α-FUNCTIONALIZATION OF TETRAHYDROISOQUINOLINES WITH ACTIVATED ALKYL BROMIDE UNDER PHOTOREDOX CATALYSIS

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1. General

^{1}H, ^{19}F NMR spectra were measured on a JEOL JNM-ECA-500 spectrometer at 500 and 470 MHz, respectively. ^{13}C NMR spectra were recorded on a JEOL JNM-ECA-500 spectrometer at 125 MHz. Chemical shifts were reported downfield from TMS (d = 0 ppm), $CDCl_3$ or CD_3CN for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in a scale relative to $CDCl_3$ or CD_3CN. For ^{19}F NMR, chemical shifts were reported in a scale relative to a $CFCl_3$ external standard (d = 0 ppm). Infrared spectra were measured on a SHIMADZU IRPrestige-21 and only diagnostic absorptions are listed. ESI-MS data were taken on a Thermo SCIENTIFIC ACCELA Exactive liquid chromatography mass spectrometer. Column chromatography was performed with silica gel N-60 (40-100 mol purchased from Kanto Chemical Co., Inc. TLC analysis was performed on Silica gel 60 F_{254}-coated glass plates (Merck). Visualization of TLC plates was carried out by means of ultraviolet (UV) irradiation at 254 nm and/or by spraying 12-molybdo(VI)phosphoric acid ethanol solution as the developing agent.

Dehydrated *N*,*N*-dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), and dichloromethane (CH_2Cl_2) were purchased from Wako Pure Chemical Industries, Ltd. Dehydrated acetonitrile (MeCN) was purchased from Sigma-Aldrich Co. LLC. Other reagents were purified by usual methods. Tetrahydroisoquinolines were prepared according to literature procedures.[1]

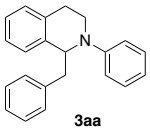
[1] D. J. Ramon, X. Marset, J. M. Perez, *Green Chem*., 2016, **18**, 826.

2. *a*-Functionalization of tetrahydroisoquinolines

2-1. Typical experimental procedure

An oven-dried test tube was charged with K_2HPO_4 (70 mg, 0.4 mmol). The test tube was equipped with a three-way stopcock, and the base was dried with a heat gun for 30 seconds under reduced pressure. $Ir(ppy)_3$ (1.3 mg, 1 mol %), *N*-phenyl tetrahydroisoquinoline (**1a**) (42 mg, 0.2 mmol), and MeCN (2 mL) were added to the tube, followed by the addition of benzyl bromide (**2a**) (51 μL, 0.4 mmol). The mixture was degassed by freeze-pump-thaw cycling (3 times). The mixture was cooled to 5 °C and irradiated with blue light for 12 h with stirring. Then, the light was switched off, and the reaction mixture was allowed to warm up to room temperature. Water was added to the tube, and the organic materials were extracted with diethyl ether (2 times). The combined organic layers were washed with brine and was dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 10/1) to provide product 1-benzyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**3aa**) (45 mg, 75%) as a yellow oil.

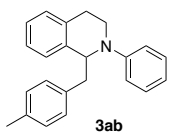
1-benzyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3aa):



3aa

Yellow oil; 45 mg, 75%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.75 (ddd, J = 5.1, 5.7, 16.4 Hz, 1H), 2.97–3.03 (m, 2H), 3.26 (dd, J = 5.7, 13.6 Hz, 1H), 3.53–3.57 (m, 1H), 3.65 (ddd, J = 5.1, 7.7, 12.2 Hz, 1H), 4.90 (dd, J = 5.7, 6.2 Hz, 1H), 6.71–6.75 (m, 2H), 6.84 (d, J = 7.9 Hz, 2H), 7.01–7.06 (m, 3H), 7.11–7.15 (m, 2H), 7.16–7.26 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.5, 42.1, 42.4, 61.5, 113.6, 117.2, 125.5, 126.2, 126.6, 127.6, 128.1, 128.2, 129.2, 129.8, 135.1, 137.6, 138.8, 149.3 ppm; IR ($CHCl_3$): 1599, 1474, 1392, 1276 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{22}H_{21}N+H]^+$: m/z = 300.1747, Found: 300.1747.

1-(4-methylbenzyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3ab):

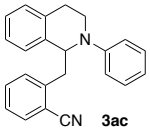


3ab

Yellow oil; 21 mg, 34%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.31 (s, 3H), 2.73–2.78 (m, 1H) , 2.92–3.02 (m, 2H), 3.21 (dd, J = 5.7, 13.8 Hz, 1H), 3.51–3.57 (m, 1H), 3.64 (ddd, J = 5.2, 7.5, 12.3 Hz, 1H), 4.88 (dd, J = 5.7, 7.2 Hz, 1H), 6.72 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.0 Hz, 2H), 7.01–7.06 (m, 3H), 7.12–7.17 (m, 2H), 7.22–7.26 ppm (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 27.5, 42.0, 42.1, 61.5, 113.6, 117.1, 125.5, 126.5, 127.7, 128.2, 128.8, 129.2, 129.6, 135.1, 135.7, 135.7, 137.8, 149.4 ppm; IR ($CHCl_3$): 1599, 1504, 1384, 1265 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{23}H_{23}N+H]^+$: m/z = 314.1903, Found: 314.1899.

1-(2-cyanobenzyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3ac):



3ac

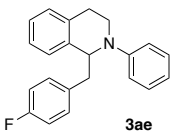
Yellow oil; 53 mg, 82%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.85 (ddd, J = 4.5, 5.1, 15.7 Hz, 1H), 3.08 (ddd, J = 5.7, 9.4, 15.7 Hz, 1H), 3.30 (dd, J = 5.4, 13.7 Hz, 1H), 3.45 (dd, J = 8.9, 13.7 Hz, 1H), 3.72 (ddd, J = 5.1, 5.7, 13.2 Hz, 1H), 3.81 (ddd, J = 4.5, 9.4, 13.2 Hz, 1H), 4.98 (dd, J = 5.4, 8.9 Hz, 1H), 6.65–6.68 (m, 3H), 6.99 (d, J = 7.9 Hz, 1H), 7.09–7.20 (m, 5H), 7.26-7.29 (m, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.47 (ddd, J = 1.1, 7.4, 7.9 Hz, 1H), 7.56 ppm (dd, J = 1.1, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.6, 41.1, 41.6, 61.2, 113.2, 114.1, 117.7, 118.2, 125.9, 126.9 (2C), 127.4, 128.8, 129.1, 130.9, 132.5, 132.6, 135.2, 137.0, 143.2, 149.3 ppm; IR ($CHCl_3$): 2226, 1597, 1502, 1395, 1327 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{23}H_{20}N_2+H]^+$: m/z = 325.1699, Found: 325.1701.

1-(4-cyanobenzyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3ad):

3ad

Yellow oil; 43 mg, 66%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.68 (ddd, J = 5.1, 5.7, 15.9 Hz, 1H), 2.98 (ddd, J = 5.7, 7.9, 15.9 Hz, 1H), 3.10 (dd, J = 6.8, 13.3 Hz, 1H), 3.28 (dd, J = 6.2, 13.3 Hz, 1H), 3.55 (ddd, J = 5.7, 5.7, 12.4 Hz, 1H), 3.62 (ddd, J = 5.1, 7.9, 12.4 Hz, 1H), 4.93 (dd, J = 6.2, 6.8 Hz, 1H), 6.75–6.83 (m, 4H), 7.07–7.20 (m, 5H), 7.22–7.25 (m, 2H), 7.50 ppm (d, J = 7.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.3, 42.2, 42.5, 61.0, 110.1, 114.1, 117.9, 119.1, 125.8, 127.0, 127.3, 128.5, 129.3, 130.5, 131.9, 135.1, 136.8, 144.5, 149.2 ppm; IR ($CHCl_3$): 2230, 1601, 1447, 1383, 1265 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{23}H_{20}N_2+H]^+$: m/z = 325.1699, Found: 325.1702.

1-(4-fluorobenzyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3ae):

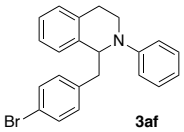


3ae

Colorles oil; 52 mg, 82%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.71 (ddd, J = 5.4, 5.7, 15.9 Hz, 1H), 2.95–3.02 (m, 2H), 3.21 (dd, J = 6.2, 13.6 Hz, 1H), 3.51–3.56 (m, 1H), 3.63 (ddd, J = 5.4, 7.7, 12.2 Hz, 1H), 4.87 (dd, J = 6.2, 6.2 Hz, 1H), 6.74 (t, J = 7.4 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.83 (d, J

= 7.9 Hz, 2H), 6.87–6.92 (m, 2H), 6.93-6.97 (m, 2H), 7.05-7.09 (m, 1H), 7.12–7.17 (m, 2H), 7.21–7.26 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.5, 41.5, 42.2, 61.4, 113.7, 114.9 (d, J = 21.6 Hz), 117.4, 125.6, 126.7, 127.6, 128.3, 129.3, 131.1 (d, J = 8.4 Hz), 134.5 (d, J = 2.4 Hz), 135.1, 137.4, 149.3, 161.6 ppm (J = 244.7 Hz); ^{19}F NMR (375 MHz, $CDCl_3$): δ = -116.8 ppm; IR ($CHCl_3$): 1603, 1510, 1240 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{22}H_{20}FN+H]^+$: m/z = 318.1653, Found: 318.1653.

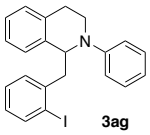
1-(4-bromobenzyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3af):



3af

Yellow oil; 33 mg, 44%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.71 (ddd, J = 5.4, 5.7, 15.9 Hz, 1H), 2.95–3.01 (m, 2H), 3.19 (dd, J = 6.0, 13.6 Hz, 1H), 3.50–3.56 (m, 1H), 3.62 (ddd, J = 5.4, 7.7, 12.2 Hz, 1H), 4.88 (dd, J = 6.0, 6.2 Hz, 1H), 6.75 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H), 6.84 (d, J = 7.9 Hz, 2H), 6.87 (d, J = 7.9 Hz, 2H), 7.08 (dt, J = 1.3, 7.4 Hz, 1H), 7.12–7.18 (m, 2H), 7.23–7.25 (m, 2H), 7.33 ppm (d, J = 7.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.4, 41.8, 42.2, 61.1, 113.8, 117.5, 120.2, 125.7, 126.7, 127.5, 128.4, 129.3, 131.2, 131.5, 135.1, 137.2, 137.8, 149.3 ppm; IR ($CHCl_3$): 1597, 1504, 1487, 1390, 1329, 1013 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{22}H_{20}BrN+H]^+$: m/z = 378.0852, Found: 378.0851.

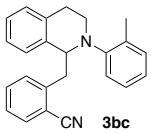
1-(2-iodobenzyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3ag):



3ag

Browish oil; 53 mg, 62%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.85 (dt, J = 4.5, 15.9 Hz, 1H), 3.11 (ddd, J = 6.2, 9.6, 15.9 Hz, 1H), 3.24 (dd, J = 5.7, 13.7 Hz, 1H), 3.36 (dd, J = 9.1, 13.7 Hz, 1H), 3.71–3.83 (m, 2H), 5.05 (dd, J = 5.7, 9.1 Hz, 1H), 6.63-6.70 (m, 3H), 6.86 (ddd, J = 1.7, 7.4, 7.4 Hz, 1H), 7.05–7.18 (m, 7H), 7.81 (dd, J = 1.1, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.7, 41.2, 46.2, 59.8, 101.2, 114.0, 117.3, 125.7, 126.7, 127.4, 128.1, 128.2, 128.6, 129.0, 131.5, 135.0, 137.6, 139.2, 141.6, 149.6 ppm; IR ($CHCl_3$): 1597, 1503, 1466, 1396, 1287 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{22}H_{20}IN+H]^+$: m/z = 426.0713, Found: 426.0714.

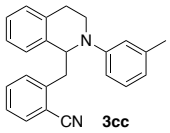
1-(2-cyanobenzyl)-2-(2-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (3bc):



3bc

Yellow oil; 43 mg, 64%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.05 (s, 3H), 2.52–2.56 (m, 1H), 2.77 (ddd, J = 5.7, 11.9, 16.7 Hz, 1H), 3.21–3.30 (m, 2H), 3.39 (dd, J = 10.5, 14.2 Hz, 1H), 3.75 (ddd, J = 4.0, 11.9, 13.9 Hz, 1H), 4.55 (dd, J = 4.0, 10.5 Hz, 1H), 6.69 (dd, J = 1.1, 7.9 Hz, 1H), 6.86–6.94 (m, 2H), 7.04 (dd, J = 1.1, 7.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 7.20–7.31 (m, 4H), 7.38 (d, J = 7.4 Hz, 1H), 7.46 (ddd, J =1.1, 7.4, 7.9 Hz, 1H), 7.58 ppm (dd, J = 1.1, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.8, 24.6, 41.9, 42.9, 62.5, 113.1, 118.5, 122.8, 123.3, 126.2, 126.2, 126.6 (2 C), 127.1, 129.2, 130.8, 130.9, 132.2, 132.4, 133.3, 135.6, 138.3, 144.3, 150.2 ppm; IR ($CHCl_3$): 2226, 1597, 1491, 1450, 1379 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{24}H_{22}N_2+H]^+$: m/z = 339.1856, Found: 339.1855.

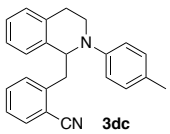
1-(2-cyanobenzyl)-2-(3-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (3cc):



3cc

Yellow oil; 39 mg, 58%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.21 (s, 3H), 2.85 (ddd, J = 4.5, 5.1, 16.1 Hz, 1H), 3.05–3.11 (m, 1H), 3.29 (dd, J = 5.1, 13.6 Hz, 1H), 3.45 (dd, J = 8.6, 13.6 Hz, 1H), 3.71 (ddd, J = 5.1, 5.7, 13.3 Hz, 1H), 3.79 (ddd, J = 4.5, 9.4, 13.3 Hz, 1H), 4.96 (dd, J = 5.1, 8.6 Hz, 1H), 6.46–6.50 (m, 3H), 6.98–7.02 (m, 2H), 7.09–7.19 (m, 3H), 7.26–7.29 (m, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.47 (dt, J =1.1, 7.4 Hz, 1H), 7.57 ppm (dd, J = 1.1, 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8, 26.7, 41.1, 41.7, 61.3, 111.2, 113.3, 114.9, 118.2, 118.6, 125.9, 126.8, 126.9, 127.4, 128.7, 128.9, 131.0, 132.4, 132.6, 135.2, 137.1, 138.7, 143.3, 149.4 ppm; IR ($CHCl_3$): 2226, 1601, 1493, 1390, 908 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{24}H_{22}N_2+H]^+$: m/z = 339.1856, Found: 339.1853.

1-(2-cyanobenzyl)-2-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (3dc):

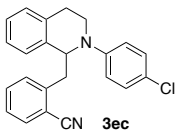


3dc

Yellow oil; 47 mg, 69%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.19 (s, 3H), 2.78 (dd, J = 4.5, 4.5, 15.9 Hz, 1H), 3.06 (ddd, J = 5.1, 9.7, 15.9 Hz, 1H), 3.29 (dd, J = 5.7, 13.6 Hz, 1H), 3.42 (dd, J = 9.1, 13.6 Hz, 1H), 3.69 (ddd, J = 4.5, 5.1, 13.2 Hz, 1H), 3.79 (ddd, J = 4.5, 9.7, 13.2 Hz, 1H), 4.90 (dd, J = 5.7, 9.1 Hz, 1H), 6.59 (d, J = 8.2 Hz, 2H), 6.93 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 7.4 Hz, 1H), 7.09–7.18 (m, 3H), 7.26–7.29 (m, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.47 (dt, J = 1.1, 7.7 Hz, 1H), 7.57 ppm

(dd, J = 1.1, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.2, 26.3, 41.1, 41.8, 61.5, 113.2, 114.8, 118.2, 125.9, 126.8 (2 C), 127.3, 127.4, 128.8, 129.6, 130.9, 132.5, 132.6, 135.2, 137.1, 143.3, 147.5 ppm; IR ($CHCl_3$): 2226, 1616, 1518, 1395 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{24}H_{22}N_2+H]^+$: m/z = 339.1856, Found: 339.1855.

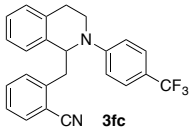
1-(2-cyanobenzyl)-2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (3ec):



3ec

Yellow oil; 51 mg, 71%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.85 (ddd, J = 4.5, 5.1, 16.1 Hz, 1H), 3.05 (dd, J = 5.7, 9.4, 16.1 Hz, 1H), 3.29 (dd, J = 5.1, 13.6 Hz, 1H), 3.43 (dd, J = 9.1, 13.6 Hz, 1H), 3.66 (ddd, J = 5.1, 5.7, 13.2 Hz, 1H), 3.79 (ddd, J = 4.5, 9.4, 13.2 Hz, 1H), 4.91 (dd, J = 5.7, 9.1 Hz, 1H), 6.52–6.59 (m, 2H), 7.00–7.05 (m, 3H), 7.10–7.22 (m, 3H), 7.29 (dt, J = 1.1, 6.8 Hz, 2H), 7.47 (dt, J = 1.1, 7.7 Hz, 1H), 7.57 ppm (dd, J = 1.7, 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.6, 41.1, 41.9, 61.2, 113.3, 115.1, 118.2, 122.4 126.1, 127.0, 127.1, 127.3, 128.8, 128.9, 130.9, 132.5, 132.7, 134.9, 136.7, 142.9, 147.9 ppm; IR ($CHCl_3$): 2226, 1595, 1495, 1395 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{23}H_{19}ClN_2+H]^+$: m/z = 359.1310, Found: 359.1309.

