

## The First Azacyclopentenylcarbinyl Radical Isomerizations (ACCRI): Independent Use of Steric and Electronic (Polarization) Effects as Gating Elements

Rajesh Viswanathan, Daniel Mutnick, and Jeffrey N. Johnston\*

Department of Chemistry, Indiana University, Bloomington, IN 47405-7102

### General Experimental Details

Flame-dried (under vacuum) glassware was used for all non-aqueous reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. Diethyl ether (Et<sub>2</sub>O), tetrahydrofuran (THF), dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), and benzene (C<sub>6</sub>H<sub>6</sub>) were dried by passage through a column of activated alumina as described by Grubbs.<sup>1</sup> Benzene was additionally passed through a column containing activated Q-5 reactant. Solvents other than benzene were degassed using the freeze-pump-thaw method when necessary. All additional solvents were dried by distillation from calcium hydride when necessary. Molecular sieves (spheres, 4Å) were calcined at 400 °C and stored at room temperature in an air-tight container. AIBN was recrystallized prior to use, and tri-*n*-butyl tin hydride ("Bu<sub>3</sub>SnH) was used as received from Aldrich.<sup>2</sup> Magnesium sulfate was used to dry organic solutions unless otherwise noted. Analytical data for **5a**, **5b**, **5g**, **5h**, **6a**, **6b**, **6g**, **6h** has been previously reported.<sup>3</sup>

Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μ) plates, and flash chromatography utilized 230–400 mesh silica gel from Scientific Adsorbents. Neutral Alumina was used as received from Scientific Adsorbents for chromatography of acid-sensitive intermediates or products. Products were visualized by UV light, iodine, and/or the use of ceric ammonium molybdate, potassium permanganate, ninhydrin, *p*-anisaldehyde, and potassium iodoplatinate solutions.

<sup>1</sup> Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

<sup>2</sup> Two lots (purchased six months apart) from Alfa Aesar failed to effect the radical reactions.

<sup>3</sup> Viswanathan, R.; Plotkin, M. A.; Prabhakaran, E. N.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *115*, 163–168.

IR spectra were recorded on a Nicolet Avatar 360 spectrophotometer. Liquids and oils were analyzed as neat films on a salt plate (transmission), whereas solids were applied to a diamond plate (ATR). Nuclear magnetic resonance spectra (NMR) were acquired on either a Varian Inova-400 or VXR-400 instrument. Chemical shifts are measured relative to tetramethylsilane, as judged by the residual partially deuterated solvent peak. Mass spectra were obtained using a Kratos MS-80 spectrometer using the ionization technique indicated. Combustion analyses were performed by Atlantic Microlab, Norcross, GA.

Ratios of diastereomers and isomeric products were measured directly from integration of  $^1\text{H}$  NMR absorptions of protons common to the components. Precision was checked by varying the relaxation delay for measurements on the same compound. Where possible, ratios were corroborated using GC-mass spectrometry. Peak assignments were made from authentic samples in every case. Ratios reported generally represent a lower limit defined by multiple runs.

### General Procedure for Ketimine Condensations

A rapidly stirred benzene solution of the amine (0.5 M), ketone (0.5 M), and 4Å MS (1:1 w/w) was stirred at 25 °C until complete conversion was achieved, as evidenced by <sup>1</sup>H NMR. The mixture was filtered through a pad of Celite and washed with Et<sub>2</sub>O or benzene. The solvent was removed *in vacuo* to give the analytically pure ketimine which was used immediately.

The same procedure was used when the benzophenone ketimine was desired, except benzophenone imine<sup>4</sup> was used in place of the ketone.<sup>5</sup>

### General Procedure for Asymmetric Phase Transfer Alkylations

A 0.34 M dichloromethane solution of benzophenone glyciny l imine *tert*-butyl ester (1 equiv), catalyst (0.1 equiv) and solid CsOH•H<sub>2</sub>O (10 equiv) was cooled to –78 °C followed by dropwise addition of benzyl halide (5 equiv). The heterogeneous mixture was stirred for the time specified while maintaining the low temperature. The solution was diluted with Et<sub>2</sub>O, washed with water, dried and concentrated prior to purification by chromatography (neutral alumina) which gave analytically pure ketimine. Absolute stereochemistry was assigned by analogy.

### General Procedure for Cyclizations Using Chiral Non-racemic Schiff Base Substrates

A benzene solution of the ketimine (1 equiv) and <sup>n</sup>Bu<sub>3</sub>SnH (2.2 equiv) was warmed to 85 °C followed by slow addition of AIBN (1.2 equiv) using a syringe pump over 4-5 hrs. The solution was refluxed for an additional hour before concentration. The residue was treated with a 1:1 (by volume) solution of Et<sub>2</sub>O and satd aq KF<sup>6</sup> and the mixture stirred vigorously until a white solid precipitated. The organic layer was washed with water, and concentrated prior to purification by silica gel chromatography to give the target indoline.

### General Procedure for Preparation of Racemic Samples

A 0.34 M dichloromethane solution of benzophenone glyciny l imine *tert*-butyl ester (1 equiv), benzyltriethyl ammonium chloride (0.2 equiv), and benzyl halide (1.2 equiv) was treated

<sup>4</sup> Pickard, P. L.; Tolbert, T. L. in "Organic Syntheses"; Wiley: NY, 1973, Collective Vol. 5, pp. 520-2.

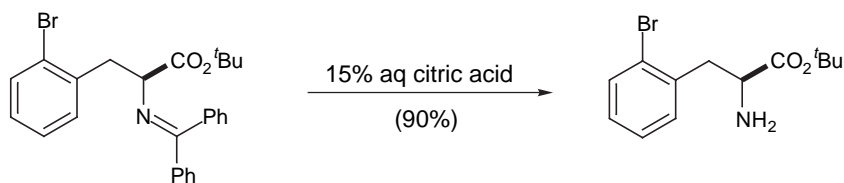
<sup>5</sup> O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, 47, 2663.

<sup>6</sup> Complete saturation by KF is necessary.

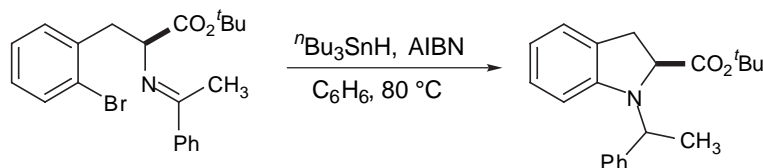
with 50% aq NaOH (20 equiv). The mixture was stirred vigorously at room temperature for 4 h. The heterogeneous mixture was diluted with Et<sub>2</sub>O, washed with water, dried, and concentrated prior to purification by column chromatography (neutral alumina) to yield pure racemic ketimines.

**General Procedure for Imine Reduction (when necessary to determine ee)**

To a 0.02 M solution of ketimine (1 equiv) in dry methanol, was added NaBH<sub>4</sub> (25 equiv) at 0 °C. The mixture was warmed up to 25 °C, and stirred for 1-1.5 h. The solution was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with water, dried, and concentrated prior to purification by silica gel chromatography to yield analytically pure amine for HPLC analysis.



**(S)-2-Amino-3-(2-bromophenyl)-propionic acid *tert*-butyl ester (S-1).**<sup>7</sup> Imine (*S*)-**5a** (599 mg, 1.29 mmol) was dissolved in THF (7.7 mL) and treated with aq 15% citric acid (3.9 mL). The mixture was stirred vigorously for 5 h at room temperature, diluted with water (10 mL) and extracted twice with ether. The pH of the aqueous layer was adjusted from 2 to 10 by dropwise addition of satd K<sub>2</sub>CO<sub>3</sub> solution. The aqueous layer was thoroughly extracted with ethyl acetate, the combined organic layers were dried and concentrated, and the residue was purified by silica gel chromatography (2% methanol in dichloromethane) to furnish the amine as a colorless oil (348 mg, 90%). *R*<sub>f</sub> = 0.67 (10% MeOH/hexanes); IR (film) 3382, 1733 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.54 (d, *J* = 8.3 Hz, 1H), 7.26–7.21 (m, 2H), 7.11–7.07 (m, 1H), 3.73 (t, *J* = 7.3 Hz, 1H), 3.20 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.87 (dd, *J* = 13.6, 8.3 Hz, 1H), 1.53 (br, s, 2H) 1.41 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) ppm 174.1, 137.4, 132.8, 131.6, 128.2, 127.2, 124.8, 81.1, 54.8, 41.7, 27.9; HRMS (EI): Exact mass calcd for C<sub>13</sub>H<sub>19</sub>BrNO<sub>2</sub> [M+H]<sup>+</sup>, 300.0599. Found 300.0647. HPLC (Chiralcel AD, 5% *i*-PrOH/hexanes, 1 mL/min): *t*<sub>r</sub> (*R*) = 9.2 m, *t*<sub>r</sub> (*S*) = 10.3 m. 95% ee: [α]<sub>D</sub><sup>21</sup> +29.3° (*c* 1.0, CHCl<sub>3</sub>).



