Supporting Information

Aerobic Direct C(sp2)-H Hydroxylation of 2-Arylpyridines by Palladium Catalysis Induced with Aldehyde Auto-Oxidation

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General Information

Unless otherwise stated, all commercially available reagents and solvents were purchased from commercial suppliers and used without further purification. DCE used for the hydroxylation reactions was freshly distilled prior to the reaction over CaH_2. All reactions were performed in oven dried round bottom flask with Teflon coated magnetic stirring bar under oxygen atmosphere. Reactions were monitored by thin layer chromatography (TLC) analysis on silica gel 60 F_{254} and visualization was accomplished with short wave UV light at 254 nm or $KMnO_4$ staining solution followed by heating, crude mixture was purified by column chromatography on Merck silica gel (100-200 mesh). ^1H and ^{13}C NMR spectra were recorded on Bruker AVANCE III 500, 400 and 300 MHz spectrometers in deuterated solvent. Proton chemical shifts are reported in ppm (δ) relative to either tetramethylsilane (TMS $\delta = 0.0$ ppm) or the residual peak of the non-deuterated solvent was used as the internal standard ($CDCl_3$ $\delta = 7.26$ ppm). NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, td = triplet of doublet, q = quartet, m = multiplet, br. s = broad singlet), coupling constants (Hz) and integration. ^{13}C chemical shifts are reported in ppm (δ) from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ $\delta = 77.0$ ppm). High resolution mass spectra were measured on Q-Tof micro MS system by electron spray ionization (ESI) technique.

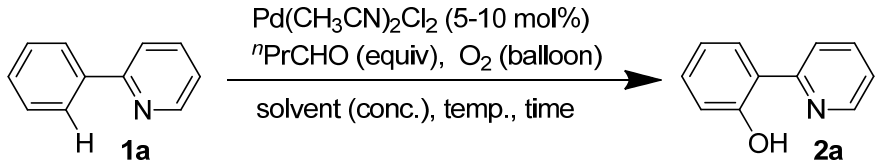
Literature Preparations

2-(4-Ethylphenyl)pyridine,[1] 2-(*p*-Tolyl)pyridine,[2] 2-(4-Chlorophenyl)pyridine,[2] 2-(4-Fluorophenyl)pyridine,[3] 2-(4-Methoxyphenyl)pyridine,[2] 2-(4-Bromophenyl)pyridine,[4] 4-(*tert*-Butyl)-2-phenylpyridine,[4] 4-(*tert*-Butyl)-2-(4-ethylphenyl)pyridine,[5] 4-(*tert*-Butyl)-2-(4-(tert-butyl)phenyl)pyridine,[6] 2-Phenylisonicotinonitrile,[5] 1-(2-Phenylpyridin-4-yl)ethanone,[7] 5-Methyl-2-phenylpyridine[3] 2-(4-Ethylphenyl)-5-methylpyridine,[1] 2-(*m*-Tolyl)pyridine,[3] 2-(4-(Benzyloxy)phenyl)pyridine,[8] 2-(2-Fluorophenyl)pyridine,[9] 5-Methyl-2-(*p*-tolyl)pyridine,[3] 2-([1,1'-Biphenyl]-4-yl)pyridine,[10] 4-Methyl-2-(*p*-tolyl)pyridine,[11] 2-([1,1'-Biphenyl]-4-yl)-4-methylpyridine,[4] 5-Methyl-2-(*m*-tolyl)pyridine,[12] 2-(3-Chlorophenyl)pyridine,[13] 4-(Pyridin-2-

yl)benzonitrile,[14] 2-(3-(Trifluoromethyl)phenyl)pyridine,[15] 4-Methyl-2-phenylpyridine,[1] Ethyl-6-phenylnicotinate,[16] 5-Nitro-2-phenylpyridine, N-(6-Phenylpyridin-2-yl)benzamide,[17] 2-(*m*-Methoxyphenyl)pyridine.[15]

Reaction Optimization

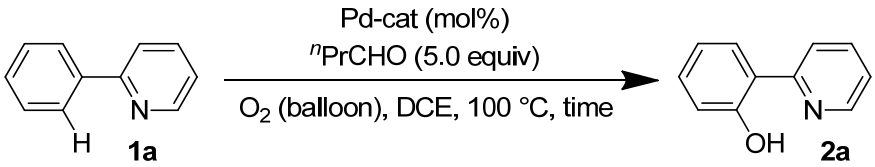
Table S1: Solvents, concentration, aldehyde (equiv), temp., cat. (mol%) screening.



Entry	Ald. (equiv)	Solvent	Conc. (M)	Temp. (°C)	Cat. (mol%)	Time (h)	Yield[a] (%)
1	10	DCE	0.15	60	10	24	80
2	10	CH_3CN	0.15	60	10	24	68
3	10	Toluene	0.15	60	10	24	trace
4	10	Dioxane	0.15	60	10	24	34
5	10	DMSO	0.15	60	10	24	trace
6	8	DCE	0.15	60	10	24	67
7	6	DCE	0.15	60	10	24	56
8	4	DCE	0.15	80	5	19	76
9	5	DCE	0.15	100	5	8	79
10	5	DCE	0.30	100	5	8	81
11	5	DCE	0.50	100	5	8	77

[a]Yields are based on the isolated material after column chromatography.

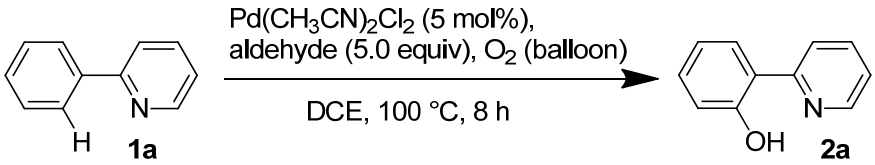
Table S2: Catalyst screening.



Entry	Catalyst (mol %)	Time (h)	Yield (%)[a]
1	$Pd(PPh_3)_2Cl_2$ (5.0)	18	75
2	$Pd(OAc)_2$ (5.0)	18	trace
3	$PdCl_2$ (5.0)	18	77
4	$Pd(CH_3CN)_2Cl_2$ (5.0)	8	81
5	$Pd(CH_3CN)_2Cl_2$ (3.5)	18	66
6	$Pd(CH_3CN)_2Cl_2$ (2.5)	18	57
7	$Pd(CH_3CN)_2Cl_2$ (1.0)	18	12

[a]Yields are based on the isolated material after column chromatography.

Table S3: Aldehyde screening.

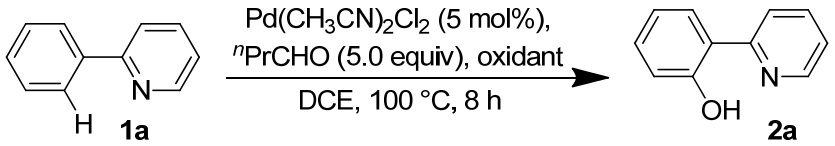


Entry	Aldehyde	Conv.(%)[a]
1	Heptanaldehyde	19
2	*n*-Butyraldehyde	100
3	Propanaldehyde	66
4	Isobutyraldehyde	91
5	Benzaldehyde	trace
6	*p*-Anisaldehyde	trace

[a]Determined by ^{1}H NMR analysis of the crude sample.

The long chain aliphatic aldehyde such as heptanaldehyde as well as aromatic aldehydes (benzaldehyde and *p*-anisaldehyde) are found to be less effective for the reaction. This is may be due to the slow aerobic oxidation of those aldehydes to the corresponding carboxylic acids. [18]

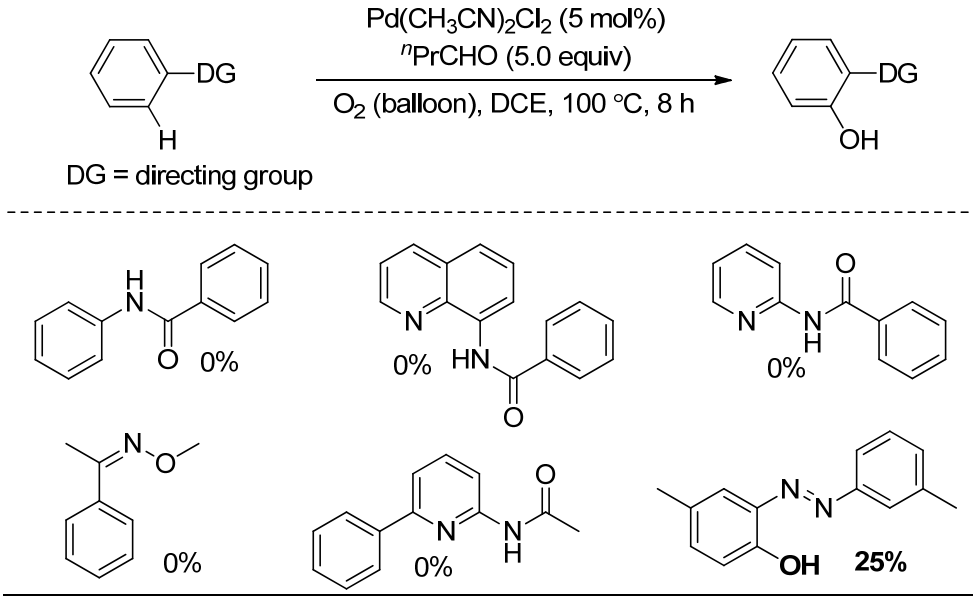
Table S4: Control experiments.



Entry	Catalyst	Aldehyde	Oxidant	Conv (%)[a]
1	-	*n*-Butyraldehyde	O_2 (balloon)	-
3	$Pd(CH_3CN)_2Cl_2$	-	O_2 (balloon)	-
4	$Pd(CH_3CN)_2Cl_2$	*n*-Butyraldehyde	Argon instead of O_2	-
5	$Pd(CH_3CN)_2Cl_2$	*n*-Butyraldehyde	Open air	40
6[b]	$Pd(CH_3CN)_2Cl_2$	*n*-Butyraldehyde	*m*-CPBA	-
7[b]	$Pd(CH_3CN)_2Cl_2$	*n*-Butyraldehyde	H_2O_2	-

[a]Determined by ^{1}H NMR analysis of the crude sample. [b]The formation of N-oxide of **2a** was realized.

Screening of Other N-Directing Groups

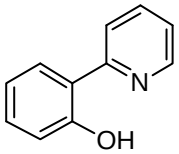


Experimental Section

General Procedure I:

To an oven dried 5.0 mL round bottom flask equipped with a magnetic stir bar, $Pd(CH_3CN)_2Cl_2$ (5 mol%) and DCE (0.13-0.3 M) were placed. The resulting solution was purged with O_2 for 7 minutes prior to the addition of substrate (1.0 equiv) and *n*-butyraldehyde (amount is specified in the individual experiment) to the solution. The reaction flask was then fitted with a reflux condenser having O_2 (balloon) on top of it and heated at 100 °C (preheated oil bath) for 8-36 h. The progress of the reaction was monitored by TLC analysis. After running the reaction to an appropriate time, the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel to afford the desired hydroxylated product**.**

2-(Pyridin-2-yl)phenol (2a)



2a

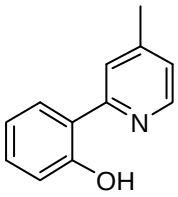
Prepared according to GP-I, combining 2-arylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 2.5% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2a** (27.6 mg, 81%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ =14.40 (br. s, 1H), 8.47 (d, *J* = 5.0 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.82-7.75 (m, 2H), 7.31 (t, *J* = 8.5 Hz, 1H), 7.23-7.18 (m, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 157.7, 145.6, 137.6, 131.3, 126.0, 121.3, 118.9, 118.7, 118.6, 118.4 ppm.

HRMS (ESI+) *m/z* calculated for $C_{11}H_{10}NO$ $[M+H]^+$ 172.0757, found 172.0756.

2-(4-Methylpyridin-2-yl)phenol (2b)



2b

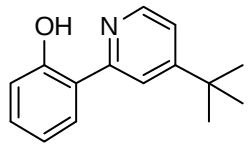
Prepared according to GP-I, combining 2-arylpyridine (33.8 mg, 0.2 mmol, 1.0 equiv) with *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 2.5% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2b** (26.6 mg, 72%) as light yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 14.51 (br. s, 1H), 8.35 (d, *J* = 5.2 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.72 (s, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.06-7.00 (m, 2H), 6.90 (t, *J* = 7.6 Hz, 1H), 2.44 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.1, 157.5, 148.9, 145.3, 131.2, 125.9, 122.5, 119.5, 118.8, 118.6, 118.5, 21.5 ppm.

HRMS (ESI+) *m/z* calculated for $C_{12}H_{12}NO$ $[M+H]^+$ 186.0913, found 186.0911.

2-(4-(*tert*-Butyl)pyridin-2-yl)phenol (2c)



2c

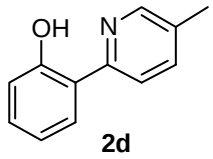
Prepared according to GP-I, combining 2-arylpyridine (42.3 mg, 0.2 mmol, 1.0 equiv) with *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2c** (34.5 mg, 76%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.43 (br. s, 1H), 8.32 (d, *J* = 5.5 Hz, 1H), 7.81 (s, 1H), 7.75 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.22-7.19 (m, 1H), 7.16 (dd, *J* = 5.5, 1.5 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.84-6.81 (m, 1H), 1.29 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.8, 160.0, 157.5, 145.5, 131.1, 125.9, 119.2, 118.9, 118.6, 118.5, 115.7, 35.1, 30.4 ppm.

HRMS (ESI+) *m/z* calculated for $C_{15}H_{18}NO$ $[M+H]^+$ 228.2111, found 228.2113.

2-(5-Methylpyridin-2-yl)phenol (2d)



2d

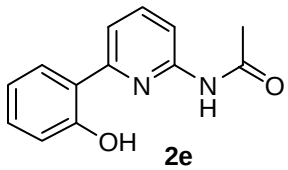
Prepared according to GP-I, combining 2-arylpyridine (33.8 mg, 0.2 mmol, 1.0 equiv) with *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2d** (26.2 mg, 71%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.33 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.77 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.64 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.30-7.26 (m, 1H), 7.02 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.91-6.87 (m, 1H), 2.38 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.6, 155.1, 145.7, 138.5, 131.2, 131.0, 125.8, 118.9, 118.6, 118.4, 18.1 ppm.

HRMS (ESI+) *m/z* calculated for $C_{12}H_{12}NO$ $[M+H]^+$ 186.0913, found 186.0911.

N-(6-(2-Hydroxyphenyl)pyridin-2-yl)acetamide (2e)



2e

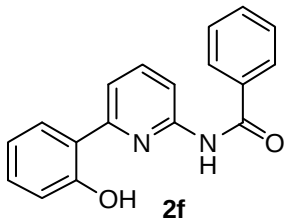
Prepared according to GP-I, combining 2-arylpyridine (42.4 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 1.3 mL of DCE (0.15 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 25% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2e** (29.0 mg, 63%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.28 (br. s, 1H), 8.35 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.82 (t, *J* = 8.0 Hz, 1H), 7.78 (dd, *J* = 8.0, 1.36 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 2.21 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.5, 158.7, 155.9, 148.4, 140.0, 131.5, 126.7, 119.4, 118.9, 118.3, 115.1, 111.7, 24.7 ppm.

HRMS (ESI+) *m/z* calculated for $C_{13}H_{13}N_2O_2$ $[M+H]^+$ 229.1097, found 229.1095.

N-(6-(2-Hydroxyphenyl)pyridin-2-yl)benzamide (2f)



2f

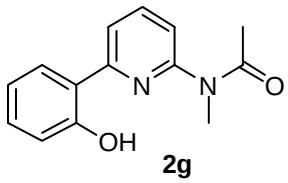
Prepared according to GP-I, combining 2-arylpyridine (54.9 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 1.3 mL of DCE (0.15 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 12% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2f** (37.8 mg, 65%) as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 13.15 (br. s, 1H), 8.61 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.94-7.84 (m, 3H), 7.78 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.32-7.26 (m, 1H), 7.01-6.89 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.8, 158.7, 156.2, 148.6, 140.0, 133.8, 132.4, 131.5, 128.8, 127.2, 126.6, 119.2, 118.9, 118.3, 115.4, 112.0 ppm.

HRMS (ESI+) *m/z* calculated for $C_{18}H_{14}N_2O_2Na$ $[M+Na]^+$ 313.0953, found 313.0951.

N-(6-(2-Hydroxyphenyl)pyridin-2-yl)-N-methylacetamide (2g)



2g

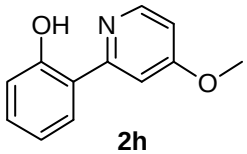
Prepared according to GP-I, combining 2-arylpyridine (45.3 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 1.3 mL of DCE (0.15 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 20% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2g** (20.3 mg, 42%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.90 (t, *J* = 8.0 Hz, 1H), 7.82-7.77 (m, 2H), 7.36-7.31 (m, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 3.44 (s, 3H), 2.16 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.4, 159.3, 157.3, 153.2, 139.7, 131.9, 126.6, 119.2, 118.6, 118.5, 118.1, 117.0, 35.6, 23.1 ppm.

HRMS (ESI+) *m/z* calculated for $C_{14}H_{15}N_2O_2$ $[M+H]^+$ 243.0427, found 243.0424.

2-(4-Methoxypyridin-2-yl)phenol (2h)



2h

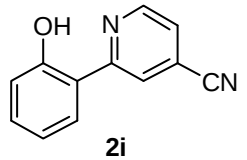
Prepared according to GP-I, combining 2-arylpyridine (37.0 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 15% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2h** (34.2 mg, 85%) as light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.65 (br. s, 1H), 8.33 (d, *J* = 5.5 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.36 (s, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.77 (dd, *J* = 5.5, 2.0 Hz, 1H), 3.92 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.8, 160.2, 159.5, 147.2, 131.4, 125.9, 118.7, 118.6, 118.5, 108.3, 104.3, 55.3 ppm.

HRMS (ESI+) *m/z* calculated for $C_{12}H_{12}NO_2$ $[M+H]^+$ 202.0863, found 202.0864.

2-(2-Hydroxyphenyl)isonicotinonitrile (2i)



2i

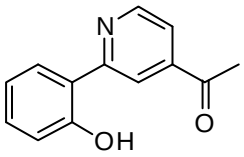
Prepared according to GP-I, combining 2-arylpyridine (36 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 5% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2i** (25.9 mg, 66%) as yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 13.31 (br. s, 1H), 8.68 (d, *J* = 5.0 Hz, 1H), 8.12 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 5.0 Hz, 1H), 7.39-7.36 (m, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 159.2, 147.2, 132.9, 126.3, 122.3, 122.2, 121.4, 119.4, 119.0, 117.3, 116.2 ppm.

H**RMS** (ESI+) *m/z* calculated for $C_{12}H_9N_2O$ $[M+H]^+$ 197.0709, found 196.0707.

1-(2-(2-Hydroxyphenyl)pyridin-4-yl)ethanone (2j)



2j

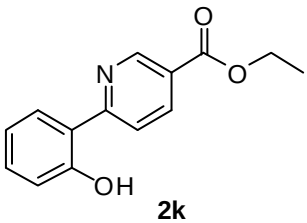
Prepared according to GP-I, combining 2-arylpyridine (39.4 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 10% EtOAc-Hexane, $R_f = 0.3$) to afford the desired hydroxylated product **2j** (29.0 mg, 68%) as light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.66 (d, *J* = 5.5 Hz, 1H), 8.33 (s, 1H), 7.87 (d, *J* = 9.5 Hz, 1H), 7.64 (d, *J* = 5.5 Hz, 1H), 7.37-7.30 (m, 1H), 7.03 (d, *J* = 9.5 Hz, 1H), 6.94 (t, *J* = 9.5 Hz, 1H), 2.69 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.8, 159.8, 159.1, 147.1, 144.2, 132.1, 126.3, 119.1, 118.9, 118.7, 118.4, 117.0, 26.7 ppm.

HRMS (ESI+) *m/z* calculated for $C_{13}H_{12}NO_2$ $[M+H]^+$ 214.0863, found 202.0865.

Ethyl 6-(2-hydroxyphenyl)nicotinate (2k)



2k

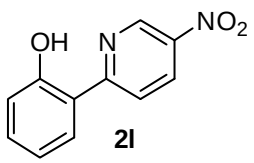
Prepared according to GP-I, combining 2-arylpyridine (45.5 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 6% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2k** (38.9 mg, 80%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 14.02 (br. s, 1H), 9.12 (s, 1H), 8.40 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.38-7.32 (m, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.6, 161.1, 160.5, 147.6, 138.3, 132.6, 126.7, 23.9, 119.0, 118.9, 118.5, 118.1, 61.5, 14.2 ppm.

HRMS (ESI+) *m/z* calculated for $C_{14}H_{14}NO_3$ $[M+H]^+$ 244.0968, found 244.0967.

2-(5-Nitropyridin-2-yl)phenol (2l)



2l

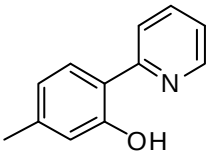
Prepared according to GP-I, combining 2-arylpyridine (40 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 5% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2l** (32.8 mg, 76%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 13.34 (s, 1H), 9.35 (d, *J* = 2.5 Hz, 1H), 8.59-8.56 (m, 1H), 8.07-8.03 (m, 1H), 7.83-7.80 (m, 1H), 7.42-7.38 (m, 1H), 7.07-7.04 (m, 1H), 6.98-6.94 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.9, 160.6, 142.5, 141.8, 133.9, 132.4, 127.2, 119.5, 119.3, 119.2, 117.4 ppm.

HRMS (ESI+) *m/z* calculated for $C_{11}H_9N_2O_3$ $[M+H]^+$ 217.0608, found 217.0606.

5-Methyl-2-(pyridin-2-yl)phenol (2m)



2m

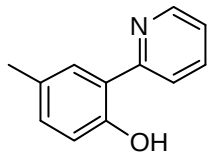
Prepared according to GP-I, combining 2-arylpyridine (33.8 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2m** (26.7 mg, 72%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.20 (br. s, 1H), 8.48 (d, *J* = 5.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.81-7.78 (m, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.21-7.18 (m, 1H), 6.85 (s, 1 H), 6.73 (d, *J* = 8.0 Hz, 1H), 2.34 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 157.9, 145.7, 142.1, 137.6, 125.9, 121.0, 119.9, 118.8, 118.7, 116.2, 21.3 ppm.

HRMS (ESI+) *m/z* calculated for $C_{12}H_{12}NO$ $[M+H]^+$ 186.0635, found 186.0632.

4-Methyl-2-(pyridin-2-yl)phenol (2n)



2n

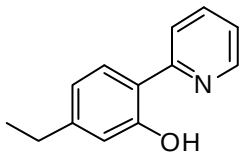
Prepared according to GP-I, combining 2-arylpyridine (33.8 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2n** (26.6 mg, 72%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.12 (s, 1H), 8.48 (d, *J* = 5.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.80 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.58 (s, 1H), 7.21-7.19 (m, 1H), 7.12 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 2.34 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 157.8, 157.6, 145.8, 137.5, 132.2, 127.5, 126.2, 121.2, 118.9, 118.4, 118.2, 20.6 ppm.

HRMS (ESI+) *m/z* calculated for $C_{12}H_{12}NO$ $[M+H]^+$ 186.1808, found 186.1806.

5-Ethyl-2-(pyridin-2-yl)phenol (2o)



2o

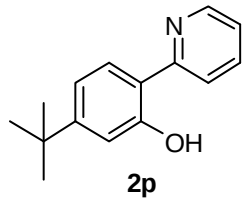
Prepared according to GP-I, combining 2-arylpyridine (36.6 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2o** (28.5 mg, 71%) as light yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 14.35 (s, 1H), 8.47 (d, *J* = 4.8 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.81-7.77 (m, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.20-7.17 (m, 1H), 6.88 (s, 1 H), 6.76 (d, *J* = 8.0 Hz, 1H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.9, 157.9, 148.3, 145.7, 137.5, 125.9, 120.9, 118.6, 117.5, 116.4, 28.6, 15.0 ppm.

HRMS (ESI+) *m/z* calculated for $C_{13}H_{14}NO$ $[M+H]^+$ 200.1070, found 200.1072.

5-(*tert*-Butyl)-2-(pyridin-2-yl)phenol (2p)



2p

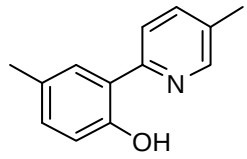
Prepared according to GP-I, combining 2-arylpyridine (42.3 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2p** (29.0 mg, 64%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.27 (s, 1H), 8.49 (d, *J* = 5.0 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.81-7.79 (m, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.21-7.18 (m, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.96 (dd, *J* = 8.5, 2.0 Hz, 1H), 1.34 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.6, 157.8, 155.3, 145.8, 137.5, 125.6, 121.0, 118.7, 116.2, 116.2, 115.4, 34.7, 31.0 ppm.

HRMS (ESI+) *m/z* calculated for $C_{15}H_{18}NO$ $[M+H]^+$ 228.1383, found 228.1382.

4-Methyl-2-(5-methylpyridin-2-yl)phenol (2q)



2q

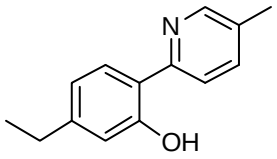
Prepared according to GP-I, combining 2-arylpyridine (36.6 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2q** (24.7 mg, 62%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.32 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 1.5 Hz, 1H), 7.09 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 2.37 (s, 3H), 2.33 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 157.3, 155.1, 145.8, 138.4, 131.8, 131.0, 127.5, 126.0, 118.6, 118.5, 118.2, 20.6, 18.1 ppm.

HRMS (ESI+) *m/z* calculated for $C_{13}H_{14}NO$ $[M+H]^+$ 200.1071, found 200.1073.

5-Ethyl-2-(5-methylpyridin-2-yl)phenol (2r)



2r

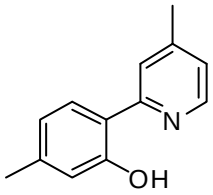
Prepared according to GP-I, combining 2-arylpyridine (39.5 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2r** (28.2 mg, 66%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.30 (s, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.62 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.87 (d, *J* = 1.5 Hz, 1H), 6.74 (dd, *J* = 8.5, 1.5 Hz, 1H), 2.64 (q, *J* = 7.5 Hz, 2H), 2.36 (s, 3H), 1.26 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ =159.0, 155.2, 147.9, 145.6, 138.4, 130.7, 125.7, 118.6, 118.3, 117.5, 116.5, 28.6, 18.1, 15.0 ppm.

HRMS (ESI+) *m/z* calculated for $C_{14}H_{16}NO$ $[M+H]^+$ 214.1223, found 214.1222.

5-Methyl-2-(4-methylpyridin-2-yl)phenol (2s)



2s

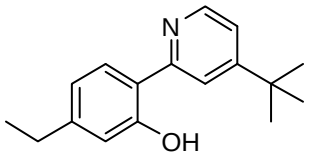
Prepared according to GP-I, combining 2-arylpyridine (36.6 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2s** (29.5 mg, 74%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.47 (s, 1H), 8.32 (d, *J* = 5.0 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 2H), 7.02 (d, *J* = 5.0 Hz, 1H), 6.84 (s, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 2.43 (s, 3H), 2.34 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.0, 157.6, 148.8, 145.2, 141.8, 125.8, 122.1, 119.8, 119.3, 118.8, 116.2, 21.6, 21.4 ppm.

HRMS (ESI+) *m/z* calculated for $C_{13}H_{14}NO$ $[M+H]^+$ 200.1070, found 200.1072.

2-(4-(*tert*-Butyl)pyridin-2-yl)-5-ethylphenol (2t)



2t

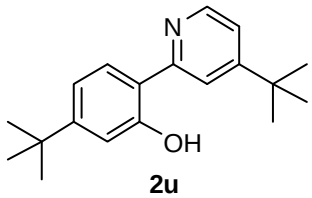
Prepared according to GP-I, combining 2-arylpyridine (47.9 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2t** (35.7 mg, 70%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.48 (s, 1H), 8.38 (d, *J* = 5.5 Hz, 1H), 7.86 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 5.5, 1.5 Hz, 1H), 6.87 (s, 1H), 6.76 (dd, *J* = 8.0, 1.5 Hz, 1H), 2.65 (q, *J* = 7.5 Hz, 2H), 1.38 (s, 9H), 1.26 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.6, 160.0, 157.7, 148.0, 145.4, 125.8, 118.5, 117.5, 116.8, 115.4, 111.4, 35.1, 30.4, 28.6, 15.1 ppm.

HRMS (ESI+) *m/z* calculated for $C_{17}H_{22}NO$ $[M+H]^+$ 256.2093, found 256.2099.

5-(*tert*-Butyl)-2-(4-(*tert*-butyl)pyridin-2-yl)phenol (2u)



2u

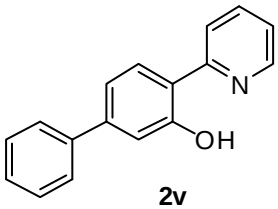
Prepared according to GP-I, combining 2-arylpyridine (53.5 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2u** (37.0 mg, 63%) as light yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 (d, *J* = 5.6 Hz, 1H), 7.87 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 1H, 7.22 (dd, *J* = 5.6, 1.6 Hz, 1H), 7.06 (s, 1H), 6.95 (dd, *J* = 8.4, 1.6 Hz, 1H), 1.37 (s, 9H), 1.33 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.8, 159.6, 157.5, 155.1, 145.4, 125.6, 118.5, 116.5, 116.0, 115.6, 115.4, 35.1, 34.7, 31.0, 30.5 ppm.

HRMS (ESI+) *m/z* calculated for $C_{19}H_{26}NO$ $[M+H]^+$ 284.2009, found 284.2008.

4-(Pyridin-2-yl)-[1,1'-biphenyl]-3-ol (2v)



2v

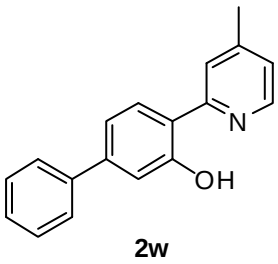
Prepared according to GP-I, combining 2-arylpyridine (46.3 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 2.5% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2v** (32.6 mg, 66%) as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.30 (br. s, 1H), 8.49 (d, *J* = 4.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.82-7.78 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 1.5 Hz, 1H), 7.21-7.19 (m, 1H), 7.13 (dd, *J* = 8.0, 1.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.2, 157.6, 145.8, 144.2, 140.2, 137.7, 128.7, 127.7, 127.0, 126.5, 121.4, 119.0, 117.8, 117.6, 116.8 ppm.

HRMS (ESI+) *m/z* calculated for $C_{17}H_{14}NO$ $[M+H]^+$ 248.0218, found 248.0221.

4-(4-Methylpyridin-2-yl)-[1,1'-biphenyl]-3-ol (2w)



2w

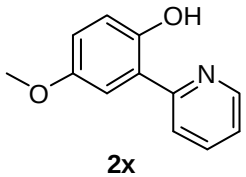
Prepared according to GP-I, combining 2-arylpyridine (49.0 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 2.5% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2w** (35.5 mg, 68%) as light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$), δ = 8.37 (d, *J* = 5.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.75 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 1.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 5.0 Hz, 1H), 2.45 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.3, 157.2, 149.0, 145.3, 143.9, 140.2, 128.7, 127.6, 126.9, 126.4, 122.5, 119.5, 117.8, 117.4, 116.7, 21.5 ppm.

HRMS (ESI+) *m/z* calculated for $C_{18}H_{16}NO$ $[M+H]^+$ 262.1227, found 262.1225.

4-Methoxy-2-(pyridin-2-yl)phenol (2x)



2x

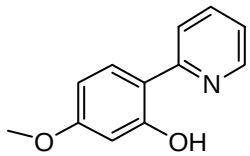
Prepared according to GP-I, combining 2-arylpyridine (37.0 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 6 h. The crude mixture was purified by column chromatography (SiO_2, 8% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2x** (20.0 mg, 49%) as light yellow liquid. *While complete consumption of the starting material was realized in 6 h, yield of the hydroxylated product* ***2x*** *was moderate. This may be due to the formation of several other unidentified side products for this particular substrate.*

^{1}H NMR (500 MHz, $CDCl_3$) δ = 13.73 (br. s, 1H), 8.44 (d, *J* = 4.5 Hz, 1H), 7.80-7.74 (m, 2H), 7.24-7.23 (m, 1H), 7.19-7.15 (m, 1H), 6.91-6.84 (m, 2H), 3.75 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.6, 154.0, 152.1, 146.0, 137.7, 121.5, 119.1, 118.8, 117.8, 111.0, 56.0 ppm.

HRMS (ESI+) *m/z* calculated for $C_{12}H_{12}NO_2$ $[M+H]^+$ 202.0863, found 202.0865.

5-Methoxy-2-(pyridin-2-yl)phenol (2y)



2y

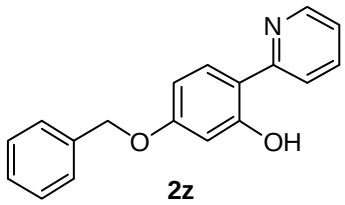
Prepared according to GP-I, combining 2-arylpyridine (37 mg, 0.2 mmol, 1.0 equiv) with *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. To improve yield of the final product, the reaction was continued for another 8 h using an additional amount of *n*-butyraldehyde (45.0 µL, 0.5 mmol, 2.5 equiv). The crude mixture was purified by column chromatography (SiO_2, 10% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2y** (26.5 mg, 65%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.64 (br. s, 1H), 8.43 (d, *J* = 5.0 Hz, 1H), 7.77 (s, 2H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.17-7.13 (m, 1H), 6.54 (d, *J* = 2.5 Hz, 1H), 6.49 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.83 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.3, 161.8, 157.7, 145.4, 137.5, 127.0, 120.4, 118.2, 112.0, 106.5, 102.1, 55.21 ppm.

HRMS (ESI+) *m/z* calculated for $C_{12}H_{12}NO_2$ $[M+H]^+$ 202.0863, found 202.0865.

5-(Benzyloxy)-2-(pyridin-2-yl)phenol (2z)



2z

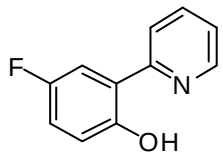
Prepared according to GP-I, combining 2-arylpyridine (52.3 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. The crude mixture was purified by column chromatography (SiO_2, 6% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2z** (41.0 mg, 74%) as white solid.