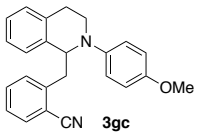
1-(2-cyanobenzyl)-2-(4-trifluoromethylphenyl)-1,2,3,4-tetrahydroisoquinoline (3fc):



3fc

Brown oil; 44 mg, 56%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.95 (ddd, J = 5.1, 5.1,16.2 Hz, 1H), 3.09 (ddd, J = 5.1, 8.2, 16.2 Hz, 1H), 3.32 (dd, J = 5.7, 13.7 Hz,1H), 3.48 (dd, J = 8.5, 13.7 Hz, 1H), 3.70–3.75 (m, 1H), 3.83 (ddd, J = 5.1, 8.2, 12.8 Hz, 1H), 5.05 (dd, J = 5.7, 8.5 Hz, 1H), 6.66 (d, J = 9.1 Hz, 2H), 7.00 (d, J = 7.4 Hz, 1H), 7.11–7.15 (m, 1H), 7.18–7.23 (m, 2H), 7.27–7.33 (m, 4H), 7.47 (ddd, J = 1.7, 7.7, 7.7 Hz, 1H), 7.56 ppm (dd, J = 1.1, 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.9, 41.0, 41.8, 60.7, 112.2, 113.2, 118.1, 118.6 (q, J = 32.4 Hz), 124.8 (q, J = 269.9 Hz), 126.2, 126.4 (q, J = 3.6 Hz), 127.2, 127.3 (2 C), 128.7, 130.9, 132.7, 132.8, 134.9, 136.4, 142.5, 151.2 ppm; ^{19}F NMR (375 MHz, $CDCl_3$): δ = -61.1 ppm; IR ($CHCl_3$): 2226, 1614, 1524, 1489, 1395, 1329, 1116 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{24}H_{19}F_3N_2+H]^+$: m/z = 393.1573, Found: 393.1571.

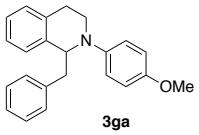
1-(2-cyanobenzyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (3gc):



3gc

Yellow oil; 18 mg, 25%; ^{1}H NMR (500 MHz, CD_3CN): δ = 2.73 (ddd, J = 4.0, 4.3, 16.8 Hz, 1H), 2.93 (ddd, J = 5.7, 10.5, 16.8 Hz, 1H), 3.24 (dd, J = 5.1, 13.7 Hz, 1H), 3.37 (dd, J = 9.1, 13.7 Hz, 1H), 3.60–3.64 (m, 4H), 3.77 (ddd, J = 4.3, 10.5, 13.9 Hz, 1H), 4.86 (dd, J = 5.1, 9.1 Hz, 1H), 6.66–6.67 (m, 4H), 7.07–7.18 (m, 4H), 7.32 (ddd, J = 1.1, 7.5, 7.9 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.53 (ddd, J = 1.1, 7.5, 7.5 Hz, 1H), 7.61 ppm (dd, J = 1.1, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.1, 41.1, 42.5, 55.6, 61.9, 113.2, 114.5, 117.4, 118.3, 125.9, 126.8, 126.8, 127.4, 128.9, 130.9, 132.4, 132.6, 135.1, 137.2, 143.6, 144.2, 152.7 ppm; IR ($CHCl_3$): 2226, 1600, 1510, 1450, 1037 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{24}H_{22}N_2O+H]^+$: m/z = 355.1805, Found: 355.1808.

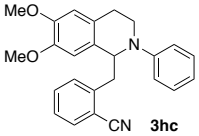
1-benzyl-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (3ga):



3ga

Yellow oil; 33 mg, 50%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.71 (ddd, J = 4.5, 5.1, 15.9 Hz, 1H), 2.94–3.02 (m, 2H), 3.20 (dd, J = 6.2, 13.3 Hz, 1H), 3.51 (ddd, J = 5.1, 5.7, 12.5 Hz, 1H), 3.61 (ddd, J = 4.5, 9.1, 12.5 Hz, 1H), 3.75 (s, 3H), 4.78 (dd, J = 6.2, 6.8 Hz, 1H), 6.74 (d, J = 7.4 Hz, 1H), 6.79–6.81 (m, 4H), 7.02–7.06 (m, 3H), 7.10–7.24 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.2, 42.1, 42.5, 55.7, 62.3, 114.7, 116.8, 125.4, 126.1, 126.4, 127.6, 128.1, 128.5, 129.7, 134.8, 137.9, 139.3, 144.3, 152.4 ppm; IR ($CHCl_3$): 1603, 1510, 1240 cm^{-1}; HRMS (ESI$^+$): Calcd. for $[C_{23}H_{23}NO+H]^+$: m/z = 330.1852, Found: 330.1855.

1-(2-cyanobenzyl)-6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3hc):

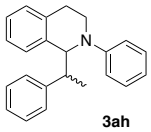


3hc

Yellow oil; 31 mg, 40%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.75 (ddd, J = 4.5, 4.5, 15.9 Hz, 1H), 3.01 (ddd, J = 5.7, 9.6, 15.9 Hz, 1H), 3.29 (dd, J = 5.7, 13.6 Hz, 1H), 3.42 (dd, J = 8.8, 13.6 Hz, 1H), 3.70–3.80 (m, 5H), 3.86 (s, 3H), 4.88 (J = 5.7, 8.8 Hz, 1H), 6.45 (s, 1H), 6.63 (s, 1H), 6.66–6.71 (m, 3H), 7.10–7.14 (m, 2H), 7.27–7.32 (m, 2H), 7.46 (dt, J = 1.1, 7.9 Hz, 1H), 7.59 ppm (dd, J = 1.1, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.1, 40.9, 41.5, 55.8 (2 C), 61.0, 110.2, 111.3, 113.2, 114.5, 117.9, 118.3, 126.8, 127.1, 128.8, 129.1, 131.1, 132.5, 132.6, 143.5, 147.0, 147.9, 149.5 ppm;

IR ($CHCl_3$): 2224, 1599, 1518, 1422, 1240, 1037 cm^{-1}; HRMS (ESI^+): Calcd. for $[C_{25}H_{24}N_2O_2+H]^+$: m/z = 385.1911, Found: 385.1904.

2-phenyl-1-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (3ah):



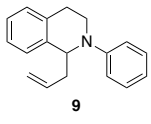
3ah

Yellow oil; 36 mg, 57%, dr = 1:1. The diastereomers were separated by Shimazu recycling preparative HPLC system [LC-20AR; column, YMC-GPC T-2000; chloroform]. However, the stereochemistries could not be determined at this time.

3ah(1): ^1H NMR (500 MHz, $CDCl_3$): δ = 1.32 (d, J = 7.4 Hz, 3H), 2.89–3.00 (m, 2H), 3.37–3.46 (m, 2H), 3.55–3.60 (m, 1H), 4.86 (d, J = 7.4 Hz, 1H), 6.66 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 7.9 Hz, 2H), 6.91 (d, J = 7.4 Hz, 1H), 7.07–7.25 ppm (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.4, 27.0, 42.8, 44.8, 64.8, 114.0, 117.0, 125.1, 126.2, 126.7, 128.0, 128.4, 128.7, 128.9, 135.5, 136.7, 144.2, 149.9 ppm; IR ($CHCl_3$): 1597, 1503, 1393, 1323, 908 cm^{-1}; HRMS (ESI^+): Calcd. for $[C_{22}H_{21}N+H]^+$: m/z = 314.1903, Found: 314.1900.

3ah(2): ^1H NMR (500 MHz, $CDCl_3$): δ = 1.44 (d, J = 7.4 Hz, 3H), 2.05 (ddd, J = 6.2, 9.1, 15.7 Hz, 1H), 2.67 (ddd, J = 5.1, 5.7, 15.7 Hz, 1H), 3.32–3.41 (m, 2H), 3.59–3.64 (m, 1H), 4.79 (d, J = 6.8 Hz, 1H), 6.60 (d, J = 7.9 Hz, 1H), 6.74 (t, J = 6.8 Hz, 1H), 6.86 (d, J = 7.9 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 6.94–6.97 (m, 1H), 6.99 (d, J = 7.9 Hz, 1H), 7.09–7.12 (m, 1H), 7.14–7.21 (m, 3H), 7.27–7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.6, 27.1, 43.0, 45.6, 64.9, 112.8, 116.6, 124.9, 126.5, 126.7, 127.7, 127.7, 127.9, 128.3, 128.8, 129.3, 135.9, 143.7, 149.5 ppm; IR ($CHCl_3$): 1597, 1504, 1395, 1327 cm^{-1}; HRMS (ESI^+): Calcd. for $[C_{22}H_{21}N+H]^+$: m/z = 314.1903, Found: 300.1904.

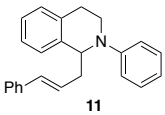
1-allyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (9):



9

Yellow oil; 31 mg, 62%; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.46–2.53 (m, 1H), 2.70–2.78 (m, 1H), 2.88 (dt, J = 5.7, 15.9 Hz, 1H), 3.03 (ddd, J = 5.7, 8.5, 15.9 Hz, 1H), 3.57–3.68 (m, 2H), 4.75 (t, J = 6.8 Hz, 1H), 5.04–5.09 (m, 2H), 5.81–5.91 (m, 1H), 6.74 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 8.5 Hz, 2H), 7.11–7.18 (m, 4H), 7.22–7.26 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.4, 40.9, 41.9, 59.3, 113.9, 117.0, 117.2, 125.7, 126.5, 127.3, 128.5, 129.2, 135.0, 135.7, 138.2, 149.5 ppm; IR ($CHCl_3$): 1599, 1491, 1447, 1383, 1350, 1263 cm^{-1}; HRMS (ESI^+): Calcd. for $[C_{18}H_{19}N+H]^+$: m/z = 250.1590, Found: 250.1590.

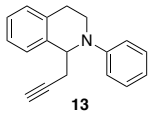
1-cinnamyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (11):



11

Yellow oil; 25 mg, 38%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.62–2.69 (m, 1H), 2.86–2.95 (m, 2H), 3.02–3.08 (m, 1H), 3.56–3.70 (m, 2H), 4.83 (t, J = 6.8 Hz, 1H), 6.19–6.24 (m, 1H), 6.40 (t, J = 15.9 Hz, 1H), 6.75 (t, J = 7.4 Hz), 6.93 (d, J = 7.9 Hz, 2H), 7.14–7.22 (m, 6H), 7.22–7.29 ppm (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.6, 40.1, 42.0, 59.8, 114.0, 117.3, 125.8, 126.1, 126.6, 127.0, 127.3, 127.4, 128.5, 128.5, 129.3, 132.0, 135.0, 137.6, 138.0, 149.5 ppm; IR ($CHCl_3$): 2924, 1597, 1504, 1393, 1329, 1261 cm^{-1}; HRMS (ESI^{+}): Calcd. for $[C_{24}H_{23}N+H]^{+}$: m/z = 326.1903, Found: 326.1900.

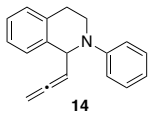
2-phenyl-1-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (13):



13

Yellow oil; 22 mg, 44%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.05 (t, J = 2.9 Hz, 1H), 2.58 (ddd, J = 2.9, 7.7, 17.0 Hz, 1H), 2.84 (ddd, J = 2.9, 5.4, 17.0 Hz, 1H), 2.93 (dt, J = 5.2, 5.7, 15.7 Hz, 1H), 3.05 (ddd, J = 5.2, 7.6, 15.7 Hz, 1H), 3.54–3.58 (m, 1H), 3.64 (ddd, J = 5.2, 7.6, 12.2 Hz, 1H), 4.91 (dd, J = 5.4, 7.7 Hz, 1H), 6.78 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 8.0 Hz, 2H), 7.16–7.22 (m, 3H), 7.26–7.33 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.0, 27.8, 42.1, 58.6, 70.9, 82.0, 114.0, 117.8, 125.9, 127.1, 127.6, 128.3, 129.3, 134.8, 136.9, 149.0 ppm; IR ($CHCl_3$): 2253, 1599, 1474, 1452, 1393, 1265 cm^{-1}; HRMS (ESI^{+}): Calcd. for $[C_{18}H_{17}N+H]^{+}$: m/z = 248.1434, Found: 248.1432.

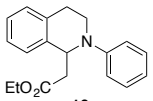
2-phenyl-1-(propa-1,2-dien-1-yl)-1,2,3,4-tetrahydroisoquinoline (14):



14

Yellow oil; 11 mg, 22%; ^{1}H NMR (500 MHz, CD_3CN): δ = 2.90 (ddd, J = 4.5, 5.4, 16.0 Hz, 1H), 3.00 (ddd, J = 5.7, 8.9, 16.0 Hz, 1H), 3.48 (ddd, J = 4.5, 8.9, 12.3 Hz, 1H), 3.64 (ddd, J = 5.4, 5.7, 12.3 Hz, 1H), 4.65–4.73(m, 2H), 5.33 (ddd, J = 6.5, 6.5, 6.8 Hz, 1H), 5.38–5.43 (m, 1H), 6.74 (t, J =7.4 Hz, 1H), 6.95 (d, J = 7.9 Hz, 2H), 7.18–7.25 ppm (m, 6H); ^{13}C NMR (125 MHz, CD_3CN): δ = 29.0, 42.7, 59.1, 77.1, 93.0, 115.8, 118.8, 126.8, 127.8, 128.6, 129.4, 130.0, 136.1, 138.0, 150.3, 209.5 ppm; IR ($CHCl_3$): 1952, 1597, 1504, 1389 cm^{-1}; HRMS (ESI^{+}): Calcd. for $[C_{18}H_{17}N+H]^{+}$: m/z = 248.1434, Found: 248.1436.

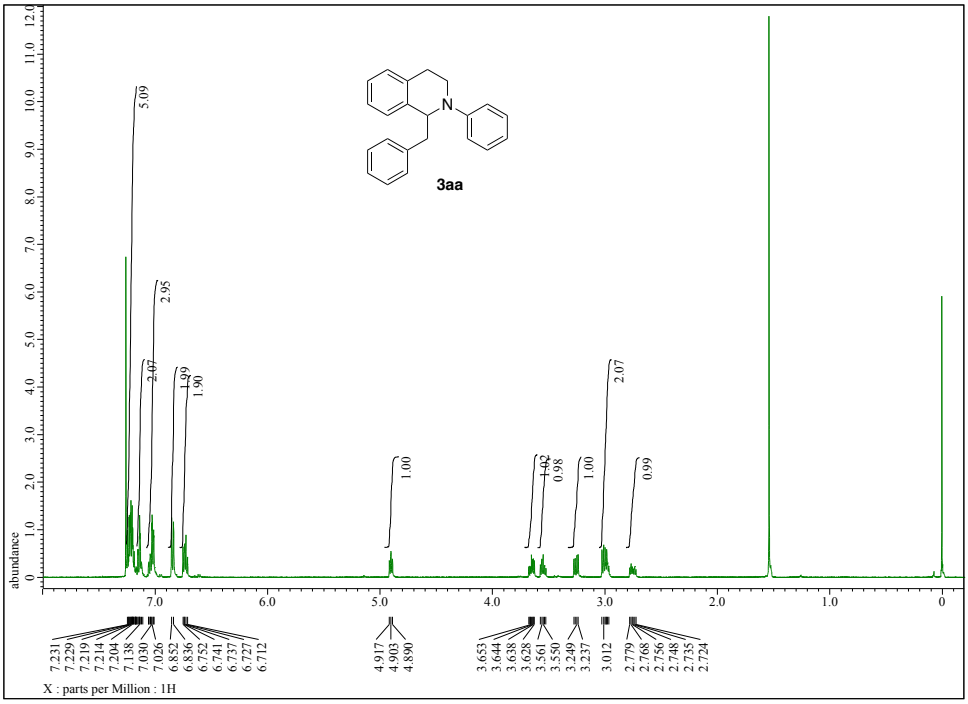
1-ethyl acetyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (16):

