Continuous-flow Reductive N-Methylation with Highly Active Heterogeneous Pd Catalysts and Sequential-flow Synthesis of N-Monomethyl Amine

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Supporting Information

Contents

1. General

• JEOL JNM-ECA 500 or ECX 600 spectrometers were used for NMR measurement. Tetramethyl silane (TMS) was used as an internal standard for ^{1}H NMR (δ = 0 ppm), and deuterated chloroform ($CDCl_3$) was used for ^{13}C NMR (δ = 77.0 ppm). In NMR analysis using deuterated dimethyl sulfoxide (DMSO-d_6) as a solvent, DMSO served as an internal standard for ^{13}C NMR (δ = 40.0 ppm). Structures of known compounds were confirmed by comparing them with data shown in literatures.

• HPLC analysis was conducted on Shimadzu LC-20AB, SPD-M20A, and DGU-20A3 with chiral columns from DAICEL Corporation.

• IR spectra were measured using JASCO FT/IR87-610 spectrometer.

• DART-MS spectra were recorded on JEOL JMS-T100TD mass spectrometer.

• Preparative thin-layer chromatography was conducted using Wakogel B-5F.

• Solvents were purchased in anhydrous grade from FUJIFILM Wako Pure Chemical Company, Kanto Chemical Co. Inc., and Tokyo Chemical Industry Co. Ltd. and used as received.

• All commercially available reagents, unless otherwise noted, were purchased from Tokyo Chemical Industry Co. Ltd.

• *p*-Anisidine and palladium acetate were purchased from Sigma-Aldrich Co. LLC.

• Formalin aqueous solution, Pd/C(5%), activated carbon, calcium phosphate, N-ethyl-*o*-toluidine were purchased from FUJIFILM Wako Pure Chemical Company.

• Pt/C(5%), Rh/C(5%), Ru/C(5%) and Ir/C(5%) were purchased from N. E. CHEMCAT Co. Ltd.

• Dimethylpolysilane was purchased from Nippon Soda Co. Ltd.

• Phenylmethylpolysilane was purchased from Nippon Paint Co.

• CARiACT Q-10 was purchased from Fuji Silysia Chemical Ltd.

• W50 cellulose was purchased from Nippon Paper Industries Co. Ltd.

• 4-Hydroxypiperidine, 4-(piperazine-1-yl) phenol and L-phenylalanine ethyl ester hydrochloride were purchased from Angene International Ltd.

• 1-(2-pyridyl) piperazine was purchased from Oakwood Products Inc.

• All liquid amines were purified by distillation before use.

• All commercially available reagents, unless otherwise noted, were used without further purification.

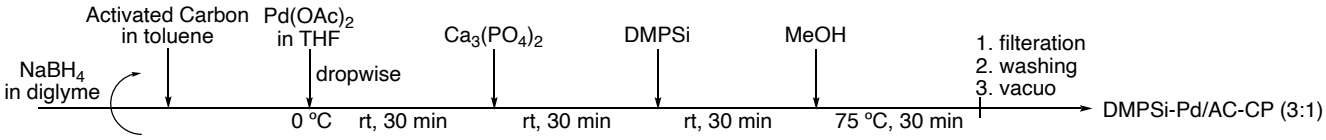
• All reactions, unless otherwise noted, were performed under argon atmosphere.

• For apparatuses for flow systems, a plunger pump (Flom KP-22-01, Flom Inc.), each size SUS column with column ends, mass flow controller, back pressure regulator, and aluminum

block heated (LCR-1300, Tokyo Rika Kikai Co.) were used. All tube were consisted of PTFE (ID 1.0 mm, OD 1/16 in.) tubes and appropriate fittings.

2. Catalyst Preparation

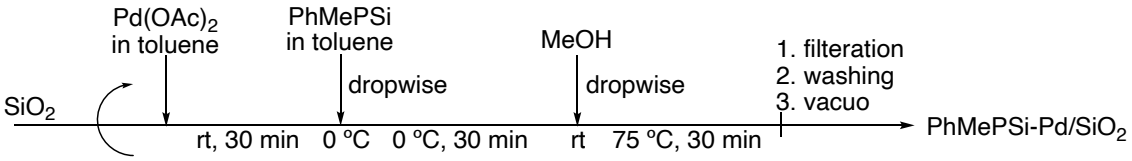
• Preparation of DMPSi-Pd/AC-CP (3:1)[1]



Scheme S1. Preparation of DMPSi-Pd/AC-CP (3:1) catalyst

A $Pd(OAc)_2$ (0.1177 g, 0.524 mmol) solution in THF (20 mL) was added dropwise at 0 °C to the mixture of activated carbon (3.38 g) and $NaBH_4$ (95.1 mg, 2.51 mmol) in toluene (75 mL) and diglyme (7.5 mL). The resulting suspension was stirred at room temperature for 30 min. Calcium phosphate (1.13 g) was added to the mixture and the mixture was kept stirring for 30 min. Dimethylpolysilane (0.51 g) was added to the mixture and the mixture was stirred for another 30 min. Methanol (25 mL) was added to the resulting mixture and the mixture was heated at 75 °C for 30 min. After the completion of the above operation, the mixture was filtered, and the resulting black powder was washed with acetone and water. Finally, the obtained material was dried under reduced pressure at 80 °C to afford dimethylpolysilane-Pd on AC-CP catalyst (DMPSi-Pd/AC-CP (3:1)) (4.88 g, 0.1 mmol/g).

• Preparation of PhMePSi-Pd/SiO_2[2]



Scheme S2. Preparation of PhMePSi-Pd/SiO_2 catalyst

CARiACT Q-10 (4.487 g) was added to the solution of $Pd(OAc)_2$ (0.1145 g, 0.51 mmol) in toluene (75 mL). The resulting suspension was stirred at room temperature for 30 min (until the liquid gets colorless). Phenylmethylpolysilane (0.499 g) in toluene (10mL) was added dropwise to the mixture at 0 °C and the mixture was kept stirring for 30 min at 0 °C. Methanol (25 mL) was added dropwise to the reaction mixture at room temperature and the mixture was heated at 75 °C for 30 min. After the completion of the above operation, the

mixture was filtered, and the resulting black powder was washed with acetone and water. Finally, the obtained material was dried under reduced pressure at 80 °C to afford phenylmethylpolysilane-Pd on SiO_2 catalyst (PhMePSi-Pd/SiO_2) (4.54 g, 0.1 mmol/g).

3. Experimental Procedures

• A procedure of N-methylation reaction of 1a under batch conditions (Table 1)

DMPSi-Pd/AC-CP (3:1) (total quantity of Pd: 0.0005 mmol, Pd: 0.25 mol%, 5.0 mg) and a magnetic stirring bar were added to a flask. The flask was sealed with a septum, evacuated, and filled with argon via an argon balloon. Afterward, THF (2 mL), di-n-octylamine **1a** (0.2 mmol, 1 eq. 48.1 mg) and formalin (0.24 mmol, 1.2 eq. 19.5 mg) were injected into the flask. A hydrogen balloon was equipped to the flask and the reaction mixture was stirred for 1 h at room temperature. After the reaction, the resulting mixture was filtered. After concentration under rotary evaporator, the resulting crude material was analyzed by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard to determine the yield of **2a**.

• A procedure of N-methylation of 1a reaction under continuous-flow optimized conditions (Figures 1, 2)

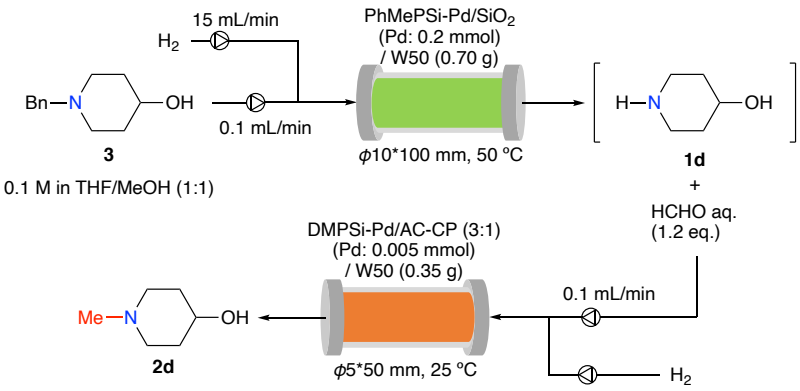
A SUS column (ID 5 mm × 50 mm) with column ends equipped with filters was used for a container of trickle-bed reactor. One of the column ends was mounted a two-way unlet tube. A PETE tube was used to connect the pump with the column. DMPSi-Pd/AC-CP (3:1) (total quantity of Pd: 0.005 mmol, 50 mg) mixed well with W50 cellulose (0.35 g) was packed into the column. THF flowed into the column by the pump (0.3 mL/min) for over 30 minutes. After that, hydrogen gas was introduced to the column at 15 mL/min flow rate. Then, the substrate solution (di-n-octylamine **1a**: 0.1 M, HCHO aq.: 0.12 M in THF and 1,3,5-trimethoxybenzene as an internal standard: 0.89 mmol, 150 mg) was introduced to the column at 0.1 mL/min flow rate. The resulting solution in an appropriate time was collected (1 mL). After concentration under rotary evaporator, the resulting crude material was analyzed by ^{1}H NMR to determine the yield of **2a**.

• A procedure of an extended-time flow reaction (Scheme 1)

A SUS column (ID 5 mm × 50 mm) with column ends equipped with filters was used for a container of trickle-bed reactor. One of the column ends was mounted a two-way unlet tube. A PETE tube was used to connect the pump with the column. DMPSi-Pd/AC-CP (3:1) (total quantity of Pd: 0.005 mmol, 50 mg) mixed well with W50 cellulose (0.35 g) was packed into the column. THF flowed into the column by the pump (0.3 mL/min) for over 30 minutes. After that, hydrogen gas was introduced to the column at 15 mL/min flow rate. Then, 1.5 L of the substrate solution (di-n-octylamine **1a**: 0.1 M, HCHO aq.: 0.12 M in THF and 1,3,5-

trimethoxybenzene as an internal standard: 8.9 mmol, 1.5 g) was introduced to the column at 0.1 mL/min flow rate. The resulting solution in an appropriate time was collected (1 mL). After concentration under rotary evaporator, the resulting crude material was analyzed by ^{1}H NMR to determine the yield of **2a**. Then, the crude material was purified by column chromatography on silica gel (eluent hexane/ethyl acetate, 20:1) to afford the product **2a** as a colorless oil (24.9 mg for 1 mL of the resulting solution, 98%). To determine the leaching of Pd, a 1 mL of solution was collected, and the solvent was removed under rotary evaporator. Then, the obtained material was treated with conc. H_2SO_4 and HNO_3 at 200 °C for 12 h. After that, the resulting material was diluted with water to 50 mL, and the solution was analyzed by ICP analysis.

• A procedure of sequential-flow reaction (Scheme 2)



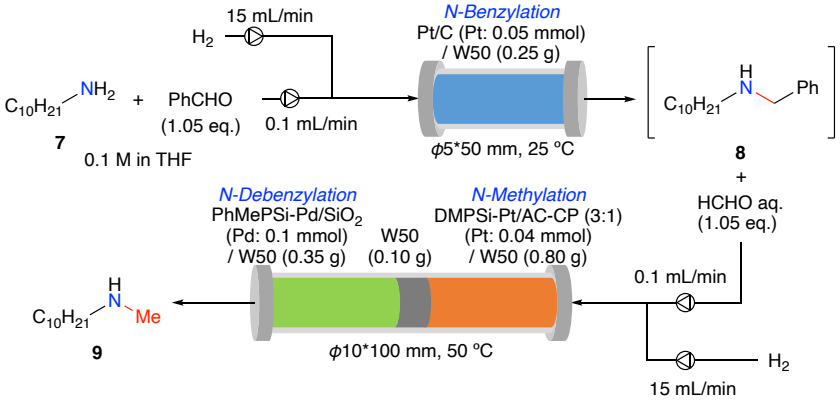
• A procedure of N-debenzylation reaction (1st step of sequential-flow reaction)

A SUS column (ID 10 mm × 100 mm) with column ends equipped with filters was used for a container of trickle-bed reactor. One of the column ends was mounted a two-way unlet tube. A PETE tube was used to connect the pump with the column. PhMePSi-Pd/SiO_2 (total quantity of Pd: 0.2 mmol, 0.20 g) mixed well with W50 cellulose (0.70 g) was packed into the column. THF flowed into the column by the pump (0.3 mL/min) for over 30 minutes. Then, hydrogen gas was introduced to the column at 15 mL/min flow rate. After that, the column heater was set to 50 °C. Then, the substrate solution (1-benzyl-4-hydroxypiperidine **3**: 0.1 M in THF and 1,3,5-trimethoxybenzene as an internal standard: 0.89 mmol, 150 mg) was introduced to the column at 0.1 mL/min flow rate. The resulting solution in an appropriate time was collected (1 mL). After concentration under rotary evaporator, the resulting crude material was analyzed by ^{1}H NMR to determine the yield of **1d**. Remaining solution was used in the next step without any treatments.

• A procedure of N-methylation reaction (2nd step of sequential-flow reaction)

A SUS column (ID 5 mm × 50 mm) with column ends equipped with filters was used for a container of trickle-bed reactor. One of the column ends was mounted a two-way unlet tube. A PETE tube was used to connect the pump with the column. DMPSi-Pd/AC-CP (3:1) (total quantity of Pd: 0.005 mmol, 50 mg) mixed well with W50 cellulose (0.35 g) was packed into the column. THF flowed into the column by the pump (0.3 mL/min) for over 30 minutes. Then, hydrogen gas was introduced to the column at 15 mL/min flow rate. After that, the resulting solution of 1st step and 1.2 equivalent of HCHO aq. was mixed and obtained solution was introduced to the column at 0.1 mL/min flow rate. The resulting solution in an appropriate time was collected (1 mL). After concentration under rotary evaporator, the resulting crude material was analyzed by ^{1}H NMR to determine the yield of **2d**.

• A procedure of sequential-flow N-monomethylation of 1-aminodecane (Scheme 4)



• A procedure of N-benzylation reaction (1st step of sequential-flow N-monomethylation)

A SUS column (ID 5 mm × 50 mm) with column ends equipped with filters was used for a container of trickle-bed reactor. One of the column ends was mounted a two-way unlet tube. A PETE tube was used to connect the pump with the column. Pt/C (total quantity of Pt: 0.05 mmol, 195.1 mg) mixed well with W50 cellulose (0.25 g) was packed into the column. THF flowed into the column by the pump (0.3 mL/min) for over 30 minutes. Then, hydrogen gas was introduced to the column at 15 mL/min flow rate. After that, the substrate solution (1-aminodecane **7**: 0.1 M, benzaldehyde: 0.105 M in THF and 1,3,5-trimethoxybenzene as an internal standard: 0.89 mmol, 150 mg) was introduced to the column at 0.1 mL/min flow rate. The resulting solution in an appropriate time was collected (1 mL). After concentration

under rotary evaporator, the resulting crude material was analyzed by ^{1}H NMR to determine the yield of **8**. Remaining solution was used in the next step without any treatments.

• A procedure of N-methylation reaction and N-debenzylation reaction (2nd and 3rd step of sequential-flow N-monomethylation)

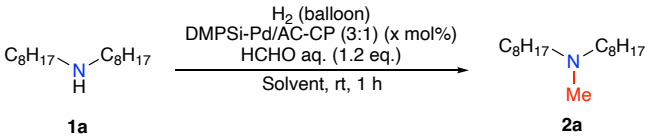
A SUS column (ID 10 mm × 100 mm) with column ends equipped with filters was used for a container of trickle-bed reactor. One of the column ends was mounted a two-way unlet tube. A PETE tube was used to connect the pump with the column. The column consisted of doubly layered catalyst, DMPSi-Pt/AC-CP (3:1) (total quantity of Pt: 0.04 mmol, 400 mg) mixed well with W50 cellulose (0.80 g) as a 1st-layer and PhMePSi-Pd/SiO_2 (total quantity of Pd: 0.1 mmol, 1.0 g) mixed well with W50 cellulose (0.35 g) as a 2nd-layer as shown in the above figure. THF flowed into the column by the pump (about 0.3 mL/min) for at least 30 minutes. Then, hydrogen gas was introduced to the column at 15 mL/min flow rate. After that, the column heater was set to 50 °C. Then , the resulting solution of 1st step and 1.05 equivalent of HCHO aq. was mixed and obtained solution was introduced to the column at 0.1 mL/min flow rate. The resulting solution in an appropriate time was collected (1 mL). After concentration under rotary evaporator, the resulting crude material was analyzed by ^{1}H NMR to determine the yield of **9**. Then, the crude material was purified by column chromatography on silica gel (eluent DCM/MeOH/Et_3N, 90:9:1) to afford the product **9** as a colorless oil (14.9 mg for 1 mL of the resulting solution, 87%).

• A procedure of catalyst reactivation

After the flow reaction for 6 h under the conditions, which is indicated as blue line in Figure 1a, the column was washed by pumping 0.1 M HCl in MeOH/H_2O (1/1, v/v) at 0.1 mL/min flow rate for 2 h at room temperature. The column was further washed by pumping THF at 0.1 mL/min flow rate for 30 min to replace the solvent inside the column completely to THF. The washed column was then reused by following the procedure described above using **1a** as substrates.

4. Supplementary Data

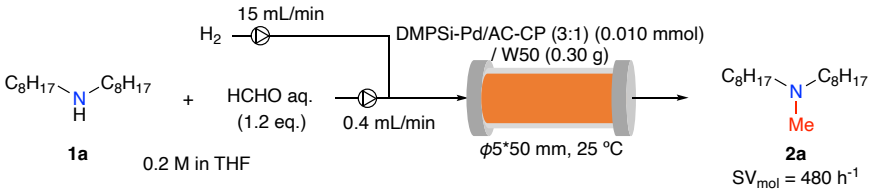
Table S1. Solvent screening of N-methylation under batch conditions



Entry	x (mol%)	Solvent	Yield (%)[a]
1	0.25	MeOH	99
2	0.25	EtOH	54
3	0.25	^{i}PrOH	56
4	0.25	THF	96
5	0.25	1,4-Dioxane	23
6	0.25	Acetone	95
7	0.25	CH_3CN	48
8	0.25	DMF	53
9	0.05	MeOH	33
10	0.05	Acetone	33
11	0.05	THF	48

[a] Determined by H NMR analysis.

・N-methylation with high SV_{mol} value under flow conditions



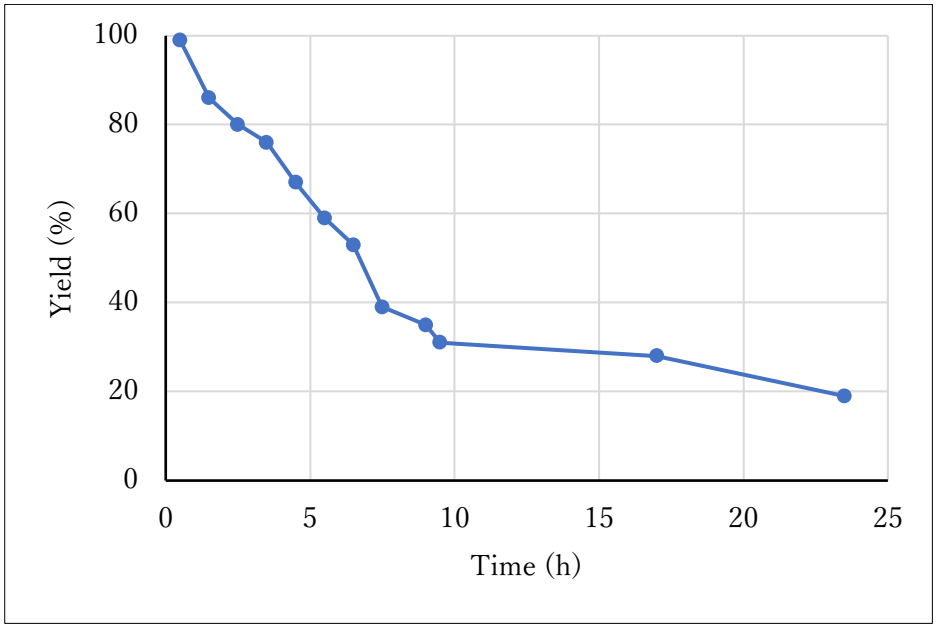
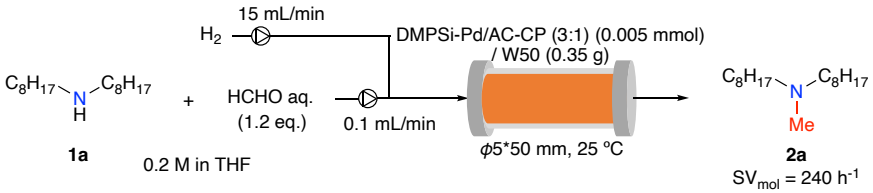


Figure S1. Reaction profile of flow reaction: yield of **2a**

・Reactivation of catalyst under flow conditions



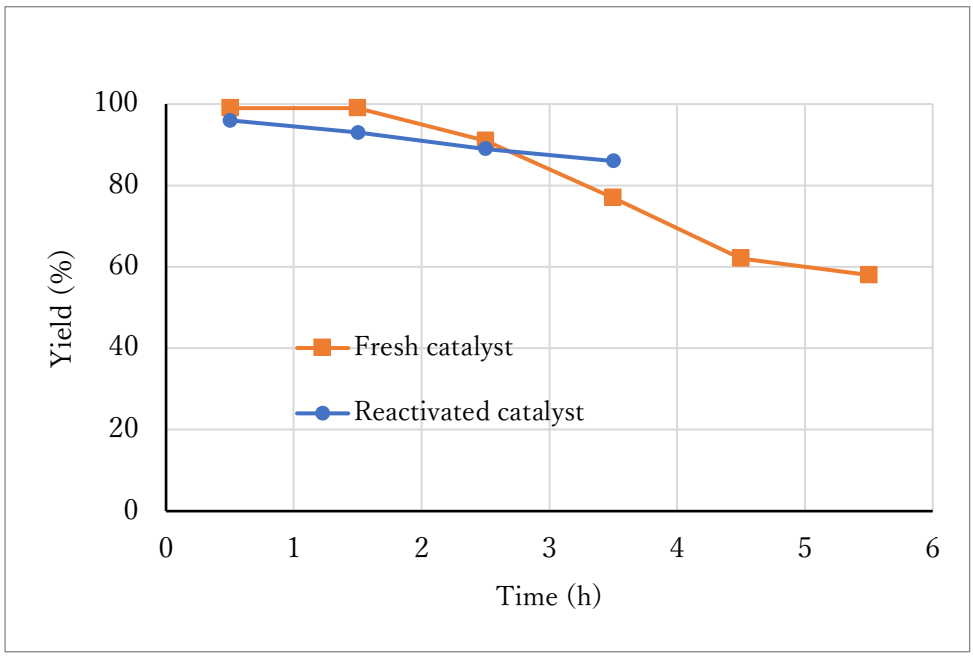
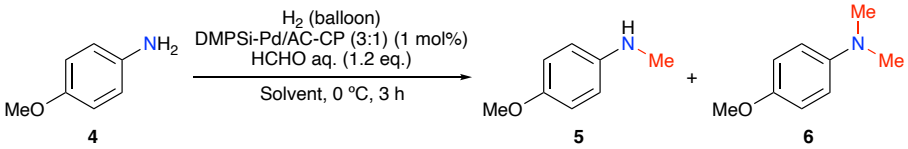


Figure S2. Reaction profile of flow reaction: yield of **2a**

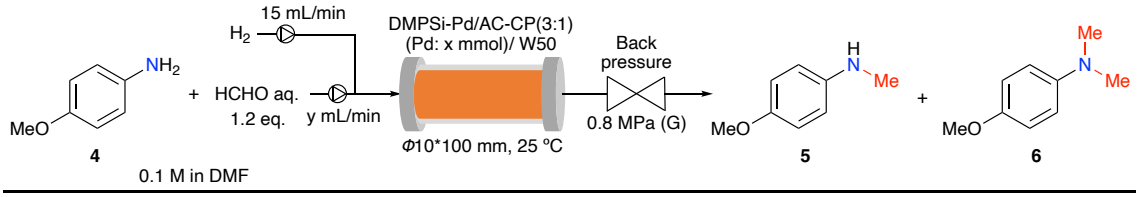
Table S2. Solvent screening of N-monomethylation under batch conditions



Entry	Solvent	Yield of **5** (%)[a]	Yield of **6** (%)[a]	Selectivity (%)[b]
1	^{i}PrOH	30	16	65
2	THF	34	12	74
3	EtOH	21	11	66
4	AcOEt	25	11	69
5	1,4-Dioxane	3	6	32
6	MeOH	16	21	43
7	CH_3CN	17	31	36
8	DMA	14	2	85
9	NMP	18	2	90
10	DMF	21	2	92

[a] Determined by H NMR analysis. [b] Yield of **5**/(Yield of **5** + Yield of **6**).

