Supporting information

Metal-free general procedure for oxidation of secondary amines to nitrones

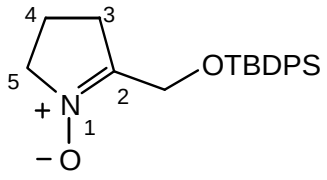
Carolina Gella, Èric Ferrer, Ramon Alibés, Félix Busqué,* Pedro de March, Marta Figueredo,* and Josep Font

Departament de Química, Universitat Autònoma de Barcelona 08193 Bellaterra, Spain
felix.busque@uab.es

Index

General Procedures. Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents. All reactions were performed avoiding moisture by standard procedures and under nitrogen atmosphere and monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated aluminum plates (0.25 mm thickness). Flash column chromatography was performed using silica gel (230-400 mesh) or Florisil® (100-200 mesh). ^{1}H-NMR spectra were recorded on several spectrometers. Proton chemical shifts are reported in ppm (δ) ($CDCl_3$, δ 7.26 or DMSO-d_6, δ2.50). ^{13}C-NMR spectra were recorded on several spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm δ) ($CDCl_3$, δ 77.2). NMR signals were assigned with the help of COSYgpqf, and HSQC experiments. Infrared peaks are reported in cm^{-1}. High resolution mass spectra (HRMS) were recorded using (ESI+).

2-*tert*-Butyldiphenylsilyloxymethyl-1-pyrroline *N*-oxide **3b**



3b

Following the general procedure, $NaHCO_3$ (5.70 g, 67.9 mmol) was added to a stirred solution of (*S*)-2-*tert*-Butyldiphenylsilyloxymethylpyrrolidine[1] (4.60 g, 13.6 mmol) in a mixture of acetonitrile-THF (4:1, 25 mL) and Na_2EDTA (0.01 M, 19 mL). The mixture was then cooled in an ice bath and Oxone® (8.76 g, 14.3 mmol) was added portionwise over 2 h. The mixture was stirred at 5 ºC for 20 min and then diluted with EtOAc (70 mL). The two phases were separated and the aqueous one was extracted with CH_2Cl_2 (3x40 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford an oil identified as a 1.3:1 mixture of nitrones (*S*)-5-*tert*-butyldiphenylsilyloxymethyl-1-pyrroline *N*-oxide **2b** and 2-*tert*-Butyldiphenylsilyloxymethyl-1-pyrroline *N*-oxide **3b** (4.30 g, 12.2 mmol, 88% yield). The ratio **2b**:**3b** was determined by ^{1}H-NMR. Pure samples of both nitrones **3b** (first eluted) and **2b** (second eluted) can be obtained by flash chromatography ($CHCl_3$/MeOH 40:1).

2b: Previously described.[2]

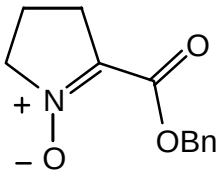
3b: IR (ATR): υ 3069, 2929, 1672, 1588, 1426, 1106, 821, 699 (cm^{-1}); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.63 (dd, *J* = 7.4, 1.7 Hz, 4H, H-Ar), 7.40 (m, 6H, H-Ar), 4.68 (m, 2H, H-1'), 3.95 (tt, *J* = 8.0, 2.3 Hz, 2H, H-5), 2.86 (tt, *J* = 7.1, 2.3 Hz, 2H, H-3), 2.09 (tt, *J* = 8.0, 7.1 Hz, 2H, H-4),

[1] Yuan, Z.-Q.; Kihlberg, J. *Tetrahedron* **2005**, *61*, 4901-4909.

[2] Sánchez-Izquierdo, F.; Blanco, P.; Busqué, F.; Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Parella, T. *Org. Lett.* **2007**, *9*, 1769-1772.

1.07 (s, 9H, *t*Bu). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 148.5, 135.4, 132.5, 129.9, 127.7, 62.7, 59.7, 29.6, 26.8, 19.2, 17.1. **HRMS** (ESI+) calcd for $C_{21}H_{27}NO_2SiNa$: 376.1703 $[M+Na]^+$; found 376.1697.

Benzy1 pyrroline-2-carboxylate *N*-oxide **13**

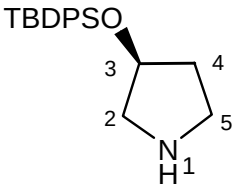


13

Following the general procedure, benzy1 pyrroline-2-carboxylate *N*-oxide **13** was obtained in a 82% yield starting from L-proline benzyl ester.

13: **IR** (ATR): υ 3366, 2950, 1723, 1552, 1218, 1165, 1009, 699 (cm^{-1}); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.39-7.33 (m, 5H, H-Ar), 5.28 (s, 2H, C*H*-Ph), 4.13 (tt, *J*=8.1, 2.1 Hz, 2H, H-5), 3.01 (tt, *J*= 7.3, 2.1 Hz, 2H, H-3), 2.13 (tt, *J*=8.1, 7.3 Hz, 2H, H-4). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.2, 135.3, 133.8, 128.5, 128.3, 126.8, 66.7, 66.6, 29.6, 16.7. **HRMS** (ESI+): calcd for $C_{12}H_{13}NO_3Na$ 242.0788 $[M+Na]^+$; found 242.0785.

(*S*)-3-*tert*-Butyldiphenylsilyloxypyrrolidine **14**



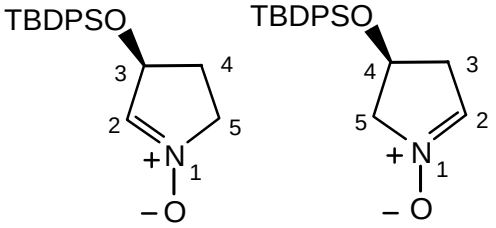
14

To a stirred solution of (*S*)-3-hydroxypyrrolidine (0.30 g, 3.45 mmol), imidazole (0.587 g, 8.63 mmol) and DMAP (21 mg, 18.93 mmol) in CH_2Cl_2 (15 mL) at 0 ºC, *tert*-butyldiphenylsilyl chloride (5.8 g, 0.17 mmol) was slowly added over 5 min and the mixture was allowed to warm up to room temperature and stirred for 16 h. At this time, the resulting precipitate was filtered off and brine (10 mL) was added. The phases were separated and the aqueous was then extracted with CH_2Cl_2 (2 x 15 ml). The whole organic phases were concentrated under reduced pressure to yield an oil which was dissolved in a mixture of CH_2Cl_2 (10 mL) and NH_3 15% (5 mL). The mixture was stirred for 1 h, the phases were separated and the aqueous phase was then extracted with CH_2Cl_2 (2 x 10 ml). The whole organic phases were dried (Na_2SO_4), concentrated under reduced pressure and purified by flash chromatography (CH_3Cl-MeOH, 20:1) to provide (*S*)-3-*tert*-butyldiphenylsilyloxypyrrolidine **14** (0.92 g, 2.83 mmol, 82 % yield).

14: $[\alpha]_D^{20}$= + 7.0 (*c* 2.0, $CHCl_3$); **IR** (ATR): υ 3069, 2930, 2856, 1427, 1417, 1107, 822, 702 (cm^{-1}); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.66 (t, *J* = 5.7 Hz, 4H, H-Ar), 7.42 (m, 6H, H-Ar), 4.40

(s br, 1H, H-3), 4.29 (s br, 1H, N*H*), 3.20 (q, *J*=7.8 Hz, 1H, H-5), 2.94 (d, *J*=11.4 Hz, 1H, H-2), 2.88 (m, 1H, H-5), 2.79 (dd, *J* = 12.4, 4.7 Hz, 1H, H-2), 1.79 (m, 2H, H-4), 1.08 (s, 9H, H-*t*Bu). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 135.6, 134.9, 134.0, 129.6, 127.7, 73.8, 55.4, 45.2, 35.6, 27.0, 19.0. **HRMS** (ESI+) calcd for $C_{20}H_{27}NOSi$: 326.1935 $[M+H]^+$; found 326.1928.