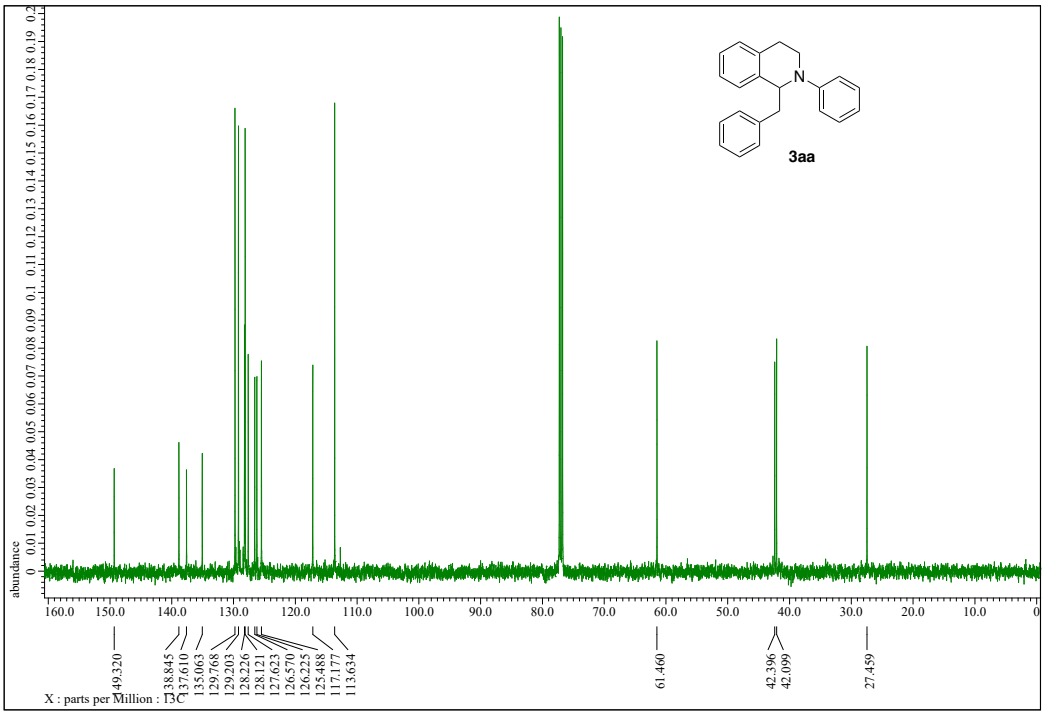


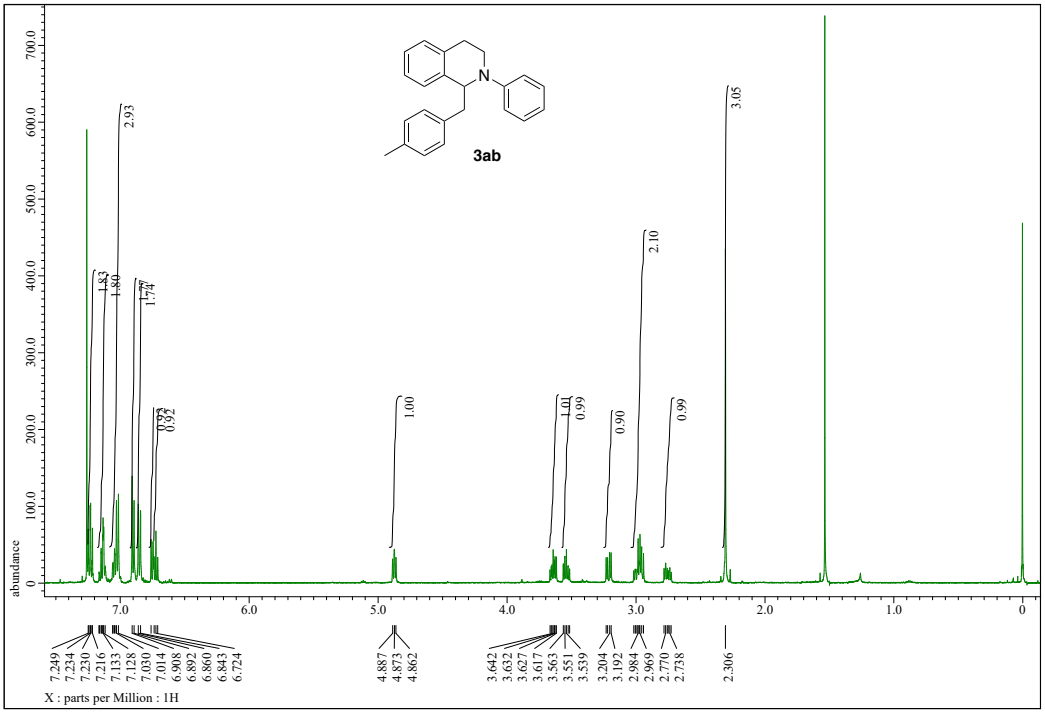
16

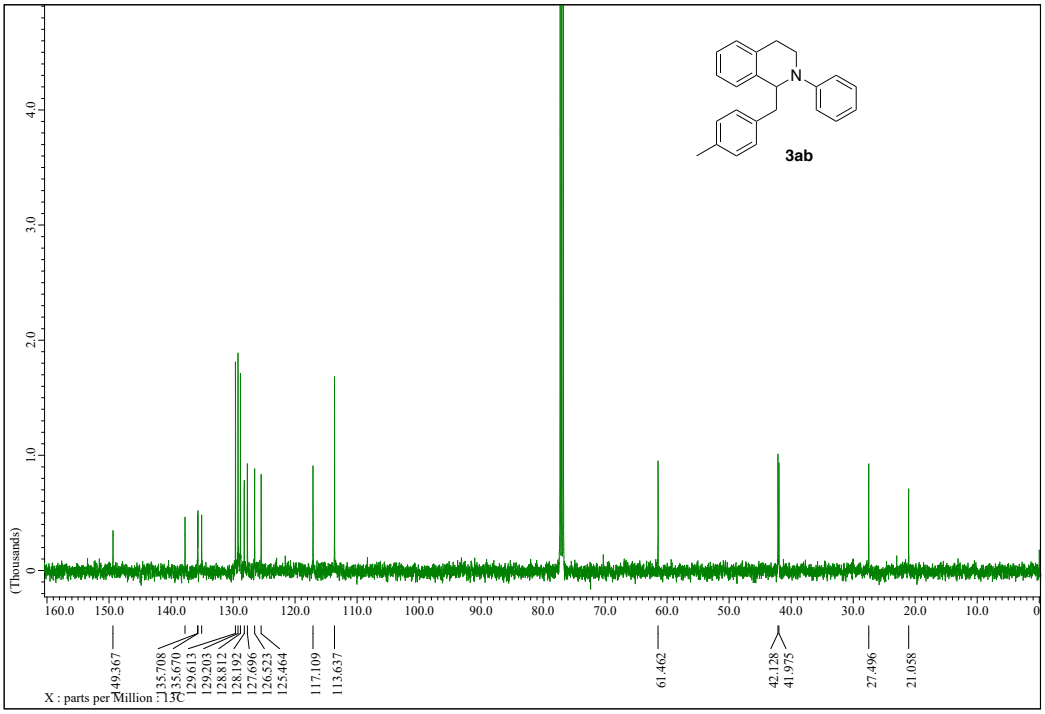
Yellow oil; 25 mg, 42%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (t, J = 6.9 Hz, 3H), 2.68 (dd, J = 6.9, 14.9 Hz, 1H), 2.82 (ddd, J = 4.6, 5.2, 15.9 Hz, 1H), 2.96 (dd, J = 6.9, 14.9 Hz, 1H), 3.07 (ddd, J = 5.7, 9.2, 15.9 Hz, 1H), 3.58 (ddd, J = 4.6, 9.2, 12.7 Hz, 1H), 3.65 (ddd, J = 5.2, 5.7, 12.7 Hz, 1H), 4.09 (q, J = 6.9 Hz, 2H), 5.34 (dd, J = 6.9, 6.9 Hz, 1H), 6.77 (t, J = 7.2 Hz, 1H), 6.98 (d, J = 8.0 Hz, 2H), 7.11–7.20 (m, 4H), 7.22–7.26 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 27.0, 41.6, 41.6, 56.2, 60.6, 114.7, 118.1, 126.1, 126.8, 127.0, 128.8, 129.3, 134.7, 137.6, 149.0, 171.5 ppm; IR ($CHCl_3$): 1663, 1510, 1483 cm^{-1}; HRMS (ESI^{+}): Calcd. for $[C_{19}H_{21}N+H]^{+}$: m/z = 296.1645, Found: 296.1643.

