Proline Based P,N Ligands in Palladium Catalyzed Asymmetric π-allyl Additions.

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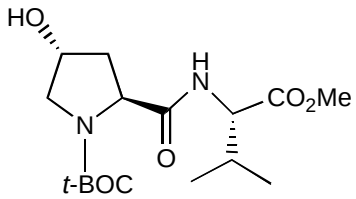
Compounds appearing in the supplementary section that are not in the body of the paper are numbered with Roman numerals.

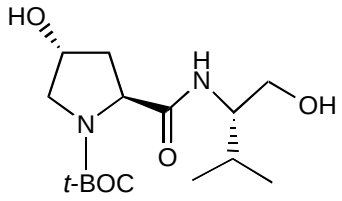
(2S, 2'S, 4R)-N-*tert*-Boc-2-[[N-[(2'-methoxycarbonyl-2'-isopropyl)methyl]-1'-amino]carbonyl]-4-hydroxyl-proline (7).



A mixture of N-*t*-Boc-L-hydroxylproline (3.50 g, 15.1 mmol), EDC (5.80 g, 30.2 mmol), and HOBt (4.10 g, 30.2 mmol) was stirred in 60 mL of dry CH_2Cl_2 at 0 ˚C for 5 min. In a separate flask, L-valine methyl ester hydrochloride (3.80 g, 22.7 mmol) and Et_3N (4.20 mL, 30.2 mmol) were stirred for 10 min in 60 mL CH_2Cl_2 after which the mixture was added to the active ester. The resulting clear solution was warmed to room temperature and stirred for 1 day. After evaporation of CH_2Cl_2 the residue was dissolved in EtOAc / H_2O (4 /1, v/v). The organic layer was washed with 1N HCl (aq.), saturated $NaHCO_3$ (aq.), H_2O and brine then dried over Na_2SO_4. The solvent was removed by evaporation leaving a residue that was subjected to column chromatography (eluant: EtOAc/*n*-hexanes (95 /5, v/v) to yield 4.68 g (90%) as a white foamy solid*: The NMR*

spectra are reported for a mixture of two rotamers, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (m, 1H), 6.85 (m, 1H), 4.40 (m, 3H), 3.66 (s, 3H), 3.50-3.20 (m, 2H), 2.08 (dqq, *J* = 6.0, 6.8 and 6.7 Hz, 1H), 1.42 (s, 9H), 0.88 (d, *J* = 6.8 Hz, 3H) 0.85 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 171.7, 155.5, 154.5, 80.2, 69.2, 68.6, 60.0, 58.2, 57.0, 54.6, 54.1, 51.6, 39.3, 36.2, 30.7, 27.9, 17.7, 17.6, 17.5, 17.3; IR (film) 3408.0, 3017.5, 2972.1, 1739.7, 1683.7, 1521.8, 1395.4, 1216.1, 1161.1, 745.1, 668.3 cm^{-1}; MS-FAB m/z (% rel intensity) 345 (MH^+, 25), 289 (22), 245 (100)**;** HRFAB Calcd for $C_{16}H_{29}N_2O_6$ (MH^+) m/e 345.2025, measured m/e 345.2036; Anal. Calcd for $C_{16}H_{28}N_2O_6$: C, 55.80; H, 8.19. Found C, 55.36; H, 7.87.

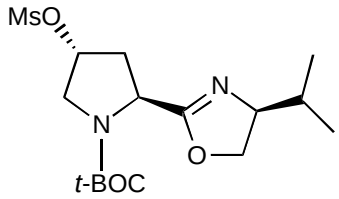
(2S, 2'S, 4R)-N-*tert*-Boc-2-[[N-[(2'-hydroxymethyl-2'-isopropyl)methyl]-1'-amino]carbonyl]-4-hydroxyl-proline (8).



To a solution of (2S, 2'S, 4R)-N-*tert*-Boc-2-[[N-[(2'-methoxycarbonyl-2'-isopropyl)methyl]-1'-amino]carbonyl]-4-hydroxyl-proline (**7**) (4.68 g, 13.4 mmol) in 200 mL of THF, lithium borohydride solution (13.4 mL, 26.6 mmol, 2M in THF) was slowly added at 0 ^{o}C. The cooling bath was removed, and stirring was continued at room temperature for 16 h. The reaction was quenched by adding 2N HCl, and THF was evaporated under reduced pressure. The residue was dissolved in EtOAc / H_2O (4/1, v/v), and the aqueous layer was extracted with EtOAc three times. The combined organic layers were then washed with a small amount of 1N NaOH and brine and dried over Na_2SO_4. Evaporation of the solvent gave 3.68 g (87%) of **5** as a white foam. This material was used for next step without further purification. The sample was judged by

NMR to be at least 90% pure: *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 and 6.72 (2 br s, 1H), 4.25 (m, 3H), 3.55-3.20 (m, 5H), 2.25 (m, 1H), 1.96 (m, 1H), 1.73 (m, 1H), 1.30 (m, 9H), 0.75 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$ + 1 drop of DMSO-d_6) δ 173.5, 172.5, 155.7, 154.5, 80.5, 69.2, 68.6, 62.7, 62.6, 58.9, 58.8, 56.9, 56.8, 54.5, 37.1, 37.0, 28.8, 28.1, 19.3, 18.8, 18.7, 18.1; IR (film) 3410.0, 3320.0, 3055.1, 2986.6, 1675.1, 1533.3, 1420.5, 1265.2, 1163.0, 895.8, 739.7, 668.3 cm^{-1}; MS-FAB m/z (% rel intensity) 317 (MH^+, 100), 303 (58); HRFAB Calcd for $C_{15}H_{29}N_2O_5$ (MH^+) m/e 317.2076, measured m/e 317.2071.

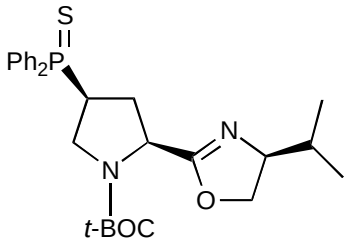
(2S, 5'S, 4R)-N-*tert*-Boc-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-(methylsulfonyl)oxyl-proline (12).



A sample of **8** (3.58 g, 11.3 mmol) was dissolved in CH_2Cl_2 / Et_3N (200 mL, 3/1, v/v) and the solution was cooled to 0 ˚C. To the solution, MsCl (3.5 mL 45.2 mmol) in 10 mL of CH_2Cl_2 was slowly added, with stirring through an addition funnel after which the reaction was stirred at room temperature for 16 h. This resulted in a dark-brownish solution with the precipitation of ammonium salt. The solvent was removed by evaporation, leaving a residue that was dissolved in EtOAc / H_2O (4/1, v/v). The organic solution was then washed with water twice and dried over Na_2SO_4. Evaporation of the solvent gave the crude product which was purified by flash chromatography (eluant: EtOAc/*n*-hexanes/Et_3N, 84/15/1) to afford a brownish viscous oil: *The NMR spectra are reported for a mixture of two rotamers*, ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (m, 1H), 4.48 (dd, *J* = 7.3 and 7.7 Hz, 1H), 4.10 (dd, *J* = 8.8 and 8.4 Hz, 1H), 3.91-3.80 (m, 2H),

3.74-3.57 (m, 2H), 2.92 (s, 3H), 2.53-2.35 (m, 1H), 2.23-2.17 (m, 1H), 1.61 (m, 1H), 1.33 (minor) and 1.29 (major) (s, 9H), 0.79 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 153.5, 80.1, 78.0, 77.6, 71.7, 71.4, 70.0, 52.9, 52.5, 52.0, 51.8, 38.3, 37.7, 36.6, 32.2, 32.0, 28.0, 18.2, 18.1, 17.6, 17.4; IR (film) 3019.4, 2970.2, 1700.2, 1690.0, 1405.1, 1368.4, 1215.1, 1173.6, 967.2, 901.7, 756.1, 668.3 cm^{-1}; MS-FAB m/z (% rel intensity) 377 (MH^+, 65), 321 (100); HRFAB Calcd for $C_{16}H_{29}N_2O_6S$ (MH^+) m/e 377.1746, measured m/e 377.1735.

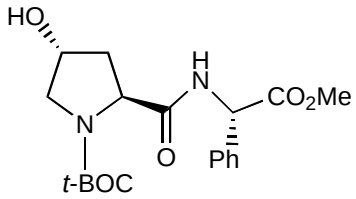
(2S, 5'S, 4S)-N-*tert*-Boc-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (15).



Ph_2PH (0.59 mL, 3.4 mmol) was added to a -78 ˚C suspension of $NaNH_2$ (0.17 g, 4.25 mmol) in degassed THF. After stirring for 15 min. the reaction mixture was allowed to warm to room temperature and stirring was continued for 3 h. To this orange solution was added a solution of **12** (0.64 g, 1.7 mmol in 15 mL of THF) and the reaction mixture was stirred at room temperature for 12 h. Next S_8 (0.11 g, 3.4 mmol in 15 mL THF) was added at 0 ˚C and the stirring was continued for 2 h at room temperature. After removal of solvent under reduced pressure, the residue was treated with NH_4Cl (sat.) and extracted with EtOAc three times. The EtOAc solutions were combined, and evaporated to the crude phosphine that was chromatographed on silica gel with EtOAc/hexane/Et_3N (66/33/1, v/v/v) to afford 0.55 g (65%) of **15** as a white solid: R_f = 0.30 (EtOH/*n*-hexanes: 2/1); mp 76 - 78 ºC; *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.81 (m, 4H), 7.54-7.44 (m, 6H), 4.52 (dd, J_{HH} = 8.1 and 8.5 Hz, 1H), 4.23 (m, 1H), 4.05 (m, 1H), 3.90 (m, 1H), 3.68 (m, 2H), 3.30

(m, 1H), 2.53 (m, 1H), 2.23 (m, 1H), 1.70 (m, 1H), 1.39 (m, 9H), 0.92 (d, J_{HH} = 6.6 Hz, 3H), 0.85 (d, J_{HH} = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 153.5, 131.8 (d, J_{CP} = 2.5 Hz), 131.1 (d, J_{CP} = 10.1 Hz), 128.8 (d, J_{CP} = 12.1 Hz), 80.2, 72.0, 70.4, 60.3, 55.3 (d, J_{CP} = 12.0 Hz), 47.4, 37.6 (d, J_{CP} = 61.4 Hz), 32.3 (d, J_{CP} = 25.1 Hz), 28.3, 18.6, 18.1; ^{31}P (120 MHz, $CDCl_3$) δ 44.12 (major) and 43.94 (minor), 44.20 (45 ^{o}C); IR (film) 3019.4, 2978.9, 1695.0, 1479.0, 1405.1, 1216.1, 1160.1, 1104.2, 758.0, 669.3 cm^{-1}; MS-FAB m/z (% rel intensity) 499 (MH^+, 100), 399 (13), 281 (25), 219 (35); HRFAB Calcd for $C_{27}H_{36}N_2O_3PS$ (MH^+) m/e 499.2184 measured m/e 499.2189; Anal. Calcd for $C_{27}H_{35}N_2O_3PS$: C, 65.04; H, 6.76. Found C, 64.89; H. 7.07.

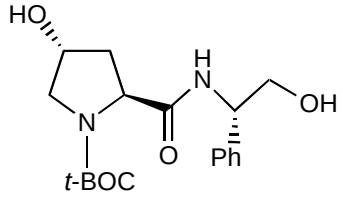
(2S, 2'S, 4R)-N-*tert*-Boc-2-[[N-[(2'-methoxycarbonyl-2'-phenyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (9).



