Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supplementary Information

Cobalt-catalyzed directed *ortho*-methylation of arenes with methyl tosylate

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Contents

Materials and Methods

General. All reactions dealing with air- or moisture-sensitive compounds were performed by standard Schlenk techniques in oven-dried reaction vessels under nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Flash column chromatography was performed using 40-63μm silica gel (Si 60, Merck). ^{1}H, ^{13}C, and ^{19}F nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV-300 (300 MHz), AV-400 (400 MHz), AV-500 (500 MHz), or BBFO-400 (400 MHz) NMR spectrometers. ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm). ^{19}F NMR spectra are referenced to external standard (CF_3CO_2H, -76.55 ppm). Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 system equipped with an FID detector and a glass capillary column, DB-5 (Agilent J&W, 0.25 mm i.d. x 30 m, 0.25 μm film thickness). High-resolution mass spectra (HRMS) were obtained with a Q-Tof Premier LC HR mass spectrometer. Melting points were determined using a capillary melting point apparatus and are uncorrected.

Materials. Unless otherwise noted, commercial reagents were purchased from Sigma-Aldrich, Alfa Aesar, or other commercial suppliers and were used as received. $Co(acac)_3$ was purchased from Alfa Aesar and used as received. 1,3-Dicyclohexyl-1*H*-benzo[*d*]imidazol-3-ium chloride (**L3**•HCl) and 1,3-*di*-*tert*-butyl-1*H*-benzo[*d*]imidazol-3-ium chloride (**L6**•HCl) were purchased from Strem Chemicals, while other imidazolium and imidazolinium salts were synthesized according to the literature procedure.[1] THF was distilled over Na/benzophenone. Methylating agents except CD_3OTs (prepared using the method reported by Poulter[2]) were purchased from TCI, Sigma-Aldrich or Merck and used as received. Grignard reagents were prepared from the corresponding alkyl halides and magnesium turnings in anhydrous THF and titrated before use.

Preparation of Starting Materials

1. Preparation of *N*-PMP imines

All *N*–PMP (*p*-methoxyphenyl) imines **1a**–**1s** (Figure S1) were synthesized according to the literature procedures,[3] and purified by recrystallization or distillation. Spectral data for these known compounds (except **1i**) showed good agreement with the literature data.[4]

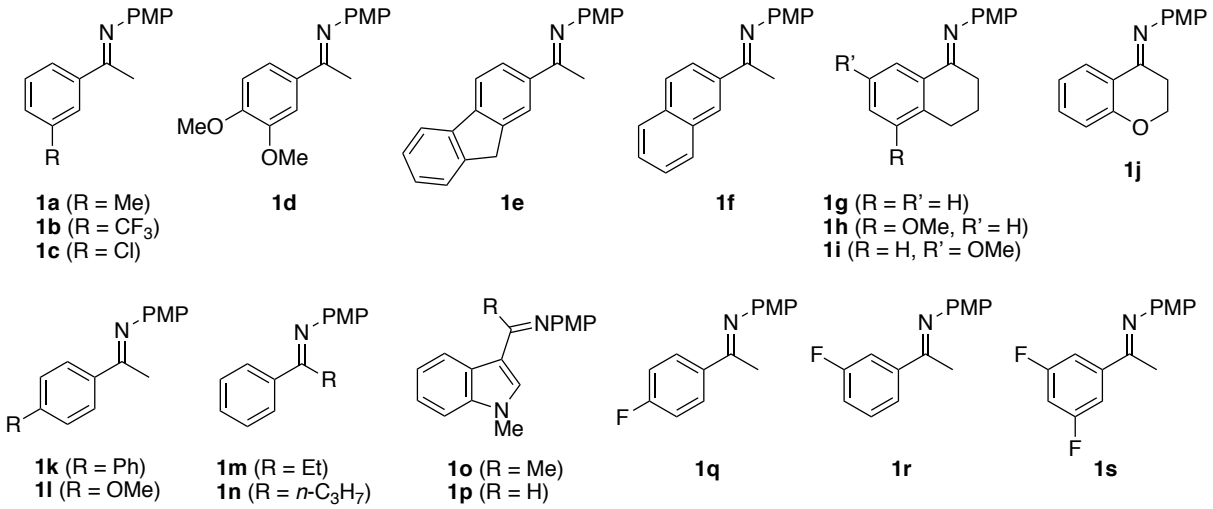
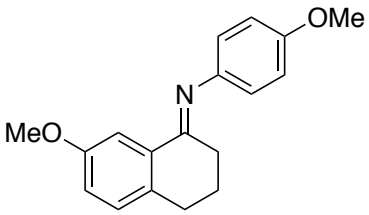


Figure S1. *N*-PMP imines used for this study.



(*E*)-7-Methoxy-*N*-(4-methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-imine (1i): Yellow solid; R_f 0.36 (hexane/EtOAc/Et_3N = 100/10/1); m.p. 81.8-84.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J* = 2.7 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.92-6.88 (m, 2H), 6.78-6.73 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 2.83 (t, *J* = 6.1 Hz, 2H), 2.53 (t, *J* = 6.4 Hz, 2H), 1.89 (quintet, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 158.2, 155.8, 144.7, 134.9, 133.8, 129.8, 120.8, 118.9, 114.3, 108.5, 55.5 (2C), 29.7, 29.2, 23.3; HRMS (ESI) Calcd for $C_{18}H_{20}NO_2$ $[M + H]^+$ 282.1494, found 282.1494.

2. Preparation of other substrates

2-Arylpyridine derivatives **3a**–**3k** except commercially available **3e** were prepared according to the literature procedure (Figure S2).[5] Spectral data for these compounds showed good agreement with the literature data.[6] N–H imine **3l** was synthesized from 3-methylbenzonitrile and *t*-BuMgCl according to the literature procedure,[7] and purified by distillation. Spectral data for **3l** showed good agreement with the literature data.[8]

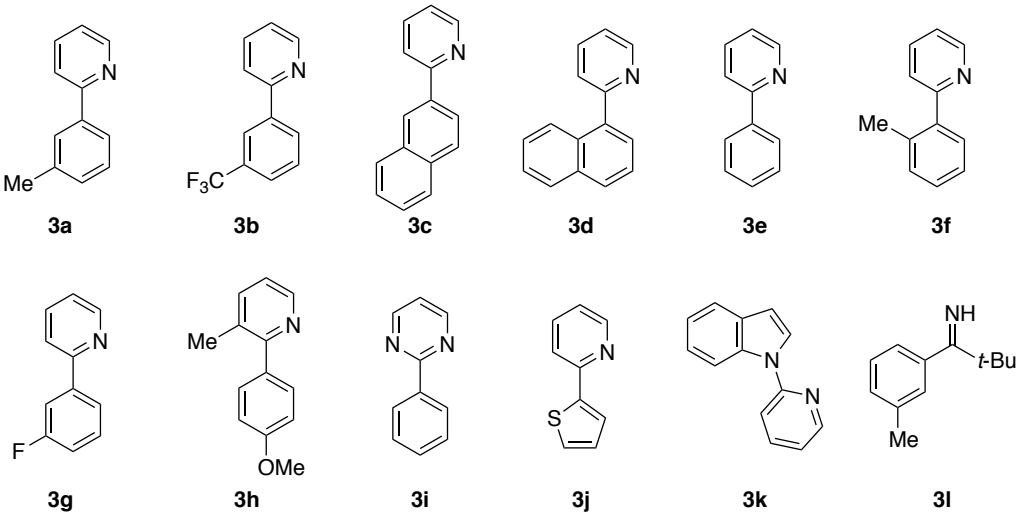
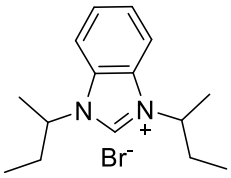


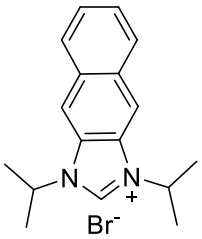
Figure S2. Other substrates used for this study.

Preparation of New *N*-Heterocyclic Carbene Precursors



1,3-Di-*sec*-butyl-1*H*-benzo[*d*]imidazol-3-ium bromide (L4•HBr; a 1:1 mixture of diastereomers): The synthesis was performed according to the procedure reported by Huynh and coworkers.[1b] A mixture of benzimidazole (2.00 g, 16.9 mmol) and K_2CO_3 (2.60 g, 18.8 mmol) was suspended in CH_3CN (10.0 mL) and stirred at ambient temperature for 1 h. To the suspension was added 2-bromobutane (5.54 mL, 50.8 mmol). The reaction mixture was stirred under reflux condition for 24 h followed by a second addition of 2-bromobutane (5.54 mL, 50.8 mmol). Stirring under reflux continued for an additional 72 h. After removing the volatiles in vacuo, CH_2Cl_2 (50 mL) was added to the residue and the resulting suspension was filtered over Celite. The filtrate was purified by silica gel chromatography (eluent: CH_2Cl_2/MeOH = 100/2 – 100/5) to afford a residue, which upon washing with ethyl acetate afforded the title compound as a white powder (3.40 g, 65%).

R_f 0.55 (CH_2Cl_2/MeOH = 3/1); m.p. 170.0-173.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.62 (s, 1H), 7.79-7.75 (m, 2H), 7.65-7.61 (m, 2H), 5.02-4.91 (m, 2H), 2.34-2.21 (m, 2H), 2.20-2.10 (m, 2H), 1.85 (d, J = 6.8 Hz, 6H), 0.92 (td, J = 7.3, 2.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.37, 141.34, 130.85, 130.84, 126.89 (two signals overlapped), 113.86, 113.84, 57.85, 57.82, 29.06, 29.00, 20.30, 20.27, 10.66, 10.59; HRMS (ESI) Calcd for $C_{15}H_{24}N_2Br$ $[M+ H]^+$ 311.1123, found 311.1127. The pairs of ^{13}C NMR signals with close chemical shifts and similar intensities indicated that the compound was obtained as a ca. 1:1 mixture of diastereomers.



1,3-Diisopropyl-1*H*-naphtho[2,3-*d*]imidazol-3-ium bromide (L7•HBr): The synthesis was

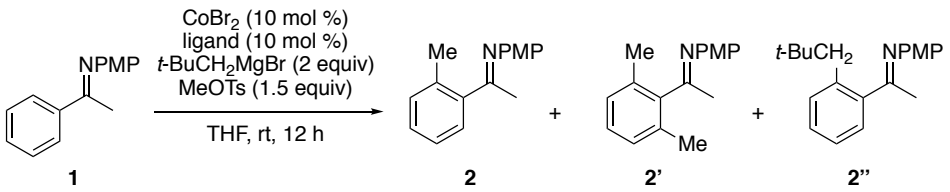
performed using 1*H*-naphtho[2,3-*d*]imidazole and 2-bromobutane (12.3 mmol scale) according to the procedure described above to afford the title compound as a white solid (3.80 g, 93%).

R$_f$ 0.48 (CH_2Cl_2/MeOH = 3/1); m.p. 235.7-236.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.67 (s, 1H), 8.22 (s, 2H), 8.10-8.06 (m, 2H), 7.67-7.63 (m, 2H), 5.30 (septet, *J* = 6.8 Hz, 2H), 1.94 (d, *J* = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 131.3, 129.7, 128.2, 127.1, 111.4, 52.4, 22.0; HRMS (ESI) Calcd for $C_{17}H_{22}N_2Br$ $[M+H]^+$ 333.0966, found 333.0964.

Cobalt-Catalyzed Directed Arene C–H Methylation with Methyl Tosylate

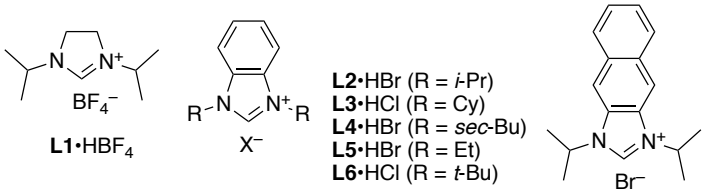
In the early stage of this study, we explored the methylation of acetophenone-derived imine **1** with methyl tosylate to identify *N*,*N*'-dialkylimidazoli(ni)um salts as effective ligands and $CoBr_2$ or $Co(acac)_3$ as suitable precatalyst (Table S1).

Table S1. Initial Results of Ligand and Precatalyst Screening[a]

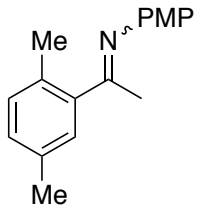


1 **2** **2'** **2"**

entry	ligand	yield (%)[b]		
		2	**2'**	**2"**
1	PPh_3	4	0	4
2	PCy_3	5	0	0
3	dppe	16	0	0
4	dppp	14	0	3
5	dppf	0	0	2
6	2,2'-bpy	6	0	3
7	1,10-phenanthroline	5	0	0
8	IMes•HCl	6	0	0
9	SIMes•HCl	6	0	0
10	IPr•HCl	7	0	0
11	SIPr•HCl	3	0	0
12	**L1**	12	1	12
13	**L2**	17	2	2
14	**L3**	44	2	4
15	**L4**	45	3	3
16	**L5**	24	3	3
17	**L6**	0	0	0
18	**L7**	48	3	3
19[c]	**L7**	34	4	1
20[d]	**L7**	21	3	2
21[e]	**L7**	37	4	2
22[f]	**L7**	45	5	0
23[g]	**L7**	28	4	0



[a]The reaction was performed on a 0.2 mmol scale (c = 0.2 M). [b]Determined by GC using *n*-tridecane as an internal standard. [c]$CoCl_2$ was used. [d]CoI_2 was used. [e]$Co(acac)_2$ was used. [f]$Co(acac)_3$ was used. [g]$Co(OAc)_2$ was used.

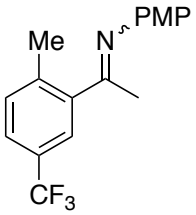


Typical Procedure: 1-(2,5-Dimethylphenyl)-*N*-(4-methoxyphenyl)ethan-1-imine (2a). In a 10 mL Schlenk tube were placed (*E*)-*N*-(4-methoxyphenyl)-1-(*m*-tolyl)ethan-1-imine (**1a**, 47.9 mg, 0.20 mmol), 1,3-*di*-*sec*-butyl-1*H*-benzo[*d*]imidazol-3-ium bromide (**L4**•HBr, 6.2 mg, 0.020 mmol), $Co(acac)_3$ (7.1 mg, 0.020 mmol), methyl tosylate (74.5 mg, 0.40 mmol, 2 equiv) and THF (0.55 mL). The resulting solution was cooled in an ice bath, followed by the addition of a THF solution of *t*-$BuCH_2MgBr$ (1.18 M, 0.45 mL, 0.53 mmol, 2.7 equiv). The resulting mixture was stirred at room temperature for 12 h, and then quenched by the addition of sat. NH_4Cl (1 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL), and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 100/2/1–100/10/1) to afford the title compound as a light yellow oil (41.1 mg, 81%), which existed as a mixture of imine *E*/*Z* isomers. The ratio of the isomers was determined to be 61:39 by ^1H NMR integrations of characteristic signals at 3.82 and 3.69 ppm.

Major isomer: R_f 0.21 (hexane/EtOAc/Et_3N = 100/10/1); ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (s, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.08 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.94-6.90 (m, 2H), 6.82-6.78 (m, 2H), 3.82 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 156.0, 144.4, 141.8, 135.2, 130.8, 130.1, 129.2, 127.7, 120.6, 114.3, 55.5, 29.4, 20.9, 19.6.

Minor isomer: R_f 0.34 (hexane/EtOAc/Et_3N = 100/10/1); ^1H NMR (400 MHz, $CDCl_3$): δ 6.95–6.88 (m, 3H), 6.64-6.59 (m, 4H), 3.69 (s, 3H), 2.43 (s, 3H), 2.28 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 155.9, 143.4, 139.3, 134.9, 131.6, 129.9, 128.8, 127.4, 122.4, 113.5, 55.2, 29.4, 21.1, 19.2.

HRMS (ESI) Calcd for $C_{17}H_{20}NO$ $[M + H]^+$ 254.1545, found 254.1548.

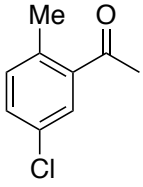


***N*-(4-Methoxyphenyl)-1-(2-methyl-5-(trifluoromethyl)phenyl)ethan-1-imine (2b):** The reaction was performed using 3 equiv of methyl tosylate and 4 equiv of *t*-BuCH_2MgBr. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 100/1/1–100/10/1) of the crude product afforded the title compound as a yellow oil (41.7 mg, 68%), which existed as a mixture of imine *E*/*Z* isomers. The ratio of the isomers was determined to be 67:33 by ^{1}H NMR integrations of characteristic signals at 3.83 and 3.69 ppm.

Major isomer: R_f 0.36 (hexane/EtOAc/Et_3N = 100/10/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.7 Hz, 1H), 6.93 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 3.83 (s, 3H), 2.53 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 156.3, 143.7, 142.3, 139.2, 131.4, 128.3 (q, $^2J_{C\text{-}F}$ = 32.4 Hz), 125.1 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 124.1 (q, $^1J_{C\text{-}F}$ = 270.2 Hz), 124.0 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 120.5, 114.4, 55.5, 21.0, 20.1; ^{19}F NMR (300 MHz, $CDCl_3$): δ -62.4.

Minor isomer: R_f 0.20 (hexane/EtOAc/Et_3N = 100/10/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.34 (m, 2H), 7.14 (d, J = 7.9 Hz, 1H), 6.63 (d, J = 8.8 Hz, 2H), 6.56 (d, J = 8.7 Hz, 2H), 3.69 (s, 3H), 2.46 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 156.2, 142.9, 139.9, 137.3, 130.8, 128.0 (q, $^2J_{C\text{-}F}$ = 32.4 Hz), 124.7 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 124.0 (two signals overlapping, q, $^1J_{C\text{-}F}$ = 270.1 Hz and q, $^3J_{C\text{-}F}$ = 3.5 Hz (partially overlapped)), 122.1, 113.7, 55.2, 29.1, 19.7; ^{19}F NMR (300 MHz, $CDCl_3$): δ –62.4.

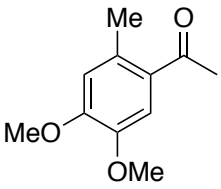
HRMS (ESI) Calcd for $C_{17}H_{17}NOF_3$ $[M + H]^+$ 308.1262, found 308.1259.



1-(5-Chloro-2-methylphenyl)ethan-1-one (2c): The reaction was performed according to the typical procedure, and then quenched by the addition of HCl (3 N, 1 mL). After stirring for 1

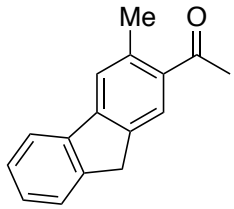
h, the resulting mixture was extracted with Et_2O (3 x 10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a colorless oil (18.8 mg, 56%).

R_f 0.48 (hexane/EtOAc = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, J = 2.2 Hz, 1H), 7.34 (dd, J = 8.2, 2.2 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 2.57 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.4, 139.0, 136.6, 133.3, 131.4, 131.3, 129.1, 29.5, 20.9; HRMS (ESI) Calcd for $C_9H_{10}OCl$ $[M + H]^+$ 169.0420, found 169.0420.



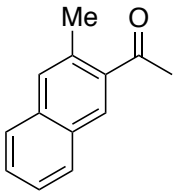
1-(4,5-Dimethoxy-2-methylphenyl)ethan-1-one (2d): [9] The reaction was performed according to the typical procedure, and the hydrolysis was performed as described for **2c**. Silica gel chromatography (eluent: hexane/EtOAc = 5/1) of the crude product afforded the title compound as a white solid (27.9 mg, 72%).

R_f 0.30 (hexane/EtOAc = 3/1); m.p. 75.0-78.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (s, 1H), 6.69 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.55 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.5, 151.6, 146.3, 133.5, 129.5, 114.6, 113.3, 56.2, 55.9, 29.4, 21.8; HRMS (ESI) Calcd for $C_{11}H_{15}O_3$ $[M + H]^+$ 195.1021, found 195.1025.



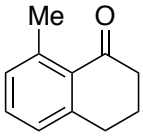
1-(3-Methyl-9*H*-fluoren-2-yl)ethan-1-one (2e): The reaction was performed according to the typical procedure, and the hydrolysis was performed as described for **2c**. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a white solid (33.0 mg, 74%).

R_f 0.29 (hexane/EtOAc = 10/1); m.p. 99.8-102.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.82 (d, J = 7.4 Hz, 1H), 7.64 (s, 1H), 7.58 (d, J = 7.4 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.36 (td, J = 7.4, 1.2 Hz, 1H), 3.92 (s, 2H), 2.65 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.3, 144.9, 144.6, 140.6, 140.3, 137.8, 135.9, 127.7, 127.0, 126.2, 125.2, 123.2, 120.6, 36.6, 29.6, 22.2; HRMS (ESI) Calcd for $C_{16}H_{15}O$ $[M + H]^+$ 223.1123, found 223.1118.



1-(3-Methylnaphthalen-2-yl)ethan-1-one (2f):[10] The reaction was performed according to the typical procedure, and the hydrolysis was performed as described for **2c**. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded a mixture of the title compound and its minor regioisomer (1-(1-methylnaphthalen-2-yl)ethan-1-one) as a light yellow solid (30.0 mg, 81%). The ratio of the regioisomers was determined to be 94:6 by ^{1}H NMR integrations of characteristic signals at 2.71 and 2.80 ppm.

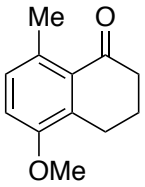
R_f 0.39 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.65 (s, 1H), 7.57-7.53 (m, 1H), 7.50-7.46 (m, 1H), 2.71 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.4, 136.3, 134.8, 134.6, 131.0, 130.6, 130.0, 128.5, 128.2, 126.9, 125.9, 29.4, 21.8; HRMS (ESI) Calcd for $C_{13}H_{13}O$ $[M + H]^+$ 185.0966, found 185.0964.



8-Methyl-3,4-dihydronaphthalen-1(2*H*)-one (2g):[11] The reaction was performed using 1.5 equiv of methyl tosylate and 2 equiv of *t*-BuCH_2MgBr, and the hydrolysis was performed as described for **2c**. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a colorless oil (21.6 mg, 67%).

R_f 0.39 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (t, J = 7.6 Hz, 1H), 7.11-7.08 (m, 2H), 2.95 (t, J = 6.1 Hz, 2H), 2.65 (t, J = 6.6 Hz, 2H), 2.64 (s, 3H), 2.08

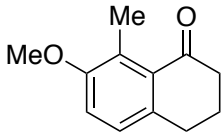
(quintet, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 145.7, 141.5, 132.2, 131.2, 130.4, 126.7, 41.0, 31.0, 23.3, 23.0; HRMS (ESI) Calcd for $C_{11}H_{13}O$ $[M + H]^+$ 161.0966, found 161.0961.



5-Methoxy-8-methyl-3,4-dihydronaphthalen-1(2*H*)-one (2h):[11] The reaction was performed according to the typical procedure, and the hydrolysis was performed as described for **2c**. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a colorless oil (31.4 mg, 83%).

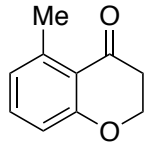
R_f 0.37 (hexane/EtOAc = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (d, J = 8.2 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H), 2.89 (t, J = 6.2 Hz, 2H), 2.62 (t, J = 6.7 Hz, 2H), 2.56 (s, 3H), 2.07 (quintet, J = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 154.8, 134.2, 132.3, 131.8, 130.0, 113.7, 55.7, 40.8, 23.6, 22.5, 22.4; HRMS (ESI) Calcd for $C_{12}H_{15}O_2$ $[M + H]^+$ 191.1072, found 191.1068.

Preparative scale synthesis of 2h: In a 100 mL Schlenk tube equipped with a stir bar were placed (*E*)-5-methoxy-*N*-(4-methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-imine (**1h**, 1.41 g, 5.0 mmol), 1,3-di-*sec*-butyl-1*H*-benzo[*d*]imidazol-3-ium bromide (**L4**•HBr, 156 mg, 0.50 mmol), $Co(acac)_3$ (178 mg, 0.50 mmol), methyl tosylate (1.86 g, 10.0 mmol, 2 equiv) and THF (17.1 mL). The resulting solution was cooled in an ice bath, followed by the addition of a THF solution of *t*-$BuCH_2MgBr$ (1.7 M, 7.9 mL, 13.5 mmol, 2.7 equiv). The resulting mixture was stirred at room temperature for 12 h, and then quenched by the addition of HCl (3 N, 25.0 mL). After stirring for 1 h, the resulting mixture was extracted with Et_2O (4 x 25 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded **2h** as a light yellow oil (0.80 g, 84%).



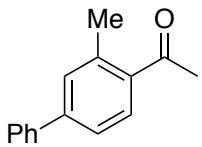
7-Methoxy-8-methyl-3,4-dihydronaphthalen-1(2*H*)-one (2i): [12] The reaction was performed according to the typical procedure, and the hydrolysis was performed as described for **2c**. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a white solid (20.8 mg, 55%).

R_f 0.32 (hexane/EtOAc = 10/1); m.p. 43.9-46.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 3.83 (s, 3H), 2.88 (t, J = 6.1 Hz, 2H), 2.63 (t, J = 6.6 Hz, 2H), 2.52 (s, 3H), 2.05 (quintet, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 156.6, 137.3, 132.4, 129.7, 126.4, 115.0, 56.1, 41.1, 30.4, 23.2, 13.2; HRMS (ESI) Calcd for $C_{12}H_{15}O_2$ $[M + H]^+$ 191.1072, found 191.1068.



5-Methylchroman-4-one (2j): The reaction was performed according to the typical procedure, and the hydrolysis was performed as described for **2c**. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil (20.0 mg, 62%).

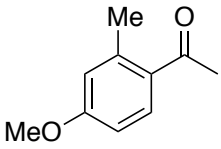
R_f 0.27 (hexane/EtOAc = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (t, J = 7.9 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 4.48 (t, J = 6.4 Hz, 2H), 2.80 (t, J = 6.4 Hz, 2H), 2.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.3, 162.9, 142.2, 134.5, 124.6, 119.9, 115.8, 66.4, 39.3, 22.9; HRMS (ESI) Calcd for $C_{10}H_{11}O_2$ $[M + H]^+$ 163.0759, found 163.0756.



1-(3-Methyl-[1,1'-biphenyl]-4-yl)ethan-1-one (2k): The reaction was performed using 1.5 equiv of methyl tosylate and 2 equiv of *t*-BuCH_2MgBr, and the hydrolysis was performed as

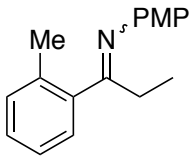
described for **2c**. Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a white solid (20.6 mg, 49%).

R_f 0.34 (hexane/EtOAc = 10/1); m.p. 60.2-63.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 7.8 Hz, 1H), 7.63-7.60 (m, 2H), 7.50-7.44 (m, 4H), 7.41-7.37 (m, 1H), 2.62 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 144.2, 140.0, 139.3, 136.1, 130.8, 130.3, 128.9, 128.0, 127.2, 124.3, 29.5, 22.0; HRMS (ESI) Calcd for $C_{15}H_{15}O$ $[M + H]^+$ 211.1123, found 211.1119.



1-(4-Methoxy-2-methylphenyl)ethan-1-one (2l):[13] The reaction was performed using 1.5 equiv of methyl tosylate and 2 equiv of *t*-BuCH_2MgBr, and the hydrolysis was performed as described for **2c**. Silica gel chromatography (eluent: hexane/EtOAc = 20/1) of the crude product afforded the title compound as a colorless oil (13.8 mg, 42%).

R_f 0.27 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.7 Hz, 1H), 6.77-6.74 (m, 2H), 3.85 (s, 3H), 2.57 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.5, 161.9, 142.2, 132.5, 130.0, 117.5, 110.6, 55.3, 29.1, 22.6; HRMS (ESI) Calcd for $C_{10}H_{13}O_2$ $[M + H]^+$ 165.0916, found 165.0920.



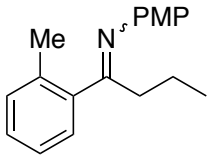
***N*-(4-methoxyphenyl)-1-(*o*-tolyl)propan-1-imine (2m):** The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 100/1/1) of the crude product afforded the title compound as a light yellow oil (33.6 mg, 66%), which existed as a mixture of imine *E*/*Z* isomers. The ratio of the isomers was determined to be 75:25 by ^{1}H NMR integrations of characteristic signals at 3.68 and 3.82 ppm.

Major isomer: R_f 0.19 (hexane/EtOAc/Et_3N = 100/10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15–7.09 (m, 2H), 7.05-7.00 (m, 2H), 6.63-6.58 (m, 4H), 3.68 (s, 3H), 2.70 (q, J = 7.3 Hz,

2H), 2.02 (s, 3H), 1.21 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 155.8, 143.6, 138.9, 133.5, 130.1, 127.8, 127.4, 125.2, 122.2, 113.4, 55.2, 35.3, 19.8, 10.4.

Minor isomer: R_f 0.26 (hexane/EtOAc/Et_3N = 100/10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.21 (m, 4H), 6.93-6.89 (m, 2H), 6.81-6.77 (m, 2H), 3.82 (s, 3H), 2.57 (q, J = 7.6 Hz, 2H), 2.46 (s, 3H), 0.94 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 155.9, 144.2, 140.2, 135.3, 130.8, 128.3, 127.1, 125.6, 120.4, 114.3, 55.5, 35.3, 26.9, 11.3.

HRMS (ESI) Calcd for $C_{17}H_{20}NO$ $[M + H]^+$ 254.1545, found 254.1549.



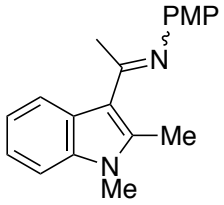
***N*-(4-methoxyphenyl)-1-(*o*-tolyl)butan-1-imine (2n):** The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 100/1/1) of the crude product afforded the title compound as a light yellow oil (34.5 mg, 65%), which existed as a mixture of *E*/*Z* isomers. The ratio of the isomers was determined to be 71:29 by ^{1}H NMR integrations of characteristic signals at 3.68 and 3.82 ppm.

R_f 0.29 (hexane/EtOAc/Et_3N = 100/10/1).

Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.08 (m, 2H), 7.05-7.00 (m, 2H), 6.63-6.57 (m, 4H), 3.68 (s, 3H), 2.65 (t, J = 7.7 Hz, 2H), 2.02 (s, 3H), 1.71-1.66 (m, 2H), 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 155.8, 143.6, 138.9, 133.5, 130.1, 127.8, 127.4, 125.2, 122.2, 113.4, 55.2, 44.3, 20.2, 19.4, 14.0.

Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.30 (m, 1H), 7.28-7.21 (m, 3H), 6.93-6.89 (m, 2H), 6.80-6.76 (m, 2H), 3.82 (s, 3H), 2.55-2.51 (m, 2H), 2.47 (s, 3H), 1.42-1.33 (m, 2H), 0.79 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 155.9, 144.2, 140.4, 135.2, 130.9, 128.3, 127.1, 125.5, 120.3, 114.2, 55.4, 35.6, 19.9, 19.8, 14.2.

HRMS (ESI) Calcd for $C_{18}H_{22}NO$ $[M + H]^+$ 268.1701, found 268.1703.



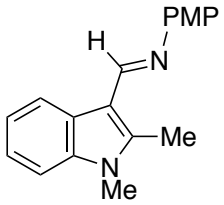
1-(1,2-Dimethyl-1*H*-indol-3-yl)-*N*-(4-methoxyphenyl)ethan-1-imine (2o): The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 90/30/1) of the crude product afforded the title compound as a brown solid (33.6 mg, 57%), which existed as a mixture of *E*/*Z* isomers. The ratio of the isomers was determined to be 87:13 by ^{1}H NMR integrations of characteristic signals at 2.74 and 2.59 ppm.

R_f 0.24 (hexane/EtOAc = 3/1).

Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.24-7.13 (m, 2H), 6.94-6.90 (m, 2H), 6.83-6.80 (m, 2H), 3.83 (s, 3H), 3.72 (s, 3H), 2.74 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 155.5, 145.3, 138.4, 136.6, 126.5, 122.4, 121.3, 121.0, 120.4 (two signals overlapping), 114.3, 109.0, 55.5, 29.5, 21.3, 12.3.

Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.7 Hz, 1H), 7.24-7.13 (m, 3H), 6.69-6.66 (m, 2H), 6.63-6.60 (m, 2H), 3.69 (s, 3H), 3.52 (s, 3H), 2.59 (s, 3H), 1.86 (s, 3H).

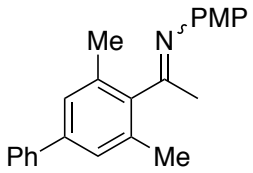
HRMS (ESI) Calcd for $C_{19}H_{21}N_2O$ $[M + H]^+$ 293.1654, found 293.1661.



(*E*)-1-(1,2-dimethyl-1*H*-indol-3-yl)-*N*-(4-methoxyphenyl)methanimine (2p): The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 90/30/1) of the crude product afforded the title compound as a mixture with minor amount of anisidine as a light yellow solid (33.2 mg). The yield was determined to be 59% based on the total weight and the ^{1}H NMR analysis of the mixture.

R_f 0.33 (hexane/EtOAc = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.51-8.47 (m, 1H), 7.32-7.24 (m, 3H), 7.23-7.20 (m, 2H), 6.95-6.92 (m, 2H), 3.84 (s, 3H), 3.72 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 152.8, 147.4, 142.1, 137.2, 125.9, 122.3, 121.8,

121.6, 121.4, 114.3, 111.4, 108.7, 55.5, 29.6, 10.7; HRMS (ESI) Calcd for $C_{18}H_{19}N_2O$ [M + H]$^+$ 279.1497, found 279.1495.

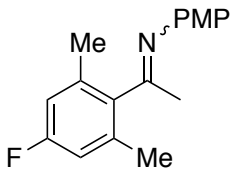


1-(3,5-Dimethyl-[1,1'-biphenyl]-4-yl)-*N*-(4-methoxyphenyl)ethan-1-imine (2k'): The reaction was performed using 4 equiv of methyl tosylate and 5.3 equiv of *t*-BuCH_2MgBr. After treatment with 3 N HCl (1.0 mL) for 1 h, the reaction mixture was neutralized with 3 N NaOH (2.0 mL) and then extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 100/2/1 – 100/5/1) to afford the title compound as a light yellow oil (33.0 mg, 50%), which existed as a mixture of *E*/*Z* isomers. The ratio of the isomers was determined to be 61:39 by ^{1}H NMR integrations of characteristic signals at 3.69 and 3.84 ppm.

Major isomer: R_f 0.26 (hexane/EtOAc/Et_3N = 100/10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.31 (m, 5H), 7.17 (s, 2H), 6.71-6.68 (m, 2H), 6.66-6.63 (m, 2H), 3.69 (s, 3H), 2.42 (s, 3H), 2.24 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 156.3, 143.0, 141.1, 140.5, 140.4, 133.6, 128.7, 127.3, 126.9, 126.2, 121.8, 113.5, 55.2, 28.6, 20.1.

Minor isomer: R_f 0.19 (hexane/EtOAc/Et_3N = 100/10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.53 (m, 5H), 7.30 (s, 2H), 6.96-6.93 (m, 2H), 6.87-6.83 (m, 2H), 3.84 (s, 3H), 2.42 (s, 6H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 156.2, 144.0, 140.9, 140.6, 138.4, 134.0, 128.7, 127.2, 127.1, 126.7, 120.7, 114.4, 55.5, 21.3, 19.3.

HRMS (ESI) Calcd for $C_{23}H_{24}NO$ [M + H]$^+$ 330.1858, found 330.1859.



1-(4-Fluoro-2,6-dimethylphenyl)-*N*-(4-methoxyphenyl)ethan-1-imine (2q): The reaction

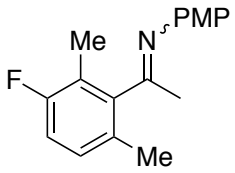
was performed using 3 equiv of methyl tosylate and 4 equiv of *t*-$BuCH_2MgBr$. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 100/1/1 – 100/10/1) of the crude product afforded the title compound as a light yellow oil (46.3 mg, 85%), which existed as a mixture of *E*/*Z* isomers. The ratio of the isomers was determined to be 56:44 by ^1H NMR integrations of characteristic signals at 3.70 and 3.83 ppm.

R_f 0.17 (hexane/EtOAc/Et_3N = 100/10/1).

Major isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 6.66-6.60 (m, 6H), 3.70 (s, 3H), 2.37 (s, 3H), 2.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 161.9 (d, $^1J_{C\text{-}F}$ = 244.0 Hz), 156.3, 142.9, 135.6 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 135.1 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 121.6, 114.3 (d, $^2J_{C\text{-}F}$ = 15.4 Hz), 113.5, 55.2, 28.6, 20.0 (d, $^4J_{C\text{-}F}$ = 1.2 Hz); ^{19}F NMR (400 MHz, $CDCl_3$): δ - 115.5.

Minor isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 6.95-6.91 (m, 2H), 6.83-6.80 (m, 2H), 6.77 (d, *J* = 9.5 Hz, 2H), 3.83 (s, 3H), 2.34 (s, 6H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 161.8 (d, $^1J_{C\text{-}F}$ = 243.5 Hz), 156.2, 143.8, 137.9 (d, $^4J_{C\text{-}F}$ = 2.7 Hz), 136.1 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 120.6, 114.4, 114.1 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 55.5, 21.4, 19.2 (d, $^4J_{C\text{-}F}$ = 1.3 Hz); ^{19}F NMR (400 MHz, $CDCl_3$): δ - 115.7.

HRMS (ESI) Calcd for $C_{17}H_{19}NOF$ $[M + H]^+$ 272.1451, found 272.1454.



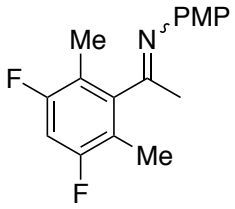
1-(3-Fluoro-2,6-dimethylphenyl)-*N*-(4-methoxyphenyl)ethan-1-imine (2r): The reaction was performed using 4 equiv of methyl tosylate and 5.3 equiv of *t*-$BuCH_2MgBr$, and worked up as described for **2k'**. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 100/2/1 – 100/10/1) to afford the title compound as a light yellow oil (36.6 mg, 67%), which existed as a mixture of *E*/*Z* isomers. The ratio of the isomers was determined to be 60:40 by ^1H NMR integrations of characteristic signals at 3.70 and 3.83 ppm.

Major isomer: R_f 0.17 (hexane/EtOAc/Et_3N = 100/10/1); ^1H NMR (400 MHz, $CDCl_3$): δ 6.95-6.91 (m, 2H), 6.66-6.61 (m, 4H), 3.70 (s, 3H), 2.37 (s, 3H), 2.12 (s, 3H), 2.09 (d, *J* = 1.5

Hz, 3H, partially overlapped); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4 (d, $^4J_{C\text{-}F}$ = 1.8 Hz), 159.5 (d, $^1J_{C\text{-}F}$ = 241.8 Hz), 156.3, 142.8, 141.1 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 128.5 (two signals overlapping, d, $^3J_{C\text{-}F}$ = 8.0 Hz and d, $^3J_{C\text{-}F}$ = 3.6 Hz (partially overlapped)), 121.5, 120.4 (d, $^2J_{C\text{-}F}$ = 17.4 Hz), 114.2 (d, $^2J_{C\text{-}F}$ = 22.5 Hz), 113.6, 55.2, 28.4, 19.3, 12.3 (d, $^3J_{C\text{-}F}$ = 4.4 Hz); ^{19}F NMR (75 MHz, $CDCl_3$): δ - 119.7.

Minor isomer: R_f 0.25 (hexane/EtOAc/Et_3N = 100/10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (dd, *J* = 8.3, 5.4 Hz, 1H), 6.89-6.77 (m, 5H), 3.83 (s, 3H), 2.31 (s, 3H), 2.26 (d, *J* = 2.1 Hz, 3H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (d, $^4J_{C\text{-}F}$ = 2.7 Hz), 159.7 (d, $^1J_{C\text{-}F}$ = 241.2 Hz), 156.3, 143.6, 143.4 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 128.9 (d, $^3J_{C\text{-}F}$ = 3.7 Hz), 128.7 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 120.8 (d, $^2J_{C\text{-}F}$ = 16.6 Hz, partially overlapped), 120.7, 114.4, 114.1 (d, $^2J_{C\text{-}F}$ = 22.4 Hz), 55.5, 21.3, 18.6, 11.1 (d, $^3J_{C\text{-}F}$ = 4.8 Hz); ^{19}F NMR (75 MHz, $CDCl_3$): δ -120.5;

HRMS (ESI) Calcd for $C_{17}H_{19}NOF$ $[M + H]^+$ 272.1451, found 272.1459.



