Selective and Multiple Functionalization of Pyridines and Alkaloids *via* Mg- and Zn-Organometallic Intermediates

Milica Jaric, Benjamin A. Haag, Sophia M. Manolikakes and Paul Knochel

Department Chemie, Ludwig-Maximilians-Universität München,
Butenandtstr. 5-13, 81377 München, Germany.

paul.knochel@cup.uni-muenchen.de

Supporting Information

Experimental Details

Table of Contents

General All reactions were carried out under argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF were continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Diethyl ether was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC (Al_2O_3,1-3 mm, ICN, Eschwege, Germany). TMPH, liquid acid chlorides and $BF_3{\cdot}OEt_2$ were distilled under argon prior to use. Yields refer to isolated yields of compounds estimated to be > 95 % pure as determined by ^{1}H-NMR (25 °C) and capillary-GC analysis. NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$) with residual chloroform (δ 7.25 ppm for ^{1}H-NMR and δ 77.0 ppm for ^{13}C-NMR) or D6-DMSO (δ 2.49 ppm for ^{1}H-NMR and δ 39.5 ppm for ^{13}C-NMR). Column chromatographical purifications were performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck if not indicated otherwise.

Typical Procedure for the metalation of heteroaromatics with hindered metal amide bases (TP1)

A dry and argon flushed 50-mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with a solution of the corresponding *N*-heteroarene (1.0 mmol) in dry THF (5 mL) and then cooled to the indicated temperature. A THF-solution of the indicated hindered metal amide base, titrated prior use, was added dropwise and the reaction mixture was stirred at the indicated temperature for the given time. Complete metalation was monitored by GC analysis of reaction aliquots, quenched with iodine in dry THF using decane as internal standard.

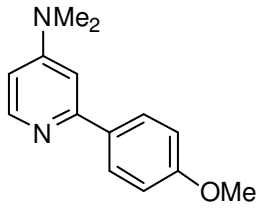
Typical Procedure for the BF_3-triggered metalation of heteroaromatics with hindered metal amide bases (TP2)

A dry and argon flushed 50-mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with a solution of the corresponding *N*-heteroarene (1.0 mmol) in dry THF (5 mL) and cooled to 0 °C. $BF_3{\cdot}OEt_2$ (156 mg, 1.1 mmol) was added dropwise and stirred for 15 min at the same temperature. The reaction mixture was cooled to the given temperature followed by dropwise addition of a THF-solution of the indicated hindered metal amide base titrated prior use, and stirring the reaction mixture at the indicated temperature for the given time. Complete metalation was monitored by GC analysis of reaction aliquots, quenched with iodine in dry THF using decane as internal standard.

Typical Procedure for the BF_3-triggered metalation of quinine (7) with TMPMgCl·LiCl (TP4)

A dry and argon flushed 50-mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with a solution of quinine (324 mg, 1.0 mmol) in dry THF (4 mL) and cooled to 0 °C. MeLi (0.61 mL 1.0 mmol, 1.63 M in diethyl ether) were added dropwise and stirred for 1 h at 25 °C. After cooling to 0 °C $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) was slowly added and stirred for 15 min at the same temperature. After dropwise addition of a THF-solution of the hindered metal amide base TMPMgCl·LiCl (**1**, 1.1 mmol), titrated prior use, the reaction mixture was stirred for further 40 min at 0 °C.

Synthesis of 2-(4-methoxyphenyl)-*N*,*N*-dimethylpyridin-4-amine (4a):



According to **TP2**, a mixture of DMAP (**2a**; 244 mg, 2.0 mmol) and $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**1**; 1.8 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 1 h). The reaction mixture was cooled to -30 °C and $ZnCl_2$ (2.2 mmol, 2.2 mL, 1 M in THF) was added dropwise. After stirring for 30 min at the same temperature $Pd(dba)_2$ (56 mg, 5 mol%) and P(*o*-fur)$_3$ (46 mg, 10 mol%) dissolved in THF (2 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-4-methoxybenzene (374 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with a sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with diethyl ether (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, isohexane / EtOAc = 1:5) afforded the product **4a** (295 mg, 81%) as yellow solid.

M.p. (°C): 120.0-125.1.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.27 (d, *J* = 6.6 Hz, 1H), 7.91-7.83 (m, 2H), 6.99-6.91 (m, 2H), 6.81 (d, *J* = 2.7 Hz, 1H), 6.45 (dd, *J* = 6.2, 2.6 Hz, 1H), 3.82 (s, 3H), 3.04 (s, 6H).

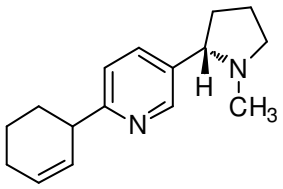
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.3, 156.7, 155.2, 148.4, 132.2, 128.3, 113.9, 105.0, 102.8, 55.3, 39.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3434, 3196, 3032, 2932, 2640, 2442, 2030, 1946, 1638, 1594, 1576, 1540, 1512, 1448, 1438, 1418, 1404, 1390, 1376, 1302, 1268, 1236, 1182, 1172, 1128, 1110, 1060, 1020, 994, 984, 960, 868, 850, 832, 804, 786, 736, 698, 646, 632.

MS (EI, 70 eV): m/z (%) = 228 [M$^+$] (99), 213 (100), 185 (43), 170 (11), 141 (9), 114 (9), 92 (4).

HRMS (EI) for **$C_{14}H_{16}N_2O$** (228.1263): 228.1258.

Synthesis of 2-(cyclohex-2-en-1-yl)-5-((S)-1-methylpyrrolidin-2-yl)pyridine (4b):



According to **TP2**, a mixture of (*S*)-nicotine (**2b**; 162 mg, 1.0 mmol) and $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) reacted with TMPMgCl·LiCl (**1**; 1.3 mL, 1.5 mmol, 1.2 M in THF) (0 °C, 2.5 h). The reaction mixture was cooled to -30 °C and CuCN·2LiCl (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise. After stirring for 30 min at the same temperature 3-bromocyclohex-1-ene (160 mg, 1.1 mmol) was added. The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with a sat. aqueous NH_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with diethyl ether (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (Al_2O_3 III, pentane / Et_2O = 1:1) afforded the product **4b** (223 mg, 92%) as red oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm) = 8.43 (s, 1H), 7.63 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 5.87-5.96 (m, 1H), 5.74-5.84 (m, 1H), 3.55-3.58 (m, 1H), 3.17-3.29 (m, 1H), 3.03-3.07 (m, 1H), 1.48-2.41 (m, 14H).

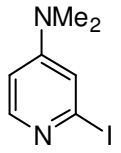
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 164.3, 149.0, 135.7, 135.2, 135.1, 128.8, 128.7, 121.7, 68.7, 68.6, 56.0, 43.7, 40.3, 35.0, 30.6, 24.9, 22.5, 21.1, 21.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}): 3018, 2934, 2874, 2858, 2836, 2774, 2720, 2664, 2362, 2340, 1734, 1674, 1616, 1596, 1566, 1480, 1456, 1448, 1420, 1400, 1374, 1344, 1332, 1314, 1288, 1250, 1216, 1210, 1152, 1132, 1116, 1086, 1044, 1026, 988, 966, 922, 902, 886, 838, 788, 764, 722, 688, 642, 610.

MS (70 eV, EI) *m/z* (%): 242 [M^+] (63), 213 (30), 185 (16), 156 (8), 133 (15), 84 (100), 42 (9).

HRMS (EI) for **$C_{16}H_{22}N_2$** (242.1783): 242.1777.

Synthesis of 2-iodo-*N*,*N*-dimethylpyridin-4-amine (4c):



According to **TP2**, a mixture of DMAP (**2a**; 244 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**1**; 1.8 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 1 h). The reaction mixture was cooled to -30 °C and a solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with a sat. NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and a sat. aqueous $Na_2S_2O_3$ (2 mL) followed by extraction with diethyl ether (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, EtOAc) afforded the product **4c** (323 mg, 72%) as yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.89 (d, *J* = 6.1 Hz, 1H), 6.88 (d, *J* = 2.2 Hz, 1H), 6.43 (dd, *J* = 6.0, 2.3 Hz, 1H), 2.96 (s, 6H).

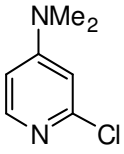
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 154.8, 149.5, 119.2, 116.4, 105.5, 39.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3008, 2882, 2816, 1580, 1506, 1436, 1394, 1372, 1294, 1260, 1220, 1124, 1064, 970, 956, 806, 780, 682.

MS (EI, 70 eV): m/z (%) = 248 [M^+] (98), 121 (78), 106 (17), 95 (14), 61 (14), 43 (100).

HRMS (EI) for **$C_7H_9IN_2$** (247.9810): (247.9808).

Synthesis of 2-chloro-*N*,*N*-dimethylpyridin-4-amine (4d):

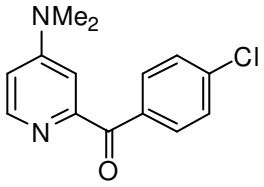


According to **TP2**, a mixture of DMAP (**2a**; 244 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**1**; 1.8 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 1 h). $C_2Cl_3F_3$ (412 mg, 2.2 mmol) dissolved in THF (3 mL) was added at 0 °C and slowly warmed

to 25 °C. The reaction mixture was quenched with a sat. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with diethyl ether (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, isohexane / EtOAc = 1:5) afforded the product **4d** (219 mg, 70%) as yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.94 (d, *J* = 5.8 Hz, 1H), 6.44 (d, *J* = 2.2 Hz, 1H), 6.38 (dd, *J* = 6.1, 2.2 Hz, 1H), 2.97 (s, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.0, 152.1, 148.9, 105.8, 105.3, 39.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2922, 2360, 1918, 1594, 1520, 1444, 1420, 1404, 1384, 1296, 1270, 1224, 1188, 1134, 1080, 1066, 980, 808, 716, 698, 612.
MS (EI, 70 eV): m/z (%) = 156 [M^+] (66), 155 (100), 119 (5), 92 (8), 57 (7).
HRMS (**EI**) for **$C_7H_9ClN_2$** (156.0454): 156.0436.

Synthesis of (4-chlorophenyl)(4-(dimethylamino)pyridin-2-yl)methanone (4e):



According to **TP2**, a mixture of DMAP (**2a**; 244 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**1**; 1.8 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 1 h). The reaction mixture was cooled to -40 °C and CuCN·2LiCl (2.2 mL, 2.2 mmol, 1 M in THF) was added and the reaction mixture was stirred for 30 min at the same temperature. Then, 4-chlorobenzoyl chloride (280 mg, 1.6 mmol) was added at -40 °C. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with diethyl ether (3x40 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, isohexane / EtOAc = 1:4) afforded the product **4e** (284 mg, 68%) as yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.17 (d, *J* = 5.8 Hz, 1H), 7.97-7.90 (m, 2H), 7.34-7.27 (m, 2H), 7.12 (d, *J* = 2.7 Hz, 1H), 6.49 (dd, *J* = 5.8, 2.7 Hz, 1H), 2.91 (s, 6H).

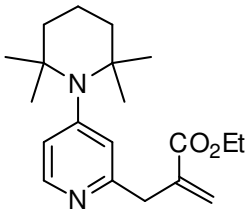
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 193.1, 154.4, 154.4, 148.1, 138.5, 134.7, 132.0, 127.8, 108.1, 106.8, 38.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3088, 2918, 2818, 1918, 1662, 1584, 1540, 1504, 1486, 1430, 1414, 1398, 1376, 1338, 1282, 1264, 1224, 1174, 1148, 1088, 1066, 1016, 980, 932, 862, 842, 818, 792, 768, 736, 724, 686.

MS (EI, 70 eV): m/z (%) = 260 [M^+] (66), 245 (64), 232 (48), 225 (45), 219 (34), 217 (100), 189 (50), 154 (20), 141 (26), 139 (83), 111 (94), 75 (36).

HRMS (EI) for **$C_{14}H_{13}ClN_2O$** (260.0716): 260.0711.

Synthesis of ethyl 2-((4-(2,2,6,6-tetramethylpiperidin-1-yl)pyridin-2-yl)methyl)acrylate (4f):



According to **TP2**, a mixture of 4-(2,2,6,6-tetramethylpiperidin-1-yl)pyridine (**2c**; 371 mg, 1.7 mmol) and $BF_3{\cdot}OEt_2$ (266 mg, 1.9 mmol) reacted with TMPMgCl·LiCl (**1**; 2.5 mL, 3 mmol, 1.2 M in THF) (0 °C, 1.5 h). The reaction mixture was cooled to -40 °C and CuCN·2LiCl (1.7 mL, 1.7 mmol, 1 M in THF) was added and the reaction mixture was stirred for 30 min at the same temperature before ethyl 2-(bromomethyl)acrylate (386 mg, 2.0 mmol) was added. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with diethyl ether (3x40 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (Al_2O_3 III, pentane / Et_2O = 4:1) afforded the product **4f** (397 mg, 71%) as colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.42 (d, *J* = 5.4 Hz, 1H), 7.03 (s, 1H), 6.98 (d, *J* = 5.4 Hz, 1H), 6.28 (s, 1H), 5.53 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 1.67-1.77 (m, 2H), 1.49-1.59 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 12H).

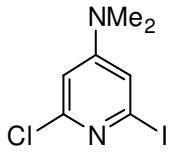
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.7, 159.0, 155.5, 149.2, 138.9, 129.0, 126.9, 126.6, 60.7, 54.1, 41.8, 40.6, 29.6, 18.1, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2970, 2930, 2870, 1716, 1632, 1588, 1542, 1474, 1456, 1446, 1428, 1378, 1364, 1326, 1294, 1272, 1244, 1186, 1174, 1130, 1096, 1034, 998, 982, 944, 926, 854, 842, 816, 778, 714.

MS (EI, 70 eV): m/z (%) = 330 [M^+] (1), 315 (100), 247 (5), 173 (4), 69 (7).

HRMS (**EI**) for **$C_{20}H_{30}N_2O_2$** (330.2307): 330.2310.

Synthesis of 2-chloro-6-iodo-*N,N*-dimethylpyridin-4-amine (4g):



According to **TP2**, a mixture of 2-chloro-*N,N*-dimethylpyridin-4-amine (**4c**; 313 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**1**; 2.5 mL, 3 mmol, 1.2 M in THF) (0 °C, 3 h). The reaction mixture was cooled to -30 °C and a solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with a sat. NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and a sat. aqueous $Na_2S_2O_3$ (2 mL) followed by extraction with diethyl ether (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, EtOAc / pentane = 1:1) afforded the product **4g** (452 mg, 80%) as white solid.

M. p. (°C): 119.0-120.1.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 6.84 (d, *J* = 2.2 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 2.98 (s, 6H).

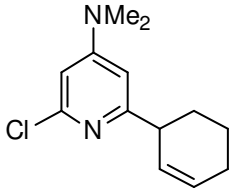
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.1, 150.2, 115.9, 115.7, 105.4, 39.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3114, 2928, 2806, 1584, 1500, 1428, 1416, 1396, 1366, 1346, 1284, 1226, 1160, 1100, 1082, 1068, 984, 964, 808, 754, 702.

MS (EI, 70 eV): m/z (%) = 282 [M^+] (100), 155 (38), 119 (7).

HRMS (**EI**) for **$C_7H_8ClIN_2$** (281.9421): 281.9419.

Synthesis of 2-chloro-6-cyclohex-2-en-1-yl-*N*,*N*-dimethylpyridin-4-amine (4h):



According to **TP2**, a mixture of 2-chloro-*N,N*-dimethylpyridin-4-amine (**4c**; 157 mg, 1.0 mmol) and BF_3·OEt_2 (156 mg, 1.1 mmol) reacted with TMPMgCl·LiCl (**1**; 1.3 mL, 1.5 mmol, 1.2 M in THF) (0 °C, 3 h). The reaction mixture was cooled to -30 °C and CuCN·2LiCl (1.1 mL, 1.1 mmol, 1 M in THF) was added dropwise. After stirring for 30 min at the same temperature 3-bromocyclohex-1-ene (193 mg, 1.2 mmol) was added. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. NH_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) and extracted with diethyl ether (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, isohexane / EtOAc = 1:1) afforded the product **4h** (185 mg, 78%) as colourless oil.

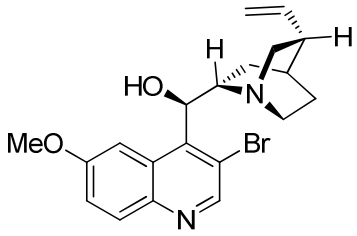
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 6.32 (d, *J* = 2.4 Hz, 1H), 6.28 (d, *J* = 2.2 Hz, 1H), 5.91-5.84 (m, 1H), 5.77-5.69 (m, 1H), 3.48-3.38 (m, 1H), 2.96 (s, 6H), 2.10-1.99 (m, 3H), 1.74-1.54 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 165.6, 156.6, 151.4, 129.1, 128.5, 103.3, 103.2, 43.7, 39.3, 30.3, 25.0, 20.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3020, 2928, 2860, 2836, 1662, 1590, 1528, 1504, 1422, 1366, 1326, 1294, 1214, 1184, 1126, 1064, 980, 934, 914, 896, 888, 822, 810, 748, 726, 710.

