Supplementary Material (ESI) for Chemical Communications

Direct Synthesis of Bicyclic Guanidines through Unprecedented Palladium(II) Catalysed Diamination with Copper Chloride as Oxidant

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SUPPORTING INFORMATION

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General: All organic reagents were purchased from Acros, if not noted otherwise. All palladium salts were purchased from Acros. *N*,*N´*-di-Boc-*N´*-trifluoromethane-sulfonylguanidine and *N*,*N*-di-Cbz-*N´*-trifluoromethane-sulfonylguanidine were purchased from Fluka. *N*,*N´*-di-Boc-*N´*-trifluoromethane-sulfonylguanidine has been synthesised from *N*-*N*-di-(tert-butoxycarbonyl)-guanidine[1] according to literature procedure.[2] Iodosobenzene diacetate was purchased from Aldrich. Dichloromethane was dried over calcium chloride and distilled from CaH_2. Absolute DMF was purchased from Fischer Chemicals and stored over 4Å molecular sieves. Column chromatography was performed with silica gel (Merck, type 60, 0.063-0.2mm). NMR spectra were recorded on Bruker Avance 400 MHz, Bruker DPX 300 MHz and Bruker DRX 500 MHz spectrometers. All chemical shifts in NMR experiments are reported as ppm downfield from TMS. The following calibrations were used: $CDCl_3$ δ = 7.26 and 77.00 ppm, C_6D_6 δ = 7.16 and 128.0 ppm. MS (ESI-LCMS) experiments were performed using an Agilent 1100 HPLC with a Bruker micro-TOF instrument (ESI). Unless other wise stated, a Supelco C8 (5cm x 4.6mm, 5µm particles) column was used with an linear elution gradient from 100% H_2O (0.5% HCO_2H) to 100% MeCN in 13min at a flow rate of 0.5mL/min. MS (EI) and HRMS experiments were performed on a Kratos MS 50 within the service centers at the Kekulé-Department, Bonn University. IR Spectra in the range of 4000-400 cm^{-1} were obtained on a Nicolet Magna 550 FT-IR Spectrometer with samples investigated as KBr pellets and the data is reported as cm^{-1}.

General Procedure for the Diamination of Guanidines

Copper bromide as oxidant:

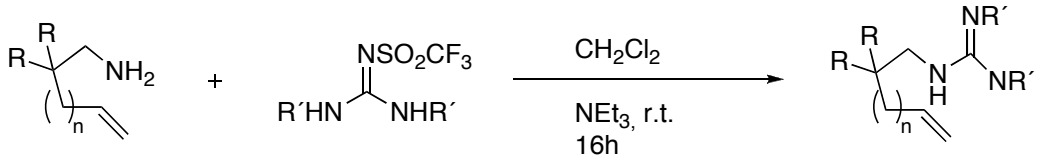
A solution of the guanidine (0.3 mmol, 1.0 eq.), $CuBr_2$ (0.9 mmol, 3.0 eq.), K_2CO_3 (0.3 mmol, 1.0 eq.) and $Pd(OAc)_2$ (0.03 mmol, 0.1 eq.) in DMF (3 mL) was stirred at room temperature until TLC control showed complete conversion of the starting material. The reaction was stopped by addition of 2 mL saturated aqueous $Na_2S_2O_3$ solution and stirred for additional 60 min. Water (5 mL) was

added and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure to yield analytically pure products.

Copper chloride as oxidant:

A solution of the guanidine (0.3 mmol, 1.0 eq.), $CuCl_2$ (0.63 mmol, 2.1 eq.), K_2CO_3 (0.3 mmol, 1.0 eq.) and $Pd(OAc)_2$ (0.03 mmol, 0.1 eq.) in DMF (3 mL) was stirred at room temperature until TLC control showed complete conversion of the starting material. The reaction was stopped by addition of 2 mL saturated aqueous $Na_2S_2O_3$ solution and stirred for additional 60 min. Water (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 20 ml). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure to yield analytically pure products.

***Synthesis of Starting Materials* 1a-f and 3a-f**

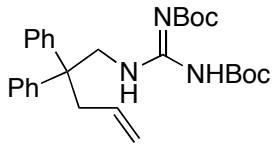


Starting materials **1a-f** and **3a-f** were synthesised by treatment of the corresponding amine[3] with *N*,*N´*-di-Boc-*N´*-trifluoromethanesulfonylguanidine or *N*,*N*-di-Cbz-*N´*-trifluoromethanesulfonylguanidine following a literature procedure.[2]

The amine (1.0 eq.) and NEt_3 (1.0 eq.) were dissolved in dry CH_2Cl_2 (4mL/mmol) and the trifluoromethanesulfonylguanidine was added in one portion. The reaction was stirred overnight at r.t. and stopped by addition of saturated $NaHCO_3$ solution (5 mL). 10 mL of CH_2Cl_2 were added and the organic phase was washed with brine. The organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo. Column chromatography (silica, hexanes/CH_2Cl_2 1:1 v/v) gave analytically pure products as white solids.

Analytical Data for New Compounds

Bis-*tert*-butyl(2,2-diphenyl-pent-4-en-1-yl)amino-methylylidene-biscarbamate

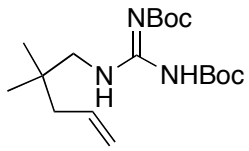


1a

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 92 % yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.34 (s, 9H), 1.42 (s, 9H), 2.85 (d, *J* = 6.8 Hz, 2H), 4.03 (d, *J* = 4.8 Hz, 2H), 4.88 (dd, *J* = 1.2, 10.4 Hz, 1H), 4.95 (dd, *J* = 1.2, 17.2, Hz, 1H), 5.36 (ddd, *J* = 6.8, 10.4, 17.2 Hz, 1H), 7.10-7.22 (m, 10H), 8.16 (br, 1NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 27.89, 28.22, 42.01, 47.87, 49.95, 79.10, 82.73, 118.52, 126.38, 128.04, 128.07, 133.54, 145.01, 152.73, 156.17. MS (EI): m/z = 479.3 (70) [M+], 423.2 (20), 406.2 (10), 367.1 (30), 350.1 (30), 326.1 (10), 264.1 (10), 220.1 (30), 216.0 (40), 207.1 (50), 178.1 (20), 160.0 (100), 129.1 (70), 116.1 (15), 91.1 (50). HRMS. calcd for $C_{28}H_{37}N_3O_4$: 479.2784, found: 479.2779. IR (KBr): ν = 3679, 3449, 3321, 3287, 3063, 3004, 2982, 2932, 1733, 1648, 1618, 1447, 1409, 1355, 1253, 1224, 1145, 1053, 908, 879, 810, 782, 757, 726, 699, 678.

Bis-*tert*-butyl(2,2-dimethyl-pent-4-en-1-yl)amino-methylylidene-biscarbamate

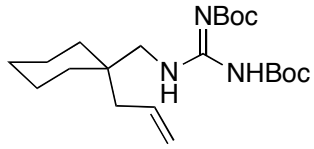


1b

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 94 % yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.88 (s, 6H), 1.43 (s, 9H), 1.44 (s, 9H), 1.95 (d, *J* = 7.6 Hz, 2H), 3.18 (d, *J* = 5.2 Hz, 2H), 5.00 (m, 2H), 5.74 (ddt, *J* = 7.6, 10.4, 17.2 Hz, 1H), 8.44 (t, *J* = 5.2 Hz, 1NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 25.03, 28.05, 28.30, 34.08, 44.37, 50.46, 79.05, 82.94, 117.80, 134.27, 153.39, 156.54, 163.68. MS (EI, eV): m/z (%): 355.2 $[M]^+$ (4), 314.2 (2), 299.1 (10), 282.1 (5), 258.1 (6), 243.1 (70), 226.1 (44), 202.0 (100), 198.1 (8), 161.0 (60), 143.0 (6), 117.0 (10), 96.0 (4), 72.0 (3), 57.0 (28). HRMS calcd for $C_{18}H_{33}N_3O_4$: 355,2471 found: 355.2473. IR (KBr): ν = 3680, 3434, 3328, 3079, 2980, 2968, 2932, 1731, 1652, 1623, 1575, 1473, 1457, 1414, 139, 1369, 1337, 1282, 1252, 1225, 1163, 1140, 1100, 1054, 809, 761, 640.

Bis-*tert*-butyl(1-allylcyclohexyl-methyl)amino-methylydene- biscarbamate

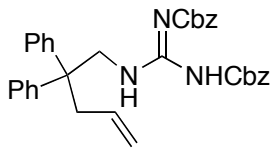


1c

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 89 % yield.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 1.25-1.57 (m, 10H), 1.49 (s, 18H), 2.09 (d, *J* = 7.6 Hz, 2H), 3.30 (d, 5.0 Hz, 2H), 5.02-5.11 (m, 2H), 5.79 (ddt, *J* = 7.6, 9.9, 17.0 Hz, 1H), 8.45 (s, 1NH). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 21.31, 26.11, 28.05, 28.30, 33.58, 36.42, 40.21, 47.29, 79.03, 82.89, 117.70, 133.97, 153.37, 156.46, 163.73. MS (EI) m/z = 395.3 $[M]^+$ (10), 354.2 (15), 339.2 (10), 298.2 (15), 283.1 (50), 266.1 (30), 242.1 (100), 217.1 (5), 186.0 (10), 161.0 (50), 148.0 (10), 143.0 (10), 99.0 (10), 95.1 (15), 81.1 (15), 57.1 (25). HRMS. calc.: 395.2784, found: 395.2780. IR (FT-IR, Ge): ν = 3335, 2978, 2928, 1718, 1639, 1415, 1366, 1330, 1134, 1056, 798.

Dibenzyl(2,2-diphenyl-pent-4-en-1-yl)amino-methylylidene-biscarbamate

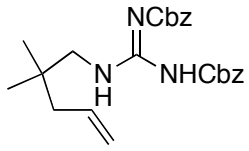


1d

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 97 % yield.

^{1}H NMR ($CDCl_3$, 400 MHz) = 2.94 (d, *J* = 7.0 Hz, 2H), 4.15 (d, *J* = 5.0 Hz, 2H), 4.98 (dd, *J* = 2.1, 10.2 Hz, 1H), 5.04 (dd, *J* = 2.1, 17.2 Hz, 1H), 5.10 (s, 2H), 5.13 (s, 2H), 5.43 (ddt, *J* = 7.0, 10.2, 17.2 Hz, 1H), 7.20-7.44 (m, 20H), 8.21 (t, *J* = 5.0 Hz, 1NH). ^{13}C NMR ($CDCl_3$, 100 MHz) = 42.05, 47.93, 49.80, 67.05, 67.95, 118.69, 126.57, 127.83, 127.95 (2C), 128.23, 128.36, 128.43, 128.57, 128.67, 133.42, 134.51, 136.82, 144.79, 153.46, 156.05, 163.61. MS (EI): m/z = 547.2 (40) [M^+], 504.1 (30), 460.1 (10), 439.2 (10), 355.1 (15), 261.1 (10), 207.1 (70), 165.1 (10), 129.1 (60), 108.1 (25), 91.1 (100), 79.1 (20). HRMS. calcd for $C_{34}H_{33}N_3O_4$: 547.2471, found: 547.2465. IR (KBr): ν = 3670, 3439, 3279, 3087, 3064, 3030, 2930, 2900, 1722, 1647, 1585, 1496, 1427, 1392, 1324, 1201, 1149, 1087, 1055, 916, 803, 756, 746, 698, 585, 497.

Dibenzyl(2,2-dimethyl-pent-4-en-1-yl)amino-methylylidene-biscarbamate



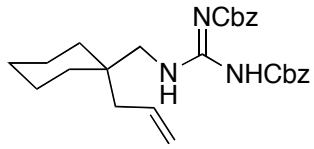
1e

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 87 % yield.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 0.84 (s, 6H), 1.94 (d, *J* = 7.6 Hz, 2H), 3.19 (d, *J* = 5.6 Hz, 2H), 4.96 (m, 1H), 5.00 (m, 1H), 5.03 (s, 2H), 5.08 (s, 2H), 5.71 (ddt, *J* = 7.6, 9.4, 17.5 Hz, 1H), 7.14-7.32 (m, 10H), 8.41 (s, 1NH). ^{13}C NMR ($CDCl_3$,

100MHz): δ = 24.80, 34.08, 44.11, 50.30, 66.90, 67.91, 117.80, 127.67, 127.88, 128.19, 128.27, 128.49, 128.57, 133.96, 134.41, 136.70, 153.83, 156.20, 163.62. MS(EI) m/z = 423.2 $[M]^+$ (10), 382.2 (5), 341.1 (5), 288.2 (7), 208.1 (15), 181.1 (10), 166.1 (5), 124.0 (5), 108.0 (25), 91.0 (100), 79.0 (25), 55.1 (10). HRMS. calc.: 423,2158, found: 423.2140. IR (FT-IR, Ge): ν = 3326, 3078, 3033, 2959, 2903, 1729, 1648, 1628, 1428, 1388, 1349, 1329, 1253, 1209, 1146, 1054, 989, 912, 749.

Dibenzyl(1-allylcyclohexyl-methyl)amino-methylydene-biscarbamate

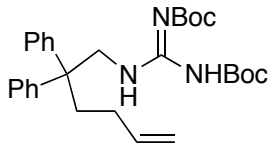


1f

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 85 % yield.

^{1}H NMR ($CDCl_3$, 400MHz): δ =1.20-1.52 (m, 10H), 2.07 (d, *J* = 7.6 Hz, 2H), 3.31 (d, *J* = 5.3 Hz, 2H), 5.00-5.08 (m, 2H), 5.09 (s, 2H), 5.14 (s, 2H), 5.76 (ddt, *J* = 7.6 , 10.2, 17.2 Hz, 1H), 7.15-7.40 (m, 10H), 8.42 (s, 1NH). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 21.16, 21.22, 25.96, 33.45, 36.47, 40.18, 66.94, 67.97, 117.83, 127.72, 127.88, 128.26, 128.33, 128.56, 128.64, 133.66, 134.46, 136.80, 153.89, 156.19, 163.69. MS (EI, eV): m/z (%): 463.3 $[M]^+$ (10), 422.2 (15), 420.1 (8), 348.2 (6), 328.2 (14), 314.1 (5), 271.1 (3), 248.1 (15), 228.1 (20), 206.1 (5), 189.1 (5), 152.1 (5), 123.1 (7), 108.0 (43), 91.0 (100), 79.0 (22), 77.0 (15), 65.1 (5), 51.0 (3). HRMS: calcd for $C_{27}H_{33}N_3O_4$: 463,2471 found: 463.2446. IR (FT-IR, Ge): ν = 2926, 2854, 1753, 1620, 1452, 1395, 1341, 1298, 1258, 1163, 1127, 1086, 1010, 740.

Bis-*tert*-butyl(2,2-diphenyl-hex-5-en-1-yl)amino-methylylidene-biscarbamate

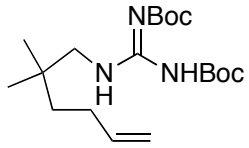


3a

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 96 % yield.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 1.40 (s, 9H), 1.50 (s, 9H), 1.79-1.87 (m, 2H), 2.13-2.20 (m, 2H), 4.14 (d, *J* = 5.0 Hz, 2H), 4.88 (d, *J* = 10.2 Hz, 1H), 4.95 (d, *J* = 17.2 Hz, 1H), 5.73 (ddt, *J* = 6.7, 10.2, 17.2 Hz, 1H), 7.14-7.32 (m, 10H), 8.09 (s, 1NH). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 27.88, 28.23, 28.77, 36.56, 47.73, 50.15, 78.99, 82.66, 114.37, 126.34, 128.00, 128.12, 138.64, 145.44, 152.62, 156.38, 163.53. MS (EI): m/z = 493.3 (50) [M+], 437.2 (10), 420.2 (10), 381.1 (15), 364.2 (30), 340.1 (15), 234.1 (30), 221.1 (80), 216.1 (50), 180.1 (30), 167.1 (50), 160.0 (100), 143.1 (20), 117.1 (20), 98.0 (15), 91.0 (30). HRMS. calcd for $C_{29}H_{39}N_3O_4$: 493.2941, found: 493.2935. IR (KBr): ν = 3678, 3433, 3322, 3290, 3090, 3065, 3025, 2979, 2951, 2932, 1725, 1647, 1578, 1449, 1410, 1359, 1340, 1272, 1253, 1225, 1145, 1057, 1016, 908, 808, 769, 756, 700, 668.

Bis-*tert*-butyl(2,2-dimethyl-hex-5-en-1-yl)amino-methylylidene-biscarbamate



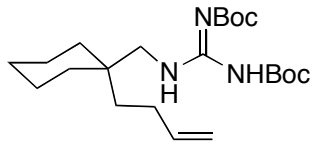
3b

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 90 % yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.92 (s, 6H), 1.31 (m, 2H), 1.47 (s, 18H), 2.01 (dtt, *J* = 1.2, 6.4, 10.4 Hz, 2H), 3.22 (d, *J* = 5.2 Hz, 2H), 4.89 (ddt, *J* = 0.8, 1.2, 10.0 Hz, 1H), 4.98 (dtt, *J* = 1.2, 1.2, 17.2 Hz, 1H), 5.76 (ddt, *J* = 6.4, 10.0, 17.2 Hz, 1H), 8.46 (br, 1NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 25.26, 28.15, 28.38, 28.45, 33.72, 38.99, 50.64, 79.17, 83.06, 114.28, 139.14, 153.48, 156.62, 163.76. MS (EI, eV): m/z (%): 369.3 $[M]^+$ (8), 313.2 (10), 296.2 (6), 273.2 (4), 257.1 (100),

240.1 (58), 212.1 (14), 203.1 (45), 196.1 (8), 161.0 (96), 148.0 (42), 143.0 (10), 117.0 (12), 98.0 (19), 86.0 (4), 69.1 (8), 57.1 (54). HRMS calcd for $C_{19}H_{35}N_3O_4$: 369.2628 found: 369.2633. IR (FT-IR, Ge): ν = 3381, 3328, 2963, 2932, 1721, 1646, 1618, 1412, 1364, 1339, 1254, 1138, 1058, 809.

Bis-*tert*-butyl(1-but-3-en-1-yl-cyclohexyl-methyl)amino-methylydene-biscarbamate

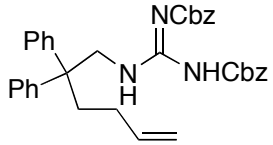


3c

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 92 % yield.

