Electronic Supplementary Material (ESI) for RSC Advances.

Proline derived Guanidine catalysts forge extensive H-bonded architectures: A solution and solid state study.

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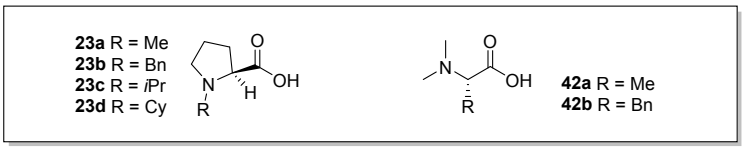
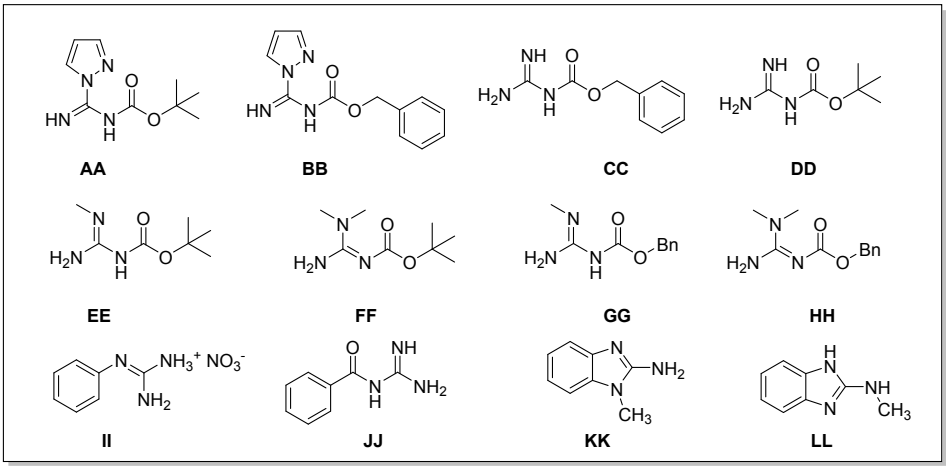
Supplementary information

Appendix I: NMR, IR, MS and HPLC data.

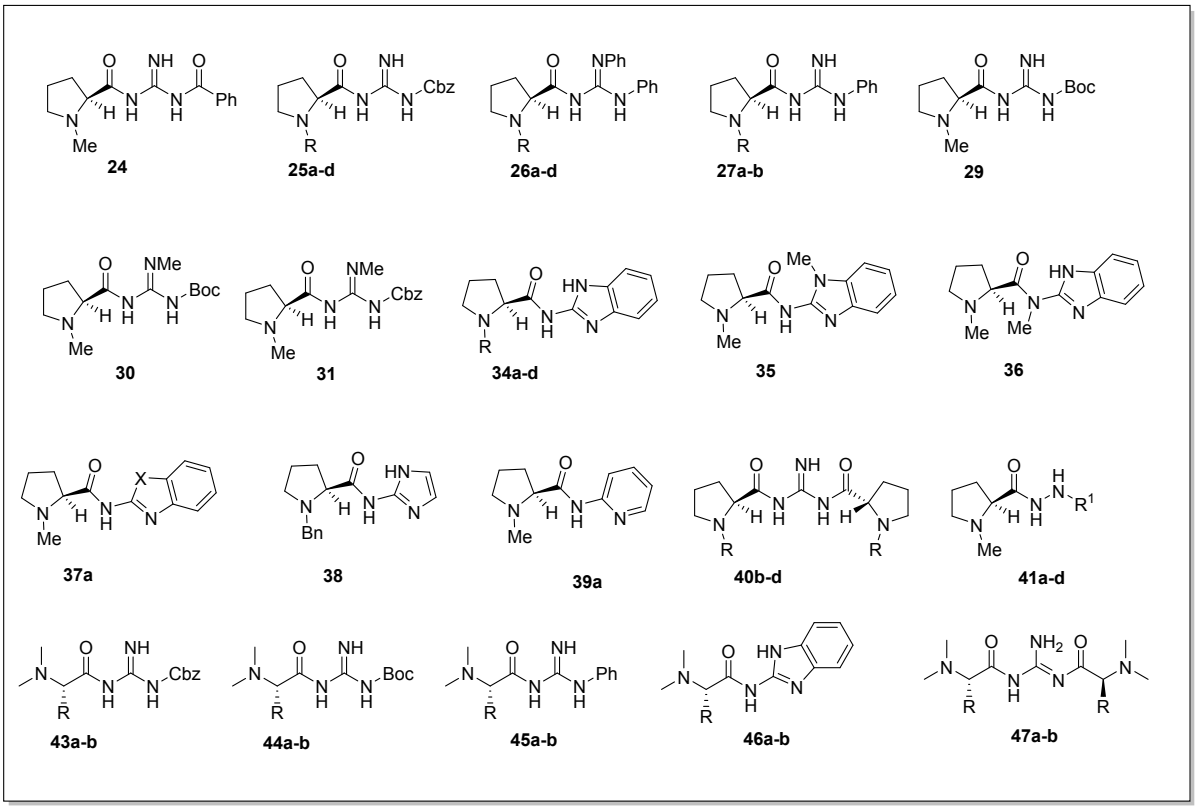
List of compounds



Amino acid derivatives



Guanidine derivatives



Catalysis structure

Experimental details

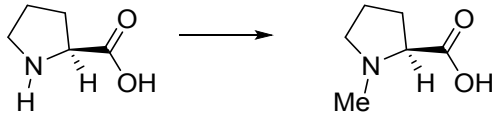
Column chromatography was carried out on silica gel (particle size 40e63 mm) and TLCs were conducted on precoated Kieselgel 60 F254 (Art. 5554; Merck) with the eluent specified in each case. All non-aqueous reactions were conducted in oven-dried apparatus under a static atmosphere of nitrogen. Diethyl ether (DE), THF and dichloromethane (DCM) were dried on a Pure Solv MD-3 solvent purification system. Dry methanol (ME) and DMF were purchased from Aldrich. Chemical shifts are reported in δ values relative to the solvent signals as an internal standard. Proton and carbon were recorded in $CDCl_3$ unless otherwise stated on a Bruker, AC400 spectrometer. Mass spectra data were obtained at the EPSRC Mass Spectrometry Service Centre at the University of Wales, Swansea. Infrared spectra were recorded as thin films (oils) on a Bruker Tensor 27 series instrument.

Abbreviations

DE = Diethyl ether
EA = Ethyl acetate
PE = Petroleum ether
CF = Chloroform
ME = Methanol
DCM = Dichloromethane
DMF = Dimethylformamide
THF = Tetrahydrofuran

Compounds **AA**,[1] **BB**,[2] and **JJ**[3] were prepared by previously reported procedures. Other guanidine and amidine derivatives were prepared by the modified literature procedures given below.

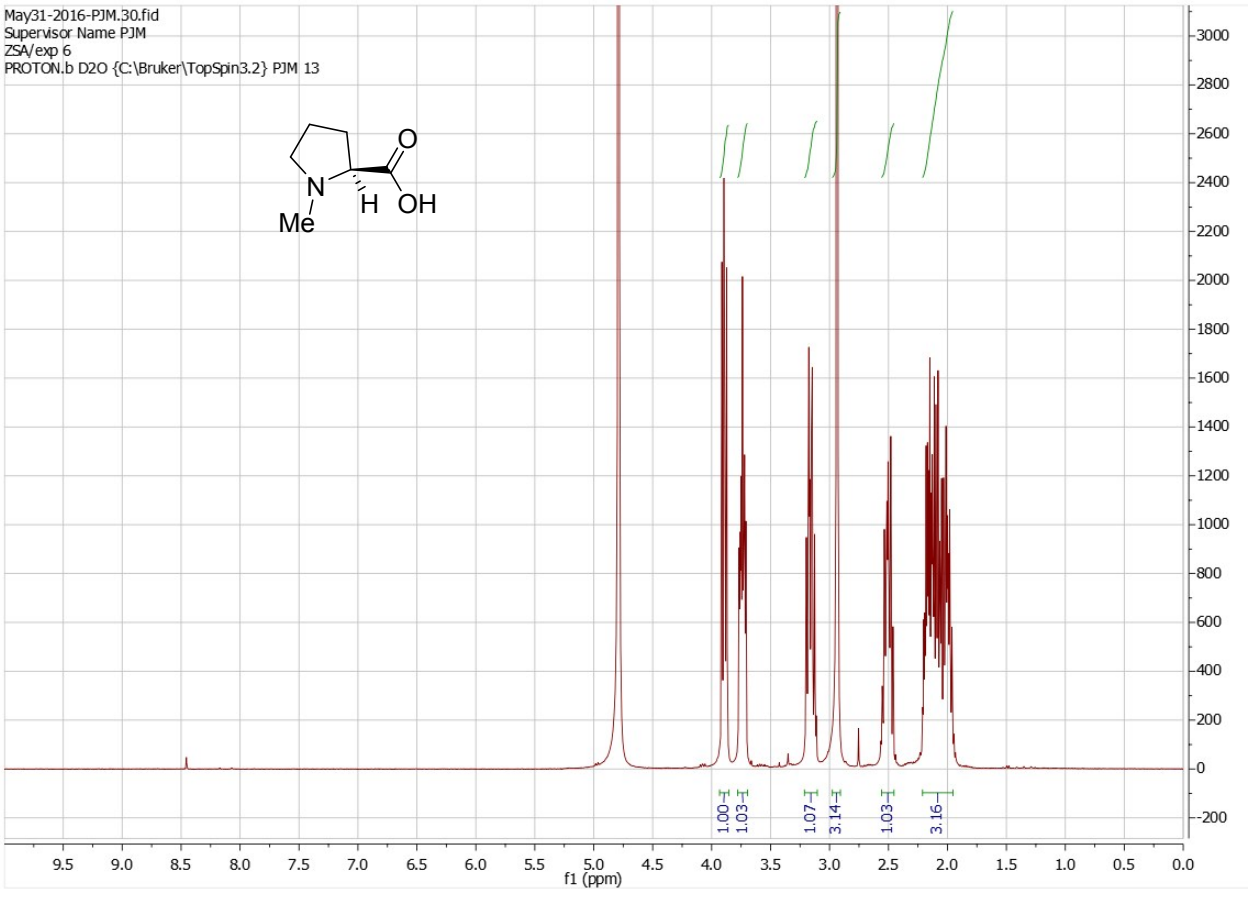
_N_-methyl-_L_-proline 23a[4]



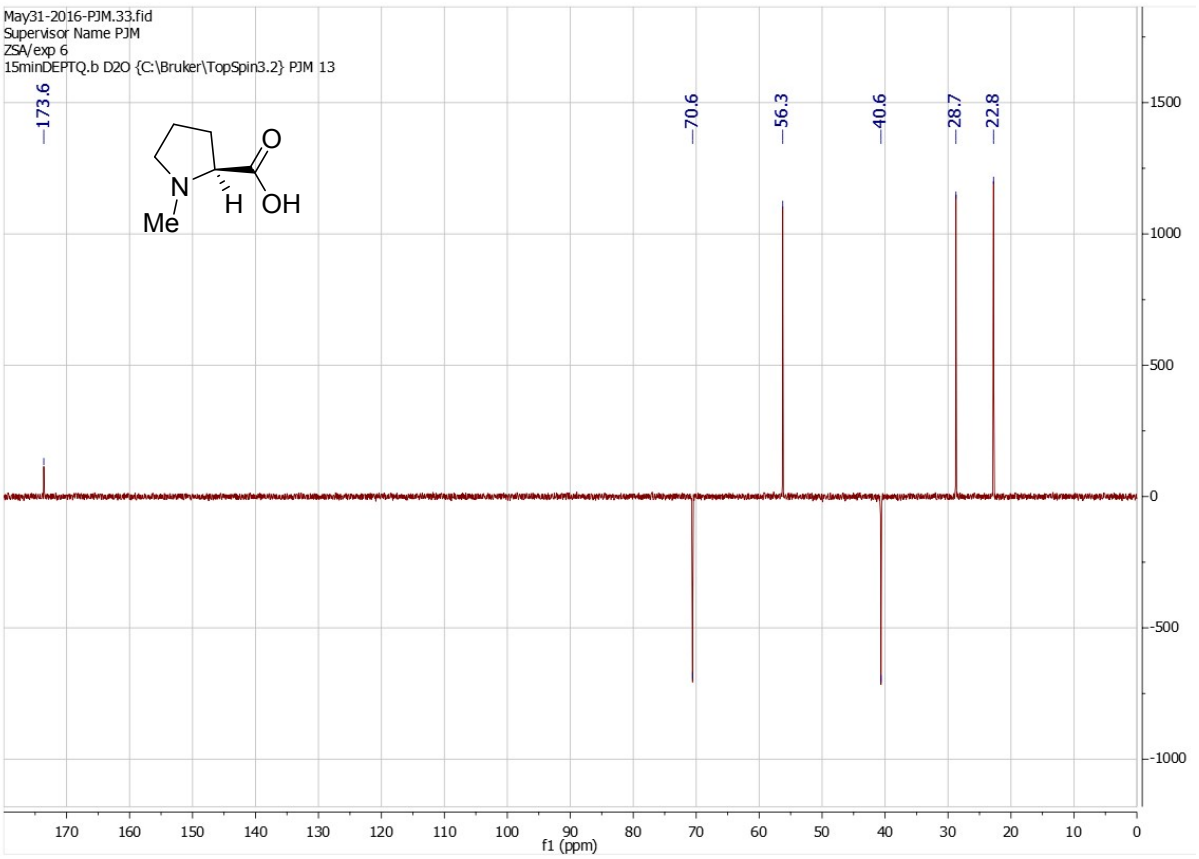
_L_-proline (10.0 g, 86.7 mmol) was dissolved in methanol (100 mL) together with formaldehyde (37 % aqueous, 7.6 mL, 95.5 mmol) and the mixture was stirred. The flask was purged with N_2 gas and 10% Pd/C (0.43 g) was added following which the flask was purged with hydrogen gas (balloon) and stirred overnight. The solution was filtered through Celite© and evaporated to dryness and the solid obtained dissolved in a minimum of methanol (ca 50 mL) and diethyl ether was added to the cloud point (ca 1 mL). The solution was cooled overnight in a freezer to give crystal of **23a**, which were removed by decanting the mother liquor. After drying under high vacuum the title compound **23a** (11.1 g, 85.9 mmol) was obtained as a white crystalline solid in 99 % yield.

R_f 0.23 (90% ME/DE); **Mp** 142-144 °C (lit.[4a] Mp 142-145 °C); **$[\alpha]_D^{22}$** -84.0 (MeOH, c = 2.0); (lit. $[\alpha]_D^{23}$ -78.0 (MeOH, c = 2.0)); **δ_H** (D_2O) 3.78 (1H, dd, _J_ 9.0, 7.2 Hz, CH), 3.56-3.52 (1H, m, CH), 2.99-2.90 (1H, m, CH), 2.75 (3H, s, Me), 2.35-2.29 (1H, m, CH), 2.00-1.79 (3H, m, CH); **δ_C** (D_2O) 173.6, 70.6, 56.3, 40.6, 28.7, 22.7; **ν_{max}** (KBr disk) 2900, 1668, 1611, 1467, 1400, 1353, 1326, 1233, 1182, 1112, 1055, 1024, 807, 774 cm^{-1}; **MS (EI, -ve ion) m/z** 128.01 (100 %, $[M-H]^-$); **HRMS m/z** found 128.0720, $C_6H_{10}NO_2$ ($[M-H]^-$) requires 128.0717.

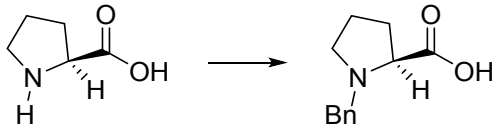
_N_-methyl-_L_-proline 23a[4]: ^{1}H NMR (D_2O)



***N*-methyl-*L*-proline 23a[4]: ^{13}C NMR (D_2O)**



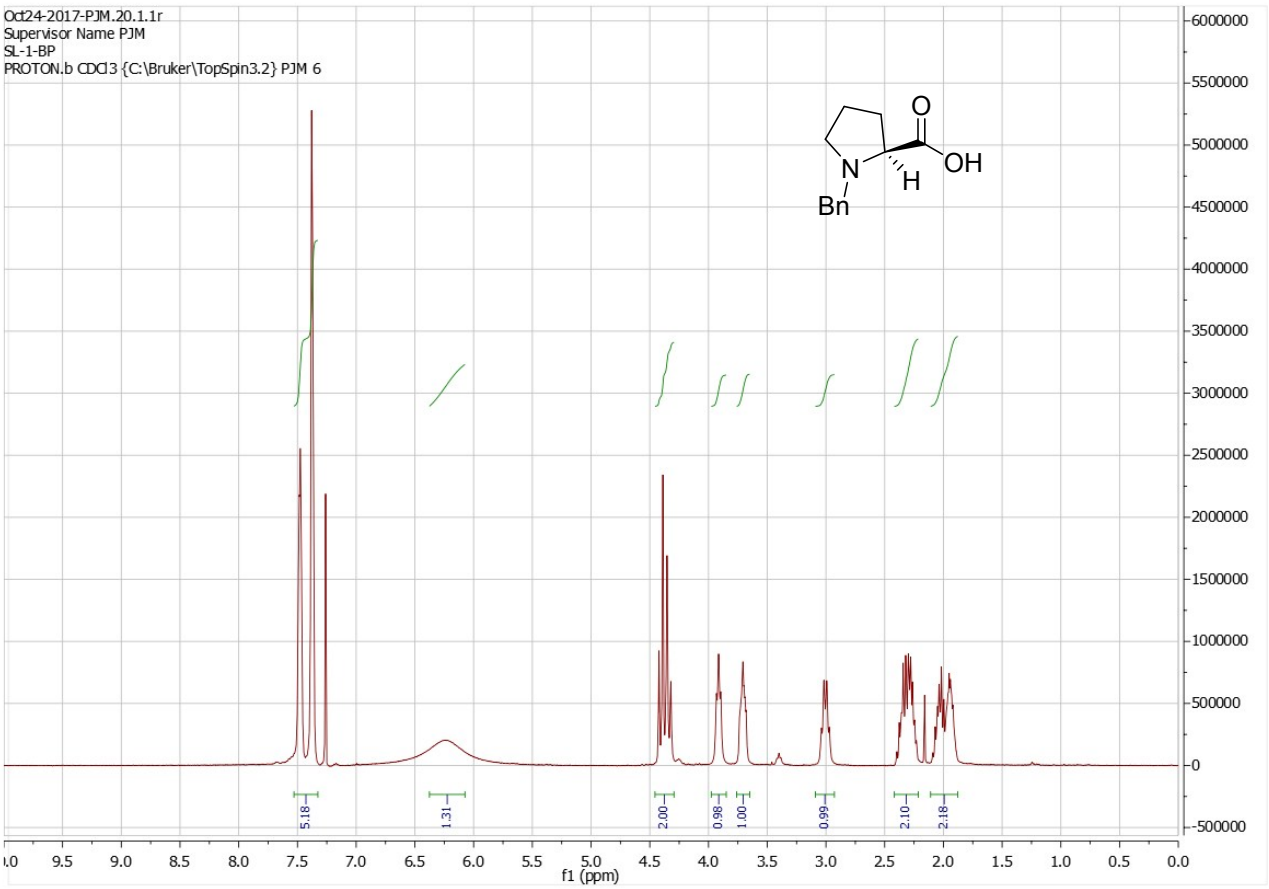
***N*-benzyl-*L*-proline 23b[4a]**



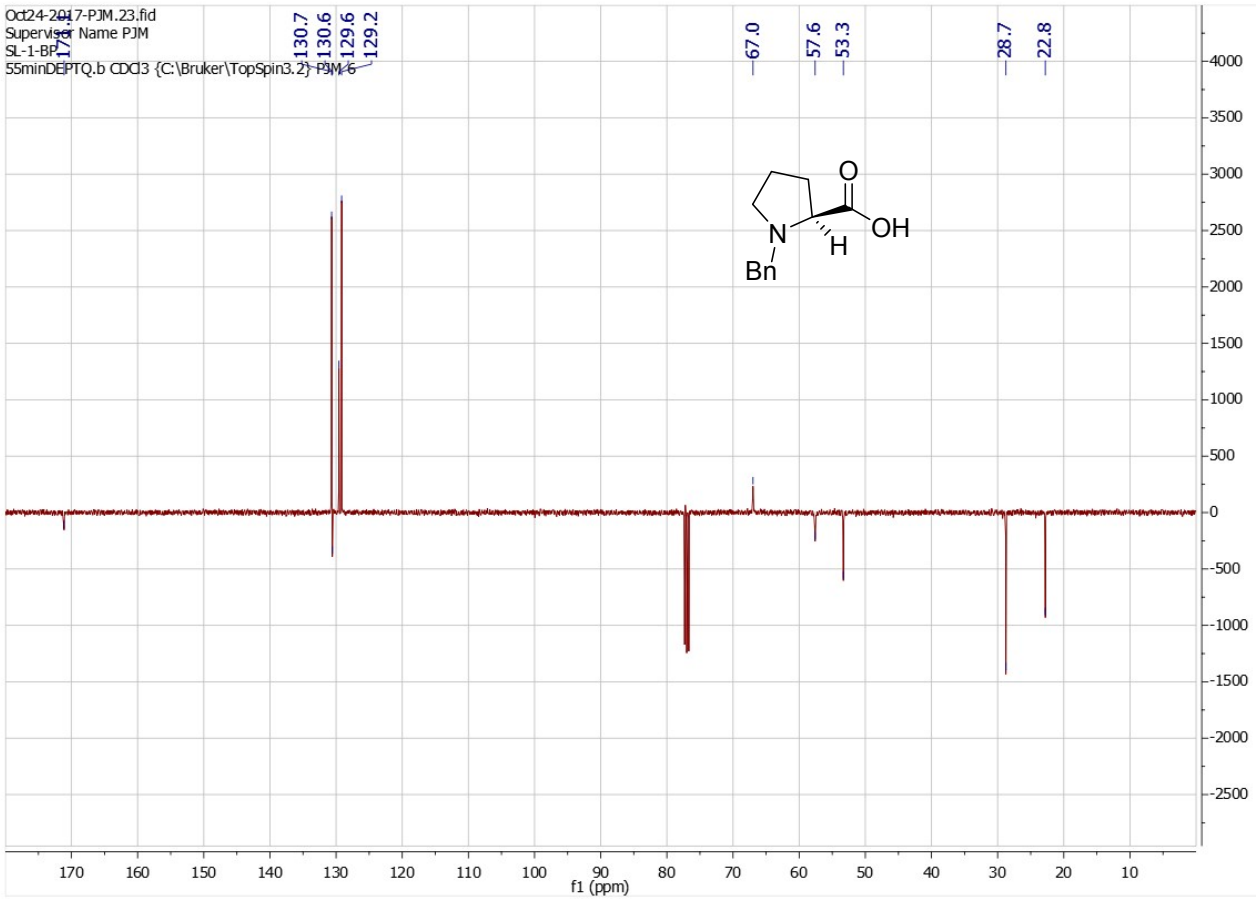
L-Proline (10.00 g, 86.86 mmol) and KOH (14.7 g, 262.06 mmol, 3.02 equiv.) were dissolved in *i*-PrOH (1 L) and heated with stirring to 40 °C. As soon as the solution became transparent, benzyl chloride (12.03 g, 10.94 mL, 95.02 mmol, 1.1 equiv.) was added in a dropwise fashion over 3 h. After 24 h, the reaction was cooled rt and neutralized using HCl (conc.) to 5-6 pH and chloroform (100 mL) was added and the mixture stirred overnight. The reaction was then filtered and the residue washed with $CHCl_3$. The filtrate was evaporated to give the crude product which was triturated with acetone (100 mL) and filtered and the solid product washed with further small portions of acetone. The solid obtained was dried under vacuum (P_2O_5) for two days to give the product **23b** (8.20 g, 40.0 mmol) as a pale yellow solid in 46 % yield.

R_f 0.36 (80% ME/EA); **Mp** 170-171 °C (lit.[4a] Mp 174-175 °C); **$[\alpha]_D^{19}$** -22.5 (EtOH, c = 1.0; lit. $[\alpha]_D^{20}$ -25.8 (EtOH, c = 1.0)); **δ_H** ($CDCl_3$) 7.51-7.44 (2H, m, 2 x CH), 7.41-7.35 (3H, m, 3 x CH), 5.84 (1H, br s OH), 4.39 (1H, d, *J* 12.9 Hz, CH), 4.31 (1H, d, *J* 12.9 Hz, CH), 3.98-3.85 (1H, m, CH), 3.71-3.60 (1H, m, CH), 3.10-2.93 (1H, m, CH), 2.42-2.21 (2H, m, 2 x CH), 2.10-1.88 (2H, m, 2 x CH); **δ_C** ($CDCl_3$) 171.1, 130.7, 130.6, 129.6, 129.2, 67.0, 57.6, 53.3, 28.7, 22.8; **ν_{max}** (KBr disk) 3432, 3036, 2873, 1745, 1634, 1394, 1321, 1203, 1005 cm^{-1}; **MS(ES, -ve) m/z** 204.1 (100 %, $[M-H]^-$) **MS(ES) m/z**,(206.1, 100%, $[M+H]^+$); **HRMS(ESI) m/z** found 204.1030, $C_{12}H_{14}NO_2$ ($[M-H]^-$) requires 204.1030.

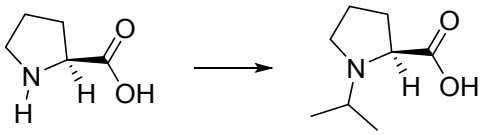
N-benzyl-*L*-proline 23b[4a]: ^{1}H NMR



N-benzyl-*L*-proline 23b[4a]: ^{13}C NMR



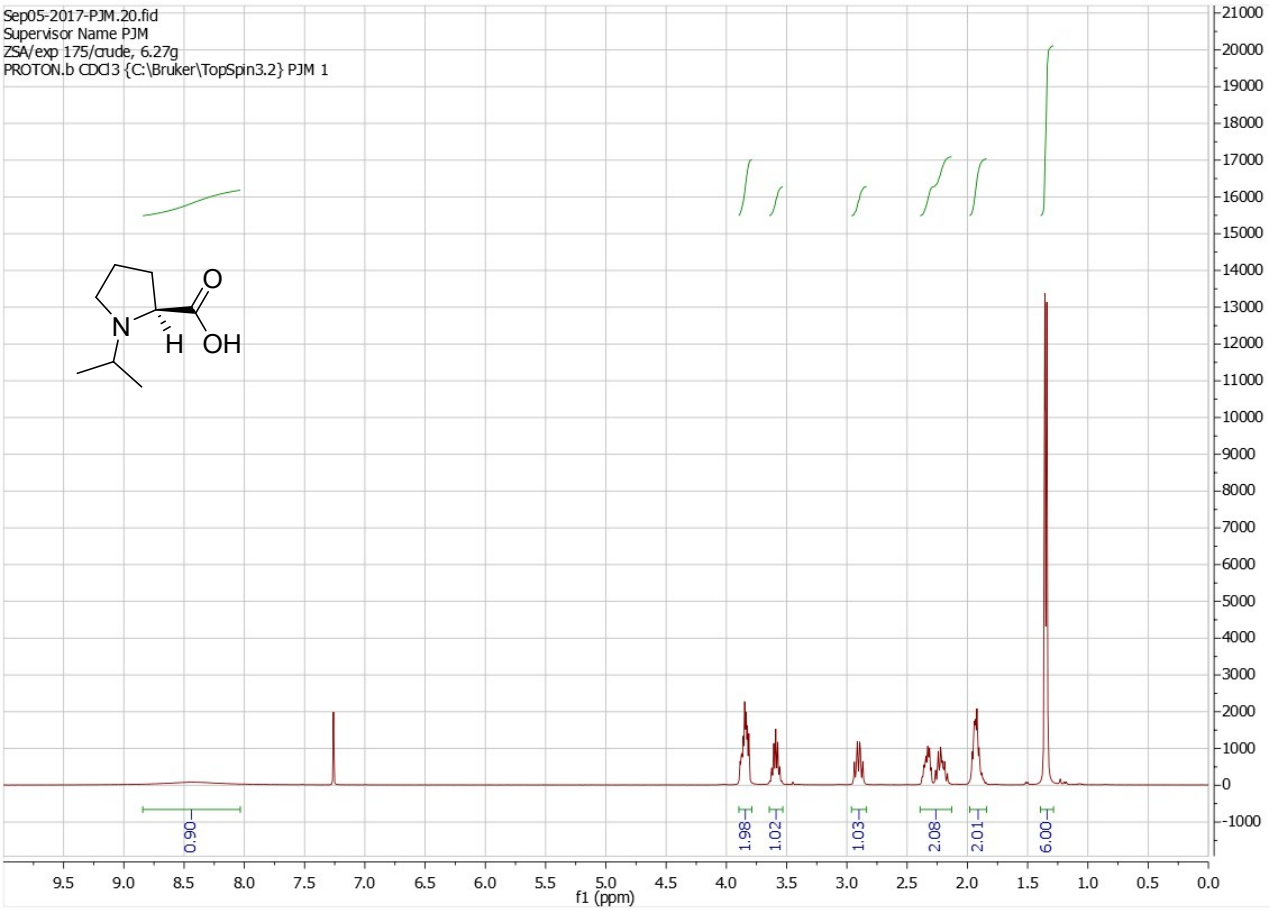
_N_-isopropyl-_L_-proline 23c[5]



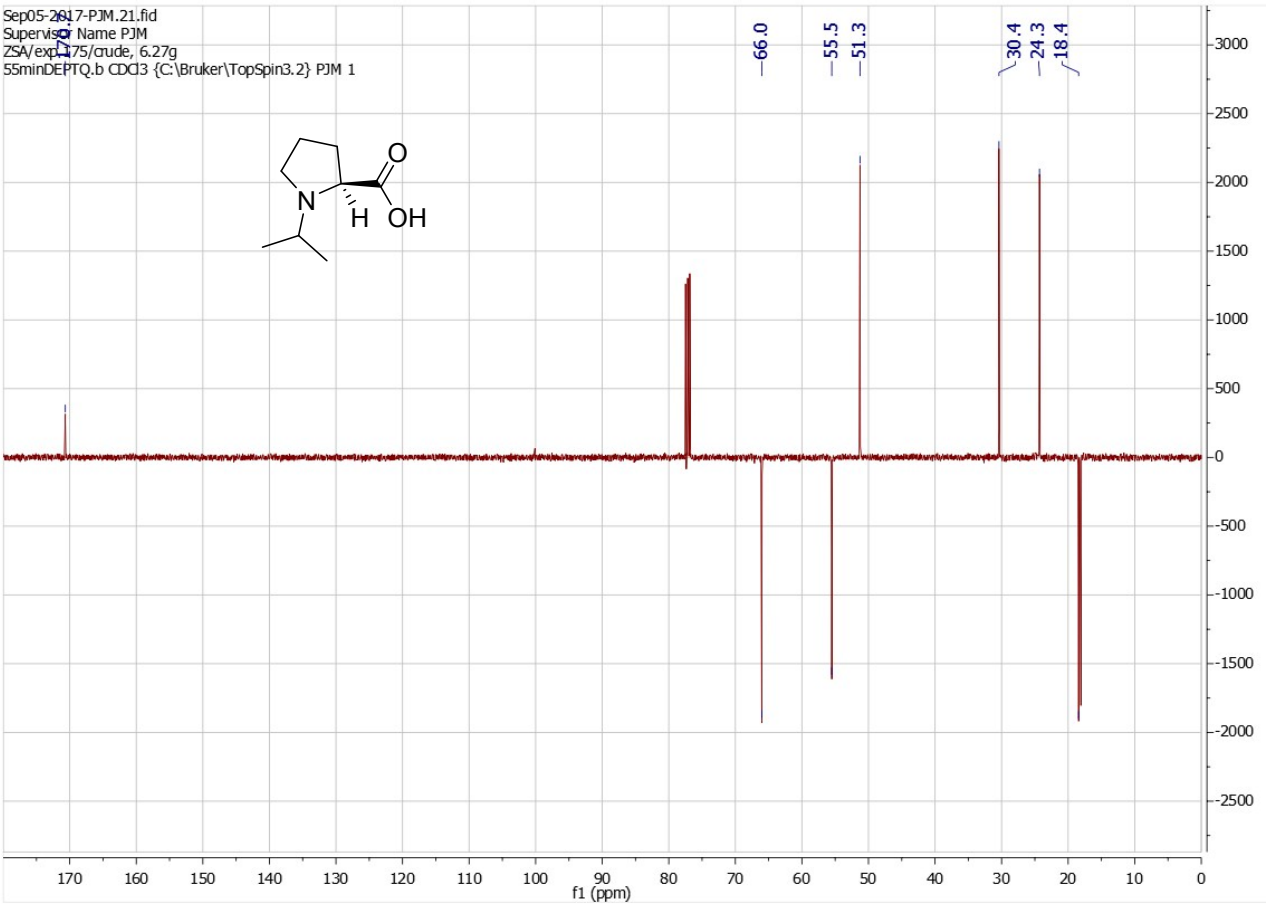
Acetone (16.6 g, 19.0 mL, 260.57 mmol, 5.0 equiv.) was added to *L*-proline (6.0 g, 52.11 mmol) and stirred for 1 h, following which dry MeOH (10 mL) was added and the mixture stirred for a further 1 h. Pd/C (0.5 g, 4.53 mmol) was cautiously added and the mixture purged with hydrogen gas and was stirred for 42 h replenishing the hydrogen as needed. The reaction was filtered through Celite© and evaporated to dryness to give a crude product which was re-dissolved in a minimum amount of methanol and the product precipitated by the addition of DE to give **23c** (7.78 g, 49.5 mmol) as yellow crystals in 95% yield.

R_f 0.21 (50 % ME/DE); **Mp** 189 °C; **$[\alpha]_D^{18}$** -68.1 (MeOH, c 1.28; Lit.[5] **$[\alpha]_D^{20}$** -55.0 (MeOH, c = 1.28)); **δ_H** 3.67 (1H, dd, *J* 4.7, 8.1 Hz, CH), 3.50 (1H, ddd, 2.7, 7.1, 11.0, CH), 3.37 (1H, septet, *J* 6.4 Hz, CH), 2.97 (1H, app dt, *J* 11.0, 6.6, CH), 1.96-2.05 (2H, m, CH_2), 1.79-1.89 (1H, m, CH), 1.52-1.67 (1H, m, CH), 1.19 (3H, d, *J* 6.4 Hz, Me), 1.17 (3H, d, *J* 6.4 Hz, Me); **δ_C** 70.7, 66.0, 55.5, 51.3, 30.4, 24.3, 18.4, 18.1; ν_{max} (KBr disk) 3432, 3036, 2873, 1634, 1394, 1321, 1203, 1080, 1005 cm^{-1}; **MS(EI, -ve)** m/z 156.1 (100 %, $[M-H]^-$); **MS(ESI) m/z** 158.1 (100 %, $[M+H]^+$); **HRMS(ESI)** m/z found 156.1032, $C_8H_{14}NO_2$ ($[M-H]^-$) requires 156.1030.

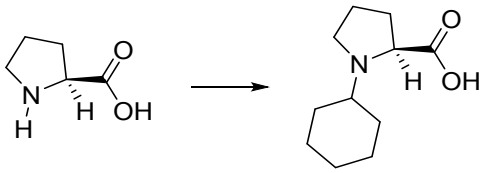
_N_-isopropyl-_L_-proline 23c[5]: ^{1}H NMR



***N*-isopropyl-*L*-proline 23c[5]: ^{13}C NMR**



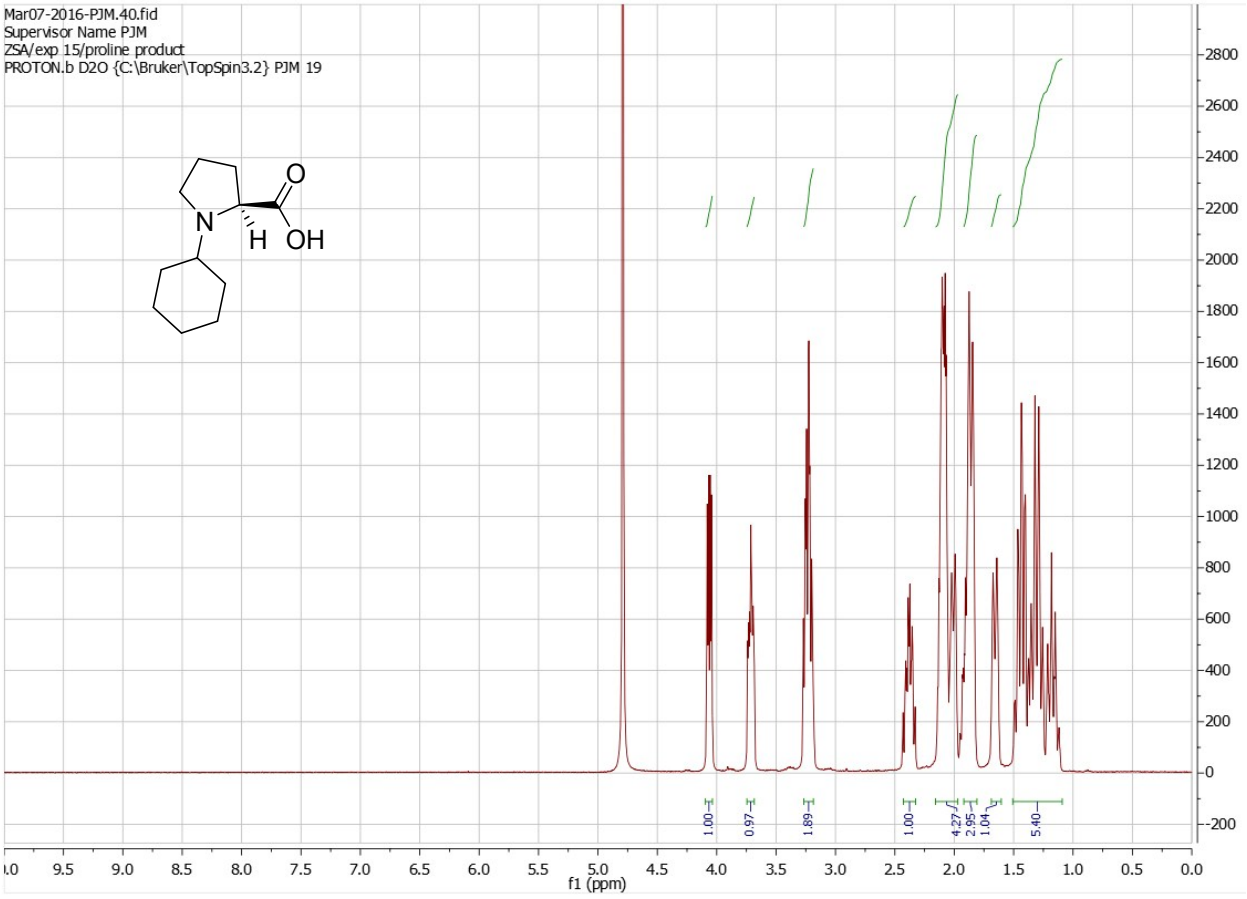
***N*-cyclohexyl-*L*-proline 23d[6]**



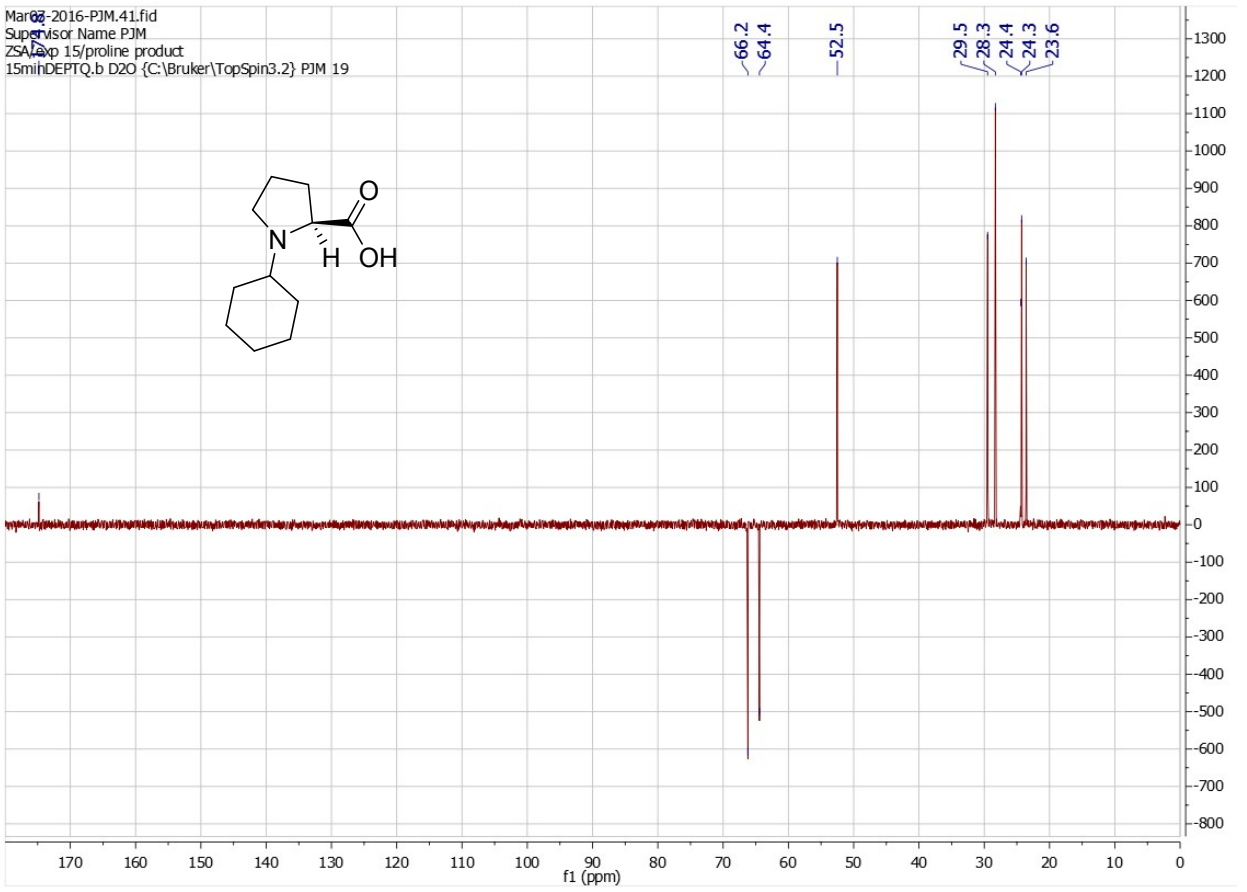
Methanol (100 mL) was added to Pd/C (10 %, 0.50 g) in a dry 500 mL RBF under a nitrogen atmosphere. *L*-Proline (11.5 g, 99.9 mmol, 1.0 equiv.) and cyclohexanone (10.8 g, 11.4 mL, 109.9 mmol, 1.1 equiv.) were then added and the reaction flask evacuated under reduced pressure and hydrogen gas was introduced (balloons). The mixture was vigorously stirred under a hydrogen atmosphere (balloons replaced as needed) overnight. The reaction was filtered through a Celite© pad which was washed with further methanol (excess). The filtrate was evaporated under reduce pressure to give **23d** (18.95 g, 96.1 mmol) as an off-white solid in 96% yield.

Rf 0.25 (5% MeOH/EtOAc); **Mp** 180-183 ^{o}C; **$[\alpha]_D^{19}$** - 36.5 (MeOH, c = 2.8); **δ_H** (D_2O) 4.06 (1H, dd, *J* 10.0, 4.7 Hz, CH), 3.74-3.69 (1H, m, CH), 3.27-3.19 (2H, m, CH), 2.43-3.33 (1H, m, CH), 1.14-1.99 (4H, m, 4 x CH), 1.93-1.83 (3H, m, 3 x CH), 1.68-1.63 (1H, m, CH), 1.50-1.11 (5H, m, 5 x CH); **δ_C** (D_2O) 174.8, 66.2, 64.4, 52.5, 29.5, 28.3, 24.4, 24.3, 23.6; **ν_{max}** 3401, 3027, 2967, 2874, 2812, 1656, 1385; **MS(EI -ve) m/z** 196.1 (100 %, $[M-H]^-$); **HRMS(ES -ve) m/z** found 196.1343, $C_{11}H_{18}NO_2$ ($[M-H]^-$) requires 196.1343.

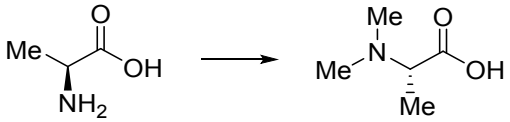
N-cyclohexyl-*L*-proline 23d[6]: ^{1}H NMR (D_2O)



N-cyclohexyl-*L*-proline 23d[6]: ^{13}C NMR (D_2O)



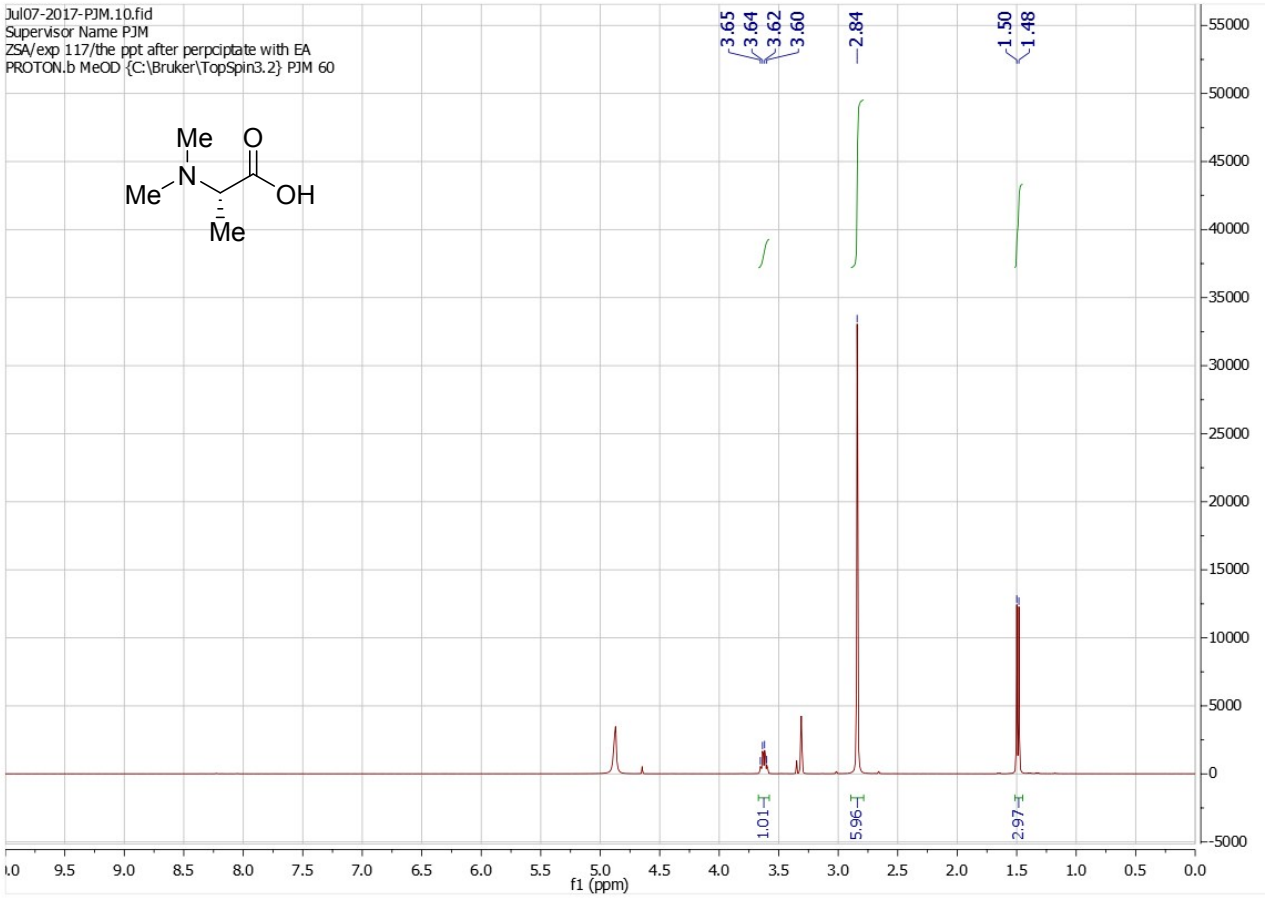
***N, N*-dimethyl-*L*-alanine 42a[7a]**



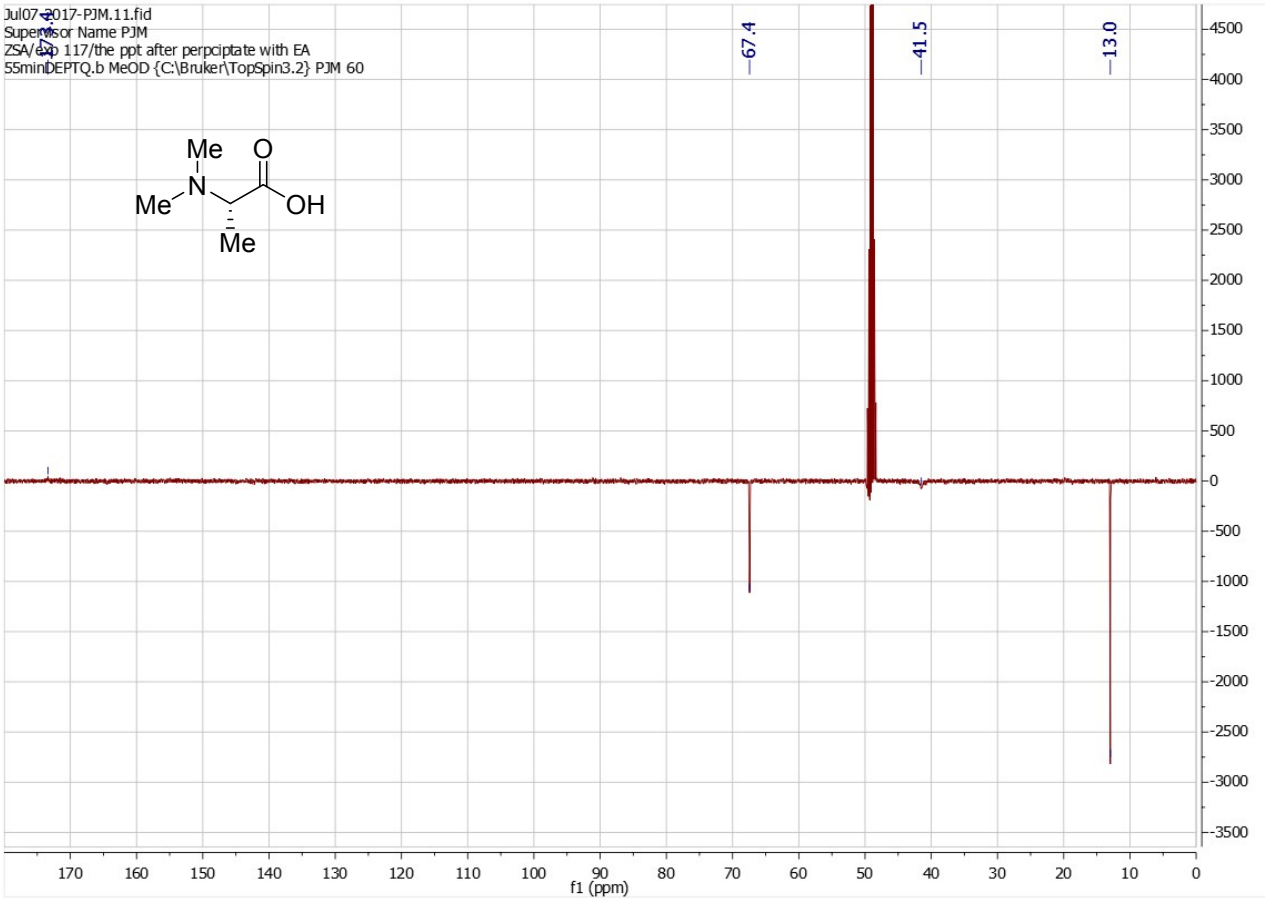
To a suspension of *L*-alanine (20.0 g, 0.225 mmol, 1.0 equiv.) dissolved in water (100 mL) was added aqueous formaldehyde 37% w/w (52.8 g, 0.65 mol, 64.8 mL, 2.9 equiv.) and palladium on charcoal (6.0 g, 10%). The flask was purged with nitrogen and then saturated with hydrogen under balloon pressure. After purging and back-filling with hydrogen three times, the reaction mixture was stirred under hydrogen at rt and atmospheric pressure for 7 days. Upon completion, the resulting aqueous slurry was heated to reflux for 30 min and then filtered while hot. The filtrate was concentrated *in vacuo* and azeotroped repeatedly with toluene to afford a white solid. The crude product was dissolved in a hot EtOH/acetone (20 mL/150 mL) mixture, then cooled overnight in a freezer. The cooled mixture was then diluted with PE until the cloud point, then kept in the freezer overnight. An initial crop of **42a** (15.4 g) was obtained as a white solid. After evaporation and recrystallization of the product in the same manner a second crop (8.53 g) was obtained. Repetition of this gave a third crop (5.33 g, 20%) to give an overall yield of 79 % (29.3 g).

Mp 184-185 °C (Lit.[7a] 184 °C); **$[\alpha]_D^{23}$** 8.3 (H_2O, c = 5.0, Lit[7b] 7.8 (H_2O, c = 5); **δ_H** (CD_3OD) 3.63 (1H, q, *J* 7.2 Hz, CH), 2.84 (6H, s, 2 x CH_3), 1.49 (3H, d, *J* 7.2 Hz, CH_3); **δ_C** (CD_3OD) 173.4, 67.4, 41.5, 13.0; **ν_{max}** 2939, 1596, 1329; **MS (ESI -ve) m/z** 59.0 (100 %), 116.1 ([M-H]$^-$, 6 %), **HRMS (ESI -ve) m/z** found 116.0718, $C_5H_{10}NO_2$ ()[M-H]$^-$) requires 116.0717.

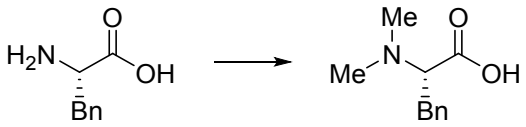
***N, N*-dimethyl-*L*-alanine 42a[7a]: ^{1}H NMR (CD_3OD)**



***N, N*-dimethyl-*L*-alanine 42a[7a]: ^{13}C NMR (CD_3OD)**



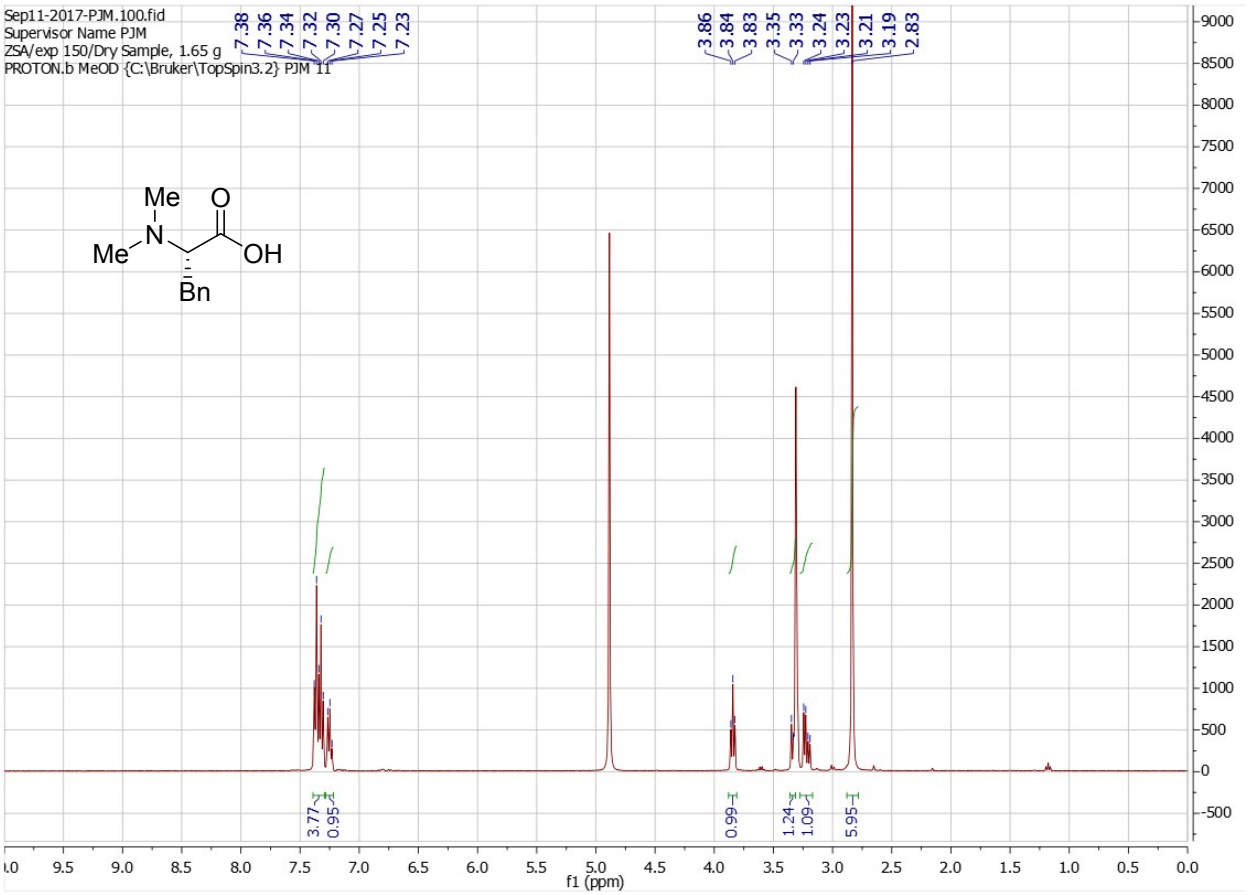
***N,N*-dimethyl-*L*-phenylalanine 42b[7b]**



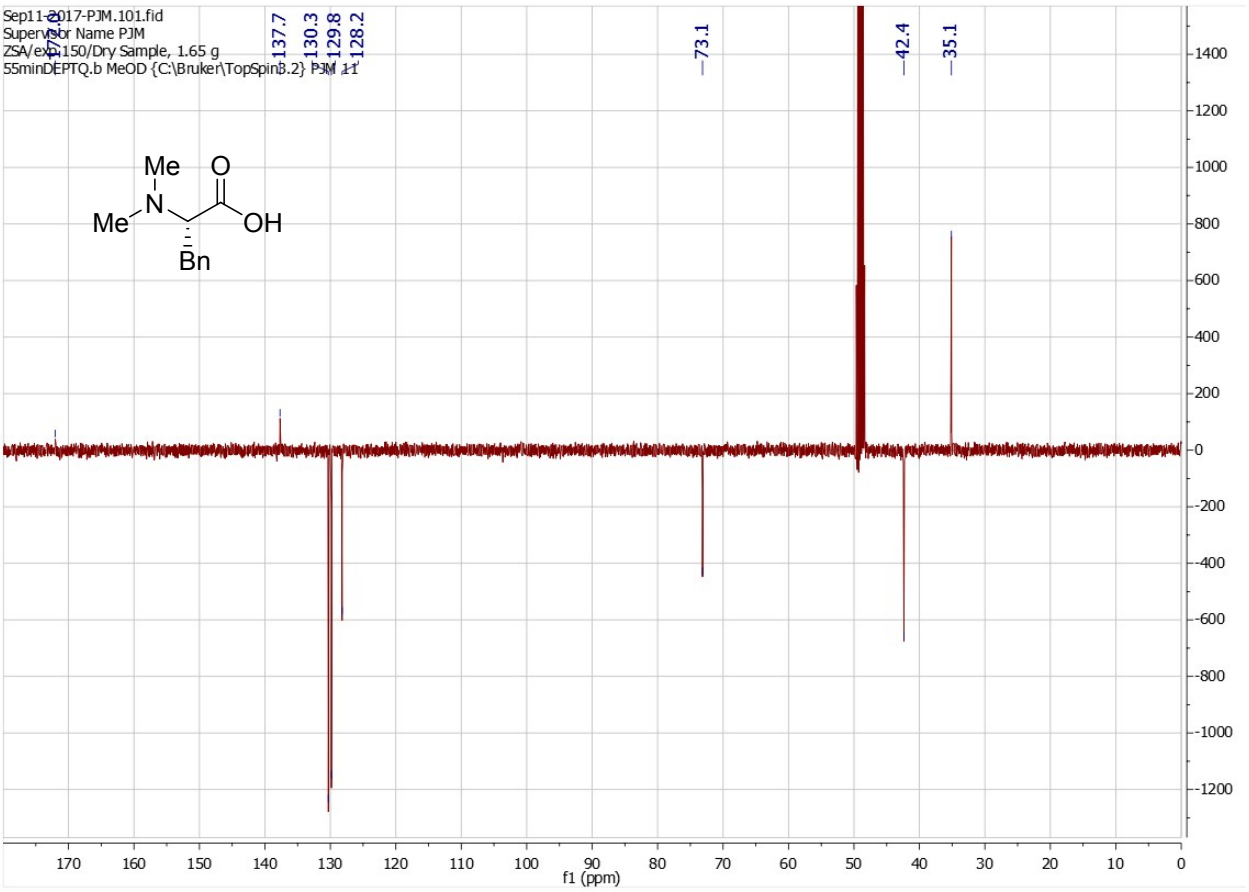
Aqueous formaldehyde (37% w/w, 6.42 g, 79.7 mmol, 5.9 mL, 6.5 equiv.) was added to a solution of *L*-phenylalanine (2.0 g, 12.1 mmol, 1.0 equiv.) dissolved in water (100 mL) and the mixture stirred for 10 min. The reaction flask was evacuated under reduced pressure, purged with nitrogen gas and Pd/C (10%, 0.60 g) was added. The reaction flask was purged with hydrogen gas (balloons), then vigorously stirred under a hydrogen atmosphere (balloons replaced as needed) for 5 days. The reaction was heated at reflux for 30 min, then filtered whilst hot through a pad of Celite©. The filtrate was concentrated *in vacuo,* then redissolved in a small volume of water (ca. 20 mL) and evaporated again to remove excess ethanol and formaldehyde. This process was repeated until a greyish solid was obtained which was then dissolved in a minimum amount of hot EtOH (ca. 35 mL), cooled to rt and left in the freezer overnight to give **42b** (1.99 g, 10.3 mmol) as off white crystals in 85 % yield.

