Generation of Tertiary α-Aminoorganolithium Reagents

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Supporting Information

Contents:

General experimental details: Air- and moisture sensitive reactions were carried out in flame- or oven-dried glassware using standard syringe/septum techniques. Glassware used for reductive lithiations was washed with concentrated potassium hydroxide/water solution, deionized water and then acetone prior to drying. Tetrahydrofuran was dried according to the method of Grubbs.[1] Electrophiles used in these experiments were freshly distilled (aldehydes and ketones) or passed through short columns of oven-dried basic alumina (alkyl halides). All other reagents were used as received or were purified accordingly.[2]

Instrumentation and chromatography: Thin layer chromatography was performed on Whatman silica gel PE SIL G/UV (0.25 mm) plates. Flash chromatography was performed using the indicated solvent system on Sorbent Technologies 230-400 mesh silica gel. Melting points were determined using an Electrothermal apparatus and are reported uncorrected. Infrared spectra were recorded on a MIDAC Prospect FT-IR. NMR spectra were recorded on Bruker DRX, Bruker GN500 and Bruker Omega500 MHz FT NMR instruments. ^{1}H NMR spectra are reported in ppm relative to tetramethylsilane or residual solvent ($CDCl_3$: δ 7.26 ppm, d_8-PhMe: δ 2.09 ppm). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad), coupling constant(s) in Hertz (Hz), and integration. Multiplets (m) are reported over the range (ppm) at which they appear. ^{13}C NMR spectra were reported in ppm relative to the solvent signal ($CDCl_3$: 77.2, d_8-PhMe: 137.9 ppm). Capillary GC analysis was performed on a Hewlett Packard Model 6890 instrument with a 30 m X 0.25 μM Alltech EC-5 (SE-54) or Restek RTX-1701 capillary column equipped with a flame ionization detector. Mass spectral data was obtained on a MicroMass Autospec E spectrometer, or a MicroMass LCT Electrospray spectrometer. Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ).

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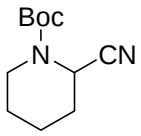
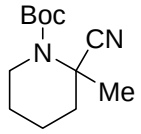
[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

[2] Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5th ed. Elsevier: Burlington, MA, 2003.



2-Cyano-piperidine-1-carboxylic acid tert-butyl ester (1). To a solution of 2-cyanopiperidine[3] (7.39 g, 67.1 mmol) in tetrahydrofuran (100 mL) was added di-*tert*-butyl dicarbonate (14.64 g, 67.1 mmol). After 48 h, volatiles were removed *in vacuo* to afford a yellow oil. Recrystallization (ethanol/water) afforded **1** as colorless crystals (12.20 g, 86%). Mp = 62–63 °C; IR (thin film) 2947, 1702 cm^{-1}; ^1H NMR (500 MHz, d8-PhMe, 350 K) δ 4.97 (br s, 1 H), 3.86 (d, *J* = 13.5 Hz, 1 H), 2.76 (ddd, *J* = 2.7, 12.9, 13.2 Hz, 1 H), 1.45–1.29 (m, 2 H), 1.34 (s, 9 H), 1.29–1.19 (m, 2 H), 1.16 (m, 1 H), 1.02 (dddd, *J* = 3.6, 3.6, 13.0, 13.0 Hz, 1 H); ^{13}C NMR (125 MHz, d8-PhMe, 350 K) δ 154.4, 117.7, 81.2, 45.0, 42.1, 28.9, 28.6, 25.13, 20.8; HRMS (CI/NH_3) calcd for $C_{11}H_{19}N_2O_2$ $[M + H]^+$ 211.1447, found 211.1441; Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 63.08; H, 8.65; N, 13.38.



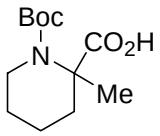
2-Cyano-2-methyl-piperidine-1-carboxylic acid tert-butyl ester (2). To a –78 °C solution of diisopropylamine (4.7 mL, 33 mmol) in tetrahydrofuran (75 mL) was added *n*-butyllithium in hexane (2.36 M, 13.1 mL, 30.9 mmol) over 5 min. After 30 min, 1,3-dimethylpropyleneurea (5.8 mL, 48 mmol) was added over 2 min followed by addition of a solution of **1** (5.00 g, 23.8 mmol) in tetrahydrofuran (20 mL) over 10 min. After 1 h, a pale yellow precipitate had formed. At this time, iodomethane (4.4 mL, 71 mmol) was added over 5 min, producing a clear, pale yellow solution. After 2 h, half-saturated ammonium chloride solution (200 mL) was added and the reaction was warmed to room temperature. The reaction was extracted with diethyl ether (3 x 75 mL) and the combined extracts were washed with saturated sodium chloride solution (50 mL), dried (magnesium sulfate) and concentrated *in vacuo* to afford a pale yellow oil. Recrystallization (ethanol/water) afforded **2** as colorless crystals (4.82 g, 90%). Mp = 58–60 °C; IR (thin film) 2947, 1704 cm^{-1}; ^1H NMR (500 MHz, d8-PhMe, 350 K) δ 3.39 (ddd, *J* = 4.5, 6.8, 13.5 Hz, 1 H), 3.06 (ddd, *J* = 4.6, 8.2, 13.2 Hz, 1 H), 1.59 (ddd, *J* = 2.8, 6.4, 9.7 Hz, 1 H), 1.46 (s, 3 H), 1.42 (s, 9 H), 1.39–1.22 (m, 3 H), 1.13 (m, 2 H); ^{13}C NMR (125 MHz, d8-PhMe, 350 K) δ 155.5, 121.5, 81.6, 53.0, 42.1, 38.1, 28.7, 25.7, 23.8, 19.3; HRMS (CI/NH_3) calcd for $C_{12}H_{21}N_2O_2$ $[M + H]^+$ 225.1603, found 225.1609; Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.25; H, 9.08; N, 12.68.

General procedure for preparation of LiDBB stock solutions. An oven-dried 15 mL round-bottom flask was equipped with a glass stir bar and septum and cooled with a purge of argon. The flask was charged with 4,4'-di-*tert*-butylbiphenyl (1.00 g, 3.75 mmol) and lithium wire (*ca.* 100 mg, 14.4 mmol, hammered into a thin sheet and cut into

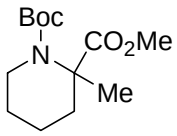
[3] (a) Bender, D. R.; Bjeldanes, L. F.; Knapp, D. R.; Rapoport, H. *J. Org. Chem.* **1975**, *40*, 1264-1269. (b) De Kimpe, N.; Stevens, C. *J. Org. Chem.* **1993,** *58*, 2904-2906.

strips) and tetrahydrofuran (7.5 mL) was added, forming a dark green solution within 2-3 min. The solution was cooled (0 °C) and stirred for 4h, producing a stock solution of lithium di-*tert*-butylbiphenylide (LiDBB) that was used assuming a concentration of 0.50 M.

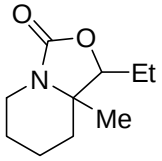
General procedure for reductive lithiation/electrophilic addition. An oven-dried 50 mL round-bottom flask was equipped with a glass stir bar and septum and cooled with a purge of argon. The flask was charged with **2** (*ca.* 100 mg, 0.446 mmol) and 1,10-phenanthroline (1 crystal) and tetrahydrofuran (5.0 mL) was then added. The solution was cooled to –78 °C and *n*-butyllithium/hexane (*ca.* 1-2 M) was added until a dark brown color persisted (typically 2–3 drops). This procedure serves to quench adventitious proton sources. LiDBB solution (0.50 M, 2.0 mL, 1.0 mmol) was added *via* gas-tight syringe in a steady stream over 30 sec to produce a dark green solution. Unless otherwise noted, the electrophile (3.0 equiv.) was added and the reaction was allowed to warm to room temperature over approximately 4 h. Saturated ammonium chloride solution (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with saturated sodium chloride solution (5 mL), dried (sodium sulfate) and concentrated *in vacuo* to afford the crude product. Purification details are provided along with characterization data. Where diastereomeric mixtures were obtained, characterization data is presented for the major diastereomer only.



