Supporting Information for

Overcoming solid handling issues in continuous flow substitution reactions through ionic liquid formation.

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Contents

1 General experimental details

Unless otherwise indicated, reagents were obtained from Sigma Aldrich, Fisher Scientific or Combi-Blocks and used as received. 2-Bromoacetophenone was recrystallized from EtOH, 4-methoxyphenol was recrystallized from benzene, and cinnamyl chloride was distilled over K_2CO_3 prior to use. Column chromatography was performed using Silicycle F60 40-63 μm silica gel. Analytical thin layer chromatography (TLC) was conducted with aluminum-backed EMD Millipore Silica Gel 60. Visualization of developed plates was performed under UV light (254 nm) and/or using $KMnO_4$, ninhydrin or I_2 stains.

1.1 Instrumentation and flow reactor details

^{1}H NMR and ^{13}C NMR were recorded on a Bruker AVANCE 400 MHz spectrometer and referenced to residual solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration. Yields for optimization studies were determined by NMR or GC analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. IR spectra were collected on a Thermo Scientific Nicolet 6700 FTIR equipped with a diamond ATR crystal (ThermoScientific) and are reported in terms of frequency of absorption (cm^{-1}). GC analysis were conducted on an Agilent Technologies 7890B GC with 30 m × 0.25 mm HP-5 column. Accurate mass data were obtained from an Agilent 5977A GC/MS using MassWorks 4.0 from CERNO bioscience.[1] Continuous flow experiments were performed using 1.0 mm inner diameter PFA tubing reactor coils heated in silicone oil baths and NE-300 syringe pumps from New Era Pump Systems Inc. equipped with 5 or 10 mL Hamilton Gastight glass syringes for reagents and 10 mL HSW Norm-Ject plastic syringes for quench streams when necessary. PEEK fittings, tee mixers and back-pressure regulators were purchased from UpChurch Scientific.

2 Solubility studies

Since the conjugate acids of organic bases are usually sparingly soluble in non-polar solvents, clogging is common even at dilute concentrations for substitution reactions that are performed with, e.g., triethylamine in toluene. When using more polar solvents, as is common for S_NAr and S_N2 reactions however, it can be difficult to predict whether or not precipitation of the conjugate acid will be problematic in a flow reaction. The likelihood of clogging depends on the choice of

solvent, temperature, concentration, base, and leaving group. These things are often optimized empirically when converting a batch procedure into flow. Because bases such as *N*-methylimidazole, tributylamine, and DBU form ionic liquids upon protonation, use of these species as bases should overcome the need to perform extensive optimization. Nonetheless, there are particular combinations of base, concentration, and temperature where-in the use of these ionic-liquid scavengers would be unnecessary.

To obtain some data to understand when the use of triethylamine would allow substitution reactions to occur in flow with NMP as a solvent, some crude solubility experiments were carried out (Table S1). For instance, when slowly heating a 0.50 M solution of triethylammonium chloride in NMP, the mixture became homogeneous at an external bath temperature of 112 °C (entry 1). A 1.0 M solution became homogeneous at 135 °C (entry 2), whereas a 2.0 M solution did not become homogeneous at 150 °C (entry 3), the maximum temperature tested. This information allowed us to focus our studies of S_NAr and S_N2 reactions at concentrations and temperatures that would otherwise lead to clogging if, e.g., triethylamine was used as a base.

However, even in cases where a reaction is carried out under conditions where the triethylammonium salt does not immediately precipitate, clogging issues can still occur upon exiting the reactor or during quench. In contrast, reactions performed herein with ionic liquid-forming bases were observed to be exceptionally robust. Furthermore, control reactions in batch with triethylamine as the base for each S_N2 reaction studied led to precipitate formation during the course of the reaction, demonstrating that clogging issues would be present with the conditions investigated in the absence of the ionic liquid-forming acid scavenger.

Table S1 Solubility studies of triethylammonium salts in NMP

entry	Compound	Concentration (M)	Temperature to dissolve on heating (°C)
1	Et_3N·HCl	0.50	112
2	Et_3N·HCl	1.0	135
3	Et_3N·HCl	2.0	not fully dissolved at 150
4	Et_3N·HBr	0.50	78
5	Et_3N·HBr	1.0	120
6	Et_3N·HBr	2.0	not fully dissolved at 150

3 General Procedures

A Acylation reactions to produce esters

B Acylation reaction to produce amides

C S_NAr reaction with N nucleophiles

D S_NAr reaction with O nucleophiles

E S_NAr reaction with S nucleophiles

F S_N2 reactions with N and S nucleophiles

G S_N2 reactions with O nucleophiles (silylations)

Note: For flow chemistry reactions, it is important to accurately determine concentration when making solutions, particularly when using minimal solvent. All solutions of 0.5 M or greater were made by diluting a weighed quantity of solute to the desired final volume in a volumetric flask or tube. Diluting, e.g., 0.5 mmol of reagent with 1.0 mL solution would result in a final concentration of significantly below 0.5 M, resulting in inaccurate stoichiometry and molar flow rates within the flow reactor.

3.1 General procedure A for acylation reactions to produce esters

Nucleophile (2.25 mmol) and base (2.25 mmol) were combined and made up to 2.00 ml with toluene to give a 1.125 M solution and loaded into a 5 mL Hamilton Gastight syringe. Electrophile (2.25 mmol) was made up to 2.00 mL with toluene to make a 1.125 M solution and loaded into a second 5 mL Hamilton Gastight syringe. The continuous flow reactor depicted in Figure S1 was used with flow rates of 89 µL/min for electrophile solution and 111 µL/min for nucleophile solution to give a residence time of 2.5 min and a 1:1.25:1.25 ratio of electrophile:nucleophile:base (*N*-methylimidazole) through a 0.5 mL reactor coil submerged in a 90 °C oil bath. To quench the reaction mixture at the end of the reactor, pump C was loaded with water with flow rate of 300 µL/min, and a 5 psi back pressure regulator was set at the end of the outlet line. The first 6 min (2.5 residence volumes) of effluent was discarded to reach steady-state, then effluent was collected for 5 min. 1 M HCl (20 mL) was added to the collected effluent and the product was extracted with DCM (3 × 40 mL). The combined organic extracts were washed with 2 M NaOH (40 mL), dried over Na_2SO_4 and the solvent evaporated. The residue was chromatographed on silica gel to yield the pure product.

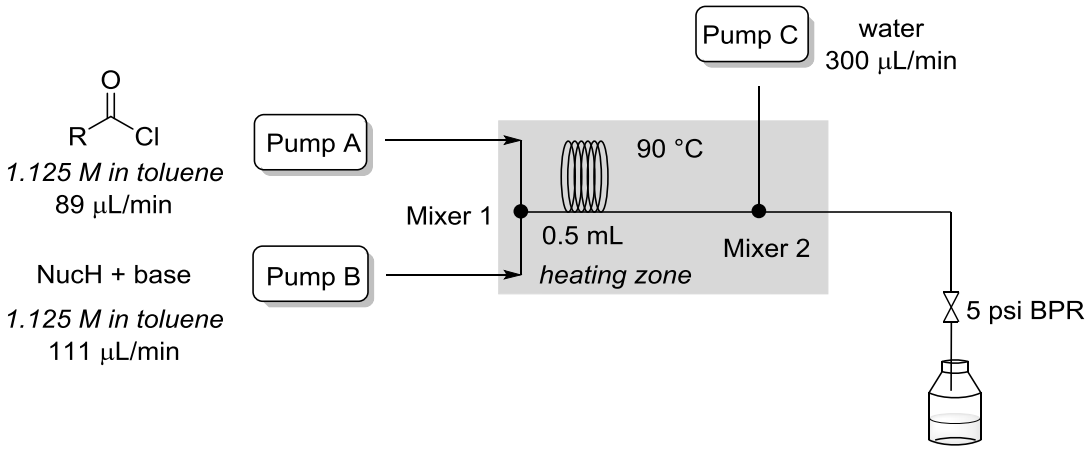


Figure S1 Schematic of flow reactor used for acylation reactions to produce esters

3.2 General procedure B for acylation reactions to produce amides

General procedure A was followed with three modifications. First, THF was used in the place of toluene for solution preparation. Second, an additional quench pump D, delivering 300 μL/min EtOAc was added as shown in Figure S2. Lastly, the back pressure was increased to 40 psi. The first 6 min (2.5 residence volumes) of effluent was discarded to reach steady-state, then effluent was collected for 5 min. 1 M HCl (30 mL) was added to the collected effluent and the product was extracted with DCM (3 × 30 mL). The combined organic extracts were washed with 1 M NaOH (20 mL), dried over Na_2SO_4 and the solvent evaporated. The white solids obtained were washed with hexanes to yield pure products when applicable, otherwise chromatographed on silica gel to yield pure compound.

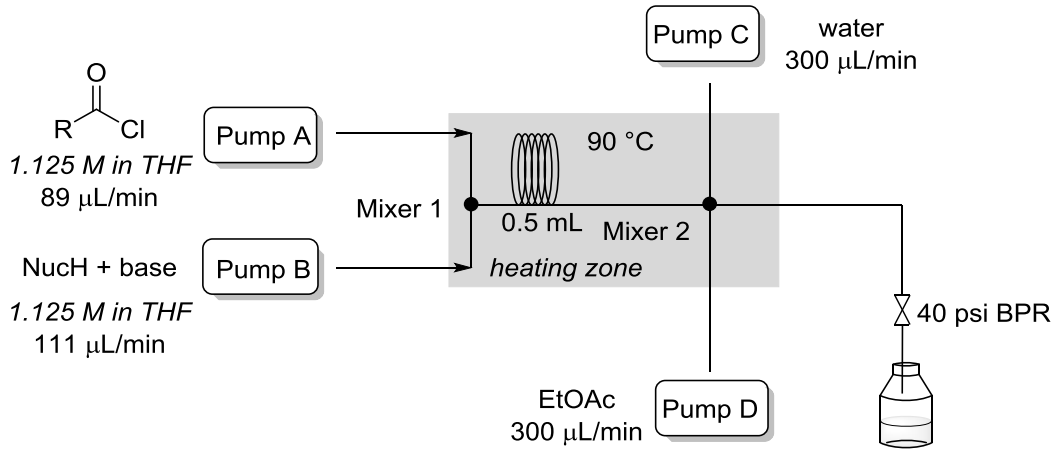


Figure S2 Schematic of flow reactor used for acylation reactions to produce amides

3.3 General procedure C for S_NAr reactions with N nucleophiles

Nucleophile (9 mmol) and base (9 mmol) were combined and made up to 3.00 mL with NMP to make a 3 M solution and loaded into a 5 mL Hamilton Gastight syringe. Electrophile (6 mmol) was made up to 3 mL with NMP to make a 2 M solution, and loaded into a second 5 mL Hamilton Gastight syringe. The continuous flow reactor depicted in Figure S3 was used with flow rates of 50 µL/min for both nucleophile and electrophile solutions, to give a residence time of 5 min and a 1:1.5:1.5 ratio of electrophile:nucleophile:base (DBU), through a 0.5 mL reactor submerged in a 115 °C oil bath. A 5 psi back pressure regulator provided back pressure for the system. The first 15 min (3 residence volumes) of effluent was discarded to reach steady-state, then effluent was collected for 5 min. DCM (60 mL) was added to the collected effluent and the organic phase was washed with water (5 × 10 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated. The residue was chromatographed on silica gel to yield the pure product.

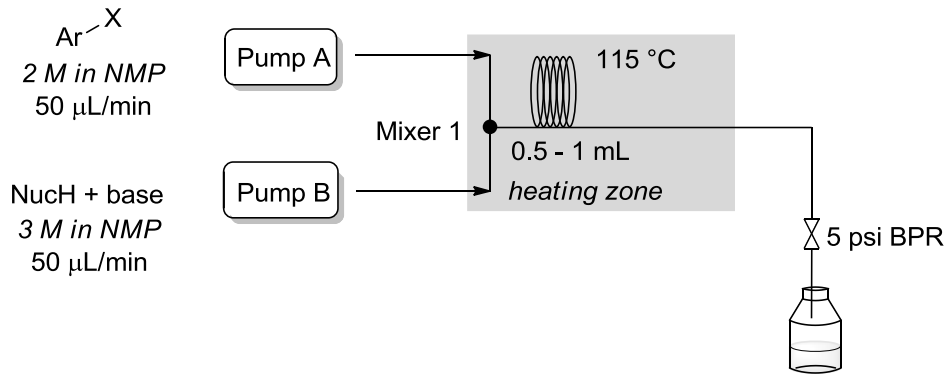


Figure S3 Schematic of flow reactor used for S_NAr reactions

3.4 General procedure D for S_NAr reactions with O nucleophiles

General procedure C was followed with three modifications. First, the flow rates of the reagent pumps were set to 16.7 µL/min instead of 50 µL/min. Second, the 0.5 mL reactor coil was replaced with a 1.0 mL reactor coil. Third, the oil bath temperature was set to 130 °C instead of 115 °C. The first 75 min (2.5 residence volumes) of effluent was discarded to reach steady-state, then effluent was collected for 30 min. DCM (60 mL) was added to the collected effluent and the organic phase was washed with water (5 × 10 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated. The residue was chromatographed on silica gel to yield the pure product.