(2S, 2'S, 4R)-N-*tert*-Boc-2-[[N-[(2'-methoxycarbonyl-2'-phenyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (**9**) was prepared by the procedure described above, using L-phenylglycine methyl ester hydrochloride in 95% yield as a white semi-solid*: The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 and 7.20 (2 broad singlets from one proton, 1H), 7.34 (m, 5H), 5.53 (m, 1H), 4.48-4.38 (m, 2H), 3.70 (s, 3H), 3.64-3.40 (m, 2H), 2.59 (br s, 1H), 2.34-2.04 (m, 2H), 1.44 and 1.33 (two broad singlets from t-Boc group, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 171.4, 170.8, 155.5, 154.4, 135.8, 128.6, 128.3, 128.2, 128.1, 127.1, 127.0, 126.9, 80.3, 69.1, 68.7, 59.0, 58.2, 56.1, 54.3, 52.4, 39.0, 36.5, 28.8, 27.5; IR 3416.7, 3019.4, 1744.5, 1683.8, 1405.1, 1216.1, 922.0, 756.1, 568.0 cm^{-1}; MS-FAB m/z

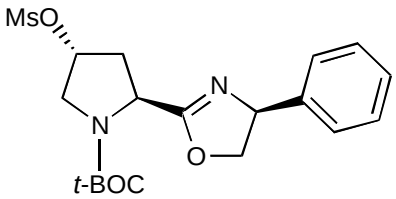
(% rel intensity) 379 (MH^+, 23), 323 (23), 279 (100); HRFAB Calcd for $C_{19}H_{27}N_2O_6$ (MH^+) m/e 379.1869, measured m/e 379.1859; Anal. Calcd for $C_{19}H_{26}N_2O_6$: C, 60.31; H, 6.93. Found C, 59.92; H, 6.80.

(2S, 2'S, 4R)-N-*tert*-Boc-2-[[N-[(2'-methoxycarbonyl-2'-phenyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (10)



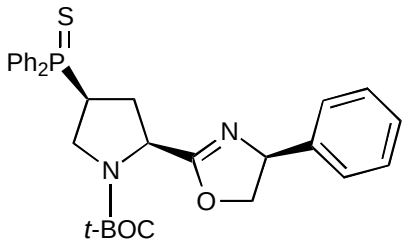
Compound **10** was prepared by the procedure described for **7**, using (2S, 2'S, 4R)-N-*tert*-Boc-2-[[N-[(2'-methoxycarbonyl-2'-phenyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (**II**). The product was obtained in 90% yield as a white foam: *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 1H), 7.31-7.21 (m, 5H), 5.10-5.01 (m, 1H), 4.44-4.36 (m, 2H), 3.89-3.00 (m, 6H), 2.32-2.06 (m, 2H), 1.47-1.26 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 173.1, 172.6, 172.2, 155.6, 155.1, 154.8, 154.6, 138.9, 138.6, 128.3, 127.2, 126.7, 126.5, 80.5, 80.4, 69.2, 68.7, 65.8, 65.0, 59.3, 58.8, 55.5, 55.3, 54.4, 39.4, 38.0, 37.0, 28.0, 27.9; IR (film) 3419.6, 3335.0, 3019.4, 1683.8, 1540.1, 1418.6, 1216.1, 1162.0, 757.0, 668.3 cm^{-1}; MS-FAB m/z (% rel intensity) 351 (MH^+, 65), 295 (55), 251 (100); HRFAB Calcd for $C_{18}H_{27}N_2O_5$ (MH^+) m/e 351.1920, measured m/e 351.1919.

(2S, 5'S, 4R)-N-*tert*-Boc-2-(4',5'-dihydro-5'-phenyl-1',3'-oxazole-2'-yl)-4-(methylsulfonyl)oxyl-proline (13).



13 was prepared by the procedure described for **12**, using the diol **10**, and was obtained in 56% yield as a yellowish vicious oil: *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.20 (m, 5H), 5.32 (m, 1H), 5.26-5.17 (m, 1H), 4.76-4.60 (m, 2H), 4.18-4.07 (m, 1H), 3.92-3.75 (m, 2H), 3.05 (2s, 3H), 2.74-2.57 (m, 1H), 2.50-2.40 (m, 1H), 1.46 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 167.7, 153.5, 153.3, 142.0, 141.7, 128.5, 128.4, 127.5, 126.5, 126.3, 126.1, 80.5, 78.0, 77.7, 75.4, 75.2, 74.9, 74.7, 69.4, 69.2, 52.9, 52.7, 52.5, 52.0, 51.8, 38.4, 38.1, 37.9, 36.9, 36.7, 28.1; IR (film) 3019.4, 1700.2, 1405.1, 1368.4, 1216.1, 1173.6, 940.0, 901.7, 764.7, 669.3 cm^{-1}; MS-FAB m/z (% rel intensity) 411 (MH^+, 30), 355 (100); HRFAB Calcd for $C_{19}H_{27}N_2O_6S$ (MH^+) m/e 411.1590, measured m/e 411.1572.

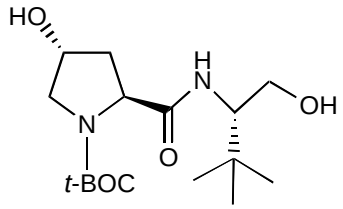
(2S, 5'S, 4S)-N-*tert*-Boc-2-(4',5'-dihydro-5'-phenyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (16).



To a -78 ˚C suspension of $NaNH_2$ (0.061 g, 1.56 mmol) in degassed THF was added Ph_2PH (0.24 mL, 1.37 mmol). After stirring for 15 min. the cooling bath was removed and the solution was allowed to warm to room temperature where stirring was continued for 3 h. During this time the solution turned deep orange. Then **13** (0.53 g, 1.30 mmol) in 15 mL of THF was transferred over via canula, stirring was continued for 12 h at room temperature. After this time the solvent was removed under reduced pressure. The residue was treated with NH_4Cl (sat.) and extracted with EtOAc three times. The EtOAc solutions were combined, and evaporated to yield the crude phosphine. The crude phosphine was treated with 15 mL of methanol and 15 mL of water containing $Na_2S_2O_3$

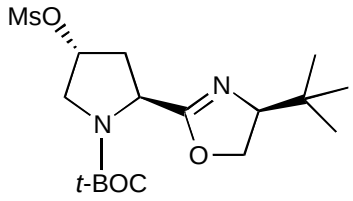
(1.60 g, 10.4 mmol) the suspension was heated to 45 - 50 ˚C, during which the solution turned clear. After stirring overnight the methanol was removed by evaporation, leaving a residue that was taken up with EtOAc / H_2O (4:1). The aqueous layer was extracted with EtOAc twice, and the EtOAc solution was washed with H_2O, brine and dried over Na_2SO_4, and evaporated to give crude phosphine sulfide that was chromatographed on silica gel by using gradient elution (EtOAc/Hexanes/Et_3N, 50/49/1 to 66/33/1, v/v/v) to yield **13** (0.25 g, 36%) as a white solid: R_f = 0.25 (EtOH/*n*-hexanes: 1/1); mp 86 - 88 ºC; *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.82 (m, 4H), 7.55-7.43 (m, 6H), 7.32-7.20 (m, 5H), 5.20 (dd, J_{HH} = 9.8 and 8.3 Hz, 1H), 4.62 (J_{HH} = 8.5 and 8.6 Hz, 1H), 4.17 (m, 2H), 3.86-3.58 (m, 2H), 3.36 (m, 1H), 2.65 (m, 1H), 2.34 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 143.4, 141.9, 131.8 (d, J_{CP} = 3.0 Hz), 131.0 (d, J_{CP} = 10.1 Hz), 128.7 (d, J_{CP} = 12.0 Hz), 128.6 (d, J_{CP} = 7.6 Hz), 127.5, 126.6, 126.4, 80.2, 75.0, 69.4, 55.2 (d, J_{CP} = 11.0 Hz), 47.3, 37.6 (d, J_{CP} = 60.1 Hz), 31.9 (d, J_{CP} = 47.1 Hz), 28,2, 28.1; ^{31}P (120 MHz, $CDCl_3$) δ 44.3 (major), 44.1 (minor); IR (film) 3019.4, 2980.8, 1695.3, 1404.1, 1216.1, 1160.1, 755.1, 668.3 cm^{-1}; MS-FAB m/z (% rel intensity) 539 (MLi^+, 49), 439 (90), 294 (20); HRFAB Calcd for $C_{30}H_{33}N_2O_3PSLi$ (MLi^+) m/e 539.2109, measured m/e 539.2115; Anal. Calcd for $C_{30}H_{33}N_2O_3PS$: C, 67.52; H, 6.42. Found C, 67.67; H. 6.21.

(2S, 2'S, 4R)-N-*tert*-Boc-2-[[N-[(2'-hydroxymethyl-2'-*tert*-butyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (11).



Compound **11** was prepared by the procedure described for (2S, 2'R, 4R)-N-*tert*-Boc-2-[[N-[(2'-hydroxymethyl-2'-isopropyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (**7**), using (S)-*tert*-lucinol. It was obtained in 87% yield as a white foam: *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 and 6.40 (2 m, 1H), 4.48 (m, 2H), 3.87-3.74 (m, 4H), 3.49-3.40 (m, 4H), 2.41 (m, 1H), 2.11 (m, 1H), 1.47 (s, 9H), 0.92 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$ + 1 drop of DMSO-d_6) δ172.6, 156.1, 80.8, 69.3, 62.3, 59.7, 59.0, 54.5, 36.9, 33.3, 28.2, 26.6; IR (film) 3365.6, 2967.3, 1675.1, 1558.4, 1405.1, 1162.0, 1047.0, 1027.0, 909.4, 732.9, 647.1 cm^{-1}; MS-FAB m/z (% rel intensity) 331 (MH^+, 100), 275 (82), 231 (100), 154 (100); HRFAB Calcd for $C_{16}H_{31}N_2O_5$ (MH^+) m/e 331.2233, measured m/e 331.2229.

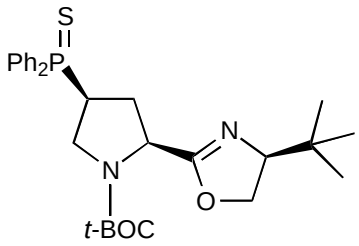
(2S, 5'S, 4R)-N-*tert*-Boc-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-(methylsulfonyl)oxyl-proline (14).



A sample of **11** (3.60 g, 10.9 mmol) was dissolved in 200 mL of CH_2Cl_2 / Et_3N (3/1, v/v) and then cooled to 0 ˚C. It was then added to a solution of MsCl (3.4 mL, 43.6 mmol) in 10 mL of CH_2Cl_2 after which the reaction mixture was refluxed for 20 h. The solvent was removed from the resulting dark-brownish solution by evaporation, leaving a residue that was dissolved in EtOAc / H_2O (4/1, v/v). The organic solution was washed with water twice and dried over Na_2SO_4. Removal of the solvent by evaporated gave the crude product that was purified by flash chromatography (eluant: EtOAc/*n*-hexanes/Et_3N, 79/20/1) to afford 3.82 g (90%) of **14** as a brownish vicious oil: *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28

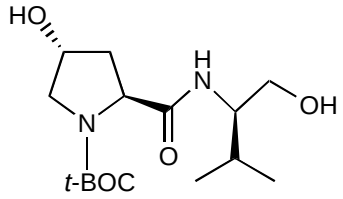
(m, 1H), 4.65 (dd, J = 7.3 and 7.7 Hz, 1H), 4.21-4.10 (m, 2H), 3.90-3.75 (m, 3H), 3.09 (s, 3H), 2.59 (m, 1H), 2.35 (m, 1H), 1.47 (minor) and 1.44 (major) (s, 9H), 0.87 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 153.3, 80.1, 78.0, 77.6, 75.4, 75.2, 68.7, 52.9, 52.5, 51.8, 38.3, 37.8, 36.6, 33.4, 28.0, 25.5; IR (film) 3019.4, 2976.9, 1700.2, 1690.0, 1405.1, 1367.5, 1216.1, 1173.6, 966.3, 901.7, 757.0, 668.3 cm^{-1}; MS-FAB m/z (% rel intensity) 391 (MH^+, 95), 335 (100); HRFAB Calcd for $C_{17}H_{31}N_2O_6S$ (MH^+) m/e 391.1903, measured m/e 391.1901.