2-Methyl-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester (4). Following the general reductive lithiation procedure, carbon dioxide gas (passed through Drierite) was blown over a solution of the organolithium reagent for 30 min prior to warming to room temperature and quenching with 10% acetic acid solution (20 mL). Purification by flash chromatography (0–10% methanol/dichloromethane) afforded **4** as a white solid (87%). Mp 92–94°C; IR (thin film) 3159, 2944, 1742, 1698 cm^{-1}; ^{1}H NMR (500 MHz, d8-PhMe, 350 K) δ 9.66 (br s, 1 H), 3.74 (ddd, *J* = 4.8, 4.8, 13.1 Hz, 1 H), 2.92 (ddd, *J* = 4.3, 9.5, 13.6 Hz, 1 H), 1.80 (ddd, *J* = 3.8, 11.0, 13.4 Hz, 1 H), 1.47 (s, 3 H), 1.44–1.28 (m, 4 H), 1.42 (s, 9 H), 1.18 (m, 1 H); ^{13}C NMR (125 MHz, d8-PhMe, 350 K) δ 180.9, 155.9, 80.8, 61.1, 41.6, 35.6, 28.8, 24.1, 20.5, 18.8; HRMS (ESI) calcd for $C_{12}H_{21}NO_4Na$ $[M + Na]^+$ 266.1368, found 266.1361; Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.55; H, 8.73; N, 5.68.



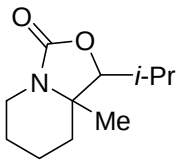
2-Methyl-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester[4] **(5).** Following the general reductive lithiation procedure, methyl chloroformate (3 equiv.) was added and the reaction was maintained at –78 °C for 15 h prior to quenching with saturated ammonium chloride solution and usual work-up. Purification by flash chromatography (20% dichloromethane/hexanes then 5–20% diethyl ether/hexanes) afforded **5** as colorless crystals (79%). Mp 43–45°C; IR (thin film) 2948, 1744, 1698 cm^{-1}; ^1H NMR (500 MHz, d8-PhMe, 350 K) δ 3.71 (ddd, *J* = 5.7, 5.7, 10.5 Hz, 1 H), 3.48 (s, 3 H), 2.95 (ddd, *J* = 4.3, 9.5, 13.6 Hz, 1 H), 1.74 (ddd, *J* = 3.9, 10.8, 13.4 Hz, 1 H), 1.47 (s, 3 H), 1.41–1.28 (m, 4 H), 1.36 (s, 9 H), 1.21 (m, 1 H); ^{13}C NMR (125 MHz, d8-PhMe, 350 K) δ 180.9, 155.9, 80.8, 61.1, 41.6, 35.6, 28.8, 24.1, 20.5, 18.8; HRMS (CI/NH_3) calcd for $C_{13}H_{24}NO_4$ $[M + H]^+$ 258.1705, found 258.1699.



1-Ethyl-8a-methyl-hexahydro-oxazolo[3,4-a]pyridin-3-one (6). Following the general reductive lithiation/electrophilic addition procedure, propionaldehyde (3.0 equiv.) was utilized as the electrophile. GC of the crude reaction mixture indicated a diastereomeric ratio of 4.5:1. Flash chromatography (20% dichloromethane/hexanes then 20% ethyl acetate/hexanes) afforded a mixture of the diastereomers as a pale yellow oil. An analytical sample of the major diastereomer was obtained as a colorless oil by additional flash chromatography. Major diastereomer: IR (thin film) 2941, 1746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.95 (dd, *J* = 3.6, 10.0 Hz, 1 H), 3.75 (dd, *J* = 5.0, 13.7 Hz, 1 H), 2.91 (ddd, *J* = 3.3, 13.4, 13.5 Hz, 1 H), 1.83–1.75 (m, 1 H), 1.73–1.62 (m, 2 H), 1.60–1.52 (m, 3 H), 1.48-1.38 (m, 1 H), 1.38–1.34 (m, 1 H), 1.33 (s, 3 H), 1.08 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 85.8, 60.0, 39.1, 28.9, 24.5, 21.5, 21.2, 20.0, 11.0; HRMS (ESI) calcd for $C_{10}H_{18}NO_2$ $[M + H]^+$ 184.1338, found 184.1333; Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.51, H, 9.53, N, 7.50.

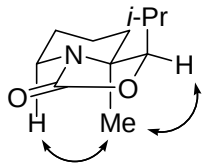
Relative stereochemistry of the major diastereomer is tentatively assigned as depicted in analogy to **7** and **8**.

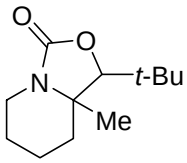
[4] Sato, T.; Yamazaki, T.; Nakanishi, Y.; Uenishi, J.-i.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, *12*, 1438-1443.



1-Isopropyl-8a-methyl-hexahydro-oxazolo[3,4-a]pyridin-3-one (7). Following the general reductive lithiation/electrophilic addition procedure, isobutyraldehyde (3.0 equiv.) was utilized as the electrophile. GC of the crude reaction mixture indicated a diastereomeric ratio of 3.7:1. Flash chromatography (20% dichloromethane/hexanes then 20% ethyl acetate/hexanes) afforded a mixture of the diastereomers as a pale yellow oil (74%). An analytical sample of the major diastereomer was obtained as a colorless oil by additional flash chromatography. Major diastereomer: IR (thin film) 2942, 1750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.75 (dd, *J* = 5.0, 13.8 Hz, 1 H), 3.65 (d, *J* = 10.0 Hz, 1 H), 2.92 (ddd, *J* = 3.4, 13.3, 13.4 Hz, 1 H), 2.01 (m, 1 H), 1.84–1.41 (m, 6 H), 1.39 (s, 3 H), 1.10 (d, *J* = 6.5 Hz, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 89.4, 60.4, 38.9, 28.6, 27.9, 24.5, 22.2, 20.5, 19.9, 19.2; HRMS (ESI) calcd for $C_{11}H_{19}NO_2Na$ $[M + Na]^+$ 220.1313, found 220.1304; Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.77, H, 9.52, N, 6.83.

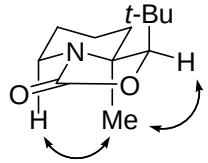
Relative stereochemistry of the major diastereomer was assigned based on the following NOESY correlations:

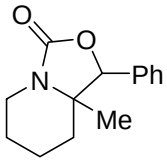




1-tert-Butyl-8a-methyl-hexahydro-oxazolo[3,4-a]pyridin-3-one (8). Following the general reductive lithiation/electrophilic addition procedure, pivalaldehyde (3.0 equiv.) was utilized as the electrophile. GC of the crude reaction mixture indicated a single diastereomer. Flash chromatography (20% dichloromethane/hexanes then 20% ethyl acetate/hexanes) afforded **8** as a pale yellow oil (59%). IR (thin film) 2955, 1749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.76 (dd, *J* = 4.6, 13.7 Hz, 1 H), 3.40 (s, 1 H), 2.45 (ddd, *J* = 3.4, 12.3, 13.7 Hz, 1 H), 1.47 (ddd, *J* = 3.6, 12.7, 12.7 Hz, 1H), 1.24–1.21 (m, 2 H), 1.11–0.98 (m, 2 H), 0.98–0.91 (m, 1 H), 0.86 (s, 3 H), 0.85 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 157.2, 90.6, 62.2, 39.0, 34.0, 30.5, 27.7, 24.6, 22.1, 20.5; HRMS (ESI) calcd for $C_{12}H_{21}NO_2Na$ $[M + Na]^+$ 234.1470, found 234.1470.

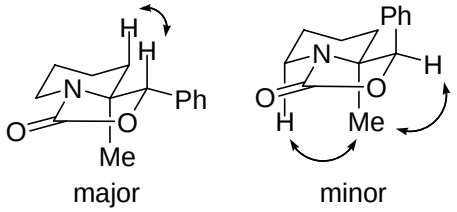
Relative stereochemistry was assigned based on the following NOESY correlations:

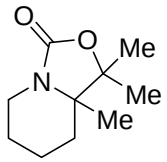




8a-Methyl-1-phenyl-hexahydro-oxazolo[3,4-a]pyridin-3-one (9). Following the general reductive lithiation/electrophilic addition procedure, benzaldehyde (3.0 equiv.) was utilized as the electrophile. GC of the crude reaction mixture indicated a diastereomeric ratio of 1.6:1. Flash chromatography (20% dichloromethane/hexanes then 50% diethyl ether/hexanes) afforded an inseparable mixture of the diastereomers as a pale yellow oil (82%). Major diastereomer: IR (thin film) 2945, 1753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5 H), 5.19 (s, 1 H), 3.81 (dd, *J* = 5.0, 13.7 Hz, 1 H), 2.95 (ddd, *J* = 3.2, 13.4, 13.6 Hz, 1 H), 1.82 (m, 1 H), 1.72 (m, 1 H), 1.65–1.53 (m, 2 H), 1.51 (s, 3 H), 1.18 (ddd, *J* = 4.3, 13.0, 13.1 Hz, 1 H), 0.72 (d, *J* = 13.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 134.6, 128.5, 128.5, 125.9, 84.9, 61.3, 39.4, 30.7, 24.3, 21.8, 20.0; HRMS (ESI) calcd for $C_{14}H_{18}NO_2$ $[M + H]^+$ 232.1338, found 232.1337; Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.91, H, 7.60, N, 6.11.