Mp 214-216 ^{o}C (Lit.^{REF} 218 ^{o}C); $\mathbf{[\alpha]_D^{19}}$ 76.8 (H_2O, c = 1.98), (Lit.[7b] 77.5 (H_2O, c = 1.98)); $\mathbf{\delta_H}$ (CD_3OD) 7.30-7.38 (4H, m, 4 x CH), 7.25 (1H, br t, *J* 7.2 Hz, CH), 3.84 (1H, dd (app triplet), *J* 6.5, 7.1 Hz, CH), 3.31 (1H, dd, *J* 14.5, 6.5 Hz, CH), 3.21 (1H, dd, *J* 14.5, 7.1 Hz, CH), 2.83 (6H, s, 2 x CH_3); $\mathbf{\delta_C}$ (CD_3OD) 172.0, 137.7, 130.3, 129.8, 128.2, 73.1, 42.4, 35.1; $\mathbf{\nu_{max}}$ 3402, 3029, 2921, 1609, 1516, 1335; **MS (ESI) m/z** 194.1 (100%, $[M+H]^+$), 161.1 (36 %), **HRMS (ESI) m/z** found 194.1183, $C_{11}H_{16}NO_2$ ($[M+H]^+$), requires 194.1176.

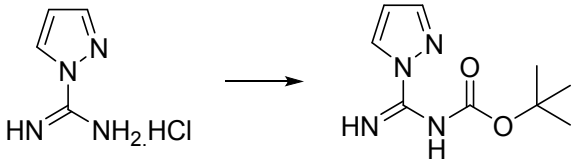
N,N-dimethyl-*L*-phenylalanine 42b[7b]: ^{1}H NMR (CD_3OD)



N,N-dimethyl-*L*-phenylalanine 42b[7b]: ^{13}C NMR (CD_3OD)



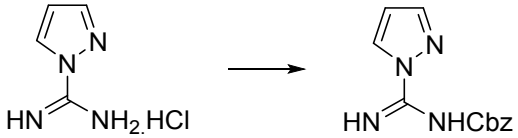
***N*-Boc-1*H*-Pyrazole-1-Carboxamide AA.**[1]



1*H*-Pyrazole-1-carboxamidine (10.0 g, 68 mmol) and di-*tert*-butyl dicarbonate (22.2 g, 102 mmol) were dissolved in anhydrous THF (40 mL) and *N*-diisopropylethylamine (23.6 mL, 136 mmol) was added. After stirring for 24 h, the reaction was diluted with water (50 mL), extracted with dichloromethane (4 × 50 mL) and the combined organic extracts washed with brine (50 mL). After drying ($MgSO_4$) the solvent was removed under reduced pressure and the crude product re-crystallised from a minimum volume of warm DE to give **AA** (10.80 g, 51.4 mmol) as a white crystalline solid 75 % yield. Data was in agreement with the literature.

Mp 100-102 °C (Lit.[1] 98-99 °C); $\boldsymbol{\delta_H}$ ($CDCl_3$) 9.05 (1H, br. s, NH), 8.46 (1H, br d, *J* 2.7 Hz, CH), 7.68 (2H, m, CH, NH), 6.40 (1H, d, *J* 1.5 Hz, CH), 1.55 (s, 9H, ^{t}Bu); $\boldsymbol{\delta c}$ ($CDCl_3$) 163.6, 155.3, 143.5, 129.0, 109.1, 80.3, 28.3; $\boldsymbol{\nu_{max}}$ 3432, 3316, 3144, 3126, 2977, 2964, 1655, 1606, 1510, 1364, 1308; **MS (ESI) m/z** 210.1 ([100%, M]$^+$), 211.1 ([91%, M+H]$^+$), 155.1 (51); **HRMS(ESI)** found 210.1123, $C_9H_{14}N_4O_2$ [M]$^+$) requires 210.1117; found 211.1197, $C_9H_{15}N_4O_2$ ([M+H]$^+$) requires 211.1190

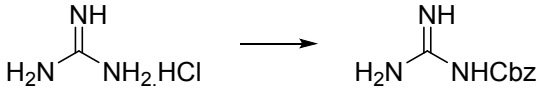
***N*-Cbz-1*H*-Pyrazole-1-Carboxamide BB.**



1*H*-pyrazole-1-carboxamidine hydrochloride (10.0 g, 68.2 mmol, 1.0 equiv.) and benzyl CFate (17.5 g, 14.6 mL, 20.6 mmol, 1.5 equiv.) were dissolved in dry THF (50 mL) and *N*-diisopropylethylamine (16.8 g, 22.6 mL, 129.6 mmol, 1.90 equiv.) was added drop-wise over 5 minutes. After 24 h the reaction was diluted with water (120 mL), extracted with dichloromethane (3 × 200 mL) and the organic phase combined and washed with brine (200 mL). After drying ($MgSO_4$) and evaporation, recrystallisation from dichloromethane yielded **BB** (13.3 g, 54.5 mmol) as rectangular transparent crystals in 80 % yield. Data was in agreement with the literature.

Mp 109 °C (lit. 107-108°C); $\mathbf{R_f}$ 0.31 (30% EtOAc in Petrol); $\boldsymbol{\delta_H}$ ($CDCl_3$) 9.05 (1H, br s, NH), 8.46 (1H, d, *J* 2.7 Hz, CH), 7.70 (1H, br d, *J* 1.6, CH), 7.65 (1H, br s, NH), 7.44 (2H, br d, *J* 7.0 Hz, 2 x CH), 7.29-7.39 (m, 3H, 3 x CH), 6.42 (1H, dd, *J* 2.7, 1.6 Hz, CH), 5.22 (s, 2H, CH_2); $\boldsymbol{\delta_C}$ ($CDCl_3$) 163.9, 155.4, 143.9, 136.4, 129.1, 128.6, 128.4, 128.3, 109.5, 67.8; $\boldsymbol{\nu_{max}}$ 3442, 3308, 3144, 3067, 2963, 1664, 1607, 1530, 1272; **m/z (ESI)** 245.1 (100%, [M+H]$^+$), 130.2 (23 %); **HRMS (ESI)** found 245.1041, $C_{12}H_{13}N_4O_2$ ([M+H]$^+$) requires 245.1039.

N-Cbz-Guanidine CC.[2]

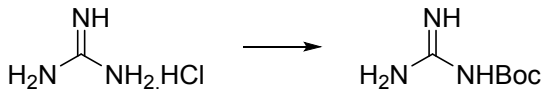


A solution of benzyl chloroformate (13.1 g, 10.9 mL, 76.5 mmol, 1 equiv.) in dioxane (25 mL) was added slowly (15 h) at 5 °C under vigorous stirring to a mixture of guanidine hydrochloride (45.7 g, 0.48 mol, 6.25 equiv.) and sodium hydroxide (19.1 g, 0.48 mol, 6.25 equiv.) dissolved in water (100 mL). The resulting suspension was stirred at rt for an additional 10 h, then extracted with

ethyl acetate (4 x 100 mL). The combined organic layers were washed with brine (2 x 50 mL), dried ($MgSO_4$) and evaporated under vacuum to give a crude product. Recrystallization from EA/PE gave **CC** (13.5 g, 69.8 mmol) as white crystals in 91 % yield. Data was in agreement with the literature.

Mp 139-142 °C (Lit[2] 140–142 °C); δ_H ($(CD_3)_2SO$) 7.25-7.60 (5H, m, Ph), 6.07-8.01 (4H, br s, 2 x NH, NH_2), 4.96 (2H, s, CH_2); δ_C ($(CD_3)_2SO$) 163.3, 163.0, 138.2, 128.2, 127.3, 64.8; ν_{max} 3450, 3405, 3306, 3065, 3040, 2954, 1621, 1591, 1522, 1290 cm^{-1}; **MS (ESI) m/z** 194.1 (100% $[M+H]^+$); HRMS **(ESI) m/z** found 194.0922, $C_9H_{11}N_3O_2$ ($[M+H]^+$) requires 194.0924.

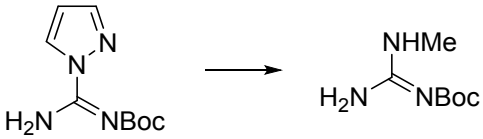
N-Boc-Guanidine DD.[2]



A solution of Boc_2O (6.01 g, 6.3 mL, 27.5 mmol, 1 equiv.) in dioxane (50 mL) was added dropwise over 8 h with vigorous stirring to a cooled (0 °C) solution of guanidinium chloride (13.15 g, 137.7 mmol, 5 equiv.) and sodium hydroxide (6.06 g, 151.4 mmol, 5.5 equiv in water (25 mL). The resulting suspension was stirred at rt for an additional 20 h and then extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine (3 x 50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude compound, which was dissolved in hot EA to which PE was added to the cloud point. Overnight cooling in the freezer gave **DD** (4.3 g, 27.0 mmol) as a white solid in 98 % yield. Data was in agreement with the literature.

Rf 0.25 (20 % DCM in ME, with 1 % NEt_3); **Mp** 167 °C (dec.) (Lit.[2] 165 ^{0} C (dec.)); δ_H ($(CD_3)_2SO$) 5.49-8.06 (4H, br s, 2 x NH, NH_2), 1.34 (9H, s, 3 x CH_3); δ_C ($(CD_3)_2SO$) 163.4, 162.7, 75.5, 28.3; ν_{max} 3441, 3402, 3315, 3139, 2975, 2935, 1656, 1533, 1308 cm^{-1}; **MS (ESI) m/z** 319.2 (100 %, $[2M+H]^+$), 341.2 (40 %, $[2M+Na]^+$), 160.1 (60 %, $[M+H]^+$), **HRMS (ESI) m/z** found 160.1077, $C_6H_{13}N_3O_2$ ($[M+H]^+$) requires 160.1081.

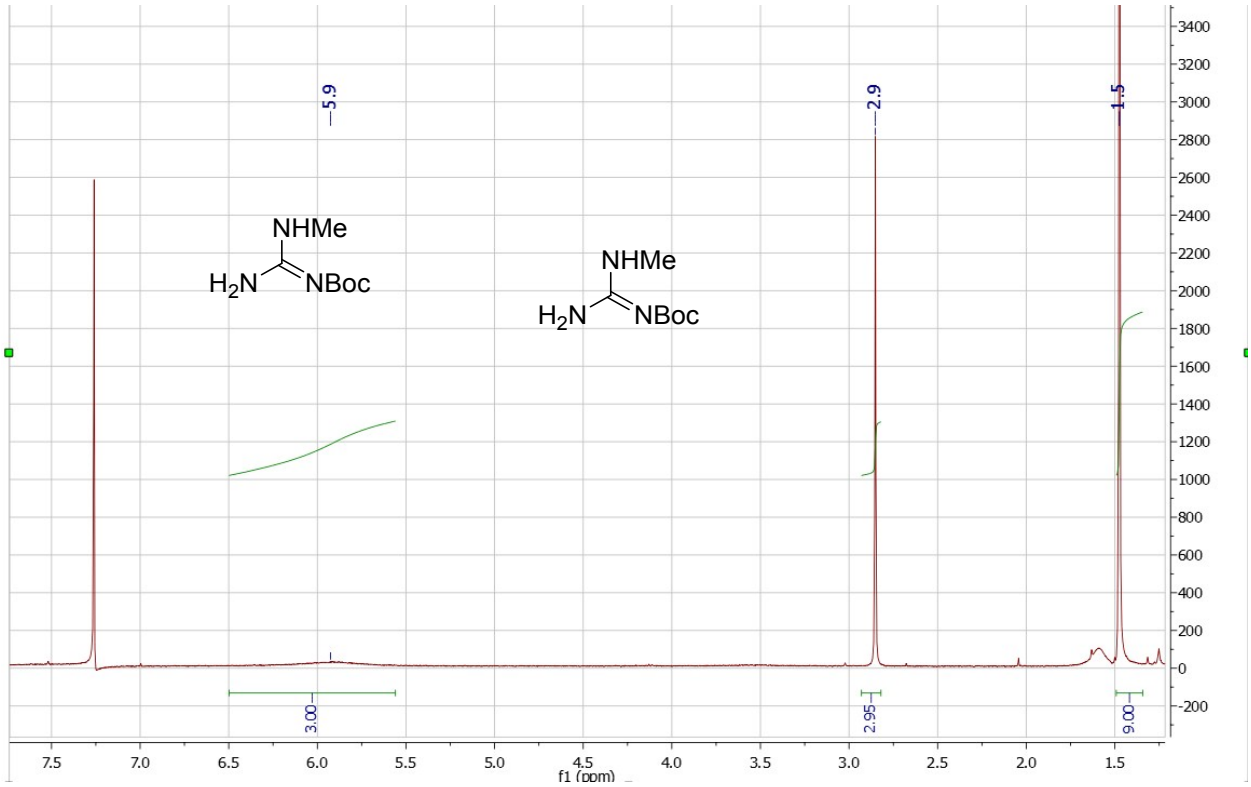
N-methyl-*N'*-Boc-guanidine EE[8]



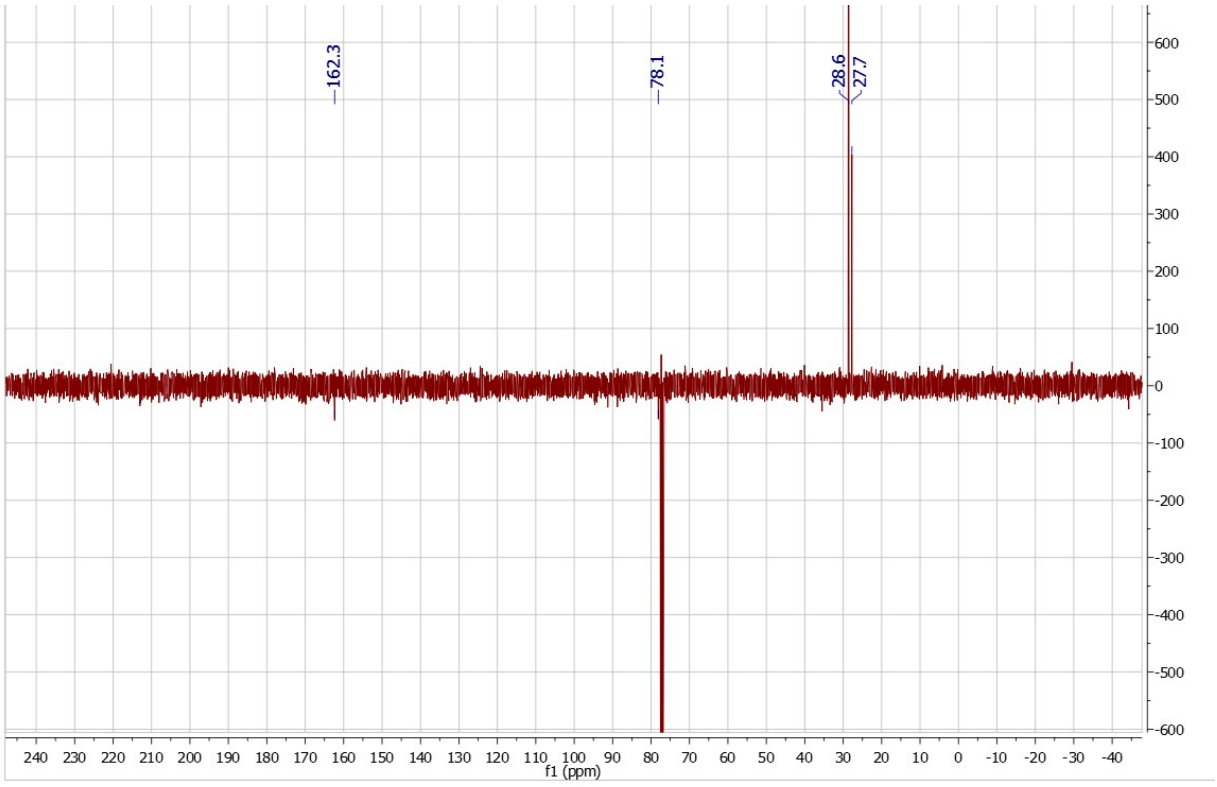
Methylamine (aq. 40 %, 3.5 mL, 2.77 g, 35.7 mmol, 3 equiv.) was added to a solution of **AA** (2.5 g, 11.9 mmol, 1.0 equiv.) in THF (25 mL) and stirring for 24 h. Water (100 mL) was added and the mixture extracted with EA (2 x 100 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL) then dried ($MgSO_4$), filtered and evaporated under vacuum. The residue was purified by silica gel chromatography (gradient elution (70-100 % EA/PE) to give **EE** (1.69 g, 82 %, 0.96 mmol) as an off-white crystalline solid. Data not reported in the literature.

Rf 0.09 (50% EA/PE); **Mp**. 176-178 °C; δ_H ($CDCl_3$) 5.93 (3H, br s, 3 x NH), 2.85 (3H, s, CH_3), 1.47 (9H, s, CH_3); δ_C ($CDCl_3$) 162.4, 78.1, 28.6, 27.7; ν_{max} 3245, 3440, 2975, 2931, 1638, 1589, 1362, 1136 cm^{-1}; **MS (ESI) m/z** 174.1(100 %, $[M+H]^+$), **HRMS (ESI) m/z** found 174.1237, $C_7H_{16}N_3O_2$ ($[M+H]^+$) requires 174.1237.

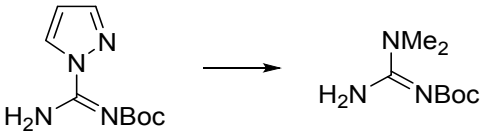
_N_-methyl-_N'_-Boc-guanidine EE[8]: ^{1}H NMR



_N_-methyl-_N'_-Boc-guanidine EE[8]: ^{13}C NMR



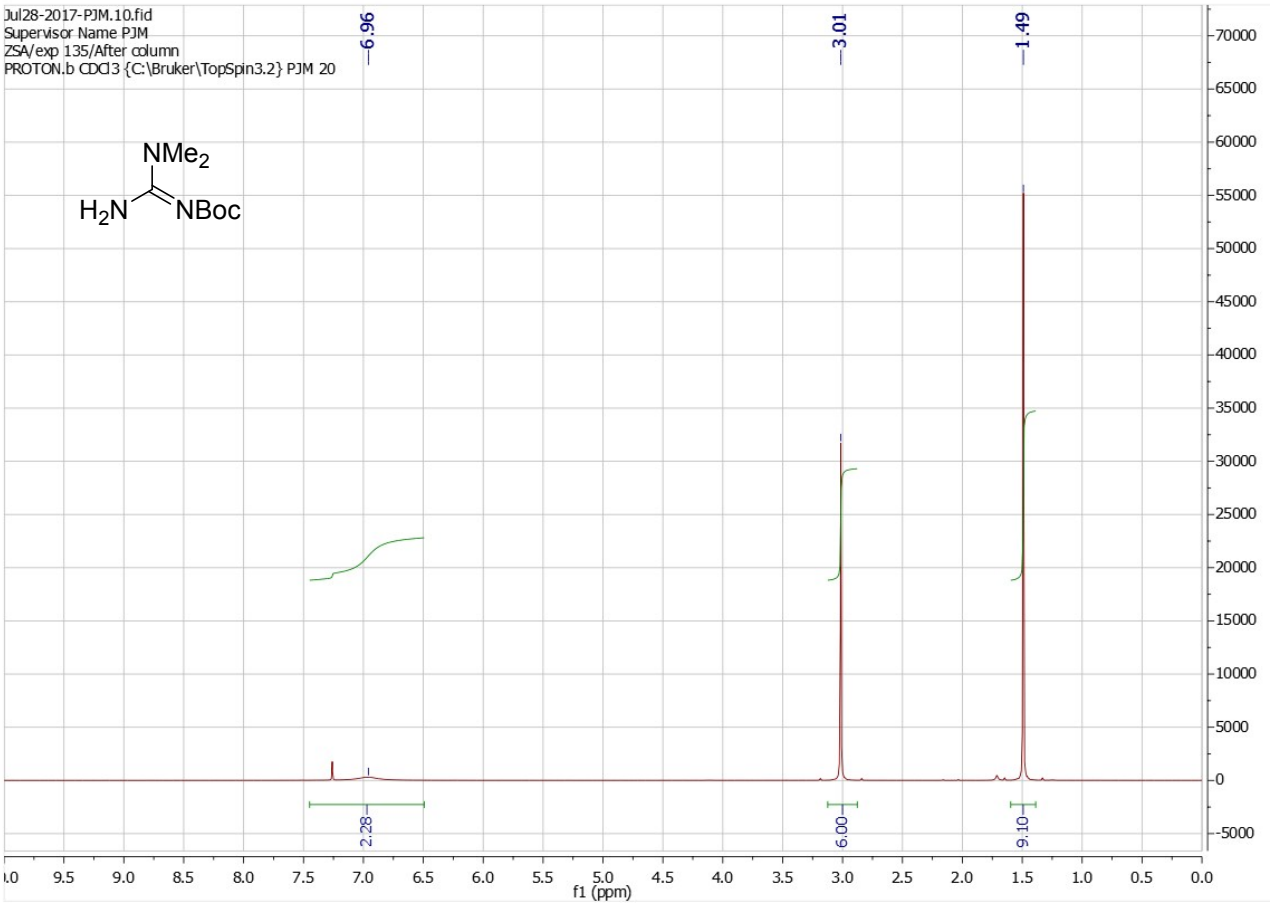
***N,N*-dimethyl-*N'*-Boc-guanidine FF.**



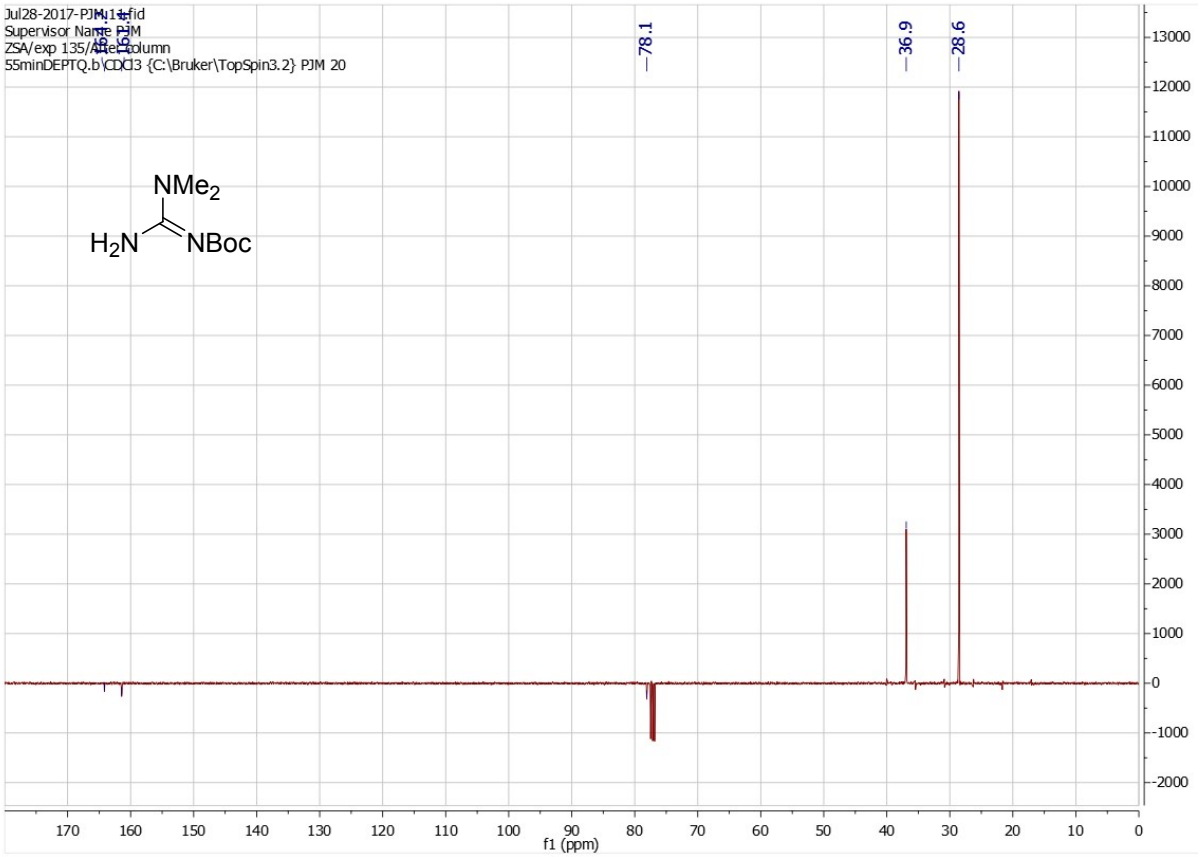
Dimethylamine (aq. 40%, 8.04 g, 71.4 mmol, 9.0 mL, 6 equiv.) was added to a solution of **AA** (2.5 g, 11.89 mmol, 1 equiv) in THF (25 mL) and the mixture stirred for 24 h. Water (150 mL) was added and the mixture extracted with EA (2 x 100 mL). The combined extracts washed with water (50 mL), brine (50 mL) and then dried ($MgSO_4$). After evaporation under vacuum, purification by silica gel chromatography (70-100 % EA/H) gave **FF** (2.19 g, 11.7 mmol) as an off-white crystalline solid in 98 % yield.

Mp 176 °C; **Rf** 0.27 (100% EA); δ_H ($CDCl_3$) 6.50-7.45 (2H, br s, NH_2), 3.01 (6H, s, 2 x CH_3), 1.49 (9H, s, 3 x CH_3); **δc** ($CDCl_3$) 164.2, 161.4, 78.1, 36.9, 28.6; ν_{max} 3370, 3231, 2976, 2933, 1651, 1589, 1317, 1268; **m/z (ESI)** 188.1 (48 %, $[M+H]^+$); **HRMS (ESI)** found 188.1393, $C_8H_{18}N_3O_2$ ($[M+H]^+$) requires 188.1394.

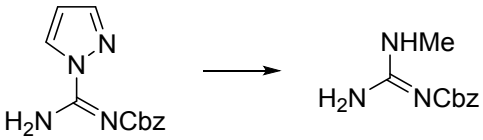
***N,N*-dimethyl-*N'*-Boc-guanidine FF ^{1}H NMR**



***N,N*-dimethyl-*N'*-Boc-guanidine FF ^{13}C NMR**



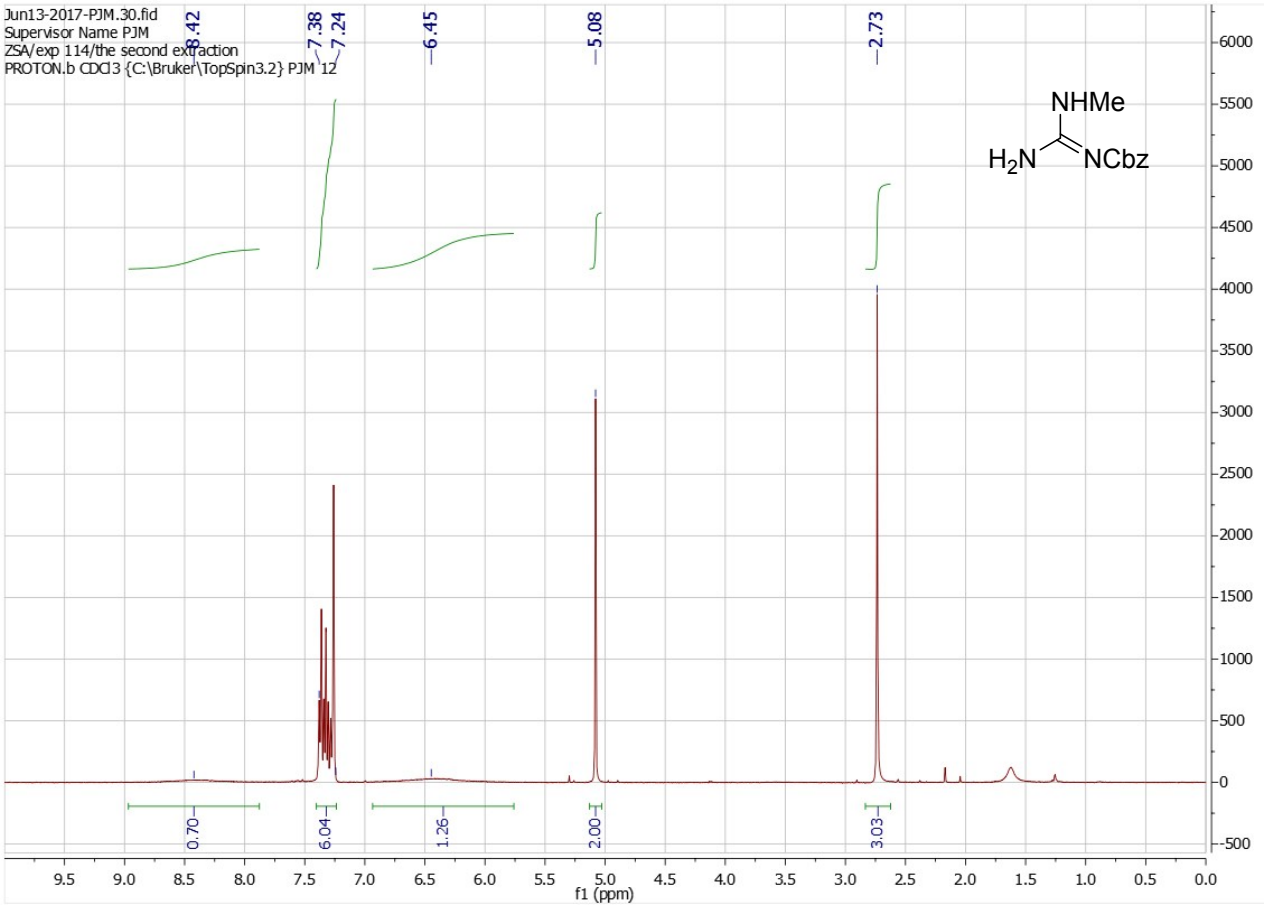
***N*-methyl-*N'*-Cbz-guanidine GG.**



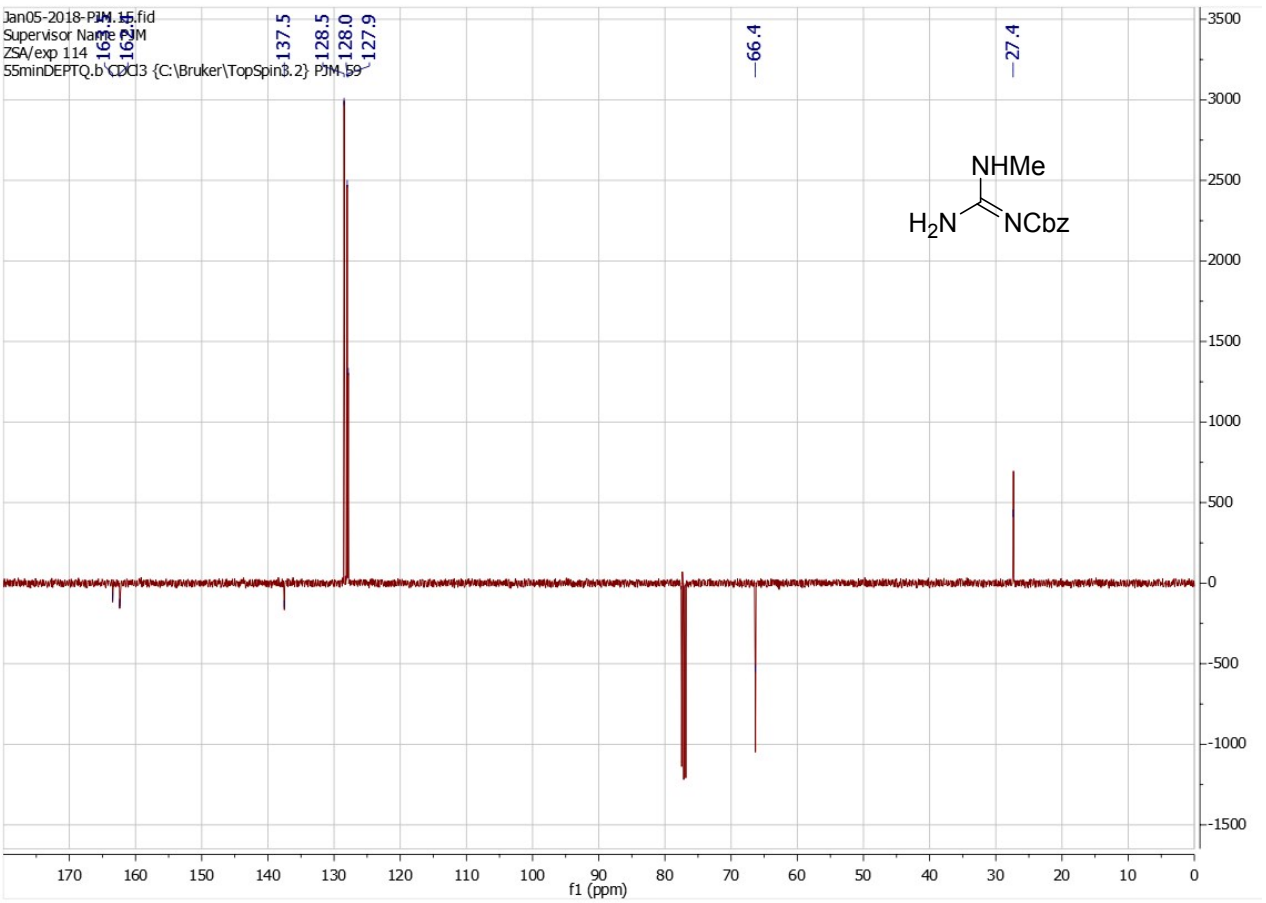
Methylamine (aq. 40 %, 1.27 g, 16.4 mmol, 1.6 mL, 2.0 equiv.) was added to a solution of **BB** (2.0 g, 8.19 mmol, 1.0 equiv.) in THF (25 mL). The reaction was vigorously stirred for 90 min, at which point TLC indicated the complete consumption of **BB**. The reaction was diluted with water (50 mL), extracted with CF (3 x 100 mL) and the combined organic extracts washed with water (2 x 50 mL) and brine (2 x 50 mL). After drying ($MgSO_4$) and evaporation under vacuum, the crude product was dissolved in the minimum volume of DCM and hexane was added to the cloud point. After standing for 24 h, filtration gave **GG** (1.39 g, 6.71 mmol) as a white crystalline solid in 82 % yield.

Mp 164 °C; **Rf** 0.15 (EA); δ_H ($CDCl_3$) 8.75-7.93 (1H, br s, NH), 7.24-7.38 (5H, m, Ph), 5.76-6.92 (2H, br s, NH_2), 5.08 (2H, s, CH_2), 2.73 (3H, s, CH_3); δ_c ($CDCl_3$) 163.5, 162.4, 137.5, 128.5, 128.0, 127.9, 66.4, 27.4; ν_{max} 3391, 3305, 3164, 2984, 2925, 1622, 1578, 1494, 1291, 1016; **MS (ESI) m/z** 208.1 (100 % $[M+H]^+$), 164.1 (67 %); **HRMS (ESI)** found 208.1091, $C_{10}H_{14}N_3O_2$ ($[M+H]^+$) requires 208.1081.

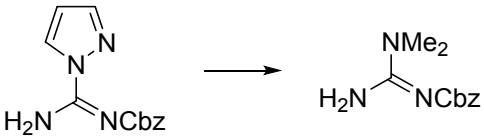
N-methyl-*N*'-Cbz-guanidine GG: ^{1}H NMR



N-methyl-*N*'-Cbz-guanidine GG: ^{13}C NMR



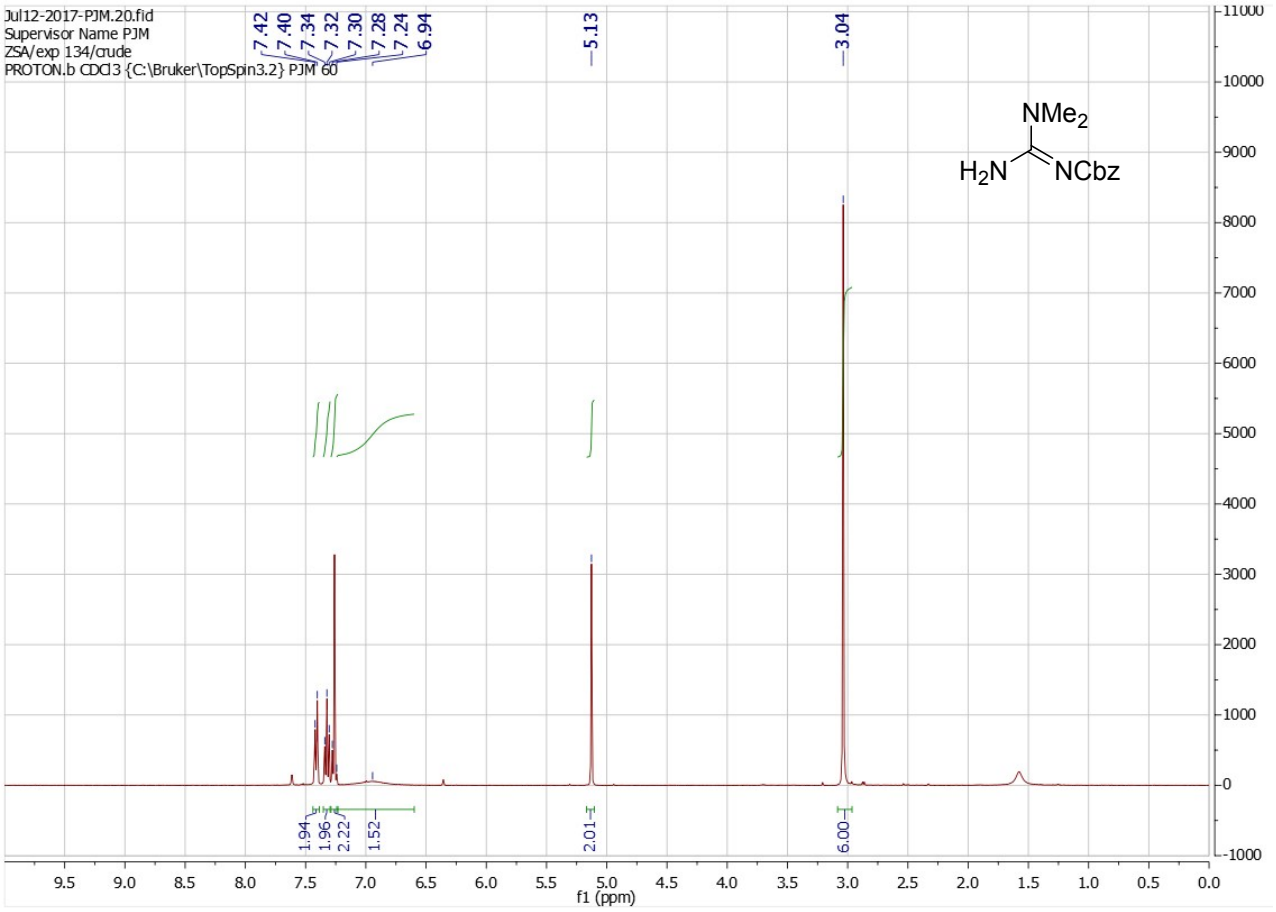
***N,N*-dimethyl-*N'*-Cbz-guanidine HH.**



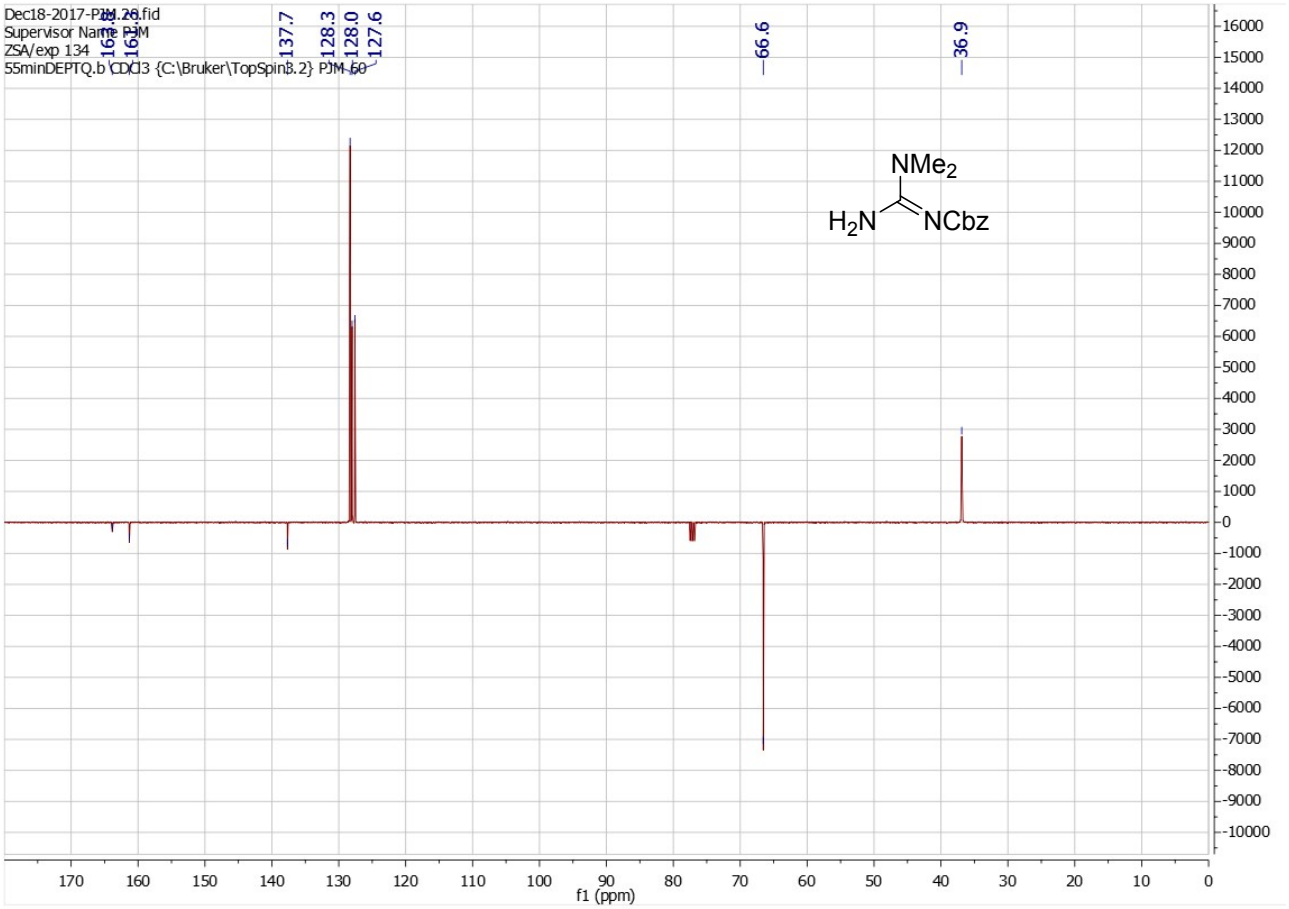
Dimethylamine (aq., 40%, 1.27 g, 16.4 mmol, 1.6 mL, 2.0 equiv.) was added to a solution of **BB** (2.50 g, 10.24 mmol, 1.0 equiv.) dissolved in THF (25 mL) and the mixture vigorously stirred for 48 h, at which point TLC indicated the complete consumption of **BB**. Water (150 mL) was added, the mixture extracted with CF (3 x 100 mL) and the combined extracts washed with water (2 x 50 mL) and brine (2 x 50 mL), then dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was dissolved in the minimum amount of DCM and hexane was added to the cloud point. After standing for 24 h, the product was collected by filtration to give **HH** (2.20 g, 9.94 mmol) as a pale yellow crystalline solid in 97 % yield.

Mp 79-81 °C; **Rf** 0.09 (50% EA in PE); δ_H ($CDCl_3$) 7.41 (2H, br d, *J* 7.3 Hz, 2 x CH), 7.32 (2H, br t, *J* 7.3 Hz, 2 x CH), 7.24-7.28 (1H, m, CH), 6.61-7.24 (2H, br s, NH_2), 5.13 (2H, s, CH_2), 3.04 (6H, s, 2 x CH_3); δ_c ($CDCl_3$) 163.8, 161.3, 137.7, 128.3, 128.0, 127.6, 66.6, 36.9; ν_{max} 3376, 3285, 3.037, 2957, 2894, 1575, 1479, 1442; **m/z (ESI)** 222.1 (100 % $[M+H]^+$); **HRMS (ESI)** found 222.1237, $C_{11}H_{16}N_3O_2$ (100 % $[M+H]^+$) requires 222.1237.

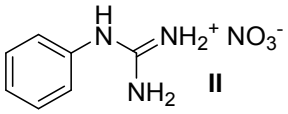
***N,N*-dimethyl-*N'*-Cbz-guanidine HH: ^{1}H NMR**



***N,N*-dimethyl-*N'*-Cbz-guanidine HH: ^{13}C NMR**



Phenylguanidinium nitrate II.[9]

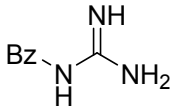


II

Aniline (9.3 g, 9.12 mL, 99.9 mmol, 1.0 equiv.) was dissolved in EtOH (75 mL) and an aqueous solution of HNO_3 (9.0 mL, 131.2 mmol, of a 65% w/w solution prepared from 90 % w/w nitric acid by slow addition to water **(CAUTION)**) was then cautiously added. An aqueous solution of cyanamide (50% w/w, 12.6 g, 11.5 mL, 148.0 mmol, 1.48 equiv.) was then added to the mixture, which was then heated to reflux for 16 h. The mixture was cooled (ice) and DE (800 mL) was added and the mixture stirred vigorously for 1 h. The grey precipitate was removed by filtration, washed with DE (excess) and dried under vacuum to give **II** (11.7 g, 85.9 mmol) as a grey solid in 86% yield.Data was in agreement with the literature.

R_f 0.28 (10 % MeOH/EA); **Mp** 112-115 °C (Lit.[9] Mp 120-122 °C); **δ_H** ($(CD_3)_2SO$) 9.62 (1H, s, NH) 7.45 (2H, br t, *J* 7.8 Hz, 2 x CH), 7.33-7.40 (4H, br s, 2 x NH_2), 7.29 (1H, br t, *J* 7.8 Hz, CH), 7.24 (2H, br d, *J* 7.8 Hz, 2 x CH); **δ_C** (DMSO) 155.7, 135.3, 129.7, 126.5, 124.5; ν_{max} 3332, 3189, 3055, 1614, 1598, 1584, 1312 cm^{-1}; MS (ESI) m/z 136.1 $[M+H]^+$, **HRMS (ESI)** m/z found 136.0867, $C_7H_{10}N_3^+$ ($[M+H]^+$) requires 136.0869.

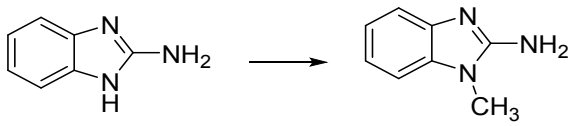
Preparation of *N*-carbamimidoylbenzamide JJ.[3]



Sodium metal (2.33g, 99.9 mmol) was added in portions to dry ethanol (60 mL) under a constant flow of nitrogen gas to produce a solution of sodium ethoxide. Guanidine carbonate (9.0 g, 49.9 mmol, 0.5 equiv.) was then added and the mixture stirred for 24 h at rt. The reaction was filtered under an inert atmosphere to remove precipitated sodium carbonate, following which ethyl benzoate **108** (10.5 g, 70.0 mmol, 0.7 equiv.) was added and the reaction stirred for a further 24 h. The reaction was evaporated to dryness at 70°C under rotary evaporation following which dioxane (ca 100 mL) was added to the residue and the mixture heated under reflux for 10 min, then hot filtered. The filtrate was cooled to rt and on standing white crystals formed, which were removed by filtration, to give **JJ** (3.68 g, 22.55 mmol) in 32 % yield Data was in agreement with the literature.

R_f 0.28 (10 % ME in EA); **Mp** 184-186 °C (Lit.[3] 211-214 °C, 158-160 °C); δ_H (CD_3OD); 7.84-7.86 (2H, m, CH), 7.42-7.51 (1H, m, CH), 7.38-7.41 (2H, t, *J* 7.5 Hz CH); **δ_C** (MeOH) 126.2, 127.0, 133.8, 134.9, 164.4, 168.9; ν_{max} (KBr disc) 3422, 3314, 3204, 1659, 1626, 1589, 1532, 1448, 1366, 1287, 1136 cm^{-1}; MS (ESI) m/z 164.0815 $[M+H]^+$, HRMS (ESI), m/z $C_8H_{10}N_3O^+$ $[M+H]^+$ requires 164.0818 found 164.0815.

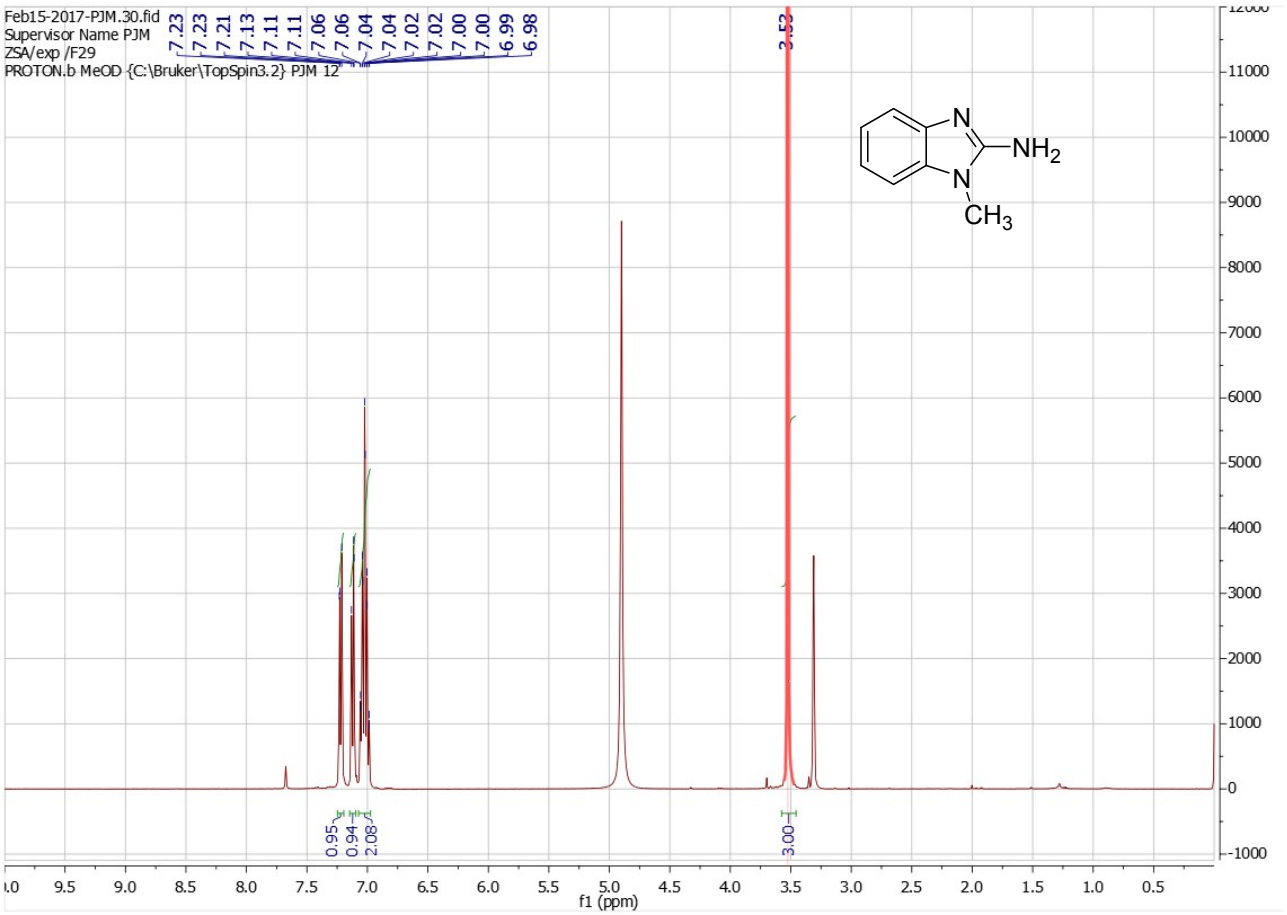
1-Methyl-1*H*-benzo[*d*]imidazol-2-amine KK.[10]



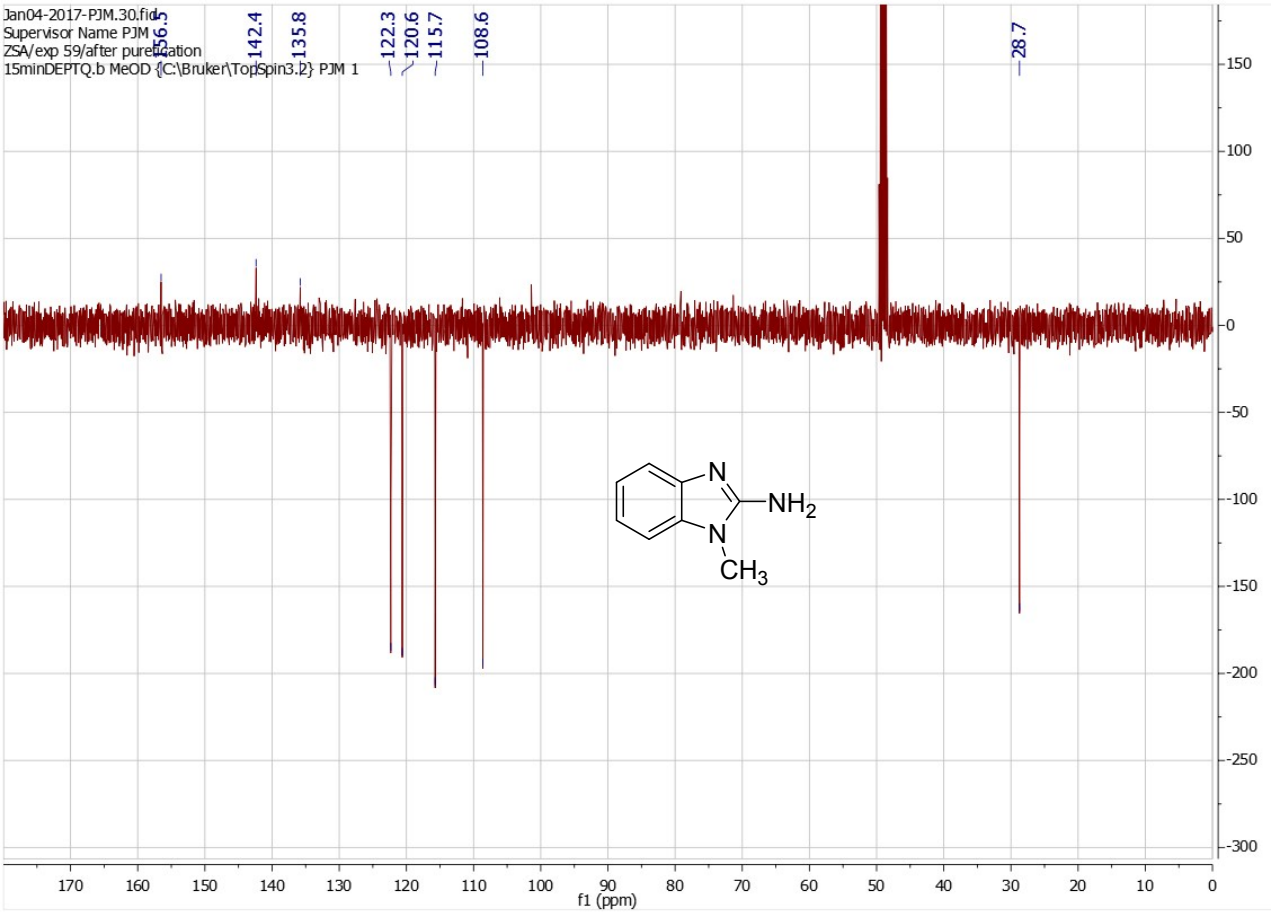
Powdered KOH (10.5 g, 187.8 mmol, 5.0 equiv.) was added to a stirred solution of 1*H*-benzo[*d*]imidazol-2-amine (5.0 g, 37.6 mmol, 1.0 equiv.) in acetone (200 mL). A thick white precipitate formed after 10 min whereupon methyl iodide (2.6 mL, 5.86 g, 41.3 mmol, 1.1 equiv.) was added and the reaction mixture stirred vigorously for 30 min. At this point, the brown solution was transferred to a separating funnel containing toluene (250 mL) and the mixture washed with water (120 mL), brine (120 mL) and then dried ($MgSO_4$). After evaporation under reduced pressure the reside was dissolved in a small volume of toluene and diluted with $CHCl_3$ to the cloud point then stored at -20 °C overnight. The solid was dissolved in dilute HCl (1M, adjusted to pH = 2) and extracted with $CHCl_3$ (3 x 100 mL). The aqueous acidic layer made alkaline with NaOH (aq. 10 % w/v) and extracted with DCM (3 x 50 mL). The DCM extract dried ($MgSO_4$) and evaporated under reduced pressure to give **KK** (1.39 g, 25%) as light brown solid. Data was in agreement with the literature.

