Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supplementary Information

Gold-catalyzed three-component spirocyclization: A one-pot approach to functionalized pyrazolidines

*Bernd Wagner, Wolf Hiller, Hiroaki Ohno and Norbert Krause**

Content

I. General Information

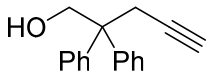
Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker DPX300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei, a Bruker DRX400 spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei, a Bruker DRX500 and a Varian Inova 500 spectrometer operating at 500 MHz for proton and 125 MHz for carbon nuclei. Fluorine (^{19}F) NMR spectra were recorded on a Bruker DRX300 spectrometer operating at 282 MHz for fluorine nuclei. 2D correlation NMR spectra were recorded on a Bruker DRX500 spectrometer.

Low resolution mass spectra were recorded with a Thermo TSQ spectrometer. High resolution mass spectrometry (ESI) was performed on an Thermo LTQ Orbitrap coupled with a Accela HPLC system.

All reagents were purchased from commercial sources and were used as supplied. Liquid aldehydes were distilled before use. Gold and silver salts were purchased from Sigma-Aldrich, Chempur and Fluorochem. 1,2-Dichloroethane, dichloromethane, toluene, and tetrahydrofuran were dried with a solvent purification system MBraun SPS-800. Unless otherwise stated, all reactions were carried out in heat dried glassware under argon atmosphere.

4-Pentyn-1-ol **1a** and 5-hexyn-1-ol **1d** were purchased from TCI Europe.

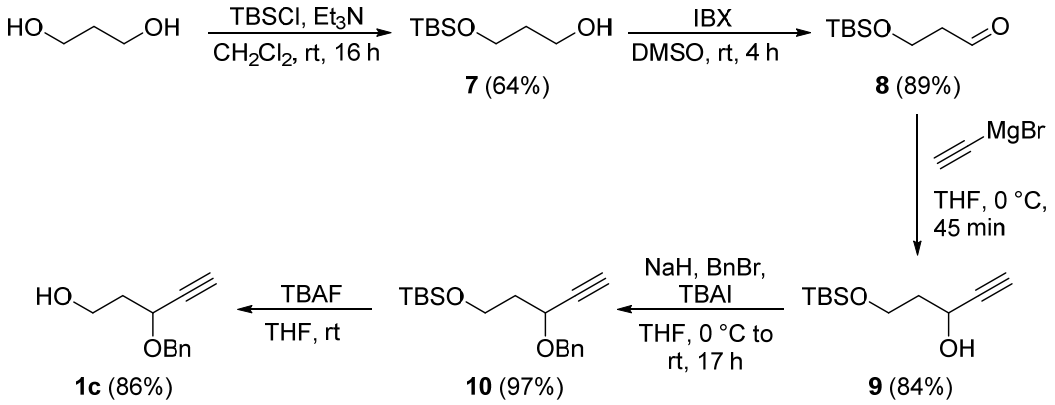
II. Synthesis of Alkynols

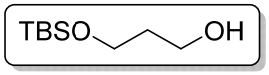


1b

2,2-diphenylpent-4-yn-1-ol (**1b**) was prepared according to literature.[1]

Synthesis of 3-(Benzyloxy)pent-4-yn-1-ol (1c)



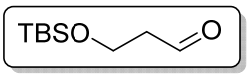


To a solution of propane-1,3-diol (3.9 mL, 4.00 g, 52.6 mmol) in 100 mL CH_2Cl_2 was added Et_3N (7.3 mL, 5.32 g, 52.6 mmol) and a solution of TBSCl (7.93 g, 52.6 mmol) in 20 mL CH_2Cl_2. After 16 h the reaction mixture was subsequently washed with 10% aqueous $NaHCO_3$-solution, brine and water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Alcohol **7** (6.38 g, 33.5 mmol, 64%) could be obtained after column chromatography (CH:EtOAc = 20:1 to 10:1 to 5:1) as a colorless oil.

^{1}H NMR (C_6D_6, 300 MHz): δ = 3.58 - 3.70 (m, 4 H), 2.92 (br. s., 1 H), 1.63 (quin, *J* = 5.9 Hz, 2 H), 0.93 (s, 9 H), 0.02 ppm (s, 6 H).

Spectral data agreed with previous data.[2]

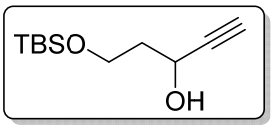
(1) Minkler, S. R. K.; Isley, N. A.; Lippincott, D. J.; Krause, N.; Lipshutz, B. H. *Org. Lett.* **2014**, *16*, 724–726.
(2) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Concon, B. D. *J. Org. Chem.* **1986**, *51*, 3388–3390.



To a solution of alcohol **7** (6.00 g, 31.5 mmol) in 100 mL DMSO IBX (15.0 g, 53.6 mmol) was added and stirred at room temperature for 4 h. After addition of 100 mL water the suspension was filtered and the filtrate extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Aldehyde **8** (5.28 g, 28.0, 89%) was obtained as a yellowish oil without further purification.

^{1}H NMR (**C_6D_6, 300 MHz**): δ = 9.39 (s, 1 H), 3.56 (t, *J* = 5.9 Hz, 2 H), 2.03 (d, *J* = 1.8 Hz, 2 H), 0.90 (m, 9 H), -0.02 ppm (m, 6 H).

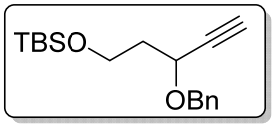
Spectral data agreed with previous data.[3]



To a solution of ethyniyl magnesium bromide (43.5 mL, 0.5M in THF) in 200 mL THF a solution of aldehyde **8** (4.1 g, 21.8 mmol) in 20 mL THF was slowly added at 0°C. After 45 min the reaction mixture was hydrolyzed with saturated aqueous NH_4Cl-solution an concentrated in vacuo. The residue was extracted with Et_2O, the organic phase dried over $MgSO_4$ and concentrated in vacuo. alcohol **9** (3.95 g, 18.4 mmol, 84%) could be obtained after column chromatography (CH:EtOAc = 20:1) as yellowish oil.

^{1}H NMR (C_6D_6, 300 MHz): δ = 4.54 (ddd, *J* = 6.9, 4.8, 2.2 Hz, 4 H), 3.80 (ddd, *J* = 10.2, 7.9, 4.6 Hz, 4 H), 3.51 - 3.61 (m, 1 H), 3.03 (br. s, 1 H), 2.12 (s, 1 H), 1.67 - 1.91 (m, 2 H), 0.89 (s, 9 H), -0.01 ppm (d, *J* = 3.3 Hz, 6 H).

Spectral data agreed with previous data.[4]

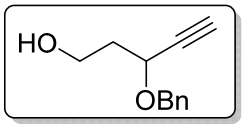


NaH (800 mg, 60% in mineral oil, 20.0 mmol)was suspended in 10 mL THF and cooled to 0°C. A solution of alkohol **9** (3.90 g, 18.2 mmol) in 20 mL of THF was added dropwise to the reaction mixture. At room temperature a solution of benzyl bromide (4.70 g, 27.3 mmol) and tetra-*N*-butylammonium iodide (55 mg, 150 µmol) in 10 mL THF was slowly added and stirred for 17 h. The reaction mixture

(3) Li, X.; Lantrip, D.; Fuchs, P. L. *J. Am. Chem. Soc.* **2003**, *125*, 14262–14263.
(4) Pearson, W. H.; Kropf, J. E.; Choy, A. L.; Lee, I. Y.; Kampf, J. W. *J. Org. Chem.* **2007**, *72*, 4135–4148.

was hydrolyzed with saturated aqueous NH_4Cl-solution and concentrated in vacuo. The residue was extracted with Et_2O, the organic phase was dried over $MgSO_4$ and concentrated in vacuo. Alkyne **10** (3.80 g, 12.5 mmol, 69%) could be obtained after column chromatography (pentane:Et_2O = 100:1) as a yellowish oil.

^{1}H-NMR (C_6D_6, 300 MHz): δ = 7.34 - 7.42 (m, 2 H), 7.12 - 7.28 (m, 4 H), 4.91 (d, *J* = 11.7 Hz, 1 H), 4.43 - 4.53 (m, 2 H), 3.70 - 3.87 (m, 2 H), 2.00 - 2.24 (m, 3 H), 0.99 (s, 9 H), 0.07 ppm (d, *J* = 1.1 Hz, 6 H). **HRMS:** Calculated for $[M+H]^+$: $C_{24}H_{33}O_2Si$ 381.2244, found: 381.2250.

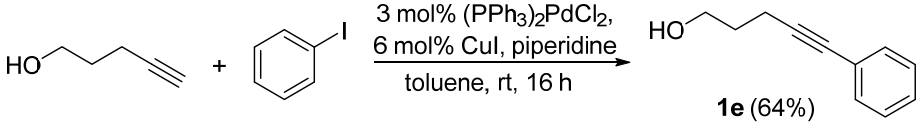


Tetra-n-butylammonium fluoride (7.88 mL, 1M in THF) was added to a solution of alkyne **10** (2.00 g, 6.57 mmol) in 50 mL THF and stirred for 8 h. After Addition of 50 mL water the mixture was extracted with CH_2Cl_2, the organic phase was dried over $MgSO_4$ and concentrated in vacuo. Alkynol **1c** (1.01 g, 5.31 mmol, 81%) could be obtained after column chromatography (pentane:Et_2O = 10:1 to 7:1 to 3:1) as a yellowish oil.

^{1}H MR (C_6D_6, 300 MHz): δ = 7.30 - 7.39 (m, 2 H), 7.13 - 7.27 (m, 3 H), 4.83 (d, *J* = 11.7 Hz, 1 H), 4.42 (d, *J* = 11.7 Hz, 1 H), 4.31 (ddd, *J* = 7.2, 5.4, 2.0 Hz, 1 H), 3.63 - 3.84 (m, 2 H), 2.58 (br. s, 1 H), 2.26 (d, *J* = 2.2 Hz, 1 H), 1.90 - 2.12 ppm (m, 2 H).

Spectral data agreed with previous data.[5]

Synthesis of 5-phenylpent-4-yn-1-ol (1e)



To a stirred solution of iodobenzene (0.06 g, 15 mmol), 4-pentyn-1-ol (1.31 g, 15.6 mmol) and piperidine (2.56g, 30.0 mmol) in 15 mL toluene was added CuI (170 mg, 900 µmol) and $(PPh_3)_2PdCl_2$ (320 mg, 450µmol)) at RT. After stirring the reaction mixture at room temperature

(5) Liu, H.; El-Salfiti, M.; Chai, D. I.; Auffret, J.; Lautens, M. *Org. Lett.* **2012**, *14*, 3648–3651.

for 16 h the solvent was removed in vacuo. Alkynol **1e** (1.60 g, 10.0 mmol, 64%) could be obtained after column chromatography (CH:EtOAc = 9:1) as a yellowish oil.

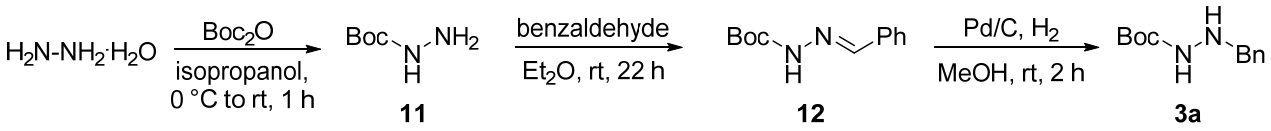
^{1}H NMR (C_6D_6, 500 MHz): δ = 7.45 (dd, *J* = 8.0, 1.5 Hz, 2 H), 6.94 - 7.04 (m, 3 H), 3.48 (t, *J* = 6.1 Hz, 2 H), 2.33 (t, *J* = 7.1 Hz, 2 H), 1.68 (br. s, 1 H), 1.55 - 1.63 ppm (m, 2 H);

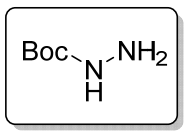
Spectral data agreed with previous data.[6]

(6) Barber, D. M.; Sanganee, H. J.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 5290–5293.

III. Synthesis of Hydrazines

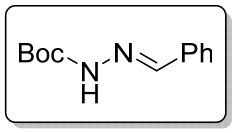
Synthesis of *tert*-butyl -2-benzylhydrazine-1-carboxylate (3a)





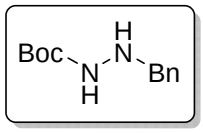
To a solution of hydrazine monohydrate (4.9 mL, 5.00 g, 100 mmol) in 20 mL of isopropanol a solution of Boc_2O (10.0 g, 45.8 mmol) dissolved in 10 mL of isopropanol was added dropwise at 0°C. After complete addition the reaction mixture was warmed up to room temperature and stirred for 1 h. The solvent was removed in vacuo, the residue was dissolved in DCM and dried over $MgSO_4$. DCM was removed in vacuo and the carbazate **11** was obtained as a white solid without further purification (5.13 g, 38.8 mmol, 85%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.89 (br. s, 1 H), 3.76 (br. s., 2 H), 1.46 ppm (s, 9 H).



The carbazate **11** (2.00 g, 15.1 mmol) was dissolved in 10 mL of dry Et_2O and freshly distilled benzaldehyde (2.08 g, 19.6 mmol) was added. The reaction mixture was stirred for 22 h. The white precipitate was collected by filtration, washed with Et_2O and dried under vacuum. The hydrazone **12** was obtained as a white solid without further purification (2.58 g, 11.7 mmol, 77%)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (br. s., 1 H), 8.14 (m, 1 H), 7.52 - 7.60 (m, 2 H), 7.29 - 7.36 (m, 3 H), 2.13 ppm (s, 9 H)



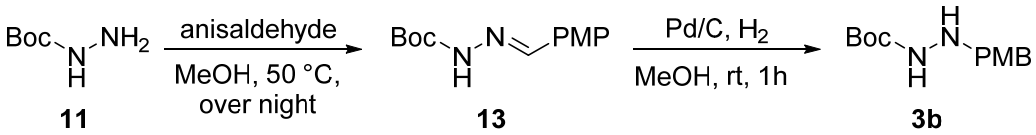
To a solution of hydrazone **12** (2.58 g, 11.7 mmol) in 20 mL dry methanol 5 mol% of Pd/C (10wt.%) was added, the flask was equipped with a hydrogen filled ballon and the reaction was stirred for 2 h. The reaction mixture was

filtered through Celite and the solvent was removed in vacuo. The hydrazine **3a** was obtained as a highly viscous oil (1.84 g, 8.31 mmol, 71%) which slowly cristallized as a white solid.

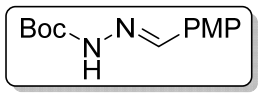
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.09 (m, 5 H), 6.15 (br. s, 1 H), 4.15 (br. s, 1 H), 3.92 (s, 1 H), 1.40 ppm (s, 9 H).

All spectral data agreed with previous data.[7]

Synthesis of tert-butyl 2-(4-methoxybenzyl)hydrazine-1-carboxylate (3b)

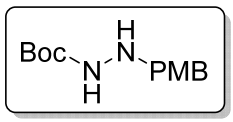


11 **13** **3b**



To a solution of Carbazate **11** (2.00 g, 15.1 mmol) dissolved in 75 mL of MeOH anisaldehyde (2.06 g, 15.1 mmol) was added and stirred over night. The white precipitate was collected by filtration, washed with pentane and dried in vacuo to obtain the hydrazone **13** as a white solid without further purification (3.63 g, 14.5 mmol, 96%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 8.05 (s, 1 H), 7.80 (s, 1 H), 7.61 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 3.81 (s, 3 H), 1.53 ppm (s, 9 H).



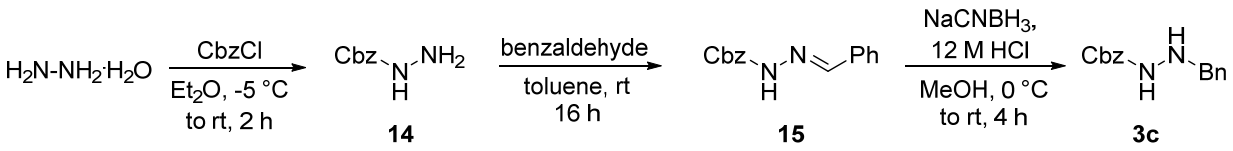
To a solution of hydrazone **13** (2.00 g, 7.99 mmol) in 40 mL MeOH 1 mol% of Pd/C (10wt.%) was added, the flask was equipped with a hydrogen filled ballon and the reaction was stirred for 1.5 h. The reaction mixture was filtered through Celite and the solvent was removed in vacuo. The hydrazine **3b** was obtained as a white solid after recrystallization in EtOH (1.16 g, 4.60 mmol, 58%).

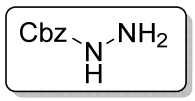
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.30 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 6.25 (br. s, 1 H), 3.96 (s, 2 H), 3.81 (s, 3 H), 3.33 (br. s, 1 H), 1.47 ppm (s, 9 H).

All spectral data agreed with previous data.[8]

(7) Mendelez, R. E.; Lubell, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 6759–6764.
(8) Burkholder, T. P.; Clayton, J. R.; Ma, L. *US2010152181 (A1)*, **2010**.

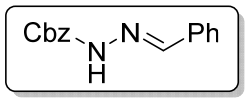
Synthesis of benzyl 2-benzylhydrazine-1-carboxylate (3c)





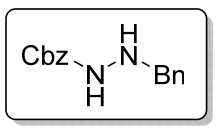
To solution of hydrazine monohydrate (3.9 mL, 4.05 g, 80.9 mmol) in 20 ml of Et_2O a solution of benzyl chloroformate (3.00 g, 17.6 mmol) in 20 mL of Et_2O was added dropwise at -5°C. After complete addition, the reaction mixture was warmed up to room temperature and stirred for further 2 h. The white precipitate was dissolved in water and the organic phase was washed with water three times. The organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was recrystallized in cyclohexane and the carbazate **14** was obtained as a white solid (1.70 g, 10.2 mmol, 58%)

^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.41-7.30 (m, 5 H), 6.09 (br. s, 1 H), 5.16 (s, 2 H), 3.63 ppm (br. s, 2 H).



Benzaldehyde (3.70 g, 34.8 mmol) was added to a solution of carbazate **14** (5.26 g, 31.6 mmol) in 60 mL of dry toluene and the reaction mixture was stirred for 16 h. The white solid was collected, washed with pentane and dried in vacuo. Hydrazone **15** was obtained as a white solid (5.57 g, 21.9 mmol, 63%).

^{1}H-NMR (CDCl3, 400 MHz): δ = 8.11 (s, 1 H), 7.87 (br. s., 1 H), 7.71-7.69 (m, 2 H), 7.44-7.35 (m, 8 H), 5.28 ppm (s, 2 H).



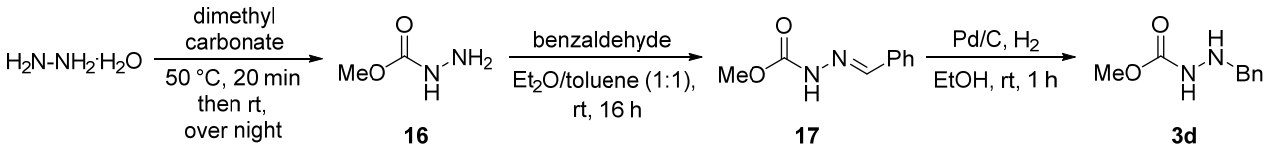
Hydrazone **15** (3.00 g, 11.8 mmol) was dissolved in 20 mL of dry methanol and sodium cyanoborohydride (1.26 g, 20.1 mmol) was added at room temperature. The reaction mixture was cooled to 0°C and 12 M aqueous HCl (2 mL, 23.6 mmol) was added dropwise. After 20 minutes, reaction mixture was warmed up to room temperature and stirred for further 4 h. The pH value was set to pH = 9 with 6 M NaOH solution

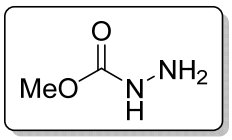
and the solvent was removed in vacuo. The residue was dissolved in DCM and washed with water. The aqueous phase was extracted five times with DCM. The collected organic phases were dried over $MgSO_4$ and the solvent was removed in vacuo. The desired hydrazine **3c** was obtained as a white solid (2.75 g, 10.7 mmol, 91%).

^{1}H-NMR (C_6D_6, 500 MHz): δ = 7.00-7.29 (m, 10 H), 6.06 (br. s., 1 H), 4.99 (s, 2 H), 4.10 (br. s., 1 H), 3.85 ppm (s., 2 H).

All spectral data agreed with previous data.[9]

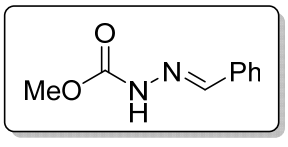
Synthesis of methyl 2-benzylhydrazine-1-carboxylate (3d)





Hydrazine monohydrate (10.0 g, 9.7 mL, 200 mmol) and dimethyl carbonate (18.9 g, 17.7 mL, 210 mmol) were mixed and stirred at 50°C for 20 minutes. The reaction mixture was cooled to room temperature and stirred over night. The crude product was dried in vacuo to obtain carbazate **16** as a white solid without further purification (17.3 g, 192 mmol, 96%).

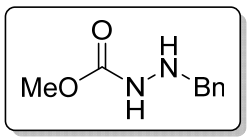
^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 6.23 (br. s, 1 H), 3.71 (s, 2 H), 3.69 ppm (s, 2 H).



To a solution of Carbazate **16** (17.3 g, 192 mmol) dissolved in 400 mL of toluene and Et_2O (1:1) benzaldehyde (22.4 g, 211 mmol) was added and stirred for 16 h. The white precipitate was collected by filtration, washed with pentane and dried in vacuo to obtain the hydrazone **17** as a white solid without further purification (23.7 g, 133 mmol, 70%).

(9) Calabretta, R.; Giordano, C.; Gallina, C.; Morea, V.; Consalvi, V.; Scandurra, R. *Eur. J. Med. Chem.* **1995**, *30*, 931–941.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.19 (br. s, 1 H), 7.87 (s, 1 H), 7.70-7-68 (m, 2 H), 7.40-7.38 (m, 3 H), 3.87 ppm (s, 3 H).



To a solution of hydrazone **17** (5.00 g, 28.1 mmol) in 20 mL dry ethanol 5 mol% of Pd/C (10wt.%) was added, the flask was equipped with a hydrogen filled ballon and the reaction was stirred for 2 h. The reaction mixture was filtered through Celite and the solvent was removed in vacuo. Hydrazine **3d** was obtained as a white solid after column chromatography (2.01 g, 11.1 mmol, 40%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.39-7.30 (m, 5 H), 6.27 (br. s., 1 H), 4.03 (s, 2 H), 3.84 (br. s., 1 H), 3.72 ppm (s, 3 H).

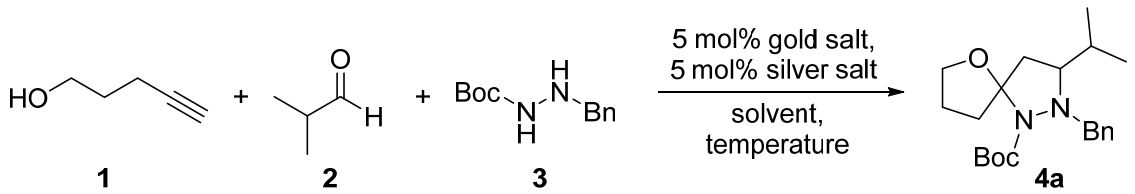
All spectral data agreed with previous data.[10]

(10) Suzuki, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2012**, *14*, 326–329.

IV. Reaction optimization

Screening of catalyst, solvent and temperature:

Under argon atmosphere, *tert*-butyl 2-benzylhydrazinecarboxylate **3a** (100 mg, 450 µmol), isobutyraldehyde (38.9 mg, 540 µmol) and 4-pentyn-1-ol (45.4 mg, 540 µmol) were dissolved in a solvent mentioned in table 1 (3 mL). To the stirred solution 5 mol% gold salt and 5 mol% of the corresponding silver salt were added and the resulting mixture was stirred at a temperature mentioned below until completion. The reaction mixture was filtered over Celite and concentrated in vacuo. The crude product was purified by column chromatography (cyclohexane:EtOAc = 30:1).

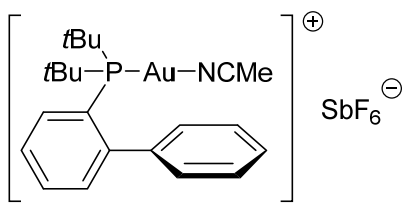


1 **2** **3** **4a**

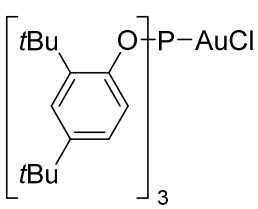
Table 1: Screening of conditions I.[a]

Entry	gold salt	silver salt	solvent	temperature	time	yield[b]
1	Ph_3PAuCl	AgOTf	1,2-DCE	rt	22 h	41%
2	Ph_3PAuCl	AgOTf	AcOH	rt	43 h	39%
3	Ph_3PAuCl	AgOTf	toluene	rt	16 h	37%
4	Ph_3PAuCl	AgOTf	DCM	rt	16 h	43%
5	Ph_3PAuCl	AgOTf	THF	rt	16 h	52%
6	Ph_3PAuCl	AgOTf	THF	50°C	3 h	40%
7	Ph_3PAuCl	AgOTf	THF	50°C	3 h	40%
8	Ph_3PAuCl	$AgBF_4$	THF	50°C	2.5 h	58%
9	Ph_3PAuCl	$AgSbF_6$	THF	50°C	3.5 h	69%
10	**A**	-	THF	50°C	4 h	65%
11	**B**	$AgSbF_6$	THF	50°C	4 h	77%
12	$Ph_3PAuNTf_2$	-	THF	50°C	4 h	75%
13	AuCl	-	THF	50°C	7 h[c]	traces
14	$AuCl_3$	-	THF	50°C	7 h[c]	traces
15	-	$AgSbF_6$	THF	50°C	4 h	traces
16	CuBr[d,e]	-	THF	50°C	14 d	traces
17	$PtCl_2$[d,e]	-	THF	50°C	24 h	57%

[a] 1.2 eq. of alkynol, 1.2 eq. of aldehyde, 1.0 eq. of hydrazine; [b] isolated yields, obtained as a diastereomeric mixture of 42:58; [c] formation of gold mirror; [d] 2.0 eq. of alkynol, 2.0 eq. of aldehyde, 1.0 eq. of hydrazine; [e] 10 mol% of catalyst.



A



B

Variation of equivalents:

Under argon atmosphere, *tert*-butyl-2-benzylhydrazinecarboxylate **3a** (100 mg, 450 µmol), isobutyraldehyde and 4-pentyn-1-ol were dissolved in THF (3 mL). To the stirred solution chloro[tris(2,4-di-tert-butylphenyl)phosphite]gold and silver hexafluoroantimonate were added and the resulting mixture was stirred at 50°C until completion. The reaction mixture was filtered over Celite and concentrated in vacuo. The crude product was purified by column chromatography (cyclohexane:EtOAc = 30:1).

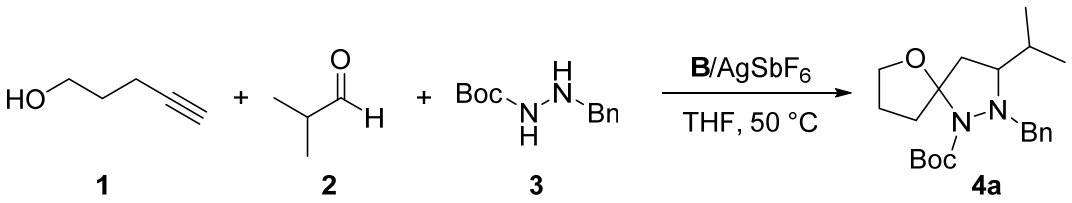


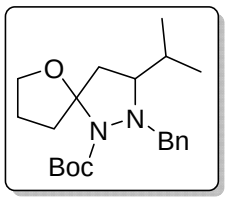
Table 2: Screening of conditions II.

entry	alkynol [eq.]	aldehyde [eq.]	hydrazine [eq.]	catalyst loading	time	yield[a]
1	1.2	1.2	1.0	5 mol%	4 h	77%
2	1.0	1.0	1.0	5 mol%	4 h	63%
3	1.2	1.0	1.0	5 mol%	4 h	64%
4	1.0	1.2	1.0	5 mol%	4 h	65%
5	1.0	1.0	1.2	5 mol%	4 h	64%
6	1.5	1.5	1.0	5 mol%	4 h	89%
7	2.0	2.0	1.0	5 mol%	4 h	92%
8	2.0	2.0	1.0	2 mol%	4 h	85%
9	2.0	2.0	1.0	1 mol%	6 h	84%

[a] isolated yield, obtained as a diastereomeric mixture of 42:58

V. Synthesis and analytical data of spiro compounds

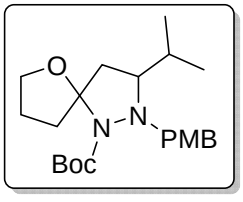
tert-Butyl 2-benzyl-3-isopropyl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4a)



Under argon atmosphere, tert-butyl 2-benzylhydrazinecarboxylate **3a** (100 mg, 450 µmol), isobutyraldehyde (64.9 mg, 900 µmol) and 4-pentyn-1-ol (75.7 mg, 900 µmol) were dissolved in THF (3 mL). To the stirred solution chloro[tris(2,4-di-tert-butylphenyl)phosphite]gold (19.8 mg, 22.5 µmol) and silver hexafluoroantimonate (7.7 mg, 22.5 µmol) were added and the resulting mixture was stirred at 50°C for 4 h. The reaction mixture was filtered over Celite and concentrated in vacuo. The crude product was purified by column chromatography (cyclohexane:EtOAc = 30:1) to afford compound **4a** (150 mg, 416 µmol, 92%, *dr* = 42:58) as a white solid.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.48 (m, 3.6 H), 7.17 - 7.26 (m, 3.8 H), 7.08 - 7.15 (m, 1.9 H), 4.29 - 4.40 (m, 1.8 H), 4.23 (q, *J* = 7.6 Hz, 1 H), 4.00 (m, 1.8 H), 3.84 (td, *J* = 7.7, 3.4 Hz, 1 H), 3.67 (td, *J* = 7.4, 4.8 Hz, 0.8 H), 3.47 (d, *J* = 12.0 Hz, 0.8 H), 3.10 (ddd, *J* = 12.0, 9.0, 6.3 Hz, 1 H), 2.81 (dt, *J* = 12.4, 8.5 Hz, 0.8 H), 2.73 (dd, *J* = 13.4, 7.9 Hz, 1 H), 2.48 - 2.56 (m, 1 H), 2.11 - 2.34 (m, 3.7 H), 1.99 - 2.07 (m, 0.8 H), 1.95 (dd, *J* = 13.7, 2.1 Hz, 1 H), 1.53 - 1.79 (m, 4 H), 1.50 (s, 7.4 H), 1.45 (s, 9 H), 0.95 (d, *J* = 6.5 Hz, 2.6 H), 0.87 (d, *J* = 6.5 Hz, 3 H), 0.72 (d, *J* = 6.3 Hz, 2.6H), 0.60 (d, *J* = 6.8 Hz, 3 H); **^{13}C-NMR (100 MHz, C_6D_6):** δ = 153.1/153.1*, 139.3/139.0*, 130.5/130.5*, 127.8/127.6*, 102.7/101.8*, 79.3/79.3*, 70.1/69.1*, 67.7/67.2*, 62.8/62.5*, 44.0, 41.7, 37.7, 35.8, 31.2, 29.4, 28.9/28.7*, 27.1/26.7*, 21.2/20.1*, 20.3/19.2* ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{21}H_{33}O_3N_2$ 361.2486, found: 361.2485; **mp:** 45°C.

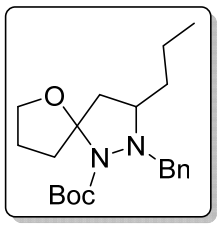
tert-Butyl-3-isopropyl-2-(4-methoxybenzyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4b)



4b (116 mg, 297 µmol, 75%, *dr* = 46:54) was synthesized according to compound **4a** with hydrazine **3b** (100 mg, 396.3 µmol), 4- pentyn-1-ol (66.7 mg, 793 µmol) and isobutyaldehyde (57.2 mg, 793 µmol) as a colorless oil.

^{1}H-NMR (500 MHz, C_6D_6): δ = 7.37 - 7.43 (m, 3.7 H), 6.80 - 6.86 (m, 3.7 H), 4.35 (q, *J* = 6.2 Hz, 0.8 H), 4.29 (d, *J* = 12.2 Hz, 1 H), 4.23 (q, *J* = 7.6 Hz, 1 H), 3.99 (dd, *J* = 12.0, 6.7 Hz, 1.8 H), 3.84 (td, *J* = 7.8, 3.4 Hz, 1 H), 3.68 (td, *J* = 7.5, 5.0 Hz, 0.8 H), 3.47 (d, *J* = 12.2 Hz, 0.8 H), 3.33 (s, 2.50 H), 3.33 (s, 3 H), 3.11 (ddd, *J* = 12.1, 8.9, 6.5 Hz, 1 H), 2.82 (dt, *J* = 12.6, 8.4 Hz, 0.8 H), 2.74 (dd, *J* = 13.6, 7.8 Hz, 1 H), 2.53 - 2.60 (m, 1 H), 2.36 (dd, *J* = 10.1, 6.7 Hz, 0.8 H), 2.23 - 2.28 (m, 2.7 H), 2.11 -2.14 (m, 1 H), 2.03 - 2.09 (m, 1 H), 1.97 (dd, *J* = 13.8, 2.3 Hz, 1 H), 1.55 - 1.80 (m, 5.7 H), 1.51 (s, 7.6 H), 1.45 - 1.49 (m, 9 H), 1.36 - 1.45 (m, 1.6 H), 0.97 (d, *J* = 6.5 Hz, 2.6 H), 0.88 (d, *J* = 6.9 Hz, 3 H), 0.74 (d, *J* = 6.9 Hz, 2.6 H), 0.63 ppm (d, *J* = 6.9 Hz, 3 H); **^{13}C-NMR (125 MHz, C_6D_6):** δ = 160.0/159.9*, 153.3/153.3*, 131.8/131.7*, 131.5/131.2*, 128.7, 114.2, 102.9/102.1*, 79.5/79.4*, 70.3/67.6*, 69.3/67.1*, 62.4/62.0, 55.1/55.1*, 44.2, 42.0, 37.9/36.0*, 31.5, 30.9, 29.7, 29.1/29.0, 27.6, 27.3, 26.9, 21.5/20.5*, 20.4/19.5* ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{22}H_{35}O_4N_2$ 391.2591, found: 39.2590.

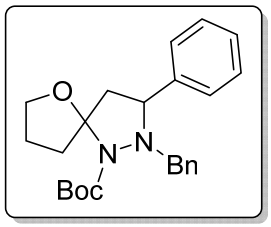
***tert*-Butyl 2-benzyl-3-(4-propylphenyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4c)**



4c (75.2 mg, 209 µmol, 46%, *dr* = 36:64) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol) and butanal (64.9 mg, 900 µmol) as a colorless oil.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.42 - 7.51 (m, 3.7 H), 7.17 - 7.25 (m, 4.5 H), 7.07 - 7.15 (m, 2.4 H), 4.20 - 4.40 (m, 2.8 H), 4.03 (d, *J* = 12.5 Hz, 1 H), 3.94 (d, *J* = 12.3 Hz, 1 H), 3.83 (td, *J* = 7.7, 3.1 Hz, 1 H), 3.68 (td, *J* = 7.4, 4.8 Hz, 0.9 H), 3.46 (d, *J* = 12.0 Hz, 0.8 H), 3.05 - 3.16 (m, 0.9 H), 2.70 - 2.89 (m, 3.8 H), 2.07 - 2.23 (m, 2.7 H), 1.98 (dtd, *J* = 13.8, 9.3, 4.8 Hz, 1 H), 1.83 (d, *J* = 13.0 Hz, 1 H), 1.68 - 1.80 (m, 2.3 H), 1.53 - 1.68 (m, 3 H), 1.48 (s, 9 H), 1.44 (s, 9 H), 1.21 - 1.41 (m, 4 H), 1.02 - 1.16 (m, 2.5 H), 0.82 - 0.95 (m, 3 H), 0.66 (t, *J* = 7.2 Hz, 3 H), 0.64 ppm (t, J = 7.2 Hz, 3 H); **^{13}C-NMR (100 MHz, C_6D_6):** δ = 153.5/153.4*, 139.5/139.3*, 130.4, 128.7/128.7*, 128.0, 127.8, 127.6, 102.8/102.0*, 79.6/79.6*, 70.3/69.5*, 62.2/62.0*, 60.5/60.4*, 47.11/44.6*, 37.8, 36.8, 36.5, 36.1, 29.1/29.0*, 28.7, 27.3/27.1*, 20.5/20.2*, 14.3/14.2* ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{21}H_{33}O_3N_2$ 361.2486, found: 361.2484.

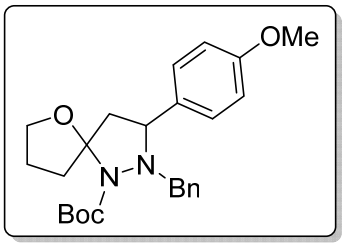
***tert*-Butyl-2-benzyl-3-phenyl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4d)**



4d (157 mg, 399 µmol, 89%, *dr = 25:75*) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol) and benzaldehyde (95.5 mg, 900 µmol,) as a white solid.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.45 - 7.56 (m, 3.4 H), 7.39 (d, *J* = 7.8 Hz, 2 H), 7.17 - 7.23 (m, 1.4 H), 6.99 - 7.15 (m, 6.3 H), 4.48 (d, *J* = 12.5 Hz, 1 H), 4.24 (dt, *J* = 9.0, 7.2 Hz, 1 H), 4.04 - 4.17 (m, 3 H), 3.71 - 3.81 (m, 1.4 H), 3.38 (td, *J* = 7.5, 4.8 Hz, 0.34 H), 3.03 (dd, *J* = 13.1, 7.8 Hz, 1 H), 2.81 (dt, *J* = 12.5, 8.5 Hz, 0.4 H), 2.71 (dt, *J* = 12.8, 8.5 Hz, 1 H), 2.25 - 2.35 (m, 0.7 H), 2.15 (dd, *J* = 13.2, 2.1 Hz, 1 H), 1.89 - 2.06 (m, 1.4 H), 1.60 - 1.72 (m, 0.6 H), 1.52 (s, 3.3 H), 1.49 (s, 9 H), 1.41 - 1.46 (m, 0.6 H), 1.25 - 1.35 ppm (m, 1 H); **^{13}C-NMR (100 MHz, C_6D_6):** δ = 153.1/152.9*, 143.2, 139.1/139.0*, 129.8, 128.9/128.9*, 128.8, 128.6, 128.0, 127.9, 127.4, 127.2, 127.0, 126.9, 102.6/101.9*, 79.9, 70.2/69.3*, 63.2/63.1*, 62.1, 48.8/46.9*, 37.7/ 35.6*, 29.1/29.0*, 27.0/27.0* ppm. **HRMS:** Calculated for $[M+H]^+$: $C_{24}H_{31}O_3N_2$ 395.2329, found: 395.2332; **mp:** 88°C.

***tert*-Butyl 2-benzyl-3-(4-methoxyphenyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4e)**

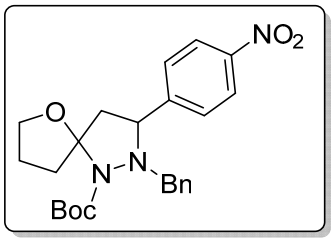


4e (155 mg, 366 µmol, 81%, *dr* = 25:75) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol) and anisaldehyde (122.5 mg, 900 µmol,) as a white solid.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.47 - 7.56 (m, 2.6 H), 7.44 (d, *J* = 8.5 Hz, 0.6 H), 7.32 (d, *J* = 8.8 Hz, 2.1 H), 7.10 - 7.15 (m, 2.6 H), 7.01 - 7.09 (m, 1.3 H), 6.80 (d, *J* = 8.5 Hz, 2.6 H), 4.48 (d, *J* = 12.5 Hz, 1 H), 4.25 (dt, *J* = 9.0, 7.2 Hz, 1 H), 4.04 - 4.18 (m, 2.8 H), 3.72 - 3.82 (m, 1.28 H), 3.45 (td, *J* = 7.4, 4.8 Hz, 0.3 H), 3.31 (s, 3 H), 3.27 (s, 0.78 H), 3.03 (dd, *J* = 13.2, 7.4 Hz, 1 H), 2.69 - 2.87 (m, 1.27 H), 2.25 - 2.38 (m, 0.6 H), 2.16 (dd, *J* = 13.1, 2.0 Hz, 1 H), 1.92 - 2.07 (m, 1.3 H), 1.64 - 1.74 (m, 0.6 H), 1.53 (s, 2.7 H), 1.50 (s, 9 H), 1.37 ppm (ddd, *J* = 12.8, 9.3, 3.8 Hz, 1.8 H); **^{13}C-NMR (100 MHz, C_6D_6):** δ = 159.3/159.2*, 153.2/152.9*, 139.2/139.1*, 134.9/134.9*, 129.9/129.8*, 128.9, 128.5, 128.1, 127.9/127.9*, 114.3/114.1*, 102.7/102.0*, 79.9, 70.2/69.3*,

62.8/62.6*, 62.0/61.9*, 55.1/55.0*, 48.7/46.9*, 37.7/35.7*, 29.1/29.0*, 27.1/27.0* ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{25}H_{33}O_4N_2$ 425.2435, found: 425.2428; **mp:** 115°C.