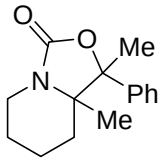
Relative stereochemistries of the diastereomers were based on the following NOESY correlations:





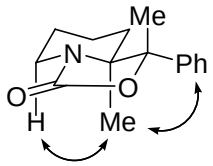
1,1,8a-Trimethyl-hexahydro-oxazolo[3,4-a]pyridin-3-one (10). Following the general reductive lithiation/electrophilic addition procedure, acetone (3.0 equiv.) was utilized as the electrophile. Flash chromatography (20% dichloromethane/hexanes then 5–50%

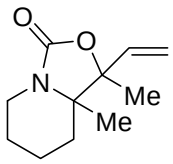
ethyl acetate/hexanes) afforded **10** as a white solid (68%). Mp 40–42 °C; IR (thin film) 2940, 1746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.72 (dd, *J* = 5.0, 13.6 Hz, 1 H), 2.86 (ddd, *J* = 3.3, 13.2, 13.3 Hz, 1 H), 1.78 (m, 1 H), 1.69–1.56 (m, 3 H), 1.49– 1.35 (m, 2 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 83.5, 61.9, 39.2, 30.1, 24.1, 23.2, 21.4, 20.3, 16.1; HRMS (ESI) calcd for $C_{10}H_{17}NO_2Na$ $[M + Na]^+$ 206.1157, found 206.1153; Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.47, H, 9.19, N, 7.56.



1,8a-Dimethyl-1-phenyl-hexahydro-oxazolo[3,4-a]pyridin-3-one (11). Following the general reductive lithiation/electrophilic addition procedure, acetophenone (3.0 equiv.) was utilized as the electrophile. GC of the crude reaction mixture indicated a diastereomeric ratio of 3.3:1. Flash chromatography (20% dichloromethane/hexanes then 5–50% ethyl acetate/hexanes) afforded a mixture of the diastereomers as a pale yellow solid (61%). An analytical sample of the major diastereomer was obtained as colorless crystals by recrystallization (diethyl ether/hexanes). Major diastereomer: Mp 120–122 °C; IR (thin film) 2942, 1754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 5 H), 3.76(dd, *J* = 5.0, 13.1 Hz, 1 H), 2.87 (ddd, *J* = 3.4, 13.0, 13.0 Hz, 1 H), 1.94 (ddd, *J* = 4.1, 12.8, 12.9 Hz, 1 H), 1.85 (m, 1 H), 1.75 (m, 1 H), 1.68 (m, 1 H), 1.66 (s, 3 H), 1.58 (ddddd, *J* = 3.2, 3.2, 13.1, 13.1, 13.1 Hz, 1 H), 1.45 (ddddd, *J* = 3.8, 5.0, 13.2, 13.2, 13.2 Hz, 1 H), 0.78 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 141.0, 128.5, 127.7, 124.9, 87.9, 62.6, 38.5, 30.1, 24.1, 24.0, 19.9, 18.3; HRMS (ESI) calcd for $C_{15}H_{20}NO_2$ $[M + H]^+$ 246.1494, found 246.1500; Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.54, H, 7.69, N, 5.68.

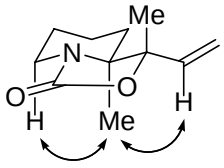
Relative stereochemistry of the major diastereomer was assigned based on the following NOESY correlations:

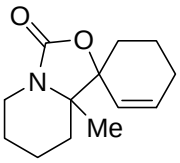




1,8a-Dimethyl-1-vinyl-hexahydro-oxazolo[3,4-a]pyridin-3-one (12). Following the general reductive lithiation/electrophilic addition procedure, methyl vinyl ketone (3.0 equiv.) was utilized as the electrophile. GC of the crude reaction mixture indicated a diastereomeric ratio of 1.5:1. Flash chromatography (20% dichloromethane/hexanes then 10–50% diethyl ether/hexanes) afforded an inseparable mixture of the diastereomers as a pale yellow oil (65%). Major diastereomer: IR (thin film) 2941, 1749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (dd, *J* = 11.0, 17.3 Hz, 1 H), 5.43 (dd, *J* = 0.6, 17.3 Hz, 1 H), 5.24 (dd, *J* = 0.6, 11.2 Hz, 1 H), 3.74 (m, 1 H), 2.86 (dddd, *J* = 3.4, 3.4, 13.4, 13.4 Hz, 1 H), 1.77 (m, 1 H), 1.70–1.50 (m, 3 H), 1.43 (m, 1 H), 1.40 (s, 3 H), 1.27 (s, 3 H), 1.26 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 135.6, 115.6, 85.1, 62.1, 39.4, 31.4, 24.0, 21.5, 20.3, 16.3; HRMS (ESI) calcd for $C_{11}H_{18}NO_2$ $[M + H]^+$ 196.1338, found 196.1337; Anal. calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.66, H, 8.63, N, 7.01.

Relative stereochemistry of the minor diastereomer was assigned based on the following NOESY correlations:

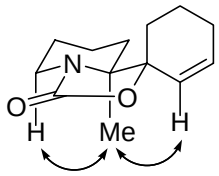




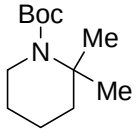
1,1-(1'-*cis*-pentenyl)-8a-methyl-hexahydro-oxazolo[3,4-a]pyridin-3-one (13). Following the general reductive lithiation/electrophilic addition procedure, 2-cyclohexenone (3.0 equiv.) was utilized as the electrophile. GC of the crude reaction mixture indicated a diastereomeric ratio of 2.2:1. Flash chromatography (20% dichloromethane/hexanes then 10–50% diethyl ether/hexanes) afforded a mixture of the diastereomers as a pale yellow oil (84%). An analytical sample of the major diastereomer was obtained as a colorless oil by additional flash chromatography. Major diastereomer: IR (thin film) 2936, 1744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (ddd, *J* = 2.7, 5.0, 10.2 Hz, 1 H), 5.78 (d, *J* = 10.2 Hz, 1 H), 3.74 (dd, *J* = 4.9, 13.8 Hz, 1 H), 2.87 (ddd, *J* = 3.7, 13.1, 13.3 Hz, 1 H), 2.11 (m, 1 H), 2.03–1.92 (m, 2 H), 1.85–1.74 (m, 2 H), 1.74–1.64 (m, 4 H), 1.59–1.42 (m, 2 H), 1.37 (dd, *J* = 3.1, 9.3 Hz, 1 H), 1.21 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 133.3, 125.3, 82.1, 62.4, 39.6, 30.0, 27.8, 24.8, 24.0,

20.3, 19.2, 16.8; HRMS (ESI) calcd for $C_{13}H_{20}NO_2$ $[M + H]^+$ 222.1494, found 222.1485; Anal. calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.70, H, 8.49, N, 6.29.

Relative stereochemistry of the major diastereomer was assigned based on the following NOESY correlations:

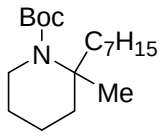


General procedure for reductive lithiation/cupration/electrophilic addition. Following the general reductive lithiation procedure, a pre-cooled (–78 °C) solution of 1-hexynylcopper[5] (2.0 equiv.) and trimethyl phophite (6.0 equiv.) in tetrahydrofuran (1.0 mL) was added *via* cannula over 1 min down the flask wall to a solution of the organolithium reagent, typically producing a dark red solution. After 30 min, the electrophile (3.0 equiv.) was added. Further experimental details are provided along with the characterization data.