Mp 203-204 °C (Lit.[10] 202-204 °C); **Rf** 0.13 (20% ME in EA); **δ_H** (CD_3OD) 7.22 (1H, br dd, *J* 6.9, 1.2 Hz, CH), 7.12 (1H, br dd, *J* 7.1, 1.4 Hz, CH), 6.98-7.06 (2H, m, 2 x CH), 3.53 (3H, s, Me); **δ_C** (CD_3OD) 156.4, 142.4, 135.8, 122.3, 120.6, 115.7, 108.6, 28.7; **ν_{max}** 3448, 3307, 3024, 2727, 1648, 1541, 1317 cm^{-1}; **MS (ESI) m/z** 148.1, (100 %, $[M+H]^+$); **HRMS (ESI) m/z** found 148.0872, $C_8H_{10}N_3$ ($[M+H]^+$) requires 148.0875.

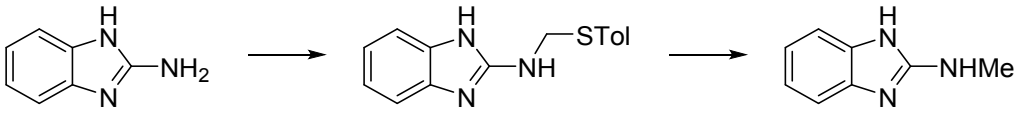
1-Methyl-1*H*-benzo[*d*]imidazol-2-amine KK[10]: ^{1}H NMR (CD_3OD)



1-Methyl-1*H*-benzo[*d*]imidazol-2-amine KK[10]: ^{13}C NMR (CD_3OD)



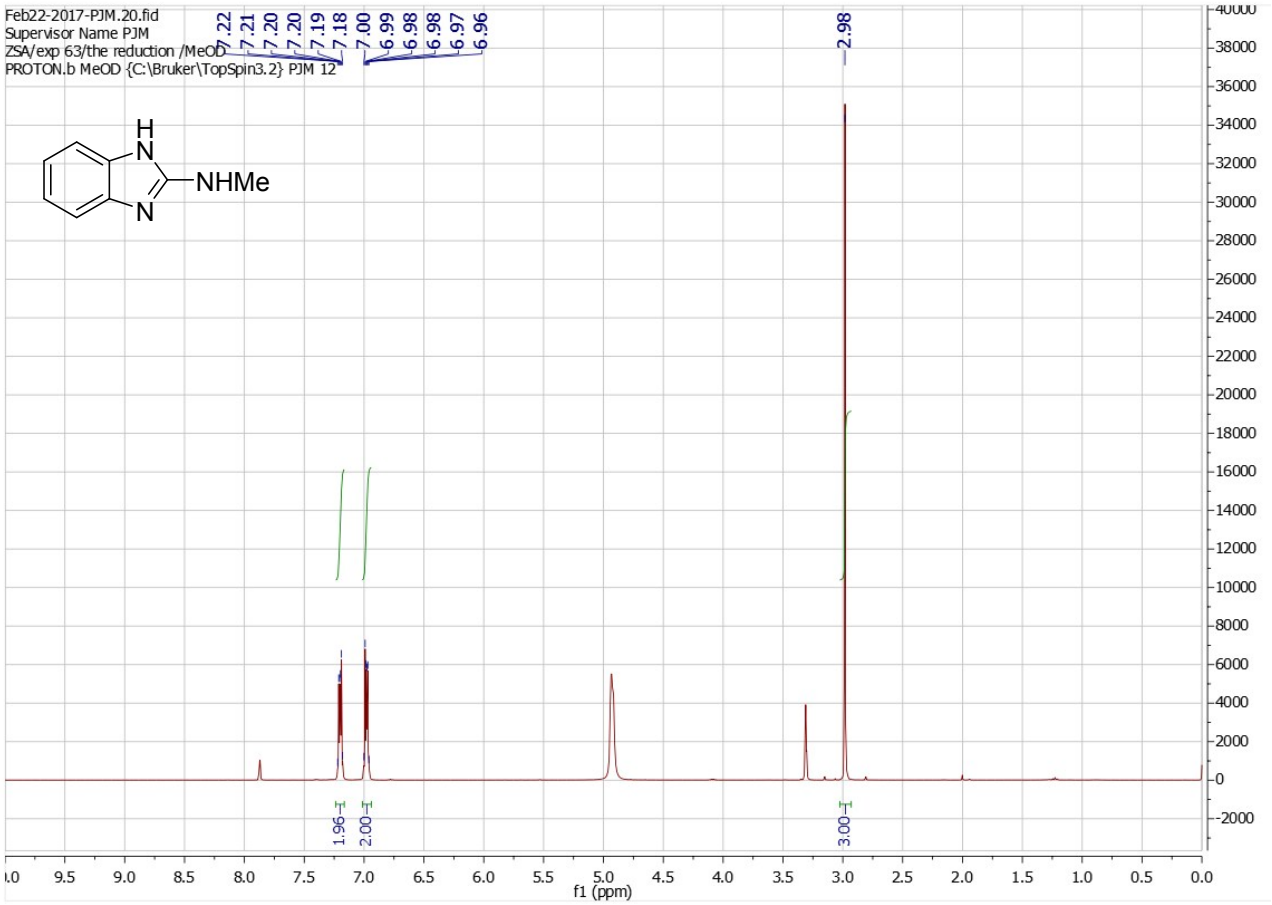
***N*-Methyl-1*H*-benzo[*d*]imidazol-2-amine LL**[11]



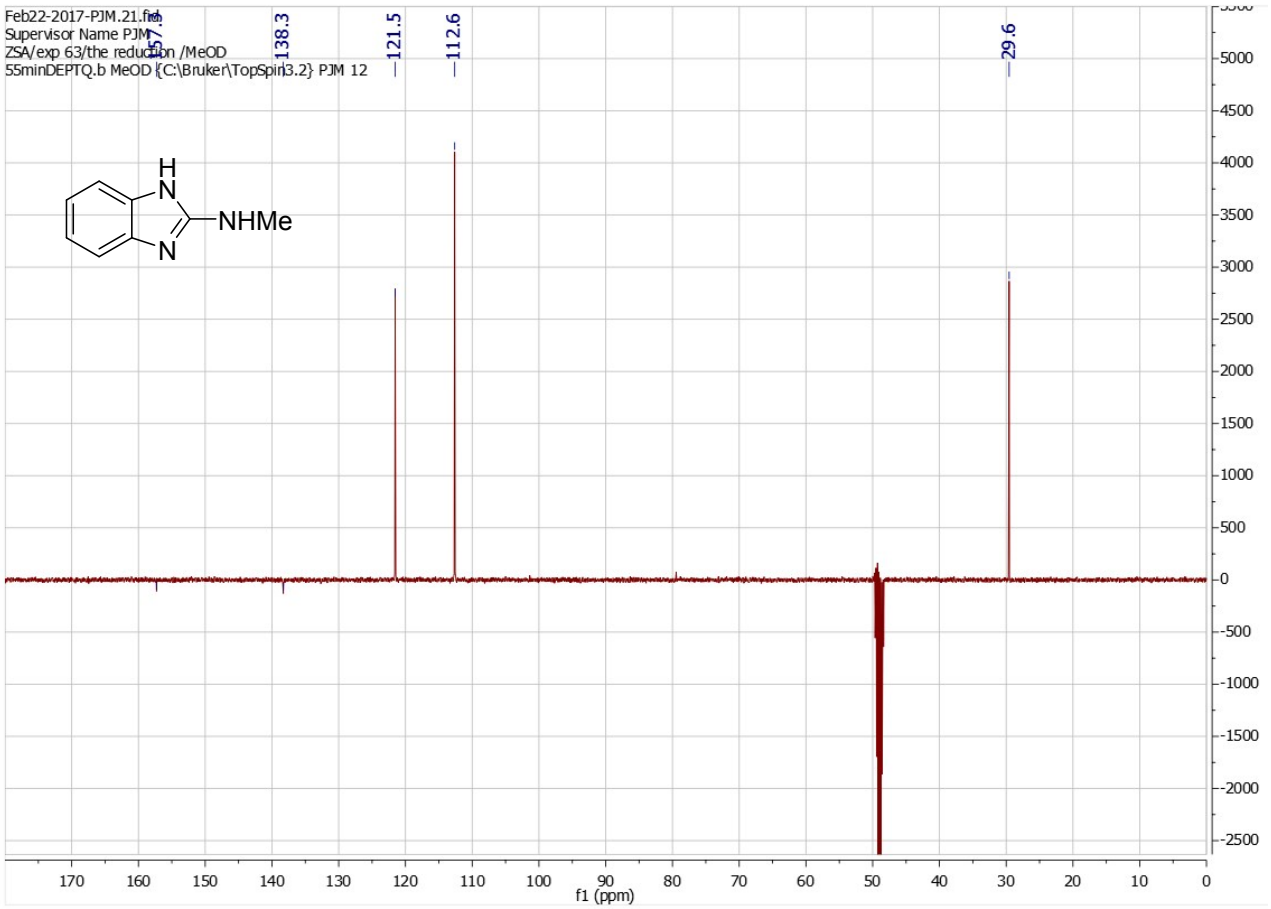
1*H*-Benzo[*d*]imidazol-2-amine (4.00 g, 30.0 mmol, 1.0 equiv.), formaldehyde (aq. 37 % w/v; 5.03 mL, 5.49 g, 67.6 mmol, 2.25 equiv.) and *p*-thiocresol (8.43 g, 68.0 mmol 2.26 equiv.) were dissolved in absolute ethanol (100 mL) and heated under reflux for 7 h. After cooling to rt, the precipitate was collected by filtration and washed with CF and recrystallized from hot ethanol to give 2-(*p*-tolylthiomethylamino)benzimidazole (6.90 g**,** 85%) as a white solid. This compound (6.90 g) was dissolved in ethanol (200 mL) and sodium borohydride (6.88 g, 0.19 mol, 7.5 equiv) was added in small portions over 1 h with stirring and the reaction was then heated under reflux for 1 h. After cooling, methanol (80 mL) was added, followed by HCl (aq. 1M, 160 mL) and the mixture concentrated under reduced pressure to give a white solid. The solid was dissolved in HCl (aq. 1M, 200 mL) and this solution was washed with DE (4 x 150 mL) before it was neutralized (pH 7-8) with sodium hydroxide (aq. 10% w/w) and extracted with EA (3 x 150 mL). The combined EA extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give **LL** (3.0 g, 20.6 mmol) as a white solid in 69 % yield over two steps. Data was in agreement with the literature.

Mp 170-173 ^oC (Lit.[11] 167-168 ^oC); δ_H (CD_3OD) 7.18-7.22 (2H, m, 2 x CH), 6.96-7.00 (2H, m, 2 x CH), 2.98 (3H, s, CH_3); δ_C (CD_3OD) 157.3, 138.3, 121.5, 112.6, 79.4, 29.6; ν_{max} 3425, 3050, 2905, 2878, 2848, 1638, 1601, 1327 cm^{-1}; **MS (ESI) m/z** 148.1 (100 %, $[M+H]^+$); **HRMS (ESI) m/z** found 148.0865, $C_8H_{10}N_3$ ($[M+H]^+$) requires 148.0869.

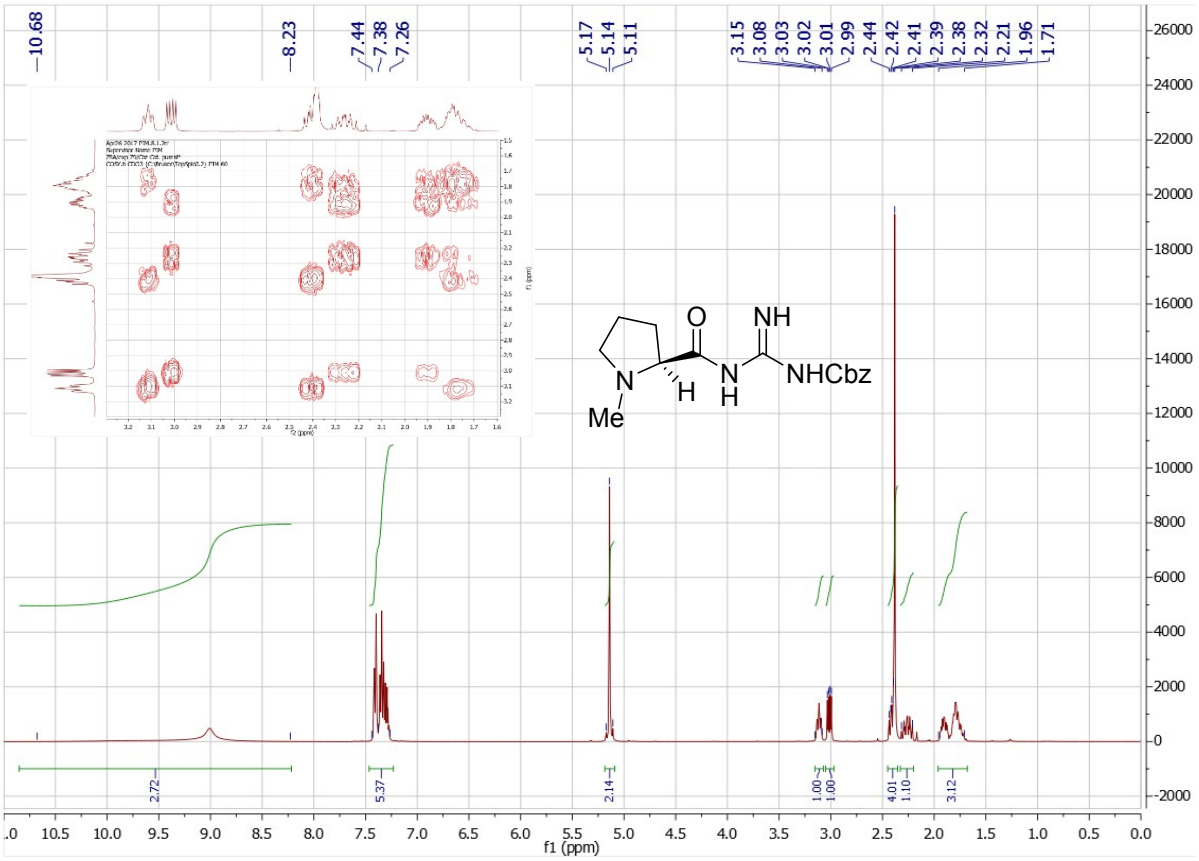
***N*-Methyl-1*H*-benzo[*d*]imidazol-2-amine LL**[11]**: ^{1}H NMR (CD_3OD)**



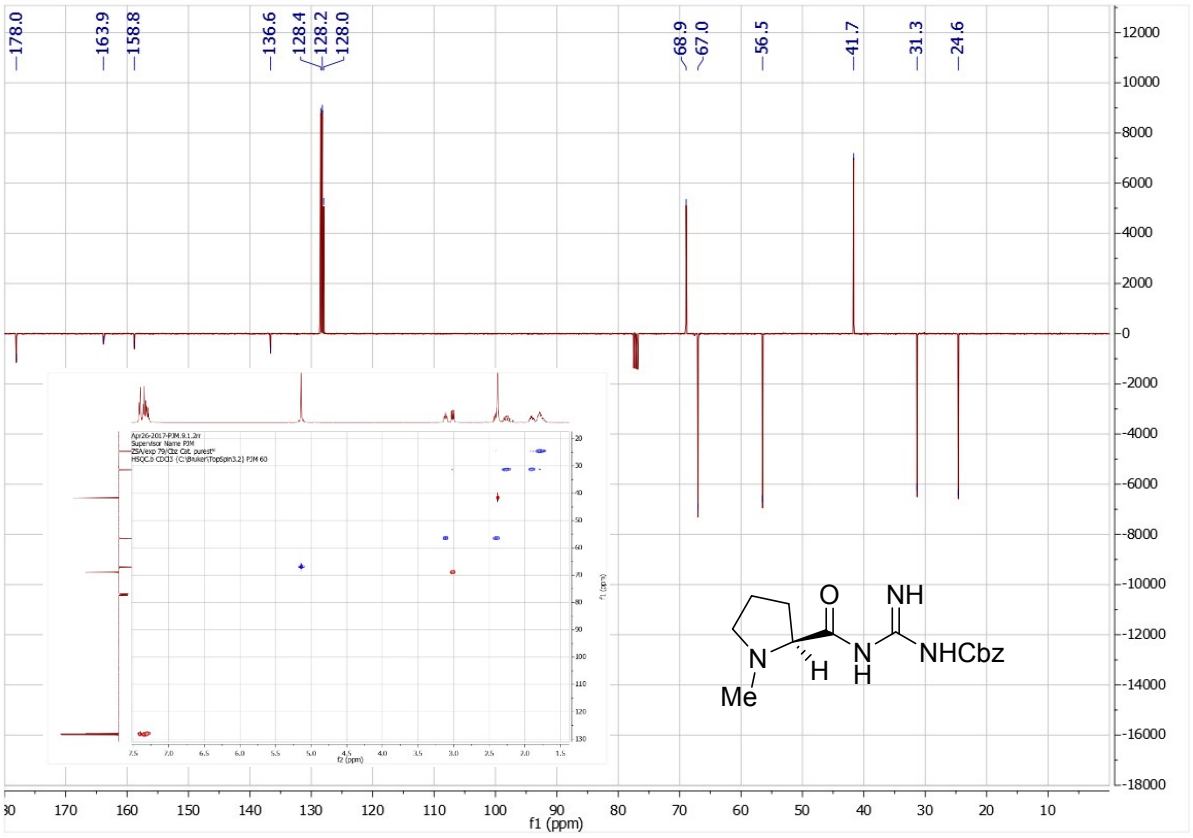
N-Methyl-1*H*-benzo[*d*]imidazol-2-amine LL[11]: ^{13}C NMR (CD_3OD)



(*S*)-*N*-Cbz-*N'*-carbamimidoyl-1-methylpyrrolidine-2-carboxamide 25a:
^{1}H NMR, COSY (insert).

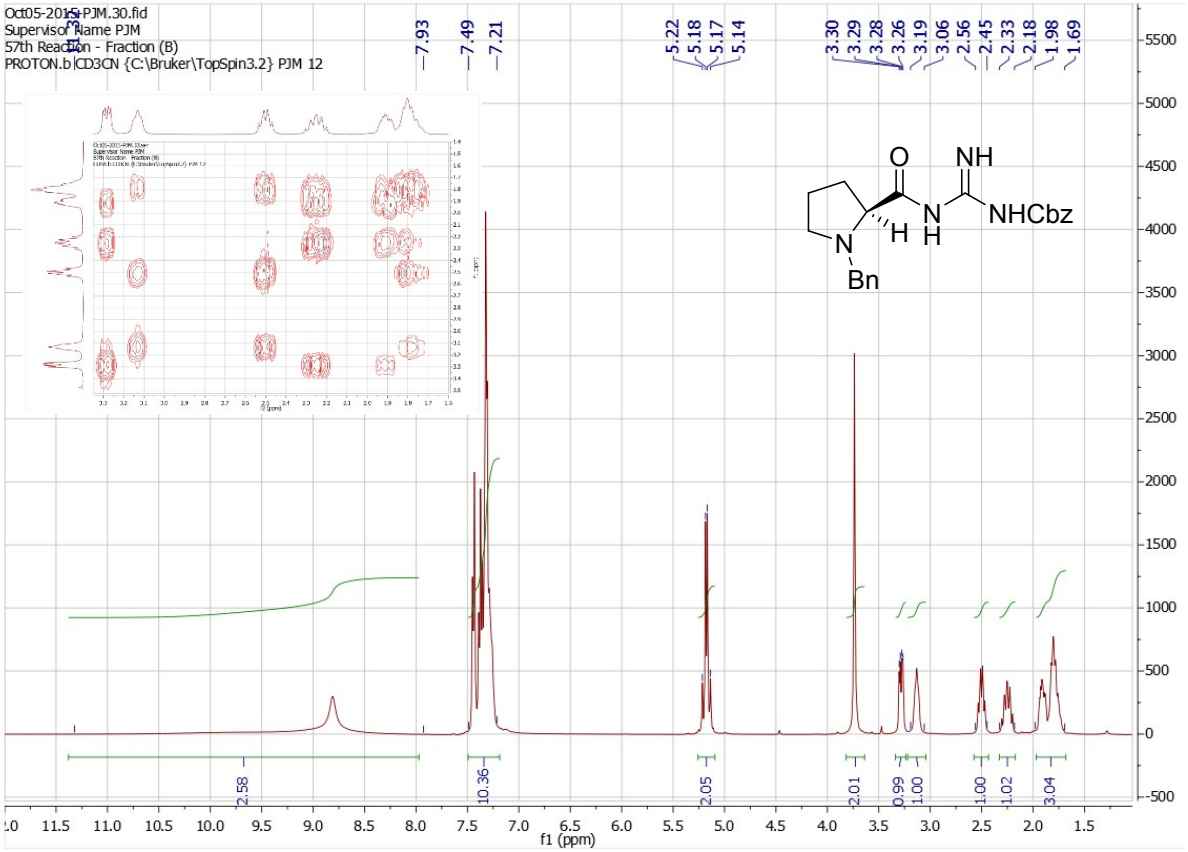


(*S*)-*N*-Cbz-*N'*-carbamimidoyl-1-methylpyrrolidine-2-carboxamide 25a:
^{13}C NMR, DEPTQ (insert)



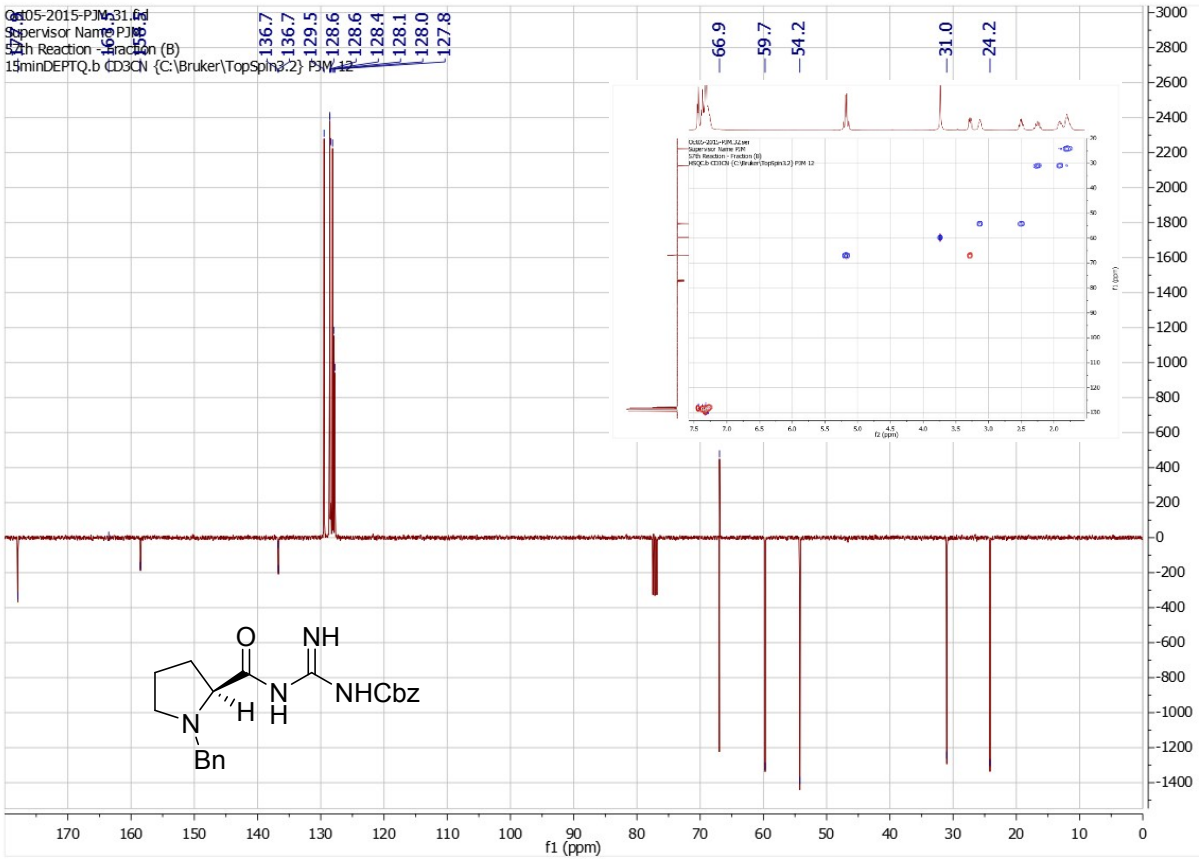
(*S*)-*N*-Cbz-1-benzyl-*N'*-carbamimidoylpyrrolidine-2-carboxamide 25b

^{1}H NMR, COSY (insert).

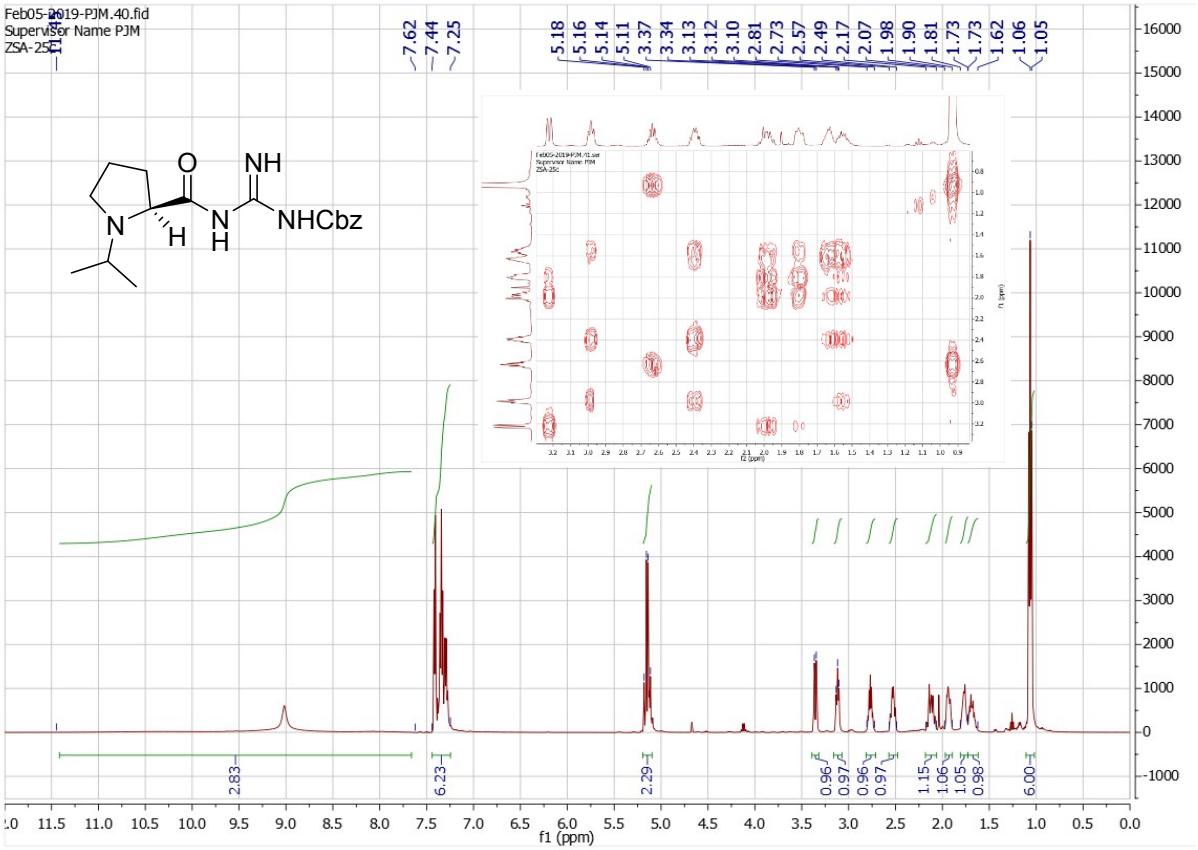


(*S*)-*N*-Cbz-1-benzyl-*N'*-carbamimidoylpyrrolidine-2-carboxamide 25b

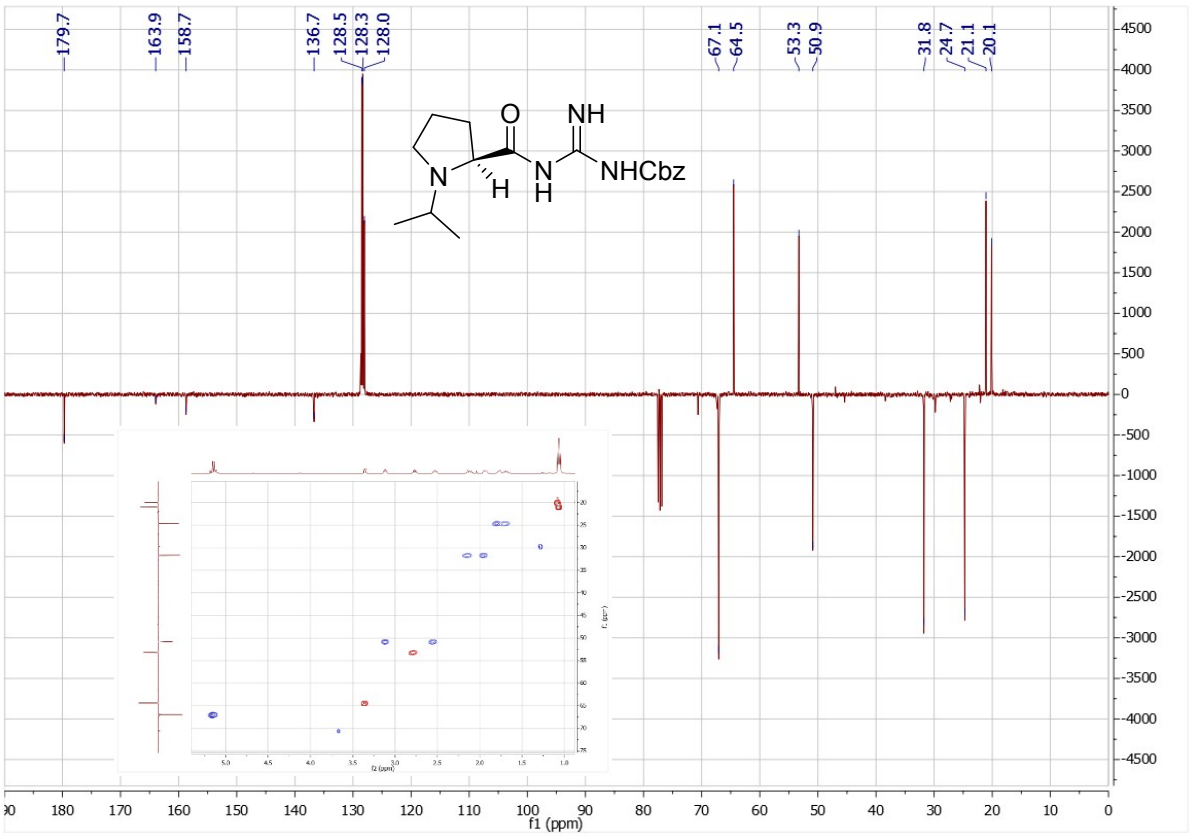
^{13}C NMR, DEPTQ (insert).



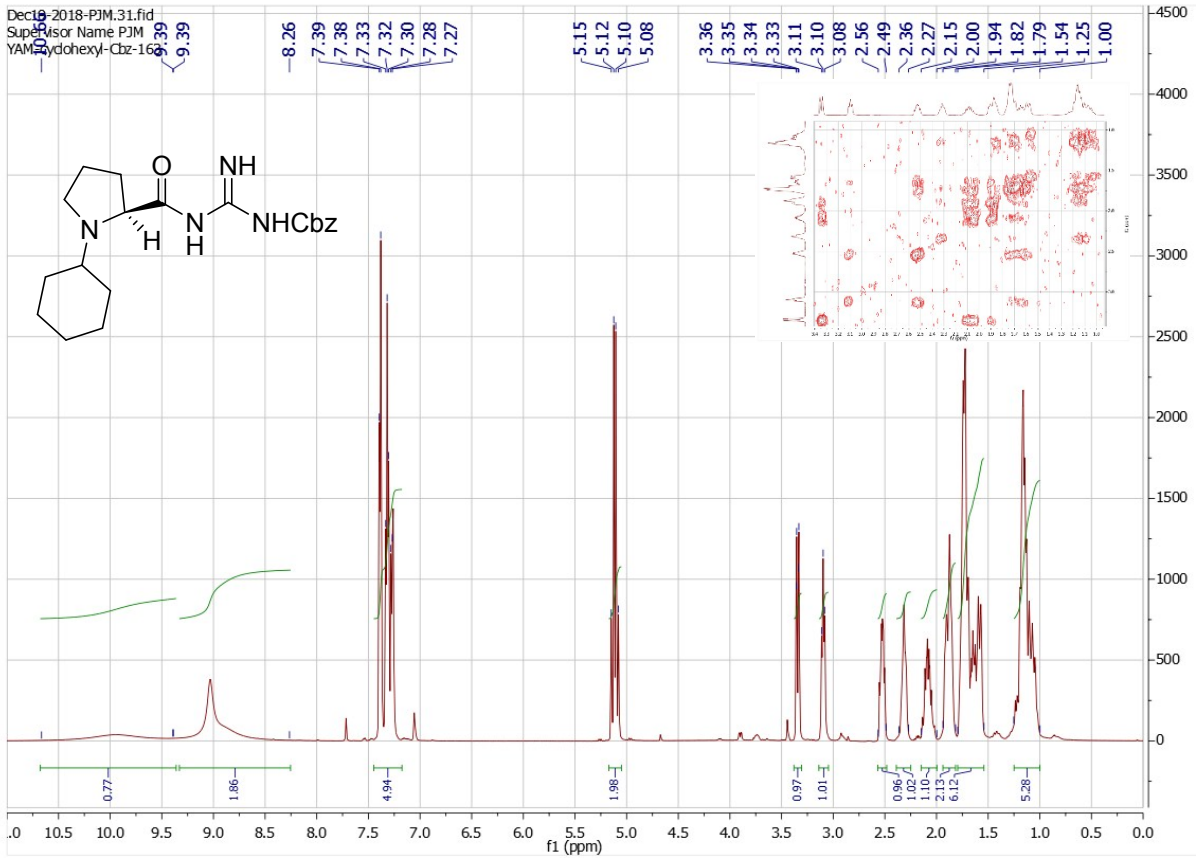
(*S*)-*N*-Cbz-*N*'-carbamimidoyl-1-isopropylpyrrolidine-2-carboxamide 25c: ^{1}H NMR, COSY (insert).



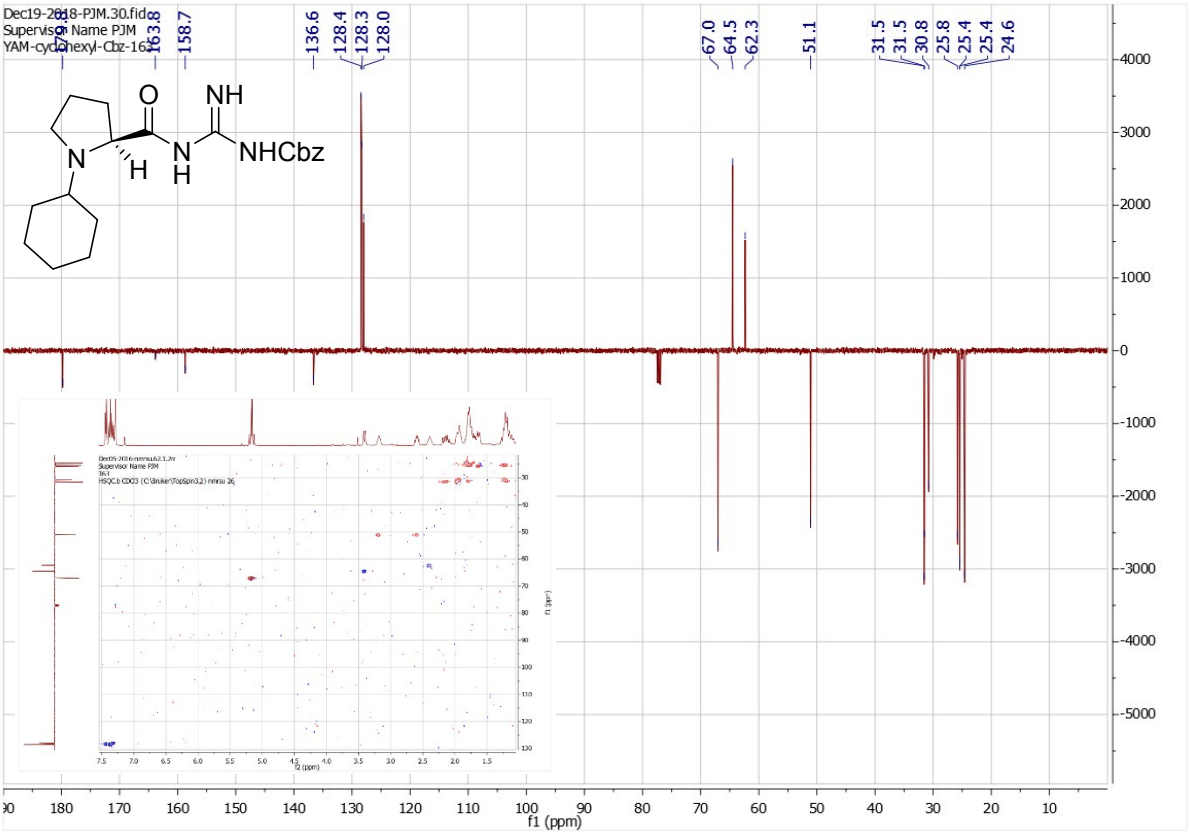
(*S*)-*N*-Cbz-*N*'-carbamimidoyl-1-isopropylpyrrolidine-2-carboxamide 25c: ^{13}C NMR, DEPTQ (insert).



(*S*)-*N*-Cbz-*N*'-carbamimidoyl-1-cyclohexylpyrrolidine-2-carboxamide 25d: ^{1}H NMR, COSY (insert).



(*S*)-*N*-Cbz-*N*'-carbamimidoyl-1-cyclohexylpyrrolidine-2-carboxamide 25d: ^{13}C NMR, DEPTQ (insert).


Dec19-2018-PJM.30.fid
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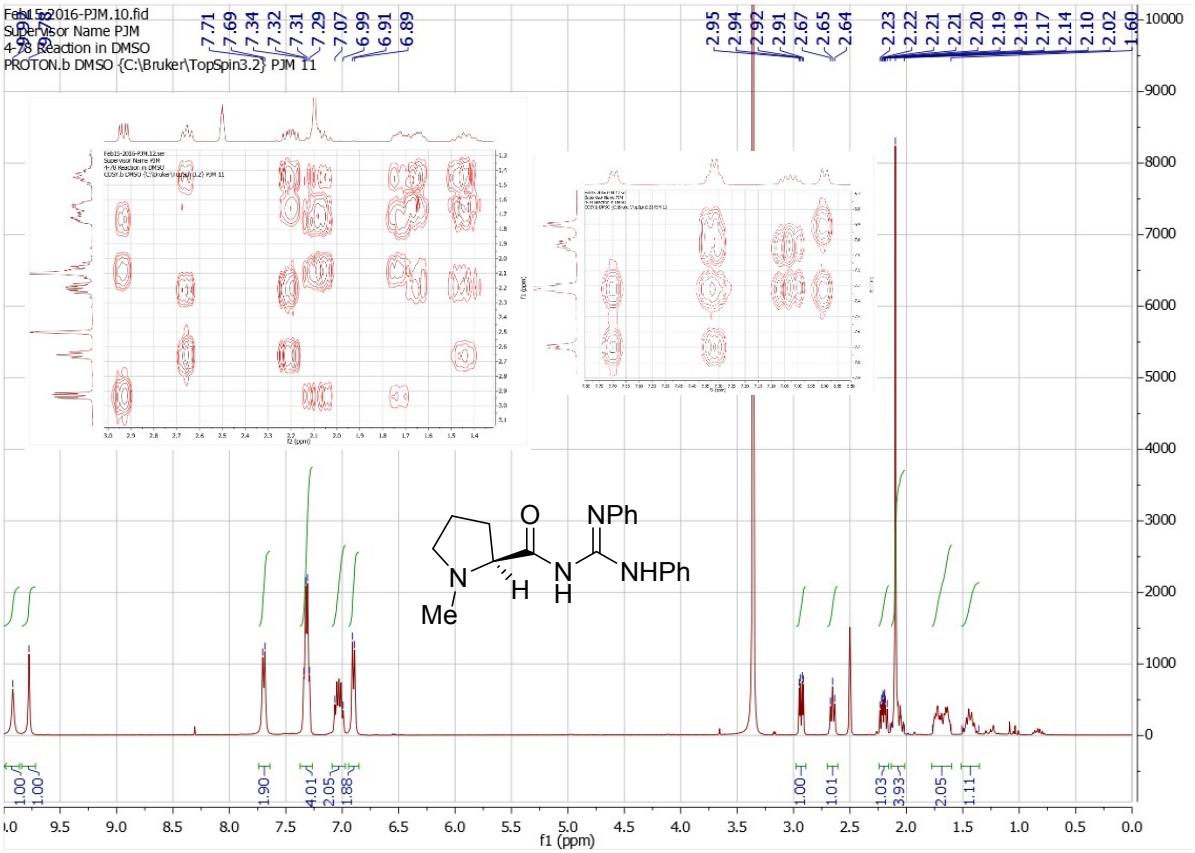
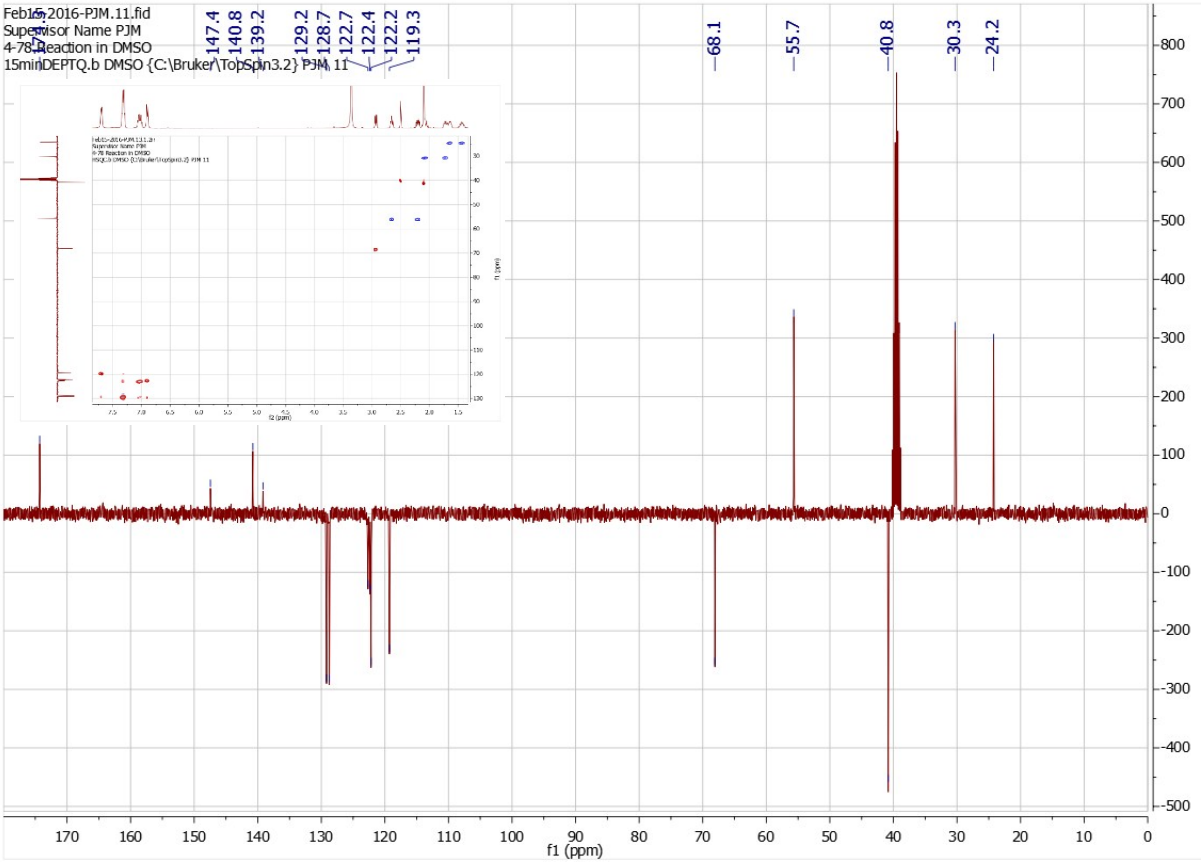
136.6
128.4
128.3
128.0
67.0
64.5
62.3
51.1
31.5
31.5
30.8
25.8
25.4
25.4
24.6
O
NH
N
H
N
H
NHCbz
f1 (ppm)

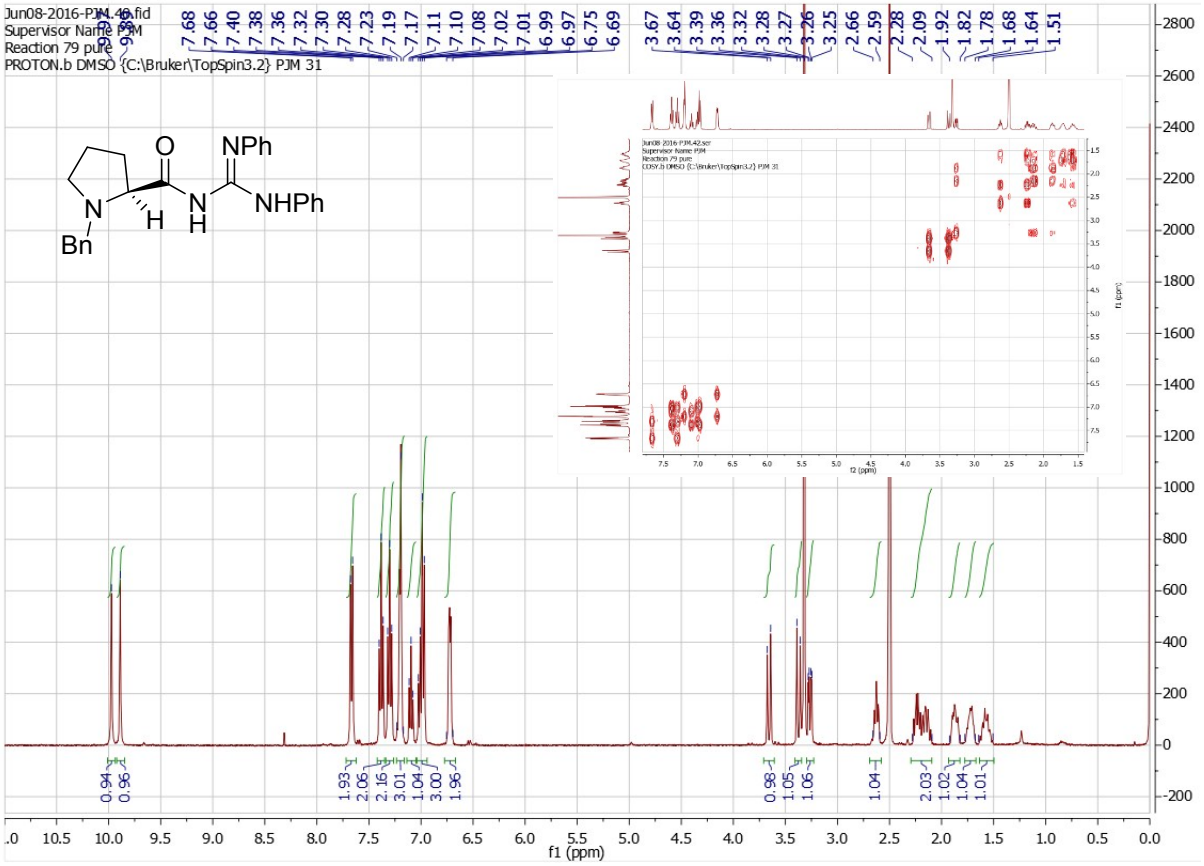
(*S*)-*N*-(*N*,*N*'-diphenylcarbamimidoyl)-1-methylpyrrolidine-2-carboxamide 26a: ^{1}H NMR, COSY (insert).



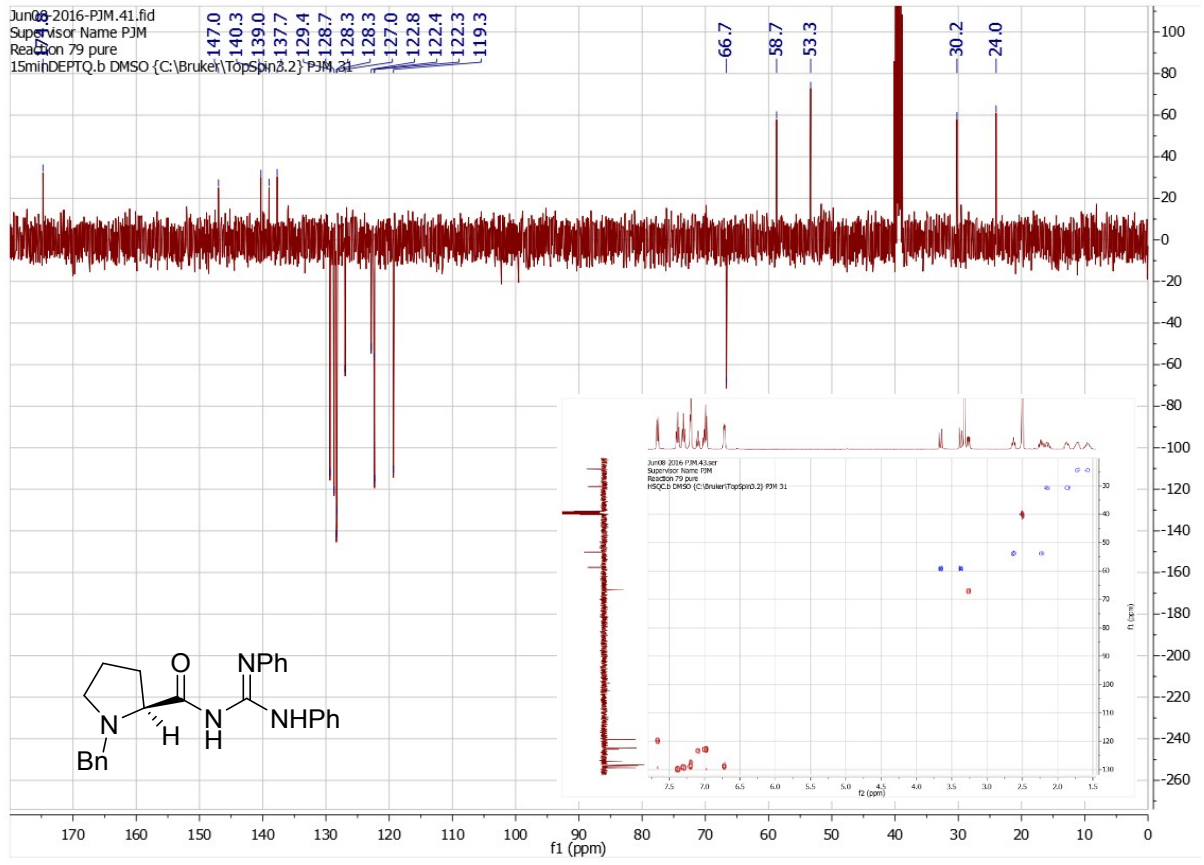
(*S*)-*N*-(*N*,*N*'-diphenylcarbamimidoyl)-1-methylpyrrolidine-2-carboxamide 26a: ^{13}C NMR, DEPTQ (insert).



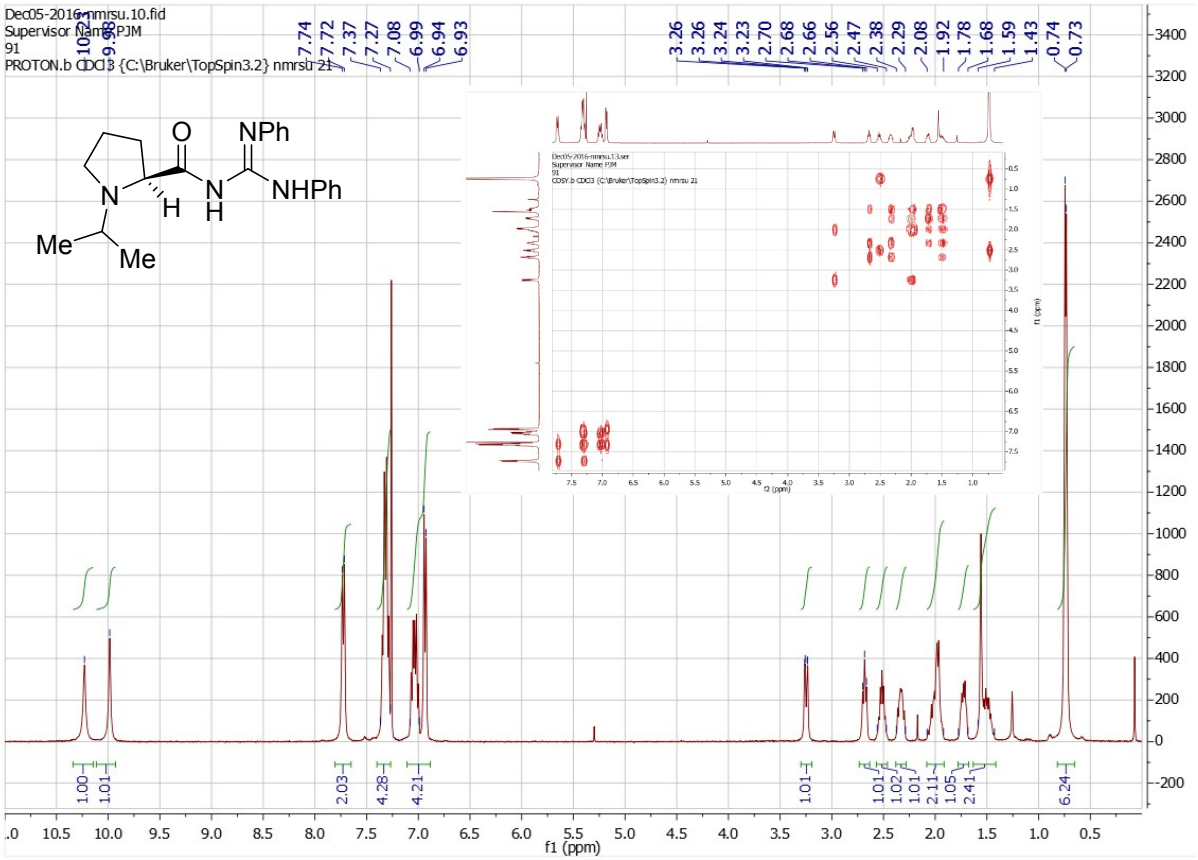
(*S*)-1-benzyl-*N*-(*N*,*N*'-diphenylcarbamimidoyl)pyrrolidine-2-carboxamide 26b
^{1}H NMR, COSY (insert).



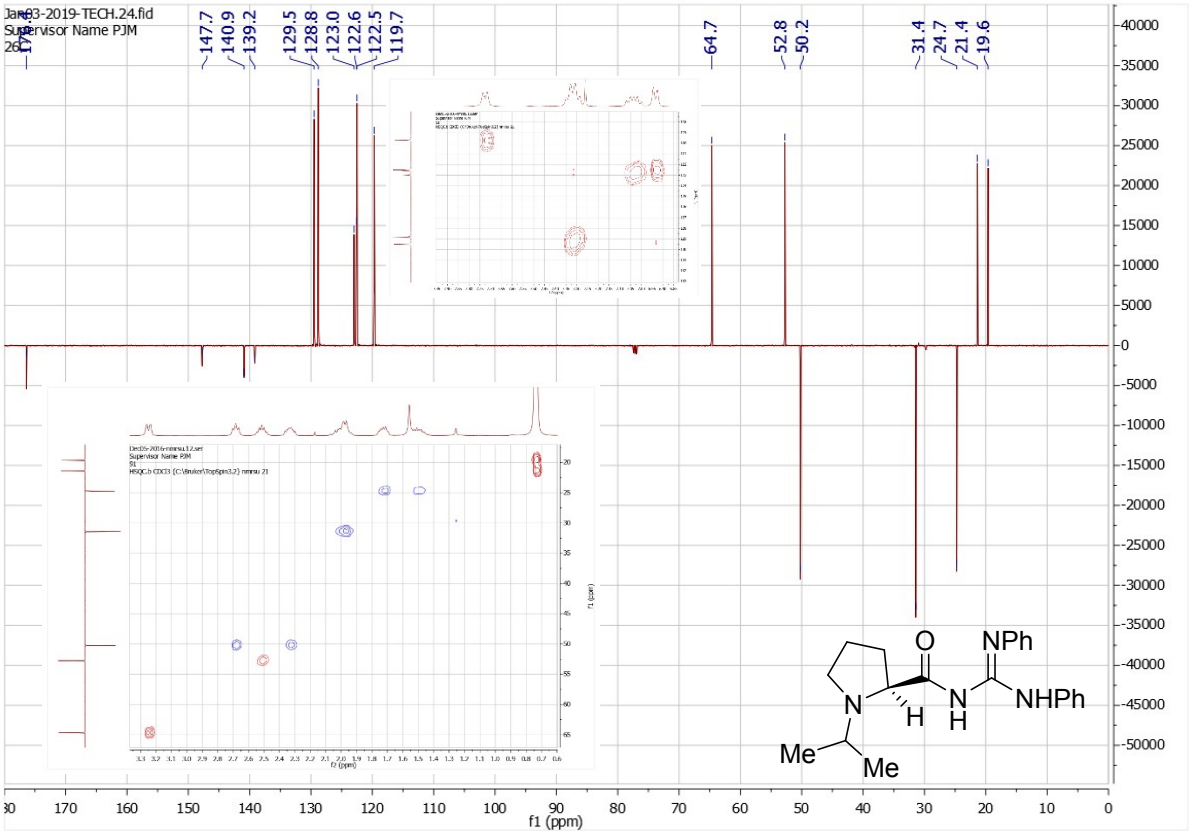
(*S*)-1-benzyl-*N*-(*N*,*N*'-diphenylcarbamimidoyl)pyrrolidine-2-carboxamide 26b
^{13}C NMR, DEPTQ (insert).