^{1}H NMR ($CDCl_3$, 400MHz): δ =1.20-1.45 (m, 12H), 1.47 (s, 18H), 1.92-2.01 (m, 2H), 3.28 (d, *J* = 5.0 Hz, 2H), 4.87 (dd, *J* = 1.8, 10.2 Hz, 1H), 4.97 (dd, *J* = 1.8, 17.0 Hz, 1H), 5.75 (ddt, *J* = 6.4, 10.2, 17.0 Hz, 1H), 8.39 (t, *J* = 5.0 Hz, 1NH). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 21.23, 26.09, 27.34, 27.94, 28.19 33.75, 34.58, 35.70, 47.02, 78.88, 82.77, 114.03, 139.11, 153.28, 156.39. 163.60. MS (ESI-LCMS): m/z (%): 410.5 $[M+H]^+$ (100). HRMS: calcd for $C_{22}H_{39}N_3O$: 409.2941, found: 409.2954 IR (FT-IR, Ge): ν = 3336, 2977, 2924, 2851, 1720, 1643, 1615, 1447, 1411, 1365, 1339, 1250, 1135, 1056, 810, 765.

Dibenzyl(2,2-diphenyl-hex-5-en-1-yl)amino-methylylidene-biscarbamate

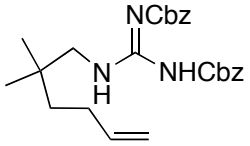


3d

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 88 % yield.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 1.82-1,92 (m, 2H), 2.19-2.26 (m, 2H), 4.22 (d, *J* = 5.3 Hz, 2H), 4.91 (dd, *J* = 1.7, 10.2 Hz, 1H), 4.96 (dd, *J* = 1.7, 17.2 Hz, 1H), 5.09 (s, 2H), 5.17 (s, 2H), 5.75 (ddt, *J* = 6.4, 10.2, 17.2 Hz, 1H), 7.21-7.46 (m, 20H), 8.12 (t, *J* = 5.3 Hz, 1NH). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 28.60, 36.59, 48.03, 49.91, 66.97, 67.86, 114.48, 126.47, 127.78, 127.88, 127.92, 128.23, 128.30, 128.36, 128.49, 128.59, 134.45, 136.74, 138.29, 145.02, 153.29, 156.10, 163.62. MS (ESI-LCMS): m/z (%): 562.6 $[M+H]^+$ (100). HRMS: calcd for $C_{35}H_{35}N_3O_4$: 561.2628, found: 561.2614 IR (FT-IR, Ge): ν = 2961, 2928, 2858, 1729, 1649, 1615, 1425, 1388, 1345, 1261, 1245, 1208, 1151, 1085, 1052, 909, 804.

Dibenzyl(2,2-dimethyl-hex-5-en-1-yl)amino-methylylidene-biscarbamate

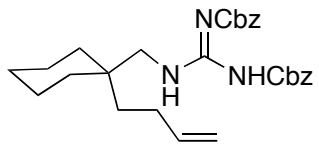


3e

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 95 % yield.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 0.85 (s, 6H), 1.22-1.29 (m, 2H), 1.91-1.99 (m, 2H), 3.20 (d, *J* = 5.3 Hz, 2H), 4.84 (ddd, *J* = 1.5, 1.9, 10.2 Hz, 1H), 4.92 (ddd *J* = 1.5, 1.9, 17.2 Hz, 1H), 5.04 (s, 2H), 5.08 (s, 2H), 5.70 (ddt, *J* = 6.4, 10.2, 17.2 Hz, 1H), 7.14-7.35 (m, 10 H), 8.40 (t, *J* = 5.3 Hz, 1NH). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 24.89, 28.14, 33.58, 38.77, 50.51, 66.87, 67.89, 114.17, 127.66, 127.88, 128.17, 128.25, 128.56, 134.39, 138.67, 153.83, 156.17, 163.60. MS (EI, eV): m/z (%): 437.3 $[M]^+$ (8), 383.2 (5), 341.2 (8), 302.2 (10), 286.2 (5), 222.1 (10), 189.1 (11), 108.0 (22), 91.0 (100), 79.0 (12), 55.1 (8). HRMS: calcd for $C_{25}H_{31}N_3O_4$: 437.2315. found: 437.2321. IR (FT-IR, Ge): ν = 3327, 3089, 3034, 2962, 3894, 1731, 1649, 1626, 1581, 1429, 1389, 1350, 1322, 1254, 1207, 1141, 1053, 911, 746.

Dibenzyl(1-but-3-en-1-yl-cyclohexyl-methyl)amino-methylidene-biscarbamate

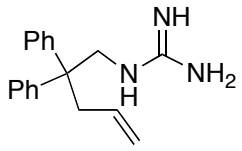


3f

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 94 % yield.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 1.16-1.43 (m, 12H), 1.86-1.95 (m, 2H), 3.27 (d, *J* = 5.3 Hz, 2H), 4.83 (dd, *J* = 1.5, 10.2 Hz, 1H), 4.91 (dd, *J* = 1.5, 17.0 Hz, 1H), 5.04 (s, 2H), 5.08 (s, 2H), 5.70 (ddt, *J* = 6.7, 10.2, 17.0 Hz, 1H), 7.14-7.32 (m, 10H), 8.35 (t, *J* = 5.3 Hz, 1NH). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 21.18, 25.98, 27.25, 33.63, 34.60, 35.68, 47.05, 66.88, 67.93, 114.19, 127.69, 127.89, 128.21, 128.30, 128.51, 128.60, 134.42, 136.75, 138.84, 153.89, 156.14, 163.64. MS (EI): m/z = 477.2 (10)[M^+], 369.2 (10), 342.2 (10), 326.2 (10), 262.1 (10), 235.1 (10), 189.1 (10), 108.0 (50), 107.0 (40), 95.1 (25), 91.0 (100), 79.1 (40), 77.0 (20). HRMS calcd for $C_{28}H_{35}N_3O_4$: 477.2628, found: 477.2625. IR (KBr): ν = 3674, 3440, 3329, 3069, 3034, 2930, 2855, 1725, 1655, 1629, 1589, 1498, 1455, 1425, 1391, 1338, 1274, 1262, 1237, 1197, 1146, 1051, 907, 804, 742, 695, 670, 584.

N-2,2-Diphenyl-pent-4-en-1-ylguanidine



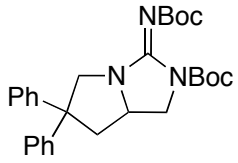
8

A 0.16 mmol sample of **1a** was stirred in 1mL TFA for 1h. Then 5 mL Et_2O and 5 mL H_2O were added and the reaction was quenched by addition of Na_2CO_3 until pH≥8 was reached. The mixture was separated and the aqueous phase extracted with Et_2O (3x10 mL). The organic extracts were combined, dried over

$MgSO_4$ and concentrated to give the free guanidine as analytically pure compound.

^{1}H NMR ($CDCl_3$/MeOD, 400MHz): δ = 2.90 (d, *J* = 6.8 Hz, 2H), 3.80 (s, 2H), 4.98 (dd, *J* = 1.2, 10.4 Hz, 1H), 5.06 (dd, *J* = 1.2, 17.2 Hz, 1H), 5.29 (ddd, *J* = 6.8, 10.4, 17.2 Hz, 1H), 6.83 (br, 1NH), 7.14 (d, *J* = 8.0 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.28 (dd, *J* = 7.6, 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$/MeOD, 100 MHz): δ = 40.94, 47.75, 49.42, 118.73, 126.67, 127.45, 128.28, 133.04, 144.21, 157.45. MS (ESI-LCMS): m/z (%): 280.6 $[M+H]^+$ (3), 179.2 (100), 165.2 (98), 91.3 (74). HRMS (MALDI-TOFTOF) calcd for $C_{18}H_{22}N_3^+$: 280.1808, found: 280.1790. IR (FT-IR, Ge): ν = 3378, 3196, 3096, 3032, 2983, 2961, 2937, 1683, 1658, 1625, 1201, 1181, 1137, 837, 801, 757, 722, 700.

tert-Butyl 3-(_tert_-butoxycarbonylimino)-6,6-diphenyltetrahydro-1_H_-pyrrolo[1,2-_c_]imidazole-2(3_H_)-carboxylate



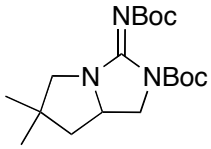
2a

Synthesised according to the general diamination procedures using $CuBr_2$ and $CuCl_2$. Isolated as a white solid, respective yields see Schemes 1 and 2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 9H), 1.51 (s, 9H), 2.37 (t, *J* = 9.2 Hz, 1H), 2.54 (dd, *J* = 4.8, 11.2 Hz, 1H), 3.52 (d, *J* = 11.2 Hz, 1H), 3.72 (dd, *J* = 7.0, 9.7 Hz, 1H), 3.97 (m, 1H), 4.05 (dd, *J* = 9.7, 9.9 Hz, 1H), 4.46 (d, *J* = 11.2 Hz, 1H), 7.15-7.32 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.93, 28.01, 43.97, 50.00, 55.86, 57.02, 57.14, 79.18, 82.53, 126.27, 126.49, 126.58, 126.70, 126.78, 128.35, 128.39, 128,47, 145.02, 149.44, 153.76. MS (EI, eV): m/z (%): 477.3 $[M]^+$ (4), 421.3 (4), 366.2 (20), 348.2 (40), 322.2 (70), 304.2 (20), 278.2 (16), 222.2 (8), 179.1 (20), 142.1 (12), 128.1 (20), 123.1 (26), 110.1 (18), 98.1 (30), 91.1 (15), 84.1 (10), 57.1 (100). HRMS calcd for $C_{28}H_{35}N_3O_4$: 477.2628,

found: 477.2632. IR (FT-IR, Ge): ν [cm^{-1}] = 3323, 3286, 3026, 3003, 2981, 2931, 1732, 1646, 1616, 1447, 1408, 1354, 1327, 1252, 1142, 1053, 810, 758, 700.

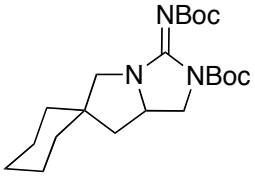
(*E*)-*tert*-Butyl 3-(*tert*-butoxycarbonylimino)-6,6-dimethyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-2(3*H*)-carboxylate



2b

Synthesised according to the general diamination procedures using $CuBr_2$ and $CuCl_2$. Isolated as a white solid, respective yields see Schemes 1 and 2.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, 6H), 1.44 (s, 18H), 1.82 (dd, *J* = 6.0, 12.0 Hz, 1H), 2.98 (d, *J* = 10.8 Hz, 1H), 3.09 (d, *J* = 10.8 Hz, 1H), 3.53 (dd, *J* = 7.2, 10.4 Hz, 1H), 4.02 (dd, *J* = 8.8, 10.4 Hz, 1H), 4.14 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.54, 28.63, 28.12, 28.24, 41.56, 46.46, 50.78, 56.92, 59.89, 78.89, 82.43, 149.69, 154.36, 159.64. MS (EI, eV): m/z (%): 354.4 $[M]^+$ (10), 298.1 (5), 280.1 (5), 254.1 (10), 242.0 (50), 224.0 (100), 198.1 (95), 180.0 (70), 154.0 (56), 123.0 (16), 110.0 (10), 98.0 (32), 83.0 (6), 57.0 (52). HRMS: calcd for $C_{18}H_{31}N_3O_4$: 353.2315 found: 353.2310. IR (FT-IR, Ge): ν [cm^{-1}] = 3000, 2969, 2958, 2930, 2871, 1737, 1681, 1616, 1382, 1367, 1315, 1260, 1147, 1097.

***tert*-Butyl 3'-(*tert*-butoxycarbonylimino)tetrahydrospiro[cyclohexane-1,6'-pyrrolo[1,2-*c*]imidazole]-2'(3'*H*)-carboxylate**

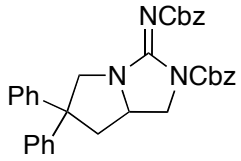


2c

Synthesised according to the general diamination procedures using $CuBr_2$ and $CuCl_2$. Isolated as a white solid, respective yields see Schemes 1 and 2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9H), 1.40 (s, 9H), 1.2-1.5 (m, 10H), 1.90 (dd, *J* = 5.8, 12.3 Hz, 1H), 2.98 (d, *J* = 11.4 Hz, 1H), 3.13 (d, *J* = 11.7 Hz, 1H), 3.46 (dd, *J* = 6.7, 10.2 Hz, 1H), 3.95 (t, *J* = 11.8 Hz, 1H), 4.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7, 23.6, 25.5, 27.8, 27.9, 35.5, 37.3, 44.2, 45.2, 50.5, 55.7, 57.2, 78.5, 82.0, 149.4, 153.9, 159.4. MS (EI, eV): m/z (%): 393.3 $[M]^+$ (10), 338.2 (5), 293.2 (5), 282.2 (50), 264.2 (90), 238.2 (100), 220.2 (60), 194.2 (40), 142.1 (20), 138.1 (40), 98.0 (15), 57.1 (30). HRMS calcd for $C_{21}H_{35}N_3O_4$: 393.2628, found: 393.2623. IR (FT-IR, Ge): ν [cm^{-1}] = 2928, 2857, 1737, 1680, 1619, 1383, 1366, 1314, 1267, 1142, 1075, 1004.

Benzyl 3-(benzyloxycarbonylimino)-6,6-diphenyltetrahydro-1*H*-pyrrolo-[1,2-*c*]imidazole-2(3*H*)-carboxylate

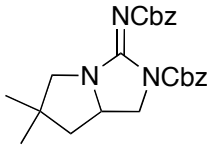


2d

Synthesised according to the general diamination procedures using $CuBr_2$ and $CuCl_2$. Isolated as a white solid, respective yields see Schemes 1 and 2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (t, *J* = 11.4 Hz, 1H), 2.57 (dd, *J* = 4.7, 11.4 Hz, 1H), 3.41 (d, *J* = 11.4 Hz, 1H), 3.73 (dd, *J* = 7.9, 10.2 Hz, 1H), 3.99 (m, 1H), 4.13 (dd *J* = 8.8, 10.2 Hz, 1H), 4.33 (d, *J* = 11.4 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 5.15 (d, *J* = 12.3 Hz, 1H), 5.16 (d, *J* = 12.3 Hz, 1H), 5.25 (d, *J* = 12.3 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 2H), 7.17-7.21 (m, 4H), 7.24-7.33 (m, 10H), 7.38-7.42 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.88, 50.18, 56.03, 56.58, 57.25, 67.25, 68.17, 126.36, 126.73, 126.90, 127.66, 128.09, 128.15, 128.20, 128.26, 128.45, 128.49, 128.57, 135.18, 136.79, 144.69, 144.95, 150.96, 153.95, 159.93. MS (ESI-LCMS): m/z: 568.2 (M+Na), 546.3 (M+H), 520.3, 478.2, 435.2, 412.2, 368.2. HRMS (ESI-MicroTOF) calcd for $C_{34}H_{32}N_3O_4^+$: 546.2393, found: 546.3284. IR (FT-IR, Ge): ν [cm^{-1}] = 2960, 2927, 1781, 1718, 1651, 1496, 1450, 1389, 1335, 1297, 1259, 1217, 1162, 1126, 1083, 913, 803, 757.

Benzyl 3-(benzyloxycarbonylimino)-6,6-dimethyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-2(3*H*)-carboxylate

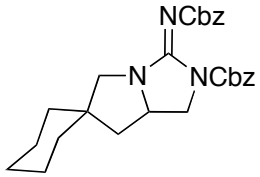


2e

Synthesised according to the general diamination procedures using $CuBr_2$ and $CuCl_2$. Isolated as a white solid, respective yields see Schemes 1 and 2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 3H), 1.12 (s, 3H), 1.43 (dd, *J* = 9.2, 12.1 Hz, 1H), 1.88 (dd, *J* = 5.6, 12.1 Hz, 1H), 2.93 (d, *J* = 11.2 Hz, 1H), 3.06 (d, *J* = 11.2 Hz, 1H), 3.06 (d, *J* = 7.0, 9.3 Hz, 1H), 4.17 (pst, *J* = 9.0 Hz, 1H), 4.23 (m, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.26 (d, *J* = 12.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.3, 27.4, 41.6, 46.0, 50.7, 56.9, 59.4, 67.1, 68.0, 127.6, 128.0, 128.1, 128.2, 128.2, 128.4, 135.2, 136.8, 151.0, 154.0, 159.8. MS (EI, eV): m/z (%): 421.2 $[M]^+$ (44), 314.2 (10), 287.2 (52), 270.2 (18), 231.1 (4), 224.1 (30), 180.1 (28), 153.1 (20), 123.0 (4), 91.0 (100), 65.1 (4), 55.1 (6). HRMS calcd for $C_{24}H_{27}N_3O_4$: 421.2002, found: 421.2006. IR (FT-IR, Ge): ν [cm^{-1}] = 3365, 3065, 3034, 2959, 2894, 1786, 1751, 1720, 1642, 1599, 1458, 1390, 1339, 1299, 1262, 1170, 1107, 1012, 802, 737.

Benzyl 3'-(benzyloxycarbonylimino)tetrahydrospiro[cyclohexane-1,6'-pyrrolo[1,2-*c*]imidazole]-2'(3'*H*)-carboxylate

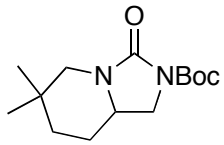


2f

Synthesised according to the general diamination procedures using $CuBr_2$ and $CuCl_2$. Isolated as a white solid, respective yields see Schemes 1 and 2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18-1.41 (m, 11 H), 1.92 (dd, *J* = 5.2, 12.4 Hz, 1H), 2.88 (d, *J* = 11.6 Hz, 1H), 3.06 (d, *J* = 11.6 Hz, 1H), 3.55 (td, *J* = 8.0, 11.2 Hz, 1H), 4.06 (m, 2H), 5.00 (d, *J* = 12.4 Hz, 1H), 5.04 (d, *J* = 12.4 Hz, 1H), 5.06 (d, *J* = 12.4 Hz, 1H), 5.14 (d *J* = 12.4 Hz, 1H), 7.17-7.34 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.68, 23.58, 25.49, 35.59, 37.34, 43.89, 45.58, 50.75, 56.15, 57.16, 67.08, 68.03, 127.57, 128.00, 128.10, 128.17, 128.39, 135.20, 136.87, 151.01, 153.98, 159.89. MS (ESI, eV): m/z: 945.5(2M+H), 812.4, 484.2(M+Na), 462.2(M+H), 328.2, 304.3, 227.0. HRMS calcd for $C_{27}H_{31}N_3O_4Na^+$: 483.2217, found: 483.2211.IR (FT-IR, Ge): ν [cm^{-1}] = 2925, 2853, 1753, 1720, 1618, 1451, 1394, 1297, 1258, 1165, 1125, 1085, 744.

tert-Butyl 6,6-dimethyl-3-oxohexahydroimidazo[1,5-*a*]pyridine-2(1*H*)-carboxylate

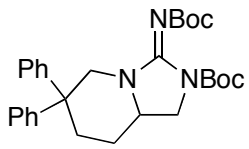


4

Synthesised according to general diamination conditions using $CuBr_2$. Isolated in 85% as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (s, 6H), 0.96 (m, 1H), 1.34 (dd, *J* = 3.6, 14.4 Hz, 1H), 1.43 (m, 1H), 1.50 (s, 9H), 1.68 (m, 1H), 2.43 (d, *J* =13.2 Hz, 1H), 3.33 (m, 2H), 3.54 (dd, *J* = 2.0, 13.2 Hz, 1H), 3.89 (td, *J* = 11.6 Hz, 4.4 Hz, 1H), 7.93 (br, 1NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.29, 27.74, 28.10, 28.24, 28.68, 30.13, 36.61, 47.38, 50.57, 51.41, 56.11, 82.00, 151.00, 153.09. MS (EI, eV): m/z (%): 268.2 $[M]^+$ (20), 253.2 (2), 212.1 (3), 195.1 (18), 168.1 (100), 153.1 (6), 139.1 (2), 125.1 (2), 112.0 (8), 99.0 (48), 85.0 (4), 69.1 (2), 57.1 (34). HRMS calcd $C_{14}H_{24}N_2O_3$: 268,1787 found: 268.1783. IR (FT-IR, Ge): ν [cm^{-1}] = 2961, 1754, 1436, 1360, 1338, 1268, 1170, 1116, 1084, 1008, 772.