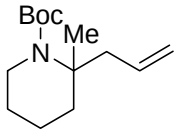


2,2-Dimethyl-piperidine-1-carboxylic acid tert-butyl ester (14). Following the general reductive lithiation/cupration procedure, iodomethane (3.0 equiv.) was added and the reaction was stirred for 16 h with gradual warming to room temperature. A saturated ammonium chloride solution (20 mL) was added, the mixture was stirred for 1 h and then extracted with diethyl ether (3 x 10 mL). Combined extracts were washed with saturated sodium chloride solution (5 mL), dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography (20% dichloromethane/hexanes then 5% diethyl ether/hexanes) afforded **14** as a colorless oil (52%). IR (thin film) 2934, 1699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.40 (m, 2 H), 1.61–1.54 (m, 4 H), 1.53–1.49 (m, 2 H), 1.46 (s, 9 H), 1.38 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 79.4, 54.7, 41.6, 39.8, 28.8, 27.1, 24.2, 18.9; HRMS (ESI) calcd for $C_{13}H_{20}NO_2$ $[M – Me]^+$ 198.1489, found 198.1496.

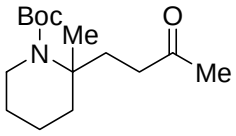
[5] 1-Hexynylcopper was prepared in an analogous fashion to the following preparation of copper phenylacetylide: Owsley, D. C.; Castro, C. E. *Org. Synth. Coll. Vol. 6*, 916.



2-Heptyl-2-methyl-piperidine-1-carboxylic acid tert-butyl ester (15). Following the general reductive lithiation/cupration procedure, iodoheptane (3.0 equiv.) was added and the reaction was stirred for 16 h with gradual warming to room temperature. A saturated ammonium chloride solution (20 mL) was added, the mixture was stirred for 1 h and then extracted with diethyl ether (3 x 10 mL). Combined extracts were washed with saturated sodium chloride solution (5 mL), dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography (20% dichloromethane/hexanes then 5% diethyl ether/hexanes) afforded **15** as a colorless oil (51%). IR (thin film) 2930, 1699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.66 (m, 1 H), 3.17 (m, 1 H), 1.91 (m, 1 H), 1.77 (m, 1 H), 1.60–1.51 (m, 5 H), 1.46 (s, 9 H), 1.38 (s, 3 H), 1.33–1.17 (m, 11 H), 0.88 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 79.2, 57.2, 41.6, 39.2, 35.8, 32.0, 30.4, 29.6, 28.8, 26.2, 24.1, 23.8, 22.8, 18.3, 14.3; HRMS (ESI) calcd for $C_{18}H_{35}NO_2Na$ $[M + Na]^+$ 320.2566, found 320.2574.

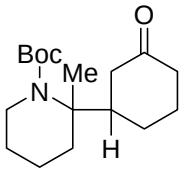


2-Allyl-2-methyl-piperidine-1-carboxylic acid tert-butyl ester (16). Following the general reductive lithiation/cupration procedure, allyl bromide (3.0 equiv.) was added and the reaction was stirred for 16 h with gradual warming to room temperature. A saturated ammonium chloride solution (20 mL) was added, the mixture was stirred for 1 h and then extracted with diethyl ether (3 x 10 mL). Combined extracts were washed with saturated sodium chloride solution (5 mL), dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography (20% dichloromethane/hexanes then 5% diethyl ether/hexanes) afforded **16** as a colorless oil (60%). IR (thin film) 2975, 2938, 1696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (dddd, *J* = 7.3, 7.3, 10.3, 17.1 Hz, 1 H), 5.09–5.00 (m, 2 H), 3.59 (ddd, *J* = 5.3, 5.3, 13.4 Hz, 1 H), 3.24 (ddd, *J* = 4.8, 8.7, 13.3 Hz, 1 H), 2.80 (dd, *J* = 6.9, 13.6 Hz, 1 H), 2.80 (dd, *J* = 6.9, 13.6 Hz, 1 H), 2.32 (dd, *J* = 7.8, 13.6 Hz, 1 H), 1.77 (m, 1 H), 1.62–1.55 (m, 4 H), 1.46 (s, 9 H), 1.40 (s, 3 H), 1.32 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 135.0, 117.7, 79.5, 57.0, 43.4, 41.7, 35.5, 28.8, 25.7, 23.6, 18.1; HRMS (ESI) calcd for $C_{14}H_{25}NO_2Na$ $[M + Na]^+$ 262.1783, found 262.1787. Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.41, H, 10.43, N, 6.02.



2-Methyl-2-(3-oxo-butyl)-piperidine-1-carboxylic acid tert-butyl ester (20). Following the general reductive lithiation/cupration procedure, chlorotrimethylsilane (5.0

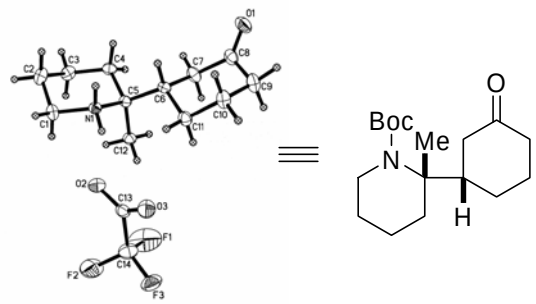
equiv.) was added followed by methyl vinyl ketone (3.0 equiv.). The reaction was stirred at –78 °C for 7.5 h, at which time 50% triethylamine/methanol (0.5 mL) was added, followed by saturated ammonium chloride solution (25 mL) and warming to room temperature. Aqueous hydrochloric acid (1 N) was added until pH 4, the mixture was stirred for 5 min and then extracted with diethyl ether (3 x 10 mL). Combined extracts were washed with saturated sodium chloride solution (5 mL), dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography (20% dichloromethane/hexanes then 5–50% diethyl ether/hexanes) afforded **20** as a colorless oil (64%). IR (thin film) 2937, 1716, 1688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.54 (m, 1 H), 3.28 (m, 1 H), 2.47 (m, 2 H), 2.30 (m, 1 H), 2.16 (s, 3 H), 1.81 (m, 1 H), 1.70–1.49 (m, 5 H), 1.45 (s, 9 H), 1.38 (s, 3 H), 1.35 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.9, 156.1, 79.5, 56.5, 41.9, 38.8, 36.2, 33.4, 30.0, 28.6, 25.5, 23.9, 18.6; HRMS (ESI) calcd for $C_{15}H_{27}NO_3Na$ $[M + Na]^+$ 292.1889, found 292.1890. Anal. calcd for $C_{15}H_{27}NO_3$: C, 66.88; H, 10.10; N, 5.20. Found: C, 67.10, H, 10.41, N, 5.22.



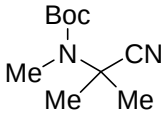
2-Methyl-2-(3-oxo-cyclohexyl)-piperidine-1-carboxylic acid tert-butyl ester (21). Following the general reductive lithiation/cupration procedure, 2-cyclohexenone (3.0 equiv.) was added followed by chlorotrimethylsilane (5.0 equiv.). The reaction was stirred for 8.5 h with gradual warming to room temperature, at which time 10% concentrated ammonium hydroxide/saturated ammonium chloride solution (10 mL) was added. After 1 h, the mixture was extracted with ethyl acetate (3 x 7.5 mL) and the combined extracts were washed with saturated sodium chloride solution (3 mL), dried (sodium sulfate) and concentrated *in vacuo*. The residue was taken up in tetrahydrofuran (5 mL) and tetra-*n*-butylammonium fluoride/tetrahydrofuran solution (1.0 M, 0.5 mL) was added. After 5 min, saturated ammonium chloride solution (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 7.5 mL). Combined extracts were washed with saturated sodium chloride solution (3 mL), dried (sodium sulfate) and concentrated *in vacuo*. ^1H NMR of the crude reaction mixture indicated a *ca.* 9:1 diastereomeric ration. Flash chromatography (20% dichloromethane/hexanes then 15–50% diethyl ether/hexanes) afforded a mixture of the diastereomers as a white solid (60%). An analytical sample of the major diastereomer was obtained by recrystallization (isooctane). Major diastereomer: IR (thin film) 2933, 1711, 1685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.89 (ddd, J = 3.7, 3.7, 6.2 Hz, 1 H), 2.93 (m, 1 H), 2.77 (m, 2 H), 2.38 (ddd, J = 2.0, 3.9, 14.4 Hz, 1 H), 2.30 (dddd, J = 2.1, 2.1, 3.9, 13.6 Hz, 1 H), 2.26–2.13 (m, 2 H), 2.10 (m, 1 H), 1.81–1.71 (m, 2 H), 1.70–1.53 (s, 6 H), 1.49 (s, 3 H), 1.45 (s, 9 H), 1.37 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.9, 155.7, 79.6, 59.4, 44.6, 42.9, 41.4, 41.2, 30.9, 28.6, 26.3, 25.6, 24.1, 22.8, 17.0. HRMS (ESI) calcd for $C_{17}H_{29}NO_3Na$ $[M + Na]^+$ 318.2045, found 318.2035.

