Kinetic Resolution in Palladium Catalyzed Asymmetric Allylic Alkylations by a P,O Ligand System

Scott R. Gilbertson*, Ping Lan.

Department of Chemistry, Washington University, One Brookings Drive
Campus 1134, Saint Louis Missouri, 63130-4899

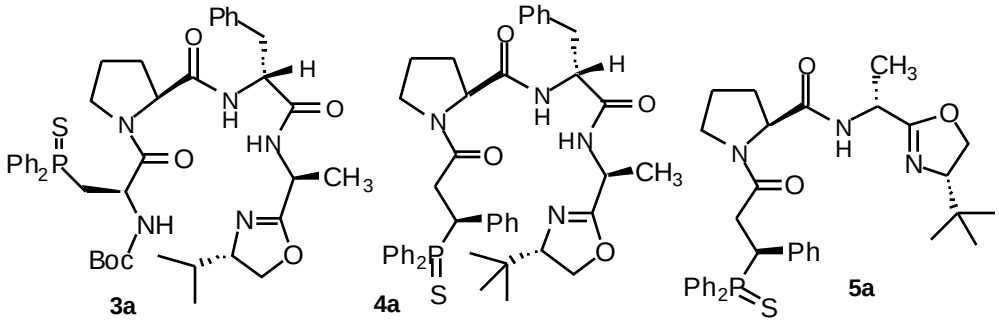
srg@wuchem.wustl.edu

General: Proton magnetic resonance spectra were recorded using either a Varian Unity 300, 500, or 600 spectrometer. Chemical shifts were reported as parts per million (ppm) downfield from tetramethylsilane in δ unit, and coupling constants were given in cycles per second (Hz). Splitting patterns were designed as s, singlet; d, doublet; t, triplet; q, quartet; m, multiple. ^{13}C spectra were obtained using the Varian 300 spectrometer at 75 MHz or Varian 600 at 125 MHz, and were reported in ppm with center line of the triplet at 77.0 ppm for chloroform-*d*. Routine ^{13}C NMR spectra were fully decoupled by broad-band waltz decoupling. ^{31}P NMR spectra were obtained in chloroform-*d* or reaction solvent with benzene-*d* sealed in capillary tube, and were reported in ppm relative to the singlet at 0.00 ppm for 10% H_3PO_4. All NMR spectra were recorded at ambient temperature unless otherwise noted. Infrared spectra (IR) were obtained using a Perkin Elmer Spectrum BX FT-IR spectrophotometer. Enantiomer ratios were determined by chiral HPLC analysis using Daicel Chemical Industries, LTD. Chiralpak AD (0.46 cm x 25 cm), Chiralcel OJ (0.46 cm x 25 cm) or Chiralcel OD (0.46 cm x 25 cm). Low-resolution fast-atom bombardment (LRFAB) and high-resolution fast-atom bombardment (HRFAB) were obtained from the Washington University Mass Spectrometry Resource Center.

Chemical reagents and starting materials were purchased from Aldrich Chemical Co., Sigma Chemical Co., Bachem, Inc., Strem Chemicals, Novabiochem, and were used without purification.

Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and acetonitrile were distilled from CaH_2. Toluene was distilled from sodium metal. Chloroform-*d* and benzene-*d* were purchased from Cambridge Isotope Laboratories (CIL).

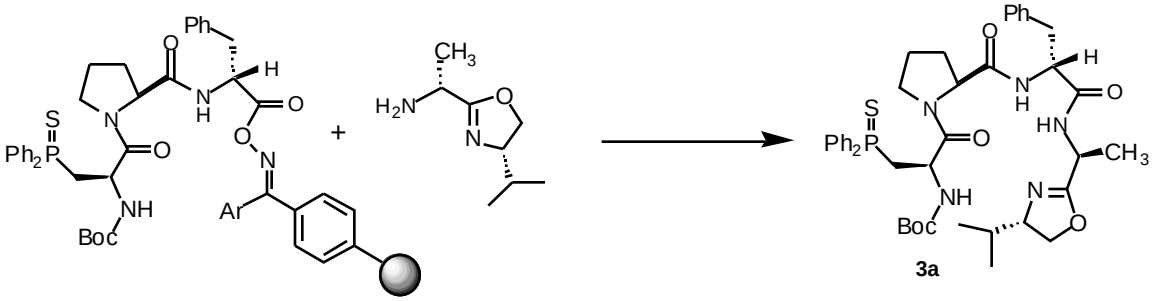
General method for solid phase synthesis of ligand phosphine sulfides **3a**-**5a** using oxime resin.



The oxime resin (ca. 0.5 mmol/g) was placed in a reaction vessel and swollen with dichloromethane (15 mL/g of resin). The solvent was drained and a mixture of the first amino acid (5 equiv.) and DCC (5 equiv.) in dichloromethane (15 mL/g) was added to the reaction vessel. The mixture was shaken for 24 h. The solution was filtered and then washed with dichloromethane × 3, DMF × 3, i-PrOH × 3 and dichloromethane × 3. The resin was dried *in vacuo*.

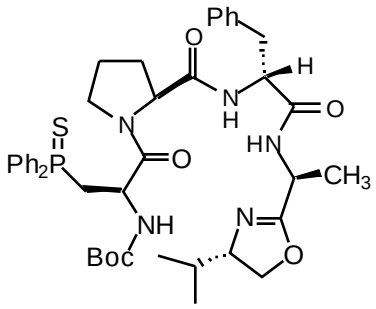
The following procedure was used for the coupling of each amino acid or phosphine-containing building block to make the extended peptide on resin: 1.) wash resin with dichloromethane × 2, 2.) wash with 25% TFA/dichloromethane, 3.) mix the resin with 25% TFA/dichloromethane and let it stand for 30 minutes, 4.) wash the resin with the following

solvents; dichloromethane × 3, *i*- PrOH × 3, dichloromethane × 3, *i*-PrOH × 3, dichloromethane × 3, DMF × 2, 5.) add Boc-amino acid or phosphine building block (3 equiv., 0.1 M in DMF) and BOP (3 equiv., 0.1 M in DMF), shake resin for 30 s, 6.) add DIEA (5.3 equiv.), shake mixture for 3 h, 7.) wash the resin with DMF × 3, dichloromethane × 3, *i*-PrOH × 3, dichloromethane × 3. The amount of solvent used for all washing was 15 mL/g, and the washing time was 1 minute.



After the synthesis was complete, a small amount of resin was removed and cleaved with amino-oxazoline nucleophile which was obtained by hydrogenation of Cbz- protected oxazoline. The cleaved peptide was filtered, the solvent evaporated, and the crude peptide was then purified by flash chromatography. The purified peptide **3a**, **4a**, or **5a** was then reduced with Raney Ni to give free phosphine-oxazoline peptide ligand **(3**, **4**, **5)** before use in catalysis.