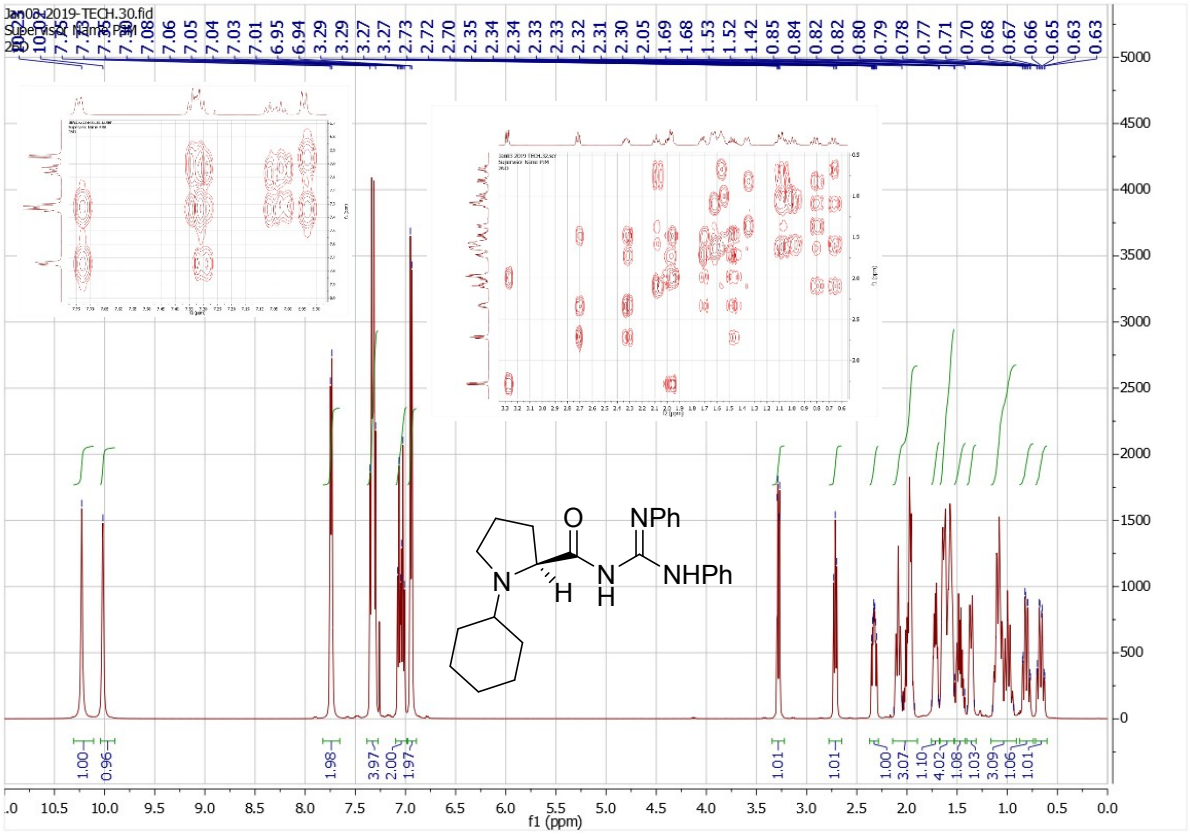
(*S*)-*N*-(*N*,*N*'-diphenylcarbamimidoyl)-1-isopropylpyrrolidine-2-carboxamide 26c
^{1}H NMR, COSY (insert).



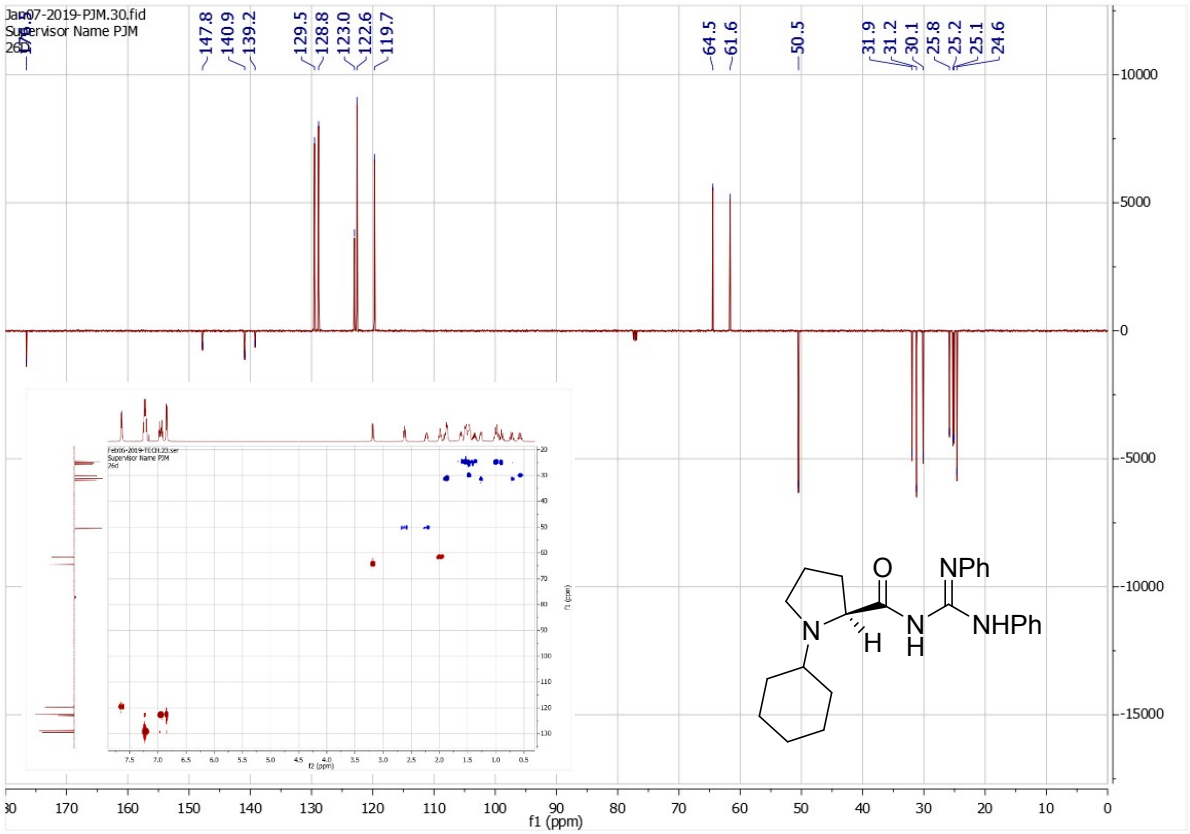
(*S*)-*N*-(*N*,*N*'-diphenylcarbamimidoyl)-1-isopropylpyrrolidine-2-carboxamide 26c
^{13}C NMR, DEPTQ (insert).



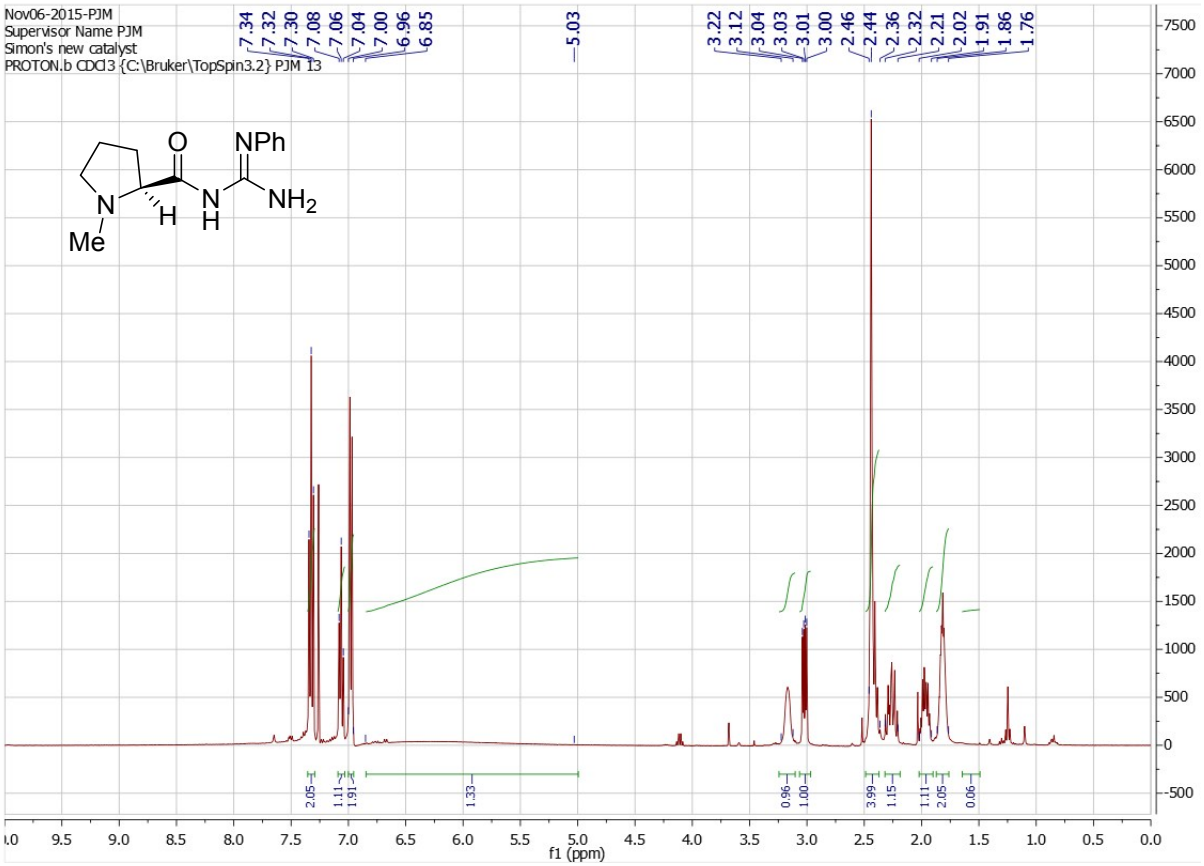
(*S*)-1-cyclohexyl-*N*-(*N*,*N*'-diphenylcarbamimidoyl)pyrrolidine-2-carboxamide 26d: ^{1}H NMR, COSY (insert).



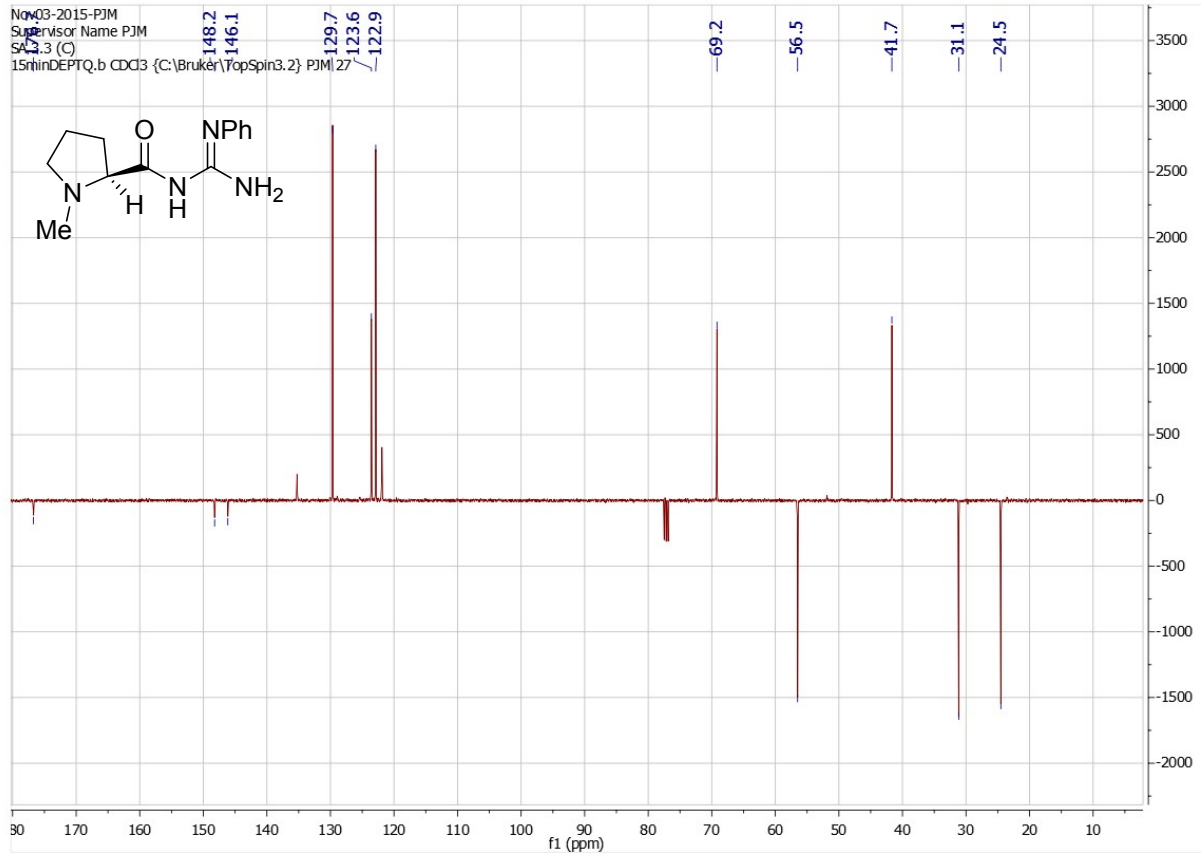
(*S*)-1-cyclohexyl-*N*-(*N*,*N*'-diphenylcarbamimidoyl)pyrrolidine-2-carboxamide 26d: ^{13}C NMR, DEPTQ (insert).



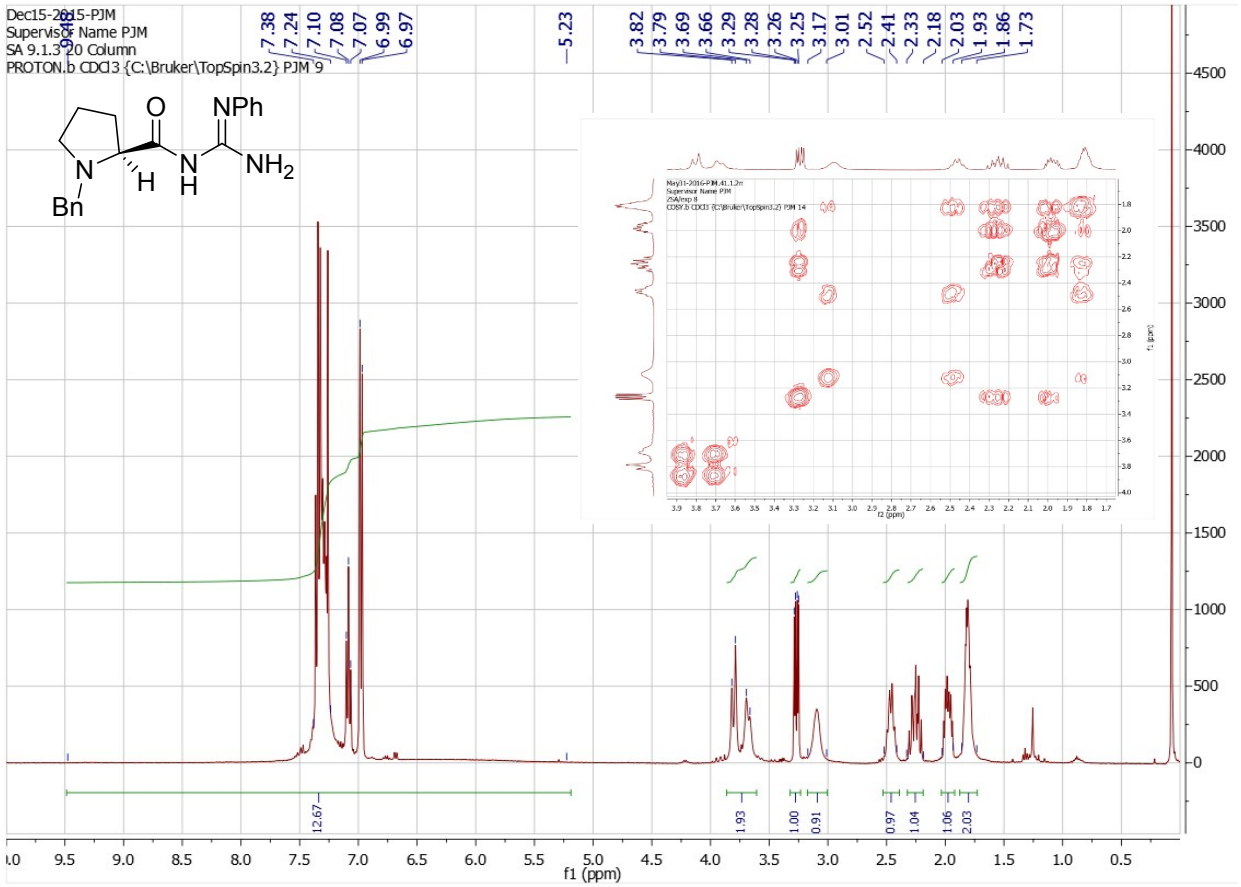
(*S*)-1-methyl-*N*-(*N*'-phenylcarbamimidoyl)pyrrolidine-2-carboxamide 27a: ^{1}H NMR.



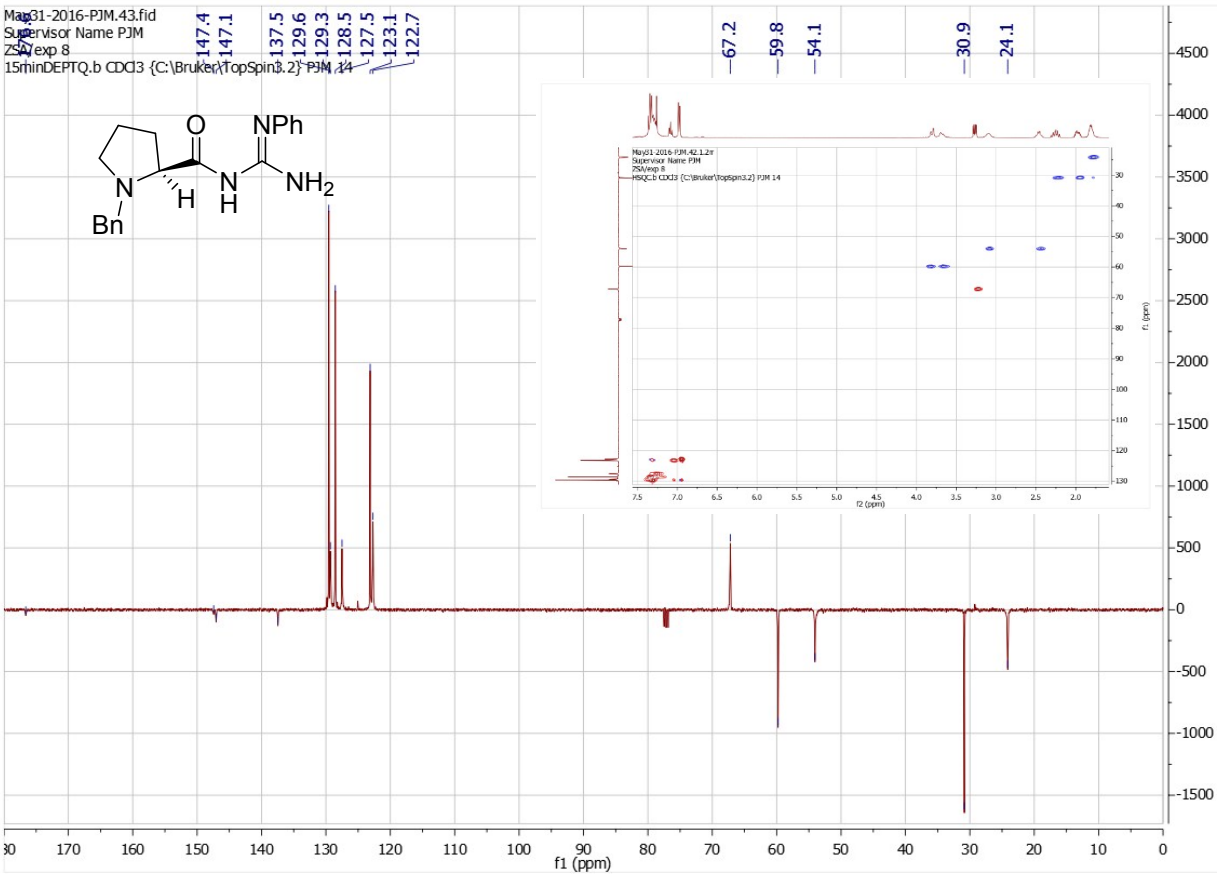
(*S*)-1-methyl-*N*-(*N*'-phenylcarbamimidoyl)pyrrolidine-2-carboxamide 27a: ^{13}C NMR.



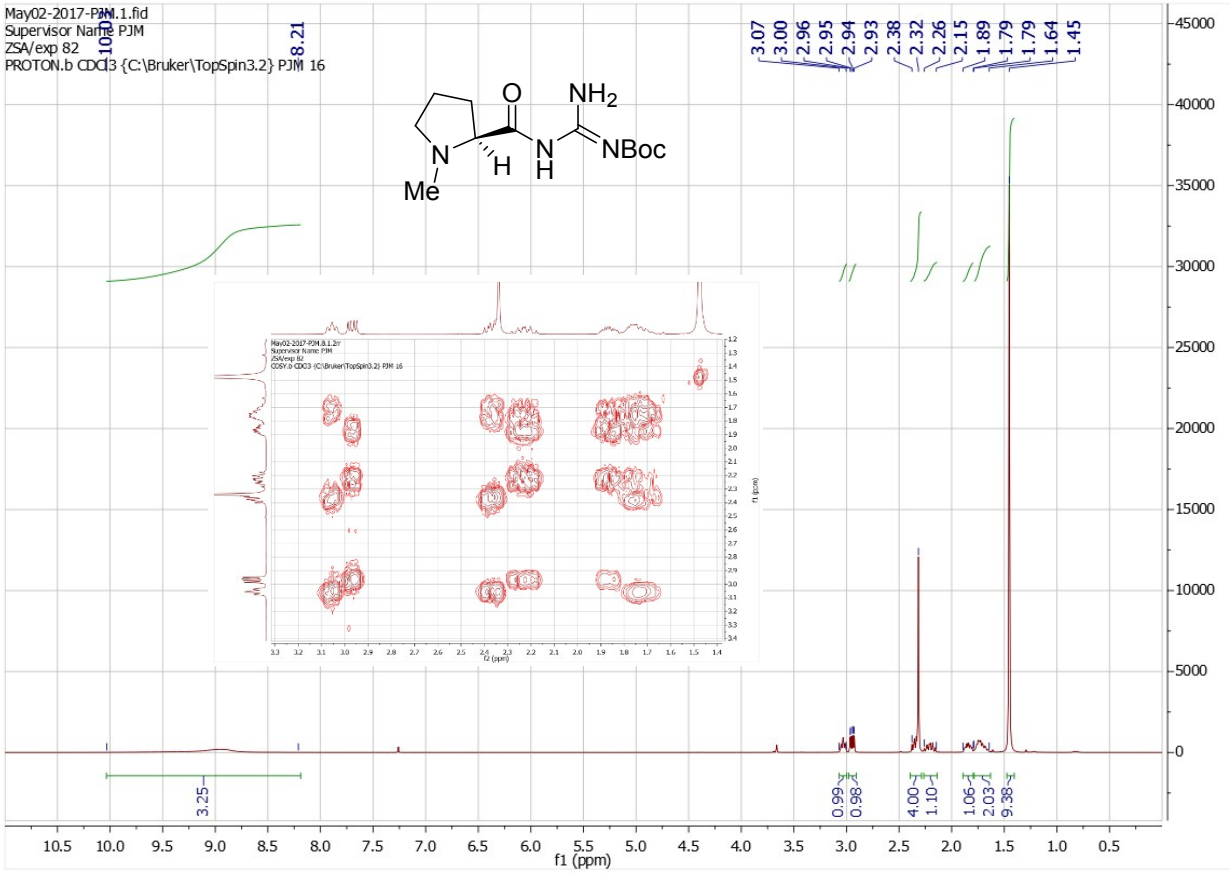
(*S*)-1-Benzyl-*N*-(*N*'-phenylcarbamimidoyl)pyrrolidine-2-carboxamide 27b: ^{1}H NMR, COSY (insert).



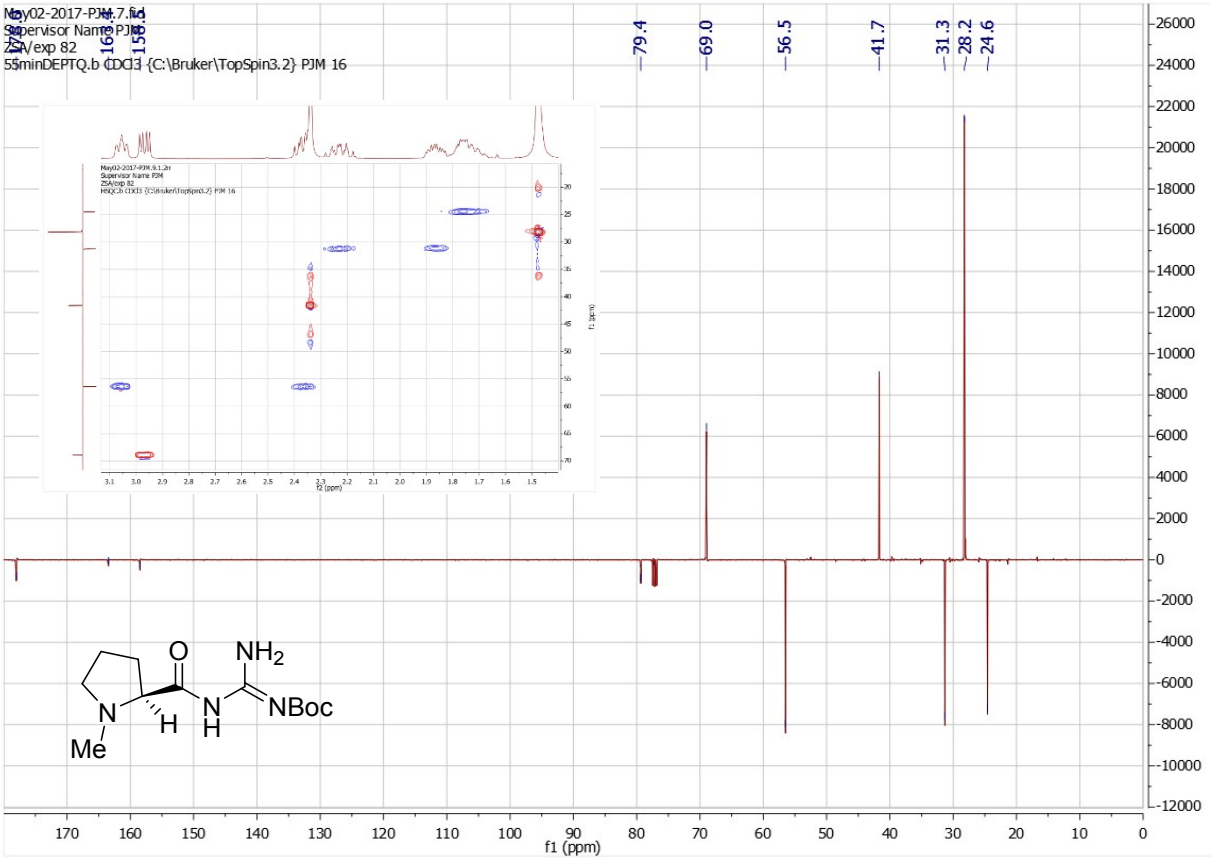
(*S*)-1-Benzyl-*N*-(*N*'-phenylcarbamimidoyl)pyrrolidine-2-carboxamide 27b: ^{13}C NMR, DEPTQ (insert).



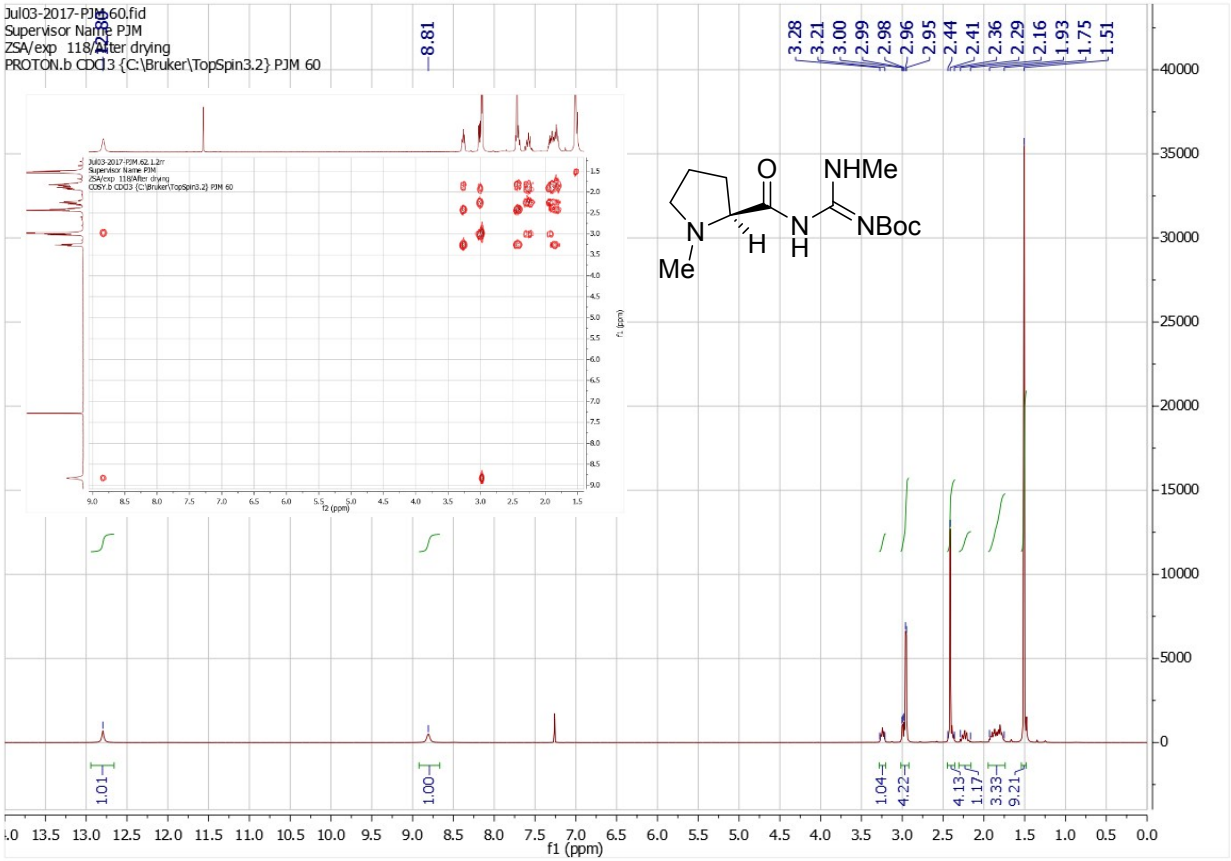
(*S*)-*N*'-Boc-*N*-carbamimidoyl-1-methylpyrrolidine-2-carboxamide 29:
^{1}H NMR, COSY (insert).



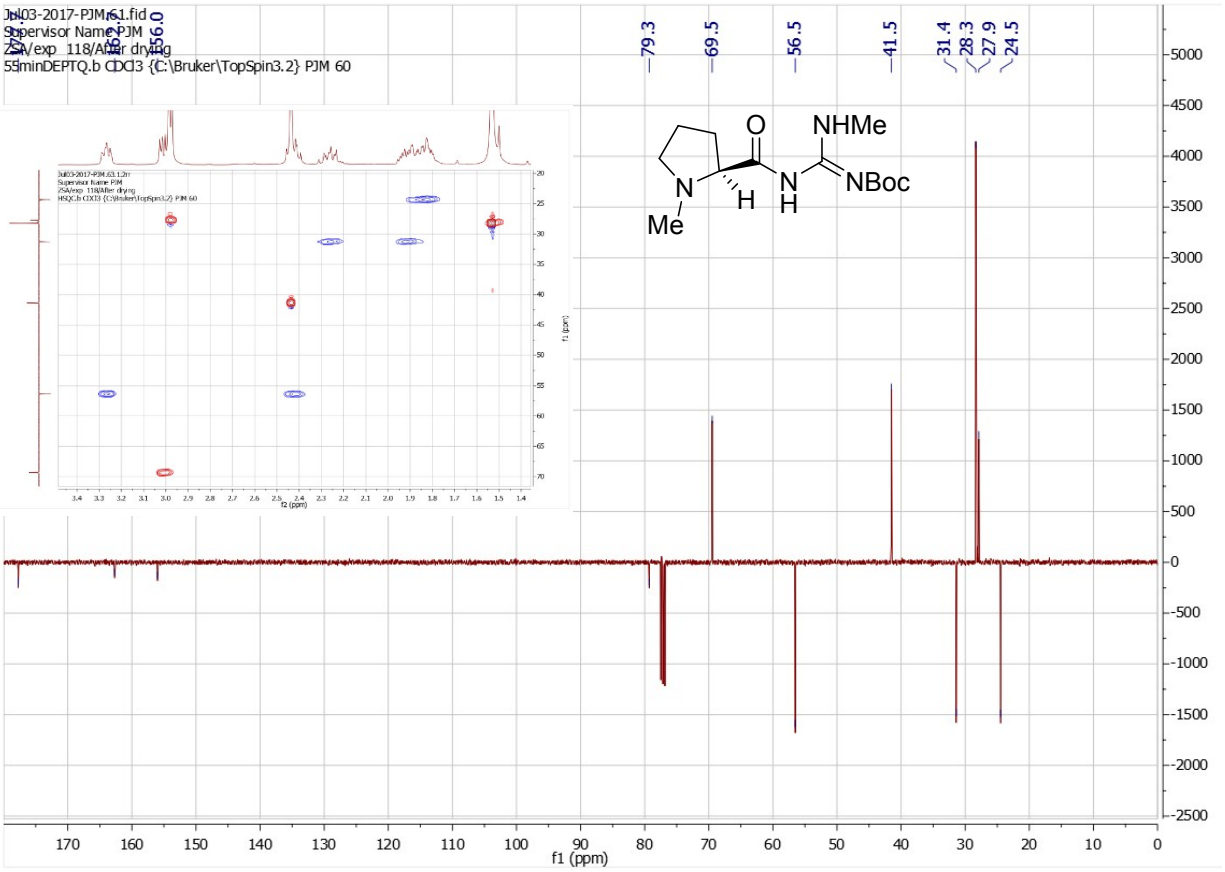
(*S*)-*N*'-Boc-*N*-carbamimidoyl-1-methylpyrrolidine-2-carboxamide 29:
^{13}C NMR, DEPTQ (insert).



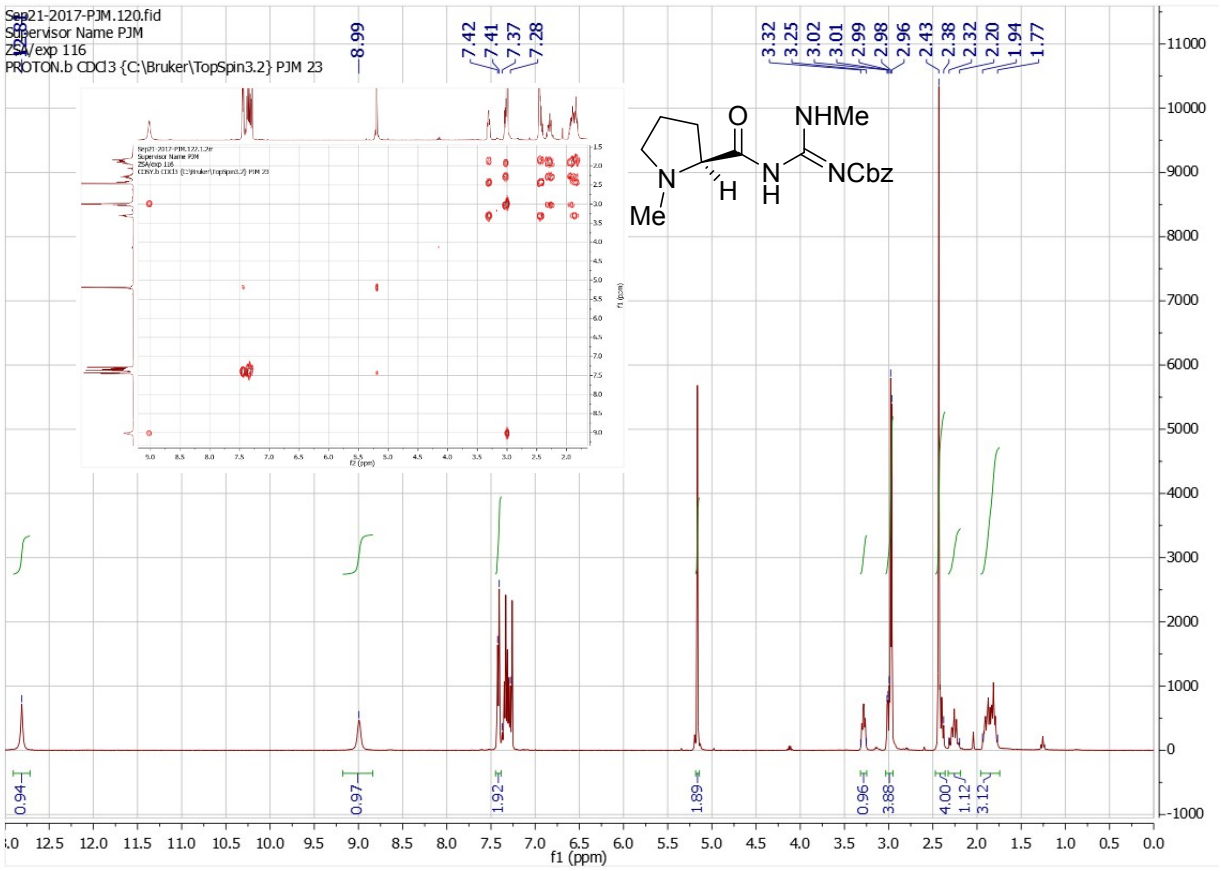
(*S*)-*N*-(*N*'-Boc-*N*-methylcarbamimidoyl)-1-methylpyrrolidine-2-carboxamide 30: ^{1}H NMR, COSY (insert).



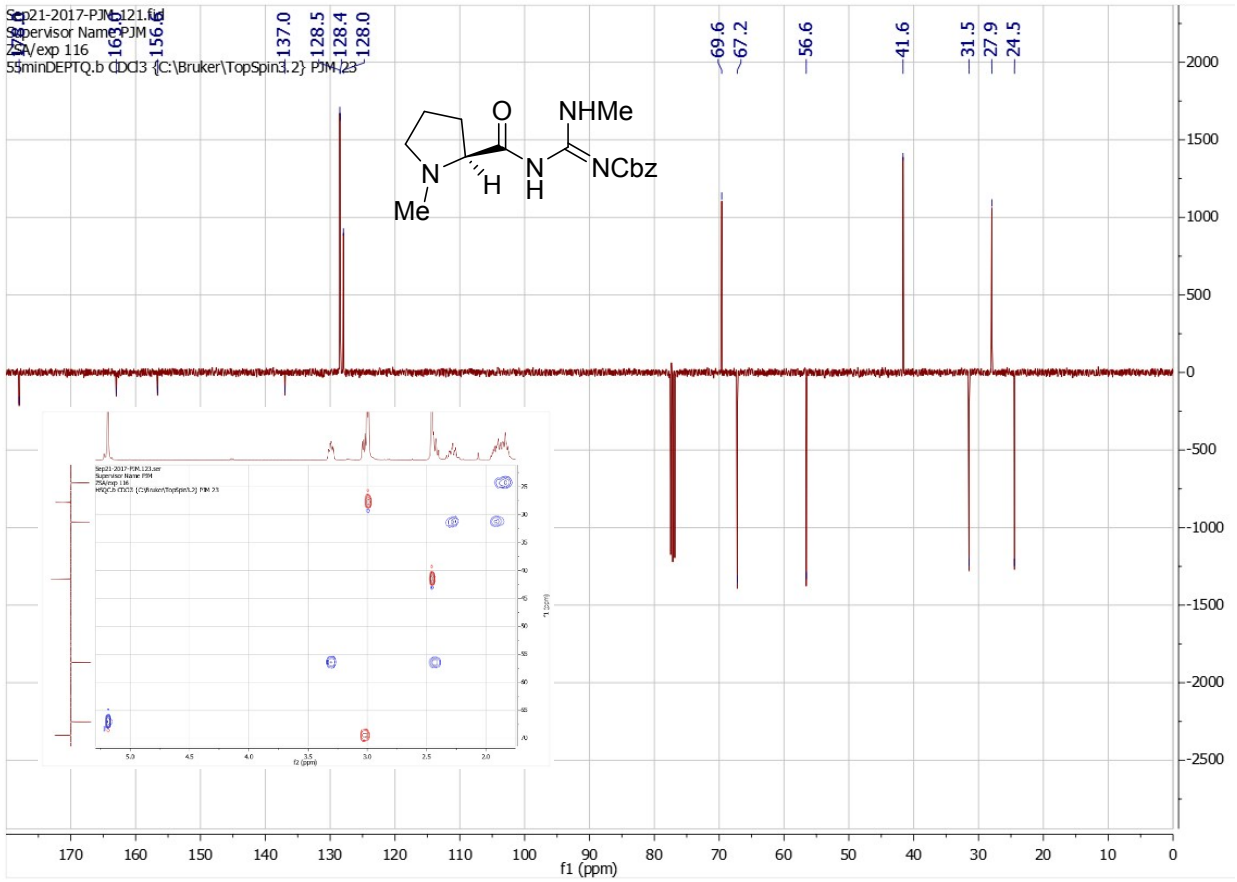
(*S*)-*N*-(*N*'-Boc-*N*-methylcarbamimidoyl)-1-methylpyrrolidine-2-carboxamide 30: ^{13}C NMR, DEPTQ (insert).



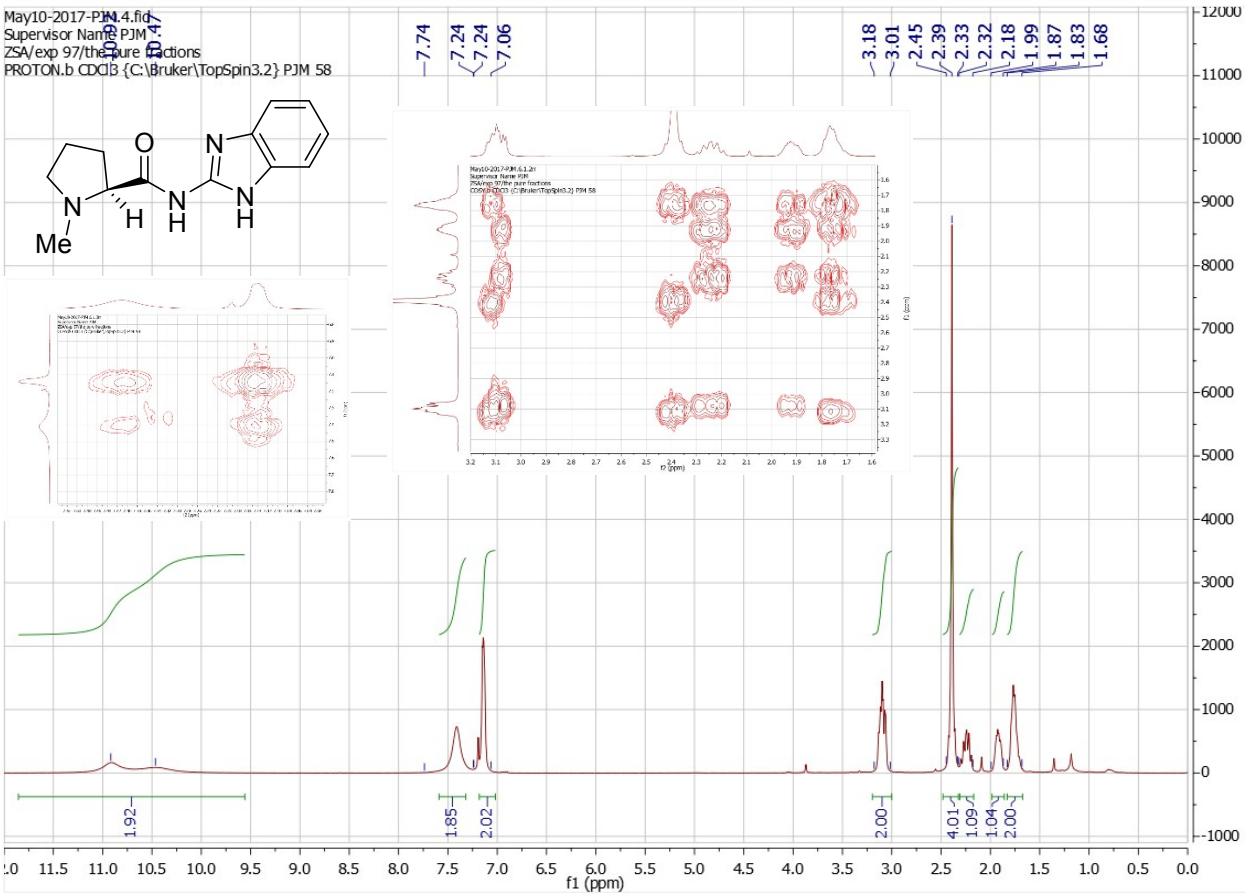
(*S*)-*N*-(*N*'-Cbz-*N*-Methylcarbamimidoyl)-1-methylpyrrolidine-2-carboxamide 31: ^{1}H NMR, COSY (insert).



(*S*)-*N*-(*N*'-Cbz-*N*-Methylcarbamimidoyl)-1-methylpyrrolidine-2-carboxamide 31: ^{13}C NMR, DEPTQ (insert).

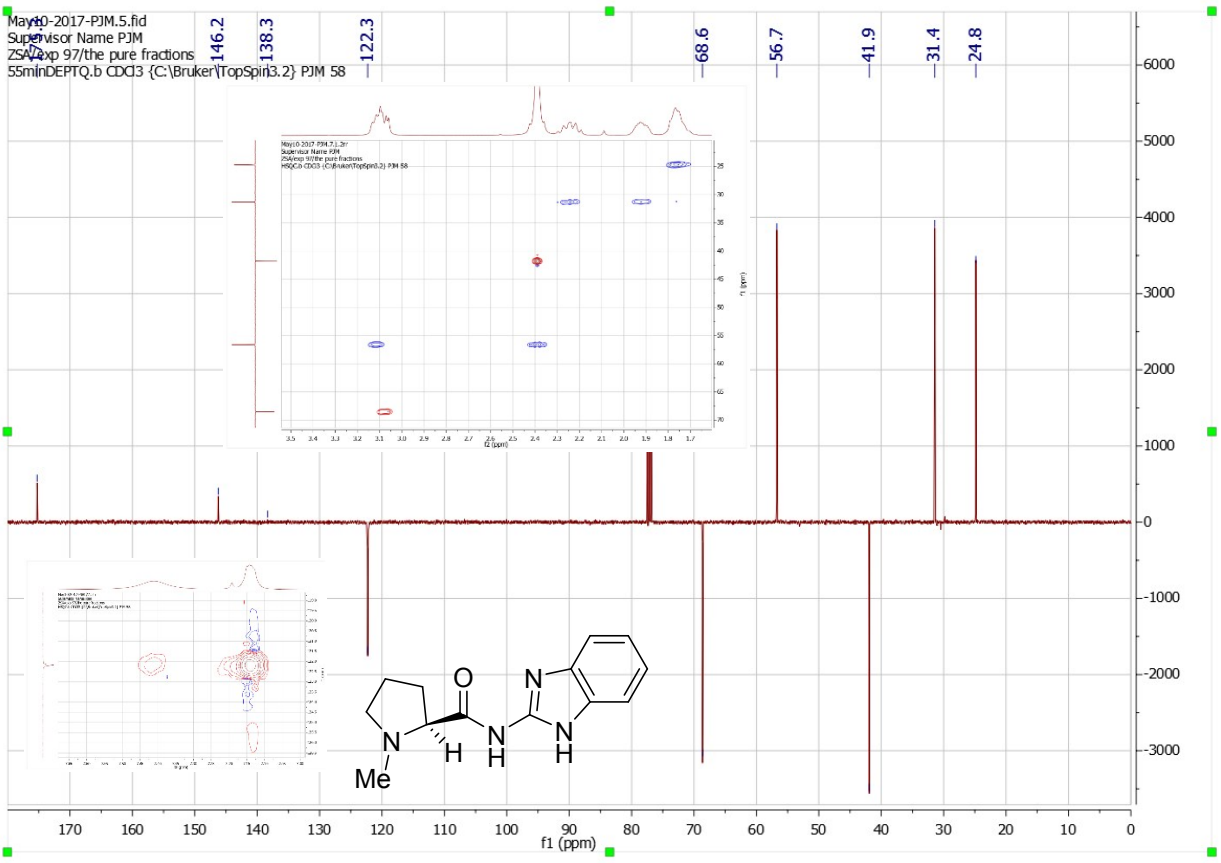


(*S*)-*N*-(1H-benzo[d]imidazol-2-yl)-1-methylpyrrolidine-2-carboxamide 34a: ^{1}H NMR, COSY (insert).



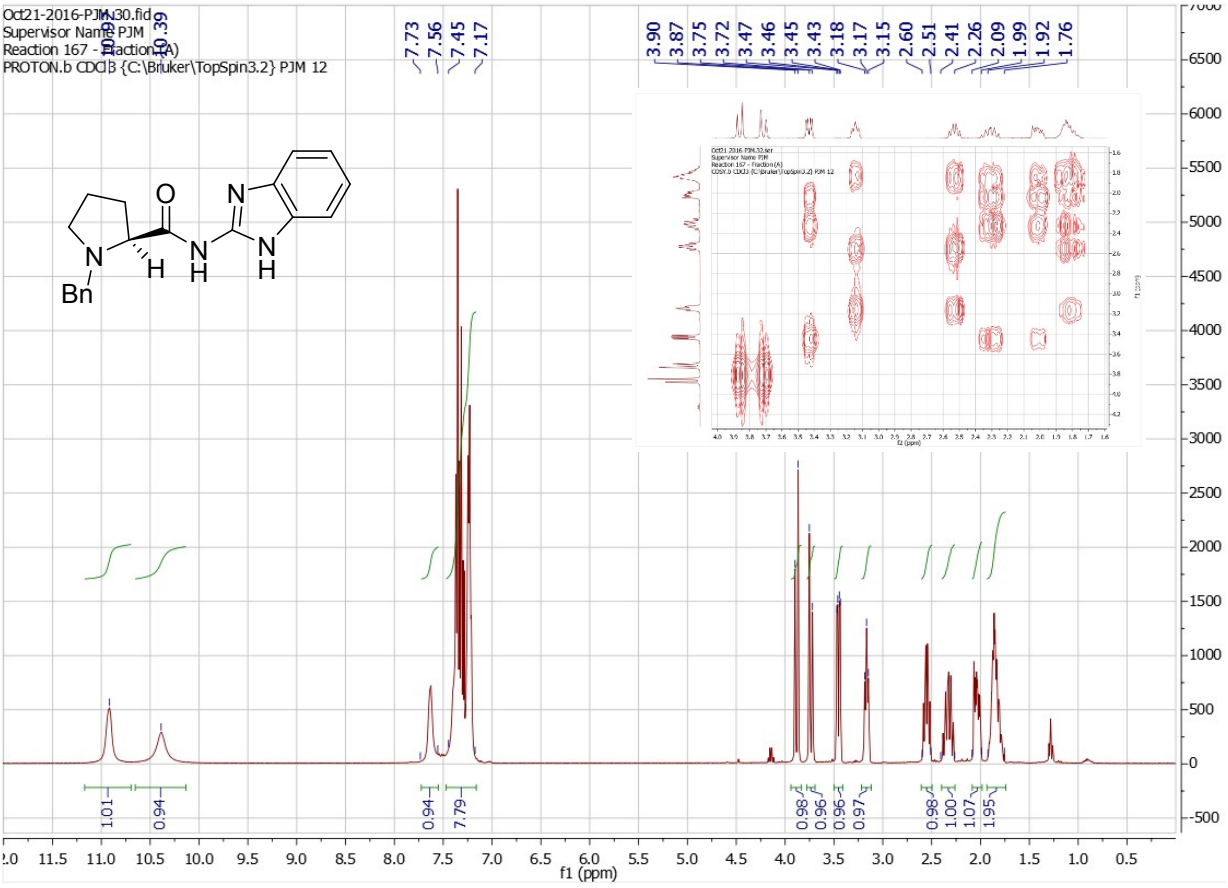
(*S*)-*N*-(1H-benzo[d]imidazol-2-yl)-1-methylpyrrolidine-2-carboxamide 34a:

^{13}C NMR, DEPTQ (insert).



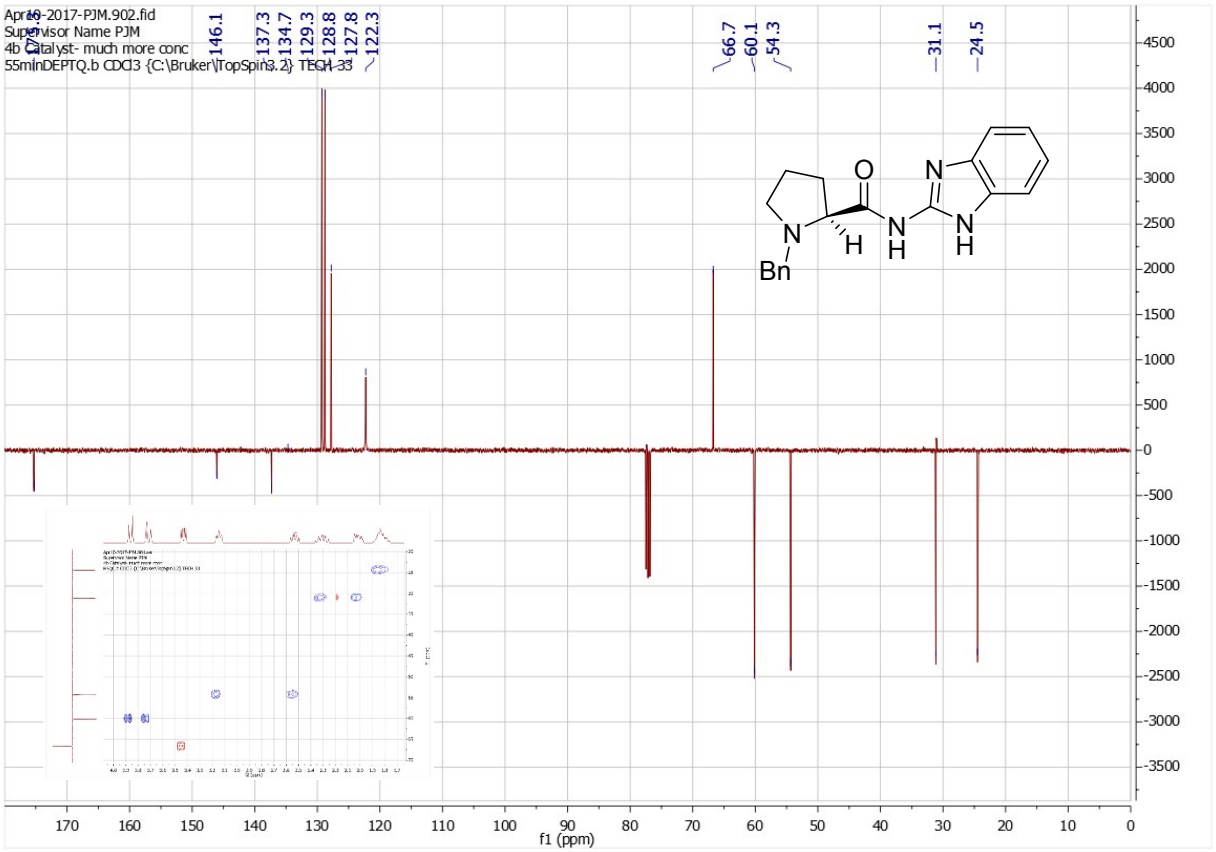
(*S*)-*N*-(1H-benzo[d]imidazol-2-yl)-1-benzylpyrrolidine-2-carboxamide 34b:

^{1}H NMR, COSY (insert).



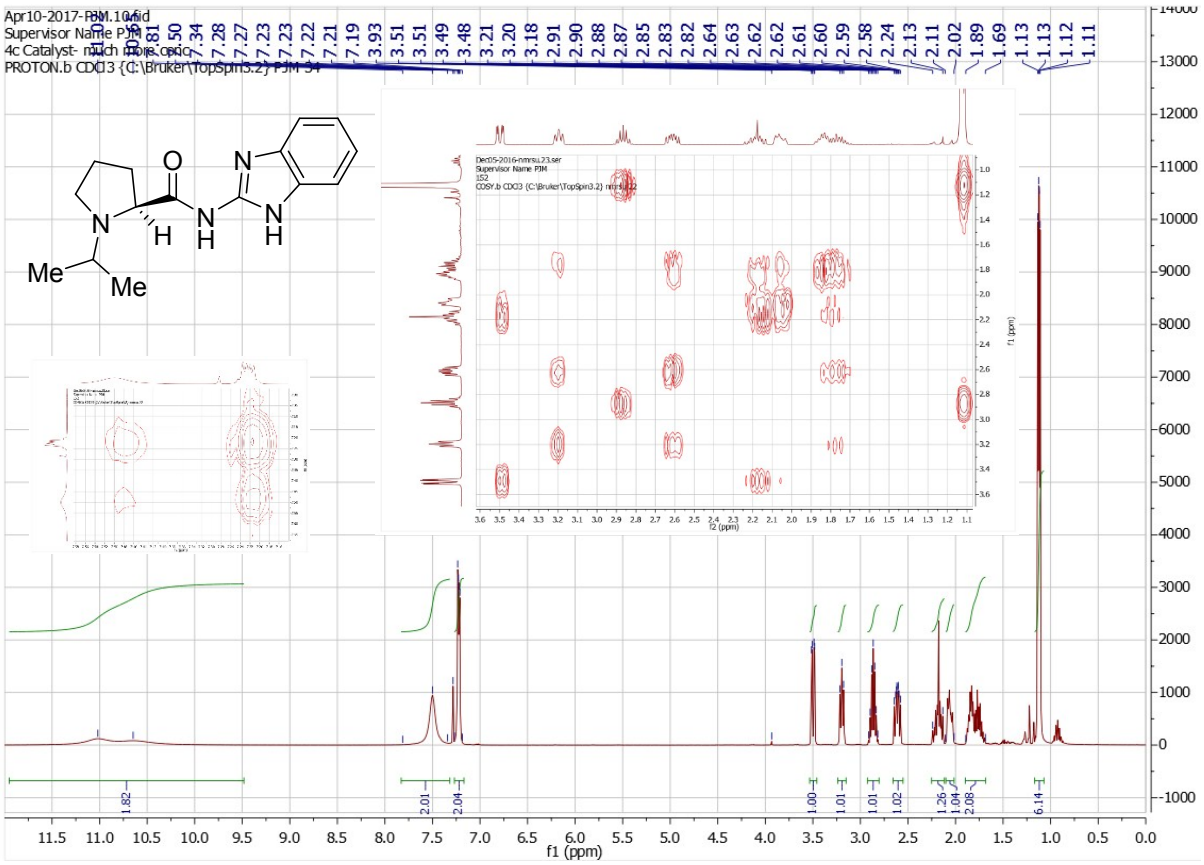
(*S*)-*N*-(1H-benzo[d]imidazol-2-yl)-1-benzylpyrrolidine-2-carboxamide 34b:

^{13}C NMR, DEPTQ (insert).



