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The Direct α-C(sp^3)-H Functionalisation of *N*-Aryl Tetrahydroisoquinolines via an Iron-Catalysed Aerobic Nitro-Mannich Reaction and Continuous Flow Processing

Martin Brzozowski, Jose A. Forni, G. Paul Savage, Anastasios Polyzos*

CSIRO Manufacturing Flagship, Private Bag 10, Clayton South, 3169, Victoria, Australia.

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1. General Information

All glassware used in moisture sensitive reactions was oven dried and then cooled under nitrogen prior to use. Anhydrous grade toluene was purchased from Merck and further dried by standing over 3 Å molecular sieves (10% w/w). Commercially available reagents were purchased at the highest quality and used without further purification. Analytical thin-layer chromatography (TLC) was performed on Merck Kieselgel $60F_{254}$ aluminium backed plates and visualized using a 254 nM UV lamp and a combination of phosphomolybdic acid, ceric ammonium molybdate or potassium permanganate stain and heat. Flash chromatography was performed on silica gel (Merck Kieselgel 60, 0.040-0.063 mm) according to the method of Still et al.[1] Dry column vacuum chromatography (DCVC) was performed on silica gel (Merck Kieselgel 60, 0.015-0.040 mm) according to the method of Sejer Pedersen et al.[2] Melting points were measured on a Gallenkamp MPD350 melting point apparatus and are uncorrected. Infrared spectra were recorded neat on a Thermo Scientific Nicolet 6700 spectrometer in attenuated total reflectance (ATR) mode. Spectra were obtained between 4000 and 400 cm^{-1} using 16 scans. NMR spectra were recorded on Bruker AV-400 instrument at 400.13 MHz for ^{1}H nuclei, at 100.61 MHz for ^{13}C nuclei and at 376.49 MHz for ^{19}F NMR nuclei. Samples were recorded in deuturated solvent as specified, and data acquired at 25 °C. Chemical shifts are reported as δ values in parts per million (ppm). In reporting spectral data the following abbreviations have been used: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; quint., quintet; m, multiplet. Low-resolution positive ion EI mass spectra were run on a ThermoQuest MAT95XL mass spectrometer using an ionization energy of 70 eV. High resolution ESI mass spectrometric analyses were performed on a Thermo Scientific Q Exactive mass spectrometer fitted with a HESI-II ion source. Positive and negative ions were recorded in an appropriate mass range set for 140,000 mass resolution. The probe was used with 0.3 mL/min flow of solvent. The nitrogen nebulizing/desolvation gas used for vaporization was heated to 350 °C in these experiments. The sheath gas flow rate was set to 35 and the auxiliary gas flow rate to 25 (both arbitrary units). The spray voltage was 3.0 kV and the capillary temperature was 300 °C. High resolution APCI mass spectrometric analyses were performed on a Thermo Scientific Q Exactive mass spectrometer fitted with an APCI ion source. Positive and negative ions were recorded in an appropriate mass range set for 70,000 mass resolution. The probe was used without flow of solvent. The nitrogen nebulizing/desolvation gas used for vaporization was heated to 450 °C in these experiments. The sheath gas flow rate was set to 25 and the auxiliary gas flow rate to 10 (both arbitrary units). The spray current was 5 μA and the capillary temperature was 320 °C. X-ray crystallography data was collected using the MX1 beamline at the Australian Synchrotron operating at 17.4 keV (λ = 0.7107 Å) with the BluIce software used to control data collection.[3] Initial data processing was conducted using XDS.[4] The structure was solved by direct methods using SHELXS-2013 and refined by least-square methods against F^2 using

[1] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
[2] D. Sejer Pedersen, C. Rosenbohm, *Synthesis*, 2001, **16**, 2431.
[3] T. M. McPhillips, S. E. McPhillips, H. J. Chiu, A. E. Cohen, A. M. Deacon, P. J. Ellis, E. Garman, A. Gonzalez, N. K. Sauter, R. P. Phizackerley, S. M. Soltis, P. Kuhn, *J. Synchrotron Rad.*, 2002, **9**, 401.
[4] W. Kabsch, *Acta Cryst.*, 2010, **D66**, 125.

SHELXL-2013.[5] The program X-Seed was used as a graphical interface for the SHELX programs.[6] All non-hydrogen atoms were refined using an anisotropic model. Hydrogen atoms were placed in idealised positions and refined using a riding model. The CIF for this structure has been deposited with the Cambridge Structural Database (CCDC = 1027557). All continuous flow reactions were performed using a Vapourtec R series Flow Chemistry system equipped with standard PTFE tubing unless stated otherwise.

2. Experimental Section

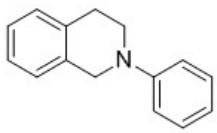
2.1 Preparation of nitro-Mannich substrates

2.1.1 General procedure for preparation of nitro-Mannich substrates

An oven-dried 50 mL flask equipped with a magnetic stirbar was charged with (±)-BINAP (5.5 mol %), evaculated and purged with argon. Dry PhMe (16 mL) was added and the mixture was heated to 100 °C (preheated oil-bath) with vigorous stirring until a homogenous solution was obtained (~5 min). The solution was cooled to room temperature, $Pd(OAc)_2$ (5 mol %) was added and the mixture stirred vigorously for 1 min. Aryl bromide (10 mmol), 1,2,3,4-tetrahydroisoquinoline (12 mmol) and potassium *tert*-butoxide (14 mmol) were added sequentially and the mixture heated at 100 °C. After 2 h the mixture was cooled to room temperature, diluted with EtOAc (50 mL) and filtered through Celite®. Concentration under reduced pressure afforded the crude product, which was purified by DCVC or flash chromatography.

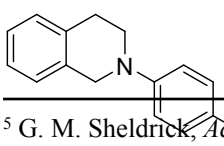
2.1.2 Characterisation of nitro-Mannich substrates

2-Phenyl-1,2,3,4-tetrahydroisoquinoline (1ab)



Bromobenzene (1.57 g, 10 mmol) was treated according to the general procedure. Purification by DCVC (id. 6 cm × h. 8 cm; 50 mL fractions, 4 × *n*-heptane, 1-10% EtOAc/*n*-heptane, 1% increments) afforded the title compound (1.53 g, 73%) as a white crystalline solid, mp 46.0-47.0 °C (lit. 44.5-45.5 °C).[7] R_f = 0.55 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.27 (m, 2H), 7.21-7.15 (m, 4H), 7.00 (dd, *J* = 8.8, 1.0 Hz, 2H), 6.84 (tt, *J* = 7.3, 1.0 Hz, 1H), 4.42 (s, 2H), 3.58 (t, *J* = 5.9 Hz, 2H), 3.00 (t, *J* = 5.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 135.0, 134.6, 129.3, 128.6, 126.7, 126.4, 126.1, 118.8, 115.3, 50.9, 46.6, 29.2. IR (neat) 3055, 2827, 1598, 1502, 1387, 1209, 934, 737, 690 cm^{-1}. MS (EI) *m/z*: 253, 210, 209, 208 (100), 206, 181, 165, 105, 104, 77.

2-(*p*-Tolyl)-1,2,3,4-tetrahydroisoquinoline (1cd)

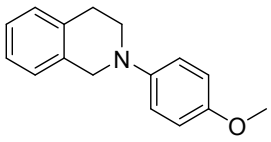


4-Bromotoluene (1.71 g, 10 mmol) was treated according to the general procedure. Purification by DCVC (id. 6 cm × h. 8 cm; 50 mL fractions,

[5] G. M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112.
[6] L. J. Barbour, *J. Supramol. Chem.*, 2001, **1**, 189.
[7] J. Meneyrol, P. Helissey, C. Tratrat, S. Giorgi-Renault, H.-P. Husson, *Synth. Commun.* 2001, **31**, 987.

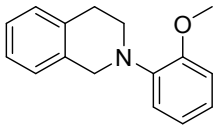
4 × *n*-heptane, 1-10% EtOAc/*n*-heptane, 1% increments) afforded the title compound (1.18 g, 53%) as a white crystalline solid, mp 36.0-37.0 °C (lit. 34.0 °C).[8] R_f = 0.50 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.09 (m, 6H), 6.94 (d, *J* = 8.4 Hz, 2H), 4.37 (s, 2H), 3.52 (t, *J* = 5.8 Hz, 2H), 3.00 (t, *J* = 5.8 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 134.9, 134.7, 129.9, 128.7, 128.6, 126.7, 126.4, 126.1, 116.0, 51.6, 47.4, 29.2, 20.5. IR (neat) 3027, 2916, 2803, 1612, 1513, 1460, 1382, 1289, 1209, 1185, 926, 804, 722 cm^{-1}. MS (EI) *m/z*: 223, 222 (100), 195, 118, 104.

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (1e)



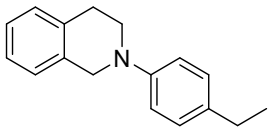
4-Bromoanisole (1.87 g, 10 mmol) was treated according to the general procedure. Purification by flash chromatography (2-5% EtOAc/*n*-heptane) afforded the title compound (895 mg, 37%) as a white crystalline solid, mp 93.5-94.5 °C (lit. 93.0-94.0 °C).[9] R_f = 0.40 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.12 (m, 4H), 7.01-6.97 (m, 2H), 6.89-6.85 (m, 2H), 4.30 (s, 2H), 3.78 (s, 3H), 3.45 (t, *J* = 5.8 Hz, 2H), 2.99 (t, *J* = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 145.5, 134.8, 134.7, 128.8, 126.7, 126.4, 126.0, 118.2, 114.7, 55.8, 52.8, 48.6, 29.2. IR (neat) 2996, 2918, 2806, 1583, 1509, 1459, 1272, 1238, 1035, 823, 754, 721 cm^{-1}. MS (EI) *m/z*: 240, 239 (100), 238, 224, 211, 135, 104, 77.

2-(2-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (1f)



2-Bromoanisole (1.87 g, 10 mmol) was treated according to the general procedure. Purification by flash chromatography (2-5% EtOAc/*n*-heptane) afforded the title compound (998 mg, 42%) as a colourless viscous oil. R_f = 0.45 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.09 (m, 4H), 7.02-7.06 (m, 2H), 6.94-6.90 (m, 2H), 4.30 (s, 2H), 3.89 (s, 3H), 3.41 (t, *J* = 5.7 Hz, 2H), 2.98 (t, *J* = 5.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 141.2, 135.2, 134.7, 129.0, 126.5, 126.2, 125.9, 123.1, 121.0, 119.1, 111.4, 55.6, 53.2, 49.1, 29.0. IR (neat) 3021, 2918, 2831, 1663, 1593, 1498, 1453, 1236, 1213, 1109, 1027, 741 cm^{-1}. MS (EI) *m/z*: 240, 239, 238 (100), 222, 208, 132, 123, 120, 104, 77.

2-(4-Ethylphenyl)-1,2,3,4-tetrahydroisoquinoline (1g)

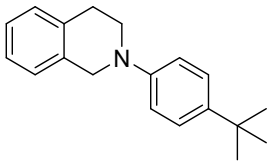


1-Bromo-4-ethylbenzene (1.85 g, 10 mmol) was treated according to the general procedure. Purification by flash chromatography (0-5% EtOAc/*n*-heptane) afforded the title compound (1.41 g, 59%) as a white crystalline solid, mp 40.0-41.0 °C. R_f = 0.46 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.14 (m, 6H), 6.96 (d, *J* = 8.6 Hz, 2H), 4.39 (s, 2H), 3.54 (t, *J* = 5.8 Hz, 2H), 3.00 (t, *J* = 5.8 Hz, 2H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 134.87, 134.86, 134.6, 128.65, 128.59, 126.6, 126.3, 126.0, 115.8, 51.4, 47.2, 29.2, 28.0, 15.9. IR (neat) 2963, 2827, 1616, 1518,

[8] A. Guram, S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 7901.
[9] A. S.-K. Tsang, K. Ingram, J. Keiser, D. B. Hibbert, M. H. Todd, *Org. Biomol. Chem.* 2013, **11**, 4921.

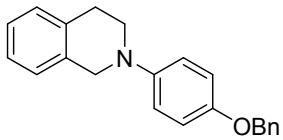
1455, 1385, 1235, 1214, 1188, 1150, 928, 818, 745 cm^{-1}. HRMS (APCI) calcd for $C_{17}H_{19}N$ ($M^{+\bullet}$): 237.1512. Found 237.1509.

2-(4-(*tert*-Butyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1h)



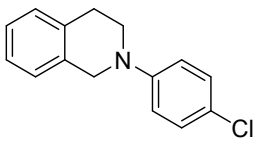
1-Bromo-4-(*tert*-butyl)benzene (2.13 g, 10 mmol) was treated according to the general procedure. Purification by flash chromatography (0-5% EtOAc/*n*-heptane) afforded the title compound (1.80 g, 75%) as a white crystalline solid, mp 76.5-77.5 °C. R_f = 0.42 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.30 (m, 2H), 7.19-7.14 (m, 4H), 6.97-6.93 (m, 2H), 4.39 (s, 2H), 3.54 (t, *J* = 5.8 Hz, 2H), 2.99 (t, *J* = 5.8 Hz, 2H), 1.3 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 141.6, 134.9, 134.7, 128.6, 126.6, 126.3, 126.07, 126.05, 115.2, 51.2, 46.8, 34.0, 31.6, 29.3. IR (neat) 2958, 2809, 1611, 1517, 1461, 1385, 1362, 1268, 1224, 1189, 932, 814, 741 cm^{-1}. MS (EI) *m/z*: 265, 264, 251, 250 (100), 248, 234, 222, 146, 118, 111, 104, 103, 91, 77.

2-(4-(Benzyloxy)phenyl)-1,2,3,4-tetrahydroisoquinoline (1i)



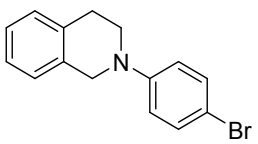
1-(Benzyloxy)-4-bromobenzene (2.63 g, 10 mmol) was treated according to the general procedure. Purification by recrystallisation (EtOH) afforded the title compound (1.86 g, 59%) as pale yellow crystalline solid, mp 88.5-89.5 °C. R_f = 0.50 (15% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.30 (m, 5H), 7.19-7.12 (m, 4H), 6.99-6.93 (m, 4H), 5.03 (s, 2H), 4.31 (s, 2H), 3.46 (t, *J* = 5.8 Hz, 2H), 2.99 (t, *J* = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 145.6, 137.5, 134.71, 134.69, 128.8, 128.7, 127.9, 127.6, 126.6, 126.4, 126.0, 117.9, 115.8, 70.7, 52.6, 48.4, 29.2. IR (neat) 3034, 2922, 2828, 1596, 1517, 1511, 1478, 1453, 1296 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{22}NO$ (M+H): 316.1696. Found 316.1699.

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (1j)



1-Bromo-4-chlorobenzene (1.91 g, 10 mmol) was treated according to the general procedure. Purification by DCVC (id. 6 cm × h. 8 cm; 50 mL fractions, 4 × *n*-heptane, 1-12% EtOAc/*n*-heptane, 1% increments) afforded the title compound (1.23 g, 50%) as a white crystalline solid, mp 67.5-68.5 °C (lit. 65.5-66.5 °C).[10] R_f = 0.42 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.14 (m, 6H), 6.91-6.87 (m, 2H), 4.38 (s, 2H), 3.54 (t, *J* = 5.8 Hz, 2H), 2.99 (t, *J* = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2, 134.8, 134.2, 129.4, 129.1, 128.7, 126.6, 126.3, 123.5, 116.3, 50.8, 46.7, 29.1. IR (neat) 2924, 2829, 1592, 1494, 1454, 1444, 1384, 1224, 1209, 1183, 818, 808, 744, 674 cm^{-1}. MS (EI) *m/z*: 242, 215, 152, 104 (100).

2-(4-Bromophenyl)-1,2,3,4-tetrahydroisoquinoline (1k)

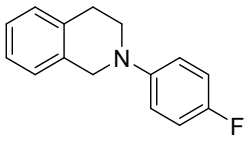


1,4-Dibromobenzene (2.36 g, 10 mmol) was treated according to the general procedure. Purification by DCVC (id. 6 cm × h. 8 cm; 50 mL fractions, 4 × *n*-heptane, 1-12% EtOAc/*n*-heptane, 1% increments)

[10] A. Rieche, E. Hoft, H. Schultze, *Chem. Ber.* 1964, **97**, 195.

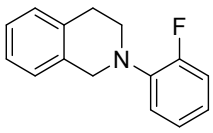
afforded the title compound (1.25 g, 43%) as a white crystalline solid, mp 71.0-72.0 °C (lit. 65.0-67.0 °C).[11] R_f = 0.38 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.35 (m, 2H), 7.22-7.15 (m, 4H), 6.86-6.82 (m, 2H), 4.38 (s, 2H), 3.54 (t, *J* = 5.8 Hz, 2H), 2.98 (t, *J* = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5, 134.8, 134.1, 132.0, 129.4, 128.6, 126.6, 126.3, 116.6, 110.6, 50.5, 46.4, 29.1. IR (neat) 3030, 2818, 1584, 1492, 1459, 1224, 1187, 804, 738, 659 cm^{-1}. MS (EI) *m/z*: 288, 286, 259, 183, 152, 115, 104 (100).

2-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (1l)



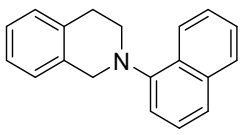
1-Bromo-4-fluorobenzene (1.75 g, 10 mmol) was treated according to the general procedure. Purification by flash chromatography (10-80% CH_2Cl_2/*n*-heptane) afforded the title compound (1.13 g, 50%) as a white crystalline solid, mp 80.0-81.0 °C. R_f = 0.35 (5% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.14 (m, 4H), 7.02-6.93 (m, 4H), 4.34 (s, 2H), 3.50 (t, *J* = 5.8 Hz, 2H), 2.99 (t, *J* = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8 (d, *J* = 261 Hz), 147.5 (d, *J* = 1.8 Hz), 134.6, 134.4, 128.7, 126.6, 126.5, 126.1, 117.2 (d, *J* = 7.8 Hz), 115.7 (*J* = 22.2 Hz), 52.0, 47.9, 29.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ -126.7 (s). IR (neat) 2926, 2824, 1507, 1386, 1269, 1225, 1205, 1188, 1153, 1112, 933, 825, 814, 808, 753, 743, 721, 701 cm^{-1}. HRMS (APCI) calcd for $C_{15}H_{14}FN$ ($M^{+\bullet}$): 227.1105. Found 227.1104.

2-(2-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (1m)



1-Bromo-2-fluorobenzene (1.75 g, 10 mmol) was treated according to the general procedure. Purification by flash chromatography (20-100% CH_2Cl_2/*n*-heptane) afforded the title compound (171 mg, 8%) as a colourless light oil (**volatile**). R_f = 0.35 (5% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.00 (m, 7H), 6.97-6.91 (m, 1H), 4.32 (s, 2H), 3.46 (t, *J* = 5.8 Hz, 2H), 3.00 (t, *J* = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, CDCl3): δ 155.9 (d, *J* = 246 Hz), 139.9 (d, *J* = 8.7 Hz), 134.57, 134.53, 129.0, 126.5, 126.4, 126.0, 124.5 (d, *J* = 3.5 Hz), 122.4 (d, *J* = 7.9 Hz), 119.5 (d, *J* = 3.0 Hz), 116.3 (d, *J* = 20.7 Hz), 52.7 (d, *J* = 2.2 Hz), 49.1 (d, *J* = 4.6 Hz), 29.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ -123.6 (s). IR (neat) 3023, 2921, 2813, 1612, 1499, 1462, 1386, 1229, 1207, 1114, 1039, 934, 809, 745 cm^{-1}. HRMS (APCI) calcd for $C_{15}H_{14}FN$ ($M^{+\bullet}$): 227.1105. Found 227.1101.

2-(Naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline (1n)

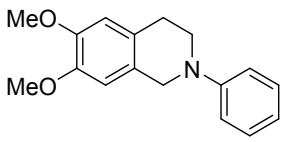


1-Bromonaphthalene (2.07 g, 10 mmol) was treated according to the general procedure. Purification by flash chromatography (10% CH_2Cl_2/*n*-heptane) afforded the title compound (649 mg, 39%) as a colourless viscous oil. R_f = 0.33 (5% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28-8.24 (m, 1H), 7.88-7.84 (m, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.50-7.41 (m, 3H), 7.26-7.18 (m, 4H), 7.13 (d, *J* = 6.5 Hz, 1H), 4.33 (s, 2H), 3.46 (br s, 2H), 3.16 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 135.4, 134.8, 134.6, 129.2, 129.1, 128.5, 126.5, 126.4, 125.98, 125.95, 125.88, 125.5, 123.8, 123.6, 115.0, 55.4, 51.6, 29.8. IR (neat) 3042,

[11] N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* 2012, **51**, 3642.

2924, 2798, 1574, 1459, 1398, 1380, 1274, 1222, 1138, 1093, 934, 799, 789, 772, 752, 739 cm^{-1}. HRMS (APCI) calcd for $C_{19}H_{17}N$ ($M^{+\bullet}$): 259.1356. Found 259.1354.

6,7-Dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (1o)



Bromobenzene (1.57 g, 10 mmol) was reacted with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[12] (2.32 g, 12 mmol) according to the general procedure. Purification by flash chromatography (30% EtOAc/*n*-heptane) afforded the title compound (2.02 g, 75%) as a white crystalline solid, mp 92.0-94.0 °C (lit. 91.0-93.0 °C).[13] R_f = 0.31 (30% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.5, 7.42 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.84 (t, *J* = 7.25 Hz, 1H), 6.66 (s, 1H), 6.65 (s, 1H), 4.34 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.55 (t, *J* = 5.83 Hz, 2H), 2.90 (t, *J* = 5.79 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 147.7, 147.6, 129.3, 126.8, 126.3, 118.9, 115.4, 111.5, 109.5, 56.10, 56.06, 50.6, 46.9, 28.7. IR (neat) 2933, 2833, 1599, 1517, 1504, 1463, 1383, 1255, 1235, 1214, 1117, 1028, 752, 693 cm^{-1}. HRMS (APCI) calcd for $C_{17}H_{20}NO_2$ ($M+H^+$): 270.1489. Found 270.1485.

[12] K. Okano, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* 2006, **128**, 7136.
[13] K. Alagiri, K. R. Prabhu, *Org. Biomol. Chem.* 2012, **10**, 835.