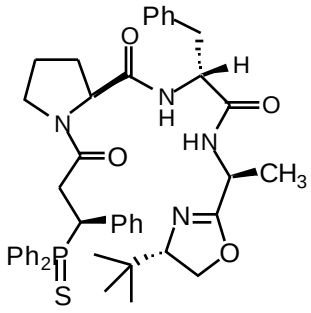
3a Boc-Pps-Pro-D-Phe-Ala-Oxa-*i*-Pr



3a: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82-7.12 (m, 15H), 6.91 (d, *J* = 7.2 Hz, 1H), 4.98-4.92 (m, 1H), 4.81 (d, *J* = 8.4 Hz, 1H), 4.64-4.59 (m, 1H), 4.55-4.52 (m, 1H), 4.28-4.26 (m, 1H), 4.17-4.14 (m, 1H), 3.91-3.89 (m, 1H), 3.79-3.75 (m, 1H), 3.62-3.56 (m, 2H), 3.11-3.00 (m, 2H), 2.84-2.65 (m, 2H), 1.94-1.80 (m, 4H), 1.68-1.61 (m, 1H), 1.27-1.18 (m, 12H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2 (d, J_{CP} = 13.6 Hz), 171.1, 169.7, 167.5, 154.2, 137.0, 131.6, 131.5, 131.4, 131.3, 130.8, 130.7, 129.8, 129.4, 129.3, 128.8, 128.7, 128.6, 128.5, 128.4, 128.1, 126.7, 126.2, 79.6, 71.5, 70.6, 60.6, 54.1, 47.7, 47.4, 43.6, 37.5, 35.2 (d, J_{CP} = 56.5 Hz), 32.3, 28.1, 27.8, 24.8, 18.5, 17.8; ^{31}P(121.5 MHz, $CDCl_3$) δ 39.7 (major), 37.5(minor); MS-FAB m/z (% rel intensity) 788 (MH^+, 80), 217 (100); HRFAB calcd for $C_{42}H_{55}N_5O_6PS$ (MH^+) m/e 788.3611, found 788.3613.

3a was converted to **3** by Raney nickel reduction. ^{31}P NMR (120 MHz, C_6D_6) δ -23.7 (major), -24.3 (minor).

4a ph-Pps-Pro-D-Phe-Ala-Oxa-*t*-Bu

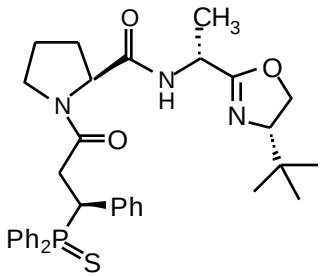


4a: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11-8.08 (m, 2H), 7.61-7.03 (m, 18H), 6.78 (m, 2H), 4.65-4.61 (m, 1H), 4.50 (t, *J* = 7.2 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 1H), 4.12 (dd, *J* = 8.7, 9.6 Hz, 1H), 4.03 (dd, *J* = 7.8, 8.7 Hz, 1H), 3.88 (dd, *J* = 3.3, 7.5 Hz, 1H), 3.74 (dd, *J* = 7.8, 9.6 Hz, 1H) 3.38-3.29 (m, 2H) 3.06-2.92 (m, 2H) 2.89 (dd, *J* = 6.6, 13.8 Hz, 1H), 2.75 (dd, *J* = 7.8, 13.8 Hz, 1H), 1.84-1.72 (m, 2H), 1.71-1.45 (m, 2H), 1.25 (d, *J* = 8.6 Hz, 3H), 0.84 (s, 9H); ^{13}C NMR (150

MHz, $CDCl_3$) δ 171.0, 170.1 (d, J_{CP} = 10.8 Hz), 169.8, 167.5, 137.0, 135.4, 132.3, 131.9, 131.8, 131.5, 131.2, 129.6, 129.3, 128.7, 128.6, 128.5, 128.4, 127.9, 127.5, 126.6, 75.1, 69.4, 60.4, 54.2, 47.6, 43.6, 42.6 (d, J_{CP} = 51.0 Hz), 37.4, 35.6, 33.6, 28.2, 25.6, 24.5, 18.6; ^{31}P(121.5 MHz, $CDCl_3$) δ 52.3; MS-FAB m/z (% rel intensity) 763 (MH^+, 100); HRFAB calcd for $C_{44}H_{52}N_4O_4PS$ (MH^+) 763.3448, found 763.3424.

4a was converted to **4** by Raney nickel reduction. ^{31}P NMR (120 MHz, C_6D_6) δ 0.8.

5a ph-Pps-D-Pro-Ala-Oxa-t-Bu

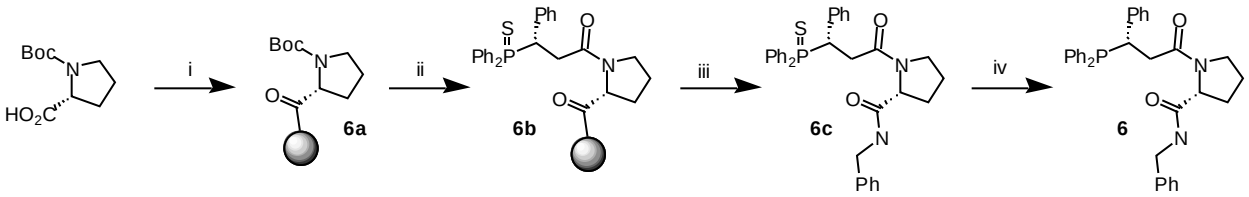


5a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19-8.12 (m, 2H), 7.56-7.05 (m, 14H), 4.74-4.61 (m, 1H), 4.55 (t, *J* = 6.9 Hz, 1H), 4.42-4.22 (m, 1H), 4.14 (dd, *J* = 8.7, 10.2 Hz, 1H) 4.03 (dd, *J* = 7.5, 8.7 Hz, 1H), 3.69 (dd, *J* = 7.5, 10.2, 1H), 3.54-3.47 (m, 1H), 3.38-3.25 (m, 2H), 2.75 (ddd, *J* = 2.7, 10.8, 16.2 Hz, 1H), 2.19-1.61 (m, 4H), 1.34 (d, *J* = 6.9 Hz, 3H), 0.79 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7 (minor) and 170.2 (major), 170.0 (d, J_{CP} = 17.0 Hz, major) and 169.9 (d, J_{CP} = 16.9 Hz, minor), 167.1 (major) and167.0 (minor), 135.0, 134.9, 132.4, 132.3, 131.9, 131.8, 131.7, 131.5, 131.4, 131.1, 130.9, 130.7, 129.8, 129.7, 129.6, 128.9, 127.9, 127.8, 127.6, 127.4, 75.2 (major) and 75.1 (minor), 69.7 (minor) and 69.4 (major), 59.8, 47.5 (minor) and 47.4 (major), 43.7 (minor) and 43.6 (major), 42.3 (d, J_{CP} = 52.6 Hz, major) and 42.2 (d, J_{CP} = 53.5 Hz, minor), 35.6, 33.6 (minor) and 33.5 (major), 27.8 (minor) and 27.7 (major), 19.2 (minor) and

19.0 (major); ^{31}P NMR (120 MHz, $CDCl_3$) δ 51.3 (major), 52.1 (minor); HRFAB calcd for $C_{35}H_{42}N_3O_3PSLi$ (MLi+) 622.2845, found 622.2832.