(*S*)-3-*tert*-Butyldiphenylsilyloxy-1-pyrroline *N*-oxide **15** and (*S*)-4-*tert*-butyldiphenylsilyloxy-1-pyrroline *N*-oxide **16**

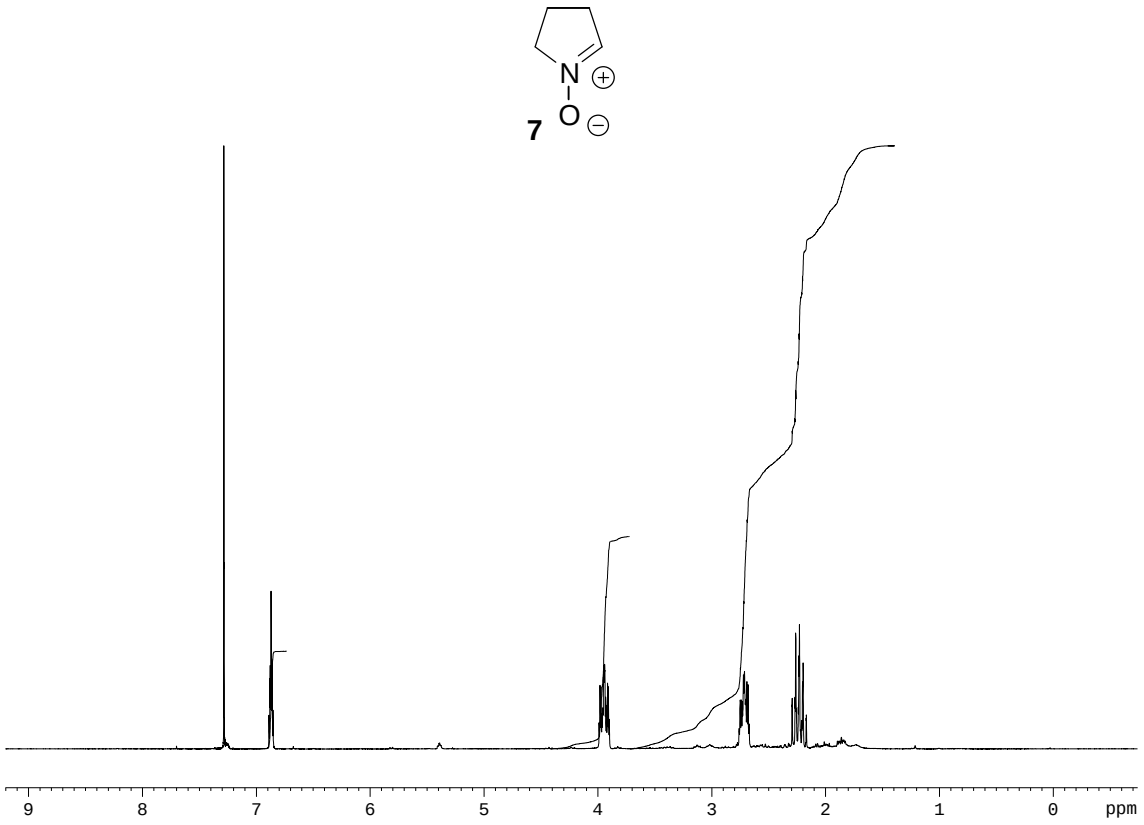


15 **16**

Following the general procedure, (*S*)-3-*tert*-butyldiphenylsilyloxypyrrolidine **14** (1.0 g, 3.08 mmol) afforded a yellow oil identified as a 2.5:1 mixture of nitrones (*S*)-3-*tert*-butyldiphenylsilyloxy-1-pyrroline *N*-oxide **15** and (*S*)-4-*tert*-butyldiphenylsilyloxy-1-pyrroline *N*-oxide **16** (0.866 g, 2.55 mmol, 83% yield). The ratio **15**:**16** was determined by ^{1}H-NMR. Pure samples of both nitrones **15** (first eluted) and **16** (second eluted) can be obtained by flash chromatography ($CHCl_3$/MeOH 30:1).

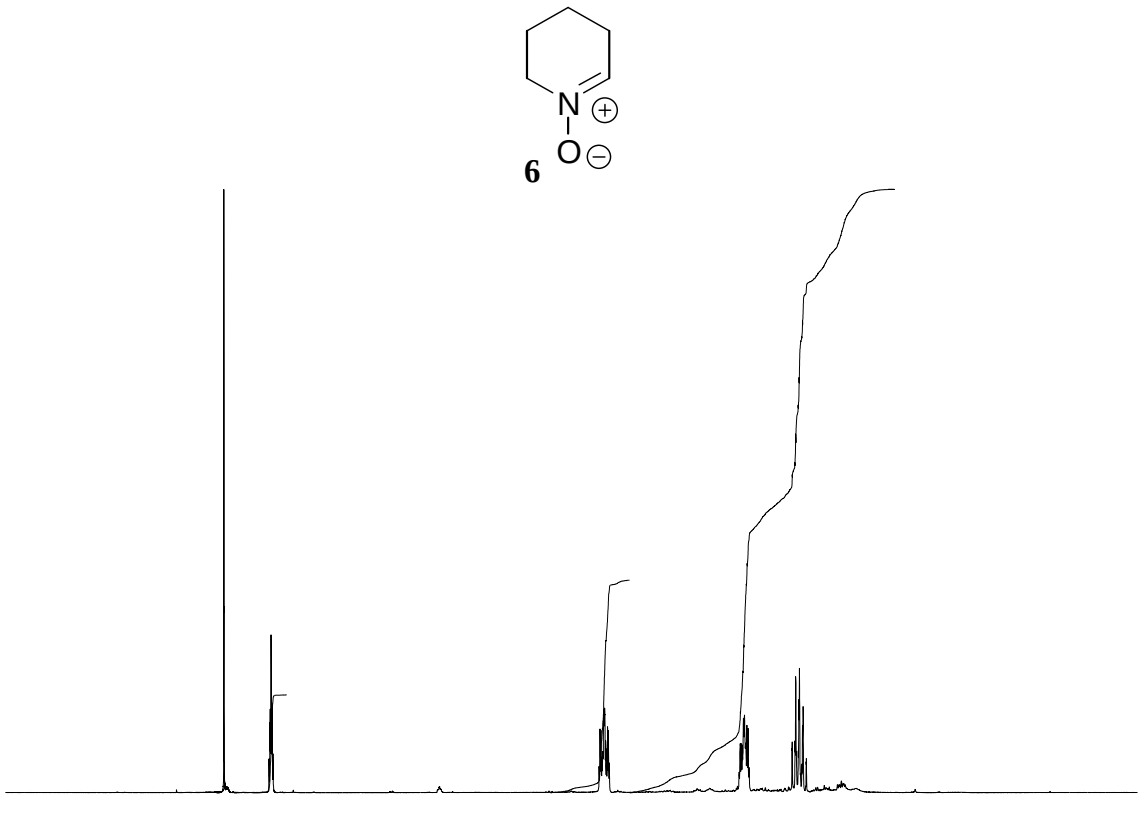
15: $[\alpha]_D^{20}$= - 42.3 (*c* 1.75, $CHCl_3$); **IR** (ATR): υ 3069, 2930, 2856, 1719, 1588, 1426, 1105, 821, 699 (cm^{-1}); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2H, H-Ar), 7.66 (d, *J* = 7.1 Hz, 2H, H-Ar), 7.43 (m, 6H, H-Ar), 6.70 (q, *J* = 2.1 Hz, 1H, H-2), 4.95 (m, 1H, H-3), 4.13 (dddt, *J* = 15.8, 9.2, 5.8, 2.0 Hz, 1H:H-5), 3.77 (dddt, *J* = 15.6, 9.0, 5.8, 1.0 Hz, 1H, H-5), 2.41 (ddd, *J* = 13.5, 9.0, 5.8 Hz, 1H, H-4), 2.19 (dddd, *J* = 13.2, 9.2, 5.7, 3.6 Hz, 1H, H-4), 1.09 (s, 9H, *t*Bu). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 136.4, 135.5, 132.8, 129.7, 127.9, 73.0, 61.0, 30.5, 26.6, 18.9. **HRMS** (ESI+) calcd for $C_{20}H_{25}NO_2SiNa$: 362.1547 $[M+Na]^+$; found 362.1546.

16: $[\alpha]_D^{20}$= - 10.0 (*c* 0.6, $CHCl_3$); **IR** (ATR): υ 3069, 2929, 2856, 1707, 1589, 1427, 1106, 821, 699 (cm^{-1}); **^{1}H-NMR** (250 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2H, H-Ar), 7.63 (d, *J* = 7.0 Hz, 2H, H-Ar), 7.43 (m, 6H, H-Ar), 6.89 (m, 1H, H-2), 4.62 (m, 1H, H-4), 3.91 (m, 2H, H-5), 2.84 (dddt, *J* = 19.0, 6.6, 2.5, 1.9 Hz, 1H, H-3), 2.71 (dtt, *J* = 19.0, 2.9, 1.6 Hz, 1H, H-3), 1.09 (s, 9H, *t*Bu). **^{13}C-NMR** (62.5 MHz, $CDCl_3$): δ 136.0, 135.3, 134.7, 133.3, 133.0, 130.6, 130.0, 128.4, 128.1, 70.5, 67.6, 40.0, 27.2, 19.4. **HRMS** (ESI+): calcd for $C_{20}H_{25}NO_2SiNa$ 362.1547 $[M+Na]^+$; found 362.1544.