MS (EI, 70 eV): m/z (%) = 236 [M^+] (88), 221 (48), 209 (40), 207 (100), 201 (39), 195 (23), 191 (15), 181 (12), 170 (38), 156 (12), 57 (19), 43 (17).
HRMS (EI) for $\mathbf{C_{13}H_{17}ClN_2}$ (236.1080): 236.1076.

Synthesis of (*R*)-(3-bromo-6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methanol (6a):



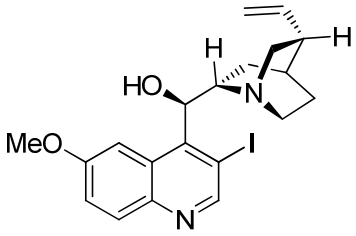
According to **TP4** quinine (**7**; 648 mg, 2.0 mmol) reacted with MeLi (1.23 mL, 2.0 mmol, 1.63 M in diethyl ether), $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**1**; 1.85 mL, 2.2 mmol, 1.19 M in THF). 1,2-Dibromo-1,1,2,2-tetrachloroethane (781 mg, 2.4 mmol) was added and the reaction mixture was stirred for 15 h at 25 °C. The reaction mixture was quenched with a sat. NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (Al_2O_3 III, isohexane / ethyl acetate = 1:1) furnished the product **8a** as off-white solid (532 mg, 66% yield).

M. p. (°C): 84.2-87.5.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = : 8.65 (s, 1H), 7.95 (s, br, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.29 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 5.92-5.77 (m, 1H), 5.59 (d, *J* = 8.8 Hz, 1H), 5.02 (s, 1H), 4.98 (d, *J* = 5.6 Hz, 1H), 3.90 (s, 3H), 3.75-3.53 (m, 1H), 3.45-3.25 (m, 1H), 2.99-2.80 (m, 1H), 2.71-2.45 (m, 2H), 2.32-2.18 (m, 1H), 1.94-1.83 (m, 1H), 1.76-1.56 (m, 2H), 1.57-1.36 (m, 2H).
^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ / (ppm) = 157.4, 149.6, 144.3, 143.9, 141.8, 131.4, 128.8, 121.5, 119.6, 114.3, 104.2, 75.8, 60.0, 55.7, 55.4, 42.8, 39.6, 27.8, 27.3, 25.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3134, 3076, 2932, 2864, 2362, 1736, 1618, 1576, 1558, 1500, 1464, 1452, 1418, 1388, 1380, 1356, 1322, 1286, 1262, 1226, 1184, 1158, 1112,

1094, 1028, 988, 950, 938, 912, 886, 870, 858, 830, 810, 784, 774, 746, 714, 686, 668, 648, 610.

HRMS (ESI) for $\mathbf{C_{20}H_{24}BrN_2O_2}$ (403.1016 [M + H^+]): 403.1014.

Synthesis of (*R*)-(3-iodo-6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methanol (6b):



According to **TP4** quinine (**7**; 648 mg, 2.0 mmol) reacted with MeLi (1.23 mL, 2.0 mmol, 1.63 M in diethyl ether), $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**1**; 1.85 mL, 2.2 mmol, 1.19 M in THF). Iodine (761 mg, 3 mmol) was added and the reaction mixture was warmed to 25 °C. The reaction solution was quenched with a sat. NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (Al_2O_3 III, isohexane / ethyl acetate = 1:1) furnished the product **8b** as off-white solid (585 mg, 65% yield).

M.p. (°C): 84.8-85.1.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.80 (s, 1H), 8.10 (s, br, 1H), 7.83 (d, *J* = 9.3 Hz, 1H), 7.27 (dd, *J* = 8.9 Hz, 2.9 Hz, 1H), 5.82-5.73 (m, 1H), 5.51-5.44 (m, 1H), 5.00 (d, *J* = 1.4 Hz, 1H), 4.98 (dt, *J* = 7.2 Hz, 1.3 Hz, 1H), 3.89 (s, 3H), 3.59-3.48 (m, 1H), 2.94-2.86 (m, 1H), 2.68-2.61 (m, 2H), 2.31-2.25 (m, 1H), 1.90-1.83 (m, 2H), 1.77-1.69 (m, 2H), 1.55-1.48 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.8, 154.6, 147.6, 144.3, 141.0, 130.9, 129.1, 121.7, 116.5, 114.6, 104.3, 81.0, 60.0, 55.3, 55.1, 43.1, 39.1, 27.2, 27.1, 24.6.

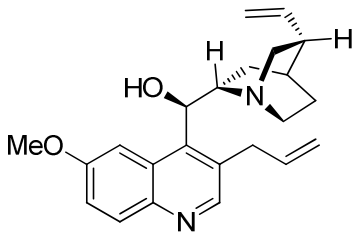
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3110, 2936, 2858, 2418, 2382, 2350, 2160, 2048, 1736, 1686, 1616, 1542, 1498, 1462, 1452, 1412, 1284, 1260, 1226, 1214, 1180, 1164, 1156,

1130, 1110, 1038, 1026, 986, 948, 908, 884, 874, 828, 808, 786, 766, 744, 734, 712, 674, 654, 640, 622, 612.

MS (EI, 70 eV): 450 [M^+] (2), 323 (17), 136 (100), 81 (7), 61 (12), 43 (16).

HRMS for $\mathbf{C_{20}H_{23}IN_2O_2}$ (450.0804): 450.0932.

Synthesis of (*R*)-(3-allyl-6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methanol (6c):



According to **TP4** quinine (**7**; 973 mg, 3.0 mmol) reacted with MeLi (1.84 mL, 3.0 mmol, 1.63 M in diethyl ether), $BF_3{\cdot}OEt_2$ (937 mg, 6.6 mmol) and TMPMgCl·LiCl (**1**; 2.77 mL, 3.3 mmol, 1.19 M in THF). CuCN·2LiCl (3.3 mL, 3.3 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for 15 min at 0 °C. After addition of allyl bromide (436 mg, 3.6 mmol) the reaction was stirred for 1.5 h at 25 °C. The reaction mixture was quenched with a sat. NH_4Cl solution (14 mL) and NH_3 (conc.) (2 mL) followed by extraction with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (Al_2O_3 III, pentane / ethyl acetate = 5:1) furnished the compound **8c** as slightly yellow resin (451 mg, 40%).

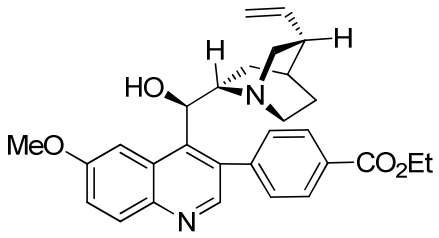
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 8.42 (s, 1H), 7.91 (d, J = 9.2Hz, 1H), 7.22-7.28 (m, 2H), 5.95-6.10 (m, 1H), 5.77-5.90 (m, 1H), 5.75-5.62 (m, 1H), 5.31-5.44 (m, 1H), 5.04-5.11 (m, 1H), 4.87-5.01 (m, 3H), 3.88 (s, 3H), 3.63-3.73 (m, 1H), 3.51-3.59 (m, 1H), 3.07-3.22 (m, 2H), 2.84-2.83 (m, 1H), 2.61-2.71 (m, 1H), 2.45-2.54 (m, 1H), 2.18-2.27 (m, 1H), 1.87-1.93 (m, 1H), 1.60-1.76 (m, 3H), 1.45-1.53 (m, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ / (ppm) = 157.7, 147.4, 144.2, 144.1, 142.0, 131.3, 130.2, 127.1, 121.5, 120.5, 116.2, 114.1, 101.0, 71.4, 60.4, 55.8, 55.3, 51.1, 42.3, 39.8, 37.6, 35.1, 30.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3134, 3076, 2932, 2864, 2362, 1736, 1618, 1576, 1558, 1500, 1464, 1452, 1418, 1388, 1380, 1356, 1322, 1286, 1262, 1226, 1184, 1158, 1112, 1094, 1028, 988, 950, 938, 912, 886, 870, 858, 830, 810, 784, 774, 746, 714, 686, 668, 648, 610 .

HRMS (ESI) for **$C_{20}H_{24}BrN_2O_2$** (403.1016 [M + H^+]): 403.1014.

Synthesis of ethyl 4-(4-((*R*)-hydroxy((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methyl)-6-methoxyquinolin-3-yl)benzoate (6d):



According to **TP4** quinine (**7**; 648 mg, 2.0 mmol) reacted with MeLi (1.2 mL, 2.0 mmol, 1.63 M in diethyl ether), $BF_3{\cdot}OEt_2$ (624 mg, 4.4 mmol) and TMPMgCl·LiCl (**1**; 1.8 mL, 2.2 mmol, 1.19 M in THF). The reaction mixture was cooled to -30 °C and $ZnCl_2$ (2.2 mmol, 2.2 mL, 1 M in THF) was added dropwise. After stirring for 30 min at the same temperature $Pd(dba)_2$ (56 mg, 5 mol%) and P(*o*-fur)$_3$ (46 mg, 10 mol%) dissolved in THF (2 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (442 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with a sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with diethyl ether (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, EtOAc / MeOH / NEt_3 = 10:1:1) afforded the product **8d** (378 mg, 50%) as yellow resin.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 8.31 (s, 1H), 8.05-8.16 (m, 2H), 7.95-8.00 (m, 1H), 7.86-7.92 (m, 1H), 7.34-7.41 (m, 2H), 7.25-7.30 (m, 1H), 5.67-5.78 (m, 1H), 5.21-5.28 (m, 1H), 4.85-4.97 (m, 2H), 4.86 (q, *J* = 6.9 Hz, 2H), 3.87 (s, 3H), 3.43-3.53 (m, 1H),

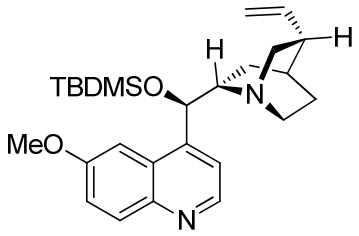
3.06-3.15 (m, 1H), 2.67-2.77 (m, 1H), 2.19-2.43 (m, 3H), 2.07-2.17 (m, 1H), 1.69-1.76 (m, 1H), 1.18-1.41 (m, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ / (ppm) = 177.1, 166.3, 157.1, 148.7, 144.5, 143.4, 141.4, 133.9, 131.0, 129.3, 127.1, 121.5, 114.2, 110.9, 105.1, 71.7, 61.0, 58.2, 55.4, 55.1, 41.8, 39.2, 29.5, 27.2, 27.1, 25.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3074, 2950, 2930, 2884, 1714 (s), 1622, 1608, 1552 (w), 1502 (m), 1462, 1422, 1396, 1390, 1366, 1352, 1308, 1264, 1230, 1176, 1102, 1072, 1028, 1020, 1004, 938, 912, 862, 852, 834, 804, 776, 732, 708, 672.

HRMS (ESI) für **$C_{29}H_{33}N_2O_4$** [M + H^+] (473.2440): 443.2436.

Synthesis of (2*S*,4*S*,8*R*)-2-((*R*)-(tert-butyldimethylsilyloxy)(6-methoxyquinolin-4-yl)methyl)-8-vinylquinuclidine (7):



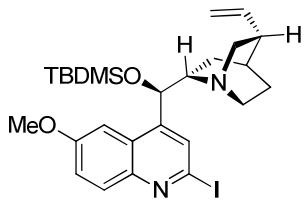
A 250 mL round bottom flask, equipped with a magnetic stirring bar, was charged with a solution of quinine (**7**; 8.0 g, 24.4 mmol) in DMF (40 mL). After addition of triethylamine (17 mL, 122.0 mmol), 4-dimethylaminopyridine (**2a**; 300 mg, 2.45 mmol) and *tert*-butyldimethylsilyl chloride (5.58 g, 37.0 mmol) the reaction mixture was stirred for 15 h at 25 °C. The reaction mixture was quenched with toluene (50 mL). The organic layer was washed with sat. $NaHCO_3$ solution (3x40 mL) and dried over $MgSO_4$. After filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, EtOAc / MeOH / NEt_3 = 9:1:1) furnished the compound **9** (10.4 g, 97%) as orange resin oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 8.72 (d, J = 4.5 Hz, 1H, major rotamer), 8.63 (d, J = 4.3 Hz, 1H, minor rotamer), 8.02 (d, J = 9.2 Hz, 1H, major rotamer), 7.97 (d, J = 9.3 Hz, 1H, minor rotamer), 8.83 (d, J = 2.6 Hz, 1H, minor rotamer), 7.51 (d, J = 4.6 Hz, 1H, major rotamer), 7.36 (dd, J = 9.3 Hz, J = 2.7 Hz 1H, major rotamer), 7.31 (dd, J = 9.3 Hz, J = 2.6 Hz, 1H, minor rotamer), 7.19 (d, J = 2.6 Hz, 1H, major rotamer), 7.10 (d, J = 4.2 Hz,

1H, minor rotamer), 5.91-5.81 (m, 1H, minor rotamer), 5.70-5.57 (m, 2H, major rotamer), 5.01-4.74 (m, 2H), 3.93 (s, 3H, major rotamer), 3.89 (s, 3H, minor rotamer), 3.57-3.41 (m, 1H), 3.06 (dd, J = 14 Hz, J = 10 Hz, 1H), 2.94-2.85 (m, 1H), 2.72-2.55 (m, 1H), 2.27-2.17 (m, 1H), 1.88-1.33 (m, 5H), 0.96 (s, 9H, major rotamer), 0.90 (s, 9H, minor rotamer), 0.12 (s, 3H, minor rotamer), 0.07 (s, 3H, major rotamer), -0.39 (s, 3H, major rotamer), -0.47 (s, 3H, minor rotamer). Ratio of rotamers determined by NMR ≈ 2/1.

^{13}C-NMR ($CDCl_3$, 100 MHz, 25 °C): δ / (ppm) = 157.9, 148.1, 147.3, 147.3, 147.2, 144.3, 142.2, 142.1, 131.8, 131.4, 129.0, 126.2, 121.5, 121.5, 121.1, 118.7, 114.2, 114.1, 104.4, 100.5, 80.1, 77.2, 72.7, 61.2, 60.8, 57.5, 56.1, 55.8, 55.3, 43.2, 41.2, 40.2, 39.9, 28.2, 27.9, 27.9, 27.8, 27.2, 25.9, 25.7, 25.7, 25.7, 21.1, 18.1, 18.0, 14.2, -3.4, -4.2, -4.7, -5.1, -5.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3076, 2998, 2948, 2930, 2884, 2858, 1916, 1620, 1592, 1574, 1508, 1472, 1462, 1432, 1408, 1390, 1360, 1322, 1302, 1254, 1240, 1228, 1184, 1172, 1130, 1102, 1074, 1030, 1004, 978, 952, 940, 912, 874, 832, 802, 776, 716, 704, 670, 642, 630, 612 .
HRMS (ESI) for **$C_{26}H_{39}N_2O_2Si$** (439.2775 [M + H^+]): 439.2772.

Synthesis of (2*S*,4*S*,5*R*)-2-((*R*)-((tert-butyldimethylsilyl)oxy)(2-iodo-6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (8a):



According to **TP2** (2*S*,4*S*,8*R*)-2-((*R*)-(tert-butyldimethylsilyloxy)(6-methoxyquinolin-4-yl)methyl)-8-vinylquinuclidine (**9**; 1.75 g, 4.0 mmol) reacted with $BF_3{\cdot}OEt_2$ (624 mg, 4.4 mmol) and TMPMgCl·LiCl (**1**; 4.8 mL, 6.0 mmol, 1.26 M in THF) (0 °C, 15 h). Iodine (2.03 g, 8 mmol) was added and the reaction mixture was stirred for 1 h at 25 °C. The reaction mixture was quenched with a sat. NH_4Cl solution (18 mL), NH_3 (conc.) (2 mL) and a sat. aqueous $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*.

Purification by flash chromatography (silica gel, EtOAc / MeOH /NEt_3 = 50:1:1) furnished the product **10a** as resin (1.00 g, 44%).

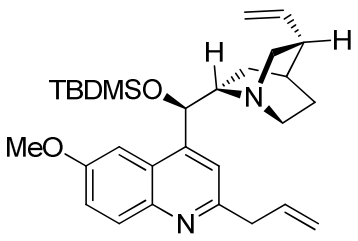
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 7.95-7.86 (m, 1H), 7.81 (s, 1H, major rotamer), 7.77 (br, 1H, minor rotamer), 7.42 (s, 1H, minor rotamer), 7.34-7.26 (m, 1H), 7.16 (br, 1H, major rotamer), 5.90-5.56 (m, 2H), 5.00-4.61 (m, 2H), 3.93 (s, 3H, major rotamer), 3.86 (s, 3H, minor rotamer), 3.57-1.36 (m, 11H), 0.96 (s, 9H, major rotamer), 0.80 (s, 9H, minor rotamer), 0.14 (s, 3H, major rotamer), 0.08 (s, 3H, minor rotamer), -0.34 (s, 3H, major rotamer), -0.43 (s, 3H, minor rotamer). Ratio of rotamers determined by NMR ≈ 3/1.