3.5 General procedure E for S_NAr reactions with S nucleophiles

Nucleophile (3.75 mmol) and base (3.75 mmol) were combined and made up to 3 ml with NMP to give a 1.25 M solution and loaded into a 5 mL Hamilton Gastight syringe. Electrophile (3.75 mmol) was made up to 3 mL with NMP to make a 1.25 M solution and loaded into a second 5 mL Hamilton Gastight syringe. The continuous flow reactor depicted in Figure S4 was used with flow rates of 10 µL/min for the electrophile solution and 15 µL/min for the nucleophile solution to give a residence time of 20 min and a 1:1.5:1.5 ratio of electrophile:nucleophile:base (*N*-metylimidazole), through a 0.5 ml reactor submerged in a 90 °C oil bath. Two quench pumps, one delivering water at 37.5 µL/min and one delivering EtOAc at 37.5 µL/min prevented precipitation upon exiting the heated zone and a 5 psi back pressure regulator provided system pressure. The first 50 min (2.5 residence volumes) of effluent was discarded to reach steady-state, then effluent was collected for 30 min. 1 M HCl (20 mL) was added to the collected effluent and the product was extracted with DCM (3 × 40 mL). The combined organic extracts were washed with 2 M NaOH (40 mL) and washed with distilled water multiple times to remove NMP from the solution then dried over Na_2SO_4 and the solvent evaporated. The residue was chromatographed on silica gel to yield the pure product.

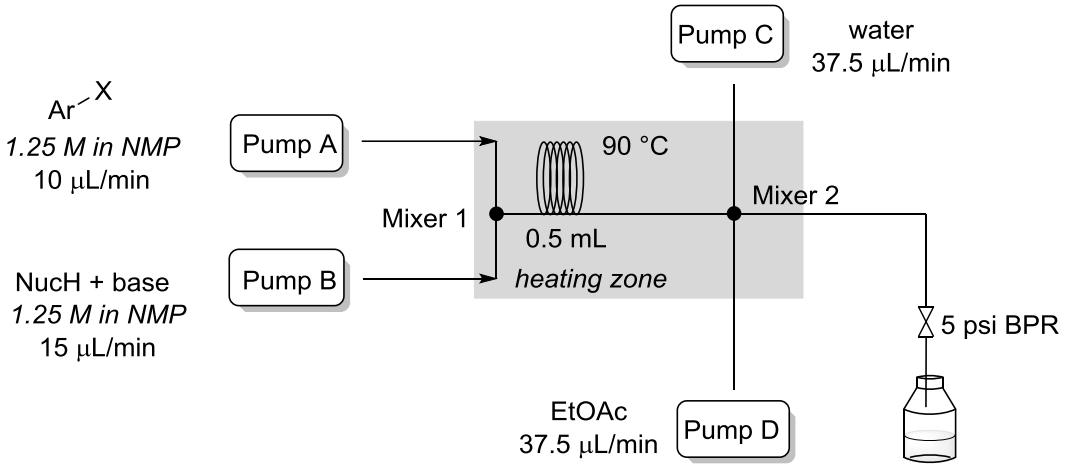


Figure S4 Schematic of flow reactor used for S_NAr reactions with S nucleophiles

3.6 General procedure F for S_N2 reactions with N and S nucleophiles

Nucleophile (10 mmol) and base (12.5 mmol) were combined neat and loaded into a 5 mL Hamilton Gastight syringe. Electrophile (12.5 mmol) was made up to 3.13 mL with NMP to make a 4.0 M solution and loaded into a second 5 mL Hamilton Gastight syringe. The continuous flow

reactor depicted in Figure S5 was used with flow rates set to give a residence time of 30 min and a 1:1.25:1.25 ratio of nucleophile:electrophile:base ($^{n}Bu_3N$ for aniline or sulfur nucleophiles, DBU for aliphatic amine nucleophiles). Flow rates differed for each reaction based on density differences between different nucleophile-base solutions. Specific flow rates used for each product are given in the Section 4 below. Reaction concentration also varied, depending on nucleophile-base solution density. Concentrations within the reactor ranged from 1.7 M to 2.1 M. and are given in Section 4 below. The first 40 min (1.33 residence volumes) of effluent was discarded to reach steady-state, then effluent was collected for 60 min. The material collected was partitioned between 0.1 M K_2CO_3 (50 mL) and 2:1 EtOAc:hexanes (20 mL). The aqueous phase was extracted with an additional 2 × 15 mL 2:1 EtOAc:hexanes and the combined organic extracts were then washed with 3 × 5 mL H_2O, dried over Na_2SO_4 and the solvent evaporated. The residue was chromatographed on silica gel to yield the pure product.

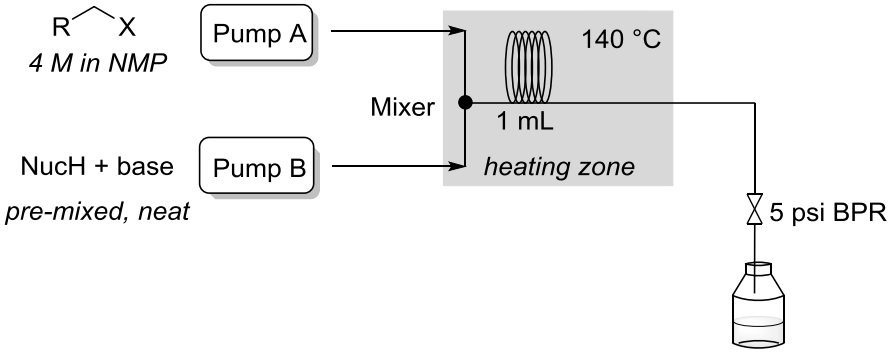


Figure S5 Schematic of flow reactor used for S_N2 reactions with N or S nucleophiles

3.7 General procedure G for S_N2 reactions with O nucleophiles (silylations)

TBSCl (5.75 mmol) was made up to 2.50 mL with DCM to give a 2.3 M solution and loaded into a 5 mL Hamilton Gastight syringe. Alcohol (5.0 mmol) and *N*-butylimidazole (10 mmol) were made up to 2.50 mL with DCM to give 2 M and 4 M concentrations respectively and loaded into another 5 mL Hamilton Gastight syringe. The continuous flow reactor and flow rates depicted in Figure S6 were used to give a residence time of 5 min and ratio of 1:1.15:2 alcohol:TBSCl:*N*-butylimidazole. The first 15 min (3 residence volumes) of effluent was discarded to reach steady-state, then effluent was collected for 15 min. Work-up varied by compound and details for each compound are given in Section 4 below.

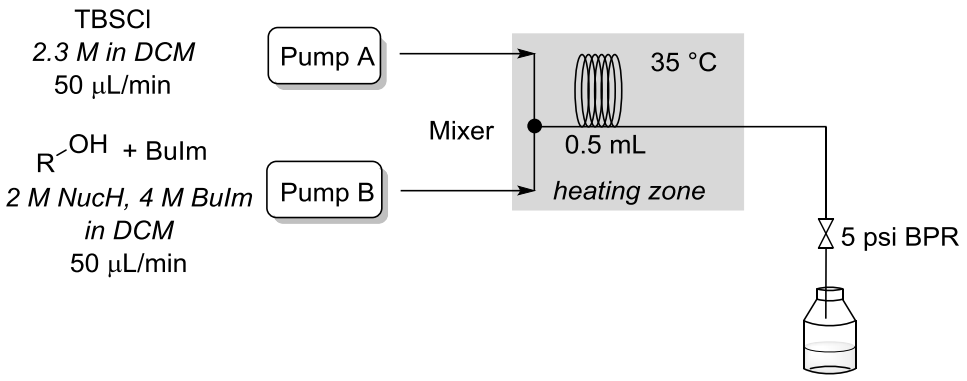
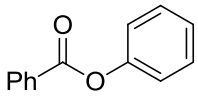


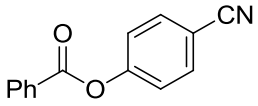
Figure S6 Schematic of flow reactor used for S_N2 reactions (silylations) with O nucleophiles

4 Substitution reactions in flow



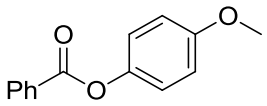
phenyl benzoate (3)

General procedure A was followed with reaction of benzoyl chloride and phenol. Column chromatography (6:1 hexanes:EtOAc) yielded the pure product as a white solid (83 mg, 83% yield). Characterization data were in agreement with the literature.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 6.9 Hz, 2 H), 7.65 (t, *J* = 8.2 Hz, 1H), 7.52 (t, *J* = 7.0 Hz, 2H), 7.44 (t, *J* = 8.3 Hz, 2H), 7.32-7.18 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.3, 151.1, 133.7, 130.3, 129.7, 129.6, 128.7, 126.0, 121.9.



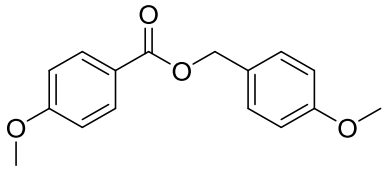
4-cyanophenyl benzoate (4)

General procedure A was followed with reaction of benzoyl chloride and 4-cyanophenol. Column chromatography (3:1 hexanes:EtOAc) yielded the pure product as a white solid (96 mg, 86% yield). Characterization data were in agreement with the literature.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.8 Hz, 2H), 7.75 (d, *J* = 9.1 Hz, 2H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.4, 154.4, 134.3, 133.9, 130.4, 128.9, 128.8, 123.1, 118.4, 110.0.



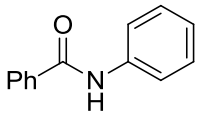
4-methoxyphenyl benzoate (5)

General procedure A was followed with reaction of benzoyl chloride and 4-methoxyphenol. Column chromatography (3:1 hexanes:EtOAc) yielded the pure product as a white solid (100 mg, 88% yield). Characterization data were in agreement with the literature.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.1 Hz, 2 H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.9 Hz, 2H) 3.82 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.7, 157.5, 144.6, 133.6, 130.3, 129.8, 128.7, 122.6, 114.7, 55.7.



4-methoxybenzyl 4-methoxybenzoate (6)

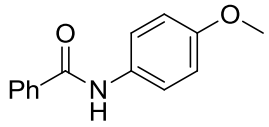
General procedure A was followed with reaction of 4-methoxybenzoyl chloride and 4-methoxybenzylalcohol. Column chromatography (10:1 hexanes:EtOAc) yielded the pure product as a colourless oil (107 mg, 78% yield). Characterization data were in agreement with the literature.[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.0 Hz, 2 H), 7.38 (d, *J* = 8.9 Hz, 2H), 7.94-6.87 (m, 4H), 5.27 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.4, 163.5, 159.7, 131.8, 130.1, 128.5, 122.8, 114.1, 113.7, 66.4, 55.5, 55.4.



***N*-phenylbenzamide (7)**

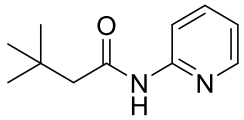
General procedure B was followed with reaction of benzoyl chloride and aniline. Washing with hexanes yielded the pure product as a white solid (80 mg, 81% yield). Characterization data were in agreement with the literature.[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 6.9 Hz, 2 H), 7.80 (br s, 1H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.5

Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 165.8, 138.1, 135.2, 131.9, 129.2, 128.9, 127.1, 124.7, 120.3.



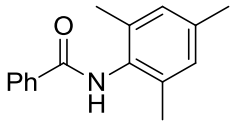
_N_-(4-methoxyphenyl)benzamide (8)

General procedure B was followed with reaction of benzoyl chloride and 4-methoxyaniline. Washing with hexanes yielded the pure product as a white solid (99 mg, 87% yield). Characterization data were in agreement with the literature.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.5 Hz, 2H), 7.75 (br s, 1H), 7.58-7.44 (m, 5H), 6.90 (d, *J* = 9.1 Hz, 2H), 3.82 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 165.8, 156.8, 135.2, 131.8, 131.1, 128.9, 127.1, 122.2, 114.4, 55.6.



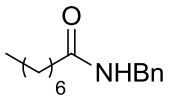
3,3-dimethyl-_N_-(pyridin-2-yl)butanamide (9)

General procedure B was followed with reaction of 3,3-dimethylbutanoyl chloride and 2-aminopyridine. Column chromatography (3:1 hexanes:EtOAc) yielded the pure product as an off-white solid (68 mg, 71% yield). mp: 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (br s, 1H), 8.35-8.37 (m, 2H), 7.75-7.64 (m, 1H), 7.08-6.97 (m, 1H), 2.24 (s, 2H), 1.06 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 151.7, 147.7, 138.6, 119.8, 114.3, 51.6. 31.4, 29.9. IR ν (cm^{-1}) 3243, 3074, 2952, 2861, 1658, 1590, 1576, 1523, 1474, 1456, 1428, 1395, 1361, 1328, 1306, 1285, 1233, 1146, 1134, 1095, 1051, 974, 952, 909, 878, 846, 805, 771, 737, 649, 618, 561. HRMS calc. for $C_{11}H_{16}N_2O$: 192.1019; found: 192.1106, spectral accuracy 99.3%.



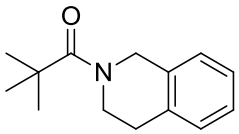
_N_-mesitylbenzamide (10)

General procedure B was followed with and the modification that DCM was used in the place of EtOAc during the quench. The product was produced by reaction of benzoyl chloride and 2,4,6-trimethylaniline. Washing with hexanes yielded the pure product as a white solid (119 mg, 99% yield). Characterization data were in agreement with the literature.[7] ^{1}H NMR (400 MHz, CDCl3) δ 7.92 (d, *J* = 7.1 Hz, 2H), 7.58 (t, *J* = 6.4 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 2H), 7.35 (br s, 1H), 6.93 (s, 2H), 2.30 (s, 3H), 2.24 (s, 6H). 13C{1H} NMR (100 MHz, CDCl3) δ 166.2, 137.2, 135.4, 134.8, 131.8, 131.3, 129.1, 128.9, 127.3, 21.1, 18.5.



