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Supporting Information

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Catalytic Enantioselective Synthesis of β^2-Amino Acids

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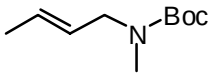
Supporting Information

General Information: ^{1}H NMR spectra were recorded at either 300, 400 or 500 MHz Varian spectrometers and ^{13}C NMR at 125 MHz in $CDCl_3$ unless otherwise noted. Mass spectral determination were carried out at 70 eV. FTIR spectra were recorded using a Nicolet Impact spectrometer. Optical rotations were measured using a Jasco DIP-370 digital polariemeter. Glassware was flame dried prior to use. All reactions were carried out under an atmosphere of argon. Elemental analysis was performed by Atlantic Microlab Inc., Norcross Georgia. Column chromatography was carried out on silica gel 60 (230-400) mesh. Commercially available reagents were used without additional purification unless noted. Degassing was carried out by bubbling Ar gas through the solution for 10 –15 min.

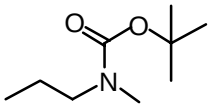


But-2-enyl-methyl-carbamic acid *tert*-butyl ester (2):

To a solution of 1-[Bis(*tert*-butoxycarbonyl)amino]-2(*E*)-butene[1] (2g, 7.96 mmol) in CH_2Cl_2 (40 mL) was added TFA (0.9 mL, 11.94 mmol) and the mixture was stirred at 23 ^oC . After 16 h, the reaction mixture was poured into Et_2O (100 mL) and washed with 10% aqueous NaOH (1 x 10 mL), brine (1 x 10 mL) and dried over Na_2SO_4. The

solution was concentrated to give the free amine that was used without further purification for the next step.

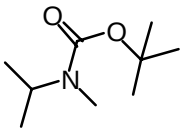
Crude amine (579 mgs, 3.4 mmol) in THF (10 mL) was added to a 60% dispersion of NaH in oil (338 mgs, 8.5 mmol) in THF (15 mL) and stirred at 23 ^{o}C. After 30 min, iodomethane (0.4 mL, 6.8 mmol) was added to the mixture and stirred at 23 ^{o}C. After 14 h, saturated NH_4Cl (10 mL) was added and the organics were extracted using Et_2O (2 x 25 mL). The combined Et_2O layers were washed with brine (1 x 25 mL) and dried (Na_2SO_4). The residue was purified by flash chromatography (SiO_2, EtOAc/Hexanes = 1:99) to give **2** (275 mgs, 1.48 mmol, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (m, 1 H), 5.41 (m, 1 H), 3.72 (m, 2 H), 2.78 (s, 3 H), 1.70 (m, 3 H), 1.45 (s, 9 H); IR (neat): 2973, 2928, 1698, 1451, 1393, 1239, 1153 cm^{-1}; Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.83; H, 10.46; N, 7.51.



Methyl-propyl-carbamic acid *tert*-butyl ester (5b):

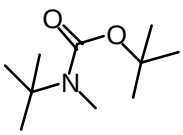
To a stirred solution of N-Methylpropylamine (2 g, 27.34 mmol), triethylamine (3.8 mL, 27.34 mmol) and DMAP (3.4 g, 27.34 mmol) at 0 ^{o}C in CH_2Cl_2 (40 mL) was slowly added di-*tert*-butyldicarbonate (7.2 g, 32.81 mmol). The mixture was allowed to warm to room temperature and stirred. After 16 h, the reaction mixture was diluted with Et_2O (30 mL) and washed with 10% HCl (2 x 25 mL), saturated K_2CO_3 (2 x 30 mL), brine (1 x 30 mL) and dried (Na_2SO_4). The solvent was concentrated by rotary evaporation to give yellow oil. Short path distillation of this residue (distillation temp = 40 ^{o}C at 0.1 mm Hg)

gave the title compound (4.4 g, 25,7 mmol, 94% yield) as clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.18 (m, 2 H), 2.83 (s, 3 H), 1.52 (m, 2 H), 1.45 (s, 9 H), 0.88 (t, *J* = 7.5 Hz, 3 H); IR (neat): 2969, 2932, 1698, 1461, 1395, 1246, 1163 cm^{-1}; Anal. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08. Found: C, 62.28; H, 11.08; N, 8.08.



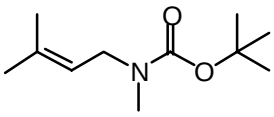
Isopropyl-methyl-carbamic acid *tert*-butyl ester (5c):

To a stirred solution of N-Methylisopropylamine (2 g, 27.34 mmol), triethylamine (3.8 mL, 27.34 mmol) and DMAP (3.4 g, 27.34 mmol) at 0 ^oC in CH_2Cl_2 (40 mL) was slowly added di-*tert*-butyldicarbonate (7.2 g, 32.81 mmol). The mixture was allowed to warm to room temperature and stirred. After 16 h, the reaction mixture was diluted with Et_2O (30 mL) and washed with 10% HCl (2 x 25 mL), saturated K_2CO_3 (2 x 30 mL), brine (1 x 30 mL) and dried over Na_2SO_4. The solvent was concentrated by rotary evaporation to give yellow oil. Short path distillation of this residue (distillation temp = 38 ^oC at 0.1 mm Hg) gave the title compound (3.0 g, 17.30 mmol, 63% yield) as clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (m, 1 H), 2.69 (s, 3 H), 1.46 (s, 9 H), 1.09 (m, 6 H); IR (neat): 2974, 2933, 1694, 1453, 1396, 1339, 1138 cm^{-1}; HRMS (EI) *m/z* calcd for $C_9H_{19}NO_2$ 173.1410, Found 173.1405.



***tert*-Butyl-methyl-carbamic acid *tert*-butyl ester (5d):**

To a stirred solution of N-Methyl-*tert*-butylamine (3 g, 34.42 mmol), triethylamine (5.0 mL, 34.42 mmol) and DMAP (5.8 g, 48.18 mmol) at 0 ^{o}C in CH_2Cl_2 (40 mL) was slowly added di-*tert*-butyldicarbonate (9.0 g, 41.30 mmol). The mixture was allowed to warm to room temperature and stirred. After 16 h, the reaction mixture was diluted with Et_2O (25 mL) and washed with 10% HCl (2 x 25 mL), saturated K_2CO_3 (2 x 30 mL), brine (1 x 30 mL) and dried (Na_2SO_4). The solvent was concentrated by rotary evaporation to give yellow oil. Short path distillation of this residue (distillation temp = 38 ^{o}C at 0.1 mm Hg) gave the title compound (3.8 g, 20.30 mmol, 59% yield) as clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (s, 3 H), 1.47 (s, 9 H), 1.36 (s, 9 H); IR (neat): 2975, 2930, 1694, 1474, 1359, 1291, 1137 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{10}H_{21}NO_2$ 187.1567, Found 187.1572.

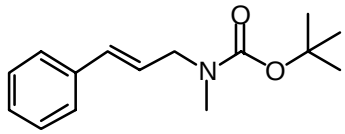


Methyl-(3-methyl-but-2-enyl)-carbamic acid *tert*-butyl ester (5f):

To a solution of 1-[Bis(*tert*-butoxycarbonyl)amino]-3-methyl-2-butene[2] (1g, 3.5 mmol) in CH_2Cl_2 (20 mL) was added TFA (0.4 mL, 5.3 mmol) and the mixture was stirred at 23 ^{o}C. After 16 h, the reaction mixture was poured into Et_2O (40 mL) and washed with 10% aqueous NaOH (1 x 10 mL), brine (1 x 40 mL) and dried over Na_2SO_4. The solution was concentrated to give the free amine that was used without further purification for the next step.

Crude amine (120 mgs, 0.7 mmol) in THF (6 mL) was added to a 60% dispersion of NaH in oil (75 mgs, 1.8 mmol) in THF (8 mL) and stirred at 23 ^{o}C. After 30 min, iodomethane (0.1 mL, 1.3 mmol) was added to the mixture and stirred at 23 ^{o}C. After 14

h, saturated NH_4Cl (10 mL) was added and the organics were extracted using Et_2O (2 x 15 mL). The combined Et_2O layers were washed with brine (1 x 10 mL) and dried (Na_2SO_4). The residue was purified by flash chromatography (SiO_2, Et_2O/Pentane = 15:85) to give **5f** (94 mgs, 0.47 mmol, 73% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 5.16 (t, *J* = 6.8 Hz, 1 H), 3.79 (m, 2 H), 2.77 (s, 3 H), 1.72 (s, 3 H), 1.67 (s, 3 H), 1.45 (s, 9 H); IR (neat): 2974, 2928, 1697, 1451, 1391, 1172, 1141 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{21}NO_2$ 199.1572, Found 199.1561.