^{1}H NMR (500 MHz, $CDCl_3$), δ = 8.45-8.44 (m, 1H), 7.79-7.78 (m, 2H), 7.71-7.70 (m, 1H), 7.46-7.31 (m, 5H), 7.18-7.15 (m, 1H), 6.65-6.64 (m, 1H), 6.58-6.55 (m, 1H), 5.10 (s, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.8, 161.5, 157.7, 145.4, 137.7, 136.7, 128.5, 127.9, 127.5, 127.1, 120.5, 118.3, 112.2, 107.2, 103.2, 69.9 ppm.

HRMS (ESI+) *m/z* calculated for $C_{18}H_{16}NO_2$ $[M+H]^+$ 278.1176, found 278.1178.

4-Fluoro-2-(pyridin-2-yl)phenol (2aa)



2aa

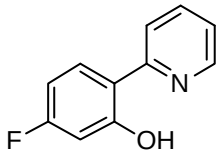
Prepared according to GP-I, combining 2-arylpyridine (34.6 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. To improve yield of the final product, the reaction was continued for another 8 h using an additional amount of *n*-butyraldehyde (45.0 µL, 0.5 mmol, 2.5 equiv). The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2aa** (20.0 mg, 53%) as light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, *J* = 4.4 Hz, 1H), 7.93-7.81 (m, 2H), 7.47 (dd, *J* = 10.0, 2.8 Hz, 1H), 7.34-7.28 (m, 1H), 7.07-6.96 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 155.9, 155.7 (d, J_{C-F} = 233.8 Hz), 153.5.0, 145.9, 138.2, 22.1, 119.6 (d, J_{C-F} = 7.5 Hz), 119.4, 118.8 (d, J_{C-F} = 7.5 Hz), 118.4 (d, J_{C-F} = 22.5 Hz), 111.9 (d, J_{C-F} = 23.7 Hz) ppm.

HRMS (ESI+) *m/z* calculated for $C_{11}H_8FNONa$ $[M+Na]^+$ = 212.0482, found 212.0484.

5-Fluoro-2-(pyridin-2-yl)phenol (2ab)



2ab

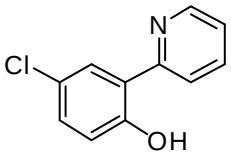
Prepared according to GP-I, combining 2-arylpyridine (34.6 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. To improve yield of the final product, the reaction was continued for another 8 h using an additional amount of *n*-butyraldehyde (45.0 μL, 0.5 mmol, 2.5 equiv). The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2ab** (26.9 mg, 72%) as light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.80 (s, 1H), 8.47 (d, *J* = 5.0 Hz, 1H), 7.84-7.78 (m, 2H), 7.74 (dd, *J* = 8.5, 6.5 Hz, 1H), 7.25-7.20 (m, 1H), 6.72 (dd, *J* = 10.5, 2.5 Hz, 1H), 6.64-6.58 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.8 (d, J_{C-F} = 248.0 Hz), 162.2 (d, J_{C-F} = 13.0 Hz), 157.4, 145.8, 138.0, 127.6 (d, J_{C-F} = 10.0 Hz), 121.5, 118.9, 115.5, 106.4 (d, J_{C-F} = 23.0 Hz), 105.3 (d, J_{C-F} = 23 Hz) ppm.

HRMS (ESI+) *m/z* calculated for $C_{11}H_9FNO$ $[M+H]^+$ 190.0663, found 190.0665.

4-Chloro-2-(pyridin-2-yl)phenol (2ac)



2ac

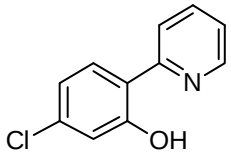
Prepared according to GP-I, combining 2-arylpyridine (37.9 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. To improve yield of the final product, the reaction was continued for another 8 h using an additional amount of *n*-butyraldehyde (45.0 μL, 0.5 mmol, 2.5 equiv). The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2ac** (25.5 mg, 62%) as light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.54 (d, *J* = 4.8 Hz, 1H), 7.91-7.86 (m, 2H), 7.76 (d, *J* = 2.8 Hz, 1H), 7.31 (dd, *J* = 8.8, 4.8 Hz, 1H), 7.28-7.23 (m, 1H), 6.98 (d, *J* = 8.8 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.5, 156.5, 145.9, 138.1, 131.2, 125.7, 123.5, 122.1, 120.0, 119.7, 119.3 ppm.

HRMS (ESI+) *m/z* calculated for $C_{11}H_9ClNO$ $[M+H]^+$ 206.0367, found 206.0365.

5-Chloro-2-(pyridin-2-yl)phenol (2ad)



2ad

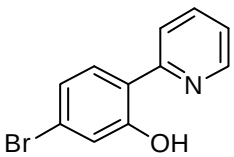
Prepared according to GP-I, combining 2-arylpyridine (37.9 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. To improve yield of the final product, the reaction was continued for another 8 h using an additional amount of *n*-butyraldehyde (45.0 μL, 0.5 mmol, 2.5 equiv). The crude mixture was purified by column chromatography (SiO_2, 4% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2ad** (29.6 mg, 72%) as light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.57 (s, 1H), 8.41 (d, *J* = 5.5 Hz, 1H), 7.76-7.75 (m, 2H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.19-7.16 (m, 1H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.79 (dd, *J* = 8.5, 2.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.8, 157.0, 145.7, 137.9, 136.7, 126.9, 121.7, 119.0, 118.9, 118.5, 117.3 ppm.

HRMS (ESI+) *m/z* calculated for $C_{11}H_9ClNO$ $[M+H]^+$ 206.0367, found 206.0365.

5-Bromo-2-(pyridin-2-yl)phenol (2ae)



2ae

Prepared according to GP-I, combining 2-arylpyridine (46.8 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. To improve yield of the final product, the reaction was continued for another 12 h using an additional amount of *n*-butyraldehyde (90.0 μL, 1.0 mmol, 5.0 equiv).The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-

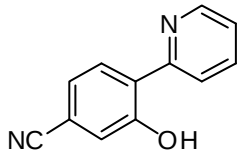
Hexane, R_f = 0.3) to afford the desired hydroxylated product **2ae** (32.0 mg, 64%) as light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.56 (br. s, 1H), 8.43 (d, *J* = 4.5 Hz, 1H), 7.81−7.76 (m, 2H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.22−7.19 (m, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 6.96 (dd, *J* = 8.5, 2.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.8, 157.1, 145.8, 137.9, 127.1, 124.9, 121.9, 121.8, 121.6, 118.9, 117.7 ppm.

HRMS (ESI+) *m/z* calculated for $C_{11}H_9BrNONa$ $[M+Na]^+$ 271.9681, found 271.9691.

2-(Pyridin-2-yl)-5-(cyano)phenol (2af)



2af

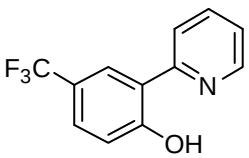
Prepared according to GP-I, combining 2-arylpyridine (36 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 1.5 mL DCE (0.13 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. To improve yield of the final product, the reaction was continued for another 8 h using an additional amount of *n*-butyraldehyde (45.0 µL, 0.5 mmol, 2.5 equiv). The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2af** (28.0 mg, 72%) as light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 15.27 (br. s, 1H), 8.55 (d, *J* = 4.0 Hz, 1H), 8.12 (s, 1H), 7.93 (s, 2H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 4.0 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 164.0, 155.9, 145.8, 138.5, 134.6, 130.9, 122.7, 119.9, 119.3, 119.2, 102.0, 84.7 ppm.

HRMS (ESI+) *m/z* calculated for $C_{12}H_9N_2O$ $[M+H]^+$ 197.0707, found 197.0709.

2-(Pyridin-2-yl)-4-(trifluoromethyl)phenol (2ag)



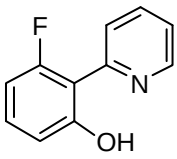
2ag

Prepared according to GP-I, combining 2-arylpyridine (44.6 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon)

atmosphere for 8 h. To improve yield of the final product, the reaction was continued for another 16 h adding additional amount of *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv) in two portions after every 8 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2ag** (30.0 mg, 63%) as light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.87 (br. s, 1H), 8.54 (d, *J* = 4.5 Hz, 1H), 8.05 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.92-7.87 (m, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 162.8, 156.6, 145.8, 138.2, 128.1 (q, J_{C-F} = 3.6 Hz), 124.5 (q, J_{C-F} = 270.9 Hz), 123.6 (q, J_{C-F} = 3.6 Hz), 122.4, 120.9 (q, J_{C-F} = 32.7 Hz), 119.2, 119.1, 118.5 ppm.
HRMS (ESI+) *m/z* calculated for $C_{12}H_9F_3NO$ $[M+H]^+$ 240.0631, found 240.0627.

3-Fluoro-2-(pyridin-2-yl)phenol (2ah)



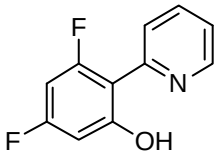
2ah

Prepared according to GP-I, combining 2-arylpyridine (34.6 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. To improve yield of the final product, additional amount of *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv) was added in two portions after every 8 h and the reaction was continued for another 28 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2ah** (25 mg, 67%) as light yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, *J* = 4.8 Hz, 1H), 8.16 (d, *J* = 10.4 Hz, 1H), 7.87 (t, *J* = 10.4 Hz, 1H), 7.33-7.27 (m, 1H), 7.25-7.17 (m, 1H), 6.84 (d, *J* = 10.4 Hz, 1H), 6.69-6.61 (m, 1H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.9 (d, J_{C-F} = 249.0 Hz), 161.4 (d, J_{C-F} = 6.0 Hz), 154.5 (d, J_{C-F} = 2.8 Hz), 145.4, 138.1 (d, J_{C-F} = 1.2 Hz), 130.9 (d, J_{C-F} = 13.0 Hz), 124.7 (d, J_{C-F} = 21.0 Hz), 122.0, 114.1 (d, J_{C-F} = 2.8 Hz), 108.7 (d, *J* = 11.0 Hz), 106.1 (d, J_{C-F} = 25.0 Hz) ppm.

HRMS (ESI+) *m/z* calculated for $C_{11}H_9FNO$ $[M+H]^+$ 190.0663, found 190.0664.

3-Fluoro-2-(pyridin-2-yl)phenol (2ai)



2ai

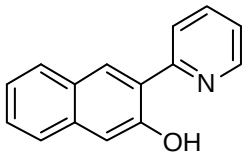
Prepared according to GP-I, combining 2-arylpyridine (38.2 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. To improve yield of the final product, additional amount of *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv) was added in two portions after every 8 h and the reaction was continued for another 28 h. The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2ai** (18.5 mg, 45%) as light yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 15.47 (s, 1H), 8.51 (d, *J* = 4.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz 1H), 7.87 (dt, *J* = 8.0, 4.0 Hz, 1H), 7.31-7.28 (m, 1H), 6.57-6.53 (m, 1H), 6.44-6.38 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6 (dd, $J_{C\text{-}F}$ = 249.1, 18.2 Hz), 163.0 (dd, $J_{C\text{-}F}$ = 15.3, 8.1 Hz), 162.6 (dd, $J_{C\text{-}F}$ = 251.3, 15.9 Hz), 154.1 (d, $J_{C\text{-}F}$ = 3.7 Hz), 145.2, 138.2, 123.9 (d, $J_{C\text{-}F}$ = 21.4 Hz), 121.9, 105.2 (d, $J_{C\text{-}F}$ = 11.3 Hz), 101.3 (dd, $J_{C\text{-}F}$ = 23.3, 3.5 Hz), 95.2 (dd, $J_{C\text{-}F}$ = 29.4, 26.4 Hz) ppm.

HRMS (ESI+) *m/z* calculated for $C_{11}H_8F_2NO$ $[M+H]^+$ 208.0568 found 208.0567.

3-(Pyridin-2-yl)naphthalen-2-ol (2aj)



2aj

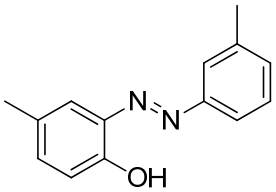
Prepared according to GP-I, combining 2-arylpyridine (40.1 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg) in 0.7 mL of DCE (0.3 M) at 100 ºC under O_2 (balloon) atmosphere for 8 h. To improve yield of the final product, the reaction was continued for another 4 h using an additional amount of *n*-butyraldehyde (45.0 µL, 0.5 mmol, 2.5 equiv). The crude mixture was purified by column chromatography (SiO_2, 3% EtOAc-Hexane, R_f = 0.3) to afford the desired hydroxylated product **2aj** (22.0 mg, 51%) as yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 14.01 (br. s, 1H), 8.57 (d, *J* = 4.4 Hz, 1H), 8.33 (s, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.95-7.84 (m, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.46-7.39 (m, 1H), 7.36 (s, 1H), 7.33-7.27 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.7, 156.8, 146.1, 137.9, 135.8, 128.2, 127.4, 127.2, 126.8, 125.9, 123.1, 122.0, 121.5, 120.0, 112.1 ppm.

HRMS (ESI+) *m/z* calculated for $C_{15}H_{12}NO$ $[M+H]^+$ 222.0913, found 222.0912.

(*E*)-4-Methyl-2-(m-tolyldiazenyl)phenol (2ak)



2ak

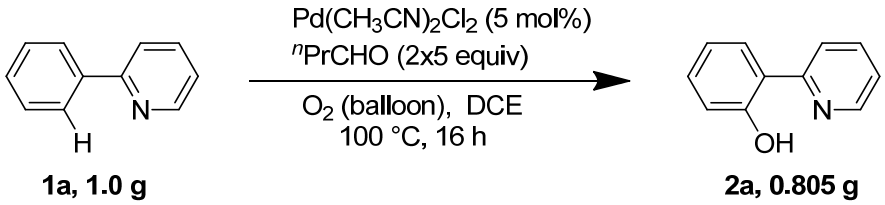
Prepared according to GP-II, combining (*E*)-1,2-di-m-tolyldiazene (21.0 mg, 0.1 mmol, 1.0 equiv) with *n*-Butyraldehyde (45.0 μL, 0.5 mmol, 5 equiv), Pd(II) catalyst (5 mol%, 1.3 mg) under O_2 (1 atm.) atmosphere in DCE (0.3 M, 0.4 mL) at 100 °C for 8 h. The crude product was purified by column chromatography (SiO_2**,** 100% Hexane, R_f = 0.5 for the product) to afford the desired ortho-hydroxylated product **2ak** (5.5 mg, 25%) as a red solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.74 (br. s, 1H), 7.75 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.16 (dd, *J* = 8.4, 2.0Hz, 1H), 6.95-6.91 (m, 1H), 2.46 (s, 3H), 2.39 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 150.9, 150.7, 139.5, 137.2, 134.3, 133.1, 132.0, 129.3, 122.5, 119.9, 117.9, 21.5, 20.4 ppm.

HRMS (ESI+) *m/z* calculated for $C_{14}H_{14}N_2O$ $[M+H]^+$ 227.1179, found 227.1176.

Gram Scale Experiment

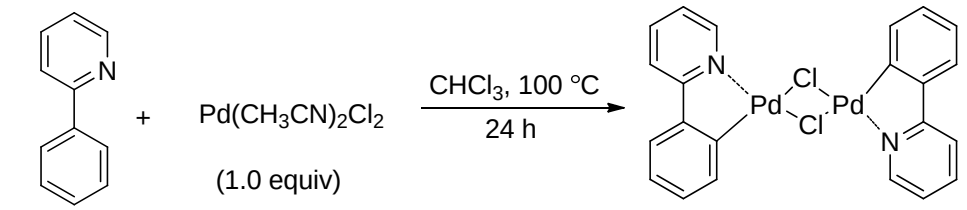


1a, 1.0 g **2a, 0.805 g**

An oven dried 50 mL round bottom flask equipped with a stirring bar, was charged with $Pd(CH_3CN)_2Cl_2$ (5 mol%, 84.0 mg), 2-phenylpyridine (930.0 µL, 6.5 mmol, 1.0 equiv) and 15.0 mL of DCE. The resulting solution was purged with O_2 for 7 minutes prior to the addition of *n*-butyraldehyde (2.93 mL, 32.5 mmol, 5.0 equiv). The flask was then fitted with a reflux condenser having O_2 (balloon) on top of it and heated at 100 °C (preheated oil bath) for 8 h. To achieve full conversion of the substrate, a second batch of *n*-butyraldehyde (2.93 mL, 32.5 mmol, 5.0 equiv) was added and the reaction was continued for another 8 h. After achieving complete consumption of the substrate, the reaction mixture was allowed to cool to room temperature and solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 2.5% EtOAc-Hexane, R_f = 0.3) to afford the desired product **2a** (805.0 mg, 74%) as light yellow liquid.

Mechanistic Investigation

Synthesis of Pd^{II}-Complex C:

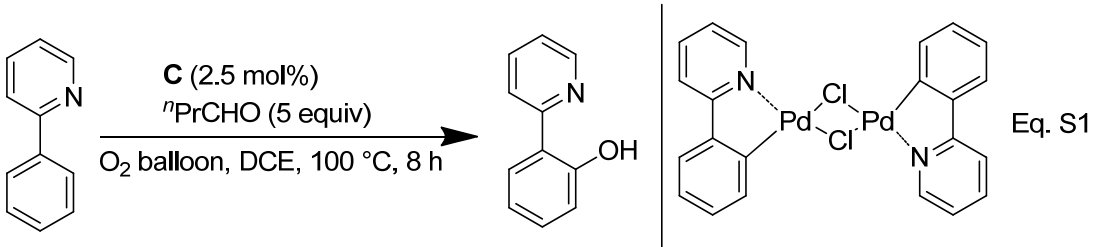


(1.1 equiv) Pd(II) complex **C**

The complex **C** was prepared according to the literature[19] by combining $Pd(CH_3CN)_2Cl_2$ (100.0 mg, 0.39 mmol, 1.0 equiv) and 2-phenylpyridine (65.8 mg, 0.43 mmol, 1.1 equiv) in $CHCl_3$ (0.35 M, 1.1 mL) at 100 °C for 24 h. The reaction mixture was cooled to room temperature, filtered, and washed with $CHCl_3$ to give palladacycle **C** as a yellow solid (83 mg, 73%). Anal. Calcd for $C_{22}H_{16}Cl_2N_2Pd_2$: C, 44.63; H, 2.72; N, 4.73. Found: C, 47.02; H, 3.35; N, 4.62. NMR spectrogram of the complex **C** could not be obtained due to very poor solubility.

a) The Aerobic C-H Hydroxylation with Pd^{II}-Complex C:

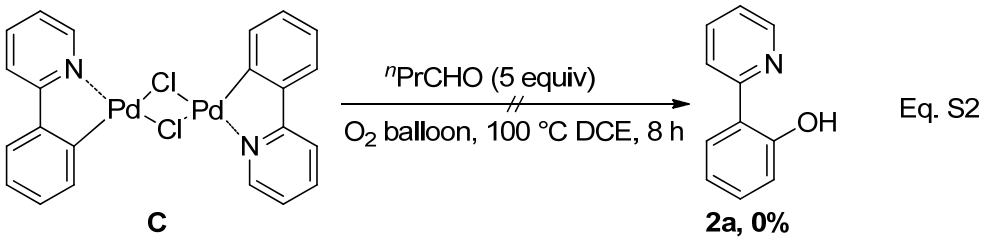
The proposed Pd(II) complex **C** was prepared according to the literature[19] and employed in the reaction as a catalyst in place of $Pd(CH_3CN)_2Cl_2$. The reaction was performed according to the GP-I using 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) complex **C** (2.5 mol%, 3.0 mg), O_2-balloon, in 0.7 mL of DCE (0.3 M) at 100°C (preheated oil bath) for 8 h. Purification of the crude material delivered the desired product **2a** in 91% yield (Eq. S1).



1a **2a, 91%** Pd(II) complex **C**

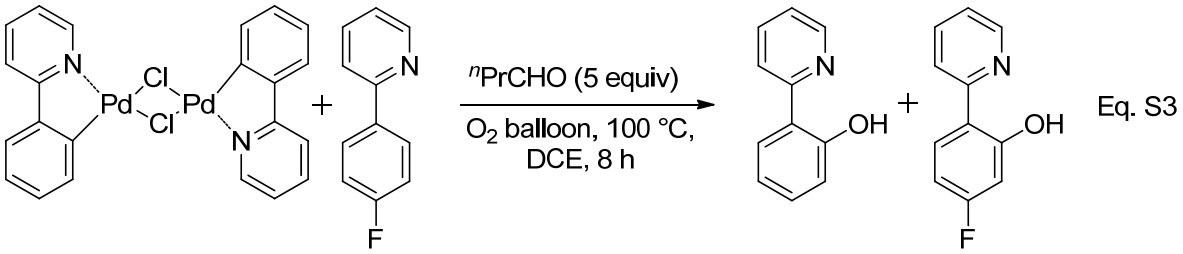
Interestingly, when the reaction was performed according to the GP-I using Pd(II) complex **C** (23.7 mg, 0.04 mmol, 1.0 equiv) alone as catalyst and substrate, *n*-butyraldehyde (18.0 µL, 0.2

mmol, 5.0 equiv), O_2-balloon, and DCE (0.13 M, 0.3 mL) at 100°C (preheated oil bath) for 8 h, no desired hydroxylated product was obtained.



C **2a, 0%** Eq. S2

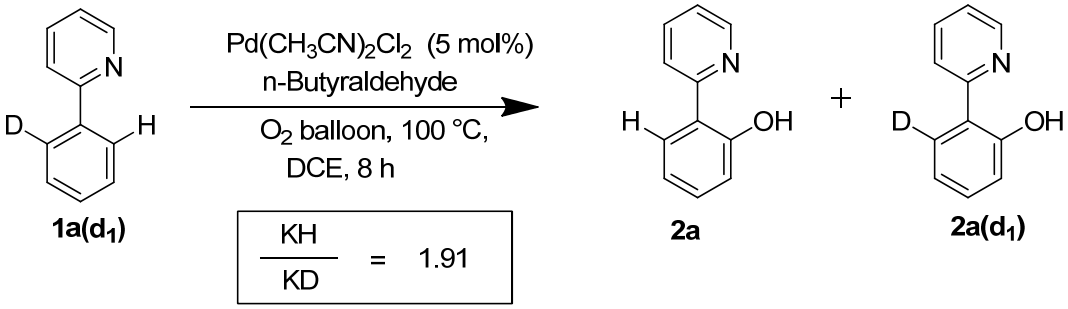
In contrast, when the experiment was repeated according to the GP-I using 2-arylpyridine **1ab** (34.6 mg, 0.2 mmol, 1.0 equiv), *n*-butyraldehyde (90.0 µL, 1 mmol, 5.0 equiv), Pd(II) complex **C** (20 mol%, 23.7 mg), O_2-balloon in DCE (0.3 M, 0.7 mL) at 100 °C (preheated oil bath) for 8 h, yielded the hydroxylated products **2a** and **2ab** in 26 and 62% yields, respectively. Based on above observations, we speculated that the decomposition of the strong dimeric Pd(II) complex **C** to form an active monomeric Pd(II) intermediate might be necessary for this transformation.



C (20 mol%) **1ab** (1 equiv) **2a, 26%** *(Based on 2-phenylpyridine in **C**)* **2ab, 62%** Eq. S3

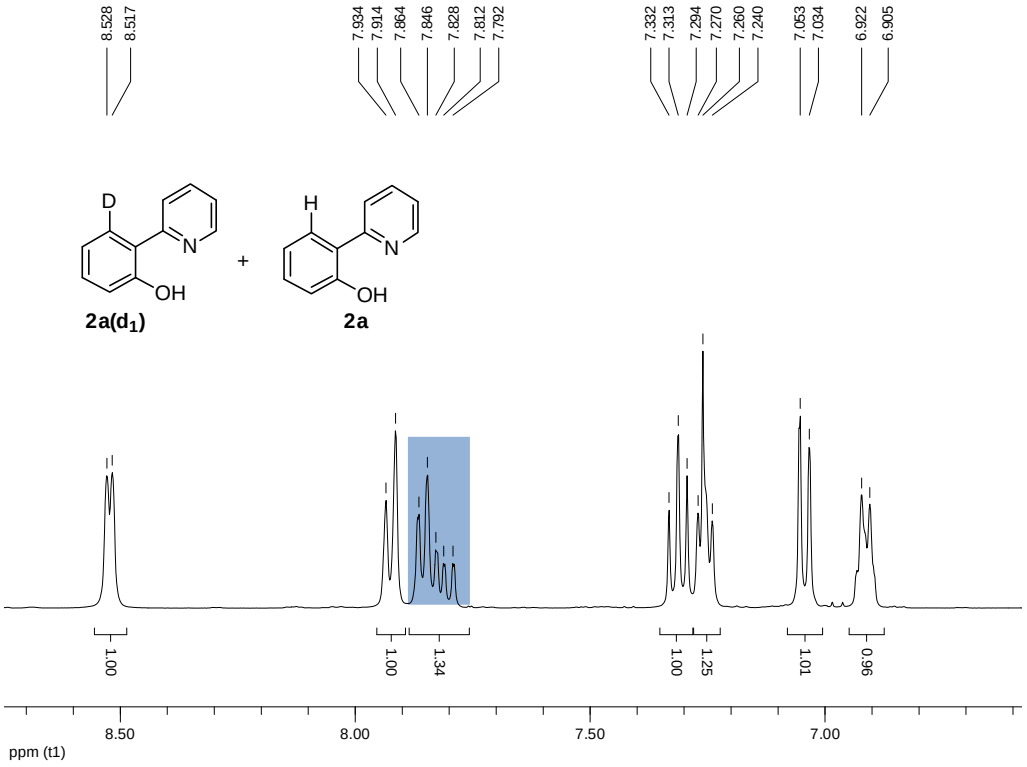
b) Studies on Kinetic Isotopic Effect (KIE)

Intramolecular Isotope Effect Experiment

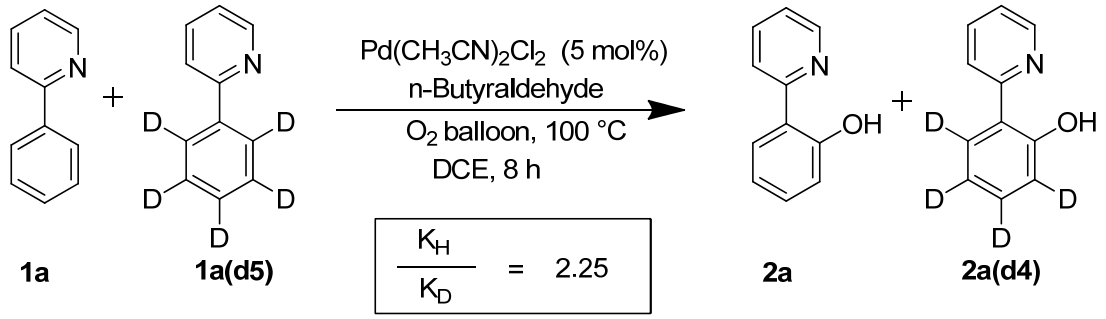


1a(d_1) **2a** **2a(d_1)**

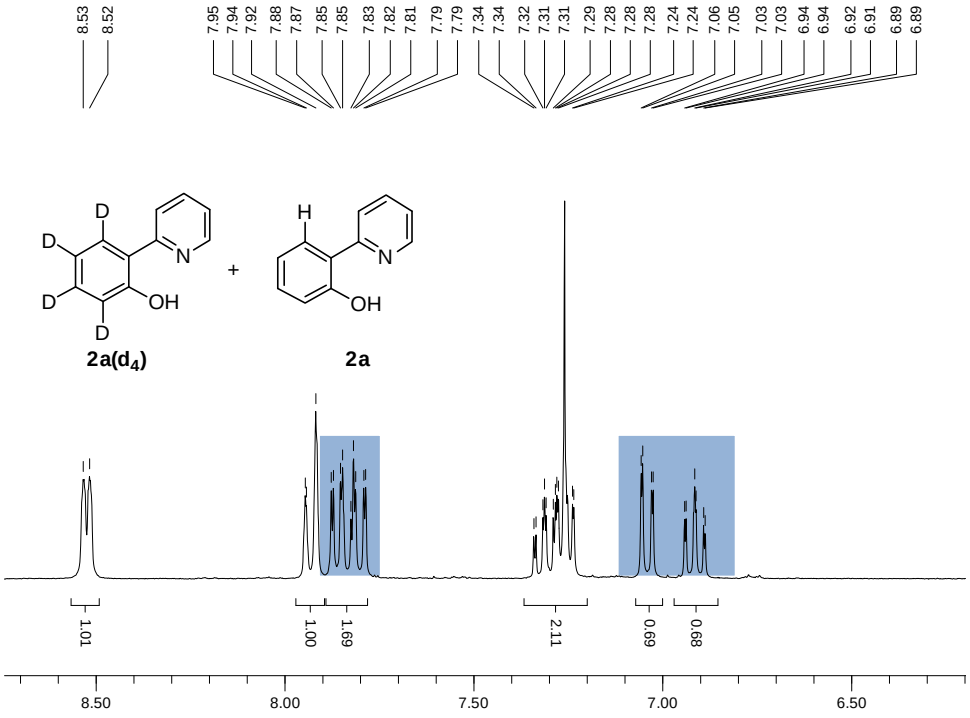
To an oven dried 5 mL round bottom flask equipped with a magnetic stir bar $Pd(CH_3CN)_2Cl_2$ (1.3 mg, 0.005 mmol) and 0.35 ml of DCE were placed. The resulting solution was cooled to 0°C and purged with O_2 for 7 min. To the solution, substrate **1a(d_1)** (15.0 mg, 0.1 mmol) and *n*-butyraldehyde (45.0 µL, 0.5 mmol, 5.0 equiv) were added. Then the reaction flask was fitted with a reflux condenser and heated at 100 °C (preheated oil bath) and continued for 8 h under O_2 (balloon). After complete consumption of the starting 2-arylpyridine, the solution was concentrated under reduced pressure. The crude mixture was purified by column chromatography to afford a mixture of hydroxylated products **2a** and **2a(d_1)** **(**13.0 mg, 80% combined yield). The ^{1}H NMR analysis of the mixture showed that the ratio of **2a** to **2a(d_1)** is 0.34:0.66 (Compared with the standard ^{1}H NMR spectrum of **2a**, the integration of the peak at 7.80 ppm was 1.34 instead of 2.00).



Intermolecular Isotope Effect Experiment

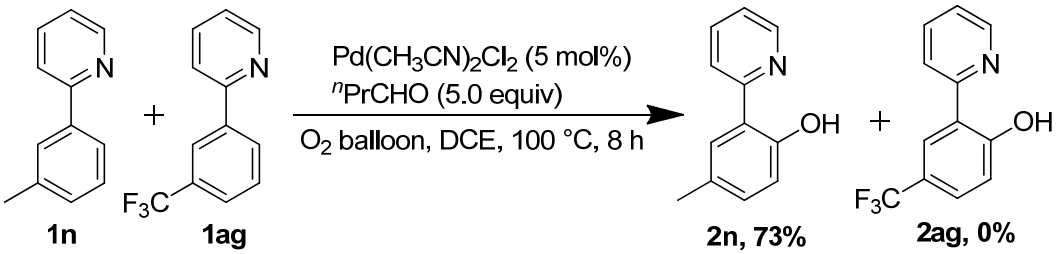


To an oven dried 5 mL round bottom flask equipped with a magnetic stir bar $Pd(CH_3CN)_2Cl_2$ (2.6 mg, 0.01 mmol) and 0.7 mL of DCE were placed. The resulting solution was cooled to 0°C and purged with O_2 for 7 minute followed by the addition of substrates **1a** (15.0 mg, 0.1 mmol) and **1a(d$_5$)** (16.0 mg, 0.1 mmol) and *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv). The formed mixture was stirred at 100 ºC under O_2 (balloon) for 2 h as monitored by TLC. The solution was then concentrated under reduced pressure. The crude mixture was purified by column chromatography to afford a mixture of hydroxylated products **2a(d$_4$)** and **2a** (10.9 mg, 32 %). The ^{1}H NMR analysis showed that ratio of **2a** to **2a(d$_4$)** 0.74:0.26 (Compared with the



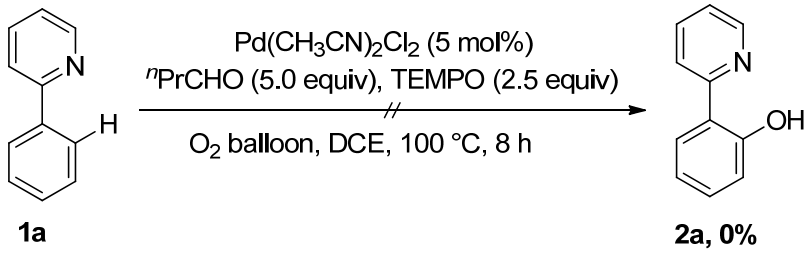
standard ^{1}H NMR spectrum of **2a**, the integration of the peak at 7.79 ppm was 1.69 instead of 2.00, the integration of the peak at 7.03 ppm was 0.69 instead of 1.00, the integration of the peak at 6.90 ppm was 0.68 instead of 1.00).

c) Competition Experiment between an Electron-rich and Electron-deficient Substrate



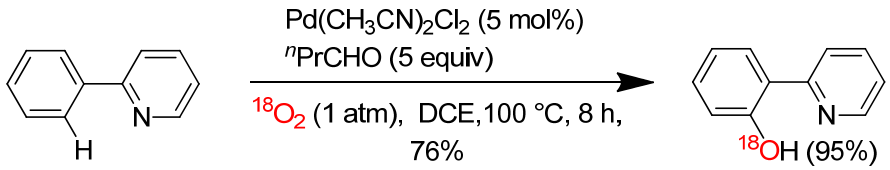
To an oven dried 5 mL round bottom flask equipped with a magnetic stir bar, $Pd(CH_3CN)_2Cl_2$ (5 mol%, 2.6 mg, 0.01 mmol) and 0.7 mL of DCE were placed. The solution was purged with O_2 for 7 minutes. To the solution, substrates **1n** (34.0 mg, 0.2 mmol), **1ag** (44.6 mg, 0.2 mmol) and *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv) were added. The reaction flask was then fitted with a reflux condenser having O_2 (balloon) on top of it and heated at 100 °C (preheated oil bath) for 8 h. The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography to afford the hydroxylated product **2n** (27 mg, 73.5 %) and substrate **1ag** (40.0 mg, 90% recovery). *This study demonstrates that the electron-rich substrate **1n** is undergoing C-H hydroxylation in a much faster rate over an electron deficient substrate **1ag** under the standard reaction conditions.*

d) C-H Hydroxylation in the Presence of a Radical Scavenger

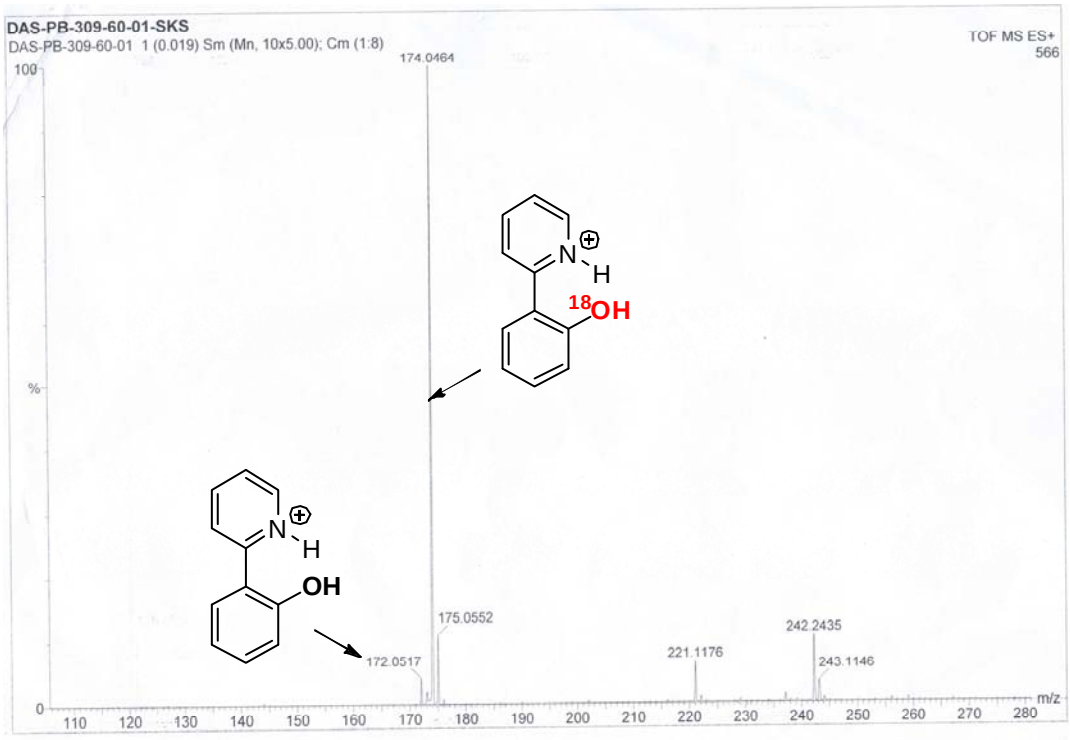


The reaction was performed according to GP-I, combining 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv), TEMPO (78.0 mg, 0.5 mmol , 2.5 equiv), *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv), Pd(II) catalyst (5 mol%, 2.6 mg), O_2-balloon in 0.7 mL of DCE (0.3 M) at 100 ºC (preheated oil bath) for 8 h. TLC analysis of the crude mixture revealed no desired hydroxylated product formation.