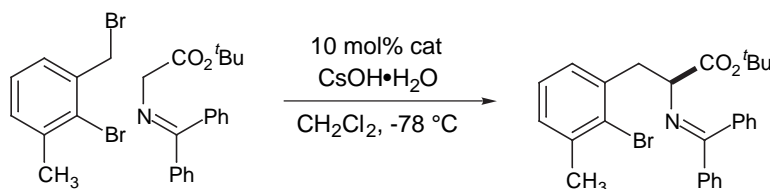
**1-(1-phenylethyl)-2,3-dihydro-1H-indole-2-carboxylic acid *tert*-butyl ester (6d).** According to the general procedure, use of **5d** (42 mg, 104 μmol), <sup>n</sup>Bu<sub>3</sub>SnH (62 μL, 229 μmol), and AIBN (13.7 mg, 83.3 μmol) provided the desired indoline after flash chromatography (SiO<sub>2</sub>, 1% ethyl acetate in hexanes) as a yellow oil (*dr* = 5:1, 25.7 mg, 76%). *R*<sub>f</sub> = 0.33 (10 % ethyl acetate in hexanes); IR (film) 2977, 2928, 1742, 1606 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (major

<sup>7</sup> Lygo, B.; Wainwright, P.G. *Tetrahedron. Lett.* **1997**, 38, 8595.

diastereomer) 7.54 (d,  $J = 7.5$  Hz, 2H), 7.34 (dd,  $J = 7.8, 7.4$  Hz, 2H), 7.24 (m, 1H), 7.02 (d,  $J = 7.3$  Hz, 1H), 6.93 (t,  $J = 7.7$  Hz, 1H), 6.64 (dd,  $J = 7.4, 7.3$  Hz, 1H), 6.21 (d,  $J = 7.9$  Hz, 1H), 4.50 (q,  $J = 7.1$  Hz, 1H), 4.40 (dd,  $J = 9.8, 9.6$  Hz, 1H), 3.43 (dd,  $J = 15.7, 10.3$  Hz, 1H), 3.09 (dd,  $J = 15.7, 9.3$  Hz, 1H), 1.54 (d,  $J = 7.0$  Hz, 3H), 1.40 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz) ppm 173.7, 151.9, 144.5, 128.7, 127.8, 127.5, 127.3, 127.1, 124.0, 118.2, 108.8, 81.3, 64.6, 58.7, 34.7, 29.9, 28.6, 28.1, 19.8; HRMS (CI,  $\text{CH}_4$ ) Exact mass calcd for  $\text{C}_{21}\text{H}_{25}\text{NO}_2$   $[\text{M}]^+$  323.1885. Found 323.1895.

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{25}\text{N}$ : C, 77.98; H, 7.79; N, 4.33. Found C, 78.03; H, 7.90; N, 4.44.

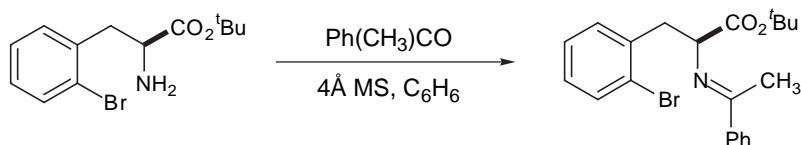
HPLC (Chiralcel AD, 5%  $i\text{PrOH}$ /hexanes, 1 mL/min): Diastereomer 1:  $t_r$  ( $S$ ) = 3.89 m,  $t_r$  ( $R$ ) = 4.03 m; Diastereomer 2:  $t_r$  ( $S$ ) = 4.65 m,  $t_r$  ( $R$ ) = 4.92 m; 92% ee:  $[\alpha]_{\text{D}}^{24} -2.2^\circ$  ( $c$  0.5,  $\text{CHCl}_3$ ).



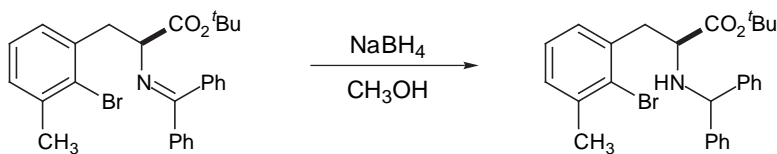
**(S)-2-(Benzhydrylideneamino)-1-(2-bromo-3-methylphenyl)propionic acid *tert*-butyl ester (5c).** Following the general procedure, 2-bromo-3-bromomethyltoluene<sup>8</sup> (750 mg, 2.84 mmol), glycyl imine (168 mg, 0.568 mmol), and  $\text{CsOH}\cdot\text{H}_2\text{O}$  (847 mg, 5.68 mmol) were stirred in  $\text{CH}_2\text{Cl}_2$  for 20 h in the presence of the cinchonidine derived catalyst (10 mol %) while maintaining a temperature  $\leq -78$  °C. Work-up according to the general procedure provided the desired product as a white solid (233 mg, 86%). mp = 92–94 °C;  $R_f$  = 0.38 (10% EtOAc/hexanes); IR (film) 3056, 1732  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 7.59 (dd,  $J = 7.9, 1.5$  Hz, 2H), 7.40–7.25 (m, 6H), 7.09–7.04 (m, 3H), 6.55 (br d,  $J = 5.0$  Hz, 2H), 4.42 (dd,  $J = 9.8, 3.9$  Hz, 1H), 3.53 (dd,  $J = 13.3, 3.9$  Hz, 1H), 3.24 (dd,  $J = 13.4, 9.9$  Hz, 1H), 2.35 (s, 3H), 1.49 (s,

<sup>8</sup> 2-Bromo-*m*-xylene was converted to the corresponding benzyl bromide: Rebek, J.; Costello, T.; Wattle, R. J. *Am. Chem. Soc.* 107, **1985**, 7487.

9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 170.8, 170.5, 139.5, 138.2, 137.8, 136.2, 130.2, 130.0, 128.8, 128.7 (2C), 128.1, 127.9 (2C), 127.6 (2C), 126.3, 81.1, 64.9, 40.2, 28.1, 23.9; HRMS (EI): Exact mass calcd for  $\text{C}_{27}\text{H}_{29}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$ , 478.1382. Found 478.1325.

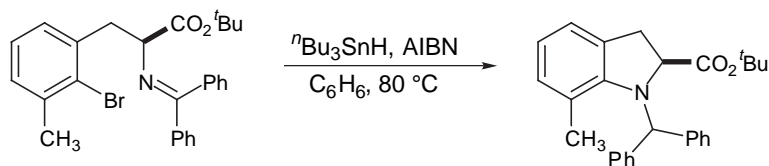


**3-(2-bromo-phenyl)-2-(1-phenyl-ethylideneamino)-propionic acid *tert*-butyl ester (5d).** According to the general procedure, use of **S-1** (179 mg, 600  $\mu\text{mol}$ ), acetophenone (77  $\mu\text{L}$ , 660  $\mu\text{mol}$ ) and 4Å MS (1.5 g), in benzene (5 ml) gave the desired imine as a yellow oil (221 mg, 92%). IR (film) 2977, 1731, 1150  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (ddd,  $J = 3.4, 3.4, 1.5$  Hz, 2H), 7.53 (dd,  $J = 7.9, 1.2$  Hz, 1H), 7.36 (m, 2H), 7.24 (m, 2H), 7.16 (m, 1H), 7.07 (m, 1H), 4.63 (dd,  $J = 8.5, 5.2$  Hz, 1H), 3.59 (dd,  $J = 13.4, 5.5$  Hz, 1H), 3.18 (dd,  $J = 13.4, 8.8$  Hz, 1H), 1.96 (s, 3H), 1.45 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 173.7, 151.9, 144.5, 128.7, 127.8, 127.5, 127.3, 127.1, 124.0, 118.2, 108.8, 81.3, 64.6, 58.7, 34.7, 29.9, 28.6, 28.1, 19.8; HRMS (EI): Exact mass calcd for  $\text{C}_{21}\text{H}_{25}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$  402.1070. Found 402.1071.