(2S, 5'S, 4S)-N-*tert*-Boc-2-(4',5'-dihydro-5'-*tert*-butyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (17).



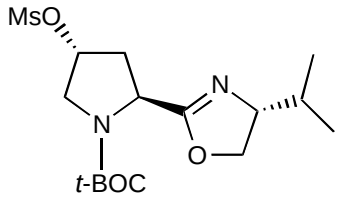
Compound **17** was prepared by the procedure described for **15**, using **14**, and was obtained in 22% yield as a white solid: R_f = 0.4 (EtOAc/*n*-hexanes: 3/2); mp 78 -80^{o}C; *The NMR spectra are reported for a mixture of two rotamers*, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.80 (m, 4H), 7.51-7.30 (m, 6H), 4.56 (dd, J_{HH} = 7.8 and 9.3 Hz, 1H), 4.20-4.12 (m, 2H). 3.84 (m, 1H), 3.65 (m, 2H), 3.30 (m, 1H), 2.50 (m, 1H), 2.24 (m, 1H), 1.40 (s, 9H), 0.85 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 153.4, 131.7 (d, J_{CP} = 3 Hz), 131.0 (d, J_{CP} = 9.8 Hz), 128.74 (d, J_{CP} = 12.0 Hz), 128.67 (d, J_{CP} = 12.0 Hz), 80.1, 75.5, 68.9, 55.3 (d, J_{CP} = 12.0 Hz), 47.3, 37.4 (d, J_{CP} = 60.2 Hz), 33.5, 32.0, 28.2, 25.6; ^{31}P (120 MHz, $CDCl_3$) δ 44.11 (major), 43.89 (minor); IR (film) 2977.0, 2905.6, 2865.0, 1693.4, 1478.4, 1404.1, 1367.5, 1246.0, 1161.1, 1104.2, 999.1, 960.0, 909.4, 731.0, 649.0 cm^{-1}; MS-FAB m/z (% rel intensity) 513 (MH^+, 100), 413 (20), 295 (25); HRFAB Calcd for $C_{28}H_{38}N_2O_3PS$ (MH^+) m/e 513.2341, measured m/e 513.2322.

(2S, 2'R, 4R)-N-*tert*-Boc-2-[[N-[(2'-hydroxymethyl-2'-isopropyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (I).



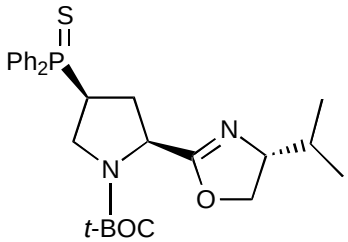
A mixture of N-*t*-Boc-L-hydroxylproline (7.40 g, 32.3 mmol), EDC (12.38 g, 64.6 mmol), HOBt 8.73 g (64.6 mmol) and D-valinol (5.00 g, 48.5 mmol) were stirred in 200 mL of CH_2Cl_2 at room temperature for 1 day. After which the CH_2Cl_2 was removed and the residue was dissolved in EtOAc. The organic layer was washed with 1N HCl (aq.), saturated $NaHCO_3$ (aq.), H_2O and brine and dried over Na_2SO_4. The solvent was removed by evaporation leaving a residue that was subjected to column chromatography (gradient eluant: EtOAc to 5% of MeOH/EtOH, v/v) to yield the product (3.65 g, 36%) as a white foam: *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 and 6.70 (2 broad singlets, 1H), 4.44 (br s, 2H), 4.33 (m, 1H), 3.71 (m, 3H), 3.60-3.46 (m, 2H), 2.20 (m, 2H), 1.85 (m., 1H), 1.44 (s, 9H), 1.10 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.6 Hz 3H), 0.91(d, J = 6.6 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$ + 1 drop of DMSO-d_6) δ 173.0, 155.4, 80.7, 69.6, 63.0, 59.2, 57.2, 55.0, 38.0, 28.9 (minor) and 28.2 (major), 19.5, 18.7; IR (film) 3416.7, 3326.1, 1675.1, 1533.8, 1419.5, 1216.1, 1163.0, 761.8, 669.3 cm^{-1}; MS-FAB m/z (% rel intensity) 317 (MH^+, 100), 217 (91); HRFAB Calcd for $C_{16}H_{29}N_2O_5$ (MH^+) m/e 317.2076, measured m/e 317.2075.

(2S, 5'R, 4R)-N-*tert*-Boc-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-(methylsulfonyl)oxyl-proline (II).



(2S, 5'R, 4R)-N-*tert*-Boc-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-(methylsulfonyl)oxyl-proline (**II**) was prepared by the procedure described for **8**, using the diol (2S, 2'R, 4R)-N-*tert*-Boc-2-[[N-[(2'-hydroxymethyl-2'-isopropyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (**I**), and was obtained in 54% yield as a brownish vicious oil: *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (m, 1H), 4.65 (m, 1H), 4.30 (m, 1H), 3.94-3.71 (m, 4H), 3.05 (s, 3H), 2.48 (m, 1H), 2.38 (m, 1H), 1.73 (m, 1H), 1.45 (s, 9H), 1.00 (m, 3H), 0.88 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 153.5, 80.4, 77.7, 72.5, 71.9, 70.8, 70.2, 52.9, 52.1, 51.7, 38.5, 38.0, 36.8, 32.9, 32.1, 28.2, 19.0; IR 3019.4, 2097.2, 1693.3, 1405.2, 1368.4, 1216.1, 1173.6, 967.2, 900.7, 758.9, 668.3 cm^{-1}; MS-FAB m/z (% rel intensity) 377 (MH^+, 70), 321 (100); HRFAB Calcd for $C_{16}H_{29}N_2O_6S$ (MH^+) m/e 377.1746, measured m/e 377.1741.

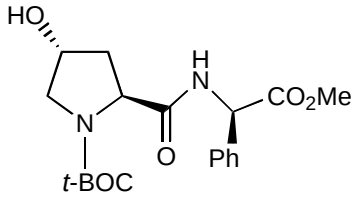
(2S, 5'R, 4S)-N-*tert*-Boc-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (The phosphine sulfide of 21).



(2S, 2'R, 4S)-N-*tert*-Boc-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (**21**) was prepared by the procedure described for **15**, using (2S, 2'R, 4R)-N-*tert*-Boc-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-

(methylsulfonyl)oxyl-proline (**II**), and was obtained in 39% yield as a white solid: R_f = 0.30 (EtOAc/*n*-hexanes: 2/1); mp 77 - 80 ºC; *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.81 (m, 4H), 7.51-7.44 (m, 6H), 4.53 (dd, J_{HH} = 8.1 and 8.0 Hz, 1H), 4.33 (dd, J_{HH} = 8.5 and 8.3 Hz, 1H), 3.90 (dd, J_{HH} = 8.8 and 8.1 Hz, 1H), 3.84-3.62 (m, 4H), 3.27 (m, 1H), 2.50 (m, 1H), 2.30 (m, 1H), 1.70 (m, 1H), 1.42 (s, 9H), 1.27 (d, J_{HH} = 6.1 Hz, 3H), 1.01 (d, J_{HH} = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 153.5, 131.8 (d, J_{CP} = 3.0 Hz), 131.8 (d, J_{CP} = 3.0 Hz),131.1 (d, J_{CP} = 10.0 Hz), 128.8 (d, J_{CP} = 12.0 Hz), 128.7 (d, J_{CP} = 12.0 Hz),80.3, 72.8, 71.2, 62.2, 54.9 (d, J_{CP} = 11.0 Hz), 47.5, 37.8 (d, J_{CP} = 61.0 Hz), 32.4 (d, J_{CP} = 51.5 Hz), 28.3, 19.4, 18.8; ^{31}P (120 MHz, $CDCl_3$) δ 44.2; IR (film) 3054.1, 2984.7, 1696.3, 1400.2, 1265.2, 1160.1, 738.7 cm^{-1}; MS-FAB m/z (% rel intensity) 505 (MLi^+, 37), 405 (66), 294 (21), 160 (100); HRFAB Calcd for $C_{27}H_{36}N_2O_3PSLi$ (MLi^+) m/e 505.2266 measured m/e 505.2274; Anal. Calcd for $C_{27}H_{35}N_2O_3PS$: C, 65.04; H, 6.76. Found C, 64.58; H. 6.87.

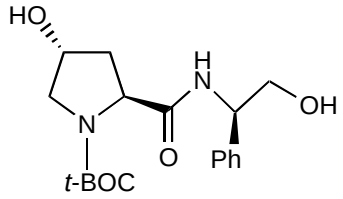
(2S, 2R', 4R)-N-*tert*-Boc-2-[[N-[(2'-methoxycarbonyl-2'-phenyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (III).



(2S, 2R', 4R)-N-*tert*-Boc-2-[[N-[(2'-methoxycarbonyl-2'-phenyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (**III**) was prepared by the procedure described above, using D-phenylglycine methyl ester hydrochloride, in 92% yield as a white semi-solid: *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 and 7.04 (2 broad singlets from one proton, 1H), 7.35 (m, 5H), 5.63-5.50

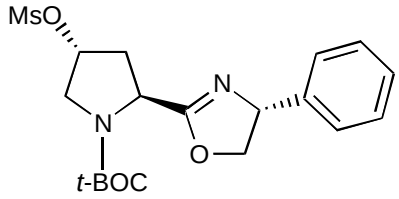
(m, 1H), 4.40 (m, 2H), 3.71(s, 3H), 3.64-3.10 (m, 3H), 2.40-2.00 (m, 2H), 1.50 and 1.30 (2 broad singlets from t-Boc group 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 171.6, 171.5, 171.0, 155.1, 136.1, 128.9, 128.7, 128.5, 128.3, 127.2, 80.8, 69.1, 69.0, 59.9, 58.4, 56.4, 55.9, 54.8, 52.6, 39.3, 36.7, 28.0; IR 3414.8, 2980.8, 1740.7, 1683.8, 1507.3, 1401.5, 1161.1, 920.0, 756.1, 568.3 cm^{-1}; MS-FAB m/z (% rel intensity) 379 (MH^+, 33), 323 (20), 279 (100); Anal. Calcd for $C_{19}H_{26}N_2O_6$: C, 60.31; H, 6.93. Found C, 60.59; H, 6.97.

(2S, 2'R, 4R)-N-*tert*-Boc-2-[[N-[(2'-hydroxymethyl-2'-phenyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (IV).