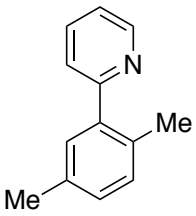
1-(3,5-Difluoro-2,6-dimethylphenyl)-*N*-(4-methoxyphenyl)ethan-1-imine (2s): The reaction was performed using 2.5 equiv of methyl tosylate and 3.3 equiv of *t*-BuCH_2MgBr. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 100/1/1) of the crude product afforded the title compound as a light yellow oil (42.9 mg, 74%), which existed as a mixture of *E*/*Z* isomers. The ratio of the isomers was determined to be 57:43 by ^{1}H NMR integrations of characteristic signals at 3.71 and 3.83 ppm.

Major isomer: R_f 0.27 (hexane/EtOAc/Et_3N = 100/10/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68-6.59 (m, 5H), 3.71 (s, 3H), 2.36 (s, 3H), 2.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1 (t, $^4J_{C\text{-}F}$ = 2.3 Hz), 159.1 (dd, $^1J_{C\text{-}F}$ = 244.5 Hz, $^3J_{C\text{-}F}$ = 12.8 Hz), 156.5, 142.7, 142.4 (t, $^3J_{C\text{-}F}$ = 4.9 Hz), 121.3, 116.1 (dd, $^2J_{C\text{-}F}$ = 13.5 Hz, $^4J_{C\text{-}F}$ = 7.5 Hz), 113.7, 102.5 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 55.2, 28.3, 11.9 (dd, *J* values were small and could not be clearly determined); ^{19}F NMR (300 MHz, $CDCl_3$): δ - 115.1.

Minor isomer: R_f 0.42 (hexane/EtOAc/Et_3N = 100/10/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ

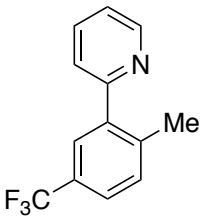
6.97-6.91 (m, 2H), 6.85-6.80 (m, 2H), 6.76 (t, J = 9.6 Hz, 1H), 3.83 (s, 3H), 2.21 (s, 6H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2 (t, $^4J_{C\text{-}F}$ = 3.4 Hz), 159.2 (dd, $^1J_{C\text{-}F}$ = 243.8 Hz, $^3J_{C\text{-}F}$ = 12.8 Hz), 156.5, 144.4 (t, $^3J_{C\text{-}F}$ = 5.3 Hz), 143.2, 120.7, 116.6 (dd, $^2J_{C\text{-}F}$ = 13.1 Hz, $^4J_{C\text{-}F}$ = 7.9 Hz), 114.4, 102.4 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 55.5, 21.3, 10.8 (dd, $^3J_{C\text{-}F}$ = 1.9 Hz, $^5J_{C\text{-}F}$ = 1.1 Hz); ^{19}F NMR (300 MHz, $CDCl_3$): δ -116.2.

HRMS (ESI) Calcd for $C_{17}H_{18}NOF_2$ $[M + H]^+$ 290.1356, found 290.1350.



2-(2,5-Dimethylphenyl)pyridine (4a):[14] The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a colorless oil (28.6 mg, 78%).

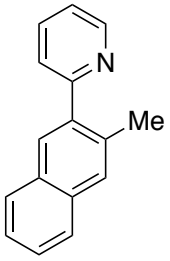
R_f 0.17 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (ddd, J = 4.8, 1.7, 1.0 Hz), 7.73 (td, J = 7.7, 1.8 Hz, 1H), 7.40 (dt, J = 7.8, 1.0 Hz), 7.25-7.22 (m, 2H), 7.17 (d, J = 7.8 Hz, 1H), 7.11 (dd, J = 7.8, 1.3 Hz, 1H), 2.36 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 149.2, 140.2, 135.9, 135.3, 132.4, 130.6, 130.2, 128.9, 124.1, 121.5, 20.9, 19.7; HRMS (ESI) Calcd for $C_{13}H_{14}N$ $[M + H]^+$ 184.1126, found 184.1125.



2-(2-Methyl-5-(trifluoromethyl)phenyl)pyridine (4b): [15] The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a colorless oil (15.6 mg, 33%).

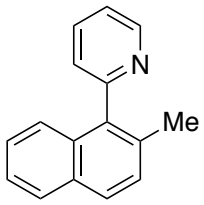
R_f 0.23 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (ddd, J = 4.8, 1.7, 1.0 Hz, 1H), 7.79 (td, J = 7.7, 1.8 Hz, 1H), 7.66 (s, 1H), 7.55 (dd, J = 8.0, 1.5 Hz, 1H), 7.43-7.39 (m, 2H), 7.30 (ddd, J = 7.6, 4.9, 1.1 Hz), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6,

149.5, 140.9, 140.1, 136.4, 131.2, 128.4 (q, $^{2}J_{C\text{-}F}$= 32.4 Hz), 126.5 (q, $^{3}J_{C\text{-}F}$ = 3.7 Hz), 124.9 (q, $^{3}J_{C\text{-}F}$ = 3.7 Hz), 124.2 (q, $^{1}J_{C\text{-}F}$ = 270.3 Hz), 124.0, 122.2, 20.3; ^{19}F NMR (400 MHz, $CDCl_3$): δ −62.3; HRMS (ESI) Calcd for $C_{13}H_{11}NF_3$ $[M + H]^+$ 238.0844, found 238.0847.



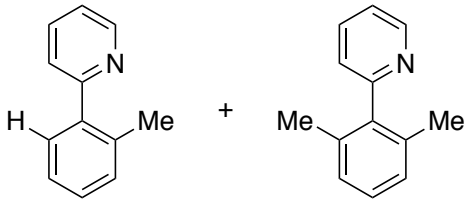
2-(3-Methylnaphthalen-2-yl)pyridine (4c):[16] The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a white solid (28.2 mg, 64%).

R_f 0.21 (hexane/EtOAc = 10/1); m.p. 69.0-71.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74 (ddd, J = 4.9, 1.5, 0.9 Hz), 7.87 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.80-7.77 (m, 2H), 7.74 (s, 1H), 7.51-7.42 (m, 3H), 7.29 (ddd, J = 7.5, 4.9, 1.0 Hz), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 149.2, 139.4, 136.2, 133.8, 133.4, 131.9, 128.8, 128.7, 127.9, 126.9, 126.3, 125.4, 124.2, 121.7, 20.8; HRMS (ESI) Calcd for $C_{16}H_{14}N$ $[M + H]^+$ 220.1126, found 220.1121.



2-(2-Methylnaphthalen-1-yl)pyridine (4d):[17] The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a light yellow solid (27.3 mg, 62%).

Rf 0.42 (hexane/EtOAc = 3/1); m.p. 81.5-84.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (d, J = 4.7 Hz, 1H), 7.87-7.80 (m, 3H), 7.43-7.28 (m, 6H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 149.8, 136.7, 136.2, 133.4, 132.4, 132.0, 128.7, 128.1, 127.8, 126.1, 125.6, 125.3, 124.8, 121.9, 20.2; HRMS (ESI) Calcd for $C_{16}H_{14}N$ $[M + H]^+$ 220.1126, found 220.1126.

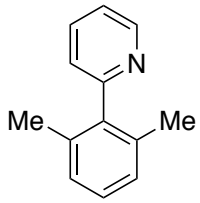


4e **4f**

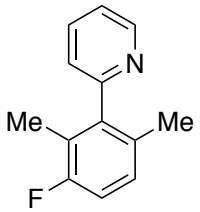
2-(*o*-Tolyl)pyridine (4e)[6e] **and 2-(2,6-dimethylphenyl)pyridine (4f):**[18] The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc = 15/1) of the crude product afforded the title compounds **4e** (12.4 mg, 37%) and **4f** (12.2 mg, 33%) as colorless oils.

4e: R_f 0.49 (hexane/EtOAc = 3/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.70 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.74 (td, J = 7.7, 1.8 Hz, 1H), 7.41-7.38 (m, 2H), 7.31-7.22 (m, 4H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 149.2, 140.4, 136.1, 135.7, 130.7, 129.6, 128.2, 125.8, 124.1, 121.6, 20.2; HRMS (ESI) Calcd for $C_{12}H_{12}N$ $[M + H]^+$ 170.0970, found 170.0965.

4f: R_f 0.46 (hexane/EtOAc = 3/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72 (d, J = 4.6 Hz, 1H), 7.76 (td, J = 7.6, 1.2 Hz, 1H), 7.28-7.17 (m, 3H), 7.10 (d, J = 7.4 Hz, 2H), 2.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 149.7, 140.5, 136.2, 135.7, 127.8, 127.5, 124.4, 121.6, 20.1; HRMS (ESI) Calcd for $C_{13}H_{14}N$ $[M + H]^+$ 184.1126, found 184.1134.



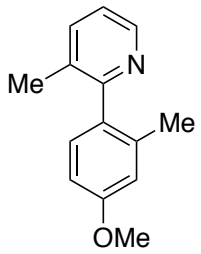
2-(2,6-Dimethylphenyl)pyridine (4f): The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound (22.0 mg, 60%) as a colorless oil.



2-(3-Fluoro-2,6-dimethylphenyl)pyridine (4g): The reaction was performed according to

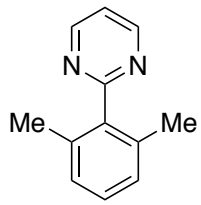
the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc = 15/1) of the crude product afforded the title compound as a colorless oil (23.0 mg, 57%).

R_f 0.19 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (ddd, J =4.9, 1.6, 0.9 Hz, 1H), 7.78 (td, J = 7.7, 1.8 Hz, 1H), 7.28 (ddd, J = 7.6, 5.0, 1.1 Hz, 1H), 7.21 (dt, J = 7.8, 1.0 Hz, 1H), 7.05 (dd, J = 8.3, 5.6 Hz, 1H), 6.96 (t, J = 8.9 Hz, 1H), 2.00 (s, 3H), 1.95 (d, J = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7 (d, $^1J_{C\text{-}F}$ = 240.4 Hz), 158.8 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 149.8, 142.1 (d, $^3J_{C\text{-}F}$ = 4.3 Hz), 136.4, 131.2 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 128.2 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 124.4, 123.0 (d, $^2J_{C\text{-}F}$ = 16.8 Hz), 122.0, 114.3 (d, $^2J_{C\text{-}F}$ = 22.7 Hz), 19.6, 11.9 (d, $^3J_{C\text{-}F}$ = 4.6 Hz); ^{19}F NMR (300 MHz, $CDCl_3$): δ -120.5; HRMS (ESI) Calcd for $C_{13}H_{13}NF$ $[M + H]^+$ 202.1032, found 202.1028.



2-(4-Methoxy-2-methylphenyl)-3-methylpyridine (4h): The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc = 5/1) of the crude product afforded the title compound as a light yellow oil (25.6 mg, 60%).

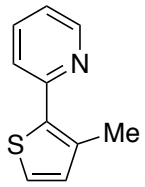
R_f 0.29 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50-8.48 (m, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.17 (dd, J = 7.6, 4.8 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 8.82-6.78 (m, 2H), 3.83 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 159.1, 146.6, 137.6, 137.1, 133.0, 131.8, 129.6, 122.0, 115.5, 111.0, 55.2, 19.6, 19.1; HRMS (ESI) Calcd for $C_{14}H_{16}NO$ $[M + H]^+$ 214.1232, found 214.1229.



2-(2,6-Dimethylphenyl)pyrimidine (4i):[14] The reaction was performed using 4 equiv of methyl tosylate and 5.3 equiv of *t*-$BuCH_2MgBr$. Silica gel chromatography (eluent:

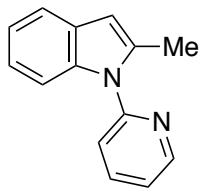
hexane/EtOAc = 5/1) of the crude product afforded the title compound as a light yellow oil (27.7 mg, 75%).

R_f 0.29 (hexane/EtOAc = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.88 (d, J = 4.9 Hz, 2H), 7.27 (t, J = 5.0 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 2H), 2.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 157.1, 139.0, 135.3, 128.4, 127.6, 118.8, 19.8; HRMS (ESI) Calcd for $C_{12}H_{13}N_2$ $[M + H]^+$ 185.1079, found 185.1083.



2-(3-Methylthiophen-2-yl)pyridine (4j): The reaction was performed using 4 equiv of methyl tosylate and 5.3 equiv of *t*-$BuCH_2MgBr$. Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light yellow oil (10.5 mg, 30%).

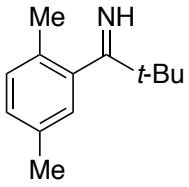
R_f 0.32 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J = 4.5 Hz, 1H), 7.71 (td, J = 7.8, 1.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 5.0 Hz, 1H), 7.15 (dd, J = 6.9, 5.1 Hz, 1H), 6.93 (d, J = 5.0 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 149.6, 138.1, 136.4, 135.3, 132.1, 125.6, 121.3, 121.2, 16.1; HRMS (ESI) Calcd for $C_{10}H_{10}NS$ $[M + H]^+$ 176.0534, found 176.0537.



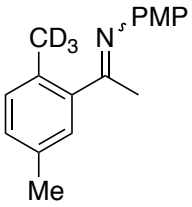
2-Methyl-1-(pyridin-2-yl)-1*H*-indole (4k):[14] The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc = 20/1) of the crude product afforded the title compound as a colorless oil (28.3 mg, 68%).

R_f 0.28 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (ddd, J = 4.9, 1.9, 0.7 Hz, 1H), 7.89 (td, J = 7.7, 1.9 Hz, 1H), 7.57-7.53 (m, 1H), 7.43 (dt, J = 8.0, 0.8 Hz, 1H), 7.39-7.35 (m, 1H), 7.32 (ddd, J = 7.5, 4.9, 1.0 Hz, 1H), 7.15-7.10 (m, 2H), 6.42 (t, J = 1.0 Hz,

1H), 2.47 (d, J = 0.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 149.5, 138.2, 137.1, 136.8, 128.7, 121.8, 121.5, 120.8, 120.6, 119.7, 110.2, 103.3, 14.0; HRMS (ESI) Calcd for $C_{14}H_{13}N_2$ $[M + H]^+$ 209.1079, found 209.1072.



1-(2,5-Dimethylphenyl)-2,2-dimethylpropan-1-imine (4l): The reaction was performed according to the typical procedure. Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 100/10/1) of the crude product afforded the title compound as a colorless oil (20.6 mg, 54%). R_f 0.17 (hexane/EtOAc/Et_3N = 100/10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.83 (s, 1H), 2.30 (s, 3H), 2.18 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 141.7, 134.3, 130.5, 130.4, 128.3, 126.5, 40.6, 28.5, 20.9, 19.6; HRMS (ESI) Calcd for $C_{13}H_{20}N$ $[M + H]^+$ 190.1596, found 190.1591.



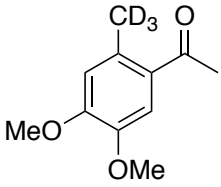
***N*-(4-Methoxyphenyl)-1-(5-methyl-2-(methyl-*d*$_3$)phenyl)ethan-1-imine (2a-*d*$_3$):** The reaction was performed as described for **2a** using CD_3OTs (75.7 mg, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 100/2/1 – 100/5/1) of the crude product afforded the title compound as a light yellow oil (41.3 mg, 81%), which existed as a mixture of *E*/*Z* isomers. The ratio of the isomers was determined to be 61:39 by ^{1}H NMR integrations of characteristic signals at 3.82 and 3.69 ppm.

Major isomer: R_f 0.17 (hexane/EtOAc/Et_3N = 100/10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (s, 1H), 7.12 (d, J = 7.7 Hz, 1H), 7.08 (dd, J = 7.7, 1.2 Hz, 1H), 6.94-6.90 (m, 2H), 6.82-6.78 (m, 2H), 3.82 (s, 3H), 2.35 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.2, 155.6, 144.2, 141.5, 134.6, 130.7, 129.9, 129.0, 127.8, 120.4, 114.4, 55.3, 29.1, 20.6, 18.5

(septet, J = 19.3 Hz).

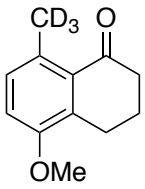
Minor isomer: R_f 0.30 (hexane/EtOAc/Et_3N = 100/10/1); ^{1}H NMR (400 MHz, $CDCl_3$: δ 6.95-6.88 (m, 3H), 6.64-6.59 (m, 4H), 3.69 (s, 3H), 2.43 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.4, 155.3, 143.5, 139.2, 134.5, 131.4, 129.2, 128.7, 127.5, 121.7, 113.6, 55.0, 29.1, 20.9, ~18.5 (not obvious due to overlap).

HRMS (ESI) Calcd for $C_{17}H_{17}D_3NO$ $[M + H]^+$ 257.1733, found 257.1733.



1-(4,5-Dimethoxy-2-(methyl-d_3)phenyl)ethan-1-one (2d-d_3): The reaction was performed as described for **2d** using CD_3OTs (75.7 mg, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 5/1) of the crude product afforded the title compound as a white solid (25.4 mg, 64%).

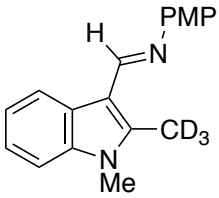
R_f 0.30 (hexane/EtOAc = 3/1); m.p. 73.0-75.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 6.70 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.5, 151.5, 146.2, 133.4, 129.4, 114.5, 113.2, 56.1, 55.8, 29.4, 21.0 (septet, J = 19.5 Hz); HRMS (ESI) Calcd for $C_{11}H_{12}D_3O_3$ $[M + H]^+$ 198.1209, found 198.1209.



5-Methoxy-8-(methyl-d_3)-3,4-dihydronaphthalen-1(2*H*)-one (2h-d_3): The reaction was performed as described for **2h** using CD_3OTs (75.7 mg, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil (31.1 mg, 81%).

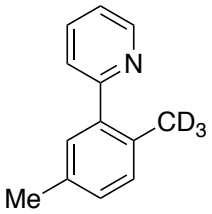
R_f 0.38 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H), 2.90 (t, J = 6.2 Hz, 2H), 2.62 (t, J = 6.6 Hz, 2H), 2.07 (quintet, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 154.8, 134.2, 132.2, 131.9,

130.0, 113.7, 55.7, 40.8, 23.5, 22.4, 21.7 (septet, J = 19.2 Hz, partially overlapped); HRMS (ESI) Calcd for $C_{12}H_{12}D_3O_2$ $[M + H]^+$ 194.1260, found 194.1256.



(*E*)-*N*-(4-methoxyphenyl)-1-(1-methyl-2-(methyl-d_3)-1*H*-indol-3-yl)methanimine (2p-d_3): The reaction was performed as described for **2p** using CD_3OTs (75.7 mg, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc/Et_3N = 90/30/1) of the crude product afforded the title compound as a mixture with minor amount of anisidine as a light yellow solid (30.6 mg). The yield was determined to be 53% based on the total weight and the ^{1}H NMR analysis of the mixture.

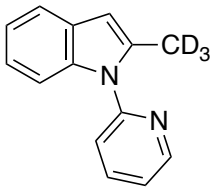
R_f 0.31 (hexane/EtOAc = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.51-8.48 (m, 1H), 7.31-7.24 (m, 3H), 7.23-7.20 (m, 2H), 6.95-6.92 (m, 2H), 3.84 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 152.9, 147.4, 142.0, 137.2, 125.9, 122.2, 121.8, 121.6, 121.4, 114.3, 111.4, 108.7, 55.5, 29.6, 9.9 (septet, J = 19.7 Hz); HRMS (ESI) Calcd for $C_{18}H_{16}D_3N_2O$ $[M + H]^+$ 282.1686, found 282.1682.



2-(5-Methyl-2-(methyl-d_3)phenyl)pyridine (4a-d_3): The reaction was performed as described for **4a** using CD_3OTs (75.7 mg, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a colorless oil (25.5 mg, 68%).

R_f 0.23 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.73 (td, J = 7.7, 1.8 Hz, 1H), 7.39 (dt, J = 7.8, 1.0 Hz, 1H), 7.25-7.22 (m, 2H), 7.17 (d, J = 7.7 Hz, 1H), 7.11 (dd, J = 7.8, 1.2 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

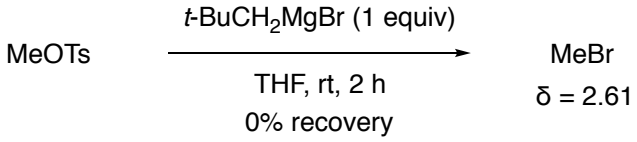
160.1, 149.2, 140.3, 135.9, 135.3, 132.3, 130.6, 130.2, 128.9, 124.1, 121.5, 20.9, 19.0 (septet, J = 19.3 Hz); HRMS (ESI) Calcd for $C_{13}H_{11}D_3N$ $[M + H]^+$ 187.1315, found 187.1312.



2-(Methyl-*d*$_3$)-1-(pyridin-2-yl)-1*H*-indole (4k-*d*$_3$): The reaction was performed as described for **4k** using CD_3OTs (75.7 mg, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1) of the crude product afforded the title compound as a colorless oil (27.2 mg, 64%).

R_f 0.23 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (dd, J = 4.8, 1.5 Hz, 1H), 7.89 (td, J = 7.7, 1.9 Hz, 1H), 7.57-7.53 (m, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.40-7.36 (m, 1H), 7.31 (dd, J = 7.4, 4.9 Hz, 1H), 7.14-7.10 (m, 2H), 6.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 149.5, 138.1, 137.1, 136.7, 128.7, 121.8, 121.5, 120.7, 120.6, 119.7, 110.2, 103.3, 13.2 (septet, J = 19.5 Hz); HRMS (ESI) Calcd for $C_{14}H_{10}D_3N_2$ $[M + H]^+$ 212.1267, found 212.1273.

Control Experiments



Reaction of methyl tosylate with *t*-BuCH$_2$MgBr (Scheme 2a): Methyl tosylate (37 mg, 0.20 mmol) and THF (0.79 mL) were placed in a Schlenk tube. To the mixture was added a THF solution of *t*-BuCH$_2$MgBr (0.96 M, 0.21 mL, 0.20 mmol). The resulting mixture was stirred at room temperature for 2 h. Then 1,1,2,2-tetrachloroethane (21.0 μL, 0.20 mmol) was added, and the mixture was diluted with $CDCl_3$ (1 mL), followed by filtration through a short pad of Celite. A part (0.1 mL) of the filtrate was transferred to an NMR tube and further diluted with $CDCl_3$ (0.5 mL) to record ^{1}H NMR spectrum, which confirmed formation of methyl bromide (δ = 2.61 ppm) and disappearance of methyl tosylate (Figure S3 and S4). The rest was treated with sat. NH_4Cl (1 mL), and then subjected to GC analysis to again confirm full consumption of methyl tosylate. The same procedure was also applied to methyl mesylate and trimethyl phosphate, and ^{1}H NMR spectra of their reactions again indicated the formation of methyl bromide (δ = 2.52 and 2.51 ppm for the reactions of MeOMs and $(MeO)_3PO$, respectively).

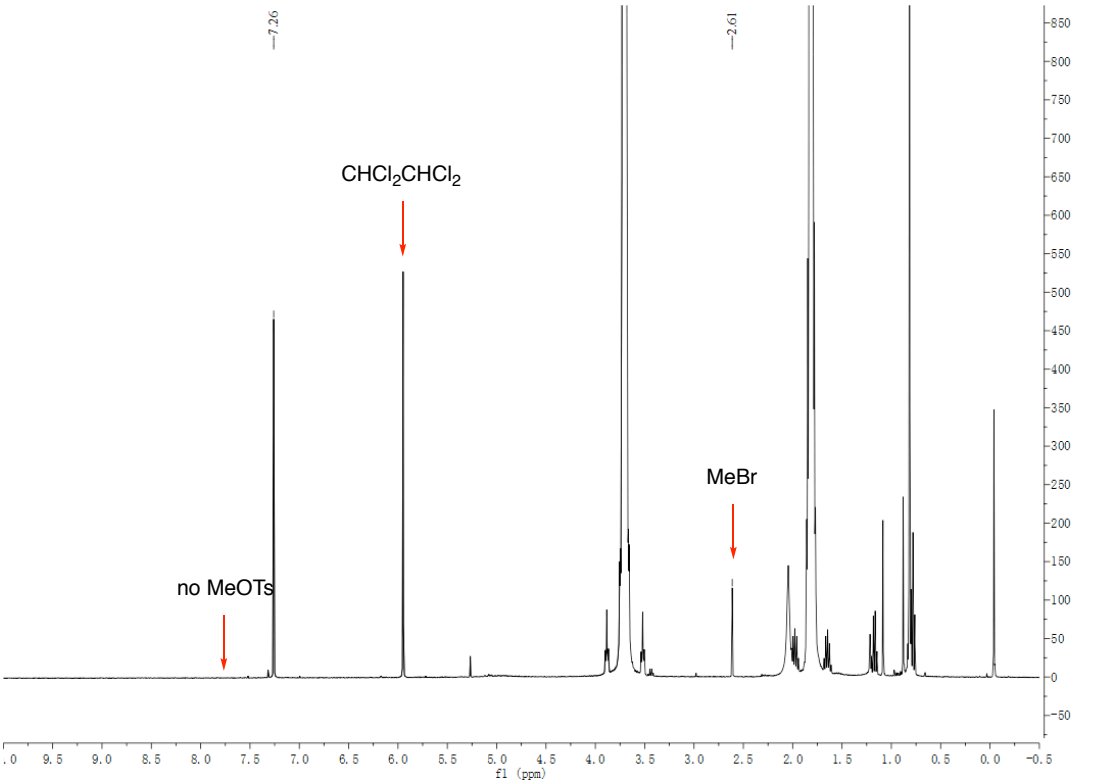


Figure S3. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the crude mixture of the reaction between MeOTs and *t*-BuCH_2MgBr.

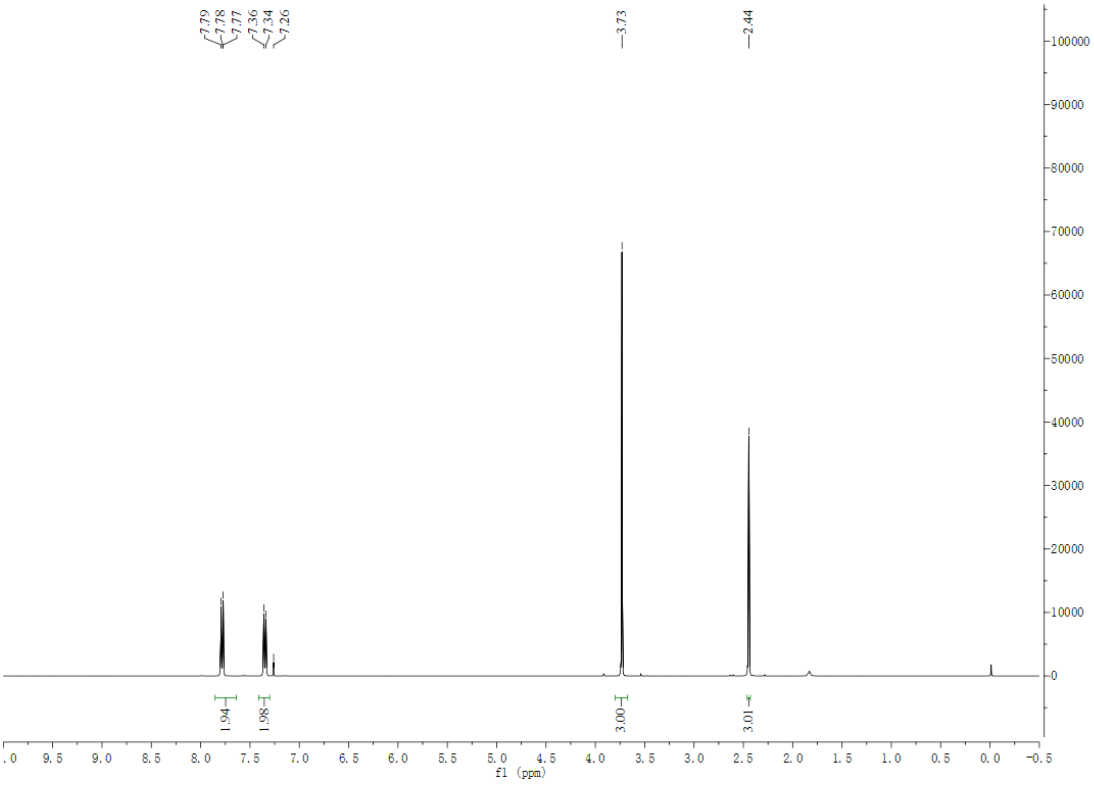
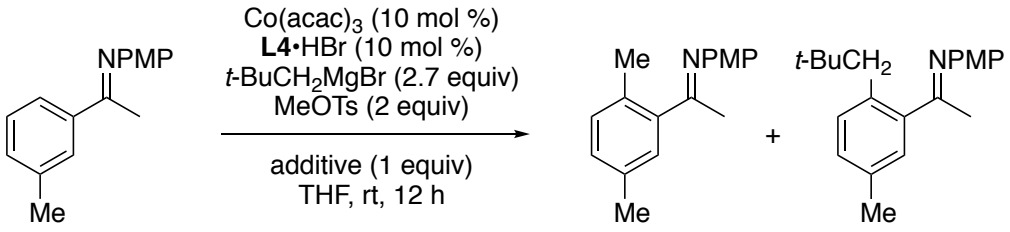
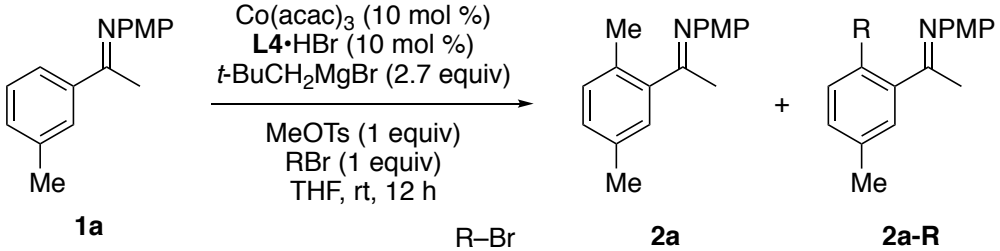


Figure S4. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of MeOTs.



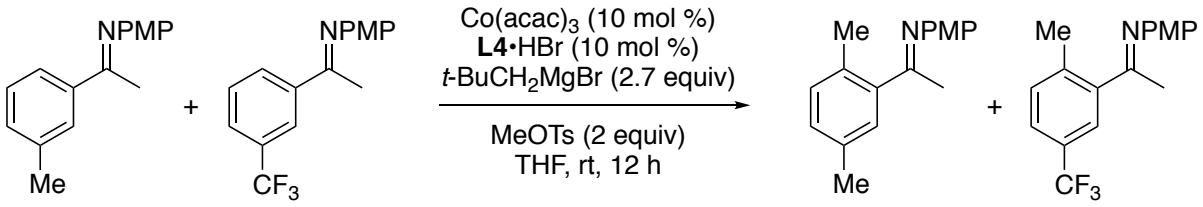
additive	**2a**	**2a'**
$Ph_2C=CH_2$	63%	2%
BHT	39%	1%
TEMPO	31%	3%

Methylation of 1a in the presence of radical scavenger (Scheme 2b): The reaction of **1a** was performed on a 0.2 mmol scale according to the typical procedure, except that a radical scavenger (1,1-diphenylethylene, BHT or TEMPO, 0.2 mmol, 1 equiv) was placed in the Schelenk tube together with the reactants and the catalysts. The quenched reaction mixture was analyzed by GC using *n*-tridecane as an internal standard to determine the yields of **2a** and **2a'**.



R–Br	**2a**	**2a-R**
n-$C_8H_{17}Br$	14%	23%
c-$C_6H_{11}Br$	20%	12%

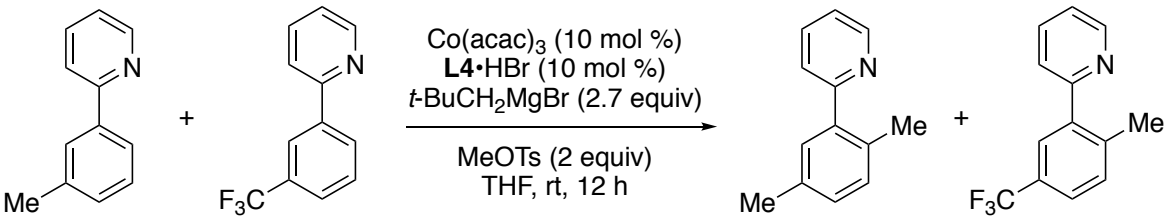
Competition between methyl tosylate and alkyl bromide (Scheme 2c): The reaction of **1a** was set up on a 0.2 mmol scale according to the typical procedure except for the following change: Instead of using 0.4 mmol (2 equiv) of methyl tosylate, 0.2 mmol (1 equiv) each of methyl tosylate and alkyl bromide (*n*-octyl bromide or cyclohexyl bromide) were placed in the Schlenk tube. The quenched reaction mixture was analyzed by GC using *n*-tridecane as an internal standard to determine the yields of **2a** and **2a-R**.



1a **1b** **2a** **2b**

run 1	10%	37%
run 2	11%	47%

Competition between 1a and 1b (Scheme 2d): A mixture of **1a** and **1b** (0.2 mmol each) was subjected to methylation according to the typical procedure. The quenched reaction mixture was analyzed by GC using *n*-tridecane as an internal standard to determine the yields of the methylated products **2a** and **2b**.



3a **3b** **4a**, 12% **4b**, 30%

Competition between 3a and 3b: A mixture of **3a** and **3b** (0.2 mmol each) was subjected to methylation according to the typical procedure. The quenched reaction mixture was analyzed by GC using *n*-tridecane as an internal standard to determine the yields of the methylated products **4a** and **4b**.

