

SUPPORTING INFORMATION

An Efficient Continuous Flow Synthesis for the Preparation of *N*-Arylhydroxylamines: Via a DMAP-Mediated Hydrogenation Process

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Supplementary data for experiments

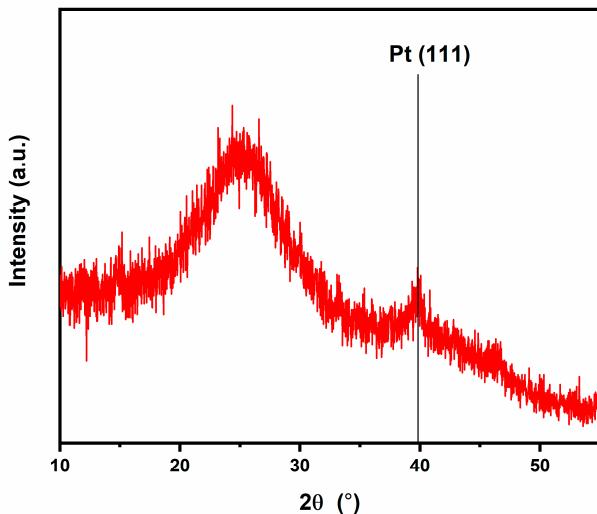


Figure S1. XRD diffractogram of 5 wt.% Pt/C

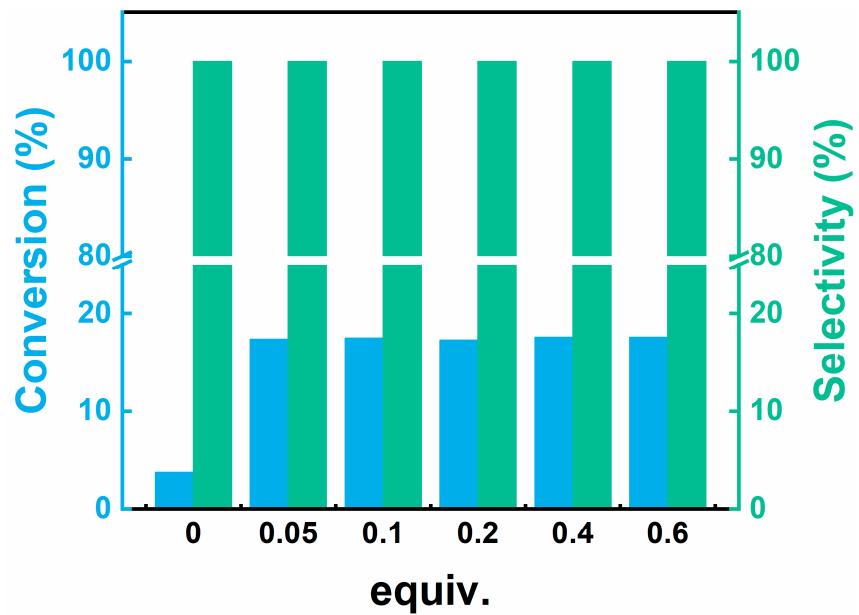


Figure S2. Inspection of DMAP equivalent in batch. Conditions: **1a** (0.78g), 5 wt. % Pt/C (5 mg), DMAP in THF (20mL), 303K, 600 rpm, 1.0 MPa H₂, 10 min reaction time.

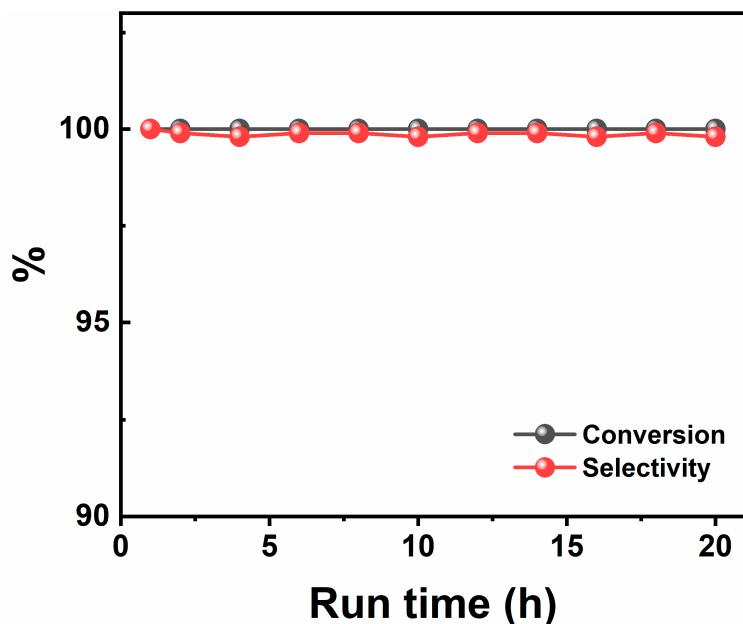


Figure S3. Run time of hydrogenation in flow. Conditions: 0.1 M solution of **1a** in THF, 5 wt.% Pt/C (1 cartridge; Ø3.0×50 mm; 0.1 g), H₂ pressure (6 bar), back pressure (4 bar), liquid flowrate (0.5 mL·min⁻¹), temperature (25 °C).

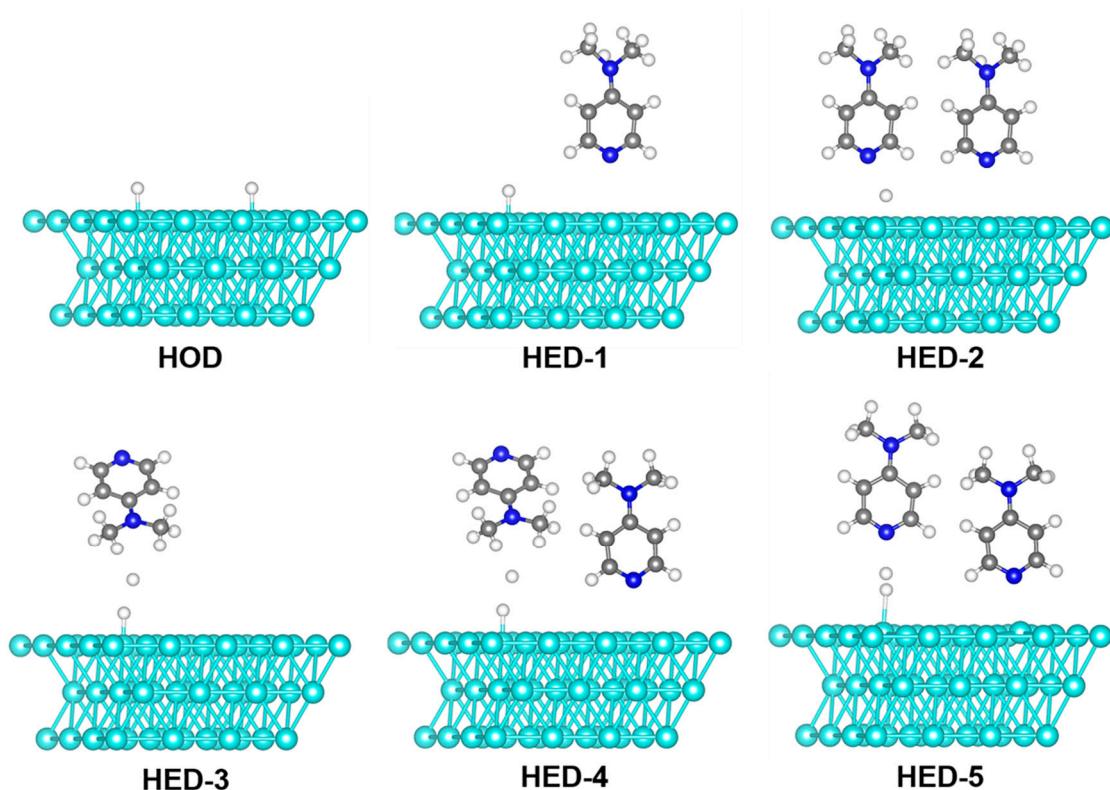


Figure S4. H₂ adsorption on the Pt surface. White, blue, and grey spheres depict H, N, and C atoms, respectively.