_N_-benzyloctanamide (11)

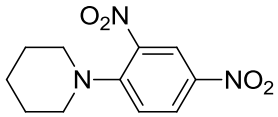
General procedure B was followed with the modification that DCM was used in the place of EtOAc during the quench and DBU was used as base instead of *N*-methylimidazole. The product was produced by reaction of octanoyl chloride and benzyl amine. Column chromatography (2:1 hexanes:EtOAc) yielded the pure product as a white solid (111 mg, 95% yield). Characterization data were in agreement with the literature.[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 5.72 (s, 1H), 4.44 (d, *J* = 5.6 Hz, 2H), 2.22 (t, *J* =7.4 Hz, 2H), 1.70-1.60 (m, 2H), 1.35-1.22 (m, 8H), 0.87 (t, *J* =6.7 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.1, 138.6, 128.8, 128.0, 127.6, 43.7, 37.0, 31.8, 29.4, 29.1, 25.9, 22.7, 14.2.



1-(3,4-dihydroisoquinolin-2(1H)-yl)-2,2-dimethylpropan-1-one (12)

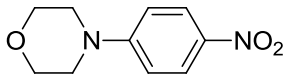
General procedure B was followed with the modification that DCM was used in the place of EtOAc during the quench and DBU was used as base instead of *N*-methylimidazole. The product was

produced by reaction of *tert*-butylacetyl chloride and 1,2,3,4-tetrahydroisoquinoline. Column chromatography (2:1 hexanes:EtOAc) yielded the pure product as a white solid (99 mg, 91% yield). Characterization data were in agreement with the literature.[9,10] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.07 (m, 4H), 4.75 (s, 2H), 3.85 (t, *J* = 5.9 Hz, 2H), 2.89 (t, *J* = 6.32 Hz, 2H), 1.32 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 176.8, 134.5, 133.7, 128.8, 126.6, 126.5, 126.4, 47.6, 43.5, 47.6, 43.5, 38.9, 29.1, 28.5.



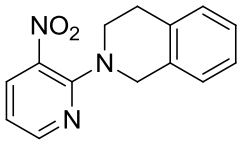
1-(2,4-dinitrophenyl)piperidine (13)

General procedure C was followed with reaction of 2,4-dinitrochlorobenzene and piperidine. Column chromatography (3:1 hexanes:EtOAc) yielded the pure product as an orange solid (117 mg, 93% yield). Characterization data were in agreement with the literature.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, *J* = 2.8 Hz, 1H), 8.21 (dd, *J* =9.4, 2.7 Hz, 1H), 7.08 (d, *J* = 9.4 Hz, 1H), 3.28-3.22 (m, 4H), 1.77-1.67 (m, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 149.9, 137.6, 128.2, 124.1, 119.2, 52.0, 25.6, 23.7.



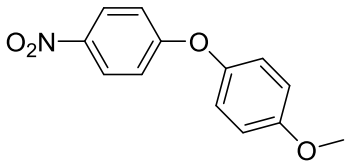
4-(4-nitrophenyl)morpholine (14)

General procedure C was followed with reaction of 4-fluoronitrobenzene and morpholine. Column chromatography (1:2 hexanes:EtOAc) yielded the pure product as a yellow solid (88 mg, 85% yield). Characterization data were in agreement with the literature.[12] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 9.4 Hz, 2H), 6.84 (d, *J* =9.4 Hz, 2H), 3.87 (t, *J* = 5.1 Hz, 4H), 3.37 (t, *J* = 5.2 Hz, 4H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 155.1, 139.2, 126.0, 112.8, 66.5, 47.3.



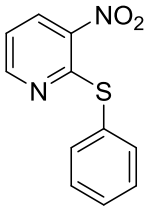
2-(3-nitropyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline (15)

General procedure C was followed with reaction of 2-chloro-3-nitro-pyridine and 1,2,3,4-tetrahydroisoquinoline. Column chromatography (3:1 hexanes:EtOAc) yielded the pure product as a yellow solid (151 mg, 85% yield). Characterization data were in agreement with the literature.[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (dd, *J* = 4.5, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.1, 1.8 Hz ,1H), 7.22-7.15 (m, 3H), 7.15-7.09 (m, 1H), 6.73 (q, *J* = 4.4 Hz,1H), 4.49 (s, 2H), 3.77 (t, *J* = 5.5 Hz, 2H), 3.02 (t, *J* = 5.8 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 152.7, 151.9, 135.8, 135.2, 133.6, 132.4, 128.6, 126.9, 126.5, 126.4, 112.8, 50.4, 46.1, 28.7.



1-methoxy-4-(4-nitrophenoxy)benzene (16)

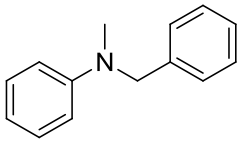
General procedure D was followed with reaction of 4-fluoronitrobenzene and 4-methoxyphenol. Column chromatography (6:1 hexanes:EtOAc) yielded the pure product as an off-white solid (218 mg, 89% yield). Characterization data were in agreement with the literature. ^{1}H NMR (400 MHz, CDCl3): δ 8.17 (d, *J* = 9.3 Hz, 2H), 7.03 (d, *J* = 9.1 Hz, 2H), 6.98-6.92 (m, 4H), 3.83 (s, 3H). ^{13}C{1H} NMR (100 MHz, CDCl3): δ 164.3, 157.3, 147.9, 142.4, 126.0, 122.0, 116.5, 115.4, 55.8.



3-nitro-2-(phenylthio)pyridine (17)

General procedure E was followed with reaction of 2-chloro-3-nitropyridine and thiophenol. Column chromatography (10:1 hexanes:EtOAc) yielded the pure product as a yellow solid (85 mg, 97% yield). Characterization data were in agreement with the literature.[14] ^{1}H NMR (400 MHz,

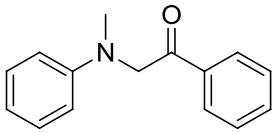
$CDCl_3$) δ 8.51-8.47 (m, 2H), 7.58-7.53 (m, 2H), 7.48-7.42 (m, 3H), 7.19-7.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 158.4, 153.5, 141.5, 136.1, 133.7, 129.7, 129.5, 129.3, 119.5.



***N*-benzyl-*N*-methylaniline (18)**

General procedure F was followed. Benzyl chloride solution flow rate was 14.3 µL/min and *N*-methylaniline/$^{n}Bu_3N$ mixture flow rate was 19.0 µL/min giving a reaction concentration of 1.7 M. Column chromatography (hexanes→2.5% EtOAc in hexanes) yielded the pure product as a colourless oil (0.51 g, 96% yield). Characterization data were in agreement with the literature.[15] ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.34 (m, 2H), 7.30–7.25 (m, 5H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.76 (t, *J* = 7.3 Hz, 1H), 4.58 (s, 2H), 3.06 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.9, 139.2, 129.3, 128.7, 127.0, 126.9, 116.4, 112.5, 56.8, 38.6.

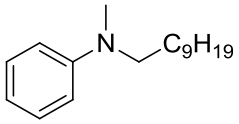
Alternatively, the reaction could be performed neat by preparing a solution of *N*-methylaniline (1.07 g, 10 mmol), benzyl chloride (1.58 g, 12.5 mmol) and $^{n}Bu_3N$ (2.31 g, 12.5 mmol) was prepared and loaded into a 5 mL Hamilton Gastight syringe. The reactor coil depicted in Figure S5 was used, fed via a single pump at 33.3 µL/min. The first 40 min of effluent were discarded then product was collected for 60 min. Work-up the same as the experiment using general procedure F. Yield: 0.63 g, 90%.



***N*-methyl-*N*-phenacylaniline (19)**

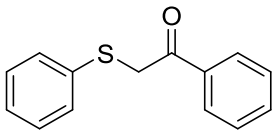
General procedure F was followed. 2-Bromoacetophenone solution flow rate was 14.3 µL/min and *N*-methylaniline/$^{n}Bu_3N$ mixture flow rate was 19.0 µL/min giving a reaction concentration of 1.7 M. Column chromatography (5%→17% EtOAc in hexanes) followed by recrystallization from hexanes yielded the pure product as yellow needles (0.43 g, 78% yield). Characterization data were in agreement with the literature.[16] ^1H NMR (400 MHz, $CDCl_3$): δ 8.01–7.99 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.23–7.20 (m, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 8.8

Hz, 2H), 4.78 (s, 2H), 3.11 (s, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.6, 149.3, 135.6, 133.7, 129.3, 128.9, 127.9, 117.2, 112.4, 59.1, 39.7.



_N_-decyl-_N_-methylaniline (20)

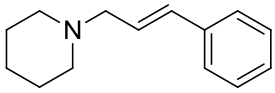
General procedure F was followed. Iododecane solution flow rate was 14.3 µL/min and *N*-methylaniline/$^{n}Bu_3N$ mixture flow rate was 19.0 µL/min giving a reaction concentration of 1.7 M. Column chromatography (hexanes→3% EtOAc in hexanes) yielded the pure product as colourless oil (0.60 g, 90% yield). Characterization data were in agreement with the literature.[17] ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.21 (m, 2H), 6.72–6.66 (m, 3H), 3.30 (t, *J* = 7.5 Hz, 2H), 2.93 (s, 3H), 1.57 (pent, *J* = 7.3 Hz, 2H), 1.32–1.28 (m, 14H), 0.90 (t, *J* = 7.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.5, 129.3, 115.9, 112.2, 53.0, 38.4, 32.0, 29.8, 29.71, 29.70, 29.5, 27.3, 26.8, 22.8, 14.3.



2-phenylthioacetophenone (21)

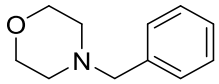
General procedure F was followed with two modifications. First, the nucleophile and base were separately dosed neat via syringe pumps equipped with 5 mL Hamilton Gastight syringes due to immiscibility. The three reagent streams: electrophile solution (4M in NMP), nucleophile and base were combined in a PEEK cross mixer and then entered the reaction coil as in Fig S4. 2-Bromoacetophenone solution flow rate was 14.6 µL/min, $^{n}Bu_3N$ flow rate 13.9 µL/min, thiophenol flow rate 4.8 µL/min giving a reaction concentration of 1.8 M. Second, 1 M HCl was used in the place of 0.1 M K_2CO_3 during the work-up steps. Column chromatography (5%→10% Et_2O in hexanes) yielded the pure product as a white solid (0.53 g, 83% yield). Characterization data were in agreement with the literature.[18] ^1H NMR (400 MHz, $CDCl_3$): δ 7.96–7.94 (m, 2H), 7.58 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.41–7.38 (m, 2H), 7.31–7.26 (m, 2H), 7.25–7.23 (m,

1H), 4.28 (s, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 191.2, 135.5, 134.9, 133.6, 130.6, 129.2, 128.8, 127.2, 41.3.



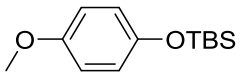
***N*-cinnamylpiperidine (22)**

General procedure F was followed. Cinnamyl chloride solution flow rate was 17.6 µL/min and piperiding/DBU mixture flow rate was 15.7 µL/min giving a reaction concentration of 2.1 M. Column chromatography over silica deactivated with Et_3N (2:1 hexanes:EtOAc) yielded the pure product as a pale yellow oil (0.58 g, 84% yield). Characterization data were in agreement with the literature.[19] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.30 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.12 (dd, *J* = 7.0, 1.2 Hz, 2H), 2.43 (br s, 4H), 1.61 (pent, *J* = 5.6 Hz, 4H), 1.45 (pent, *J* = 5.2 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 137.2, 132.7, 128.7, 127.5, 127.4, 126.4, 62.1, 54.8, 26.2, 24.5.



***N*-benzylmorpholine (23)**

General procedure F was followed. Benzyl chloride solution flow rate was 17.8 µL/min and morpholine/DBU flow rate was 15.5 µL/min giving a reaction concentration of 2.1 M. Column chromatography (30%→50% EtOAc in hexanes) yielded the pure product as a pale yellow oil (0.63 g, 94% yield). Characterization data were in agreement with the literature.[20] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.26 (m, 5H), 3.71 (t, *J* = 4.6 Hz, 4H), 3.50 (s, 2H), 2.44 (t, *J* = 4.5 Hz, 4H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 137.9, 129.3, 128.4, 127.3, 67.2, 63.6, 53.8.



***tert*-butyl(4-methoxyphenoxy)dimethylsilane (24)**

General procedure G was followed with reaction of TBSCl and 4-methoxyphenol. A photograph of the biphasic effluent is shown in Figure S7 below. To the collected biphasic effluent, DCM (40 mL) was added and the mixture washed with 3 × 20 mL of 1 M HCl. The organic phase was then

dried over Na_2SO_4, the solvent evaporated and the product purified on silica gel (6:1, hexanes:EtOAc) to yield the pure product as colourless oil (0.35 g, 97% yield). Characterization data were in agreement with the literature.[21] ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (s, 4H), 3.76 (s, 3H), 0.99 (s, 9H), 0.18 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.2, 149.5, 120.7, 114.6, 55.7, 25.9, 18.3, –4.3.