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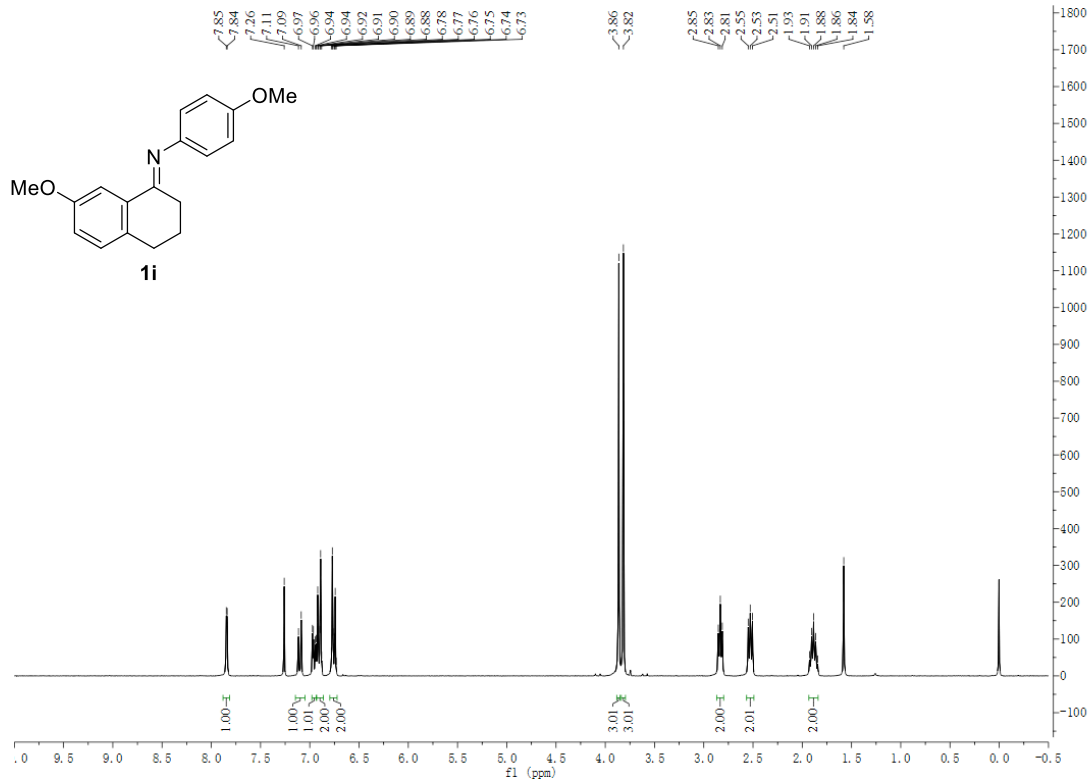
NMR Spectra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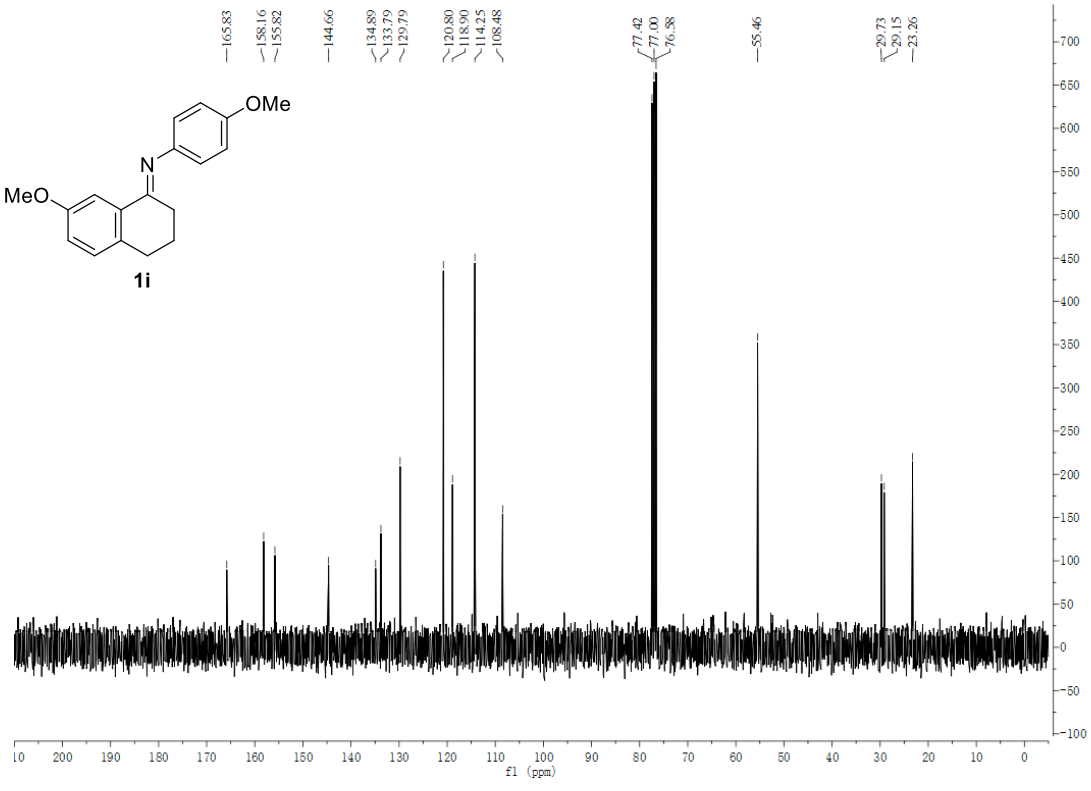
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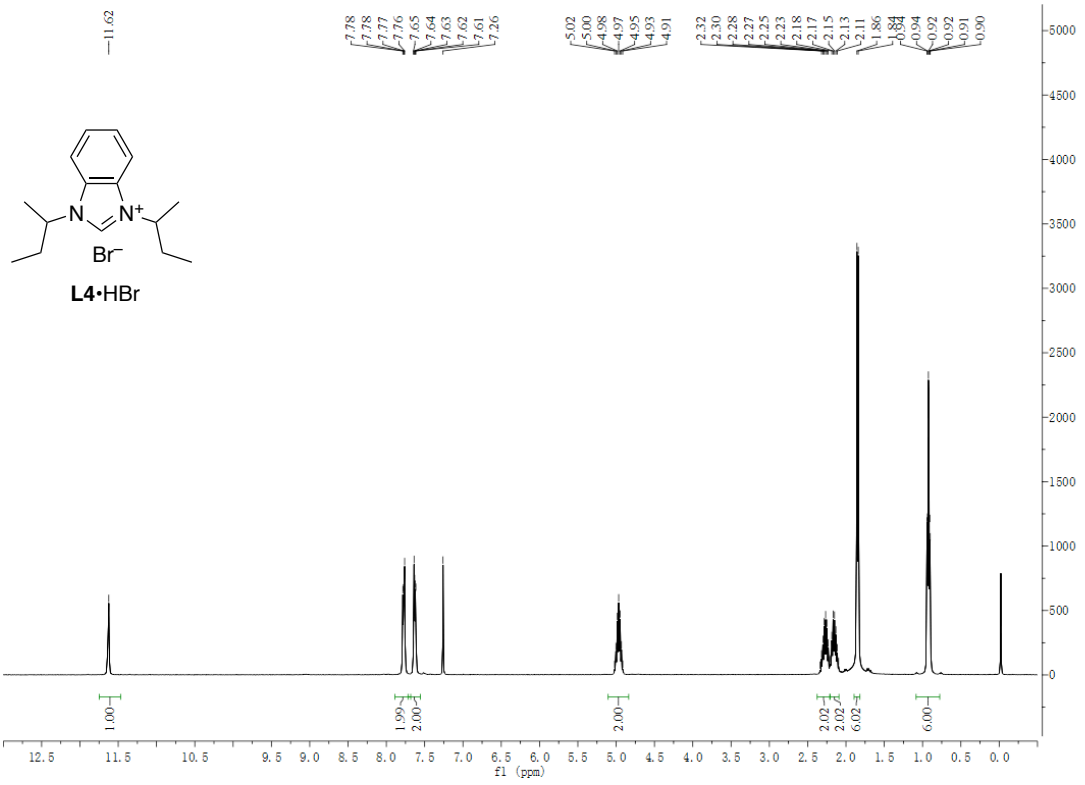
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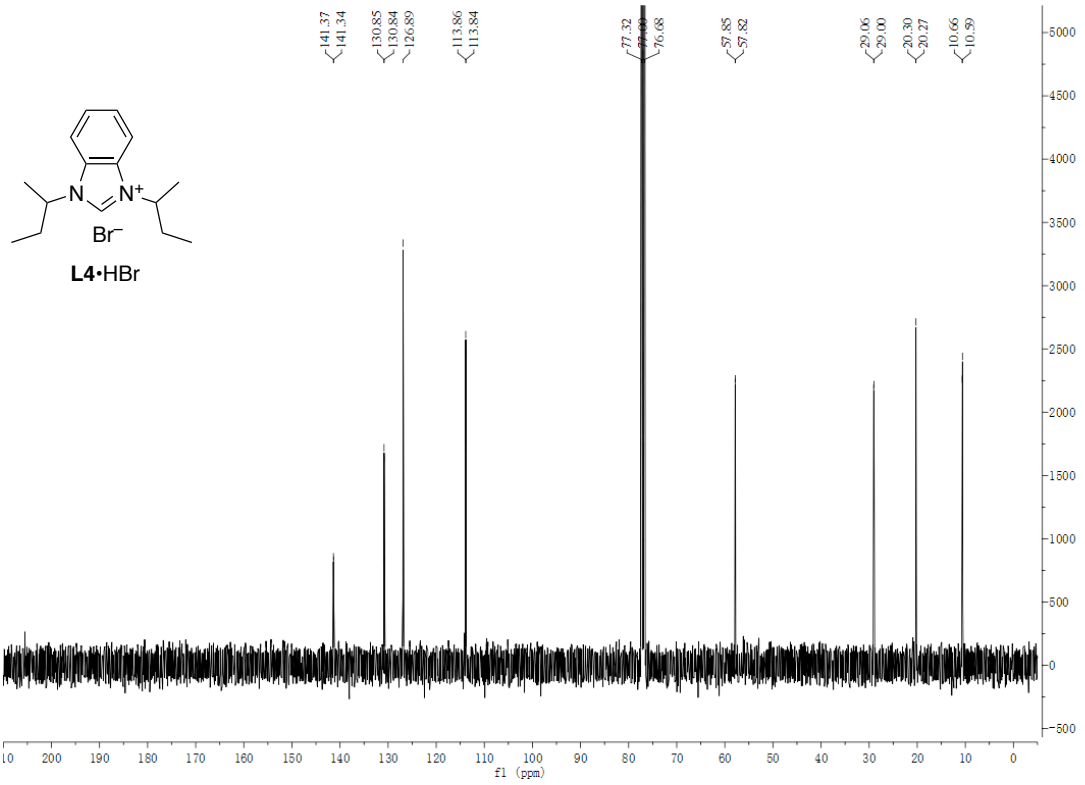
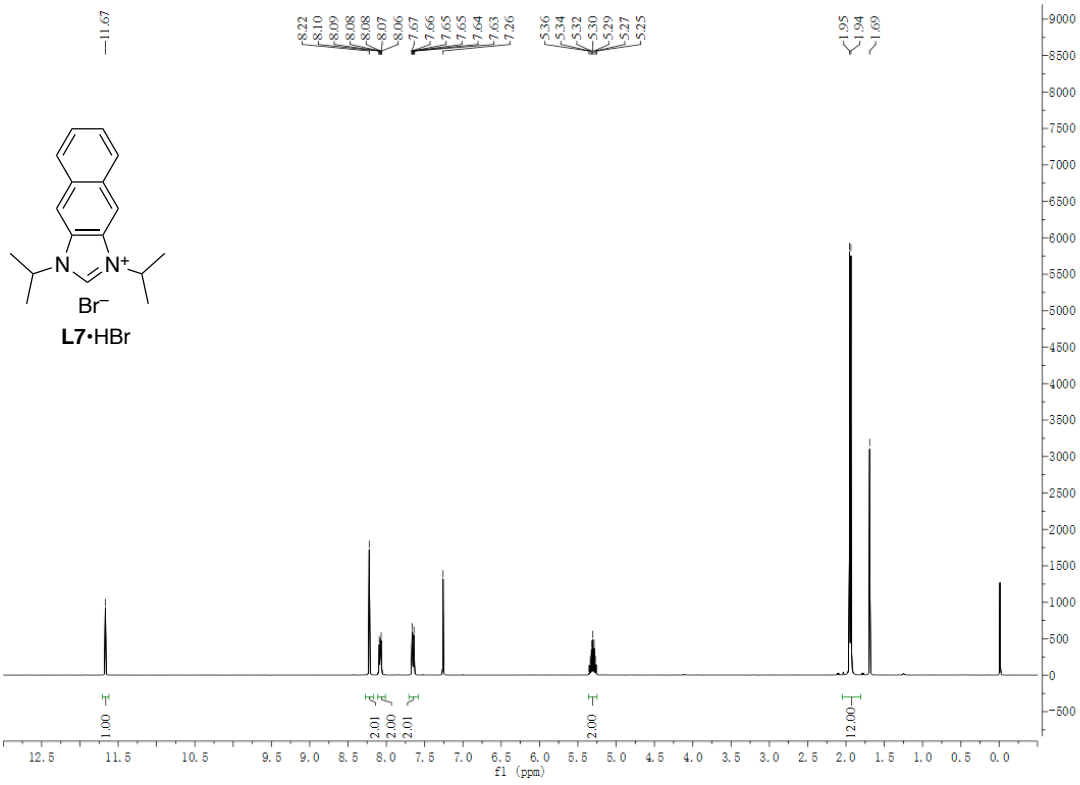
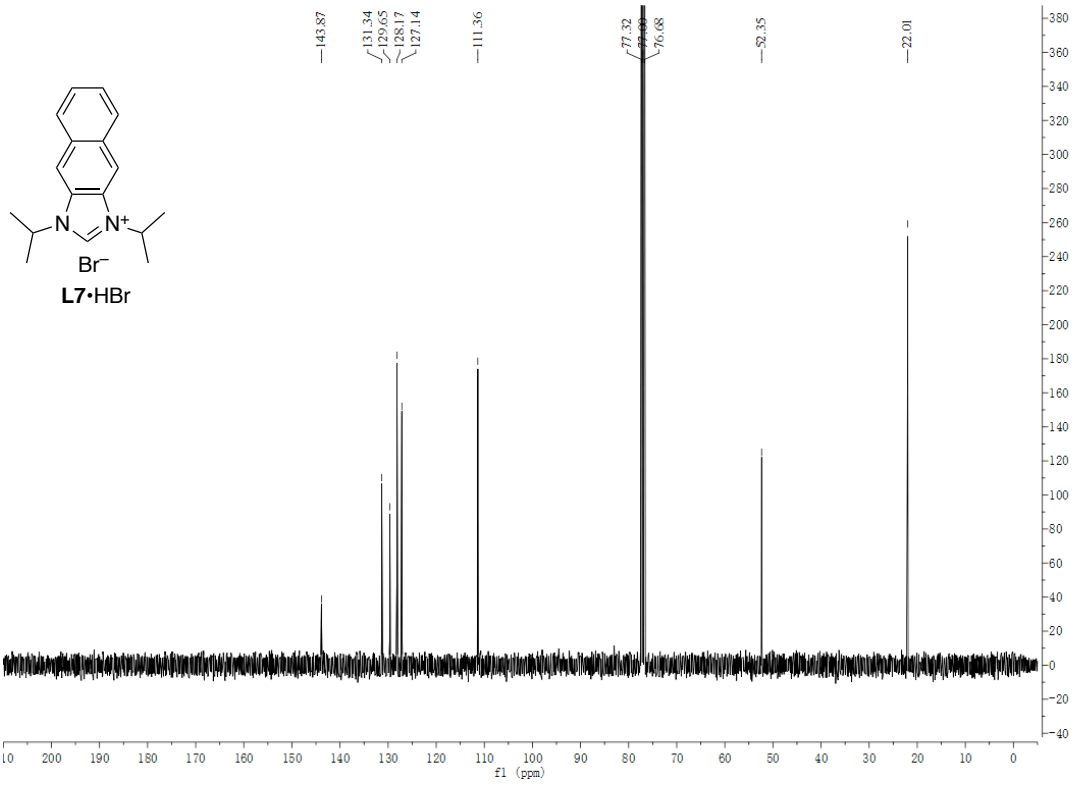
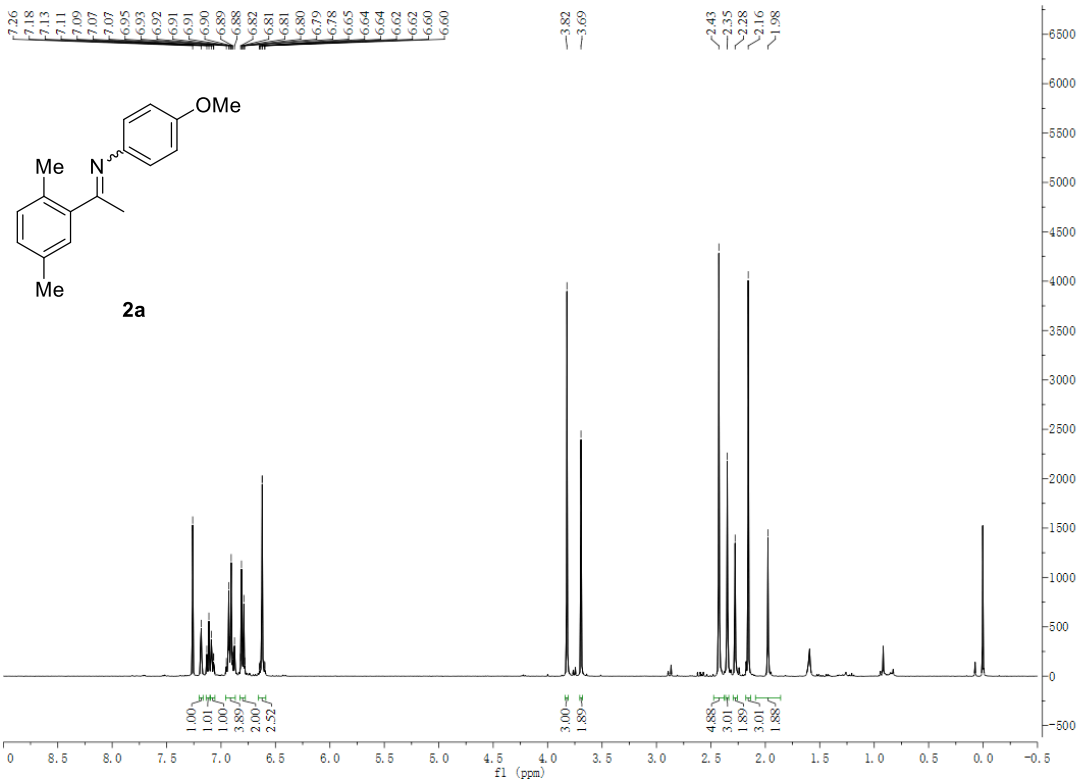
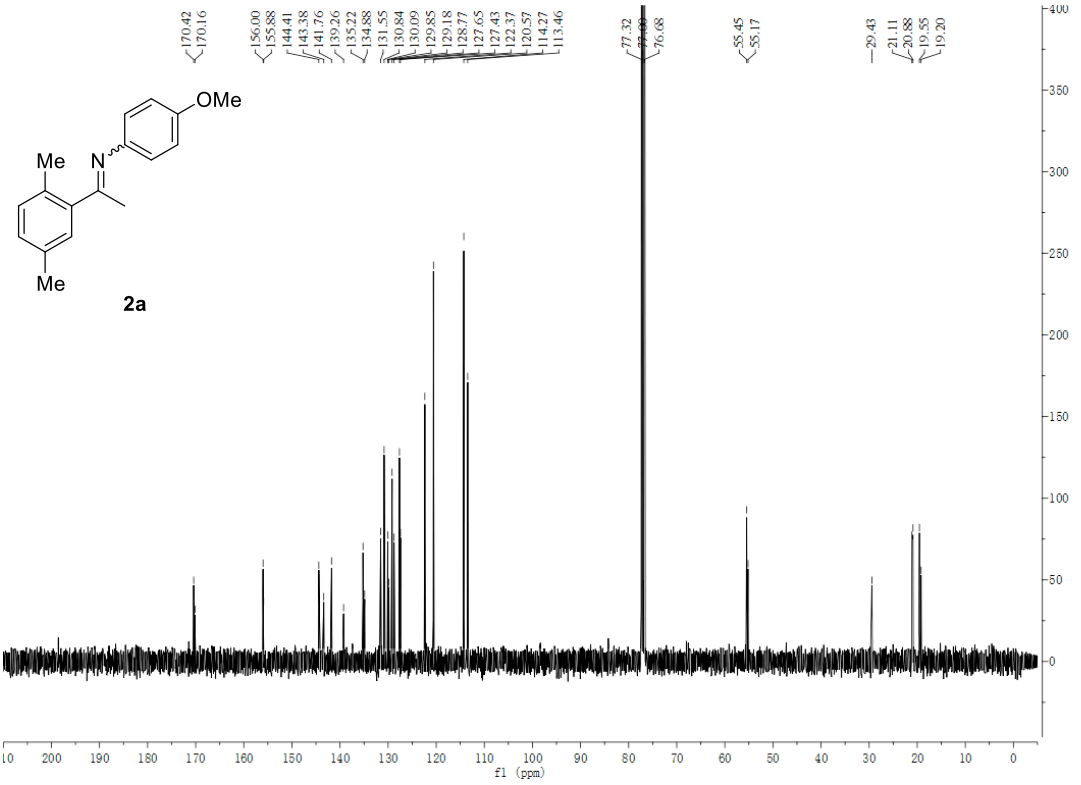
6.00
f1 (ppm)

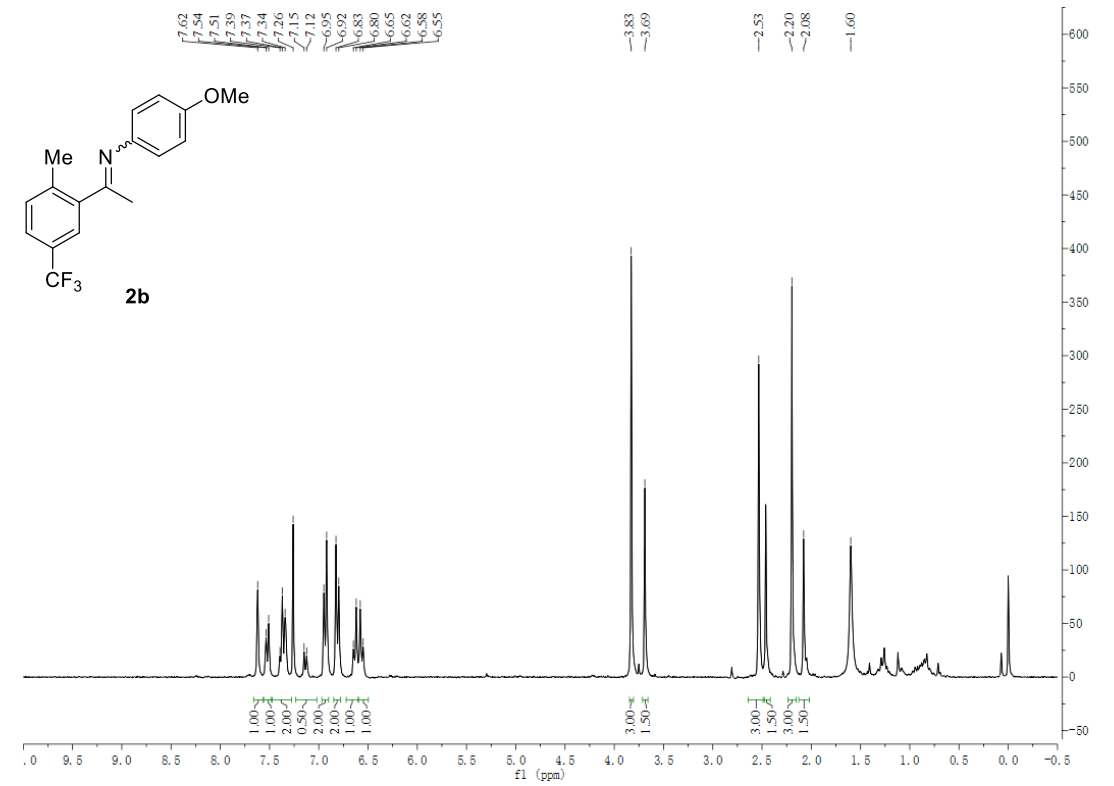

141.37
141.34
130.85
130.84
126.89
113.86
113.84
77.32
77.00
76.68
57.85
57.82
29.06
29.00
20.30
20.27
10.66
10.59
N
N+
Br−
L4·HBr
f1 (ppm)

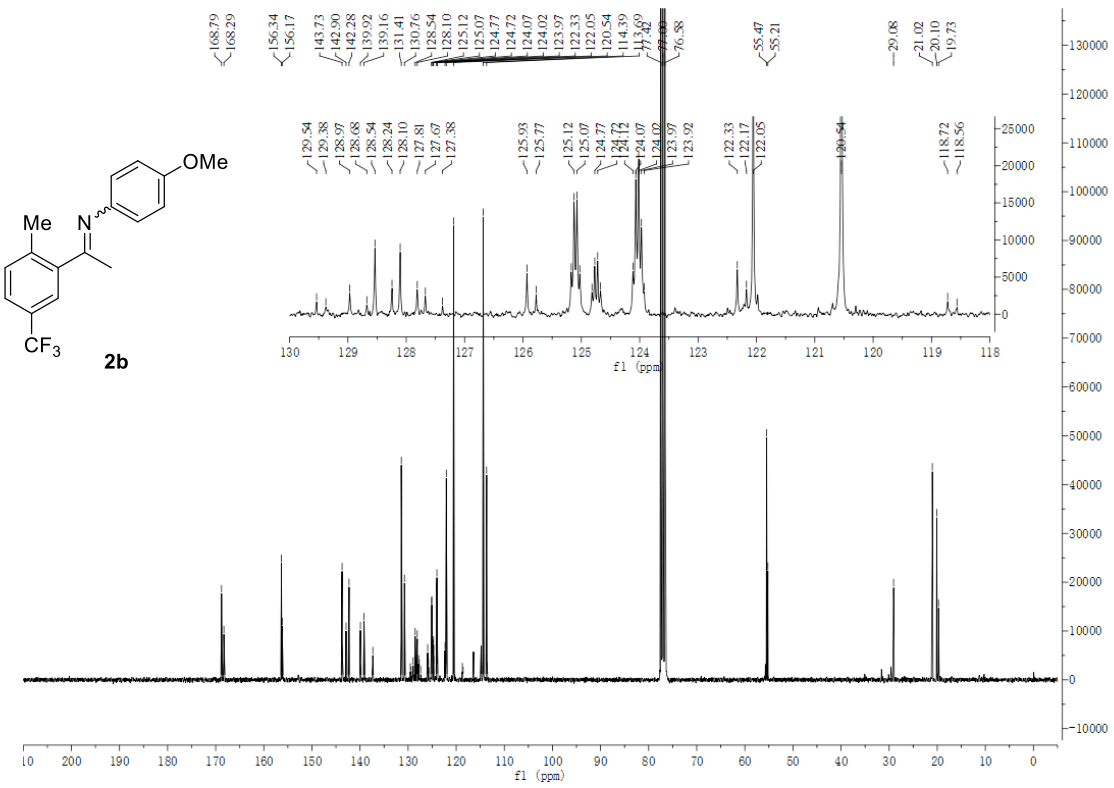

11.67
8.22
8.10
8.09
8.08
8.08
8.07
8.06
7.67
7.66
7.65
7.65
7.64
7.63
7.26
5.36
5.34
5.32
5.30
5.29
5.27
5.25
1.95
1.94
1.69
Br⁻
L7•HBr
1.00
2.01
2.00
2.01
2.00
12.00
f1 (ppm)

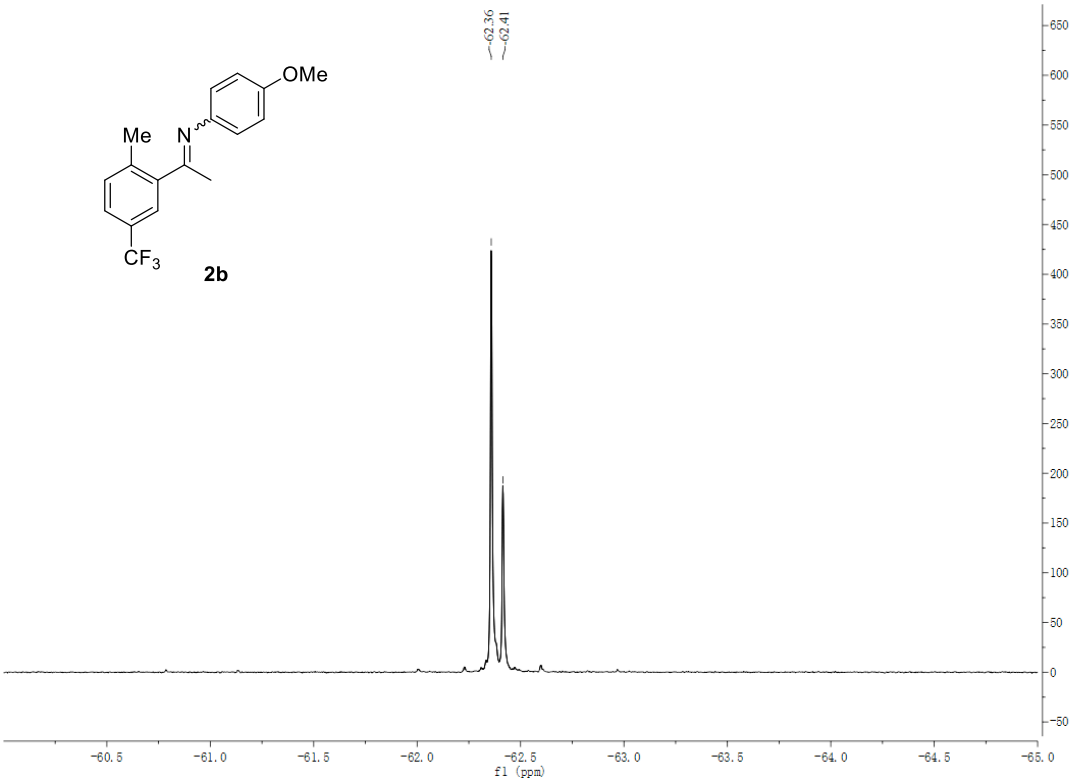

143.87
131.34
129.65
128.17
127.14
111.36
77.32
76.68
52.35
22.01
Br⁻
L7•HBr
f1 (ppm)

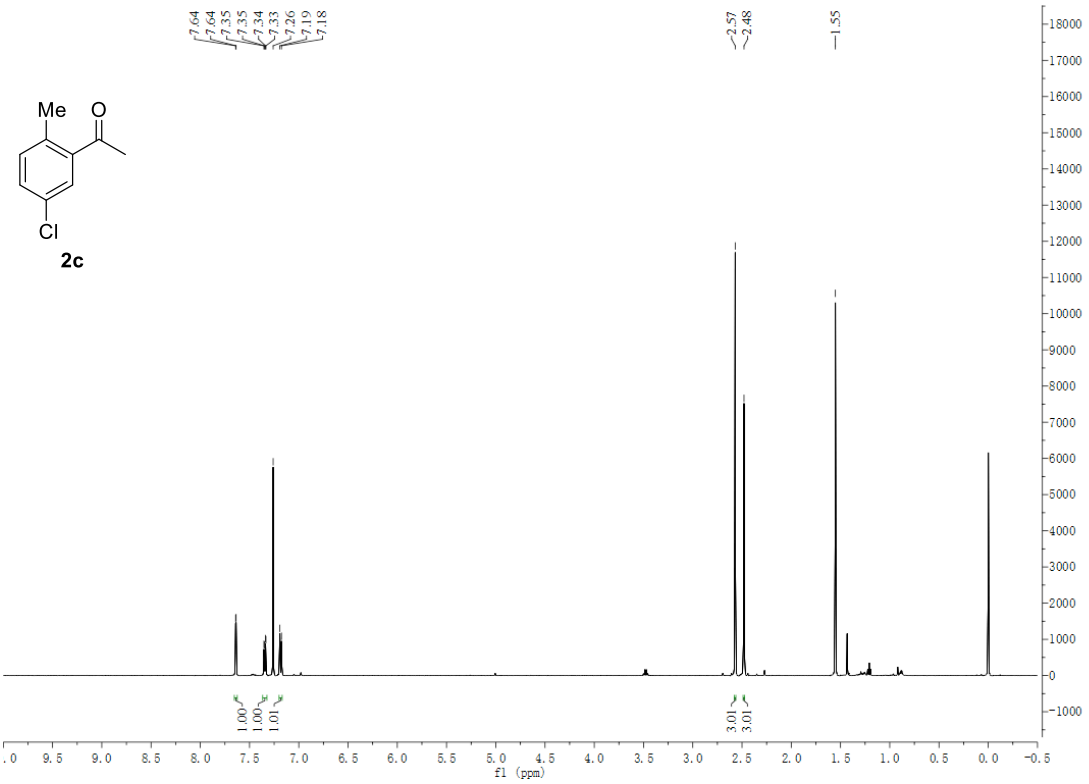

OMe
Me
N
Me
2a
f1 (ppm)

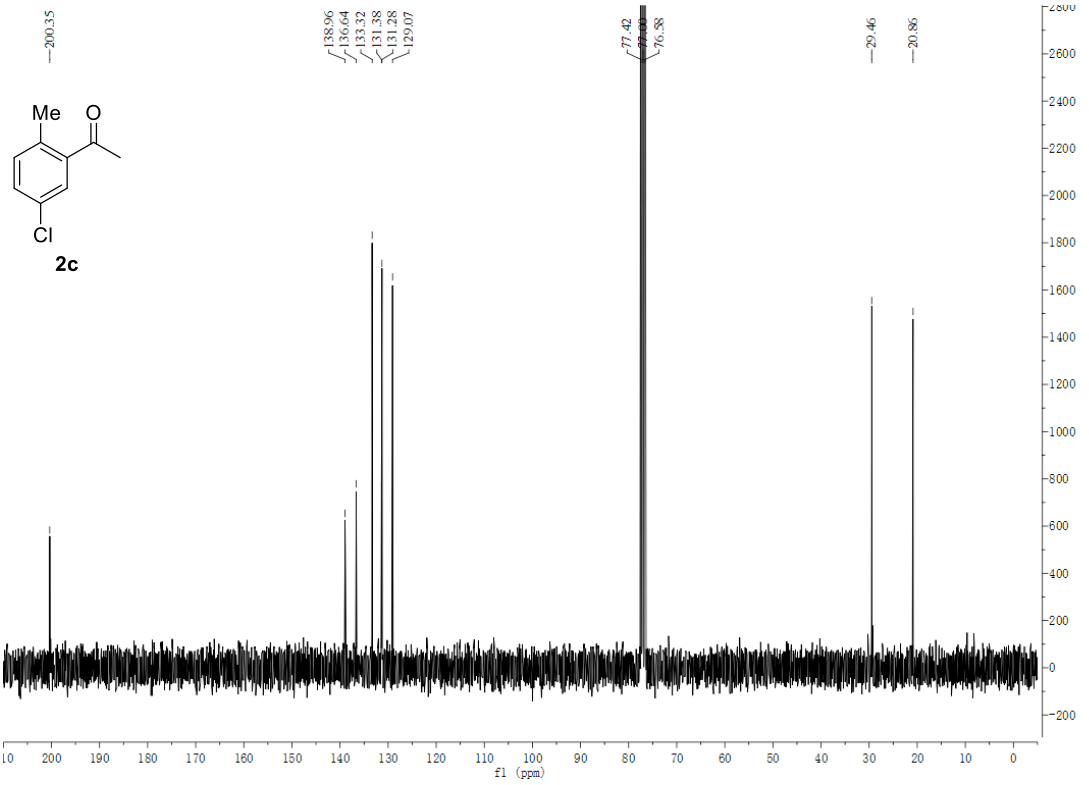

OMe
Me
N
Me
2a
f1 (ppm)

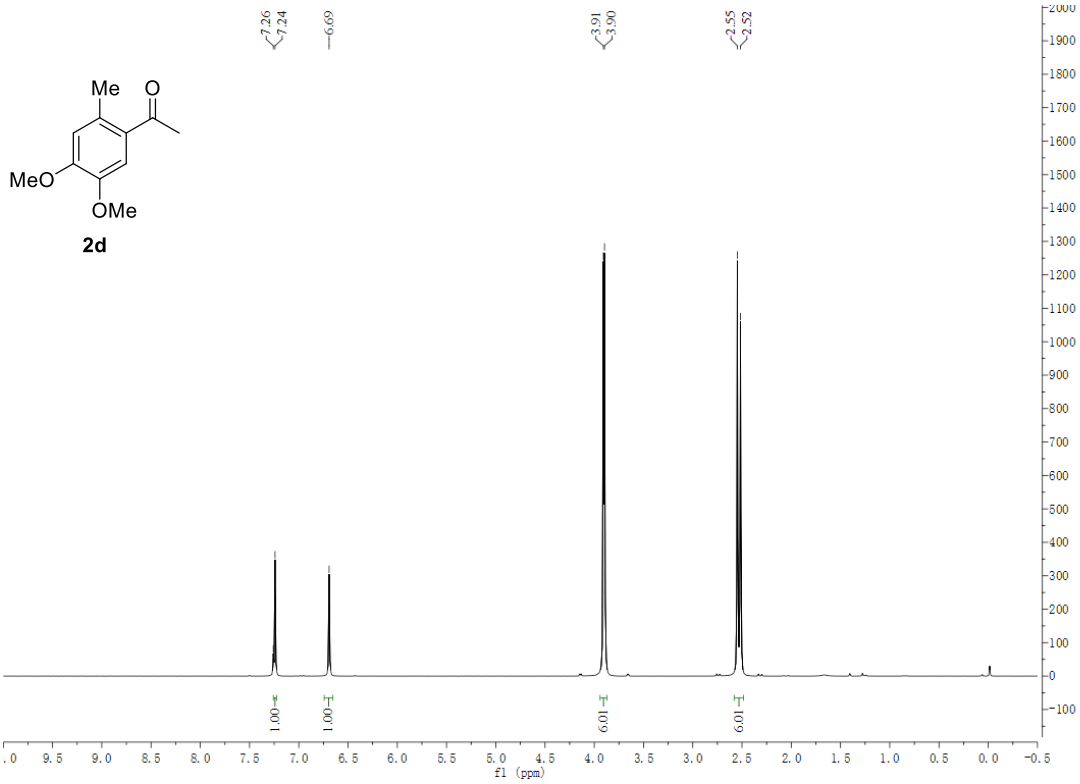

OMe
Me
N
CF3
2b
7.62
7.54
7.51
7.39
7.37
7.34
7.26
7.15
7.12
6.95
6.92
6.83
6.80
6.65
6.62
6.58
6.55
3.83
3.69
2.53
2.20
2.08
1.60
f1 (ppm)

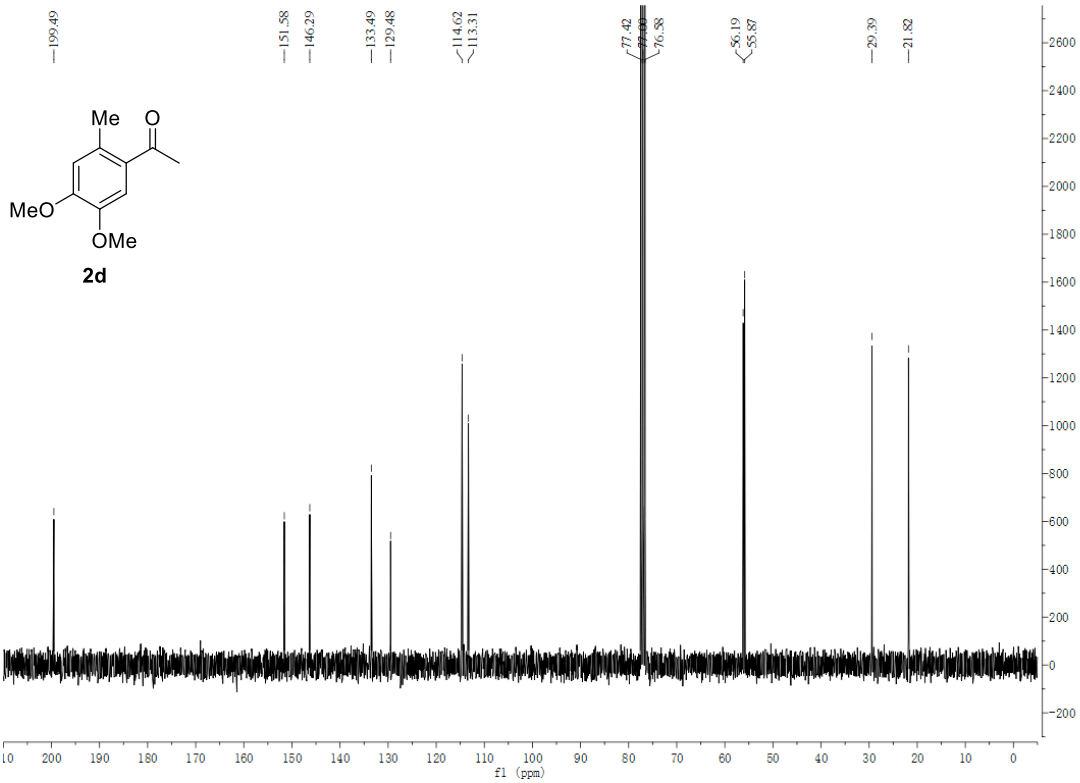

OMe
Me
N
CF3
2b
168.79
168.29
156.34
156.17
143.73
142.90
142.28
139.92
139.16
131.41
130.76
128.54
128.10
125.12
125.07
124.77
124.72
124.07
124.02
123.97
122.33
122.05
120.54
114.39
113.69
77.42
77.00
76.58
55.47
55.21
29.08
21.02
20.10
19.73
129.54
129.38
128.97
128.68
128.54
128.24
128.10
127.81
127.67
127.38
125.93
125.77
125.12
125.07
124.77
124.72
124.12
124.07
124.02
123.97
123.92
122.33
122.17
122.05
120.54
118.72
118.56
f1 (ppm)

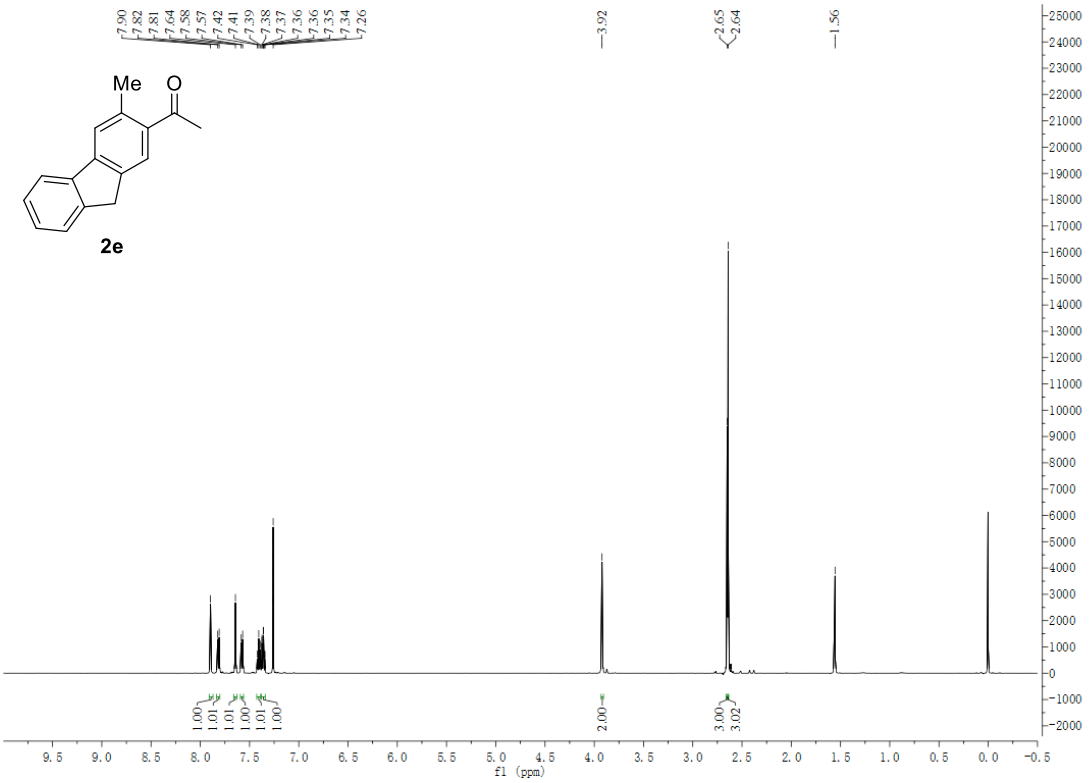

-62.36
-62.41
OMe
Me
N
CF3
2b
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-60.5
-61.0
-61.5
-62.0
-62.5
-63.0
-63.5
-64.0
-64.5
-65.0
f1 (ppm)

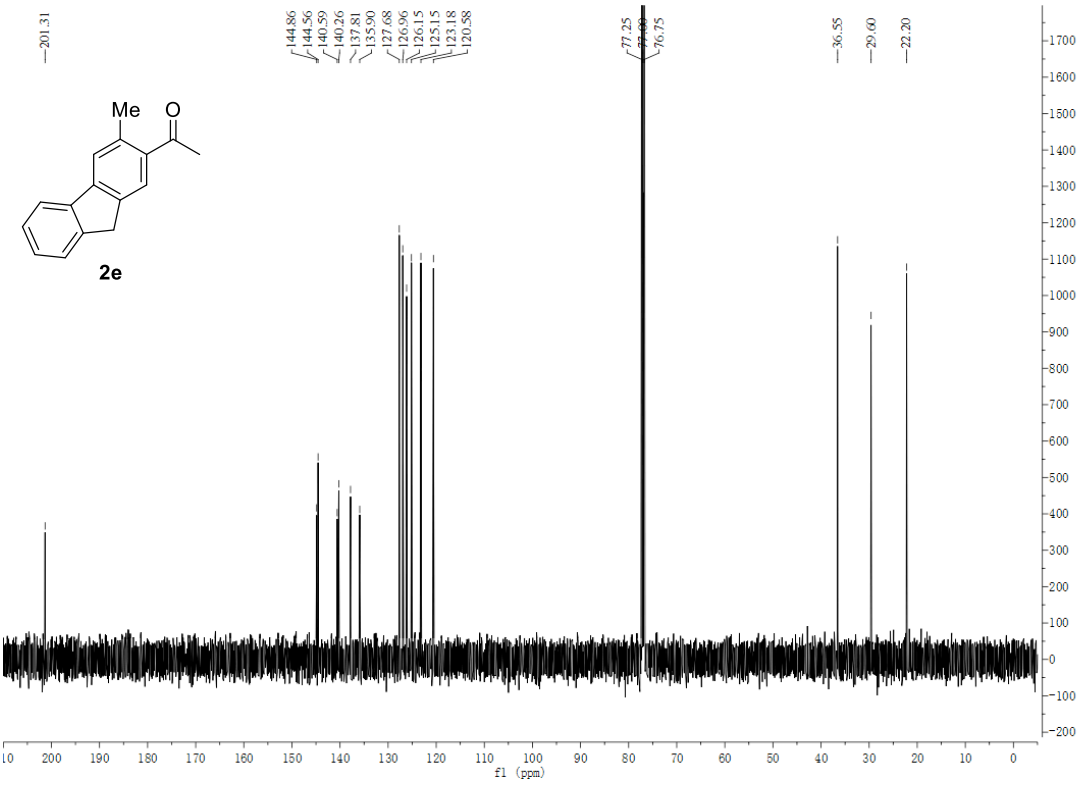

7.64
7.64
7.35
7.35
7.34
7.33
7.26
7.19
7.18
2.57
2.48
1.55
Me
O
Cl
2c
1.00
1.00
1.01
3.01
3.01
f1 (ppm)