Table S1. Control experiments

Entry	Condition	Conv. (%)
1	No 5 wt% Pt/C	0
2	No H ₂	0

Conditions: **1a** (0.78g), 5 wt. % Pt/C (5 mg), DMAP (0.078g) in THF (20mL), 303K, 600 rpm, 1.0 MPa H₂, 1 h reaction time.

Table S2. Bader charge analysis

	Charge distribution (Q _{H1} , Q _{H2})	
HOD	-0.13	-0.13
HED-1	-0.11	0.37
HED-2	-0.12	0.39
HED-3	-0.19	0.43
HED-4	/	/
HED-5	-0.09	0.33

Table S3. Investigation of TEA equivalent in batch

Entry	Equivalent of TEA	Conv. (%)
1	None	4
2	0.05 eq. TEA	15
3	0.1 eq. TEA	24

Conditions: **1a** (0.78g), 5 wt. % Pt/C (5 mg), DMAP (0.078g) in THF (20mL), 303K, 600 rpm, 1.0 MPa H₂, 10 min reaction time.

Data of products

N-(2-chlorophenyl)hydroxylamine (1b)¹

¹H NMR (600 MHz, DMSO-*d*₆): 8.55 (s, 1H), 8.18 (s, 1H), 7.25-7.17 (m, 3H), 6.79-6.76 (td, *J* = 7.8, 1.8 Hz, 1H).

¹³C NMR (150 MHz, DMSO-*d*₆): 147.4, 128.4, 127.4, 119.7, 116.8, 114.0.

N-(4-chlorophenyl)hydroxylamine (2b)¹

¹H NMR (600 MHz, DMSO-*d*₆): 8.43 (s, 1H), 8.39 (s, 1H), 7.20-7.18 (d, *J* = 8.4 Hz, 2H), 6.85-6.84 (d, *J* = 8.4 Hz, 2H).

¹³C NMR (150 MHz, DMSO-*d*₆): 151.0, 128.3, 122.5, 114.4.

N-(3-chlorophenyl)hydroxylamine (3b)²

¹H NMR (600 MHz, DMSO-*d*₆): 8.51 (s, 1H), 8.49 (s, 1H), 7.17-7.14 (t, *J* = 7.8 Hz, 1H), 6.85 (s, 1H), 6.76-6.74 (dd, *J* = 7.8, 1.8 Hz, 2H).

¹³C NMR (150 MHz, DMSO-*d*₆): 153.7, 133.3, 130.0, 118.6, 112.1, 111.4.

N-(2-bromophenyl)hydroxylamine (4b)²

¹H NMR (600 MHz, DMSO-*d*₆): 8.58 (s, 1H), 7.97 (s, 1H), 7.41-7.40 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.28-7.25 (m, 1H), 7.17-7.15 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.74-6.71 (td, *J* = 7.2, 1.2 Hz, 1H).

¹³C NMR (150 MHz, DMSO-*d*₆): 148.6, 131.8, 128.2, 120.7, 114.6, 106.7.

N-(2-iodophenyl)hydroxylamine (5b)³

¹H NMR (600 MHz, DMSO-*d*₆): 8.59 (s, 1H), 7.64-7.62 (m, 2H), 7.30-7.27 (m, 1H), 7.11-7.09 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.61-6.58 (td, *J* = 7.2, 1.8 Hz, 1H).

¹³C NMR (150 MHz, DMSO-*d*₆): 150.9, 138.2, 128.8, 121.6, 114.2, 81.6.

ethyl 2-(hydroxyamino)benzoate (6b)²

¹H NMR (600 MHz, DMSO-*d*₆): 8.95 (s, 1H), 8.66 (s, 1H), 7.79-7.77 (d, *J* = 9.0 Hz, 2H), 6.85-6.84 (d, *J* = 9.0 Hz, 2H), 3.76 (s, 3H).

¹³C NMR (150 MHz, DMSO-*d*₆): 166.3, 156.0, 130.5, 119.2, 111.3, 51.5.

1-(4-(hydroxyamino)phenyl)ethanone (7b)⁴

¹H NMR (600 MHz, DMSO-*d*₆): 8.99 (s, 1H), 8.69 (s, 1H), 7.80-7.79 (d, *J* = 9.0 Hz, 2H), 6.84-6.83 (d, *J* = 9.0 Hz, 2H), 2.44 (s, 3H).

¹³C NMR (150 MHz, DMSO-*d*₆): 195.8, 156.0, 129.9, 127.8, 111.0, 26.1.

N-phenylhydroxylamine (8b)¹

¹H NMR (600 MHz, DMSO-*d*₆): 8.28 (s, 1H), 8.23 (s, 1H), 7.18-7.15 (t, *J* = 7.8 Hz, 2H), 6.86-6.84 (d, *J* = 8.4 Hz, 2H), 6.76-6.73 (t, *J* = 7.8 Hz, 1H).

¹³C NMR (150 MHz, DMSO-*d*₆): 152.1, 128.4, 119.2, 113.0.

N-(2-tolyl)hydroxylamine (9b)¹

¹H NMR (600 MHz, DMSO-*d*₆): 8.22 (s, 1H), 7.90 (s, 1H), 7.11-7.09 (m, 2H), 6.98-6.97 (d, *J* = 7.2 Hz, 1H), 6.72-6.69 (td, *J* = 6.6, 2.4 Hz, 1H), 2.08 (s, 3H).

¹³C NMR (150 MHz, DMSO-*d*₆): 149.7, 129.4, 126.3, 121.9, 119.1, 112.1, 16.9.

N-(2-((1-(4-chlorophenyl)-1H-pyrazol-3-yl)oxy)methyl)phenyl)hydroxylamine (10b)⁵

¹H NMR (600 MHz, DMSO-*d*₆): 8.40 (s, 1H), 8.37 (d, *J* = 3.0 Hz, 1H), 8.15 (s, 1H), 7.78-7.77 (d, *J* = 9.0 Hz, 2H), 7.52-7.50 (d, *J* = 9.0 Hz, 2H), 7.32-7.31 (d, *J* = 6.0 Hz, 1H), 7.26-7.23 (t, *J* = 7.8 Hz, 1H), 7.20-7.19 (d, *J* = 7.8 Hz, 1H), 6.83-6.80 (t, *J* = 7.8 Hz, 1H), 6.09 (d, *J* = 3.0 Hz, 1H), 5.21 (s, 2H).

¹³C NMR (150 MHz, DMSO-*d*₆): 163.9, 149.5, 138.5, 129.5, 129.3, 129.1, 128.8, 128.6, 121.0, 119.2, 118.7, 112.9, 94.7, 67.0.

o-Chloroaniline (1c)¹

¹H NMR (600 MHz, DMSO-*d*₆): 7.17-7.16 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.02-6.99 (td, *J* = 6.0, 1.8 Hz, 1H), 6.80-6.78 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.54-6.51 (td, *J* = 7.2, 1.2 Hz, 1H), 5.29 (s, 2H).

¹³C NMR (150 MHz, DMSO-*d*₆): 144.6, 129.0, 127.6, 117.1, 116.8, 115.4.

Aniline (1d)¹

¹H NMR (600 MHz, DMSO-*d*₆): 7.02-7.00 (t, *J* = 15.6 Hz, 2H), 6.8-6.56 (dd, *J* = 8.4, 1.2 Hz, 2H), 6.51-6.48 (t, *J* = 14.4 Hz, 1H), 4.98 (s, 2H).

¹³C NMR (150 MHz, DMSO-*d*₆): 148.6, 128.8, 115.7, 113.9.