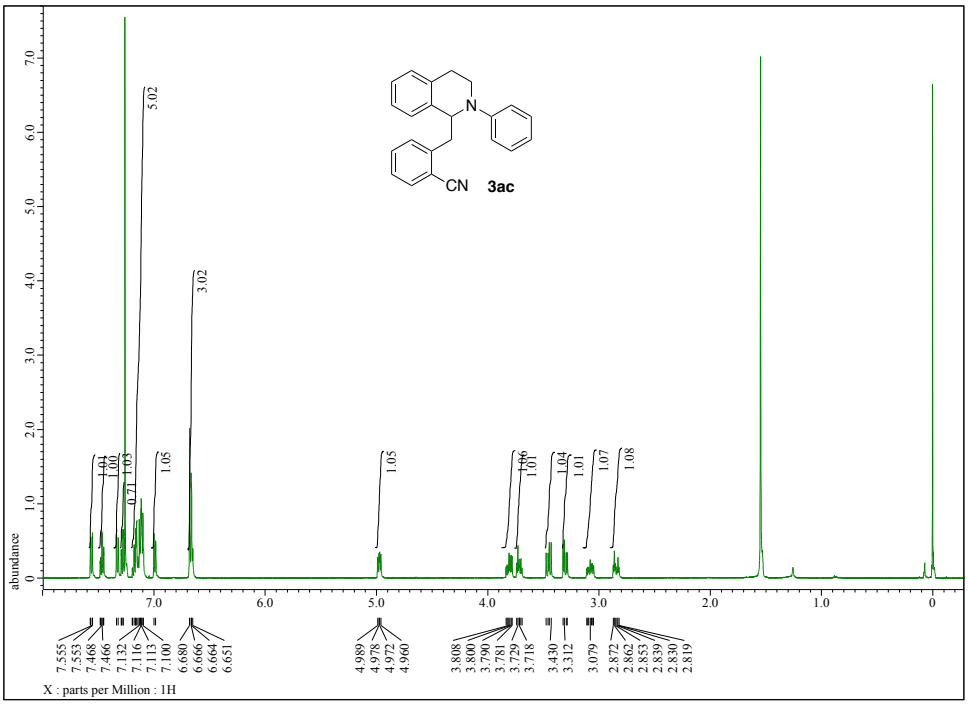
3. NMR spectra

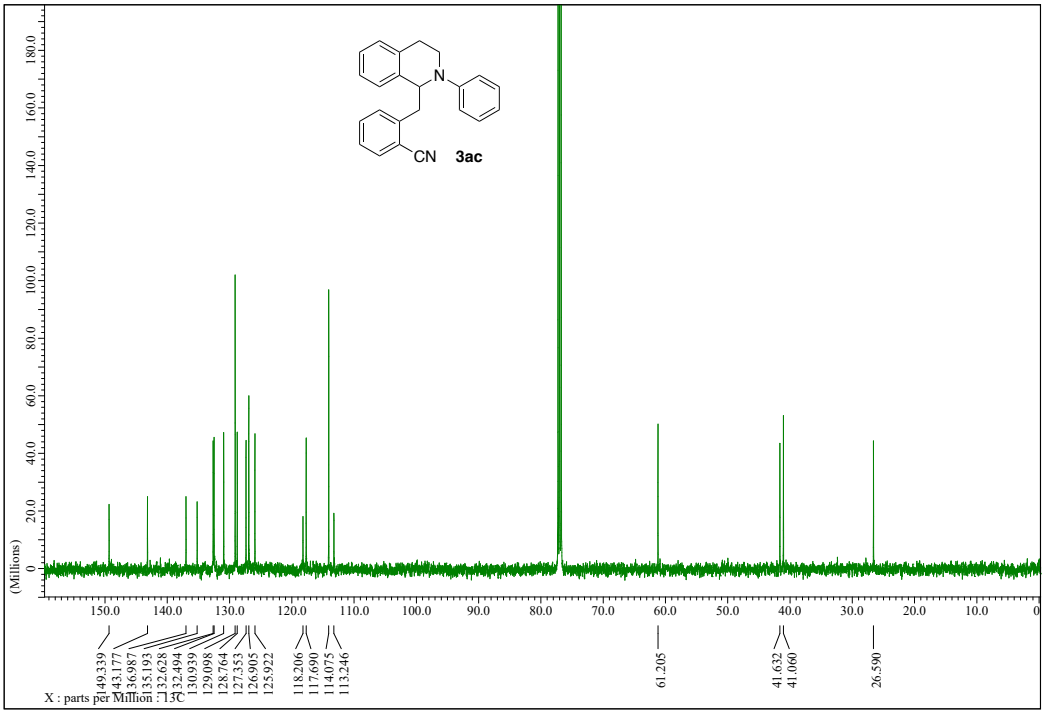


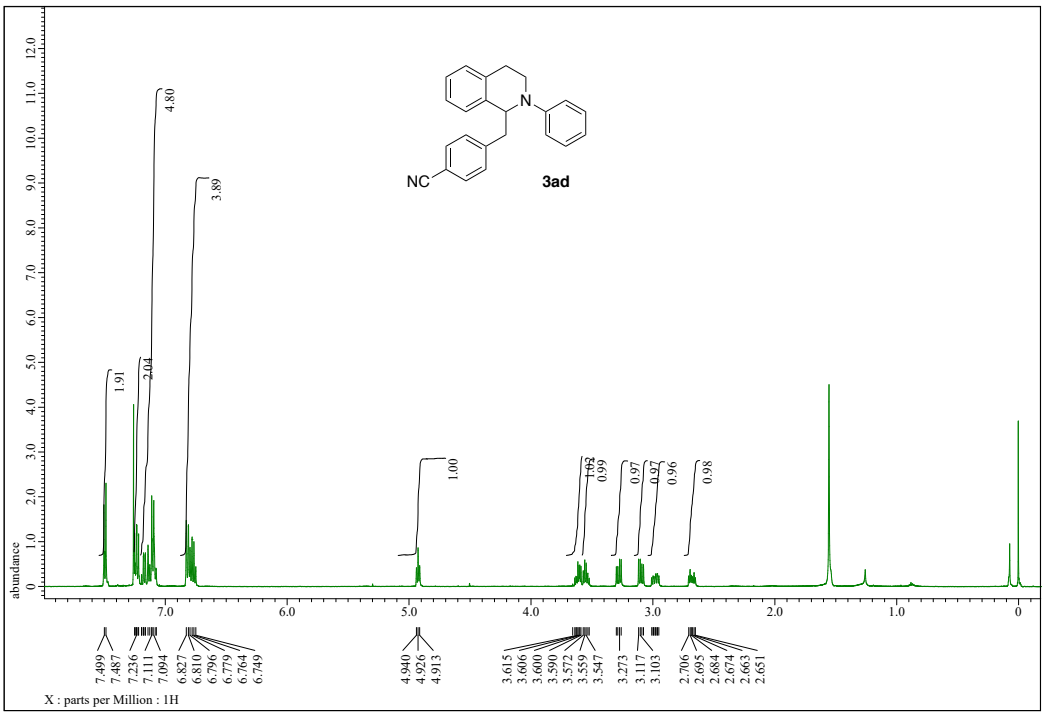



3ab
abundance
X : parts per Million : 1H


3ab
(Thousands)
X : parts per Million : 13C


CN 3ac
abundance
X : parts per Million : 1H


CN 3ac
(Millions)
X : parts per Million : 13C


abundance
4.80
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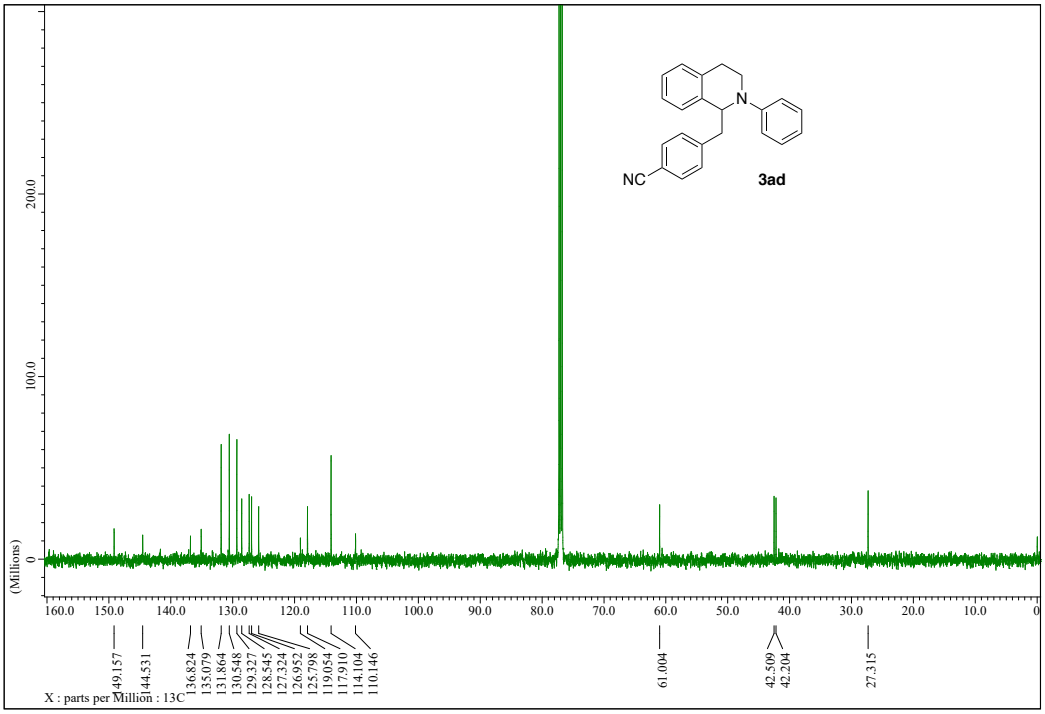
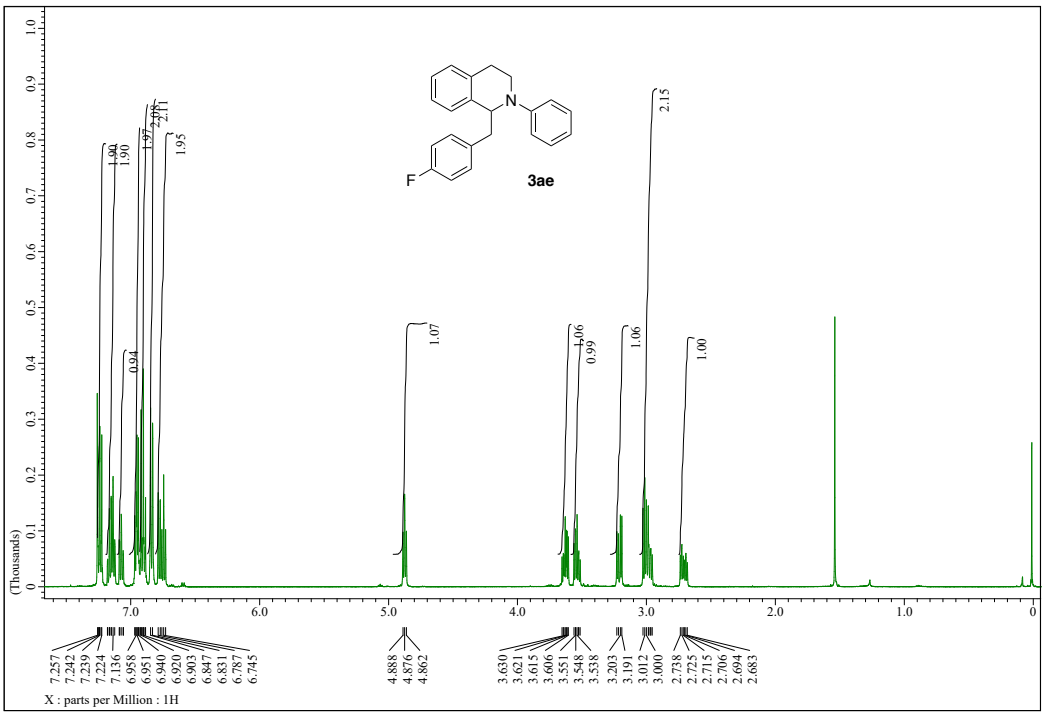
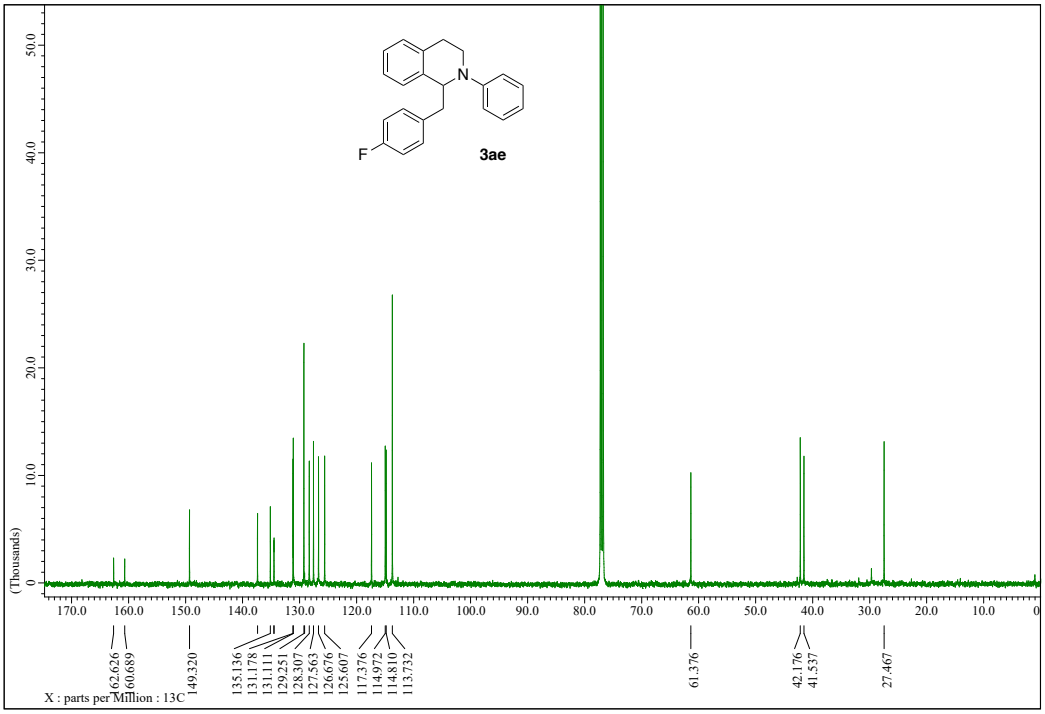
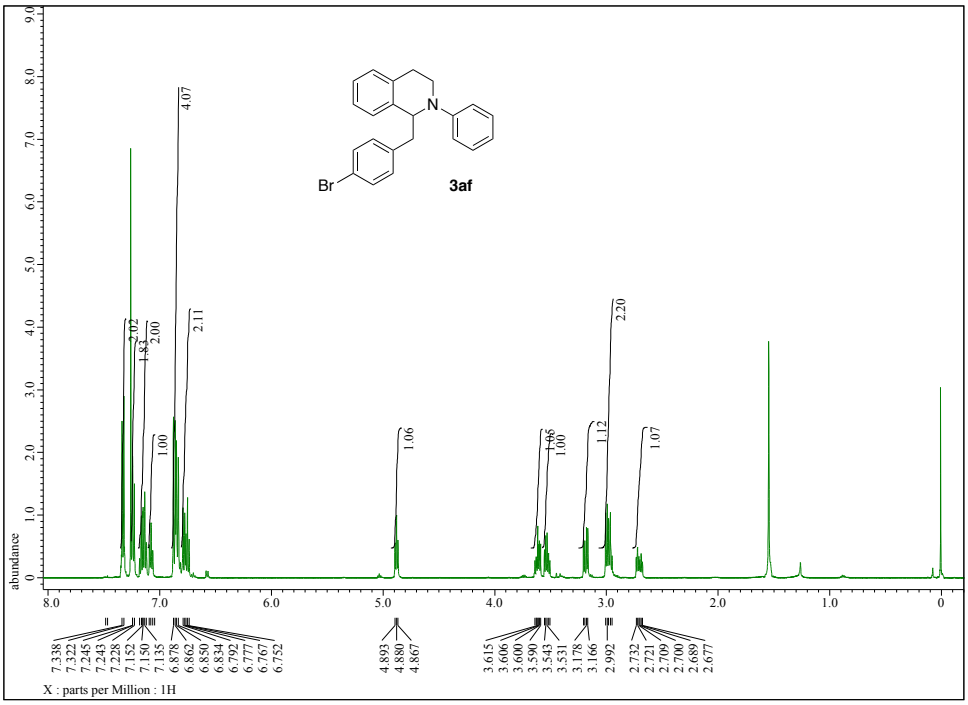
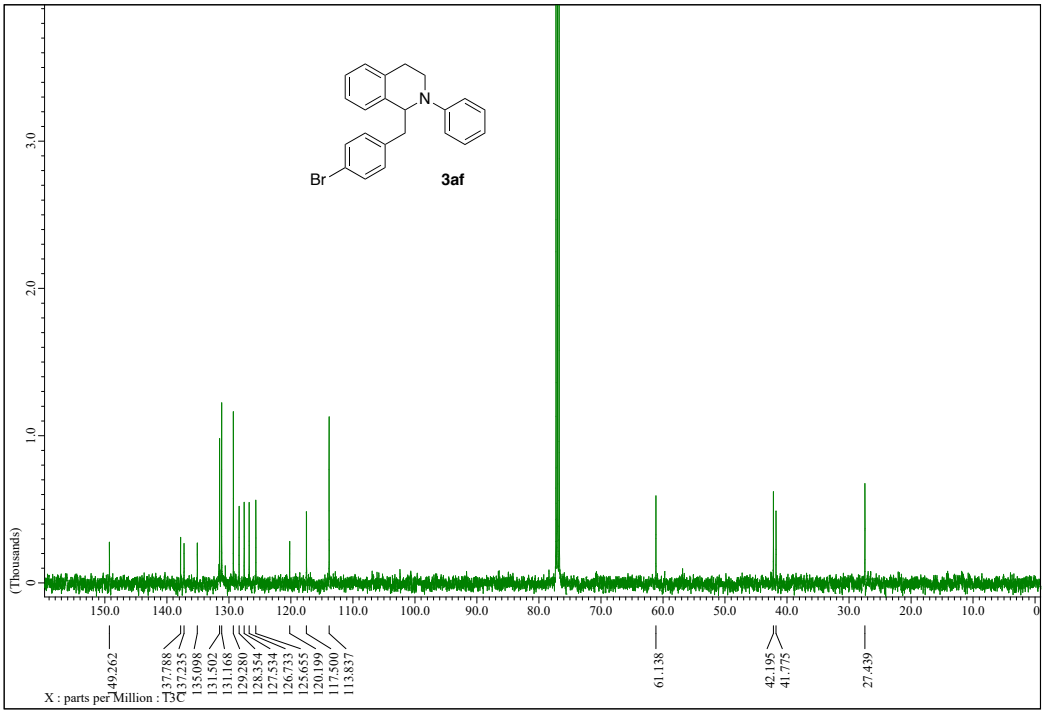
2.04
1.91
1.00
1.03
0.99
0.97
0.97
0.96
0.98
7.499
7.487
7.236
7.111
7.094
6.827
6.810
6.796
6.779
6.764
6.749
4.940
4.926
4.913
3.615
3.606
3.600
3.590
3.572
3.559
3.547
3.273
3.117
3.103
2.706
2.695
2.684
2.674
2.663
2.651
NC
3ad
X : parts per Million : 1H

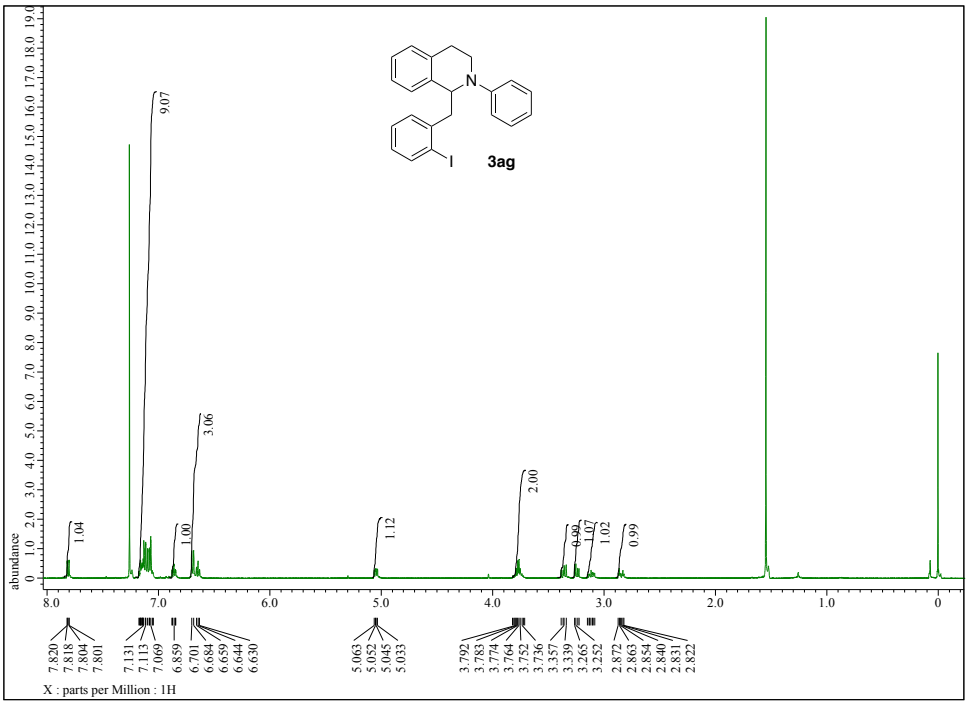

(Millions)
149.157
144.531
136.824
135.079
131.864
130.548
129.327
128.545
127.324
126.952
125.798
119.054
117.910
114.104
110.146
61.004
42.509
42.204
27.315
NC
3ad
X : parts per Million : 13C