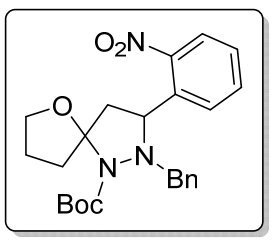
***tert*-Butyl-2-benzyl-3-(4-nitrophenyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4f)**



4f (166 mg, 377 µmol, 84%, *dr* = 43:57) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol) and 4-nitrobenzaldehyde (136 mg, 900 µmol) as a yellow solid

^{1}H-NMR (500 MHz, C_6D_6): δ = 7.81 - 7.90 (m, 3.4 H), 7.38 - 7.45 (m, 3.3 H), 7.27 (d, *J* = 8.4 Hz, 1.3 H), 6.98 - 7.15 (m, 6 H), 4.43 (d, *J* = 12.6 Hz, 1 H), 4.19 (dt, *J* = 8.4, 7.5 Hz, 1 H), 4.12 (d, *J* = 12.6 Hz, 0.6 H), 4.04 (d, *J* = 12.6 Hz, 1 H), 3.99 (q, *J* = 7.4 Hz, 1 H), 3.91 (dd, *J* = 7.6, 1.9 Hz, 1 H), 3.85 (d, *J* = 7.6 Hz, 0.6 H), 3.77 (td, *J* = 7.8, 3.4 Hz, 1 H), 3.60 (d, *J* = 12.6 Hz, 0.6 H), 3.30 (td, *J* = 7.6, 4.8 Hz, 0.6 H), 2.92 (dd, *J* = 13.4, 8.0 Hz, 1 H), 2.77 (dt, *J* = 12.6, 8.6 Hz, 0.6 H), 2.63 (dt, *J* = 13.0, 8.4 Hz, 1 H), 2.24 (dd, *J* = 13.0, 7.6 Hz, 0.6 H), 1.94 - 2.07 (m, 2.34 H), 1.90 (dd, *J* = 13.2, 2.5 Hz, 1 H), 1.66 (ddd, *J* = 12.9, 8.3, 4.8 Hz, 0.6 H), 1.52 - 1.55 (m, 0.6 H), 1.50 (s, 5.9 H), 1.46 (s, 9 H), 1.40 - 1.44 (m, 0.6 H), 1.17 ppm (ddd, *J* = 13.0, 9.2, 4.2 Hz, 1 H); **^{13}C-NMR (125 MHz, C_6D_6)**: δ = 153.1/152.1*, 150.5/150.3*, 147.6/147.5, 138.5, 129.8/129.7*, 129.1/129.0*, 128.7, 127.8/127.6*, 123.8/123.7*, 102.3/101.7*, 80.4, 70.2/69.4*, 62.8/62.5*, 62.2/62.2*, 48.7/46.5*, 37.2/35.5, 29.0/28.9*, 26.9/26.8 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{24}H_{29}O_5N_3$ 440.2180, found: 440.2182; **mp:** 58°C.

***tert*-Butyl-2-benzyl-3-(2-nitrophenyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4g)**

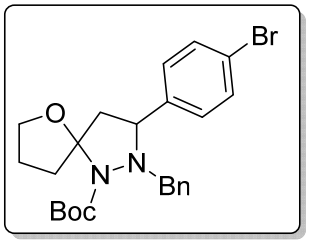


4g (150 mg, 343 µmol, 76%, *dr* = 25:75) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol) and 2-nitrobenzaldehyde (136 mg, 900 µmol) as a yellow solid.

^{1}H NMR (500 MHz, C_6D_6): δ = 7.23 - 7.53 (m, 5 H), 6.92 - 7.14 (m, 3.6 H), 6.53 - 6.71 (m, 3.2 H), 5.04 - 5.12 (m, 1.3 H), 4.42 - 4.49 (m, 1 H), 4.05 - 4.16 (m, 2.3 H), 3.83 - 3.89 (m, 0.3 H), 3.74

- 3.80 (m, 0.3 H), 3.66 - 3.73 (m, 1 H), 3.26 - 3.33 (m, 1 H), 3.11 - 3.19 (m, 0.3 H), 2.64 - 2.74 (m, 1.3 H), 2.45 - 2.56 (m, 0.3 H), 2.06 - 2.13 (m, 0.3 H), 1.93 - 2.04 (m, 2 H), 1.83 - 1.92 (m, 0.3 H), 1.52 (s, 5 H), 1.45 - 1.50 (m, 9 H), 1.40 (m, 2.3 H), 1.25 – 1.32(m, 1 H) 1.14 - 1.22 ppm (m, 1 H); **^{13}C-NMR (100 MHz, C_6D_6):** δ =153.1*/152.4, 148.3/147.9, 133.4*/133.3, 131.8/131.1*, 130.0*/129.9, 129.9*/128.8, 128.3*/128.4, 128.0/127.7*, 125.2/125.1*, 102.0/101.1*, 80.4*/80.4, 70.0*/69.1, 63.0/62.4*, 61.9/61.4*, 49.6/47.8*, 36.7*/35.1, 29.0*/28.9, 26.7*/26.5 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{24}H_{30}O_5N_3$ 440.2180, found: 440.2182; **mp:** 50°C.

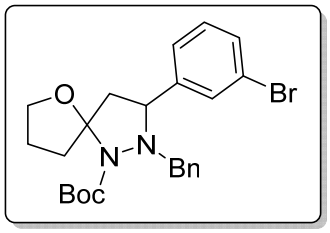
***tert*-Butyl-2-benzyl-3-(4-bromophenyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4h)**



4h (157 mg, 399 µmol, 71%, *dr* = 27:73) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol) and 4-bromobenzaldehyde (167 mg, 900 µmol,) as a white solid.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.43 (d, *J* = 7.3 Hz, 3 H), 7.19 - 7.30 (m, 4.1 H), 7.00 - 7.15 (m, 6.4 H), 4.42 (d, *J* = 12.5 Hz, 1 H), 4.16 - 4.25 (m, 1 H), 4.00 - 4.13 (m, 2 H), 3.91 (d, *J* = 6.5 Hz, 1 H), 3.86 (d, *J* = 7.3 Hz, 0.5 H), 3.76 (td, *J* = 7.8, 3.0 Hz, 0.5 H), 3.64 (d, *J* = 12.8 Hz, 0.5 H), 3.34 (td, *J* = 7.5, 4.5 Hz, 1 H), 2.95 (dd, *J* = 13.2, 7.7 Hz, 1 H), 2.78 (dt, *J* = 12.5, 8.5 Hz, 0.5 H), 2.63 (dt, *J* = 12.8, 8.5 Hz, 1 H), 2.19 - 2.27 (m, 0.5 H), 2.09 - 2.16 (m, 0.5 H), 1.89 - 2.05 (m, 2.6 H), 1.58 - 1.70 (m, 1 H), 1.50 (s, 4.5 H), 1.45 (s, 9 H), 1.27 - 1.42 (m, 2 H), 1.21 ppm (ddd, *J* = 12.9, 9.3, 4.1 Hz, 1 H); **^{13}C-NMR (100 MHz, C_6D_6):** δ = 153.1/152.7*, 142.4/142.2*, 138.8/138.8*, 131.8/131.6*, 129.8/129.7*, 129.1/129.0*, 128.9/128.9*, 128.0, 121.1/120.9*, 102.5/101.8*, 80.1/80.1*, 70.2/69.3*; 62.5/62.0*, 48.6/46.6*, 37.5/35.7, 29.0/29.0*, 27.0/27.0* ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{24}H_{30}O_3N_2Br$ 473.1434, found: 4753.1438; $C_{24}H_{30}O_3N_2{}^{81}Br$ 475.1414, found: 475.1409; **mp:** 109°C.

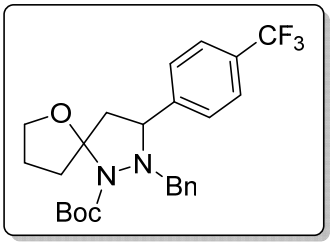
***tert*-Butyl-2-benzyl-3-(3-bromophenyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4i)**



4i (170 mg, 360 µmol, 80%, *dr* = 29:91) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol) and 3-bromobenzaldehyde (167 mg, 900 µmol,) as a white solid.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.74 - 7.89 (m, 1.4 H), 7.39 - 7.47 (m, 2.9 H), 6.95 - 7.15 (m, 7 H), 6.72 - 6.85 (m, 1.6 H) , 4.39 (d, *J* = 12.5 Hz, 1 H), 4.15 - 4.24 (m, 1 H), 3.97 - 4.10 (m, 1.9 H), 3.86 - 3.97 (m, 2.5 H), 3.75 (td, *J* = 7.8, 3.0 Hz, 1 H), 3.64 (d, *J* = 12.8 Hz, 0.45 H), 3.31 (td, *J* = 7.5, 4.6 Hz, 0.45 H), 2.95 (dd, *J* = 13.2, 7.7 Hz, 1 H), 2.77 (dt, *J* = 12.6, 8.4 Hz, 0.45 H), 2.62 (dt, *J* = 12.9, 8.5 Hz, 2 H), 2.20 - 2.28 (m, 0.45 H), 2.09 - 2.15 (m, 0.45 H), 1.89 - 2.04 (m, 2.6 H), 1.56 (s, 4 H), 1.52 (s, 9 H), 1.35 - 1.49 (m, 2.3 H), 1.21 ppm (ddd, *J* = 13.0, 9.3, 4.0 Hz, 1.45 H); **^{13}C-NMR (100 MHz, C_6D_6):** δ = 153.2/152.8*, 146.0/145.8*, 138.7/138.6*, 130.6, 130.4, 130.3, 130.2, 130.1, 130.0, 129.9, 129.8, 129.0/128.9*, 128.0, 125.8/125.5*, 123.4, 123.1*, 102.4, 101.8*, 80.2, 70.3/69.3*, 62.7/62.6*, 62.3/62.1*, 60.4, 48.8/46.7*, 37.6/35.5*, 29.9/29.0*, 27.0/27.* ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{24}H_{30}O_3N_2Br$ 473.1434, found: 475.1437; $C_{24}H_{30}O_3N_2{}^{81}Br$ 475.1414, found: 475.1409; **mp:** 105°C.

***tert*-Butyl-2-benzyl-3-(4-(trifluoromethyl)phenyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4j)**

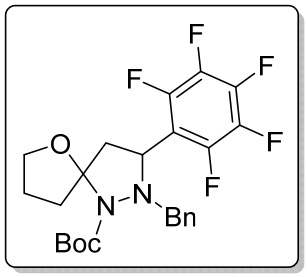


4j (185 mg, 401 µmol, 89%, *dr* = 33:67) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol) and 4-(trifluoromethyl)benzaldehyde (157 mg, 900 µmol) as a yellowish oil.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.32 - 7.49 (m, 7.1 H), 7.23 (d, *J* = 8.3 Hz, 2 H), 6.99 - 7.15 (m, 4.5 H), 4.44 (d, *J* = 12.5 Hz, 1 H), 4.11 - 4.24 (m, 1.53 H), 4.07 (d, *J* = 12.5 Hz, 1 H), 3.89 - 4.03 (m, 2.1 H), 3.76 (td, *J* = 7.8, 3.0 Hz, 1 H), 3.64 (d, *J* = 12.8 Hz, 0.5 H), 3.29 (td, *J* = 7.7, 4.5 Hz, 1 H), 2.97 (dd, *J* = 13.2, 7.9 Hz, 1 H), 2.79 (dt, *J* = 12.7, 8.6 Hz, 0.52 H), 2.61 (dt, *J* = 12.8, 8.5 Hz, 1 H), 2.27 (dd, *J* = 12.9, 7.7 Hz, 0.52 H), 2.12 (d, *J* = 13.1 Hz, 0.6 H), 1.88 - 2.03 (m, 2.7 H), 1.58 - 1.72 (m, 1.7 H), 1.52 (s, 5 H), 1.47 (s, 9 H), 1.27 - 1.39 (m, 4.2 H), 1.09 - 1.21 ppm (m, 2 H);

^{13}C-NMR (100 MHz, C_6D_6): 153.1/152.6*, 147.6/147.4*, 138.7/138.7*, 129.8/129.7*, 129.0/129.0*, 127.6/127.4*, 125.7/125.5* (q, *J* = 3.9 Hz), 102.4/101.7*, 80.2, 70.2/69.4*, 62.7/62.6*, 62.2/62.1*, 48.8/46.6*, 37.3/35.5*, 29.0/29.0*, 27.6/27.6*, 27.0/26.9* ppm; **^{19}F-NMR (282 MHz, C_6D_6):** δ = -61,0/-61.1 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{25}H_{30}O_3N_2F_3$ 463.2203, found: 463.2198.

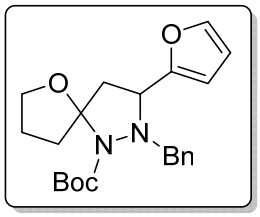
***tert*-Butyl-2-benzyl-3-(perfluorophenyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4k)**



4k (155 mg, 320 µmol, 71%, *dr* = 20:80) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol) and 2,3,4,5,6-pentafluorobenzaldehyde (176 mg, 900 µmol) as a yellowish oil.

^{1}H-NMR (500 MHz, C_6D_6): δ = 7.45 (d, *J* = 7.3 Hz, 0.35 H), 7.27 (d, *J* = 6.9 Hz, 2 H), 6.86 - 7.07 (m, 3.4 H), 4.43 - 4.57 (m, 2 H), 4.31 (d, *J* = 7.6 Hz, 0.16 H), 4.17 - 4.26 (m, 0.33 H), 4.04 (d, *J* = 11.9 Hz, 1 H), 3.93 - 4.01 (m, 1 H), 3.72 - 3.80 (m, 1 H), 3.56 (d, *J* = 12.6 Hz, 0.16 H), 3.41 - 3.48 (m, 0.16 H), 3.25 - 3.36 (m, 1 H), 2.87 (dt, *J* = 12.6, 8.6 Hz, 0.16 H), 2.29 - 2.44 (m, 2 H), 2.13 - 2.26 (m, 1.2 H), 2.05 (m, 0.35 H), 1.61 - 1.74 (m, 2.4 H), 1.57 (s, 1.7 H), 1.48 (s, 9 H), 1.28 - 1.40 ppm (m, 1.2 H); **^{13}C-NMR (125 MHz, C_6D_6):** δ = 153.0, 138.0, 130.1, 129.8, 129.1, 128.7, 128.4, 128.1, 101.8, 80.4/80.2*, 68.3, 65.4, 57.0, 36.3, 33.1, 29.0/28.9*, 27.0/26.0* ppm; **^{19}F-NMR (282 MHz, C_6D_6)**: δ = -142.1 (d, *J* = 16.1 Hz), -142.7 (d, *J* = 13.8 Hz), -156.8 (t, *J* = 20.7 Hz), -157.3 (t, *J* = 20.7 Hz), -162.89 (td, *J* = 20.7, 6.9 Hz), -163.1 (td, *J* = 20.7, 6.9 Hz) ppm **HRMS:** Calculated for $[M+H]^+$: $C_{24}H_{26}O_3N_2F_5$ 485.1858, found: 485.1860.

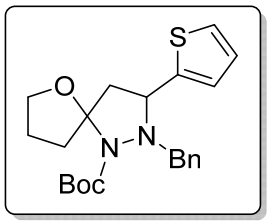
***tert*-Butyl-2-benzyl-3-(furan-2-yl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4l)**



4l (142 mg, 369 µmol, 82%, *dr* = 23:77) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol) and furfural (86.5 mg, 900 µmol) as a yellowish oil.

^{1}H-NMR (500 MHz, C_6D_6): δ = 7.43 - 7.50 (m, 2.7 H), 7.12 - 7.19 (m, 2.7 H), 7.03 - 7.10 (m, 1.7 H), 7.01 (d, *J* = 0.8 Hz, 1 H), 6.62 (s., 0.29 H), 6.41 (d, *J* = 2.7 Hz, 1 H), 6.09 (dd, *J* = 2.9, 1.7 Hz, 0.29 H), 6.05 (dd, *J* = 3.3, 1.7 Hz, 1 H), 4.33 (d, *J* = 12.6 Hz, 1 H), 3.97 - 4.26 (m, 4 H), 3.76 (td, *J* = 7.4, 2.9 Hz, 1 H), 3.69 (d, *J* = 13.0 Hz, 0.29 H), 3.55 (td, *J* = 7.5, 4.6 Hz, 0.34 H), 2.77 - 2.91 (m, 2.35 H), 2.62 (dd, *J* = 12.8, 2.1 Hz, 0.28 H), 2.46 (dd, *J* = 13.4, 2.3 Hz, 1 H), 2.10 (dd, *J* = 13.0, 7.3 Hz, 0.34 H), 1.98 - 2.07 (m, 1.34 H), 1.47 - 1.68 (m, 3.6 H), 1.45 (s, 3 H), 1.43 (s, 9 H), 1.15 - 1.37 ppm (m, 3 H); **^{13}C-NMR (125 MHz, C_6D_6):** δ = 155.7, 153.3/153.1*, 142.0/141.9*, 139.0/138.8*, 129.9/129.9*, 128.8/128.8*, 128,7, 127.9/127.9*, 111.1/111.0*, 107.7/107.1*, 102.7/101.9*, 79.8/79.8*, 61.7/61.5*, 58.9/58.8*, 45.6/44.3*, 37.4/35.7*, 29.0/28.9*, 27.1/27.0* ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{22}H_{29}O_4N_2$ 385.2122, found: 385.2141.

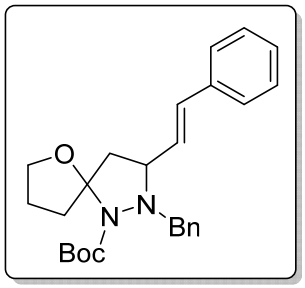
***tert*-Butyl 2-benzyl-3-(thiophen-2-yl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4m)**



4m (175 mg, 437 µmol, 97%, *dr* = 20:80) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol) and thiophene-2-carbaldehyde (101 mg, 900 µmol,) as a yellowish oil.

^{1}H-NMR (500 MHz, C_6D_6): δ = 7.48 - 7.55 (m, 2.48 H), 7.13 - 7.21 (m, 2 H), 7.04 - 7.11 (m, 1.27 H), 6.90 - 6.93 (m, 0.24 H), 6.85 (d, *J* = 5.0 Hz, 1.24 H), 6.76 (dd, *J* = 5.0, 3.4 Hz, 0.24 H), 6.72 (dd, *J* = 5.2, 3.6 Hz, 1 H), 6.64 - 6.67 (m, 1 H), 4.40 (d, *J* = 13.0 Hz, 1 H), 4.22 - 4.27 (m, 1 H), 4.13 - 4.19 (m, 1.48 H), 4.11 (d, *J* = 12.6 Hz, 0.24 H), 4.05 (d, *J* = 13.0 Hz, 1 H), 3.77 (td, *J* = 7.7, 3.3 Hz, 1 H), 3.63 (d, *J* = 12.6 Hz, 0.24 H), 3.50 (td, *J* = 7.5, 4.6 Hz, 0.24 H), 2.97 (dd, *J* = 13.0, 7.3 Hz, 1 H), 2.75 - 2.90 (m, 1.24 H), 2.39 (dd, *J* = 13.0, 1.1 Hz, 0.24 H), 2.19 - 2.26 (m, 1.24 H), 1.98 - 2.09 (m, 1.24 H), 1.67 (ddd, *J* = 12.7, 8.3, 5.0 Hz, 0.4 H), 1.53 - 1.62 (m, 2.24 H), 1.51 (s, 2.3 H), 1.49 (s, 9 H), 1.23 - 1.35 ppm (m, 1.6 H); **^{13}C-NMR (125 MHz, C_6D_6):** δ = 153.1/153.0*, 148.5, 138.9, 130.0/129.8*, 128.9/128.9*, 128.7, 128.0, 127.2, 124.8/124.6*, 124.1/123.8*, 102.9/102.0*, 79.9/79.9*, 70.3/69.5*, 61.7, 60.1/60.1*, 48.7/46.8*, 37.8/36.0*, 29.0/29.0*, 27.1/27.0* ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{22}H_{29}O_3N_2S$ 401.1893, found: 401.1881.

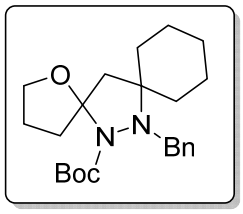
***tert*-Butyl (*E*)-2-benzyl-3-styryl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4n)**



4n (62.5 mg, 149 µmol, 33%, *dr* = 44:56) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol) and cinnamaldehyde (119 mg, 900 µmol) as a yellow solid.

^{1}H NMR (400 MHz, C_6D_6): δ = 7.46 - 7.60 (m, 3 H), 7.44 (d, *J* = 7.5 Hz, 0.5 H), 7.17 - 7.26 (m, 6 H), 6.94 - 7.15 (m, 8 H), 6.72 (d, *J* = 15.8 Hz, 1 H), 6.44 - 6.49 (m, 1 H), 5.81 (dd, *J* = 15.8, 4.5 Hz, 1 H), 4.40 (d, *J* = 12.5 Hz, 1 H), 4.23 - 4.35 (m, 1.5 H), 4.14 (d, *J* = 12.8 Hz, 0.5 H), 4.03 (d, *J* = 12.5 Hz, 1 H), 3.79 (td, *J* = 7.5, 3.0 Hz, 1 H), 3.54 - 3.75 (m, 2.5 H), 2.84 - 3.02 (m, 1.5 H), 2.75 (dd, *J* = 13.1, 7.5 Hz, 1 H), 2.00 - 2.17 (m, 2.5 H), 1.82 (dd, *J* = 13.1, 3.0 Hz, 1 H), 1.52 - 1.75 (m, 5 H), 1.45 - 1.51 (m, 13.5 H), 1.25 - 1.39 (m, 6 H), 0.82 - 1.02 ppm (m, 3 H); **^{13}C-NMR (100 MHz, C_6D_6):** δ = 153.2/153.0*, 139.2/139.2*, 138.2/138.1*, 133.4, 131.0, 139.6, 130.5, 130.3, 130.0, 130.0, 129.7, 129.2, 129.1, 129.1, 129.0, 128.9, 128.9, 128.0, 127.9, 127.8, 127.6, 127.3, 127.2, 127.1, 127.1, 102.4/102.0*, 80.6, 80.0/79.9*, 70.3/69.4*, 66..3, 63.1, 62.9, 62.8, 62.0, 61.8, 61.6, 46.9/45.7*, 37.1/35.9*, 30.8, 30.6, 29.9, 29.0/29.0*, 28.6, 27.6, 17.2, 27.1 ppm **HRMS:** Calculated for $[M+H]^+$: $C_{26}H_{33}O_3N_2$ 421.2486, found: 421.2478; mp: 101°C.

***tert*-Butyl 13-benzyl-1-oxa-13,14-diazadispiro[4.1.57.25]tetradecane-14-carboxylate (4o)**

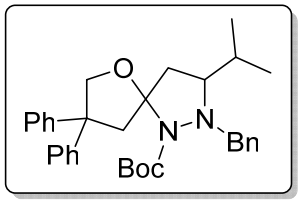


4o (60.9 mg, 158 µmol, 35%) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 4-pentyn-1-ol (75.7 mg, 900 µmol), cyclohexanone (353 mg, 3.60 mmol) and $Yb(OTf)_3$ (27.9 mg, 45 µmol) in the presence of 4Å molecular sieve as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6): δ = 7.57 (d, *J* = 7.3 Hz, 2 H), 7.22 (t, *J* = 7.6 Hz, 2 H), 7.10 - 7.15 (m, 1 H), 4.25 (q, *J* = 7.5 Hz, 1 H), 3.99 (d, *J* = 12.6 Hz, 1 H), 3.77 - 3.87 (m, 2 H), 2.88 - 2.96 (m, 1 H), 2.42 (d, *J* = 13.0 Hz, 1 H), 2.17 - 2.26 (m, 1 H), 1.89 (d, *J* = 13.4 Hz, 1 H), 1.72 - 1.80 (m, 1 H), 1.63 - 1.72 (m, 2 H), 1.44 - 1.61 (m, 4 H), 1.30 (s, 9 H), 1.16 - 1.27 ppm (m, 5 H); **^{13}C-NMR (125 MHz, C_6D_6):** δ = 154.2, 140.3, 131.0, 128.4, 127.3, 102.7, 79.0, 69.4, 65.6, 56.8, 35.7, 34.4,

28.7, 27.6, 26.7, 23.6, 23.4 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{23}H_{35}O_3N_2$ 387.2642, found: 387.2651.

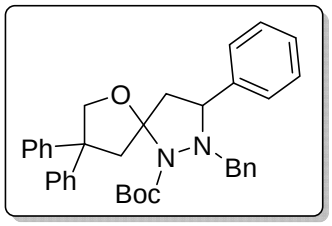
***tert*-Butyl 2-benzyl-3-isopropyl-8,8-diphenyl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4p)**



4p (194 mg, 378 µmol, 84%, *dr* = 34:66) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), alkynol **1b** (213 mg, 900 µmol) and isobutyraldehyde (64.9 mg, 900 µmol) as a white solid.

^{1}H NMR (300 MHz, C_6D_6): δ = 7.46 (d, *J* = 7.3 Hz, 3 H), 7.35 (d, *J* = 7.3 Hz, 3 H), 6.97 - 7.25 (m, 16.5 H), 4.76 - 4.85 (m, 2 H), 4.54 (d, *J* = 12.4 Hz, 0.5 H), 4.39 (d, *J* = 12.4 Hz, 0.5 H), 4.22 (m, 1 H), 4.05 (d, *J* = 11.7 Hz, 1 H), 3.92 (d, *J* = 12.1 Hz, 0.5 H), 3.40 (d, *J* = 12.1 Hz, 1 H), 2.39 - 2.56 (m, 2 H), 2.11 - 2.32 (m, 2.5 H), 1.83 - 1.92 (m, 1 H), 1.66 - 1.78 (m, 1 H), 1.50 - 1.58 (m,1 H), 1.46 (m, 13.5 H), 1.27 - 1.40(m, 1 H), 0.94 (d, J = 6.1 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 1.5 H), 0.68 (d, *J* = 6.2 Hz, 3 H), 0.40 ppm (d, *J* = 7.0 Hz, 1.5 H); **^{13}C-NMR (125 MHz, C_6D_6):** δ = 146.9*/146.1, 145,5/145,3*, 139.0*/138.8, 130.5/130.3*, 128.9, 128.6, 128.6, 128.5, 128.5, 127.9, 127.8, 127.7, 127.8*/126.7*, 126.6/126.6*, 102.7*/102.0, 79.9*/79.7, 77.3*/76.6, 67.7/66.8*, 62.6, 56.9, 50.2/48.7*, 43.5/42.0*, 30.0*/29.6, 28.9/28.8*, 21.1/20.8*, 20.1/19.5* ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{33}H_{41}O_3N_2$ 513.3112, found: 513.3103; **mp:** 137°C.

***tert*-Butyl 2-benzyl-3,8,8-triphenyl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4q)**

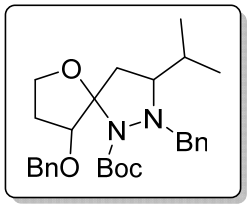


4q (197 mg, 360 µmol, 80%, *dr* = 29:71) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), alkynol **1b** (213 mg, 900 µmol) and benzaldehyde (95.5 mg, 900 µmol) as a white solid.

^{1}H NMR (500 MHz, C_6D_6): δ = 7.46 - 7.53 (m, 3.8 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.18 - 7.27 (m, 3.8 H), 6.90 - 7.14 (m, 20 H), 4.78 - 4.83 (m, 1 H), 4.72 - 4.77 (m, 1.4 H), 4.50 - 4.57 (m, 1.4 H),

4.21 (dd, *J* = 12.4, 6.3 Hz, 0.8 H), 4.08 (d, *J* = 11.9 Hz, 2 H), 3.87 - 3.98 (m, 1.4 H), 3.67 (d, *J* = 12.6 Hz, 0.4 H), 2.82 ppm (dd, *J* = 13.8, 7.6 Hz, 1 H)2.46 - 2.46 (m, 1 H), 2.46 (d, *J* = 12.6 Hz, 0.4 H), 2.14 - 2.17 (m, 0.4 H), 2.04 – 2.08 (m, 0.4 H), 1.99 (d, *J* = 12.6 Hz, 1 H), 1.79 (d, *J* = 13.4 Hz, 1 H), 1.48 - 1.50 (m, 13 H); **^{13}C-NMR (75 MHz, C_6D_6):** δ = 153.4*/152.8, 146.9, 146.7, 146.6, 145.7, 145.3, 143.5, 142.5, 139.0/138.8*, 129.8, 129.6, 129.2, 129.2, 129.0, 129.0, 128.9, 128.9, 128.9, 128.8, 128.8, 128.7, 128.3, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.3, 127.2, 127.0, 126.9, 126.8, 126.8, 126.7, 126.7, 102.7/102.1*, 80.4/80.3*, 77.1*/76.3, 65.4/63.1, 62.1/61.2*, 56.9*/56.8, 53.8/52.2*, 50.5*/47.8, 35.6*/35.0, 31.8*/31.7, 31.0/30.8*, 29.1*/29.0 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{36}H_{39}O_3N_2$ 547.2955, found: 547.2949; **mp:** 73°C.

***tert*-Butyl-2-benzyl-9-(benzyloxy)-3-isopropyl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4r)**

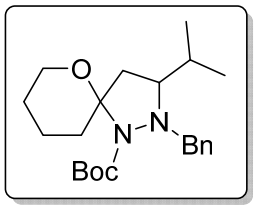


4r (174 mg, 374 µmol, 83%, *dr* = 44:56) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), alkynol **1c** (171 mg, 900 µmol) and isobutyraldehyde (64.9 mg, 900 µmol) as a colorless oil.

^{1}H-NMR (500 MHz, C_6D_6): δ = 7.38 - 7.48 (m, 3.5 H), 7.28 - 7.34 (m, 2 H), 7.17 - 7.24 (m, 12.5 H), 7.05 - 7.15 (m, 5 H), 5.17 (t, *J* = 6.3 Hz, 0.7 H), 4.85 (t, *J* = 7.3 Hz, 1 H), 4.43 (d, *J* = 11.9 Hz, 1 H), 4.11 - 4.34 (m, 5 H), 3.98 - 4.06 (m, 1.7 H), 3.91 (td, *J* = 8.2, 3.4 Hz, 0.7 H), 3.77 (td, *J* = 7.8, 3.4 Hz, 1 H), 3.56 (d, *J* = 11.9 Hz, 1 H), 2.98 - 3.09 (m, 1.7 H), 2.54 (d, *J* = 9.6 Hz, 1 H), 2.46 (dtd, *J* = 11.9, 6.9, 3.1 Hz, 1 H), 2.37 (dd, *J* = 10.1, 7.5 Hz, 1 H), 2.15 - 2.30 (m, 2 H), 2.02 (d, *J* = 13.8 Hz, 1 H), 1.50 - 1.78 (m, 2.7 H), 1.47 (s, 9 H), 1.44 (s, 6.3 H), 0.96 (d, *J* = 6.5 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 2.5 H), 0.75 (d, *J* = 6.9 Hz, 3 H), 0.65 (d, *J* = 6.5 Hz, 2.5 H) ppm; **^{13}C-NMR (125 MHz, C_6D_6):** 153.8/153.7*, 139.4/139.3*, 139.2/139.3*, 130.7/130.7*, 129.0, 128.8, 128.6, 128.5, 128.3, 128.1, 127.9, 127.8, 105.5/103.5*, 82.2/81.9*, 79.8/, 79.7*, 72.8/72.4*, 68.2/68.0*, 67.2, 37.3, 35.1, 33.6, 33.1, 31.0, 29.9, 29.0/28.9*, 21.4/20.7*, 20.3/19.8*;

HRMS: Calculated for $[M+H]^+$: $C_{28}H_{39}O_4N_2$ 467.2904, found: 467.2905.

***tert*-Butyl 2-benzyl-3-isopropyl-6-oxa-1,2-diazaspiro[4.5]decane-1-carboxylate (4s)**



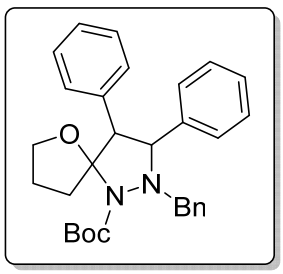
4s (126 mg, 338 µmol,75%) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 450 µmol), 5-hexyn-1-ol (88.7 mg, 900 µmol) and isobutyraldehyde (64.9 mg, 900 µmol) as a diastereomeric mixture of 25:75. The diastereomers were separated by column chromatography (CH:EtOAc = 30:1) obtaining *anti*-**4s** (95.1 mg, 254 µmol, 56%) and *syn*-**4s** (31.2 mg, 83.3 µmol, 19%) as colorless oils. The minor diastereomer slowly crystallized at -12°C.

Major diastereomer: **^{1}H-NMR (500 MHz, C_6D_6):** δ = 7.53 (d, *J* = 7.3 Hz, 5 H), 7.21 (t, *J* = 7.5 Hz, 5 H), 7.10 - 7.15 (m, 2 H), 4.36 (d, *J* = 12.2 Hz, 1 H), 4.01 (d, *J* = 12.6 Hz, 1 H), 3.74 - 3.80 (m, 1 H), 3.48 - 3.55 (m, 1 H), 2.78 - 2.88 (m, 2 H), 2.25 (dd, *J* = 12.8, 7.8 Hz, 2 H), 1.62 - 1.69 (m, 2 H), 1.47 (s, 9 H), 1.27 - 1.43 (m, 5 H), 0.73 ppm (dd, *J* = 16.3, 6.7 Hz, 6 H); **^{13}C-NMR (125 MHz, C_6D_6):** δ = 154.7, 140.2, 130.6, 127.7, 96.5, 79.5, 68.3, 65.5, 63.6, 43.0, 32.5, 32.3, 28.9, 25.7, 22.3, 20.2 18.1 ppm.

Minor diastereomer: **^{1}H-NMR (500 MHz, C_6D_6):** δ = 7.52 (d, *J* = 7.3 Hz, 2 H), 7.21 (t, *J* = 7.5 Hz, 2 H), 7.09 - 7.15 (m, 1 H), 4.08 (d, *J* = 11.9 Hz, 1 H), 3.76 - 3.83 (m, 1 H), 3.46 (d, *J* = 12.2 Hz, 1 H), 3.28 (td, *J* = 11.9, 2.7 Hz, 1 H), 3.00 - 3.11 (m, 1 H), 2.29 - 2.37 (m, 2 H), 2.08 - 2.19 (m, *J* = 10.4, 6.6, 6.6 Hz, 1 H), 1.69 - 1.76 (m, 1 H), 1.58 - 1.69 (m, 4 H), 1.52 (s, 9 H), 1.14 - 1.43 (m, 9 H), 0.91 (d, *J* = 6.5 Hz, 5 H), 0.65 ppm (d, *J* = 6.5 Hz, 3 H); **^{13}C-NMR (125 MHz, C_6D_6):** δ = 153.0, 139.3, 130.8, 128.0, 95.2, 79.4, 67.6, 65.3, 63.1, 44.1, 36.1, 34.1, 32.7, 30.9, 30.6, 29.9, 29.1, 27.6, 25.7, 23.1, 21.7, 20.3 ppm;

HRMS: Calculated for $[M+H]^+$: $C_{22}H_{35}O_3N_2$ 375.2642, found: 375.2648.

***tert*-Butyl 2-benzyl-3,4-diphenyl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4t)**

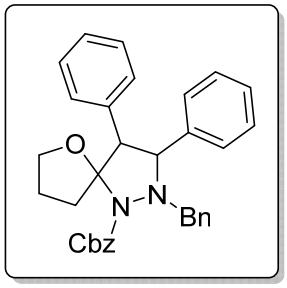


4t (49.6 mg, 105 µmol, 27%, *dr* = 42:58) was synthesized according to compound **4a** with hydrazine **3a** (100 mg, 390 µmol), alkynol **1e** (141 mg, 780 µmol) and isobutyraldehyde (56.2 mg, 780 µmol) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6): δ = 7.41 - 7.48 (m, 3.7 H), 7.38 (d, *J* = 7.3 Hz, 2 H), 7.23 - 7.32 (m, 5.4 H), 7.18 (m. 0.7 H), 6.99 - 7.13 (m, 17 H),

6.82 - 6.99 (m, 14 H), 6.74 - 6.81 (m, 1 H), 5.08 (d, *J* = 7.3 Hz, 1 H), 4.58 - 4.66 (m, 1.4 H), 4.29 - 4.42 (m, 3.7 H), 4.22 (d, *J* = 7.6 Hz, 1.7 H), 4.10 (d, *J* = 13.0 Hz, 1 H), 3.98 (td, *J*=7.9, 5.2 Hz, 1.7 H), 3.78 (br. s., 1 H), 3.54 - 3.65 (m, 2 H), 3.38 (q, *J* = 7.6 Hz, 0.7 H), 3.28 (td, *J* = 7.6, 5.2 Hz, 1 H), 3.22 (d, *J* = 10.7 Hz, 0.7 H), 3.13 (ddd, *J* = 12.7, 8.3, 2.7 Hz, 0.7 H), 2.91 (br. s., 1 H), 2.55 (br. s., 0.7 H), 2.23 - 2.37 (m, 1 H), 1.98 (br. s., 0.7 H), 1.76 - 1.86 (m, 1 H), 1.53 - 1.64 (m, 3 H), 1.51 (s, 7 H), 1.47 (s, 9 H), 1.40 (s, 14 H), 1.22 - 1.34 (m, 1.4 H), 0.88 - 0.99 ppm (m, 1.4 H); **^{13}C NMR (125 MHz, C_6D_6):** δ = 153.7*/153.3, 140.4, 138.8/138.4*, 138.0/137.7*, 136.1, 134.8, 134.2, 133.0, 131.6, 131.6, 130.9, 130.5, 129.8, 129.7, 129.2, 128.9, 128.7, 128.5, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 126.9, 103.3/103.0*, 80.3/80.1*, 73.5, 69.6, 68.9, 67.8, 63.0, 37.4, 32.6, 32.1, 29.2, 29.0, 28.9, 25.9, 25.5, 25.5 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{30}H_{35}O_3N_2$ 471.2642, found: 471.2643.

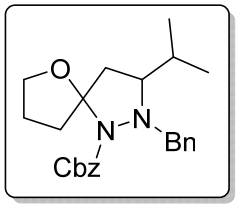
Benzyl 2-benzyl-3,4-diphenyl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4u)



4u (103 mg, 203 µmol, 52%, *dr* = 44:56) was synthesized according to compound **4a** with hydrazine **3b** (100 mg, 390 µmol), alkynol **1e** (141 mg, 780 µmol) and benzaldehyde (82.8 mg, 780 µmol) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6): δ = 6.83 - 7.43 (m, 34 H), 5.22 - 5.40 (m, 3.5 H), 5.08 (d, *J* = 6.9 Hz, 0.7 H), 5.04 (d, *J* = 12.2 Hz, 1 H), 4.88 (d, *J* =10.3 Hz, 0.7 H), 4.59 (dd, *J* = 19.1, 11.5 Hz, 2 H), 4.34 (dd, *J* = 12.0, 5.2 Hz, 2 H), 4.26 (d, *J* = 7.3 Hz, 2 H), 4.11 (br. s., 1 H), 3.93 (td, *J* = 8.0, 5.0 Hz, 1.5 H), 3.74 (br. s., *J* = 2.3 Hz, 0.7 H), 3.59 (br. s., 0.7 H), 3.51 (d, *J* = 7.6 Hz, 1 H), 3.36 (q, *J* = 7.4 Hz, 1 H), 3.14 - 3.30 (m, 1.7 H), 3.08 (ddd, *J* = 12.8, 8.2, 2.3 Hz, 1 H), 2.78 - 2.95 (m, 0.7 H), 2.49 - 2.71 (m, 0.7 H), 2.23 - 2.36 (m, 1 H), 1.96 - 2.17 (m, 0.7 H), 1.72 - 1.85 (m, 1 H), 1.44 - 1.62 (m, 2.5 H), 1.17 - 1.34 (m, 1 H), 0.91 ppm (br. s., 1 H); **^{13}C NMR (125 MHz, C_6D_6):** δ = 154.3*/153.9, 140.1, 138.4, 137.9, 137.8, 137.6, 135.8, 134.5, 133.0, 131.5, 131.5, 130.8, 130.4, 129.8, 129.2, 129.1, 129.0, 129.0, 128.9, 128.8, 128.7, 128.5, 128.5, 128.3, 128.1, 128.0, 128.0, 127.9, 127.9, 127.7, 127.5, 127.4, 127.4, 127.3, 127.0, 103.5*/103.0, 73.5, 69.0, 68.1, 67.5, 67.4, 65.2, 62.8, 37.3*/32.0, 25.5*/25.3 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{33}H_{33}O_3N_2$ 505.2486, found: 505.2481.

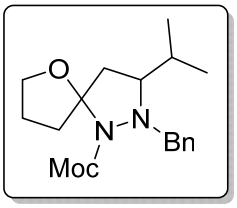
Benzyl 2-benzyl-3-isopropyl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4v)



4v (119 mg, 302 µmol, 78%, *dr* = 50:50) was synthesized according to compound **4a** with hydrazine **3b** (100 mg, 390 µmol), alkynol **1a** (65.6 mg, 780 µmol) and isobutyraldehyde (56.2 mg, 780 µmol) as a colorless oil.

