Supporting Information

Practical and Regioselective Synthesis of C4-Alkylated Pyridines

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1. General Information

Reagents were purchased at Combi-Blocks, Sigma-Aldrich, Acros Organic, Strem and Alfa Aesar and used without further purification unless otherwise stated. Isolated yields refer to chromatographically and NMR yields refer to spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated. Acetonitrile (MeCN), and diethyl ether were obtained by passing the previously degassed solvents through an activated alumina column. Other solvents for reaction such as dichloroethane (DCE), water and ethanol were used HPLC grade. For determination of ^{1}H NMR yields, dimethyl sulfone or 1,3,5-trimethoxybenzene were used as internal standards (automatic baseline correction was applied). All electrochemical reactions were run using a commercial potentiostat, an IKA ElectraSyn 2.0 unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Merck Milipore Sigma silica plates (60 F_{254}), using short-wave, long-wave UV light (254 nm, 365 nm) for visualization, and *p*-anisaldehyde or potassium permanganate as developing agents. Flash column chromatography was performed using Merck Milipore Sigma silica gel (60, particle size 0.043–0.063 mm). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX400 instruments, and chemical shifts for ^{1}H and ^{13}C NMR are reported relative to the solvent peaks (7.26 ppm for ^{1}H NMR in $CDCl_3$, 77.16 ppm for ^{13}C NMR in $CDCl_3$). ^{19}F{^{1}H} NMR data were calibrated using trichlorofluoromethane as an external reference (0.0 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. High–resolution mass spectra (HRMS) were recorded on a Waters LC-TOF (I-Class and G2-XS) mass spectrometer using ESI or APCI ion sources, a Thermo Fisher Scientific LTQ Orbitrap XL mass spectrometer using ESI ion source and an Agilent Technologies 6230 TOF LC/MS with a Dual AJS ESI ion source.

2. Initial Screening to C-2 Blocking Groups

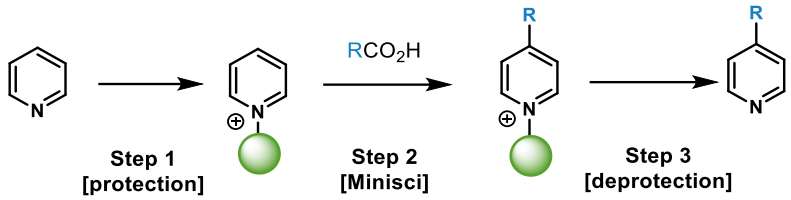


Figure S1. General scheme for screening pyridine C-2 blocking groups

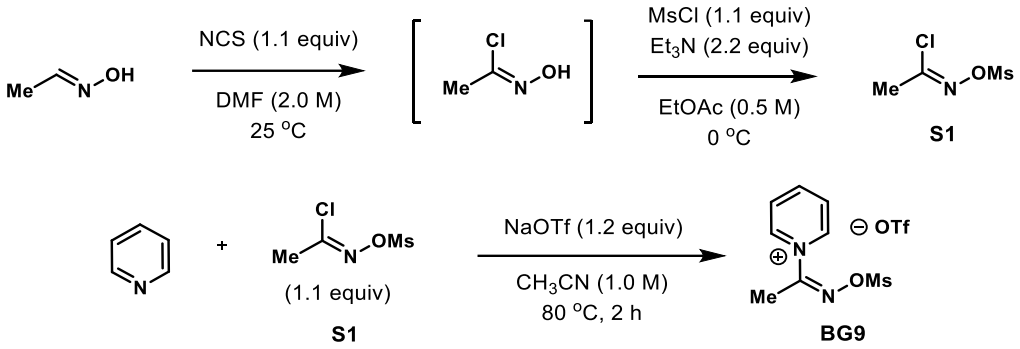


Figure S2. Synthesis of known pyridinium salt, **BD9**[1]

Acetaldehyde oxime (2.5 g, 42.3 mmol, 1.00 equiv.) was dissolved in DMF (20 mL) at room temperature. *N*-chlorosuccinimide (5.93 g, 44.4 mmol, 1.05 equiv.) was added as a solid in 5 portions over approximately 1 h. After complete addition, the reaction mixture was stirred for 20 minutes, and then poured into 50 mL of EtOAc. The mixture was washed 2 x 15 mL brine, 2 x 25 mL water, 1 x 15 mL brine. The organic solution was dried over $MgSO_4$ and concentrated on a rotavap to approximately 50 mL (Note: high concentration was avoided due to the potential loss of the product). The mixture was transferred to a 500 mL round bottom flask with large magnetic stirring bar. The mixture was diluted with EtOAc (total volume 100 mL) and cooled in an ice bath to 0 ºC. After that triethylamine (13 mL, 93.0 mmol, 2.2 equiv.) was added dropwise over 5 minutes. During this time, a thick slurry was formed, which cannot be stirred efficiently with a stir bar. Methanesulfonyl chloride (3.6 mL, 47.0 mmol, 1.1 equiv.) was then added dropwise over 10 minutes, and the resulting white solid (Et_3N-HCl) was filtered and rinsed with EtOAc. The filtrate is transferred to a separatory funnel and washed first with 2 x 40 mL water, then with 15 mL brine. The organic solution was dried over $MgSO_4$ and dried under refused pressure. The residue is mixed with heptane (300 mL) to afford a solid suspension. The solid is collected and washed twice with heptane and dried to afford a white crystalline solid **S1** (3.829 g, 53% overall yield).

^{1}H NMR (500 MHz, CD_3CN) δ 3.24 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (126 MHz, CD_3CN) δ 148.80, 36.34, 22.92.

To a 5 mL culture tube equipped with a screw cap and magnetic stir bar, pyridine (161 µL, 2.0 mmol, 1.0 equiv.), *N*-((methylsulfonyl)oxy)acetimidoyl chloride (**S1**, 377.5 mg, 2.2 mmol, 1.1 equiv.), sodium trifluoromethanesulfonate (NaOTf, 413 mg, 2.4 mmol, 1.2 equiv.) in acetonitrile (2 mL, 1.0 M) were added. The vial was sealed and heated at 80 ˚C with rapid stirring for 2 h (>80% conversion). The reaction mixture was cooled to room temperature and then diluted with ethyl acetate, and a pale yellow

[1] Pier, P. S. *J. Am. Chem. Soc.* **2017**, *139*, 9499−9502.

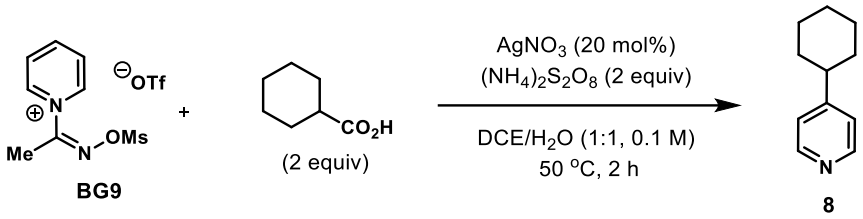
precipitate was formed. This solid was filtered, washed twice with ethyl acetate, dried under reduced pressure, obtaining the desired product **BG9** as a pale yellowish solid (426 mg, 55% yield). This solid was used further step without further purification.

^{1}H NMR (500 MHz, CD_3CN) δ 8.90 – 8.86 (m, 2H), 8.80 (tt, *J* = 7.9, 1.4 Hz, 1H), 8.30 (dd, *J* = 8.0, 6.7 Hz, 2H), 3.34 (s, 3H), 2.71 (s, 3H).

^{13}C NMR (126 MHz, CD_3CN) δ 151.70, 149.95, 142.89, 128.88, 36.82, 19.42

HRMS $[M]^+ = C_8H_{11}N_2O_3S^+$: calculated for 215.0490, found 215.0490

2.1 Reaction with Pyridinium Salt BG9



To a 15 mL culture tube equipped with Teflon septum screw cap and containing a stir bar, the pyridinium salt **BG9** (0.5 mmol, 182 mg, 1 equiv), cyclohexane carboxylic acid (128 mg, 1.0 mmol, 2 equiv), $(NH_4)_2S_2O_8$ (228 mg, 1.0 mmol, 2 equiv) and $AgNO_3$ (17 mg, 0.1 mmol, 20 mol%) and dichloroethane (2.5 mL) and H_2O (2.5 mL) were added and stirred at 50 °C for 2 h. The reaction was monitored by crude NMR or LCMS. Upon completion, the crude was diluted with dichloromethane (1 mL) and saturated aqueous $NaHCO_3$ (3 mL). The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was analyzed by NMR dissolved in $CDCl_3$. Dimethyl sulfone (0.5 mmol) was used as an internal standard. The desired product **8** was observed in 39% NMR yield. The C-2 alkylated product was not observed in crude NMR spectrum.

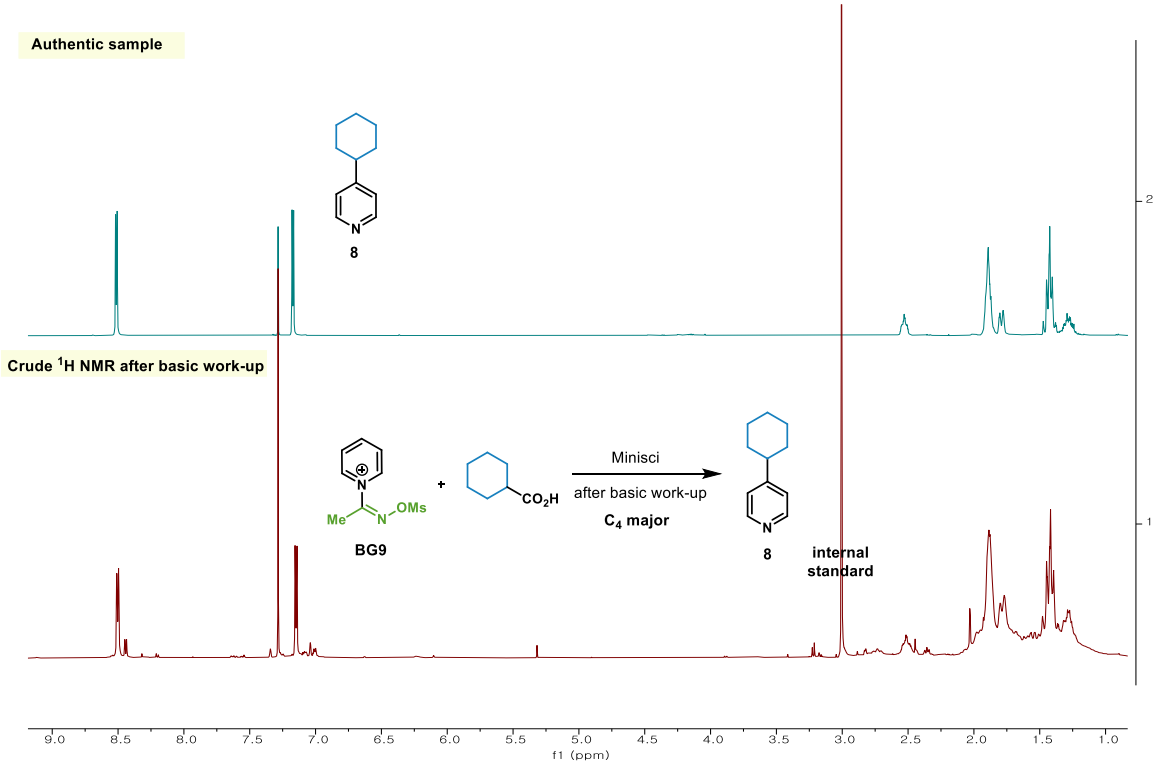
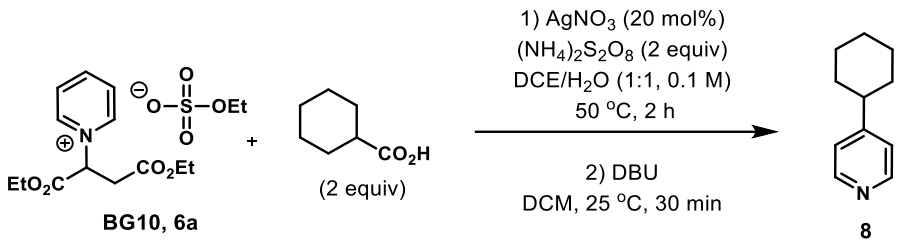


Figure S3. Crude NMR after Minisci reaction using the **BG9**

2.2 Reaction Discovery Using Fumarate-derived Pyridinium 6a



To a 15 mL culture tube equipped with Teflon septum screw cap and containing a stir bar, pyridinium salt **BG10**, **6a** (0.5 mmol, 188 mg, 1 equiv), cyclohexane carboxylic acid (128 mg, 1.0 mmol, 2 equiv), $(NH_4)_2S_2O_8$ (228 mg, 1.0 mmol, 2 equiv), $AgNO_3$ (17 mg, 0.1 mmol, 20 mol%), dichloroethane (2.5 mL) and H_2O (2.5 mL) were added and stirred at 50 °C for 2 h. The reaction was monitored by crude NMR or LCMS. Upon completion, the reaction was diluted with dichloromethane (1 mL). The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was dissolved again in dichloromethane (5 mL), treated with DBU (3 equiv, 225 uL) at 25 °C for 30 min. The reaction mixture was analyzed by NMR dissolved in $CDCl_3$. Dimethyl sulfone (0.5 mmol) was used as an internal standard. The desired product **8** was observed in 83% NMR yield. The C-2 alkylated product was not observed in crude NMR spectrum.

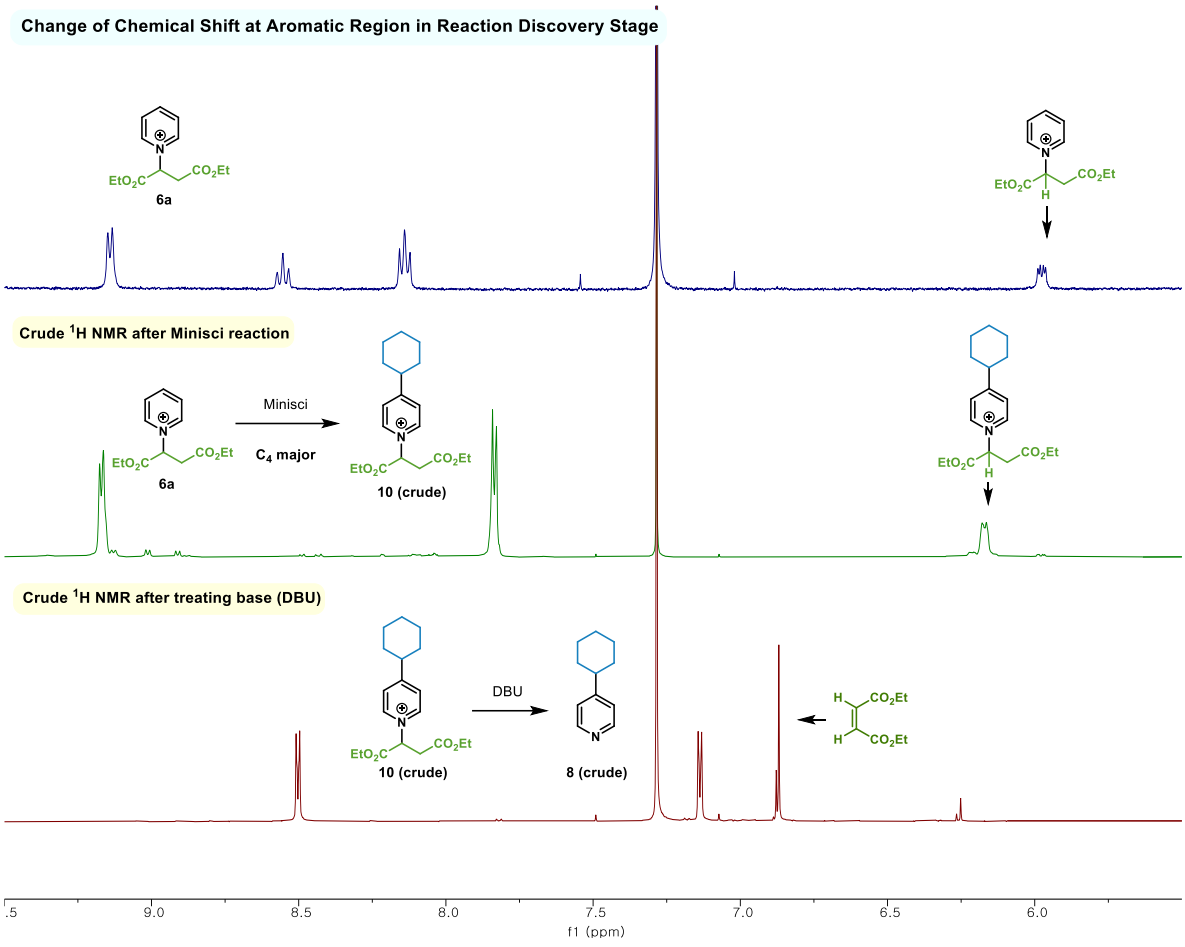
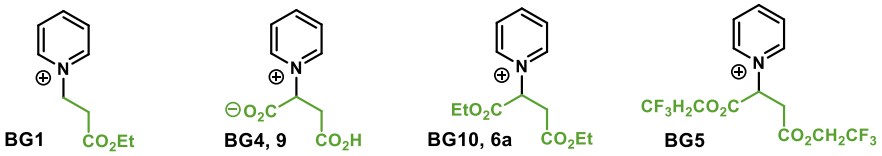


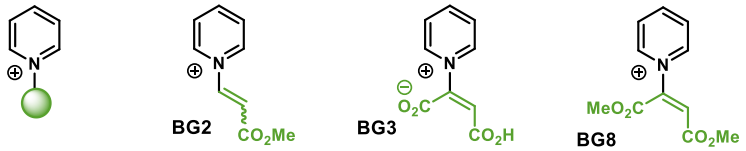
Figure S4. Reaction discovery: change chemical shift after Minisci reaction using the **BG10 (6a)**

2.3 Summary of Experimental Results Using Blocking Groups

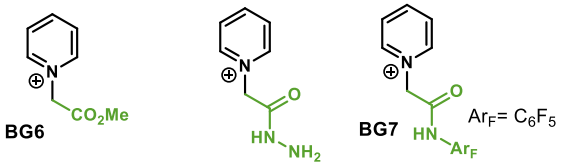
Adopting known procedures, different **BG**s were synthesized. In some cases, pure products could not be obtained (**BG2, BG5, BG8**) due to their instabilty at room temperature. When Minisci reaction was carried out, low conversion (**BG1, BG2, BG4, BG6**) and/or decomposition (**BG5, BG 3, BG7**) were observed.



Step 1 (protection)	• react with alkyl halide • scalable	• react with maleic acid • scalable	• esterification from **9**	• failed to isolating pure compound
Step 2 (Minisci)	• low conversion (<10%) • high regioselectivity (>10:1)	• moderate conversion (50%) • high regioselectivity (>10:1)	• full conversion • high regioselectivity (exclusive C4)	decomposed
Step 3 (deprotection)	not tested	not tested	clean, very fast (DBU, 25 °C, 15 min)	not tested



Step 1 (protection)	• react with alkyne • *E*:*Z* = 0.6:1 mixture	• react with alkynyl diacid • scalable	• react with alkyne • unstable at r.t.
Step 2 (Minisci)	• low conversion (<30%) • high regioselectivity (>5:1)	• no conversion • decomposition	not tested



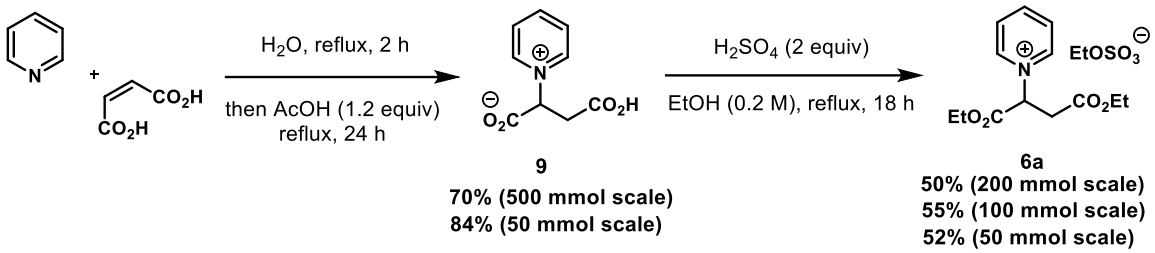
Step 1 (protection)	• react with alkyl halide	• commercially available	• react with alkyl halide
Step 2 (Minisci)	• low conversion (<10%) • high regioselectivity (exclusive C4)	• no conversion • decomposition	• no conversion • decomposition

Figure S5. Synthetic trial and Minisci reaction screening to blocking groups

Regarding other possible blocking groups, acyl pyridinium species were not considered based on their relative instability, as they are used as acyl transfer reagents.[2] On the other hand, chloroformates have been studied in the past as transient blocking groups for selective nucleophilic addition to pyridines. However, they were not considered as potential candidates because of their lack in selectivity and their inefficient back-oxidation to generate the desired pyridine.[3]

[2] Zipse, H., Held, I., & Xu, S. *Synthesis*, **2007**, 8, 1185–1196.
[3] Akiba, K.; Nishihara, Y.; Wada, M.; *Tetrahedron Lett.* **1983**, *24*, 5269–5272.

3. Practical Synthesis of Pyridinium Salt 6a



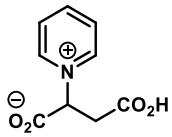
9
70% (500 mmol scale)
84% (50 mmol scale)

6a
50% (200 mmol scale)
55% (100 mmol scale)
52% (50 mmol scale)

The procedure was developed and modified based on known literature. [4]

3.1 Step 1: Synthesis of Pyridinium 9

A solution of maleic acid (58.05 g, 500 mmol) and pyridine (1 equiv., 40.26 mL, 500 mmol) in H_2O (250mL) was stirred at 90 ˚C for 2 h. After a crystalline solid appeared in reaction mixture, acetic acid (34.3 mL, 1.2 equiv., 600 mmol) was added. The suspension was kept under stirring at the same temperature for 24 h. The crude reaction mixture was cooled down to room temperature, filtered and washed with MeOH and EtOAc. The resulting white solid was dried under reduced pressure by rotary evaporator and high vacuum for overnight. The product **9** (68.3 g, 70% yield) was obtained as a white solid. The resulting product was used for next step without further purification.



3-carboxy-2-(pyridin-1-ium-1-yl)propanoate (9)

^{1}H NMR (500 MHz, D_2O) δ 8.87 – 8.84 (m, 2H), 8.53 – 8.49 (m, 1H), 8.02 (t, *J* = 6.8 Hz, 2H), 5.59 (ddd, *J* = 9.7, 3.8, 2.1 Hz, 1H), 3.60 – 3.42 (m, 1H), 3.43 – 3.24 (m, 1H).

HRMS [M] = $C_9H_9NO_4$: calculated for 196.0610, found 196.0612

3.2 Step 2: Esterification; Synthesis of Pyridinium Salt 6a

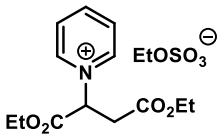
A solution of pyridinium carboxylate **9** (50 mmol, 9.758 g) in EtOH (250 mL, 0.2 M) with concentrated sulfuric acid (2 equiv., 100 mmol, 5.25 mL) was stirred at 90 ˚C for 18 h. The reaction was monitored by TLC and LCMS (30% conversion, 15 min, 70% conversion, 1 h, 95% conversion after 18 h). After the reaction was done, the solvent (EtOH) was evaporated by reduced pressure at least 15 min. The concentrated crude mixture was diluted in dichloromethane (200 mL) and H_2O (50 mL) and extracted by dichloromethane with monitoring TLC both aqueous and organic phase. (Approximately 50 mL x 10 times, total organic phase volume = 750 mL). [*Note: when less amount of water was employed (below 10 mL), the yield was higher above 90%. However, the crude material was obtained as sticky*

[4] Uemura, K.; Sano, K.; Matsumoto, A.; Yoshida, Y.; Mino, T.; Sakamoto, M. *Chem. Asian J.* **2019**, *14*, 4150−4153.

oil containing the mono-esterified product (below 5%) and residual CH_2Cl_2.] The combined organic phase was dried by Na_2SO_4, filtered and concentrated under reduced pressure. To the resulting colorless liquid anhydrous diethyl ether (30 mL) was added and subsequently dried by reduced pressure. After the residual solvent was totally evaporated by reduced pressure, the product was obtained as a white solid (9.76 g, 52% yield). The resulting product was used for next step without further purification.

For 100 mmol scale reaction, a solution of pyridinium carboxylate inner salt **9** (100 mmol, 19.517 g) in EtOH (500 mL, 0.2 M) with concentrated sulfuric acid (2 equiv., 200 mmol, 10.5 mL) was stirred at 90 ˚C for 18 h. After the work-up, the product was obtained as a white solid (20.87 g, 55 % yield).

For 200 mmol scale reaction, a solution of pyridinium carboxylate inner salt **9** (200 mmol, 39.03 g) in EtOH (1000 mL, 0.2 M) with concentrated sulfuric acid (2 equiv., 400 mmol, 21.0 mL) was stirred at 90 ˚C for 18 h. After the work-up, the product was obtained as a white solid (37.65 g, 50 % yield).



Pyridinium Salt (6a)

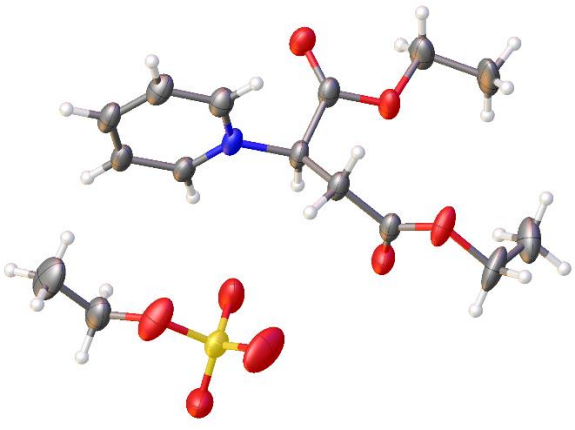
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (d, *J* = 5.6 Hz, 2H), 8.58 – 8.53 (m, 1H), 8.09 (dd, *J* = 7.9, 6.7 Hz, 2H), 6.30 – 6.24 (m, 1H), 4.43 – 4.24 (m, 2H), 4.22 – 4.09 (m, 5H), 3.78 (dd, *J* = 18.9, 8.0 Hz, 1H), 3.52 (dd, *J* = 18.9, 3.2 Hz, 1H), 1.28 (td, J = 7.1, 5.5 Hz, 6H), 1.23 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 166.3, 146.5, 128.1, 68.6, 63.8, 63.7, 62.1, 37.2, 15.2, 14.0, 13.9.

LRMS $[M]^+ = C_{13}H_{18}NO_4^+$: calculated for 252.12, found 252.16.

HRMS $[M]^+ = C_{13}H_{18}NO_4^+$: calculated for 252.1236, found 252.1236

3.3. X-ray Structure of Pyridinium 6a



Experimental Summary

The single crystal X-ray diffraction studies were carried out on a Bruker APEX II diffractometer equipped with Cu K_α radiation (λ=1.54178 Å).

Crystals of the subject compound were used as received (grow from DCM).

A 0.200 x 0.200 x 0.180 mm colorless crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ϖ scans. Crystal-to-detector distance was 40 mm and exposure time was 1.0, 2.0, 3.0 and 4.0 seconds (depending on the 2θ range) per frame using a scan width of 1.50°. Data collection was 97.8% complete to 67.500° in θ. A total of 26320 reflections were collected covering the indices, -10<=h<=10, -10<=k<=10, -15<=l<=15. 3309 reflections were found to be symmetry independent, with a R_{int} of 0.0413. Indexing and unit cell refinement indicated a **Primitive**, **Triclinic** lattice. The space group was found to be ***P-1***. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Good data and refinement, minor disorder on CH2-CH3 atoms
P-1 "Racemic" space group

SI-Table 1. Crystal data and structure refinement for Baran785 (**6a**).

Report date	2021-04-30	
Identification code	baran785 (**6a**)	
Empirical formula	C15 H23 N O8 S	
Molecular formula	C13 H18 N O4, C2 H5 O4 S	
Formula weight	377.40	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.7948(2) Å	α= 88.7630(10)°.
	b = 8.8282(2) Å	β= 75.8870(10)°.
	c = 12.7065(3) Å	γ = 75.0200(10)°.
Volume	923.36(4) $Å^3$	
Z	2	
Density (calculated)	1.357 Mg/m^3	
Absorption coefficient	1.936 mm^{-1}	
F(000)	400	
Crystal size	0.2 x 0.2 x 0.18 mm^3	
Crystal color, habit	colorless block	
Theta range for data collection	3.590 to 68.241°.	
Index ranges	-10<=h<=10, -10<=k<=10, -15<=l<=15	
Reflections collected	26320	
Independent reflections	3309 [R(int) = 0.0413]	
Completeness to theta = 67.500°	97.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7533 and 0.5841	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3309 / 1 / 249
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0483, wR2 = 0.1230
R indices (all data)	R1 = 0.0586, wR2 = 0.1321
Largest diff. peak and hole	0.786 and -0.319 e.Å^{-3}

SI-Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for Baran785. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5680(3)	2083(3)	6301(2)	31(1)
N(1)	7184(2)	1889(2)	5419(2)	31(1)
O(1)	1688(2)	4679(2)	7176(2)	46(1)
C(2)	4387(3)	3588(3)	6208(2)	33(1)
O(2)	2341(2)	2171(2)	6598(2)	46(1)
C(3)	2711(3)	3377(3)	6686(2)	34(1)
O(3)	4751(2)	2226(2)	8173(1)	39(1)
C(4)	6115(3)	2009(3)	7394(2)	34(1)
O(4)	7459(2)	1803(2)	7523(1)	40(1)
C(5)	6(3)	4595(4)	7598(3)	56(1)
C(6)	-193(4)	3792(4)	8642(3)	63(1)
C(9)	7677(3)	620(3)	4739(2)	31(1)
C(10)	9080(3)	423(3)	3916(2)	35(1)
C(11)	9962(3)	1519(3)	3810(2)	38(1)
C(12)	9428(3)	2810(3)	4527(2)	39(1)
C(13)	8026(3)	2992(3)	5329(2)	36(1)
C(7)	4950(20)	1899(15)	9275(9)	47(3)
C(8)	3274(7)	2301(9)	9984(4)	72(2)
C(7A)	4920(30)	2436(15)	9288(11)	41(3)
C(8A)	4859(9)	4069(8)	9659(5)	54(2)
S(1)	4179(1)	2384(1)	3083(1)	36(1)
O(5)	5765(2)	2645(3)	2289(2)	63(1)
O(6)	4693(2)	1606(3)	3994(2)	62(1)
O(7)	3159(3)	3921(3)	3353(3)	84(1)
O(8)	3562(2)	1403(3)	2514(2)	58(1)
C(14)	6984(3)	1278(4)	1801(2)	53(1)
C(15)	8505(4)	1750(5)	1240(3)	74(1)

SI-Table 3. Bond lengths [Å] and angles [°] for Baran785 (**6a**).

C(1)-H(1)	1.0000
C(1)-N(1)	1.484(3)
C(1)-C(2)	1.533(3)
C(1)-C(4)	1.523(3)
N(1)-C(9)	1.342(3)
N(1)-C(13)	1.355(3)
O(1)-C(3)	1.320(3)
O(1)-C(5)	1.466(3)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(2)-C(3)	1.509(3)
O(2)-C(3)	1.205(3)
O(3)-C(4)	1.329(3)
O(3)-C(7)	1.467(9)
O(3)-C(7A)	1.481(11)
C(4)-O(4)	1.200(3)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(5)-C(6)	1.484(4)
C(6)-H(6A)	0.9800
C(6)-H(6B)	0.9800
C(6)-H(6C)	0.9800
C(9)-H(9)	0.9500
C(9)-C(10)	1.383(3)
C(10)-H(10)	0.9500
C(10)-C(11)	1.374(4)
C(11)-H(11)	0.9500
C(11)-C(12)	1.381(4)
C(12)-H(12)	0.9500
C(12)-C(13)	1.371(3)
C(13)-H(13)	0.9500
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(7)-C(8)	1.49(2)
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(7A)-H(7AA)	0.9900
C(7A)-H(7AB)	0.9900
C(7A)-C(8A)	1.510(15)
C(8A)-H(8AA)	0.9800
C(8A)-H(8AB)	0.9800
C(8A)-H(8AC)	0.9800
S(1)-O(5)	1.577(2)
S(1)-O(6)	1.440(2)
S(1)-O(7)	1.416(2)
S(1)-O(8)	1.424(2)
O(5)-C(14)	1.425(4)
C(14)-H(14A)	0.9900

C(14)-H(14B)	0.9900
C(14)-C(15)	1.511(4)
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
N(1)-C(1)-H(1)	107.7
N(1)-C(1)-C(2)	112.04(18)
N(1)-C(1)-C(4)	109.06(18)
C(2)-C(1)-H(1)	107.7
C(4)-C(1)-H(1)	107.7
C(4)-C(1)-C(2)	112.43(19)
C(9)-N(1)-C(1)	119.0(2)
C(9)-N(1)-C(13)	121.9(2)
C(13)-N(1)-C(1)	119.1(2)
C(3)-O(1)-C(5)	115.3(2)
C(1)-C(2)-H(2A)	109.6
C(1)-C(2)-H(2B)	109.6
H(2A)-C(2)-H(2B)	108.1
C(3)-C(2)-C(1)	110.2(2)
C(3)-C(2)-H(2A)	109.6
C(3)-C(2)-H(2B)	109.6
O(1)-C(3)-C(2)	112.2(2)
O(2)-C(3)-O(1)	124.1(2)
O(2)-C(3)-C(2)	123.7(2)
C(4)-O(3)-C(7)	115.8(8)
C(4)-O(3)-C(7A)	115.3(10)
O(3)-C(4)-C(1)	108.25(19)
O(4)-C(4)-C(1)	125.6(2)
O(4)-C(4)-O(3)	126.2(2)
O(1)-C(5)-H(5A)	109.4
O(1)-C(5)-H(5B)	109.4
O(1)-C(5)-C(6)	111.1(3)
H(5A)-C(5)-H(5B)	108.0
C(6)-C(5)-H(5A)	109.4
C(6)-C(5)-H(5B)	109.4
C(5)-C(6)-H(6A)	109.5
C(5)-C(6)-H(6B)	109.5
C(5)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
N(1)-C(9)-H(9)	120.2
N(1)-C(9)-C(10)	119.5(2)
C(10)-C(9)-H(9)	120.2
C(9)-C(10)-H(10)	120.1
C(11)-C(10)-C(9)	119.8(2)
C(11)-C(10)-H(10)	120.1
C(10)-C(11)-H(11)	120.3
C(10)-C(11)-C(12)	119.3(2)
C(12)-C(11)-H(11)	120.3
C(11)-C(12)-H(12)	120.0

C(13)-C(12)-C(11)	120.0(2)
C(13)-C(12)-H(12)	120.0
N(1)-C(13)-C(12)	119.4(2)
N(1)-C(13)-H(13)	120.3
C(12)-C(13)-H(13)	120.3
O(3)-C(7)-H(7A)	110.8
O(3)-C(7)-H(7B)	110.8
O(3)-C(7)-C(8)	104.9(10)
H(7A)-C(7)-H(7B)	108.8
C(8)-C(7)-H(7A)	110.8
C(8)-C(7)-H(7B)	110.8
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
O(3)-C(7A)-H(7AA)	108.0
O(3)-C(7A)-H(7AB)	108.0
O(3)-C(7A)-C(8A)	117.2(8)
H(7AA)-C(7A)-H(7AB)	107.2
C(8A)-C(7A)-H(7AA)	108.0
C(8A)-C(7A)-H(7AB)	108.0
C(7A)-C(8A)-H(8AA)	109.5
C(7A)-C(8A)-H(8AB)	109.5
C(7A)-C(8A)-H(8AC)	109.5
H(8AA)-C(8A)-H(8AB)	109.5
H(8AA)-C(8A)-H(8AC)	109.5
H(8AB)-C(8A)-H(8AC)	109.5
O(6)-S(1)-O(5)	105.64(12)
O(7)-S(1)-O(5)	103.98(14)
O(7)-S(1)-O(6)	113.41(17)
O(7)-S(1)-O(8)	114.61(15)
O(8)-S(1)-O(5)	107.30(13)
O(8)-S(1)-O(6)	111.04(15)
C(14)-O(5)-S(1)	117.02(19)
O(5)-C(14)-H(14A)	109.9
O(5)-C(14)-H(14B)	109.9
O(5)-C(14)-C(15)	108.9(3)
H(14A)-C(14)-H(14B)	108.3
C(15)-C(14)-H(14A)	109.9
C(15)-C(14)-H(14B)	109.9
C(14)-C(15)-H(15A)	109.5
C(14)-C(15)-H(15B)	109.5
C(14)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5

SI-Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Baran785 (**6a**). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(1)	37(1)	25(1)	4(1)	2(1)	0(1)
N(1)	21(1)	38(1)	27(1)	6(1)	-2(1)	1(1)
O(1)	26(1)	36(1)	60(1)	12(1)	9(1)	5(1)
C(2)	24(1)	38(1)	29(1)	7(1)	-1(1)	1(1)
O(2)	30(1)	59(1)	43(1)	-12(1)	3(1)	-10(1)
C(3)	25(1)	43(1)	26(1)	6(1)	-2(1)	2(1)
O(3)	30(1)	54(1)	24(1)	5(1)	-1(1)	3(1)
C(4)	27(1)	34(1)	30(1)	4(1)	-1(1)	4(1)
O(4)	29(1)	50(1)	36(1)	6(1)	-8(1)	1(1)
C(5)	25(1)	47(2)	73(2)	14(2)	14(1)	6(1)
C(6)	58(2)	60(2)	50(2)	-4(2)	22(1)	-12(2)
C(9)	22(1)	39(1)	28(1)	3(1)	-6(1)	0(1)
C(10)	23(1)	48(2)	26(1)	3(1)	-4(1)	4(1)
C(11)	23(1)	53(2)	30(1)	12(1)	-1(1)	0(1)
C(12)	28(1)	44(2)	41(1)	12(1)	-4(1)	-6(1)
C(13)	30(1)	37(1)	34(1)	7(1)	-5(1)	-2(1)
C(7)	41(4)	62(8)	25(3)	7(4)	-5(3)	5(7)
C(8)	48(3)	124(6)	19(2)	-1(3)	-2(2)	15(3)
C(7A)	41(4)	46(8)	24(4)	16(4)	-7(3)	7(7)
C(8A)	59(4)	58(4)	31(3)	-6(3)	-7(3)	5(3)
S(1)	24(1)	37(1)	40(1)	-4(1)	-6(1)	2(1)
O(5)	36(1)	59(1)	83(2)	30(1)	-2(1)	-7(1)
O(6)	38(1)	96(2)	36(1)	2(1)	-3(1)	4(1)
O(7)	45(1)	41(1)	152(3)	-17(1)	-18(2)	10(1)
O(8)	36(1)	81(2)	53(1)	-24(1)	-3(1)	-14(1)
C(14)	36(1)	79(2)	34(1)	6(1)	-1(1)	-5(1)
C(15)	46(2)	112(3)	54(2)	30(2)	6(2)	-19(2)

SI-Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Baran785 (**6a**).

	x	y	z	U(eq)
H(1)	5224	1174	6232	37
H(2A)	4545	4472	6598	39
H(2B)	4501	3842	5435	39
H(5A)	-305	4017	7060	67
H(5B)	-726	5669	7708	67
H(6A)	479	2707	8525	94
H(6B)	-1335	3796	8923	94
H(6C)	146	4345	9168	94
H(9)	7068	-139	4821	38
H(10)	9432	-466	3426	42
H(11)	10930	1391	3249	46
H(12)	10034	3571	4464	47
H(13)	7647	3885	5819	43
H(7A)	5601	2553	9486	56
H(7B)	5503	779	9325	56
H(8A)	2722	3389	9878	108
H(8B)	3317	2185	10745	108
H(8C)	2676	1596	9794	108
H(7AA)	5967	1728	9349	49
H(7AB)	4047	2085	9800	49
H(8AA)	5764	4412	9195	80
H(8AB)	4945	4063	10413	80
H(8AC)	3829	4792	9607	80
H(14A)	6600	768	1267	64
H(14B)	7216	520	2363	64
H(15A)	8809	2358	1754	111
H(15B)	8305	2391	624	111
H(15C)	9390	807	977	111

4. Graphical Procedure for Pyridinium Salt 6a Synthesis

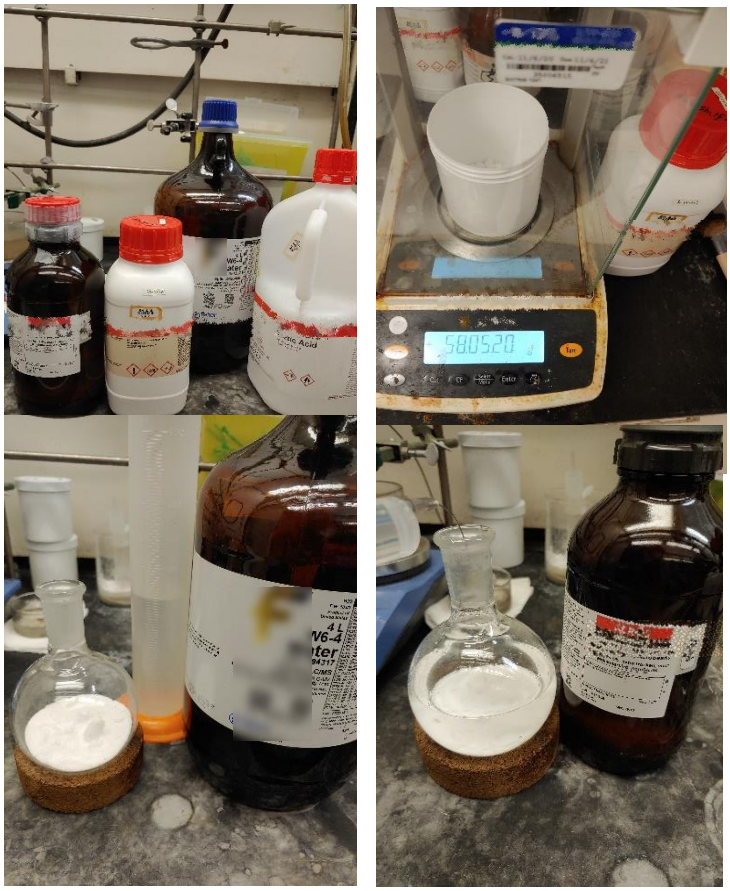


Fig. S6. Reaction set-up for the 1st step of the synthesis of pyridinium salt 6a.. Reagents and solvent (upper left), weigh mass of 500 mmol maleic acid (upper right), maleic acid and stir bar in 500 mL RBF (bottom left), added 250 mL water and 500 mmol pyridine (bottom right).

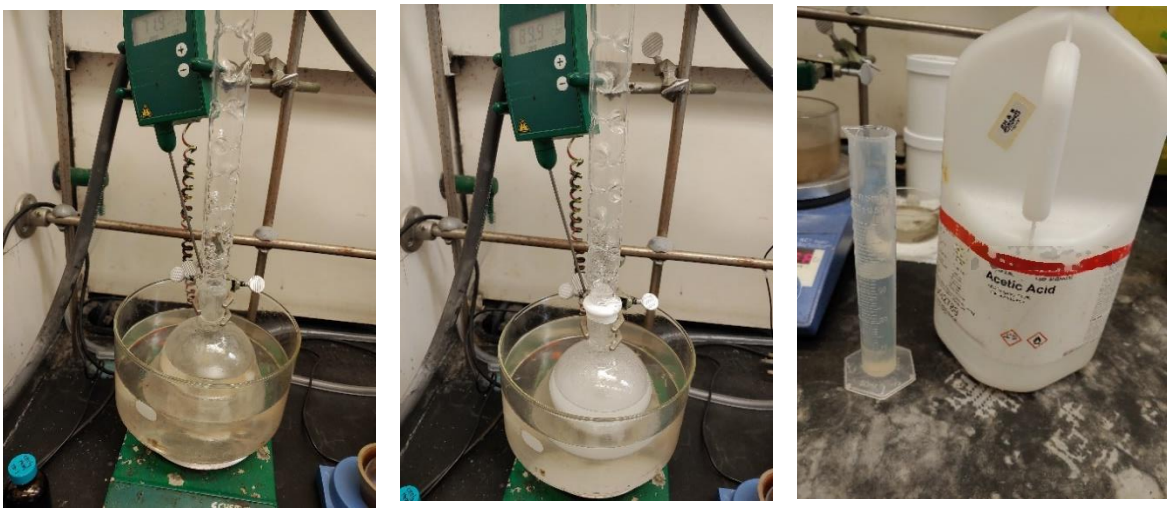


Fig. S7. Reaction set-up for the 1st step of the synthesis of pyridinium salt 6a. (continued). Observed homogeneous solution under heating with Vigreux condenser (left), white solid formation after 2 h (center), addition of 600 mmol of AcOH (right).

Fig. S8. Work-up procedure for the 1st step of the synthesis of pyridinium salt 6a. Filtration of the white solid using Büchner funnel (upper left, center). The resulting solid was dried by rotary evaporator and high vacuum. (upper right), The pyridinium salt **9** was stored in 100 mL Nalgene bottle, stable in ambient temperature (bottom).

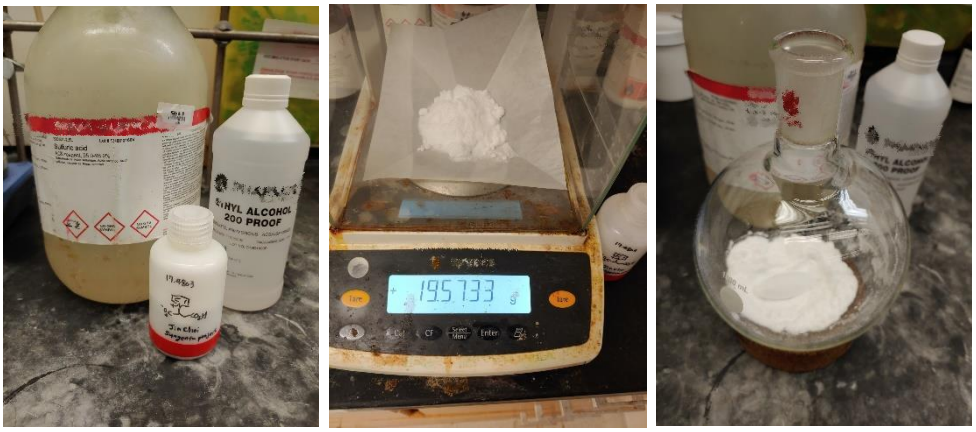


Fig. S9. Reaction set-up for the 2nd step of the synthesis pyridinium salt 6a. Reagents and solvent (left), weigh mass of 100 mmol pyridinium **9** (center), pyridinium **9** and stirring bar in 1000 mL RBF (right)

Fig S10. Reaction set-up for the 2nd step of the synthesis pyridinium salt 6a (continued). 500 mL EtOH (left), 10.5 mL concentrated H_2SO_4 (right)

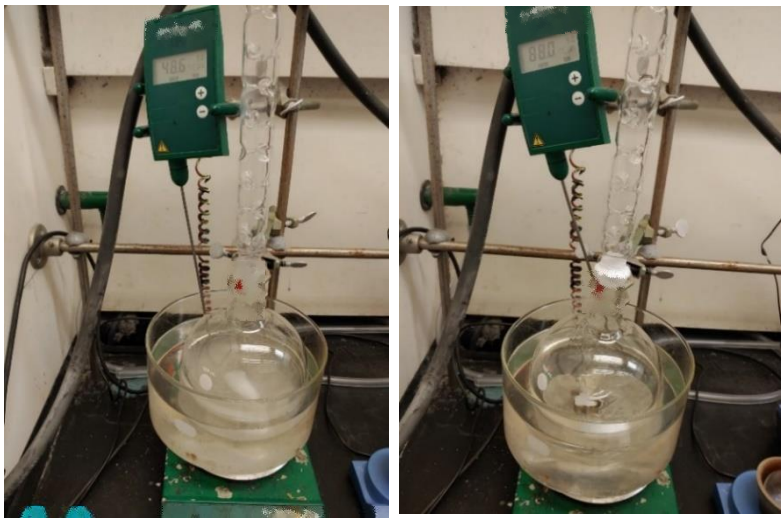


Fig. S11. Reaction set-up for the 2nd step of the synthesis pyridinium salt 6a (continued). Heterogeneous mixture at the beginning of the reaction (left), Homogeneous mixture under heating was observed (right).

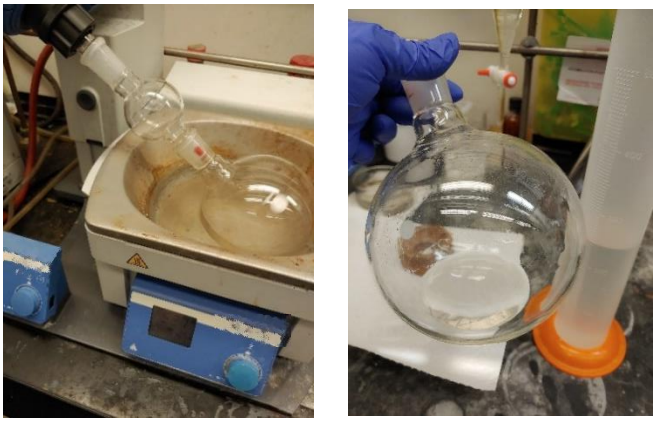


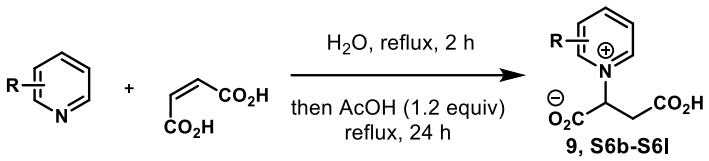
Fig. S12. Work-up procedure for 2nd step of pyridinium salt 6a synthesis. Evaporation of the solvent using rotatory evaporator after complete reaction (left), crude liquid after evaporating solvent (right).

Fig. S13. Work-up procedure for to 2nd step of pyridinium salt 6a synthesis (continued). Extraction with CH_2Cl_2 and H_2O (left), organic layers dried with Na_2SO_4 (center), filtration and evaporation of the residual solvent by rotary evaporator (right).

Fig. S14. Isolation of pyridinium salt 6a. Anhydrous Et_2O was added to the oil to remove the residual solvent (left), dried product obtained as a white solid (center), The resulting salt **6a** was stored in 20 mL vial, stable in ambient temperature (right).

5. General Procedure for Pyridinium Feedstock (6b – 6i) Synthesis

General Procedure A



A solution of maleic acid (1.16 g, 10 mmol) and substituted pyridine (1 equiv., 10 mmol) in H_2O (5 mL) was stirred at 90 °C for 2 h. After a crystalline solid appeared in reaction mixture, acetic acid (686 µL, 1.2 equiv. 12 mmol) was added. The solution was kept in suspension with stirring at the same temperature for 24 h. The crude reaction mixture was cooled down to room temperature, filtered, washed with small amount of MeOH and EtOAc. The resulting white solid was dried under reduced pressure by rotary evaporator and high vacuum for overnight. The product was obtained and used for next step without further purification.

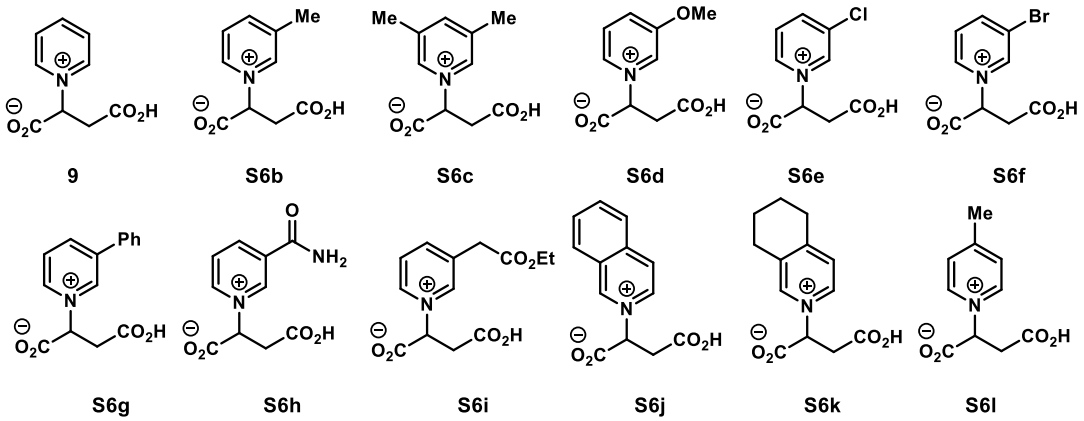
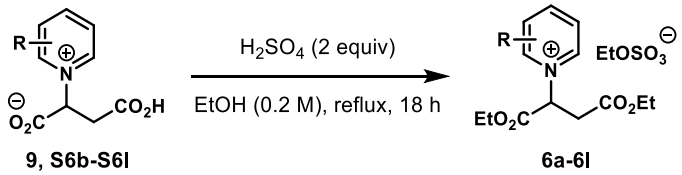


Figure S15. Synthesized pyridinium salts followed by general procedure A

General Procedure B [5]



A solution of pyridinium carboxylate salt (2.5 mmol, 1 equiv.) in EtOH (12.5 mL, 0.2 M) with concentrated sulfuric acid (2 equiv., 5 mmol, 260 µL) was stirred at 90 °C for 18 h. Upon completion, the solvent (EtOH) was evaporated under reduced pressure. The concentrated crude mixture was diluted in dichloromethane (15 mL) and H_2O (2 mL) and extracted by dichloromethane monitoring by TLC both aqueous and organic phase until no desired product in the aqueous phase was observed. The

[5] Regarding the toxicity of ethylsulfate, this anion does not rise any significant concern according to the MSDS of sodium ethylsulfate (see: https://www.sigmaaldrich.com/US/en/product/aldrich/901275).

No trace of diethyl sulfate could be observed in the ^{1}H, ^{13}C NMR and LC-MS of any pyridinium crude material. Furthermore, a literature research on that regard revealed that harsh conditions are required to generate dialkylsulfates starting from the corresponding monoalkylated one (see Sun Guibin, Zhang Rongnan, Li Hecun, Hu Lei, Zhang Xuede, Bian Binghui, Wang Jiawang, Environmentally-Friendly Diethyl Sulfate Production Process, 2020, CN201910839415 20190905).

combined organic phase was dried by Na_2SO_4, filtered, concentrated under reduced pressure. The resulting colorless liquid was used for next step without further purification.

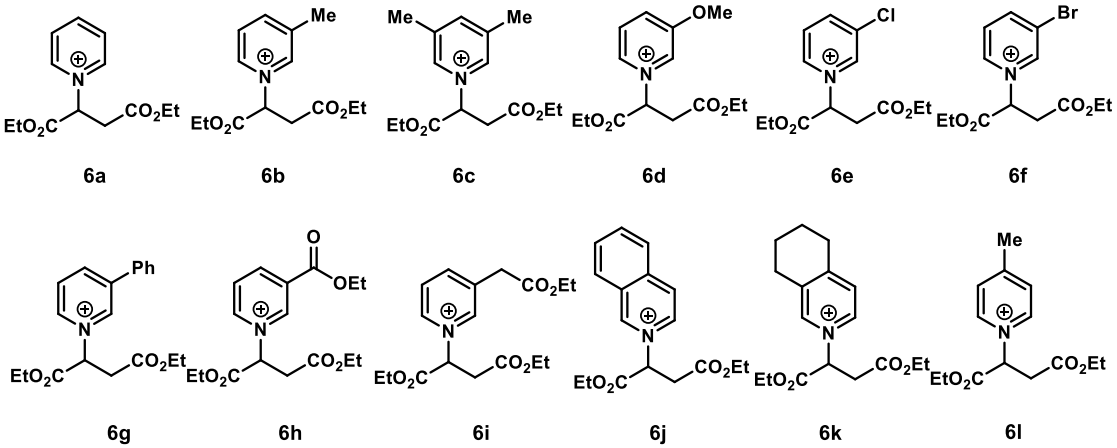
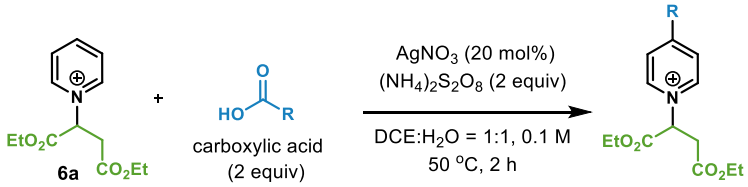


Figure S16. Synthesized pyridinium salts **6** according to general procedure B
Counter-anion = ethyl sulfate ($EtOSO_3^-$).

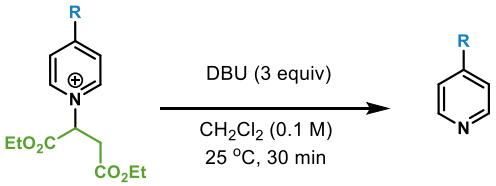
6. General Procedure for Minisci (type) and Deprotection Reactions

General Procedure C: Minisci Reaction



To a 15 mL culture tube equipped with Teflon septum screw cap and containing a stir bar pyridinium, **6a** (0.5 mmol, 188 mg, 1 equiv), carboxylic acid (1.0 mmol, 2 equiv), $(NH_4)_2S_2O_8$ (228 mg, 1.0 mmol, 2 equiv) and $AgNO_3$ (16.7 mg, 0.1 mmol, 20 mol%) were added, together with dichloroethane (2.5 mL) and H_2O (2.5 mL). The biphasic mixture was stirred at 50 °C for 2 hours. The reaction and ist regioselectivity were monitored by NMR or LCMS. Upon completion, the reaction was diluted with dichloromethane (1 mL). The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude material was used next step without further purification.

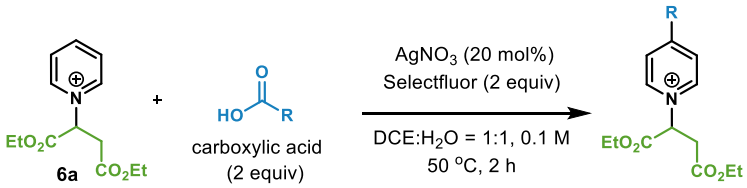
General Procedure D: Base-promoted Deprotection Reaction



The crude alkylated product was added DBU (225 µL, 1.5 mmol, 3 equiv) in dichloromethane (5 mL, 0.1 M). and the reaction mixture was stirred at room temperature for 30 min. Upon the reaction completion, the reaction mixture was transferred to a separatory funnel containing 1 *N* NaOH (3 mL) for adjusting pH >10 [Note: In case of base sensitive substrate, aq. NaOH could be changed by aq. $NaHCO_3$]. The aqueous phase was extracted with dichloromethane (3 x 3 mL) and combined organic phase was washed with brine. The resulting combined organic layers were dried over Na_2SO_4, filtered,

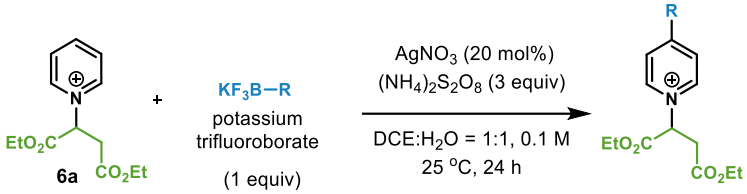
and concentrated in *vacuo*. The crude material was purified by silica gel chromatography to yield the desired product.

General Procedure E: Minisci-type Reaction Reported by Baxter Group[6]



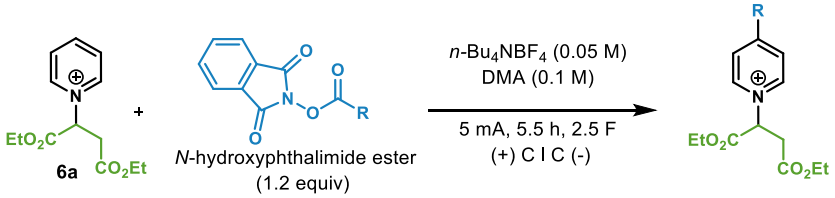
To a 15 mL culture tube equipped with Teflon septum screw cap and containing a stir bar, pyridinium **6a** (0.5 mmol, 188 mg, 1 equiv), carboxylic acid (1.0 mmol, 2 equiv), Selectfluor (177 mg, 1.0 mmol, 2 equiv) and $AgNO_3$ (16.7 mg, 0.1 mmol, 20 mol%) were added, together with dichloroethane (2.5 mL) and H_2O (2.5 mL). The biphasic mixture was stirred at 50 °C. The reaction and ist regioselectivity were monitored by NMR or LCMS. Upon completion, the reaction was diluted with dichloromethane (1 mL). The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude material was used next step without further purification.

General Procedure F: Minisci-type Reaction Reported by Molander Group[7]



To a 15 mL culture tube equipped with Teflon septum screw cap and containing a stir bar, pyridinium **6a** (0.5 mmol, 188 mg, 1 equiv), potassium alkyltrifluoroborate (0.5 mmol, 1 equiv), $(NH_4)_2S_2O_8$ (337 mg, 1.5 mmol, 3 equiv) and $AgNO_3$ (16.7 mg, 0.1 mmol, 20 mol%) were added, together with dichloroethane (2.5 mL) and H_2O (2.5 mL). The biphasic mixture was stirred at room temperature for 24 h. Upon completion, the reaction was diluted with dichloromethane (1 mL). The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was used next step without further purification.

General Procedure G: Minisci-type Reaction Reported by Lei & Wang Group (e-chem)[8], [9]

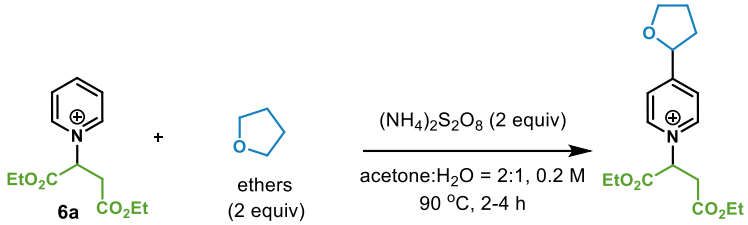


To an oven-dried 5 mL ElectraSyn vial, equipped with two graphite electrodes and a magnetic stirbar, the corresponding pyridinium **6a** (188 mg, 0.5 mmol, 1.0 equiv.), the *N*-hydroxyphthalimide ester (0.6 mmol, 1.2 equiv.) and *n*-Bu_4NBF_4 (82.3 mg, 0.05 M, 0.25 mmol) were added, together with DMA (5 mL) was added. The reaction mixture was stirred and electrolyzed at a constant current of 5.0 mA under

[6] Galloway, J. D.; Mai, D. N.; Baxter, R. D. *Org. Lett.* **2017**, *19*, 5772−5775.
[7] Presset, M.; Fleury-Brégeot, N.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2013**, *78*, 4615−4619.
[8] Liu, Y.; Xue, L.; Shi, B.; Bu, F.; Wang, D.; Lu, L.; Shi, R.; Lei, A. *Chem. Commun.*, **2019**, *55*, 14922−14925.
[9] Niu, K.; Song, L.; Hao, Y.; Liu, Y.; Wang, Q. *Chem. Commun.*, **2020**, *56*, 11673−11676.

room temperature for 5.5 h (approximately 2.5 F). The reaction was quenched with saturated sodium bicarbonate aqueous solution (10 mL) and extracted with EtOAc (3 × 10 mL). Then the combined organic layers were filtered, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was used next step without further purification.

General Procedure H: Minisci-type Reaction using Unactivated Ether[10]

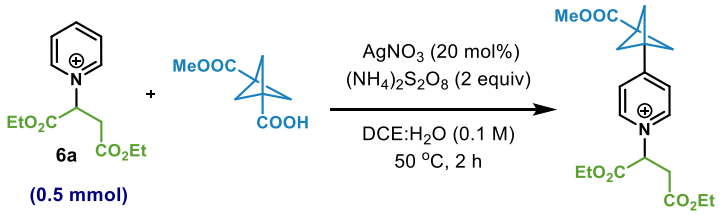


To a 15 mL culture tube equipped with Teflon septum screw cap and containing a stir bar, pyridinium **6a** (0.5 mmol, 188 mg, 1 equiv), ether (1.0 mmol, 2 equiv) and $(NH_4)_2S_2O_8$ (228 mg, 1.0 mmol, 2 equiv) were added, together with acetone (1.7mL) and H_2O (0.8 mL). The reaction mixture was stirred for at 90 °C for 2-4 h. Upon completion, the reaction was evaporated by reduced pressure, diluted with dichloromethane (1 mL). The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was used next step without further purification.

[10] McCallum, T.; Jouanno, L-A.; Cannilo, A.; Barriault, L. *Synlett* **2016**, *27*, 1282−1286.

7. Optimization Screening for Expensive Carboxylic Acids

After a reoptimization of the reaction, we observed that valuable carboxylic acid can be employed as limiting reagents for the alkylation in similar yields compared to the standard conditions (**Figure S17)**. Furthermore, higher concentrations can be used with similar results compared to our benchmark reaction.

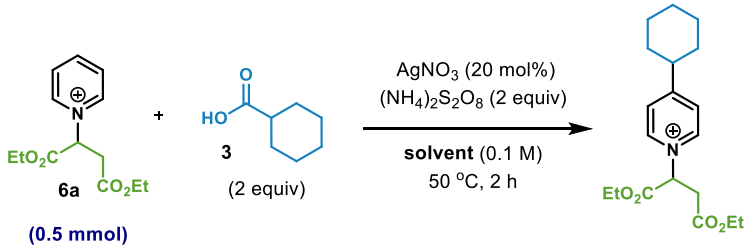


Variations	%NMR yield (isolated)
None	34% (32%)
$K_2S_2O_8$	16%
$AgNO_3$ two additions	28%
Acid limiting reagent	**40% (38%)**
80°C	Trace
80°C, Acid limiting reagent	Trace
80°C, 30 min	9%
80°C, Acid lim. reag., 30 min	14%
0.05 M	33%
0.2 M	35%
0.3 M	**44% (42%)**
0.4 M	44%

Figure S17. Reaction screening for low yield example using expensive carboxylic acid

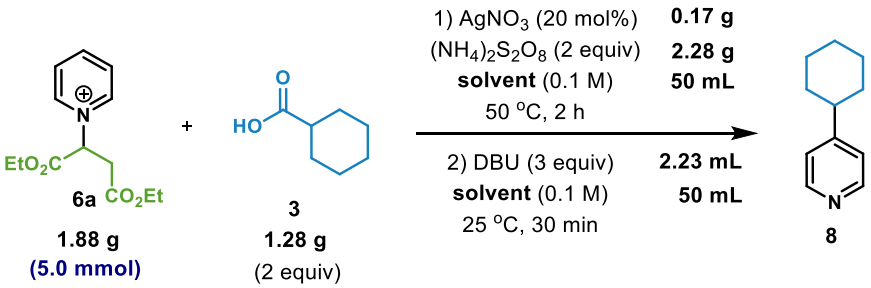
8. Solvent Screening for Process Chemistry

For potential application in process chemistry setting, alternative, non-halogenated solvents were investigated. As a result, different, non-halogenated solvents can be used for this Minisci transformation with similar outcome compared to the benchmark reaction (**Figure S18-S19**).



solvent	%NMR yield (isolated)
DCE:H_2O (1:1)	83% (81%)
acetone:H_2O (1:1)	61%
CH_3CN:H_2O (1:1)	38%
EtOAc:H_2O (1:1)	65%
$PhCF_3$:H_2O (1:1)	53%
H_2O	53%

Figure S18. Solvent screening



1st step solvent	2nd step solvent	%yield (amount)
DCE:H_2O (1:1)	**CH_2Cl_2**	**77% (621 mg)**
EtOAc:H_2O (1:1)	**EtOAc**	**56% (451 mg)**

Figure S19. Comparision of scale-up result between standard and green solvent

9. Comparison with One-pot Protocol

In order to minimize the downstream steps of te protocol, a one-pot procedure was tested (**Figure S20**). As a result, a drop in the isolated yield of the desired product was observed.

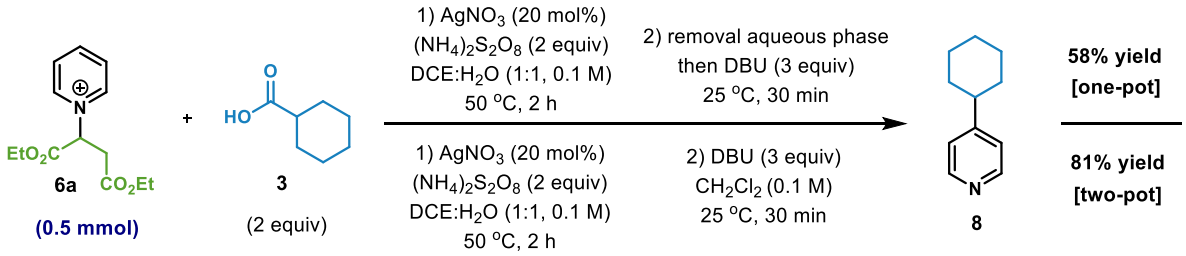
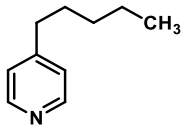


Figure S20. Trial and result for one-pot protocol

10. Characterization of Products in Table 1



4-pentylpyridine (11)

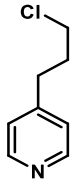
Following the modified general procedure C and D, *n*-hexanoic acid (232 mg, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450 µL, 3.0 mmol, 6 equiv) was used in procedure D [**Table 1**, **footnote b**]. The compound **11** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 3:1), obtained as an orange liquid (42.1 mg, 56% yield).

R_f = 0.42 (*n*-hexane:EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, J = 6.0 Hz, 2H), 7.12 (d, J = 6.0 Hz, 2H), 2.66 – 2.58 (t, J = 7.7 Hz, 3H), 1.65 (p, J = 7.5 Hz, 2H), 1.40 – 1.29 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.80, 149.60, 123.92, 35.22, 31.35, 29.98, 22.45, 13.96.

HRMS $[M+H]^+ = C_{10}H_{16}N^+$: calculated for 150.1283, found 150.1284



4-(3-chloropropyl)pyridine (12)

Following the modified general procedure C and D, 4-chlorobutyric acid (197 µL, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450 µL, 3.0 mmol, 6 equiv) was used in procedure D [**Table 1**, **footnote b**]. The compound **12** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 2:1), obtained as a yellow liquid (25.4 mg, 33% yield).

For scale-up reaction (5.0 mmol scale)

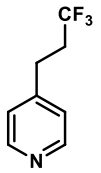
Following the modified general procedure C and D, pyridinium **6a** (1.88 g, 5.0 mmol, 1 equiv), 4-chlorobutyric acid (1.97 mL, 20.0 mmol, 4 equiv), $AgNO_3$ (167 mg, 1.0 mmol, 20 mol%), $(NH_4)_2S_2O_8$ (2.28 g, 10.0 mmol, 2 equiv) was added in dichloroethane (25 mL) and H_2O (25 mL) in procedure C and DBU (4.5 mL, 30.0 mmol, 6 equiv) was used in procedure D [**Table 1**, footnote **b**]. The compound **12** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 2:1), obtained as pale brown liquid (302.3 mg, 39% yield).

R_f = 0.45 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 6.1 Hz, 2H), 7.16 (d, *J* = 6.0 Hz, 2H), 3.56 (t, *J* = 6.3 Hz, 2H), 2.85 – 2.79 (m, 2H), 2.23 – 2.03 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.86, 149.73, 123.97, 43.80, 32.81, 32.09.

HRMS $[M+H]^+ = C_8H_{11}ClN^+$: calculated for 156.0580, found 156.0582



4-(3,3,3-trifluoropropyl)pyridine (13)

Following the modified general procedure C and D, carboxylic acid (284 mg, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450 µL, 3.0 mmol, 6 equiv) was used in procedure D [**Table 1**, **footnote b**]. The compound **13** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 4:1 to 3:2), obtained as a yellow liquid (20.3 mg, 23% yield). *[Caution: this compound was quite volatile, all of the solvent evaporating step was performed below 40 °C, above 100 mbar]*

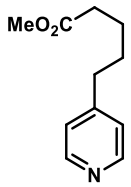
R_f = 0.25 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 5.4 Hz, 2H), 7.16 (d, *J* = 5.3 Hz, 2H), 2.94 – 2.84 (m, 2H), 2.44 (ddd, *J* = 10.5, 8.2, 5.7 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.10, 147.81, 126.38 (q, *J* = 276.6 Hz), 123.56, 34.38 (q, *J* = 29.1 Hz), 27.58 (q, *J* = 3.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -69.24.

HRMS $[M+H]^+ = C_8H_9F_3N^+$: calculated for 176.0687, found 176.0688



methyl 5-(pyridin-4-yl)pentanoate (14)

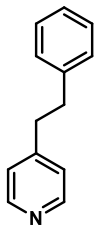
Following the modified general procedure C and D (0.3 M, DCE:H_2O 1:1), adipic acid monomethyl ester (160 mg, 1.0 mmol, 2 equiv) was used in procedure C and DBU (225 µL, 1.5 mmol, 3 equiv) was used in procedure D [**Table 1**, **footnote e**]. The compound **14** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a yellow solid (37.7 mg, 39% yield).

R_f = 0.15 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 – 8.39 (m, 2H), 7.09 (d, *J* = 5.3 Hz, 2H), 3.66 (s, 3H), 2.65 – 2.59 (m, 2H), 2.34 (h, *J* = 3.6, 3.0 Hz, 2H), 1.66 (p, *J* = 3.6 Hz, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.81, 150.92, 149.75, 123.84, 51.56, 34.86, 33.75, 29.65, 24.43.