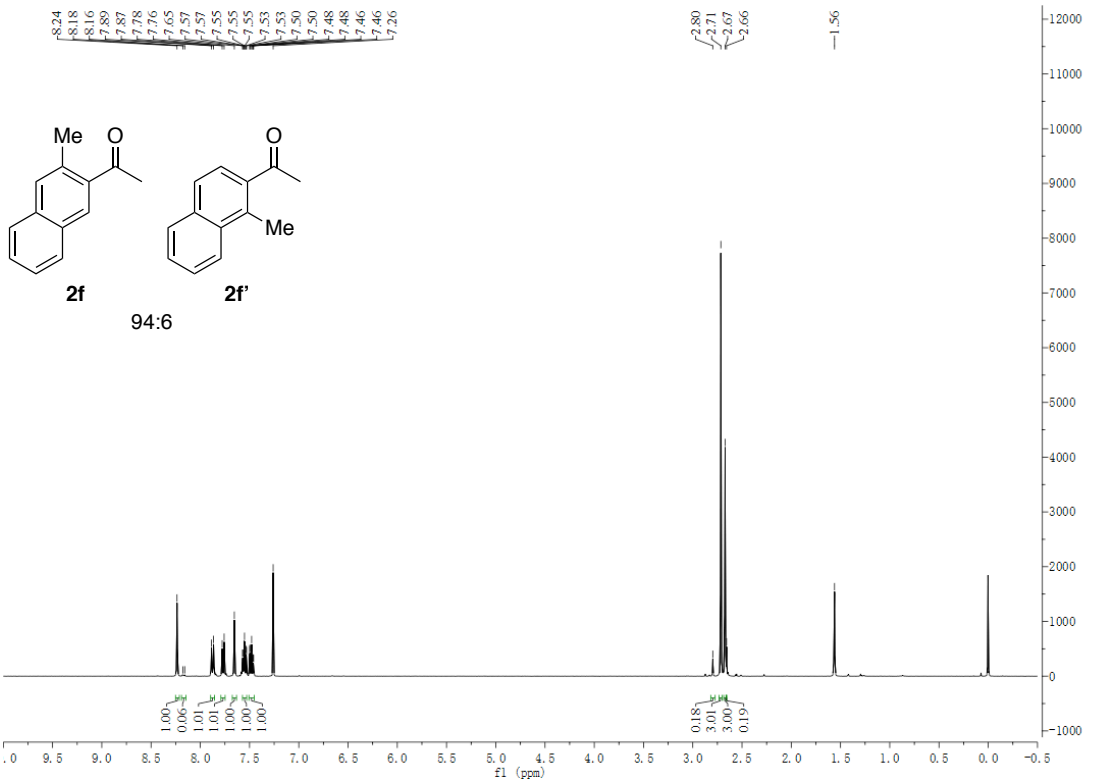

200.35
138.96
136.64
133.32
131.38
131.28
129.07
77.42
77.00
76.58
29.46
20.86
Me
O
Cl
2c
f1 (ppm)

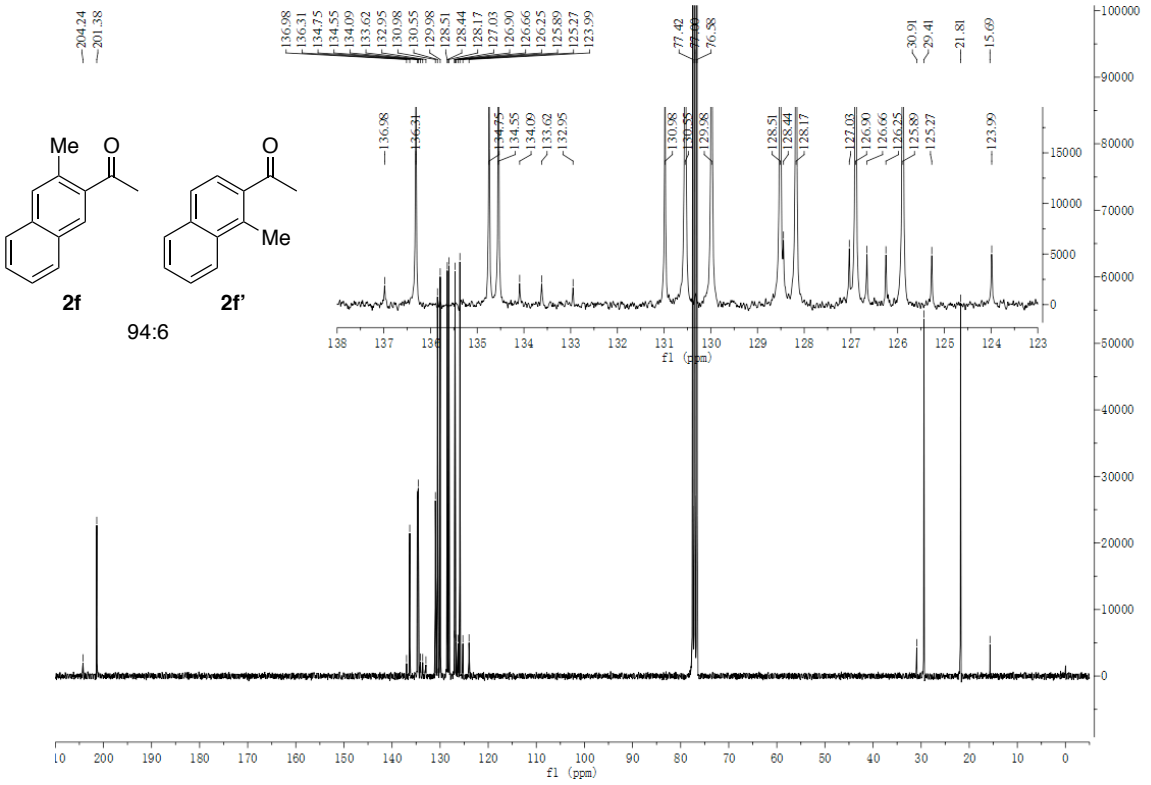

Me
O
MeO
OMe
2d
7.26
7.24
6.69
3.91
3.90
2.55
2.52
1.00
1.00
6.01
6.01
f1 (ppm)

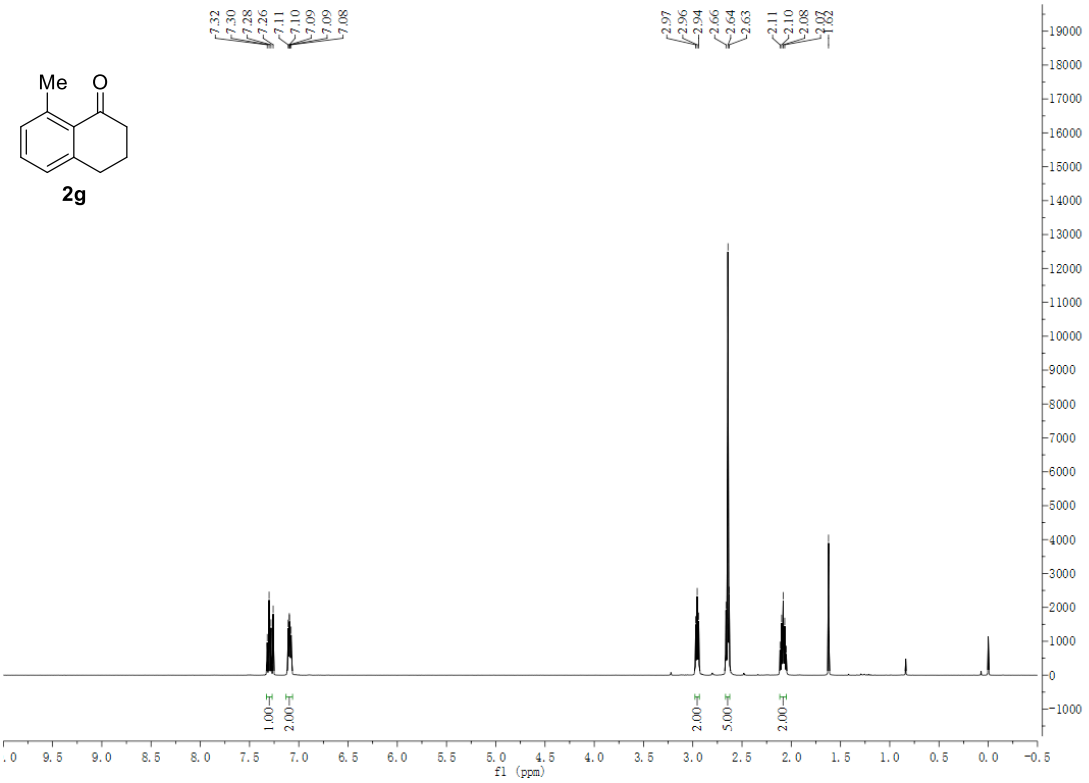

Me
O
MeO
OMe
2d
199.49
151.58
146.29
133.49
129.48
114.62
113.31
77.42
77.00
76.58
56.19
55.87
29.39
21.82
f1 (ppm)

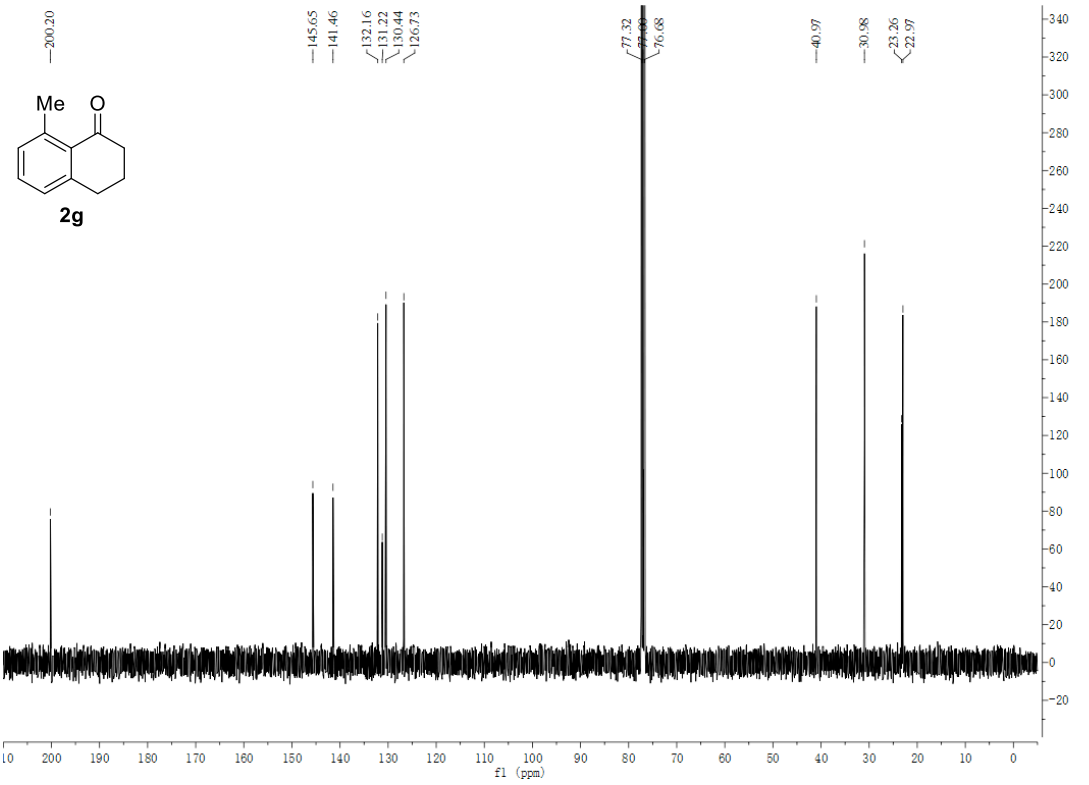

7.90
7.82
7.81
7.64
7.58
7.57
7.42
7.41
7.39
7.38
7.37
7.36
7.36
7.35
7.34
7.26
3.92
2.65
2.64
1.56
Me
O
2e
1.00
1.01
1.01
1.00
1.01
1.00
2.00
3.00
3.02
f1 (ppm)

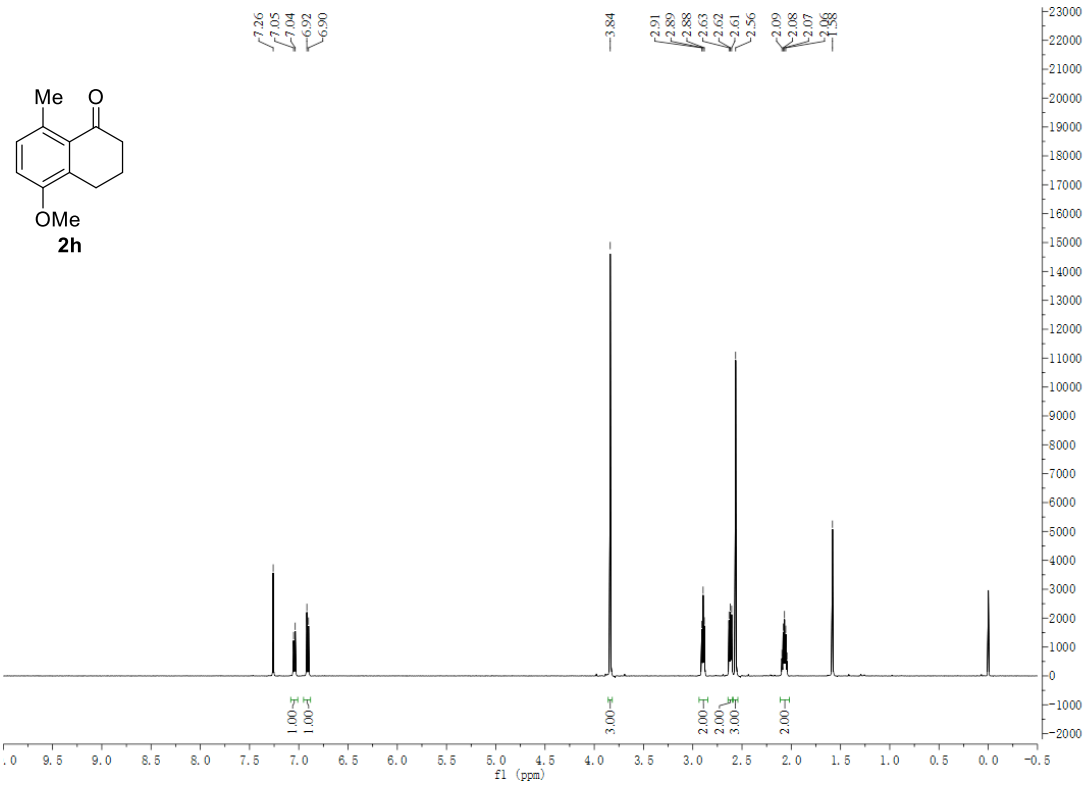

201.31
144.86
144.56
140.59
140.26
137.81
135.90
127.68
126.96
126.15
125.15
123.18
120.58
77.25
77.00
76.75
36.55
29.60
22.20
Me
O
2e
f1 (ppm)

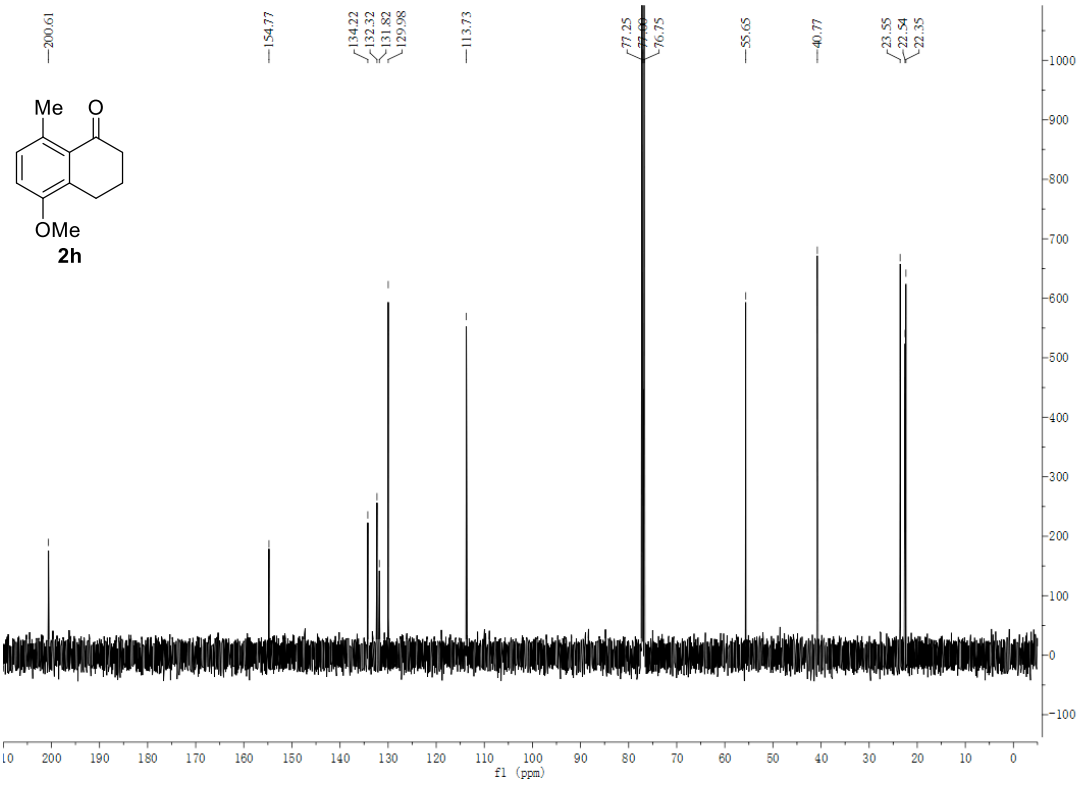

Me
O
O
Me
2f
2f'
94:6
f1 (ppm)

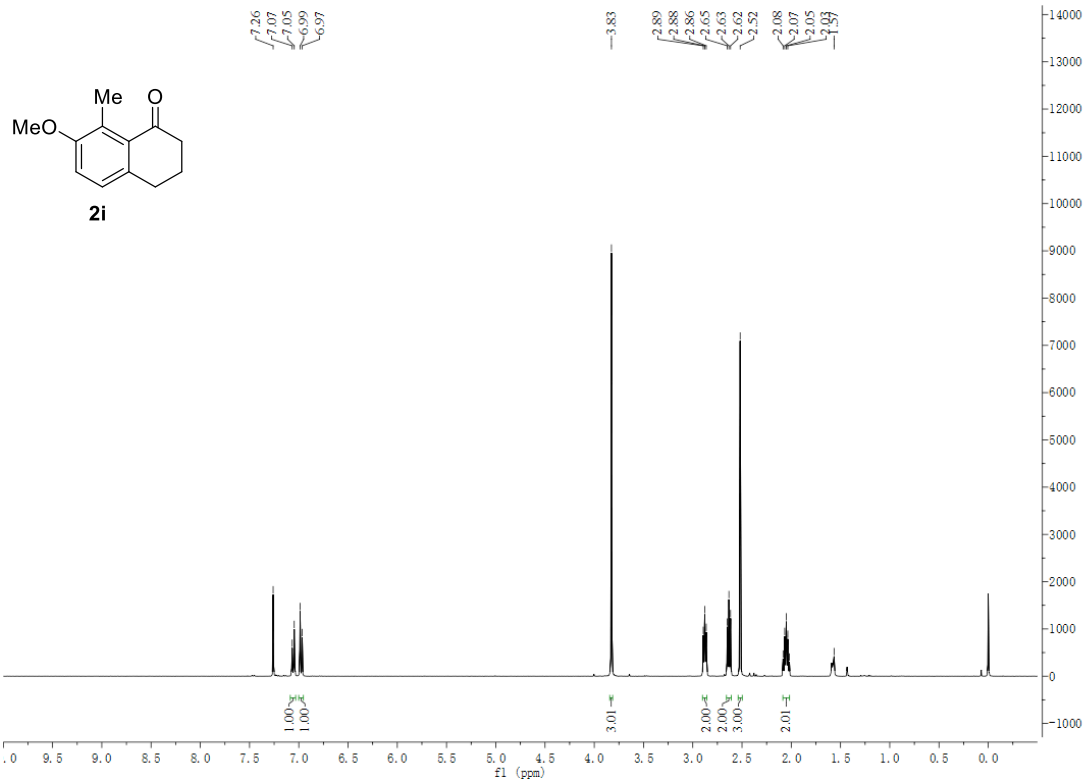

Me
O
O
Me
2f
2f'
94:6
f1 (ppm)

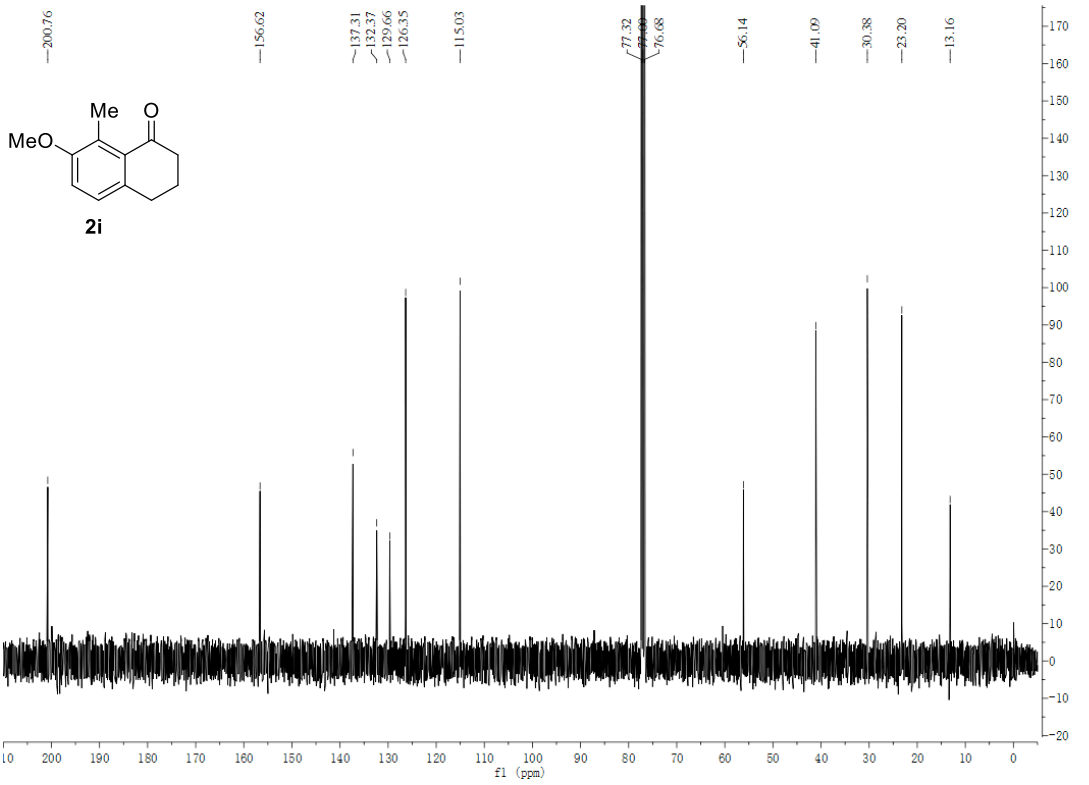

Me
O
2g
7.32
7.30
7.28
7.26
7.11
7.10
7.09
7.09
7.08
2.97
2.96
2.94
2.66
2.64
2.63
2.11
2.10
2.08
2.07
1.62
1.00
2.00
2.00
5.00
2.00
f1 (ppm)

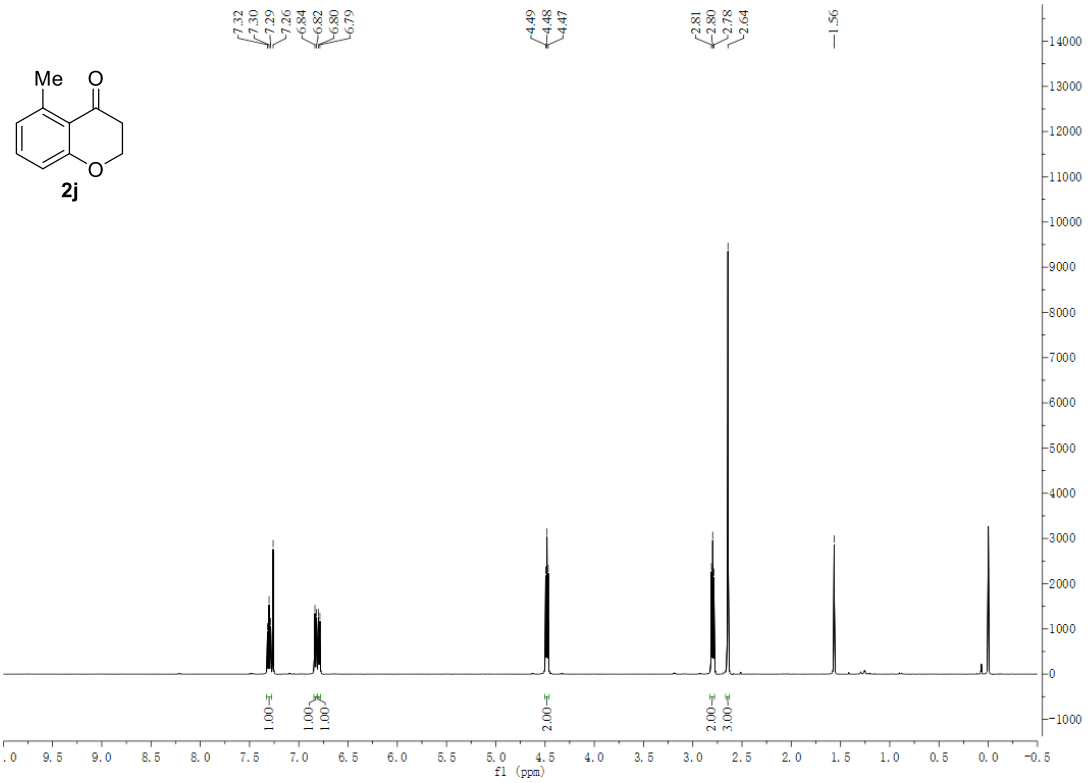

Me
O
2g
200.20
145.65
141.46
132.16
131.22
130.44
126.73
77.32
77.00
76.68
40.97
30.98
23.26
22.97
f1 (ppm)

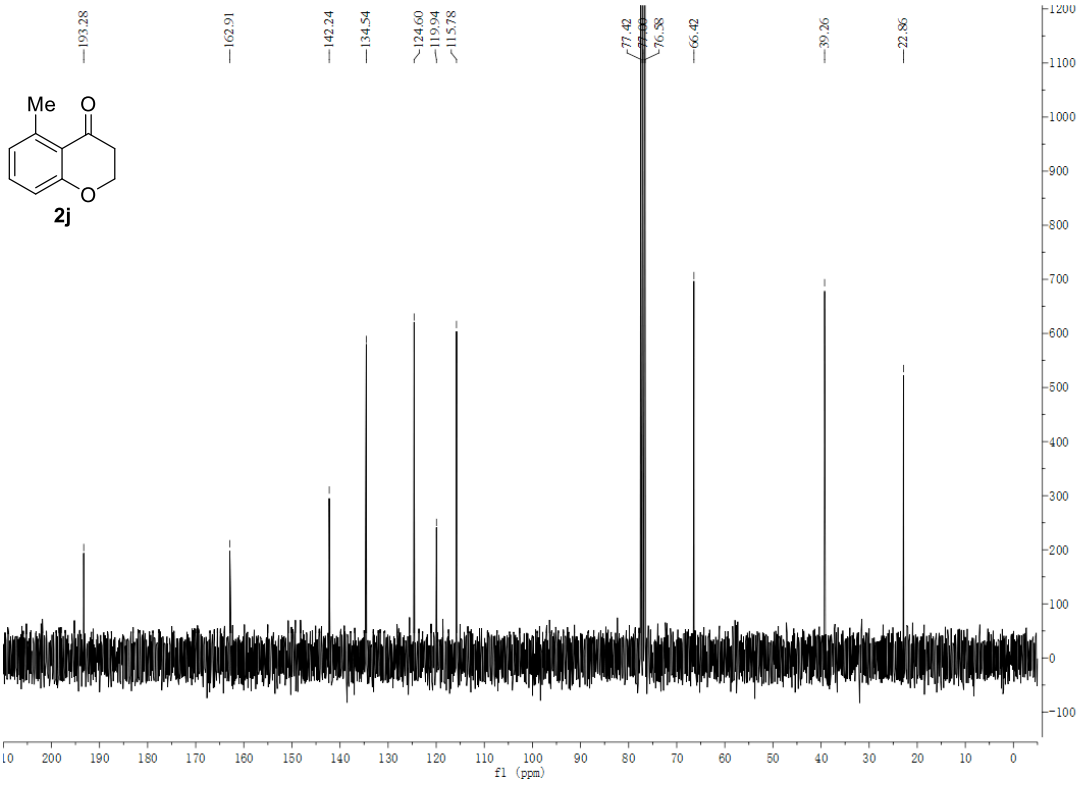

Me
O
OMe
2h
7.26
7.05
7.04
6.92
6.90
3.84
2.91
2.89
2.88
2.63
2.62
2.61
2.56
2.09
2.08
2.07
1.88
1.00
1.00
3.00
2.00
3.00
2.00
f1 (ppm)

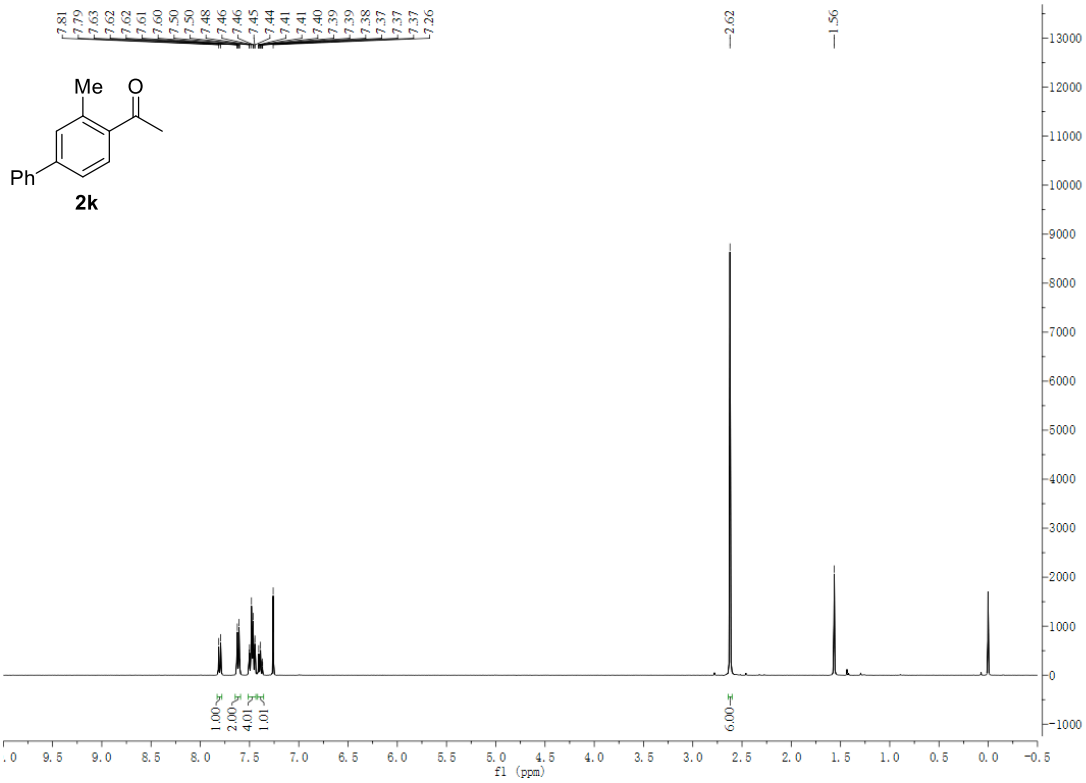

Me
O
OMe
2h
200.61
154.77
134.22
132.32
131.82
129.98
113.73
77.25
76.75
55.65
40.77
23.55
22.54
22.35
f1 (ppm)

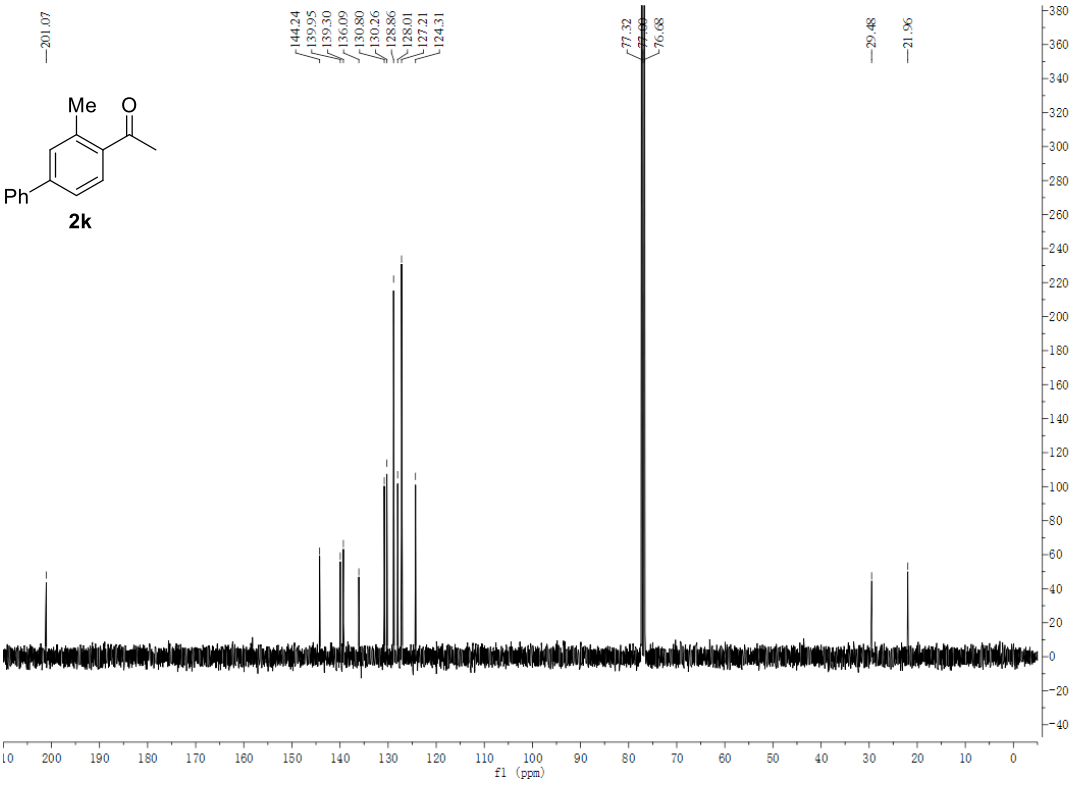

Me
O
MeO
2i
7.26
7.07
7.05
6.99
6.97
3.83
2.89
2.88
2.86
2.65
2.63
2.62
2.52
2.08
2.07
2.05
1.93
1.97
1.00
1.00
3.01
2.00
2.00
3.00
2.01
f1 (ppm)

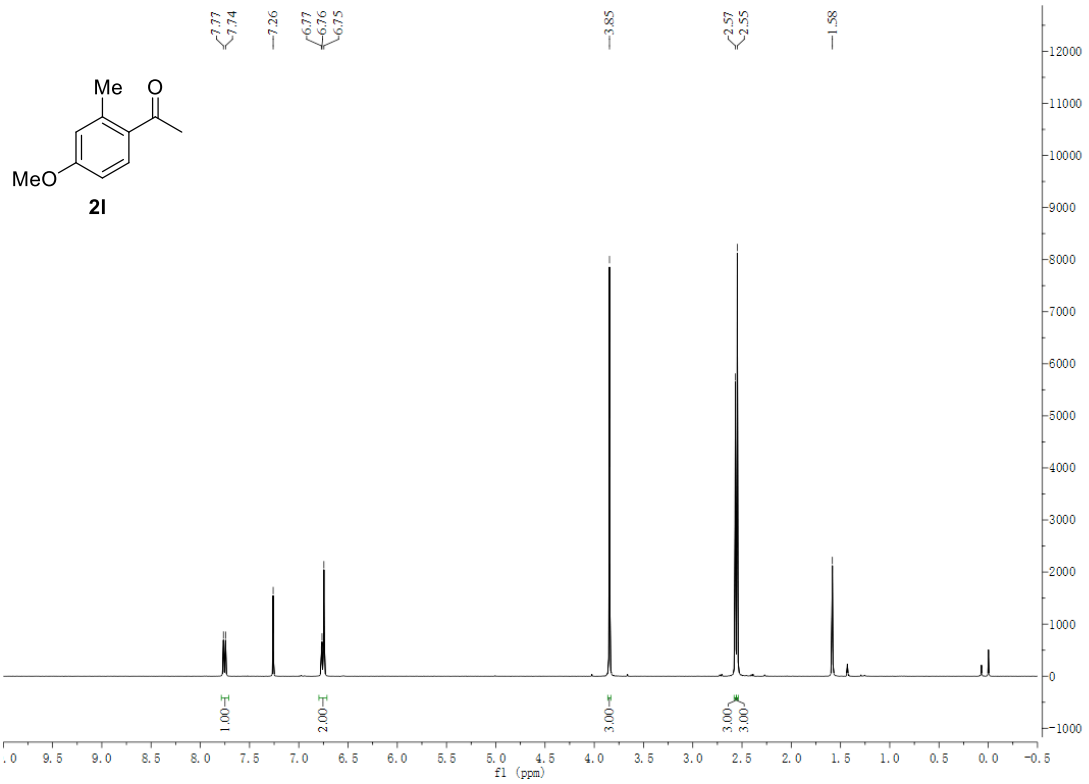

Me
O
MeO
2i
200.76
156.62
137.31
132.37
129.66
126.35
115.03
77.32
77.00
76.68
56.14
41.09
30.38
23.20
13.16
f1 (ppm)

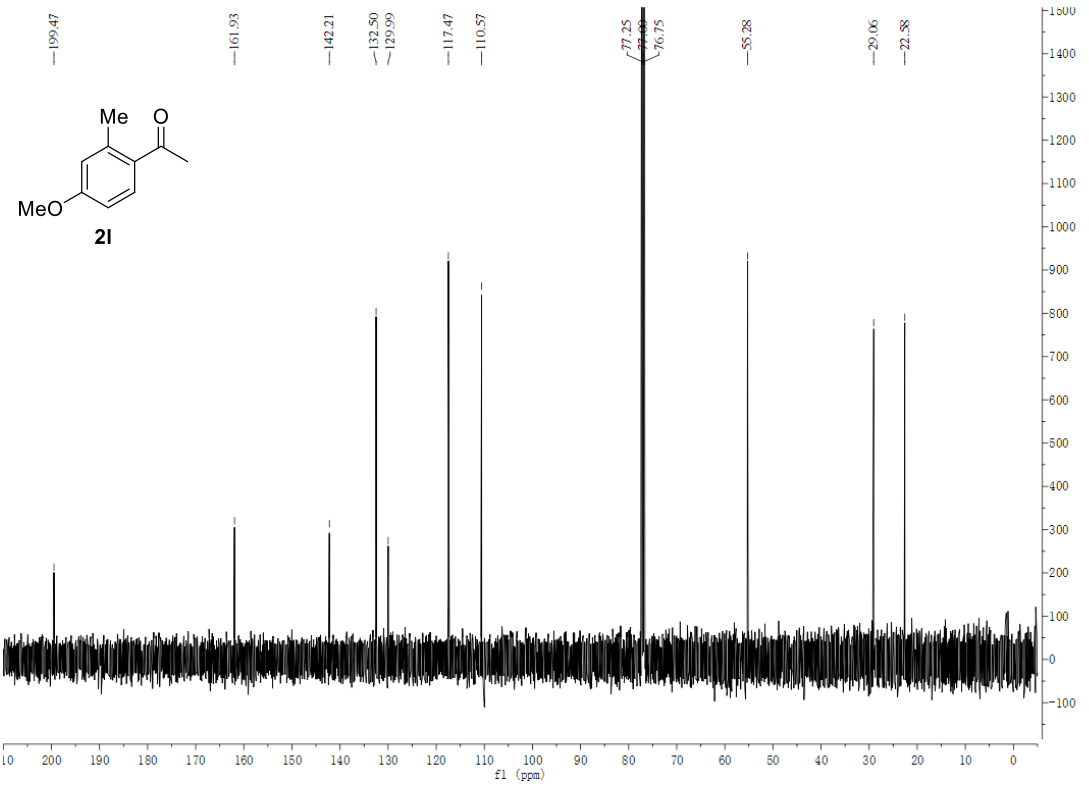

Me
O
O
2j
7.32
7.30
7.29
7.26
6.84
6.82
6.80
6.79
4.49
4.48
4.47
2.81
2.80
2.78
2.64
1.56
1.00
1.00
1.00
2.00
2.00
3.00
f1 (ppm)