^{1}H-NMR (300 MHz, C_6D_6): δ = 7.28 - 7.53 (m, 8 H), 7.05 - 7.23 (m, 12 H), 5.03 - 5.32 (m, 4 H), 4.19 - 4.46 (m, 3 H), 3.97 - 4.12 (m, 2 H), 3.90 (td, *J* = 7.8, 3.5 Hz, 1 H), 3.73 (td, *J* = 7.2, 5.3 Hz, 1 H), 3.54 (d, *J* = 12.4 Hz, 1 H), 3.04 - 3.21 (m, 1 H), 2.70 - 2.91 (m, 2 H), 2.60 (td, *J* = 8.3, 2.0 Hz, 1 H), 1.96 - 2.44 (m, 7 H), 1.33 - 1.87 (m, 6 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.77 (d, *J* = 6.2 Hz, 3 H), 0.63 ppm (d, *J* = 6.6 Hz, 3 H); **^{13}C-NMR (75 MHz, C_6D_6):** δ = 153.9/153.8*, 139.0/138.7*, 138.0/137.9*, 130.7/130.6*, 128.9, 128.6, 128.6, 128.5, 128.3, 128.0, 127.9, 103.1/102.3*, 70.5, 69.5, 68.1, 67.5, 67.2/67.2*, 63.3/62.8*, 53.7, 43.8/41.6*, 37.8/35.9*, 31.2/29.6*, 27.2/26.8*, 21.4, 20.5, 20.3, 19.3 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{24}H_{31}O_3N_2$ 395.2329, found: 395.2325.

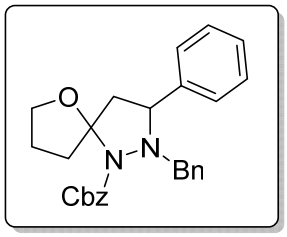
Methyl 2-benzyl-3-isopropyl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4w)



4w (138 mg, 433 µmol, 75%, *dr* = 42:58) was synthesized according to compound **4a** with hydrazine **3c** (100 mg, 555 µmol), alkynol **1a** (93.4 mg, 1.11 mmol) and isobutyraldehyde (80.0 mg, 1.11 mmol) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.32 - 7.41 (m, 3 H), 7.17 - 7.31 (m, 5 H), 4.03 - 4.19 (m, 6 H), 3.76 - 3.95 (m, 8 H), 3.68 (s, 2 H), 3.61 (s, 3 H), 2.81 - 2.92 (m, 1 H), 2.64 - 2.76 (m, 2 H), 2.53 - 2.62 (m, 1 H), 2.37 (m, 1 H), 2.11 - 2.28 (m, 4 H), 1.76 - 2.03 (m, 4 H), 1.40 - 1.53 (m, 1 H), 0.65 - 0.74 (m, 10 H) ppm; **^{13}C-NMR (75 MHz, $CDCl_3$):** δ =154.0/153.9*, 137.9/137.6*, 129.8/129.7*, 127.9/127.8*, 127.3/127.1*, 102.3/, 101.5*, 69.5/68.9*, 67.3/66.8*, 52.1/52.0*, 42.9, 37.0, 35.2, 30.2, 28.9, 26.5/26.1*, 20.5/19.6*, 19.9/18.9* ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{18}H_{27}O_3N_2$ 319.2016, found: 319.2011.

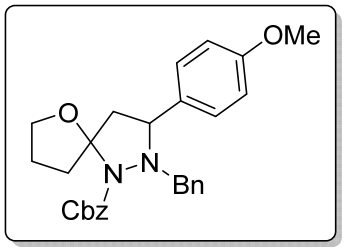
Benzyl 2-benzyl-3-phenyl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4x)



4x (114 mg, 265 µmol, 68%, *dr* = 42:58) was synthesized according to compound **4a** with hydrazine **3b** (100 mg, 390 µmol), alkynol **1a** (65.6 mg, 780 µmol) and benzaldehyde (82.8 mg, 780 µmol) as a colorless oil.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.52 (d, *J* = 7.8 Hz, 0.67 H), 7.38 - 7.45 (m, 2.66 H), 7.32 (dd, *J* = 11.8, 7.5 Hz, 4.8 H), 6.95 - 7.14 (m, 12 H), 5.21 - 5.31 (m, 1.3 H), 5.09 - 5.18 (m, 3.2 H), 5.02 (d, *J* = 12.3 Hz, 1 H), 4.47 (d, *J* = 12.8 Hz, 1 H), 3.98 - 4.26 (m, 4 H), 3.70 - 3.82 (m, 1.32 H), 3.36 (td, *J* = 7.4, 5.3 Hz, 0.32 H), 3.00 (dd, *J* = 13.2, 7.7 Hz, 1 H), 2.62 - 2.80 (m, 1.3 H), 2.20 - 2.35 (m, 0.64 H), 2.13 (dd, *J* = 13.2, 2.4 Hz, 1 H), 1.84 - 2.03 (m, 1.34 H), 1.65 (ddd, *J* = 12. 9, 8.2, 5.0 Hz, 0.32 H), 1.25 - 1.55 ppm (m, 2.8 H); **^{13}C-NMR (100 MHz, C_6D_6):** δ = 153.8/153.4*, 142.9/142.8*, 138.7/138.6*, 137.9/137.9*, 129.8/129.8*, 129.0, 129.0, 128.9, 128.8, 128.7, 128.0/127.9*, 127.3/127.2*, 127.0/127.0*, 102.9/102.2*, 70.4/69.4*, 67.3/67.3*, 66.3, 63.3/63.2*, 62.3/62.2*, 48.5/46.7*, 37.7/35.6*, 26.9/26.9* ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{27}H_{29}O_3N_2$ 429.2173, found: 429.2166.

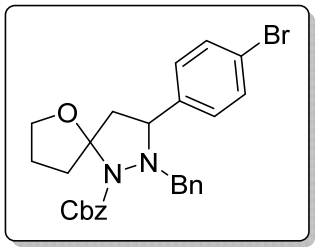
Benzyl 2-benzyl-3-(4-methoxyphenyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4y)



4y (172 mg, 374 µmol, 96%, *dr* = 37:63) was synthesized according to compound **4a** with hydrazine **3b** (100 mg, 390 µmol), alkynol **1a** (65.6 mg, 780 µmol) and anisaldehyde (106 mg, 780 µmol) as a colorless oil.

^{1}H NMR (300 MHz, C_6D_6): δ = 7.37 - 7.48 (m, 3.4 H), 7.20 - 7.36 (m, 4 H), 6.96 - 7.19 (m, 9 H), 6.64 - 6.80 (m, 3 H), 5.10 - 5.32 (m, 1.8 H), 5.03 (d, *J* = 12.4 Hz, 1 H), 4.45 (d, *J* = 12.8 Hz, 1 H), 3.95 - 4.26 (m, 4 H), 3.68 - 3.82 (m, 1.8 H), 3.36 - 3.50 (m, 1.4 H), 3.27 - 3.33 (m, 4.7 H), 3.00 (dd, *J* = 13.0, 7.5 Hz, 1 H), 2.68 (m, 1.4 H), 2.20 - 2.43 (m, 1 H), 2.16 (dd, *J* = 13.2, 2.2 Hz, 1 H), 2.08 (m, 0.8 H), 1.93 (m, 1.8 H), 1.30 - 1.74 ppm (m, 5 H); **^{13}C NMR (75 MHz, C_6D_6):** δ = 159.3/159.2*, 153.8*/153.5, 138.8/138.7*, 137.9/137.9*, 134.6*/134.4, 129.9*/129.8, 129.0/128.8*, 128.7, 128.0/127.9*, 114.3/114.2*, 103.0/102.4*, 70.3*/69.4, 67.3/66.2*, 62.9*/62.7, 62.2*/62.0, 55.1/55.0*, 48.3/46.6*, 37.8*/35.7, 27.4*/26.9 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{28}H_{31}O_4N_2$ 459.2278, found: 459.2273.

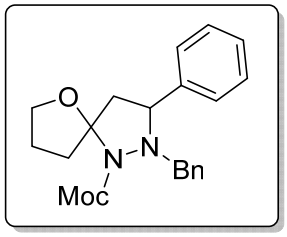
Benzyl 2-benzyl-3-(4-bromophenyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4z)



4z (156 mg, 308 µmol, 79%, *dr* = 34:66) was synthesized according to compound **4a** with hydrazine **3b** (100 mg, 390 µmol), alkynol **1a** (65.6 mg, 780 µmol) and 4-bromobenzaldehyde (106 mg, 780 µmol) as a colorless oil

^{1}H NMR (300 MHz, C_6D_6): δ = 7.36 (d, *J*=7.0 Hz, 3 H), 7.17 - 7.32 (m, 7 H), 6.94 - 7.13 (m, 12 H), 5.25 (d, *J* = 12.1 Hz, 1.5 H), 5.06 - 5.14 (m, 0.5 H), 4.99 (d, *J* = 12.1 Hz, 1 H), 4.41 (d, *J* = 12.8 Hz, 1 H), 4.18 (dt, *J* = 9.0, 7.0 Hz, 1 H), 3.85 - 4.11 (m, 4 H), 3.75 (td, *J* = 7.8, 3.1 Hz, 1 H), 3.65 (d, *J* = 12.8 Hz, 0.5 H), 3.34 (td, *J* = 7.5, 4.8 Hz, 0.5 H), 2.92 (dd, *J* = 13.2, 7.7 Hz, 1 H), 2.72 (dt, *J* = 12.8, 8.4 Hz, 0.5 H), 2.61 (dt, *J* = 12.8, 8.4 Hz, 1 H), 2.16 - 2.26 (m, 0.5 H), 2.07 - 2.15 (m, 0.5 H), 1.85 - 2.04 (m, 2.5 H), 1.65 (ddd, *J* = 12.9, 8.3, 5.1 Hz, 0.5 H), 1.34 - 1.54 (m, 2 H), 1.23 ppm (ddd, *J* = 13.1, 9.2, 4.4 Hz, 1 H); **^{13}C NMR (75 MHz, C_6D_6):** δ = 153.7*/153.3, 142.0*/141.8, 138.4/138.4*, 137.7*/137.7, 131.9/131.7*, 129.8*/129.7, 129.1*/129.0, 129.0*/128.9, 128.8, 128.8, 128.7, 128.6, 128.5, 121.2/121.0*, 102.7/102.1*, 70.4*/69.5, 67.4/67.4*, 62.6/62.2*, 48.2/46.4*, 37.5*/35.6, 26.9*/26.8 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{27}H_{28}O_3N_2Br$ 507.1278, found: 507.1290; calculated for $[M+H]^+$: $C_{27}H_{28}O_3N_2{}^{81}Br$ 509.1257, found: 509.1260.

Methyl 2-benzyl-3-phenyl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4aa)

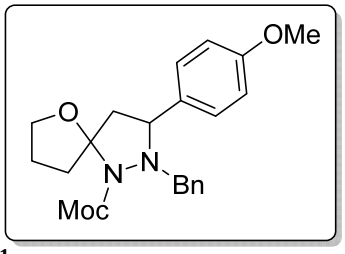


4aa (147 mg, 416 µmol, 75%, *dr* = 30:70) was synthesized according to compound **4a** with hydrazine **3c** (100 mg, 555 µmol), alkynol **1a** (93.4 mg, 1.11 mmol) and benzaldehyde (118 mg, 1.11 mmol) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6): δ = 7.51 (d, *J* = 8.0 Hz, 0.5 H), 7.40 - 7.47 (m, 2.5 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 6.98 - 7.20 (m, 8 H), 4.40 (d, *J* = 13.0 Hz, 1 H), 4.22 (dt, *J* = 8.4, 7.5 Hz, 1 H), 4.03 - 4.17 (m, 2.6 H), 3.78 (td, *J* = 7.8, 3.1 Hz, 1 H), 3.72 - 3.75 (m, 0.3 H), 3.50 (s, 0.7 H), 3.47 (s, 3 H), 3.41 (td, *J* = 7.5, 5.0 Hz, 3 H), 2.98 (dd, J = 13.0, 7.6 Hz, 1 H), 2.76 (dt, *J* = 12.6, 8.4 Hz, 0.3 H), 2.69 (dt, *J* = 13.0, 8.4 Hz, 1 H), 2.30 - 2.36 (m, 0.3 H), 2.24 - 2.30 (m, 0.3 H), 2.14 (dd, *J* = 13.4, 2.7 Hz, 1 H), 1.92 - 2.06 (m, 1.3 H), 1.68 (ddd, *J* = 13.0, 8.4, 5.4 Hz, 0.3 H), 1.43 - 1.56 (m, 1.6 H), 1.34 ppm (ddd, *J* = 13.0, 9.2, 4.2 Hz, 1.3 H); **^{13}C**

NMR (125 MHz, C_6D_6): δ = 154.2*/153.9, 142.7*/138.5, 129.7*/129.6, 128.7, 128.6, 128.5, 127.8, 127.7, 127.2*/127.1, 126.9*/126.8, 102.6/102.0*, 70.1*/69.2, 63.3*/63.3, 62.1/61.9*, 52.2/52.2*, 48.4/46.5*, 37.4*/35.4, 26.8*/26.7 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{21}H_{25}O_3N_2$ 353.1860, found: 353.1857.

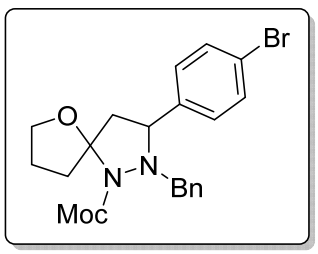
Methyl 2-benzyl-3-(4-methoxyphenyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4ab)



4ab (168 mg, 438 µmol, 79%, *dr* = 26:74) was synthesized according to compound **4a** with hydrazine **3c** (100 mg, 555 µmol), alkynol **1a** (93.4 mg, 1.11 mmol) and anisaldehyde (151 mg, 1.11 mmol) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6): δ = 7.39 - 7.50 (m, 3 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.08 - 7.14 (m, 2.6 H), 7.03 (m, 1.6 H), 6.72 - 6.79 (m, 2.6 H), 4.40 (d, *J* = 12.6 Hz, 1 H), 4.24 (dt, *J* = 8.6, 7.2 Hz, 1 H), 4.03 - 4.16 (m, 2.6 H), 3.79 (td, *J* = 7.6, 3.1 Hz, 1 H), 3.75 (d, *J* = 12.6 Hz, 0.3 H), 3.51 (s, 1 H), 3.49 (s, 3 H), 3.31 (s, 3 H), 3.27 - 3.29 (m, 1 H), 2.98 (dd, *J* = 13.2, 7.5 Hz, 1 H), 2.69 - 2.81 (m, 1.3 H), 2.35 (d, *J* = 1.5 Hz, 0.3 H), 2.23 - 2.29 (m, *J* = 7.3 Hz, 0.3 H), 2.16 (dd, *J* = 13.2, 2.5 Hz, 1 H), 1.94 - 2.08 (m, *J* = 6.7, 3.6 Hz, 1.3 H), 1.60 - 1.74 (m, 0.6 H), 1.46 - 1.59 (m, 1.6 H), 1.37 - 1.45 ppm (m, 1.3 H); **^{13}C-NMR (125 MHz, C_6D_6):** δ = 159.4/159.3*, 154.4*/154.1, 138.9/138.8*, 134.6, 129.9, 129.8, 129.7, 128.9, 128.8, 128.8, 128.7, 128.5, 128.1, 128.0, 127.9, 114.4/114.3*, 102.9/102.4*, 70.3*/69.4, 63.2*/63.0, 62.1/61.9*, 55.1/55.0*, 52.4/52.4*, 48.5/46.6*, 37.7*/35.7, 27.0*/27.0 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{22}H_{27}O_4N_2$ 383.1965, found: 383.1967.

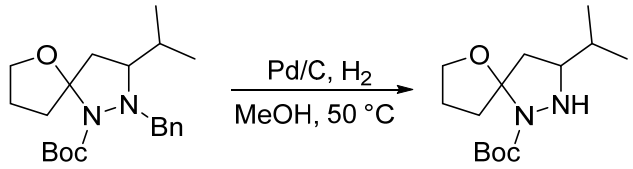
Methyl 2-benzyl-3-(4-bromophenyl)-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (4ac)



4aa (182 mg, 422 µmol, 76%, *dr* = 32:68) was synthesized according to compound **4b** with hydrazine **3c** (100 mg, 555 µmol), alkynol **1a** (93.4 mg, 1.11 mmol) and 4-bromobenzaldehyde (205 mg, 1.11 mmol) as a colorless oil.

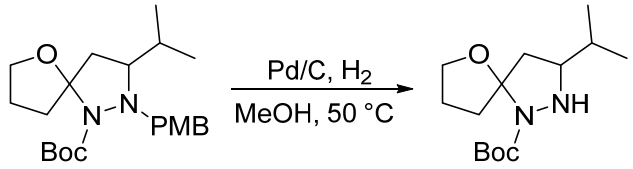
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 - 7.47 (m, 6 H), 7.20 - 7.34 (m, 7.5 H), 4.35 (d, *J* = 12.5 Hz, 1 H), 4.01 - 4.25 (m, 4.5 H), 3.87 - 3.98 (m, 1.5 H), 3.80 (s, 1.5 H), 3.78 (s, 3 H), 3.66 (td, *J* = 7.5, 5.1 Hz, 0.5 H), 3.14 (dd, *J* = 13.2, 7.7 Hz, 1 H), 2.73 - 2.86 (m, *J* = 12.7, 8.3, 8.3 Hz, 0.5 H), 2.69 (dd, *J* = 13.1, 7.5 Hz, 0.5 H), 2.48 - 2.59 (m, 1.5 H), 2.39 (dd, *J* = 13.2, 2.1 Hz, 1 H), 2.07 - 2.24 (m, 1.5 H), 2.02 (ddd, *J* = 12.8, 8.2, 4.9 Hz, 0.5 H), 1.77 - 1.91 (m, 1.5 H), 1.44 - 1.53 ppm (m, 1 H); **^{13}C-NMR (100 MHz, C_6D_6):** δ = 153.5*/153.3, 140.8*/140.5, 137.2/137.0*, 131.2/131.0*, 129.1*/128.9, 128.2*/128.1, 127.9, 127.5*/127.3, 120.4/120.2*, 101.9/101.3*, 69.5*/68.8, 61.8*/61.6, 61.1*/61.0, 52.4/52.3*, 47.4/46.0*, 36.8*/34.8, 26.2*/26.0 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{21}H_{24}O_3N_2Br$ 431.0965, found: 431.0968; calculated for $[M+H]^+$: $C_{21}H_{24}O_3N_2{}^{81}Br$ 433.0944, found: 433.0938.

***tert*-Butyl 3-isopropyl-6-oxa-1,2-diazaspiro[4.4]nonane-1-carboxylate (5)**



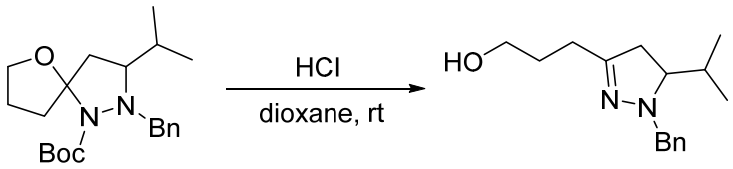
To a solution of **4a** (100 mg, 277 µmol) in 3 mL of MeOH was added palladium on charcoal (100 mg, 10 wt%), the flask was equipped with a hydrogen-filled ballon and stirred for 2 h at 50°C. The reaction mixture was filtrated over a pad of celite and concentrated in vacuo. The deprotected spirocyclic compound **5** (74.1 mg, 274µmol, 99%) could be obtained after column chromatography (CH:EtOAc = 25:1 to 10:1) as a white solid.

^{1}H NMR (500 MHz, C_6D_6): δ = 4.21 - 4.28 (m, 0.5 H), 4.17 (q, *J* = 7.0 Hz, 1 H), 3.92 (br. s., 1 H), 3.76 - 3.78 (m, 0.5 H), 3.62 (td, *J* = 7.6, 5.5 Hz, 1 H), 2.95 - 3.03 (m, 1 H), 2.82 - 2.89 (m, 4 H), 2.57 - 2.65 (m, 1.5 H), 2.47 - 2.56 (m, 0.5 H), 2.13 - 2.24 (m, 1 H), 1.99 (m, 1.5 H), 1.76 - 1.89 (m, 1 H), 1.53 - 1.72 (m, 3 H), 1.41 - 1.51 (m, 13.5 H), 1.16 - 1.25 (m, 1.5 H), 0.81 - 0.87 (m, 4.5 H), 0.61 - 0.67 ppm (m, 4.5 H); **^{13}C-NMR (100 MHz, C_6D_6):** δ =153.2, 102.7*/101.3, 79.8/79.7*, 69.7*/69.5, 63.5*/62.5, 49.7*/48.3, 36.1*/34.5, 32.0/31.3*, 29.0*/29.0, 27.2*/26.9, 20.9*/20.8, 19.9*/19.8 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{14}H_{27}O_3N_2$ 271.2016, found: 271.2011; **mp:** 56°C.



To a solution of **4b** (100 mg, 256 µmol) in 3 mL of MeOH was added palladium on charcoal (100 mg, 10 wt%), the flask was equipped with a hydrogen-filled ballon and stirred for 2 h at 50°C. The reaction mixture was filtrated over a pad of celite and concentrated in vacuo. The deprotected spirocyclic compound **5** (66.5 mg, 246µmol, 96%) could be obtained after column chromatography (CH:EtOAc = 25:1 to 10:1) as a white solid.

3-(1-Benzyl-5-isopropyl-4,5-dihydro-1H-pyrazol-3-yl)propan-1-ol (6)

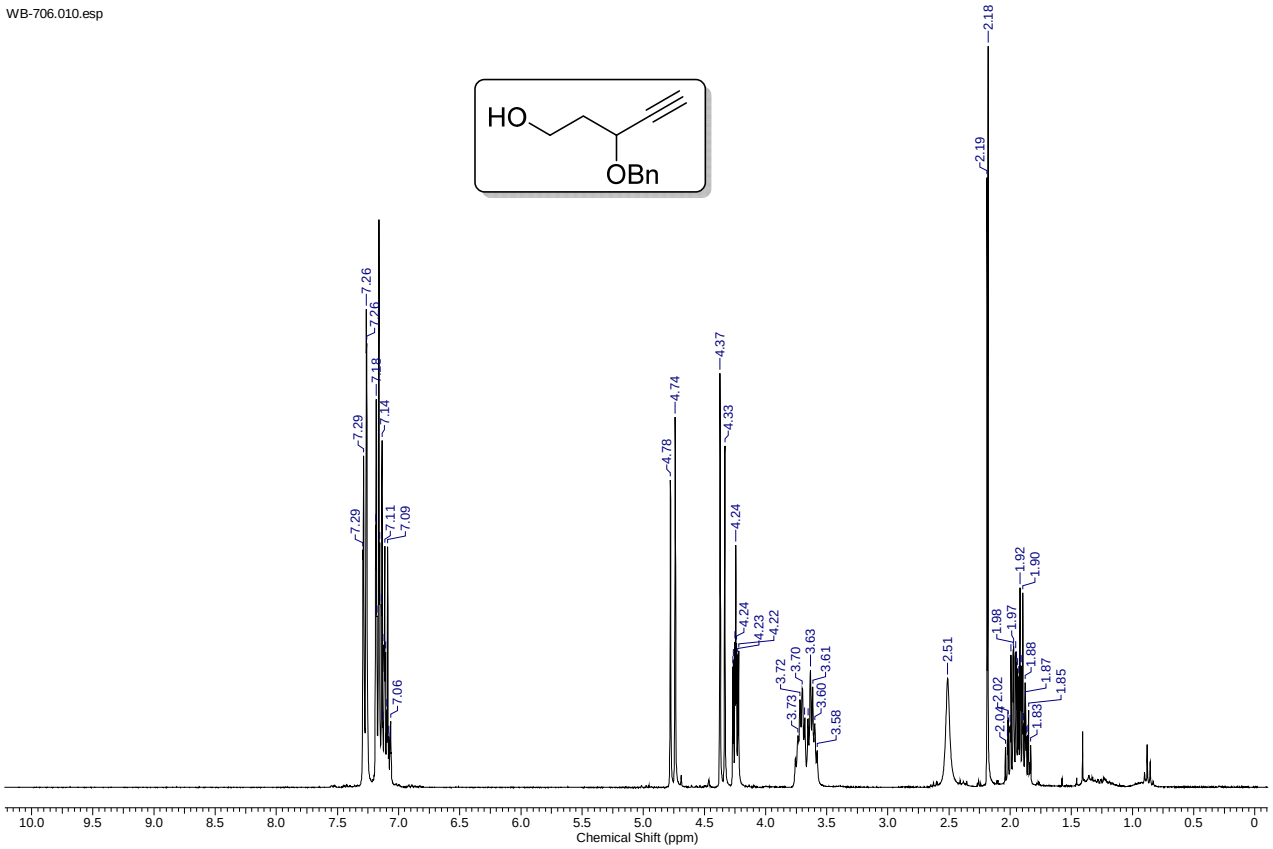


To **4a** (253 mg, 702 µmol) was slowly added a solution HCl (0.5 mL, 4 N in dioxane) and the resulting reaction mixture was stirred at room temperature for 2 h. 10 mL saturated aqueous Na_2CO_3-solution was added, the mixture was extracted with Et_2O and the organic phase was dried over $MgSO_4$. Compound **6** (91.1 mg, 350µmol, 50%) could be obtained after column chromatography (CH:EtOAc 5:1) as a yellowish oil.

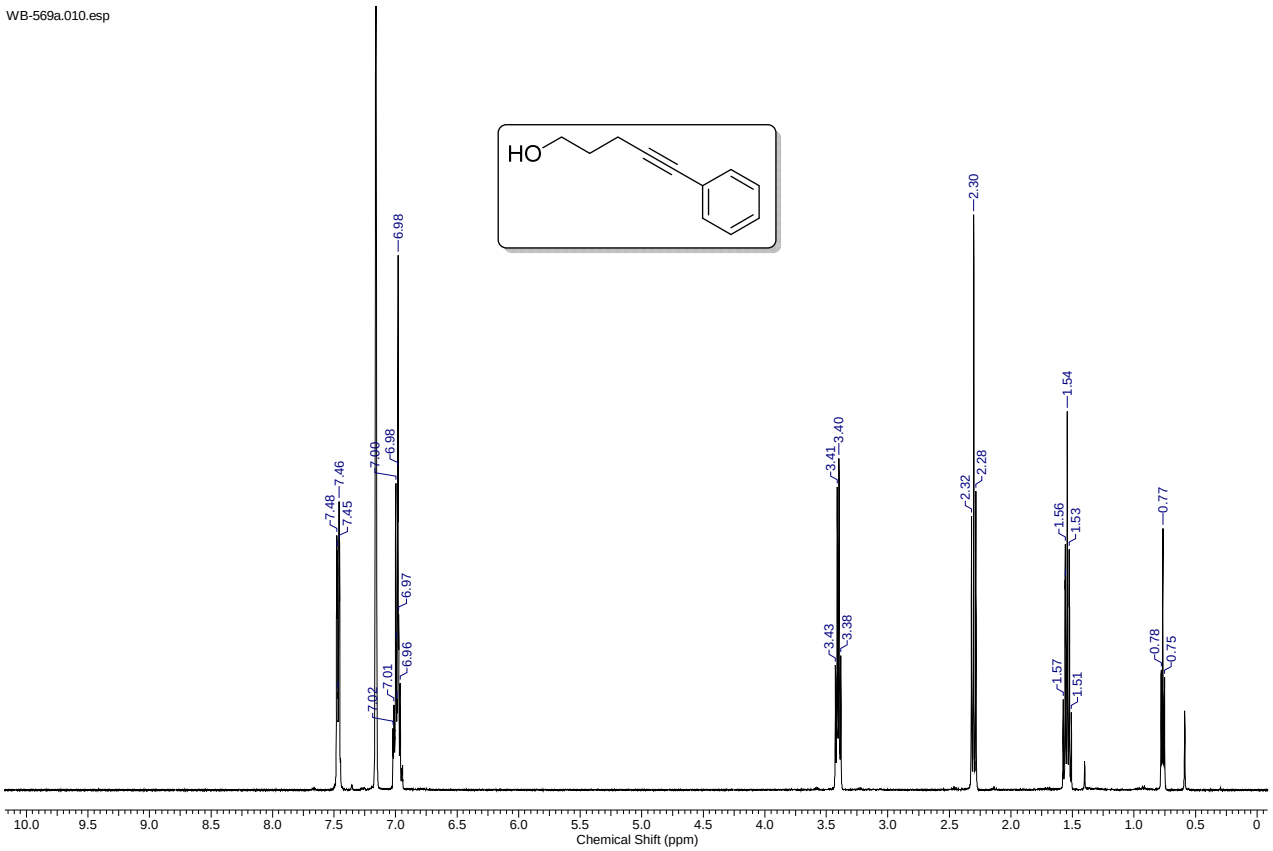
^{1}H NMR (500 MHz, C_6D_6): δ = 7.40 (d, *J* = 7.6 Hz, 2 H), 7.21 (t, *J* = 7.6 Hz, 2 H), 7.07 - 7.13 (m, 4 H), 4.17 (d, *J* = 14.1 Hz, 1 H), 3.95 (d, *J* = 14.1 Hz, 1 H), 3.53 (td, *J* = 5.9, 1.5 Hz, 2 H), 3.40 (br. s., 1 H), 2.83 (ddd, *J* = 13.1, 10.2, 4.6 Hz, 1 H), 2.17 (t, *J* = 7.3 Hz, 2 H), 2.02 - 2.10 (m, 1 H), 1.89 - 1.98 (m, 1 H), 1.62 - 1.73 (m, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H), 0.70 ppm (d, *J*=6.9 Hz, 3 H); **^{13}C-NMR (125 MHz, C_6D_6):** δ = 154.3, 139.0, 130.0, 128.7, 127.6, 71.0, 62.2, 59.1, 36.6, 30.1, 29.1, 28.1, 20.8, 17.1 ppm; **HRMS:** Calculated for $[M+H]^+$: $C_{16}H_{24}ON_2$ 261.1961, found: 261.1960.

VI. NMR Spectra

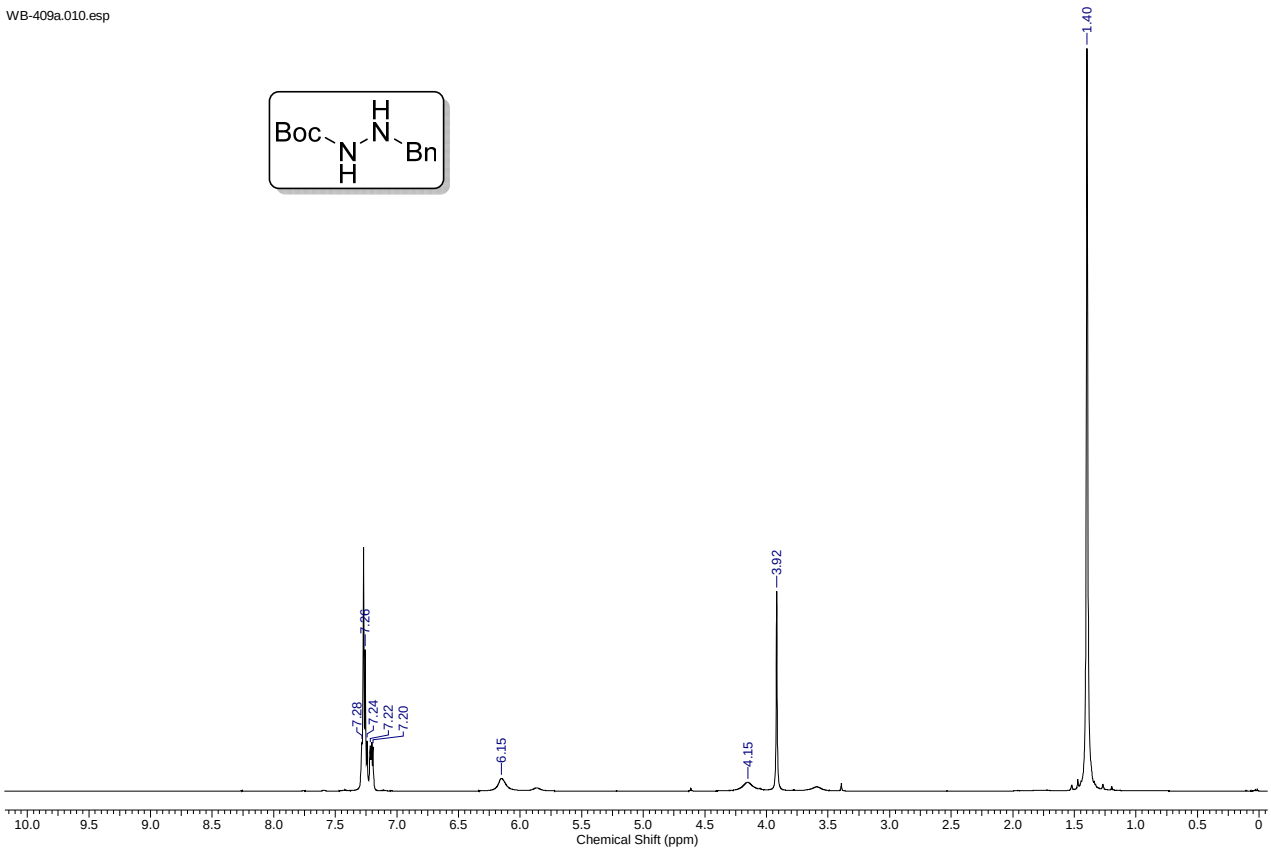
1c



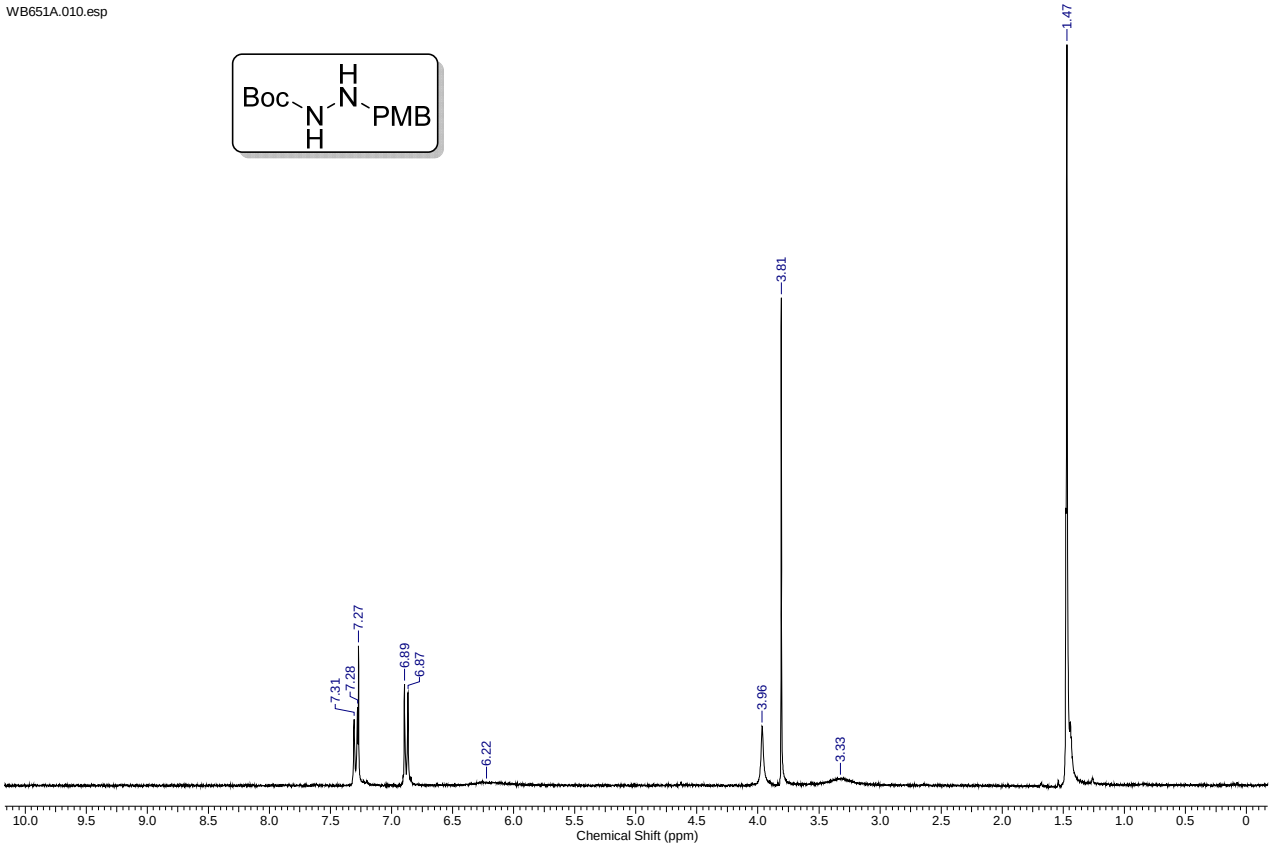
1e


WB-569a.010.esp
HO
7.48
7.46
7.45
7.02
7.01
7.00
6.98
6.98
6.97
6.96
3.43
3.41
3.40
3.38
2.32
2.30
2.28
1.57
1.56
1.54
1.53
1.51
0.78
0.77
0.75
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

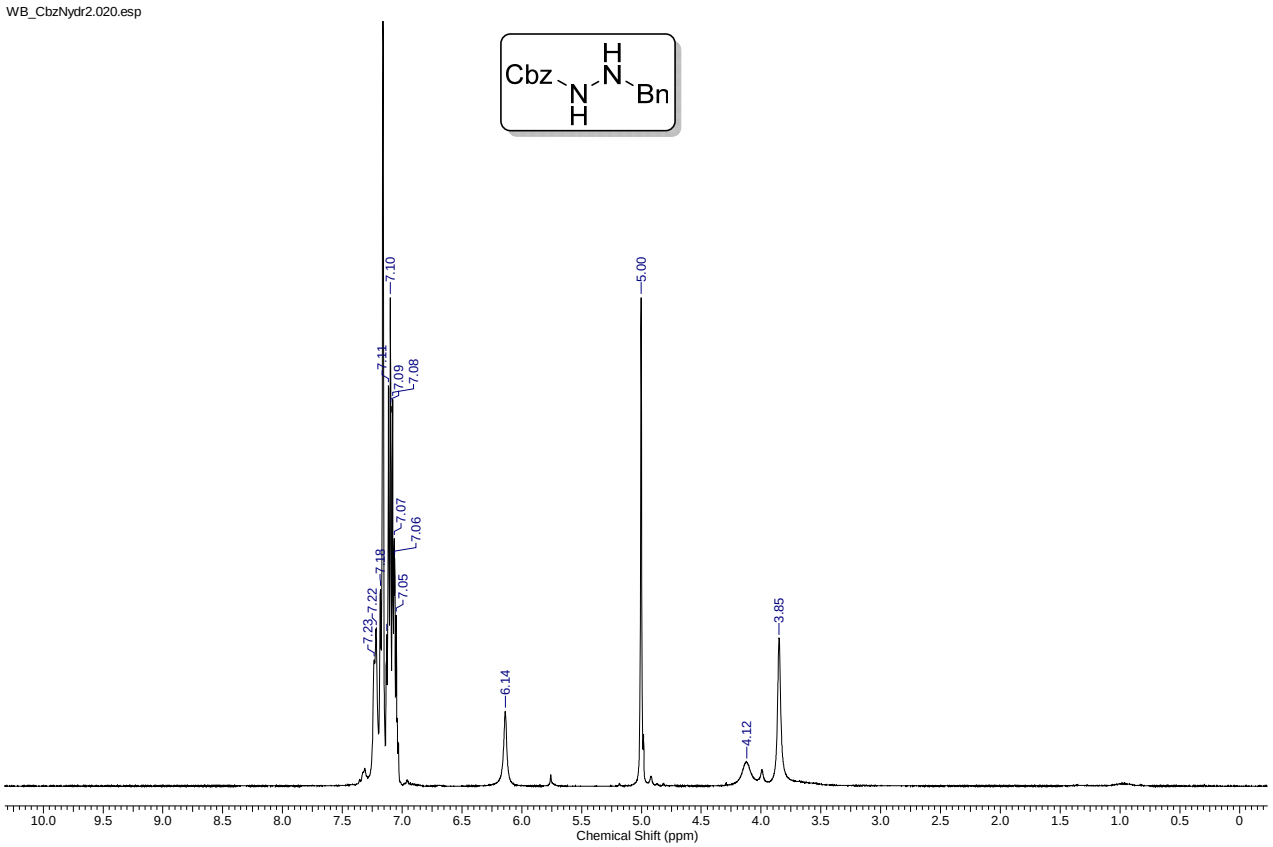
3a


WB-409a.010.esp
Boc
N
H
H
N
Bn
1.40
3.92
7.28
7.24
7.22
7.20
6.15
4.15
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