HRMS $[M+H]^+ = C_{11}H_{16}NO_2^+$: calculated for 194.1181, found 194.1182



4-phenethylpyridine (15)

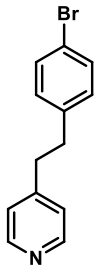
Following the general procedure C and D, hydrocinnamic acid (300 mg, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450 µL, 3.0 mmol, 6 equiv) was used in procedure D [**Table 1**, **footnote b**]. The compound **15** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a brown solid (38.0 mg, 41% yield).

R_f = 0.40 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 – 8.39 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.23 – 7.18 (m, 1H), 7.16 – 7.12 (m, 2H), 7.11 – 7.08 (m, 2H), 2.93 (s, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.14, 149.32, 140.64, 128.58, 128.49, 126.38, 124.18, 37.17, 36.60.

HRMS $[M+H]^+ = C_{13}H_{14}N^+$: calculated for 184.1126, found 184.1126



4-(4-bromophenylethyl)pyridine (16)

Following the general procedure C and D, 3-(4-bromophenyl)-propanoic acid (458 mg, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450 µL, 3.0 mmol, 6 equiv) was used in procedure D [**Table 1**, **footnote b**]. The compound **16** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a brown solid (34.1 mg, 26% yield).

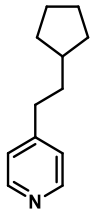
Following the modified general procedure C and D (0.3 M, DCE:H_2O= 1:1), 3-(4-bromophenyl)-propanoic acid (458 mg, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450 µL, 3.0 mmol, 6 equiv) was used in procedure D [**Table 1**, **footnote e**]. The compound **16** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a brown solid (47.2 mg, 36% yield).

R_f = 0.20 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 – 8.41 (m, 2H), 7.44 – 7.33 (m, 1H), 7.18 – 7.05 (m, 1H), 7.00 (d, J = 8.3 Hz, 1H), 2.91 (tt, J = 8.1, 4.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9, 139.4, 131.7, 130.3, 124.4, 120.3, 37.0, 36.0.

HRMS $[M+H]^+$= $C_{13}H_{13}BrN^+$: calculated for 262.0231, found 262.0240



4-(2-cyclopentylethyl)pyridine (17)

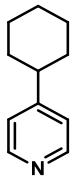
Following the modified general procedure C and D (0.3 M, DCE:H_2O = 1:1), 3-cyclopentyl propanoic acid (142 mg, 1.0 mmol, 2 equiv) was used in procedure C and DBU (225 µL, 1.5 mmol, 3 equiv) was used in procedure D [**Table 1**, **footnote e**]. The compound **17** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 2:1), obtained as a yellow solid (36.2 mg, 41% yield).

R_f = 0.55 (*n*-hexane: EtOAc = 2:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 – 8.42 (m, 2H), 7.15 – 7.03 (m, 2H), 2.67 – 2.52 (m, 2H), 1.84 – 1.72 (m, 3H), 1.67 – 1.58 (m, 4H), 1.55 – 1.48 (m, 2H), 1.18 – 1.06 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.11, 149.67, 124.01, 39.71, 36.97, 34.59, 32.71, 25.31.

HRMS $[M+H]^+$= $C_{12}H_{18}N^+$: calculated for 176.1439, found 176.1443



4-cyclohexylpyridine (8)

Following the general procedure C and D, cyclohexane carboxylic acid (128 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **8** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 3:1 to 2:1), obtained as an orange liquid (65.1 mg, 81% yield).

For scale-up reaction (5.0 mmol scale)

Following the general procedure C and D, pyridinium **6a** (1.88 g, 5.0 mmol, 1 equiv), cyclohexane carboxylic acid **3** (1.28 g, 10.0 mmol, 2 equiv), $AgNO_3$ (167 mg, 1.0 mmol, 20 mol%), $(NH_4)_2S_2O_8$ (2.28 g, 10.0 mmol, 2 equiv) was added in dichloroethane (25 mL) and H_2O (25 mL) in procedure C and DBU (2.25 mL, 15.0 mmol, 3 equiv) was used in procedure D. The compound **8** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 2:1), obtained as a yellow liquid (621 mg, 77% yield).

For scale-up reaction using non-halogenated solvent (5.0 mmol scale)

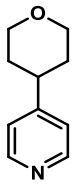
Following the general procedure C and D, pyridinium **6a** (1.88 g, 5.0 mmol, 1 equiv), cyclohexane carboxylic acid **3** (1.28 g, 10.0 mmol, 2 equiv), $AgNO_3$ (167 mg, 1.0 mmol, 20 mol%), $(NH_4)_2S_2O_8$ (2.28 g, 10.0 mmol, 2 equiv) was added in ethyl acetate (25 mL) and H_2O (25 mL) in procedure C and DBU (2.25 mL, 15.0 mmol, 3 equiv) was used in procedure D. The compound **8** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 3:1), obtained as a yellow liquid (452 mg, 56% yield).

R_f = 0.43 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, *J* = 6.2 Hz, 2H), 7.15 (d, *J* = 6.2 Hz, 2H), 2.54 – 2.47 (m, 1H), 1.87 (tq, *J* = 6.6, 3.8 Hz, 4H), 1.79 – 1.73 (m, 1H), 1.40 (td, *J* = 9.5, 2.5 Hz, 4H), 1.30 – 1.21 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.35, 149.32, 122.65, 44.02, 33.63, 26.64, 26.05.

HRMS $[M+H]^+ = C_{11}H_{16}N^+$: calculated for 162.1283, found 162.1288



4-(tetrahydro-2H-pyran-4-yl)pyridine (18)

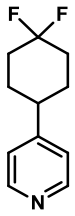
Following the general procedure C and D, tetrahydro-2H-pyran-4-carboxylic acid (130 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **18** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 2:1 to 1:2), obtained as a pale yellow liquid (61.8 mg, 76% yield).

R_f = 0.13 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 6.1 Hz, 2H), 7.19 (d, *J* = 6.1 Hz, 2H), 4.15 – 4.08 (m, 2H), 3.62 – 3.51 (m, 2H), 2.80 (dt, *J* = 10.8, 5.2 Hz, 1H), 1.81 (dt, *J* = 6.0, 3.7 Hz, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.90, 149.55, 122.32, 67.98, 40.90, 32.91.

HRMS $[M+H]^+ = C_{10}H_{14}NO^+$: calculated for 164.1075, found 164.1078



4-(4,4-difluorocyclohexyl)pyridine (19)

Following the general procedure C and D, 4,4-difluorocyclohexane-1-carboxylic acid (164 μL, 1.0 mmol, 2 equiv) was used in procedure C. The compound **19** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 3:1 to 1:1), obtained as a yellow liquid (70.1 mg, 71% yield).

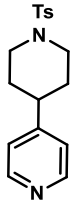
R_f = 0.20 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 6.2 Hz, 2H), 7.16 (d, *J* = 6.1 Hz, 2H), 2.62 (td, *J* = 9.8, 8.1, 5.6 Hz, 1H), 2.30 – 2.19 (m, 2H), 1.97 – 1.78 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.84 (d, *J* = 2.5 Hz), 149.99, 122.73 (dd, *J* = 243.0, 239.4 Hz), 122.21, 41.76, 33.77 (dd, *J* = 25.7, 23.0 Hz), 29.44 (d, *J* = 10.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -94.31, -94.94, -104.75, -105.38.

HRMS $[M+H]^+ = C_{11}H_{14}F_2N^+$: calculated for 198.1094, found 198.1100



4-(1-tosylpiperidin-4-yl)pyridine (20)

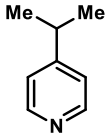
Following the general procedure C and D, 1-tosylpiperidine-4-carboxylic acid (283 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **20** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 3:1 to 1:3), obtained as a yellow liquid (58.0 mg, 37% yield).

R_f = 0.10 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 6.1 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 6.1 Hz, 2H), 3.97 (d, *J* = 11.7 Hz, 1H), 2.48 (s, 3H), 2.38 (td, *J* = 11.9, 2.9 Hz, 4H), 1.94 – 1.78 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.72, 149.88, 143.67, 133.10, 129.71, 127.77, 122.17, 46.47, 41.17, 31.71, 21.56.

HRMS $[M+H]^+ = C_{17}H_{21}N_2O_2S^+$: calculated for 317.1324, found 317.1332



4-isopropylpyridine (21)

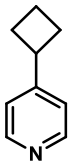
Following the general procedure C and D, isobutyric acid (92 µL, 1.0 mmol, 2 equiv) was used in procedure C. The compound **21** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 3:1), obtained as a yellow liquid (31.7 mg, 52% yield). *[Caution: this compound was quite volatile, all of the solvent evaporating step was performed below 40 °C, above 100 mbar]*

R_f = 0.35 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 6.1 Hz, 2H), 7.17 (d, J = 6.1 Hz, 2H), 2.91 (hept, *J* = 7.0 Hz, 1H), 1.28 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.50, 149.78, 121.99, 33.56, 23.10.

HRMS $[M+H]^+ = C_8H_{12}N^+$: calculated for 122.0964, found 122.0964



4-cyclobutylpyridine (22)

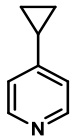
Following the general procedure C and D, cyclobutane carboxylic acid (100 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **22** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 2:1), obtained as a pale yellow liquid (46.1 mg, 69% yield).

R_f = 0.35 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 6.1 Hz, 2H), 7.13 (d, *J* = 5.9 Hz, 2H), 3.55 (p, *J* = 8.5 Hz, 1H), 2.43 – 2.34 (m, 2H), 2.21 – 2.12 (m, 2H), 2.13 – 2.04 (m, 1H), 1.95 – 1.87 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.90, 149.62, 121.70, 39.33, 28.93, 18.36.

HRMS $[M+H]^+ = C_9H_{12}N^+$: calculated for 134.0964, found 134.0963



4-cyclopropylpyridine (23)

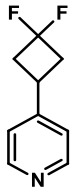
Following the general procedure C and D, cyclopropane carboxylic acid (86 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **23** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 4:1 to 1:1), obtained as an orange liquid (36.0 mg, 60% yield). *[Caution: this compound was quite volatile, all of the solvent evaporating step was performed below 40 °C, above 100 mbar]*

$\mathbf{R_f}$ = 0.35 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 6.1 Hz, 2H), 6.97 (d, *J* = 6.1 Hz, 2H), 1.87 (tt, *J* = 8.3, 4.9 Hz, 1H), 1.15 – 1.05 (m, 2H), 0.81 (dt, *J* = 7.0, 4.8 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.76, 149.43, 120.73, 14.95, 10.53.

HRMS $[M+H]^+ = C_8H_{10}N^+$: calculated for 120.0808, found 120.0812



4-(3,3-difluorocyclobutyl)pyridine (24)

Following the general procedure C and D, 3,3-difluoro cyclopropane carboxylic acid (272 mg, 2.0 mmol, 4 equiv) was used in procedure C (4 equiv, 450 µL). [**Table 1**, **footnote b**]. The compound **24** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as an orange liquid (37.0 mg, 44% yield).

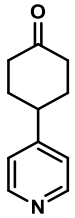
$\mathbf{R_f}$ = 0.25 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 – 8.54 (m, 2H), 7.22 – 7.12 (m, 2H), 3.38 (pt, *J* = 6.8, 3.5 Hz, 1H), 3.10 – 2.98 (m, 2H), 2.75 – 2.62 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 149.6, 122.1, 121.7 – 116.1 (m), 42.0 (dd, *J* = 23.9, 22.7 Hz), 27.4 (dd, *J* = 14.7, 4.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -85.24 (d, J = 195.0 Hz), -100.98 (d, J = 194.3 Hz).

HRMS $[M+H]^+ = C_9H_{10}F_2N^+$: calculated for 170.0781, found 170.0781



4-(pyridin-4-yl)cyclohexan-1-one (25)

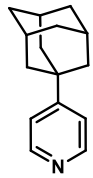
Following the general procedure C and D, 4-oxocyclohexane-1-carboxylic acid (142 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **25** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 2:1 to 1:2), obtained as an orange liquid (22.2 mg, 25% yield).

R_f = 0.18 (ethyl acetate only)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 6.2 Hz, 2H), 7.20 (d, *J* = 6.2 Hz, 2H), 3.09 – 2.99 (m, 1H), 2.55 (dd, *J* = 7.6, 3.1 Hz, 4H), 2.31 – 2.21 (m, 2H), 2.04 – 1.89 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 210.00, 153.55, 150.03, 122.16, 41.98, 40.97, 33.04.

HRMS $[M+H]^+$= $C_{11}H_{14}NO^+$: calculated for 176.1075, found 176.1077



4-(adamantan-1-yl)pyridine (26)

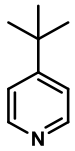
Following the general procedure C and D, 1-adamantyl carboxylic acid (180 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **26** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 2:1), obtained as a pale yellow solid (95.9 mg, 89% yield).

R_f = 0.55 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 6.3 Hz, 2H), 7.27 (d, *J* = 6.3 Hz, 2H), 2.17 – 2.11 (m, 3H), 1.91 (d, *J* = 2.9 Hz, 6H), 1.85 – 1.74 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.91, 149.68, 120.37, 42.36, 36.58, 36.24, 28.63.

HRMS $[M+H]^+$= $C_{15}H_{20}N^+$: calculated for 214.1596, found 214.1602



4-(*tert*-butyl)pyridine (27)

Following the general procedure C and D, pivalic acid (102 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **27** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 4:1 to 2:1), obtained as a pale yellow liquid (47.0 mg, 70% yield). *[Caution: this compound was quite volatile, all of the solvent evaporating step was performed below 40 °C, above 100 mbar]*

For scale-up reaction (5.0 mmol scale)

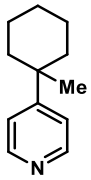
Following the modified general procedure C and D, pyridinium **6a** (1.88 g, 5.0 mmol, 1 equiv), pivalic acid (1.02 mL, 10.0 mmol, 2 equiv), $AgNO_3$ (167 mg, 1.0 mmol, 20 mol%), $(NH_4)_2S_2O_8$ (2.28 g, 10.0 mmol, 2 equiv) was added in dichloroethane (25 mL) and H_2O (25 mL) in procedure C and DBU (2.3 mL, 15.0 mmol, 3 equiv) was used in procedure D. The compound **27** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a pale yellow liquid (452 mg, 67% yield).

R_f = 0.35 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 6.3 Hz, 2H), 7.31 (d, *J* = 6.3 Hz, 2H), 1.34 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.26, 149.42, 120.81, 34.70, 30.50

HRMS $[M+H]^+ = C_9H_{14}N^+$: calculated for 136.1126 found 136.1122



4-(1-methylcyclohexyl)pyridine (28)

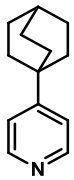
Following the general procedure C and D, 1-methylcyclohexane-1-carboxylic acid (142 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **28** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 3:1), obtained as an orange liquid (52.3 mg, 60% yield).

R_f = 0.55 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 6.1 Hz, 2H), 7.28 (d, J = 6.1 Hz, 2H), 1.99 (dq, *J* = 8.6, 4.3, 3.1 Hz, 2H), 1.65 – 1.54 (m, 4H), 1.49 – 1.36 (m, 4H), 1.19 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.06, 149.81, 121.42, 38.06, 37.17, 30.00, 26.13, 22.48.

HRMS $[M+H]^+ = C_{12}H_{18}N^+$: calculated for 176.1439, found 176.1445



4-(bicyclo[2.2.2]octan-1-yl)pyridine (29)

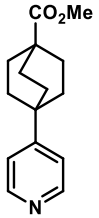
Following the general procedure C and D, bicyclo[2.2.2]octane-1-carboxylic acid (154 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **29** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as an orange liquid (37 mg, 40% yield).

R_f = 0.30 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 – 8.44 (m, 2H), 7.23 – 7.18 (m, 2H), 1.79 – 1.73 (m, 6H), 1.72 – 1.65 (m, 7H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 149.5, 121.3, 34.5, 31.6, 26.3, 24.4.

HRMS $[M+H]^+ = C_{13}H_{18}N^+$: calculated for 188.1439, found 188.1441



methyl 4-(pyridin-4-yl)bicyclo[2.2.2]octane-1-carboxylate (30)

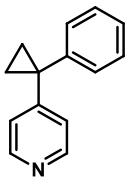
Following the general procedure C and D, 4-(methoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid (212 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **30** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 4:1 to 1:1), obtained as an orange liquid (94.5 mg, 77% yield).

R_f = 0.20 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 6.3 Hz, 2H), 7.22 (d, *J* = 6.3 Hz, 2H), 3.69 (s, 3H), 1.95 (dd, *J* = 10.4, 5.2 Hz, 6H), 1.86 (dd, *J* = 10.4, 5.2 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.99, 158.11, 149.59, 120.97, 51.80, 39.04, 34.75, 31.09, 28.46.

HRMS $[M+H]^+ = C_{15}H_{20}NO_2^+$: calculated for 246.1494, found 246.1502



4-(1-phenylcyclopropyl)pyridine (31)

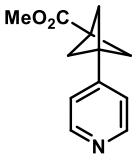
Following the general procedure C and D, 1-phenylcyclopropane-1-carboxylic acid (162 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **31** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 3:1), obtained as a pale brown liquid (41.8 mg, 43% yield).

R_f = 0.35 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 6.3 Hz, 1H), 7.39 – 7.29 (m, 3H), 6.96 – 6.94 (m, 2H), 1.45 (d, *J* = 2.1 Hz, 1H), 1.38 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.53, 149.47, 143.03, 129.80, 128.63, 126.96, 121.79, 29.13, 17.71.

HRMS $[M+H]^+$= $C_{14}H_{14}N^+$: calculated for 196.1126, found 196.1133



Methyl 3-(pyridine-4-yl)bicyclo[1.1.1]pentane-1-carboxylate (32)

Following the general procedure C and D, 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (170 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **32** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a yellow liquid (32.0 mg, 32% yield).

For reaction with carboxylic acid as limiting reagent

Following the modified general procedure C and D, using 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid as limiting reagent (85 mg, 0.5 mmol) and 2 equiv of the pyridinium salt (376 mg, 1.0 mmol, 2 equiv) was used in procedure C [**Table 1. Footnote d**]. The compound **32** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a yellow liquid (38.0 mg, 38% yield).

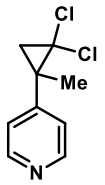
For reaction on concentrated solution (0.3 M)

Following the modified general procedure C and D (0.3 M, DCE:H_2O=1:1), 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (170 mg, 1.0 mmol, 2 equiv) was used in procedure C and DBU (225 µL, 1.5 mmol, 3 equiv) was used in procedure D [**Table 1**, **footnote e**]. The compound **32** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a yellow solid (42.3 mg, 42% yield).

R_f = 0.30 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.9 Hz, 2H), 7.13 (d, *J* = 4.2 Hz, 2H), 3.71 (s, 3H), 2.35 (s, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 149.5, 148.6, 121.6, 53.3, 51.9, 40.9, 37.4.

HRMS $[M+H]^+ = C_{12}H_{14}NO_2^+$: calculated for 204.1025, found 204.1031



4-(2,2-dichloro-1-methylcyclopropyl)pyridine. (33)

Following the modified general procedure C and D (0.3 M, DCE:H_2O=1:1), 2,2-dichloro-1-methylcyclopropane-1-carboxylic acid (169 mg, 1.0 mmol, 2 equiv) was used in procedure C and DBU (225 µL, 1.5 mmol, 3 equiv) was used in procedure D [**Table 1**, **footnote e**]. The compound **33** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a yellow solid (37.0 mg, 37% yield).

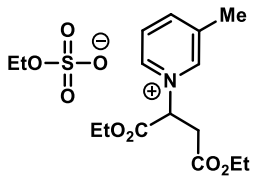
R_f = 0.45 (*n*-hexane: EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.1 Hz, 2H), 7.25 – 7.23 (m, 2H), 1.99 (d, *J* = 7.5 Hz, 1H), 1.68 (s, 3H), 1.65 (d, *J* = 7.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.1, 149.9, 123.8, 35.7, 31.6, 24.6.

HRMS $[M+H]^+ = C_9H_{10}Cl_2N^+$: calculated for 202.0190, found 202.0195

11. Characterization of Substituted Pyridinium Salts 6b-6l



Pyridinium Salt 6b

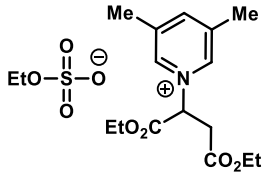
Following the general procedure B, the starting pyridinium **S6b** (523 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 18 h. The title compound **6b** was obtained as a colorless liquid (919 mg, 94% yield).

R_f = 0.25 (CH_2Cl_2: MeOH= 5: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (d, *J* = 1.8 Hz, 1H), 9.17 (d, *J* = 6.0 Hz, 1H), 8.33 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.99 (dd, *J* = 8.0, 6.2 Hz, 1H), 6.25 (dd, *J* = 7.8, 3.2 Hz, 1H), 4.38 – 4.25 (m, 2H), 4.13 (dd, *J* = 24.8, 7.1 Hz, 4H), 3.80 (dd, *J* = 19.0, 7.8 Hz, 1H), 3.52 (dd, *J* = 19.0, 3.2 Hz, 1H), 2.65 (s, 3H), 1.30 (dt, *J* = 8.6, 7.1 Hz, 6H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.25, 166.39, 147.00, 146.10, 143.45, 139.59, 127.40, 68.33, 63.68, 63.38, 61.93, 37.17, 18.76, 15.18, 14.00, 13.91.

HRMS $[M]^+ = C_{14}H_{20}NO_4^+$: calculated for 266.1392, found 266.1396



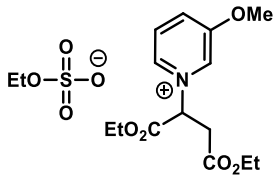
Pyridinium Salt 6c

Following the general procedure B, the starting pyridinium **S6c** (558 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 18 h. The title compound **6c** was obtained as a colorless liquid (1.01 g, >99% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 2H), 8.09 (s, 1H), 6.20 (dd, *J* = 7.5, 3.2 Hz, 1H), 4.32 (ddd, *J* = 35.2, 10.7, 7.1 Hz, 2H), 4.21 – 4.06 (m, 4H), 3.79 (dd, *J* = 19.0, 7.6 Hz, 1H), 3.50 (dd, *J* = 19.0, 3.2 Hz, 1H), 2.59 (s, 6H), 1.29 (m, 6H, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.43, 166.50, 147.49, 143.15, 138.74, 68.14, 63.70, 63.58, 61.89, 37.24, 18.61, 15.13, 14.01, 13.91.

HRMS $[M]^+ = C_{15}H_{22}NO_4^+$: calculated for 280.1549, found 280.1558



Pyridinium Salt 6d

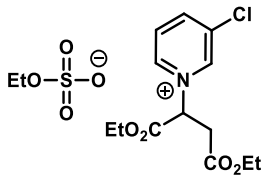
Following the general procedure B, the starting pyridinium **S6d** (564 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 18 h. The title compound **6d** was obtained as a colorless liquid (895 mg, 88% yield).

R_f = 0.20 (CH_2Cl_2: MeOH= 5: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (d, *J* = 1.2 Hz, 1H), 8.91 (d, *J* = 6.1 Hz, 1H), 8.10 – 8.07 (m, 1H), 7.99 (dd, *J* = 8.8, 6.0 Hz, 1H), 6.27 (dd, *J* = 7.8, 3.2 Hz, 1H), 4.31 (dd, *J* = 21.1, 7.1 Hz, 2H), 4.15 (d, *J* = 7.2 Hz, 2H), 4.10 (s, 3H), 4.10 – 4.06 (m, 2H), 3.77 (dd, *J* = 18.9, 7.8 Hz, 1H), 3.50 (dd, *J* = 18.9, 3.2 Hz, 1H), 1.32 – 1.22 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.17, 166.25, 158.67, 138.55, 132.95, 132.80, 128.28, 68.68, 63.74, 63.64, 61.93, 57.90, 37.18, 15.09, 13.99, 13.89.

HRMS $[M]^+ = C_{14}H_{20}NO_5^+$: calculated for 282.1341, found 282.1349



Pyridinium Salt 6e

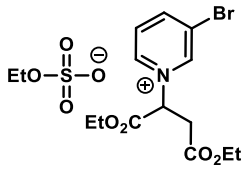
Following the general procedure B, the starting pyridinium **S6e** (574 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 18 h. The title compound **6e** was obtained as a yellow liquid containing of diethyl maleate as a impurity (752 mg, 73% yield).

R_f = 0.30 (CH_2Cl_2: MeOH= 5: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (d, *J* = 6.3 Hz, 1H), 9.36 (s, 1H), 8.58 – 8.52 (m, 1H), 8.23 (dd, *J* = 8.5, 6.2 Hz, 1H), 6.31 (dd, *J* = 7.8, 3.1 Hz, 1H), 4.35 (d, *J* = 7.1 Hz, 2H), 4.29 (dd, *J* = 20.2, 7.2 Hz, 2H), 4.20 – 4.13 (m, 2H), 3.77 (dd, *J* = 19.0, 7.8 Hz, 1H), 3.59 (dd, *J* = 19.0, 3.1 Hz, 1H), 1.44 – 1.21 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.24, 166.06, 146.65, 145.59, 145.09, 135.48, 129.18, 68.94, 63.91, 63.89, 62.08, 36.90, 15.07, 13.99, 13.89.

HRMS $[M]^+ = C_{13}H_{17}ClNO_4^+$: calculated for 286.0846, found 286.0848



Pyridinium Salt 6f

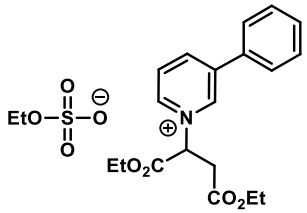
Following the general procedure B, the starting pyridinium **S6f** (2.74 mg, 10 mmol) was reacted with sulfuric acid (1.05 mL, 20 mmol) in EtOH (50 mL) at 90 °C for 24 h. The title compound **6f** was obtained as a yellow liquid after a filtration over a silica plug (first EtOAc, then CH_2Cl_2:MeOH=8:2) (3.07 g, 67% yield).

R_f = 0.50 (CH_2Cl_2: MeOH= 4: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (dt, *J* = 6.2, 1.3 Hz, 1H), 9.44 (t, *J* = 1.6 Hz, 1H), 8.67 (ddd, *J* = 8.3, 1.9, 1.0 Hz, 1H), 8.14 (dd, *J* = 8.4, 6.2 Hz, 1H), 6.33 (dd, *J* = 7.9, 3.0 Hz, 1H), 4.38 – 4.22 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.77 (dd, *J* = 19.0, 7.9 Hz, 1H), 3.55 (dd, *J* = 19.0, 3.0 Hz, 1H), 1.31 – 1.21 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 166.2, 149.5, 147.2, 146.1, 129.4, 122.6, 69.0, 64.0, 63.5, 62.2, 37.1, 15.3, 14.1, 14.0.

HRMS $[M]^+ = C_{13}H_{17}BrNO_4^+$: calculated for 330.0341, found 330.0343



Pyridinium Salt 6g

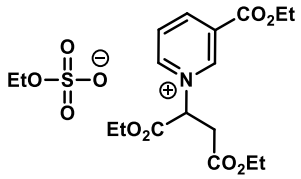
Following the general procedure B, the starting pyridinium **S6g** (678 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 24 h. The title compound **6g** was obtained as a colorless liquid (1.105 g, 98% yield).

R_f = 0.45 (CH_2Cl_2: MeOH= 5: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 9.28 (d, *J* = 6.3 Hz, 1H), 8.71 (d, *J* = 8.1 Hz, 1H), 8.19 (dd, *J* = 8.2, 6.2 Hz, 2H), 7.75 (d, *J* = 6.9 Hz, 2H), 7.55 – 7.45 (m, 3H), 6.40 (dd, *J* = 8.0, 3.1 Hz, 2H), 4.31 (dd, *J* = 21.0, 7.1 Hz, 2H), 4.16 – 4.02 (m, 4H), 3.81 (dd, *J* = 18.9, 8.0 Hz, 1H), 3.55 (dd, *J* = 18.9, 3.1 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.22 (dt, *J* = 9.9, 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.23, 166.45, 144.17, 144.10, 144.06, 141.12, 132.80, 130.48, 129.81, 129.79, 128.46, 127.55, 68.58, 63.69 (2 carbon), 61.92, 37.14, 15.09, 13.98, 13.91.

HRMS $[M]^+ = C_{19}H_{22}NO_4^+$: calculated for 328.1549, found 328.1558



Pyridinium Salt 6h

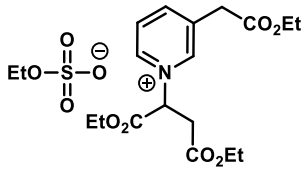
Following the general procedure B, the starting pyridinium **S6h** (595 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 24 h. The title compound **6h** was obtained as a yellow liquid (1.049 g, 93% yield).

R_f = 0.35 (CH_2Cl_2: MeOH= 5: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 9.63 (d, *J* = 6.3 Hz, 1H), 9.04 (d, *J* = 8.1 Hz, 1H), 8.37 (dd, *J* = 8.1, 6.2 Hz, 1H), 6.35 (dd, *J* = 7.7, 3.2 Hz, 1H), 4.51 (qd, *J* = 7.2, 1.5 Hz, 2H), 4.40 – 4.27 (m, 2H), 4.16 (t, *J* = 7.1 Hz, 2H), 4.03 (q, *J* = 7.1 Hz, 4H), 3.79 (dd, *J* = 18.9, 7.7 Hz, 1H), 3.64 (dd, *J* = 18.9, 3.2 Hz, 1H), 1.45 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.25 (td, *J* = 7.1, 4.7 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.22, 166.27, 161.14, 150.21, 146.80, 146.54, 130.59, 128.92, 68.96, 63.91, 63.62, 63.46, 62.09, 36.84, 15.06, 14.07, 13.98, 13.89.

HRMS $[M]^+ = C_{16}H_{22}NO_6^+$: calculated for 324.1447, found 324.1455



Pyridinium Salt 6i

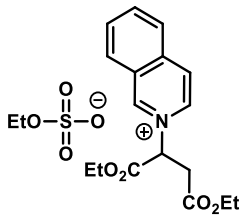
Following the general procedure B, the starting pyridinium **S6i** (706 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 24 h. The title compound **6i** was obtained as a colorless liquid (804.6 mg, 70% yield, >80% purity).

R_f = 0.50 (CH_2Cl_2: MeOH= 5: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (s, 1H), 9.21 (d, *J* = 6.3 Hz, 1H), 8.50 (d, *J* = 8.1 Hz, 1H), 8.05 (dd, *J* = 8.1, 6.2 Hz, 2H), 6.20 (dd, *J* = 7.8, 3.4 Hz, 1H), 4.38 – 4.24 (m, 2H), 4.21 (m, 2H), 4.15 (m, 2H), 4.11 (m, 2H), 4.02 (s, 2H), 3.75 (dd, *J* = 18.8, 7.8 Hz, 1H), 3.53 (dd, *J* = 18.8, 3.4 Hz, 1H), 1.32 – 1.27 (m, 12H), 1.25 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.05, 169.15, 166.24, 147.83, 146.78, 144.56, 135.92, 127.46, 68.51, 63.95, 63.75, 61.96, 37.23, 37.07, 15.07, 14.07, 13.97, 13.88.

HRMS $[M]^+ = C_{17}H_{24}NO_6^+$: calculated for 338.1604, found 338.1613



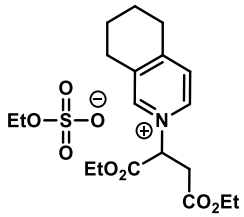
Pyridinium Salt 6j

Following the general procedure B, the starting pyridinium **S6j** (613 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 24 h. The title compound **6j** was obtained as a colorless liquid (948 mg, 89% yield).

R_f = 0.54 (CH_2Cl_2: MeOH= 5: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.87 (dd, *J* = 6.9, 1.6 Hz, 1H), 8.65 – 8.62 (m, 1H), 8.35 (d, *J* = 6.9 Hz, 1H), 8.10 (dd, *J* = 5.7, 1.4 Hz, 2H), 7.87 (s, 1H), 6.42 – 6.37 (m, 1H), 4.30 (dd, *J* = 14.9, 7.3 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.06 (dd, *J* = 7.1, 5.3 Hz, 2H), 3.84 (dd, *J* = 18.7, 8.9 Hz, 1H), 3.57 (dd, *J* = 18.7, 3.5 Hz, 1H), 1.26 (dt, *J* = 10.2, 7.1 Hz, 6H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.70, 166.47, 152.42, 137.88, 137.84, 134.96, 132.00, 131.22, 127.67, 127.03, 125.87, 68.29, 63.68, 63.53, 61.76, 36.82, 15.14, 13.93, 13.88.

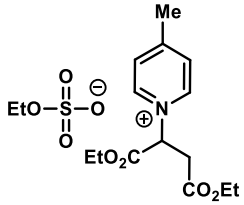


Pyridinium Salt 6k

Following the general procedure B, the starting pyridinium **S6k** (623 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 24 h. The title compound **6k** was obtained as a yellow liquid (820 mg, 76% yield).

R_f = 0.58 (CH_2Cl_2: MeOH= 5: 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.90 (dd, *J* = 6.5, 1.7 Hz, 1H), 7.67 (d, *J* = 6.5 Hz, 1H), 6.13 (dd, *J* = 7.4, 3.2 Hz, 1H), 4.35 – 4.23 (m, 3H), 4.18 – 4.08 (m, 3H), 3.77 (dd, *J* = 19.0, 7.4 Hz, 1H), 3.49 (dd, *J* = 18.9, 3.2 Hz, 1H), 3.02 (t, *J* = 6.3 Hz, 4H), 1.91 (t, *J* = 3.3 Hz, 4H), 1.34 – 1.22 (m, 9H).



Pyridinium Salt 6l

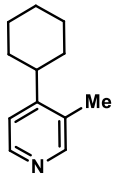
Following the general procedure B, the starting pyridinium **S6l** (523 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 18 h. The title compound **6l** was obtained as a colorless liquid (1.16 g, 84% yield).

R_f = 0.55 (CH_2Cl_2: MeOH= 5: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (d, *J* = 6.9 Hz, 2H), 7.86 (d, *J* = 6.4 Hz, 2H), 6.18 (dd, *J* = 7.9, 3.2 Hz, 1H), 4.32 (dd, *J* = 18.7, 7.2 Hz, 2H), 4.13 (dd, *J* = 16.9, 7.1 Hz, 4H), 3.76 (dd, *J* = 18.9, 7.8 Hz, 1H), 3.51 (dd, *J* = 18.9, 3.2 Hz, 1H), 2.70 (s, 3H), 1.30 (td, *J* = 7.1, 3.5 Hz, 6H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.23, 166.46, 160.61, 145.41, 128.47, 67.70, 63.68, 63.63, 61.93, 37.09, 22.38, 15.15, 14.00, 13.91.

12. Characterization of Products in Table 1 [3,4-Substituted Pyridines]



4-cyclohexyl-3-methylpyridine (34)

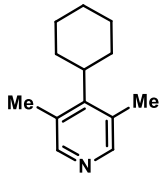
Following the general procedure C and D, the pyridinium **6b** (196 mg, 0.5 mmol) was reacted. The alkylated product **34** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 3:1), obtained as a yellow liquid (69.4 mg, 79% yield, 2 steps).

R_f = 0.30 (*n*-hexane:EtOAc = 1: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 5.1 Hz, 1H), 8.34 (s, 1H), 7.10 (d, *J* = 5.2 Hz, 1H), 2.69 (dd, *J* = 7.4, 4.1 Hz, 1H), 2.31 (s, 3H), 1.92 – 1.74 (m, 4H), 1.48 – 1.37 (m, 4H), 1.30 (dt, *J* = 12.6, 3.6 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.38, 150.73, 147.82, 130.68, 120.32, 39.79, 32.75, 26.78, 26.11, 16.02.

HRMS $[M+H]^+ = C_{12}H_{18}N^+$: calculated for 176.1439, found 176.1445



4-cyclohexyl-3,5-dimethylpyridine (35)

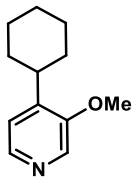
Following the procedure C and D, the pyridinium **6c** (203 mg, 0.5 mmol) was reacted. The alkylated product **35** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 3:1), obtained as a pale yellowish liquid (49.8 mg, 53% yield, 2 steps).

R_f = 0.30 (*n*-hexane:EtOAc = 1: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 2H), 3.00 – 2.89 (m, 1H), 2.37 (s, 6H), 1.91 – 1.76 (m, 4H), 1.71 – 1.64 (m, 2H), 1.43 – 1.25 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.47, 147.43 (suppressed broad peak), 130.79, 41.61, 29.73, 27.29, 26.21, 18.39 (suppressed broad peak)

HRMS $[M+H]^+ = C_{13}H_{20}N^+$: calculated for 190.1596, found 190.1601



4-cyclohexyl-3-methoxypyridine (36)

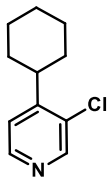
Following the procedure C and D, the pyridinium **6d** (204 mg, 0.5 mmol) was reacted. The alkylated product **36** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 2:1), obtained as a pale yellowish liquid (57.8 mg, 60% yield, 2 steps).

R_f = 0.25 (*n*-hexane:EtOAc = 1: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 4.8 Hz, 1H), 8.20 (s, 1H), 7.11 (d, *J* = 4.9 Hz, 1H), 3.93 (s, 3H), 3.02 – 2.78 (m, 1H), 1.88 – 1.75 (m, 4H), 1.48 – 1.22 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.21, 144.50, 142.93, 132.88, 121.17, 55.98, 36.40, 32.34, 26.72, 26.20.

HRMS $[M+H]^+ = C_{12}H_{18}NO^+$: calculated for 192.1388, found 192.1394



3-chloro-4-cyclohexylpyridine (37)

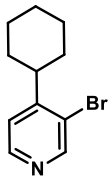
Following the procedure C and D, the pyridinium **6e** (206 mg, 0.5 mmol) was reacted. The alkylated product **37** was isolated by silica gel chromatography (*n*-hexane: diethyl ether = 4:1 to 3:1), obtained as a pale yellowish liquid (53.2 mg, 54% yield, 2 steps).

R_f = 0.20 (*n*-hexane: diethyl ether= 3: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 7.19 (d, *J* = 5.1 Hz, 1H), 3.04 – 2.96 (m, 1H), 1.93 – 1.86 (m, 4H), 1.83 – 1.78 (m, 1H), 1.52 – 1.22 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.32, 149.29, 147.91, 131.63, 121.96, 40.13, 32.17, 26.49, 25.98.

HRMS $[M+H]^+ = C_{11}H_{15}ClN^+$: calculated for 196.0893, found 196.0900



3-bromo-4-cyclohexylpyridine (38)

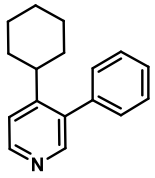
Following the procedure C and D, the pyridinium **6f** (228 mg, 0.5 mmol) was reacted. The alkylated product **38** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 10:1), obtained as a pale yellow liquid (82 mg, 68% yield, 2 steps).

R_f = 0.40 (*n*-hexane:EtOAc = 7:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 7.15 (d, *J* = 5.2 Hz, 1H), 2.98 – 2.84 (m, 1H), 1.87 (t, *J* = 11.1 Hz, 5H), 1.78 (d, *J* = 13.5 Hz, 1H), 1.49 – 1.19 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 152.0, 148.6, 123.1, 122.5, 43.0, 32.4, 26.6, 26.1.

HRMS $[M+H]^+ = C_{11}H_{15}BrN^+$: calculated for 240.0388, found 240.0394



4-cyclohexyl-3-phenylpyridine (39)

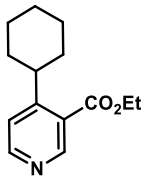
Following the general procedure C and D, the pyridinium **6g** (227 mg, 0.5 mmol) was reacted. The alkylated product **39** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 10:1 to 5:1), obtained as a pale yellowish liquid (82.3 mg, 69% yield, 2 steps).

R_f = 0.24 (*n*-hexane:EtOAc = 4: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 5.3 Hz, 1H), 8.42 (s, 1H), 7.51 – 7.41 (m, 3H), 7.34 – 7.25 (m, 2H, 1H), 2.76 – 2.64 (m, 1H), 1.82 – 1.67 (m, 5H), 1.44 (dd, *J* = 12.3, 3.3 Hz, 2H), 1.31 – 1.15 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.89, 150.38, 148.70, 138.09, 136.95, 129.44, 128.34, 127.50, 121.20, 39.63, 33.79, 26.40, 25.93.

HRMS $[M+H]^+ = C_{17}H_{20}N^+$: calculated for 238.1596, found 238.1603



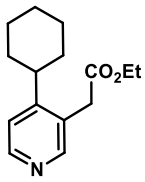
Ethyl 4-cyclohexylnicotinate (40)

Following the procedure C and D, the pyridinium **6h** (225 mg, 0.5 mmol) was reacted. The alkylated product **40** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 10:1 to 5:1), obtained as a pale yellowish liquid (74.3 mg, 64% yield, 2 steps).

R_f = 0.35 (*n*-hexane:EtOAc = 4: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.61 (d, *J* = 5.3 Hz, 1H), 7.30 (d, *J* = 5.3 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.62 – 3.22 (m, 1H), 1.93 – 1.76 (m, 5H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.50-1.28 (m, 5H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.69, 157.53, 152.15, 151.10, 126.12, 121.54, 61.29, 39.77, 33.54, 26.63, 26.05, 14.26.

HRMS $[M+H]^+$= $C_{14}H_{20}NO_2^+$: calculated for 234.1494, found 234.1502



Ethyl 2-(4-cyclohexylpyridin-3-yl)acetate (41)

Following the general procedure C and D, the pyridinium **6i** (232 mg, 0.5 mmol) was reacted. The alkylated product **41** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 4:1 to 2:1), obtained as a pale yellowish liquid (79.0 mg, 64% yield, 2 steps).

R_f = 0.22 (*n*-hexane:EtOAc = 1: 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 5.2 Hz, 1H), 8.40 (s, 1H), 7.19 (d, *J* = 5.2 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 2H), 2.72 – 2.66 (m, 1H), 1.90 – 1.84 (m, 2H), 1.84 – 1.74 (m, 3H), 1.49 – 1.35 (m, 5H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.97, 155.15, 151.29, 148.94, 127.68, 121.23, 61.15, 39.90, 36.16, 33.28, 26.66, 25.99, 14.16.

HRMS $[M+H]^+$= $C_{15}H_{22}NO_2^+$: calculated for 248.1651, found 248.1658

13. Unsuccessful or Challenging Substrates in Minisci Reaction

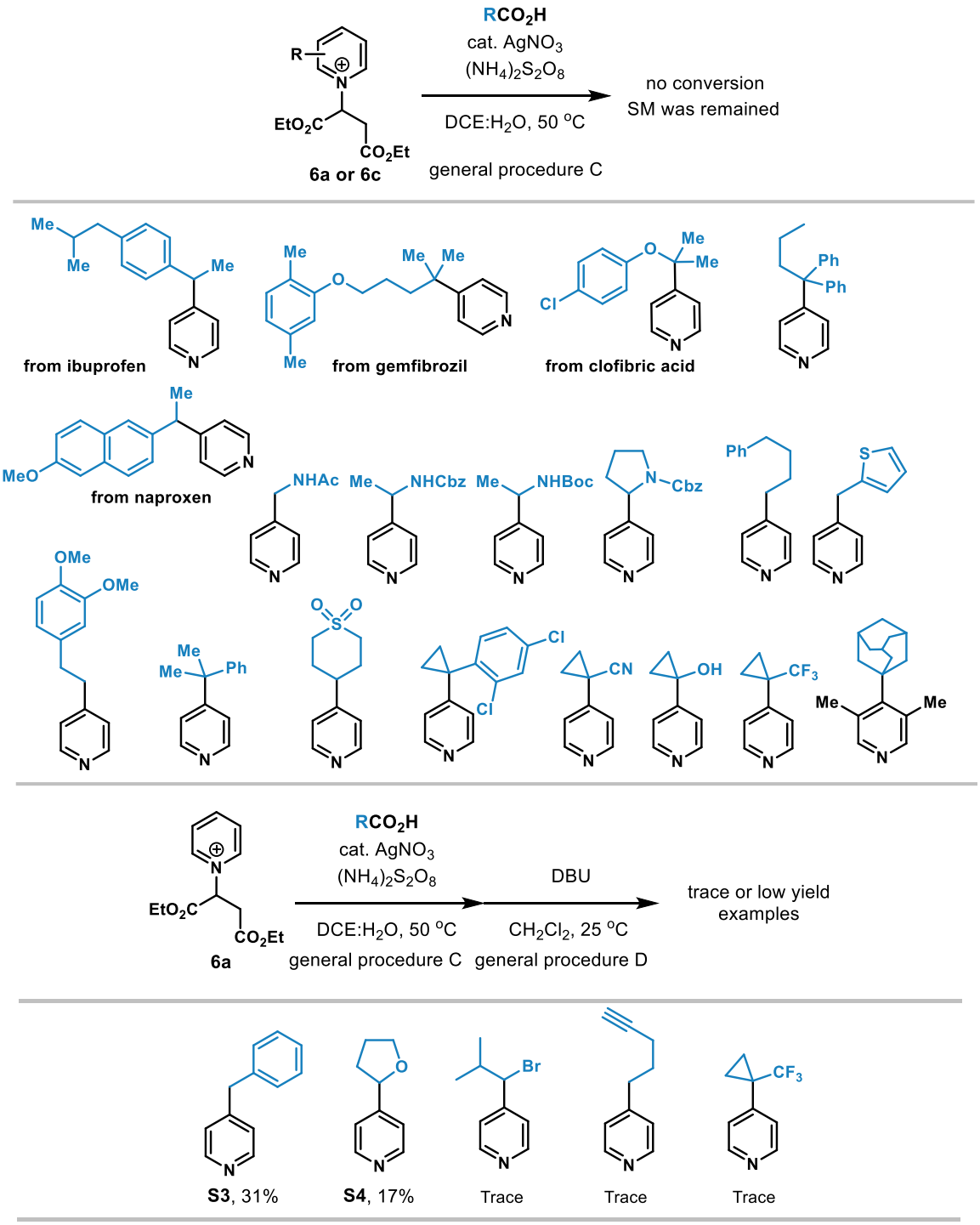


Figure S21. Unsuccessful or challenging substrates in Minisci reaction

For certain carboxylic acids tested with our product, no desired product was obserced (**Figure S21, top**). Some of the unsuccessful subtrates showed poor solubility of the carboxylic acid in the organic phase (i.e. ibuprofen, gemfibrozil, clofibric acid and naproxen), for others complete degradation of the selected starting materdial was observed (i.e. amino acids and α-functionalized cyclopropyl carboxylic acids). With other substrates, low yield or just traces of product were observed (**Figure S21, bottom**).

14. Unsuccessful or Challenging Substrates in Substituted Pyridine Examples

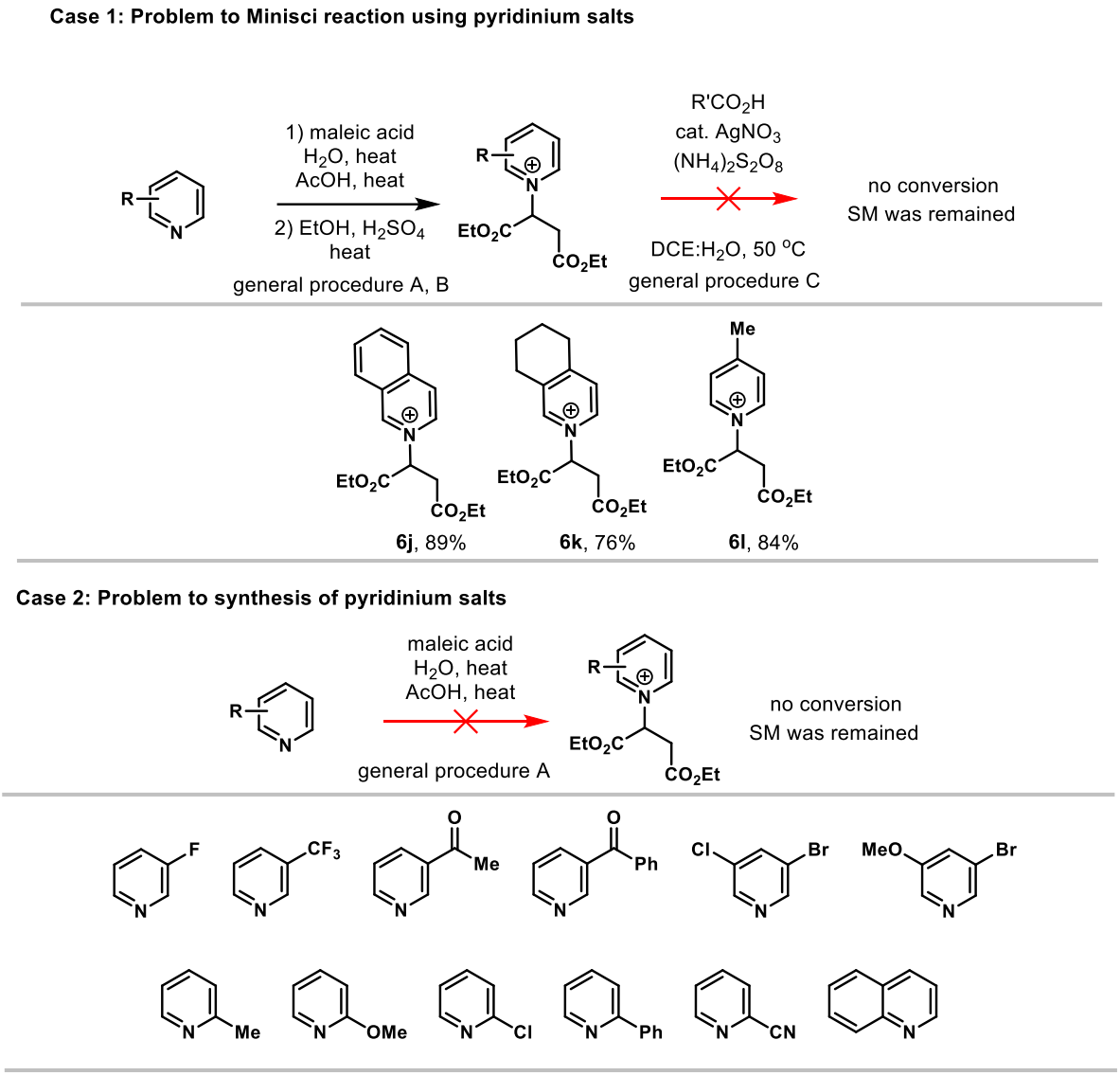


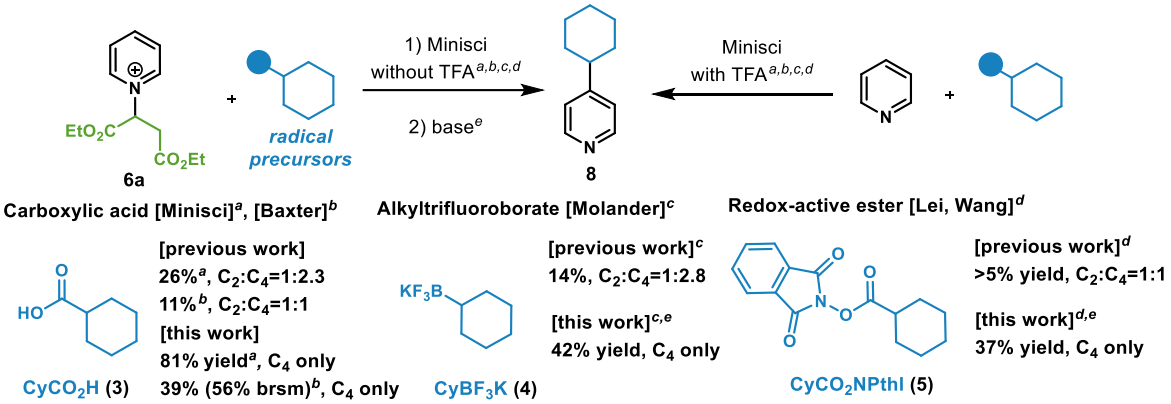
Figure S22. Unsuccessful or challenging substrates in substituted pyridine examples

In order to explore the possibilites of the pyridinium precursor, different salts were prepared as showed in the sections above. However, some limitations of our protocol were observed during the screening. 4-substituted pyridinum salts could be synthesized successfully (**Figure S22, 6j-6l**), but no product was observed when these substrates were subjected to the Minisci alkylation reaction (**Figure S22, top**).

Furthermore, no desired pyridinium carboxylate salt was obtained for certain substituted pyridines (**Figure S22, bottom**). For 2-substituted pyridines, 3-substituted, electronpoor pyridines and 3,5-disubstituted pyridines our protocol resulted ineffective and no product formation was observed.

15. Experimental Procedure and Characterization of Compounds in Applications

15.1 Comparison with Simple Pyridine Substrate in Figure 1C



a) **6a** (0.5 mmol), **3** (1.0 mmol), $AgNO_3$ (20 mol%), $(NH_4)_2S_2O_8$ (1.0 mmol), TFA (1 equiv), DCE:H_2O=1:1, 0.1 M, 50 °C, 2 h
b) **6a** (0.5 mmol), **3** (1.0 mmol), $AgNO_3$ (20 mol%), SelectFluor (1.0 mmol), TFA (1 equiv), DCE:H_2O=1:1, 0.1 M, 50 °C, 24 h
c) **6a** (0.5 mmol), **4** (0.5 mmol), $AgNO_3$ (20 mol%), $(NH_4)_2S_2O_8$ (1.5 mmol), TFA (2 equiv), DCE:H_2O=1:1, 0.1 M, 25 °C, 24 h
d) **6a** (0.5 mmol), **5** (0.6 mmol), (+)C | C(-), nBu_4NBF_4 (0.05 M), 5 mA/cm^2, TFA (1 equiv), DMA (0.1 M), 25 °C, 20 h
e) DBU (3 equiv), CH_2Cl_2 (0.1 M), 25 °C, 30 min.

Figure S23. Comparison experiments between **6a** and simple pyridine

Using 6a

Following the general procedures written above (from C to H) followed by the procedure D, the alkyl precursor radical partners were used accordingly. The compound **8** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 3:1 to 2:1), obtained as an orange liquid.

Using pyridine

Following the general procedures written above (from C to H), pyridine (40.2 µL, 0.5 mmol, 1 equiv), TFA (19 µL, 0.5 mmol, 1 equiv) the alkyl precursor radical partners were used accordingly. The regioselectivity was determined by crude ^{1}H NMR using $CDCl_3$ or CD_3OD. When possible , the compound **8** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 3:1 to 2:1), obtained as an orange liquid.

15.2 Comparison with Literature Examples

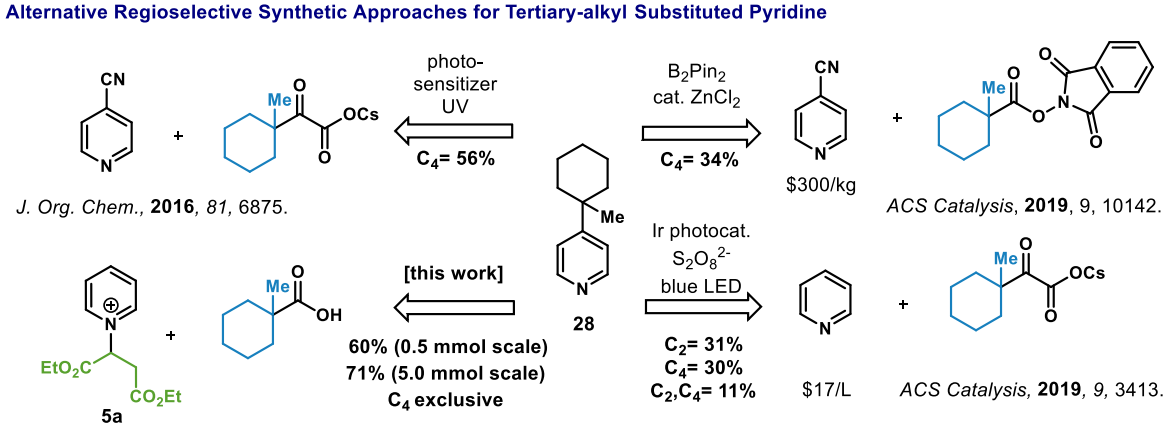
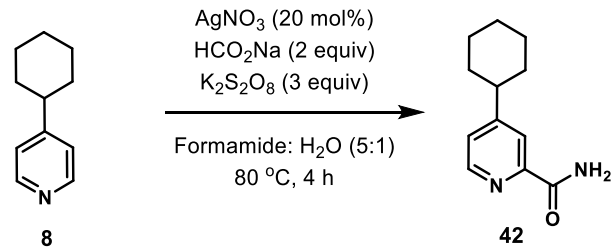


Figure S24. Alternative regioselective synthetic route

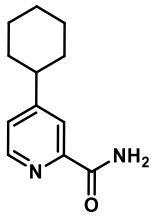
15.3 Two-Stage Derivatization

15.3.1. C-2 Carbamoylation



8 42

Following the literature procedure[11], to a 5 mL culture tube equipped with screw cap and magnetic stirbar, $AgNO_3$ (8.7 mg, 0.05 mmol, 20 mol%), $K_2S_2O_8$ (202 mg, 0.75 mmol, 3 equiv), HCOONa (34 mg, 0.5 mmol, 2 equiv) and corresponding pyridine **8** (40.3 mg, 0.25 mmol) were added, together with formamide (1 mL), and H_2O (0.2 mL). The resulting mixture was stirred at 80 °C for 4 h. At the end of the reaction, the reaction mixture was cooled to room temperature, poured into a sat. aq NaCl solution (7 mL), and extracted with EtOAc (3 × 7 mL). The organic phases were combined, evaporated in a rotary evaporator. The residue was purified by flash column chromatography on silica gel (*n*-hexane: EtOAc = 5:1 to 2:1) to afford the corresponding product **42** as colorless liquid (26.4 mg, 52% yield).



4-cyclohexylpicolinamide (42)

R_f = 0.12 (*n*-hexane:EtOAc = 2: 1)

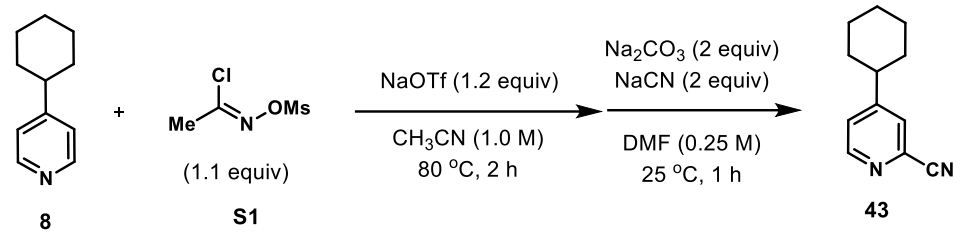
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 5.0 Hz, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 7.86 (br, 1H), 7.27 (d, *J* = 1.8 Hz, 1H), 5.77 (br, 1H), 2.63 – 2.52 (m, 1H), 1.92 – 1.82 (m, 4H), 1.80 – 1.72 (m, 1H), 1.50 – 1.37 (m, 4H), 1.35 – 1.19 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.31, 158.45, 149.61, 148.44, 125.30, 121.24, 44.10, 33.55, 26.59, 25.99.

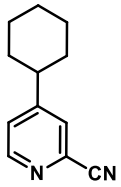
HRMS $[M+H]^+ = C_{12}H_{17}N_2O^+$: calculated for 205.1341, found 205.1348

[11] Han, W.; Jin, F.; Zhao, Q.; Du, H.; Yao, L. *Synlett* **2016**, *27*, 1854.

15.3.2. C-2 Cyanation



Following the literature procedure[1], to a 5 mL culture tube equipped with screw cap and magnetic stirbar, 4-cyclohexyl pyridine (40.3 mg, 0.25 mmol, 1.0 equiv), *N*-((methylsulfonyl)oxy)acetimidoyl chloride (**S1**, 47.2 mg, 0.275 mmol, 1.1 equiv) and sodium trifluoromethanesulfonate (NaOTf, 51.6 mg, 0.30 mmol, 1.2 equiv) were added, together with MeCN (0.25 mL, 1.0 M). Subsequently, the vial was sealed and heated at 80 °C with rapid stirring for 2 h. The reaction mixture was cooled to room temperature and diluted with DMF (1 mL), followed by the addition of Na_2CO_3 (53 mg, 0.50 mmol, 2.0 equiv) and NaCN (24.5 mg, 0.50 mmol, 2.0 equiv). The vial was sealed and stirred at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate, and washed twice with water and once with brine. The organic solution was dried over $MgSO_4$, and the product was purified on silica gel (hexane: ethyl acetate = 10:1 to 4:1). The resulting product **43** was obtained as a colorless liquid (18.3 mg, 39% yield) and starting material **8** was recovered (12.9 mg, 32%)



4-cyclohexylpicolinonitrile (43)

R_f = 0.52 (*n*-hexane:EtOAc = 4:1)

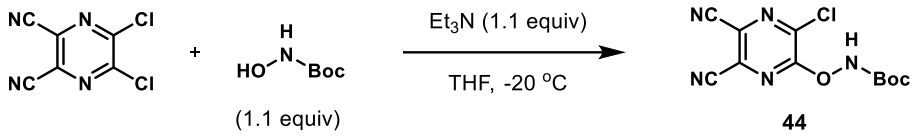
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.1 Hz, 1H), 7.57 (s, 1H), 7.39 – 7.34 (m, 1H), 2.59 (s, 1H), 1.91 (d, *J* = 8.0 Hz, 3H), 1.81 (d, *J* = 13.3 Hz, 1H), 1.43 (dt, *J* = 11.5, 6.6 Hz, 4H), 1.35 – 1.20 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.15, 150.98, 133.96, 127.38, 125.59, 117.54, 43.58, 33.31, 26.29, 25.69.

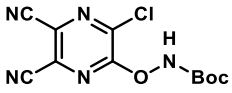
HRMS $[M+H]^+ = C_{12}H_{15}N_2^+$: calculated for 187.1235, found 187.1237

15.3.3. C-2 Amidation

Following the litearature procedure[12], Compound **45** was synthesized from the aminating reagent **44**.



Into a 100 mL round-bottom flask, 5,6-dichloropyrazine-2,3-dicarbonitrile (1.989 g, 10 mmol, 1.00 equiv), BocNHOH (1.414 g, 11 mmol, 1.10 equiv), and THF (20 mL) were added. The mixture was cooled to -20 °C and Et_3N (1.53 mL, 11 mmol, 1.10 equiv) was added dropwise over 5 min. The resulting solution was stirred for 20 min at -20 °C, the solids were filtered off, and the filtrate concentrated. The residue was purified on silica gel chromatography (*n*-hexane:ethyl acetate = 100:0 to 4:1). The desired product **44** was obtained as a pale yellow solid (1.64 g, 55% yield).



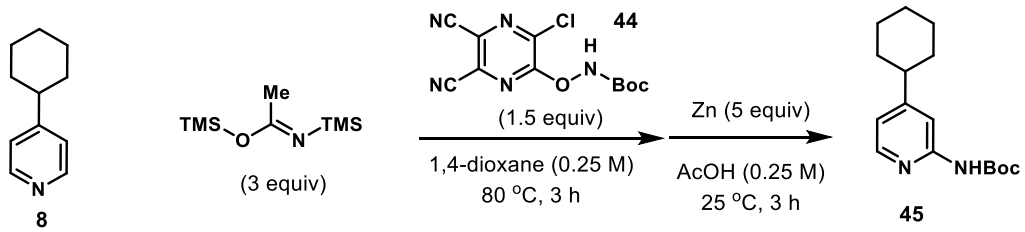
***Tert*-butyl ((3-chloro-5,6-dicyanopyrazin-2-yl)oxy)carbamate (44)**

R_f = 0.35 (*n*-hexane:EtOAc = 4:1)

^{1}H NMR (500 MHz, CD_3CN) δ 9.35 (s, 1H), 1.50 (s, 9H).

^{13}C NMR (126 MHz, CD_3CN) δ 157.8, 154.9, 140.5, 129.1, 126.5, 112.7, 112.6, 83.7, 27.2.

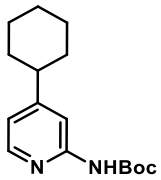
HRMS $[M-H]^-$= $C_{11}H_9ClN_5O_3^-$: calculated for 294.0394, found 294.0392



To a 5 mL culture tube equipped with screw cap and magnetic stirbar, pyridine substrate (40.3 mg, 0.25 mmol, 1.0 equiv), *N*,*O*-bis(trimethylsilyl)acetamide (183 µL, 0.75 mmol, 3.0 equiv), and anhydrous 1,4-dioxane (1 mL, 0.25 M) were added, followed by *tert*-butyl ((3-chloro-5,6-dicyanopyrazin-2-yl)oxy)carbamate (**44**, 111 mg, 1.5 equiv). Subsequently, the vial was sealed and heated at 80 °C for 3 h. The reaction mixture was then cooled to ambient temperature, diluted with glacial AcOH (1 mL), and Zn powder (81.7 mg, 1.25 mmol, 5.0 equiv) was added at once. The resulting slurry was stirred vigorously for 3 h at ambient temperature. The mixture was concentrated to dryness, and the product

[12] Fier, P. S.; Kim, S.; Cohen, R. D. *J. Am. Chem. Soc.* **2020**, *142*, 8614−8618.

was purified on silica gel (*n*-hexane: ethyl acetate = 10:1 to 1:1). The resulting product **45** was obtained as a white solid (47.8 mg, 69% yield).



***Tert*-butyl (4-cyclohexylpyridin-2-yl)carbamate (45)**

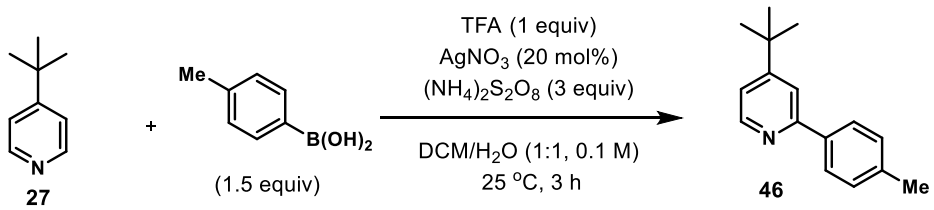
R_f = 0.58 (*n*-hexane:EtOAc = 4:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (br, 1H), 8.22 (d, *J* = 5.3 Hz, 1H), 7.88 (s, 1H), 6.82 (dd, *J* = 5.3, 1.6 Hz, 1H), 2.58 – 2.49 (m, 1H), 1.88 (dd, *J* = 19.9, 13.8 Hz, 4H), 1.82 – 1.74 (m, 1H), 1.57 (s, 9H), 1.48 – 1.35 (m, 4H), 1.35 – 1.24 (m, 1H).

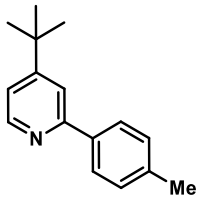
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.30, 152.90, 152.68, 147.46, 117.02, 110.90, 80.56, 44.38, 33.48, 28.41, 26.57, 25.94.

HRMS $[M\text{-}Boc+2H]^+ = C_{11}H_{16}N_2^+$: calculated for 177.1392, found 177.1394

15.3.4. C-2 Arylation



To a 5 mL culture tube equipped with screw cap and magnetic stirbar, 4-*tert*-butylpyridine (**27**, 0.35 mmol, 47 mg, 1 equiv), 4-methylphenyl boronic acid (0.525 mmol, 1.5 equiv, 71 mg), $(NH_4)_2S_2O_8$ (239 mg, 1.05 mmol, 3 equiv), $AgNO_3$ (11.7 mg, 0.07 mmol, 20 mol%) and TFA (27 µL, 0.35 mmol, 1 equiv) were added, together with dichloromethane (1.75 mL) and H_2O (1.75 mL). The resulting biphasic mixture was stirred at room tempeerature for 3 h. The reaction was monitored by TLC or LCMS. Upon completion, the reaction was neutralized with aqueous $NaHCO_3$ (5 mL) for adjusting basic pH. (pH >8). The crude mixture was diluted by dichloromethane (5 mL). The aqueous phase was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified on silica gel chromatography (*n*-Hex:EtOAc = 40:1 to 25:1). The desired product **46** was obtained as a colorless oil (41.1 mg, 52% yield). [Overall yield from **6a**, 36% yield]



4-(*tert*-butyl)-2-(p-tolyl)pyridine (46)

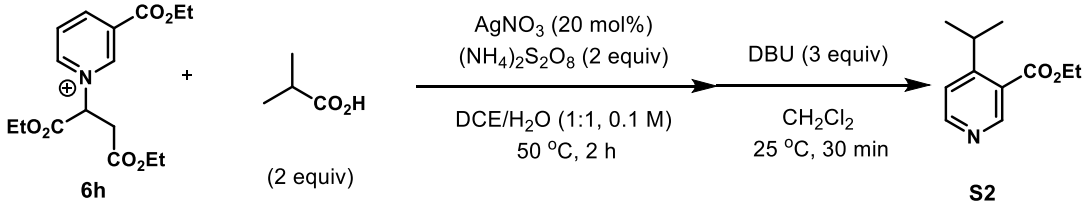
R_f = 0.35 (*n*-hexane:EtOAc = 10:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, *J* = 5.2 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.71 (s, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.23 (dd, *J* = 5.3, 1.8 Hz, 1H), 2.44 (s, 3H), 1.39 (s, 9H).

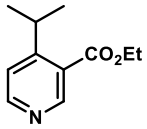
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.64, 157.53, 149.46, 138.68, 137.23, 129.42, 126.91, 119.07, 117.45, 34.86, 30.62, 21.27.

HRMS $[M+H]^+ = C_{16}H_{20}N^+$: calculated for 226.1596, found 226.1599

15.3.5. Sequential C-2 Functionalization



Following the general procedure C and D, **6h** (228 mg, 0.5 mmol, 1 equiv) and isobutyric acid (92 µL, 1.0 mmol, 2 equiv) was used in procedure C. The compound **S2** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 10:1 to 6:1), obtained as a yellow liquid (52.5 mg, 54% yield).



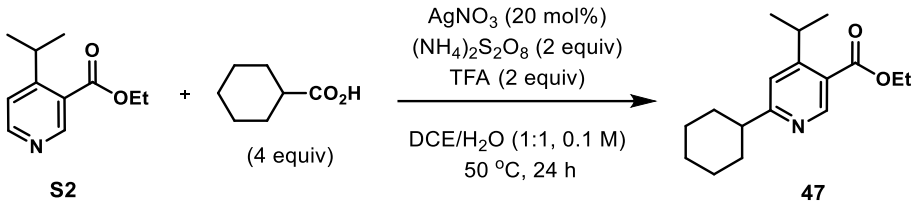
Ethyl 4-isopropylnicotinate (S2)

R_f = 0.30 (*n*-hexane:EtOAc = 4:1)

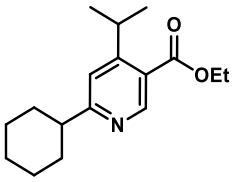
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.64 (d, *J* = 5.3 Hz, 1H), 7.34 (d, *J* = 5.3 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.82 (hept, *J* = 6.8 Hz, 1H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.29 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.60, 158.82, 152.21, 150.97, 126.03, 121.01, 61.34, 29.26, 23.12, 14.23.

HRMS $[M+H]^+ = C_{11}H_{16}NO_2^+$: calculated for 194.1181, found 194.1187



To a 8 mL culture tube equipped with screw cap and magnetic stirbar, compound **S2** (0.25 mmol, 48.3 mg, 1 equiv), cyclohexane carboxylic acid (128 mg, 1.0 mmol, 4 equiv), TFA (38 µL, 0.5 mmol, 2 equiv), $(NH_4)_2S_2O_8$ (114 mg, 0.5 mmol, 2 equiv) and $AgNO_3$ (8.3 mg, 0.05 mmol, 20 mol%) were added, together with dichloroethane (1.25 mL) and H_2O (1.25 mL). The resulting biphasic mixture was then stirred at 50 °C for 24 h. Upon completion, the reaction was diluted with dichloromethane (2 mL), saturated aq. $NaHCO_3$ (2 mL) and checked the pH above 7. The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified using silica column chromatography (n-hexane: EtOAc = 30:1 to 10:1). The resulting product **47** was obtained as a colorless liquid (44.6 mg, 65% yield) [Overall yield from **6h**, 35% yield] The minor C-2 regioisomer was determined by crude NMR, but couldn't characterize pure product (C6:C2 =10:1)



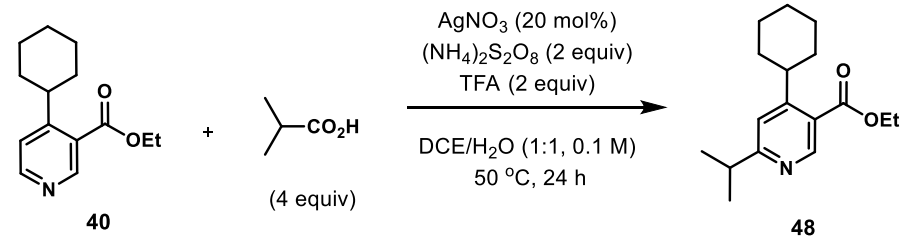
Ethyl 6-cyclohexyl-4-isopropylnicotinate (47)

R_f = 0.60 (*n*-hexane:EtOAc = 4:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.17 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.83 (hept, *J* = 6.9 Hz, 1H), 2.74 (tt, *J* = 11.9, 3.4 Hz, 1H), 2.00 – 1.84 (m, 4H), 1.78 (dtt, *J* = 12.8, 3.3, 1.5 Hz, 1H), 1.57 (qd, *J* = 12.5, 3.2 Hz, 2H), 1.50 – 1.38 (m, 5H), 1.33 (tt, *J* = 12.6, 3.4 Hz, 1H), 1.27 (d, *J* = 6.8 Hz, 6H).