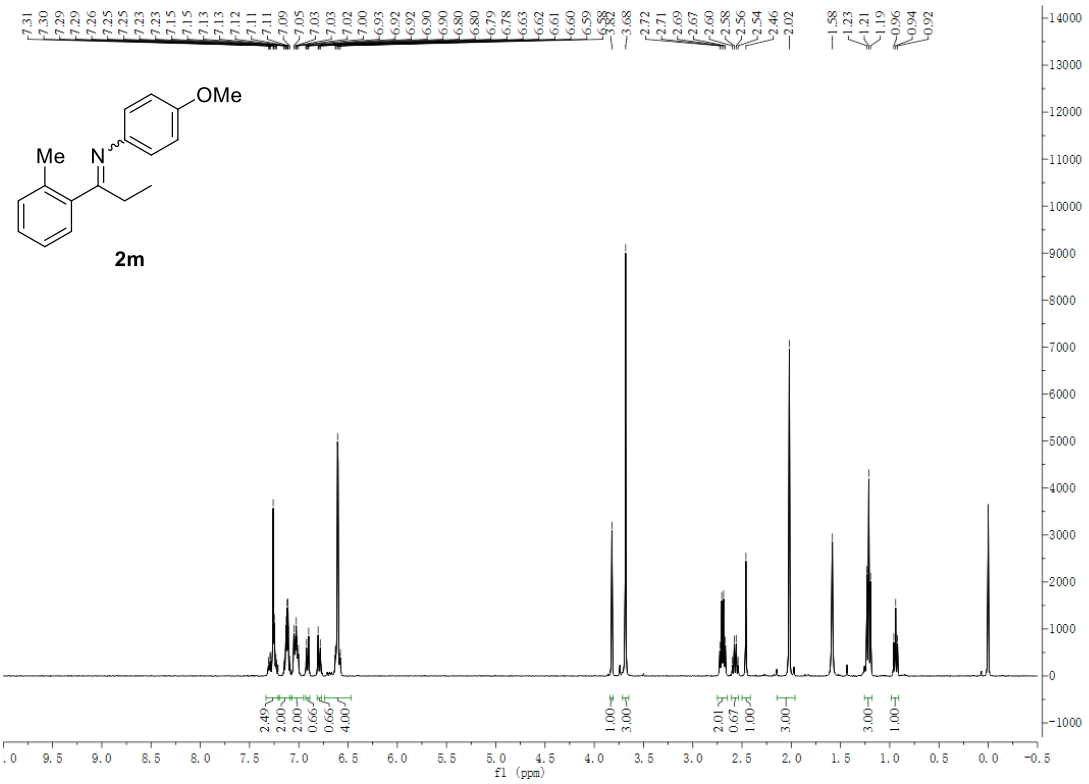

Me
O
O
2j
193.28
162.91
142.24
134.54
124.60
119.94
115.78
77.42
77.00
76.58
66.42
39.26
22.86
f1 (ppm)

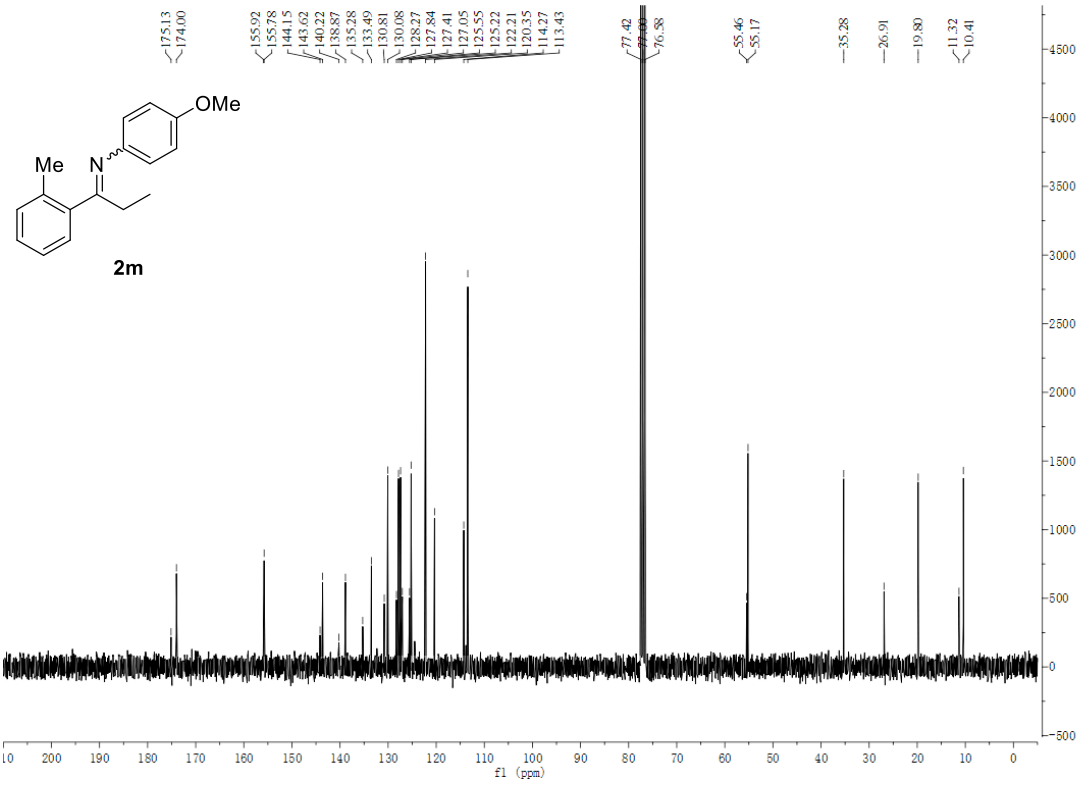

7.81
7.79
7.63
7.62
7.62
7.61
7.60
7.50
7.50
7.48
7.46
7.46
7.45
7.44
7.41
7.41
7.40
7.39
7.38
7.37
7.37
7.37
7.26
2.62
1.56
Me
O
Ph
2k
1.00
2.00
4.01
1.01
6.00
f1 (ppm)

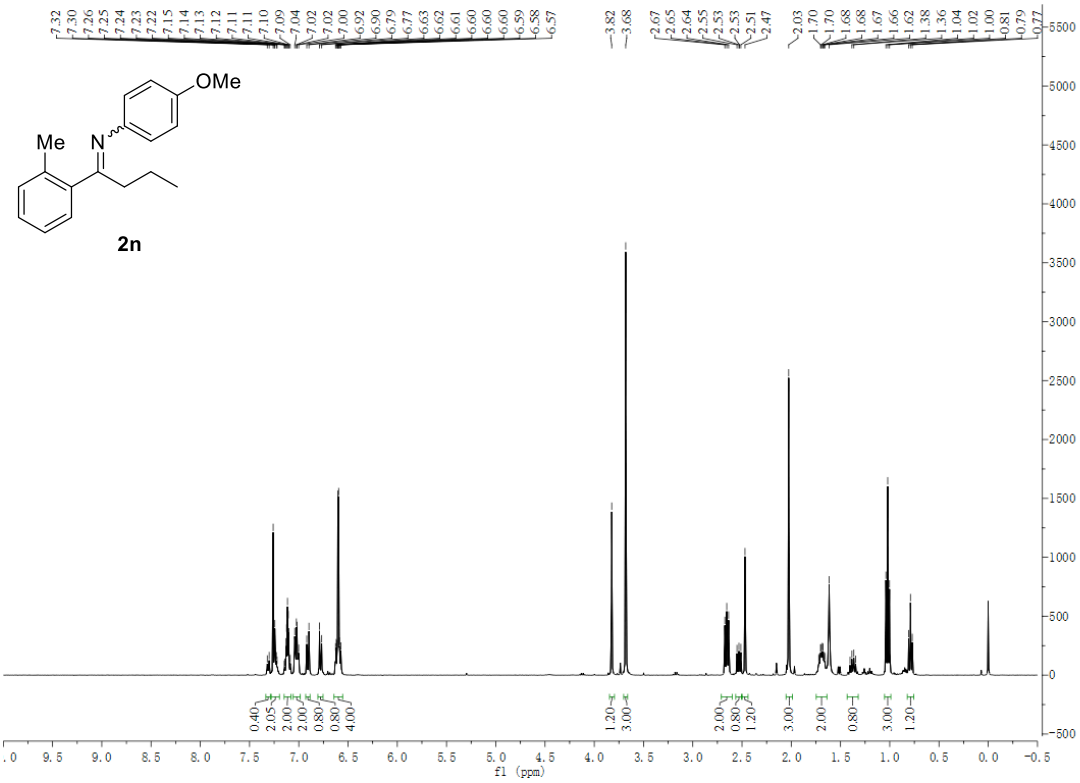

201.07
144.24
139.95
139.30
136.09
130.80
130.26
128.86
128.01
127.21
124.31
77.32
77.00
76.68
29.48
21.96
Me
O
Ph
2k
f1 (ppm)

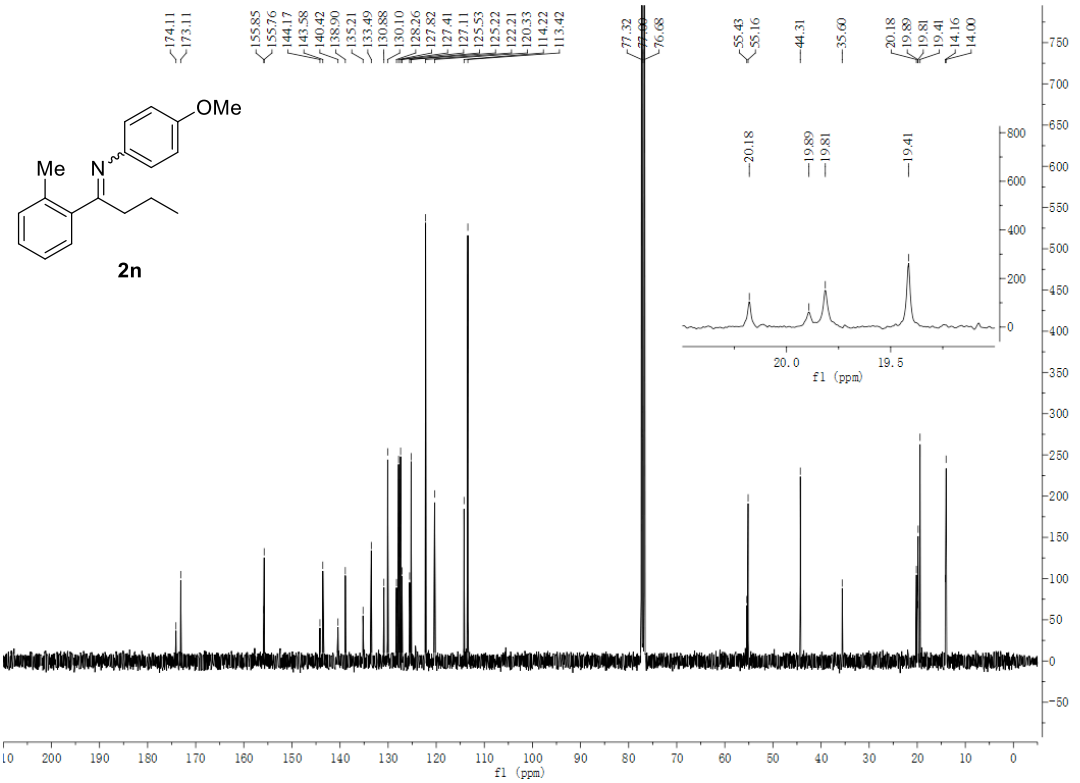

Me
O
MeO
2l
7.77
7.74
7.26
6.77
6.76
6.75
3.85
2.57
2.55
1.58
1.00
2.00
3.00
3.00
3.00
f1 (ppm)

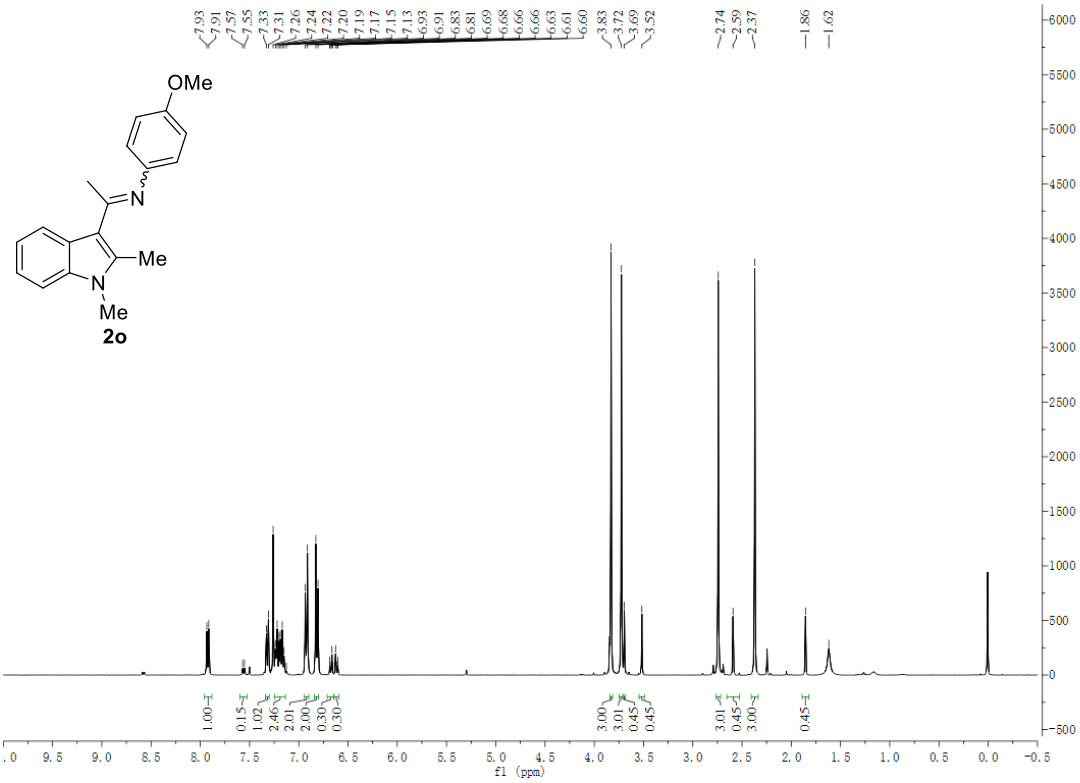

Me
O
MeO
2l
199.47
161.93
142.21
132.50
129.99
117.47
110.57
77.25
76.75
55.28
29.06
22.58
f1 (ppm)

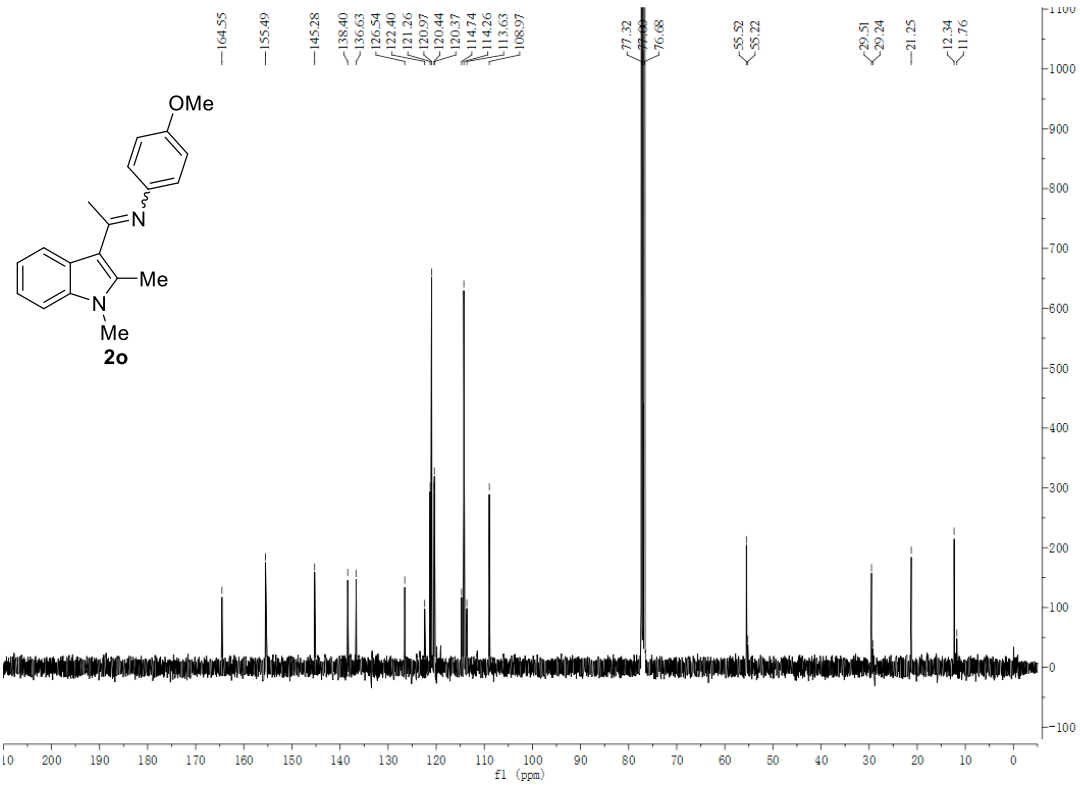

OMe
Me
N
2m
f1 (ppm)

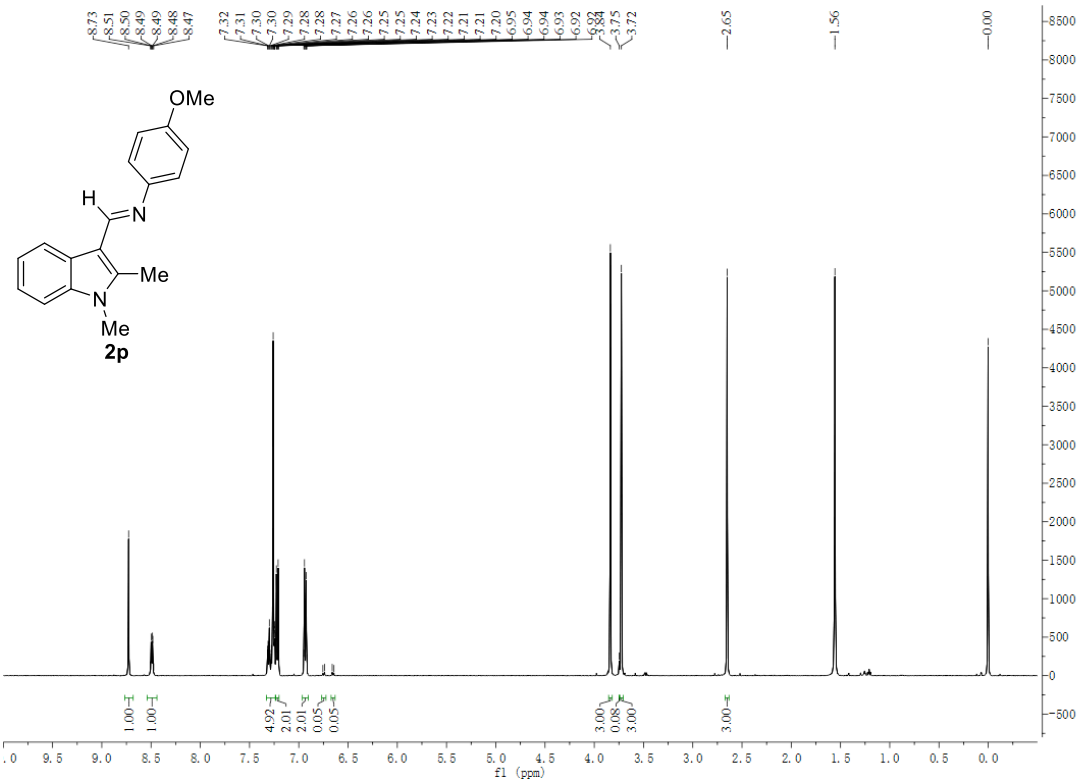

OMe
Me
N
2m
f1 (ppm)

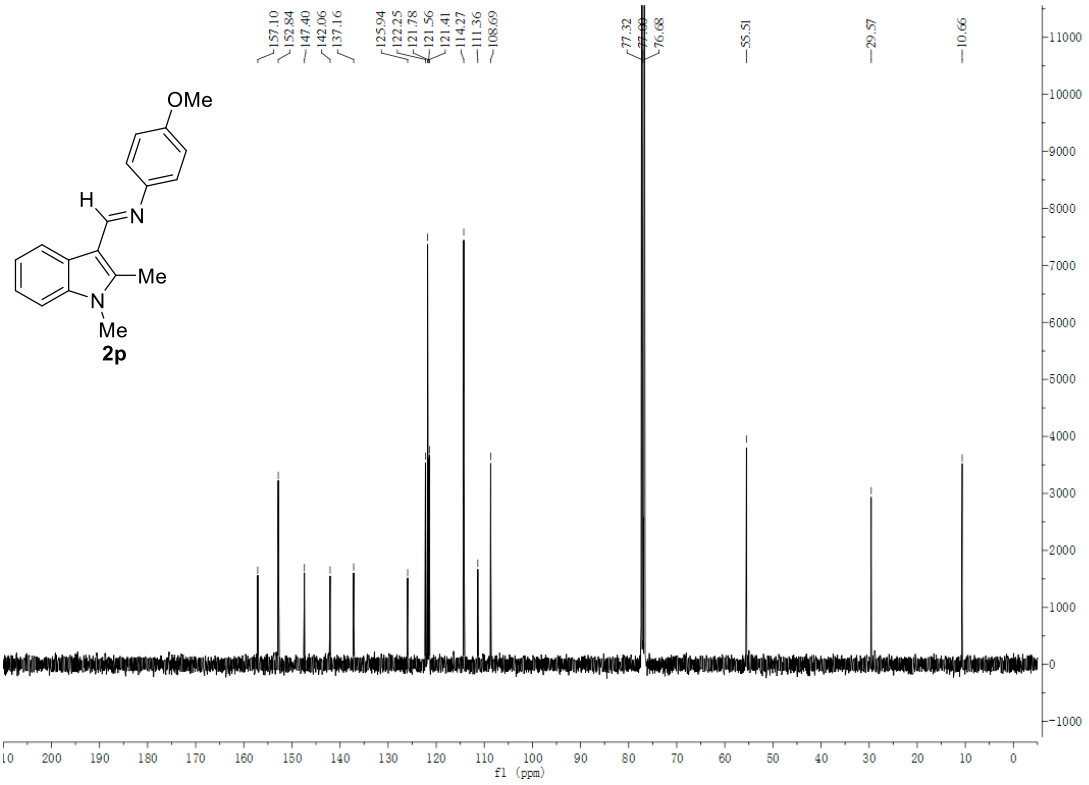

OMe
Me
N
2n
f1 (ppm)

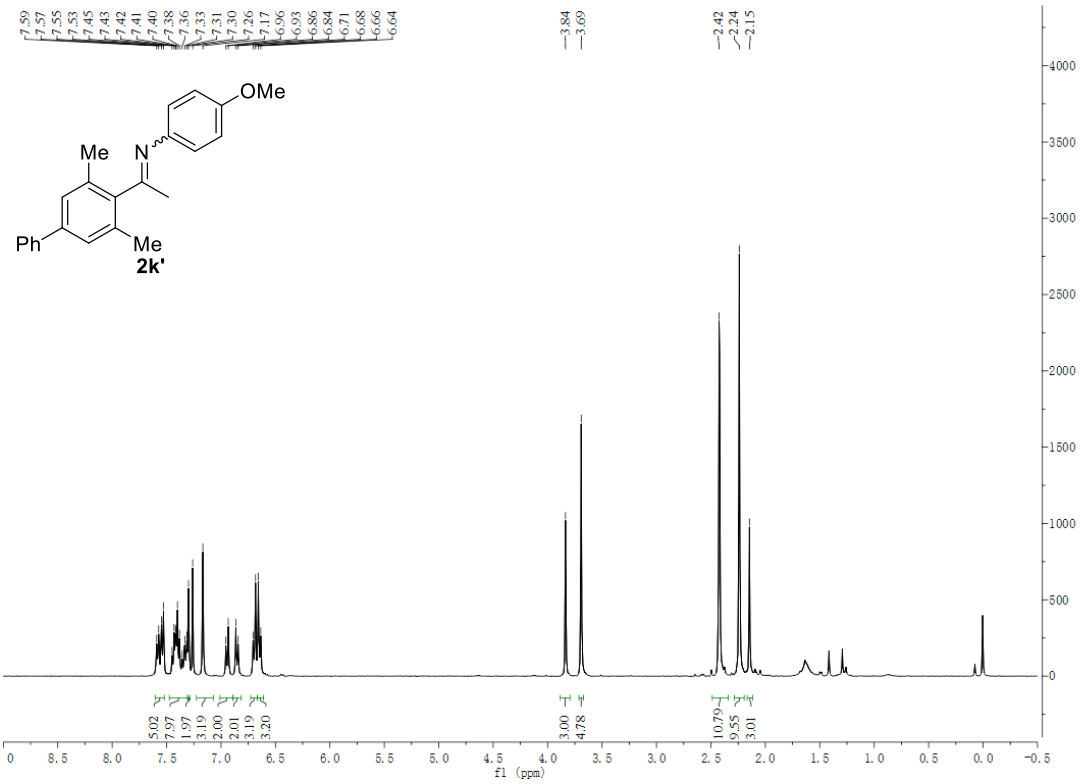

OMe
Me
N
2n
f1 (ppm)


OMe
N
Me
N
Me
2o
7.93
7.91
7.57
7.55
7.33
7.31
7.26
7.24
7.22
7.20
7.19
7.17
7.15
7.13
6.93
6.91
6.83
6.81
6.69
6.68
6.66
6.66
6.63
6.61
6.60
3.83
3.72
3.69
3.52
2.74
2.59
2.37
1.86
1.62
1.00
0.15
1.02
2.46
2.01
2.00
0.30
0.30
3.00
3.01
0.45
0.45
3.01
0.45
3.00
0.45
f1 (ppm)


OMe
N
Me
N
Me
2o
164.55
155.49
145.28
138.40
136.63
126.54
122.40
121.26
120.97
120.44
120.37
114.74
114.26
113.63
108.97
77.32
77.00
76.68
55.52
55.22
29.51
29.24
21.25
12.34
11.76
f1 (ppm)


OMe
H
N
Me
N
Me
2p
f1 (ppm)


OMe
H
N
Me
N
Me
2p
f1 (ppm)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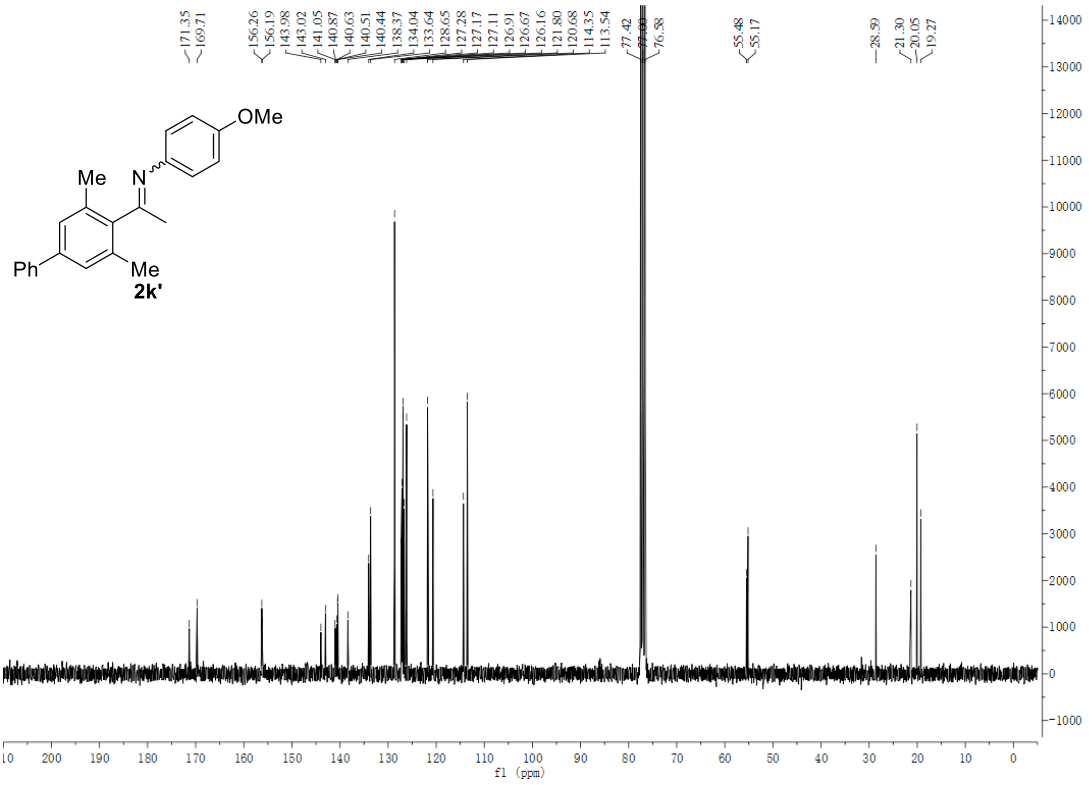
7.41
7.40
7.38
7.36
7.33
7.31
7.30
7.26
7.17
6.96
6.93
6.86
6.84
6.71
6.68
6.66
6.64
3.84
3.69
2.42
2.24
2.15
OMe
Me
N
Ph
Me
2k'
5.02
7.97
1.97
3.19
2.00
2.01
3.19
3.20
3.00
4.78
10.79
9.55
3.01
f1 (ppm)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143.02
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140.87
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140.51
140.44
138.37
134.04
133.64
128.65
127.28
127.17
127.11
126.91
126.67
126.16
121.80
120.68
114.35
113.54
77.42
76.58
55.48
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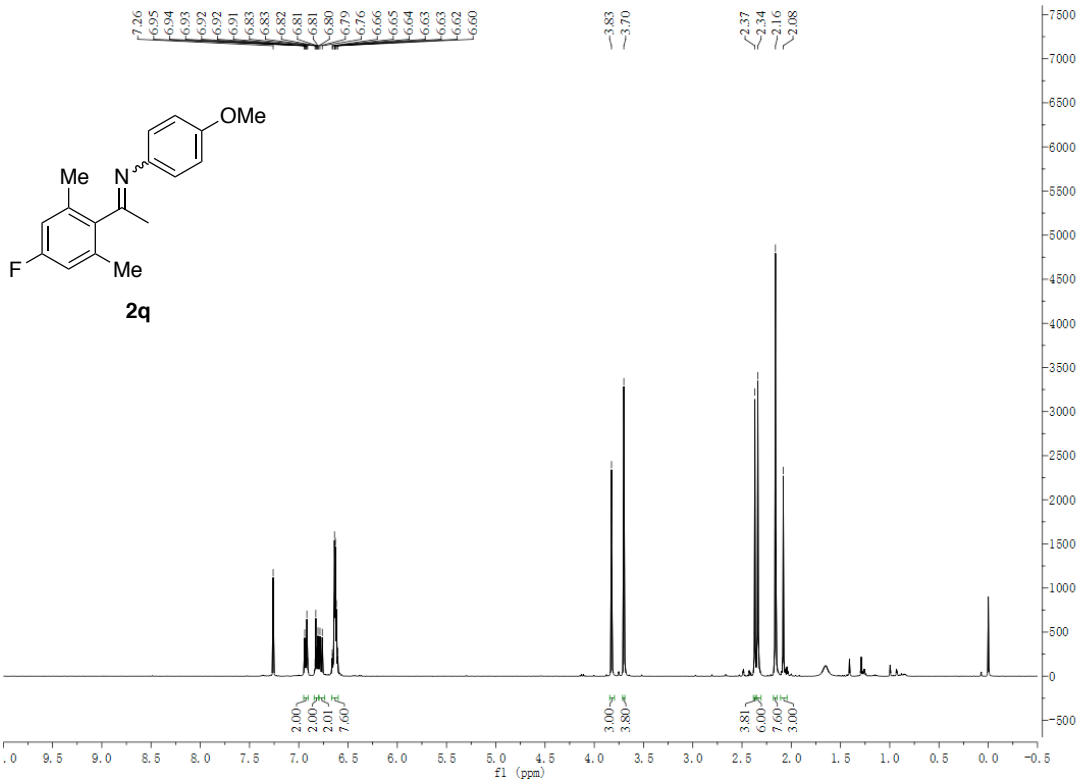
28.59
21.30
20.05
19.27
OMe
Me
N
Ph
Me
2k'
f1 (ppm)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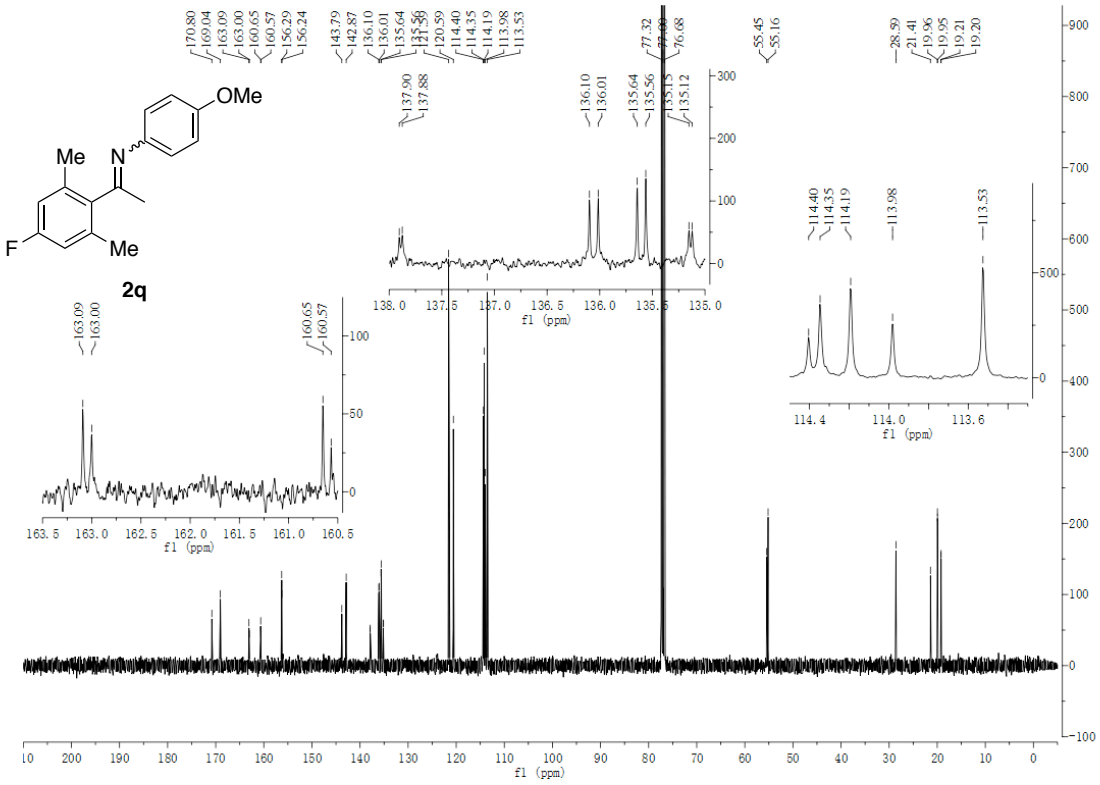
N
F
Me
2q
f1 (ppm)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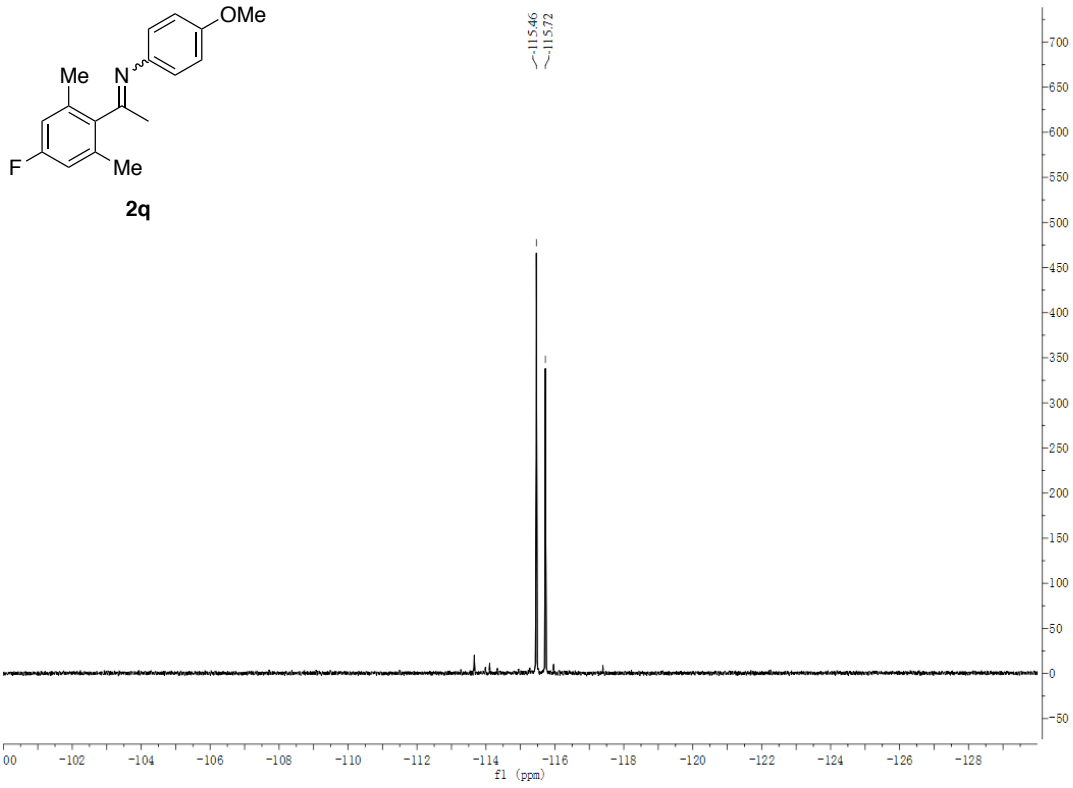
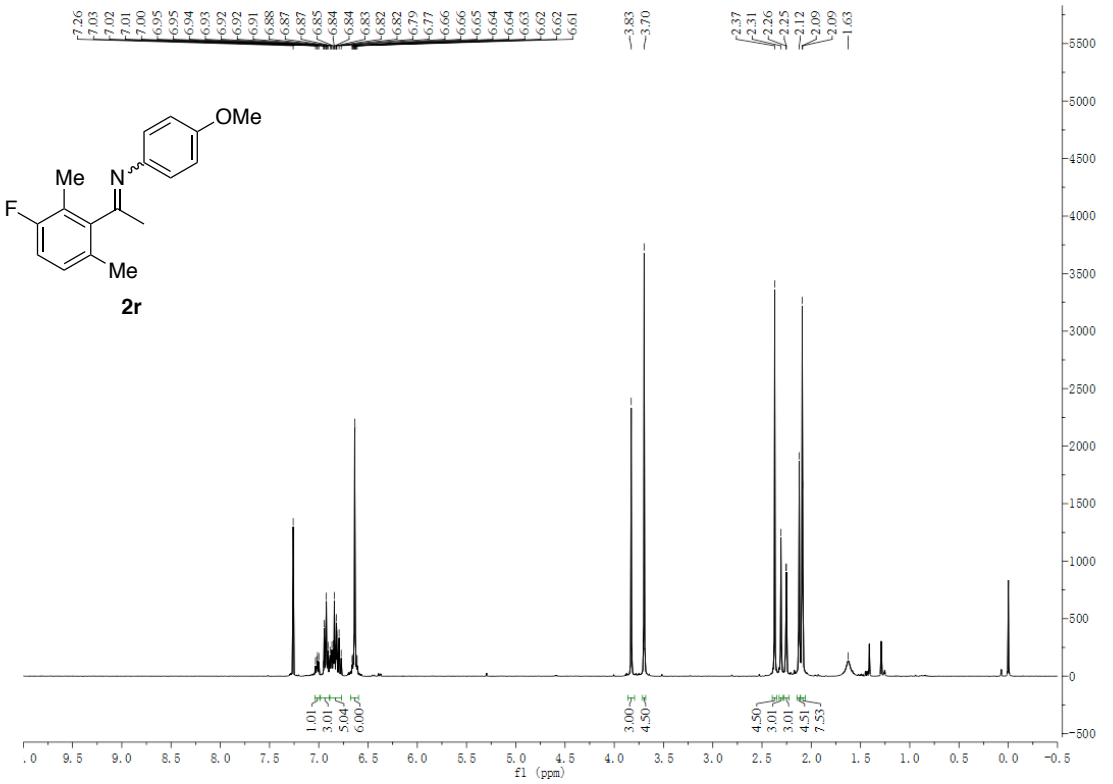
Me
N
F
Me
2q
f1 (ppm)