^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ (ppm) = 158.3, 156.9, 149.0, 145.7, 142.1, 131.1, 130.8, 129.6, 126.3, 125.4, 122.3, 122.0, 115.3, 114.6, 114.1, 104.8, 101.0, 79.3, 77.2, 61.1, 60.6, 57.1, 56.1, 56.0, 55.3, 54.7, 43.1, 41.2, 39.8, 28.1, 27.7, 27.2, 25.9, 25.7, 25.7, 20.7, 18.0, -3.4, -4.2, -4.6, -5.0, -5.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 3000, 2948, 2930, 2882, 2858, 2362, 2328, 1738, 1618, 1576, 1548, 1502, 1470, 1462, 1432, 1404, 1388, 1362, 1322, 1284, 1256, 1232, 1092, 1030, 1004, 952, 944, 912, 880, 870, 834, 804, 776, 726, 710, 672, 646.

HRMS (ESI) for **$C_{26}H_{38}IN_2O_2Si$** (565.1742 [M + H^+]): 565.1737.

Synthesis of (2*S*,4*S*,5*R*)-2-((*R*)-(2-allyl-6-methoxyquinolin-4-yl)((tert-butyldimethylsilyl)oxy)methyl)-5-vinylquinuclidine (8b):



According to TP2 (2*S*,4*S*,8*R*)-2-((*R*)-(tert-butyldimethylsilyloxy)(6-methoxyquinolin-4-yl)methyl)-8-vinylquinuclidine (**9**; 877 mg, 2.0 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.0 mmol) and TMPMgCl·LiCl (**1**; 2.5 mL, 3.0 mmol, 1.22 M in THF) (0 °C, 15 h). CuCN·2LiCl (2.2 mL, 2.2 mmol, 1 M in THF) was added and the reaction mixture was stirred for 15 min at 0 °C. After addition of allyl bromide (387 mg, 3.2 mmol) the reaction was stirred for 4 h at 25 °C. The reaction mixture was quenched with a sat. NH_4Cl solution (10 mL) and NH_3 (conc.) (2 mL) followed by extraction with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, pentan / EtOAc / NEt_3 = 20:1:1) furnished the compound **10b** as slightly brown honey like oil (379 mg, 41%).

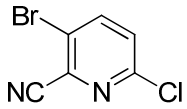
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 8.00-7.89 (m, 1H), 7.79 (br, 1H, minor rotamer), 7.45 (s, 1H, major rotamer), 7.36-7.25 (m, 1H), 7.17 (br, 1H, major rotamer), 7.03 (s, 1H, minor rotamer), 6.17-6.00 (m, 1H), 5.94-5.54 (m, 2H), 5.23-5.08 (m, 2H), 5.02-4.71 (m, 2H), 3.93 (s, 3H, major rotamer), 3.88 (s, 3H, minor rotamer), 3.72-1.28 (m, 13H), 0.96 (s, 9H, major rotamer), 0.80 (s, 9H, minor rotamer), 0.13 (s, 3H, major rotamer), 0.07 (s, 3H, minor rotamer), -0.40 (s, 3H, major rotamer), -0.48 (s, 3H, minor rotamer). Ratio of rotamers determined by NMR ≈ 3/1.

^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ / (ppm) = 157.6, 157.2, 144.0, 142.2, 135.6, 131.2, 124.7, 121.3, 118.9, 117.0, 114.3, 114.1, 100.7, 77.2, 72.7, 61.1, 57.5, 55.8, 43.7, 43.3, 40.2, 39.8, 28.0, 27.8, 25.9, 25.7, 20.7, 18.0, -4.2, -5.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3076, 2998, 2948, 2930, 2884, 2858, 1916, 1620, 1592, 1574, 1508, 1472, 1436, 1410, 1378, 1356, 1320, 1304, 1260, 1232, 1166, 1104, 1066, 1034, 1012, 996, 968, 910, 882, 832, 796, 768, 734, 678, 652.

HRMS (ESI) for **$C_{29}H_{43}N_2O_2Si$** [M + H^+] (479.3088): 479.3084.

Synthesis of 3-bromo-6-chloropicolinonitrile (11):



According to **TP1**, 5-bromo-2-chloropyridine (**11**; 385 mg, 2.0 mmol) reacted with TMPMgCl·LiCl (**1**; 1.96 mL, 2.2 mmol, 1.12 M in THF) (-40 °C, 3 h). After addition of tosyl cyanide (435 mg, 2.4 mmol) the reaction was stirred for 30 min at 25 °C. The reaction mixture was quenched with a sat. NH_4Cl solution (10 mL) followed by extraction with diethyl ether (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, isohexane / Et_2O = 5:1) furnished the compound **13** as white solid (295 mg, 68%).

M. p. (°C): 92.3-94.1.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 7.96 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H).

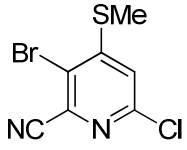
^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ / (ppm) = 150.9, 143.0, 134.4, 129.1, 123.2, 114.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3106, 3058, 2948, 2920, 2850, 2360, 2340, 2240, 1950, 1810, 1740, 1676, 1542, 1484, 1440, 1414, 1364, 1348, 1302, 1260, 1186, 1148, 1136, 1126, 1022, 976, 864, 834, 738, 682, 674 .

MS (70 eV, EI): *m/z* (%): 218 (100), 216 [M^+] (73), 101 (20), 75 (27), 50 (12), 43 (22).

HRMS for **$C_6H_2BrClN_2$** (215.9090): 215.9086.

Synthesis of 3-bromo-6-chloro-4-(methylthio)picolinonitrile (13):



According to **TP1**, 3-bromo-6-chloropicolinonitrile (**13**; 595 mg, 2.6 mmol) reacted with TMPMgCl·LiCl (**1**; 2.4 mL, 2.8 mmol, 1.19 M in THF) (-78 °C, 10 min). After addition of S-methyl methanesulfonothioate (390 mg, 3.0 mmol,) the reaction was stirred for 50 min at

25 °C. The reaction mixture was quenched with a sat. NH_4Cl solution (15 mL) followed by extraction with diethyl ether (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, isohexane / Et_2O = 10:1) furnished the compound **15** as white solid (555 mg, 81%).

M. p. (°C): 149.4-151.0.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 7.10 (s, 1H), 2.54 (s, 3H).

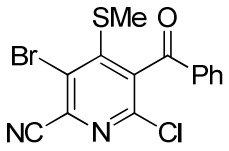
^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ / (ppm) = 157.1, 150.7, 133.7, 121.6, 121.5, 114.7, 15.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3098, 2924, 2482, 2362, 2244, 1744, 1558, 1534, 1506, 1454, 1420, 1382, 1344, 1326, 1244, 1236, 1214, 1204, 1184, 1158, 1150, 1068, 1038, 1018, 978, 958, 890, 876, 824, 778, 766, 730, 716, 656, 616 .

MS (70 eV, EI): *m/z* (%): 264 (100), 262 [M^+](75), 221 (13), 220 (12), 179 (16), 166 (17), 146 (12), 75 (11), 47 (19), 45 (12).

HRMS for **$C_7H_4BrClN_2S$** (261.8967): 261.8961.

Synthesis of 5-benzoyl-3-bromo-6-chloro-4-(methylthio)picolinonitrile (16):



According to **TP1**, 3-bromo-6-chloro-4-(methylthio)picolinonitrile (**15**; 132 mg, 0.5 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**16**; 1.04 mL, 0.75 mmol, 0.72 M in THF) (-20 °C, 4 h). CuCN·2LiCl (0.75 mL, 0.75 mmol, 1 M in THF) was added and the reaction mixture was stirred for 15 min at the same temperature. After addition of benzoyl chloride (113 mg, 0.8 mmol) the reaction mixture was stirred for 14 h at 25 °C and was quenched with a sat. NH_4Cl solution (2.0 mL) followed by extraction with diethyl ether (3x10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, isohexane / Et_2O = 10:1) furnished the compound **15** as white solid (112 mg, 61%).

M. p. (°C): decomp. at 112.3.

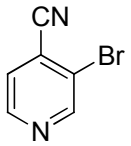
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 7.76 (d, J = 7.1 Hz, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.53 (t, J = 7.5 Hz, 2H), 2.35 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ / (ppm) = 189.5, 150.1, 147.2, 142.0, 135.1, 135.0, 134.9, 130.0, 129.6, 129.4, 129.4, 19.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964, 2908, 1678, 1596, 1582, 1522, 1496, 1450, 1416, 1302, 1260, 1224, 1192, 1176, 1046, 1012, 884, 864, 792, 720, 700, 686, 662, 640, 616.

HRMS (ESI) for **$C_{14}H_9BrClN_2OS$** (366.9302 [M + H^+]): 366.9295.

Synthesis of 3-bromoisonicotinonitrile (17):



According to **TP2**, a mixture of isonicotinonitrile (**18;** 208 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**16**; 3.1 mL, 2.2 mmol, 0.71 M in THF) (-20 °C, 3 h). The reaction mixture was cooled to -78 °C and Br_2 (352 mg, 2.2 mmol) dissolved in CCl_4 (2 mL) was added dropwise. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 30 min . The reaction mixture was quenched with a mixture of sat. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, pentane / Et_2O = 4:1) furnished the product **19** as white solid (234 mg, 64%).

M. p. (°C): 96.6-98.2.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm)= 8.91 (s, 1H), 8.69 (d, J = 4.9 Hz), 8.54 (d, J = 4.9 Hz).

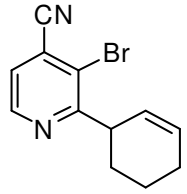
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm)= 152.7, 148.5, 126.8, 123.3, 122.2, 114.8, 99.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3752, 3108, 3078, 3014, 2964, 2362, 2340, 2238, 1972, 1918, 1772, 1740, 1704, 1572, 1534, 1498, 1470, 1402, 1280, 1218, 1204, 1104, 1088, 1026, 848, 784, 730, 694, 668.

MS (EI, 70 eV) m/z (%): 183 [M^+] (100), 181 (97) , 103 (88), 76 (31), 75 (14).

HRMS for **$C_6H_3BrN_2$** (181.9480): 181.9483.

Synthesis of 3-bromo-2-cyclohexylisonicotinonitrile (18):



According to **TP1**, 3-bromoisonicotinonitrile (**19;** 366 mg, 2.0 mmol) reacted with TMPMgCl·LiCl (**1**; 1.85 mL, 2.2 mmol, 1.2 M in THF) (-78 °C, 1 h). CuCN·2LiCl (2.2 mL, 2.2 mmol, 1 M in THF) was added and the reaction mixture was stirred for 30 min at the same temperature before 3-bromocyclohexene (258 mg, 1.6 mmol) was added at -78 °C. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with diethyl ether (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, pentane / Et_2O = 5:1) furnished the compound **20** as yellowish oil (274 mg, 65% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm) = 8.63 (d, *J* = 4.9 Hz, 1H), 7.84 (d, *J* = 4.9 Hz, 1H), 5.90-5.98 (m, 1H), 5.61-5.68 (m, 1H), 4.08-4.15 (m, 1H), 2.00-2.17 (m, 3H), 1.78-1.89 (m, 1H), 1.53-1.72 (m, 2H).

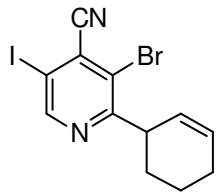
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 165.2, 148.3, 129.0, 127.1, 124.6, 124.3, 122.2, 115.5, 42.6, 28.4, 24.5, 21.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3026, 2932, 2860, 2836, 2238, 2192, 1680, 1650, 1568, 1536, 1446, 1432, 1394, 1382, 1344, 1326, 1298, 1266, 1238, 1192, 1156, 1136, 1114, 1082, 1060, 1048, 1022, 944, 916, 892, 838, 810, 784, 760, 744, 720, 702, 634, 618.

MS (70 eV, EI) *m/z* (%): 262 [M^+] (33), 235 (100), 223 (16), 198 (21), 183 (20), 155 (11), 142 (10), 79 (5), 67 (19).

HRMS (EI) for **$C_{12}H_{11}BrN_2$** (262.0106): 262.0115.

Synthesis of 3-bromo-2-(cyclohex-2-en-1-yl)-5-iodoisonicotinonitrile (20):



According to **TP1**, 3-bromo-2-(cyclohex-2-en-1-yl)isonicotinonitrile (**21;** 526 mg, 2.0 mmol) reacted with TMPMgCl·LiCl (**1**; 2.5 mL, 3.0 mmol, 1.2 M in THF) (-30 °C, 4 h). A solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with a sat. NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and a sat. aqueous $Na_2S_2O_3$ (2 mL) followed by extraction with diethyl ether (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, pentane / Et_2O = 10:1) furnished the compound **22** as yellow oil (521 mg, 67%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm) = 8.90 (s, 1H), 5.90-6.07 (m, 1H), 5.56-5.72 (m, 1H), 2.00-2.22 (m, 3H), 1.80-1.94 (m, 1H), 1.54-1.75 (m, 2H).

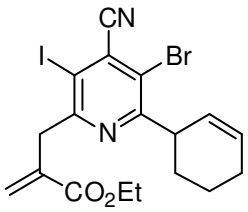
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 164.1, 155.5, 130.9, 129.5, 123.3, 116.7, 93.6, 42.5, 28.5, 24.6, 21.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3746, 3736, 3024, 3018, 3004, 2970, 2942, 2936, 2906, 2896, 2362, 2340, 2284, 1792, 1736, 1718, 1540, 1508, 1496, 1490, 1482, 1474, 1436, 1420, 1406, 1364, 1340, 1320, 1294, 1264, 1228, 1214, 1164, 1142, 1128, 1044, 1024, 934, 822, 722, 640, 624, 610.

MS (EI, 70 eV) m/z (%): 389 [M^+] (65), 360 (99), 359 (100), 321 (23), 308 (40), 154 (21).

HRMS (EI) for **$C_{12}H_{10}BrIN_2$** (387.9072): 387.9049.

Synthesis of ethyl 2-((5-bromo-4-cyano-6-(cyclohex-2-en-1-yl)-3-iodopyridin-2-yl)methyl)acrylate (21):



According to **TP1**, 3-bromo-2-(cyclohex-2-en-1-yl)-5-iodoisonicotinonitrile (**22**; 389 mg, 1.0 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**16**; 1.5 mmol, 2.0 mL, 0.75 M in THF) (25 °C, 20 h). The reaction mixture was cooled to -30 °C and CuCN·2LiCl (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise. After stirring for 30 min at the same temperature ethyl 2-(bromomethyl)acrylate (232 mg, 1.2 mmol) was added. The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with a sat. aqueous NH_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with diethyl ether (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, pentane / Et_2O = 20:1) afforded the product **23** as yellow oil (311 mg, 62%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm) = 6.27-6.32 (m, 1H), 5.77-5.88 (m, 1H), 5.50-5.58 (m, 1H), 5.43-5.46 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.92-4.03 (m, 3H), 2.00-2.12 (m, 2H), 1.90-1.98 (m, 1H), 1.80-1.89 (m, 1H), 1.59-1.75 (m, 2H), 1.14-1.31 (m, 4H).

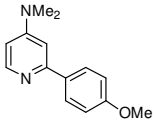
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 166.8, 163.3, 161.0, 137.8, 132.3, 129.1, 127.1, 127.1, 120.4, 117.9, 96.8, 61.2, 44.3, 42.5, 28.1, 25.0, 21.6, 14.6.

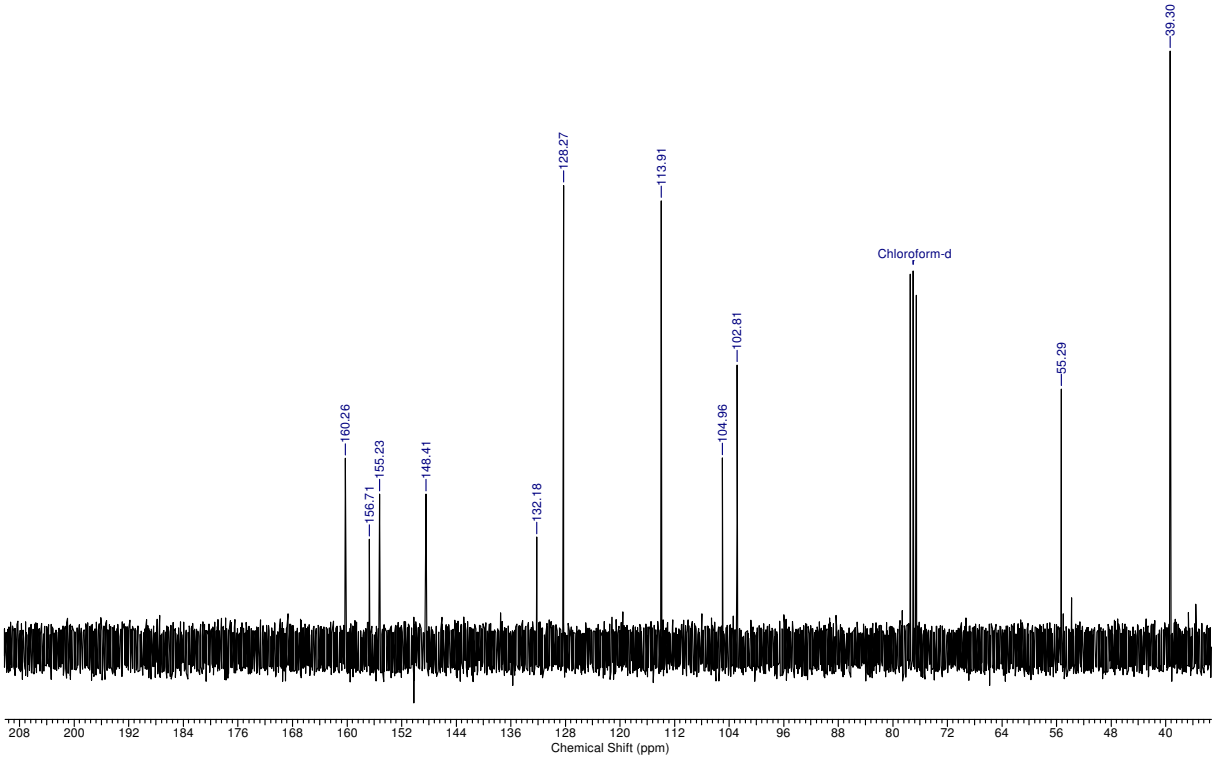
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2934, 2838, 2360, 2340, 1718, 1654, 1646, 1630, 1540, 1522, 1506, 1430, 1414, 1388, 1368, 1338, 1324, 1296, 1258, 1216, 1184, 1148, 1114, 1096, 1044, 1026, 956, 916, 894, 858, 838, 824, 784, 768, 668, 658.