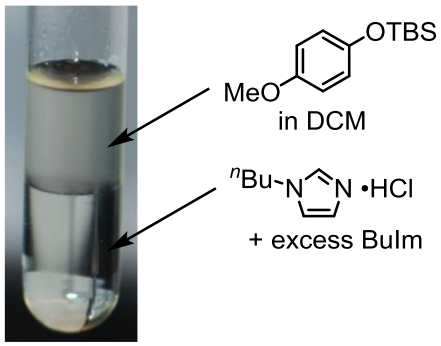
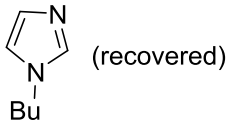
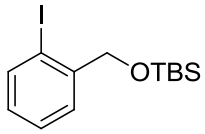


Figure S7 Photograph of the biphasic reaction mixture after production of silyl ether **24**



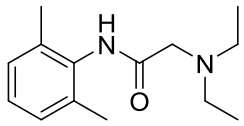
Recovered *N*-butylimidazole

The aqueous acidic extracts (combined 60 mL) from the work-up of **24** were basified by the addition of 2 M NaOH (60 mL) and extracted with 3 × 40 mL of DCM. The combined organic phases were dried over Na_2SO_4 and the solvent evaporated to yield 0.1769 g of analytically pure *N*-butylimidazole, 95%. Characterization data were in agreement with the literature.[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (s, 1H), 6.99 (s, 1H), 6.85 (s, 1H), 3.88 (t, J = 7.1, 2H), 1.71 (m, 2H), 1.28 (m, 2H), 0.89 (t, J = 7.4, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 137.1, 129.4, 118.8, 46.7, 33.1, 19.7, 13.5.



***tert*-butyl((2-iodobenzyl)oxy)dimethylsilane (25)**

General procedure G was followed with reaction of TBSCl and 2-iodobenzyl alcohol. The biphasic effluent collected was partitioned between 1 M HCl (20 mL) and 2:1 EtOAc:hexanes (20 mL). The aqueous phase was extracted with an additional 2×15 mL 2:1 EtOAc:hexanes and the combined organic extracts were washed with 5 mL brine, dried over Na_2SO_4 and the solvent evaporated. The residue was chromatographed on silica gel (hexanes) to yield the pure product as colourless oil (0.50 g, 95% yield). Characterization data were in agreement with the literature.[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.51 (d *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.8, 1H), 4.63 (s, 2H), 0.98 (s, 9H), 0.14 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 142.9, 138.6, 128.5, 128.2, 127.4, 95.8, 69.4, 26.0, 18.4, –5.3.



lidocaine

The conditions used were based on the literature batch procedure[24] with minimal modifications necessary to allow telescoping in flow. Specifically, toluene was used as the solvent for both reaction steps to facilitate telescoping without solvent switching, both reaction steps were performed at 90 °C in the same heated zone to prevent crystallization of the amide intermediate produced in the first acylation step, and ^{n}Bu$_3$N and DBU respectively were used as acid scavengers to prevent precipitate formation during both reactions.

2,6-Dimethylaniline (0.61 g, 5.0 mmol) and ^{n}Bu$_3$N (0.93 g, 5.0 mmol) were made up to 5.00 mL with toluene and loaded into a 5 mL Hamilton Gastight syringe. Chloroacetyl chloride (0.63 g, 5.5 mmol) was made up to 5.00 mL with toluene and loaded into another 5 mL Hamilton Gastight syringe. Et_2NH (1.01 g, 15 mmol) and DBU (1.51 g, 10 mmol) were combined neat and loaded into a third 5 mL Hamilton Gastight syringe. The continuous flow reactor depicted in Figure S8 was used to give a residence time of 1.25 min for the acylation and 9.5 min for the S_N2 reaction.

Reaction stoichiometry was 2,6-Dimethylaniline with 1.1 eq. of chloroacetyl chloride and 1 eq. of $^{n}Bu_3N$ for the acylation reaction, then 3 eq. of Et_2NH and 2 eq. of DBU (1 eq. consumed by $^{n}Bu_3N{\cdot}HCl$ from the previous acylation step) for the S_N2 reaction.

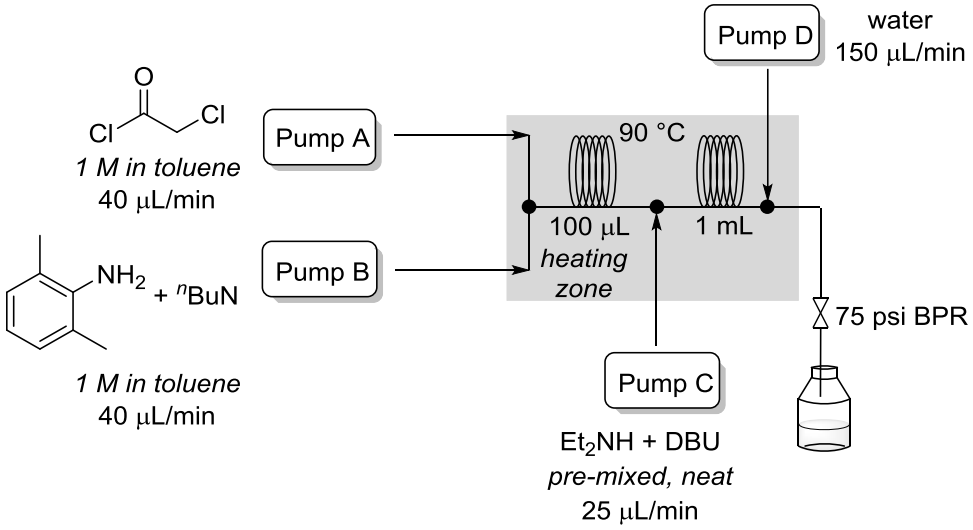
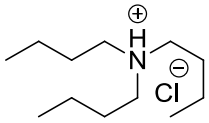


Figure S8 Schematic of flow reactor used for telescoped synthesis of Lidocaine

The first 20 min (~2 residence volumes) of effluent was discarded to reach steady-state, then effluent was collected for 60 min. All material collected was partitioned between 1 M NaOH (20 mL) and 2:1 EtOAc:hexanes (20 mL). The aqueous phase was extracted with an additional 2 × 15 mL 2:1 EtOAc:hexanes and the combined organic extracts were washed with 3 × 5 mL water, then extracted with 5×5 mL 1M HCl. The combined aqueous extracts were washed with 5 mL Et_2O then the *p*H was raised to >14 by addition of 50% NaOH. The solution was extracted with 4 × 5 mL hexanes and the combined extracts were dried over Na_2SO_4. The solvent was evaporated and the residue chromatographed on Et_3N deactivated silica gel (25 × 150 mm column, 10%→30% EtOAc in hexanes eluent) to yield the pure product as a white powder (0.37 g, 66% yield). Characterization data were in agreement with the literature.[25] ^1H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 7.09 (m, 3H), 3.22 (s, 2H), 2.69 (q, *J* = 7.1 Hz, 4H), 2.23 (s, 6H), 1.14 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.4, 135.2, 134.1, 128.3, 127.2, 57.6, 49.1, 18.7, 12.8.

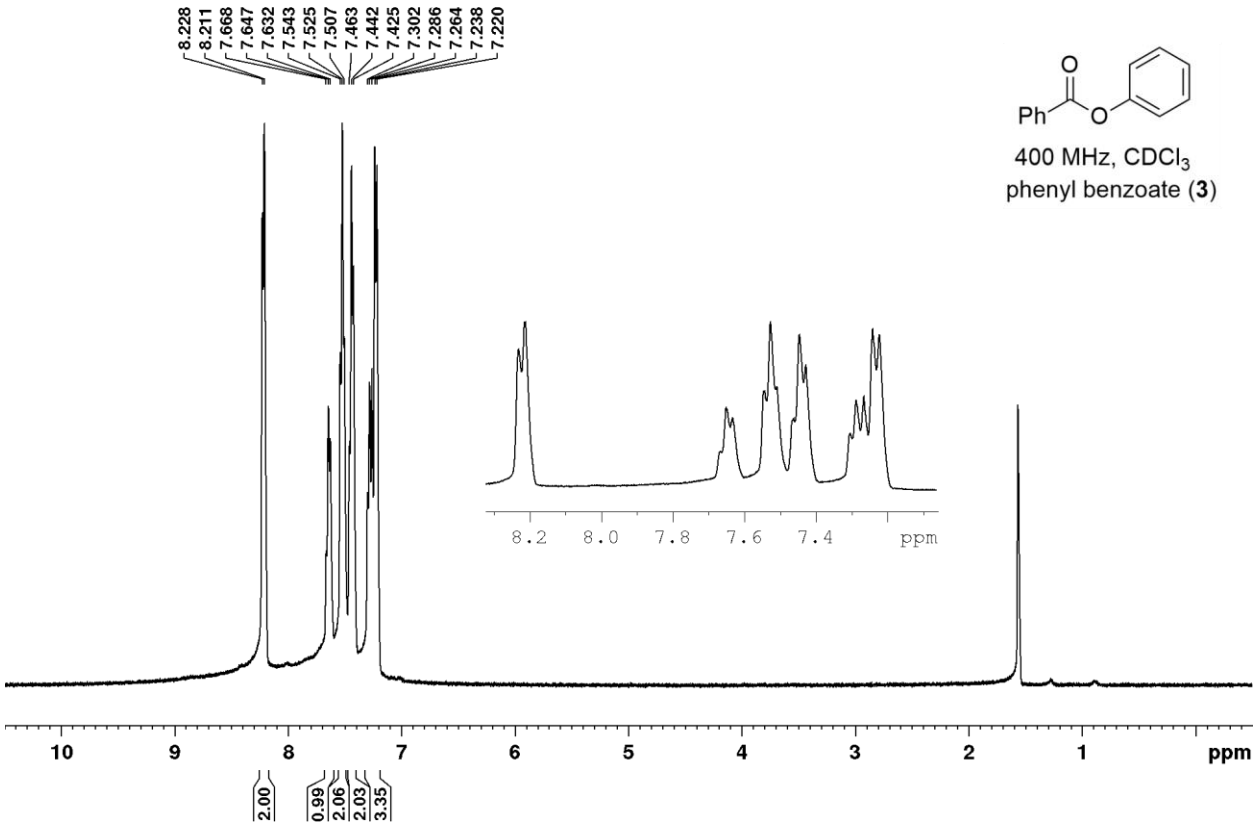
5 Determination of tributylammonium chloride melting point