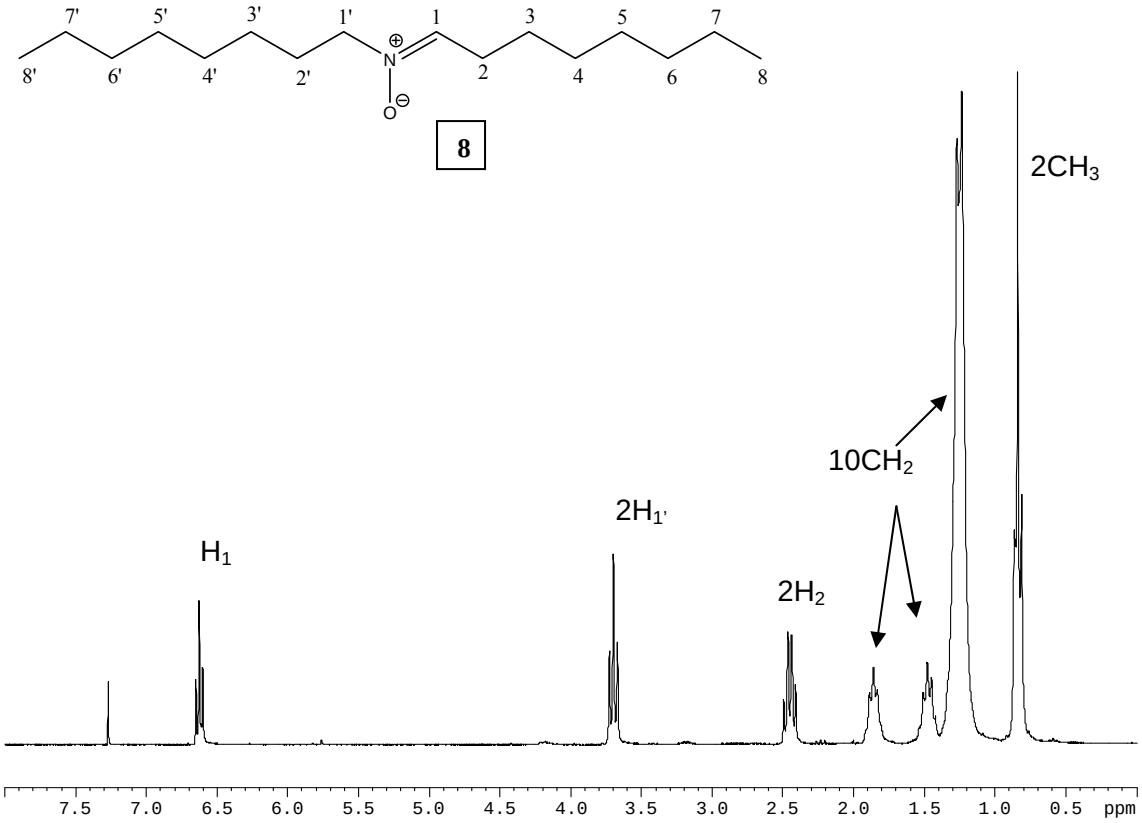
7

^{1}H-NMR (250 MHz, $CDCl_3$)



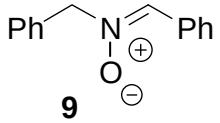
6

^{1}H-NMR (250 MHz, $CDCl_3$)

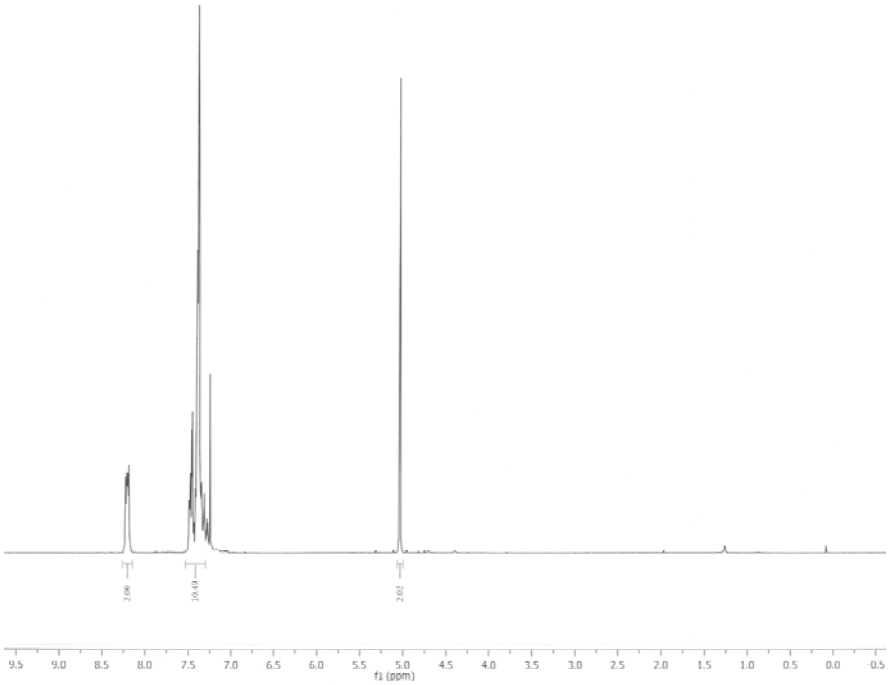


8

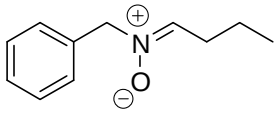
^{1}H-NMR (250 MHz, $CDCl_3$)



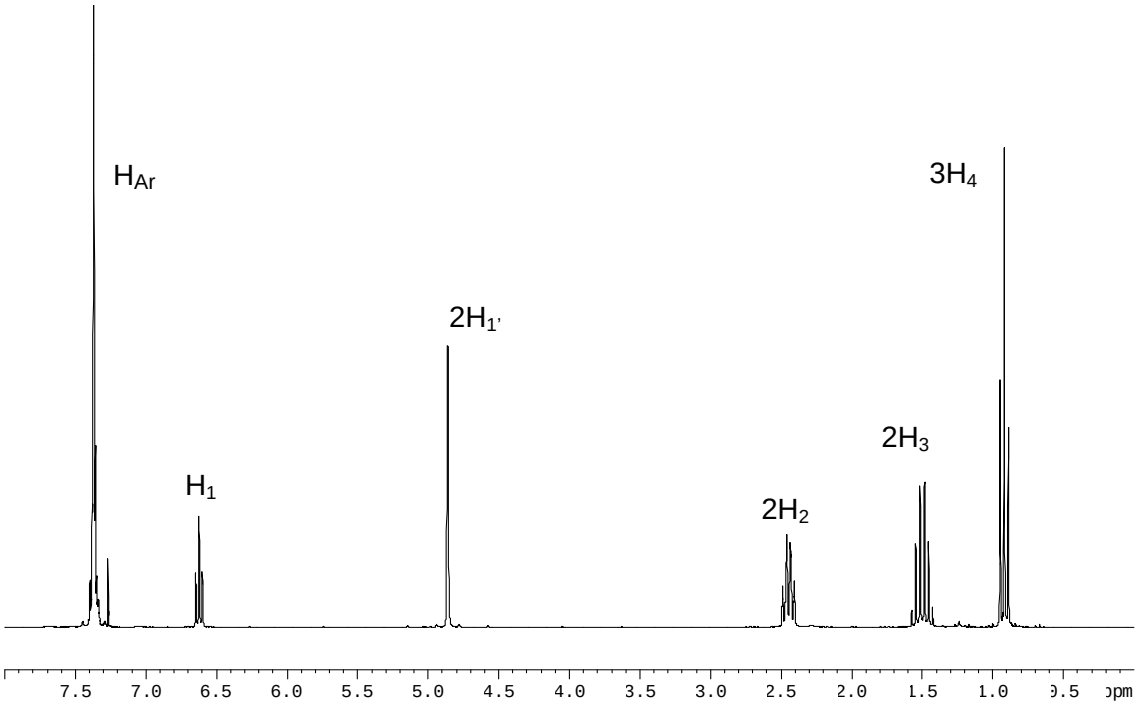
9



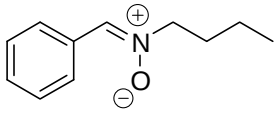
^{1}H-NMR (250 MHz, $CDCl_3$)



