Methyl 1-(diphenylphosphino)-2-naphthoate

To a solution of 2.86 g (10.8 mmol) of methyl 1-bromo-2-naphthoate and 58 mg (0.15 mmol) of $(PhCN)_2PdCl_2$ in 16 mL of toluene was added 3.1 mL (16.5 mmol) of trimethylsilyldiphenylphosphine. The dark purple solution was heated at 120°C for 48 h. The reaction mixture was diluted with 60 mL of chloroform and the organic layer was washed with saturated $NaHCO_3$ (1 x 30 mL), water (1 x 20 mL) and brine (1 x 20 mL) and was dried over $MgSO_4$. After removing the solvent *in vacuo*, the residue was mixed with silica gel and chromatographied on silica gel (ethyl acetate). After removing most of the solvent, dark yellow crystals were obtained and the brown residue was mixed with about double the amount of silica gel and chromatographied on 30 g of silica gel with hexanes/ethyl acetate (4:1) to give 2.67 g (66%) of yellow crystals, mp. 155-156°C, R_f 0.29 (10% ethyl acetate/hexanes). IR ($CDCl_3$): 1726, 1482, 1462, 1434, 1368, 1317 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): 8.19 (dd, J = 8.7, 2.9 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.62 (dd, J = 8.4, 2.3 Hz, 1H), 7.42 (m, 5H), 7.27 (m, 7H), 3.62 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, C-P coupling not removed): δ 170.25, 170.19, 140.87, 140.34, 135.82, 135.01, 134.87, 134.48, 132.66, 132.29, 132.19, 131.68, 131.35, 128.72, 128.46, 128.35, 128.12, 126.96, 126.68, 124.79, 124.64, 52.01. HRMS: Calcd for $C_{24}H_{19}O_2P$-CH_3: 355.0888. Found: 355.0880.

1-(diphenylphosphino)-2-naphthoic acid

A solution of methyl 1-(diphenylphosphino)-2-naphthoate (0.572 g, 1.54 mmol) and lithium hydroxide (0.113 g, 2.69 mmol) in a mixture of absolute ethanol (6 mL) and water (2 mL) was heated at 82°C for 7 h and then allowed to cool to room temperature.

Aqueous hydrochloric acid (20 mL, 1N) was added and the mixture was extracted with dichloromethane (2x20 mL). The organic layer was washed with saturated aqueous sodium chloride (15 mL) and dried over sodium sulfate. Removal of solvent *in vacuo* afforded 0.554 g (quant.) of the acid as a solid, mp 169-172° (dec), R_f 0.19 (30% ethyl acetate/hexanes). IR ($CDCl_3$): 3100 (b), 1698, 1652, 1481, 1464, 1436, 1354, 1312, 766, 745, 732, 696 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.81 (s, 1H), 8.0-8.3 (m, 6H), 9.09 (d, J = 8.6 Hz, 1H), 7.71 (m, 2H), 7.42 (m, 6H), 7.26 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$, all C-P coupling are not removed): δ 166.78 (d, J = 4.8 Hz), 138.24, 138.01, 136.54, 136.31, 135.86, 135.79, 135.27, 134.99, 134.77, 133.58, 132.36, 132.30, 131.89, 131.48, 130.66, 130.04, 129.19, 129.01, 128.87, 128.54, 128.39, 128.13, 127.83, 126.64, 124.67, 123.68, 124.54, 122.72. HRMS: Calcd for $C_{23}H_{17}O_2P$: 356.0967. Found: 356.0957.

(1R,2R)-Diamino-(1N,2N)-bis(1'-(diphenylphosphino)-2-naphthoyl)cyclohexane (16)

A solution of 26 mg (0.23 mmol) of (1R,2R)-diaminocyclohexane, 200 mg (0.55 mmol) of 1-(diphenylphosphino)-2-naphthoic acid and 6 mg (0.05 mmol) DMAP in 1.5 mL of methylene chloride was cooled to –25° C (precipitation) and 106 mg (0.51 mmol) of DCC were added. The solution was allowed to warm to room temperature and stirred for 19 h. The urea was filtered through a celite pad and the filter cake was washed with 20 mL of methylene dichloride. The organic phase was washed with 1N aqueous hydrochloric acid (1x5 mL), water (1x5 mL) and brine (1x5 mL) and was dried over magnesium sulfate. The solvent was removed in the presence of 0.5 g of silica gel and the residue was chromatographied on 15 g of silica gel eluting with 120 mL hexanes/ethyl acetate (3:1) and 240 mL hexanes/ethyl acetate (2:1) to afford the ligand as a yellow glass (153 mg, 85%), [α] = -81.9° (c = 0.4, CH_2Cl_2, R_f = 0.42 (1:1 hexanes/ethyl

