High Asymmetric Induction with π -turn Derived Palladium Phosphine Complexes

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General: Proton, carbon and phosphorus NMR spectra were performed using either a Varian Mercury 300 or Varian Inova 600 MHz spectrometer. ^1H chemical shifts were reported in ppm (δ) downfield from TMS, and coupling constants are reported in Hz. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, broad and dd, doublet of doublets. ^{13}C spectra were acquired at 100 MHz (300) and 125 MHz (600), and were reported in ppm downfield from TMS. ^{31}P NMR spectra were acquired at 120 MHz and reported in ppm with respect to 85% H_3PO_4 as an external reference. IR spectra were obtained on a Perkin Elmer Spectrum BX FT-IR spectrophotometer. Enantiomeric excesses were determined by ^1H NMR with the chiral shift reagent $\text{Eu}(\text{hfc})_3$. EI, FAB and MALDI mass spectral data were obtained from the Washington University Mass Spectrometry Resource Center. Reactions were monitored by TLC using Aldrich polyester silica gel 60 F_{254} plates (0.25 mm). Flash chromatography was performed using ICN Silitech 32–63 D, 60 Å. Chemical starting materials were purchased from Aldrich, Bachem, Strem, Novabiochem, and were used without further purification. Mimotopes, a Fisher Scientific Company, supplied Mimotopes Synphase Crowns. THF was distilled from sodium benzophenone ketyl. Dichloromethane and acetonitrile were distilled from CaH_2 . Deuterated solvents were purchased from Cambridge Isotope Laboratories.

General procedure for preparation of Boc-phosphine sulfide-Methyl esters:

A flask charged with zinc dust (<10 micron) (0.3 g, 1.5 mmol, 3.0 equiv) was gently heated in-vacuo, allowed to cool and back filled with nitrogen. THF (1 mL), DMF (0.24 mL, 3.0 mmol, 2 equiv) and 1,2-dibromoethane (16 μL , 0.18 mmol, 4% to Zn) were added via syringe. The flask was heated to ebullition with a heat gun, while stirred vigorously,

and allowed to cool to room temperature. This process was repeated four times. TMSCl (18 μ l, 0.14 mmol, 3% to zinc) was added and allowed to stir for 30 min. In a separate flask Boc protected 3-iodo alanine methyl ester (0.5 g, 1.5 mmol, 1 equiv) was dissolved in THF (2 mL) and added dropwise via syringe to the zinc suspension. The flask and syringe was then rinsed with THF (1 mL) and added to the reaction. Upon near completion of the zinc insertion determined by TLC (typically about 2 hours) stirring was halted to allow the zinc to settle (about 30 min). In a separate flask charged with CuCN $\cdot$ 2LiCl (CuCN: 0.14 g, 1.5 mmol, 1 equiv; LiCl: 0.13 g, 3.0 mmol, 2 equiv), which had been heated to 140 – 150° C in an oil bath under vacuum for at least 2 hours, was added THF (3 ml). After the salts had dissolved the solution was cooled to 0° C and the solution of the zinc iodide was transferred via cannula dropwise into the copper solution. The reaction was stirred for 15 min. and then the phosphine chloride (3.0 mmol, 2 equiv) was added dropwise via syringe. The reaction was allowed to stir at 0° C for 10 min. then allowed to stir at room temperature for 2 hours. S₈ (0.14 g, 4.5 mmol, 3 equiv) was added to the reaction as a solid and the reaction was allowed to stir for 15 hours. The insoluble material was filtered and the THF was removed at reduced pressure. The remaining material was loaded onto silica gel and filtered through a short column of silica gel with an EtOAc/hexane solvent system. The crude product was loaded onto silica gel and chromatographed with EtOAc/hexane as solvent.

Spectral data for Boc-phosphine sulfide-Methyl esters:

^1H NMR (300 MHz, CDCl_3) δ 8.56 (dd, $J = 6.6, 17.6$ Hz, 1H), 8.39 (dd, $J = 7.1, 17.0$ Hz, 1H), 8.03 (dd, $J = 8.2, 30$ Hz, 2H), 7.93 (d, $J = 7.7$ Hz, 2H), 7.77 (br-s, 2H), 7.54 (q $J = 9.1$ Hz, 2H), 7.31 (t, $J = 7.1$ Hz, 2H), 7.21 (t, $J = 7.2$ Hz, 2H), 5.41 (d, $J = 7.4$ Hz, 1H), 4.76 (ddt, $J = 20.2, 7.4, 13.7$ Hz, 1H), 3.63 (dd, $J = 6.0, 9.9$ Hz, 2H), 3.52 (s, 3H), 1.20 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.8 (d, $J_{\text{CP}} = 11.7$ Hz), 154.96 (s), 134.21 (d, $J_{\text{CP}} = 8.6$ Hz), 133.69 (d, $J_{\text{CP}} = 2.8$ Hz), 132.00 (d, $J_{\text{CP}} = 8.6$ Hz), 129.67 (s), 127.27 (s), 126.53 (d, $J_{\text{CP}} = 6.9$ Hz), 125.75 (d, $J_{\text{CP}} = 6.5$ Hz), 125.58 (d, $J_{\text{CP}} = 5.7$ Hz), 125.28 (d, $J_{\text{CP}} = 14.3$ Hz), 125.15 (d, $J_{\text{CP}} = 14.3$ Hz), 79.95 (s), 52.76 (s), 50.47 (s), 33.18 (d, $J_{\text{CP}} = 58.1$ Hz), 28.30 (s). ^{31}P NMR (120 MHz, CDCl_3) δ 37.04. IR (KBr, cm^{-1}) 3364, 3056, 2977, 1742, 1717, 1507, 1366, 1217, 1165, 1049, 1026, 801, 772. FAB-MS; $[\text{M} + \text{Li}]$ calcd. 526.1793, obsd. 526.1797. $R_f = 0.2$ (30% EtOAc in hexane)