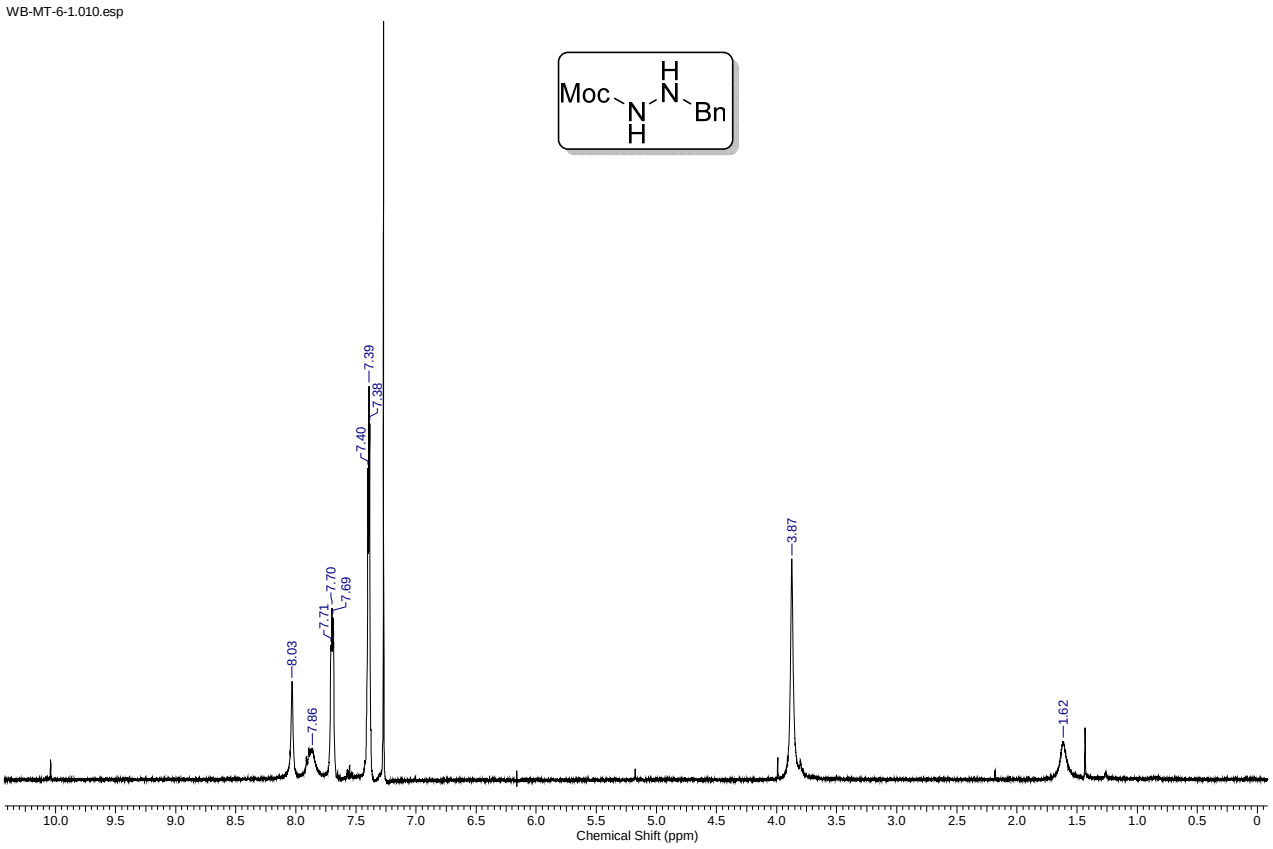
3b


WB651A.010.esp
Boc
N
H
H
N
PMB
1.47
3.81
7.27
7.31
7.28
6.89
6.87
6.22
3.96
3.33
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

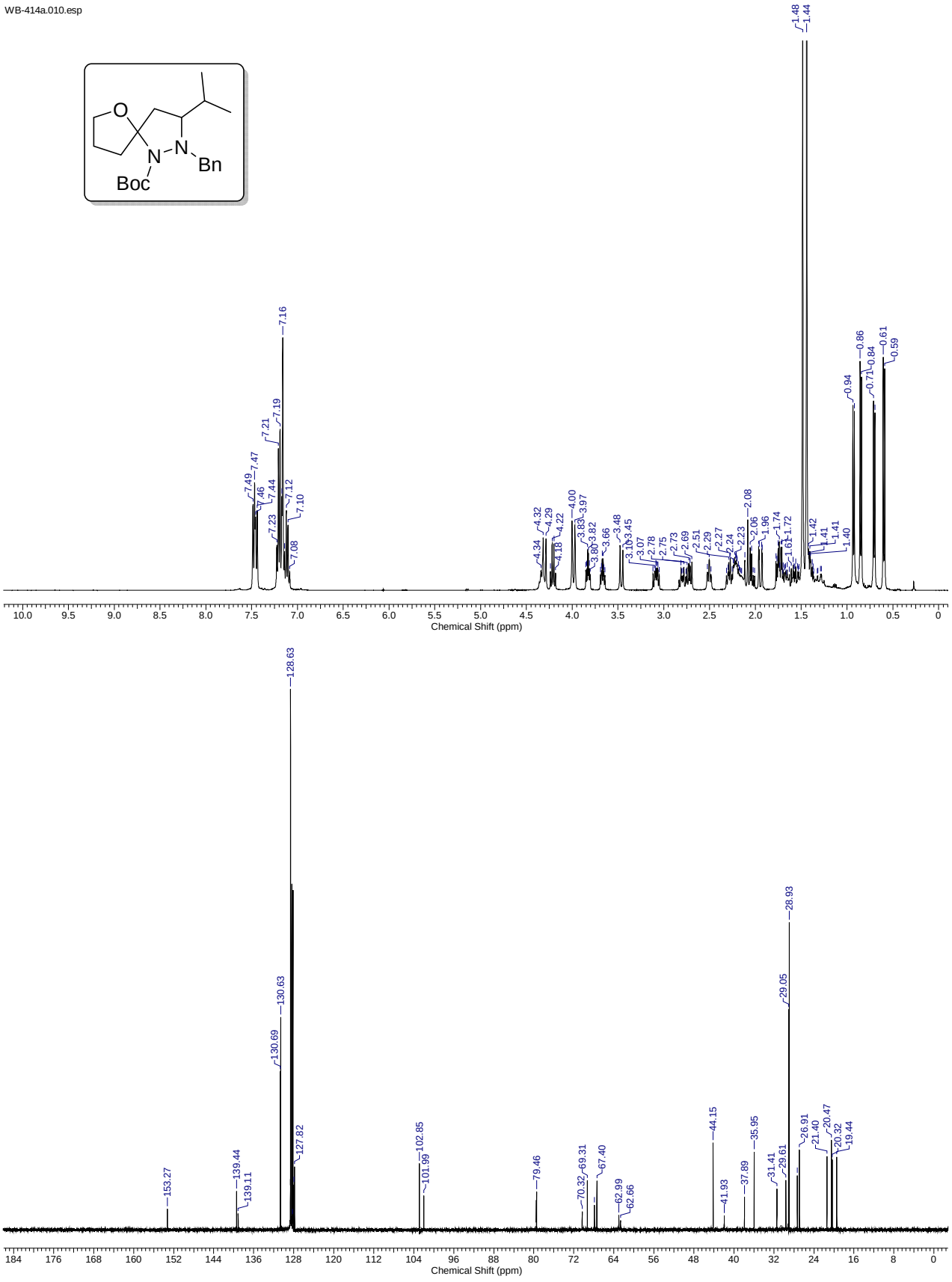
3c


WB_CbzNydr2.020.esp
Cbz
N
H
H
N
Bn
7.10
7.11
7.09
7.08
7.07
7.06
7.18
7.05
7.23
7.22
6.14
5.00
4.12
3.85
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

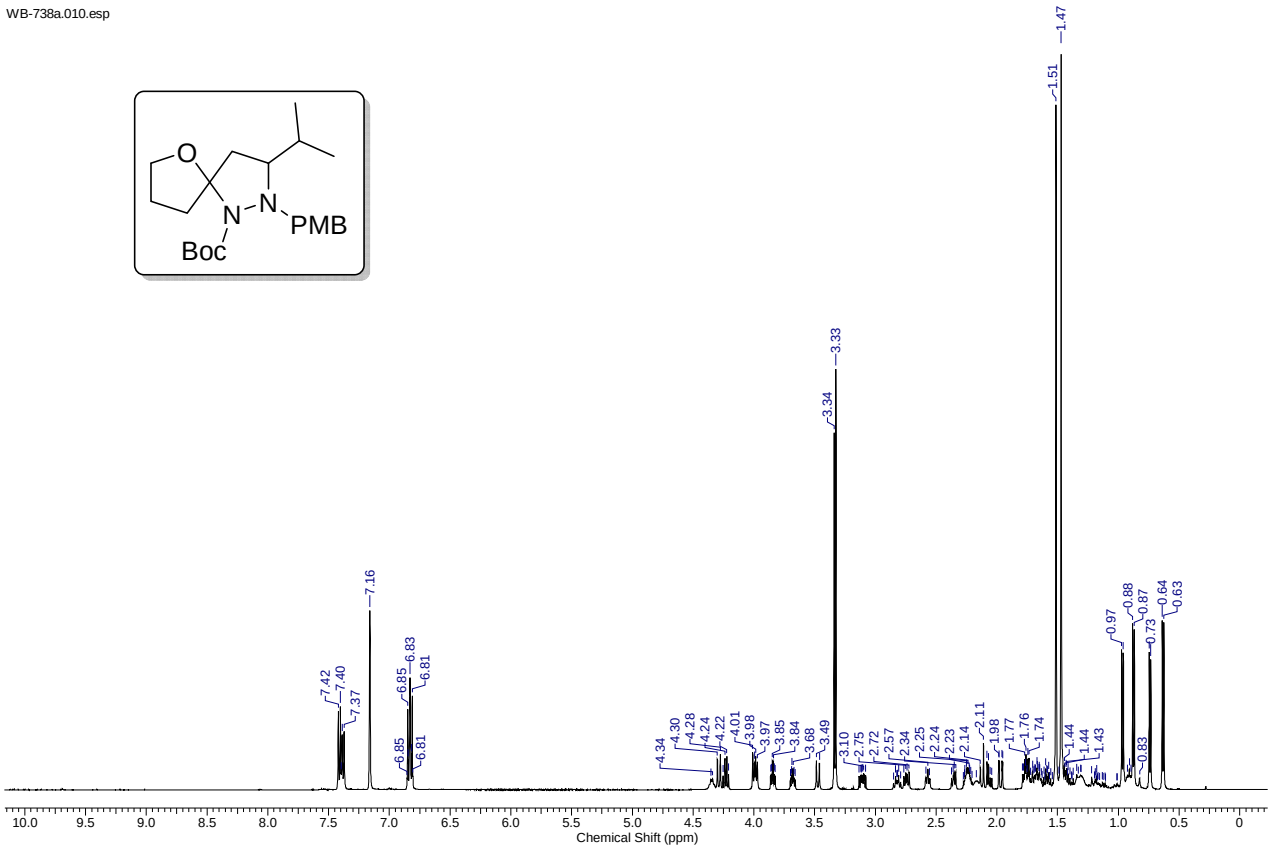
3d

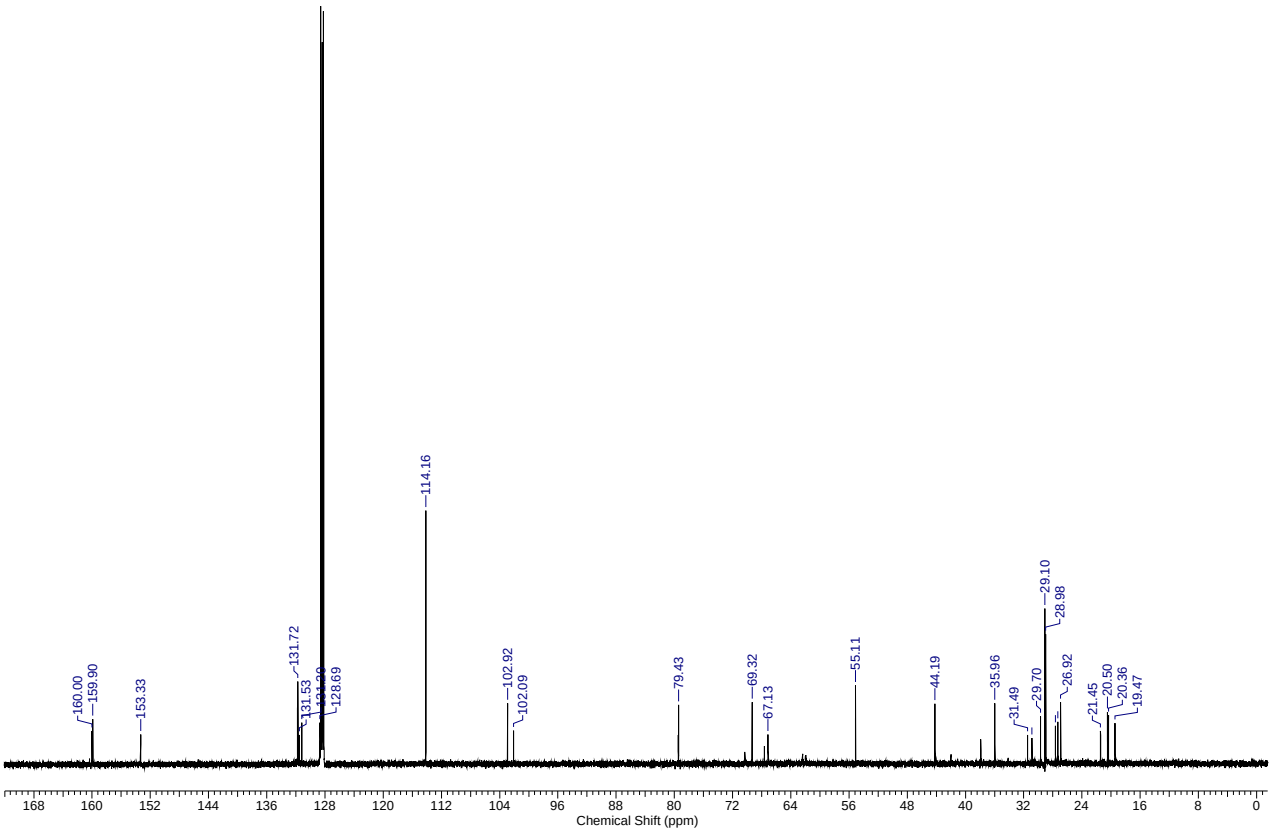

WB-MT-6-1.010.esp
Moc
N
H
H
N
Bn
8.03
7.86
7.71
7.70
7.69
7.40
7.39
7.38
3.87
1.62
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

4a

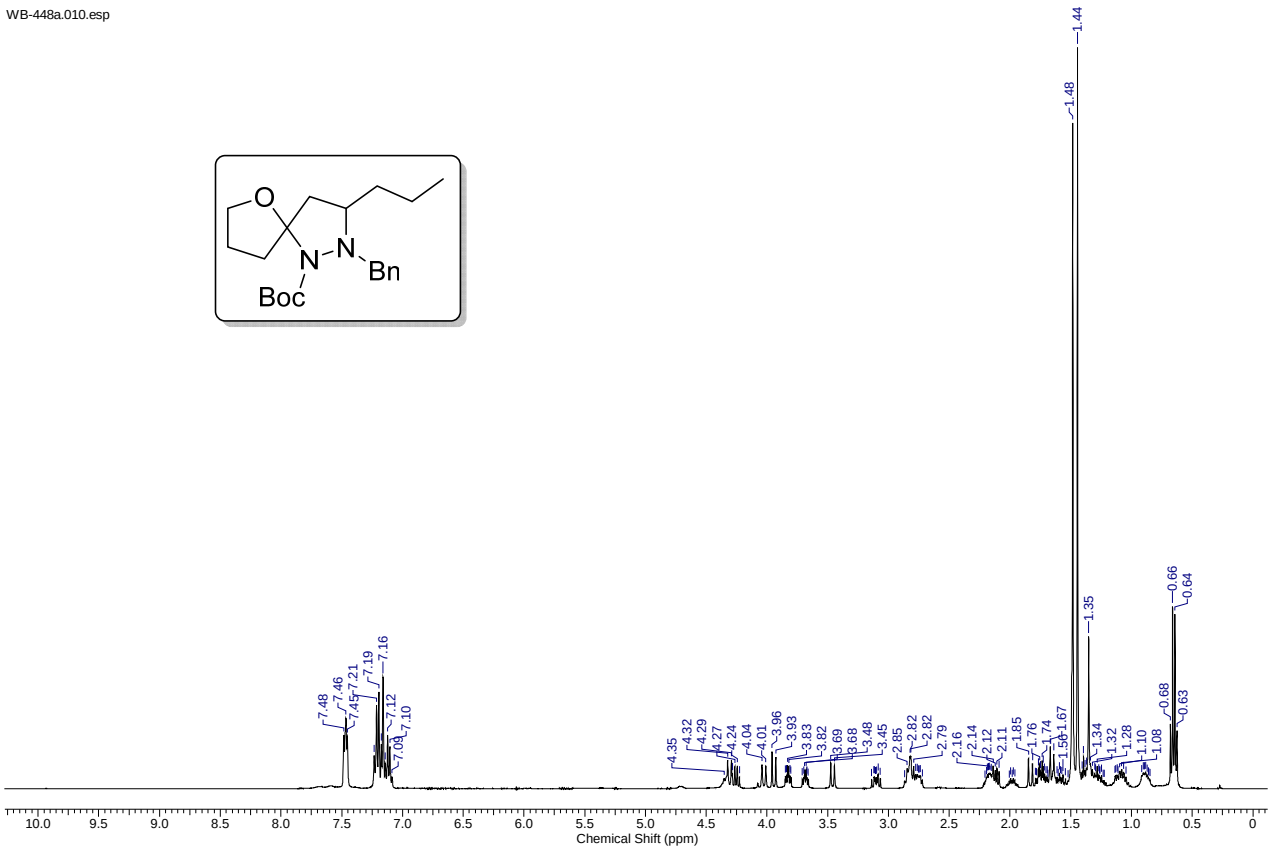

WB-414a.010.esp
O
N
N
Bn
Boc
Chemical Shift (ppm)
Chemical Shift (ppm)

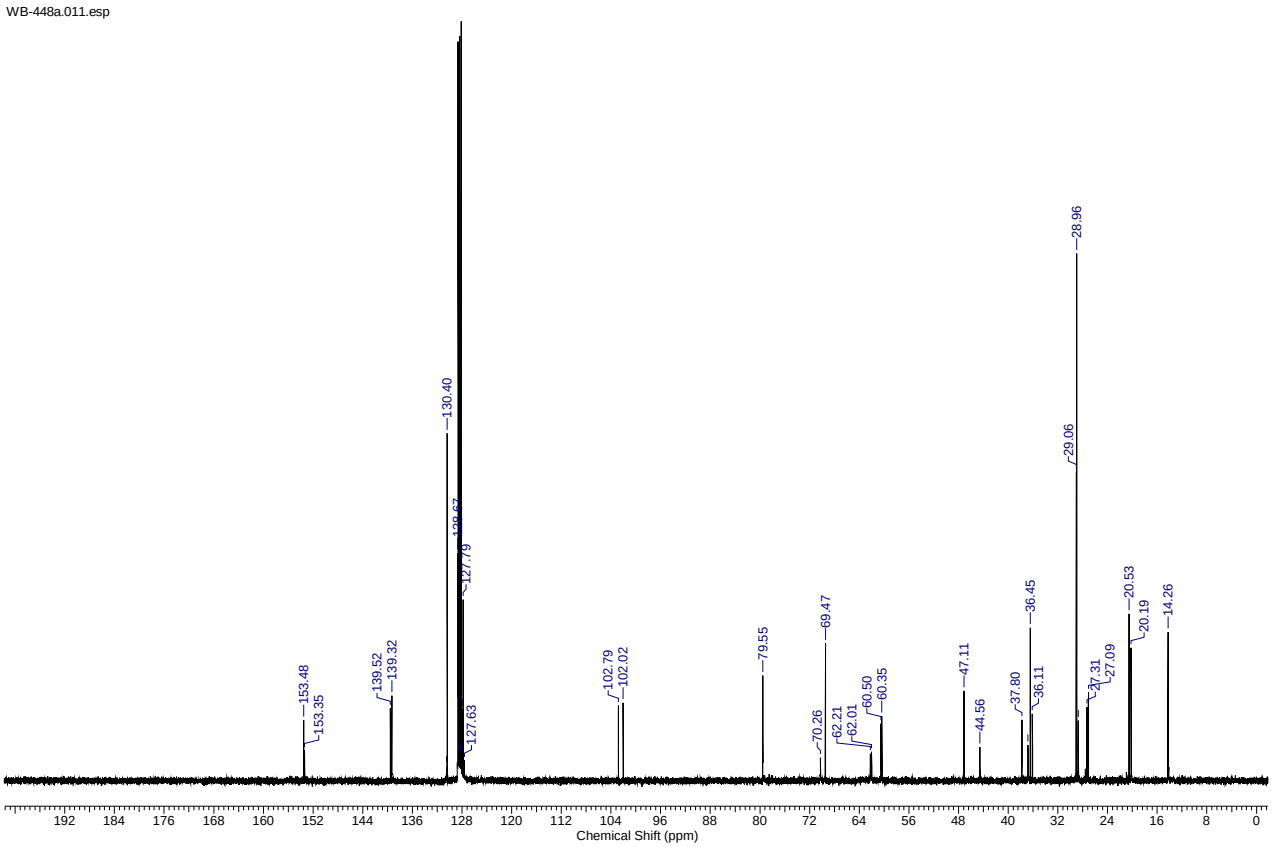
4b


WB-738a.010.esp
O
N
N
PMB
Boc
1.47
1.51
3.33
3.34
7.16
7.42
7.40
7.37
6.85
6.83
6.81
6.85
6.81
4.34
4.30
4.28
4.24
4.22
4.01
3.98
3.97
3.85
3.84
3.68
3.49
3.10
2.75
2.72
2.57
2.34
2.25
2.24
2.23
2.14
2.11
1.98
1.77
1.76
1.74
1.44
1.44
1.43
0.97
0.88
0.87
0.83
0.73
0.64
0.63
Chemical Shift (ppm)

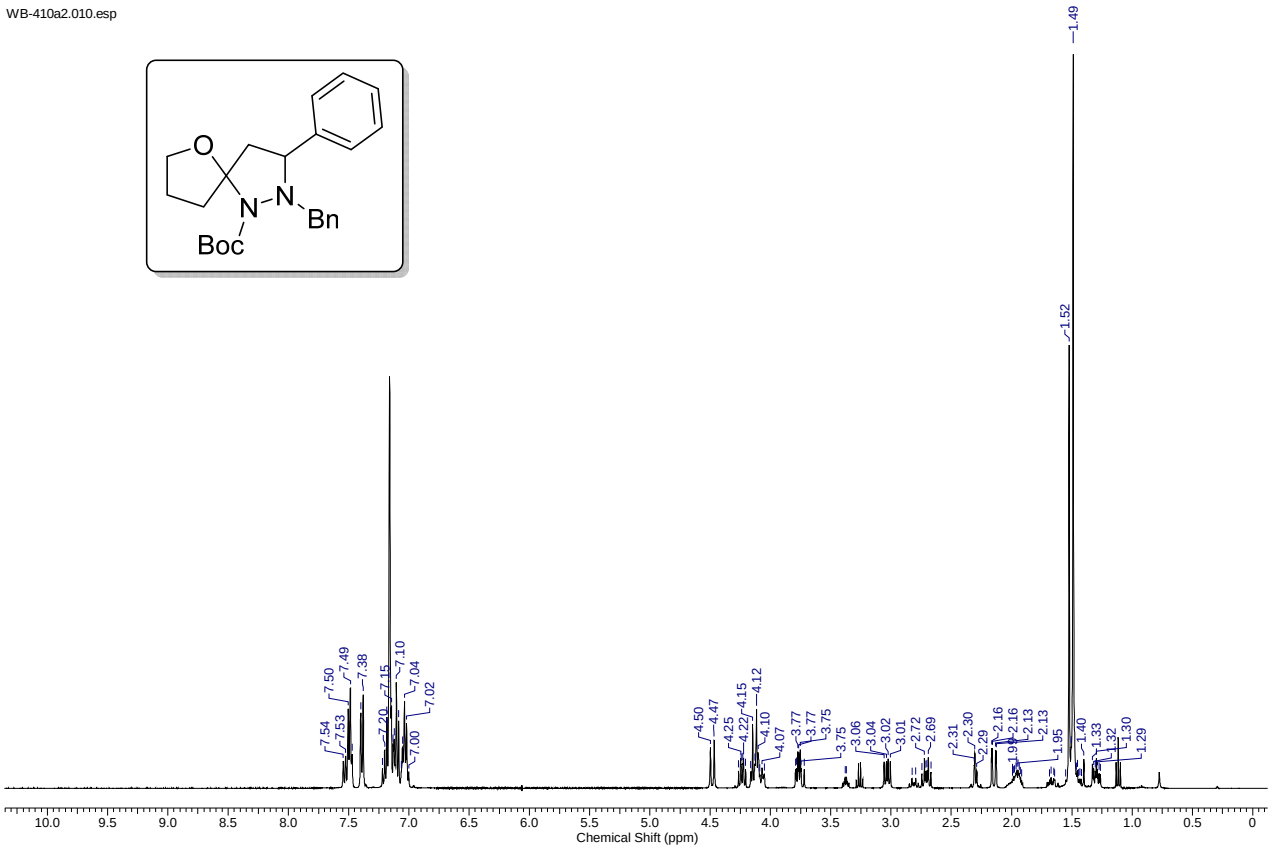

160.00
159.90
153.33
131.72
131.53
128.69
114.16
102.92
102.09
79.43
69.32
67.13
55.11
44.19
35.96
31.49
29.70
29.10
28.98
26.92
21.45
20.50
20.36
19.47
Chemical Shift (ppm)

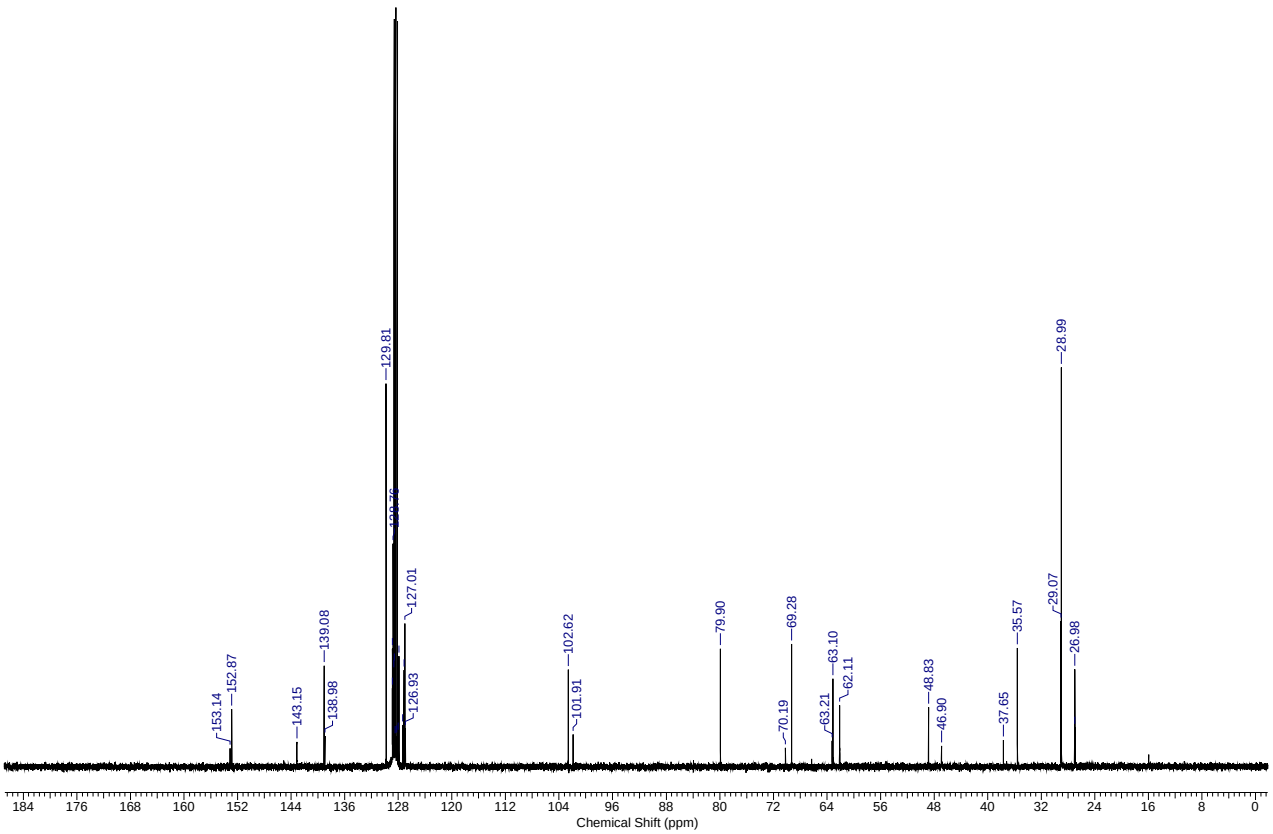
4c


WB-448a.010.esp
O
N
N
Bn
Boc
7.48
7.46
7.45
7.21
7.19
7.16
7.12
7.10
7.03
4.35
4.32
4.29
4.27
4.24
4.04
4.01
3.96
3.93
3.83
3.82
3.69
3.68
3.48
3.45
2.85
2.82
2.82
2.79
2.16
2.14
2.12
2.11
1.85
1.76
1.74
1.67
1.58
1.44
1.48
1.35
1.34
1.32
1.28
1.10
1.08
0.68
0.66
0.64
0.63
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

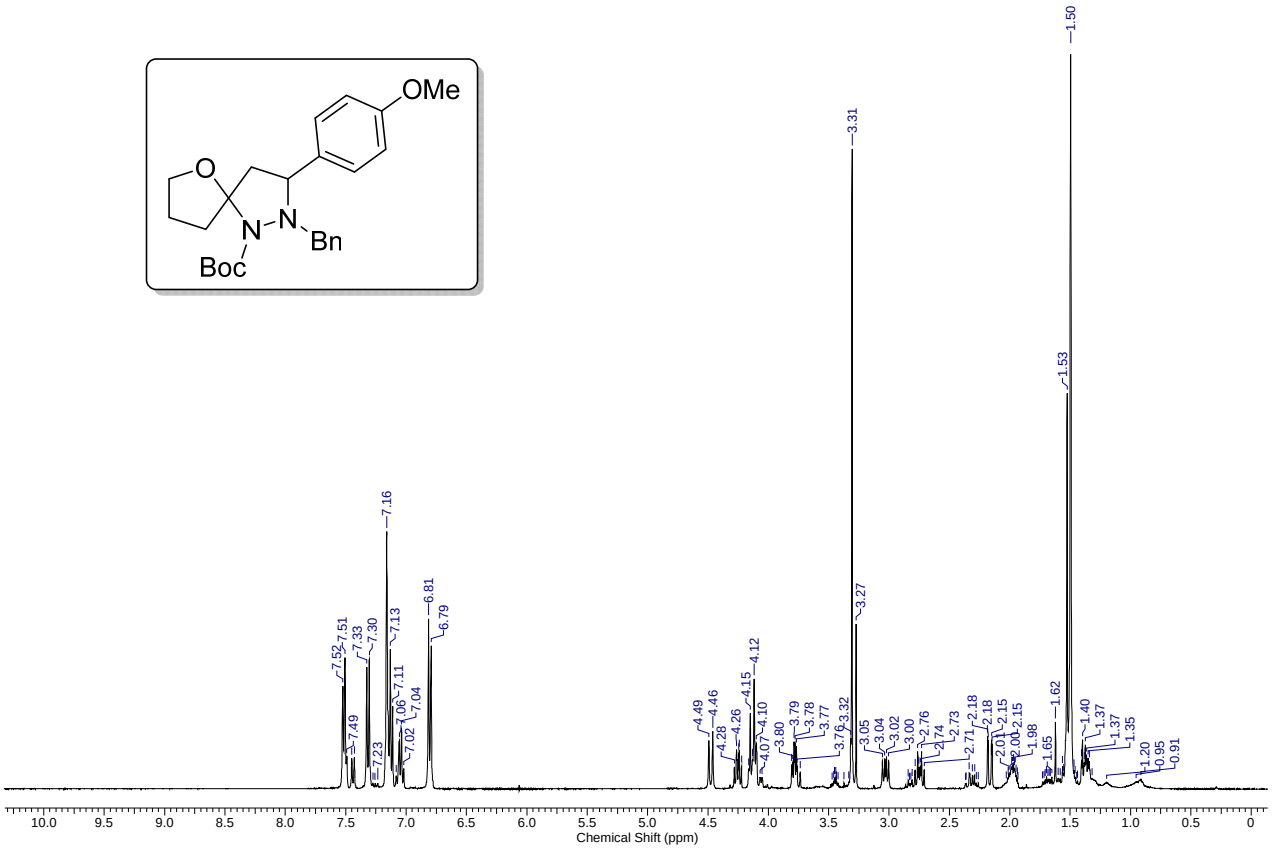

WB-448a.011.esp
153.48
153.35
139.52
139.32
130.40
128.67
127.79
127.63
102.79
102.02
79.55
70.26
69.47
62.21
62.01
60.50
60.35
47.11
44.56
37.80
36.45
36.11
29.06
28.96
27.31
27.09
20.53
20.19
14.26
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

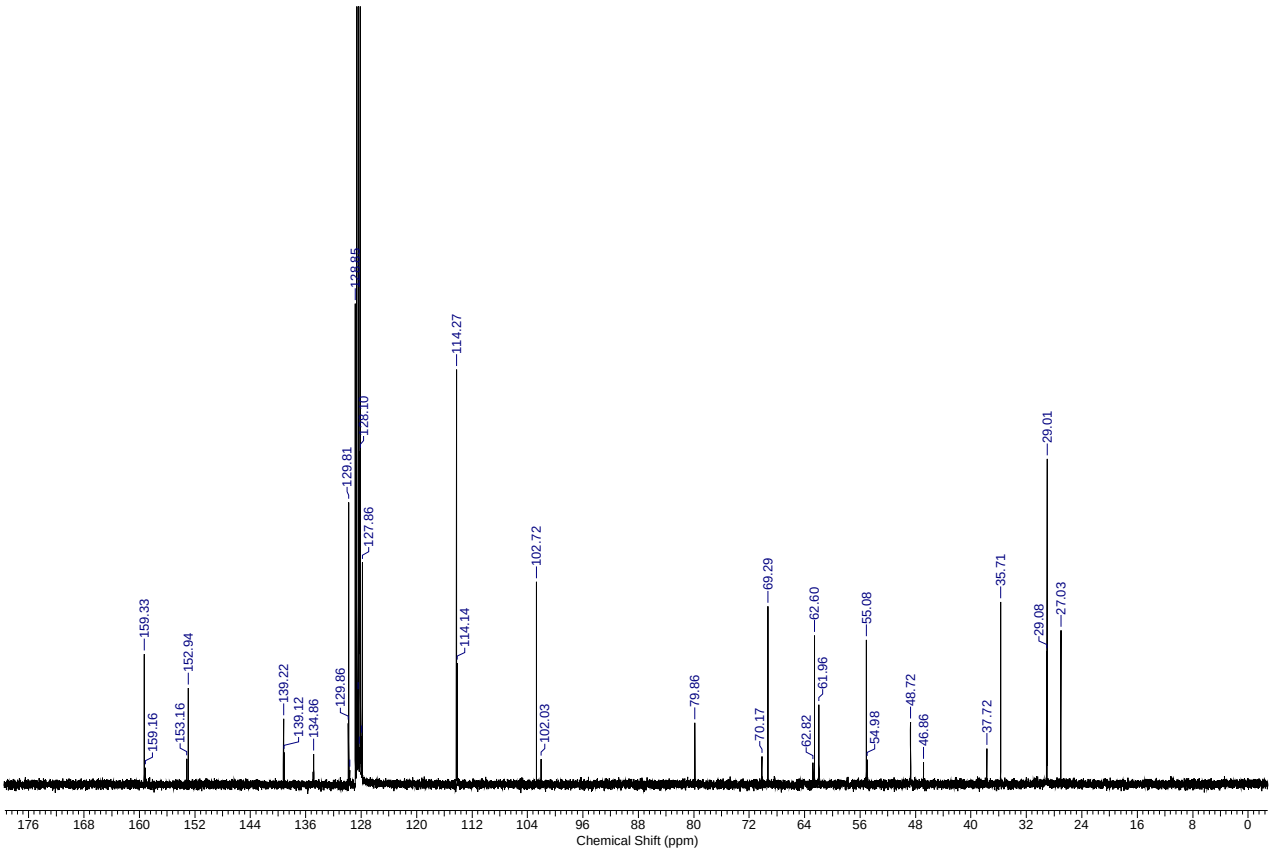
4d


WB-410a2.010.esp
O
N
N
Bn
Boc
Chemical Shift (ppm)

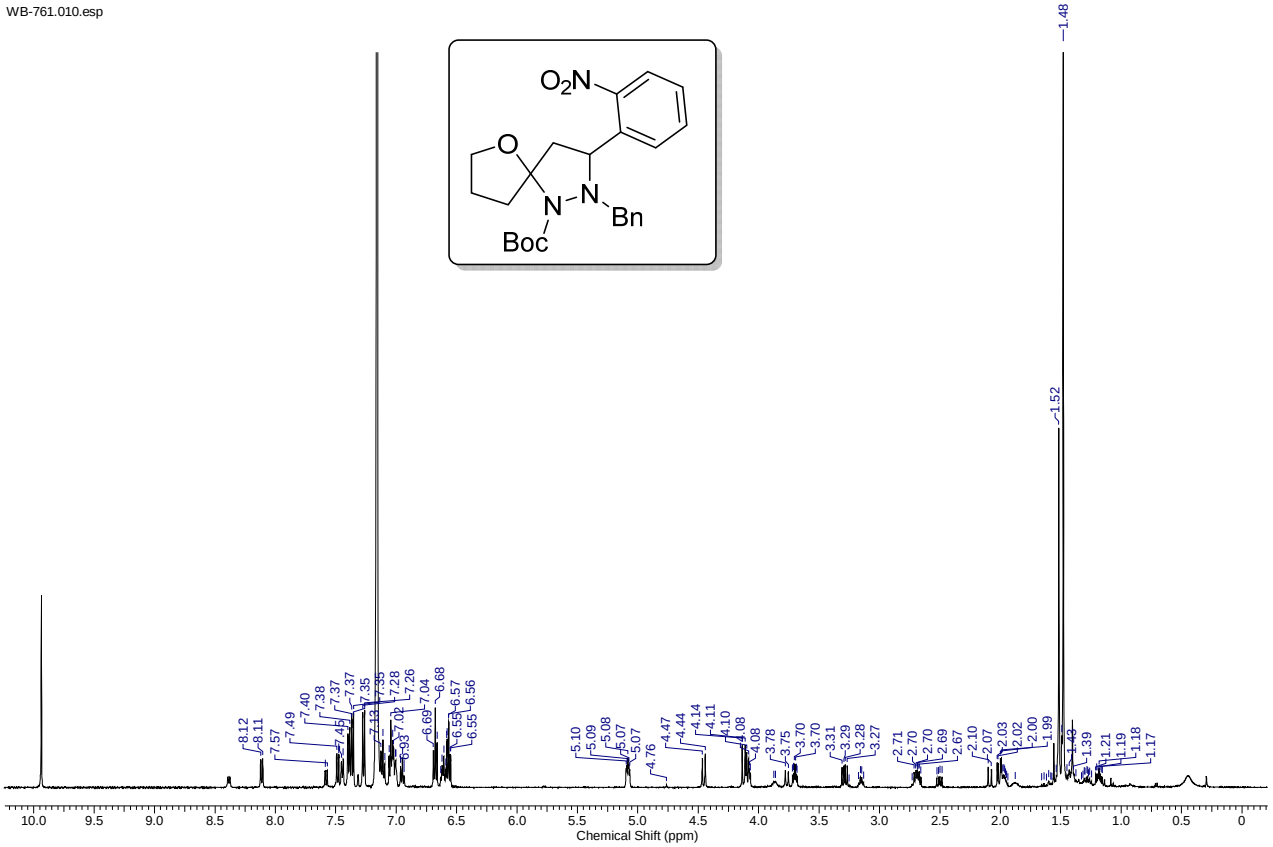

Chemical Shift (ppm)