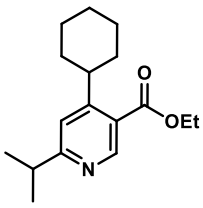
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.61, 166.76, 159.28, 150.70, 123.38, 118.19, 61.04, 46.72, 32.71, 29.22, 26.49, 25.99, 23.17, 14.24.

HRMS $[M+H]^+ = C_{17}H_{26}NO_2^+$: calculated for 276.1964, found 276.1971



To a 8 mL culture tube equipped with screw cap and magnetic stirbar, compound **40** (0.25 mmol, 58.3 mg, 1 equiv), isobutyric acid (88 mg, 1.0 mmol, 4 equiv), TFA (38 µL, 0.5 mmol, 2 equiv), $(NH_4)_2S_2O_8$ (114 mg, 0.5 mmol, 2 equiv) and $AgNO_3$ (8.3 mg, 0.05 mmol, 20 mol%) were added, together with

dichloroethane (1.25 mL) and H_2O (1.25 mL). The resulting biphasic mixture was stirred at 50 °C for 24 h. Upon completion, the reaction was diluted with dichloromethane (2 mL), saturated aq. $NaHCO_3$ (2 mL) and checked the pH above 7. The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified using silica column chromatography (*n*-hexane: EtOAc = 30:1 to 10:1). The resulting product **48** was obtained as a colorless liquid (28.2 mg, 41% yield) and the starting material **40** was recovered (23.3 mg, 40% yield). [Overall yield from **6h**, 27% yield]
The minor C-2 regioisomer was detected trace amount in crude NMR, but couldn't characterize pure product (C6:C2 =>20:1)



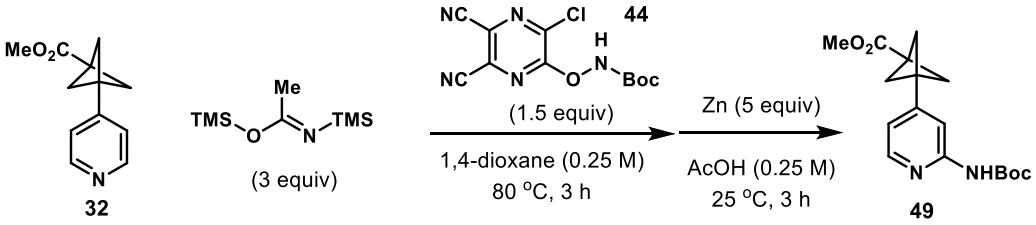
Ethyl 4-cyclohexyl-6-isopropylnicotinate (48)

R_f = 0.55 (*n*-hexane:EtOAc = 4:1)

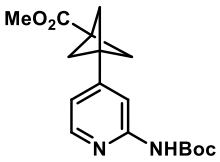
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.16 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.49 – 3.39 (m, 1H), 3.14 – 3.02 (m, 1H), 1.94 – 1.84 (m, 5H), 1.80 (d, *J* = 12.8 Hz, 1H), 1.53 – 1.36 (m, 6H), 1.32 (d, *J* = 6.9 Hz, 7H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.37, 166.86, 158.06, 150.90, 123.48, 118.38, 61.01, 39.78, 36.51, 33.61, 26.71, 26.12, 22.41, 14.26.

HRMS $[M+H]^+ = C_{17}H_{26}NO_2^+$: calculated for 276.1964, found 276.1973



To a 5 mL culture tube equipped with screw cap and magnetic stirbar, the pyridine substrate **32** (50.1 mg, 0.25 mmol, 1.0 equiv), *N*,*O*-bis(trimethylsilyl)acetamide (183 µL, 0.75 mmol, 3.0 equiv), and anhydrous 1,4-dioxane (1 mL, 0.25 M) were added, followed by the addition of *tert*-butyl ((3-chloro-5,6-dicyanopyrazin-2-yl)oxy)carbamate (**44**, 111 mg, 1.5 equiv) Subsequently, the vial was sealed and heated at 80 °C for 3 h. The reaction mixture was cooled to ambient temperature, diluted with glacial AcOH (1 mL), and Zn powder (81.7 mg, 1.25 mmol, 5.0 equiv) was added at once. The resulting slurry was stirred vigorously for 3 h at ambient temperature. The mixture was concentrated to dryness, and the product was purified on silica gel (*n*-hexane: ethyl acetate = 2:1 to 1:1). The resulting product **49** was obtained as a white solid (66.3 mg, 83% yield) [Overall yield from **6a**, 35% yield]



Methyl 3-(2-((tert-butoxycarbonyl)amino)pyridin-4-yl)bicyclo[1.1.1]pentane-1-carboxylate (49)

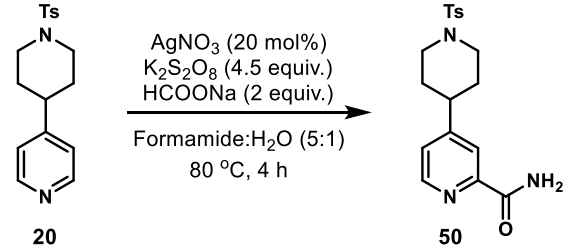
R_f = 0.55 (*n*-hexane:EtOAc = 2:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.22 (dd, *J* = 5.2, 0.9 Hz, 1H), 7.79 (s, 1H), 6.78 (dd, *J* = 5.1, 1.5 Hz, 1H), 3.71 (s, 3H), 2.35 (s, 6H), 1.54 (s, 9H).

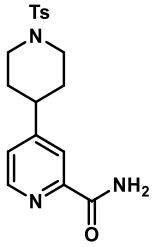
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.40, 152.79, 152.74, 150.73, 147.72, 116.16, 109.91, 81.04, 53.40, 51.91, 41.29, 37.29, 28.51, 28.36.

HRMS $[M+H]^+ = C_{17}H_{23}N_2O_4^+$: calculated for 319.1658, found 319.1655

15.3.6. Intermediate Synthesis For Oomycetes Fungicide Candidate



Following a modified literature procedure [8], to a 5 mL culture tube equipped with screw cap and magnetic stirbar, $AgNO_3$ (9.0 mg, 0.05 mmol, 20 mol%), $K_2S_2O_8$ (101 mg, 0.375 mmol, 1.5 equiv), HCOONa (34 mg, 0.5 mmol, 2 equiv) and corresponding pyridine **20** (40.3 mg, 0.25 mmol) were added, together with formamide (1 mL), and H_2O (0.2 mL). While the resulting mixture was stirred at 80 °C other 2 portions of $K_2S_2O_8$ (2x101 mg, 0.375 mmol, 1.5 equiv) were added after 1 hour and 2 hours. The mixture was then stirred at the same temperature for other 2 hours. At the end of the reaction, the reaction mixture was cooled to room temperature, poured into a sat. aq NaCl solution (7 mL), and extracted with EtOAc (3 × 7 mL). The organic phases were combined, evaporated in a rotary evaporator. The residue was purified by flash column chromatography on silica gel (EtOAc) to afford the corresponding product **50** as white solid (53.9 mg, 60% yield).



4-(1-tosylpiperidin-4-yl)picolinamide (50)

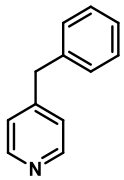
R_f = 0.60 (EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 – 8.46 (m, 1H), 8.01 (d, *J* = 1.8 Hz, 1H), 7.86 (br, 1H), 7.71 – 7.65 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.24 (dd, *J* = 5.1, 1.9 Hz, 1H), 5.73 (br, 1H), 3.95 (dp, *J* = 11.7, 1.9 Hz, 2H), 2.52 (tt, *J* = 12.0, 3.9 Hz, 1H), 2.45 (s, 3H), 2.37 (td, *J* = 12.0, 2.8 Hz, 2H), 1.97 – 1.78 (m, 5H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.73, 155.48, 149.82, 148.71, 143.86, 133.26, 129.88, 127.87, 124.68, 121.39, 46.49, 41.33, 31.72, 21.69.

HRMS $[M+H]^+ = C_{18}H_{22}N_3O_3S^+$: calculated for 360.1382, found 360.1391

15.4 Limitation: Unsuccessful or Low Yield Examples

15.4.1. Minisci (type) Reaction



4-benzylpyridine (S3)

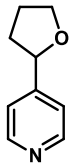
Following the general procedure C and D, phenylacetic acid (272 mg, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450 µL, 3.0 mmol, 6 equiv) was used in procedure D [**Table 1, footnote b**]. The compound **S3** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a brown solid (25.9 mg, 26% yield).

R_f = 0.25 (*n*-hexane:EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.2 Hz, 4H), 7.32 (t, *J* = 7.4 Hz, 4H), 7.24 (t, *J* = 7.0 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 4H), 7.12 (d, *J* = 5.2 Hz, 4H), 3.98 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 149.6, 138.9, 129.2, 128.9, 126.9, 124.4, 41.4.

HRMS $[M+H]^+ = C_{12}H_{12}N^+$: calculated for 170.0970, found 170.0974



4-(tetrahydrofuran-2-yl)pyridine (S4)

Reaction with the tetrahydrofuran-2-carboxylic acid as a radical precursor

Following the general procedure C and D, tetrahydrofuran-2-carboxylic acid (116 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **S4** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 2:1 to 1:3), obtained as an orange liquid (12.5 mg, 17% yield).

Reaction with THF as a radical precursor

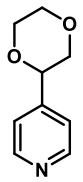
Following the general procedure H and D, tetrahydrofuran (81 µL, 1.0 mmol, 2 equiv) was used in procedure H. The compound **S4** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 2:1 to 1:3), obtained as a pale yellow solid (25.4 mg, 34% yield).

$\mathbf{R_f}$ = 0.15 (*n*-hexane:EtOAc = 1:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 5.1 Hz, 2H), 7.28 (d, *J* = 5.5 Hz, 2H), 4.93 (t, *J* = 7.2 Hz, 1H), 4.15 – 4.07 (m, 1H), 3.99 (q, *J* = 7.4 Hz, 1H), 2.41 (dq, *J* = 13.2, 6.9 Hz, 1H), 2.03 (tt, *J* = 13.8, 5.8 Hz, 2H), 1.79 (dq, *J* = 12.4, 7.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.94, 149.61, 120.53, 79.08, 68.97, 34.32, 25.83.

HRMS $[M+H]^+ = C_9H_{12}NO^+$: calculated for 150.0919, found 150.0919



4-(1,4-dioxan-2-yl)pyridine (S5)

Following the general procedure H and D, 1,4-dioxane (85 µL, 1.0 mmol, 2 equiv) was used in procedure H. The compound **S5** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:2), obtained as a pale yellow solid (37.1 mg, 45% yield).

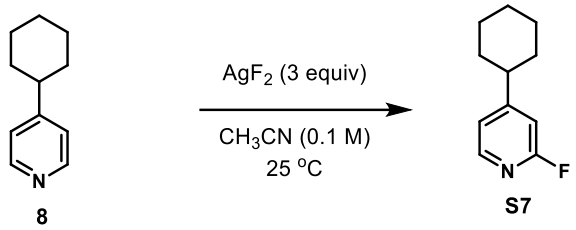
$\mathbf{R_f}$ = 0.35 (*n*-hexane:EtOAc = 1:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, *J* = 6.1 Hz, 2H), 7.31 – 7.26 (m, 2H), 4.65 (dd, *J* = 10.1, 2.9 Hz, 1H), 3.93 (ddd, *J* = 22.6, 12.3, 2.8 Hz, 3H), 3.85 – 3.70 (m, 2H), 3.40 (dd, *J* = 11.7, 10.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.91, 146.97, 120.88, 76.27, 71.84, 66.86, 66.35.

HRMS $[M+H]^+ = C_9H_{12}NO_2^+$: calculated for 166.0868, found 166.0873

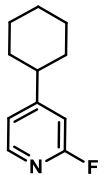
15.4.2. C2-Fluorination



8 S7

The reaction was performed followed by Fier & Hartwig procedure[13]

To an oven-dried 5 mL culture tube, 4-cyclohexylpyridine **8** (40.3 mg, 0.25 mmol, 1 equiv) and anhydrous acetonitrile (2.5 mL) were added. While the solution was stirring rapidly, AgF_2 (109 mg, 0.75 mmol, 3 equiv) was added at once. The reaction vial was sealed with a Teflon-lined cap with Ar balloon and stirred at room temperature for 2 h. The reaction was completed, poured into a separatory funnel containing 10 mL of saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was washed once with 10 mL of brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by silica gel chromatography (*n*-Hex:EtOAc = 50:1 to 30:1) to obtained the title compound **S7** as a colorless liquid (4.9 mg, 11% yield, 85% starting material (**8**) was remained)



4-cyclohexyl-2-fluoropyridine (S7)

R_f = 0.42 (*n*-hexane:EtOAc = 10:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 5.2 Hz, 1H), 7.03 (d, *J* = 4.8 Hz, 1H), 6.77 (s, 1H), 2.62 – 2.52 (m, 1H), 1.90 (t, *J* = 6.1 Hz, 4H), 1.83 – 1.75 (m, 1H), 1.42 (dd, *J* = 11.7, 8.8 Hz, 4H), 1.34 – 1.22 (m, 1H).

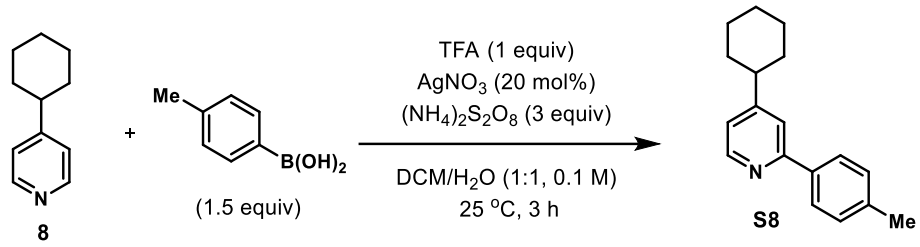
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.21 (d, *J* = 237.5 Hz), 162.76 (d, *J* = 7.4 Hz), 147.28 (d, *J* = 15.3 Hz), 120.21 (d, *J* = 3.9 Hz), 107.47 (d, *J* = 36.6 Hz), 43.80 (d, *J* = 2.7 Hz), 33.41, 26.40, 25.84.

^{19}F NMR (376 MHz, $CDCl_3$) δ -71.78.

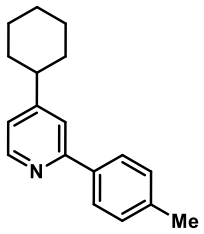
HRMS $[M+H]^+ = C_{11}H_{15}FN^+$: calculated for 180.1189, found 180.1193

[13] Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 10139–10147.

15.4.3. C-2 Borono Minisci Arylation



To a 5 mL culture tube equipped with screw cap and magnetic stirbar, 4-cyclohexylpyridine **8** (0.25 mmol, 40.3 mg, 1 equiv), 4-methylphenyl boronic acid (0.375 mmol, 1.5 equiv, 51 mg), $(NH_4)_2S_2O_8$ (171 mg, 0.75 mmol, 3 equiv), $AgNO_3$ (8 mg, 0.05 mmol, 20 mol%) and TFA (19 µL, 0.25 mmol, 1 equiv) were added, together with dichloromethane (1.25 mL) and H_2O (1.25 mL). The resulting biphasic mixture was stirred at room temperature for 3 h. The reaction was monitored by TLC or LCMS. Upon completion, the reaction was neutralized with aqueous $NaHCO_3$ (5 mL) for adjusting basic pH above 8. The crude mixture was diluted by dichloromethane (5 mL). The aqueous phase was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified on silica gel chromatography (*n*-Hex:EtOAc = 30:1 to 15:1). The desired product **S8** was obtained as a colorless oil (8.9 mg, 14% yield).



4-cyclohexyl-2-(p-tolyl)pyridine (S8)

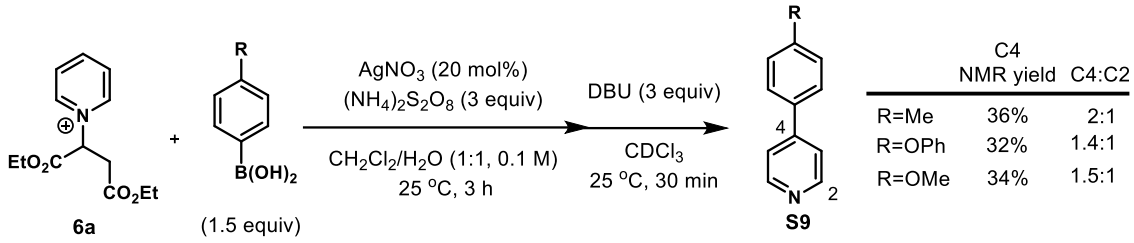
R_f = 0.24 (*n*-hexane:EtOAc = 15:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, *J* = 5.1 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 2H), 7.56 (s, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.07 (dd, *J* = 5.1, 1.7 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.43 (s, 3H), 1.98 – 1.85 (m, 4H), 1.81 (dt, *J* = 13.1, 1.6 Hz, 1H), 1.53 – 1.24 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.50, 157.29, 149.50, 138.69, 136.98, 129.41, 126.84, 120.61, 119.10, 44.16, 33.62, 26.60, 25.99, 21.27.

HRMS $[M+H]^+ = C_{18}H_{22}N^+$: calculated for 252.1752, found 252.1757

15.4.4. Borono-Minisci Arylation with pyridinium 6a



	C4 NMR yield	C4:C2
R=Me	36%	2:1
R=OPh	32%	1.4:1
R=OMe	34%	1.5:1

Following the known literature procedure for borono-Minisci reaction[14], to a 5 mL culture tube equipped with screw cap and magnetic stirbar, pyridinium salt **6a** (0.5 mmol, 188 mg, 1 equiv), 4-substituted aryl- boronic acid (0.75 mmol, 1.5 equiv), $(NH_4)_2S_2O_8$ (342 mg, 1.5 mmol, 3 equiv) and $AgNO_3$ (17 mg, 0.1 mmol, 20 mol%) were added, together with dichloromethane (2.5 mL) and H_2O (2.5 mL). The resulting biphasic mixture was stirred at room temperature for 3 h. Upon completion, the crude mixture was diluted by dichloromethane (5 mL). The aqueous phase was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The obtained crude mixture was used without further purification step. The regioselectivity was determined by crude ^{1}H NMR in $CDCl_3$.

To the crude mixture in $CDCl_3$ (5 mL, 0.1 M) DBU (225 µL, 1.5 mmol, 3 equiv) was added, and the reaction mixture was stirred at room temperature for 30 min. Upon the reaction completion, dimethyl sulfone (23.6 mg, 0.25 mmol, 0.5 equiv.) was added to reaction mixture as an internal standard for NMR analysis. The resulting mixture was directly analyzed by ^{1}H NMR to determine NMR yield and regioselectivity. Chemical shifts of crude mixture could be matched with known spectrum data from literature.[14], [15]

General Procedure for Reaction Screening

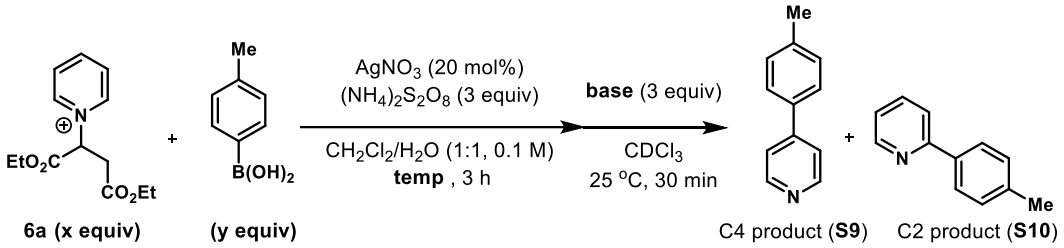
To a 5 mL vial equipped with screw cap and magnetic stirbar, pyridinium salt **6a** (0.25 mmol, 94 mg, 1 equiv), 4-methyl phenyl boronic acid (0.375 mmol, 1.5 equiv), $(NH_4)_2S_2O_8$ (171 mg, 0.75 mmol, 3 equiv) and $AgNO_3$ (8 mg, 0.05 mmol, 20 mol%) were added, together with dichloromethane (1.25 mL) and H_2O (1.25 mL). The resulting biphasic mixture was stirred at the chosen temperature for 3 h. Upon completion, the crude mixture was diluted by dichloromethane (2.5 mL). The aqueous phase was extracted with dichloromethane (3 x 2.5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was added bases (0.75 mmol, 3 equiv) in $CDCl_3$ (2.5 mL, 0.1 M). and the reaction mixture was stirred at room temperature for 30 min. Upon the reaction completion, dimethyl sulfone (11.8 mg, 0.125 mmol, 0.5 equiv.) was added to reaction mixture as an internal standard for NMR analysis. The resulting mixture was directly analyzed by ^{1}H NMR, determeined NMR yield and regioselectivity.

[14] Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010,** *132*, 13194-13196

[15] Bartolomeu, A. d. A.; Silva, R. C.; Brocksom, T. J.; Noël, T.; de Oliveira, K. T. *J. Org. Chem*. **2019**, *84*, 10459-10471.

In order to investigate the Borono-Minisci Arylation, different reaction temperatures (from 0°C to 50°C, Figure S25) were screened. As a result, room temperature led to the best performarce, but in all cases low selectivity was observed. Similar outcome was observed during the optimization of the reaction stoichiometry. Finally, different bases for the deprotection step were tested in order to maximise the yield of the final product, revealing that sodium methoxide can efficiently release the BG leading to the mixture of C-2/C-4 products in good yield.

In conclusion, low regioselectivity of borono Minisci reaction employing Csp^2(aryl)-centered radical was observed. Nevertheless, the C-4/C-2 product ratio seems improved comparing the results with the original method (C-4/C-2 1.6:1 vs 1:2 observed in the original method), proving the efficacy of the BG approach even in this case. The lower selectivity can be attributed to the reduced hindrance of the aryl radical compared to the alkyl ones. For this reason, the efficacy of the BG installed on the pyridine ring results attenuated.



temp.	x:y	base	C4 NMR yield	C4:C2
0 °C	1:1.5	DBU	22%	2.2:1
25 °C	1:1.5	DBU	36%	1.7:1
50 °C	1:1.5	DBU	31%	1.5:1
25 °C	1:1.5	K_2CO_3	trace	N/D
		Cs_2CO_3	trace	N/D
		K_3PO_4	trace	N/D
		KOH	0%	N/D
		NMP	0%	N/D
		TEA	26%	1.6:1
		DMAP	35%	1.5:1
		KO*t*Bu	20%	N/D
		NaOMe	54%	1.6:1
25 °C	1 : 2	DBU	33%	1.6:1
	1 : 2	**NaOMe**	**60%**	**1.6:1**
	2 : 1	NaOMe	N/D	1.3:1

Figure S25. Optimization of borono-Minisci reaction with pyridinium salt **6a**

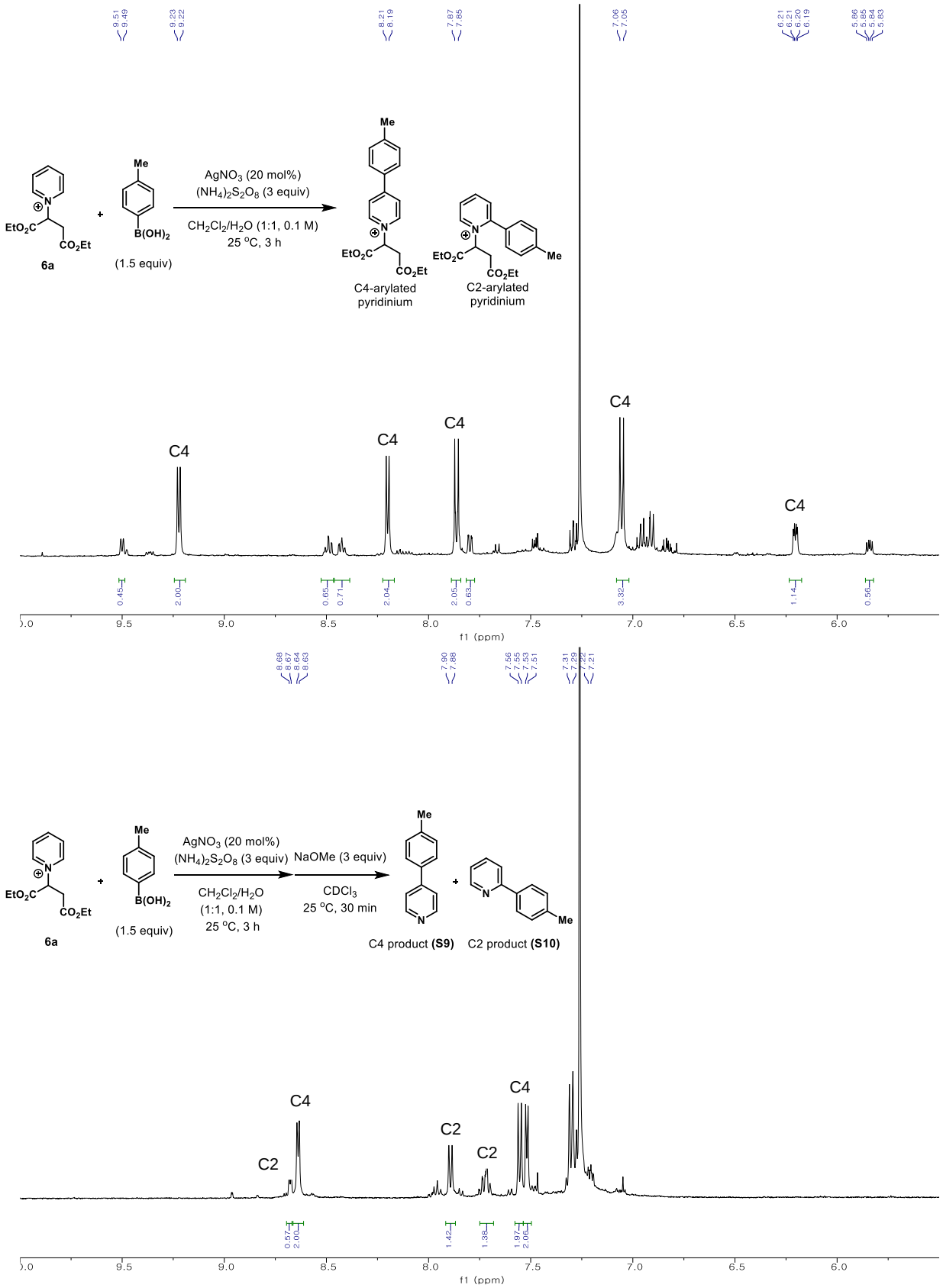


Figure S26. Crude ^{1}H NMR spectrum in $CDCl_3$ after borono-Minisci reaction (**top**) deprotection reaction using NaOMe (**bottom**)

15.5 Mock Medicinal Chemistry and Process Chemistry [Figure 3C]

Following the general procedure C and D, pyridinium **6a** (1.88 g, 5.0 mmol, 1 equiv), 1-adamantyl carboxylic acid (1.80 g, 10.0 mmol, 2 equiv), $AgNO_3$ (167 mg, 1.0 mmol, 20 mol%), $(NH_4)_2S_2O_8$ (2.28 g, 10.0 mmol, 2 equiv) was added in dichloroethane (25 mL) and H_2O (25 mL) in procedure C and DBU (2.25 mL, 15.0 mmol, 3 equiv) was used in procedure D. After the deprotection step, the crude mixture was washed by brine (20 mL x 3 times), dried using anhydrous sodium sulfate, filtered and concentrated by rotavap. The crude mixture was dissolved in hexane (100 mL) and aq. 1 *N* HCl (50 mL) to adjust pH below 1. These two phase mixture was poured into seperatory funnel, washed hexane (50 mL x 3 times). The aqueous layer was treated by aq. 1 *N* NaOH to adjust pH above 10, extracted by ethyl acetate (25 mL x 3 times). The combined organic layer was dried by anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The desired product **26** was obtained as a yellow crystalline solid (1.012 g, 94% yield, 93% NMR purity).

16. Troubleshooting: Frequently Asked Questions

Question 1: Which precautions need to be taken to run this reaction?
Answer: All the employed reagents were used without any special handling. The reaction was performed under air without degassing. All of the solvent were used in HPLC grade.

Question 2: How important is stirring for this reaction?
Answer: Since the classical Minisci reaction is a biphasic reaction, stirring is important for the reaction rate. Our preferred stirring rate is above 1000 rpm which was sufficent to mix efficiently the two phases.

Question 3: What are the observed byproducts of this reaction?
Answer: Most of the crude NMR of the performed Minisci reactions were very clean. An excess of carboxylic acid and unreacted starting material remained in the organic layer but we could not trace any byproduct in aqueous phase. In the deprotection step using DBU, we observed that a stoichiometic amount of diethyl maleate was formed. This nonpolar product could be isolated and recovered by column chromatography. We also observed a yellow colored byproduct in low yield entries which was containing aliphatic moieties after the deprotection step.

Question 4: What can I do if I observe poor conversion in the Minisci reaction?
Answer: You can increase the reaction time. Alternatively, you can use more carboxylic acid such as 4 equiv. instead of 2, this usually helps to get a better yield. We also found concentrated reaction conditions (0.3 M) would be helpful to improve the conversion rate. We would not recommend to increase the temperature as leads to less efficient reactions, based on experimental result (see, **Figure S17**, page S24).

Question 5: How do I monitor the reaction?
Answer: We have optimized the reaction time for the benchmark reaction, indicating 1.5 h is enough for full conversion in 0.5 mmol scale. For this reason, we chose a reaction time of 2 hours for each substrate. However, if you observe partial conversion for your reaction, you can use TLC analysis with UV visualization (254 nm) to see the starting material if it is UV active and $KMnO_4$ stain for non-UV active substrates. Also, we frequently analyzed aliquot of organic phase using ^1H NMR in $CDCl_3$ to conversion and regioselectivity.

Question 6: Does longer reaction time cause a drop in yield?
Answer: We did not observe any loss in yield within 12 h. However, in the case of compound **19** we left the reaction running for 48 h and a yield drop was observed (71% to 38%). Therefore we recommend to monitor your reaction if longer time is needed.

Question 7: Are the alkylated products volatile?
Answer: Some alkylated products with low molecular weight or without funtional groups are generally volatile. All the information regarding the volatile products obtained in this manuscript were mentioned in characterization section of each compound. You can keep the temperature of rotavap water bath below 40 °C and the pressure of rotavap higher than 100 mbar.

Question 8: The Minisci reaction is two-phase reaction. Does the yield drop in a larger scale?
Answer: We obtained similar yield when scaling up the reaction to gram scale. Larger scale was not tested.

Question 9: What are the limitations of this regioselective Minisci reaction?

Answer: "Polar carboxylic acid" (we define "polar" carboxylic acids as some acid substrates bearing polar group such as N, O heteroatom) are generally not compatible with this method. This is probably due to the behaviour of this polar acids which are not prone to go the organic phase, therefore the reaction does not proceed. Primary carboxylic acid gave low yield when they used standard condition, so we changed equivalent of carboxylic acid (from 2 equiv to 4 equiv), observing improved yields. Please see "Unsuccessful or Challenging Substrates in This Study" section (see **Figure S21**., page S49) for the problematic substrates we have tried.

Question 10: What are the limitations of the pyridinium salts preparation protocol?

Answer: Please see " Unsuccessful or Challenging Substrates in Substituted Pyridine Examples" section (see **Figure S22**., page S50) for the problematic substrates we have tried. Most of observed byproduct in unsuccessful cases is the salt formed by the maleic acid and 3-substituted pyridine. All of the 2-substituted pyridine and quinoline were recovered without any conversion.

Question 11: How do I choose the appropriate conditions if I am using an expensive carboxylic acid?

Answer: The criteria for how to choose conditions depend on the value of the substrates. More specifically, if the carboxylic acid is more precious than the pyridiniunìm salt such as compound **32**, you should choose the conditions where the carboxylic acid is employed as limiting reagent (see General procedure C).

Question 12: How can I scale-up these Minisci reactions?

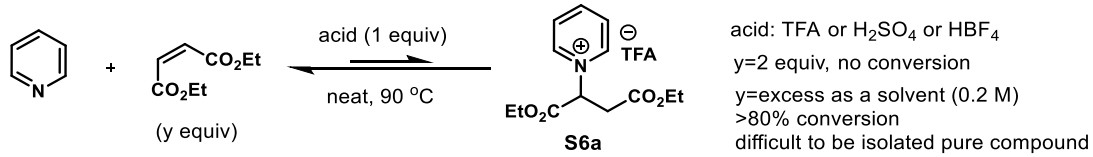
Answer: You can scale up to gram-scale both of the Minisci and the deprotection reaction, according to the procedures we provided (see **Figure S19.**, page S24). Larger scale reactions than what reported in the manuscript have not been tested. For 5 mmol scale reaction, the deprotection step using DBU is slightly exothermic, so we recommend to keep the temperature of the vessel below 30 °C using water bath.

Question 13: Why do we need an extraction for both the steps?

Answer: We tried to develope the one-pot reaction without an intermediate extraction step, however all our attempts led to less efficient processes. We think that the role of extraction in the Minisci step is essential to eliminate the water soluble sulfates, persulfates and silver salts, which are detrimental for the deprotection step. Furthermore, the role of extraction step in the deprotection reaction is to remove excess of carboxylic acid and DBU, facilitating the isolation of the desired product.

Question 14: Is it possible to obtain the pyridinium salt 6a via one-step procedure using diethyl fumarate or maleate?

Answer: We tried to test reaction at the early-stage to adopt this approach. Several attempts were performed in acidic media, but we could only get the product **S6a** with diethyl maleate as a solvent [1 equiv TFA, 1 equiv pyridine, diethyl maleate (0.2 M), neat, 90 °C, 12 h]. This procedure had several limitations regarding the elimination of the excess of diethyl maleate and the purification of **S6a**. Based on the experimental results, we could not apply this procedure at large scale because of the reversibility of the Micheal addition.

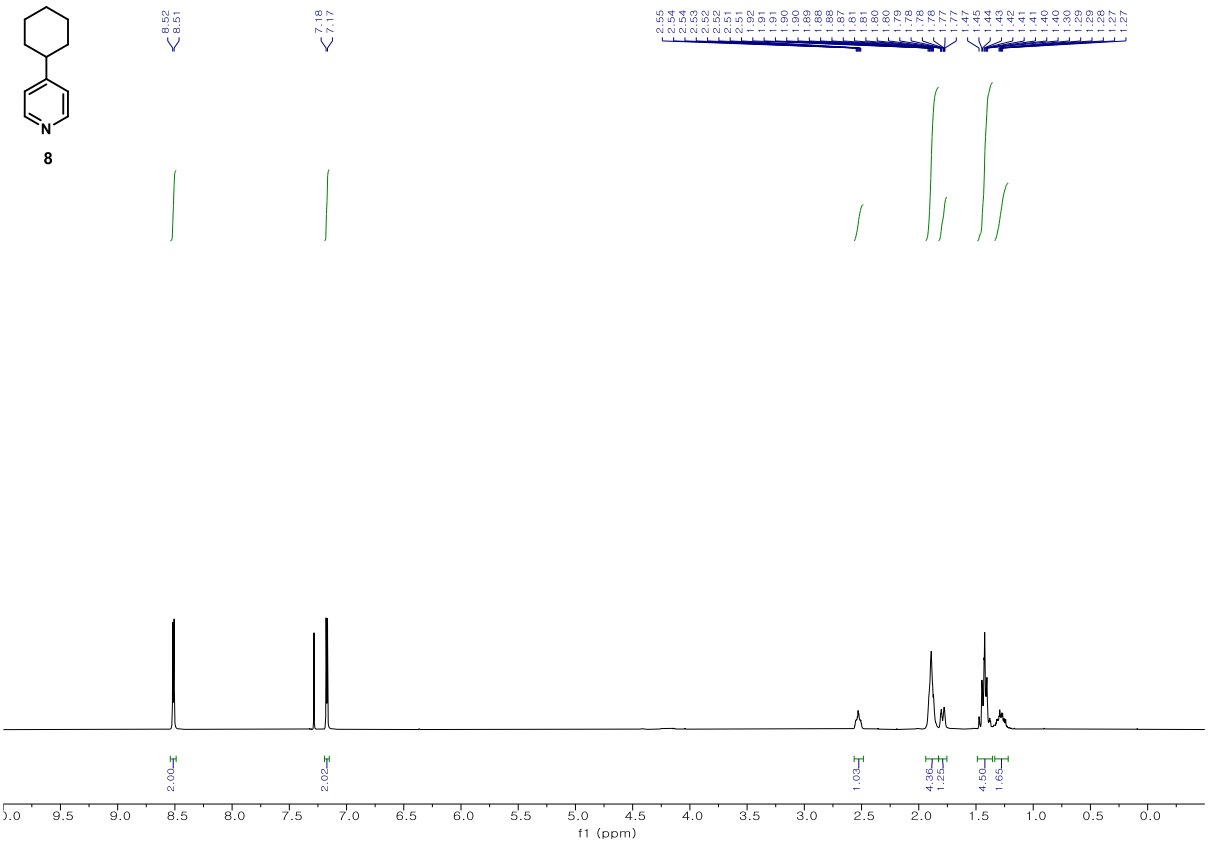


Question 15: Is it possible to obtain the pyridinium salt 6a via one-pot procedure without isolating the carboxylate intermediate?

Answer: We tried to carry out the synthesis one pot, but the presence of water undermines the esterification step. Therefore is recommended to isolate and dry the carboxylate intermediate to guarantee the success of the esterification step.