^1H NMR (300 MHz, CDCl_3) δ 8.56 (dd, $J = 7.4, 15.7$ Hz, 2H), 7.7-8.0 (m, 8H), 7.5-7.6 (m, 4H), 5.44 (d, $J = 7.4$ Hz, 1H), 4.7-4.9 (m, 1H), 3.65 (s, 3H), 3.25-3.60 (m, 2H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.75 (d, $J_{\text{CP}} = 10.6$ Hz), 154.93 (s), 134.65 (s),

133.40 (d, J_{CP} = 10.5 Hz), 133.10 (d, J_{CP} = 10.3 Hz), 132.75 (d, J_{CP} = 13.7 Hz), 129.27 (d, J_{CP} = 2.9 Hz), 128.91 (d, J_{CP} = 24.0 Hz), 128.74 (d, J_{CP} = 24.0 Hz), 127.96 (s), 127.34 (s), 126.00 (d, J_{CP} = 10.9 Hz), 79.96 (s), 52.92 (s), 50.54 (s), 33.16 (d, J_{CP} = 58.7 Hz), 28.07 (s). ^{31}P NMR (120 MHz, CDCl_3) δ 38.84. IR (KBr, cm^{-1}) 3362, 3053, 2976, 1743, 1711, 1500, 1366, 1341, 1251, 1165, 1080, 816, 747, 477. FAB-MS; $[\text{M} + \text{Li}]$ calcd. 526.1793, obsd. 526.1772. R_f = 0.3 (35% EtOAc in hexane)

^1H NMR (300 MHz, CDCl_3) δ 7.39 (d, J = 13.7 Hz, 4H), 7.07 (s, 2H), 5.51 (d, J = 7.4 Hz, 1H), 4.59-4.72 (m, 1H), 3.63 (s, 3H), 3.02-3.23 (m, 2H), 2.30 (s, 12H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.85 (d, J_{CP} = 10.9 Hz), 155.00 (s), 138.63 (d, J_{CP} = 9.4 Hz), 138.46 (d, J_{CP} = 9.4 Hz), 133.56 (s), 128.64 (d, J_{CP} = 10.3 Hz), 79.92 (s), 52.76 (s), 50.51 (s), 33.25 (d, J_{CP} = 57.8 Hz), 28.32 (s), 21.58 (s). ^{31}P NMR (120 MHz, CDCl_3) δ 38.35. IR (KBr, cm^{-1}) 3358, 2977, 2923, 1718, 1600, 1500, 1167, 1049, 1020, 850, 692, 627. FAB-MS; $[\text{M} + \text{Li}]$ calcd. 482.2106, obsd. 482.2111. R_f = 0.33 (30% EtOAc in hexane)

^1H NMR (300 MHz, CDCl_3) δ 6.75-6.84 (m, 4H), 6.06 (br-d, J = 4.7 Hz, 1H), 3.92-4.09 (m, 1H), 3.68 (s, 3H), 3.44-3.57 (m, 1H), 2.91-3.04 (m, 1H), 2.44 (s, 6H), 2.32 (s, 6H), 2.23 (s, 6H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 172.47 (d, J_{CP} = 16.4 Hz),

154.94 (s), 141.62 (d, $J_{\text{CP}} = 10.0$ Hz), 139.52 (d, $J_{\text{CP}} = 10.3$ Hz), 132.47 (d, $J_{\text{CP}} = 11.2$ Hz), 131.99 (d, $J_{\text{CP}} = 11.5$ Hz), 80.00 (s), 52.85 (s), 51.88 (s), 41.10 (d, $J_{\text{CP}} = 53.0$ Hz), 28.47 (s), 23.68 (d, $J_{\text{CP}} = 4.9$ Hz), 21.04 (d, $J_{\text{CP}} = 5.2$ Hz). ^{31}P NMR (120 MHz, CDCl_3) δ 39.44. IR (KBr, cm^{-1}) 3343, 2974, 2930, 1717, 1603, 1501, 1452, 1366, 1248, 1219, 1168, 1046, 1027, 855, 649. FAB-MS; $[\text{M} + \text{H}]$ calcd. 504.2337, obsd. 504.2331. $R_f = 0.3$ (30% EtOAc in hexane)

