SUPPORTING INFORMATION

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Introducing the New Class of **N**-*Phosphoryl Ynamides via Cu(I)-Catalyzed Amidations of Alkynyl Bromides.*

authored by

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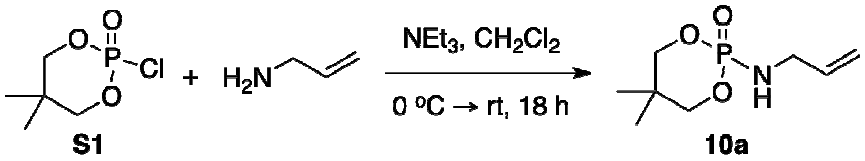
GENERAL EXPERIMENTAL INFORMATION

All reactions were performed in flame-dried glassware under a nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased from Aldrich, Acros, Alfa Aesar, or TCI unless otherwise noted. Chromatographic separations were performed using Dynamic Adsorbants, Inc. 32-63 μm SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-400 and VI-500 spectrometers using $CDCl_3$ with TMS or residual solvent as standard unless otherwise noted. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained on a Bruker EQUINOX 55 FTIR. TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and $KMnO_4$ stains. Low-resolution mass spectra were obtained using an Agilent 1100 series LS/MSD and are APCI. All spectral data obtained for new compounds are reported here.

General Procedure for the Preparation of Phosphoramidates[1] 10a–10c:



To a flame-dried 25-mL RB-flask was added CH_2Cl_2 (4 mL, 0.6 M in allyl amine), allyl amine (0.17 mL, 2.26 mmol), and NEt_3 (0.50 mL, 3.40 mmol) under a nitrogen atmosphere. The reaction flask was cooled to 0 °C and 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide **S1** (500.0 mg, 2.71 mmol) was added slowly dropwise. Once the addition was complete, the reaction was allowed to warm to rt and stir overnight. After the reaction was judged to be complete by TLC, water (10 mL) was added, the organic layer separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phase was washed with sat. NaCl and dried over Na_2SO_4. The crude product **10a** (498 mg, 2.26 mmol, ≥95%) was clean by ^1H NMR and further purification was not necessary.

10a: R_f = 0.18 [1:1 EtOAc:CH_2Cl_2]; white solid; mp = 75–76 °C;

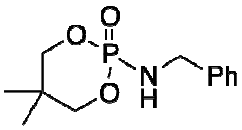
^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.21 (s, 3H), 2.82 (s, 1H), 3.62 (dddt, 2H, *J* = 1.4, 5.6, 7.2, 10.8 Hz), 3.81 (ddt, 2H, *J* = 1.4, 10.8, 20.0 Hz), 4.30 (dd, 2H, *J* = 4.0, 10.8 Hz), 5.13 (dd, 1H, *J* = 1.4, 10.4 Hz), 5.25 (dq, 1H, *J* = 1.4, 16.8 Hz), 5.89 (ddt, 1H, *J* = 5.6, 10.4, 16.8 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 22.3, 32.10 (d, *J* = 5.1 Hz), 44.1, 76.4 (d, *J* = 5.5 Hz), 116.1, 135.9 (d, *J* = 5.7 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ 6.38;

IR (film) cm^{-1} 3024brm, 2964w, 2932w, 2877m, 1650w, 1454m, 1226s, 1212s;

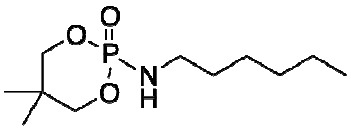
mass spectrum (APCI): m/e (% relative intensity) 206 (100) $(M+H)^+$.



10b

Phosphoramidate **10b** (1.19 g, 4.67 mmol) was prepared from benzyl amine (0.51 mL, 4.67 mmol) and **S1** (1.04 g, 5.61 mmol) in ≥95% yield. *Further purification via flash silica gel column chromatography (1:4:1 hexanes/EtOAc/CH_2Cl_2) was required.*

10b: R_f = 0.15 [1:4:1 hexanes:EtOAc:CH_2Cl_2]; white solid; mp = 120–122 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.21 (s, 3H), 3.06 (s, 1H), 3.83 (ddd, 2H, *J* = 1.2, 11.2, 20.0 Hz), 4.20 (dd, 2H, *J* = 6.8, 10.4 Hz), 4.33 (dd, 2H, *J* = 4.0, 11.2 Hz), 7.27–7.30 (m, 1H), 7.31–7.36 (m, 4H);
^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 22.3, 32.1, 45.6, 76.5 (d, *J* = 5.4 Hz), 127.5, 127.7, 128.9, 157.6;
^{31}P NMR (162 MHz, $CDCl_3$) δ 6.10;
IR (film) cm^{-1} 3149brm, 2959m, 2877m, 1494w, 1455m, 1224s, 1211s;
mass spectrum (APCI): m/e (% relative intensity) 256 (100) $(M+H)^+$.

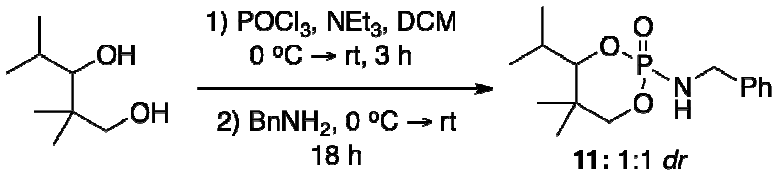


10c

Phosphoramidate **10c** (1.23 g, 4.95 mmol) was prepared from hexyl amine (0.65 mL, 4.95 mmol) and **S1** (1.10 g, 5.94 mmol) in ≥95% yield. *Further purification via flash silica gel column chromatography (1:4 hexanes/EtOAc) was required.*

10c: R_f = 0.24 [1:1 EtOAc:CH_2Cl_2]; white solid; mp = 52–54 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 8.0 Hz), 0.89 (s, 3H), 1.21 (s, 3H), 1.27–1.34 (m, 6H), 1.51 (pent, 2H, *J* = 7.2 Hz), 2.97 (dt, 2H, *J* = 7.2, 10.4 Hz), 3.13 (brs, 1H), 3.80 (ddt, 2H, *J* = 1.4, 11.2, 20.0 Hz), 4.29 (dd, 2H, *J* = 4.0, 11.2 Hz);
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.9, 22.2, 22.7, 26.4, 31.6, 31.8 (d, *J* = 5.9 Hz), 32.0 (d, *J* = 5.3 Hz), 41.7 (d, *J* = 1.1 Hz), 76.2 (d, *J* = 5.4 Hz);
^{31}P NMR (162 MHz, $CDCl_3$) δ 6.81;
IR (film) cm^{-1} 3167brm, 2957m, 2929m, 2871m, 1462m, 1224s, 1210s;
mass spectrum (APCI): m/e (% relative intensity) 250 (100) $(M+H)^+$.

General Procedure for the preparation of Phosphoramidate 11 and Phosphordiamidates[2] 18 and 20.