OMe
Me
N
F
Me
2q
-115.46
-115.72
f1 (ppm)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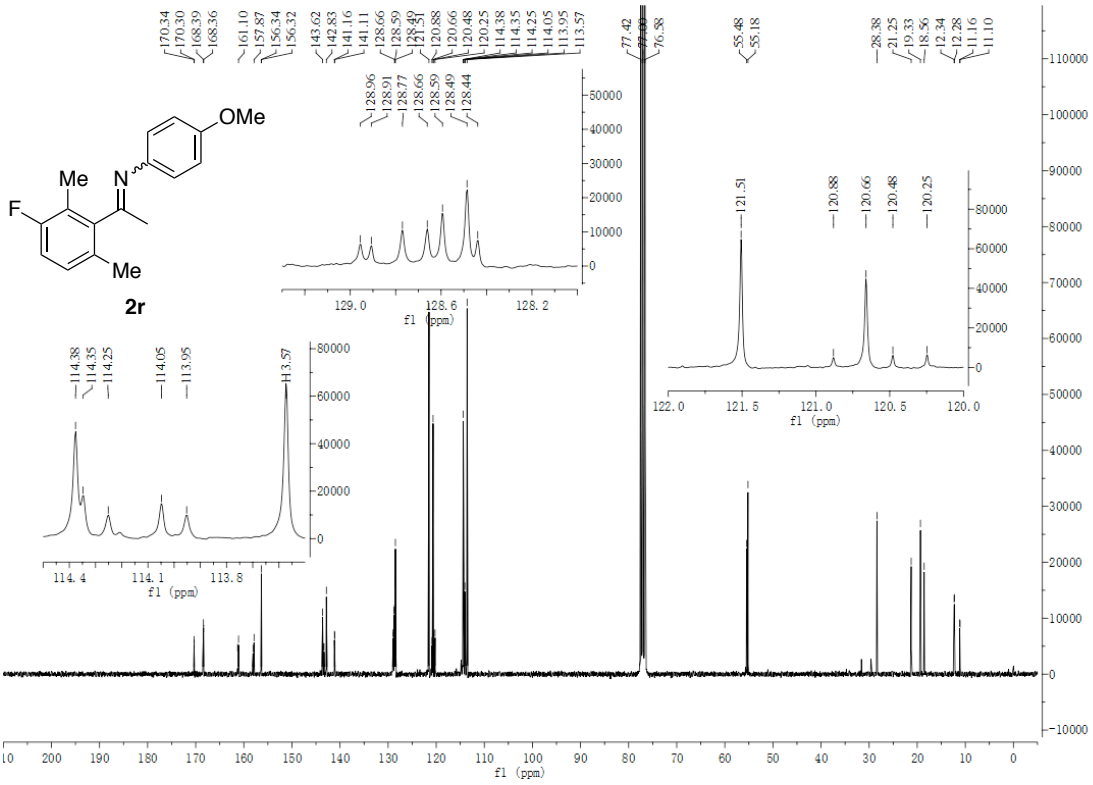
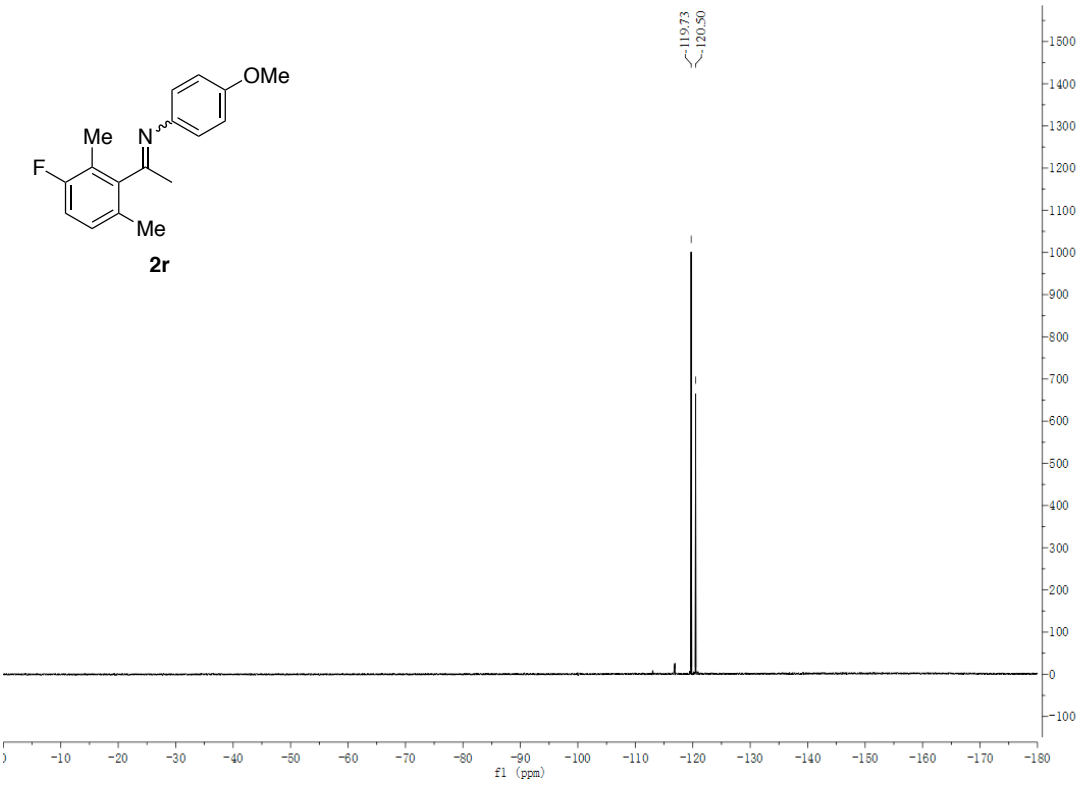
Me
N
F
Me
2r
f1 (ppm)


OMe
Me
N
F
Me
2r
f1 (ppm)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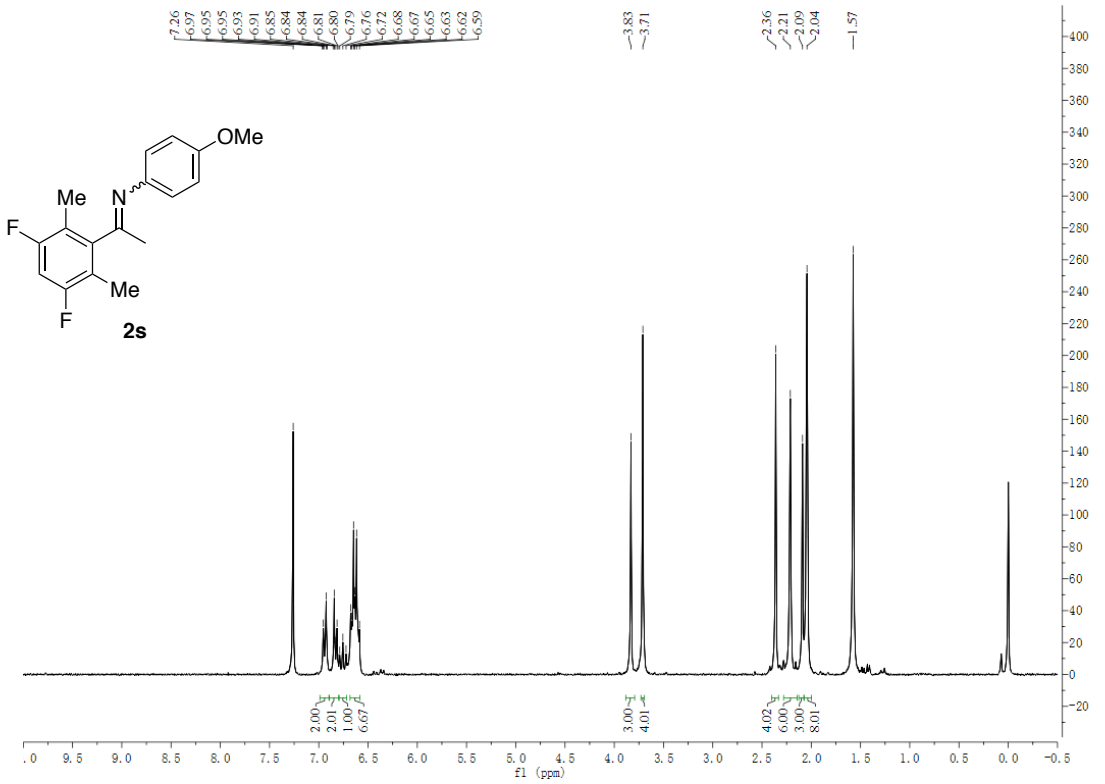
N
F
Me
2r
119.73
120.50
f1 (ppm)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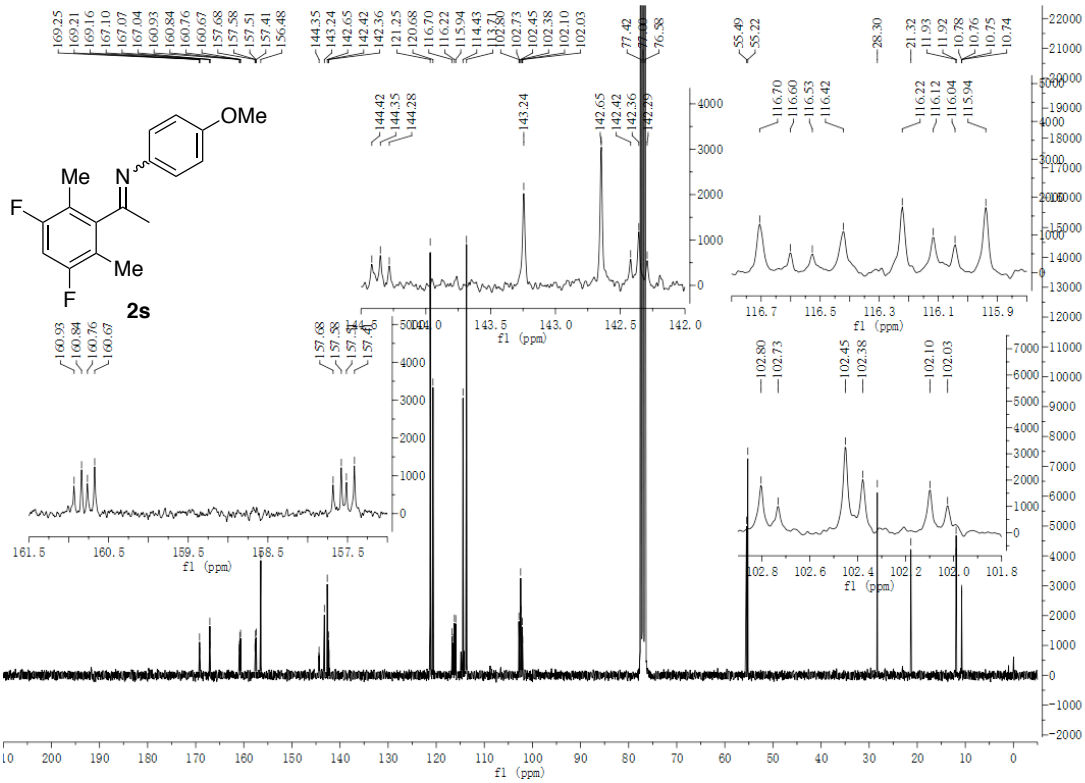
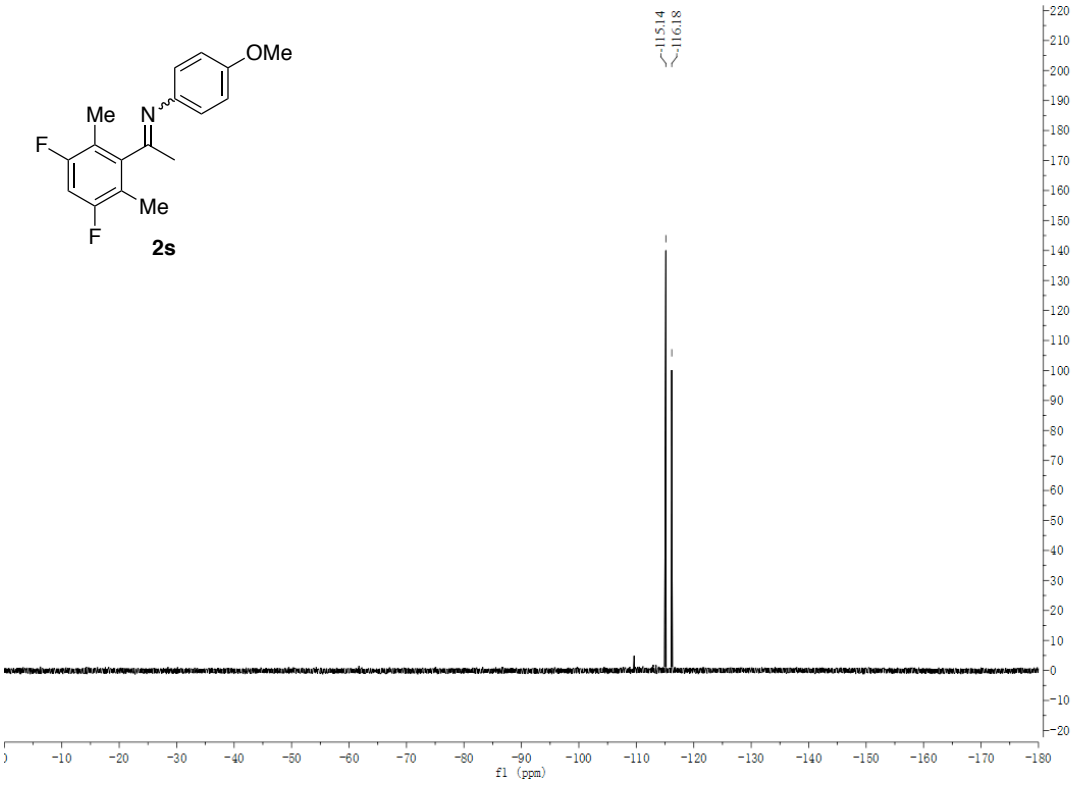
Me
N
F
Me
F
2s
f1 (ppm)


OMe
Me
N
F
Me
F
2s
f1 (ppm)


OMe
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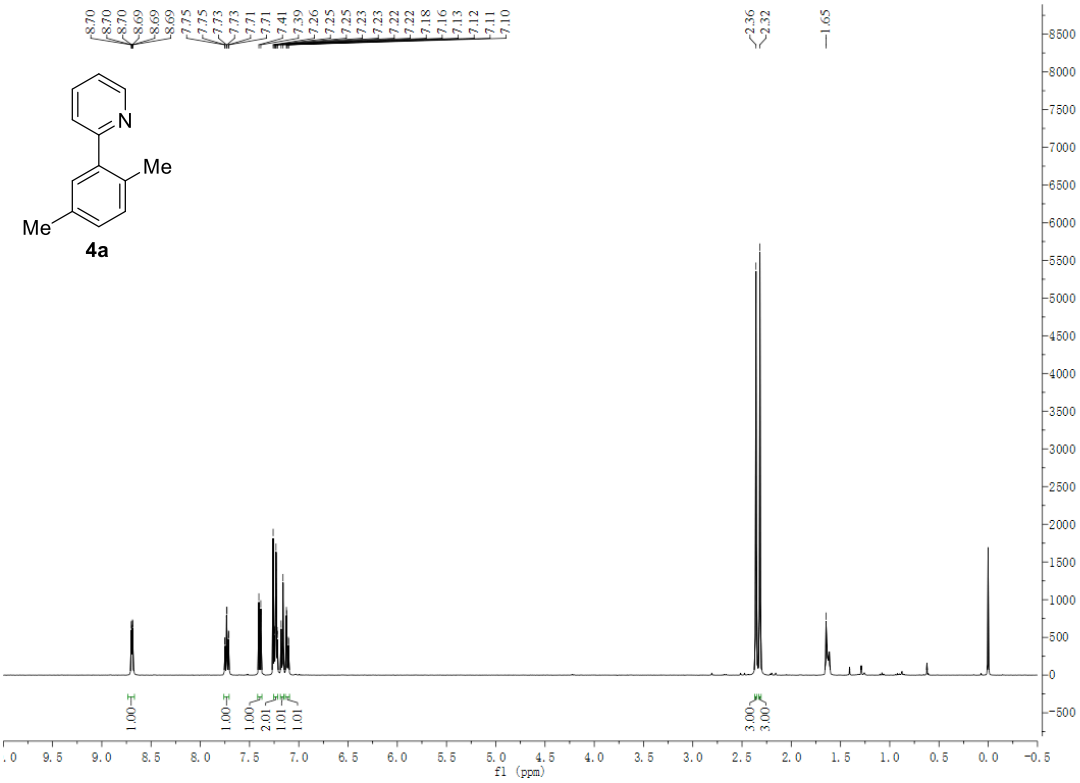
Me
F
Me
F
2s
-115.14
-116.18
f1 (ppm)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8.69
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7.71
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7.41
7.39
7.26
7.25
7.25
7.23
7.23
7.22
7.22
7.18
7.16
7.13
7.12
7.11
7.10
2.36
2.32
1.65
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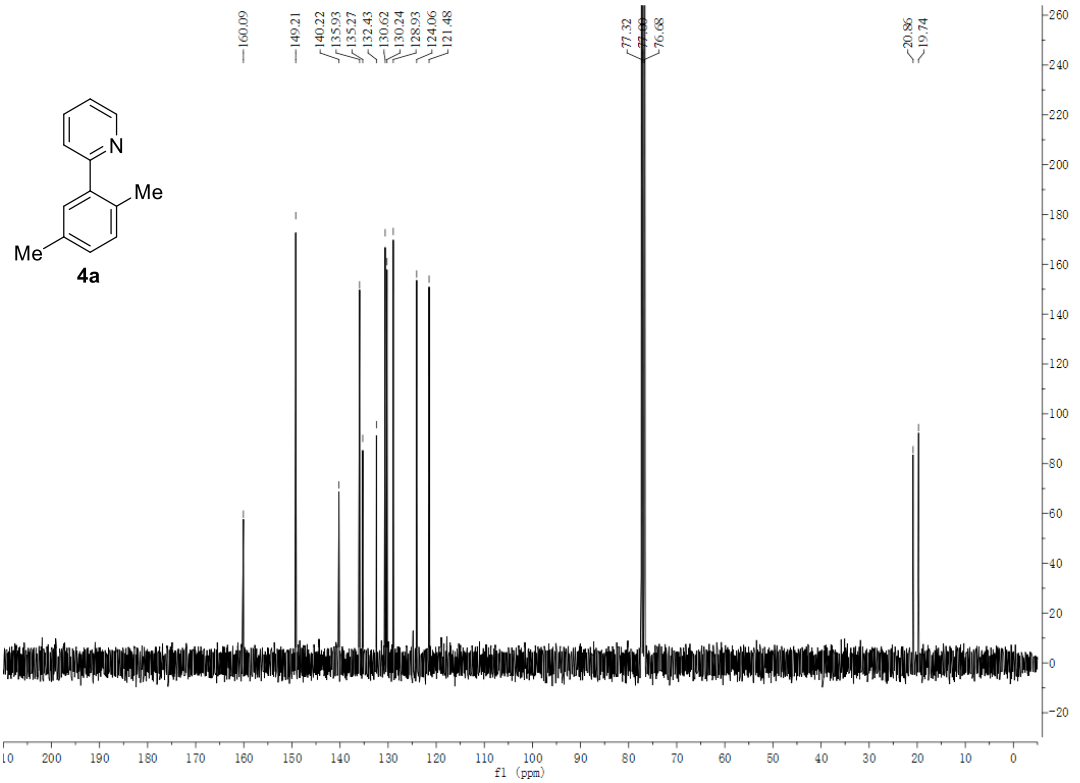
Me
Me
4a
1.00
1.00
1.00
2.01
1.01
1.01
3.00
3.00
f1 (ppm)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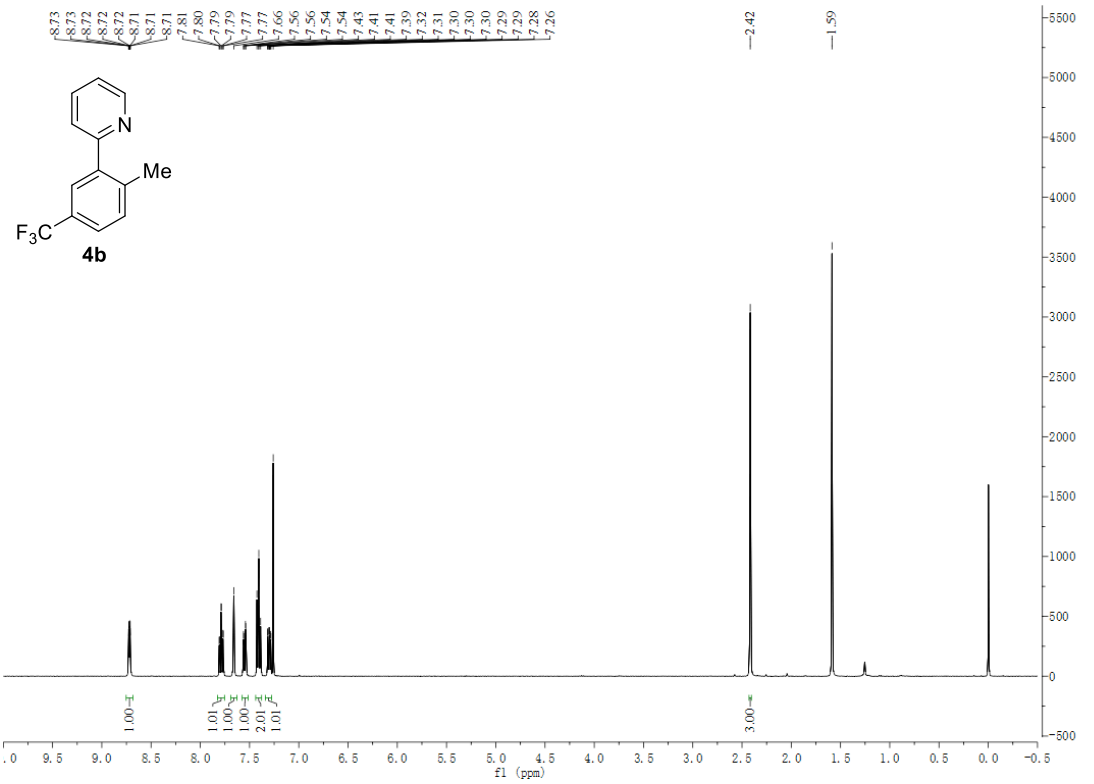
135.27
132.43
130.62
130.24
128.93
124.06
121.48
77.32
77.00
76.68
20.86
19.74
N
Me
Me
4a
f1 (ppm)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7.39
7.32
7.31
7.30
7.30
7.30
7.29
7.29
7.28
7.26
2.42
1.59
N
Me
F3C
4b
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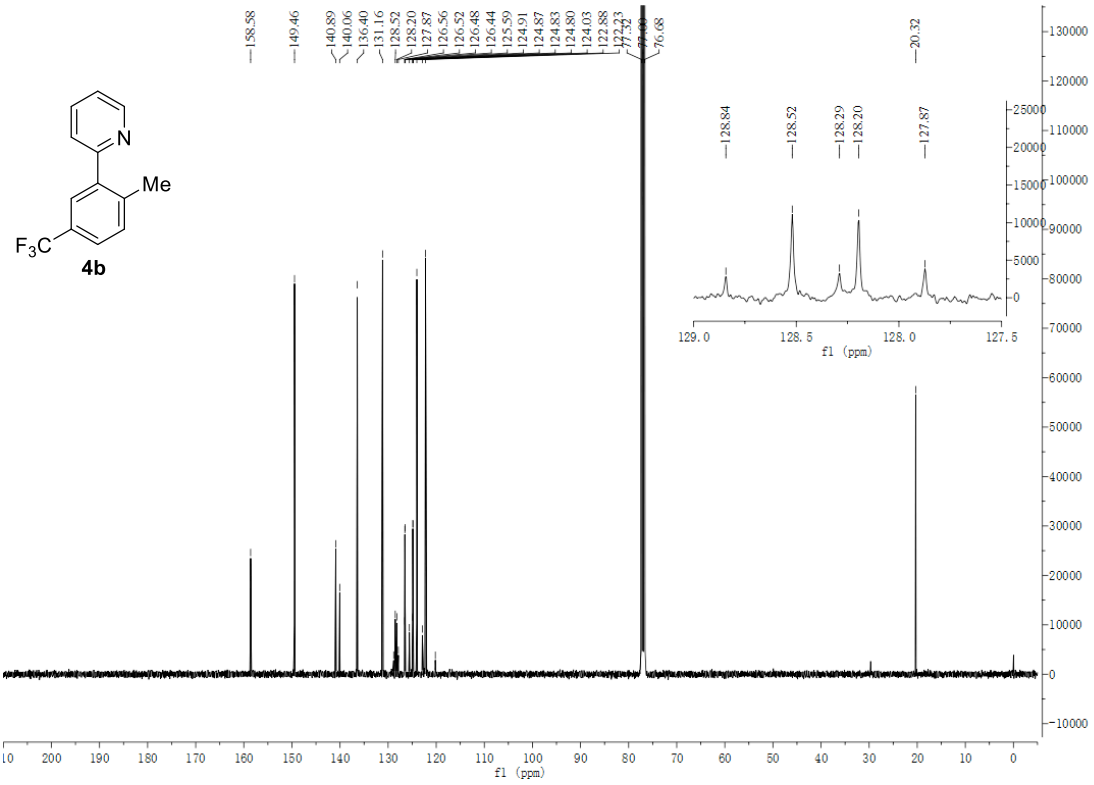
1.01
1.00
1.00
2.01
1.01
3.00
f1 (ppm)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128.20
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126.56
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126.48
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124.91
124.87
124.83
124.80
124.03
122.88
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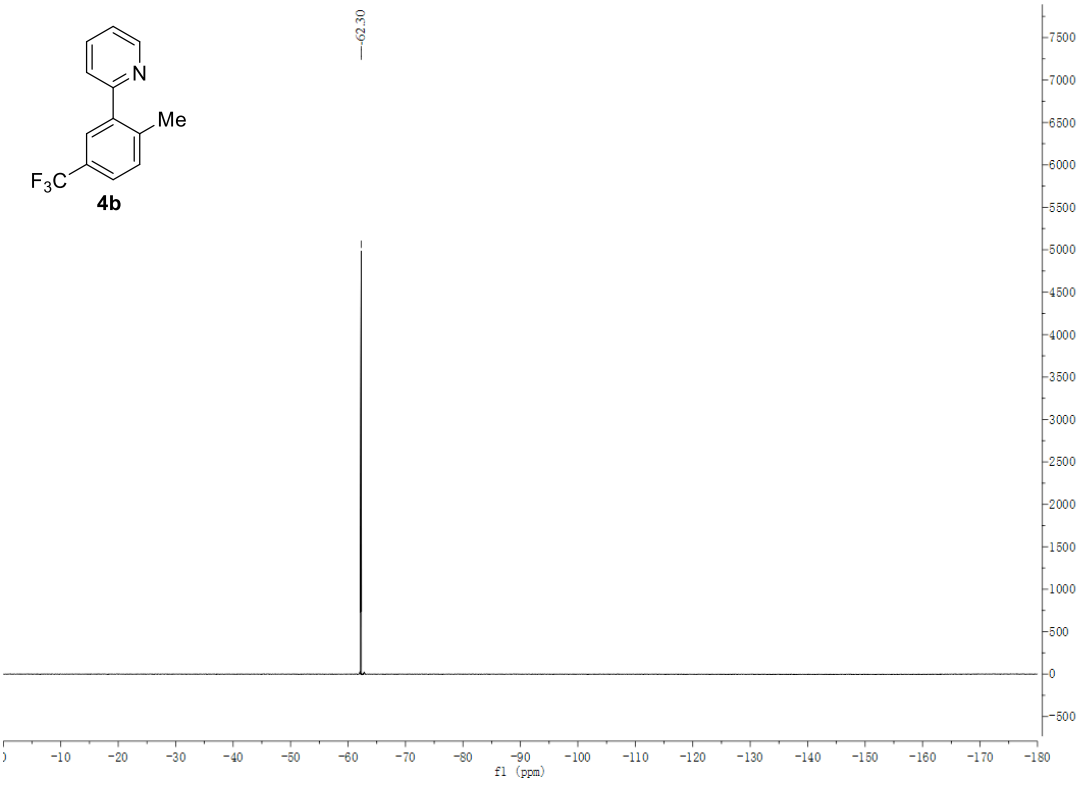
128.52
128.29
128.20
127.87
N
Me
F3C
4b
f1 (ppm)


N
Me
F3C
4b
-62.30
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-10
-20
-30
-40
-50
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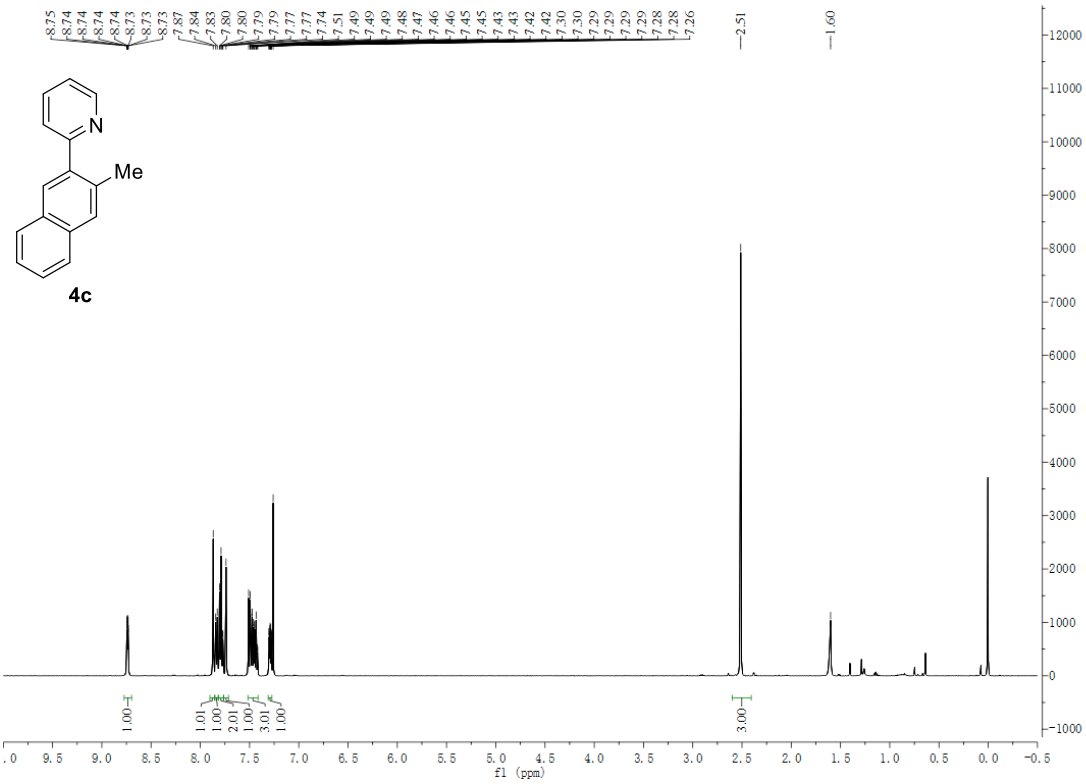
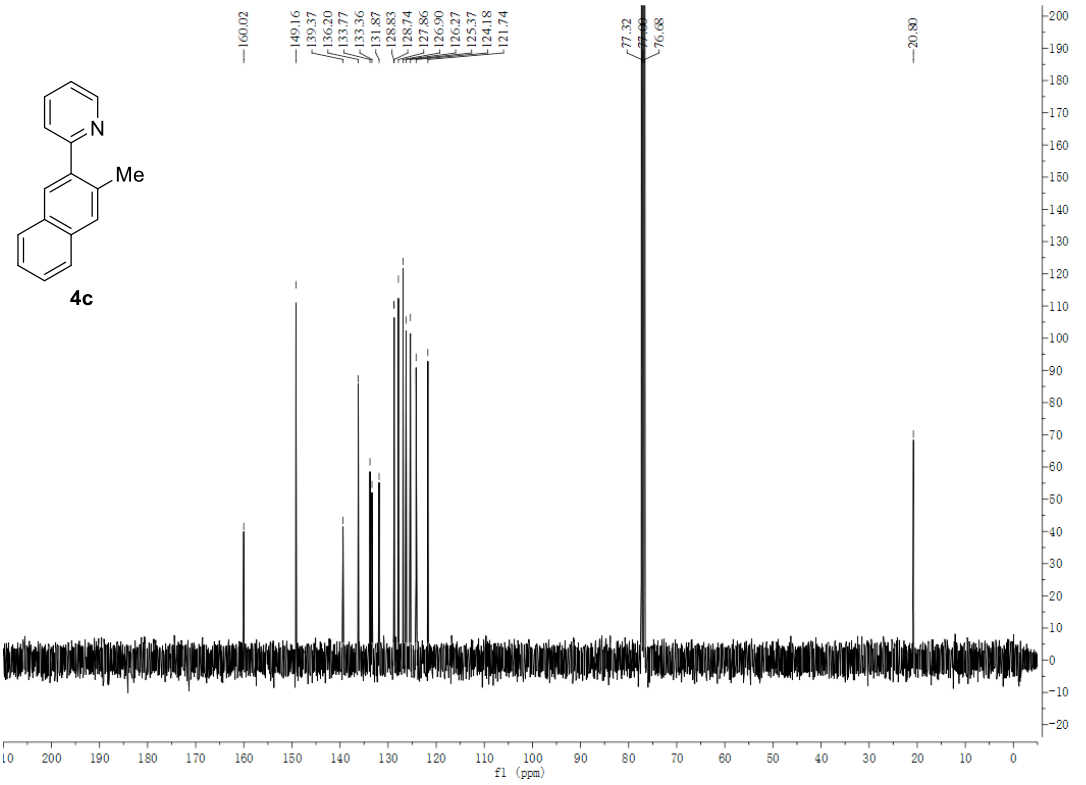
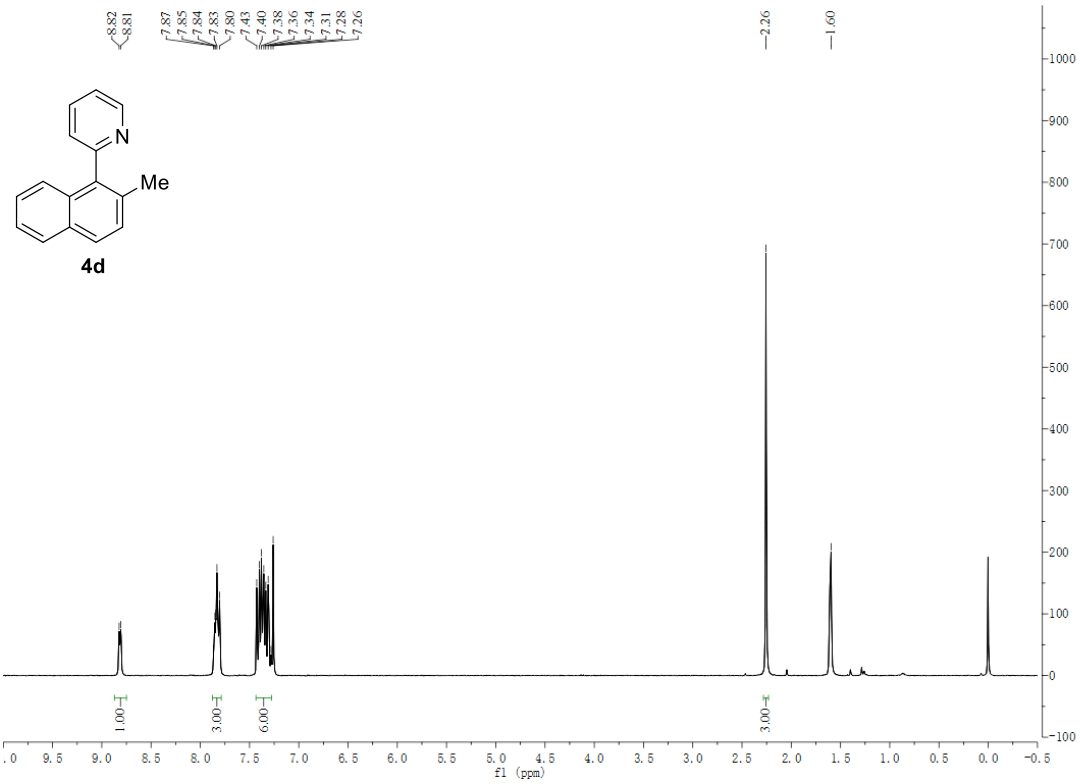
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)


N
Me
4c
f1 (ppm)