MS (EI, 70 eV) m/z (%): 501 [M^+] (99), 500 (27), 470 (65), 426 (56), 374 (100), 346 (19), 219 (11), 192 (21).

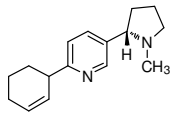
HRMS (EI) for **$C_{18}H_{18}BrIN_2O_2$** (499.9596): 499.9589.

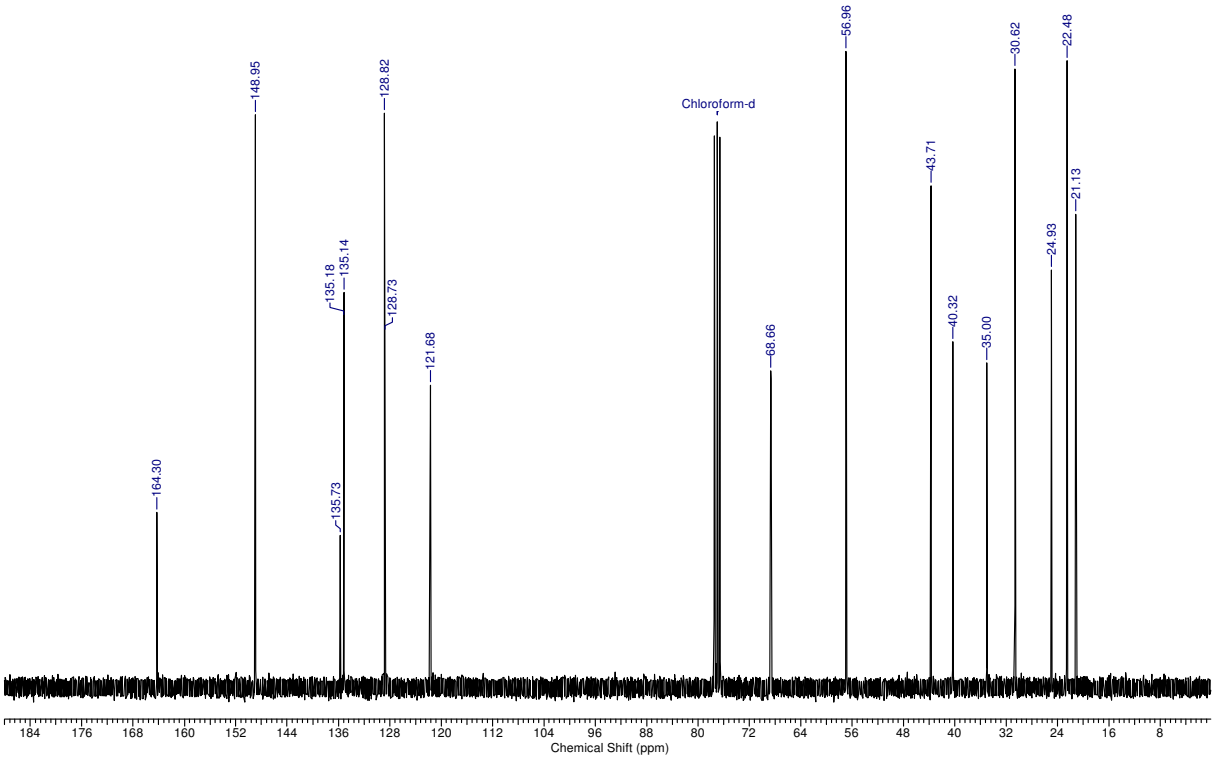
Synthesis of 2-(4-methoxyphenyl)-*N*,*N*-dimethylpyridin-4-amine (4a)



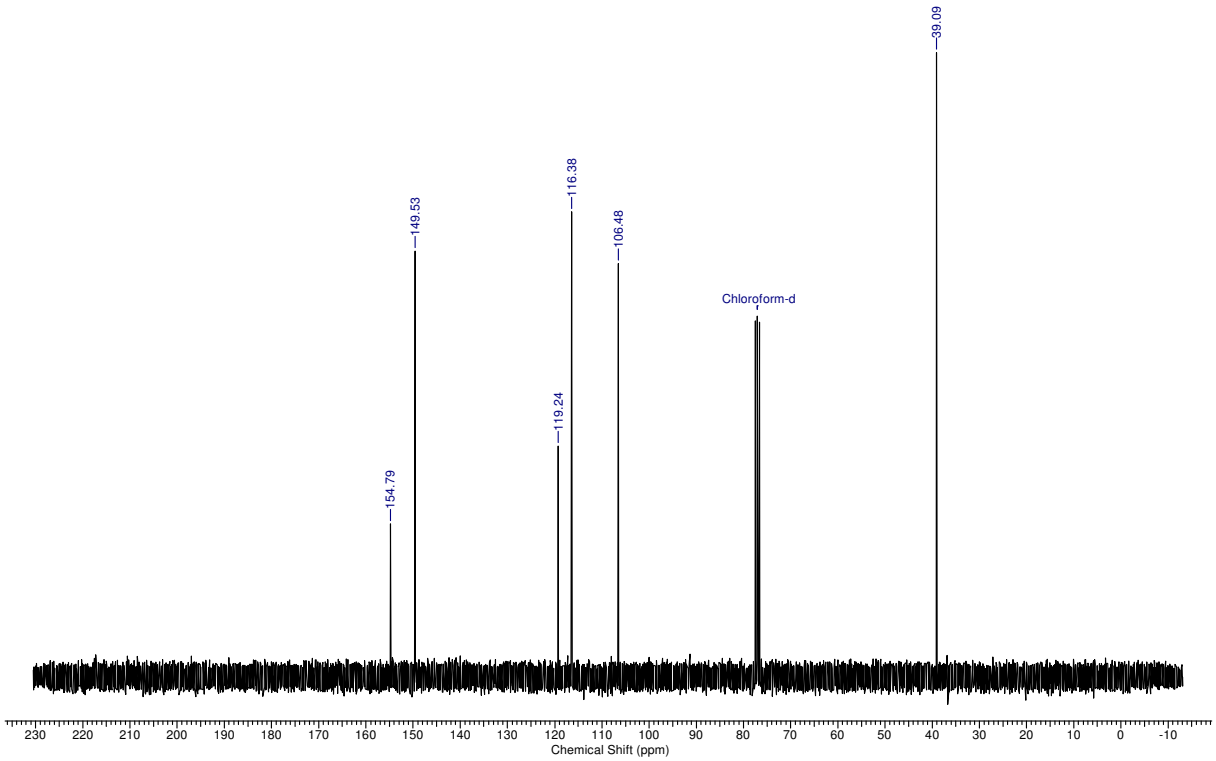


Synthesis of 2-(cyclohex-2-en-1-yl)-5-((S)-1-methylpyrrolidin-2-yl)pyridine (4b)

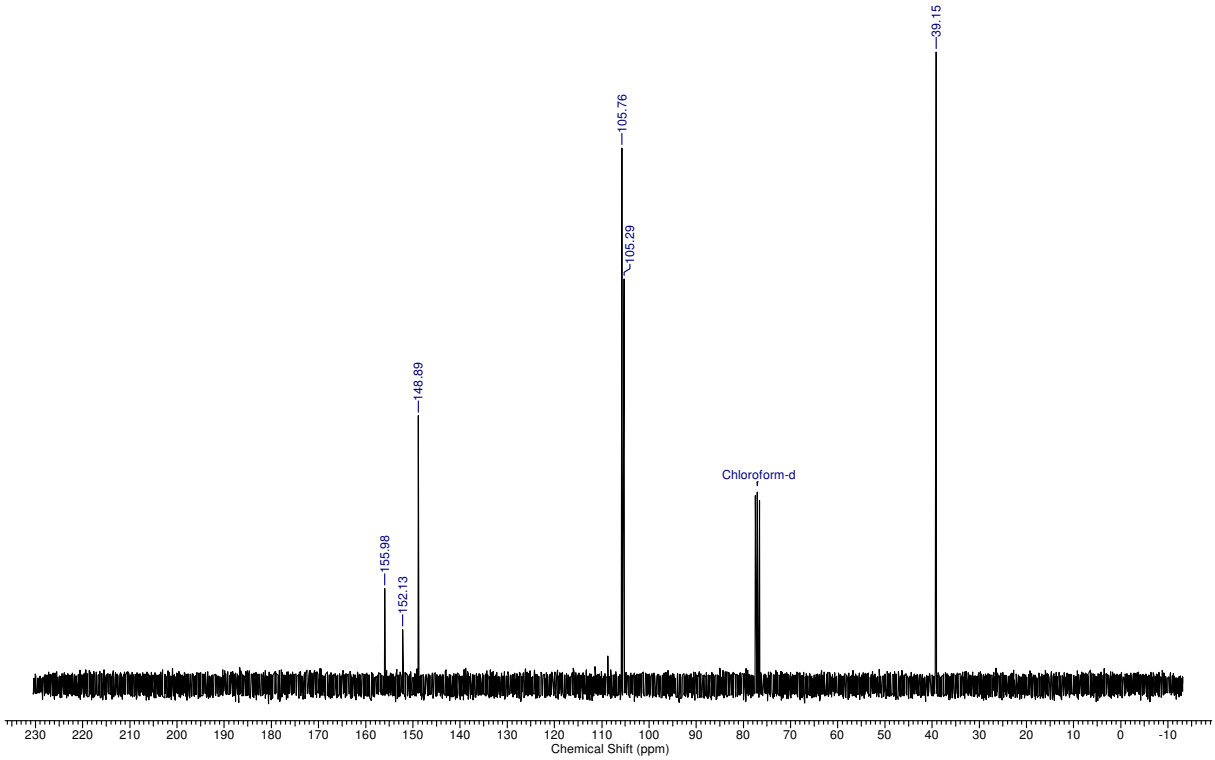




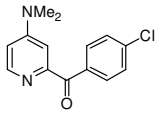
Synthesis of 2-iodo-*N*,*N*-dimethylpyridin-4-amine (4c)

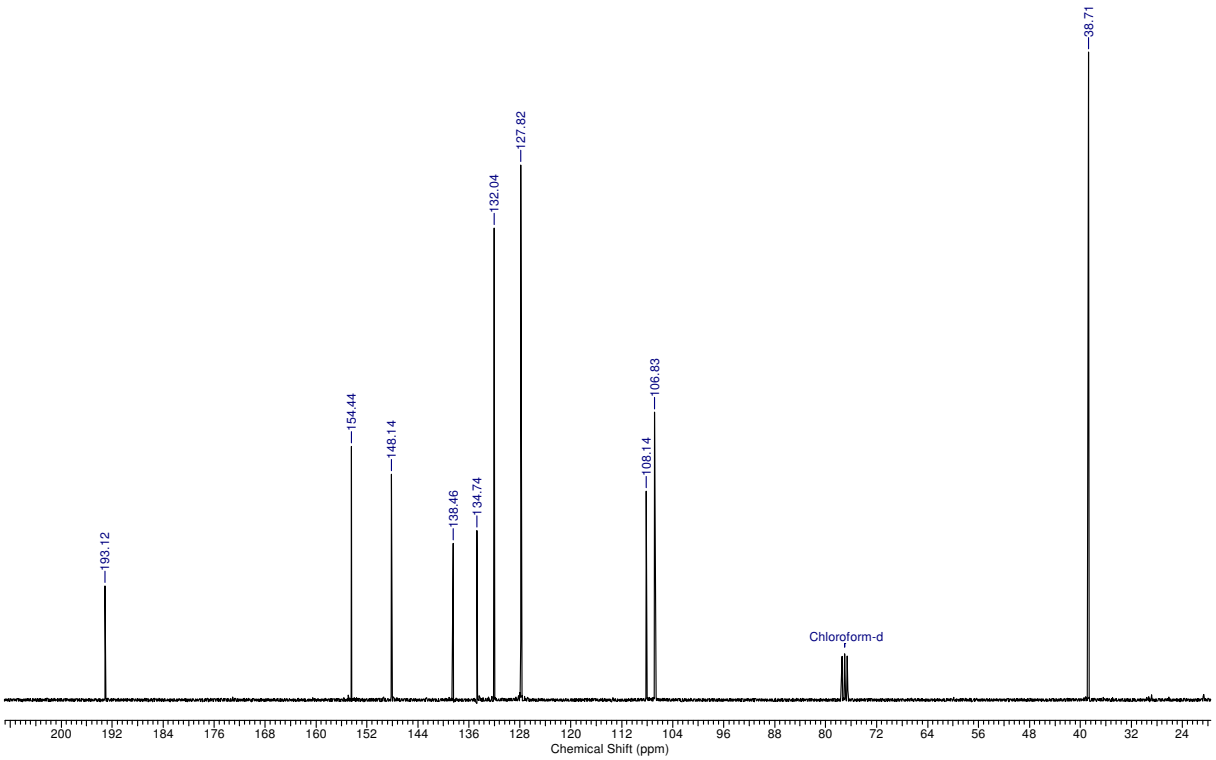


Synthesis of 2-chloro-*N*,*N*-dimethylpyridin-4-amine (4d)

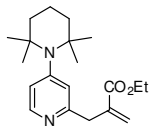


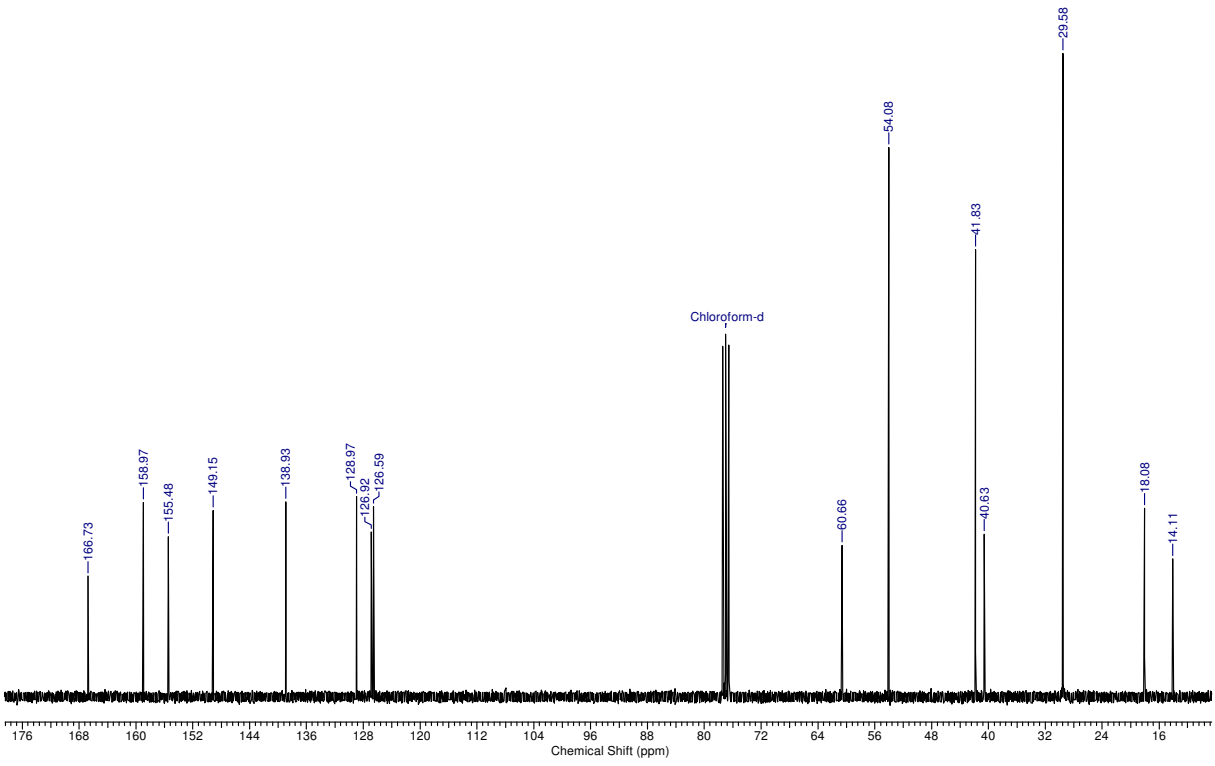
Synthesis of (4-chlorophenyl)(4-(dimethylamino)pyridin-2-yl)methanone (4e)