11: 1:1 *dr*

To a flame-dried 25-mL RB-flask was added CH_2Cl_2 (15 mL, 0.1 M in diol), $POCl_3$ (0.14 mL, 1.50 mmol), and NEt_3 (0.68 mL, 4.95 mmol) under a nitrogen atmosphere. The reaction flask was cooled to 0 °C and a solution of the 1,3-diol (219.0 mg, 1.5 mmol) in 1 mL CH_2Cl_2 was added slowly dropwise. Once the addition was complete, the reaction was allowed to warm to rt and stir for 3 h. The reaction flask was then cooled to back to 0 °C and a solution of benzyl amine (0.16 mL, 1.65 mmol) in 1 mL CH_2Cl_2 was added dropwise. Once the addition was complete, the reaction was allowed to warm to rt overnight. After the reaction was judged to be complete by TLC, water (10 mL) was added, the organic layer separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phase was washed with sat. NaCl and dried over Na_2SO_4. The crude residue was purified by flash silica gel column chromatography (1:4:1 hexanes/EtOAc/CH_2Cl_2) to afford the pure phosphoramide **11** (290.9 mg, 0.98 mmol, 65%) as a 1:1 mixture of diastereomers.

11-*fast band*: R_f = 0.28 [1:4:1 hexanes:EtOAc:CH_2Cl_2]; white solid; mp = 125–127 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.98 (d, 3H, *J* = 6.8 Hz), 1.01 (d, 3H, *J* = 6.8 Hz), 1.21 (s, 3H), 1.93–2.03 (m, 1H), 2.90–2.96 (m, 1H), 3.73 (dd, 1H, *J* = 10.8, 21.6 Hz), 3.84 (t, 1H, *J* = 3.6 Hz), 3.92 (dd, 1H, *J* = 4.0, 10.8 Hz), 4.13 (td, 2H, *J* = 2.4, 8.0 Hz), 7.24–7.30 (m, 2H), 7.32–7.37 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 19.0, 22.2, 22.6, 29.4 (d, *J* = 7.6 Hz), 36.3 (d, *J* = 4.7 Hz), 45.2, 79.4 (d, *J* = 6.3 Hz), 91.2 (d, *J* = 7.7 Hz), 127.7, 127.8, 128.8, 139.7 (d, *J* = 7.7 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ 4.41;

IR (film) cm^{-1} 3223w, 2967w, 1454m, 1401w, 1371w, 1257s;

mass spectrum (APCI): m/e (% relative intensity) 298 (100) $(M+H)^+$.

11-*slow band*: R_f = 0.12 [1:4:1 hexanes:EtOAc:CH_2Cl_2]; white solid; mp = 93–97 °C;

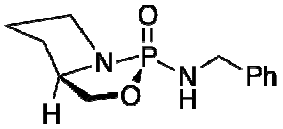
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 3H), 0.94 (d, 3H, *J* = 6.4 Hz), 1.06 (d, 3H, *J* = 6.4 Hz), 1.14 (s, 3H), 1.96 (s, 1H), 3.16–3.23 (m, 1H), 3.65 (dd, *J* = 11.2, 24.0 Hz), 4.18 (d, 2H, *J* = 5.2 Hz), 4.23 (dd, 2H, *J* = 11.2, 23.2 Hz), 7.22–7.40 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 18.9, 21.7, 22.8, 29.3 (d, *J* = 8.4 Hz), 35.6 (d, *J* = 2.8 Hz), 45.7, 78.0 (d, *J* = 5.1 Hz), 88.7 (d, *J* = 5.7 Hz), 127.4, 127.6, 128.7, 139.5;

^{31}P NMR (162 MHz, $CDCl_3$) δ 7.66;

IR (film) cm^{-1} 3217w, 2967m, 2937w, 2880w, 1495m, 1469m, 1371w, 1228s;

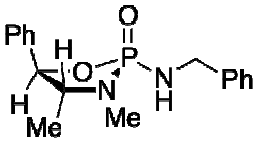
mass spectrum (APCI): m/e (% relative intensity) 298 (100) $(M+H)^+$.



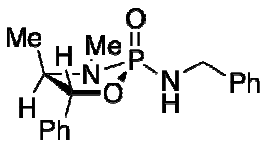
18

The phosphordiamidate **18** (889.0 mg, 3.52 mmol) was prepared as a single diastereomer from *L*-proline (0.38 mL, 4.0 mmol), $POCl_3$ (0.37 mL, 4.0 mmol), and benzyl amine (0.48 mL, 4.4 mmol) following the general procedure in 89% yield. After column chromatography (isocratic eluent: 1:3 EtOAc/CH_2Cl_2 + 5% MeOH), recrystallization from Et_2O afforded a white solid.

18: R_f = 0.14 [1:3 EtOAc:CH_2Cl_2 + 5% MeOH]; white solid; mp = 45–47 °C; $[\alpha]_D^{20}$ = +36.8 (*c* 1.0, CH_2Cl_2);
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62–1.66 (m, 1H), 1.89–1.99 (m, 3H), 2.80–2.88 (m, 1H), 2.95 (s, 1H), 3.57–3.63 (m, 1H), 3.80 (td, 1H, *J* = 2.0, 9.0 Hz), 3.90–3.99 (m, 1H), 4.10 (dd, 2H, *J* = 7.0, 11.0 Hz), 4.24 (ddd, 1H, *J* = 7.0, 9.0, 22.0 Hz), 7.24–7.27 (m, 1H), 7.31–7.34 (m, 3H);
^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8 (d, *J* = 2.7 Hz), 30.5 (d, *J* = 3.2 Hz), 45.4, 45.5 (d, *J* = 2.4 Hz), 62.7 (d, *J* = 10.8 Hz), 69.9 (d, *J* = 4.7 Hz), 127.3, 127.4, 128.7, 140.1 (d, *J* = 5.9 Hz);
^{31}P NMR (162 MHz, $CDCl_3$) δ 31.36;
IR (film) cm^{-1} 3226m, 2877m, 1453s, 1202s;
mass spectrum (APCI): m/e (% relative intensity) 253 (100) $(M+H)^+$.



20a (*major*)



20b (*minor*)

The phosphordiamidate **20** (712 mg, 2.25 mmol) was prepared as a 3:1 mixture of diastereomers from 1*R*,2*R*-(–)-pseudoephedrine (413.0 mg, 2.5 mmol), $POCl_3$ (0.23 mL, 2.5 mmol), and benzyl amine (0.30 mL, 2.75 mmol) following the general procedure in 90% yield. The minor diastereomer **20b** could be crystallized from the mixture with Et_2O as 16:1 **20b**:**20a** leaving the mother liquor with 5:1 **20a**:**20b**.

20a (*major*, 5:1 *dr*): R_f = 0.17 [1:3 EtOAc:CH_2Cl_2 + 5% MeOH]; colorless foam; $[\alpha]_D^{20}$ = –26.3 (*c* 1.0, CH_2Cl_2);
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, 3H, *J* = 6.0 Hz), 2.59 (d, 3H, *J* = 11.0 Hz), 3.23–3.27 (m, 1H), 3.31 (dq, 1H, *J* = 6.0, 9.0 Hz), 4.15 (dd, 2H, *J* = 7.0, 11.5 Hz), 4.61 (dd, 1H, *J* = 2.5, 9.0 Hz), 7.25–7.29 (m, 2H), 7.30–7.41 (m, 6H), 7.42 (dd, 2H, *J* = 1.5, 8.0 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 (d, *J* = 9.8 Hz), 28.8, 45.7, 61.8 (d, *J* = 11.7 Hz), 85.7, 127.1, 127.5, 127.6, 128.8, 128.9, 129.1, 137.9, 139.9;

^{31}P NMR (162 MHz, $CDCl_3$) δ 27.34;

IR (film) cm^{-1} 3219brm, 3029m, 2971m, 2900m, 1453m, 1284s, 1228s;

mass spectrum (APCI): m/e (% relative intensity) 317 (100) $(M+H)^+$.