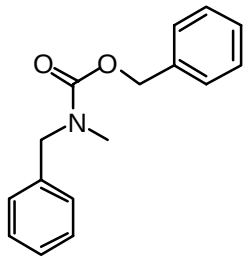


Methyl-(3-phenyl-allyl)-carbamic acid *tert*-butyl ester (5g):

To a solution of 1-[Bis(*tert*-butoxycarbonyl)amino]-1-phenyl-1-propene[2] (425 mgs, 1.27 mmol) in CH_2Cl_2 (25 mL) was added TFA (0.15 mL, 1.9 mmol) and the mixture was stirred at 23 ^oC. After 16 h, the reaction mixture was poured into Et_2O (40 mL) and washed with 10% aqueous NaOH (1 x 10 mL), brine (1 x 40 mL) and dried over Na_2SO_4. The solution was concentrated to give the free amine that was used without further purification for the next step.

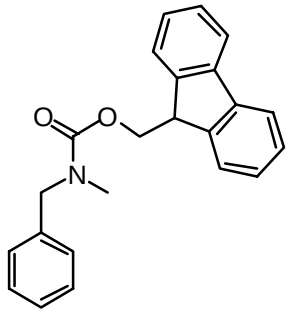
Crude amine (297 mgs, 1.27 mmol) in THF (8 mL) was added to a 60% dispersion of NaH in oil (240 mgs, 6.0 mmol) in THF (10 mL) and stirred at 23 ^oC. After 30 min, iodomethane (0.2 mL, 3.2 mmol) was added to the mixture and stirred at 23 ^oC. After 14 h, saturated NH_4Cl (20 mL) was added and the organics were extracted using Et_2O (2 x 20 mL). The combined Et_2O layers were washed brine (1 x 20 mL) and dried (Na_2SO_4). The residue was purified by flash chromatography (SiO_2, Et_2O/Pentane =

10:90) to give **5g** (180 mgs, 0.73 mmol, 57% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.0 Hz, 2 H), 7.32 (t, *J* = 7.5 Hz, 2 H), 7.37 (t, *J* = 7.5 Hz, 1 H), 6.47 (m, 1 H), 6.16 (m, 1 H), 3.97 (m, 2 H), 2.86 (s, 3 H), 1.47 (s, 9 H); IR (neat): 3014, 2974, 2928, 1694, 1391, 1144 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{21}NO_2$ 247.1575, Found 247.1572.



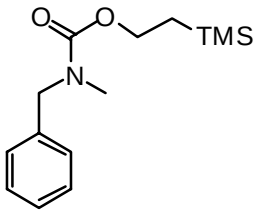
Benzyl-methyl-carbamic acid benzyl ester (8a):

To a stirred solution of *N*-benzylmethylamine (2.0 mL, 15.5 mmol) in CH_2Cl_2 (15 mL) at -78 ^{o}C was slowly added benzylchloroformate (2.2 mL, 18.6 mmol), followed by triethylamine (3.6 mL, 26.35 mmol). The mixture was allowed to warm to room temperature and stirred. After 16 h, 1M HCl (40 mL) was added and the organics were extracted using CH_2Cl_2 (3 x 40 mL). The combined CH_2Cl_2 layers were washed with 1M HCl (1 x 50 mL), brine (1 x 50 mL) and dried (Na_2SO_4). The residue was purified by flash chromatography (SiO_2, Et_2O/Pentane = 10:90) to give **8a** (3.1 g, 12.14 mmol, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.17 (m, 10 H), 5.18 (s, 2 H), 4.50 (s, 2 H), 2.91 (s, 3 H); IR (neat): 3062, 3031, 2942, 1702, 1480, 1403, 1223, 1141, 1051 cm^{-1}; Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.54; H, 6.84; N, 5.63.



Benzyl-methyl-carbamic acid 9*H*-fluoren-9-ylmethyl ester (8b):

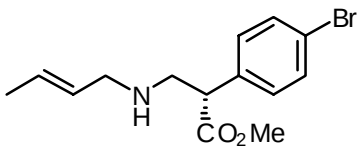
To a stirred solution of *N*-benzylmethylamine (500 mgs, 4.13 mmol) and K_2CO_3 (1.7 g, 12.4 mmol) in THF/H_2O (3:1) (15 mL) at 0 ^oC was slowly added 9-Fluorenyl-methylchloroformate (2.1 g, 8.25 mmol). The mixture was stirred at 0 ^oC for 45 min and allowed to warm to room temperature and stirred. After 1 h, H_2O (20 mL) was added and the organics were extracted using Et_2O (3 x 20 mL). The combined Et_2O layers were washed with brine (1 x 40 mL) and dried (Na_2SO_4). The residue was purified by flash chromatography (SiO_2, Et_2O/Pentane = 10:90) to give **8b** (980 mgs, 2.86 mmol, 69% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2 H), 7.61 (d, *J* = 7.2 Hz, 1 H), 7.48 (d, *J* = 7.2 Hz, 1 H), 7.39 – 7.20 (m, 8 H), 7.04 (m, 1 H), 4.50 (m, 1 H), 4.36 (m, 1 H), 4.27 (m, 1 H), 2.89 (s, 3 H); IR (neat): 3061, 3033, 2945, 1701, 1480, 1450, 1229, 1142 cm^{-1}; Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.19; H, 6.21; N, 4.05.



Benzyl-methyl-carbamic acid 2-(trimethyl-silanyl)-ethyl ester (8c):

To a stirred solution of N-benzylmethylamine (52 mgs, 0.43 mmol) in CH_2Cl_2 (8 mL) at 23 ^oC was added 1-[[2-(Trimethylsilyl)ethoxy]carbonyl]imidazole[3] (2.1 g, 8.25 mmol).

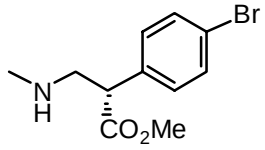
After 48 h at 23 ^{o}C, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, Et_2O/Pentane = 20:80) to give the title compound (57 mgs, 0.22 mmol, 50% yield) as clear oil, which was identical to previously prepared material.[4]



2*S*-(4-Bromo-phenyl)-3-but-2-enylamino-propionic acid methyl ester (4):

Methyl 4-bromo phenyldiazoacetate **(3)** (295 mgs, 1.15 mmol) in 2,2-dimethylbutane (10 mL) was added dropwise over 4 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (22 mgs, 0.01mmol) and But-2-enyl-methyl-carbamic acid *tert*-butyl ester **(2)** (107 mgs, 0.58 mmol) in 2,2-dimethylbutane (10 mL). After the addition, the resulting solution was stirred at 23^{o} C for 1 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (10 mL) and TFA (0.25 mL) and stirred for 12 h at 23^{o} C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (20 mL), extracted with 10% HCl (3 x 10 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (1 x 20 mL), brine (1 x 20 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 25:35:2) to give the title compound (104 mgs, 0.33 mmol, 58% yield). $[\alpha]^{25}_{D}$ = -39.6^{o} (c 1.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.5 Hz, 2 H), 7.18 (d, *J* = 8.5 Hz, 2 H), 5.59 (m, 1 H), 5.45 (m, 1 H), 3.78 (dd, *J* = 6.5, 7.5 Hz, 1 H), 3.67 (s, 3 H), 3.23 – 3.16 (m, 3 H), 2.87 (dd, *J* = 6.5, 12.0 Hz, 1 H), 1.67 (m, 3 H); ^{13}C NMR (DEPT) (125

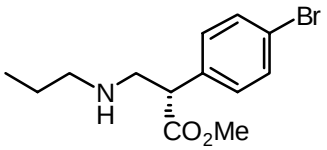
MHz, $CDCl_3$) δ 173.2 (C), 136.3 (C), 131.9 (CH), 129.8 (CH), 129.0 (CH), 127.7 (CH), 121.6 (C), 52.2 (CH_3), 51.7 (CH), 51.5 (CH_2), 51.4 (CH_2), 17.7 (CH_2); IR (neat): 3329, 3001, 2948, 2846, 1735, 1487, 1442, 1164 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{14}H_{18}NBrO_2$ 313.0500, Found 313.0486. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **4**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/Pentane = 20:80) gave the amide in 85% ee (HPLC, Whelk column, 0.8% 2-propanol in hexanes, 0.8 mL/min, 1 mg/mL, t_R = 20.88 (major) and 23.43 (minor) min, UV 254 nm); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 5.63 – 5.58 (m, 1 H), 5.24 – 5.20 (m, 1 H), 4.16 (t, *J* = 7.6 Hz, 1 H), 3.88 (m, 2 H), 3.68 (s, 3 H), 3.57 – 3.52 (m, 2 H), 1.71 (d, *J* = 6.4 Hz, 1 H); IR (neat): 2923, 2854, 1736, 1690, 1487, 1441, 1205, 1155 cm^{-1}; EI-MS *m/z* (relative intensity) 407 (M^+, 1%), 377, 242.