Labeling Experiment



HRMS data



To an oven dried 5.0 mL Schlenk tube equipped with a magnetic stir bar, $Pd(CH_3CN)_2Cl_2$ (2.6 mg, 0.01 mmol) was placed. The tube was evacuated under vacuum and back refilled with argon (3 times). To the tube, freshly distilled 0.7 mL of DCE (0.3 M), 2-phenylpyridine (31.0 mg, 0.2 mmol, 1.0 equiv) and *n*-butyraldehyde (90.0 µL, 1.0 mmol, 5.0 equiv) were placed. The mixture

was degassed by the freeze-pump-thaw procedure for three times. Finally the tube was evacuated while placing it in a liquid nitrogen bath and filled with $^{18}O_2$ (provided from a 98% $^{18}O_2$ cylinder). The solution was heated at 100°C for 8 hours. The solution was allowed to cool to room temperature and concentrated under vacuum. The crude mixture was purified by column chromatography on silica gel (SiO_2**,** 2.5% EtOAc-Hexane, $R_f = 0.3$) to afford the desired product (26.0 mg, 76 %). The 95% incorporation of ^{18}O in the product was confirmed by HRMS of the sample.

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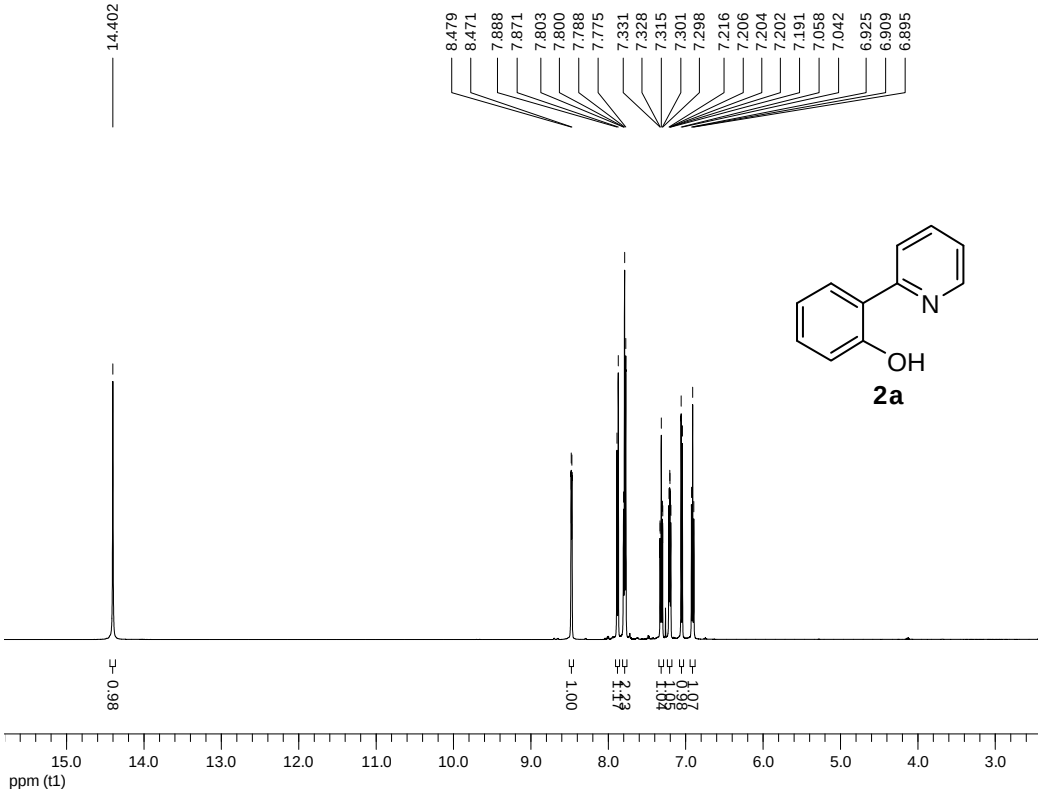
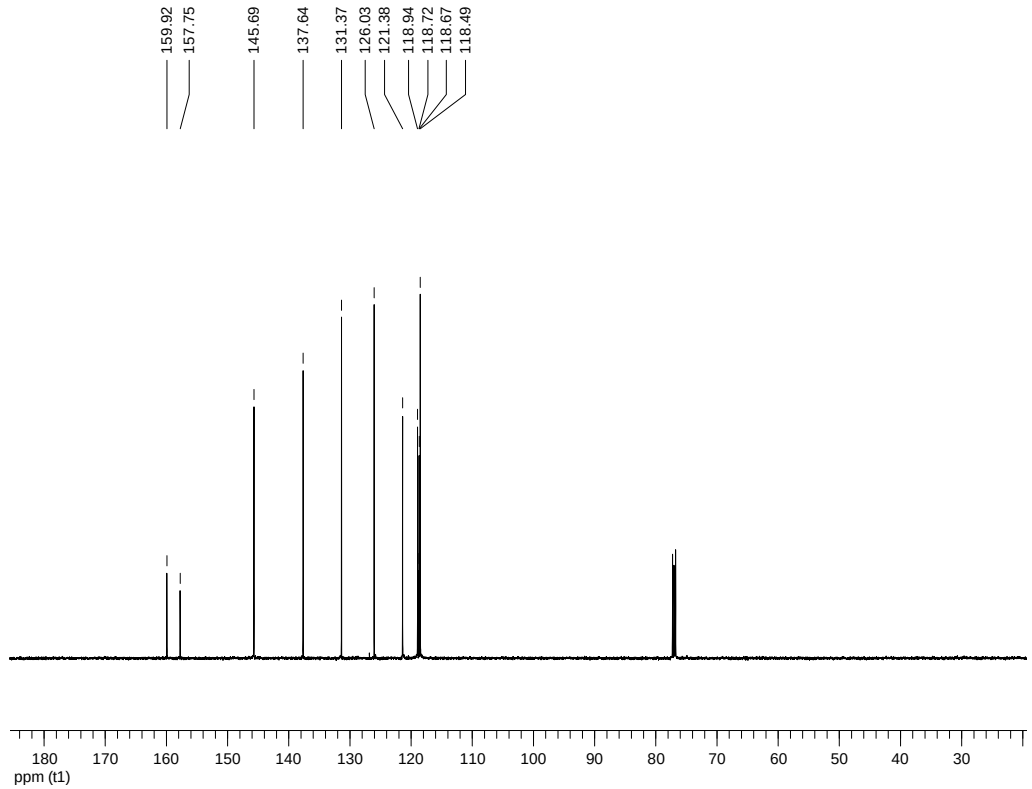
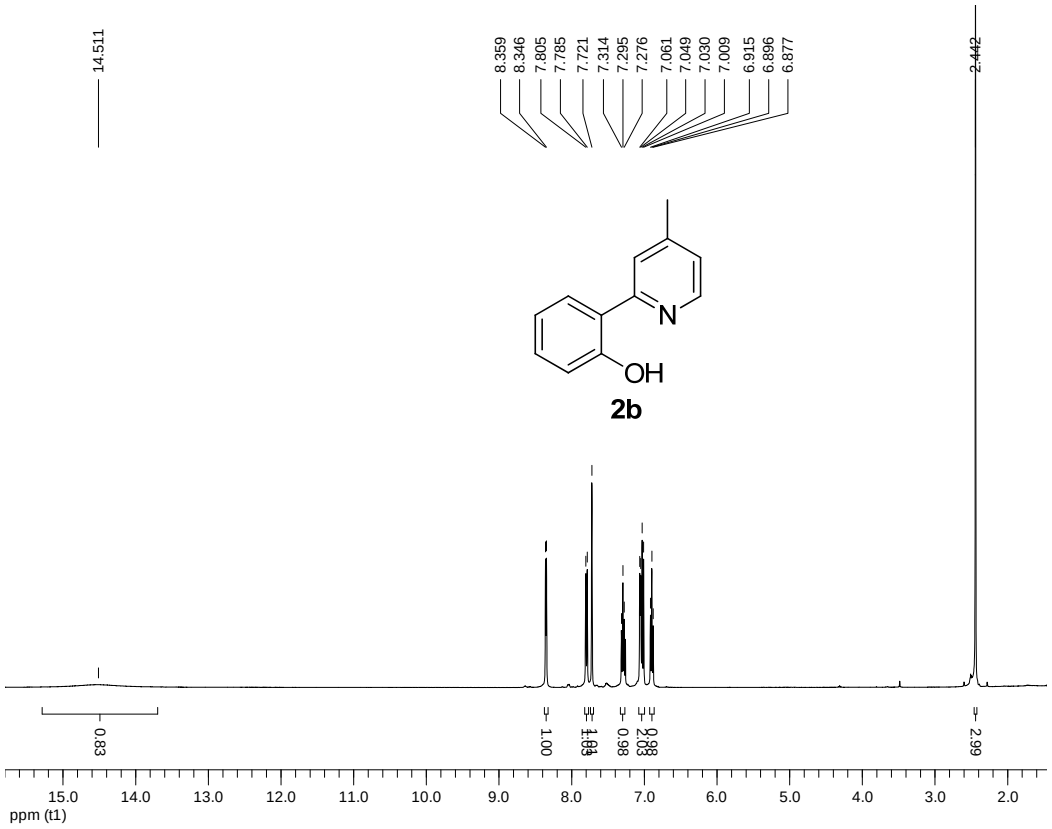
^{1}H and ^{13}C NMR spectra



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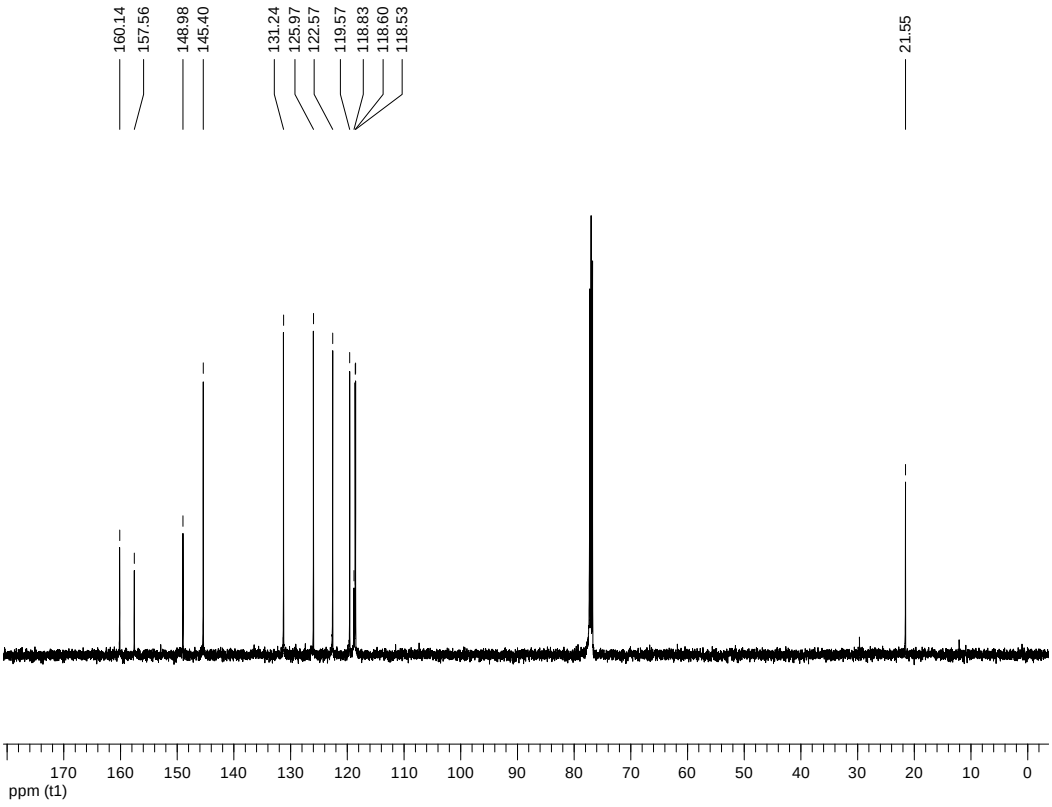
7.049
7.030
7.009
6.915
6.896
6.877
2.442
N
OH
2b
0.83
1.00
1.01
1.01
0.98
2.03
2.03
2.99
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)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160
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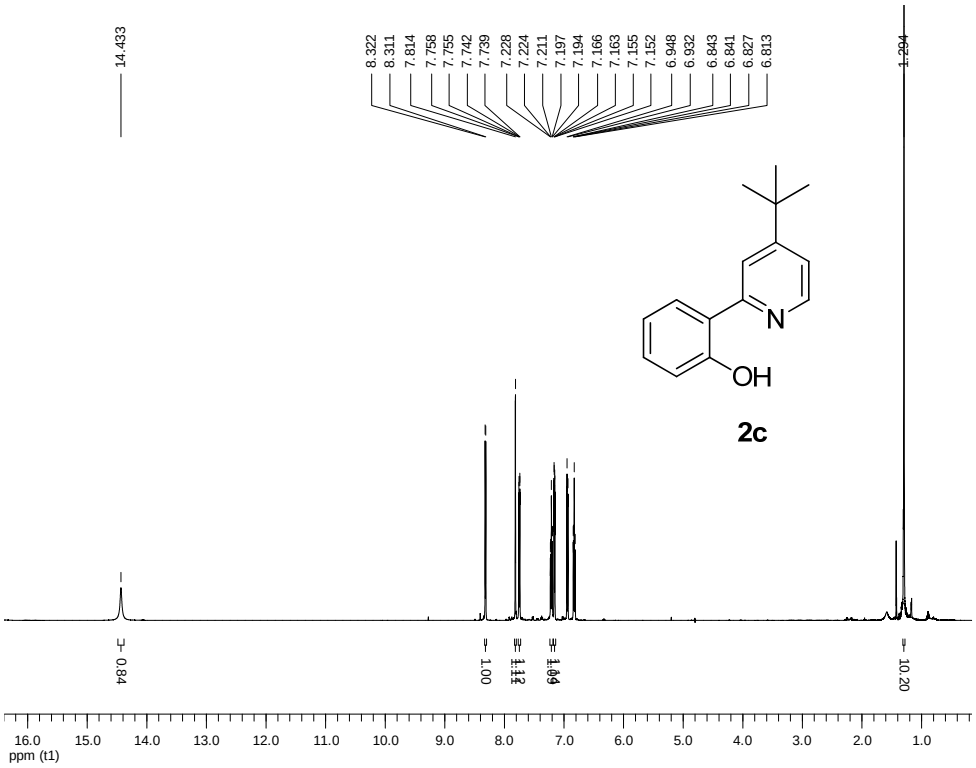
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (t1)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7.155
7.152
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6.932
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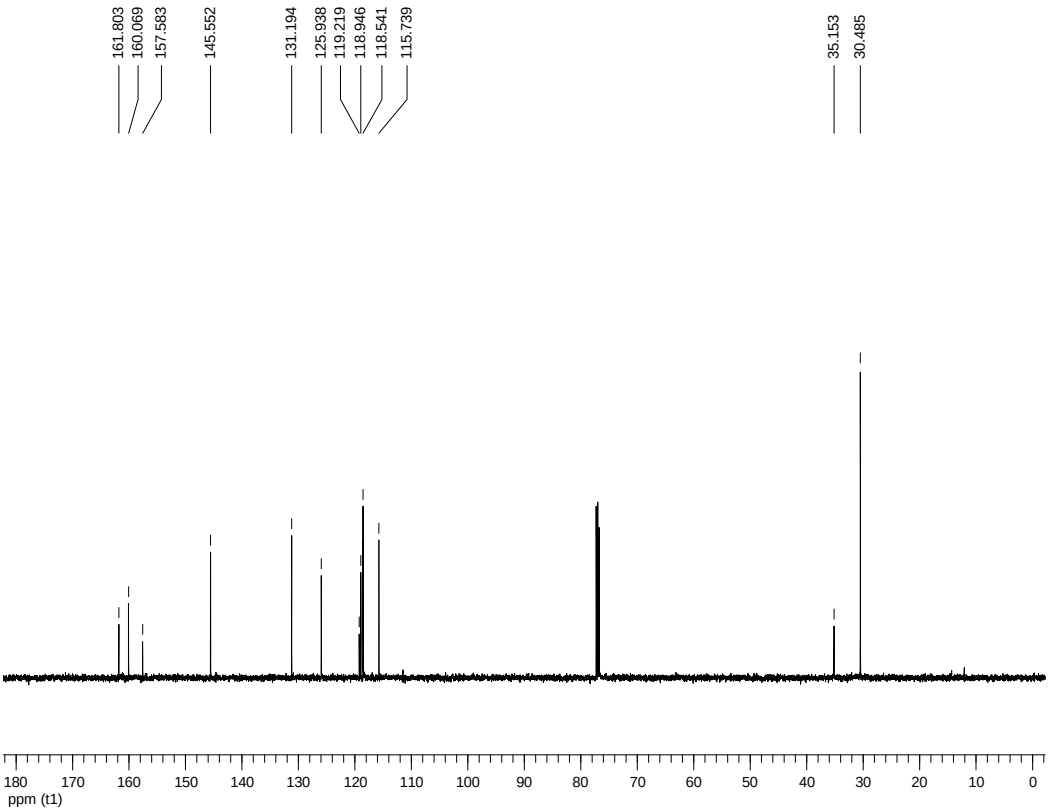
ppm (t1)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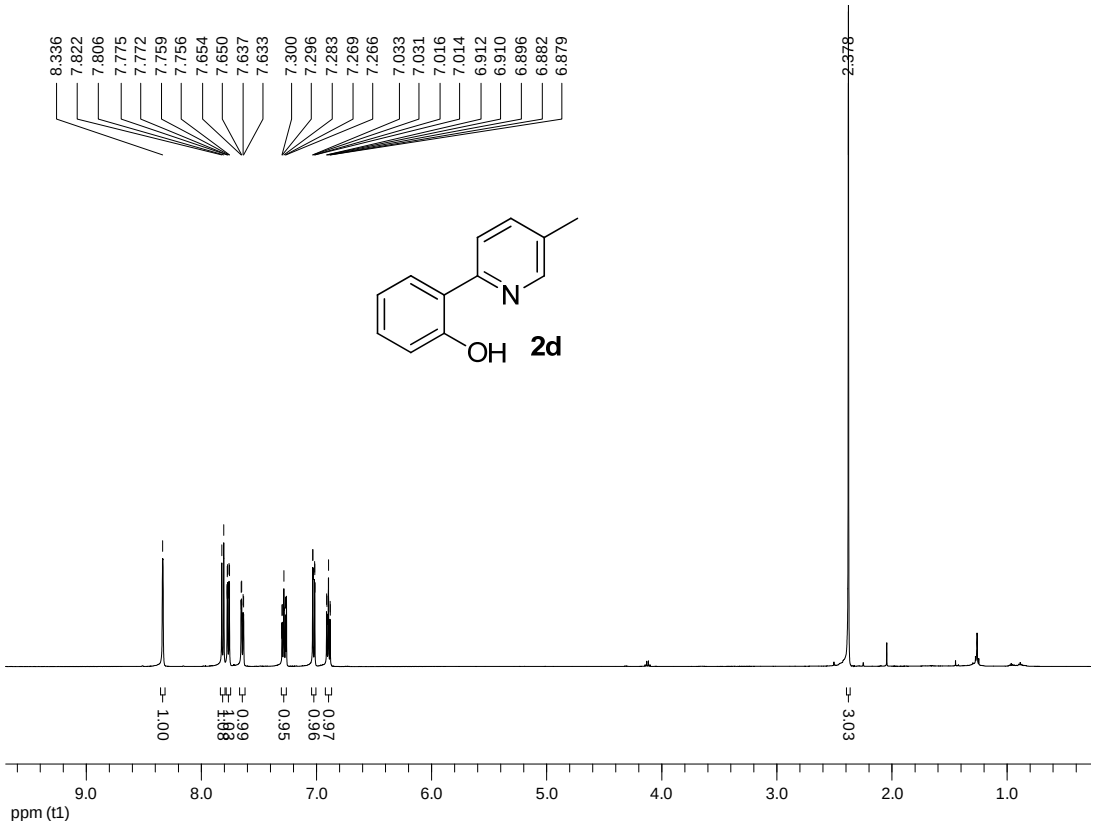
ppm (t1)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7.806
7.775
7.772
7.759
7.756
7.654
7.650
7.637
7.633
7.300
7.296
7.283
7.269
7.266
7.033
7.031
7.016
7.014
6.912
6.910
6.896
6.882
6.879
2.378
N
OH
2d
1.00
1.08
0.99
0.95
0.96
0.97
3.03
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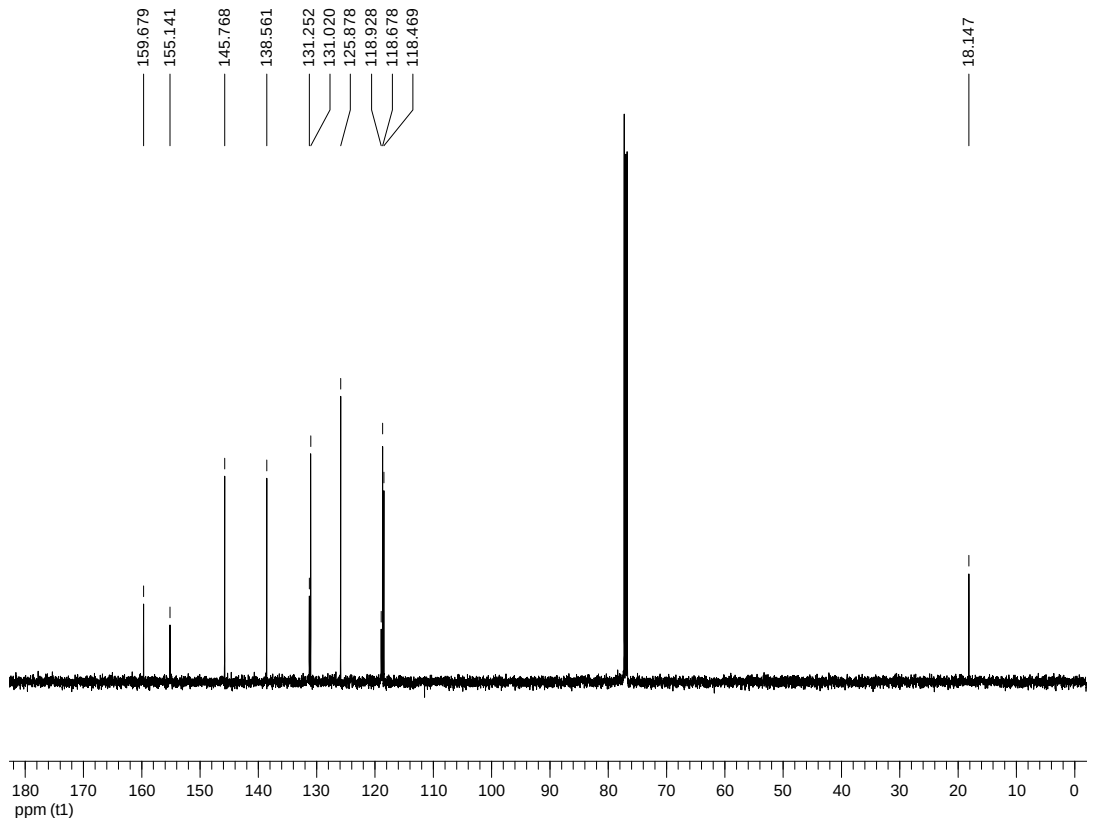
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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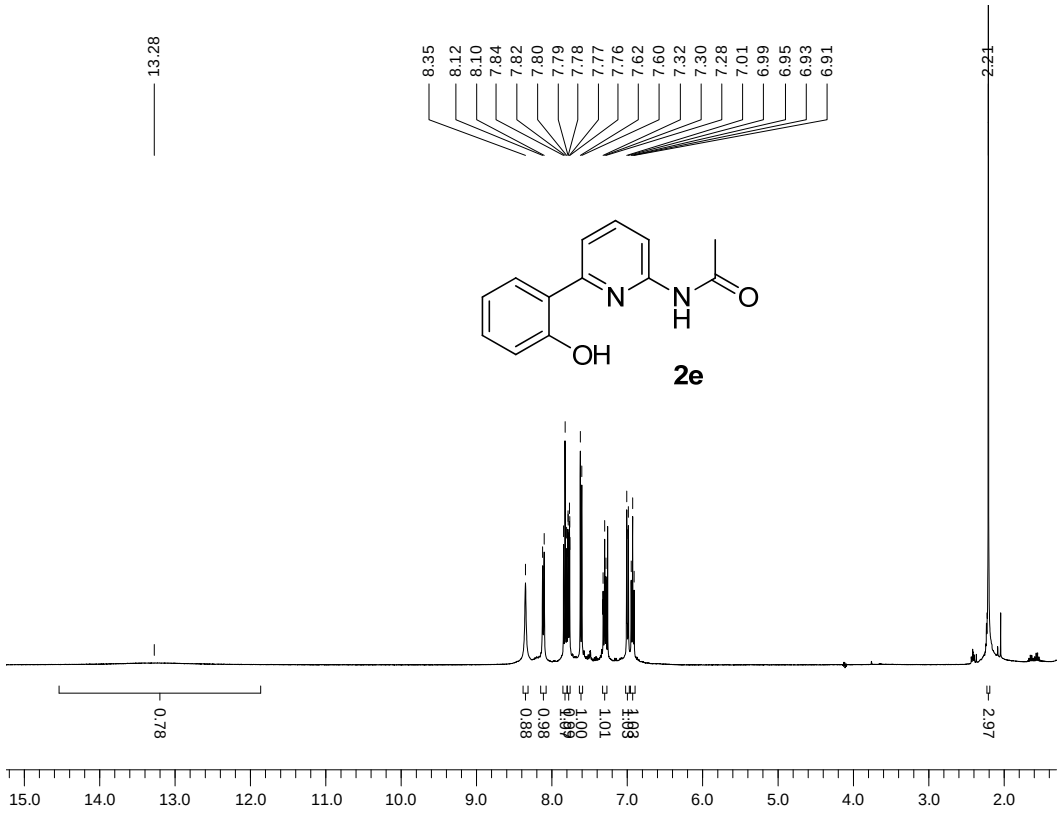
155.141
145.768
138.561
131.252
131.020
125.878
118.928
118.678
118.469
18.147
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (t1)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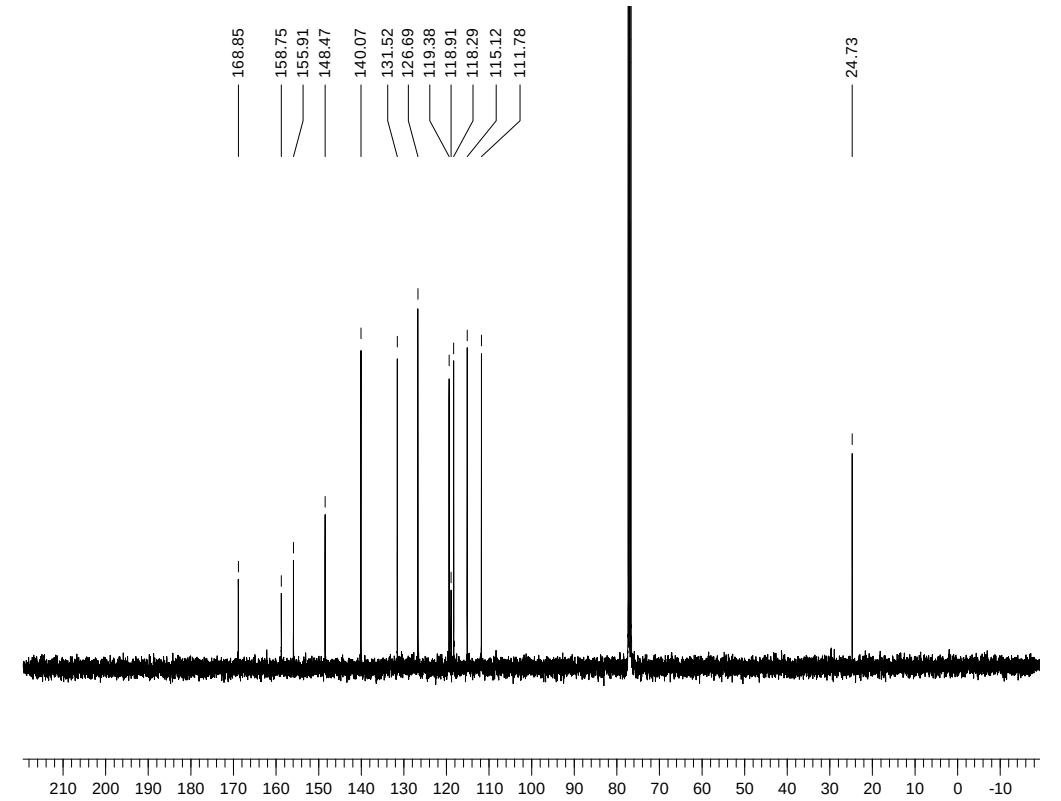
8.35
8.12
8.10
7.84
7.82
7.80
7.79
7.78
7.77
7.76
7.62
7.60
7.32
7.30
7.28
7.01
6.99
6.95
6.93
6.91
2.21
N
N
H
O
OH
2e
0.78
0.88
0.98
1.00
1.01
2.97
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0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155.91
148.47
140.07
131.52
126.69
119.38
118.91
118.29
115.12
111.78
24.73
210
200
190
180
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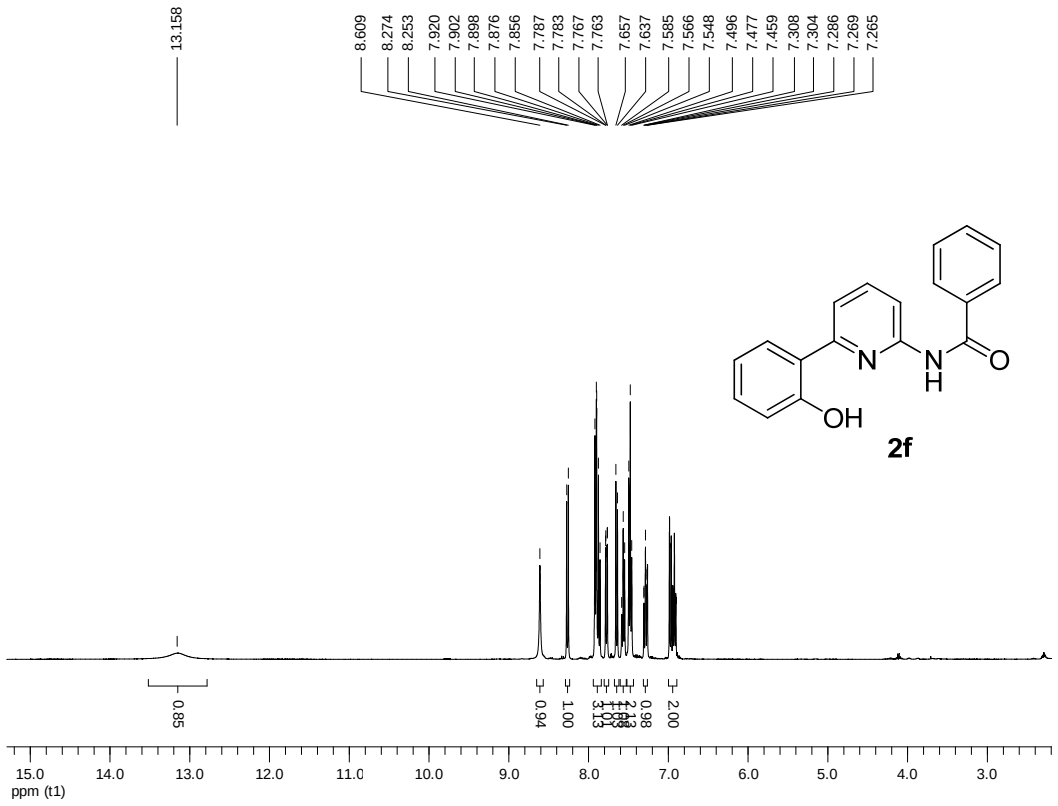
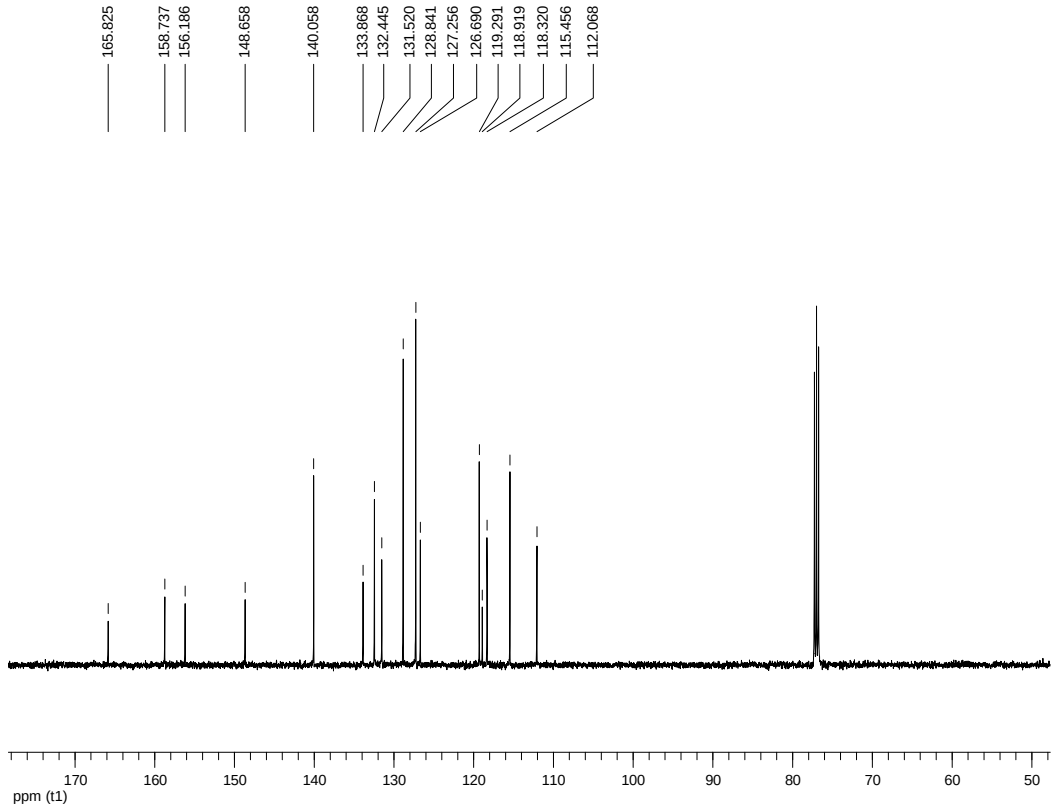
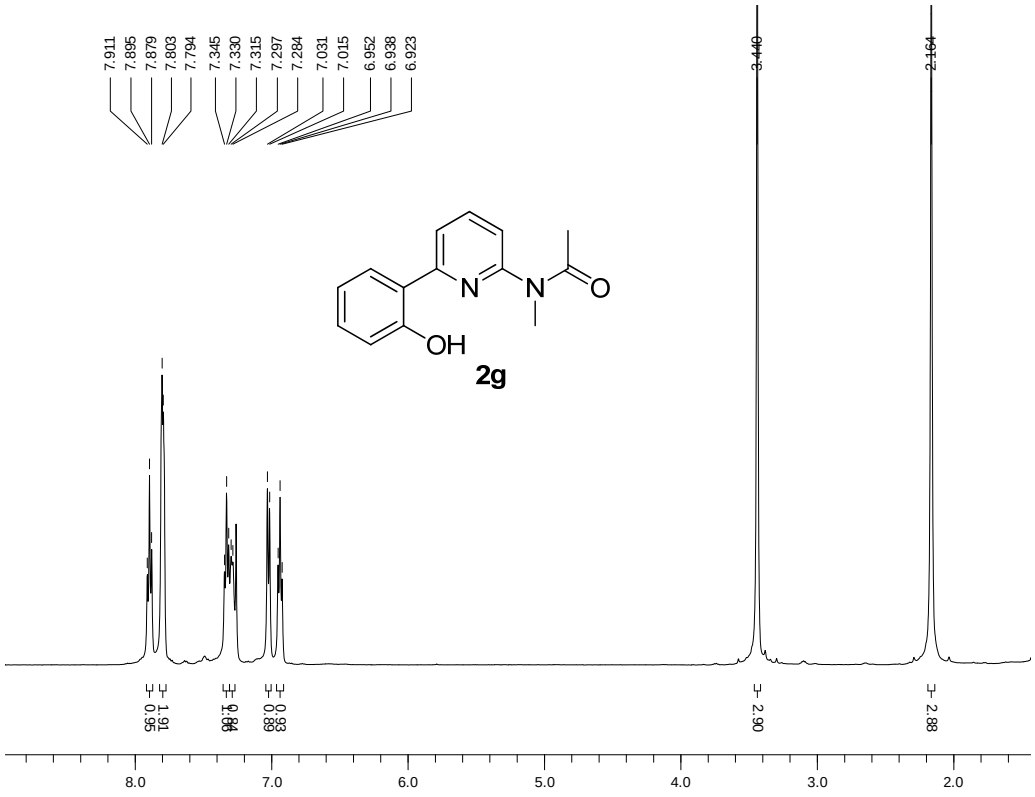
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