2.2 Continuous flow reactor configuration

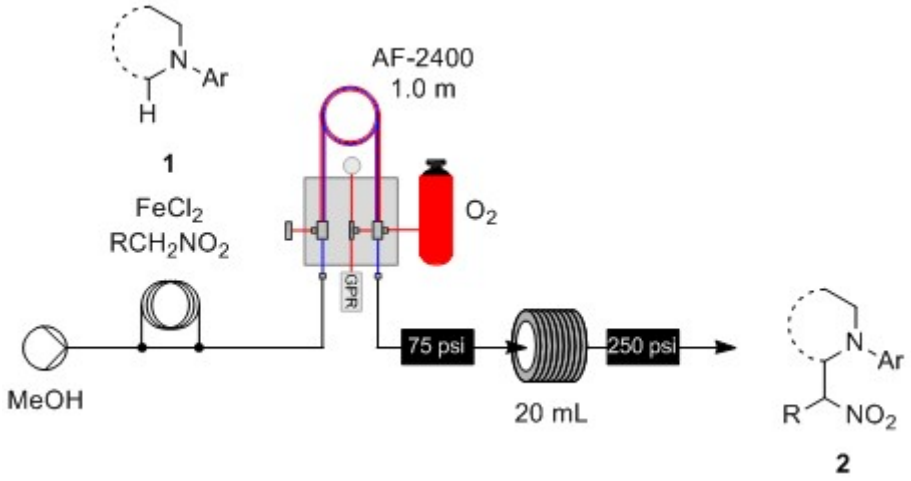


Figure S1 Schematic of continuous flow reaction configuration.

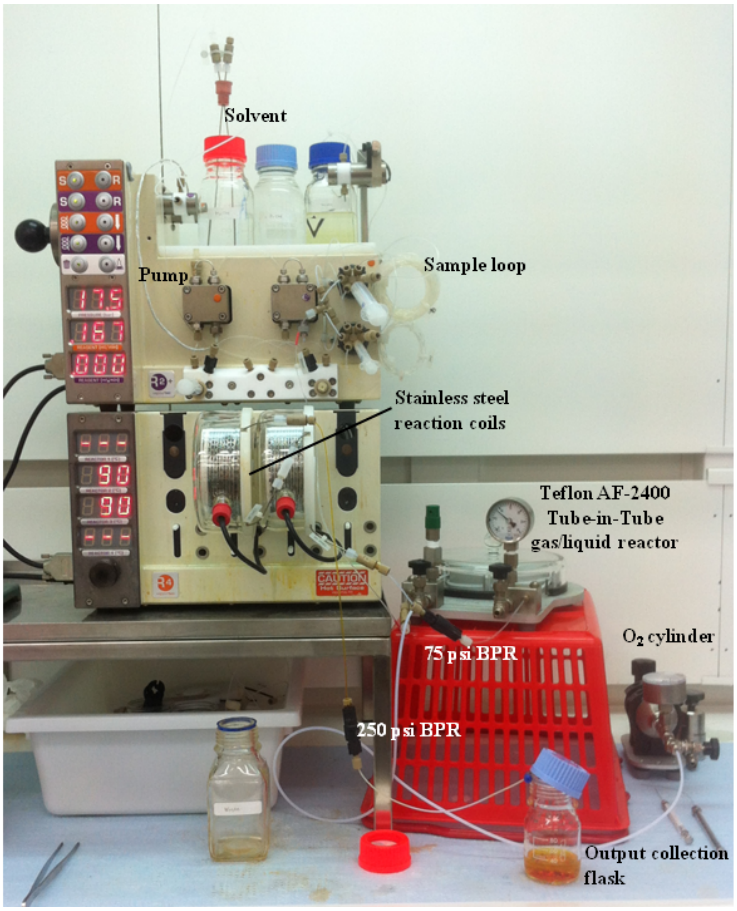
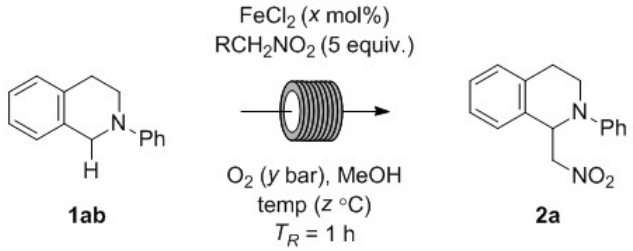


Figure S2 Continuous flow reactor employed for the aerobic nitro-Mannich reaction.

2.3 Reaction optimisation

2.3.1 General procedure for reaction condition screening (Table 1)



A solution of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (0.1 mmol), nitromethane and transition metal catalyst in MeOH (2 mL) was passed successively through a Teflon AF-2400 based tube-in-tube gas/liquid reactor pressurized with O_2 and two 10 mL stainless steel reaction coils. Back pressure regulators were required in line after the gas/liquid reactor (75 psi) and the reaction coils (250 psi) to prevent solution outgassing. The reaction stream was concentrated under reduced pressure filtered through a plug of silica (eluting with EtOAc) and then analysed by ^{1}H NMR.

2.3.2 Reaction condition screening results

Table S1. Transition metal screening[a]

Entry	Catalyst (°C)	Conversion (%)[b]
1	$CuCl_2$	>95
2	$FeCl_3$	89
3	$FeCl_2$	>95
4	$NiCl_2.6H_2O$	92
5	$CoCl_2.6H_2O$	>95
6	$ZnBr_2$	39

[a]Reaction conditions: **1a** (0.1 mmol), catalyst (10 mol%), $MeNO_2$ (0.5 mmol), O_2 (7 bar), 2 mL MeOH, 1 h. [b]Determined by ^{1}H NMR.

Table S2. Temperature screening[a]

Entry	Temperature (°C)	Conversion (%)[b]
1	100	>95
2	90	>95
3	80	91
4	70	87
5	60	57
6	50	37

[a]Reaction conditions: **1a** (0.1 mmol), $FeCl_2$ (10 mol%), $MeNO_2$ (0.5 mmol), O_2 (7 bar), 2 mL MeOH, 1 h. [b]Determined by ^{1}H NMR.

Table S3. Residence time screening[a]

Entry	Residence time (min)	Conversion (%)[b]
1	120	>95
2	60	>95
3	45	>95
4	30	88
5	15	70
6	5	5

[a]Reaction conditions: **1a** (0.1 mmol), $FeCl_2$ (10 mol%), $MeNO_2$ (0.5 mmol), O_2 (7 bar), 2 mL MeOH, 90 °C. [b]Determined by ^1H NMR.

Table S4. Amount of catalyst[a]

Entry	Catalyst loading (mol%)	Conversion (%)[b]
1	10	>95
2	5	40
3	2	26
4	1	11
5	0.5	9
6	0.1	7

[a]Reaction conditions: **1a** (0.1 mmol), $MeNO_2$ (0.5 mmol), O_2 (7 bar), 2 mL MeOH, 90 °C, 1 h. [b]Determined by ^1H NMR.

Table S5. Amount of nitromethane[a]

Entry	Nitromethane equiv.	Conversion (%)[b]
1	5	>95
2	4	63
3	3	45
4	2	34
5	1.5	27
6	1	11

[a]Reaction conditions: **1a** (0.1 mmol), $FeCl_2$ (10 mol%), O_2 (7 bar), 2 mL MeOH, 90 °C, 1 h. [b]Determined by ^1H NMR.

Table S6. Pressure screening[a]

Entry	O_2 pressure (bar)	Conversion (%)[b]
1	7	>95
2	5	72
3	3	36
4	1	18

[a]Reaction conditions: **1a** (0.1 mmol), $FeCl_2$ (10 mol%), $MeNO_2$ (0.5 mmol), 2 mL MeOH, 90 °C, 1 h. [b]Determined by ^1H NMR.

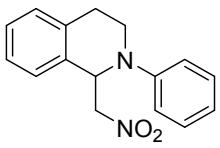
2.4 Continuous flow iron-catalysed aerobic nitro-Mannich reaction

2.4.1 General procedure for continuous flow iron-catalysed aerobic nitro-Mannich reaction

A solution of 2-aryl-1,2,3,4-tetrahydroisoquinoline (1 mmol), nitroalkane (5 mmol) and anhydrous $FeCl_2$ (12.7 mg, 0.1 mmol, 10 mol %, 99.95% Alfa Aesar) in MeOH (20 mL) was passed successively through a Teflon AF-2400 based tube-in-tube gas/liquid reactor pressurized with O_2 (7 bar) and two 10 mL stainless steel reaction coils heated to 90 °C at a rate of 0.167 mL/min^{-1}. Back pressure regulators were required in line after the gas/liquid reactor (75 psi) and the reaction coils (250 psi) to prevent solution outgassing. The reaction stream was collected into a flask containing Et_3N (279 μL, 2 mmol), concentrated under reduced pressure and then purified by flash chromatography.

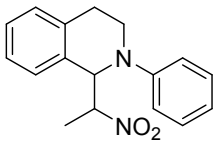
2.4.2 Characterisation of nitro-Mannich products

1-(Nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (2a)



2-Phenyl-1,2,3,4-tetrahydroisoquinoline (209 mg, 1 mmol) was treated with nitromethane (271 μL, 5 mmol) according to the general procedure, except the R2+ pumping module was set to a flow rate of 0.222 mL/min (T_R = 1.5 h). Purification by flash chromatography (10% EtOAc/*n*-heptane) afforded the title compound (194 mg, 72%) as a yellow crystalline solid, mp 104.0-105.0 (lit. 89.0-90.0 °C).[14] R_f = 0.25 (15% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.12 (m, 6H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.89-6.85 (m, 1H), 5.56 (t, *J* = 7.1 Hz, 1H), 4.90 (dd, *J* = 12.0, 7.7 Hz, 1H), 4.58 (dd, *J* = 12.0, 6.6 Hz, 1H), 3.71-3.60 (m, 2H), 3.09 (ddd, *J* = 16.3, 8.3, 6.0 Hz, 1H), 2.84 (dt, 16.3, 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 135.4, 133.1, 129.6, 129.3, 128.3, 127.1, 126.8, 119.6, 115.2, 78.9, 58.3, 42.2, 26.6. IR (neat) 2975, 1595, 1543, 1494, 1381, 1331, 1009, 754, 746, 692 cm^{-1}. MS (EI) *m/z*: 268, 209, 208 (100), 206, 193, 104, 77.

1-(Nitroethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (2b)

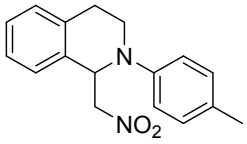


2-Phenyl-1,2,3,4-tetrahydroisoquinoline (209 mg, 1 mmol) was treated with nitroethane (359 μL, 5 mmol) according to the general procedure. Purification by flash chromatography (10% EtOAc/*n*-heptane) afforded the title compound (182 mg, 65%) as a yellow viscous oil. Ratio of diastereoisomers is 1.6. R_f = 0.25 (15% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.10 (m, 6H), 7.02-6.98 (m, 2H), 6.84-6.80 (m, 1H), 5.26-5.23 (m, 1H), [5.08-5.02 (m), 4.92-4.86 (m), 1H)], [3.87-3.81 (m), 3.63-3.53 (m), 2H], [3.09-3.02 (m), 2.95-2.85 (m), 2H], [1.70 (d, *J* = 6.7 Hz), 1.54 (d, *J* = 6.7 Hz), 3H]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 149.0, 135.7, 134.9, 133.9, 132.1, 129.5, 129.4, 129.2, 128.8, 128.5, 128.3, 127.3, 126.7, 126.2, 119.4, 118.9, 115.5, 114.6, 89.1, 85.5, 62.8, 61.3, 43.6, 42.8, 26.8, 26.5, 17.5, 16.5. IR (neat)

[14] Z. Li, C.-Z. Li, *J. Am. Chem. Soc.* 2005, **127**, 3672.

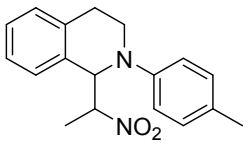
2918, 1783, 1648, 1597, 1503, 1358, 1198, 750, 692 cm^{-1}. MS (EI) *m/z*: 282, 236, 209, 208 (100), 206, 128, 115, 104, 77.

1-(Nitromethyl)-2-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline (2c)



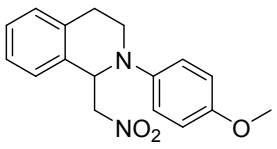
2-(*p*-Tolyl)-1,2,3,4-tetrahydroisoquinoline (223 mg, 1 mmol) was treated with nitromethane (271 μL, 5 mmol) according to the general procedure. Purification by flash chromatography (6% EtOAc/*n*-heptane) afforded the title compound (218 mg, 77%) as a pale yellow crystalline solid, mp 96.5-98.5 °C (lit. 94-96 °C).[15] R_f = 0.35 (15% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.12 (m, 4H), 7.09-7.06 (m, 2H), 6.91-6.87 (m, 2H), 5.50 (t, *J* = 7.1 Hz, 1H), 4.85 (dd, *J* = 11.8, 8.0 Hz, 1H), 4.56 (dd, *J* = 11.8, 6.4 Hz, 1H), 3.67-3.55 (m, 2H), 3.10-3.02 (m, 1H), 2.76 (dt, *J* = 16.2, 4.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5, 135.5, 133.1, 130.1, 129.4, 129.3, 128.1, 127.1, 126.8, 116.1, 79.0, 58.5, 42.5, 26.4, 20.5. IR (neat) 3028, 2919, 1616, 1548, 1514, 1378, 1209, 810, 753 cm^{-1}. MS (EI) *m/z*: 282, 222 (100), 128, 118, 91.

1-(Nitroethyl)-2-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline (2d)



2-(*p*-Tolyl)-1,2,3,4-tetrahydroisoquinoline (112 mg, 0.5 mmol) was treated with nitroethane (180 μL, 2.5 mmol) according to the general procedure. Purification by flash chromatography (2-10% EtOAc/*n*-heptane) afforded the title compound (55 mg, 39%) as a yellow viscous oil. Ratio of diastereoisomers is 1.6. R_f = 0.25 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.01 (m, 6H), 6.92-6.89 (m, 2H), 5.21-5.17 (m, 1H), [5.08-5.01 (m), 4.93-4.86 (m), 1H], [3.86-3.79 (m), 3.61-3.55 (m), 2H], [3.08-3.01 (m), 2.91-2.83 (m), 2H], [2.28 (s), 2.26 (s), 3H], [1.72 (s), 1.70 (s), 1H], 1.57-1.54 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 146.9, 135.8, 135.0, 133.9, 132.2, 130.0, 129.9, 129.3, 129.0, 128.9, 128.56, 128.51, 128.2, 127.4, 126.6, 126.2, 116.2, 115.3, 89.1, 85.6, 63.0, 61.6, 44.0, 43.1, 26.7, 26.4, 20.46, 20.41, 17.5, 16.5. IR (neat) 3029, 1616, 1550, 1516, 1386, 1358, 1196, 1115, 947, 754 cm^{-1}. HRMS (APCI) calcd for $C_{18}H_{21}N_2O_2$ ($M+H^+$): 297.1598. Found 297.1598.

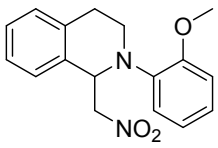
2-(4-Methoxyphenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2e)



2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (239 mg, 1 mmol) was treated with nitromethane (271 μL, 5 mmol) according to the general procedure. Purification by flash chromatography (10% EtOAc/*n*-heptane) afforded the title compound (201 mg, 67%) as a yellow viscous oil. R_f = 0.22 (15% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.13 (m, 4H), 6.94-6.90 (m, 2H), 6.84-6.80 (m, 2H), 5.39 (dd, *J* = 8.6, 5.8 Hz, 1H), 4.83 (dd, *J* = 11.9, 8.6 Hz, 1H), 4.56 (dd, *J* = 11.9, 5.8 Hz, 1H), 3.75 (s, 3H), 3.61-3.52 (m, 2H), 3.06-2.98 (m, 1H), 2.70 (dt, *J* = 16.5, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 143.2, 135.6, 133.0, 129.6, 128.0, 127.0, 126.7, 119.0, 114.8, 79.1, 59.0, 55.7, 43.2, 25.9. IR (neat) 2931, 2833, 1547, 1511, 1378, 1242, 1033, 823, 776, 752 cm^{-1}. MS (EI) *m/z*: 298, 238 (100), 193, 115.

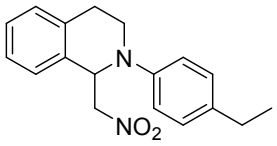
[15] X.-Z. Shu, X.-F. Xia, Y.-F. Yang, K.-G. Ji, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.* 2009, **74**, 7464.

2-(2-Methoxyphenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2f)



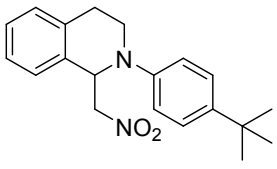
2-(2-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (239 mg, 1 mmol) was treated with nitromethane (271 μL, 5 mmol) according to the general procedure. Purification by flash chromatography (10% EtOAc/*n*-heptane) afforded the title compound (172 mg, 58%) as a white crystalline solid, mp 103.0-104.0 °C (lit. 103.0-104.0 °C).[9] R_f = 0.35 (15% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.20 (m, 2H), 7.17-7.15 (m, 2H), 7.06-7.02 (m, 1H), 6.96-6.93 (m, 1H), 6.90-6.83 (m, 2H), 5.52 (dd, *J* = 8.0, 5.0 Hz, 1H), 4.86 (dd, *J* = 12.2, 8.3 Hz, 1H), 4.56 (dd, *J* = 12.2, 5.0 Hz, 1H), 3.83 (s, 3H), 3.66-3.60 (m, 1H), 3.50 (ddd, *J* = 13.3, 11.0, 4.1 Hz, 1H), 3.03-2.95 (m, 1H), 2.79-2.74 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 139.0, 135.5, 133.8, 129.7, 127.7, 127.0, 126.6, 124.3, 122.1, 121.2, 112.7, 79.3, 58.3, 55.9, 43.2, 27.0. IR (neat) 2923, 2834, 1593, 1548, 1498, 1378, 1240, 1026, 748 cm^{-1}. MS (EI) *m/z*: 298, 239, 238 (100), 236, 222, 207, 169, 115, 84, 82.

2-(4-Ethylphenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2g)



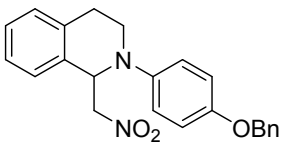
2-(4-Ethylphenyl)-1,2,3,4-tetrahydroisoquinoline (119 mg, 0.5 mmol) was treated with nitromethane (135 μL, 2.5 mmol) according to the general procedure. Purification by flash chromatography (5-10% EtOAc/*n*-heptane) afforded the title compound (83 mg, 56%) as a yellow viscous oil. R_f = 0.27 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.14 (m, 6H), 6.95 (d, *J* = 8.5 Hz, 2H), 5.54 (t, *J* = 7.2 Hz, 1H), 4.89 (dd, *J* = 11.8, 8.0 Hz, 1H), 4.59 (dd, *J* = 11.8, 6.4 Hz, 1H), 3.72-3.59 (m, 2H), 3.11 (ddd, *J* = 16.0, 9.4, 6.2 Hz, 1H), 2.79 (dt, *J* = 16.0, 4.6 Hz, 1H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 135.7, 135.5, 133.1, 129.4, 128.9, 128.1, 127.1, 126.7, 115.8, 78.9, 58.5, 42.4, 27.9, 26.4, 15.9. IR (neat) 2961, 2926, 1613, 1547, 1514, 1378, 1217, 1114, 1009, 939, 824, 776, 752, 630 cm^{-1}. HRMS (APCI) calcd for $C_{18}H_{20}N_2O_2$ ($M^{+\bullet}$): 296.1519. Found 296.1524.

2-(4-(*tert*-Butyl)phenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2h)



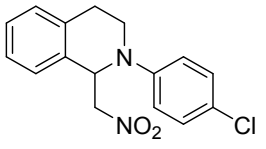
2-(4-(*tert*-butyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (121 mg, 0.5 mmol) was treated with nitromethane (135 μL, 2.5 mmol) according to the general procedure. Purification by flash chromatography (5-10% EtOAc/*n*-heptane) afforded the title compound (104 mg, 64%) as a yellow viscous oil. R_f = 0.28 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.77 Hz, 2H), 7.30-7.15 (m, 4H), 6.97 (d, *J* = 8.8 Hz, 2H), 5.57 (t, *J* = 7.2 Hz, 1H), 4.90 (dd, *J* = 11.8, 7.9 Hz, 1H), 4.59 (dd, *J* = 11.8, 6.6 Hz, 1H), 3.73-3.61 (m, 2H), 3.13 (ddd, *J* = 16.0, 9.2, 6.2 Hz, 1H), 2.81 (dt, *J* = 16.0, 4.8 Hz, 1H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 142.3, 135.5, 133.2, 129.3, 128.1, 127.1, 126.5, 126.4, 114.9, 79.0, 58.5, 42.1, 34.0, 31.5, 26.5. IR (neat) 2960, 1612, 1550, 1518, 1394, 1378, 1269, 1216, 1010, 823, 777, 757 cm^{-1}. HRMS (APCI) calcd for $C_{20}H_{24}N_2O_2$ ($M^{+\bullet}$): 324.1832. Found 324.1833.

2-(4-(Benzyloxy)phenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2i)



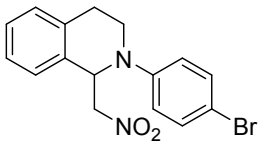
2-(4-(benzyloxy)phenyl)-1,2,3,4-tetrahydroisoquinoline (157 mg, 0.5 mmol) was treated with nitromethane (135 μL, 2.5 mmol) according to the general procedure. Purification by flash chromatography (15-20% EtOAc/*n*-heptane) afforded the title compound (90 mg, 48%) as a yellow viscous oil. R_f = 0.36 (15% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.29 (m, 5H), 7.25-7.13 (m, 4H), 6.92-6.87 (m, 4H), 5.39 (dd, *J* = 8.5, 5.9 Hz, 1H), 5.00 (s, 2H), 4.83 (dd, *J* = 11.9, 8.6 Hz, 1H), 4.56 (dd, *J* = 11.9, 5.9 Hz, 1H), 3.62-3.52 (m, 2H), 3.02 (ddd, *J* = 16.4, 9.2, 7.0 Hz, 1H), 2.70 (dt, *J* = 16.4, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 137.4, 135.5, 133.0, 129.6, 128.7, 128.05, 128.01, 127.6, 127.1, 126.7, 118.7, 115.9, 79.1, 77.5, 77.2, 76.8, 70.6, 59.0, 43.2, 25.9. IR (neat) 2924, 1532, 1510, 1467, 1383 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{23}N_2O_3$ ($M+H^+$): 375.1703. Found 375.1706.

2-(4-Chlorophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2j)



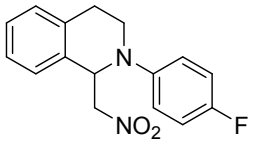
2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (244 mg, 1 mmol) was treated with nitromethane (271 μL, 5 mmol) according to the general procedure. Purification by flash chromatography (5-10% EtOAc/*n*-heptane) afforded the title compound (221 mg, 73%) as a pale yellow crystalline solid, mp 99.0-100.0°C. R_f = 0.18 (15% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.13 (m, 6H), 6.91-6.87 (m, 2H), 5.49 (t, *J* = 7.3 Hz, 1H), 4.85 (dd, *J* = 11.9, 8.1 Hz, 1H), 4.57 (dd, *J* = 11.9, 6.3 Hz, 1H), 3.67-3.57 (m, 2H), 3.11-3.03 (m, 1H), 2.78 (dt, *J* = 16.3, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 135.2, 132.6, 129.4, 128.4, 127.1, 127.0, 124.5, 116.6, 78.8, 58.3, 42.3, 26.3. IR (neat) 2916, 1595, 1547, 1493, 1376, 1330, 1216, 807, 749, 645 cm^{-1}. MS (EI) *m/z*: 302, 242 (100), 227, 138, 115, 110, 77.