Table S3. Continuous-flow N-monomethylation reaction



Entry	Cat. (mmol)	F. R. (mL/min)	Yield of **5** (%)[a]	Yield of **6** (%)[a]	Selectivity (%)[b]
1	0.010	0.1	43	4	91
2	0.020	0.1	56	8	88
3	0.010	0.05	59	6	90
4	0.020	0.05	58	11	84

[a] Determined by H NMR analysis. [b] Yield of **5**/(Yield of **5** + Yield of **6**).

5. STEM analysis and EDS mapping

Figure S3. STEM image of DMPSi-Pd/AC-CP (3:1) before use

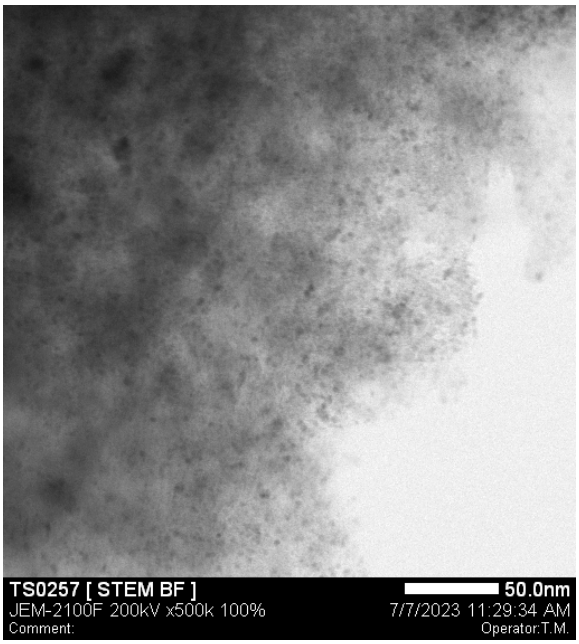


Figure S4. STEM image of DMPSi-Pd/AC-CP (3:1) after the flow reaction

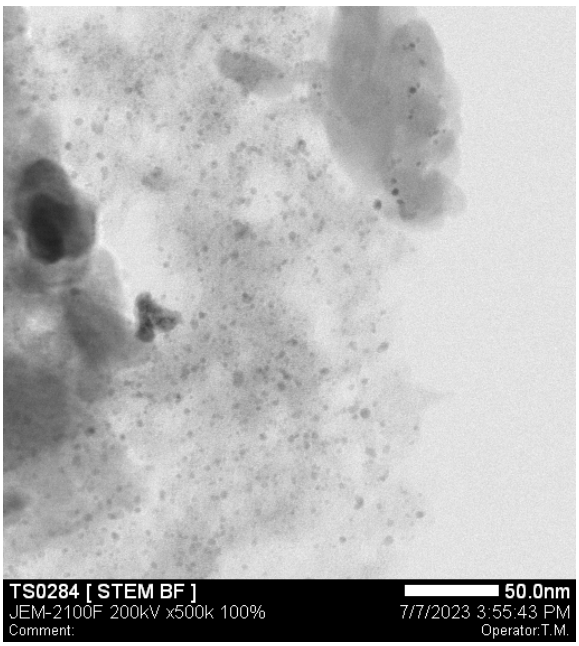


Figure S5. EDS mapping of DMPSi-Pd/AC-CP (3:1) before use

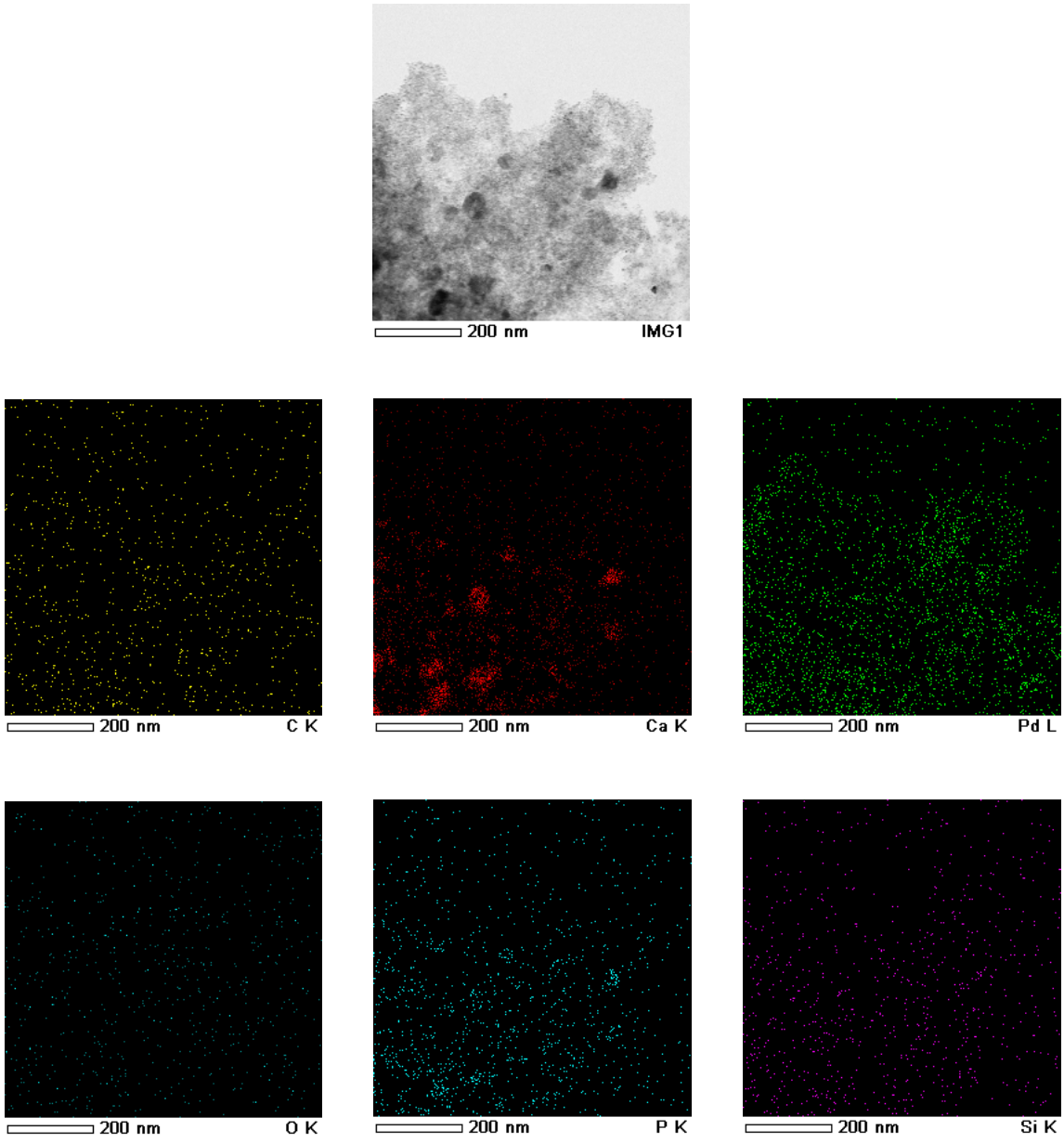


Figure S6. EDS mapping of DMPSi-Pd/AC-CP (3:1) after the flow reaction

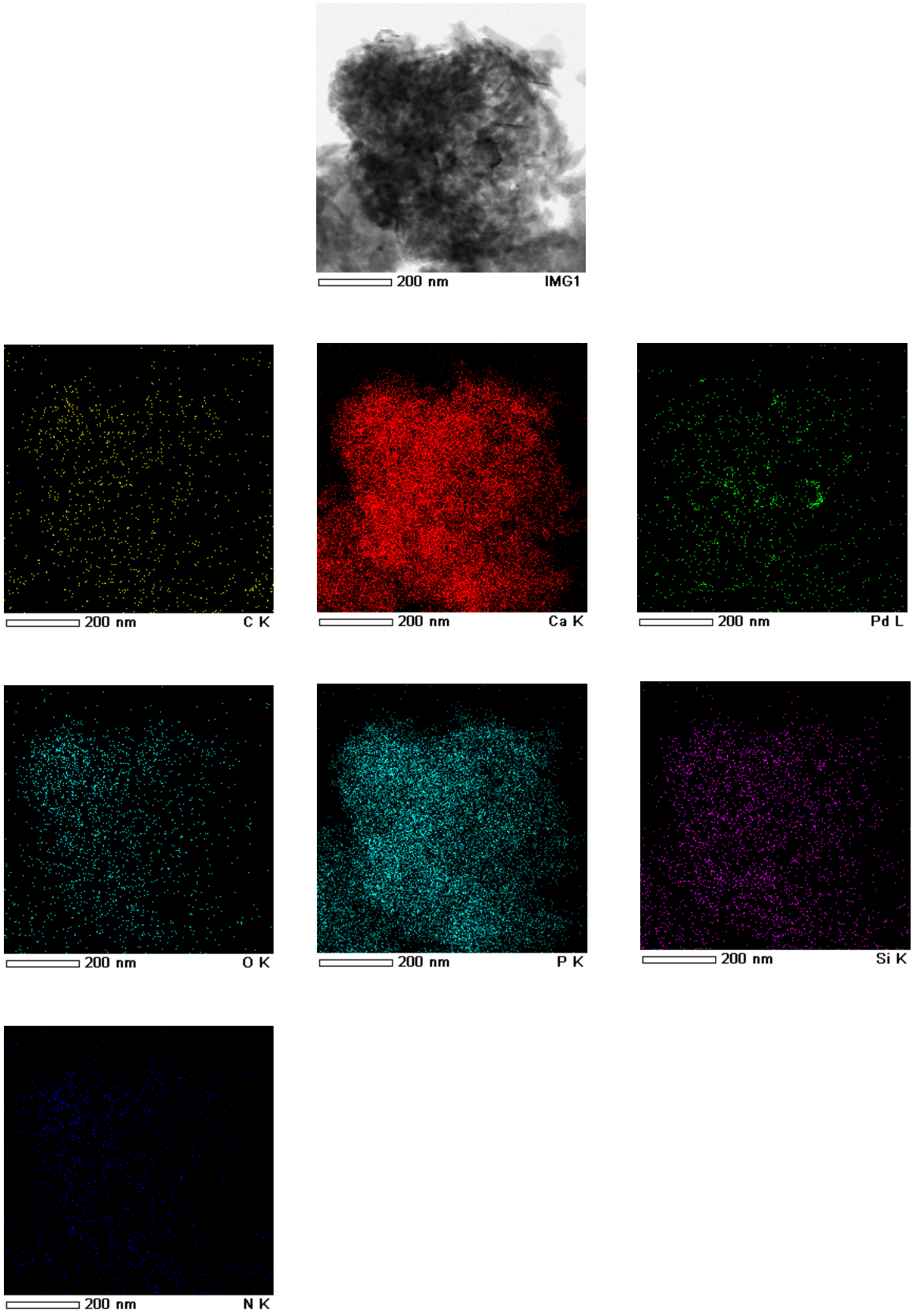
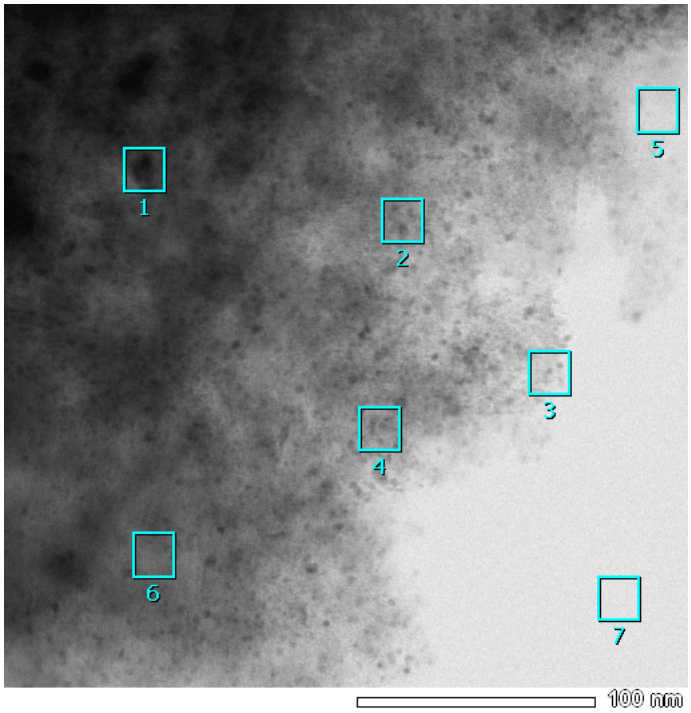
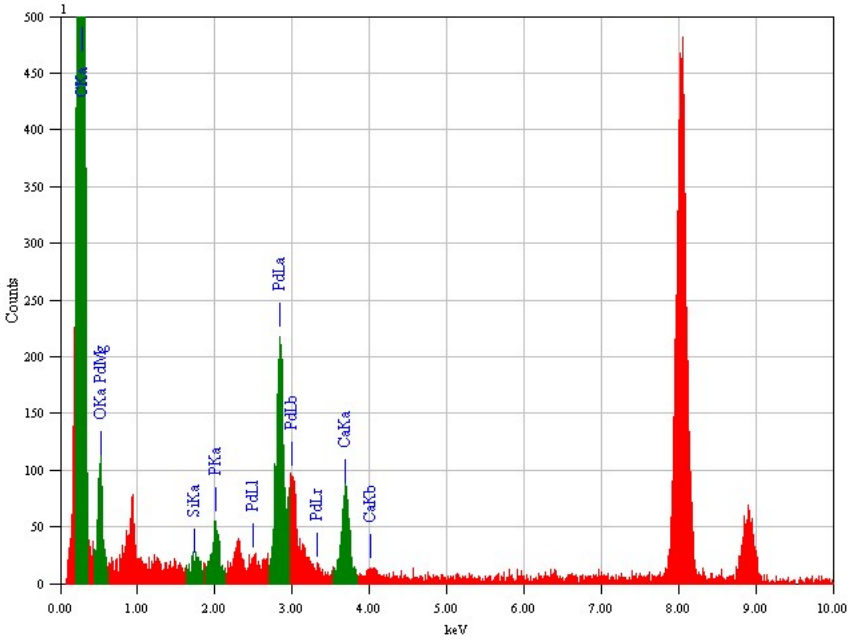


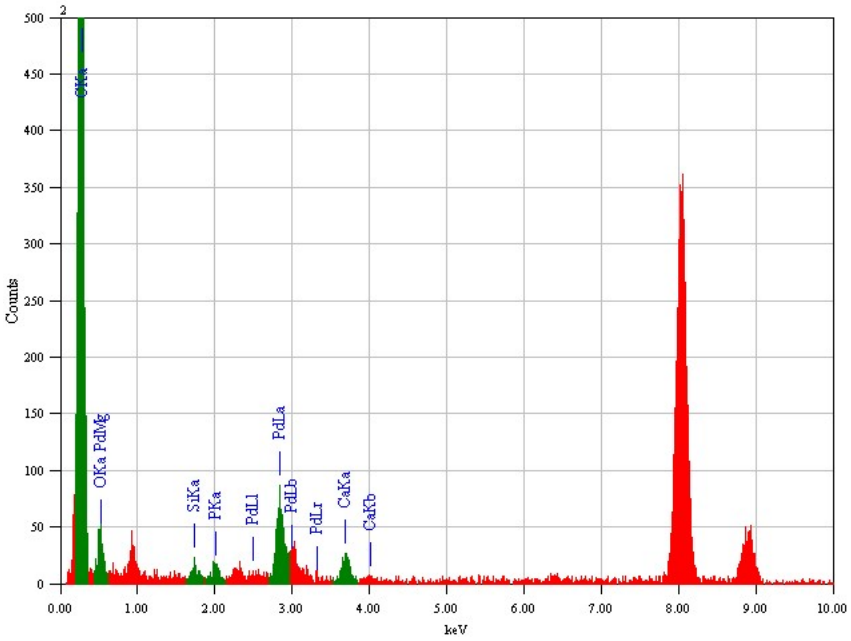
Figure S7. STEM area analysis of DMPSi-Pd/AC-CP (3:1) before use



・Area 1



· Area 2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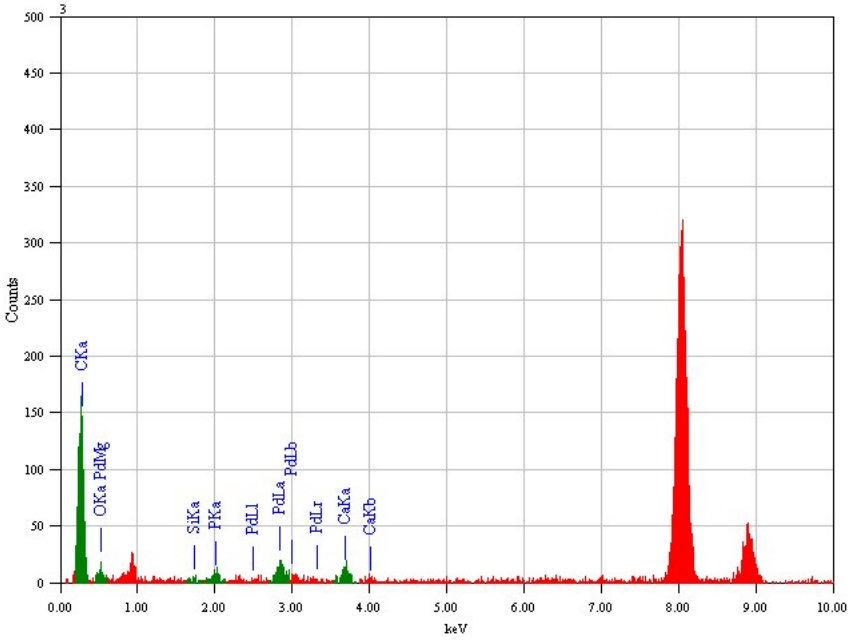
· Area 3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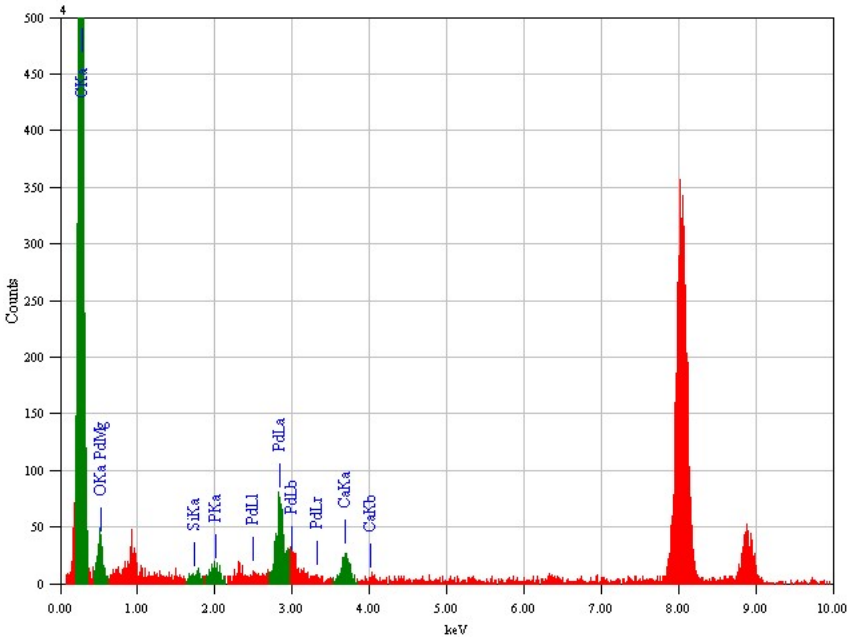
・Area 4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keV
OKa
OKa PdMg
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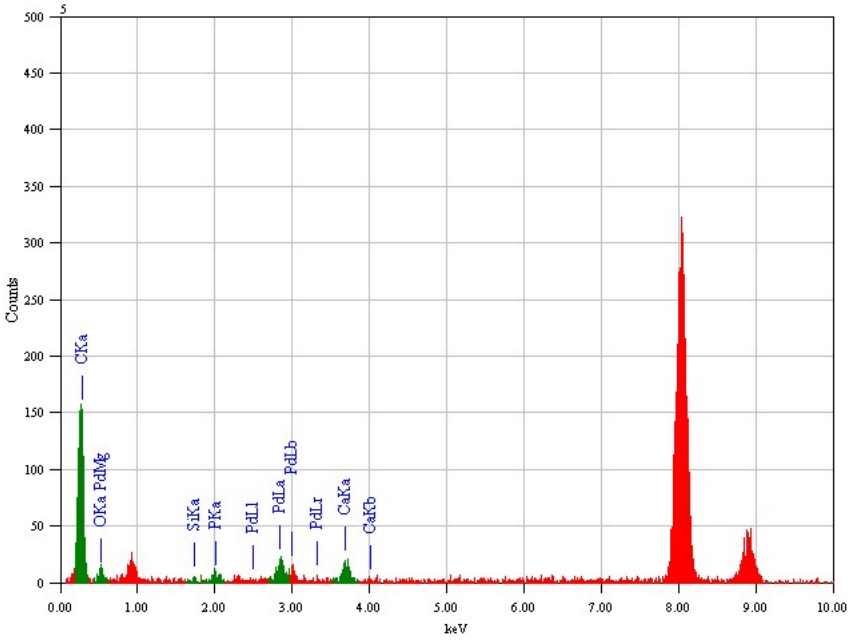
・Area 5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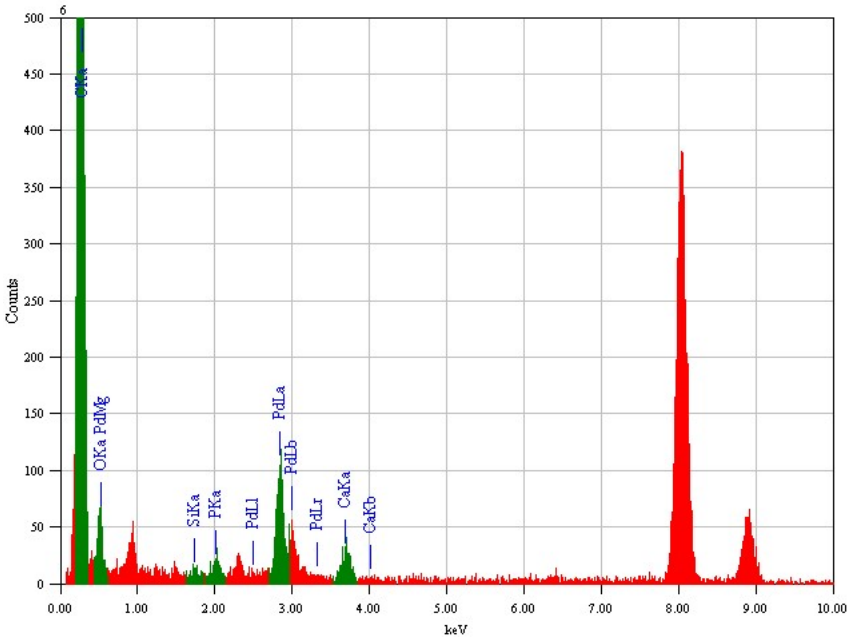
· Area 6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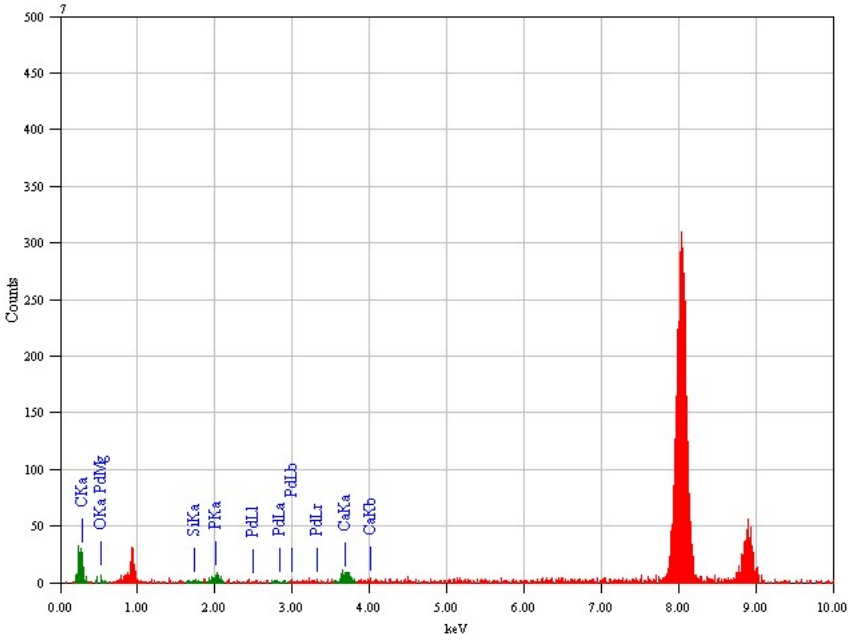
· Area 7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Counts
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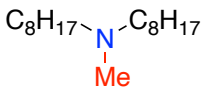
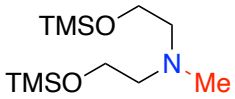
6. Spectroscopic Information of the Products