***tert*-Butyl 3-(*tert*-butoxycarbonylimino)-6,6-diphenylhexahydroimidazo-[1,5-*a*]pyridine-2(1*H*)-carboxylate**

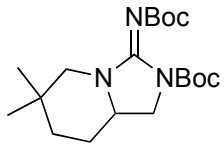


5a

Synthesised according to the general diamination procedure using $CuCl_2$. Isolated as a white solid, respective yields see Scheme 2.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.47 (s, 9H), 1.50 (m, 1), 1.57 (s, 9H), 1.91 (dq, *J* = 3.2, 13.2 Hz, 1H), 2.32 (dt, *J* = 2.6, 13.2 Hz, 1H), 2.66 (dq, *J* = 2.9, 13.8 Hz, 1H), 2.82 (d, *J* = 14 Hz, 1H), 3.23 (t, *J* = 10.2 Hz, 1H), 3.59-3.69 (m, 1H), 4.05 (dd, *J* = 8.2, 10.2 Hz, 1H), 4.92 (dd, *J* = 2.1, 14.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 26.71, 28.03, 28.27, 33.68, 45.71, 49.64, 50.78, 53.10, 78.78, 82.32, 126.07, 126.51, 126.60, 127.64, 128.29, 128.57, 143.74, 146.45, 149.87, 150.45, 159.12. MS (EI, eV): m/z (%): 491.2 (40), 435.2 (25), 391.2 (40), 362.1 (100), 335.1 (70), 318.1 (40), 291.1 (50), 180.1 (40), 165.0 (25), 142.0 (15), 124.0 (60), 98.0 (20), 91.0 (15), 57.1 (30). HRMS calcd for $C_{29}H_{37}N_3O_4$: 491.2784, found: 491.2791. IR (FT-IR, Ge): ν [cm^{-1}] = 3061, 2975, 2929, 2865, 1750, 1679, 1617, 1450, 1368, 1274, 1142, 800.

***tert*-Butyl 3-(*tert*-butoxycarbonylimino)-6,6-dimethylhexahydroimidazo-[1,5-*a*]pyridine-2(1*H*)-carboxylate**



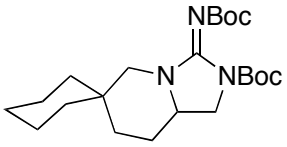
5b

Synthesised according to the general diamination procedure using $CuCl_2$. Isolated as a white solid, respective yields see Scheme 2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (s, 3H), 0.91 (s, 3H), 1.28 (m, 1H), 1.44 (s, 9H), 1.46 (s, 9H), 1.45 (m, 2H), 1.71 (dd, *J* = 3.6 Hz, 12.8 Hz, 1H), 2.41 (d, *J* = 12.8 Hz, 1H), 3.37 (m, 2H), 3.68 (dd, *J* = 1.6 Hz, 12.8 Hz, 1H), 4.01 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.20, 27.13, 27.91, 28.14, 28.55, 29.98, 36.29, 50.68, 52.36, 53.27, 78.51, 82.12, 149.97, 151.21, 159.28. MS (EI, eV): m/z (%) = 368.5 $[M]^+$ (1), 312.4 (4), 255.9 (1), 212.2 (100), 168.2 (35). HRMS calcd for $C_{19}H_{33}N_3O_4$: 367.2471, found: 367.2479. IR (FT-IR, Ge): ν [cm^{-1}] = 2961, 2930, 1752, 1700, 1434, 1392, 1361, 1269, 1250, 1160, 1117, 1082, 1050, 1025, 1008, 854, 773.

tert-Butyl 3'-(_tert_-butoxycarbonylimino)tetrahydro-1'_H_-spiro[cyclohexane-1,6'-imidazo[1,5-_a_]pyridine]-2'(3'_H_)-carboxylate

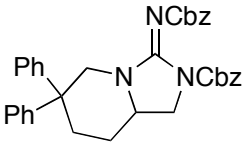


5c

Synthesised according to the general diamination procedure using $CuCl_2$. Isolated as a white solid, respective yields see Scheme 2.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.12-1.54 (m, 12H), 1.45 (s, 9H), 1.47 (s, 9H), 1.65-1.72 (m, 2H), 2.31 (d, *J* = 13.2 Hz, 1H), 3.35-3.46 (m, 2H), 3.97-4.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.24, 21.35, 26.35, 26.49, 28.00, 30.65, 32.57, 34.20, 37.88, 50.12, 50.72, 53.51, 78.42, 82.14, 149.99, 151.38, 159.21. MS (EI, eV): m/z (%): 408.3 $[M]^+$ (10), 407.2 (25), 351.2 (25), 295.1 (55), 278.1 (100), 251.1 (75), 208.1 (25), 206.1 (20), 143.0 (20), 57.1 (20). HRMS calcd for $C_{22}H_{38}N_3O_4^+$: 408.2857, found: 408.2865. IR (FT-IR, Ge): ν [cm^{-1}] = 2973, 2927, 2847, 1774, 1741, 1706, 1678, 1619, 1450, 1363, 1259, 1160, 1104, 1012, 855, 769.

Benzyl 3-(benzyloxycarbonylimino)-6,6-diphenylhexahydroimidazo[1,5-_a_]-pyridine-2(1_H_)-carboxylate

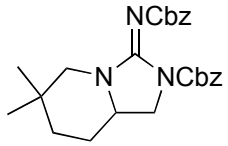


5d

Synthesised according to the general diamination procedure using $CuCl_2$. Isolated as a white solid, respective yields see Scheme 2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (ddd, *J* = 2.4 Hz, 12.4, 13.6 Hz, 1H), 1.90 (qd, *J* = 3.2 Hz, 13.6 Hz, 1H), 2.32 (dt, *J* = 3.2 Hz, 13.6 Hz, 1H), 2.69 (qd, *J* = 2.8 Hz, 12.4 Hz, 1H), 2.88 (d, *J* = 14.0 Hz, 1H), 3.32 (t, *J* = 10.4 Hz, 1H), 3.66 (m, 1H), 4.16 (dd, *J* = 8.4 Hz, 10.4 Hz, 1H), 4.95 (dd, 2.4 Hz, 14.0 Hz, 1H), 5.07 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 7.13- 7.45 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.72, 33.52, 45.73, 49.67, 50.48, 52.98, 67.23, 68.20, 126.16, 126.38, 126.56, 127.40, 127.55, 128.16, 128.21, 128.36, 128.42, 128.47, 128.63, 135.03, 137.06, 143.35, 146.16, 149.95, 151.13, 159.44. MS (EI, eV): m/z (%): 560.5 $[M]^+$ (100), 516.5 (28), 473.4 (12), 452.3 (10), 408.3 (4), 380.3 (4), 91.3 (11). HRMS calcd for $C_{35}H_{33}N_3O_4$: 559.2471, found: 559.2470. IR (FT-IR, Ge): ν [cm^{-1}] = 3064, 2948, 2886, 1761, 1669, 1613, 1487, 1403, 1269, 1190, 1165, 1147, 1116, 1099, 1041, 736.

Benzyl 3-(benzyloxycarbonylimino)-6,6-dimethylhexahydroimidazo-[1,5-*a*]pyridine-2(1*H*)-carboxylate



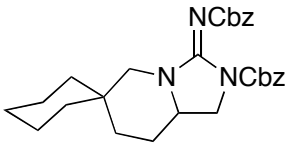
5e

Synthesised according to the general diamination procedure using $CuCl_2$. Isolated as a white solid, respective yields see Scheme 2.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.86 (s, 3H), 0.87 (s, 3H), 1.25 (dd, *J* = 10.8, 14.4 Hz, 1H), 1.44 (ddd, *J* = 3.6, 10.8, 14.0 Hz, 2H), 1.68 (m, 1H), 2.39 (d, *J* = 13.2 Hz, 1H), 3.37 (m, 1H), 3.42 (dd, *J* = 8.4, 10.0 Hz, 1H), 3.63 (dd, *J* = 1.6, 12.8 Hz, 1H), 4.06 (dd, *J* = 8.0, 9.6 Hz, 1H), 4.97 (s, 2H), 5.02 (d, *J* = 12.0 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 7.15-7.31 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.16, 27.20, 28.53, 30.09, 36.13, 50.39, 52.50, 53.10, 67.12, 68.14, 127.44, 128.05, 128.19, 128.29, 128.34, 128.43, 135.09, 137.04, 150.80, 151.29, 159.64. MS (EI,

eV): m/z (%) = 435.2 $[M]^+$ (4), 302.2 (60), 257.2 (5), 195.1 (7), 168.1 (100), 151.1 (12), 108.0 (24), 91.0 (77), 79.0 (11), 65.0 (6). HRMS calcd for $C_{25}H_{29}N_3O_4$: 435.2158, found: 435.2163. IR (FT-IR, Ge): ν [cm^{-1}] = 3035, 2950, 1759, 1674, 1622, 1454, 1400, 1337, 1268, 1219, 1177, 1154, 1115, 1042, 753, 733, 711.

Benzyl 3'-(benzyloxycarbonylimino)tetrahydro-1'*H*-spiro[cyclohexane-1,6'-imidazo[1,5-*a*]pyridine]-2'(3'*H*)-carboxylate



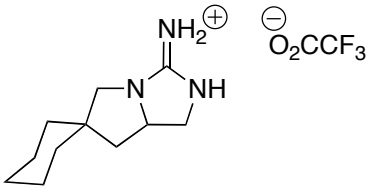
5f

Synthesised according to the general diamination procedure using $CuCl_2$. Isolated as a white solid, respective yields see Scheme 2.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.09-1.51 (m, 12H), 1.64 (dt, *J* = 2.8, 14.3 Hz, 2H), 2.28 (d, *J* = 13.5 Hz, 1H), 3.38-3.46 (m, 2H), 3.97-4.09 (m, 2H), 4.97 (s, 2H), 5.00 (d, *J* = 12.3 Hz, 1H), 5.09 (d, *J* = 12.3 Hz, 1H), 7.14-7.32 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.28, 21.42, 26.31, 26.57, 30.67, 32.68, 34.33, 37.89, 50.05, 50.50, 53.49, 67.15, 68.20, 127.47, 128.11, 128.20, 128.37, 128.40, 128.50, 135.19, 137.20, 150.94, 151.38, 159.72. MS (ESI-LCMS): m/z (%): 476 $[M+H]^+$ (100). HRMS (MALDI-TOFTOF) calcd for $C_{28}H_{34}N_3O_4^+$: 476.2544, found: 476.2501. IR (FT-IR, Ge): ν [cm^{-1}] = 2926, 2850, 1761, 1671, 1617, 1452, 1400, 1267, 1175, 1156, 1109, 1042, 753.

Deprotection procedures

Tetrahydro-1'*H*-spiro[cyclohexane-1,6'-pyrrolo[1,2-*c*]imidazole]-2'(3'*H*)-imine hydrotrifluoroacetate

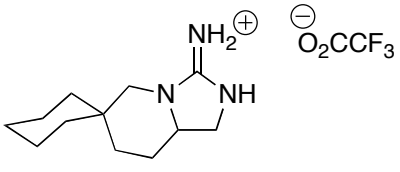


6

The *N*,*N'*-bis-Boc protected guanidine **2c** (0.15 mmol) is treated with trifluoroacetic acid (1 mL) in dichloromethane (1 mL) and stirred for 60 min at room temperature. The solution is then concentrated under reduced pressure to yield the analytically pure deprotected guanidine in 99% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36-1.61 (m, 11H), 2.05 (dd, *J* = 6.1, 12.6 Hz, 1H), 3.15 (d, *J* = 11.1 Hz, 1H), 3.22 (d, *J* = 11.1 Hz, 1H), 3.53 (dd, *J* = 4.1, 9.1 Hz, 1H), 3.87 (pst, *J* = 9.3 Hz, 1H), 4.28 (m, 1H), 6.5-7.7 (br, 2NH), 8.46 (s, 1NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.86, 23.62, 25.44, 35.60, 37.63, 43.09, 45.90, 47.39, 57.36, 60.98, 161.59 (TFA anion not detected).

Tetrahydro-1'H-spiro[cyclohexane-1,6'-imidazo[1,5-a]pyridin]-3'(2'H)-imine hydrotrifluoroacetate



7

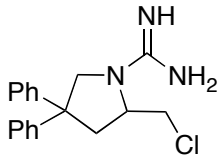
The *N*,*N'*-bis-Boc protected guanidine **5c** (0.5 mmol) is treated with neat trifluoroacetic acid (1 mL) and stirred for 30 min at room temperature. Diethyl ether (10 mL) is added and the reaction is quenched by careful addition of solid

Na_2CO_3. When the CO_2 evolution ceases, 10 mL of H_2O are added and the addition of Na_2CO_3 is continued until pH = 11. The organic layer is separated and the aqueous phase is extracted with diethyl ether (3 x 15 mL), dried and concentrated under reduced pressure to yield the analytically pure deprotected guanidine in 99% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20-1.50 (m, 11H), 1.91 (m, 2H), 1.86 (d, *J* = 14.0 Hz, 1H), 2.62 (d, *J* = 13.6 Hz, 1H), 3.23 (dd, *J* = 6.4, 8.8 Hz, 1H), 3.69 (m, 1H), 3.72 (d, *J* = 14.0 Hz, 1H), 3.77 (d, *J* = 8.8 Hz, 1H), 7.76 (br, 2NH), 8.53 (br, 1NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.05, 21.31, 25.84, 26.22, 30.55, 33.04, 33.25, 37.34, 47.33, 50.99, 58.37, 158.00 (TFA anion not detected). MS (ESI-LCMS): m/z (%): 208.3 (100), 84.1 (8). HRMS (MALDI-TOFTOF) calcd for $C_{12}H_{22}N_3^+$: 208.1808, found: 208.1824. IR (FT-IR, Ge): ν [cm^{-1}] = 3355, 2931, 2853, 1668, 1579, 1452, 1202, 1133, 836, 801, 720.

Aminochlorination and Aminoacetoxylation Procedures

2-(Chloromethyl)-4,4-diphenylpyrrolidine-1-carboximidamide



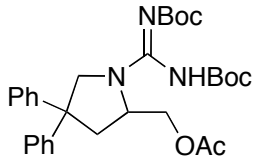
9

Synthesised under the conditions of the general diamination procedure for guanidines using $CuCl_2$ as oxidant.

^{1}H NMR (MeOH-d_4, 400 MHz): δ = 2.78 (dd, *J* = 8.8, 12.8 Hz, 1H), 2.95 (ddd, *J* = 1.6, 6.8, 12.8 Hz, 1H), 3.59 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.83 (m, 2H), 4.14 (ddd, *J* = 2.0, 6.8, 12.4 Hz, 1H), 4.40 (dd, *J* = 1.6, 10.8 Hz, 1H), 7.10-7.26 (m, 10H). ^{13}C NMR (MeOH-d_4, 100 MHz): δ = 40.47, 43.55, 52.58, 56.81, 57.84, 125.65, 126.16, 126.71, 128.16, 128.51, 128.65, 143.33, 143.63, 155.02. MS (ESI-LCMS): m/z (%): 314.3 $[M+H]^+$ (63), 196.2 (27), 91.5 (27), 78.39 (100). HRMS (MALDI-TOFTOF) calcd for $C_{18}H_{21}ClN_3^+$: 314.1419, found: 314.1435. IR (FT-IR,

Ge): ν [cm^{-1}] = 3351, 3168, 2957, 2936, 1660, 612, 1497, 1437, 1388, 1202, 1180, 1132, 802, 730.

(1-(*N*,*N*'-bis(*tert*-Butoxycarbonyl)carbamimidoyl)-4,4-diphenylpyrrolidin-2-yl)methyl ethanoate



10

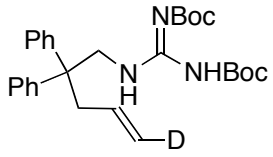
A solution of the precursor **1a** (0.45 mmol, 1.0 eq.), oxidant (0.90 mmol, 2.0 eq.), sodium acetate (0.45 mmol, 1.0 eq.) and $Pd(OAC)_2$ (0.045 mmol, 10% mol) in CH_2Cl_2 (4.5 mL) was stirred overnight at room temperature. The reaction was quenched by addition of sat. aqueous $Na_2S_2O_3$ solution, the organic phase was separated and the aqueous phase extracted with dichloromethane several times. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by flash-chromatography on silica gel (dichloromethane) to give compound **10** in 90% yield.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 18H), 1.99 (s, 3H), 2.56 (dd, *J* = 10.4, 12.0 Hz, 1H), 2.71 (ddd, *J* = 1.6, 6.8, 12.4 Hz, 1H), 3.92 (d, *J* = 12.0 Hz, 4.18 (t, *J* = 10.4 Hz), 4.33 (br, 1H), 4.53 (br, 1H), 7.05-7.23 (10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.90, 28.11, 52.61, 56.32, 59.66, 63.04, 79.20, 81.96, 126.26, 126.59, 126.65, 126.65, 128.54, 128.69, 143.97, 145.01, 150.31, 154.01, 170.96. MS (EI, eV): m/z (%): 537.4 $[M]^+$(18), 477.4 (20), 425.3 (3), 408.3 (5), 390.3 (2), 381.3 (10), 363.3 (12), 347.2 (2), 338.2 (5), 320.2 (10), 290.2 (30), 276.2 (4), 260.2 (40), 222.2 (30), 205.2 (45), 192.1 (13), 180.1 (25), 165.1 (20), 144.1 (12), 141.1 (20), 123.1 (20), 97.1 (8), 91.1 (22), 69.1 (5), 59.1 (100), 56.1 (58). HRMS calcd for $C_{30}H_{39}N_3O_6$: 537.2839, found: 537.2847. IR (FT-IR, Ge): ν [cm^{-1}] =

3055, 3028, 3009, 2978, 2931, 2899, 1745, 1636, 1611, 1419, 1367, 1295, 1233, 1141, 1116, 1061.