5a was converted to **5** by Raney nickel reduction. ^{31}P NMR (120 MHz, C_6D_6) δ -1.75 (major), -0.55 (minor).

Synthesis of ligand **6**



i.) DCC, oxime resin; ii.) 25% TFA/DCM; Ph-Pps-OH, BOP, DIEA; iii.) benzyl amine, THF; iv.) Raney Ni

6a: The oxime resin (ca. 0.53 mmol/g) was placed in a reaction vessel and swollen with dichloromethane (15 mL/g of resin). The solvent was drained and a slurry of Boc-D-Pro-OH (5 equiv.) and DCC (5 equiv.) in dichloromethane (15 mL/g) was added to the reaction vessel. The mixture was shaken for 24 h. The solution was filtered and then washed 3 times each with dichloromethane, DMF, *i*-PrOH and dichloromethane. The resin was then dried *in vacuo*.

6b: The general method for solid phase synthesis on oxime resin was used. After the synthesis of **6b** was complete, the weigh of the resin was determined and the loading was found to be 0.5 mmol/g.

6c: 50 mg of resin **6b** was placed in a small vial, followed by addition of benzyl amine (29 μL, 10 equiv.) and THF (1 mL). The vial was put on shaker. After 1 day, the mixture was filtered, washed with more dichloromethane, and then concentrated. The oil residue was purified by flushing through a silica-gel filled pipette with a mixture of hexane/EtOAc (20/80) as the eluant to give **6c** (11 mg, 100%) as a colorless oil which solidified at low temperature. ^{1}H NMR

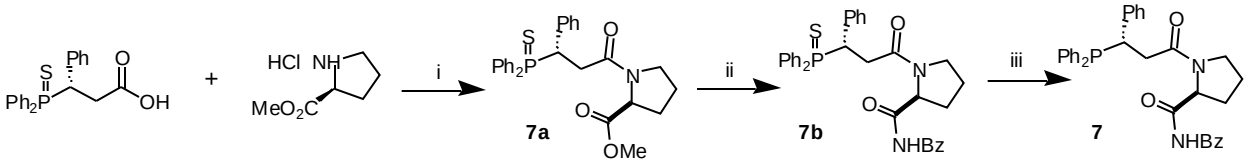
(300MHz, $CDCl_3$) δ 8.18-8.11 (m, 2H), 7.56-7.02 (m, 18H), 6.22 (m, 1H), 4.70 (dt, *J* = 7.4, 10.2, 1H), 4.47 (dd, *J* = 6.3, 15.0 Hz, 1H), 4.37 (d, *J* = 7.5, 1H), 4.30 (dd, *J* = 5.7, 15.0 Hz, 1H), 3.54-3.51 (m, 1H), 3.49-3.26 (m, 2H), 2.84-2.74 (m, 1H), 2.31-1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 170.5 (d, J_{CP} = 16.5 Hz), 138.7, 135.3 (d, J_{CP} = 4.0 Hz), 132.1, 132.0, 131.8, 131.7, 131.4, 130.8, 130.7, 129.9, 129.3, 129.1, 128.8, 128.2, 127.6, 127.5, 60.1, 47.8, 43.5, 42.5 (d, J_{CP} = 52.6 Hz), 35.9, 27.7, 25.0; ^{31}P NMR (120MHz, $CDCl_3$) δ 52.1(minor), 51.6(major). IR (film) cm^{-1} 3305, 3053, 2919, 1639, 1538, 1494, 1435, 1099, 909, 730, 694.

6c was converted to **6** by Raney nickel reduction. ^{31}P NMR (120 MHz, C_6D_6) δ 0.76(minor), -1.2(major).

Synthesis of ligand **7**

7 was synthesized by both solid phase synthesis (the same procedure as **6**) and solution synthesis.

Solution synthesis of **7**:



i.) EDC, HOBT, Et_3N, DCM; ii.) a.) LiOH, H_2O, MeOH/THF, b.) $KHSO_4$ (aq) c.) EDC, HOBT, benzylamine, DCM; iii.) Raney Ni

7a: A mixture of acid Ph-Pps-OH (500 mg, 1 equiv.), proline methyl ester, HCl (271 mg, 1.2 equiv.), EDC (314 mg, 1.2 equiv.) and HOBT (222 mg, 1.2 equiv.) in 14 mL of dichloromethane was stirred at 0 °C for 5 minutes followed by addition of Et_3N (229 μL, 1.2 equiv.). The solution was warmed to room temperature and stirred over night. The solvent was

removed and ethyl acetate (80 mL) was added. The mixture was washed with water (40 mL), 1N HCl (30 mL), sat. $NaHCO_3$ (40 mL) and brine (40 mL) then dried over Na_2SO_4. After removal of solvent, the residue was purified by column chromatography with a mixture of hexane/EtOAc (30/70) as eluant to give **7a** (466 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24-8.12 (m, 2H), 7.56-7.44 (m, 5H), 7.35-7.08 (m, 8H), 4.77 (dt, *J* = 4.8, 8.7 Hz, 1H), 4.26 (dd, *J* = 2.8, 8.0 Hz, 1H, minor) and 4.15 (dd, *J* = 4.4, 8.2 Hz, 1H, major), 3.59 (s, 3H, minor isomer) and 3.44 (s, 3H, major isomer), 3.50-3.37 (m, 2H), 3.19-2.87 (m, 2H), 2.04-1.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 168.8 (d, J_{CP} = 13.0 Hz), 135.3 (d, J_{CP} = 4.5 Hz), 132.1 (d, J_{CP} = 9.1 Hz), 131.6, 131.3, (d, J_{CP} = 9.5 Hz), 131.2, 131.0, 130.6, 130.2, 129.7, (d, J_{CP} = 5.5 Hz), 128.5 (d, J_{CP} = 11.6 Hz), 127.8 (d, J_{CP} = 12.0 Hz), 127.6 (d, J_{CP} = 2.5 Hz), 127.1 (d, J_{CP} = 2.5 Hz), 59.1 (minor) and 58.7 (major), 52.4 (minor) and 51.8 (major), 46.9 (major) and 46.2 (minor), 42.4 (d, J_{CP} = 52.0 Hz), 35.5, 28.9, 24.4; ^{31}P NMR (120 MHz, $CDCl_3$) δ 52.2 (major), 51.2 (minor); IR (film) cm^{-1} 3054, 2951, 2873, 1742, 1641, 1432, 1308, 1194, 1173, 912;MS-FAB m/z (% rel intensity) 484 (MLi^+, 90), 160 (100); HRFAB calcd. for $C_{27}H_{29}NO_3PS$ (MH^+) m/e 478.1606, found: 478.1589.