Appendix

Spectra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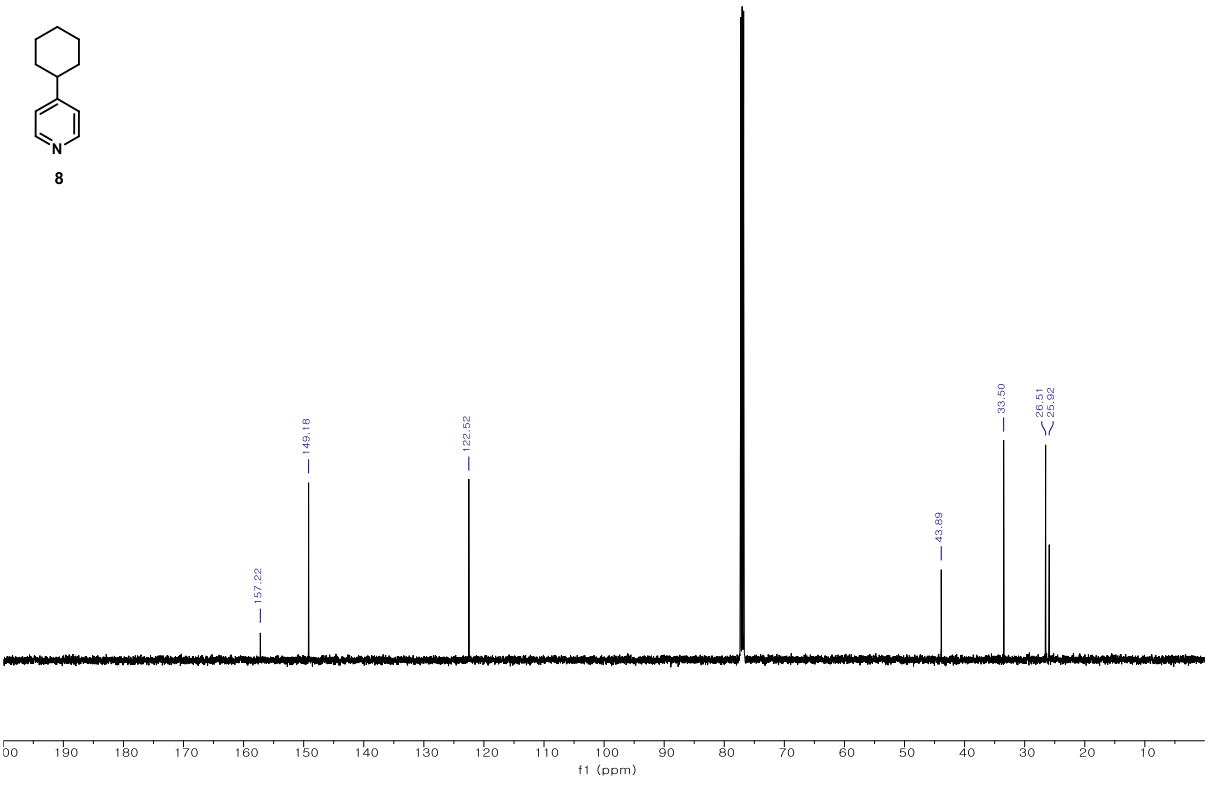
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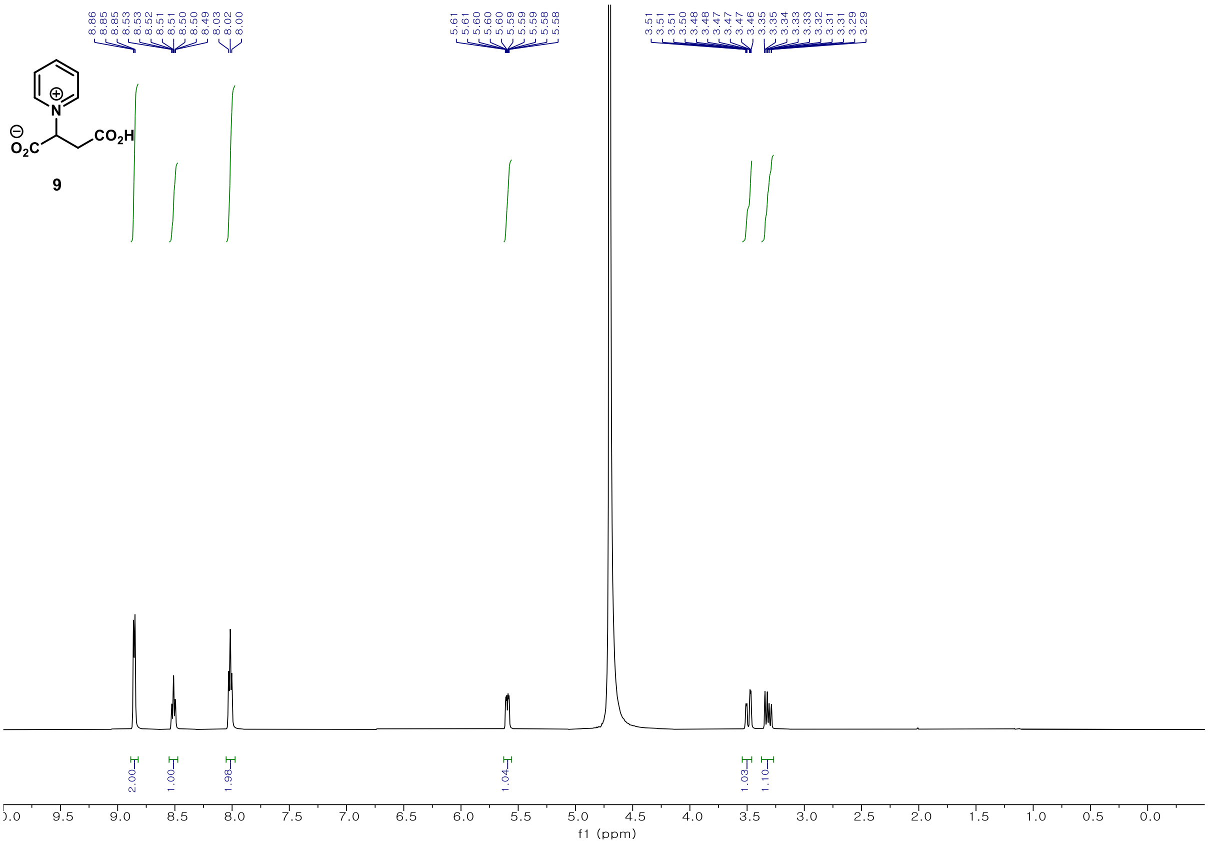
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3.29
3.29
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O2C
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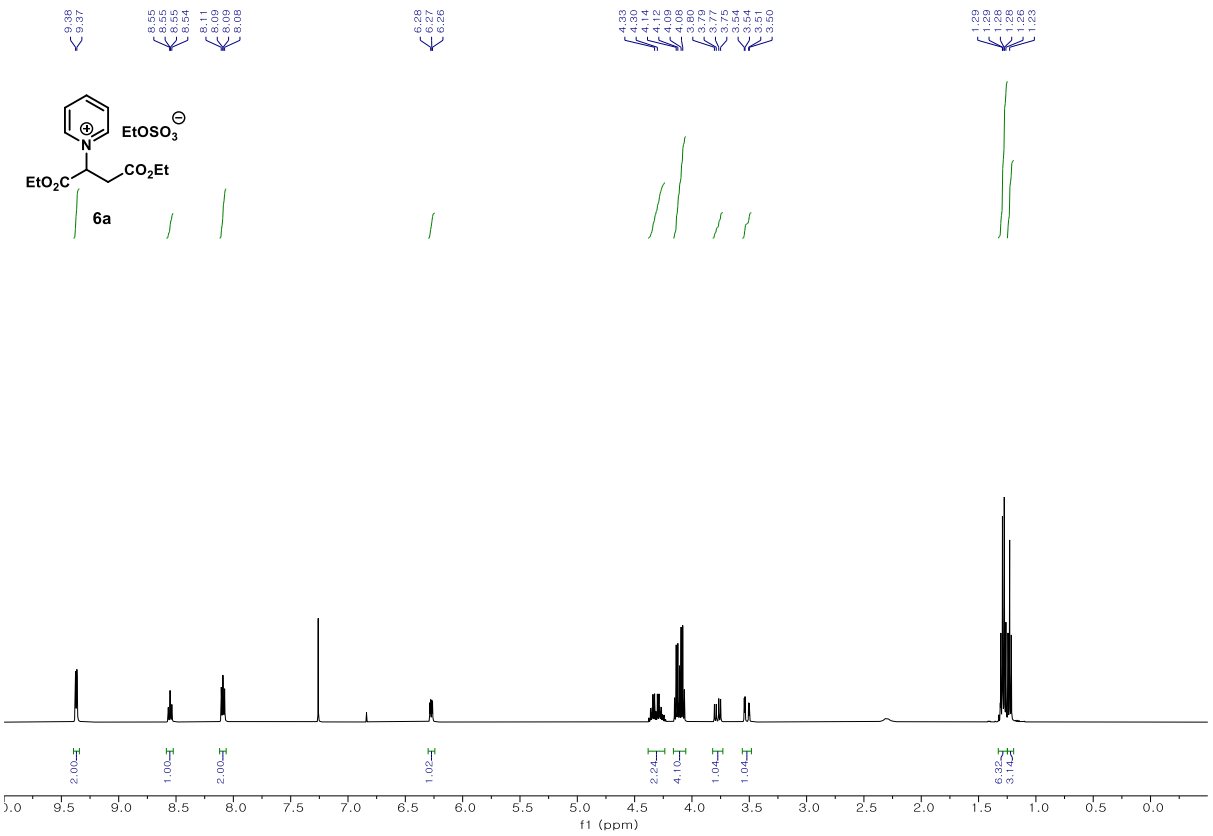
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CO2Et
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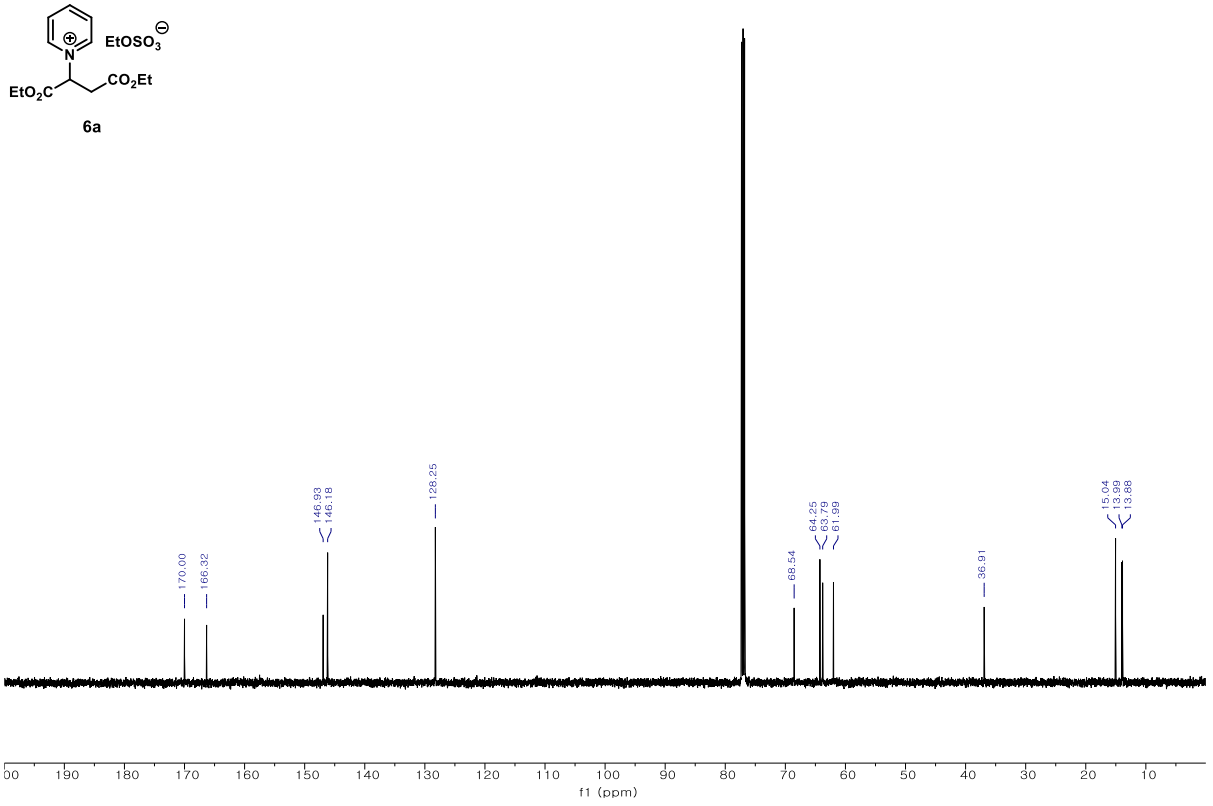
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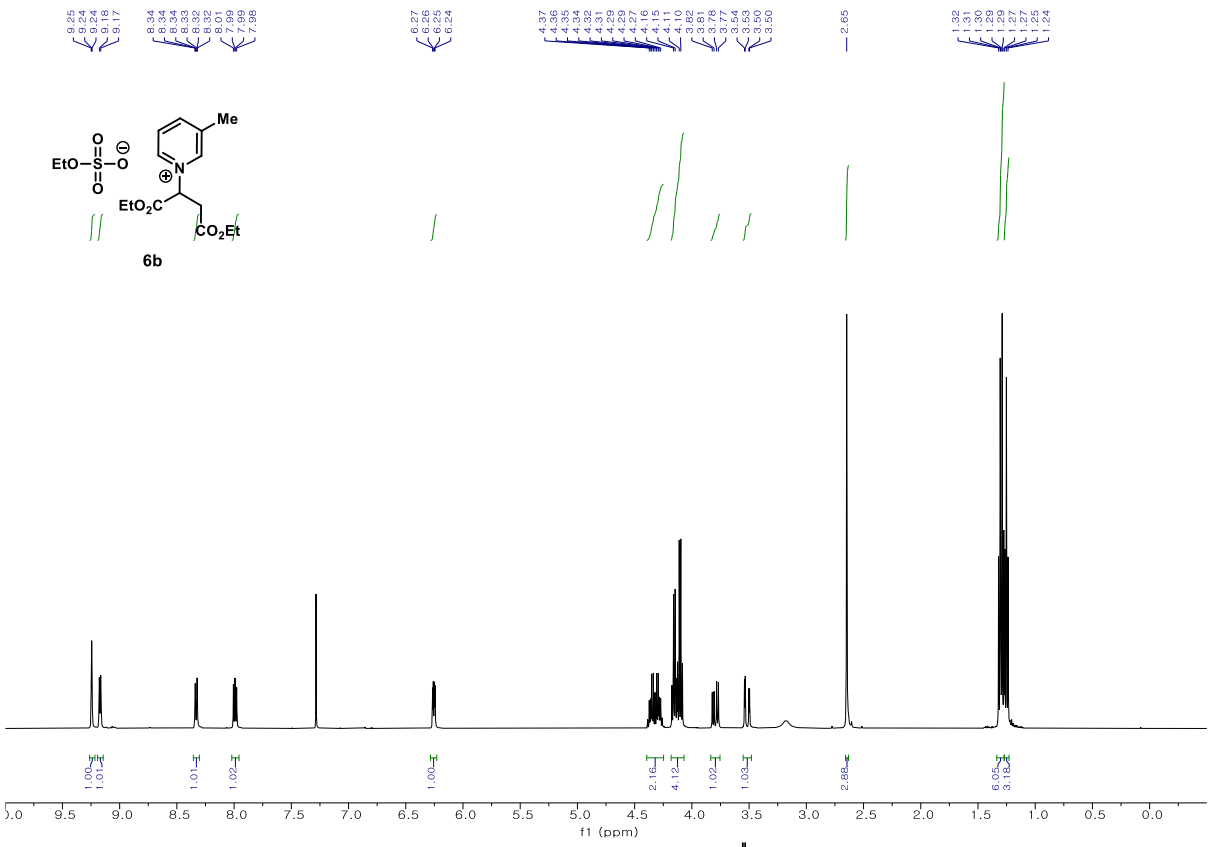
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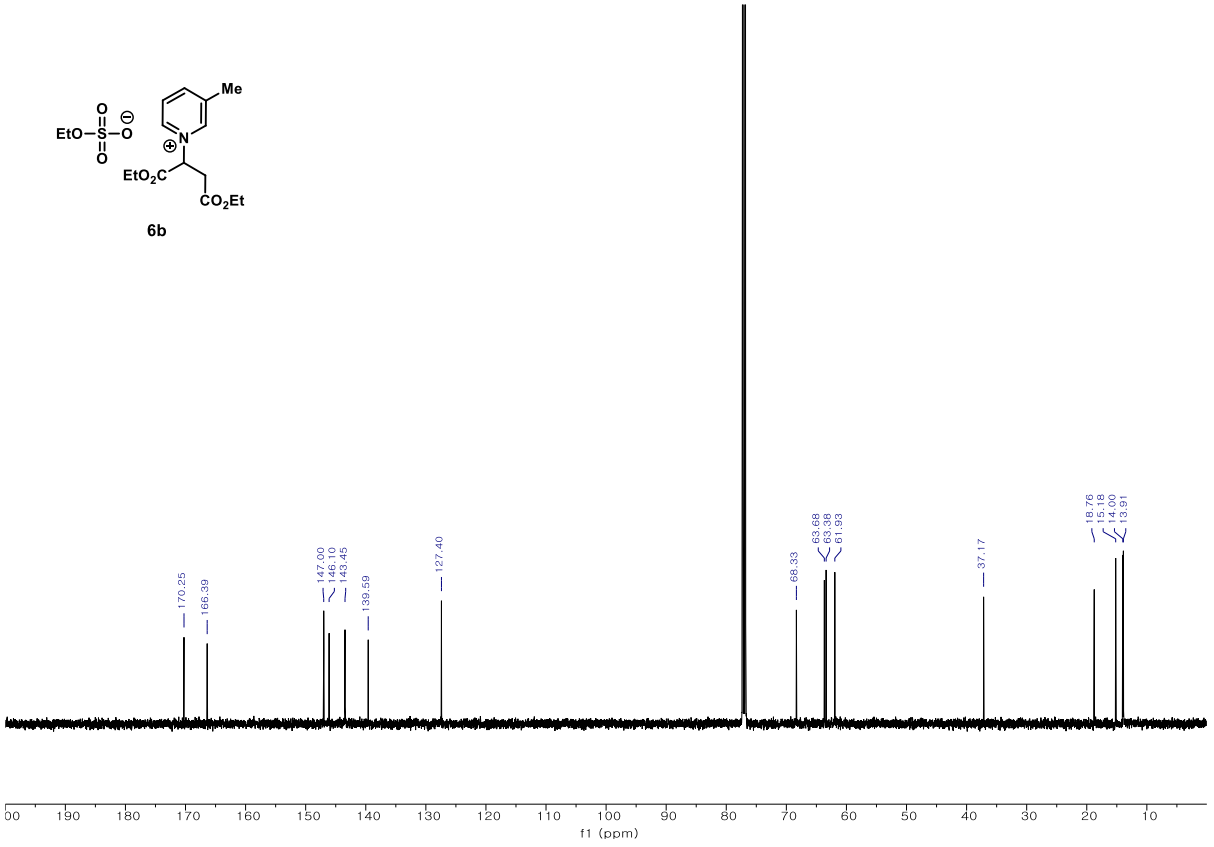
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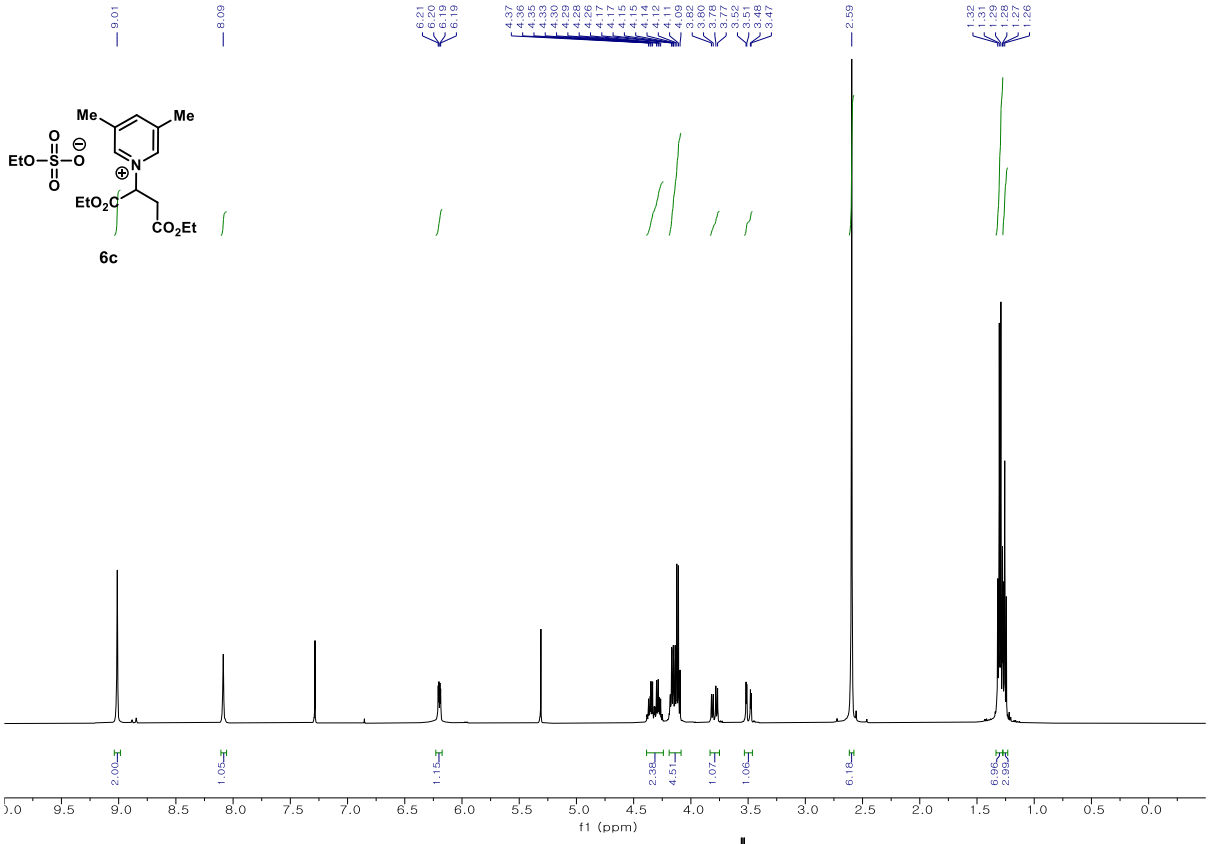
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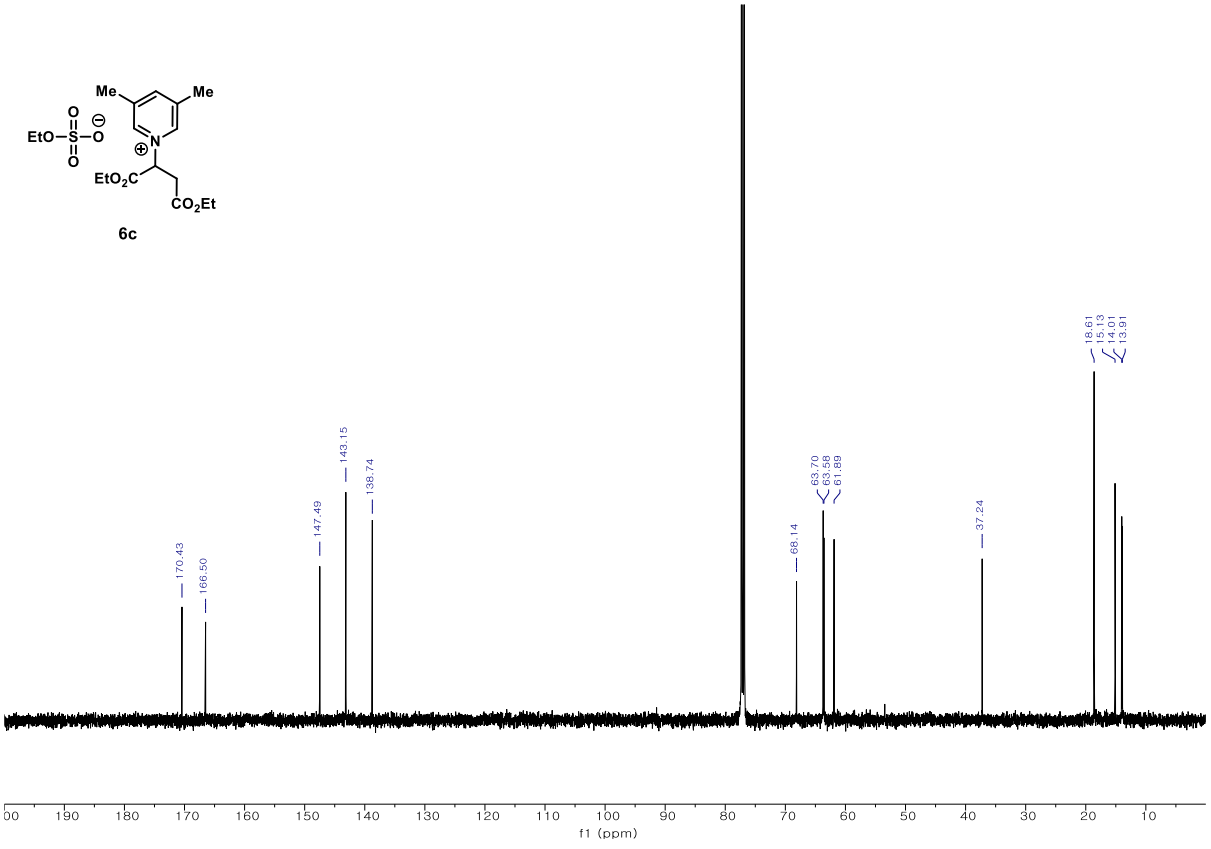
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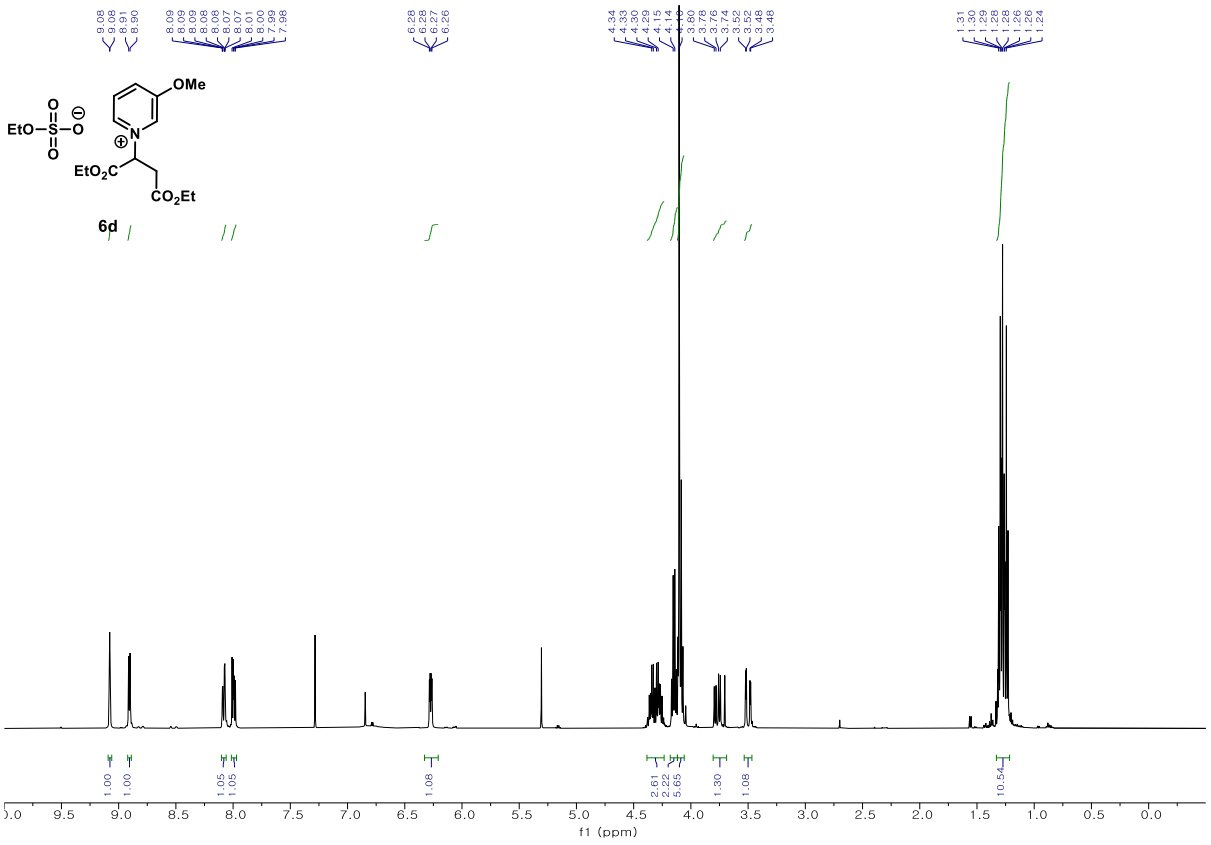
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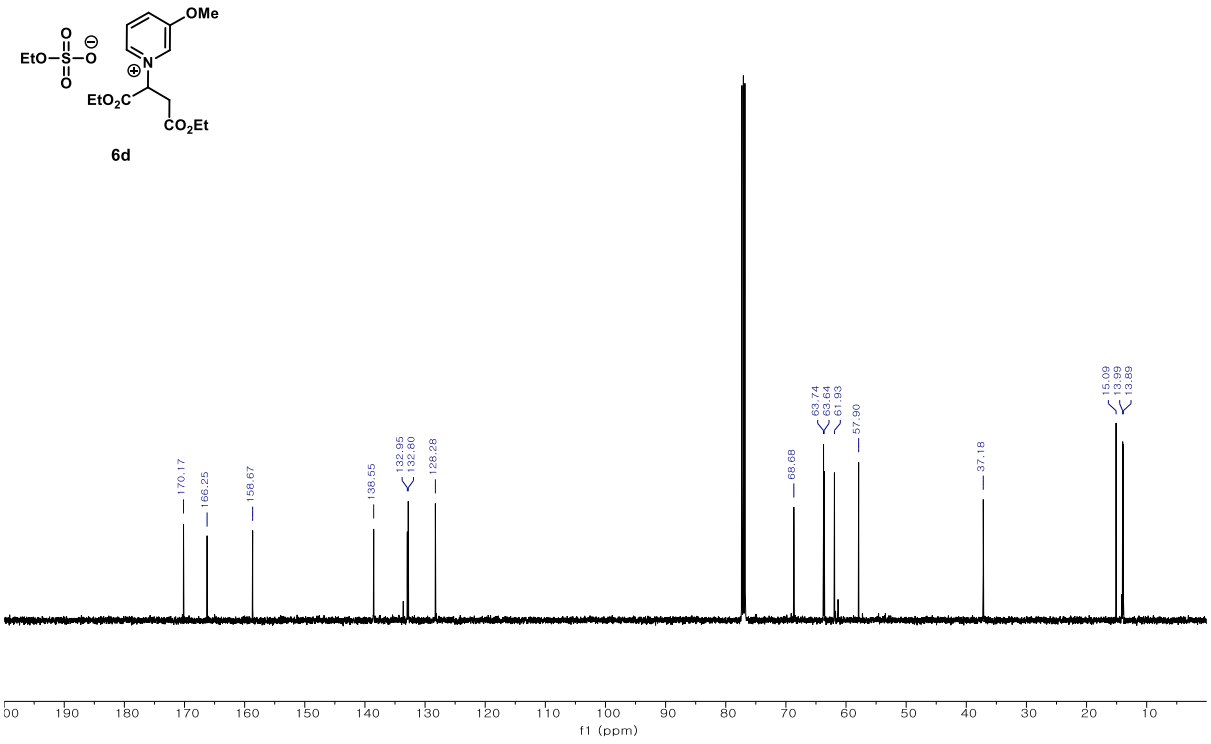
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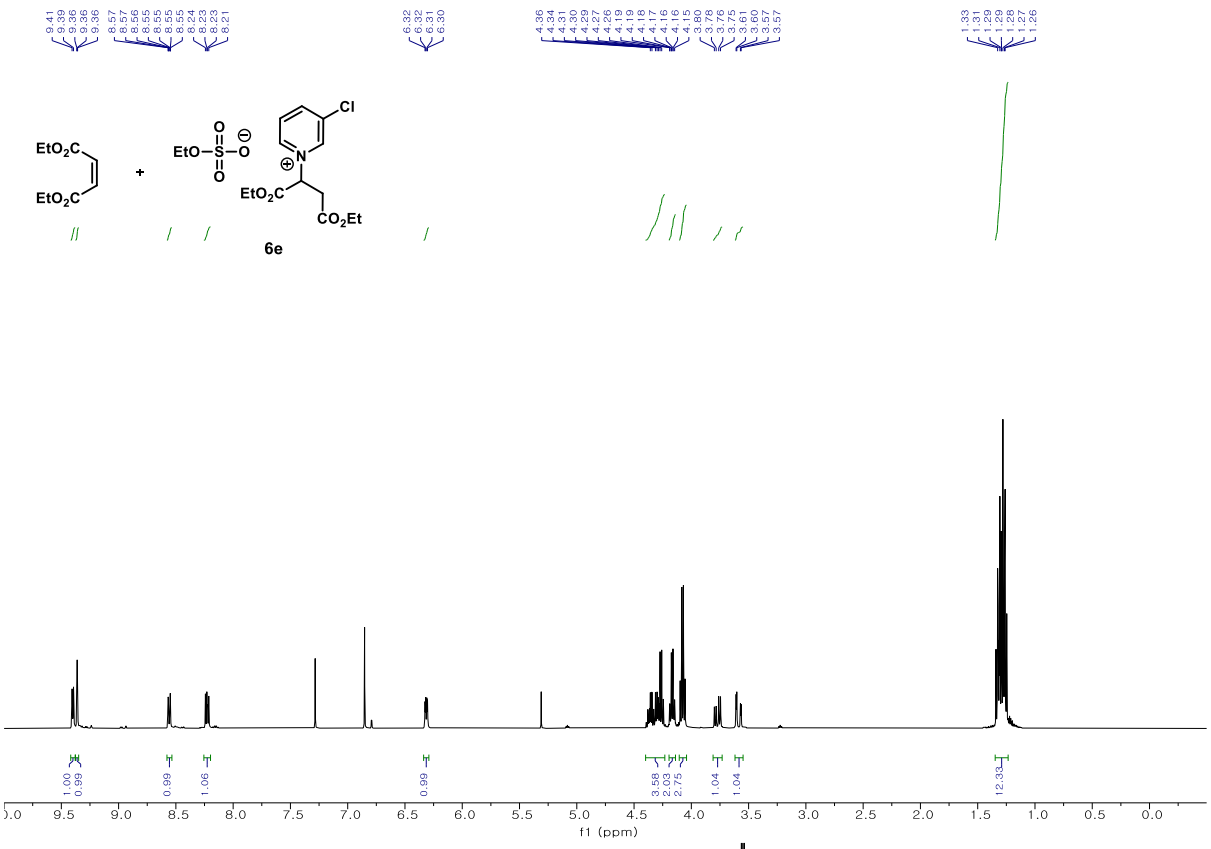
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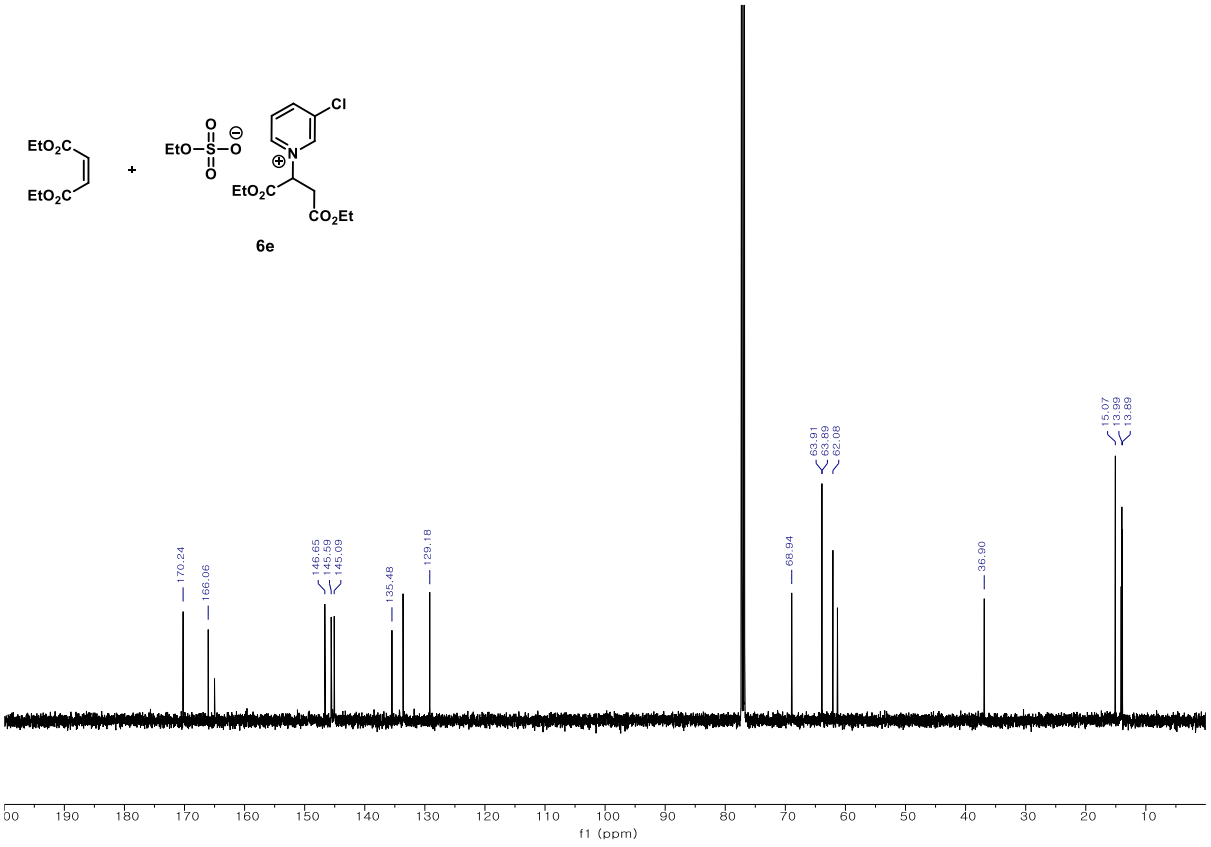
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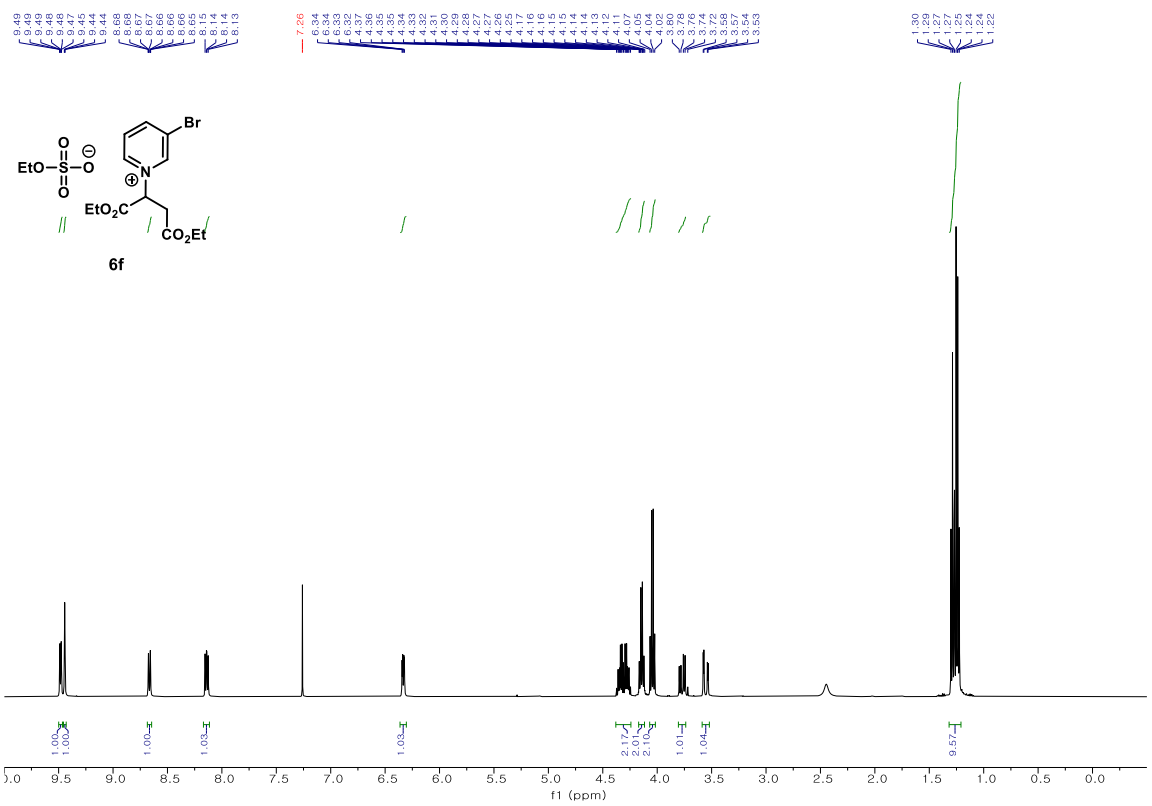
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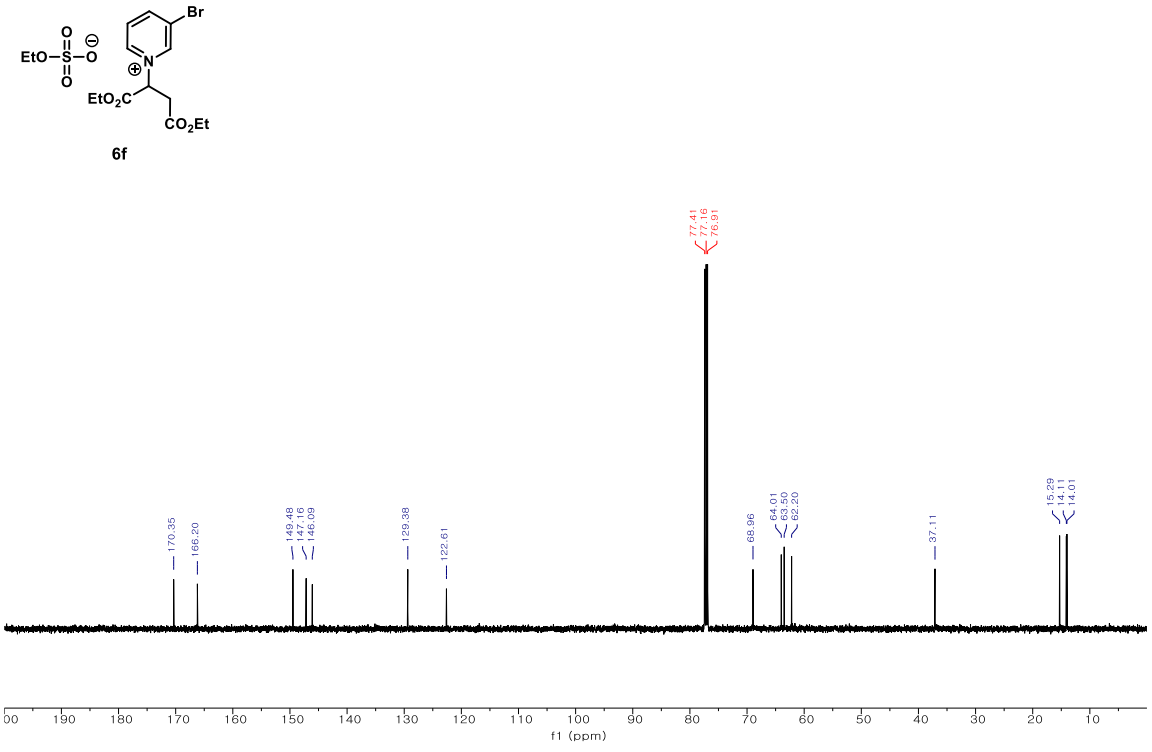
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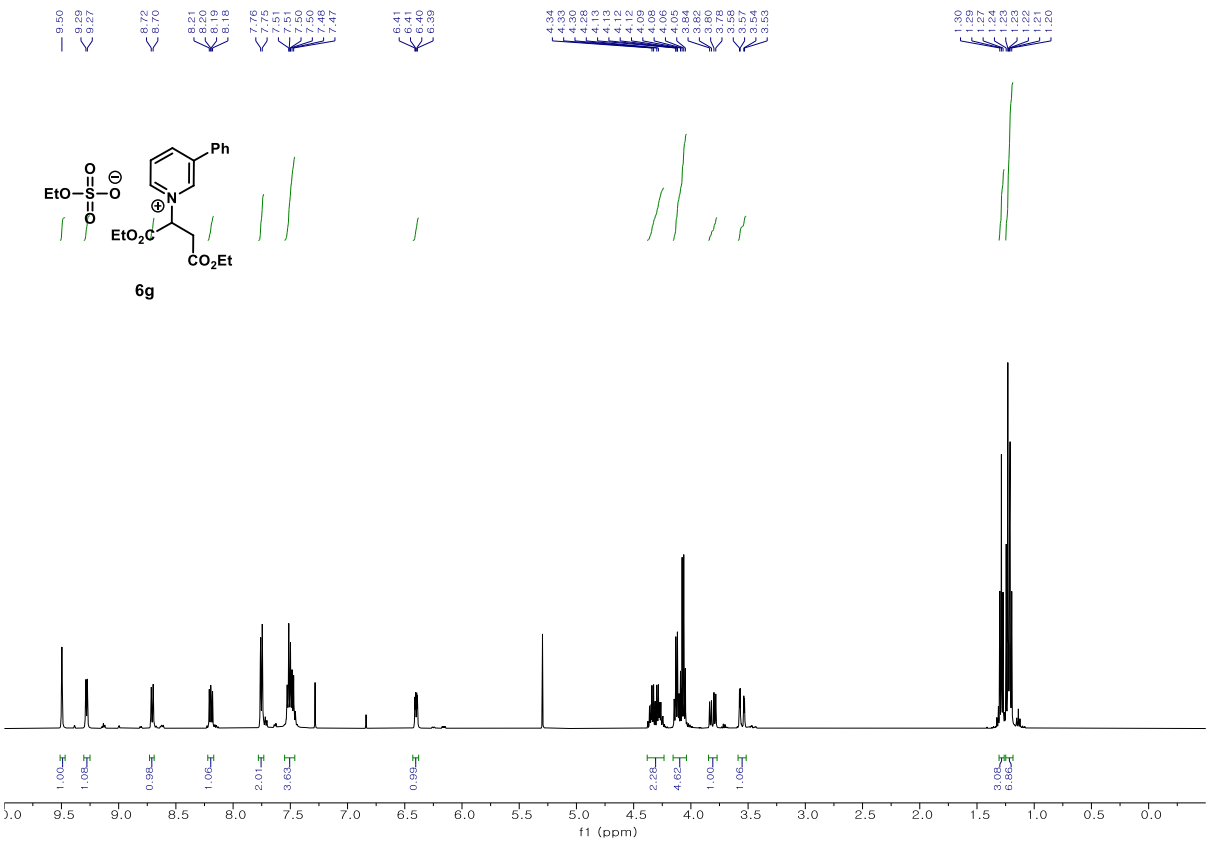
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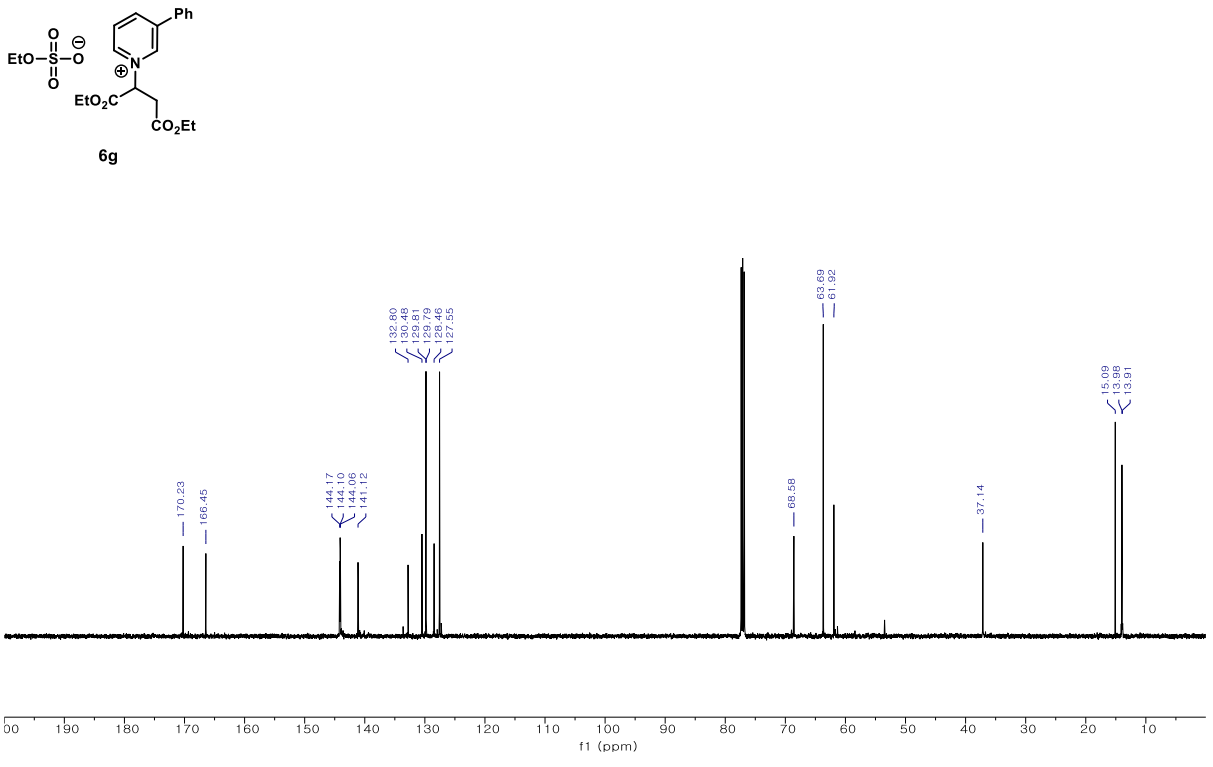
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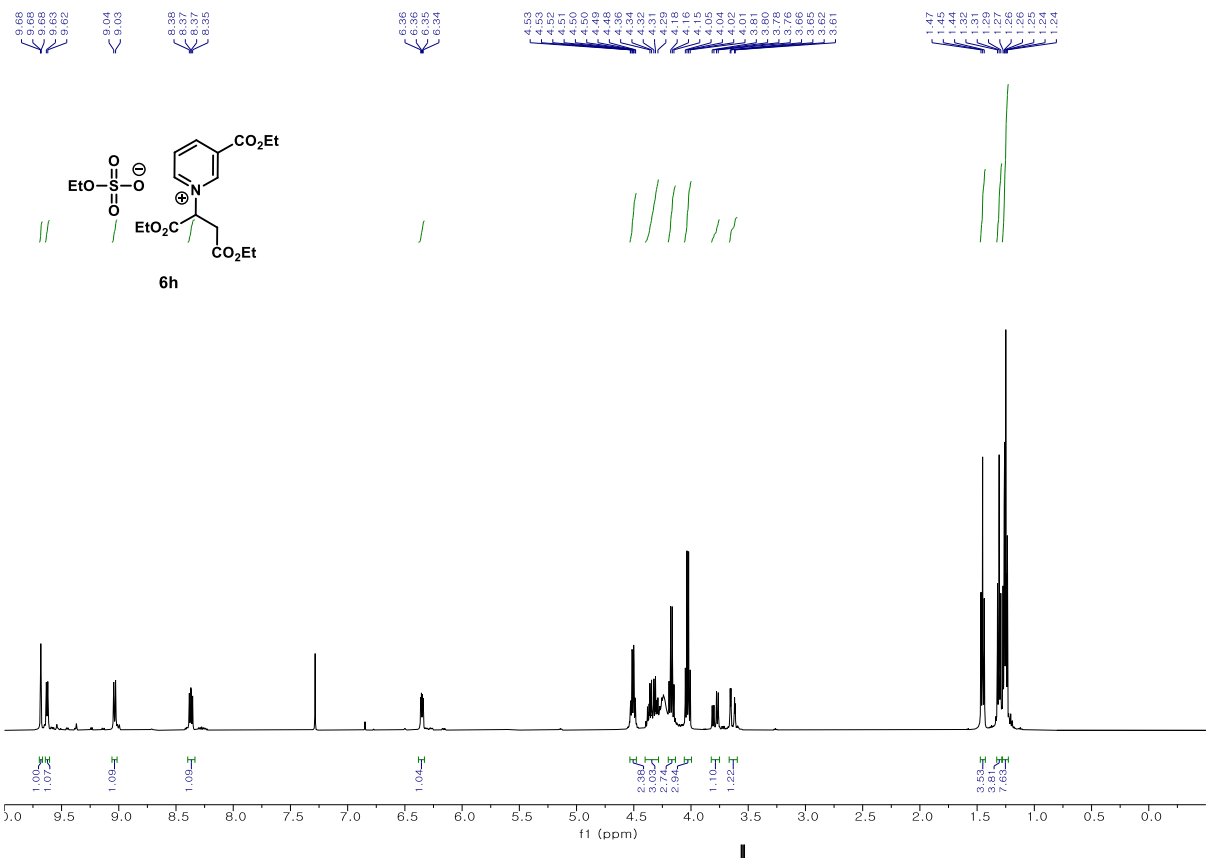
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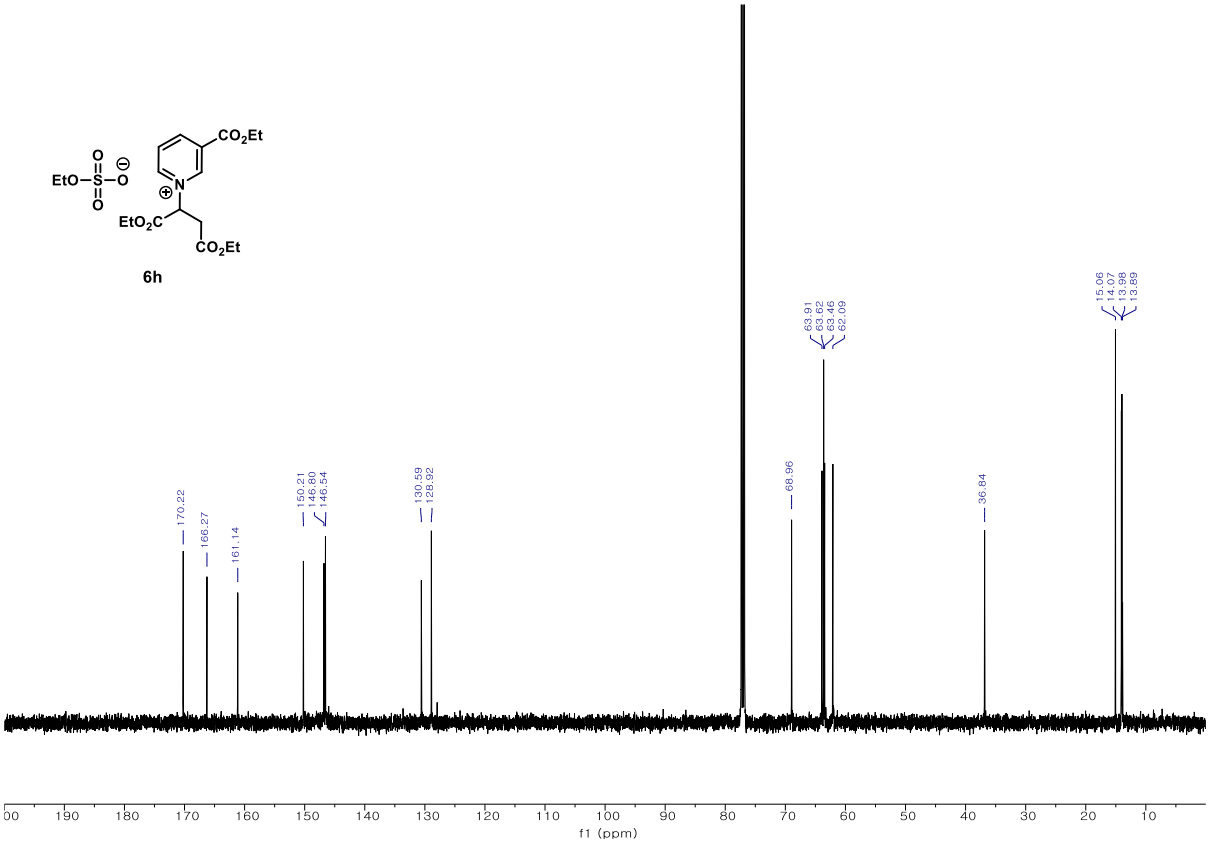
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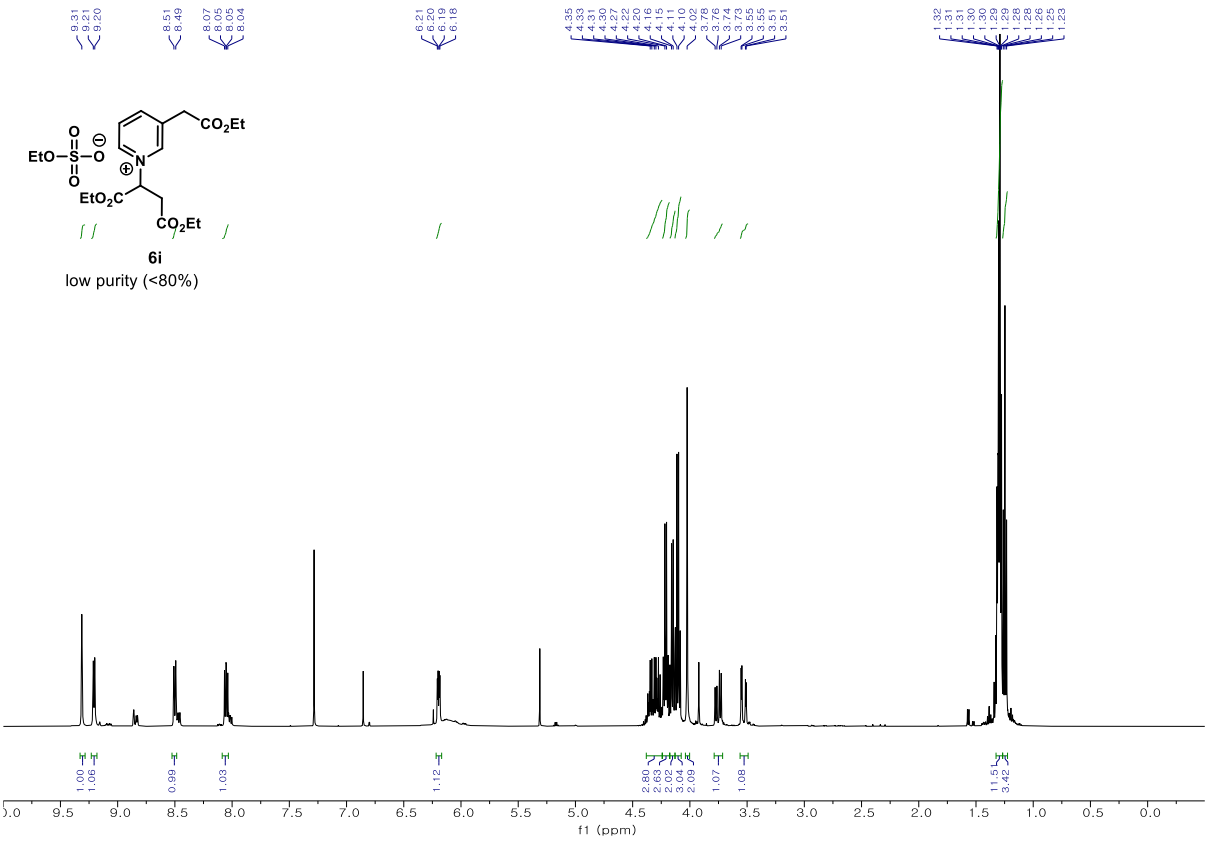
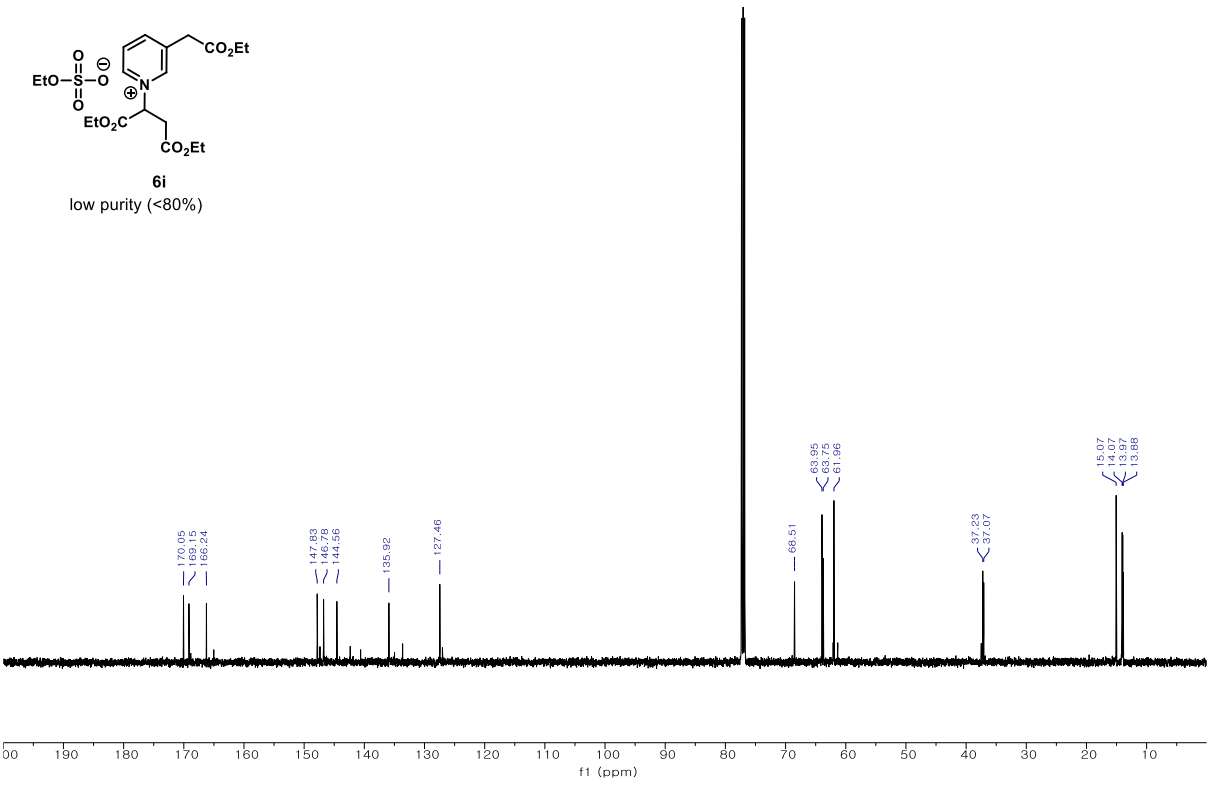
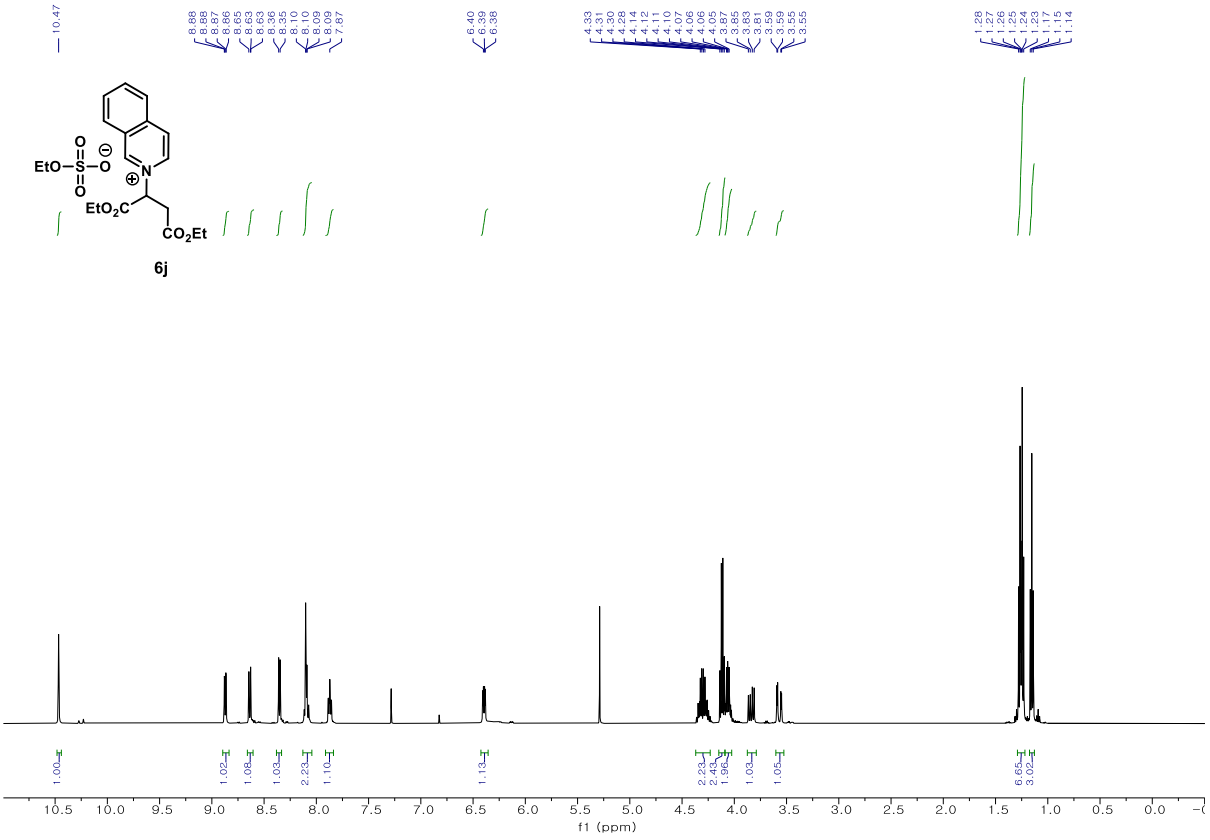
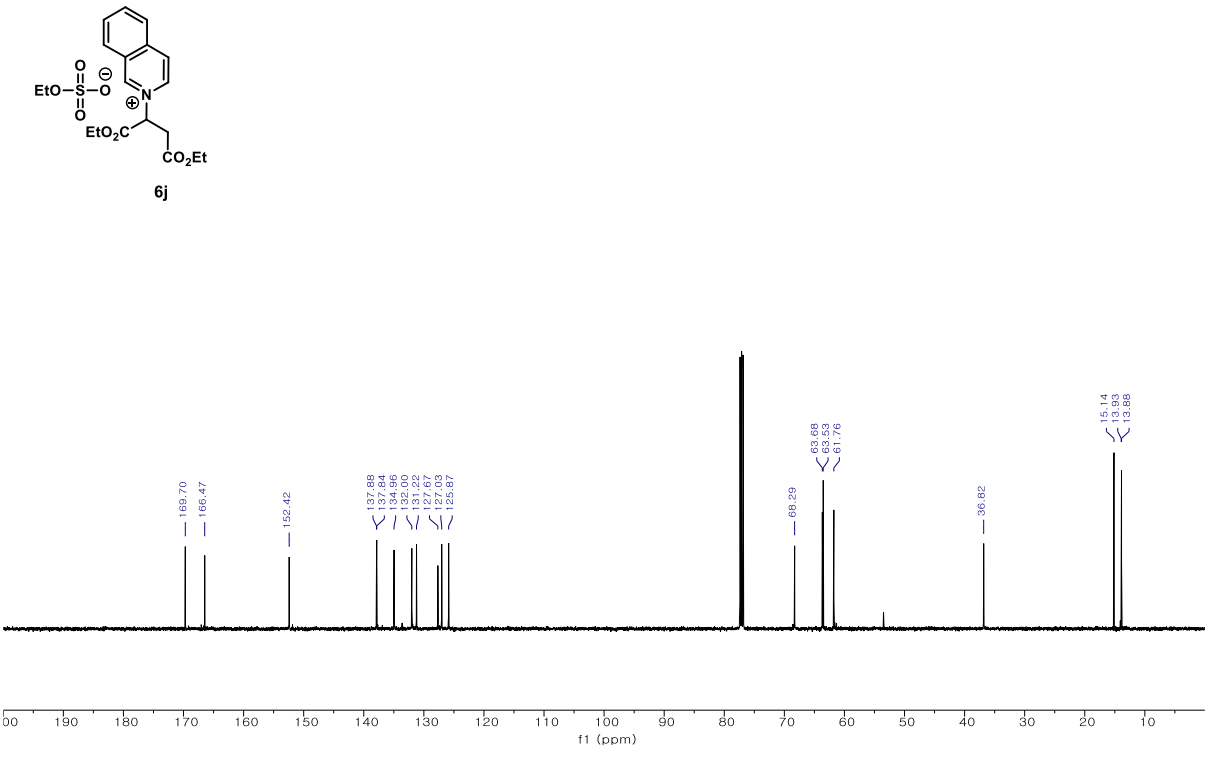
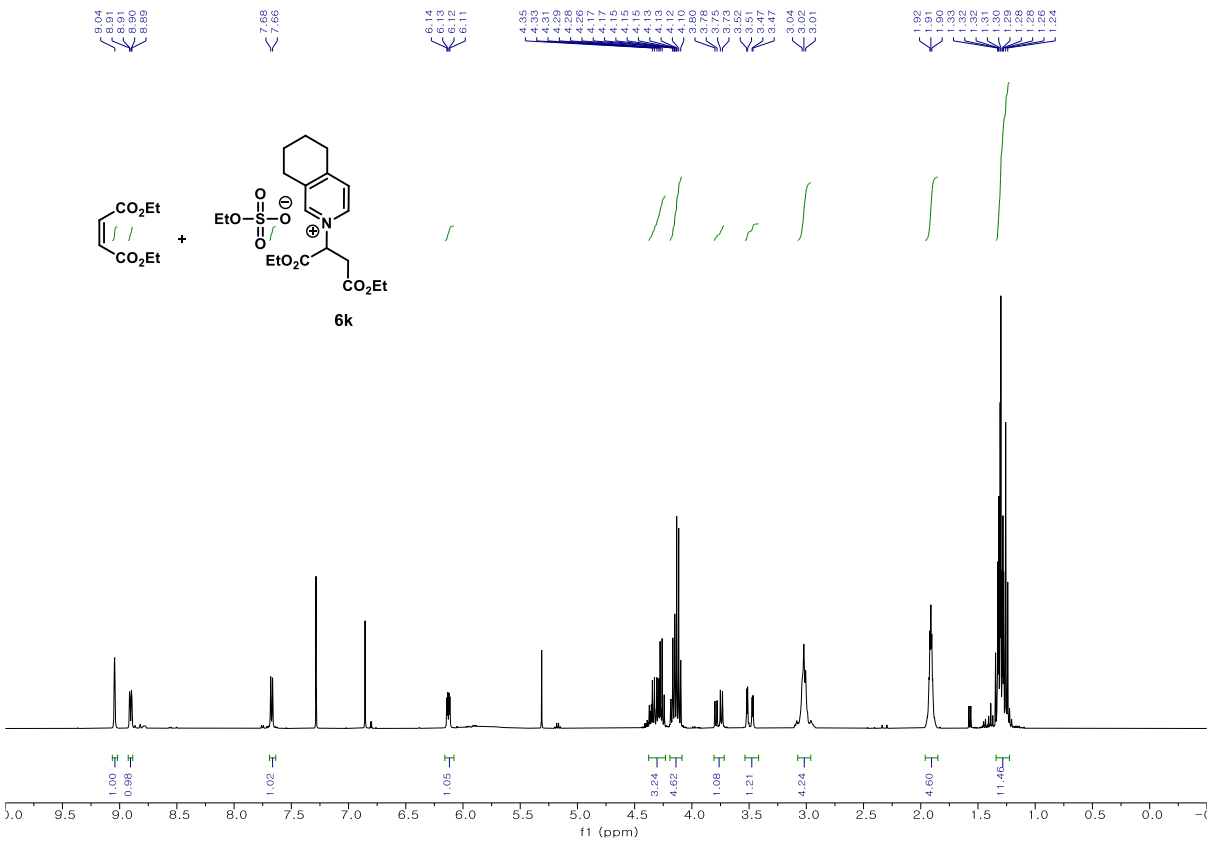
128.92
68.96
63.91
63.82
63.46
62.09
36.84
15.06
14.07
13.98
13.89
f1 (ppm)

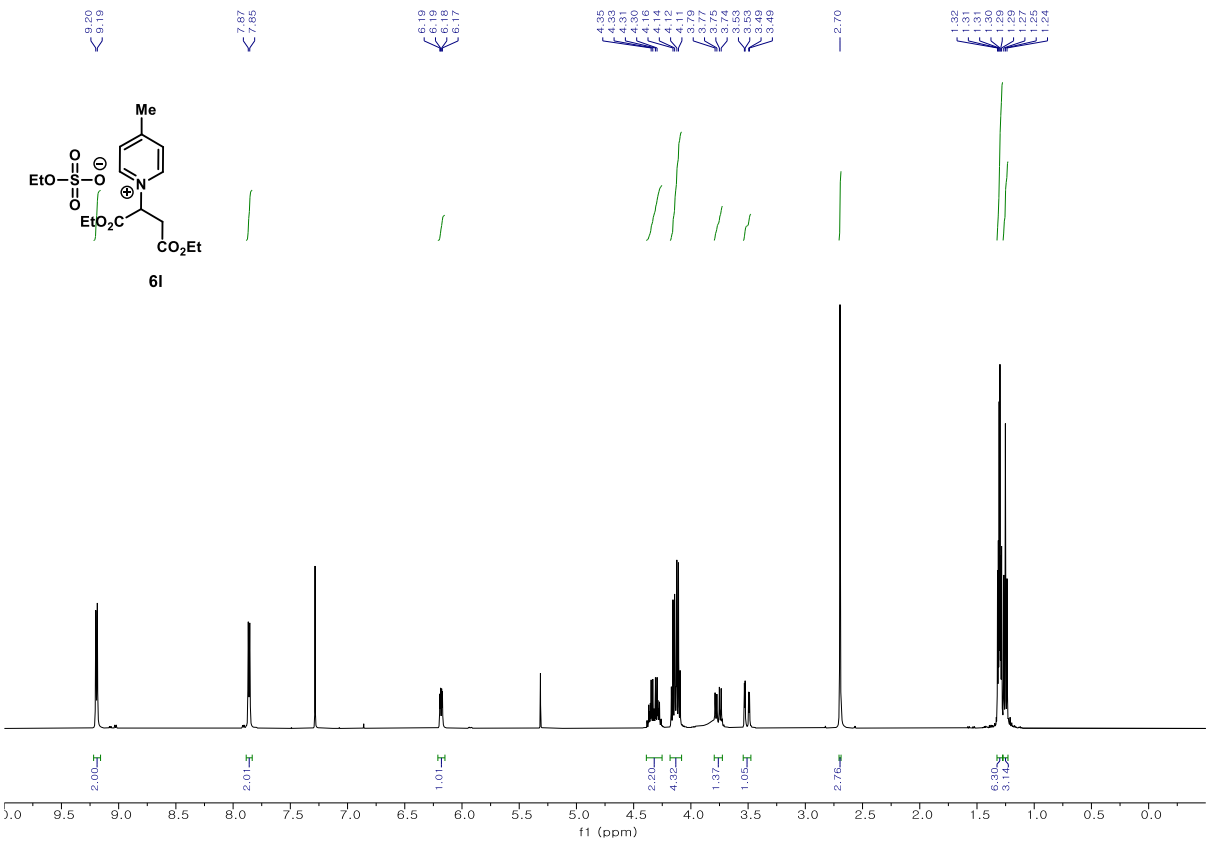

6i
low purity (<80%)
f1 (ppm)

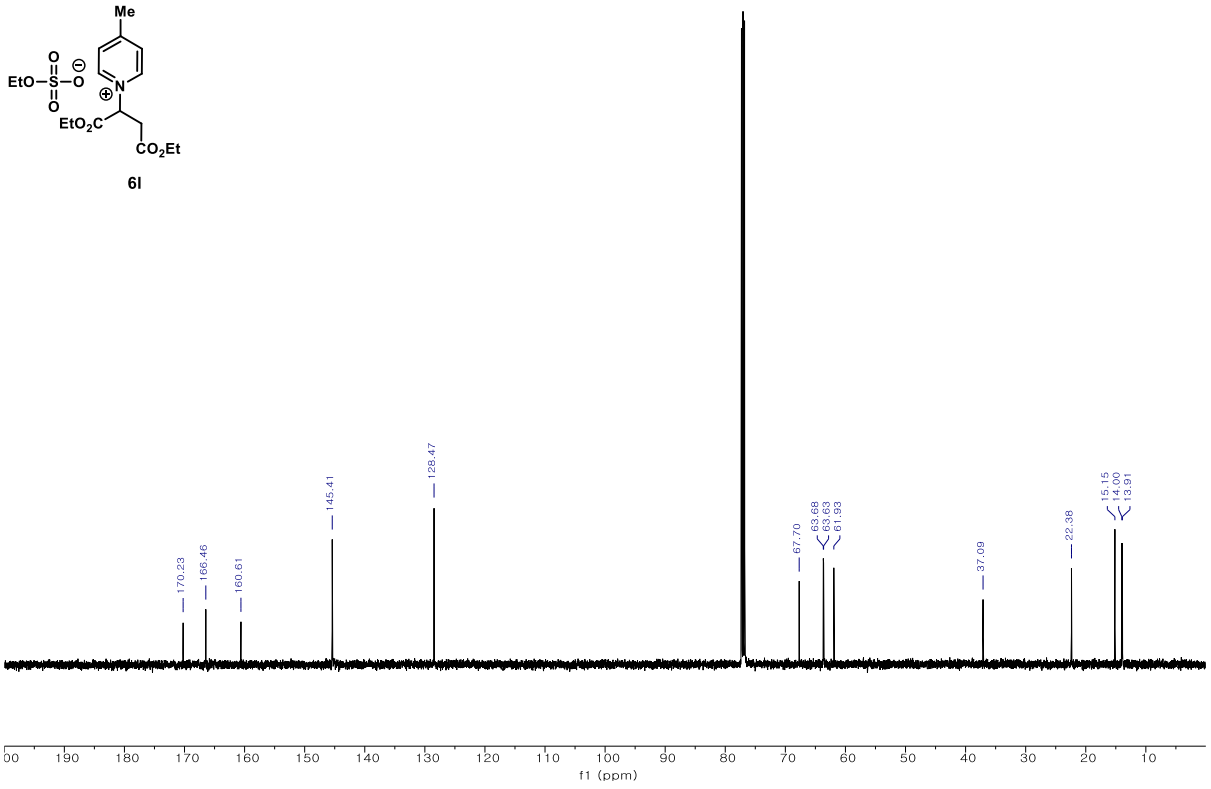

6i
low purity (<80%)
f1 (ppm)

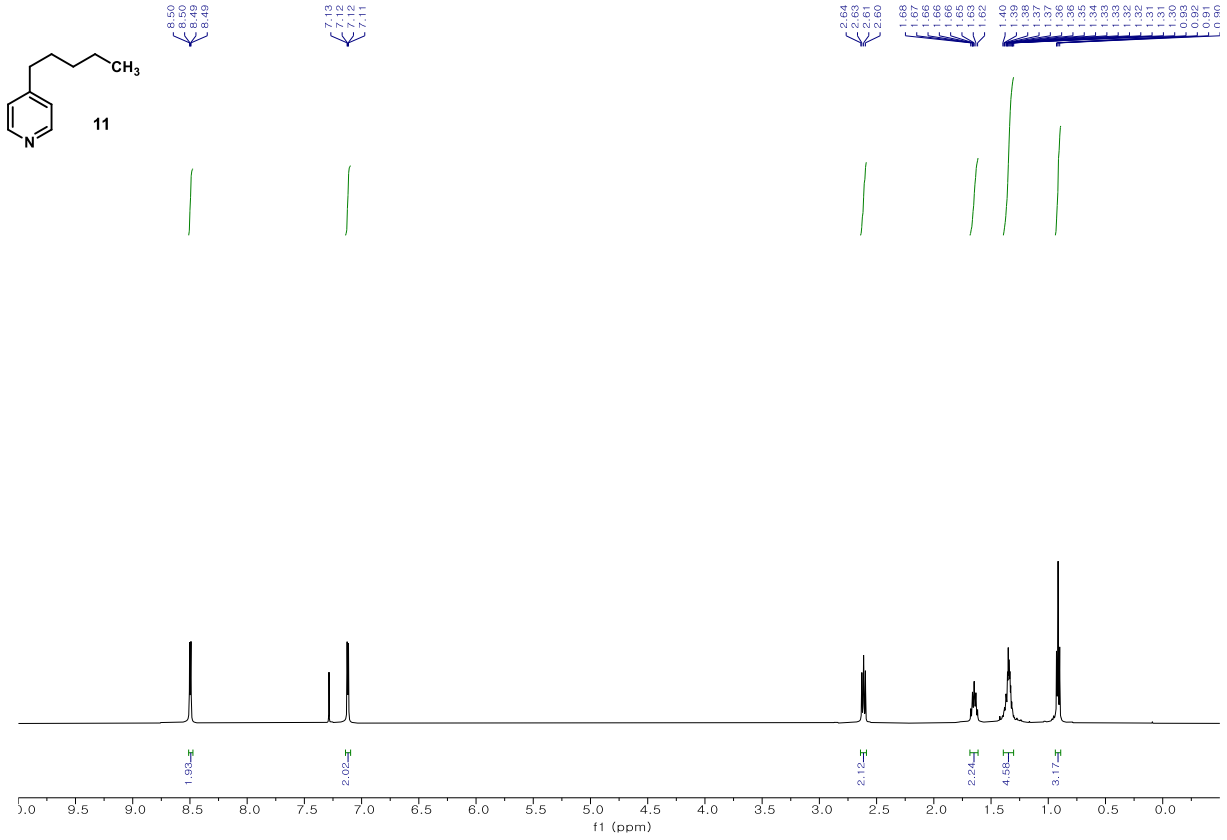

10.47
8.88
8.88
8.87
8.87
8.86
8.65
8.63
8.63
8.36
8.35
8.10
8.10
8.09
8.09
7.87
6.40
6.39
6.38
4.33
4.31
4.30
4.28
4.14
4.12
4.11
4.10
4.07
4.07
4.06
4.06
4.05
3.87
3.85
3.83
3.81
3.59
3.59
3.55
3.55
1.28
1.27
1.26
1.25
1.24
1.23
1.17
1.15
1.14
EtO
O
S
O
O
O
N
EtO2C
CO2Et
6j
1.00
1.02
1.08
1.03
2.23
1.10
1.13
2.23
2.43
1.96
1.03
1.05
6.65
3.02
f1 (ppm)

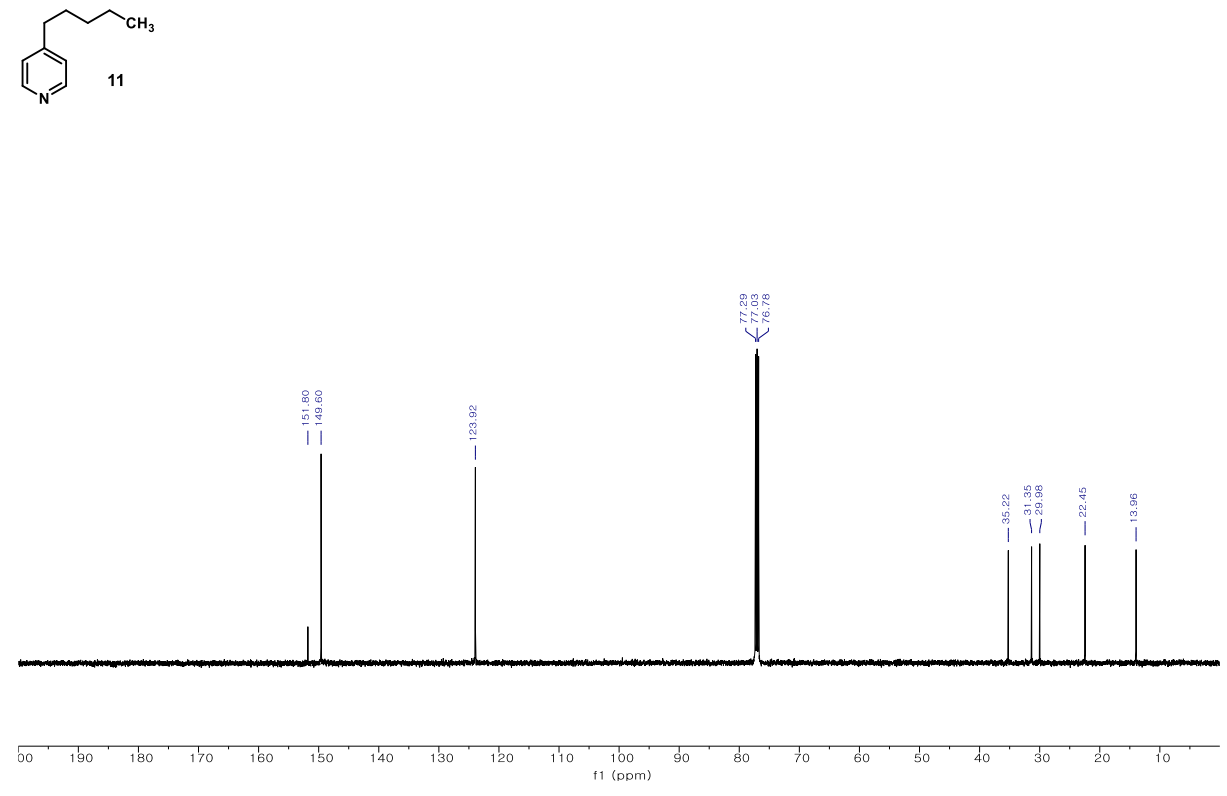

EtO
O
S
O
O
O
N
EtO2C
CO2Et
6j
169.70
166.47
152.42
137.88
137.84
134.96
132.00
131.22
127.67
127.03
125.87
68.29
63.68
63.53
61.76
36.82
15.14
13.93
13.88
f1 (ppm)

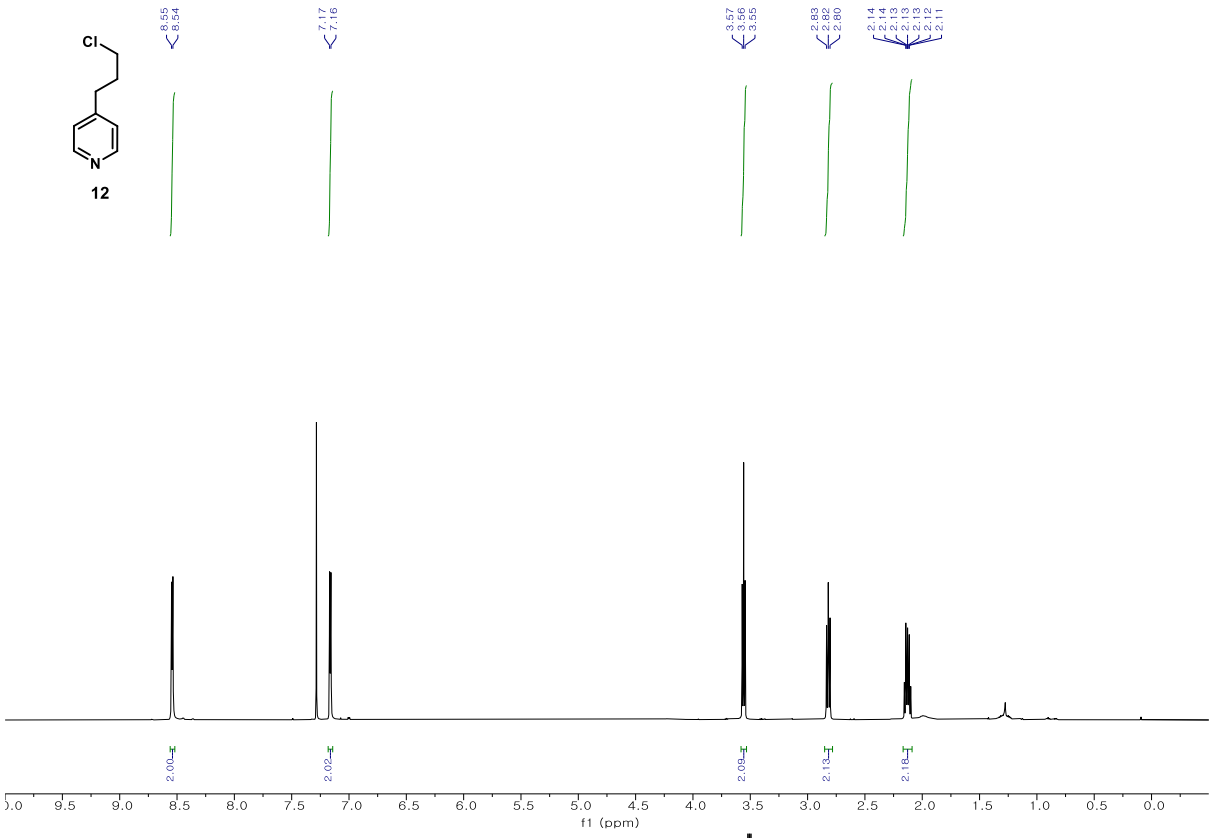

9.04
8.91
8.91
8.90
8.89
7.68
7.66
6.14
6.13
6.12
6.11
4.35
4.33
4.31
4.29
4.28
4.26
4.17
4.17
4.15
4.15
4.15
4.13
4.12
4.10
3.80
3.78
3.75
3.73
3.52
3.51
3.47
3.04
3.02
3.01
1.92
1.91
1.90
1.33
1.32
1.32
1.31
1.30
1.29
1.28
1.28
1.26
1.24
CO2Et
CO2Et
+
EtO
S
O
O
O
N
EtO2C
CO2Et
6k
1.00
0.98
1.02
1.05
3.24
4.62
1.08
1.21
4.24
4.60
11.46
f1 (ppm)

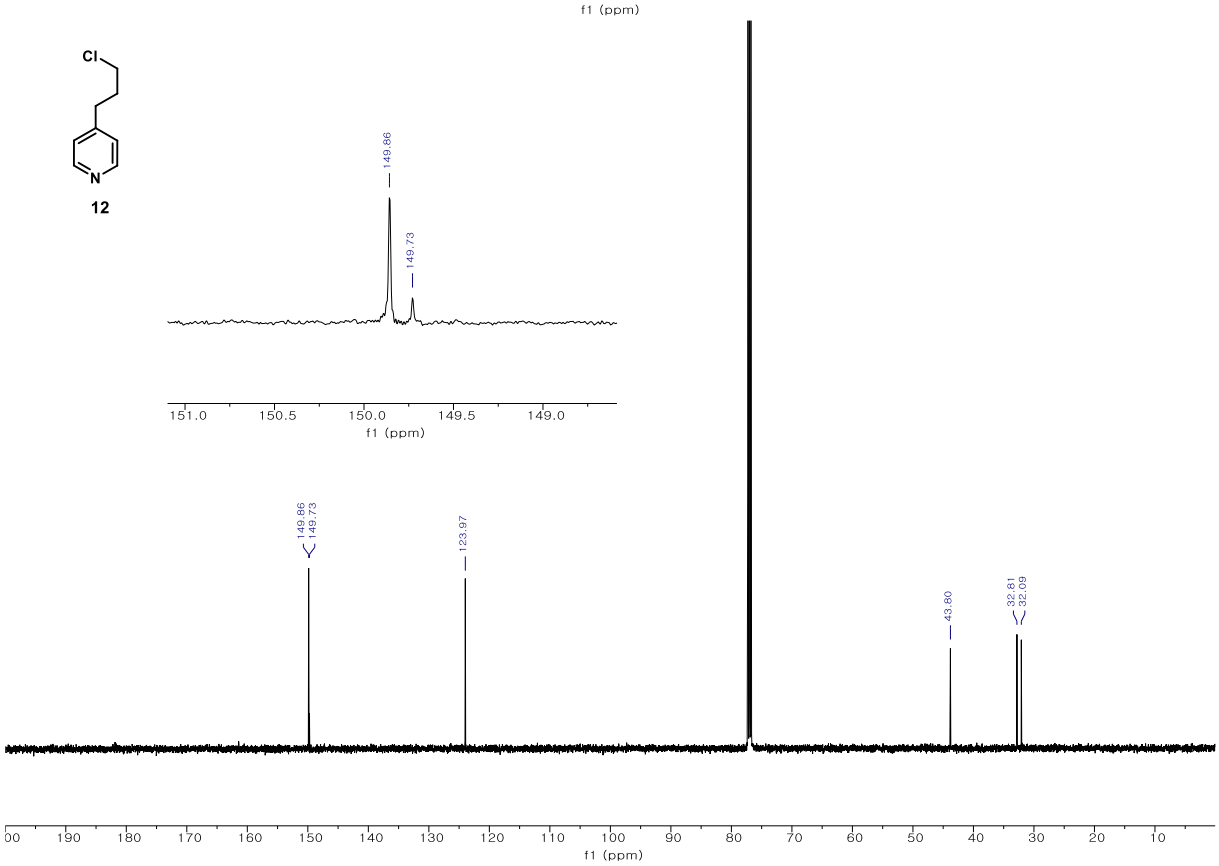

9.20
9.19
7.87
7.85
6.19
6.19
6.18
6.17
4.35
4.33
4.31
4.30
4.16
4.14
4.12
4.11
3.79
3.77
3.75
3.74
3.53
3.53
3.49
3.49
2.70
1.32
1.31
1.31
1.30
1.29
1.29
1.27
1.25
1.24
Me
EtO
EtO2C
CO2Et
6l
2.00
2.01
1.01
2.20
4.32
1.37
1.05
2.76
6.30
3.14
f1 (ppm)

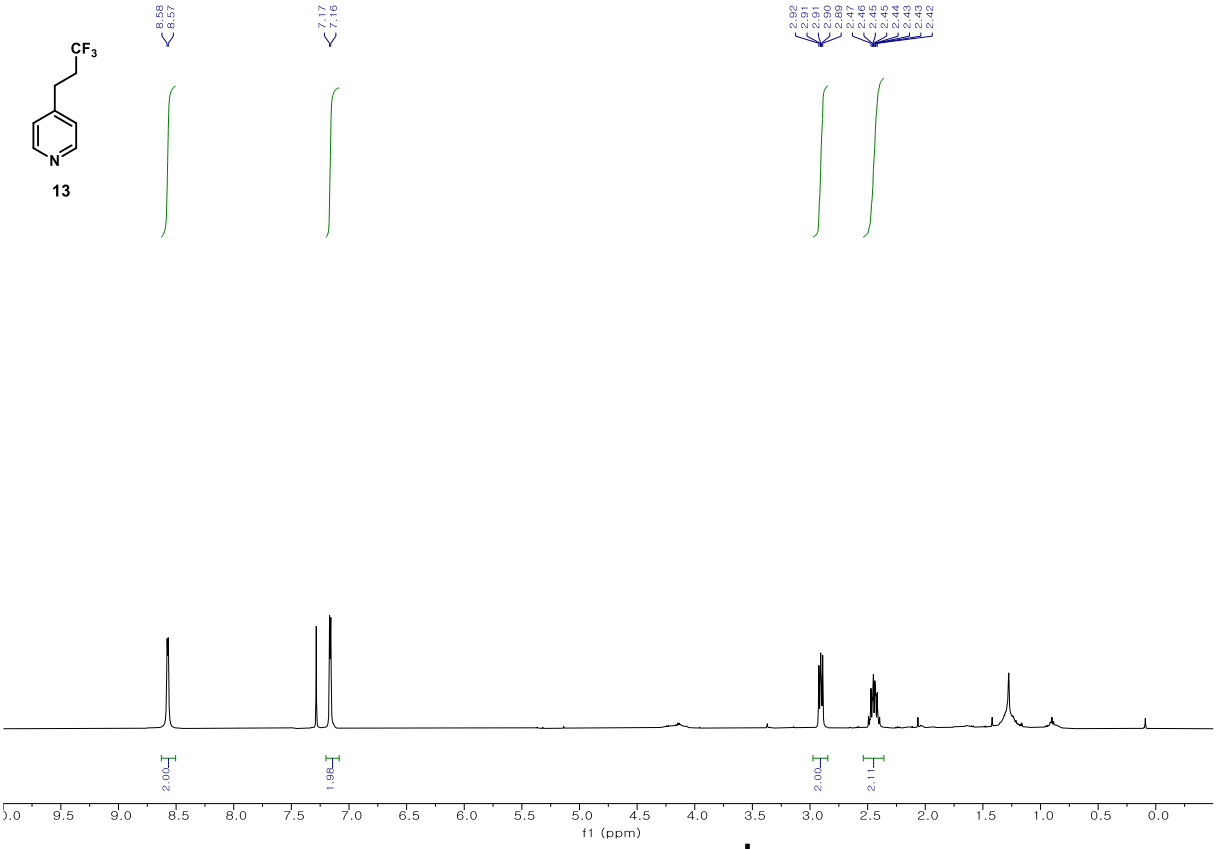

Me
EtO
EtO2C
CO2Et
6l
170.23
166.46
160.61
145.41
128.47
67.70
63.68
63.63
61.93
37.09
22.38
15.15
14.00
13.91
f1 (ppm)

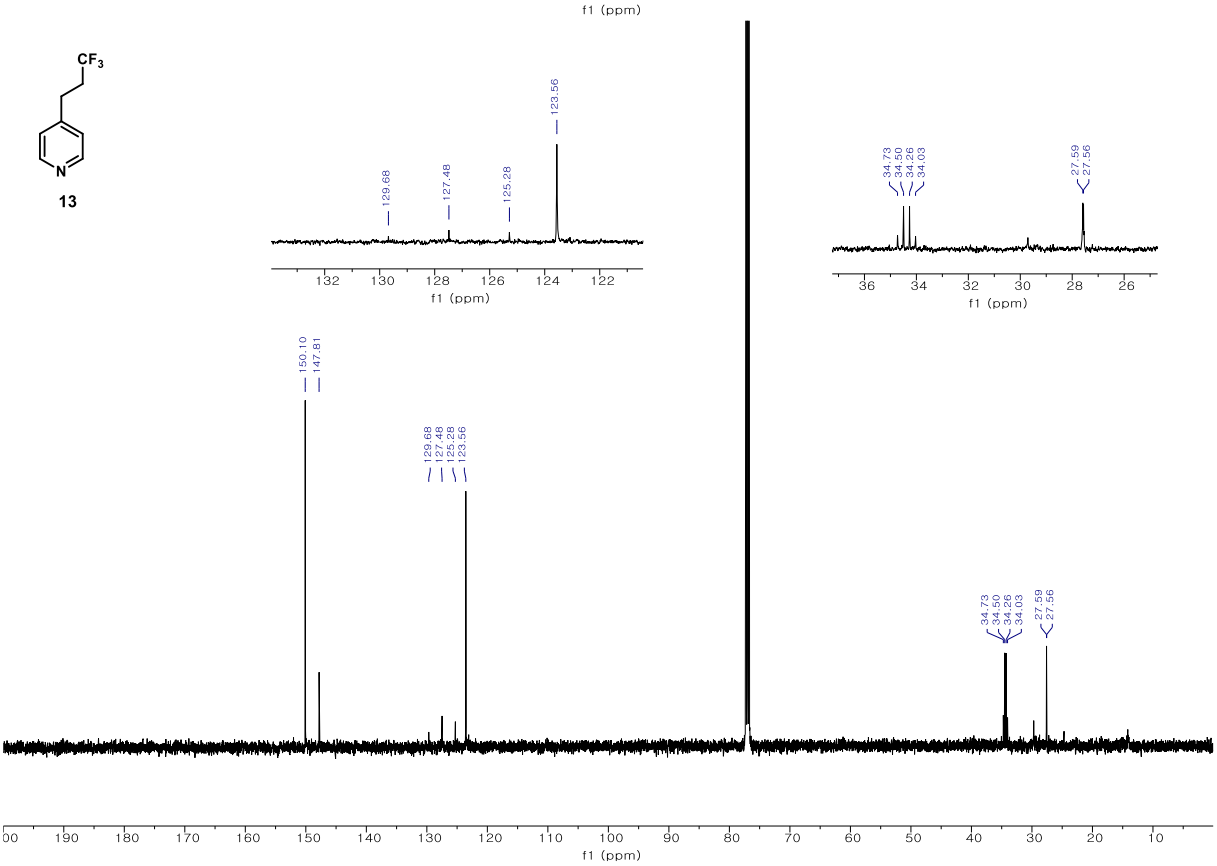

CH3
N
11
8.50
8.50
8.49
8.49
7.13
7.12
7.12
7.11
2.64
2.63
2.61
2.60
1.68
1.67
1.66
1.66
1.65
1.65
1.63
1.62
1.40
1.39
1.38
1.37
1.37
1.36
1.36
1.35
1.34
1.33
1.33
1.32
1.32
1.31
1.31
1.30
0.93
0.92
0.91
0.90
1.93
2.02
2.12
2.24
4.58
3.17
f1 (ppm)

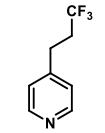

CH3
N
11
77.29
77.03
76.78
151.80
149.60
123.92
35.22
31.35
29.98
22.45
13.96
f1 (ppm)


Cl
N
12
8.55
8.54
7.17
7.16
3.57
3.56
3.55
2.83
2.82
2.80
2.14
2.14
2.13
2.13
2.13
2.12
2.11
2.00
2.02
2.09
2.13
2.18
f1 (ppm)


Cl
N
12
149.86
149.73
f1 (ppm)
149.86
149.73
123.97
43.80
32.81
32.09
f1 (ppm)

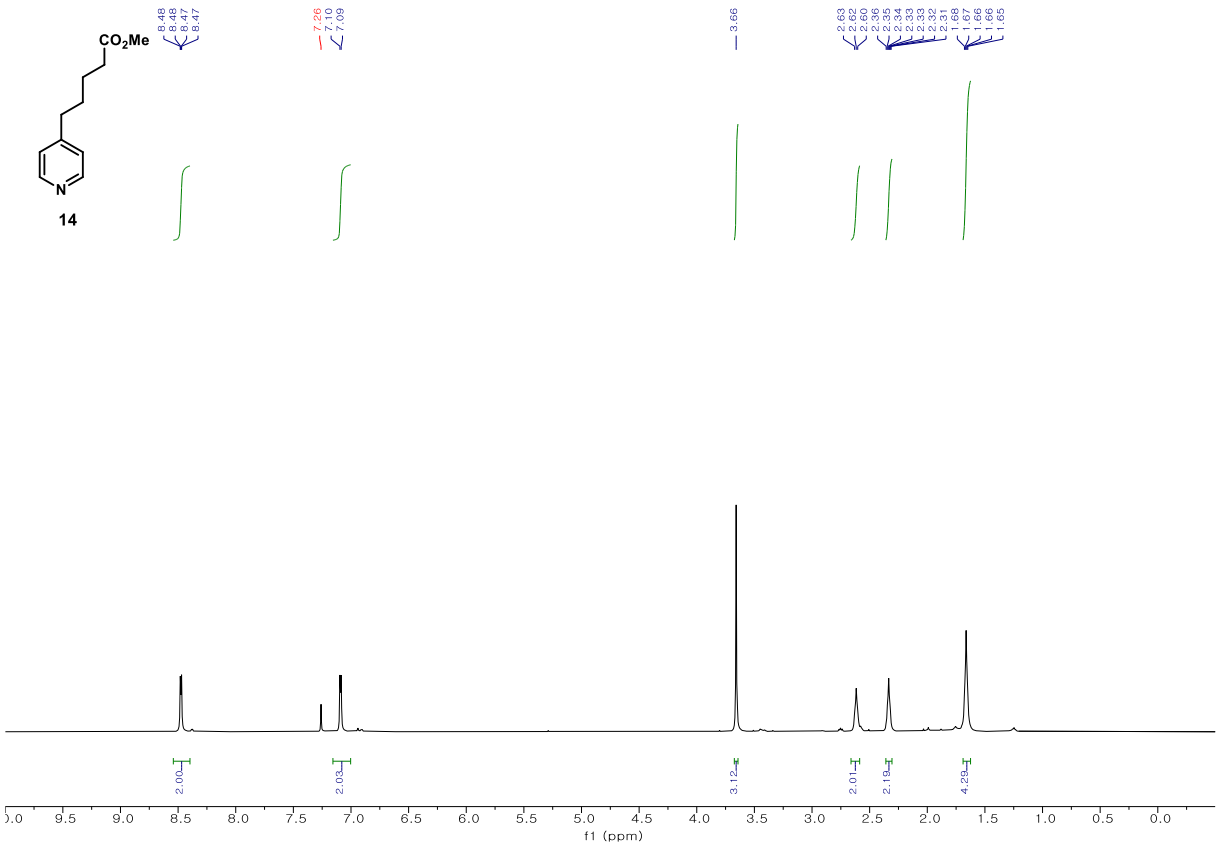

CF3
N
13
8.58
8.57
7.17
7.16
2.92
2.91
2.91
2.90
2.89
2.47
2.46
2.45
2.45
2.44
2.43
2.43
2.42
2.00
1.98
2.00
2.11
f1 (ppm)

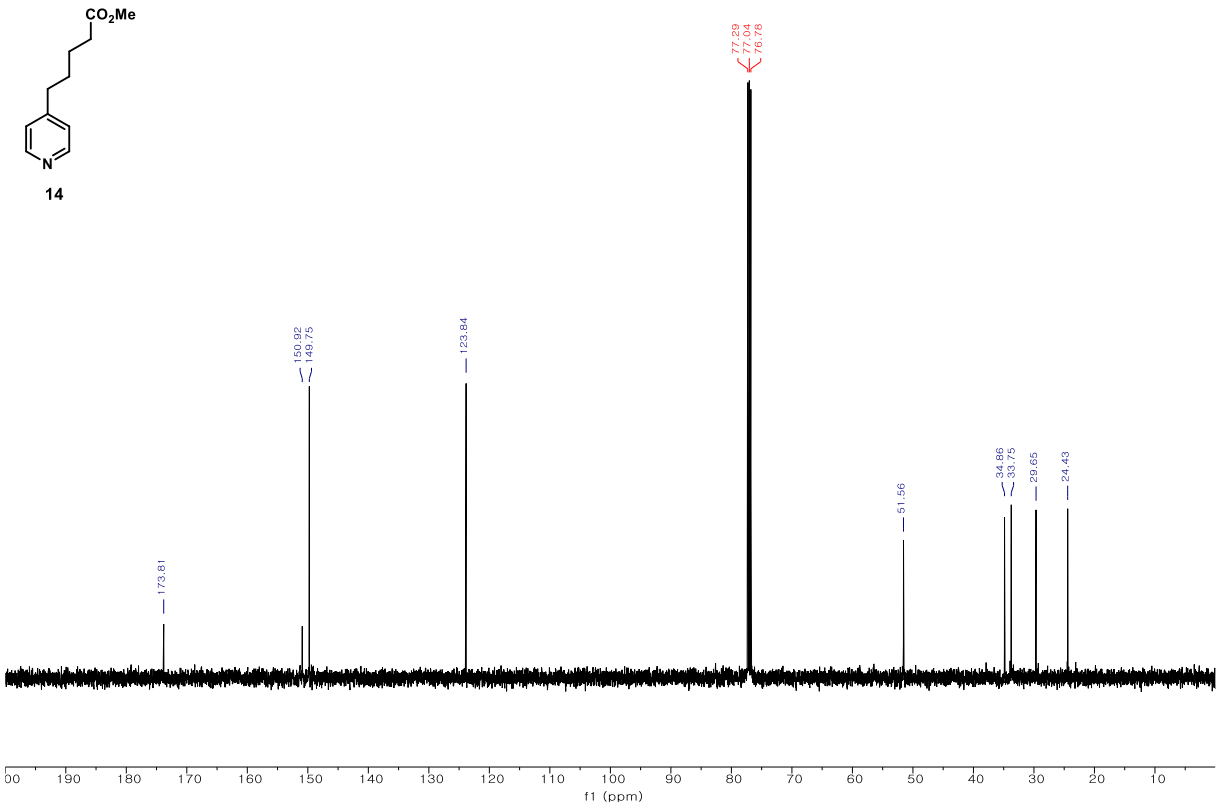

CF3
N
13
129.68
127.48
125.28
123.56
34.73
34.50
34.26
34.03
27.59
27.56
f1 (ppm)
150.10
147.81
129.68
127.48
125.28
123.56
34.73
34.50
34.26
34.03
27.59
27.56
f1 (ppm)