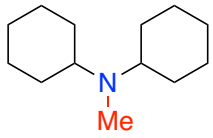
2a

N-Methyl-di-*n*-octylamine (2a)[3]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 2.31 (t, 4H, J = 7.56 Hz), 2.21 (s, 3H), 1.48-1.40 (m, 4H), 1.32-1.18 (m, 20H), 0.88 (t, 6H, J = 6.87 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 57.9, 42.3, 31.8, 29.6, 29.3, 27.6, 27.2, 22.6, 14.1.



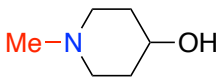
2b

N-Methyl-bis[2-(trimethylsilyloxy)ethyl]amine (2b)[4]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 3.56 (t, 4H, J = 6.53 Hz), 2.46 (t, 4H, J = 6.53 Hz), 2.20 (s, 3H), 0.00 (s, 18H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 61.2, 60.5, 44.2, 0.2.



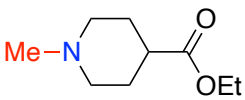
2c

N-Methyl-dicyclohexylamine (2c)[5]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 2.57-2.47 (m, 2H), 2.24 (s, 3H), 1.77-1.70 (m, 8H), 1.61-1.60 (m, 2H), 1.26-1.21 (m, 8H), 1.15-1.03 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 59.2, 32.8, 30.5, 26.2, 26.1.



2d

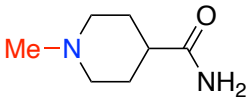
N-Methyl-4-hydroxypiperidine (2d)[6]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 3.63-3.57 (m, 1H), 2.71-2.61 (m, 2H), 2.21 (s, 3H), 2.10-2.02 (m, 2H), 1.86-1.80 (m, 2H), 1.59-1.51 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 66.6, 53.1, 45.8, 34.2.



2e

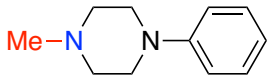
Ethyl N-methyl-4-piperidinecarboxylate (2e)[7]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 4.13

(q, 2H, J = 7.10 Hz), 2.83-2.82 (m, 2H), 2.29-2.22 (m, 4H), 2.02-2.01 (m, 2H), 1.93-1.90 (m, 2H), 1.80-1.76 (m, 2H), 1.25 (t, 3H, J = 6.87 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 174.9, 60.2, 54.8, 46.2, 40.3, 28.0, 14.1.



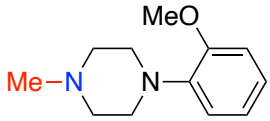
2f

N-Methyl-4-piperidinecarboxamide (2f)[8]: ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm): 7.19 (s, 1H), 6.70 (s, 1H), 2.73 (d, 2H, J = 11.00 Hz), 2.11 (s, 3H), 1.99-1.95 (m, 1H), 1.78 (t, 2H, J = 11.00 Hz), 1.66-1.62 (m, 2H), 1.54-1.39 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm): 176.6, 54.9, 46.2, 41.1, 28.5.



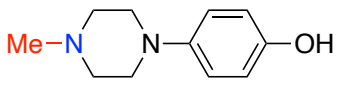
2g

N-Methyl-N'-phenylpiperazine (2g)[9]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.25-7.23 (m, 2H), 6.93-6.91 (m, 2H), 6.85-6.84 (m, 1H), 3.20 (t, 4H, J = 5.15 Hz), 2.56 (t, 4H, J = 5.15 Hz), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 151.1, 128.9, 119.5, 115.9, 55.0, 48.9, 46.0.



2h

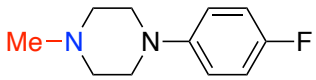
N-Methyl-N'-(2-methoxyphenyl) piperazine (2h)[10]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 6.93-6.80 (m, 3H), 6.78-6.75 (m, 1H), 3.78 (s, 3H), 3.09-2.96 (m, 4H), 2.58-2.51 (m, 4H), 2.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 152.1, 141.2, 122.7, 120.8, 118.1, 111.0, 55.23, 55.19, 50.5, 46.1.



2i

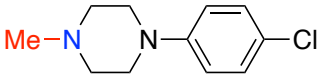
N-Methyl-N'-(4-hydroxyphenyl) piperazine (2i)[11]: ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm): 8.79 (br s, 1 H), 6.75 (d, 2H, J = 7.56 Hz), 6.63 (d, 2H, J = 8.25 Hz), 2.94-2.92 (m, 4H), 2.44-2.40 (m, 4H), 2.19 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm): 150.8,

144.2, 117.6, 115.4, 54.8, 49.8, 45.7.



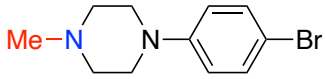
2j

N-Methyl-N'-(4-fluorophenyl) piperazine (2j)[9]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 6.94-6.89 (m, 2H), 6.86-6.82 (m, 2H), 3.09 (t, 4H, J = 4.81 Hz), 2.53 (t, 4H, J = 4.81 Hz), 2.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 157.9, 156.3, 147.9, 117.7 (d, J = 28.7 Hz), 115.4 (d, J = 86.2 Hz), 55.1, 50.1, 46.1; ^{19}F NMR (471 MHz, $CDCl_3$): δ (ppm): -124.5.



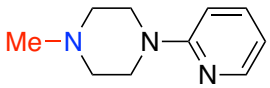
2k

N-Methyl-N'-(4-chlorophenyl) piperazine (2k)[12]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.13 (d, 2H, J = 8.50 Hz), 6.77 (d, 2H, J = 8.50 Hz), 3.10 (t, 4H, J = 4.12 Hz), 2.50 (t, 4H, J = 4.47 Hz), 2.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 149.8, 128.9, 124.5, 117.2, 54.9, 49.0, 46.0.



2l

N-Methyl-N'-(4-chlorophenyl) piperazine (2l)[13]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.25 (d, 2H, J = 8.25 Hz), 6.70 (d, 2H, J = 8.25 Hz), 3.09 (t, 4H, J = 4.47 Hz), 2.47 (t, 4H, J = 4.81 Hz), 2.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 150.3, 131.8, 117.6, 111.7, 54.9, 48.9, 46.1.

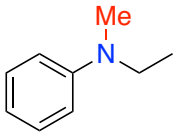


2m

N-Methyl-N'-(2-pyridyl) piperazine (2m)[13]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 8.20-8.18 (m, 1H), 7.47 (ddd, 1H, J = 8.90, 7.10, 2.00 Hz), 6.66-6.60 (m, 2H), 3.56 (t, 4H, J = 5.15 Hz), 2.52 (t, 4H, J = 5.15 Hz), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 159.5, 147.9, 137.3, 113.2, 107.0, 54.8, 46.2, 45.1.

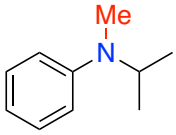
2n

N-Methyl-N-ethyl-benzylamine (2n)[15]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.26-7.22 (m, 4H), 7.19-7.15 (m, 1H), 3.41 (s, 2H), 2.38 (q, 2H, J = 7.10 Hz), 2.12 (s, 3H), 1.03 (t, 3H, J = 7.22 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 139.1, 129.0, 128.1, 126.8, 61.9, 51.1, 41.6, 12.4.



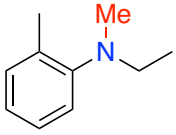
2o

N-Methyl-N-ethylaniline (2o)[3]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.25-7.22 (m, 2H), 6.74-6.69 (m, 3H), 3.40 (q, 2H, J = 7.10 Hz), 2.90 (s, 3H), 1.12 (t, 3H, J = 7.10 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 148.9, 129.1, 116.1, 112.4, 46.7, 37.4, 11.1.



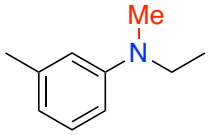
2p

N-methyl-N-isopropylaniline (2p)[16]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.25-7.22 (m, 2H), 6.81 (d, 2H, J = 7.56 Hz), 6.71 (t, 1H, J = 7.22 Hz), 4.12-4.09 (m, 2H), 2.74 (s, 3H), 1.17 (d, 6H, J = 6.19 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 150.1, 129.0, 116.4, 113.3, 48.9, 29.7, 19.2.



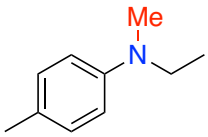
2q

N-Methyl-N-ethyl-*o*-toluidine (2q)[3]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.16 (q, 2H, J = 7.56 Hz), 7.04 (d, 1H, J = 8.25 Hz), 6.95 (t, 1H, J = 7.22 Hz), 2.91 (q, 2H, J = 7.10 Hz), 2.68 (s, 3H), 2.31 (s, 3H), 1.10 (t, 3H, J = 7.22 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 152.2, 133.1, 131.0, 126.2, 122.6, 119.8, 50.4, 40.9, 18.3, 12.8.



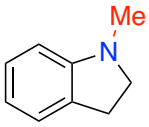
2r

N-Methyl-N-ethyl-*m*-toluidine (2r)[3]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.19-7.16 (m, 1H), 6.60-6.58 (m, 3H), 3.43 (q, 2H, J = 7.10 Hz), 2.93 (s, 3H), 2.37 (s, 3H), 1.16 (t, 3H, J = 7.10 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 149.1, 138.7, 129.0, 117.1, 113.2, 109.7, 46.8, 37.4, 21.9, 11.2.



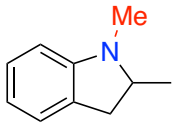
2s

N-Methyl-N-ethyl-*p*-toluidine (2s)[3]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 6.96 (d, 2H, J = 8.25 Hz), 6.61-6.57 (m, 2H), 3.28 (q, 2H, J = 7.10 Hz), 2.78 (s, 3H), 2.18 (s, 3H), 1.01 (t, 3H, J = 7.10 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): 147.1, 129.6, 125.4, 112.9, 47.1, 37.6, 20.1, 11.0.



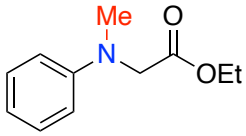
2t

1-Methylindoline (2t): ^{1}H NMR (600 MHz, $CDCl_3$) [3]: δ (ppm): 7.09-7.06 (m, 2H), 6.66 (t, 1H, J = 7.22 Hz), 6.48 (d, 1H, J = 8.25 Hz), 3.28 (t, 2H, J = 8.25 Hz), 2.93 (t, 2H, J = 7.90 Hz), 2.75 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 153.4, 130.3, 127.3, 124.2, 117.7, 107.2, 56.1, 36.2, 28.7.



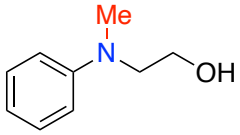
2u

1,2-Dimethylindoline (2u)[5]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.08-7.03 (m, 2H), 6.65 (t, 1H, J = 7.22 Hz), 6.44 (d, 1H, J = 8.25 Hz), 3.42-3.36 (m, 1H), 3.07 (q, 1H, J = 7.79 Hz), 2.70 (s, 3H), 2.59 (dd, 1H, J = 15.12, 10.31 Hz), 1.32 (d, 3H, J = 6.19 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 153.5, 129.2, 127.3, 124.0, 117.8, 107.1, 62.8, 37.3, 33.7, 18.7.



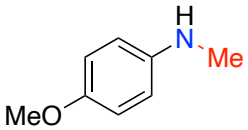
2v

N-Methyl-N-phenylglycine ethyl ester (2v)[17]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.22 (m t, 2H, J = 7.90 Hz), 6.74 (t, 1H, J = 7.22 Hz), 6.68 (d, 2H, J = 8.25 Hz), 4.16 (q, 2H, J = 7.10 Hz), 4.05 (s, 2H), 3.06 (s, 3H), 1.23 (t, 3H, J = 6.87 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 170.9, 148.8, 129.0, 117.2, 112.2, 60.7, 54.4, 39.4, 14.1.



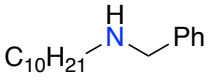
2w

2-(N-Methylanilino)-ethanol (2w)[18]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.24 (t, 2H, J = 7.90 Hz), 6.83-6.72 (m, 3H), 3.78 (t, 2H, J = 5.50 Hz), 3.45 (t, 2H, J = 5.84 Hz), 2.95 (s, 3H), 2.04 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 149.8, 129.1, 117.0, 112.8, 59.8, 55.2, 38.6.



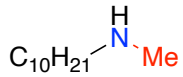
5

N-methyl-*p*-anisidine (5): ^{1}H NMR (600 MHz, $CDCl_3$)[19]: δ (ppm): 6.80 (d, 2H, J = 8.94 Hz), 6.59 (d, 2H, J = 8.94 Hz), 3.75 (s, 3H), 3.42 (br, 1H), 2.80 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 152.0, 143.7, 114.9, 113.6, 55.8, 31.6.



8

N-Benzyl-*n*-decylamine (8)[20]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 7.24-7.22 (m, 4H), 7.17-7.15 (m, 1H), 3.70 (s, 2H), 2.54 (t, 2H, J = 7.22 Hz), 2.12 (br s, 1H), 1.45-1.41 (m, 2H), 1.25-1.02 (m, 14H), 0.79 (t, 3H, J = 6.87 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 139.2, 128.43, 128.38, 127.1, 53.6, 49.0, 31.9, 29.56, 29.53, 29.47, 29.38, 29.29, 27.3, 22.7, 14.1.



9

N-Methyl-*n*-decylamine (9)[21]: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 2.54 (t, 2H, J = 7.22 Hz), 2.41 (s, 3H), 1.48-1.43 (m, 2H), 1.29-1.21 (m, 15H), 0.85 (t, 3H, J = 6.87 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 52.0, 36.2, 31.8, 29.6, 29.51, 29.48, 29.2, 27.2, 22.6, 14.0.

7. References

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[2] Saito, Y.; Nishizawa, K.; Laroche, B.; Ishitani, H.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2022**, e202115643

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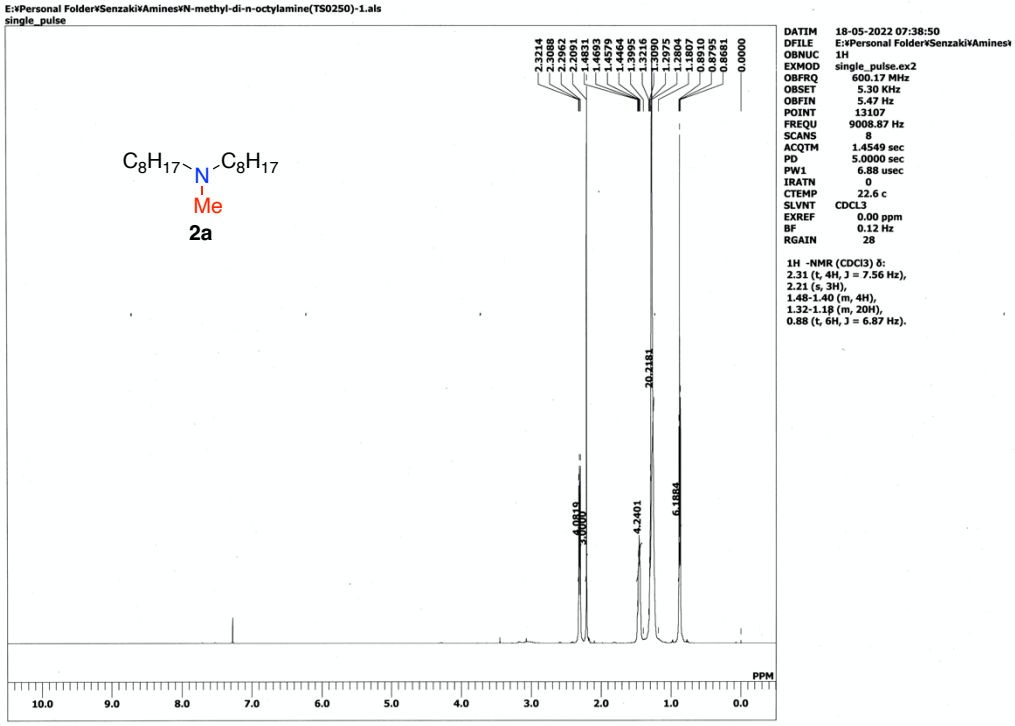
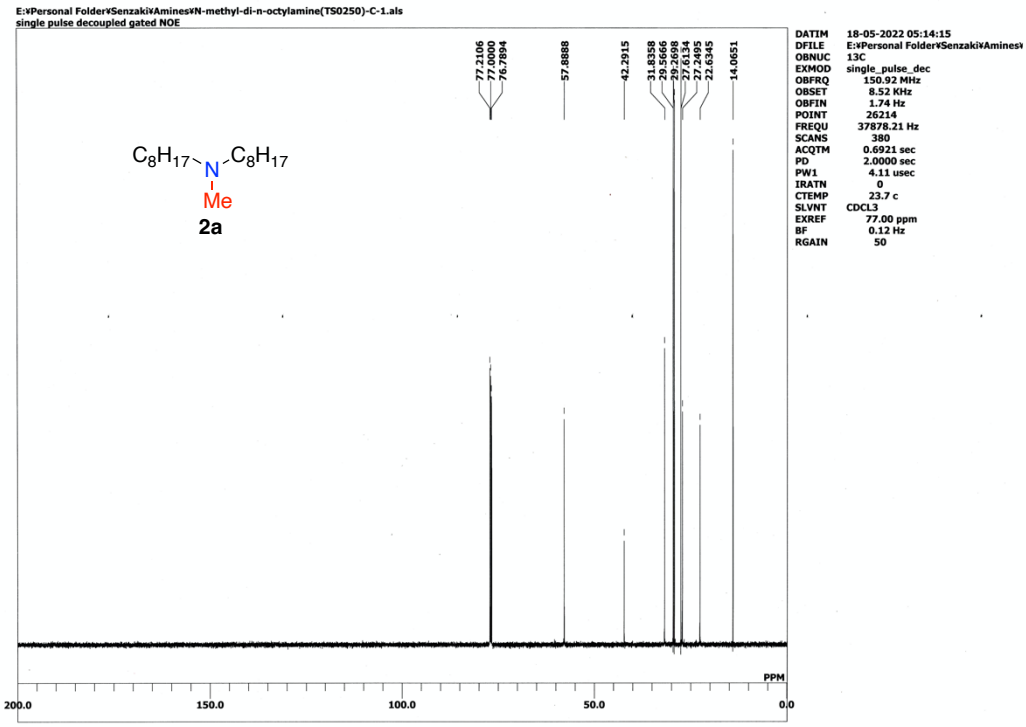
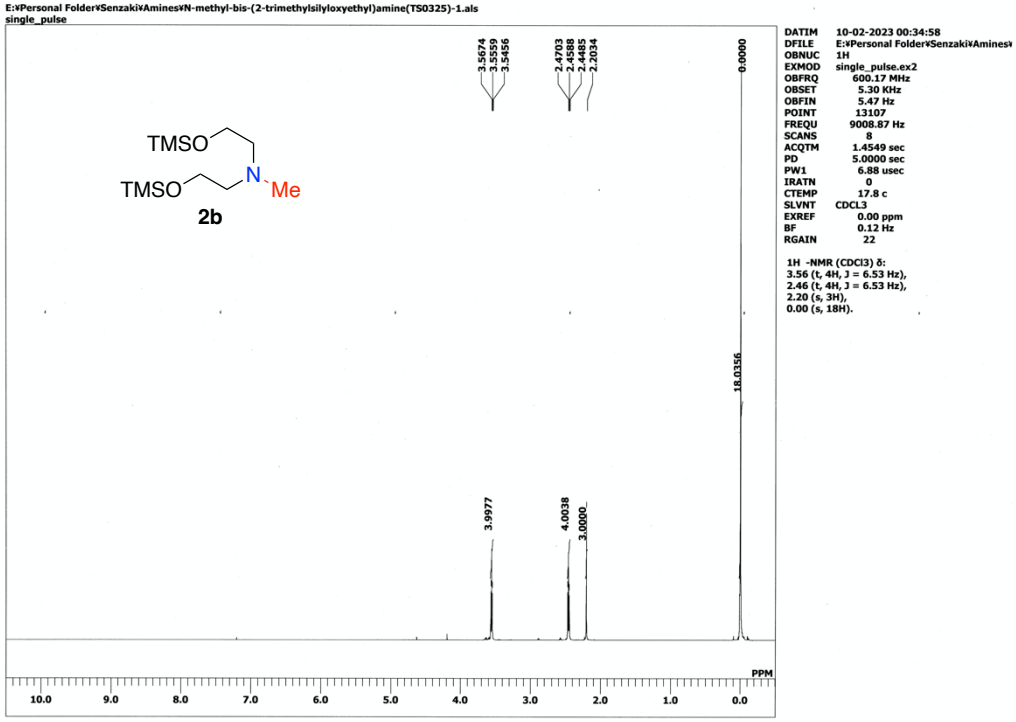
8. NMR Charts