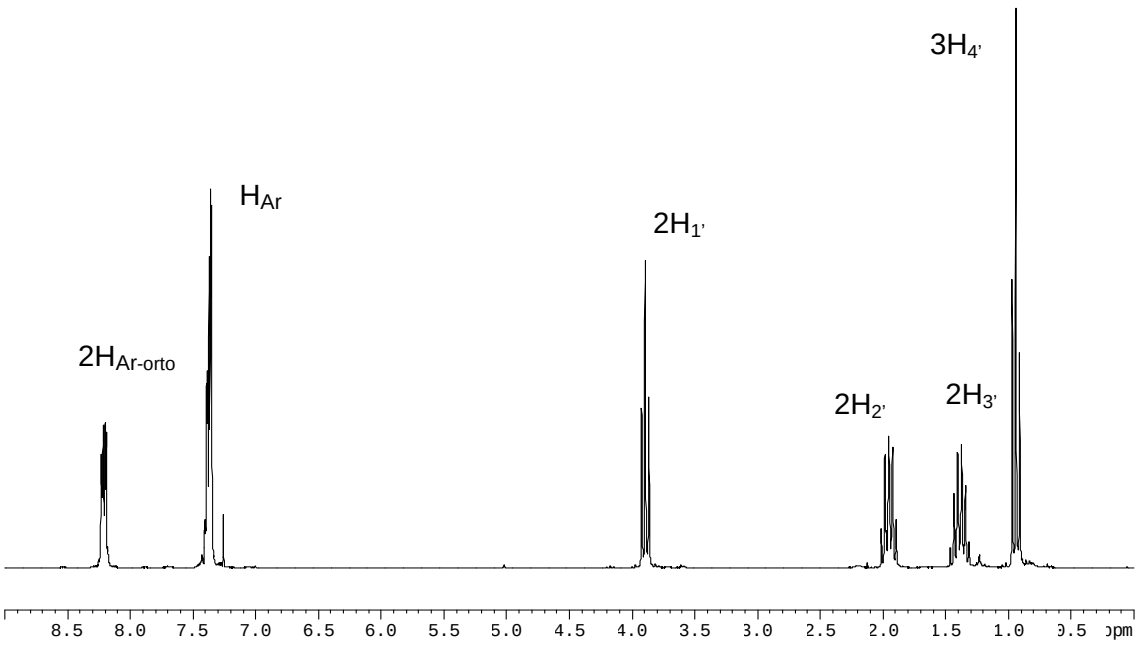
10



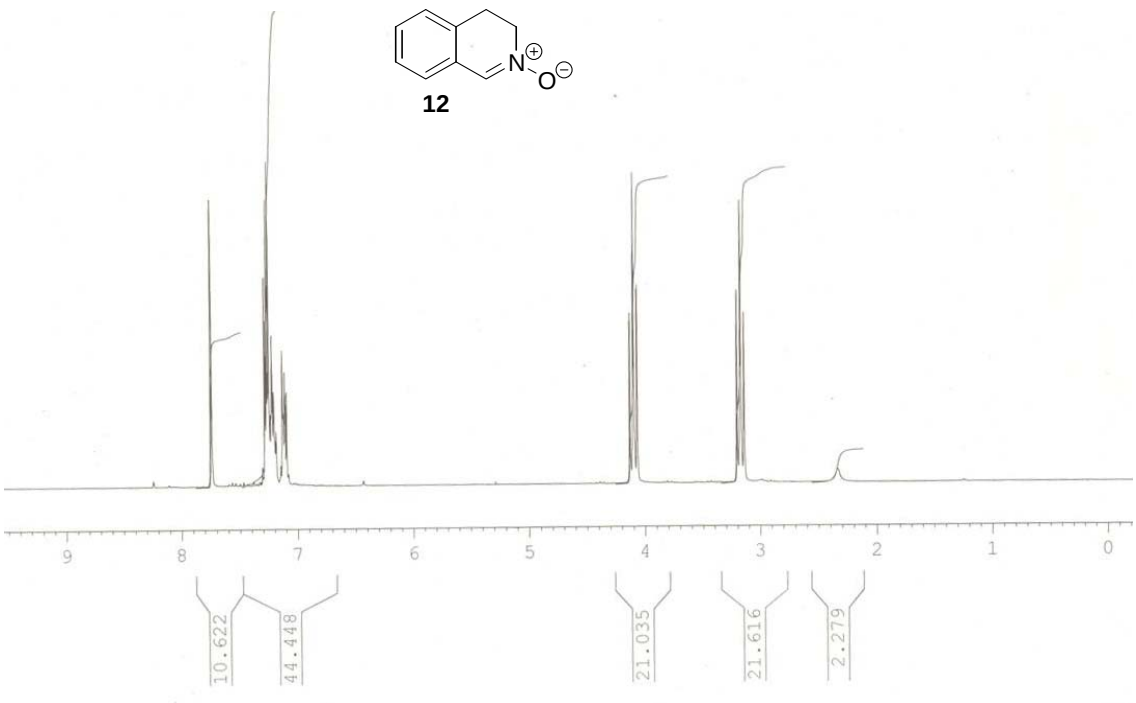
^{1}H-NMR (250 MHz, $CDCl_3$)



11

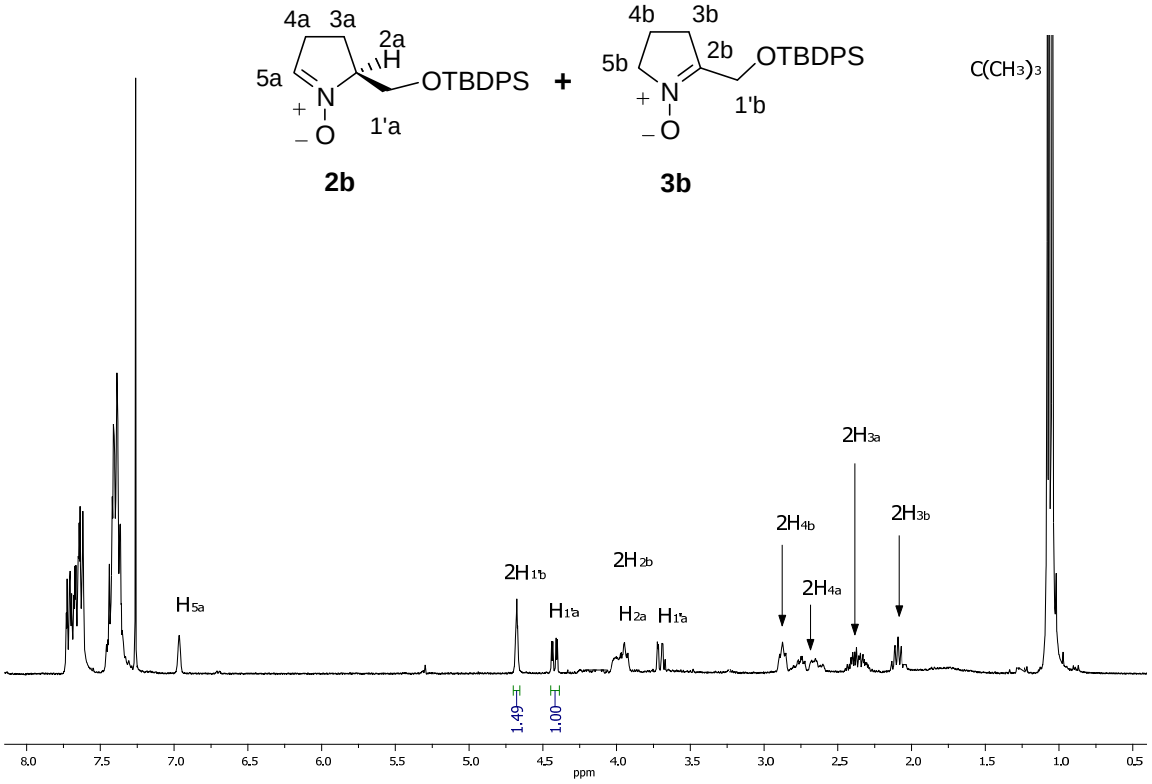


^{1}H-NMR (250 MHz, $CDCl_3$)