2-(4-Bromophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2k)



2-(4-Bromophenyl)-1,2,3,4-tetrahydroisoquinoline (288 mg, 1 mmol) was treated with nitromethane (271 μL, 5 mmol) according to the general procedure. Purification by flash chromatography (5-10% EtOAc/*n*-heptane) afforded the title compound (246 mg, 71%) as a viscous yellow oil. R_f = 0.15 (15% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.32 (m, 2H), 7.29-7.12 (m, 4H), 6.87-6.83 (m, 2H), 5.49 (t, *J* = 7.2 Hz, 1H), 4.85 (dd, *J* = 11.9, 8.1 Hz, 1H), 4.57 (dd, *J* = 11.9, 6.4 Hz, 1H), 3.67-3.56 (m, 2H), 3.11-3.03 (m, 1H), 2.79 (dt, *J* =16.45, 4.83 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 135.1, 132.5, 132.3, 129.4, 128.4, 127.1, 126.9, 116.9, 111.6, 78.7, 58.2, 42.1, 26.3. IR (neat) 2917, 1588, 1542, 1492, 1377, 1331, 1217, 805, 755, 737 cm^{-1}. MS (EI) *m/z*: 346, 286 (100), 219, 184, 115, 103.

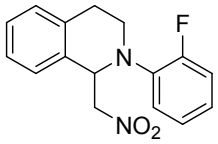
2-(4-Fluorophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2l)



2-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (114 mg, 0.5 mmol) was treated with nitromethane (135 μL, 2.5 mmol) according to the general procedure. Purification by flash chromatography (2-5% EtOAc/*n*-heptane) afforded the title compound (77 mg, 54%) as a yellow oil. R_f = 0.10 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.17 (m, 4H), 7.00-6.92 (m, 4H), 5.46 (dd, *J* = 8.5, 6.0 Hz, 1H), 4.87 (dd, *J* = 12.0, 8.7 Hz, 1H), 4.60

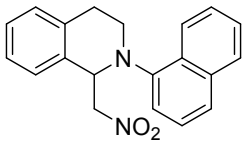
(dd, *J* = 12.0, 5.9 Hz, 1H), 3.68-3.58 (m, 2H), 3.06 (dt, *J* = 16.4, 8.0 Hz, 1H), 2.76 (dt, *J* = 16.4, 4.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3 (d, *J* = 239.2 Hz), 145.4 (d, *J* = 2.2 Hz), 135.3, 132.6, 129.5, 128.2, 127.0, 126.8, 118.0 (d, *J* = 7.7 Hz), 115.9 (d, *J* = 22.2 Hz), 78.9, 58.8, 42.9, 25.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ –125.46 (s). IR (neat) 2922, 1547, 1507, 1379, 1230, 1163, 1005, 816, 777, 753, 629 cm^{-1}. HRMS (APCI) calcd for $C_{16}H_{16}FN_2O_2$ ($M+H^+$): 287.1190. Found 287.1192.

2-(2-Fluorophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2m)



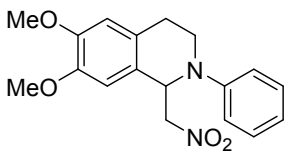
2-(2-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (114 mg, 0.5 mmol) was treated with nitromethane (135 μL, 2.5 mmol) according to the general procedure. Purification by flash chromatography (2-5% EtOAc/*n*-heptane) afforded recovered starting material (19 mg, 17%) and the title compound (29 mg, 20%, 31% brsm) as an opaque viscous oil. R_f = 0.20 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-6.86 (m, 8H), 5.37 (dd, *J* = 9.3, 4.8 Hz, 1H), 4.85 (dd, *J* = 12.2, 9.3 Hz, 1H), 4.59 (dd, *J* = 12.2, 4.8 Hz, 1H), 3.64-3.52 (m, 2H), 2.92 (ddd, *J* = 17.0, 11.0, 6.3 Hz, 1H), 2.67 (dt, *J* = 16.5, 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2 (d, *J* = 247 Hz), 137.8 (d, *J* = 9.1 Hz), 135.6, 132.8, 129.8, 127.9, 126.89, 126.86, 124.5 (d, *J* = 3.8 Hz), 123.9 (d, *J* = 7.9 Hz), 122.7 (d, *J* = 2.3 Hz), 116.6 (d, *J* = 20.8 Hz), 79.2, 58.4 (d, *J* = 2.6 Hz), 43.5 (d, *J* = 3.4 Hz), 26.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ –122.94 (s). IR (neat) 2926, 1610, 1554, 1500, 1454, 1378, 1229, 1141, 1101, 1038, 1005, 812, 752, 654 cm^{-1}. HRMS (APCI) calcd for $C_{16}H_{16}FN_2O_2$ ($M+H^+$): 287.1190. Found 287.1190.

2-(Naphthalen-1-yl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2n)



2-(naphthalene-1-yl)-1,2,3,4-tetrahydroisoquinoline (130 mg, 0.5 mmol) was treated with nitromethane (135 μL, 2.5 mmol) according to the general procedure. Purification by flash chromatography (2-10% EtOAc/*n*-heptane) afforded recovered starting material (71 mg, 55%) and the title compound (43 mg, 27%, 60% brsm) as a colourless viscous oil. R_f = 0.27 (10% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.53 (quint., *J* = 6.9 Hz, 2H), 7.35-7.21 (m, 5H), 6.89 (d, *J* = 6.6, 1H), 5.39 (dd, *J* = 10.4, 4.2 Hz, 1H), 4.98 (t, *J* = 11.2 Hz, 1H), 4.71 (dd, *J* = 11.9, 4.3 Hz, 1H), 3.75 (td, *J* = 13.0, 3.6 Hz, 1H), 3.56 (dd, *J* = 14.1, 5.1 Hz, 1H), 2.85 (br s, 1H), 2.57 (d, *J* = 15.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 136.1, 134.9, 133.1, 130.0, 129.6, 128.4, 127.9, 126.9, 126.7, 126.24, 126.17, 125.5, 124.9, 126.7, 118.8, 79.7, 60.2, 44.8, 24.5. IR (neat) 3046, 2922, 1551, 1399, 1379, 1214, 1099, 906, 802, 776, 753, 730 cm^{-1}. HRMS (APCI) calcd for $C_{20}H_{18}N_2O_2$ ($M^{+\bullet}$): 318.1363. Found 318.1364.

6,7-Dimethoxy-1-(nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (2o)

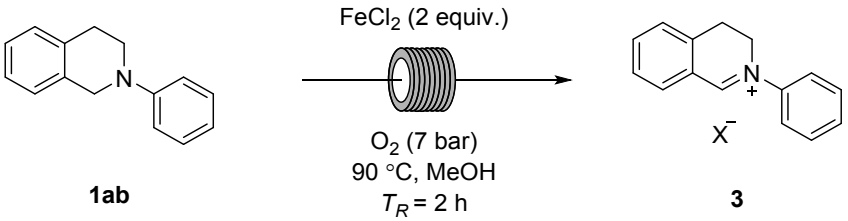


6,7-Dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (135 mg, 0.5 mmol) was treated with nitromethane (135 μL, 2.5 mmol) according to the general procedure. Purification by flash chromatography (30-50% EtOAc/*n*-heptane) afforded recovered starting material (53 mg, 39%) and the title compound (80 mg, 49%, 70% brsm) as a yellow viscous oil. R_f = 0.28 (30% EtOAc/*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H), 6.97 (d, *J* = 8.0

Hz, 2H), 6.85 (t, J = 7.3 Hz, 1H), 6.64 (s, 1H), 6.60 (s, 1H), 5.46 (t, J = 7.2 Hz, 1H), 4.85 (dd, J = 11.8, 8.0 Hz, 1H), 4.56 (dd, J = 11.8, 8.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.71-3.55 (m, 2H), 3.00 (ddd, J = 15.9, 9.8, 5.8 Hz, 1H), 2.68 (dt, J = 16.2, 4.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 148.7, 147.9, 129.6, 127.5, 124.7, 119.7, 115.6, 111.8, 109.7, 78.9, 58.1, 56.2, 56.0, 42.2, 25.9. IR (neat) 2937, 1548, 1513, 1452 cm^{-1}. (APCI) calcd for $C_{18}H_{21}N_2O_4$ ($M+H^+$): 329.1496. Found 329.1498.

2.5 Evidence of iminium intermediate

2.5.1 Preparation of iminium intermediate (3)



A solution of **1ab** (120 mg, 0.57 mmol) and anhydrous $FeCl_2$ (145.3 mg, 1.15 mmol, 2 equiv., 99.95% Alfa Aesar) in MeOH (10 mL) was passed successively through a Teflon AF-2400 based tube-in-tube gas/liquid reactor pressurized with O_2 (7 bar) and two 10 mL stainless steel reaction coils heated to 90 °C at a rate of 0.167 mL/min^{-1}. Back pressure regulators were required in line after the gas/liquid reactor (75 psi) and the reaction coils (250 psi) to prevent solution outgassing. One drop of the reaction output was removed for analysis by ESI MS. The reaction stream was concentrated under reduced pressure, diluted with MeOH (3 mL) and filtered. The resulting solution was left to stand at rt for 30 days, after which crystals were observed.

HRMS (ESI, positive mode) calcd for $C_{15}H_{14}N$ (M^+): 208.1121. Found 208.1122. HRMS (ESI, negative mode) calcd for $FeCl_3$ (X^-): 160.8420. Found 160.8417.

Crystal data for 2[**3**]$^+$[Fe_2OCl_6]$^{2-}$: $C_{30}H_{28}Cl_6Fe_2N_2O$, M = 756.94, yellow block, 0.030 x 0.030 x 0.020 mm^3, space group $P2_1/c$ (No. 14), V = 3230.3(11) Å^3, Z = 4, D_c = 1.556 g/cm^3, F_{000} = 1536, T = 100(2)K, $2\theta_{max}$ = 55.8°, 30010 reflections collected, 7370 unique (R_{int} = 0.0538). Final *GooF* = 1.049, *R1* = 0.0386, *wR2* = 0.0927, *R* indices based on 6290 reflections with I > 2(I), 370 parameters, 0 restraints. Lp and absorption corrections applied, μ = 1.422 mm^{-1}.

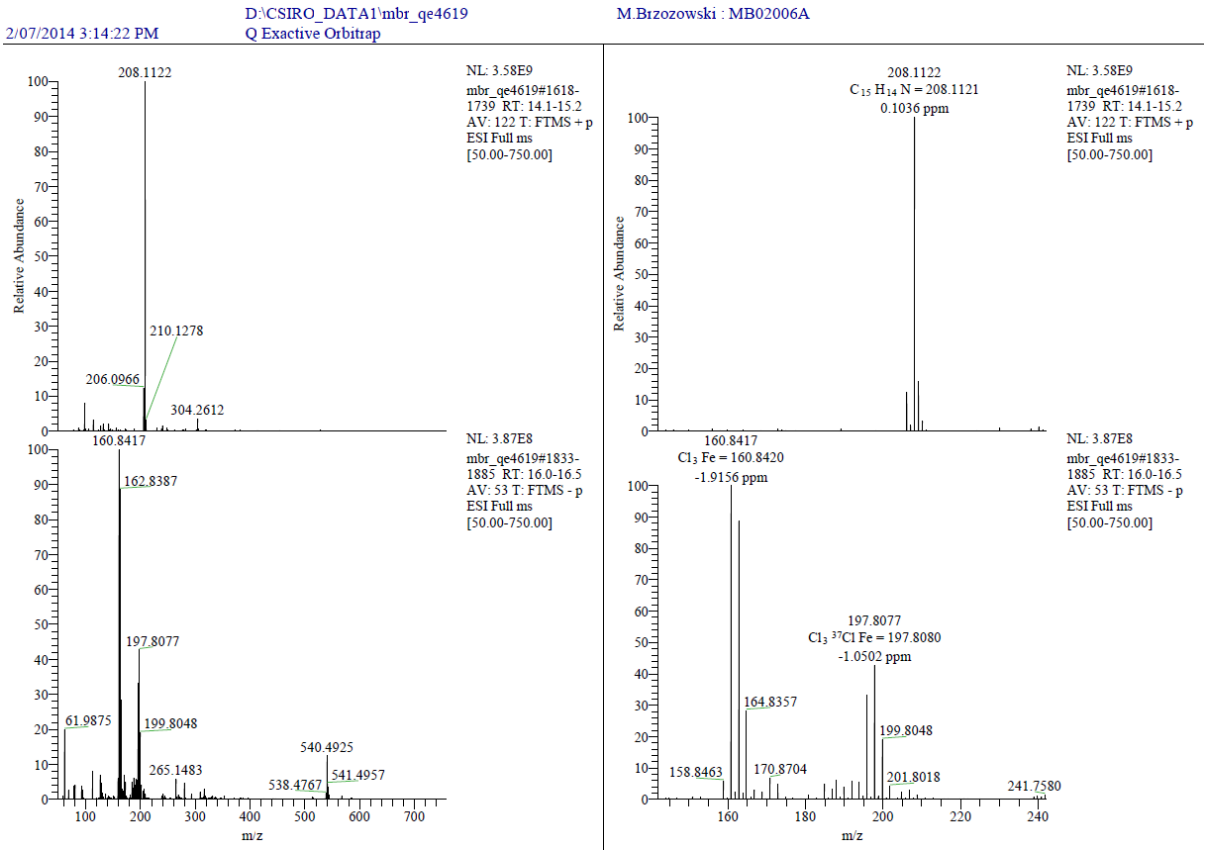


Figure S3 ESI mass spectrum of $[\mathbf{3}]^{+}[FeCl_3]^{-}$.

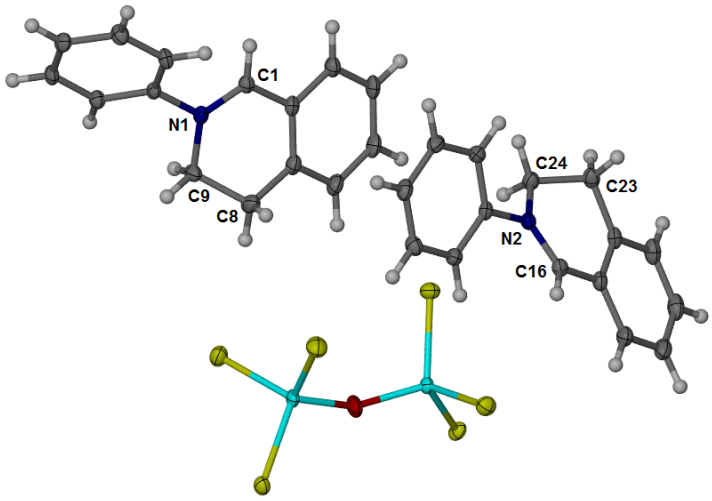
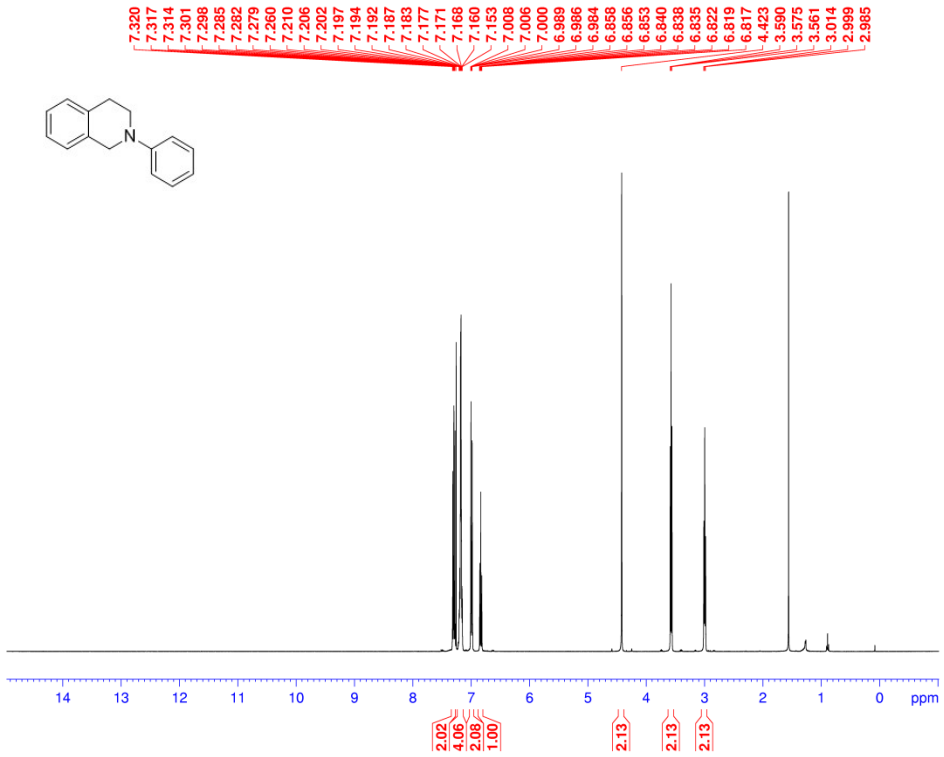
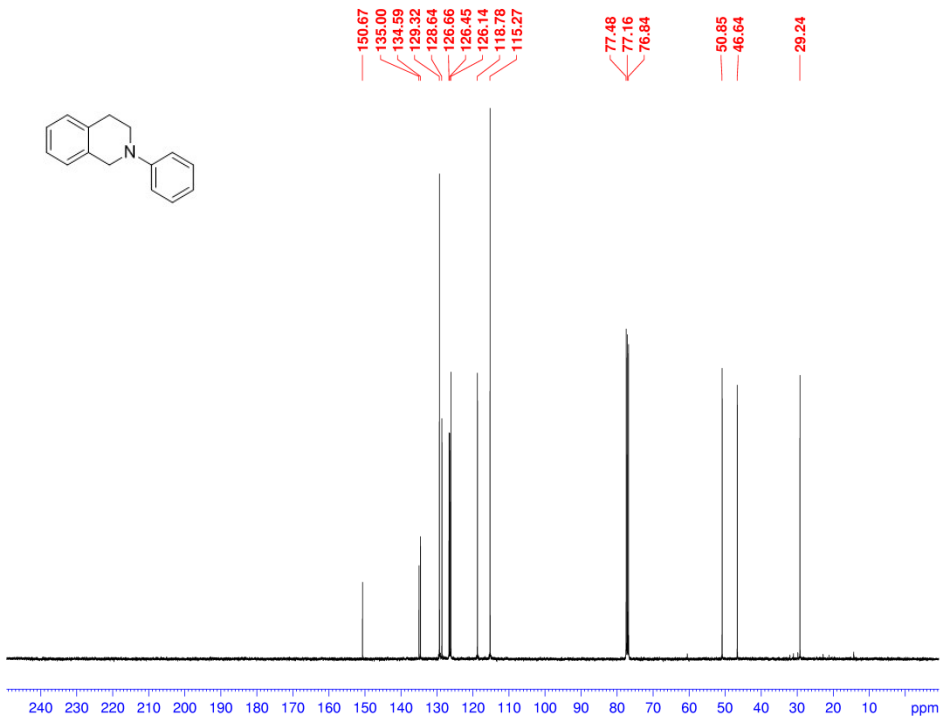


Figure S4 The asymmetric unit of $2[\mathbf{3}]^{+}[Fe_2OCl_6]^{2-}$ with displacement ellipsoids displayed at the 50% probability levels. Selected atom labelling is shown.

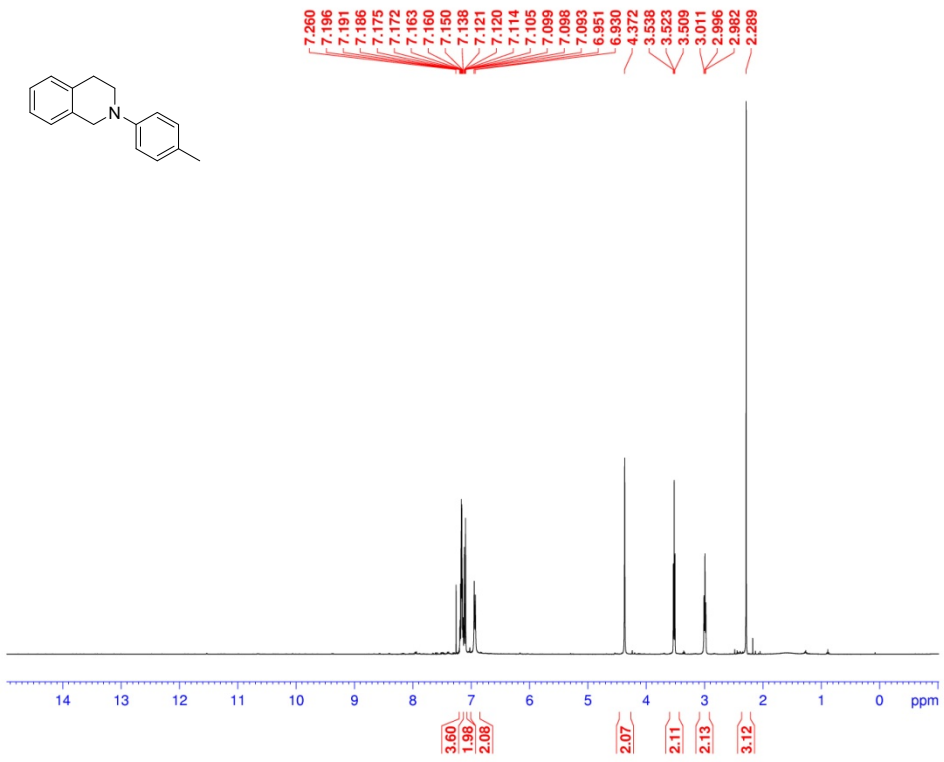
3. NMR Spectra

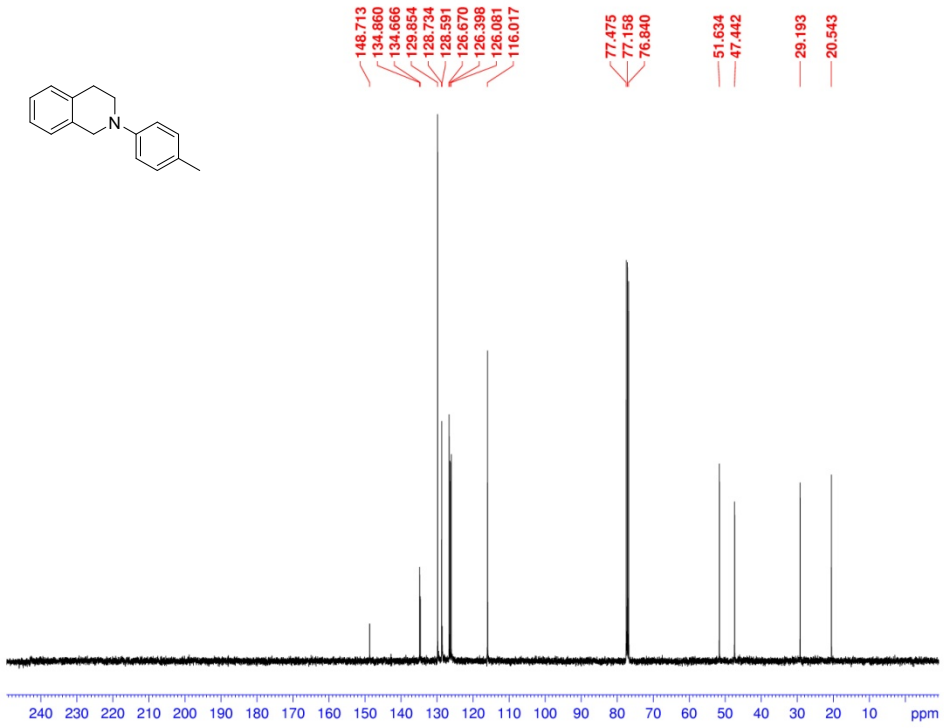
2-Phenyl-1,2,3,4-tetrahydroisoquinoline (1ab)