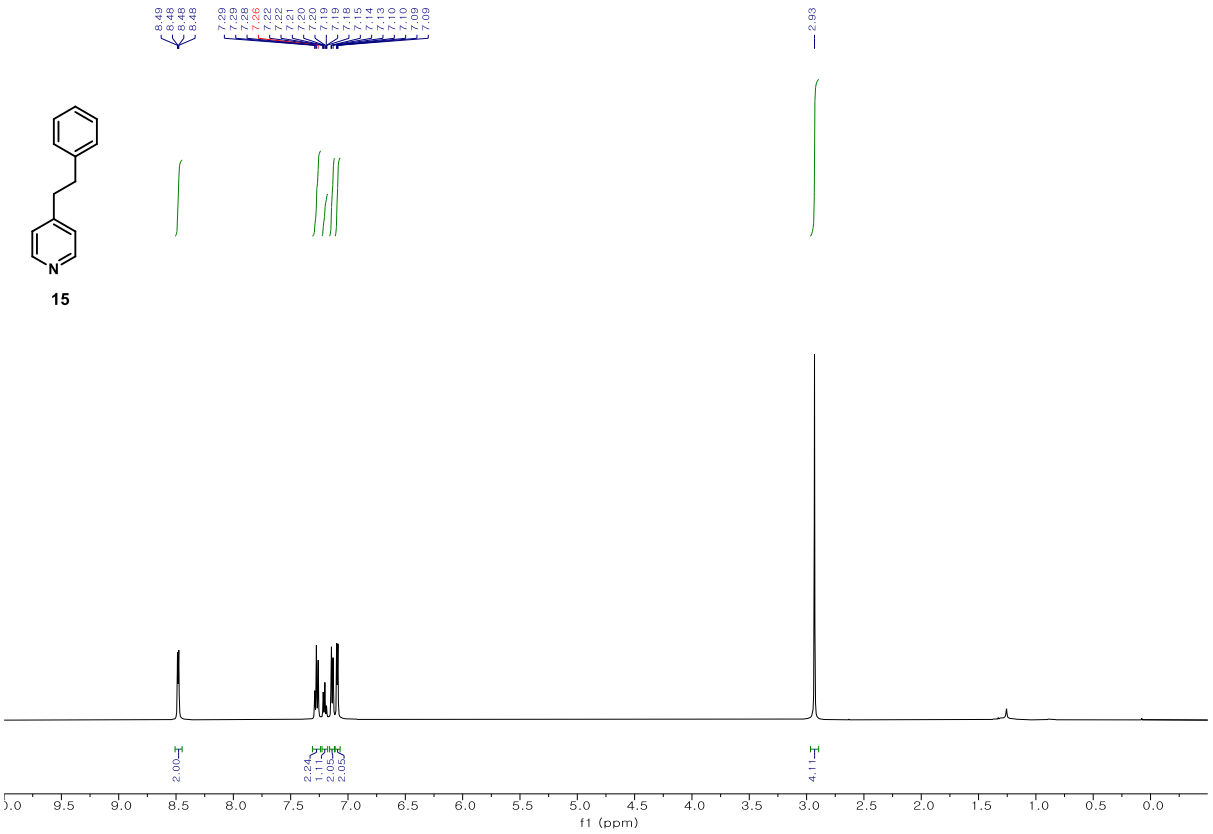

CF3
N

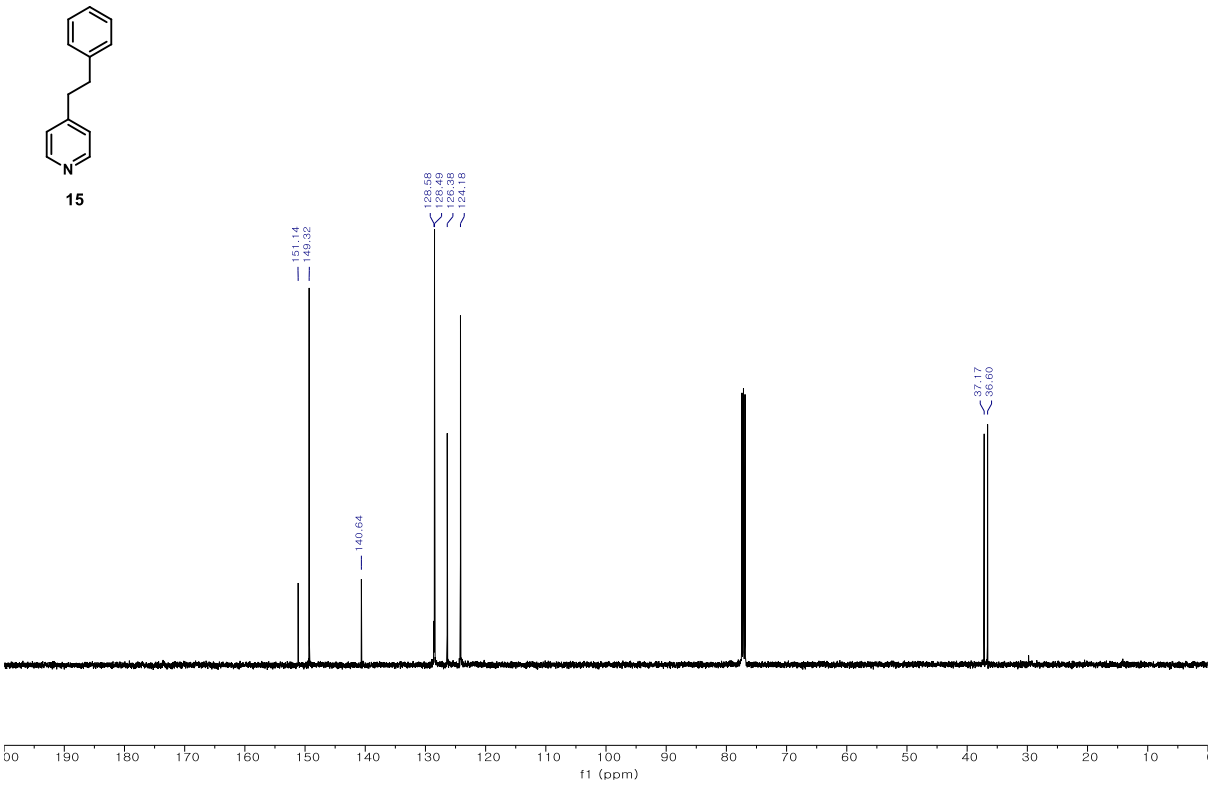
13

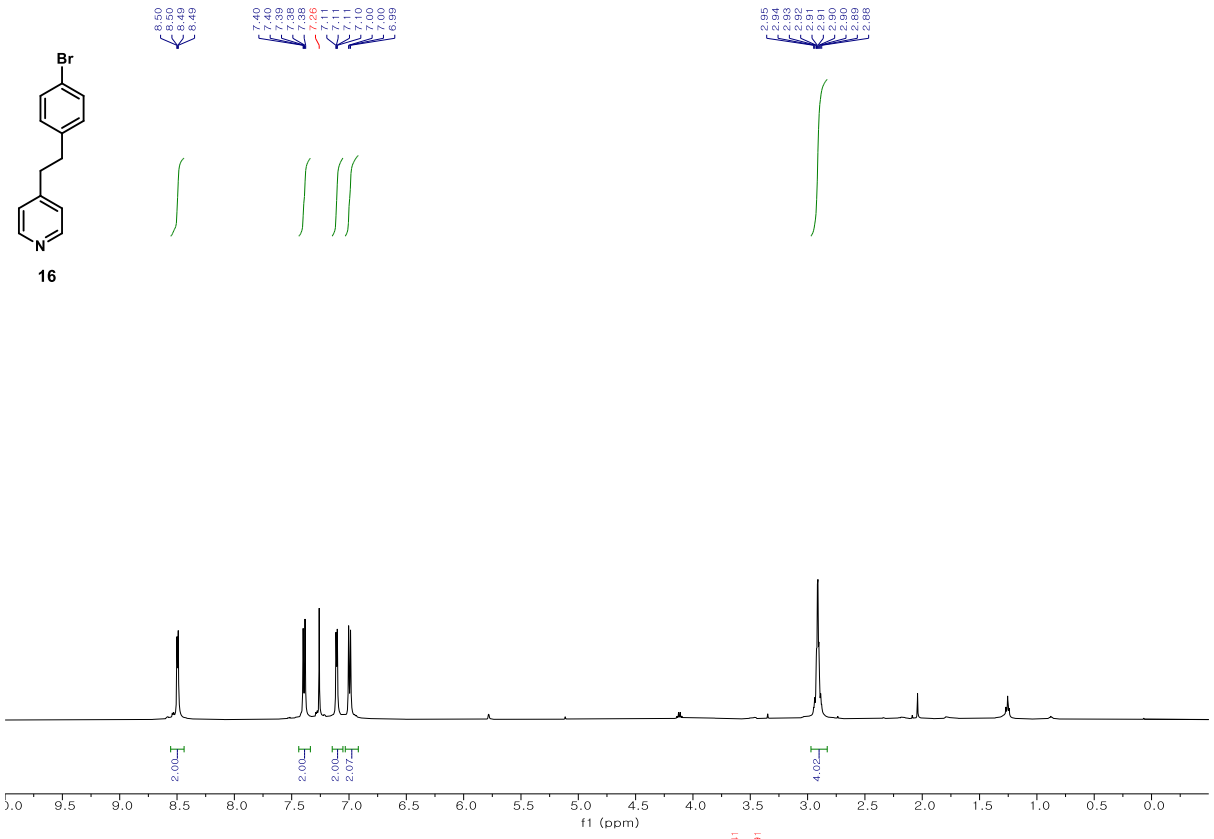
-69.24
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

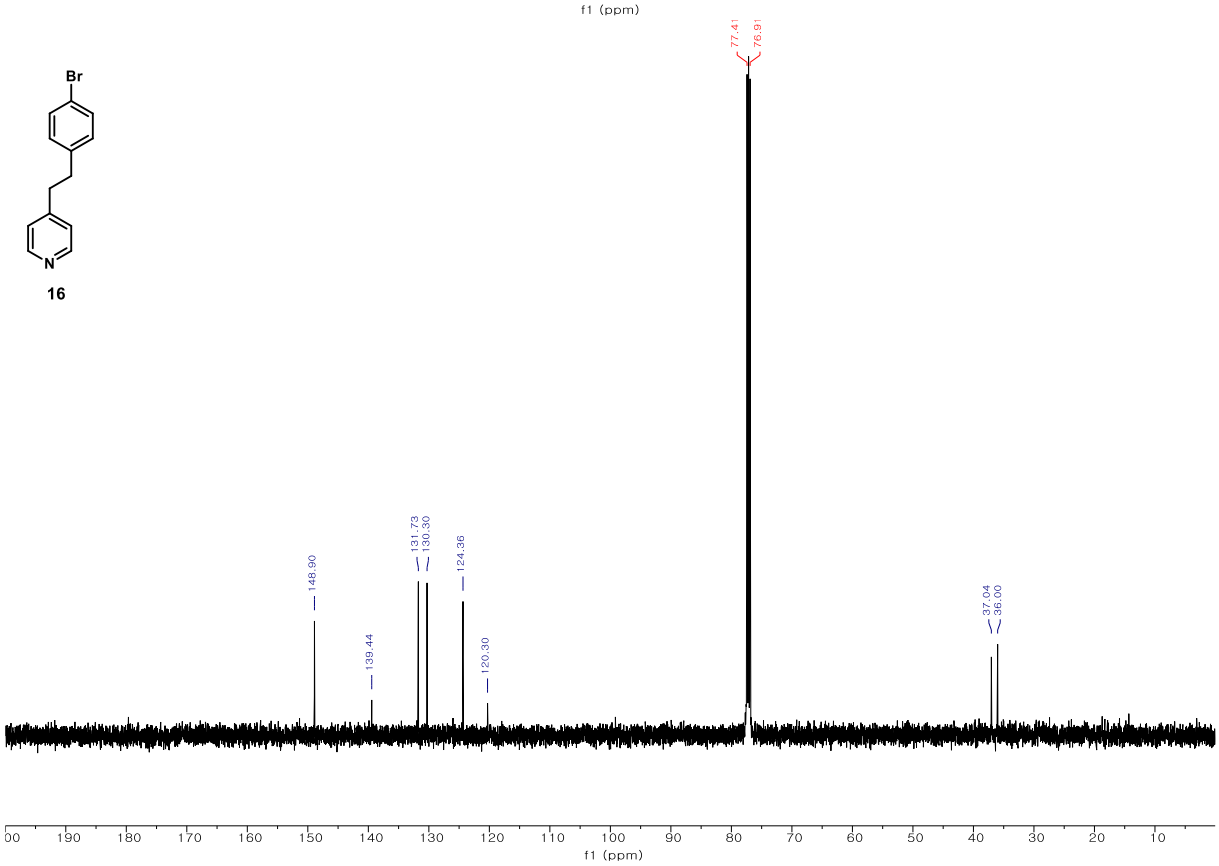

CO2Me
N
14
8.48
8.48
8.47
8.47
7.26
7.10
7.09
3.66
2.63
2.62
2.60
2.36
2.35
2.34
2.33
2.32
2.31
1.68
1.67
1.66
1.66
1.65
2.00
2.03
3.12
2.01
2.19
4.28
f1 (ppm)

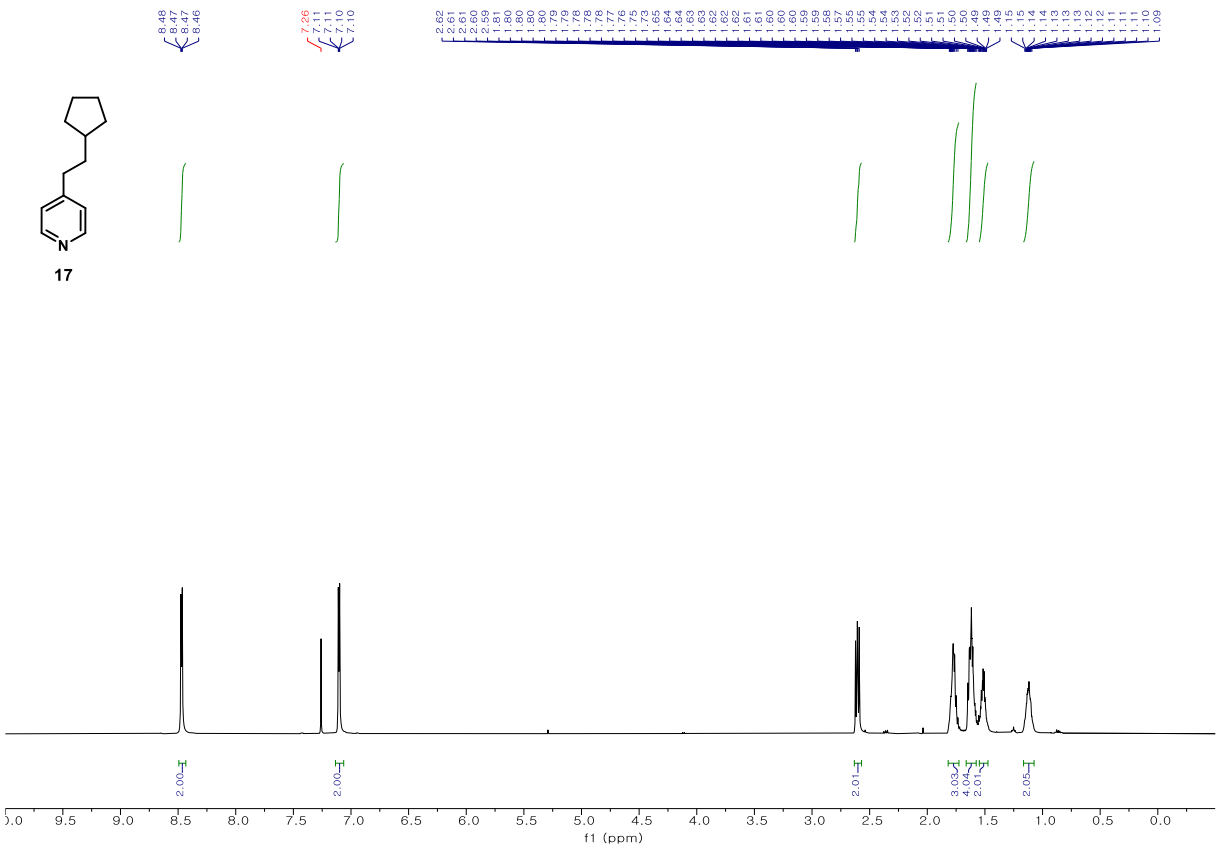

CO2Me
N
14
77.29
77.04
76.78
150.92
149.75
123.84
173.81
51.56
34.86
33.75
29.65
24.43
f1 (ppm)

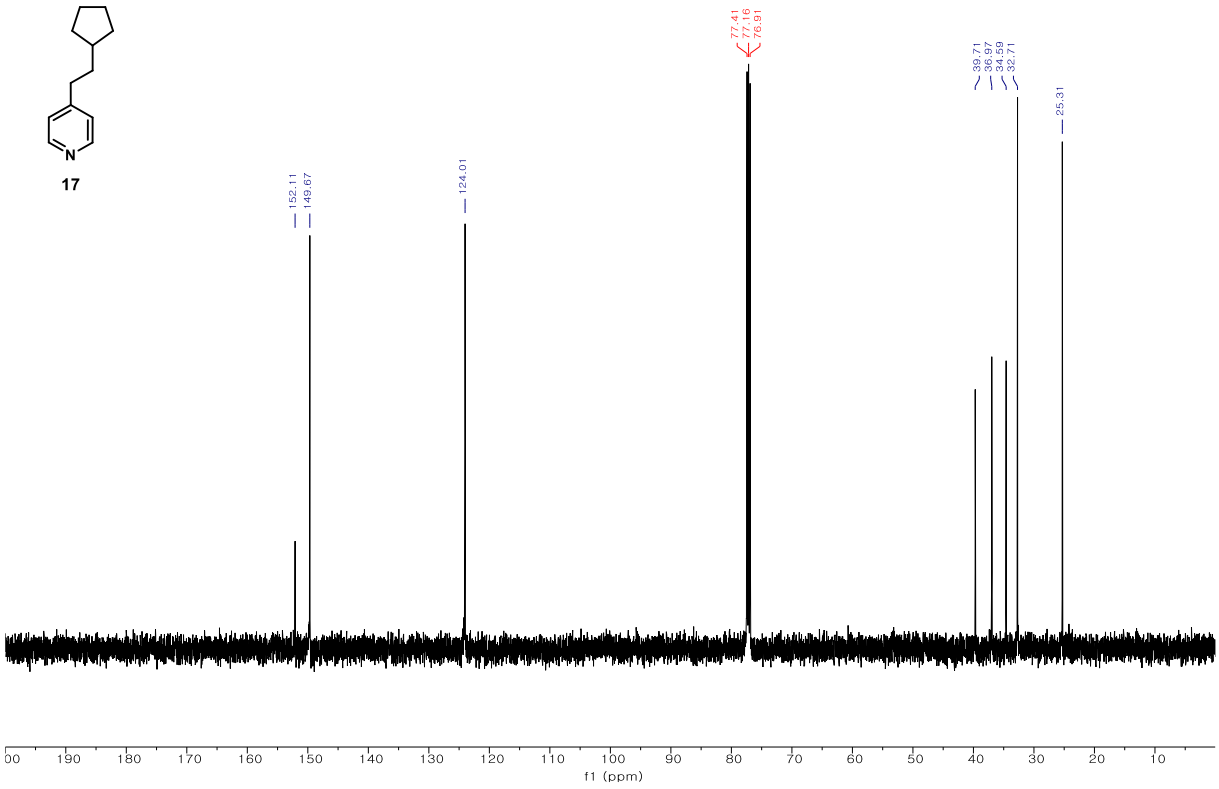

8.49
8.48
8.48
8.48
7.29
7.29
7.28
7.26
7.22
7.21
7.20
7.20
7.19
7.19
7.18
7.15
7.14
7.13
7.10
7.10
7.09
7.09
2.93
15
2.00
2.24
1.11
1.15
2.05
4.11
f1 (ppm)

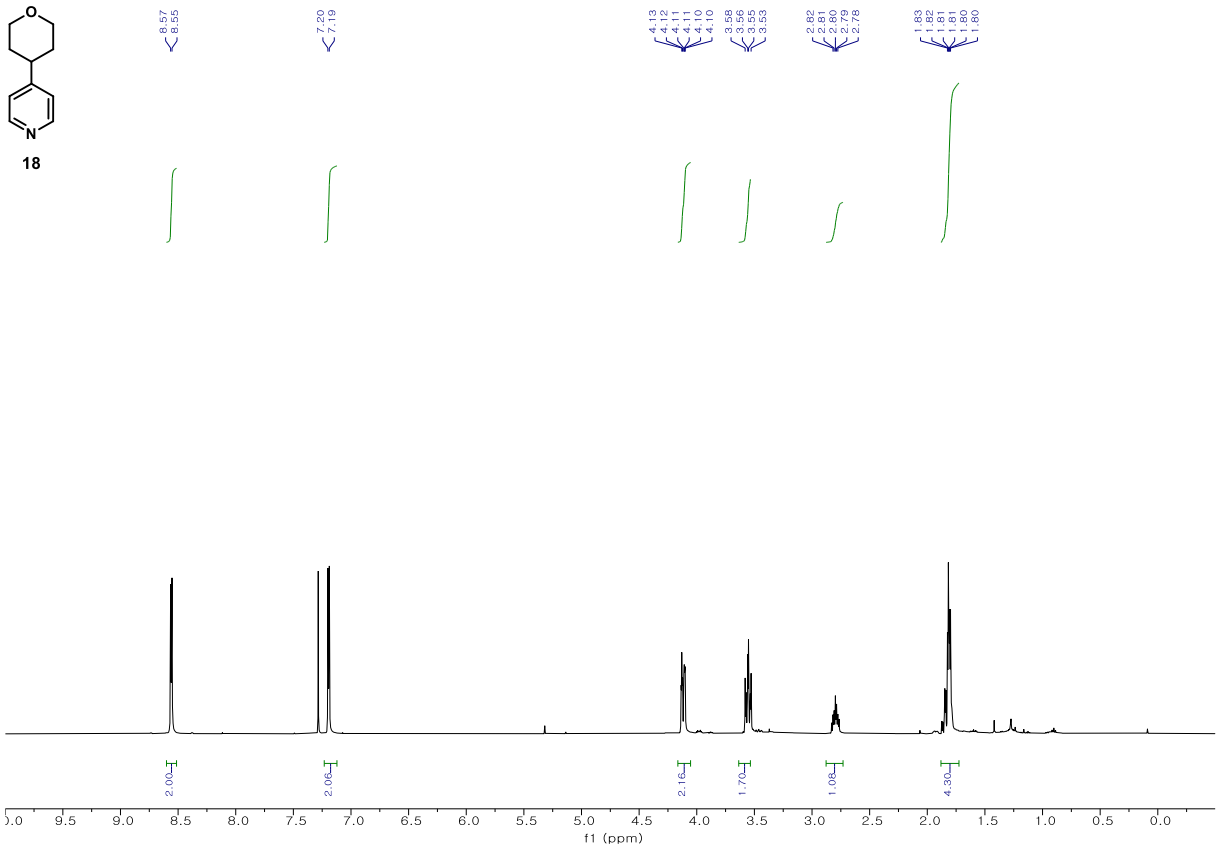

15
151.14
149.32
140.64
128.58
128.49
126.38
124.18
37.17
36.60
f1 (ppm)

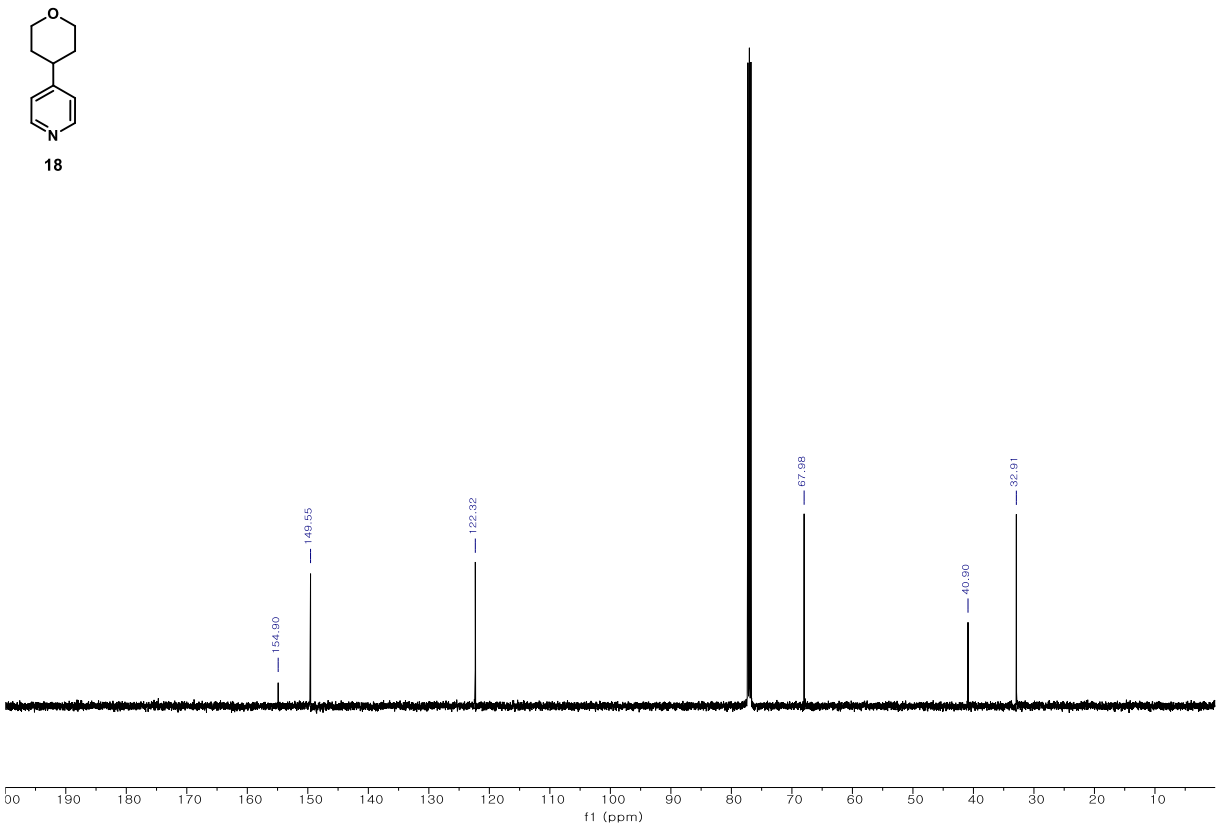

8.50
8.50
8.49
8.49
7.40
7.40
7.39
7.38
7.38
7.26
7.11
7.11
7.10
7.00
7.00
6.99
2.95
2.94
2.93
2.92
2.91
2.91
2.90
2.90
2.89
2.88
Br
N
16
2.00
2.00
2.00
2.07
4.02
f1 (ppm)

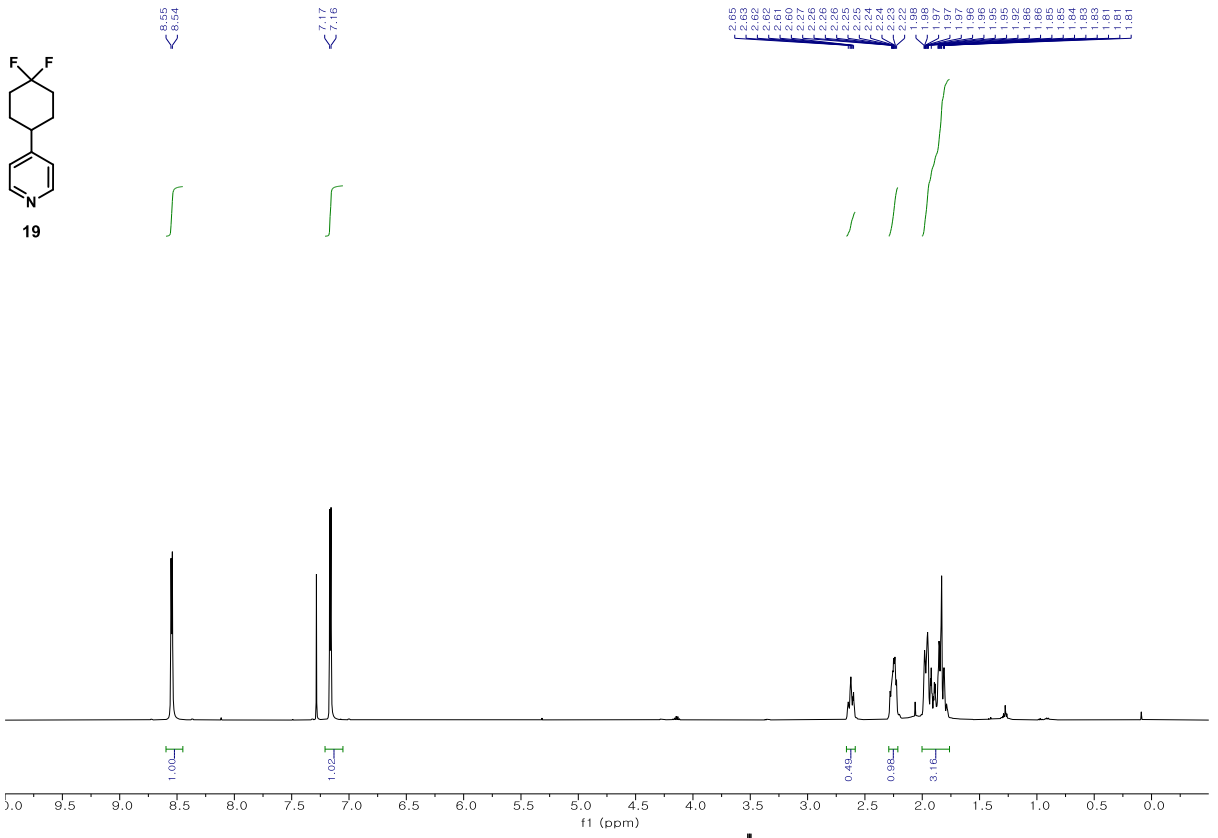

77.41
76.91
Br
N
16
148.90
139.44
131.73
130.30
124.36
120.30
37.04
36.00
f1 (ppm)

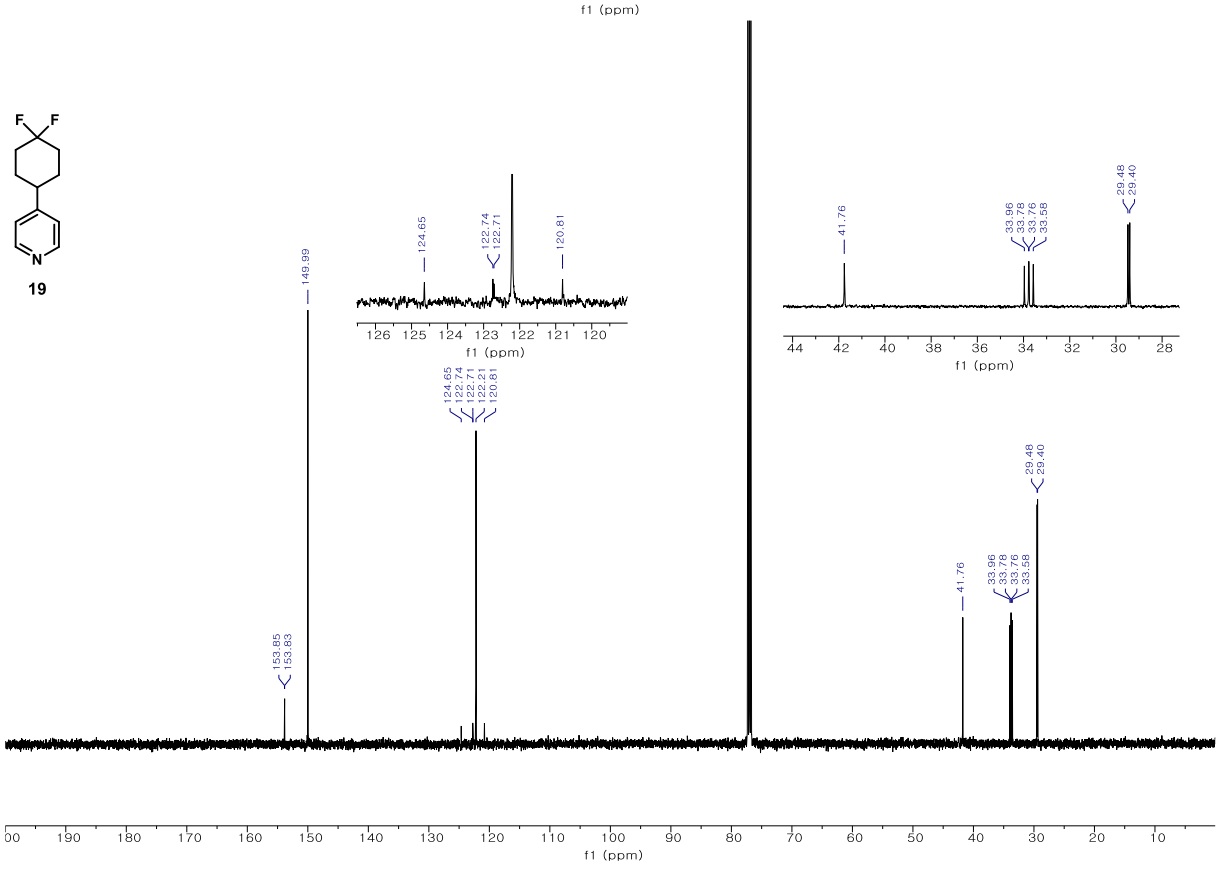

17
f1 (ppm)

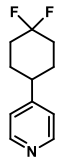

17
f1 (ppm)


18
8.57
8.55
7.20
7.19
4.13
4.12
4.11
4.11
4.10
4.10
3.58
3.56
3.55
3.55
2.82
2.81
2.80
2.79
2.78
1.83
1.82
1.81
1.81
1.80
1.80
2.00
2.06
2.16
1.70
1.08
4.30
f1 (ppm)


18
154.90
149.55
122.32
67.98
40.90
32.91
f1 (ppm)

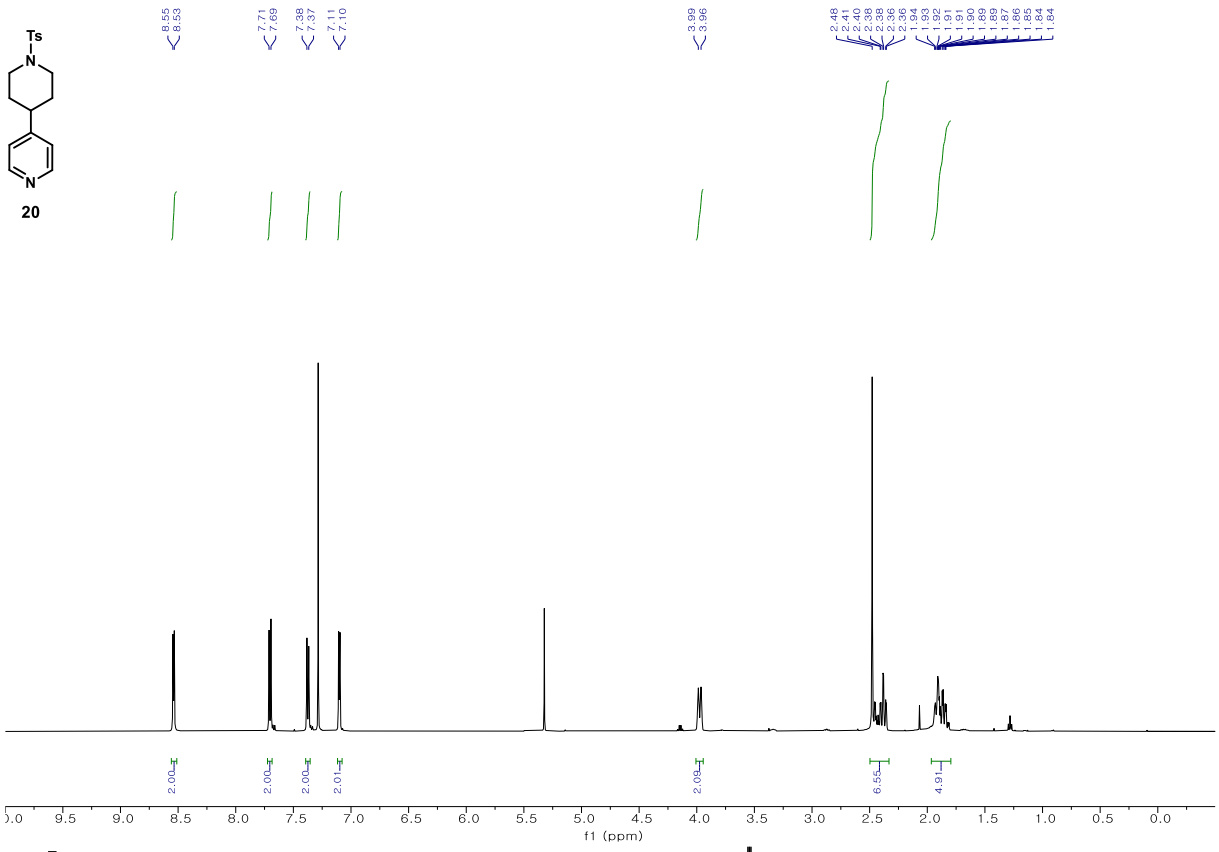

F
F
N
19
8.55
8.54
7.17
7.16
2.65
2.63
2.62
2.62
2.61
2.60
2.27
2.26
2.26
2.25
2.25
2.24
2.24
2.23
2.23
1.98
1.97
1.97
1.97
1.96
1.96
1.95
1.95
1.92
1.86
1.86
1.85
1.85
1.84
1.83
1.83
1.81
1.81
1.81
1.00
1.02
0.49
0.98
3.16
f1 (ppm)


F
F
N
19
149.99
124.65
122.74
122.71
120.81
153.85
153.83
41.76
33.96
33.78
33.76
33.58
29.48
29.40
f1 (ppm)


F
F
N

19

-94.31
-94.94
-104.75
-105.38
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


Ts
N
N
20
8.55
8.53
7.71
7.69
7.38
7.37
7.11
7.10
3.99
3.96
2.48
2.41
2.40
2.38
2.38
2.36
2.36
1.94
1.93
1.92
1.91
1.91
1.90
1.89
1.89
1.87
1.86
1.85
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1.84
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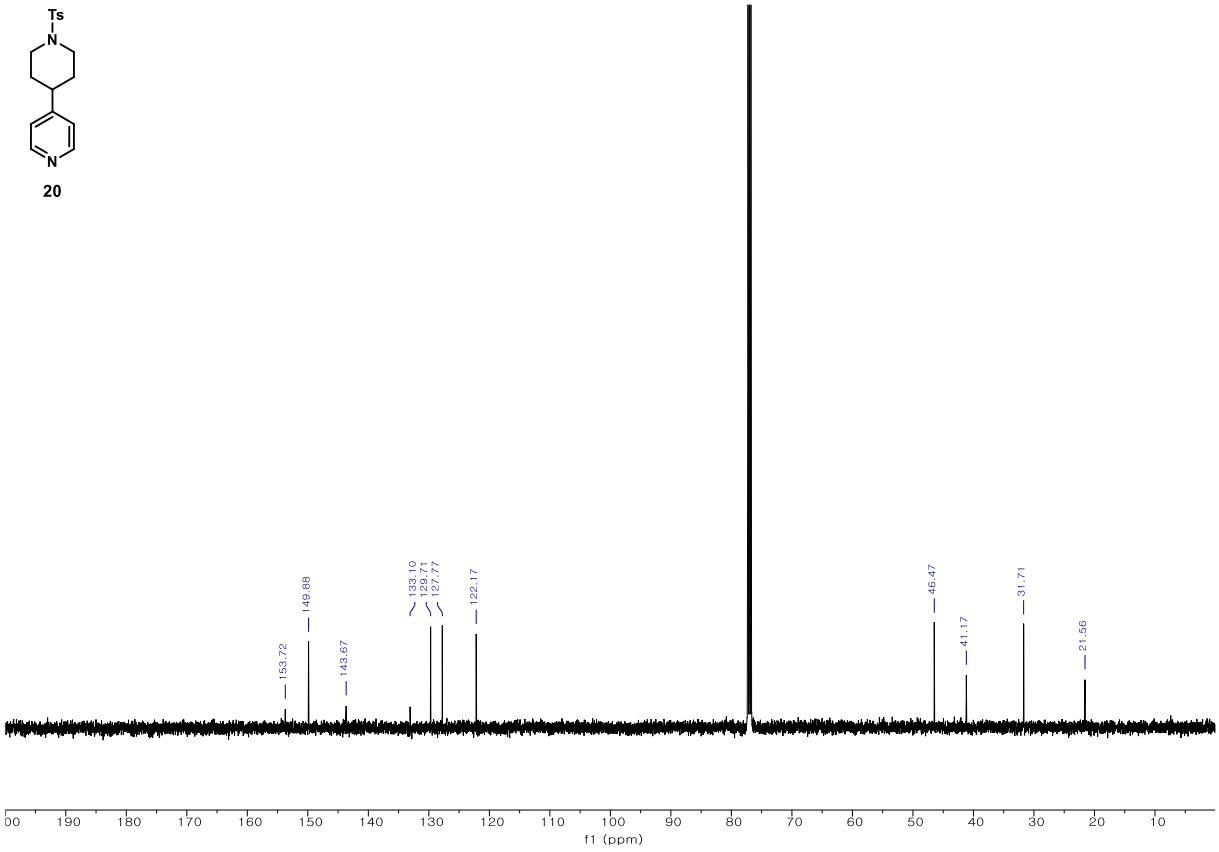
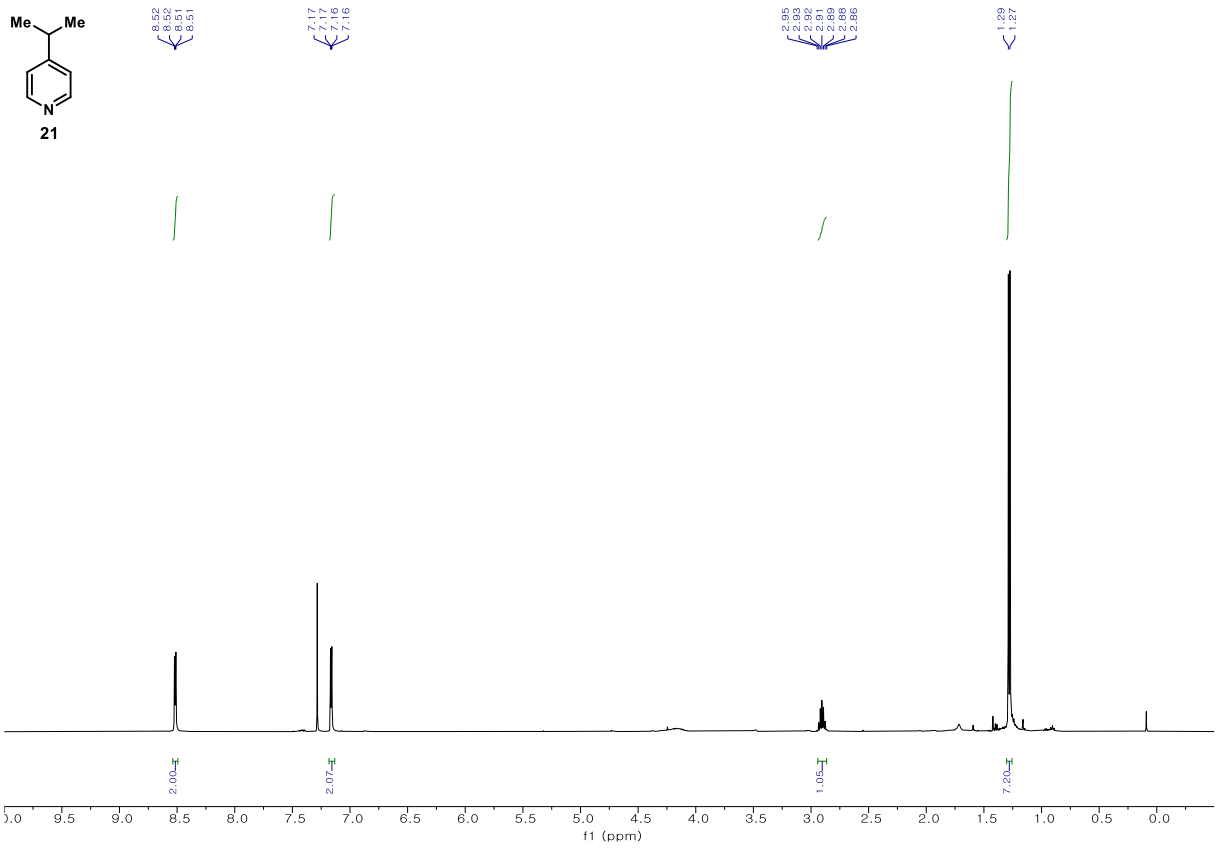
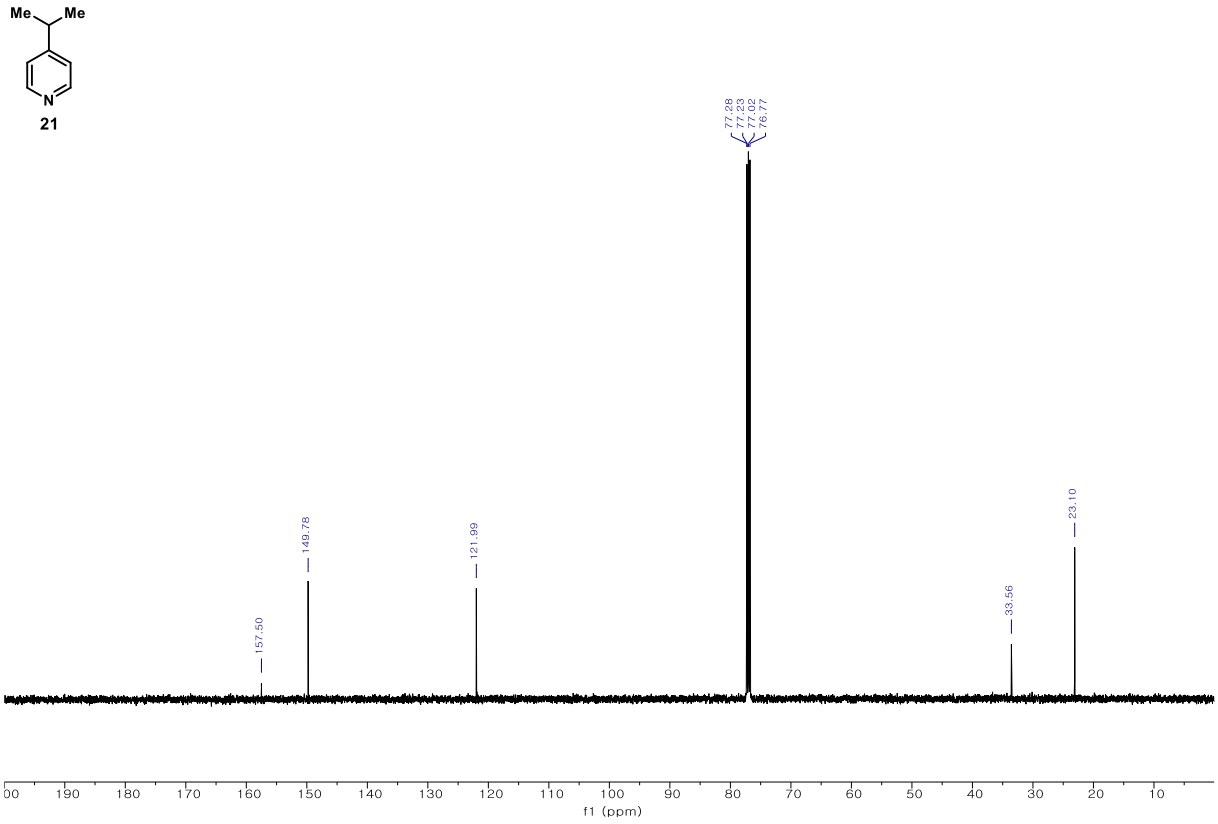
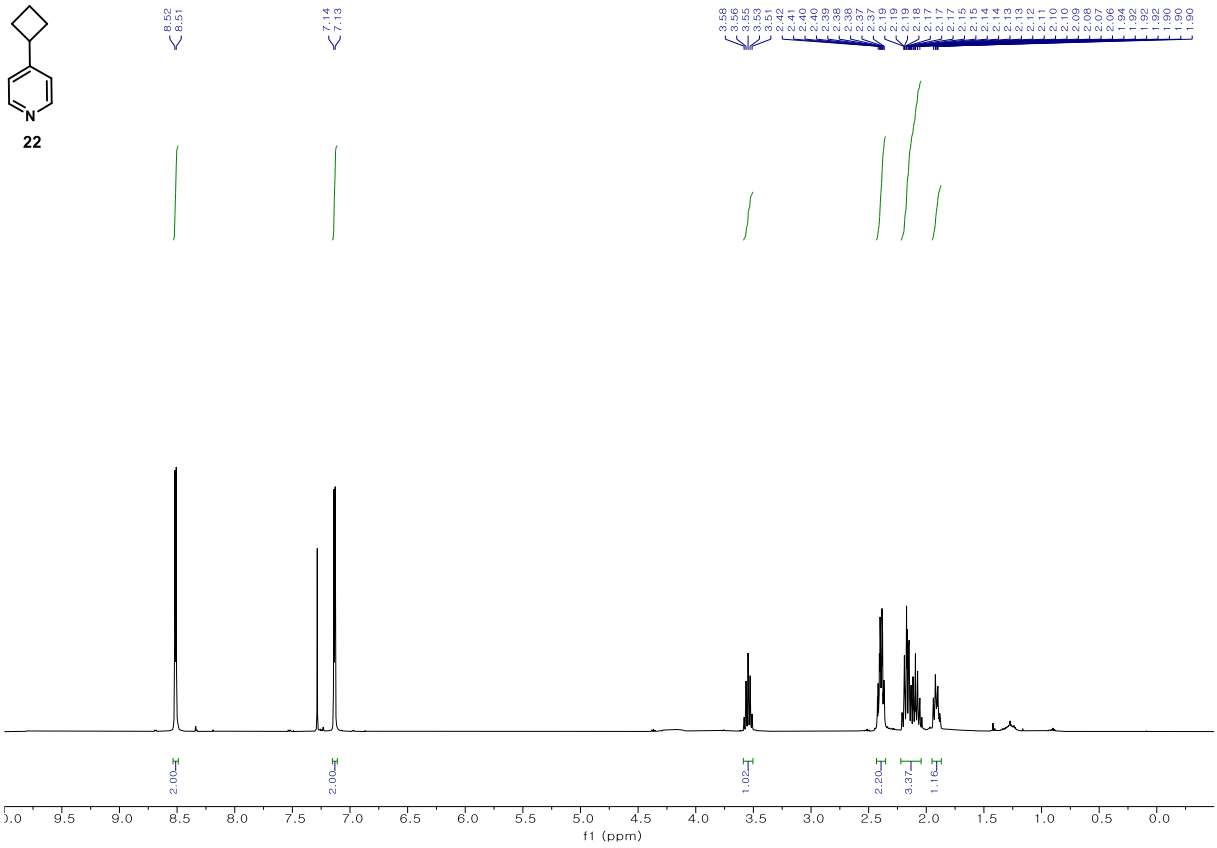
2.00
2.00
2.01
2.08
6.55
4.91
f1 (ppm)


Ts
N
N
20
153.72
149.88
143.67
133.10
129.71
127.77
122.17
46.47
41.17
31.71
21.56
f1 (ppm)


Me
Me
N
21
8.52
8.52
8.51
8.51
7.17
7.17
7.16
7.16
2.95
2.93
2.92
2.91
2.89
2.88
2.86
1.29
1.27
2.00
2.07
1.05
7.20
f1 (ppm)


Me
Me
N
21
77.28
77.23
77.02
76.77
157.50
149.78
121.99
33.56
23.10
f1 (ppm)