20b (*minor*, 16:1 *dr*): R_f = 0.31 [1:3 EtOAc:CH_2Cl_2 + 5% MeOH]; white solid; mp = 140–142 °C;

$[\alpha]_D^{20}$ = –48.6 (*c* 1.0, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, 3H, *J* = 6.0 Hz), 2.62 (d, 3H, *J* = 9.6 Hz), 3.10–3.16 (m, 1H), 3.34–3.41 (m, 1H), 4.07–4.25 (m, 2H), 4.95 (d, 1H, *J* = 8.8 Hz), 7.27–7.31 (m, 3H), 7.33–7.40 (m, 7H);

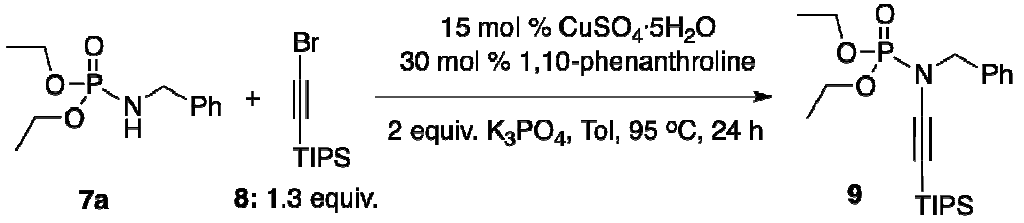
^{13}C NMR (125 MHz, $CDCl_3$) δ 16.7 (d, *J* = 6.1 Hz), 28.3 (d, *J* = 5.7 Hz), 45.4, 62.8 (d, *J* = 12.3 Hz), 83.9 (d, *J* = 1.6 Hz), 126.8, 127.1, 127.4, 127.5, 127.7, 128.9, 128.9, 129.1, 137.6 (d, *J* = 8.7 Hz), 139.8 (d, *J* = 5.9 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ 26.58;

IR (film) cm^{-1} 3194brm, 3065m, 30312, 2973m, 2901m, 1454m, 1229s;

mass spectrum (APCI): m/e (% relative intensity) 317 (100) $(M+H)^+$.

General Procedure for the Synthesis of *N*-Phosphoryl Ynamides 9 and 12–17 from Phosphoramidates.



To a flame-dried screw-cap vial filled with nitrogen were added phosphoramidate **7a** (100.0 mg, 0.412 mmol), $CuSO_4$•$5H_2O$ (13.9 mg, 0.062 mmol), 1,10-phenanthroline (22.2 mg, 0.124 mmol), and K_3PO_4 (175.0 mg, 0.824 mmol). The vial was evacuated under vacuum and backfilled with nitrogen two times, then toluene (1 mL, 0.4 M in phosphoramidate) and alkynyl bromide **8** (140.0 mg, 0.536 mmol) were added. The vial was again evacuated under vacuum and backfilled with nitrogen three times before sealing and heating to 95 °C overnight with vigorous stirring. When the reaction was judged to be complete by TLC, the reaction mixture was filtered through Celite™ and the solvent was removed *in vacuo*. Purification of the crude residue by flash silica gel column chromatography (isocratic eluent: 4:1 hexanes/EtOAc + 5% NEt_3 buffer) afforded the pure ynamide **9** (118.0 mg, 0.280 mmol, 68% yield) as a colorless oil.

9: R_f = 0.41 [2:1 hexanes:EtOAc]; colorless oil;

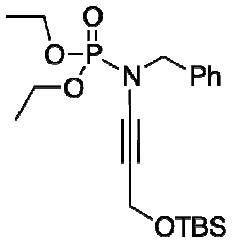
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 18H), 0.98 (s, 3H), 1.27 (t, 6H, *J* = 7.2 Hz), 3.97–4.14 (m, 4H), 4.43 (d, 2H, *J* = 8.8 Hz), 7.27–7.33 (m, 3H), 7.43 (dd, 2H, *J* = 1.2, 7.2 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 16.1 (d, *J* = 7.1 Hz), 18.7, 55.4 (d, *J* = 5.1 Hz), 63.5 (d, *J* = 4.0 Hz), 63.8 (d, *J* = 6.0 Hz), 100.1 (d, *J* = 4.0 Hz), 128.2, 128.5, 129.2, 136.9 (d, *J* = 1.6 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ –4.00;

IR (film) cm^{-1} 2942m, 2864m, 2163m, 1462w, 1268m;

mass spectrum (APCI): m/e (% relative intensity) 424 (100) $(M+H)^+$.



12a

Ynamide **12a** (102.5 mg, 0.249 mmol) was prepared from phosphoramidate **7a** (100.0 mg, 0.412 mmol) following the general procedure in 61% yield.

12a: R_f = 0.30 [2:1 hexanes:EtOAc]; colorless oil;

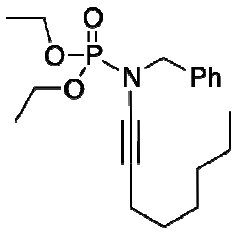
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.83 (s, 9H), 1.26 (td, 6H, *J* = 0.8, 7.2 Hz), 3.93–4.03 (m, 4H), 4.31 (d, 2H, *J* = 3.6 Hz), 4.38 (d, 2H, *J* = 8.8 Hz), 7.25–7.31 (m, 3H), 7.37–7.39 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ –4.9, 16.2 (d, *J* = 7.3 Hz), 18.4, 26.0, 52.1 (d, *J* = 1.3 Hz), 55.1 (d, *J* = 5.5 Hz), 63.8 (d, *J* = 5.8 Hz), 64.8 (d, *J* = 5.1 Hz), 81.4 (d, *J* = 4.9 Hz), 128.1, 128.6, 128.9, 137.1 (d, *J* = 1.6 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ 4.98;

IR (film) cm^{-1} 2929m, 2857m, 2244m, 1471w, 1264s;

mass spectrum (APCI): m/e (% relative intensity) 312 (100) $(M–OTBS+MeOH+H)^+$.

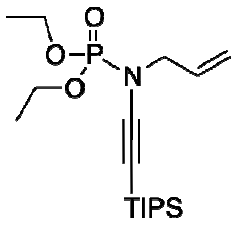


12b

Ynamide **12b** (100.0 mg, 0.285 mmol) was prepared from phosphoramidate **7a** (100.0 mg, 0.412 mmol) following the general procedure in 69% yield.