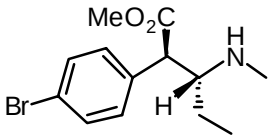
2S-(4-Bromo-phenyl)-3-methylamino-propionic acid methyl ester (6a):

Methyl 4-bromo phenyldiazoacetate **(3)** (351 mgs, 1.37 mmol) in 2,2-dimethylbutane (8 mL) was added dropwise over 4 h using a syringe pump to a solution of Rh_2(*R*-DOSP)$_4$ (25 mgs, 0.01mmol) and Dimethyl-carbamic acid *tert*-butyl ester **(5a)**[5] (100 mgs, 0.69 mmol) in 2,2-dimethylbutane (10 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue

was reconstituted in CH_2Cl_2 (10 mL) and TFA (0.3 mL, 3.4 mmol) and stirred for 12 h at 23^o C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (20 mL), extracted with 10% HCl (3 x 10 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (1 x 20 mL), brine (1 x 20 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 35:35:2) to give the title compound (114 mgs, 0.42 mmol, 61% yield). $[\alpha]^{25}_D$ = -19.7^o (c 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.5 Hz, 2 H), 7.19 (d, *J* = 8.5 Hz, 2 H), 3.80 – 3.77 (dd, *J* = 7.0, 8.5 Hz, 1 H), 3.67 (s, 3 H), 3.23 – 3.19 (dd, *J* = 8.5, 12.0 Hz, 1 H), 2.87 – 2.83 (dd, *J* = 7.0, 12.5 Hz, 1 H), 2.42 (s, 3 H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) δ 173.0 (C), 136.1 (C), 131.8 (CH), 129.7 (CH), 121.5 (C), 54.5 (CH_2), 52.1 (CH_3), 51.1 (CH), 36.2 (CH_3); IR (neat): 3334, 2948, 2845, 1734, 1486, 1439, 1205 cm^{-1}; Anal. Calcd for $C_{11}H_{15}NBrClO_2$: C, 42.81; H, 4.90; N, 4.54. Found: C, 43.13; H, 5.06; N, 4.37. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **6a**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/Pentane = 20:80) gave the amide in 31% ee (HPLC, Chiralcel-OD-H column, 5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 9.54 (minor) and 10.24 (major) min, UV 254 nm); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.0 Hz, 2 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 4.11 (t, *J* = 8.0 Hz, 1 H), 3.93 (dd, *J* = 8.0, 13.5 Hz, 1 H), 3.73 (dd, *J* = 8.0, 13.5 Hz, 1 H), 3.69 (s, 3 H), 2.98 (s, 3 H); IR (neat): 2953, 1736, 1694, 1488, 1436, 1194, 1148 cm^{-1}; EI-MS *m/z* (relative intensity) 367 (M^+, 1%), 337, 240.



6b



7

2*S*-(4-Bromo-phenyl)-3-propylamino-propionic acid methyl ester (6b) and 2*S*-(4-Bromo-phenyl)-3*R*-methylamino-pentanoic acid methyl ester (7):

Methyl 4-bromo phenyldiazoacetate **(3)** (600 mgs, 2.35 mmol) in 2,2-dimethylbutane (12 mL) was added dropwise over 4 h using a additional funnel to a solution of Rh_2(*S*-DOSP)$_4$ (44 mgs, 0.01mmol) and Methyl-propyl-carbamic acid *tert*-butyl ester (**5b**) (240 mgs, 1.38 mmol) in 2,2-dimethylbutane (20 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (25 mL) and TFA (0.5 mL, 6.9 mmol) and stirred for 16 h at 23^o C. The solution was concentrated in *vacuo,* and the residue was dissolved in Et_2O (30 mL), extracted with 10% HCl (3 x 25 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8–9) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (1 x 30 mL) and brine (1 x 30 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the title regioisomers **6b** and **7** (>94% de by ^{1}H-NMR) in the ratio of 5:1 respectively (by ^{1}H-NMR). The regioisomers were separated by preparative TLC (SiO_2, Et_2O/Pentane/NEt_3= 30:35:3).

Major: 2*S*-(4-Bromo-phenyl)-3-propylamino-propionic acid methyl ester (6b): (169 mgs, 0.56 mmol, 46% yield); $[\alpha]^{25}_D$ = -32.81^o (c 2.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2 H), 7.19 (d, *J* = 8.5 Hz, 2 H), 3.79 – 3.76 (dd, *J* = 7.0, 8.5

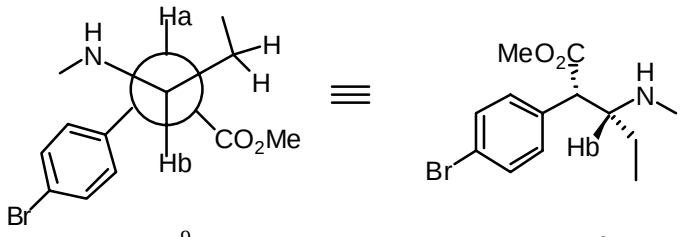
Hz, 1 H), 3.67 (s, 3 H), 3.26 – 3.22 (dd, *J* = 8.5, 12.5 Hz, 1 H), 2.89 – 2.85 (dd, *J* = 6.5, 12.0 Hz, 1 H), 2.58 (m, 2 H), 1.47 – 1.41 (m, 3 H), 0.87 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) 173.1 (C), 136.2 (C), 131.8 (CH), 129.7 (CH), 121.4 (C), 52.4 (CH_2), 52.0 (CH_3), 51.4 (CH_2), 51.4 (CH_2), 22.9 (CH_2), 11.6 (CH_3); IR (neat): 3328, 2954, 2873, 1734, 1486, 1201 cm^{-1}; HRMS (FAB) $(m+H)^+$ calcd for $C_{13}H_{19}NBrO_2$ 300.0594, Found 300.0590. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **6b**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 20:80) gave the amide in 64% ee (HPLC, Chiralcel-OD-H column, 1.5% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 6.16 (major) and 6.71 (minor) min, UV 254 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 10.5 Hz, 2 H), 7.16 (d, *J* = 10.5 Hz, 2 H), 4.20 – 4.16 (t, *J* = 9.5 Hz, 1 H), 3.90 – 3.84 (m, 1 H), 3.68 (s, 3 H), 3.63 – 3.58 (m, 1 H), 3.31 – 3.24 (m, 1 H), 3.01 – 2.93 (m, 1 H), 1.54 (m, 2 H), 0.87 (t, *J* = 9.5 Hz, 3 H); IR (neat): 2961, 2877, 1736, 1689, 1487, 1440, 1211, 1148 cm^{-1}; EI-MS *m/z* (relative intensity) 397 (M^+, 1%), 336.

Minor: 2*S*-(4-Bromo-phenyl)-3*R*-methylamino-pentanoic acid methyl ester (7): (32 mgs, 0.11 mmol, 8% yield). [24% ee (HPLC, Whelk column, 18.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 4.32 (major) and 6.14 (minor) min, UV 254 nm); $[\alpha]^{25}_D$ = -16.39^o (c 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.5 Hz, 2 H), 3.66 (s, 3 H), 3.64 (d, *J* = 9.5 Hz, 1 H), 3.10 – 3.06 (m, 1 H), 2.20 (s, 3 H), 1.57 – 1.47 (m, 2 H), 0.96 (t, *J* = 8.0 Hz, 3 H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) 173.1 (C), 135.6 (C), 131.7 (CH), 130.5 (CH), 121.6 (C), 62.0 (CH), 54.7(CH), 52.0 (CH_3), 32.74 (CH_3), 23.53 (CH_2), 9.35 (CH_3); IR (neat): 3350, 2952,

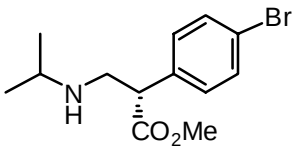
2794, 1732, 1486, 1145, 1075 cm^{-1}; HRMS (FAB) $(M+H)^+$ calcd for $C_{13}H_{19}NBrO_2$ 300.0594, Found 300.0594. The stereochemical assignment for the minor regioisomer **7** was based on the distinctive coupling constants.[9] It is well established that the Rh_2(S-DOSP)$_4$-catalyzed C-H insertions generate the (*S*)-configuration at the stereogenic center formed at the original carbenoid site.[10] The large coupling constant value between Ha and Hb (J = 9.5 Hz) indicates that the protons preferentially exist in an antiperiplanar conformation (A, Figure 1).

Furthermore the NMR signals for the *N*-methyl protons of **7** are shifted from δ 2.45 ppm to 2.20 ppm. This clearly shows the shielding effect of the aromatic ring on N-Methyl

Figure 1



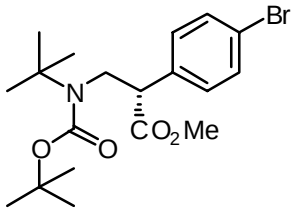
protons as shown in the Figure 1.[9] Also the proton NMR signals for the methylene group did not shift downfield, indicates the lack of shielding due to the aromatic ring. Based on this argument the configuration at C3 is *R*.