Relative stereochemistry of the major diastereomer was established using X-ray crystallography *via* cleavage of the Boc protecting group (trifluoroacetic acid,

dichloromethane, 0 ºC) and crystallization of the resulting trifluoroacetate salt ($MeOH/Et_2O$):



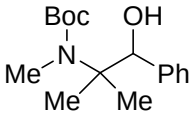
Additional X-ray data follows the experimental section.



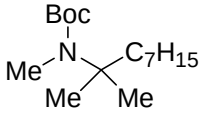
(Cyano-dimethyl-methyl)-methyl-carbamic acid tert-butyl ester (23). To a –78 °C solution of diisopropylamine (1.4 mL, 10 mmol) in tetrahydrofuran (20 mL) was added *n*-butyllithium in hexane (2.36 M, 4.2 mL, 9.8 mmol) over 5 min. After 30 min, 1,3-dimethylpropyleneurea (0.953 mL, 7.88 mmol) was added over 1 min followed by addition of a solution of cyanomethyl-methyl-carbamic acid tert-butyl ester[6] (0.970 g, 3.94 mmol) in tetrahydrofuran (5 mL) over 5 min. After 1 h., iodomethane (0.981 mL, 15.8 mmol) was added over 2 min. After 4 h, half-saturated ammonium chloride solution (100 mL) was added and the reaction was warmed to room temperature. The reaction was extracted with diethyl ether (3 x 30 mL) and the combined extracts were washed with saturated sodium chloride solution (25 mL), dried (magnesium sulfate) and concentrated *in vacuo* to afford a pale yellow oil. Flash chromatography (5–15% diethyl ether/hexanes) afforded the monoalkylated aminonitrile (0.539 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96 (s, 1 H), 1.55 (s, 3 H), 1.53 (s, 9 H). To a –78 °C solution of diisopropylamine (0.623 mL, 4.45 mmol) in tetrahydrofuran (10 mL) was added *n*-butyllithium in hexane (2.36 M, 1.8 mL, 4.2 mmol) over 5 min. After 30 min., 1,3-dimethylpropyleneurea (0.672 mL, 5.56 mmol) was added over 1 min. followed by addition of a solution of the monoalkylated aminonitrile (0.513 g, 2.78 mmol) in tetrahydrofuran (4 mL) over 5 min. After 1.5 h, iodomethane (0.519 mL, 8.34 mmol) was added over 2 min. After 4 h, half-saturated ammonium chloride solution (50 mL) was added and the reaction was warmed to room temperature. The reaction was extracted with diethyl ether (3 x 25 mL) and the combined extracts were washed with saturated sodium chloride solution (15 mL), dried (magnesium sulfate) and concentrated *in vacuo* to afford a pale yellow oil. Flash chromatography (20% diethyl ether/hexanes) afforded **23** as a white solid (0.469 g, 85%). Mp 44–46 ºC; IR (thin film) 2979, 1702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (s, 3 H), 1.70 (s, 6 H), 1.52 (s, 9 H); ^{13}C NMR (125

[6] Kruijtzer, J. A. W.; Lefeber, D. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **1997**, *38*, 5335-5338.

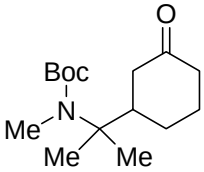
MHz, $CDCl_3$) δ 154.8, 122.2, 82.1, 51.8, 30.4, 28.5, 27.0. HRMS (ESI) calcd for $C_{10}H_{18}N_2O_2Na$ $[M + Na]^+$ 221.1266, found 221.1267. Anal. calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.36, H, 8.79, N, 14.30.



(2-Hydroxy-1,1-dimethyl-2-phenyl-ethyl)-methyl-carbamic acid tert-butyl ester (24). Following the general reductive lithiation/electrophilic addition procedure with aminonitrile **23**, benzaldehyde (3.0 equiv.) was utilized as the electrophile, maintaining at –78 °C for 2 h prior to usual work-up. Flash chromatography (20% dichloromethane/hexanes then 5–20% diethyl ether/hexanes) afforded **24** as a colorless oil (75%). IR (thin film) 3460, 2977, 1662 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 4.83 (s, 1 H), 2.39 (s, 3 H), 1.51 (s, 9 H), 1.49 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 142.0, 127.8, 127.6, 127.4, 80.3, 62.4, 32.9, 28.7, 26.0, 24.3; HRMS (ESI) calcd for $C_{16}H_{26}NO_3$ $[M + H]^+$ 280.1913, found 280.1917. Anal. calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 69.00, H, 9.08, N, 5.21.

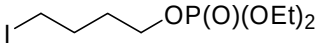


(1,1-Dimethyl-octyl)-methyl-carbamic acid tert-butyl ester (25). Following the general reductive lithiation/cupration procedure with aminonitrile **23**, iodoheptane (3.0 equiv.) was added and the reaction was stirred for 16 h with gradual warming to room temperature. A saturated ammonium chloride solution (20 mL) was added, the mixture was stirred for 1 h and then extracted with diethyl ether (3 x 10 mL). Combined extracts were washed with saturated sodium chloride solution (5 mL), dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography (20% dichloromethane/hexanes then 5% diethyl ether/hexanes) afforded **25** as a colorless oil (38%). IR (thin film) 2927, 1698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.85 (s, 3 H), 1.73 (m, 1 H), 1.46 (s, 9 H), 1.31 (s, 6 H), 1.30–1.17 (m, 10 H), 0.89 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 79.3, 57.7, 41.2, 32.3, 32.1, 30.3, 29.6, 28.8, 28.0, 24.5, 22.9, 14.3; HRMS (ESI) calcd for $C_{16}H_{33}NO_2Na$ $[M + Na]^+$ 294.2409, found 294.2396.

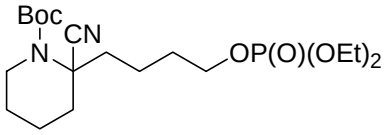


Methyl-[1-methyl-1-(3-oxo-cyclohexyl)-ethyl]-carbamic acid tert-butyl ester (26). Following the general reductive lithiation/cupration procedure with aminonitrile **23**, 2-cyclohexenone (3.0 equiv.) was added followed by chlorotrimethylsilane (5.0 equiv.). The reaction was stirred for 8.5 h with gradual warming to room temperature, at which

time 10% concentrated ammonium hydroxide/saturated ammonium chloride solution (10 mL) was added. After 1 h, the mixture was extracted with ethyl acetate (3 x 7.5 mL) and the combined extracts were washed with saturated sodium chloride solution (3 mL), dried (sodium sulfate) and concentrated *in vacuo*. The residue was taken up in tetrahydrofuran (5 mL) and tetra-*n*-butylammonium fluoride/tetrahydrofuran solution (1.0 M, 0.5 mL) was added. After 5 min, saturated ammonium chloride solution (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 7.5 mL). Combined extracts were washed with saturated sodium chloride solution (3 mL), dried (sodium sulfate) and concentrated *in vacuo*. ^{1}H NMR of the crude reaction mixture indicated a *ca.* 9:1 diastereomeric ration. Flash chromatography (20% dichloromethane/hexanes then 15–50% diethyl ether/hexanes) afforded **26** as a pale yellow oil (57%). IR (thin film) 2972, 1711, 1687 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (s, 3 H), 4.83 (s, 1 H), 2.37 (m, 1 H), 2.31 (dddd, *J* = 2.2, 2.2, 4.2, 13.5 Hz, 1 H), 2.22 (m, 1 H), 2.09 (m, 2 H), 1.81 (d, *J* = 12.9 Hz, 1 H), 1.59 (m, 1 H), 1.44 (s, 9 H), 1.37 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 155.8, 79.7, 60.2, 45.3 43.8, 41.4, 32.7, 28.7, 26.7, 25.4, 24.8, 24.4; HRMS (ESI) calcd for $C_{15}H_{27}NO_3Na$ $[M + Na]^+$ 292.1889, found 292.1891. Anal. calcd for $C_{15}H_{27}NO_3$: C, 66.88; H, 10.10; N, 5.20. Found: C, 67.09, H, 10.28, N, 5.25.