Compounds spectra

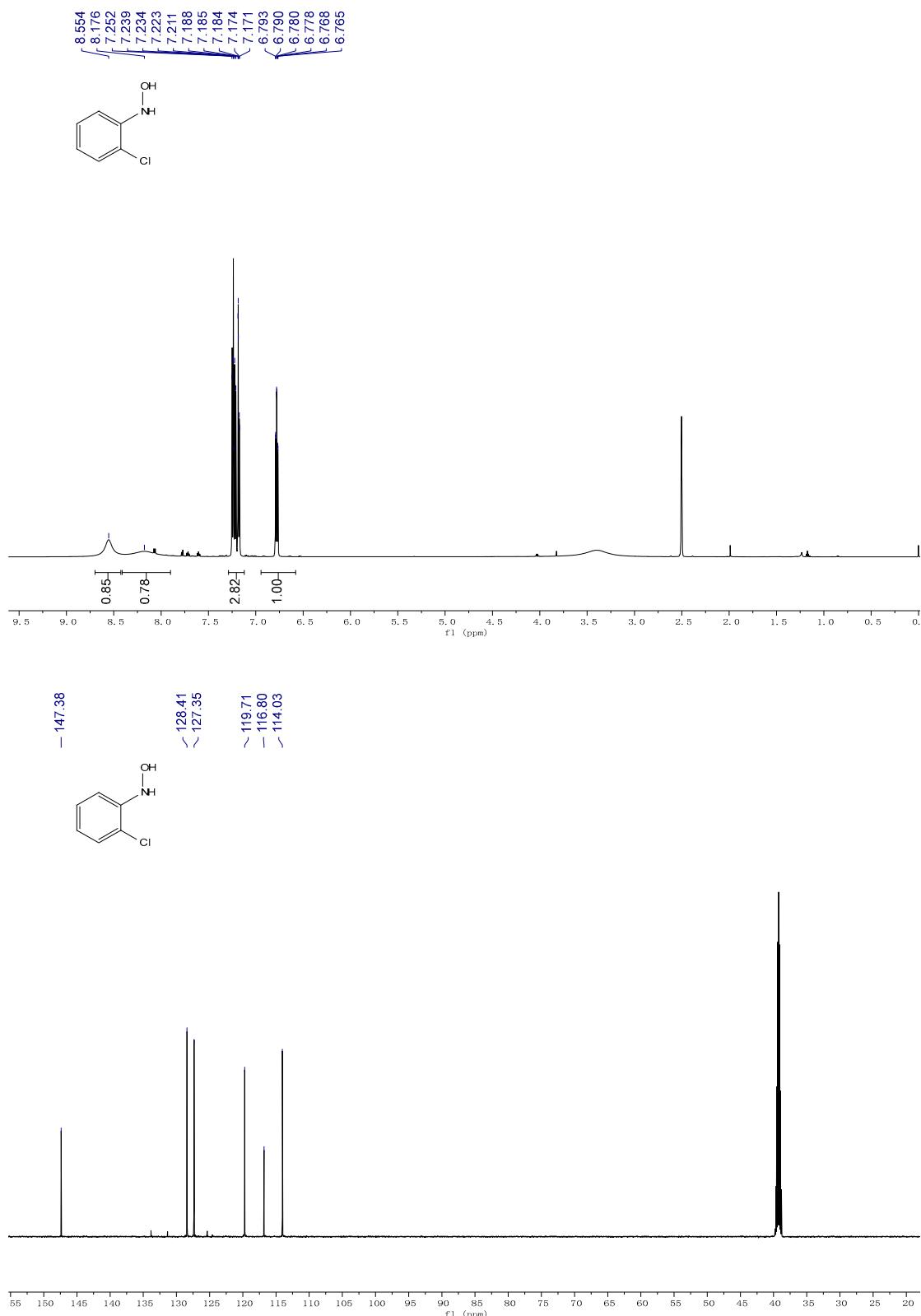


Figure S5. ^1H and ^{13}C NMR spectra of *N*-(2-chlorophenyl)hydroxylamine

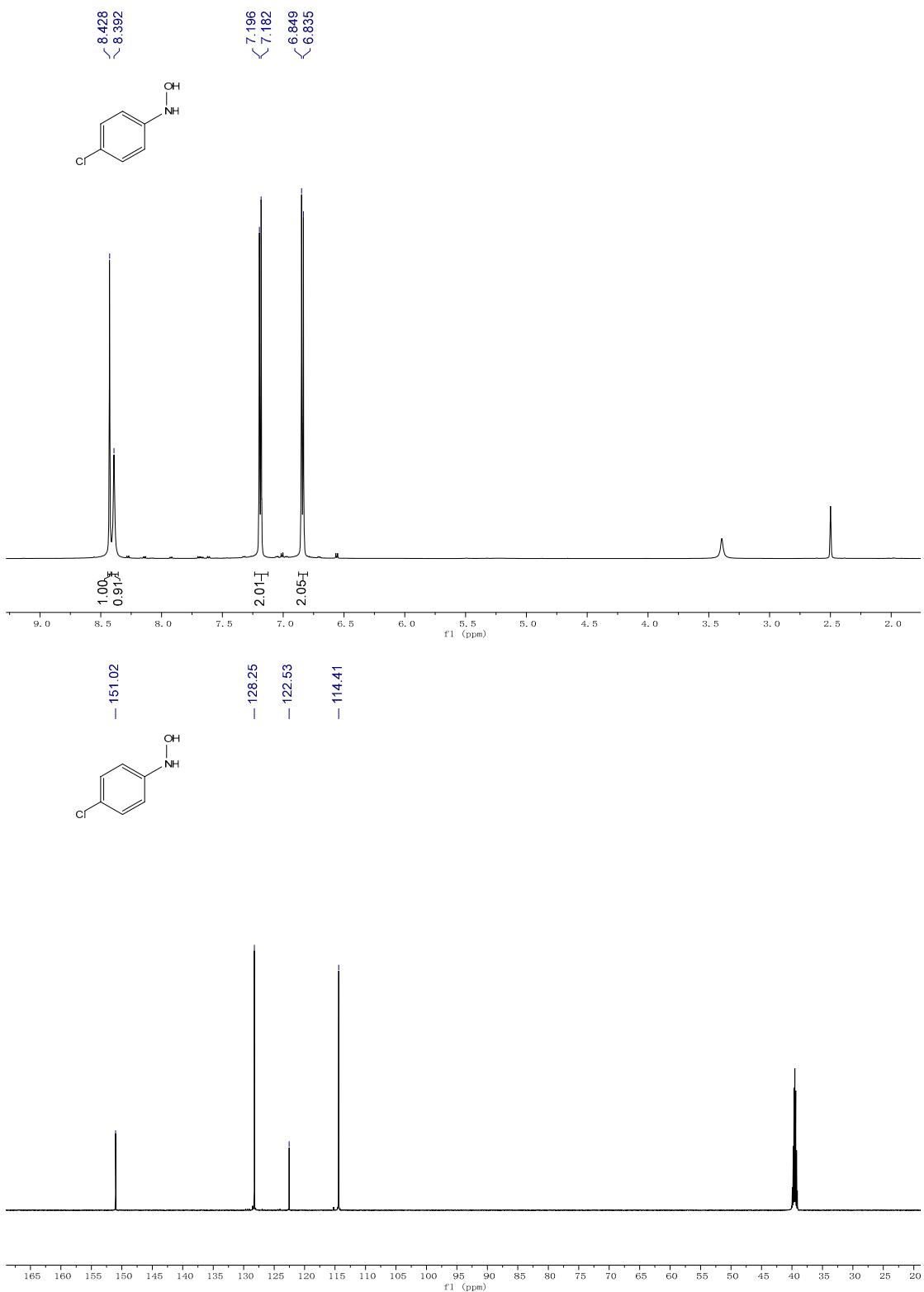


Figure S6. ¹H and ¹³C NMR spectra of *N*-(4-chlorophenyl)hydroxylamine