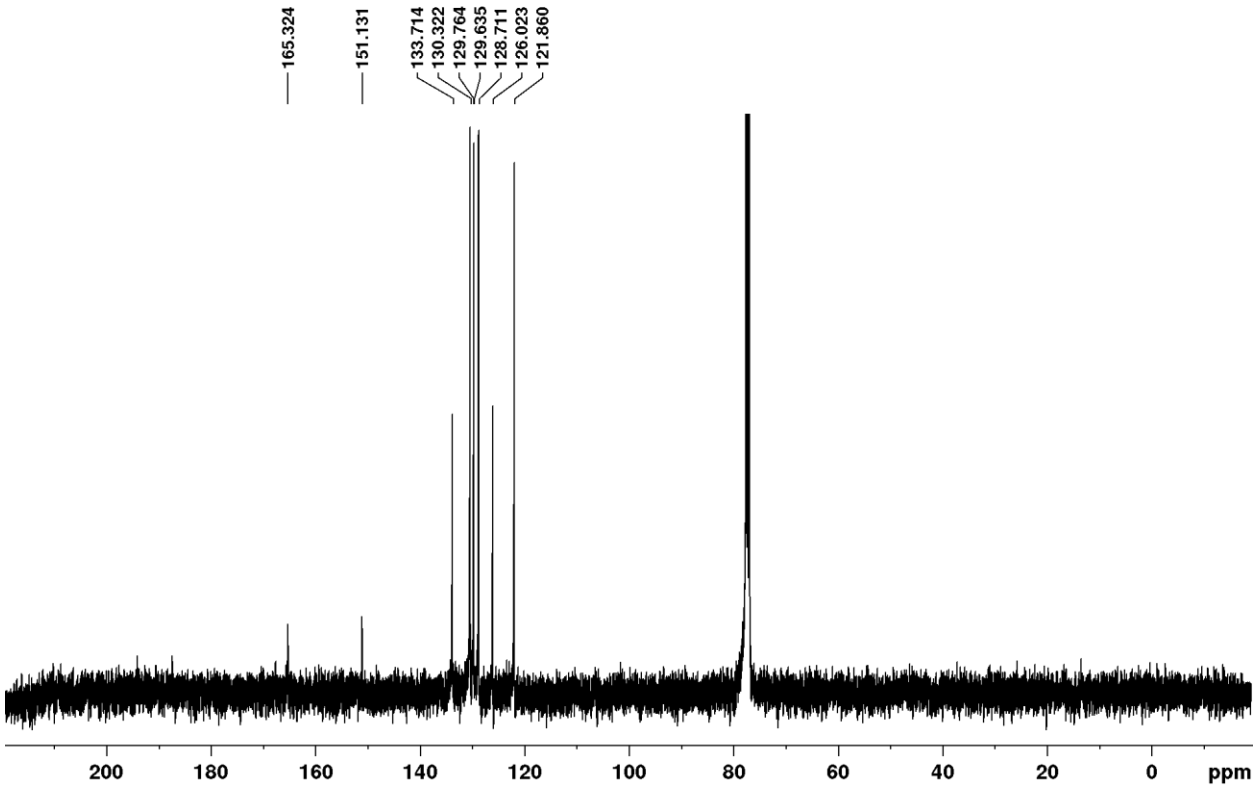


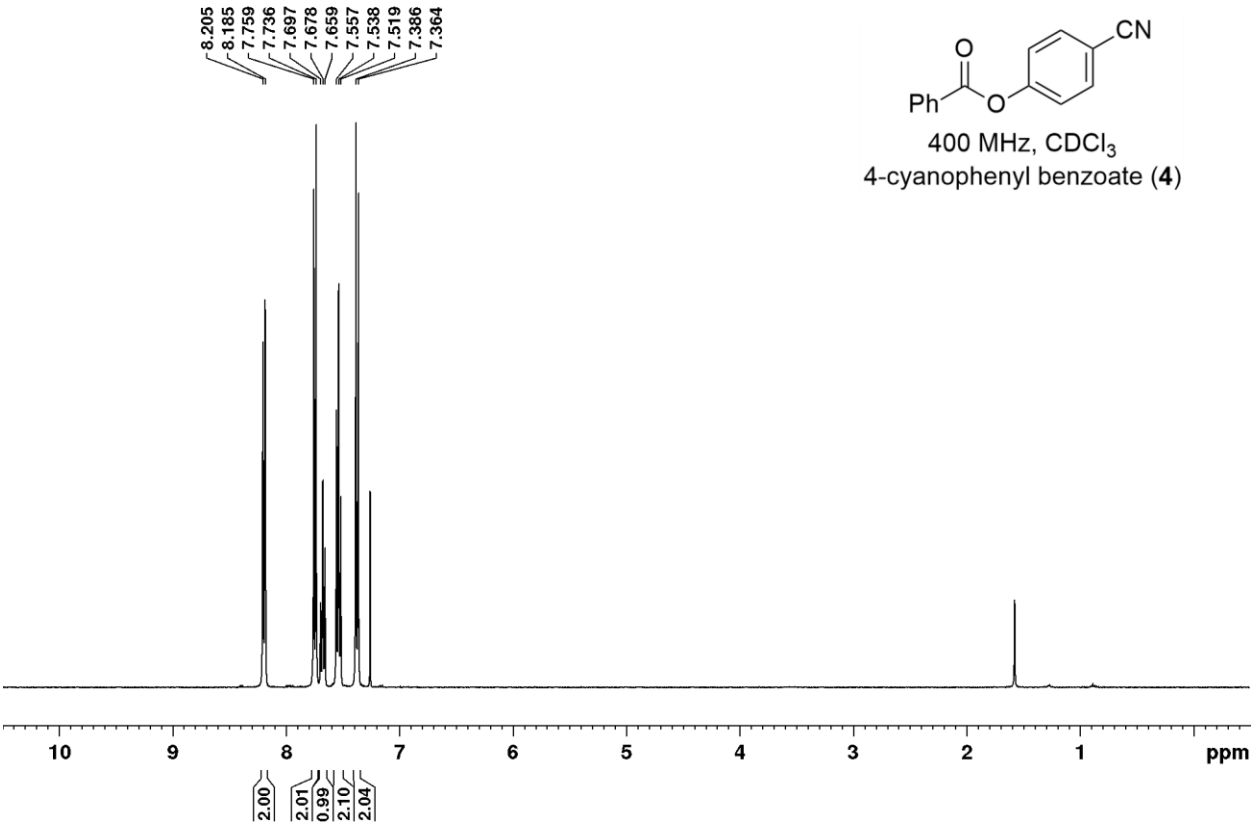
Tributylammonium chloride

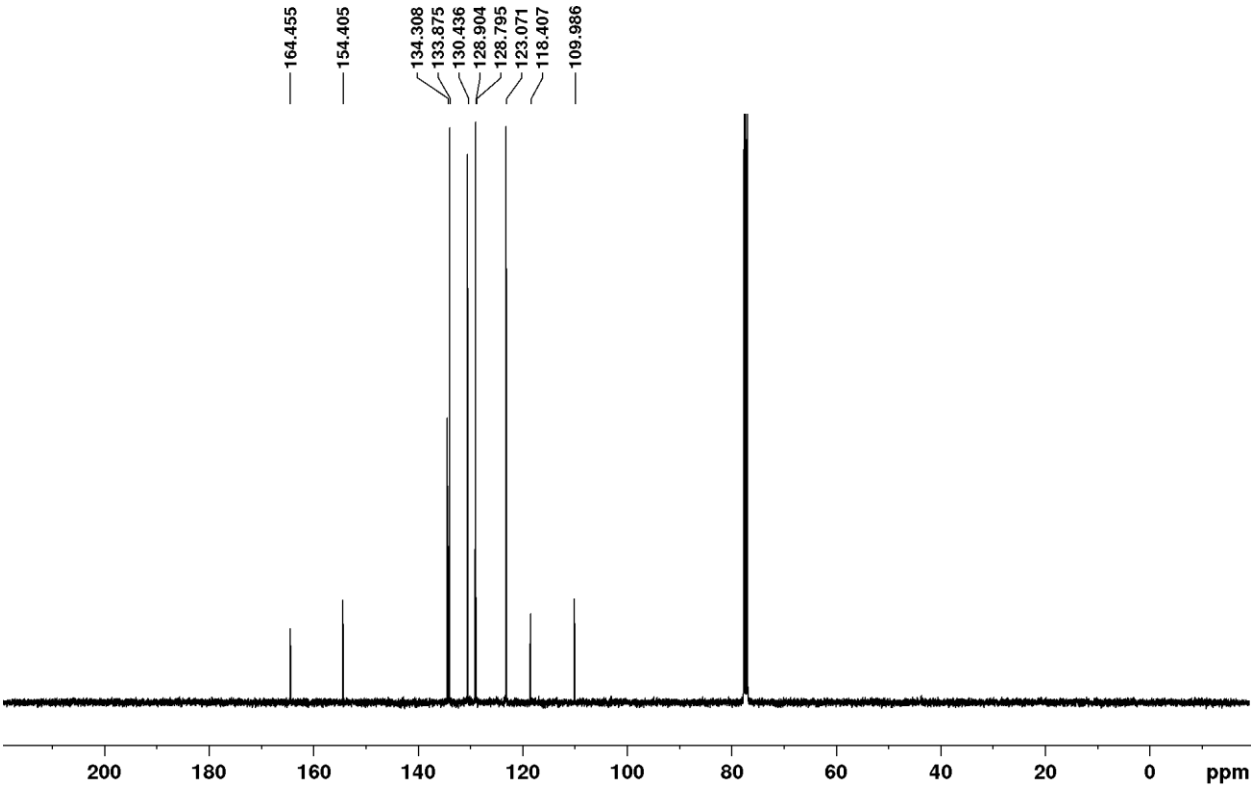
4 M HCl (8 mmol) in dioxane was added dropwise to tributylamine (8 mmol) in diethyl ether and stirred for 20 minutes in room temperature. Removing volatile chemicals under reduced pressure and recrystallizing from mixture of hexane and ethyl acetate gave tributylammonium chloride as white needles. Characterization data were in agreement with the literature.[26] mp: 58–62 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.43 (br s, 1H), 3.02–2.93 (m, 6H), 1.68–1.57 (m, 6H), 1.36–1.25 (m, 6H), 0.91 (t, *J* = 7.3 Hz, 9H).

