REVISED Supporting Information

A Temporary Phosphorus Tether/Ring-Closing Metathesis Strategy to Functionalized 1,4-Diamines

Kevin T. Sprott, Matthew D. McReynolds, and Paul R. Hanson*

Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, KS 66045-7582
phanson@KU.edu

Experimental Section

General Methods.

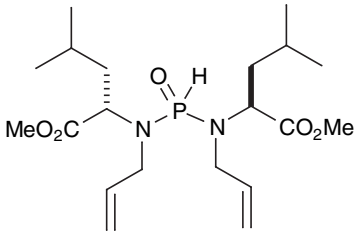
All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon using standard gas-tight syringes, cannulaes, and septa. CH_2Cl_2 was purified by distillation over CaH_2 or by passage through a Solv-Tek (www.solvtek.com) purification system employing activated Al_2O_3 (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518). THF and Et_2O were purified by passage through the Solv-Tek purification system employing activated Al_2O_3. Benzene was purified by distillation over CaH_2. Et_3N was distilled from CaH_2 and stored over KOH. DMAP was purchased from Reilly Chemicals and was not further purified. All amino acid precursors were purchased from Advanced Chem Tech. Thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5717, Merck). Visualization of TLC spots was effected using $KMnO_4$ stain. Flash column chromatography was performed with Merck silica gel (EM-9385-9, 230-400 mesh). Deuterochloroform ($CDCl_3$) was purchased from Cambridge Isotope Laboratories and stored over molecular sieves (4 Å) at room temperature. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$

(unless otherwise mentioned) on either a Bruker DRX-400 MHz spectrometer operating at 400 MHz and 100 MHz, respectively; or a Bruker Avance-500 MHz spectrometer operating at 500 MHz and 126 MHz, respectively. All ^{31}P spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on a Bruker DRX-400 MHz spectrometer operating at 162 MHz. High resolution mass spectrometry (HRMS) and FAB spectra were performed by the Mass Spectrometry Laboratory at the University of Kansas using a VG Instrument ZAB double-focusing mass spectrometer.

General Procedure for the Formation of Acyclic Phosphorus Acid Diamides 8a-d

A solution of Et_3N, *N*-allylated amino acid ester, 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 was cooled to 0°. PCl_3 was added dropwise, and the reaction mixture was heated to reflux for 3 hours, then concentrated under reduced pressure. The crude salty mixture was diluted with diethyl ether and water; the layers were separated and the water layer was washed with diethyl ether (2X). The organic layers were combined, dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The resulting oils were purified by flash chromatography.

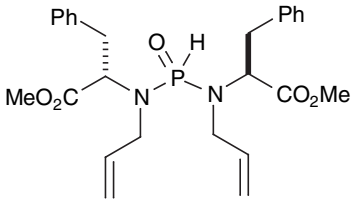
Acyclic Leucine-Derived Phosphorus Acid Diamide 8a



This compound was not re-synthesized using the new, higher yielding method**:** A solution of PCl_3 (50 µL, 0.57 mmol) and Et_2O (5 mL) was cooled in a –10 °C (NaCl saturated) ice bath. *N*-allylated leucine methyl ester (**7a**) (477 mg, 2.58 mmol) in Et_2O (2 mL) was added via cannulae. After addition, the solution was warmed to reflux and heated overnight. The reaction was concentrated under reduced pressure and purified by flash chromatography (1:1 hexanes/EtOAc) to afford 112 mg (47%) of **8a** as a colorless oil. $[\alpha]^{25} = +8.9$ (c = 0.12, $CHCl_3$); FTIR (neat) 1740, 1436, 1369, 1219 (P=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J_{HP} = 593.4 Hz, 1H), 5.83-5.72 (m, 2H), 5.16-5.01 (m, 4H), 4.18-4.08 (m, 2H), 3.74-3.53 (m, 4H), 3.65 (s, 3H), 3.64 (s, 3H), 1.75-1.64 (m, 6H), 0.91-0.88 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.55 (d, J_{CP} =

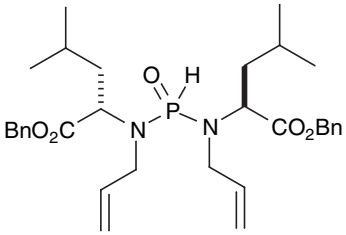
2.2 Hz), 173.44 (d, J_{CP} = 4.2 Hz), 135.84 (d, J_{CP} = 2.2 Hz), 135.47 (d, J_{CP} = 2.5 Hz), 117.64, 117.06, 55.31 (d, J_{CP} = 4.9 Hz), 55.64 (d, J_{CP} = 7.3 Hz), 51.82, 51.82, 46.91 (d, J_{CP} = 5.9 Hz), 45.17 (d, J_{CP} = 4.4 Hz), 39.91 (d, J_{CP} = 3.0 Hz), 37.95 (d, J_{CP} = 3.0 Hz), 24.61, 24.08, 22.76, 22.58, 21.84, 21.40; ^{31}P NMR (100 MHz, $CDCl_3$) δ 21.92; HRMS calcd for $C_{20}H_{38}N_2O_5P$ $(M+H)^+$ required 417.2518, found 417.2525.