^1H NMR (300 MHz, CDCl_3) δ 8.18 (d, $J = 8.2$ Hz, 1H), 8.01 (d, $J = 8.3$ Hz, 1H), 7.87 (d, $J = 8.2$ Hz, 1H), 7.74 (dd, $J = 6.6, 13.5$ Hz, 2H), 7.5-7.58 (m, 1H), 7.35-7.45 (m, 6H), 5.54 (d, $J = 6.9$ Hz, 1H), 4.62-4.78 (m, 1H), 3.62 (s, 3H), 3.42-3.58 (m, 1H), 3.23-3.38 (m, 1H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.72 (d, $J_{\text{CP}} = 10.3$ Hz), 155.09 (s), 134.40 (d, $J_{\text{CP}} = 8.8$ Hz), 134.24 (s), 133.72 (s), 133.55 (s), 133.15 (s), 131.83 (d, $J_{\text{CP}} = 2.9$ Hz), 131.00 (d, $J_{\text{CP}} = 10.6$ Hz), 129.65 (s), 129.20 (d, $J_{\text{CP}} = 12.6$ Hz), 128.45 (s), 127.24 (s), 126.55 (s), 126.47 (s), 124.85 (d, $J_{\text{CP}} = 14.1$ Hz), 80.11 (s), 52.83 (s), 50.56 (s), 33.30 (d, $J_{\text{CP}} = 57.8$ Hz), 28.37 (s). ^{31}P NMR (120 MHz, CDCl_3) δ 38.06. IR (KBr, cm^{-1}) 3361, 3055, 2977, 1743, 1709, 1508, 1437, 1366, 1217, 1165, 1049, 1026, 829, 801, 774, 748, 713, 693. FAB-MS; $[\text{M} + \text{Li}]$ calcd. 476.1637, obsd. 476.1616. $R_f = 0.2$ (30% EtOAc in hexane)

The other diastereomer from the reaction that formed **7f** and **7f'**.

^1H NMR (300 MHz, CDCl_3) δ 8.27 (d, $J = 8.5$ Hz, 1H), 8.09 (dd, $J = 6.9, 16.2$ Hz, 1H), 8.00 (d, $J = 8.2$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.77 (dd, $J = 6.6, 20.3$ Hz, 2H), 7.48-7.57 (m, 1H), 7.32-7.47 (m, 5H), 5.44 (d, $J = 7.7$ Hz, 1H), 4.72-4.89 (m, 1H), 3.64 (s, 3H), 3.30-3.48 (m, 2H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.91 (d, $J_{\text{CP}} = 11.8$ Hz), 155.05 (s), 134.50 (d, $J_{\text{CP}} = 9.2$ Hz), 133.74 (d, $J_{\text{CP}} = 3.2$ Hz), 132.45 (d, $J_{\text{CP}} = 9.7$ Hz), 131.98 (d, $J_{\text{CP}} = 8.6$ Hz), 131.72 (s), 131.21 (d, $J_{\text{CP}} = 11.2$ Hz), 129.63 (s), 129.06 (d, $J_{\text{CP}} = 12.6$ Hz), 128.89 (s), 127.82 (s), 127.24 (s), 126.62 (s), 126.54 (s), 124.70 (d, $J_{\text{CP}} = 13.7$ Hz), 80.09 (s), 52.91 (s), 50.44 (s), 33.48 (d, $J_{\text{CP}} = 58.4$ Hz), 28.39 (s). ^{31}P NMR (120 MHz, CDCl_3) δ 37.57. IR (KBr, cm^{-1}) 3361, 3059, 2983, 2946, 2932, 1757, 1690, 1527, 1436, 1390, 1365, 1350, 1284, 1249, 1211, 1169, 1052, 1024, 829, 803, 776, 689, 608. FAB-MS; $[\text{M} + \text{Li}]$ calcd. 476.1637, obsd. 476.1619. $R_f = 0.2$ (30% EtOAc in hexane)

^1H NMR (300 MHz, CDCl_3) δ 7.67 (dd, $J = 14.3, 14.3$ Hz, 4H), 5.84 (d, $J = 6.3$ Hz, 1H), 4.53-4.69 (m, 1H), 3.68 (d, $J = 2.5$ Hz, 6H), 3.57 (s, 3H), 2.93-3.05 (m, 1H), 1.39 (d, $J =$

3.9 Hz, 36H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 172.01 (d, $J_{\text{CP}} = 10.6$ Hz), 162.88 (d, $J_{\text{CP}} = 12.8$ Hz), 155.34 (s), 144.50 (d, $J_{\text{CP}} = 12.3$ Hz), 144.27 (s), 130.14 (d, $J_{\text{CP}} = 12.1$ Hz), 80.07 (s), 64.66, 64.63, 52.60, 50.83, 36.35, 36.33, 35.26, 34.50, 32.11, 28.48. ^{31}P NMR (120 MHz, CDCl_3) δ 39.50. IR (KBr, cm^{-1}) 3340, 2963, 2874, 1748, 1718, 1499, 1449, 1410, 1393, 1365, 1267, 1227, 1167, 1143, 1116, 1008, 880, 733. FAB-MS; $[\text{M} + \text{H}]$ calcd. 703.4035, obsd. 703.4021. $R_f = 0.2$ (15% EtOAc in hexane)