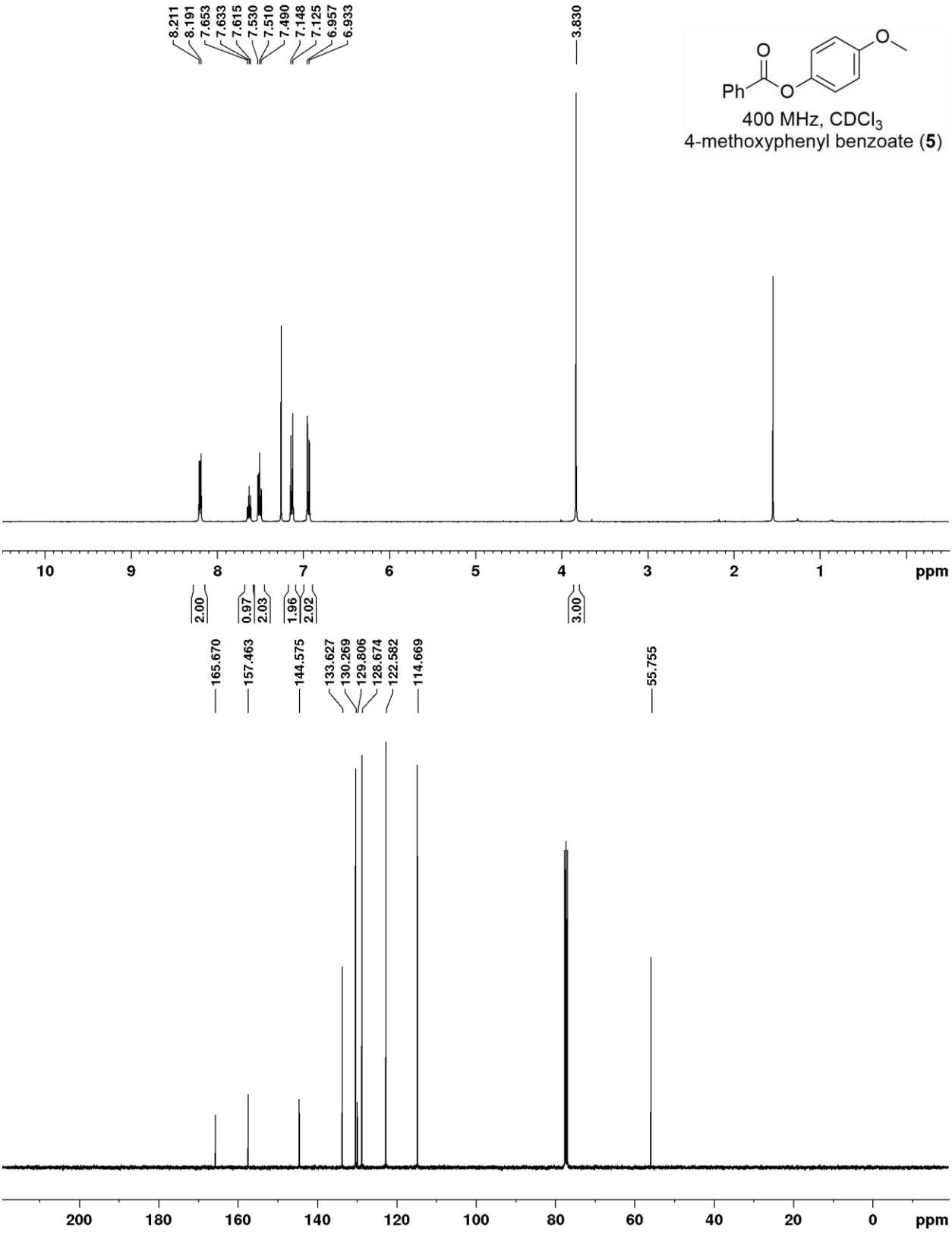
6 NMR Spectra

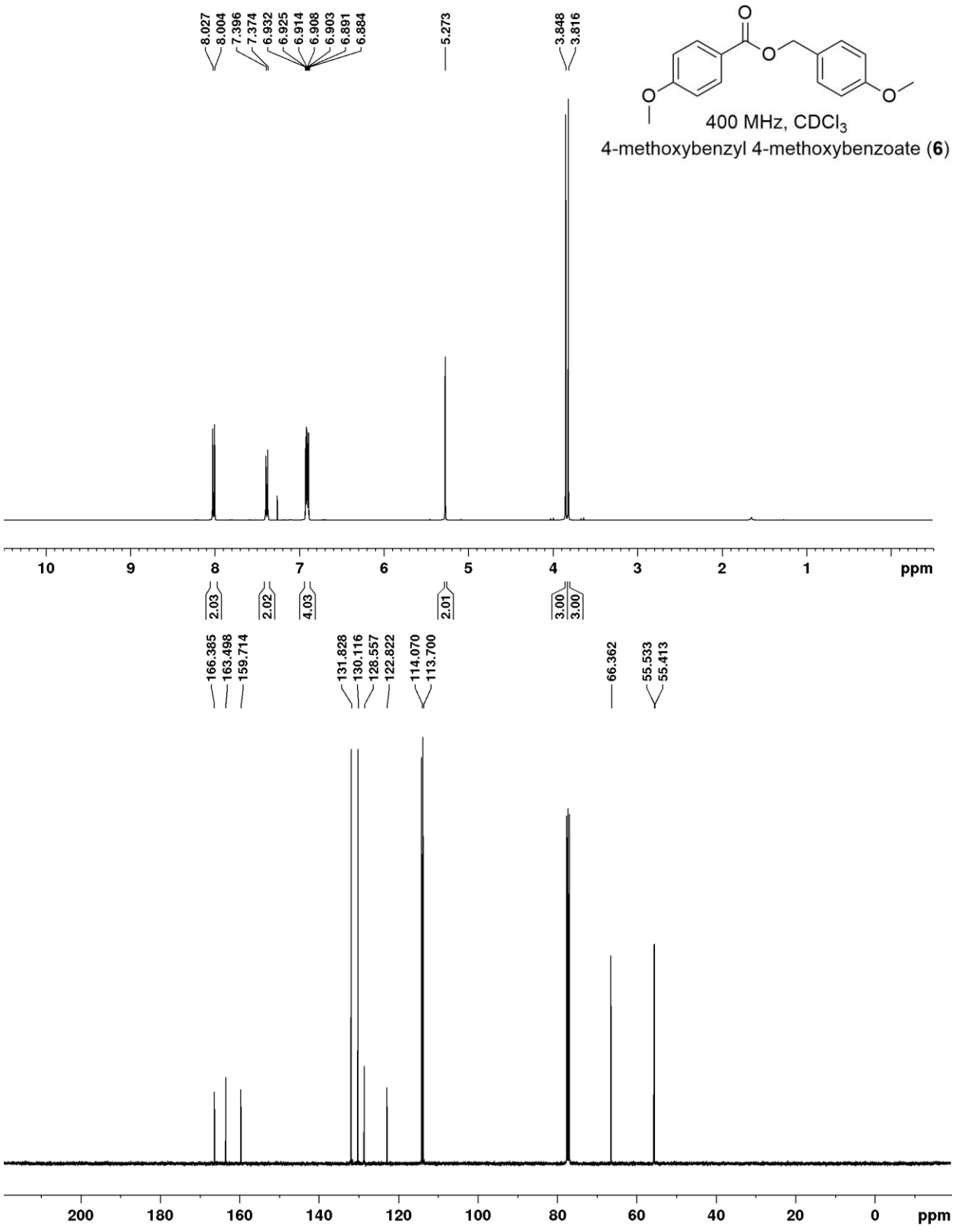


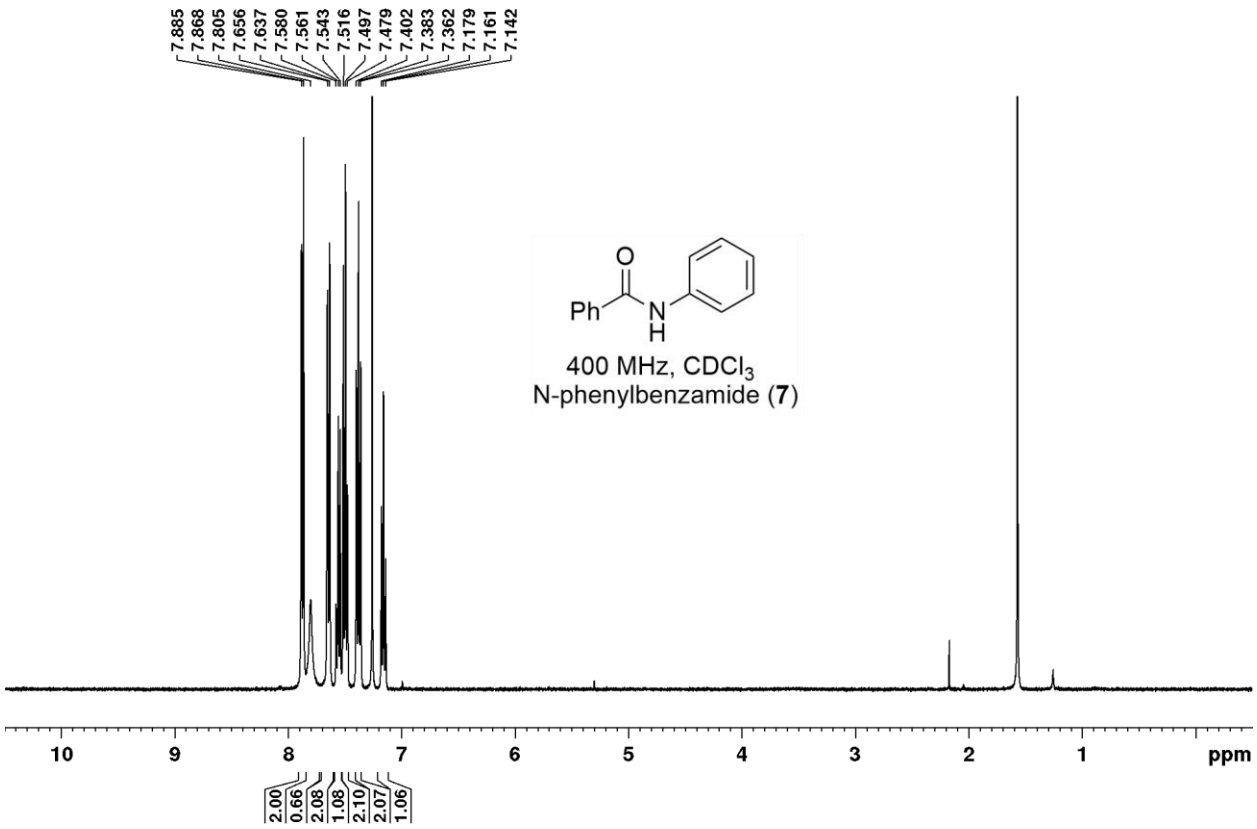


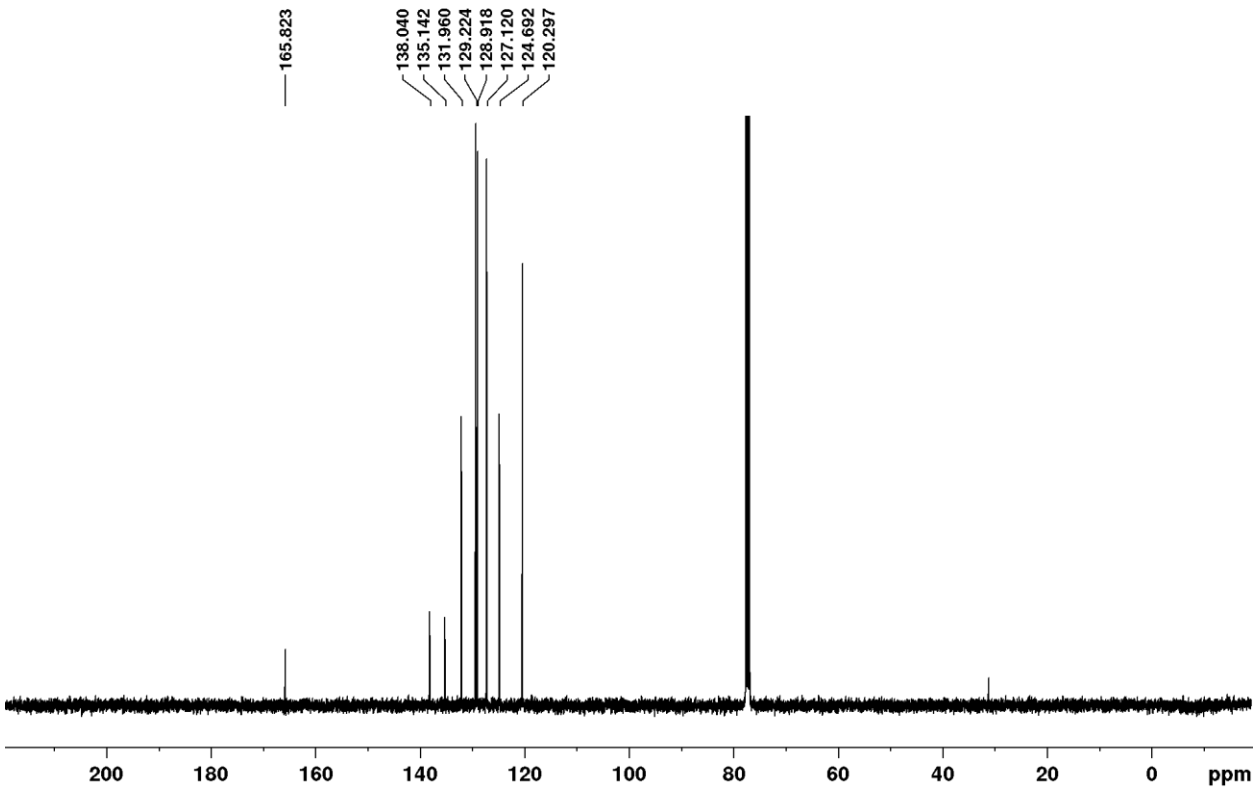

8.205
8.185
7.759
7.736
7.697
7.678
7.659
7.557
7.538
7.519
7.386
7.364
O
Ph
O
CN
400 MHz, CDCl3
4-cyanophenyl benzoate (4)
10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.01
0.99
2.10
2.04

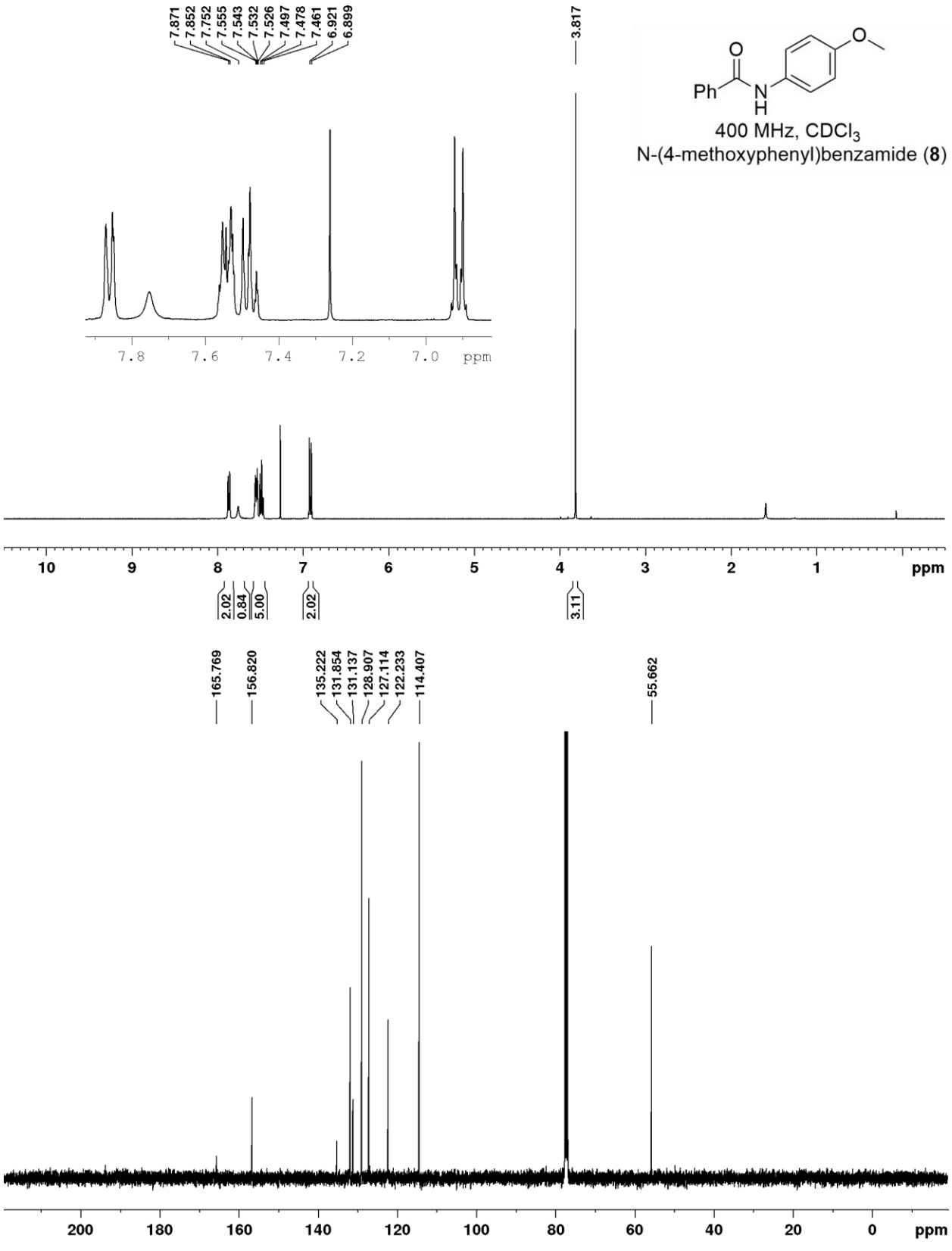

164.455
154.405
134.308
133.875
130.436
128.904
128.795
123.071
118.407
109.986
200
180
160
140
120
100
80
60
40
20
0
ppm

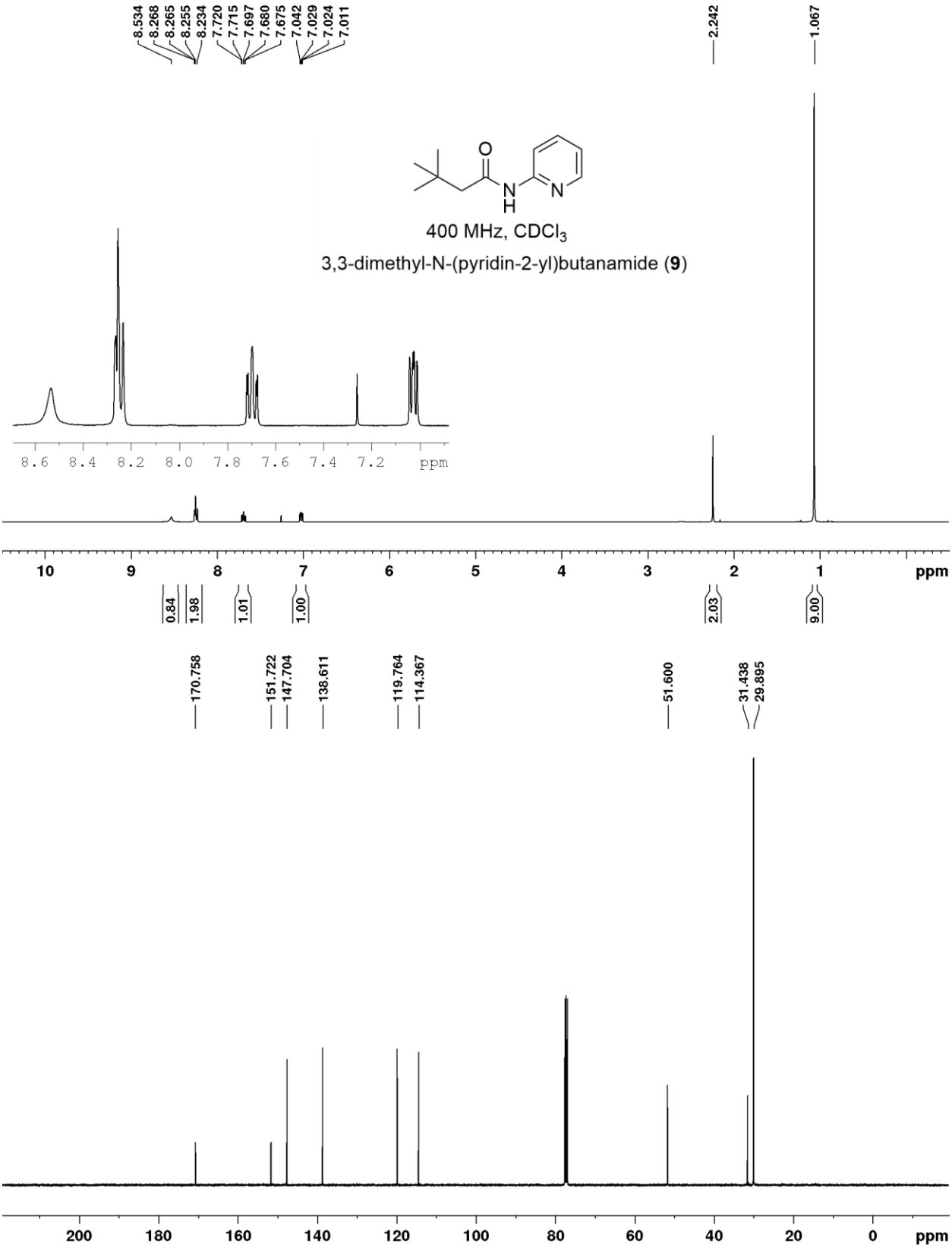

8.211
8.191
7.653
7.633
7.615
7.530
7.510
7.490
7.148
7.125
6.957
6.933
3.830
O
O
Ph
O
400 MHz, CDCl3
4-methoxyphenyl benzoate (5)
10
9
8
7
6
5
4
3
2
1
ppm
2.00
0.97
2.03
1.96
2.02
3.00
165.670
157.463
144.575
133.627
130.269
129.806
128.674
122.582
114.669
55.755
200
180
160
140
120
100
80
60
40
20
0
ppm