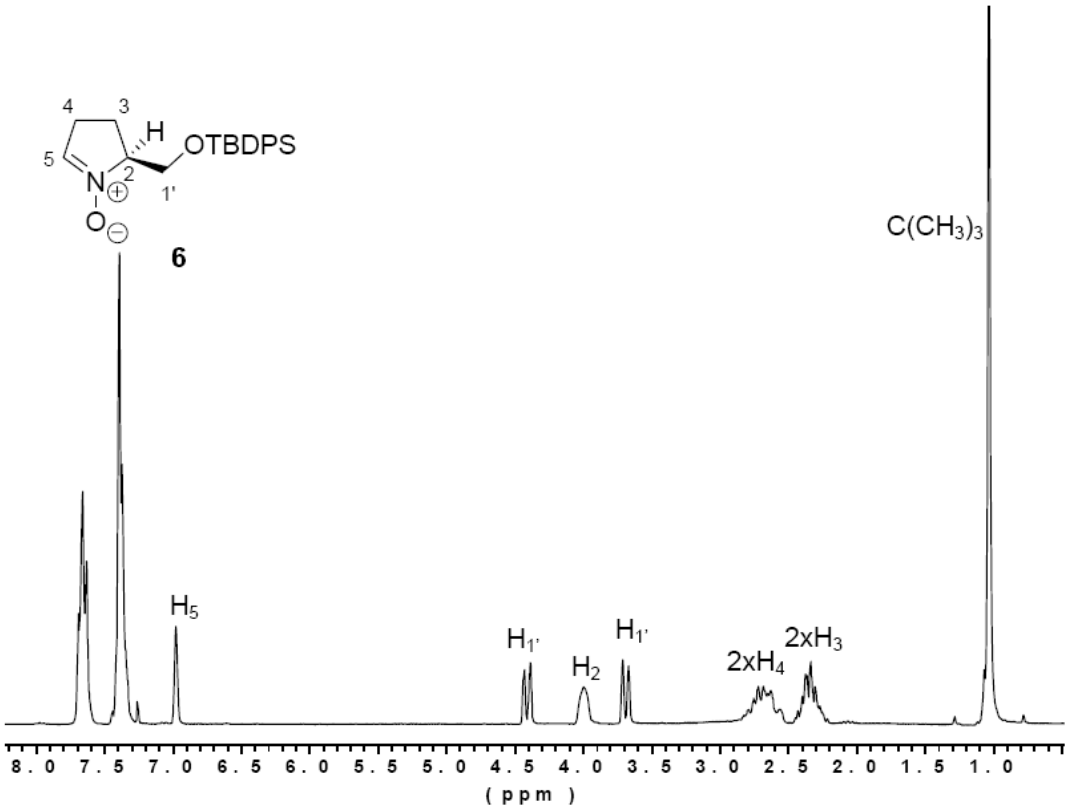


^{1}H-NMR (250 MHz, $CDCl_3$)

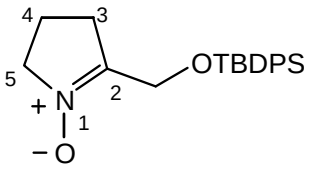
^{1}H-NMR spectrum of nitrones **2b** and **3b** (reaction mixture)



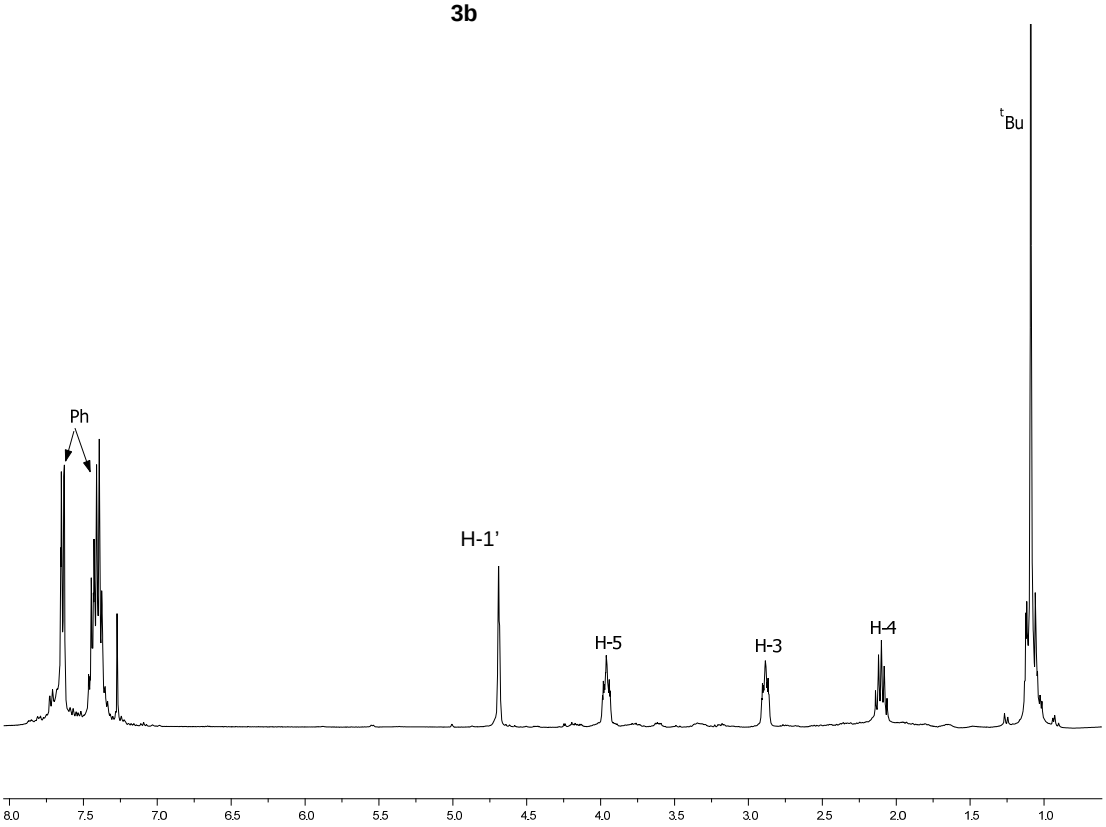
^{1}H-NMR (250 MHz, $CDCl_3$)



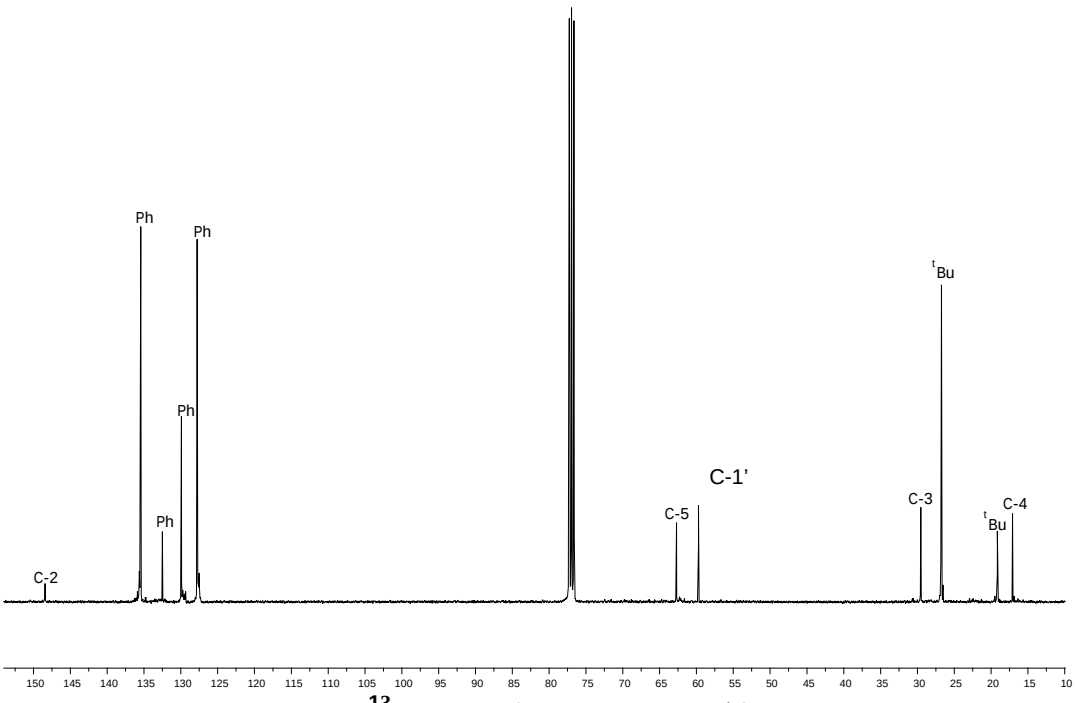
^{1}H-NMR (250 MHz, $CDCl_3$)



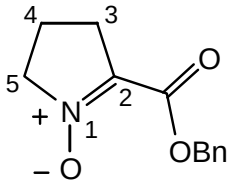
3b



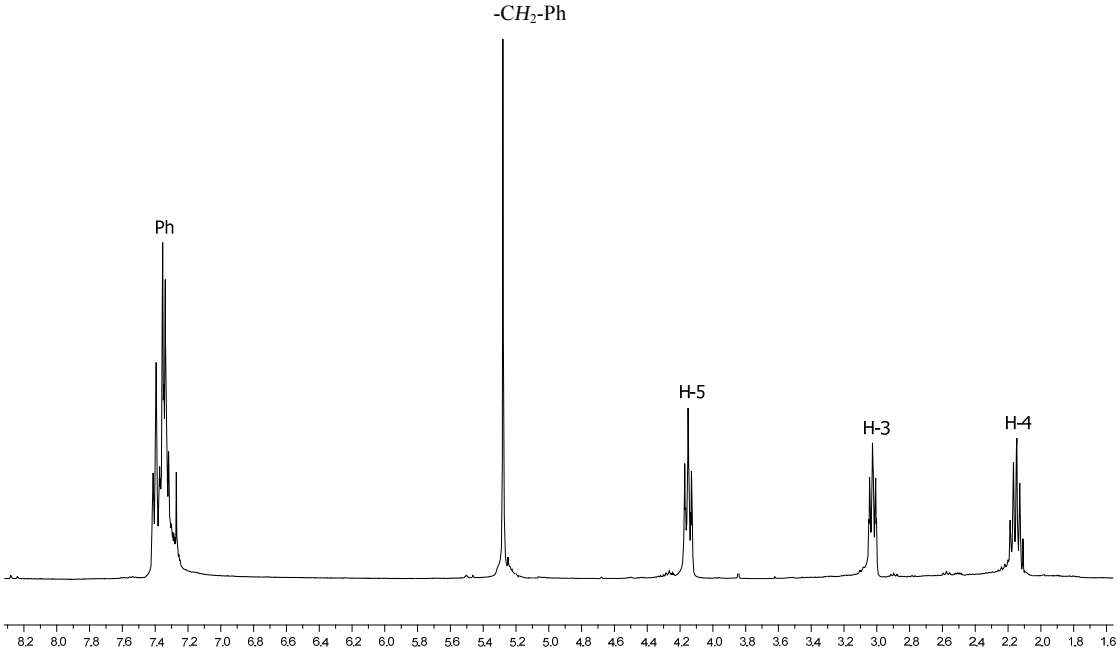
^{1}H-NMR (400 MHz, $CDCl_3$)