**(S)-2-(Benzhydrylamino)-3-(2-bromo-3-methylphenyl)propionic acid *tert*-butyl ester (S-2).** The enantiomeric ratio was determined after reduction of the ketimine. Addition of  $\text{NaBH}_4$  (3.77 mg, 99.5  $\mu\text{mol}$ ) to imine (9.50 mg, 19.9  $\mu\text{mol}$ ) in MeOH (1.0 mL) furnished, after flash chromatography ( $\text{SiO}_2$ , 2% ethyl acetate in hexanes), the amine as a white solid (8 mg, 83%). mp 116–118  $^\circ\text{C}$ ;  $R_f$ =0.43 (10% EtOAc/hexanes); IR (film) 3323, 1723  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 (dd,  $J = 8.2, 1.5$  Hz, 2H), 7.28 (td,  $J = 6.3, 1.8$  Hz, 2H), 7.22 (t,  $J = 1.3$  Hz, 1H), 7.20–7.13, (m, 7H), 7.09–7.07 (m, 1H), 4.81 (s, 1H), 3.50 (t,  $J = 7.7$  Hz, 1H), 3.13 (dd,

$J = 13.4, 6.9$  Hz, 1H), 3.06 (dd,  $J = 13.4, 5.0$  Hz, 1H), 2.43 (s, 3H), 2.21 (br s, 1H), 1.42 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 174.1, 138.4, 138.0, 129.6, 128.9, 128.4, 128.2, 127.7, 127.4, 127.3, 127.1, 126.3, 117.9, 112.8, 95.4, 81.1, 65.4, 59.4, 41.0, 28.0, 24.0; HRMS (EI): Exact mass calcd for  $\text{C}_{27}\text{H}_{31}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$  480.1538. Found 480.1560. HPLC (Chiralcel OD, 2%  $i$ PrOH/hexanes, 1 mLmin):  $t_r$  ( $S$ ) = 4.9 m,  $t_r$  ( $R$ ) 5.6 m. ( $S$ )- 88% ee  $[\alpha]_{\text{D}}^{23} -35.2$  ( $c$  0.8,  $\text{CHCl}_3$ ). ( $R$ )- 86% ee,  $[\alpha]_{\text{D}}^{24} +33.2$  ( $c$  0.5,  $\text{CHCl}_3$ ).

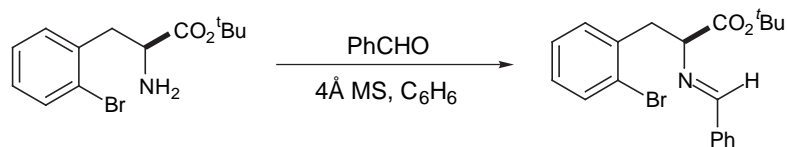


**1-Benzhydryl-7-methyl-2,3-dihydro-1H-indole-2-carboxylic acid *tert*-butyl ester (6c).** Following the general procedure, use of the ketimine (41.0 mg, 86.0  $\mu\text{mol}$ ),  $n\text{Bu}_3\text{SnH}$  (51.0  $\mu\text{L}$ , 0.189 mmol), and AIBN (17 mg, 0.103 mmol) provided, following chromatography ( $\text{SiO}_2$ , 1% ethyl acetate in hexanes), the racemic indoline as a colorless oil (5.00 mg, 15%).<sup>9</sup>  $R_f$  = 0.40 (10% EtOAc/hexanes); IR (film) 3059, 1743  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 (d,  $J = 7.9$  Hz, 2H), 7.39-7.30 (m, 4H), 7.26-7.20 (m, 2H), 6.97 (td,  $J = 7.8, 1.1$  Hz, 3H), 6.85 (d,  $J = 7.1$  Hz, 1H), 6.79 (t,  $J = 7.4$  Hz, 1H), 5.95 (s, 1H), 4.05 (dd,  $J = 7.3, 5.2$  Hz, 1H), 2.61 (d,  $J = 5.9$  Hz, 2H), 2.37 (s, 3H), 1.39 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 173.2, 150.9, 141.2, 140.4, 132.1, 130.1, 128.9, 128.7, 128.2, 128.0, 127.4, 126.9, 123.6, 121.6, 121.5, 80.5, 68.2, 61.7, 35.0, 27.9, 18.5; HRMS (EI): Exact mass calcd for  $\text{C}_{27}\text{H}_{29}\text{NO}_2$   $[\text{M}]^+$ , 399.2198. Found 399.2203.

HPLC (Chiralcel AD, 0.5%  $i$ PrOH/hexanes, 0.5 mLmin):  $t_r$  ( $S$ ) = 10.0 m,  $t_r$  ( $R$ ) = 10.6 m.

<sup>9</sup> The mass balance consisted of un-reacted starting material and reduced aryl bomide (ArH).

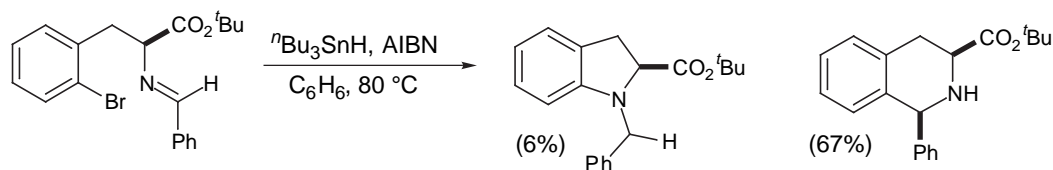




**2-(Benzylidene amino)-3-(2-bromophenyl)-propionic acid *tert*-butyl ester (5e).**

Following the general procedure (Method A), amine **S-1** (250 mg, 833  $\mu$ mol), benzaldehyde (85.0  $\mu$ L, 833  $\mu$ mol), and 4Å MS in benzene (0.8 mL) after 10 h provided the aldimine (330 mg, 100%), as a >95: 5 mixture of stereoisomers and a colorless oil. IR (film) 3062, 1733, 1641  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.00 (s, 1H), 7.71 (dd,  $J = 7.7, 1.5$  Hz, 2H), 7.53 (d,  $J = 7.8$  Hz, 1H), 7.42–7.35 (m, 3H); 7.21 (d,  $J = 7.5$  Hz, 1H), 7.14 (t,  $J = 7.4$  Hz, 1H), 7.04 (td,  $J = 8.9, 1.3$  Hz, 1H), 4.25 (dd,  $J = 8.2, 5.8$  Hz, 1H), 3.56 (dd,  $J = 13.6, 5.8$  Hz, 1H), 3.19 (dd,  $J = 13.6, 8.3$  Hz, 1H) 1.45 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 170.5, 163.5, 137.1, 135.7, 132.6, 130.9, 128.4, 128.3, 128.2, 127.0, 124.8, 81.4, 72.9, 39.8, 28.0; HRMS (EI): Exact mass calcd for  $\text{C}_{20}\text{H}_{23}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$ , 388.0912. Found 388.0917.

HPLC (Chiralcel OD, 2%  $i$ PrOH/hexanes, 1 mL/min):  $t_r$  (*S*) = 5.4 m,  $t_r$  (*R*) = 6.3 m. (*S*)-94% ee  $[\alpha]_{\text{D}}^{21} -140.1^\circ$  ( $c$  1.5,  $\text{CHCl}_3$ ).



Following the general procedure, use of aldimine **5e** (224 mg, 577  $\mu$ mol),  $n\text{Bu}_3\text{SnH}$  (171  $\mu$ L, 635  $\mu$ mol), and AIBN (76.0 mg, 462  $\mu$ mol) furnished, after silica gel chromatography (3–5% ethyl acetate in hexanes, the indoline **6e** (10.4 mg, 6%) as a colorless oil and tetrahydroisoquinoline **S-3** (119.0 mg, 67%) as a colorless solid.