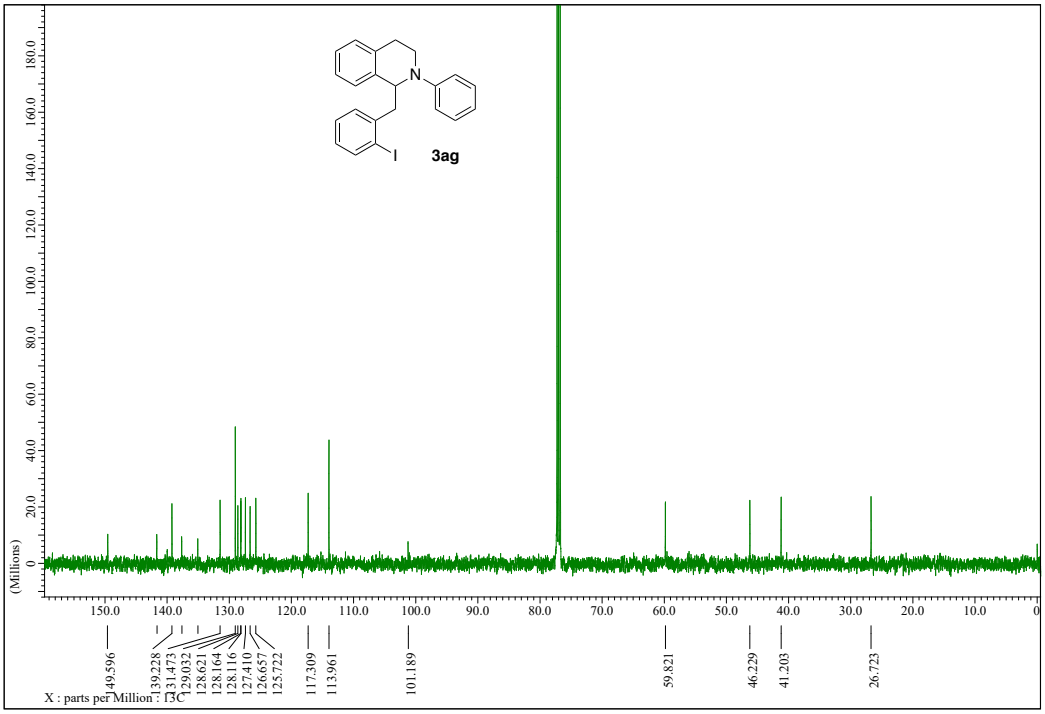

3ae
F
N
(Thousands)
X : parts per Million : 1H

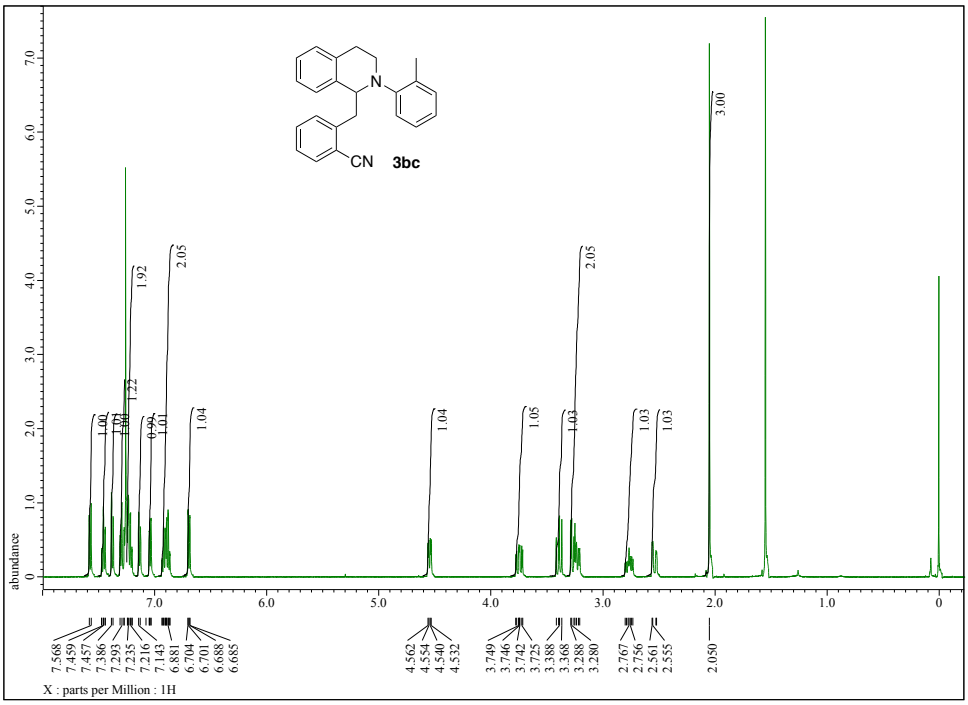

3ae
F
N
(Thousands)
X : parts per Million : 13C

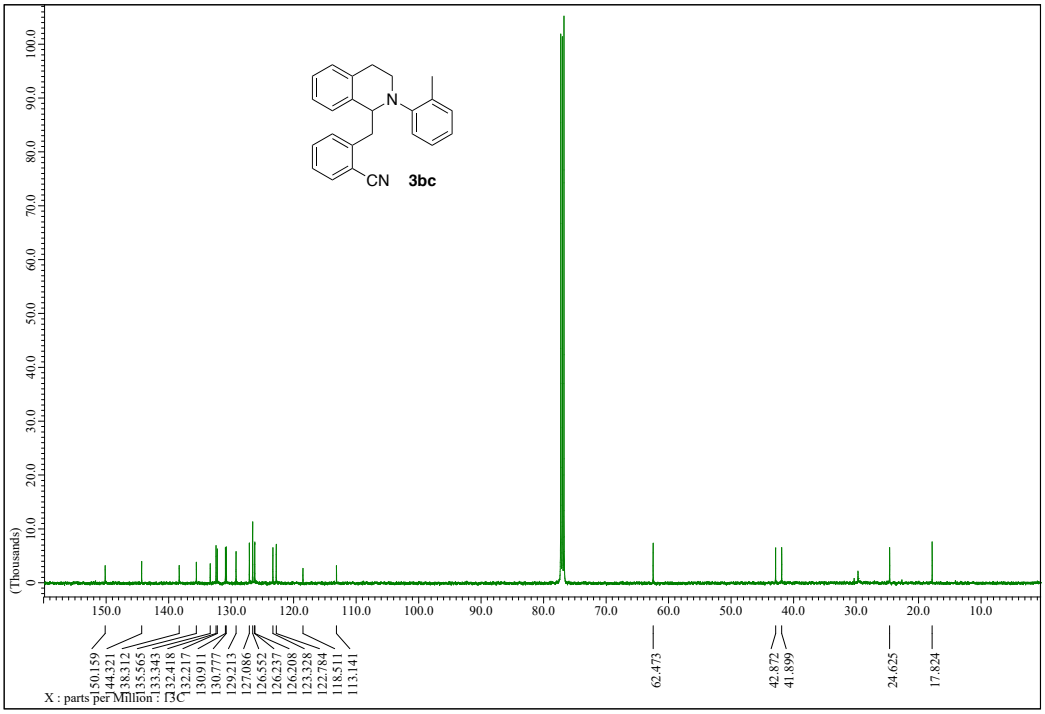

Br
N
3af
abundance
X : parts per Million : 1H

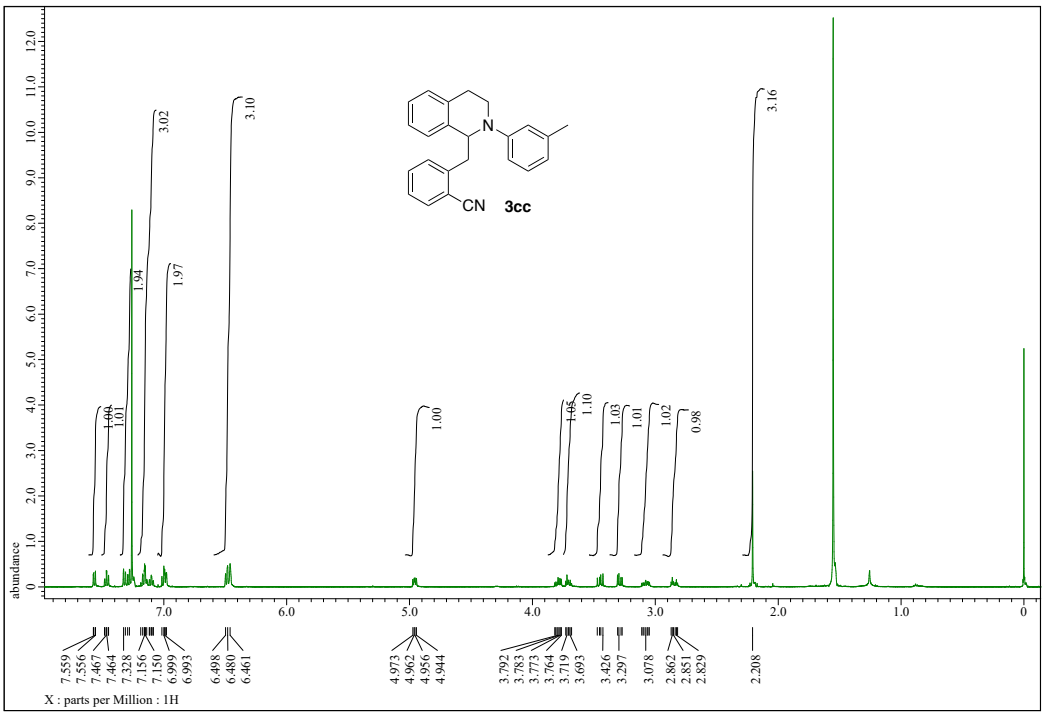

Br
N
3af
(Thousands)
X : parts per Million : 13C

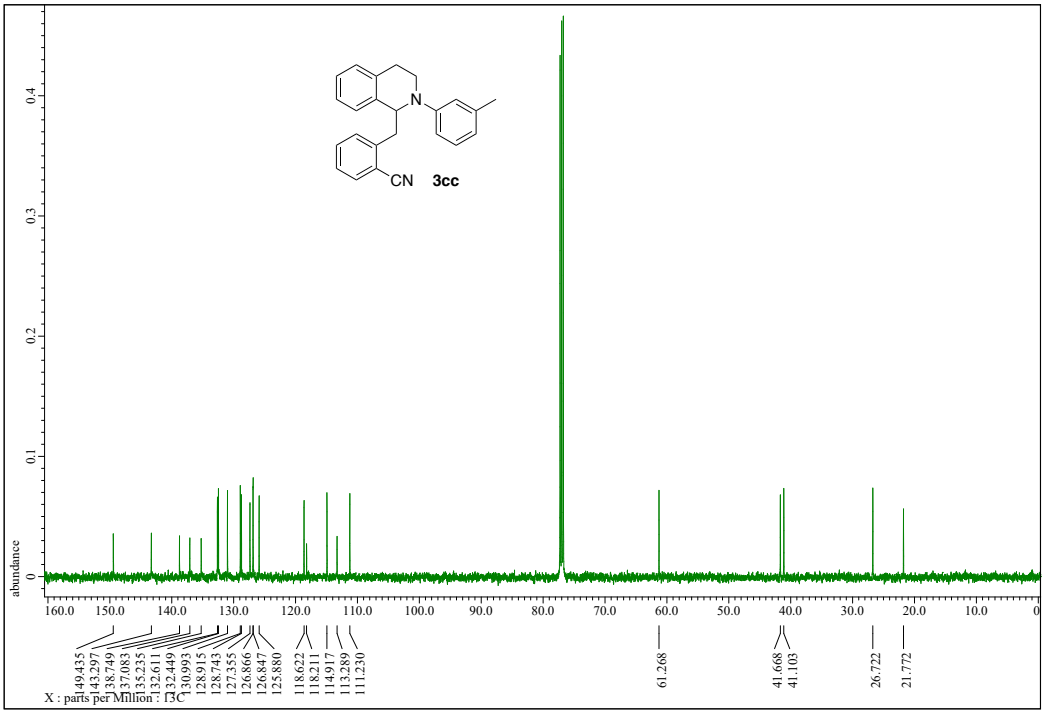

3ag
abundance
X : parts per Million : 1H

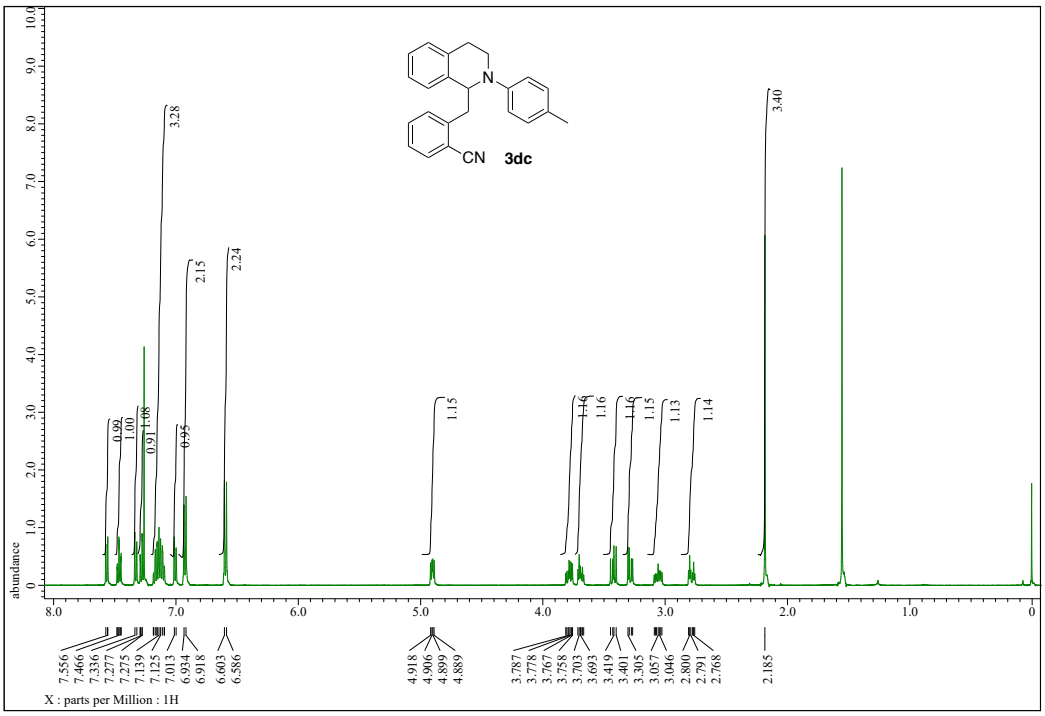

3ag
(Millions)
X : parts per Million : 13

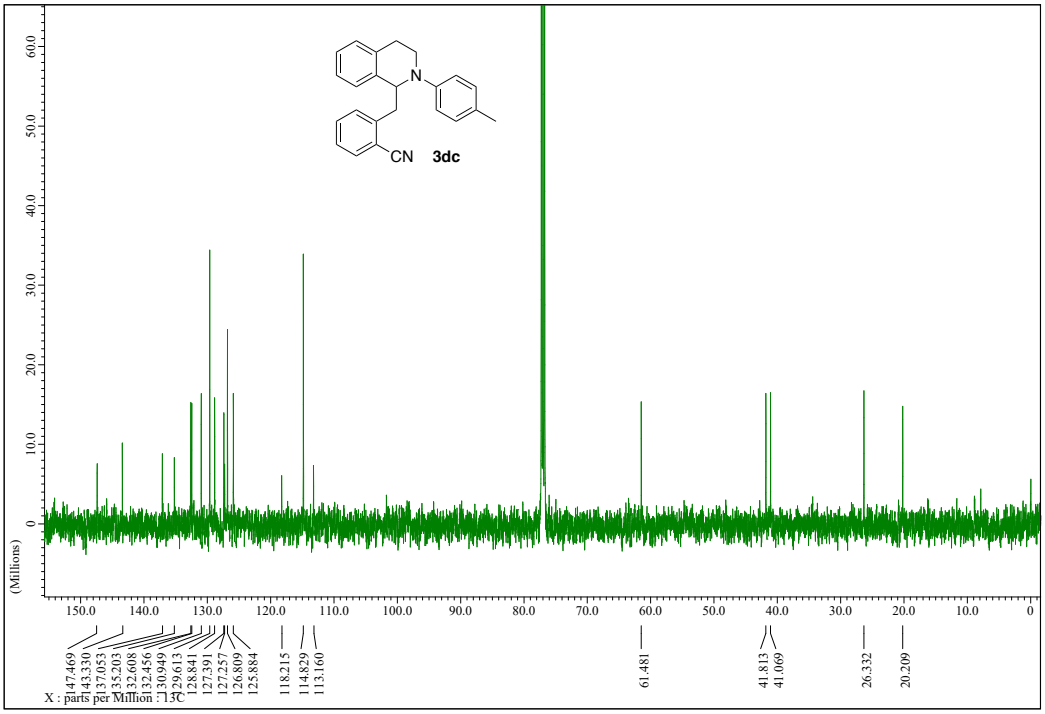

CN 3bc
abundance
X : parts per Million : 1H

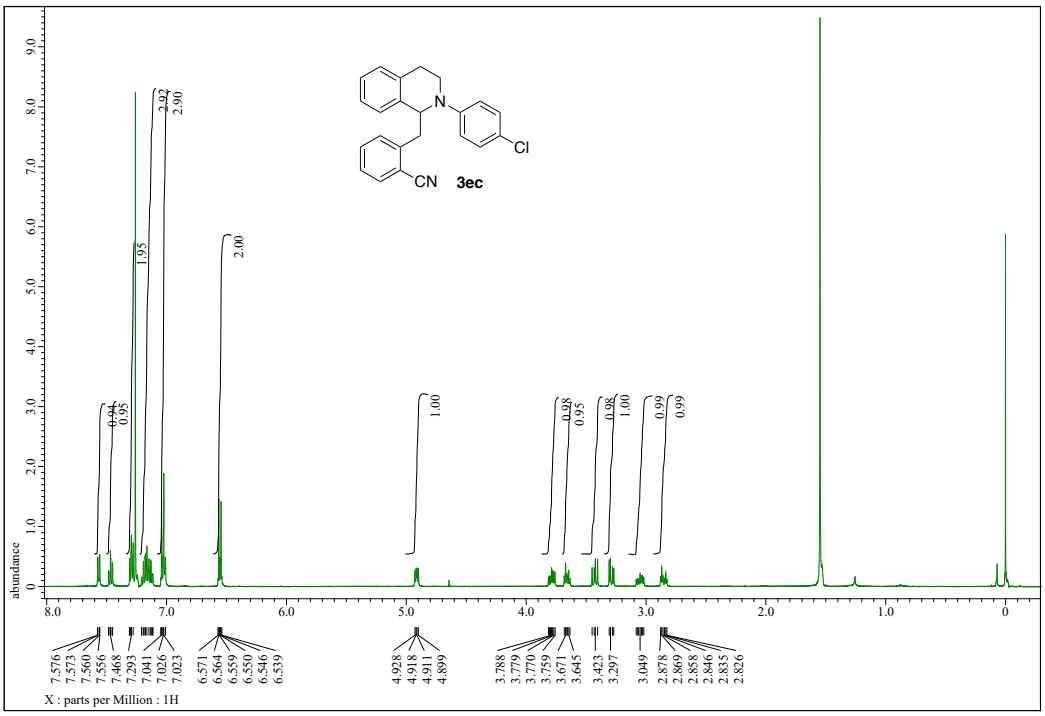

CN 3bc
(Thousands)
X : parts per Million : 13C

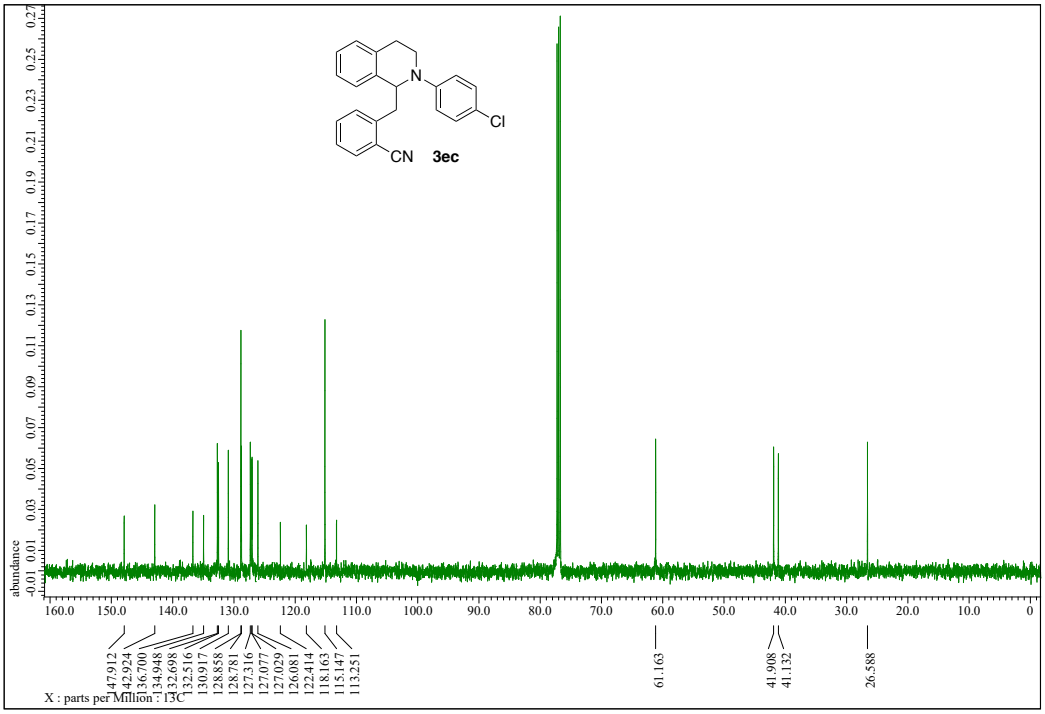

abundance
CN 3cc
3.16
3.10
3.02
1.97
1.94
1.00
1.01
1.00
1.05
1.10
1.03
1.01
1.02
0.98
7.559
7.556
7.467
7.464
7.328
7.156
7.150
6.999
6.993
6.498
6.480
6.461
4.973
4.962
4.956
4.944
3.792
3.783
3.773
3.764
3.719
3.693
3.426
3.297
3.078
2.862
2.851
2.829
2.208
X : parts per Million : 1H

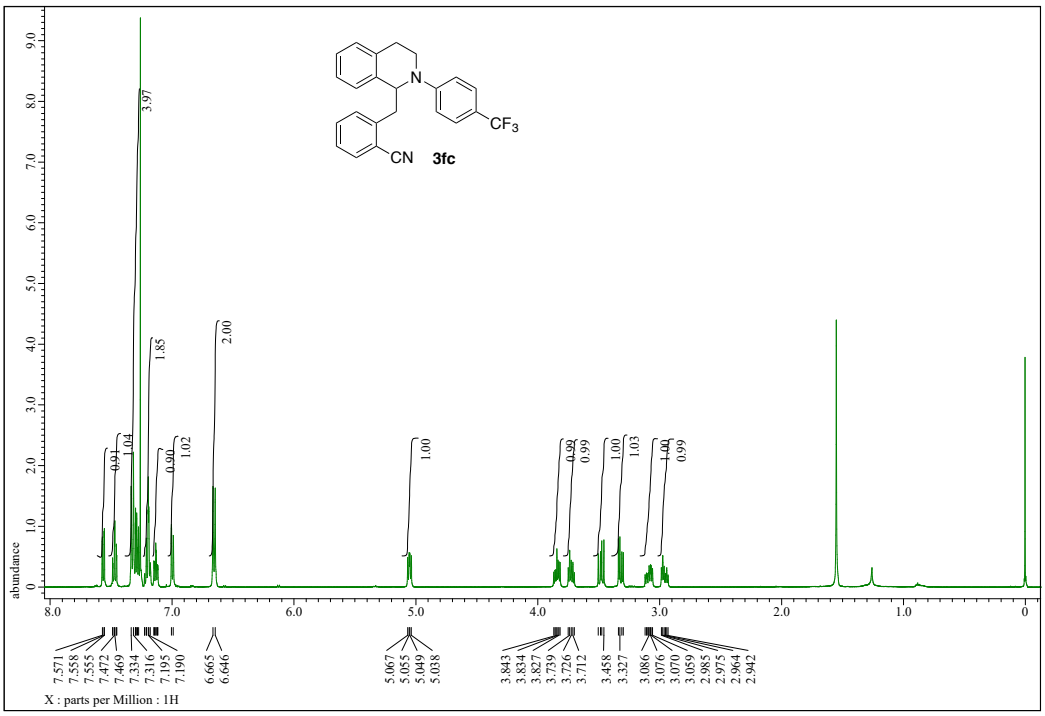

abundance
CN 3cc
149.435
143.297
138.749
137.083
135.235
132.611
132.449
130.993
128.915
128.743
127.355
126.866
126.847
125.880
118.622
118.211
114.917
113.289
111.230
61.268
41.668
41.103
26.722
21.772
X : parts per Million : 13C