12b: R_f = 0.38 [2:1 hexanes:EtOAc]; colorless oil;

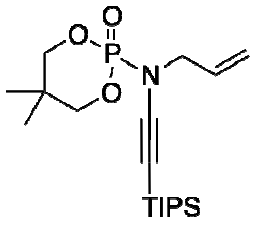
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J* = 6.8 Hz), 1.17–1.32 (m, 8H), 1.30 (t, 6H, *J* = 7.2 Hz), 2.16 (td, 2H, *J* = 2.8, 6.8 Hz), 3.96–4.15 (m, 4H), 4.39 (d, 2H, *J* = 9.2 Hz), 7.27–7.37 (m, 3H), 7.40–7.44 (m, 2H);
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 16.2 (d, *J* = 7.3 Hz), 18.4, 22.6, 28.4, 29.2, 31.4, 55.1 (d, *J* = 5.9 Hz), 63.6 (d, *J* = 5.5 Hz), 65.0 (d, *J* = 4.7 Hz), 76.0 (d, *J* = 4.8 Hz), 127.8, 128.3, 128.7, 137.3 (d, *J* = 1.5 Hz);
^{31}P NMR (162 MHz, $CDCl_3$) δ 5.68;
IR (film) cm^{-1} 2929m, 2858m, 2253m, 1455w, 1263s;
mass spectrum (APCI): m/e (% relative intensity) 384 (95) $(M+MeOH+H)^+$.



13

Ynamide **13** (113.0 mg, 0.303 mmol) was prepared from phosphoramidate **7b** (150.0 mg, 0.777 mmol) following the general procedure in 39% yield.

13: R_f = 0.36 [2:1 hexanes:EtOAc]; colorless oil;
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 18H), 1.04 (s, 3H), 1.35 (ddd, 6H, *J* = 0.8, 6.8, 7.6 Hz), 3.89 (ddd, 2H, *J* = 1.2, 7.2, 8.0 Hz), 4.09–4.21 (m, 4H), 5.24 (d, 1H, *J* = 10.2 Hz), 5.31 (d, 1H, *J* = 17.2 Hz), 5.86–5.96 (m, 2H);
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 16.2 (d, *J* = 7.4 Hz), 18.8, 54.0 (d, *J* = 5.3 Hz), 62.7 (d, *J* = 4.0 Hz), 63.9 (d, *J* = 6.0 Hz), 66.1 (d, *J* = 3.9 Hz), 119.2, 132.8;
^{31}P NMR (162 MHz, $CDCl_3$) δ 4.16;
IR (film) cm^{-1} 2942m, 2865m, 2164s, 1463w, 1270s;
mass spectrum (APCI): m/e (% relative intensity) 374 (100) $(M+H)^+$.



14

Ynamide **14** (86.1 mg, 0.224 mmol) was prepared from phosphoramidate **10a** (80.6 mg, 0.391 mmol), CuTC (14.9 mg, 0.078 mmol), DMEDA (16.8 μL, 0.156 mmol), K_3PO_4 (166.0 mg, 0.782 mmol), dioxane (1.0 mL, 0.4

M), and alkynyl bromide **8** (132.7 mg, 0.508 mmol) in 57% yield (95% *brsm*). *Alternatively, **10a** (113.5 mg, 0.294 mmol) could be prepared in 75% yield following the general procedure for ynamide **19a**.*

14: R_f = 0.17 [2:1 hexanes:EtOAc]; colorless oil;

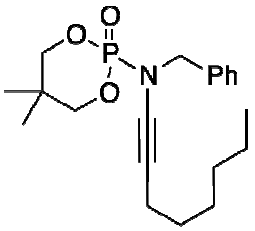
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 18H), 1.06 (s, 3H), 1.08 (s, 3H), 1.14 (s, 3H), 3.93 (dd, 2H, *J* = 6.8, 8.8 Hz), 4.11–4.25 (m, 4H), 5.27 (d, 1H, *J* = 10.0 Hz), 5.35 (d, 1H, *J* = 16.8 Hz), 5.96 (ddt, 1H, *J* = 6.8, 10.0, 16.8 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 18.7, 21.2, 21.4, 32.3 (d, *J* = 6.8 Hz), 53.8 (d, *J* = 6.1 Hz), 60.4, 63.4 (d, *J* = 4.6 Hz), 78.3 (d, *J* = 6.9 Hz), 99.5 (d, *J* = 3.8 Hz), 119.1, 132.3 (d, *J* = 1.6 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ –2.20;

IR (film) cm^{-1} 2942m, 2865m, 2163m, 1740w, 1464m, 1373w, 1313m, 1277s;

mass spectrum (APCI): m/e (% relative intensity) 386 (100) $(M+H)^+$.



15a

Ynamide **15a** (119.0 mg, 0.328 mmol) was prepared from phosphoramidate **10b** (100.0 mg, 0.391 mmol) following the general procedure in 84% yield.

15a: R_f = 0.18 [2:1 hexanes:EtOAc]; white solid; mp = 44–46 ^oC;

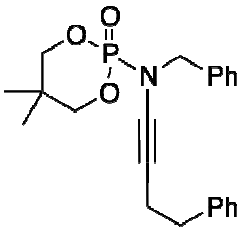
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J* = 7.2 Hz), 1.04 (s, 3H), 1.14 (s, 3H), 1.18–1.29 (m, 6H), 1.38 (quint, 2H, *J* = 7.2 Hz), 2.14 (td, 2H, *J* = 3.2, 7.2 Hz), 4.06 (dd, 2H, *J* = 11.2, 14.4 Hz), 4.21 (dd, 2H, *J* = 9.2, 11.2 Hz), 4.44 (d, 2H, *J* = 9.2 Hz), 7.28 (t, 1H, *J* = 7.2 Hz), 7.33 (t, 2H, *J* = 7.2 Hz), 7.39 (d, 2H, *J* = 7.2 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 18.4 (d, *J* = 1.4 Hz), 21.3, 21.4, 22.7, 28.6, 29.2, 31.5, 32.3 (d, *J* = 6.3 Hz), 54.7 (d, *J* = 6.4 Hz), 65.9 (d, *J* = 5.4 Hz), 75.4 (d, *J* = 4.6 Hz), 78.0 (d, *J* = 6.5 Hz), 127.9, 128.5, 128.6, 136.9;

^{31}P NMR (162 MHz, $CDCl_3$) δ 0.80;

IR (film) cm^{-1} 2958m, 2929m, 2858w, 2256w, 1467m, 1271s;

mass spectrum (APCI): m/e (% relative intensity) 396 (100) $(M+MeOH+H)^+$.



15b

Ynamide **15b** (137.0 mg, 0.358 mmol) was prepared from phosphoramidate **10b** (100.0 mg, 0.391 mmol) following the general procedure in 92% yield.

15b: R_f = 0.15 [2:1 hexanes:EtOAc]; white solid; mp = 62–63 ^{o}C;

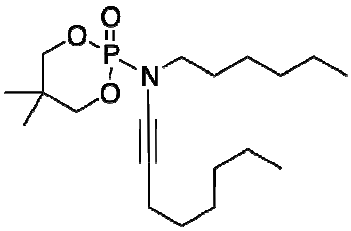
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 6H), 2.46 (td, 2H, *J* = 3.2, 7.2 Hz), 2.70 (t, 2H, *J* = 7.2 Hz), 3.95 (dd, 2H, *J* = 11.2, 14.0 Hz), 4.13 (dd, 2H, *J* = 9.6, 11.2 Hz), 4.41 (d, 2H, *J* = 9.6 Hz), 7.09–7.12 (m, 2H), 7.16–7.20 (m, 1H), 7.22–7.27 (m, 2H), 7.27–7.35 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8 (d, *J* = 1.3 Hz), 21.4 (d, *J* = 3.8 Hz), 32.3 (d, *J* = 6.2 Hz), 35.6 (d, *J* = 1.3 Hz), 54.8 (d, *J* = 6.5 Hz), 64.6, 65.2 (d, *J* = 4.9 Hz), 76.5 (d, *J* = 4.7 Hz), 78.1 (d, *J* = 6.4 Hz), 126.4, 128.0, 128.5, 128.6, 128.7, 128.7, 136.9 (d, *J* = 1.8 Hz), 141.0;

^{31}P NMR (162 MHz, $CDCl_3$) δ 0.37;

IR (film) cm^{-1} 2970m, 2256m, 1453m, 1290s;

mass spectrum (APCI): m/e (% relative intensity) 384 (100) $(M+H)^+$.