acetate). IR (C_6D_6): 3398, 3304, 1659, 1585, 1515, 1503, 1481, 1434 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ 8.14 (d, J = 8.7 Hz, 2H), 7.78 (d, d, J = 8.4, 3.4 Hz, 2H), 7.64 (m, 4H), 7.45 (m, 6H), 7.37 (d, J = 8.4 Hz, 2H), 7.02 (t, J = 8.0 Hz, 2H), 6.89 (m, 14H), 6.73 (d, J = 7.1 Hz, 2H), 4.02 (m, 2H), 2.09 (m, 2H), 1.36 (m, 4H), 1.03 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6): 171.2 (d, J = 6.7 Hz), 148.4 (d, J = 41.5 Hz), 138.1 (d, J = 16.4 Hz), 137.2 (d, J = 15.5 Hz), 135.3, 135.2 (d, J = 21.8 Hz), 132.5 (d, J = 21.8 Hz), 132.4, 131.0 (d, J = 26.3 Hz), 130.1 (br), 129.8, 129.00 (d, J = 10.5 Hz), 128.99, 128.2, 126.7 (d, J = 11.8 Hz), 125.3 (d, J = 10.6 Hz), 54.5, 32.1, 25.1. HRMS: Calcd for $C_{52}H_{44}N_2O_2P_2$: 790.2878. Found: 790.2872.

Preparation of 3-carbomethoxy-2-naphthyl trifluoromethanesulfonate

A solution of 31.1 g (110.3 mmol) of trifluoromethanesulfonyl anhydride in 58 mL of dichloromethane was added over 1 h to a solution of 18.5 g (91.5 mmol) of methyl 3-hydroxy-2-naphthoate in 18.6 mL of pyridine and 106 mL of dichloromethane at –78°C. The reaction was warmed to 0°C and then stirred for 14 h during which it warmed to room temperature. The reaction was diluted with 600 mL of diethyl ether and filtered through a sintered glass funnel to remove the pyridinium trifluoromethanesulfonate. The organic phase was washed with 2x100 mL of 2 N aqueous hydrochloric acid, 2x100 mL of water, and 1x150 mL of saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes) to give 35.5 g of a white solid which was recrystallized from 50 mL of ethanol to give 23.74 g (78%) of the product as yellow white plates, mp 59-60°C, R_f 0.48 (4:1 hexanes/ethyl acetate). IR ($CDCl_3$): 1730, 1634, 1602, 1428, 1337 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.68 (s, 1H),

8.01 (d, J = 8.0, 1H), 7.91 (d, J = 8.0, 1H), 7.76 (s, 1H), 7.68 (m, 2H), 4.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 145.0, 135.1, 135.0, 131.5, 129.9, 129.2, 128.2, 127.8, 122.1, 121.1, 118.8 (t, J = 322 Hz), 52.5. HRMS: Calcd for $C_{13}H_9O_5F_3S$: 334.0123. Found: 334.0134.

Preparation of methyl 3-diphenylphosphino-2-naphthoate

A solution of 5.1 g (15.2 mmol) of 3-carbomethoxy-2-naphthyl trifluoromethanesulfonate, 146 mg (0.38 mmol) of bis(benzonitrile)palladium dichloride and 6.67 g (26 mmol) of trimethylsilyldiphenylphosphine (added in that order) in 38 mL of toluene was heated at reflux for 26 h. After cooling to room temperature, the reaction was diluted with 100 mL of chloroform. The organic phase was washed with 1x50 mL of saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The product was absorbed onto 10 g of silica gel and purified by flash chromatography on silica gel (5 cm x 12 cm, 10% ethyl aceate in hexanes) to give 3.08 g (55%) of the phosphine which can be recrystallized from methylene chloride to give pale yellow crystals. IR (neat from $CDCl_3$): 3051, 1714, 1433, 1284, 1241, 1223, 1106, 1008, 746, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.94-7.91 (m, 1H), 7.58-7.50 (m, 4H), 7.38-7.30 (m, 11H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6 (d, J = 2.7 Hz), 138.2 (d, J = 11.2 Hz), 135.9 (d, J = 26.2 Hz), 135.1, 134.6, 134.1 (d, J = 21.0 Hz), 132.13 (br), 131.0 (d, J = 18.9 Hz), 128.8, 128.7, 128.6 (d, J = 7.2 Hz), 128.5, 128.0, 127.3, 51.9. Anal Calcd for $C_{24}H_{19}O_2P$: C, 77.83; H, 5.17; P, 8.36; MW, 370.1123. Found: C, 77.73; H, 5.33; P, 8.08; MW, 370.1121.