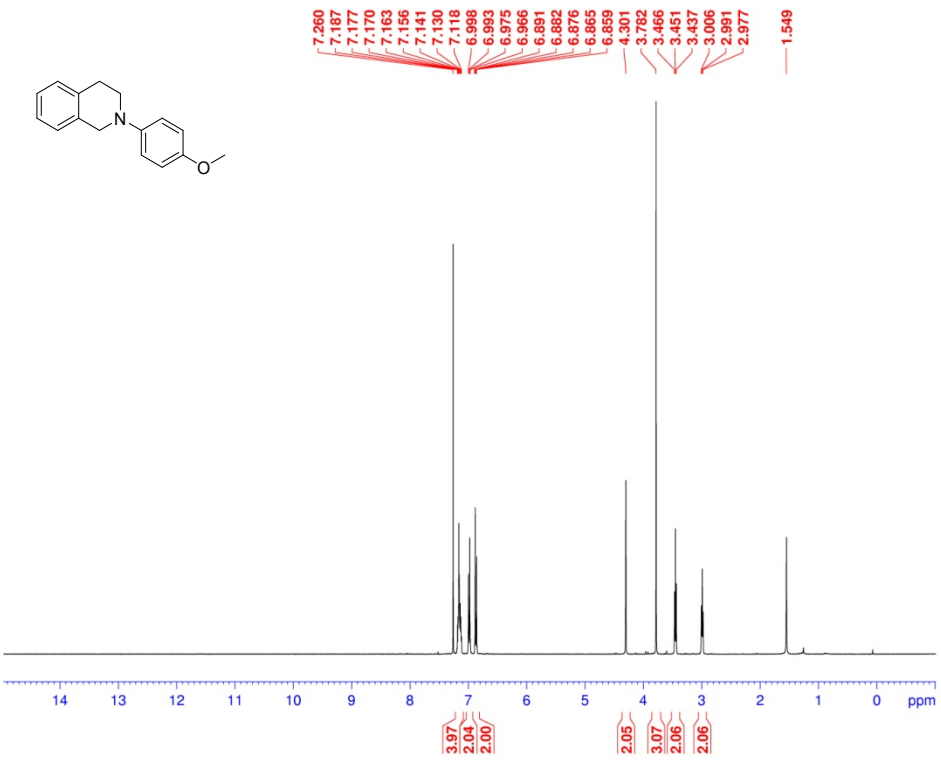


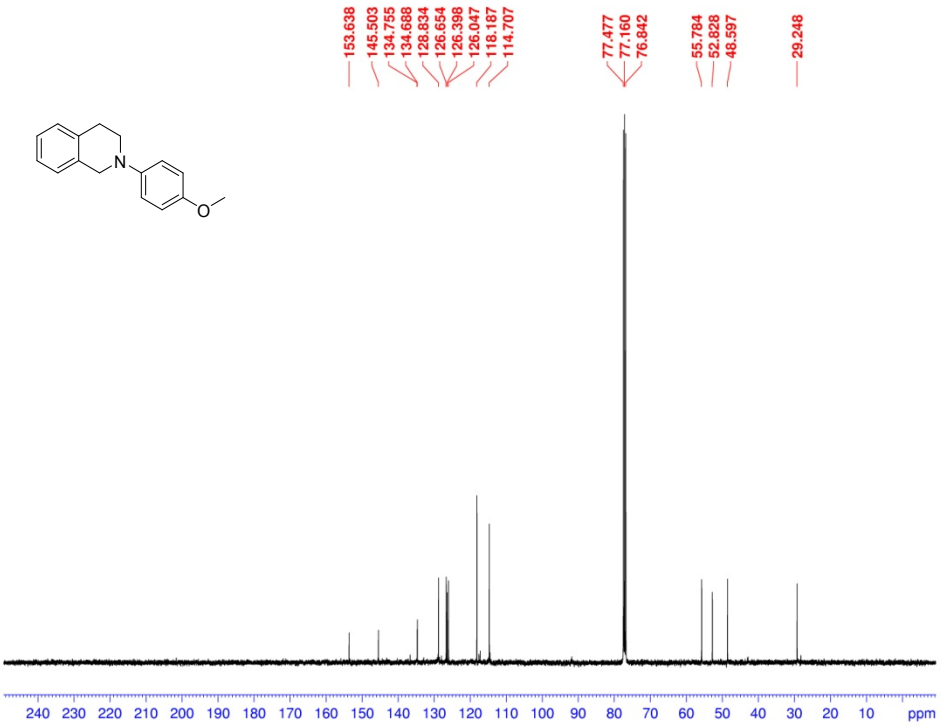
2-(*p*-Tolyl)-1,2,3,4-tetrahydroisoquinoline (1cd)



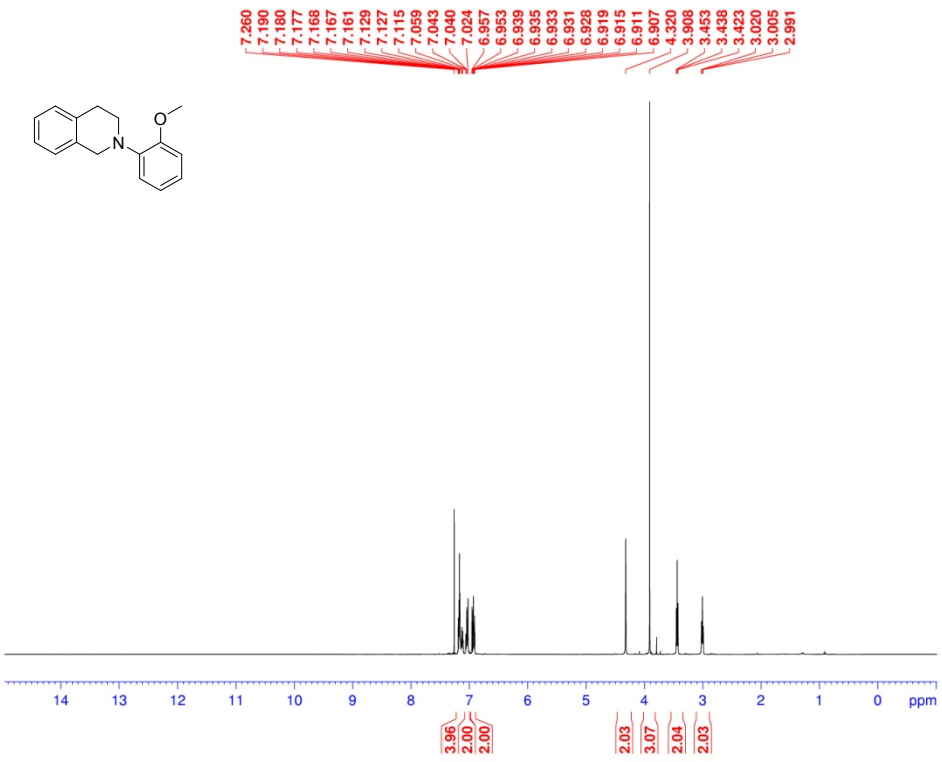


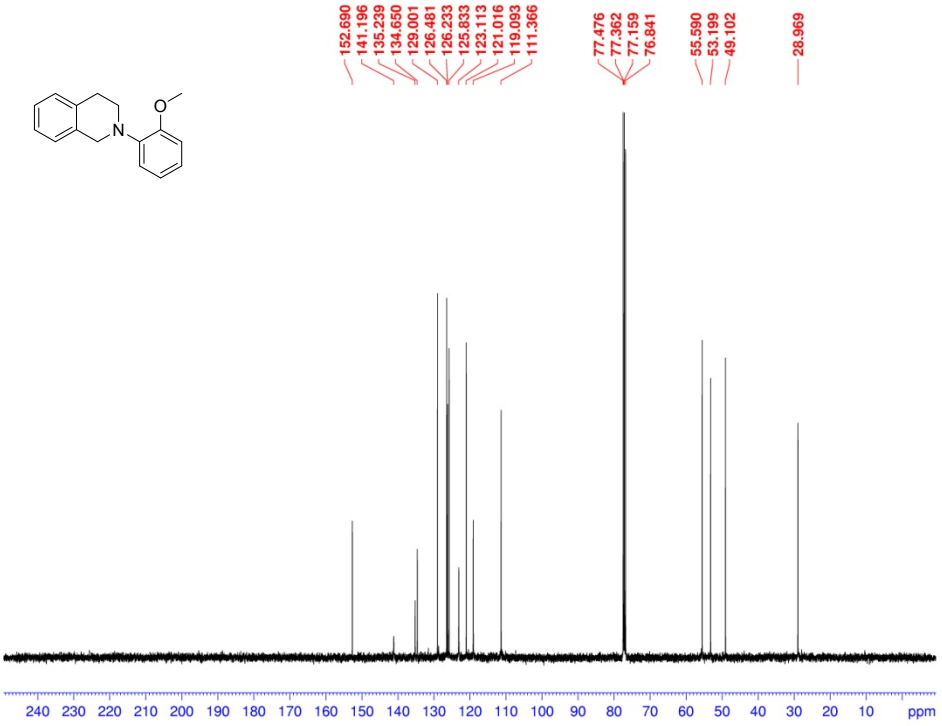
2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (1e)



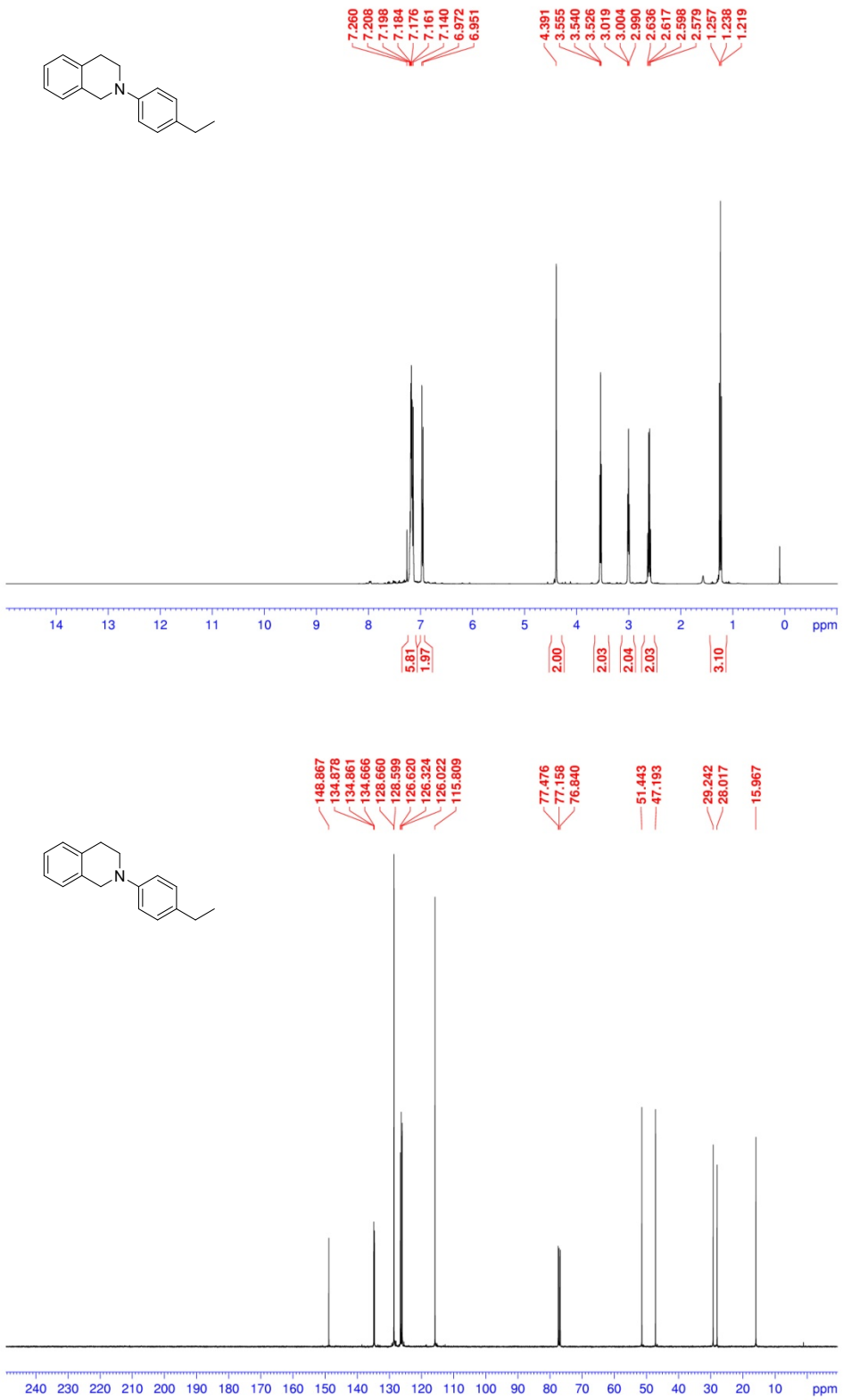


2-(2-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (1f)

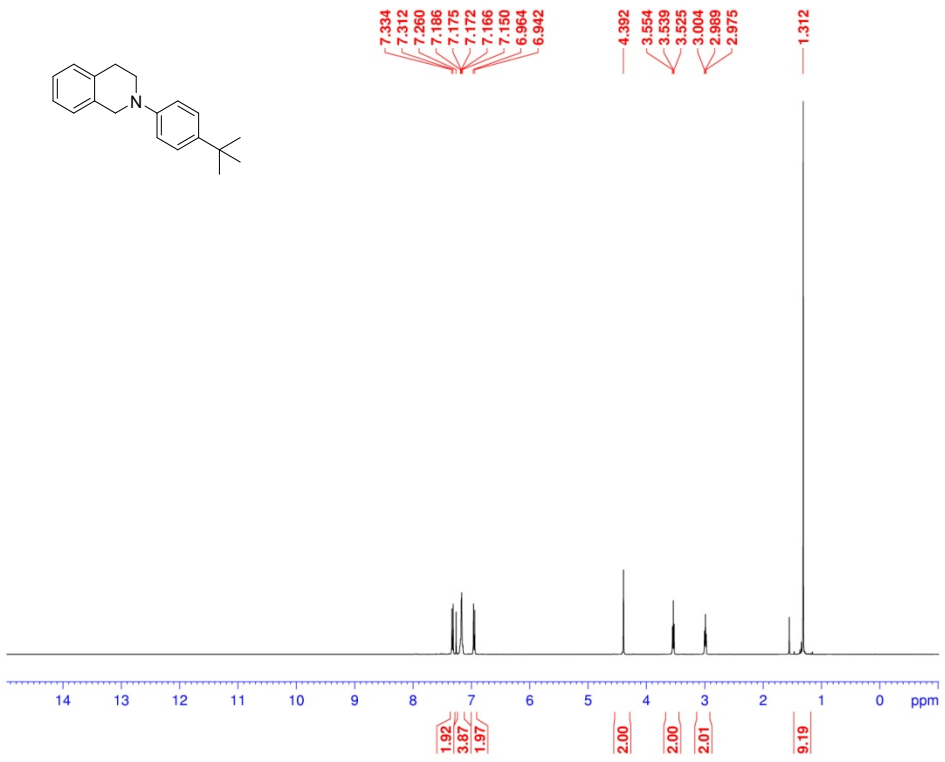


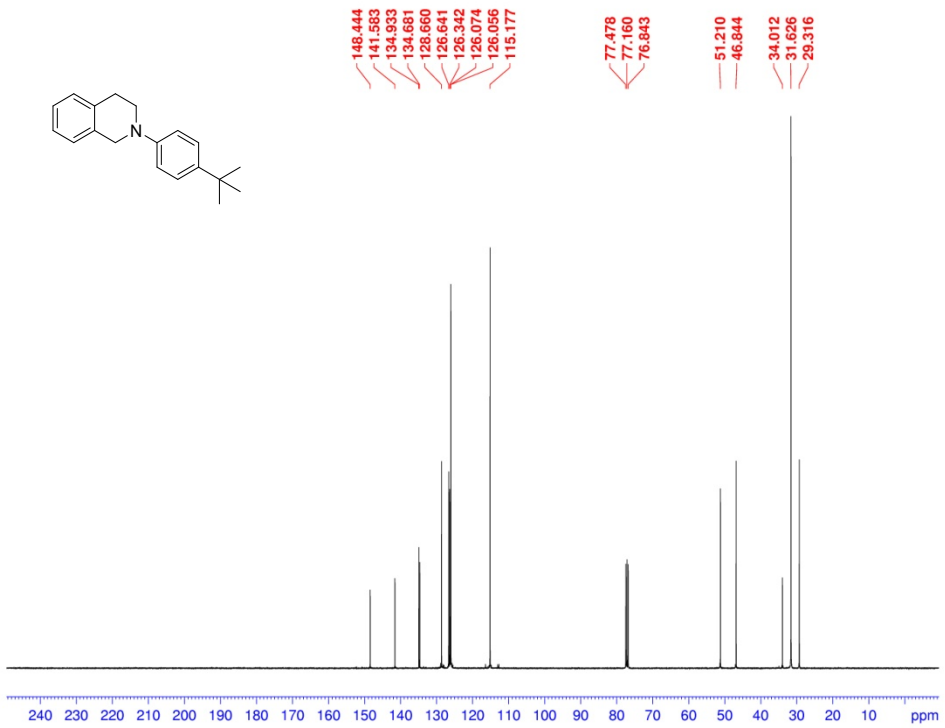


2-(4-Ethylphenyl)-1,2,3,4-tetrahydroisoquinoline (1g)

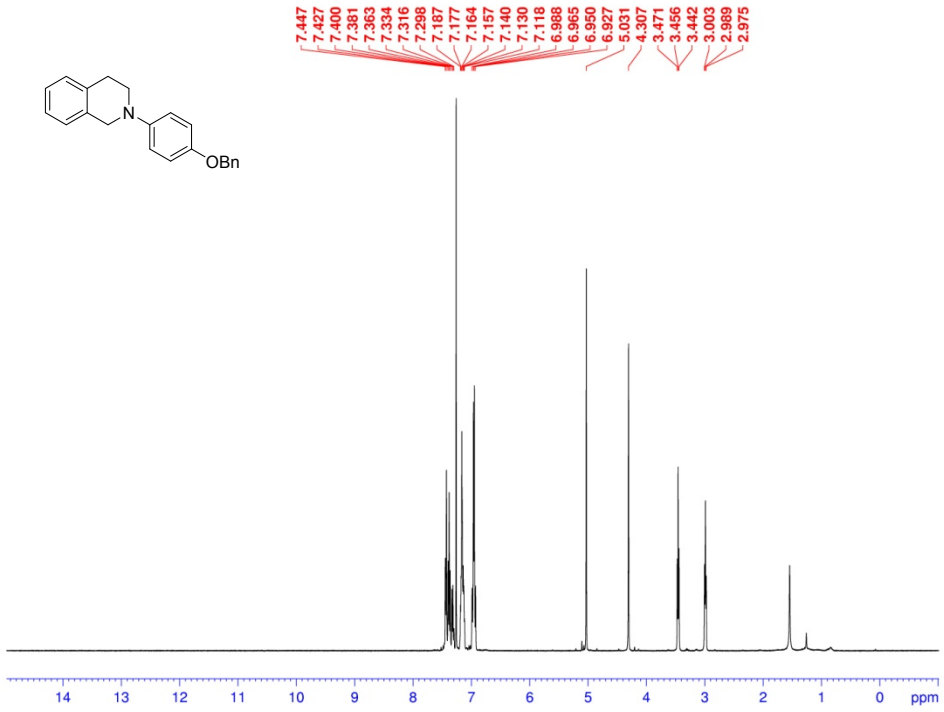


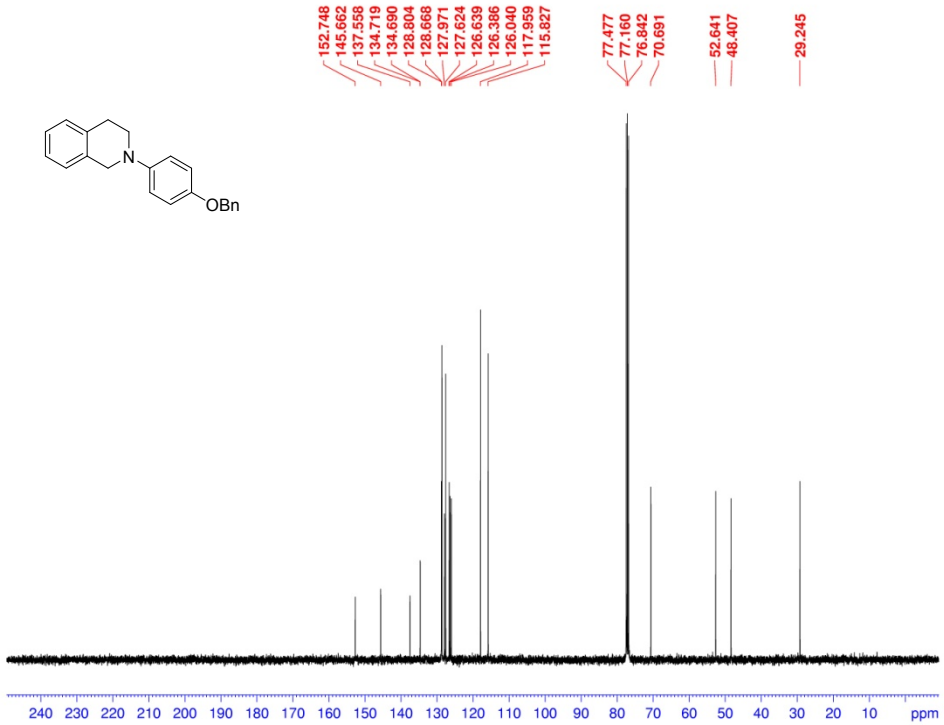
2-(4-(*tert*-Butyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (1h)