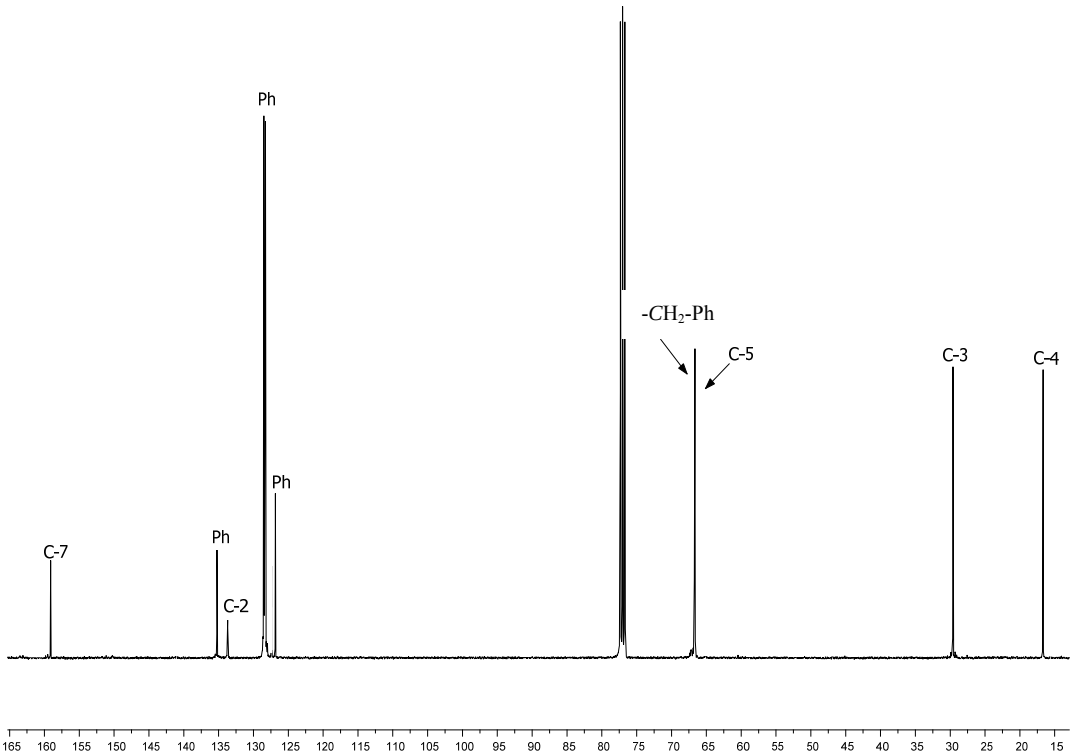
^{13}C-NMR (100 MHz, $CDCl_3$)



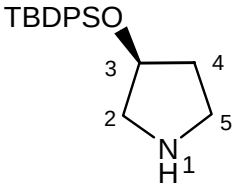
13



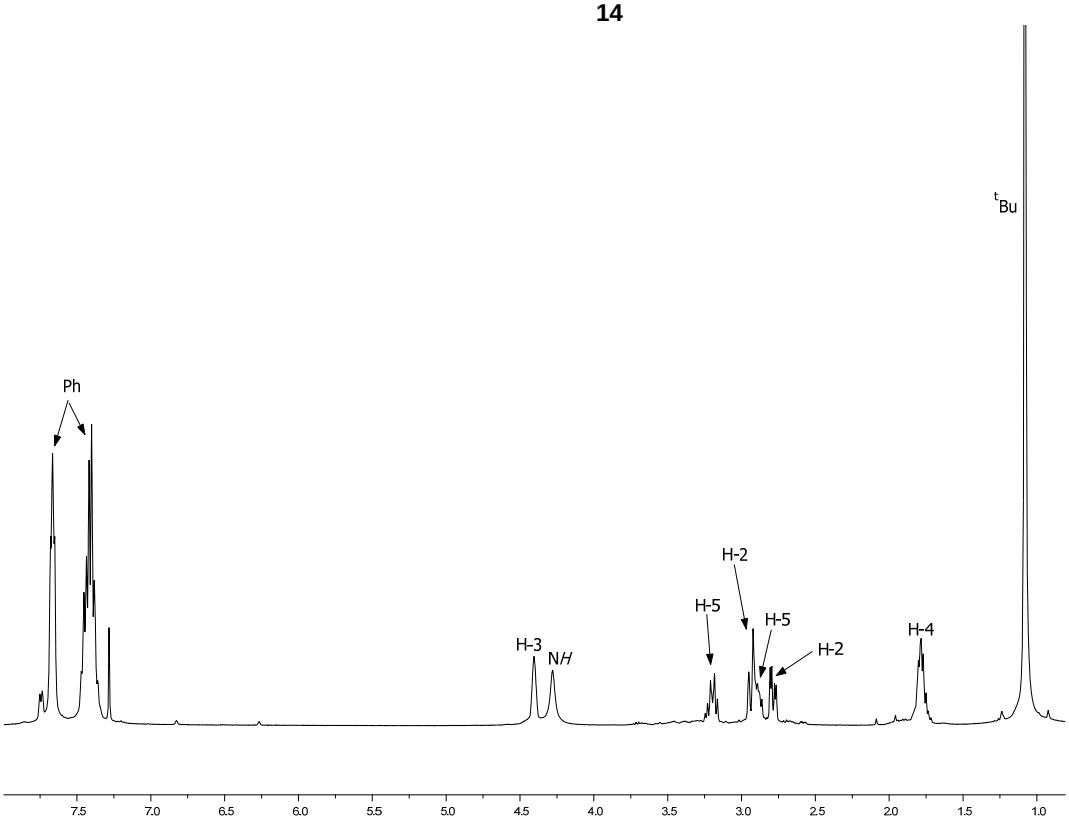
^{1}H-NMR (400 MHz, $CDCl_3$)



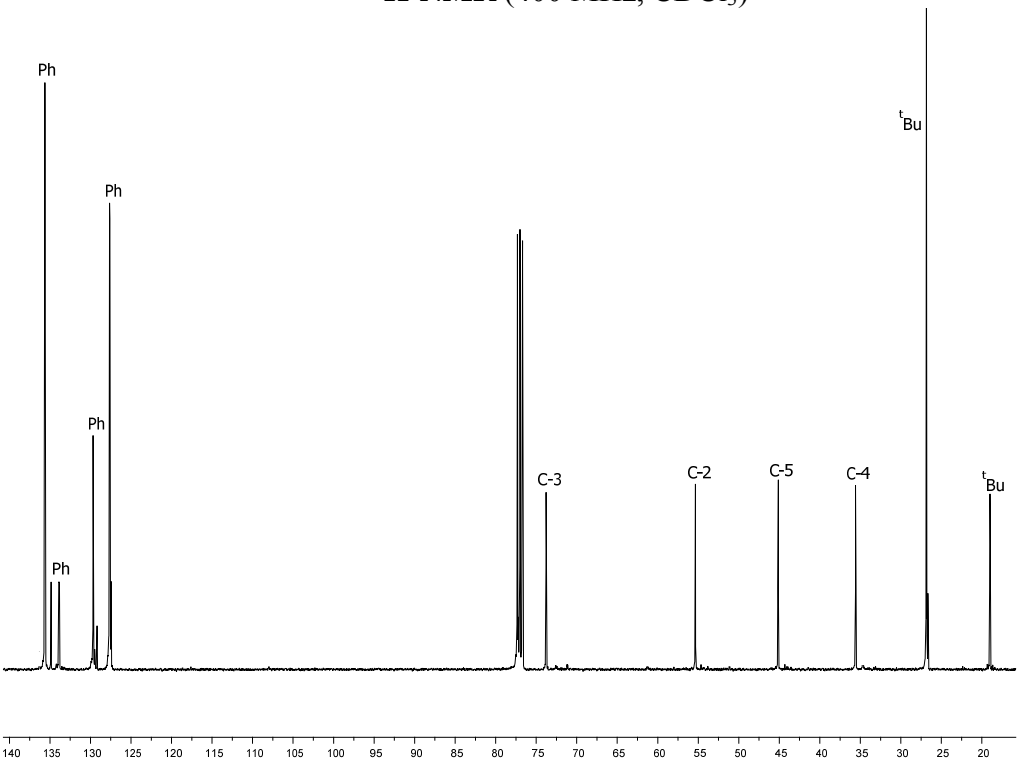
^{13}C-NMR (100 MHz, $CDCl_3$)