Stereochemical Analysis

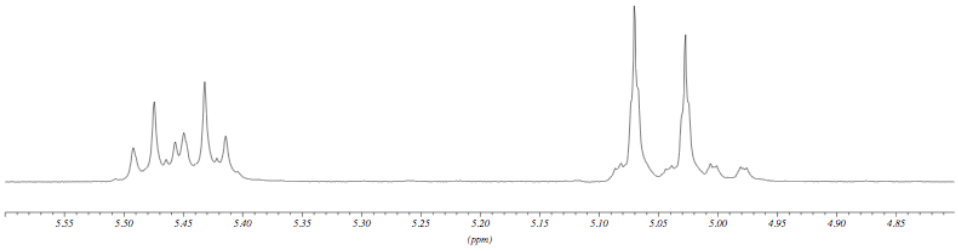
Synthesis of labelled compound (*E*)-1a-d_1: Selectively deuterated guanidine **(*E*)-1a-d_1**, was prepared according to the general procedure for starting material synthesis using selectively labelled allylic bromide.[4] The latter was obtained following a literature procedure using Schwartz reagent. The labelled allylic bromide was used as described before to obtain the guanidines.



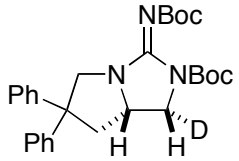
(*E*)-1a-d_1

90% Deuteration grade.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 1.49 (s, 9H, 2.92 (dd, *J* = 1.2, 7.2 Hz, 2H), 4.10 (d, *J* = 4.8 Hz, 2H), 5.00 (dd, *J* = 1.6, 17.2 Hz, 1H), 5.42 (td, *J* = 7.2, 17.2 Hz, 1H), 7.18-7.33 (m, 10H), 8.23 (t, *J* = 4.8 Hz, 1NH). ^{13}C NMR (100 MHz, CDCL3): δ = 27.83, 28.17, 41.92, 47.75, 49.87, 78.94, 82.64, 118.20 (t, *J* = 25.0 Hz), 126.33, 128.00, 128.02, 133.37, 144.99, 152.70, 156.17. IR (FT-IR, Ge): ν = 3305, 2980, 2935, 1786, 1726, 1634, 1560, 1415, 1367, 1324, 1136, 1057, 814, 756, 701.

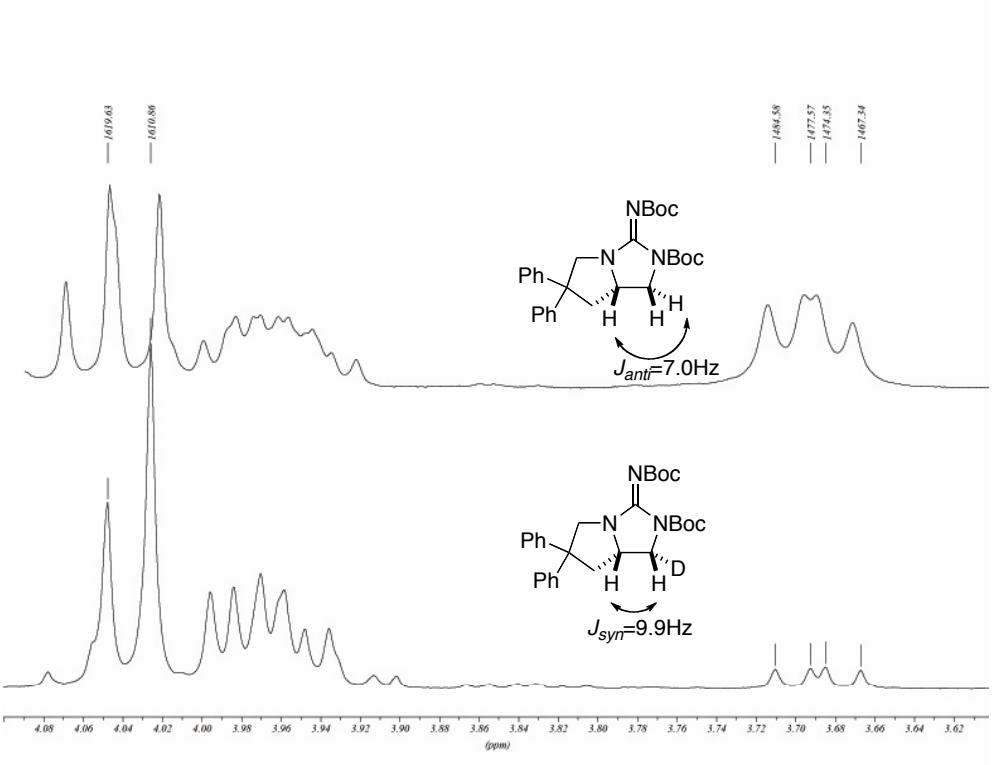


Deuterated compound **(*E*)-1a-d$_1$** underwent clean diamination to a single diastereomeric product. From the coupling constant of the resulting isomer of **2a-d$_1$** the relative *syn*-configuration could be unambiguously determined.



2a-d$_1$

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 9H), 1.42 (s, 9H), 2.24 (dd, *J* = 10.4, 11.2 Hz, 1H), 2.44 (dd, *J* = 4.8, 11.2 Hz, 1H), 3.41 (d, *J* = 11.2 Hz, 1H), 3.87 (ddd, *J* = 4.8 Hz, 9.2 Hz, 10.4 Hz, 1H), 3.94 (d, J_{syn} = 9.2 Hz, 1H), 4.35 (d, *J* = 11.2 Hz, 1H), 7.06-7.24 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.97, 28.05, 44.03, 49.66 (t, *J* = 21.5 Hz), 55.63, 56.98, 57.14, 78.99, 82.40, 126.27, 126.60, 126.74, 126.80, 128.41, 128.51, 145.15, 145.35, 149.45, 153.82, 159.66. MS (ESI-LCMS): m/z (%): 479.3 $[M+H]^+$ (1), 423.4 (5), 367.3 (22), 323.4 (100), 297.3 (5), 279.3 (67), 237.2 (5). IR (FT-IR, Ge): ν [cm^{-1}] = 2966, 2930, 1748, 1635, 1559, 1451, 1368, 1255, 1128, 847, 771.



Data on X-Ray Structure Determination

Compound 5d:

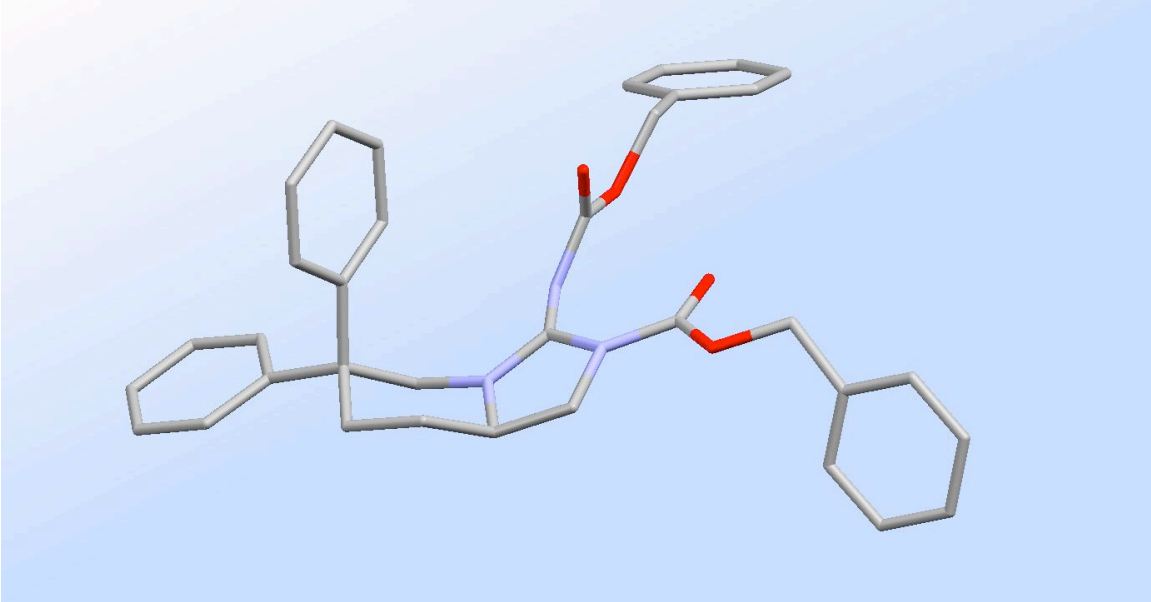


Table S-1. Crystal data and structure refinement for **5d**.

Identification code	streuff1
Empirical formula	C33 H33 N3 O4
Formula weight	559.64
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 9.9630(5)A alpha = 89.717(3) deg. b = 10.0620(5)A beta = 76.596(3)deg. c = 15.7850(5)A gamma = 67.802(2)deg
Volume	1419.21(11)A^3
Z, Calculated density	2, 1.310 Mg/m^3
F(000)	592

Crystal size	0.40 x 0.35 x 0.30 mm
Diffractometer	Nonius KappaCCD
Theta range for data collection	1.33 to 27.50 deg.
Reflections collected / unique	9485 / 6465 [R(int) = 0.0218]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6465 / 0 / 388
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0480, wR2 = 0.1300
R indices (all data)	R1 = 0.0755, wR2 = 0.1162

Compound 7:

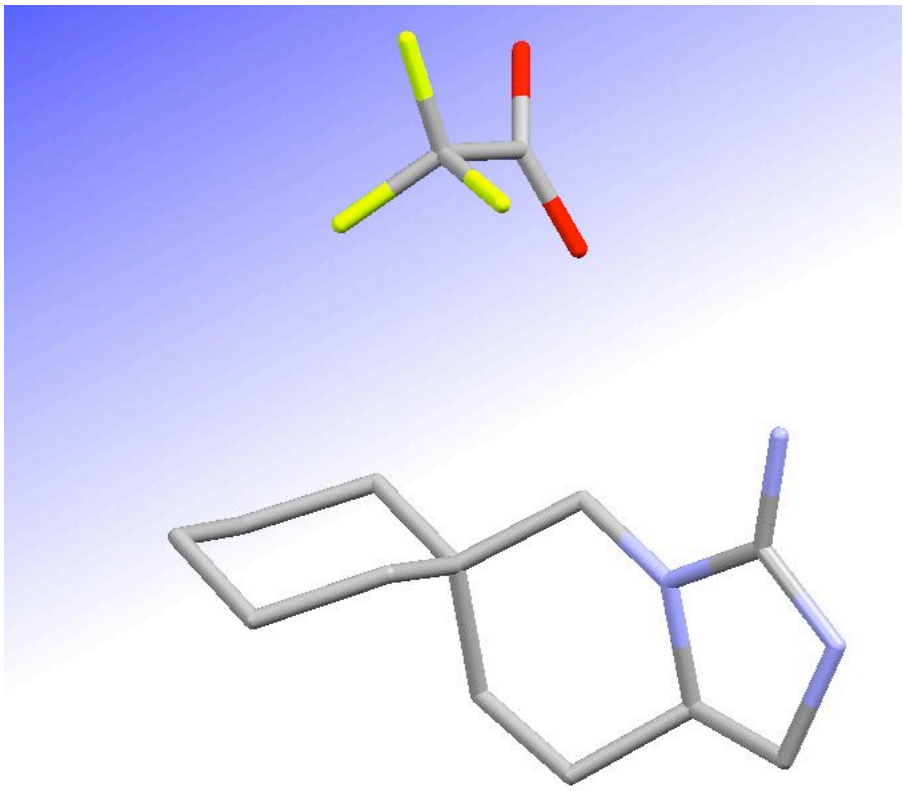
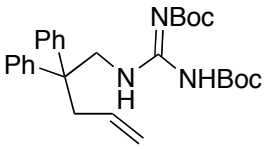


Table S-1. Crystal data and structure refinement for **7**.

Identification code	streuff6
Empirical formula	C14 H22 F3 N3 O2
Formula weight	321.35
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, *P* $2_1/c$
Unit cell dimensions	a = 13.8901(9)A b = 5.9564(2) beta = 120.178(3)deg. c = 22.1517(11)A
Volume	1584.33(14)A^3

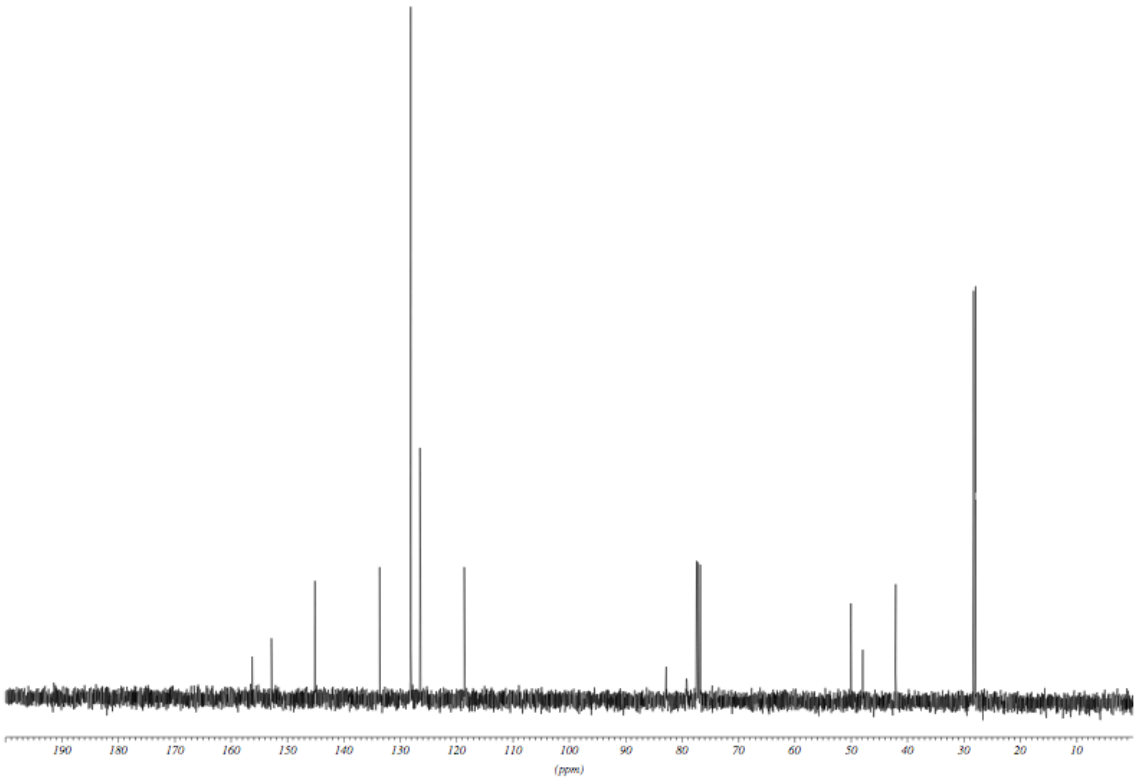
Z, Calculated density	4, 1.347 Mg/m^3
Absorption coefficient	0.114 mm^-1
Absorption coefficient	0.086 mm^-1
F(000)	680
Crystal size	0.30 x 0.20 x 0.10 mm
Diffractometer	Nonius KappaCCD
Theta range for data collection	1.70 to 27.54 deg.
Reflections collected / unique	9509 / 3631 [R(int) = 0.0515]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3631 / 0 / 208
Goodness-of-fit on F^2	1.038
Final R indices [I>2sigma(I)]	R1 = 0.0710, wR2 = 0.2096
R indices (all data)	R1 = 0.1240, wR2 = 0.1798

Spectral Reproduction of Starting Materials and Products


NBoc
Ph
Ph
N
H
NHBoc

1a

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


190
180
170
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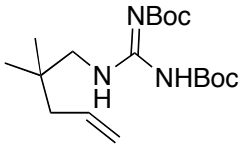
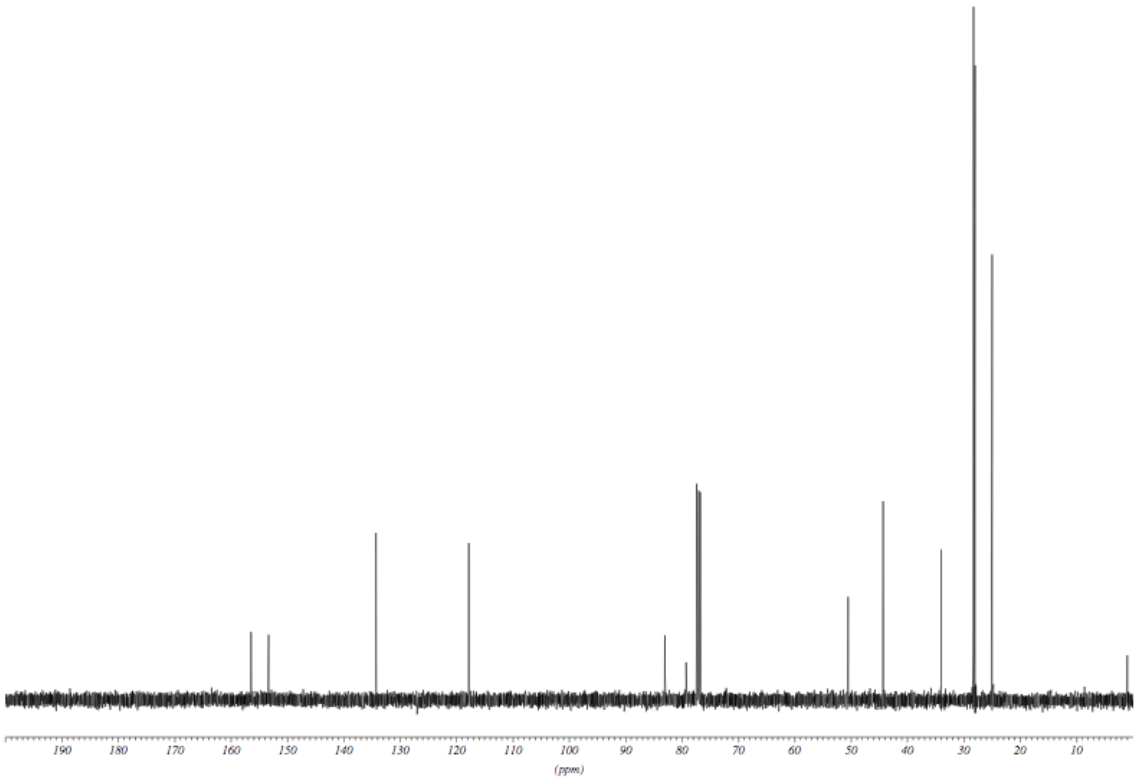
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