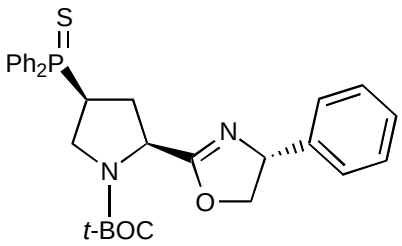
(2S, 2'R, 4R)-N-*tert*-Boc-2-[[N-[(2'-hydroxymethyl-2'-phenyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (**IV**) was prepared by the procedure described for **8**, using (2S, 2R', 4R)-N-*tert*-Boc-2-[[N-[(2'-methoxycarbonyl-2'-phenyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (**III**). The product was obtained in 90% yield as a white foam: *The NMR spectra are reported for a mixture of two rotamers*, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 and 7.40 (2 broad singlets, 1H), 7.26 (m, 5H), 5.05 (m, 1H), 4.46-4.29 (m, 4H), 3.74 (m, 2H), 3.50-3.42 (m, 2H), 2.21-1.98 (m, 2H), 1.39 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.7, 155.2, 154.9, 138.9, 138.6, 128.4, 127.3, 126.6, 88.5, 69.5, 68.7, 65.7, 65.2, 59.5, 59.0, 55.4, 55.1, 39.3, 38.0, 28.1; IR (film) 3410.9, 3328.9, 2980.0, 3935.5, 1672.2, 1536.2, 1417.6, 1368.4, 909.4, 730.0, 649.0 cm^{-1}; MS-FAB m/z (% rel intensity) 351 (MH^+, 25), 295 (28), 251 (100); HRFAB Calcd for $C_{18}H_{27}N_2O_5$ (MH^+) m/e 351.1920, measured m/e 351.1930.

(2S, 5'R, 4R)-N-tert-Boc-2-(4',5'-dihydro-5'-phenyl-1',3'-oxazole-2'-yl)-4-(methylsulfonyl)oxyl-proline (V).



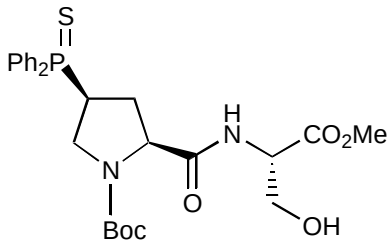
(2S, 5'R, 4R)-N-tert-Boc-2-(4',5'-dihydro-5'-phenyl-1',3'-oxazole-2'-yl)-4-(methylsulfonyl)oxyl-proline (**V**) was prepared by the procedure described for **16**, using the diol (2S, 2'R, 4R)-N-*tert*-Boc-2-[[N-[(2'-hydroxymethyl-2'-phenyl)methyl]-1'-amino]-carbonyl]-4-hydroxyl-proline (**IV**), and was obtained in 60% yield as a yellowish viscous oil: *The NMR spectra are reported for a mixture of two rotamers*, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H), 5.32 (m, 1H), 5.20 (m, 1H), 4.77-4.63 (m, 2H), 4.15-4.07 (m, 1H), 3.92-3.75 (m, 2H), 3.04 (s, 3H), 2.74-2.57 (m, 1H), 2.50-2.42 (m, 1H), 1.47 and 1.44 (2 s, overlap), 9H); ^{13}C (75 MHz, $CDCl_3$) δ 167.8, 167.6, 153.5, 141.9, 141.4, 128.5, 127.5, 126.5, 126.3, 80.5, 78.0, 77.7, 75.2, 74.7, 69.5, 52.8, 52.1, 51.7, 38.4, 38.2, 36.8, 28.1; IR (film) 3020.4, 2981.8, 1697.3, 1402.2, 1368.4, 1216.1, 1174.6, 966.3, 909.4, 752.2, 668.3 cm^{-1}; MS-FAB m/z (% rel intensity) 411 (MH^+, 30); HRFAB Calcd for $C_{19}H_{27}N_2O_6S$ (MH^+) m/e 411.1590, measured m/e 411.1572.

(2S, 5'R, 4S)-N-*tert*-Boc-2-(4',5'-dihydro-5'-phenyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (The phosphine sulfide of 22).



(2S, 2'R, 4S)-N-*tert*-Boc-2-(4',5'-dihydro-5'-phenyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (**XI**) was prepared by the procedure described for **12**, using (2S, 2'R, 4R)-N-tert-Boc-2-(4',5'-dihydro-5'-phenyl-1',3'-oxazole-2'-yl)-4-(methylsulfonyl)oxyl-proline (**VII**), and was obtained in 35% yield as a white solid: R_f = 0.25 (EtOAc/*n*-hexanes: 1/1); mp 85 - 87 ^oC; *The NMR spectra are reported for a mixture of two rotamers*, ^1H NMR (300 MHz, $CDCl_3$) δ 7.91-7.82 (m, 4H), 7.50-7.45 (m, 6H), 7.32-7.20 (m, 5H), 5.20 (dd, J_{HH} = 9.0 and 9.0 Hz, 1H), 4.62 (dd, J_{HH} = 8.1 and 8.6 Hz, 2H), 4.16 (m, 1H), 3.75 (m. 2H), 3.38 (m, 1H), 2.70 (m, 1H), 2.33 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 153.4, 141.9, 131.8 (d, J_{CP} = 3.0 Hz), 131.0 (d, J_{CP} = 10.0 Hz), 128.8 (d, J_{CP} = 12.1 Hz), 128.7 (d, J_{CP} = 7.0 Hz), 127.5, 126.7, 126.4, 80.3, 75.0, 69.4, 54.3 (d, J_{CP} = 145.2 Hz), 47.3, 37.6 (d, J_{CP} = 59.6 Hz), 31.9 (d, J_{CP} = 47.6 Hz), 28.2; ^{31}P (120 MHz, $CDCl_3$) δ 44.3 (major), 44.1 (minor); IR (film) 3019.4, 2980.8, 1695.3, 1405.1, 1216.1, 1160.1, 756.1, 668.3 cm^{-1}; MS-FAB m/z (% rel intensity) 533 (MH^+, 100), 433 (30), 315 (25), 259 (27), 219 (30), 154 (25); HRFAB Calcd for $C_{30}H_{34}N_2O_3PS$ (MH^+) m/e 533.2028, measured m/e 533.2032.

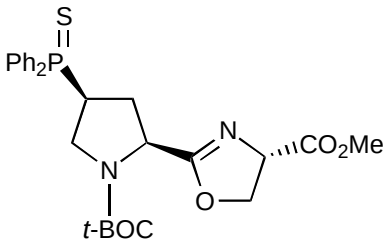
(2S, 2'S, 4S)-N-*tert*-Boc-2-[[N-[(2'-hydroxymethyl-2'-methoxycarbonyl)methyl]-1'-amino]-carbonyl]-4-diphenylphosphinothioyl-proline (VI)



A mixture of (2S, 4S)-N-Boc-2-carboxyl-4-diphenylphosphinothioyl-proline (0.45 g, 1.04 mmol), EDC (0.4 g, 2.1 mmol), HOBt (0.28 g, 2.1 mmol) was stirred in 10 mL of CH_2Cl_2 at 0 ^oC for 5 min. In a separated flask, L-Serine methyl ester hydrochloride (0.24 g, 1.5 mmol) and Et_3N (0.28 mL, 0.2 mol) in 10 mL of CH_2Cl_2 were

stirred for 10 min after which the mixture was added to the active ester. The resulting clear solution was warmed to room temperature and stirred for 1 day. After evaporation of CH_2Cl_2 and the residue was dissolved in EtOAc / H_2O (4 /1, v/v). The organic layer was washed with 1N HCl (aq.), saturated $NaHCO_3$ (aq.), H_2O and brine and dried over Na_2SO_4. The solvent was removed by evaporation leaving a residue that was subjected to column chromatography (eluant: EtOAc/*n*-hexanes (90/10, v/v) to yield 0.53 g (96%) of **VI** as a white foamy solid: *The NMR spectra are reported for a mixture of two rotamers*, ^1H NMR (300 MHz, $CDCl_3$) δ 7.90-7.81 (m, 4H), 7.51-7.44 (m, 6H), 6.92 (d, J = 7.5 Hz, 1H), 4.61 (br s, 1H), 4.30 (br s, 1H), 3.94 (br s, 3H), 3.75 (s, 3H), 3.70 (br s, 2H), 2.55 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ171.0, 170.4, 154.1, 131.9, 131.7, 131.6, 131.1 (d, J_{CP} = 10.1 Hz), 130.0 (d, J_{CP} = 10.1 Hz), 130.5, 128.8 (d, J_{CP} = 12.0 Hz), 128.7 (d, J_{CP} = 12.0 Hz), 81.3, 62.6, 61.2, 54.6, 52.5, 47.7, 37.5, 30.7, 28.1; ^{31}P (120 MHz, $CDCl_3$) δ 46.6, 45.7 and 44.8; IR (film) 3414.8, 3019.7, 2980.5, 1745.3, 1678.6, 1518.8, 1413.5, 1438.1, 1392.6, 1217.9, 1162.2, 1102.8, 1050.5, 928.9, 771.7, 668.9; MS-FAB m/z (% rel intensity) 553 (MH^+, 45), 433 (100); HRFAB Calcd for $C_{26}H_{33}N_2O_6PS$ (MH^+) m/e 533.1875, Found 533.1879.

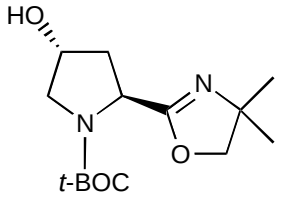
(2S, 5'R, 4S)-N-*tert*-Boc-2-(4',5'-dihydro-5'-methoxylcarbonyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (The phosphine sulfide of 23).



To a solution of (2S, 2'S, 4S)-N-*tert*-Boc-2-[[N-[(2'-hydroxymethyl-2'-methoxycarbonyl)methyl]-1'-amino]-carbonyl]-4-diphenylphosphinothioyl-proline **(VI)** (0.63 g, 1.2 mmol) in 15 mL of THF, Burgess reagent (0.37 g, 1.5 mmol) in 10 mL of

THF was slowly added at 0 ^{o}C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 1 h. After which the solution was heated to reflux for 3 h. After cooling down the THF solvent was removed and the residue was subjected to column chromatograph (eluent: EtOAc/Hexanes/Et_3N, 66/33/1) to afford 0.57 g (93%) as a white solid: mp 80 ^{o}C (gel); *The NMR spectra are reported for a mixture of two rotamers*, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.82 (m, 4H), 7.52-7.43 (m, 6H), 4.75-4.68 (m, 1H), 4.61-4.45 (m, 3H), 3.77 (s, 3H), 3.76 (m, 2H), 3.34 (m, 1H), 2.65-2.45 (m, 1H), 2.27-2.19 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ170.9, 169.7, 153.5, 140.0 (d, J_{CP} = 10.1 Hz), 131.8, 131.7, 128.7 (d, J_{CP} = 12.0 Hz), 80.5, 69.4, 68.0, 54.8 (d, J_{CP} = 11.5 Hz), 52.4, 47.3 (d, J_{CP} = 6.0 Hz), 37.5 (d, J_{CP} = 60.1 Hz), 32.3, 28.0; ^{31}P (120 MHz, $CDCl_3$) δ 44.3; IR (film) 3054.4, 2987.1, 1742.5, 1696.3, 1551.9, 1421.9, 1265.0, 1159.3, 896.0, 737.0, 703.7; MS-FAB m/z (% rel intensity) 515 (MH^+, 100), 415 (53), 219 (65); HRFAB Calcd for $C_{26}H_{32}N_2O_6PS$ (MH^+) m/e 515.1769, Found 515.1767.