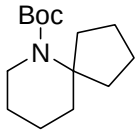
Phosphoric acid diethyl ester 4-iodo-butyl ester (27). To a 0 ºC solution of 4-iodo-1-butanol[7] (5.50 g, 27.5 mmol) in dichloromethane (50 mL) was added diethyl chlorophosphate (11.9 mL, 82.5 mmol) followed by pyridine (8.9 mL, 111 mmol) and *N*,*N*-dimethylaminopyridine (0.135 g, 1.38 mmol). The reaction was stirred for 18 h at 0 ºC and 2 h at room temperature. Diethyl ether (150 mL) was added and the solution was washed with 1N sodium bisulfate solution (3 x 25 mL), saturated sodium bicarbonate solution (2 x 25 mL), saturated sodium chloride solution (25 mL), dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography (50% diethyl ether/hexanes then diethyl ether) afforded **27** as a yellow oil (7.32 g, 79%). IR (thin film) 2981, 1269, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (p, *J* = 7.1 Hz, 4 H), 4.04 (q, *J* = 6.3 Hz, 2 H), 3.20 (t, *J* = 6.8 Hz, 2 H), 1.93 (m, 2 H), 1.78 (m, 2 H), 1.32 (dt, *J* = 0.5, 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.6 (d, *J* = 5.9 Hz), 64.2 (d, *J* = 5.9 Hz), 31.5 (d, *J* = 7.0 Hz), 29.9, 16.6 (d, *J* = 6.6 Hz), 6.2; HRMS (CI/NH_3) calcd for $C_8H_{19}IO_4P$ $[M + H]^+$ 337.0066, found 337.0072.



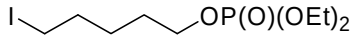
2-Cyano-2-[4-(diethoxy-phosphoryloxy)-butyl]-piperidine-1-carboxylic acid tert-butyl ester (29). To a –78 °C solution of diisopropylamine (0.107 mL, 0.763 mmol) in

[7] Wakita, H.; Matsumoto, K.; Yoshiwara, H.; Hosono, Y.; Hayashi, R.; Nishiyama, H.; Nagase, H. *Tetrahedron* **1999**, *55*, 2449-2474.

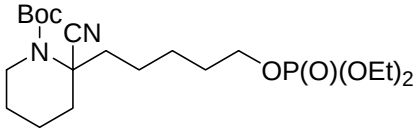
tetrahydrofuran (5 mL) was added *n*-butyllithium in hexane (2.55 M, 0.277 mL, 0.707 mmol) over 5 min. After 30 min, 1,3-dimethylpropyleneurea (0.137 mL, 1.13 mmol) was added over 2 min. followed by addition of a solution of **1** (0.143 g, 0.678 mmol) in tetrahydrofuran (1 mL) over 5 min. After 1 h, **27** (0.190 mg, 0.565 mmol) in tetrahydrofuran (1 mL) was added over 5 min. After 8 h, saturated ammonium chloride solution (1 mL) was added and the reaction was warmed to room temperature and then diluted with water (10 mL). The reaction was extracted with ethyl acetate (3 x 5 mL) and the combined extracts were washed with saturated sodium chloride solution (3 mL), dried (sodium sulfate) and concentrated *in vacuo* to afford a pale yellow oil. Flash chromatography (30% ethyl acetate/hexanes) afforded **29** as a colorless oil (0.197 g, 83%). IR (thin film) 2977, 1699, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.12 (p, *J* = 7.1 Hz, 4 H), 4.06 (q, *J* = 6.5 Hz, 2 H), 3.82 (ddd, *J* = 4.0, 4.0, 13.0 Hz, 1 H), 3.04 (ddd, *J* = 4.3, 10.3, 14.0 Hz, 1 H), 2.13–1.95 (m, 4 H), 1.80–1.61 (m, 6 H), 1.56 (m, 1 H), 1.51 (s, 9 H), 1.34 (t, *J* = 7.1 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 121.0, 81.9, 67.1 (d, *J* = 6.0 Hz), 63.9 (d, *J* = 5.8 Hz), 56.1, 40.6, 35.1, 33.5, 30.2 (d, *J* = 6.9 Hz), 22.8, 20.5, 17.9, 16.3 (d, *J* = 6.7); HRMS (ESI) calcd for $C_{19}H_{36}N_2O_6P$ $[M + H]^+$ 419.2311, found 419.2297. Anal. calcd for $C_{19}H_{35}N_2O_6P$: C, 54.53; H, 8.43; N, 6.69. Found: C, 54.38, H, 8.45, N, 6.55.



6-Aza-spiro[4.5]decane-6-carboxylic acid tert-butyl ester (31). An oven-dried 50 mL round-bottom flask was equipped with a glass stir bar and septum and cooled with a purge of argon. The flask was charged with 1,10-phenanthroline (1 crystal) and a solution of **29** (0.098 mg, 0.234 mmol) in tetrahydrofuran (4.0 mL) was then added. The solution was cooled to –78 °C and *n*-butyllithium/hexane (*ca.* 1-2 M) was added until a dark brown color persisted (2 drops). LiDBB solution (0.30 M, 3.1 mL, 0.94 mmol) was added *via* gas-tight syringe in a steady stream over 30 sec to produce a dark green solution. After 4 h, the reaction was quenched with methanol (0.2 mL), saturated ammonium chloride solution (1 mL) and water (15 mL) were added and the mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3 x 5 mL) and the combined extracts were washed with saturated sodium chloride solution (3 mL), dried (sodium sulfate) and concentrated *in vacuo*. Flash chromatography (50% dichloromethane/hexanes then 5% diethyl ether/hexanes) afforded **31** as a colorless oil (0.053 mg, 95%). IR (thin film) 2933, 1702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.46 (m, 2 H), 2.01 (m, 2 H), 1.88 (m, 2 H), 1.75 (m, 2 H), 1.58–1.48 (m, 6 H), 1.46 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 79.2, 66.2, 44.4, 37.5, 34.6, 28.8, 24.7, 23.9, 20.3; HRMS (ESI) calcd for $C_{14}H_{25}NO_2Na$ $[M + Na]^+$ 262.1783, found 262.1779.

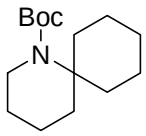


Phosphoric acid diethyl ester 4-iodo-pentyl ester (28). To a 0 ºC solution of 5-iodo-1-pentanol[8] (9.55 g, 44.6 mmol) in dichloromethane (100 mL) was added pyridine (14.4 mL, 178 mmol) followed by diethyl chlorophosphate (19.3 mL, 134 mmol). The reaction was stirred for 2.5 h at 0 ºC. Diethyl ether (300 mL) was added and the solution was washed with 1N sodium bisulfate solution (2 x 100 mL), saturated sodium bicarbonate solution (100 mL), saturated sodium chloride solution (100 mL), dried (sodium sulfate) and concentrated *in vacuo*. Flash chromatography (50–80% ethyl acetate/hexanes) afforded **28** as a pale yellow oil (12.34 g, 79%). IR (thin film) 2981, 1272, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.10 (p, *J* = 7.1 Hz, 4 H), 4.02 (q, *J* = 6.9 Hz, 2 H), 3.18 (t, *J* = 6.9 Hz, 2 H), 1.84 (m, 2 H), 1.69 (m, 2 H), 1.49 (m, 2 H), 1.33 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 67.6 (d, *J* = 5.9 Hz), 64.1 (d, *J* = 5.8 Hz), 33.3, 29.6 (d, *J* = 6.9 Hz), 26.9, 16.6 (d, *J* = 6.6 Hz), 6.9; HRMS (ESI) calcd for $C_9H_{21}IO_4P$ $[M + H]^+$ 351.0222, found 351.0213.