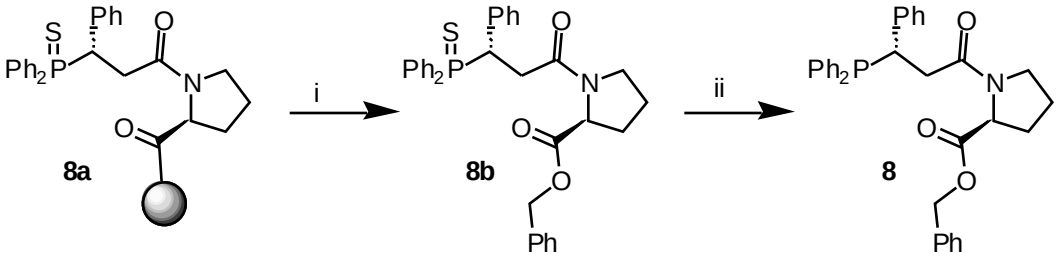
7b: An aqueous solution of $LiOH.H_2O$ (5 equiv.) was added into the mixture of **7a** (416 mg, 1 equiv.), MeOH (4 mL) and THF (4 mL) drop wise at 0 °C. The reaction was stirred at 0 °C and monitored by TLC. Upon completion (3 h), aqueous $KHSO_4$ solution was added to the mixture until pH was 2. The mixture was concentrated and then extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography using a mixture of hexane/EtOAc/acetic acid (70/30/1) as eluant to give the acid (378 mg, 94%) as white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.86 (s, 1H), 8.25-8.11 (m, 2H), 7.55-7.09 (m, 13H), 4.74 (dt, *J* = 6.3, 9.3 Hz, 1H), 4.17-4.14 (m, 1H), 3.47-3.39 (m, 2H), 3.10 (d, *J* = 12.7 Hz, 1H), 3.08 (d, *J* = 12.9 Hz, 1H), 2.08-1.66 (m,

4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 171.1 (d, J_{CP} = 12.5 Hz), 135.0 (d, J_{CP} = 4.0 Hz), 132.1 (d, J_{CP} = 9.5 Hz), 131.8, 131.7, 131.4, (d, J_{CP} = 9.5 Hz), 131.2, 131.0, 130.1 (d, J_{CP} = 21.5 Hz), 129.5 (d, J_{CP} = 5.6 Hz), 128.6 (d, J_{CP} =11.6 Hz), 127.9, 127.7, 127.4, 59.2, 47.6, 42.5 (d, J_{CP} = 51.1 Hz), 35.6, 27.8, 24.3; ^{31}P NMR (120 MHz, $CDCl_3$) δ 51.9 (major), 50.9 (minor); IR (film) cm^{-1} 3100-2800 (br.), 1727, 1609, 1451, 1436, 1189, 1100, 912, 695; MS-FAB m/z (% rel intensity) 464 (MH^+, 25), 349 (75), 154 (100); HRFAB calcd. for $C_{26}H_{27}NO_3PS$ (MH^+) 464.1449, found 464.1448.

A mixture of the above acid (187 mg, 1 equiv.), EDC (93 mg, 1.2 equiv.) and HOBT (66 mg, 1.2 equiv.) in 4 mL of dichloromethane was cooled to 0 °C followed by addition of benzyl amine (53 μL, 1.2 equiv.). The mixture was warmed to room temperature and stirred over night. After the removal of solvent, water (20mL) was added and the mixture was extracted with ethyl acetate (40 mL x 2). The combined extracts were washed with 1N HCl (20 mL), sat. $NaHCO_3$ (20 mL), brine (40 mL), and dried over $MgSO_4$. The crude product was purified by column chromatography with a mixture of hexane/EtOAc (25/75) as eluant to afford **7b** (206 mg, 92%) as white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21-8.17 (m, 2H), 7.56-7.01 (m, 18H), 6.45-6.42 (m, 1H), 4.68 (dt, *J* = 3.8, 9.5 Hz, 1H), 4.45 (dd, *J* = 2.0, 8.0 Hz, 1H), 4.17 (dd, *J* = 6.5, 15.0 Hz, 1H), 3.92 (dd, *J* = 5.8, 15.0 Hz, 1H), 3.51-3.41 (m, 2H), 3.31 (ddd, *J* = 8.7, 10.2, 15.6 Hz, 1H), 2.79 (ddd, *J* = 3.9, 9.9, 15.6 Hz, 1H), 2.34-2.31 (m, 1H), 1.89-1.85 (m, 2H), 1.74-1.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7 (d, J_{CP} = 15.2 Hz), 170.5, 138.2, 134.7, 132.0, 131.9, 131.4, 131.3, 131.2, 130.9, 130.7, 130.3, 129.6, 129.5, 128.9, 128.8, 128.4, 128.0, 127.9, 127.6, 127.0, 126.9, 60.0, 47.8, 43.1, 43.0 (d, J_{CP} = 52.7 Hz), 35.4 (d, J_{CP} = 4.2 Hz), 27.5, 24.5; ^{31}P NMR (120 MHz, $CDCl_3$) δ 51.0 (major), 50.8 (minor); IR (film) cm^{-1} 3411, 3302, 3054, 2920, 1643, 1525,

1434, 1308, 1098, 910; MS-FAB m/z (% rel intensity) 559 (MLi^+, 85), 160 (100); HRFAB calcd for $C_{33}H_{33}N_2O_2PSLi$ (MLi^+) m/e 559.2160, found 559.2169. $[\alpha]_D$ (c) = -205.8 (0.0152)

7b was converted to ligand **7** by Raney nickel reduction. ^{31}P NMR (120 MHz, C_6D_6) δ -0.2 (major), -1.9 (minor).



i.) DBU, benzyl alcohol, THF; ii.) Raney Ni

Synthesis of **8**

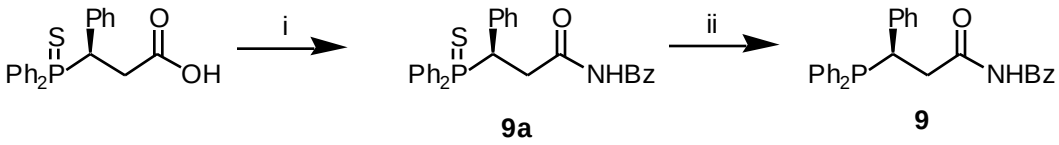
Oxime resin **8a** was synthesized by the same method as was used for **6b**.