2*S*-(4-Bromo-phenyl)-3-isopropylamino-propionic acid methyl ester (6c):

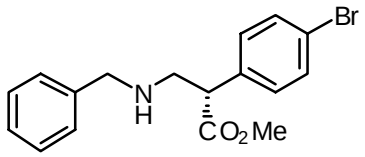
Methyl 4-bromo phenyldiazoacetate **(3)** (294 mgs, 1.15 mmol) in 2,2-dimethylbutane (8 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (22 mgs, 0.01mmol) and Isopropyl-methyl-carbamic acid *tert*-butyl ester **(5c)** (100 mgs, 0.58 mmol) in 2,2-dimethylbutane (5 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (10 mL) and TFA (0.25 mL, 2.8 mmol) and stirred for 16 h at 23^o C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (25 mL), extracted with 10% HCl (3 x 15 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (1 x 15 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 25:35:2) to give the title compound (98 mgs, 0.37 mmol, 57% yield). $[\alpha]^{25}_D$ = -29.05^o (c 0.84, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.5 Hz, 2 H), 7.19 (d, *J* = 8.5 Hz, 2 H), 3.74 (t, *J* = 8.0 Hz, 1 H), 3.67 (s, 3 H), 3.25 – 3.21 (dd, *J* = 8.5, 12.0 Hz, 1 H), 2.88 – 2.84 (dd, *J* = 6.5, 12.0 Hz, 1 H), 2.80 (m, 1 H), 1.04 and 1.02 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) δ 173.2 (C), 136.3 (C), 131.8 (CH), 129.7 (CH), 121.5 (C), 52.1 (CH_3), 51.6 (CH), 49.9 (CH_2), 48.4 (CH), 22.9 (CH_3), 22.8 (CH_3); IR (neat): 3321, 2961, 2844, 1735, 1486, 1438, 1165, 1073 cm^{-1}; HRMS (EI) [M^+–2H] calcd for $C_{13}H_{16}NBrO_2$ 297.0364, Found 297.0356; HRMS (EI) [M^+–CH_3] calcd for $C_{12}H_{15}NBrO_2$ 284.02861, Found 284.0283. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **6c**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/Pentane = 20:80) gave the amide in 82%

ee (HPLC, Chiralcel-OD-H column, 5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 4.75 (major) and 5.58 (minor) min, UV 254 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 4.24 (t, *J* = 6.8 Hz, 1 H), 4.1 (m, 1 H), 3.93 – 3.98 (dd, *J* = 6.4, 13.6 Hz, 1 H), 3.68 (s, 3 H), 3.41 – 3.36 (dd, *J* = 7.6, 14.0 Hz, 1 H), 1.17 (d, *J* = 6.8 Hz, 3 H), 0.78 (d, *J* = 6.0 Hz, 3 H); IR (neat): 2974, 2360, 2338, 1736, 1687, 1197, 1149 cm^{-1}; EI-MS *m/z* (relative intensity) 395 (M^+, 1%), 240, 168.



2*S*-(4-Bromo-phenyl)-3-(*tert*-butoxycarbonyl-*tert*-butyl-amino)-propionicacidmethyl ester (6d): Methyl 4-bromo phenyldiazoacetate **(3)** (272 mgs, 1.07 mmol) in 2,2-dimethylbutane (8 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (20 mgs, 0.01mmol) and *tert*-Butyl-methyl-carbamic acid *tert*-butyl ester **(5d)** (100 mgs, 0.53 mmol) in 2,2-dimethylbutane (6 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, Et_2O/Pentane= 10:90) to give the title compound (130 mgs, 0.31 mmol, 58% yield). Enantiomeric excess of **6d** was determined by ^{1}H-NMR using by Eu tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorate]) as a chiral shift reagent and was found to be 54% ee. $[\alpha]^{25}_D$ = -29.82^o (c 1.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 2 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 4.00 (t, *J* = 7.0 Hz, 1 H), 3.92 – 3.89 (dd, *J* = 7.0, 14.5 Hz,

1 H), 3.67 (s, 3 H), 3.56 – 3.52 (dd, *J* = 7.0, 14.5 Hz, 1 H), 1.46 (s, 9 H), 1.24 (s, 9 H); IR (neat): 2971, 1734, 1697, 1487, 1364, 1328, 1160 cm^{-1}; Anal. Calcd for $C_{19}H_{28}NBrO_4$: C, 53.28; H, 6.81; N, 3.38. Found: C, 53.28; H, 6.97; N, 3.26.



3-Benzylamino-2S-(4-bromo-phenyl)-propionic acid methyl ester (6e):

Reaction between Methyl 4-bromo phenyldiazoacetate and Benzyl-methyl-carbamic acid *tert*-butyl ester (5e): Methyl 4-bromo phenyldiazoacetate **(3)** (230 mgs, 0.90 mmol) in 2,2-dimethylbutane (7 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (17 mgs, 0.01mmol) and Benzyl-methyl-carbamic acid *tert*-butyl ester (**5e**)[6] (100 mgs, 0.45 mmol) in 2,2-dimethylbutane (5 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (10 mL) and TFA (0.2 mL, 2.26 mmol) and stirred for 16 h at 23^o C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (20 mL), extracted with 10% HCl (3 x 15 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (1 x 15 mL), brine (1 x 20 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 25:35:2) to give the title compound **6e** (97 mgs, 0.28 mmol, 62% yield). $[\alpha]^{25}_D$ = -44.71^o (c 1.36, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 2 H), 7.32 – 7.22 (m, 5 H), 7.16 (d, *J* = 7.0 Hz, 2 H), 3.8 (s,

2 H), 3.77 (m, 1 H), 3.66 (s, 3 H), 3.26 (m, 1 H), 2.91 (dd, *J* = 6.5, 11.5 Hz, 1 H)); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) δ 173.1 (C), 139.8 (C), 136.1 (C), 131.8 (CH), 129.7 (CH), 128.3 (CH), 127.9 (CH), 126.9 (CH), 121.4 (CH), 53.5 (CH_2), 52.1 (CH_3), 51.7 (CH_2), 51.5 (CH); IR (neat): 3328, 3024, 2948, 2844, 1730, 1490, 1455, 1163, 1011 cm^{-1}; Anal. Calcd for $C_{17}H_{18}NBrO_2$: C, 58.63; H, 5.21; N, 4.02. Found: C, 58.76; H, 5.25; N, 4.06. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **6e**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 15:85) gave the amide in 95% ee (HPLC, Chiralcel-AD-RH column, 5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 4.62 (major) and 8.16 (minor) min, UV 254 nm); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.5 Hz, 2 H), 7.37 – 7.32 (m, 3 H), 7.13 – 7.10 (m, 4 H), 4.65 (s, 3 H), 4.24 (m, 2 H), 3.87 – 3.77 (m, 1 H), 3.68 (s, 3 H), 3.52 – 3.48 (dd, *J* = 7.0 Hz, 13.5 Hz, 1 H); IR (neat): 3041, 2948, 1735, 1691, 1210, 1166, 1144 cm^{-1}; EI-MS *m/z* (relative intensity) 443 (M^+, 1%), 346, 240.

Reaction between Methyl 4-bromo phenyldiazoacetate and Benzyl-methyl-carbamic acid benzyl ester (8a): Methyl 4-bromo phenyldiazoacetate **(3)** (200 mgs, 0.78 mmol) in 2,2-dimethylbutane (6 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (17 mgs, 0.01mmol) and Benzyl-methyl-carbamic acid benzyl ester **(8a)** (100 mgs, 0.39 mmol) in 2,2-dimethylbutane (5 mL). After the addition, the resulting solution was stirred at 23^o C for 4 h. The solvent was removed under reduced pressure and the residue was reconstituted in acetic acid (2 mL) at 0 ^{o}C under Ar and 30% HBr in acetic acid (2.5 mL) was added. After 3 h at 0 ^{o}C, reaction mixture was diluted with Et_2O (10 mL) extracted with H_2O (3 x 15 mL). The combined aqueous

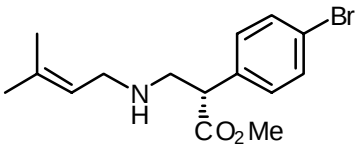
layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined EtOAc layers were washed with brine (1 x 30 mL) and dried (Na_2SO_4). The residue was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 25:35:2) to give the title compound **6e** (91 mgs, 0.26 mmol, 67% yield). To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **6e**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 15:85) gave the amide in 90% ee (HPLC, Chiralcel-AD-RH column, 5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 4.62 (major) and 8.16 (minor) min, UV 254 nm).