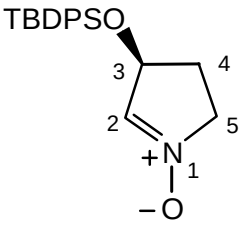
14



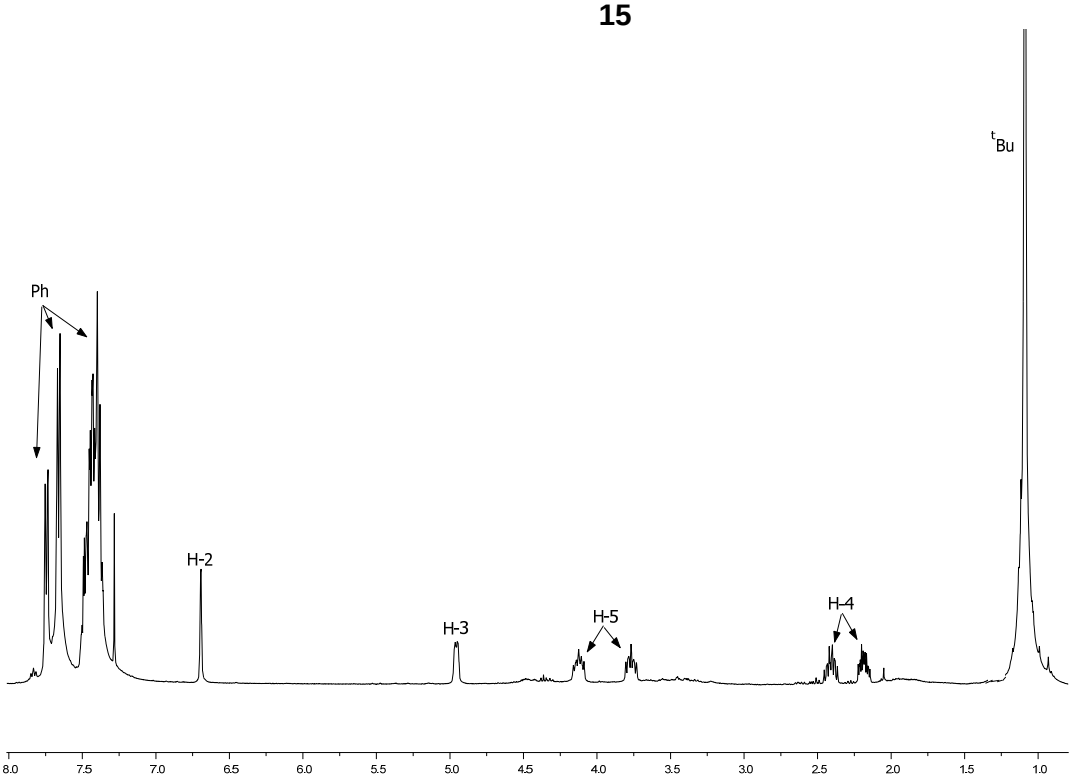
^{1}H-NMR (400 MHz, $CDCl_3$)



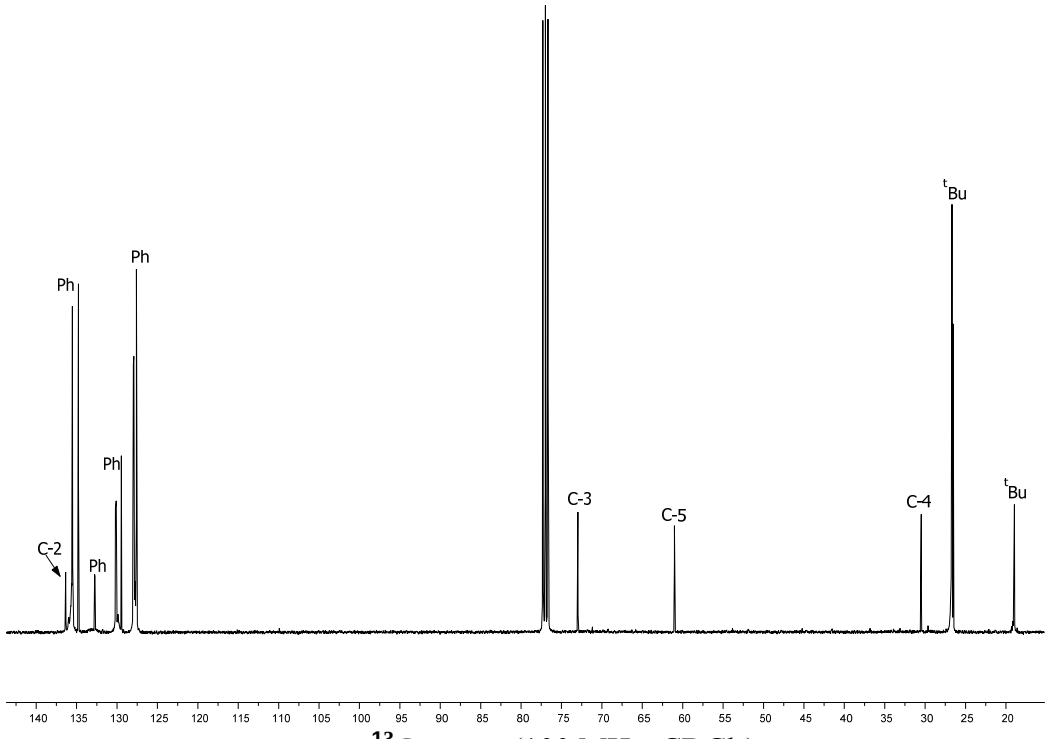
^{13}C-NMR (100 MHz, $CDCl_3$)



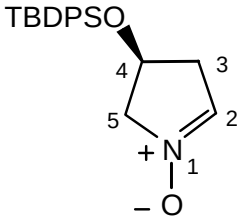
15



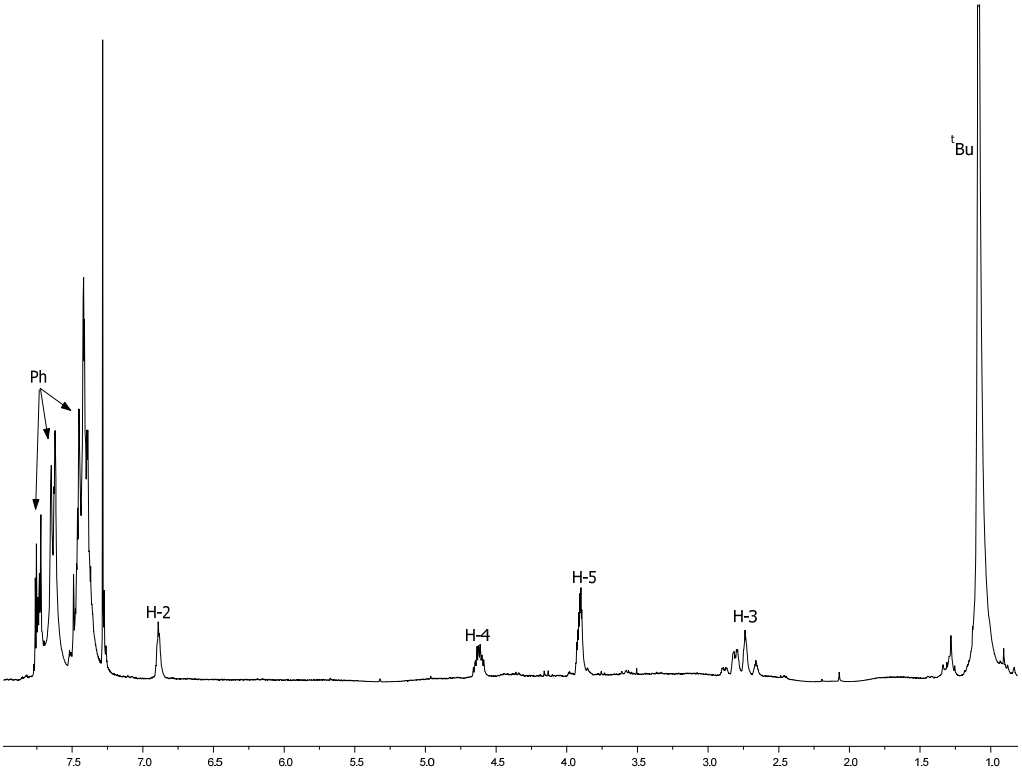
^{1}H-NMR (400 MHz, $CDCl_3$)