8b: 50 mg of resin **8a** was measured into a small vial and mixed with THF (1 mL), DBU (10 μL, 10 equiv.) and benzyl alcohol (27 μL, 10 equiv.). The vial was put on shaker for over night. Then the mixture was filtered and washed with dichloromethane. The filtrate was concentrated and the residue purified by passing through a silica-gel filled pipette with hexane/EtOAc (80/20) as eluant to give **8b** (10 mg, 72%) as oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.24-8.11 (m, 2H), 7.56-7.07 (m, 18H), 5.02 (d, *J* = 12.3 Hz, 1H), 4.84 (d, *J* = 12.3 Hz, 1H), 4.80-4.75 (m, 1H, major) and 4.69 (dt, *J* = 2.1, 10.5 Hz, 1H, minor), 4.29 (dd, *J* = 3.2, 8.2 Hz, 1H, minor) and 4.20 (dd, *J* = 4.0, 7.6 Hz, 1H, major), 3.52-3.28 (m, 2H), 3.17-2.58 (m, 2H), 2.04-1.66 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6 (minor) and 171.5 (major), 168.9 (d, J_{CP} = 14.8 Hz), 135.8, 135.5, 132.3, 132.2, 131.9, 131.8, 131.7, 131.6, 131.5, 131.4, 131.1, 129.9, 129.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.3, 67.4 (minor) and 66.4 (major), 59.4 (minor) and 58.9 (major), 47.0 (major) and 46.4 (minor), 42.4 (d, J_{CP} = 62.5 Hz), 35.6, 31.0 (minor) and 29.0 (major), 24.5 (minor) and 22.4 (major); ^{31}P (120 MHz,

$CDCl_3$) δ 52.4 (major), 51.1 (minor); IR cm^{-1} 3059, 2919, 1740, 1639, 1435, 1166, 1096, 694; MS-FAB m/z (% rel intensity) 560 (MLi^+, 6), 313 (18), 160 (100); HRFAB calcd. for $C_{33}H_{32}NO_3PSLi$ (MLi^+) m/e 560.2001, found 560.2008.

8b was converted to **8** by Raney nickel reduction. ^{31}P NMR (120 MHz, C_6D_6) δ 0.1 (major), -1.4 (minor).

Synthesis of **9**



9a **9**

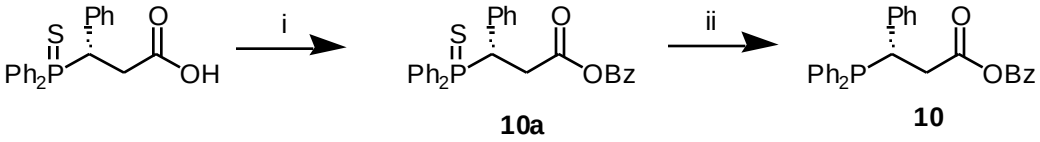
i.) EDC, HOBT, DCM, benzylamine; ii.) Raney Ni

9a: A mixture of acid ph-(*R*)-Pps-OH (150 mg, 1 equiv.), HOBT (66 mg, 1.2 equiv.) and EDC (94 mg, 11.2 equiv.) in 4 mL of dichloromethane was cooled to 0 °C followed by addition of benzyl amine (67 μL, 1.5 equiv.). The mixture was warmed to room temperature and stirred over night. After the removal of solvent, the residue was mixed with water (20 mL) and extracted with ethyl acetate (40 mL x 2). The combined extracts were washed with 1N HCl, sat. $NaHCO_3$, brine (20 mL each) and dried over Na_2SO_4. The crude product was purified by column chromatography using hexane/EtOAc (60/40) as eluant to give **9a** (130 mg, 70%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.24-8.17 (m, 2H), 7.58-7.09 (m, 16H), 6.80-6.76 (m, 2H), 5.90 (m, 1H), 4.63 (dt, *J* = 4.2, 10.2 Hz, 1H), 4.31 (dd, *J* = 6.7, 15.3 Hz, 1H), 3.91 (dd, *J* = 5.0, 15.0 Hz, 1H), 3.07-2.95 (m, 1H), 2.89-2.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (d, J_{CP} = 16.5 Hz), 137.8, 135.5, 132.3, 132.2, 131.9, 131.8, 131.7, 131.6, 131.5, 131.4, 131.1, 129.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.3, 43.5, 43.3 (d, J_{CP} = 52.1

Hz), 38.2 (d, J_{CP} = 2.5 HZ); ^{31}P NMR (120 MHz, $CDCl_3$) δ 51.1; IR (film) cm^{-1} 3287, 3054, 2915, 1646, 1550, 1434, 1109, 910; MS-FAB m/z (% rel intensity) 462 (MLi^+, 60), 160 (100); HRFAB calcd. for $C_{28}H_{26}NOPSLi$ (MLi^+) m/e 462.1633, found 462.1632. $[\alpha]_D$ (c) = +157.6 (0.0252)

9a was converted to ligand **9** by Raney nickel reduction. ^{31}P NMR (120 MHz, C_6D_6) δ -0.3.

Synthesis of **10**



10a **10**

i.)DCC, DMAP, DCM, benzyl alcohol; ii.) Raney Ni

10a: A mixture of the acid Ph-(*S*)-Pps-OH (200 mg, 1 equiv.), benzyl alcohol (85 μL, 1.5 equiv.) and DMAP (33 mg, 0.5 equiv.) in 4 mL of dichloromethane was cooled to 0 °C followed by addition of DCC (135 mg, 1.2 equiv.). The mixture was warmed to room temperature and stirred over night, producing a precipitate. The suspension was filtered and washed with small amount of dichloromethane two times. The filtrate was poured into a separatory funnel, washed with water (50 mL x 2), citric acid (50 mL), sat. $NaHCO_3$ (50 mL), brine (50 mL) and dried over $MgSO_4$. After removal of solvent, the residue was purified by column chromatography using hexane/EtOAc (80/20) as eluant to give **10a** (150 mg, 60%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18-8.11 (m, 2H), 7.58-7.04 (m, 18H), 4.91 (s, 2H), 4.47 (dt, *J* = 3.3, 11.4 Hz, 1H), 3.31 (ddd, *J* = 7.2, 11.7, 16.5 Hz, 1H), 2.89 (ddd, *J* = 3.3, 9.6, 16.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4 (d, J_{CP} = 19.6 Hz), 135.7, 134.3, (d, J_{CP} = 4.6 Hz), 132.3, 132.2, 132.1, 131.9, 131.8, 131.6, 131.5 (d, J_{CP} = 3.1 Hz), 131.2, 130.6, 130.2, 130.0 (d, J_{CP} = 5.4 Hz), 129.2, 129.1, 128.7, 128.3, (d, J_{CP} = 4.8 Hz), 128.2, 127.9, (d, J_{CP} = 2.8 Hz), 66.8, 43.5 (d, J_{CP} = 51.5 Hz), 35.7

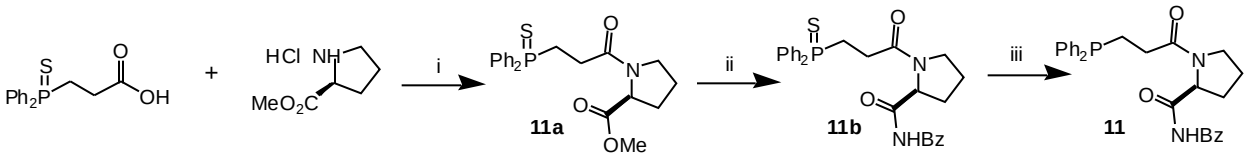
(d, J_{CP} = 3.7 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 51.0; IR (film) cm^{-1} 3550-3142 (br.), 3054, 2920, 1734, 1600, 1584, 1434, 1215, 1098; MS-FAB m/z (% rel intensity) 463 (MLi^+, 30), 160 (100); HRFAB calcd. for $C_{28}H_{25}O_2PSLi$ (MLi^+) 463.1473, found 463.1467. $[\alpha]_D$ (c) = -173.6 (0.0248)

10a was converted to **10** by Raney nickel reduction. ^{31}P NMR (120 MHz, C_6D_6) δ -0.3.