Reaction between Methyl 4-bromo phenyldiazoacetate and Benzyl-methyl-carbamic acid 9*H*-fluoren-9-ylmethyl ester (8b): Methyl 4-bromo phenyldiazoacetate **(3)** (149 mgs, 0.58 mmol) in 2,2-dimethylbutane (6 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (17 mgs, 0.01mmol) and Benzyl-methyl-carbamic acid 9*H*-fluoren-9-ylmethyl ester **(8b)** (100 mgs, 0.39 mmol) in 2,2-dimethylbutane/CH_2Cl_2 (5:1) (6 mL). After the addition, the resulting solution was stirred at 23^o C for 5 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_3CN (10 mL) at 0 ^{o}C under Ar and Et_2NH (0.2 mL) was added. After 3 h at 23 ^{o}C, reaction mixture was diluted with Et_2O (25 mL) extracted with 10% HCl (3 x 15 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined EtOAc layers were washed with brine (1 x 30 mL) and dried (Na_2SO_4). The residue was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 10:90:2) to give the title compound **6e** (21 mgs, 0.06 mmol, 21% yield). To measure the enantiomeric excess of the above

compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **6e**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 15:85) gave the amide in 69% ee (HPLC, Chiralcel-AD-RH column, 5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 4.62 (major) and 8.16 (minor) min, UV 254 nm).

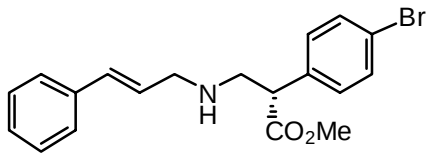
Reaction between Methyl 4-bromo phenyldiazoacetate and Benzyl-methyl-carbamic acid 2-(trimethyl-silanyl)-ethyl ester (8c): Methyl 4-bromo phenyldiazoacetate **(3)** (192 mgs, 0.75 mmol) in 2,2-dimethylbutane (6 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (14 mgs, 0.01mmol) and Benzyl-methyl-carbamic acid 2-(trimethyl-silanyl)-ethyl ester[4] (**8c**) (100 mgs, 0.37 mmol) in 2,2-dimethylbutane (6 mL). After the addition, the resulting solution was stirred at 23^o C for 8 h. The solvent was removed under reduced pressure and the residue was reconstituted in THF (10 mL) at 23 ^{o}C under Ar and 1M tetrabutylammonium fluoride in THF (2.5 mL) was added. After 3 h at 23 ^{o}C, reaction mixture was concentrated under pressure and diluted with Et_2O (30 mL) extracted with 10% HCl (3 x 15 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined EtOAc layers were washed with water (1 x 30 mL), brine (1 x 30 mL) and dried (Na_2SO_4). The residue was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 20:80:2) to give the title compound **6e** (34 mgs, 0.098 mmol, 26% yield). To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **6e**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 15:85) gave the amide in 94% ee (HPLC, Chiralcel-AD-RH column,

5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 4.72 (major) and 8.08 (minor) min, UV 254 nm).



2*S*-(4-Bromo-phenyl)-3-(3-methyl-but-2-enylamino)-propionicacid methyl ester (6f): Methyl 4-bromo phenyldiazoacetate **(3)** (271 mgs, 1.06 mmol) in 2,2-dimethylbutane (7 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (20 mgs, 0.01mmol) and Methyl-(3-methyl-but-2-enyl)-carbamic acid tert-butyl ester **(5f)** (106 mgs, 0.53 mmol) in 2,2-dimethylbutane (6 mL). After the addition, the resulting solution was stirred at 23^o C for 3 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (8 mL) and TFA (0.3 mL, 4.25 mmol) and stirred for 12 h at 23^o C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (20 mL), extracted with 10% HCl (3 x 10 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (1 x 15 mL), brine (1 x 15 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 25:35:2) to give the title compound (108 mgs, 0.33 mmol, 62% yield). $[\alpha]^{25}_D$ = -7.38^o (c 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 5.18 (m, 1 H), 3.78 (dd, *J* = 6.5, 8.0 Hz, 1 H), 3.67 (s, 3 H), 3.25 – 3.19 (m, 3 H), 2.89 (dd, *J* = 7.0, 12.5 Hz, 1 H), 1.70 (s, 3 H), 1.62 (s, 3 H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) δ 173.2 (C), 136.3 (C), 134.6 (C), 131.8 (CH), 129.7 (CH), 122.5 (CH), 121.5 (C), 52.1 (CH_3), 51.9 (CH_2), 51.4 (CH), 46.9 (CH_2), 25.7

(CH_3), 17.8 (CH_3); IR (neat): 3324, 2949, 2849, 1735, 1487, 1441, 1163 cm^{-1}; HRMS (EI) [M^+–2H] calcd for $C_{15}H_{18}NBrO_2$ 323.0521, Found 323.0517. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **6f**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 20:80) gave the amide in 87% ee (HPLC, Chiralcel-OD-H column, 0.7% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 5.20 (major) and 5.79 (minor) min, UV 254 nm); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 4.94 (m, 1 H), 4.16 (t, *J* = 7.6 Hz, 1 H), 3.99 (dd, *J* = 7.2, 16.0 Hz, 1 H), 3.83 – 3.77 (dd, *J* = 8.0, 13.6 Hz, 1 H), 3.68 (s, 3 H), 3.60 – 3.56 (dd, *J* = 8.8, 15.6 Hz, 1 H), 3.49 (dd, *J* = 7.2, 13.6 Hz, 1 H), 1.72 (s, 3 H), 1.65 (s, 3 H); IR (neat): 2951, 2914, 1736, 1691, 1442, 1205, 1150 cm^{-1}; EI-MS *m/z* (relative intensity) 421 (M^+, 4%), 362, 240.

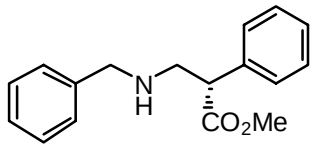


2*S*-(4-Bromo-phenyl)-3-(3-phenyl-allylamino)-propionic acid methyl ester (6g):

Methyl 4-bromo phenyldiazoacetate **(3)** (175 mgs, 0.69 mmol) in 2,2-dimethylbutane (5 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (13 mgs, 0.01mmol) and Methyl-(3-phenyl-allyl)-carbamic acid tert-butyl ester **(5g)** (85 mgs, 0.34 mmol) in 2,2-dimethylbutane (5 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (8 mL) and TFA (0.1 mL, 4.25 mmol) and stirred for

14 h at 23^{o} C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (15 mL), extracted with 10% HCl (3 x 15 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (1 x 15 mL), brine (1 x 20 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 25:35:2) to give the title compound (80 mgs, 0.21 mmol, 60% yield). $[\alpha]^{25}_{D}$ = -38.99^{o} (c 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 7.5 Hz, 2 H), 7.30 (t, *J* = 7.0 Hz, 2 H), 7.23 (d, *J* = 7.5 Hz, 1 H), 7.19 (d, *J* = 8.5 Hz, 2 H), 6.51 (d, *J* = 15.5 Hz, 1 H), 6.25 – 6.19 (m, 1 H), 3.81 (t, *J* = 7.0 Hz, 1 H), 3.68 (s, 3 H), 3.42 (m, 2 H), 3.31 (dd, *J* = 8.5, 12.0 Hz, 1 H), 2.94 (dd, *J* = 6.5, 10.5 Hz, 1 H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) δ 173.2 (C), 136.9 (C), 136.2 (C), 131.9 (CH), 131.6 (CH), 129.7 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 126.3 (CH), 121.6 (C), 52.2 (CH_2), 51.8 (CH_3), 51.6 (CH), 51.6 (CH_2); IR (neat): 3025, 2947, 2843, 1734, 1488, 1346, 1164 cm^{-1}; Anal. Calcd for $C_{19}H_{20}NBrO_2$: C, 60.97; H, 5.39; N, 3.74. Found: C, 60.83; H, 5.43; N, 3.60. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **6g**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/Pentane = 20:80) gave the amide in 87% ee (HPLC, Chiralcel-OD-H column, 0.7% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 18.26 (major) and 22.72 (minor) min, UV 254 nm); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2 H), 7.34 – 7.26 (m, 5 H), 7.16 (d, *J* = 9.0 Hz, 2 H), 6.49 (d, *J* = 16.0 Hz, 1 H), 5.93 – 5.87 (m, 1 H), 4.21 (t, *J* = 7.5 Hz, 1 H), 4.13 (dd, *J* = 7.0, 16.5 Hz, 1 H), 3.95 (dd, *J* = 8.0, 13.5 Hz, 1 H), 3.87 – 3.83 (dd, *J* = 5.0 Hz, 15.5 Hz, 1 H), 3.68 (s, 3 H),

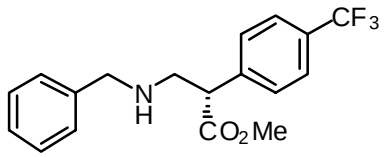
3.62 (m, 1 H); IR (neat): 2952, 2925, 1735, 1691, 1488, 1205, 1153 cm^{-1}; EI-MS *m/z* (relative intensity) 469 (M^+, 23%), 407, 341.