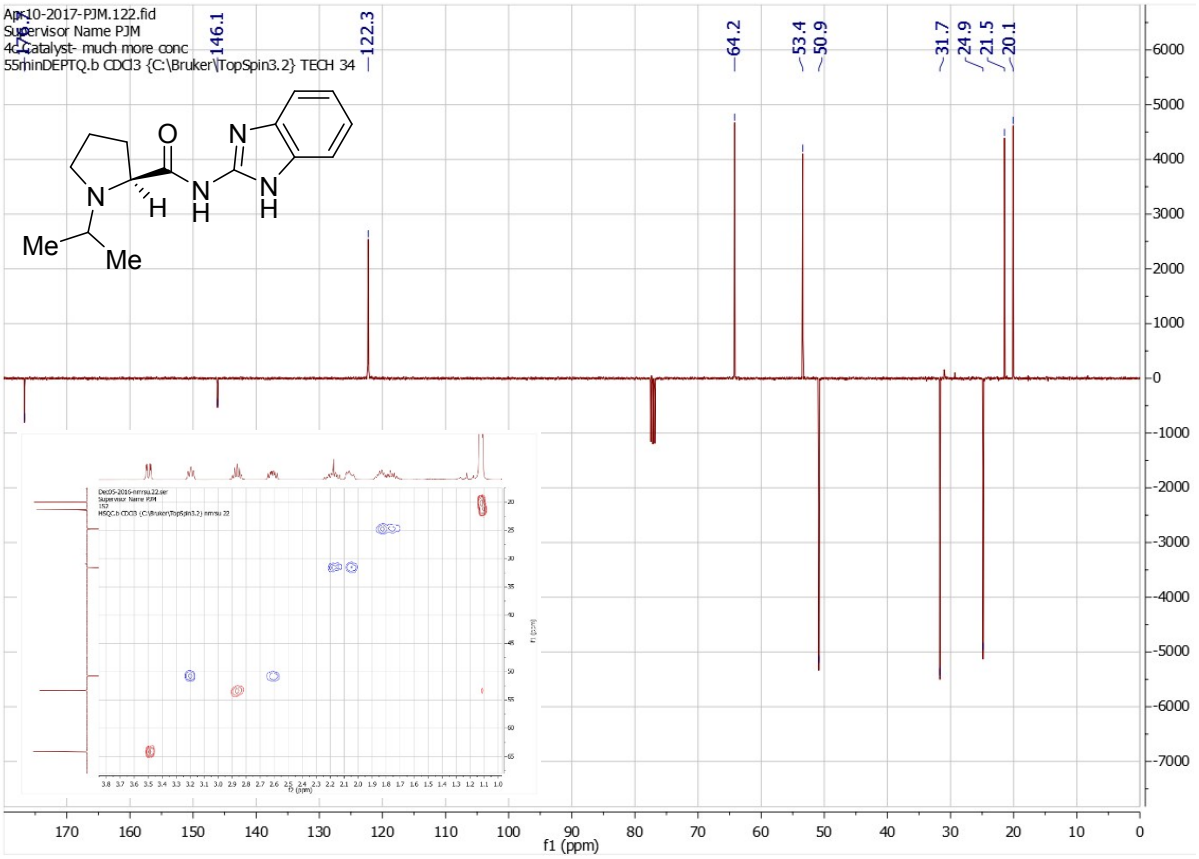
(*S*)-*N*-(1H-benzo[d]imidazol-2-yl)-1-isopropylpyrrolidine-2-carboxamide 34c

^{1}H NMR, COSY (insert).



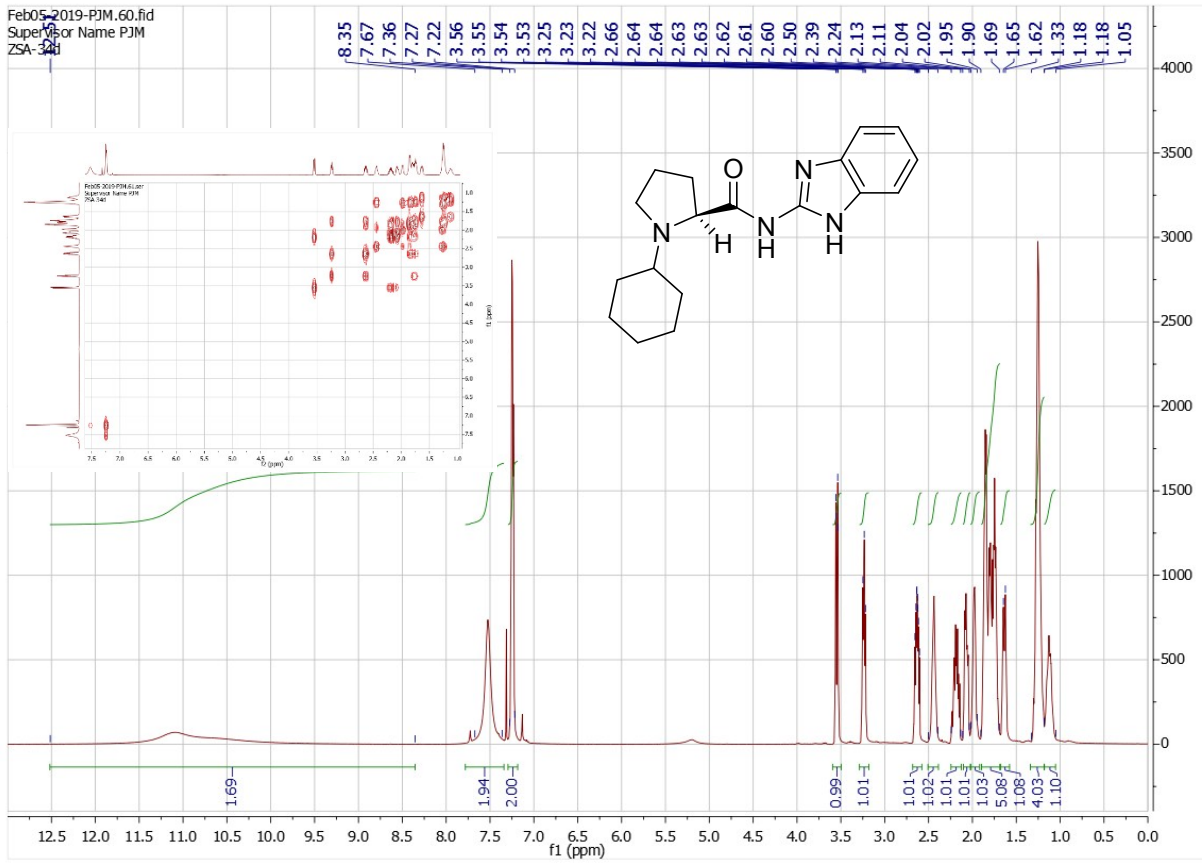
(*S*)-*N*-(1H-benzo[d]imidazol-2-yl)-1-isopropylpyrrolidine-2-carboxamide 34c

^{13}C NMR, DEPTQ (insert).

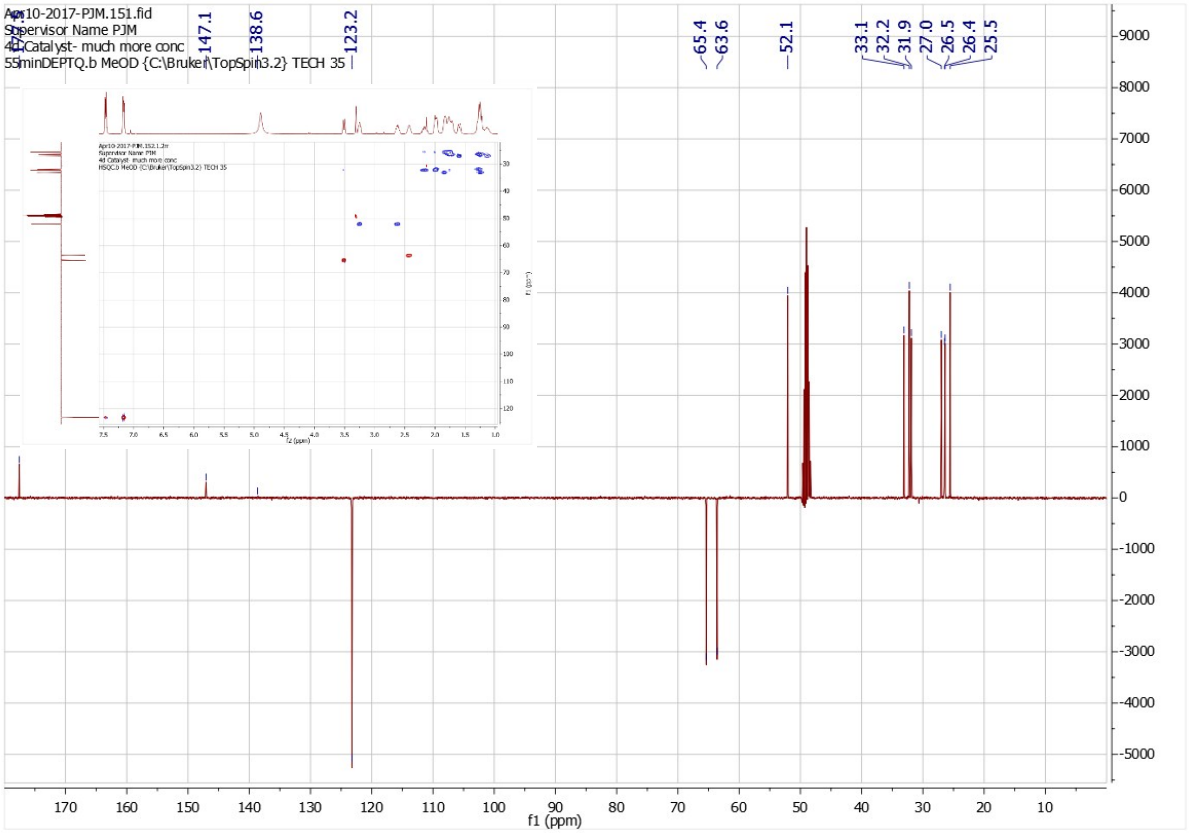


(*S*)-*N*-(1H-benzo[d]imidazol-2-yl)-1-cyclohexylpyrrolidine-2-carboxamide 34d

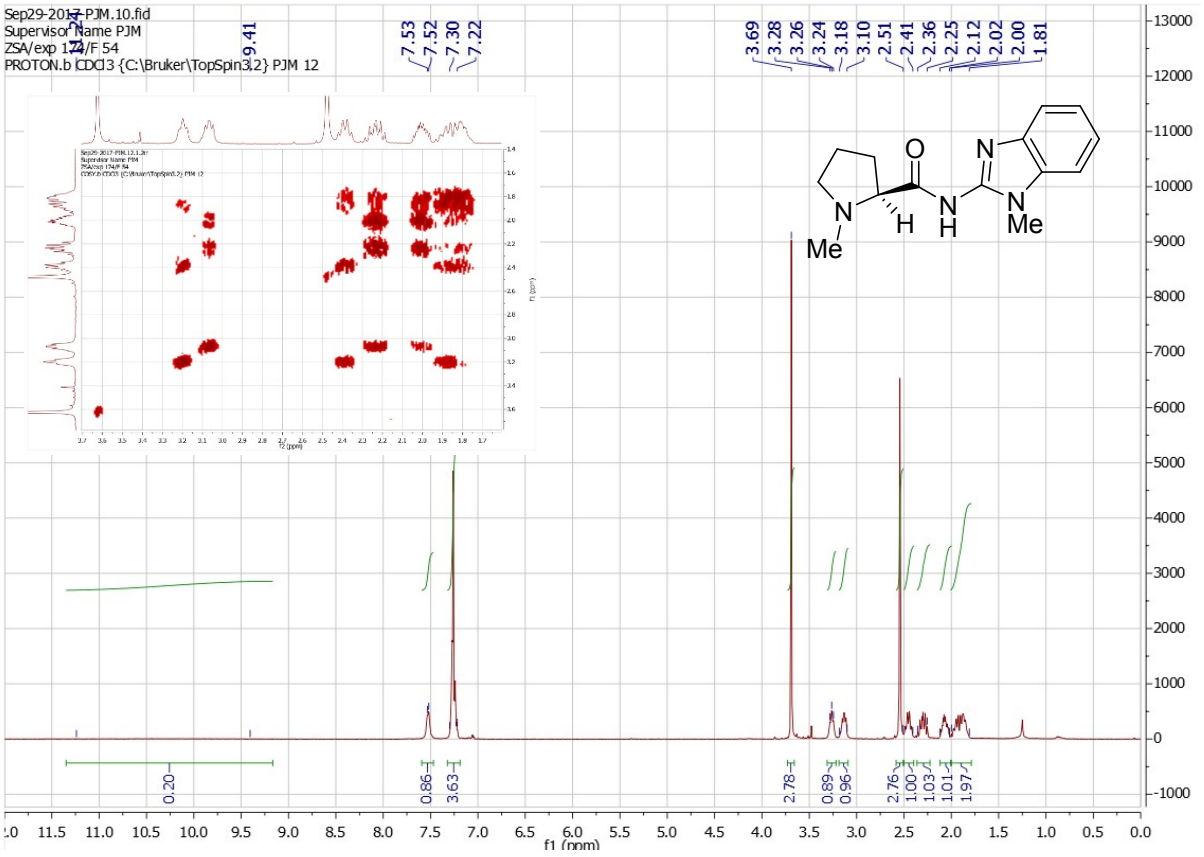
^{1}H NMR, COSY (insert).



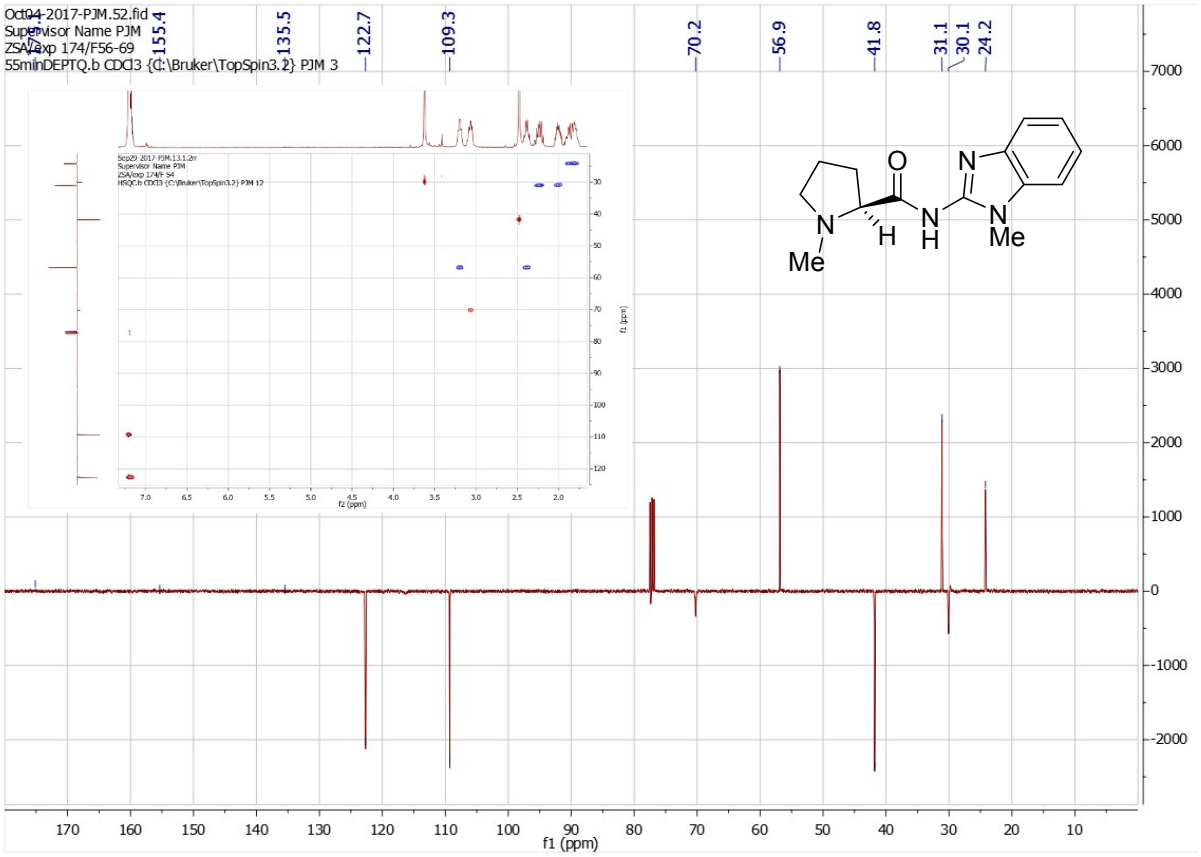
(*S*)-*N*-(1H-benzo[d]imidazol-2-yl)-1-cyclohexylpyrrolidine-2-carboxamide 34d
^{13}C NMR, DEPTQ (insert).



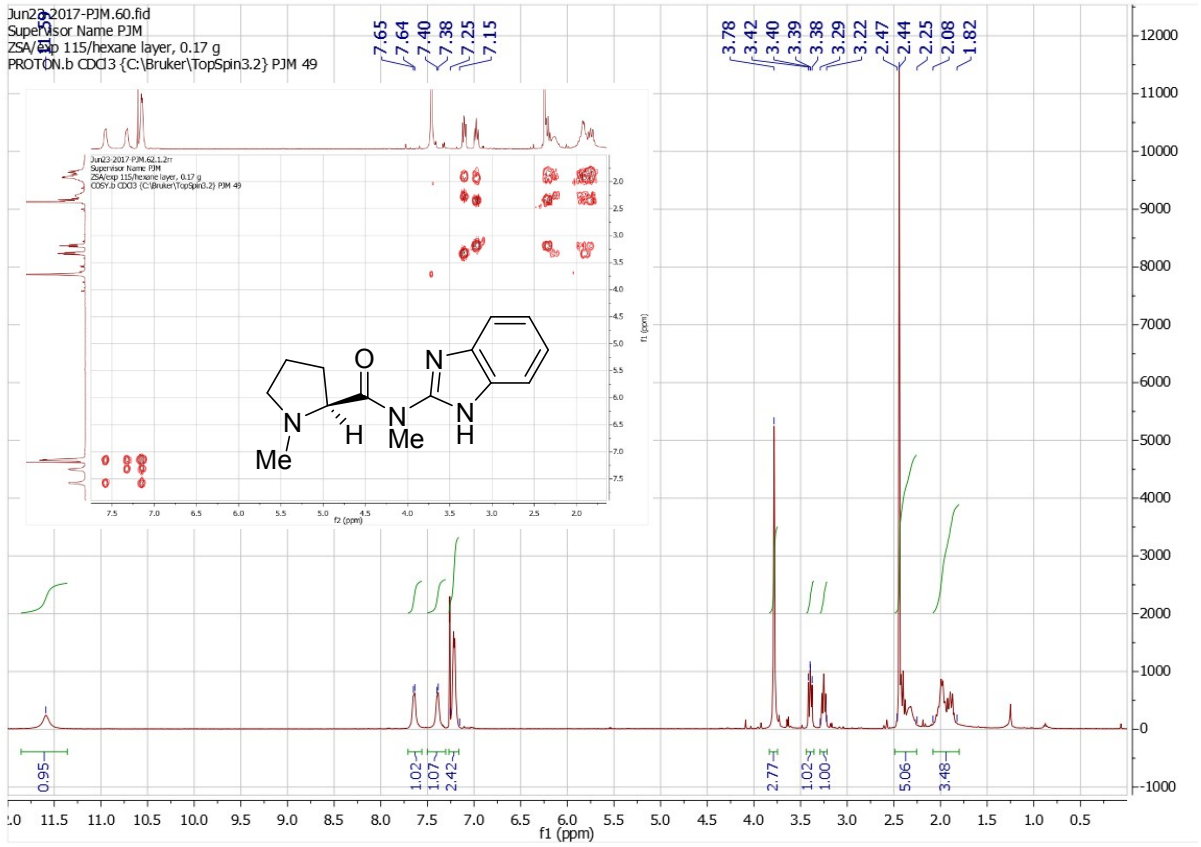
(*S*)-*N*-(1H-benzo[d]imidazol-2-yl)-1-methylpyrrolidine-2-carboxamide 35:
^{1}H NMR, COSY (insert).



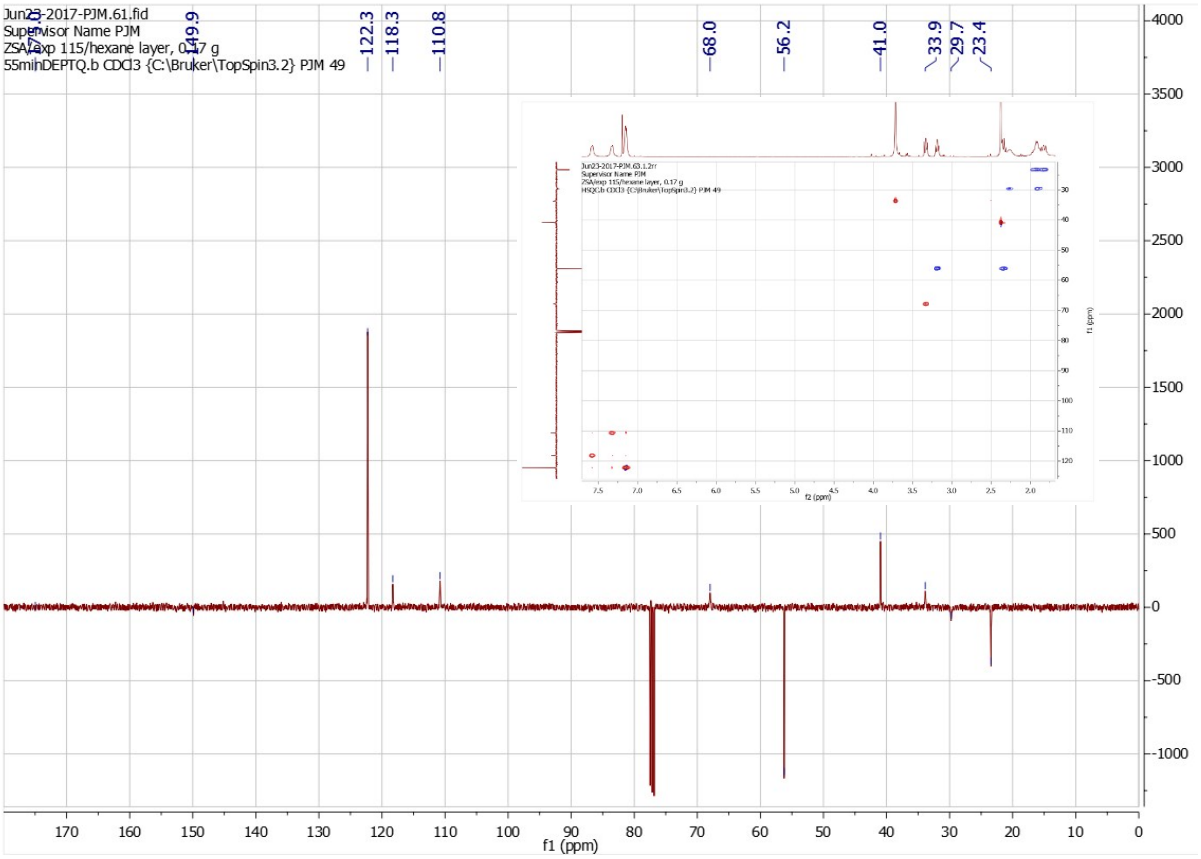
(*S*)-*N*-(1H-benzo[d]imidazol-2-yl)-1-methylpyrrolidine-2-carboxamide 35: ^{13}C NMR, DEPTQ (insert).



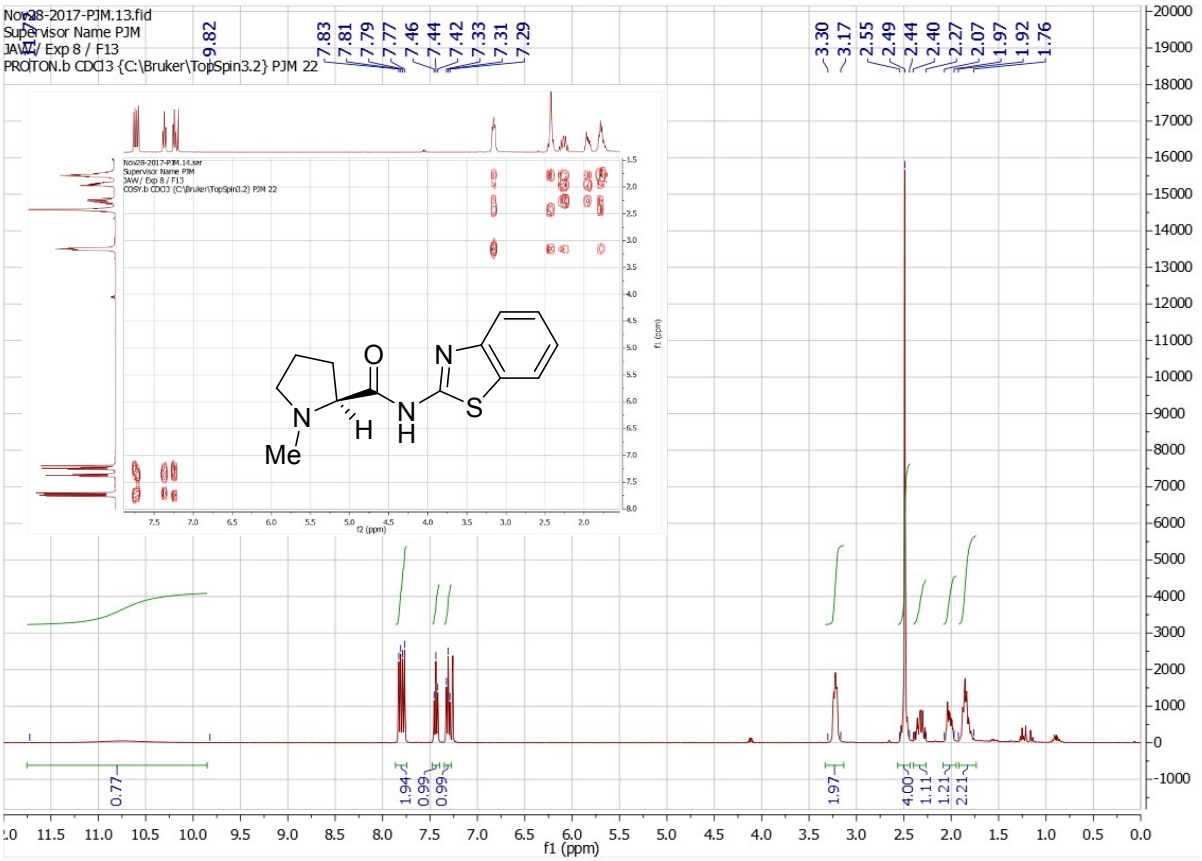
(*S*)-*N*-(1H-Benzo[d]imidazol-2-yl)-*N*,1-dimethylpyrrolidine-2-carboxamide 36: ^{1}H NMR, COSY (insert).



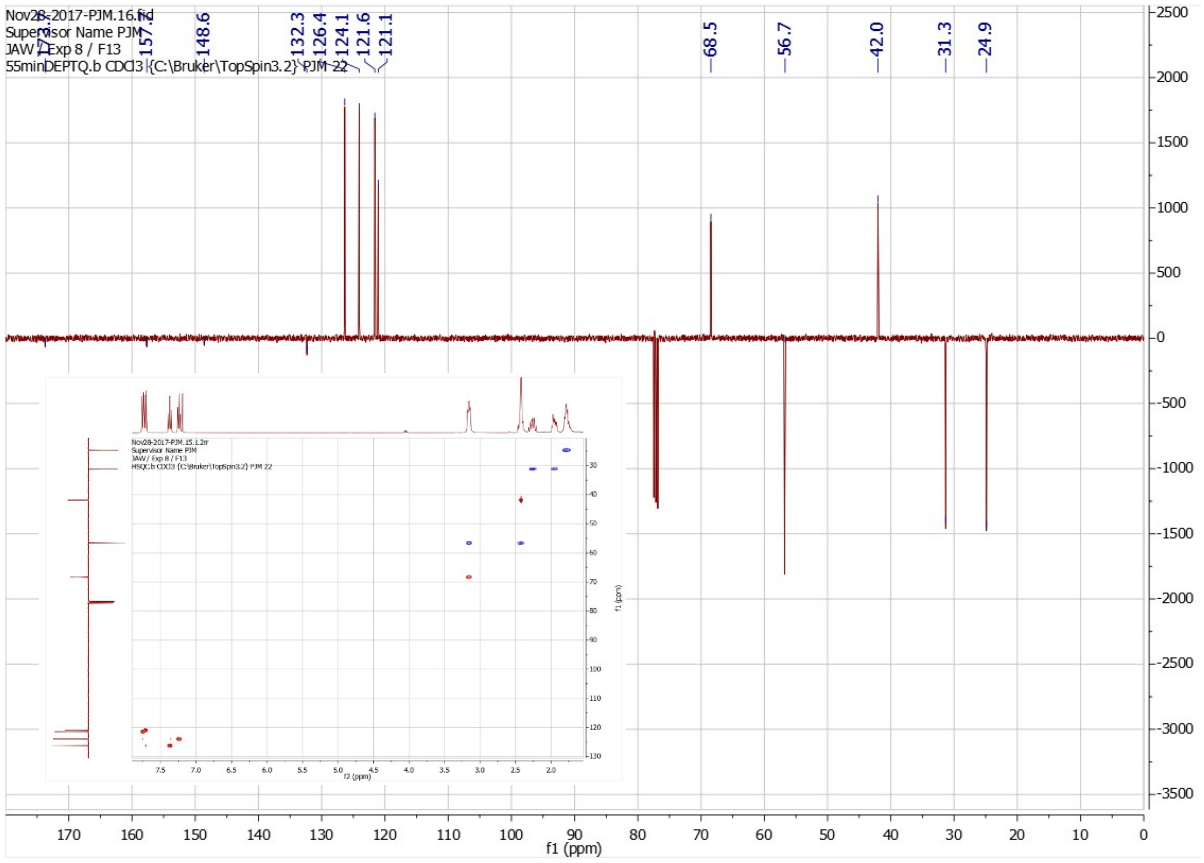
(*S*)-*N*-(1H-Benzo[d]imidazol-2-yl)-*N*,1-dimethylpyrrolidine-2-carboxamide 36: ^{13}C NMR, DEPTQ (insert).



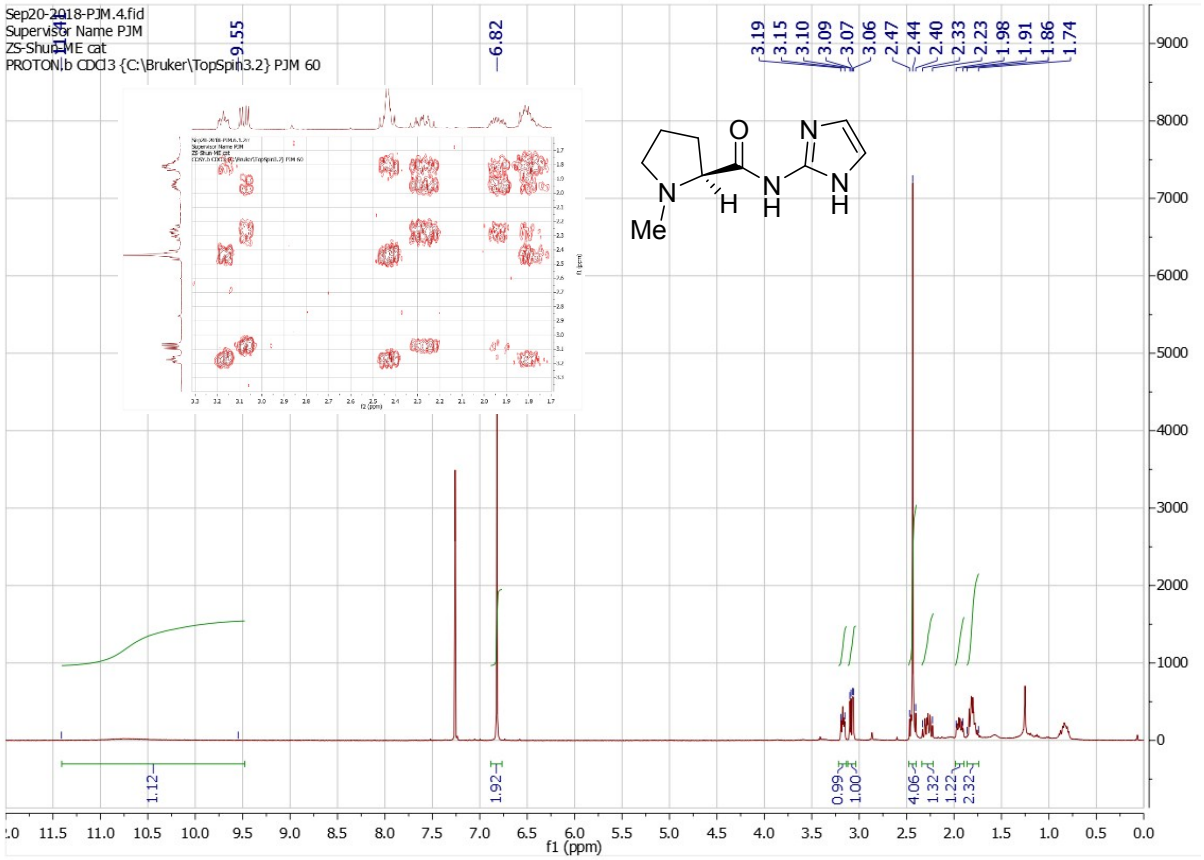
(S)-*N*-(benzo[*d*]thiazol-2-yl)-1-methylpyrrolidine-2-carboxamide 37a. ^{1}H NMR, COSY (insert).



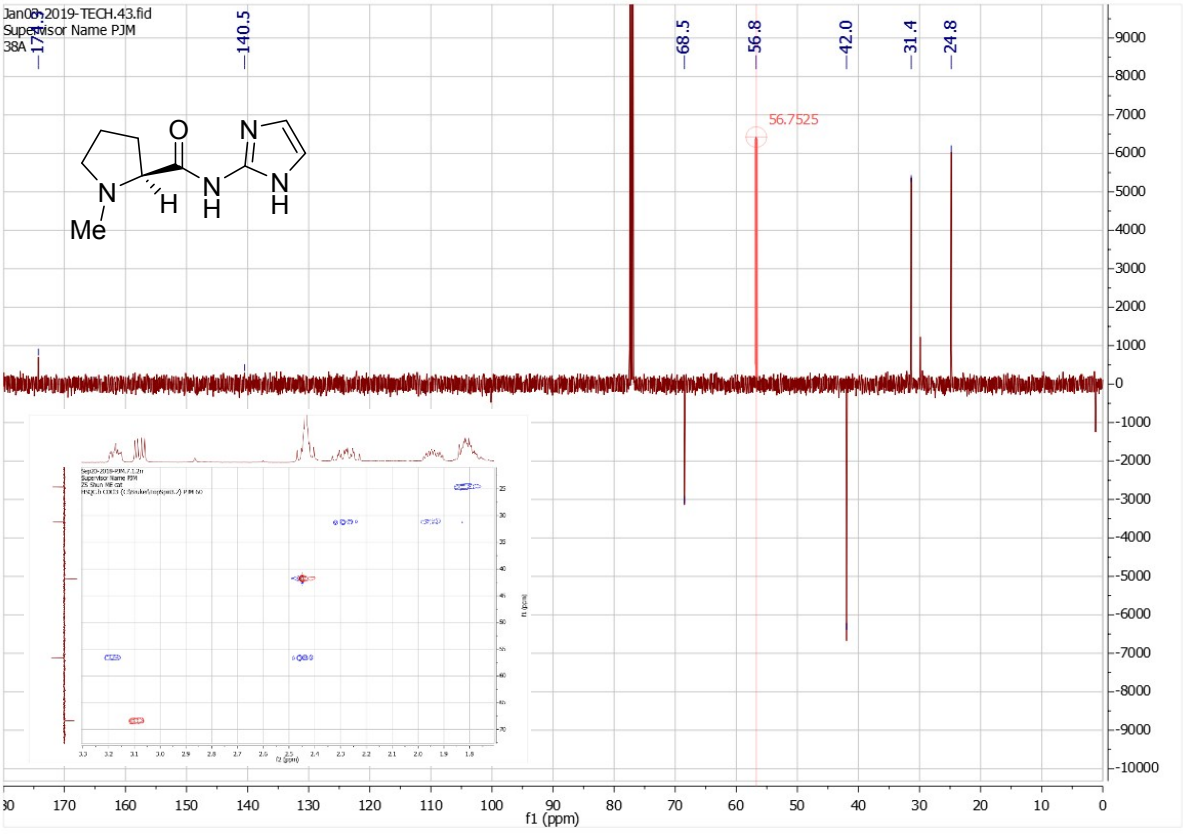
(S)-*N*-(benzo[*d*]thiazol-2-yl)-1-methylpyrrolidine-2-carboxamide 37a.
^{13}C NMR, DEPTQ (insert).



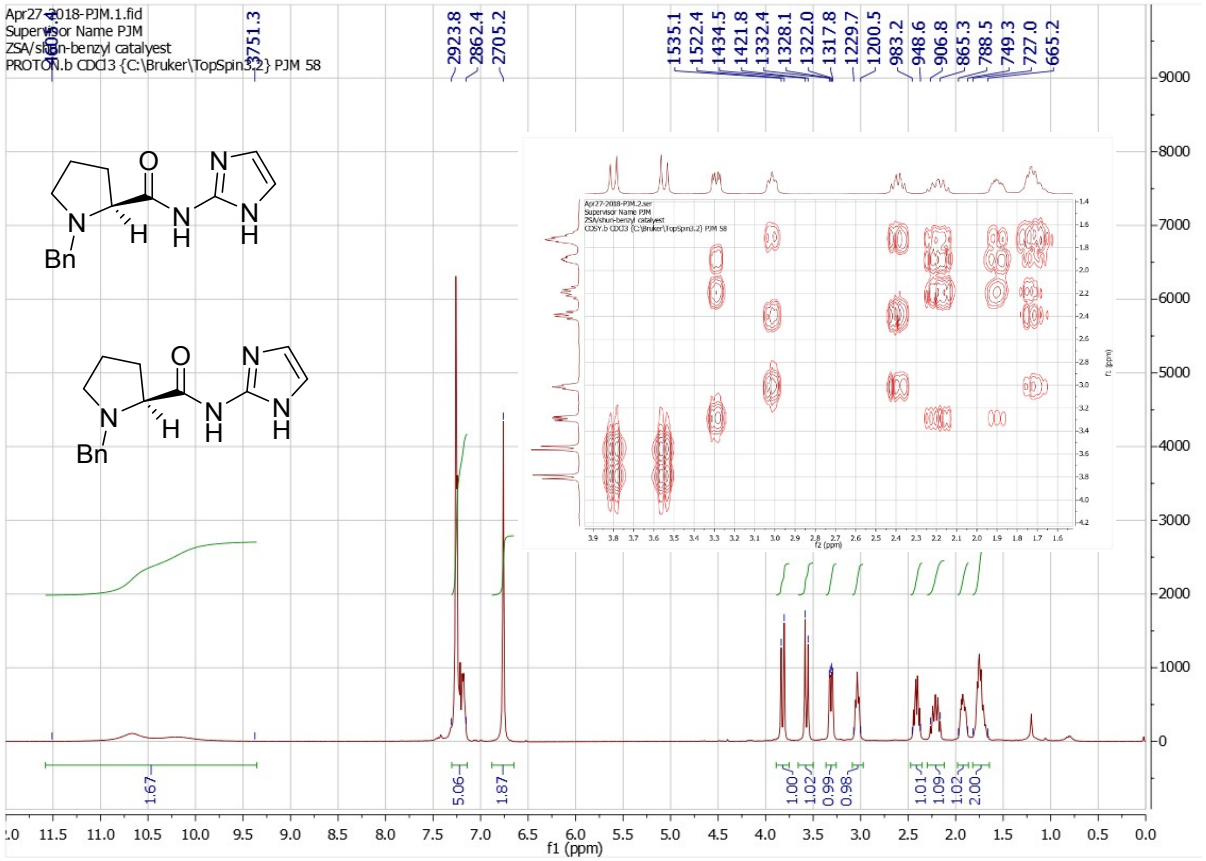
***(S)*-1-Methyl-*N*-(1*H*-imidazol-2-yl)pyrrolidine-2-carboxamide 38a**
^{1}H NMR, COSY (insert).



***(S)*-1-Methyl-*N*-(1*H*-imidazol-2-yl)pyrrolidine-2-carboxamide 38a**
^{13}C NMR, DEPTQ (insert).

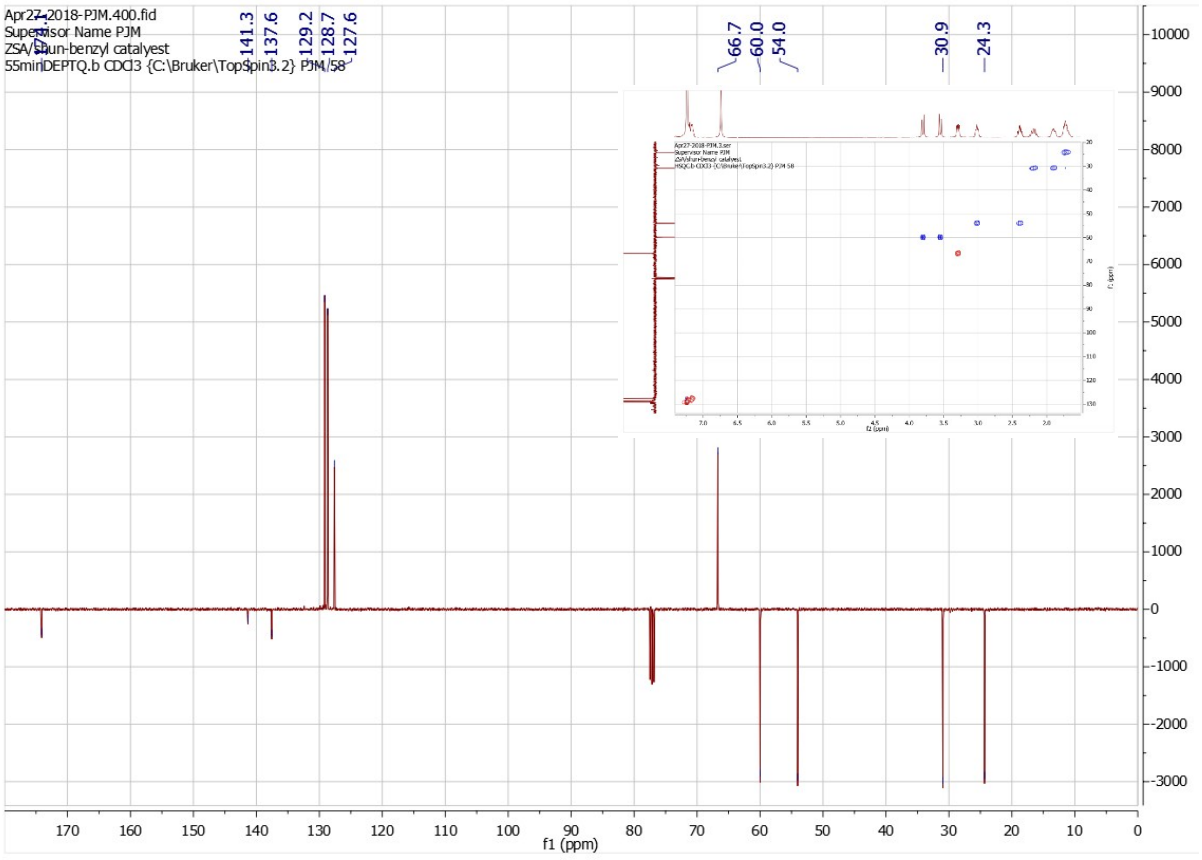


***(S)*-1-Benzyl-*N*-(1*H*-imidazol-2-yl)pyrrolidine-2-carboxamide 38b:**
^{1}H NMR, COSY (insert).



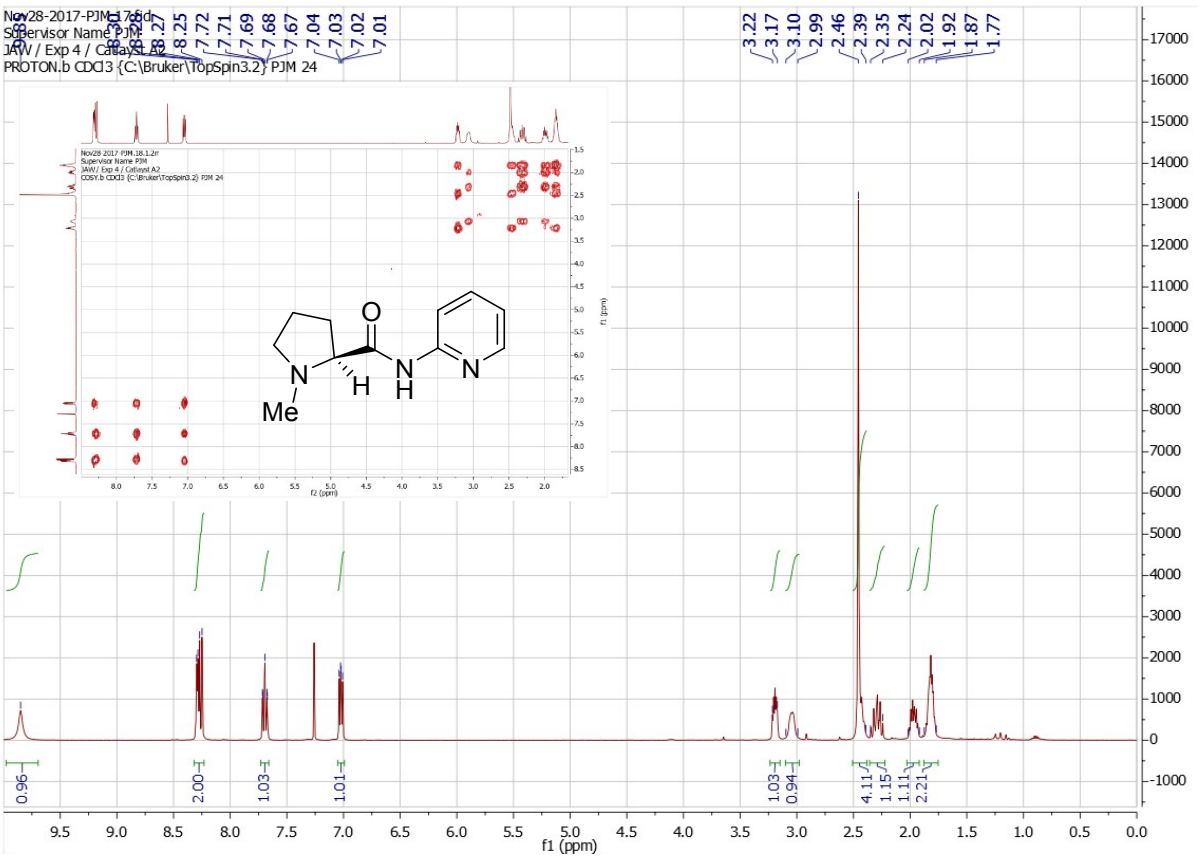
***(S)*-1-Benzyl-*N*-(1*H*-imidazol-2-yl)pyrrolidine-2-carboxamide 38b**

^{13}C NMR, DEPTQ (insert).

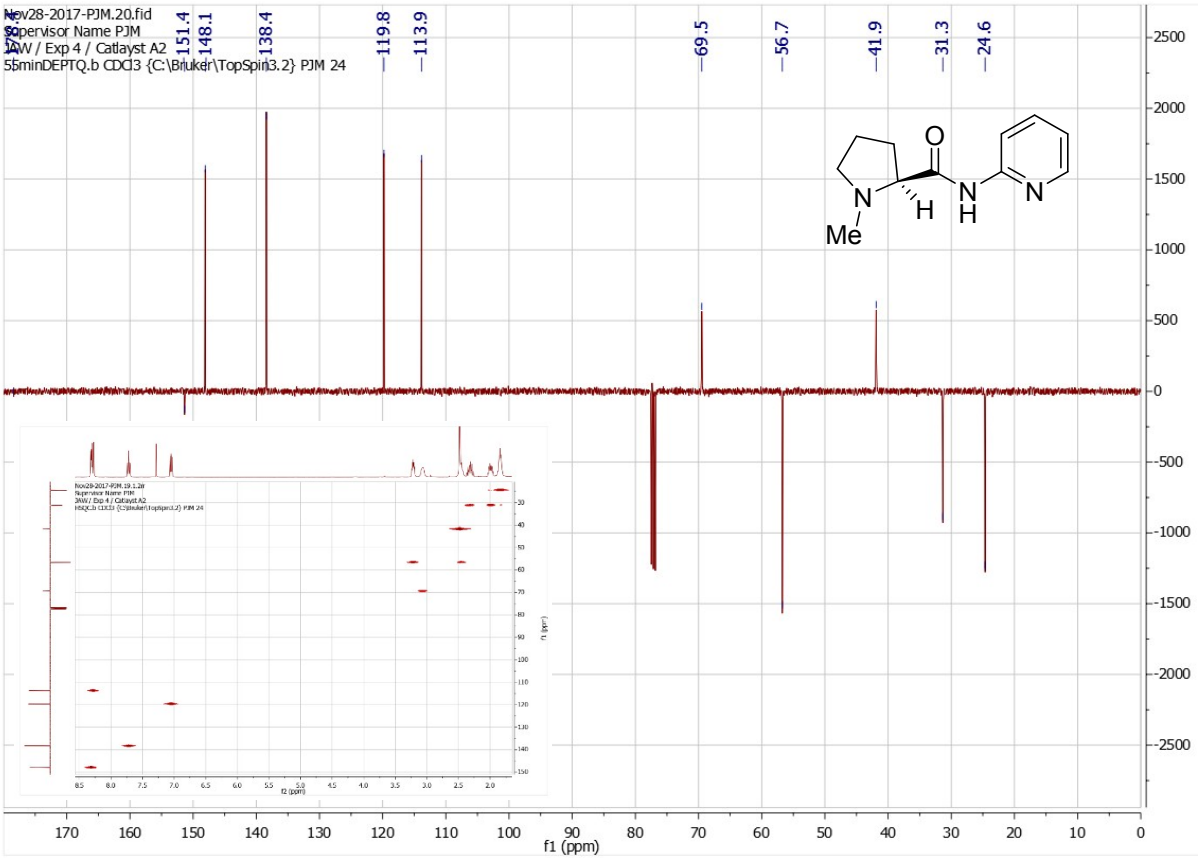


(S)-1-Methyl-*N*-(pyridine-2-yl)pyrrolidine-2-carboxamide 39a:

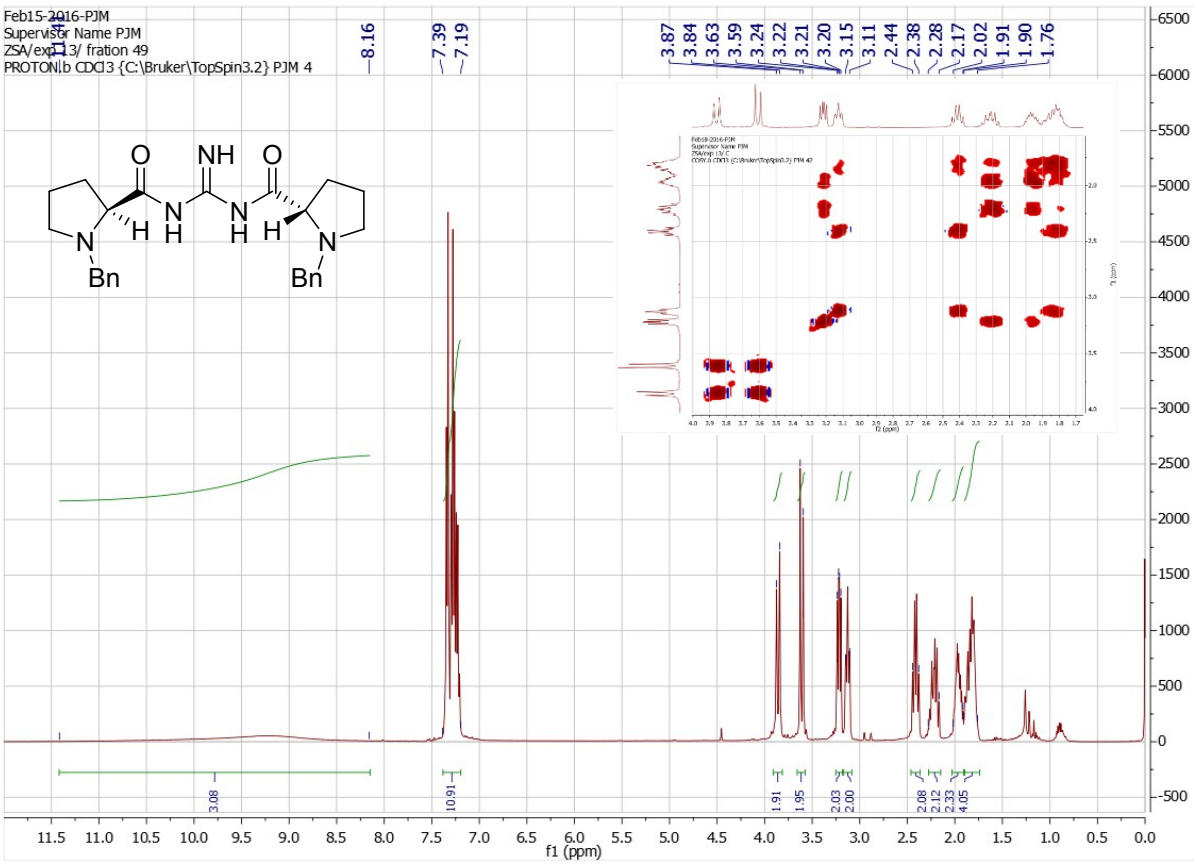
^{1}H NMR, COSY (insert).



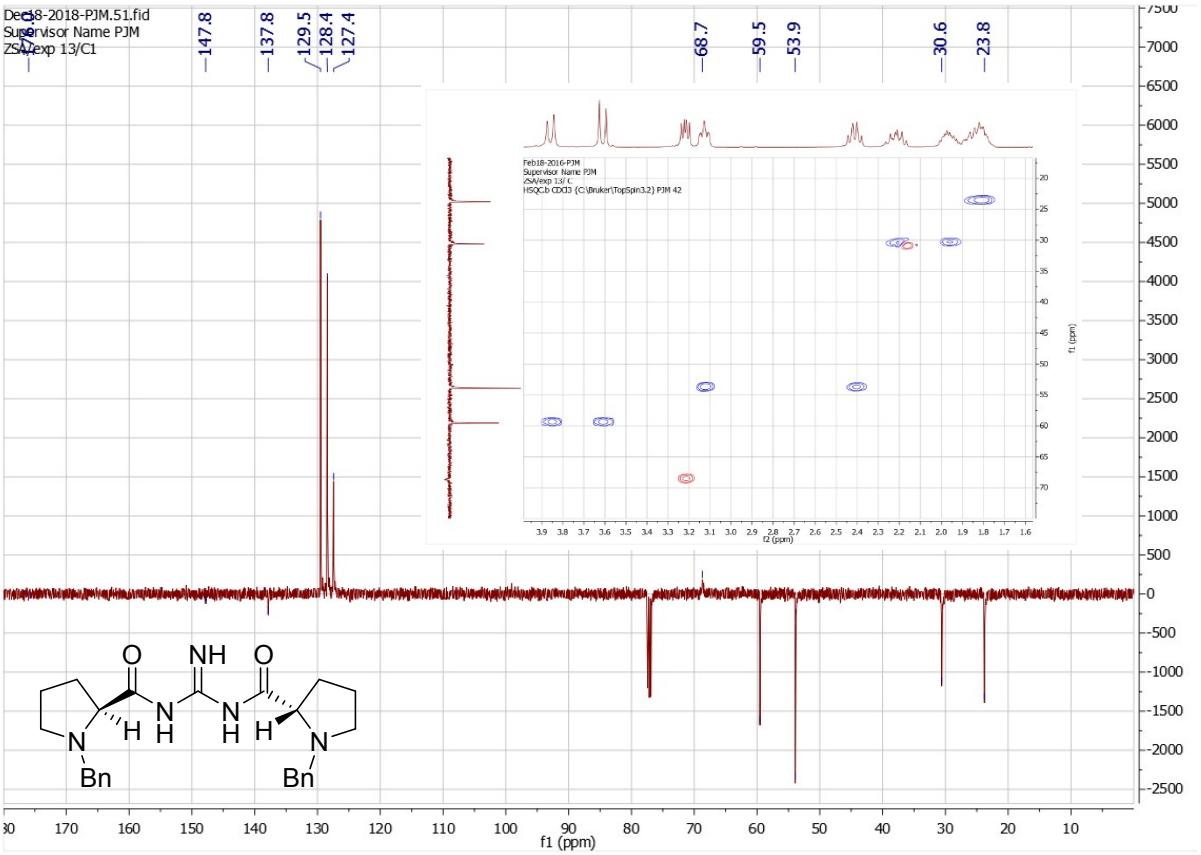
(S)-1-Methyl-*N*-(pyridine-2-yl)pyrrolidine-2-carboxamide 39a:
^{13}C NMR, DEPTQ (insert).



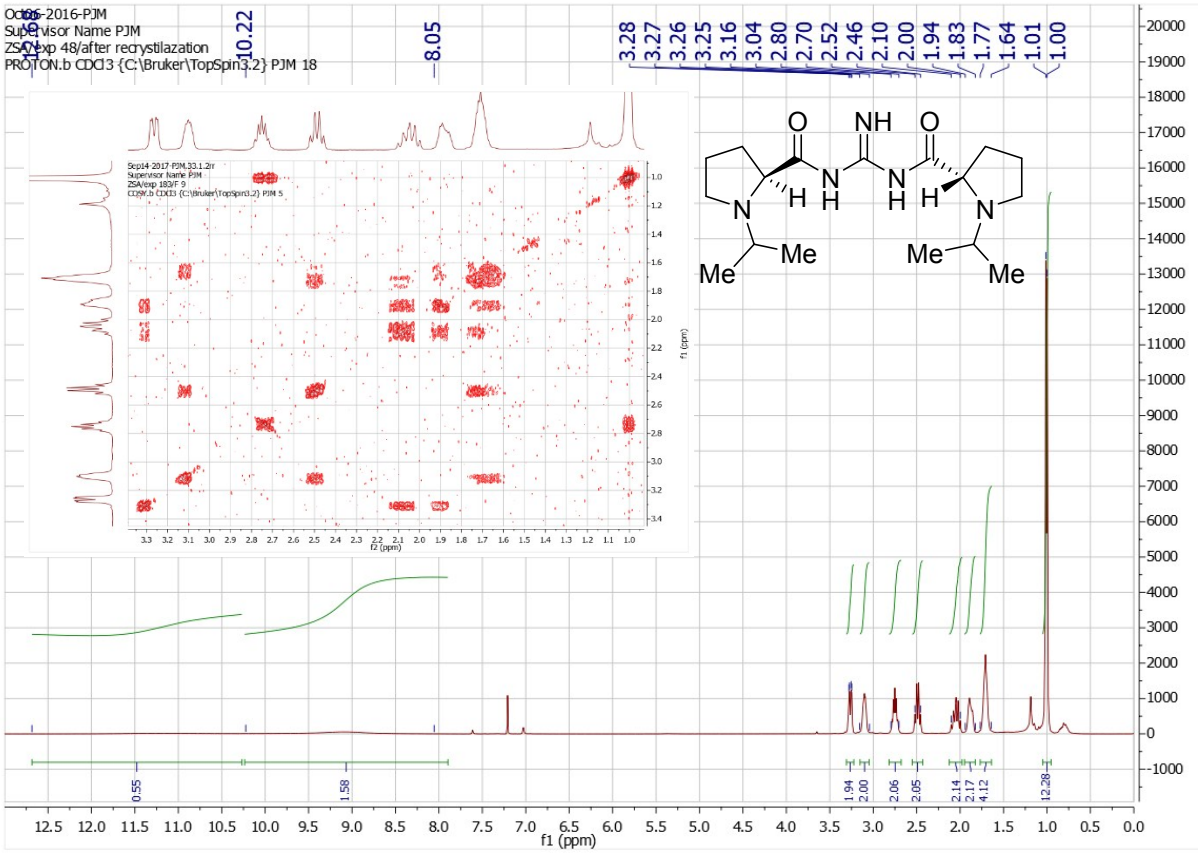
***(2S,2'S)*-*N,N'*-(Iminomethylene)bis(1-benzylpyrrolidine-2-carboxamide) 40b:**
^{1}H NMR, COSY (insert).