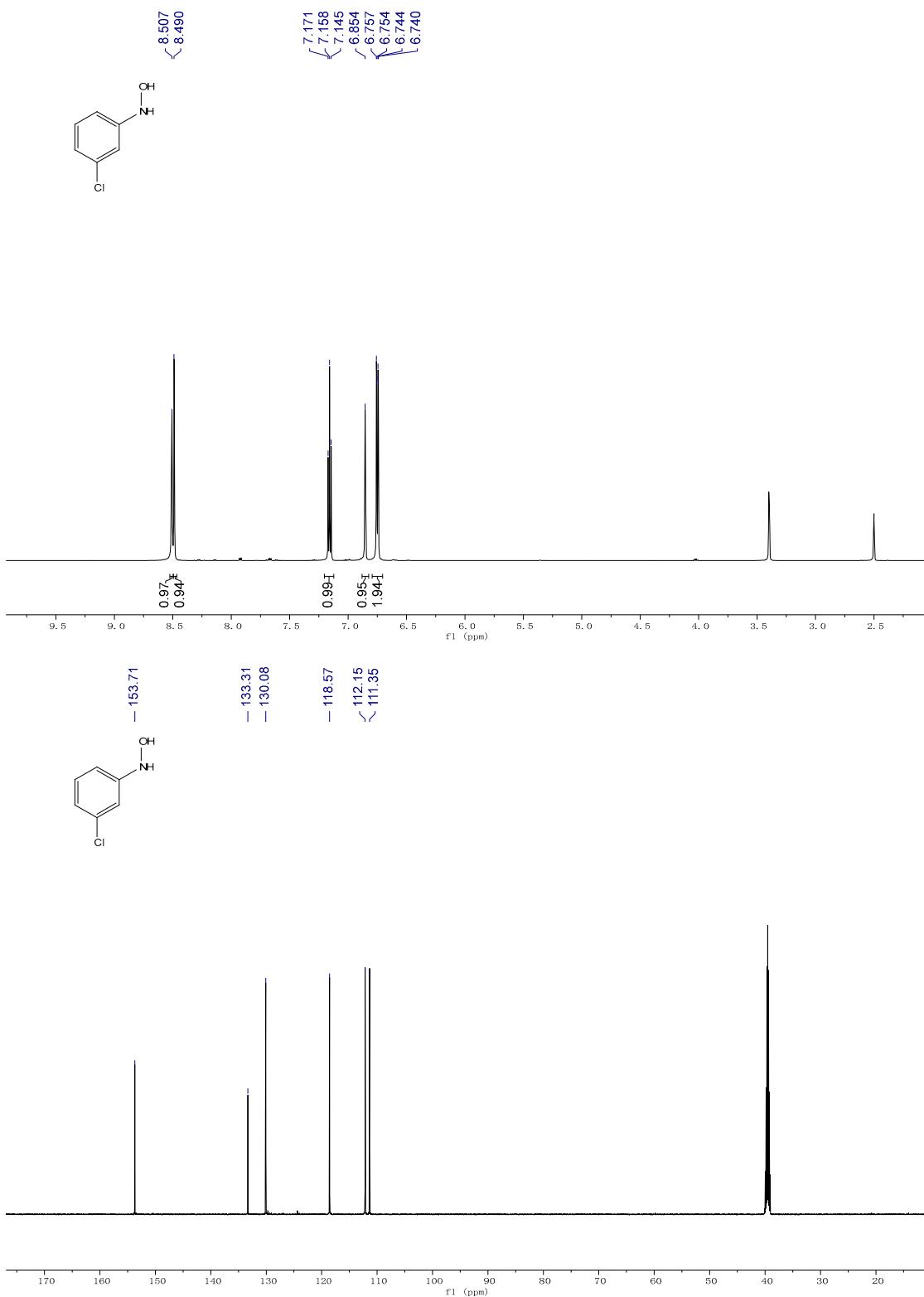


Figure S7. ^1H and ^{13}C NMR spectra of *N*-(3-chlorophenyl)hydroxylamine

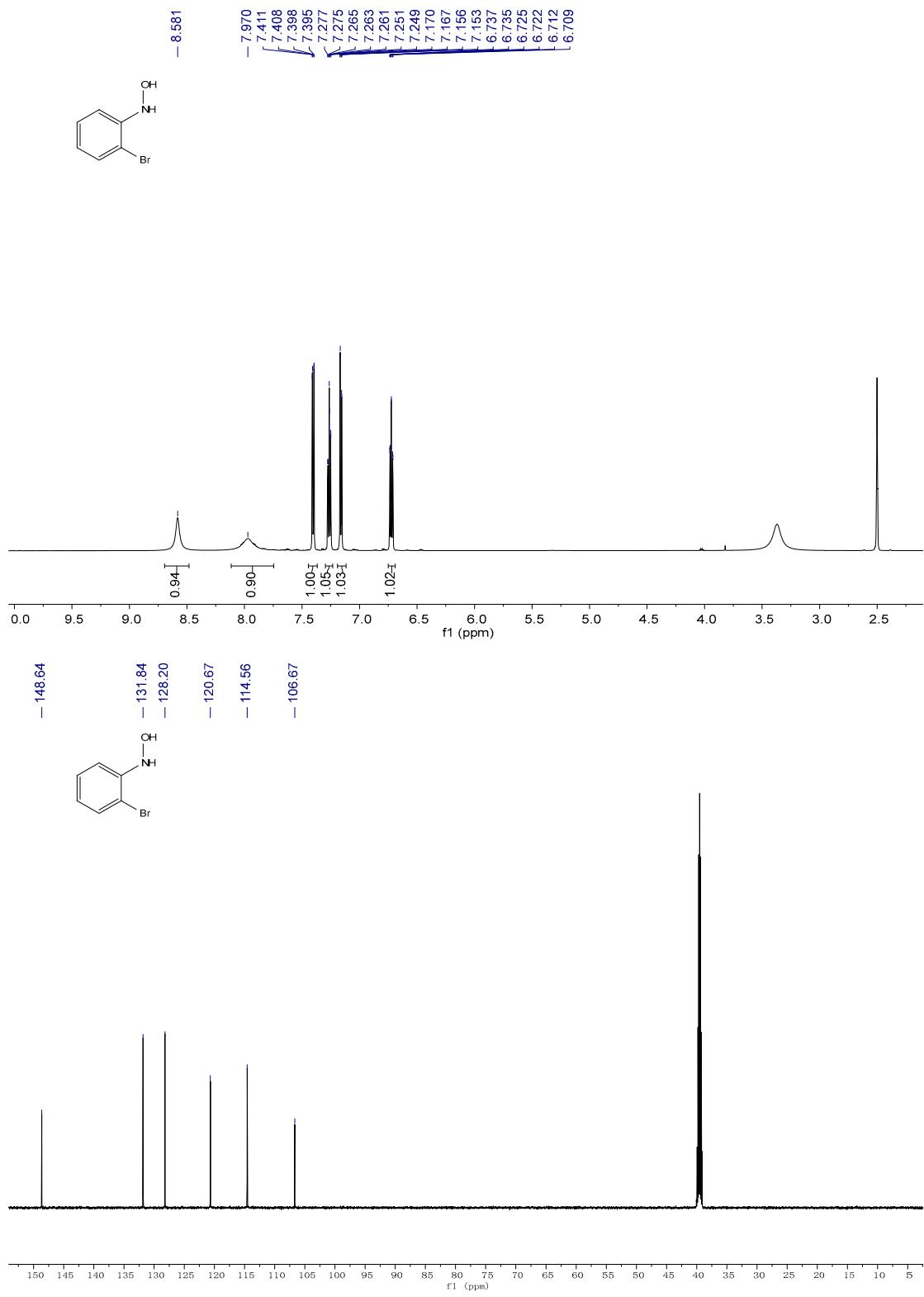


Figure S8. ¹H and ¹³C NMR spectra of *N*-(2-bromophenyl)hydroxylamine