3-Benzylamino-2*S*-phenyl-propionic acid methyl ester (10a):

Methyl phenyldiazoacetate **(9a)** (159 mgs, 0.90 mmol) in 2,2-dimethylbutane (8 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (17 mgs, 0.01mmol) and Benzyl-methyl-carbamic acid *tert*-butyl ester **(5e)**[6] (100 mgs, 0.45 mmol) in 2,2-dimethylbutane (5 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (10 mL) and TFA (0.2 mL, 2.26 mmol) and stirred for 16 h at 23^o C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (20 mL), extracted with 10% HCl (3 x 15 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (1 x 15 mL), brine (1 x 20 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 25:35:2) to give the title compound (80 mgs, 0.30 mmol, 67% yield). $[\alpha]^{25}_D$ = -42.36^o (c 0.76, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 10 H), 3.85 – 3.82 (dd, *J* = 6.5, 8.5 Hz, 1 H), 3.80 (s, 2 H), 3.66 (s, 3 H), 3.30 (dd, *J* = 8.5, 12.0 Hz, 1 H), 2.90 (dd, *J* = 6.5, 12.0 Hz, 1 H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) δ 173.5 (C), 139.9 (C), 137.1 (C), 128.7 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 126.9 (CH), 53.5 (CH_2), 52.0

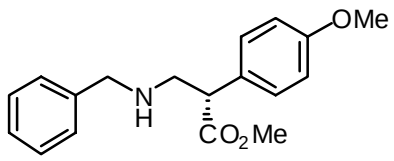
(CH_3), 51.9 (CH), 51.9 (CH_2); IR (neat): 3334, 3061, 3028, 2948, 2839, 1733, 1494, 1452, 1164 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{17}H_{19}NO_2$ 269.1415, Found 269.1412. HRMS (EI) [M^+-2H] calcd for $C_{17}H_{17}NO_2$ 267.1259, Found 267.1259. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **10a**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/Pentane = 20:80) gave the amide in 96% ee (HPLC, Chiralcel-AD-RH column, 5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 4.09 (major) and 6.17 (minor) min, UV 254 nm); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 8 H), 7.09 (m, 2 H), 4.64 – 4.57 (m, 2H), 4.24 – 4.20 (m, 1 H), 4.09 – 4.05 (m, 1 H), 3.85 – 3.80 (s, 3 H), 3.53 – 3.47 (m, 1H); IR (neat): 3032, 2953, 1734, 1691, 1449, 1205, 1151 cm^{-1}; EI-MS *m/z* (relative intensity) 365 (M^+, 3%), 268.



3-Benzylamino-2*S*-(4-trifluoromethyl-phenyl)-propionic acid methyl ester (10b):

Methyl 4-trifluorophenyldiazoacetate **(9b)** (221 mgs, 0.90 mmol) in 2,2-dimethylbutane (6 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (17 mgs, 0.01mmol) and Benzyl-methyl-carbamic acid *tert*-butyl ester **(5e)**[6] (100 mgs, 0.45 mmol) in 2,2-dimethylbutane (5 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (10 mL) and TFA (0.2 mL, 2.26 mmol) and stirred for 16 h

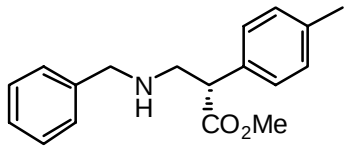
at 23^{o} C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (20 mL), extracted with 10% HCl (3 x 15 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (1 x 15 mL), brine (1 x 20 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 25:35:2) to give the title compound (84 mgs, 0.25 mmol, 55% yield). $[\alpha]^{25}_{D}$ = -1.99^{o} (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.32 – 7.24 (m, 5 H), 3.90 – 3.87 (dd, *J* = 6.5, 8.0 Hz, 1 H), 3.80 (s, 2 H), 3.68 (s, 3 H), 3.31 – 3.26 (dd, *J* = 8.0, 12.0 Hz, 1 H), 2.94 – 2.91 (dd, *J* = 6.5, 12.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 141.1, 139.7, 128.5, 128.4, 127.9, 125.6, 53.5, 52.3, 51.9, 51.7; IR (neat): 2924, 2861, 1736, 1619, 1326, 1165 cm^{-1}; HRMS (EI) [M^{+}-2H] calcd for $C_{18}H_{16}NF_3O_2$ 333.1133, Found 335.1119. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **10b**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 20:80) gave the amide in 92% ee (HPLC, Chiralcel-AD-RH column, 5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 3.82 (major) and 6.05 (minor) min, UV 254 nm); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2 H), 7.38 – 7.32 (m, 5 H), 7.13 - 7.11 (d, *J* = 7.0 Hz, 2 H), 4.61 (m, 1 H), 4.33 – 4.27 (m, 2 H), 3.83 – 3.78 (dd, *J* = 8.5, 14.0 Hz, 1 H), 3.69 (s, 3 H), 3.57 – 3.53 (dd, *J* = 6.0, 13.5 Hz, 1 H); IR (neat): 3033, 2956, 1737, 1692, 1447, 1326, 1163 cm^{-1}; EI-MS *m/z* (relative intensity) 433 (M^{+}, 2%), 336.



3-Benzylamino-2*S*-(4-methoxy-phenyl)-propionic acid methyl ester (10c):

Methyl 4-methoxyphenyldiazoacetate **(9c)** (187 mgs, 0.90 mmol) in 2,2-dimethylbutane/toluene (4:1) (7.5 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (17 mgs, 0.01mmol) and Benzyl-methyl-carbamic acid *tert*-butyl ester **(5e)**[6] (100 mgs, 0.45 mmol) in 2,2-dimethylbutane (5 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (10 mL) and TFA (0.2 mL, 2.26 mmol) and stirred for 16 h at 23^o C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (20 mL), extracted with 10% HCl (3 x 15 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (1 x 15 mL), brine (1 x 20 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 25:35:2) to give the title compound (82 mgs, 0.27 mmol, 61% yield). $[\alpha]^{25}_D$ = -50.99^o (c 0.60, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 5 H), 7.21 – 7.10 (d, *J* = 9.0 Hz, 2 H), 6.86 – 6.84 (d, *J* = 9.0 Hz, 2 H), 3.79 – 3.77 (m, 6 H), 3.65 (s, 3 H), 3.26 – 3.22 (dd, *J* = 8.5, 12.0 Hz, 1 H), 2.91 – 2.87 (dd, *J* = 7.0, 12.0 Hz, 1 H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) δ 173.8 (C), 158.9 (C), 139.9 (C), 129.1 (C), 129.0 (C), 128.3 (CH), 127.9 (CH), 126.9 (CH), 114.1 (CH), 55.2 (CH_3), 53.6 (CH_2), 51.9 (CH_2), 51.0 (CH); IR (neat): 2949, 2837, 1731, 1512,

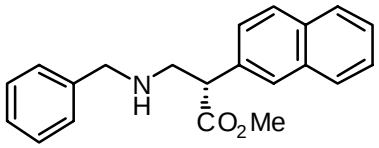
1454, 1249, 1170 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{21}NO_3$ 299.1521, Found 299.1528. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **10c**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 20:80) gave the amide in 92% ee (HPLC, Chiralcel-AD-RH column, 5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 6.10 (major) and 8.25 (minor) min, UV 254 nm); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 3 H), 7.17 (m, 2 H), 7.11 (m, 2 H), 6.89 – 6.86 (m, 2 H), 4.61 – 4.58 (m, 1 H), 4.18 – 4.08 (m, 2 H), 3.83 – 3.79 (m, 4 H), 3.67 (s, 3 H), 3.49 – 3.45 (dd, *J* = 7.5, 13.5 Hz, 1 H); IR (neat): 3032, 2955, 2842, 1733, 1691, 1512, 1254, 1205, 1162 cm^{-1}; EI-MS *m/z* (relative intensity) 395 (M^+, 1%), 336.



3-Benzylamino-2*S*-*p*-tolyl-propionic acid methyl ester (10d):

4-Methyl phenyldiazoacetate **(9d)** (172 mgs, 0.90 mmol) in 2,2-dimethylbutane (6 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (17 mgs, 0.01mmol) and Benzyl-methyl-carbamic acid *tert*-butyl ester **(5e)**[6] (100 mgs, 0.45 mmol) in 2,2-dimethylbutane (5 mL). After the addition, the resulting solution was stirred at 23° C for 30 min. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (10 mL) and TFA (0.2 mL, 2.26 mmol) and stirred for 16 h at 23° C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (20 mL), extracted with 10% HCl (3 x 15 mL). The combined aqueous layers

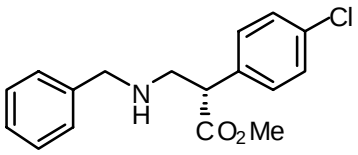
were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (1 x 15 mL), brine (1 x 20 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 25:35:2) to give the title compound (85 mgs, 0.30 mmol, 66% yield). $[\alpha]^{25}_D$ = -57.14^o (c 0.84, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 5 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 3.81 – 3.78 (m, 3 H), 3.64 (s, 3 H), 3.28 (dd, *J* = 9.0, 12.5 Hz, 1 H), 2.91 (dd, *J* = 7.0, 12.5 Hz, 1 H), 2.31 (s, 3 H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) δ 173.7 (C), 140.0 (C), 137.1 (C), 134.1 (C), 129.4 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 126.9 (CH), 53.6 (CH), 51.9 (CH_3), 51.8 (CH_2), 51.5 (CH_2), 20.9 (CH_3); IR (neat): 3332, 3024, 2952, 2836, 1734, 1459, 1163 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{21}NO_2$ 238.1572, Found 238.1567. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **10d**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 5:95) gave the amide in 95% ee (HPLC, Chiralcel-AD-RH column, 5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 4.20 (major) and 8.05 (minor) min, UV 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 3 H), 7.14 (m, 6 H), 4.63 (m, 1 H), 4.21 – 4.06 (m, 2 H), 3.85 (m, 1 H), 3.66 (s, 3 H), 3.51 (dd, *J* = 7.5, 13.8 Hz, 1 H), 2.34 (s, 3 H); IR (neat): 3030, 2953, 1735, 1692, 1448, 1206, 1161 cm^{-1}; EI-MS *m/z* (relative intensity) 379 (M^+, 1%), 347.