16

Ynamide **16** (81.4 mg, 0.228 mmol) was prepared from phosphoramidate **10c** (100.0 mg, 0.400 mmol) following the general procedure in 57% yield.

16: R_f = 0.21 [2:1 hexanes:EtOAc]; colorless oil;

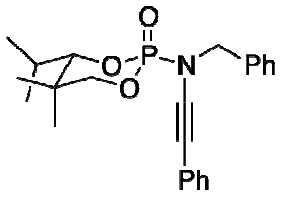
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 6.8 Hz), 0.89 (t, 3H, *J* = 6.9 Hz), 1.03 (s, 3H), 1.17 (s, 3H), 1.25–1.42 (m, 12H), 1.49 (pent, 2H, *J* = 7.2 Hz), 1.68 (pent, 2H, *J* = 7.2 Hz), 2.24 (td, 2H, *J* = 3.2, 6.8 Hz), 3.27 (td, 2H, *J* = 7.2, 8.0 Hz), 4.05 (dd, 2H, *J* = 10.8, 14.8 Hz), 4.21 (dd, 2H, *J* = 9.2, 10.8 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2 (d, *J* = 4.7 Hz), 18.6 (d, *J* = 1.6 Hz), 21.3, 21.5, 22.7, 22.8, 26.0, 28.7 (d, *J* = 1.6 Hz), 28.7, 29.4 (d, *J* = 1.3 Hz), 31.5, 31.6, 32.3, 32.3, 50.9 (d, *J* = 5.7 Hz), 65.0 (d, *J* = 5.6 Hz), 75.5 (d, *J* = 4.5 Hz), 77.8 (d, *J* = 6.3 Hz);

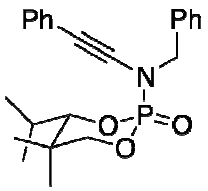
^{31}P NMR (162 MHz, $CDCl_3$) δ 1.28;

IR (film) cm^{-1} 2959m, 2928s, 2858m, 2255m, 1467m, 1275s;

mass spectrum (APCI): m/e (% relative intensity) 390 (100) $(M+MeOH+H)^+$.



17-eq



17-ax

A 1:1 separable mixture of ynamides **17** (318.0 mg, 0.801 mmol) was prepared from a 1:1 mixture of phosphoramidates **11** (250.0 mg, 0.841 mmol) following the general procedure in 95% yield.

17-eq: R_f = 0.11 [2:1 hexanes:EtOAc]; pale yellow solid; mp = 53–55 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.01 (d, 3H, *J* = 6.8 Hz), 1.05 (d, 3H, *J* = 6.4 Hz), 1.26 (s, 3H), 1.96–2.03 (m, 1H), 3.89 (dd, 1H, *J* = 11.2, 22.8 Hz), 4.26 (dd, 1H, *J* = 2.4, 10.8 Hz), 4.40 (dd, 1H, *J* = 2.4, 4.0 Hz), 4.53 (d, 2H, *J* = 8.0 Hz), 7.19–7.26 (m, 5H), 7.30–7.40 (m, 3H), 7.46–7.49 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 18.8, 21.8, 22.5, 29.6 (d, *J* = 7.1 Hz), 36.1 (d, *J* = 5.4 Hz), 55.1 (d, *J* = 5.0 Hz), 66.7 (d, *J* = 5.5 Hz), 80.9 (d, *J* = 7.2 Hz), 86.4 (d, *J* = 5.1 Hz), 93.8 (d, *J* = 8.8 Hz), 123.7 (d, *J* = 1.6 Hz), 127.3, 128.2, 128.4, 128.6, 129.1, 130.9 (d, *J* = 1.7 Hz), 136.4 (d, *J* = 2.1 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ –3.87;

IR (film) cm^{-1} 2970w, 2234m, 1471w, 1373w, 1289s;

mass spectrum (ESI): m/e (% relative intensity) 430 (100) $(M+MeOH+H)^+$.

17-ax: R_f = 0.16 [2:1 hexanes:EtOAc]; white solid; mp = 126–130 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.03 (d, 3H, *J* = 6.8 Hz), 1.08 (d, 3H, *J* = 7.2 Hz), 1.29 (s, 3H), 1.98–2.07 (m, 1H), 3.84 (dd, 1H, *J* = 11.2, 24.4 Hz), 4.24 (dd, 1H, *J* = 1.2, 3.6 Hz), 4.29 (dd, 1H, *J* = 2.0, 10.8 Hz), 4.62 (dd, 1H, *J* = 9.6, 14.4 Hz), 4.70 (dd, 1H, *J* = 9.6, 14.4 Hz), 7.21 (s, 5H), 7.29–7.38 (m, 3H), 7.47 (d, 2H, *J* = 7.2 Hz);

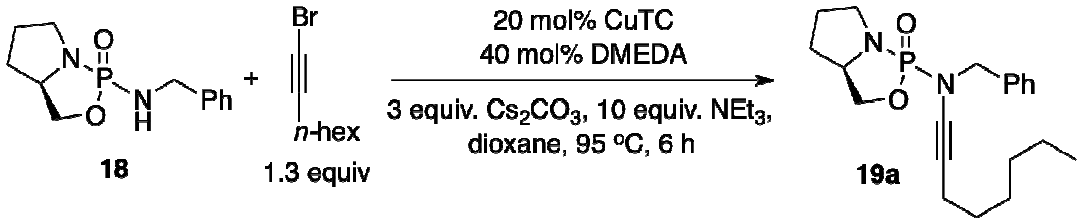
^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 18.7, 21.9, 22.8, 29.6 (d, *J* = 8.4 Hz), 36.1 (d, *J* = 3.8 Hz), 55.1 (d, *J* = 6.9 Hz), 66.9 (d, *J* = 5.4 Hz), 78.9 (d, *J* = 5.3 Hz), 85.3 (d, *J* = 3.8 Hz), 90.5 (d, *J* = 6.9 Hz), 123.9 (d, *J* = 2.3 Hz), 127.2, 128.1, 128.3, 128.7, 128.7, 131.0 (d, *J* = 1.6 Hz), 136.8;

^{31}P NMR (162 MHz, $CDCl_3$) δ –1.11;

IR (film) cm^{-1} 2969w, 2242m, 1455w, 1370m, 1352m, 1267s;

mass spectrum (ESI): m/e (% relative intensity) 430 (100) $(M+MeOH+H)^+$.

General Procedure for the Synthesis of Ynamides 19 and 23–25.