13.158
8.609
8.274
8.253
7.920
7.902
7.898
7.876
7.856
7.787
7.783
7.767
7.763
7.657
7.637
7.585
7.566
7.548
7.496
7.477
7.459
7.308
7.304
7.286
7.269
7.265
N
N
H
O
OH
2f
0.85
0.94
1.00
3.03
0.98
2.00
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
ppm (t1)


165.825
158.737
156.186
148.658
140.058
133.868
132.445
131.520
128.841
127.256
126.690
119.291
118.919
118.320
115.456
112.068
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm (t1)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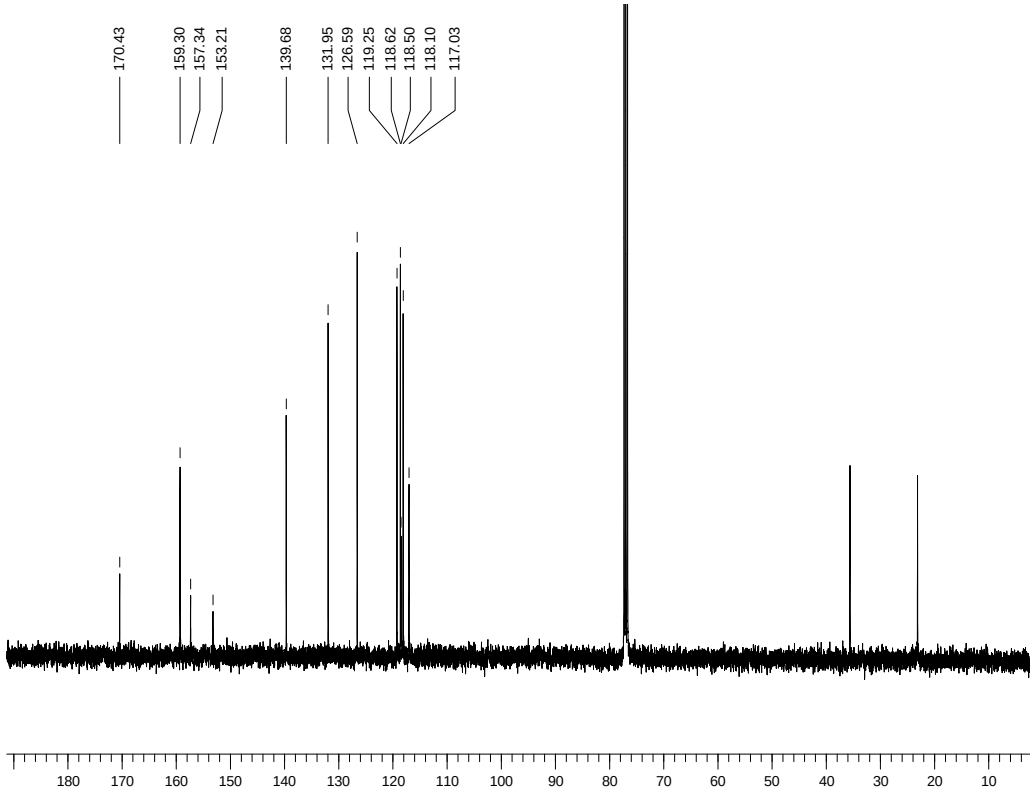
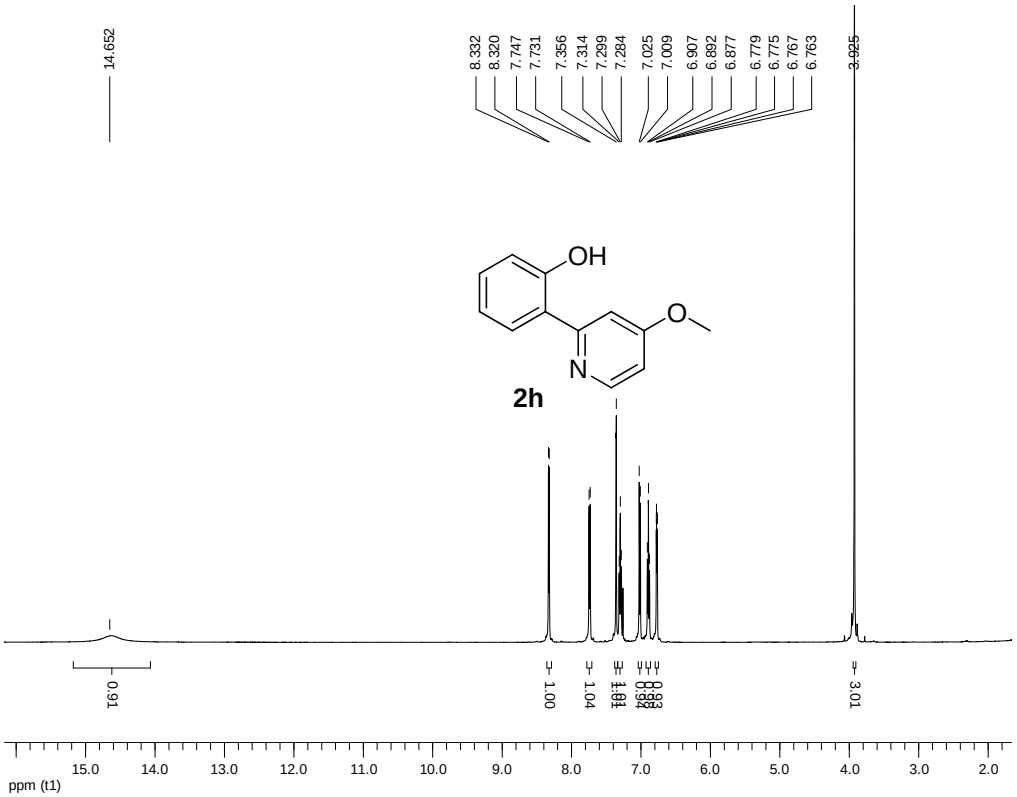
7.895
7.879
7.803
7.794
7.345
7.330
7.315
7.297
7.284
7.031
7.015
6.952
6.938
6.923
3.440
2.164
N
N
O
OH
2g
1.91
0.95
0.93
0.89
2.90
2.88
8.0
7.0
6.0
5.0
4.0
3.0
2.0


170.43
159.30
157.34
153.21
139.68
131.95
126.59
119.25
118.62
118.50
118.10
117.03
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10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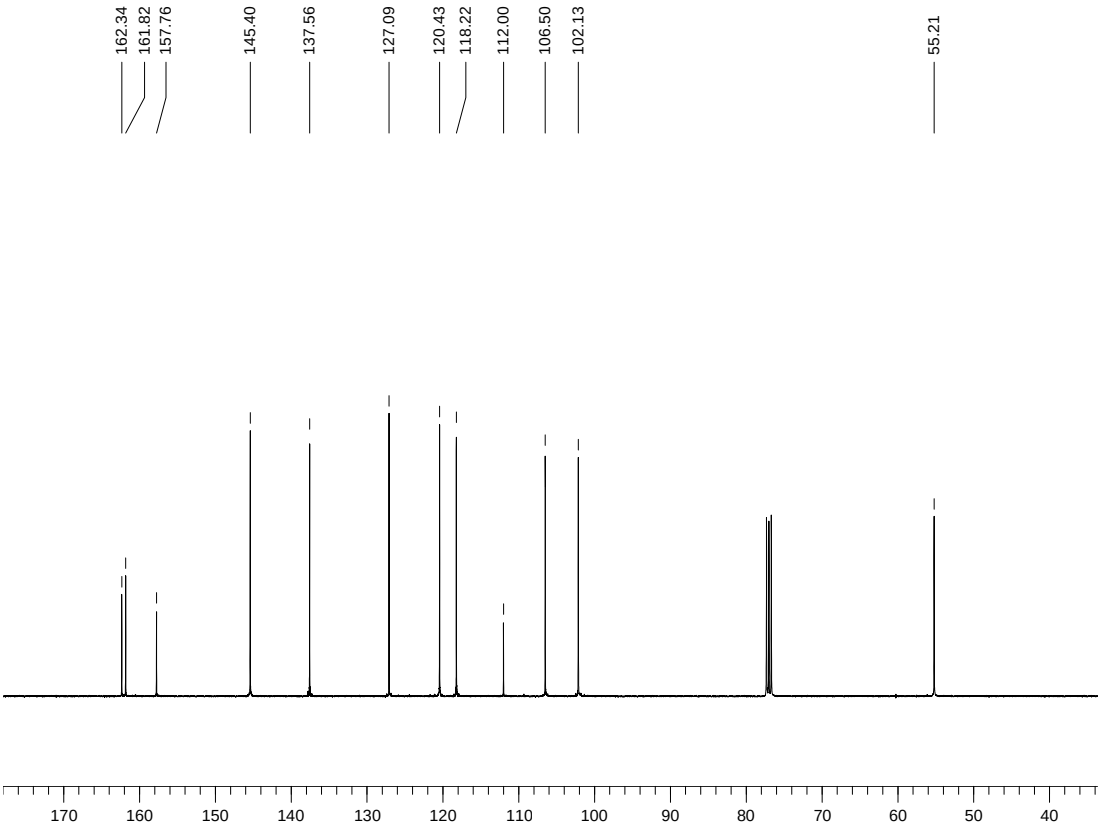
8.332
8.320
7.747
7.731
7.356
7.314
7.299
7.284
7.025
7.009
6.907
6.892
6.877
6.779
6.775
6.767
6.763
3.925
OH
O
N
2h
0.91
1.00
1.04
3.01
ppm (t1)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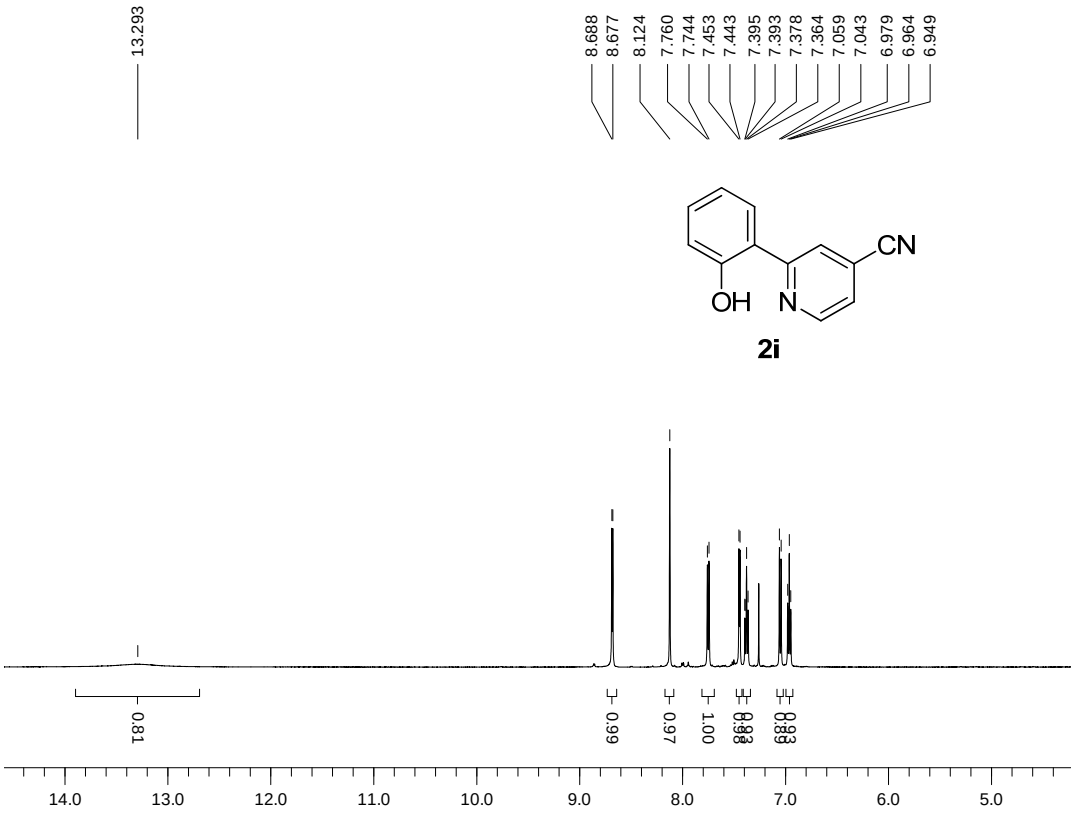
161.82
157.76
145.40
137.56
127.09
120.43
118.22
112.00
106.50
102.13
55.21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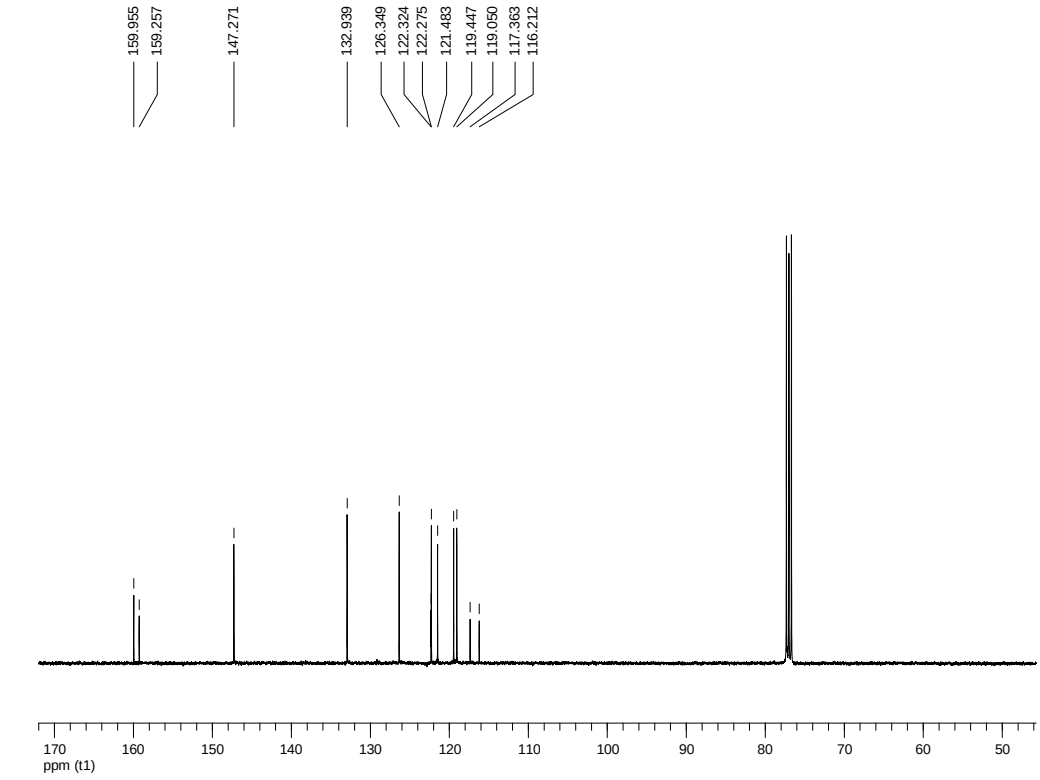
8.688
8.677
8.124
7.760
7.744
7.453
7.443
7.395
7.393
7.378
7.364
7.059
7.043
6.979
6.964
6.949
CN
OH
N
0.81
0.99
0.97
1.00
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0

2i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159.257
147.271
132.939
126.349
122.324
122.275
121.483
119.447
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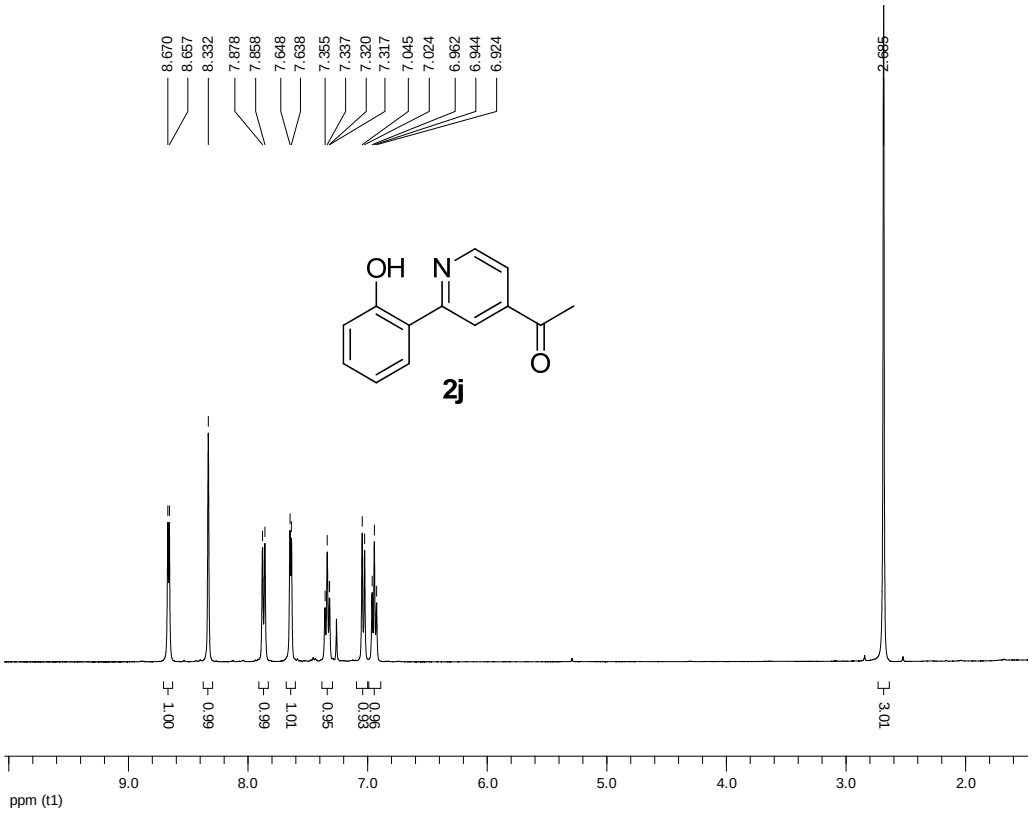
117.363
116.212
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm (t1)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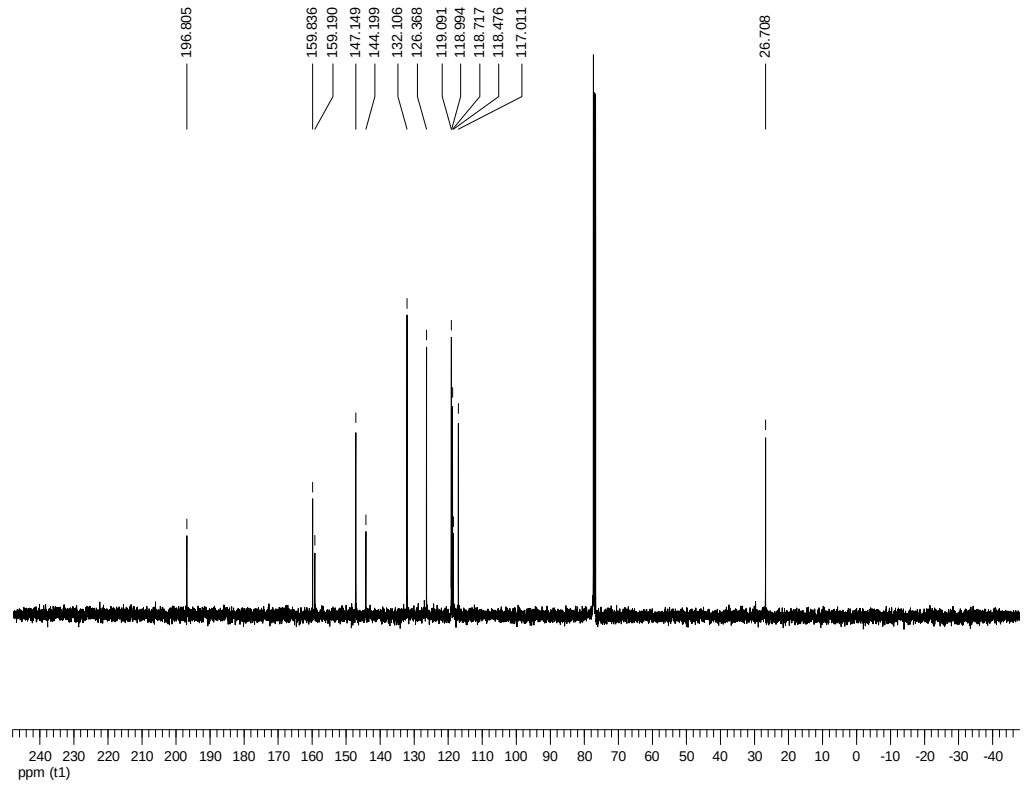
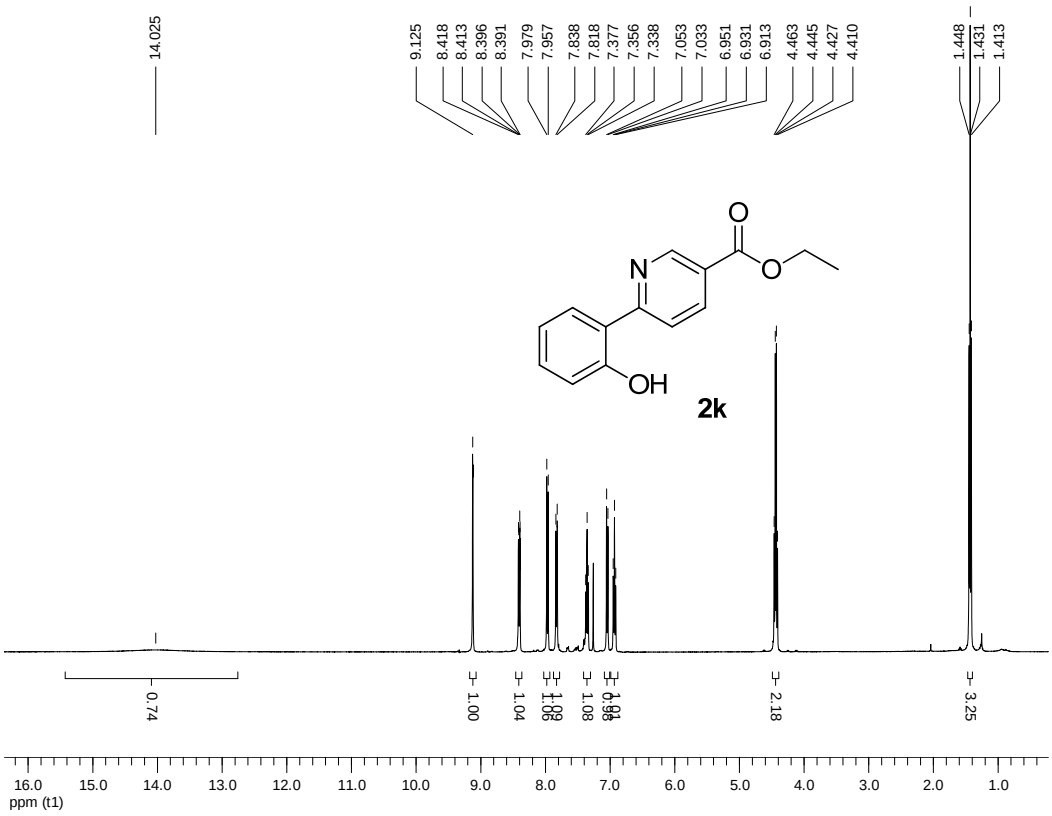
8.332
7.878
7.858
7.648
7.638
7.355
7.337
7.320
7.317
7.045
7.024
6.962
6.944
6.924
2.685
OH
N
O
2j
1.00
0.99
0.99
1.01
0.95
0.93
0.96
3.01
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)


196.805
159.836
159.190
147.149
144.199
132.106
126.368
119.091
118.994
118.717
118.476
117.011
26.708
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
ppm (t1)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8.418
8.413
8.396
8.391
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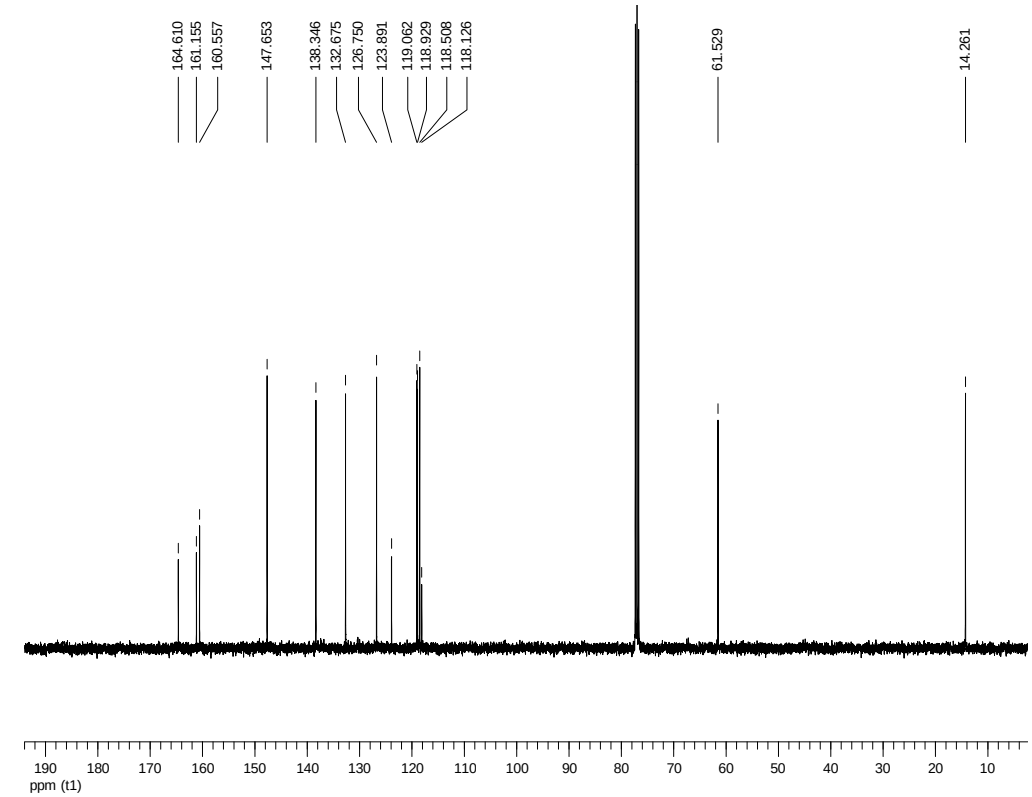
7.957
7.838
7.818
7.377
7.356
7.338
7.053
7.033
6.951
6.931
6.913
4.463
4.445
4.427
4.410
1.448
1.431
1.413
O
N
O
OH
2k
0.74
1.00
1.04
1.08
1.08
1.08
2.18
3.25
16.0
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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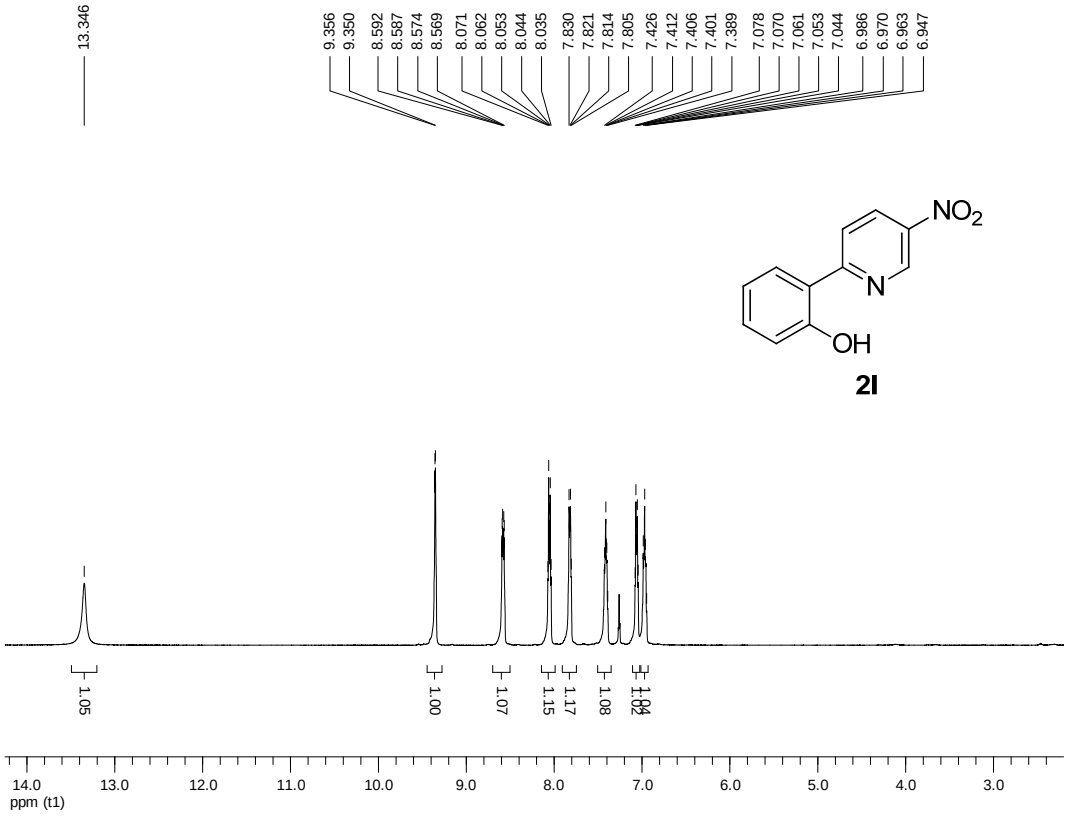
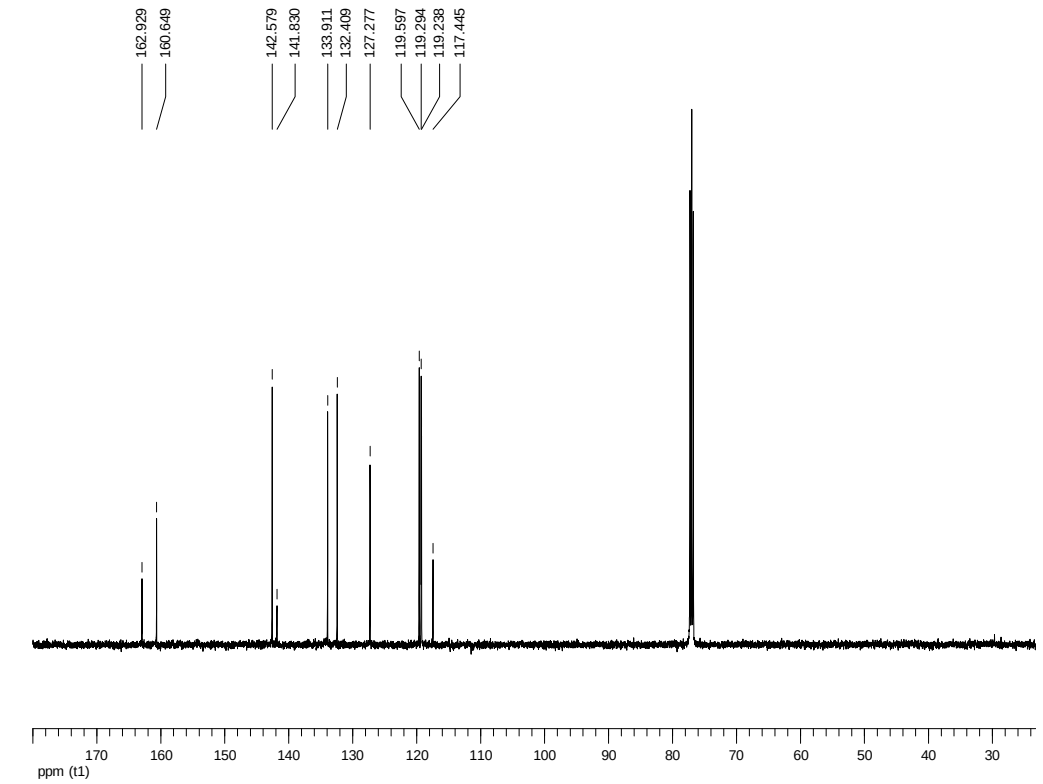
160.557
147.653
138.346
132.675
126.750
123.891
119.062
118.929
118.508
118.126
61.529
14.261
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)