Acyclic Phenylalanine-Derived Phosphorus Acid Diamide 8b



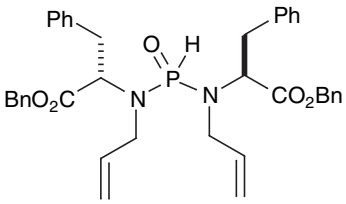
Following the general procedure for the formation of acyclic phosphorus acid diamides**,** *N*-allylated phenylalanine methyl ester (**7b**) (6.0 g, 27.3 mmol), Et_3N (13.3 mL, 95.5 mmol), DMAP (111 mg, 0.91 mmol), CH_2Cl_2 (50 mL); and PCl_3 (0.791 mL, 9.1 mmol), yielded 3.18 g (72%) of **8b** as a colorless oil after purification by flash chromatography (2:1, hexanes/EtOAc). $[\alpha]_{25}$ = -46.7 (c = 1.42, $CHCl_3$); FTIR (neat) 1737, 1437, 1217 (P=O), 748, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.14 (m, 10H), 6.83 (d, J_{HP} = 597.4 Hz, 1H), 5.65 (dddd, *J* = 16.8, 10.1, 6.6, 6.6 Hz, 1H), 5.53 (dddd, *J* = 16.8, 10.0, 6.6, 6.6 Hz, 1H), 5.13-5.02 (m, 4H), 4.46 (ddd, J_{HP} = 9.1 Hz, J_{HH} = 6.7, 6.7 Hz, 1H), 4.14 (ddd, J_{HP} = 15.4 Hz, J_{HH} = 7.6, 7.6 Hz, 1H), 3.65 (s, 3H), 3.61 (s, 3H), 3.51-3.46 (m, 2H), 3.34-3.26 (m, 4H), 3.07 (dd, *J* = 14.0, 7.8 Hz, 1H), 2.99 (dd, *J* = 16.3, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.53 (d, J_{CP} = 3.5 Hz), 172.35 (d, J_{CP} = 2.7 Hz), 137.59, 137.28, 135.45, 135.03, 129.23, 129.08, 128.43, 128.37, 126.63, 126.60, 117.86, 117.48, 59.13 (d, J_{CP} = 5.7 Hz), 58.43 (d, J_{CP} = 6.0 Hz), 51.92, 51.92, 46.70 (d, J_{CP} = 4.9 Hz), 45.83 (d, J_{CP} = 5.1 Hz), 37.25 (d, J_{CP} = 3.3 Hz), 35.61 (d, J_{CP} = 3.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.67; HRMS calcd for $C_{26}H_{34}N_2O_5P$ $(M + H)^+$ required 485.2205, found 485.2204.

Acyclic Leucine-Derived Phosphorus Acid Diamide 8c



Following the general procedure for the formation of acyclic phosphorus acid diamides**,** *N*-allylated leucine benzyl ester (**7c**) (4.8 g, 18.4 mmol), Et_3N (9.0 mL, 64.4 mmol), DMAP (75 mg, 0.61 mmol), CH_2Cl_2 (35 mL); and PCl_3 (0.53 mL, 6.1 mmol), yielded 2.86 g (82%) of **8c** a colorless oil after purification by flash chromatography (4:1, hexanes/EtOAc to 2:1, hexanes/EtOAc). $[\alpha]_{25}$ = +21.1 (c = 1.77, $CHCl_3$); FTIR (neat) 1736, 1456, 1386, 1216 (P=O), 751, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 10H), 6.98 (d, J_{HP} = 593.7 Hz, 1H), 5.69 (dddd, *J* = 16.9, 10.0, 6.9, 6.9 Hz, 1H), 5.68 (dddd, *J* = 16.8, 10.0, 6.8, 6.8 Hz, 1H), 5.09 (s, 4H), 5.12-5.00 (m, 3H), 4.93-3.99 (m, 1H), 4.24-4.10 (m, 2H), 3.73-3.46 (m, 4H), 1.83-1.67 (m, 6H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.91-0.88 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.94 (d, J_{CP} = 2.8 Hz), 172.84 (d, J_{CP} = 4.6 Hz), 135.75 (d, J_{CP} = 3.3 Hz), 135.41 (d, J_{CP} = 2.7 Hz), 135.36, 135.36, 128.49, 128.47, 128.42, 128.39, 128.30, 128.27, 117.71, 117.23, 66.82, 66.79, 55.85 (d, J_{CP} = 2.8 Hz), 55.80, 46.95 (d, J_{CP} = 6.3 Hz), 45.11 (d, J_{CP} = 4.0 Hz), 39.92, 37.74, 24.63, 23.99, 22.85, 22.59, 21.91, 21.33; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.32; HRMS calcd for $C_{32}H_{46}N_2O_5P$ $(M + H)^+$ required 569.3144, found 569.3120.