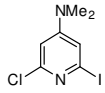


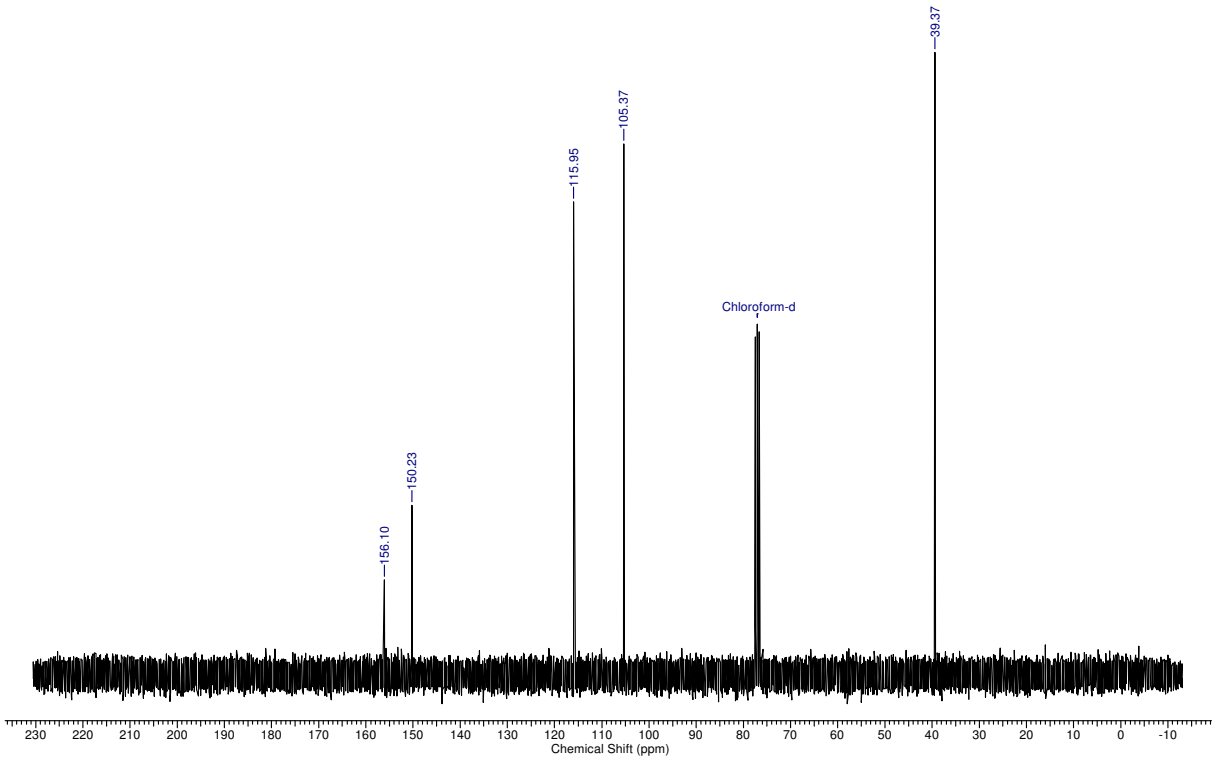
Synthesis of ethyl 2-((4-(2,2,6,6-tetramethylpiperidin-1-yl)pyridin-2-yl)methyl)acrylate (4f)



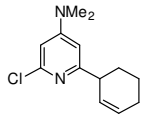


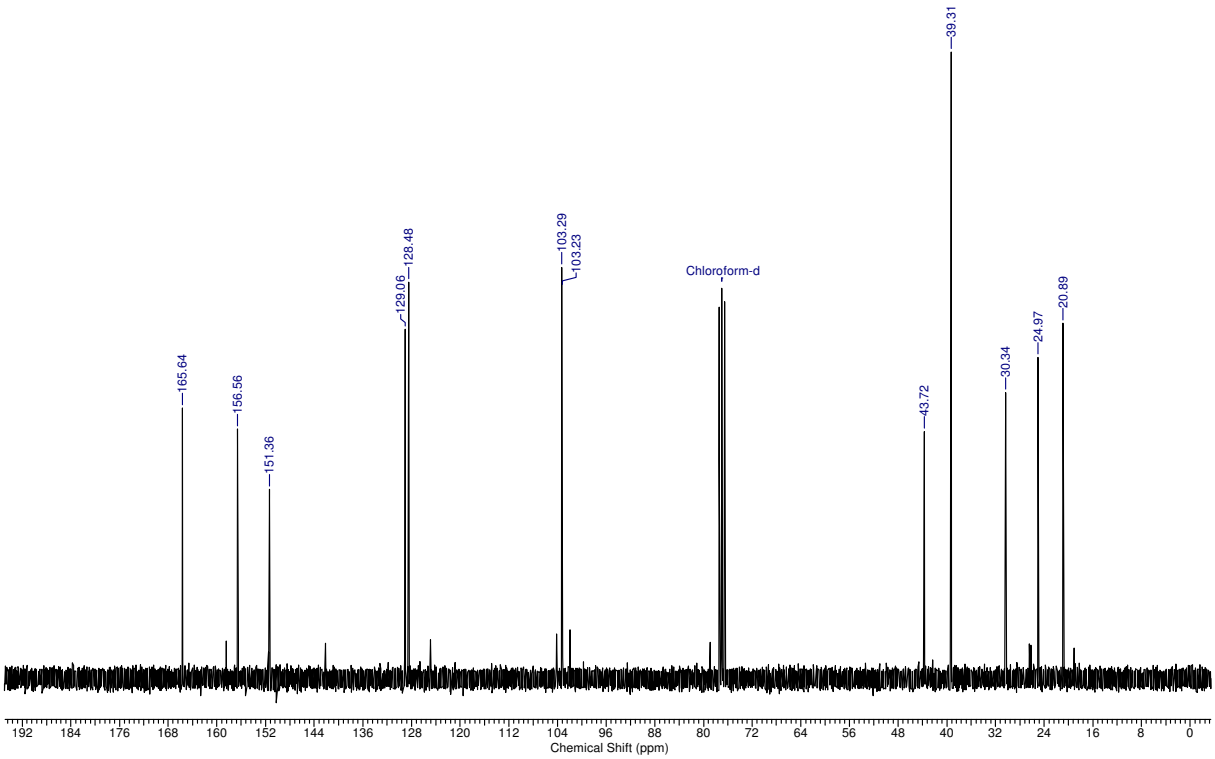
Synthesis of 2-chloro-6-iodo-*N*,*N*-dimethylpyridin-4-amine (4g)



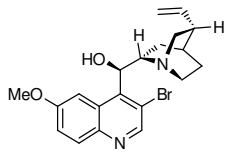


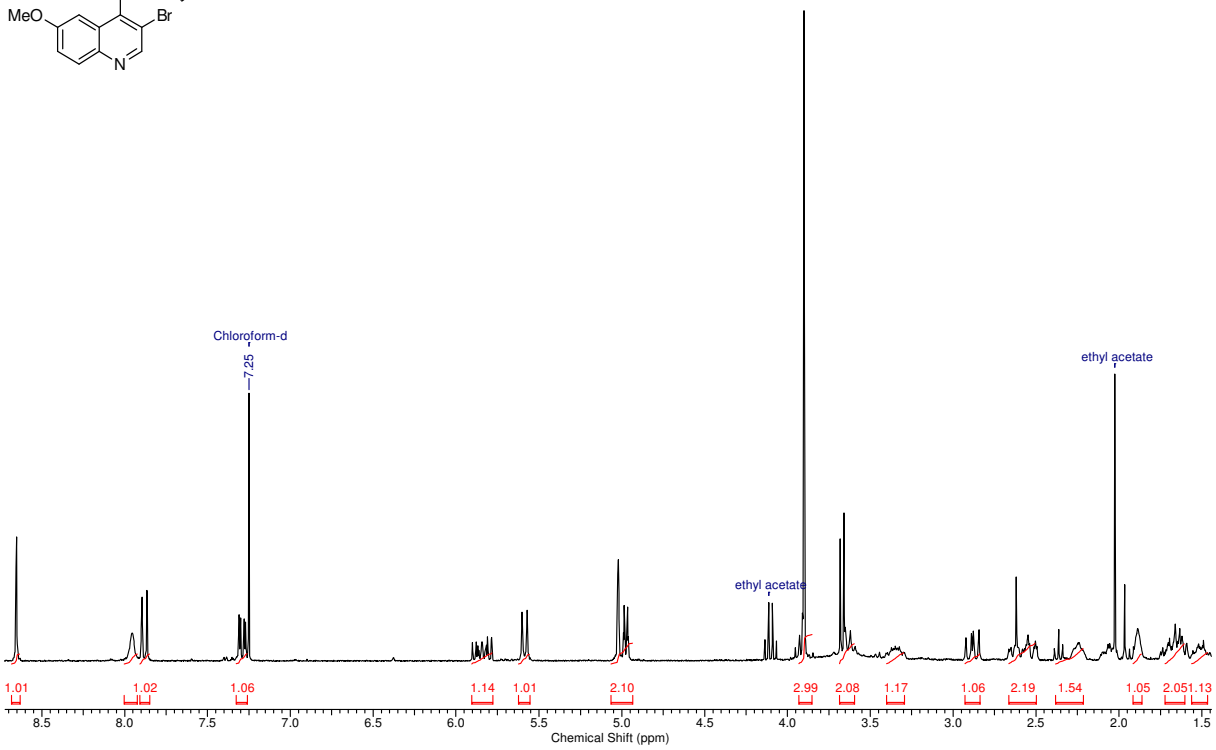
Synthesis of 2-chloro-6-cyclohex-2-en-1-yl-*N*,*N*-dimethylpyridin-4-amine (4h)

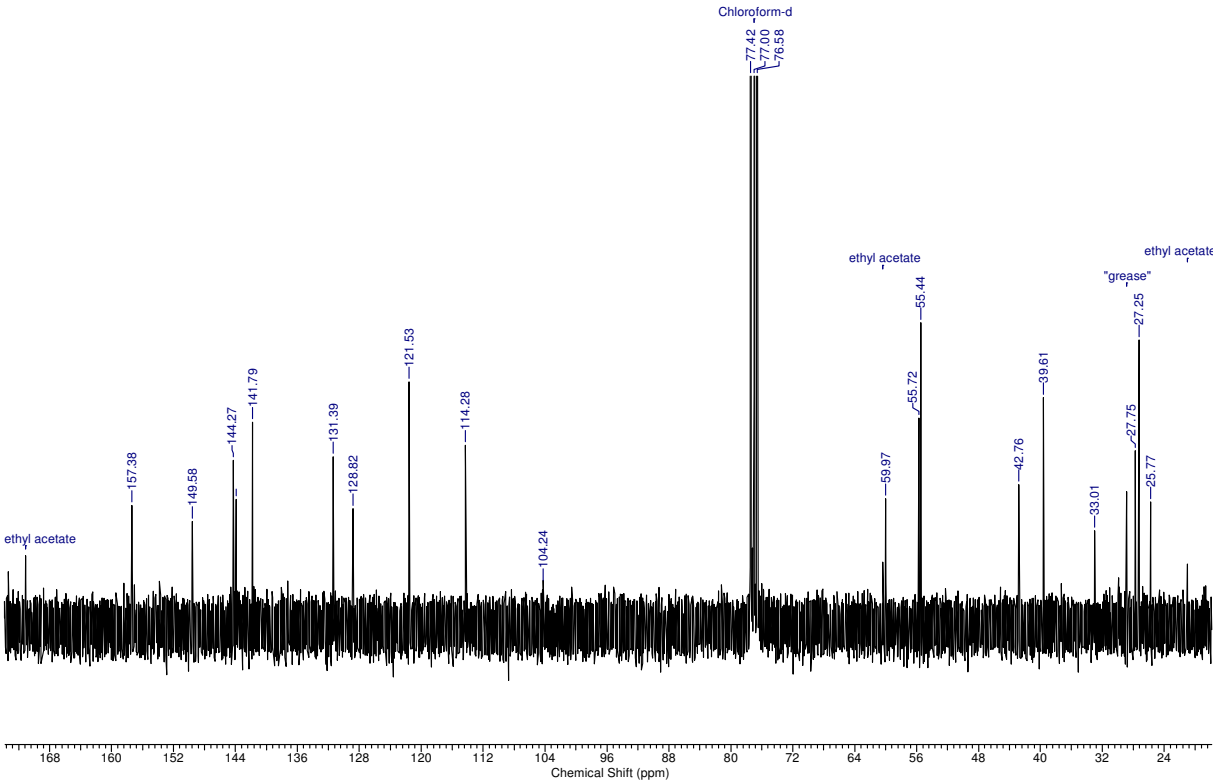




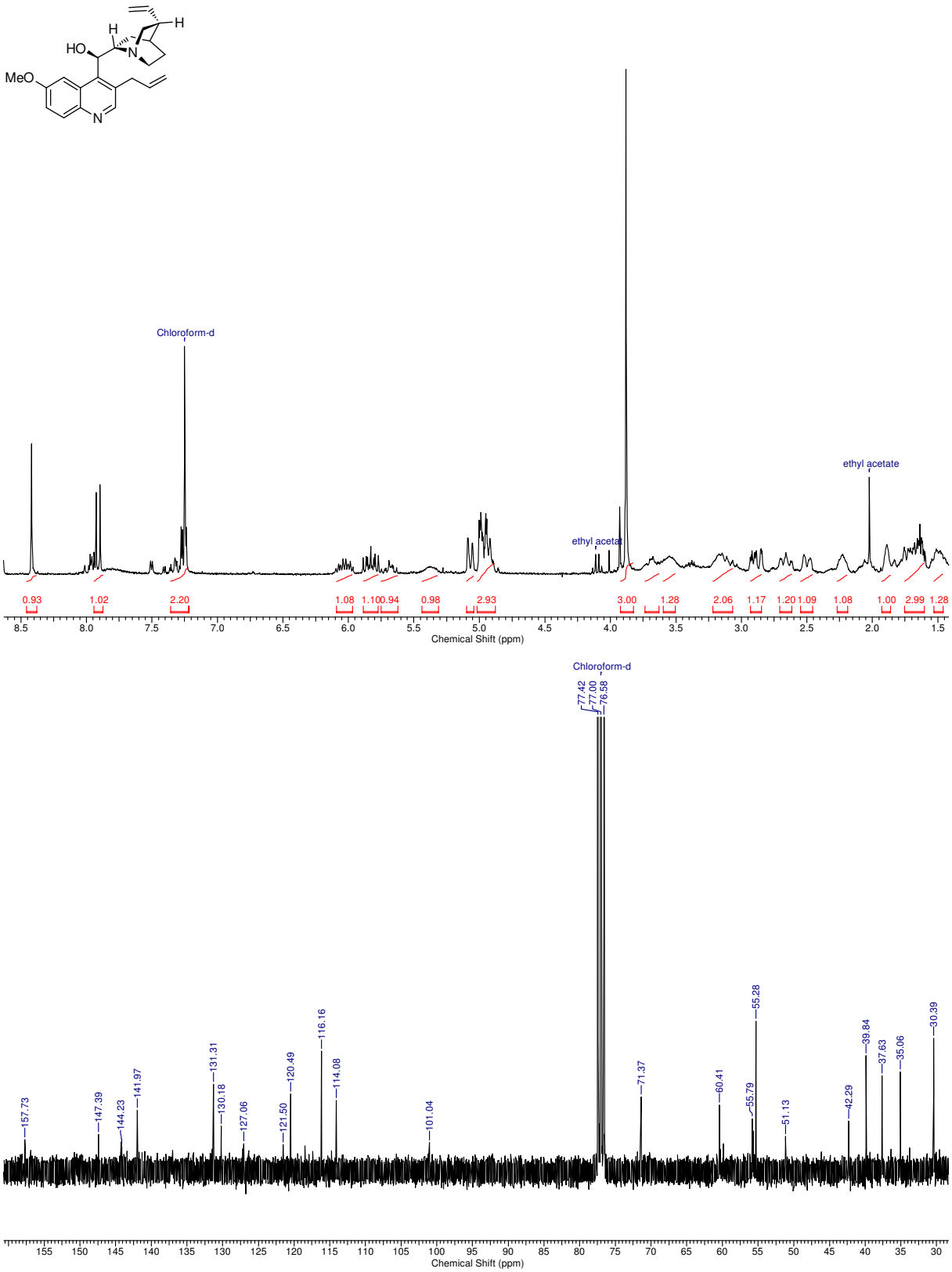
(*R*)-(3-Bromo-6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methanol (6a)