To a flame-dried 5-mL RB-flask was added phosphordiamidate **18** (139.0 mg, 0.557 mmol), CuTC (21.0 mg, 0.111 mmol), DMEDA (24 μL, 0.223 mmol), and Cs_2CO_3 (545 mg, 1.67 mmol). The flask was evacuated under vacuum and backfilled two times with nitrogen, followed by addition of dioxane (1.4 mL, 0.4 M) and the 1-ocynyl bromide (137.0 mg, 0.724 mmol). The flask was again evacuated under vacuum and backfilled with nitrogen three times, followed by addition of NEt_3 (0.77 mL, 5.57 mmol). The flask was sealed under nitrogen and heated to 95 °C for 6 hours. Once the reaction appeared complete by TLC, the reaction mixture was filtered through Celite™ and the solvent was removed *in vacuo*. Purification of the crude residue via flash silica gel column chromatography (2:1:1 hexanes/EtOAc/CH_2Cl_2 + 5% NEt_3 buffer) afforded ynamide **19a** (75.0 mg, 0.209 mmol, 38%).

19a: R_f = 0.15 [2:1:1 hexanes:EtOAc:CH_2Cl_2]; colorless oil; $[\alpha]_D^{20}$ = +61.4 (*c* 0.50, CH_2Cl_2);

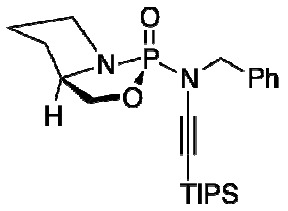
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J* = 7.0 Hz), 1.20–1.33 (m, 6H), 1.40 (pent, 2H, *J* = 7.2 Hz), 1.63–1.69 (m, 1H), 1.91–2.02 (m, 3H), 2.16 (td, 2H, *J* = 3.2, 6.8 Hz), 2.87–2.96 (m, 1H), 3.57–3.65 (m, 1H), 3.83 (td, 1H, *J* = 3.6, 8.4 Hz), 3.98–4.08 (m, 1H), 4.32 (ddd, 1H, *J* = 6.8, 8.8, 19.2 Hz), 4.38–4.49 (m, 2H), 7.27 (t, 1H, *J* = 7.2 Hz), 7.33 (t, 2H, *J* = 7.2 Hz), 7.39 (d, 2H, *J* = 7.2 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 18.7 (d, *J* = 1.5 Hz), 22.8, 27.5 (d, *J* = 3.0 Hz), 28.6, 29.5, 30.6 (d, *J* = 3.8 Hz), 31.6, 45.9 (d, *J* = 2.7 Hz), 54.8 (d, *J* = 6.6 Hz), 62.9 (d, *J* = 11.5 Hz), 65.0 (d, *J* = 4.7 Hz), 71.1 (d, *J* = 4.0 Hz), 76.6 (d, *J* = 3.9 Hz), 127.7, 128.4, 128.5, 137.9 (d, *J* = 1.4 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ 29.59;

IR (film) cm^{-1} 2927s, 2251m, 1266s;

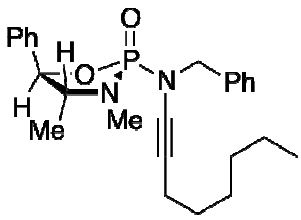
mass spectrum (ESI): m/e (% relative intensity) 393 (100) $(M+MeOH+H)^+$.



19b

Ynamide **19b** (66.0 mg, 0.154 mmol) was prepared in 28% yield from phosphoramidate **18** (139.0 mg, 0.557 mmol) in 8 h following the general procedure.

19b: R_f = 0.26 [2:1:1 hexanes:EtOAc:CH_2Cl_2]; colorless oil; $[\alpha]_D^{20}$ = +39.8 (*c* 1.0, CH_2Cl_2);
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 18H), 1.02–1.07 (m, 3H), 1.90–1.98 (m, 3H), 2.85–2.94 (m, 1H), 3.55–3.63 (m, 1H), 3.84 (td, 1H, *J* = 3.8, 8.4 Hz), 3.96–4.06 (m, 1H), 4.31 (ddd, 1H, *J* = 7.2, 8.4, 18.8 Hz), 4.47 (d, 2H, *J* = 9.6 Hz), 7.25 (t, 1H, *J* = 7.2 Hz), 7.30 (t, 2H, *J* = 7.2 Hz), 7.39 (d, 2H, *J* = 7.2 Hz);
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 18.2, 18.8, 27.6, 30.8 (d, *J* = 3.8 Hz), 45.6 (d, *J* = 3.0 Hz), 55.1 (d, *J* = 6.0 Hz), 62.9 (d, *J* = 12.2 Hz), 71.1 (d, *J* = 3.8 Hz), 127.8, 128.5, 128.7, 137.3 (d, *J* = 1.3 Hz);
^{31}P NMR (162 MHz, $CDCl_3$) δ 28.32;
IR (film) cm^{-1} 2941m, 2864m, 2161m, 1630m, 1462m, 1272m;
mass spectrum (ESI): m/e (% relative intensity) 433 (100) $(M+H)^+$.



23

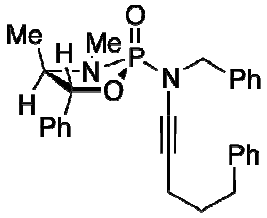
Ynamide **23** (139.0 mg, 0.328 mmol) was prepared in 59% yield from phosphoramidate **20a** (176.0 mg, 0.557 mmol) in 6 h following the general procedure.

23: R_f = 0.26 [3:1:1 hexanes:EtOAc:CH_2Cl_2]; colorless oil; $[\alpha]_D^{20}$ = –31.8 (*c* 1.0, CH_2Cl_2);
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 6.8 Hz), 1.20 (d, 3H, *J* = 6.2 Hz), 1.23–1.34 (m, 7H), 1.44 (pent, 2H, *J* = 6.8 Hz), 2.21 (td, 2H, *J* = 3.2, 6.8 Hz), 2.58 (d, 3H, *J* = 10.0 Hz), 3.43 (qd, 1H, *J* = 6.2, 7.2 Hz), 4.50 (d, 2H, *J* = 9.2 Hz), 4.93 (dd, 1H, *J* = 1.8, 8.4 Hz), 7.25–7.40 (m, 10H);
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 16.1 (d, *J* = 7.7 Hz), 18.7, 22.8, 28.1 (d, *J* = 5.3 Hz), 28.7, 29.6, 31.6, 55.2 (d, *J* = 5.7 Hz), 61.9 (d, *J* = 13.3 Hz), 65.0 (d, *J* = 4.7 Hz), 77.1 (d, *J* = 4.6 Hz), 87.0, 126.9, 127.8, 128.5, 128.6, 128.8, 129.1, 137.7 (d, *J* = 7.1 Hz), 138.0 (d, *J* = 1.5 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ 24.84;

IR (film) cm^{-1} 2928m, 2857m, 2250m, 1455m, 1260s;

mass spectrum (ESI): m/e (% relative intensity) 457 (100) $(M+MeOH+H)^+$.



24

Ynamide **24** (16.0 mg, 0.035 mmol) was prepared in 41% yield from phosphoramidate **20b** (26.0 mg, 0.085 mmol) in 24 h following the general procedure.