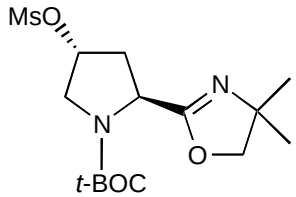
(2S, 4R)-N-*tert*-Boc-2-(4',5'-dihydro-5',5'-dimethyl-1',3'-oxazole-2'-yl)-4-hydroxyl-proline (VII)[1]**.**



The oxazoline ring was formed by the procedure reported by Vorbriiggen, and Krolikiewicz (*Tetrahedron Lett.* **1981**, *45*, 4471). N-*t*-Boc-4-hydroxylproline (10 g, 0.043 mol), 2-amino-2-methyl-1-propanol (6.2 mL, 0.065 mol), Et_3N (18.1 mL, 0.13 mol) and CCl_4 (12.5 mL, 0.13 mol) were mixed together in CH_3CN / pyridine (150 mL, 1:1). After

cooling the solution to 0 ˚C, Ph_3P (34 g, 0.13 mol) in CH_3CN / pyridine (150 mL, 1:1) was added through an addition funnel. The cooling bath was removed, and the mixture was allowed to stir at room temperature for 24 h. After removal of the precipitate, by filtration, the filtrate was evaporated and the residue was dissolved in EtOAc. The organic solution was washed with H_2O, brine and dried over Na_2SO_4. The EtOAc was removed in vacuo to yield a white solid. The desired product was purified by silica gel chromatography, first using EtOAc to removed the PPH_3 and $PH_3P(O)$, than using gradient eluant (1-4% MeOH / EtOAc) to gave the product (10.8 g, 88%) as a white semi-solid: *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 and 6.47 (2 br s, 1H), 4.44 (m, 1H), 4.28 (dd, *J* = 8.7 and 7.5 Hz, 1H), 3.95 (dd, *J* = 8.7 and 8.1 Hz, 2H), 3.61-3.45 (m, 2H), 2.28-2.05 (m, 2H), 1.45 and 1.44 (2s, 9H), 1.27 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 155.5, 80.7, 80.1, 79.3, 66.9, 59.5, 55.6, 39.8, 37.8, 28.2, 27.9; IR (film) 3405.1, 2973.1, 2935.5, 1700.0, 1684.7, 1457.1, 1419.5, 1216.1, 1047.3, 758.0, 668.3 cm^{-1}; MS-FAB m/z (% rel intensity) 285 (MH^+, 100), 229 (73); HRFAB Calcd for $C_{14}H_{25}N_2O_4$ (MH^+) m/e 285.1814, measured m/e 285.1815.

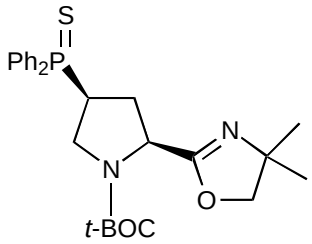
(2S, 4R)-N-*tert*-Boc-2-(4',5'-dihydro-5',5'-dimethyl-1',3'-oxazole-2'-yl)-4-(methyl-sulfonyl)oxyl-proline (VIII).



To a solution of (2S, 4R)-N-*tert*-Boc-2-(4',5'-dihydro-5',5'-dimethyl-1',3'-oxazole-2'-yl)-4-hydroxyl-proline (**VII**) (10.50 g, 0.037 mol) in 100 mL of CH_2Cl_2 was added Et_3N (15.40 mL, 0.11 mol), followed by addition of MsCl (4.30 mL, 0.055 mol) at 0 ºC.

The reaction was stirred for 2h. After which the solvent was removed under vacuo to yield a residue that was then subjected to chromatography using 1% Et_3N / EtOAc, affording the desired product (8.2 g, 60%) as a brownish vicious oil: *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (m, 1H), 4.58 (dd, *J* = 6.1 and 6.1 Hz, 1H), 3.99 (d, *J* = 8.1 Hz, 1H), 3.92 (d, *J* = 8.1 Hz, 1H), 3.83-3.71 (m, 2H), 3.06 (s, 3H), 2.60 (m, 1H), 2.38-2.29 (m, 1H), 1.46 (s, 9H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 153.5, 80.5, 79.3, 77.7, 67.2, 52.9, 51.9, 38.6, 38.0, 28.2, 28.0; IR (film) 3020.4, 2977.0, 1597.3, 1400.0, 1363.6, 1216.1, 1173.6, 970.1, 906.5, 765.7, 667.3 cm^{-1}; MS-FAB m/z (% rel intensity) 363 (MH^+, 75), 307 (100); HRFAB Calcd for $C_{15}H_{26}N_2O_6S(MH^+)$ m/e 363.1590, measured m/e 363.1670; Anal. Calcd for $C_{15}H_{26}N_2O_6S$: C, 49.71; H, 7.23; Found C, 49.88; H, 6.97.

(2S, 4S)-N-*tert*-Boc-2-(4',5'-dihydro-5',5'-dimethyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (Phosphine sulfide of 24).

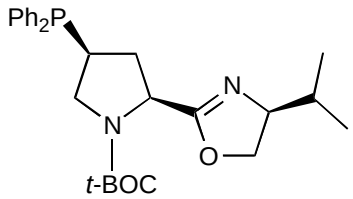


(2S, 4S)-N-*tert*-Boc-2-(4',5'-dihydro-5',5'-dimethyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (**24**) was prepared by the procedure described for **15**, using (2S, 4R)-N-*tert*-Boc-2-(4',5'-dihydro-5',5'-dimethyl-1',3'-oxazole-2'-yl)-4-(methylsulfonyl)-oxyl-proline (**VIII**), and was obtained in 25% yield as a white solid after recrystallization from CH_2Cl_2-*n*-hexanes: R_f = 0.2 (EtOAc/*n*-hexanes: 3/2); mp = 89 -91°C; *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.81 (m, 4H), 7.51-7.42 (m, 6H), 4.50 (dd, J_{HH} = 8.3 and 8.3 Hz,

1H), 4.02 (d, J_{HH} = 8.1, 1H), 3.91 (d, J_{HH} = 8.1, 1H), 3.70 (m, 2H), 3.30 (m, 1H), 2.55 (m, 1H), 2.22 (m, 1H), 1.42 (s, 9H), 1.31 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 153.5, 131.8 (d, J_{CP} = 3.0 Hz), 131.1 (d, J_{CP} = 10.1 Hz), 128.8 (d, J_{CP} = 12.1 Hz), 128.5 (d, J_{CP} = 27.5 Hz), 80.3, 79.4, 67.1, 55.0 (d, J_{CP} = 11.1 Hz), 47.4 (d, J_{CP} = 6.1 Hz), 37.6 (d, J_{CP} = 60.0 Hz), 33.2, 28.3, 28.1; ^{31}P (120 MHz, $CDCl_3$) δ 44.1; IR (film) 3019.4, 2977.0, 1695.3, 1404.1, 1216.1, 1160.1, 758.0, 668.3 cm^{-1}; MS-FAB m/z (% rel intensity) 485 (MH^+, 100), 368 (48), 267 (15); HRFAB Calcd for $C_{26}H_{33}N_2O_3PS$ (M^+) m/e 484.1949, measured m/e 484.1949.

Sample procedure for Raney nickel reduction.

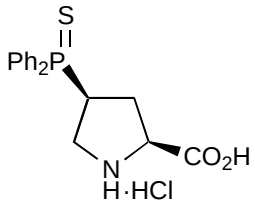
(2S, 5'S, 4S)-N-*tert*-Boc-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-diphenylphosphino-proline (18).



Phosphine sulfide **15** (50 mg, 0.1 mmol) was added to Raney nickel (0.5 g), in CH_3CN (6 mL), that had been washed with methanol (three times), ether (three times), and degassed CH_3CN (three times). The reaction mixture was stirred at room temperature for 8 h, by which time the ^{31}P NMR spectrum indicated the complete reduction of the phosphine sulfide to the phosphine. The Raney nickel was then filtrated through a syringe filter. Evaporation of solvent afforded 40 mg (86%) of **18** as a white solid that was ready to use for catalysis: *The NMR spectra are reported for a mixture of two rotamers*, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 10H), 4.39 (dd, J = 7.8 and 8.4 Hz, 1H), 4.13 (m, 1H), 3.94-3.83 (m, 2H), 3.64 (m, 1H), 3.29 (m, 1H), 2.80 (m, 1H), 2.26 (m, 1H), 1.92 (m, 1H), 1.64 (m, 1H), 1.33 (s, 9H), 0.84 (d, J = 6.3 Hz, 3H), 0.77 (d, J = 6.9 Hz, 3H);

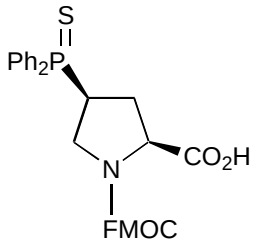
^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 153.6, 133.33 (J_{CP} = 11.6 Hz), 133.0 (J_{CP} = 19.1 Hz), 129.1, 128.6 (J_{CP} = 6.8 Hz), 79.9, 71.9, 70.2, 55.64 (d, J_{CP} = 8.0 Hz), 50.7 (d, J_{CP} = 28.0 Hz), 36.3 (d, J_{CP} = 20.0 Hz), 35.2 (d, J_{CP} = 9.0 Hz), 32.5, 28.3, 18.6, 17.9; ^{31}P (120 MHz, $CDCl_3$) δ -9.24 (major) and -10.0 (minor); MS-FAB m/z (% rel intensity) 467 (MH^+, 100), 411 (30), 254 (37), 185 (50); HRFAB Calcd for $C_{27}H_{36}N_2O_3P$ (MH^+) m/e 467.2463, measured m/e 467.2471.

(2S, 4S)-2-carboxyl-4-diphenylphosphinothioyl-proline hydrochloride (25)



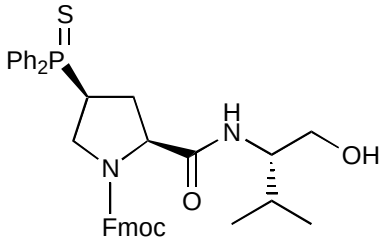
A suspension of 50 mL of 3N $HCl_{(aq)}$ containing 1.1 g (2.20 mmol) of (2S, 2'S, 4S)-N-*tert*-Boc-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (**15**) was heated to reflux. After all materials dissolved in solution, refluxing was continued for another 2h. The reaction was cooled down to room temperature and stored at -20 ^oC overnight and the resulting white precipitate was collected by filtration. Recrystallization from H_2O gave a 0.60 g (75%) of **35** as needle crystals: mp 133 -136 ^oC; ^1H NMR (300 MHz, $CDCl_3$ + 2 drops of DMSO-d_6) δ 8.80 (br s, 1H), 7.96-7.84 (m, 4H), 7.50-7.44 (m, 6H), 5.43 (br s, 2H), 4.64 (dd, J_{HH} = 8.4 and 9.0 Hz, 1H), 4.06 (m, 1H), 3.58 (m, 2H), 5.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + 2 drops of DMSO-d_6) δ 169.6, 131.96 (d, J_{CP} = 3.0 Hz), 131.1, 130.9, 130.8, 129.9 (d, J_{CP} = 10.1 Hz), 128.8 (d, J_{CP} = 12.0 Hz), 128.7 (d, J_{CP} = 12.0 Hz), 59.1 (d, J_{CP} = 10.0 Hz), 46.7, 37.3 (d, J_{CP} = 79.3 Hz), 29.5; ^{31}P (120 MHz, $CDCl_3$+ 2 drops of DMSO-d_6) δ 45.5;
MS-FAB Calcd for $C_{17}H_{19}NO_2PS$ m/z (% rel intensity) 332 (MH^+, 100); HRFAB Calcd for $C_{17}H_{19}NO_2PS$ (MH^+) m/e 332.0874, measured 322.0872.