2-Cyano-2-[4-(diethoxy-phosphoryloxy)-pentyl]-piperidine-1-carboxylic acid tert-butyl ester (30). To a –78 °C solution of diisopropylamine (0.512 mL, 3.65 mmol) in tetrahydrofuran (10 mL) was added *n*-butyllithium in hexane (1.60 M, 2.12 mL, 3.39 mmol) over 5 min. After 30 min., 1,3-dimethylpropyleneurea (0.631 mL, 5.22 mmol) was added over 2 min followed by addition of a solution of **1** (0.548 g, 2.61 mmol) in tetrahydrofuran (5.0 mL) over 3 min. After 1 h, **28** (0.829 mg, 2.37 mmol) in tetrahydrofuran (2.5 mL) was added over 5 min. After 3.5 h, half-saturated ammonium chloride solution (50 mL) was added and the reaction was warmed to room temperature and extracted with ethyl acetate (3 x 15 mL). The combined extracts were washed with saturated sodium chloride solution (10 mL), dried (sodium sulfate) and concentrated *in vacuo* to afford a pale yellow oil. Flash chromatography (50–75% ethyl acetate/hexanes) afforded **30** as a colorless oil (0.682 g, 67%). IR (thin film) 2940, 1700, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.10 (p, *J* = 7.1 Hz, 4 H), 4.02 (q, *J* = 6.7 Hz, 2 H), 3.81 (d, *J* = 14.1 Hz, 1 H), 3.02 (m, 1 H), 2.08–1.90 (m, 4 H), 1.79–1.59 (m, 6 H), 1.50 (s, 9 H), 1.47–1.37 (m, 4 H), 1.33 (t, *J* = 7.1 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 121.2, 82.0, 67.4 (d, *J* = 6.0 Hz), 63.9 (d, *J* = 5.8 Hz), 56.3, 40.6, 35.6, 33.6, 30.3 (d, *J* = 6.9 Hz), 28.5, 25.6, 24.1, 22.9, 18.0, 16.3 (d, *J* = 6.6); HRMS (ESI) calcd for $C_{20}H_{37}N_2O_6PNa$ $[M + Na]^+$ 455.2287, found 455.2269. Anal. calcd for $C_{20}H_{37}N_2O_6P$: C, 55.54; H, 8.62; N, 6.48. Found: C, 55.70, H, 8.80, N, 6.44.

[8] Kobayashi, Y.; Shimazaki, T.; Taguchi, H.; Sato, F. *J. Org. Chem.* **1990**, *55*, 5324-5335.



1-Aza-spiro[5.5]undecane-1-carboxylic acid tert-butyl ester (32). An oven-dried 50 mL round-bottom flask was equipped with a glass stir bar and septum and cooled with a purge of argon. The flask was charged with 1,10-phenanthroline (1 crystal) and a solution of **30** (0.160 mg, 0.370 mmol) in tetrahydrofuran (5.0 mL) was then added. The solution was cooled to –78 °C and *n*-butyllithium/hexane (*ca.* 1-2 M) was added until a dark brown color persisted (2 drops). LiDBB solution (0.50 M, 1.6 mL, 0.81 mmol) was added *via* gas-tight syringe in a steady stream over 30 sec to produce a dark green solution. After 15 min, the reaction was warmed to –40 °C over 15 min, maintained at that temperature for 1 h, and then warmed to room temperature over 2h. Half-saturated ammonium chloride solution (20 mL) was added, the mixture was extracted with ethyl acetate (3 x 10 mL) and the combined extracts were washed with saturated sodium chloride solution (5 mL), dried (sodium sulfate) and concentrated *in vacuo*. Flash chromatography (20% dichloromethane/hexanes then 5% ethyl acetate/hexanes) afforded **32** as a colorless oil (0.045 mg, 45%). IR (thin film) 2928, 1692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 (m, 2 H), 2.56 (m, 2 H), 1.66 (m, 2 H), 1.56 (m, 6 H), 1.45–1.29 (m, 10 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 79.2, 58.7, 40.9, 33.4, 31.1, 28.8, 25.9, 23.6, 23.1, 17.3; HRMS (ESI) calcd for $C_{15}H_{27}NO_2Na$ $[M + Na]^+$ 276.1939, found 276.1929.

X-ray Data Collection, Structure Solution and Refinement for compound **21**.

A colorless crystal of approximate dimensions 0.18 x 0.25 x 0.25 mm was mounted on a glass fiber and transferred to a Bruker CCD platform diffractometer. The SMART[1] program package was used to determine the unit-cell parameters and for data collection (25 sec/frame scan time for a sphere of diffraction data). The raw frame data was processed using SAINT[2] and SADABS[3] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[4] program. The diffraction symmetry was 2/*m* and the systematic absences were consistent with the centrosymmetric monoclinic space group $P2_1/n$ which was later determined to be correct.

The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. The analytical scattering factors[5] for neutral atoms were used throughout the analysis. Hydrogen atoms were located from a difference-Fourier map and refined (x,y,z and U_{iso}). At convergence, wR2 = 0.1098 and Goof = 1.070 for 278 variables refined against 3678 unique data. As a comparison for refinement on F, R1 = 0.0422 for those 2805 data with $I > 2.0\sigma(I)$.

References.

1. SMART Software Users Guide, Version 5.1, Bruker Analytical X-Ray Systems, Inc.; Madison, WI 1999.

2. SAINT Software Users Guide, Version 6.0, Bruker Analytical X-Ray Systems, Inc.; Madison, WI 1999.

3. Sheldrick, G. M. SADABS, Version 2.05, Bruker Analytical X-Ray Systems, Inc.; Madison, WI 2001.

4. Sheldrick, G. M. SHELXTL Version 6.12, Bruker Analytical X-Ray Systems, Inc.; Madison, WI 2001.

5. International Tables for X-Ray Crystallography 1992, Vol. C., Dordrecht: Kluwer AcademicPublishers.

Definitions:

$wR2 = [\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

$R1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$

Goof = $S = [\Sigma[w(F_o^2-F_c^2)^2] / (n-p)]^{1/2}$ where n is the number of reflections and p is the total number of parameters refined. The thermal ellipsoid plot is shown at the 50% probability level.

Table 1. Crystal data and structure refinement for sdr13.

Identification code	sdr13	
Empirical formula	$C_{14}\ H_{22}\ F_3\ N\ O_3$	
Formula weight	309.33	
Temperature	163(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 8.8599(9) Å	α= 90°.
	b = 20.656(2) Å	β= 114.216(2)°.
	c = 9.0612(9) Å	γ = 90°.
Volume	1512.4(3) $Å^3$	
Z	4	
Density (calculated)	1.359 Mg/m^3	
Absorption coefficient	0.118 mm^{-1}	
F(000)	656	
Crystal size	0.25 x 0.25 x 0.18 mm^3	
Theta range for data collection	2.65 to 28.30°.	
Index ranges	$-11 \le h \le 11$, $-27 \le k \le 26$, $-12 \le l \le 12$	
Reflections collected	15886	
Independent reflections	3678 [R(int) = 0.0324]	
Completeness to theta = 28.30°	98.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9791 and 0.9711	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3678 / 0 / 278	
Goodness-of-fit on F^2	1.070	
Final R indices [I>2sigma(I)]	R1 = 0.0422, wR2 = 0.0958	
R indices (all data)	R1 = 0.0633, wR2 = 0.1098	
Largest diff. peak and hole	0.472 and -0.355 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for sdr13. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	270(2)	816(1)	-1755(2)	17(1)
O(1)	-5774(1)	2058(1)	-2027(2)	33(1)
C(1)	1407(2)	722(1)	-2591(2)	23(1)
C(2)	517(2)	895(1)	-4363(2)	28(1)
C(3)	-37(2)	1598(1)	-4510(2)	25(1)
C(4)	-1180(2)	1705(1)	-3646(2)	21(1)
C(5)	-461(2)	1490(1)	-1862(2)	16(1)
C(6)	-1878(2)	1409(1)	-1279(2)	18(1)
C(7)	-2910(2)	2032(1)	-1521(2)	25(1)
C(8)	-4372(2)	1919(1)	-1091(2)	24(1)
C(9)	-3966(2)	1627(1)	547(2)	30(1)
C(10)	-2837(2)	1034(1)	835(2)	27(1)
C(11)	-1329(2)	1179(1)	471(2)	22(1)
C(12)	907(2)	1946(1)	-794(2)	21(1)
C(13)	2809(2)	420(1)	2622(2)	21(1)
C(14)	4219(2)	854(1)	3775(2)	30(1)
O(3)	2040(1)	111(1)	3258(1)	30(1)
O(2)	2618(1)	450(1)	1190(1)	33(1)
F(1)	3820(2)	1477(1)	3463(2)	75(1)
F(2)	5623(1)	764(1)	3585(1)	56(1)
F(3)	4584(1)	759(1)	5332(1)	41(1)

Table 3. Bond lengths [Å] and angles [°] for sdr13.