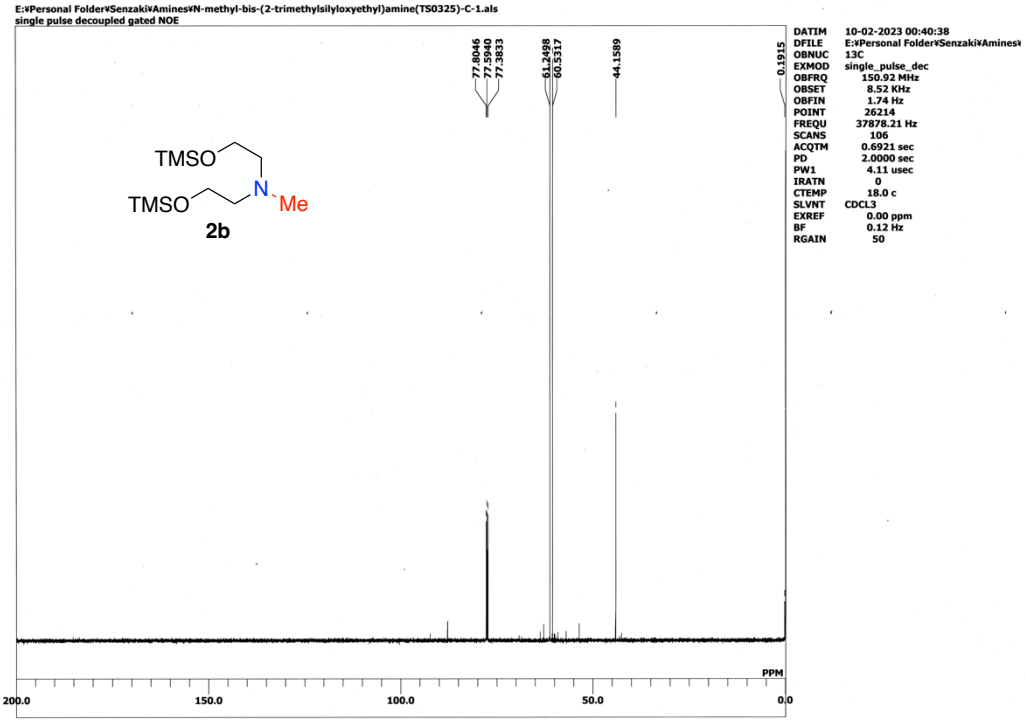
N-Methyl-di-*n*-octylamine (2a)



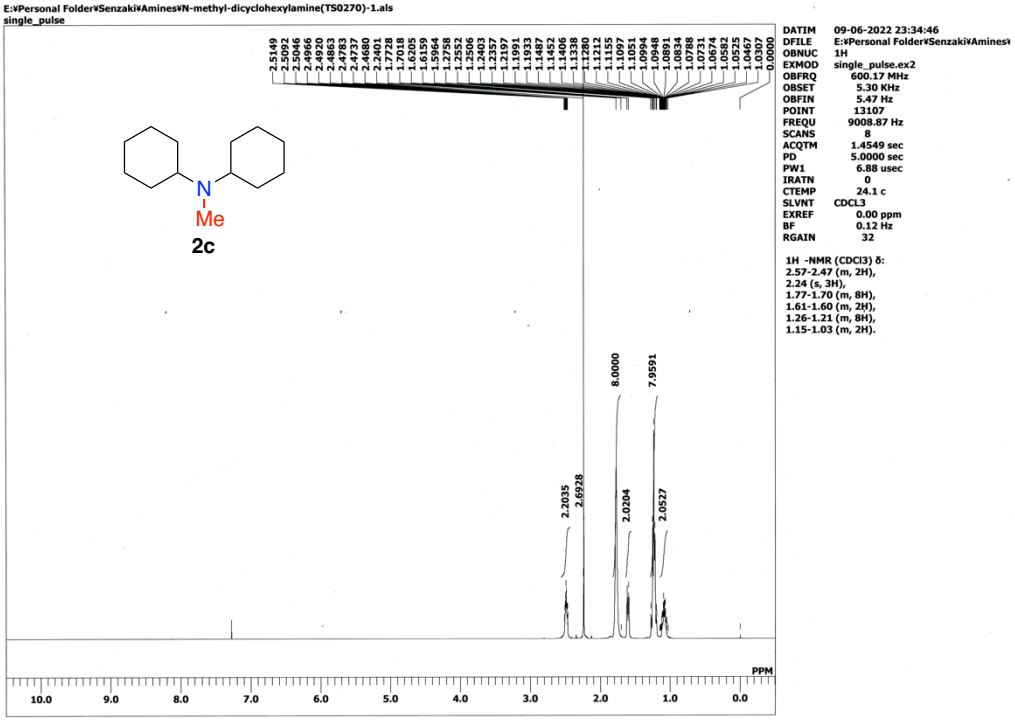


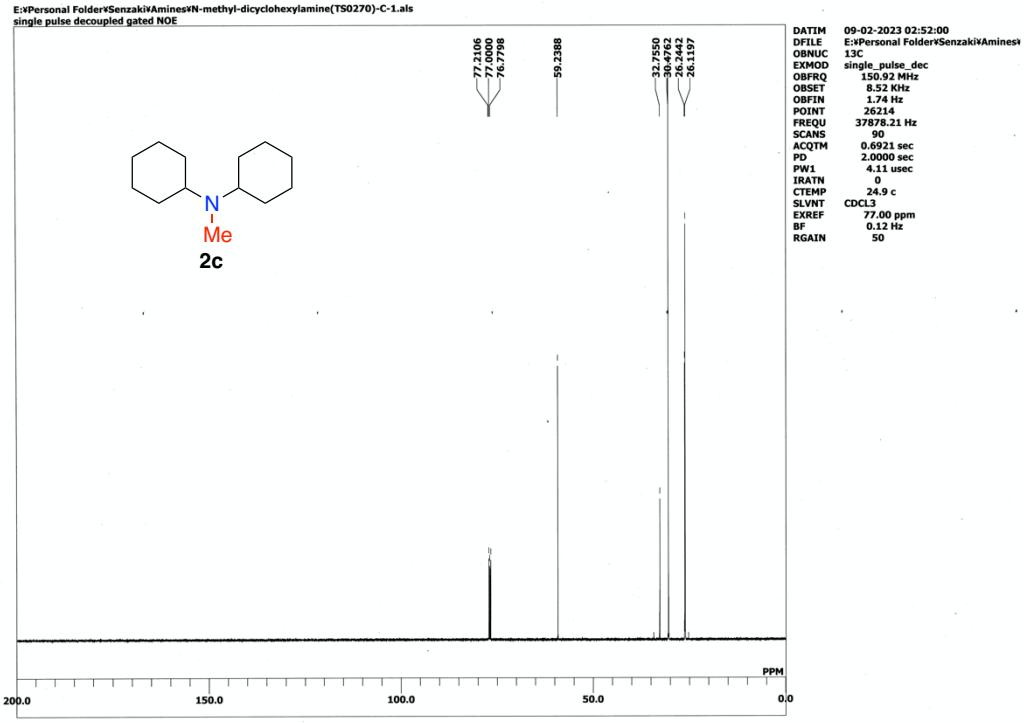
N-Methyl-bis[2-(trimethylsilyloxy)ethyl]amine (2b)





N-Methyl-dicyclohexylamine (2c)





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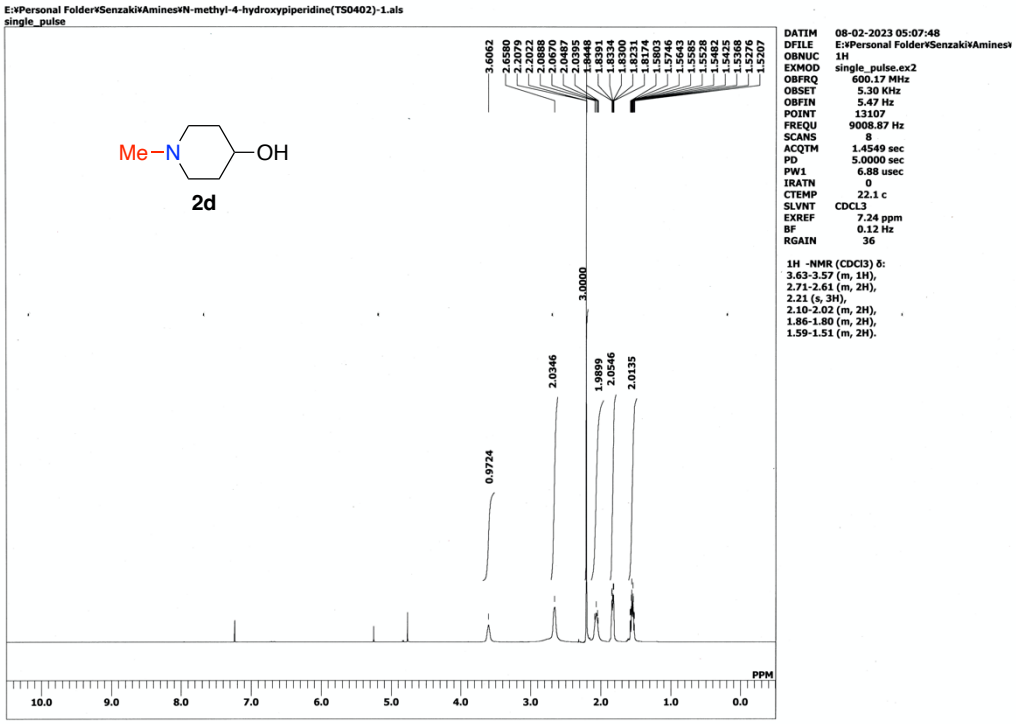
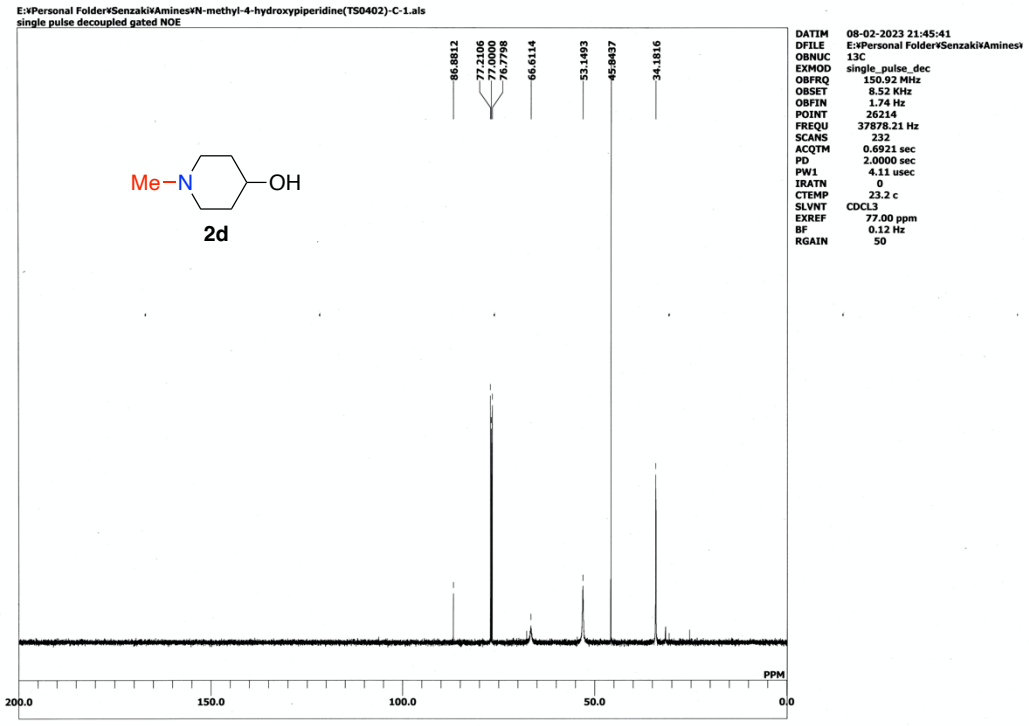
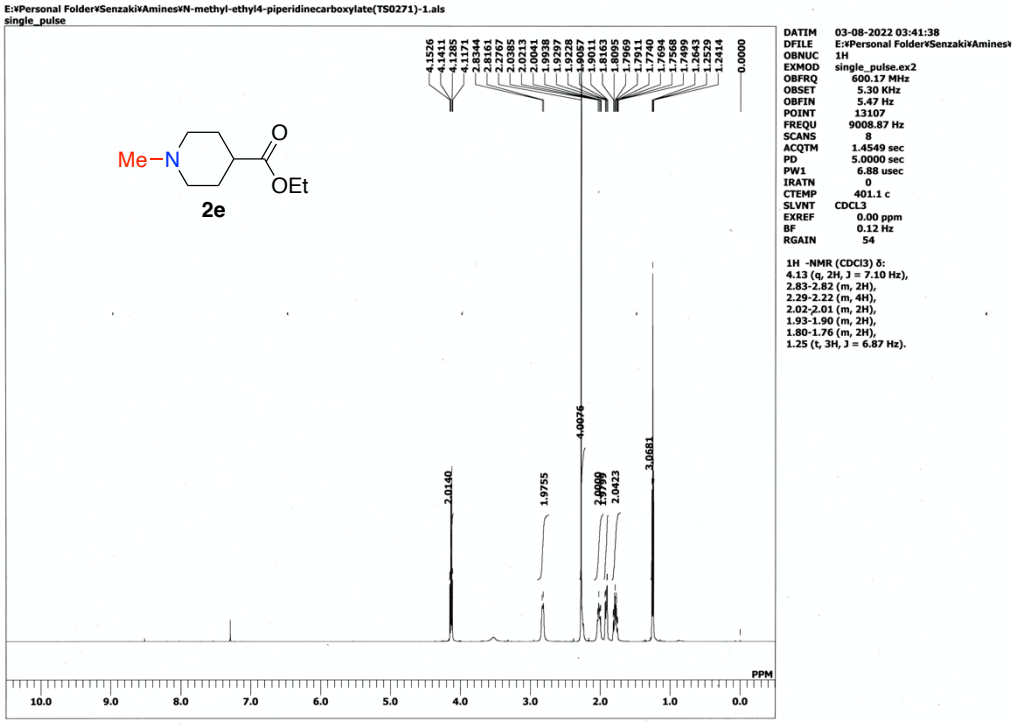
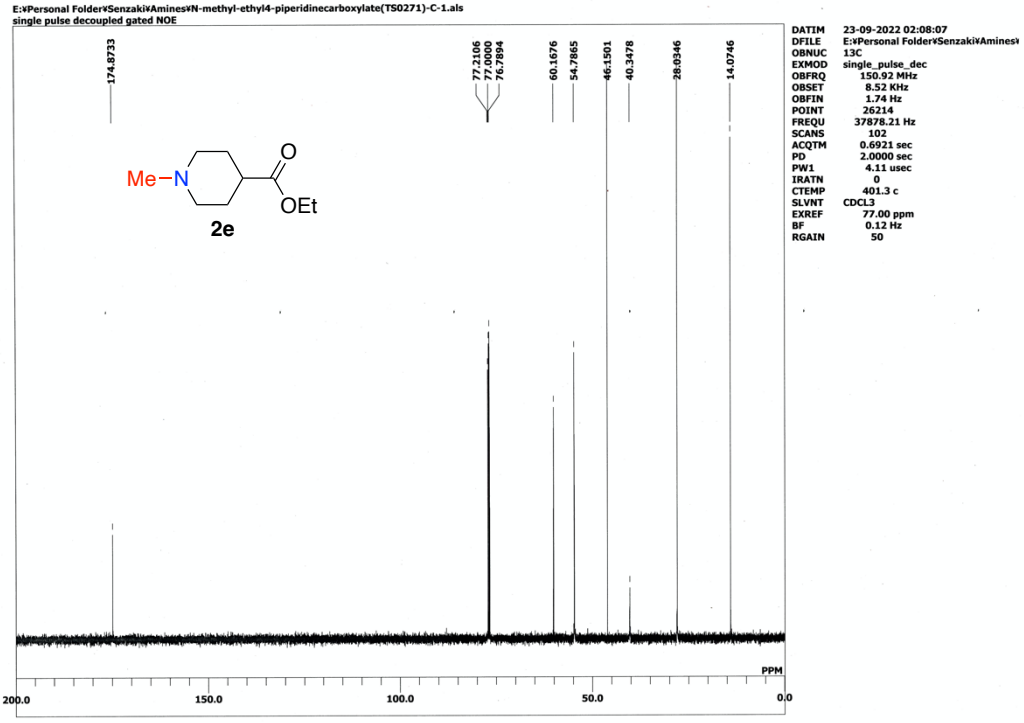




Ethyl N-methyl-4-piperidinecarboxylate (2e)





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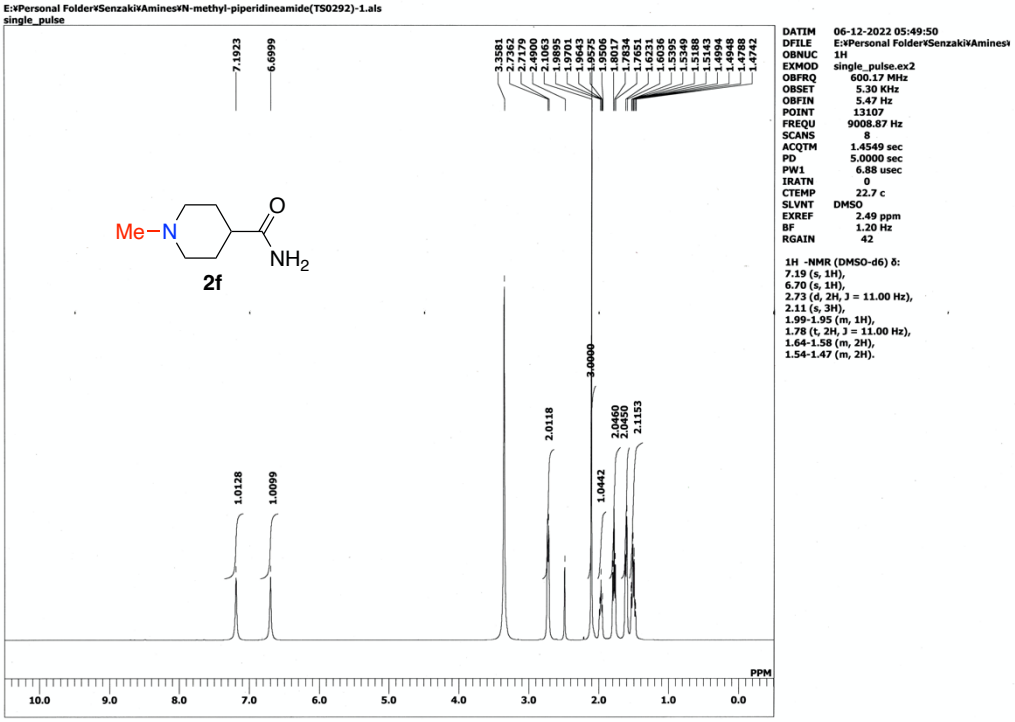