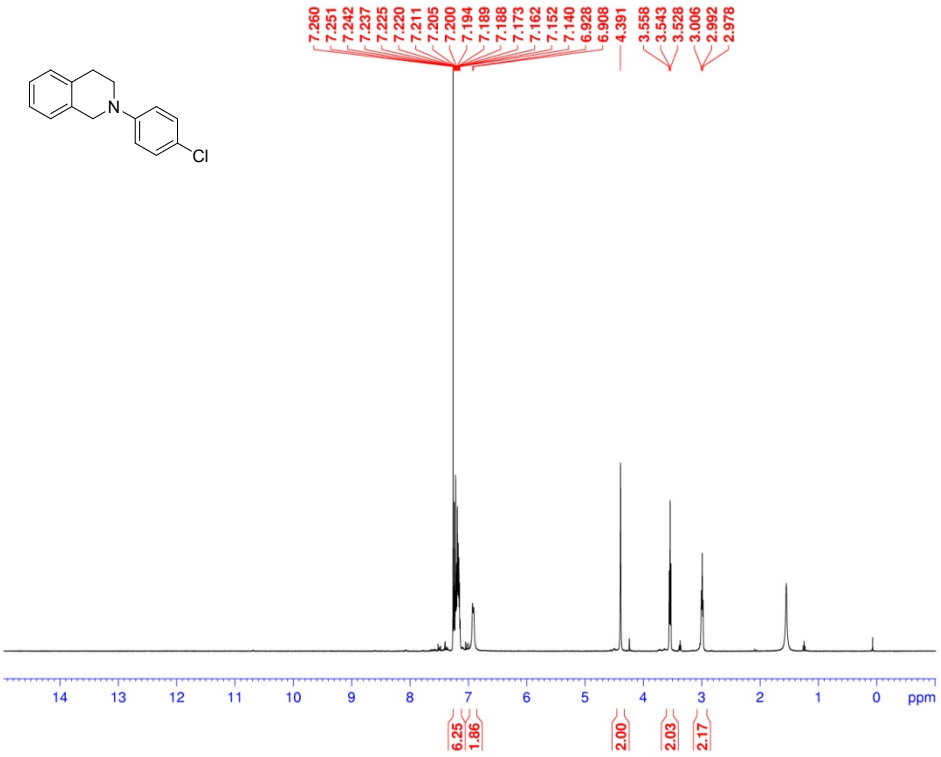


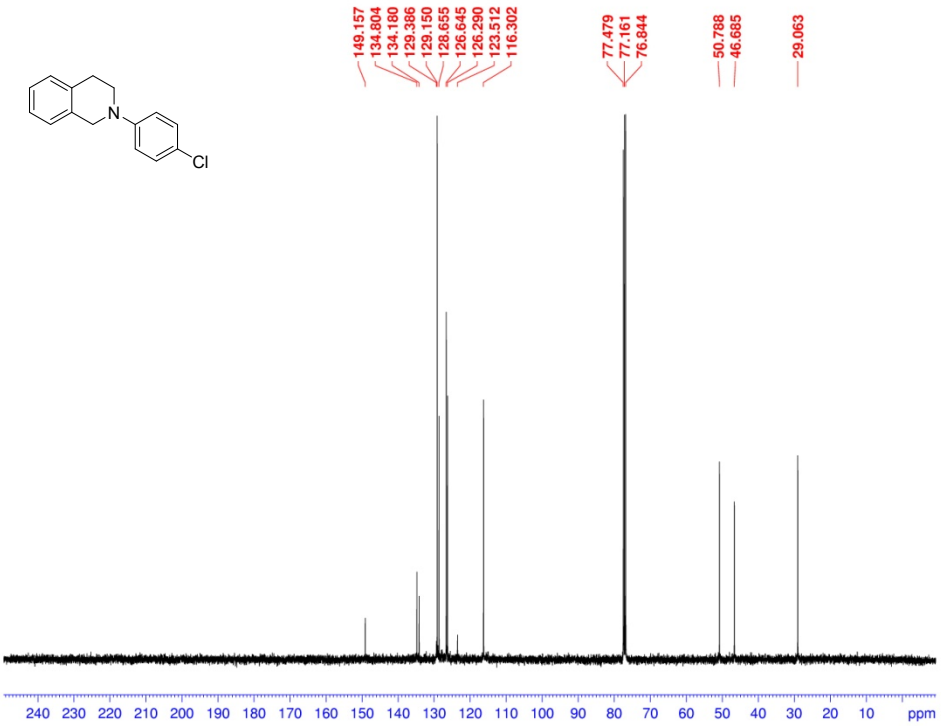
2-(4-(Benzyloxy)phenyl)-1,2,3,4-tetrahydroisoquinoline (1i)



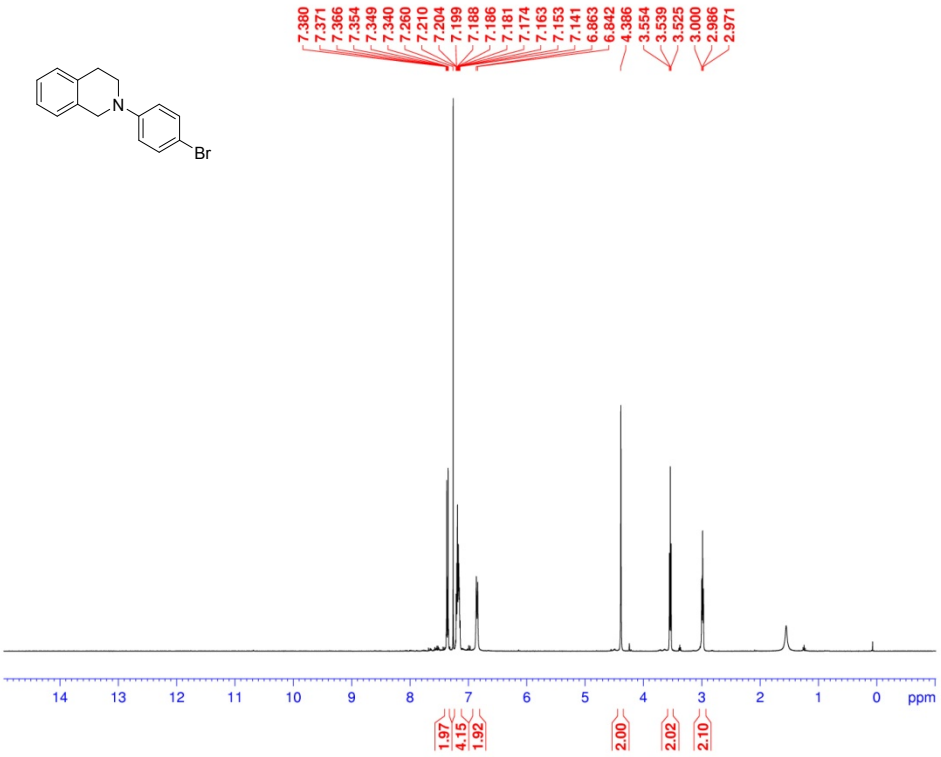


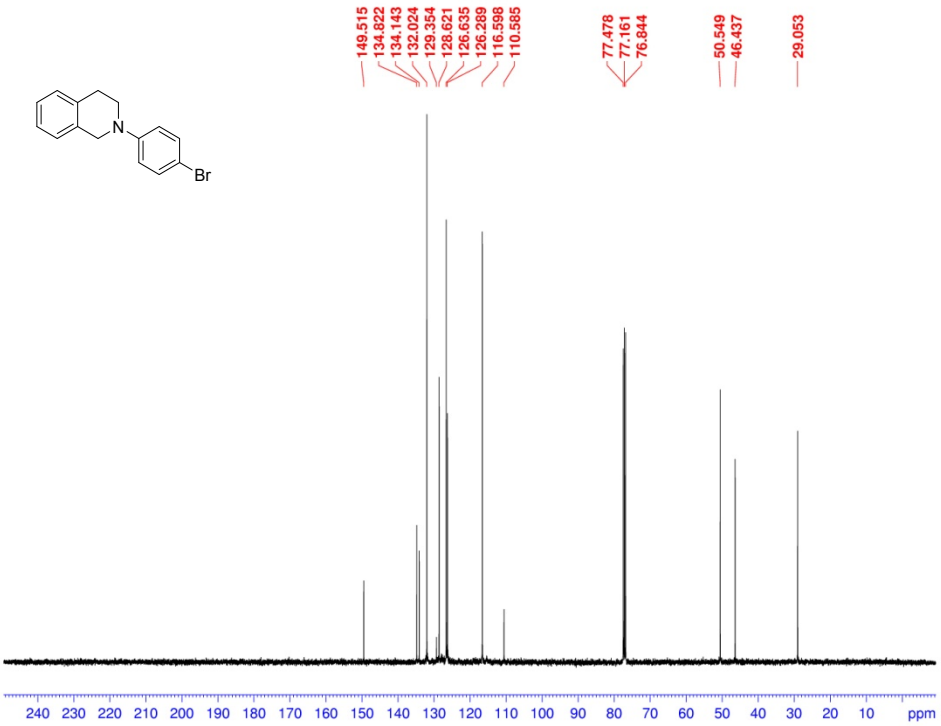
2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (1j)



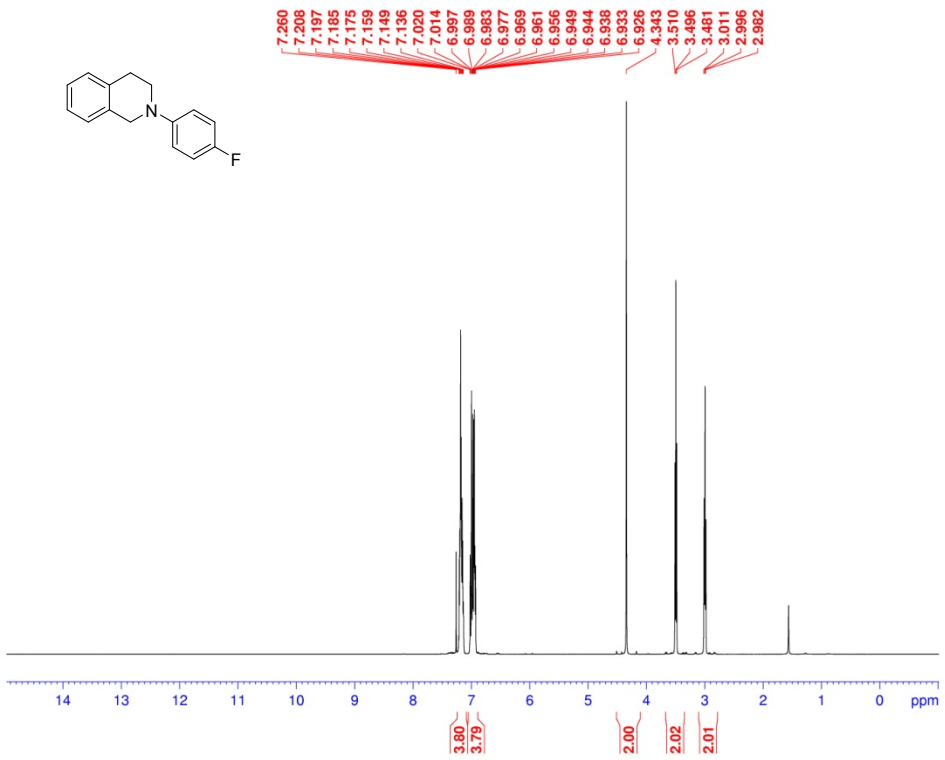


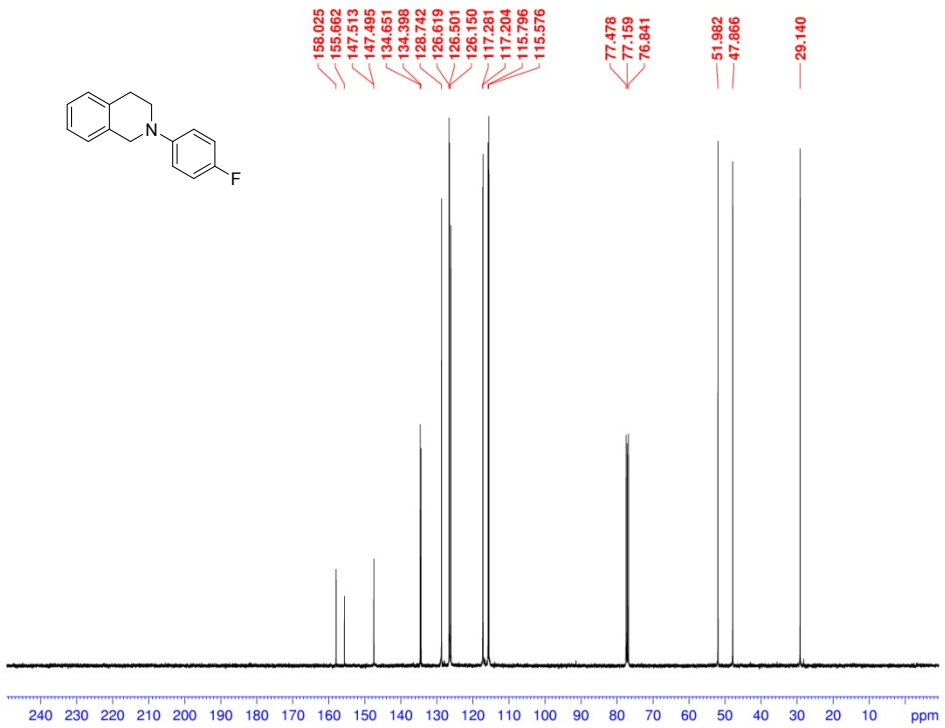
2-(4-Bromophenyl)-1,2,3,4-tetrahydroisoquinoline (1k)





2-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (1l)






-123.75
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F
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0
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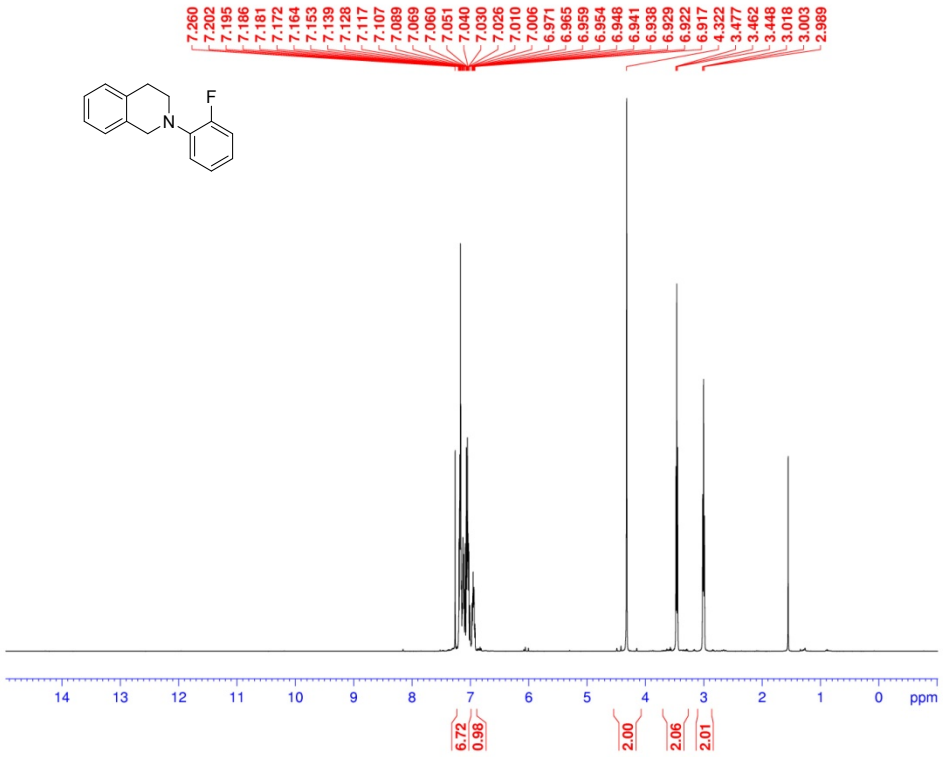
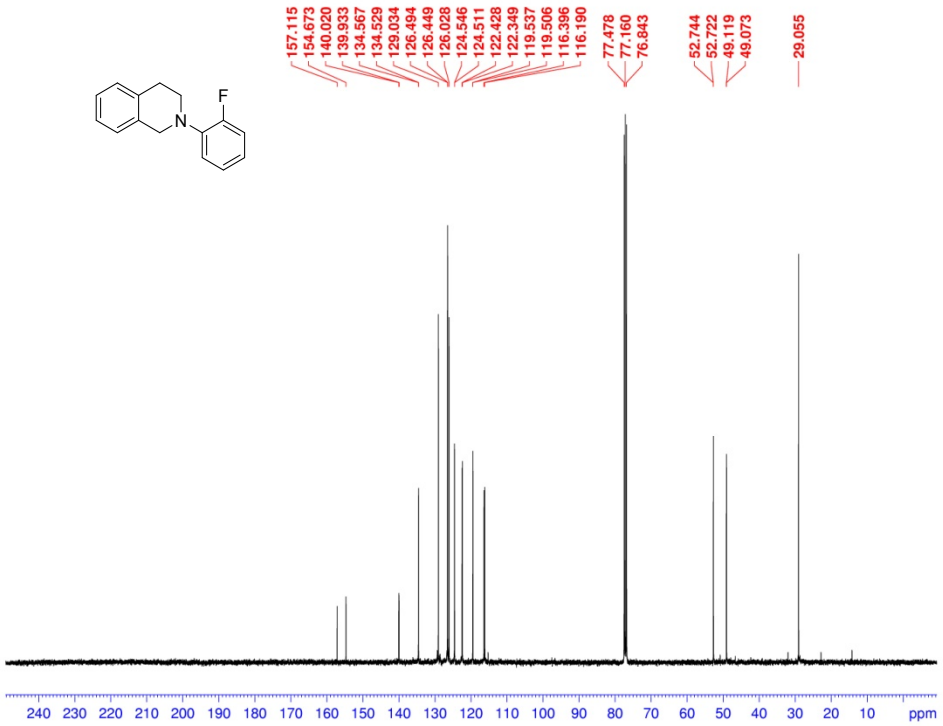
-100
-150
-200
ppm

2-(2-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (1m)






F
N
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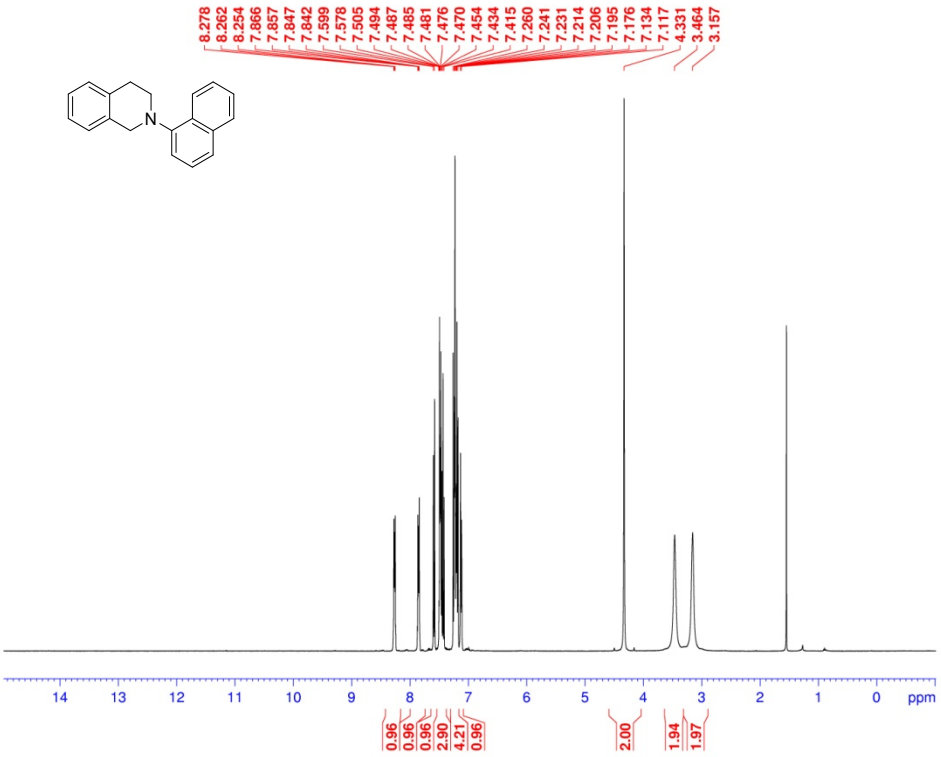
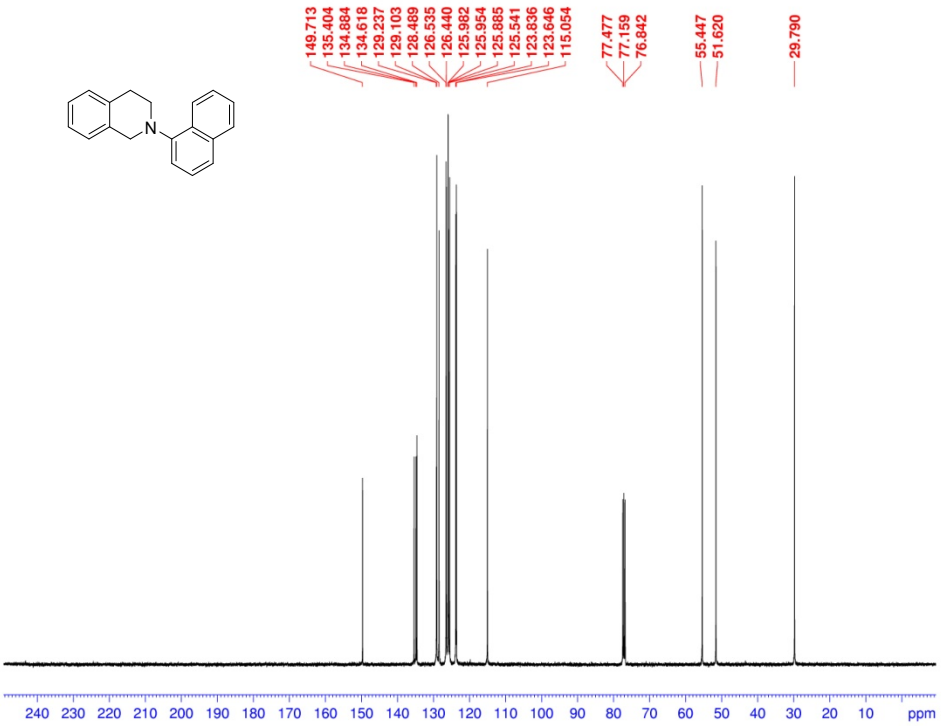
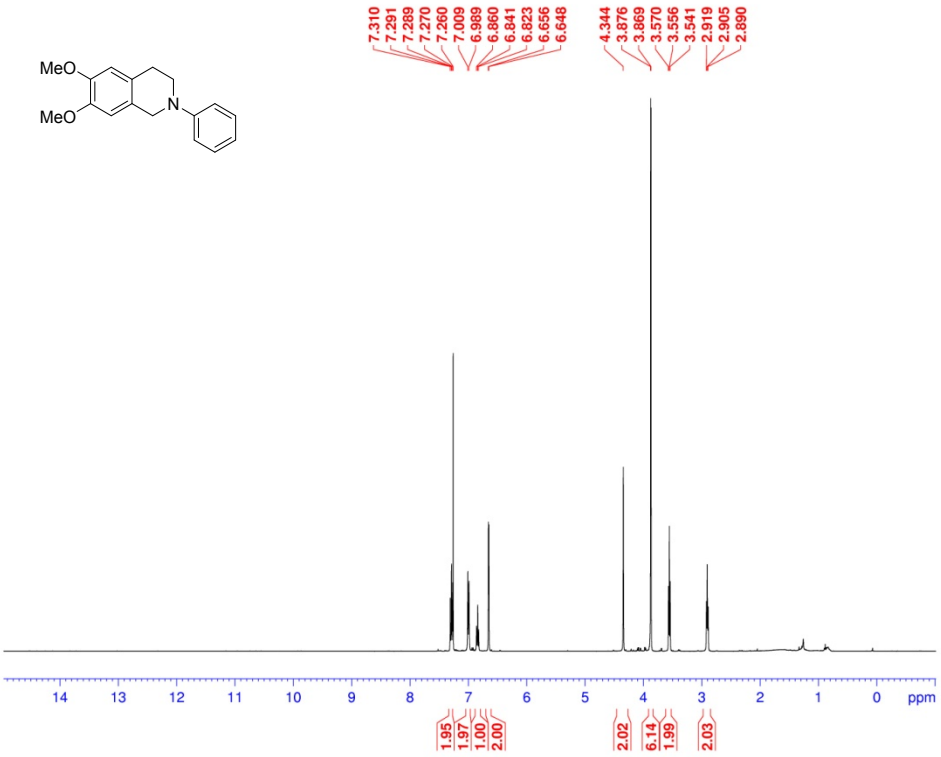
-200
ppm