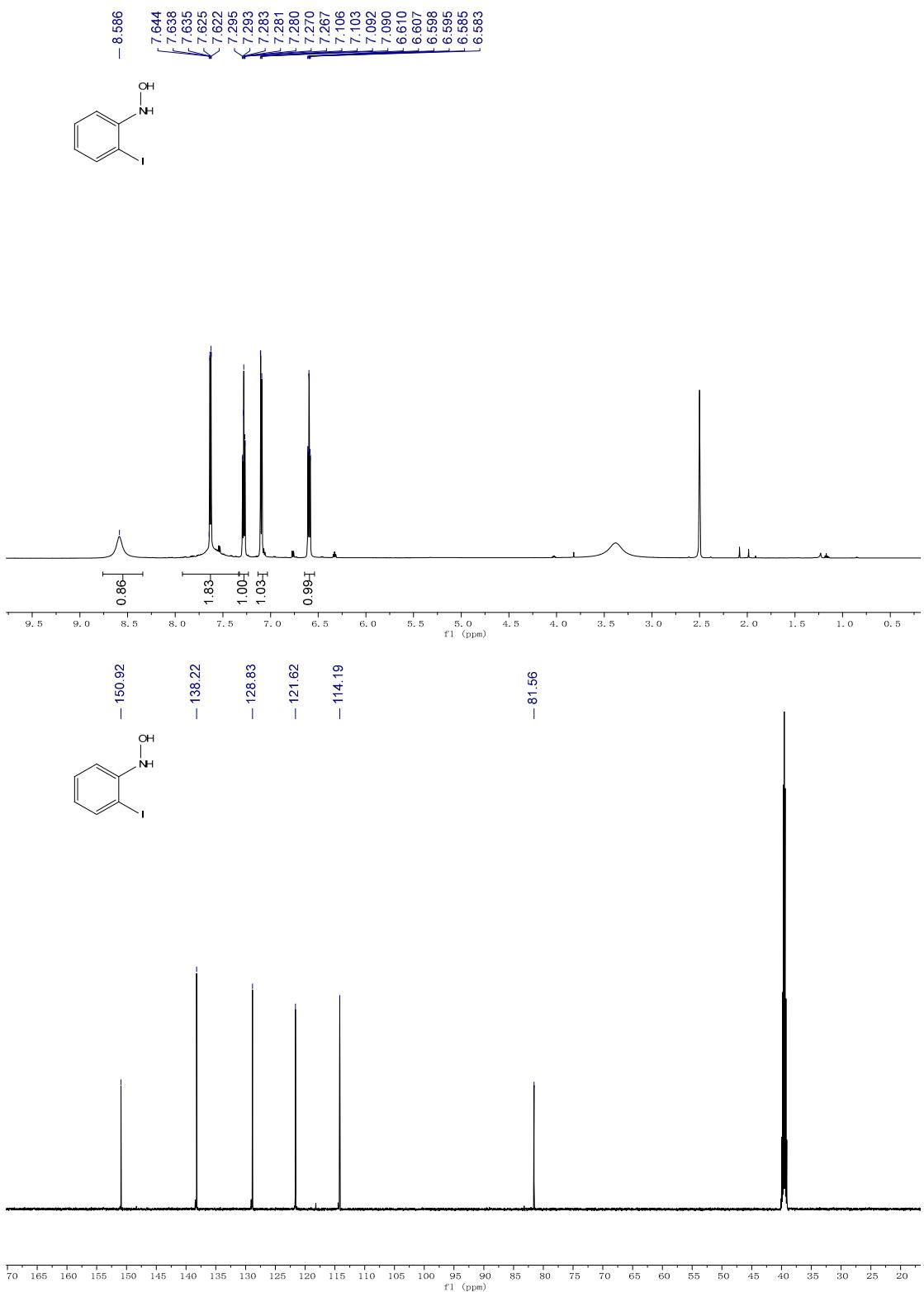


Figure S9. ^1H and ^{13}C NMR spectra of *N*-(2-iodophenyl)hydroxylamine

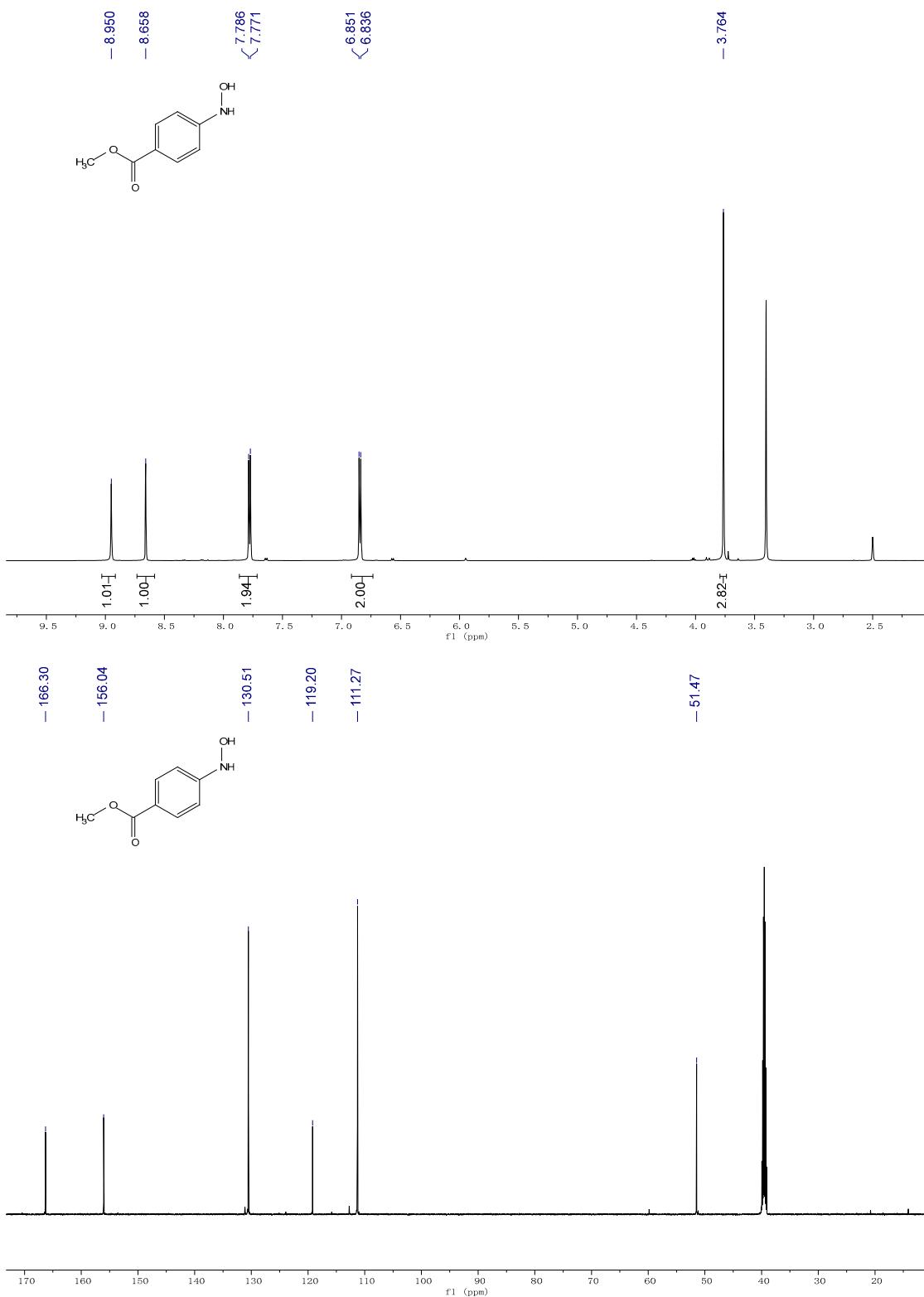


Figure S10. ¹H and ¹³C NMR spectra of ethyl 2-(hydroxyamino)benzoate