Preparation of 3-diphenylphosphino-2-naphthoic acid

A solution of 1.56 g (4.2 mmol) of methyl 3-diphenylphosphino-2-naphthoate and 0.31 g (7.4 mmol) of lithium hydroxide in 5 mL of water and 16 mL of ethanol was heated at reflux for 16 h. After cooling to room temperature, the reaction was diluted with 50 mL of 1 N hydrochloric acid. The aqueous phase was extracted with 3x40 mL of dichloromethane. The combined organic phases were concentrated *in vacuo* to give 1.40 g (94%) of the acid as a yellow white solid which was used without further purification, mp 230°C (dec.). ^{1}H NMR (300 MHz, DMSO-d6): δ 8.67 (d, J = 3.8 Hz, 1H), 8.11 (m, 1H), 7.62-7.55 (m, 3H), 7.38 (m, 6H), 7.25-7.19 (m, 5H). ^{13}C NMR (75 MHz, CF_3COOD): 174.0, 144.6 (d, J = 11.4 Hz), 139.75 (d, J = 7.9 Hz), 138.0 (d, J = 2.9 Hz), 137.5 (d, J = 2.5 Hz), 137.0 (d, J = 15.6 Hz), 135.5 (d, J = 11.4 Hz), 134.67, 134.56, 133.0 (d, J = 13.8 Hz), 132.3, 131.5, 127.2 (d, J = 5.3 Hz), 119.2 (d, J = 92.5 Hz), 113.0 (d, J = 91.6 Hz). HRMS: Calcd for $C_{23}H_{17}O_2P$: 356.0966. Found: 356.0982.

(-)-1*R*,2*R*-diamino-1*N*,2*N*-bis(3'-diphenylphosphino-2'-naphthoyl)cyclohexane (18)

To a solution of 1.07 g (3.0 mmol) of 3-diphenylphosphino-2-naphthoic acid in 15 mL of dichloromethane at 0°C was added 1.01 g (10.0 mmol) of triethylamine followed by 0.89 g (3.3 mmol) of diphenylchlorophosphate over 2-3 min. After warming to room temperature over 3 h, the mixture was transferred via cannula to a solution of 171 mg (1.5 mmol) of (1*R*,2*R*)-diaminocyclohexane in 15 mL of dichloromethane and stirred at 25°C for 16 h. The reaction mixture was then diluted with 30 mL of dichloromethane, washed with 1x30 mL of saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (30% ethyl acetate in hexanes) to give 0.60 g (51%) of a yellow foam which was

crystallized from 5 mL of 1:1 chloroform:hexanes as a white powder, mp 154-158°C, $[\alpha]_D$ = -53.9° (c 2.14, CH_2Cl_2), R_f 0.61 (50% ethyl acetate in hexanes). IR (solution, $CDCl_3$): 3426, 1651, 1626, 1519, 1435, 1324 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.1 (d, J = 3.8 Hz, 2H), 7.6 (m, 2H), 7.5 (m, 2H), 7.4 (m, 4H), 7.2-7.3 (m, 22H), 6.6 (d, J = 7.1 Hz, 2H), 3.9 (m, 2H), 1.9 (m, 2H), 1.6-1.7 (m, 2H), 1.25 (m, 2H), 1.1 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 137.7, 134.9, 134.0 (d, J = 18.8 Hz), 133.7 (d, J = 9.8 Hz), 133.5 (d, J = 11.7 Hz), 132.4, 128.7, 128.5 (d, J = 6.9 Hz), 128.4 (d, J = 6.5 Hz), 128.3, 127.8, 127.5 (d, J = 4.8 Hz), 127.4, 127.1, 54.0, 32.0, 24.7. Anal. Calcd for $C_{52}H_{44}N_2O_2P_2$: C, 78.97; H, 5.61; N, 3.54; P, 7.83. Found: C, 78.77; H, 5.80; N, 3.40; P, 7.57.