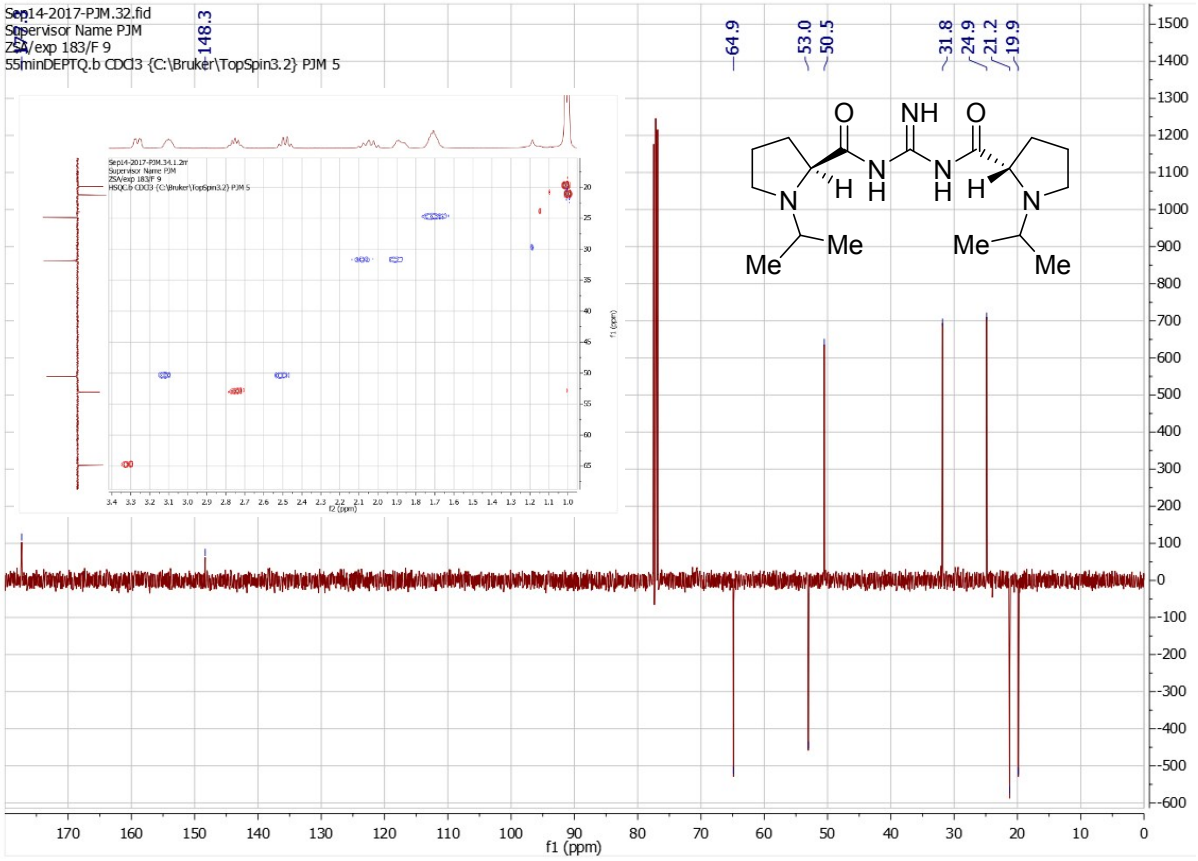
***(2S,2'S)*-*N,N'*-(Iminomethylene)bis(1-benzylpyrrolidine-2-carboxamide) 40b: ^{13}C NMR, DEPTQ (insert).**



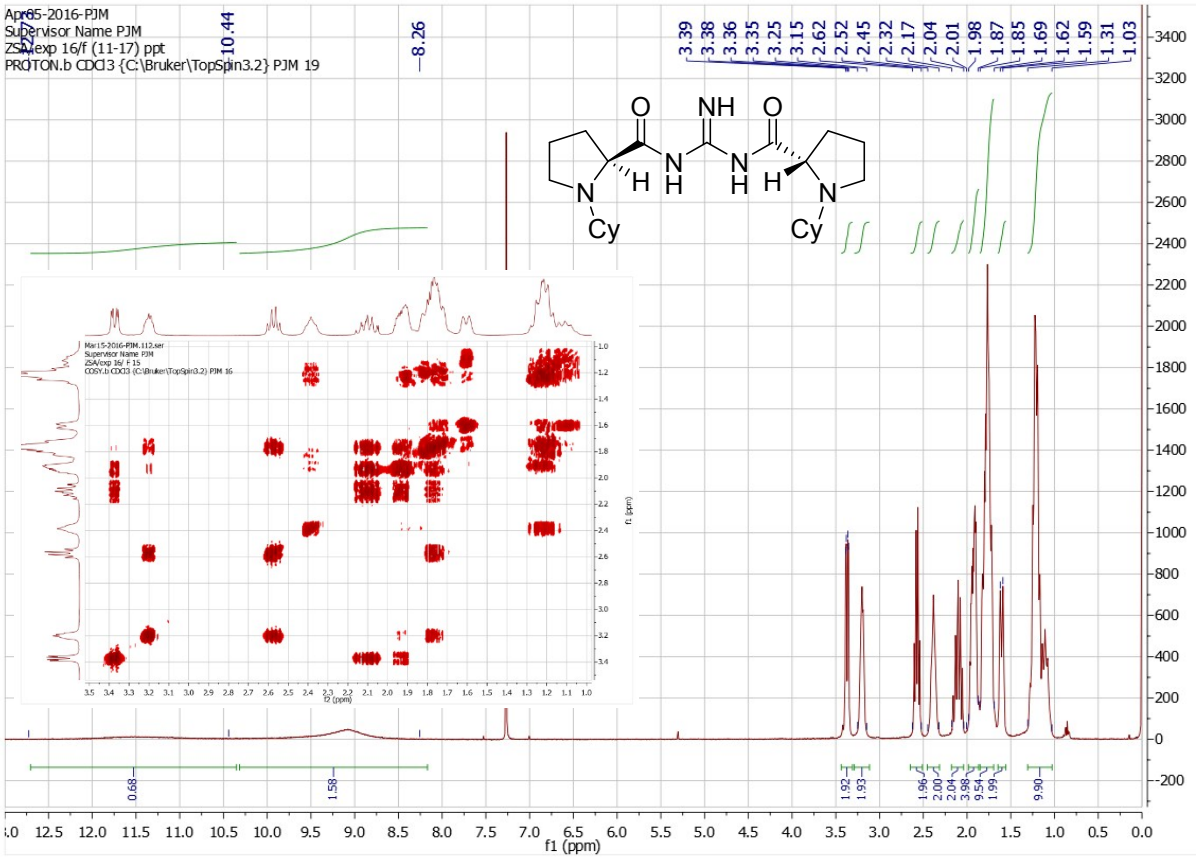
(*2S,2'S*)-*N,N'*-(Iminomethylene)bis(1-isopropylpyrrolidine-2-carboxamide) 40c: ^{1}H NMR, COSY (insert).



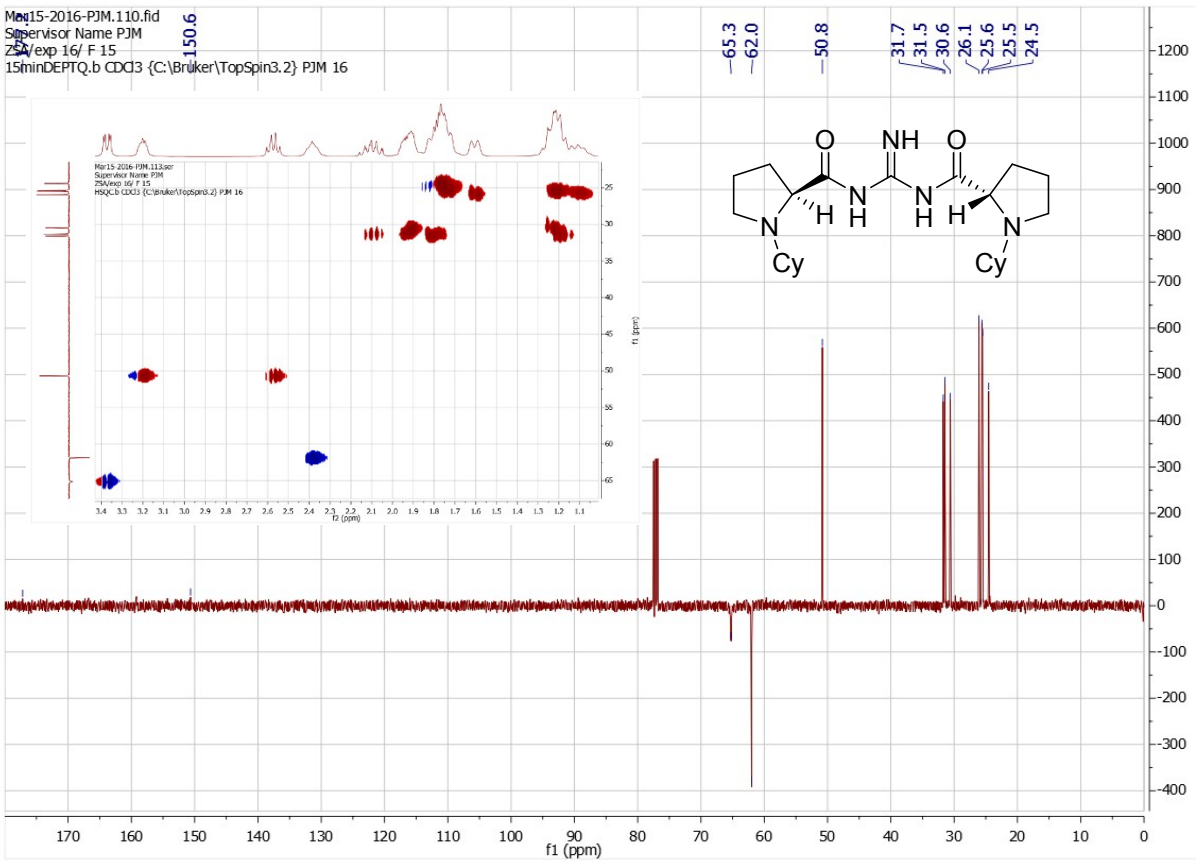
(*2S,2'S*)-*N,N'*-(Iminomethylene)bis(1-isopropylpyrrolidine-2-carboxamide) 40c: ^{13}C NMR, DEPTQ (insert).



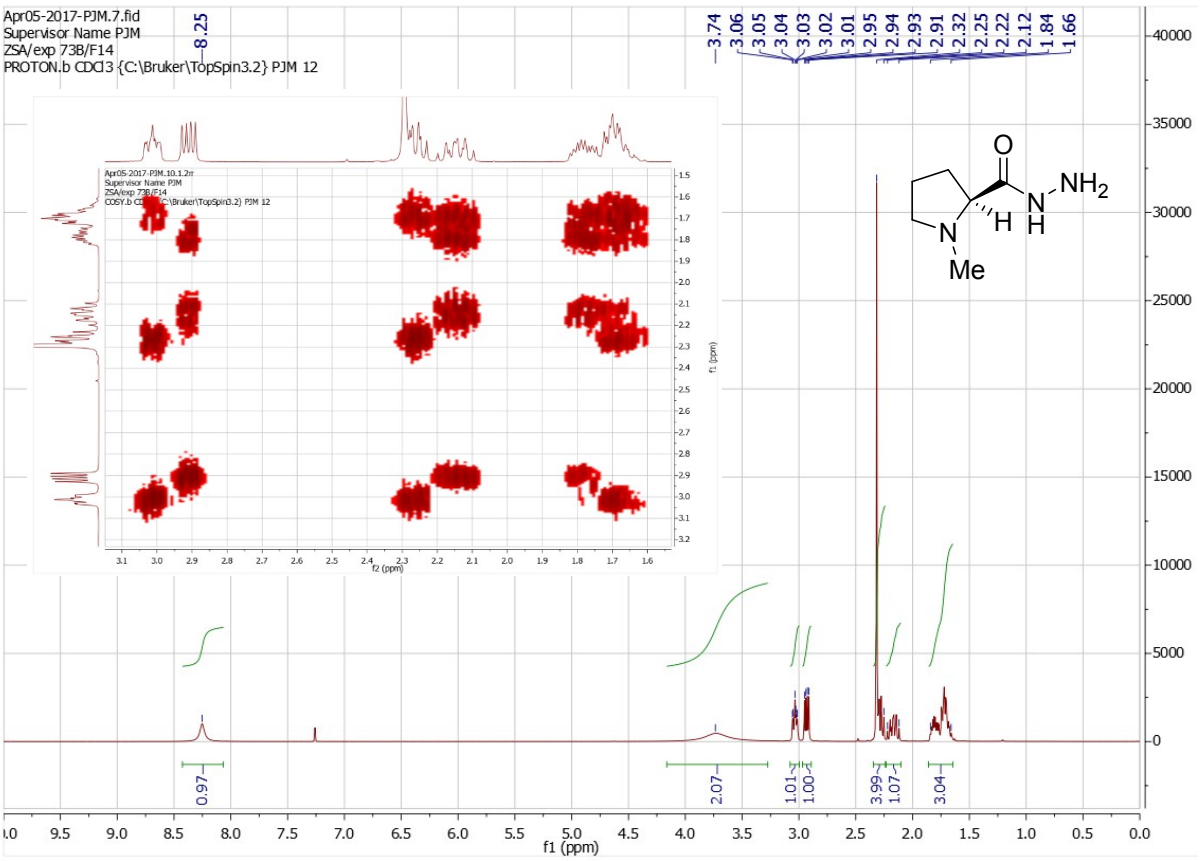
(*2S,2'S*)-*N,N'*-(Iminomethylene)bis(1-cyclohexylpyrrolidine-2-carboxamide) 40d: ^{1}H NMR, COSY (insert).



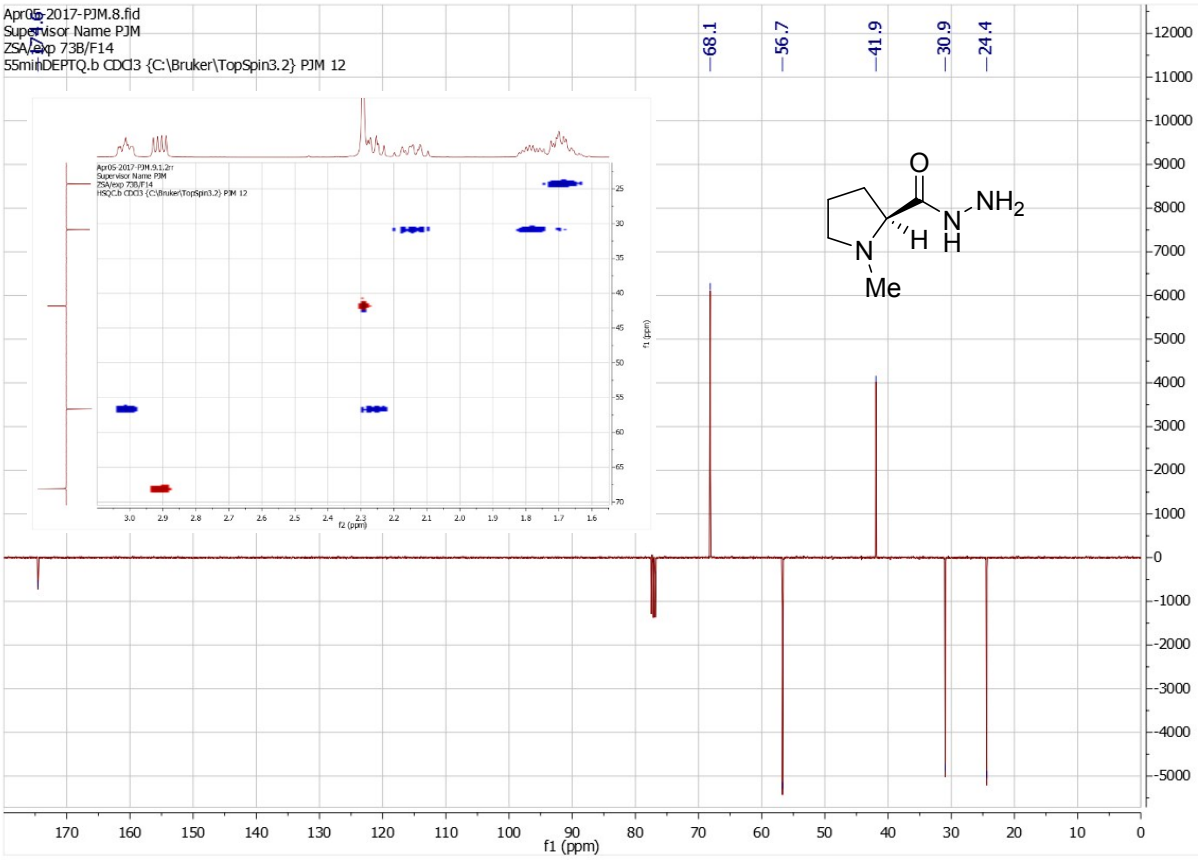
(*2S,2'S*)-*N,N'*-(Iminomethylene)bis(1-cyclohexylpyrrolidine-2-carboxamide) 40d: ^{13}C NMR, DEPTQ (insert).



(*S*)-1-Methylpyrrolidine-2-carbohydrazide 41a (Method D): ^{1}H NMR, COSY (insert).

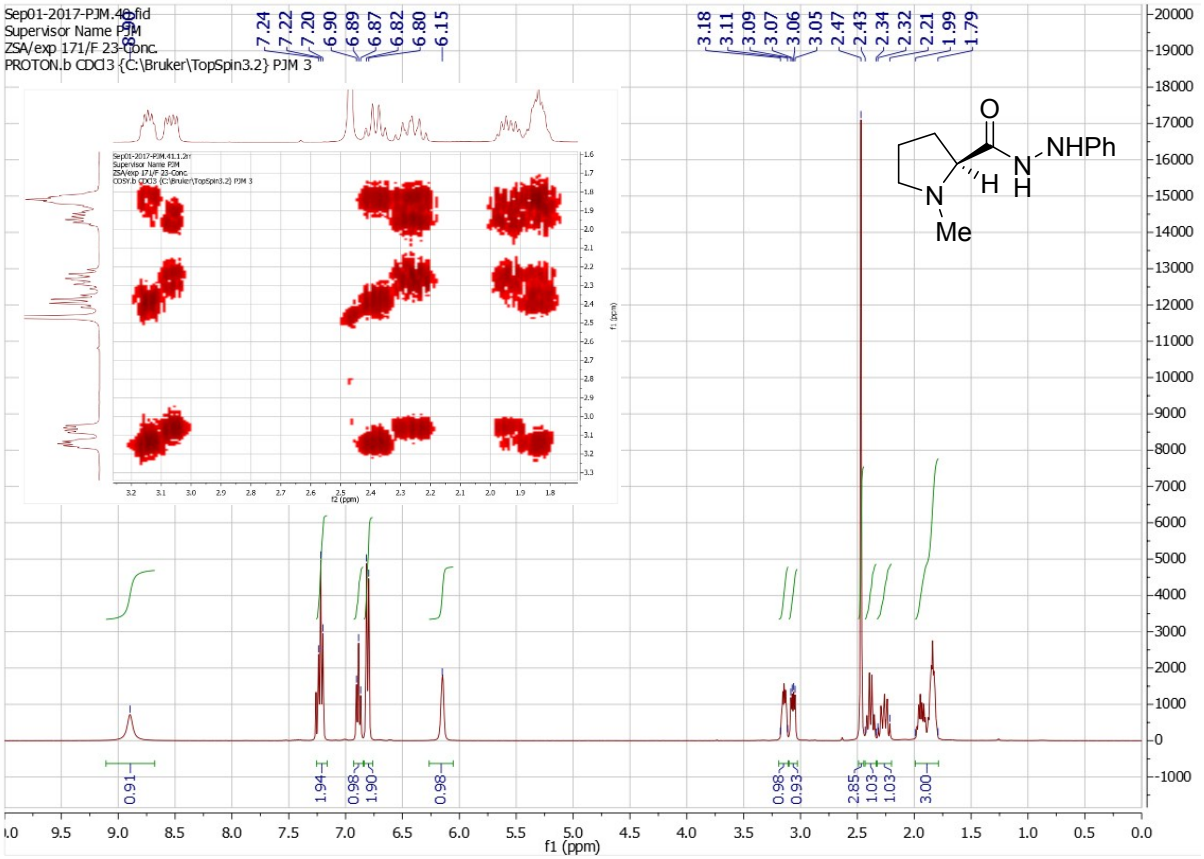


(*S*)-1-Methylpyrrolidine-2-carbohydrazide 41a (Method D): ^{13}C NMR, DEPTQ (insert).



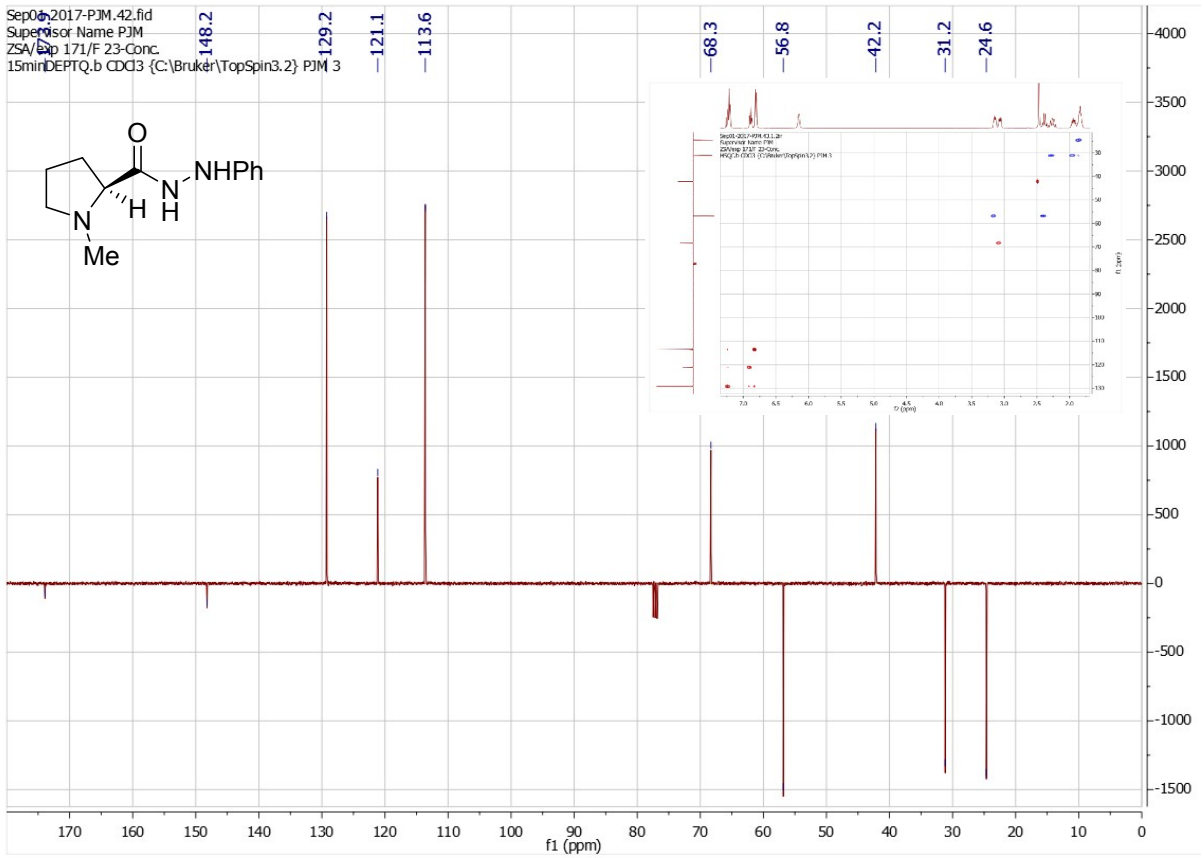
(*S*)-1-methyl-N'-phenylpyrrolidine-2-carbohydrazide 41b:

^{1}H NMR, COSY (insert).



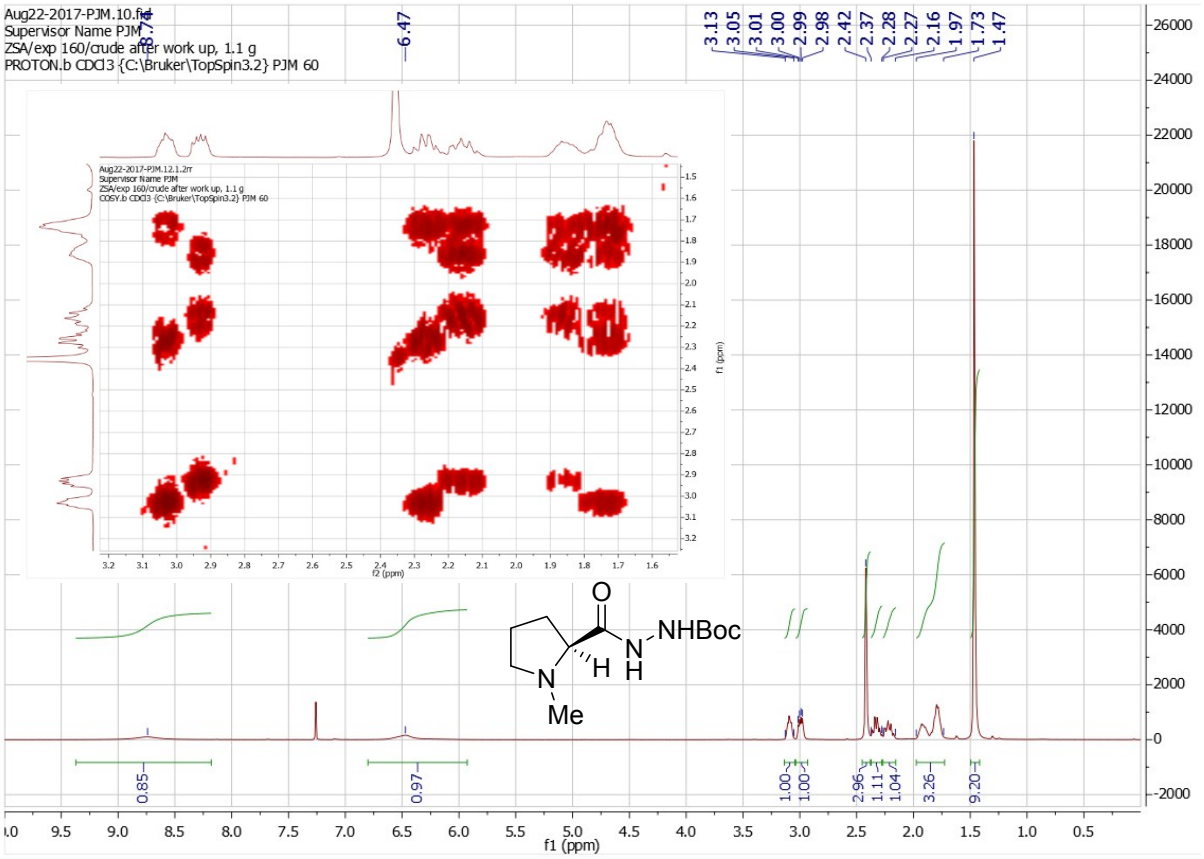
(*S*)-1-methyl-N'-phenylpyrrolidine-2-carbohydrazide 41b:

^{13}C NMR, DEPTQ (insert).



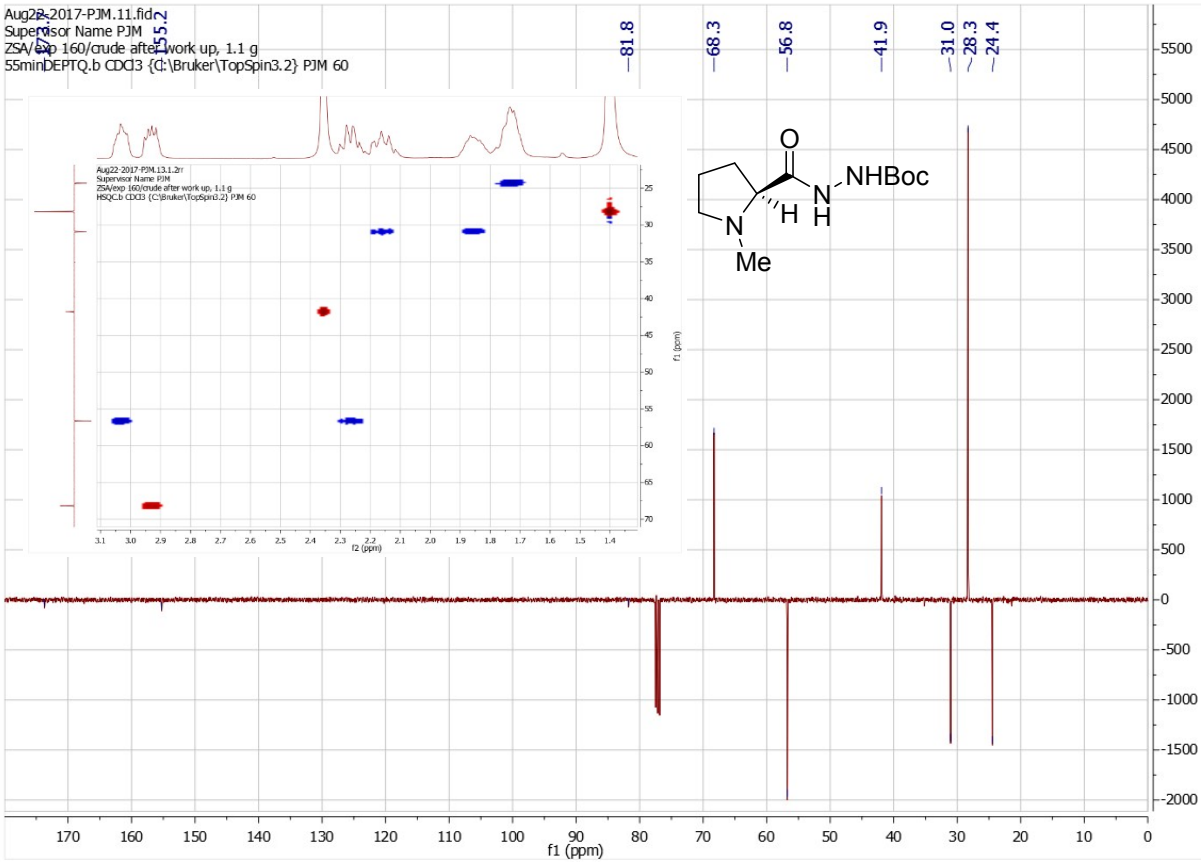
***tert*-Butyl 2-(methyl-*L*-prolyl)hydrazine-1-carboxylate 41c:**

^{1}H NMR, COSY (insert).



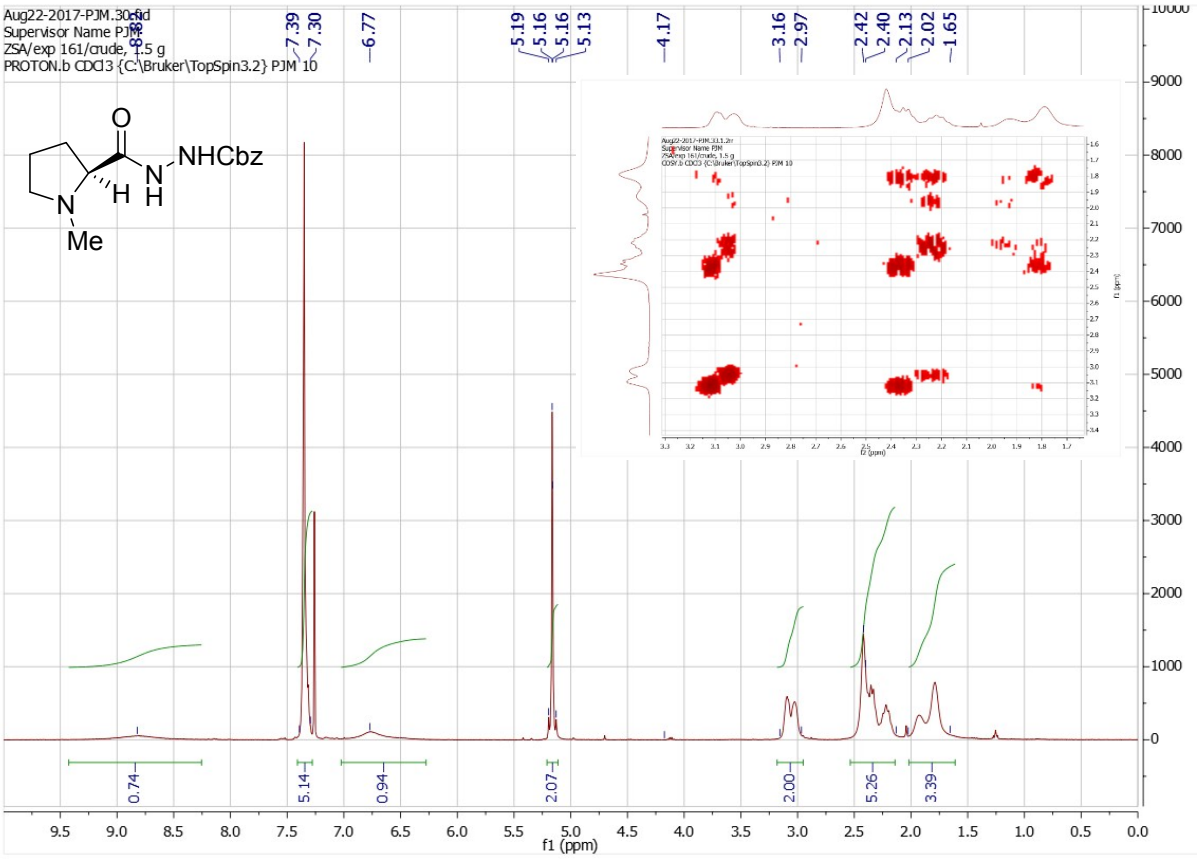
***tert*-Butyl 2-(methyl-*L*-prolyl)hydrazine-1-carboxylate 41c:**

^{13}C NMR, DEPTQ (insert).



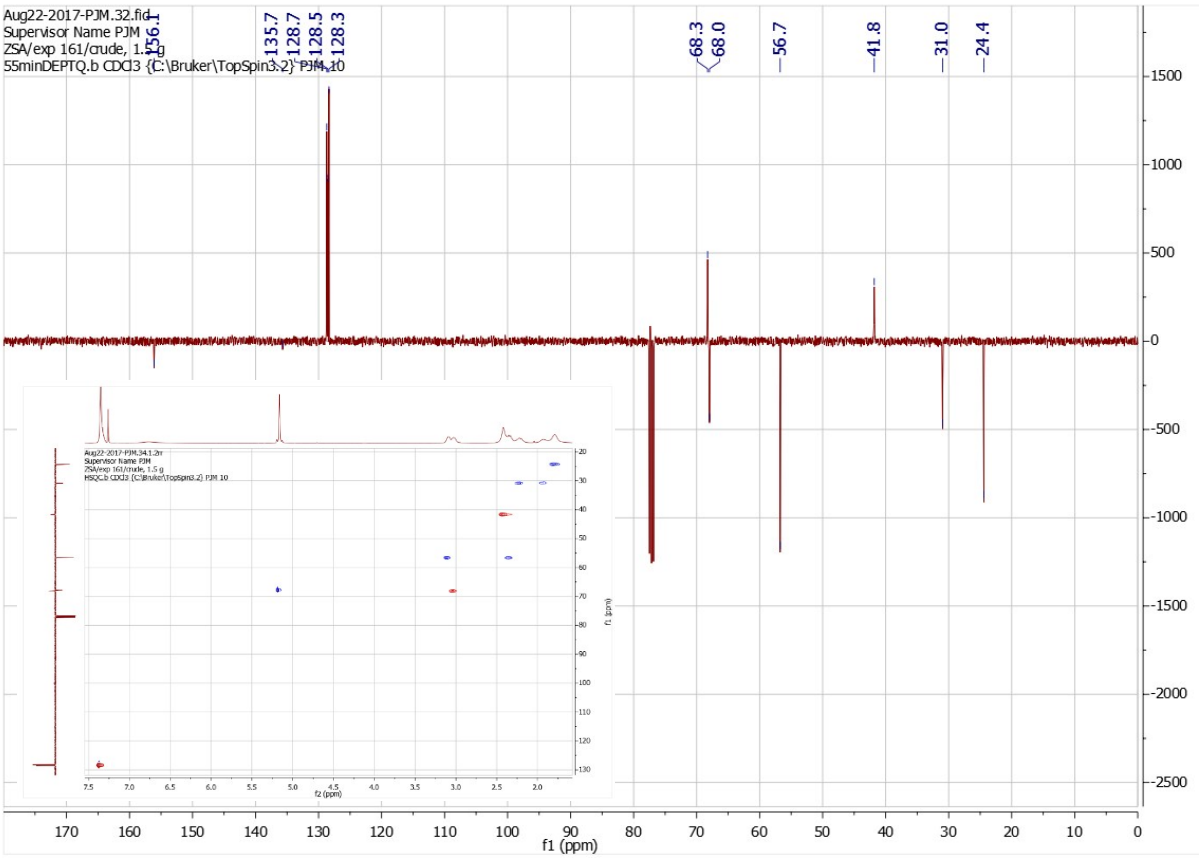
Benzyl 2-(methyl-*L*-prolyl)hydrazine-1-carboxylate 41d:

^{1}H NMR, COSY (insert).



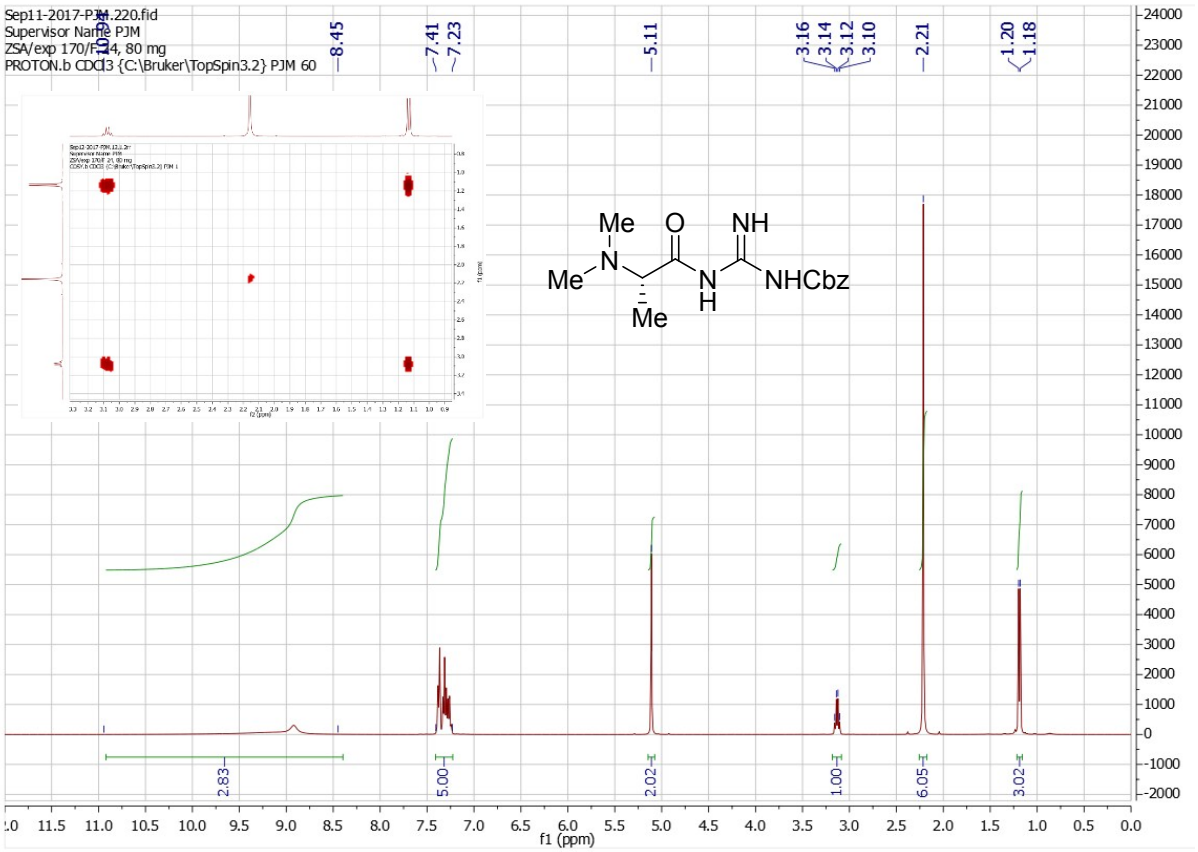
Benzyl 2-(methyl-*L*-prolyl)hydrazine-1-carboxylate 41d:

^{13}C NMR, DEPTQ (insert).



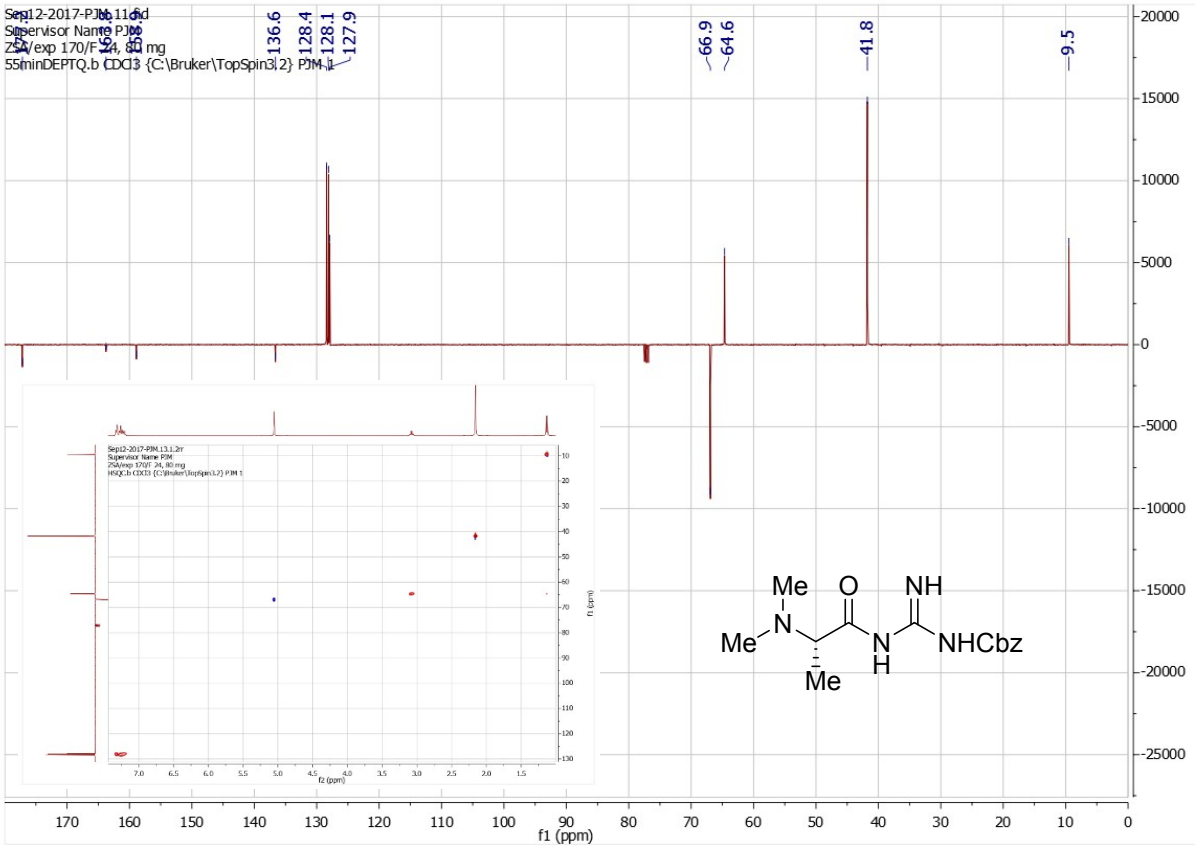
(*S*)-*N*-Cbz-*N'*-carbamimidoyl-2-(dimethylamino)propanamide 43a:

^{1}H NMR, COSY (insert).



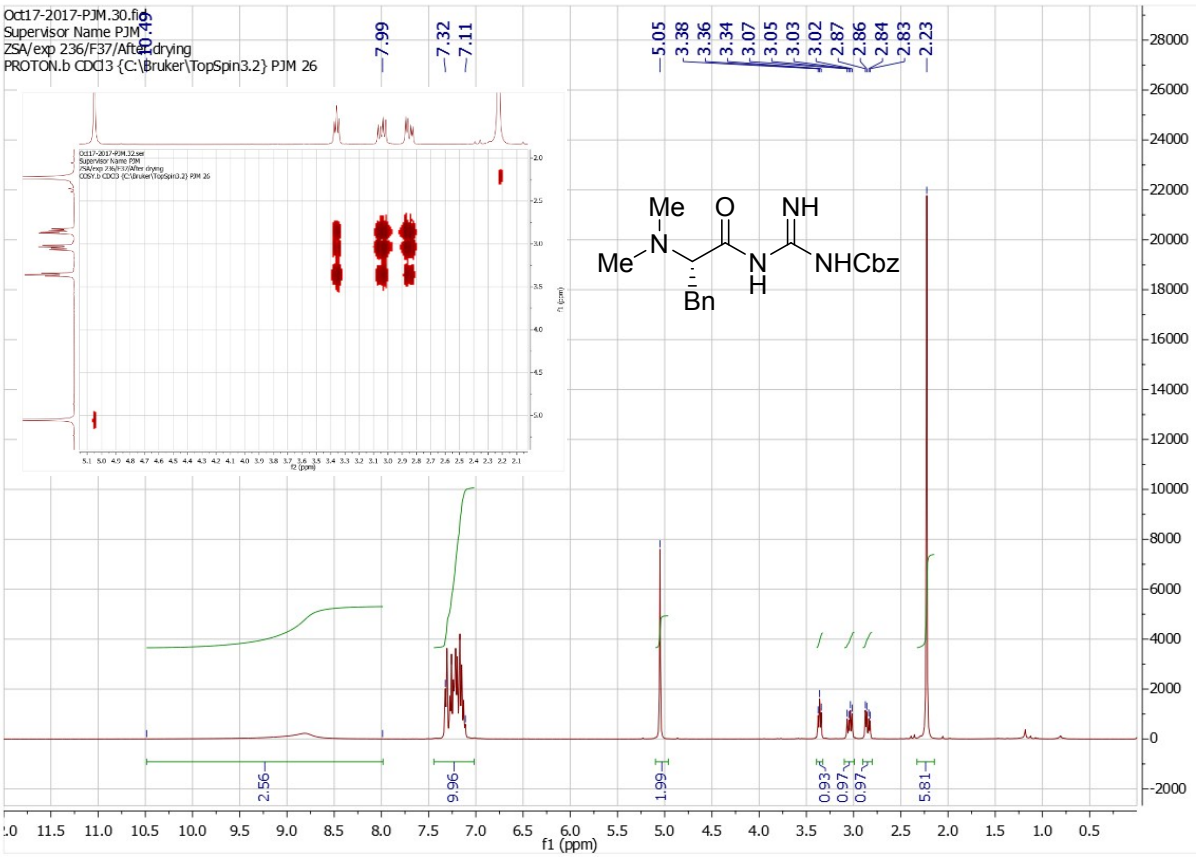
(*S*)-*N*-Cbz-*N'*-carbamimidoyl-2-(dimethylamino)propanamide 43a:

^{13}C NMR, DEPTQ (insert).



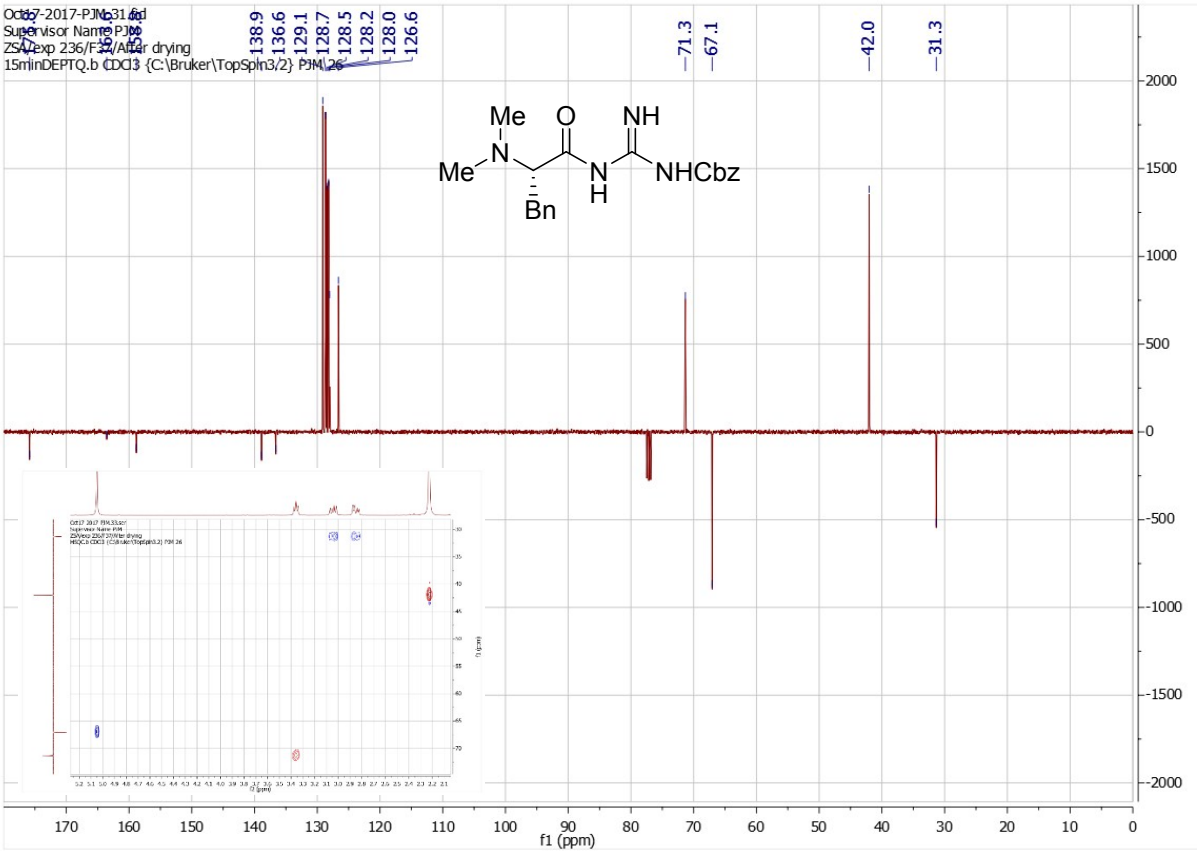
(*S*)-*N*-Cbz-*N'*-Carbamimidoyl-2-(dimethylamino)-3-phenylpropanamide 43b:

^{1}H NMR, COSY (insert).

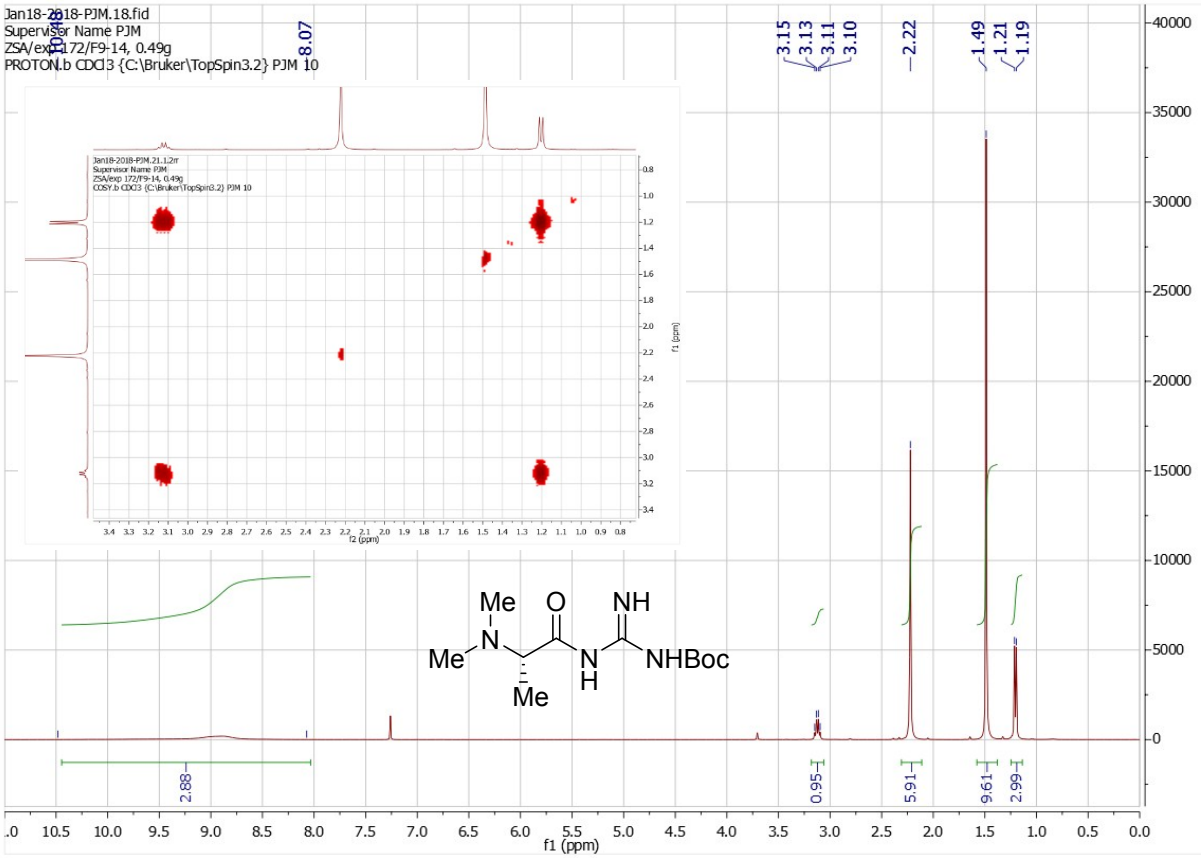


(*S*)-*N*-Cbz-*N'*-Carbamimidoyl-2-(dimethylamino)-3-phenylpropanamide 43b:

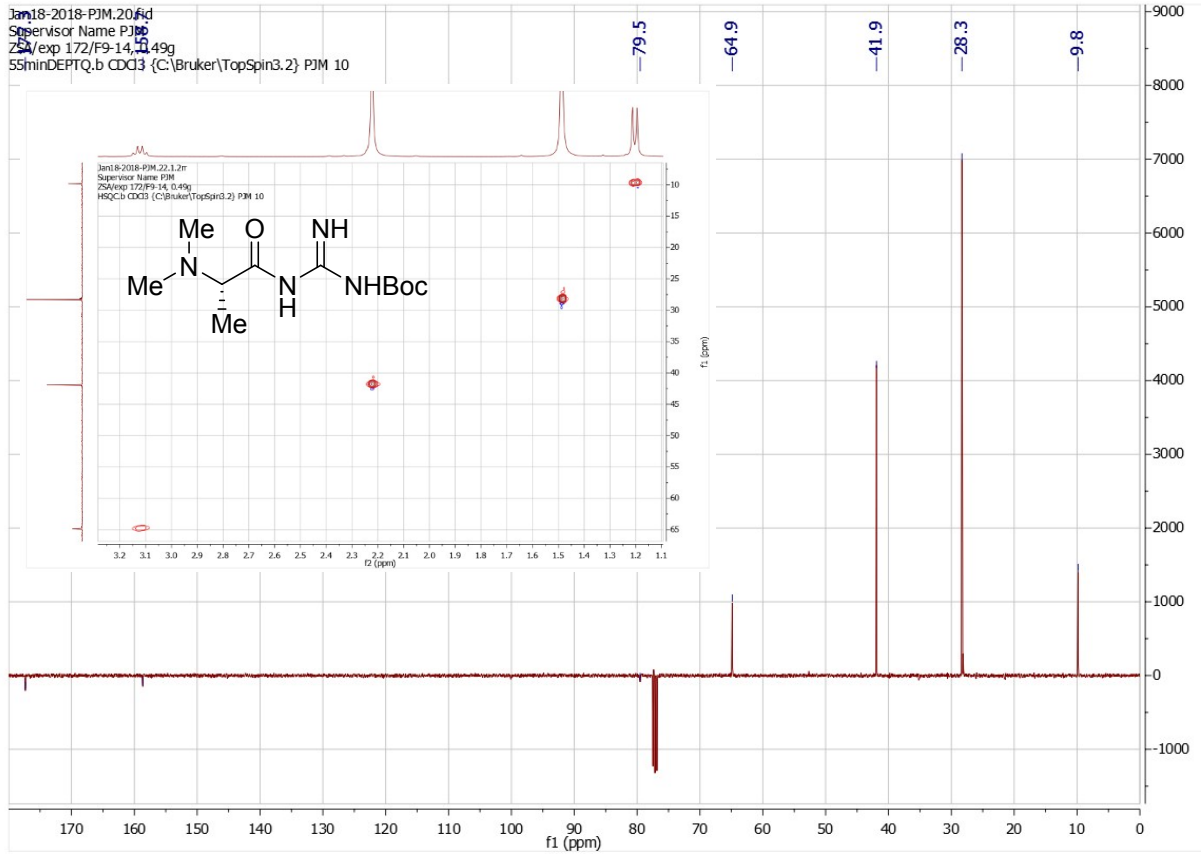
^{13}C NMR, DEPTQ (insert).