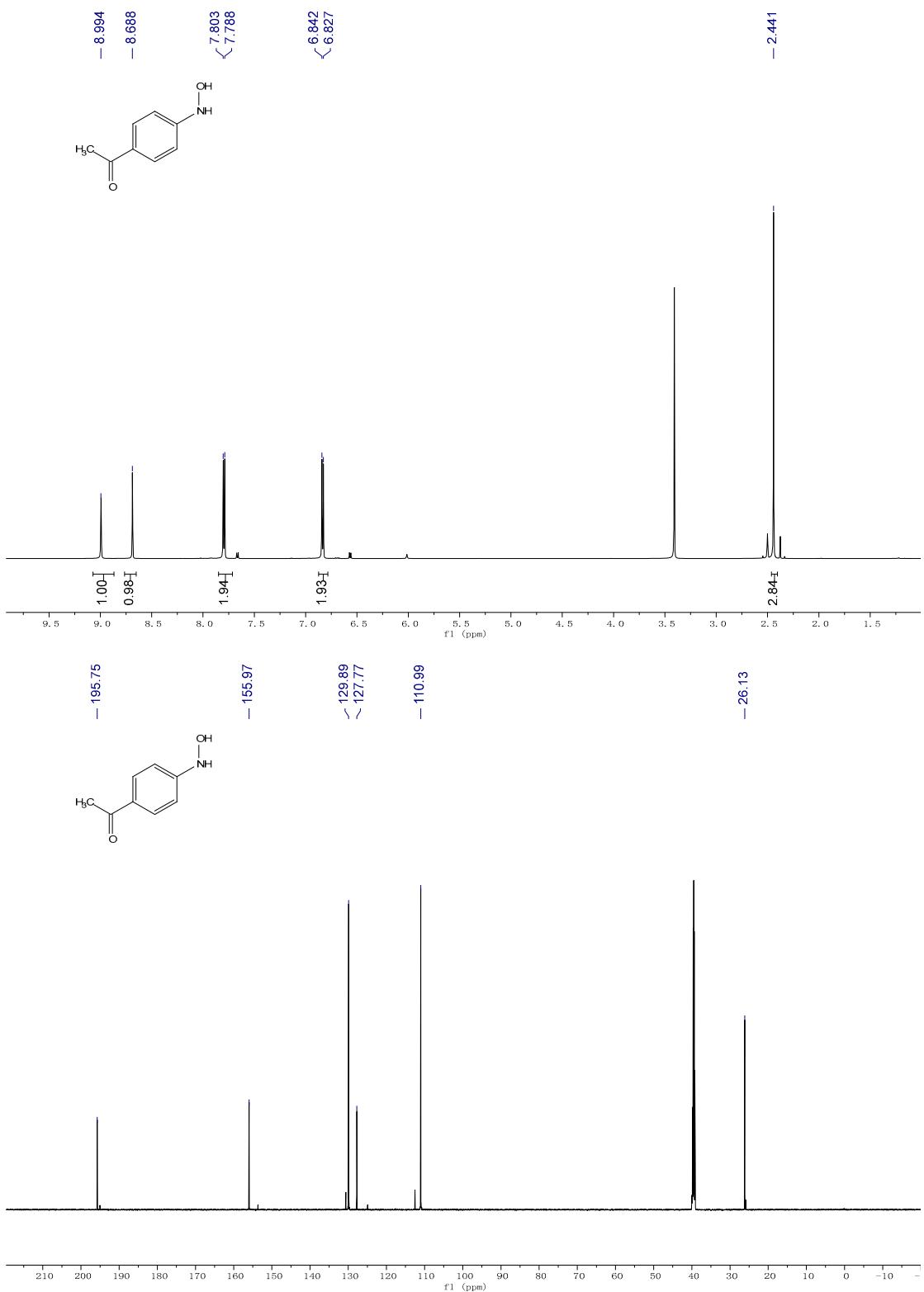


Figure S11. ^1H and ^{13}C NMR spectra of 1-(4-(hydroxyamino)phenyl)ethanone

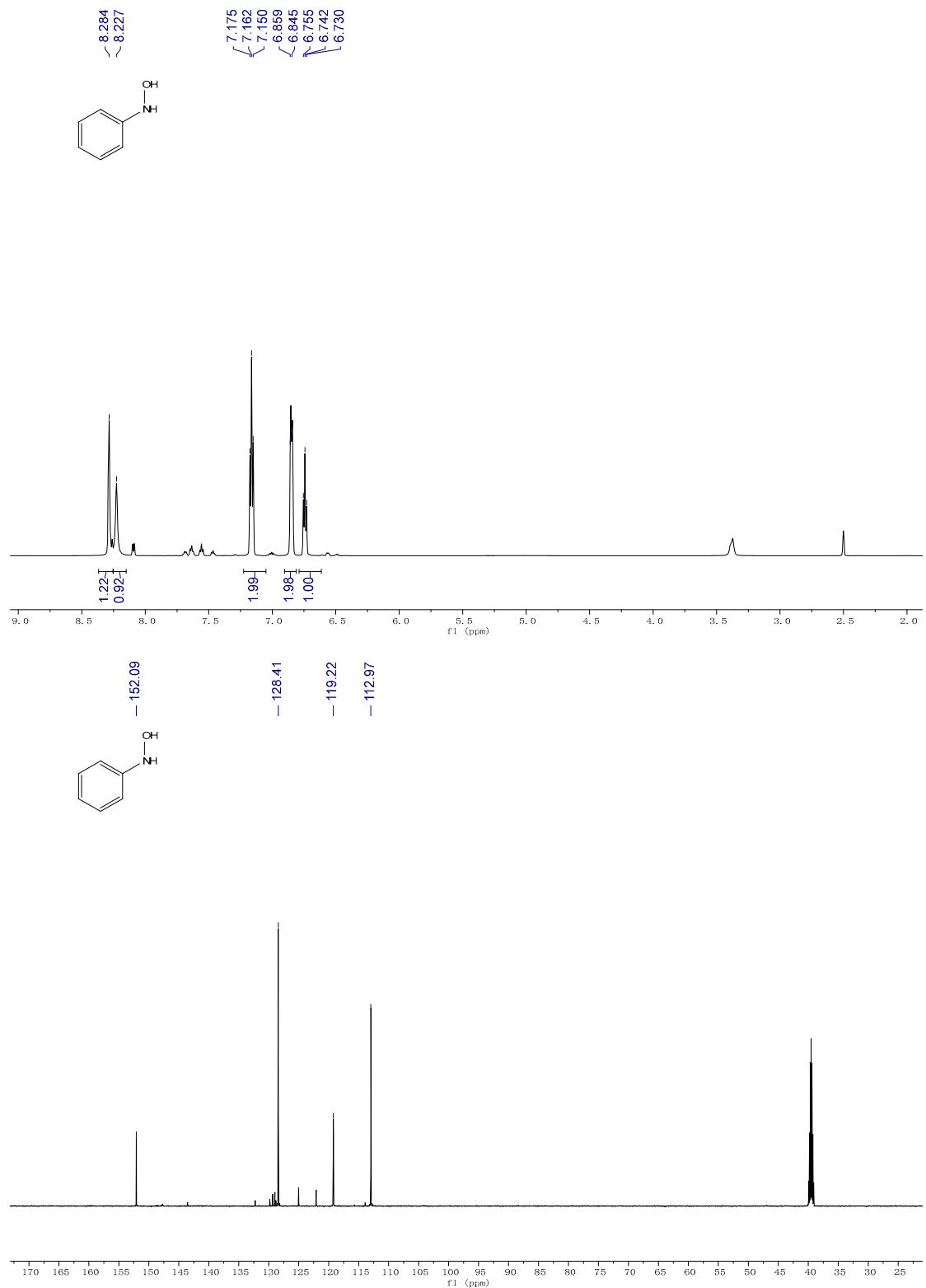


Figure S12. ^1H and ^{13}C NMR spectra of *N*-phenylhydroxylamine

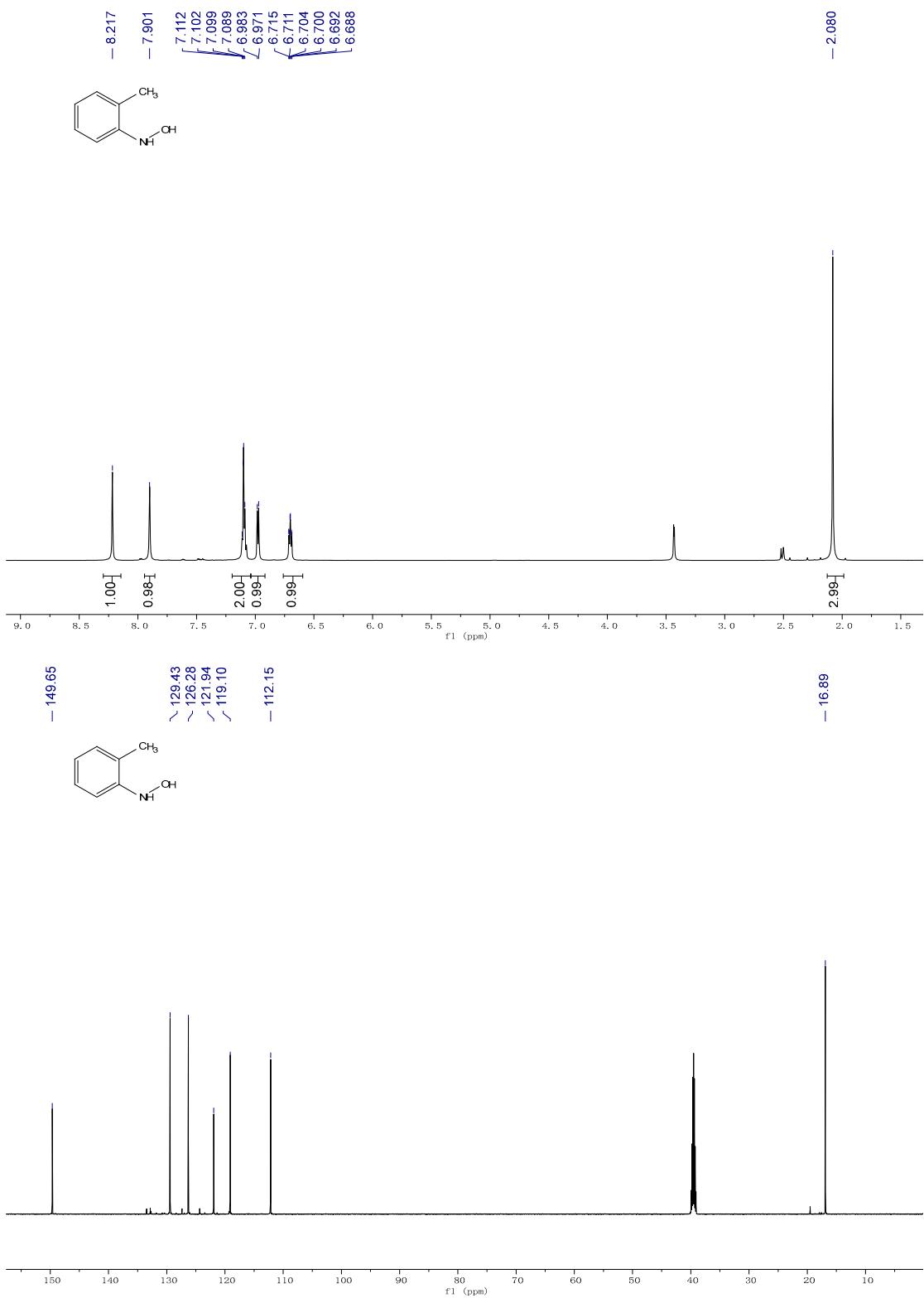