Acyclic Phenylalanine-Derived Phosphorus Acid Diamide 8d



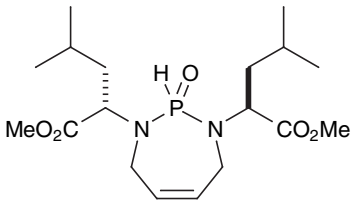
Following the general procedure for the formation of acyclic phosphorus acid diamides**,** *N*-allylated phenylalanine benzyl ester (**7d**) (3.28 g, 11.1 mmol), Et_3N (5.4 mL, 38.8 mmol), DMAP (45 mg, 0.37 mmol), CH_2Cl_2 (22 mL); and PCl_3 (0.32 mL, 3.7 mmol), yielded 1.74 g (74%) of **8d** a colorless oil after purification by flash chromatography (4:1, hexanes/EtOAc to

1:1, hexanes/EtOAc). $[\alpha]_{25}$ = -24.5 (c = 1.38, $CHCl_3$); FTIR (neat) 1736, 1455, 1217 (P=O), 748, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.31 (m, 5H), 7.27-7.12 (m, 15H), 6.81 (d, J_{HP} = 598.7 Hz, 1H), 5.60 (ddd, J = 10.0, 6.7, 6.7 Hz, 1H), 5.47 (ddd, J = 10.1, 6.7, 6.7 Hz, 1H), 5.10 (d, J = 8.1 Hz, 1H), 5.05 (d, J = 8.1 Hz, 1H), 5.06-4.96 (m, 6H), 4.48 (ddd, J_{HP} = 11.0 Hz, J_{HH} = 6.8, 6.8 Hz, 1H), 4.20 (ddd, J_{HP} = 15.0 Hz, J_{HH} = 7.6, 7.6 Hz, 1H), 3.49-3.46 (m, 2H), 3.33-3.28 (m, 4H), 3.10 (dd, J = 13.9, 7.4 Hz, 1H), 2.99 (dd, J = 14.3, 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.79 (d, J_{CP} = 3.8 Hz), 171.67 (d, J_{CP} = 3.2 Hz), 137.60, 137.20, 135.63, 135.22, 135.11, 135.04 (d, J_{CP} = 2.2 Hz), 129.35, 129.11, 128.46, 128.46, 128.45, 128.45, 128.41, 128.34, 128.30, 128.26, 126.60, 126.55, 117.88, 117.47, 66.90, 66.90, 59.21 (d, J_{CP} = 3.9 Hz), 58.83 (d, J_{CP} = 4.8 Hz), 47.02 (d, J_{CP} = 4.4 Hz), 45.86 (d, J_{CP} =3.8 Hz), 37.46, 35.74; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.91; HRMS calcd for $C_{38}H_{42}N_2O_5P$ $(M + H)^+$ required 637.2831, found 637.2826.

General Procedure for the Formation of 1,3,2-Diazaphosphepine 2-oxides 10a-d

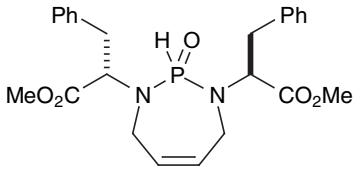
The acyclic phosphorus acid diamide (**8a-d**) was dissolved in benzene and heated to reflux. The second generation, 4,5-dihydroimidazol-2-ylidene-derived Grubbs catalyst (**9**) was added, and the reaction was monitored by TLC (2.5 mol % catalyst; reaction time typically 2-5 minutes). Once complete, the reaction mixture was concentrated under reduced pressure, and the resulting oils were purified by flash chromatography.

Cyclic Leucine-Derived 1,3,2-Diazaphosphepine 2-oxide 10a



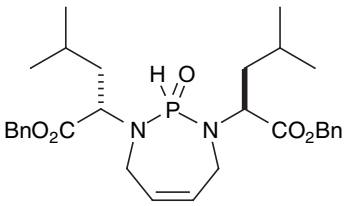
Following the general procedure for the formation of 1,3,2-diazaphosphepine 2-oxides, acyclic phosphorus acid diamide **8a** (390 mg, 0.94 mmol), Grubbs catalyst **9** (20 mg, 0.023 mmol), and benzene (50 mL) yielded a colorless oil. Only a small portion of the resulting oil was purified by flash chromatography (1:1, hexanes/EtOAc) for characterization of cyclic *P*-H compound **10a**. The remaining oil was hydrolyzed with methanolic HCl to yield diamine **1a**. Total yield after hydrolysis is 97%. Compound **10a** was identical in all respects to the compound we have published in the literature.[6b]

Cyclic Phenylalanine-Derived 1,3,2-Diazaphosphepine 2-oxide 10b



Following the general procedure for the formation of 1,3,2-diazaphosphepine 2-oxides, acyclic phosphorus acid diamide **8b** (1.10 g, 2.06 mmol), Grubbs catalyst **9** (44 mg, 0.05 mmol), and benzene (85 mL) yielded 1.02 g (>99%) of **10b** as a colorless oil after purification by flash chromatography (1:1, hexanes/EtOAc). $[\alpha]_{25}$ = -66.7 (c = 1.69, $CHCl_3$); FTIR (neat) 1736, 1454, 1358, 1222 (P=O), 746, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.14 (m, 10H), 6.56 (d, J_{HP} = 599.7 Hz, 1H), 5.41 (bs, 2H), 4.44 (ddd, J_{HP} = 11.9 Hz, J_{HH} = 7.4, 7.4 Hz, 1H), 4.33 (ddd, J_{HP} = 9.7 Hz, J_{HH} = 6.0, 6.0 Hz, 1H), 3.65 (d, J_{HP} = 0.8 Hz, 3H), 3.59 (d, J_{HP} = 0.7 Hz, 3H), 3.56-3.41 (m, 2H), 3.34-3.24 (m, 3H), 3.15 (dd, J = 14.3, 6.0 Hz, 1H), 2.84 (dd, J = 14.3, 9.7 Hz, 1H), 2.80 (dd, J = 14.5, 8.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 171.94 (d, J_{CP}= 4.3 Hz), 171.83 (d, J_{CP} = 2.3 Hz), 136.68, 136.62, 129.13, 129.13, 128.31, 128.15, 127.79, 127.42, 126.71, 126.46, 59.08 (d, J_{CP} = 8.5 Hz), 58.52 (d, J_{CP} = 8.0 Hz), 52.07, 51.93, 39.67 (d, J_{CP} = 5.0 Hz), 39.63 (d, J_{CP} = 5.5 Hz), 36.21 (d, J_{CP} = 4.2 Hz), 36.07 (d, J_{CP} = 2.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.91; HRMS calcd for $C_{24}H_{30}N_2O_5P$ $(M + H)^+$ required 457.1892, found 457.1904.