**(*S*)-1-Benzyl-2,3-dihydro-1-H-indole-2-carboxylic acid *tert*-butyl ester (6e).**

$R_f$ =0.42 (10% EtOAc/hexanes); IR (film) 3026, 1736  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 (d,  $J = 7.0$  Hz, 1H), 7.33 (t,  $J = 7.0$  Hz, 2H), 7.28–7.24 (m, 2H), 7.07–7.01 (m, 2H), 6.68 (t,  $J = 7.5$  Hz, 1H), 6.40 (d,  $J = 7.8$  Hz, 1H), 4.56 (d,  $J = 15.6$  Hz, 1H), 4.30 (d,  $J = 15.7$  Hz, 1H)

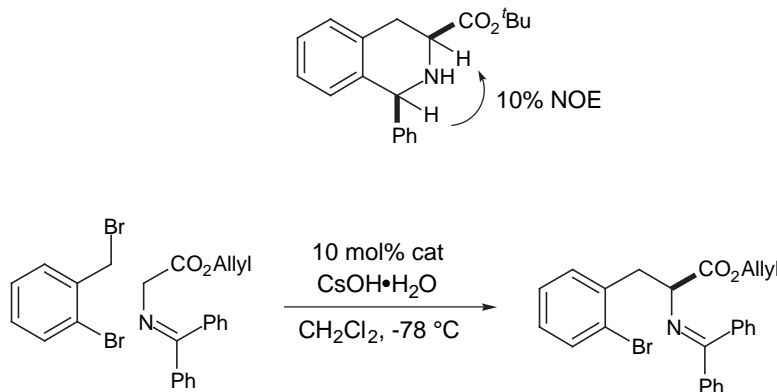
4.16 (dd  $J = 10.2, 8.2$  Hz, 1H), 3.36 (dd,  $J = 15.9, 10.2$  Hz, 1H), 3.19 (dd,  $J = 15.9, 8.2$  Hz, 1H), 1.43 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 171.9, 151.6, 130.3, 128.5, 127.71, 127.67, 127.1, 124.1, 122.4, 117.9, 107.0, 81.4, 66.2, 52.1, 33.4, 28.0; HRMS (EI): Exact mass calcd for  $\text{C}_{20}\text{H}_{23}\text{NO}_2$   $[\text{M}]^+$ , 309.1729. Found 309.1744.

HPLC (Chiralcel OD, 1%  $i$ PrOH/hexanes, 0.5 mL/min):  $t_r$  ( $S$ ) = 14.5 m,  $t_r$  ( $R$ ) = 17.7 m. ( $S$ )- 81% ee,  $[\alpha]_{\text{D}}^{25} -5.3^\circ$  ( $c$  0.3,  $\text{CHCl}_3$ ).

**( $S$ )-1-Phenyl-1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid *tert*-butyl ester ( $S$ -3).** mp 116-119  $^\circ\text{C}$ ;  $R_f$  = 0.25 (10% EtOAc/hexanes); IR (film) 2975, 1726  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.30 (m, 5H), 7.16 (dd,  $J = 14.4, 7.5$  Hz, 2H), 7.05 (td,  $J = 7.9, 1.9$  Hz, 1H), 6.72 (d,  $J = 7.8$  Hz, 1H), 5.14 (s, 1H), 3.81 (dd,  $J = 9.0, 6.5$  Hz, 1H), 3.15 (d,  $J = 6.9$  Hz, 2H), 2.47 (br, s, 1H), 1.54 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 171.7, 143.9, 138.5, 134.1, 129.1, 128.8, 128.4, 127.6, 127.5, 126.2, 125.9, 81.5, 63.2, 57.0, 32.8, 28.0; HRMS (EI): Exact mass calcd for  $\text{C}_{20}\text{H}_{23}\text{NO}_2$   $[\text{M}]^+$ , 309.1729. Found 309.1715.

*Anal.* Calcd for  $\text{C}_{20}\text{H}_{23}\text{NO}_2$ : C, 77.64, H, 7.49, N, 4.53. Found : C, 77.36, H, 7.55, N, 4.43.

HPLC (Chiralcel AD, 10%  $i$ PrOH/hexanes, 1.0 mL/min):  $t_r$  ( $S$ ) = 6.0 m,  $t_r$  ( $R$ ) = 8.9 m. ( $S$ )- 95% ee,  $[\alpha]_{\text{D}}^{25} -8.8^\circ$  ( $c$  1.0,  $\text{CHCl}_3$ ).

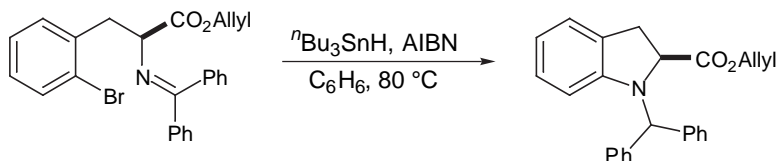


**2-(Benzhydrylidene-amino)-3-(2-bromophenyl)-propionic acid allyl ester ( $5f$ ).**

Following the general procedure, *ortho*-bromobenzyl bromide (501 mg, 1.79  $\mu\text{mol}$ ), glycine allyl

ester benzophenone imine (100 mg, 357  $\mu\text{mol}$ ),  $\text{CsOH}\cdot\text{H}_2\text{O}$  (532 mg, 3.57 mmol), and the cinchonidine derived catalyst (21.8 mg, 36.0  $\mu\text{mol}$ ) were stirred in  $\text{CH}_2\text{Cl}_2$  (1.05 mL) at  $-78\text{ }^\circ\text{C}$  for 7 hours. Workup according to the general procedure and flash chromatography (neutral alumina, 4% ethyl acetate in hexanes) gave the desired phenyl alanine derivative as a colorless oil (100 mg, 62% yield).  $R_f = 0.20$  (10% EtOAc/hexanes); IR (film) 3062, 1748, 1618  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64 (d,  $J = 7.3$  Hz, 2H), 7.45 (d,  $J = 7.9$  Hz, 1H), 7.39 (t,  $J = 6.3$  Hz, 2H), 7.36–7.30 (m, 4H), 7.23 (d,  $J = 7.5$  Hz, 1H), 7.16 (t,  $J = 7.3$  Hz, 1H), 7.06 (td,  $J = 8.8$ , 1.5, Hz, 1H), 6.62 (bs s, 2H), 5.94 (ddd,  $J = 18.3$ , 10.5, 5.6 Hz, 1H), 5.34 (dd,  $J = 18.3$ , 1.1 Hz, 1H), 5.25 (d,  $J = 10.5$  Hz, 1H); 4.74–4.65 (m, 2H), 4.58 (dd,  $J = 9.8$ , 3.8 Hz, 1H), 3.58 (dd,  $J = 13.2$ , 4.2 Hz, 1H), 3.31 (dd,  $J = 13.2$ , 10.0 Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 171.2, 171.1, 139.1, 137.0, 135.7, 132.7, 132.5, 131.9, 130.9, 130.0, 128.7, 128.3, 128.2, 128.1 (2C), 127.5, 126.9, 118.0, 65.5, 64.3, 39.5; HRMS (EI): Exact mass calcd for  $\text{C}_{25}\text{H}_{23}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$ , 448.0912. Found 448.0915.

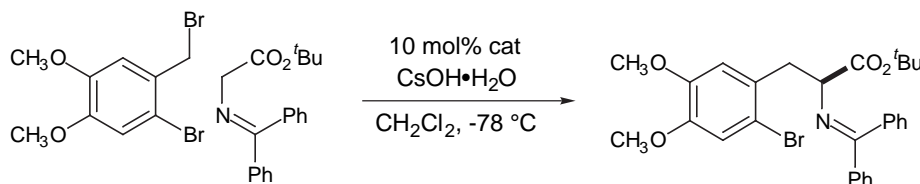
HPLC (Chiralcel OD, 2%  $i\text{PrOH}$ /hexanes, 1 mL/min):  $t_r$  ( $R$ ) = 5.9 m,  $t_r$  ( $S$ ) = 6.6 m. ( $S$ )-76% ee  $[\alpha]_D^{21} -265.5^\circ$  ( $c$  0.5,  $\text{CHCl}_3$ ).



**1-Benzhydryl-2,3-dihydro-1H-indole-2-carboxylic acid allyl ester (6f).** According to the general procedure, Schiff base (40.2 mg, 94.0  $\mu\text{mol}$ ),  $n\text{Bu}_3\text{SnH}$  (55.7  $\mu\text{L}$ , 0.207 mmol) and AIBN (12.3 mg, 75.0  $\mu\text{mol}$ ) furnished after workup and chromatography ( $\text{SiO}_2$ , 4% ethyl acetate in hexanes), ( $S$ )-**4** as a colorless oil (26.0 mg, 75% yield).  $R_f = 0.35$  (10% EtOAc/hexanes); IR (film) 3055, 1744  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (d,  $J = 1.6$  Hz, 2H), 7.46–7.24 (m, 8H), 7.05 (d,  $J = 7.2$  Hz, 1H), 6.91 (t,  $J = 7.6$  Hz, 1H), 6.61 (t,  $J = 7.2$  Hz, 1H), 6.07 (d,  $J = 4.0$  Hz, 1H), 5.83–5.73 (m, 1H), 5.66 (s, 1H), 5.21 (d,  $J = 1.2$  Hz, 1H), 5.18 (dd,  $J = 4.8$ , 1.2 Hz, 1H), 4.44–4.35 (m, 2H), 4.27 (dd,  $J = 10.0$ , 5.6 Hz, 1H), 3.45 (dd,  $J = 15.6$ , 10.4 Hz,

1H), 3.07 (dd,  $J = 16.0, 5.6$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 173.2, 151.1, 140.8, 140.6, 131.7, 129.0, 128.6, 128.5 (3C), 127.5 (2C), 127.4, 123.9, 118.4, 118.2, 109.3, 67.2, 65.3, 64.5, 34.0; HRMS (EI): Exact mass calcd for  $\text{C}_{25}\text{H}_{23}\text{NO}_2$   $[\text{M}]^+$  369.1729. Found 369.1745.