(2S, 4S)-N-Fmoc-2-carboxyl-4-diphenylphosphinothioyl-proline (X)



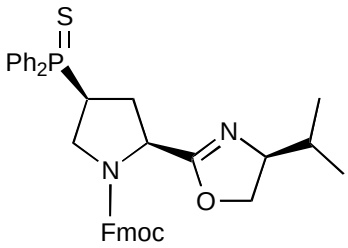
To a solution of 0.16 g (0.436 mmol) of **25** in 10 mL of acetone was added 0.19 g (2.26 mmol) of $NaHCO_3$ in 5 mL of H_2O, followed by addition of FMOC-OSu (0.183 g, 0.54 mmol), and the reaction mixture was allowed to stir overnight. Evaporation of acetone and the aqueous residue was acidified with 0.5 N of HCl to pH = 3-4, and was extracted with ethyl acetate (3 X 15 mL). The combined organic layer was washed with brine and dried over Na_2SO_4 and evaporated to give a white foamy solid. The crude product was purified by column chromatography, first using EtOAc / hexanes (1/1, v/v) to remove the excess FMOC-OSu, then using EtOAc/ hexanes/HOAC (60/40/1, v/v/v) to collect 0.26 g (100%) of **X** as a white solid: mp 118 ^oC (shrink), 121 ^oC (gel); *The NMR spectra are reported for a mixture of two rotamers*, ^1H NMR (300 MHz, $CDCl_3$) δ 9.22 (br s, 1H), 7.91-7.79 (m, 4H), 7.69-7.63 (m, 2H), 7.58-7.46 (m, 8H), 7.37-7.15 (m, 4H), 4.52-4.30 (m, 2H), 4.27-4.04 (m, 2H), 3.85-3.61 (m, 2H), 3.30 (m, 1H), 2.55 (m, 1H), 2.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 175.4, 154.8, 154.1, 143.8, 143.5, 143.4, 141.1, 132.0, 131.1 (d, J_{CP} = 10.1 Hz), 128.9 (d, J_{CP} = 12.5 Hz), 127.6, 127.0 (d, J_{CP} = 7.6 Hz), 124.88 (d, J_{CP} = 27.1 Hz), 124.85 (d, J_{CP} = 7.0 Hz), 119.8, 67.8, 67.6, 59.1 (d, J_{CP} = 10.0 Hz), 58.4 (d, J_{CP} = 10.0 Hz), 38.5 (d, J_{CP} = 61.1 Hz), 38.0 (d, J_{CP} = 59.1 Hz), 31.7, 30.4; ^{31}P (120 MHz, $CDCl_3$) δ 43.87 and 43.77; ^{31}P (120 MHz, $CDCl_3$) δ 43.87 and 43.77; IR (film) 3019.6, 1704.8, 1522.5, 1475.1, 1423.0, 1214.9, 1103.4, 1037.8, 924.8, 768.0, 669.2; MS-FAB m/z (% rel intensity) 554 (MH^+, 12), 292 (78), 266 (100); HRFAB Calcd for $C_{32}H_{29}NO_4PS$ (MH^+) m/e 544.1572, measured 544.1564.

(2S, 2'S, 4S)-N-Fmoc-2-[[N-[(2'-hydroxymethyl-2'-isopropyl)methyl]-1'-amino]-carbonyl]-4-diphenylphosphinothioyl-proline (XI).



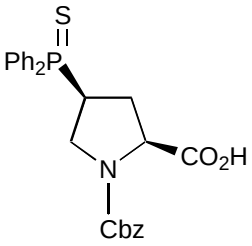
A mixture of (2S, 4S)-N-Fmoc-2-carboxyl-4-diphenylphosphinothioyl-proline (**X**) (0.70 g, 1.3 mmol), EDC (0.50 g, 2.6 mmol), HOBt (0.35 g, 2.6 mmol) was stirred in 20 mL of CH_2Cl_2 at 0 ^oC for 5 min. To this solution (S)-valinol (0.20 g, 2.0 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 1 day. After evaporation of CH_2Cl_2 and the residue was dissolved in EtOAc / H_2O (4 /1, v/v). The organic layer was washed with 1N HCl (aq.), saturated $NaHCO_3$ (aq.), H_2O and brine and dried over Na_2SO_4. The solvent was removed by evaporation leaving a residue that was subjected to column chromatography (eluant: EtOAc) to yield 0.78 g (93%) as a white solid: mp 105-107 ^oC; *The NMR spectra are reported for a mixture of two rotamers*, ^1H NMR (300 MHz, $CDCl_3$) δ 7.89-7.24 (m, 18H), 6.22(d, J = 8.7 Hz, 1H), 4.56-4.28 (m, 3H), 4.17 (m, 6H), 2.63-2.46 (m, 1H), 2.35 (br s, 1H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ171.1, 155.4, 143.5, 141.2, 132.0, 132.1, 131.1, 130.9, 128.9 (d, J_{CP} = 12.0 Hz), 127.0, 124.9, 120.0, 119.9, 68.1, 63.3, 62.0, 57.3, 48.1, 47.0, 37.7 (d, J_{CP} = 59.1Hz), 31.1, 28.9, 19.5, 19.0; ^{31}P (120 MHz, $CDCl_3$) δ 44.8; IR (film) 3054.4, 2986.9, 1688.6, 1517.7, 1421.7, 1267.5, 1106.4, 896.0, 730.5; MS-FAB m/z (% rel intensity) 639 (MH^+, 30), 179 (100); HRFAB Calcd for $C_{37}H_{40}N_2O_4PS$ (MH^+) m/e 639.2446, Found 639.2443.

(2S, 5'R, 4S)-N-Fmoc-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline sulfide (26).



was prepared by the procedure described above for **15**, using **XI**, in 86% yield as a white solid: mp 70 ^{o}C (gel); *The NMR spectra are reported for a mixture of two rotamers,* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.16 (m, 18 H), 4.91-3.61 (m, 8H), 3.35 (m, 1H), 2.57 (m, 1H), 2.30 (m, 1H), 1.66 (m, 1H), 1.30 (m, 1H), 0.90-0.79 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 165.3, 154.2, 153.9, 143.9, 143.8, 143.6, 143.4, 141.0, 131.8, 131.7, 131.0, 130.8, 128.7 (d, J_{CP} = 12.0Hz), 127.5, 126.8, 125.0, 124.8, 119.7; ^{31}P (120 MHz, $CDCl_3$) δ 44.3; IR (film) 3054.4, 2986.9, 1705.6, 1421.7, 1353.8, 1264.6, 1165.8, 1104.3, 896.1, 747.3; MS-FAB m/z (% rel intensity) 621 (MH^+, 100), 403 (30); HRFAB Calcd for $C_{37}H_{38}N_2O_3PS$ (MH^+) m/e 621.2341, Found 621.2337.

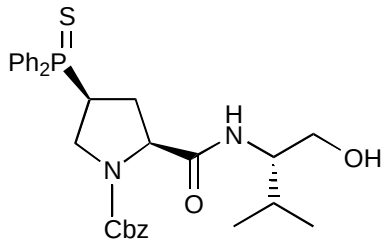
(2S, 4S)-N-Cbz-2-carboxyl-4-diphenylphosphinothioyl-proline (XII).



To a solution of 0.60 g (1.64 mmol) of **25** in 20 mL of acetone was added 0.69 g (8.18 mmol) of $NaHCO_3$ in 10 mL of H_2O, followed by addition of benzyl chloroformate (0.31 g, 1.80 mmol), and the reaction mixture was allowed to stir overnight. Evaporation of acetone and the aqueous residue was acidified with 0.5 N of HCl to pH = 3-4, and was extracted with ethyl acetate (3 X 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4 and evaporated to give a white foamy solid. The crude product was purified by column chromatography using EtOAc/ hexanes/HOAC (50/50/1, v/v/v) to collect 0.74 g (97%) of **25** as a white solid: mp 85 ^{o}C (gel); *The NMR spectra*

are reported for a mixture of two rotamers, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (br s, 1H), 7.88 - 7.81 (m, 4H), 7.46 (m, 6H), 7.29 - 7.14 (m, 5H), 5.10 (d, J_{HH} = 8.1 Hz, 2H), 4.39 (m, 1H), 3.79 (m, 2H), 3.35 (m, 1H), 2.53 (m, 1H), 2.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 175.5, 154.8, 154.0, 135.9, 131.9, 131.0 (d, J_{CP} = 12.5 Hz), 128.80 (d, J_{CP} = 12.5 Hz), 128.0, 127.9, 127.7, 125.2, 67.5, 67.4, 59.2 (d, J_{CP} = 10.1 Hz), 58.6 (d, J_{CP} = 10.4 Hz), 47.6 (d, J_{CP} = 38.6 Hz), 38.4 (d, J_{CP} = 59.6 Hz), 37.9 (d, J_{CP} = 59.6 Hz), 31.5, 30.5; ^{31}P (120 MHz, $CDCl_3$) δ 44.1 and 43.92; IR (film) 3019.7, 3000.0, 1704.7 1525.2, 1422.5, 1216.9, 1402.4, 928.9, 771.6, 669.1; MS-FAB m/z (% rel intensity) 466 (MH^+, 100), 422 (10); HRFAB Calcd for $C_{25}H_{25}NO_4PS$ (MH^+) m/e 466.1242, measured 422.1253. Anal. Calcd for $C_{25}H_{24}NO_4PS$: C, 64.51; H, 5.20. Found C, 63.64; H. 4.91.

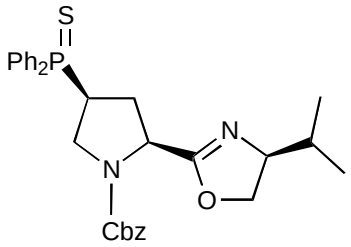
(2S, 2'S, 4s)-N-Cbz-2-[[N-[(2'-hydroxymethyl-2'-isopropyl)methyl]-1'-amino]-carbonyl]-4-diphenylphosphinothioyl-proline (XIII).



was prepared by the procedure described above for **15**, using (2S, 4S)-N-Cbz-2-carboxyl-4-diphenylphosphinothioyl-proline, in 90% yield as a white foam: *The NMR spectra are reported for a mixture of two rotamers*, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.79 (m, 4H), 7.54-7.46 (m, 6H), 7.33(m, 5H), 6.09 (br s, 1H), 5.11(br s, 1H), 4.34 (dd, *J* = 8.7 and 8.4 Hz), 3.85-3.40 (m, 6H), 2.60-2.37 (m, 2H), 1.17 (m, 2H), 0.91 (d, *J* = 7.5 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ171.4, 155.2, 135.9, 131.8, 131.1(d, *J*cp = 12.1 Hz), 131.0 (d, *J*cp = 10.6 Hz), 128.8 (d, *J*cp = 12.6 Hz), 128.7 (d, *J*cp = 12.5 Hz), 128.5, 128.2, 128.1, 67.6, 63.1, 61.9, 57.0, 48.3, 37.7 (d, *J*cp = 59.0 Hz), 28.7, 19.5, 18.9; ^{31}P (120 MHz, $CDCl_3$) δ 45.4;IR (film) 3054.5, 2987.3, 1689.3, 1422.1,

1263.0, 1183.0, 896.1, 731.8; MS-FAB m/z (% rel intensity) 550 (M+, 75), 333 (23), 219 (22), 154 (100); HRFAB Calcd for $C_{30}H_{35}N_2O_4PS$ (MH^+) m/e 550.2055, Found 550.2036.