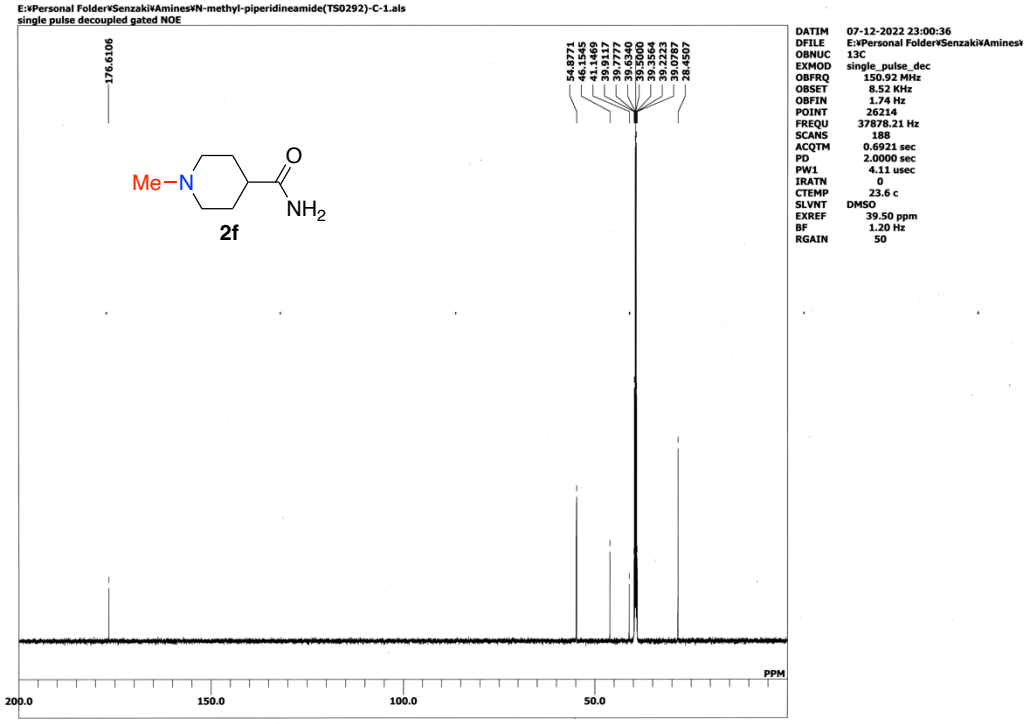

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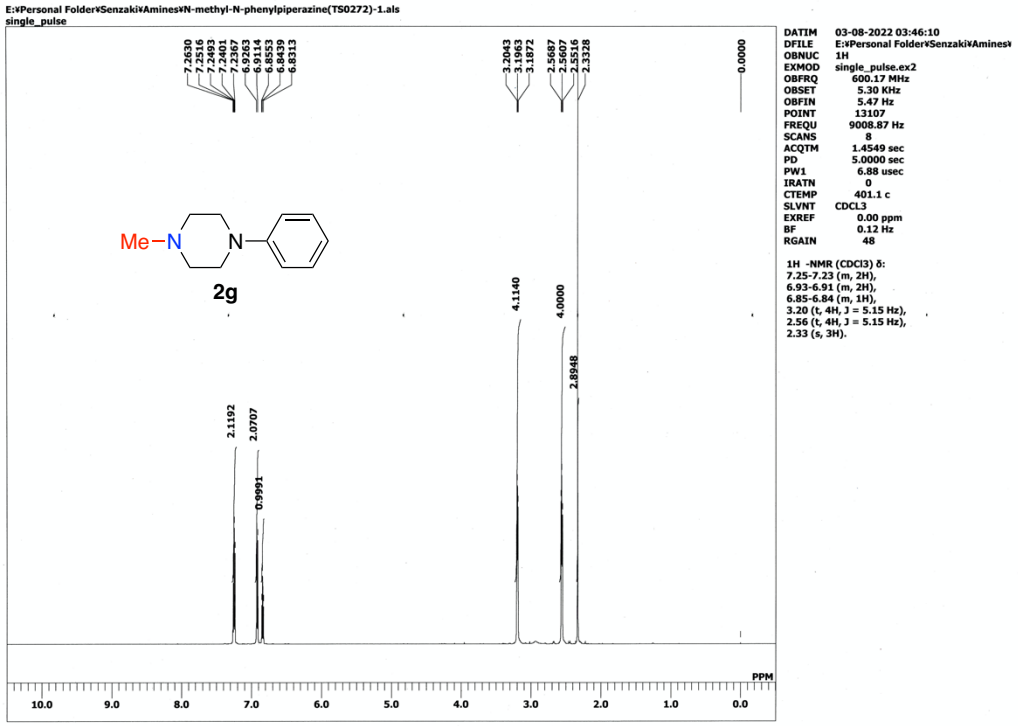
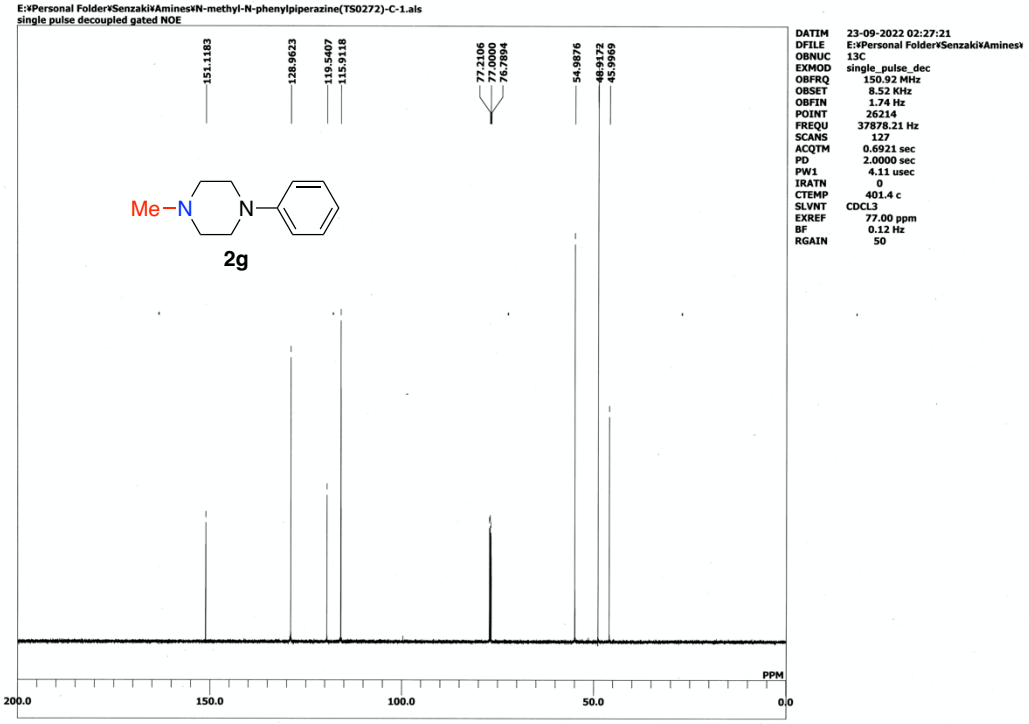
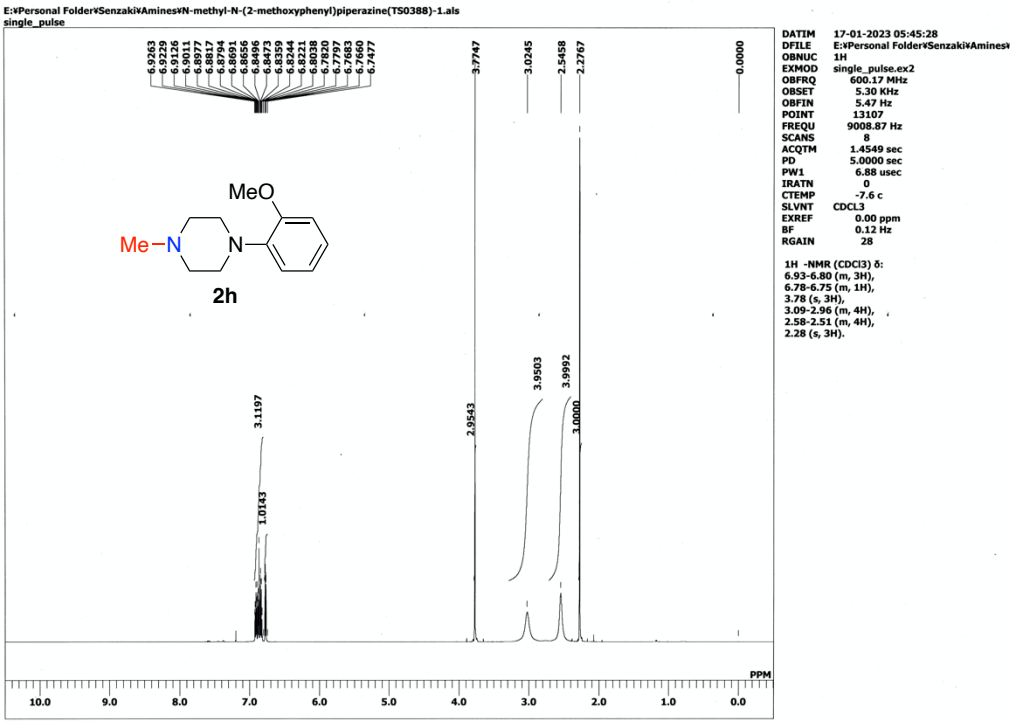
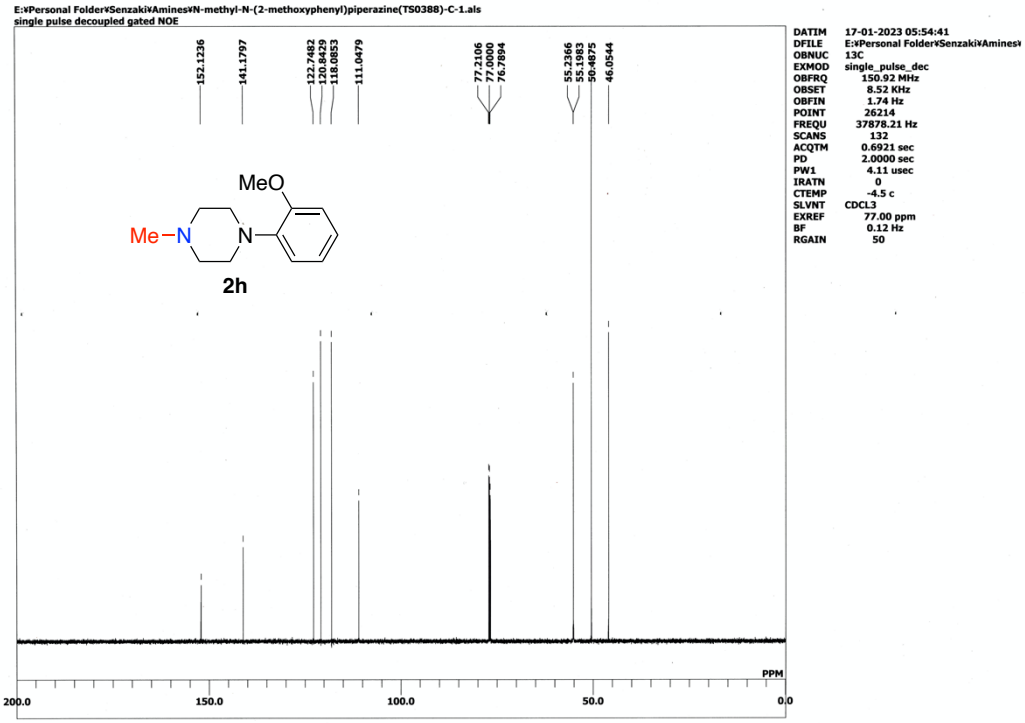




N-Methyl-N'-(2-methoxyphenyl) piperazine (2h)





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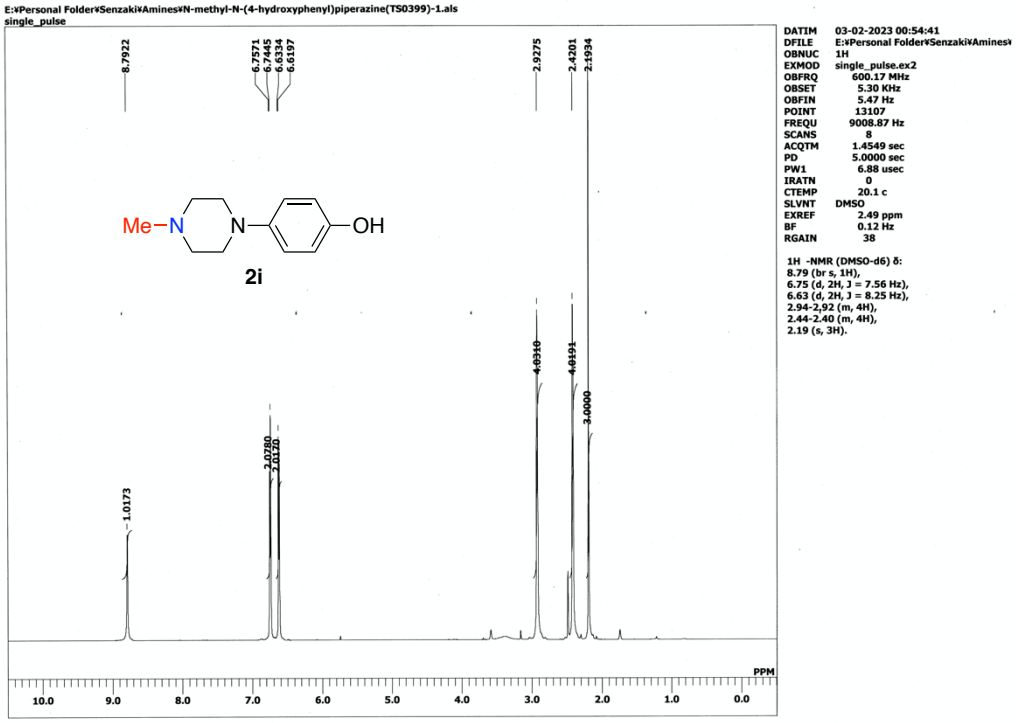
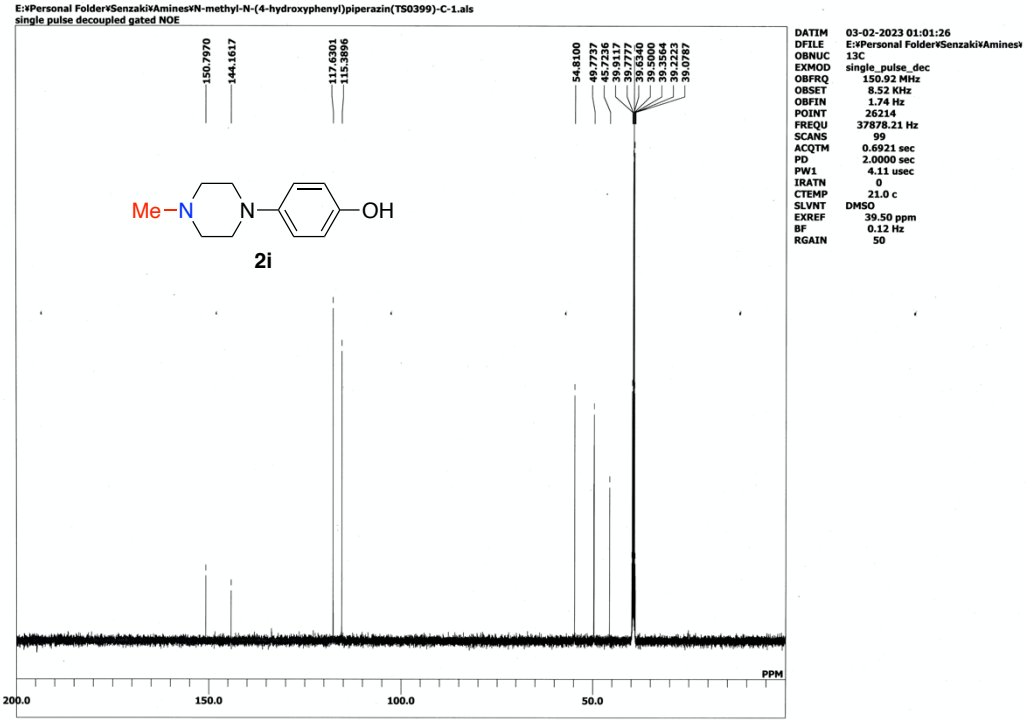
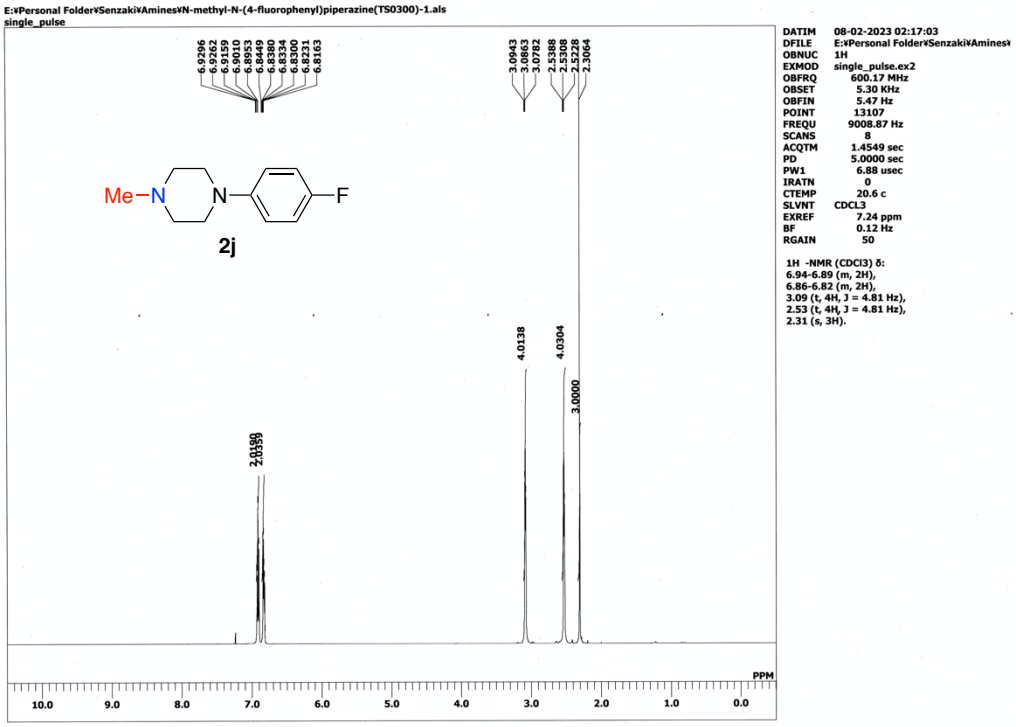
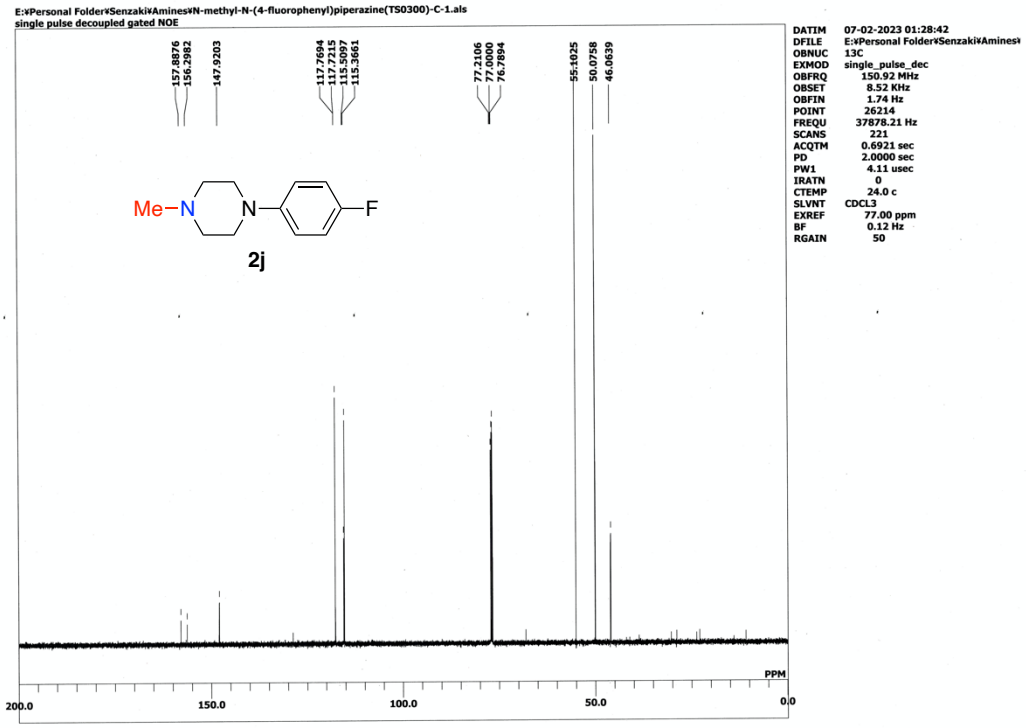
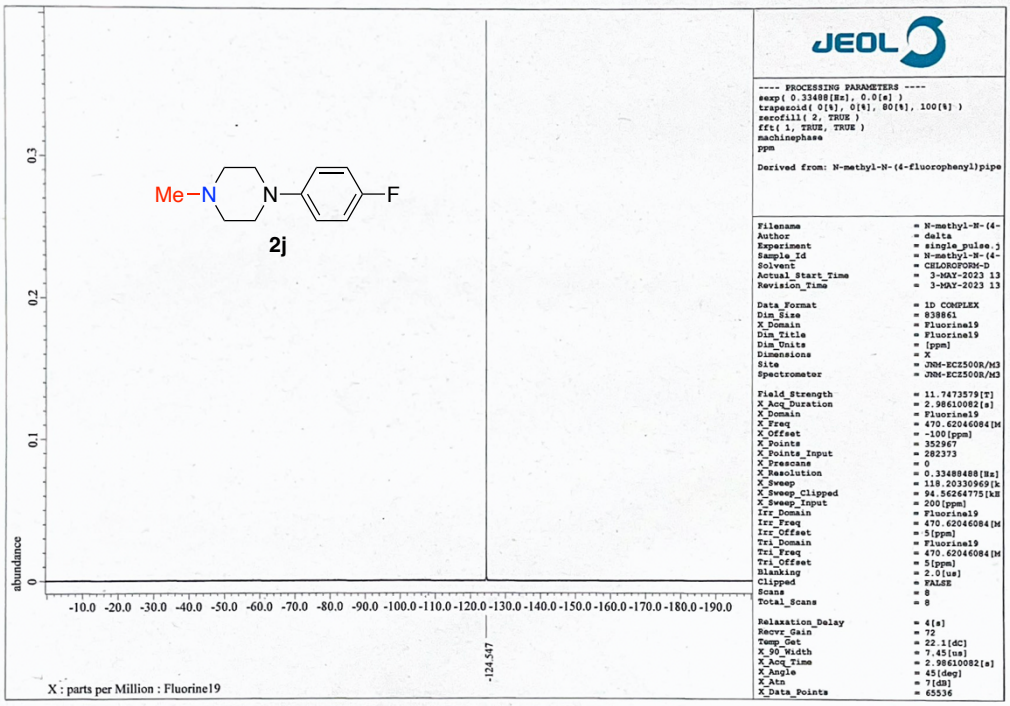




N-Methyl-N'-(4-fluorophenyl) piperazine (2j)