HPLC (Chiralcel AD, 2%  $i$ PrOH/hexanes, 1 mL/min):  $t_r$  ( $R$ ) = 6.6 m,  $t_r$  ( $S$ ) = 10.6 m. ( $S$ )-38% ee  $[\alpha]_{\text{D}}^{21} -17.9^\circ$  ( $c$  0.7,  $\text{CHCl}_3$ ).

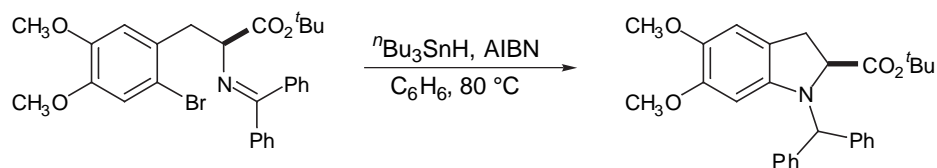


**( $S$ )-2-(Benzhydrylideneamino)-3-(2-bromo-4,5-dimethoxyphenyl)propionic acid *tert*-butyl ester (**5i**).** Following general procedure, 1-bromo-2-bromomethyl-4,5-dimethoxybenzene<sup>10</sup> (787 mg, 2.54 mmol), the glycinyl imine (150 mg, 0.508 mmol), and  $\text{CsOH}\cdot\text{H}_2\text{O}$  (757 mg, 5.08 mmol) were stirred in  $\text{CH}_2\text{Cl}_2$  for 15 h in the presence of the cinchonidine derived catalyst (10 mol %) while maintaining a temperature  $\leq -65^\circ\text{C}$ . Work-up according to the general procedure provided the desired product as a white solid (226 mg, 85%). mp 99–100  $^\circ\text{C}$ ;  $R_f$  = 0.13 (10% EtOAc/hexanes); IR (film) 3057, 1732  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63 (d,  $J = 7.3$  Hz, 2H), 7.39–7.28 (m, 6H), 6.92 (s, 1H), 6.71 (s, 1H), 6.62 (br d,  $J = 6.5$  Hz, 2H), 4.29 (dd,  $J = 9.9, 3.8$  Hz, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 3.39 (dd,  $J = 13.4, 3.8$  Hz, 1H), 3.20 (dd,  $J = 13.3, 10.1$  Hz, 1H), 1.48 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 170.6, 170.4, 148.0, 147.7, 139.3, 136.0, 130.2, 129.5, 128.7, 128.2, 128.0, 127.9, 127.7, 115.0, 114.8, 81.2, 65.4, 56.1, 55.7, 39.0, 28.0; HRMS (EI): Exact mass calcd for  $\text{C}_{28}\text{H}_{31}\text{BrNO}_4$   $[\text{M}+\text{H}]^+$ , 524.1436. Found 524.1418.

Similarly, use of cinchonine derived catalyst gave the enantiomer as a white solid (256 mg, 95%).

HPLC (Chiralcel OD, 2%  $i$ PrOH/hexanes, 1 mL/min):  $t_r$  ( $S$ ) = 7.1 m,  $t_r$  ( $R$ ) = 8.5 m. ( $S$ )-92% ee,  $[\alpha]_{\text{D}}^{23} -202.5^\circ$  ( $c$  1.4,  $\text{CHCl}_3$ ). ( $R$ )-97% ee,  $[\alpha]_{\text{D}}^{25} +214.3^\circ$  ( $c$  0.8,  $\text{CHCl}_3$ ).

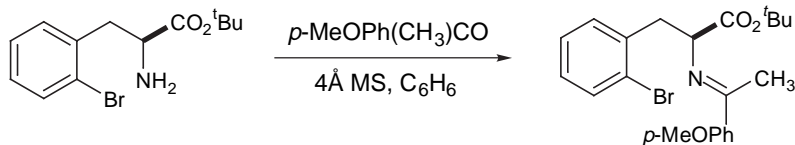
<sup>10</sup> Landais, Y.; Robin, J. P.; Lebron, A. *Tetrahedron* **1991**, 47, 3787.



**(S)-1-Benzhydryl-5,6-dimethoxy-2,3-dihydro-1H-indole-2-carboxylic acid *tert*-butyl ester (6i).** Following the general procedure, the ketimine (41.6 mg, 79.0  $\mu$ mol),  $n$ -Bu<sub>3</sub>SnH (107  $\mu$ L, 397  $\mu$ mol), and AIBN (15.6 mg, 95.0  $\mu$ mol) gave, following chromatography (neutral alumina, 5% EtOAc in hexanes), the indoline as a colorless oil (18.0 mg, 50%).  $R_f$  = 0.13 (10% EtOAc/hexanes); IR (film) 3061, 1733  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 (dd,  $J$  = 6.9, 5.5 Hz, 4H), 7.34–7.22 (m, 6H), 6.67 (s, 1H), 5.65 (s, 1H), 5.62 (s, 1H), 4.10 (dd,  $J$  = 10.1, 5.2 Hz, 1H), 3.78 (s, 3H), 3.41 (s, 3H), 3.35 (dd,  $J$  = 15.6, 10.3 Hz, 1H), 2.93 (dd,  $J$  = 15.0, 5.1 Hz, 1H), 1.36 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 172.6, 148.4, 145.6, 141.7, 141.5, 140.7, 132.4, 130.1, 129.1, 128.5, 128.4, 128.3, 127.4, 127.2, 118.2, 109.8, 96.3, 80.9, 67.5, 65.5, 57.0, 55.5, 33.7, 27.9; HRMS (EI): Exact mass calcd for  $\text{C}_{28}\text{H}_{31}\text{NO}_4$   $[\text{M}]^+$ , 445.2253. Found, 445.2167.

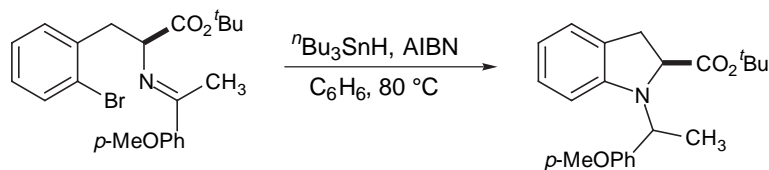
The enantiomeric indoline was similarly prepared (27.7 mg, 50%).

HPLC (Chiralcel AD, 2%  $i$ -PrOH/hexanes, 1 mL/min):  $t_r$  ( $R$ ) = 7.9 m,  $t_r$  ( $S$ ) = 8.6 m. ( $S$ )- 82% ee,  $[\alpha]_{\text{D}}^{25}$   $-18.0^\circ$  ( $c$  0.8,  $\text{CHCl}_3$ ). ( $R$ )- 82% ee,  $[\alpha]_{\text{D}}^{25}$   $+18.5^\circ$  ( $c$  2.2,  $\text{CHCl}_3$ ).



**(S)-3-(2-bromophenyl)-2-[1-(4-methoxyphenyl)-ethylideneamino]-propionic acid *tert*-butyl ester (5j).** Following the general procedure, amine **S-1** (107 mg, 356  $\mu$ mol), *para*-methoxyacetophenone (53.0 mg, 356  $\mu$ mol), and 4Å MS in toluene (0.36 mL) after 36 h at reflux provided the desired ketimine as a colorless oil (115 mg, 75%) and > 95:5 mixture of stereoisomers ( $^1\text{H}$  NMR); IR (film) 2974, 1730, 1678  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (d,  $J$  = 8.9 Hz, 2H), 7.28–7.21 (m, 2H), 7.17–7.11 (m, 2H), 6.85 (d,  $J$  = 8.9 Hz, 2H), 4.58 (dd,

$J = 8.9, 5.5$  Hz, 1H), 3.85 (s, 3H), 3.55 (dd,  $J = 13.4, 5.2$  Hz, 1H), 3.15 (dd,  $J = 13.4, 8.9$  Hz, 1H), 1.91 (s, 3H), 1.42 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 166.8, 137.7, 132.8, 130.1, 129.0, 128.5, 128.3, 128.2, 128.1, 127.3, 113.6, 113.3, 81.1, 63.8, 55.3, 40.0, 29.7, 28.0; HRMS (EI): Exact mass calcd for  $\text{C}_{22}\text{H}_{27}\text{BrNO}_3$   $[\text{M}+\text{H}]^+$ , 432.1174. Found 432.1172. (*S*)- 87% ee  $[\alpha]_{\text{D}}^{21} -43.1^\circ$  ( $c$  0.7,  $\text{CHCl}_3$ ).