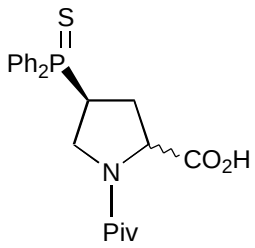
(2S, 5'R, 4S)-N-Cbz-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (27).



A sample of (2S, 2'S, 4s)-N-Cbz-2-[[N-[(2'-hydroxymethyl-2'-isopropyl)methyl]-1'-amino]-carbonyl]-4-diphenylphosphinothioyl-proline **(XIII)** (0.28 g, 0.51 mmol) was dissolved in CH_2Cl_2/Et_3N (20 mL, 3/1, v/v) and the solution was cooled to 0 ^oC. To the solution, MsCl (0.18 g, 0.15 mmol) was slowly added. The cooling bath was removed and the mixture was stirred for 16 h resulting in a dark-brownish solution with the precipitation of ammonium salt. The solvent removed by evaporation, leaving a residue that was dissolved in EtOAc / H_2O (4/1, v/v). The organic solution was then washed with water twice and dried over Na_2SO_4 and evaporated to give a crude product that was purified by flash chromatography (eluant: EtOAc/*n*-hexanes/Et_3N, 74/25/1) to afford 0.23 g (85%) of **27** as a white foam: *The NMR spectra are reported for a mixture of two rotamers*, ^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 4H), 7.48 (m, 6H), 7.30 (m, 5H), 5.26-4.95 (m, 2H), 4.62 (dd, J = 7.8 and 8.7 Hz, 1H), 4.21-3.65 (m, 5H), 3.35 (m, 1H), 2.54 (m, 1H), 2.25 (m, 1H), 1.70-1.57 (m, 1H), 0.87-0.77 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 154.0, 136.4, 131.8, 131.7, 131.0, 130.9, 128.7 (d, J_{CP} = 12.0 Hz), 128.2, 127.8, 71.8, 70.3, 55.3 (d, J_{CP} = 11.0 Hz), 55.1 (d, J_{CP} = 11.0 Hz), 47.9, 47.3, 38.3 (d, J_{CP} = 61.1 Hz), 37.6 (d, J_{CP} = 60.2 Hz), 32.2, 32.1, 31.2, 18.5, 17.9; ^{31}P (120 MHz, $CDCl_3$) δ 44.0; IR 3054.4, 2987.1, 1705.3, 1603.7, 1551.9, 1437.0, 1421.8, 1359.3,

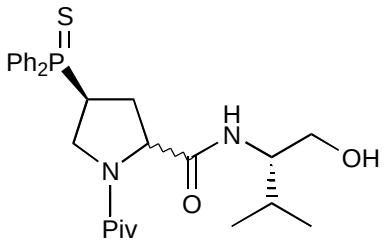
1262.9, 1170.4, 896.1, 743.0; MS-FAB m/z (% rel intensity) 532 (MH^+, 77), 315 (28), 154 (100); HRFAB Calcd for $C_{30}H_{33}N_2O_3PS$ (MH^+) m/e 532.1949, Found 532.1940.

4S-N-Piv-2-carboxyl-4-diphenylphosphinothioyl-proline (XIV, mixture of two diastereoisomers)



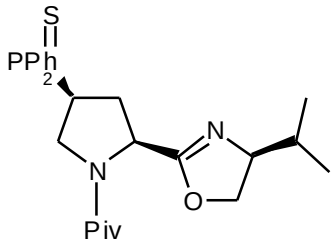
To a suspension of CH_2Cl_2 containing **25** (0.30 g, 0.82 mmol) was added Et_3N (0.45 mL, 3.24 mmol), and stirred for 15 min., followed by the addition of pivaloyl chloride (0.30 mL, 2.44 mmol) at 0 ºC. The resulting clear solution was stirred at room temperature for 2 h. The reaction was quenched by addition of 2N HCl and stirred for 10 minutes. The organic layer was washed with water and brine and dried over Na_2SO_4. Evaporation of solvent gave a crude product that was purified by flash column (EtOAc/Hexanes/HOAc, 50/49/1) to give 0.31 g (91%) as a white solid (mixtures of two diastereoisomers: ratio, ca 1/1): mp 82 ºC (gel); ^1H NMR (300 MHz, $CDCl_3$) d 9.85 (br s, 2H), 7.96-7.82 (m, 8H), 7.58-7.49(m, 12H), 4.77 (d, *J* = 8.4 Hz, 1H), 4.56 (dd, *J* = 8.4 Hz and 9.3 Hz, 1H), 4.17-3.72 (m, 5H), 3.3 (m, 1H), 2.45 (m, 2H), 2.14 (m, 2H), 1.22 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ177.6, 176.9, 175.4, 132.09, 132.05, 131.17 (d, J_{CP} = 10.1 Hz), 131.14 (d, J_{CP} = 10.5 Hz), 131.0, 130.8, 129.1, 129.0, 128.9, 128.8, 62.0, 62.1, 60.9, 49.0, 48.4, 40.1, 39.3, 39.1, 38.6, 38.2, 27.2, 27.1; ^{31}P (120 MHz, $CDCl_3$) δ 48.66 and 46.73; IR (film) 3019.7, 1731.4, 1611.6, 1531.4, 1415.6, 1352.6, 1215.5, 1103.4, 1045.3, 929.2, 765.8, 669.2; MS-FAB m/z (% rel intensity) 416 (MH^+, 100), 332 (20), 279 (18), 185 (37), 154 (72); HRFAB Calcd for $C_{22}H_{27}NO_3PS$ (MH^+) m/e 416.1449, Found 416.1444.

(2'S, 4s)-N-Piv-2-[[N-[(2'-hydroxymethyl-2'-isopropyl)methyl]-1'-amino]-carbonyl]-4-diphenylphosphinothioyl-proline (29 and 31, mixtures of two diastereoisomers)

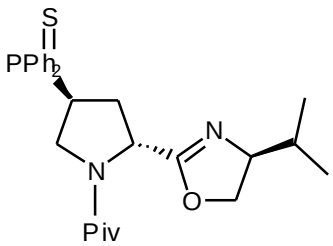


was prepared by the procedure described above for **11**, using 4S-N-Piv-2-carboxyl-4-diphenylphosphinothioyl-proline (**XIV**), in 90% yield as a white solid: mp 70 ^{o}C (shrink), 80 ^{o}C (gel); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.82(m, 8H), 7.58-7.46(m, 12H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.31 (d, *J* = 8.1 Hz, 1H), 4.74 (d, *J* = 8.1 Hz, 1H), 4.62 and 4.59 (dd, J = 8.4 Hz and 8.7 Hz, 1H), 4.11-3.95 (m, 4H), 3.73-3.50 (m, 6H), 3.33 (m, 2H), 2.71-2.56 (m, 4H), 2.32-2.40 (m, 2H), 1.89-1.80(m, 2H), 1.20 (s, 9H), 1.19 (s, 9H), 0.95-0.89 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ178.3, 178.1, 172.6, 171.1, 133.0, 132.07, 132.04, 131.9, 131.87, 131.27, 131.25, 1341.14, 131.11, 131.0, 130.8, 129.1, 129.0, 128.9, 128.8, 128.75, 128.77, 63.5 (d, J_{CP} = 9.5Hz), 62.5 (d, J_{CP} = 10.0Hz), 57.7, 57.2, 49.3 (d, J_{CP} = 6.0Hz), 48.1, 39.7, 39.1, 39.0, 38.3, 29.0, 28.9, 28.0, 27.4, 27.3, 19.6, 19.5, 18.8, 18.6; ^{31}P (120 MHz, $CDCl_3$) δ 46.2 and 43.7; IR (film) 3420.1, 3019.6, 1670.4, 1603.7, 1529.6, 1477.8, 1414.8, 1351.9, 1215.3, 1044.4, 925.9, 774.9, 669.2; MS-FAB m/z (% rel intensity) 501 (MH^+, 78), 398 (16), 283 (25), 219 (50), 152 (100); HRFAB Calcd for $C_{27}H_{38}N_2O_3PS$ (MH^+) m/e 501.2341, Found 501.2323.

(2S, 5'R, 4S)-N-Piv-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (28) and (2R, 5'R, 4S)-N-Piv-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (31).



28



31

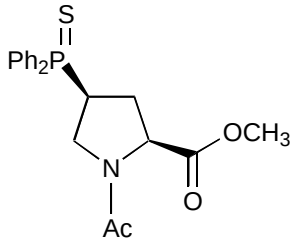
was prepared by the procedure described above for **12**, using (2'S, 4S)-N-Piv-2-[[N-[(2'-hydroxymethyl-2'-isopropyl)methyl]-1'-amino]-carbonyl]-4-diphenylphosphinothioyl-proline **(17)**. The crude mixture was separated and purified by column chromatograph (eluent: EtOAc/Et3N, 99/1) to afford two diastereoisomers.

Compound **28** (39%): R_f = 0.12 (EtOAc); mp 117 ^oC (gel); *The NMR spectra are reported for a mixture of two rotamers,* ^1H NMR (300 MHz, $CDCl_3$) δ 7.90-7.77 (m, 4H), 7.53-7.41 (m, 6H), 4.81 (dd, J = 8.4 and 8.4 Hz, 1H), 4.18-4.09 (m, 1H), 3.96-3.80 (m, 4H), 3.36-3.23 (m., 1H), 2.39-2.14 (m, 2H), 1.71-1.60 (m, 1H), 1.12 (s, 9H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ176.1, 166.2, 131.94 (d, J_{CP} = 6.0 Hz), 311.90 (d, J_{CP} = 6.0 Hz), 131.1, 131.0, 130.8, 128.9 (d, J_{CP} = 12.0 Hz), 128.8 (d, J_{CP} = 12.0 Hz), 71.7, 70.2, 56.4 (d, J_{CP} = 11.0 Hz), 48.7 (d, J_{CP} = 6.5 Hz), 39.4 (d, J_{CP} = 60.2 Hz), 38.7, 32.4, 29.7, 27.3, 18.6, 18.0; ^{31}P (120 MHz, $CDCl_3$) δ 43.0; IR 3054.4, 2987.1, 1670.4, 1625.9, 1548.1, 1440.0, 1421.9, 1264.9, 896.0, 739.9, 710.0; MS-FAB m/z (% rel intensity) 483 (MH^+, 100), 265 (175), 152 (43); HRFAB Calcd for $C_{27}H_{36}N_2O_2PS$ (MH^+) m/e 483.2235, Found 483.2233.

Compound 31 (36%): R_f = 0.24 (EtOAc); *The NMR spectra are reported for a mixture of two rotamers,* ^1H NMR (300 MHz, $CDCl_3$) δ 7.93-7.81 (m, 4H), 7.53-7.42 (m, 6H), 4.92 (d, *J* = 8.7 Hz, 1H), 4.30-4.22 (m, 1H), 4.05-3.85 (m, 5H), 2.48 (br s, 1H), 1.82-1.76 (m, 2H), 1.20 (s, 9H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ176.2, 167.2, 131.9 (d, J_{CP} = 7.0 Hz), 131.8 (d, J_{CP} = 7.0 Hz), 131.2, 131.0, 130.9, 128.9 (d, J_{CP} = 13.5 Hz), 128.7 (d, J_{CP} = 12.2 Hz), 71.6, 70.0, 56.2, 47.9,

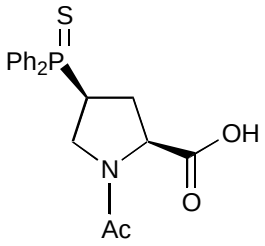
38.9, 38.0, 32.2, 29.6, 27.4, 18.6, 17.6; ^{31}P (120 MHz, $CDCl_3$) δ 45.8; IR (film) 3054.5, 2986.9, 1675.3, 1640.0, 1532.2, 1421.9, 1265.1, 896.0, 736.8, 705.1; MS-FAB m/z (% rel intensity) 483 (MH^+, 100), 256 (40), 219 (30), 152 (43); HRFAB Calcd for $C_{27}H_{36}N_2O_2PS$ (MH^+) m/e 483.2235, Found 483.2231.