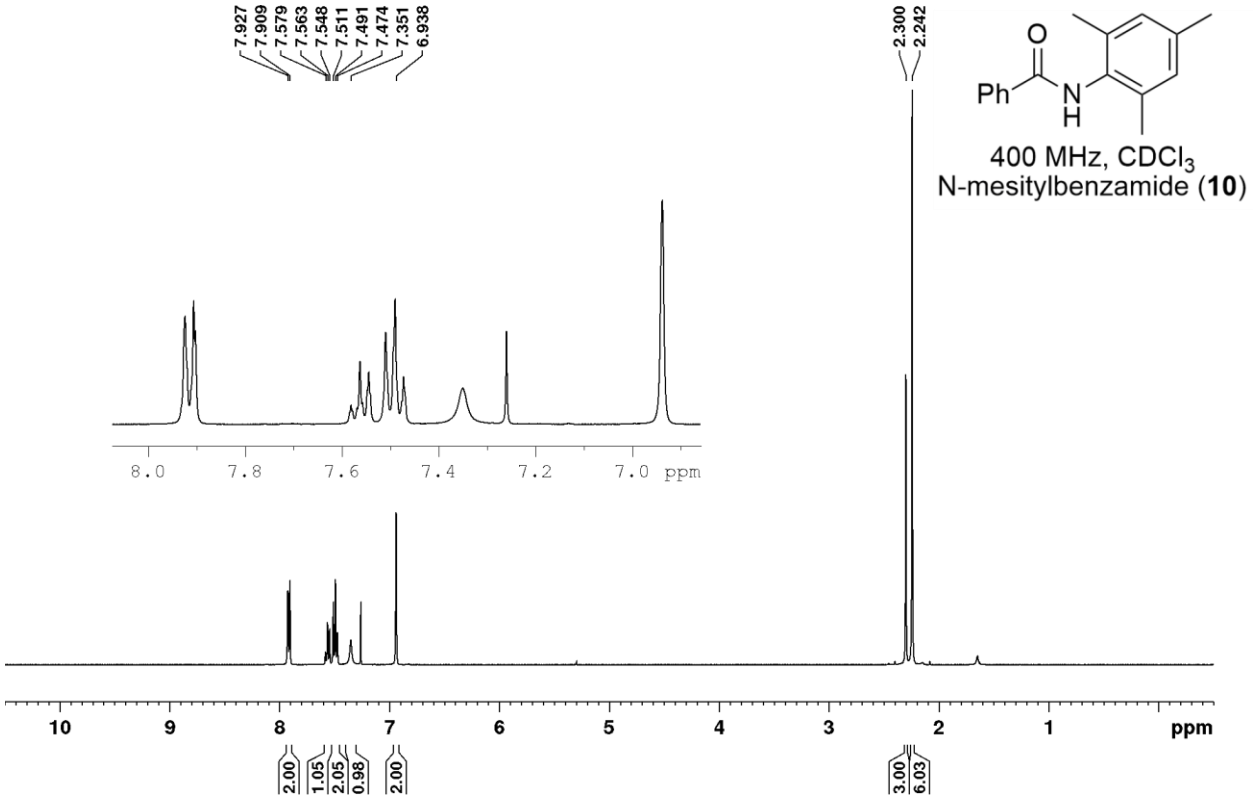

8.027
8.004
7.396
7.374
6.932
6.925
6.914
6.908
6.903
6.891
6.884
5.273
3.848
3.816
400 MHz, CDCl3
4-methoxybenzyl 4-methoxybenzoate (6)
10
9
8
7
6
5
4
3
2
1
ppm
2.03
2.02
4.03
2.01
3.00
3.00
166.385
163.498
159.714
131.828
130.116
128.557
122.822
114.070
113.700
66.362
55.533
55.413
200
180
160
140
120
100
80
60
40
20
0
ppm

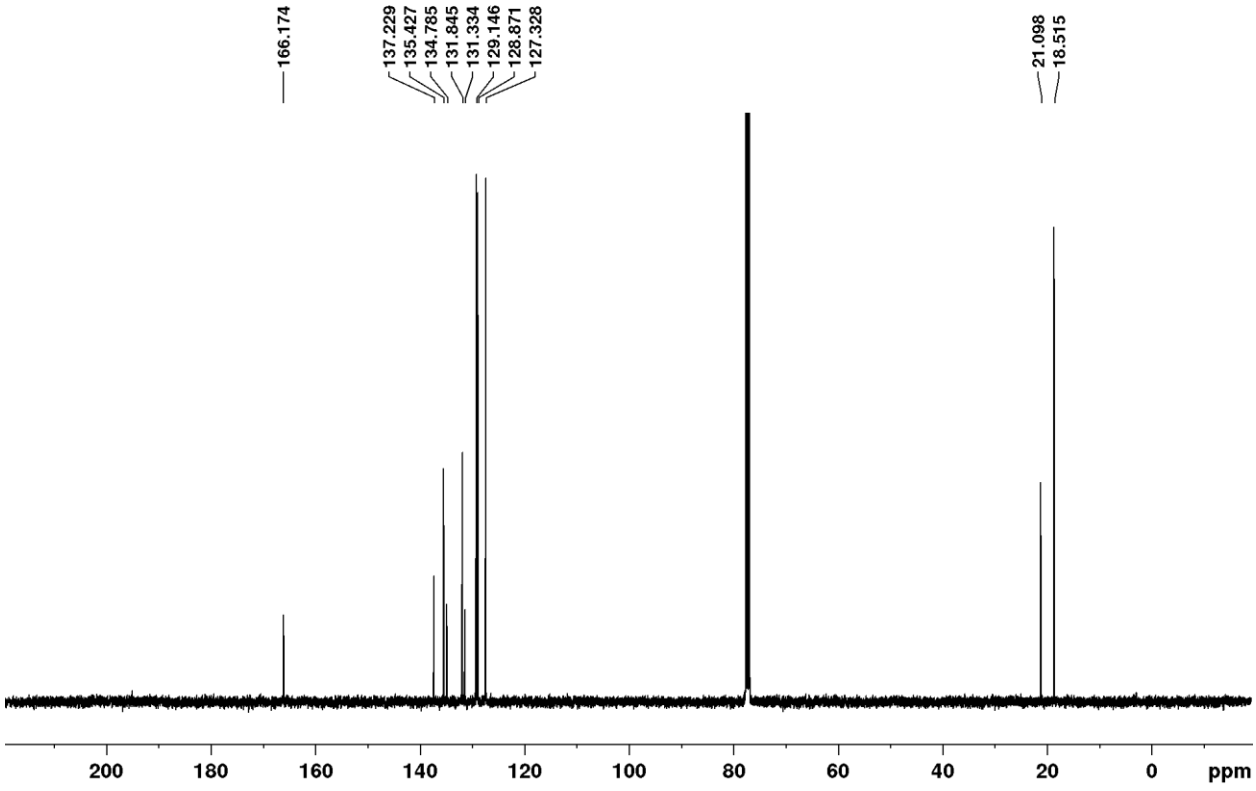

7.885
7.868
7.805
7.656
7.637
7.580
7.561
7.543
7.516
7.497
7.479
7.402
7.383
7.362
7.179
7.161
7.142
O
Ph
N
H
400 MHz, CDCl3
N-phenylbenzamide (7)
10
9
8
7
6
5
4
3
2
1
ppm
2.00
0.66
2.08
1.08
2.10
2.07
1.06

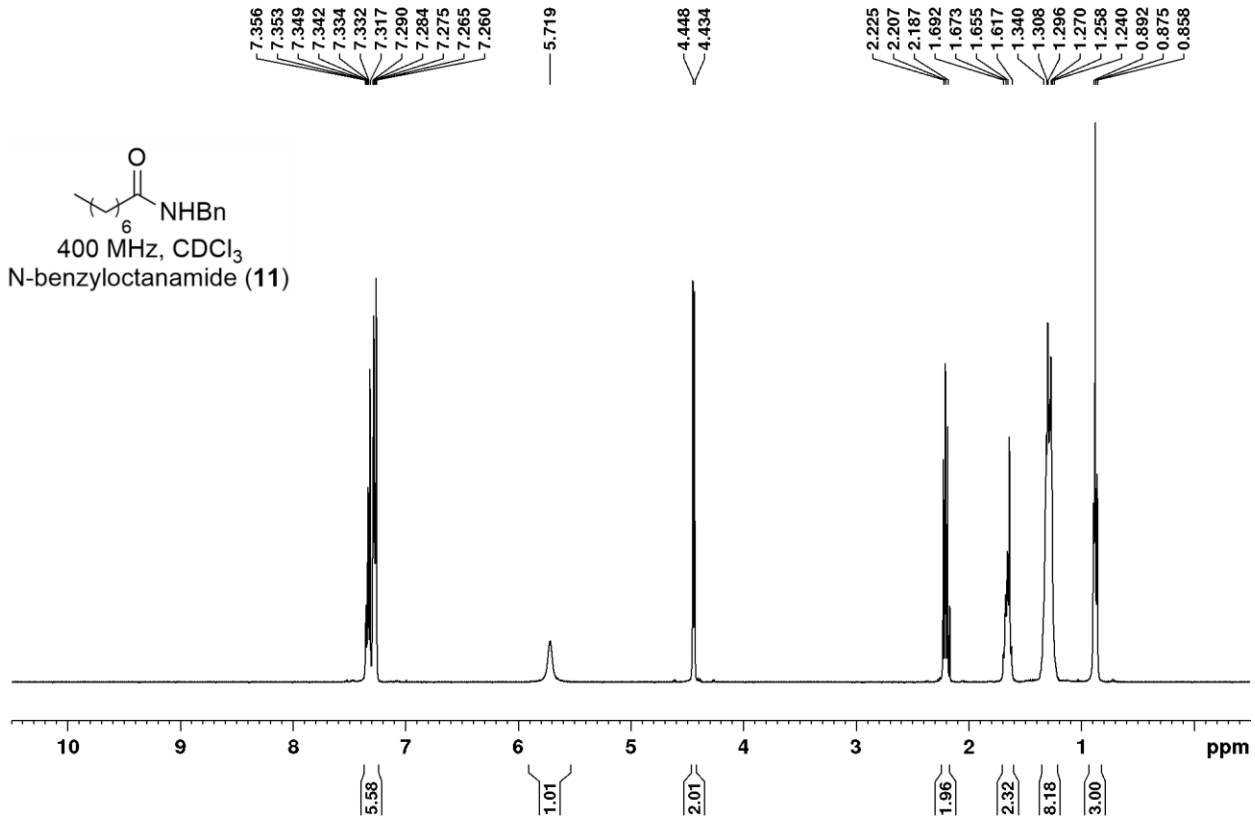

165.823
138.040
135.142
131.960
129.224
128.918
127.120
124.692
120.297
200
180
160
140
120
100
80
60
40
20
0
ppm