3-Benzylamino-2-naphthalen-2-yl-propionic acid methyl ester (10e):

Methyl 2-naphthyldiazoacetate **(9e)** (204 mgs, 0.90 mmol) in 2,2-dimethylbutane/toluene (4:1) (7.5 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (17 mgs, 0.01mmol) and Benzyl-methyl-carbamic acid *tert*-butyl ester **(5e)**[6] (100 mgs, 0.45 mmol) in 2,2-dimethylbutane (5 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (10 mL) and TFA (0.2 mL, 2.26 mmol) and stirred for 16 h at 23^o C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (20 mL), extracted with 10% HCl (3 x 15 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (1 x 15 mL), brine (1 x 20 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 15:85:2) to give the title compound (79 mgs, 0.25 mmol, 55% yield). $[\alpha]^{25}_D$ = -57.14^o (c 0.80, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.78 (m, 3 H), 7.73 (s, 1 H), 7.47 – 7.40 (m, 3 H), 7.30 – 7.22 (m, 5 H), 4.01 – 3.99 (dd, *J* = 7.0, 7.5 Hz, 1 H), 3.81 (m, 2 H), 3.66 (s, 3 H), 3.39 – 3.35 (dd, *J* = 8.5, 12.5 Hz, 1 H), 3.04 – 3.00 (dd, *J* = 7.0, 12.5 Hz, 1H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) δ 173.5 (C), 139.9 (C), 134.5 (C), 133.3 (C), 132.7 (C), 128.3 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 127.0 (CH), 126.9 (CH), 126.3 (CH), 125.9 (CH), 125.8 (CH), 53.6 (CH_2), 52.1 (CH),

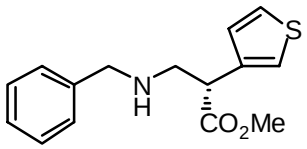
52.0 (CH_3), 51.8 (CH_2); IR (neat): 3329, 3054, 3025, 2947, 2839, 1731, 1449, 1166 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{12}H_{21}NO_2$ 319.1572, Found 319.1579. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **10e**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 20:80) gave the amide in 87% ee (HPLC, Chiralcel-AD-RH column, 10.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 3.40 (major) and 4.70 (minor) min, UV 254 nm); ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 3 H), 7.69 (s, 1 H), 7.52 – 7.49 (m, 2 H), 7.38 – 7.30 (m, 4 H), 7.12 – 7.08 (m, 2 H), 4.60 (m, 1 H), 4.41 – 4.38 (t, *J* = 8.0 Hz, 1 H), 4.09 – 4.05 (m, 1 H), 3.96 – 3.92 (dd, *J* = 7.5, 13.5 Hz, 1 H), 3.69 (s, 3 H), 3.62 – 3.58 (dd, *J* = 7.5, 14.0 Hz, 1 H); IR (neat): 3032, 2957, 1734, 1690, 1204, 1157 cm^{-1}; EI-MS *m/z* (relative intensity) 415 (M^+, 1%), 348.



3-Benzylamino-2*S*-(4-chloro-phenyl)-propionic acid methyl ester (10f):

Methyl 4-chlorophenyldiazoacetate **(9f)** (190 mgs, 0.90 mmol) in 2,2-dimethylbutane (6 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (17 mgs, 0.01mmol) and Benzyl-methyl-carbamic acid *tert*-butyl ester **(5e)**[6] (100 mgs, 0.45 mmol) in 2,2-dimethylbutane (5 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (10 mL) and TFA (0.2 mL, 2.26 mmol) and stirred for 16 h

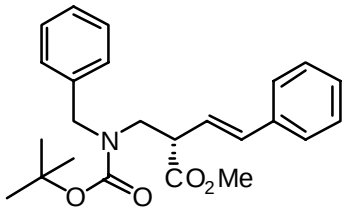
at 23^{o} C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (20 mL), extracted with 10% HCl (3 x 15 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (1 x 20 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 25:35:2) to give the title compound (85 mgs, 0.28 mmol, 62% yield). $[\alpha]^{25}_{D}$ = -52.43^{o} (c 0.82, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.20 (m, 9 H), 3.78 (m, 3 H), 3.66 (s, 3 H), 3.26 – 3.22 (dd, *J* = 9.0, 12.0 Hz, 1 H), 2.91 – 2.87 (dd, *J* = 7.0, 12.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1 (C), 139.8 (C), 135.6 (C), 133.3 (C), 129.3 (CH), 128.8 (CH), 128.3 (CH), 127.9 (CH), 126.9 (CH), 53.5 (CH_2), 52.0 (CH_2), 51.7 (CH_2), 51.3 (CH); IR (neat): 3336, 3060, 3027, 2948, 2839, 1734, 1491, 1165 cm^{-1}; HRMS (EI) [M^{+}-2H] calcd for $C_{17}H_{16}NClO_2$ 301.0869, Found 301.0879. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **10f**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 20:80) gave the amide in 96% ee (HPLC, Chiralcel-AD-RH column, 5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 4.77 (major) and 8.05 (minor) min, UV 254 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 5 H), 7.18 (d, *J* = 10.5 Hz, 2 H), 7.11 (d, *J* = 8.5 Hz, 2 H), 4.61 – 4.57 (m, 1 H), 4.23 – 4.17 (m, 1 H), 3.81 – 3.76 (dd, *J* = 10.0, 17.0 Hz, 1 H), 3.67 (s, 3 H), 3.52 – 3.47 (dd, *J* = 9.0, 17.5 Hz, 1 H); IR (neat): 3030, 2956, 1735, 1691, 1492, 1447, 1206 cm^{-1}; EI-MS *m/z* (relative intensity) 399 (M^{+}, 1%), 340.



3-Benzylamino-2*S*-thiophen-3-yl-propionic acid methyl ester (10g):

Methyl thiophen-3-yldiazoacetate **(9g)** (165 mgs, 0.90 mmol) in 2,2-dimethylbutane (8 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (17 mgs, 0.01mmol) and Benzyl-methyl-carbamic acid *tert*-butyl ester **(5e)**[6] (100 mgs, 0.45 mmol) in 2,2-dimethylbutane (5 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue was reconstituted in CH_2Cl_2 (10 mL) and TFA (0.2 mL, 2.26 mmol) and stirred for 16 h at 23^o C. The solution was concentrated in *vacuo*, and the residue was dissolved in Et_2O (20 mL), extracted with 10% HCl (5 x 15 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (1 x 15 mL), brine (1 x 20 mL) and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/Pentane/NEt_3= 25:35:2) to give the title compound (68 mgs, 0.26 mmol, 58% yield). $[\alpha]^{25}_D$ = -12.44^o (c 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 6 H), 7.16 (m, 1 H), 7.04 (d, *J* = 5.0 Hz, 1 H), 4.00 – 3.97 (dd, *J* = 7.0, 8.5 Hz, 1 H), 3.80 (s, 2 H), 3.69 (s, 3 H), 3.26 – 3.22 (dd, *J* = 8.5, 12.0 Hz, 1 H), 2.96 – 2.92 (dd, *J* = 6.5, 11.5 Hz, 1 H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) δ 173.3 (C), 139.7 (C), 137.1 (C), 128.4 (CH), 128.0 (CH), 127.1 (CH), 127.0 (CH), 125.9 (CH), 122.4 (CH), 53.4 (CH_2), 52.1 (CH_3), 51.5 (CH_2), 47.3 (CH); IR (neat): 3101, 2947, 2847, 1732, 1443, 1196, 1165 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{17}NSO_2$ 275.0980, Found 275.0958. To measure the

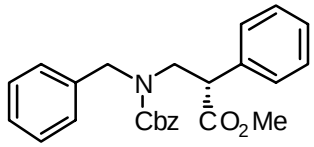
enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **10g**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 20:80) gave the amide in 90% ee (HPLC, Chiralcel-AD-RH column, 5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 5.08 (major) and 8.09 (minor) min, UV 254 nm); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 4 H), 7.16 – 7.11 (m, 3 H), 7.02 (d, *J* = 5.0 Hz, 1 H), 4.69 – 4.57 (m, 1 H), 4.37 (t, *J* = 7.5 Hz, 1 H), 4.16 (m, 1 H), 3.83 – 3.78 (dd, *J* = 7.5, 13.5 Hz, 1 H), 3.70 (s, 3 H), 3.53 – 3.49 (dd, *J* = 7.5, 14.0 Hz, 1 H); IR (neat): 2959, 2919, 1735, 1690, 1451, 1211, 1162 cm^{-1}; EI-MS *m/z* (relative intensity) 371 (M^+, 2%), 276.