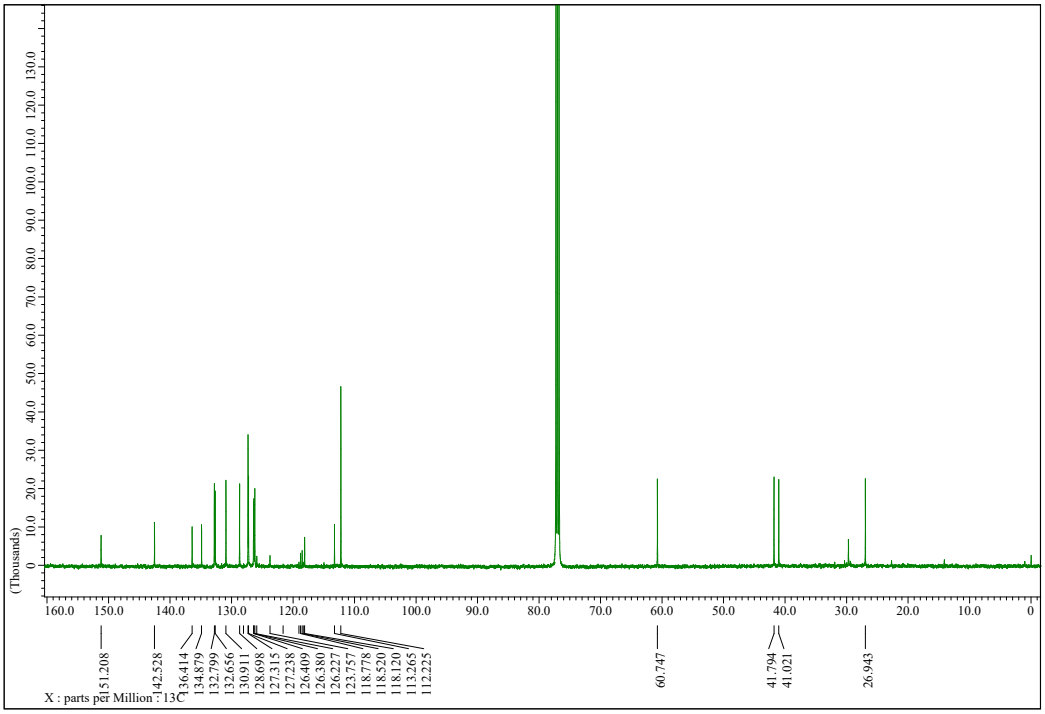

3dc
CN
abundance
X : parts per Million : 1H

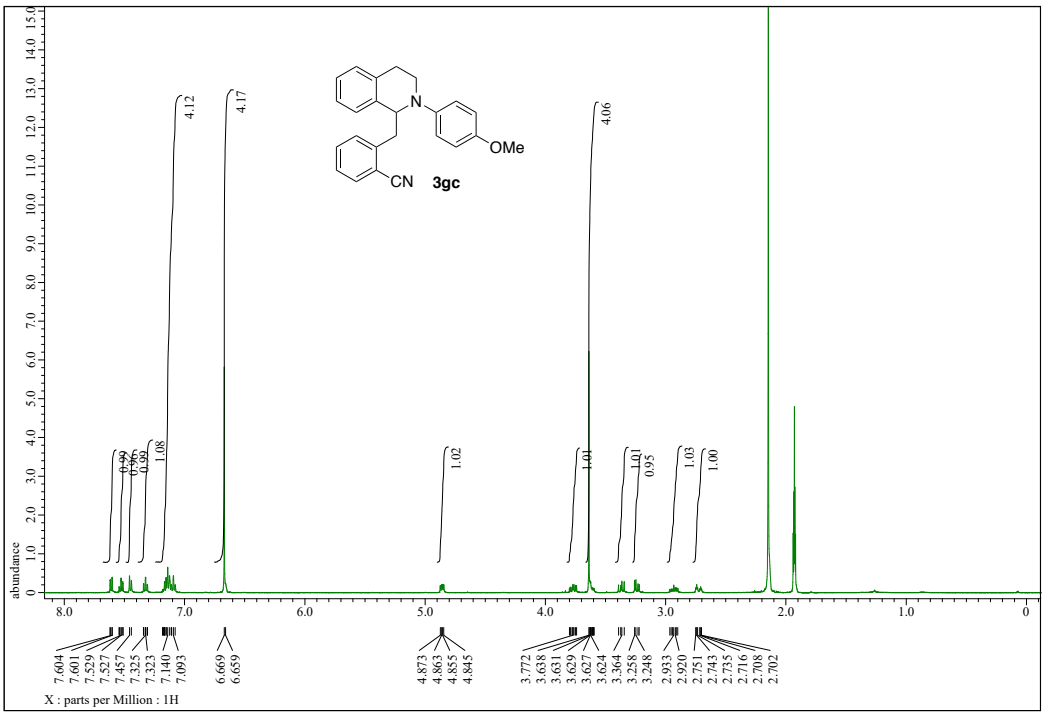

3dc
CN
(Millions)
X : parts per Million : 13C

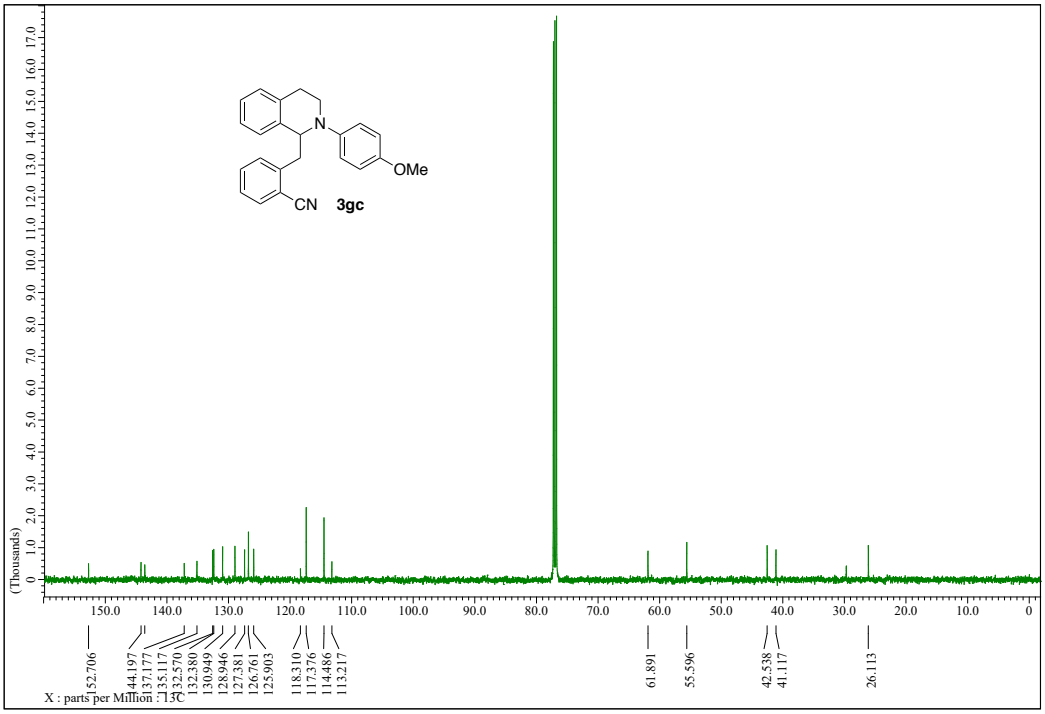

N
Cl
CN
3ec
abundance
X : parts per Million : 1H

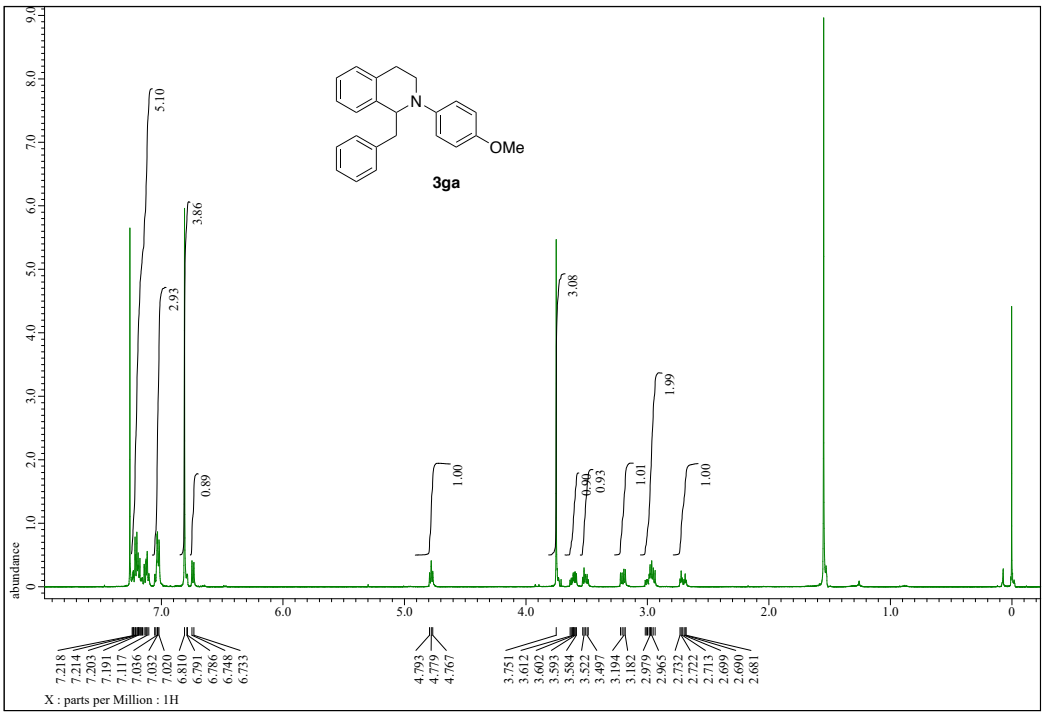

N
Cl
CN
3ec
abundance
X : parts per Million : 13C

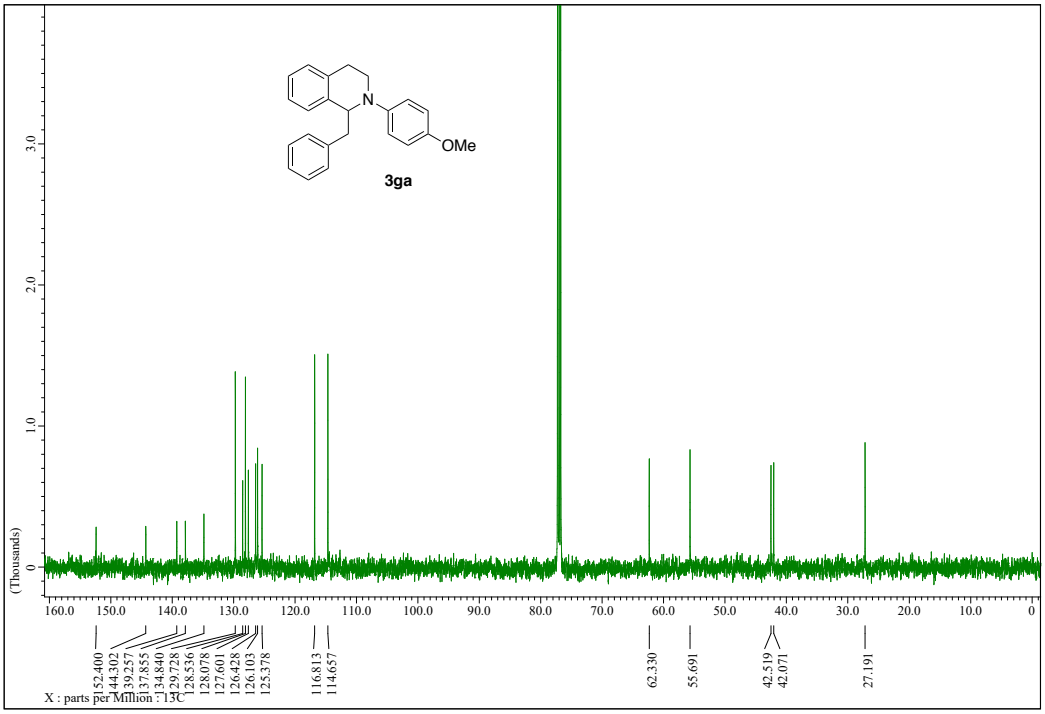

N
CF3
CN
3fc
abundance
3.97
1.85
2.00
0.91
1.04
0.90
1.02
1.00
0.98
0.99
1.00
1.03
1.00
0.99
7.571
7.558
7.555
7.472
7.469
7.334
7.316
7.195
7.190
6.665
6.646
5.067
5.055
5.049
5.038
3.843
3.834
3.827
3.739
3.726
3.712
3.458
3.327
3.086
3.076
3.070
3.059
2.985
2.975
2.964
2.942
X : parts per Million : 1H

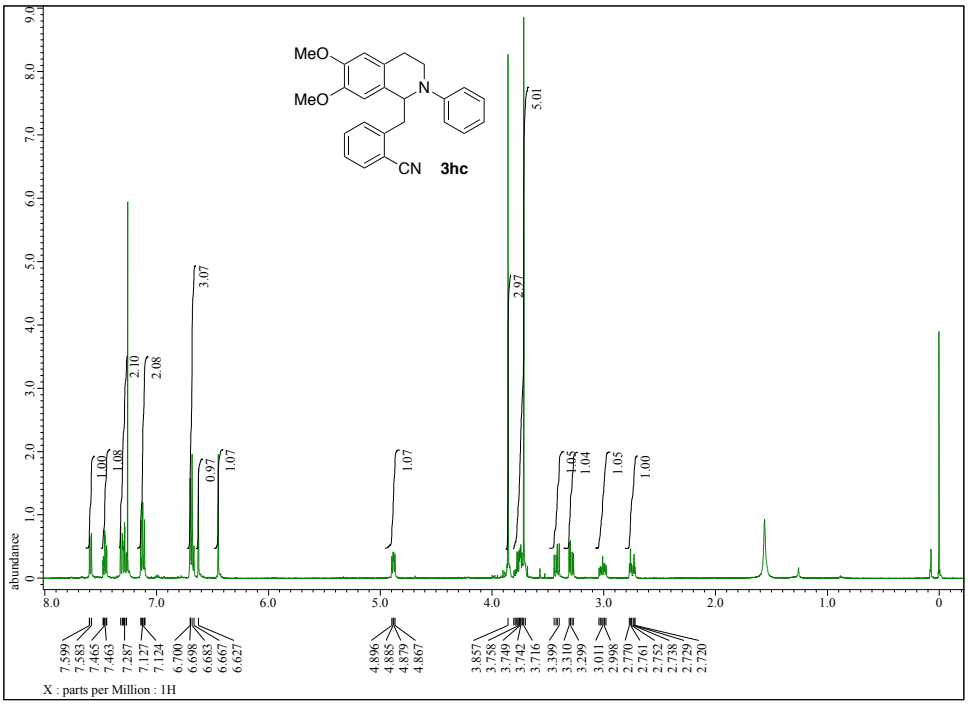

(Thousands)
151.208
142.528
136.414
134.879
132.799
132.656
130.911
128.698
127.315
127.238
126.409
126.380
126.227
123.757
118.778
118.520
118.120
113.265
112.225
60.747
41.794
41.021
26.943
X : parts per Million : 13C

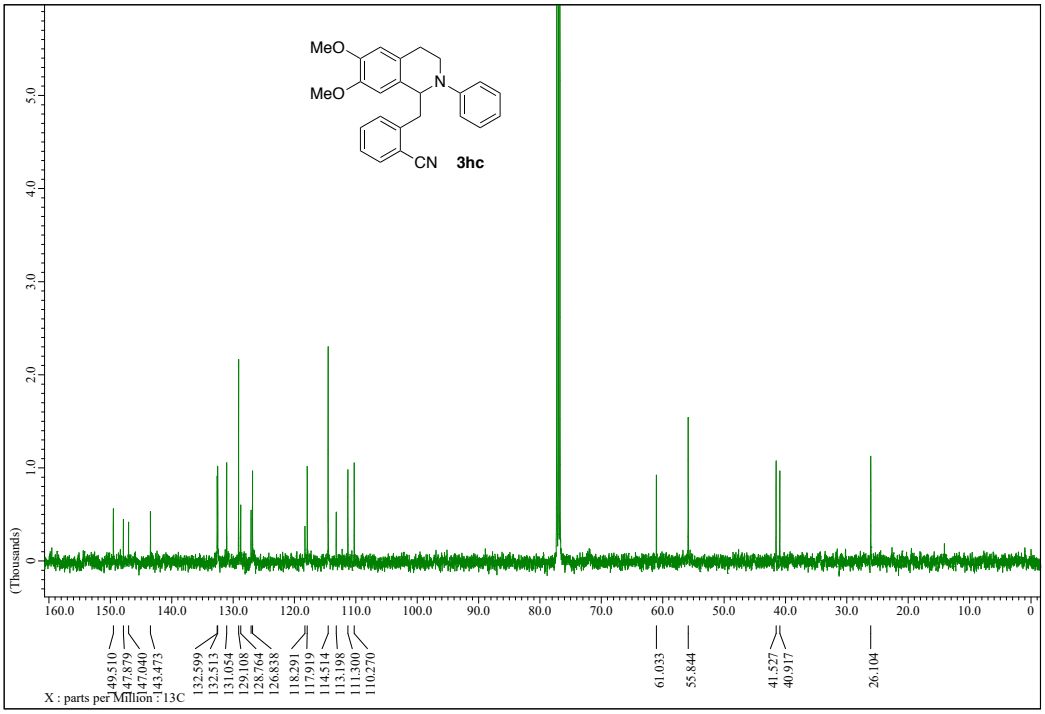

abundance
4.12
4.17
4.06
1.02
1.01
1.08
1.03
1.00
0.95
0.99
0.96
0.92
OMe
CN
3gc
7.604
7.601
7.529
7.527
7.457
7.325
7.323
7.140
7.093
6.669
6.659
4.873
4.863
4.855
4.845
3.772
3.638
3.631
3.629
3.627
3.624
3.364
3.258
3.248
2.933
2.920
2.751
2.743
2.735
2.716
2.708
2.702
X : parts per Million : 1H

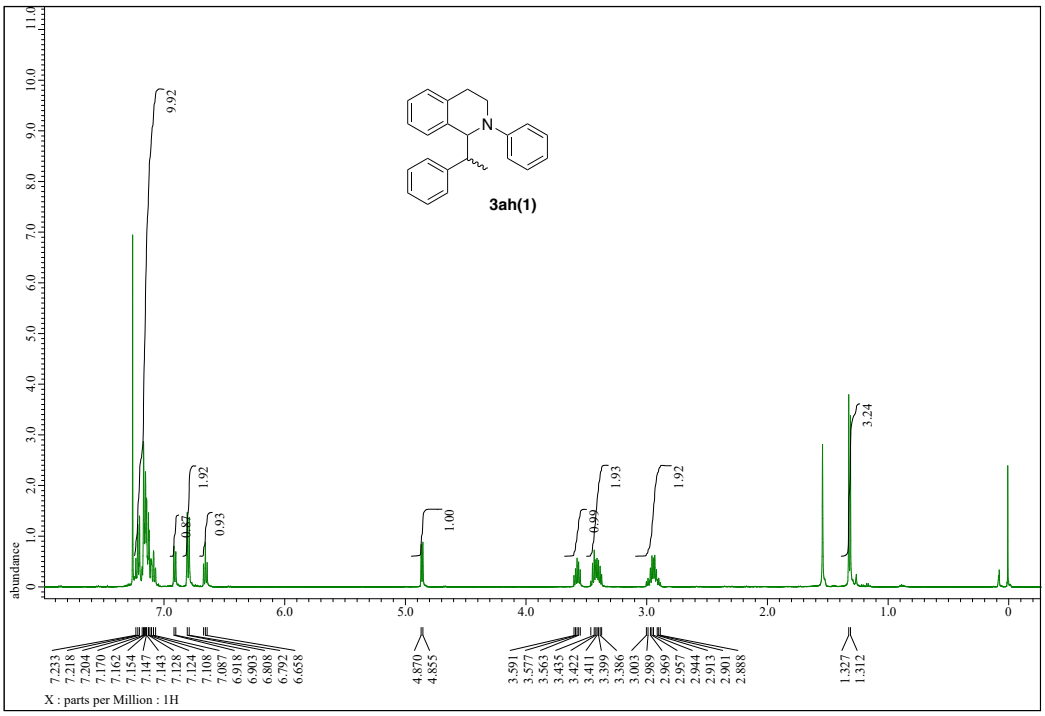

(Thousands)
OMe
CN
3gc
152.706
144.197
137.177
135.117
132.570
132.380
130.949
128.946
127.381
126.761
125.903
118.310
117.376
114.486
113.217
61.891
55.596
42.538
41.117
26.113
X : parts per Million : 13C