^1H NMR (300 MHz, CDCl_3) δ 7.9 (t, $J = 15.7$ Hz, 2H), 7.15-7.25 (m, 2H), 7.01 (dd, $J = 7.8, 13.2$ Hz, 2H), 5.39 (d, $J = 7.1$ Hz, 1H), 4.44-4.60 (m, 1H), 3.66 (s, 3H), 3.22-3.37 (m, 2H), 2.38 (s, 6H), 1.98 (d, $J = 7.7$ Hz, 6H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 172.00 (d, $J_{\text{CP}} = 10.4$ Hz), 155.07 (s), 137.47 (d, $J_{\text{CP}} = 8.9$ Hz), 137.15 (d, $J_{\text{CP}} = 9.5$ Hz), 136.17 (d, $J_{\text{CP}} = 12.3$ Hz), 133.17-132.25 (m), 131.07 (d, $J_{\text{CP}} = 20.1$ Hz), 130.01 (d, $J_{\text{CP}} = 21.2$ Hz), 80.02 (s), 52.84 (s), 50.41 (s), 31.91 (d, $J_{\text{CP}} = 58.1$ Hz), 28.36 (s), 21.06 (d, $J_{\text{CP}} = 24.0$ Hz). ^{31}P NMR (120 MHz, CDCl_3) δ 36.81. IR (KBr, cm^{-1}) 3362, 2976, 2926, 1714, 1487, 1366, 1217, 1166, 1048, 911, 818, 620. FAB-MS; $[\text{M} + \text{Li}]$ calcd. 482.2106, obsd. 482.2089. $R_f = 0.17$ (20% EtOAc in hexane)

General procedure for preparation of Fmoc-phosphine sulfide-acids:

To a 0.4 – 0.5 M THF solution of the Boc-phosphine sulfide-Methyl ester at 0° was added 2 equivalents of aqueous LiOH (0.2 M), at 0° , dropwise via cannula. Upon completion,

as determined by TLC, the reaction was neutralized with conc. HCl. The THF was removed under reduced pressure and the resulting material was extracted two times with DCM, dried with Na₂SO₄, filtered and concentrated to a white foam. The resulting Boc-acid was treated with 50% TFA in DCM until complete removal of the Boc group as judged by TLC. The reaction mixture was then concentrated, dissolved in toluene and concentrated, dissolved in chloroform and concentrated and finally dissolved in DCM and concentrated before drying in-vacuo for 30 minutes. To the resulting unprotected amino acid, dissolved in a 1:1 acetone: water mixture, was added 2 equivalents of NaHCO₃ and 1 equivalent of Fmoc-OSu. The reaction was allowed to stir overnight before neutralizing with conc. HCl and removal of the MeOH under reduced pressure. The resulting material was extracted twice with DCM, dried with Na₂SO₄, filtered, concentrated and chromatographed with a MeOH/DCM solvent system.

Spectral data for Fmoc-phosphine sulfide acids:

¹H NMR (300 MHz, CDCl₃) □ 11.2 (br-s, 1H), 8.34-8.90 (m, 2H), 8.23 (d, *J* = 7.7 Hz, 1H), 8.1 (d, *J* = 7.1 Hz, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.4 Hz, 2H), 7.68 (d, *J* = 7.1 Hz, 2H) 7.21-7.66 (m, 12H), 5.95 (br-s, 1H), 4.75-4.96 (br-m, 1H), 3.67-4.15 (m, 5H). ¹³C NMR (100 MHz, CDCl₃) □ 175.16 (d, *J*_{CP} = 14.3 Hz), 155.75 (s), 144.02 (d, *J*_{CP} = 11.2 Hz), 143.81 (s), 141.47 (s), 141.43 (s), 134.35 (d, *J*_{CP} = 8.9 Hz), 134.12 (d, *J*_{CP} = 6.8 Hz), 133.86 (s), 132.13 (d, *J*_{CP} = 8.3 Hz), 131.07 (d, *J*_{CP} =

8.7 Hz), 129.72 (s), 128.05 (s), 127.44 (s), 126.62 (d, $J_{\text{CP}} = 5.7$ Hz), 125.70 (s), 125.37 (d, $J_{\text{CP}} = 10.5$ Hz), 120.24 (s), 67.52 (s), 50.60 (s), 47.08 (s), 33.07 (d, $J_{\text{CP}} = 58.1$ Hz). ^{31}P NMR (120 MHz, CDCl_3) δ 37.22. IR (KBr, cm^{-1}) 3294, 3059, 2588, 1954, 1719, 1508, 1330, 1249, 1046, 801, 772, 759, 741. FAB-MS; $[\text{M} + 2\text{Li} - \text{H}]$ calcd. 640.1875, obsd. 640.1848. $R_f = 0.13$ (50% EtOAc in hexane)