(2S, 4S)-N-acetyl-2-methoxycarbonyl-4-diphenylphosphinothioyl-proline (23)



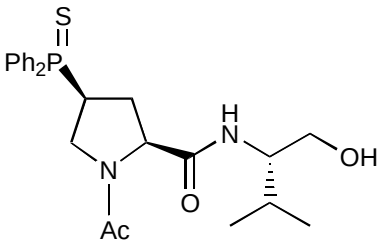
To a solution of (2S, 4S)-2-methoxycarbonyl-4-diphenylphosphinothioyl-proline (**25**) (0.14 g, 0.41 mmol) in 10 mL of dry CH_2Cl_2 was added 0.11 mL (1.2 mmol) of acetic anhydride at 0 ^oC. The reaction mixture was then stirred at room temperature for 2 hours. A small amount of ice-water was added to quench the reaction. The organic layer was washed with 1N HCl, $NaHCO_{3(sat)}$, brine and dried over Na_2SO_4 and evaporated to give a residue which was subjected to column chromatography using 5% of MeOH in EtOAc to collect a 0.15 g (96%) of white foamy solid: *The NMR spectra are reported for a mixture of two rotamers (trans / cis: 3/1),* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 - 7.75 (m, 4H), 7.51 - 7.38 (m, 6H), 4.46 - 4.35 (m, 1H), 4.05 - 3.83 (m, 1 and 1/3H), 3.69 and 3.63 (s, 3H), 3.50 (m, 1 and 1/3H), 3.29 (m, 1/3H), 2.64 -2.29 (m, 1 and 1/3H), 2.17 (m, 2/3H), 1.93 and 1.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 171.0, 169.2, 168.7, 131.9, 131.8, 131.2, 130.8 (d, *J*cp = 10.0 Hz), 130.5, 130.1, 128.9, 128.7, 128.6, 59.7, 58.9 (d, *J*cp = 10.5 Hz), 52.7, 52.2, 48.4 (d, *J*cp = 5.9 Hz), 46.9, 38.6 (d, *J*cp = 59.2 Hz), 32.0, 30.0, 22.2, 21.7; ^{31}P (120 MHz, $CDCl_3$) δ 45.4, 44.2; IR (film) 2983.4., 1744.1, 1658.1, 1466.0, 1446.4, 1373.7, 1244.9, 1051.5, 917.5, 847.1, 738.9; MS-FAB m/z (% rel intensity) 388 (MH^+, 45), 328 (45), 218 (100); HRFAB Calcd for $C_{20}H_{23}NO_3PS$ (MH^+) m/e 388.1136, Found 388.1130.

(2S, 4S)-N-Acetyl-2-carboxyl-4-diphenylphosphinothioyl-proline (XV).



Lithium hydroxide monohydrate (76 mg, 1.80 mmol) was added to a stirred solution of (2S, 4S)-N-acetyl-2-methoxycarbonyl-4-diphenylphosphinothioyl-proline (**26**) (0.14 g, 0.36 mmol) in 15 mL of THF/MeOH/H_2O (10/3/2, v/v/v). After warming back to room temperature, the reaction mixture was continued to stir for 2 hours. Evaporation of organic solvent and the aqueous residue was acidified with 0.5 N HCl to pH = 3 - 4 and extracted with diethyl ether. The ether layer was then washed with brine, dried over Na_2SO_4 and evaporated to give 0.13 g (97%) of product as a white solid: mp 100 ^oC (shrink), 110 ^oC (gel); *The NMR spectra are reported for a mixture of two rotamers*, ^1H NMR (300 MHz, $CDCl_3$) δ 10.9 (br s, 1H), 7.97 -7.81 (m, 4H), 7.52 -7.44 (m, 6H), 4.88 -4.36 (m, 1H), 4.07 - 3.89 (m, 1H), 3.58 - 3.29 (m, 2H), 2.43 (m, 1H), 2.21 (m, 1H), 1.96 and 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 170.8, 131.8 (m), 131.3 - 130.8 (m), 129.0, 128.9, 128.8, 128.7, 59.4, 48.9, 47.2; ^{31}P (120 MHz, $CDCl_3$) δ 45.0 and 44.0, IR (film) 3054.5, 2987.1, 1736.4, 1649.9, 1605.1, 1437.2, 1421.9, 1262.9, 1103.0, 896.1, 738.4, 644.1; MS-FAB m/z (% rel intensity) 374 (MH^+, 45), 185 (38); HRFAB Calcd for $C_{19}H_{21}NO_3PS$ (MH^+) m/e 374.0980, Found m/e 374.0976.

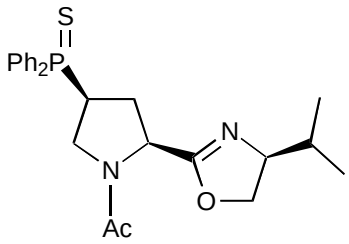
(2S, 2'S, 4S)-N-Acetyl-2-[[N-[(2'-hydroxymethyl-2'-isopropyl)methyl]-1'-amino]-carbonyl]-4-diphenylphosphinothioyl-proline (XVI)



A mixture of (2S, 4S)-N-Acetyl-2-carboxyl-4-diphenylphosphinothioyl-proline (**XV**) (0.13 g, 0.35 mmol), EDC (0.13 g, 0.70 mmol), HOBt (95 mg, 0.70 mmol) was

stirred in 20 mL of CH_2Cl_2 at 0 ^oC for 5 min. To this solution (S)-valinol (72 mg, 0.70 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 1 day. After evaporation of CH_2Cl_2 and the residue was dissolved in EtOAc / H_2O (4 /1, v/v). The organic layer was washed with 1N HCl (aq.), saturated $NaHCO_3$ (aq.), H_2O and brine and dried over Na_2SO_4. The solvent was removed by evaporation leaving a residue that was subjected to column chromatography (eluant: 5% MeOH in EtOAc) to yield 0.15 g (91%) in 90% yield as a white solid: mp 75 ^oC (shrink), 85 ^oC (gel); *The NMR spectra are reported for a mixture of two rotamers,* ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 - 7.82 (m, 4H), 7.55 - 7.43 (m, 6H), [6.73 (d, *J* = 9.0 Hz) and 6.47 (d, *J* = 8.4 Hz), 1H], 4.41 (dd, *J*= 7.2 Hz and 10.2 Hz, 1H), [4.11 (m) and 3.96 (m), 1H], 3.76 -3.49 (m, 5H), 3.29 (m, 1H), [2.65 - 2.48 (m) and 2.30 -2.21 (m), 2H], 2.03 and 2.00 (s, 3H), 1.87 - 1.75 (m, 1H), 0.94 - 0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ171.6, 171.3, 170.9, 170.6, 132.0 (m), 131.3 -130.9 (m), 129.0 - 128.8 (m), 63.1, 63.0, 62.7, 61.5 (d, *J*cp = 10.5 Hz), 57.5, 56.8, 49.2, 47.6, 38.1 (d, *J*cp = 59.6 Hz), 33.4, 30.4, 28.8, 22.7, 21.7, 19.5, 19.0; ^{31}P (120 MHz, $CDCl_3$) δ 45.6 and 45.3; IR (film) 3019.7, 2978.0, 1651.0, 1601.8, 1521.5, 1601.8, 1521.5, 1476.7, 1422.2, 1211.6, 1045.6, 928.9, 767.8, 669.2, 627.6; MS-FAB m/z (% rel intensity) 459 (MH^+, 52), 328 (46), 219 (100), 110 (100); HRFAB Calcd for $C_{24}H_{32}N_2O_3PS$ (MH^+) m/e 459.1871, Found m/e 459.1872.

(2S, 5'R, 4S)-N-Acetyl-2-(4',5'-dihydro-5'-isopropyl-1',3'-oxazole-2'-yl)-4-diphenylphosphinothioyl-proline (phosphine sulfide of 30)



To a solution of (2S, 2'S, 4S)-N-Acetyl-2-[[N-[(2'-hydroxymethyl-2'-isopropyl)methyl]-1'-amino]-carbonyl]-4-diphenylphosphinothioyl-proline (**XVI**) (0.14 g, 0.31 mmol) in 15 mL of THF, Burgess reagent (95 mg, 0.40 mmol) was slowly added at 0 ^oC. The reaction mixture was allowed to warm to room temperature and stirring was

continued for 1 h. After which the solution was heated to reflux for 3 h. After cooling down the THF solvent was removed and the residue was subjected to column chromatograph (eluent: EtOAc/methanol/Et_3N, 92/7/1) to afford 0.10 g (75%) as a white foam: *The NMR spectra are reported for a mixture of two rotamers,* ^1H NMR (300 MHz, CDCl3) δ 7.89 -7.76 (m, 4H), 7.50 -7.39 (m, 6H), 4.66 -4.55 (m, 1H), 4.26 -4.11 (m, 1H), 4.05 -3.84 (m, 3H), 3.60 -3.18 (m, 2H), 2.71 -2.15 (m, 2H), 1.95 and 1.94 (s, 3H), 1.71 - 1.60 (m, 1H), 0.89 - 0.76 (m, 6H); ^{13}C NMR (75 MHz, CDCl3) d169.6, 168.7, 165.4, 132.1 - 131.7 (m), 131.1 - 130.8 (m), 129.0 - 128.7 (m), 72.0, 71.7, 70.8, 70.2, 55.7 (d, *J*cp = 11.0 Hz) 48.6, 46.9, 38.4 (d, *J*cp = 60.1 Hz), 37.1 (d, *J*cp = 59.6 Hz), 32.4, 32.2, 30.9, 22.5, 21.7, 18.6, 18.5, 18.1, 17.8; 31P (120 MHz, CDCl3) d 44.5 and 43.9; IR (film) 3054.1, 2986.7, 1650.9, 1551.1, 1436.4, 1421.9, 1265.0, 1102.1, 909.0, 947.9, 650.7; MS-FAB m/z (% rel intensity) 441 (MH+, 100), 328 (10), 218 (32); HRFAB Calcd for $C_{24}H_{30}N_2O_2PS$ (MH^+) m/e 441.1766, Found m/e 441.1777.

Procedure for π-ally allylation. The phosphine oxazoline ligand was mixed with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in degassed solvent, followed by addition of the cyclic allylic acetate. To this mixture a solution containing dimethyl malonate (3 eq.), TBAF (3 eq.) and BSA (3 eq.) was added slowly through a addition funnel (30 minutes). After the reaction was completed, water was added to quench the reaction and the organic solvent was removed by evaporation. The water layer was then extracted with dimethyl ether twice and the ether solution was washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. Evaporation of solvent gave a residue that was chromatographed by using EtOAc/*n*-hexanes (10/90, v/v) as an eluant to afford a colorless oil.