Me
N
N
F
2j
abundance
0.3
0.2
0.1
0
-10.0 -20.0 -30.0 -40.0 -50.0 -60.0 -70.0 -80.0 -90.0 -100.0 -110.0 -120.0 -130.0 -140.0 -150.0 -160.0 -170.0 -180.0 -190.0
-124.547
X : parts per Million : Fluorine19
JEOL
---- PROCESSING PARAMETERS ----
sexp(0.33408[Hz], 0.0[s])
trapezoid(0[%], 0[%], 80[%], 100[%])
zerofill(2, TRUE)
fft(1, TRUE, TRUE)
machinephase
ppm
Derived from: N-methyl-N-(4-fluorophenyl)pipe
Filename = N-methyl-N-(4-
Author = dalta
Experiment = single_pulse.j
Sample_Id = N-methyl-N-(4-
Solvent = CHLOROFORM-D
Actual_Start_Time = 3-MAY-2023 13
Revision_Time = 3-MAY-2023 13
Data_Format = 1D COMPLEX
Dim_Size = 838861
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Dim_Title = Fluorine19
Dim_Units = [ppm]
Dimensions = X
Site = JNM-ECZ500R/M3
Spectrometer = JNM-ECZ500R/M3
Field_Strength = 11.7473579[T]
X_Acq_Duration = 2.98610082[s]
X_Domain = Fluorine19
X_Freq = 470.62046084[M
X_Offset = -100[ppm]
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X_Points_Input = 282373
X_Prescans = 0
X_Resolution = 0.33489488[Hz]
X_Sweep = 118.20330969[k
X_Sweep_Clipped = 94.56264775[kH
X_Sweep_Input = 200[ppm]
Irr_Domain = Fluorine19
Irr_Freq = 470.62046084[M
Irr_Offset = 5[ppm]
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Tri_Offset = 5[ppm]
Blanking = 2.0[us]
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Total_Scans = 8
Relaxation_Delay = 4[s]
Recvr_Gain = 72
Temp_Get = 22.1[dC]
X_90_Width = 7.45[us]
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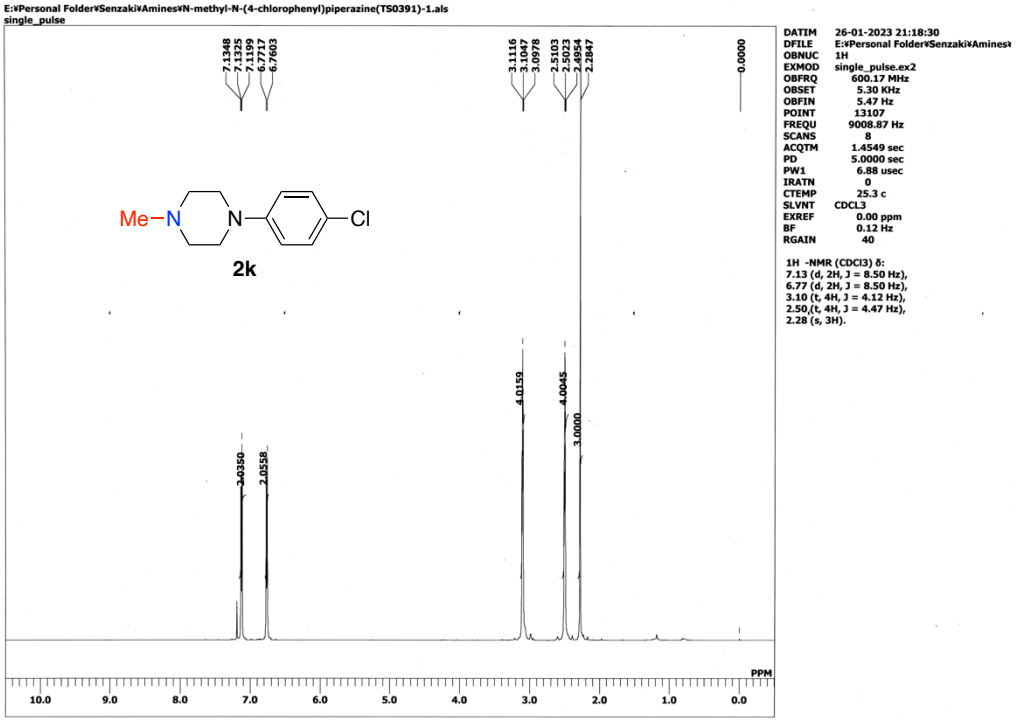
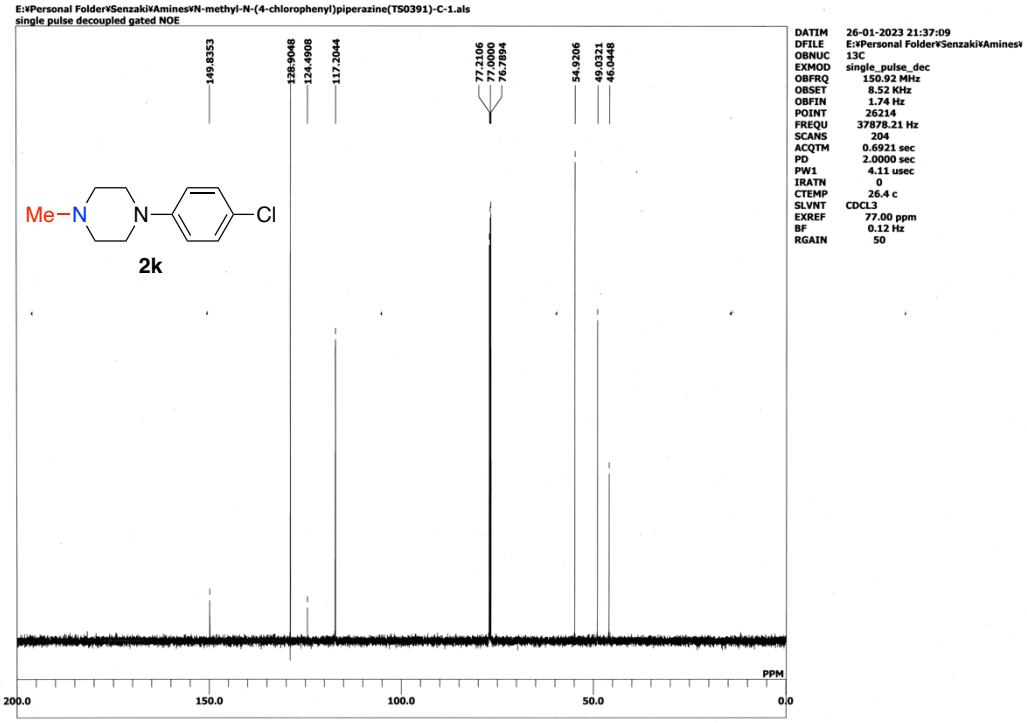
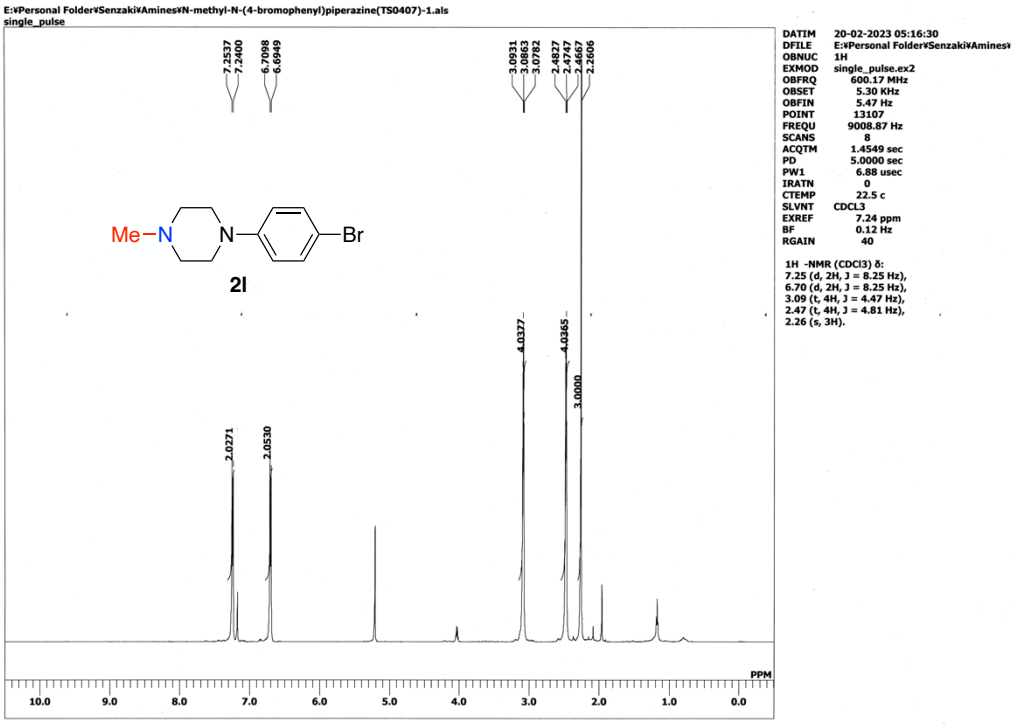
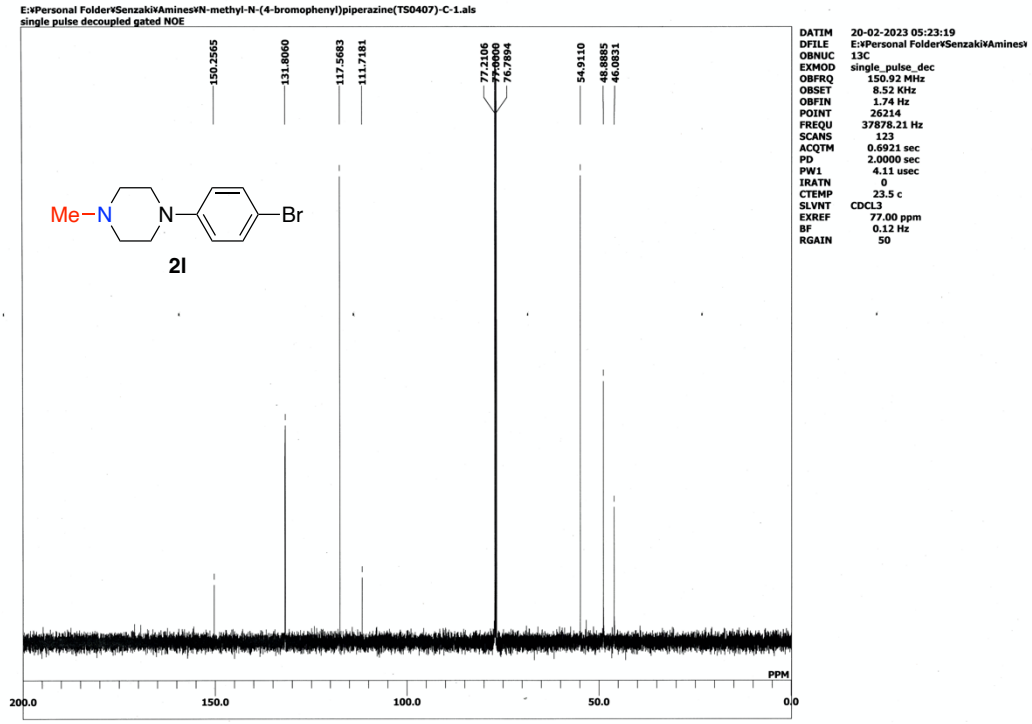
N-Methyl-N'-(4-chlorophenyl) piperazine (2k)



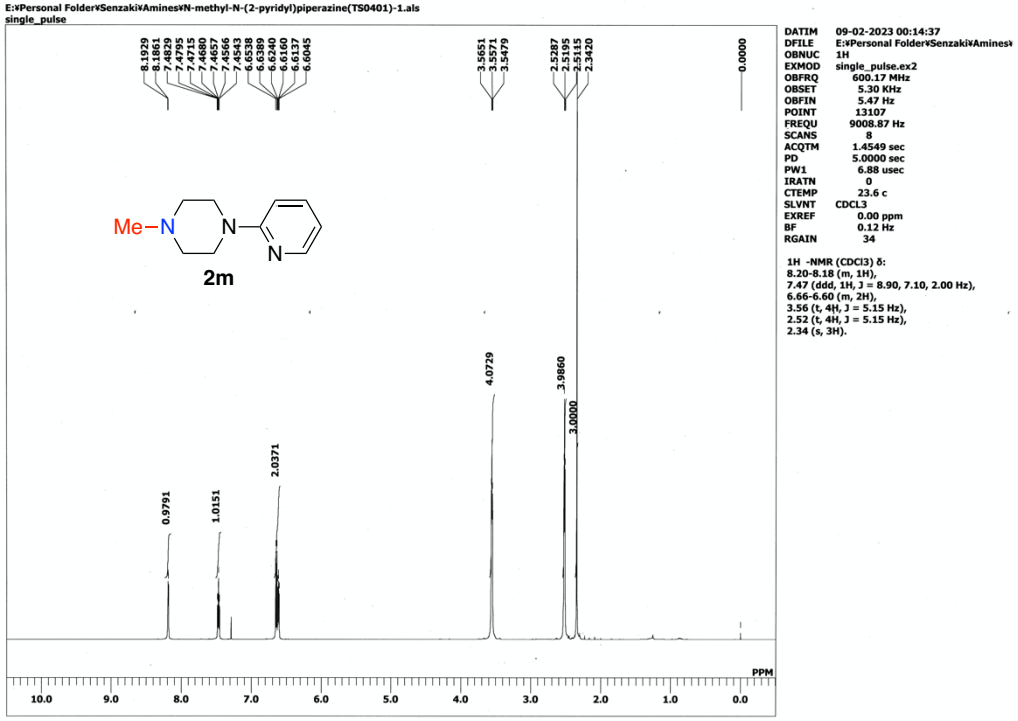


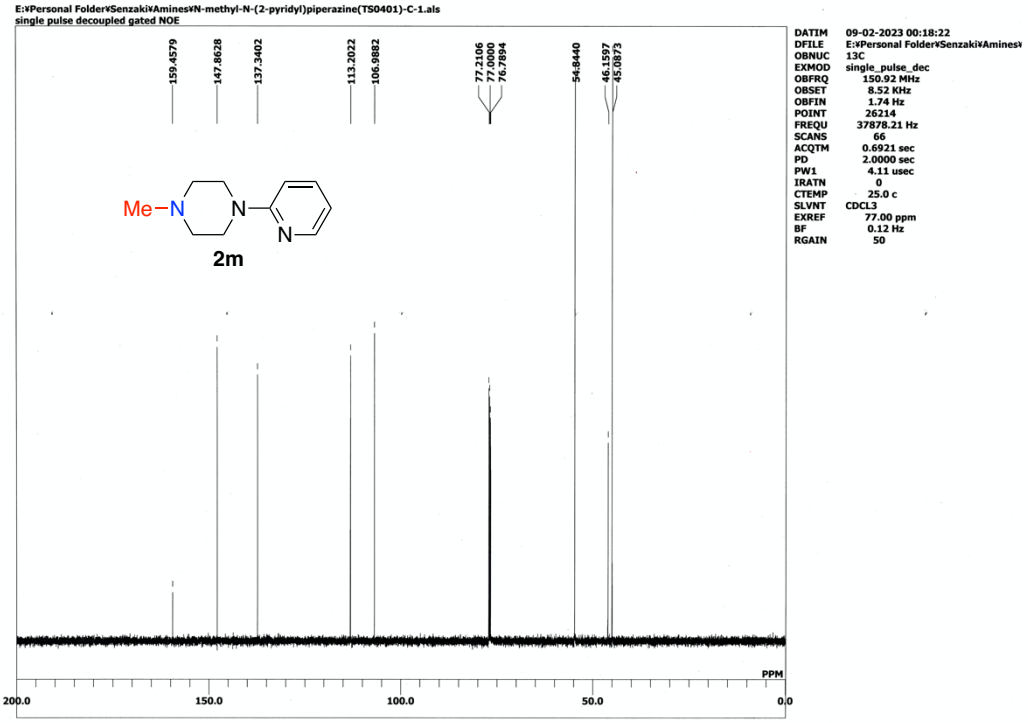
N-Methyl-N'-(4-bromophenyl) piperazine (2l)





N-Methyl-N'-(2-pyridyl) piperazine (2m)





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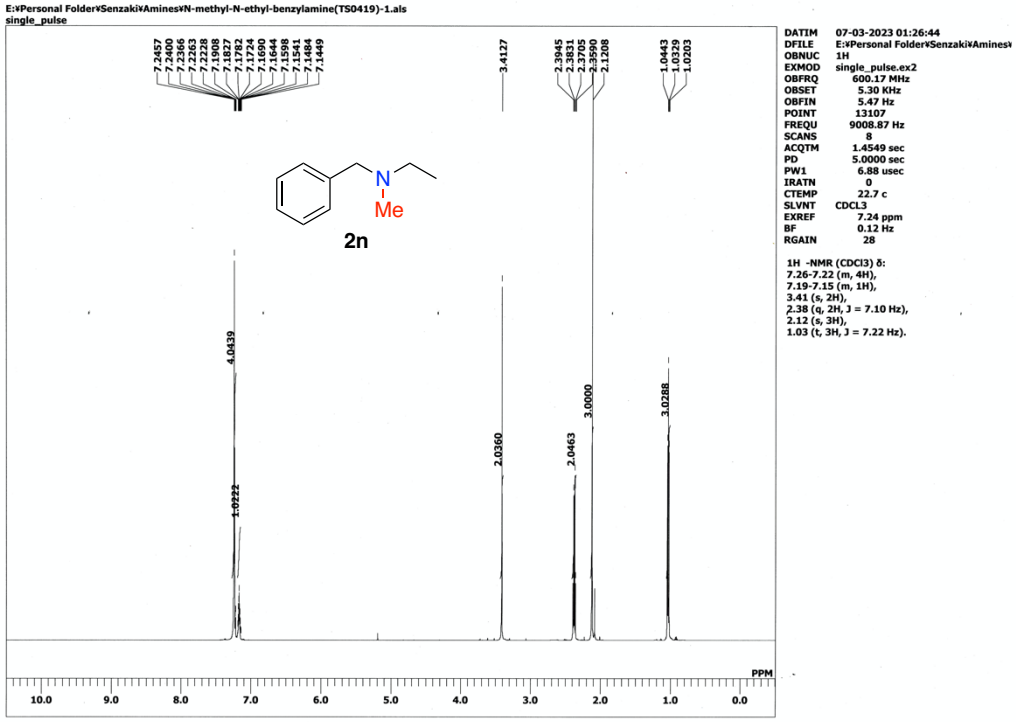

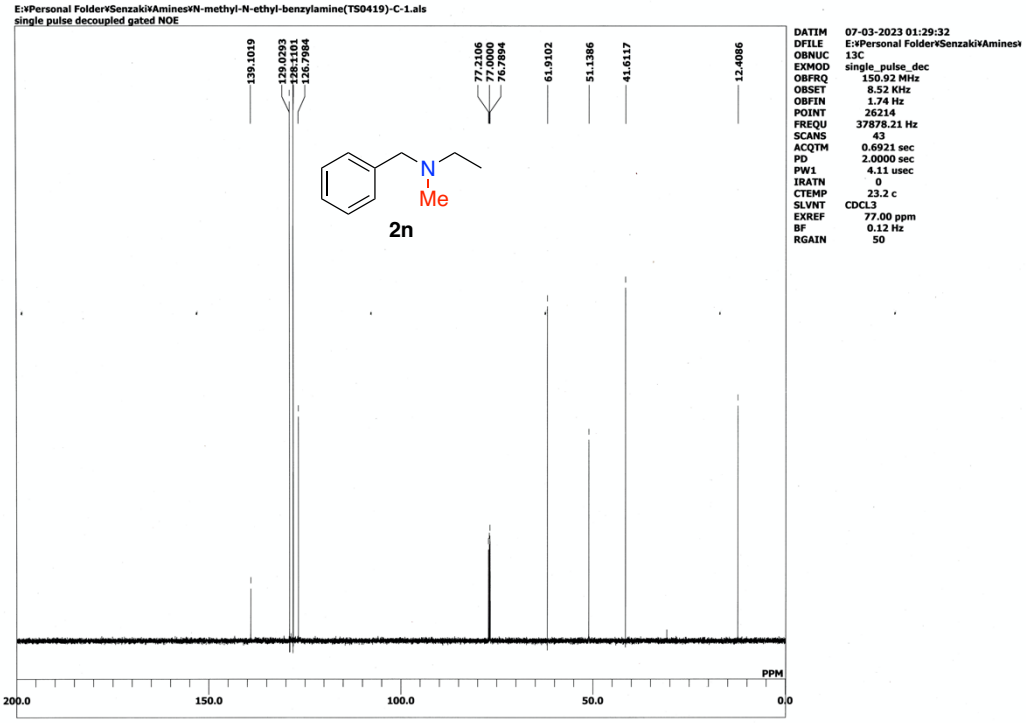

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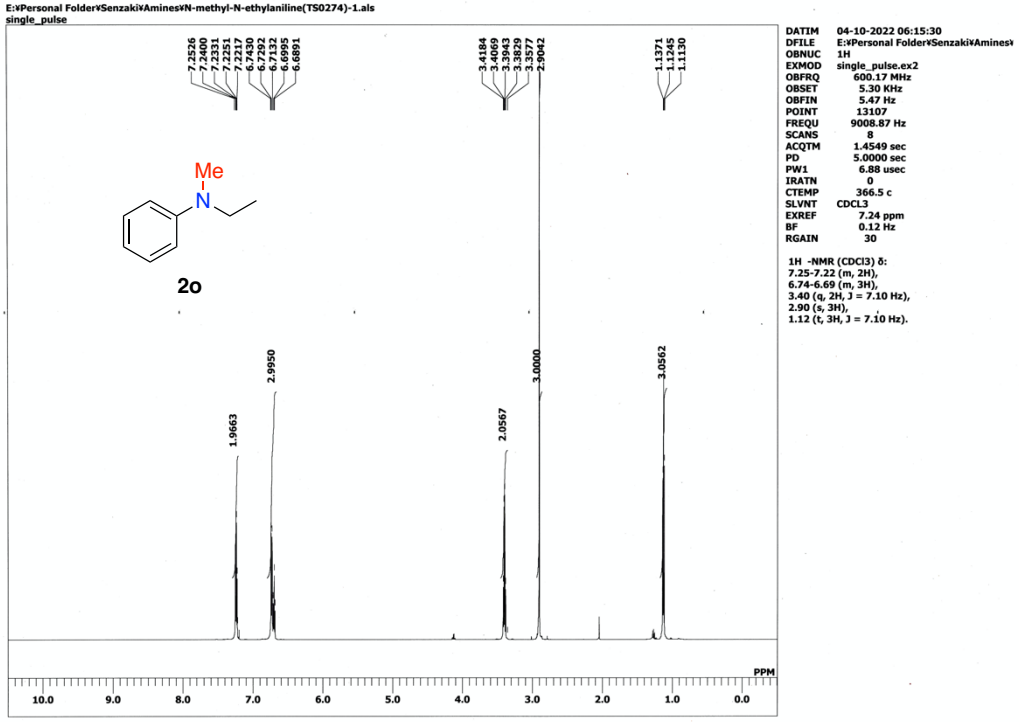

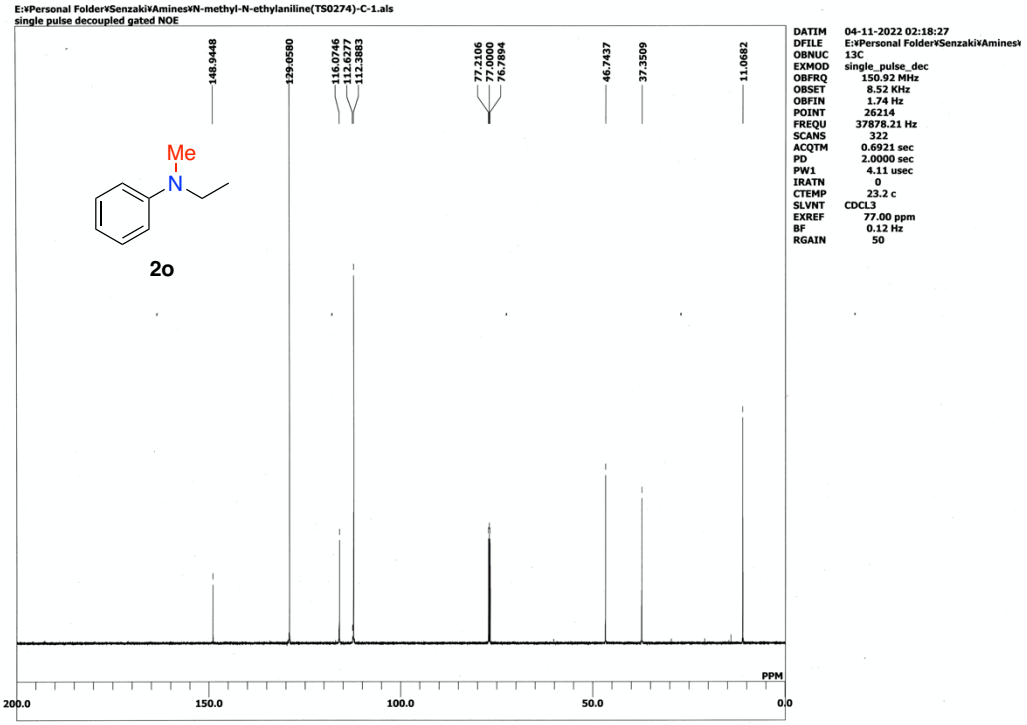

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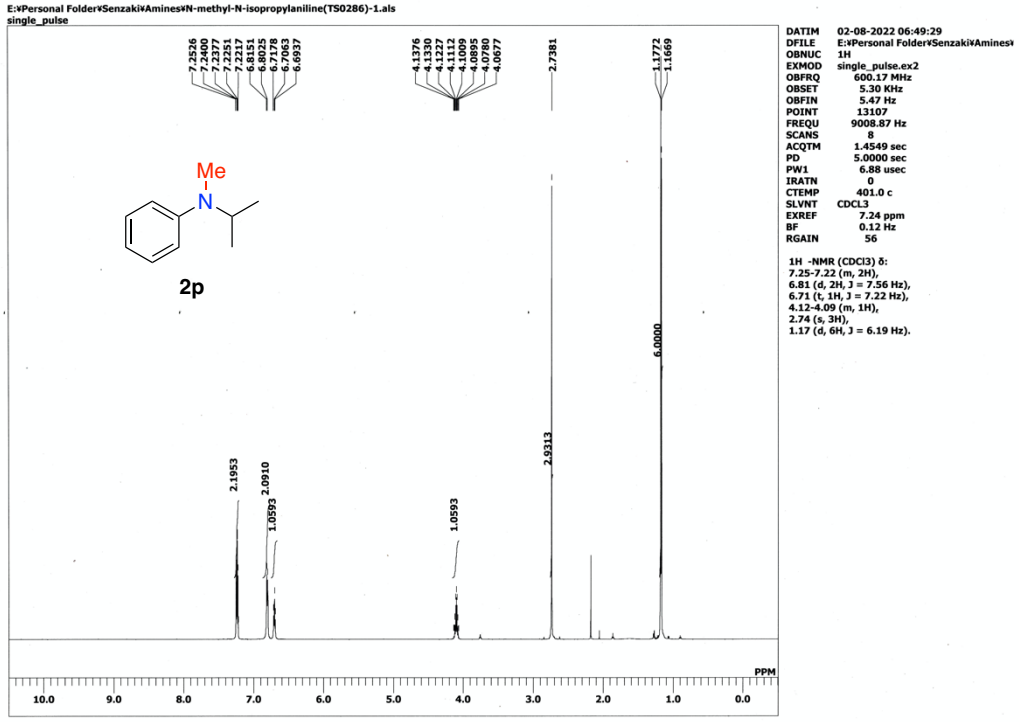