22
8.52
8.51
7.14
7.13
3.58
3.56
3.55
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3.51
2.42
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2.40
2.40
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2.38
2.38
2.37
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2.19
2.18
2.17
2.17
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2.15
2.14
2.14
2.13
2.13
2.12
2.11
2.10
2.10
2.09
2.08
2.07
2.06
1.94
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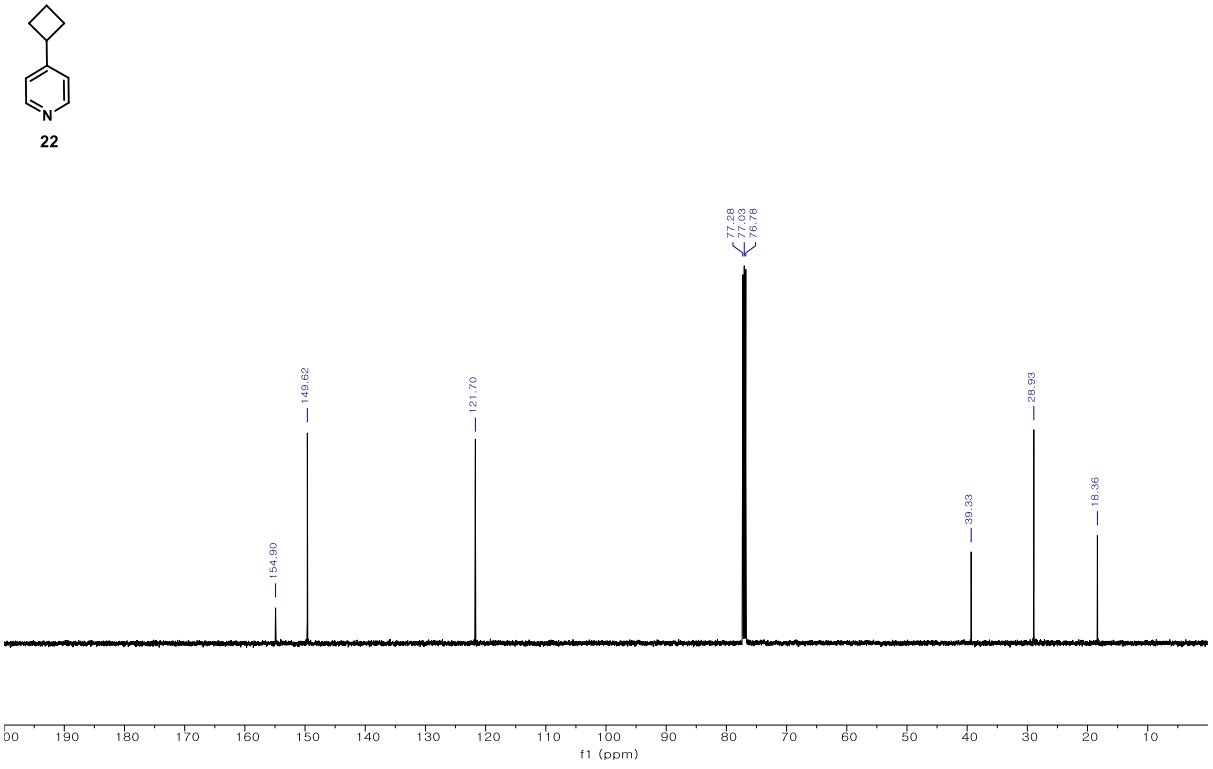
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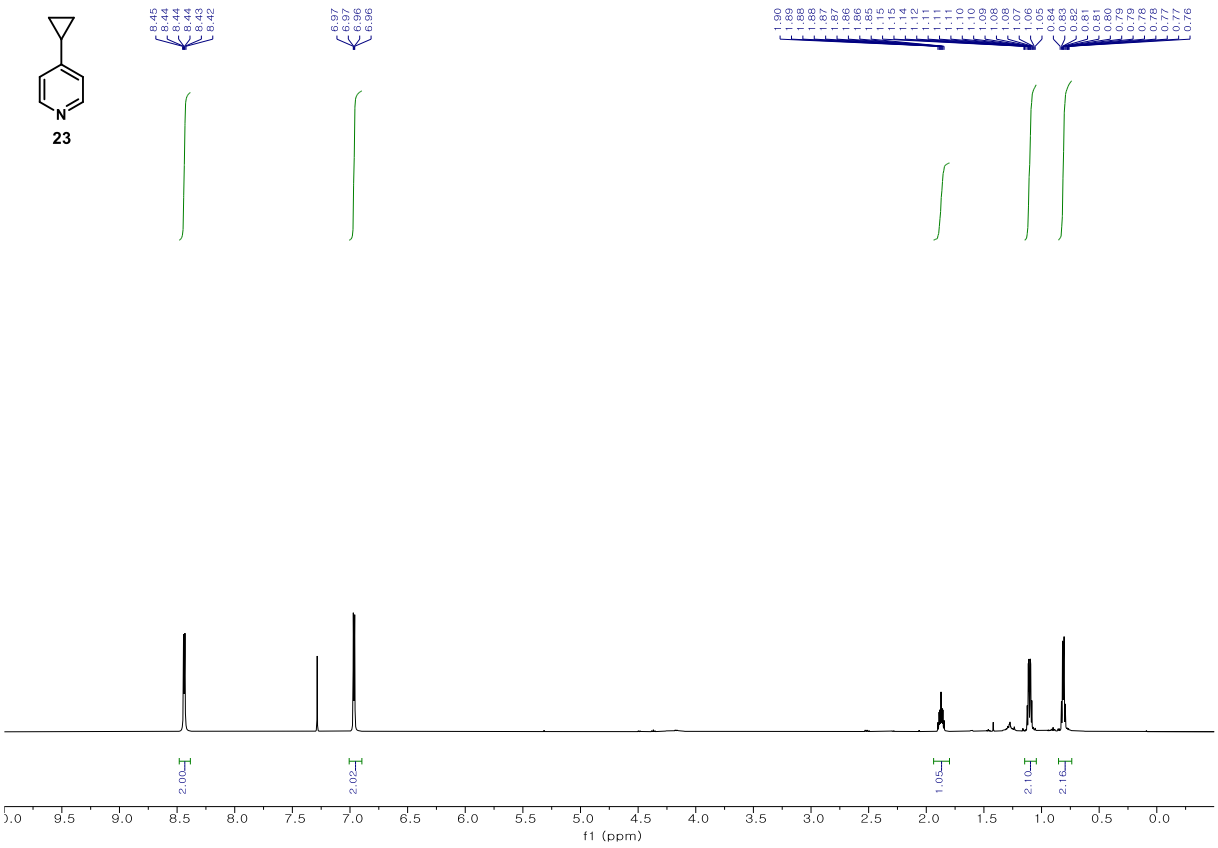
18.36
154.90
f1 (ppm)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6.96
6.96
1.90
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1.88
1.88
1.87
1.87
1.86
1.85
1.15
1.15
1.14
1.12
1.11
1.11
1.11
1.10
1.10
1.09
1.08
1.08
1.07
1.06
1.05
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0.82
0.81
0.81
0.80
0.79
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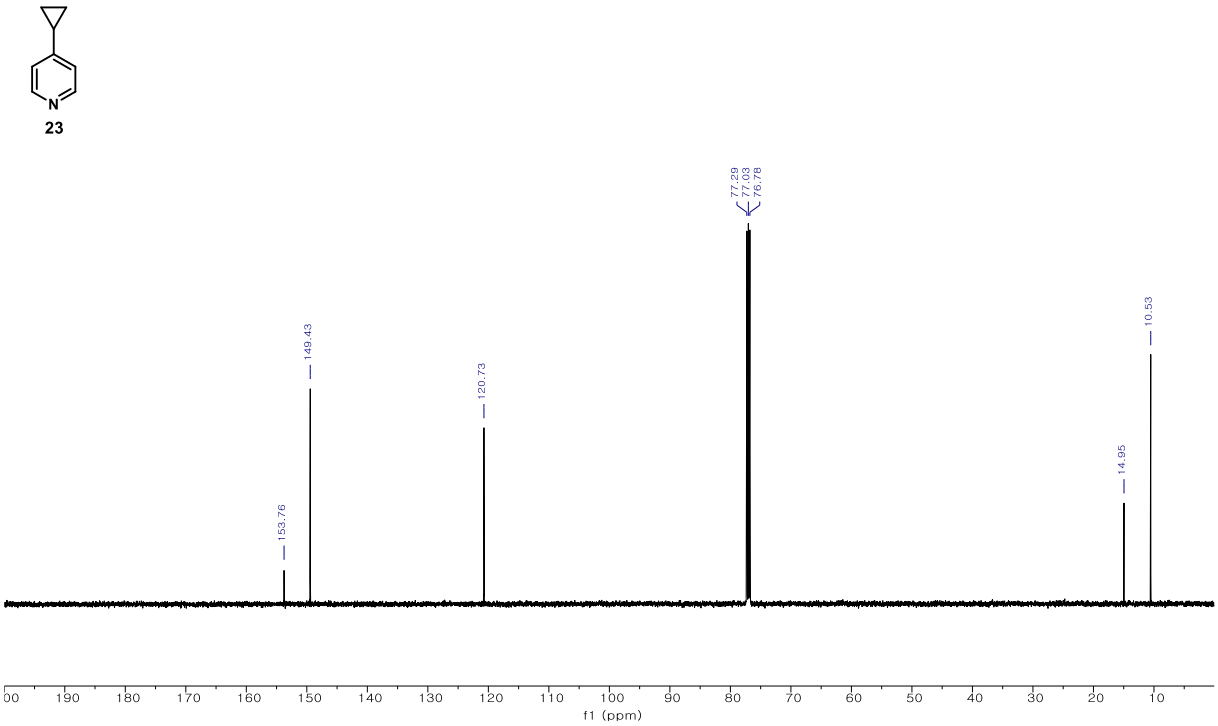
1.05
2.10
2.16
f1 (ppm)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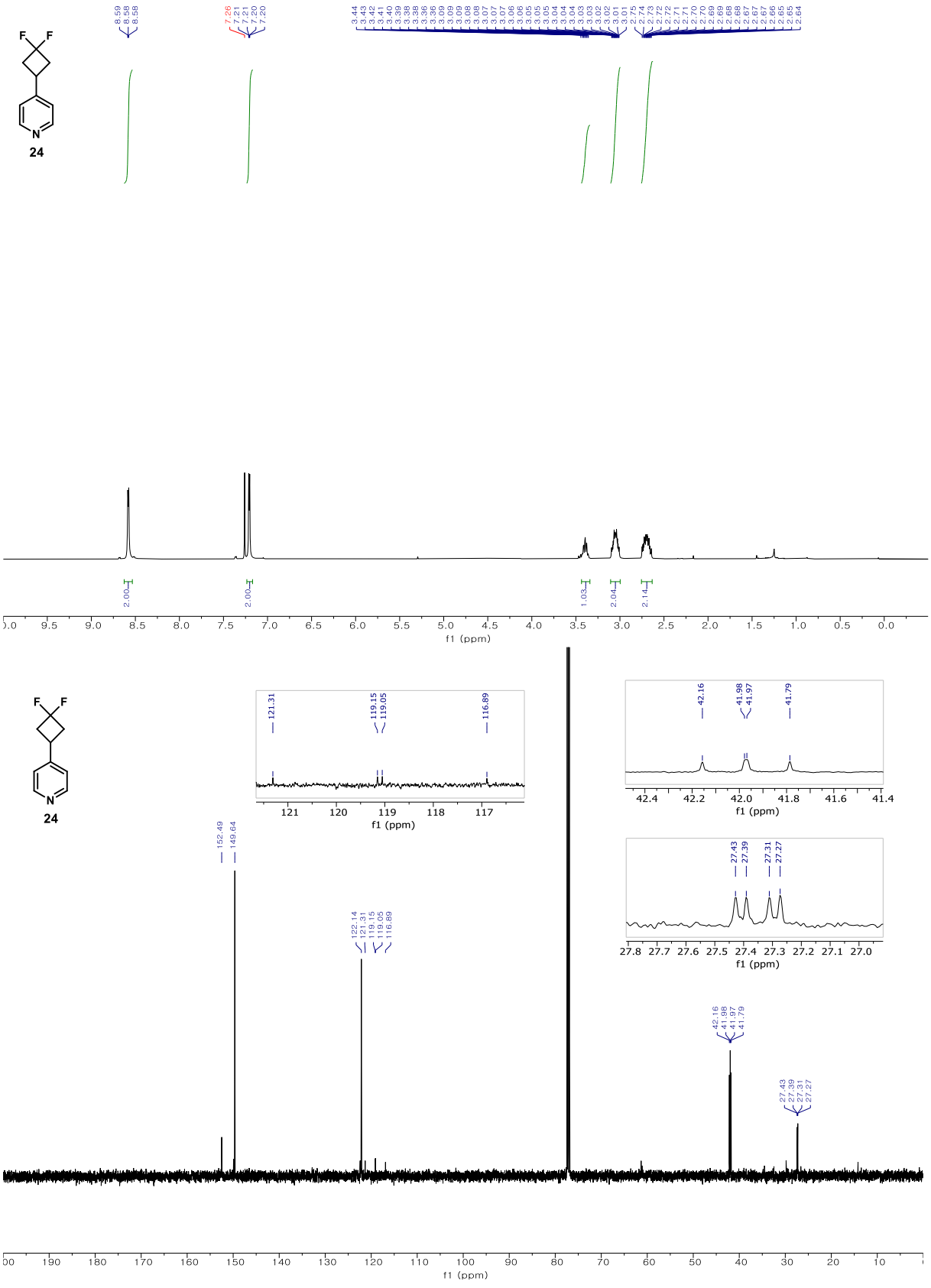
f1 (ppm)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7.20
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3.42
3.41
3.40
3.39
3.38
3.38
3.36
3.36
3.09
3.09
3.09
3.08
3.08
3.07
3.07
3.07
3.06
3.06
3.05
3.05
3.05
3.04
3.04
3.04
3.03
3.03
3.02
3.02
3.01
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2.67
2.67
2.66
2.65
2.65
2.64
2.00
2.00
1.03
2.04
2.14
f1 (ppm)
121.31
119.15
119.05
116.89
f1 (ppm)
42.16
41.98
41.97
41.79
f1 (ppm)
27.43
27.39
27.31
27.27
f1 (ppm)
152.49
149.64
122.14
121.31
119.15
119.05
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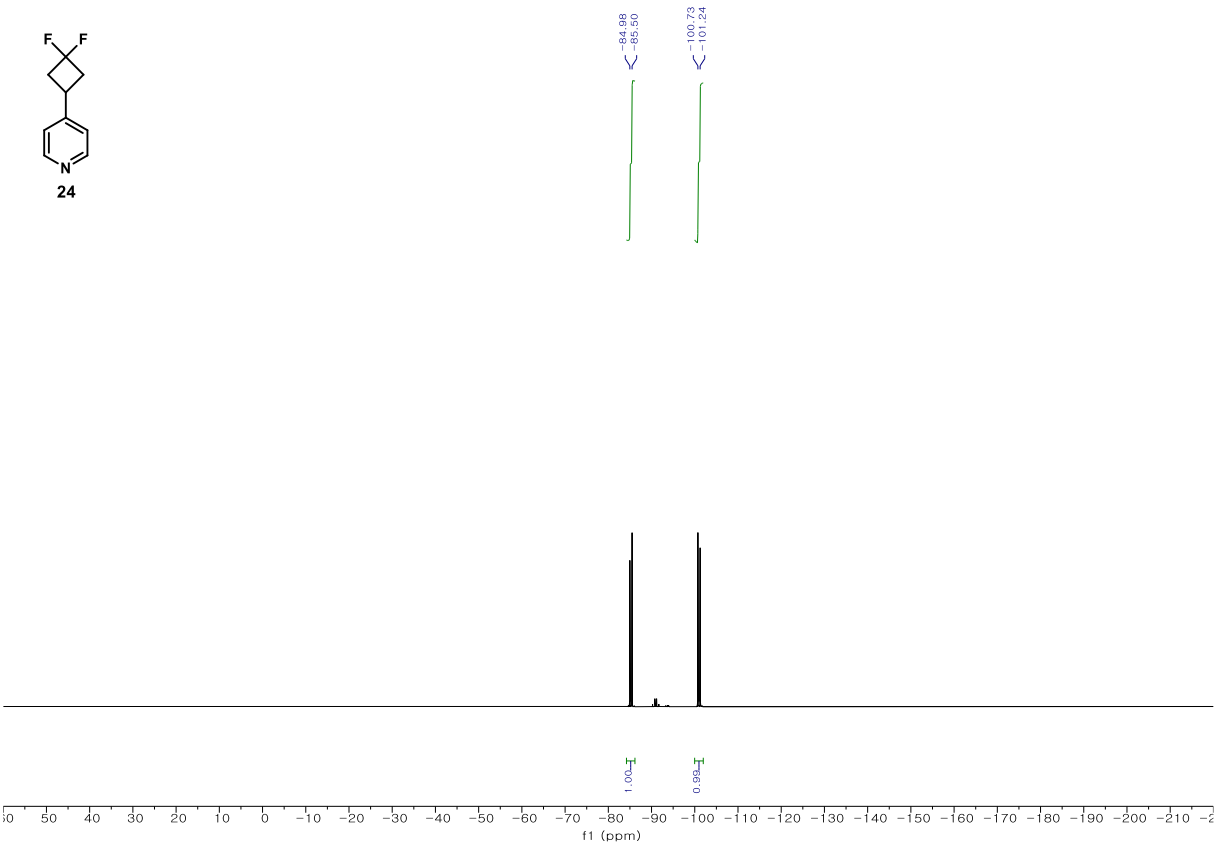
42.16
41.98
41.97
41.79
27.43
27.39
27.31
27.27
f1 (ppm)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F
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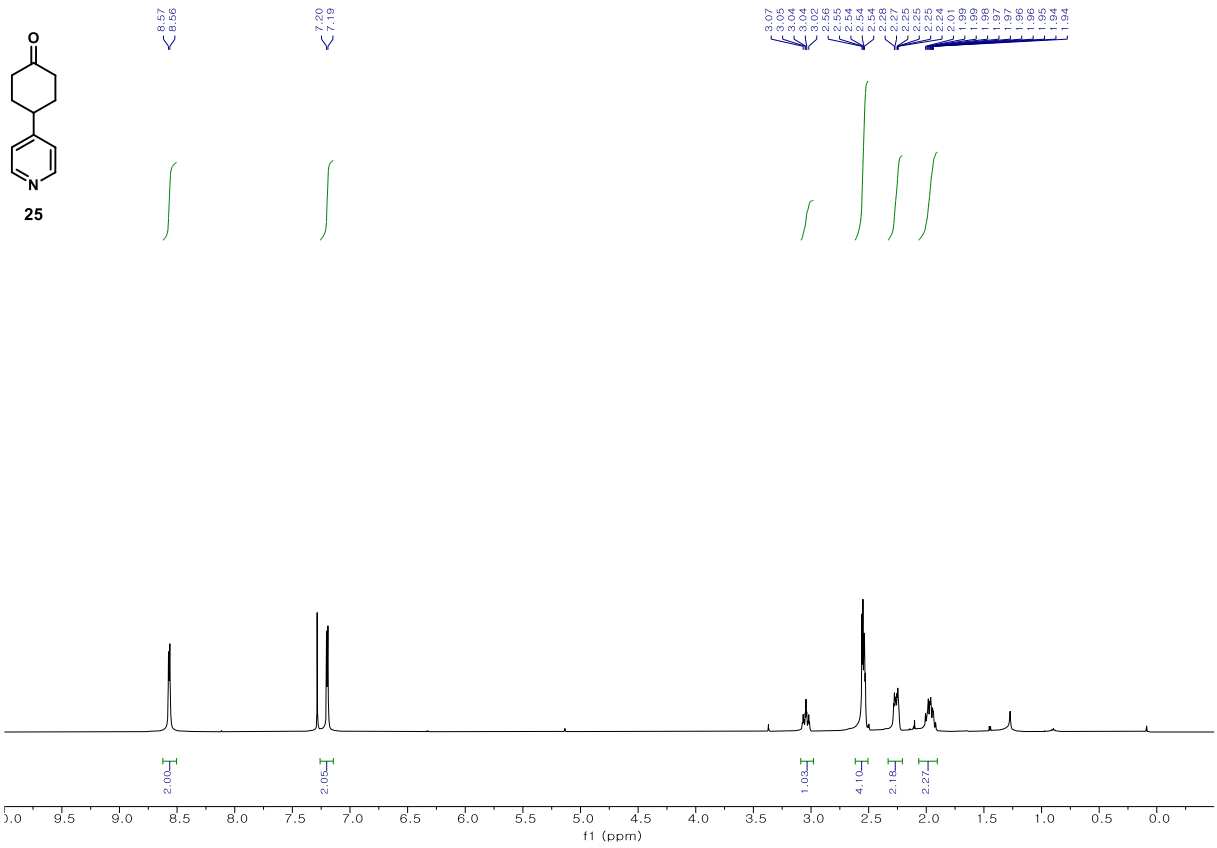
1.00
0.99
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)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3.04
3.04
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2.54
2.54
2.54
2.28
2.27
2.25
2.25
2.25
2.24
2.01
1.99
1.98
1.98
1.97
1.97
1.96
1.96
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1.94
1.94
2.00
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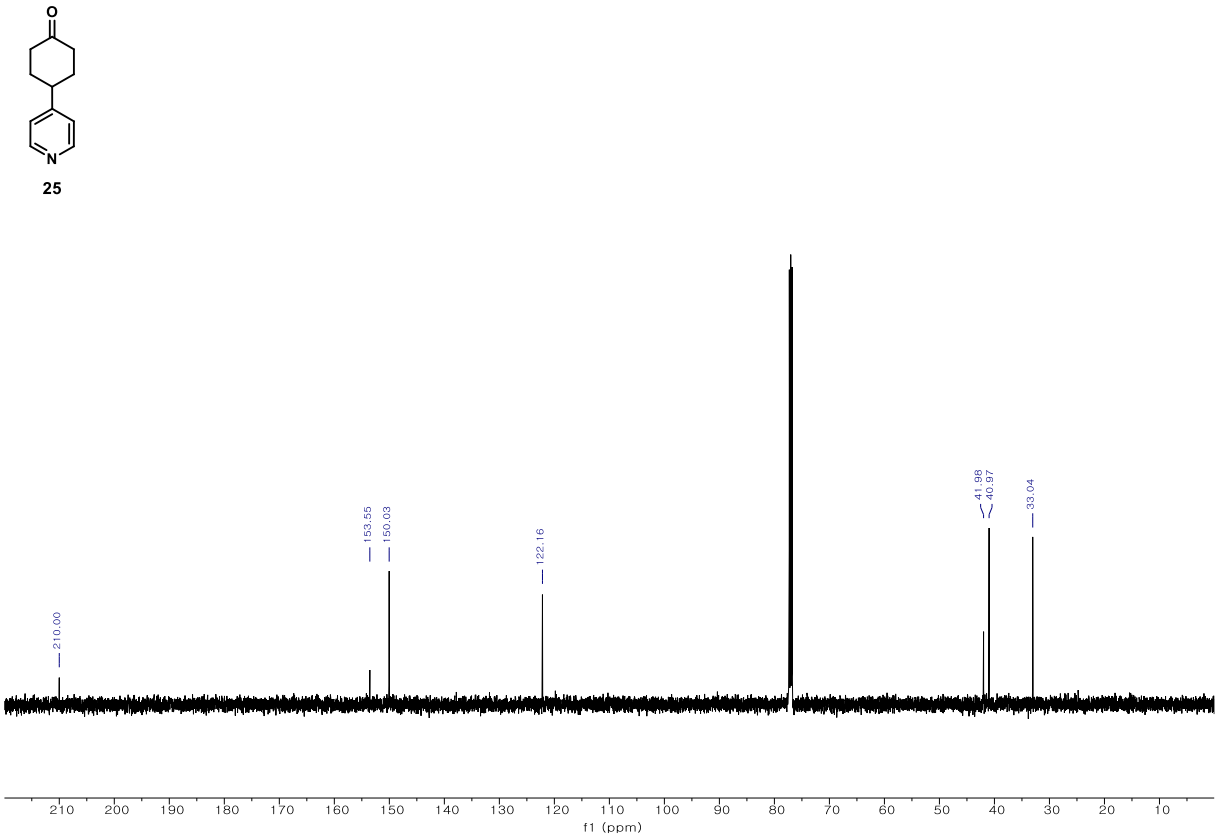
1.03
4.10
2.18
2.27
f1 (ppm)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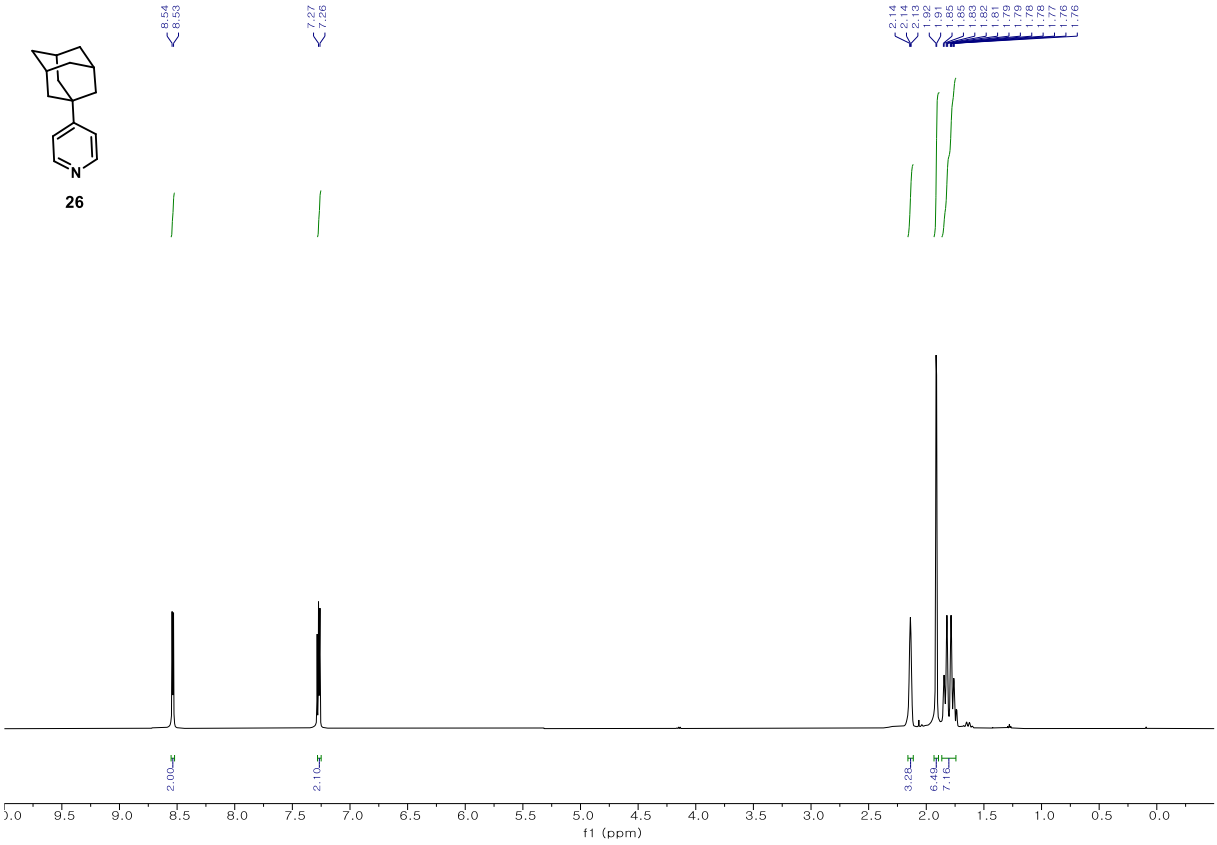
150.03
122.16
41.98
40.97
33.04
f1 (ppm)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2.14
2.13
1.92
1.91
1.85
1.85
1.83
1.82
1.81
1.79
1.79
1.78
1.78
1.77
1.76
1.76
N
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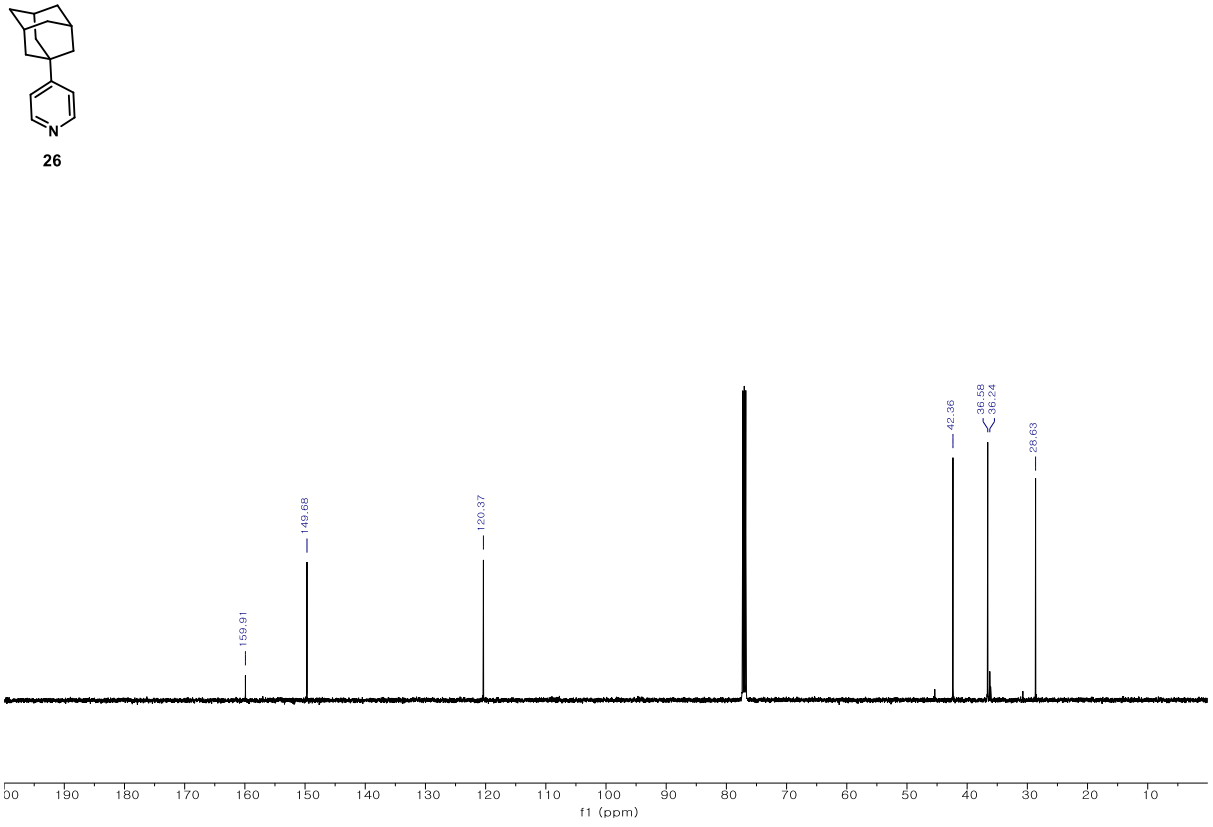
2.10
3.28
6.48
7.16
f1 (ppm)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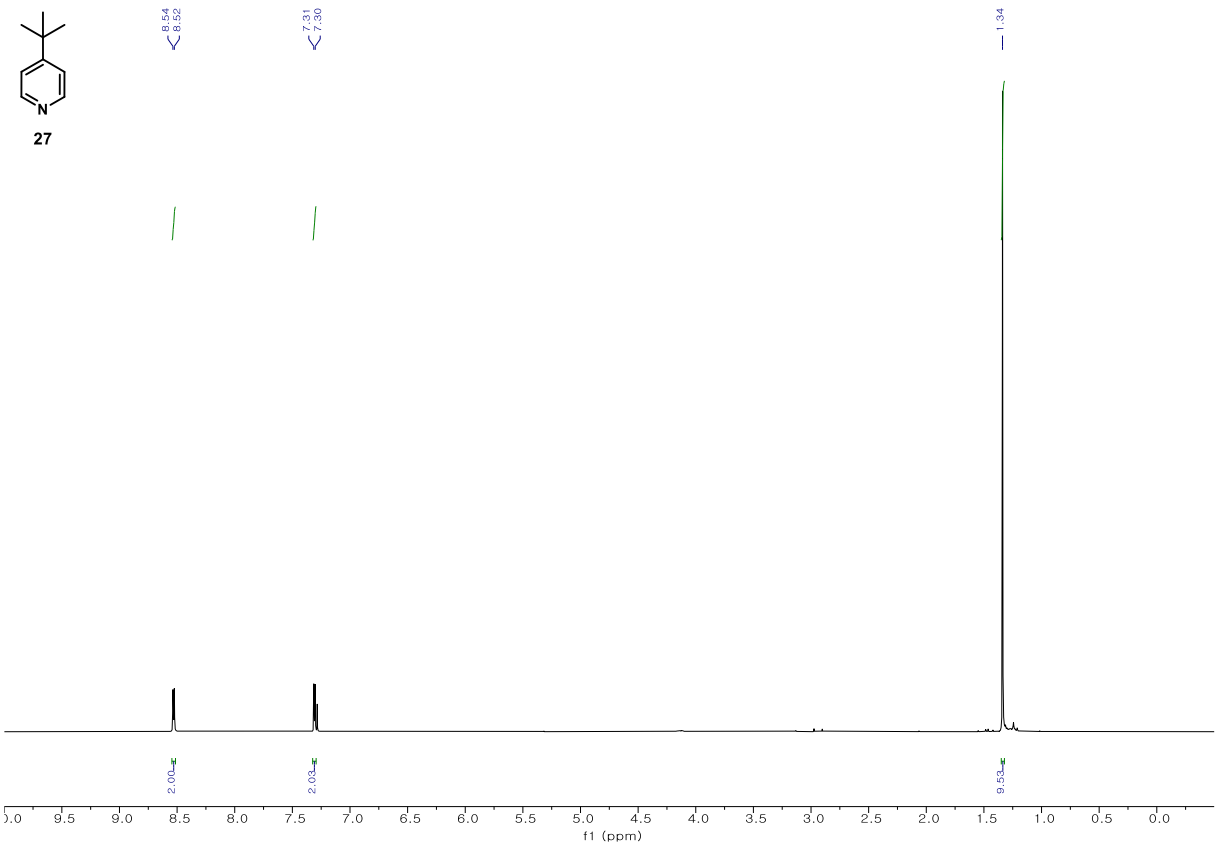
120.37
42.36
36.58
36.24
28.63
f1 (ppm)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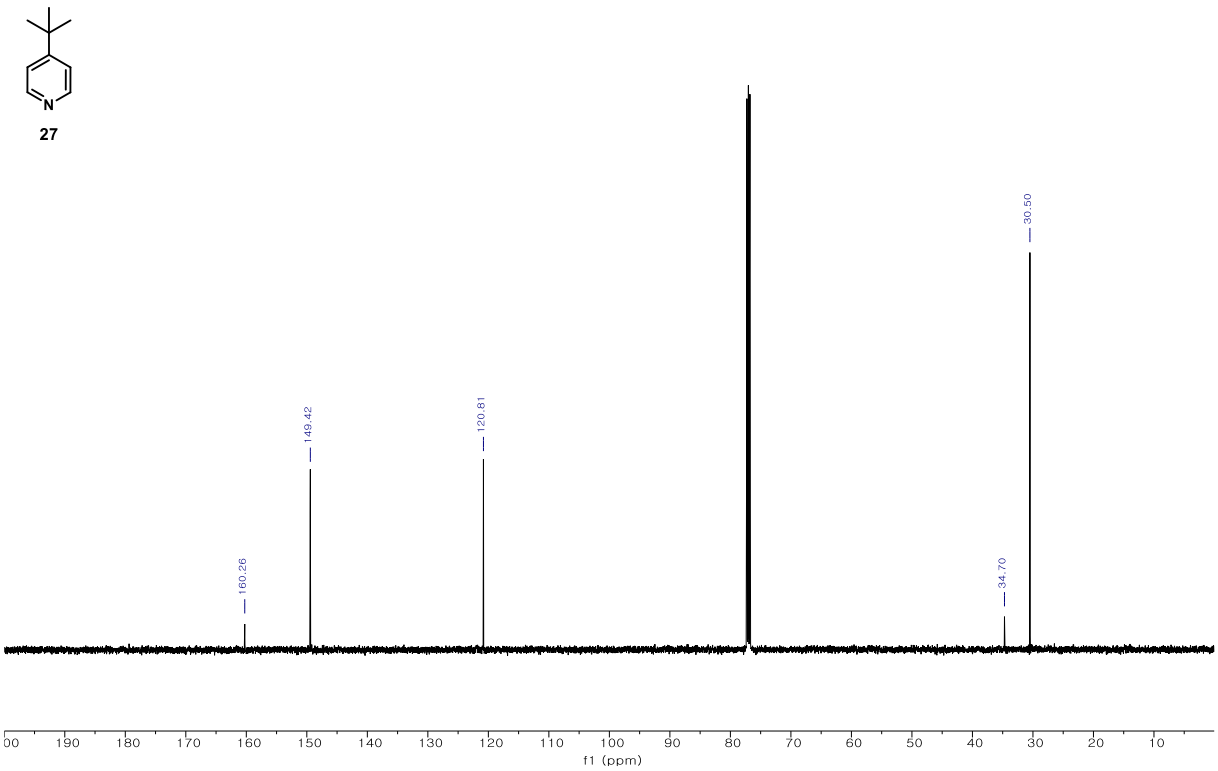
7.30
1.34
2.00
2.03
9.53
f1 (ppm)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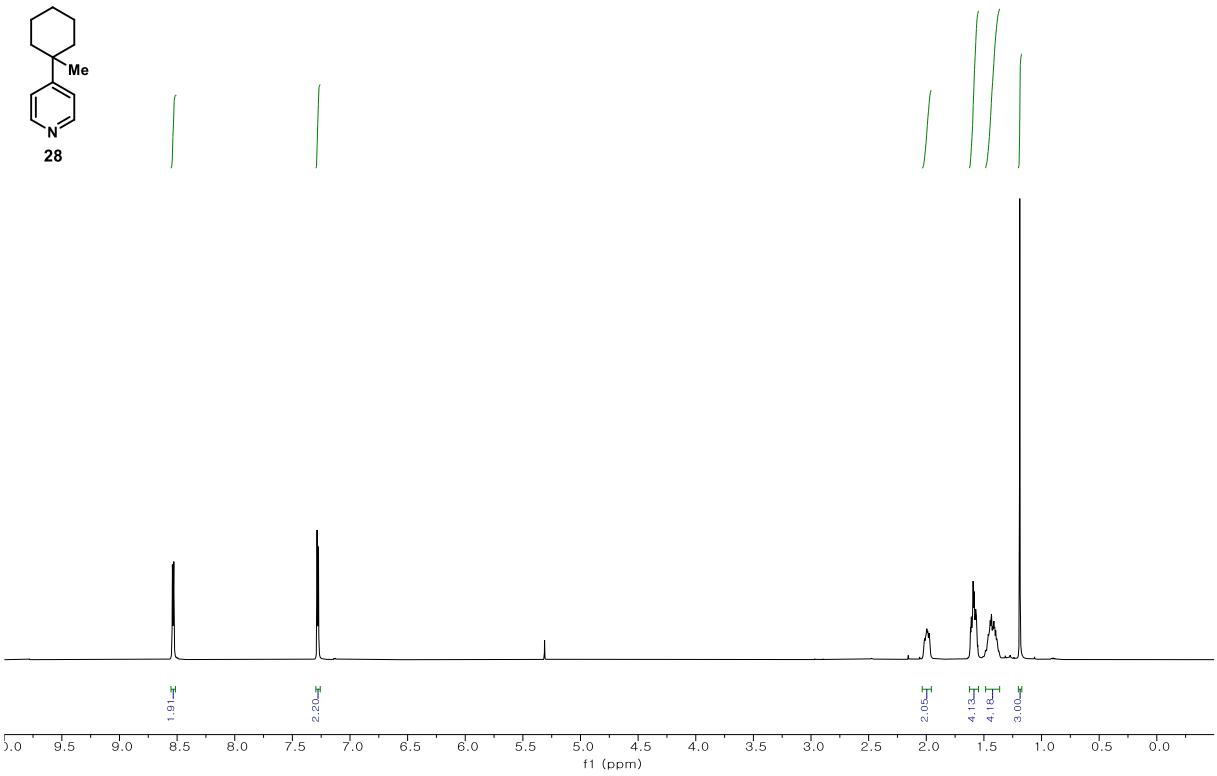
34.70
30.50
f1 (ppm)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N
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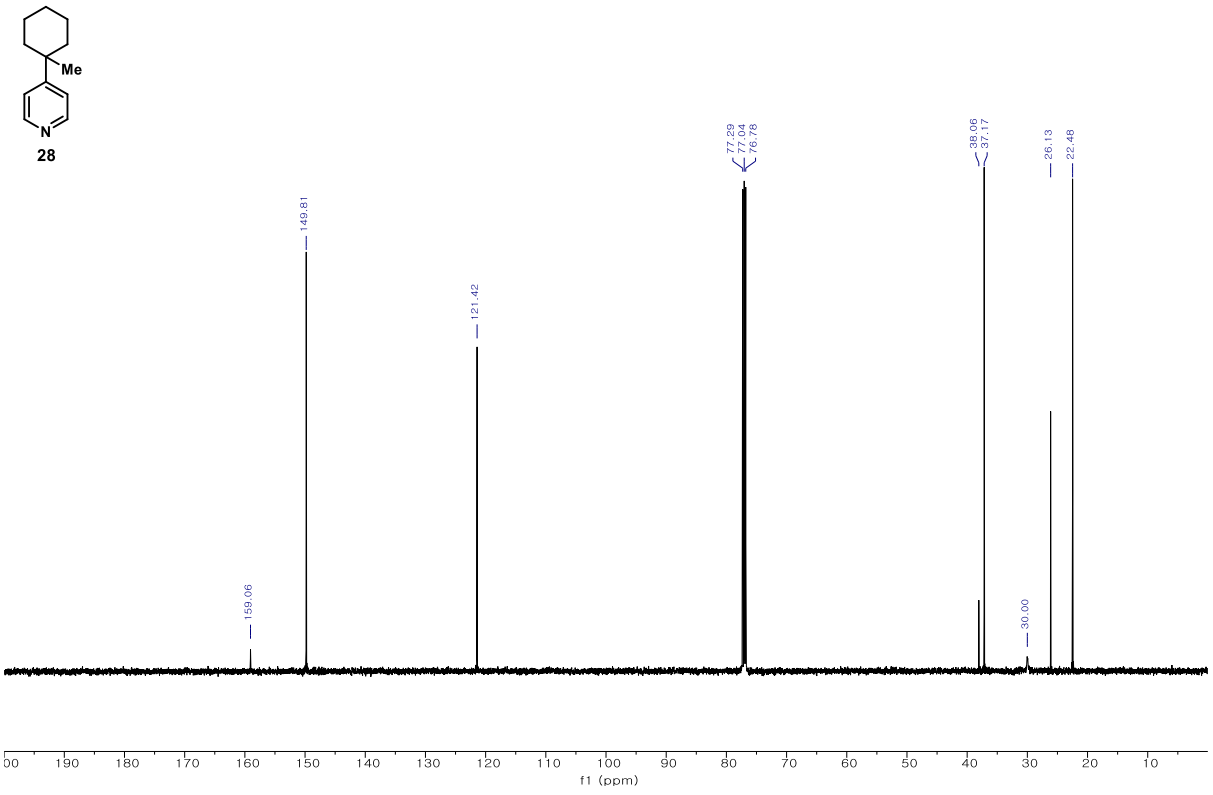
1.91
2.20
2.05
4.13
4.18
3.00
f1 (ppm)


Me
N
28
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121.42
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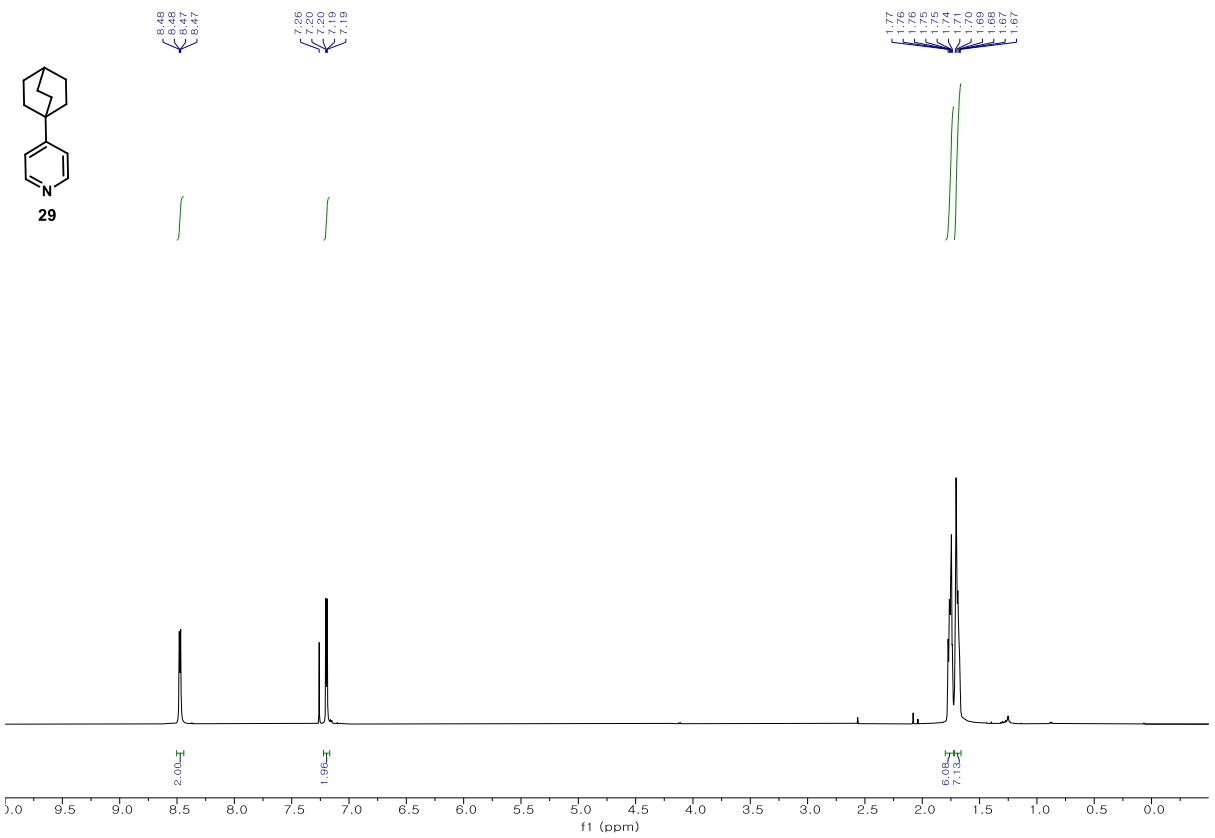
76.78
38.06
37.17
30.00
26.13
22.48
f1 (ppm)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7.19
7.19
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1.76
1.76
1.75
1.75
1.74
1.71
1.70
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1.68
1.67
1.67
N
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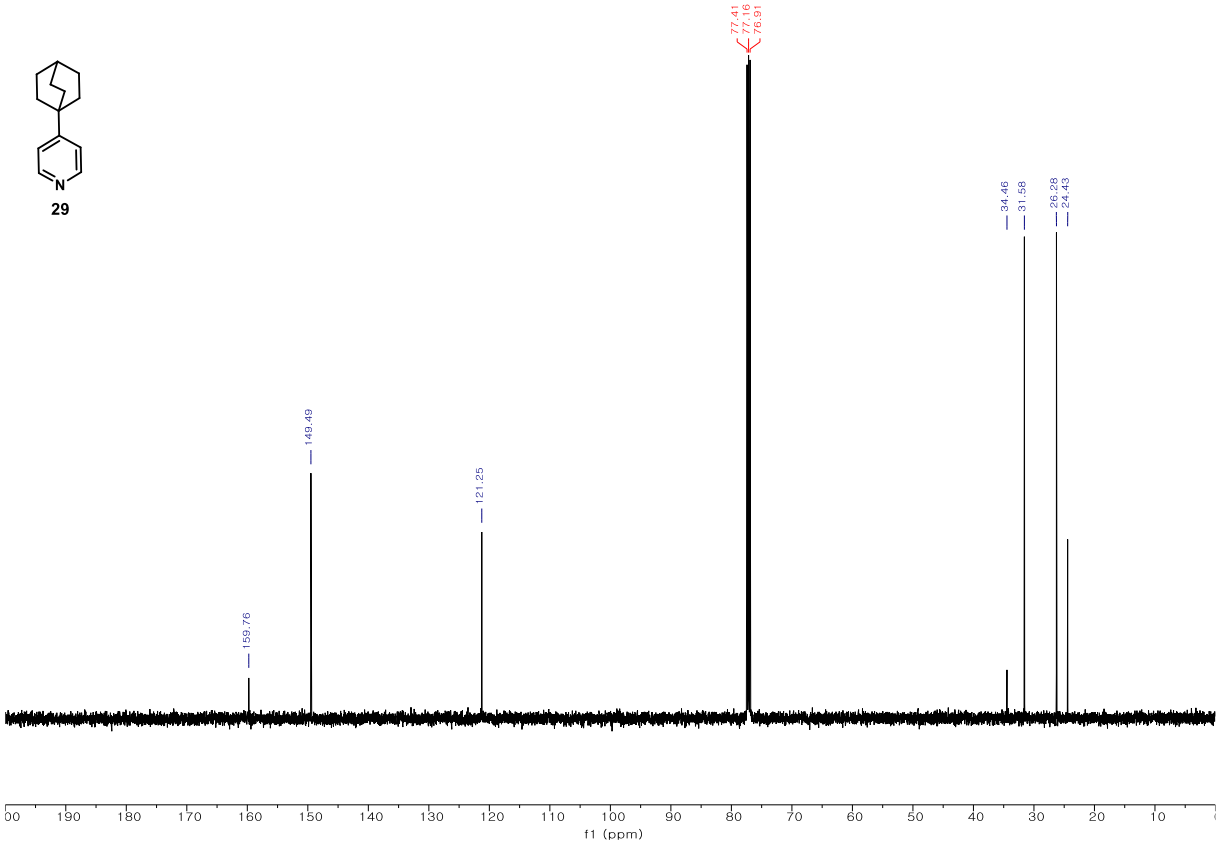
1.96
6.08
7.13
f1 (ppm)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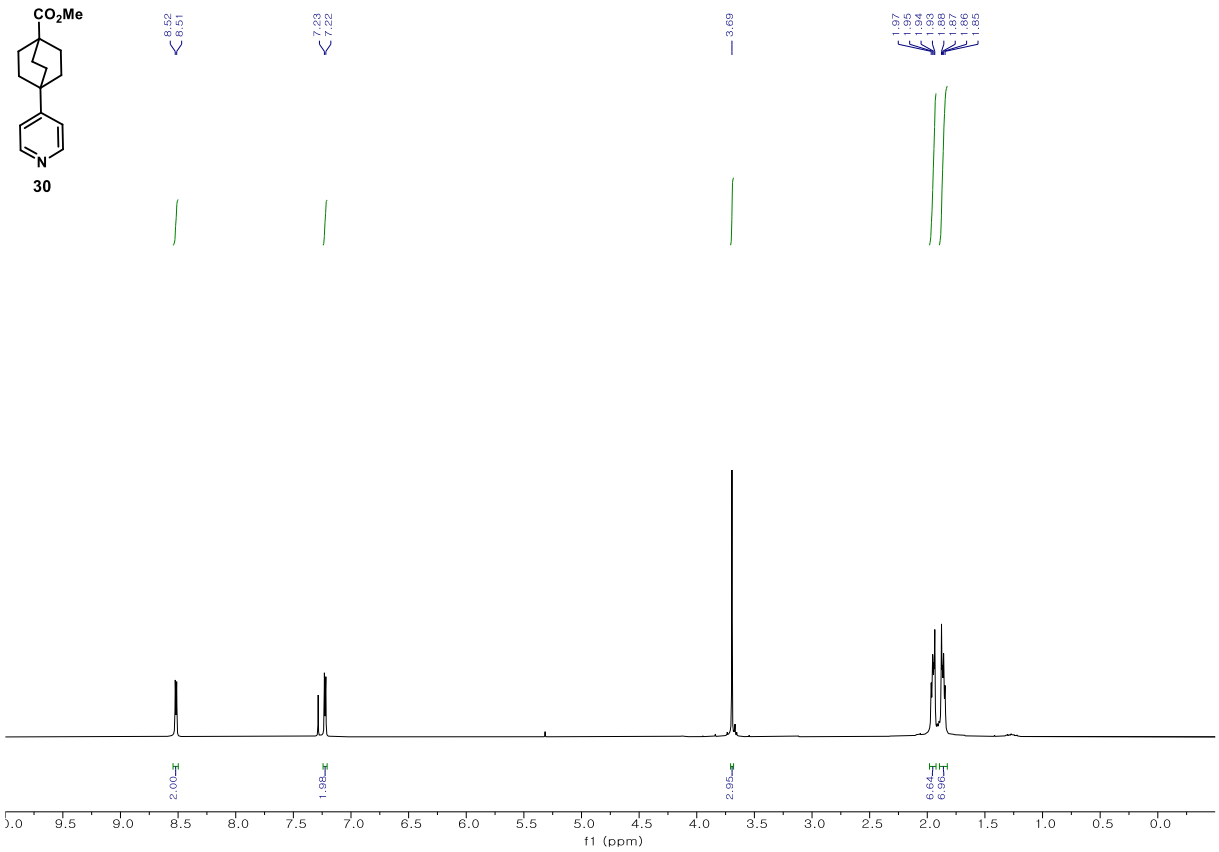
31.58
26.28
24.43
149.49
121.25
159.76
N
29
f1 (ppm)


CO2Me
N
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8.51
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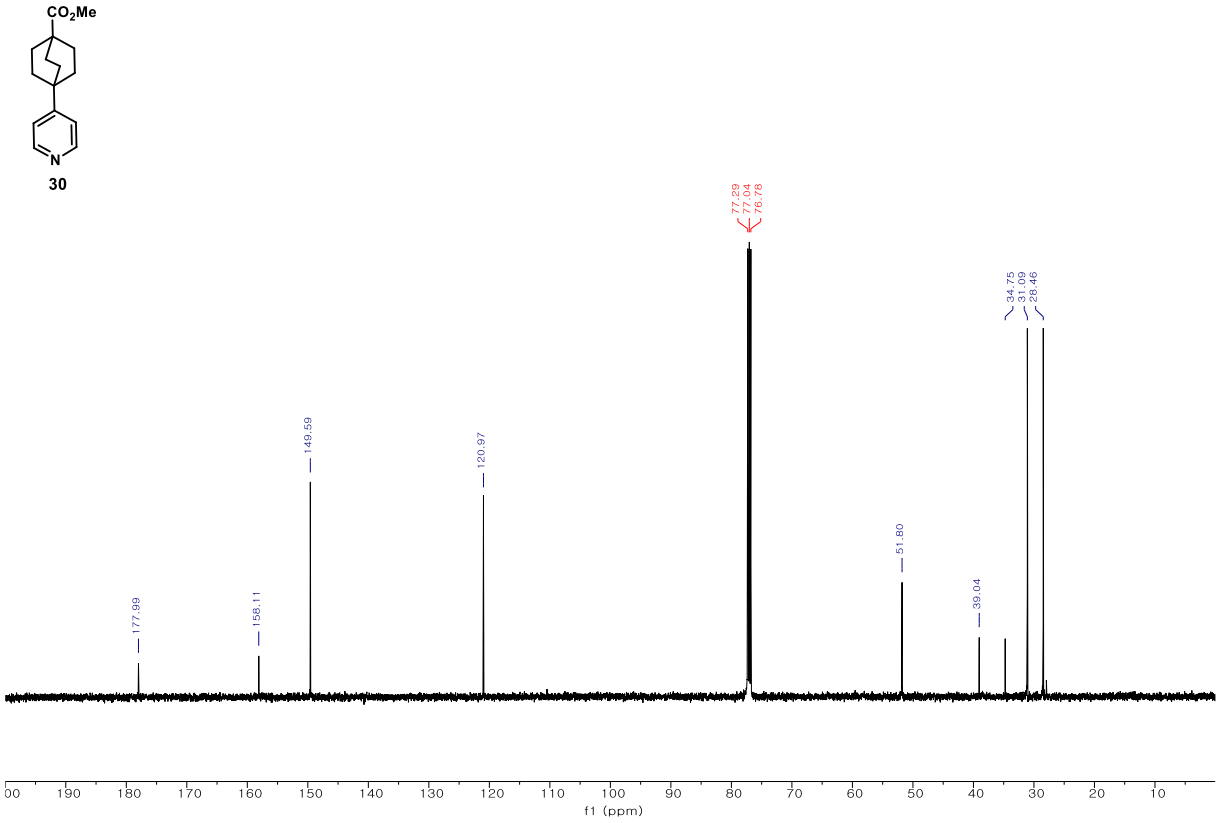
7.22
3.69
1.97
1.95
1.94
1.93
1.88
1.87
1.86
1.85
2.00
1.98
2.95
6.64
6.96
f1 (ppm)


CO2Me
N
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77.29
77.04
76.78
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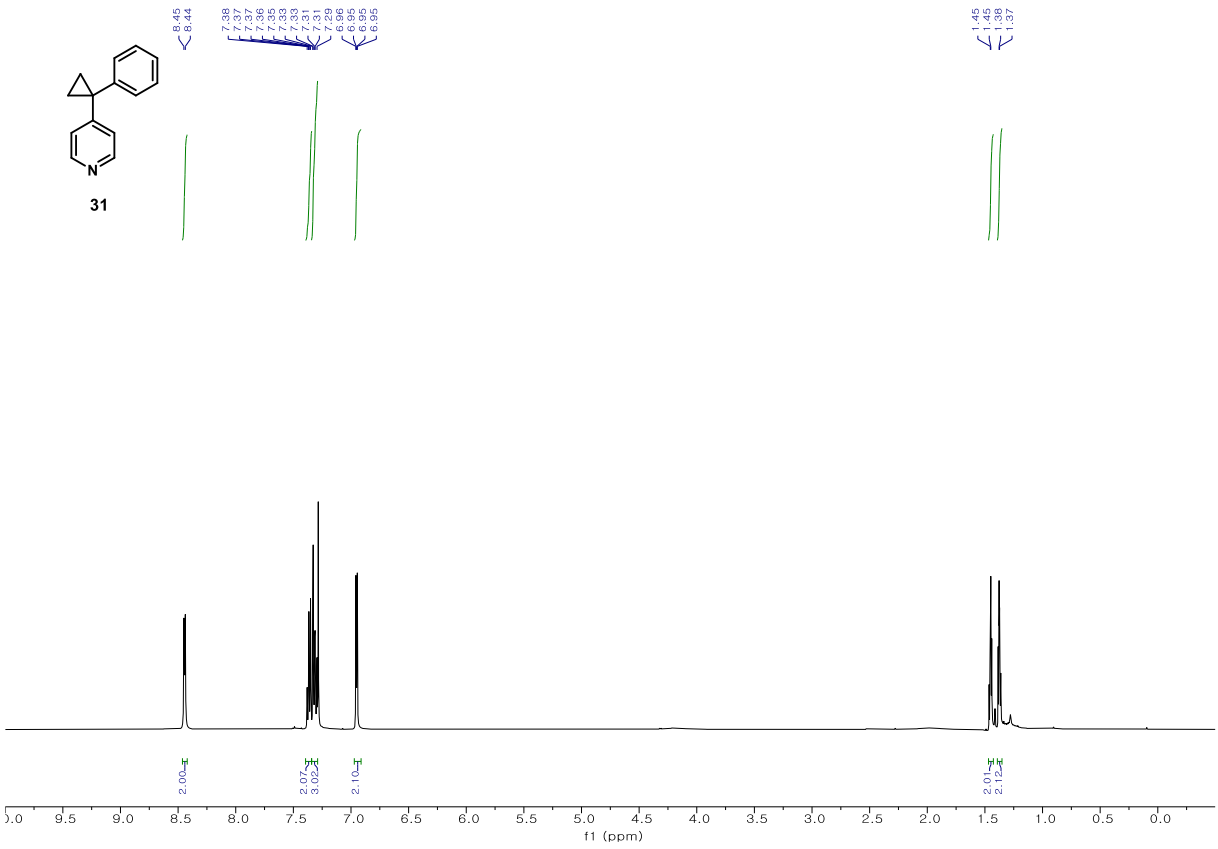
149.59
120.97
51.80
39.04
34.75
31.09
28.46
f1 (ppm)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7.33
7.33
7.31
7.31
7.29
6.96
6.95
6.95
6.95
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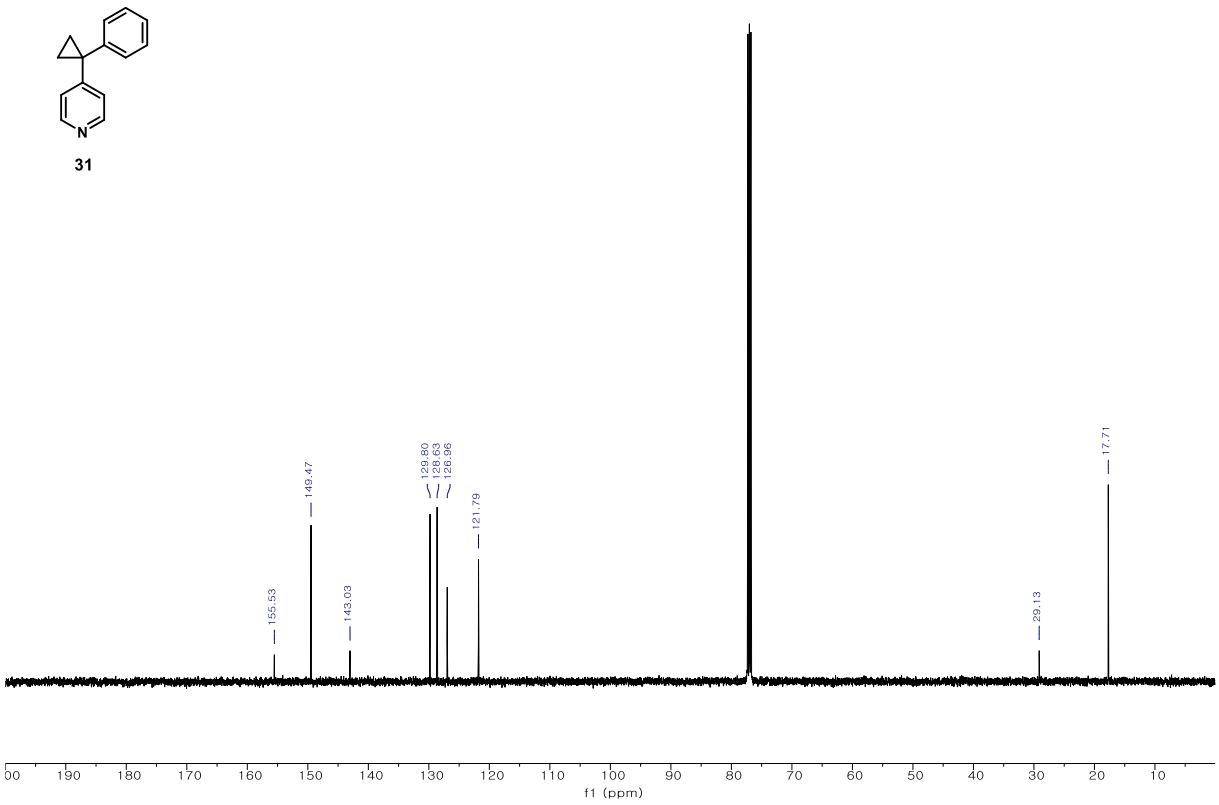
1.45
1.38
1.37
31
2.00
2.07
3.02
2.10
2.01
2.12
f1 (ppm)


31
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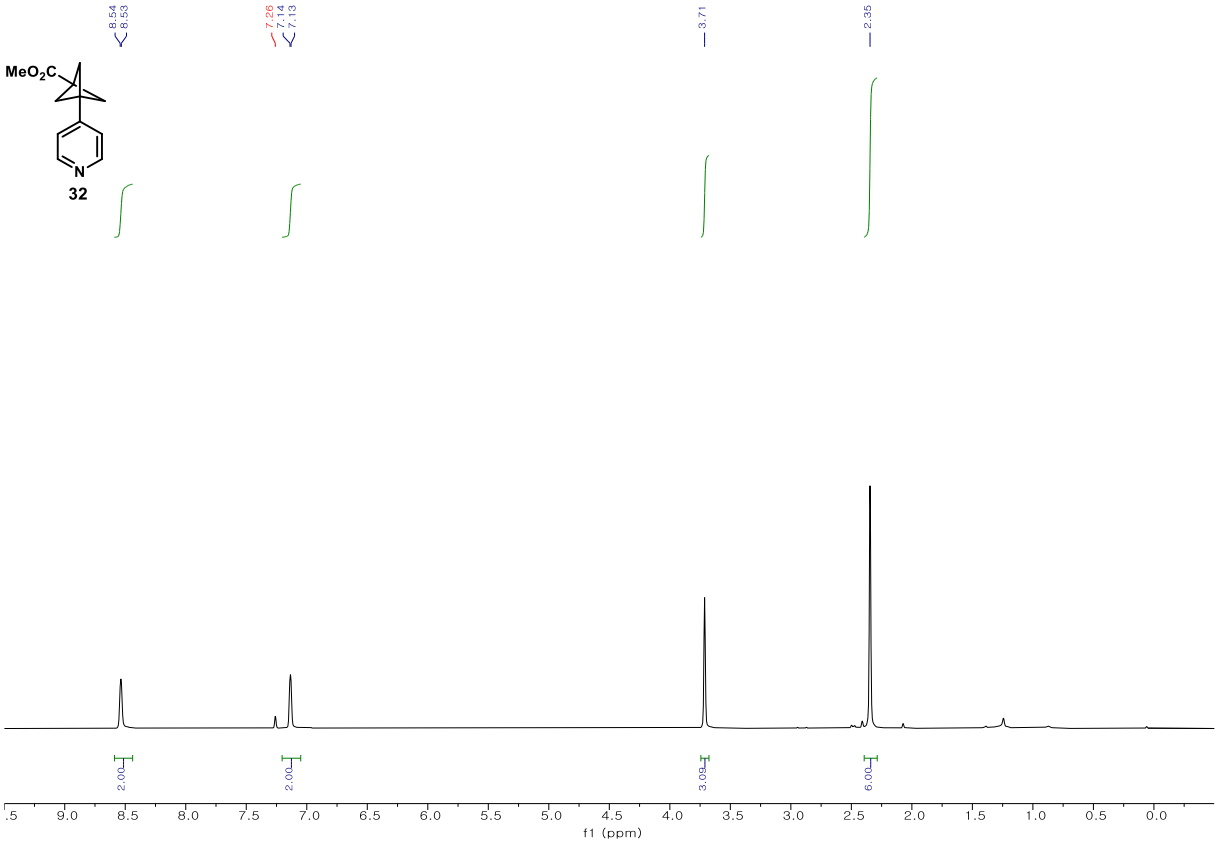
143.03
129.80
128.63
126.96
121.79
29.13
17.71
f1 (ppm)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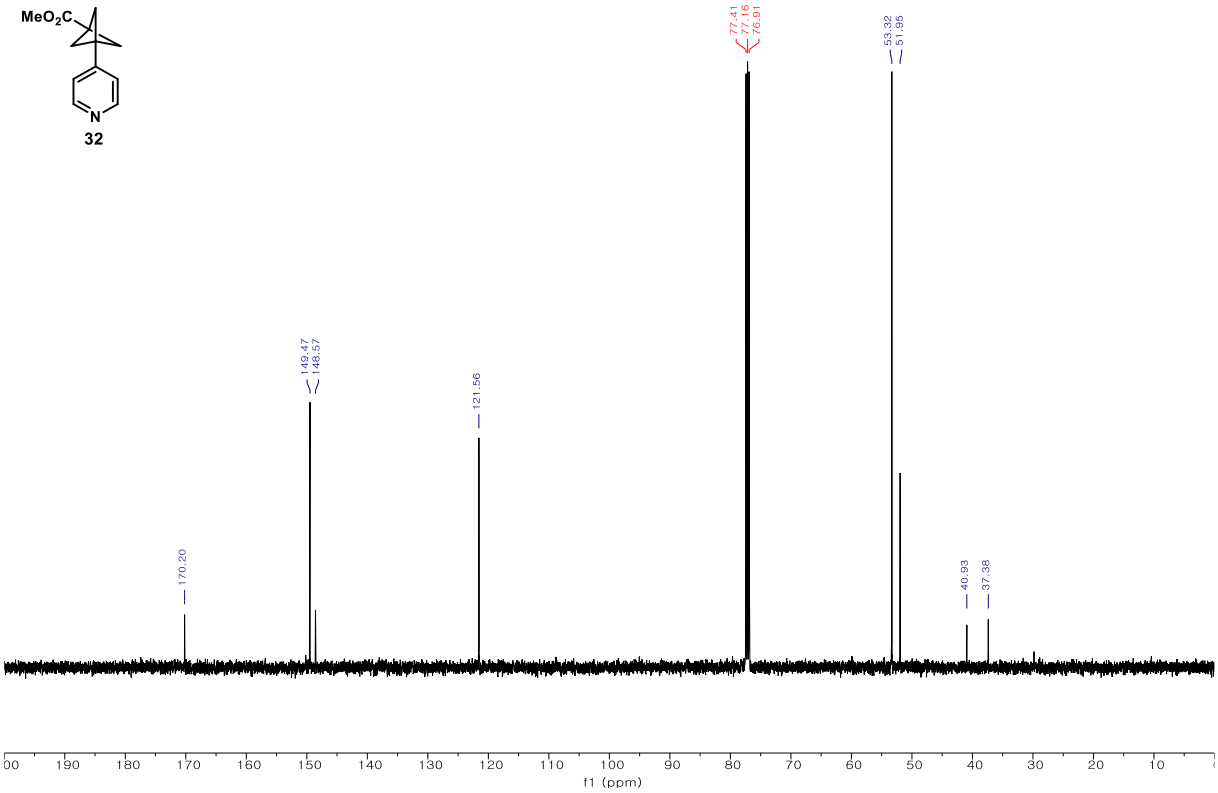
8.53
7.26
7.14
7.13
3.71
2.35
MeO2C
N
32
2.00
2.00
3.09
6.00
f1 (ppm)


MeO2C
N
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77.16
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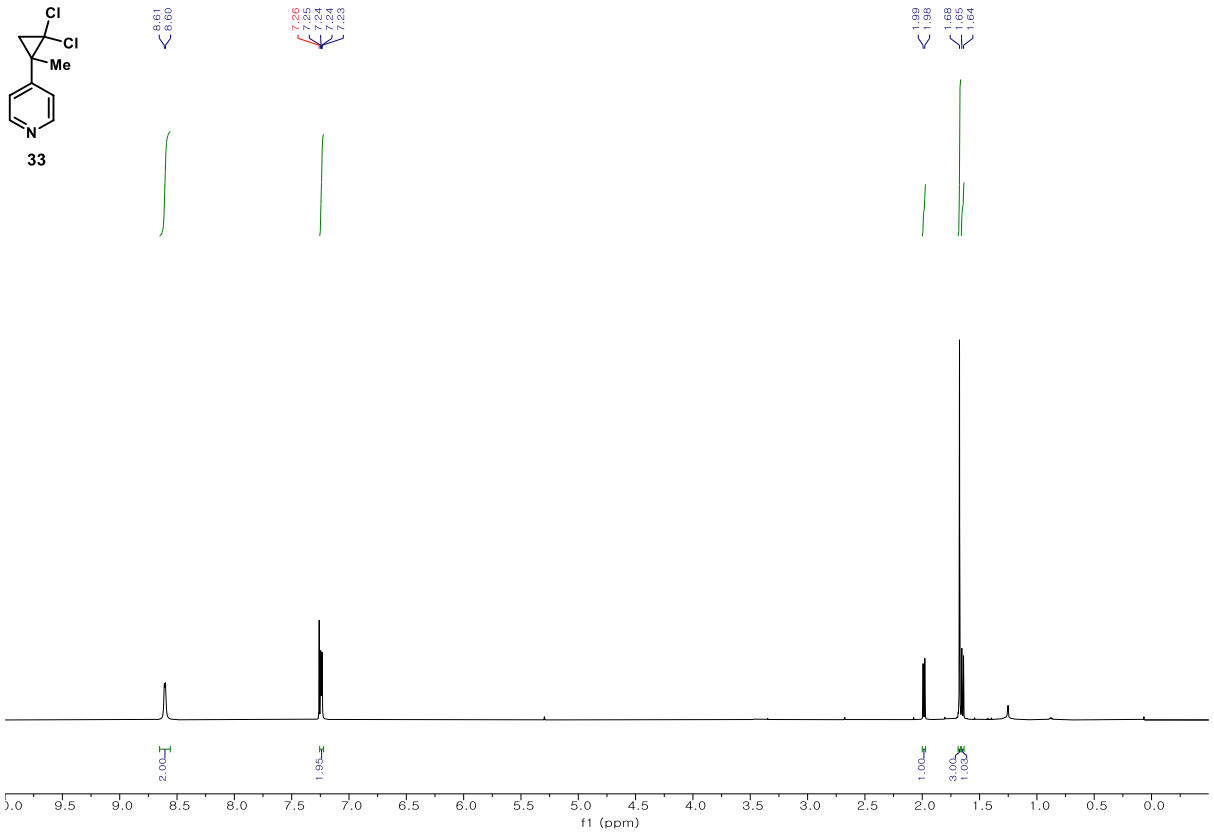
170.20
40.93
37.38
f1 (ppm)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Cl
Me
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7.25
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7.24
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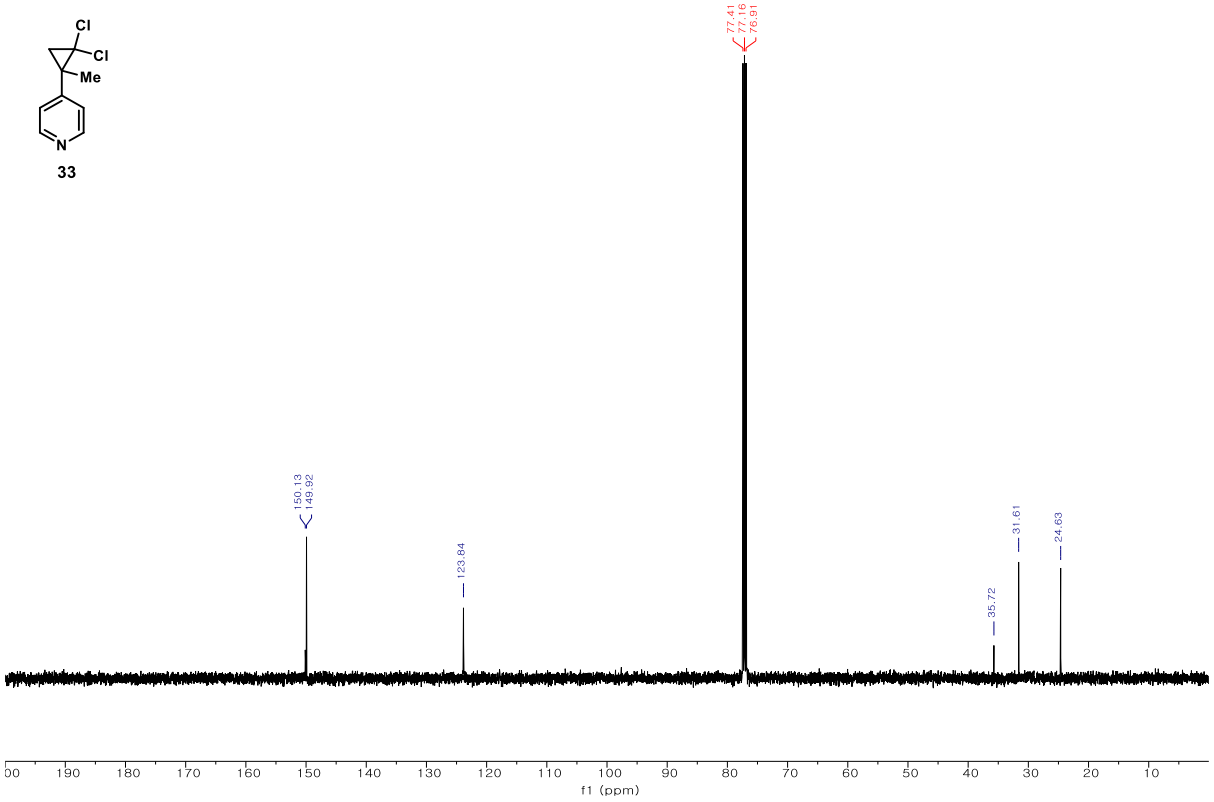
1.68
1.65
1.64
2.00
1.95
1.00
3.00
1.03
f1 (ppm)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Cl
Me
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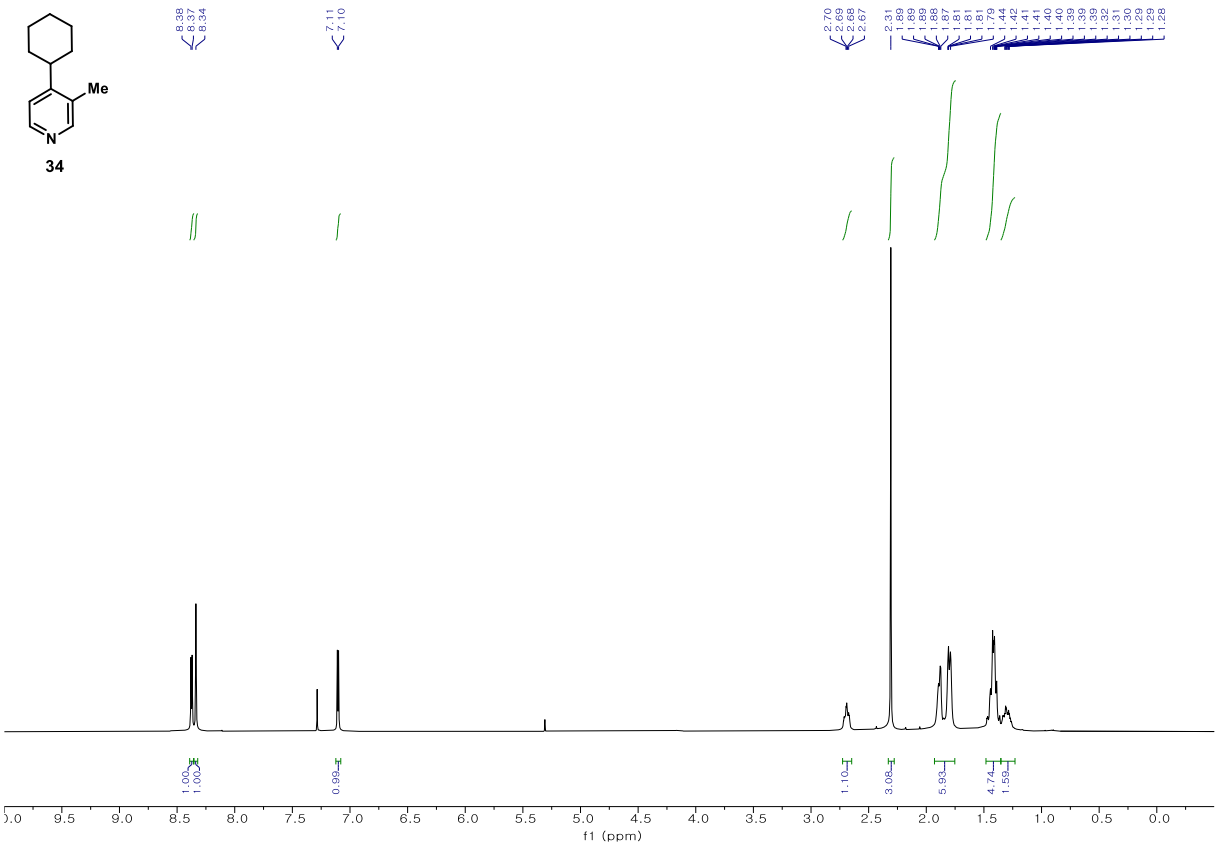
77.16
76.91
150.13
149.92
123.84
35.72
31.61
24.63
f1 (ppm)


Me
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8.37
8.34
7.11
7.10
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2.69
2.68
2.67
2.31
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1.89
1.89
1.88
1.87
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1.81
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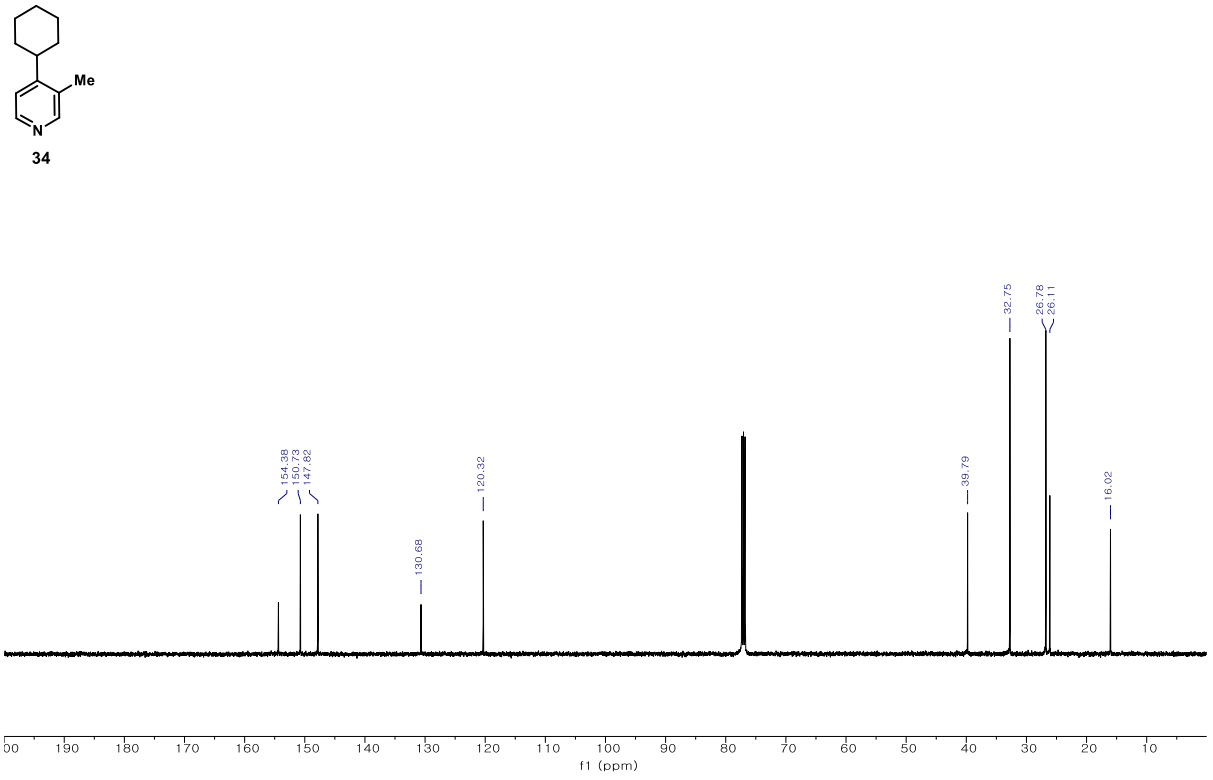
1.40
1.39
1.39
1.39
1.32
1.31
1.30
1.29
1.29
1.28
1.00
1.00
0.99
1.10
3.08
5.93
4.74
1.59
f1 (ppm)


Me
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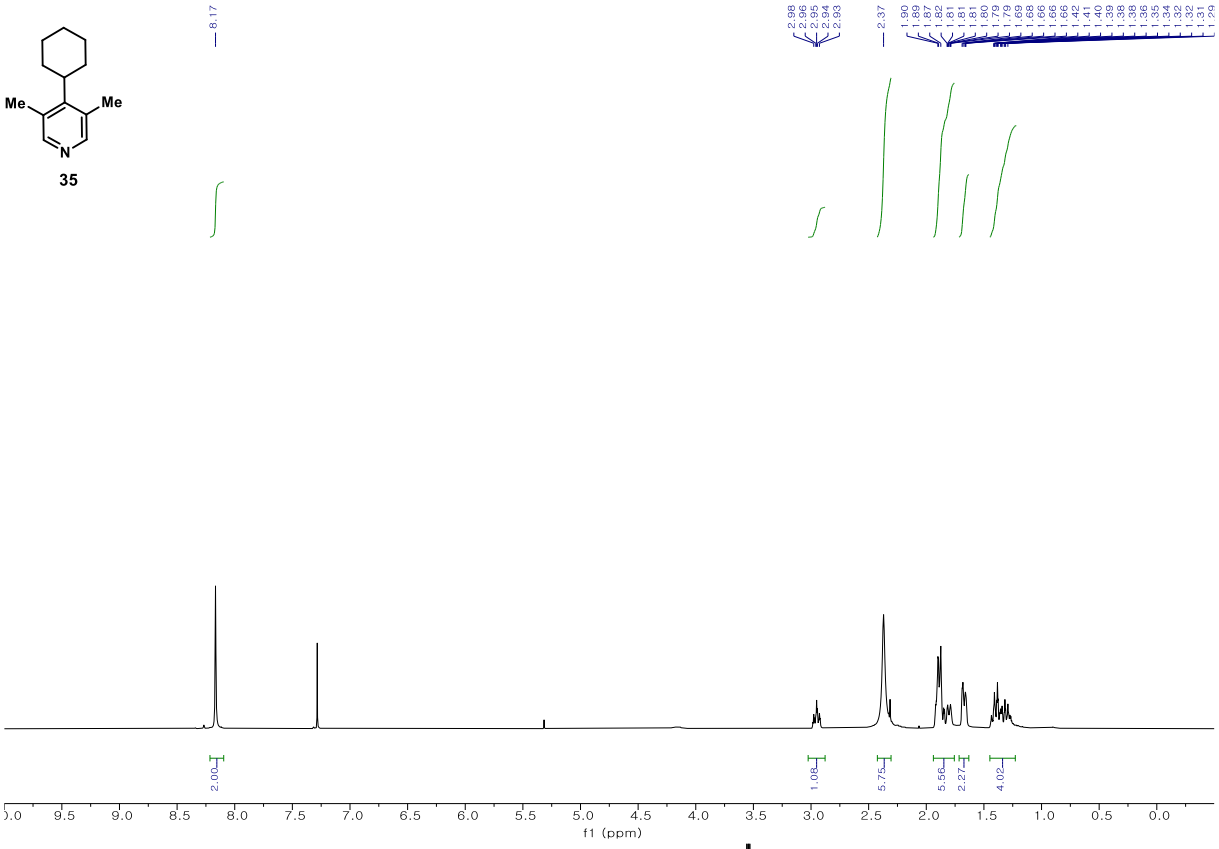
120.32
39.79
32.75
26.78
26.11
16.02
f1 (ppm)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Me
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2.96
2.95
2.94
2.93
2.37
1.90
1.89
1.87
1.82
1.81
1.81
1.81
1.80
1.79
1.79
1.69
1.68
1.68
1.66
1.66
1.42
1.41
1.40
1.39
1.38
1.38
1.36
1.35
1.34
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1.31
1.29
2.00
1.08
5.75
5.56
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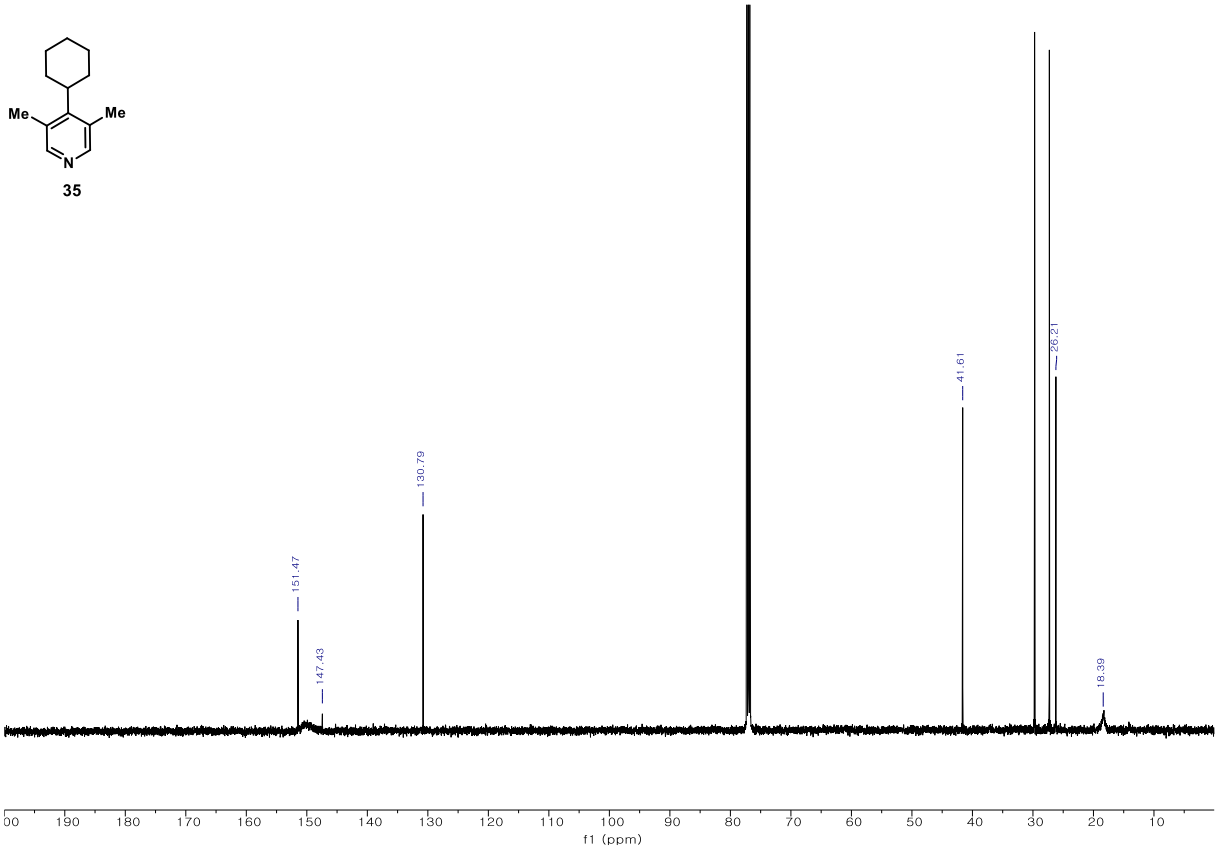
4.02
f1 (ppm)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Me
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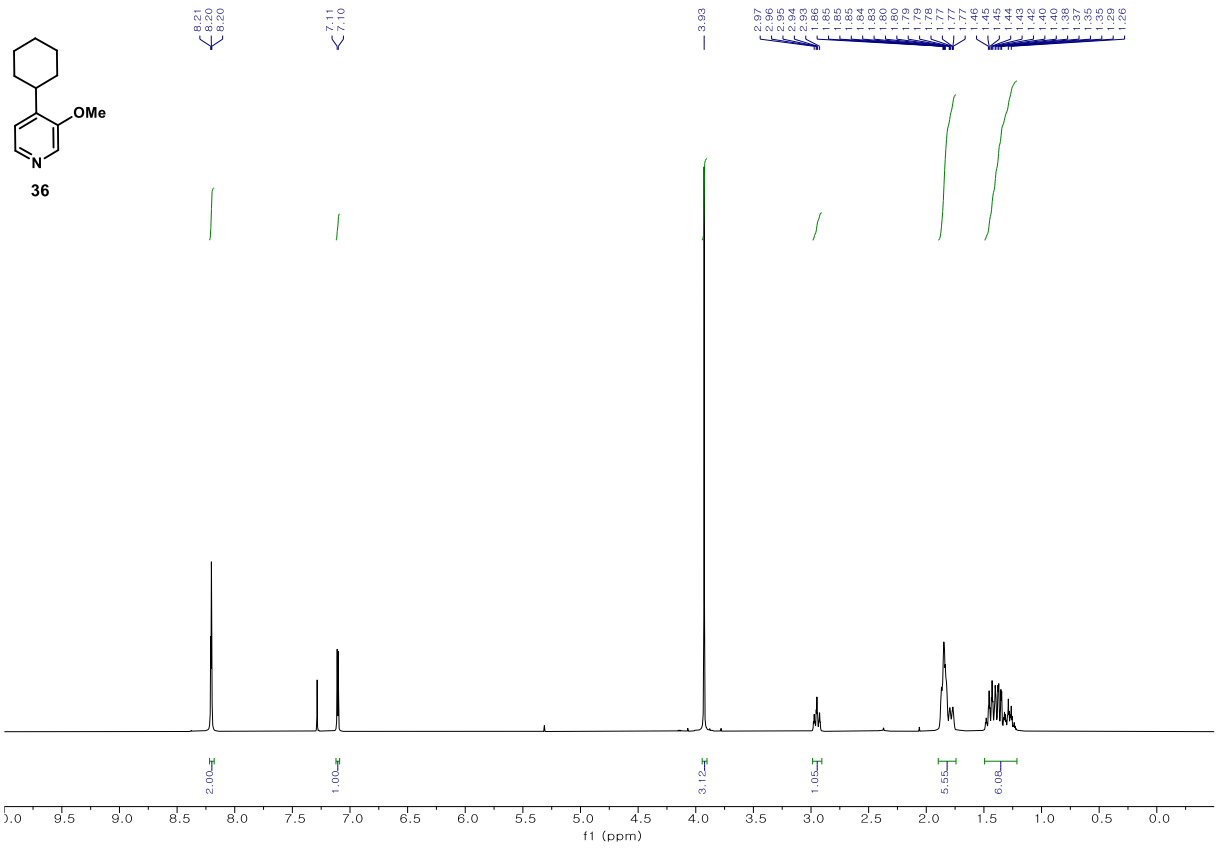
147.43
130.79
41.61
26.21
18.39
f1 (ppm)