Synthesis of **11**

11 was made by using either solid phase synthesis (the same procedure as **6**) or solution synthesis.

Solution synthesis of **11**:



i.) EDC, HOBT, Et_3N, DCM; ii.) a.) LiOH, H_2O, MeOH/THF, b.) $KHSO_4$ (aq) c.) EDC, HOBT, benzylamine, DCM; iii.) Raney Ni

11a: Et_3N (264 μL, 1.1 equiv.) was added to a mixture of the acid building block (500 mg, 1 equiv.), proline methyl ester. HCl salt (314 mg, 1.1 equiv.), EDC (364 mg, 1.1 equiv.) and HOBT (256 mg, 1.1 equiv.) in 17 mL of dichloromethane. The solution was stirred over night. After removal of solvent, the residue was mixed with water (40 mL) and extracted with ethyl acetate (40 mL x 2). The combined extracts were washed with 1N HCl (30 mL), sat. $NaHCO_3$ (40 mL), brine (40 mL) and dried over $NaSO_4$. The crude product was purified by column chromatography using hexane/EtOAc (30/70) as eluant to give **11a** (548 mg, 79%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.78 (m, 4H), 7.51-7.40 (m, 6H), 4.42-4.36 (m, 1H), 3.70 (s, 3H, major) and 3.64 (s, 3H, minor), 3.59-3.41 (m, 2H), 2.92-2.56 (m, 4H), 2.16-1.82 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 170.1 (d, J_{CP} = 17.5 Hz), 133.0, 132.0, 131.9, 131.4,

131.3, 131.2, 129.0, 128.9, 128.8, 59.4 (minor) and 59.0 (major), 52.8 (minor) and 52.4 (major), 47.1 (major) and 46.7 (minor), 29.4, 27.7, 27.6 (d, J_{CP} = 59.1 Hz), 24.9; ^{31}P NMR (120 MHz, $CDCl_3$) δ 43.5 (minor), 43.4 (major); IR (film) cm^{-1} 3468, 3054, 2951, 2873, 1742, 1643, 1434, 1313, 1197, 1176, 1101, 742, 693; MS-FAB m/z (% rel intensity) 408 (MLi^+, 100); HRFAB calcd. for $C_{21}H_{24}NO_3PSLi$ (MLi^+) 408.1375, found 408.1371.

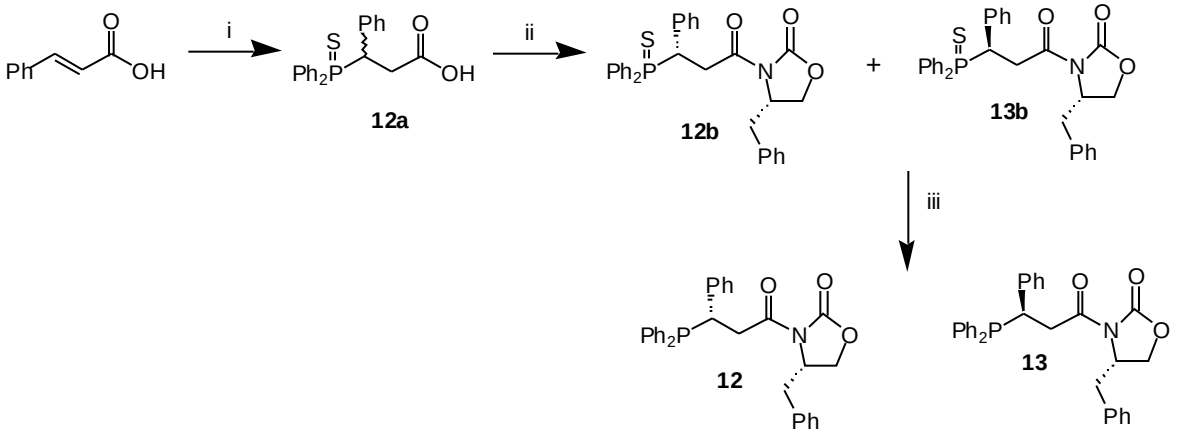
11b: An aqueous solution of $LiOH.H_2O$ was added to a mixture of **11a** (498 mg, 1 equiv.), MeOH (5 mL) and THF (5 mL) at 0 °C. The reaction was monitored with TLC. Upon completion (3 h), a solution of $KHSO_4$ (aq.) was added until the solution was pH 2. The mixture was concentrated and then extracted twice with ethyl acetate. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of solvent, the crude product was purified by column chromatography using hexane/EtOAc/acetic acid (20/80/1) as eluant to give the desired acid (353 mg, 74%) as white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.89-7.12 (m, 10H), 4.50-4.40 (m, 1H), 3.56-3.40 (m, 2H), 2.99-2.60 (m, 4H), 2.17-1.79 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 174.4, 171.2 (d, J_{CP} = 16.8 Hz), 132.5, 131.6, 131.4, 131.1, 131.0, 130.9, 130.8, 128.9, 128.7, 128.6, 128.5, 128.1, 125.2, 59.4 (minor) and 59.1 (major), 47.2 (major) and 46.6 (minor), 28.6, 27.4, 27.2 (d, J_{CP} = 58.6 Hz), 24.4; ^{31}P NMR (120 MHz, $CDCl_3$) δ 43.6 (minor), 43.4 (major); IR (film) cm^{-1} 3648-2367 (br.), 3049, 2971, 2920, 2878, 1734, 1638, 1605, 1450, 1434, 1318, 1189, 1104, 912; MS-FAB m/z (% rel intensity) 394 (MLi^+, 15), 160 (100); HRFAB calcd. for $C_{20}H_{22}NO_3PSLi$ (MLi^+) 394.1218. found 394.1224.