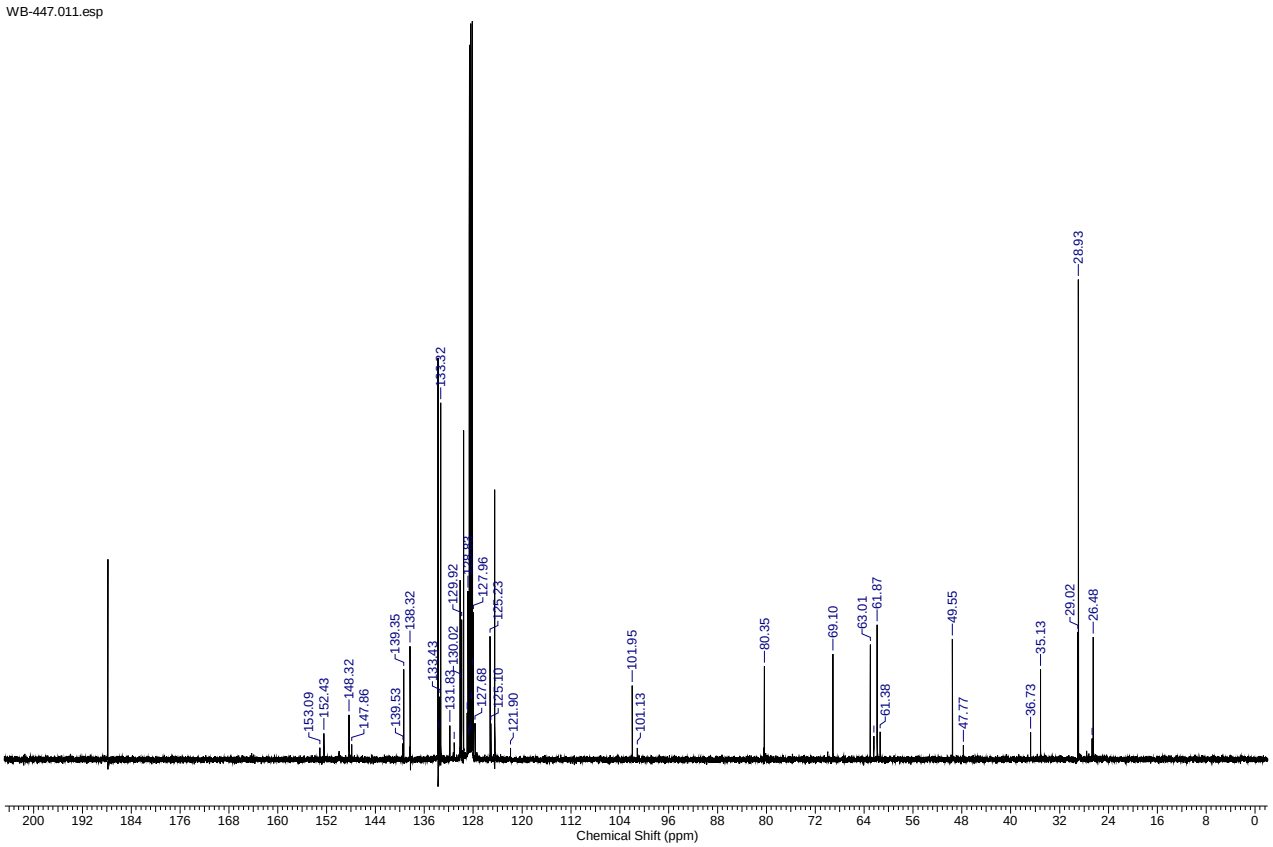
4e



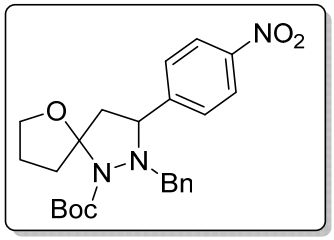


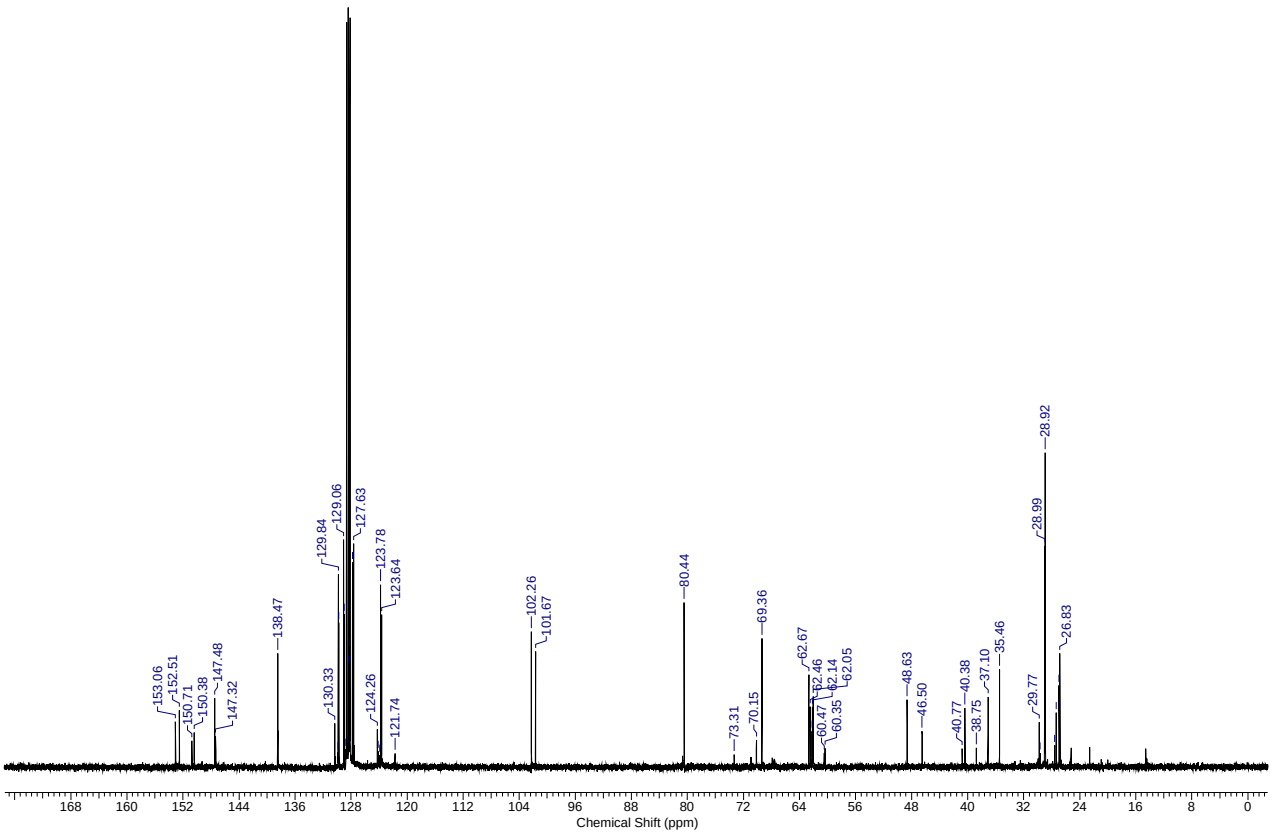
4f


WB-761.010.esp
O2N
O
N
N
Bn
Boc
Chemical Shift (ppm)

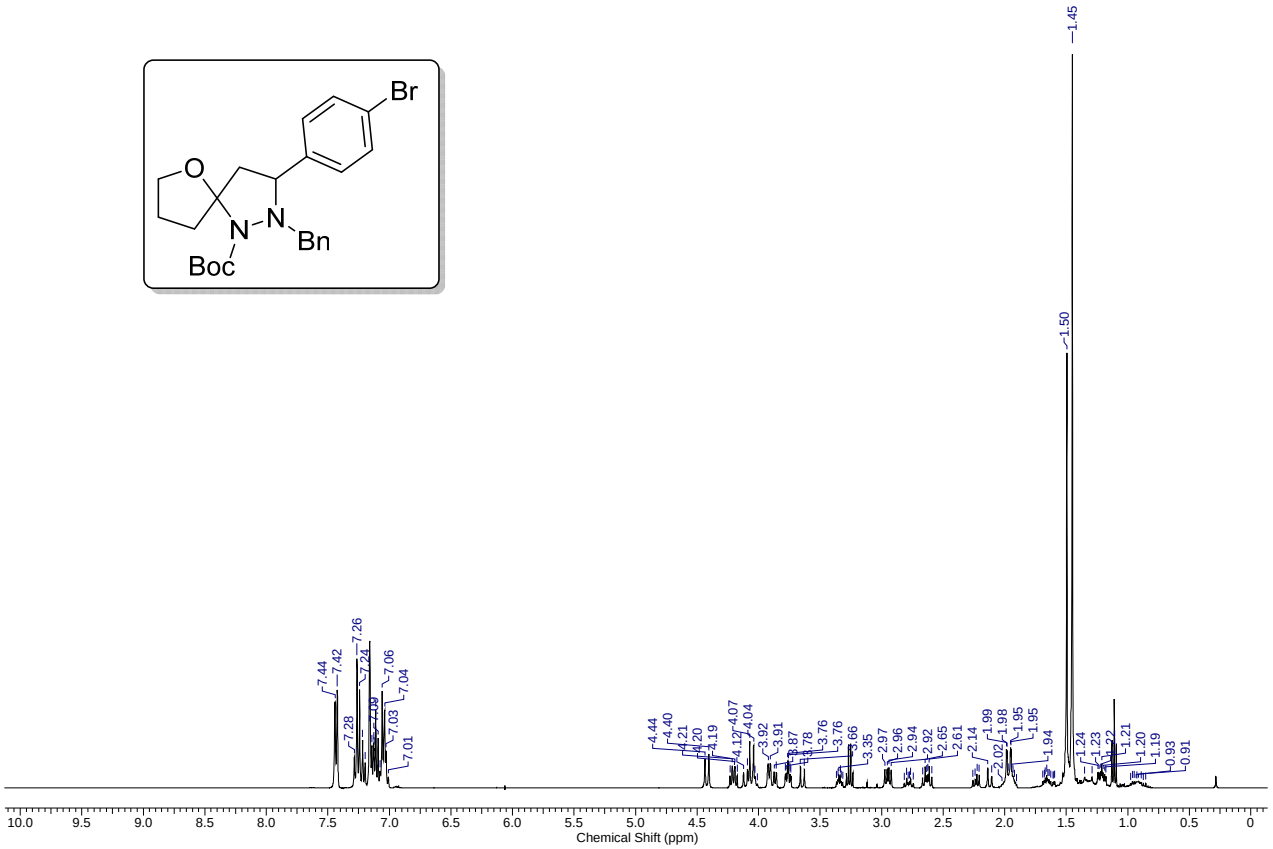

WB-447.011.esp
Chemical Shift (ppm)

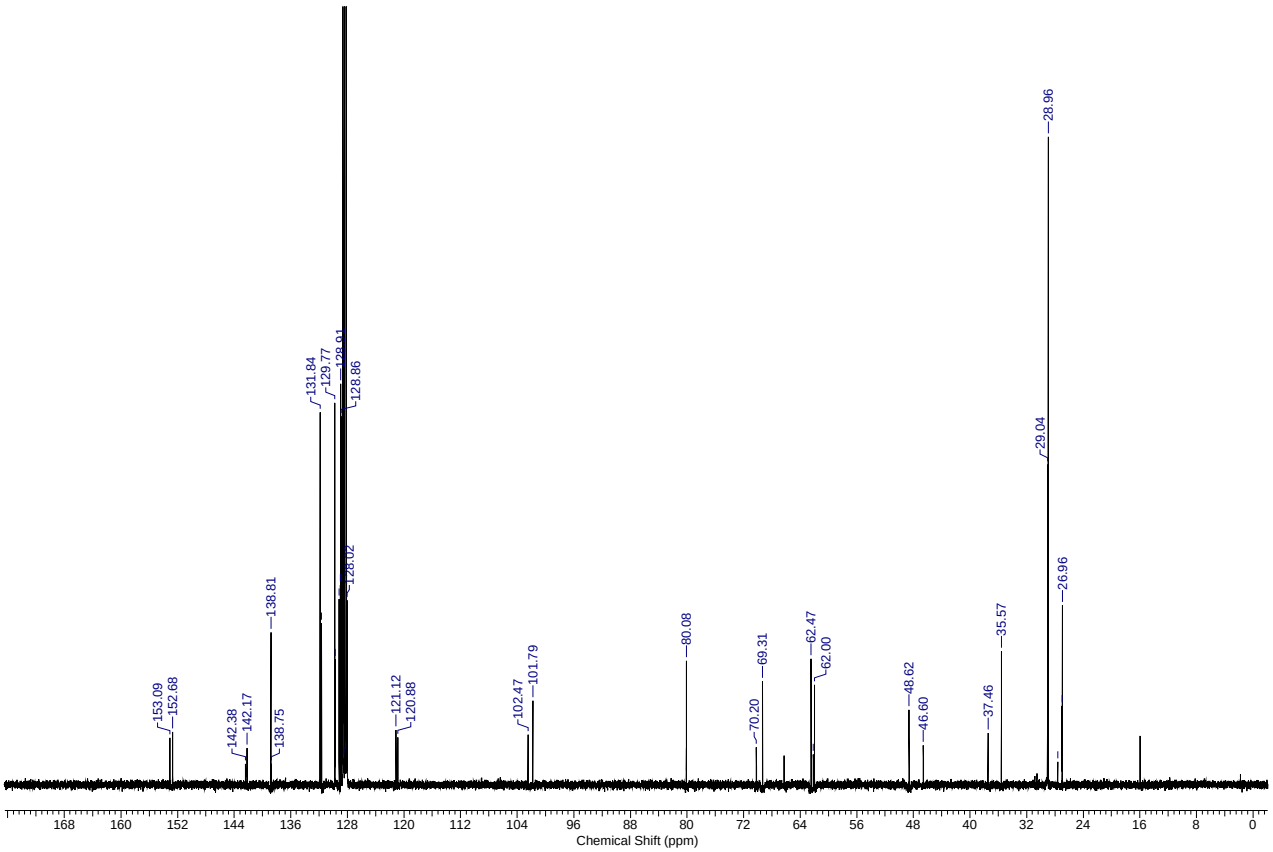
4g



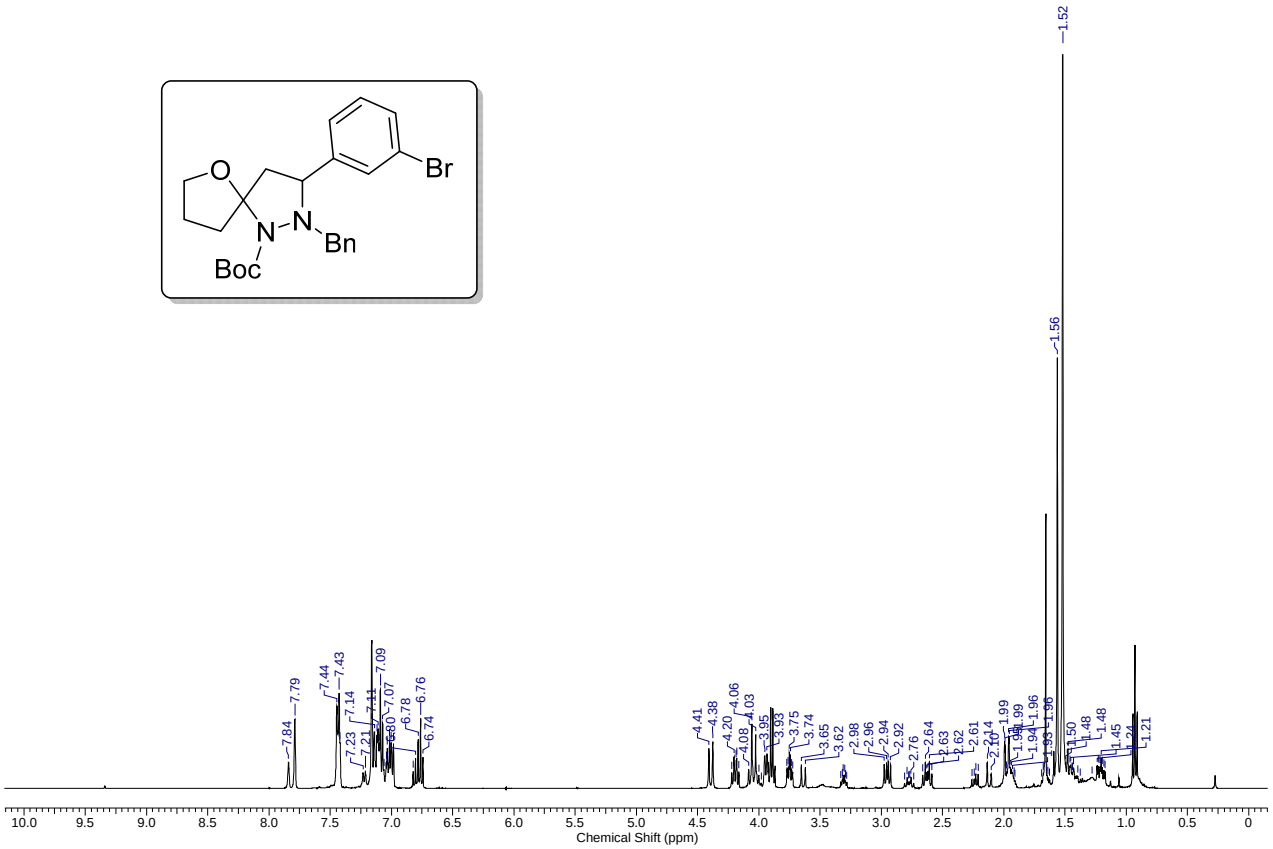


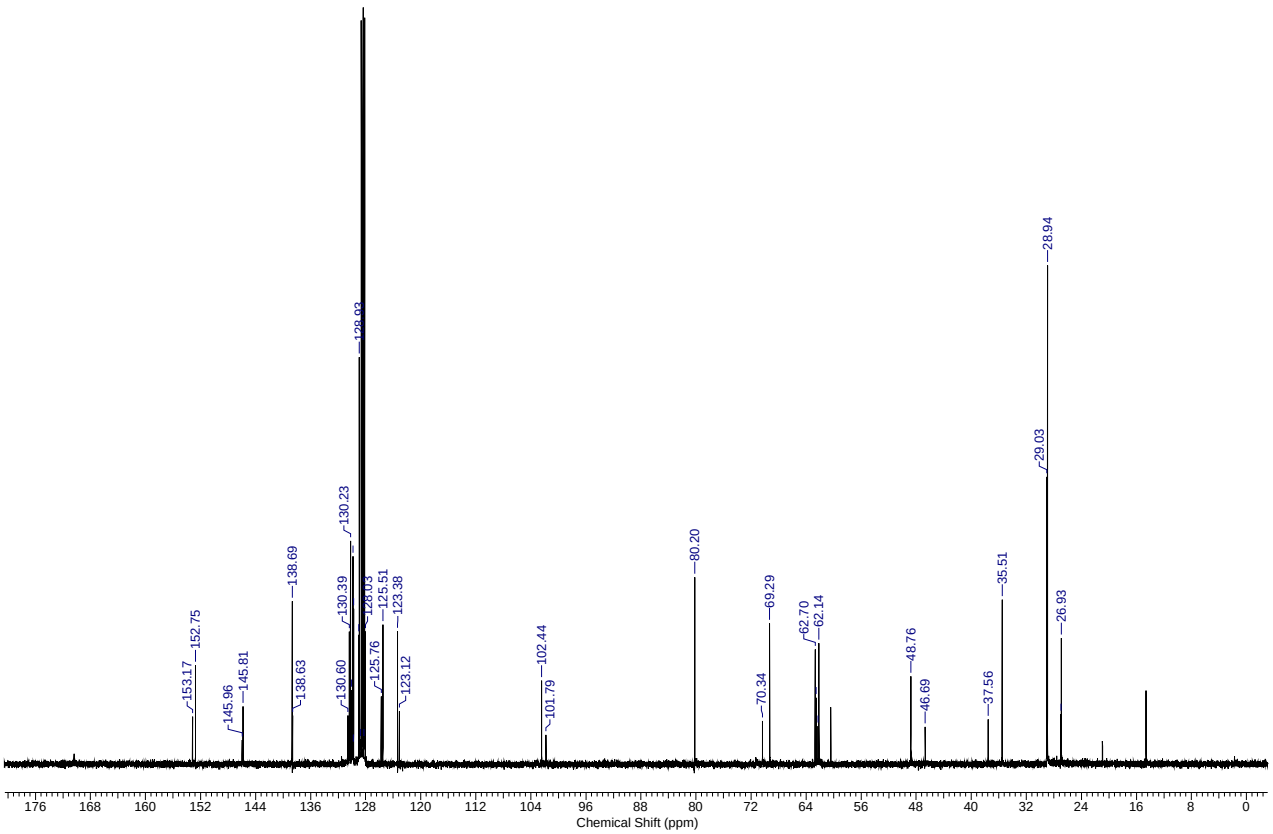
4h



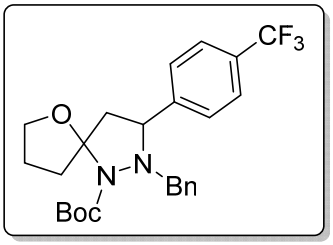


4i

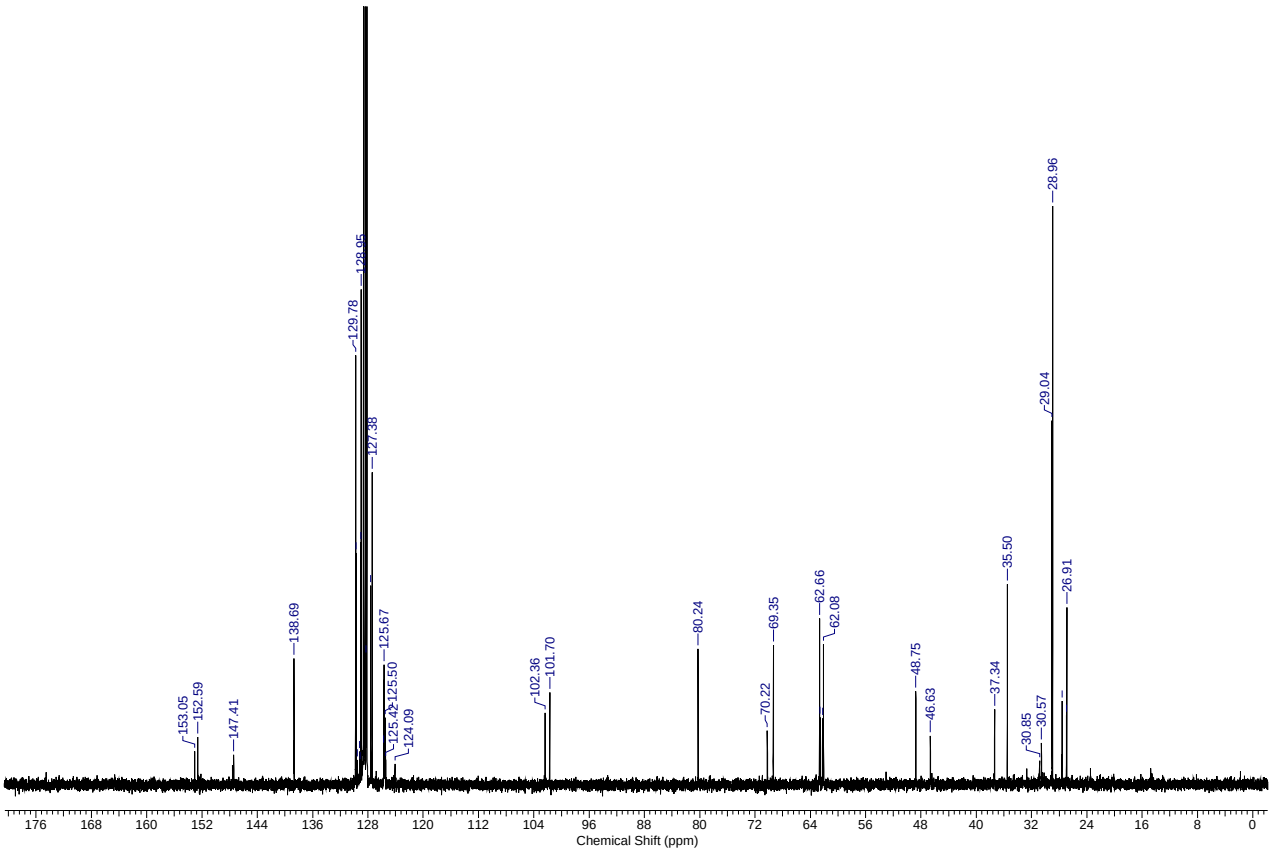


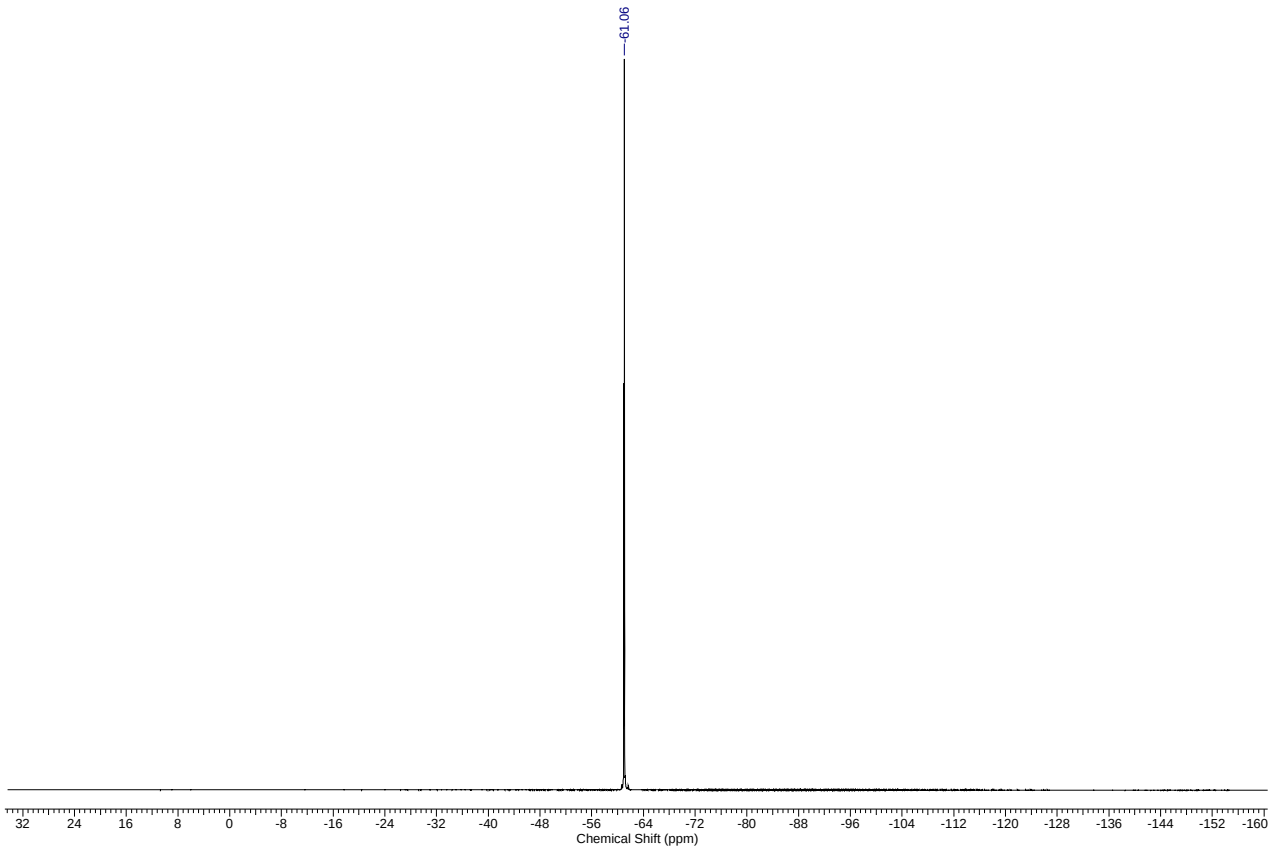


4j


CF3
O
N
N
Bn
Boc

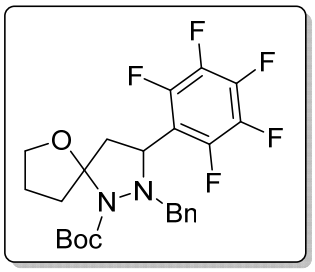
7.44
7.43
7.39
7.38
7.36
7.34
7.24
7.11
7.09
7.04
7.02
7.00
4.46
4.43
4.21
4.12
4.09
4.06
3.98
3.97
3.93
3.78
3.77
3.76
3.66
3.00
2.98
2.96
2.94
2.63
2.60
2.14
1.99
1.98
1.95
1.92
1.95
1.67
1.65
1.52
1.47
1.35
1.19
1.18
1.17
1.16
1.15
Chemical Shift (ppm)


153.05
152.59
147.41
138.69
129.78
129.05
127.38
125.67
125.42
125.50
124.09
102.36
101.70
80.24
70.22
69.35
62.66
62.08
48.75
46.63
37.34
35.50
30.85
30.57
29.04
28.96
26.91
Chemical Shift (ppm)

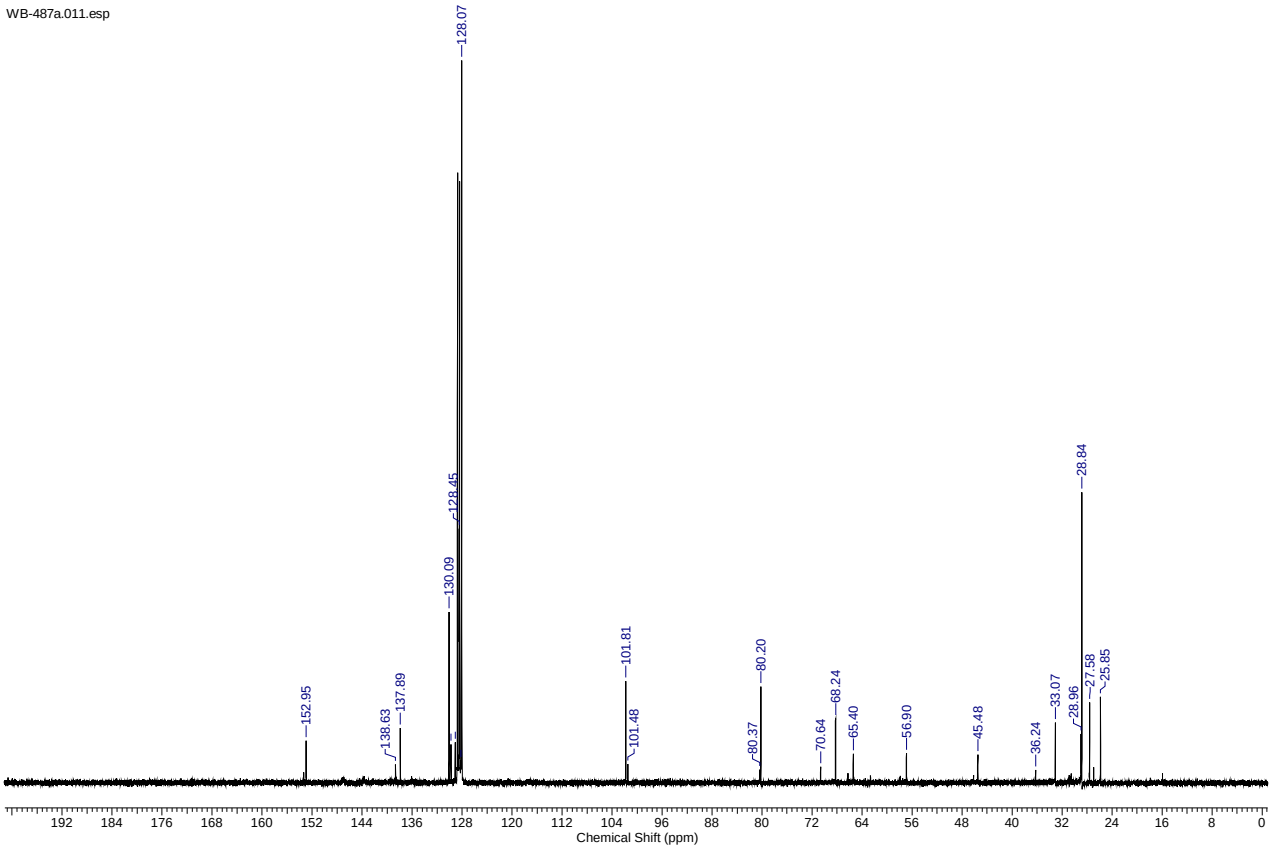

-61.06
32 24 16 8 0 -8 -16 -24 -32 -40 -48 -56 -64 -72 -80 -88 -96 -104 -112 -120 -128 -136 -144 -152 -160
Chemical Shift (ppm)

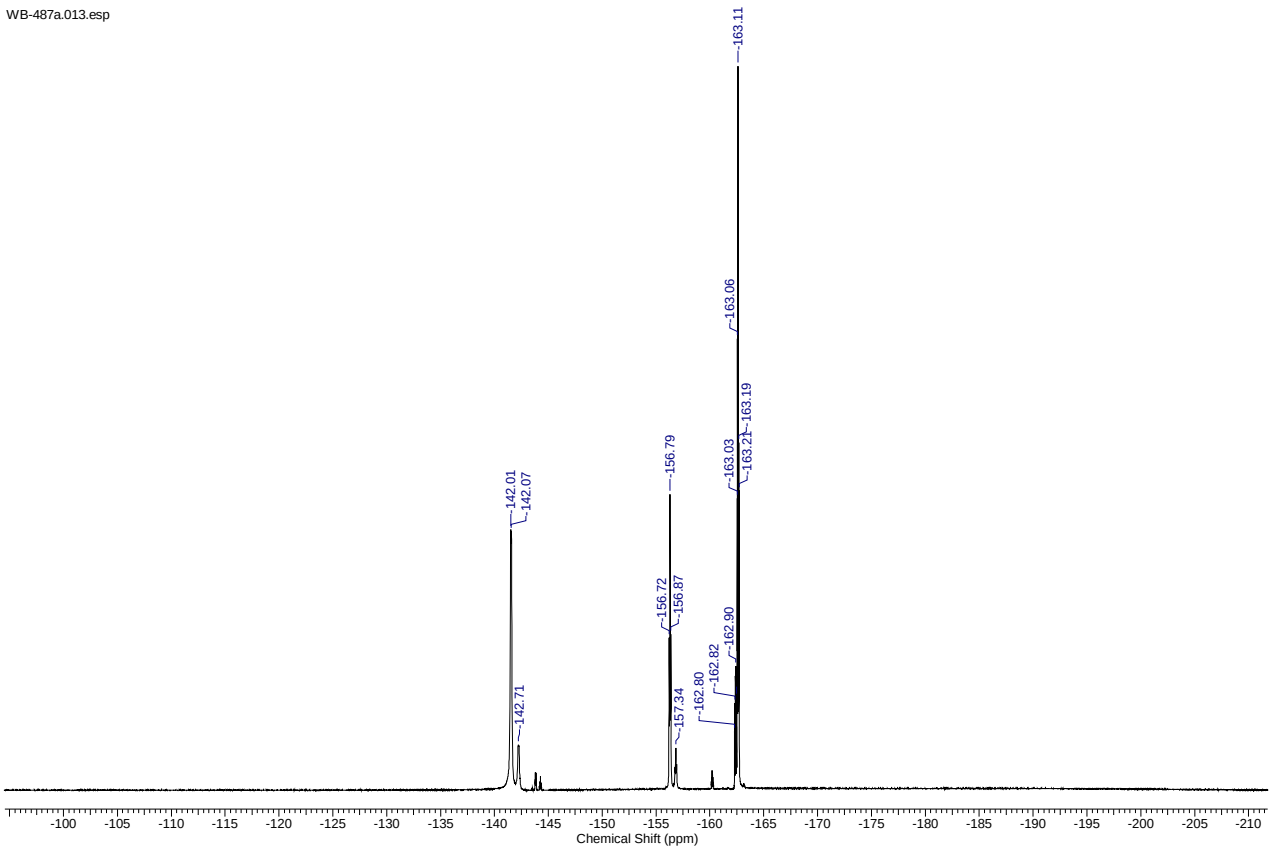
4k

WB-487a.010.esp

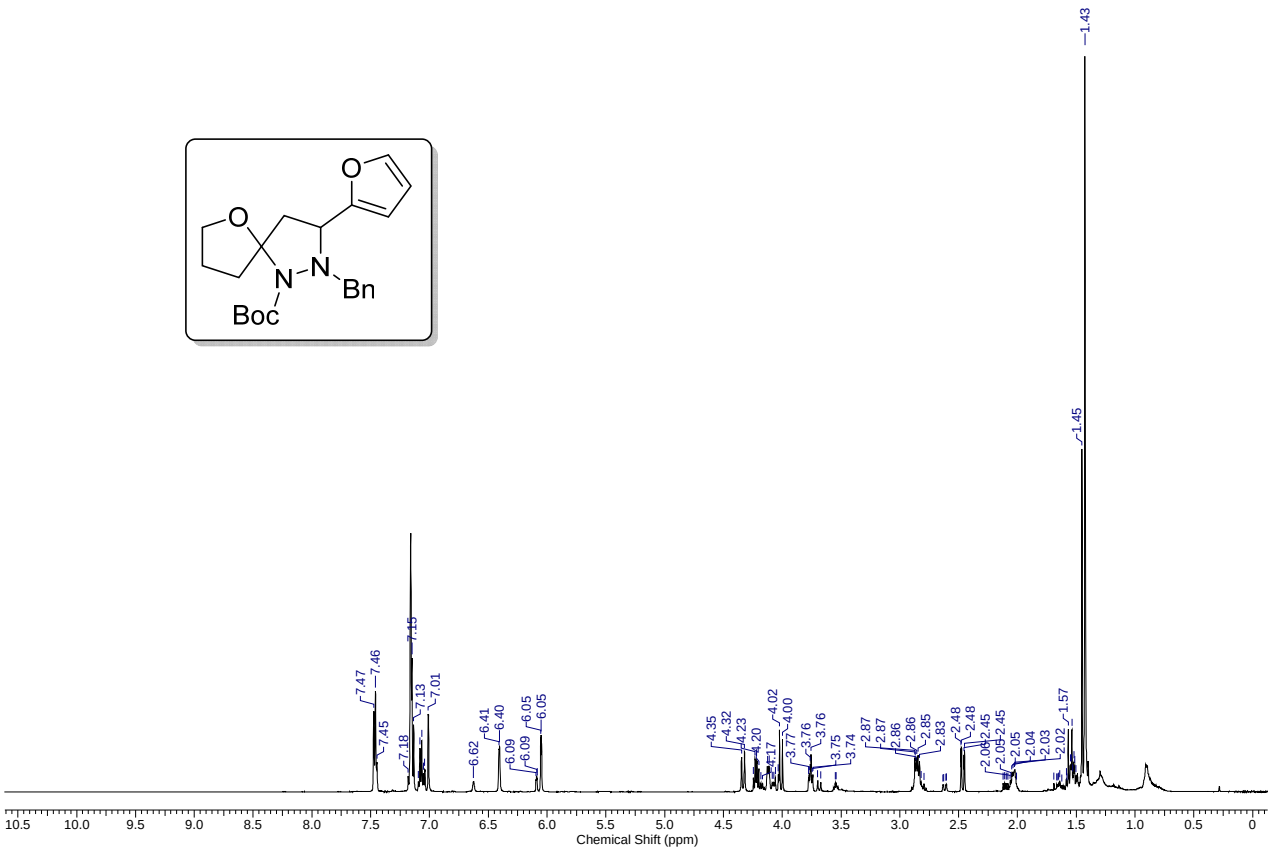


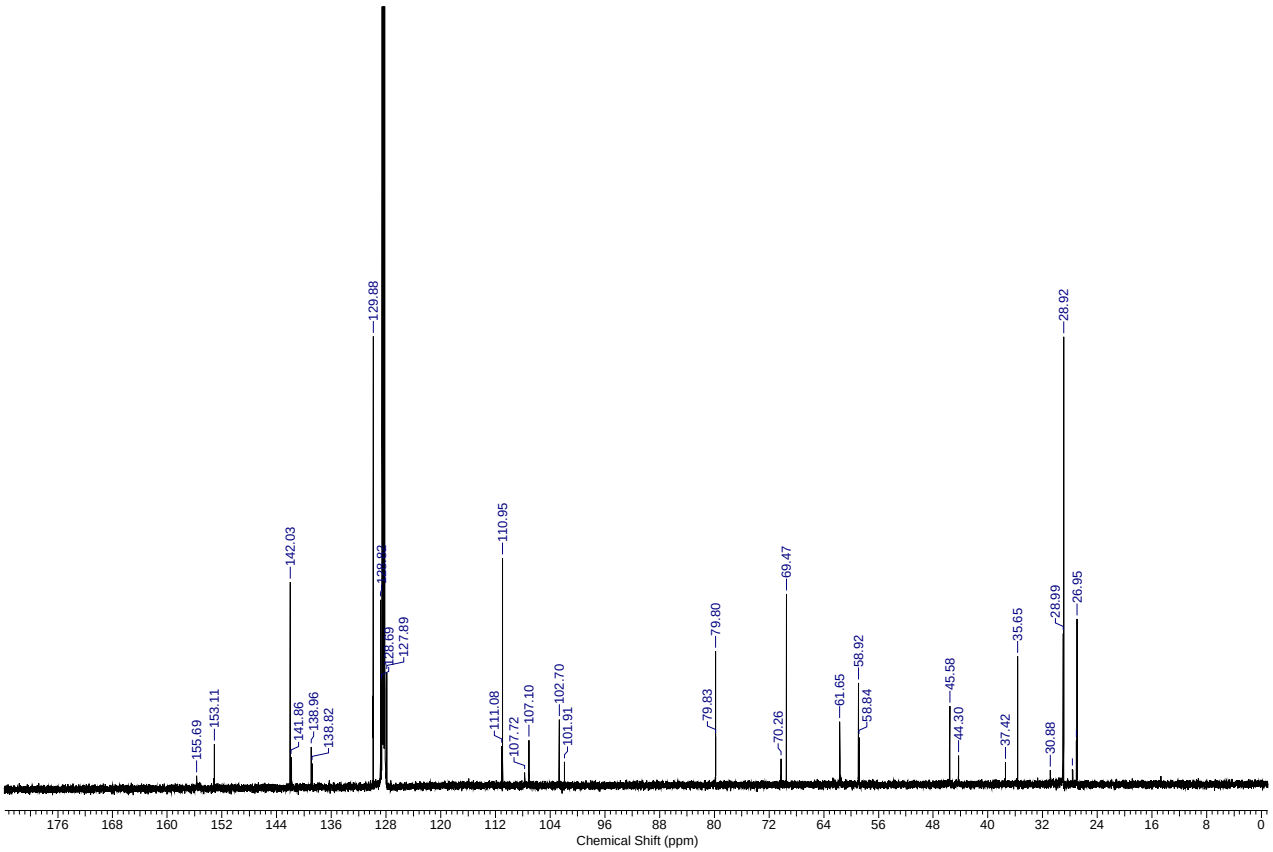
WB-487a.011.esp



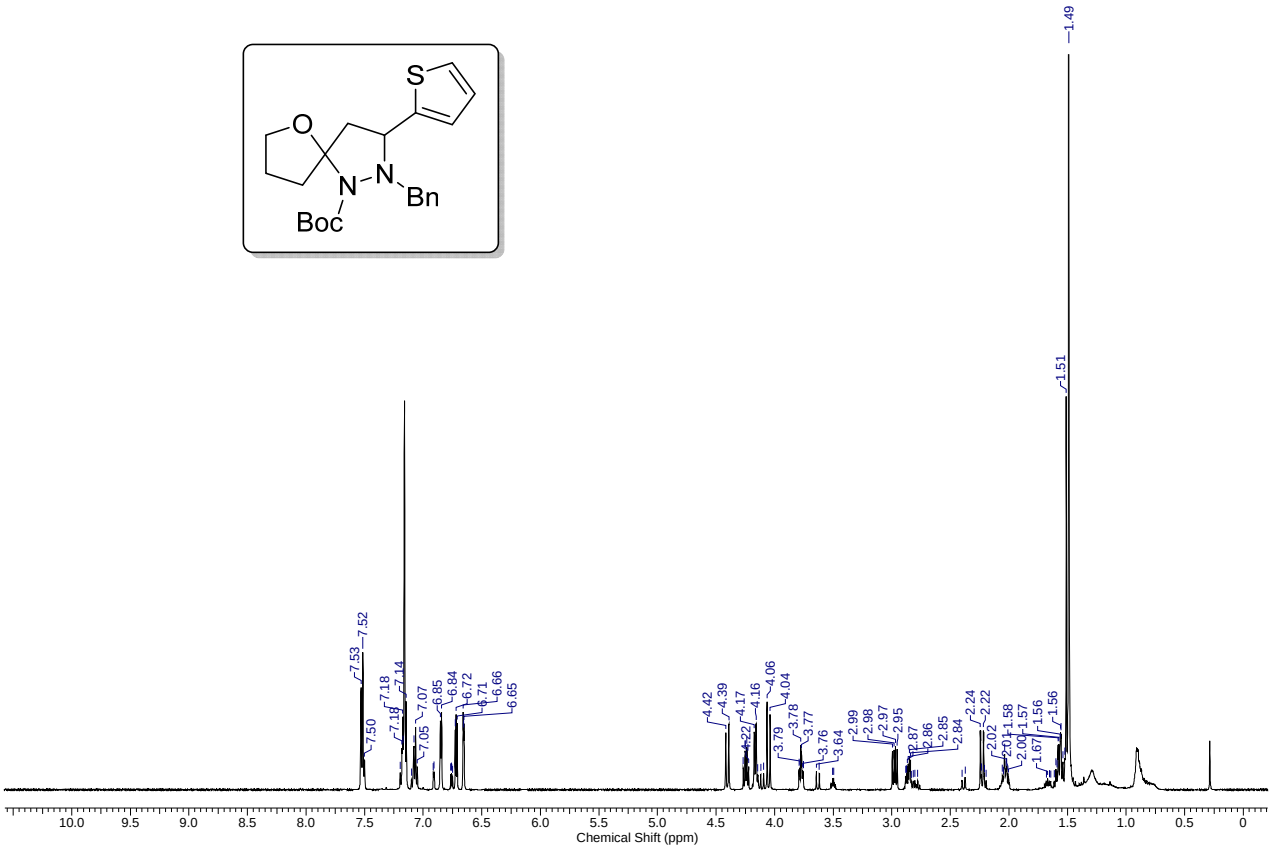

WB-487a.013.esp
163.11
163.06
163.19
163.21
163.03
156.79
142.01
142.07
156.72
156.87
162.90
162.82
162.80
142.71
157.34
-100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195 -200 -205 -210
Chemical Shift (ppm)