**(*S*)-1-[1-(4-methoxy phenyl) ethyl]-2,3-dihydro-1H-indole-2-carboxylic acid *tert*-butyl ester (**6j**)**. Following the general procedure, the ketimine (36.0 mg, 86.0  $\mu\text{mol}$ ),  $n\text{-Bu}_3\text{SnH}$  (51.0  $\mu\text{L}$ , 189  $\mu\text{mol}$ ), and AIBN (11.3 mg, 69.0  $\mu\text{mol}$ ) furnished, after silica gel chromatography (1% ether in hexanes), the desired indoline (15.0 mg, 50%) as a 3:1 mixture of diastereomers.

*Minor diastereomer*:  $R_f = 0.55$  (10% EtOAc/hexanes); IR (film) 2974, 1741  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 (d,  $J = 8.6$  Hz, 2H), 7.01 (d,  $J = 7.0$  Hz, 1H), 6.95 (t,  $J = 7.6$  Hz, 1H), 6.86 (d,  $J = 8.6$  Hz, 2H), 6.63 (t,  $J = 7.0$  Hz, 1H), 6.26 (d,  $J = 7.9$  Hz, 1H), 4.49 (q,  $J = 7.0$  Hz, 1H), 4.36 (t,  $J = 9.5$  Hz, 1H), 3.80 (s, 3H), 3.42 (dd,  $J = 15.9, 10.4$  Hz, 1H), 3.06 (dd,  $J = 15.9, 9.2$  Hz, 1H), 1.51 (d,  $J = 7.0$  Hz, 3H), 1.39 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 173.5, 158.5, 151.7, 136.2, 128.2 (2C), 127.5, 123.8, 117.9, 113.8, 108.6, 81.0, 64.2, 57.6, 55.2, 34.5, 27.9, 19.3; HRMS (EI): Exact mass calcd for  $\text{C}_{22}\text{H}_{27}\text{NO}_3$   $[\text{M}]^+$ , 353.1991. Found 353.2008.

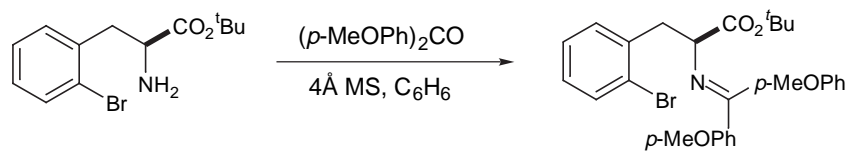
HPLC (Chiralcel OD, 2%  $i\text{-PrOH}$ /hexanes, 0.5 mL/min):  $t_r$  (2*S*) = 11.0 m,  $t_r$  (2*R*) = 13.2 m. (*S*)- 32% ee,  $[\alpha]_{\text{D}}^{21} +2.1^\circ$  ( $c$  0.5,  $\text{CHCl}_3$ ).

*Major diastereomer*:  $R_f = 0.45$  (10% EtOAc/hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (d,  $J = 8.7$  Hz, 2H), 6.99 (d,  $J = 7.0$  Hz, 1H), 6.87-6.83 (m, 3H), 6.58 (t,  $J = 6.9$  Hz, 1H), 6.08 (d,  $J = 7.9$  Hz, 1H), 4.60 (q,  $J = 7.0$  Hz, 1H), 4.28 (dd,  $J = 10.3, 7.4$  Hz, 1H), 3.80 (s, 3H), 3.37 (dd,  $J = 16.0, 10.5$  Hz, 1H), 3.08 (dd,  $J = 15.9, 7.4$  Hz, 1H), 1.51 (d,  $J = 6.9$  Hz, 3H), 1.47 (s,

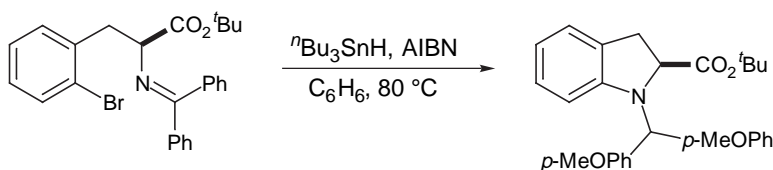
9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 173.4, 148.1, 139.3, 127.9 (2C), 127.2, 124.0, 117.5, 113.7 (2C), 108.9, 64.4, 62.9, 55.2, 55.1, 33.8, 28.0, 16.5.

*Anal.* Calcd for  $\text{C}_{22}\text{H}_{27}\text{NO}_3$ : C, 74.76; H, 7.70; N, 3.96. Found: C, 74.77; H, 7.77; N, 3.95.

HPLC (Chiralcel OD, 2%  $i$ -PrOH/hexanes, 0.5 mL/min):  $t_r$  (2*S*) = 13.0 m,  $t_r$  (2*R*) = 15.0 m. (2*S*)- 32% ee,  $[\alpha]_{\text{D}}^{21} -7.2^\circ$  (c 1.1,  $\text{CHCl}_3$ ).



**2-[[bis-(4-Methoxyphenyl)-methylene]-amino-3-(2-bromophenyl)-propionic acid *tert*-butyl ester (5k).** According to the general procedure, use of **S-1** (52.2 mg, 175  $\mu\text{mol}$ ), *bis*-4-methoxybenzophenone imine (41.6 mg, 173  $\mu\text{mol}$ ), 4 Å sieves (1.5 g), and benzene (6 ml), gave the desired product as a white solid (87 mg, 96%). mp 109–113°C; IR (film) 2975, 1730  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 (d,  $J$  = 8.6 Hz, 2H), 7.42 (d,  $J$  = 7.8 Hz, 1H), 7.19 (d,  $J$  = 6.7 Hz, 1H), 7.11 (t,  $J$  = 7.3 Hz, 1H), 7.01 (t,  $J$  = 7.0 Hz, 1H), 6.80 (m, 2H), 6.53 (d,  $J$  = 7 Hz, 2H), 4.35 (dd,  $J$  = 9.7, 4.0 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.43 (dd,  $J$  = 13.4, 4.0 Hz, 1H), 3.20 (m, 1H), 1.45 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz) ppm 171.2, 161.4, 159.6, 138.0, 134.2, 132.9, 132.7, 130.7, 129.4, 128.8, 128.1, 127.1, 125.4, 114.9, 113.6, 113.4, 81.3, 65.2, 55.5, 39.9, 28.3; HRMS (CI,  $\text{CH}_4$ ) Exact mass calcd for  $\text{C}_{28}\text{H}_{31}^{81}\text{BrNO}_4$   $[\text{M}+\text{H}]^+$  524.1438. Found 526.1419.

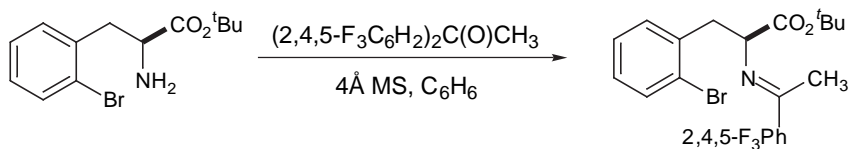


**1-[[bis-(4-methoxy-phenyl)-methyl]-2,3-dihydro-1*H*-indole-2-carboxylic acid *tert*-butyl ester (6k).** According to the general procedure, use of **5k** (31.1 mg, 59.5  $\mu\text{mol}$ ),

$n\text{Bu}_3\text{SnH}$  (35  $\mu\text{L}$ , 330  $\mu\text{mol}$ ), and AIBN (7.8 mg, 47.6  $\mu\text{mol}$ ) provided the desired indoline after flash chromatography ( $\text{SiO}_2$ , 2% ethyl acetates in hexanes) as a colorless oil (18.7 mg, 71%).  $R_f=0.18$  (10% ethyl acetate in hexanes); IR (film) 2929, 1735, 1510  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 (d,  $J = 8.7$  Hz, 2H), 7.23 (d,  $J = 8.6$  Hz, 2H), 7.00 (d,  $J = 6.6$  Hz, 1H), 6.83 (m, 5H), 6.61 (dd,  $J = 13.9, 7.0$  Hz, 1H), 6.01 (d,  $J = 7.8$  Hz, 1H), 5.54 (s, 1H), 4.08 (dd,  $J = 10.5, 5.9$  Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.38 (dd,  $J = 15.8, 10.5$  Hz, 1H), 2.98 (dd,  $J = 15.8, 5.8$  Hz, 1H), 1.34 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz) ppm 173.0, 158.9, 151.5, 133.8, 133.6, 130.3, 129.8, 128.0, 127.6, 124.0, 118.0, 114.0, 109.5, 81.1, 66.1, 65.2, 55.5, 34.3, 30.0, 28.2; HRMS (EI): Exact mass calcd for  $\text{C}_{28}\text{H}_{31}\text{NO}_4$   $[\text{M}]^+$ , 445.2253. Found 445.2263.