Preparation of (*S*)-2-phthalimido-3-butenyl (*S*)-*O*-methylmandelate (14)

A solution of 10.9 mg (0.05 mmol) of (*S*)-2-phthalimido-3-buten-1-ol, 10.1 mg (0.06 mmol) of (*S*)-*O*-methylmandelic acid, 14.4 mg (0.07 mmol) of DCC and 0.5 mg (0.005 mmol) of DMAP in 0.5 mL of dichloromethane was stirred at 25°C for 12 h, filtered through cotton, and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (40% diethyl ether in pentane) to give 18.0 mg (98%) of the ester as a clear oil in 98% de as determined by HPLC analysis (Dynamax, 8 μ SiO_2, 60 Å pore size, 4.6 mm x 250 mm, 15% ethyl acetate in hexane, 1.0 mL/min, λ = 254 nm), $[\alpha]_D$ = +4.2° (c 1.80, CH_2Cl_2), R_f 0.62 (30% ethyl acetate in hexanes). IR (film): 3064, 3032, 2990, 2933, 2830, 1756, 1714, 1468, 1455, 1385, 1256, 1174, 1113, 1013 cm^{-1}. ^1H NMR (330 MHz, $CDCl_3$): δ 7.8-7.7 (m, 4H), 7.2 (m, 2H), 7.0 (m, 3H), 6.15-6.0 (m, 1H), 5.3 (m, 2H), 5.0 (m, 1H), 4.7 (m, 2H), 4.4 (dd, J = 11.0, 5.3 Hz, 1H), 3.3 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 167.4, 135.8, 133.9, 131.6, 130.8, 128.4, 128.2, 126.8, 123.3,

120.1, 82.1, 63.1, 57.3, 52.1. Anal. Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.88; H, 5.41; N 3.98.

Preparation of *N*-(benxyloxycarbonyl)-(*S*)-2-amino-3-buten-1-ol (20)

A solution of 35.7 mg (0.16 mmol) of (*S*)-2-phthalimido-3-buten-1-ol (98% de) and 16 mg (0.32 mmol) of hydrazine in 1 mL of ethanol was heated at reflux for 2 h. Then, 3 mL of 6 N aqueous hydrochloric acid was added and the reaction heated at reflux for 1 h. After cooling to 0°C, the mixture was filtered through glass wool to remove the phthalhydrazide and concentrated *in vacuo* to give the amine hydrochloride salt **19** as a white solid which was directly derivatized.

To the crude amine hydrochloride salt in 0.5 mL of dichloromethane at 0°C was added 49 mg (0.48 mmol) of triethylamine and 34.1 mg (0.20 mmol) of benzyl chloroformate. The reaction was stirred at 0°C for 1 h. The reaction mixture was directly purified by flash chromatography on silica gel (75% diethyl ether in pentane) to give 22.2 mg (62% for 2 steps) of the (*S*)-carbamate **20** as a clear oil, $[\alpha]_D$ = -32.2° (c 1.47, $CHCl_3$), (lit.[7d] $[\alpha]_D$ = -32.1° (c 3.1, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H), 5.8 (ddd, J = 15.9, 10.6, 5.4 Hz, 1H), 5.3 (m, 2H), 5.15 (bd, 9.5 Hz, 1H), 5.1 (s, 2H), 4.3 (m, 2H), 3.7 (m, 2H).

Preparation of 4-iodo-3-phthalimido-2-butene (22)

To a solution of 0.23 g (1.05 mmol) of 2-phthalimido-3-butene-1-ol in 1 mL of acetonitrile and 1.5 mL of diethyl ether at 0°C was added 93 mg (1.37 mmol) of imidazole, 317 mg (1.21 mmol) of triphenylphosphine, and 373 mg (1.47 mmol) of iodine sequentially. The reaction was allowed to warm to room temperature and stirred for 5 h. The reaction mixture was diluted with 10 mL of water and extracted with 3x20

mL of dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (20% ethyl acetate in hexanes) to give 293 mg (85%) of the iodide as a white solid, mp 72-73°C, R_f 0.77 (30% ethyl acetate in hexanes). IR ($CDCl_3$): 1714, 1470, 1384, 1111, 1075 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.9 (m, 2H), 7.75 (m, 2H), 6.2 (ddd, J = 17.2, 9.5, 7.0 Hz, 1H), 5.3 (m, 1H), 5.0 (m, 1H), 4.0 (t, J = 10.2 Hz, 1H), 3.5 (dd, J = 10.2, 5.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 134.1, 132.9, 131.5, 123.4, 119.5, 55.6, 4.8. HRMS: Calcd for $C_{12}H_{10}NO_2I$: 326.9756. Found: 326.9749.