24: R_f = 0.24 [2:1:1 hexanes:EtOAc:CH_2Cl_2]; colorless oil; $[\alpha]_D^{20}$ = +37.5 (*c* 0.61, CH_2Cl_2);

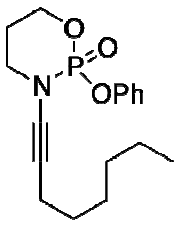
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, 3H, *J* = 6.0 Hz), 1.65–1.75 (m, 4H), 2.18 (td, 2H, *J* = 3.6, 6.8 Hz), 2.57 (d, 3H, *J* = 10.8 Hz), 3.45 (dq, 1H, *J* = 6.0, 9.2 Hz), 4.51 (dd, 1H, *J* = 8.0, 14.4 Hz), 4.58 (dd, 1H, *J* = 9.5, 14.4 Hz), 4.93 (d, 1H, *J* = 9.2 Hz), 7.05 (d, 2H, *J* = 6.8 Hz), 7.18 (t, 1H, *J* = 7.2 Hz), 7.23–7.37 (m, 9H), 7.47–7.53 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 18.1, 28.1, 31.0, 34.9, 42.5, 55.6 (d, *J* = 4.4 Hz), 64.3 (d, *J* = 10.7 Hz), 65.1, 85.1, 126.1, 127.1, 128.0, 128.5, 128.6, 128.7, 128.8, 128.9, 129.2, 137.3, 137.9, 141.7;

^{31}P NMR (162 MHz, $CDCl_3$) δ 22.70;

IR (film) cm^{-1} 2926m, 2249m, 1495m, 1454m, 1262s;

mass spectrum (ESI): m/e (% relative intensity) 459 (5) $(M+H)^+$, 491 (100) $(M+MeOH+H)^+$.

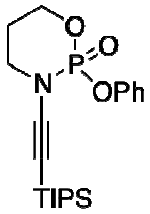


25a

Ynamide **25a** (79.0 mg, 0.246 mmol) was prepared in 62% yield from phosphoramidate **22** (85.0 mg, 0.397 mmol), CuTC (14.9 mg, 0.079 mmol), DMEDA (16.8 μL, 0.159 mmol), 3:1 toluene:EtOAc (1 mL, 0.4 M), and 1-octynyl bromide (96.3 mg, 0.516 mmol) in 24 h following the general procedure.

25a: R_f = 0.19 [2:1 hexanes:EtOAc]; colorless oil;

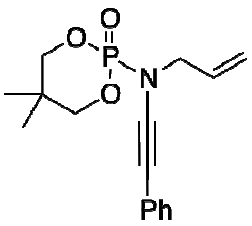
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 6.8 Hz), 1.24–1.38 (m, 7H), 1.46 (dt, 2H, *J* = 7.2, 14.8 Hz), 1.81 (d, 1H, *J* = 14.8 Hz), 2.20 (td, 2H, *J* = 3.6, 7.2 Hz), 2.24–2.32 (m, 1H), 3.42–3.59 (m, 1H), 3.66 (tt, 1H, *J* = 2.8, 11.6 Hz), 4.36–4.50 (m, 2H), 7.18 (t, 1H, *J* = 7.2 Hz), 7.29 (d, 2H, *J* = 7.2 Hz), 7.34 (t, 2H, *J* = 7.2 Hz);
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 18.6 (d, *J* = 1.9 Hz), 22.8, 25.6, 28.8, 29.3 (d, *J* = 1.1 Hz), 31.6, 50.7, 52.8, 64.5 (d, *J* = 5.5 Hz), 70.2 (d, *J* = 8.0 Hz), 120.3 (d, *J* = 5.3 Hz), 125.2, 129.9, 150.9;
^{31}P NMR (162 MHz, $CDCl_3$) δ –5.26;
IR (film) cm^{-1} 2929m, 2857m, 2257m, 1593m, 1489m, 1296s;
mass spectrum (ESI): m/e (% relative intensity) 354 (100) $(M+MeOH+H)^+$.



25b

Ynamide **25b** (74.6 mg, 0.190 mmol) was prepared in 81% yield from phosphoramidate **22** (50.0 mg, 0.234 mmol) following the general procedure in 20 h.

25b: R_f = 0.15 [3:1 hexanes:EtOAc]; colorless oil;
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 21H), 1.85 (dt, 1H, *J* = 3.2, 14.8 Hz), 2.23–2.34 (m, 1H), 3.61 (ddt, 1H, *J* = 4.0, 12.0, 16.8 Hz), 3.72 (tt, 1H, *J* = 2.8, 12.0 Hz), 4.41–4.53 (m, 2H), 7.17 (t, 1H, *J* = 7.8 Hz), 7.29 (d, 2H, *J* = 7.8 Hz), 7.34 (t, 2H, *J* = 7.8 Hz);
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 18.9, 25.5 (d, *J* = 3.9 Hz), 53.0, 62.6 (d, *J* = 4.6 Hz), 70.3 (d, *J* = 8.3 Hz), 99.8 (d, *J* = 14.5 Hz), 120.3 (d, *J* = 4.7 Hz), 125.3, 130.00, 150.7;
^{31}P NMR (162 MHz, $CDCl_3$) δ –6.85;
IR (film) cm^{-1} 2942m, 2865m, 2167s, 1593w, 1491m, 1300s;
mass spectrum (ESI): m/e (% relative intensity) 394 (20) $(M+H)^+$; 426 (100) $(M+MeOH+H)^+$.

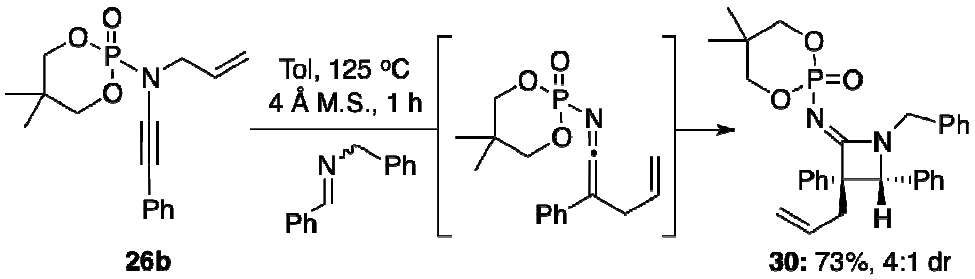


26b

Ynamide **26b** was prepared in 71% yield from phosphoramidate **10a** (220.0 mg, 1.07 mmol) using CuTC (44.0 mg, 0.214 mmol), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (68.0 µL, 0.428 mmol) as the ligand, Cs_2CO_3 (698.0 mg, 2.14 mmol), and dioxane (2.7 mL) for 48 h at 60 °C following the general procedure.