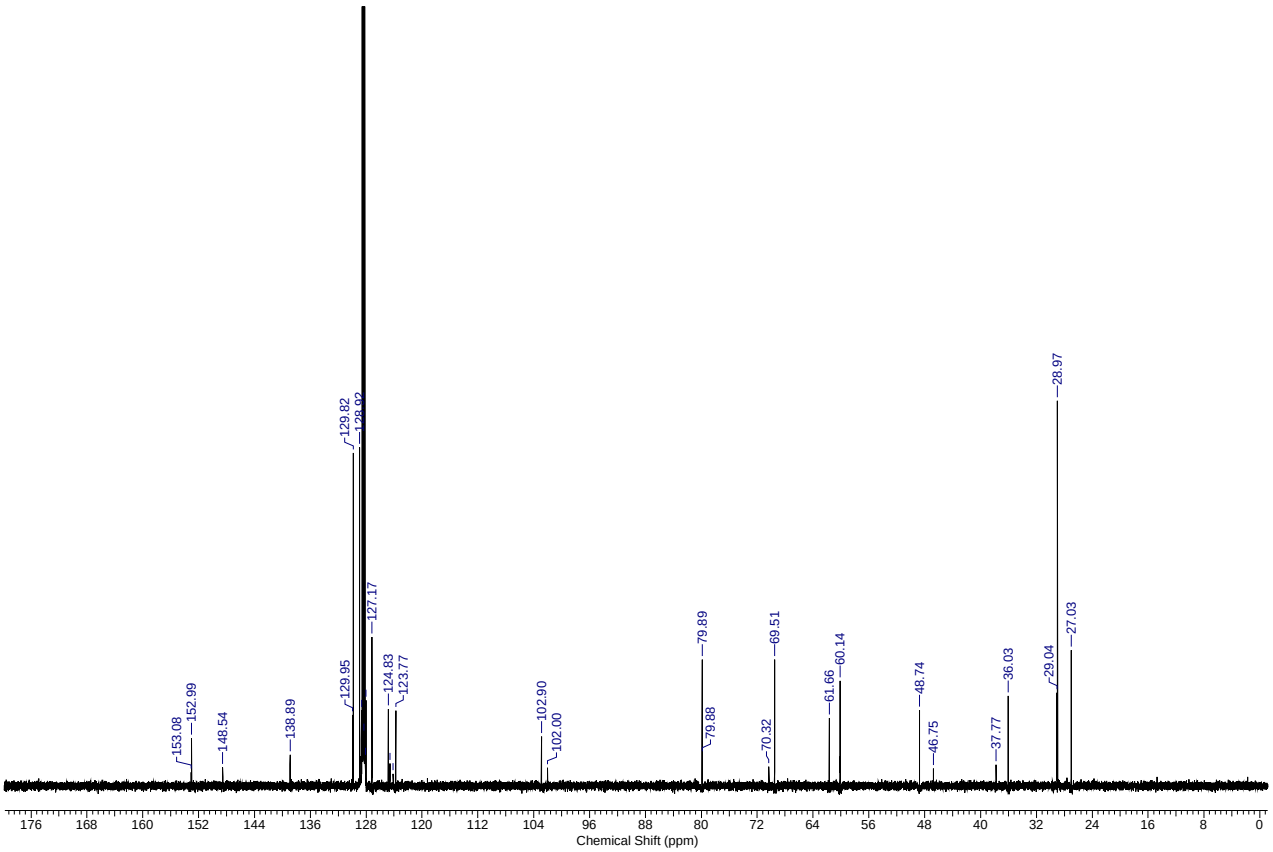
4l


O
O
N
N
Bn
Boc
1.43
1.45
7.47
7.46
7.45
7.18
7.15
7.13
7.01
6.62
6.41
6.40
6.09
6.09
6.05
6.05
4.35
4.32
4.23
4.20
4.17
4.02
4.00
3.77
3.76
3.76
3.75
3.74
2.87
2.87
2.86
2.86
2.85
2.83
2.48
2.48
2.45
2.45
2.05
2.05
2.04
2.03
2.02
1.57
Chemical Shift (ppm)


155.69
153.11
142.03
141.86
138.96
138.82
129.88
129.09
128.69
127.89
111.08
110.95
107.72
107.10
102.70
101.91
79.83
79.80
70.26
69.47
61.65
58.92
58.84
45.58
44.30
37.42
35.65
30.88
28.99
28.92
26.95
Chemical Shift (ppm)

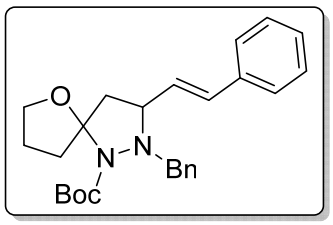
4m


S
O
N
N
Bn
Boc
1.49
1.51
7.53
7.52
7.50
7.18
7.14
7.18
7.07
7.05
6.85
6.84
6.72
6.71
6.66
6.65
4.42
4.39
4.17
4.22
4.16
4.06
4.04
3.79
3.78
3.77
3.76
3.64
2.99
2.98
2.97
2.95
2.87
2.86
2.85
2.84
2.24
2.22
2.02
2.01
1.58
2.00
1.57
1.67
1.56
1.56
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

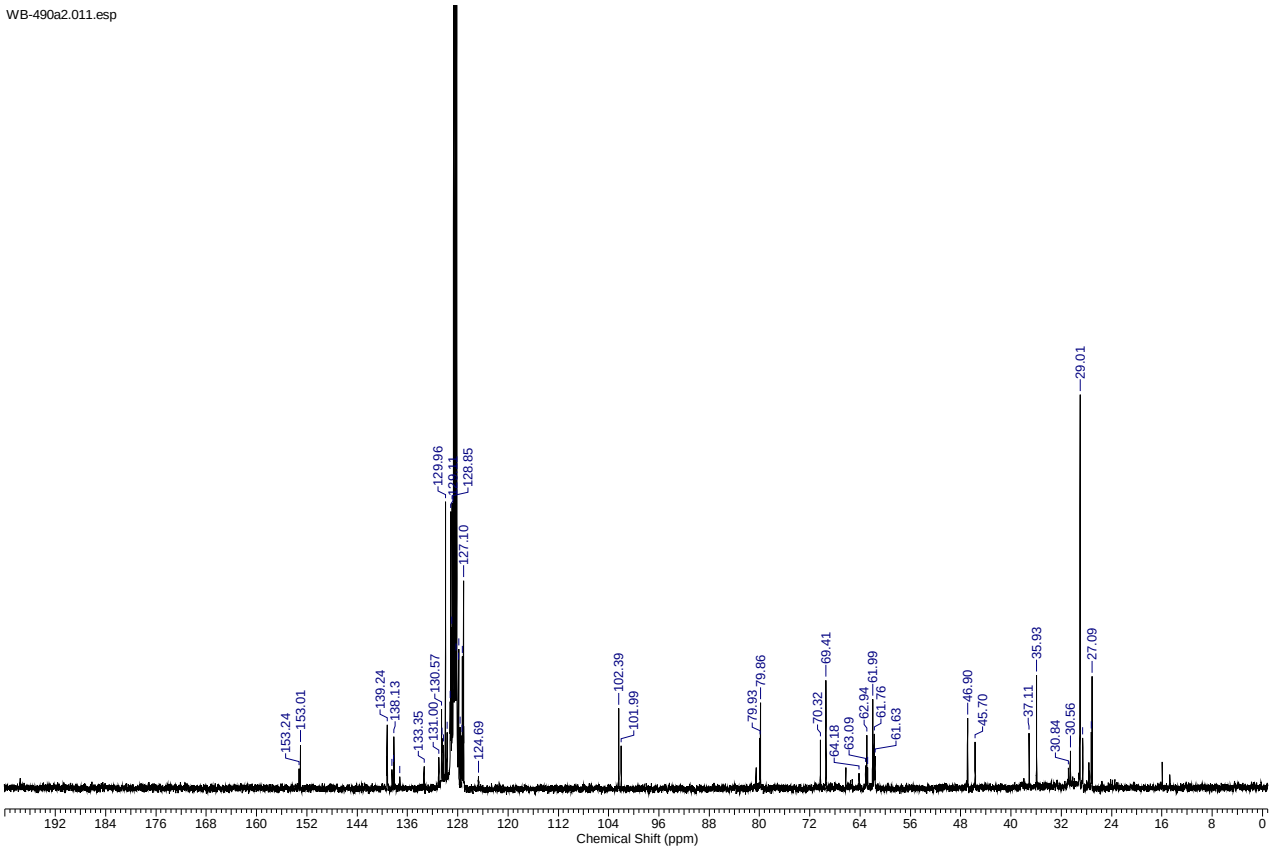

28.97
129.82
128.92
127.17
153.08
152.99
148.54
138.89
129.95
124.83
123.77
102.90
102.00
79.89
79.88
70.32
69.51
61.66
60.14
48.74
46.75
37.77
36.03
29.04
27.03
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

4n

WB-490a2.010.esp

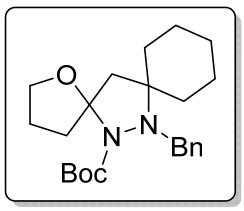


WB-490a2.011.esp

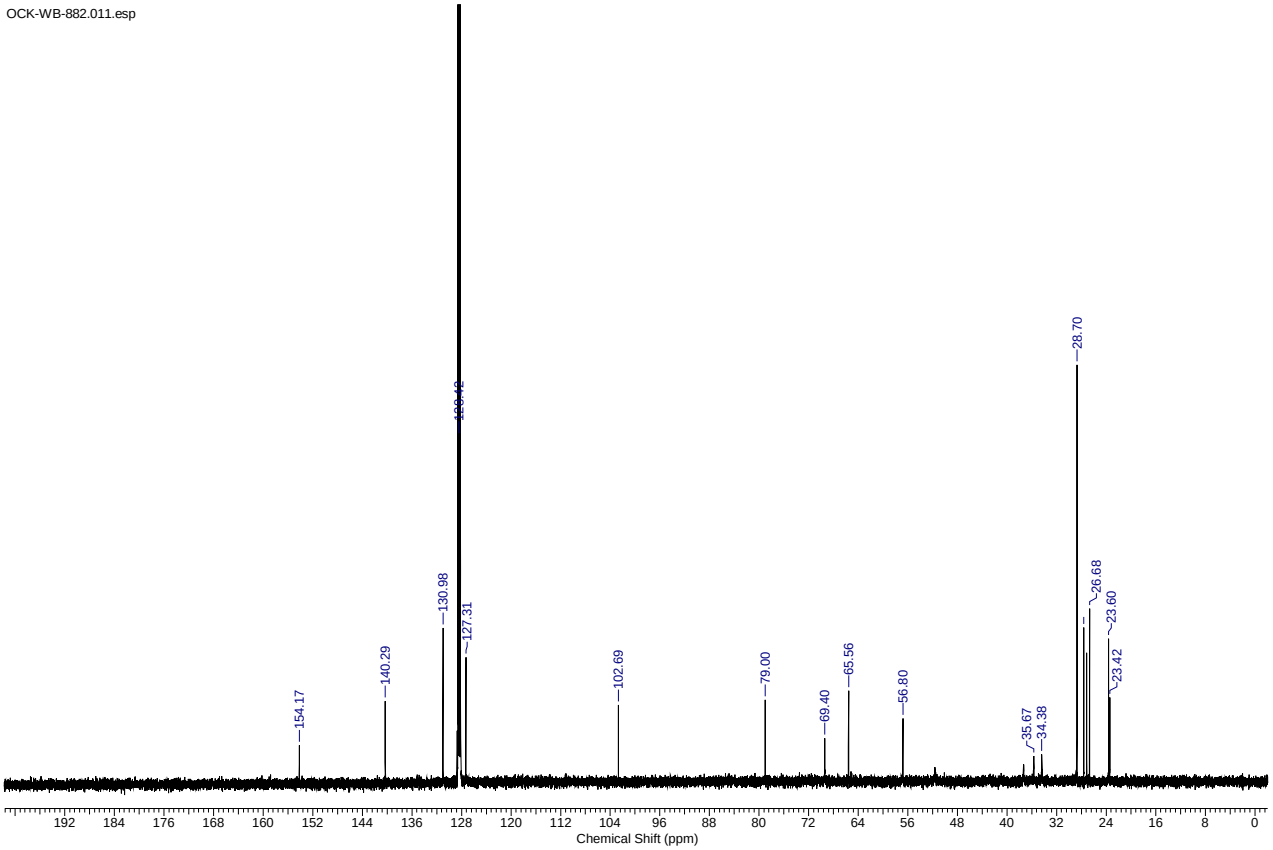


4o

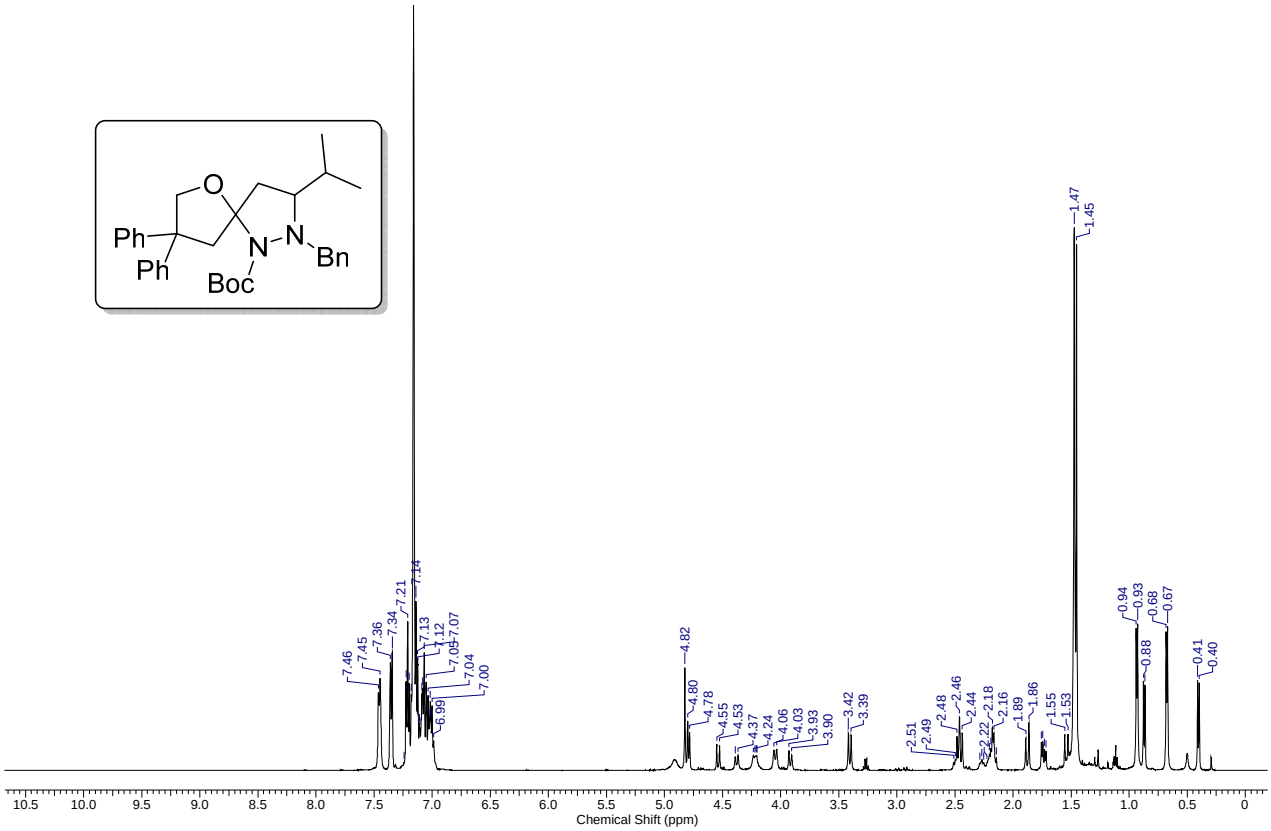
OCK-WB-882.010.esp

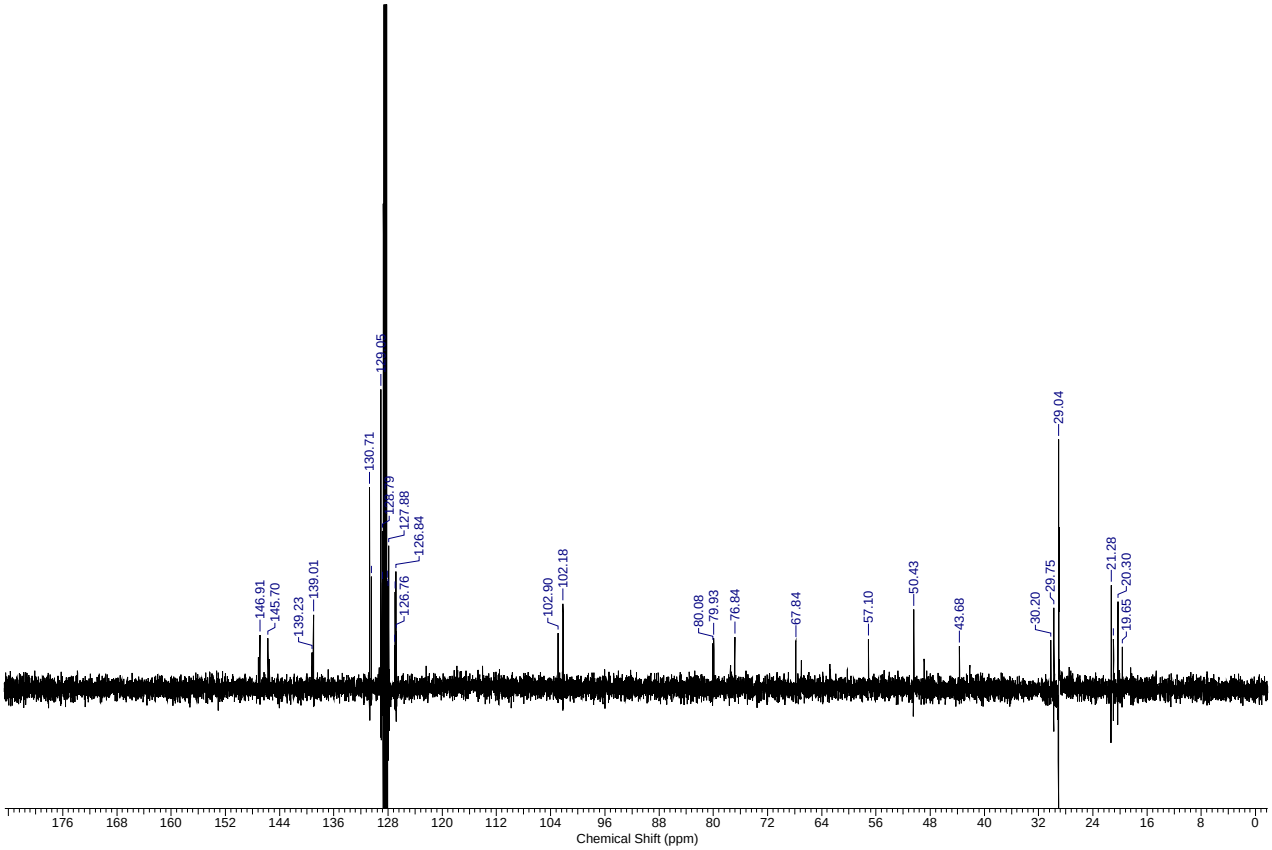


OCK-WB-882.011.esp

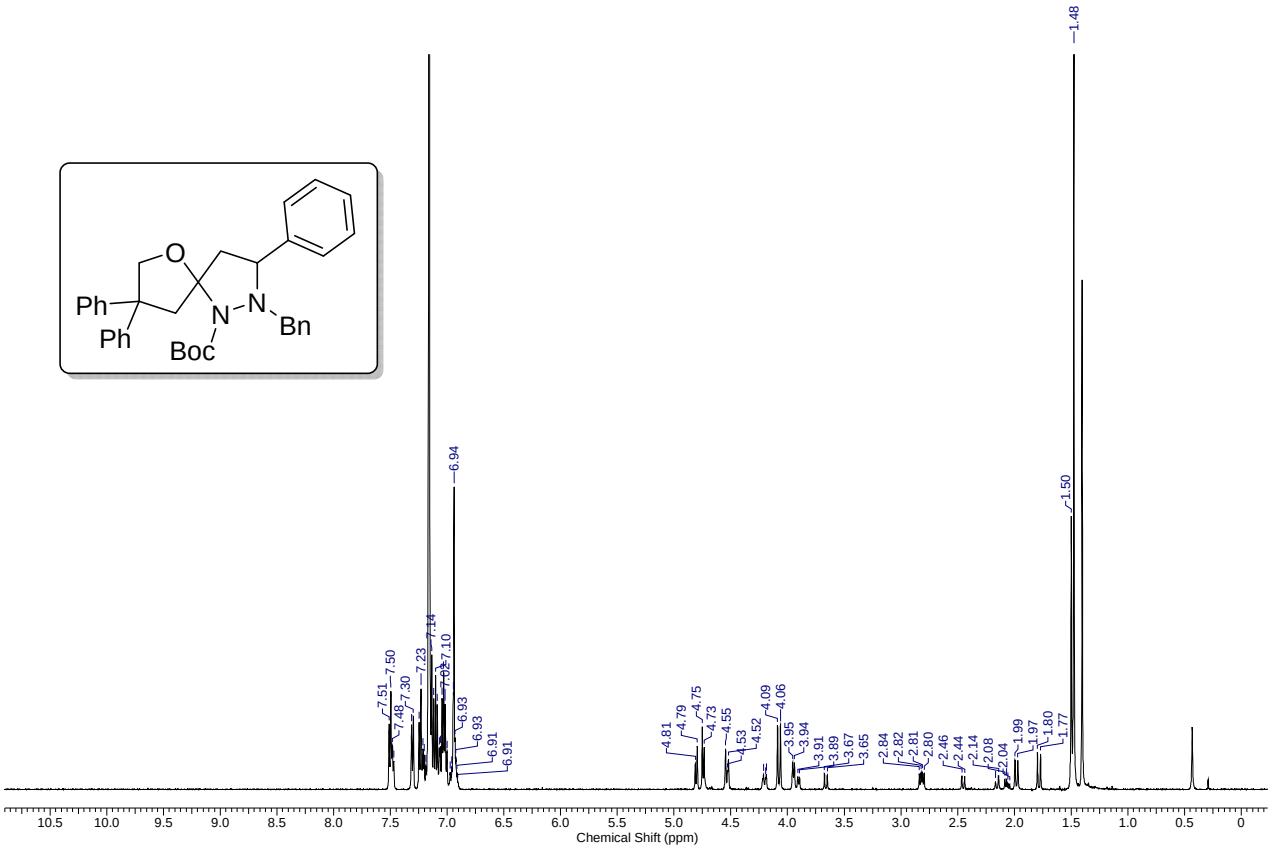


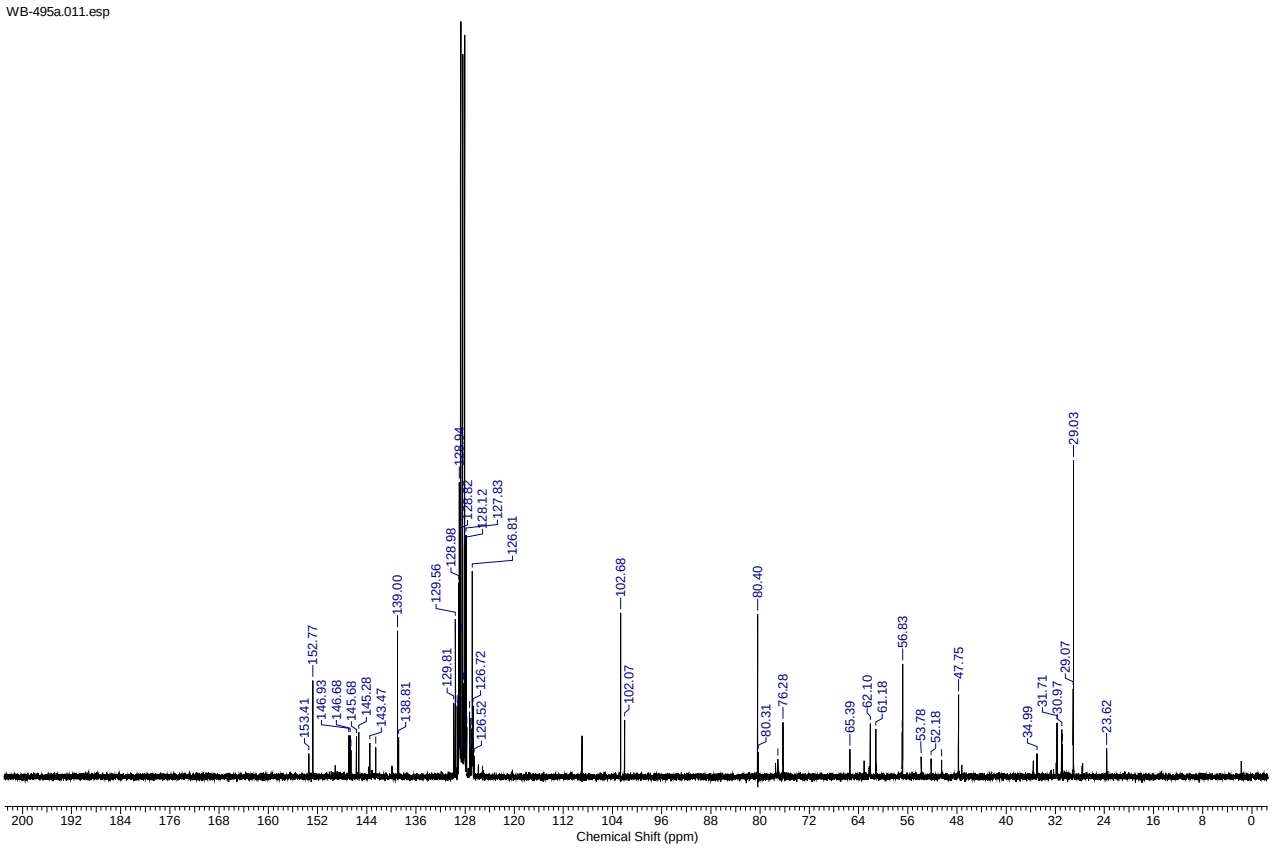
4p


Ph
Ph
O
N
N
Bn
Boc
7.46
7.45
7.36
7.34
7.21
7.14
7.13
7.12
7.09
7.07
7.04
7.00
6.99
4.82
4.80
4.78
4.55
4.53
4.37
4.24
4.06
4.03
3.93
3.90
3.42
3.39
2.51
2.49
2.48
2.46
2.44
2.22
2.18
2.16
1.89
1.86
1.55
1.53
1.47
1.45
0.94
0.93
0.88
0.68
0.67
0.41
0.40
Chemical Shift (ppm)

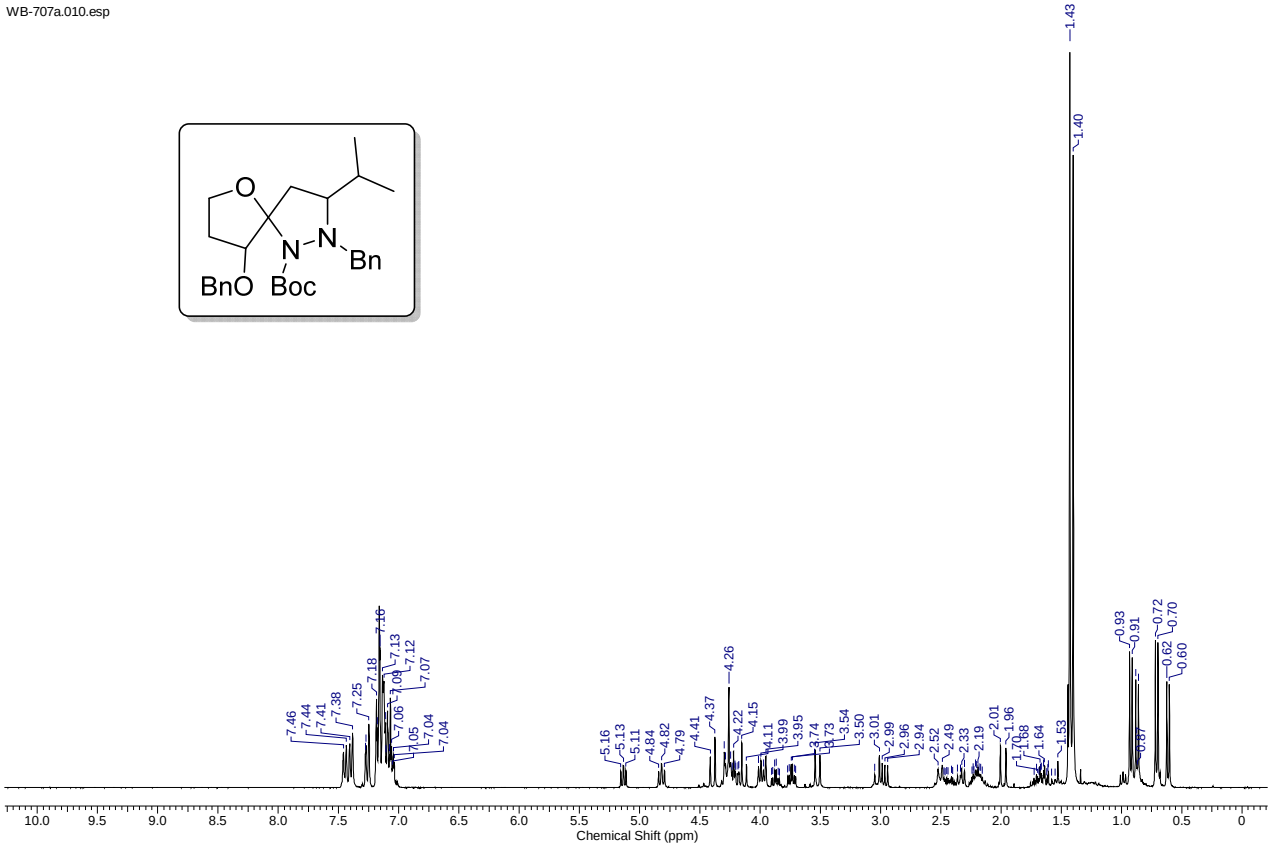

146.91
145.70
139.23
139.01
130.71
129.05
128.79
127.88
126.84
126.76
102.90
102.18
80.08
79.93
76.84
67.84
57.10
50.43
43.68
30.20
29.75
29.04
21.28
20.30
19.65
Chemical Shift (ppm)

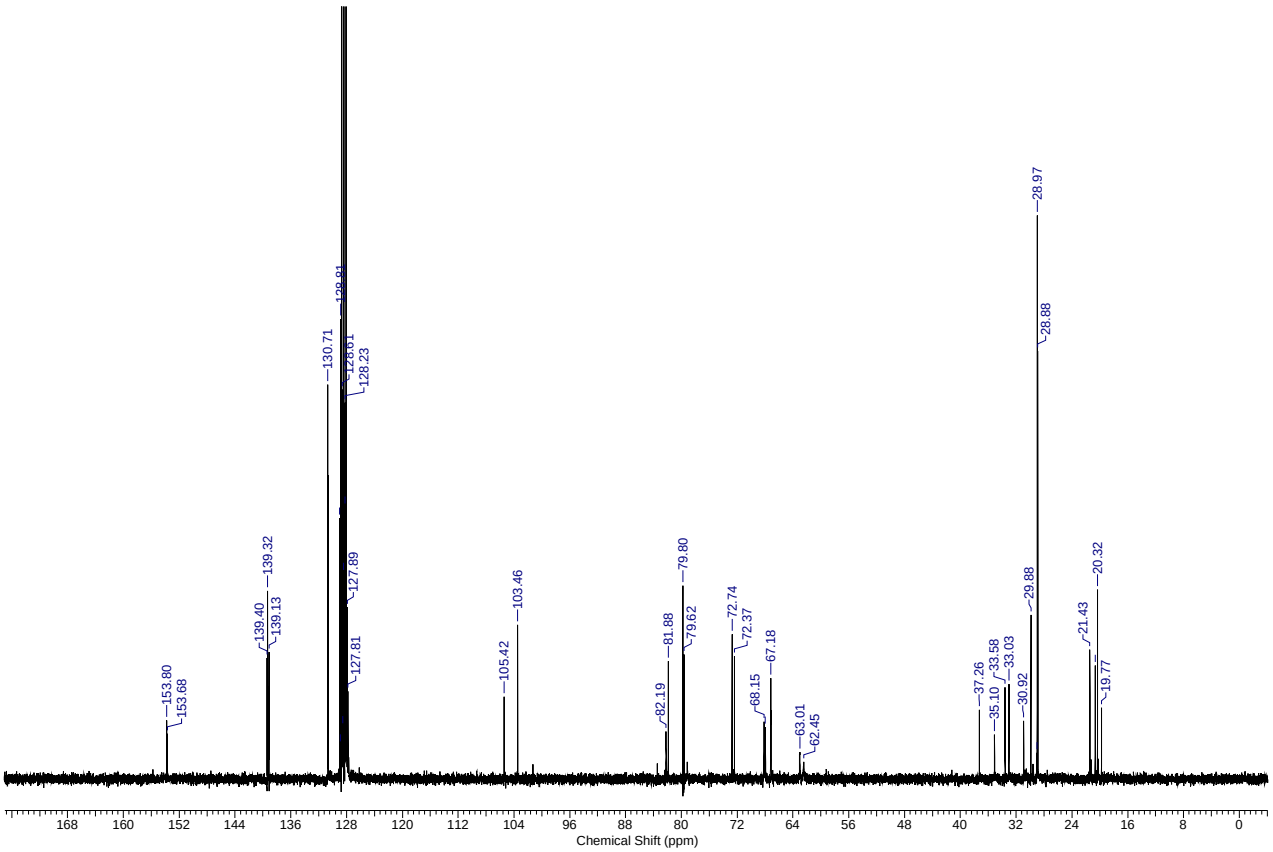
4q


Ph
Ph
O
N
N
Bn
Boc
Chemical Shift (ppm)

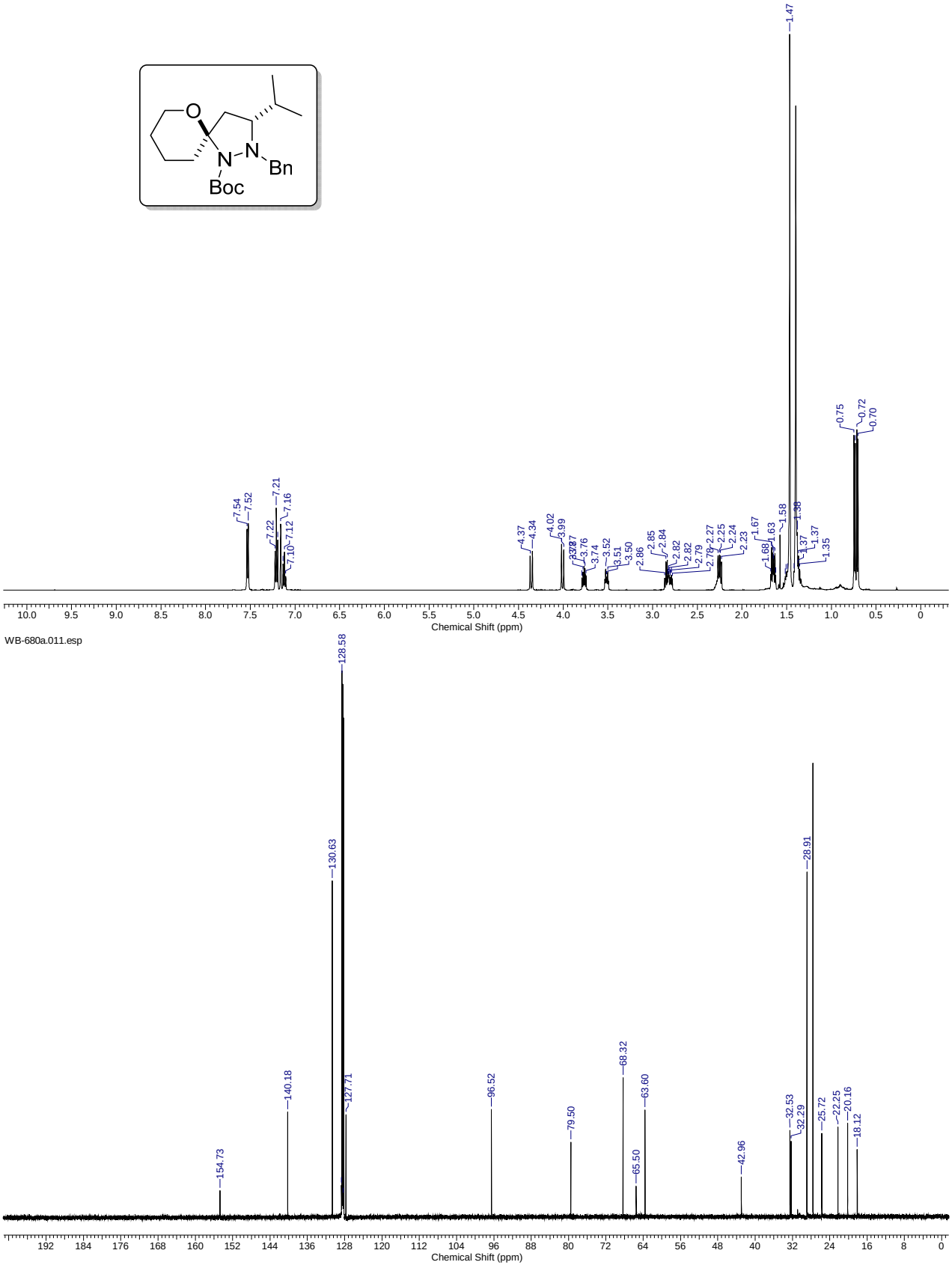

WB-495a.011.esp
Chemical Shift (ppm)