S-2-Amino-1-butanol (32)

(S)-2-*N*-phthalimidoyl-3-buten-1-ol (0.217 g, 1 mmol) in 1 ml of absolute ethanol was added, under hydrogen (1 atm, balloon) to a suspension of 10% palladium on carbon in 1 mL of absolute ethanol. The resulting mixture was stirred at room temperature, under hydrogen (1 atm, balloon) for 16 h, before being purged with nitrogen, and filtered over celite. The filtrate was evaporated *in vacuo* to give 0.21 g (96%) of (S)-2-*N*-phthalimidoyl-1-butanol (**31**) which was used directly in the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (m, 2H), 7.73 (m, 2H), 4.28 (m, 2H), 4.06 (ddd, J = 11.8, 8.7, 7.4 Hz, 1H), 3.88 (dt, J = 11.8, 3.3 Hz, 1H), 2.76 (bdd, J = 8.8, 3.3 Hz, 1H), 1.89 (m, 2H), 0.93 (t, J = 7.5 Hz. 3H).

Ethylenediamine (130 μL, 1.94 mmol) was added to a solution of (S)-2-*N*-phthalimidoyl-1-butanol (0.21 g, 0.958 mmol) in 5 mL of absolute ethanol. The resulting mixture was stirred at reflux for 18 h before being cooled to 0°C, and filtered through celite. The filtrate was evaporated *in vacuo* to give a residue that was applied onto a DOWEX-50-W (H^+) column (1x5 cm). The column was first flushed with water (50 mL),

and then eluted with a 0.6 M solution of ammonium hydroxide (60 mL, 1 mL fractions). The pure fractions were combined and evaporated *in vacuo* to give 78.6 mg (92% yield) of (S)-2-amino-1-butanol (**32**) whose spectra were identical to an authentic sample.

2-(S)-*N*-Acetamido-3-buten-1-yl acetate (29)

A mixture of **12** (250 mg, 1.15 mmol) and ethylenediamine (150 μL, 2.24 mmol) in 5 mL of absolute ethanol was stirred at reflux for 14 h. The white precipitate was filtered and the filtrate was evaporated *in vacuo*. The residue was taken up in 2 mL of a 1/1 mixture of pyridine and acetic anyhydride. After stirring at room temperature for 12 h, 1 mL of methanol was added and the resulting mixture was evaporated *in vacuo* and then coevaporated three times with toluene. The residue was purified by flash chromatography (gradient ethyl acetate/hexanes 6/4 to 7/3) to give 157 mg (77% yield) of **29** as a white solid which could be recrystallized in diisopropyl ether, mp =72-73°C, $[\alpha]_D^{27}$ = -55 (c 1.19, CH_2Cl_2). IR (KBr): 3290, 1742, 1670, 1286 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (ddd, J = 17.3, 10.4, 5.2 Hz, 1H), 5.69 (m, 1H), 5.24 (bd, J = 17.3 Hz, 1H), 5.22 (bd, J = 10.4 Hz, 1H), 4.79 (m, 1H), 4.23 (dd, J = 11.3, 5.9 Hz, 1H), 4.09 (dd, J = 11.3, 4.3 Hz, 1H), 2.07 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.17, 169.74, 134.28, 116.93, 65.37, 50.39, 23.14, 20.62. HRMS: Cacld for $C_8H_{13}NO_3$: 171.0895. Found: 171.0894.

Methyl 2-(R)-2-*N*-acetamido-3-hydroxy-propanoate (30)

To a solution of **29** (51.4 mg, 0.3 mmol) in 5 mL of a 4/1 mixture of methylene chloride and methanol was added 400 μL of a 2.5 M methanolic solution of sodium hydroxide. Ozone was bubbled through the reaction mixture, at –78°C, for 30 min. The white precipitate was filtered off and the filtrate was evaporated *in vacuo*. The residue

was purified by flash chromatograph (pure ethyl acetate) to give 29.6 mg (61% yield) of **30** as a colorless oil, $[\alpha]_D^{30}$ = -18 (c 3.02, CH_2Cl_2). IR (neat): 3390, 1742, 1285, 1239 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.57 (m, 1H), 4.67 (ddd, J = 7.4, 3.8, 3.4 Hz, 1H), 3.98 (dd, J = 11.2, 3.8 Hz, 1H), 3.91 (dd, J = 11.2, 3.4 Hz, 1H), 3.79 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.16, 170.83, 63.35, 54.67, 62.72. HRMS: Calcd for $C_6H_{11}NO_4$ ($-H_2O$): 143.0582. Found: 143.0579.