26b: R_f = 0.23 [1:1 hexanes:EtOAc]; pale yellow solid; mp = 108–109 °C;
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.19 (s, 3H), 4.02 (ddt, 2H, *J* = 1.6, 6.2, 9.2 Hz), 4.14–4.22 (m, 4H), 5.30 (d, 1H, *J* = 10.4 Hz), 5.39 (dd, 1H, *J* = 1.6, 17.2 Hz), 5.97 (ddt, 1H, *J* = 6.2, 10.4, 17.2 Hz), 7.23–7.30 (m, 3H), 7.31–7.34 (m, 2H);
^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 21.5, 32.5, 53.9 (d, *J* = 6.1 Hz), 66.3 (d, *J* = 5.7 Hz), 78.3 (d, *J* = 6.3 Hz), 85.3 (d, *J* = 4.1 Hz), 119.2, 123.7 (d, *J* = 2.1 Hz), 127.5, 128.5, 131.2 (d, *J* = 1.5 Hz), 132.8 (d, *J* = 1.4 Hz);
^{31}P NMR (162 MHz, $CDCl_3$) δ 1.01;
IR (film) cm^{-1} 3081w, 2970w, 2896w, 2244s, 1370m, 1326m, 1254s;
mass spectrum (ESI): m/e (% relative intensity) 306 (100) $(M+H)^+$;

Synthesis of *N*-Phosphoryl Azetidin-2-imine 30:



26b **30:** 73%, 4:1 dr

To a flame-dried screw-cap vial containing 4 Å M.S. (30 mg) were added ynamide **26b** (30.6 mg, 0.10 mmol), imine (37.5 µL, 0.20 mmol), and anhyd toluene (0.33 mL, 0.33 M in ynamide) under dry N_2. The vial was sealed and heated to 125 °C for 1 h at which time TLC analysis revealed that the ynamide had been completely consumed. The reaction mixture was filtered through Celite™ to remove the sieves and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography [isocratic eluent: 1:1 hexanes:EtOAC + 2% NEt_3] afforded a 4:1 diastereomeric mixture of the azetidine-2-imine **30** (36.3 mg, 0.073 mmol, 73% yield).

30: R_f = 0.42 [1:2 hexanes:EtOAc]; pale yellow solid;

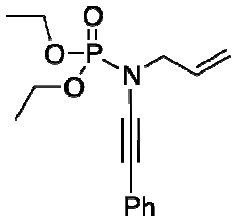
^{1}H NMR (500 MHz, $CDCl_3$) *major diastereomer* δ 0.97 (s, 3H), 1.23 (s, 3H), 2.75 (dd, 1H, *J* = 9.0, 14.0 Hz), 3.15 (dd, 1H, *J* = 5.5, 14.0 Hz), 3.90 (d, 2H, *J* = 14.5 Hz), 3.99 (dd, 2H, *J* = 11.0, 17.0 Hz), 4.17 (m, 2H), 4.70 (s, 1H), 5.01 (d, 1H, *J* = 10.0 Hz), 5.18 (d, 1H, *J* = 17.0 Hz), 5.33 (d, 1H, *J* = 14.5 Hz), 6.83 (d, 2H, *J* = 6.5 Hz), 6.98–7.08 (m, 6H), 7.18–7.33 (m, 6H), 7.46 (m, 1H); *selected resonances from minor diastereomer* δ 0.87 (s, 3H), 1.27 (s, 3H), 2.39 (dd, 1H, *J* = 7.5, 14.5 Hz), 2.70 (dd, 1H, *J* = 7.5, 22.0 Hz), 4.44 (d, 1H, *J* = 17.0 Hz), 4.64 (d, 1H, *J* = 10.0 Hz), 4.81 (s, 1H), 5.28–5.35 (m, 1H), 5.62 (d, 1H, *J* = 15.0 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) *major diastereomer* δ 21.4, 22.2, 32.7 (d, *J* = 5.5 Hz), 41.4, 46.7, 66.3 (d, *J* = 12.9 Hz), 66.6, 77.2 (d, *J* = 4.9 Hz), 119.8, 126.8, 127.2, 127.8, 127.9, 128.1, 128.2, 128.3, 128.8, 128.9, 129.5, 133.6, 134.7, 135.1, 137.1, 167.7;

^{31}P NMR (162 MHz, $CDCl_3$) *major diastereomer* δ –1.94; *minor diastereomer* δ –2.82;

IR (film) cm^{-1} 3062w, 3030w, 2961w, 2881w, 1670s, 1456m, 1269s;

mass spectrum (ESI): m/e (% relative intensity) 501 (100) $(M+H)^+$.



i

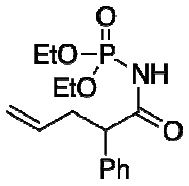
Ynamide **i** (26.8 mg, 0.091 mmol) was prepared from phosphoramidate **7b** (150.0 mg, 0.777 mmol) following the general procedure in 12% yield after 39% conversion of the starting material.

Footnote compound i: R_f = 0.24 [2:1 hexanes:EtOAc]; colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (td, 6H, *J* = 1.2, 7.2 Hz), 3.98 (ddd, 2H, *J* = 1.2, 6.4, 8.4 Hz), 4.16–4.25 (m, 4H), 5.29 (d, 1H, *J* = 10.2 Hz), 5.38 (d, 1H, *J* = 17.2 Hz), 5.98 (ddtd, 1H, *J* = 0.8, 6.4, 10.2, 16.8 Hz), 7.22–7.29 (m, 3H), 7.32–7.34 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3 (d, *J* = 7.1 Hz), 54.0 (d, *J* = 5.3 Hz), 64.1 (d, *J* = 5.8 Hz), 65.7 (d, *J* = 5.4 Hz), 85.8 (d, *J* = 5.3 Hz), 119.2, 124.1, 127.2, 128.4, 131.1 (d, *J* = 1.4 Hz), 133.0 (d, *J* = 1.5 Hz);

mass spectrum (APCI): m/e (% relative intensity) 294 (20) $(M+H)^+$, 326 (100) $(M+MeOH+H)^+$.



ii

Amide **ii** (27.0 mg, 0.092 mmol, 12%) was isolated as a byproduct from the synthesis of ynamide **i**.

Footnote compound ii: R_f = 0.11 [2:1 hexanes:EtOAc]; colorless oil;
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (td, 3H, *J* = 0.8, 7.2 Hz), 1.34 (td, 3H, *J* = 0.8, 7.2 Hz), 2.46 (dt, 1H, *J* = 6.8, 14.4 Hz), 2.85 (dddt, 1H, *J* = 1.2, 7.2, 8.4, 14.4 Hz), 3.67 (t, 1H, *J* = 7.6 Hz), 3.82 (ddq, 1H, *J* = 7.2, 8.0, 10.2 Hz), 3.95 (ddq, 1H, *J* = 7.2, 8.0, 10.2 Hz), 4.08–4.24 (m, 2H), 4.97 (dd, 1H, *J* = 1.8, 10.2 Hz), 5.06 (dq, 1H, *J* = 1.8, 17.2 Hz), 5.70 (ddt, 1H, *J* = 7.2, 10.2, 17.2 Hz), 7.22–7.31 (m, 3H), 7.34–7.37 (m, 2H), 8.68 (brs, 1H);
^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (d, *J* = 6.9 Hz), 16.3 (d, *J* = 7.0 Hz), 37.2, 53.3 (d, *J* = 10.0 Hz), 64.0 (d, *J* = 5.8 Hz), 64.4 (d, *J* = 5.9 Hz), 117.1, 127.7, 128.3, 128.9, 135.6, 138.9, 174.8 (d, *J* = 4.2 Hz);
mass spectrum (APCI): m/e (% relative intensity) 312 (100) $(M+H)^+$.

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1. Hammerschmidt, F.; Hanbauer, M. *J. Org. Chem.* **2000**, *65,* 6121.
2. Setzer, W. N.; Black, B. G.; Hovanes, B. A; Hubbard, J. L. *J. Org. Chem.* **1989**, *54*, 1709.