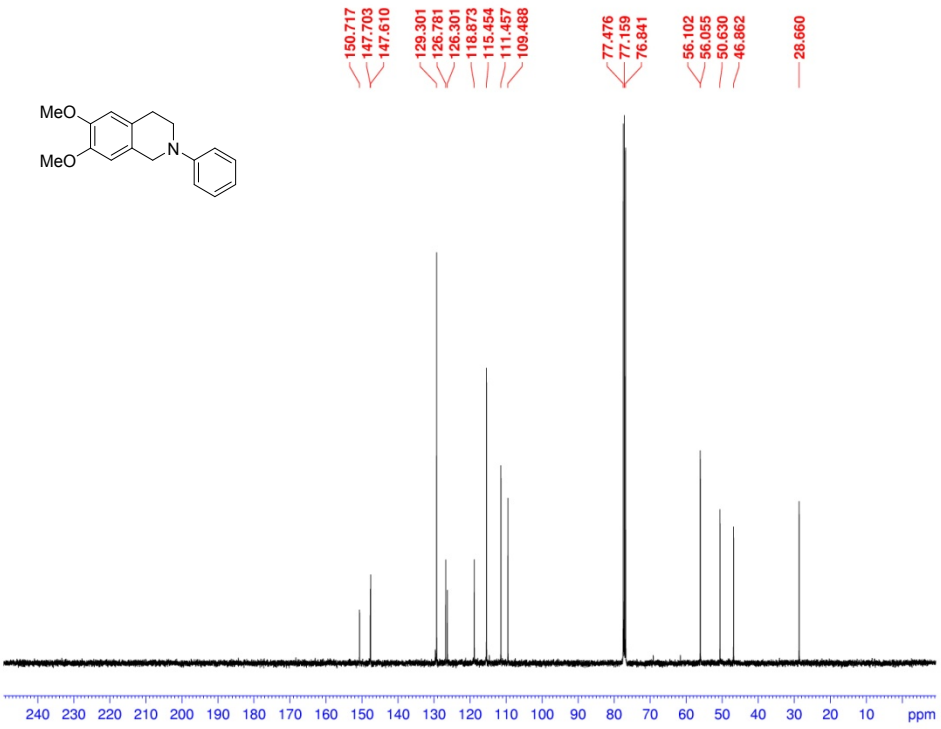
2-(Naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline (1n)



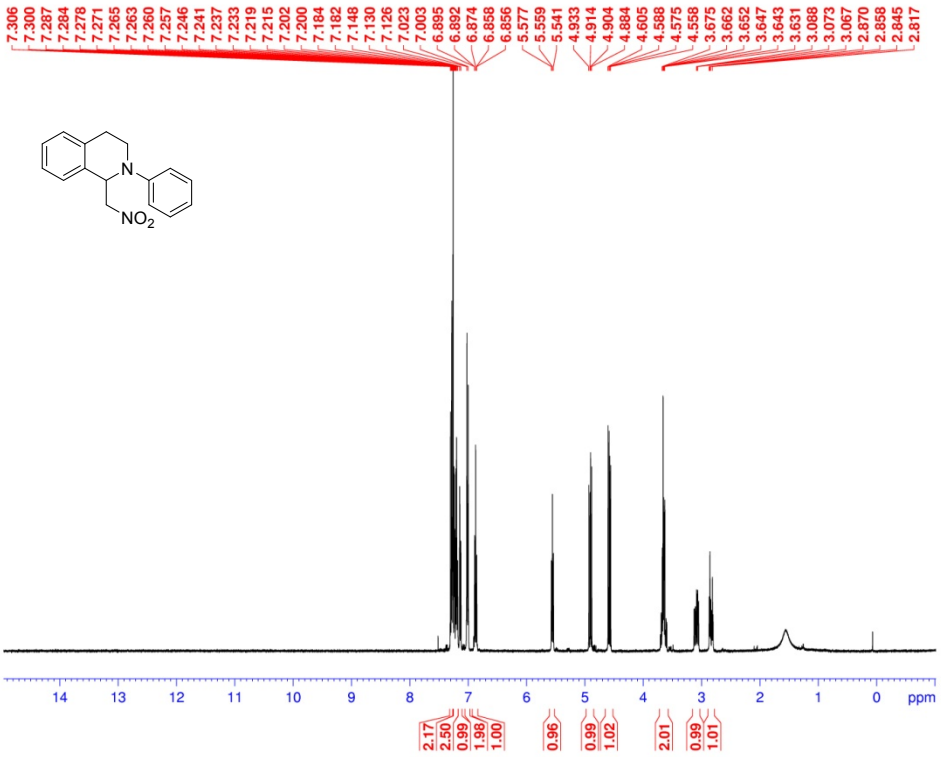


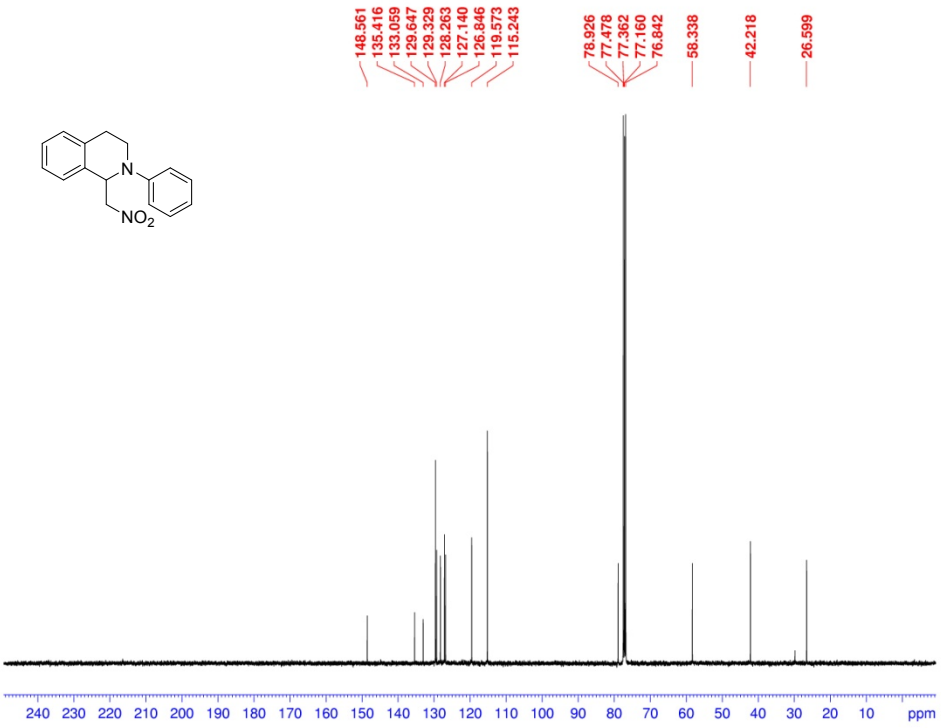
6,7-Dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (1o)



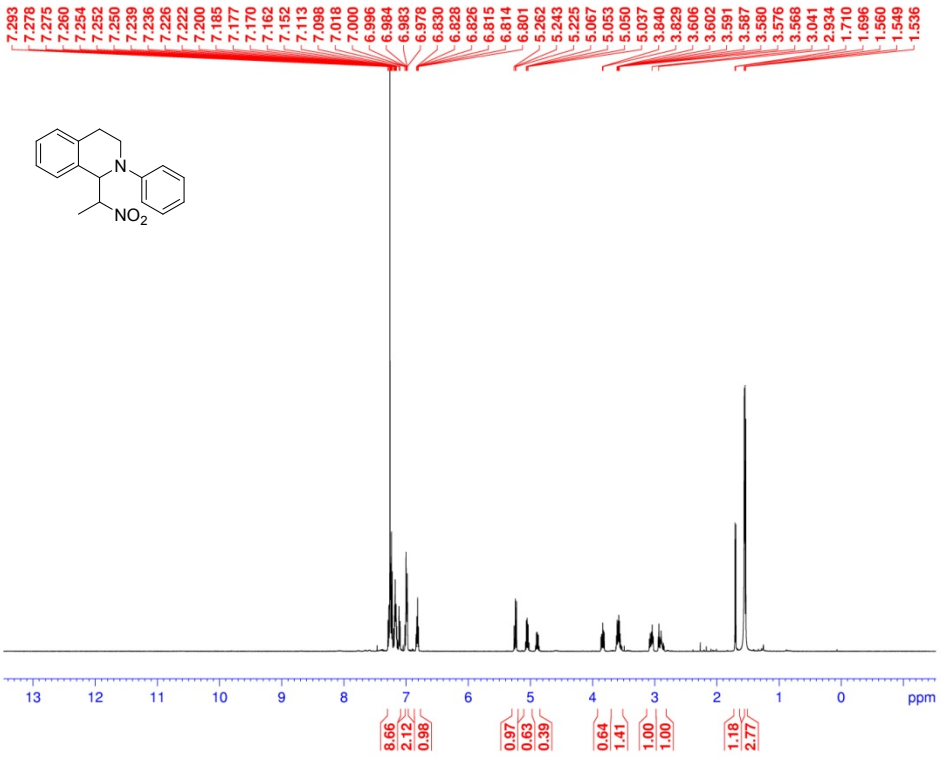


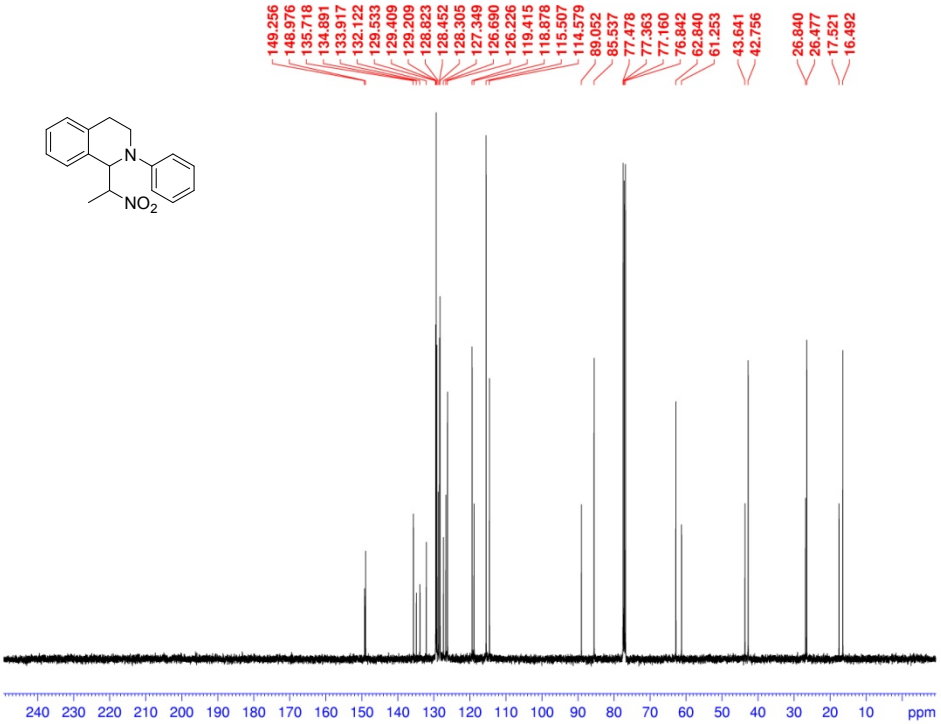
1-(Nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (2a)



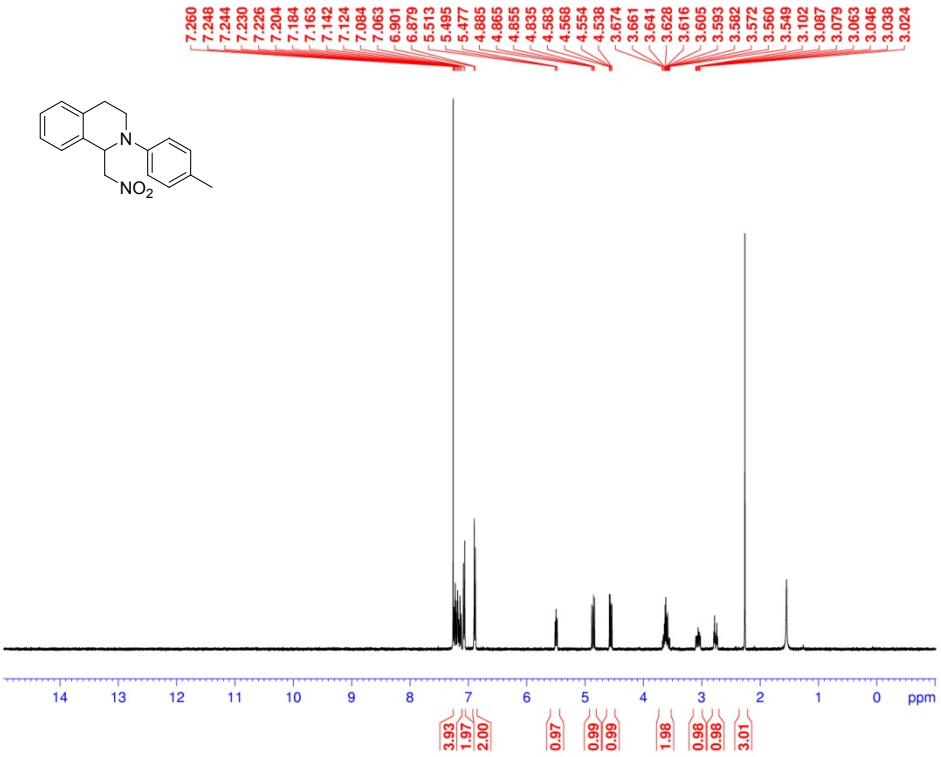


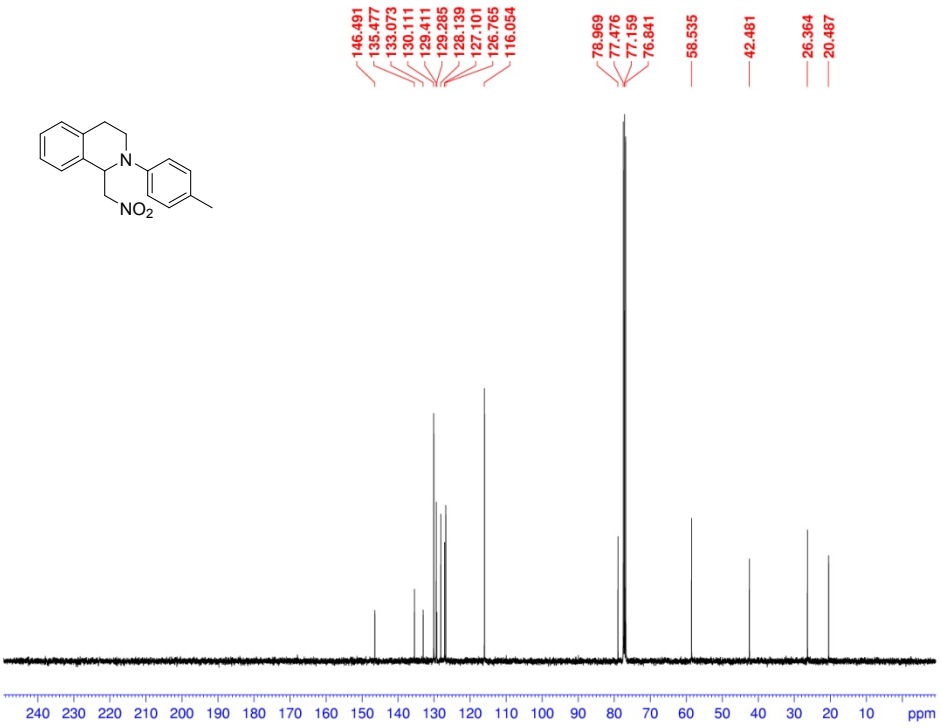
1-(Nitroethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (2b)



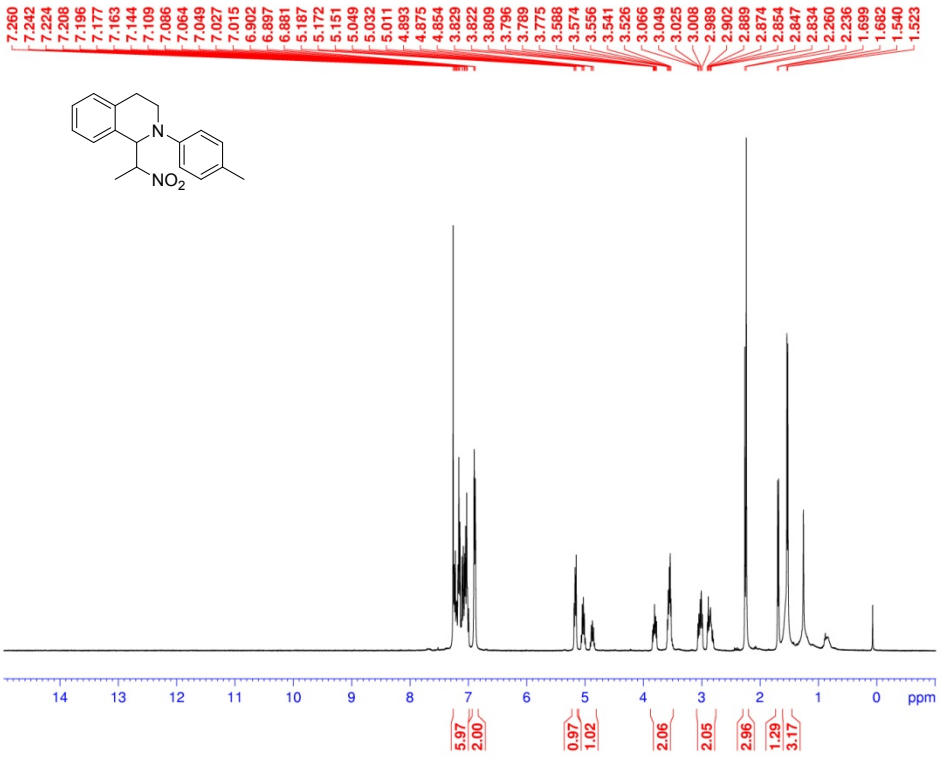


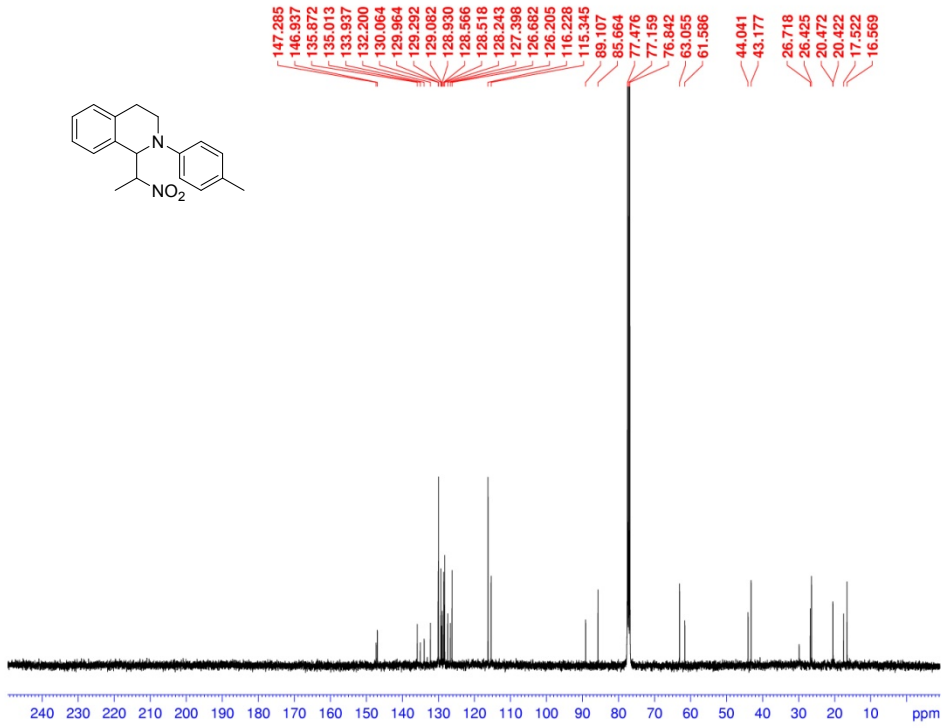
1-(Nitromethyl)-2-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline (2c)