N
Me
4c
f1 (ppm)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7.36
7.34
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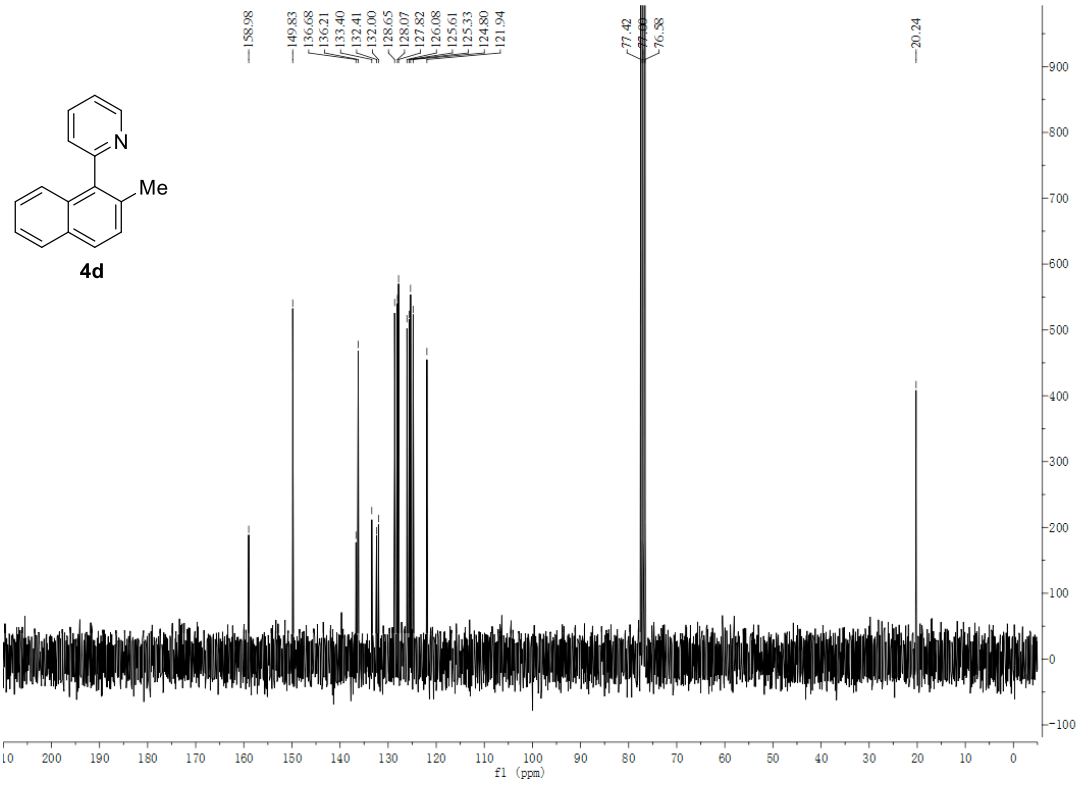
2.26
1.60
N
Me
4d
1.00
3.00
6.00
3.00
f1 (ppm)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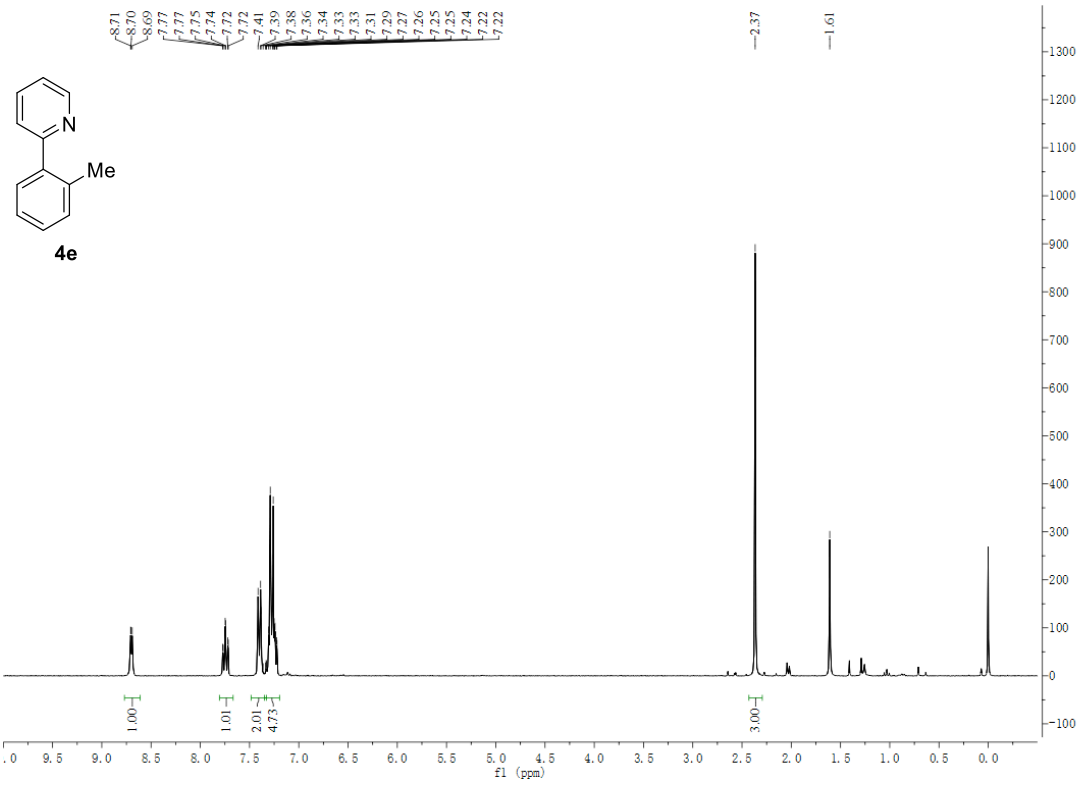
121.94
77.42
77.00
76.58
20.24
N
Me
4d
f1 (ppm)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7.33
7.31
7.29
7.27
7.26
7.25
7.25
7.24
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7.22
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1.61
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Me
4e
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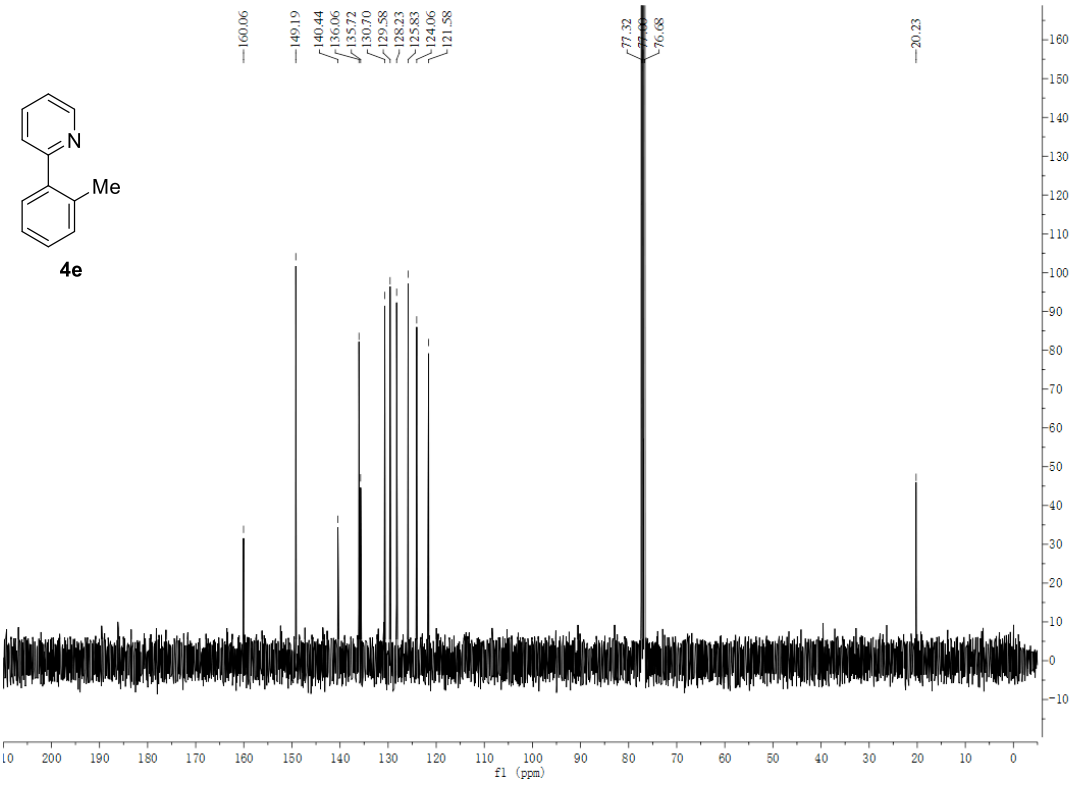
1.01
2.01
4.73
3.00
f1 (ppm)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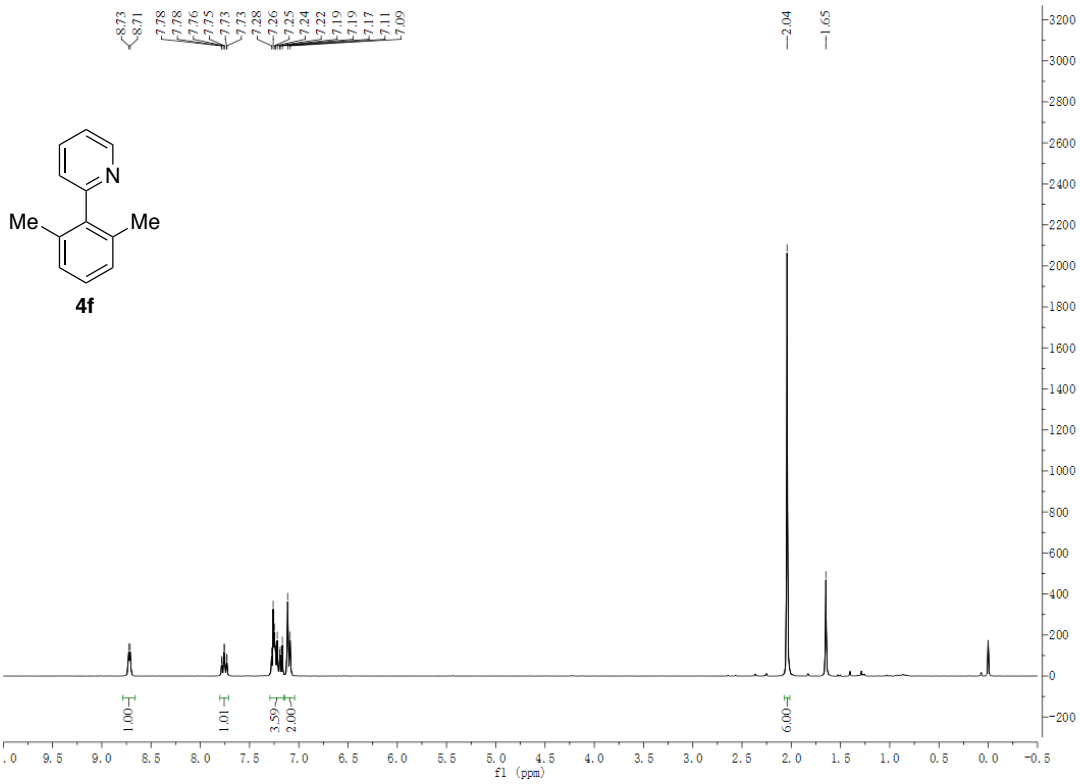
77.32
77.00
76.68
20.23
N
Me
4e
f1 (ppm)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7.25
7.24
7.22
7.19
7.19
7.17
7.11
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N
Me
Me
4f
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1.01
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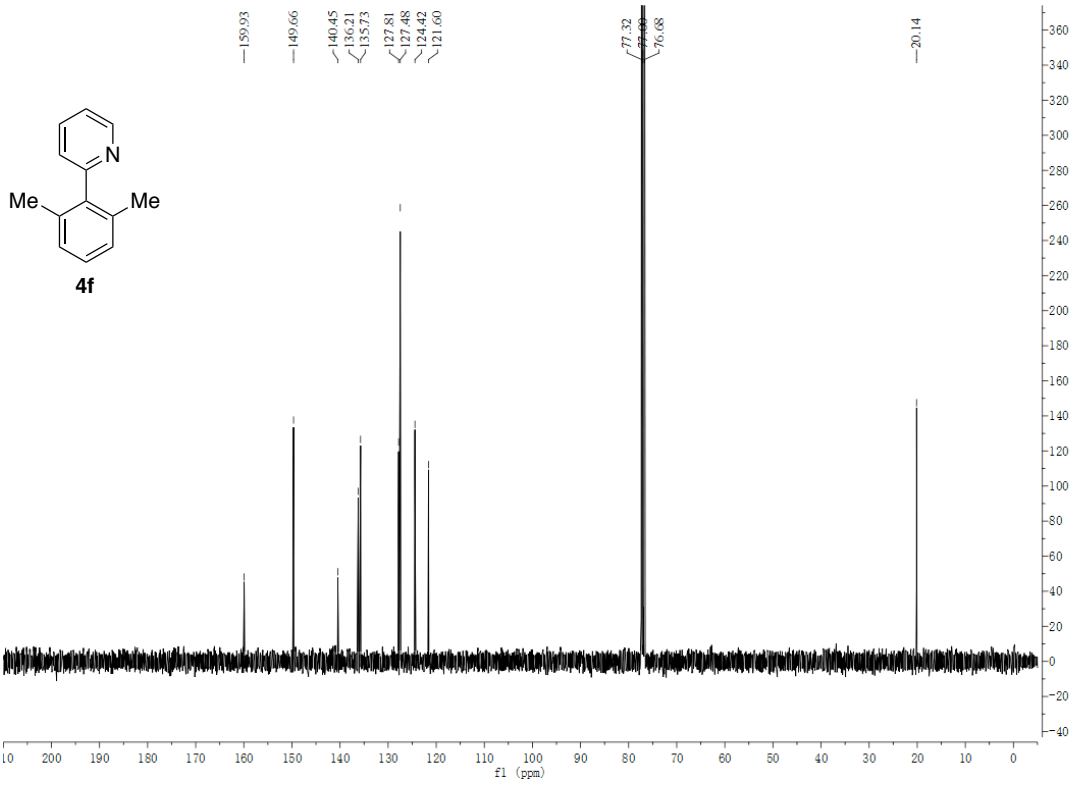
2.00
6.00
f1 (ppm)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20.14
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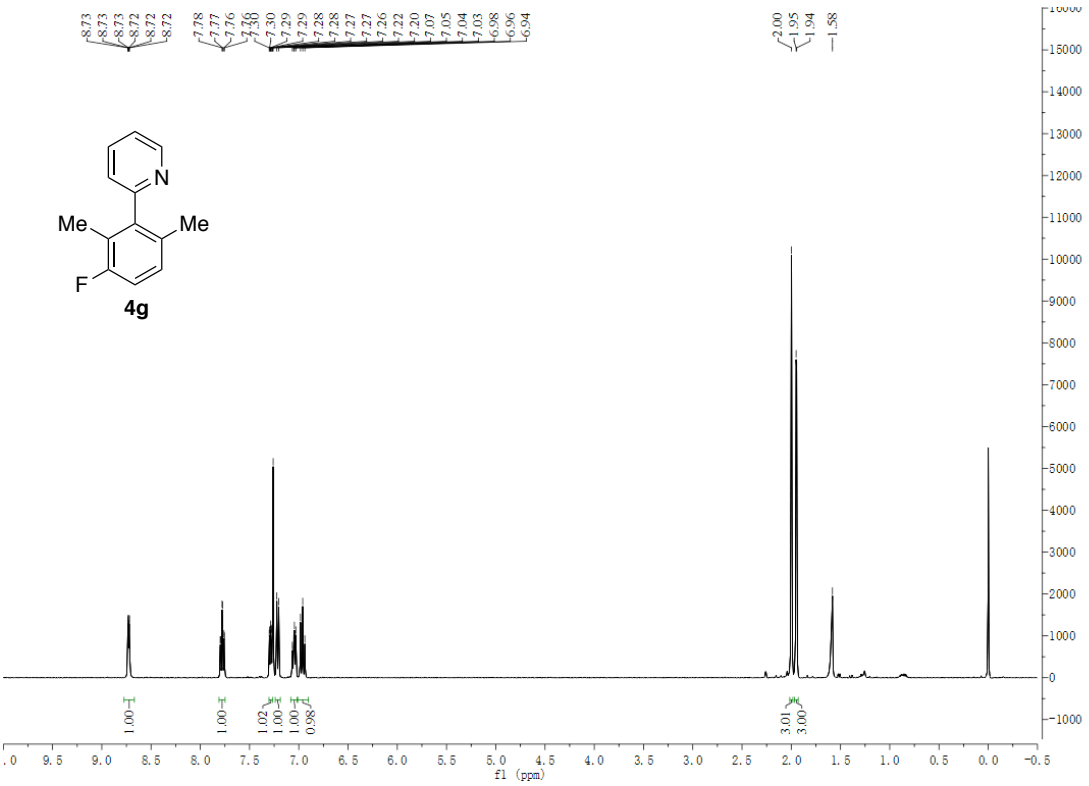
Me
Me
4f
f1 (ppm)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7.29
7.28
7.28
7.27
7.27
7.26
7.22
7.20
7.07
7.05
7.04
7.03
6.98
6.96
6.94
2.00
1.95
1.94
1.58
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Me
Me
F
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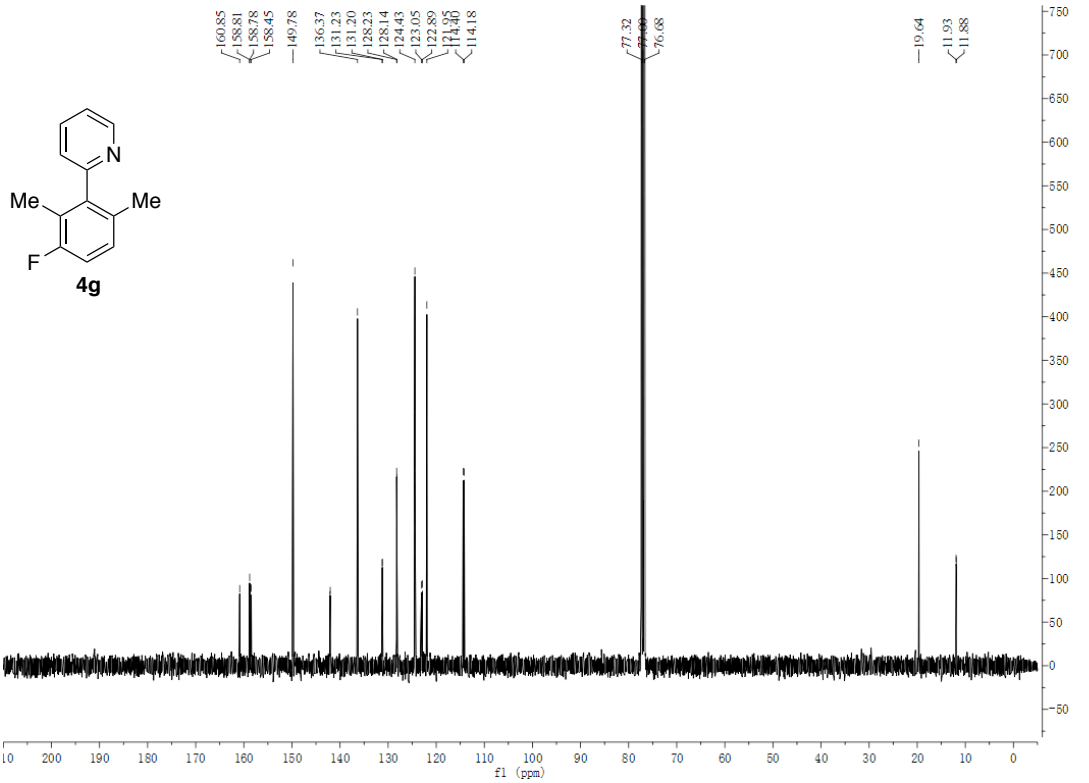
1.00
1.00
0.98
3.01
3.00
f1 (ppm)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122.89
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77.00
76.68
19.64
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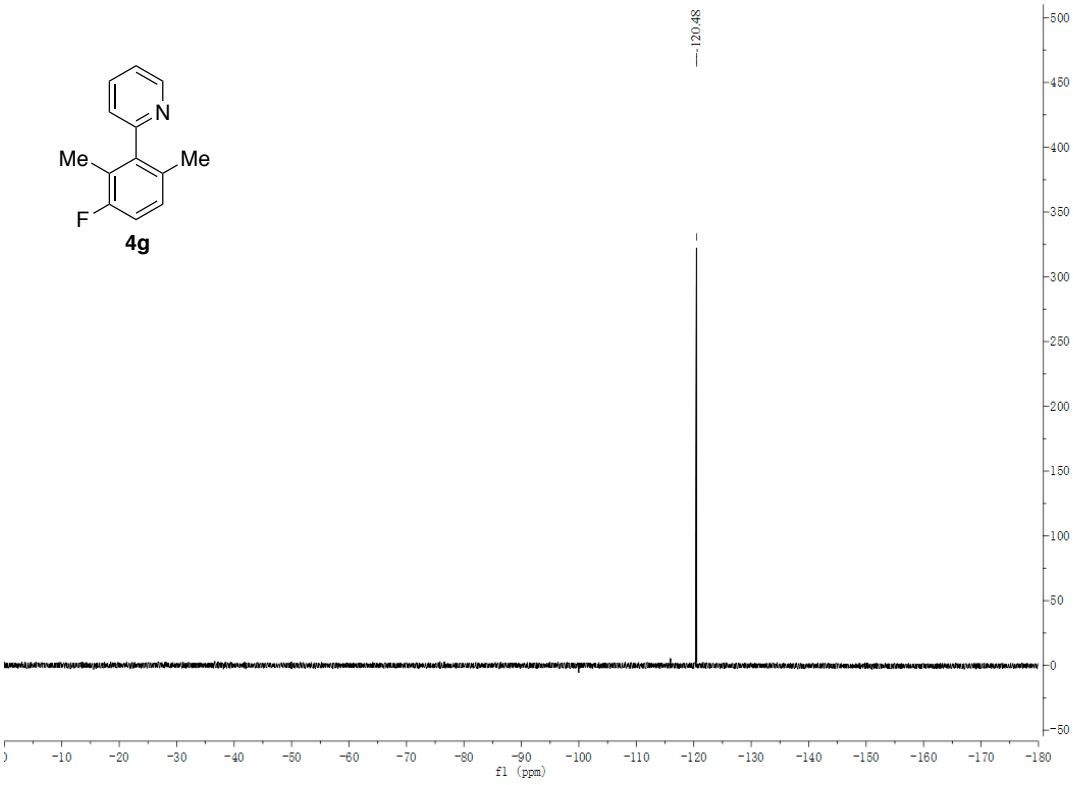
N
Me
Me
F
4g
f1 (ppm)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Me
F
4g
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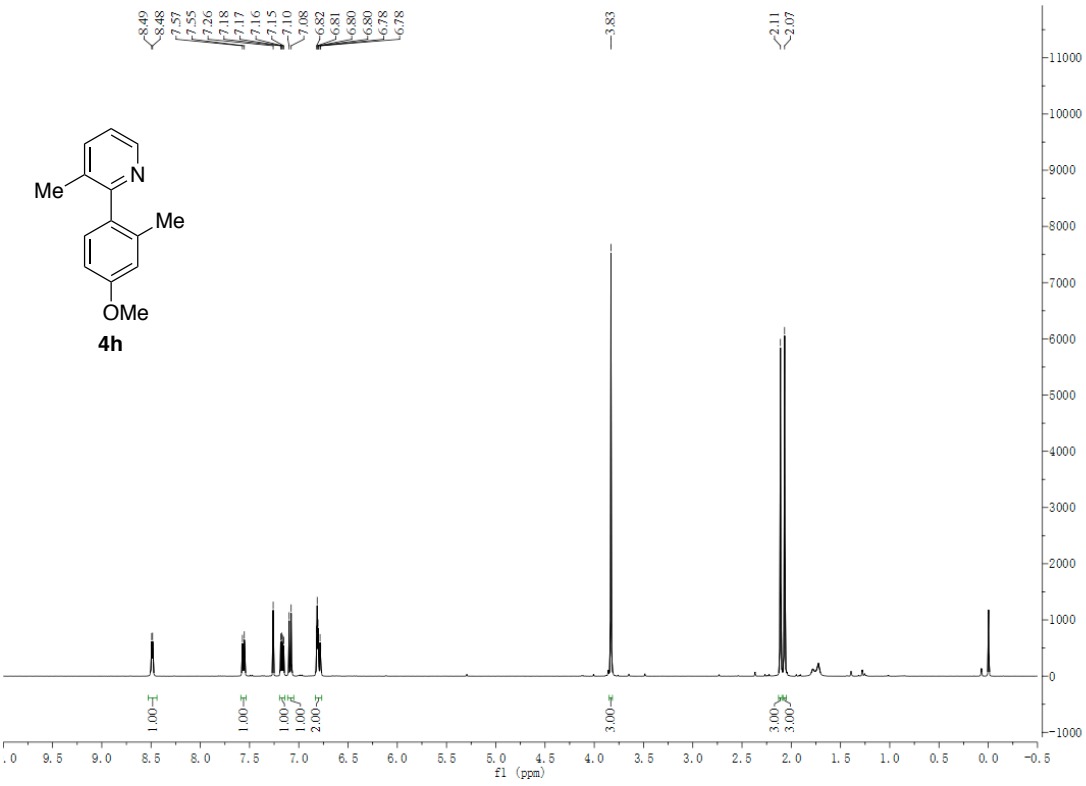
f1 (ppm)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6.81
6.80
6.80
6.78
6.78
3.83
2.11
2.07
Me
N
Me
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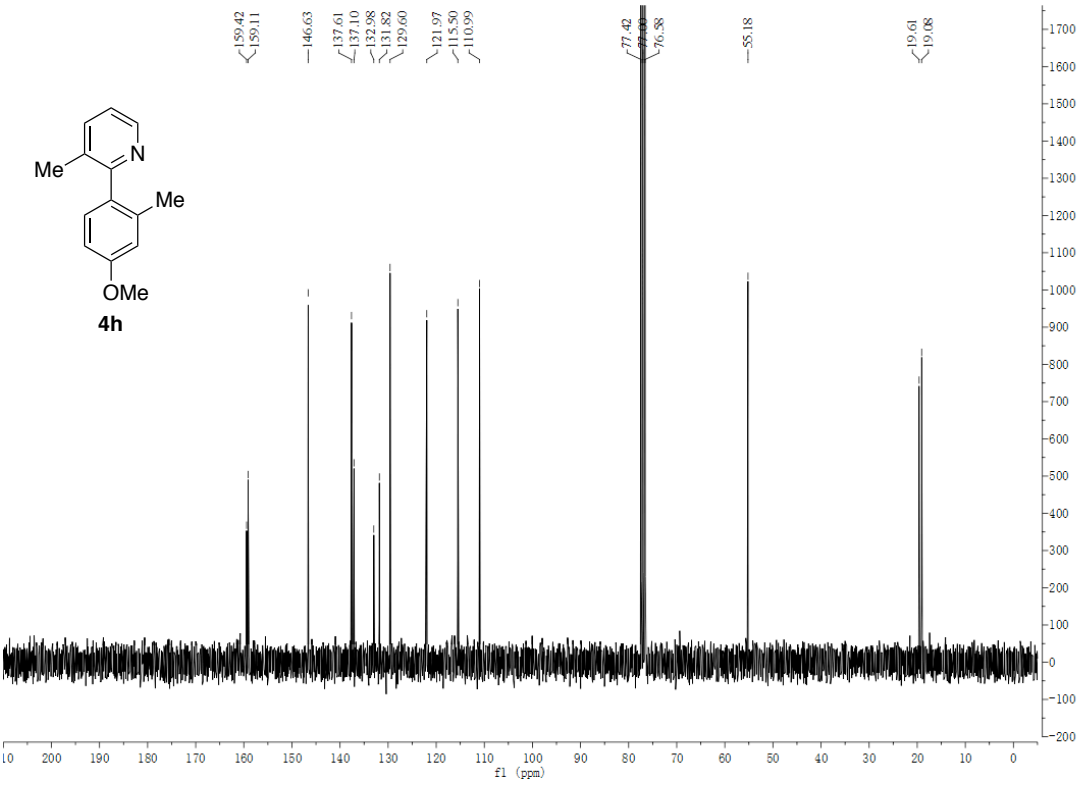
1.00
1.00
1.00
2.00
3.00
3.00
3.00
f1 (ppm)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115.50
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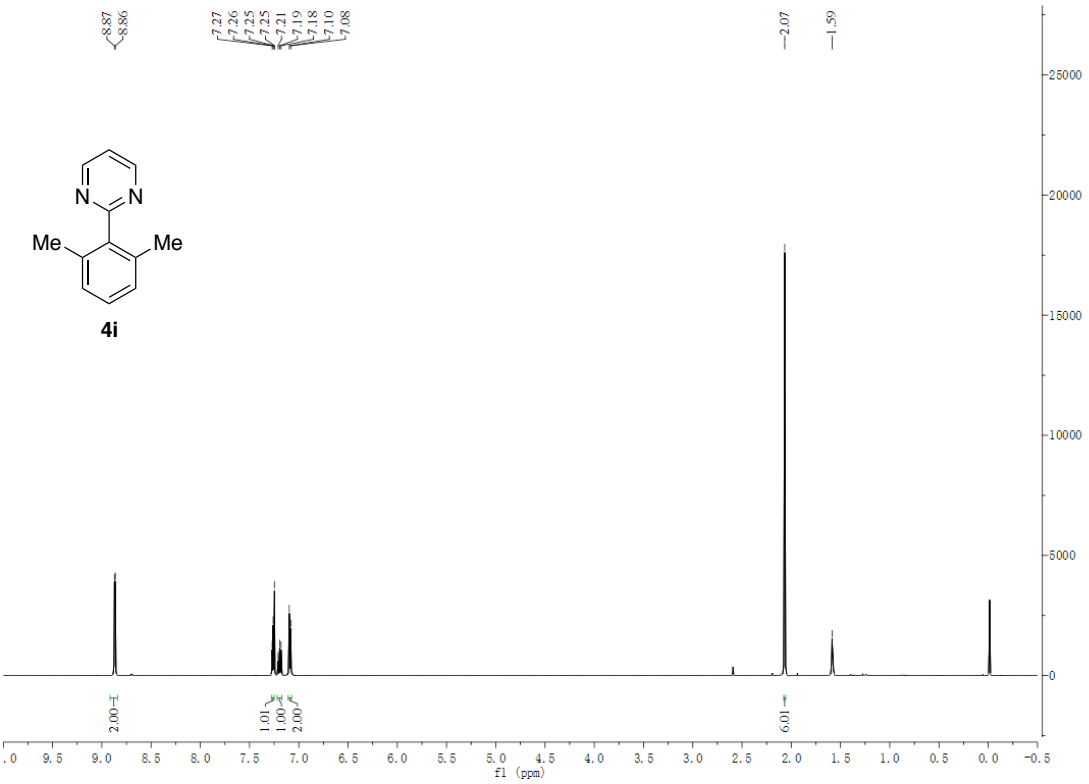
77.00
76.58
55.18
19.61
19.08
Me
N
Me
OMe
4h
f1 (ppm)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7.10
7.08
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N
N
Me
Me
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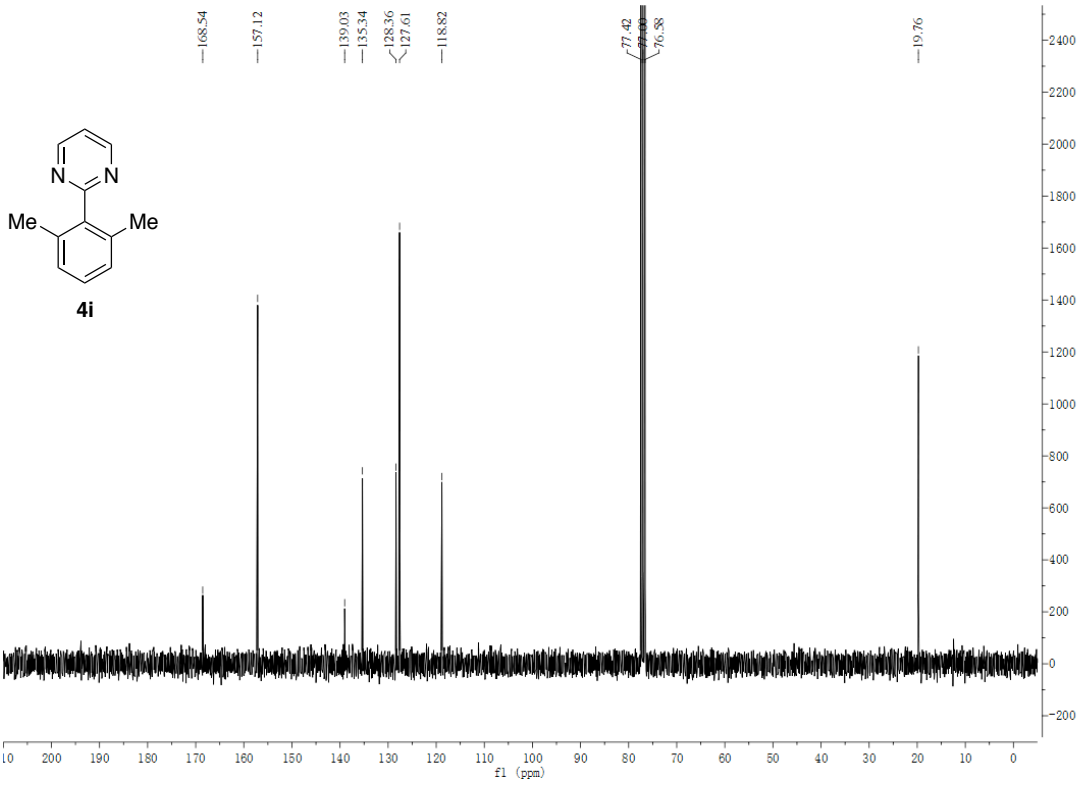
2.00
1.01
1.00
2.00
6.01
f1 (ppm)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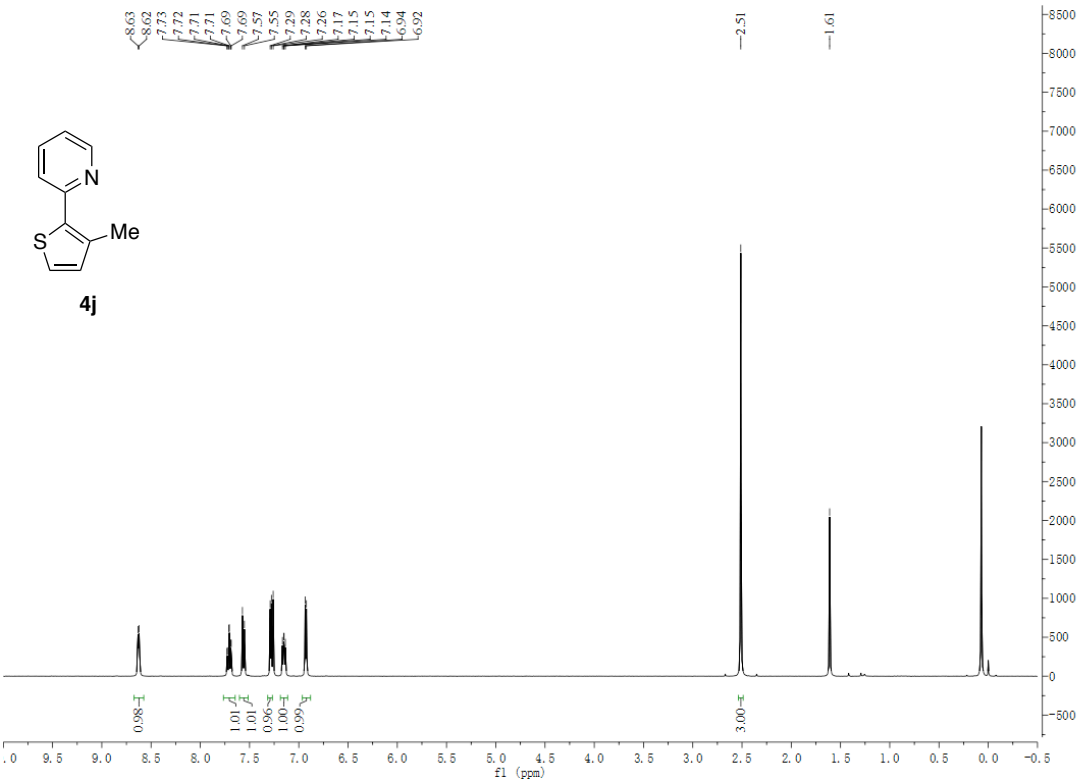
77.00
76.58
19.76
N
N
Me
Me
4i
f1 (ppm)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7.71
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7.69
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7.55
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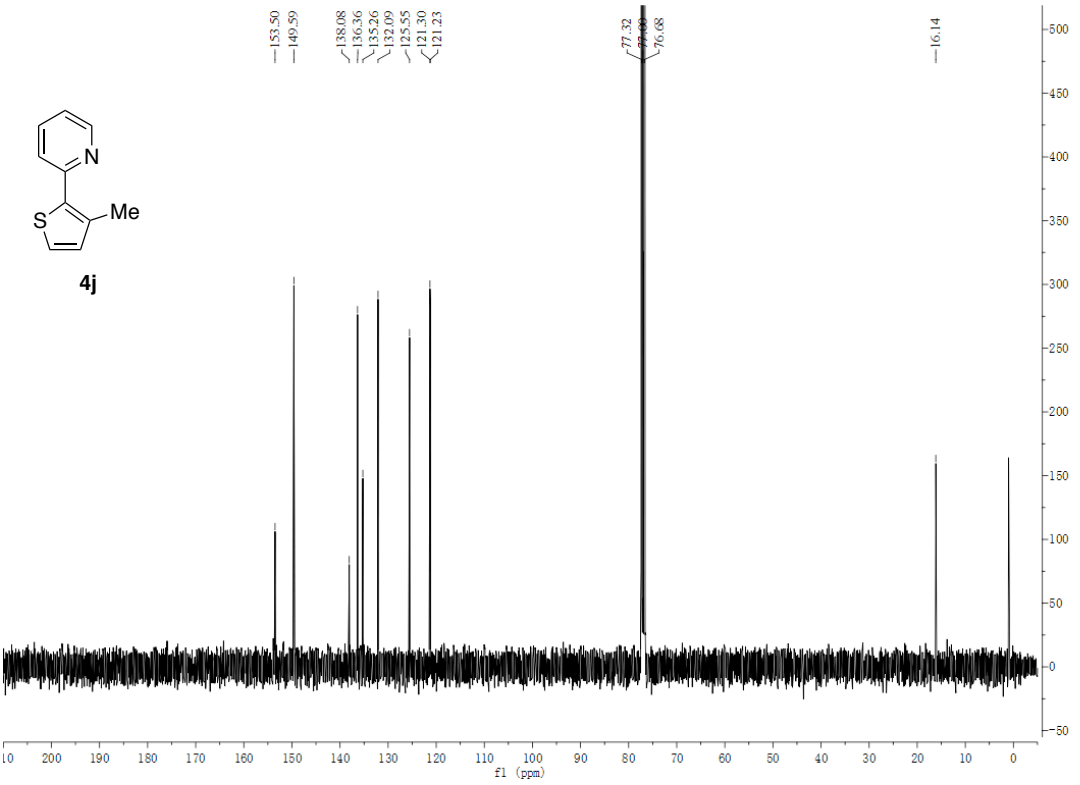
7.28
7.26
7.17
7.15
7.15
7.14
6.94
6.92
2.51
1.61
N
S
Me
4j
0.98
1.01
1.01
0.96
1.00
0.99
3.00
f1 (ppm)