13.346
9.356
9.350
8.592
8.587
8.574
8.569
8.071
8.062
8.053
8.044
8.035
7.830
7.821
7.814
7.805
7.426
7.412
7.406
7.401
7.389
7.078
7.070
7.061
7.053
7.044
6.986
6.970
6.963
6.947
NO2
N
OH
2l
1.05
1.00
1.07
1.15
1.17
1.08
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
ppm (t1)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142.579
141.830
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132.409
127.277
119.597
119.294
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117.445
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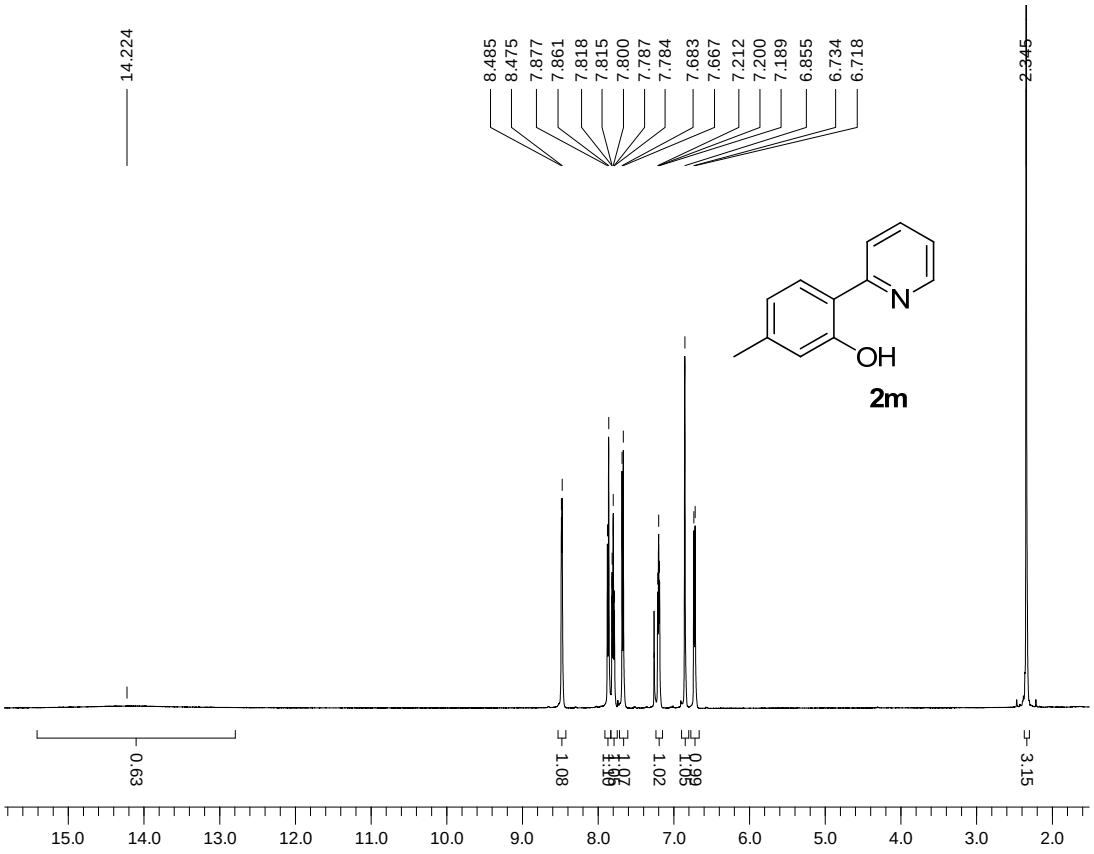
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm (t1)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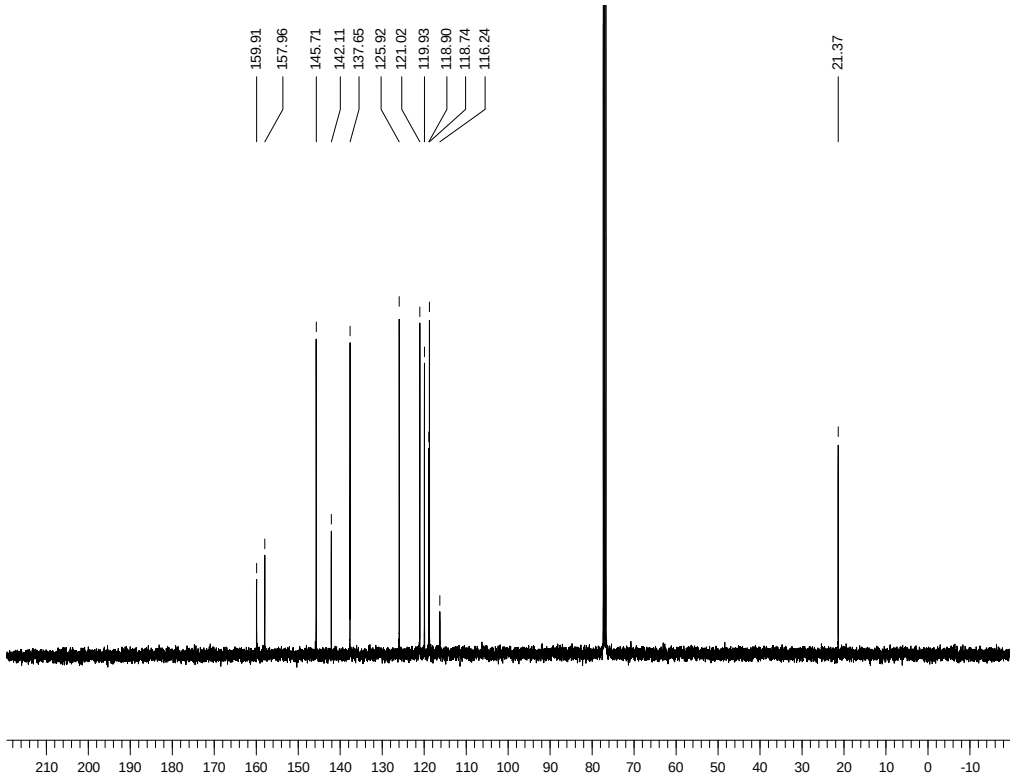
7.818
7.815
7.800
7.787
7.784
7.683
7.667
7.212
7.200
7.189
6.855
6.734
6.718
2.345
N
OH
2m
0.63
1.08
1.02
3.15
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0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157.96
145.71
142.11
137.65
125.92
121.02
119.93
118.90
118.74
116.24
21.37
210
200
190
180
170
160
150
140
130
120
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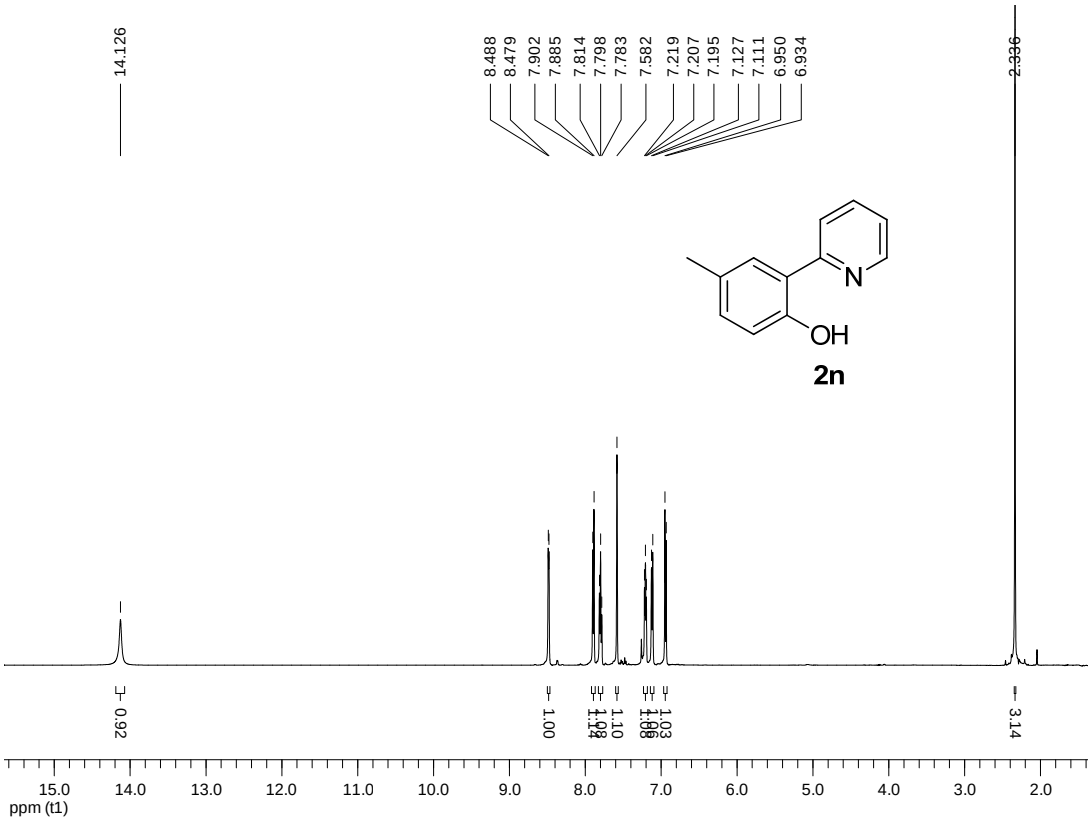
100
90
80
70
60
50
40
30
20
10
0
-10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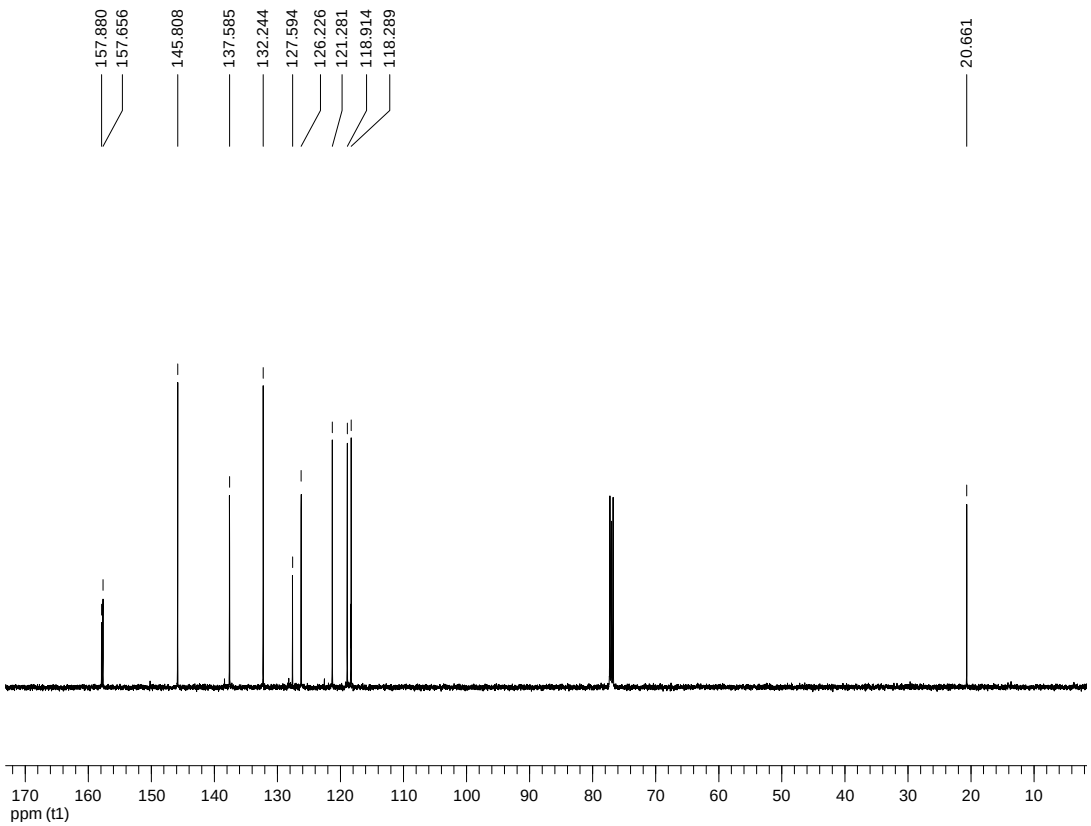
7.885
7.814
7.798
7.783
7.582
7.219
7.207
7.195
7.127
7.111
6.950
6.934
2.336
N
OH
2n
0.92
1.00
1.10
1.03
3.14
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)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157.656
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137.585
132.244
127.594
126.226
121.281
118.914
118.289
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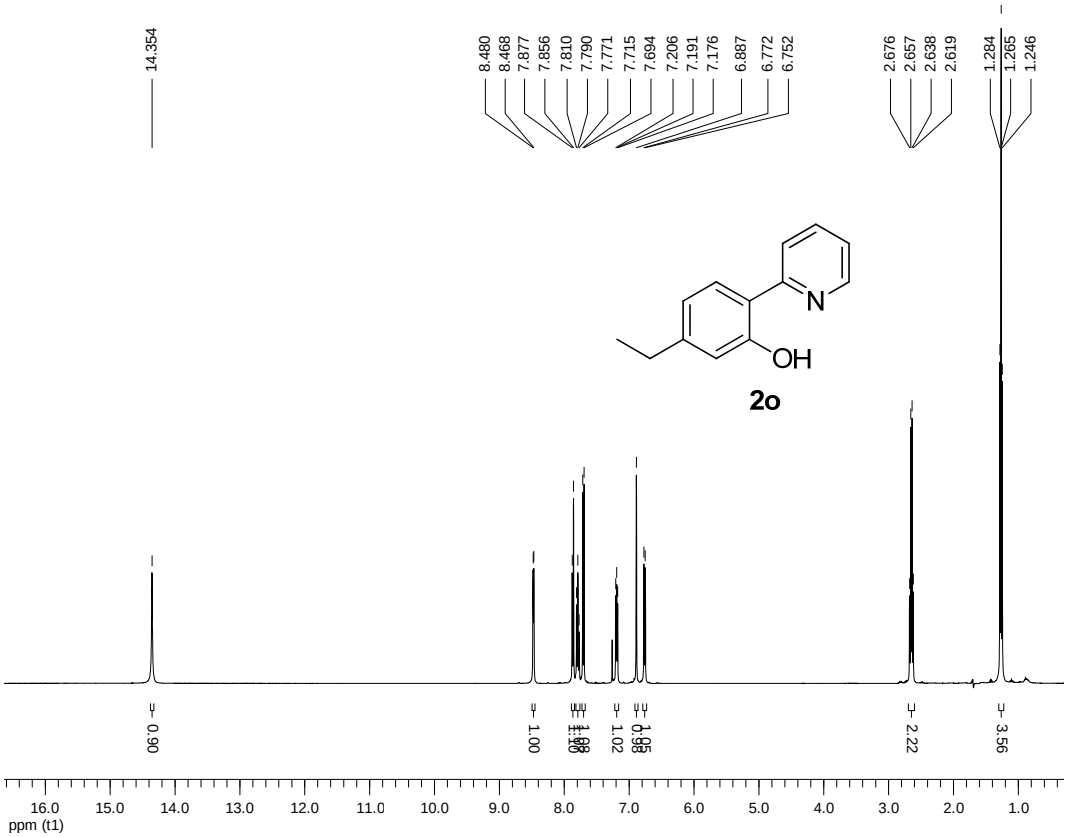
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)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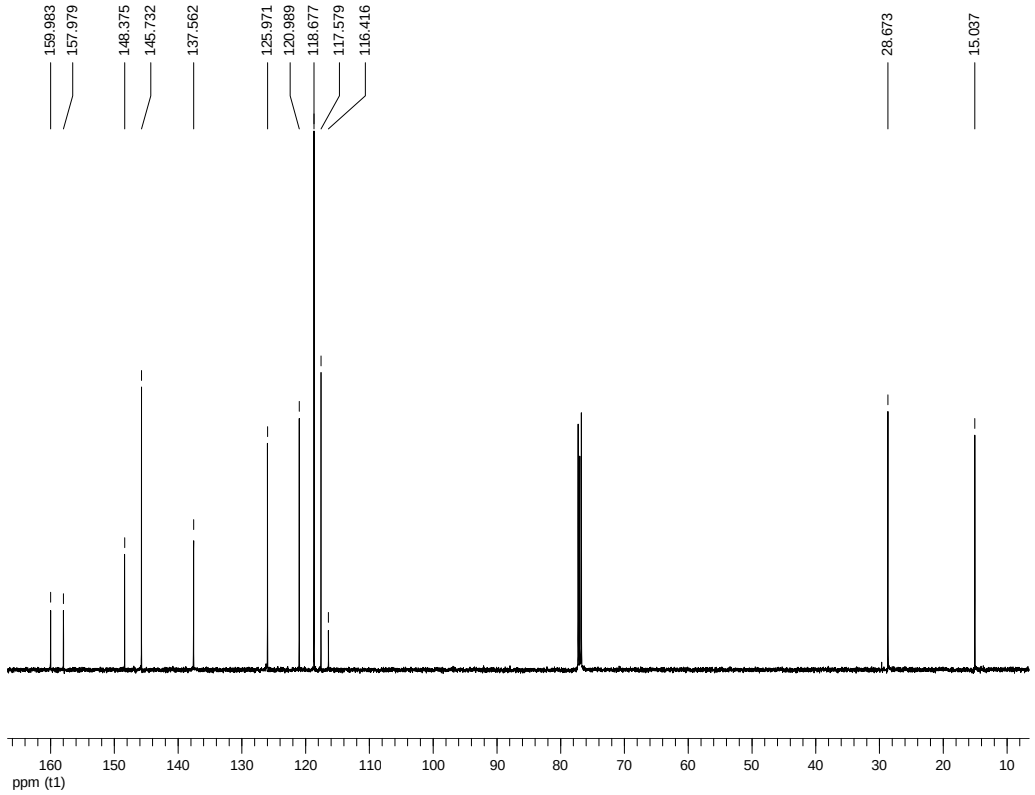
7.810
7.790
7.771
7.715
7.694
7.206
7.191
7.176
6.887
6.772
6.752
2.676
2.657
2.638
2.619
1.284
1.265
1.246
N
OH
2o
0.90
1.00
1.02
2.22
3.56
16.0
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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148.375
145.732
137.562
125.971
120.989
118.677
117.579
116.416
28.673
15.037
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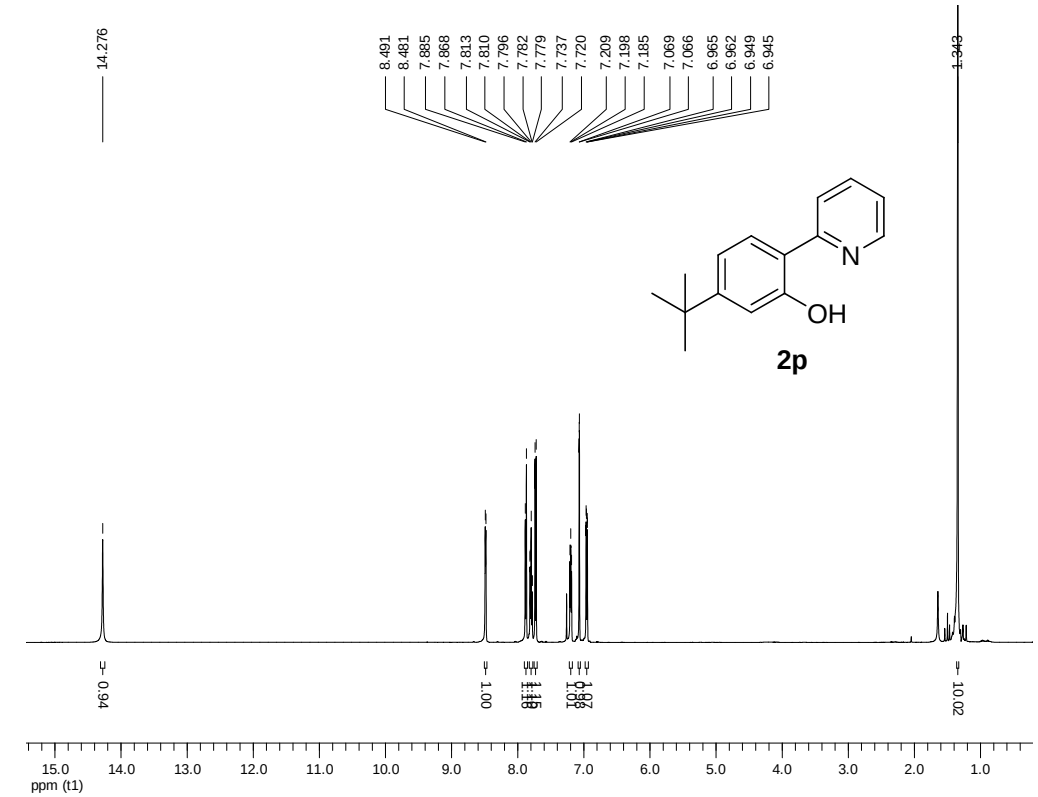
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)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7.885
7.868
7.813
7.810
7.796
7.782
7.779
7.737
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7.209
7.198
7.185
7.069
7.066
6.965
6.962
6.949
6.945
1.343
N
OH
2p
0.94
1.00
1.15
0.98
1.05
2.07
10.02
15.0
14.0
13.0
12.0
11.0
10.0
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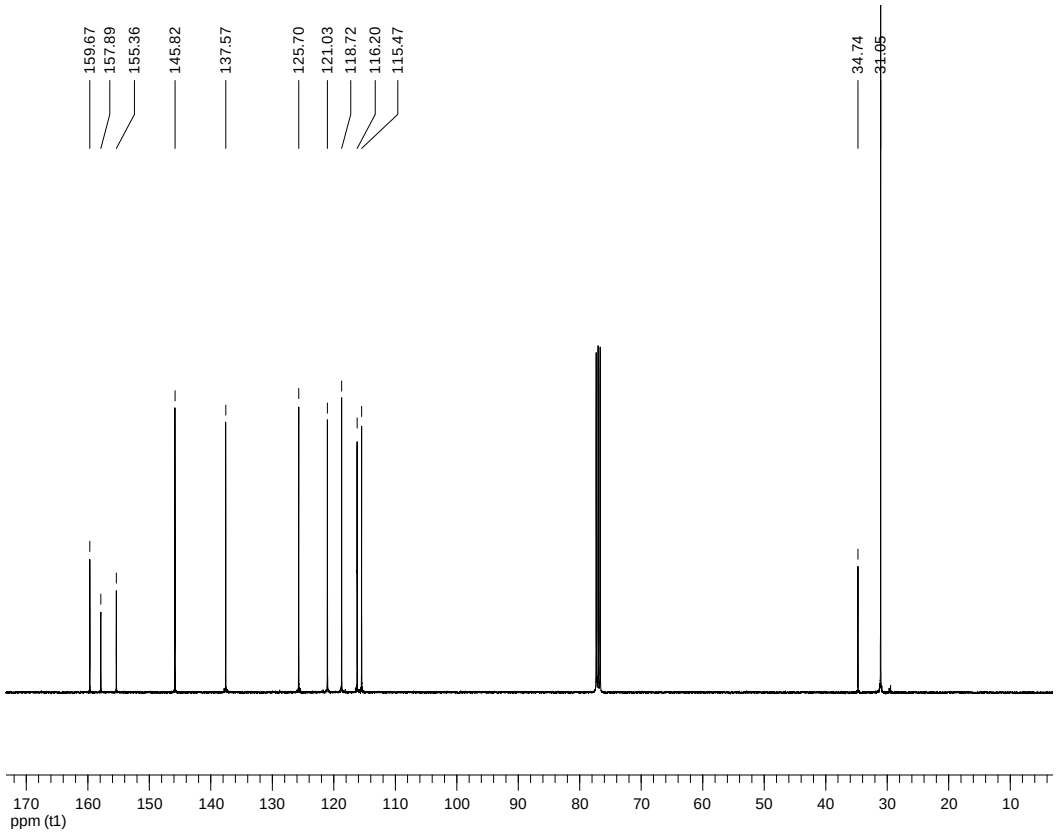
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