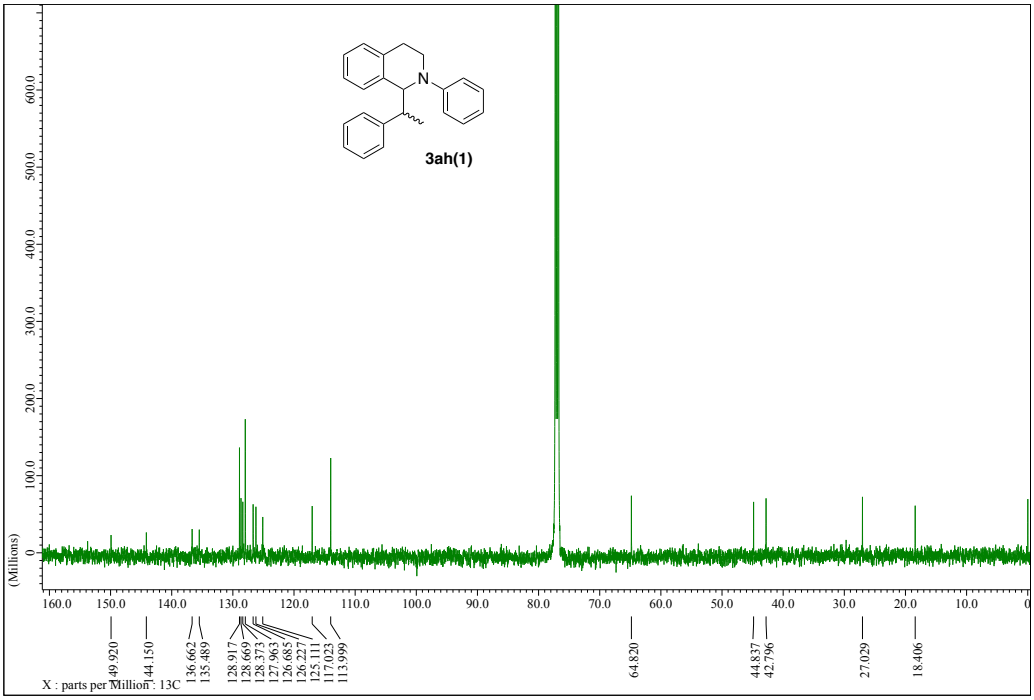

3ga
OMe
N
abundance
X : parts per Million : 1H

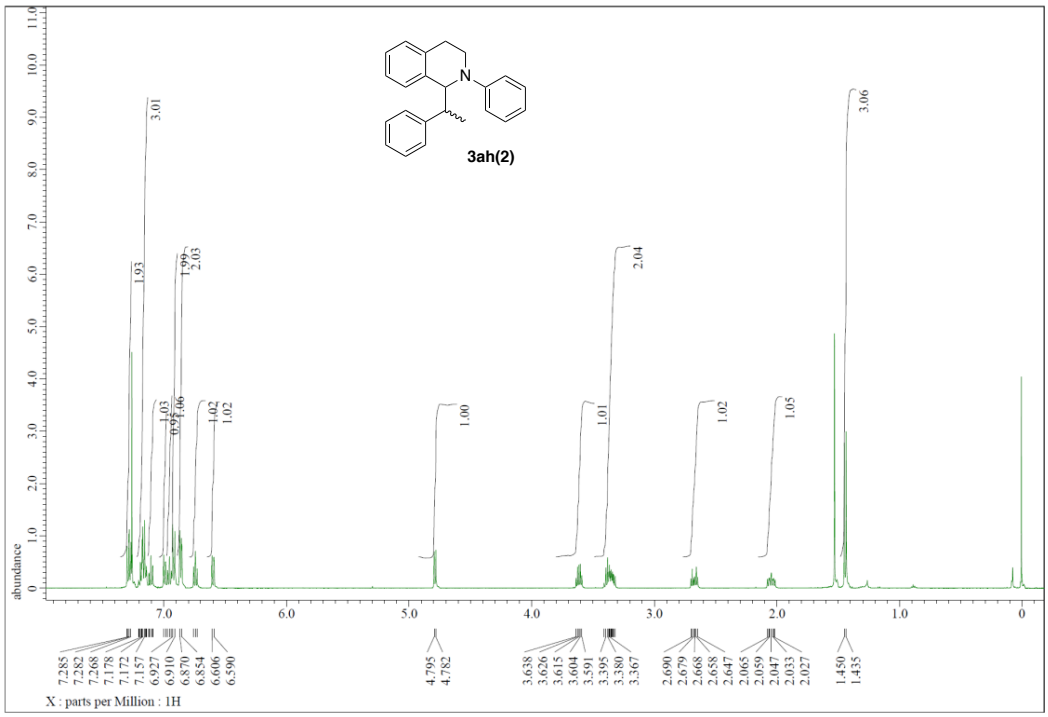

3ga
OMe
N
(Thousands)
X : parts per Million : 13C

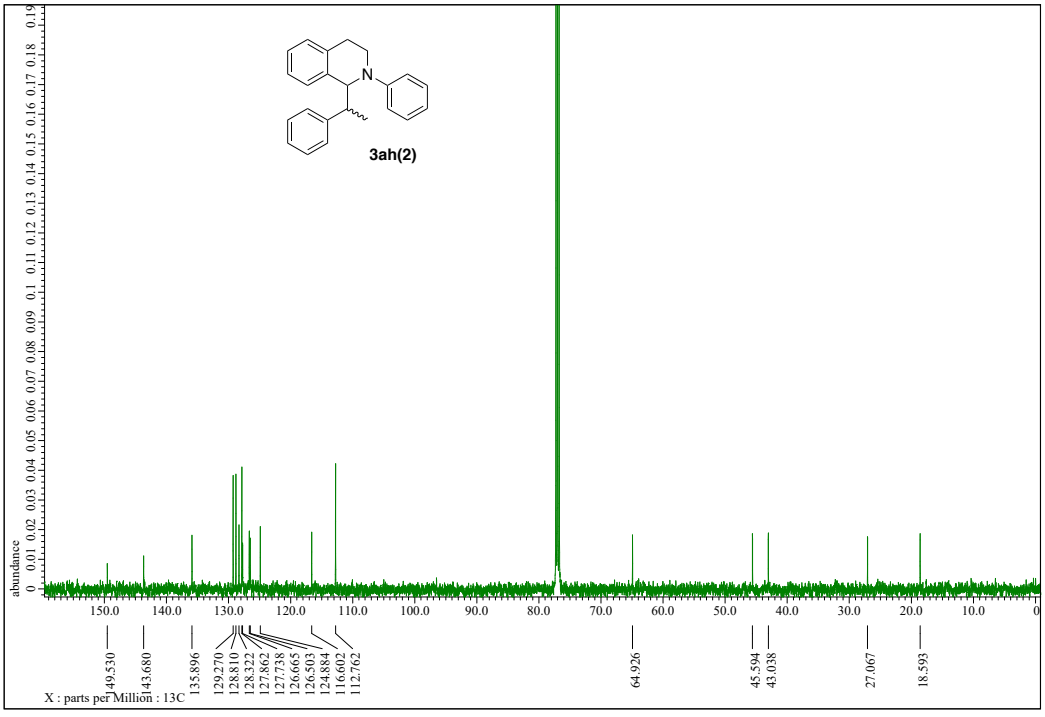

MeO
MeO
N
CN
3hc
abundance
X : parts per Million : 1H

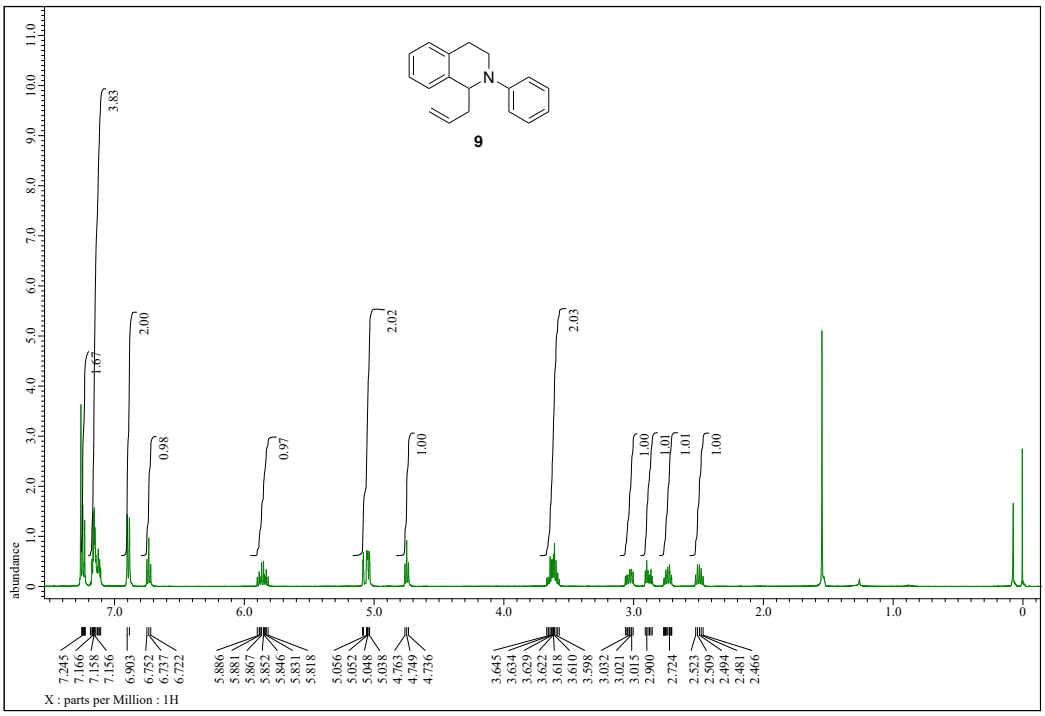

MeO
MeO
N
CN
3hc
(Thousands)
X : parts per Million : 13C

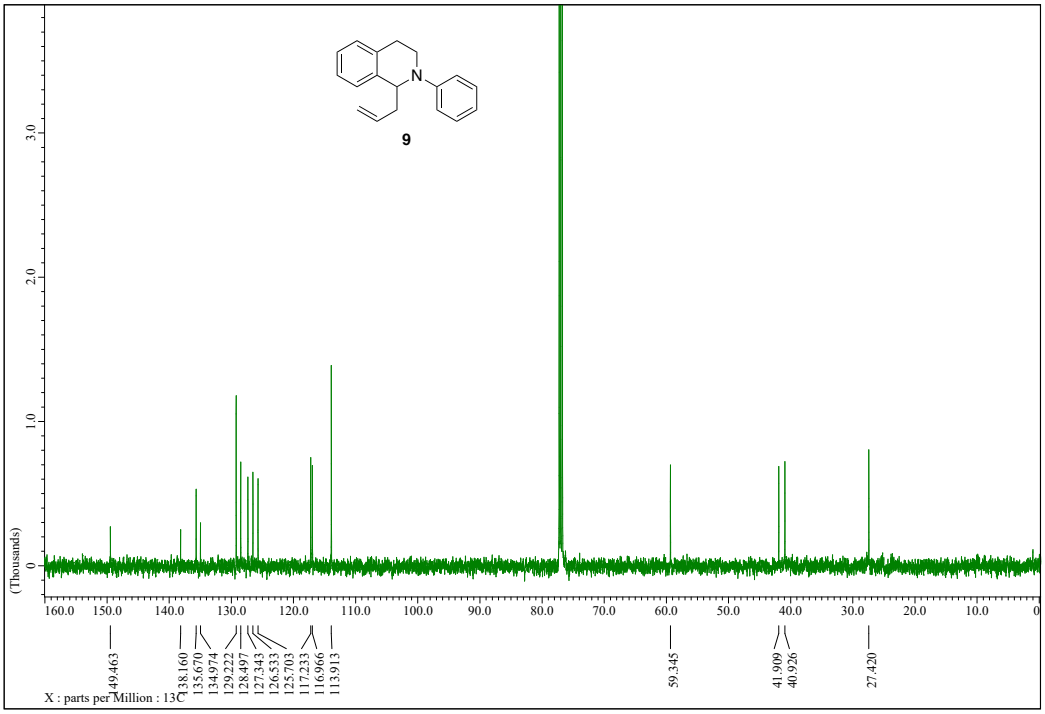

3ah(1)
abundance
X : parts per Million : 1H

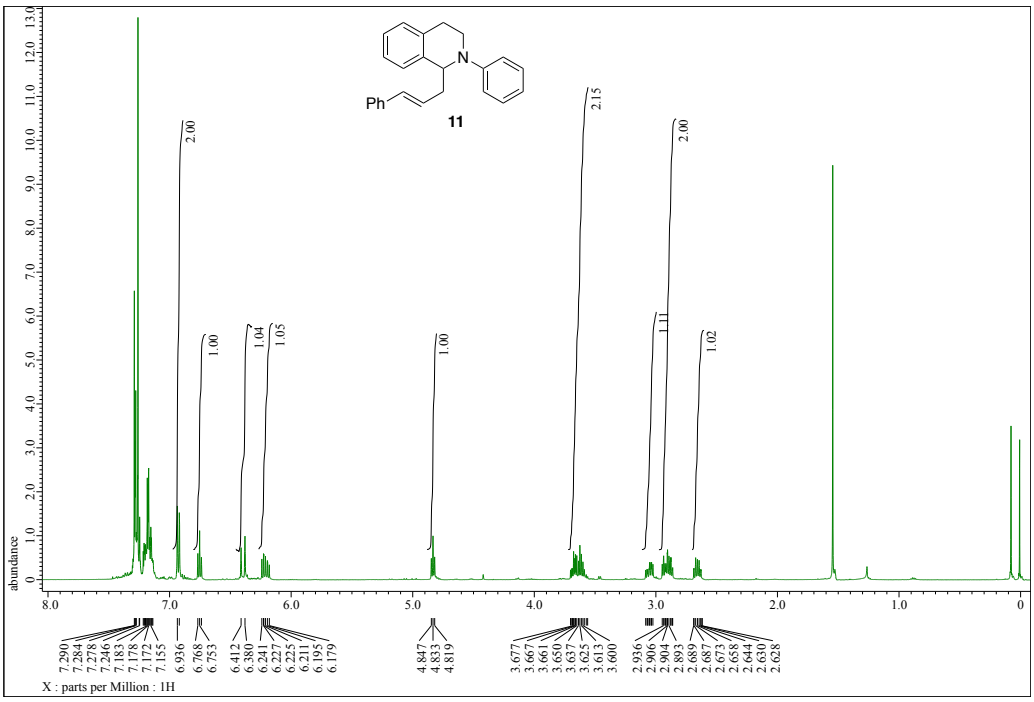

3ah(1)
(Millions)
X : parts per Million : 13C

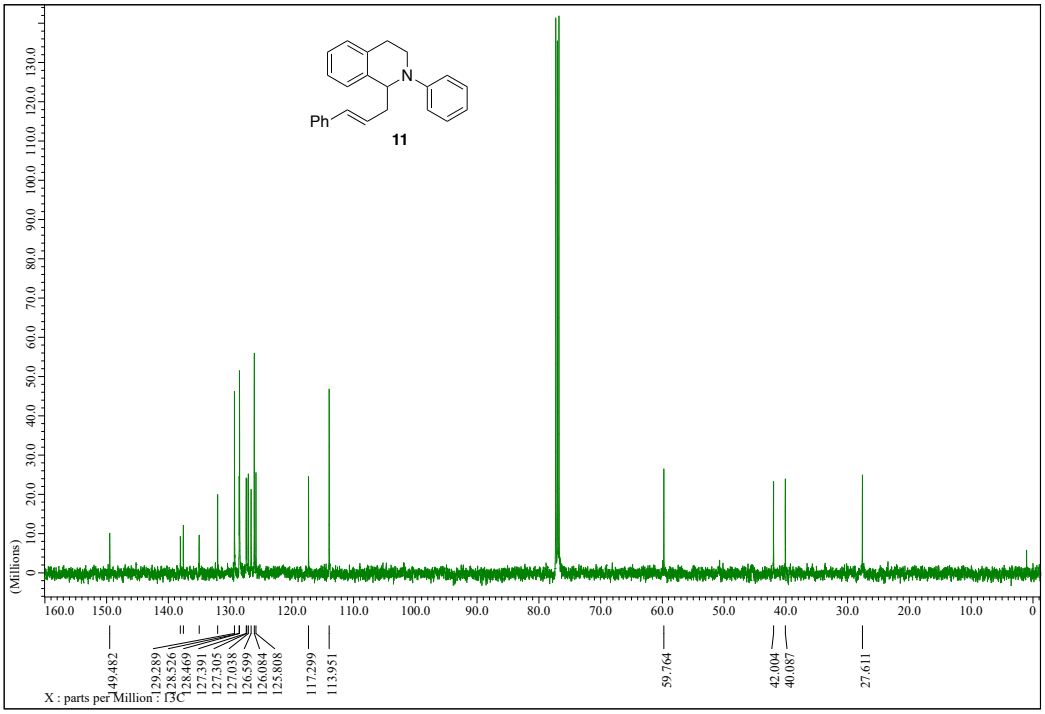

3ah(2)
abundance
X : parts per Million : 1H

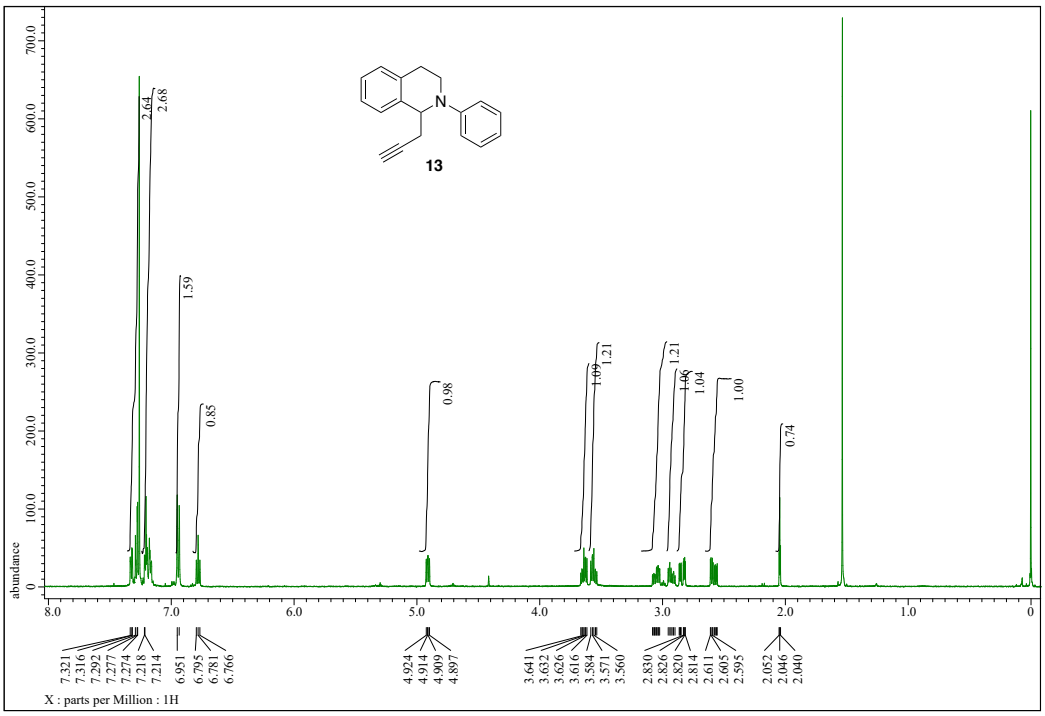

3ah(2)
abundance
X : parts per Million : 13C

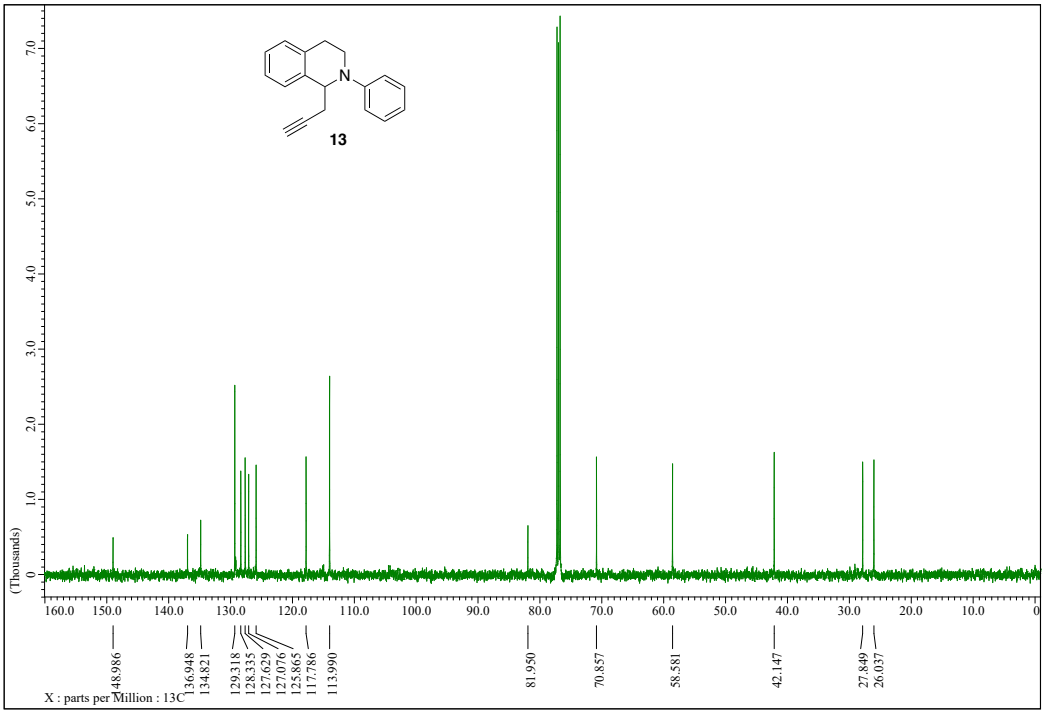

9
abundance
3.83
1.67
2.00
0.98
0.97
2.02
1.00
2.03
1.00
1.01
1.01
1.00
7.245
7.166
7.158
7.156
6.903
6.752
6.737
6.722
5.886
5.881
5.867
5.852
5.846
5.831
5.818
5.056
5.052
5.048
5.038
4.763
4.749
4.736
3.645
3.634
3.629
3.622
3.618
3.610
3.598
3.032
3.021
3.015
2.900
2.724
2.523
2.509
2.494
2.481
2.466
X : parts per Million : 1H

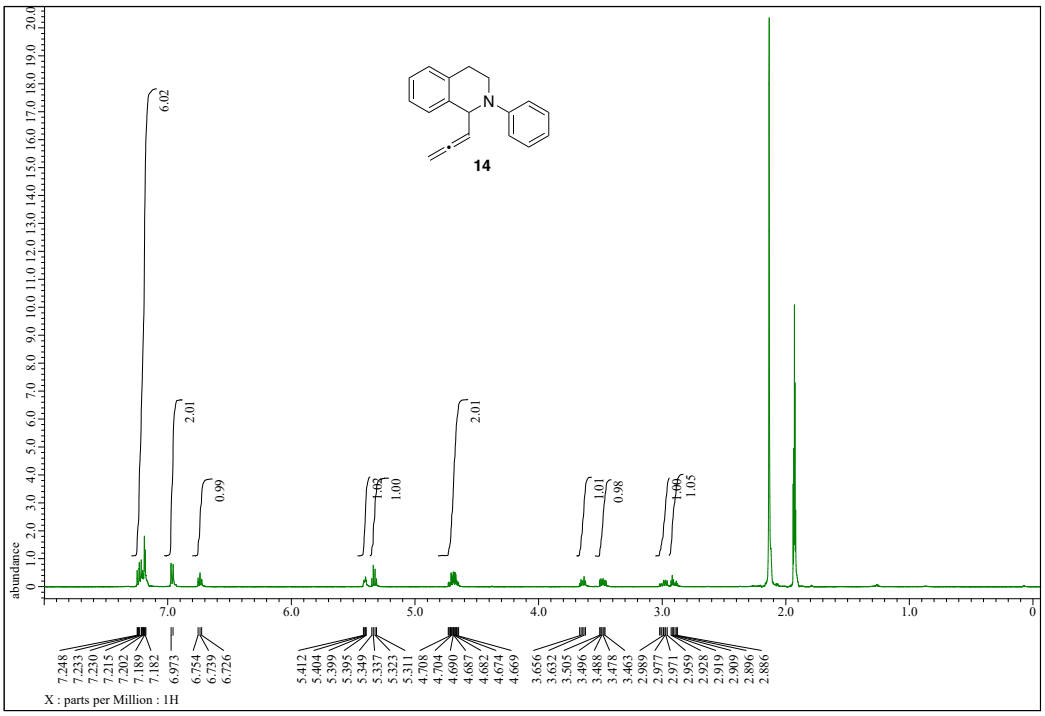

9
(Thousands)
149.463
138.160
135.670
134.974
129.222
128.497
127.343
126.533
125.703
117.233
116.966
113.913
59.345
41.909
40.926
27.420
X : parts per Million : 13C

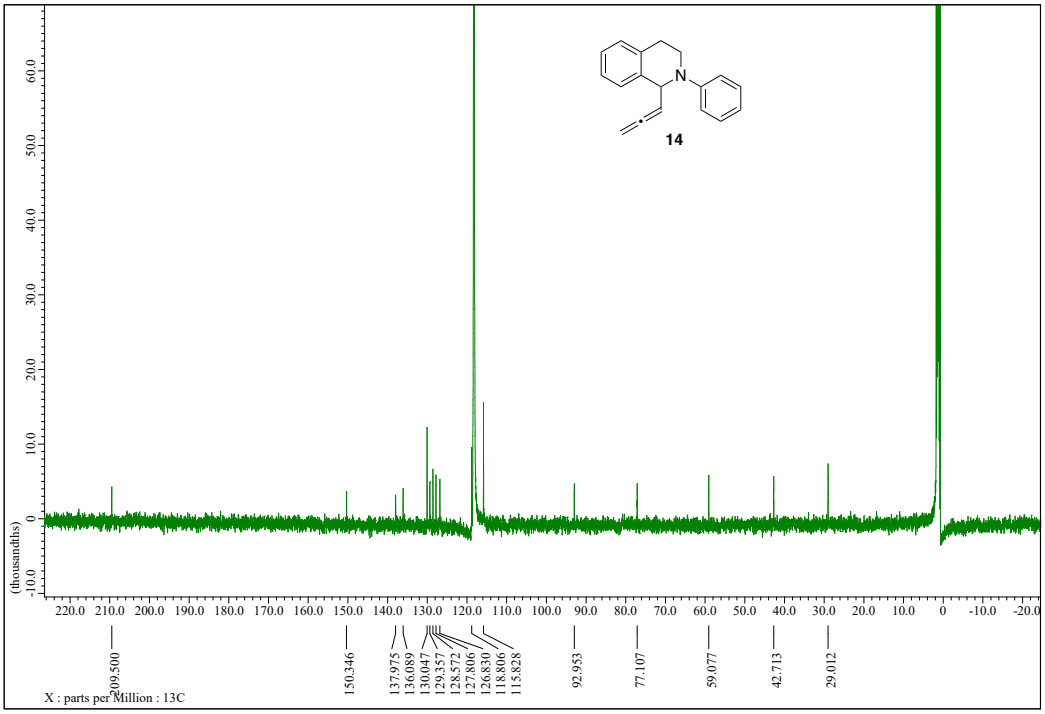

Ph
N
11
abundance
2.00
1.00
1.04
1.05
1.00
2.15
1.11
2.00
1.02
7.290
7.284
7.278
7.246
7.183
7.178
7.172
7.155
6.936
6.768
6.753
6.412
6.380
6.241
6.227
6.225
6.211
6.195
6.179
4.847
4.833
4.819
3.677
3.667
3.661
3.650
3.637
3.625
3.613
3.600
2.936
2.906
2.904
2.893
2.689
2.687
2.673
2.658
2.644
2.630
2.628
X : parts per Million : 1H

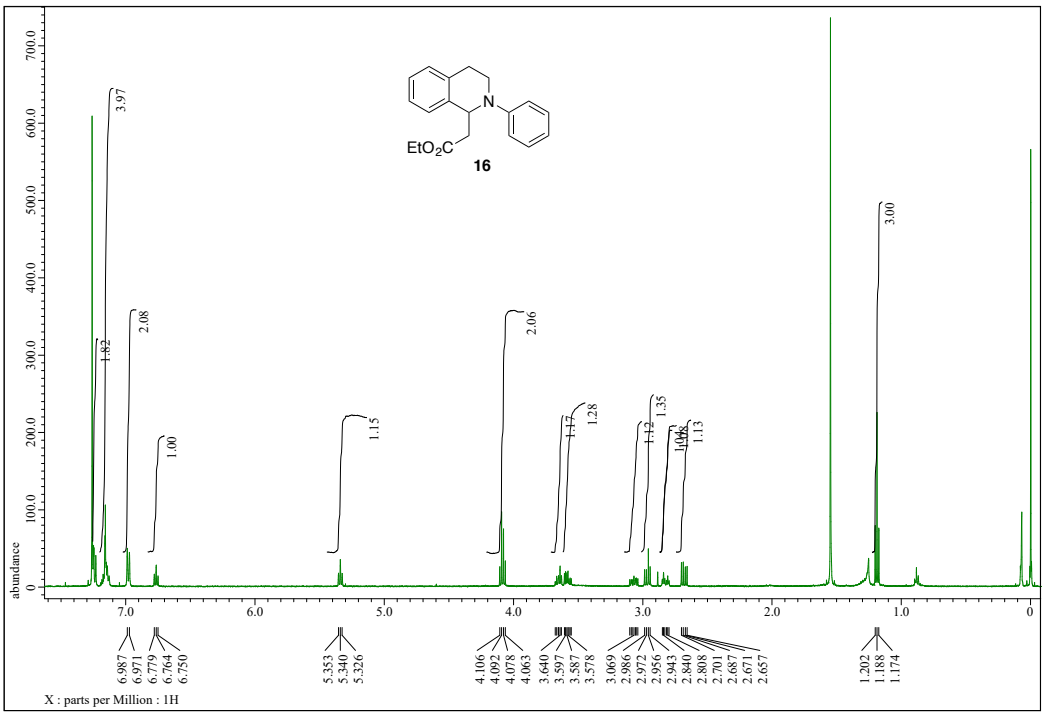

Ph
N
11
(Millions)
49.482
129.289
128.526