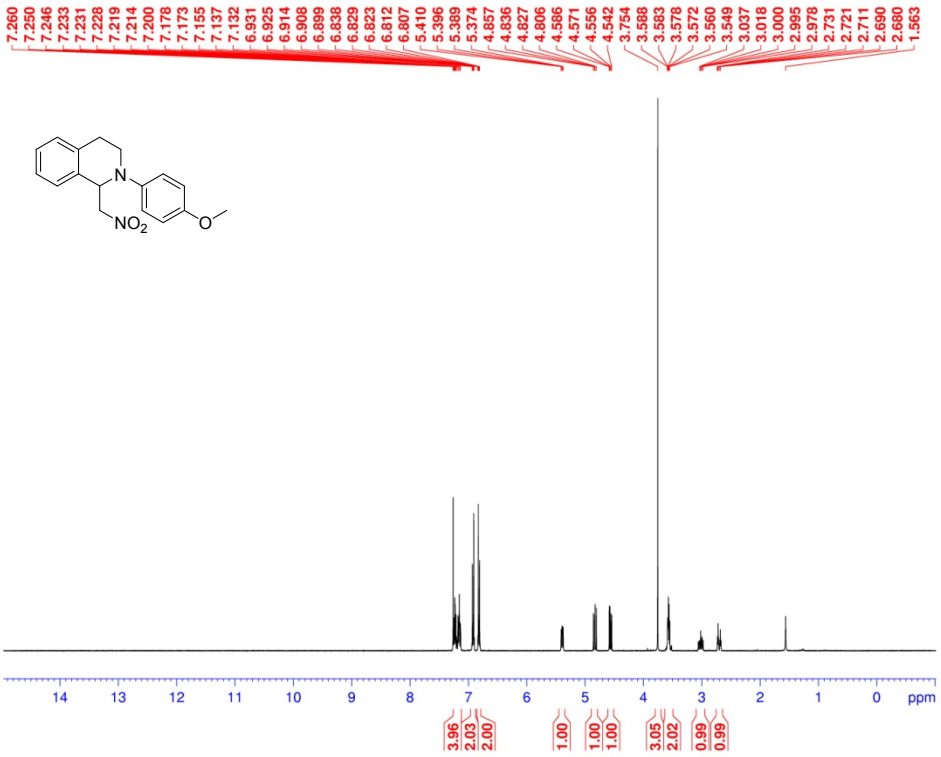


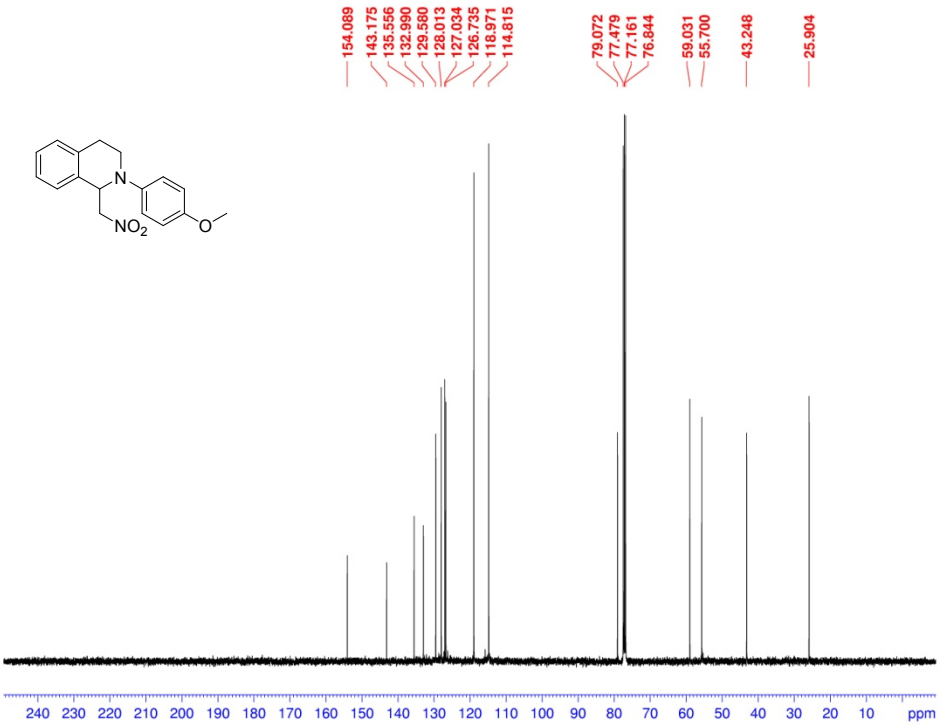
1-(Nitroethyl)-2-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline (2d)



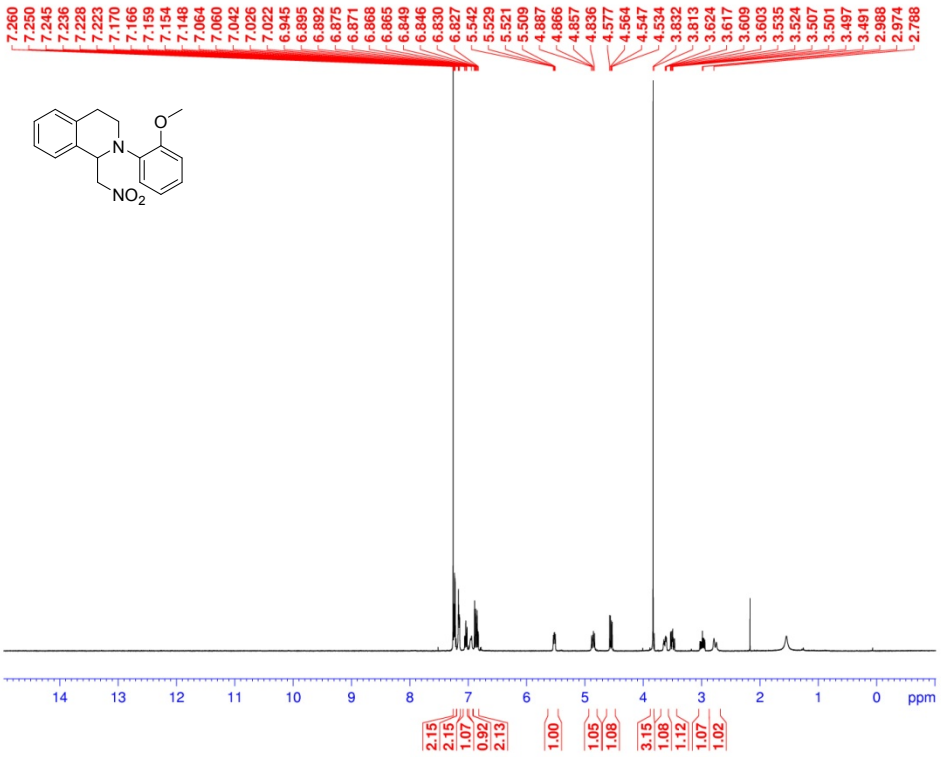


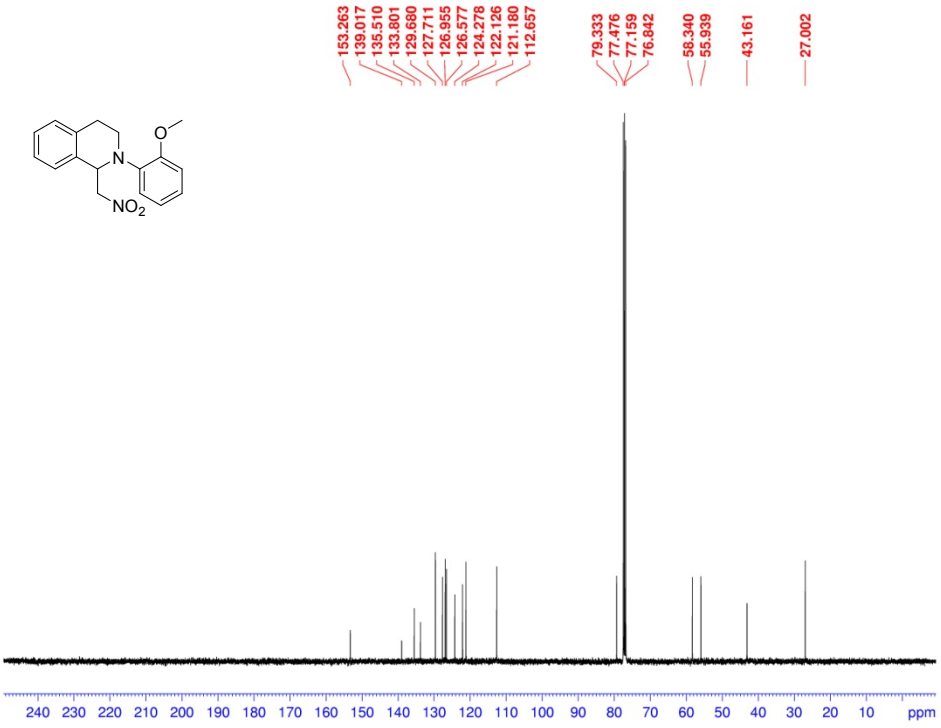
2-(4-Methoxyphenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2e)



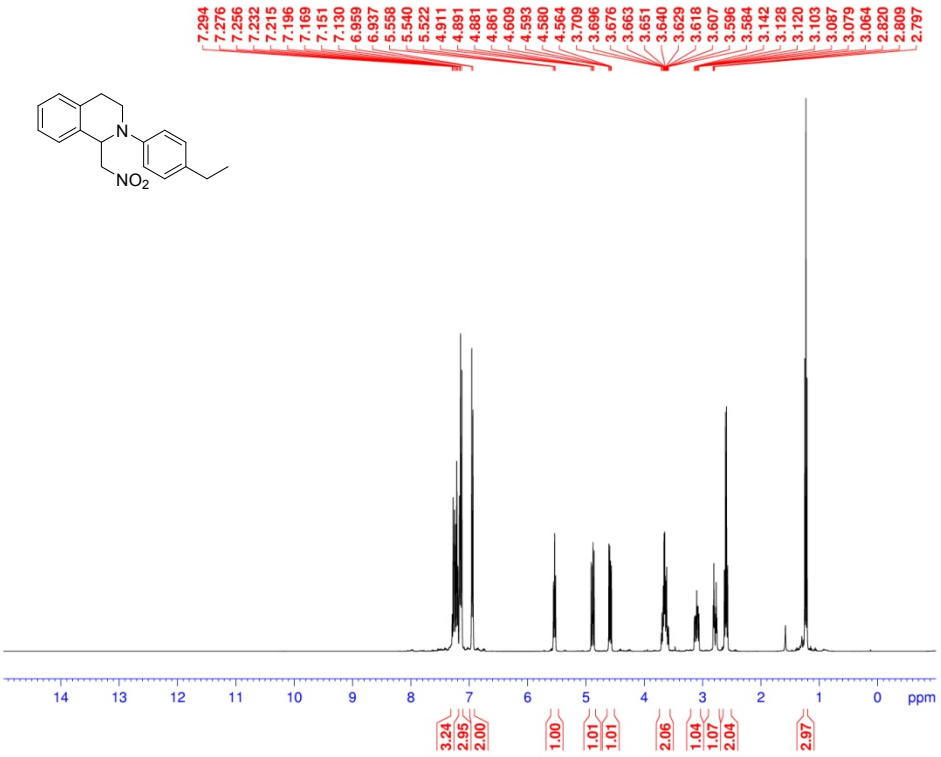


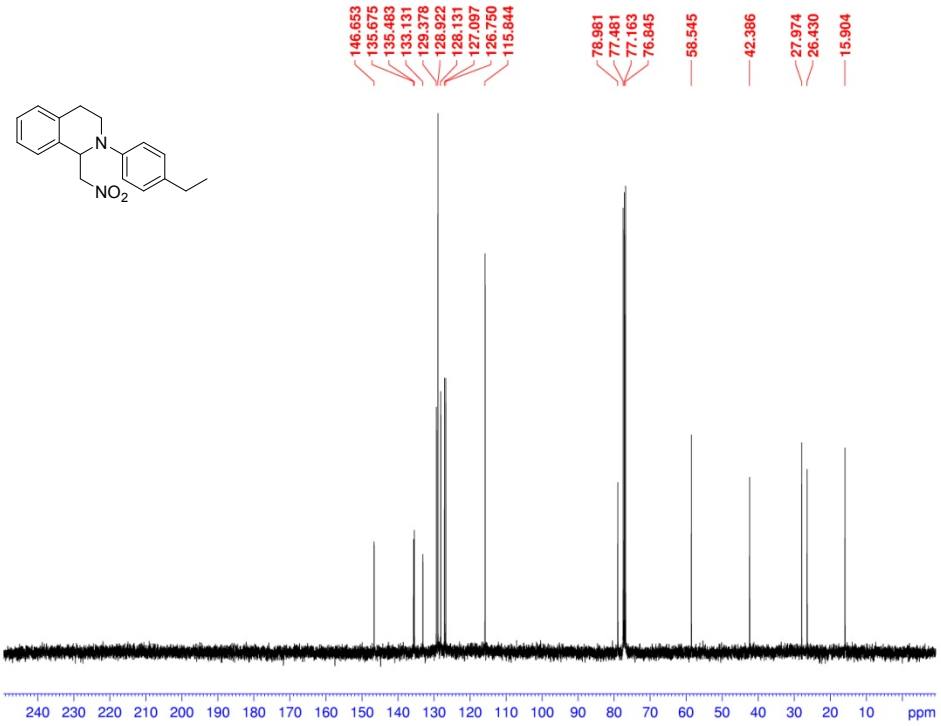
2-(2-Methoxyphenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2f)



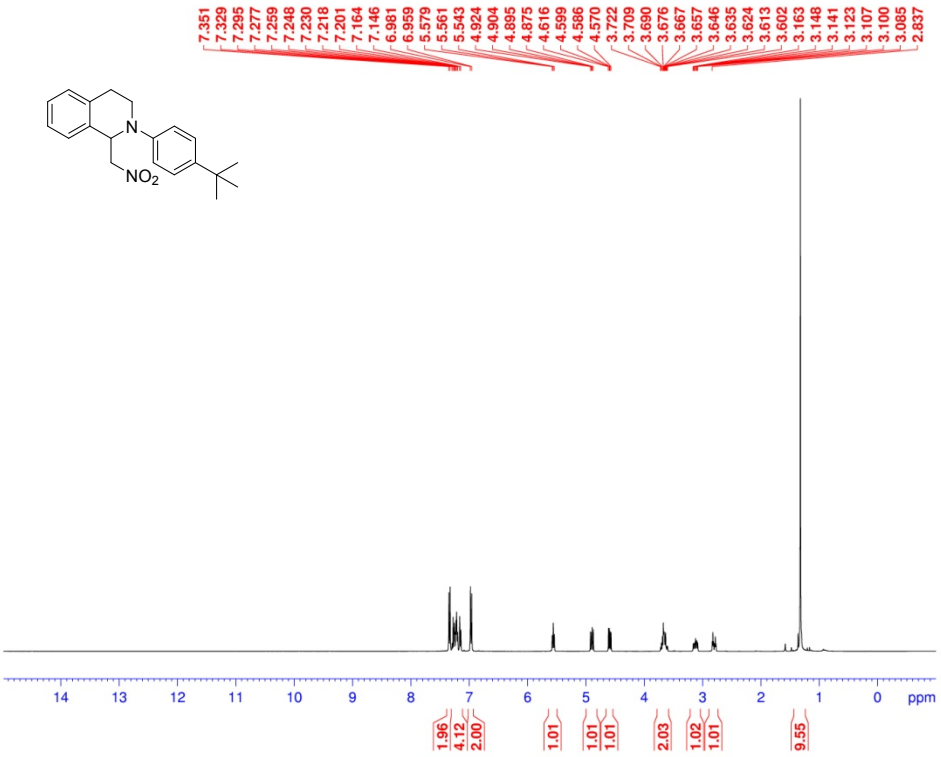


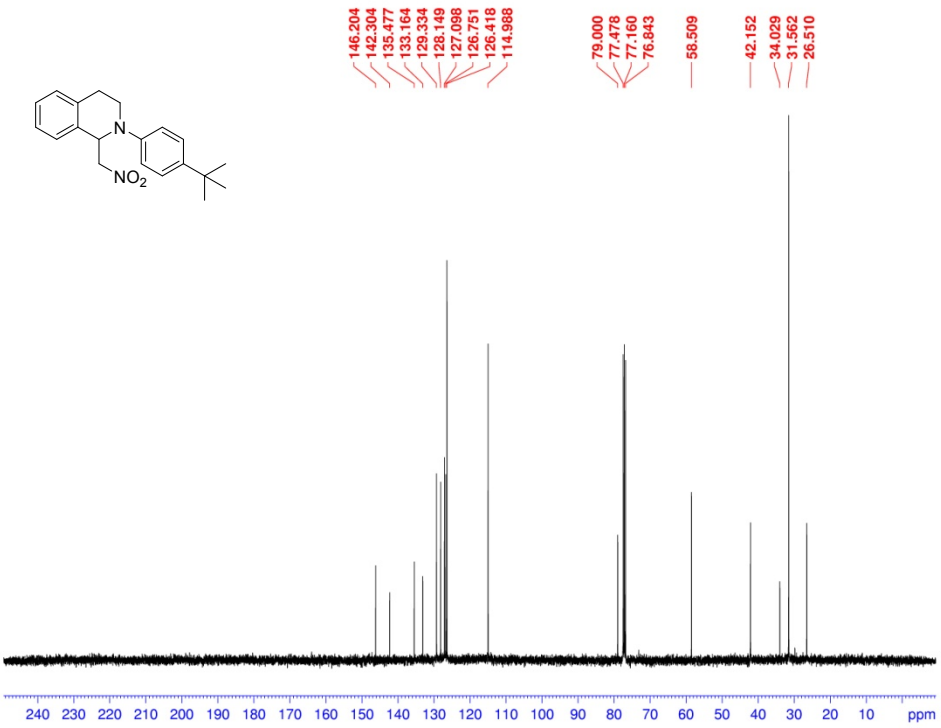
2-(4-Ethylphenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2g)



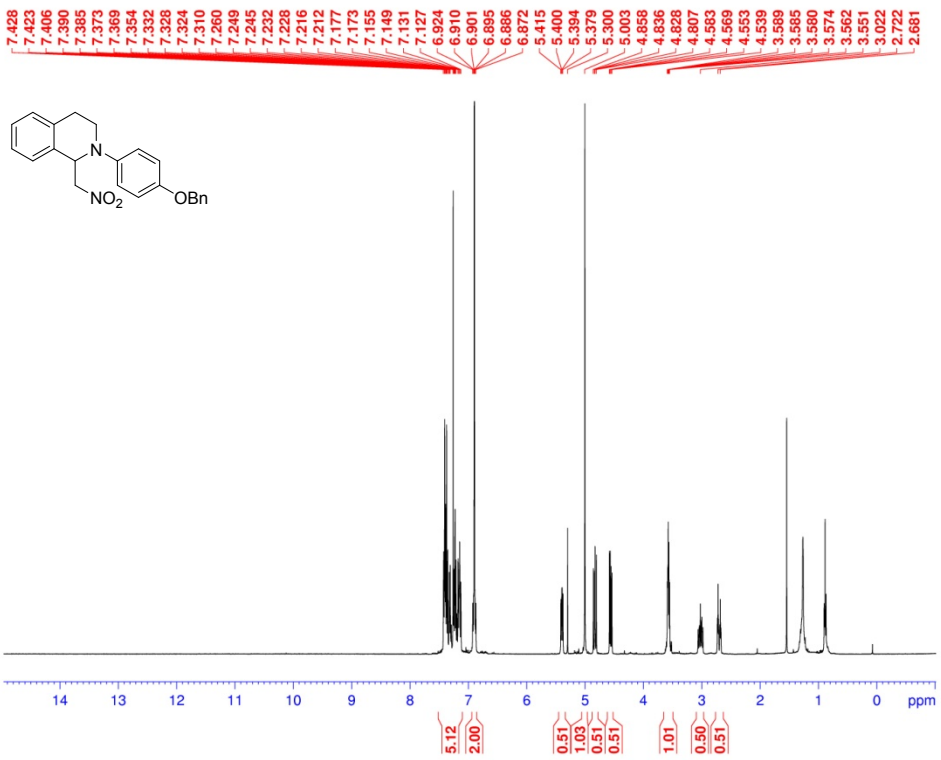


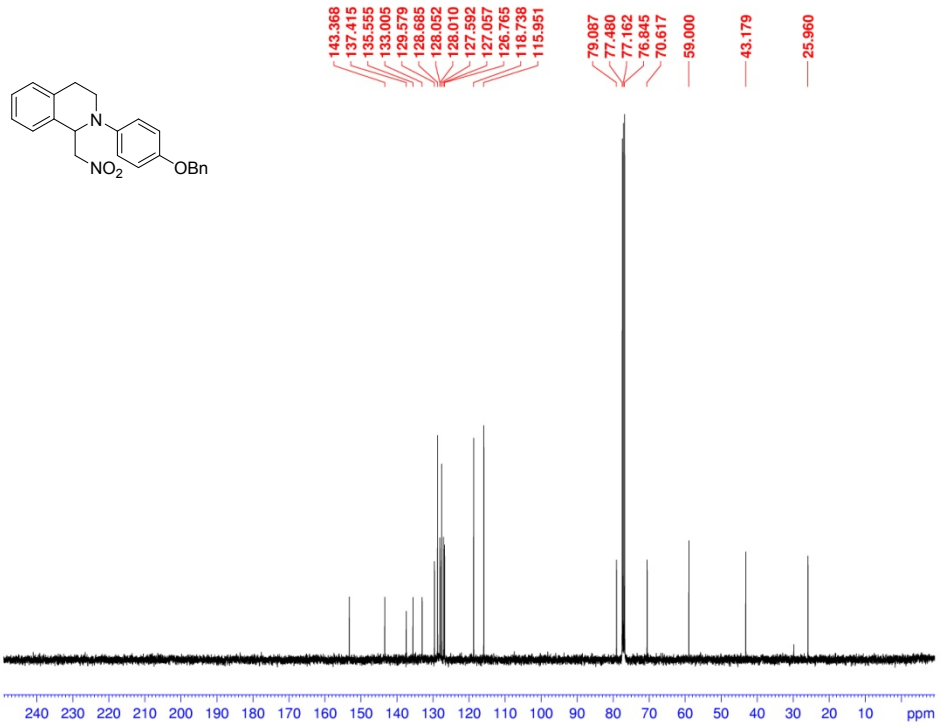
2-(4-(*tert*-Butyl)phenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2h)