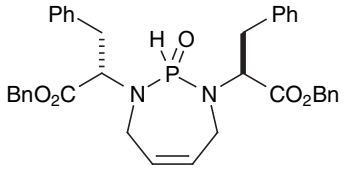
Cyclic Leucine-Derived 1,3,2-Diazaphosphepine 2-oxide 10c



Following the general procedure for the formation of 1,3,2-diazaphosphepine 2-oxides, acyclic phosphorus acid diamide **8c** (2.38 g, 4.21 mmol), Grubbs catalyst **9** (35 mg, 0.042 mmol), and benzene (200 mL) yielded a colorless oil. Only a small portion of the resulting oil was purified by flash chromatography (1:1, hexanes/EtOAc) for characterization of cyclic *P*-H compound **10c**. The remaining oil was hydrolyzed with methanolic HCl to yield diamine **1c**. Total yield after hydrolysis is 95% (see compound **1c**). $[\alpha]_{25}$ = -31.3 (c = 1.95, $CHCl_3$); FTIR (neat) 1735, 1455, 1387, 1253 (P=O), 752, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 10H), 7.02 (d, J_{HP}

= 592.1 Hz, 1H), 5.50-5.43 (m, 2H), 5.16-5.05 (m, 4H), 4.40 (ddd, J_{HP} = 10.1 Hz, J_{HH} = 8.4, 8.4 Hz, 1H), 4.05-3.95 (m, 2H), 3.70-3.62 (m, 1H), 3.48-3.31 (m, 2H), 1.73-1.52 (m, 6H), 0.96 (d, *J* = 6.3 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.68 (d, J_{CP} = 2.1 Hz), 172.12, 135.41, 135.41, 128.48, 128.41, 128.30, 128.27, 128.27, 128.16, 127.98, 127.70, 66.79, 66.79, 56.48 (d, J_{CP} = 9.0 Hz), 56.32 (d, J_{CP} = 6.6 Hz), 40.15 (d, J_{CP} = 3.2 Hz), 40.00 (d, J_{CP} = 5.3 Hz), 39.08 (d, J_{CP} = 5.4 Hz), 37.98 (d, J_{CP} = 3.3 Hz), 24.45, 24.42, 23.24, 22.89, 21.60, 21.23; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.77; HRMS calcd for $C_{30}H_{42}N_2O_5P$ $(M + H)^+$ required 541.2831, found 541.2842.

Cyclic Phenylalanine-Derived 1,3,2-Diazaphosphepine 2-oxide 10d

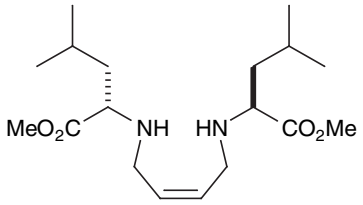


Following the general procedure for the formation of 1,3,2-diazaphosphepine 2-oxides, acyclic phosphorus acid diamide **8d** (1.67 g, 2.62 mmol), Grubbs catalyst **9** (46 mg, 0.052 mmol), and benzene (130 mL) yielded a colorless oil. Only a small portion of the resulting oil was purified by flash chromatography (1:1, hexanes/EtOAc) for characterization of cyclic *P*-H compound **10d**. The remaining oil was hydrolyzed with methanolic HCl to yield diamine **1d**. Total yield after hydrolysis is >99% (see compound **1d**). $[\alpha]_{25}$ = -30.8 (c = 4.49, $CHCl_3$); FTIR (neat) 1735, 1454, 1218 (P=O), 746, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.10 (m, 20H), 6.51 (d, J_{HP} = 603.5 Hz, 1H), 5.30-5.27 (m, 2H), 5.11 (d, *J* = 12.2 Hz, 1H), 5.06 (d, *J* = 12.2 Hz, 1H), 5.04 (d, *J* = 12.1 Hz, 1H), 4.99 (d, *J* = 12.1 Hz, 1H), 4.48 (ddd, J_{HP} = 12.1 Hz, J_{HH} = 7.8, 7.8 Hz, 1H), 4.38 (ddd, J_{HP} = 9.6 Hz, J_{HH} = 5.9, 5.9 Hz, 1H), 3.48-3.13 (m, 6H), 2.83 (dd, J = 13.7, 9.9 Hz, 1H), 2.79 (dd, *J* = 12.3, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.29 (d, J_{CP} = 3.5 Hz), 171.26 (d, J_{CP} = 2.2 Hz), 136.73, 136.62, 135.26, 135.18, 129.25, 129.23, 128.49, 128.43, 128.35, 128.35, 128.33, 128.30, 128.23, 128.21, 127.79, 127.50, 126.77, 126.51, 66.92, 66.88, 59.44 (d, J_{CP} = 6.7 Hz), 58.64 (d, J_{CP} = 6.5 Hz), 39.88 (d, J_{CP} = 3.2 Hz), 39.56 (d, J_{CP} = 3.8 Hz), 36.35 (d, J_{CP} = 3.2 Hz), 36.17; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.80; HRMS calcd for $C_{36}H_{38}N_2O_5P$ $(M + H)^+$ required 609.2518, found 609.2506.