OMe
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3.93
2.97
2.96
2.95
2.94
2.93
1.86
1.85
1.85
1.85
1.84
1.83
1.80
1.80
1.79
1.78
1.78
1.77
1.77
1.46
1.45
1.45
1.44
1.43
1.42
1.40
1.40
1.38
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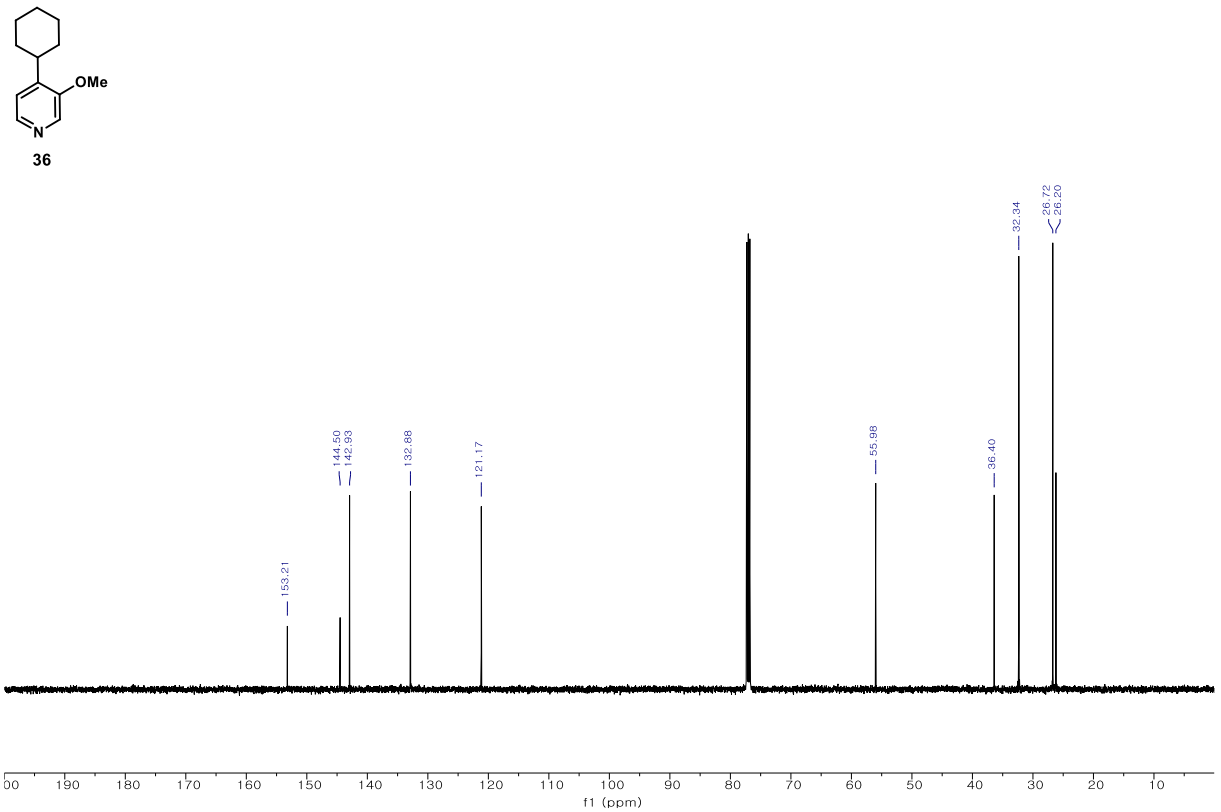
1.29
1.26
2.00
1.00
3.12
1.05
5.55
6.08
f1 (ppm)


OMe
N
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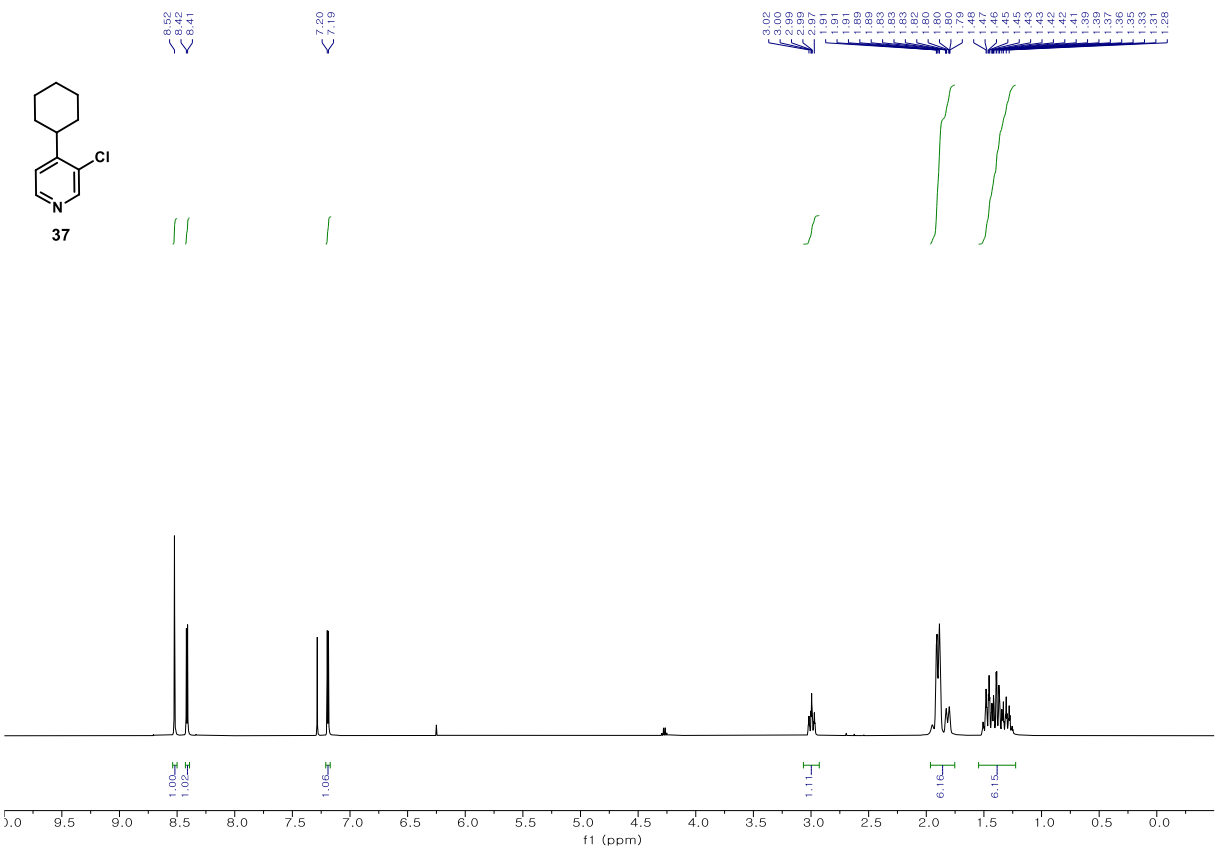
132.88
121.17
55.98
36.40
32.34
26.72
26.20
f1 (ppm)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1.91
1.91
1.89
1.89
1.83
1.83
1.82
1.80
1.80
1.78
1.48
1.47
1.46
1.45
1.45
1.43
1.43
1.42
1.42
1.41
1.39
1.39
1.37
1.36
1.35
1.33
1.31
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Cl
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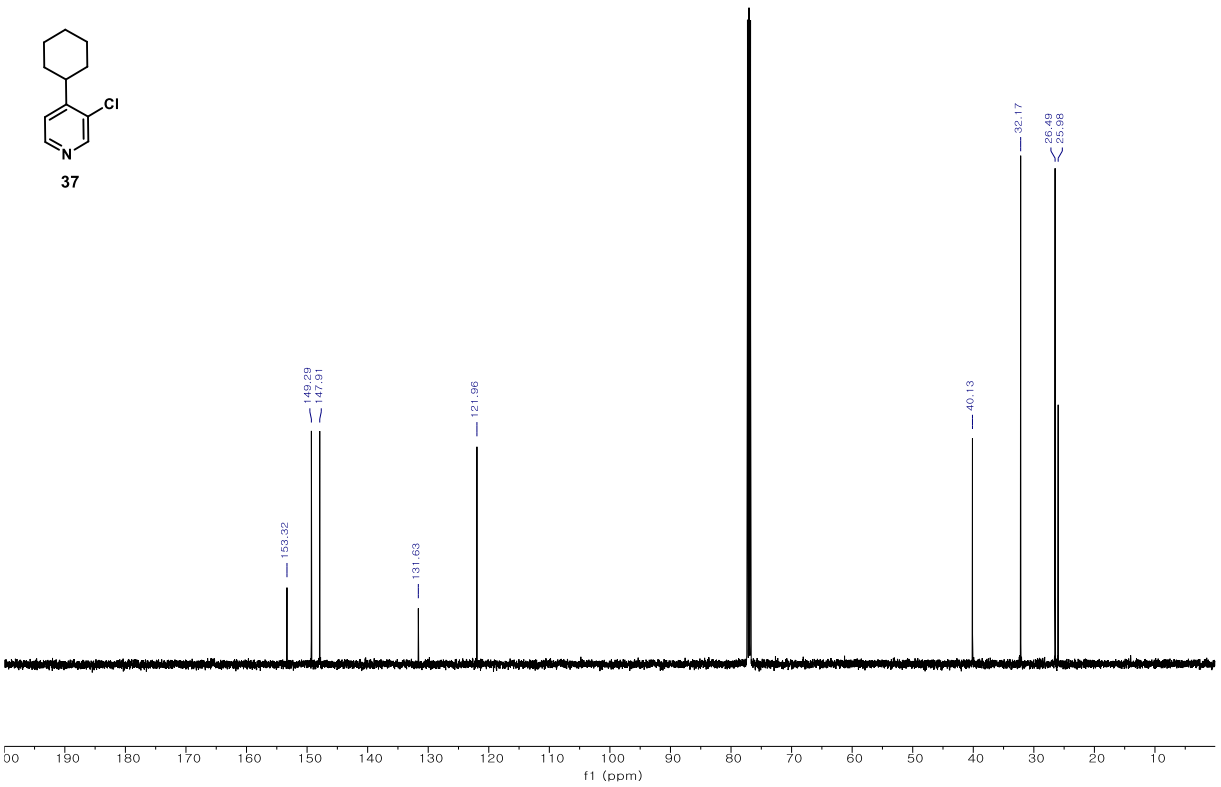
1.00
1.02
1.06
1.11
6.16
6.15
f1 (ppm)


Cl
N
37
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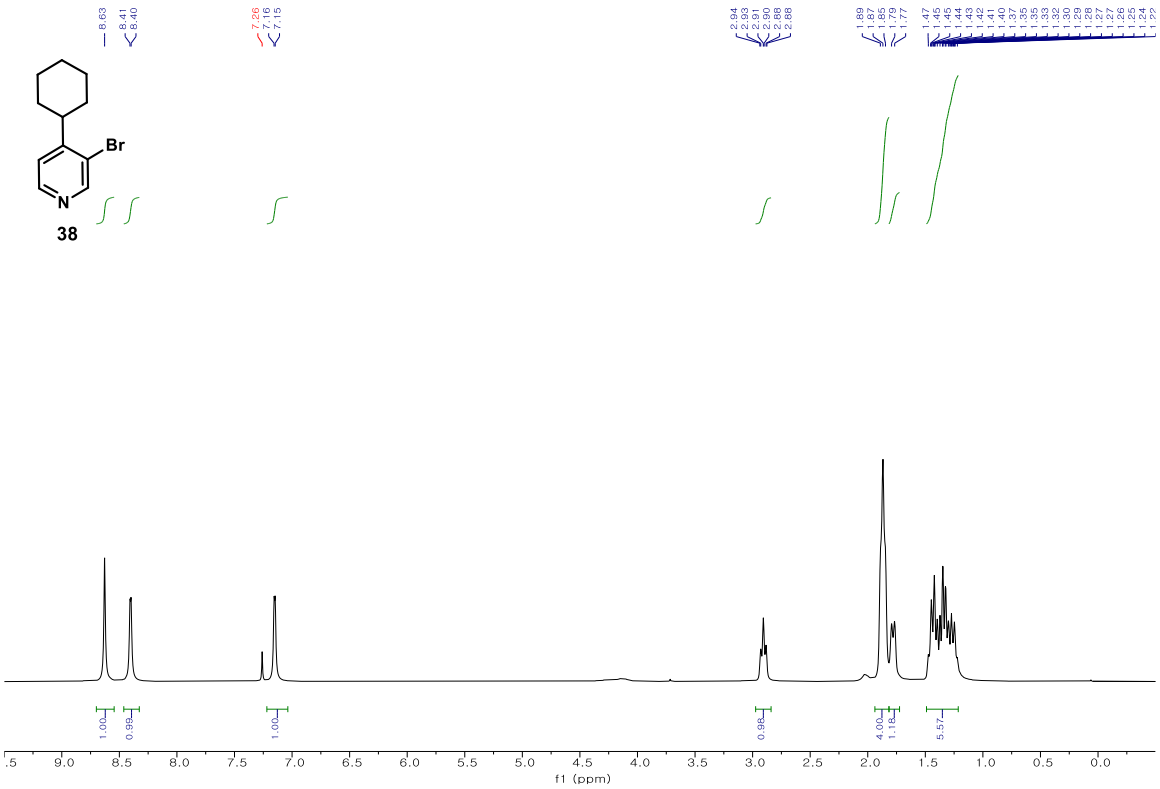
149.29
147.91
131.63
121.96
40.13
32.17
26.49
25.98
f1 (ppm)


8.63
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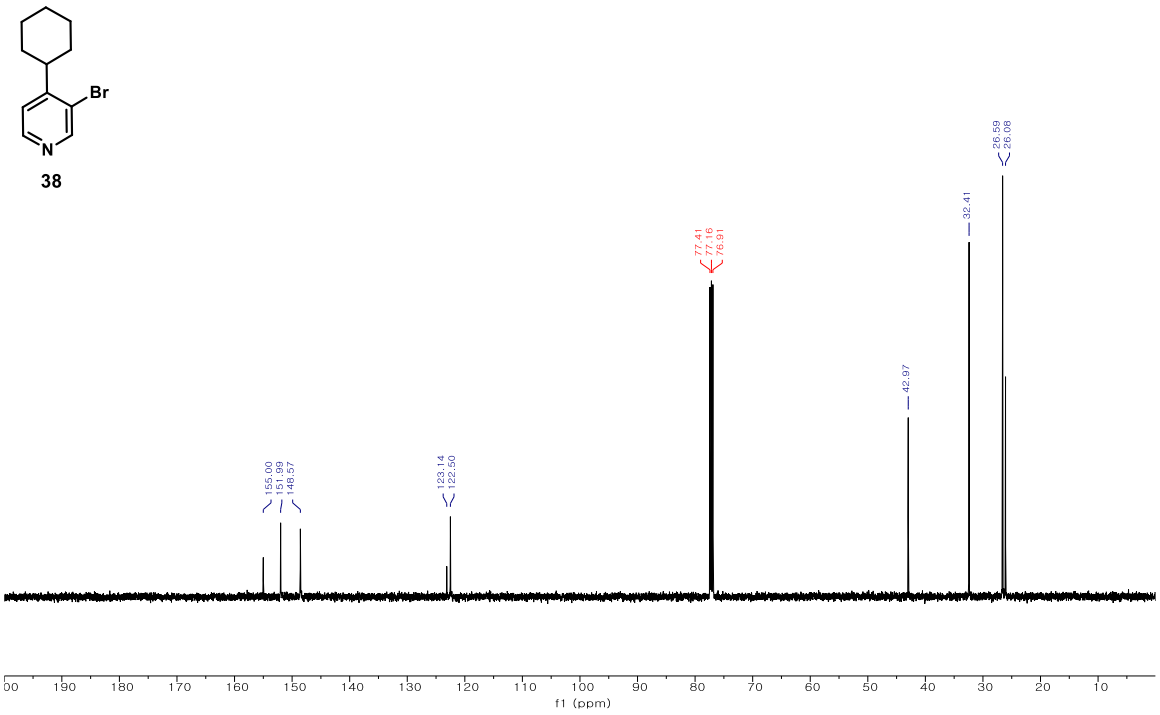
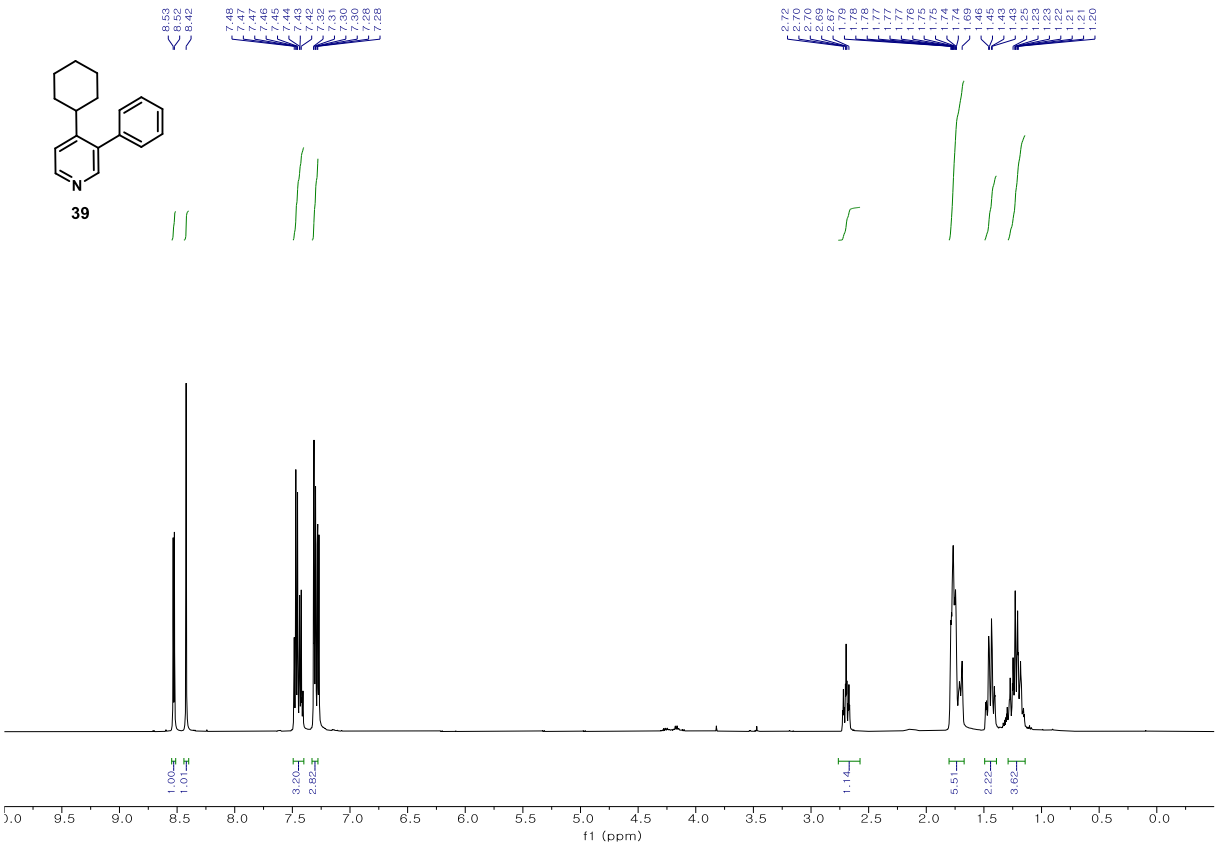
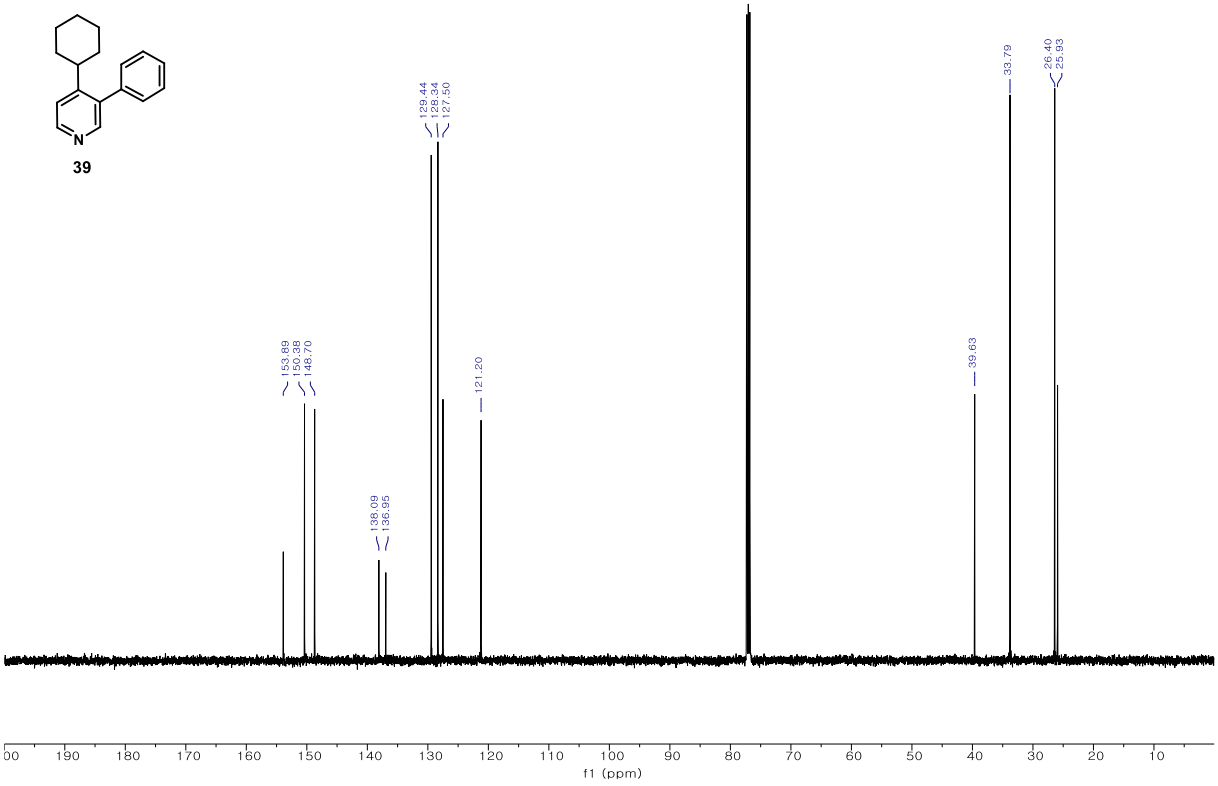
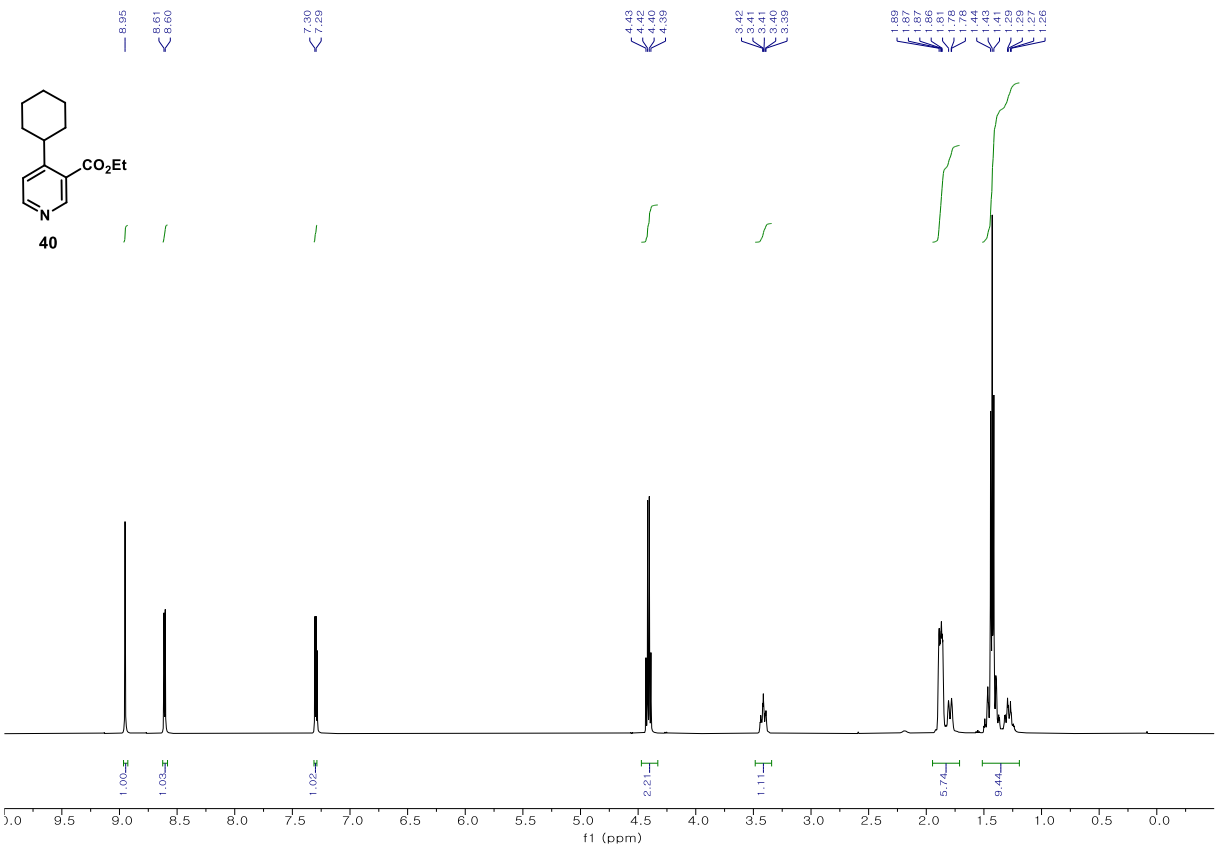
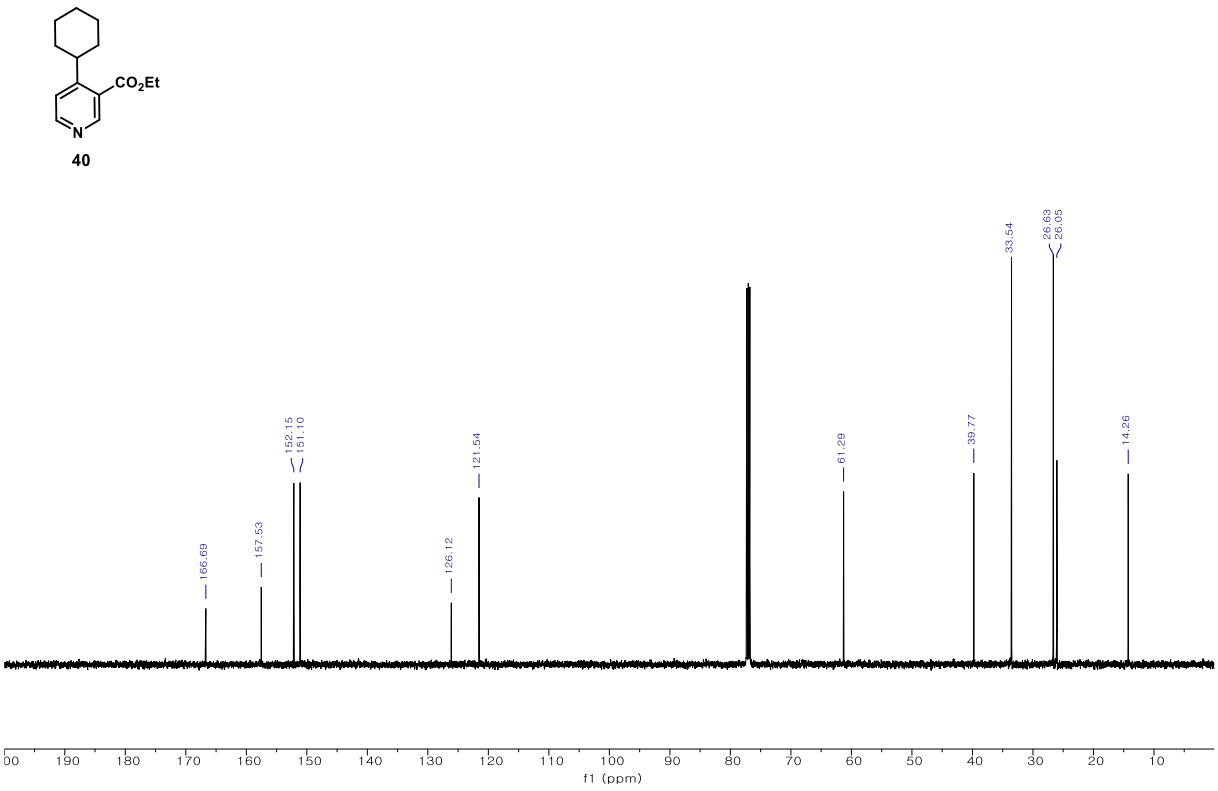
7.26
7.16
7.15
2.94
2.93
2.91
2.90
2.88
2.88
1.89
1.87
1.85
1.79
1.77
1.47
1.45
1.45
1.44
1.43
1.42
1.41
1.40
1.37
1.35
1.35
1.33
1.32
1.30
1.29
1.28
1.27
1.27
1.26
1.25
1.24
1.22
Br
N
38
1.00
0.98
1.00
0.98
4.00
1.18
5.57
f1 (ppm)

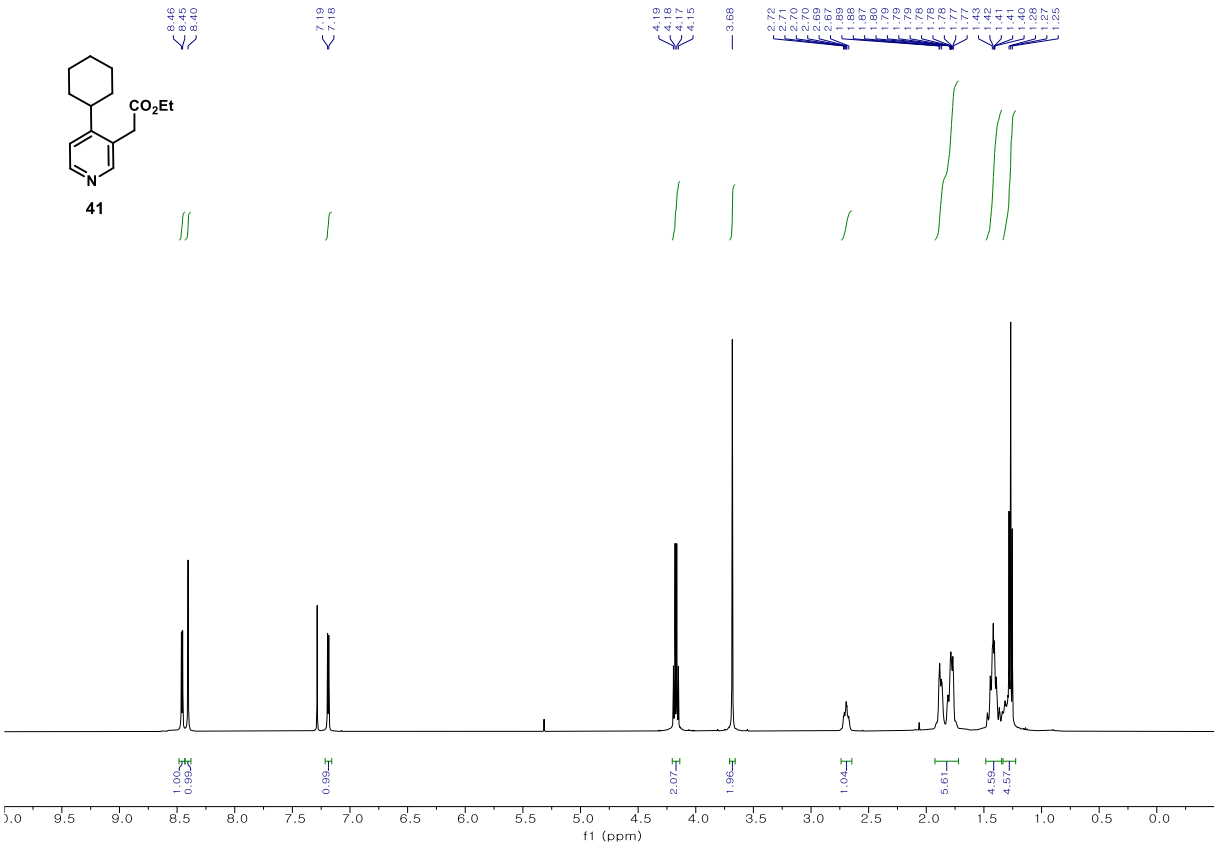

Br
N
38
155.00
151.99
148.57
123.14
122.50
77.41
77.16
76.91
42.97
32.41
26.59
26.06
f1 (ppm)

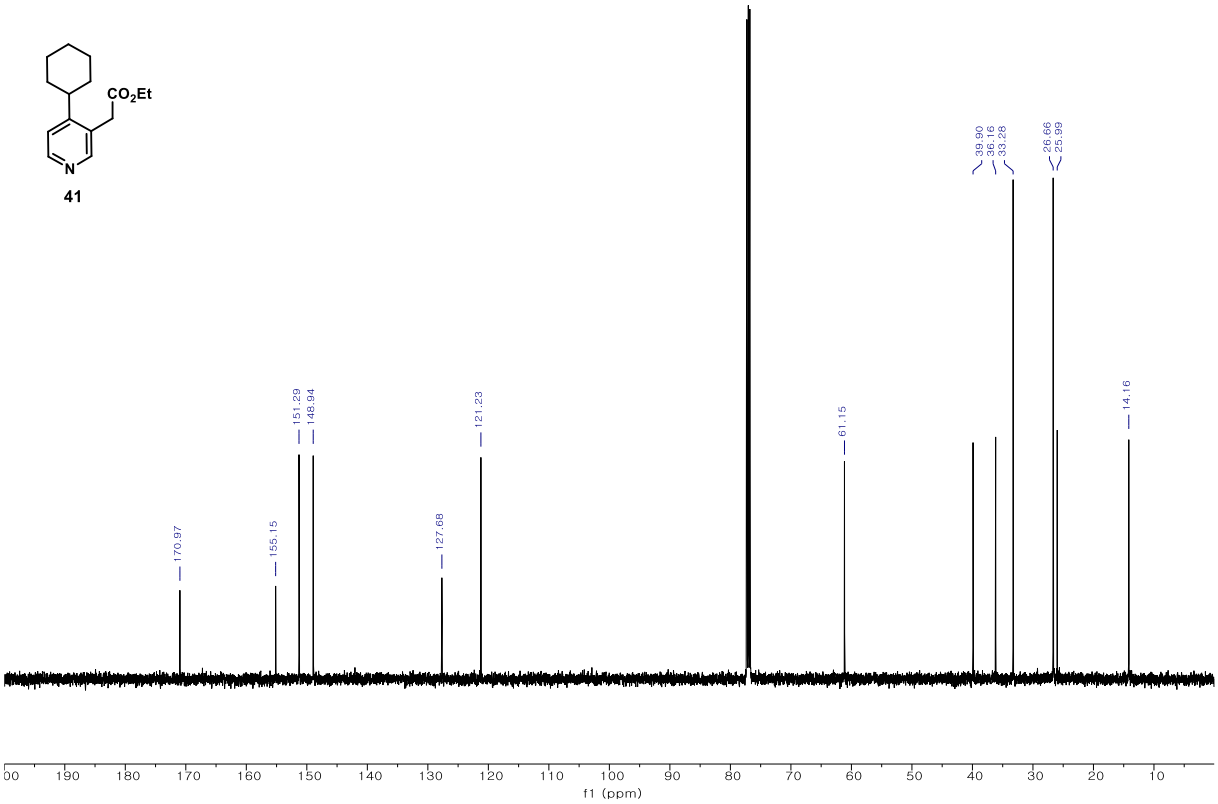

39
8.53
8.52
8.42
7.48
7.47
7.47
7.46
7.45
7.44
7.43
7.42
7.32
7.31
7.30
7.30
7.28
7.28
2.72
2.70
2.70
2.69
2.67
1.79
1.78
1.78
1.77
1.77
1.77
1.76
1.75
1.75
1.75
1.74
1.69
1.46
1.45
1.43
1.43
1.25
1.23
1.23
1.22
1.21
1.21
1.20
1.00
1.01
3.20
2.82
1.14
5.51
2.22
3.62
f1 (ppm)

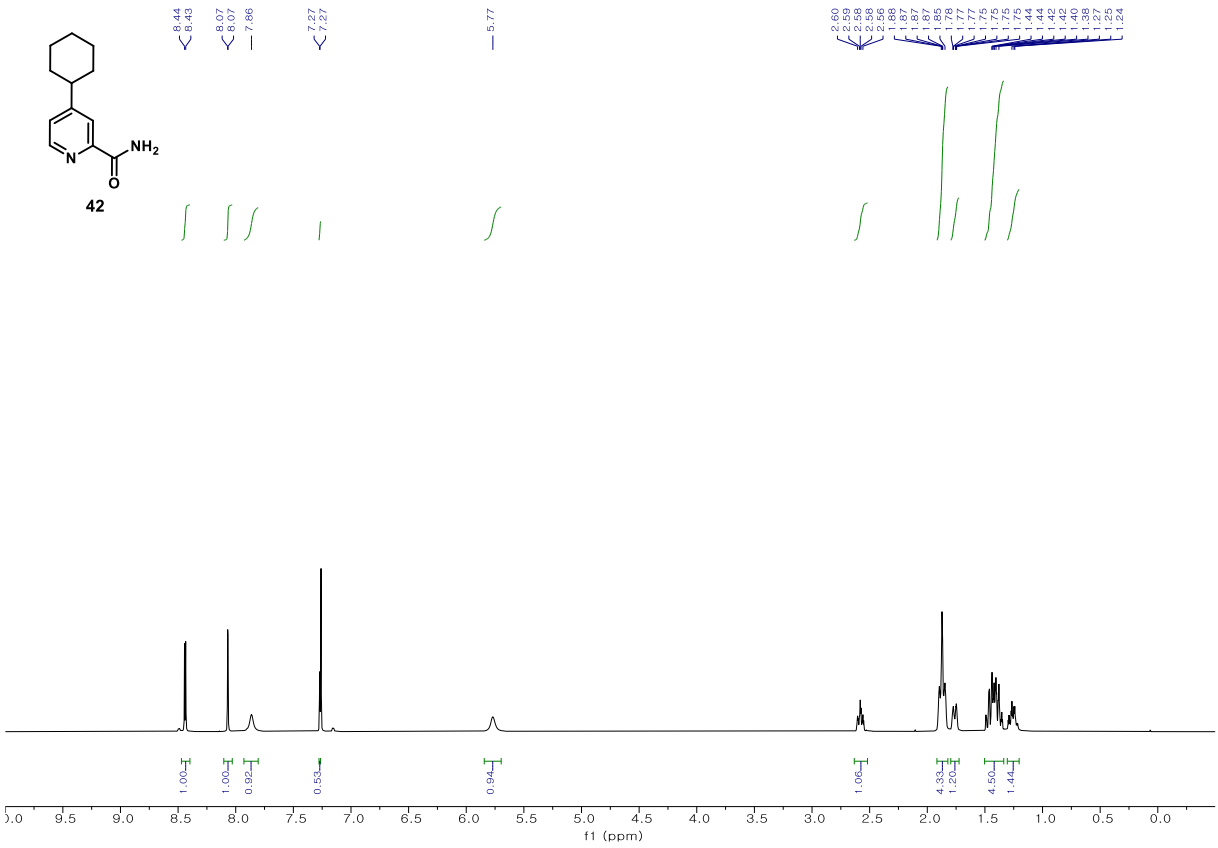

39
153.89
150.38
148.70
138.09
136.95
129.44
128.34
127.50
121.20
39.63
33.79
26.40
25.93
f1 (ppm)

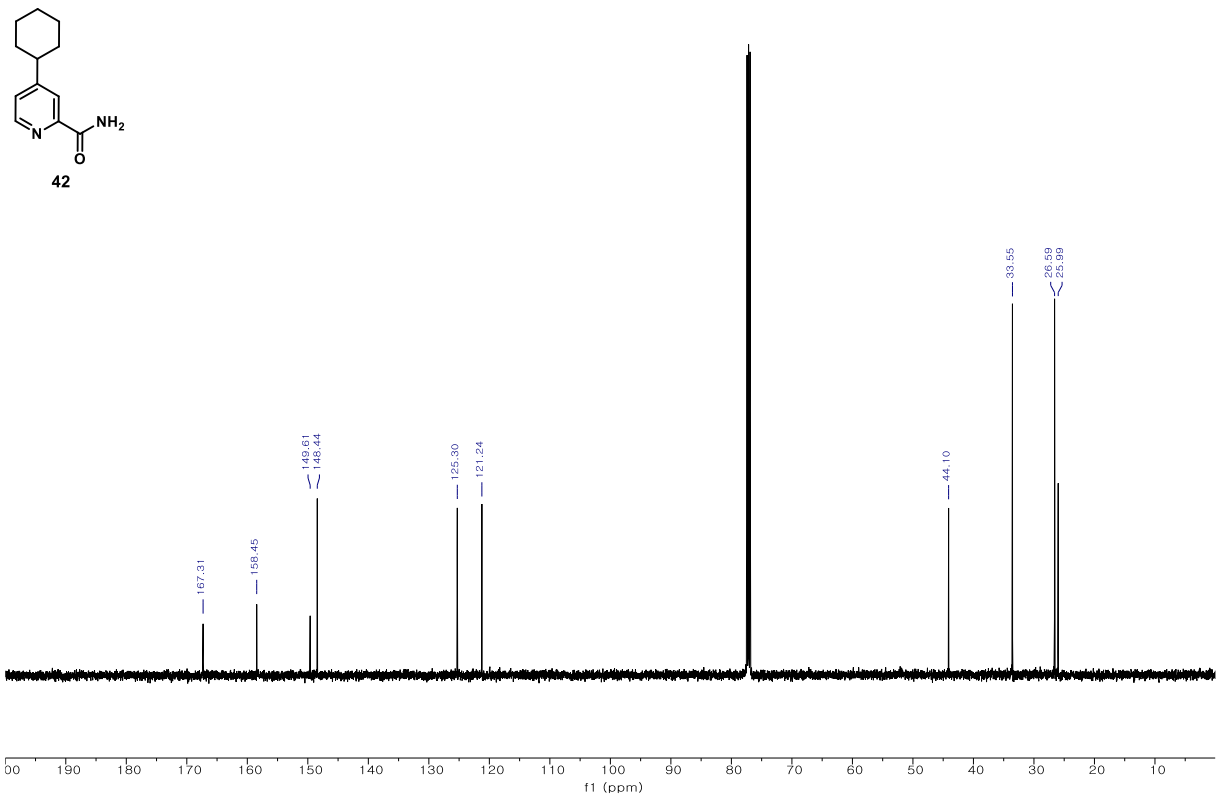

8.95
8.61
8.60
7.30
7.29
4.43
4.42
4.40
4.39
3.42
3.41
3.41
3.40
3.39
1.89
1.87
1.87
1.86
1.81
1.78
1.78
1.44
1.43
1.41
1.29
1.29
1.27
1.26
CO2Et
N
40
1.00
1.03
1.02
2.21
1.11
5.74
9.44
f1 (ppm)

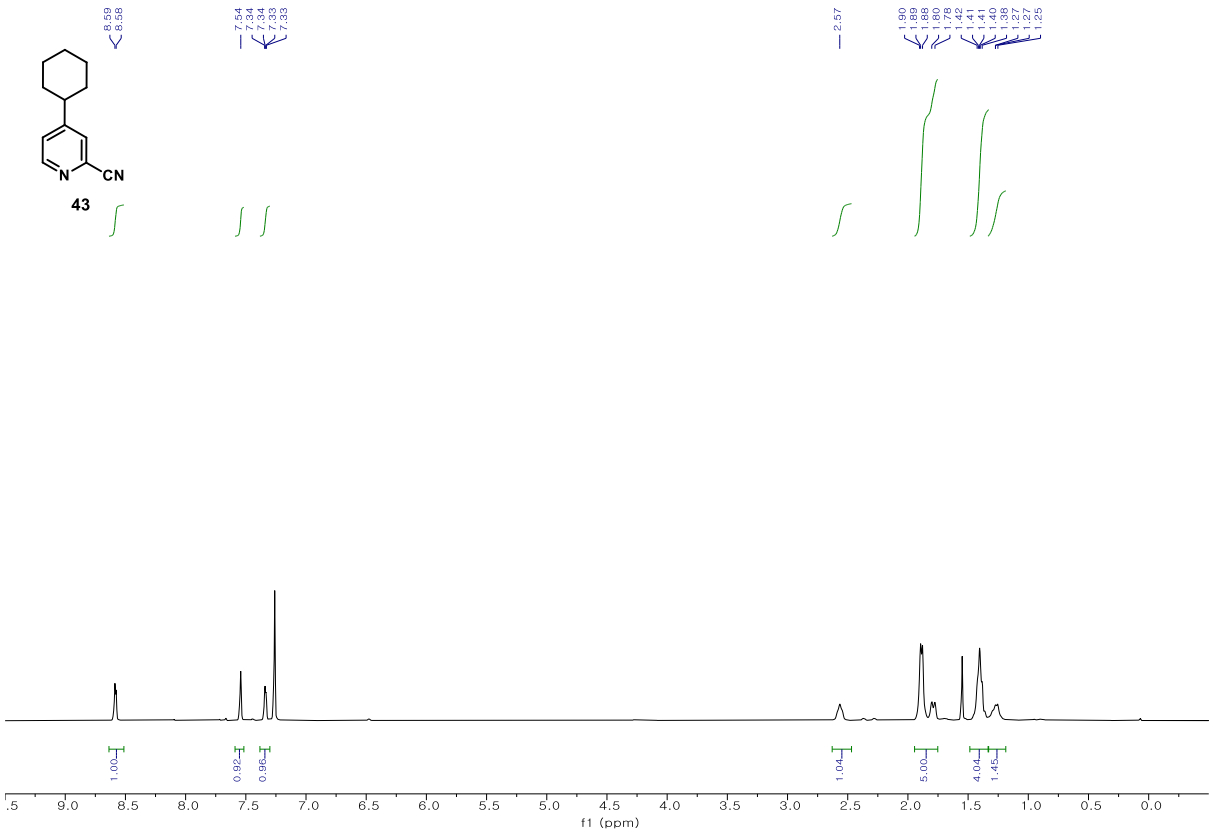

CO2Et
N
40
166.69
157.53
152.15
151.10
126.12
121.54
61.29
39.77
33.54
26.63
26.05
14.26
f1 (ppm)

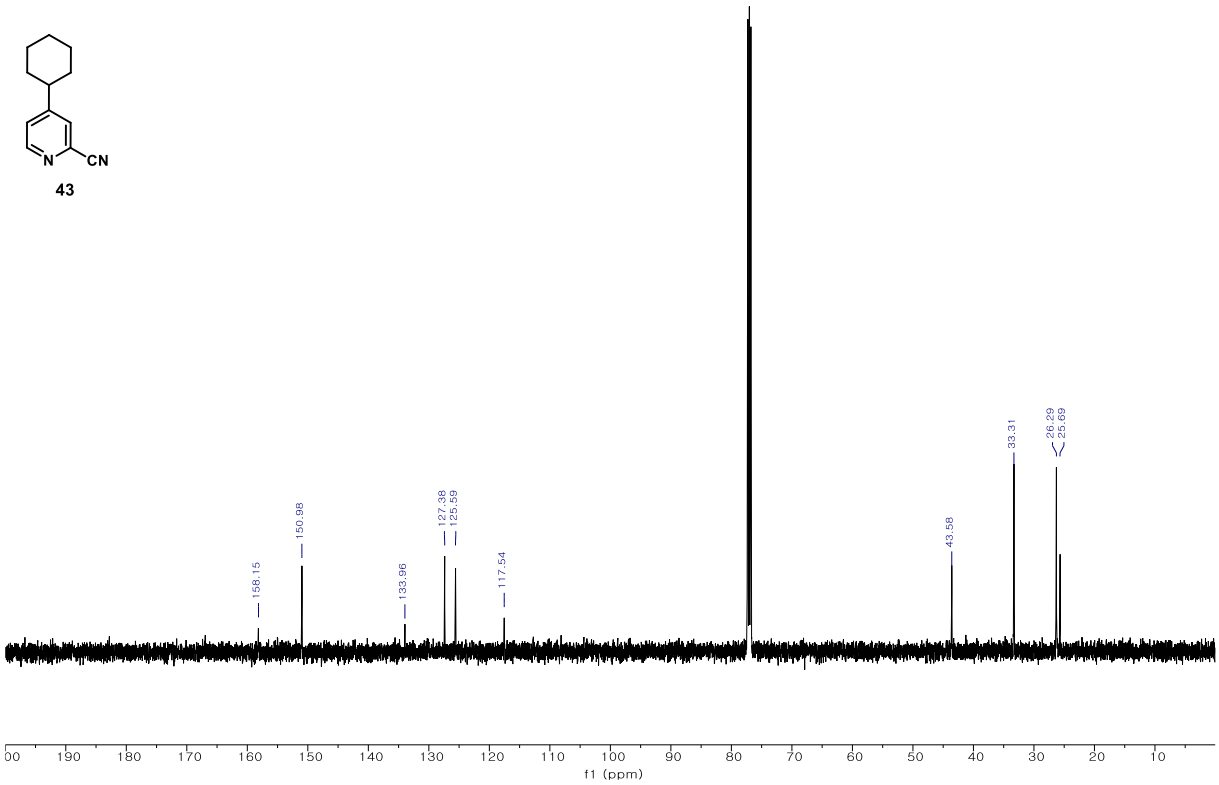

8.46
8.45
8.40
7.19
7.18
4.19
4.18
4.17
4.15
3.68
2.72
2.71
2.70
2.70
2.69
2.67
1.89
1.88
1.87
1.80
1.79
1.79
1.79
1.78
1.78
1.78
1.77
1.77
1.43
1.42
1.41
1.41
1.40
1.28
1.27
1.25
CO2Et
N
41
1.00
0.99
0.99
2.07
1.96
1.04
5.61
4.59
4.57
f1 (ppm)

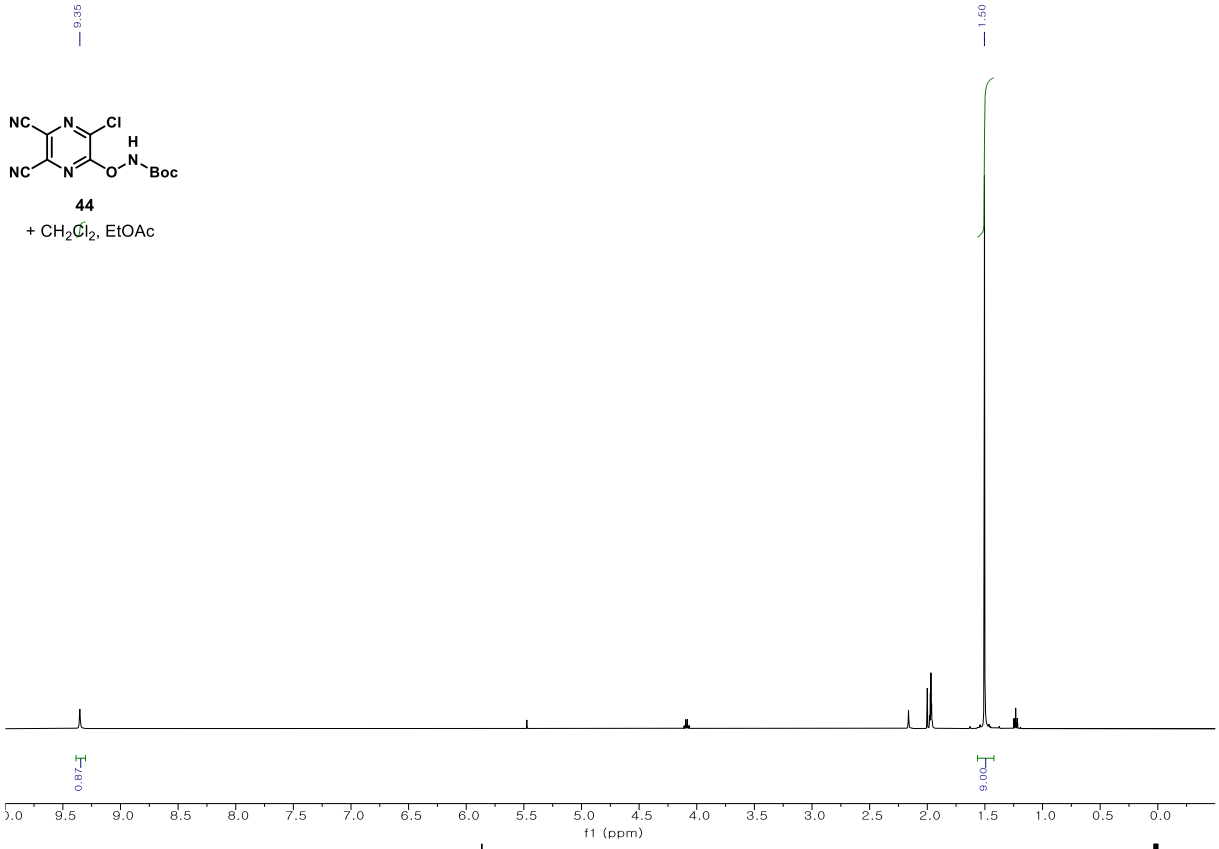

CO2Et
N
41
39.90
38.16
33.28
26.66
25.99
170.97
155.15
151.29
148.94
127.68
121.23
61.15
14.16
f1 (ppm)

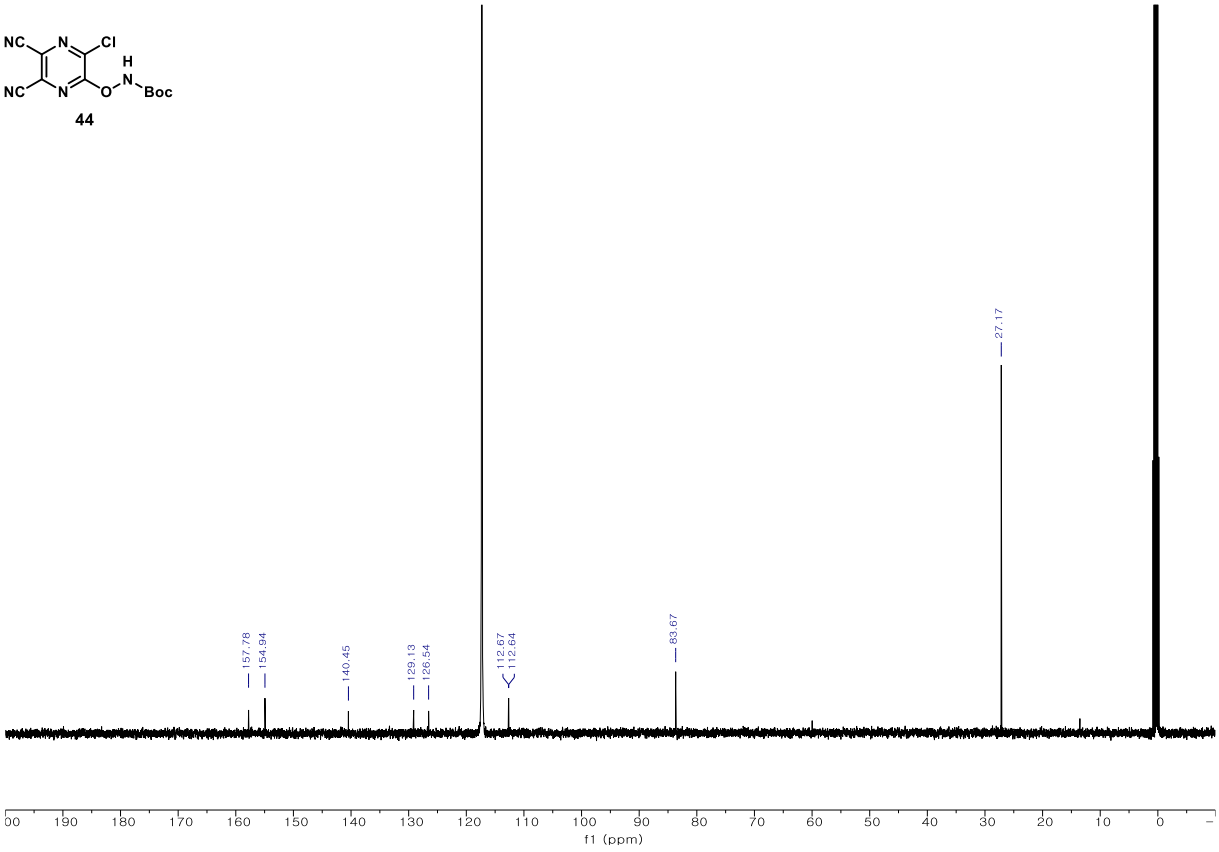

8.44
8.43
8.07
8.07
7.86
7.27
7.27
5.77
2.60
2.59
2.58
2.58
2.56
1.88
1.87
1.87
1.85
1.78
1.77
1.77
1.75
1.75
1.75
1.73
1.45
1.44
1.42
1.42
1.40
1.38
1.27
1.25
1.24
NH2
O
N
42
1.00
1.00
0.92
0.53
0.94
1.06
4.33
1.20
4.50
1.44
f1 (ppm)

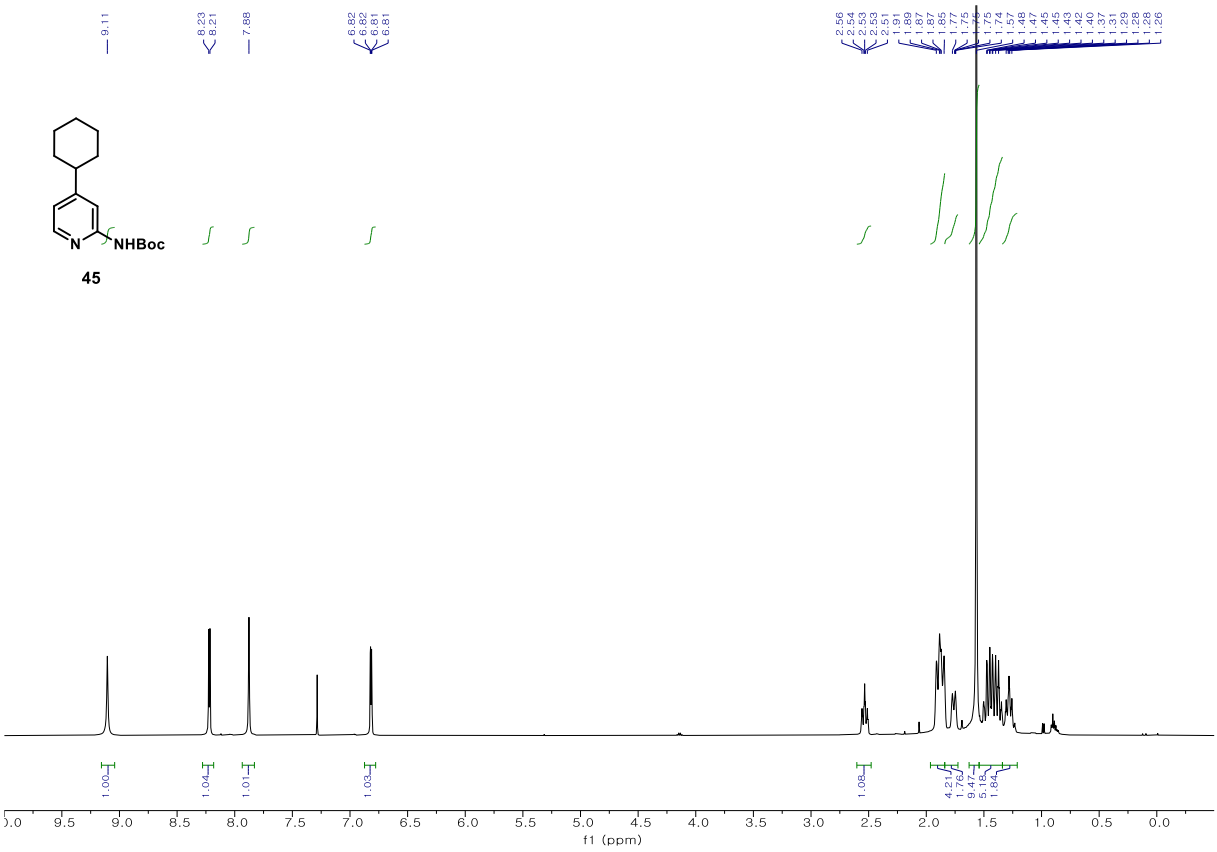

NH2
O
N
42
167.31
158.45
149.61
148.44
125.30
121.24
44.10
33.55
26.59
25.99
f1 (ppm)

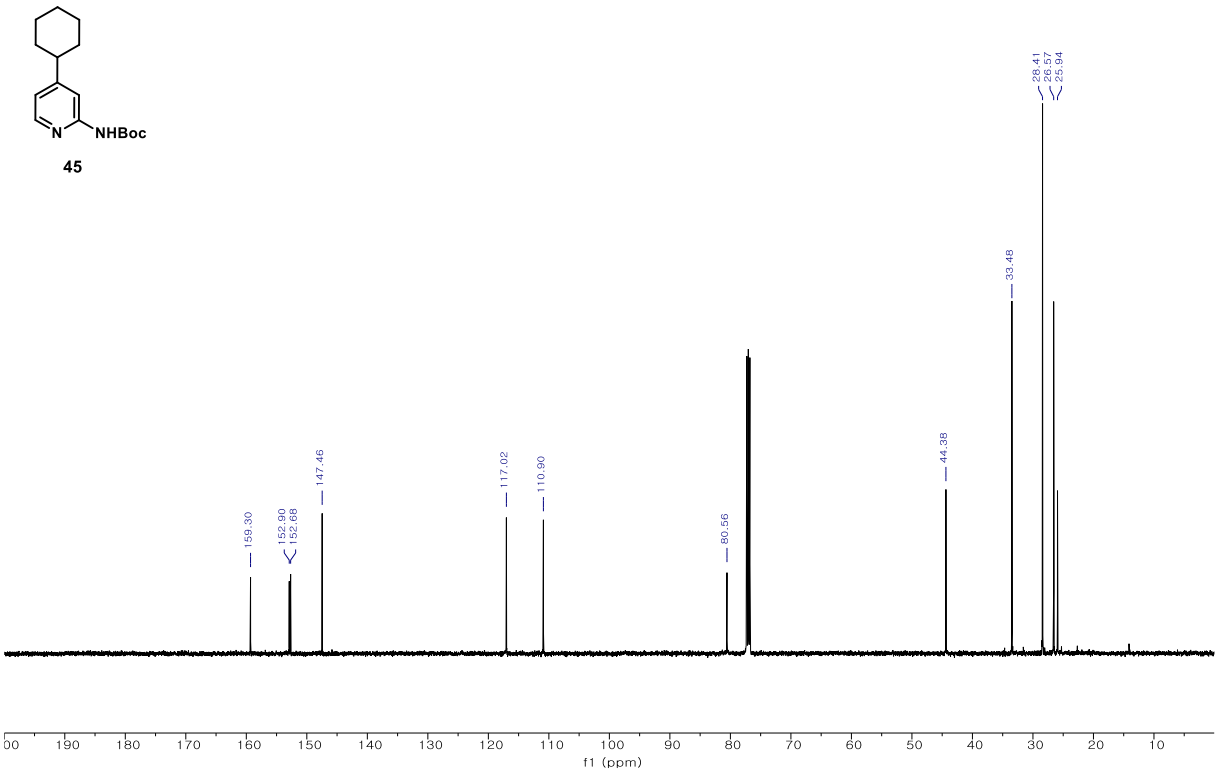

8.59
8.58
7.54
7.34
7.34
7.34
7.33
2.57
1.90
1.89
1.88
1.80
1.78
1.42
1.41
1.41
1.40
1.38
1.27
1.25
N
CN
43
1.00
0.92
0.96
1.04
5.00
4.04
1.45
f1 (ppm)

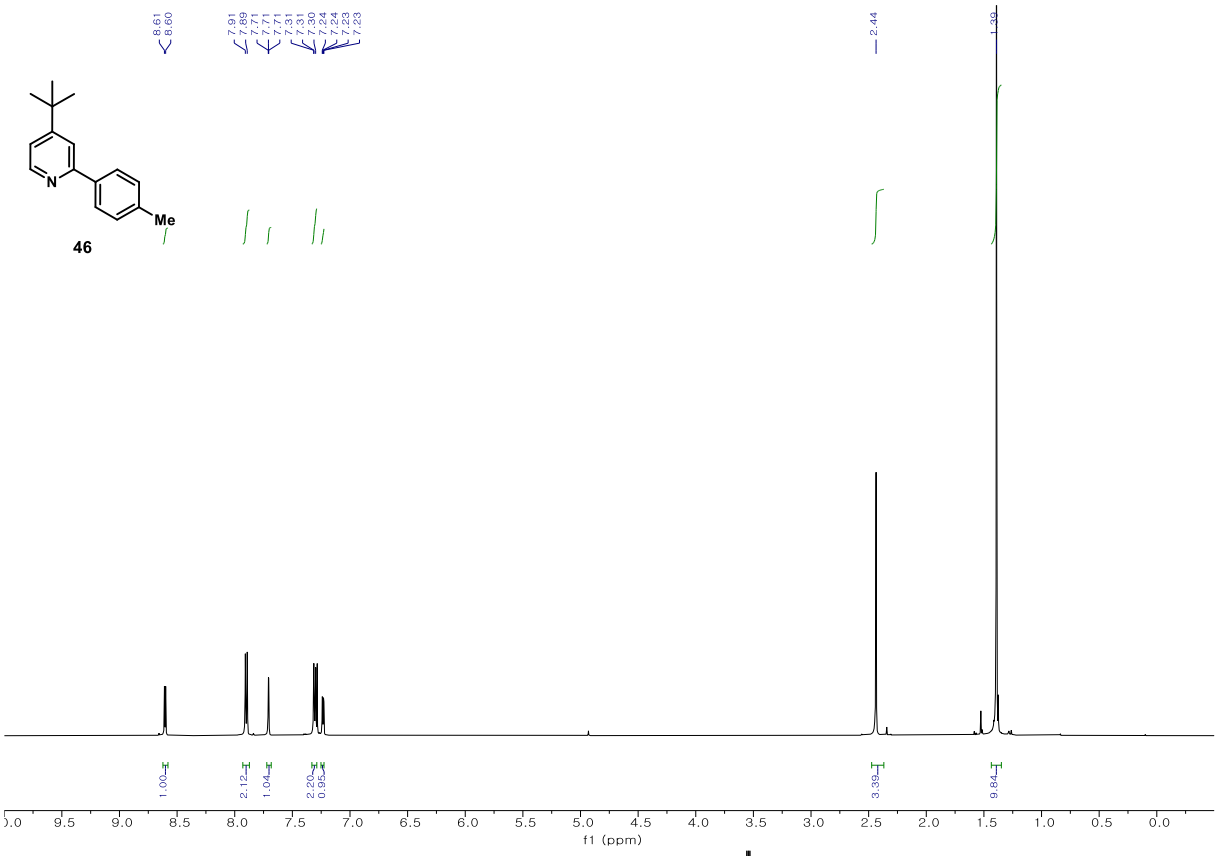

N
CN
43
158.15
150.98
133.96
127.38
125.59
117.54
43.58
33.31
26.29
25.69
f1 (ppm)

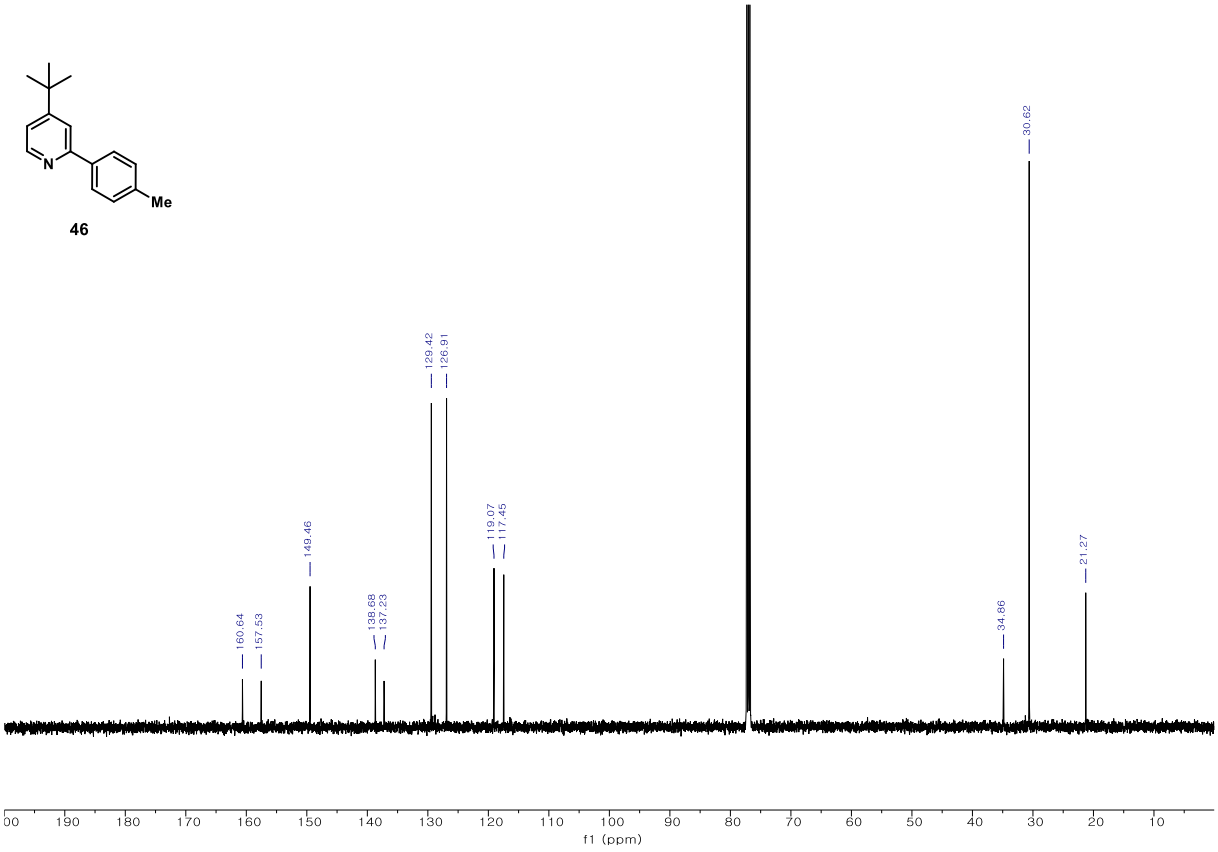

9.35
1.50
NC
N
Cl
H
N
NC
N
O
Boc
44
+ CH2Cl2, EtOAc
0.87
9.00
f1 (ppm)

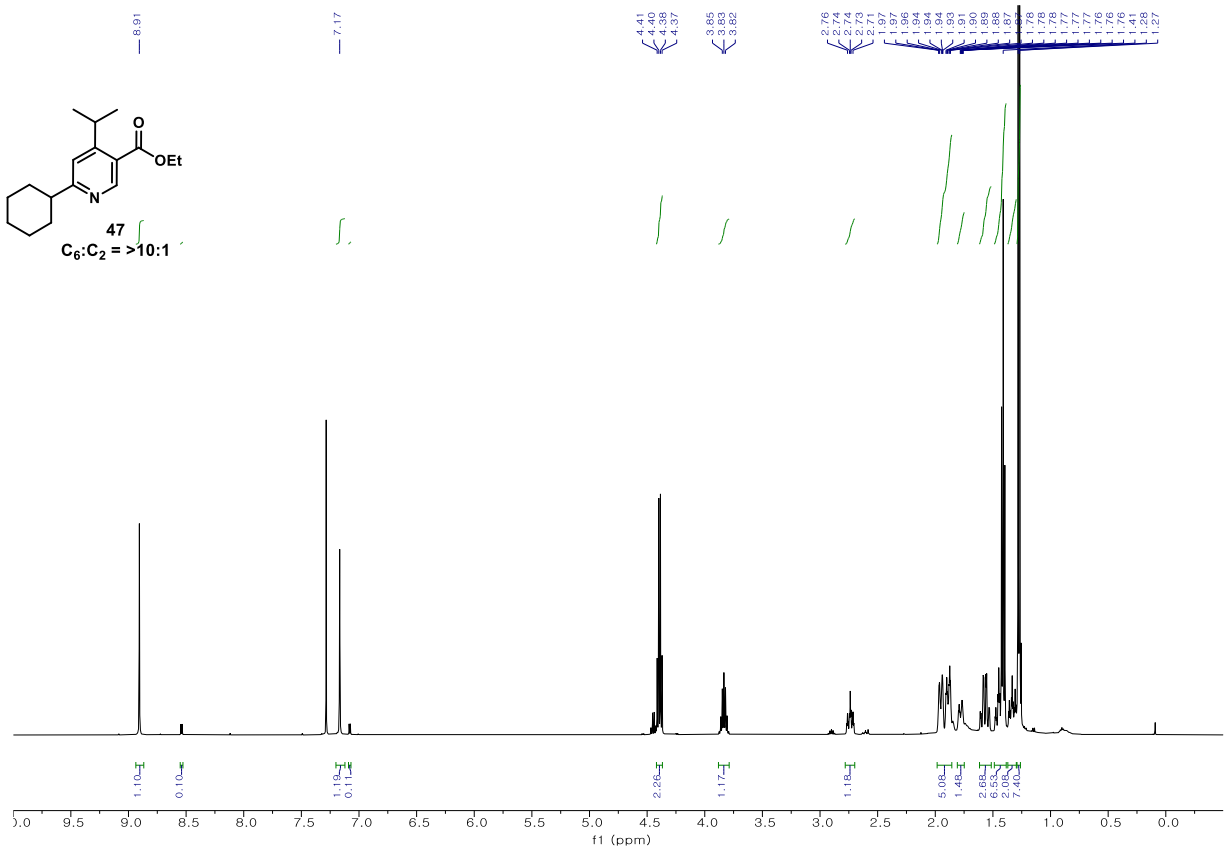

NC
N
Cl
H
N
NC
N
O
Boc
44
27.17
157.78
154.94
140.45
129.13
126.54
112.67
112.64
83.67
f1 (ppm)