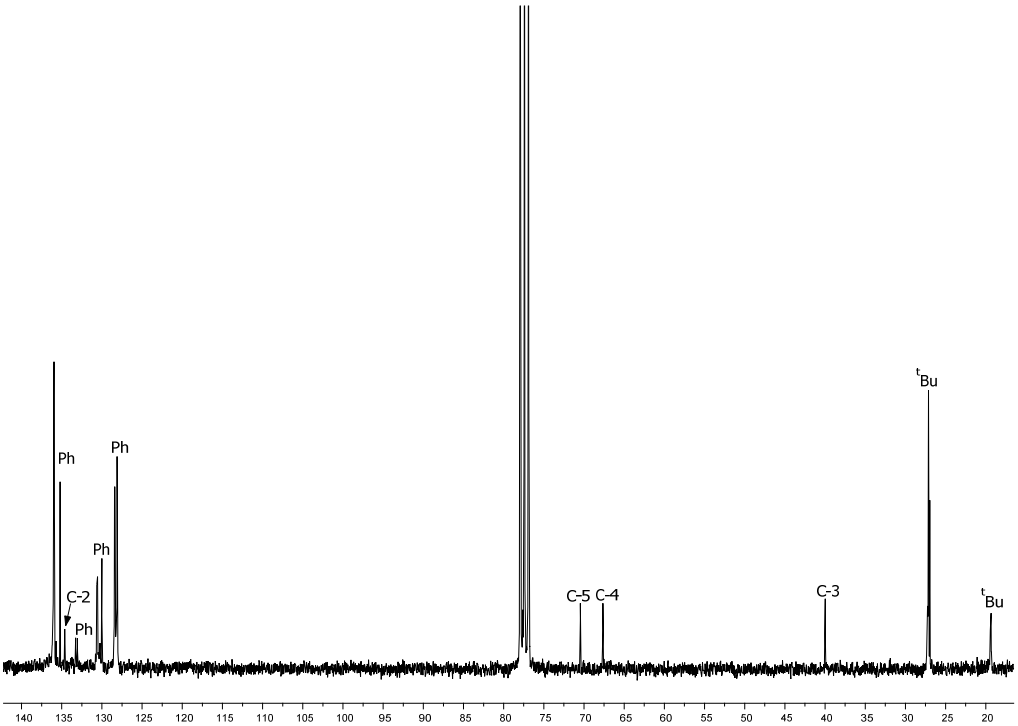
^{13}C-NMR (100 MHz, $CDCl_3$)



16



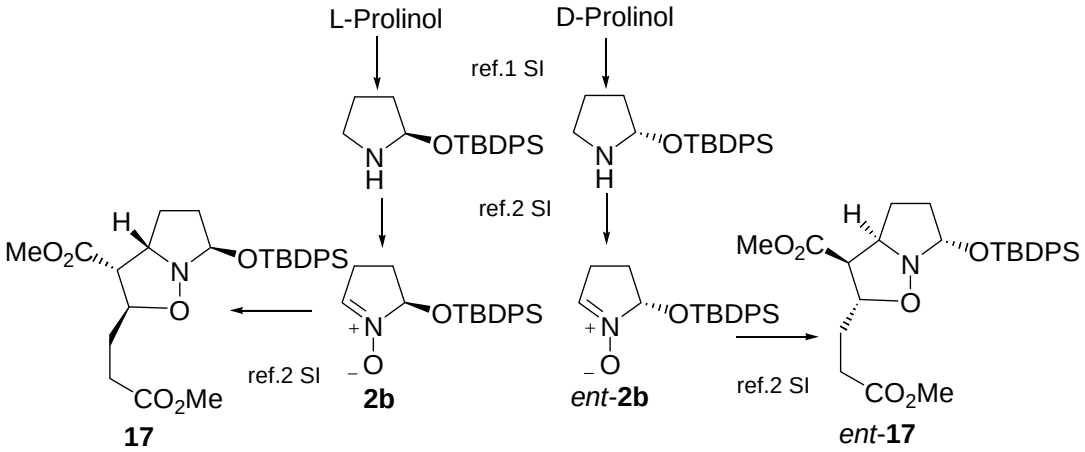
^{1}H-NMR (250 MHz, $CDCl_3$)

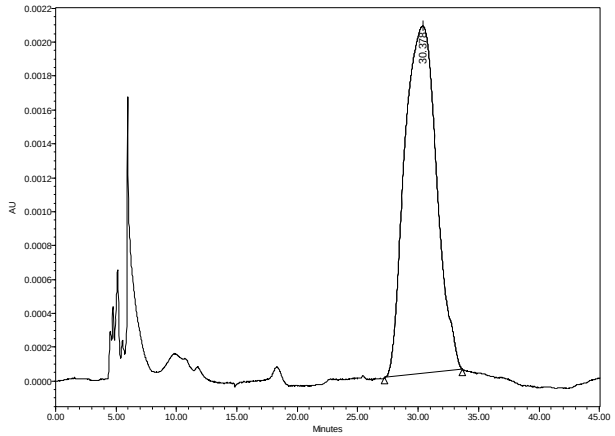


^{13}C-NMR (62.5 MHz, $CDCl_3$)

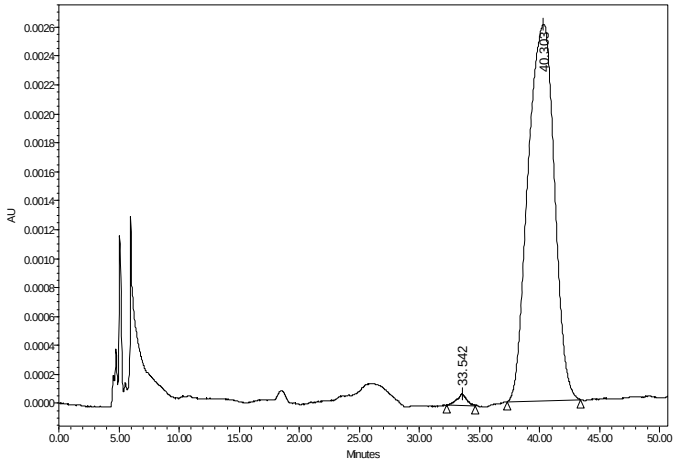
Chiral HPLC chromatograms of *endo* cycloadducts of nitrones **2b** and *ent*-**2b** with (*E*)-2-hexenedioic acid dimethyl ester

The enantiomeric purity of nitrones **2b** and *ent*-**2b** can be confirmed by chiral HPLC of the corresponding *endo* cycloadducts **17** and *ent*-**17** derived from the 1,3-dipolar cycloaddition with (*E*)-2-hexenedioic acid dimethyl ester.[2] Chromatogram A of cycloadduct **17** clearly shows the lack of a peak at 40 minutes, where compound *ent*-**17** appears according chromatogram B.

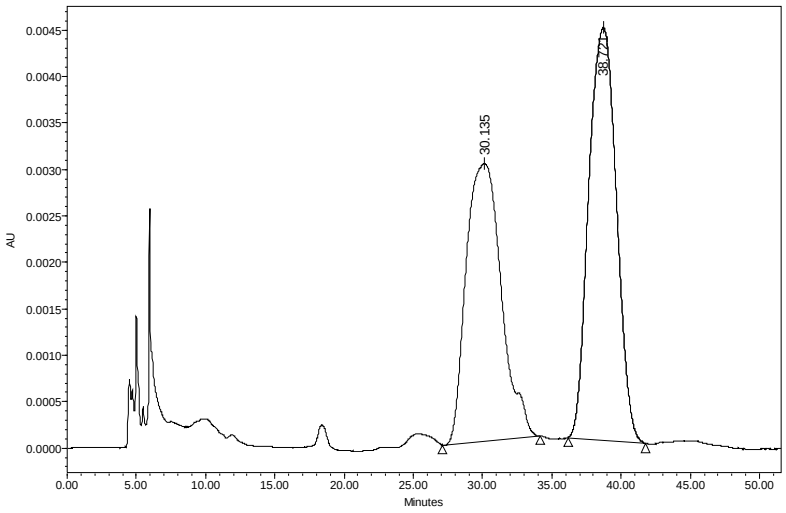




Chromatogram A: Cycloadduct **17** derived from L-prolinol.



Chromatogram B: Cycloadduct *ent*-**17** derived from D-prolinol.



Chromatogram C: Approximately 1:1 mixture of cycloadducts **17** and *ent*-**17**.

- HPLC condicions: Daicel Chiralpak AD-H 4.6x250 mm column, *i*PrOH-Hexane 1:99, 0.8 mL/min flow.