NBoc
N
H
NHBoc

1b

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)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180
170
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90
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70
60
50
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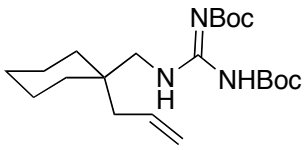
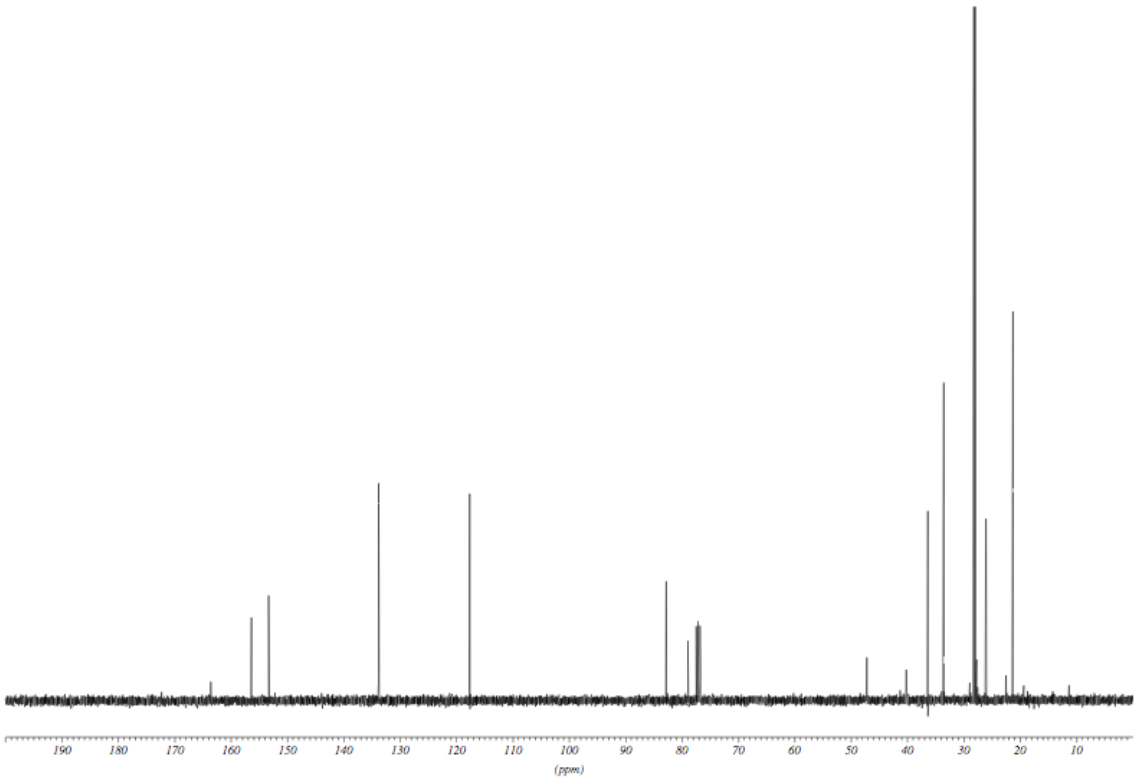
30
20
10
(ppm)


NBoc
N
H
NHBoc

1c

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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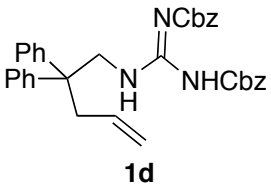
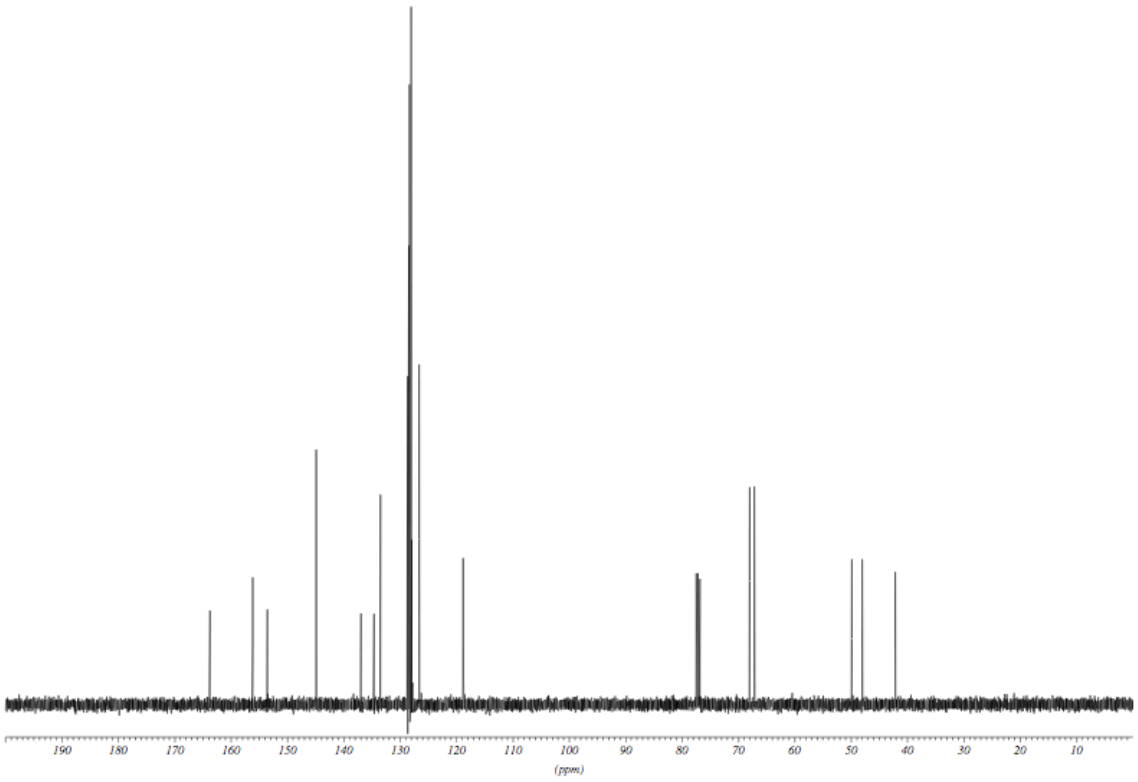
(ppm)


NCbz
Ph
Ph
N
H
NHCbz

1d

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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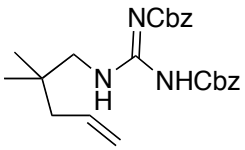
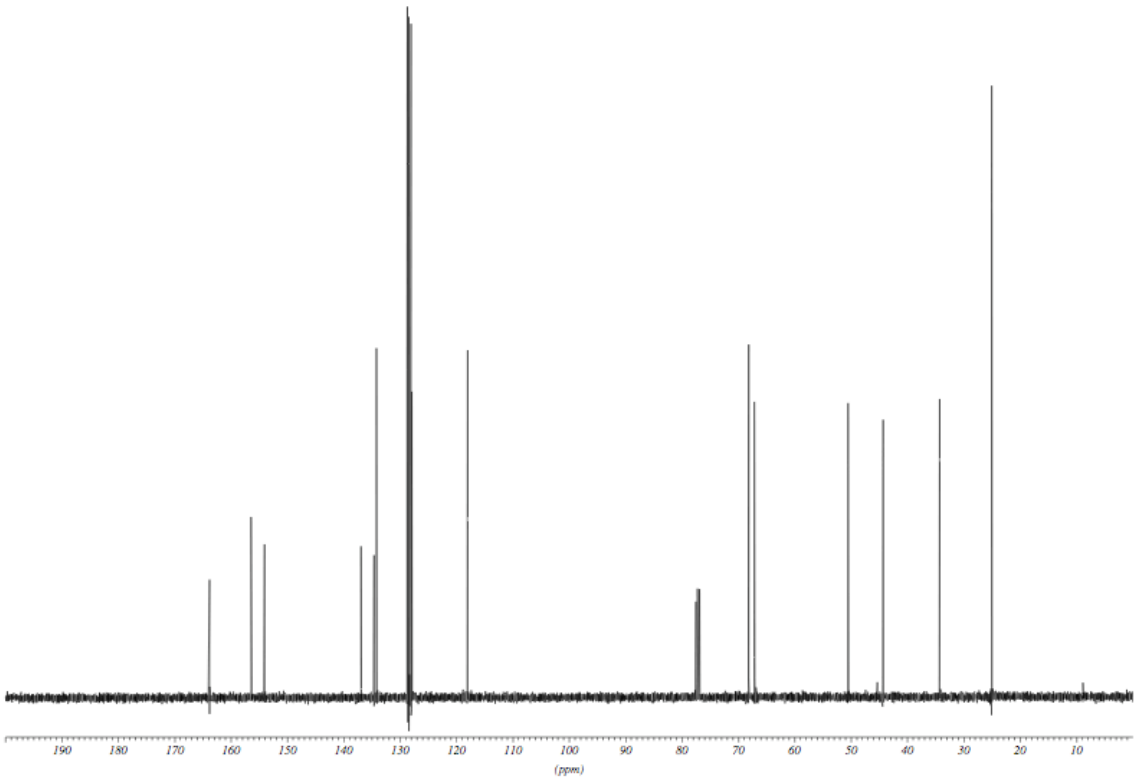
(ppm)


NCbz
N
H
NHCbz

1e

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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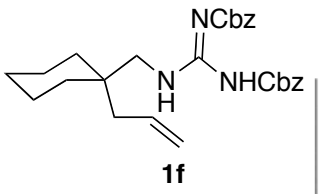
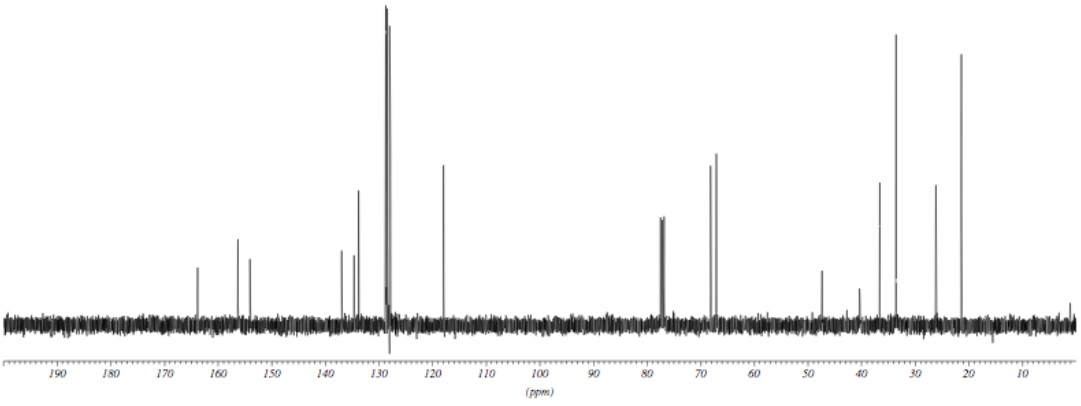
(ppm)


NCbz
N
H
NHCbz

1f

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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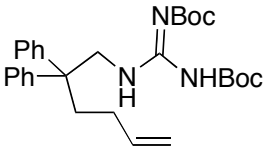
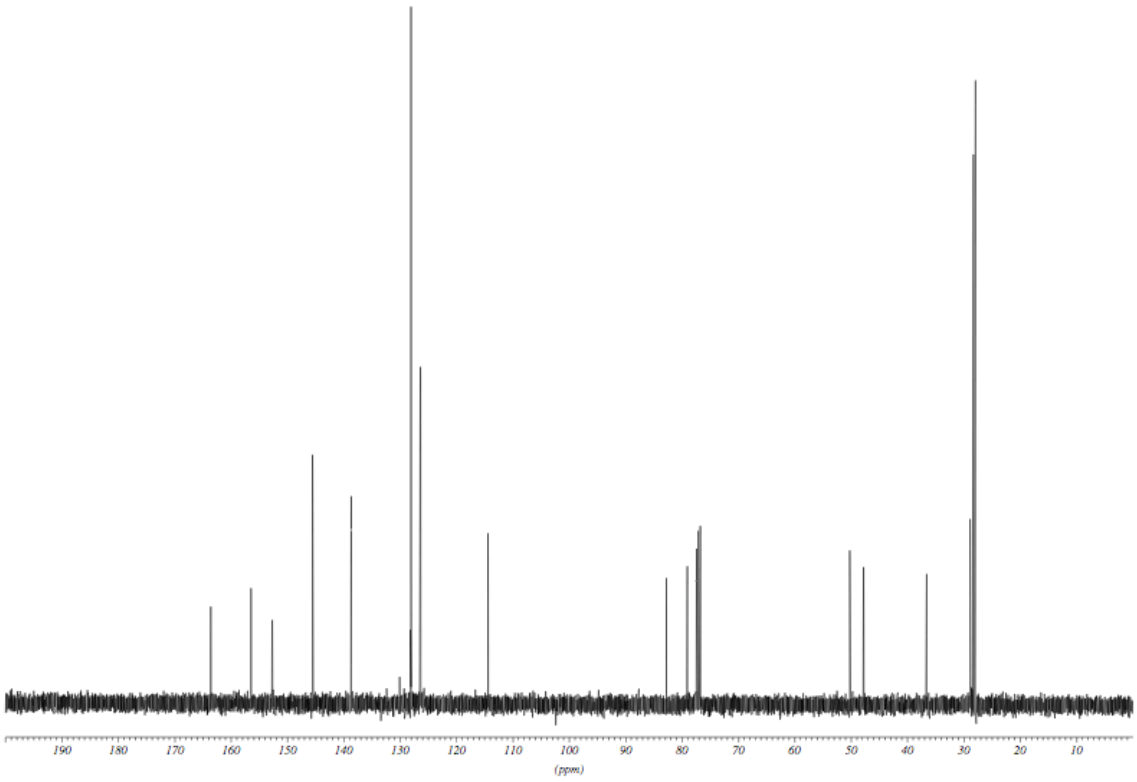
(ppm)


NBoc
Ph
Ph
N
H
NHBoc

3a

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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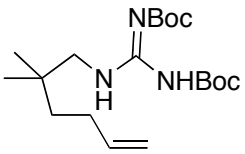
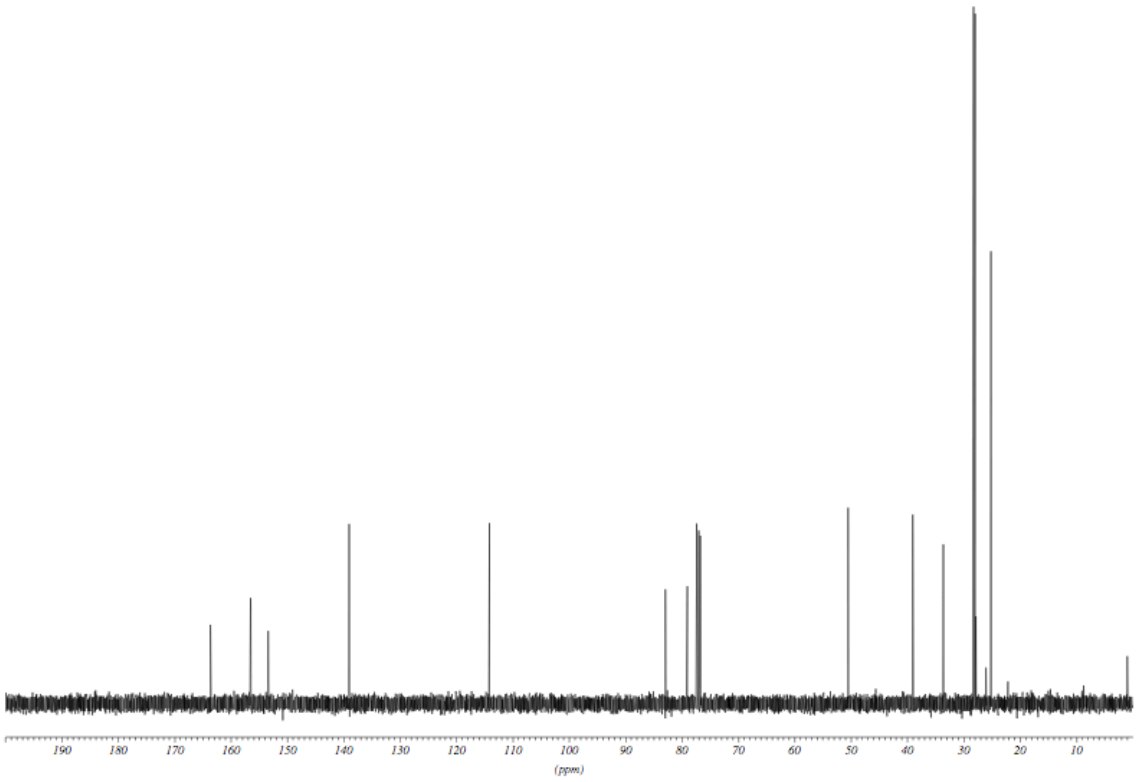
(ppm)