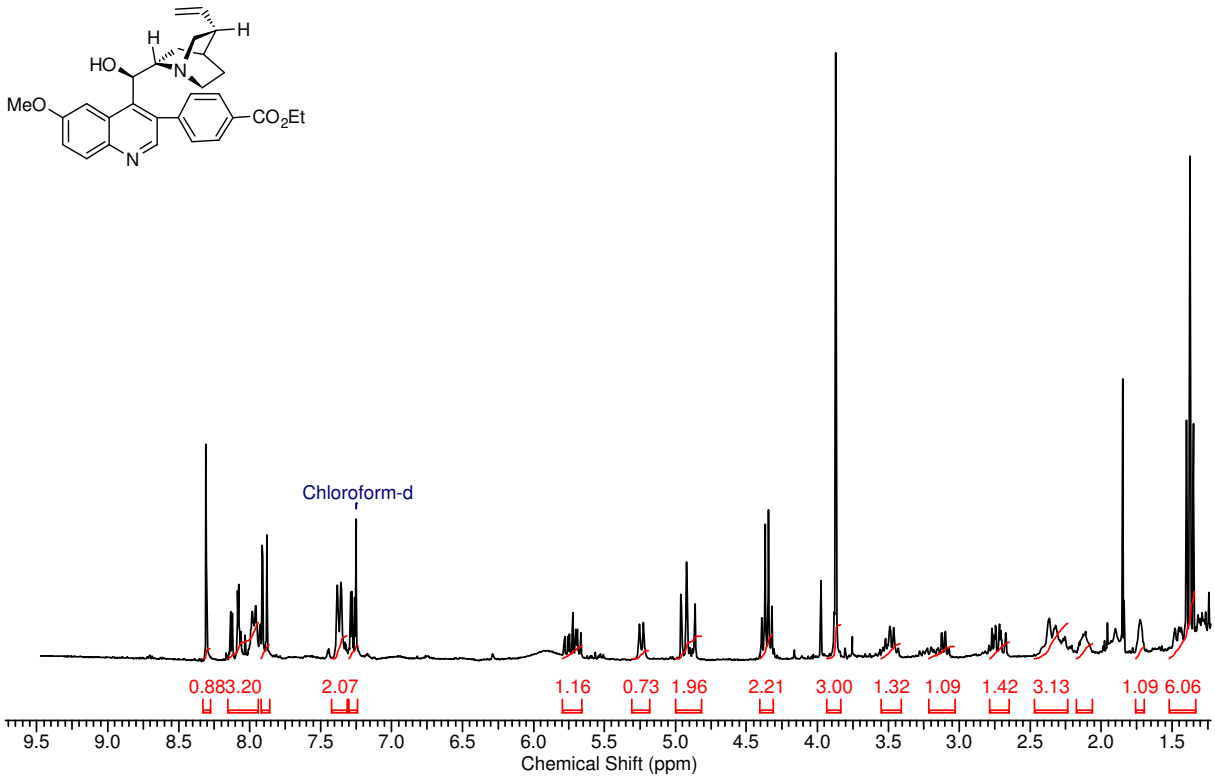


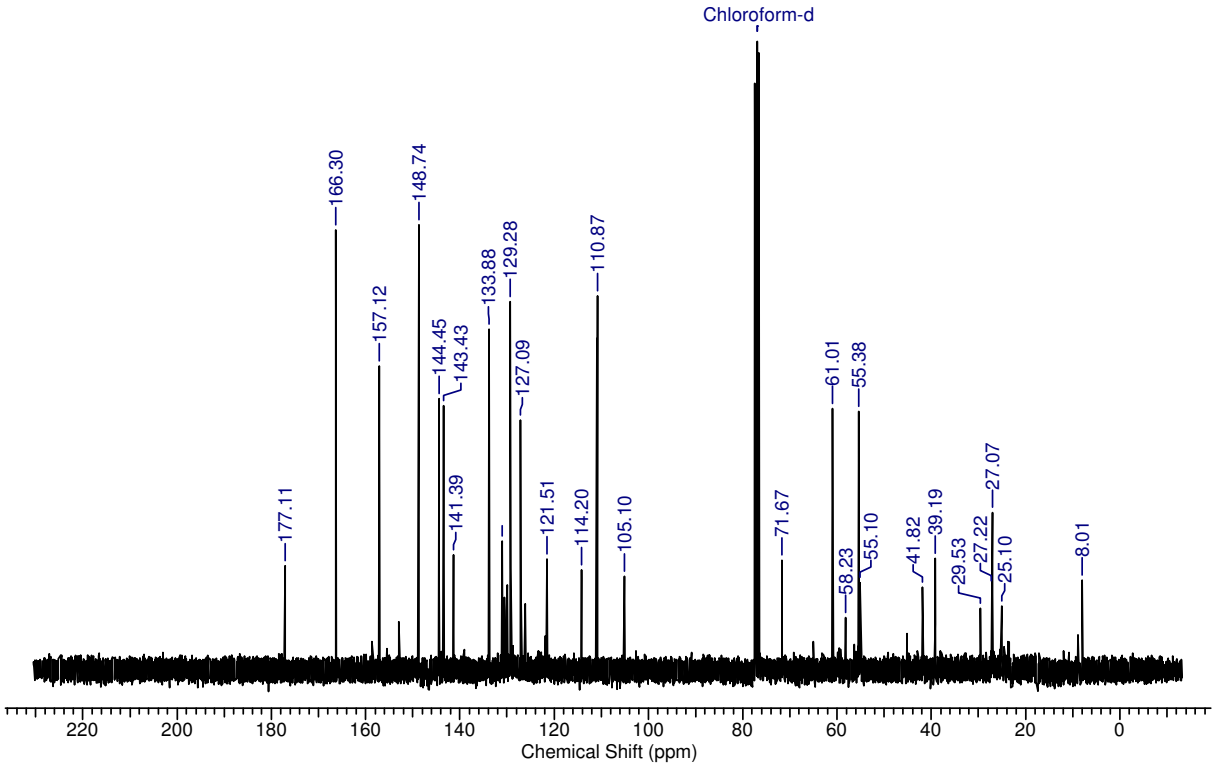


(*R*)-(3-Allyl-6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methanol (6c)

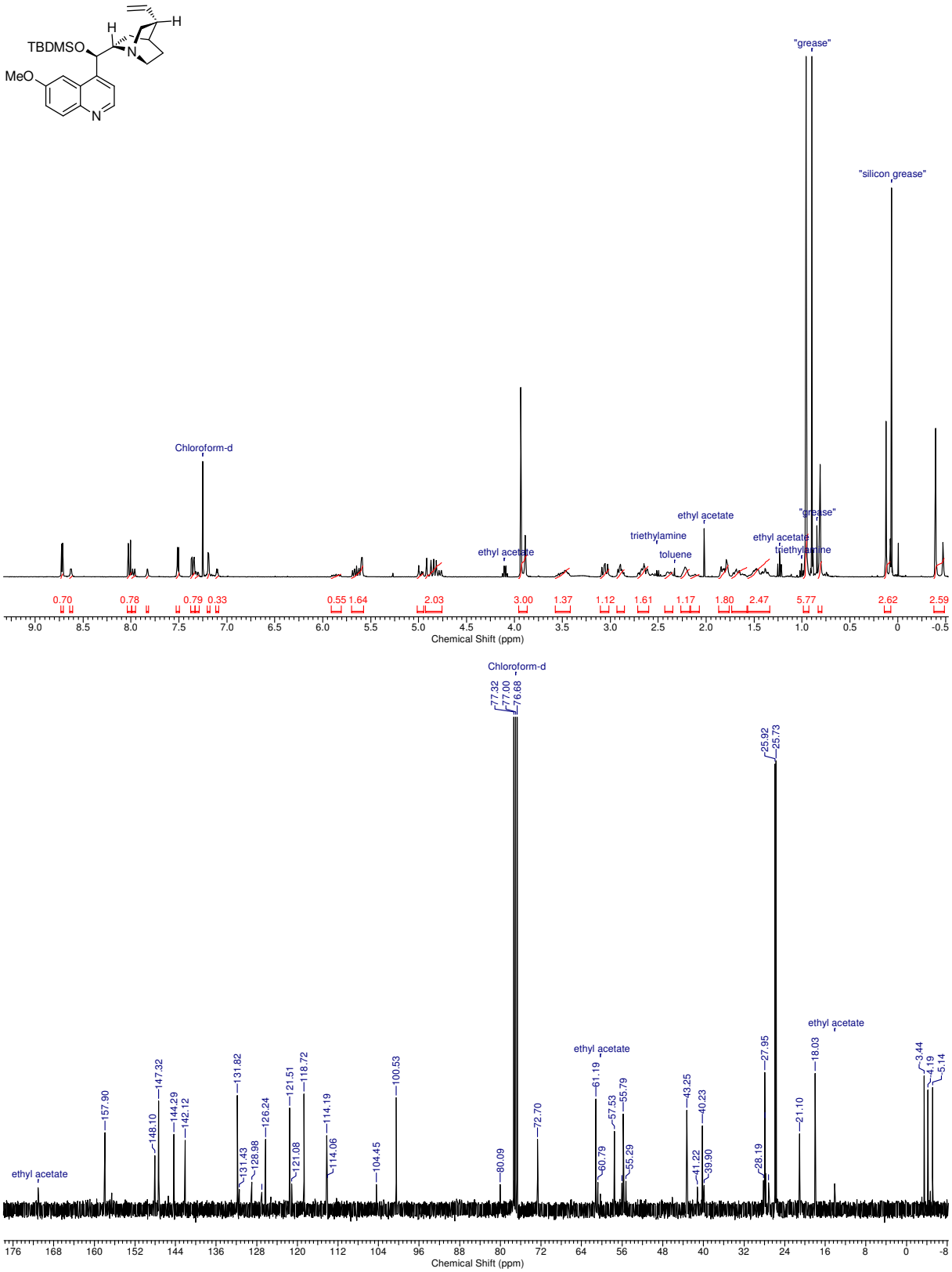


Ethyl 4-(4-((*R*)-hydroxy((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methyl)-6-methoxyquinolin-3-yl)benzoate (6d)

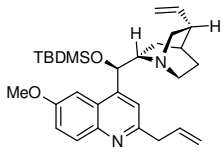


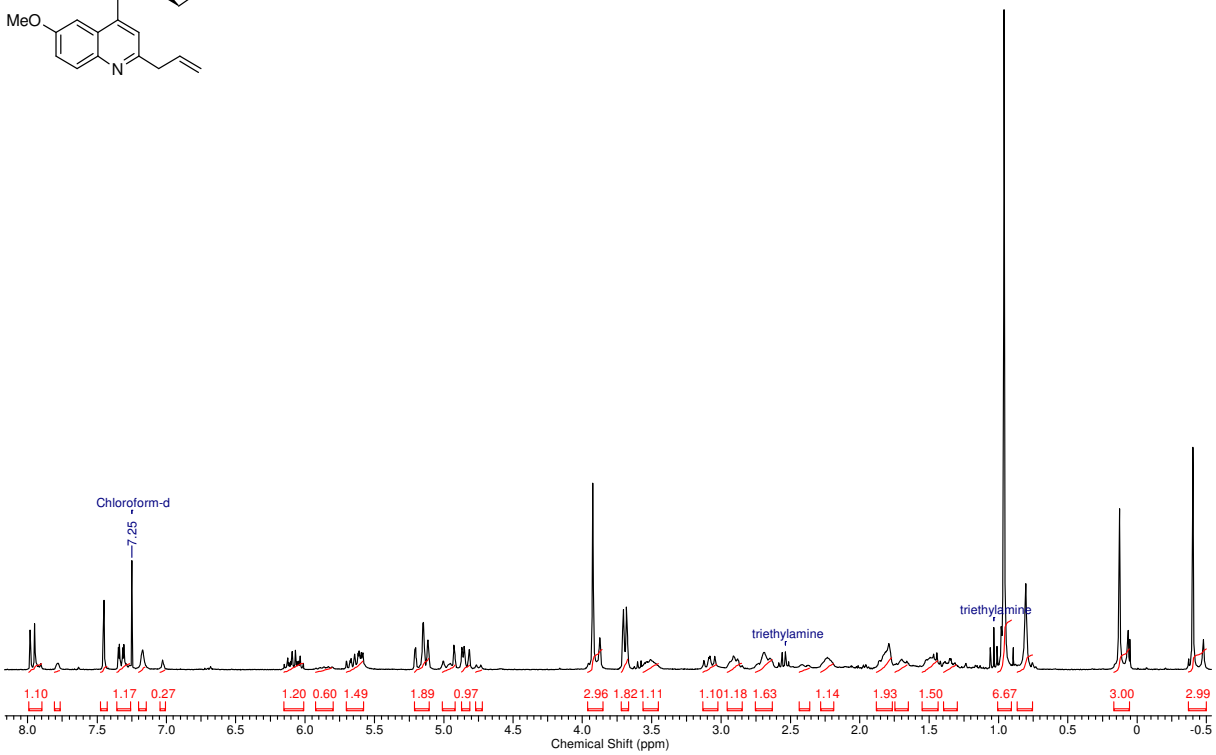


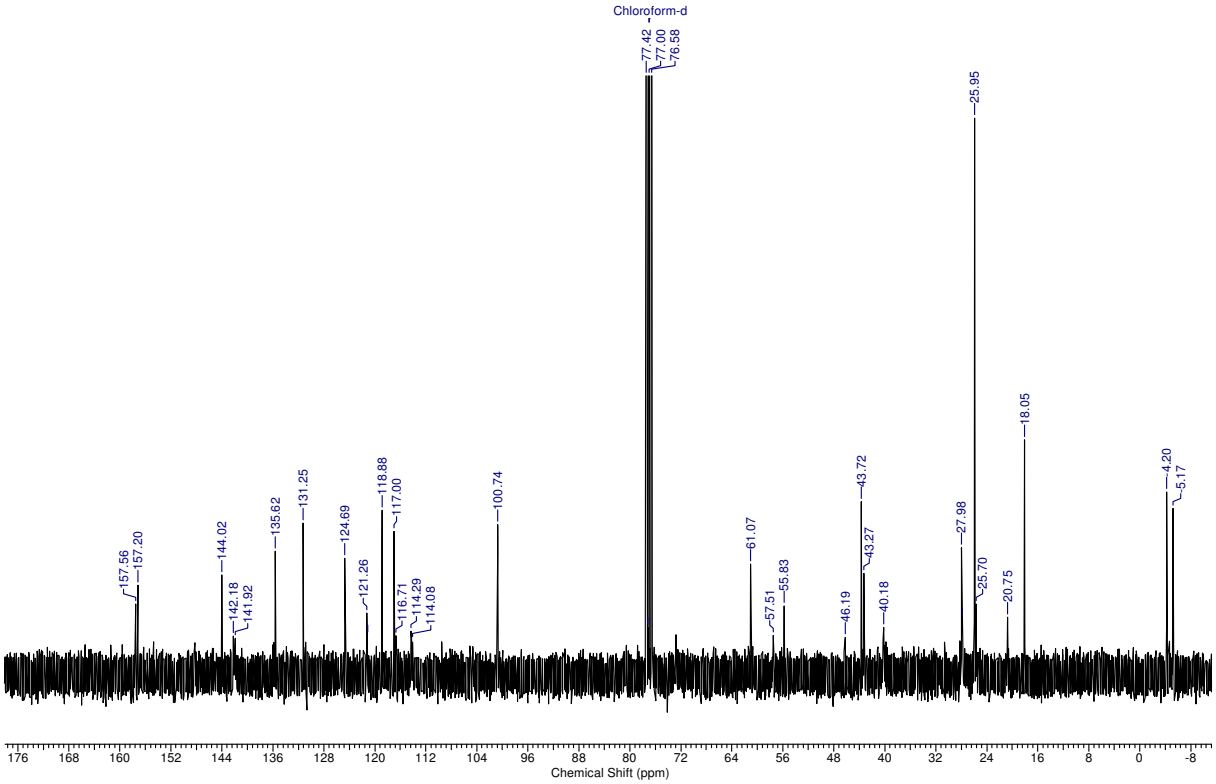
(2*S*,4*S*,8*R*)-2-((*R*)-(Tert-butyldimethylsilyloxy)(6-methoxyquinolin-4-yl)methyl)-8-vinylquinuclidine (7)



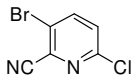
(2*S*,4*S*,5*R*)-2-((*R*)-(2-allyl-6-methoxyquinolin-4-yl)((tert-butyldimethylsilyl)oxy)methyl)-5-vinylquinuclidine (8b)