General procedure for the formation of 1,4-Diamines 1a-d

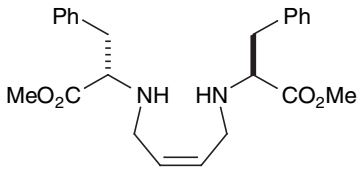
1,3,2-Diazaphosphepine 2-oxides **10a-d** were individually dissolved in HCl saturated MeOH and stirred at room temperature for 1 hour. (1,3,2-Diazaphosphepine 2-oxides **10a-d** need not be purified after metathesis; rather, the crude mixture was concentrated and treated with methanolic HCl). The solution was diluted with EtOAc and the organic layer was washed water (3X). The water layer was neutralized with aqueous $NaHCO_3$, then extracted 3 times with ethyl acetate. The organic portions were combined, washed with brine, dried (Na_2SO_4), filtered, then concentrated. Acid/base extraction afforded **1a-d** in >95% purity by NMR (^1H, ^{13}C, and ^{31}P) and >99% by GC spectral analysis. Therefore, no further purification was necessary.

Leucine Methyl Ester-Derived 1,4-Diamine 1a



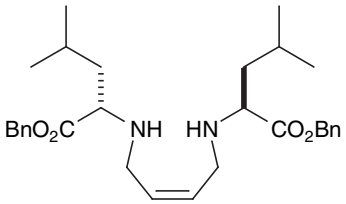
Following the general procedure for the formation of 1,4-diamines, crude 1,3,2-diazaphosphepine 2-oxide **10a** (309 mg, 0.80 mmol) and methanolic HCl (3 mL) yielded 264 mg (97%) of the pure 1,4-diamine **1a** as a colorless oil. $[\alpha]^{25} = +12.0$ (c = 0.05, $CHCl_3$); FTIR (neat) 1737, 1468, 1433, 1368 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.56 (dd, *J* = 4.5, 4.5 Hz, 2H), 3.72 (s, 6H), 3.29-3.21 (m, 4H), 3.09 (dd, *J* = 13.2, 4.8 Hz, 2H), 1.76-1.66 (m, 2H), 1.54 (bs, 2H), 1.47-1.43 (m, 4H), 0.92 (d, *J* = 6.6 Hz, 6H), 0.89 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.44, 130.17. 59.34, 51.60, 44.62, 42.85, 24.90, 22.66, 22.35; HRMS calcd for $C_{18}H_{35}N_2O_4$ $(M+H)^+$ required 343.2597, found 343.2619.

Phenylalanine Methyl Ester Derived 1,4-Diamine 1b



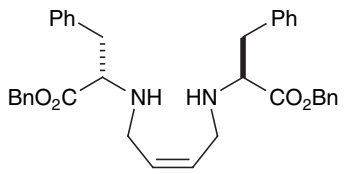
Following the general procedure for the formation of 1,4-diamines, crude 1,3,2-diazaphosphepine 2-oxide **10b** (420 mg, 0.92 mmol) and methanolic HCl (3 mL) yielded 396 mg (>99%) of the pure 1,4-diamine **1b** as a colorless oil. $[\alpha]_{25}$ = +23.4 (c =1.37, $CHCl_3$); FTIR (neat) 3428 (broad), 1734, 1455, 744, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.14 (m, 10H), 5.49 (ddd, *J* = 10.9, 6.1, 6.1 Hz, 2H), 3.62 (s, 6H), 3.49 (dd, *J* = 6.9, 6.9 Hz, 2H), 3.19 (dd, *J* = 13.4, 4.3 Hz, 2H), 3.07 (dd, *J* = 13.7, 5.2 Hz, 2H), 2.92 (d, *J* = 6.8 Hz, 4H), 1.56 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.79, 137.01, 129.94, 129.00, 128.31, 126.61, 62.12, 51.50, 44.43, 39.59; HRMS calcd for $C_{24}H_{31}N_2O_4$ $(M + H)^+$ required 411.2284, found 411.2306.

Leucine Benzyl Ester Derived 1,4-Diamine 1c



Following the general procedure for the formation of 1,4-diamines, crude 1,3,2-diazaphosphepine 2-oxide **10c** (2.07 g, 3.8 mmol) and methanolic HCl (3 mL) yielded 1.80 g (95%) of the pure 1,4-diamine **1c** as a colorless oil. $[\alpha]_{25}$ = -17.3 (c = 3.12, $CHCl_3$); FTIR (neat) 3330 (bs), 1732, 1456, 1367, 751, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 10H), 5.53 (dd, *J* = 15.3, 10.9 Hz, 2H), 5.16 (s, 4H), 3.29 (dd, *J* = 7.3, 7.3 Hz, 2H), 3.19 (dd, *J* = 13.1, 4.1 Hz, 2H), 3.06 (dd, *J* = 13.4, 5.0 Hz, 2H), 1.69 (ddqq, *J* = 6.7, 6.7, 6.7, 6.7 Hz, 2H), 1.52 (bs, 2H), 1.49-1.39 (m, 4H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.65, 135.74, 130.05, 128.42, 128.15 (2), 66.18, 59.26, 44.44, 42.67, 24.73, 22.53, 22.24; HRMS calcd for $C_{30}H_{43}N_2O_4$ $(M + H)^+$ required 495.3223, found 495.3227.