^1H NMR (300 MHz, CDCl_3) δ 10.4 (br-s, 1H), 8.53 (dd, $J = 15.5, 21.3$ Hz, 2H), 7.75-7.95 (m, 8H), 7.68 (d, $J = 7.4$ Hz, 2H), 7.4-7.6 (m, 4H), 7.15-7.4 (m, 6H), 6.02 (d, $J = 7.4$ Hz, 1H), 4.75-4.95 (m, 1H), 3.5-3.81 (m, 4H), 3.26-3.45 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 175.51 (d, $J_{\text{CP}} = 12.3$ Hz), 155.79 (s), 143.83 (s), 141.30 (d, $J_{\text{CP}} = 3.1$ Hz), 134.69 (d, $J_{\text{CP}} = 6.3$ Hz), 133.58 (d, $J_{\text{CP}} = 10.6$ Hz), 132.97 (d, $J_{\text{CP}} = 10.5$ Hz), 132.70 (d, $J_{\text{CP}} = 13.7$ Hz), 132.59 (d, $J_{\text{CP}} = 13.5$ Hz), 129.22 (s), 128.95 (d, $J_{\text{CP}} = 15.5$ Hz), 128.66 (s), 127.93 (d, $J_{\text{CP}} = 10.9$ Hz), 127.30 (d, $J_{\text{CP}} = 12.9$ Hz), 126.10 (d, $J_{\text{CP}} = 13.1$ Hz), 125.93 (d, $J_{\text{CP}} = 12.2$ Hz), 125.44 (d, $J_{\text{CP}} = 4.3$ Hz), 120.04 (s), 67.37 (s), 50.81 (s), 46.72 (s), 32.44 (d, $J_{\text{CP}} = 59.8$ Hz). ^{31}P NMR (120 MHz, CDCl_3) δ 39.32. IR (KBr, cm^{-1}) 3305, 3054, 2605, 1719, 1508, 1251, 1080, 741. FAB-MS; $[\text{M} + \text{H}]$ calcd. 628.1711, obsd. 628.1701. $R_f = 0.27$ (3% MeOH in DCM)

^1H NMR (300 MHz, CDCl_3) δ 7.74 (d, $J = 7.4$ Hz, 2H), 7.22-7.55, (m, 10H), 7.06 (d, $J = 15.4$ Hz, 2H), 6.07 (d, $J = 6.1$ Hz, 1H), 4.60-4.72 (m, 1H), 3.98-4.21 (m, 3H), 3.05-3.35 (m, 2H), 2.28 (s, 12H). ^{13}C NMR (100 MHz, CDCl_3) δ 176.17 (br-s), 156.19 (s), 144.00 (s), 141.35 (s), 138.60 (d, $J_{\text{CP}} = 28.6$ Hz), 138.64 (s), 133.72 (s), 128.80 (d, $J_{\text{CP}} = 22.9$ Hz), 128.78 (s), 127.62 (d, $J_{\text{CP}} = 38$ Hz), 125.63 (s), 120.08 (s), 67.63 (s), 51.10 (s), 47.08 (s), 32.60 (d, $J_{\text{CP}} = 55.6$ Hz), 21.55 (s). ^{31}P NMR (120 MHz, CDCl_3) δ 39.21. IR (KBr, cm^{-1}) 3298, 3037, 2918, 1718, 1522, 1449, 1251, 1124, 1048, 851, 759, 740, 691. FAB-MS; $[\text{M} + \text{Li}]$ calcd. 590.2106, obsd. 590.2092. $R_f = 0.3$ (3% MeOH in DCM)

^1H NMR (300 MHz, CDCl_3) δ 7.76 (d, $J = 7.4$ Hz, 2H), 7.62 (dd, $J = 7.2, 16.2$ Hz, 2H), 7.28-7.45 (m, 4H), 6.74-6.88 (m, 4H), 4.02-4.33 (m, 4H), 3.52-3.65 (m, 1H), 3.02-3.19 (m, 1H), 2.38 (d, $J = 21.7$ Hz, 12H), 2.19 (d, $J = 10.7$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 176.36 (s), 156.27 (s), 144.00 (d, $J_{\text{CP}} = 17.8$ Hz), 141.46 (d, $J_{\text{CP}} = 5.7$ Hz), 140.88 (s), 139.58 (d, $J_{\text{CP}} = 10$ Hz), 132.63 (d, $J_{\text{CP}} = 10.3$ Hz), 132.00 (d, $J_{\text{CP}} = 8.9$ Hz), 127.97 (s), 127.40 (s), 125.80 (d, $J_{\text{CP}} = 20$ Hz), 120.16 (s), 67.84 (s), 52.40 (s), 47.20 (s), 40.40 (d, $J_{\text{CP}} = 51.8$ Hz), 23.65 (d, $J_{\text{CP}} = 9.8$ Hz), 21.05 (d, $J_{\text{CP}} = 5.7$ Hz). ^{31}P NMR (120 MHz, CDCl_3) δ 39.83. IR (KBr, cm^{-1}) 3294, 3025, 2967, 2924, 1725, 1604, 1517, 1450, 1401, 1247, 1046, 910, 851, 759, 739, 648. FAB-MS; $[\text{M} + \text{H}]$ calcd. 612.2337, obsd. 612.2331. $R_f = 0.32$ (3% MeOH in DCM)