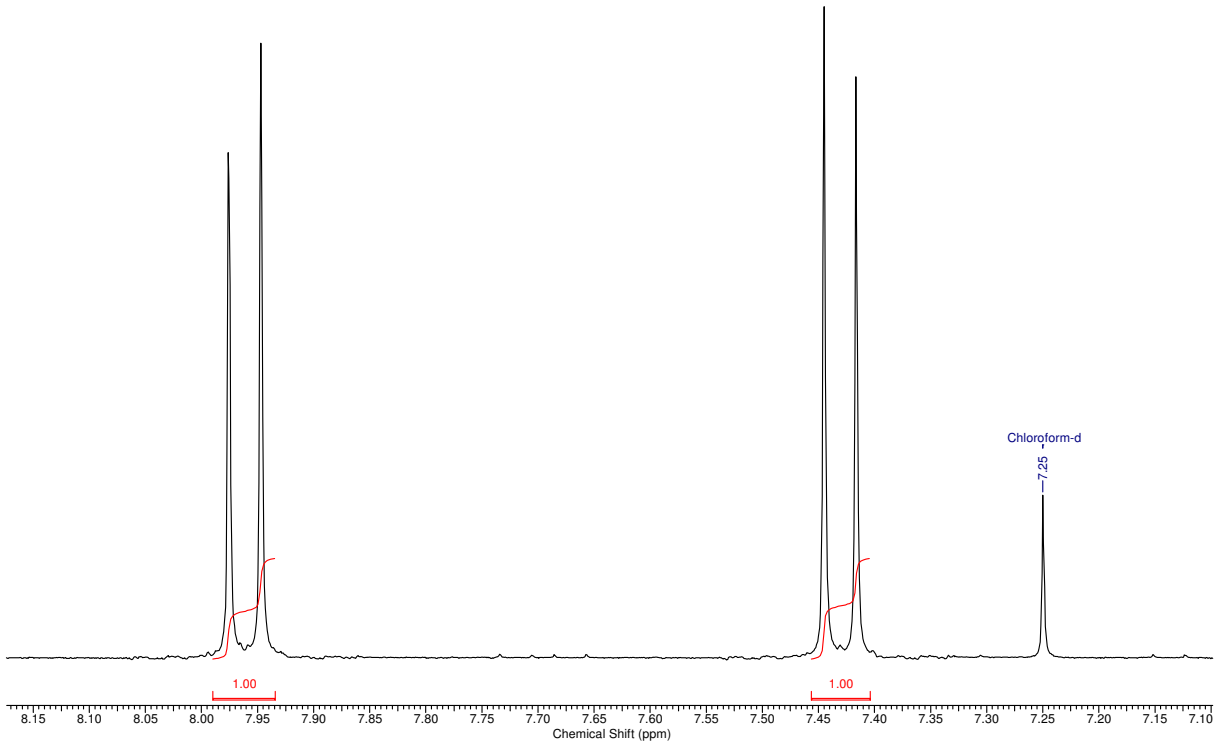


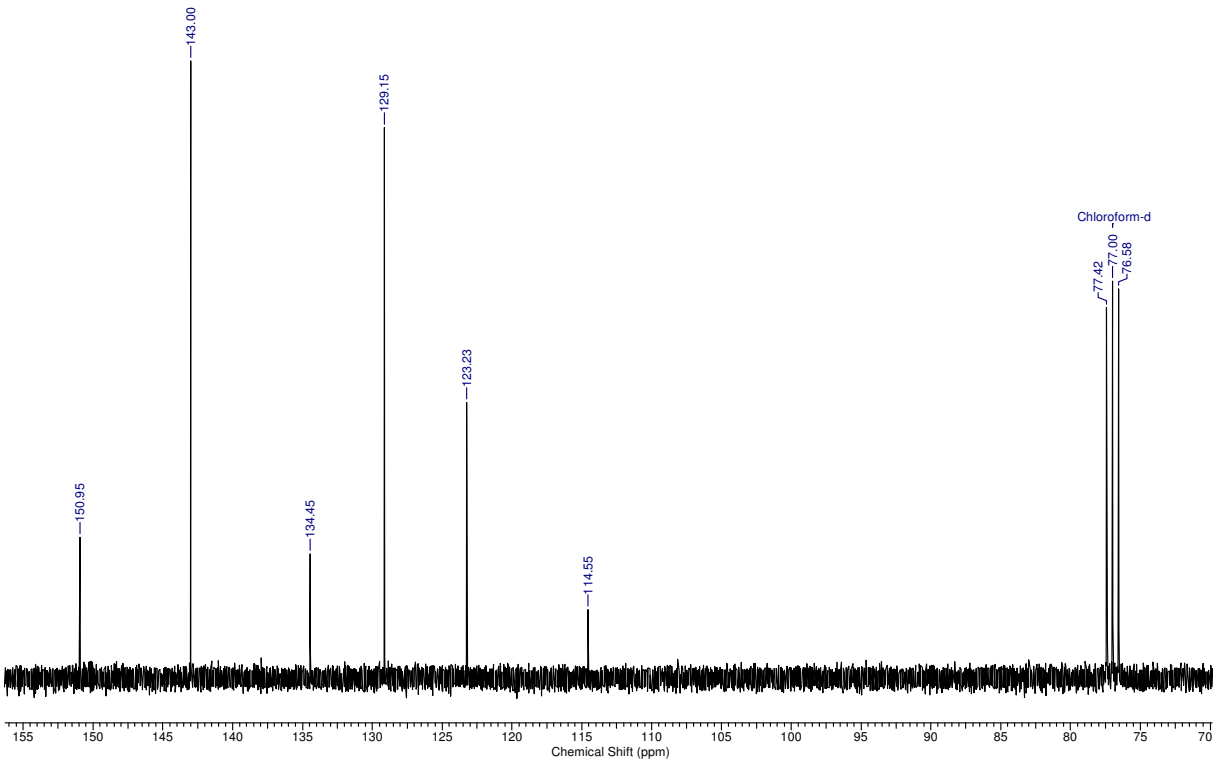




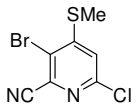
3-Bromo-6-chloropicolinonitrile (11)

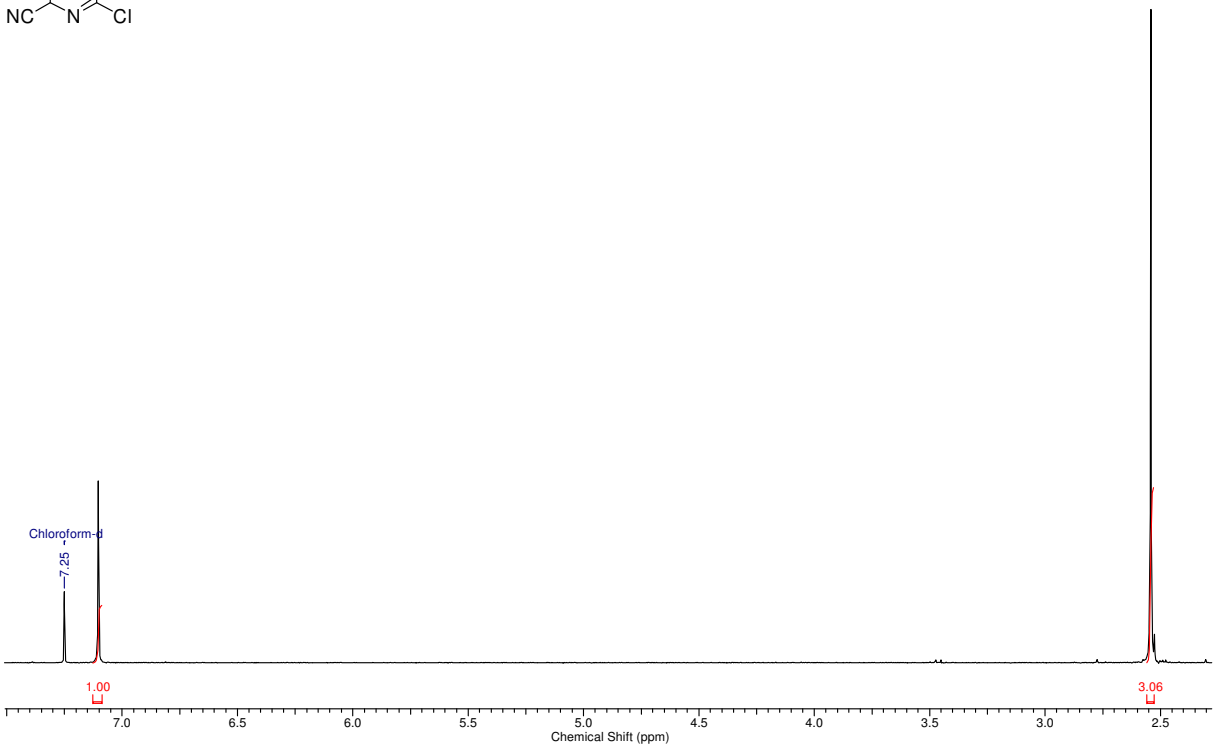


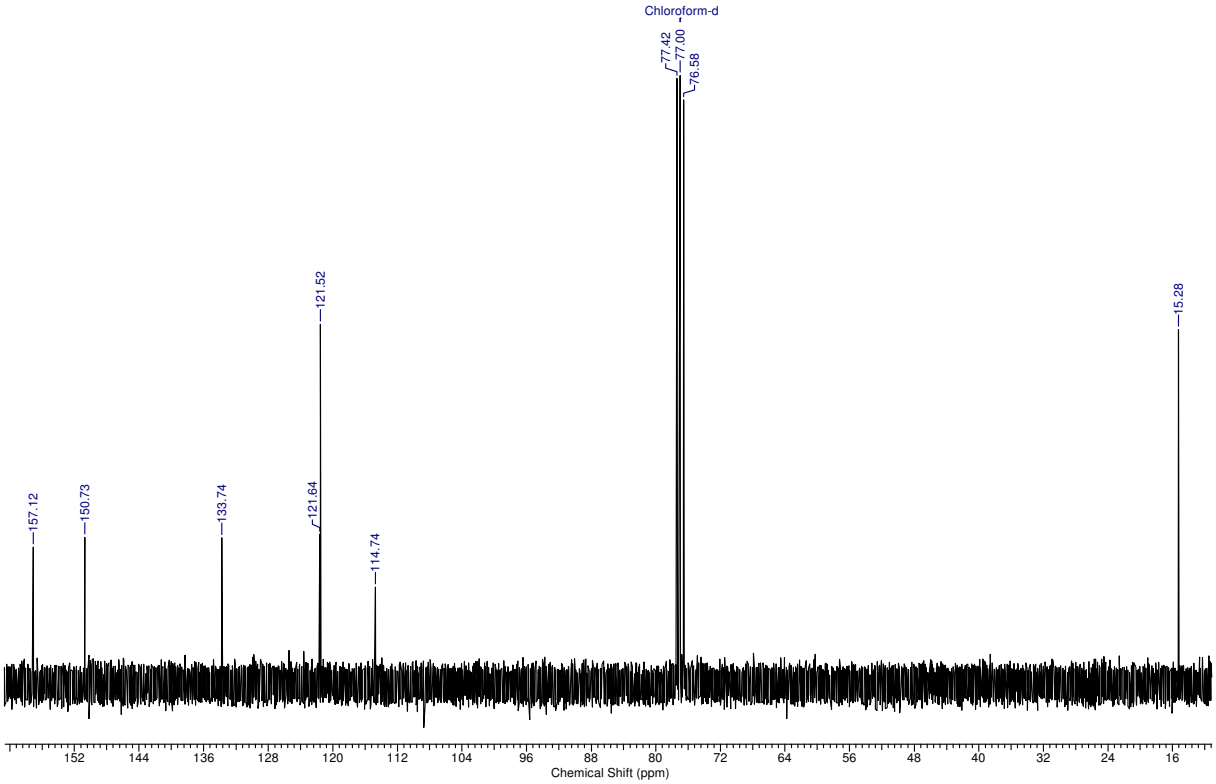




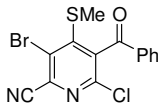
3-bromo-6-chloro-4-(methylthio)picolinonitrile (13)

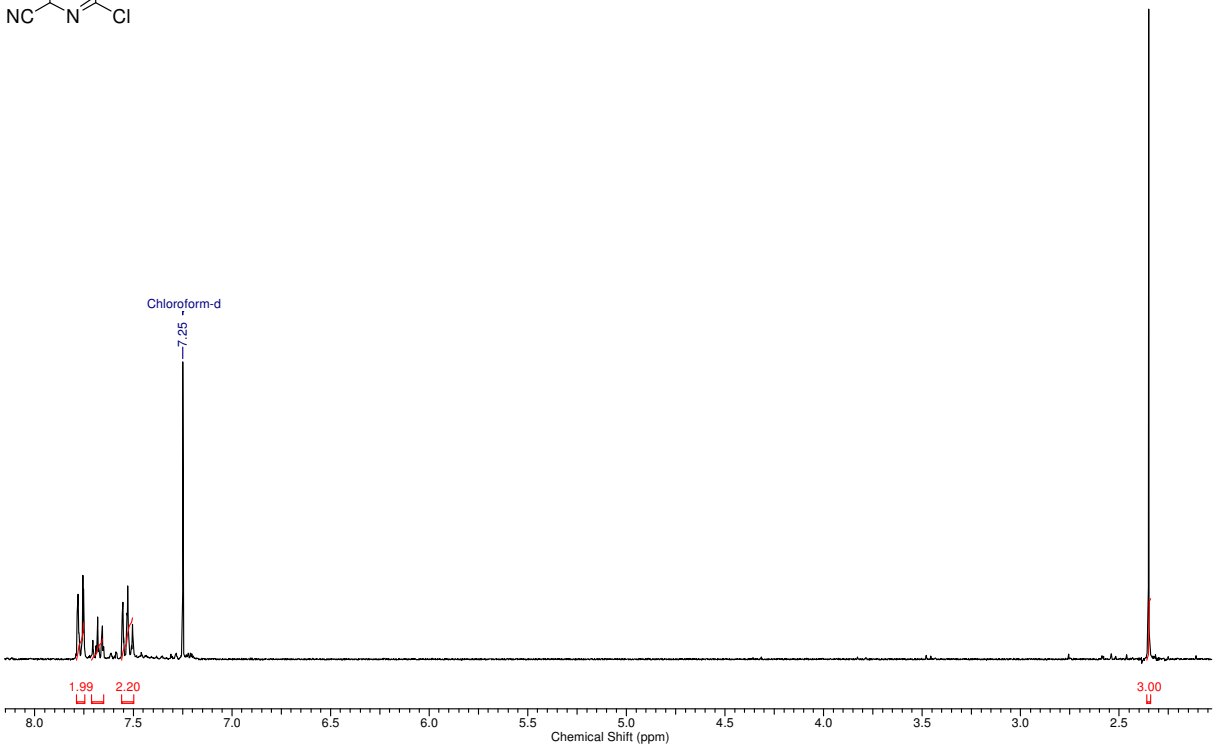


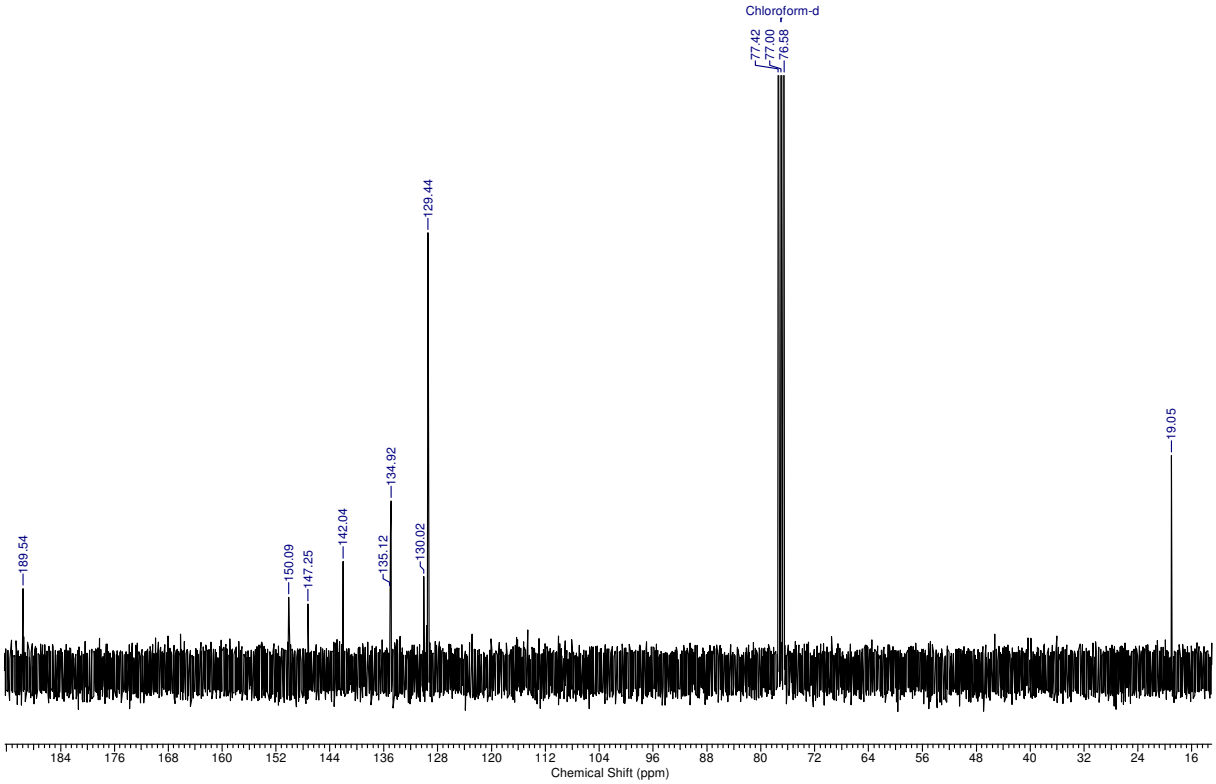




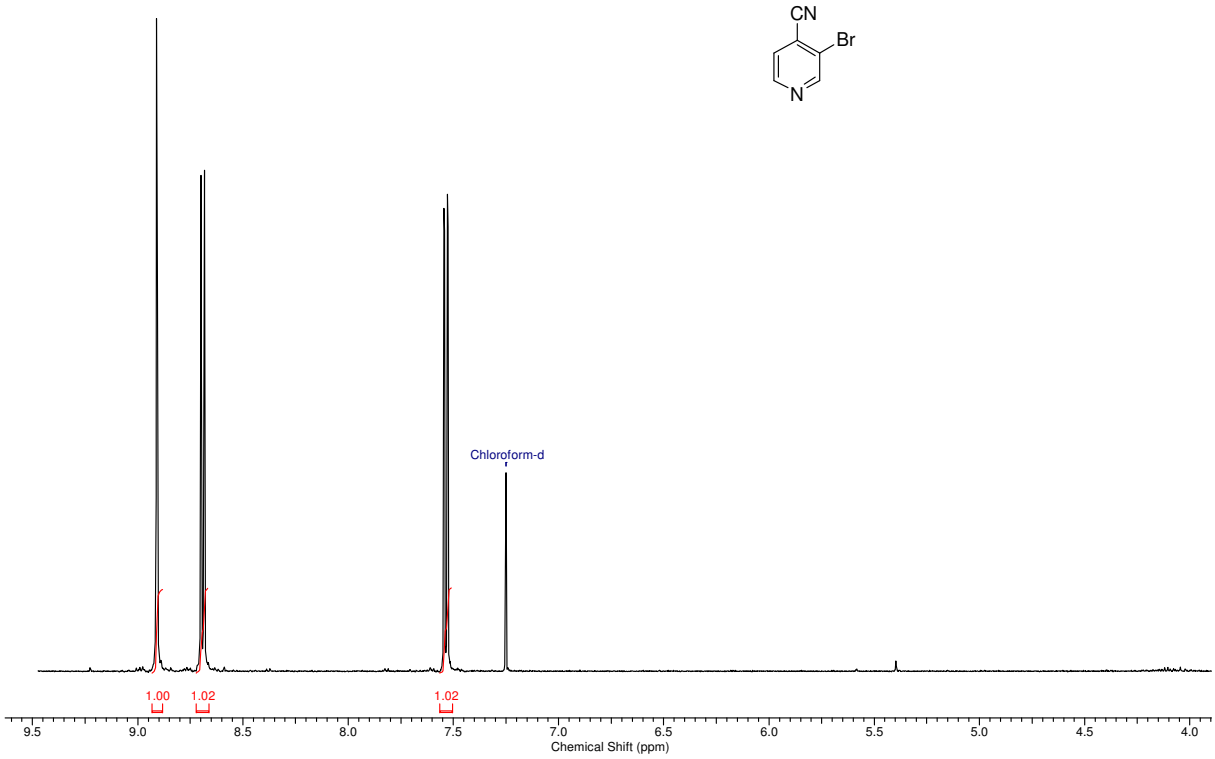
5-benzoyl-3-bromo-6-chloro-4-(methylthio)picolinonitrile (16)