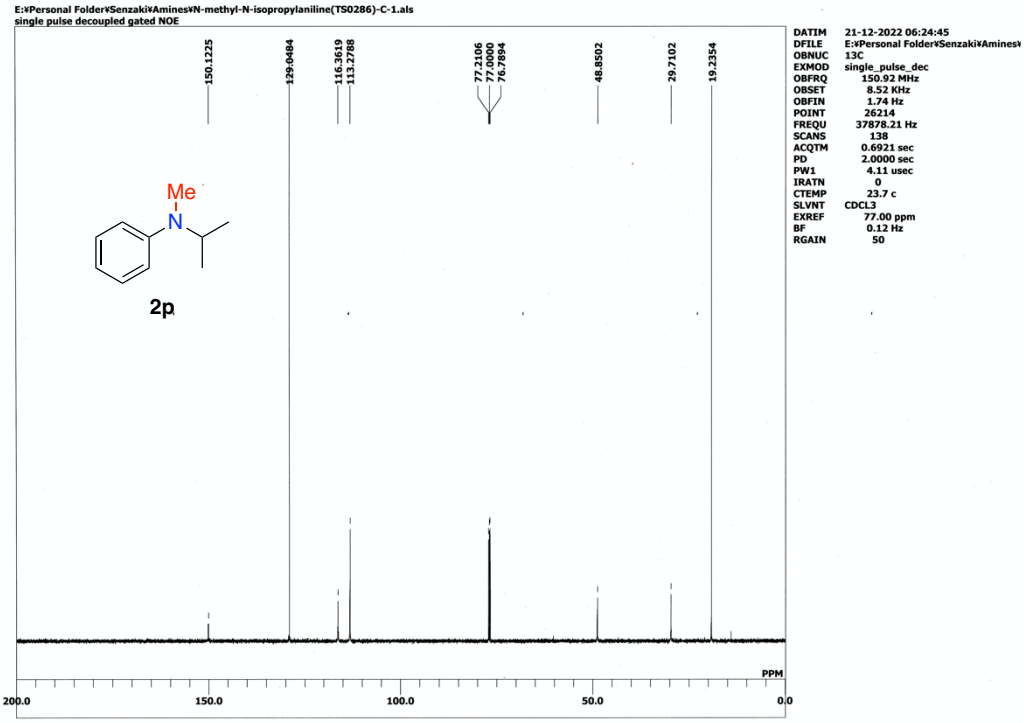

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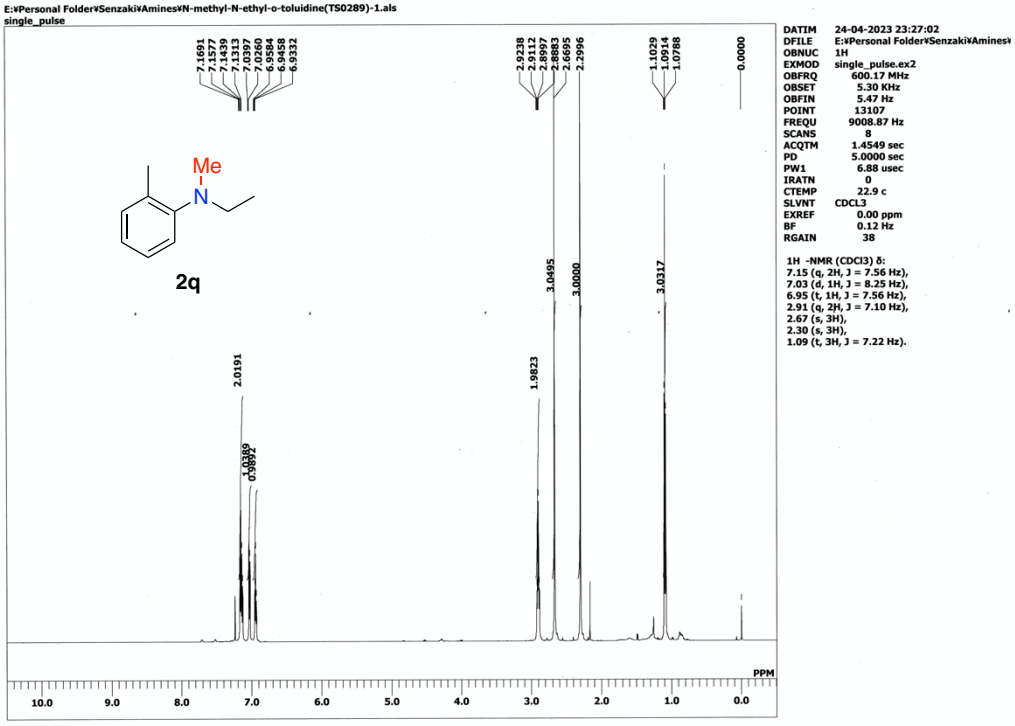

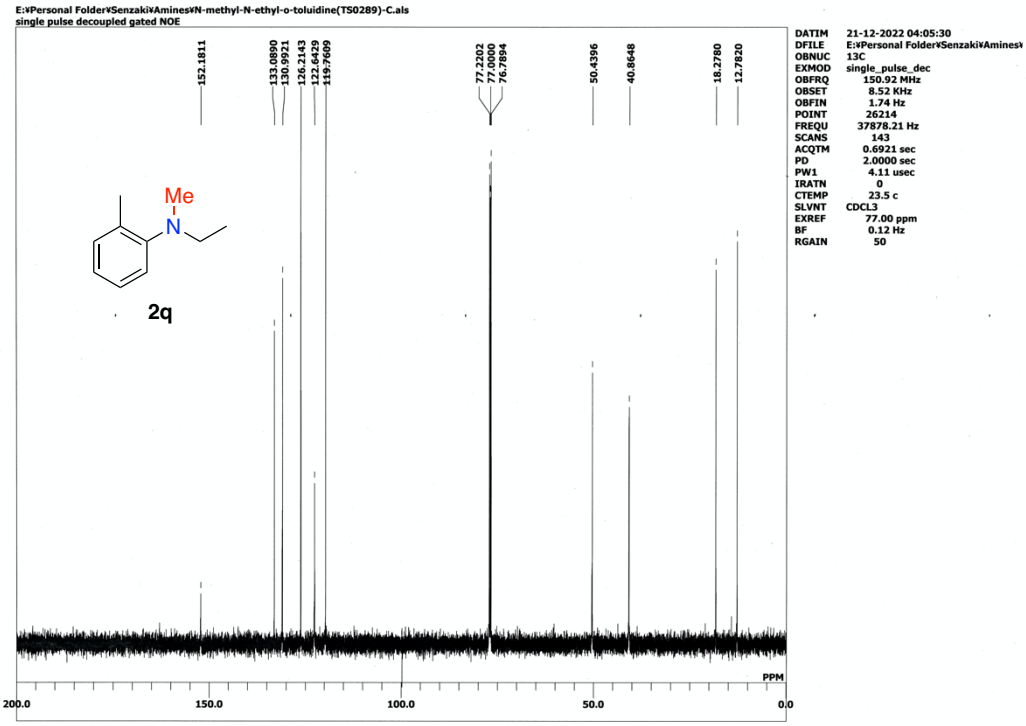

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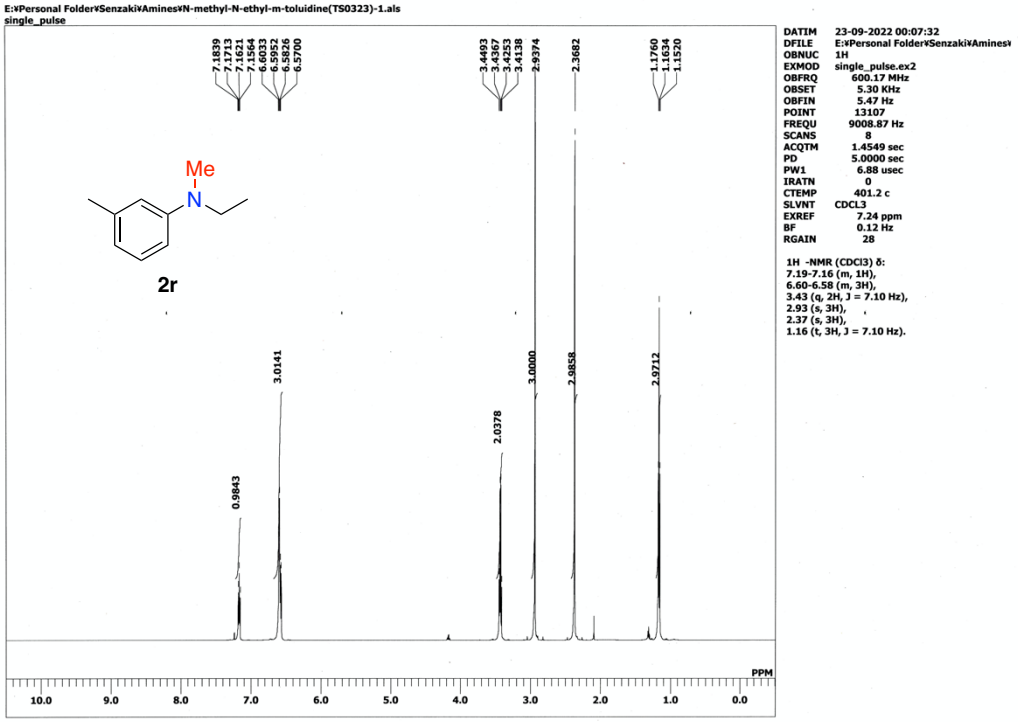

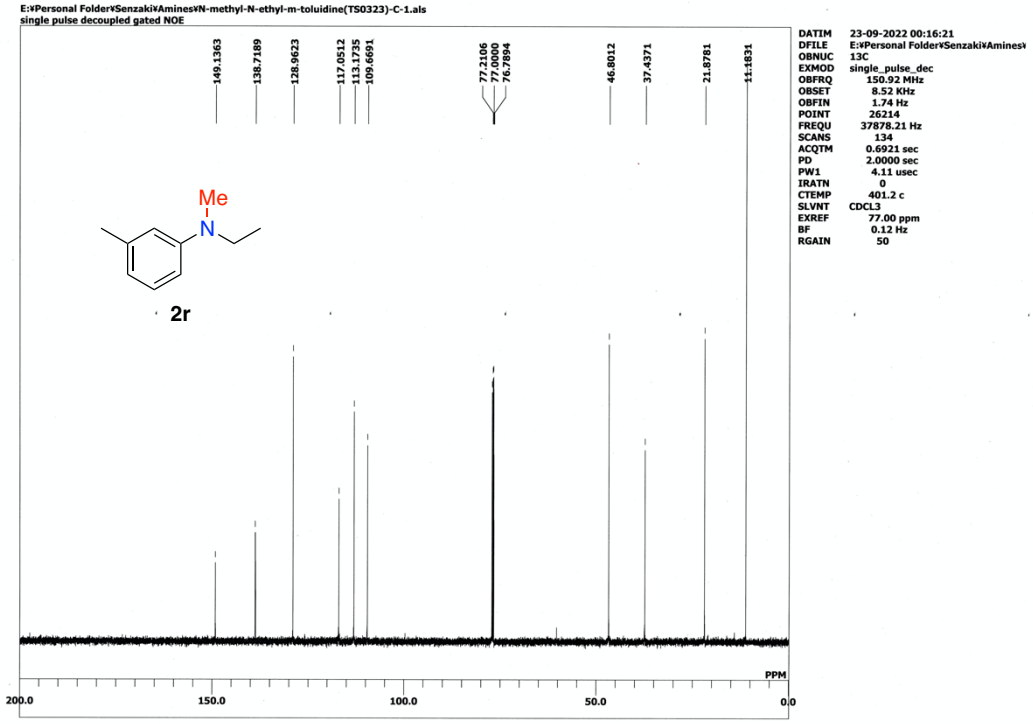

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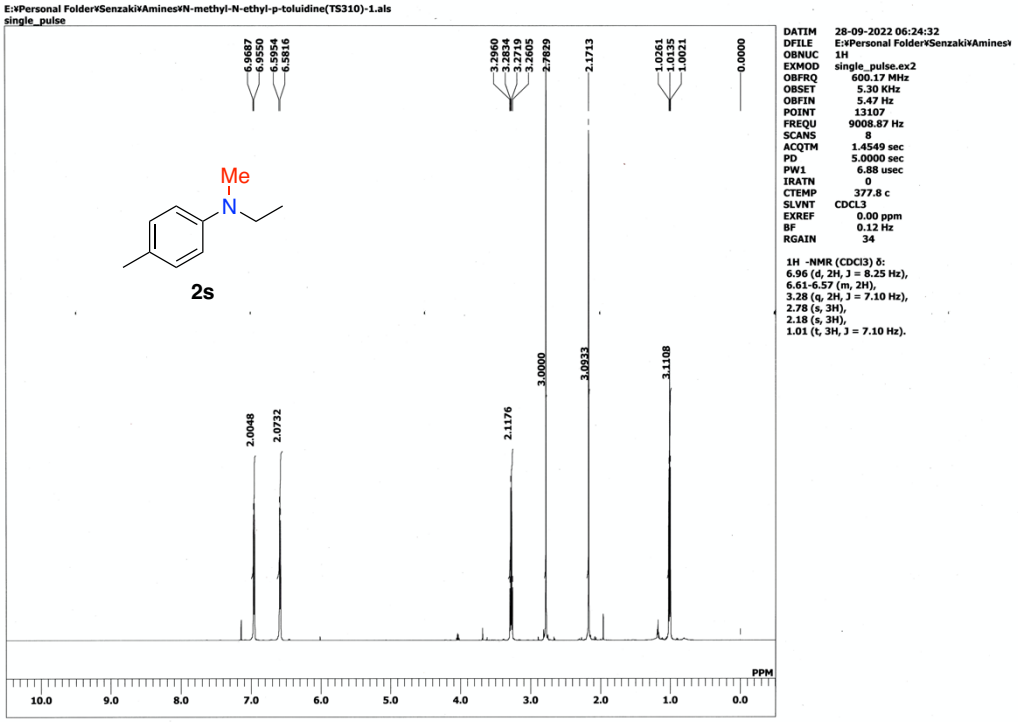
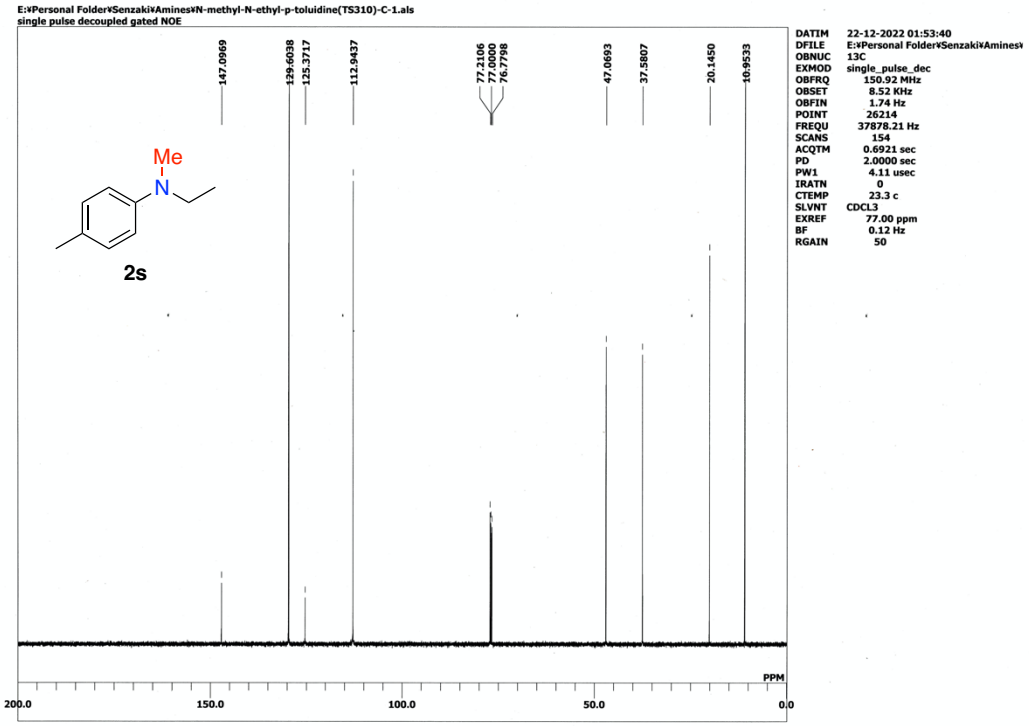
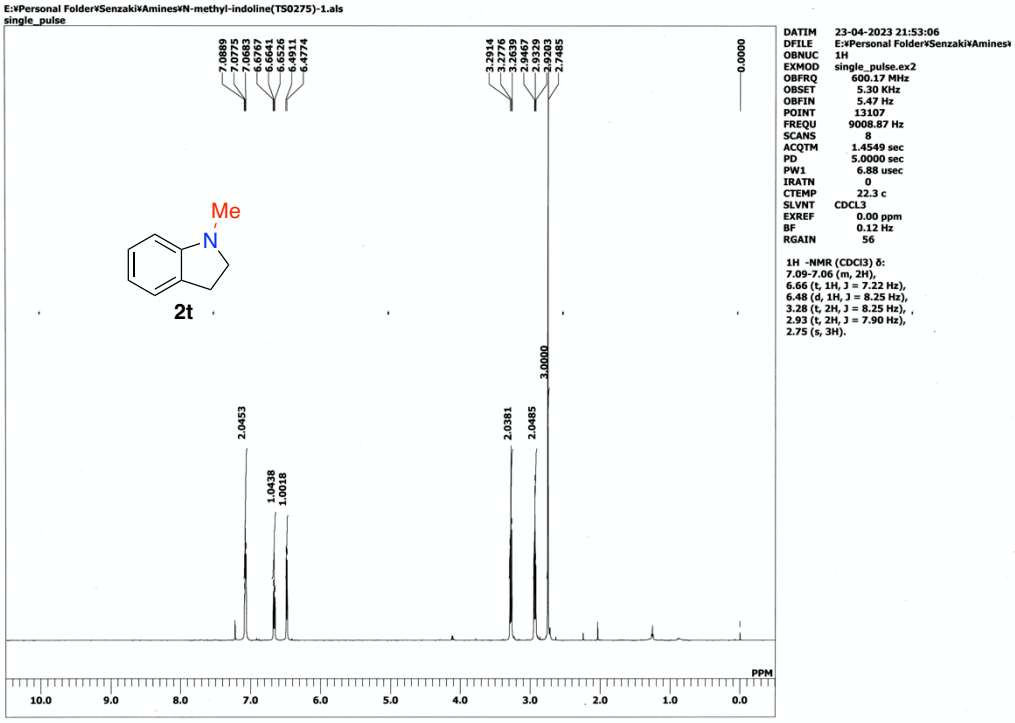
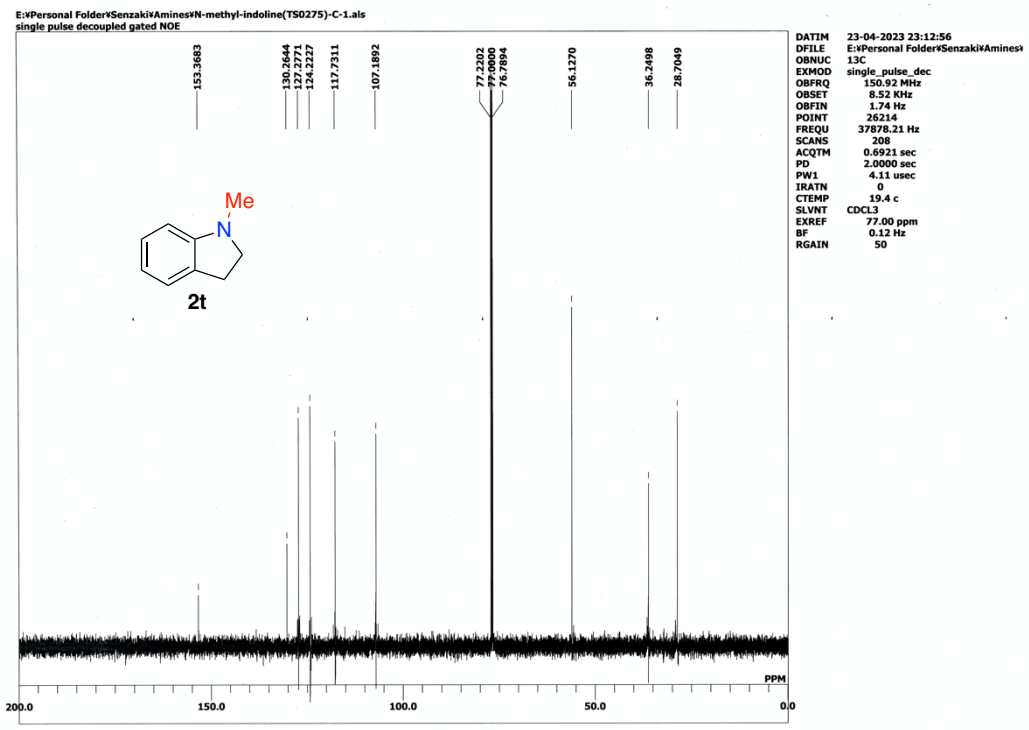