4r

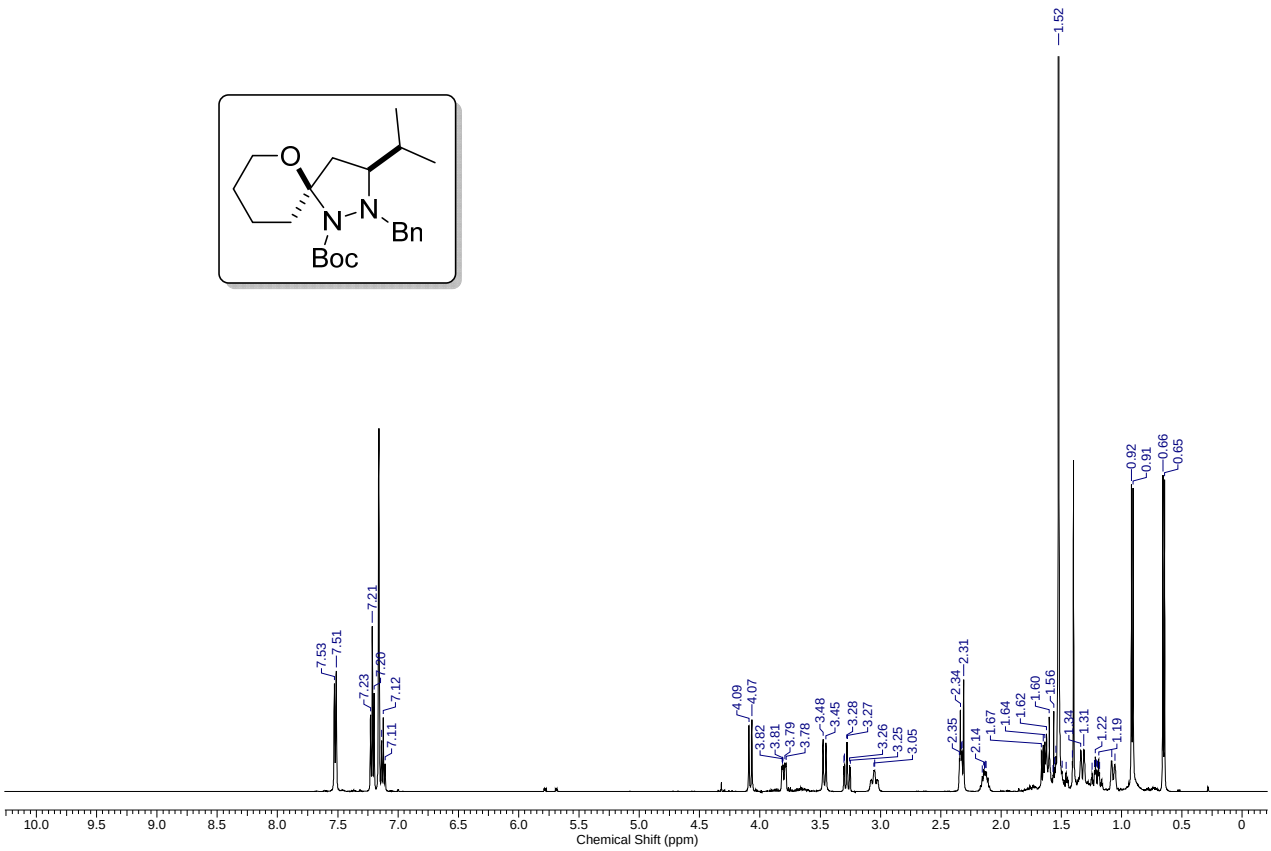

WB-707a.010.esp
O
N
N
Bn
BnO
Boc
Chemical Shift (ppm)

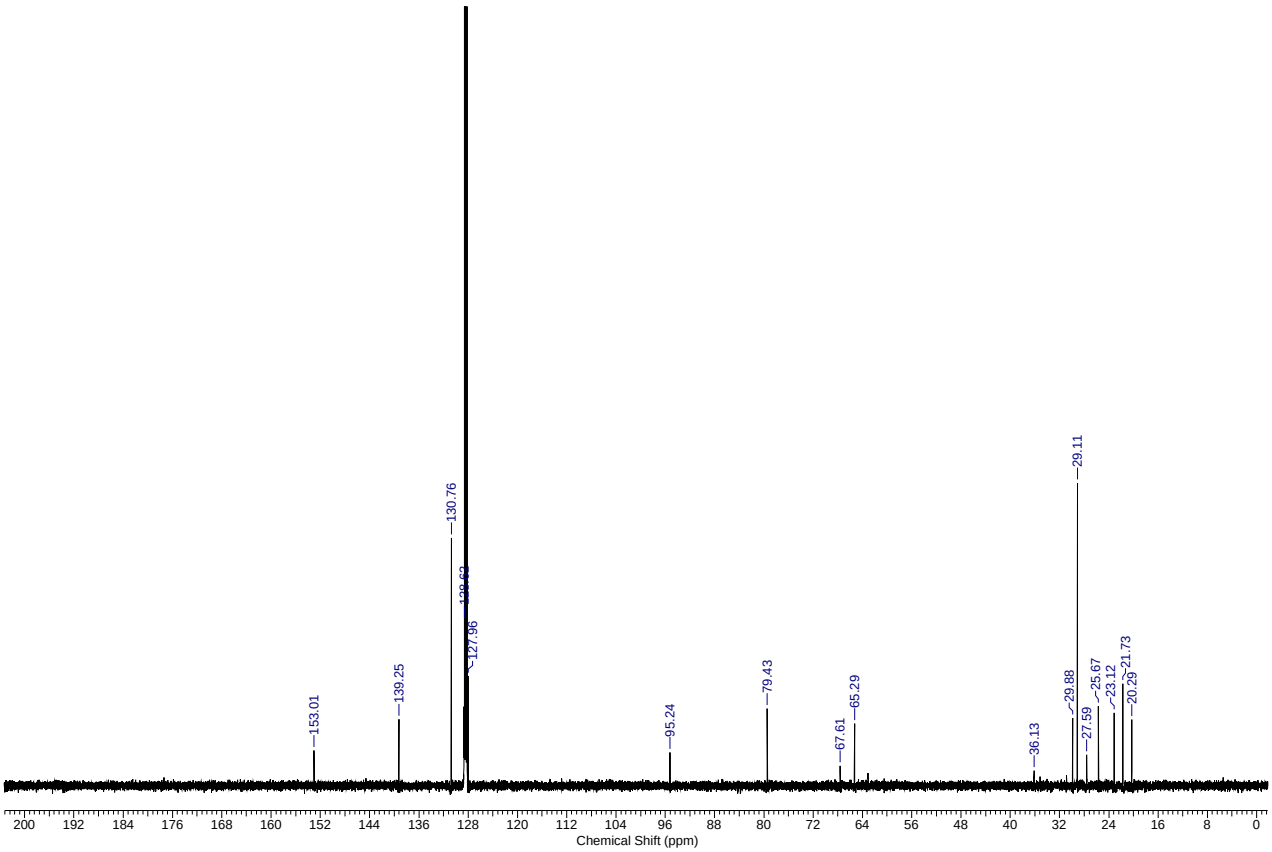

Chemical Shift (ppm)

***(anti)*-4s**


O
N
N
Bn
Boc
1.47
0.75
0.72
0.70
7.54
7.52
7.21
7.22
7.16
7.12
7.10
4.37
4.34
4.02
3.99
3.76
3.74
3.52
3.51
3.50
2.86
2.85
2.84
2.82
2.79
2.27
2.25
2.24
2.23
1.67
1.63
1.58
1.38
1.37
1.35
Chemical Shift (ppm)
WB-680a.011.esp
128.58
130.63
140.18
127.71
154.73
96.52
79.50
68.32
65.50
63.60
42.96
32.53
32.29
28.91
25.72
22.25
20.16
18.12
Chemical Shift (ppm)

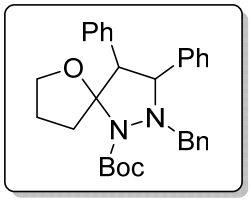
***(syn)*-4s**


O
N
N
Bn
Boc
1.52
7.53
7.51
7.21
7.23
7.20
7.12
7.11
4.09
4.07
3.82
3.81
3.79
3.78
3.48
3.45
3.28
3.27
3.26
3.25
3.05
2.35
2.34
2.31
2.14
1.67
1.64
1.62
1.60
1.56
1.34
1.31
1.22
1.19
0.92
0.91
0.66
0.65
Chemical Shift (ppm)

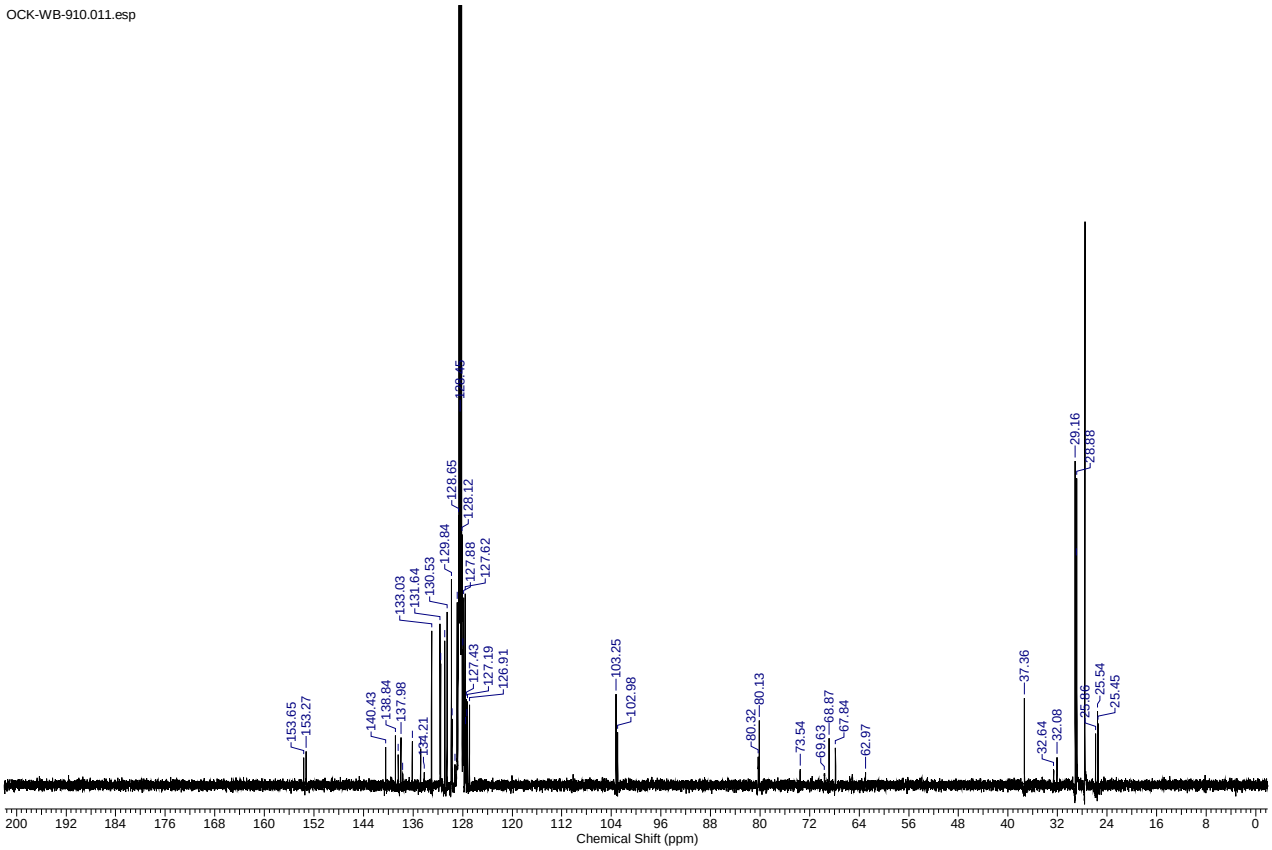

153.01
139.25
130.76
128.63
127.96
95.24
79.43
67.61
65.29
36.13
29.88
29.11
27.59
25.67
23.12
21.73
20.29
Chemical Shift (ppm)

4t

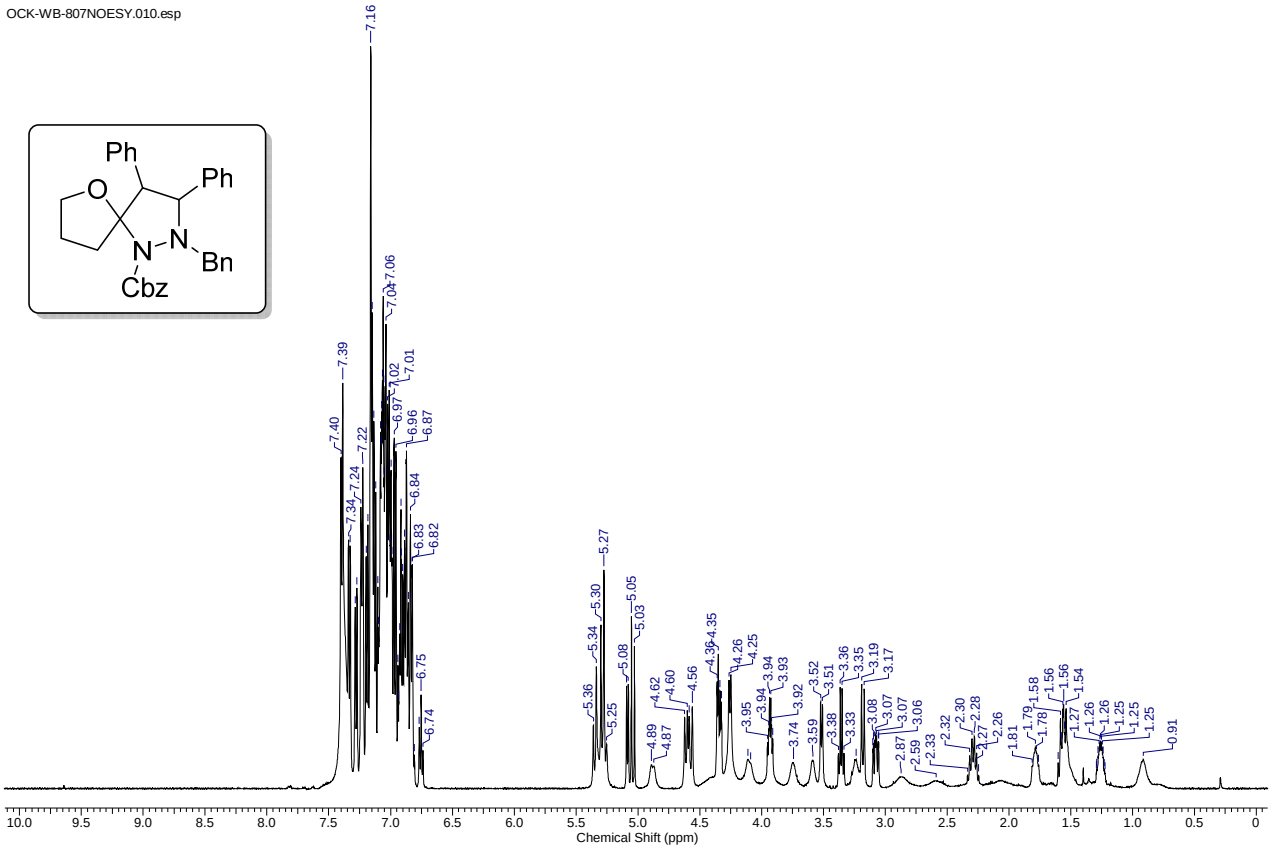
OCK-WB-910.010.esp

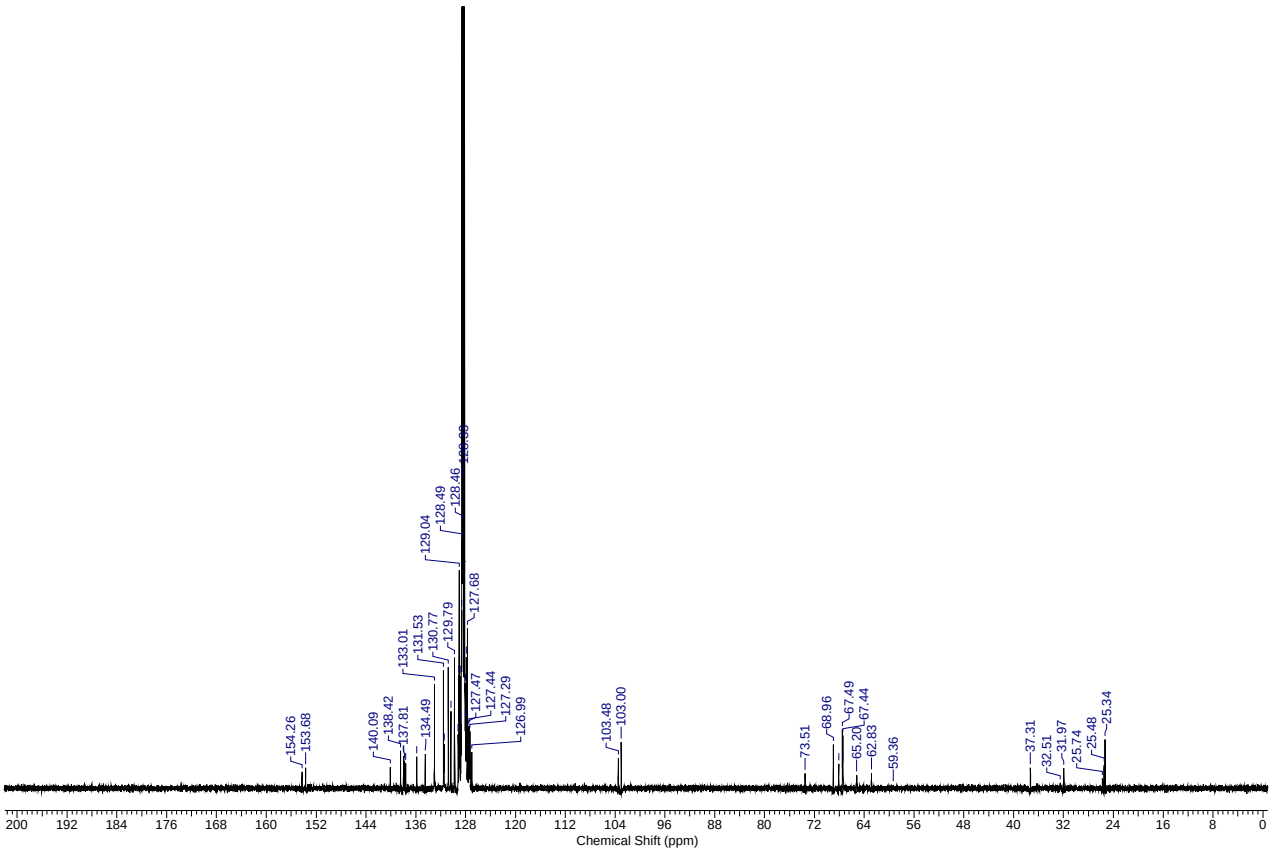


OCK-WB-910.011.esp

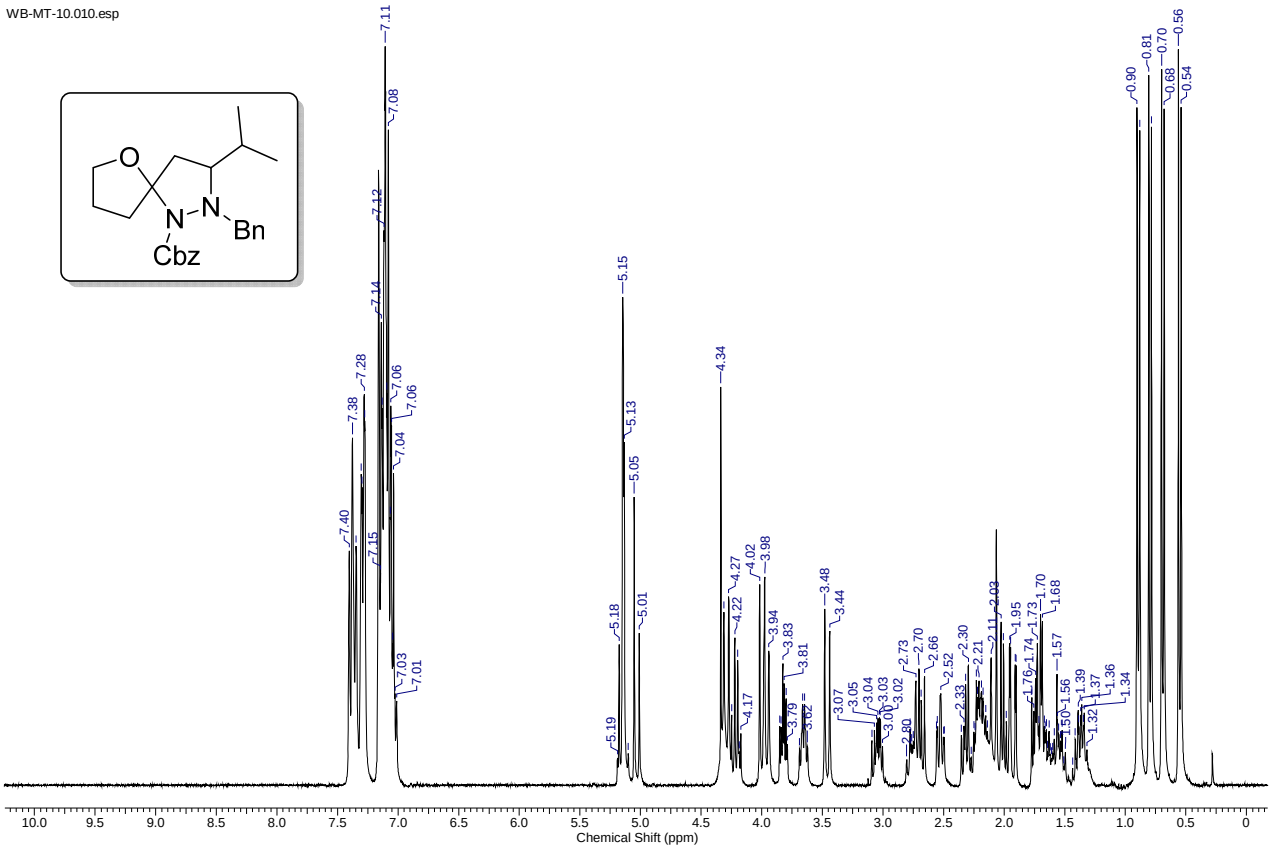


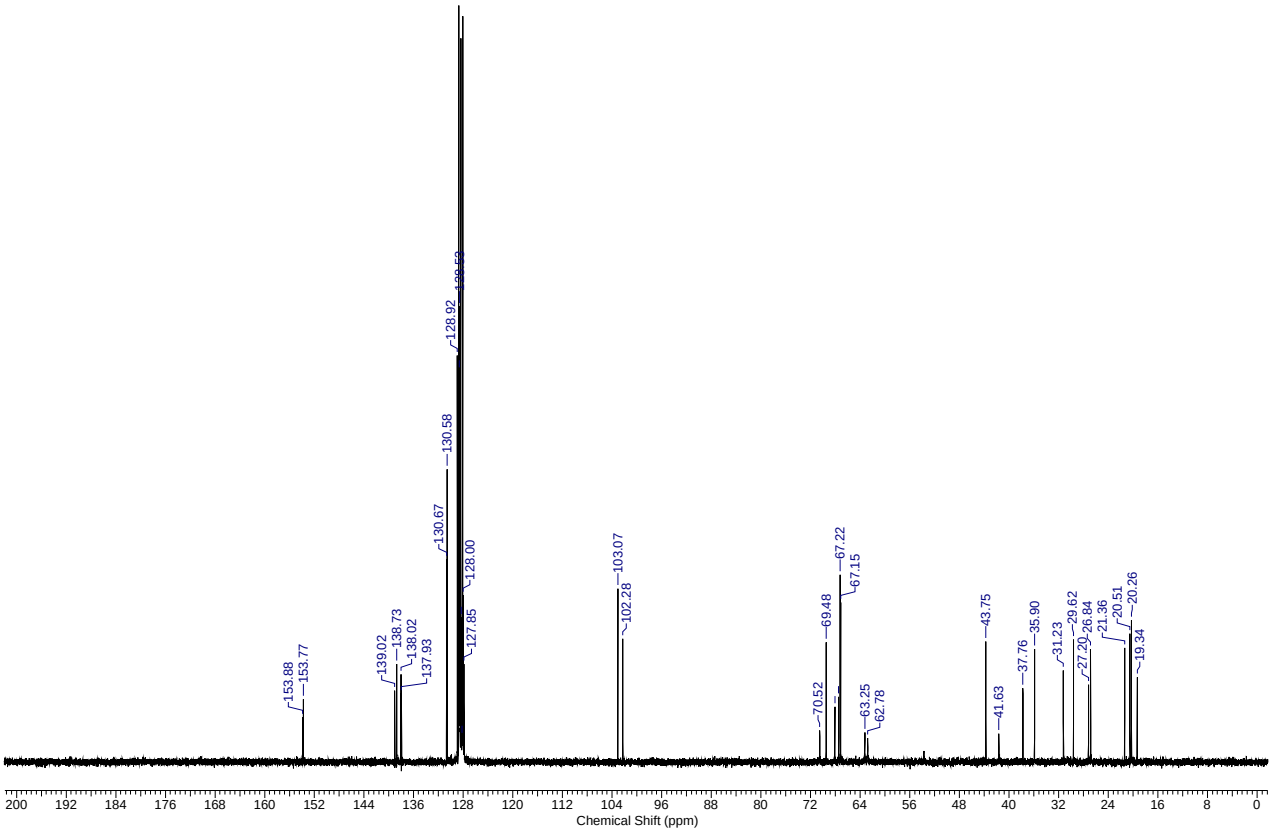
4u


OCK-WB-807NOESY.010.esp
Ph
Ph
O
N
N
Bn
Cbz
Chemical Shift (ppm)

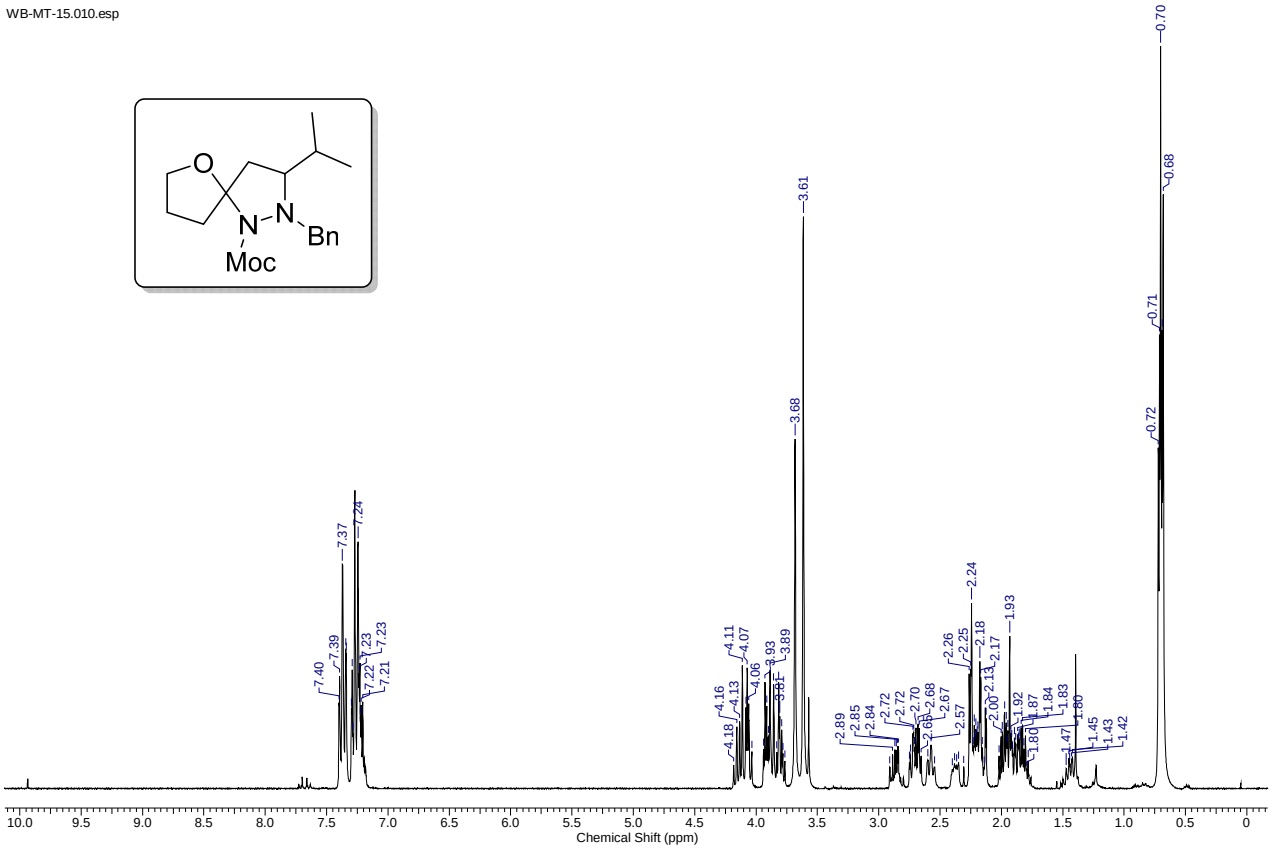

Chemical Shift (ppm)

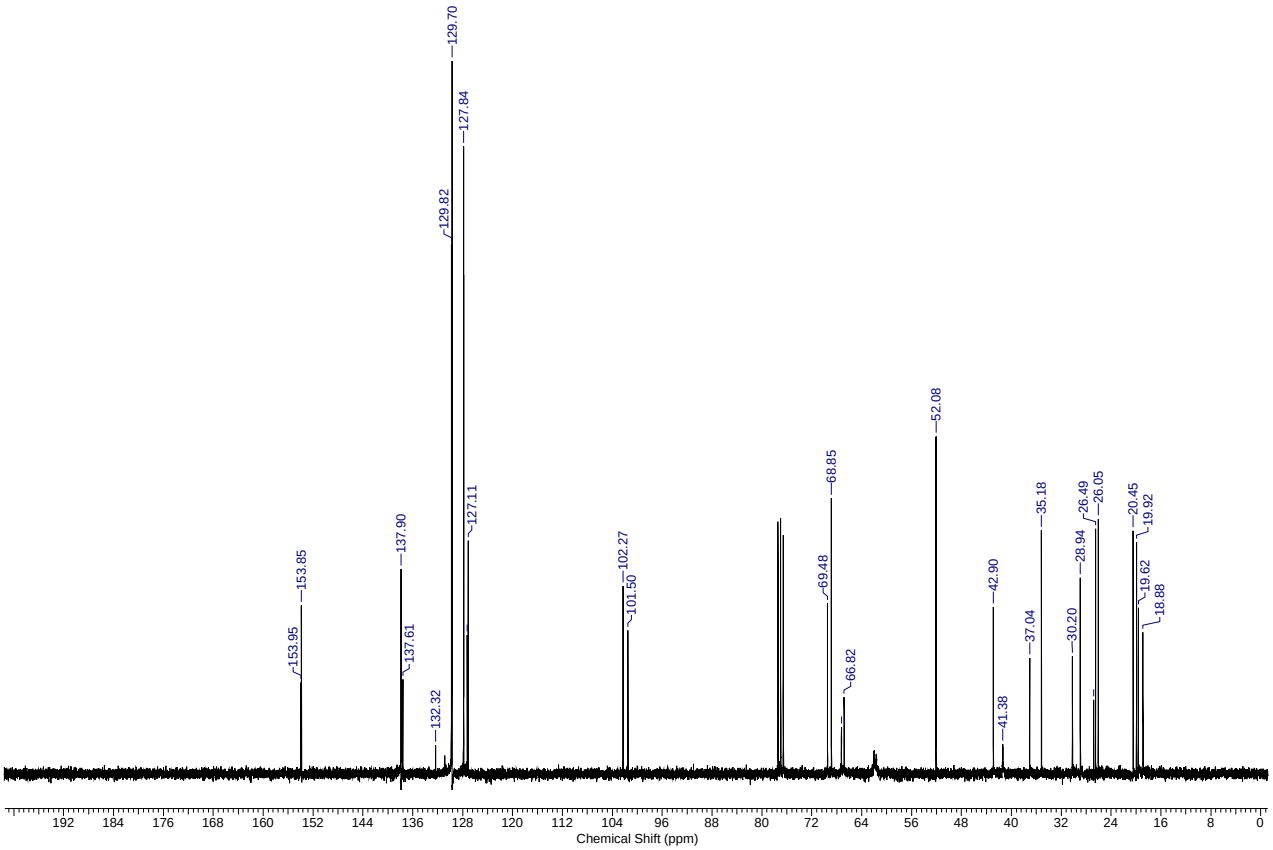
4v


WB-MT-10.010.esp
O
N
N
Bn
Cbz
Chemical Shift (ppm)

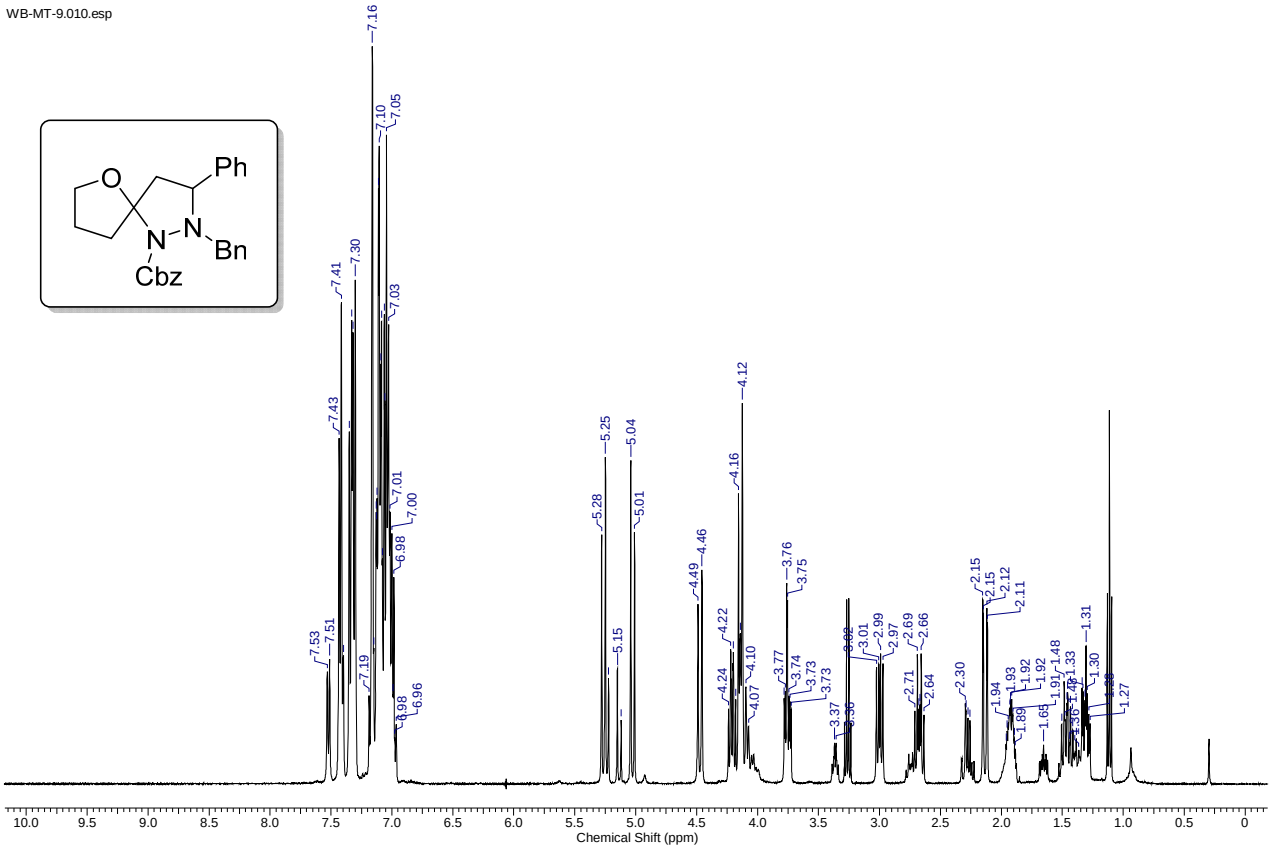

Chemical Shift (ppm)

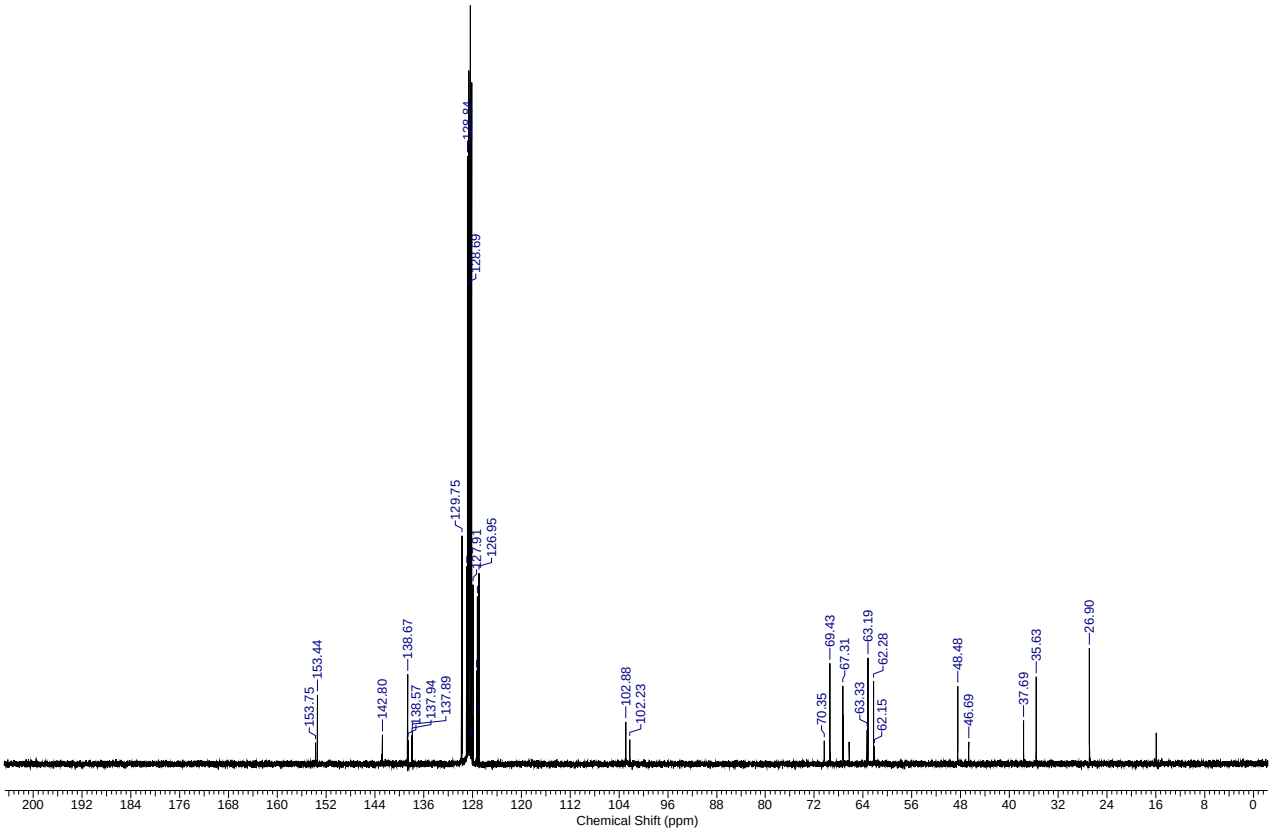
4w


WB-MT-15.010.esp
O
N
N
Bn
Moc
Chemical Shift (ppm)