153.50
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135.26
132.09
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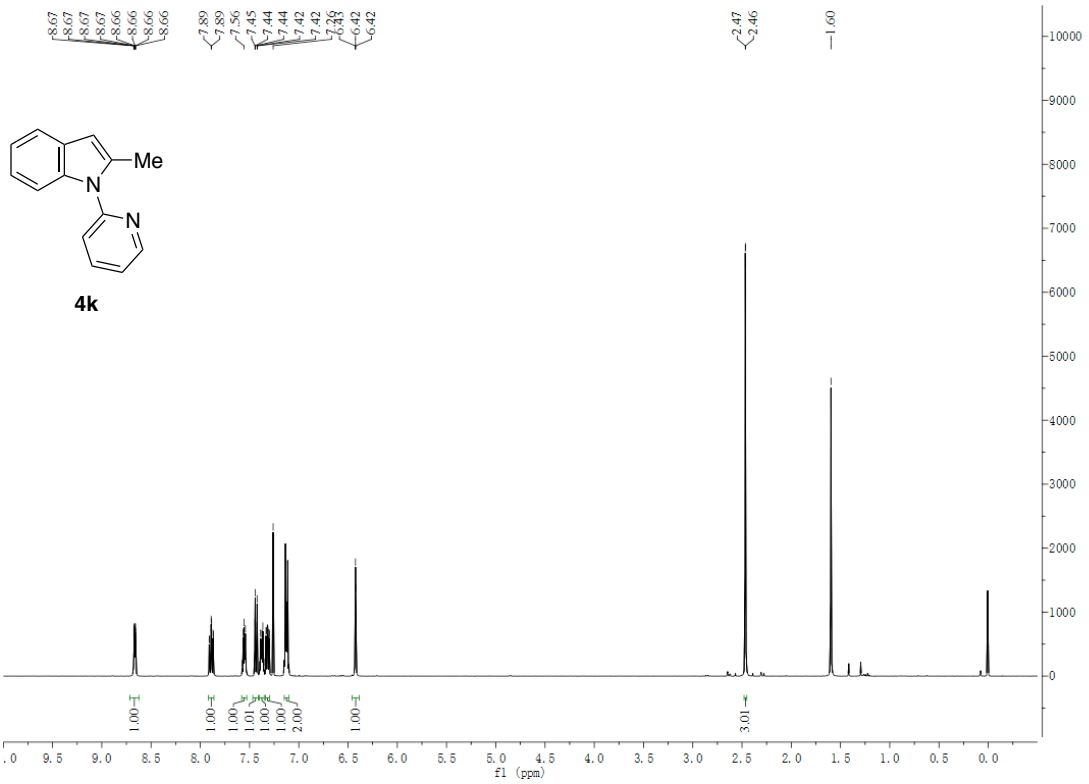
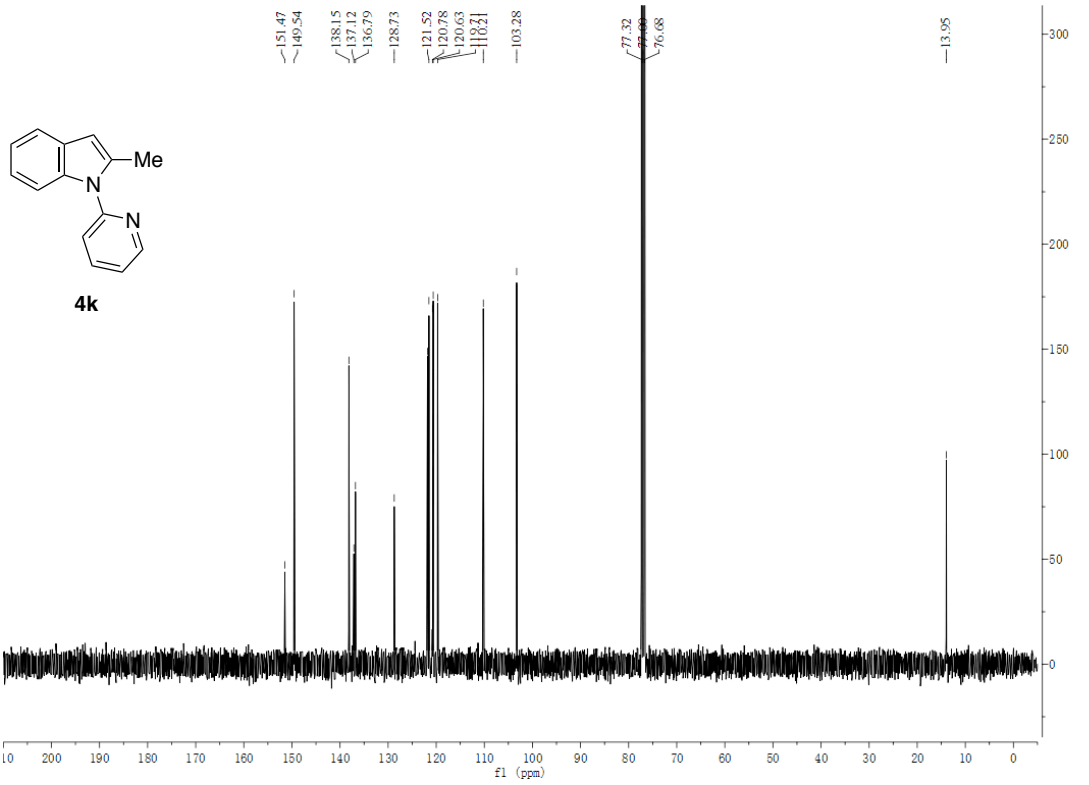
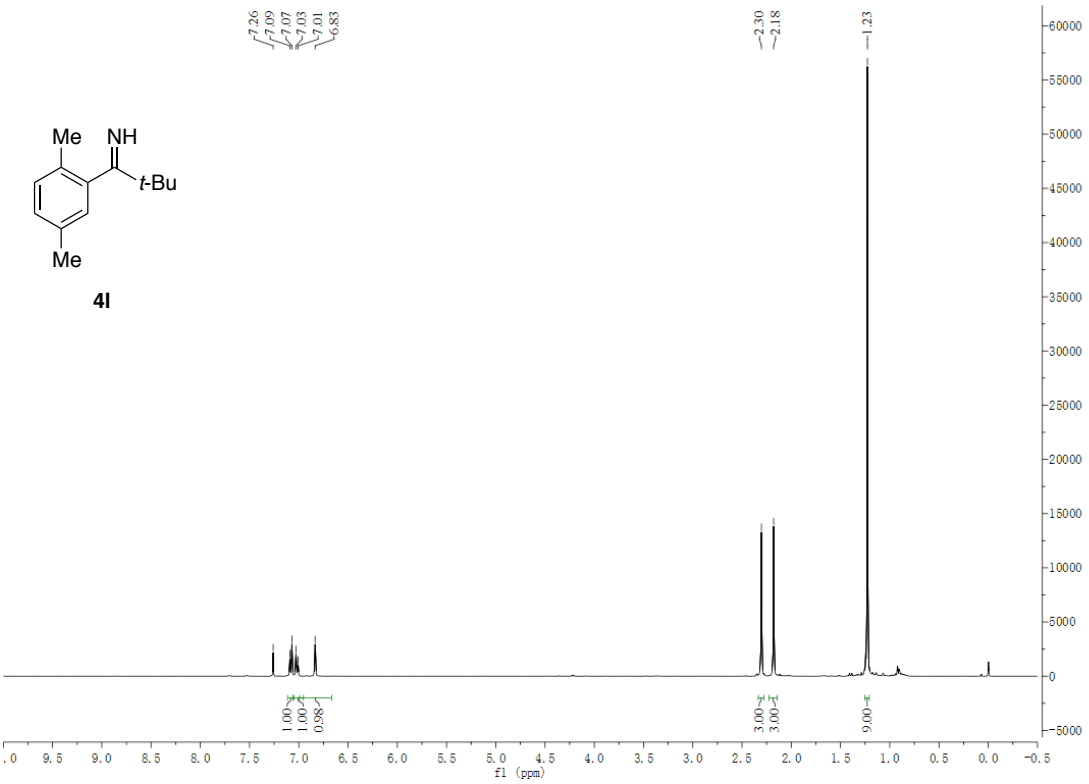
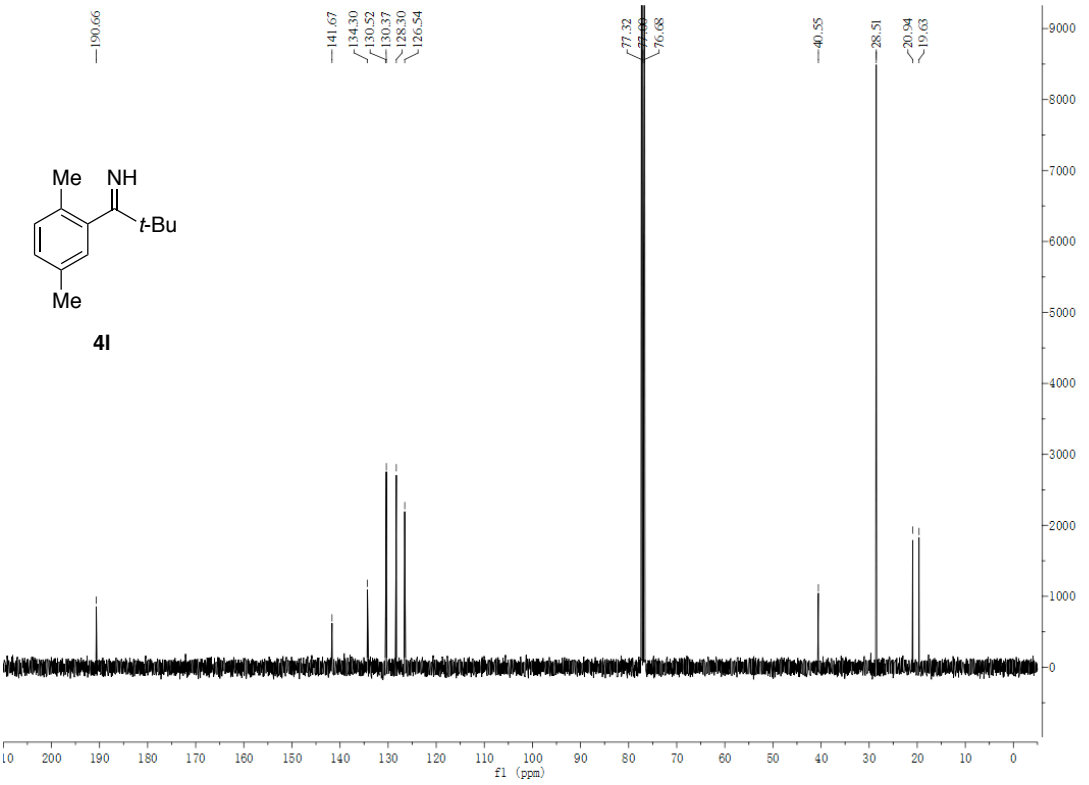
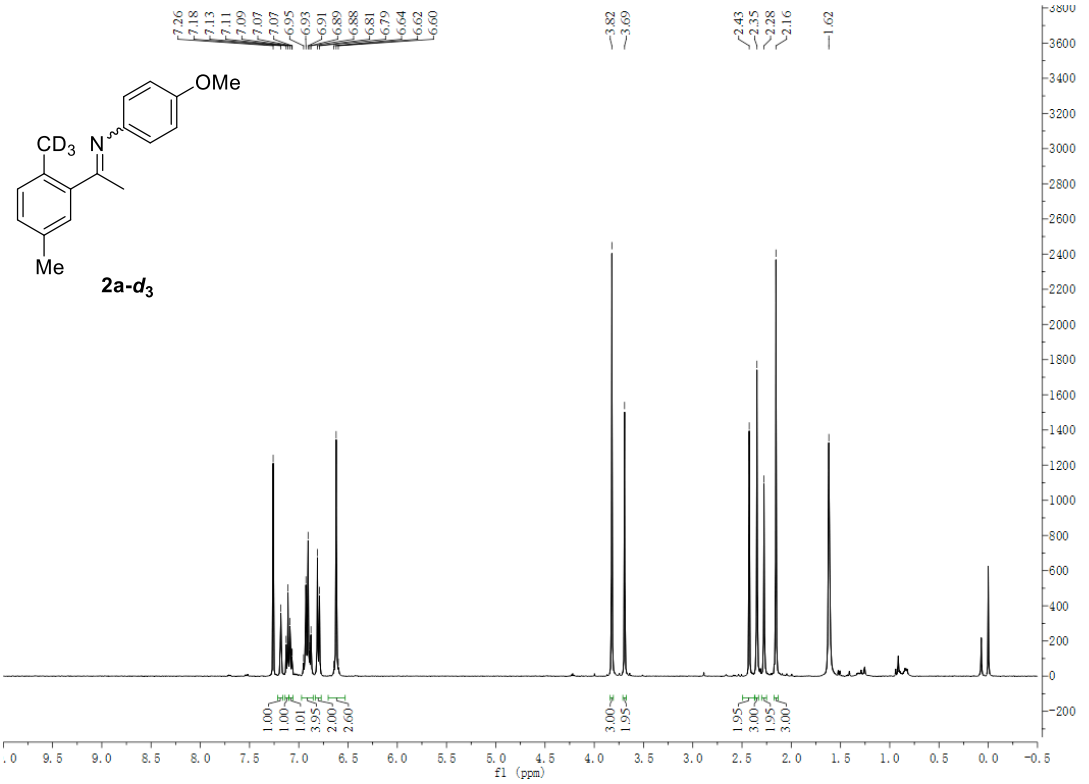
121.23
77.32
77.00
76.68
16.14
N
S
Me
4j
f1 (ppm)

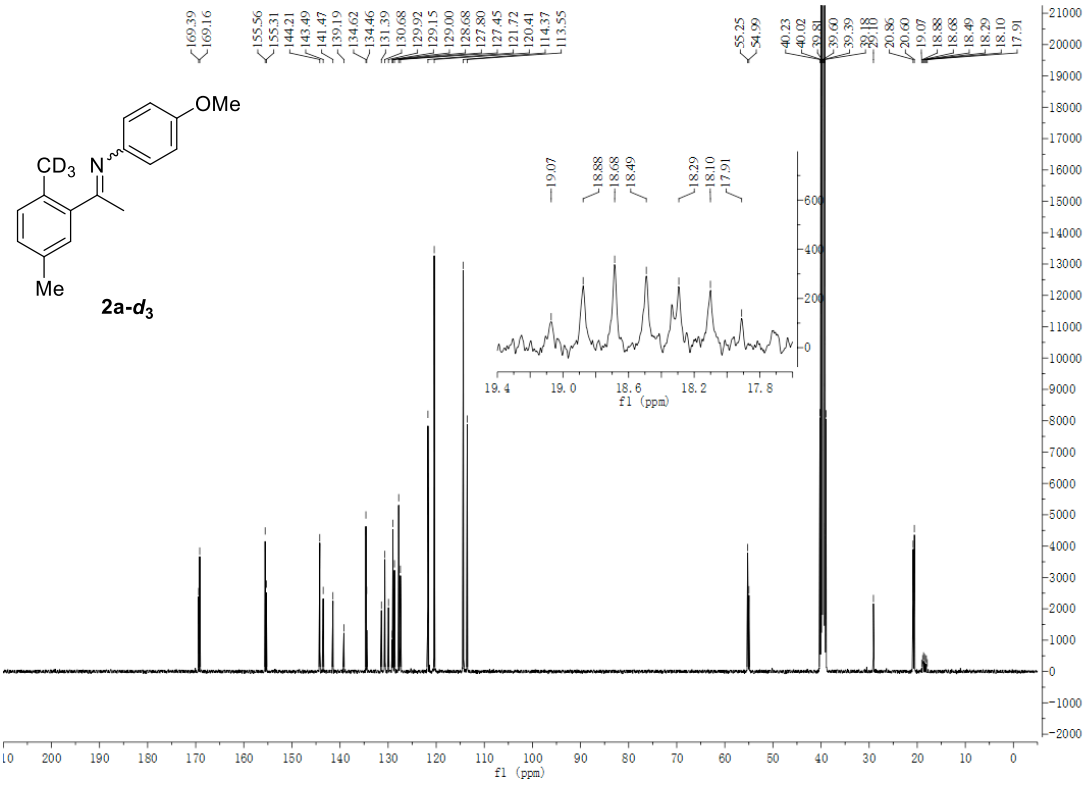

8.67
8.67
8.67
8.67
8.66
8.66
8.66
7.89
7.89
7.56
7.45
7.44
7.44
7.42
7.42
7.26
6.43
6.42
6.42
2.47
2.46
1.60
Me
N
N
4k
1.00
1.00
1.00
1.01
1.00
1.00
2.00
1.00
3.01
f1 (ppm)

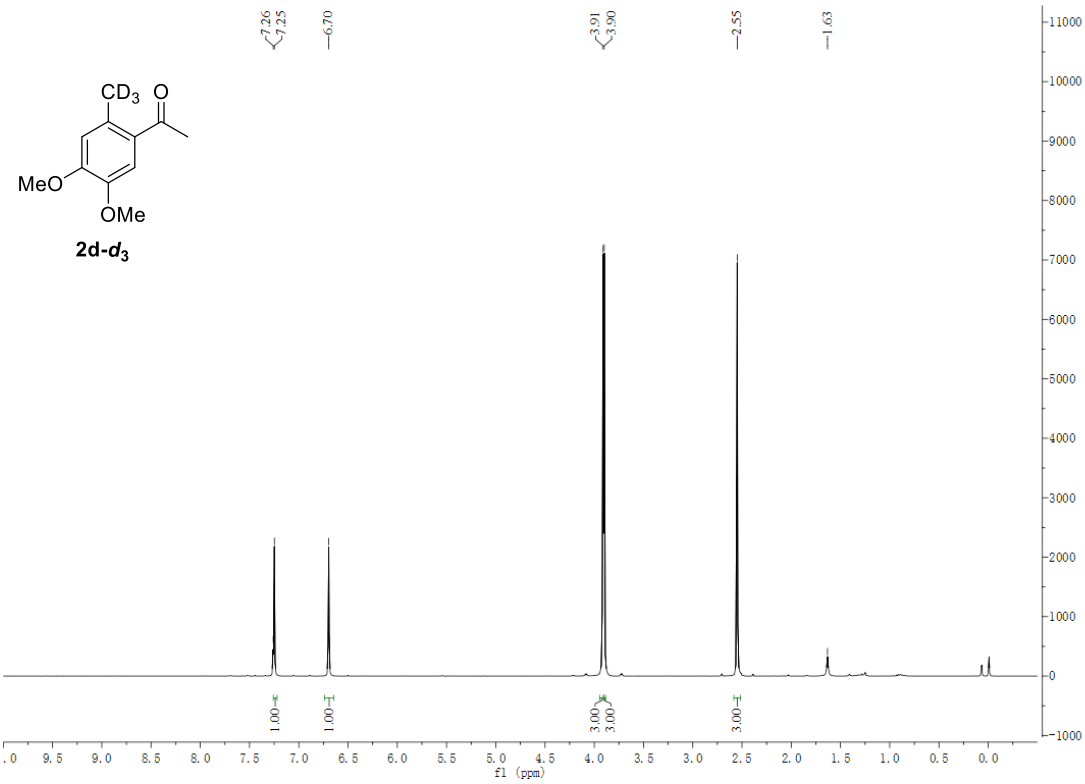

151.47
149.54
138.15
137.12
136.79
128.73
121.52
120.78
120.63
118.21
103.28
77.32
76.68
13.95
Me
N
N
4k
f1 (ppm)

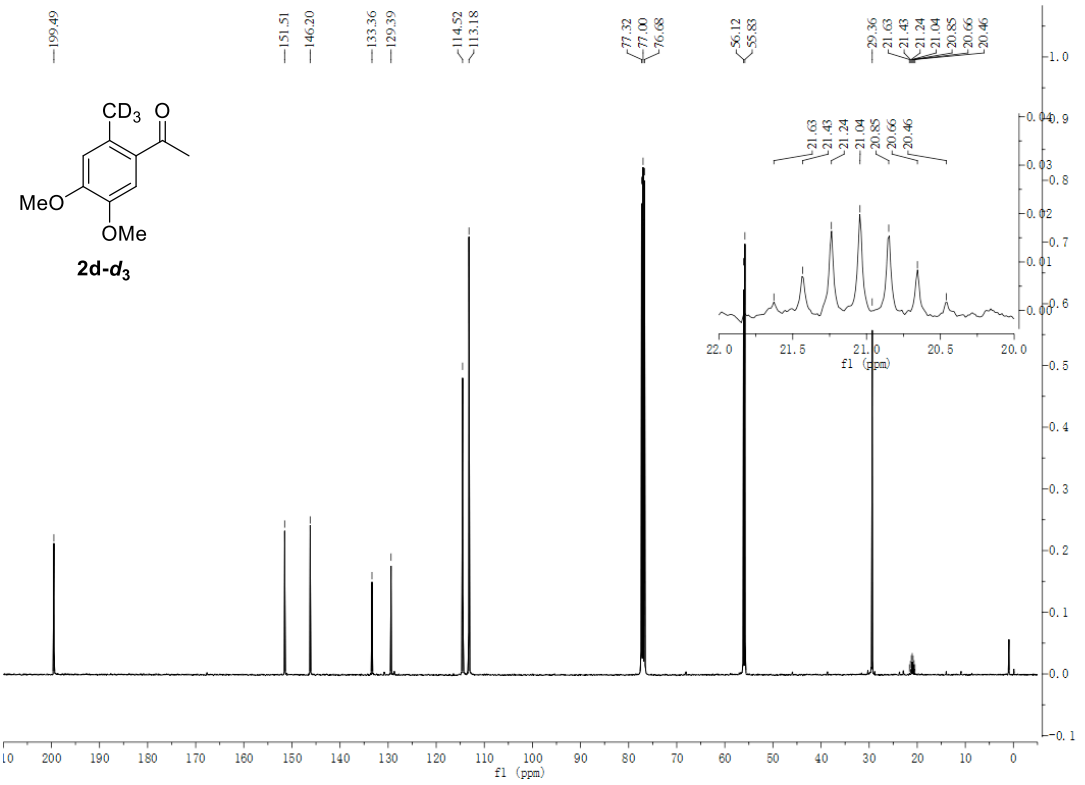

Me
NH
t-Bu
Me
4l
7.26
7.09
7.07
7.03
7.01
6.83
2.30
2.18
1.23
1.00
1.00
0.98
3.00
3.00
9.00
f1 (ppm)

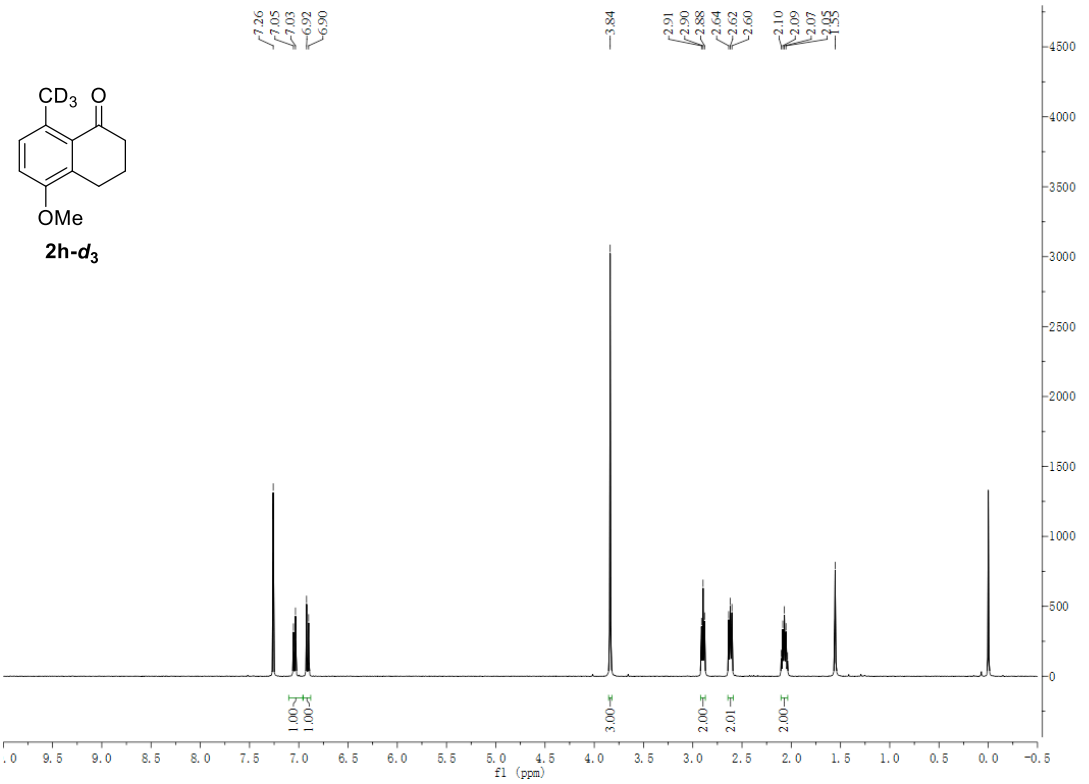

Me
NH
t-Bu
Me
4l
190.66
141.67
134.30
130.52
130.37
128.30
126.54
77.32
76.68
40.55
28.51
20.94
19.63
f1 (ppm)

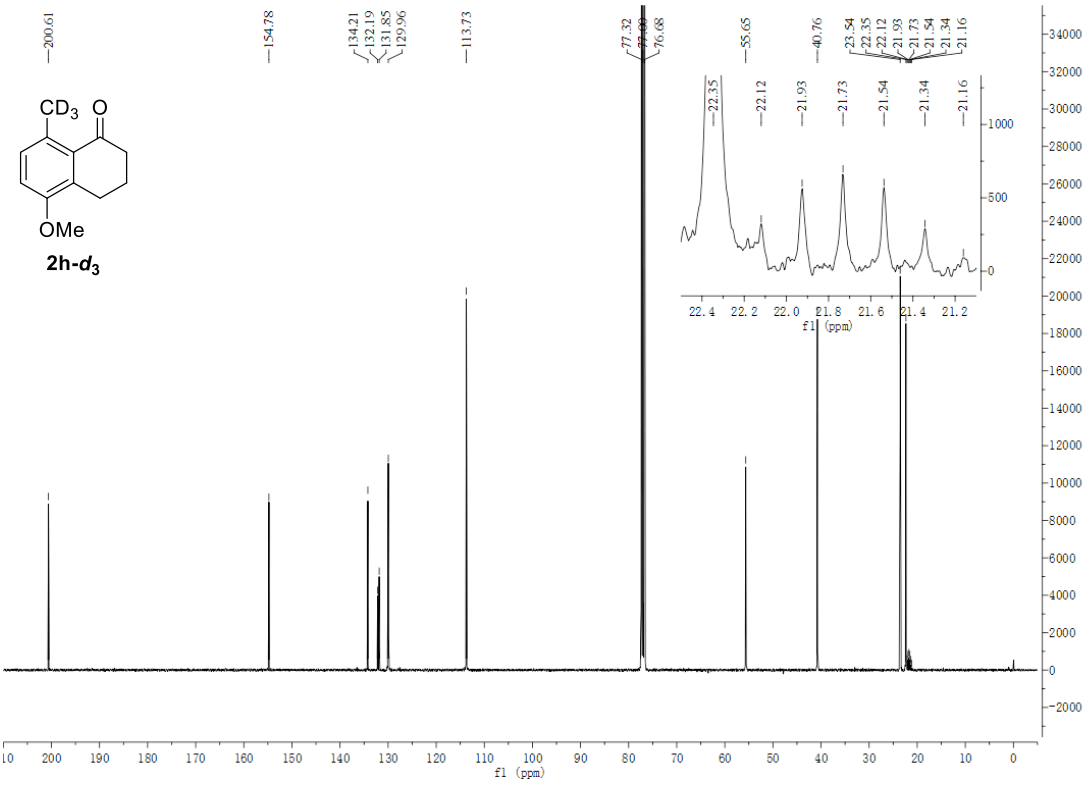

OMe
CD3
N
Me
2a-d3
f1 (ppm)

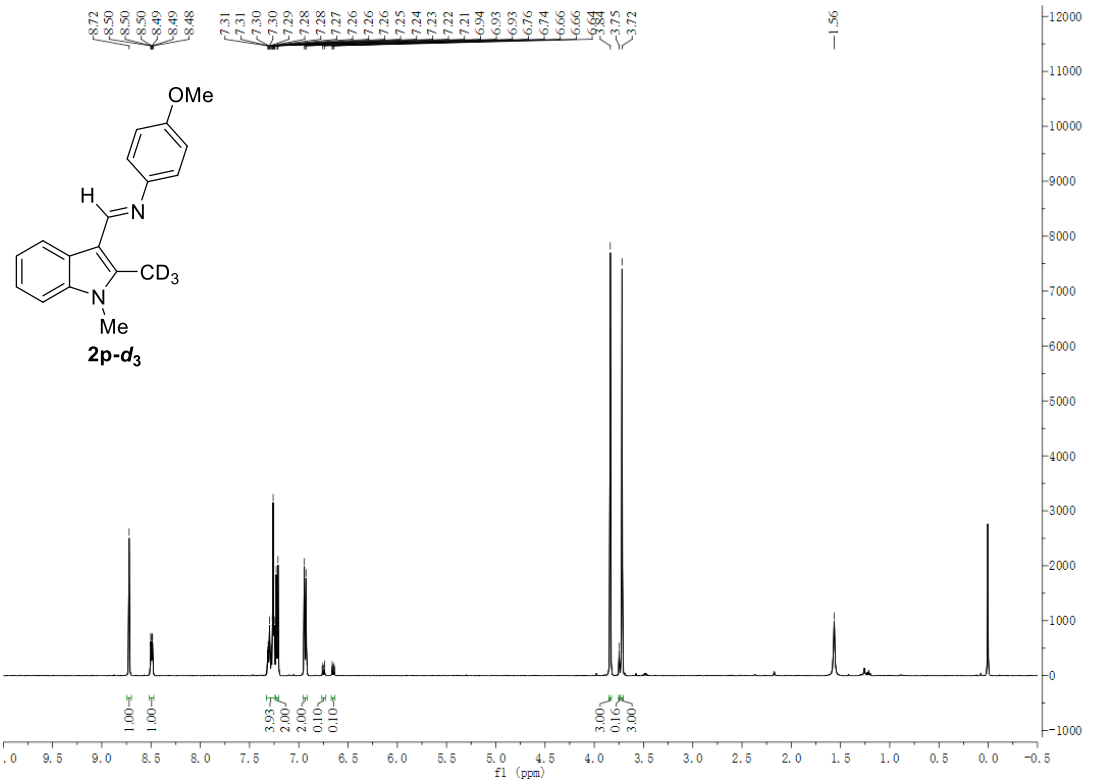

OMe
CD3
N
Me
2a-d3
f1 (ppm)

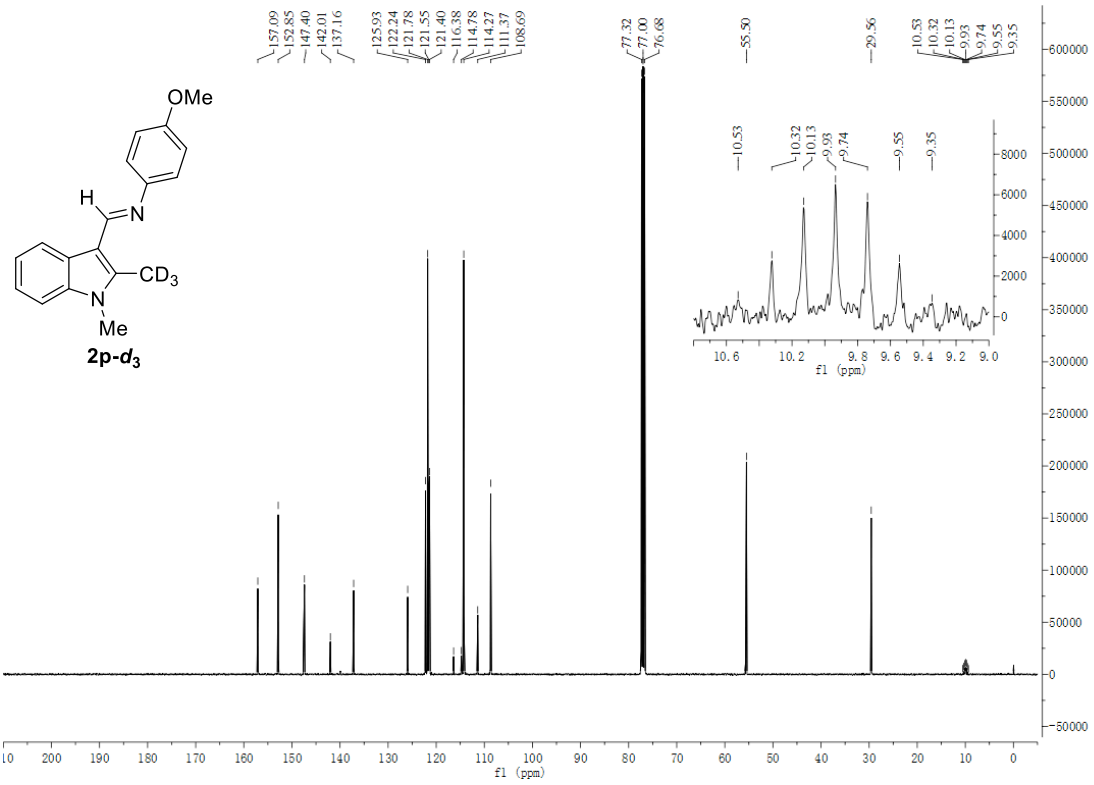

CD3 O
MeO
OMe
2d-d3
7.26
7.25
6.70
3.91
3.90
2.55
1.63
1.00
1.00
3.00
3.00
3.00
f1 (ppm)

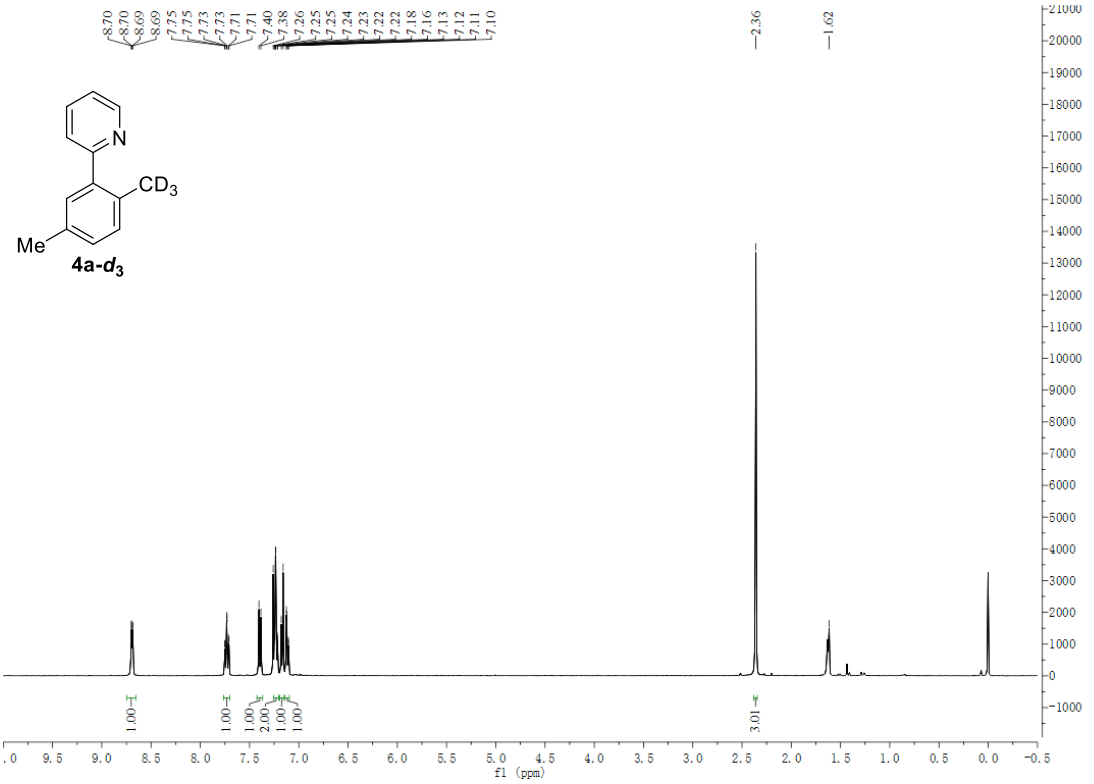

CD3 O
MeO
OMe
2d-d3
199.49
151.51
146.20
133.36
129.39
114.52
113.18
77.32
77.00
76.68
56.12
55.83
29.36
21.63
21.43
21.24
21.04
20.85
20.66
20.46
f1 (ppm)


CD3 O
OMe
2h-d3
7.26
7.05
7.03
6.92
6.90
3.84
2.91
2.90
2.88
2.64
2.62
2.60
2.10
2.09
2.07
1.95
1.00
1.00
3.00
2.00
2.01
2.00
f1 (ppm)


CD3 O
OMe
2h-d3
200.61
154.78
134.21
132.19
131.85
129.96
113.73
77.32
77.00
76.68
55.65
40.76
23.54
22.35
22.12
21.93
21.73
21.54
21.34
21.16
f1 (ppm)


OMe
H
N
CD3
N
Me
2p-d3
f1 (ppm)


OMe
H
N
CD3
N
Me
2p-d3
f1 (ppm)


8.70
8.70
8.69
8.69
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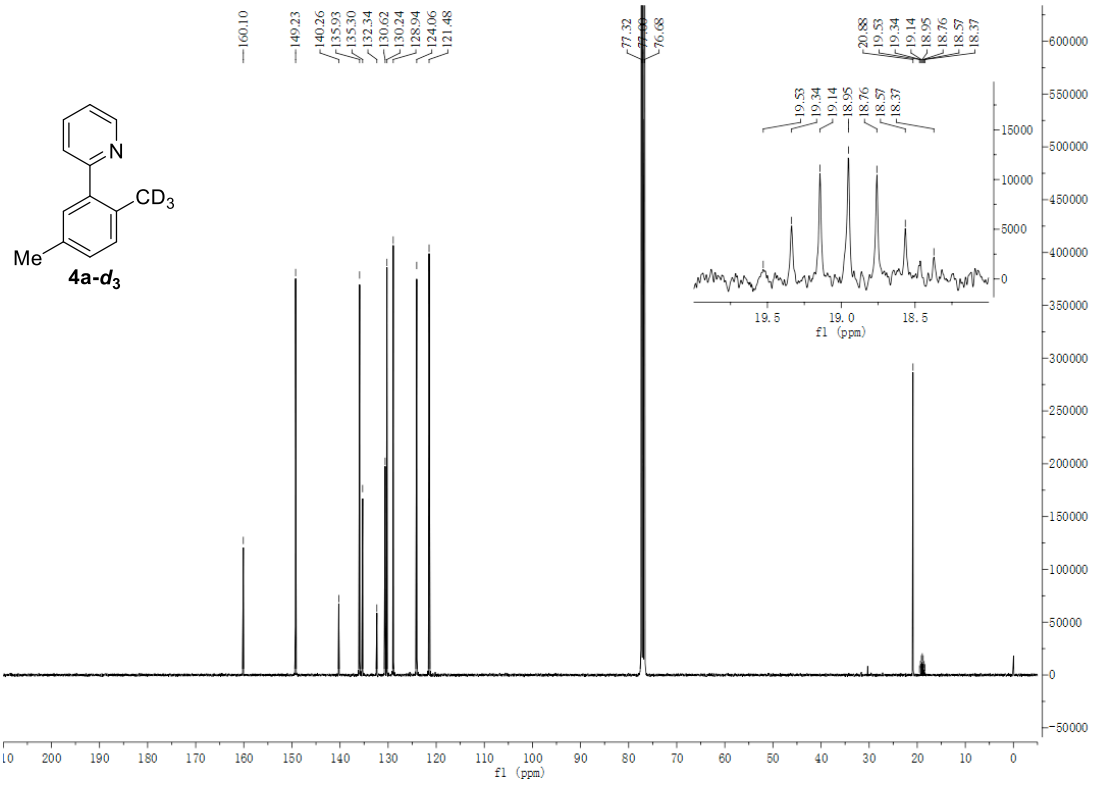
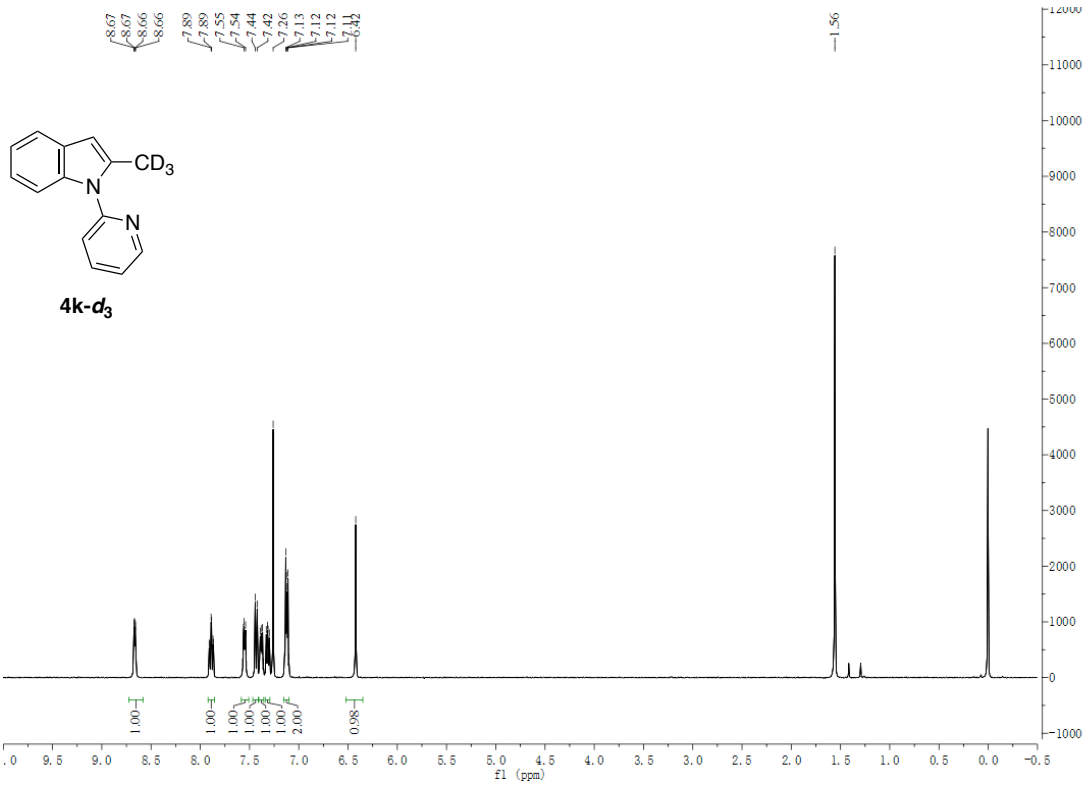
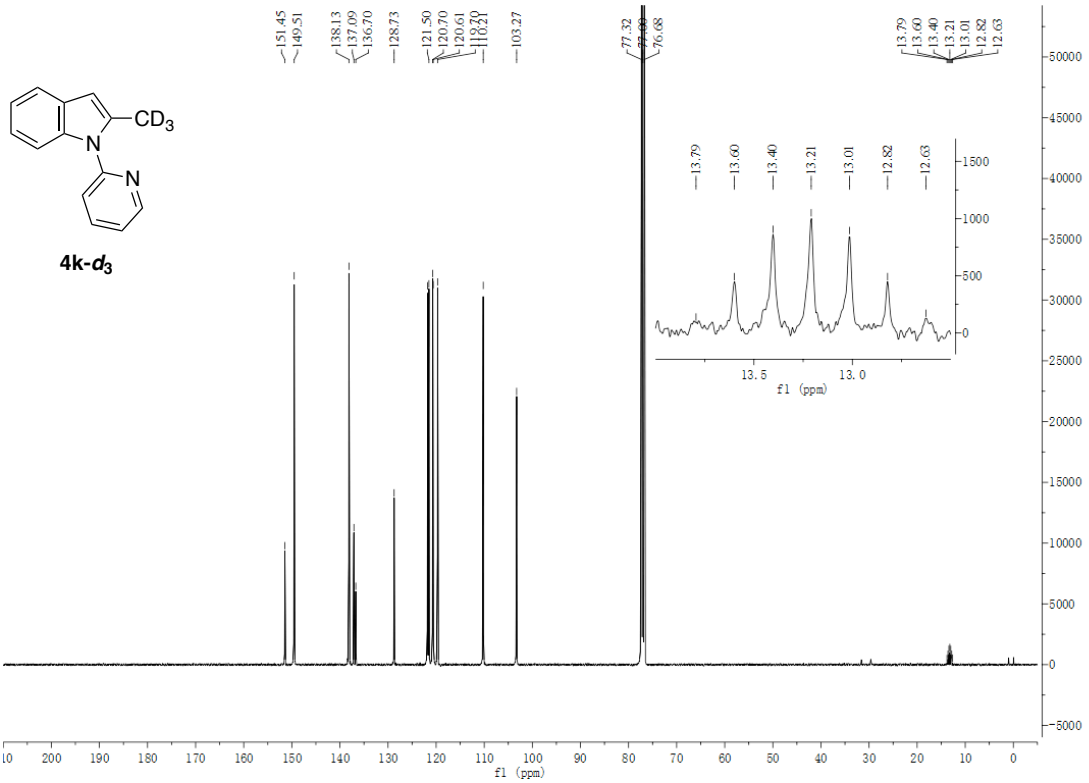
7.75
7.73
7.73
7.71
7.71
7.40
7.38
7.26
7.25
7.25
7.24
7.23
7.22
7.22
7.18
7.16
7.13
7.12
7.11
7.10
2.36
1.62
N
CD3
Me
4a-d3
1.00
1.00
1.00
2.00
1.00
1.00
3.01
f1 (ppm)


160.10
149.23
140.26
135.93
135.30
132.34
130.62
130.24
128.94
124.06
121.48
77.32
77.00
76.68
20.88
19.53
19.34
19.14
18.95
18.76
18.57
18.37
N
CD3
Me
4a-d3
f1 (ppm)


8.67
8.67
8.66
8.66
7.89
7.89
7.55
7.54
7.44
7.42
7.26
7.13
7.12
7.12
7.11
6.42
1.56
CD3
N
N
4k-d3
1.00
1.00
1.00
1.00
1.00
2.00
0.98
f1 (ppm)


151.45
149.51
138.13
137.09
136.70
128.73
121.50
120.70
120.61
118.21
118.20
103.27
77.32
77.00
76.68
13.79
13.60
13.40
13.21
13.01
12.82
12.63
CD3
N
N
4k-d3
f1 (ppm)