2-[(Benzyl-*tert*-butoxycarbonyl-amino)-methyl]-4-phenyl-but-3-enoic acid methyl ester (10h):

2-diazo-4-phenyl-3-butenoate **(9h)** (183 mgs, 0.90 mmol) in 2,2-dimethylbutane (8 mL) was added dropwise over 3 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (17 mgs, 0.01mmol) and Benzyl-methyl-carbamic acid *tert*-butyl ester **(5e)**[6] (100 mgs, 0.45 mmol) in 2,2-dimethylbutane (6 mL). After the addition, the resulting solution was stirred at 23^o C for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, Et_2O/Pentane= 10:90) to give the title compound (98 mgs, 0.25 mmol, 56% yield) in 96% ee (HPLC, Whelk column, 5.0% 2-

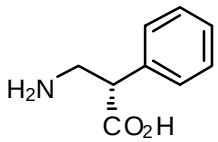
propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 12.33 (major) and 16.21 (minor) min, UV 254 nm);. $[\alpha]^{25}_D$ = -88.27^o (c 2.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 10 H), 6.47 (m, 1 H), 6.19 – 6.10 (m, 1 H), 4.57 – 4.37 (m, 2 H), 3.68 (s, 3 H), 3.56 (m, 2H), 1.49 (s, 9 H); IR (neat): 3027, 2975, 1735, 1694, 1365, 1163 cm^{-1}; Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 73.30; H, 7.37; N, 3.44.



3-(Benzyl-benzyloxycarbonyl-amino)-2*S*-phenyl-propionic acid methyl ester (11):

Methyl phenyldiazoacetate **(9a)** (703 mgs, 4.0 mmol) in 2,2-dimethylbutane (15 mL) was added dropwise over 4 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (66 mgs, 0.008 mmol) and Benzyl-methyl-carbamic acid *tert*-butyl ester **(8a)**[6] (600 mgs, 2.35 mmol) in 2,2-dimethylbutane (25 mL). After the addition, the resulting solution was stirred at 23^o C for 8 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, Et_2O/Pentane= 10:90) to give the title compound X (725 mgs, 1.80 mmol, 77% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.07 (m, 15 H), 5.18 (m, 2 H), 4.43 - 4.21 (m, 3 H), 3.82 (m, 1 H), 3.62 – 3.54 (m, 4 H). To a solution of **11** (155 mgs, 0.38 mmol) in acetic acid (1 mL) at 0 ^{o}C under Ar was added 30% HBr in acetic acid (2.5 mL). After 4h at 0 ^{o}C, reaction mixture was diluted with Et_2O (50 mL) and extracted with 10% HCl (2 x 25 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 20 mL). The combined EtOAc layers were washed with brine (1 x 30 mL) and dried

(Na_2SO_4). The solvent was removed under reduced pressure to give the amine **10a** (100 mgs, 0.37 mmol, 97% yield), which required no further purification. To measure the enantiomeric excess of the above compound, it was converted to its trifluoroacetamide. Trifluoroacetamide of **10a**: Acylation of a small sample of the free amine from above with TFAA and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 20:80) gave the amide in 93% ee (HPLC, Chiralcel-AD-RH column, 5.0% 2-propanol in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 4.15 (major) and 8.00 (minor) min, UV 254 nm).

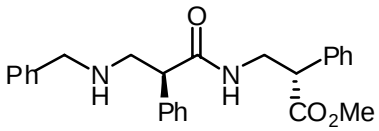


3-Amino-2*S*-phenyl-propionic acid (12):

To a solution of **11** (200 mgs, 0.49 mmol) in THF/H_2O (4:1) (7.5 mL) at 23 ^oC was added LiOH•H_2O (63 mgs, 1.5 mmol). After 6h at 23 ^oC, reaction mixture was acidify to pH = 2 with 0.5M HCl (approximately 20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined CH_2Cl_2 layers were washed with brine (1 x 30 mL) and dried over Na_2SO_4. The evaporation of the solvent gave the crude acid that was used without further purification for the next step.

To a solution of crude acid in methanol (8 mL) was added 10% palladium in carbon (30 mgs) and ammonium formate (378 mgs). The resulting mixture was heated to 70 ^oC. After 2 h at 70 ^oC, the resulting mixture was cooled to 23 ^oC, filtered through the celite using methanol washes and the filtrate was concentrated. Recrystallization from ethanol/water gave the title compound **12** as white crystals (54 mgs, 0.33 mmol, 66% yield). $[\alpha]^{25}_D$ = -86.15^o (c 0.13, H_2O) [lit.[7] $[\alpha]^{30}_D$ = +94^o (c 0.2, H_2O), lit.[8] +85^o (c 0.2,

H_2O); ^1H NMR (500 MHz, D_2O) δ 7.35 – 7.19 (m, 5 H), 3.66 (t, *J* = 7.5 Hz, 1 H), 3.36 – 3.31 (dd, *J* = 7.5, 13.0 Hz, 1 H), 3.17 – 3.13 (dd, *J* = 7.0, 12.5 Hz, 1 H).



3-(3-Benzylamino-2*S*-phenyl-propionylamino)-2*S*-phenyl-propionic acid methyl ester (15):

To a solution of **11** (367 mgs, 0.91 mmol) in acetic acid (3 mL) at 0 ^oC under Ar was added 30% HBr in acetic acid (5 mL). After 4h at 0 ^oC, reaction mixture was diluted with Et_2O (100 mL) and extracted with 10% HCl (3 x 25 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8-9) and extracted with EtOAc (3 x 30 mL). The combined EtOAc layers were washed with brine (1 x 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give the amine in quantitative yield that was used without further purification for the next step.

Hydrogenation of above crude in ethanol (12 mL) and 10% palladium in carbon (94 mgs) under 1 atm pressure (H_2, balloon) for 16 h, followed by filtration through the celite and the removal of solvent under reduced pressure gave primary amine **14** which was used further without purification.

To a solution of **11** (390 mgs, 0.96 mmol) in THF/H_2O (4:1) (12 mL) at 23 ^oC was added LiOH•H_2O (122 mgs, 2.9 mmol). After 7h at 23 ^oC, the reaction mixture was acidify to pH = 2 with 0.5M HCl (approximately 35 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined CH_2Cl_2 were washed with brine (1 x 30 mL) and dried over Na_2SO_4. The

evaporation of the solvent gave the crude acid that was used without further purification for the next step.

To a solution of acid **13** in CH_2Cl_2 (20 mL) at 0 ^oC was added amine **14** in CH_2Cl_2 (8 mL) and HOBt (137 mgs, 1.01 mmol). After 5 min at 0 ^oC, EDC (194 mgs, 1.01 mmol) was added and the solution was slowly warmed to 23 ^oC and stirred. After 20 h, the reaction mixture was diluted with CH_2Cl_2 and washed with 0.1N citric acid (25 mL), saturated $NaHCO_3$ (25 mL), brine (25 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was reconstituted in acetic acid (10 mL) and at 0 ^oC under Ar was added 30% HBr in acetic acid (2.5 mL). After 3 h at 23 ^oC, reaction mixture was diluted with EtOAc (30 mL) and washed with ice cold 10% NaOH (2 x 25 mL). The combined aqueous layers were basified to pH 8-9 with 10% NaOH and extracted with EtOAc (2 x 20 mL). The combined EtOAc layers were washed with brine (1 x 30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, Et_2O/Pentane/Et_3N= 20:40:4) to give the title compound (230 mgs, 0.55 mmol, 67% yield). $[\alpha]^{25}_D$ = -68.06^o (c 2.48, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.15 (m, 15 H), 3.91 (t, *J* = 7.5 Hz, 1 H), 3.71 (s, 2 H), 3.66 (m, 2 H), 3.58 – 3.56 (m, 1 H), 5.52 (s, 3 H), 3.22 (dd, *J* = 7.5, 12.0 Hz, 1 H), 2.87 – 2.84 (dd, *J* = 5.0, 12.5 Hz, 1 H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$) δ 173.0(C), 172.8 (C), 139.7 (C), 138.2 (C), 136.1 (C), 128.7 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 126.9 (CH), 53.7 (CH_2), 52.5 (CH), 51.9 (CH_3), 51.7 (CH_2), 50.6 (CH), 42.0 (CH_2); IR (neat): 3306, 3061, 3029, 2946, 2842, 1733, 1654, 1542, 1201, 1171 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{26}H_{28}N_2O_3$ 416.2099, Found 416.2080.

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