159.67
157.89
155.36
145.82
137.57
125.70
121.03
118.72
116.20
115.47
34.74
31.05
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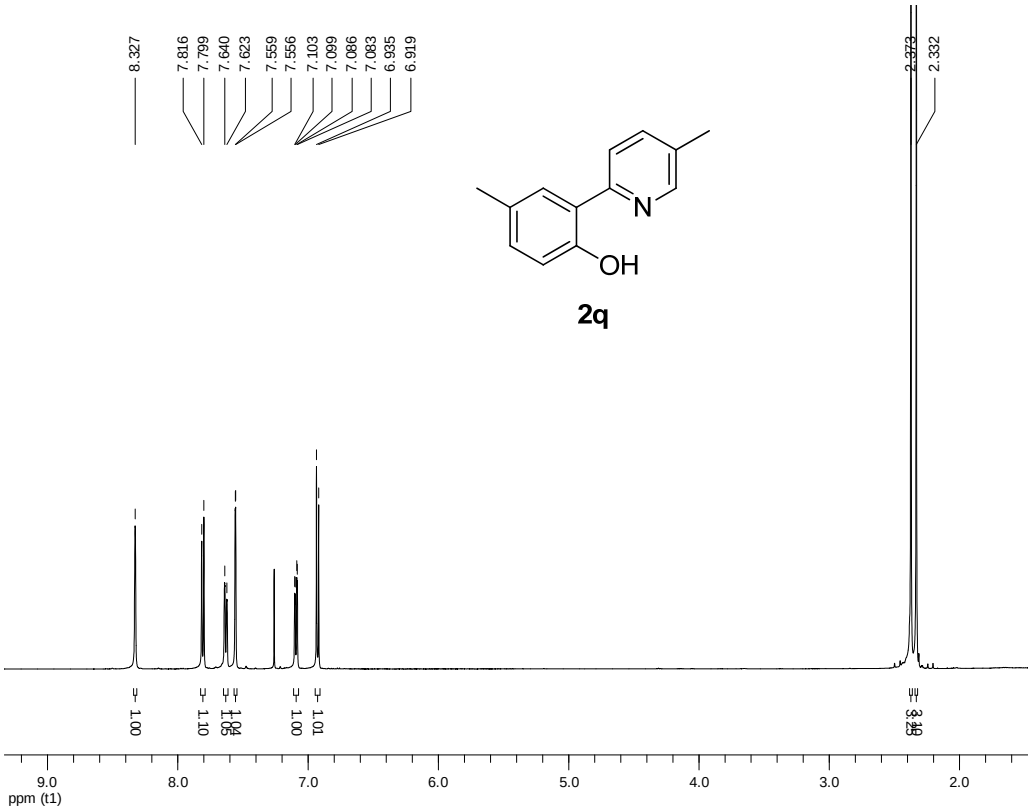
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)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7.623
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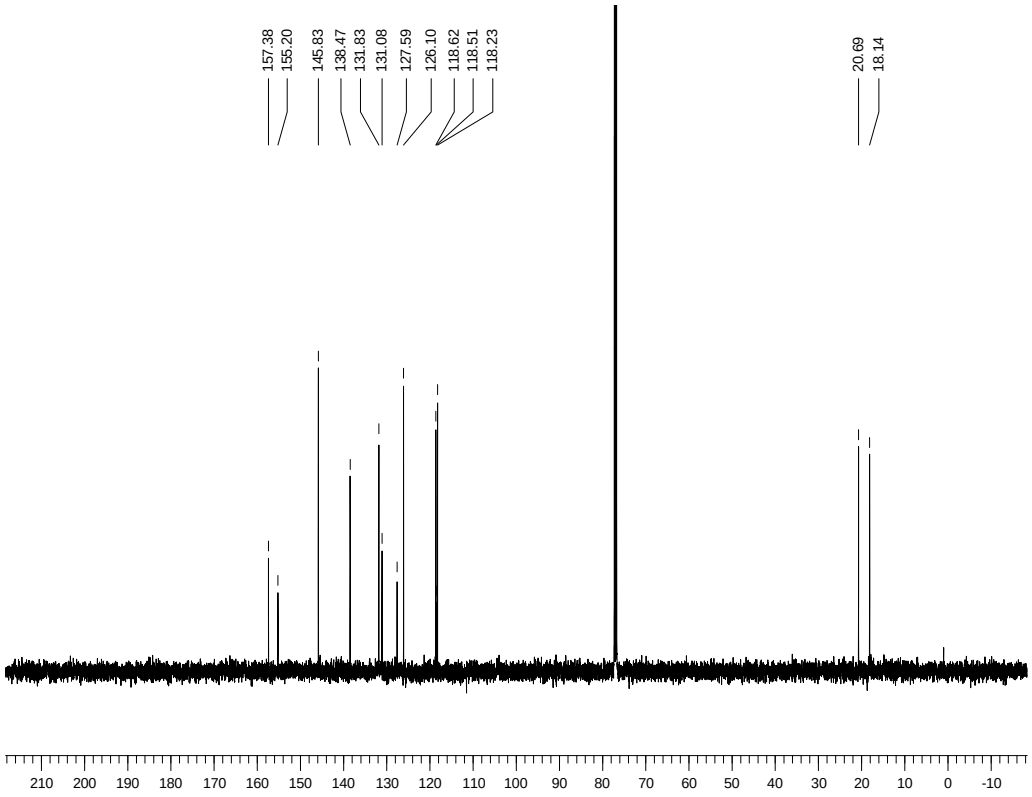
7.556
7.103
7.099
7.086
7.083
6.935
6.919
2.373
2.332
N
OH
2q
1.00
1.10
1.04
1.00
1.01
3.45
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)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131.08
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126.10
118.62
118.51
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18.14
210
200
190
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50
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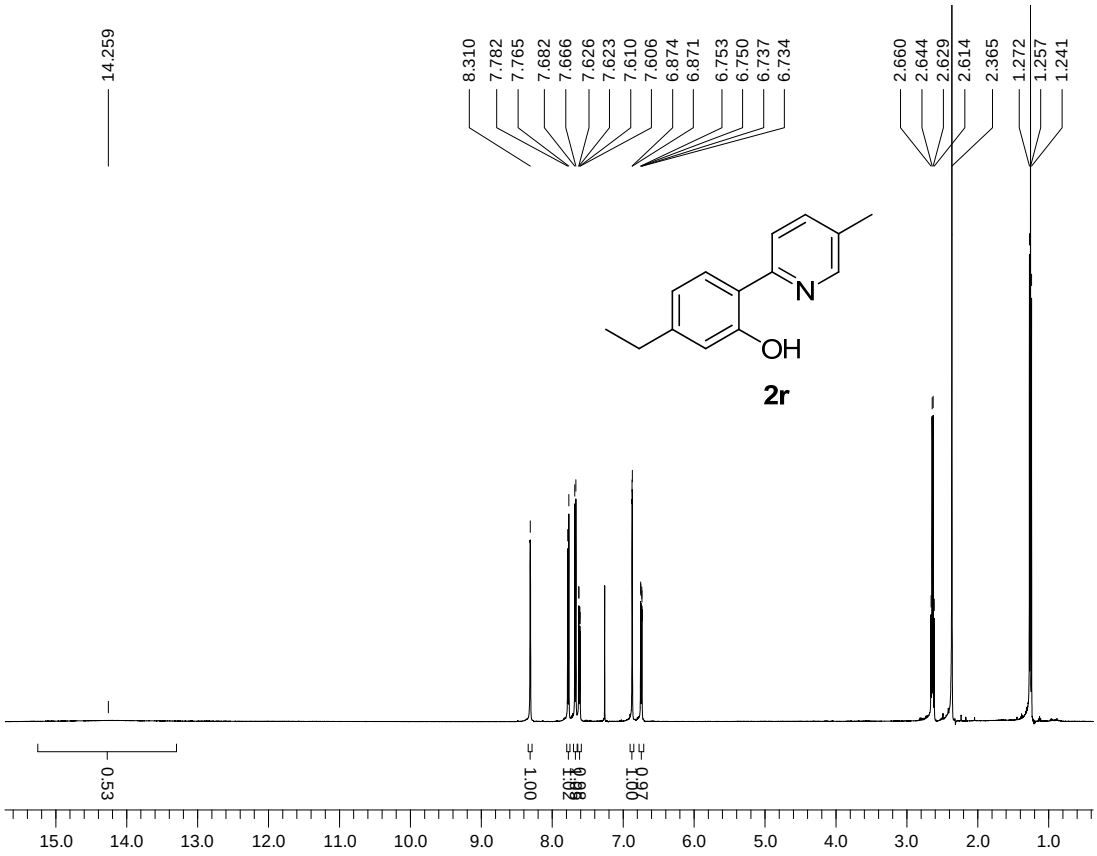
0
-10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7.623
7.610
7.606
6.874
6.871
6.753
6.750
6.737
6.734
2.660
2.644
2.629
2.614
2.365
1.272
1.257
1.241
N
OH
2r
0.53
1.00
2.07
1.00
15.0
14.0
13.0
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7.0
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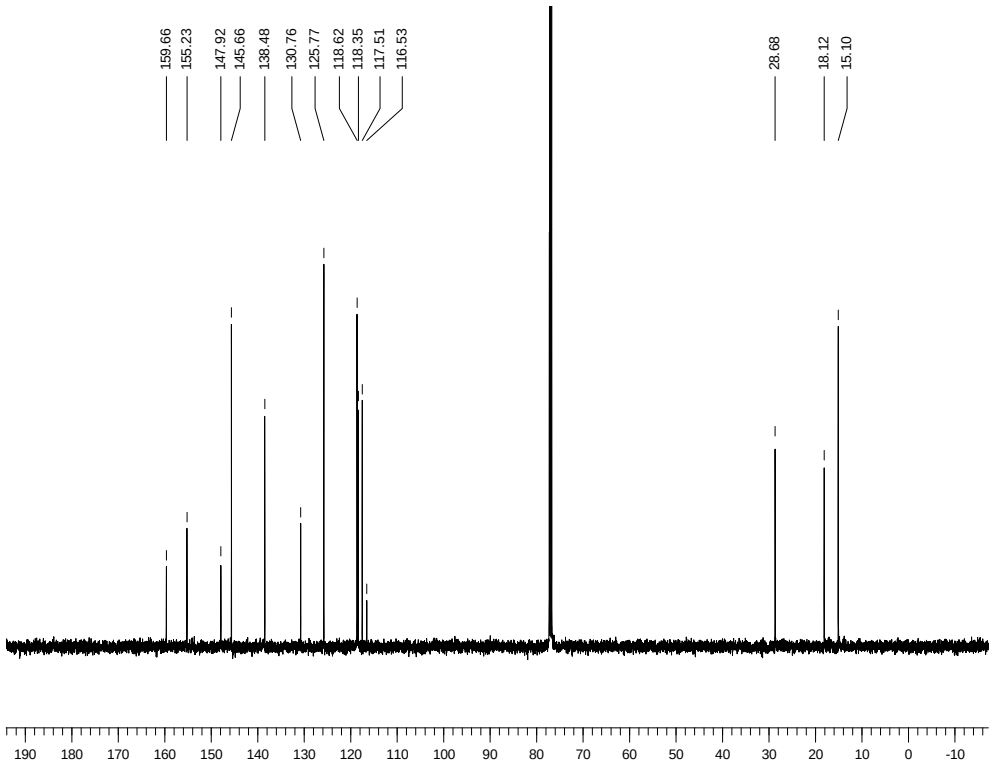
2.0
1.0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125.77
118.62
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117.51
116.53
28.68
18.12
15.10
190
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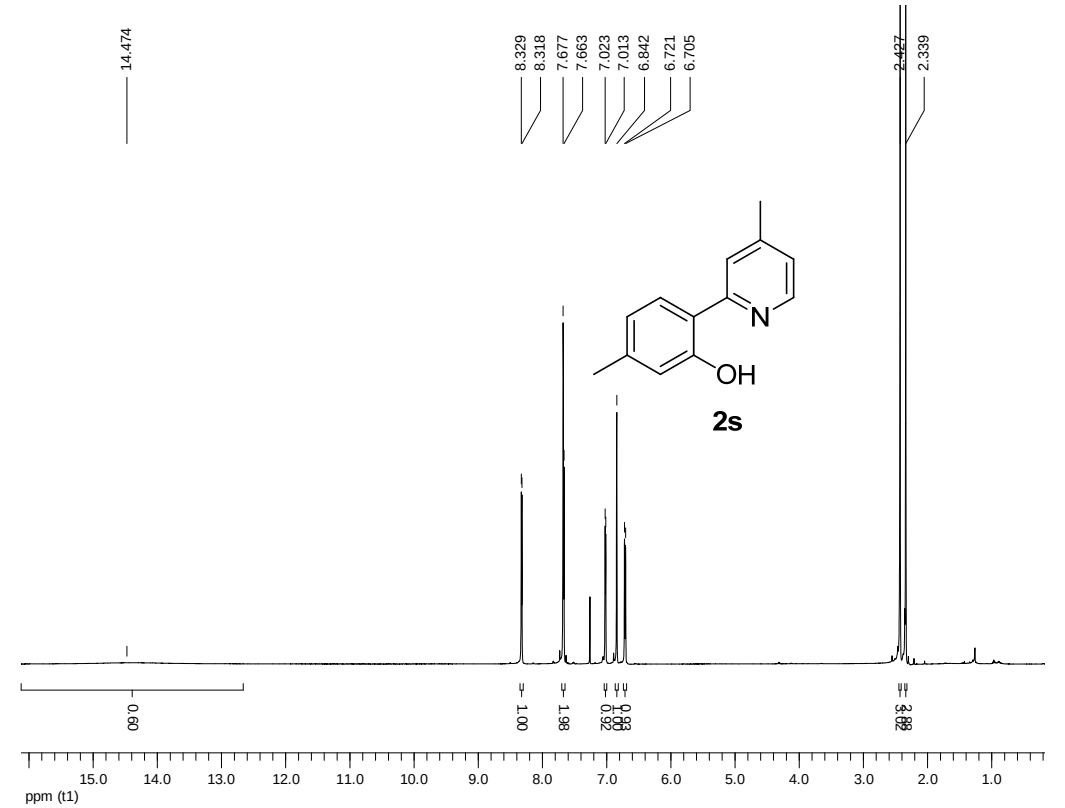
0
-10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6.842
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6.705
2.427
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0.92
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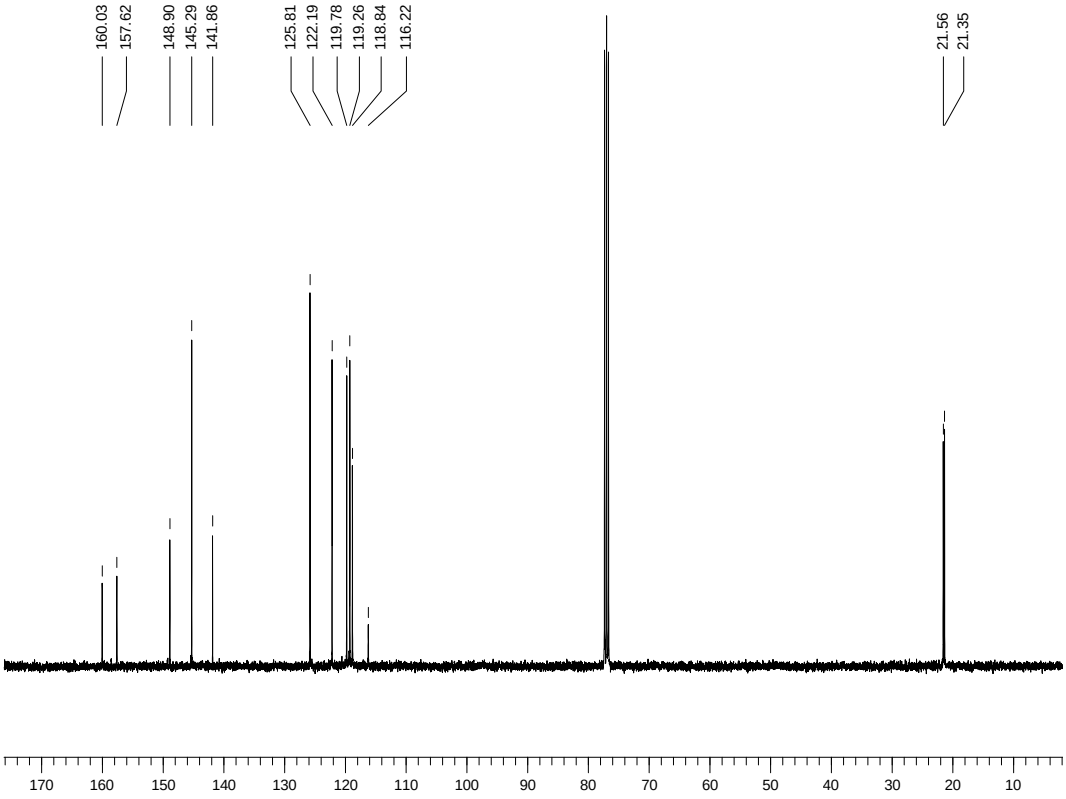
ppm (t1)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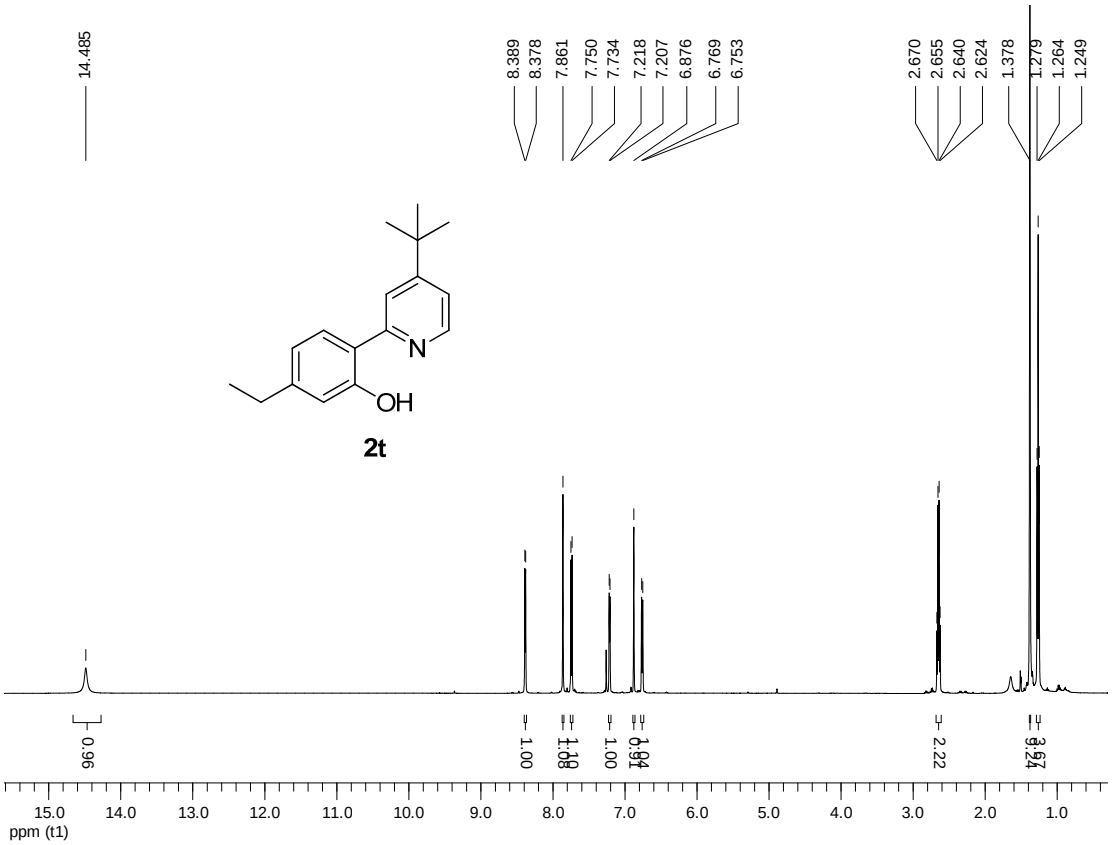
21.35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7.734
7.218
7.207
6.876
6.769
6.753
2.670
2.655
2.640
2.624
1.378
1.279
1.264
1.249
N
OH
0.96
1.00
1.08
1.00
1.04
2.22
9.27
15.0
14.0
13.0
12.0
11.0
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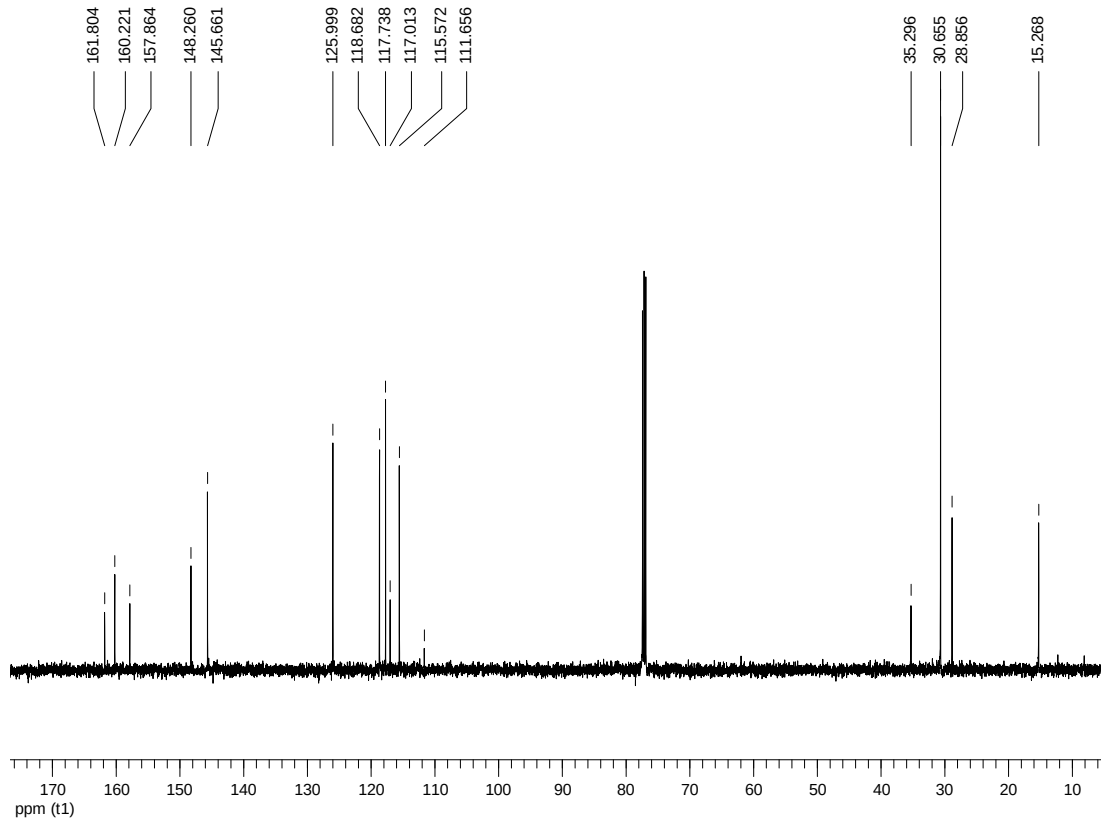
3.0
2.0
1.0
ppm (t1)