Benzyl amine (55 μL, 1.2 equiv.) was added to a mixture of the acid (163 mg, 1 equiv.), EDC (97 mg, 1.2 equiv.) and HOBT (68 mg, 1.2 equiv.) in 4 mL of dichloromethane at 0 °C. The mixture was warmed to room temperature and stirred over night. After removal of solvent, the residue was mixed with water (20 mL) and extracted with ethyl acetate (40 mL x 2). The

combined extracts were washed with 1N HCl (20 mL), sat. $NaHCO_3$ (20 mL), brine (40 mL) and dried over $MgSO_4$. The crude product was purified by column chromatography using hexane/EtOAc (15/85) as eluant to give **11b** (184 mg, 92%) as white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.21 (m, 15H), 6.35 (m, 1H), 4.52-4.49 (m, 1H), 4.46 (dd, *J* = 6.3, 15.0 Hz, 1H), 4.33 (dd, *J* = 5.6, 15.0 Hz, 1H), 3.56-3.49 (m, 1H), 3.43-3.37 (m, 1H), 2.88-2.78 (m, 2H), 2.70-2.62 (m, 2H), 2.42-2.36 (m, 1H), 2.15-1.74 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 171.0 (d, J_{CP} = 15.4 Hz), 138.4, 132.6, (d, J_{CP} = 13.3 Hz),131.7, 131.6, 131.5, 131.1, 131.0, 130.8, 128.8, 128.7, 128.6, 128.4, 127.3, 127.1 60.8 (minor) and 60.1 (major), 47.3 (major) and 46.9 (minor), 43.3 (minor) and 43.1 (major), 28.1, 27.6, 27.3 (d, J_{CP} = 58.3 Hz), 24.6; ^{31}P NMR (120 MHz, $CDCl_3$) δ 43.6 (minor), 43.4 (major); IR (film) cm^{-1} 3297, 3054, 2920, 2873, 2641, 1532, 1434, 1315, 1238, 1103, 910; MS-FAB m/z (% rel intensity) 483 (MLi^+, 90), 160 (100); HRFAB calcd. for $C_{27}H_{29}N_2O_2PSLi$ (MLi^+) 483.1847, found 483.1858.

11b was converted to **11** by Raney nickel reduction. ^{31}P NMR (120 MHz, C_6D_6) δ -14.5 (minor), -14.7 (major).

Synthesis of **12** and **13**



i.) a.) 1.0 equiv. *n*-BuLi, 3h, b.) Ph_2PH, 1.5 equiv. *n*-BuLi, 3h, c.) $Na_2S_2O_3$, H_2O; ii.) a.) pivoyl chloride, DIPEA, b.) *n*-BuLi, (*S*)-(-)-4-benzyl -2-oxazolidinone, -78°C; iii.) Raney Ni

12a: Diphenylphosphine (8.7 mL, 49.5 mmol, 1.5 equiv.) was added to 150 mL of THF

under N_2 at –78 °C, followed by *n*-BuLi (19.8 mL, 49.5 mmol, 1.5 equiv.), producing a deep red solution. The reaction was warmed to 25 °C and stirred for 3 h. In a separate flask, cinnamic acid (4.94 g, 33.3 mmol, 1 equiv.) was dissolved in THF and cooled to –78 °C after which *n*-BuLi (13.3 mL, 33.3 mmol, 1 equiv.) was added. A thick yellow solid was initially formed which dissolved into solution upon warming the reaction flask to 25 °C. After both solutions were stirred for 3 h, the cinnamic acid solution was added to the diphenylphosphine anion solution, resulting in a dark brown solution. The reaction was stirred for 16 h, and the color was light orange and thick with solid. At this time, a sodium thiosulfate solution (26.32 g, 0.167 mol dissolved in 150 mL of degassed distilled water) was transferred by cannula to the flask containing the phosphine acid. The reaction was stirred for 8 h. Dichloromethane (200 mL) was added to the reaction flask, and the entire mixture was poured into separatory funnel. A yellow third layer formed between the aqueous layer and organic layer. The organic layer was discarded and the other two layers were acidified with 2N HCl and extracted with dichloromethane (100 mL). The two organic layers were washed with brine and dried over $MgSO_4$. After concentration *in vacuo*, a crude white solid resulted. Both layers contain the desired product, but the 'third layer' was more pure, yielding 4.0 g (33%) of crude white solid. The solid could be further purified by recrystallization from EtOAc/hexane mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17-8.10 (m, 2H), 7.58-7.10 (m, 13H), 4.40 (dt, *J* = 3.3, 10.5 Hz, 1H), 3.29-3.17 (m, 1H), 2.87 (ddd, *J* = 3.0, 10.5, 17.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 133.8-127.6, 42.7 (d, J_{CP} = 52 Hz), 35.1 (d, J_{CP} = 3.5 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 50.6; IR (film) cm^{-1} 1700, 1651, 1558, 1418, 891; HRFAB calcd. for $C_{21}H_{20}O_2PS$ (MH^+) 367.0922, found 367.0927. **12b** $[\alpha]_D$ (c) = -124.7 (0.0121); **13b** $[\alpha]_D$ (c) = +191.2 (0.0121)

12b and **13b**: **12a** (5.57 g, 15.2 mmol) was dissolved in dry THF (90 mL) and cooled to –78 °C. DIPEA (3.2 mL, 18.0 mmol) and trimethylacetyl chloride (2.0 mL, 16.0 mmol) were added to the mixture, which was then slowly warmed to 0 °C and stirred for 90 min, producing a cloudy solution of the mixed anhydride. In a separate flask, the lithium salt of (S)-(-)-4-benzyl-2-oxazolidinone was prepared by addition of *n*-BuLi (6.1 mL of a 2.5M solution in hexane) to the oxazolidinone (2.69 g, 15.2 mmol dissolved in 60 mL of dry THF) at –78 °C. The mixed anhydride solution was warmed to room temperature, and following filtration was transferred under N_2 to the oxazolidinone solution. THF (30 mL) was used to rinse the remaining anhydride from the amine hydrochloride salt. The golden solution was stirred at –78 °C for 30 min, and at 0 °C for 2 h. The reaction was quenched with NH_4Cl (60 mL) and THF was exchanged with EtOAc (250 mL). The organic layer was then washed with sat. $NaHCO_3$ solution, 1N HCl, and brine. The combined aqueous layers were extracted with EtOAc (2 x 100 mL) and the combined organic layers were dried over $MgSO_4$. Column chromatography (EtOAc/hexane=35/65, R_f (**12b**)=0.33, R_f (**13b**)=0.22) was used to purify the resulting crude white solid, yielding 2.08 g of **12b** as a white foam and 2.4 g of diastereomer **13b** as white foam, overall yield: 4.58 g (56%). **12b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29-8.20 (m, 2H), 7.62-7.01 (m, 18H), 4.83 (dt, *J* = 3.6, 10.8 Hz, 1H), 4.49-4.41 (m, 1H), 4.13-3.98 (m, 3H), 3.37 (ddd, *J* = 3.6, 9.6, 17.4 Hz, 1H), 2.90 (dd, *J* = 3.3, 13.5 Hz, 1H), 2.44 (dd, *J* = 9.6, 13.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (d, J_{CP} = 18.5 Hz), 153.0, 134.9, 134.1 (d, J_{CP} = 4.6 Hz), 132.2, 132.0, 131.8 (d, J_{CP} = 3.0 Hz), 131.5, 131.4, 131.1 (d, J_{CP} = 3.0 Hz), 130.8, 130.5, 130.1, 130.0, 129.8, 129.1, 128.8, 128.6, 127.9, 127.7 (d, J_{CP} = 4.0 Hz), 127.6, 127.4 (d, J_{CP} = 3.0 Hz), 127.2, 66.1, 54.8, 42.3 (d, J_{CP} = 51.6 Hz), 37.2, 36.7 (J_{CP} = 5.0 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 51.5; IR (film) cm^{-1} 3060, 3029, 2978, 1780, 1700, 1387, 1215, 751; HRFAB calcd. for $C_{31}H_{29}NO_3PS$ (MH^+) m/e 526.1606,