^1H NMR (300 MHz, CDCl_3) δ 8.20 (d, $J = 7.4$ Hz, 1H), 8.14 (d, $J = 6.3$ Hz, 1H), 7.95 (d, $J = 8.2$ Hz, 1H), 7.78-7.87 (m, 2H), 7.76 (d, $J = 7.7$ Hz, 3H), 7.46-7.54 (m, 3H), 7.35-7.54 (m, 6H), 7.25-7.54 (m, 3H), 6.03 (d, $J = 6.6$ Hz, 1H), 4.61-4.75 (m, 1H), 3.92-4.10 (m, 3H), 3.45-3.62 (m, 1H), 3.28-3.62 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 175.13 (d, $J_{\text{CP}} = 12.8$ Hz), 155.96 (s), 143.92 (s), 143.85 (s), 141.44 (s), 134.32 (d, $J_{\text{CP}} = 9.2$ Hz), 133.97 (s), 133.63 (d, $J_{\text{CP}} = 10.9$ Hz), 133.24 (s), 132.13 (s), 131.80 (s), 131.14 (d, $J_{\text{CP}} = 10.9$ Hz), 129.66 (s), 129.31 (d, $J_{\text{CP}} = 12.3$ Hz), 127.98 (s), 127.37 (s), 126.64 (s), 126.47 (s), 125.61 (s), 124.97 (s), 124.78 (s), 120.18 (s), 67.68 (s), 50.82 (s), 47.06 (s), 32.80 (d, $J_{\text{CP}} = 58.1$ Hz). ^{31}P NMR (120 MHz, CDCl_3) δ 38.20. IR (KBr, cm^{-1}) 3300, 3059, 2588, 1719, 1508, 1449, 1437, 1332, 1250, 773, 760, 741. FAB-MS; $[\text{M} + \text{Li}]$ calcd. 584.1637, obsd. 584.1625. $R_f = 0.2$ (2% MeOH in DCM)

^1H NMR (300 MHz, CDCl_3) δ 8.33 (d, $J = 8.2$ Hz, 1H), 8.06 (dd, $J = 7.2, 16.2$ Hz, 1H), 7.97 (d, $J = 8.2$ Hz, 1H), 7.80-7.90 (m, 2H), 7.74 (d, $J = 8.1$ Hz, 3H), 5.89 (d, $J = 7.1$ Hz, 1H), 4.81-4.95 (m, 1H), 3.83-4.17 (m, 3H), 3.34-3.54 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 175.76 (s), 155.88 (s), 143.88 (s), 141.42 (s), 134.50 (d, $J_{\text{CP}} = 9.2$ Hz), 133.91

(s), 133.30 (s), 132.42 (s), 132.22 (s), 132.04 (d, $J_{\text{CP}} = 8.9$ Hz), 131.89 (s), 131.34 (d, $J_{\text{CP}} = 11.1$ Hz), 129.66 (s), 128.97 (d, $J_{\text{CP}} = 12.9$ Hz), 127.98 (s), 127.35 (s), 126.71 (s), 126.49 (d, $J_{\text{CP}} = 8.0$ Hz), 125.63 (s), 124.85 (s), 124.67 (s), 120.16 (s), 67.61 (s), 50.64 (s), 47.03 (s), 33.00 (d, $J_{\text{CP}} = 54.4$ Hz). ^{31}P NMR (120 MHz, CDCl_3) δ 37.56. IR (KBr, cm^{-1}) 3305, 3058, 2588, 1718, 1508, 1450, 1437, 1332, 1251, 1102, 1048, 908, 798, 773, 760, 740. FAB-MS; $[\text{M} + 2\text{Li} - \text{H}]$ calcd. 590.1719, obsd. 590.1710. $R_f = 0.2$ (2% MeOH in DCM)

^1H NMR (300 MHz, CDCl_3) δ 7.69-7.82 (m, 6H), 7.55-7.62 (m, 2H), 7.23-7.40 (m, 4H), 6.48 (br-d, $J = 4.7$ Hz, 1H), 4.53-4.67 (m, 1H), 4.1-4.26 (m, 3H), 6.48 (d, $J = 10.4$ Hz, 6H), 3.00-3.21 (m, 2H), 1.41 (s, 36H). ^{13}C NMR (100 MHz, CDCl_3) δ 175.90 (d, $J_{\text{CP}} = 15.8$ Hz), 162.98 (d, $J_{\text{CP}} = 12.0$ Hz), 156.19 (s), 144.73 (d, $J_{\text{CP}} = 12.3$ Hz), 144.52 (d, $J_{\text{CP}} = 12.3$ Hz), 143.90 (s), 141.40 (s), 130.30 (s), 130.04 (s), 127.92 (s), 127.42 (s), 125.65 (s), 120.12 (s), 67.63 (s), 64.71 (s), 51.43 (s), 47.16 (s), 36.38 (s), 33.98 (d, $J_{\text{CP}} = 57.3$ Hz), 32.13 (s). ^{31}P NMR (120 MHz, CDCl_3) δ 40.33. IR (KBr, cm^{-1}) 3289, 2962, 1725, 1509, 1450, 1410, 1362, 1262, 1228, 1142, 1116, 1006, 740. FAB-MS; $[\text{M} + \text{H}]$ calcd. 812.4114, obsd. 812.4100. $R_f = 0.3$ (2% MeOH in DCM)