NBoc
N
H
NHBoc

3b

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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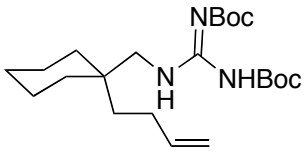
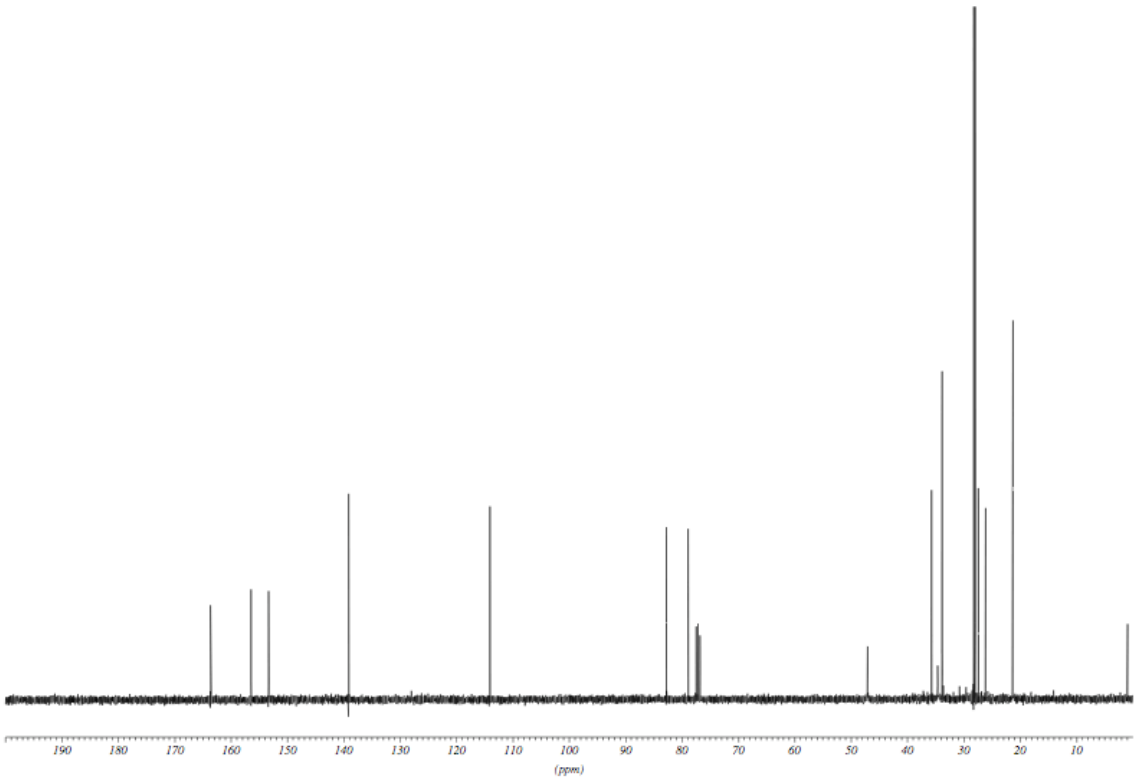
(ppm)


NBoc
N
H
NHBoc

3c

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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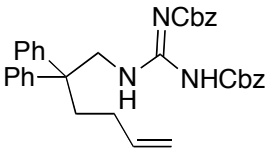
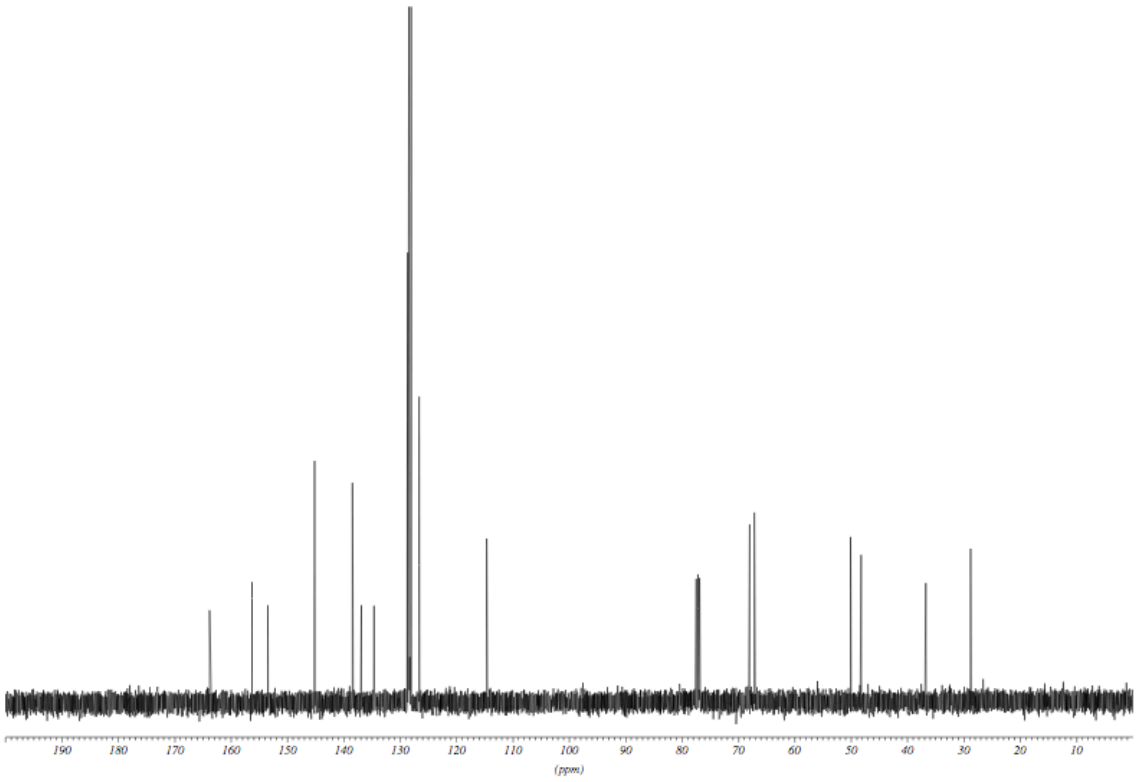
(ppm)


NCbz
Ph
Ph
N
H
NHCbz

3d

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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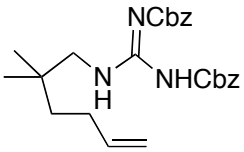
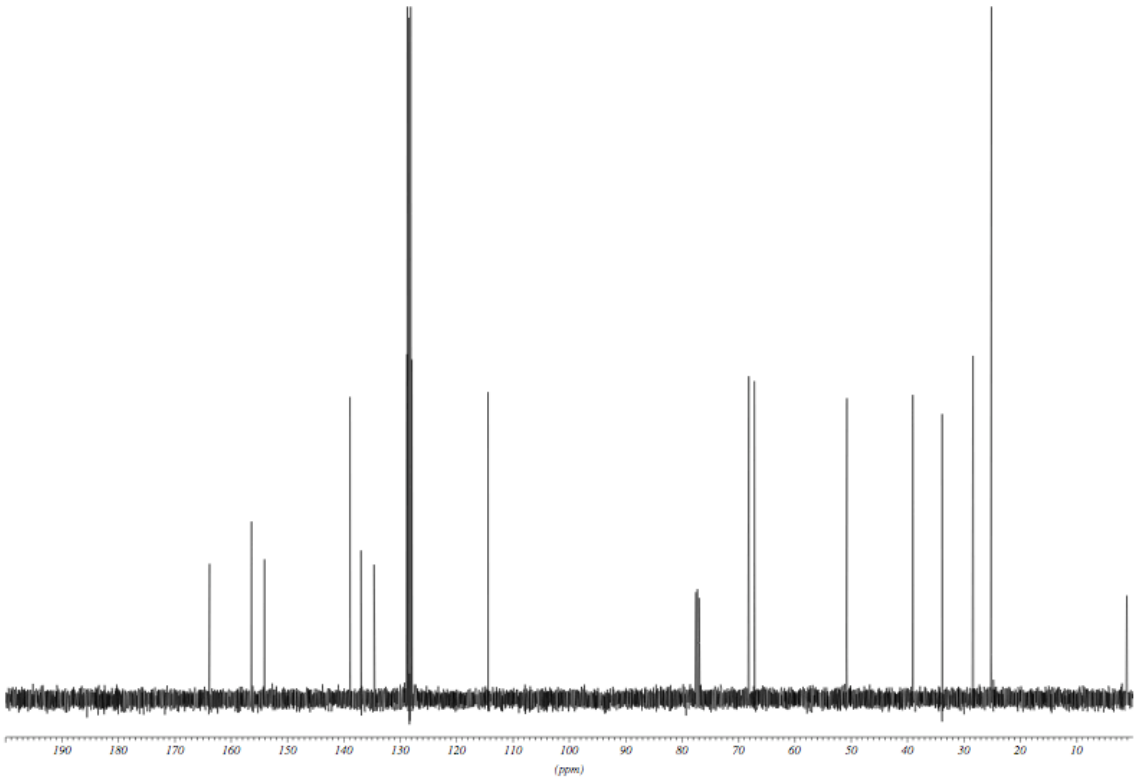
(ppm)


NCbz
N
H
NHCbz

3e

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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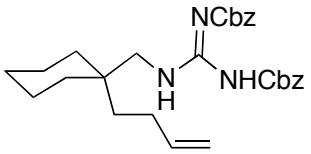
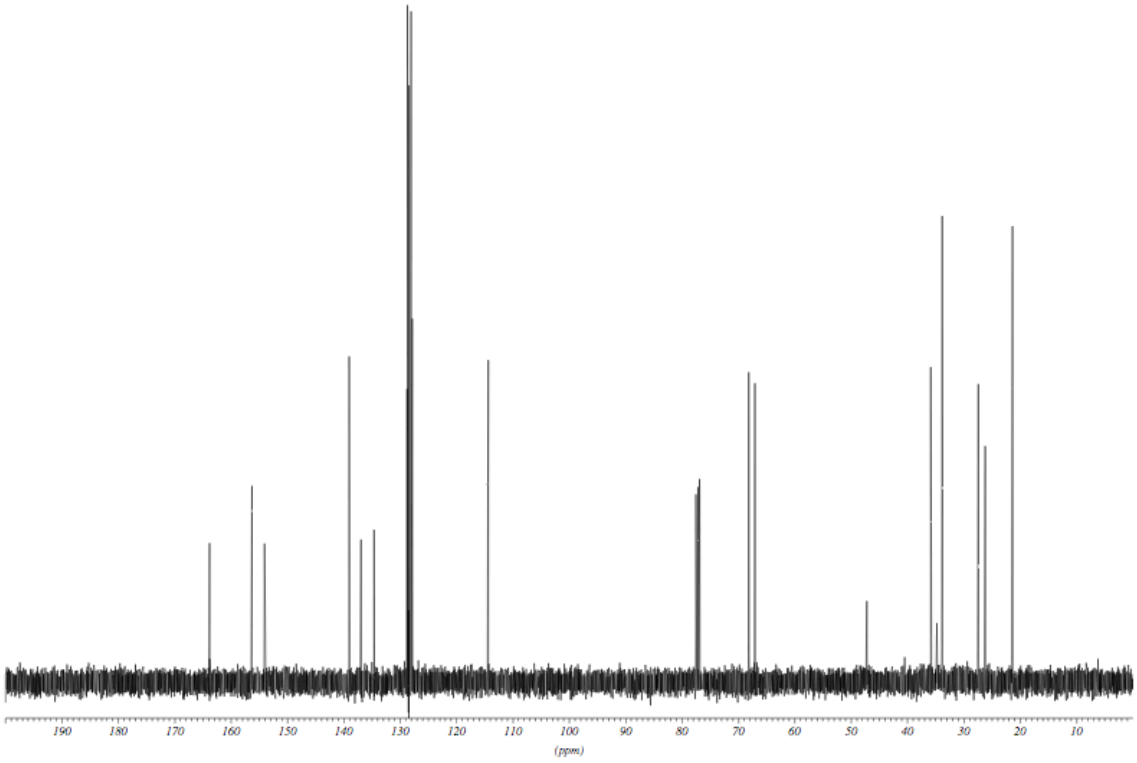
(ppm)


NCbz
N
H
NHCbz

3f

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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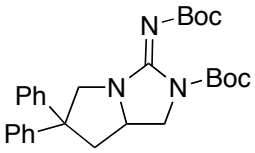
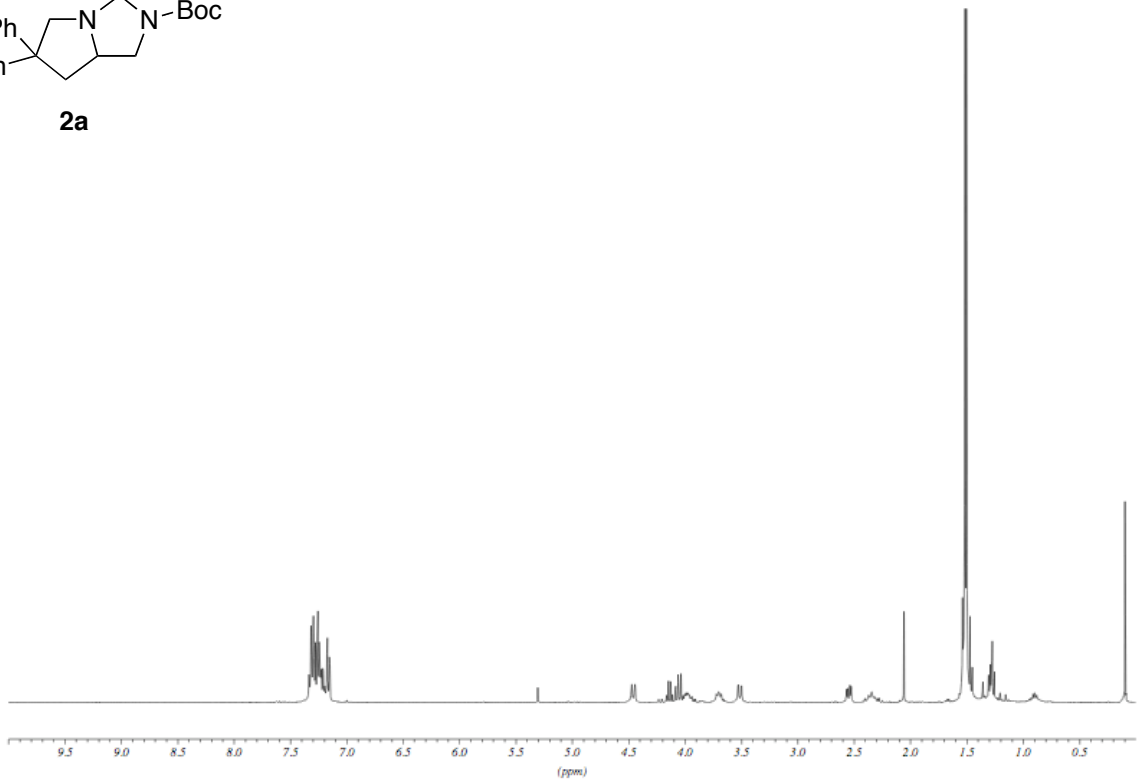
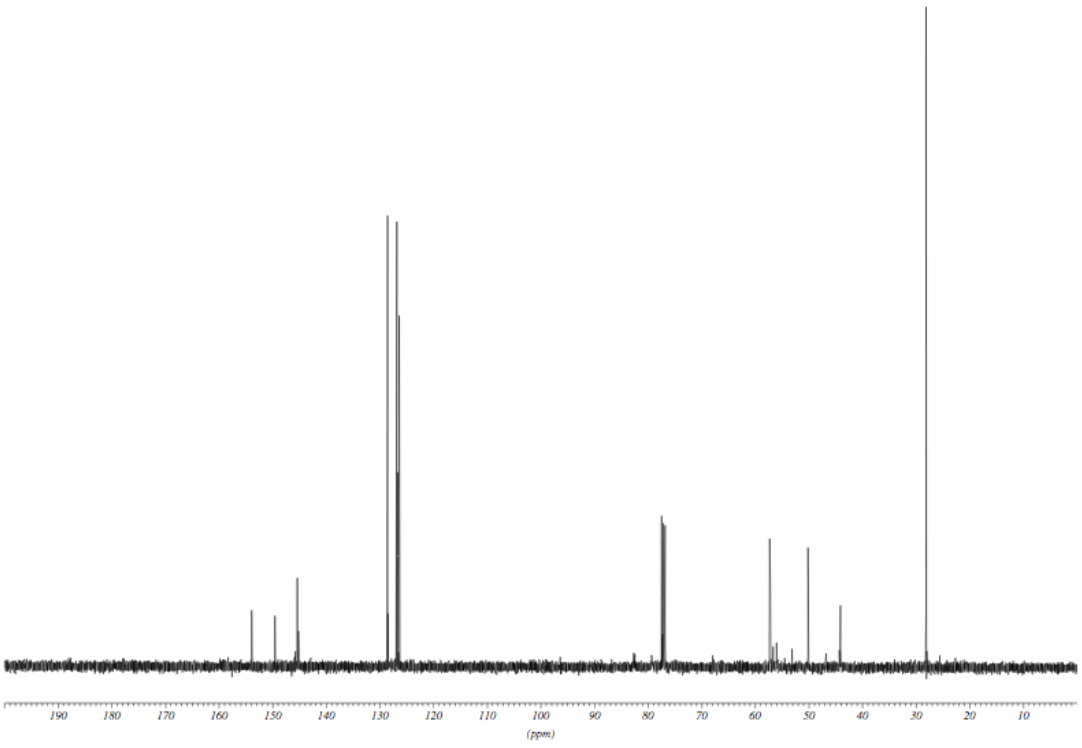
(ppm)


N–Boc
N
N–Boc
Ph
Ph

2a


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)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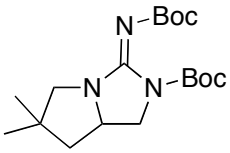
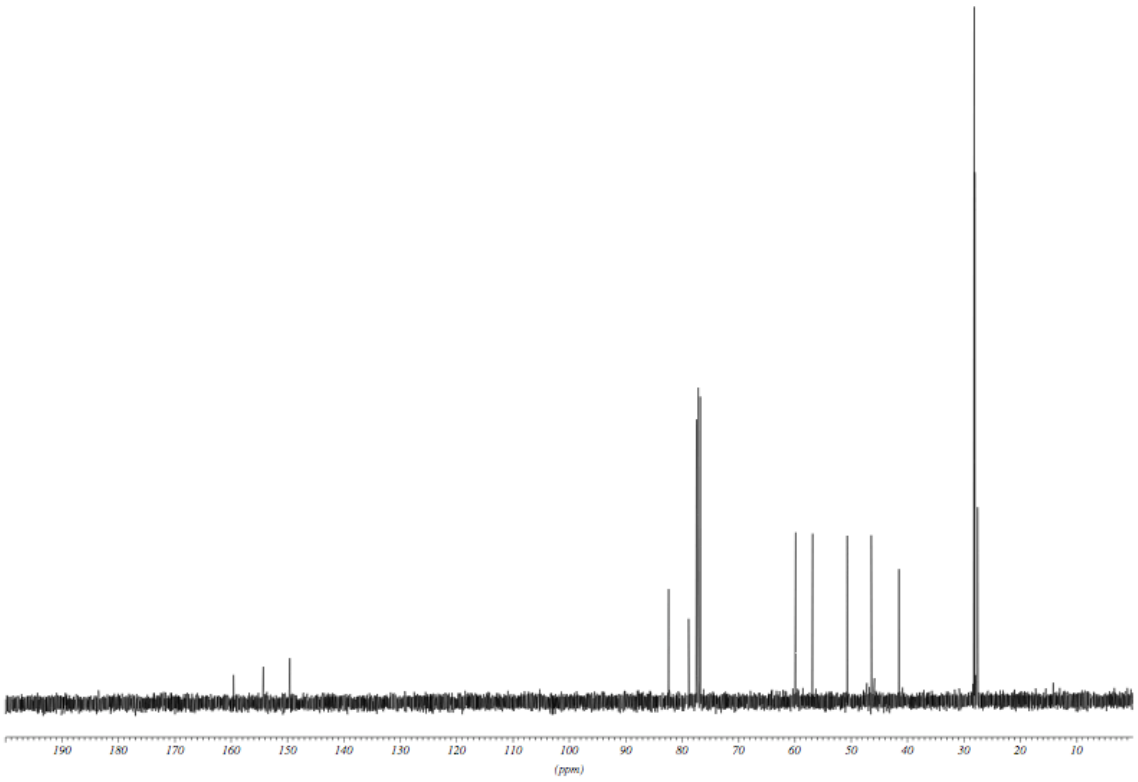
(ppm)