Figure S13. ¹H and ¹³C NMR spectra of *N*-(2-tolyl)hydroxylamine

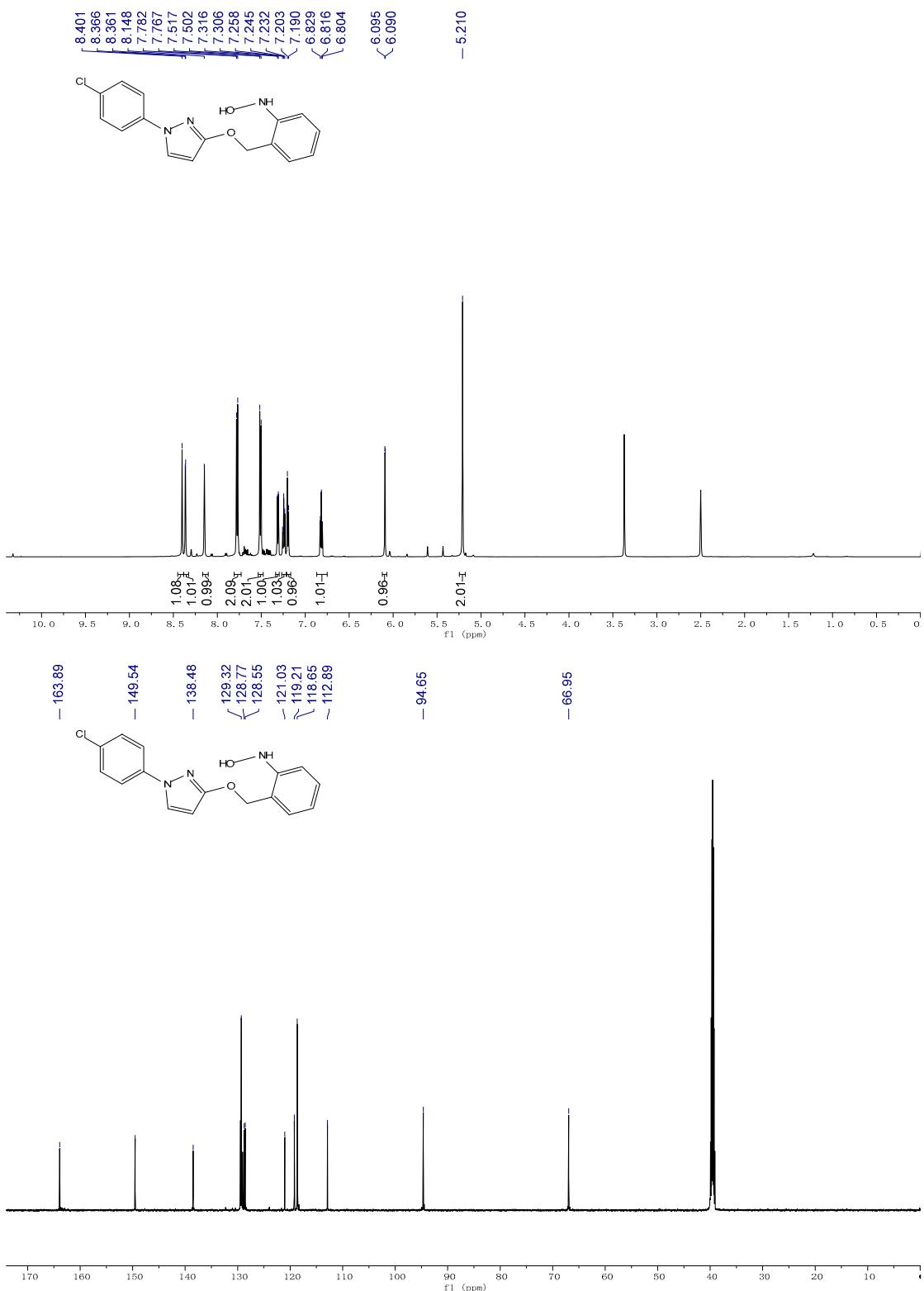


Figure S14. ¹H and ¹³C NMR spectra of *N*-(2-((1-(4-chlorophenyl)-1*H*-pyrazol-3-yl)oxy)methyl)phenyl)hydroxylamine