N(1)-C(1)	1.5008(18)
N(1)-C(5)	1.5212(17)
O(1)-C(8)	1.2168(19)
C(1)-C(2)	1.513(2)
C(2)-C(3)	1.521(2)
C(3)-C(4)	1.529(2)
C(4)-C(5)	1.5399(19)
C(5)-C(12)	1.5271(19)
C(5)-C(6)	1.5575(19)
C(6)-C(11)	1.531(2)
C(6)-C(7)	1.541(2)
C(7)-C(8)	1.516(2)
C(8)-C(9)	1.502(2)
C(9)-C(10)	1.534(2)
C(10)-C(11)	1.531(2)
C(13)-O(3)	1.2362(19)
C(13)-O(2)	1.2396(19)
C(13)-C(14)	1.544(2)
C(14)-F(3)	1.3264(19)
C(14)-F(1)	1.334(2)
C(14)-F(2)	1.337(2)
C(1)-N(1)-C(5)	116.31(11)
N(1)-C(1)-C(2)	109.86(13)
C(1)-C(2)-C(3)	109.09(13)
C(2)-C(3)-C(4)	110.56(13)
C(3)-C(4)-C(5)	114.87(12)
N(1)-C(5)-C(12)	108.52(11)
N(1)-C(5)-C(4)	108.20(11)
C(12)-C(5)-C(4)	111.49(12)
N(1)-C(5)-C(6)	105.18(11)
C(12)-C(5)-C(6)	113.07(12)
C(4)-C(5)-C(6)	110.07(11)
C(11)-C(6)-C(7)	108.90(12)

C(11)-C(6)-C(5)	115.26(11)
C(7)-C(6)-C(5)	112.10(12)
C(8)-C(7)-C(6)	110.76(12)
O(1)-C(8)-C(9)	123.09(14)
O(1)-C(8)-C(7)	121.29(15)
C(9)-C(8)-C(7)	115.62(13)
C(8)-C(9)-C(10)	111.32(13)
C(11)-C(10)-C(9)	111.92(13)
C(10)-C(11)-C(6)	110.45(13)
O(3)-C(13)-O(2)	130.44(15)
O(3)-C(13)-C(14)	115.62(13)
O(2)-C(13)-C(14)	113.92(14)
F(3)-C(14)-F(1)	107.20(15)
F(3)-C(14)-F(2)	106.44(14)
F(1)-C(14)-F(2)	106.65(15)
F(3)-C(14)-C(13)	114.26(13)
F(1)-C(14)-C(13)	110.24(14)
F(2)-C(14)-C(13)	111.65(14)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for sdr13. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	17(1)	15(1)	18(1)	-1(1)	6(1)	-1(1)
O(1)	20(1)	36(1)	41(1)	-1(1)	11(1)	4(1)
C(1)	25(1)	20(1)	30(1)	0(1)	16(1)	2(1)
C(2)	38(1)	25(1)	27(1)	-2(1)	19(1)	-1(1)
C(3)	30(1)	24(1)	22(1)	3(1)	11(1)	-3(1)
C(4)	20(1)	20(1)	20(1)	2(1)	5(1)	0(1)
C(5)	16(1)	13(1)	19(1)	0(1)	5(1)	1(1)
C(6)	15(1)	17(1)	20(1)	0(1)	5(1)	0(1)
C(7)	22(1)	22(1)	32(1)	7(1)	12(1)	5(1)
C(8)	22(1)	18(1)	34(1)	-3(1)	13(1)	2(1)
C(9)	29(1)	29(1)	37(1)	3(1)	20(1)	6(1)
C(10)	30(1)	25(1)	31(1)	4(1)	18(1)	4(1)
C(11)	22(1)	22(1)	23(1)	3(1)	10(1)	4(1)
C(12)	18(1)	18(1)	23(1)	-3(1)	6(1)	-2(1)
C(13)	16(1)	20(1)	23(1)	-3(1)	4(1)	3(1)
C(14)	30(1)	28(1)	28(1)	-1(1)	7(1)	-9(1)
O(3)	28(1)	28(1)	34(1)	-9(1)	14(1)	-10(1)
O(2)	27(1)	45(1)	21(1)	-1(1)	4(1)	7(1)
F(1)	93(1)	21(1)	76(1)	-4(1)	0(1)	-12(1)
F(2)	29(1)	96(1)	43(1)	-8(1)	15(1)	-27(1)
F(3)	35(1)	58(1)	24(1)	-12(1)	5(1)	-14(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for sdr13.

	x	y	z	U(eq)
H(1)	850(20)	707(9)	-710(20)	26(5)
H(2)	-570(20)	508(10)	-2190(20)	30(5)
H(1A)	2380(20)	993(9)	-2040(20)	26(5)
H(1B)	1720(20)	268(9)	-2440(20)	26(4)
H(2A)	1260(20)	803(9)	-4880(20)	35(5)
H(2B)	-430(20)	615(10)	-4870(20)	31(5)
H(3A)	-600(20)	1726(9)	-5630(20)	26(4)
H(3B)	940(20)	1877(9)	-4050(20)	28(5)
H(4A)	-1440(20)	2153(9)	-3660(20)	20(4)
H(4B)	-2200(20)	1469(9)	-4210(20)	31(5)
H(6A)	-2590(20)	1083(8)	-1960(20)	19(4)
H(7A)	-2220(20)	2372(10)	-780(20)	32(5)
H(7B)	-3330(20)	2178(9)	-2610(20)	32(5)
H(9A)	-4970(30)	1518(10)	660(30)	44(6)
H(9B)	-3360(20)	1960(10)	1370(20)	32(5)
H(10A)	-3480(20)	668(9)	120(20)	28(5)
H(10B)	-2470(20)	878(9)	1960(20)	32(5)
H(11A)	-660(20)	791(9)	680(20)	25(4)
H(11B)	-620(20)	1516(9)	1220(20)	30(5)
H(12A)	1750(20)	1997(9)	-1230(20)	25(4)
H(12B)	1430(20)	1780(9)	300(20)	25(4)
H(12C)	390(20)	2358(10)	-780(20)	32(5)

Table 6. Torsion angles [°] for sdr13.

C(5)-N(1)-C(1)-C(2)	-57.18(17)
N(1)-C(1)-C(2)-C(3)	59.55(17)
C(1)-C(2)-C(3)-C(4)	-58.82(18)
C(2)-C(3)-C(4)-C(5)	54.43(18)
C(1)-N(1)-C(5)-C(12)	-71.96(15)
C(1)-N(1)-C(5)-C(4)	49.17(15)
C(1)-N(1)-C(5)-C(6)	166.77(12)
C(3)-C(4)-C(5)-N(1)	-47.23(16)
C(3)-C(4)-C(5)-C(12)	72.03(16)
C(3)-C(4)-C(5)-C(6)	-161.66(12)
N(1)-C(5)-C(6)-C(11)	62.18(15)
C(12)-C(5)-C(6)-C(11)	-56.06(16)
C(4)-C(5)-C(6)-C(11)	178.52(12)
N(1)-C(5)-C(6)-C(7)	-172.49(12)
C(12)-C(5)-C(6)-C(7)	69.26(15)
C(4)-C(5)-C(6)-C(7)	-56.16(16)
C(11)-C(6)-C(7)-C(8)	-56.57(17)
C(5)-C(6)-C(7)-C(8)	174.69(12)
C(6)-C(7)-C(8)-O(1)	-127.74(16)
C(6)-C(7)-C(8)-C(9)	52.21(18)
O(1)-C(8)-C(9)-C(10)	131.49(16)
C(7)-C(8)-C(9)-C(10)	-48.5(2)
C(8)-C(9)-C(10)-C(11)	50.43(19)
C(9)-C(10)-C(11)-C(6)	-57.91(18)
C(7)-C(6)-C(11)-C(10)	60.35(16)
C(5)-C(6)-C(11)-C(10)	-172.70(12)
O(3)-C(13)-C(14)-F(3)	10.1(2)
O(2)-C(13)-C(14)-F(3)	-171.12(14)
O(3)-C(13)-C(14)-F(1)	-110.71(17)
O(2)-C(13)-C(14)-F(1)	68.10(19)
O(3)-C(13)-C(14)-F(2)	130.93(15)
O(2)-C(13)-C(14)-F(2)	-50.26(19)