2t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157.864
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118.682
117.738
117.013
115.572
111.656
35.296
30.655
28.856
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140
130
120
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60
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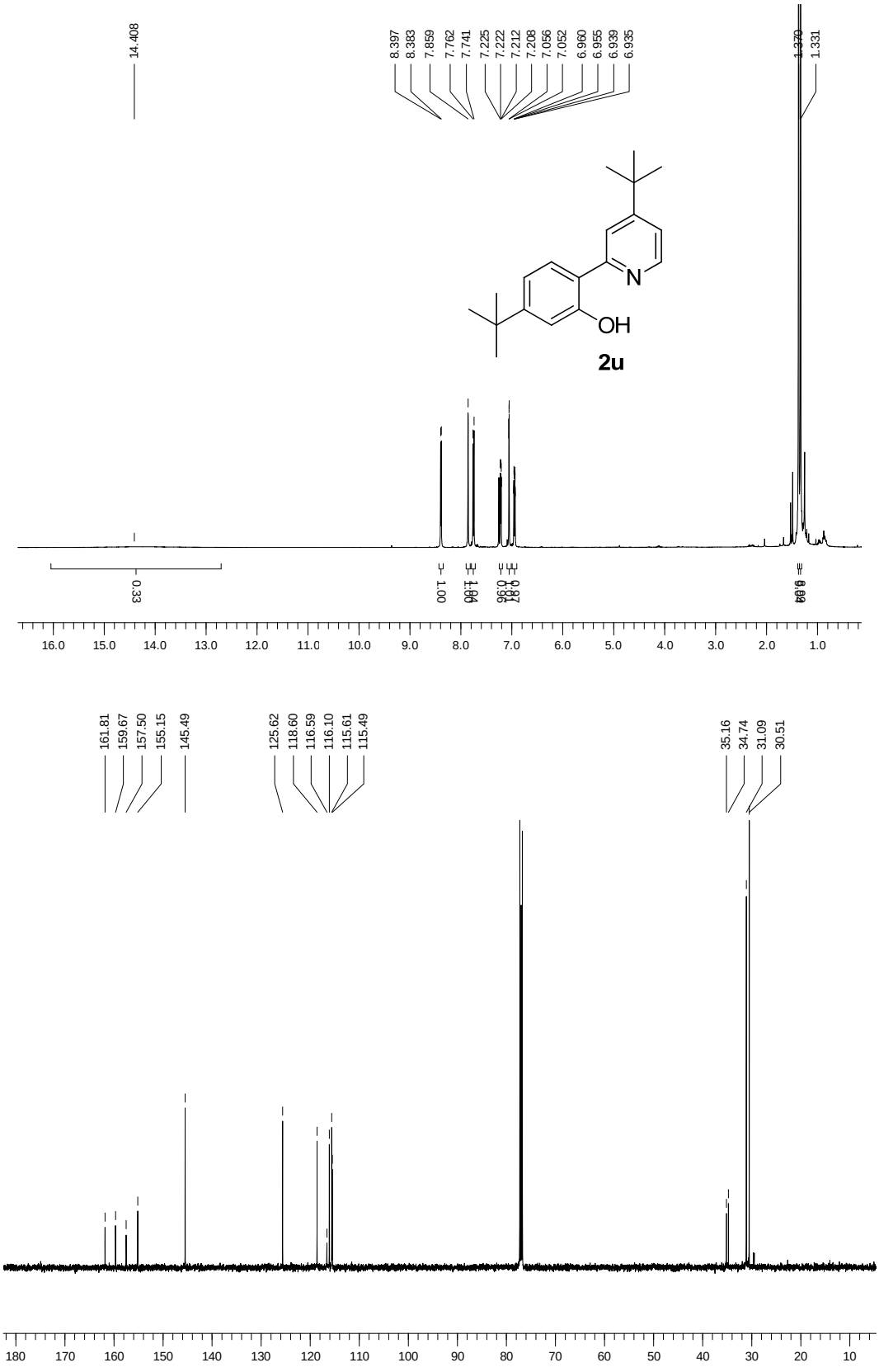
30
20
10
ppm (t1)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7.741
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7.222
7.212
7.208
7.056
7.052
6.960
6.955
6.939
6.935
1.370
1.331
N
OH
2u
0.33
1.00
16.0
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
161.81
159.67
157.50
155.15
145.49
125.62
118.60
116.59
116.10
115.61
115.49
35.16
34.74
31.09
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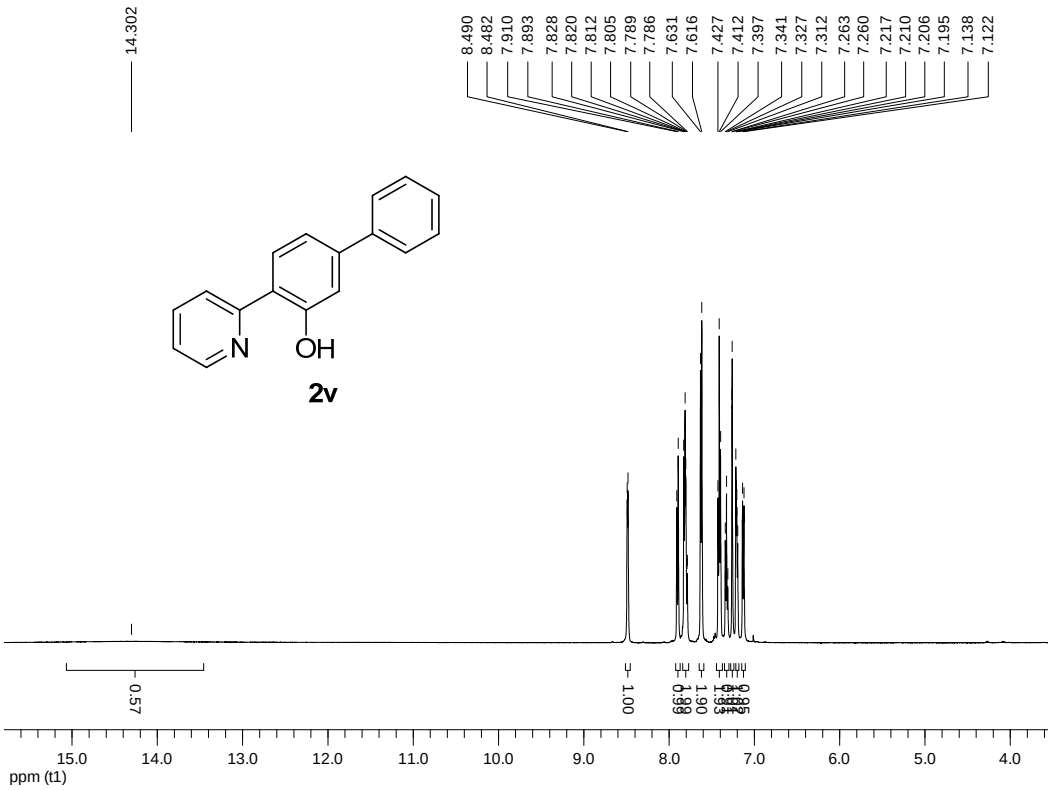
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8.482
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7.893
7.828
7.820
7.812
7.805
7.789
7.786
7.631
7.616
7.427
7.412
7.397
7.341
7.327
7.312
7.263
7.260
7.217
7.210
7.206
7.195
7.138
7.122
N
OH
2v
0.57
1.00
1.90
15.0
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11.0
10.0
9.0
8.0
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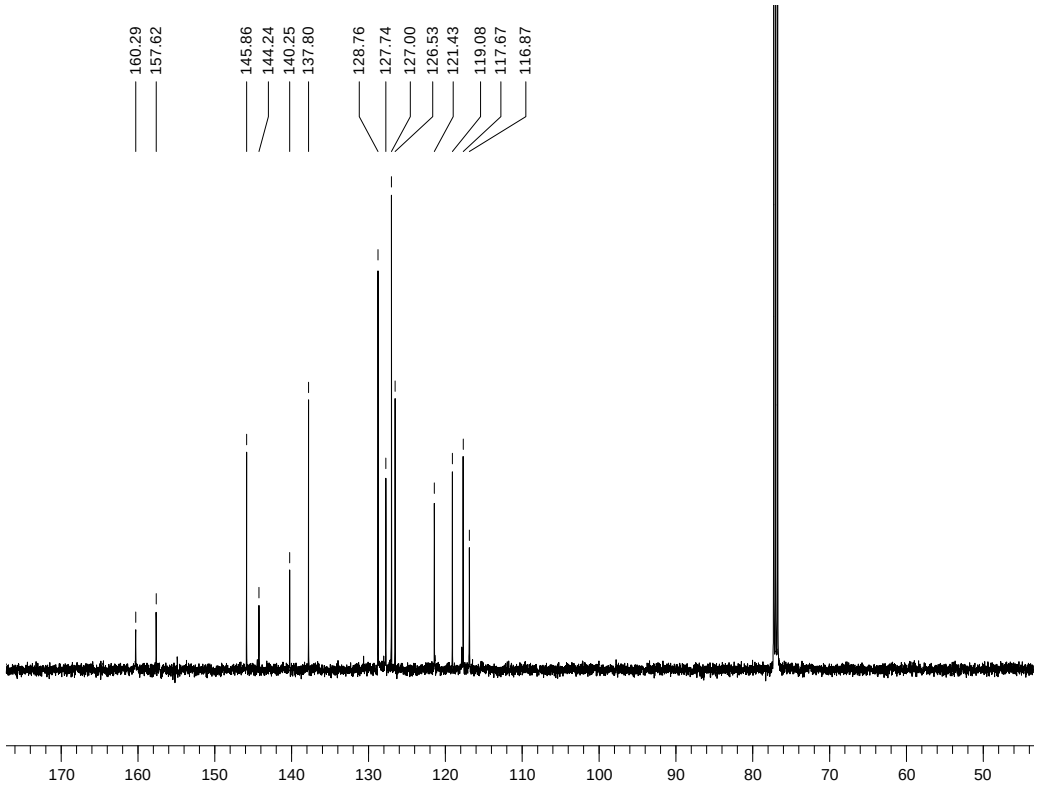
6.0
5.0
4.0
ppm (t1)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127.74
127.00
126.53
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116.87
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160
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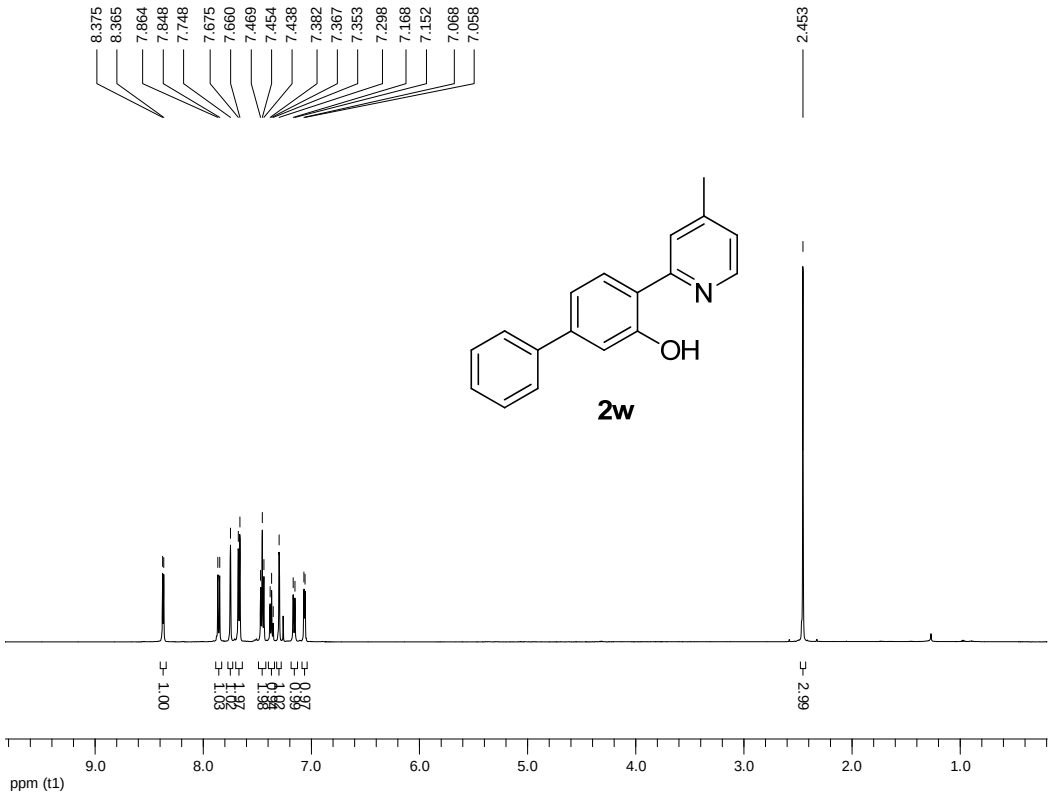
140
130
120
110
100
90
80
70
60
50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7.864
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7.748
7.675
7.660
7.469
7.454
7.438
7.382
7.367
7.353
7.298
7.168
7.152
7.068
7.058
2.453
N
OH
2w
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2.99
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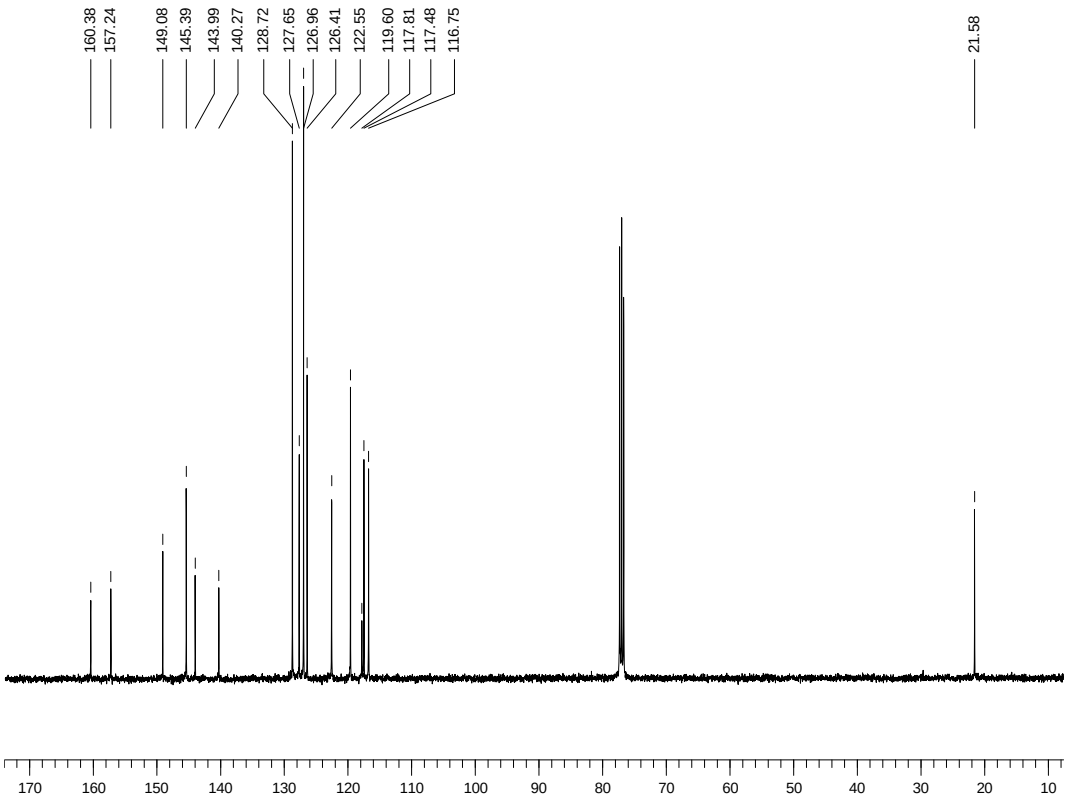
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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122.55
119.60
117.81
117.48
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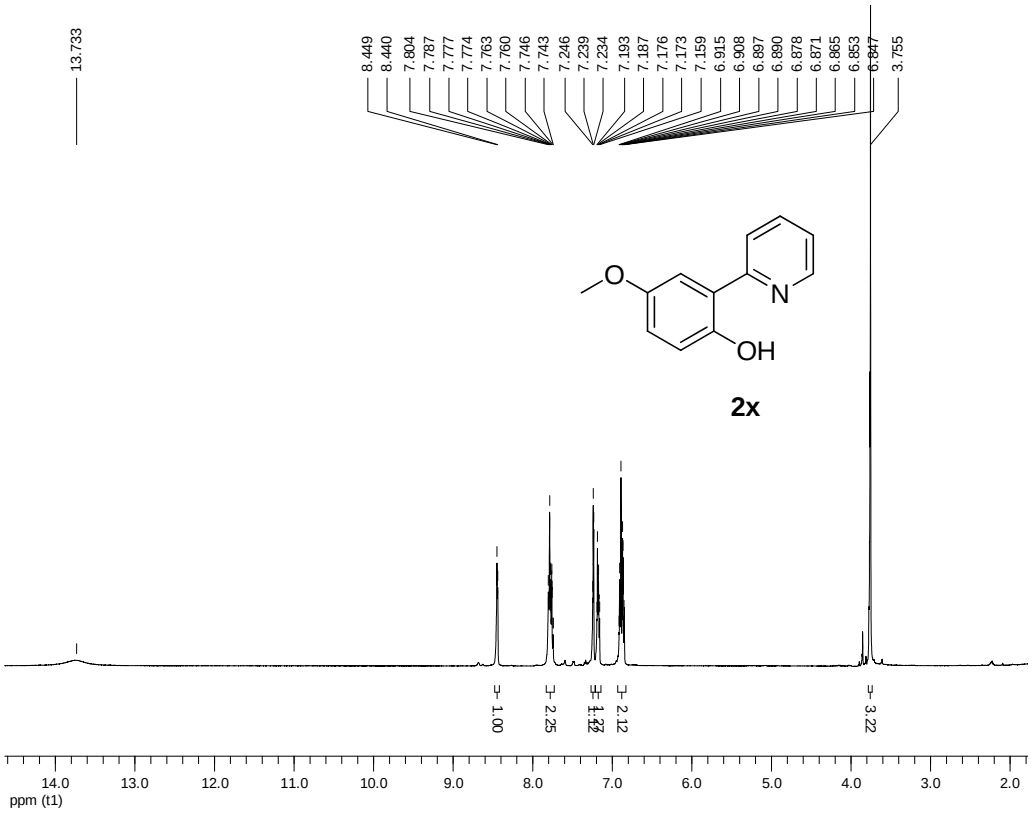
20
10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7.774
7.763
7.760
7.746
7.743
7.246
7.239
7.234
7.193
7.187
7.176
7.173
7.159
6.915
6.908
6.897
6.890
6.878
6.871
6.865
6.853
6.847
3.755
O
N
OH
2x
1.00
2.25
1.12
1.27
2.12
3.22
14.0
13.0
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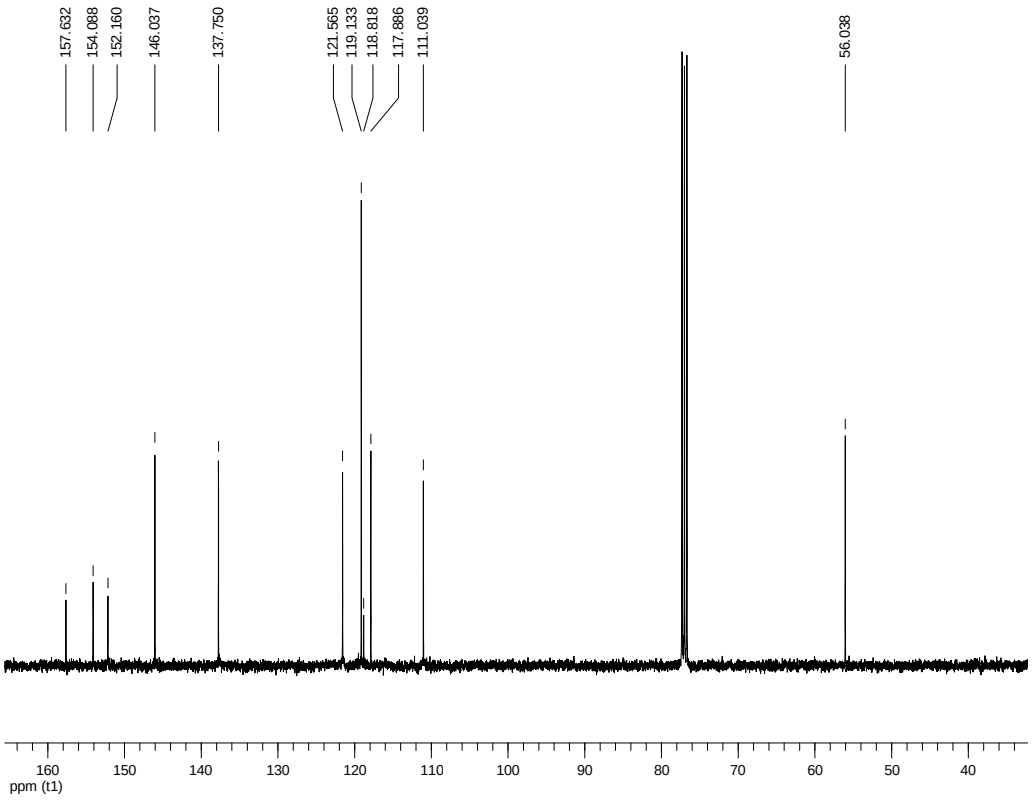
ppm (t1)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152.160
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118.818
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160
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90
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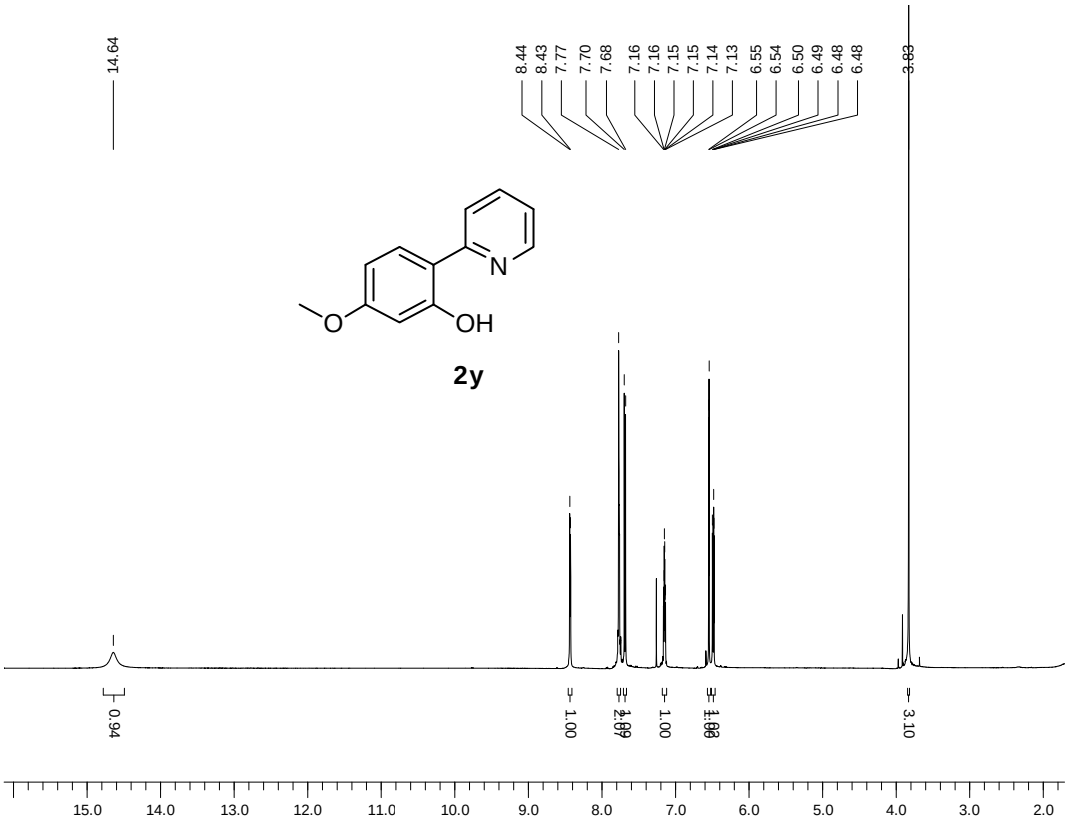
50
40
ppm (t1)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7.15
7.14
7.13
6.55
6.54
6.50
6.49
6.48
6.48
3.83
N
O
OH
2y
0.94
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2.17
1.00
1.00
3.10
15.0
14.0
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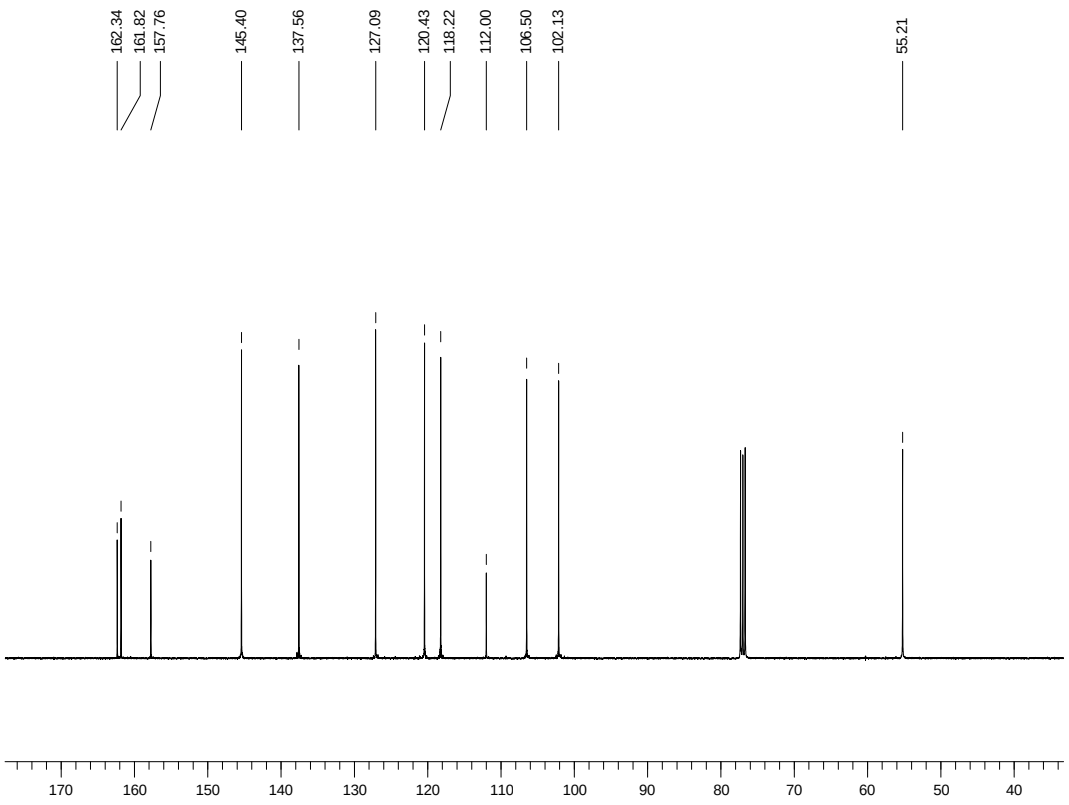
2.0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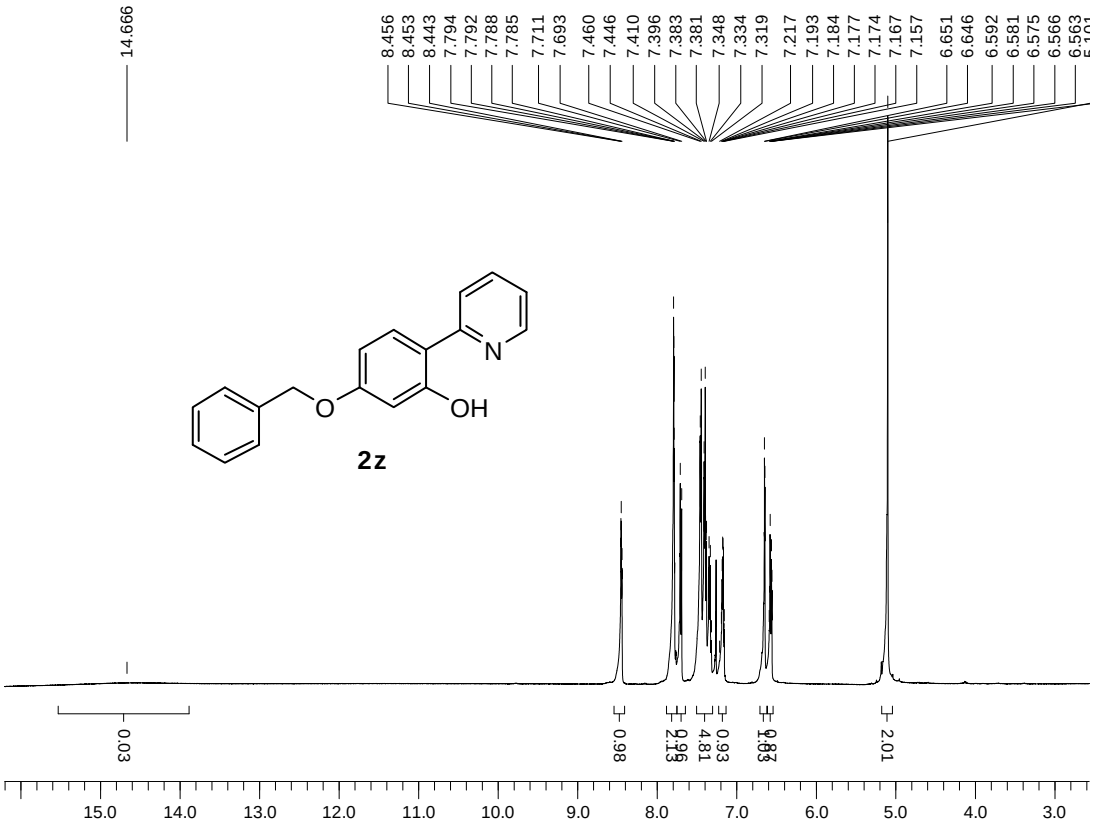
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7.410
7.396
7.383
7.381
7.348
7.334
7.319
7.217
7.193
7.184
7.177
7.174
7.167
7.157
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6.646
6.592
6.581
6.575
6.566
6.563
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O
OH
2z
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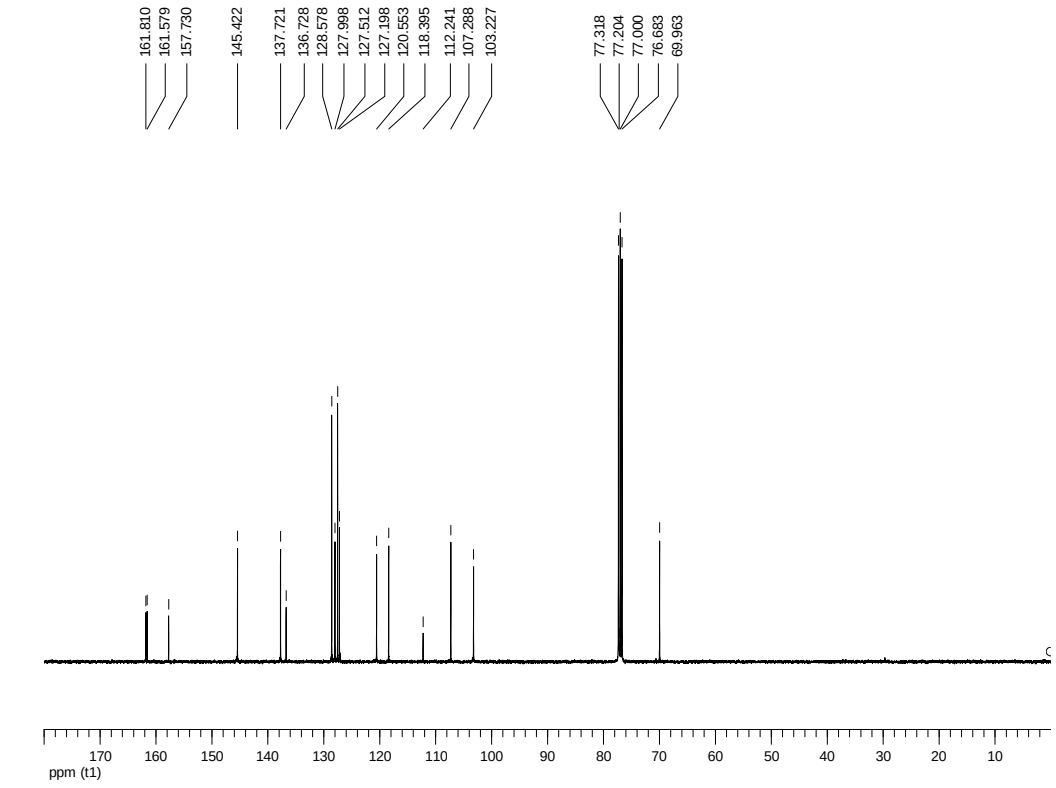
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107.288
103.227
77.318
77.204
77.000
76.683
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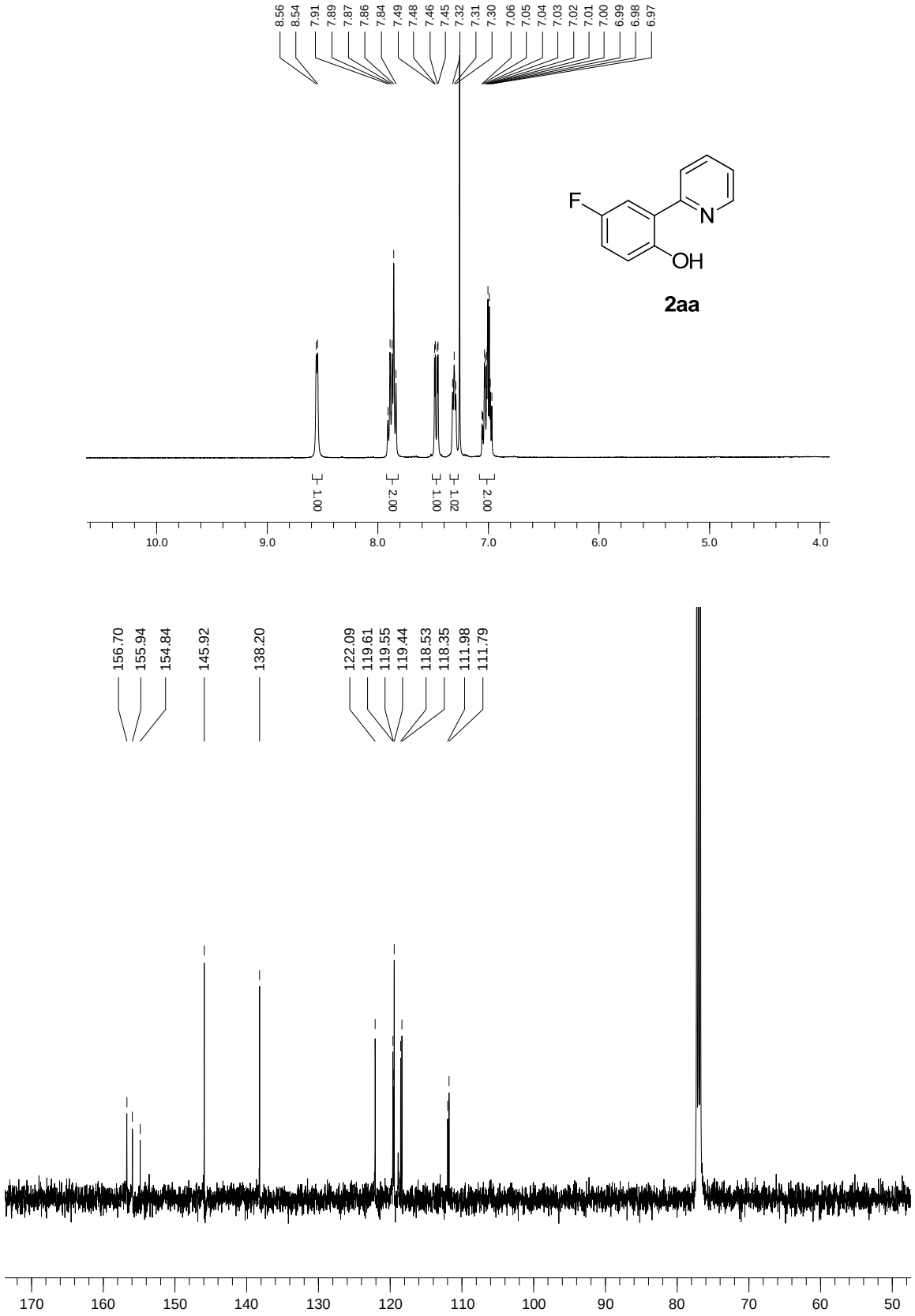
ppm (t1)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7.06
7.05
7.04
7.03
7.02
7.01
7.00
6.99
6.98
6.97
F
N
OH
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2.00
1.00
1.02
2.00
10.0
9.0
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4.0
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138.20
122.09
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119.55
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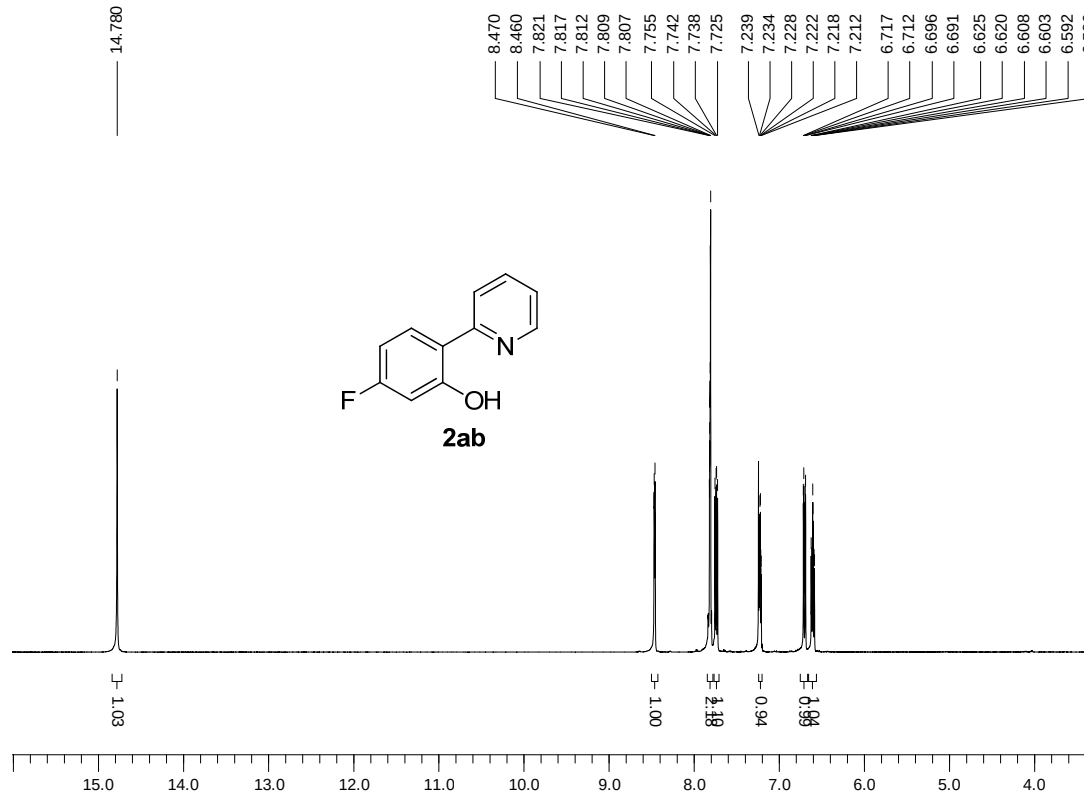
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7.222
7.218
7.212
6.717
6.712
6.696
6.691
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6.620
6.608
6.603
6.592
F
OH
N
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1.00
2.18
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1.04
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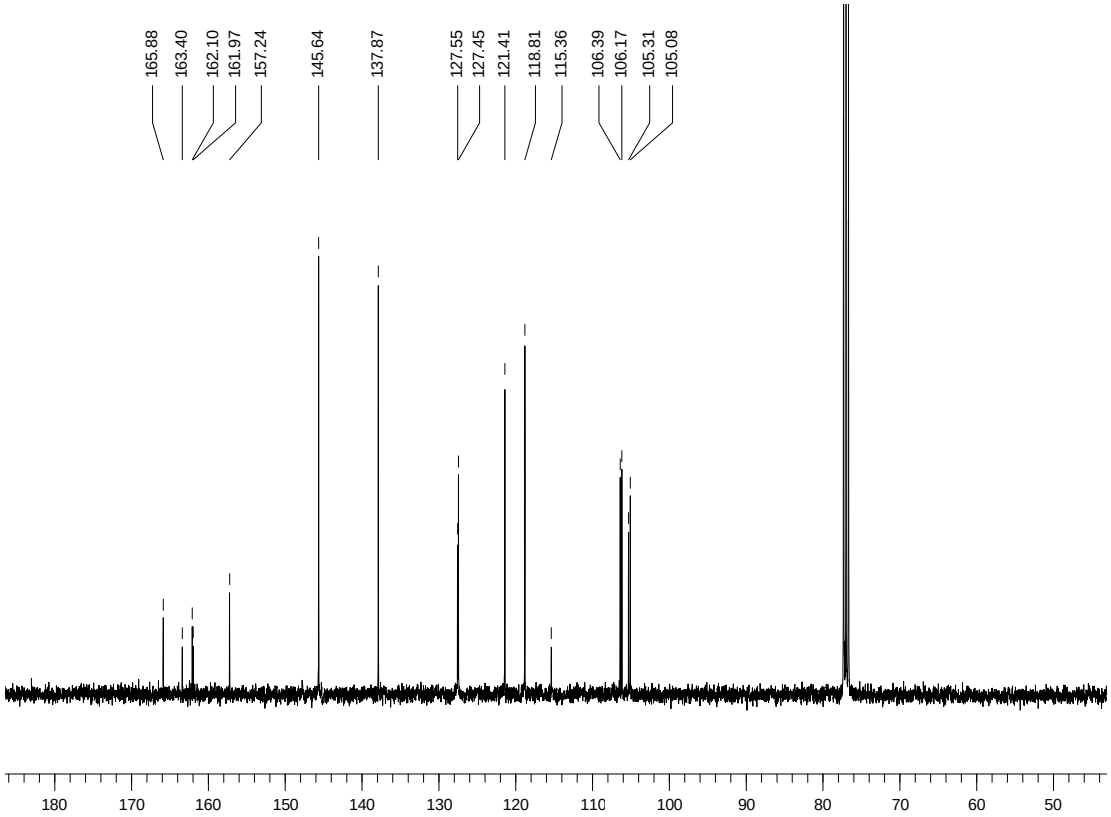
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120
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60
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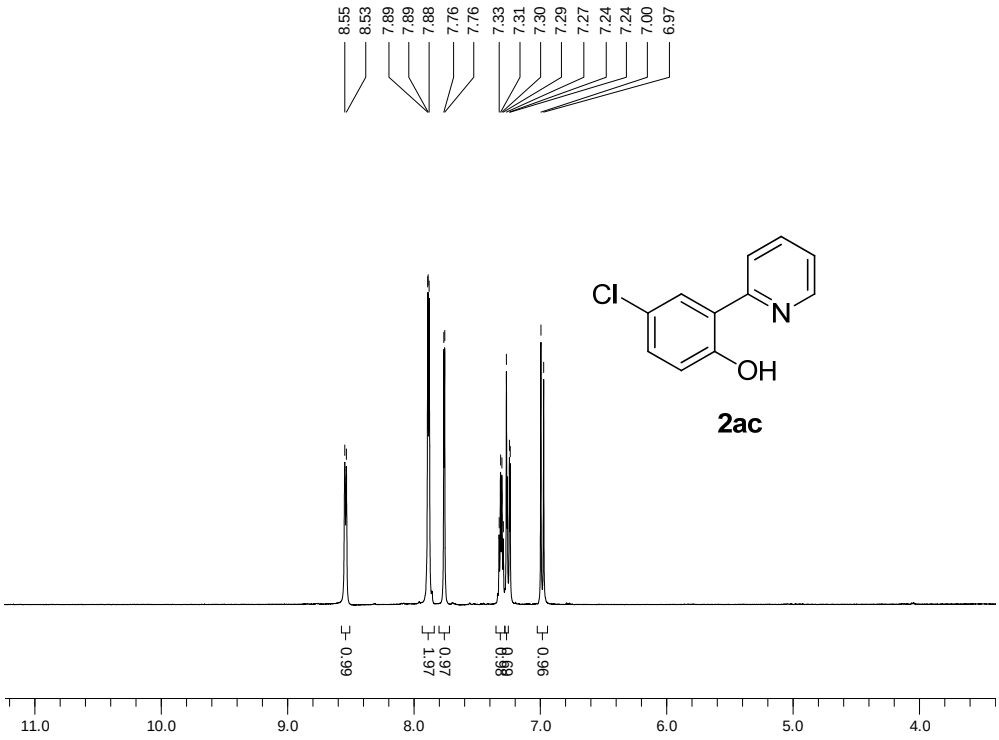
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7.30
7.29
7.27
7.24
7.24
7.00
6.97
Cl
N
OH
2ac
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0.96
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10.0
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8.0
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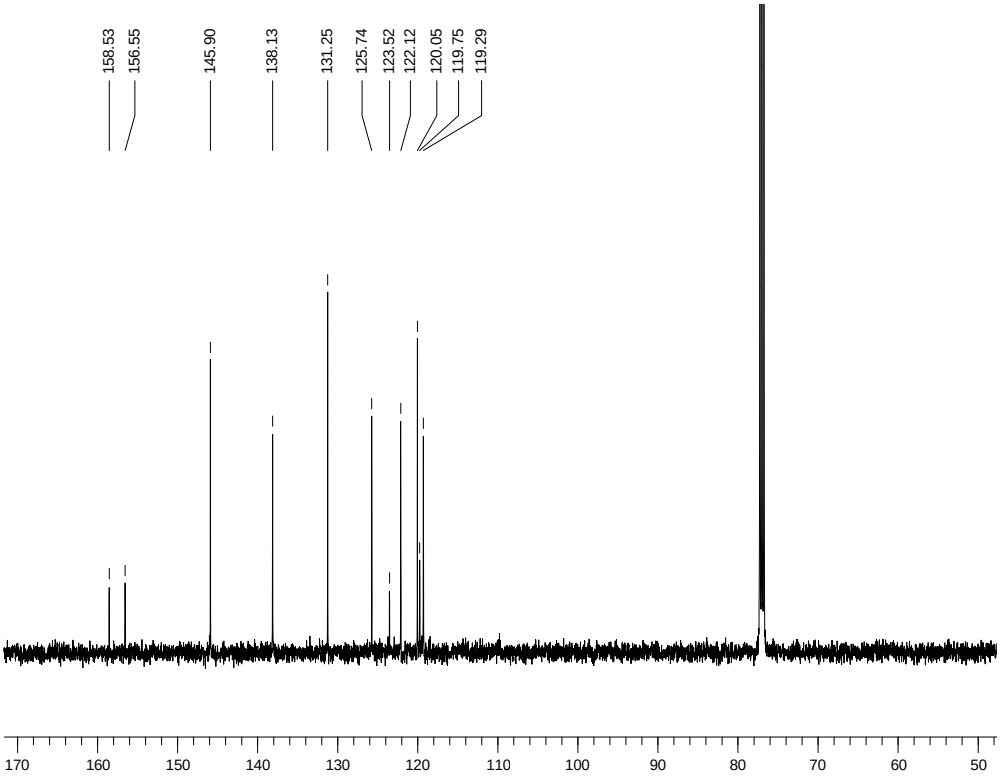
4.0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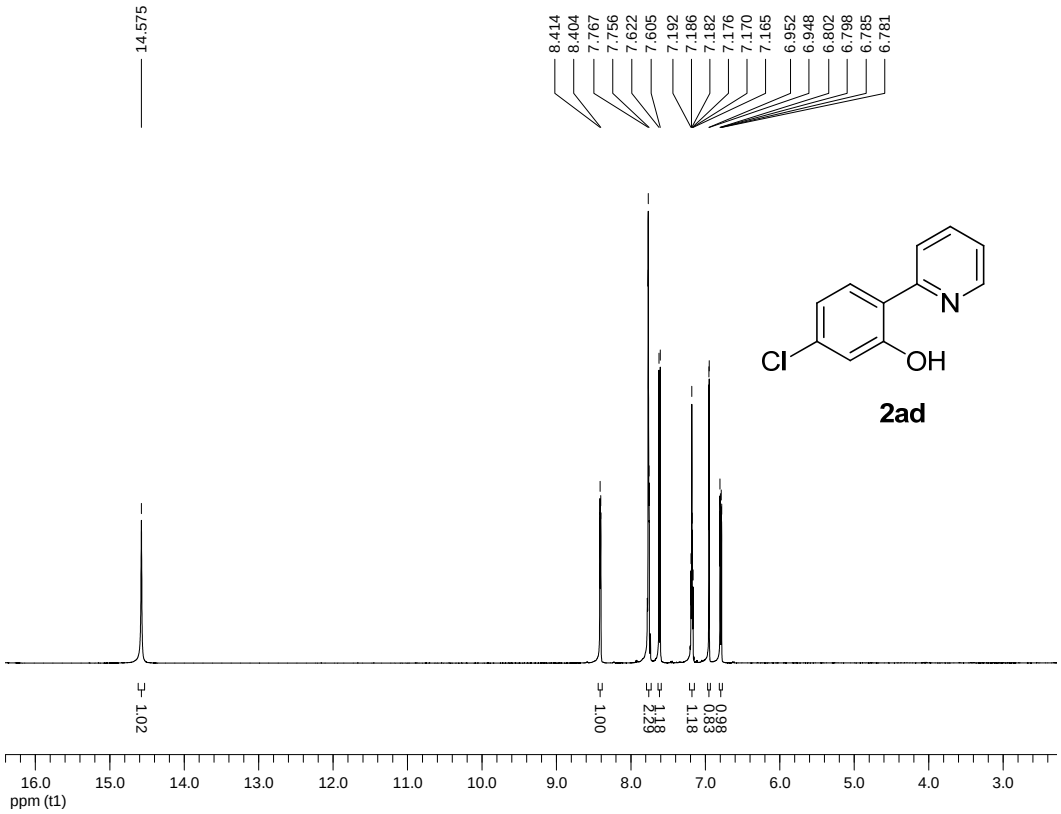
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7.170
7.165
6.952
6.948
6.802
6.798
6.785
6.781
Cl
OH
N
2ad
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1.00
2.28
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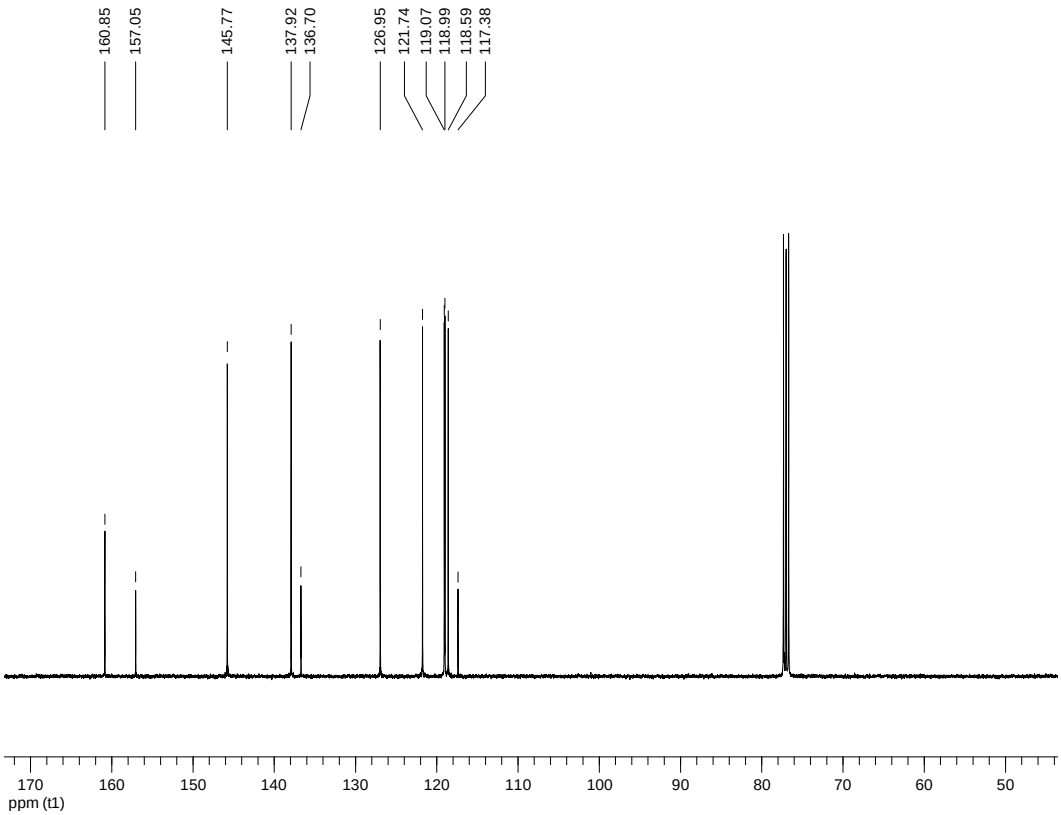
7.0
6.0
5.0
4.0
3.0
ppm (t1)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160
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140
130
120
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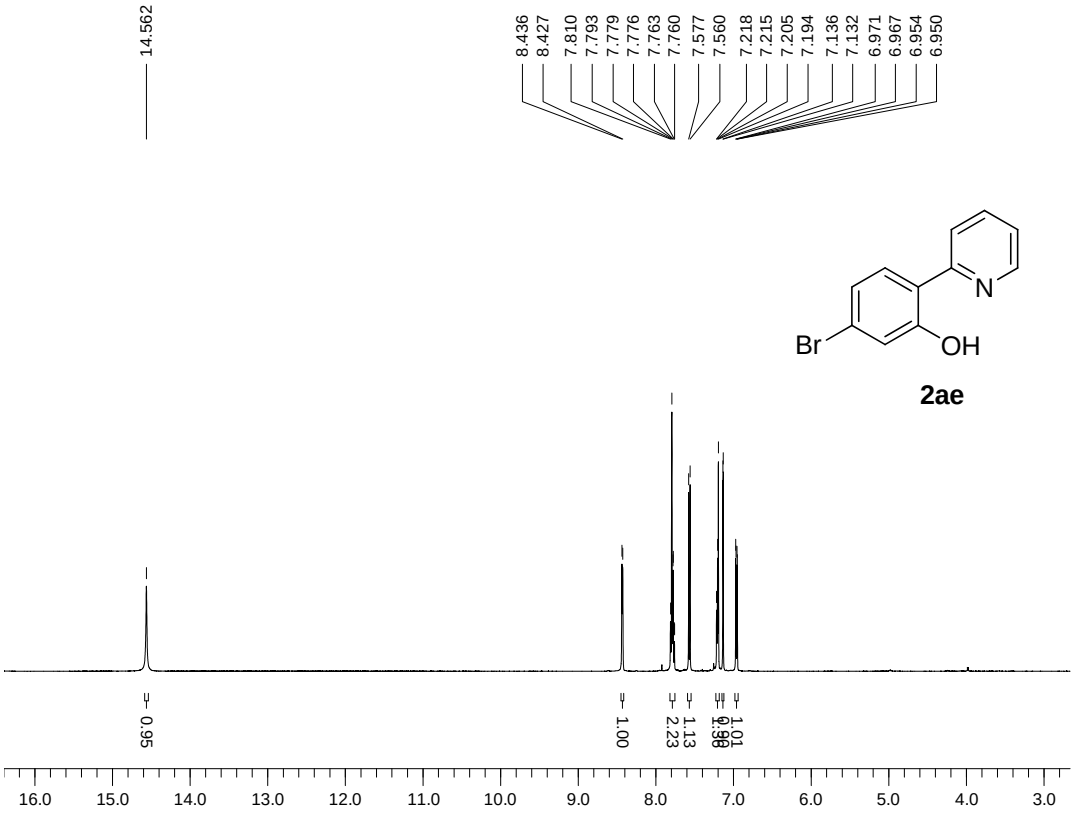
100
90
80
70
60
50
ppm (t1)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7.560
7.218
7.215
7.205
7.194
7.136
7.132
6.971
6.967
6.954
6.950
N
Br
OH
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2.23
1.13
1.01
16.0
15.0
14.0
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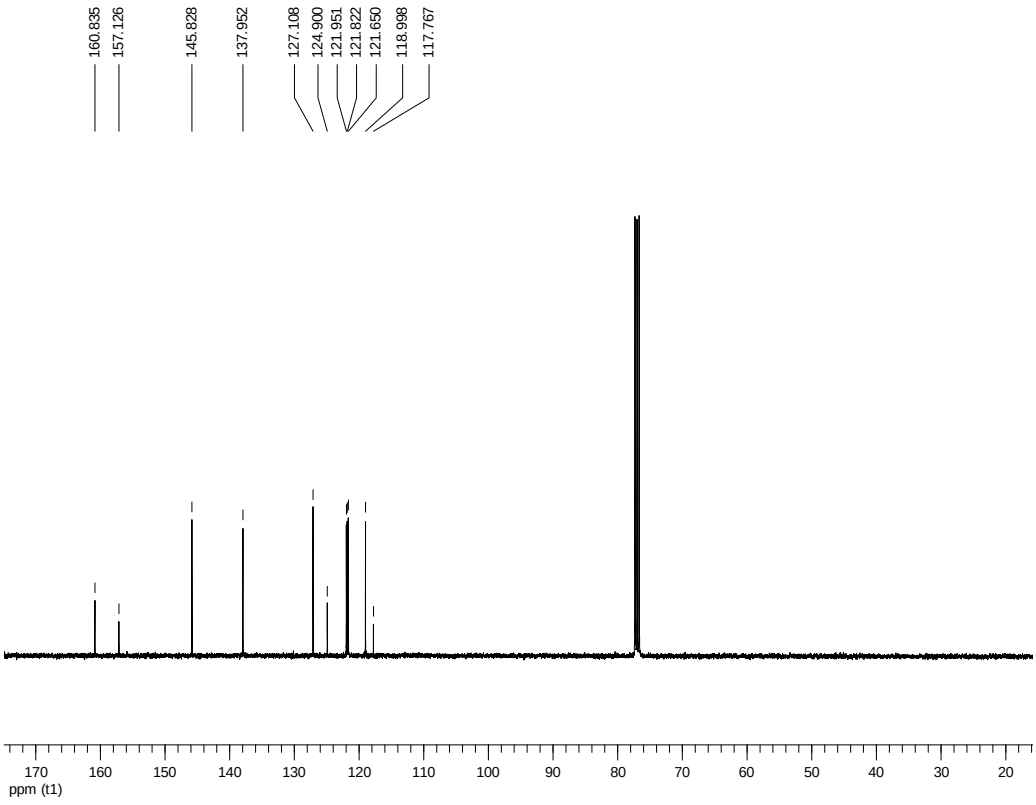
2ae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121.951
121.822
121.650
118.998
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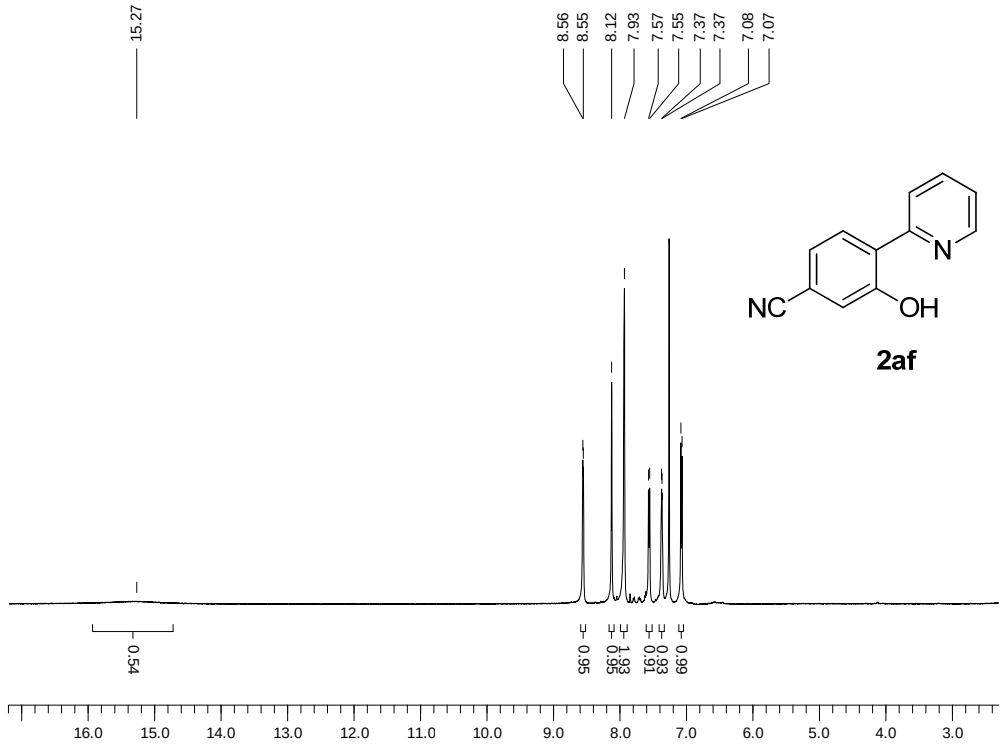
ppm (t1)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NC
OH
2af
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0.95
1.93
0.95
0.91
0.93
0.99
16.0
15.0
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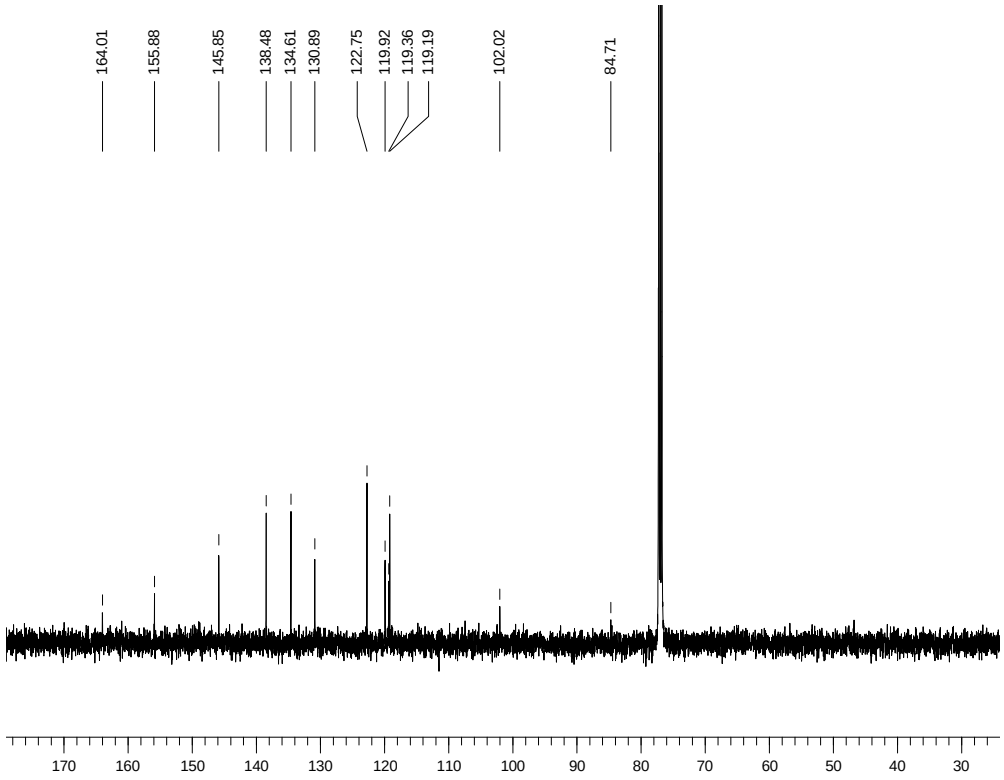
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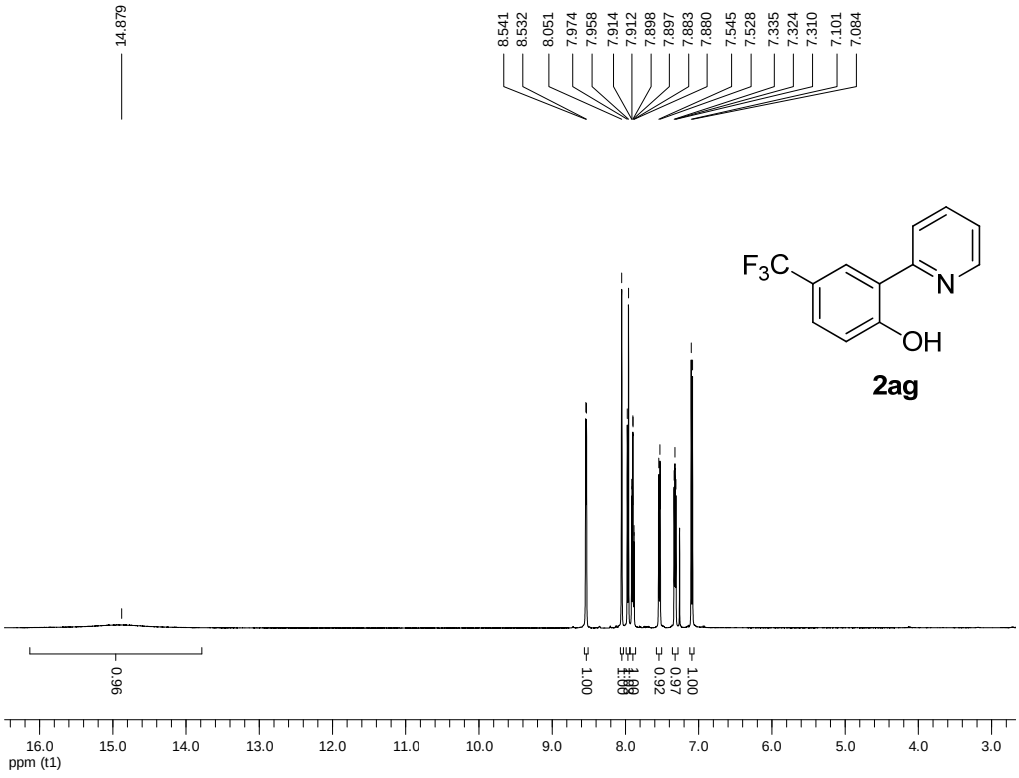
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8.051
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7.914
7.912
7.898
7.897
7.883
7.880
7.545
7.528
7.335
7.324
7.310
7.101
7.084
F3C
N
OH
2ag
0.96
1.00
0.92
0.97
1.00
16.0
15.0
14.0
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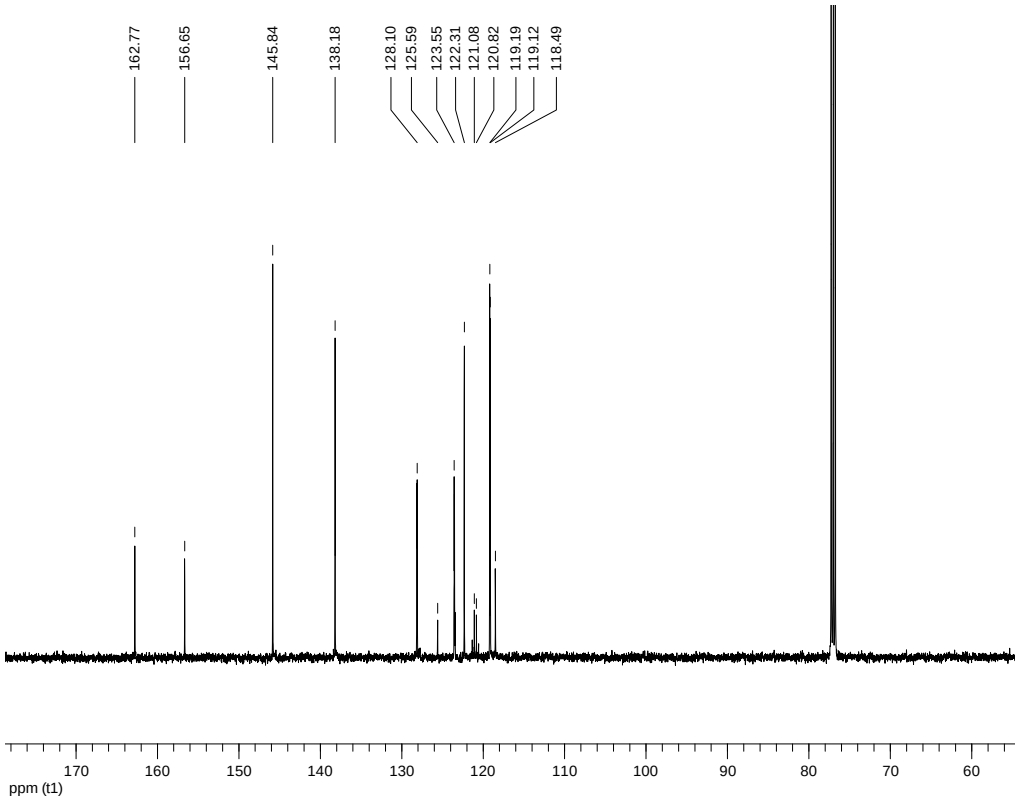
ppm (t1)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125.59
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122.31
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170
160
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140
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120
110
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80
70
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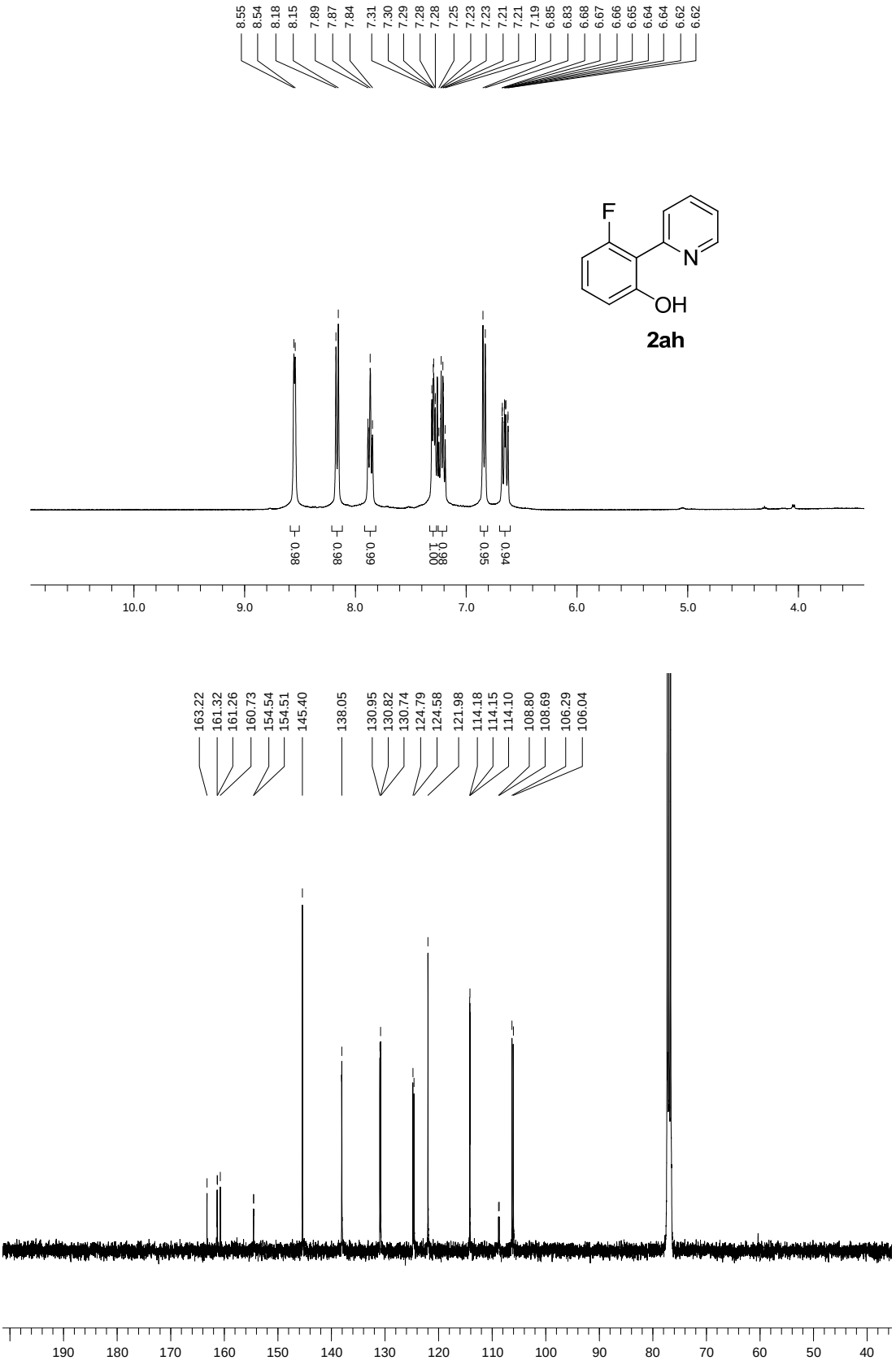
ppm (t1)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7.31
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7.28
7.28
7.25
7.23
7.23
7.21
7.21
7.19
6.85
6.83
6.68
6.67
6.66
6.65
6.64
6.64
6.62
6.62
F
N
OH
2ah
0.98
0.98
0.99
1.00
0.95
0.94
10.0
9.0
8.0
7.0
6.0
5.0
4.0
163.22
161.32
161.26
160.73
154.54
154.51
145.40
138.05
130.95
130.82
130.74
124.79
124.58
121.98
114.18
114.15
114.10
108.80
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180
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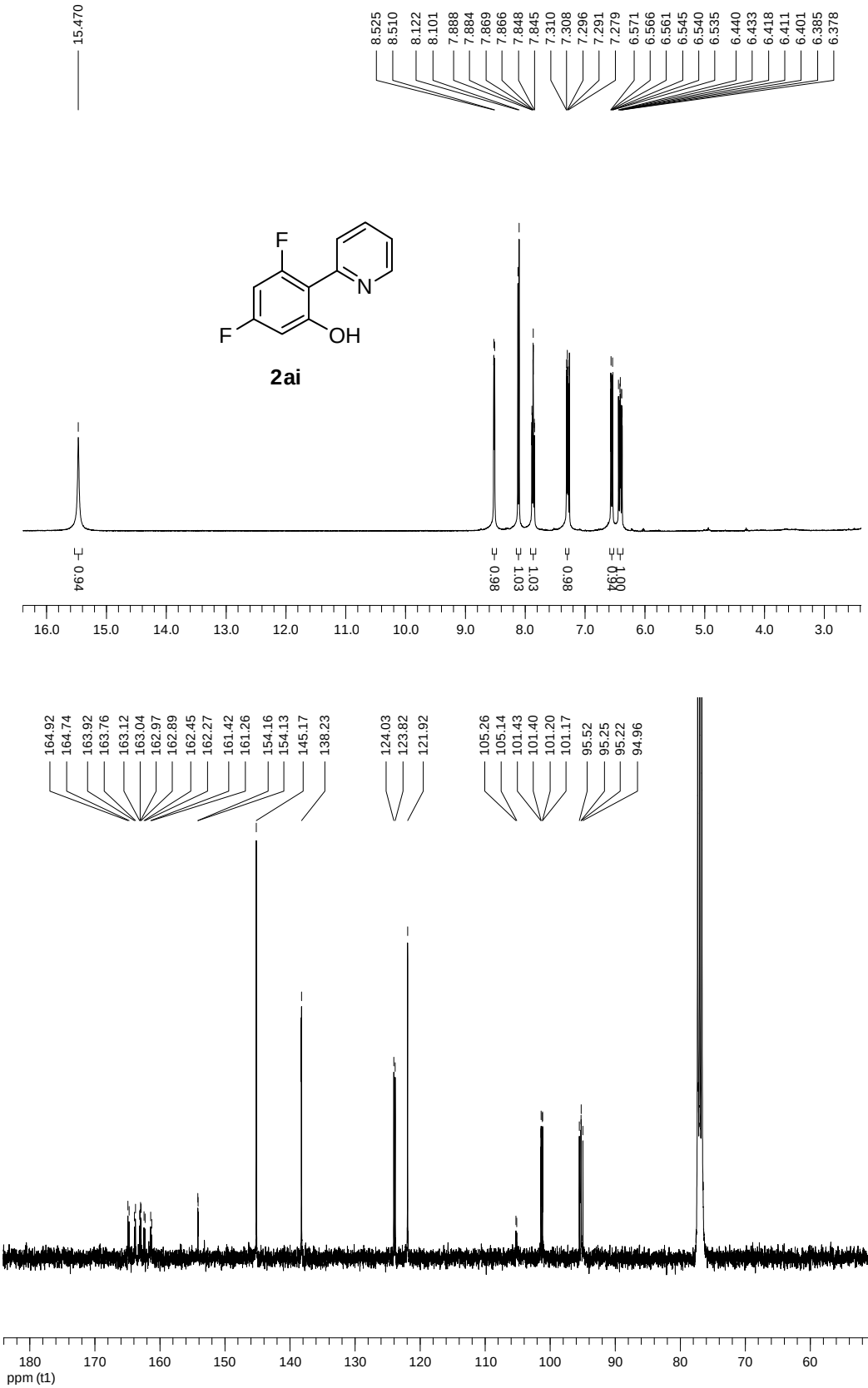
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7.308
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7.291
7.279
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6.545
6.540
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6.418
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F
N
F
OH
2ai
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0.98
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1.03
0.98
1.00
0.94
16.0
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
164.92
164.74
163.92
163.76
163.12
163.04
162.97
162.89
162.45
162.27
161.42
161.26
154.16
154.13
145.17
138.23
124.03
123.82
121.92
105.26
105.14
101.43
101.40
101.20
101.17
95.52
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150
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110
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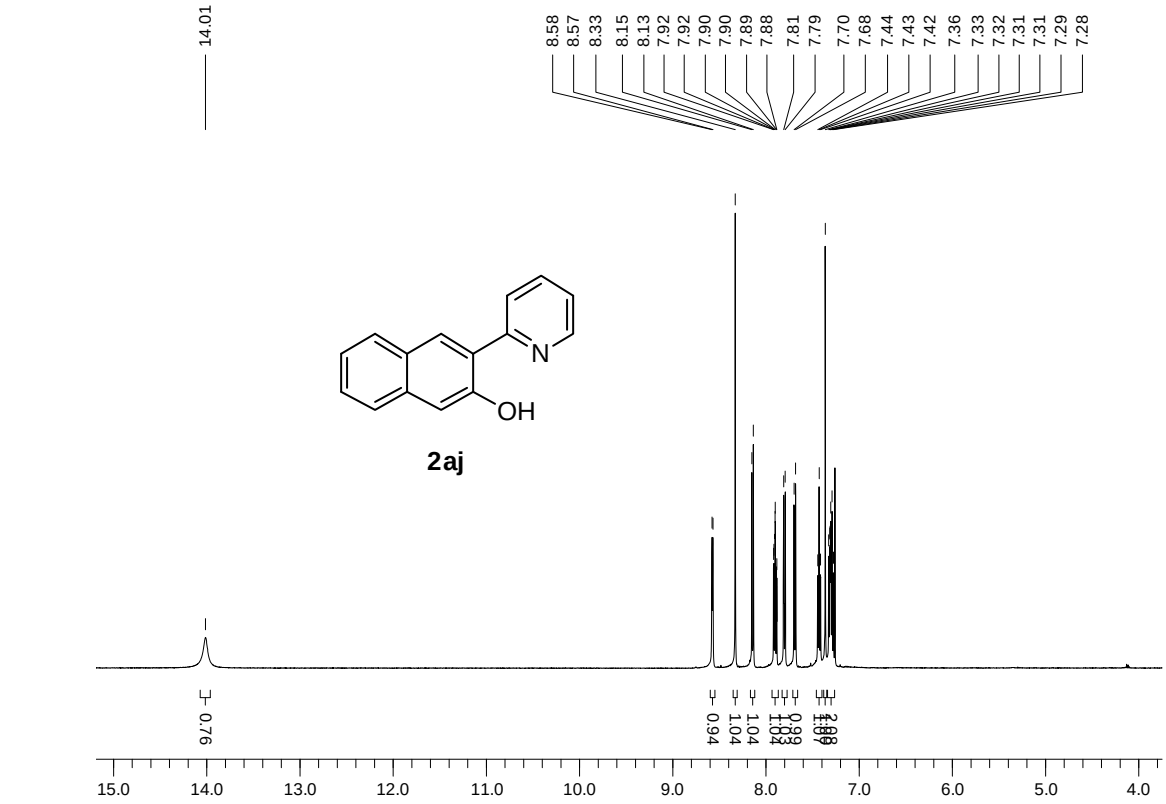
70
60
ppm (t1)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8.13
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7.92
7.90
7.90
7.89
7.88
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7.79
7.70
7.68
7.44
7.43
7.42
7.36
7.33
7.32
7.31
7.31
7.29
7.28
N
OH
0.76
0.94
1.04
1.04
0.99
2.08
4.00
15.0
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12.0
11.0
10.0
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7.0
6.0
5.0
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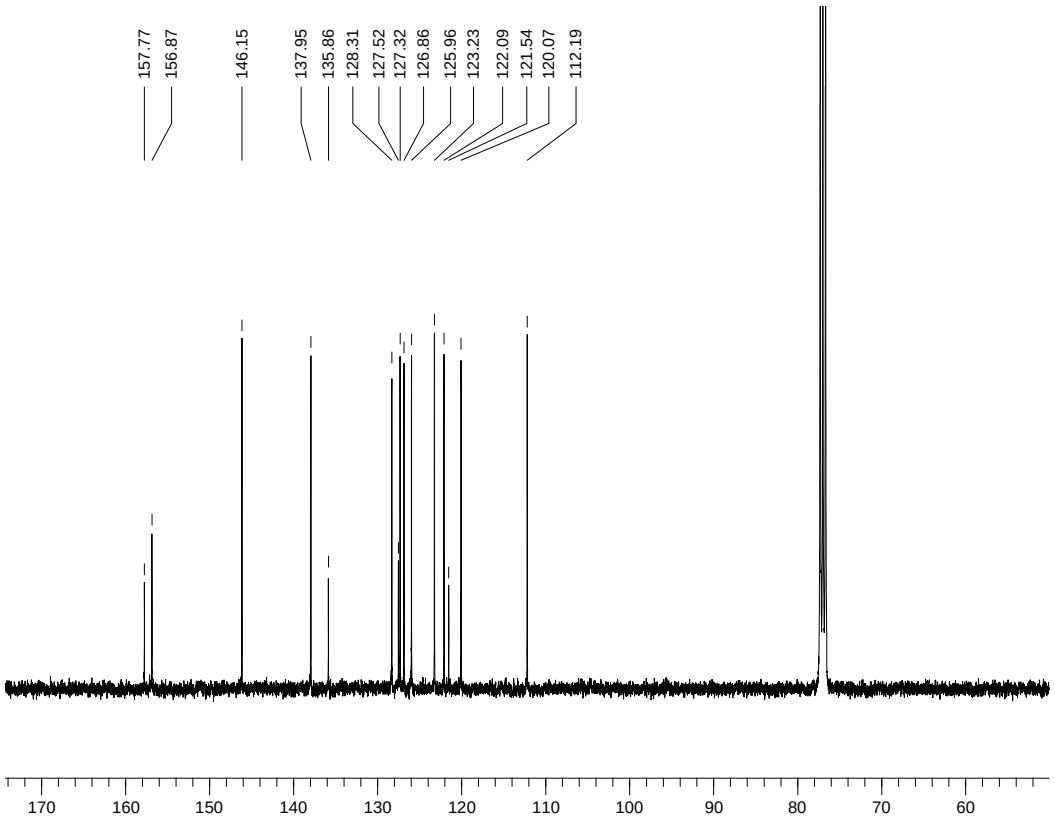
2aj