*Anal.* Calcd for  $\text{C}_{28}\text{H}_{31}\text{NO}_4$ : C, 75.48; H, 7.11; N, 3.17. Found: C, 75.19; H, 7.11; N, 3.17.

HPLC: Chiralcel AD (2%  $i\text{PrOH}$ /hexanes, 1mL/min, 254 nm),  $t_r$  (Peak 1) 12.9 min,  $t_r$  (Peak 2) 17.8 min; 83.9 % ee:  $[\alpha]_D^{21} -12.2^\circ$  ( $c$  0.8,  $\text{CDCl}_3$ ).

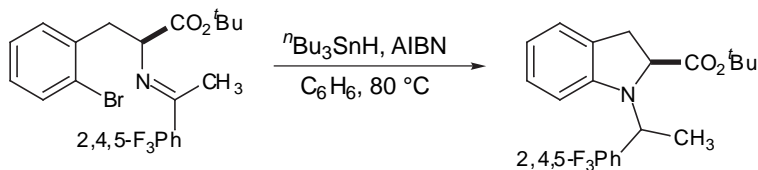


**(S)-3-(2-Bromophenyl)-2-[1-(2',4',5'-trifluorophenyl)-ethylideneamino]-**

**propionic acid *tert*-butyl ester (51).** Following the general procedure, amine **S-1** (107 mg, 356  $\mu\text{mol}$ ), 2',4',5'-trifluoroacetophenone (46.6  $\mu\text{L}$ , 356  $\mu\text{mol}$ ), and 4Å MS in toluene (0.36 mL) after 30 h at reflux provided the desired ketimine (115 mg, 70%) as a colorless oil; IR (film) 3065, 1734, 1618  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56 (d,  $J = 7.7$  Hz, 1H), 7.24-7.23 (m, 2H), 7.14-7.10 (m, 2H), 6.90 (td,  $J = 9.9, 6.3$  Hz, 1H), 4.65 (dd,  $J = 9.1, 5.1$  Hz, 1H), 3.61 (dd,  $J = 13.4, 5.1$  Hz, 1H), 3.19 (dd,  $J = 13.4, 9.1$  Hz, 1H), 1.96 (d,  $J = 3.4$  Hz, 3H), 1.48 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 169.9, 165.0, 155.2, 150.6, 137.1, 132.6 (2C), 128.4, 127.1, 127.0, 124.7, 117.8 ( $J_{\text{C-F}} = 14.5$  Hz, 1C), 105.7 (m, 2C), 81.7, 65.6, 63.3, 39.6, 28.0; HRMS (EI): Exact mass calcd for  $\text{C}_{21}\text{H}_{22}\text{BrF}_3\text{NO}_2$   $[\text{M}+\text{H}]^+$ , 456.0786. Found 456.0781.



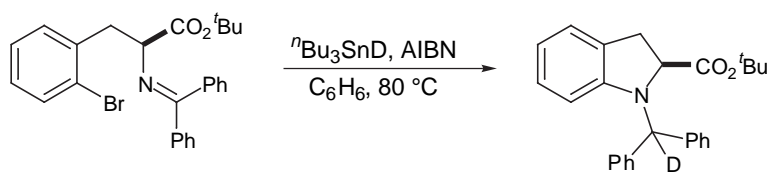
HPLC (Chiralcel OD, 2% *i*PrOH/hexanes, 0.5 mL/min):  $t_r$  (*S*) = 8.6 m,  $t_r$  (*R*) = 11.8 m. (*S*)- 87% ee,  $[\alpha]_D^{21}$   $-66.4^\circ$  (*c* 0.6, CHCl<sub>3</sub>).



**(*S*)-1-[1-(2,4,5-trifluorophenyl)ethyl]-2,3-dihydro-1H-indole-2-carboxylic acid *tert*-butyl ester (6l).** Following the general procedure, the ketimine (90.0 mg, 196  $\mu$ mol),  $n$ Bu<sub>3</sub>SnH (116  $\mu$ L, 434  $\mu$ mol), and AIBN (26.0 mg, 158  $\mu$ mol) furnished after silica gel chromatography (1% ethyl acetate in hexanes) the desired indoline (52.0 mg, 70%) as a colorless oil and a 3:1 inseparable mixture of diastereomers.  $R_f$  = 0.58 (10% EtOAc/hexanes); IR (film) 3062, 1737 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.87-7.80 (m, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 7.00-6.91 (m, 2H), 6.70 (t, *J* = 6.8 Hz, 1H), 6.08 (d, *J* = 7.9 Hz, 1H), 4.71 (dd, *J* = 14.0, 7.0 Hz, 1H), 4.48 (t, *J* = 10.2 Hz, 1H), 3.48 (dd, *J* = 15.7, 10.2 Hz, 1H), 3.13 (dd, *J* = 15.8, 10.1 Hz, 1H), 1.51-1.50 (m, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) ppm 173.4, 151.1, 128.5, 127.7, 127.4, 127.0, 124.0, 123.9, 118.6, 118.1 (*d J*<sub>C-F</sub> = 19.7 Hz, 1C), 107.9, 105.3 (m 2C), 81.7, 64.1, 51.9, 34.5, 27.9, 18.4; HRMS (EI): Exact mass calcd for C<sub>21</sub>H<sub>22</sub>NF<sub>3</sub>O<sub>2</sub> [M]<sup>+</sup>, 377.1603. Found 377.1599.

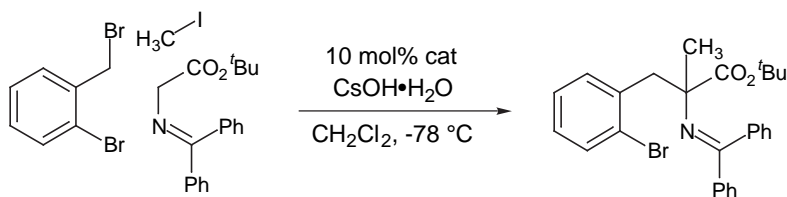
*Anal.* Calcd for C<sub>21</sub>H<sub>22</sub>NF<sub>3</sub>O<sub>2</sub>: C, 66.83; H, 5.88; N, 3.71. Found: C, 66.86; H, 5.80; N, 3.62.

HPLC (Chiralcel AD, 1% *i*PrOH/hexanes, 0.25 mL/min): major diastereomer:  $t_r$  (2*S*) = 17.2 m,  $t_r$  (2*R*) = 20.2 m; minor diastereomer :  $t_r$  (2*S*) = 18.6 m,  $t_r$  (2*R*) = 19.5 m. (2*S*)- 82% ee,  $[\alpha]_D^{21}$   $-4.9^\circ$  (*c* 0.7, CHCl<sub>3</sub>).