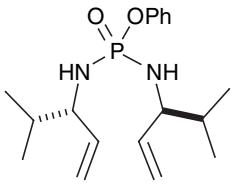
Phenylalanine Benzyl Ester Derived 1,4-Diamine 1d



Following the general procedure for the formation of 1,4-diamines, crude 1,3,2-diazaphosphepine 2-oxide **10d** (1.37 g, 2.44 mmol) and methanolic HCl (4 mL) yielded 1.325 g (>99%) of the pure

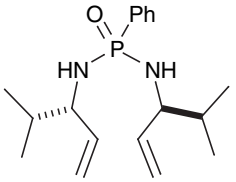
1,4-diamine **1d** as a colorless oil. $[\alpha]_{25}$ = +6.9 (c = 2.38, $CHCl_3$); FTIR (neat) 1732, 750, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.09 (m, 20H), 5.47 (ddd, *J* = 15.5, 15.5, 11.1 Hz, 2H), 5.04 (s, 4H), 3.52 (dd, *J* = 7.0, 7.0 Hz, 2H), 3.17 (dd, *J* = 13.4, 4.3 Hz, 2H), 3.04 (dd, *J* = 13.6, 5.1 Hz, 2H), 2.94 (dd, *J* = 13.5, 6.6 Hz, 2H), 2.88 (dd, *J* = 13.5, 7.3 Hz, 2H), 1.58 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.28, 136.95, 135.45, 130.00, 129.11, 128.40, 128.32, 128.30, 128.18, 126.58, 66.34, 62.17, 44.42, 39.66; HRMS calcd for $C_{36}H_{39}N_2O_4$ $(M + H)^+$ required 563.2910, found 563.2910.

Acyclic Valine-Derived Diamidophosphate 13a



The procedure for the synthesis of **13a**, as well as characterization data, was identical in all respects as we have published in the literature.[6b]

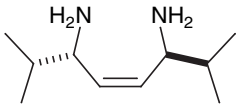
Acyclic Valine-Derived Phosphonamide 13b



A solution of phenylphosphonic dichloride (**12b**) (69 mg, 0.35 mmol) and CH_2Cl_2 (3.5 mL) was cooled in a 0 °C ice bath. Et_3N (358 mg, 3.54 mmol) was added slowly, followed by a catalytic amount of DMAP (4 mg, 35 µmol), and the solution was stirred at 0 °C for 5 minutes. L-Valine-derived allylic ammonium salt **11** (97 mg, 0.72 mmol) was added, and the solution was stirred at room temperature for 3 hours. The crude product was partitioned between CH_2Cl_2 and water, the layers were separated, and the aqueous layer was washed with CH_2Cl_2 (3X). The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (EtOAc) yielded 95 mg (84%) of **13b** as a white foam. $[\alpha]^{25}$ = +42.3 (c = 1.21, $CDCl_3$); FTIR (neat) 3219, 3077, 1465, 1437, 1386, 1368, 1190 (P=O), 748, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85-7.77 (m, 2H), 7.46-7.35 (m, 3H), 5.75 (ddd, *J* = 16.8, 10.4, 6.0 Hz, 1H), 5.63 (ddd, *J* = 16.9, 10.4, 6.3 Hz, 1H), 5.10 (ddd, *J* = 17.2, 1.5, 1.5 Hz, 1H),

5.07 (ddd, J = 10.3, 1.4, 1.4 Hz, 1H), 5.00 (ddd, J = 17.2, 1.4, 1.4 Hz, 1H), 4.96 (ddd, J = 10.1, 1.3, 1.3 Hz, 1H), 3.68-3.59 (m, 1H), 3.55-3.48 (m, 1H), 2.54-2.46 (m, 2H), 1.80-1.67 (m, 2H), 0.83 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.04 (J_{CP} = 3.6 Hz), 138.62 (J_{CP} = 3.6 Hz), 133.70 (J_{CP} = 154.7 Hz), 131.86 (J_{CP} = 9.4 Hz), 131.22 (J_{CP} = 2.8 Hz), 128.02 (J_{CP} = 13.3 Hz), 115.07, 114.86, 58.70, 58.23, 33.53 (J_{CP} = 5.0 Hz), 33.40 (J_{CP} = 5.0 Hz), 18.31, 18.31, 17.97, 17.97; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.42; HRMS calcd for $C_{18}H_{30}N_2OP$ $(M+H)^+$ required 321.2086, found 321.2086.