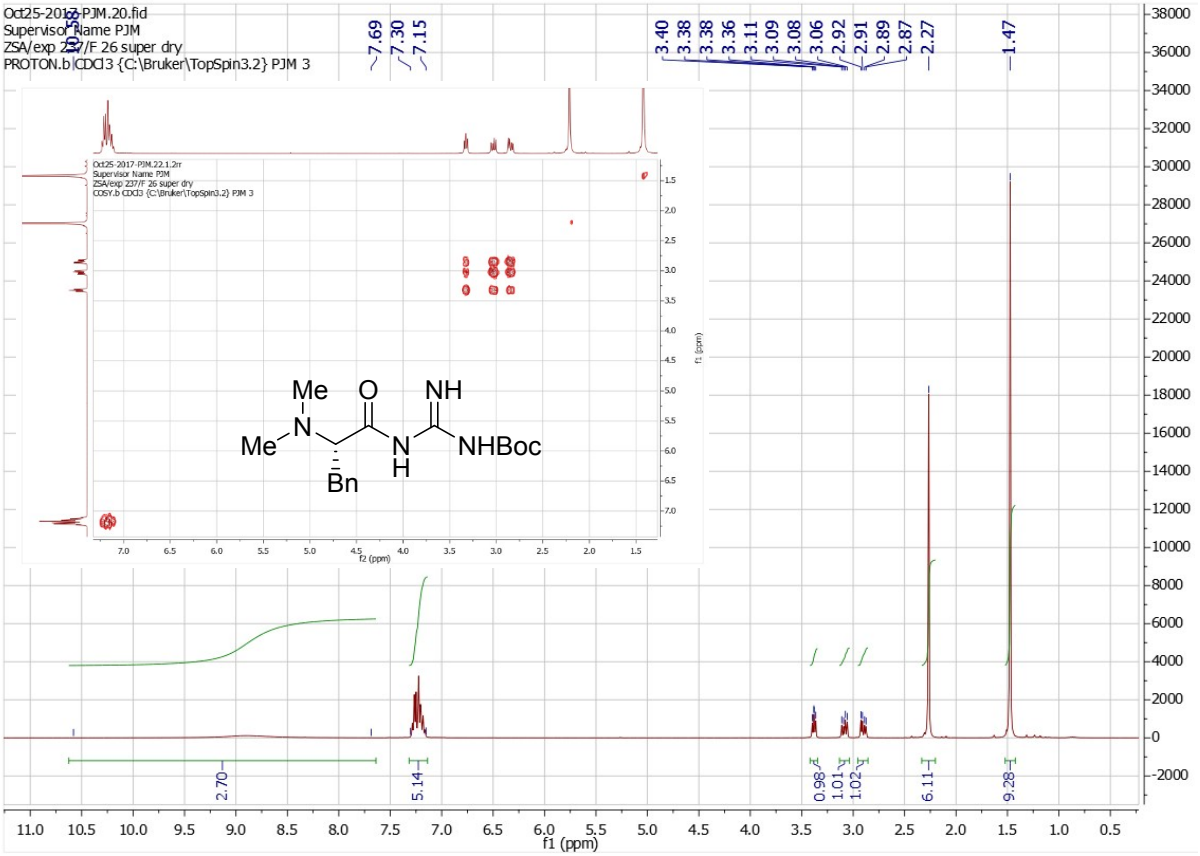
(*S*)-*N*-Boc-*N'*-Carbamimidoyl-2-(dimethylamino)propanamide 44a:
^{1}H NMR, COSY (insert).



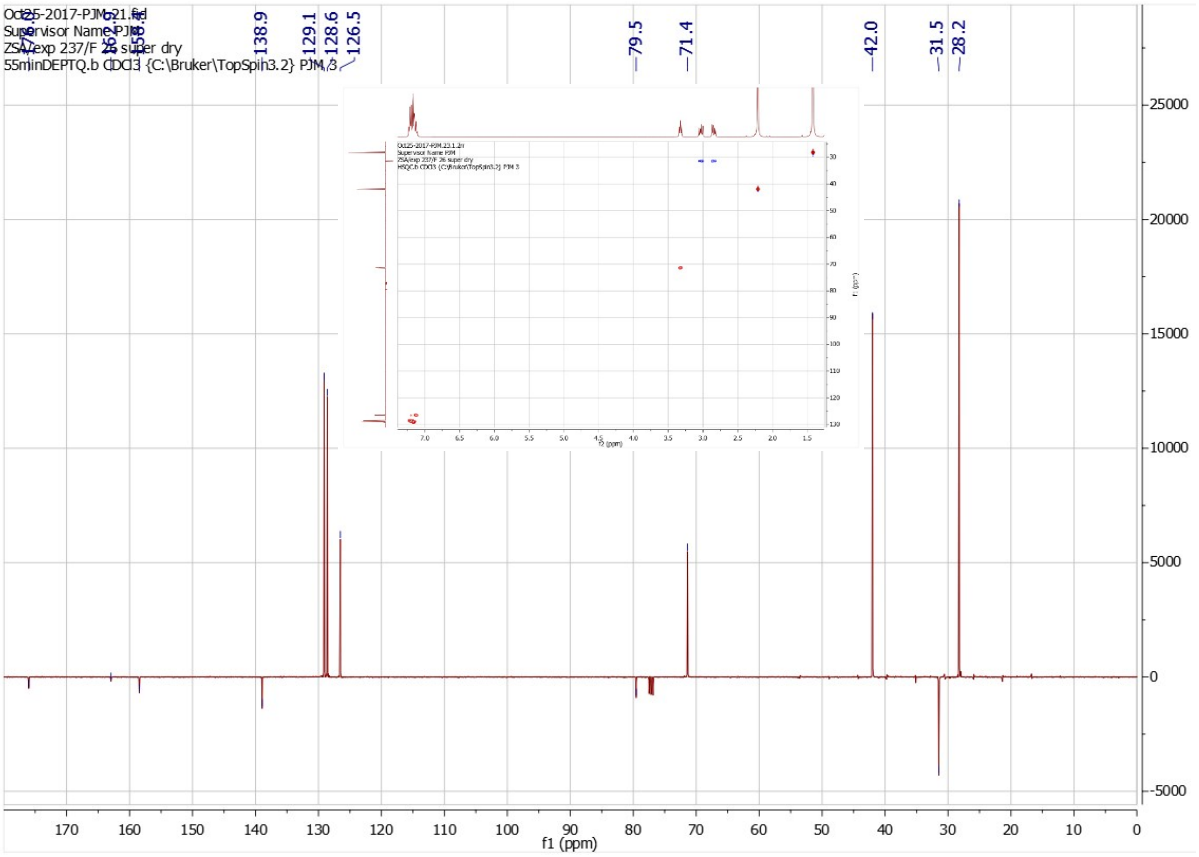
(*S*)-*N*-Boc-*N'*-Carbamimidoyl-2-(dimethylamino)propanamide 44a
^{13}C NMR, DEPTQ (insert).



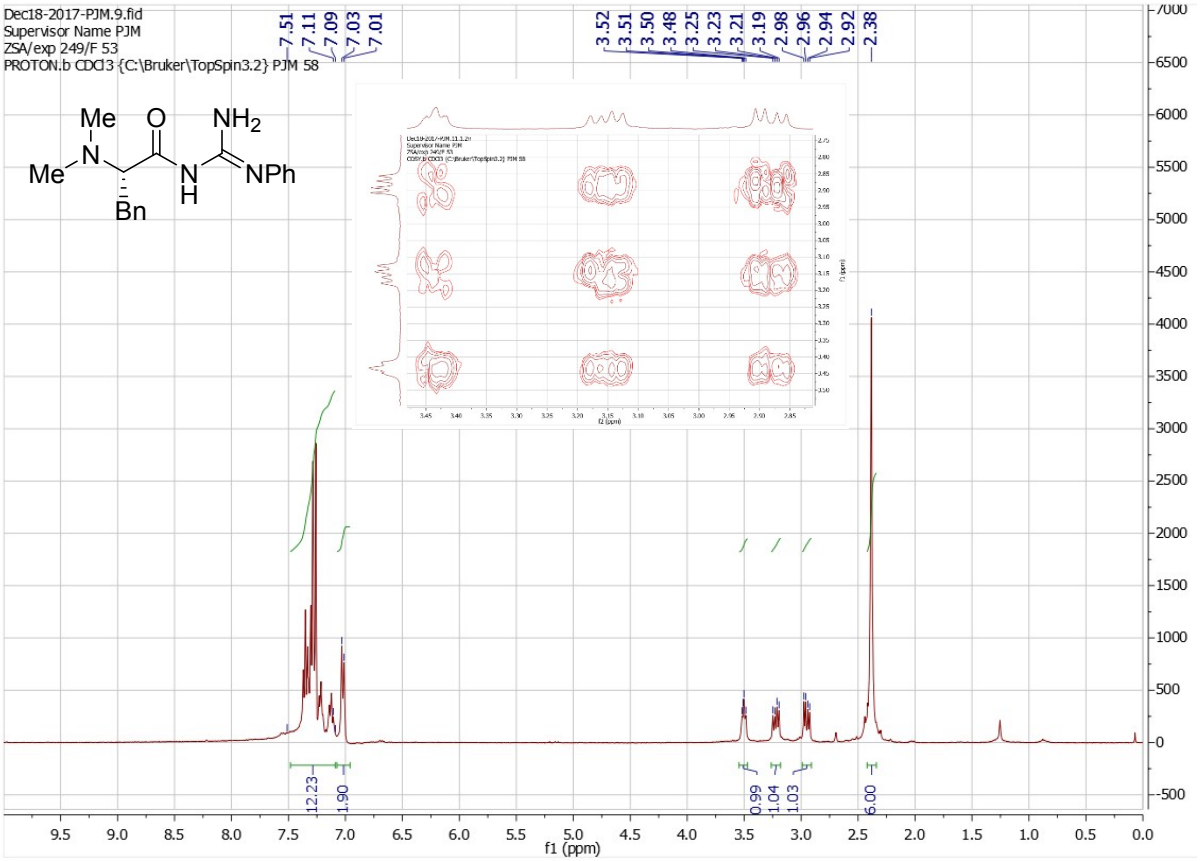
(*S*)-*N*-Boc-*N'*-Carbamimidoyl-2-(dimethylamino)-3-phenylpropanamide 44b: ^{1}H NMR, COSY (insert).



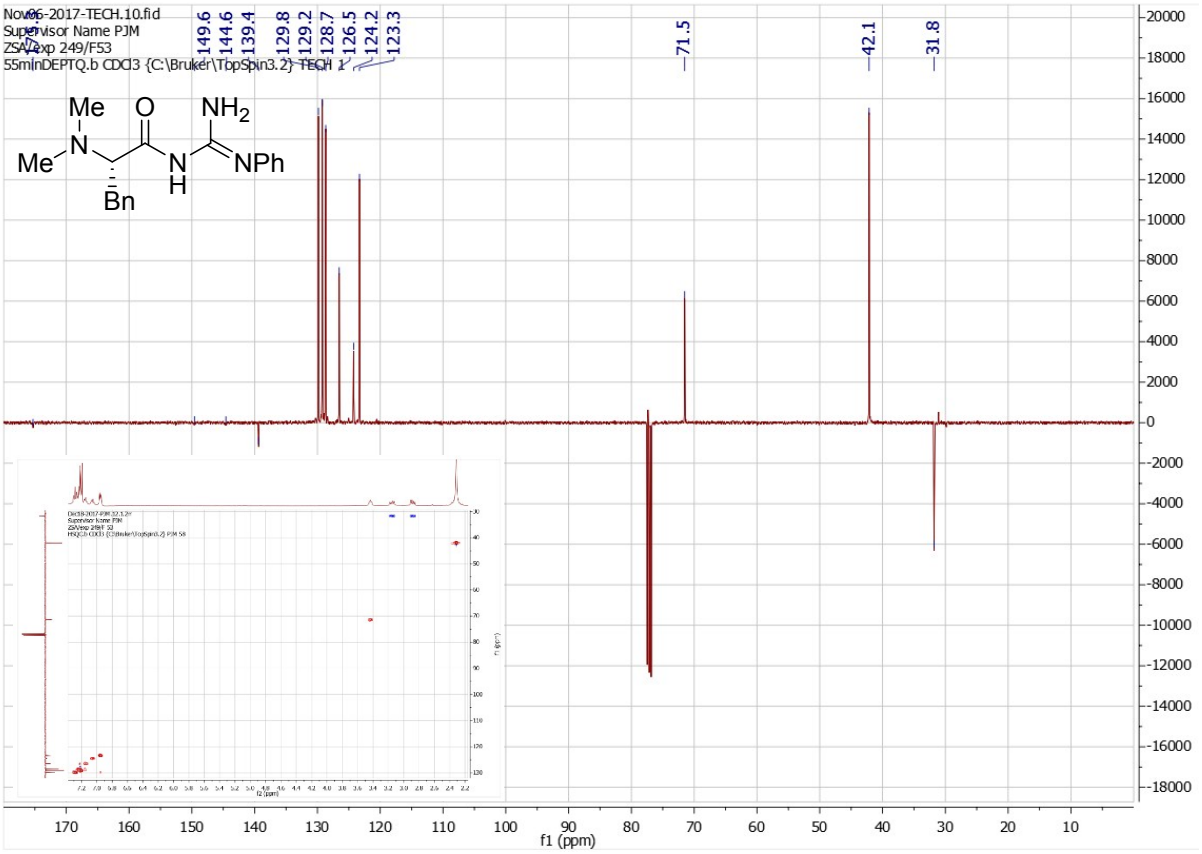
(*S*)-*N*-Boc-*N'*-Carbamimidoyl-2-(dimethylamino)-3-phenylpropanamide 44b: ^{13}C NMR, DEPTQ (insert).



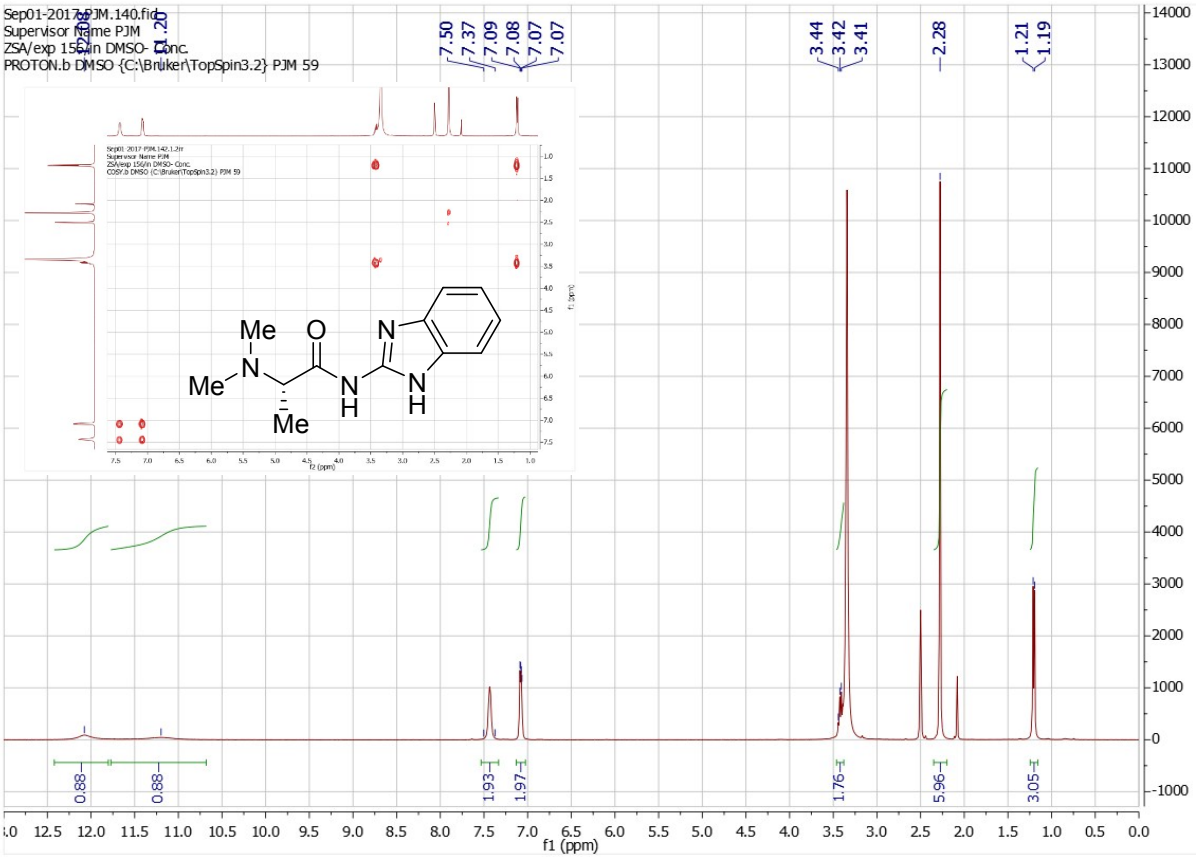
(*S*)-2-(dimethylamino)-3-phenyl-*N*-(*N*′-phenylcarbamimidoyl)propanamide 45b: ^{1}H NMR, COSY (insert).



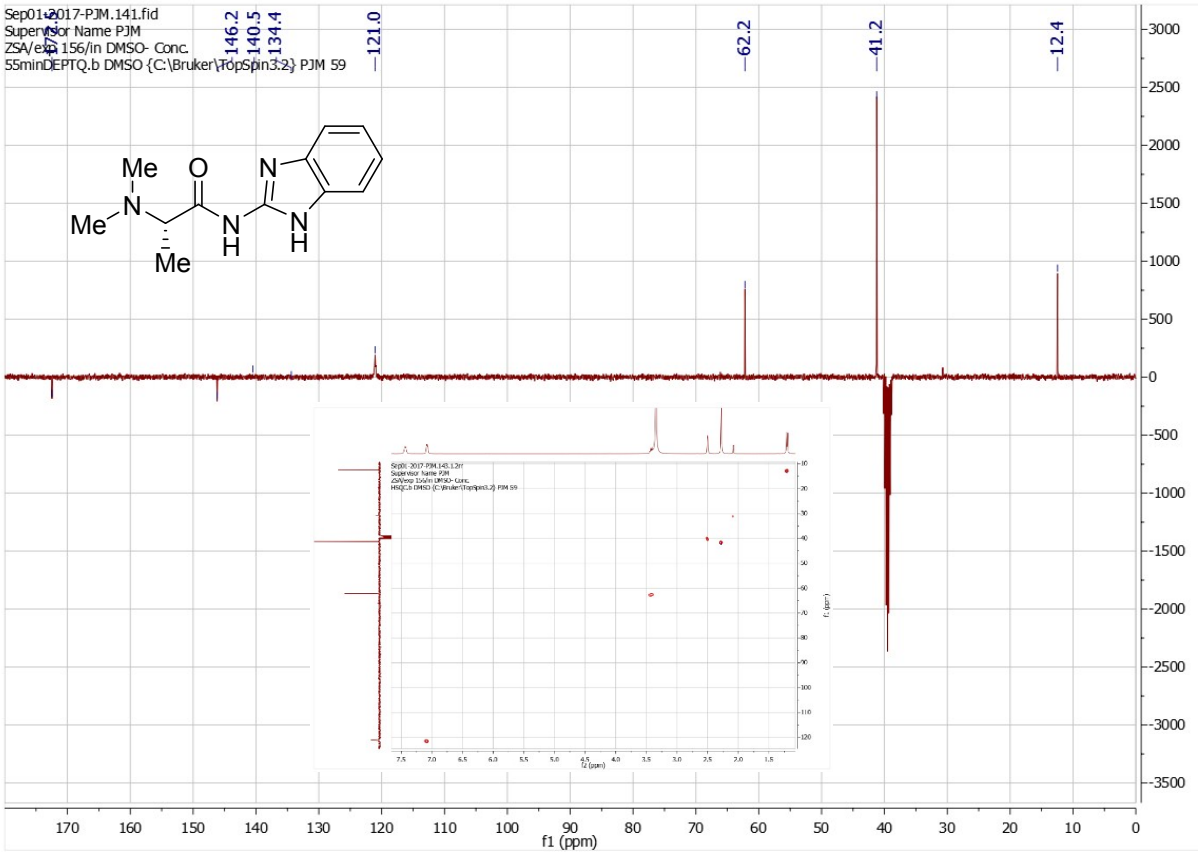
(*S*)-2-(dimethylamino)-3-phenyl-*N*-(*N*′-phenylcarbamimidoyl)propanamide 45b ^{13}C NMR, DEPTQ (insert).



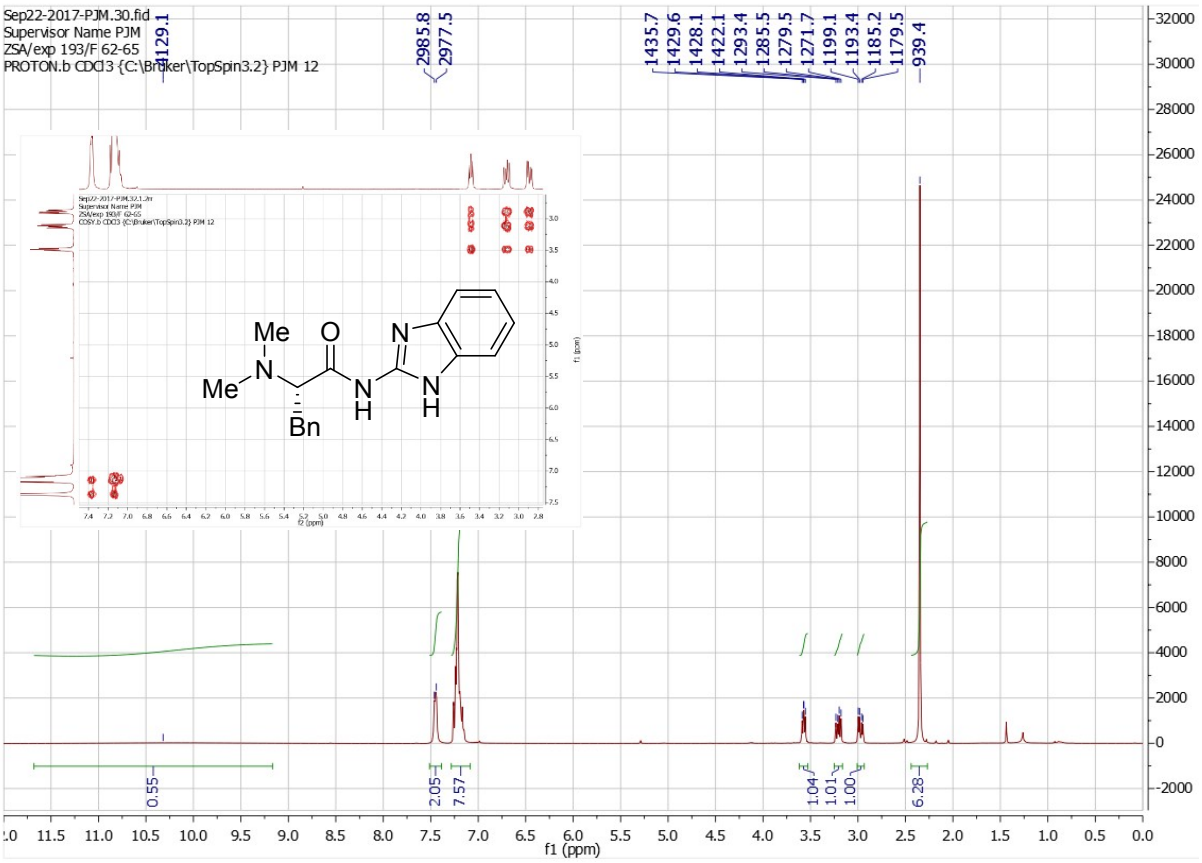
(*S*)-*N*-(1*H*-Benzo[*d*]imidazol-2-yl)-2-(dimethylamino)propanamide 46a:
^{1}H NMR, COSY (insert).



(*S*)-*N*-(1*H*-Benzo[*d*]imidazol-2-yl)-2-(dimethylamino)propanamide 46a:
^{13}C NMR, DEPTQ (insert).

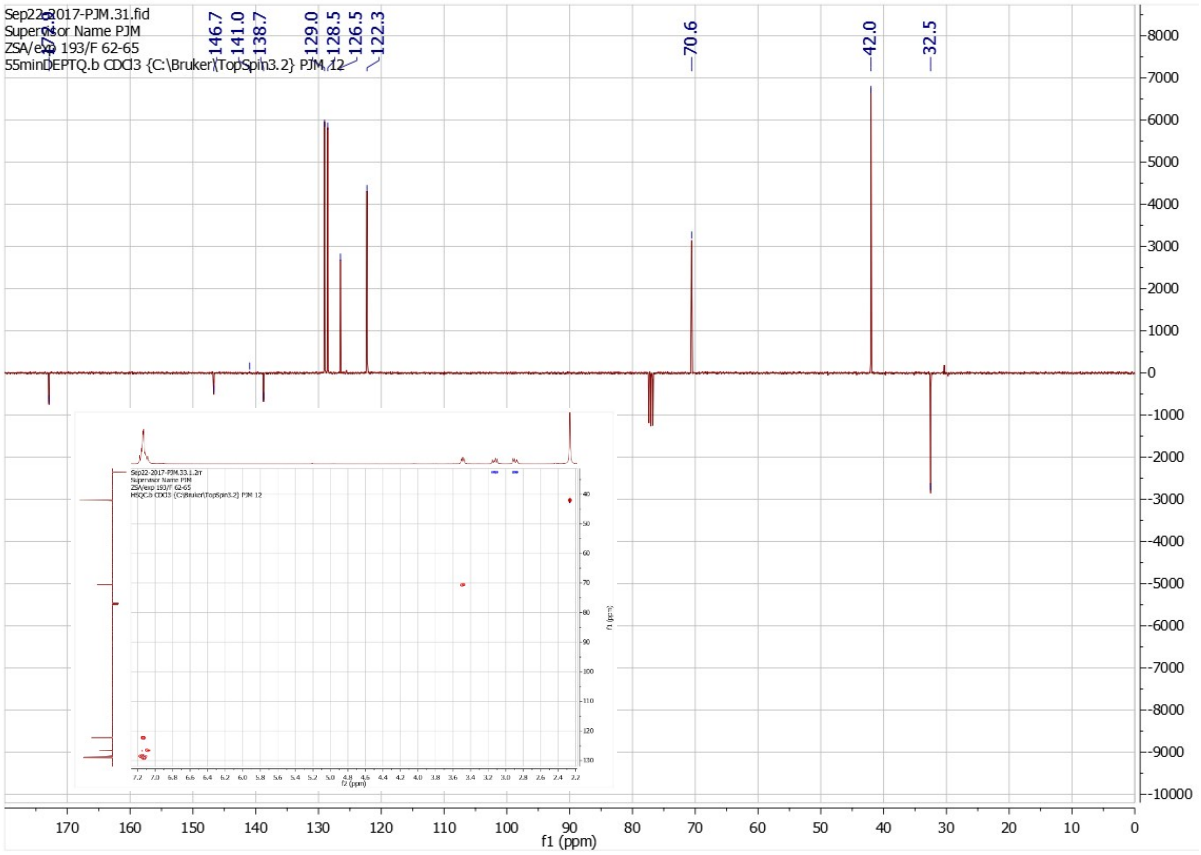


(*S*)-*N*-(1*H*-Benzo[*d*]imidazol-2-yl)-2-(dimethylamino)-3-phenylpropanamide 46b: ^{1}H NMR, COSY (insert).

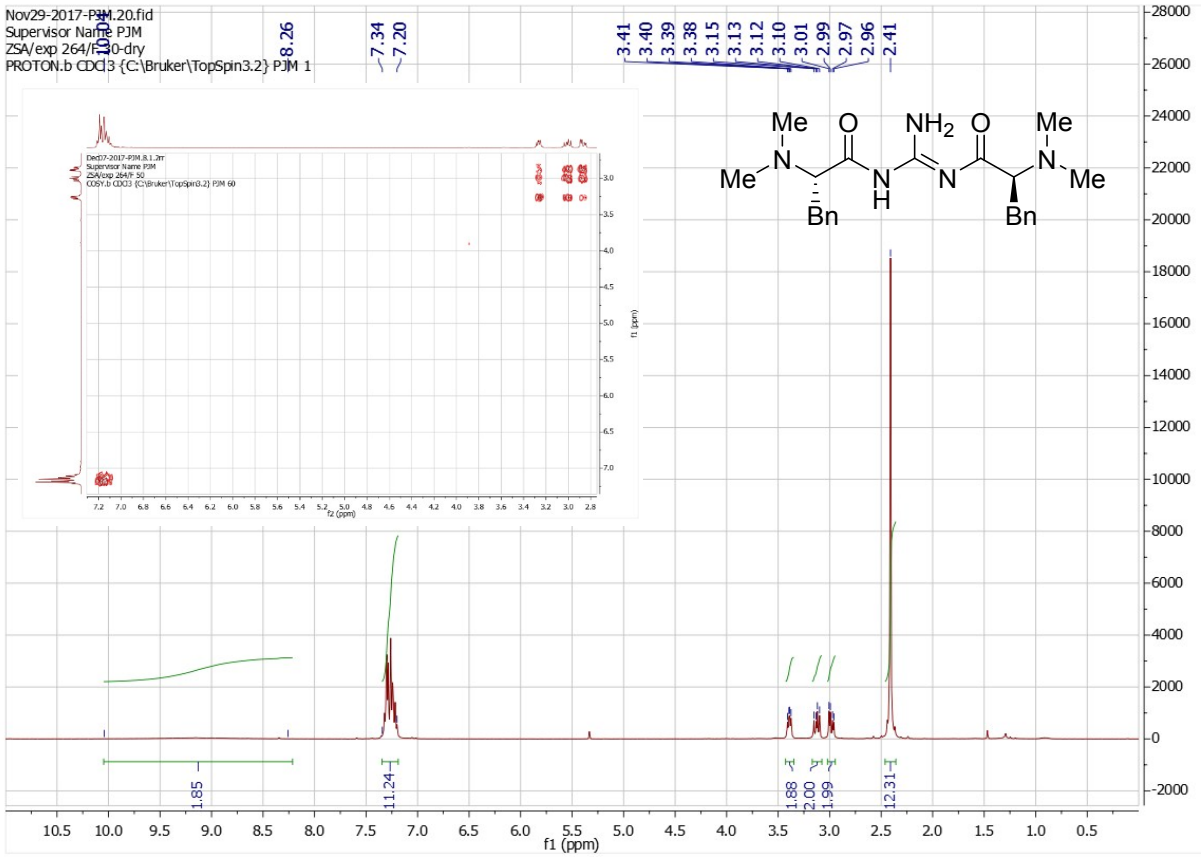


(*S*)-*N*-(1*H*-Benzo[*d*]imidazol-2-yl)-2-(dimethylamino)-3-phenylpropanamide 46b:

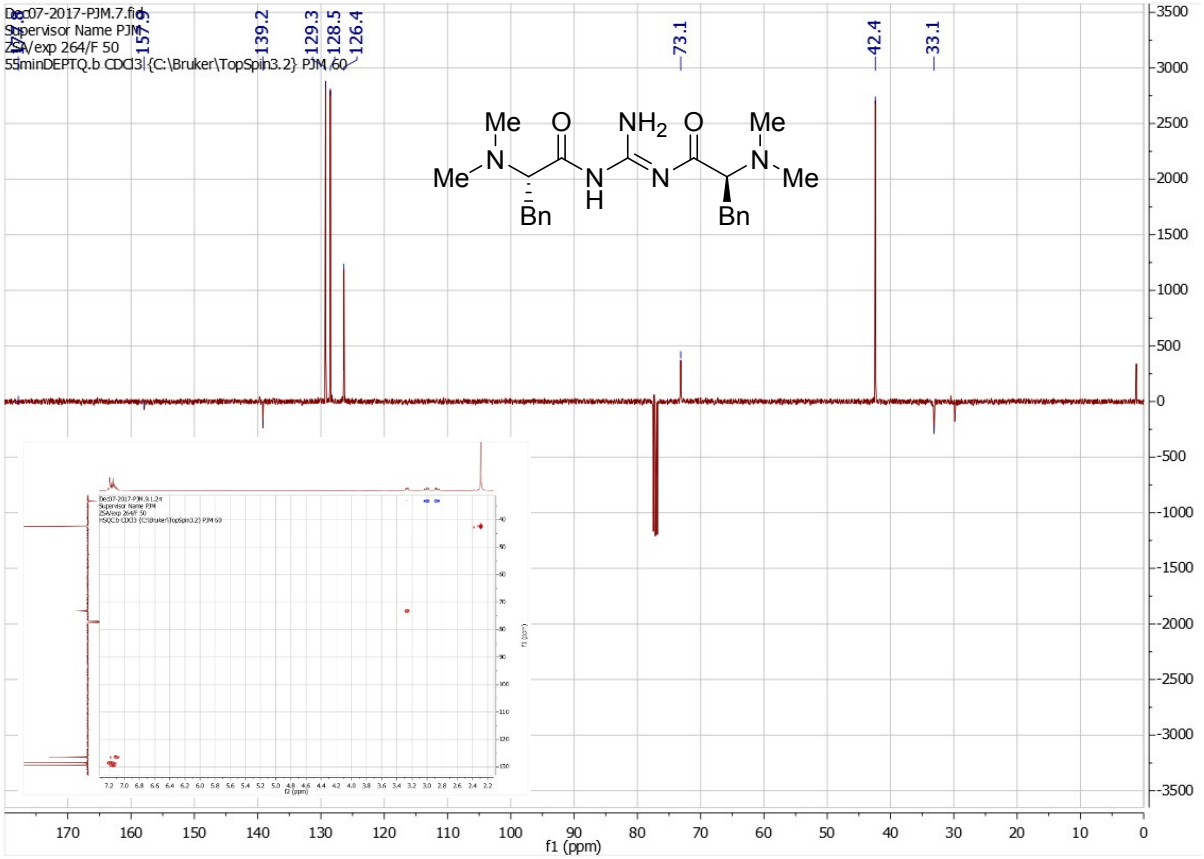
^{13}C NMR, DEPTQ (insert).



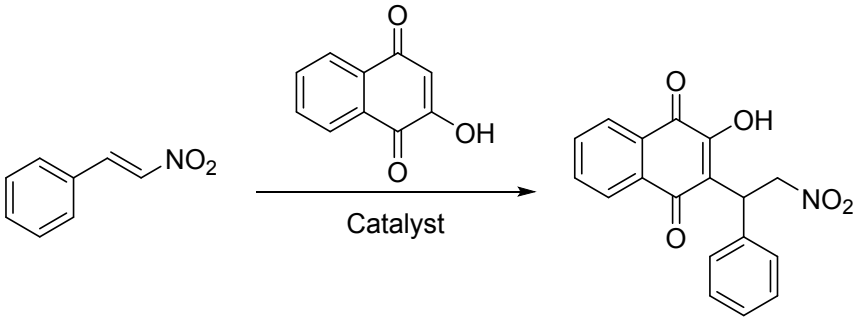
(*S*)-*N*-(Amino((*S*)-2-(dimethylamino)-3-phenylpropanamido)methylene)-2-(dimethylamino)-3-phenylpropanamide 47b: ^{1}H NMR, COSY (insert).



(*S*)-*N*-(Amino((*S*)-2-(dimethylamino)-3-phenylpropanamido)methylene)-2-(dimethylamino)-3-phenylpropanamide 47b: ^{13}C NMR, DEPTQ (insert).



HPLC of reaction β-nitrostyrene 52 and 2-hydroxy-1,4-napthoquinone



2-Hydroxy-1,4-napthoquinone **1** (100 mg, 0.574 mmol) and the required catalyst (0.04-0.1 equiv.) were dissolved in the required solvent and cooled to the required temperature (-20 to 0 ^{o}C, see text and table **A1**). β-Nitrostyrene **2** (128.5 mg, 0.861 mmol, 1.5 equiv) was then added and the mixture stirred for the required time and temperature. Reaction progress was determined by sampling and determination by H NMR. On completion the solvent was evaporated to give a deep red residue which was purified by column chromatography eluting firstly with 2-4% EA in petrol to remove excess **2** then followed with DCM to give the product 6 as a yellow solid. Illustrative example from catalyst **25a**; 56% ee, $[\alpha]_D^{25}$ -16.0 (acetone, c = 1.46); Lit. $[\alpha]_D^{17}$ -44.8 (acetone, c = 1.0);[12] Lit. $[\alpha]_D^{25}$ -34.0 (acetone, c = 1.46).[13] Enantiomeric excess were determined either on a Chiralpak IA (250 x 4.6 mm, mobile phase 90 % hexane, 8 % ethanol, 2 % dichloromethane, 0.1% TFA, 1 mL/min, detecting at 254 nm; R enantiomer 19.5 min, S enantiomer 27.2 min), or a Chiralcel AS-H IA (250 x 4.6 mm, mobile phase 96 % hexane, 4 % isopropanol, 0.1% TFA, 1.5 mL/min at 40 ^{o}C, detecting at 254 nm; R enantiomer 23.5 min, S enantiomer 26.2 min) or Phenomenex Lux Amylose-1 (250 x 4.6 mm,

mobile phase 70 % hexane, 30 % isopropanol, 0.5 mL/min at 40 °C, detecting at 254 nm; R enantiomer 13.2 min, S enantiomer 14.3 min). (See SI-HPLC)

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Appendix II: Crystallographic information.

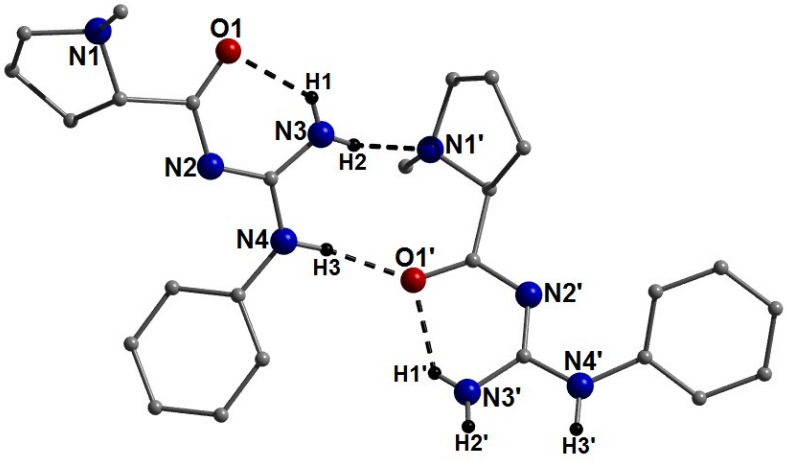


Fig. S1 Two crystallographically related units of **27a** connected through intermolecular H-bonding interactions (dashed lines) at distances of 1.87 Å (N4(H3)···O1′) and 2.07 Å (N3(H2)···N1′). The intramolecular H-bond lies at a distance of 2.02 Å (N3(H1)···O1).

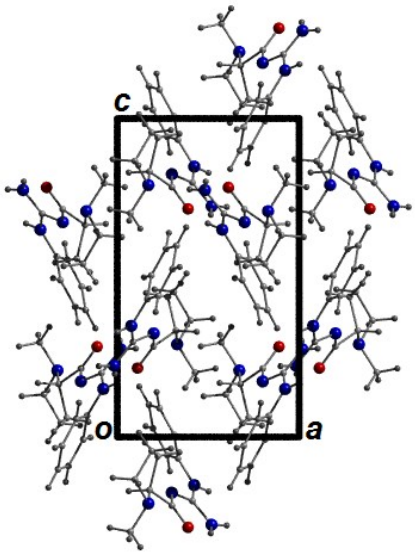


Fig. S2 Unit cell packing arrangement in **27a** as viewed along the *b* unit cell direction.

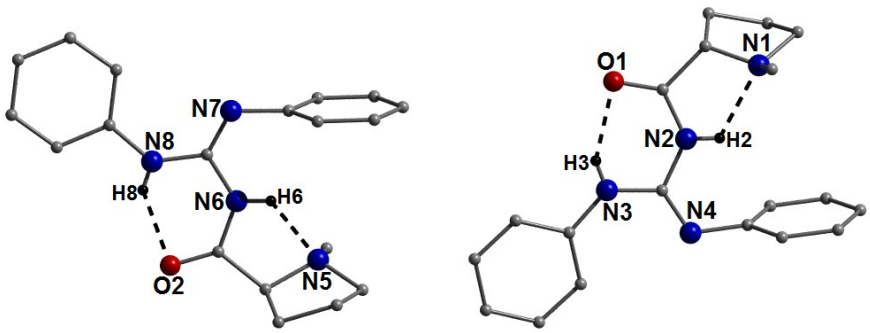


Fig. S3 Crystal structure highlighting the two organic moieties comprising the asymmetric unit in **26a**. The dashed lines represent the intramolecular H-bonding interactions: N8(H8)···O2 = 2.029 Å; N6(H6)···N5 = 2.071 Å; N3(H3)···O1 = 2.005 Å and N2(H2)···N1 = 2.149 Å.

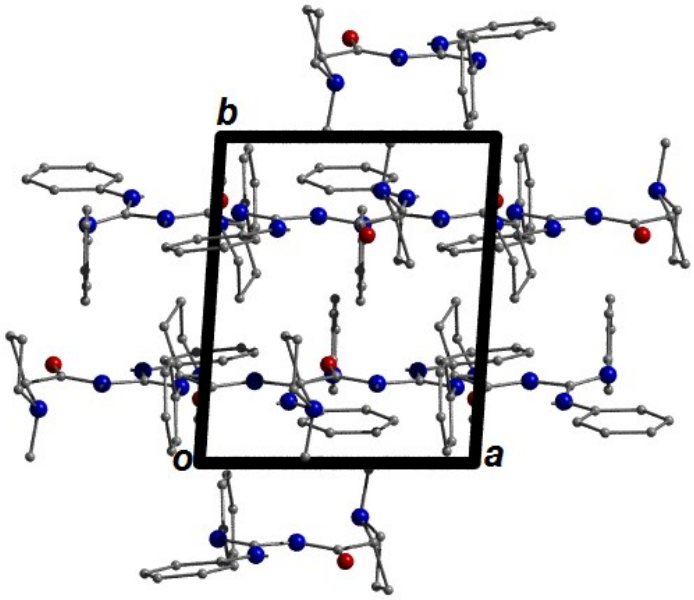


Fig. S4 Packing arrangement in the unit cell of **26a** as viewed along the *c* unit cell direction.

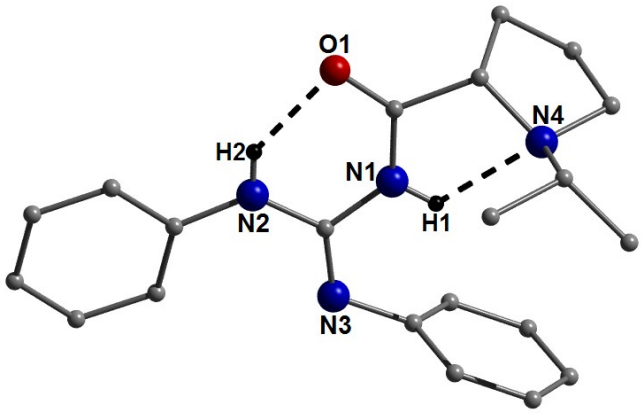


Fig. S5 Crystal structure of **26c** highlighting the intramolecular H-bonding as dashed lines (N2(H2)···O1 = 2.05 Å and N1(H1)···N4 = 2.21 Å).

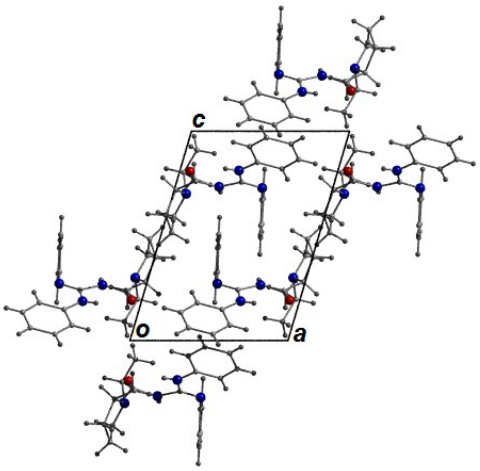


Fig. S6 Unit cell packing arrangement in **26c** as viewed along the *b* unit cell direction.

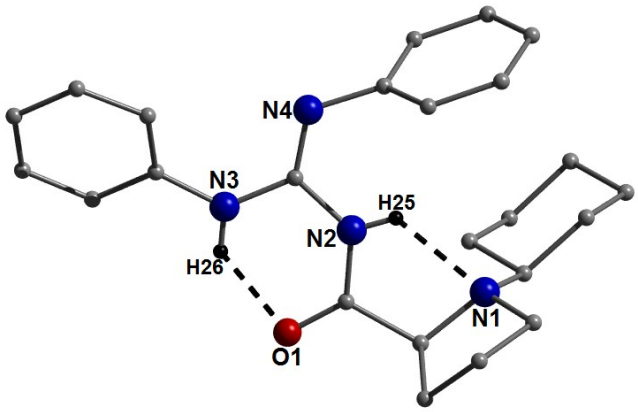


Fig. S7 Crystal structure of **26d** highlighting the intramolecular H-bonding as dashed lines with distances of 1.97 Å (N3(H26)···O1) and 2.14 Å (N2(H25)···N1).

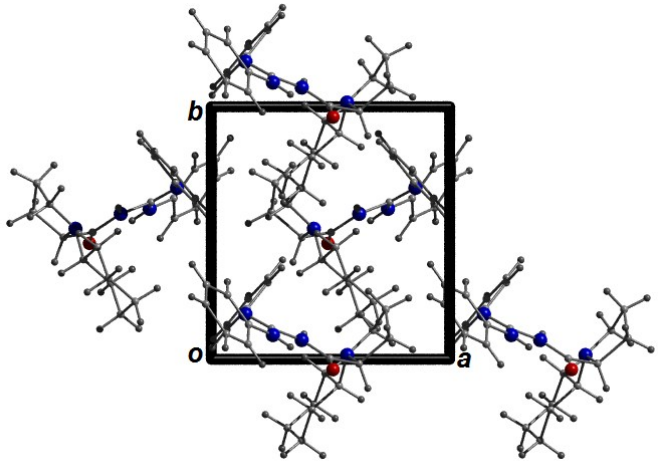


Fig. S8 Unit cell packing arrangement in **26d** as viewed along the *c* unit cell direction.

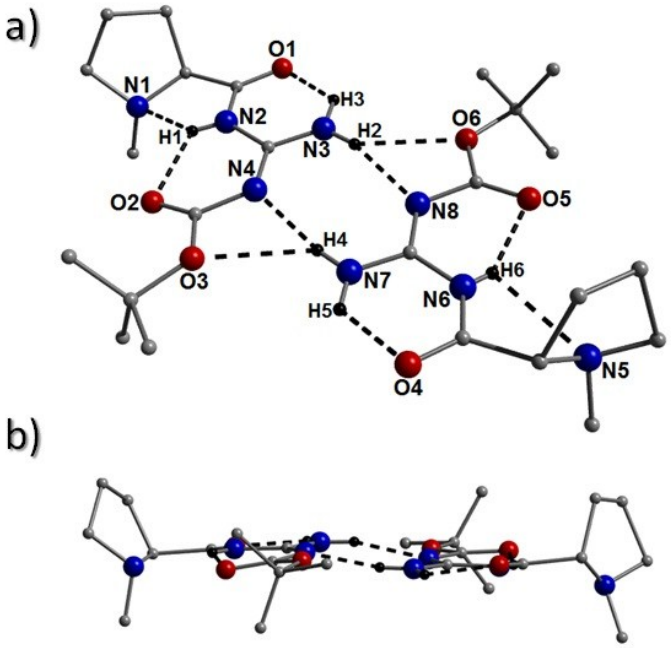


Fig. S9 A H-bonded dimer comprising the asymmetric unit in **29**. The dashed lines represent the intra-(N2(H1)···O2 = 2.09 Å; N2(H1)···N1 = 2.10 Å; N3(H3)···O1 = 1.94 Å; N6(H6)···O5 = 2.05 Å; N6(H6)···N5 = 2.49 Å; N7(H5)···O4 = 2.06 Å) and intermolecular hydrogen bonding interaction (N4···(H4)N7 = 2.04 Å; N3(H2)···N8 = 2.06 Å; O3···(H4)N7 = 2.58 Å; N3(H2)···O6 = 2.54 Å).

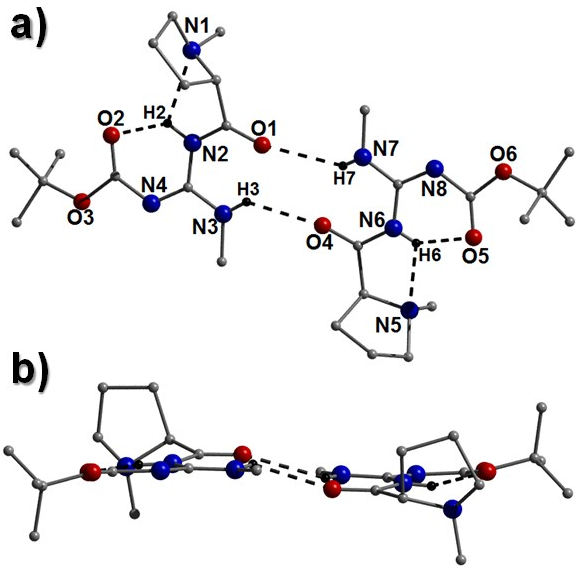


Fig. S10 A H-bonded dimeric unit observed in the asymmetric unit of **30**. The dashed lines represent the intra-(N2(H2)···O2 = 1.92 Å; N6(H6)···O5 = 2.02 Å; N2(H2)···N1 = 2.37 Å; N6(H6)···N5 = 2.33 Å) and intermolecular hydrogen bonding interactions (N3(H3)···N4′ = 2.37 Å; O1···(H7)N7 = 2.48 Å).

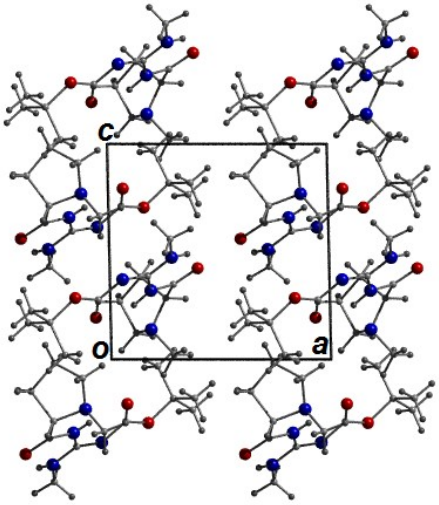


Fig. S11 Unit cell packing arrangement in **30** as viewed along the *b* unit cell direction.

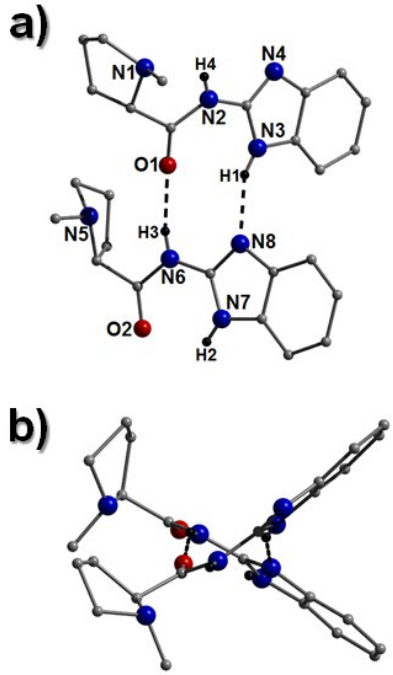


Fig. S12 Crystal structure showing the two moieties comprising the asymmetric unit in **34a** as viewed approximately perpendicular (a) and parallel (b) to their benzimidazole aromatic rings. The dashed lines represent the H-bonding interactions connecting the two units at distances 2.37 Å (N6(H3)···O1) and 2.01 Å (N8···(H1)N3). The intramolecular H-bonding distances (not shown) are: N2(H4)···N1 = 2.21 Å; N3(H1)···O1 = 2.35 Å; N6(H3)···N5 = 2.34 Å and N7(H2)···O2 = 2.26 Å.

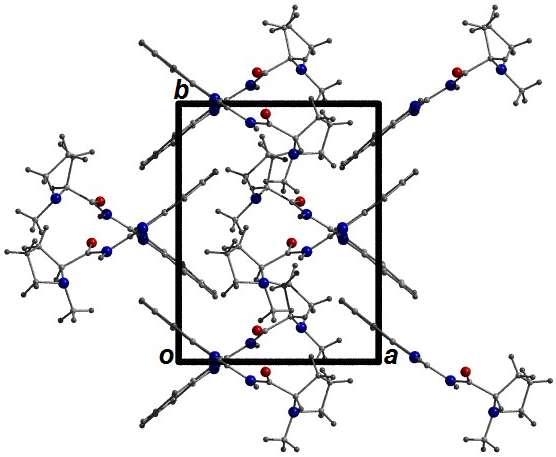


Fig. S13 Crystal packing arrangement in **34a** as viewed along the *c* direction of the unit cell.

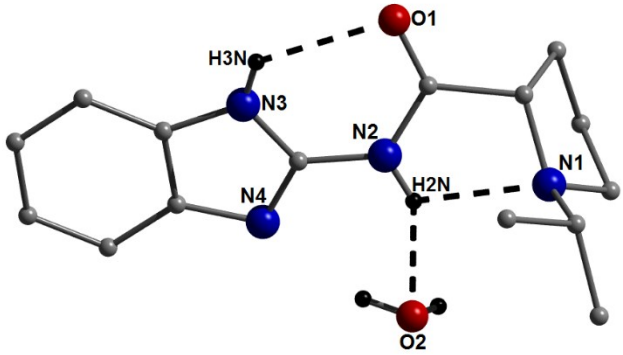


Fig. S14 Crystal structure of **34c** showing intramolecular H-bonding (dashed lines) at distances of 2.12 Å (N2(H2N)···N1) and 2.28 Å (N3(H3N)···O1) along with two intermolecular interaction with a water solvent of crystallisation (N2(H2N)···O2 = 2.15 Å and N4···H20(O2) = 2.09 Å).

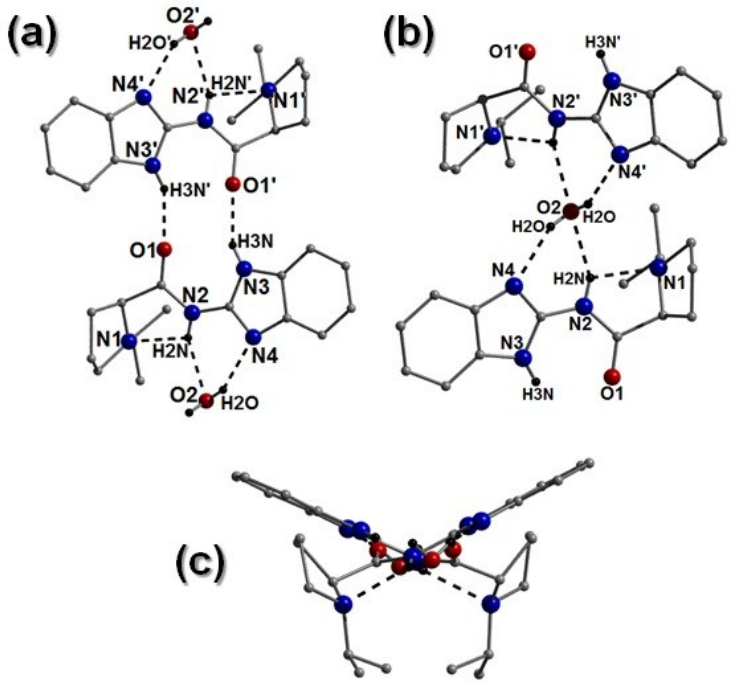


Fig. S15 Crystal structure of **34c** showing the intermolecular H-bonding (dashed lines) between each organic unit (a) and (b) via the waters of crystallisation (labelled O2) as they propagate along the *a* direction of the unit cell (c). Selected H-bonding distances: O1···(H3N′)N3′ = 2.03 Å; N4···(H20)O2 = 2.09 Å and N2(H2N)···O2 = 2.15 Å.

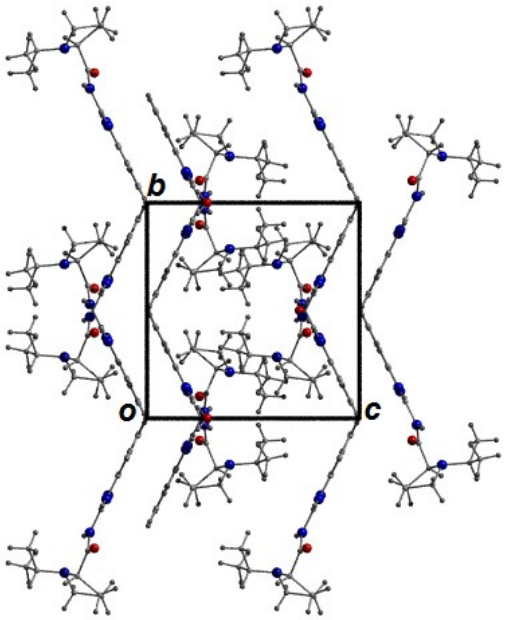


Fig. S16 Crystal packing motif observed in **34c** as viewed along the *a* unit cell direction.

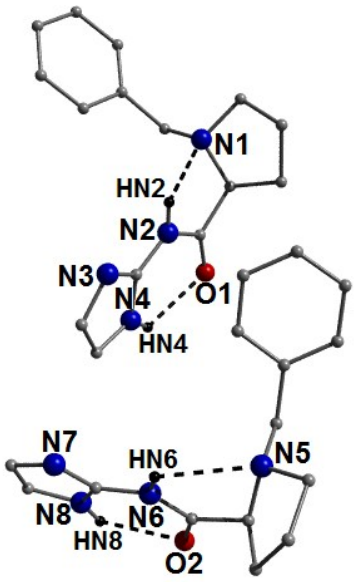


Fig. S17 Asymmetric unit in **38**. Selected intramolecular H-bond distances (dashed lines): N4(HN4)···O1 = 2.24 Å, N2(HN2)···N1 = 2.36 Å, N6(HN6)···N5 = 2.51 Å and N8(HN8)···O2 = 2.26 Å.

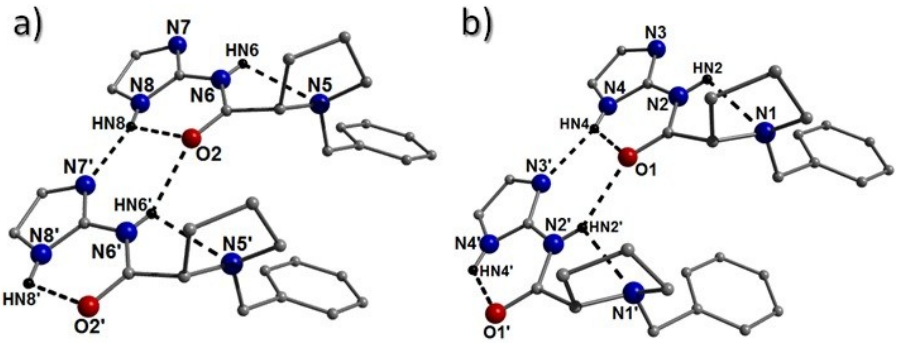


Fig. S18 Intermolecular H-bonding observed by both moieties (a and b, respectively) in the asymmetric unit of **38**. Dashed lines represent intermolecular H-bonding at distances (Å): 2.16 (O1···HN2′(N2′)), 2.16 (N4(HN4)···N3′), 2.22 (O2···HN6′(N6′)) and 2.06 (N8(HN8)···N7′). Intramolecular H-bonds also shown (see Fig. S17 for bond lengths).

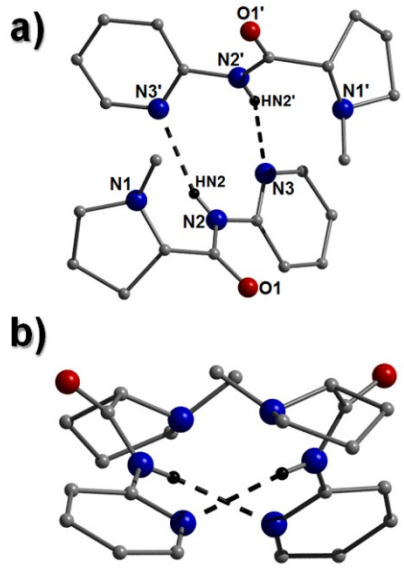


Fig. S19 Crystal structure representation of a pair of crystallographically related units in **39a**. The intermolecular H-bonded interactions are represented as dashed lines (N2(HN2)···N3′ = 2.35 Å).