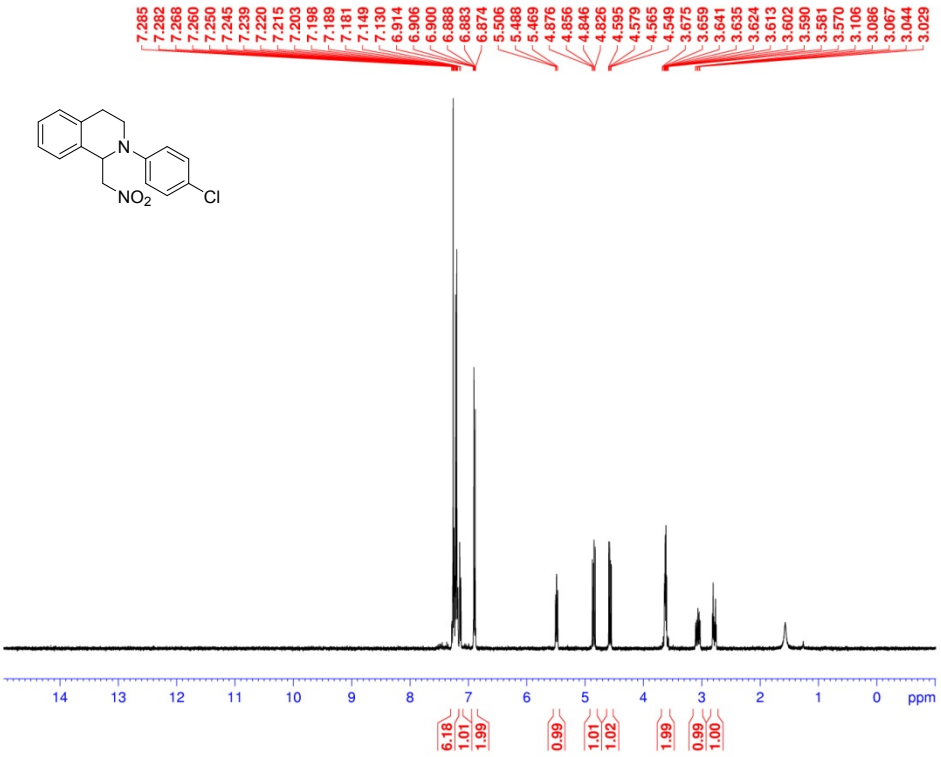


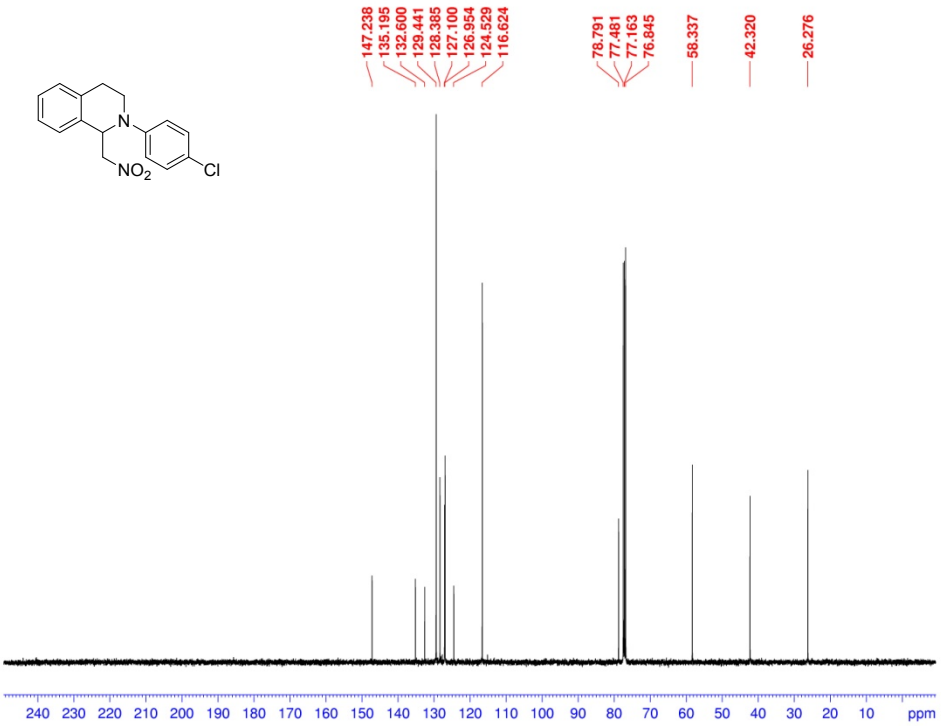
2-(4-(Benzyloxy)phenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2i)



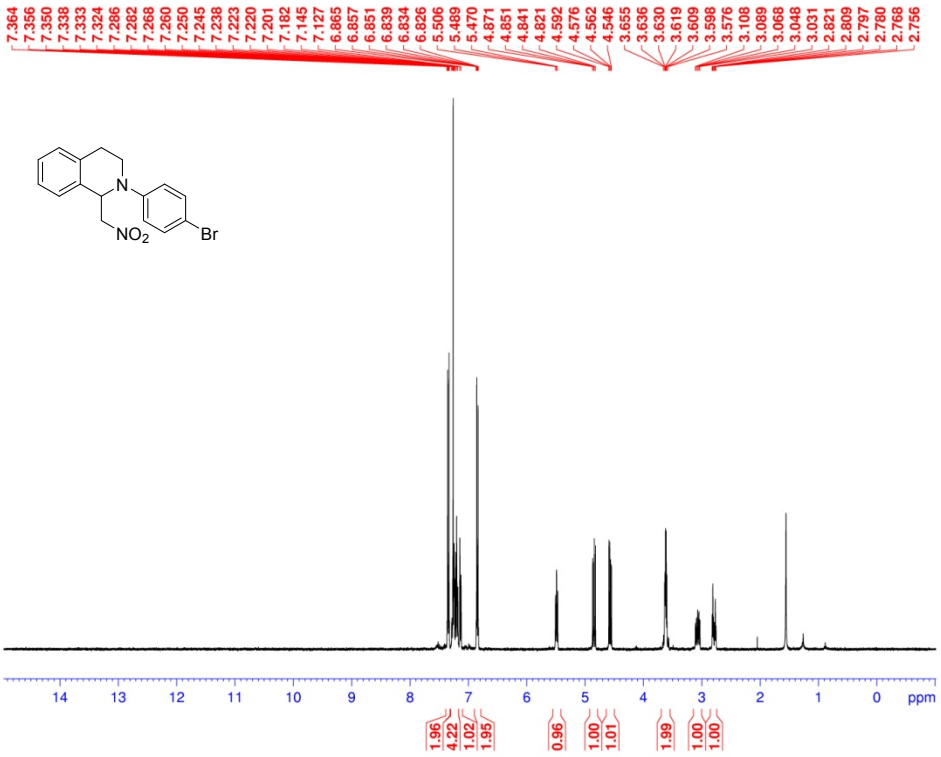


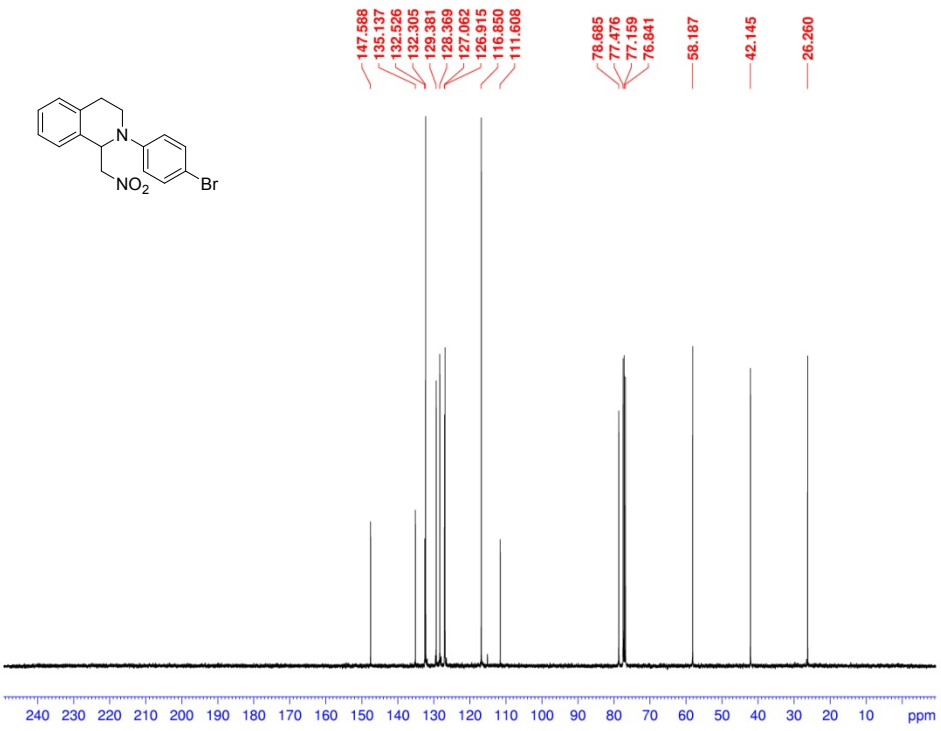
2-(4-Chlorophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2j)



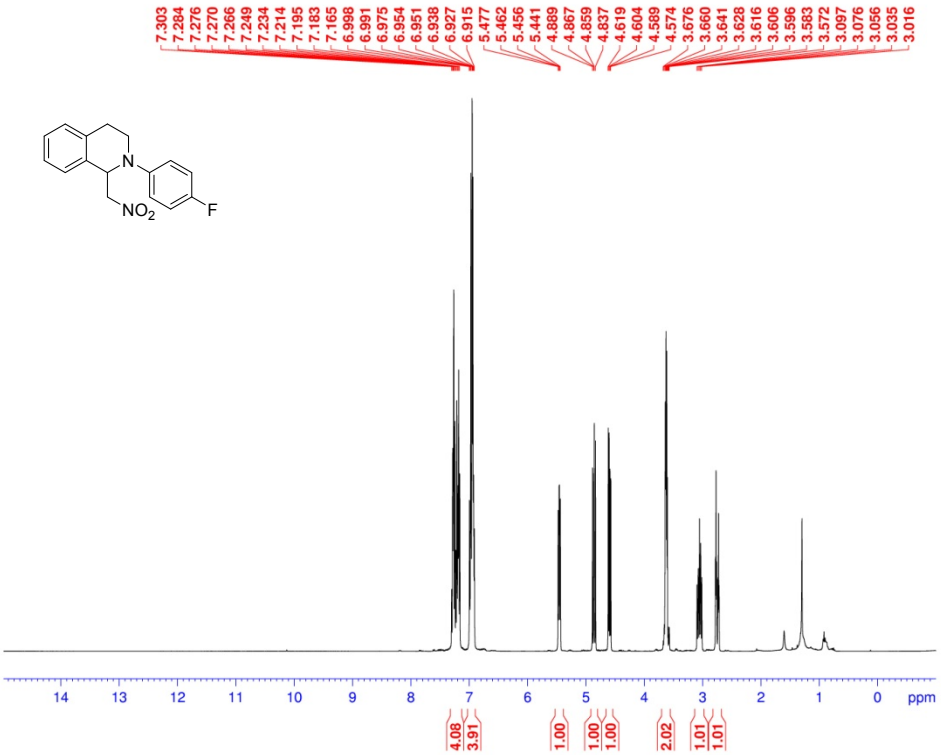


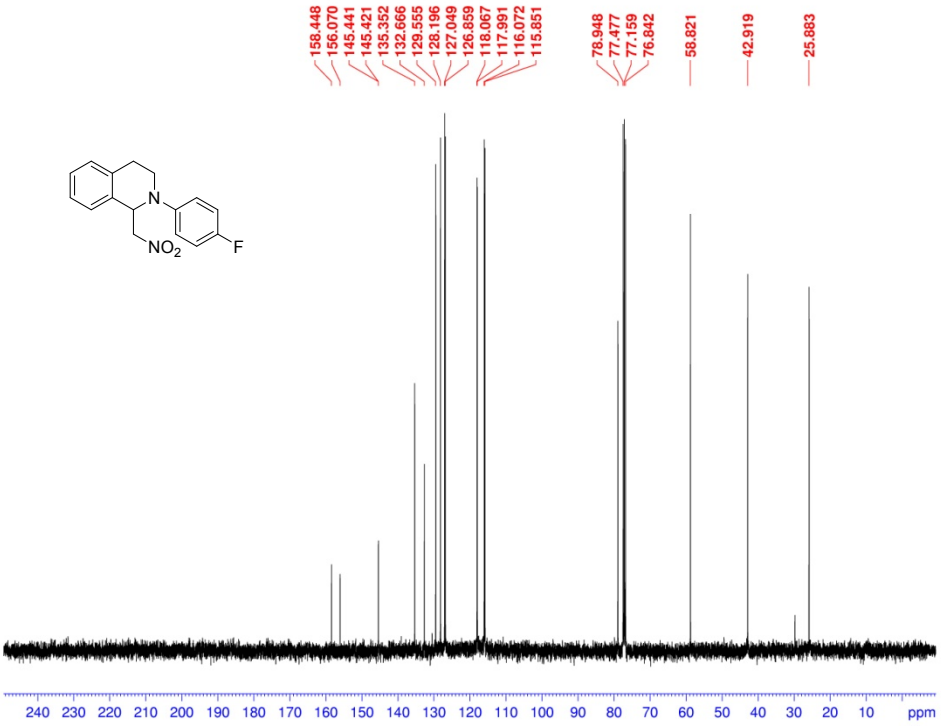
2-(4-Bromophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2k)

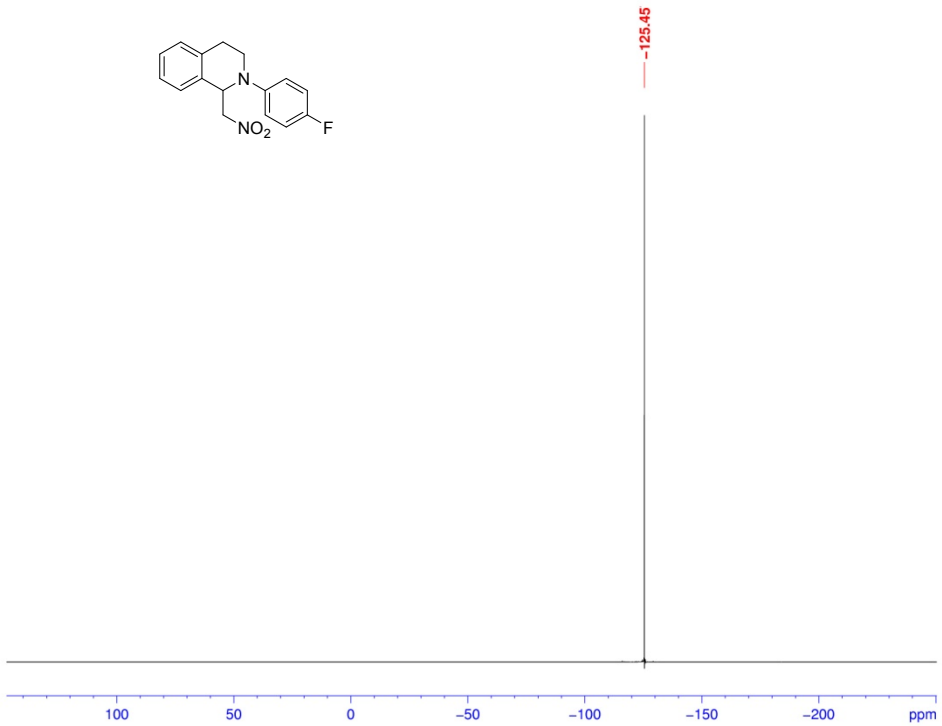




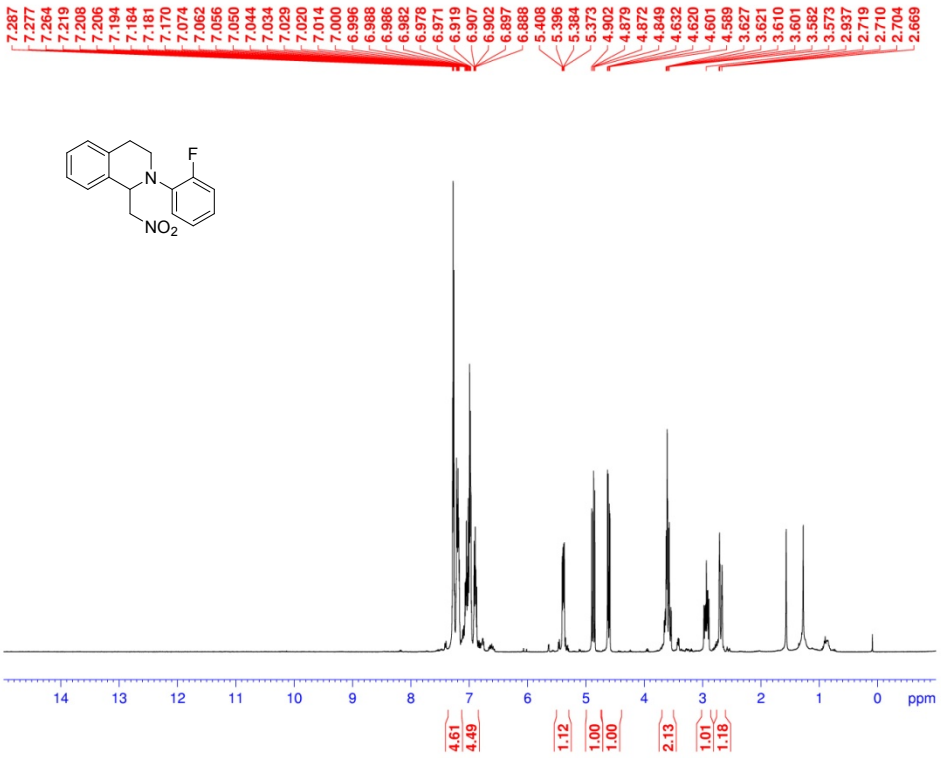
2-(4-Fluorophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2l)

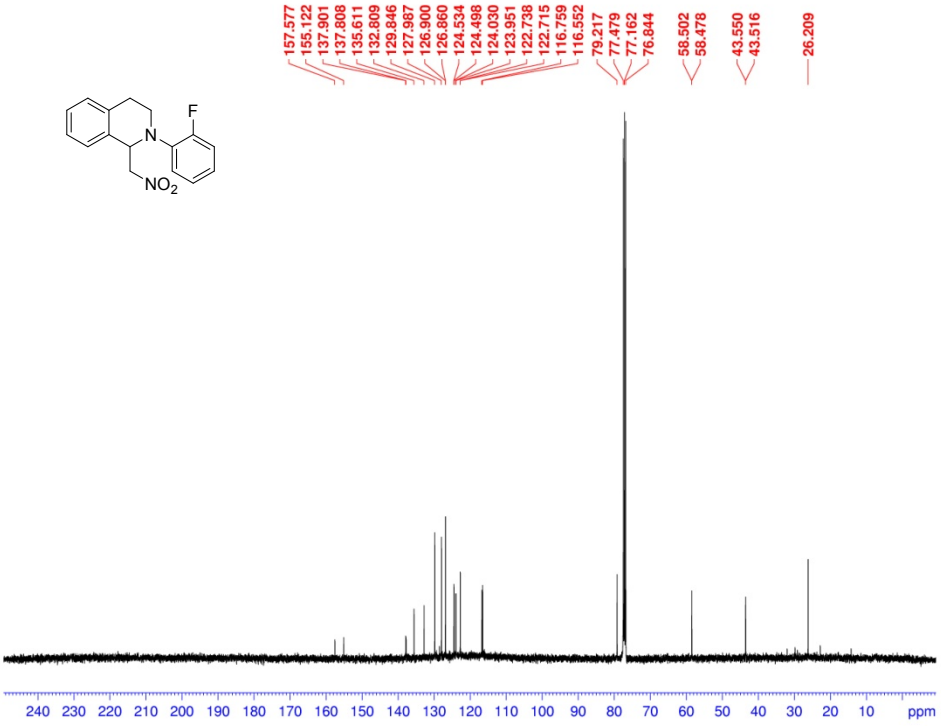





N
NO2
F
-125.45
100
50
0
-50
-100
-150
-200
ppm

2-(4-Fluorophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2m)






F
N
NO2
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100
50
0
-50
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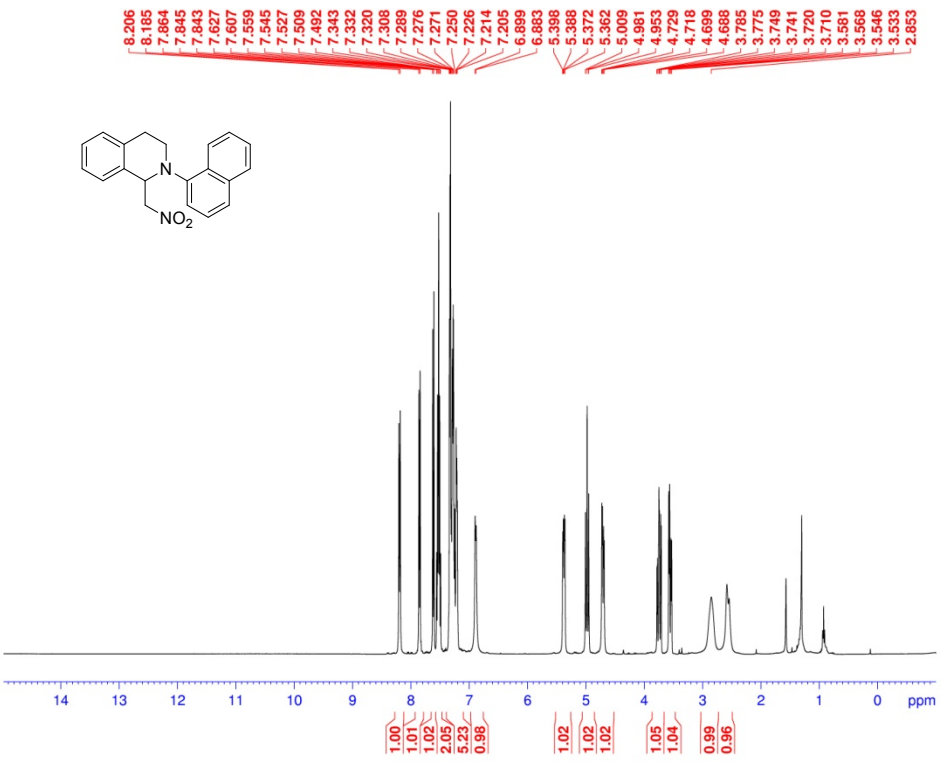
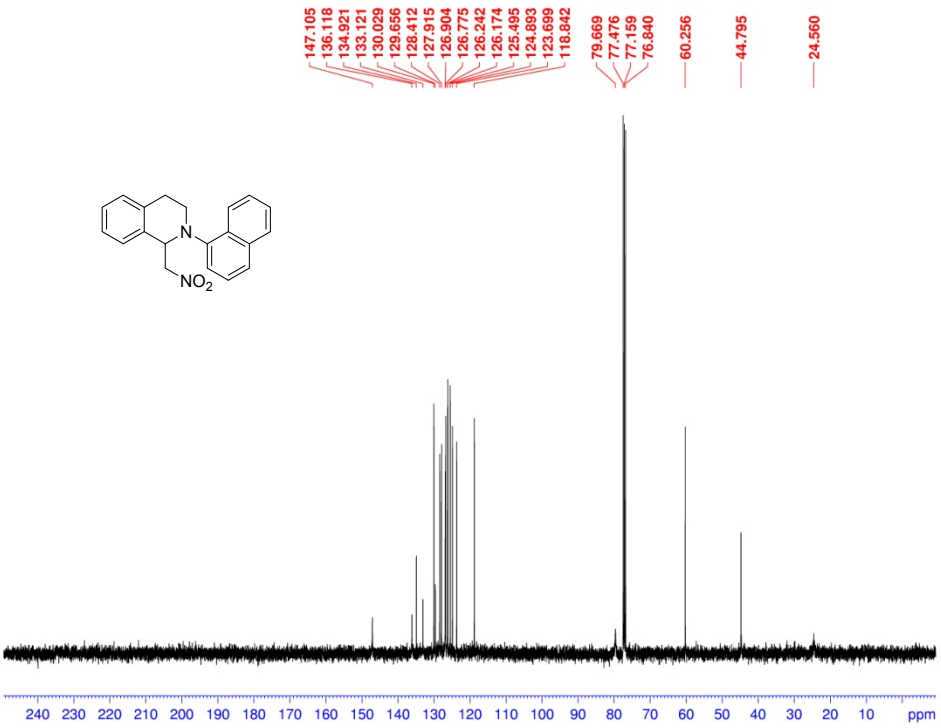
-200
ppm

2-(Naphthalen-1-yl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2n)





6,7-Dimethoxy-1-(nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (2o)