Valine-Derived 1,4-Diamine 2 from 13a

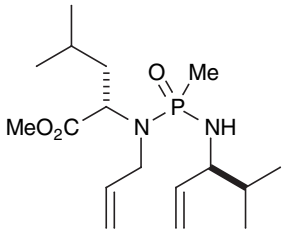


A solution of acyclic diamidophosphate **13a** (46 mg, 0.14 mmol) and benzene (14 mL) was purged with argon for 10 minutes. Grubbs catalyst **9** (1 mg, 1 μmol) was added, and the solution was brought to reflux and monitored by TLC. Upon disappearance of starting material by TLC (about 1 hour), the reaction was concentrated under reduced pressure. The crude metathesis product was dissolved in THF (2 mL) and 2.0 M HCl (2 mL) and the solution was stirred in a 50 °C oil bath for 3 hrs. The solution was diluted with EtOAc and the organic layer was washed with water (3X). The water layer was neutralized with K_2CO_3(aq, sat'd), brought to a pH of 10 with K_2CO_3(s), then extracted with CH_2Cl_2 (3X). The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated to yield 21 mg (91%) of **2** as an orange oil. Acid/base extraction afforded **2** in >95% purity by NMR (^{1}H, ^{13}C, and ^{31}P) and >99% by GC spectral analysis. Therefore, no further purification was necessary. $[\alpha]^{25}$ = +35.4 (c = 1.45, $CHCl_3$); FTIR (neat) 3357 (broad), 3260 (broad), 1574, 1468, 1368, 1307, 1289 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (dd, J = 6.6, 2.2 Hz, 2H), 3.33 (ddd, J = 6.8, 6.8, 2.2 Hz, 2H), 1.60-1.48 (m, 2H), 1.34-1.15 (bs, 4H), 0.96 (d, J = 6.7 Hz, 6H), 0.88 (d, J = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.59, 54.41, 34.00, 18.95, 18.83; HRMS calcd for $C_{10}H_{23}N_2$ $(M+H)^+$ required 171.1861, found 171.1872.

Valine-Derived 1,4-Diamine 2 from 13b

A solution of acyclic phosphonamide **13b** (114 mg, 0.36 mmol) and benzene (36 mL) was purged with argon for 10 minutes. Grubbs catalyst **9** (9 mg, 11 µmol) was added, and the solution was brought to reflux and monitored by TLC. Upon disappearance of starting material by TLC (about 2 hrs), the reaction was concentrated under reduced pressure. The crude metathesis product was dissolved in THF (3 mL) and 2.0 M HCl (3 mL), and the solution was stirred in a 50 °C oil bath for 3 hrs. The solution was diluted with EtOAc and the organic layer was washed with water (3X). The water layer was neutralized with K_2CO_3(aq, sat'd), brought to a pH of 10 with K_2CO_3(s), then extracted with CH_2Cl_2 (3X). The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated to yield 42 mg (70%) of **2** as an orange oil. The product need not be further purified. The product was identical in all respects to **2** from **13a**.

Acyclic Leucine/Valine-Derived Phosphonamide 16



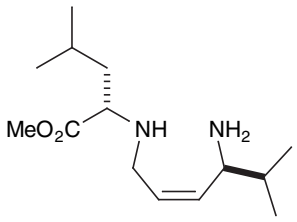
A solution of both leucine-derived methyl phosphonamidic monochloridate diastereomers **15P$_S$S** and **15P$_R$S** (*dr* ~ 1.1:1.0) (78 mg, 0.28 mmol) and CH_2Cl_2 (1 mL) was cooled in a 0 °C ice bath. Et_3N (70 mg, 0.69 mmol) was added slowly, followed by a catalytic amount of DMAP (2 mg, 12 µmol), and the solution was stirred at 0 °C for 5 minutes. Valine-derived allylic ammonium salt **11** (39 mg, 0.29 mmol) was added, and the solution was stirred at 0 °C for 2 hours. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc, filtered, and re-concentrated. ^{31}P analysis of the crude reaction mixture revealed a 6.6:1.0 mixture of diastereomers. Flash chromatography (EtOAc) yielded 50 mg (53%) of major diastereomer **16-major** (either **16P$_S$SS** or **16P$_R$SS**) as a colorless oil, and 34 mg (35%) of a 2.6:1.0 mixture of major and minor diastereomers **16-mixture** (**16P$_S$SS** and **16P$_R$SS**), respectively, as a colorless oil. **16-major** was characterized and carried on to the next step to give **3**. **16-mixture** was not fully characterized, but immediately carried on to the next step to give **3**.

16-major: R_f = 0.51 (5% MeOH in EtOAc); $[\alpha]^{25}$ = +13.6 (c = 0.68, $CHCl_3$); FTIR (neat) 3321 (broad), 3077, 1740, 1640, 1468, 1435, 1385, 1368, 1194 (P=O) cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 5.84-5.76 (m, 1H), 5.74 (ddd, *J* = 16.8, 10.3, 6.4 Hz, 1H), 5.17 (ddd, *J* = 17.0, 1.5, 1.5 Hz, 1H), 5.13 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.11 (ddd, *J* = 10.3, 1.3, 1.3 Hz, 1H), 5.06 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.62-4.56 (m, 1H), 3.76-3.67 (m, 1H), 3.67 (s, 3H), 3.56-3.46 (m, 2H), 2.87 (dd, J_{HP} = 9.2 Hz, J_{HH} = 3.2 Hz, 1H), 1.85-1.74 (m, 1H), 1.72-1.61 (m, 3H), 1.45 (d, J_{HP} = 15.3 Hz, 3H), 0.95 (d, *J* = 6.1 Hz, 3H), 0.92 (d, *J* = 5.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.76, 138.75 (d, J_{CP} = 4.1 Hz), 136.67, 116.35, 114.91, 58.14, 55.43 (d, J_{CP} = 3.1 Hz), 51.71, 47.23 (d, J_{CP} = 4.5 Hz), 38.02 (d, J_{CP} = 4.1 Hz), 33.39 (d, J_{CP} = 4.9 Hz), 24.22, 22.83, 20.93, 18.17, 17.70, 14.26 (d, J_{CP} = 120.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.12; HRMS calcd for $C_{17}H_{34}N_2O_3P$ $(M+H)^+$ required 345.2307, found 345.2307.