found 526.1600. **13b**: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.23-8.16 (m, 2H), 7.61-7.54 (m, 5H), 7.39-7.13 (m, 11H), 6.92-6.85 (m, 2H), 4.78 (dt, *J* = 3.6, 10.5 Hz, 1H), 4.50-4.41 (m, 1H), 4.25 (ddd, *J* = 7.8, 10.8, 17.1, 1H), 4.15-4.01 (m, 2H), 3.27 (ddd, *J* = 3.3, 10.2, 17.4 Hz, 1H), 2.82 (dd, *J* = 3.6, 13.5, 1H), 2.55 (dd, *J* = 8.5, 13.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (d, J_{CP} = 18 Hz), 153.3, 134.5, 134.4 (d, J_{CP} = 4.5 Hz), 132.1, 132.0, 131.7 (d, J_{CP} = 4.0 Hz), 131.6, 131.5, 131.4, 131.2 (d, J_{CP} = 4.0 Hz), 131.0, 130.4, 130.0 (d, J_{CP} = 5.0 Hz), 129.2, 128.7, 128.6, 127.9, 127.8 (d, J_{CP} = 4.0 Hz), 127.7, 127.5 (d, J_{CP} = 4.0 Hz), 127.1, 66.2, 55.2, 43.2 (d, J_{CP} = 54.6 Hz), 37.4, 36.6; ^{31}P NMR (120 MHz, $CDCl_3$) δ 51.0; IR (film) cm^{-1} 3059, 3029, 2980, 1781, 1696, 1390, 1210, 1103, 752, 697; HRFAB calcd. for $C_{31}H_{29}NO_3PS$ (MH^+) 526.1606, found 526.1609.

12b and **13b** were converted to **12** and **13** by Raney nickel reduction. ^{31}P NMR (120 MHz, C_6D_6) δ 0.68 (**12**), -0.39 (**13**).

General procedure of Raney nickel reduction.

Raney nickel (0.8 g) was weighed into a Schlenk tube and washed with methanol (2 mL x 5), ether (2 mL x 3) and degassed CH_3CN (2 mL x 3), then a phosphinesulfide-containing compound (ca. 0.1 mmol) in degassed CH_3CN (1.5 mL) was added. The Schlenk tube was capped immediately and freeze-thaw for three times to get rid of trace air. The mixture was stirred with the tube tightly sealed at room temperature until the reduction was complete (monitored by ^{31}P NMR, the reaction was usually finished within 1 h). The supernatant solution was drawn into a syringe and injected through a syringe filter into a weighed flask charged with nitrogen. A small amount of degassed CH_3CN was used to wash the residue of Raney nickel and then combined with the previous CH_3CN through a syringe filter. The solvent can be removed *in vacuo* and replaced with the solvent of choice before use.

General procedure of π- allyl addition.

The reduced phosphine ligand was mixed with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (Pd:L=1:3) in degassed solvent, followed by addition of the 1,3-diphenyl acetate (10 equiv. to ligand) to make a solution at 0.1 M. To this solution was added a mixture of dimethyl malonate (20 equiv.), TBAF (20 equiv.) and BSA (20 equiv.) at the temperature of choice. The reaction was monitored by HPLC and stopped when conversion was ca. 50-60% to determine the enantiomer ratios of reactant and product.

HPLC condition:

Chiralpak AD: solvent: *i*-PrOH/hexane = 10/90; flow rate: 1 mL/min; detection: UV 204 nm; temp. = 25°C; retention time: t_R(**1**-(*S*)) = 5.7 min, t_R(**1**-(*R*)) = 5.9 min, t_R(**2**-(*R*)) = 10.0 min, t_R(**2**-(*S*)) = 13.7 min. Or use Chiracel OJ to determine the ratios of recovered starting material: solvent: *i*-PrOH/hexane = 1/99; flow rate: 1 mL/min; detection: UV 204 nm; temp. = 25°C; retention time: t_R(**1**-(*S*)) = 27.4 min, t_R(**1**-(*R*)) = 32.9 min.

Synthesis of complex **15**

A suspension of reduced ligand **13** (64 mg, 0.1298 mmol) and Pd dimer **14** (43 mg, 0.065 mmol) in 3 mL of degassed dichloromethane was stirred in a Schlenk tube at room temperature for 5 h. The suspension dissolved mostly. A solution of $AgPF_6$ (32 mg, 0.1298 mmol) in 1 mL of degassed dichloromethane was added into the orange suspension and precipitate forming observed immediately. The mixture was stirred for 1 h and the supernatant was injected through a syringe filter into a flask charged with nitrogen. Wash the precipitate with dichloromethane for

couple times and combine with the previous solution in the flask by injecting through a syringe filter. The bright orange solution was concentrated i*n vacuo* to give **15** (134 mg, ca. 100%) as orange solid. ^{1}H NMR (600 MHz, THF-D_8) δ 8.2-6.42 (m, 30H), 6.9 (m, 1H), 6.4 (m, 1H), 5.0 (m, 1H), 4.7 (m, 1H), 4.5 (m, 1H), 4.2 (m, 1H), 4.1 (m, 1H), 4.0 (m, 1H), 3.3 (m, 1H), 2.5 (m, 2H); ^{13}C NMR (150 MHz, THF-D_8) δ 178, 151, 136.4, 135.6, 134.2, 131.2, 130.7, 129.2, 128.6, 128.5, 128.3, 127.8, 127.7, 127.6, 127.5, 127.3, 126.8, 126.3, 126.2, 125.8, 125.7, 125.3, 125.2, 125.0, 124.9, 122.0, 121.8, 110, 103 (d, J_{CP} = 17.0 Hz), 71, 67, 56, 38, 37, 36; ^{31}P NMR (120 MHz, THF-D_8) δ 45.2 (s, major), 40.9 (s, minor); IR (film) cm^{-1} 3714-3216 (br.), 3641, 3053, 3025, 2958, 2919, 2851, 1773, 1698, 1611, 1387, 1259, 1097, 1018, 906, 833, 797; ESI-MS (capillary temp. = 45 °C): 792 (100, [M-PF_6]$^{+}$), ^{106}Pd isotope cluster 788-798, relative intensity calcd. (obs.) 2.6 (2), 1.2 (1.5), 29.1 (27.2), 70.9 (64), 100.0 (100.0), 37.7 (44.5), 77.9 (82.3), 32.0 (42.0), 38.0 (45.0), 14.7 (21.0), 3.2 (4.5).