N
Boc
N
N
Boc

2b

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


190
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170
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150
140
130
120
110
100
90
80
70
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50
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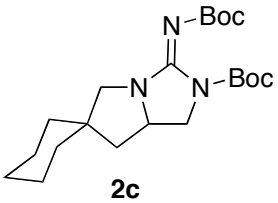
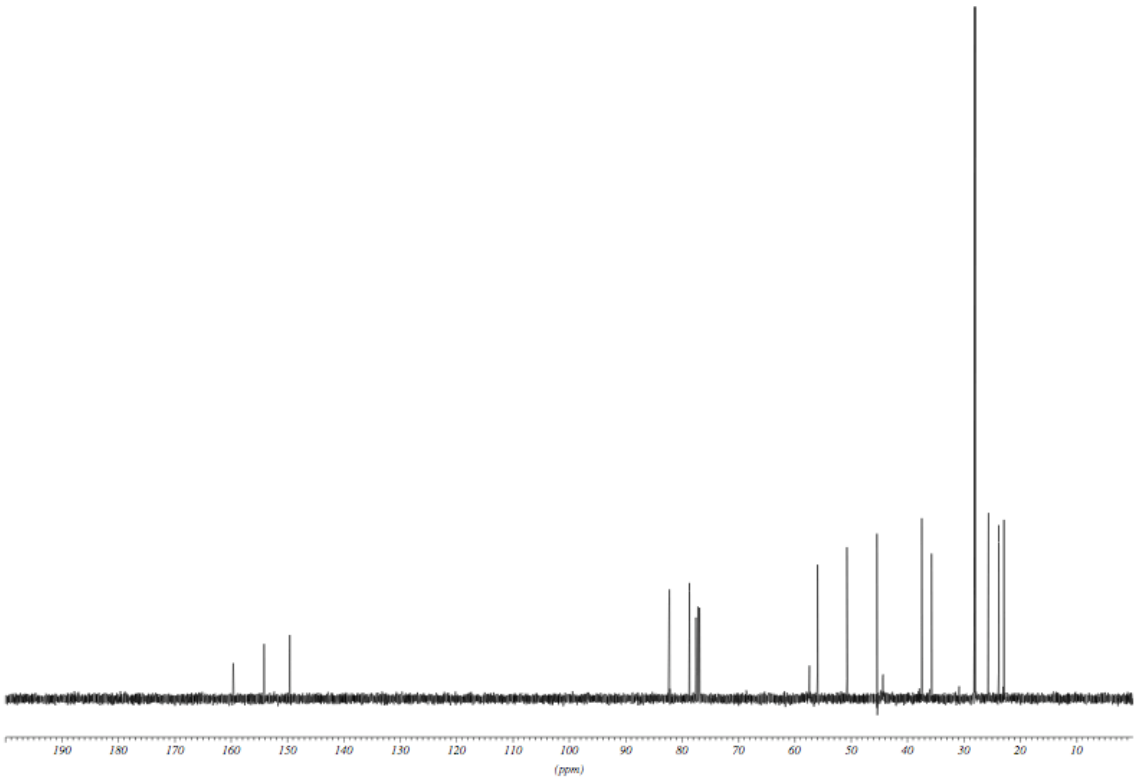
30
20
10
(ppm)


N-Boc
N
N-Boc

2c

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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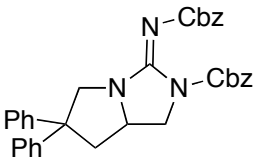
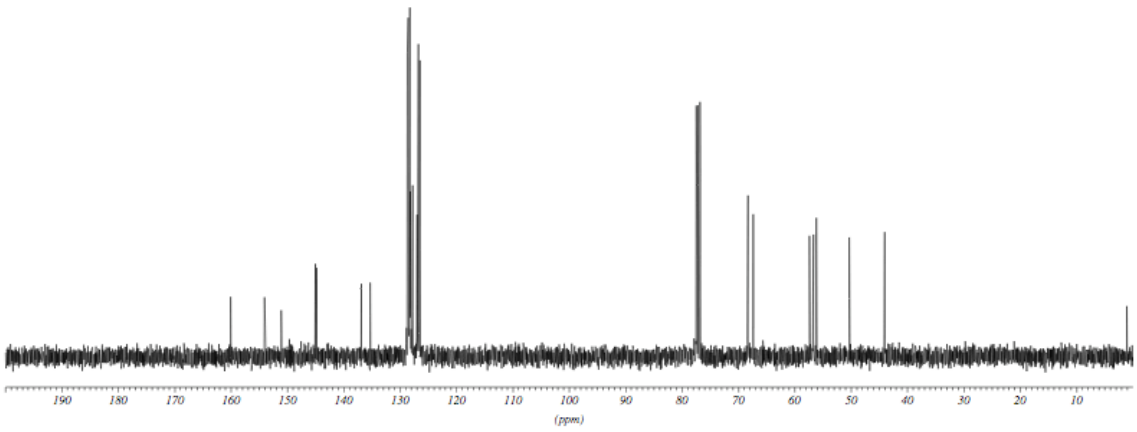
(ppm)


N
Cbz
N
N
Cbz
Ph
Ph

2d

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)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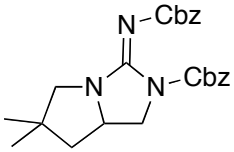
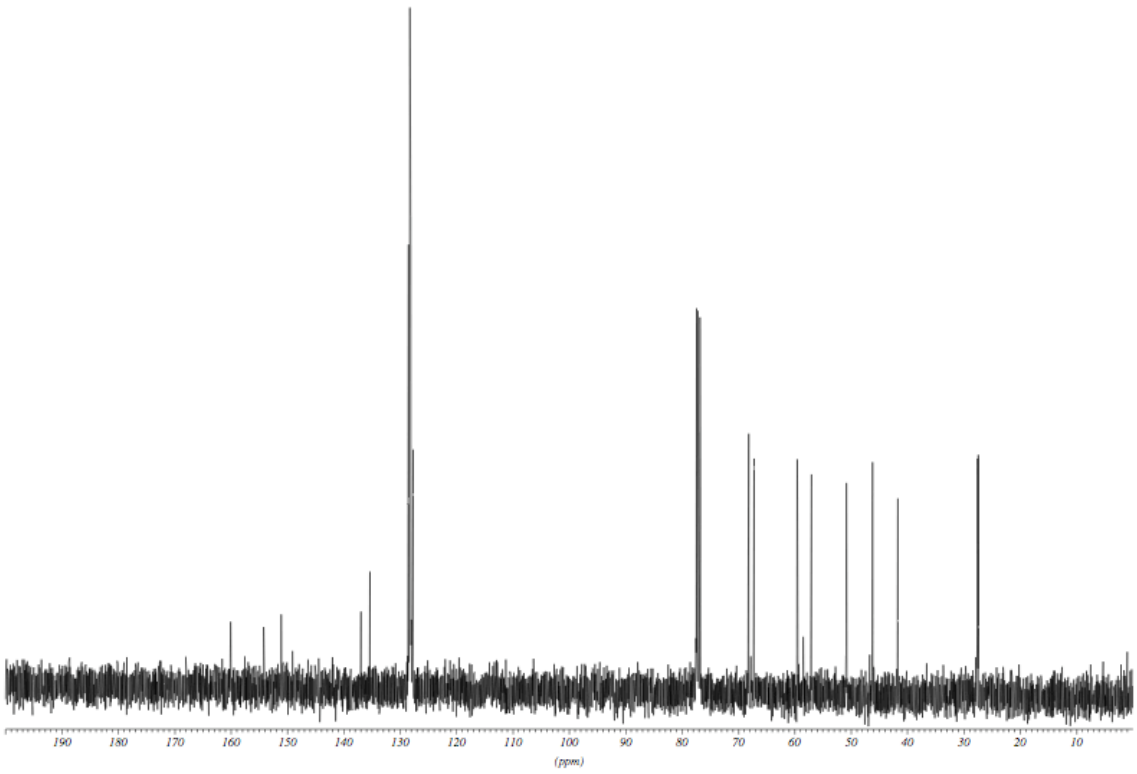
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


N–Cbz
N
N–Cbz

2e

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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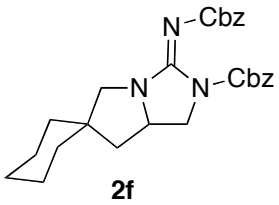
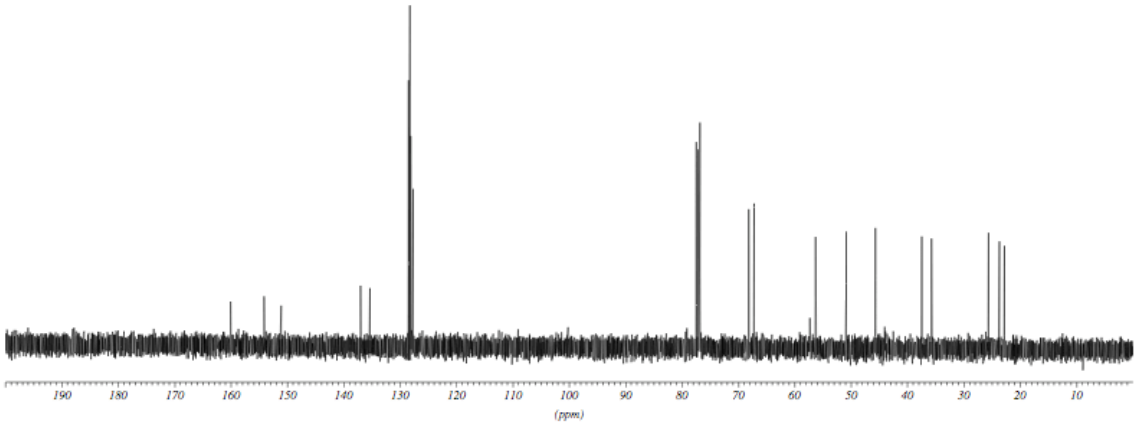
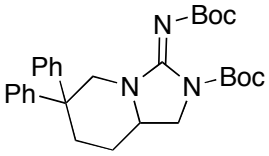
(ppm)


N–Cbz
N
N–Cbz

2f

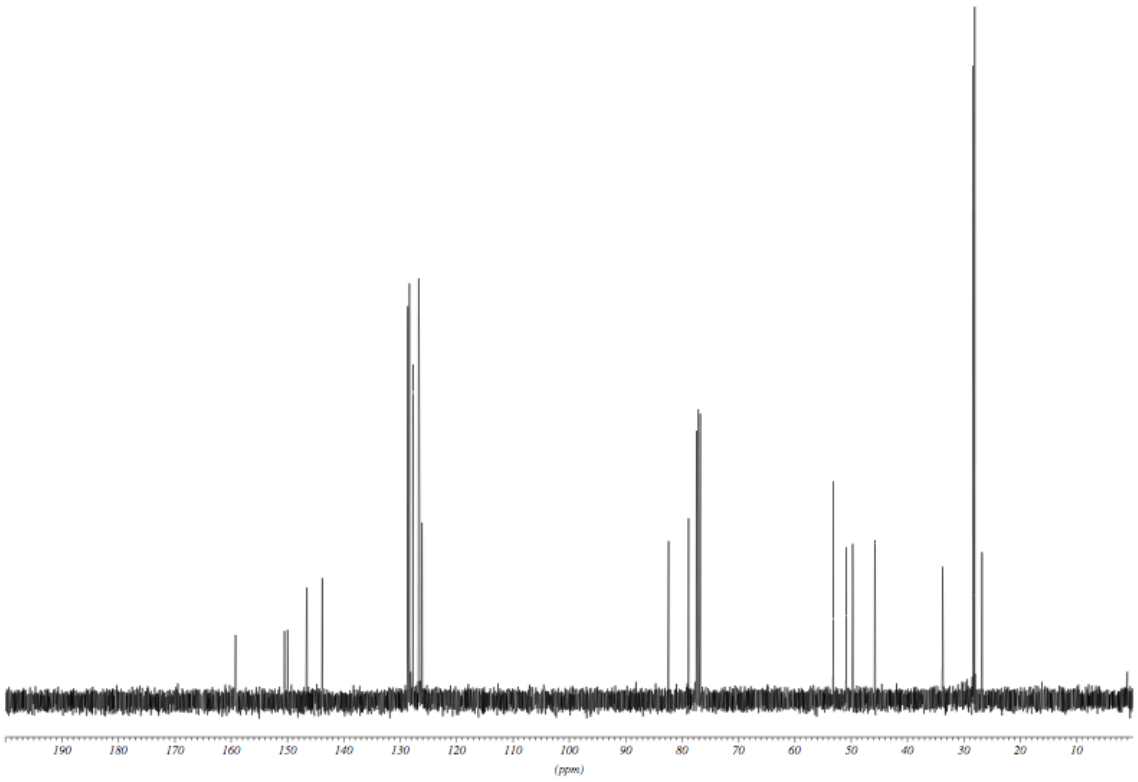
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


N
Boc
Ph
Ph
N
N
Boc

5a

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


190
180
170
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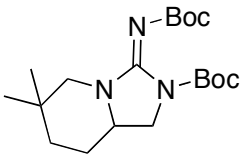
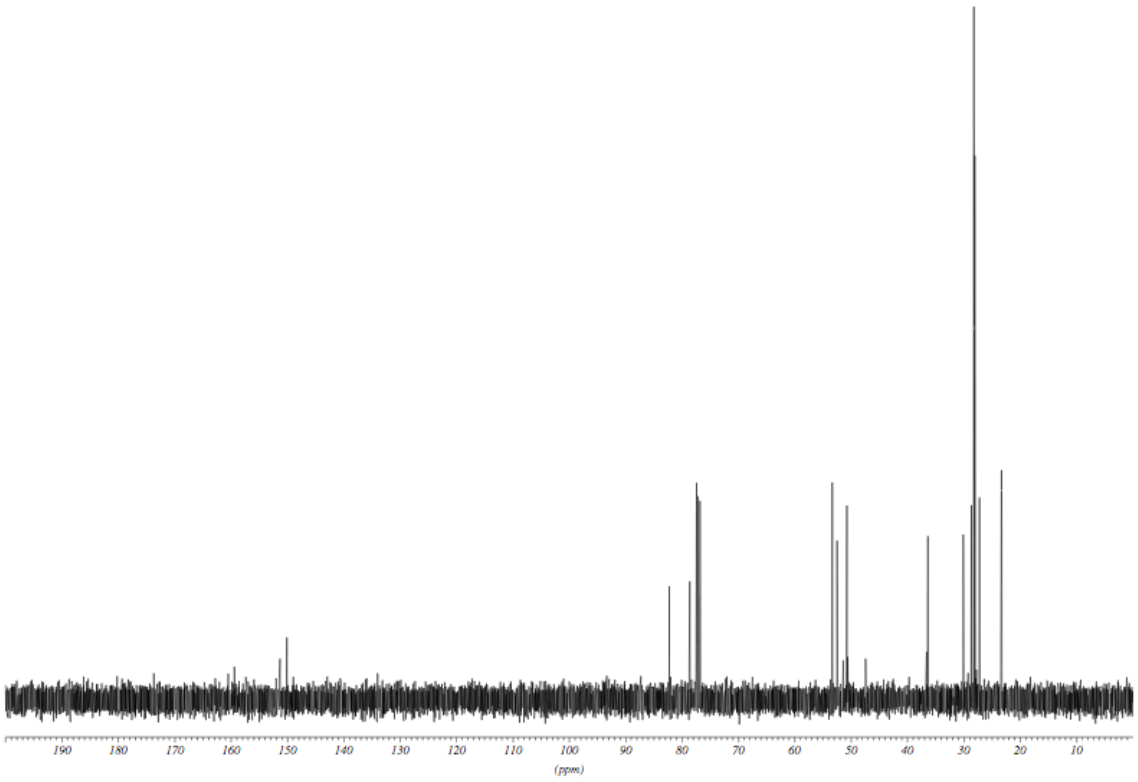
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


