-(2-Methyl-2,3-dihydro-1H-3a-aza-cyclopenta[a]inden-8-yl)-ethanone (36). Reaction of **23** (150 mg, 0.496 mmol) using chiral ligand **16b** according to the general procedure for enantioselective cyclization (125 °C, 16 h) afforded the desired product as the N-benzyl imine **24**. After removal of the toluene solvent, hydrolysis and purification were accomplished in one step by dry-loading the imine onto a silica column and eluting with 33% EtOAc/Hex. Thus, ketone **(R)-(-)-36** was obtained as an off-white solid in 64% yield (68 mg). ¹H NMR (500 MHz): δ 8.27 (d, *J* = 7.7 Hz, 1H), 7.26-7.21 (m, 3H), 4.28 (dd, *J* = 8.0, 10.1 Hz, 1H), 3.68 (dd, *J* = 6.6, 10.2, 1H), 3.51 (dd, *J* = 8.2, 17.0 Hz, 1H), 3.22-3.14 (m, 1H), 2.92 (dd, *J* = 6.6, 17.0 Hz, 1H), 2.52 (s, 3H), 1.34 (d, *J* = 6.9 Hz, 3H). ¹³C{H} NMR (100 MHz): δ 192.8, 151.7, 132.8, 130.3, 122.2, 122.2, 122.1, 110.4, 109.6, 51.4, 36.0, 35.7, 29.4, 19.8. Chiral HPLC (Chiralcel OD column, 12% *i*PrOH/Hex, 1 mL/min): major, 17.416 min; minor, 21.274 min; 68% ee. $[\alpha]_D^{25}$ -3.8 (c 1.00, CHCl₃). Maximum $[\alpha]_D^{25}$ -5.6 (c 1.00, CHCl₃).

1-Chloro-3-isopropenyloxy-benzene (38). A flame-dried 50 mL round bottom flask was charged with 3-chloro-phenol (2.00 g, 15.6 mmol), CH₂Cl₂ (13 mL), and pyridine (1.26 mL, 15.6 mmol). After cooling the flask to 0 °C, acetyl chloride was added dropwise over 10 min. The reaction mixture was stirred for 2 h at the same temperature and then diluted with CH₂Cl₂ (13 mL). This mixture was washed once with

1N HCl (aq) and then dried, filtered and concentrated to an oil *in vacuo*. Chromatography (SiO₂) using 12% EtOAc/Hex as the eluent gave 1.81 g (70%) of **37** as a colorless oil. ¹H NMR (400 MHz): δ 7.32 (m, 1H), 7.21 (m, 1H), 7.13 (m, 1H), 7.00 (m, 1H), 2.30 (s, 3H). This material (1.50 g, 8.79 mmol) was then added to a flame-dried round bottom flask equipped with a rubber septum and stir bar. The flask was then cooled to 0 °C, and Tebbe's reagent¹² (17.6 mL of a 0.5 M solution in toluene) was added all at once. The mixture was stirred for 30 min, at which time 130 mL of dry Et₂O was added, followed by ~10 drops of dry MeOH to destroy active aluminum compounds. After stirring for 15 min, the resulting deep red solution was filtered twice through a celite cake, rinsed with hexanes, and the volatiles removed *in vacuo*. The concentrate was then dry-loaded onto a basic Al₂O₃ column and eluted with 5% Et₂O/pentane to yield 1.13 g (76%) of **38** as a colorless oil. IR: 2922, 1590, 1472, 1256, 1221, 967 cm⁻¹. ¹H NMR (500 MHz): δ 7.27 (m, 1H), 7.09 (m, 1H), 7.06 (m, 1H), 6.94 (m, 1H), 4.27 (m, 1H), 4.07 (m, 1H), 1.97 (s, 3H). ¹³C{H} NMR (100 MHz): δ 158.9, 156.2, 134.8, 130.3, 123.9, 120.8, 118.6, 91.6, 19.8. EI-HRMS Calcd. for C₉H₉ClO [M]⁺: 169.0420. Found: 169.0419.

1-(3-Isopropenyloxy-phenyl)-ethanone (39). A flame-dried 25 mL round bottom flask fitted with a rubber septum was charged with Rieke Mg¹³ (9.7 mL of a solution of 2.5 g in 100 mL of THF, 9.96 mmol) using an 18-gauge syringe needle. Aryl chloride **38** (600 mg, 3.56 mmol) was weighed into a syringe and added to the flask all at once. The reaction mixture became warm after one minute and the Mg turned a darker grey color. After stirring for 3 h at rt, the resulting Grignard solution was transferred dropwise via cannula into a dry flask containing acetic anhydride (1.00 mL, 10.7 mmol)

and THF (10 mL) at -78°C . The reaction mixture was stirred for 2 h at the same temperature, at which time it was diluted with Et_2O (30 mL) and quenched with H_2O (50 mL). The cold bath was then removed and replaced with a rt bath to thaw the mixture. After 10 min of stirring at rt, the layers were separated, the water layer was extracted with Et_2O (2x), and the organic layers were combined, dried, filtered and concentrated to a yellow oil. Chromatography (basic Al_2O_3) using 10% EtOAc/Hex as the eluent provides 456 mg (73%) of **39** as a light yellow oil. IR: 1689, 1585, 1438, 1256, 959 cm^{-1} . ^1H NMR (400 MHz): δ 7.71 (d, $J = 8.0\text{ Hz}$, 1H), 7.63 (m, 1H), 7.44 (t, $J = 8.0\text{ Hz}$, 1H), 7.25 (m, 1H), 4.25 (s, 1H), 4.00 (s, 1H), 2.60 (s, 3H), 2.01 (s, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz): δ 197.4, 159.2, 155.8, 138.8, 129.8, 125.3, 123.8, 120.1, 91.0, 26.7, 19.9. Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{O}_2$: C, 74.98; H, 6.86. Found: C, 75.09; H, 7.06.