^1H NMR (300 MHz, CDCl_3) δ 10.01 (br-s, 1H), 7.97 (t, $J = 15.4$ Hz, 2H), 7.76 (d, $J = 7.2$ Hz, 2H), 7.61 (dd, $J = 7.2, 15.4$ Hz, 2H), 7.29-7.45 (m, 4H), 7.12-7.25 (m, 2H), 6.98-7.08 (m, 2H), 6.32 (d, $J = 6.6$ Hz, 1H), 4.48-6.63 (m, 1H), 4.08-4.24 (m, 3H), 3.30-3.51 (m, 2H), 2.30 (d, $J = 24.7$ Hz, 6H), 2.06 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 175.88 (d, $J_{\text{CP}} = 14.1$ Hz), 156.03 (s), 143.85 (s), 141.48 (s), 137.45 (d, $J_{\text{CP}} = 11.5$ Hz), 137.32 (d, $J_{\text{CP}} = 9.1$ Hz), 136.40 (d, $J_{\text{CP}} = 12.6$ Hz), 136.32 (d, $J_{\text{CP}} = 12.6$ Hz), 133.09 (d, $J_{\text{CP}} = 6.6$ Hz), 132.32 (d, $J_{\text{CP}} = 12.6$ Hz), 128.03 (s), 127.44 (d, $J_{\text{CP}} = 4.3$ Hz), 125.70 (d, $J_{\text{CP}} = 16.3$ Hz), 120.26 (s), 67.75 (s), 50.82 (s), 47.12 (s), 31.62 (d, $J_{\text{CP}} = 57.0$ Hz), 21.30 (d, $J_{\text{CP}} = 10.0$ Hz), 25.10 (d, $J_{\text{CP}} = 8.9$ Hz). ^{31}P NMR (120 MHz, CDCl_3) δ 37.37. IR (KBr, cm^{-1}) 3289, 3037, 2922, 2599, 1719, 1517, 1486, 1450, 1248, 1046, 909, 816, 740. FAB-MS; $[\text{M} + 2\text{Li} - \text{H}]$ calcd. 596.2188, obsd. 596.2179. $R_f = 0.3$ (3% MeOH in DCM)

General method for solid phase peptide synthesis and phosphine deprotection:

Fmoc protected crowns were deprotected with 20% piperidine in DMF for 30 min. The crowns were then washed with DMF 3 X, MeOH 3 X and DMF 3 X. Peptide couplings were carried out in DMF, as concentrated as possible, with 5 equivalents of Fmoc-amino acid, DIC and HOBt for 3 hours. This procedure was repeated 5 times and the peptide was acetylated for 30 min. with 20% Ac_2O , 5% DIPEA in DMF. Following acetylation, the wash sequence was ended with DCM 3 X and the crowns were dried in-vacuo. Prior to phosphine deprotection the crowns were placed in 20-mL scintillation vials and sealed

with rubber septa under N₂. Throughout the deprotection sequence the crowns were kept under nitrogen.

The deprotection sequence was started by first treating with 10 equivalents of MeOTf in DCM overnight. The crowns were next washed with DCM 3 X and THF 3 X, and then treated with 10 equivalents of HMPT in THF for 2 hours. The crowns were washed with THF 3 X and MeCN 3 X and finally treated with 1 equivalent of [Pd(allyl)Cl]₂ for 30 min. in MeCN. After a final wash with MeCN 6 X the crowns were dried in-vacuo and transferred to individual 20-mL scintillation vials sealed under N₂.

General method for solution phase peptide synthesis and phosphine deprotection:

To a Boc-protected amino acid in DCM was added 1.5 equiv. of PyBOP and an ammonium salt of an amino ester. 3 equiv. of DIPEA were added and the reaction was allowed to stir for 30 minutes. The reaction mixture was then washed with 3N HCl, sat. sodium bicarb., and brine. The DCM solution was dried with Na₂SO₄, filtered, concentrated and chromatographed on silica gel. The Boc-methyl ester protected dipeptide was then treated with a 50% solution of TFA in DCM until complete removal of the Boc group as judged by TLC. The reaction mixture was then concentrated, dissolved in toluene and concentrated, dissolved in chloroform and concentrated and finally dissolved in DCM and concentrated before drying in-vacuo for 30 minutes. This coupling/deprotection sequence was repeated until the desired Boc-methyl ester protected six-mer. was attained.

10 μ mol of the bis-phosphine ligands were treated with 400 mg of Raney-Ni* in MeCN (under N₂) for 2 hours (6-membered ring) or until complete by TLC (5-membered ring).

The Raney-Ni was allowed to settle and the solution was syringe filtered into a schlenk tube. The Raney-Ni was washed with MeCN 3 X 3 mL and syringe filtered into the schlenk tube and concentrated in-vacuo.

*Prior to deprotection, the Raney-Ni slurry was washed with MeOH until the MeOH was clear and then washed with MeCN 3 X.

Spectral data of peptide ligands:

^1H NMR (600 MHz, CDCl_3) δ 7.68-7.83 (m, 3H), 7.20-7.50 (m, 20H), 7.08 (s, 2H), 5.57-5.62 (m, 1H), 4.90-5.00 (m, 1H), 4.70-4.80 (m, 1H), 4.60-4.64 (m, 1H), 4.35-4.42 (m, 2H), 3.88-3.94 (m, 1H), 3.68 (s, 3H), 3.44-3.50 (br-s, 2H), 3.27-3.35 (m, 1H), 3.11-3.20 (m, 1H), 2.95-3.04 (m, 2H), 2.30 (s, 6H), 2.27 (s, 6H), 2.14-2.22 (m, 1H), 1.95-2.40 (m, 2H), 1.80-1.86 (m, 1H), 1.46-1.62 (m, 4H), 1.37-1.44 (m, 9H), 0.80-0.92 (m, 12H). ^{13}C NMR (100 MHz, CDCl_3) δ 173.05, 171.81, 170.98, 170.67, 170.51, 170.28, 170.11, 170.02, 155.07, 138.53, 138.49, 138.44, 138.41, 133.68, 133.60, 132.65, 132.13, 131.93, 131.66, 131.55, 131.40, 131.20, 131.12, 131.04, 128.77, 128.69, 128.64, 128.56, 128.50, 128.44, 128.37, 128.14, 127.86, 127.80, 127.17, 79.97, 60.91, 58.75, 58.28, 52.12, 51.09, 49.46, 48.39, 47.50, 40.57, 33.31, 32.93, 28.86, 28.22, 24.96, 24.56, 22.59, 22.00, 21.79, 21.24, 21.18, 19.77, 17.58. ^{31}P NMR (120 MHz, CDCl_3) δ 43.67, 40.67. IR (KBr, cm^{-1})

3300, 3042, 2952, 2924, 2868, 1737, 1676, 1519, 1435, 1362, 1242, 1161, 848, 691.

MALDI-MS; calcd. 1204.5, obsd. [M + Na] 1227.5.

^1H NMR (300 MHz, CDCl_3) δ 7.38-7.63 (m, 10H), 7.05-7.15 (m, 4H), 6.84 (br-d, $J = 5.8$ Hz, 1H), 6.70 (br-d, $J = 7.4$ Hz, 1H), 5.20-5.30 (m, 1H), 4.60-4.79 (m, 2H), 4.19-4.25 (m, 1H), 3.89-4.09 (m, 2H), 3.68-3.83 (m, 4H), 3.57 (s, 3H), 3.22-3.51 (m, 3H), 3.09-3.22 (m, 2H), 2.85-3.01 (m, 1H), 2.27-2.37 (m, 24H), 1.80-2.15 (m, 4H), 1.42 (s, 9H), 1.11 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 172.34, 171.82, 171.00, 170.92, 170.62, 170.53, 169.97, 168.43, 155.43, 138.57, 138.53, 138.48, 138.45, 138.37, 138.22, 138.14, 133.53, 133.46, 133.21, 132.43, 131.89, 131.58, 131.06, 128.96, 128.89, 128.77, 128.69, 128.63, 128.57, 128.35, 128.28, 128.06, 79.82, 61.11, 52.02, 50.24, 50.09, 47.74, 46.86, 43.45, 41.07, 34.63, 34.27, 32.50, 32.12, 28.44, 28.23, 25.05, 21.23, 21.21, 16.02. ^{31}P NMR (120 MHz, CDCl_3) δ 40.65, 39.57. IR (KBr, cm^{-1}) 3294, 3025, 2975, 2919, 2241, 1748, 1715, 1667, 1525, 1441, 1362, 1239, 1208, 1166, 1122, 1041, 848, 727, 691, 632. MALDI-MS; calcd. 1100.4434, obsd. [M + Na] 1123.67.

General allylic substitution procedure:

Heterogeneous Catalysis: To the metallated crown (5-6 μ mol) under N_2 was added 1-2 mL of solvent and 200 μ mol of substrate. In a separate flask under N_2 600 μ mol BSA was added dropwise to 600 μ mol of dimethyl malonate and 600 μ mol TBAF (1M in THF). This exothermic reaction is allowed to cool to room temperature and is then added dropwise to the catalyst and substrate. The reactions were monitored by TLC using $KMnO_4$ stain. Upon completion, or after overnight stirring, the reactions were concentrated and chromatographed on silica gel with 10% EtOAc in Hexane. Samples for evaluating enantioselectivity were prepared by adding 0.5 – 0.6 mL of C_6D_6 to ~5 mg of product and 10 – 15 mg of $Eu(hfc)_3$. Enantiomeric excesses were determined by integrating the two pairs of singlets (4.1 – 4.6 ppm for the 5-membered ring and 3.7 – 4.5 ppm for the 6-membered ring) corresponding to the malonate methyl esters.

Homogeneous Catalysis: The ligand (6%), $[Pd(allyl)Cl]_2$ (2%) and 200 μ mol of substrate were stirred in 1-2 mL of solvent. The rest of the procedure is the same as previously described except for only 300 μ mol of nucleophile were used.

 1H NMR for allylic substitution products:

Propanedioic acid, 2-cyclopentene-1-yl-dimethyl ester

1H NMR (300 MHz, $CDCl_3$) δ 5.82-5.85 (m, 1H), 5.64-5.67 (m, 1H), 3.75 (s, 6H), 3.26-3.37 (m, 2H), 2.30-2.38 (m, 2H), 2.09-2.16 (m, 1H), 1.54-1.63 (m, 1H).

Propanedioic acid, 2-cyclohexene-1-yl-dimethyl ester ^1H NMR (300 MHz, CDCl_3) $\square$

5.74-5.82 (m, 1H), 5.52 (dd, $J = 2.3, 10.2$ Hz, 1H), 3.75 (s, 6H), 3.29 (d, $J = 9.2$ Hz, 1H),

2.86-2.95 (m, 1H), 1.96-2.06 (m, 2H), 1.26-1.81 (m, 4H).