128.469
127.391
127.305
127.038
126.599
126.084
125.808
117.299
113.951
59.764
42.004
40.087
27.611
X : parts per Million : 13C

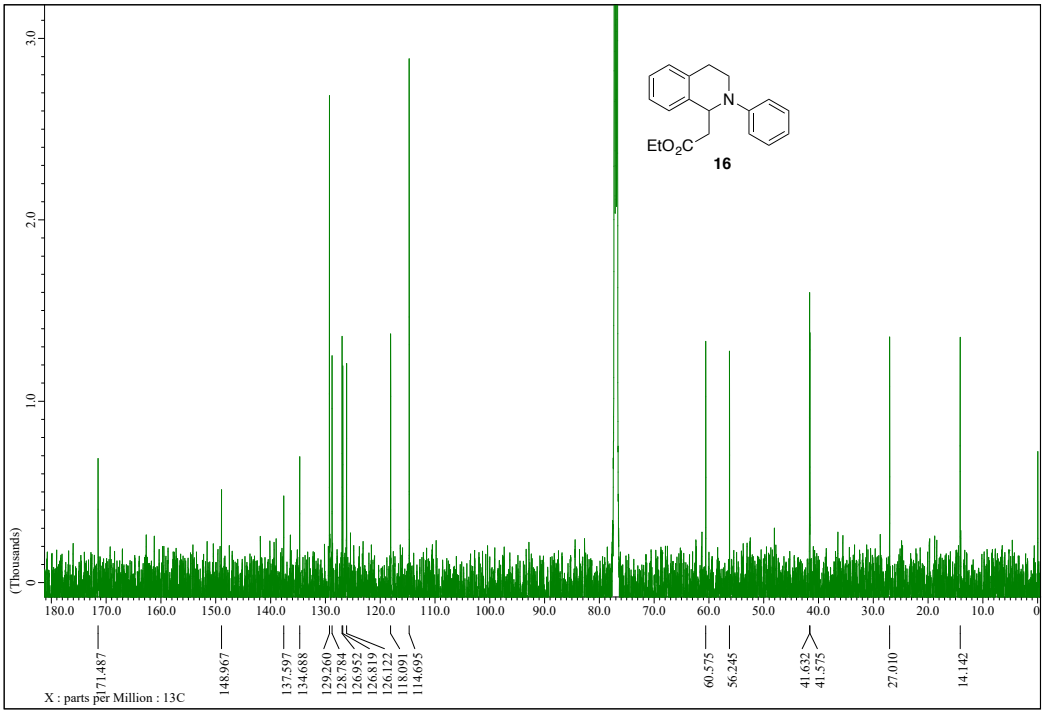

13
abundance
2.64
2.68
1.59
0.85
0.98
1.09
1.21
1.21
1.06
1.04
1.00
0.74
7.321
7.316
7.292
7.277
7.274
7.218
7.214
6.951
6.795
6.781
6.766
4.924
4.914
4.909
4.897
3.641
3.632
3.626
3.616
3.584
3.571
3.560
2.830
2.826
2.820
2.814
2.611
2.605
2.595
2.052
2.046
2.040
X : parts per Million : 1H


13
(Thousands)
148.986
136.948
134.821
129.318
128.335
127.629
127.076
125.865
117.786
113.990
81.950
70.857
58.581
42.147
27.849
26.037
X : parts per Million : 13C


14
abundance
6.02
2.01
0.99
1.03
1.00
2.01
1.01
0.98
1.02
1.05
7.248
7.233
7.230
7.215
7.202
7.189
7.182
6.973
6.754
6.739
6.726
5.412
5.404
5.399
5.395
5.349
5.337
5.323
5.311
4.708
4.704
4.690
4.687
4.682
4.674
4.669
3.656
3.632
3.505
3.496
3.488
3.478
3.463
2.989
2.977
2.971
2.959
2.928
2.919
2.909
2.896
2.886
X : parts per Million : 1H


14
(thousandths)
209.500
150.346
137.975
136.089
130.047
129.357
128.572
127.806
126.830
118.806
115.828
92.953
77.107
59.077
42.713
29.012
X : parts per Million : 13C


abundance
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0
3.97
2.08
1.82
1.00
1.15
2.06
1.28
1.35
1.13
3.00
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
6.987
6.971
6.779
6.764
6.750
5.353
5.340
5.326
4.106
4.092
4.078
4.063
3.640
3.597
3.587
3.578
3.069
2.986
2.972
2.956
2.943
2.840
2.808
2.701
2.687
2.671
2.657
1.202
1.188
1.174
X : parts per Million : 1H
EtO2C
16


(Thousands)
3.0
2.0
1.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
171.487
148.967
137.597
134.688
129.260
128.784
126.952
126.819
126.122
118.091
114.695
60.575
56.245
41.632
41.575
27.010
14.142
X : parts per Million : 13C
EtO2C
16