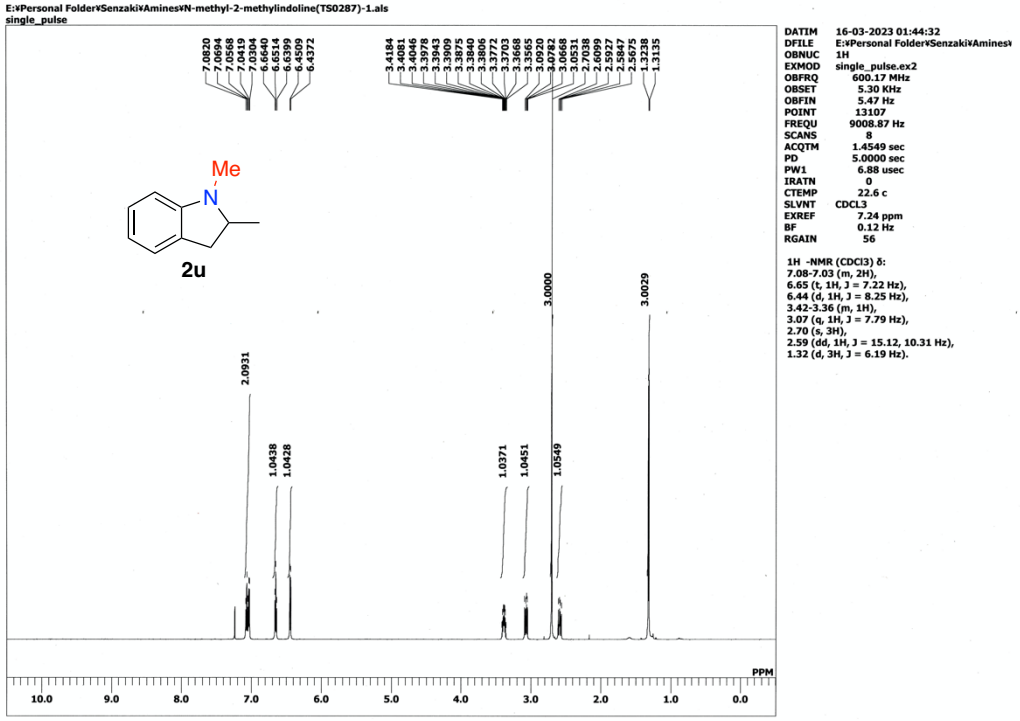


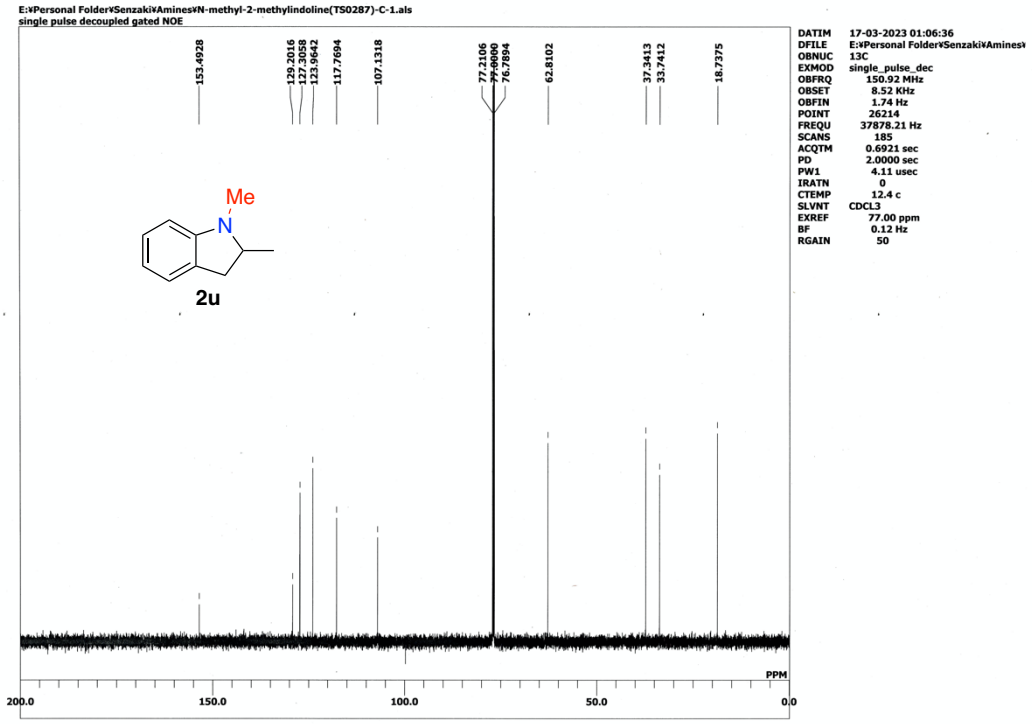
1-Methylindoline (2t)



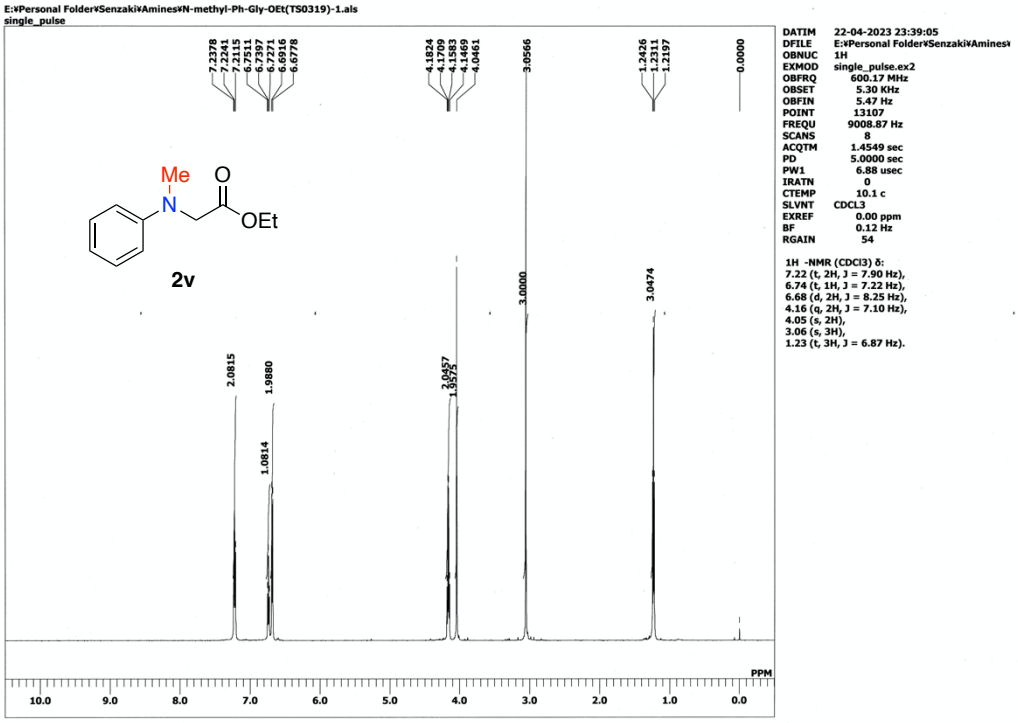


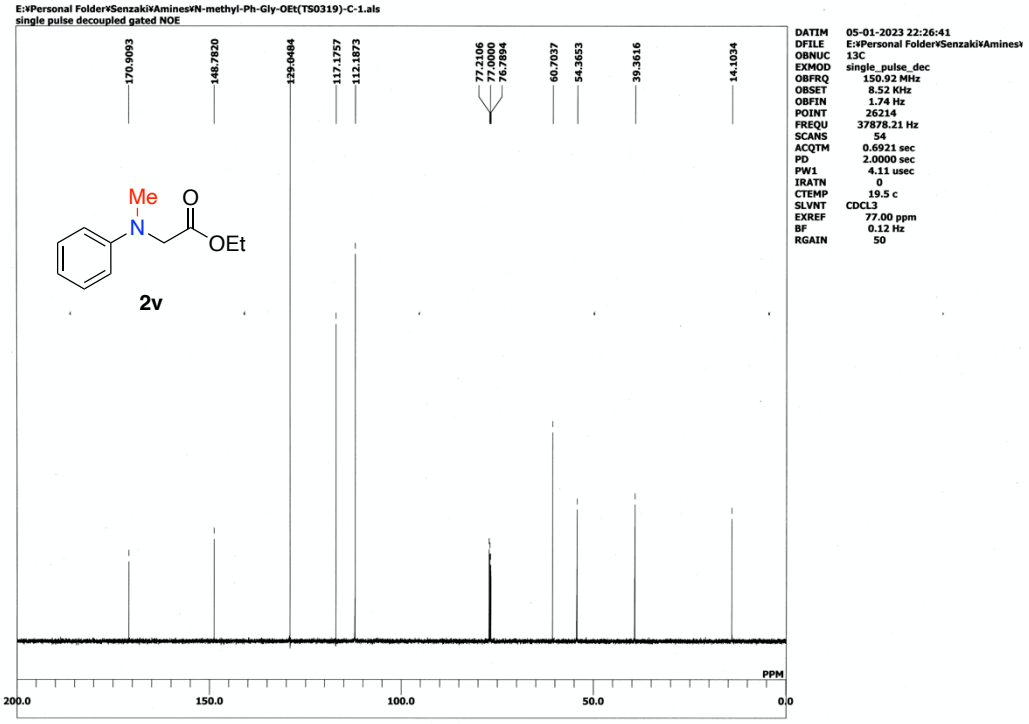
1,2-Dimethylindoline (2u)



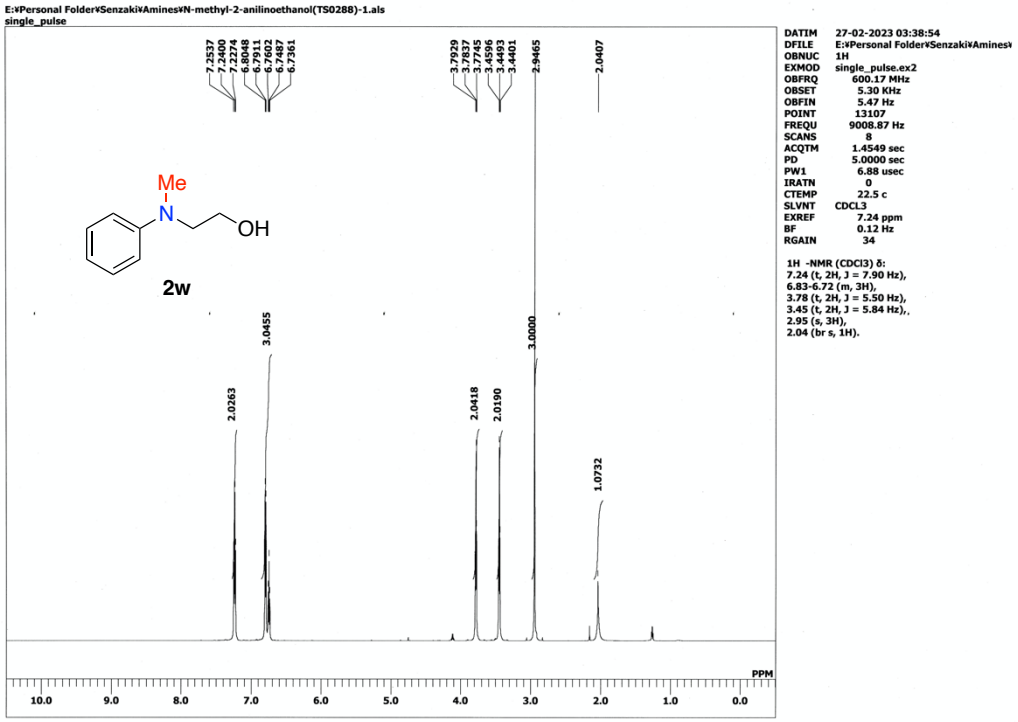


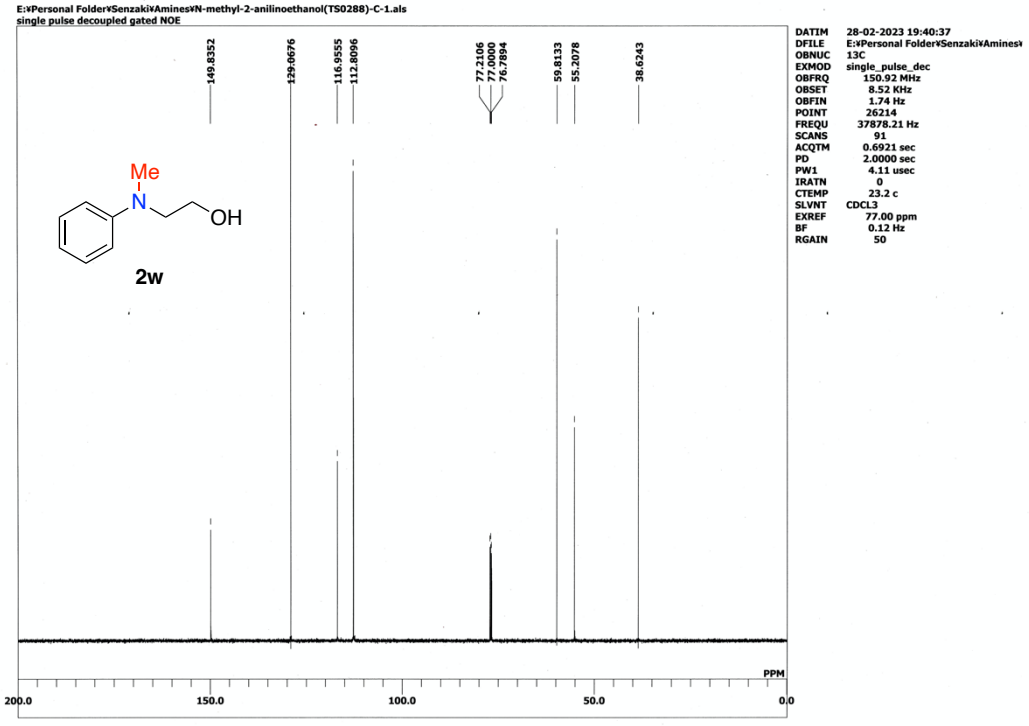
N-Methyl-N-phenylglycine ethyl ester (2v)



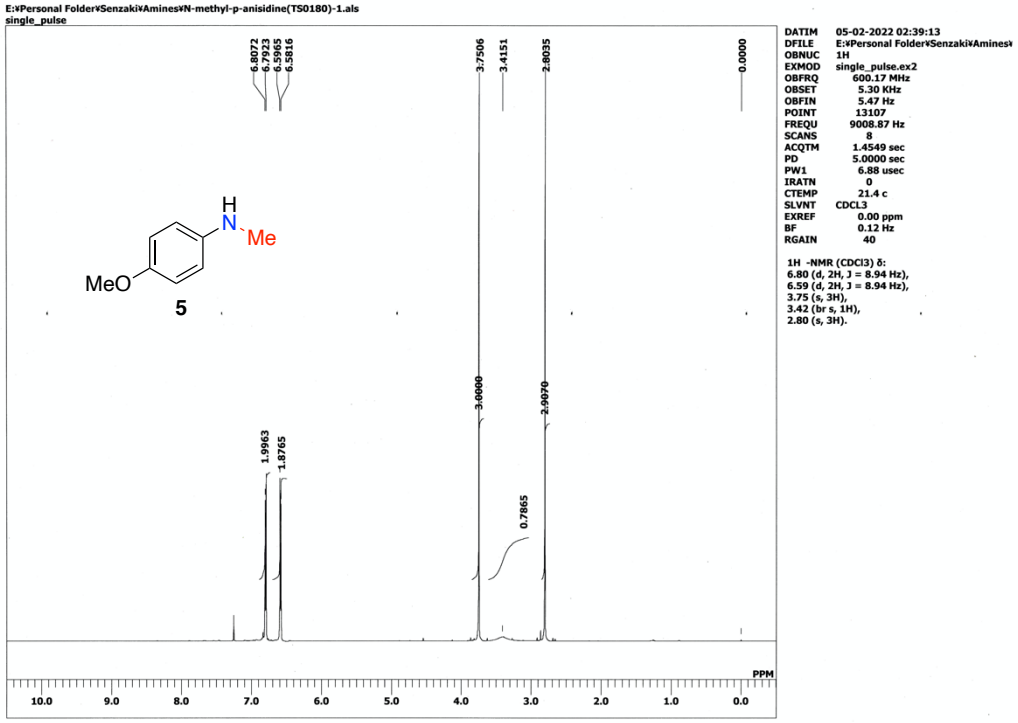


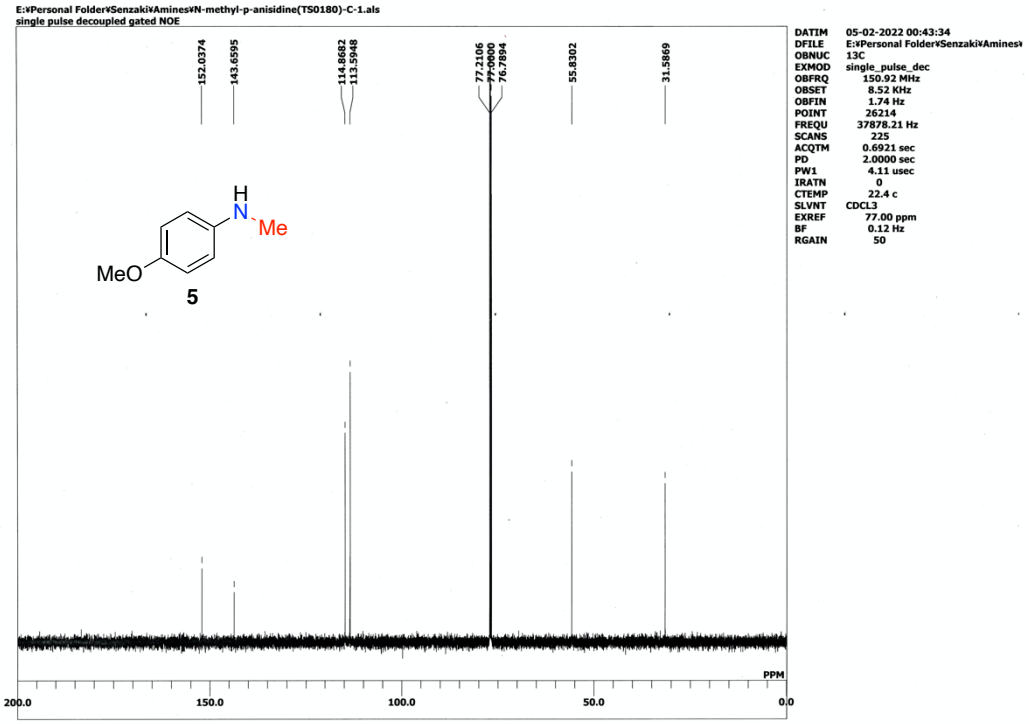
2-(N-Methylanilino)-ethanol (2w)



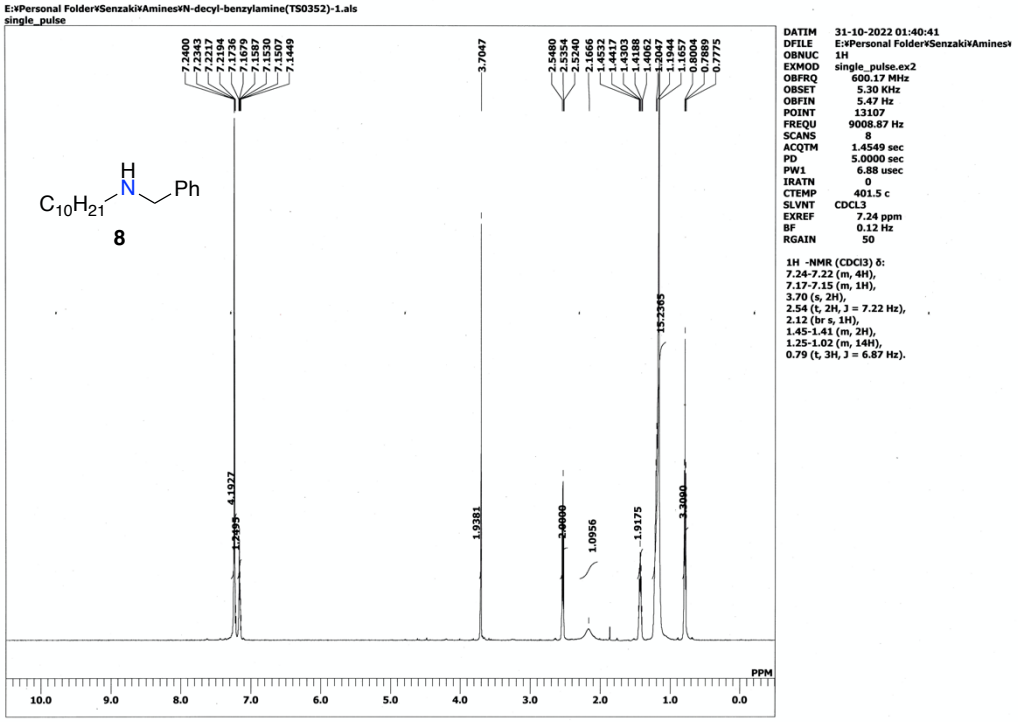


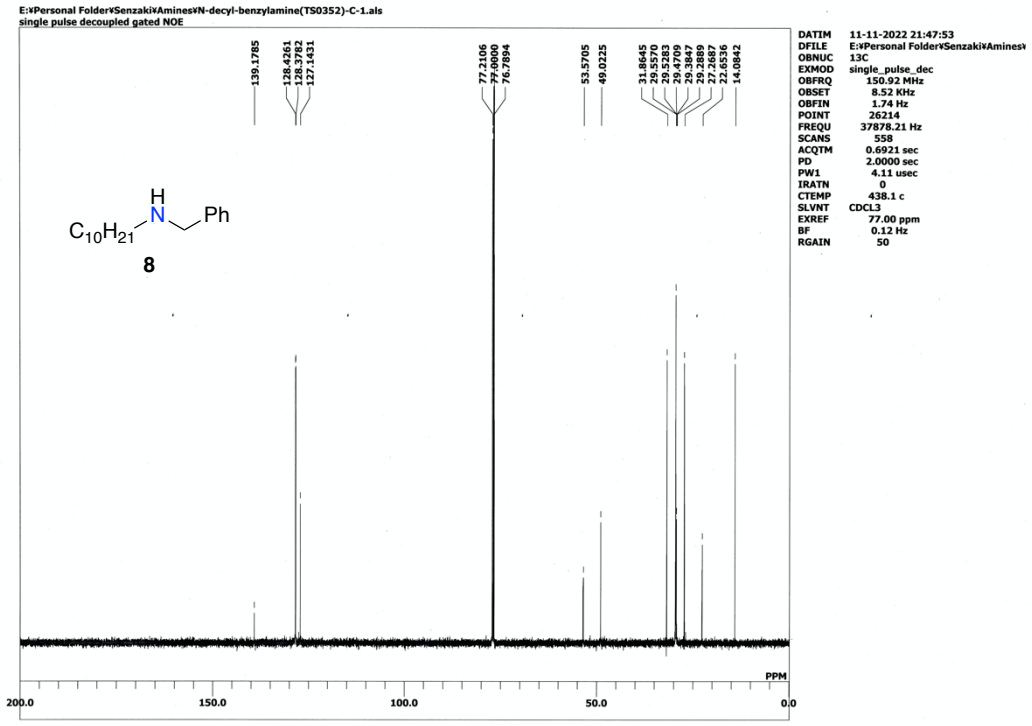
N-methyl-*p*-anisidine (5)





N-Benzyl-*n*-decylamine (8)





N-Methyl-*n*-decylamine (9)