**(S)-1-Benzhydryl-2,3-dihydro-1D-indole-2-carboxylic acid *tert*-butyl ester (9).**

According to the general procedure, the Schiff base (18.6 mg, 40.0  $\mu\text{mol}$ ),  $n\text{-Bu}_3\text{SnH}$  (23.8  $\mu\text{L}$ , 0.088 mmol) and AIBN (5.25 mg, 0.032 mmol) furnished after chromatography ( $\text{SiO}_2$ , 2% ethyl acetate in hexanes) the desired product as a colorless oil (13.9 mg, 90% yield).  $R_f$  = 0.42 (10% EtOAc/hexanes); IR (film) 3061, 1730  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (d,  $J$  = 7.1 Hz, 2H), 7.37 (d,  $J$  = 7.1 Hz, 2H), 7.34–7.23 (m, 6H), 7.03 (d,  $J$  = 7.1 Hz, 1H), 6.87 (t,  $J$  = 7.7 Hz, 1H), 6.64 (t,  $J$  = 7.3 Hz, 1H), 6.01 (d,  $J$  = 7.9 Hz, 1H), 4.11 (dd  $J$  = 10.5, 5.4 Hz, 1H), 3.42 (dd,  $J$  = 15.9, 10.5 Hz, 1H), 3.00 (dd,  $J$  = 15.9, 5.4 Hz, 1H), 1.33 (s, 9H);  $^2\text{H}$  NMR (60 MHz,  $\text{CDCl}_3$ )  $\delta$  5.60 (br s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 172.6, 151.2, 141.1, 140.6, 129.2, 128.5 (2C), 128.4 (2C), 127.7, 127.3, 127.2, 123.8, 117.9, 109.2, 80.8, 66.6 (t,  $J$  = 21.3 Hz), 65.0, 34.0, 27.9; HRMS (EI): Exact mass calcd for  $\text{C}_{26}\text{H}_{26}\text{DNO}_2$   $[\text{M}]^+$ , 386.2104. Found 386.2102.

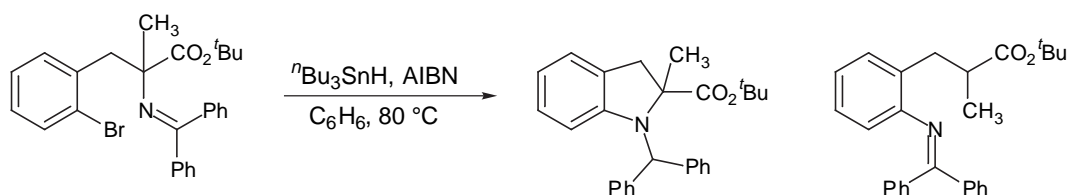


**2-(Benzhydrylidene-amino)-3-(2-bromophenyl)-2-methyl-propionic acid *tert*-butyl ester (10).**

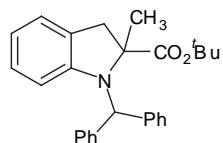
As an adaptation of the general procedure, methyl iodide (22.2  $\mu\text{L}$ , 355  $\mu\text{mol}$ ), Schiff base (100 mg, 339  $\mu\text{mol}$ ),  $\text{CsOH}\cdot\text{H}_2\text{O}$  (126 mg, 845  $\mu\text{mol}$ ), and cinchonidine derived catalyst (20.6 mg, 34.0  $\mu\text{mol}$ ), were stirred in toluene (1 mL) at room temperature for 3.5 h. Additional  $\text{CsOH}\cdot\text{H}_2\text{O}$  (252 mg, 1.69 mmol), catalyst (20.6 mg, 34.0  $\mu\text{mol}$ ) and *ortho*-bromobenzyl bromide (114 mg, 407  $\mu\text{mol}$ ), were added and the reaction mixture was stirred vigorously for an additional 18 h at room temperature. The reaction mixture was diluted with ether and water (1:1). The organic

layer was separated, the aqueous layer was extracted with ether, and the combined ether layers were dried and concentrated. Flash chromatography (neutral alumina, 0.50% ethyl acetate in hexanes) gave the desired ketimine as a colorless oil (76.0 mg, 46%). The catalyst was recovered by washing the aqueous layer with  $\text{CH}_2\text{Cl}_2$ .  $R_f=0.40$  (10% EtOAc/hexanes); IR (film) 3058, 1730, 1628  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 7.68 (dd,  $J = 7.3, 1.6$  Hz, 1H), 7.56 (d,  $J = 8.4$  Hz, 2H), 7.54 (t,  $J = 8.4$  Hz, 1H), 7.34–7.28 (m, 6H), 7.21 (td,  $J = 8.8, 0.8$  Hz, 1H), 7.06 (d,  $J = 6.4$  Hz, 3H), 3.48 (d,  $J = 14.0$ , Hz, 1H), 3.38 (d,  $J = 14.0$ , Hz, 1H), 1.32 (s, 9H), 1.17 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 173.7, 166.5, 141.5, 138.5, 137.6, 132.6, 129.8, 128.5, 128.5, 128.3, 128.1, 127.9, 127.8 (2C), 126.8, 126.4, 81.0, 68.3, 46.6, 27.9, 23.7; HRMS (EI): Exact mass calcd for  $\text{C}_{27}\text{H}_{29}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$  478.1382. Found 478.1363.

HPLC (Chiralcel OD, 1%  $i$ PrOH/hexanes, 0.5 mL/min):  $t_r$  (minor) = 8.9 m,  $t_r$  (major) = 10.8 m. (*S*)-22% ee.



Following the general procedure, Schiff base (41.0 mg, 86.0  $\mu\text{mol}$ ),  $n\text{Bu}_3\text{SnH}$  (51.0  $\mu\text{L}$ , 0.189 mmol) and AIBN (11.3 mg, 69  $\mu\text{mol}$ ) furnished after chromatography (neutral alumina, 20% dichloromethane in hexanes), the indoline as a colorless oil (16.0 mg, 48% yield) and the aryl imine as a yellow oil (15.0 mg, 45% yield).



**1-Benzhydryl-4-bromo-2-methyl-2,3-dihydro-1H-indole-2-**

**carboxylic acid *tert*-butyl ester (11).**  $R_f=0.54$  (10% EtOAc/hexanes); IR (film) 3065, 1727  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37–7.26 (m, 10H),

7.02 (d,  $J = 7.2$  Hz, 1H), 6.72 (t,  $J = 7.6$  Hz, 1H), 6.54 (t,  $J = 8.0$  Hz, 1H),

5.80 (s, 1H), 5.75 (d,  $J = 8.0$  Hz, 1H), 3.67 (d,  $J = 16.0$  Hz, 1H), 3.03 (d,  $J = 16.0$  Hz, 1H),

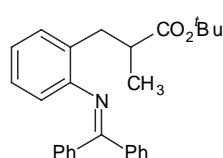
1.40 (s, 9H), 1.37 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 173.7, 148.7, 142.2, 140.7,

128.64, 127.59, 128.4, 128.1, 127.1, 126.9, 126.8, 125.7, 123.9, 116.2, 108.8, 81.6, 71.2,

62.3, 42.5, 27.8, 24.8; HRMS (EI): Exact mass calcd. for  $C_{27}H_{29}NO_2$   $[M]^+$ , 399.2198. Found 399.2185.

*Anal.* Calcd for  $C_{27}H_{29}NO_2$ : C, 81.17; H, 7.32; N, 3.51. Found: C, 81.15; H, 7.52; N, 3.47.

HPLC (Chiralcel AD, 1% *i*PrOH/hexanes, 1.0 mL/min):  $t_r$  = 3.8 m, 4.0 m.



**3-[2-(Benzhydrylidene-amino)-phenyl]-2-methyl-propionic acid**

***tert*-butyl ester (12).**  $R_f$ =0.17 (50%  $CH_2Cl_2$ /hexanes); IR (film) 3058,

1723, 1621  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.82 (d,  $J$  = 7.2 Hz, 2H),

7.48 (d,  $J$  = 7.2 Hz, 1H), 7.32–7.25 (m, 3H), 7.15 (dd,  $J$  = 7.2, 1.6 Hz, 2H), 7.10 (d,  $J$  = 7.2 Hz, 1H), 6.92 (td,  $J$  = 7.2, 1.2 Hz, 1H), 6.87 (td,  $J$  = 7.2, 1.2 Hz, 1H), 6.40 (d,  $J$  = 8.0 Hz, 1H), 2.95–2.83 (m, 2H), 2.63 (dd,  $J$  = 12.4, 6.8 Hz, 1H), 1.36 (s, 9H), 1.14 (d,  $J$  = 6.8, Hz, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ) ppm 176.1, 166.6, 139.5, 130.7, 130.5, 129.9, 129.3, 129.0 (2C), 128.6, 128.1, 127.9, 126.3, 123.2, 119.9, 79.8, 39.9, 36.4, 29.7, 28.0, 17.2; HRMS (EI): Exact mass calcd. for  $C_{27}H_{29}NO_2$   $[M]^+$ , 399.2198. Found 399.2212.

*Anal.* Calcd for  $C_{27}H_{29}NO_2$ : C, 81.17; H, 7.32; N, 3.51. Found: C, 81.37; H, 7.36; N, 3.46.

HPLC (Chiralcel AD, 1% *i*PrOH/hexanes, 1.0 mL/min):  $t_r$  = 4.7 m, 5.1 m.