N
Boc
N
N
Boc

5b

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


190
180
170
160
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140
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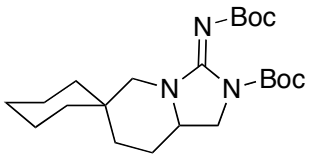
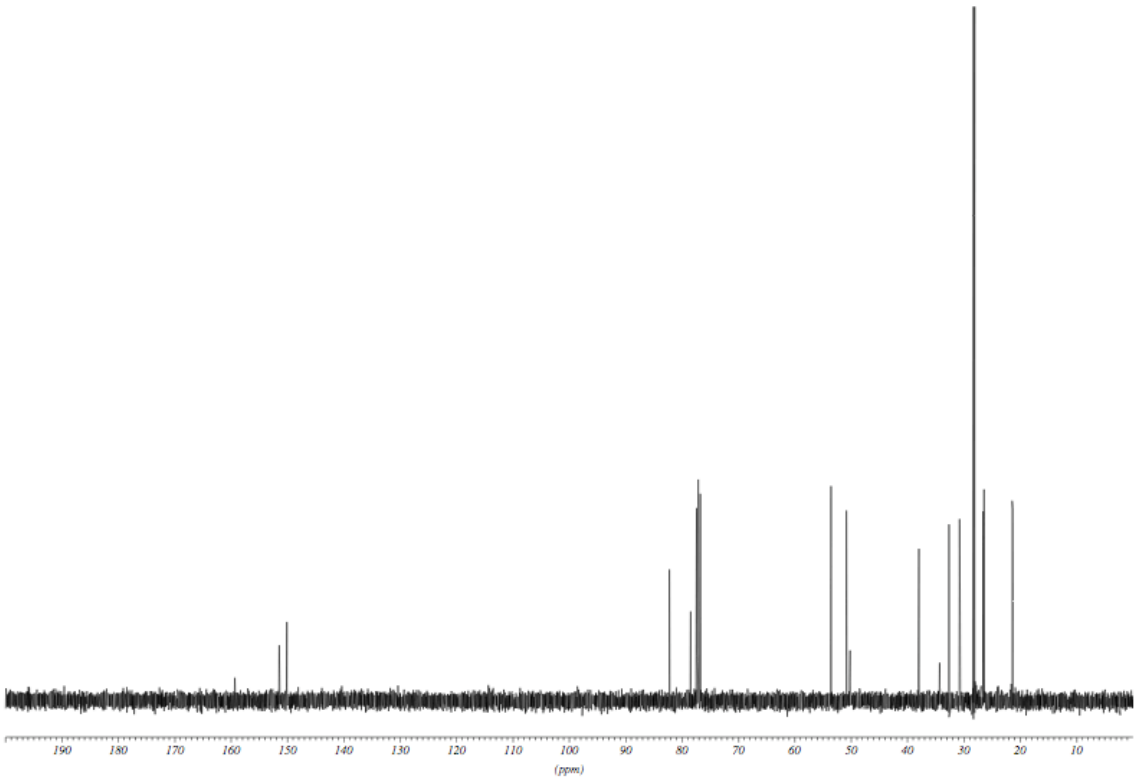
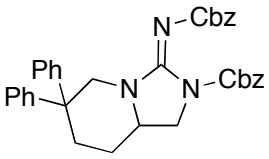
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


N
Boc
N
N
Boc

5c

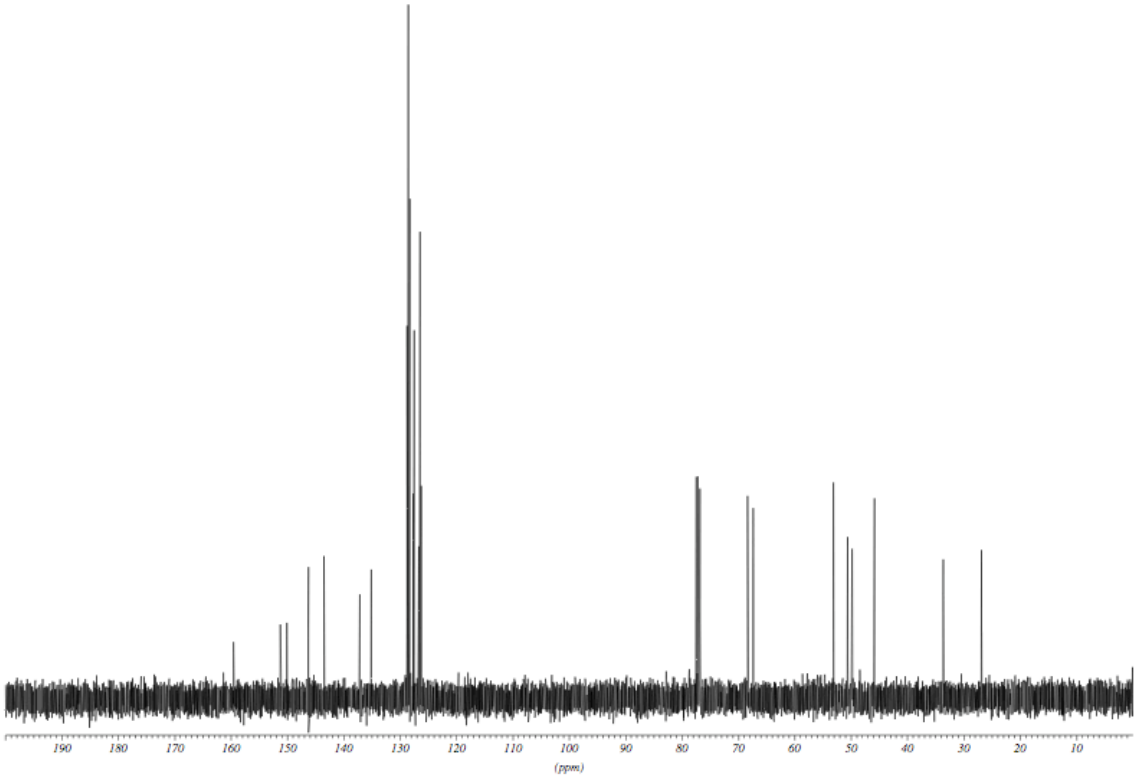
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

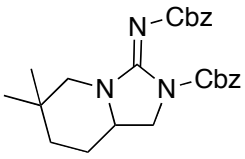

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


N
Cbz
Ph
Ph
N
N
Cbz

5d

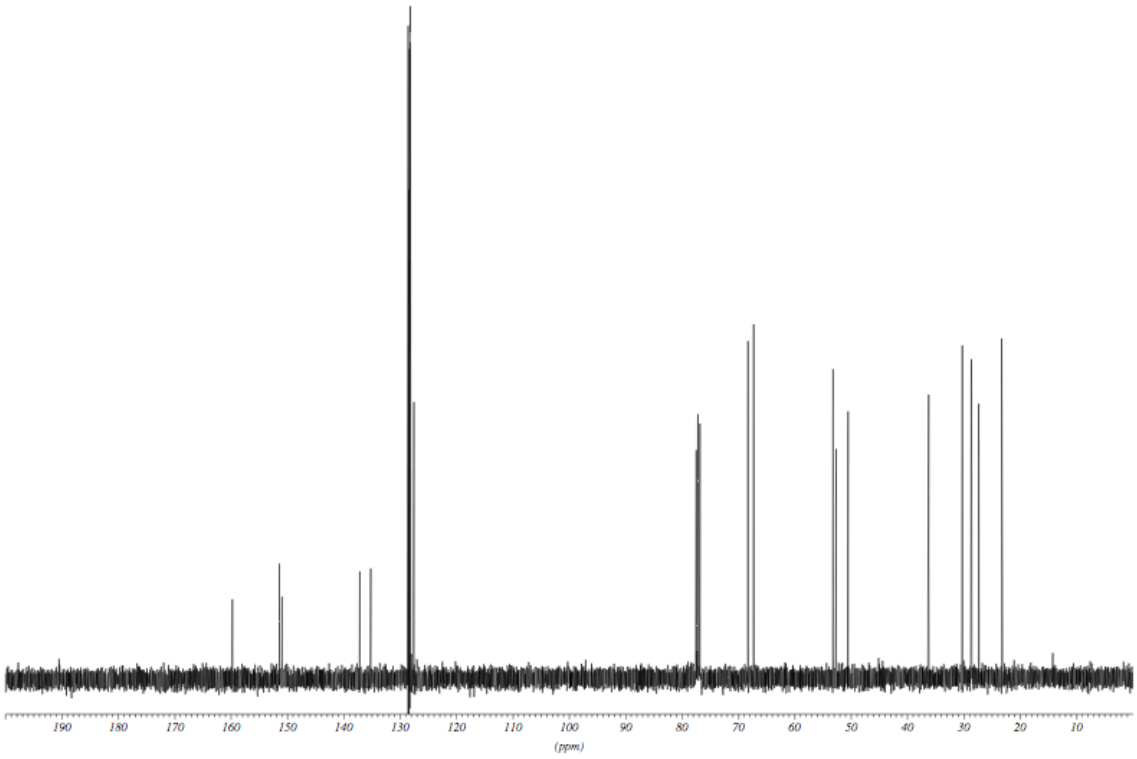
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

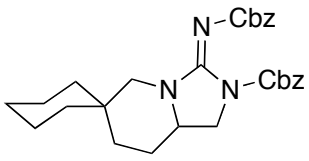

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


N
Cbz
N
N
Cbz

5e

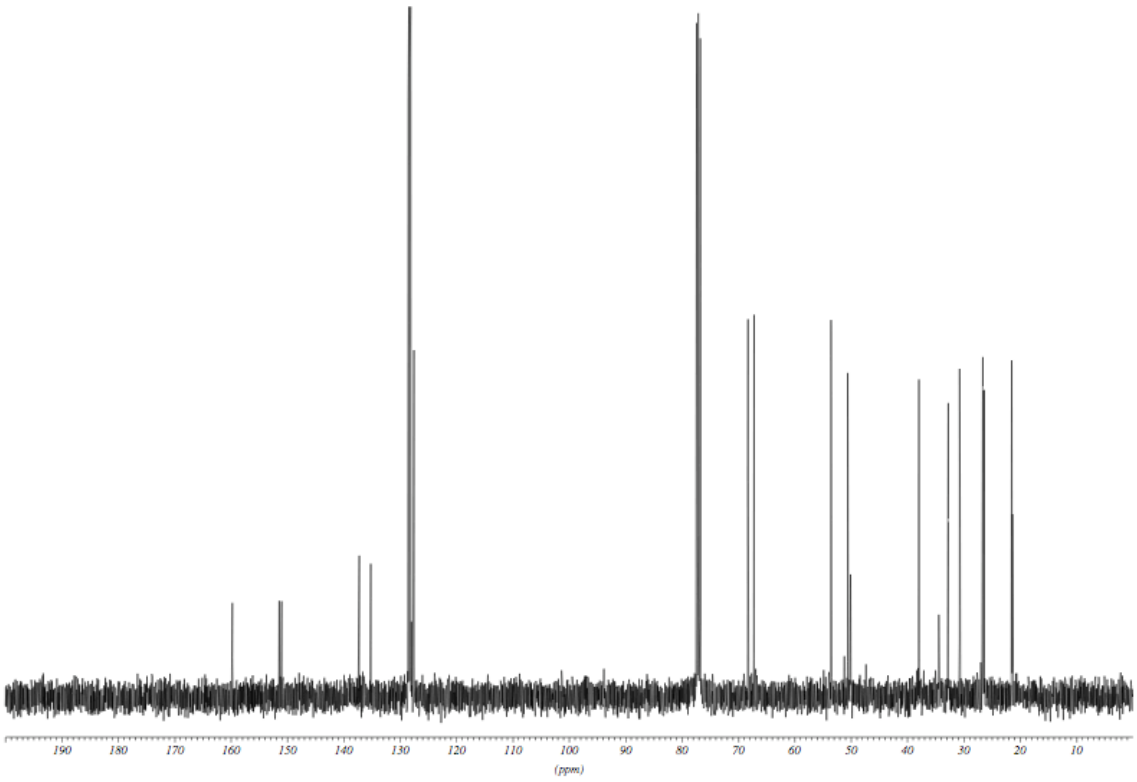
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

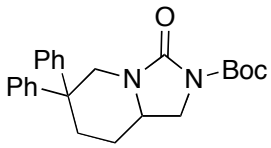

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


N
Cbz
N
N
Cbz

5f

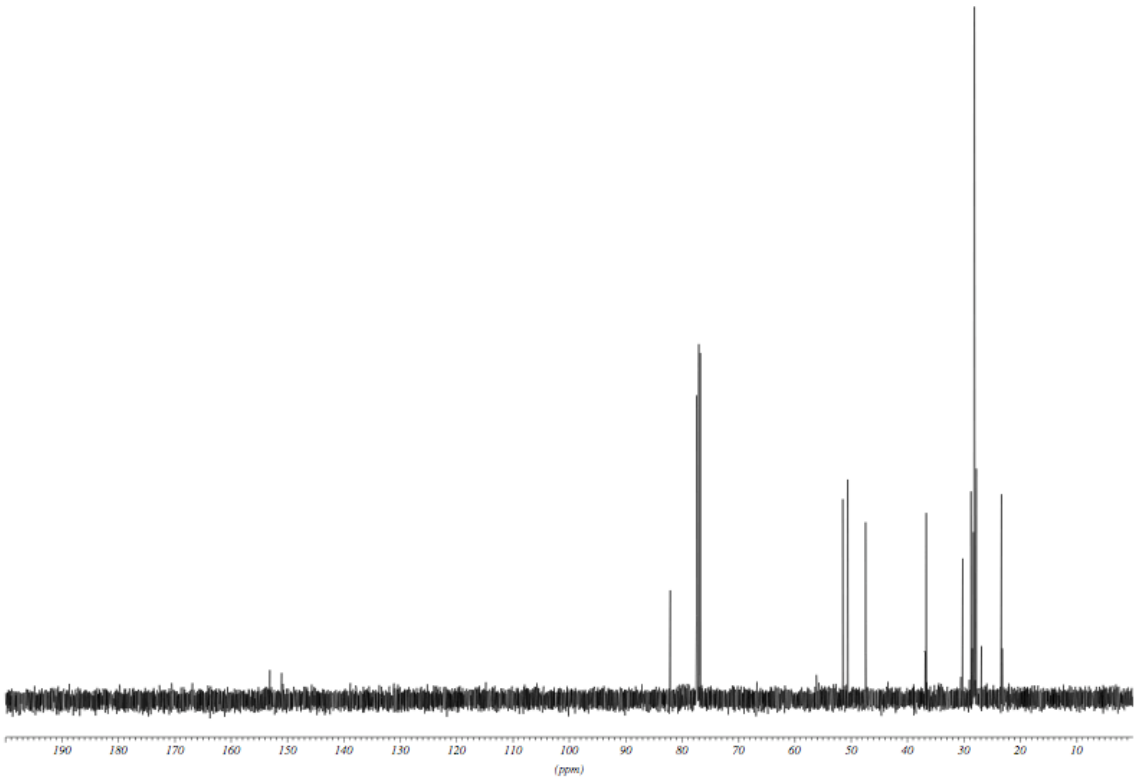
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

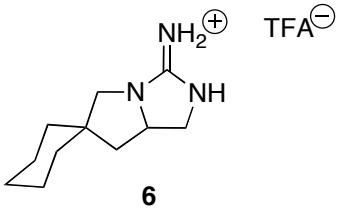

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


O
Ph
Ph
N
N
Boc

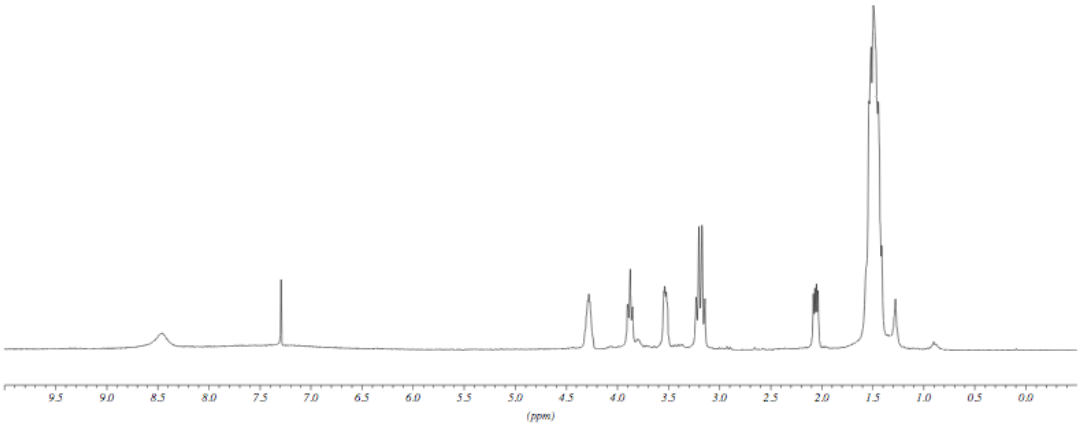
4

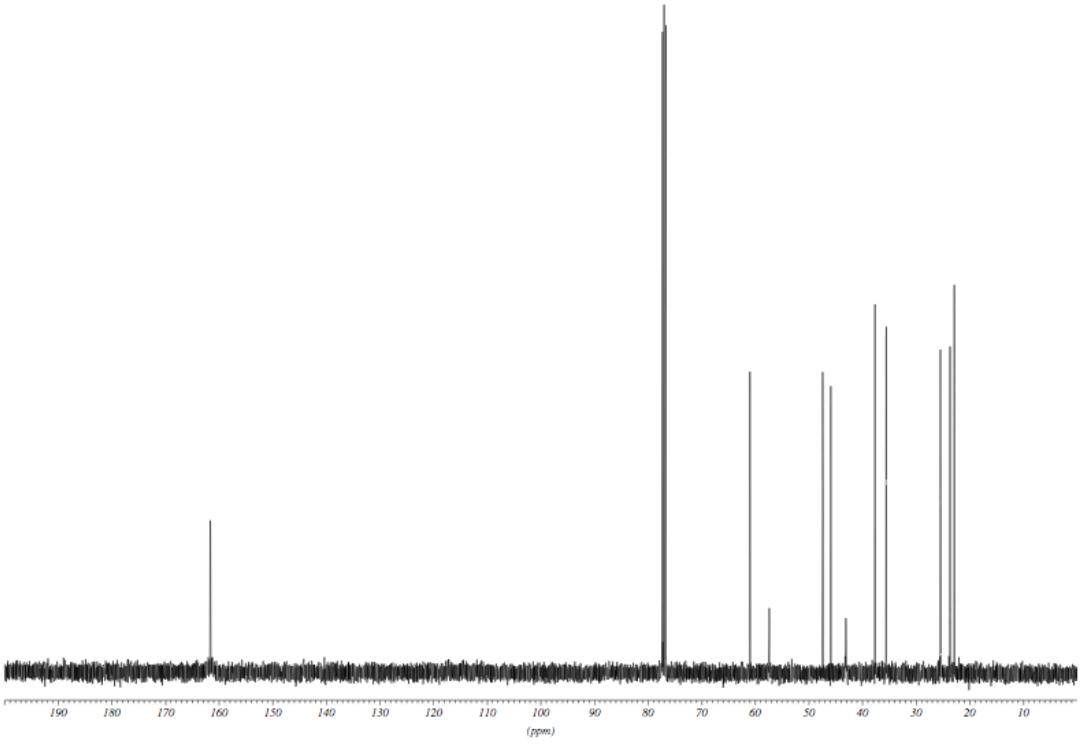
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

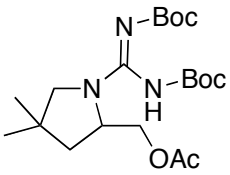

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


NH2
TFA
N
NH

6


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)



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[2] K. Feichtinger, H. L. Sings, T. J. Baker, K. Matthews, M. Goodman *J. Org. Chem.* 1998**, 63***,* 8432

[3] For a general synthesis of these amines see: Y. Tamaru, M. Hojo, H. Higashimura, Z.-I. Yoshida *J. Am. Chem. Soc.* 1988, **110**, 3994.

[4] D. Orain, J.-C. Guillemin *J. Org. Chem.* 1999, **64**, 3563.