157.77
156.87
146.15
137.95
135.86
128.31
127.52
127.32
126.86
125.96
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120.07
112.19
170
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120
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100
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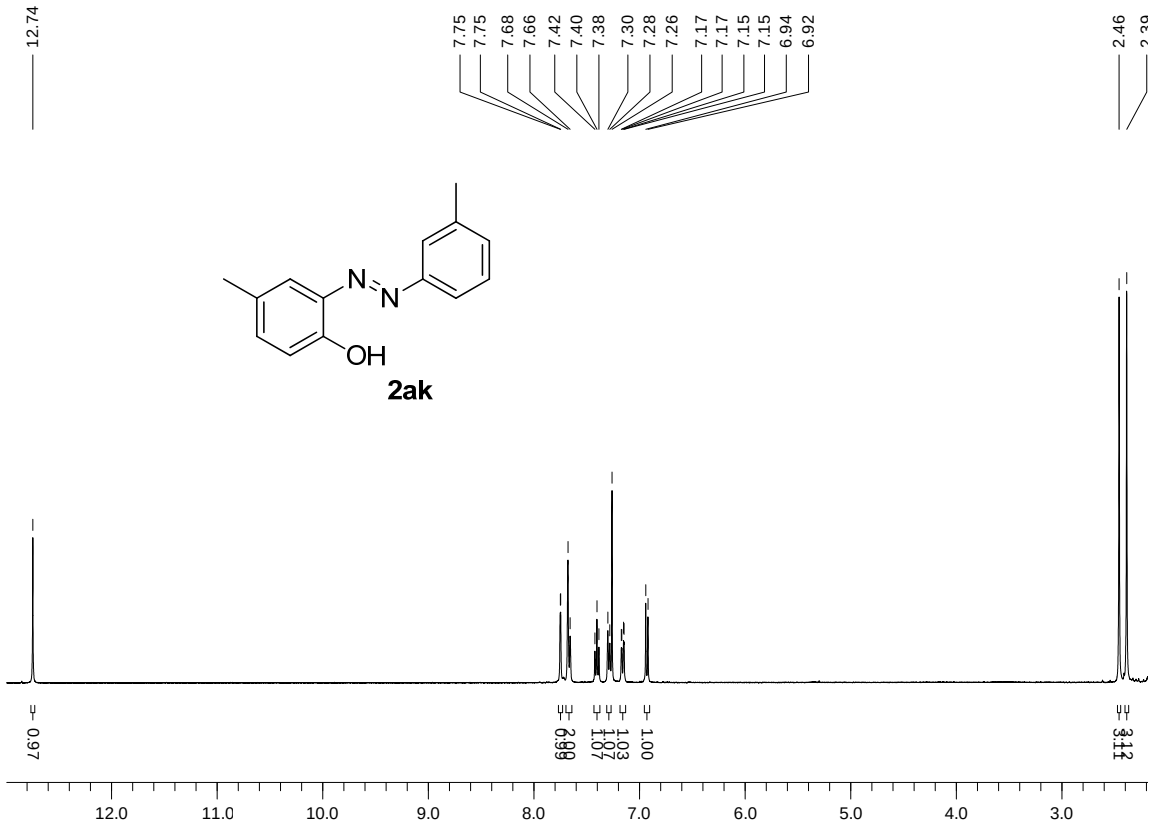
60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7.66
7.42
7.40
7.38
7.30
7.28
7.26
7.17
7.17
7.15
7.15
6.94
6.92
2.46
N
N
OH
2ak
0.97
2.99
1.07
1.03
1.00
3.12
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0