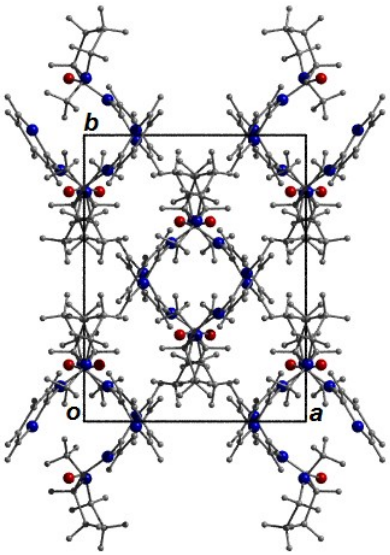


Fig. S20 The packing arrangement observed in **39a** as viewed along the *c* unit cell direction.

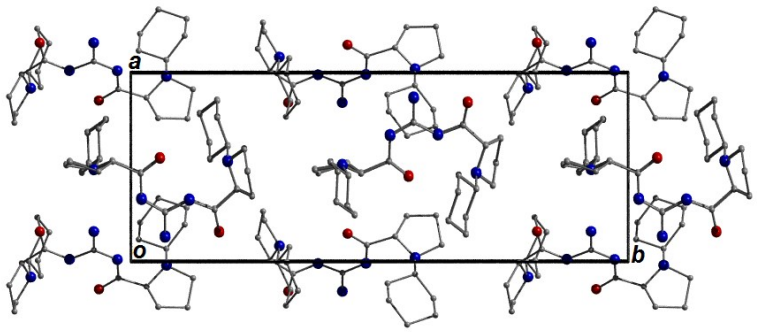


Fig. 21 Packing arrangement observed in the crystal structure of **40d** as viewed along the *c* direction of the unit cell.

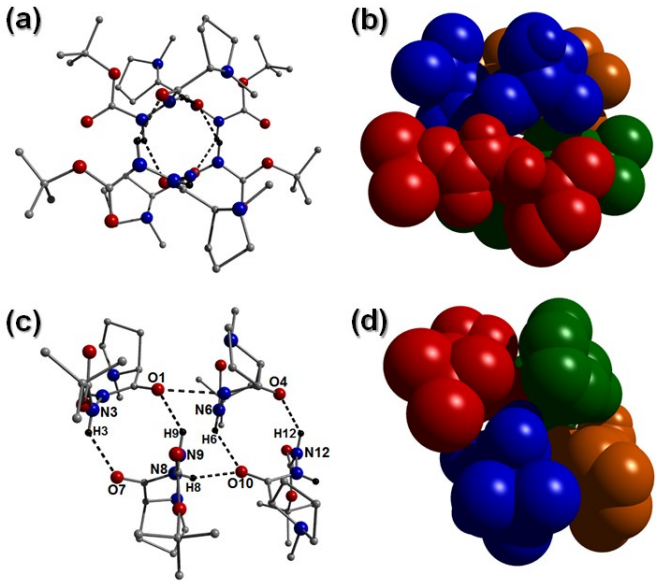


Fig. S22 (a) Crystal structure highlighting the four organic units that make up the asymmetric unit in **41c** (*crystal 2*) as viewed along the *a* (figure a) and *c* (figure c) unit cell directions, respectively. Figures b and d represent their equivalent space-fill representations where each colour denotes a single molecule of **41c**. Selected intermolecular H-bonding interactions (dashed lines): N3(H3)···O7 = 2.16 Å, N6(H6)···O10 = 2.21 Å, N9(H9)···O1 = 2.13 Å and N12(H12)···O4 = 2.20 Å.

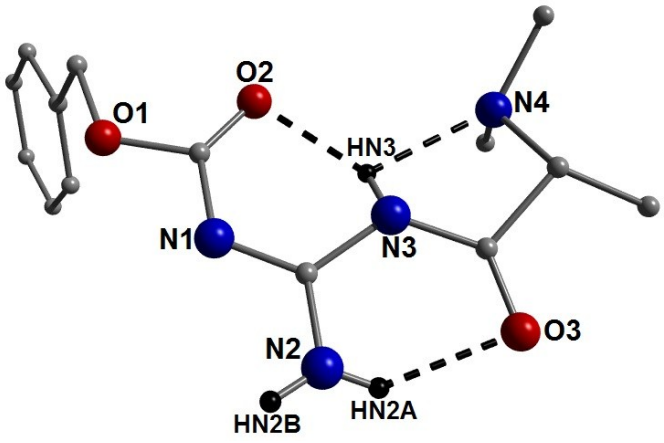


Fig. S23 The crystal structure obtained from **43a** highlighting (dashed line) the intramolecular H-bonding interactions (N2(HN2A)···O3 =2.07 Å; N3(HN3)···O2 = 1.96 Å and N3(HN3)···N4 = 2.30 Å. The majority of hydrogen atoms have been omitted for clarity.

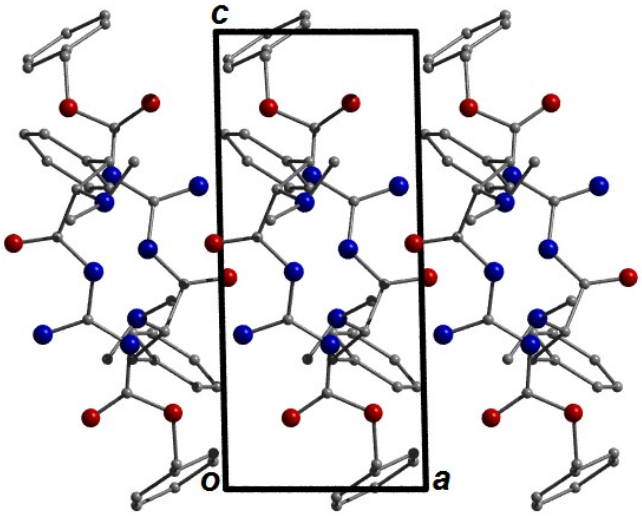


Fig. S24 The packing arrangement observed in **43b** as viewed along the *b* unit cell direction.

Powder X-ray diffraction

All PXRD samples were collected at room temperature on a Rigaku MiniFlex600 (CuK_{α} radiation, 40.0 kV, 15.0 mA), over a 2θ range of 5 to 40°.

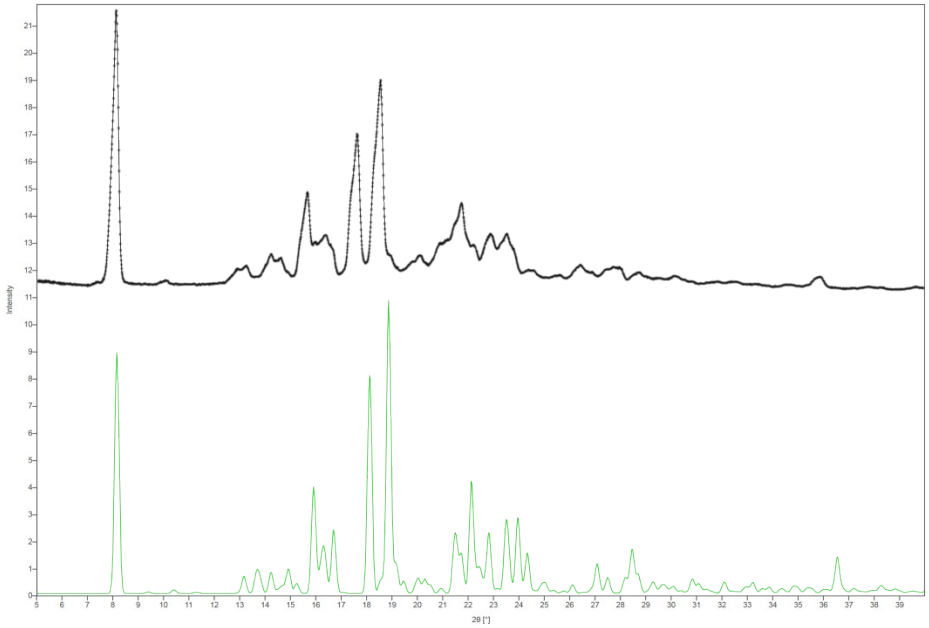
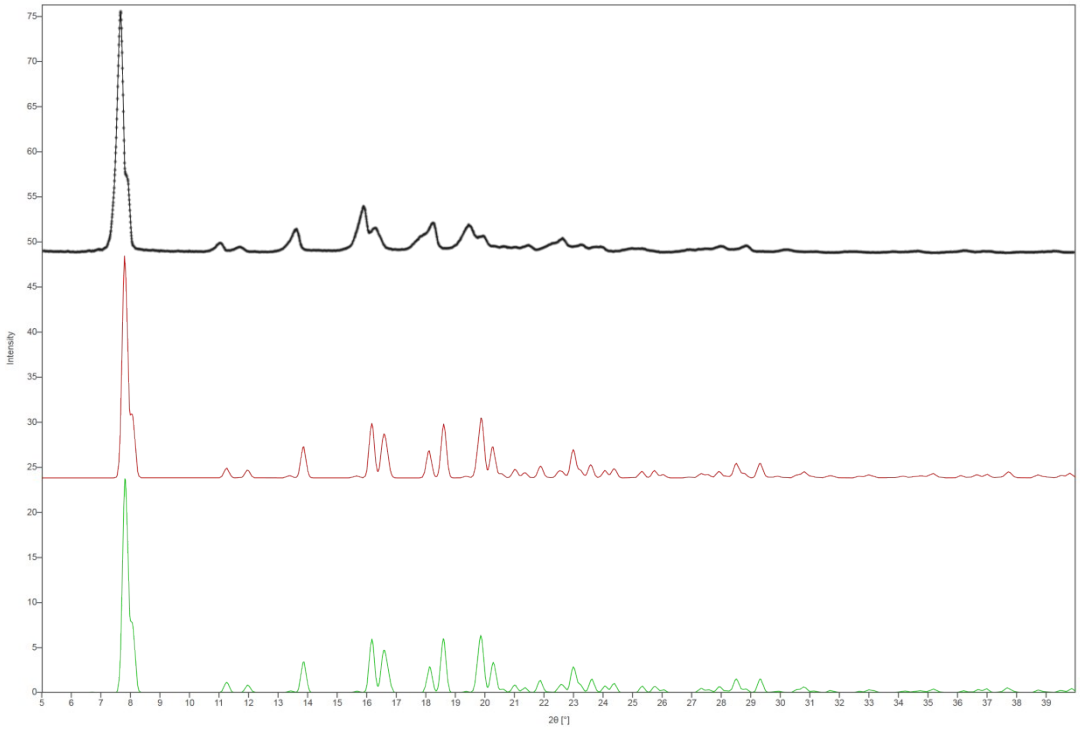


Fig. S25 Powder X-ray diffraction spectrum obtained from a polycrystalline sample of **26a** (black trace) and a simulated pXRD spectrum obtained using single crystal data of sample **26a** (green trace).



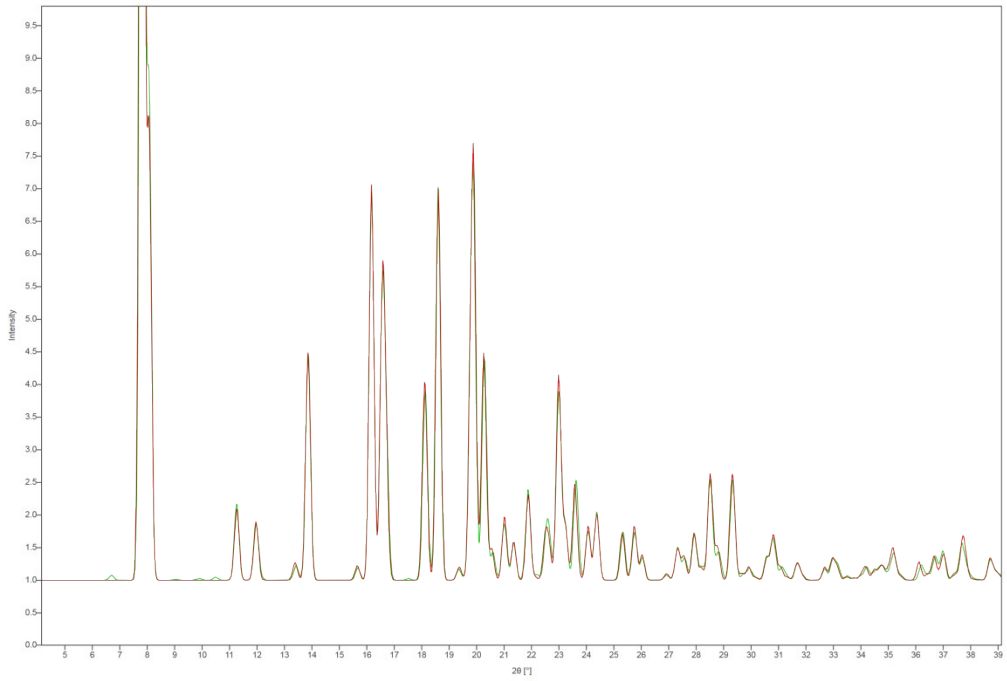


Fig. S26 41c (Top) The pXRD spectrum obtained from a polycrystalline sample of **41c** (black trace) along with the simulated spectra originating from the single crystal structures of ***41c-crystal 1*** (red trace) and **41c-*crystal 2*** (green trace). (Bottom) An overlay of the simulated spectra from the single crystal data of ***41c-crystal 1*** (red trace) and **41c-*crystal 2*** (green trace).

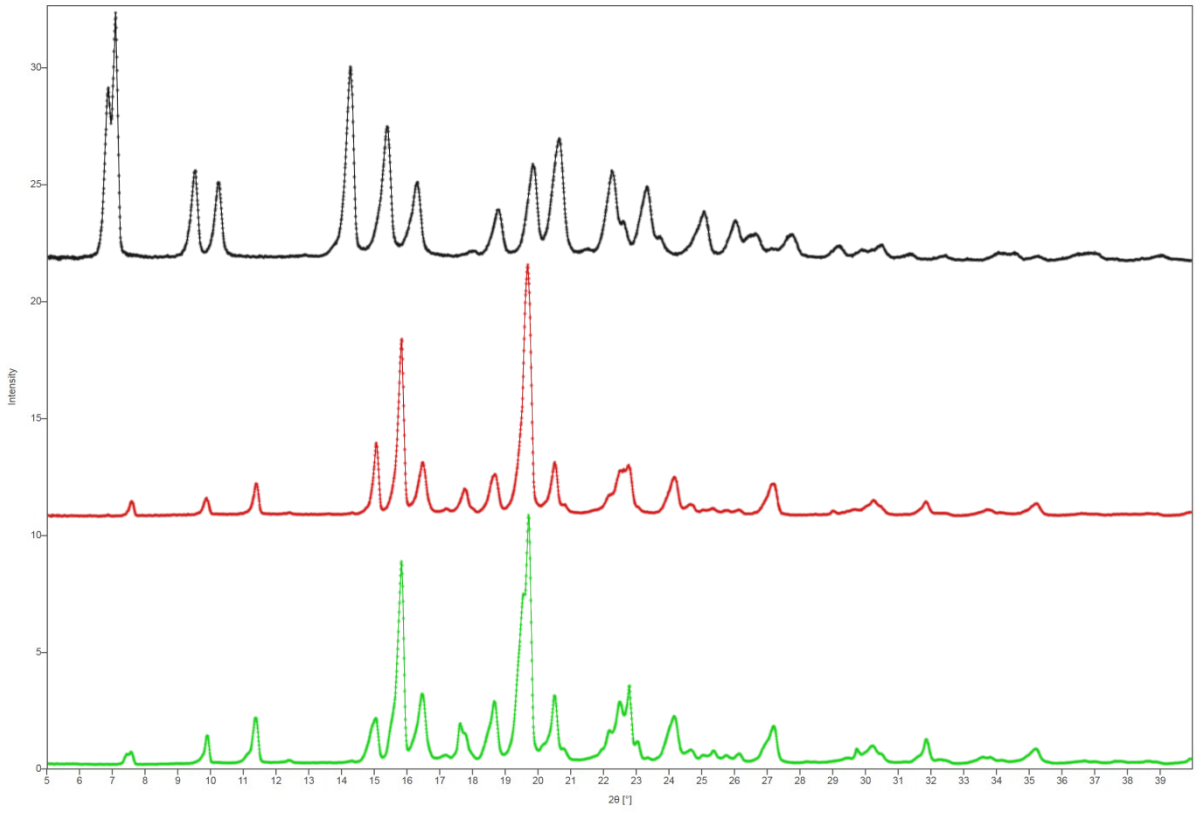


Fig. S27 (Top) The pXRD spectrum obtained from a polycrystalline racemic sample of **25a** (black trace). (Middle and bottom) pXRD spectra obtained from an 86%ee (93:7 S:R; red trace) and 100%ee (all S; green trace) samples of **25a** obtained from HPLC.

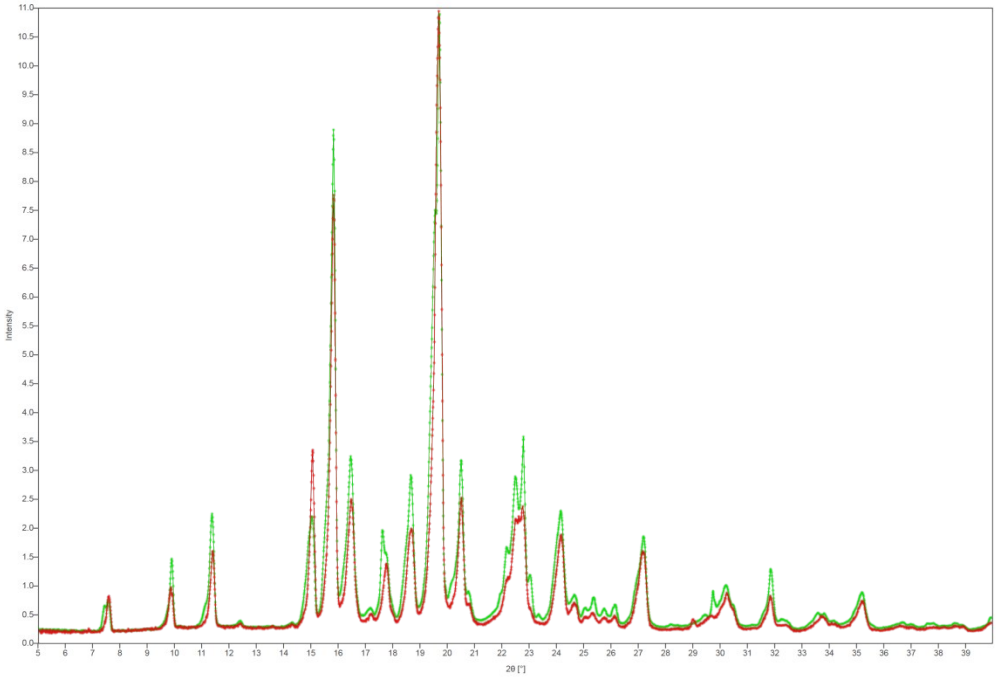


Fig. S28 25a Overlay of the pXRD spectra obtained from an 86%ee (93:7 S:R; red trace) and 100%ee (all S; green trace) sample of **25a** obtained from HPLC.

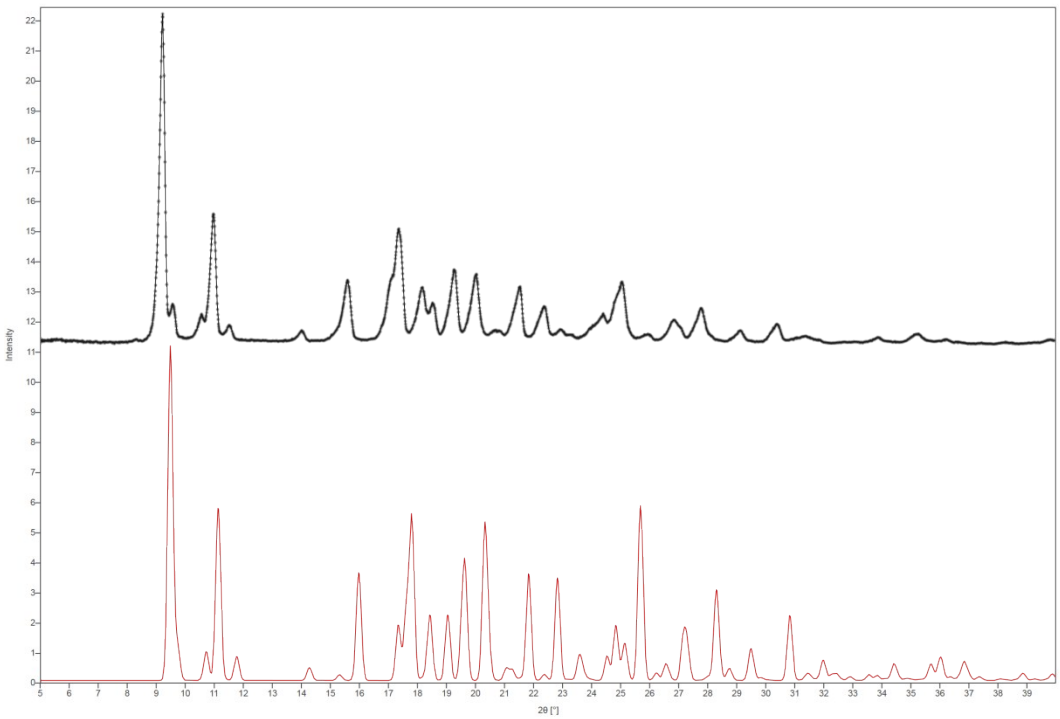


Fig. S29 The pXRD spectrum obtained from a polycrystalline sample of **31** (black trace) along with a simulated spectrum obtained from its corresponding single crystal data (red trace).

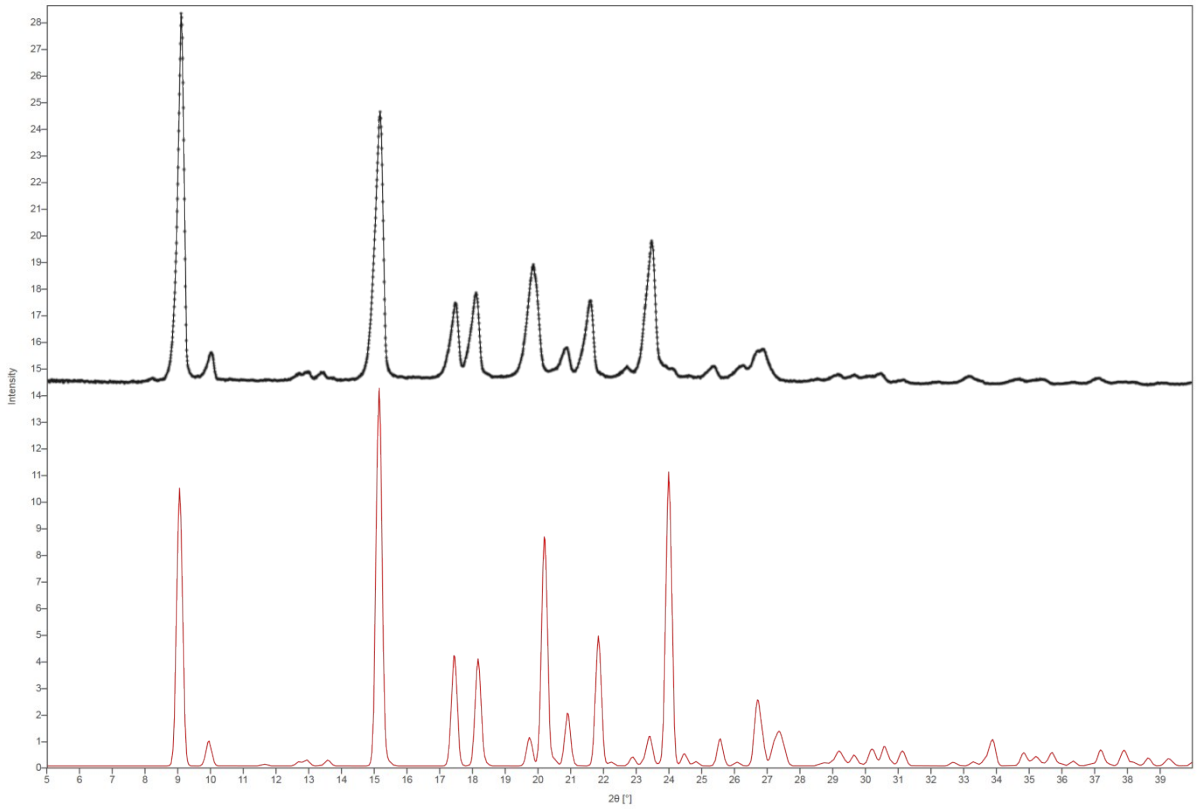


Fig. S30 The pXRD spectrum of **41b** (black trace) along with its corresponding simulation spectrum obtained from its single crystal data (red trace).

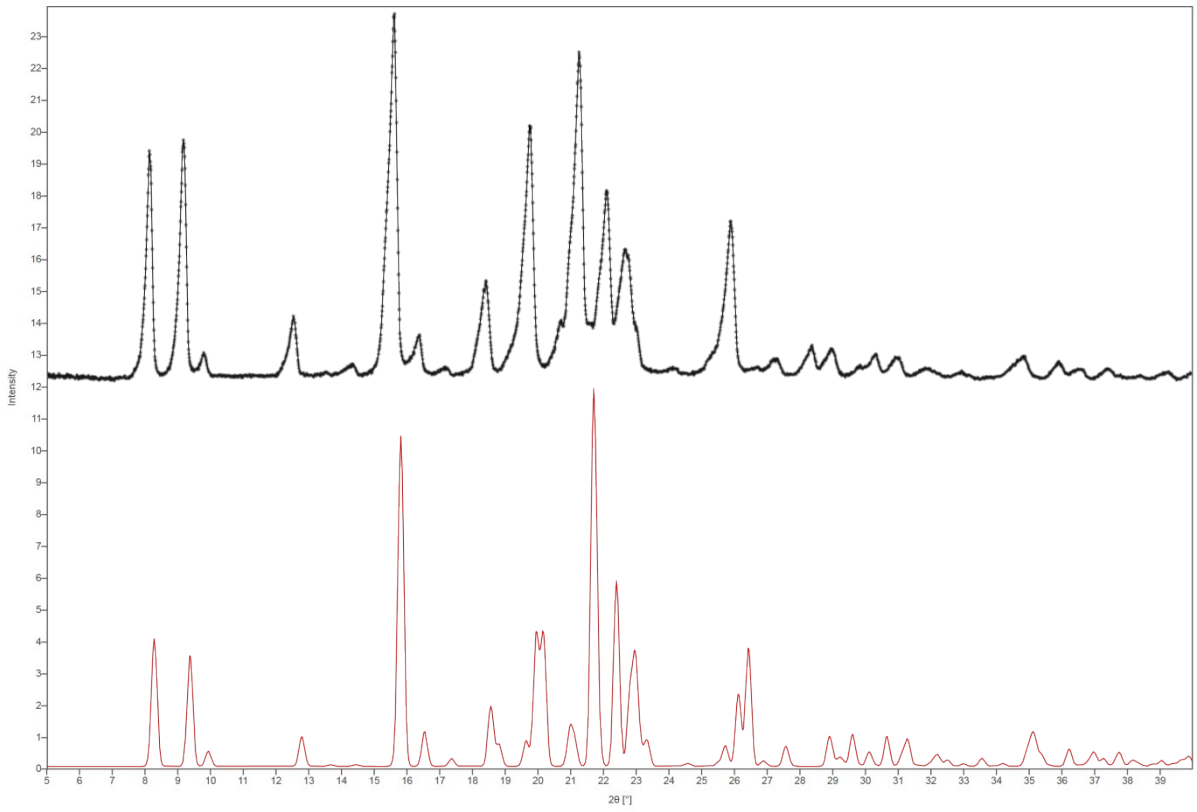


Fig.S31 Powder XRD spectrum of **43a** (top) along with its corresponding simulation using single crystal data (bottom).

Table S1 Selected crystal data obtained from **25a**, **26a**, **26c** and **26d**.

	25a	**26a**	**26c**	**26d**
Formula[a]	$C_{15}H_{20}N_4O_3$	$C_{19}H_{22}N_4O_1$	$C_{21}H_{26}N_4O_1$	$C_{24}H_{30}N_4O_1$
M_W	304.35	322.41	350.46	390.52
Crystal System	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	$P2_1$	P-1	$P2_1$	$P2_1$
a/Å	5.5616(3)	8.27490(10)	8.600(3)	9.3748(2)
b/Å	17.9003(13)	9.89550(10)	9.896(4)	9.6012(2)
c/Å	15.5410(9)	21.8743(3)	11.880(3)	12.5616(3)
α/°	90	82.1070(10)	90	90
β/°	94.111(5)	86.6940(10)	106.38(2)	104.848(2)
γ/°	90	85.7750(10)	90	90
V/Å^3	1543.19	1767.32	970.018	1092.91
Z	4	4	2	2
T/K	100(2)	30(2)	100(2)	100(2)
λ[b]/Å	0.71073	0.6889	0.6889	0.6889
D_c/g cm^{-3}	1.310	1.212	1.200	1.187
μ(Mo-Ka)/ mm^{-1}	0.094	0.073	0.072	0.074
Meas./indep. (R_{int}) refl.	30287 / 8146 (0.855)	30447 / 15842 (0.0939)	17850 / 4416 (0.0907)	11102 / 4942 (0.0627)
Restraints, Parameters	1, 423	0, 551	1, 245	1, 1.014
wR2 (all data)[c]	0.1447	0.2295	0.1311	0.1321
R1[d,e]	0.0684	0.0817	0.0491	0.0519
Goodness of fit on F^2	1.004	1.162	1.094	1.014

[a] Includes guest molecules. [b] Mo-Kα radiation, graphite monochromator. [c] wR2= [Σw(IF$_o^2$I- IF$_c^2$I)^2/ ΣwIF$_o^2$I^2]$^{1/2}$. [d]For observed data. [e] R1= ΣIIF$_o$I- IF$_c$II/ ΣIF$_o$I

Table S2 Selected crystal data obtained from **27a** and **29-31**.

	27a	**29**	**30**	**31**
Formula[a]	$C_{13}H_{18}N_4O_1$	$C_{12}H_{22}N_4O_3$	$C_{13}H_{24}N_4O_3$	$C_{16}H_{22}N_4O_3$
M_W	246.31	270.33	284.36	318.37
Crystal System	Orthorhombic	Monoclinic	Triclinic	Triclinic
Space group	$P2_12_12_1$	$P2_1$	P1	P-1
a/Å	7.98857(9)	9.62820(10)	9.1851(3)	8.9903(5)
b/Å	11.71525(11)	13.8844(2)	9.3856(2)	10.1684(6)
c/Å	13.99640(13)	11.73000(10)	9.6867(3)	10.7191(7)
α/°	90	90	68.200(2)	104.553(6)
β/°	90	102.9130(10)	89.701(2)	110.229(6)
γ/°	90	90	86.138(2)	105.243(6)
V/Å^3	1309.9	1528.43	773.411	821.31(10)
Z	4	4	2	2
T/K	100(2)	100(2)	100(2)	100(2)
λ[b]/Å	0.6889	0.9028	1.54184	0.9028
D_c/g cm^{-3}	1.249	1.175	1.221	1.287
μ(Mo-Ka)/ mm^{-1}	0.083	0.086	0.721	0.165
Meas./indep. (R_{int}) refl.	28908 / 6422 (0.0444)	14738 / 6228 (0.0696)	26740 / 5379 (0.0619)	7772 / 5673 (0.1676)
Restraints, Parameters	0, 176	1, 375	3, 387	12, 455
wR2 (all data)[c]	0.1235	0.2109	0.1750	0.2073
R1[d,e]	0.0474	0.0747	0.0609	0.0767
Goodness of fit on F^2	1.071	1.037	1.077	0.956

[a] Includes guest molecules. [b] Mo-Kα radiation, graphite monochromator. [c] wR2= [Σw(IF$_o^2$I- IF$_c^2$I)^2/ ΣwIF$_o^2$I^2]$^{1/2}$. [d]For observed data. [e] R1= ΣIIF$_o$I- IF$_c$II/ ΣIF$_o$I

Table S3 Selected crystal data obtained from **34a**, **34b**, **34c** and **38b**.

	34a	**34b**	**34c**·H_2O	**38b**
Formula[a]	$C_{13}H_{16}N_4O_1$	$C_{19}H_{20}N_4O_1$	$C_{30}H_{42}N_8O_3$	$C_{15}H_{18}N_4O_1$
M_W	244.30	320.39	562.72	270.33
Crystal System	Monoclinic	Hexagonal	Orthorhombic	Monoclinic
Space group	$P2_1$	$P6_5$	$P2_12_12$	$P2_1$
a/Å	9.8292(2)	9.8466(4)	12.0576(2)	15.4703(10)
b/Å	12.6358(4)	9.8466(4)	11.3774(2)	5.1282(2)
c/Å	10.1195(2)	29.7164(12)	11.1889(2)	19.1266(13)
α/°	90	90	90	90
β/°	94.835(2)	90	90	112.939(5)
γ/°	90	120	90	90
V/Å^3	1252.37	2495.17	1534.94	1397.41
Z	4	6	2	4
T/K	100(2)	100(2)	100(2)	100(2)
λ[b]/Å	1.54184	0.6889	0.71073	0.6889
D_c/g cm^{-3}	1.296	1.279	1.213	1.285
μ(Mo-Ka)/ mm^{-1}	0.695	0.082	0.081	0.079
Meas./indep. (R_{int}) refl.	11865 / 4184 (0.0523)	25029 / 3740 (0.1031)	33986 / 4257 (0.0475)	19276 / 6319 (0.1359)
Restraints, Parameters	1, 343	7, 221	0, 200	1, 377
wR2 (all data)[c]	0.1207	0.1919	0.0998	0.1584
R1[d,e]	0.0451	0.0650	0.0386	0.0633
Goodness of fit on F^2	1.033	0.948	1.066	0.861

[a] Includes guest molecules. [b] Mo-Kα radiation, graphite monochromator. [c] wR2= [Σw(IF$_o^2$I- IF$_c^2$I)^2/ ΣwIF$_o^2$I^2]$^{1/2}$. [d]For observed data. [e] R1= ΣIIF$_o$I- IF$_c$II/ ΣIF$_o$I

Table S4 Selected crystal data obtained from **39**, **40b**, **49d** and **41b**.

	39	**40b**	**40d**	**41b**
Formula[a]	$C_{11}H_{15}N_3O_1$	$C_{25}H_{31}N_5O_2$	$C_{23}H_{39}N_5O_2$	$C_{12}H_{17}N_3O_1$
M_W	205.26	433.55	417.59	219.28
Crystal System	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic
Space group	$C222_1$	$P2_12_12_1$	$P2_1$	C2
a/Å	9.88050(10)	6.83130(10)	10.0504(6)	12.7286(3)
b/Å	12.7554(2)	9.9682(2)	24.8719(7)	13.6712(3)
c/Å	17.4319(2)	34.4021(7)	10.3198(6)	15.1669(4)
α/°	90	90	90	90
β/°	90	90	114.323(7)	113.349(3)
γ/°	90	90	90	90
V/Å^3	2196.94	2342.64	2350.69	2423.14
Z	8	4	4	8
T/K	100(2)	100(2)	100(2)	100(2)
λ[b]/Å	1.54184	0.71073	0.71073	1.54184
D_c/g cm^{-3}	1.241	1.229	1.180	1.202
μ(Mo-Ka)/ mm^{-1}	0.663	0.080	0.077	0.632
Meas./indep. (R_{int}) refl.	6642 / 2053 (0.0233)	32332 / 75609 (0.0842)	73118 / 12524 (0.0833)	53582 / 4618 (0.0717)
Restraints, Parameters	0, 141	0, 301	1, 542	9, 324
wR2 (all data)[c]	0.1094	0.1189	0.3114	0.0980
R1[d,e]	0.0415	0.0482	0.1049	0.0357
Goodness of fit on F^2	1.069	1.049	1.255	1.051

[a] Includes guest molecules. [b] Mo-Kα radiation, graphite monochromator. [c] wR2= [Σw(IF$_o^2$I- IF$_c^2$I)^2/ ΣwIF$_o^2$I^2]$^{1/2}$. [d]For observed data. [e] R1= ΣIIF$_o$I- IF$_c$II/ ΣIF$_o$I

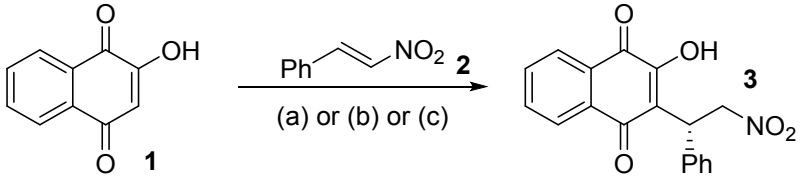
Table S5 Selected crystal data obtained from **41c**, **43a**, **43b** and **44**.

	41c-*crystal 1*	**41c**-*crystal 2*	**43a**	**43b**	**44b**
Formula[a]	$C_{11}H_{21}N_3O_3$	$C_{11}H_{21}N_3O_3$	$C_{14}H_{20}N_4O_3$	$C_{36}H_{45}N_8O_2$	$C_{20}H_{24}N_4O_3$
M_W	243.31	243.31	292.34	621.80	368.43
Crystal System	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$Pnma2_1$	$P2_1$	I2/a	$P2_1$	$P2_1$
a/Å	9.7621(4)	9.7687(5)	12.4402(4)	12.4470(4)	5.41730(10)
b/Å	13.2127(4)	21.9014(12)	12.9330(4)	12.0122(5)	13.9827(2)
c/Å	21.9038(7)	13.1820(7)	19.1393(6)	24.2818(6)	12.3897(2)
α/°	90	90	90	90	90
β/°	90	89.865(5)	99.889(3)	102.043(2)	91.2540(10)
γ/°	90	90	90	90	90
V/Å^3	2825.23(17)	2820.3(3)	3033.55(17)	3550.61	938.276
Z	8	8	8	4	2
T/K	100(2)	100(2)	100(2)	35(2)	100(2)
λ[b]/Å	1.54184	0.6889	1.54184	0.6889	1.54184
D_c/g cm^{-3}	1.144	1.146	1.280	1.163	1.304
μ(Mo-Ka)/ mm^{-1}	0.689	0.079	0.758	0.070	0.729
Meas./indep. (R_{int}) refl.	21112 / 4209 (0.1546)	17512 / 9516 (0.1767)	11819 /2837 (0.0597)	14653 / 9041 (0.1237)	12000 / 3534 (0.0308)
Restraints, Parameters	69, 280	1, 629	0, 205	397, 940	1, 256
wR2 (all data)[c]	0.3834	0.1955	0.2952	0.1969	0.0682
R1[d,e]	0.1390	0.0743	0.1348	0.0721	0.0278
Goodness of fit on F^2	1.477	0.676	1.126	0.918	1.039

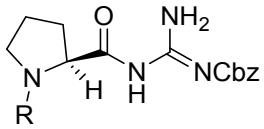
[a] Includes guest molecules. [b] Mo-Kα radiation, graphite monochromator. [c] wR2= [Σw(IF$_o^2$I- IF$_c^2$I)^2/ ΣwIF$_o^2$I^2]$^{1/2}$. [d]For observed data. [e] R1= ΣIIF$_o$I- IF$_c$II/ ΣIF$_o$I

Appendix III: Detailed information on catalytic reactions.

Data for catalysts studied in the reaction of **1** with **2** to give **5** in all solvents studied. Results are given as ee (% yield/time in h).



Catalysts **25a**, **25b**, **25c** and **25d**



25a R = Me
25b R = Bn
25c R = *i*-Pr
25d R = Cy

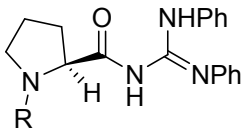
(a) Catalyst (0.1 eqv), at 0 °C 7-8 h then rt, (b) -78 °C to -20 °C, see (Table I)

Table I: Entries and results.

Entry	Cat.	Cons.	Acetonitrile	DCM	THF	Toluene	EtOAc	PhH	Xylene
1	**25a**	a b	34 (88/93)	37 (88/99) 13 (61/50)	18 (100/50)	44 (100/75)	31(100/76)	26 (72/48) 28 (18/36)	---- 9(18/81)
2	**25b**	a	7 (5/93)	8 (47/90)	15 (100/94)	13 (100/86)	5 (100/92)	-----	-----
3	**25c**	a	15 (10//89)	5 (20/90)	1 (20/89)	5 (32/90)	4 (20/90)	----	----
4	**25d**	a	1 (39/99)	4 (39/89)	----	----	----	----	----

(i) Precipitate formation during reaction.

Catalysts **26a-d**



26a R = Me
26b R = Bn
26c R = *i*-Pr
26d R = Cy

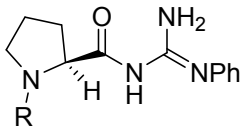
(a) Catalyst (0.1 eqv), at 0 °C for 7-8 h then rt, see (Table II)

Table II: Entries and results.

Entry	Catalyst	Cons.	Acetonitrile	DCM	THF	Toluene	EtOAc
1	**26a**[(i)]	a	4 (42/90)	1 (72/93)	3 (100/41)	3 (100/38)	4 (100/40)
2	**26b**	a	6 (38/72)	3 (38/76)	1 (72/51)	1 (72/35)	3 (72/97)
3	**26c**	a	3 (22/95)	5 (22/68)	----	----	----
	26d	a	1 (58/81)	1 (58/90)	----	----	----

i) Using with 0.04 eqv of catalyst **26a**.

Catalysts **27a-b**:



27a R = Me
27b R = Bn

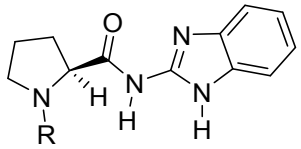
(a) Catalyst **27a-b**; 0.1 eqv, entries 1-3 at 0 °C, see (Table III).

Table III: Entries and results.

Entry	Catalyst	Cons.	Acetonitrile	DCM	THF	Toluene	EtOAc
1	**27a**	a	16 (21/93)	21 (4/91)	16 (96/85)	NR[(i)]	22 (96/87)
2	**27a**	a	----	25 (54/92)	----	----	----
3	**27b**	a	1 (48/91)	1 (48/93)	2 (48/36)	2 (48/90)	4 (68/82)

i) Catalyst **27a** was insoluble in toluene.

Catalysts **34a-d**



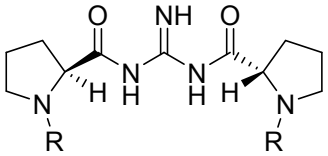
34a R = Me
34b R = Bn
34c R = i-Pr
34d R = Cy

(a) Catalyst **34a-d**; 0.1 eqv, at 0 °C for 7-8 h then rt, see (Table IV).

Table IV: Entries and results.

Entry	Catalyst	Cons.	Acetonitrile	DCM	Toluene
1	**34a**	a	7 (39/90)	27 (39/88)	32 (100/87)
2	**34b**	a	3 (58/89)	12 (58/92)	----
3	**34c**	a	2 (88/81)	(100/90)	----
4	**34d**	a	2 (58/91)	9 (85/96)	----

Catalysts **40b-d**



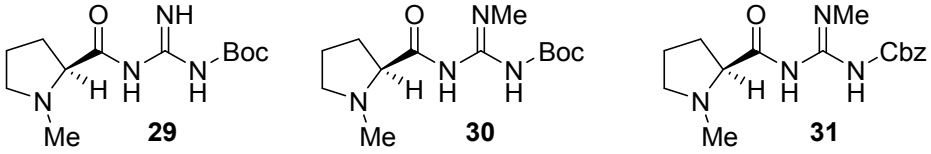
40b R = Bn
40c R = i-Pr
40d R = Cy

(a) Conditions: Catalyst **40b-d** (0.1 eqv), then either (a) 0 °C, 7-8 h then rt or (b) -78 °C to -20 °C, or (c) with benzoic acid (BA); see table **V**

Table V: Entries and results.

Entry	Cat.	Cons.	DCM	MeCN	THF	PhMe	Xylenes	PhH
1	**40b**	a	6 (96/91)	----	----	----	7 (24/82)	----
		b	4 (48/92)	----	----	----	----	----
2	**40c**	a	4 (29/81)	4 (5/60)	4 (72/80)	4 (5/48)	4 (5/67)	4 (5/37)
		b	3 (5/48)	----	----	4 (5/53)	----	----
3	**40d**	a	1(46/100)	2 (24/87)	1 (144/91)	2 (72/39)	2 (48/65)	2 (72/75)
		b	7 (48/89)	----	----	----	----	----
		c	1 (24/63)	----	----	1 (24/41)	1 (24/53)	----

Catalysts **29**, **30 and 31**.

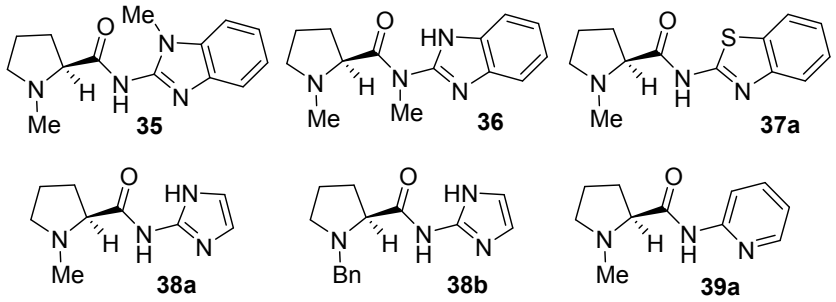


(a) Conditions: Catalyst **29**, **30** or **31** (0.1 eqv) then either (a) 0 °C, 7-8 h then rt, or (b) with benzoic acid (BA, 0.1 eqv), or (c); -78 °C - -20 °C; see table VI

Table VI: Entries and results.

Entry	Cat.	Cons.	DCM	PhMe	Xylene	Et_2O	PhH	CCl_4
1	**29**	a	19 (28/75)	22 (2/89)	22 (2/80)	19 (124/80)	17 (4/90)	21 (28/64)
		b	28 (168/63)	37 (48/90)	----	----	----	----
		c	----	18 (24/38)	----	----	----	----
2	**30**	a	9 (120/86)	7 (48/70)	4 (48/91)	5 (120/54)	7 (48/85)	3 (120/55)
3	**31**	a	5 (120/65)	4 (46/7)	----	1 (120/22)	----	----

Catalysts **35**, **36**, **37a**, **38a**, **38b** and **39**.

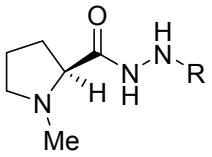


Conditions: Catalyst (0.1 eqv) then either (a) 0 °C, 7-8 h then rt, or (b) with benzoic acid (BA); see table VII

Table VII: Entries and results.

Entry	Cat.	Cons.	DCM	PhMe	Xylenes	Et_2O	PhH
1	**35**	a	4 (48/91)	5 (49/86)	----	3 (120/55)	----
2	**36**	a	6 (120/75)	14 (48/19)	10 (22/48)	8 (48/48)	10 (48/80)
3	**37a**	a	3 (48/25)	0 (48/14)	----	----	4 (48/37)
4	**38a**	a	16 (100/69)	16 (120/54)	----	----	----
5	**38b**	a	13 (96/70)	5 (96/67)	----	----	----
6	**39a**	a	2 (48/78)	2 (48/16)	----	----	0 (48/87)

Catalysts **41a-d**.



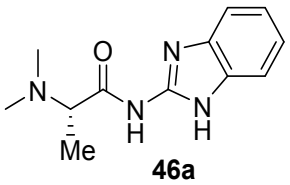
41a R = H
41b R = Ph
41c R = Boc
41d R = Cbz

Conditions: Catalyst **41a-d** (0.1 eqv) then either (a) 0 °C, 7-8 h then rt or (b) -78 °C - -20 °C, see table VIII

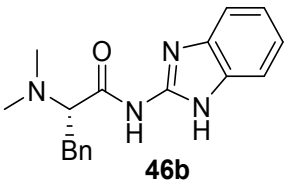
Table VIII: Entries and results.

Entry	Cat.	Cons.	DCM	PhMe	Xylenes	Et_2O	PhH
1	**41a**	a	3 (100/70)	5 (2/71)	4 (72/68)	4 (124/41)	NR
2	**41b**	a	3 (48/87)	3 (1/86)	3 (1/59)	----	2 (1/56)
		b	----	17 (24/63)	----	----	----
3	**41c**	a	4 (168/42)	13 (168/19)	10 (168/10)	2 (168/28)	9 (168/71)
4	**41d**	a	2 (10/66)	10 (10/27)	5 (48/74)	4 (96/36)	8 (10/72)
		b	3 (48/80)	----	----	----	----

Catalysts **46a-b**:



46a



46b

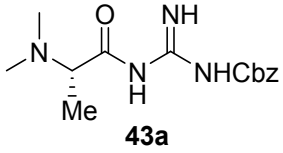
Conditions: Catalysts **46a,b** (0.1 eqv), 0 °C, 7-8 h then rt, see table IX.

Table IX: Entries and results.

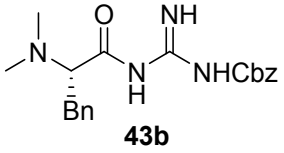
Entry[i]	Cat.	DCM	PhMe	Xylenes	THF	Ether	PhH	CCl_4
1	**46a**	10 (168/88)	16 (168/37)	14 (168/48)	10 (168/54)	9 (168/88)	----	9 (168/67)
2	**46b**	10 (120/79)	20 (120/57)	28 (120/41)	17 (120/75)	9 (120/81)	9 (72/65)	15 (72/49)

i) Results are given as ee (time (h)/yield (%))

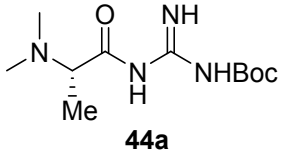
Catalysts **43a**, **43b**, **44a**, **44b, 45b** and **47b**.



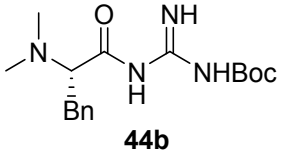
43a



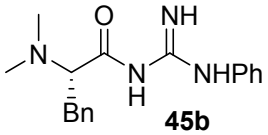
43b



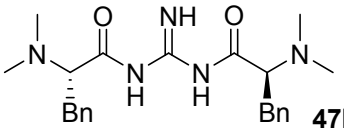
44a



44b



45b



47b

Conditions: Catalyst **43a**, **43b**, **44a**, **44b, 45b** or **47b** (0.1 eqv) then either (a) 0 °C, 7-8 h, then rt, or (b) with (BA); or (c); -78 °C to -20 °C; see table X.

Table X: Entries and results.

Entry	Cat.		DCM	PhMe	Xylenes	THF	Et_2O	PhH	CCl_4
1	**43a**	a	7 (96/88)	13 (18/88)	10 (40/65)	9 (96/60)	8 (96/69)	10(18/75)	7 (96/67)
		b	7 (96/88)	----	----	----	----	----	----
2	**43b**	a	4 (28/92)	15 (72/43)	15 (72/33)	6 (72/99)	6 (48/43)	9 (2/97)	7 (99/75)
		b	7(120/34)	25 (2/67)	21 (2/44)	----	----	----	----
		c		22 (10/54)	----	----	----	----	----
3	**44a**	a	10 (44/65)	11 (20/40)	15 (20/39)	10 (72/77)	10 (20/44)	11 (20/54)	11 (44/76)
		b	8 (24/75)	-----	----	----	----	----	----
4	**44b**	a	9 (8/49)	18 (1/46)	20 (15/41)	15 (10/85)	11 (10/57)	13 (15/63)	6 (8/89)
		b	----	30 (48/91)	----	----	----	----	----
		c	-----	31(10/40)	----	--------	----	----	----
5	**45b**	a	18 (8/81)	21 (10/96)	21 (8/100)	21 (10/66)	----	21 (10/76)	18 (10/36)
6	**47b**	a	21 (2/67)	23 (2/59)	24 (2/61)	21 (18/95)	----	25 (2/54)	----
		c	25(24/33)	25 (72/42)	----	----	----	----	----

Appendix IV: HPLC analysis, representative examples.

Racemic **5**.

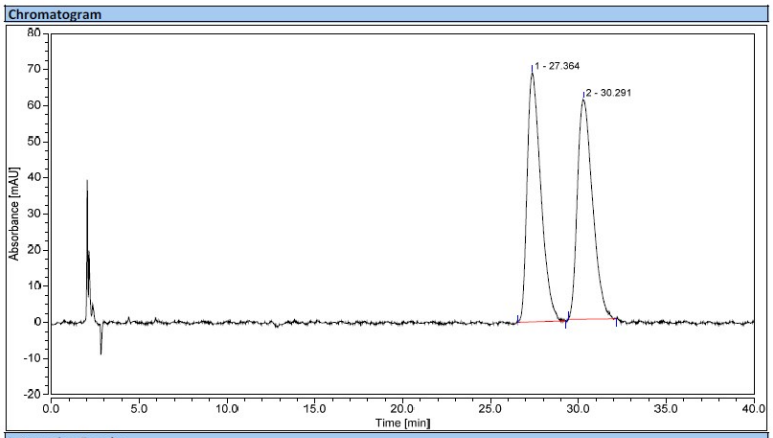
Instrument:U3000 Sequence:Zahraa 02.08.2017 Page 1 of 1

Chromatogram and Results

Injection Details

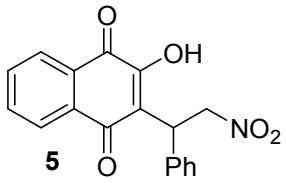
Injection Name:	**Racemic**	*Run Time (min):*	**40.00**
Vial Number:	**RC8**	*Injection Volume:*	**20.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_1**
Calibration Level:		*Wavelength:*	**254.0**
Instrument Method:	**Chiracel AS-H**	*Bandwidth:*	**n.a.**
Processing Method:	**New ProcMethod**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**03/Aug/17 06:30**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		27.364	62.254	68.958	50.57	53.13	n.a.
2		30.291	60.860	60.841	49.43	46.87	n.a.
Total:			**123.114**	**129.798**	**100.00**	**100.00**	



Racemic (AS-H Column)

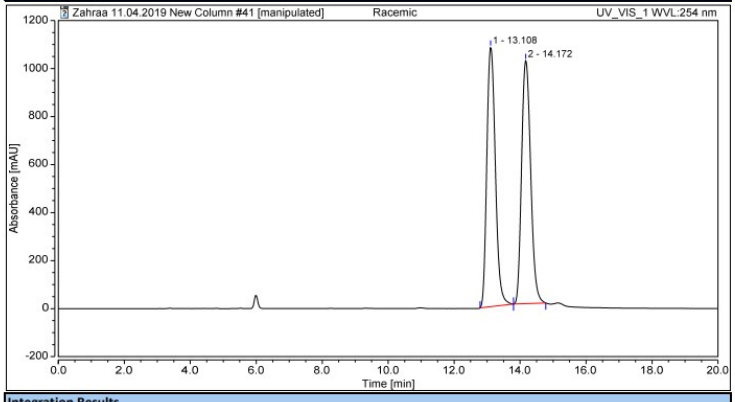
Instrument:U3000 Sequence:Zahraa 11.04.2019 New Column Page 1 of 1

Chromatogram and Results

Injection Details

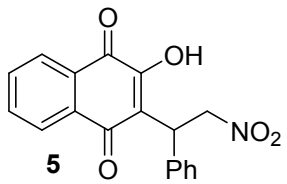
Injection Name:	**Racemic**	*Run Time (min):*	**20.00**
Vial Number:	**RE7**	*Injection Volume:*	**10.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_1**
Calibration Level:		*Wavelength:*	**254.0**
Instrument Method:	**Phen-Amy-1**	*Bandwidth:*	**n.a.**
Processing Method:	**New ProcMethod**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**22/May/19 15:38**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13.108	324.113	1081.028	50.09	51.64	n.a.
2		14.172	323.006	1012.528	49.91	48.36	n.a.
Total:			**647.118**	**2093.556**	**100.00**	**100.00**	



Racemic (Phen-Amy-1 Column)

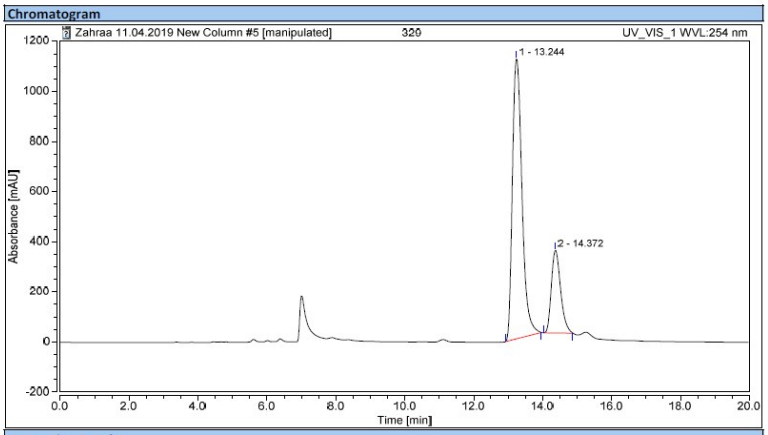
Results with catalysts **25a** and **29**.

Chromatogram and Results

Injection Details

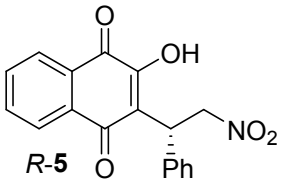
Injection Name:	**329**	*Run Time (min):*	**20.00**
Vial Number:	**RA5**	*Injection Volume:*	**10.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_1**
Calibration Level:		*Wavelength:*	**254.0**
Instrument Method:	**Phen-Amy-1**	*Bandwidth:*	**n.a.**
Processing Method:	**New ProcMethod**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**12/Apr/19 00:41**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13.244	358.729	1118.116	77.73	77.17	n.a.
2		14.372	102.788	330.849	22.27	22.83	n.a.
Total:			**461.517**	**1448.965**	**100.00**	**100.00**	



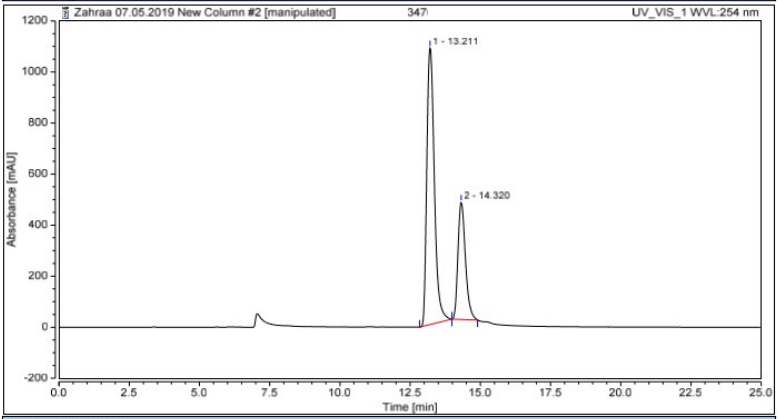
56% ee catalyst **25a** (PhMe)

Chromatogram and Results

Injection Details

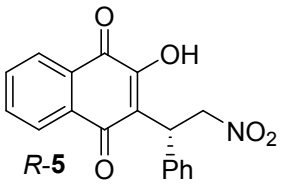
Injection Name:	**347**	*Run Time (min):*	**25.00**
Vial Number:	**RA2**	*Injection Volume:*	**10.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_1**
Calibration Level:		*Wavelength:*	**254.0**
Instrument Method:	**Phen-Amy-1**	*Bandwidth:*	**n.a.**
Processing Method:	**New ProcMethod**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**07/May/19 17:32**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13.211	337.181	1084.036	70.38	70.20	n.a.
2		14.320	141.890	460.077	29.62	29.80	n.a.
Total:			**479.071**	**1544.112**	**100.00**	**100.00**	



41% ee catalyst **29** (PhMe)