Benzyl-[1-(3-isopropenyloxy-phenyl)-ethylidene]-amine (25). Prepared according to the general procedure for imine formation from **39** (500 mg, 2.83 mmol). Isolated as a light yellow oil after distillation (120°C , 0.15 mm Hg) in 80% yield (603 mg) as a mixture of *E/Z* isomers (11.1:1 by ^1H NMR). *E* isomer: ^1H NMR (500 MHz): δ 7.66-7.10 (m, 9H), 4.74 (s, 2H), 4.18 (s, 1H), 3.98 (s, 1H), 2.33 (s, 3H), 2.01 (s, 3H). *Z* isomer: ^1H NMR (500 MHz): δ 7.66-6.87 (m, 9H), 4.44 (s, 2H), 4.24 (s, 1H), 4.04 (s, 1H), 2.37 (s, 3H), 2.01 (s, 3H).

(±)-1-(2-Methyl-2,3-dihydro-benzofuran-4-yl)-ethanone (40). Reaction of **25** (75.0 mg, 0.283 mmol) according to the general procedure for imine cyclization with Wilkinson's catalyst (125 °C, 45 min) afforded **(±)-40** as a white solid (45 mg, 90% yield) after imine hydrolysis and silica gel chromatography (10% EtOAc/Hex). Mp: 40-41 °C. IR: 2972, 2929, 1669, 1585, 1451, 1237 cm⁻¹. ¹H NMR (500 MHz): δ 7.36 (d, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 4.96 (m, 1H), 3.67 (d, *J* = 8.9, 17.5 Hz, 1H), 3.13 (dd, *J* = 7.5, 17.6 Hz, 1H), 2.58 (s, 3H), 1.47 (d, *J* = 6.3 Hz, 3H). ¹³C{H} NMR (100 MHz): δ 199.1, 160.6, 134.0, 128.4, 128.1, 121.4, 113.6, 80.2, 38.5, 27.8, 21.9. Anal. Calcd. for C₁₁H₁₂O₂: C, 74.98; H, 6.86. Found: C, 75.03; H, 7.04.

(R)-(+)-1-(2-Methyl-2,3-dihydro-benzofuran-4-yl)-ethanone (40). Reaction of **25** (60.0 mg, 0.226 mmol) using chiral ligand **16b** according to the general procedure for enantioselective imine cyclization (50 °C, 1.5 h) afforded **(R)-(+)-40** as a white solid (25 mg, 63% yield) after imine hydrolysis and silica gel chromatography (10% EtOAc/Hex). MP: 52-54 °C. ¹H NMR (500 MHz): δ 7.36 (d, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 4.96 (m, 1H), 3.67 (dd, *J* = 8.9, 17.5 Hz, 1H), 3.13 (dd, *J* = 7.5, 17.6 Hz, 1H), 2.58 (s, 3H), 1.47 (d, *J* = 6.3 Hz, 3H). ¹³C{H} NMR (125 MHz): δ 199.0,

160.6, 134.0, 128.4, 128.0, 121.3, 113.5, 80.2, 38.5, 27.8, 21.9. Chiral HPLC (Chiralcel AS column, 1% *i*PrOH/Hex, 1 mL/min): major, 8.856 min; minor, 7.010 min; 95% ee. $[\alpha]_D^{25} +22.98$ (c 1.04, CHCl₃). Maximum $[\alpha]_D^{25} +24.19$ (c 1.04, CHCl₃).

(S_S, R)-2,4,6-Trimethyl-benzenesulfinic acid [1-(2-methyl-2,3-dihydrobenzofuran-4-yl)-ethylidene]-amide (**41**). To a dry glass reaction vessel was added **41** (95% ee, 30.0 mg, 0.170 mmol), (S)-(+)-2,4,6-trimethylbenzenesulfinamide¹⁴ (34.3 mg, 0.187 mmol), THF (0.34 mL), and Ti(OEt)₄ (0.083 mL of an 85% solution in isopropanol, 0.340 mmol). This mixture was refluxed overnight (15h), cooled to rt, and poured onto rapidly stirring brine (0.50 mL). It was then filtered through a plug of celite and rinsed with ethyl acetate. The organic layer was dried (Na₂SO₄), concentrated, and eluted on a silica gel column (60% Hexanes/EtOAc) to give 31 mg (53% yield) of a light yellow solid. Recrystallization by vapor diffusion (ether/pentane) yielded x-ray quality crystals of **41**. The crystal structure identified the absolute configuration of (R)-(+)-**40**. MP: 120-122 °C. IR: 1565, 1442, 1234, 1082 cm⁻¹. ¹H NMR (500 MHz): δ 7.15 (m, 1H), 7.09 (m, 1H), 6.87-6.84 (m, 3H), 4.88 (m, 1H), 3.62 (dd, *J* = 9.0, 17.0 Hz, 1H), 3.02 (dd, *J* = 7.0, 17.0 Hz, 1H), 2.66 (s, 6H), 2.66 (s, 3H), 2.28 (s, 3H), 1.38 (d, *J* = 6.5 Hz, 3H). ¹³C{H} NMR (125 MHz): δ 173.3, 160.3, 141.5, 138.7, 137.9, 135.3, 130.6, 128.0, 127.3, 119.7, 112.3, 79.8, 38.8, 21.8, 21.3, 21.1, 19.4. HRMS (FAB) Calcd. for C₂₀H₂₄NO₂S (M⁺+H): 342.1528. Found: 342.1533.

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