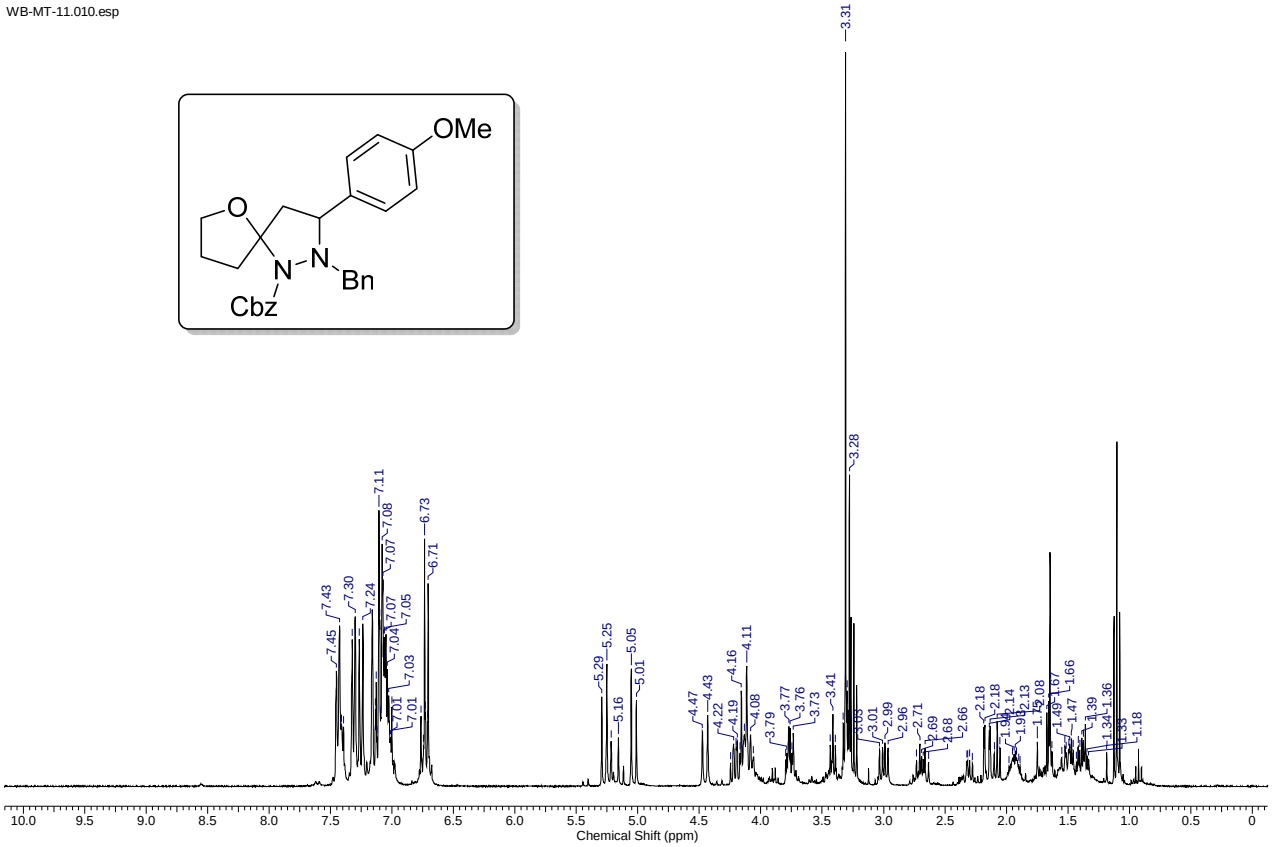

Chemical Shift (ppm)

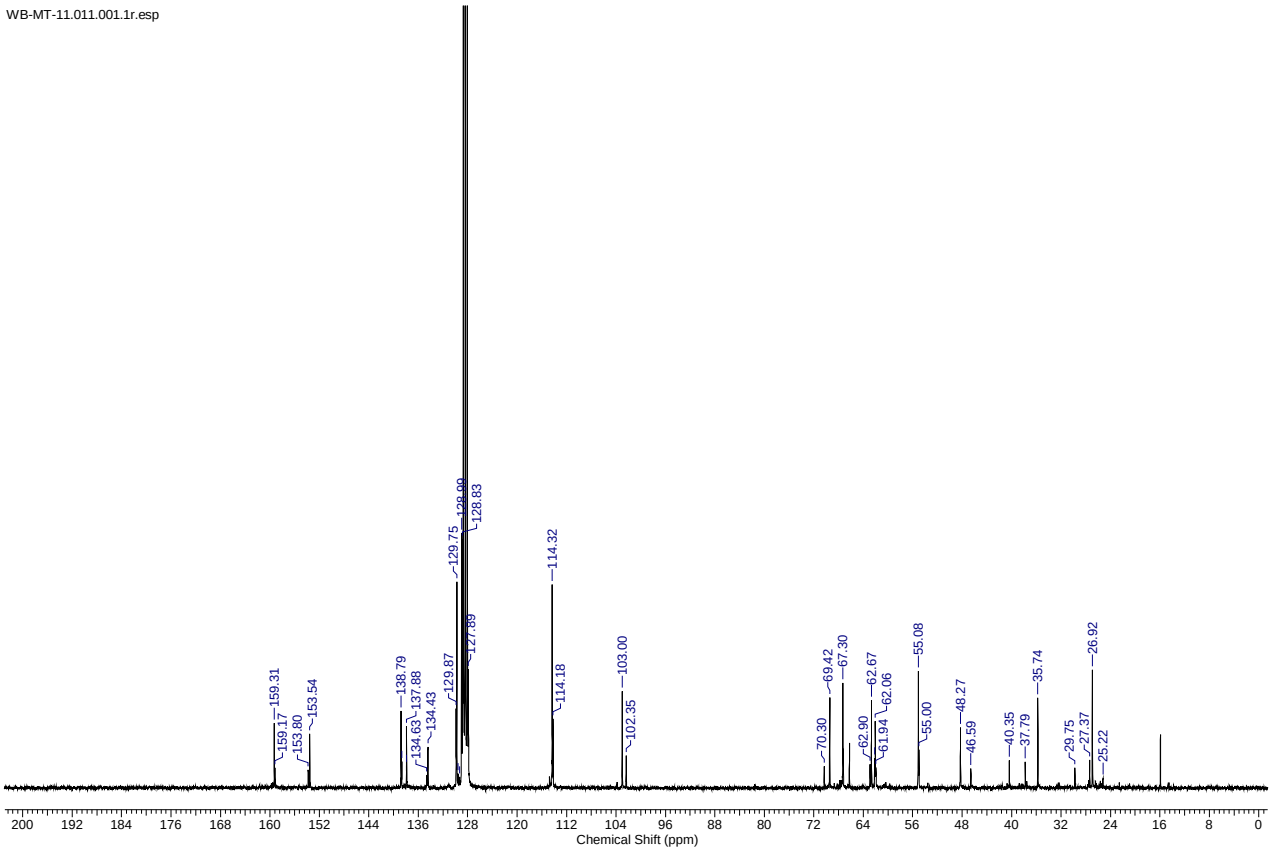
4x


WB-MT-9.010.esp
O
Ph
N
N
Bn
Cbz
Chemical Shift (ppm)

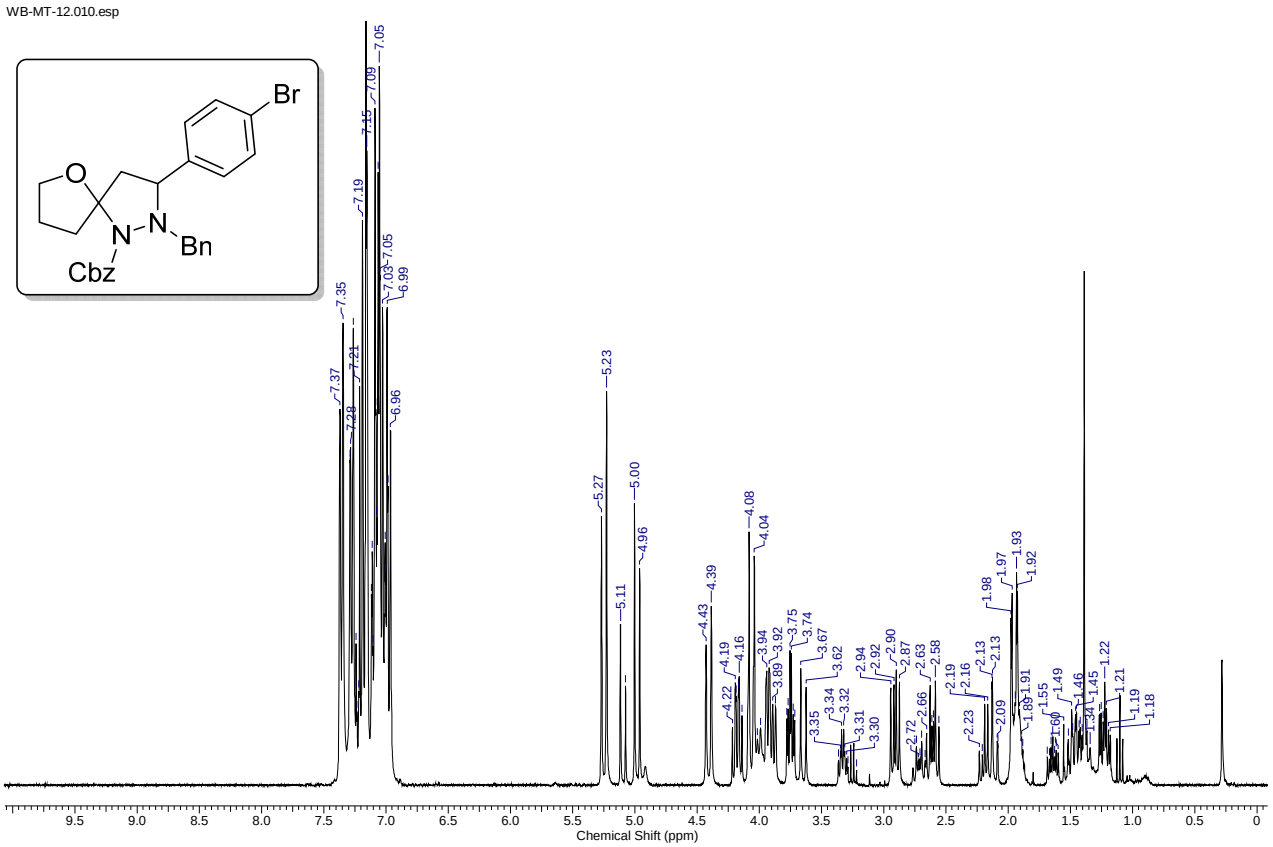

Chemical Shift (ppm)

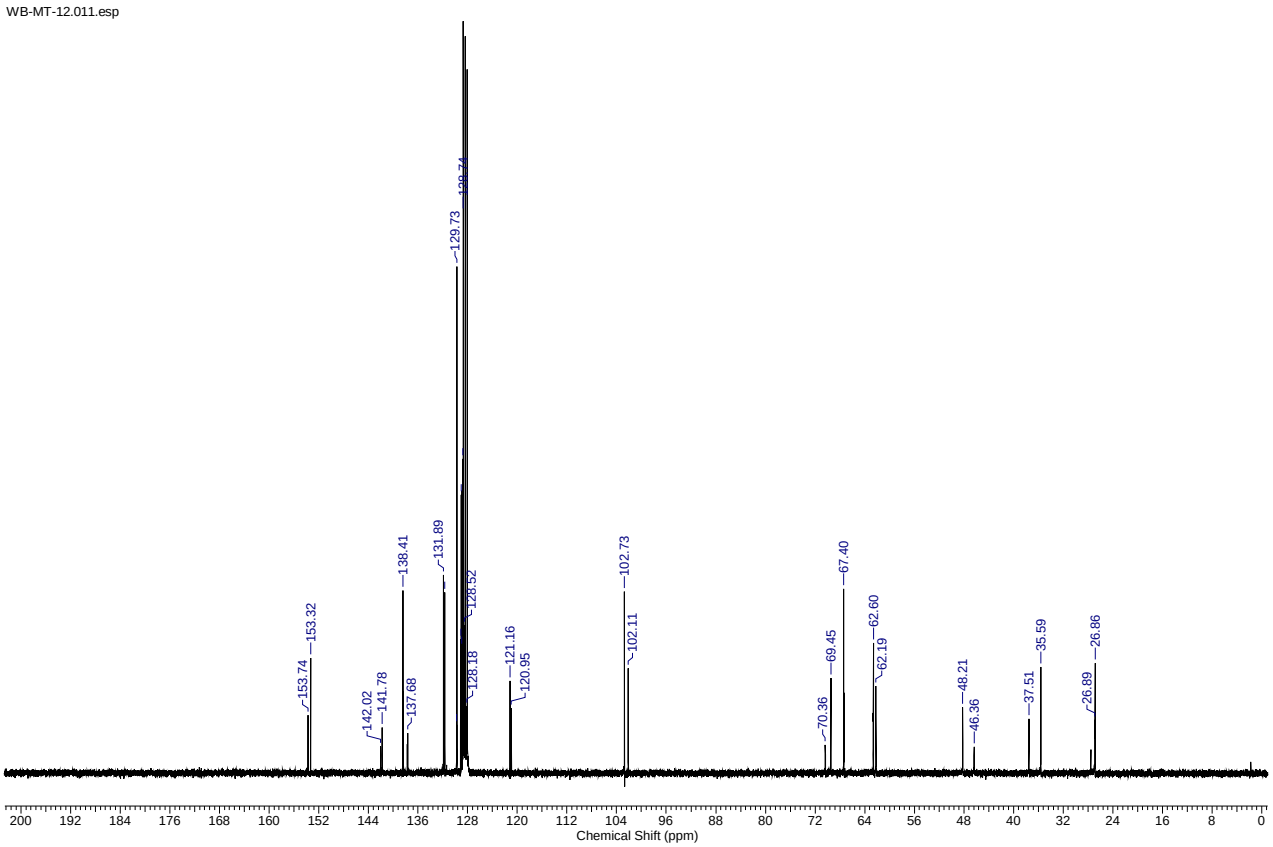
4y


WB-MT-11.010.esp
OMe
O
N
N
Bn
Cbz
Chemical Shift (ppm)

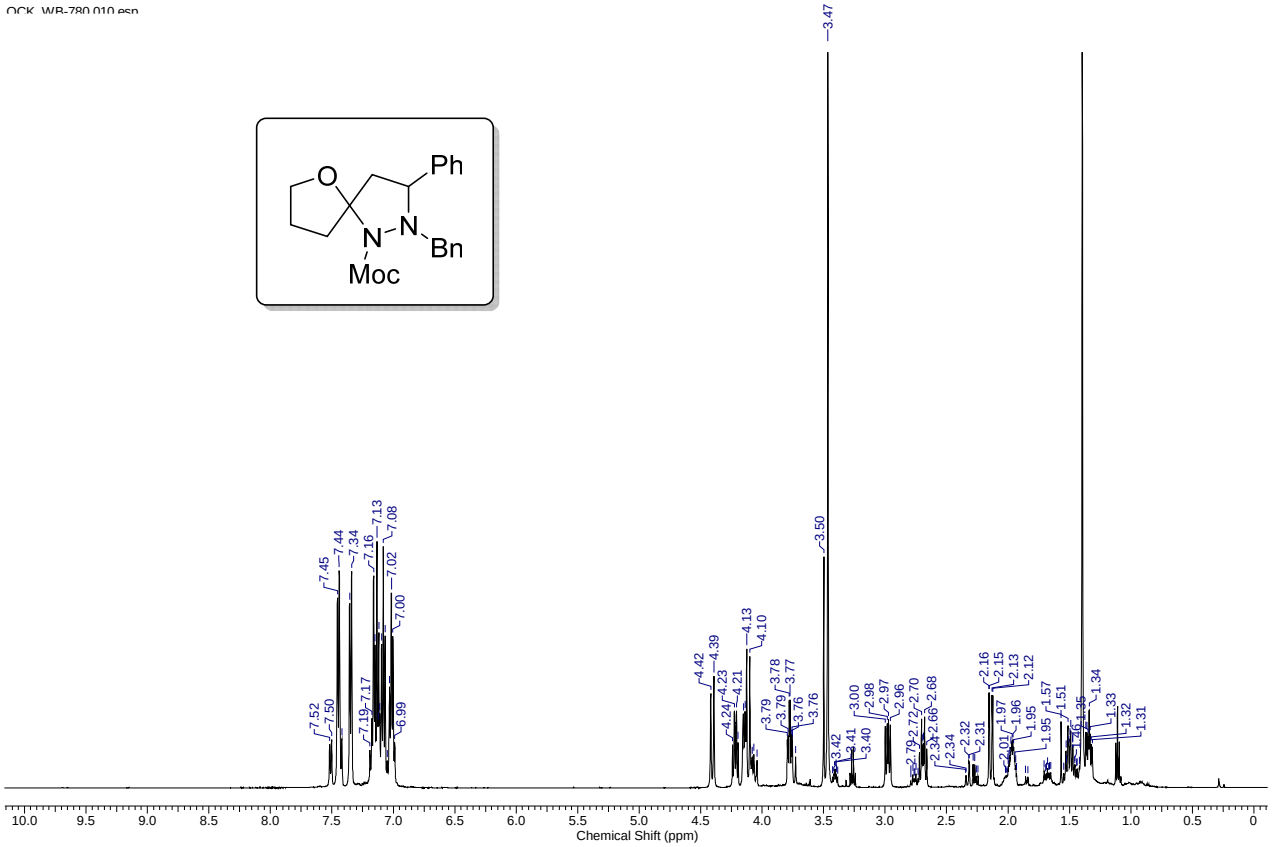

WB-MT-11.011.001.1r.esp
Chemical Shift (ppm)

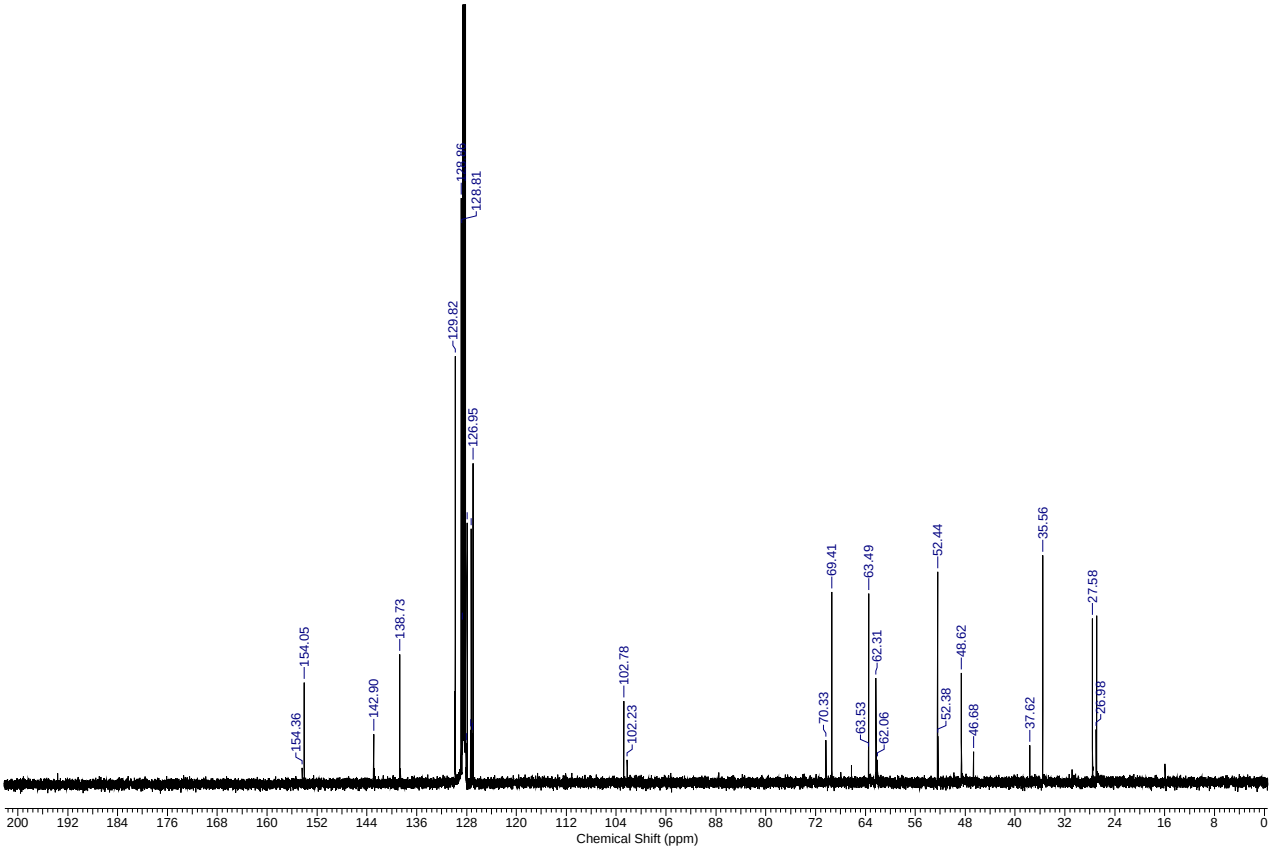
4z


WB-MT-12.010.esp
Br
O
N
N
Bn
Cbz
Chemical Shift (ppm)

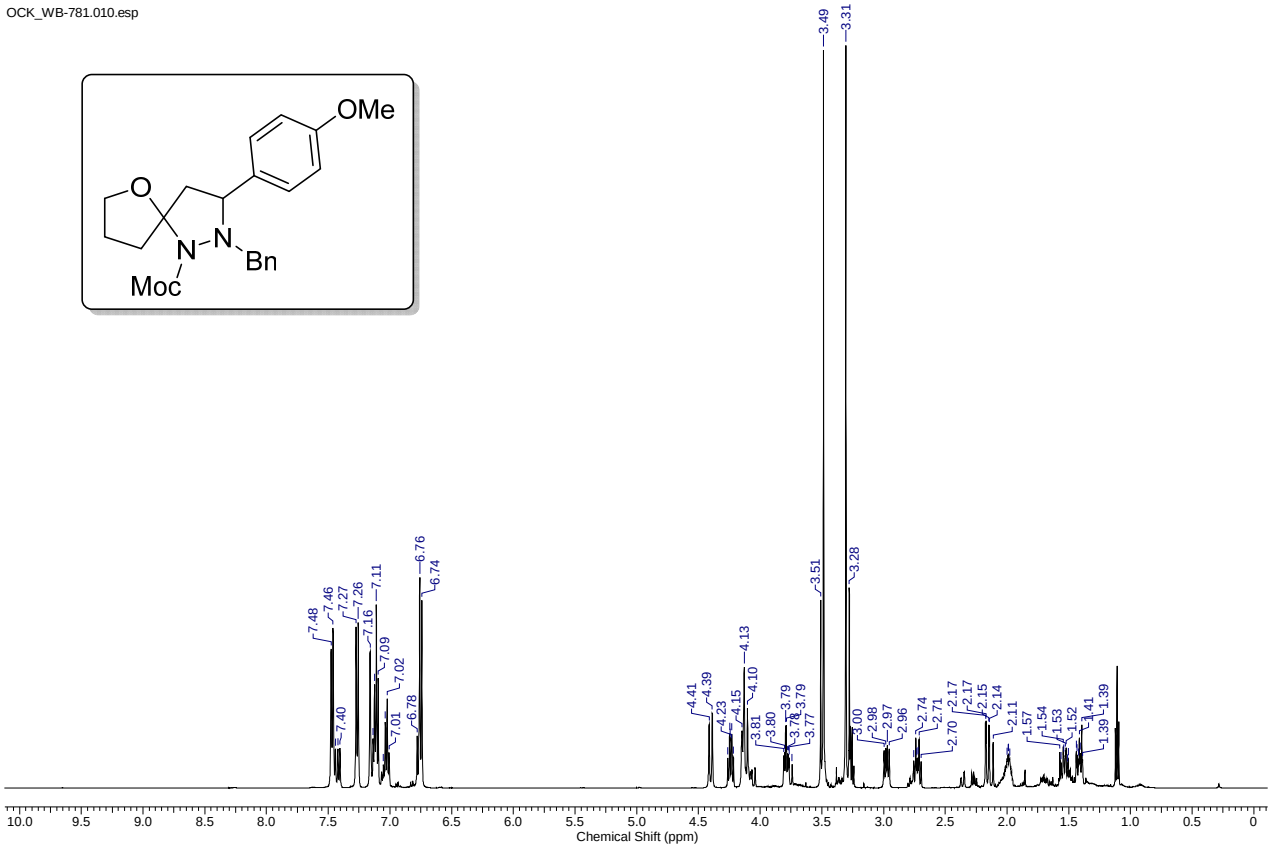

WB-MT-12.011.esp
Chemical Shift (ppm)

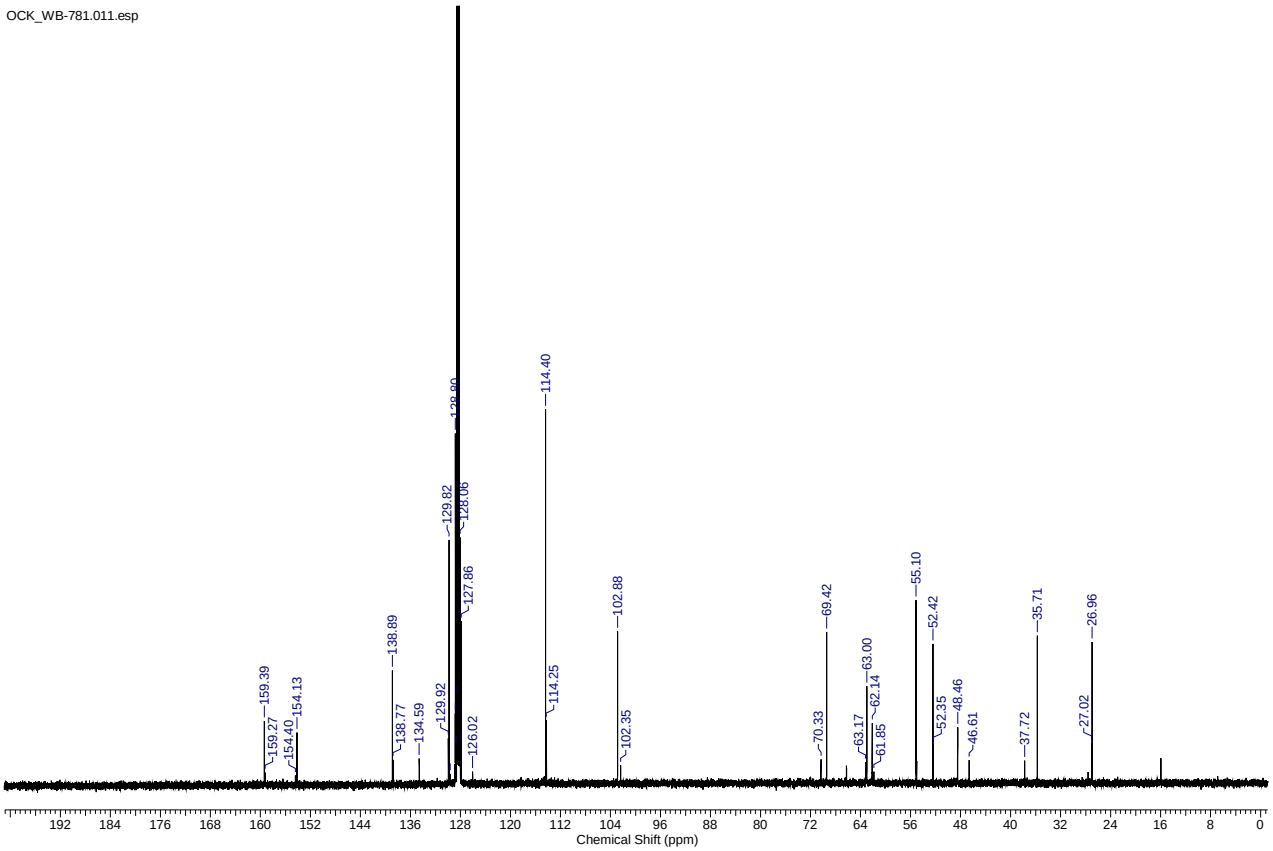
4aa


OCK_WB-780.010.esp
Ph
O
N
N
Bn
Moc
Chemical Shift (ppm)

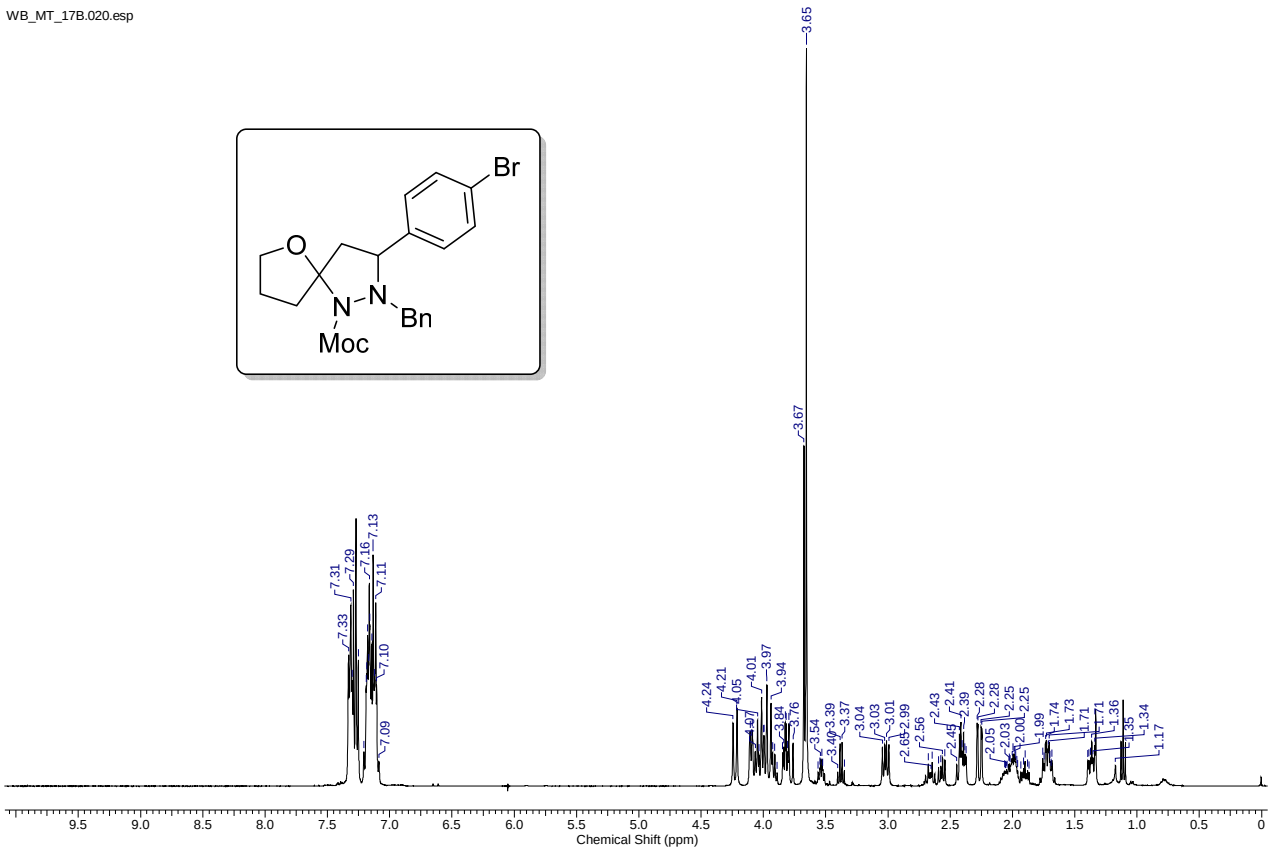

Chemical Shift (ppm)

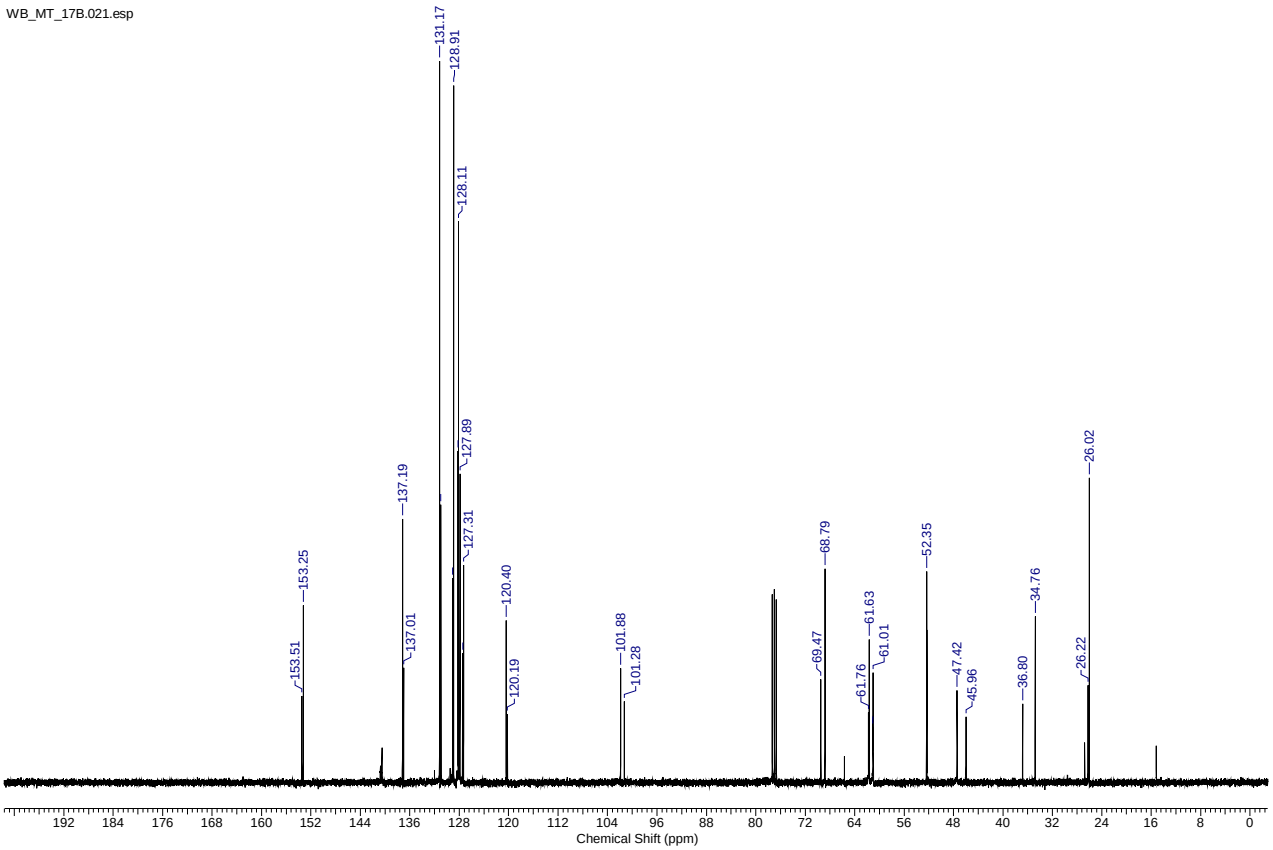
4ab


OCK_WB-781.010.esp
OMe
O
N
N
Bn
Moc
Chemical Shift (ppm)


OCK_WB-781.011.esp
Chemical Shift (ppm)

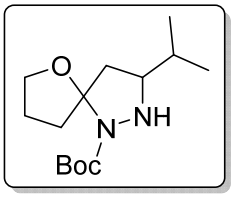
4ac


WB_MT_17B.020.esp
Br
O
N
N
Bn
Moc
Chemical Shift (ppm)

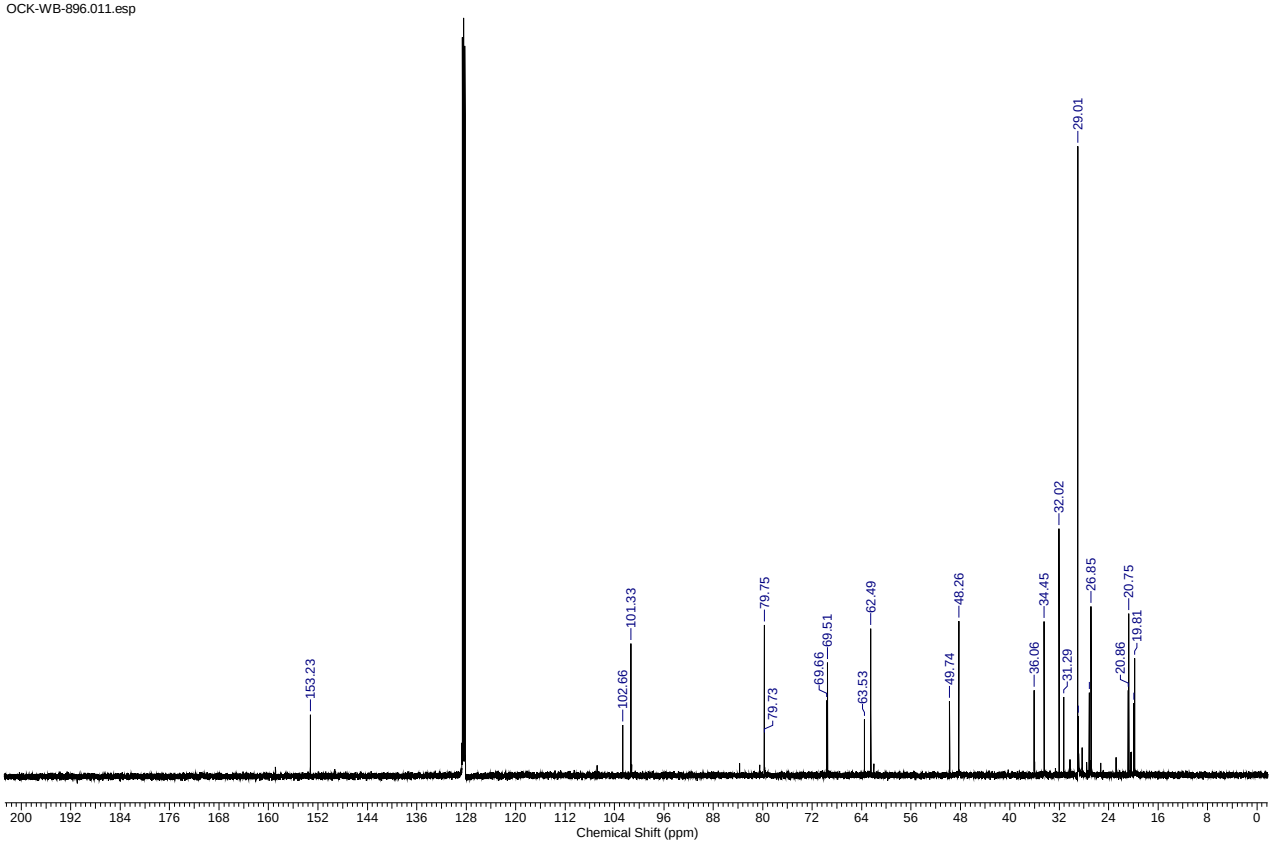

WB_MT_17B.021.esp
Chemical Shift (ppm)

5

OCK-WB-896.010.esp

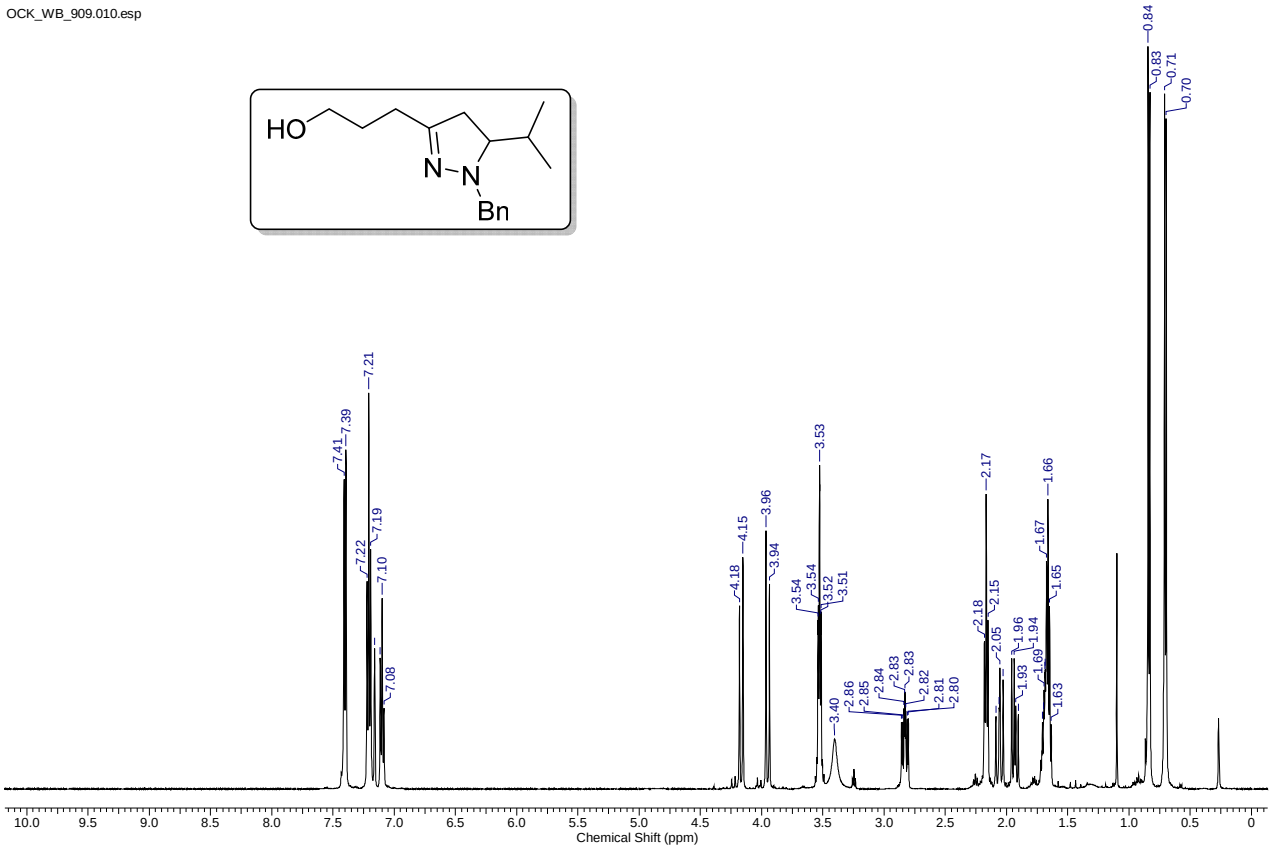


OCK-WB-896.011.esp



6

OCK_WB_909.010.esp



OCK_WB_909.011.esp