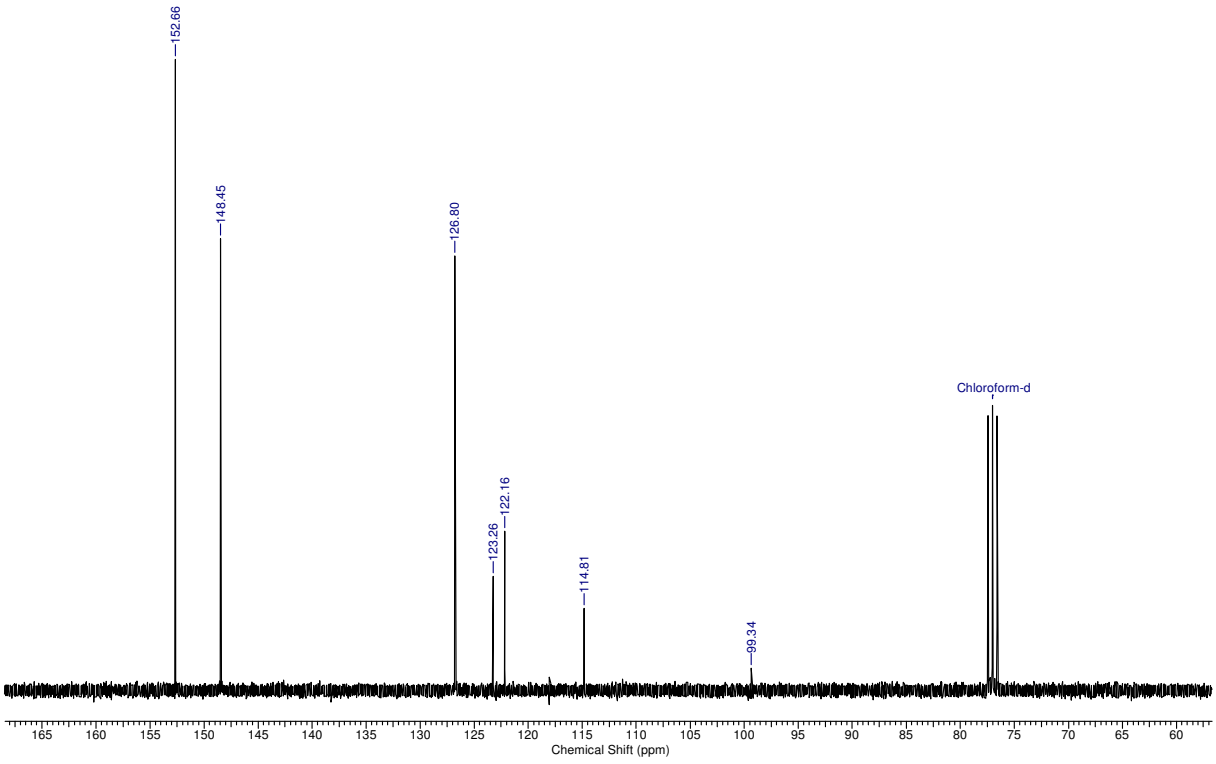




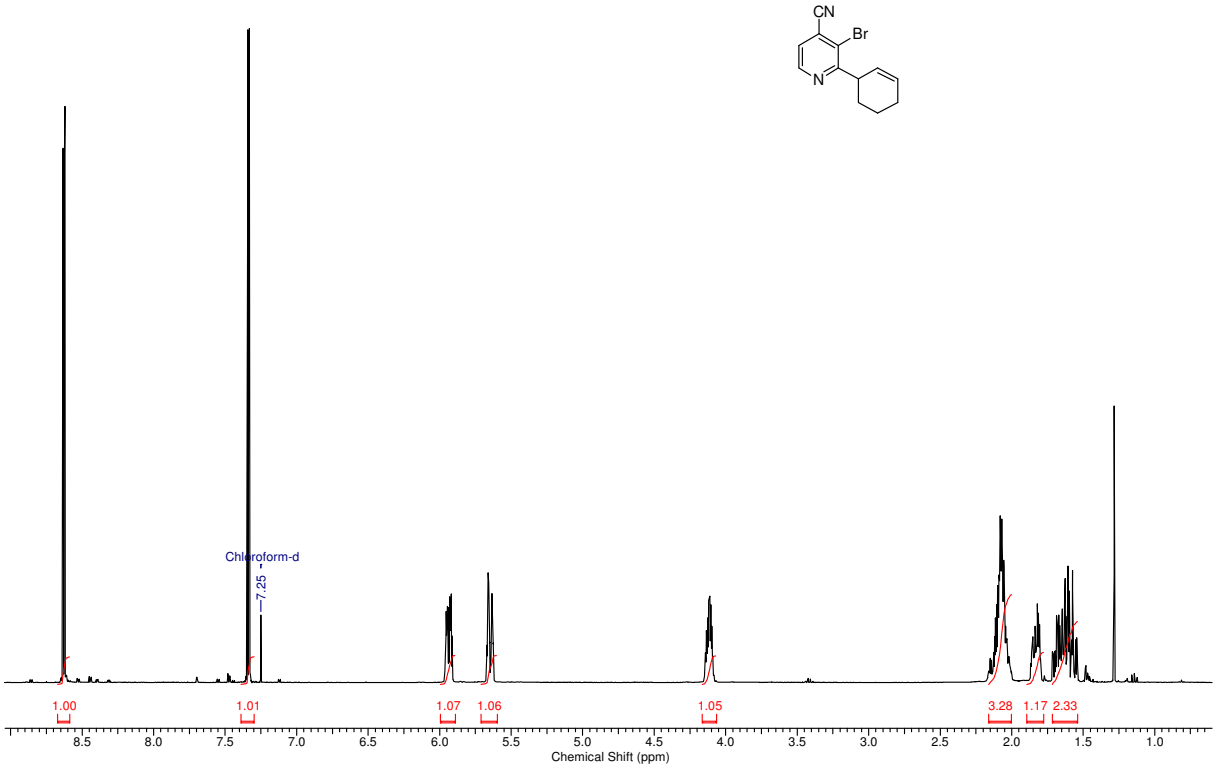


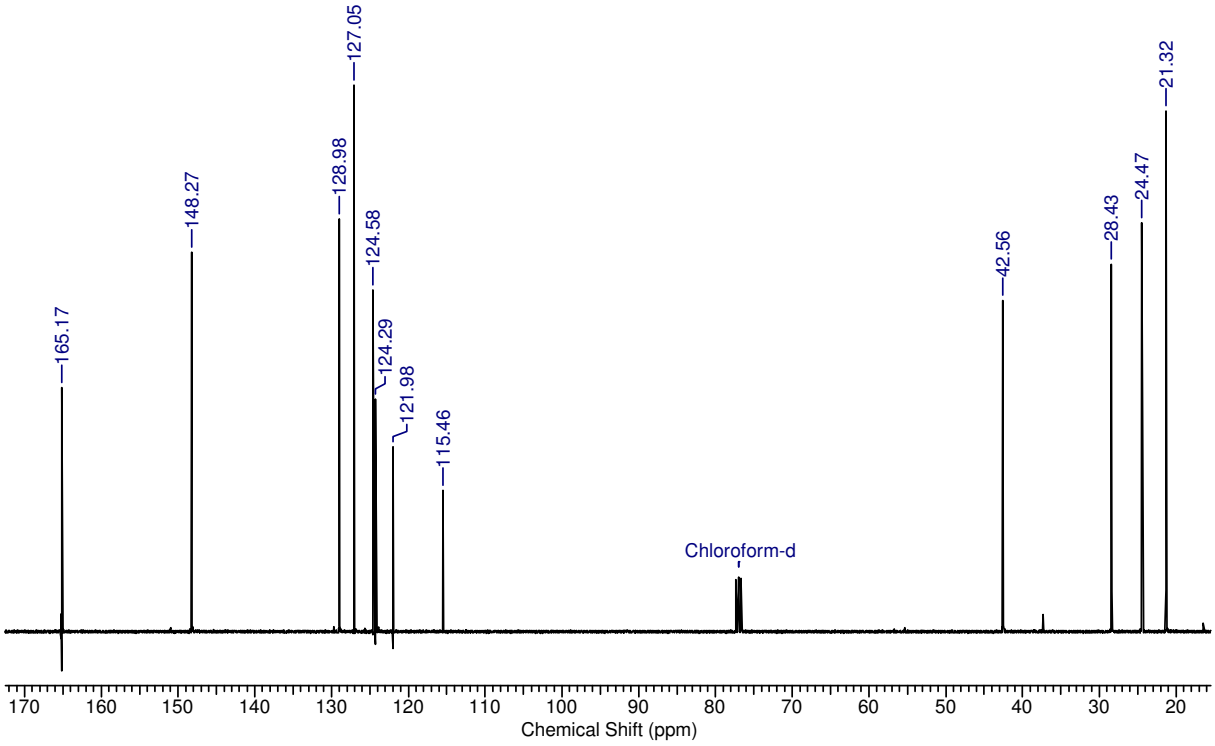
3-bromoisonicotinonitrile (17)



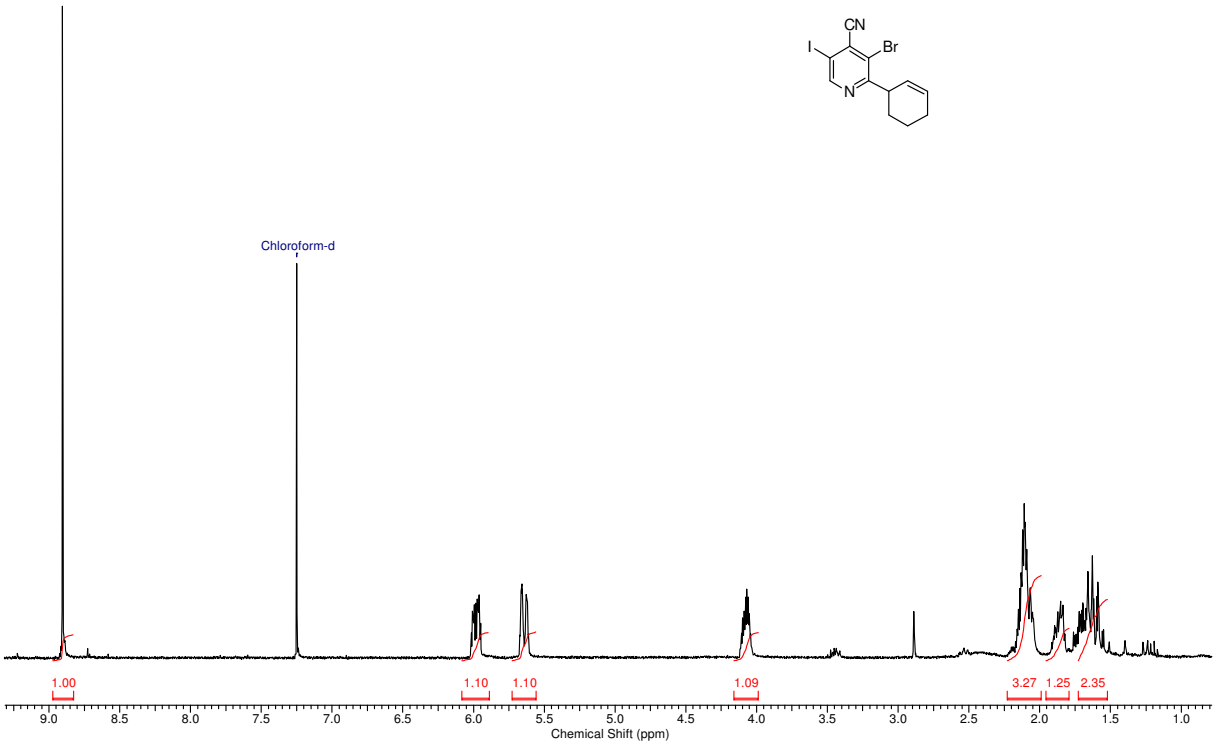


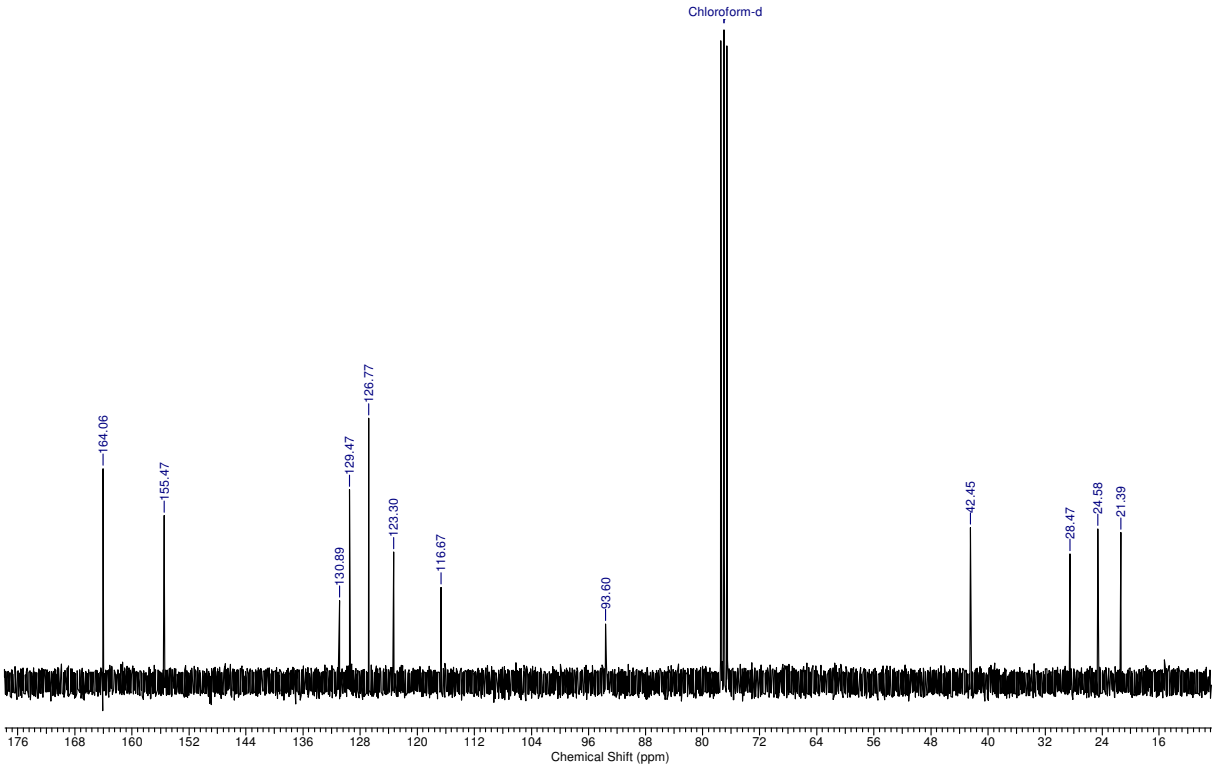
3-bromo-2-cyclohexylisonicotinonitrile (18):





3-Bromo-2-(cyclohex-2-en-1-yl)-5-iodoisonicotinonitrile (20):





3-bromo-2-(cyclohex-2-en-1-yl)-5-iodoisonicotinonitrile (21):