16-minor: R_f = 0.49 (5% MeOH in EtOAc); ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.41.

Leucine/Valine-Derived Unsymmetric 1,4-Diamine 3



A solution of acyclic phosphonamide **16** (51 mg, 0.15 mmol) and CH_2Cl_2 (15 mL) was purged with argon for 10 minutes. Grubbs catalyst **17** (6 mg, 7 µmol) was added, and the solution was brought to reflux and monitored by TLC. Upon disappearance of starting material by TLC, the reaction was concentrated under reduced pressure. The crude metathesis product was dissolved in HCl saturated MeOH (2 mL), and the solution was stirred in a 50 °C oil bath for 3 hrs. The solution was diluted with EtOAc and the organic layer was washed with water (3X). The water layer was neutralized with K_2CO_3(aq, sat'd), brought to a pH of 10 with K_2CO_3(s), then extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated to yield 37 mg (97%) of **3** as a yellow oil. Acid/base extraction afforded **3** in >95% purity by NMR (^{1}H, ^{13}C, and ^{31}P) and >99% by GC spectral analysis. Therefore, no further purification was necessary. $[\alpha]^{25}$ = -6.5 (c = 1.32, $CHCl_3$); FTIR (neat) 3317 (broad), 1736, 1468, 1434, 1385, 1367 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52-5.46 (m, 1H), 5.39 (overlapping dd, *J* = 10.9, 9.5 Hz, 1H), 3.71 (s, 3H), 3.35-3.25 (m, 1H), 3.32 (dd, *J* = 13.3, 7.3 Hz, 1H), 3.27 (dd, *J* = 7.3, 7.3 Hz, 1H), 3.11 (dd, *J* = 13.3, 6.2 Hz, 1H), 1.78-1.64 (m,

1H), 1.59-1.50 (m, 1H), 1.49-1.31 (m, 3H), 1.45 (dd, *J* = 6.9, 6.9 Hz, 2H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6, 90 °C) δ 174.92, 134.72, 127.64, 58.50, 53.11, 50.53, 43.78, 41.63, 33.31, 24.01, 22.06, 21.63, 17.94, 17.94; HRMS calcd for $C_{14}H_{29}N_2O_2$ $(M+H)^+$ required 257.2229, found 257.2235.

Summary of unsuccessful attempts at using other temporary tethers:

Secondary Amine	*Tether reagent*	*Conditions*	*Coupling Pdt Observed?*	*RCM Pdt Observed?*
7a	$SiPh_2Cl_2$	CH_2Cl_2, 0 °C	no (only **7a** by TLC)	N/A
7a	$SiPh_2Cl_2$	NaH, THF, -78 °C to RT	no (only **7a** by TLC)	N/A
7a	$SiMe_2Cl_2$	Et_3N, CH_2Cl_2, 0 °C	no (only **7a** by TLC)	N/A
7a	$SiHCl_3$	CH_2Cl_2, 0 °C	no (only **7a** by TLC)	N/A
7a	$SiCl_4$	NaH, THF, -78 °C to RT	no (only **7a** by TLC)	N/A
7a	$PhBCl_2$	Et_3N, CH_2Cl_2, -78 °C to RT	no (only **7a** by TLC)	N/A
7a	BCl_3	Et_3N, CH_2Cl_2, -78 °C to RT	no (only **7a** by TLC)	N/A
7a	$(CCl_3O)_2CO$	Et_3N, CH_2Cl_2, -78 °C to RT	yes	minimal (TLC) 24-48 hrs.
7a	[a]$Cu(OAc)_2$	CH_2Cl_2, 0 °C	N/A	no (only **7a** by TLC)
7a	[a]$Fe(OAc)_2$	CH_2Cl_2, 0 °C	N/A	no (only **7a** by TLC)
7a	[a]$MnCl_2$	CH_2Cl_2, 0 °C	N/A	no (only **7a** by TLC)
7a	[a]$Mg(OTf)_2$	CH_2Cl_2, 0 °C	N/A	no (only **7a** by TLC)
7a	[a]$NiCl_2$	NaH, THF, -78 °C to RT	N/A	no (only **7a** by TLC)
7a	[a]$Ni(acac)_2$	NaH, THF, -78 °C to RT	N/A	no (only **7a** by TLC)

[a] When evaluating the metal-derived tethers, the first generation Grubbs catalyst was added to the crude coupling reaction mixture, and the solution was brought to reflux. The reaction was monitored by quenching an aliquot of the crude solution with methanolic HCl, neutralizing, and testing the aliquot by TLC to observe the presence or absence of the 1,4-diamine.