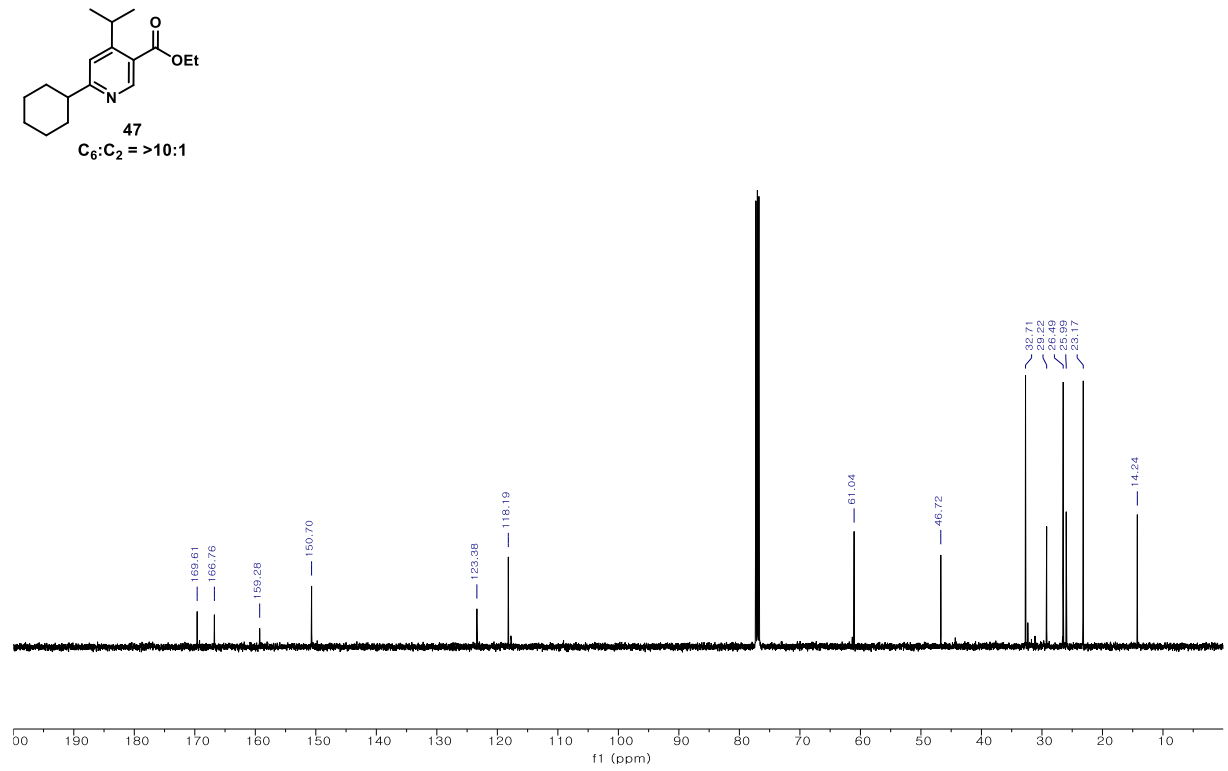

9.11
8.23
8.21
7.88
6.82
6.82
6.81
6.81
2.56
2.54
2.53
2.53
2.51
1.91
1.89
1.87
1.87
1.85
1.77
1.75
1.74
1.57
1.48
1.47
1.45
1.45
1.43
1.42
1.40
1.37
1.31
1.29
1.28
1.28
1.26
NHBoc
45
1.00
1.04
1.01
1.03
1.08
4.21
1.82
9.47
5.18
1.84
f1 (ppm)

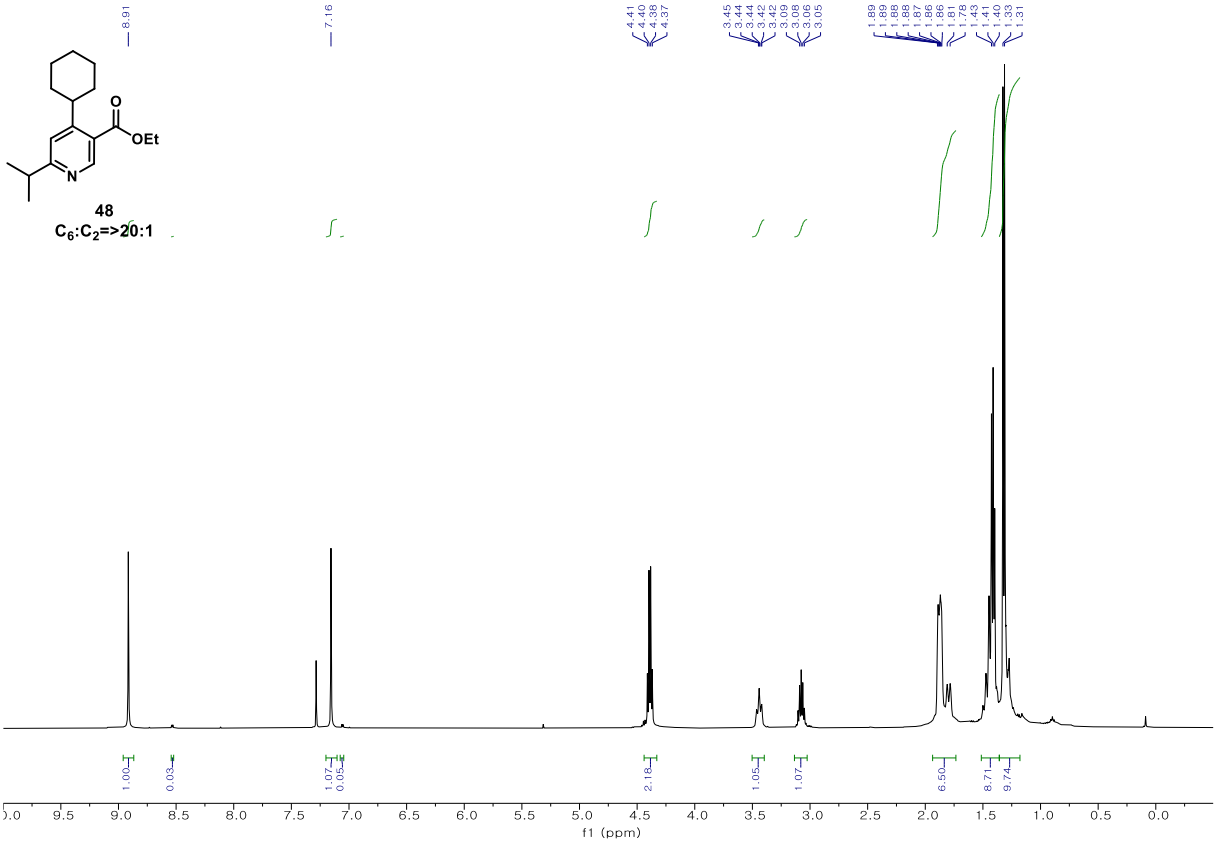

NHBoc
45
28.41
26.57
25.94
33.48
44.38
159.30
152.90
152.68
147.46
117.02
110.90
80.56
f1 (ppm)


8.61
8.60
7.91
7.89
7.71
7.71
7.71
7.31
7.31
7.30
7.24
7.24
7.23
7.23
2.44
1.39
N
Me
46
1.00
2.12
1.04
2.20
0.95
3.39
9.84
f1 (ppm)

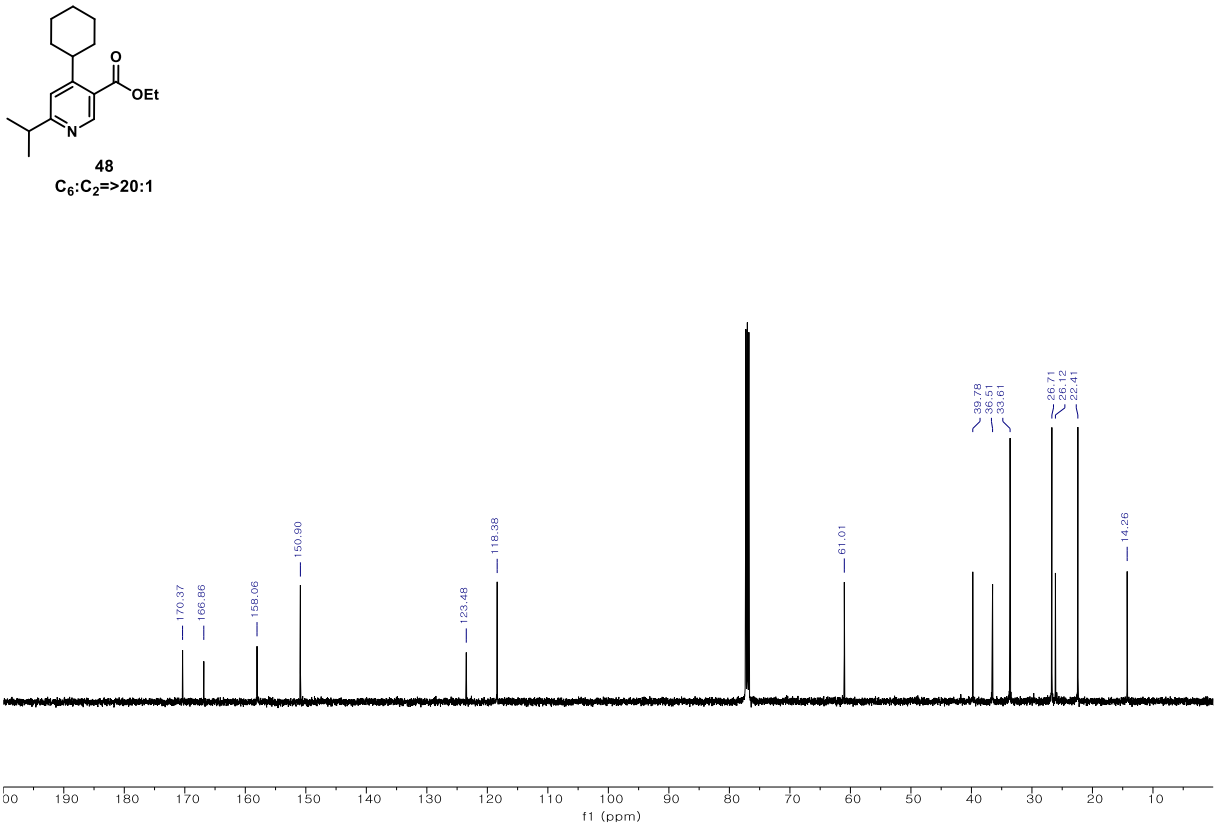

N
Me
46
160.64
157.53
149.46
138.68
137.23
129.42
126.91
119.07
117.45
34.86
30.62
21.27
f1 (ppm)


47
C6:C2 = >10:1
f1 (ppm)

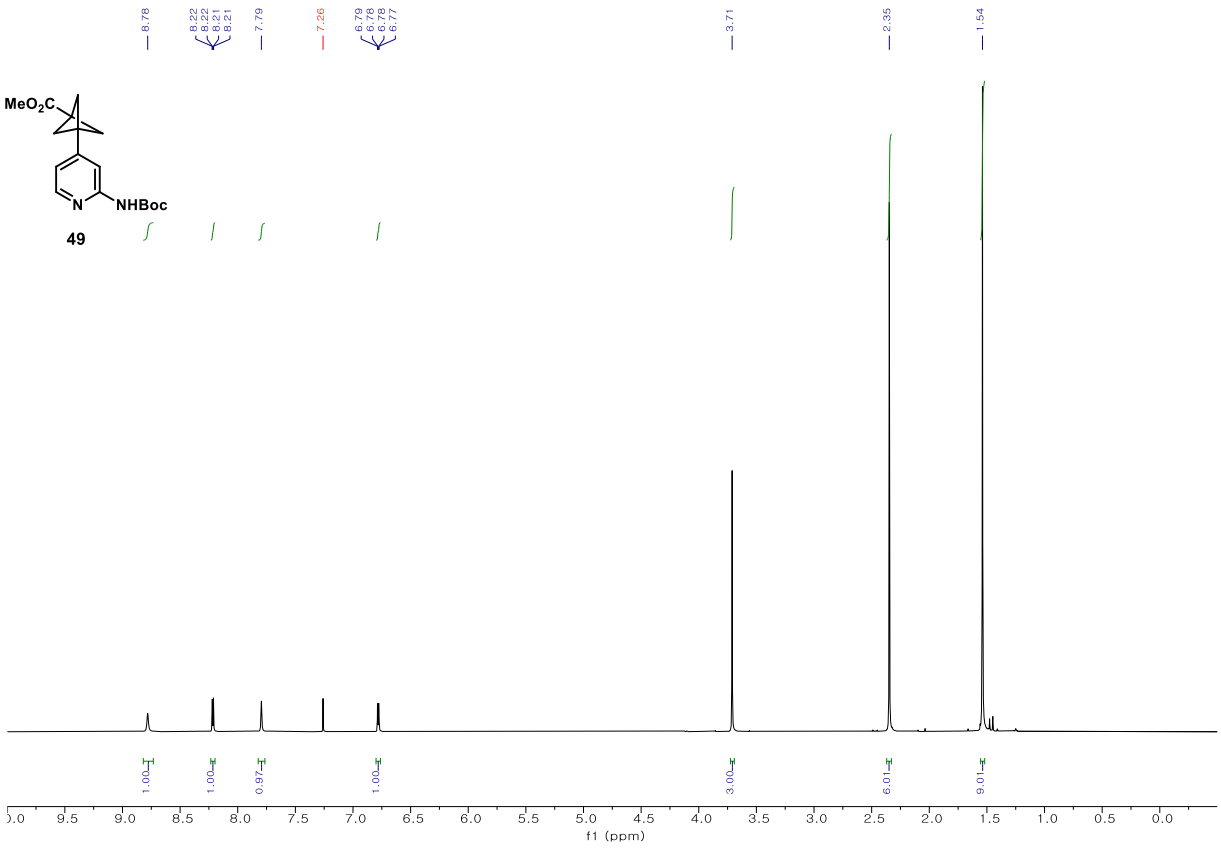

47
C6:C2 = >10:1
f1 (ppm)

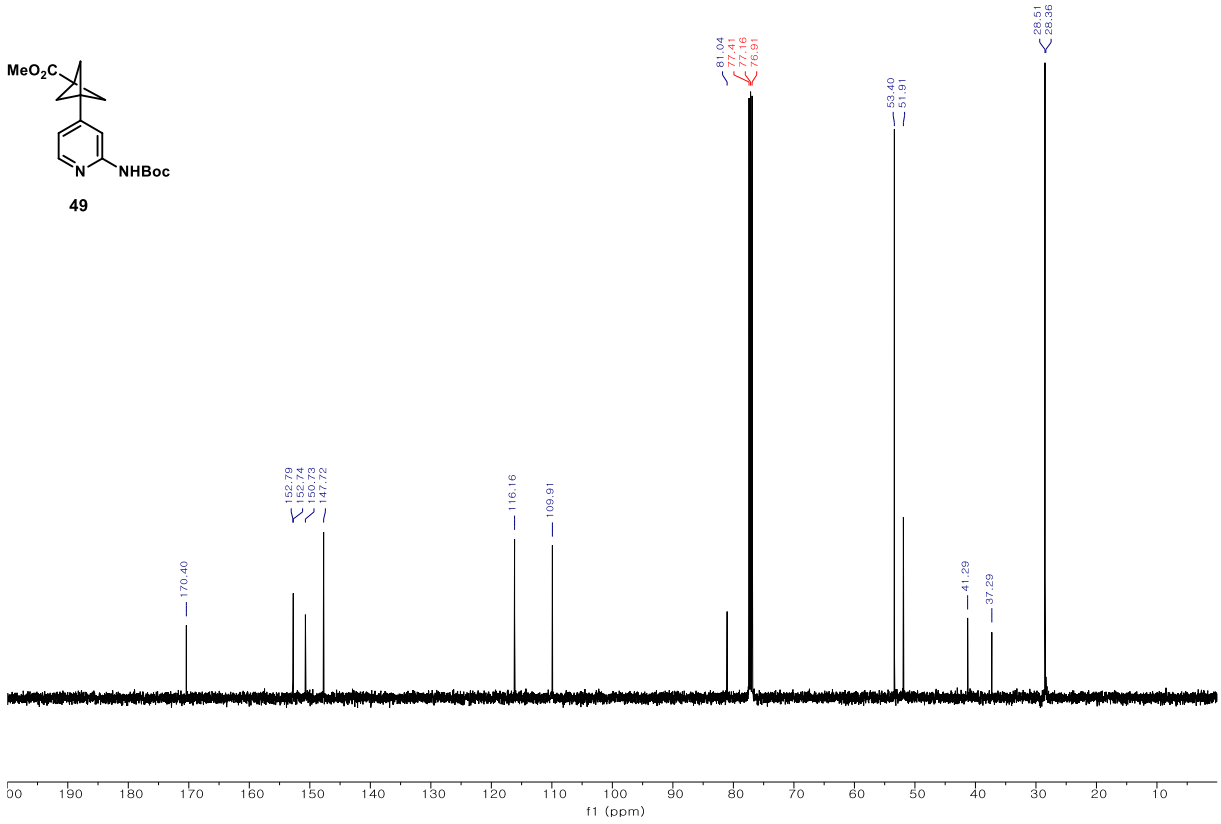


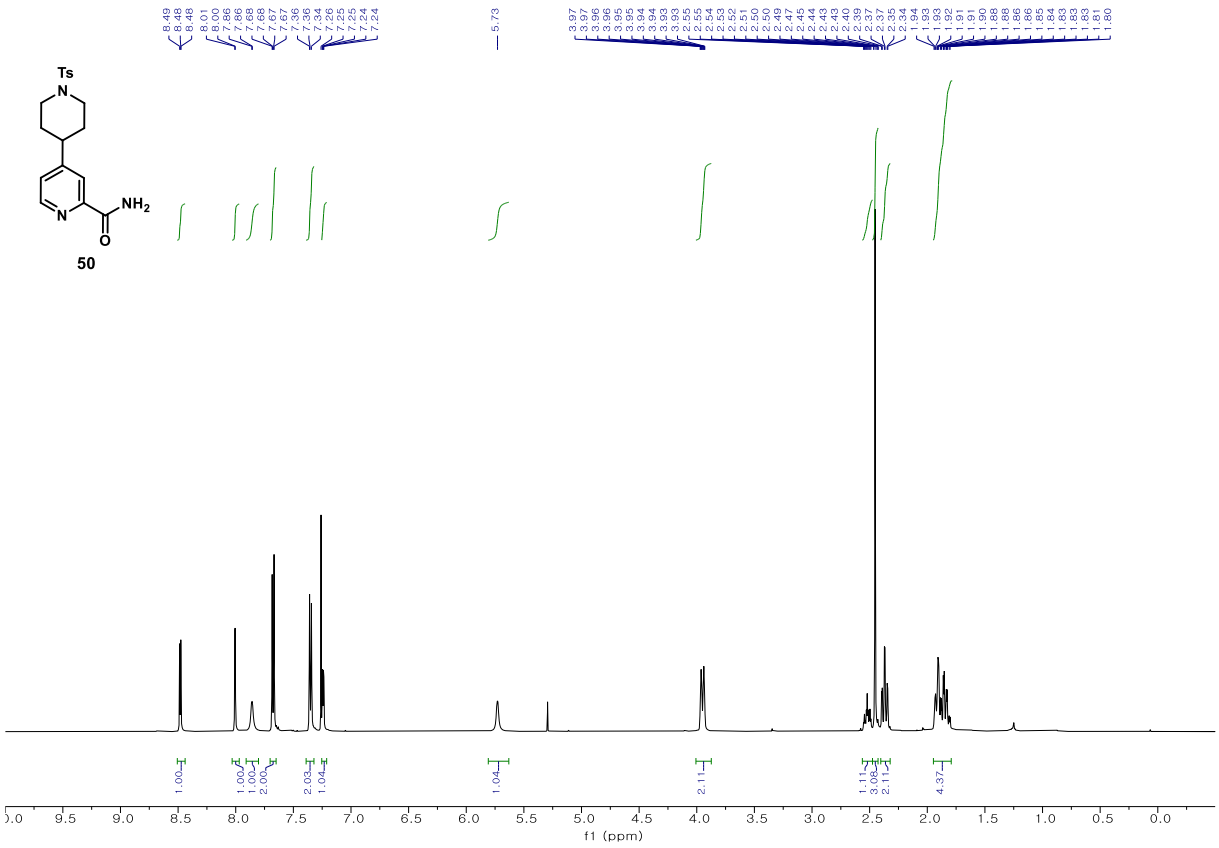
48
C_6:C_2=>20:1

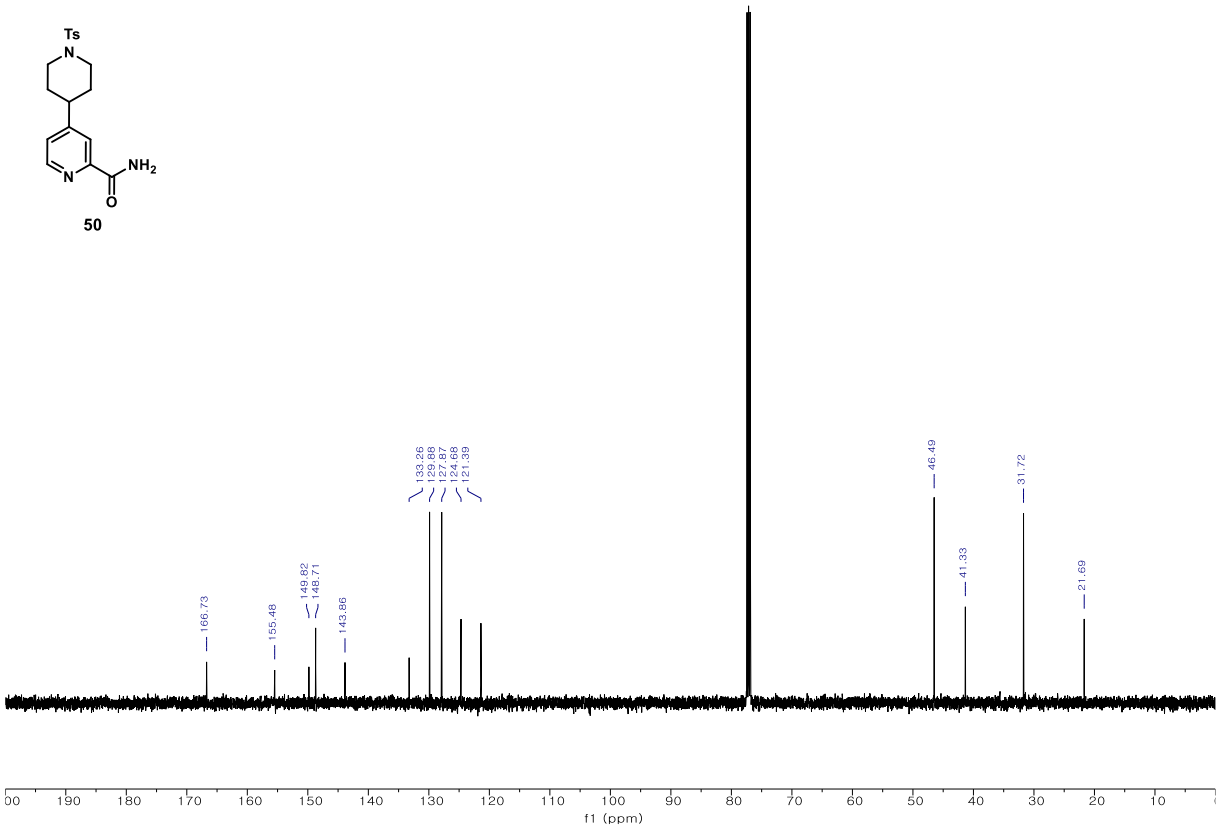


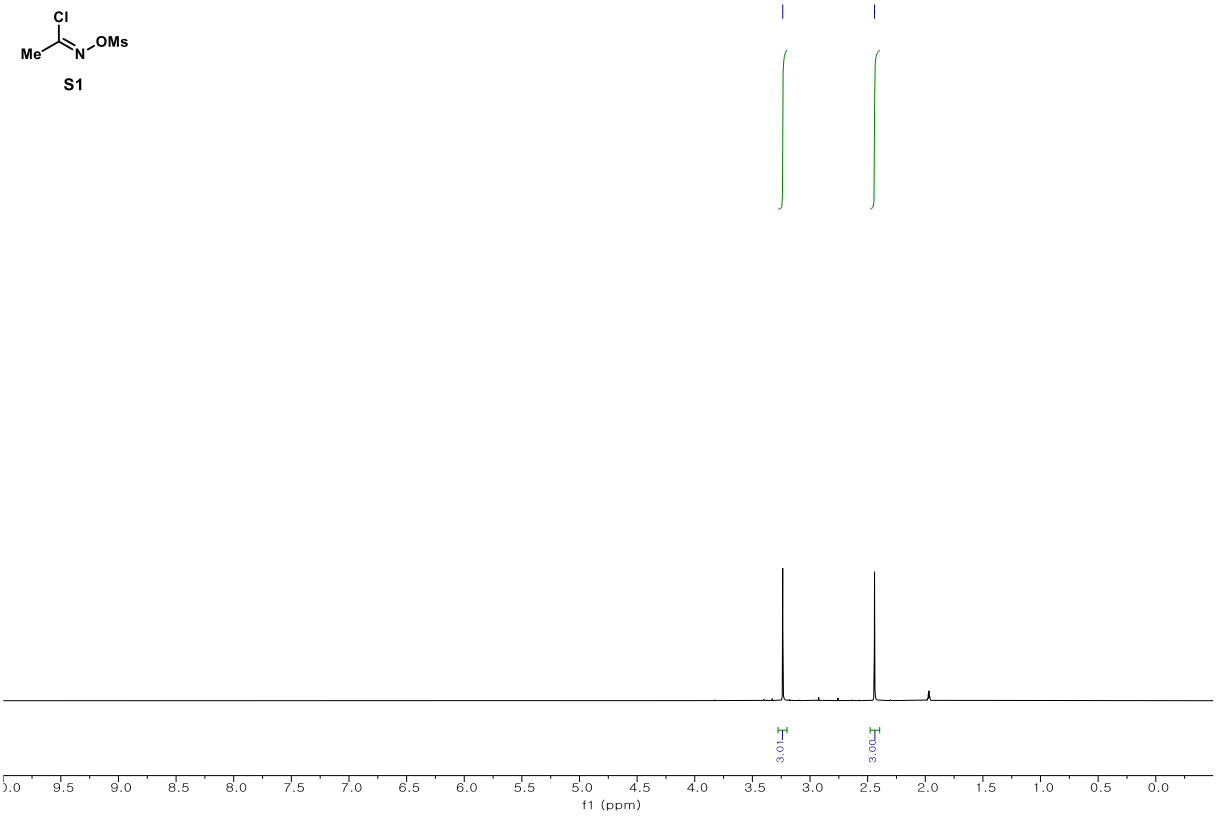
48
C_6:C_2=>20:1

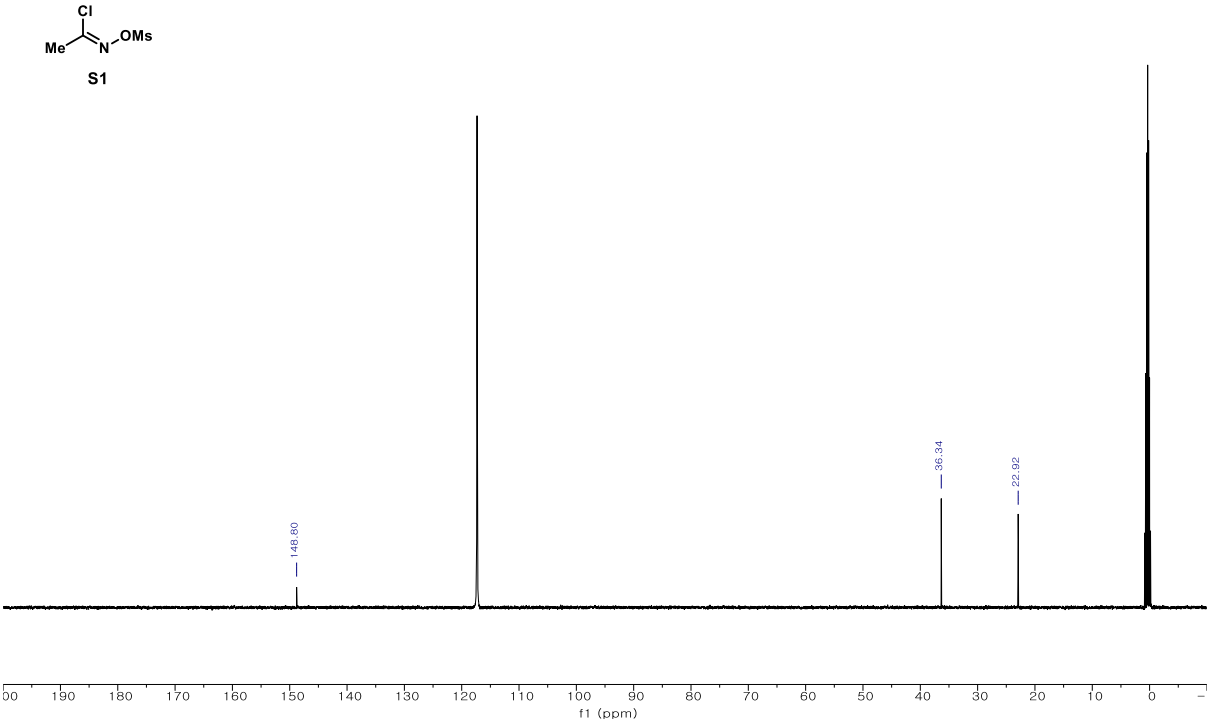

8.78
8.22
8.22
8.21
8.21
7.79
7.26
6.79
6.78
6.78
6.77
3.71
2.35
1.54
MeO2C
N
NHBoc
49
1.00
1.00
0.97
1.00
3.00
6.01
9.01
f1 (ppm)

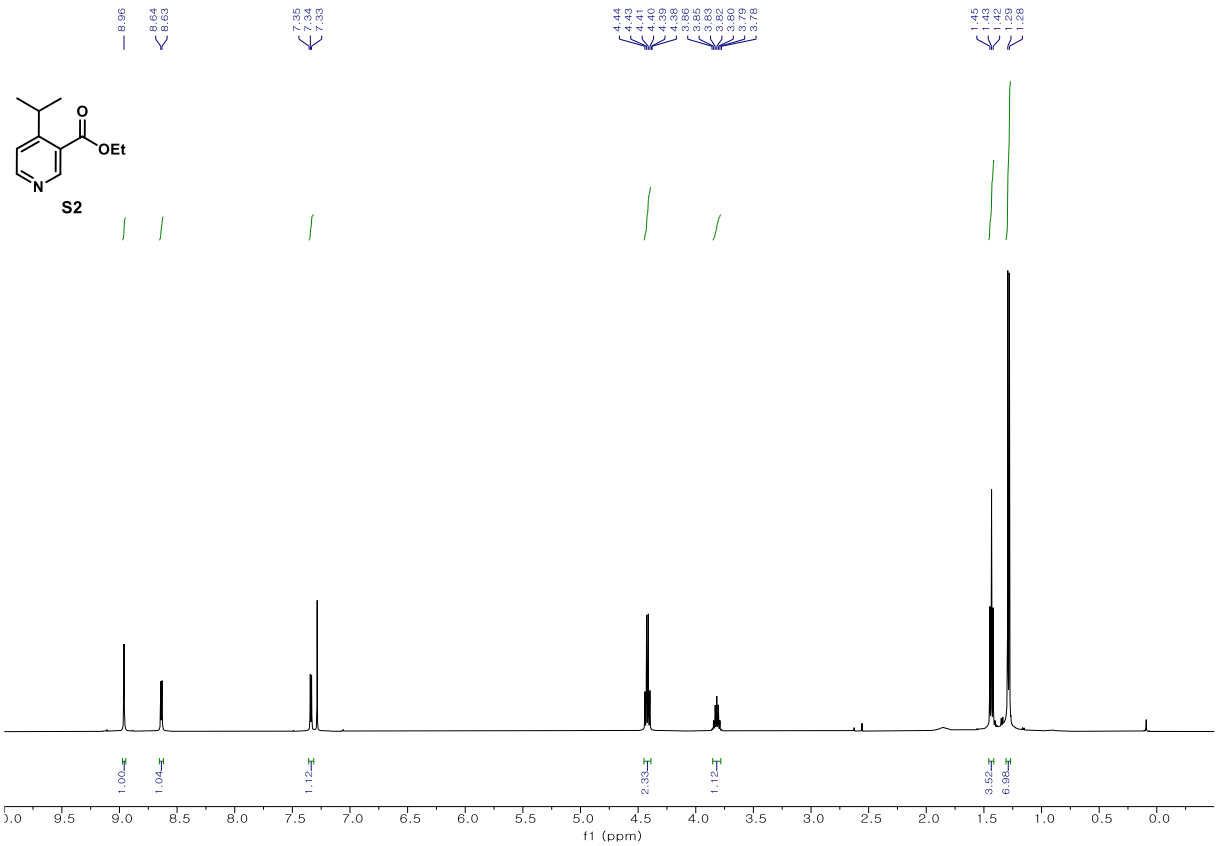

81.04
77.41
77.16
76.91
53.40
51.91
28.51
28.36
152.79
152.74
150.73
147.72
116.16
109.91
170.40
41.29
37.29
MeO2C
N
NHBoc
49
f1 (ppm)

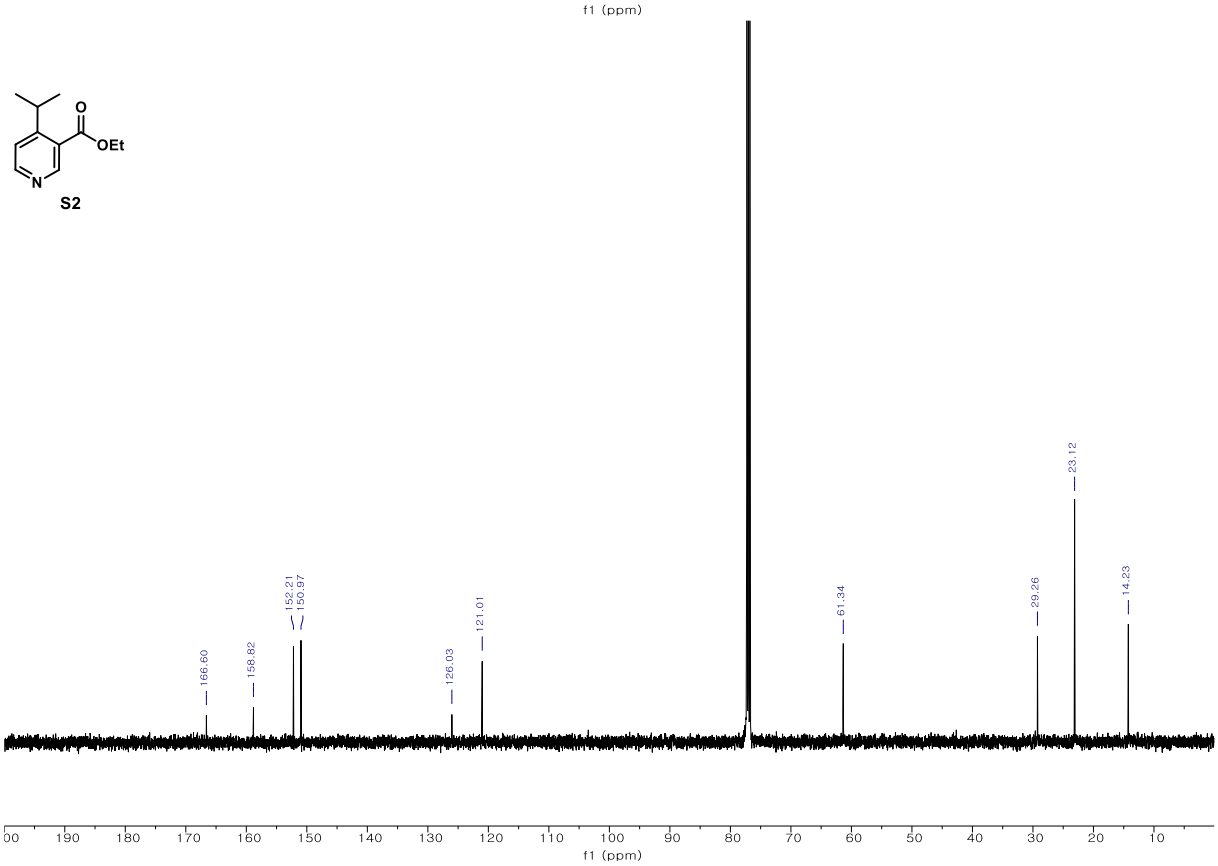

8.49
8.48
8.46
8.01
8.00
7.86
7.68
7.68
7.67
7.67
7.36
7.34
7.26
7.25
7.24
7.24
5.73
3.97
3.97
3.96
3.96
3.95
3.95
3.94
3.94
3.93
3.93
2.55
2.54
2.54
2.52
2.51
2.50
2.50
2.49
2.47
2.45
2.44
2.43
2.40
2.40
2.39
2.37
2.37
2.35
2.34
1.94
1.93
1.93
1.92
1.91
1.91
1.90
1.88
1.88
1.86
1.86
1.85
1.84
1.83
1.83
1.83
1.81
1.80
Ts
N
N
NH2
O
50
1.00
1.00
1.00
2.00
2.03
1.04
1.04
2.11
1.11
3.08
2.11
4.37
f1 (ppm)

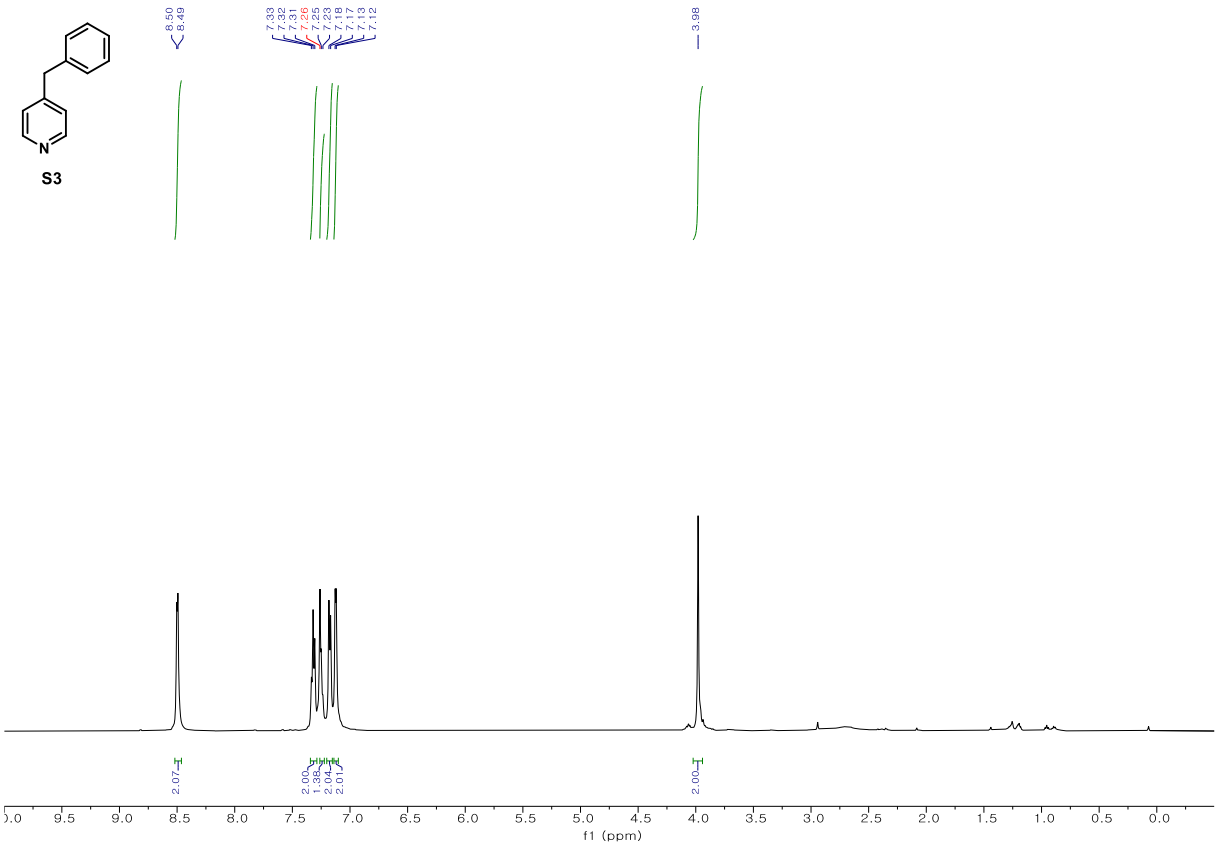

Ts
N
N
NH2
O
50
133.26
129.88
127.87
124.68
121.39
166.73
155.48
149.92
148.71
143.86
46.49
41.33
31.72
21.69
f1 (ppm)

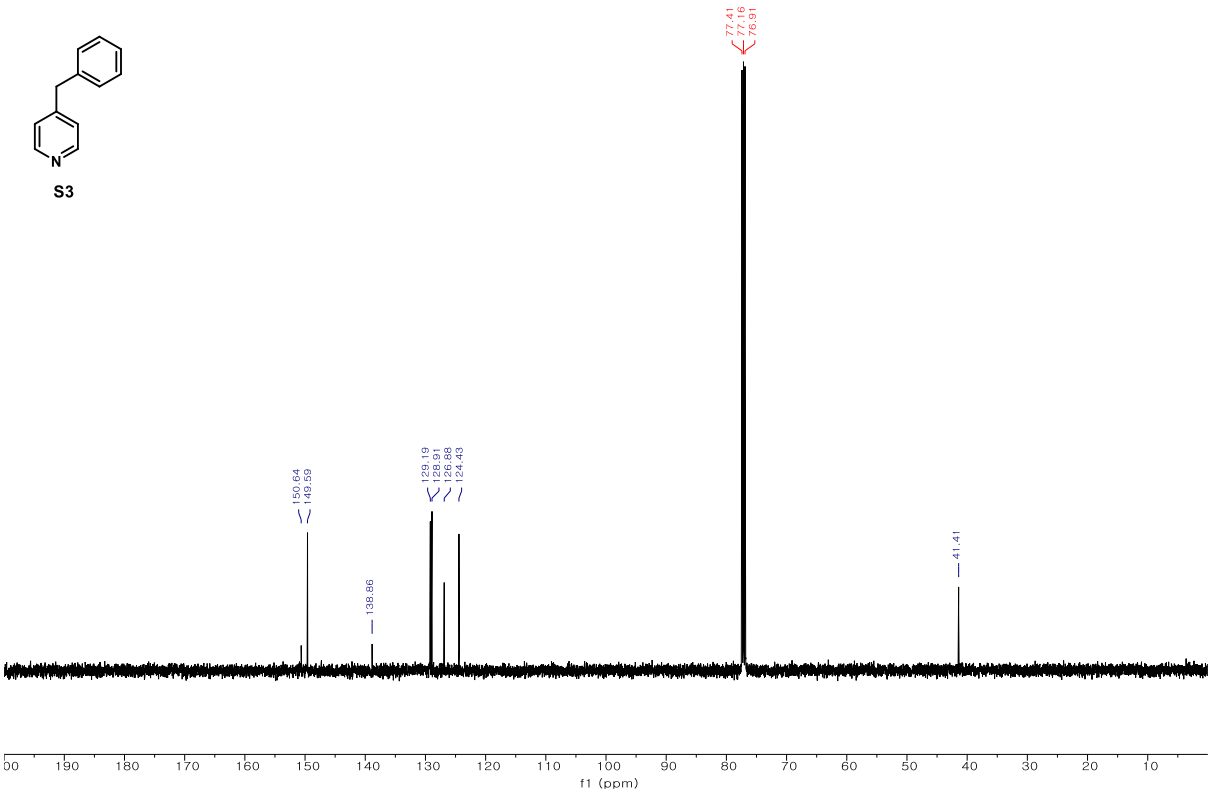

Cl
Me
N
OMs
S1
3.24
2.44
3.01
3.00
f1 (ppm)

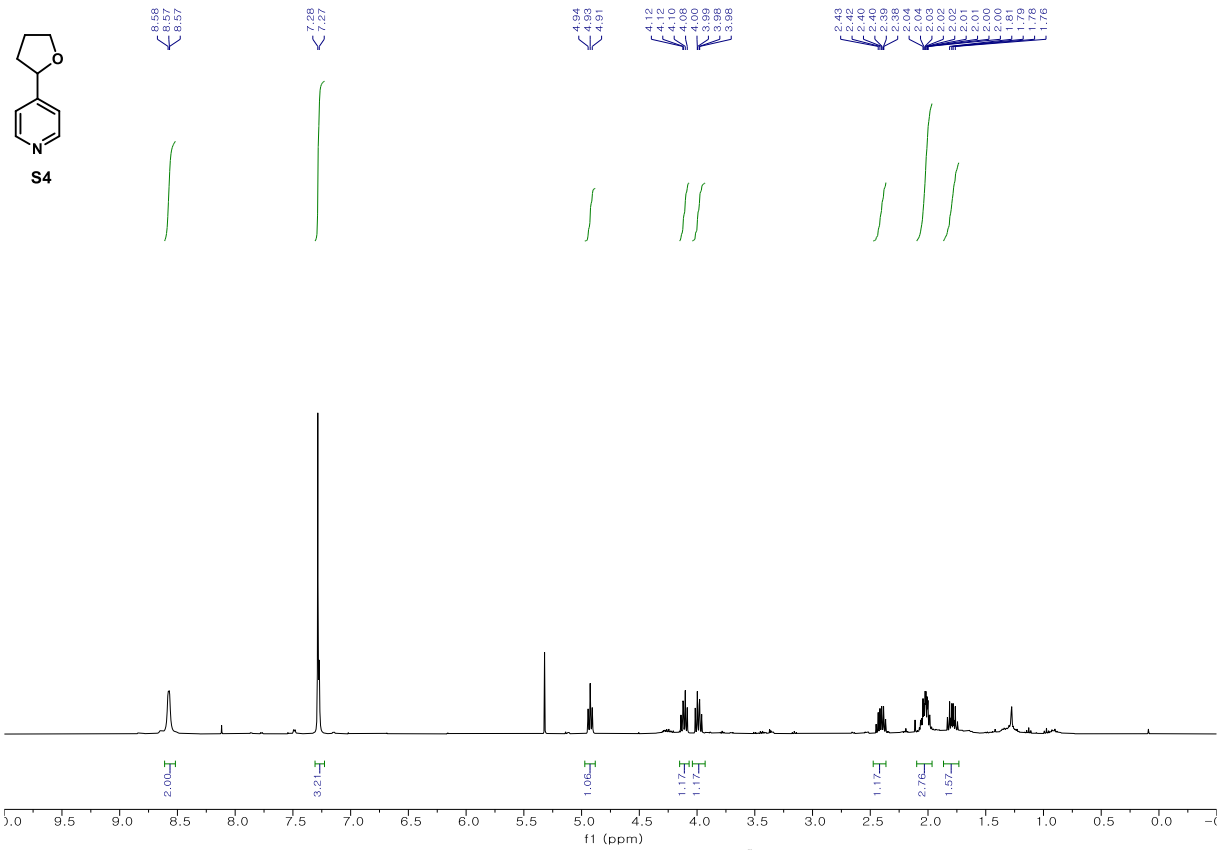

Cl
Me
N
OMs
S1
148.80
36.34
22.92
f1 (ppm)

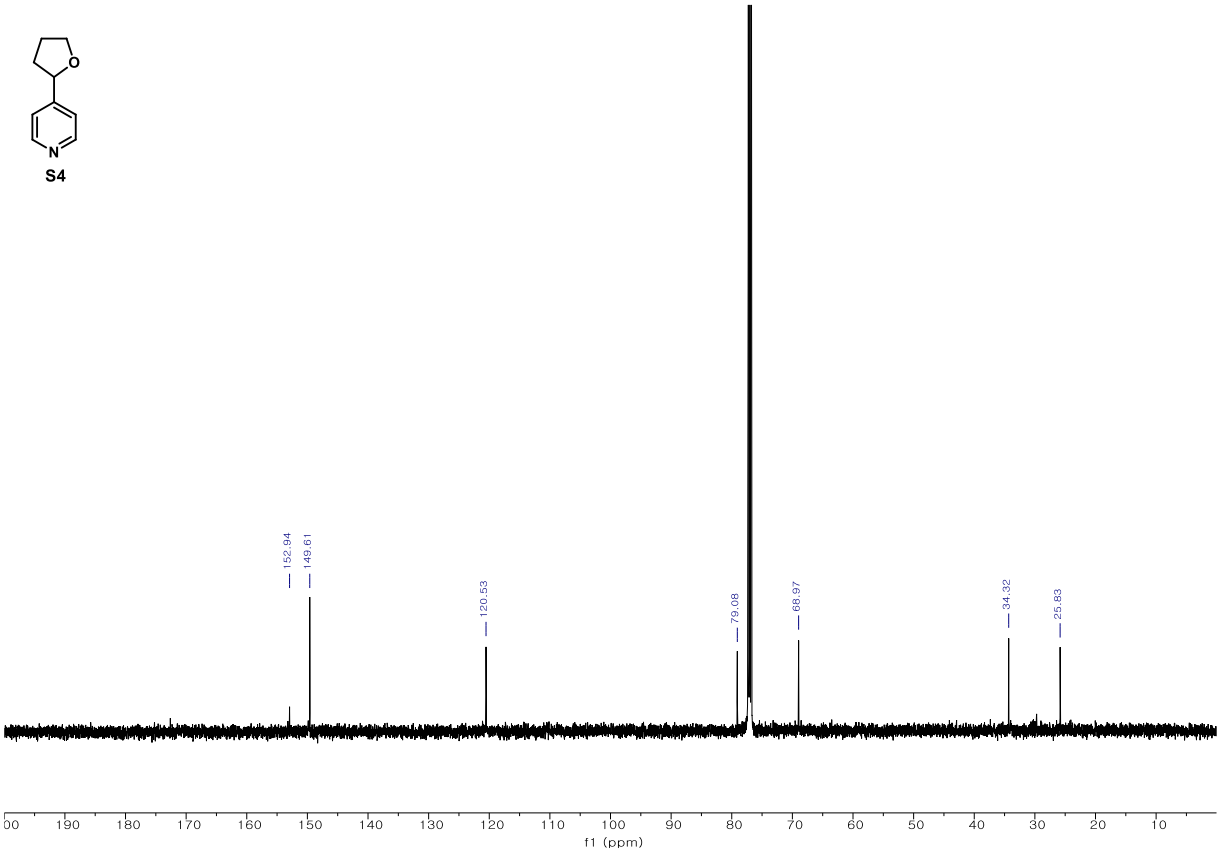

8.96
8.64
8.63
7.35
7.34
7.33
4.44
4.43
4.41
4.40
4.39
4.38
3.86
3.85
3.83
3.82
3.80
3.79
3.78
1.45
1.43
1.42
1.29
1.28
O
OEt
N
S2
1.00
1.04
1.12
2.33
1.12
3.52
6.98
f1 (ppm)

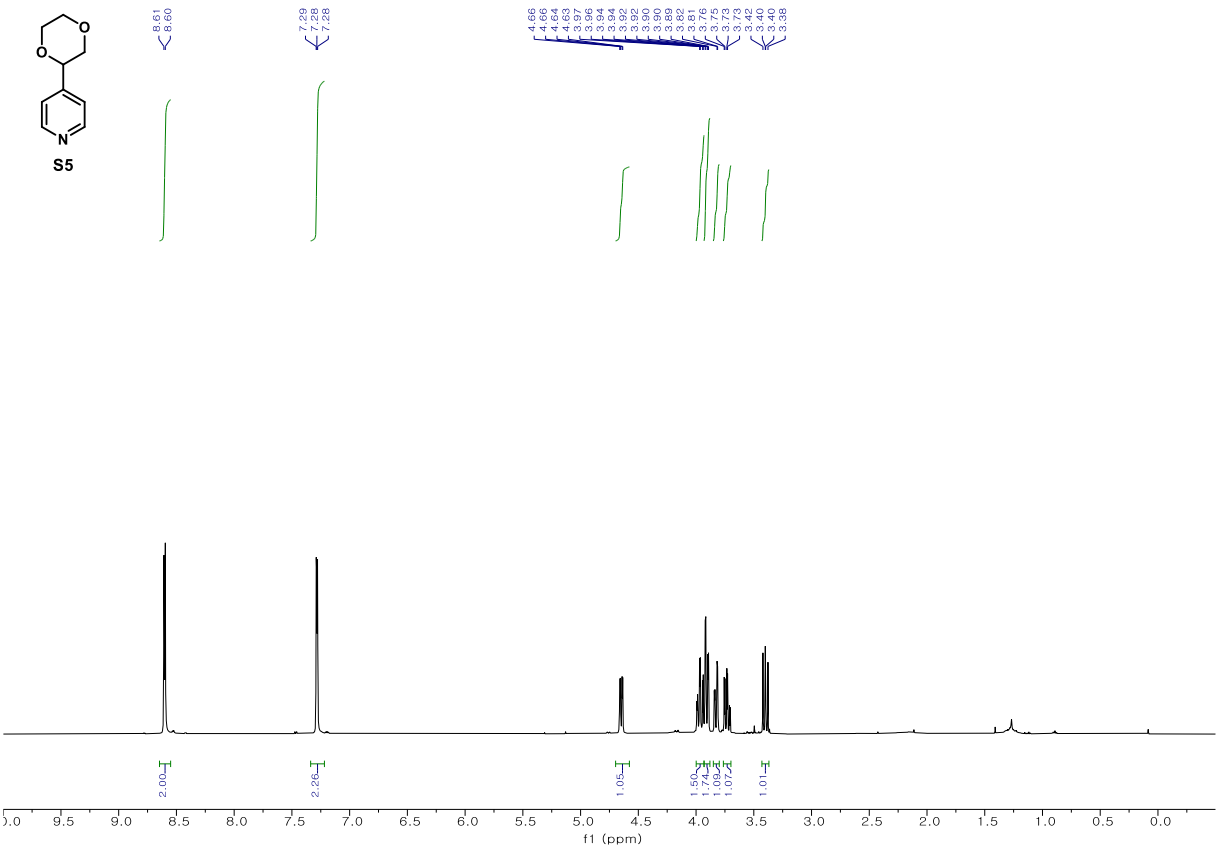

O
OEt
N
S2
166.60
158.82
152.21
150.97
126.03
121.01
61.34
29.26
23.12
14.23
f1 (ppm)

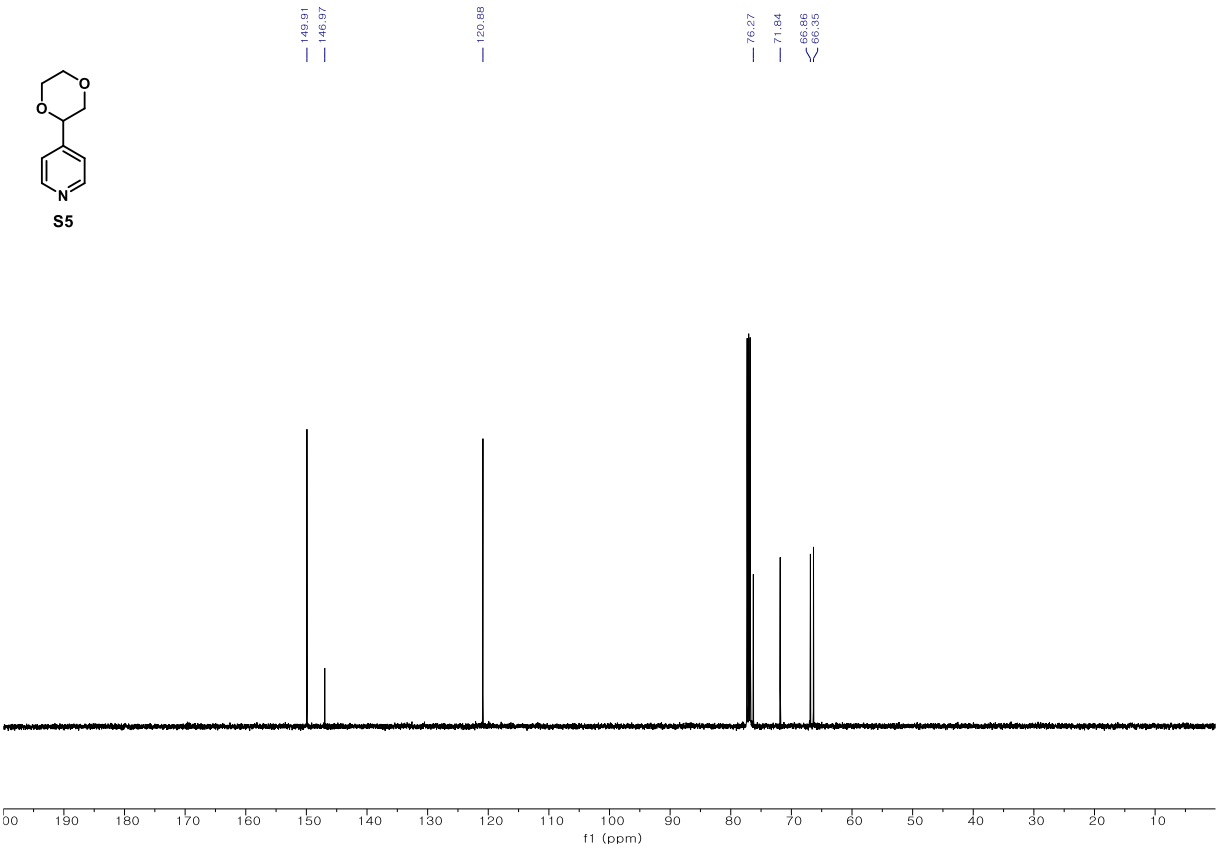

S3
8.50
8.49
7.33
7.32
7.31
7.26
7.25
7.23
7.18
7.17
7.13
7.12
3.98
2.07
2.00
1.84
1.84
2.01
2.00
f1 (ppm)

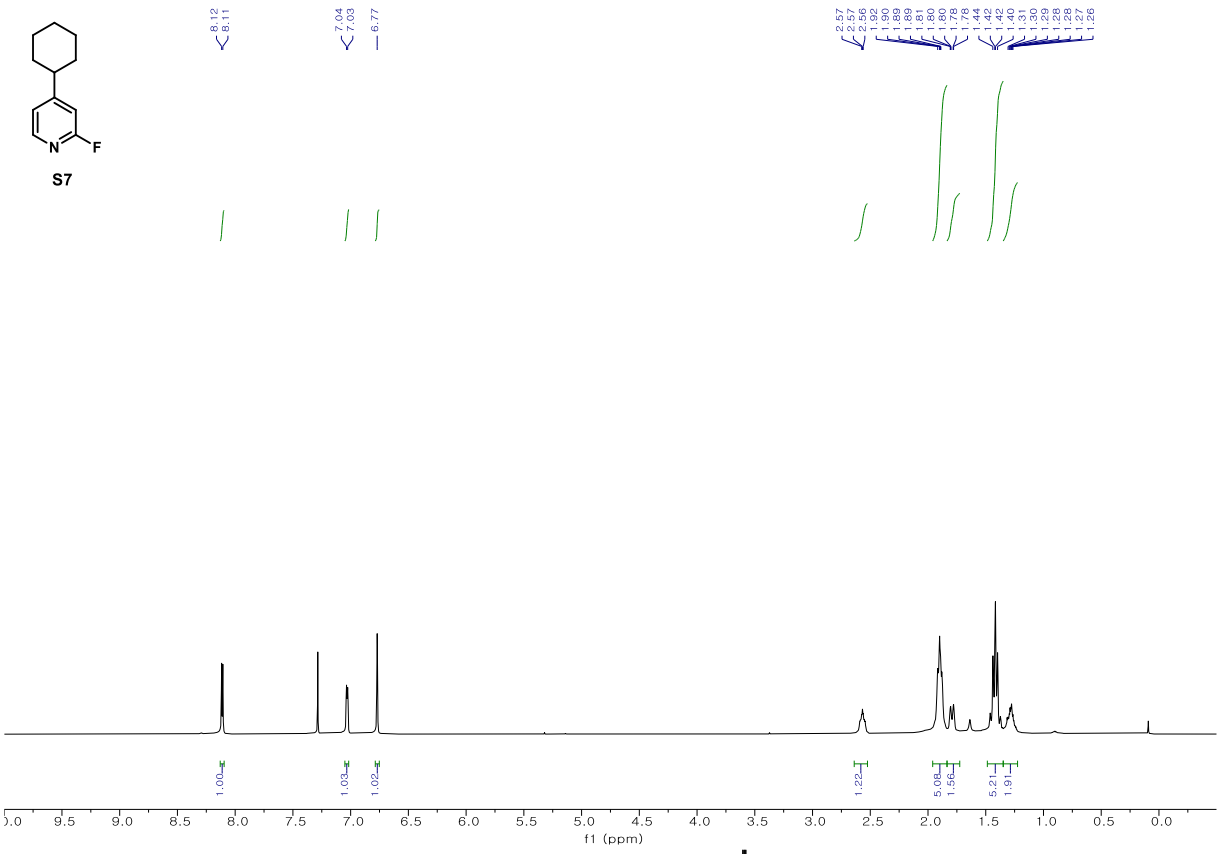

S3
77.41
77.16
76.91
150.64
149.59
138.86
129.19
128.91
126.88
124.43
41.41
f1 (ppm)

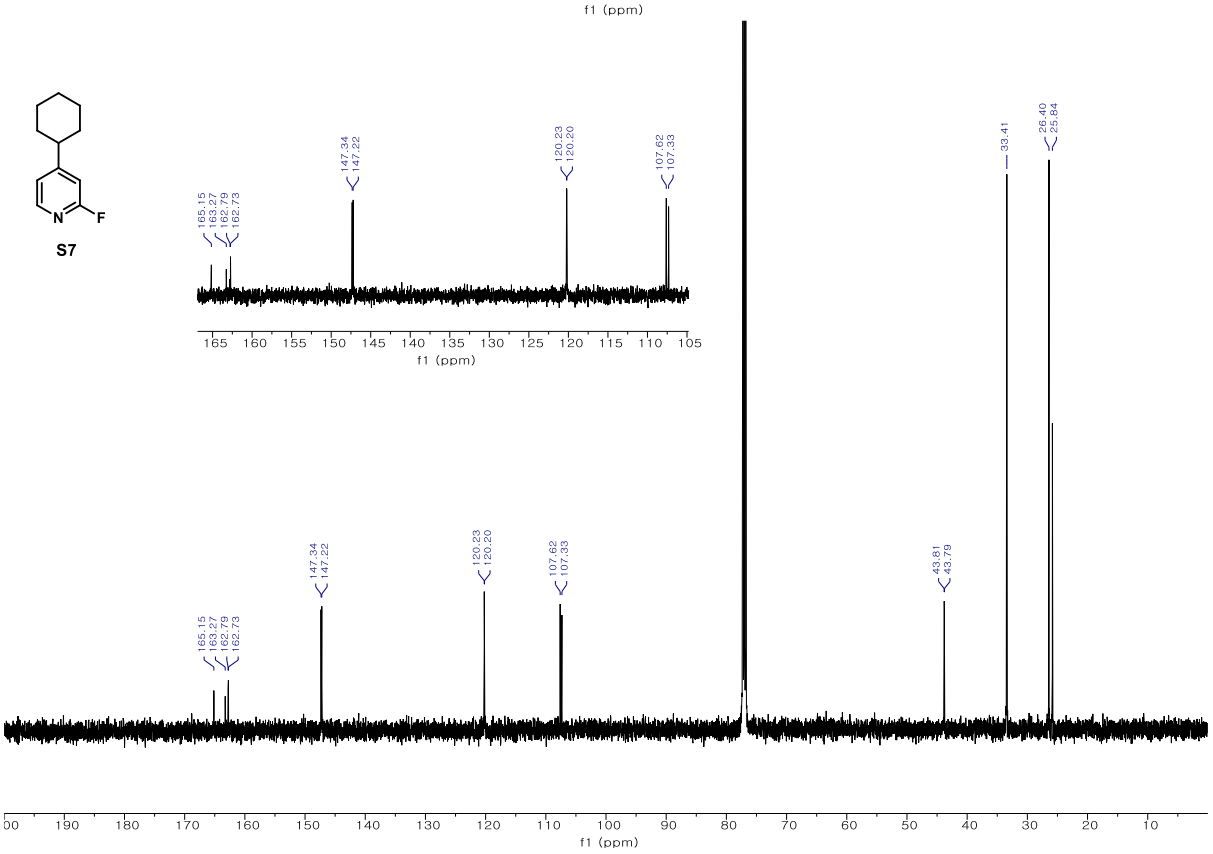

S4
8.58
8.57
8.57
7.28
7.27
4.94
4.93
4.91
4.12
4.12
4.10
4.08
4.00
3.99
3.98
3.98
2.43
2.42
2.40
2.40
2.39
2.38
2.04
2.04
2.03
2.02
2.02
2.01
2.01
2.00
2.00
1.81
1.79
1.78
1.76
2.00
3.21
1.06
1.17
1.17
1.17
2.76
1.57
f1 (ppm)

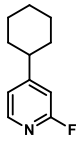

S4
152.94
149.61
120.53
79.08
68.97
34.32
25.83
f1 (ppm)


S5
8.61
8.60
7.29
7.28
7.28
4.66
4.66
4.64
4.63
3.97
3.96
3.94
3.94
3.92
3.92
3.90
3.90
3.89
3.82
3.81
3.76
3.75
3.73
3.73
3.42
3.40
3.40
3.38
2.00
2.26
1.05
1.50
1.74
1.09
1.07
1.01
f1 (ppm)


S5
149.91
146.97
120.88
76.27
71.84
66.86
66.35
f1 (ppm)

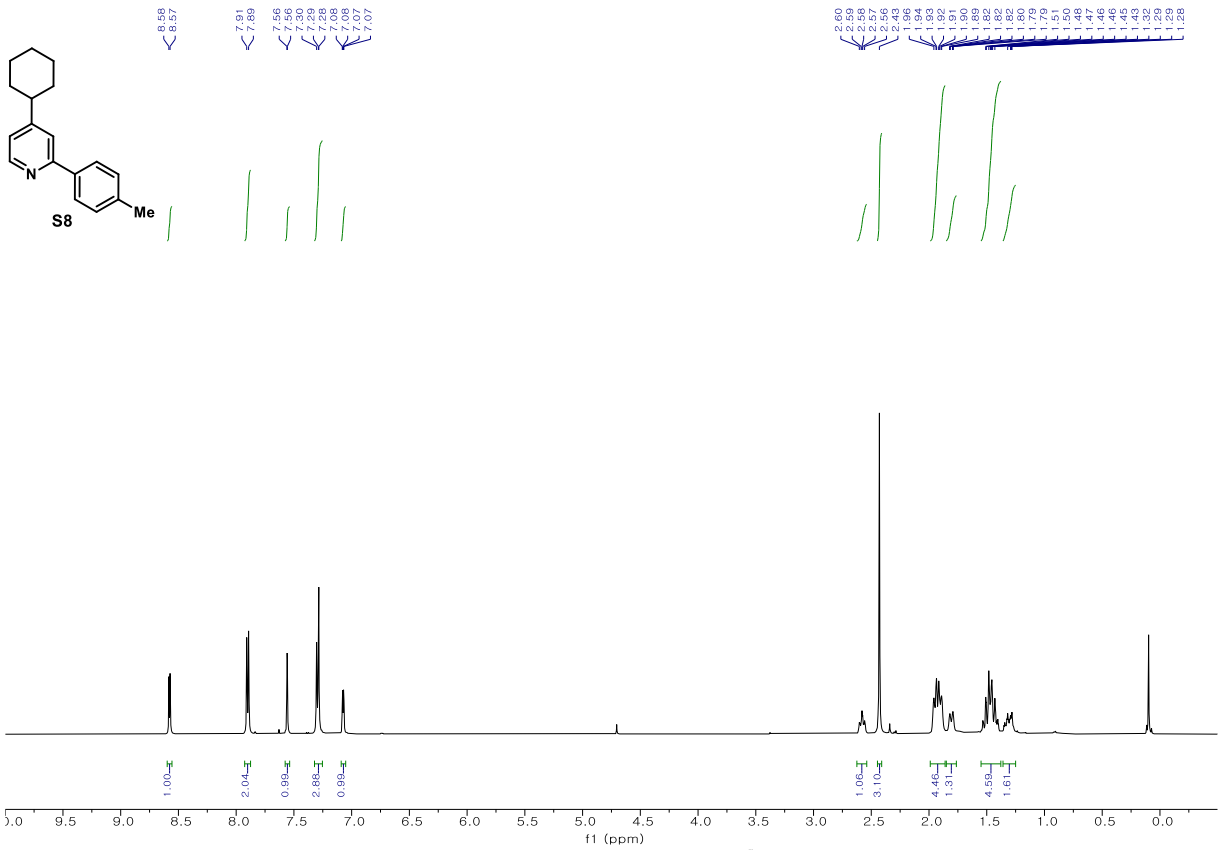

S7
8.12
8.11
7.04
7.03
6.77
2.57
2.57
2.56
2.56
1.90
1.89
1.89
1.81
1.80
1.80
1.78
1.44
1.42
1.42
1.40
1.31
1.30
1.29
1.28
1.28
1.27
1.26
1.00
1.03
1.02
1.22
5.08
1.56
5.21
1.91
f1 (ppm)

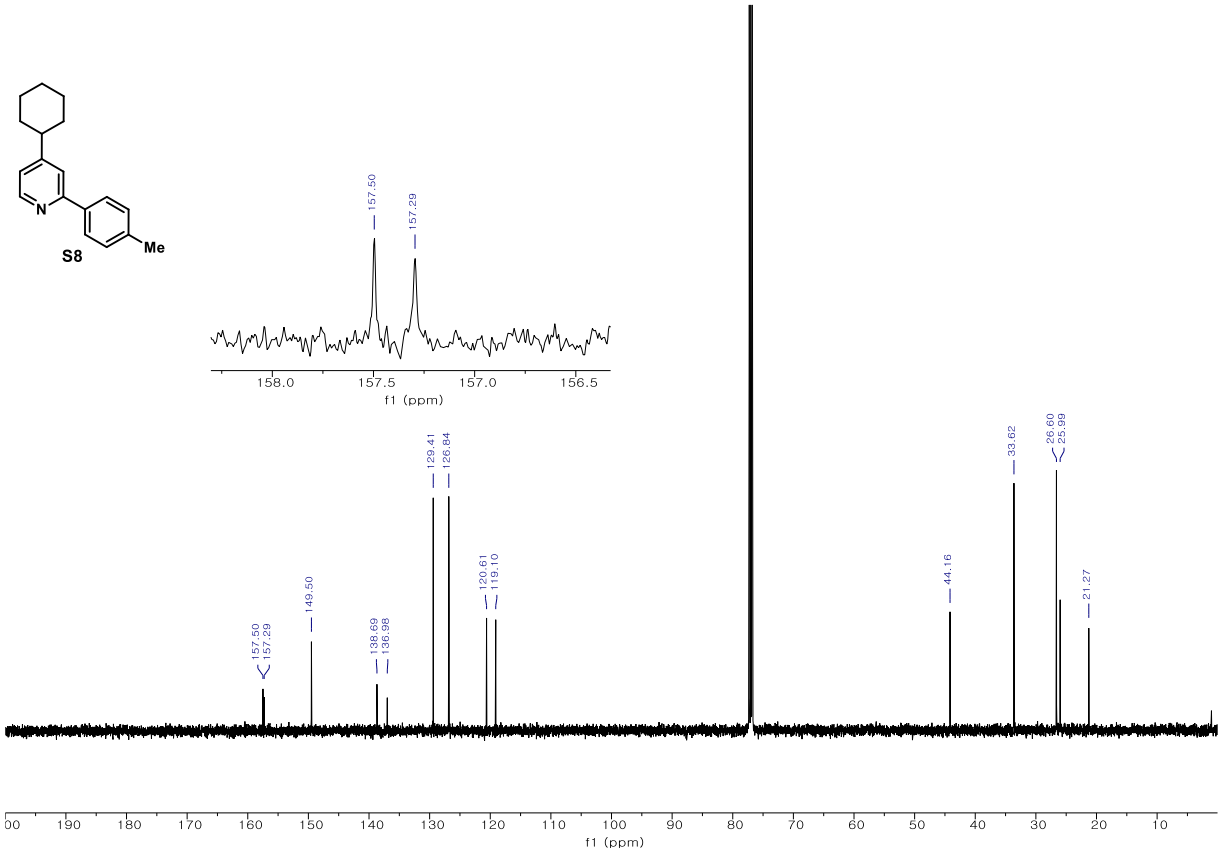

S7
165.15
163.27
162.79
162.73
147.34
147.22
120.23
120.20
107.62
107.33
33.41
26.40
25.84
43.81
43.79
f1 (ppm)


N
F

S7

-71.78
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


8.58
8.57
7.91
7.89
7.56
7.55
7.30
7.29
7.28
7.08
7.08
7.07
7.07
2.60
2.59
2.58
2.57
2.56
2.43
1.96
1.94
1.93
1.92
1.91
1.90
1.89
1.82
1.82
1.80
1.79
1.79
1.51
1.50
1.48
1.47
1.46
1.46
1.45
1.43
1.32
1.29
1.29
1.28
N
Me
S8
1.00
2.04
0.99
2.88
0.99
1.06
3.10
4.46
1.31
4.59
1.61
f1 (ppm)


N
Me
S8
157.50
157.29
158.0
157.5
157.0
156.5
f1 (ppm)
129.41
126.84
120.61
119.10
157.50
157.29
149.50
138.69
136.98
44.16
33.62
26.60
25.99
21.27
f1 (ppm)