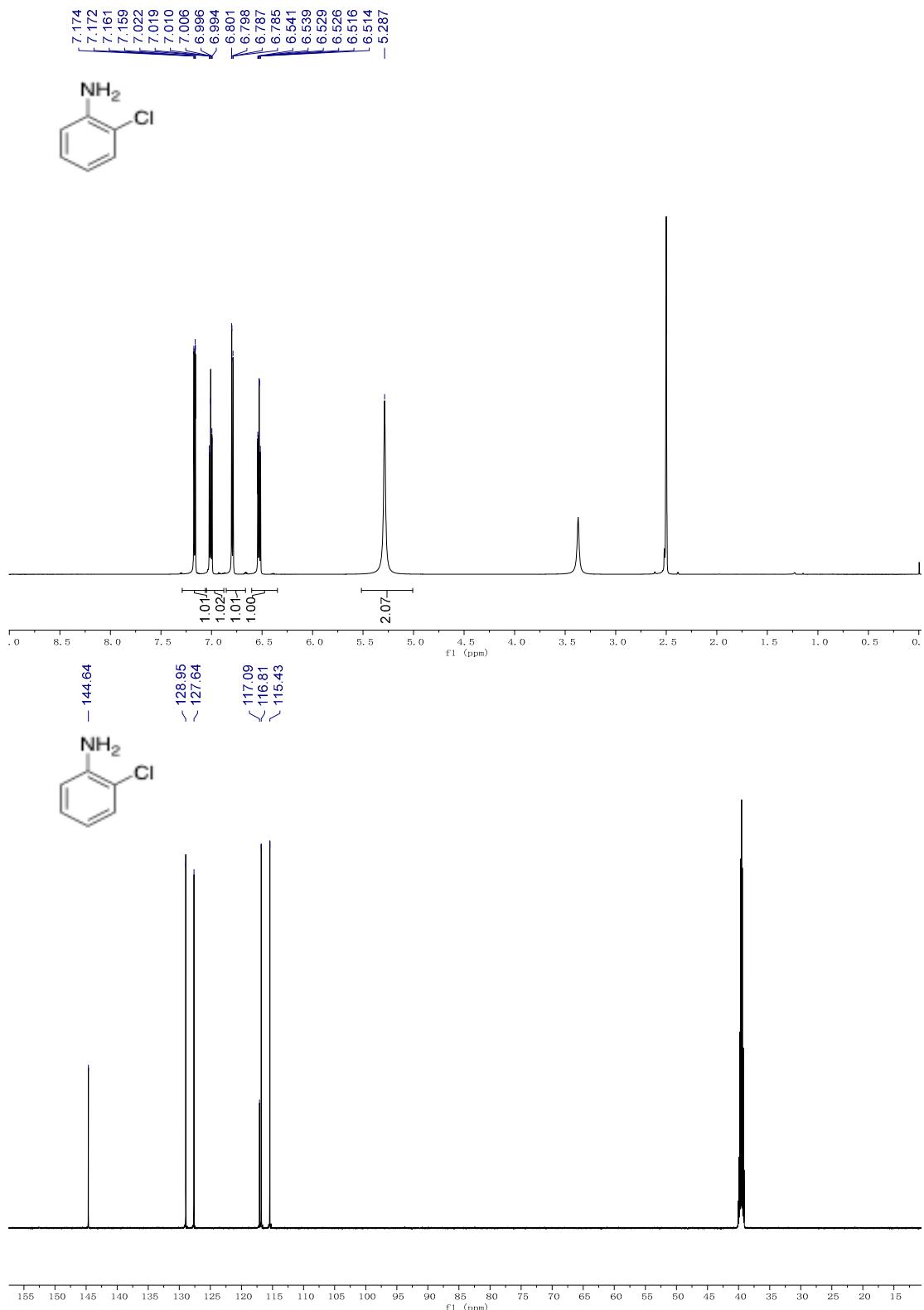


Figure S15. ¹H and ¹³C NMR spectra of *o*-Chloroaniline

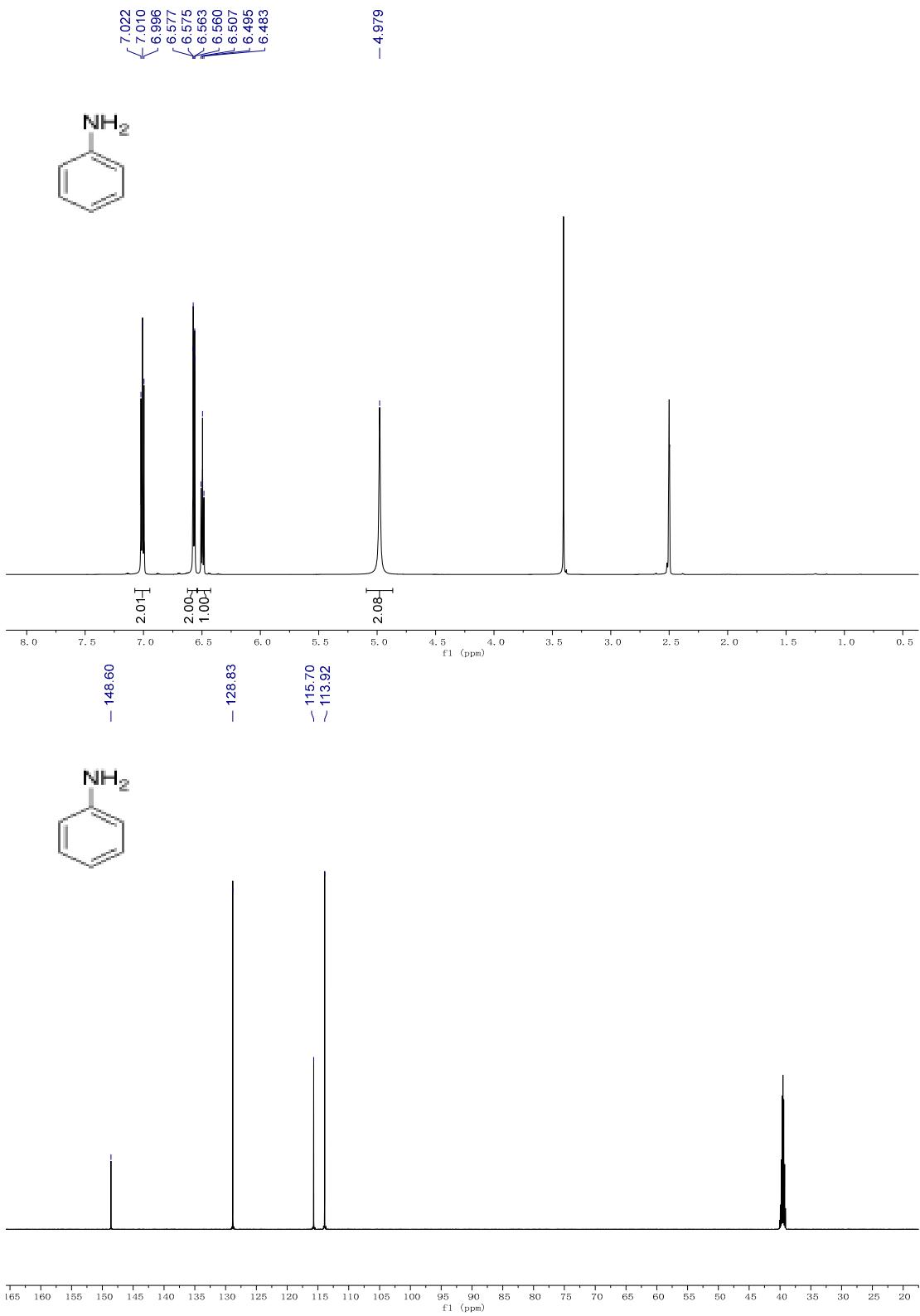


Figure S16. ¹H and ¹³C NMR spectra of aniline

+MS, 28.4min #3396

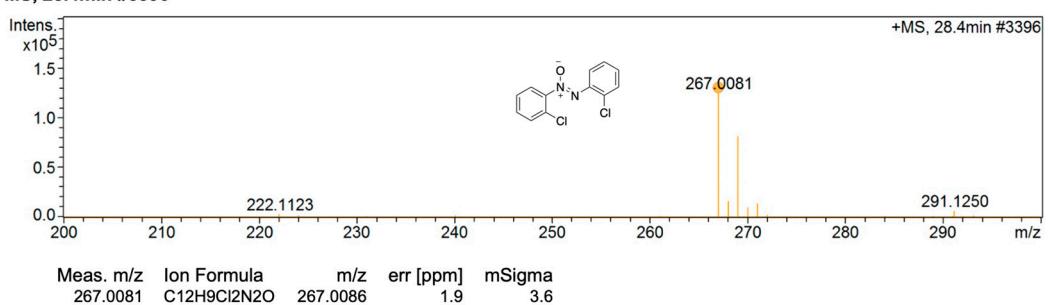


Figure S17. LC-MS spectra of AZO

References

- 1 Doherty, S.; Knight, J.G.; Backhouse, T.; Summers, R.J.; Abood, E.; Simpson, W.; Paget, W.; Bourne, R.A.; Chamberlain, T.W.; Stones, R.; et al. Highly selective and solvent-dependent reduction of nitrobenzene to N-phenylhydroxylamine, azoxyben-zene, and aniline catalyzed by phosphino-modified polymer immobilized ionic liquid-stabilized AuNPs. *ACS Catal.* **2019**, *9*, 4777–4791. <https://doi.org/10.1021/acscatal.9b00347>.
- 2 Sharma, S.D.; Gogoi, P.; Konwar, S. A highly efficient and green method for the synthesis of 3,4-dihydropyrimidin-2-ones and 1,5-benzodiazepines catalyzed by dodecyl sulfonic acid in water. *Indian J. Chem. Sect. B Org. Chem. Incl. Med. Chem.* **2007**, *46B*, 1672–1678.
- 3 Chuang, H.Y.; Schupp, M.; Meyrelles, R.; Maryasin, B.; Maulide, N. Redox-Neutral Selenium-Catalysed Isomerisation of para-Hydroxamic Acids into para-Aminophenols. *Angew. Chemie-Int. Ed.* **2021**, *60*, 13778–13782.
- 4 Kallitsakis, M.G.; Ioannou, D.I.; Terzidis, M.A.; Kostakis, G.E.; Lykakis, I.N. Selective Photoinduced Reduction of Nitroarenes to N-Arylhydroxylamines. *Org. Lett.* **2020**, *22*, 4339–4343.
- 5 Xu, F.; Chen, J.L.; Jiang, Z.J.; Cheng, P.F.; Yu, Z.Q.; Su, W.K. Selective hydrogenation of nitroaromatics to N-arylhydroxylamines in a micropacked bed reactor with passivated catalyst. *RSC Adv.* **2020**, *10*, 28585–28594.