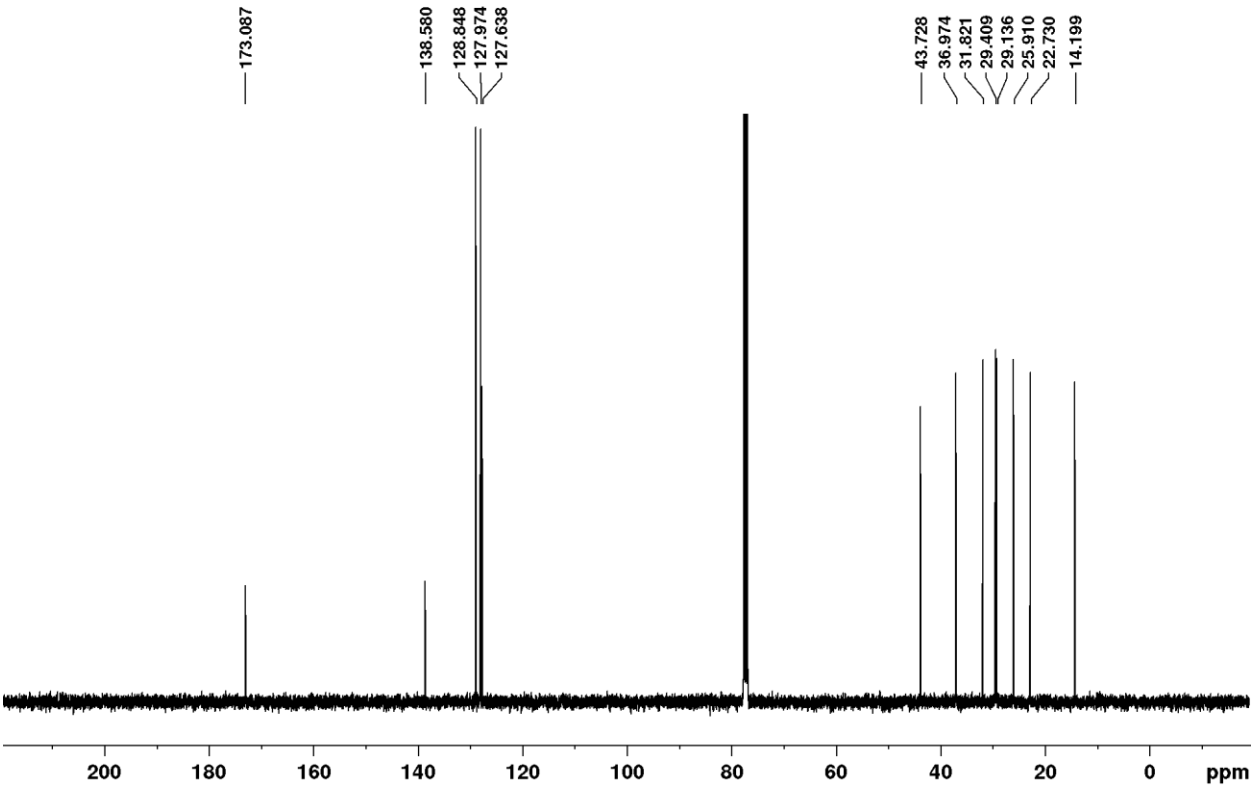

7.871
7.852
7.752
7.555
7.543
7.532
7.526
7.497
7.478
7.461
6.921
6.899
3.817
7.8
7.6
7.4
7.2
7.0
ppm
O
Ph
N
H
O
400 MHz, CDCl3
N-(4-methoxyphenyl)benzamide (8)
10
9
8
7
6
5
4
3
2
1
ppm
2.02
0.84
5.00
2.02
3.11
165.769
156.820
135.222
131.854
131.137
128.907
127.114
122.233
114.407
55.662
200
180
160
140
120
100
80
60
40
20
0
ppm

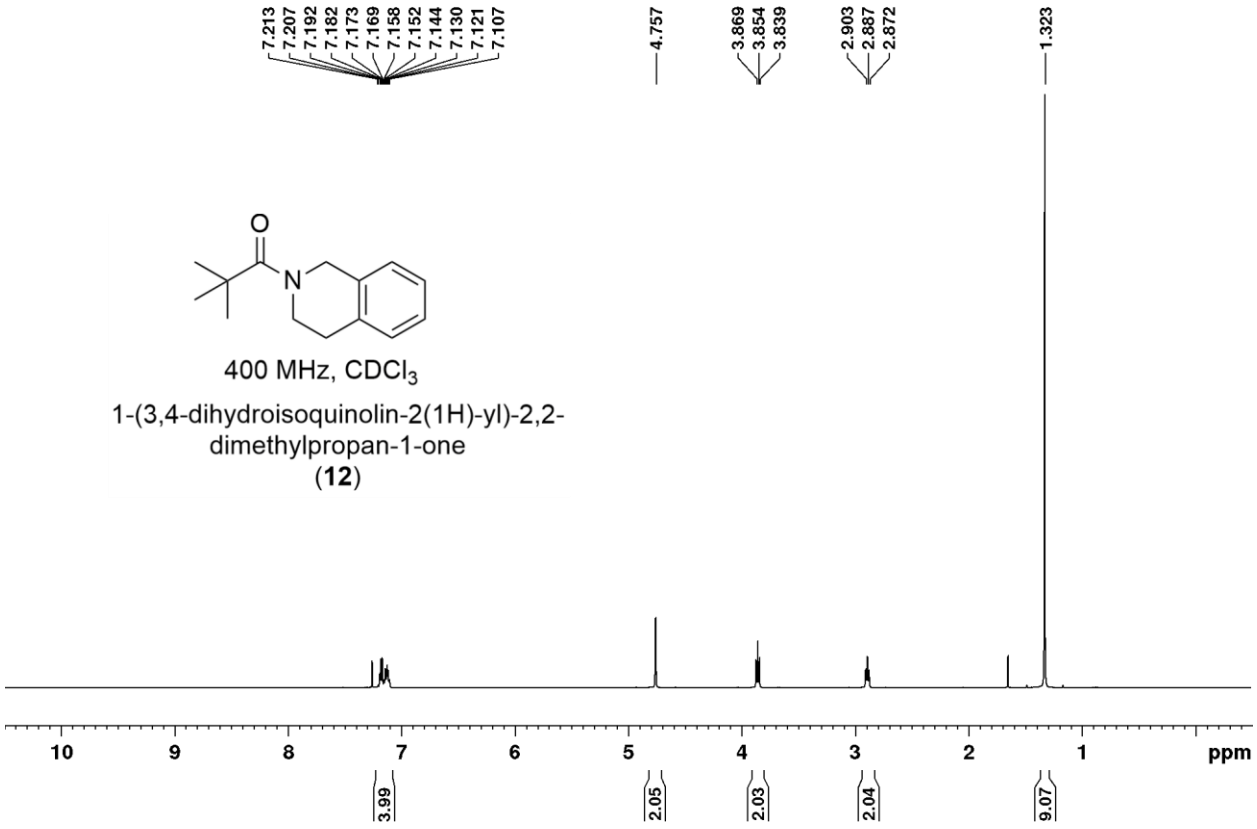

8.534
8.268
8.265
8.255
8.234
7.720
7.715
7.697
7.680
7.675
7.042
7.029
7.024
7.011
2.242
1.067
400 MHz, CDCl3
3,3-dimethyl-N-(pyridin-2-yl)butanamide (9)
8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 ppm
10 9 8 7 6 5 4 3 2 1 ppm
0.84
1.98
1.01
1.00
2.03
9.00
170.758
151.722
147.704
138.611
119.764
114.367
51.600
31.438
29.895
200 180 160 140 120 100 80 60 40 20 0 ppm

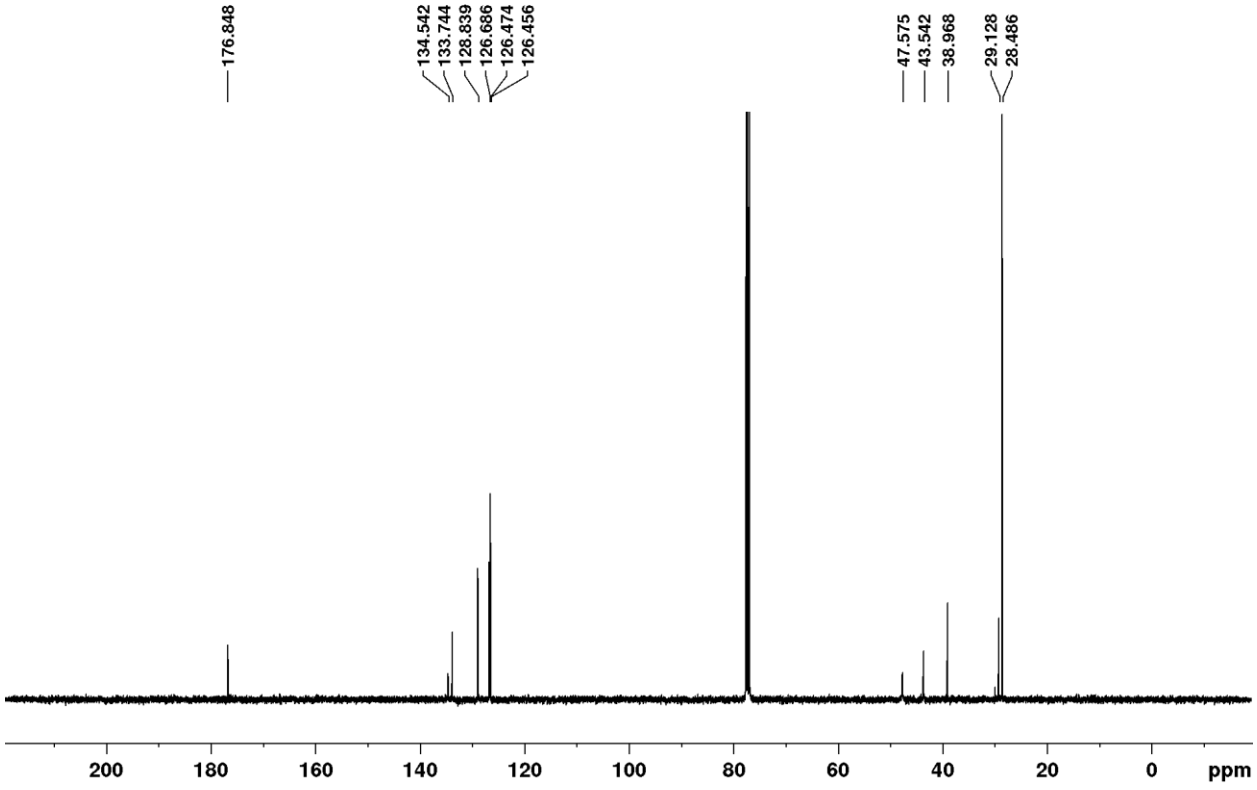

7.927
7.909
7.579
7.563
7.548
7.511
7.491
7.474
7.351
6.938
2.300
2.242
O
Ph
N
H
400 MHz, CDCl3
N-mesitylbenzamide (10)
8.0
7.8
7.6
7.4
7.2
7.0 ppm
10
9
8
7
6
5
4
3
2
1
ppm
2.00
1.05
2.05
0.98
2.00
3.00
6.03

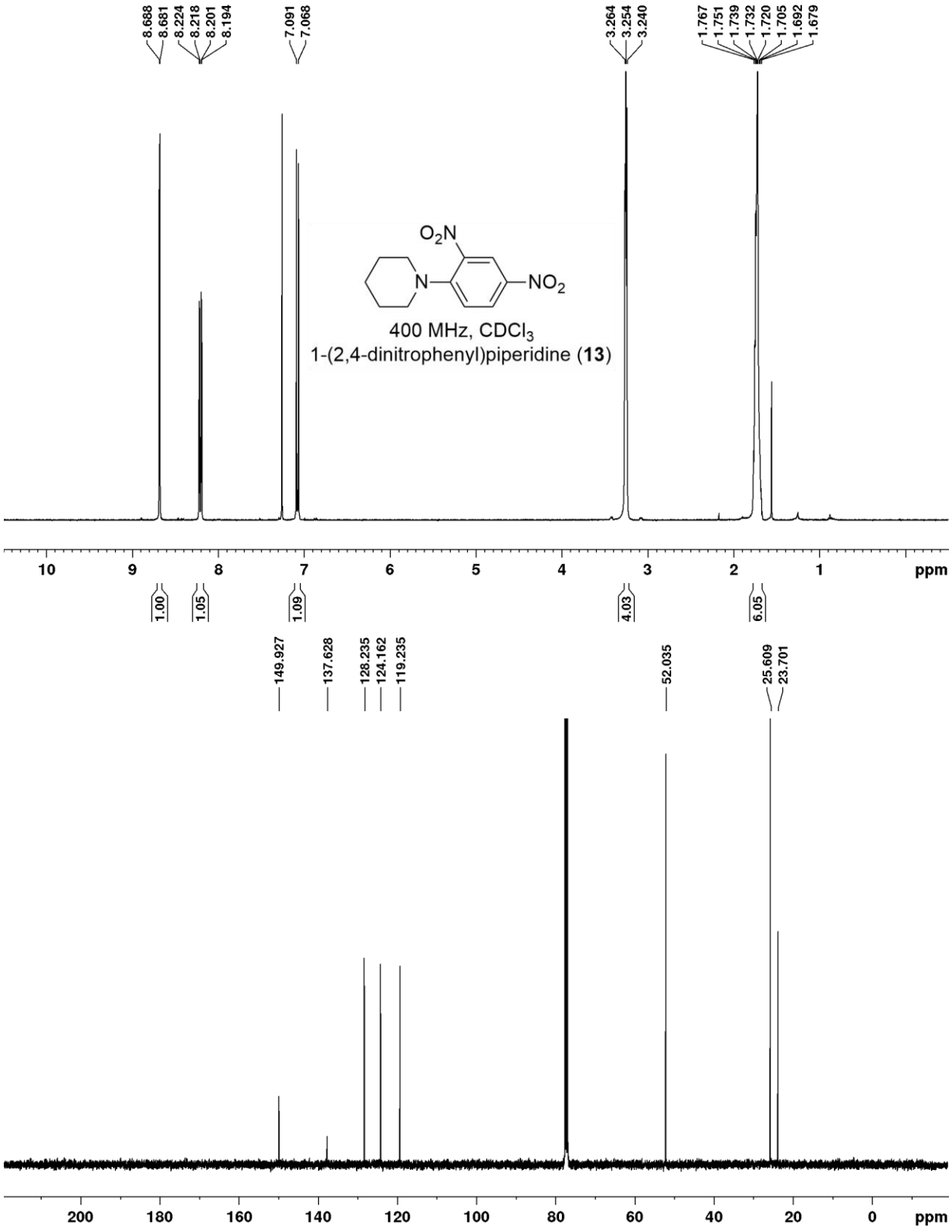

166.174
137.229
135.427
134.785
131.845
131.334
129.146
128.871
127.328
21.098
18.515
200
180
160
140
120
100
80
60
40
20
0
ppm

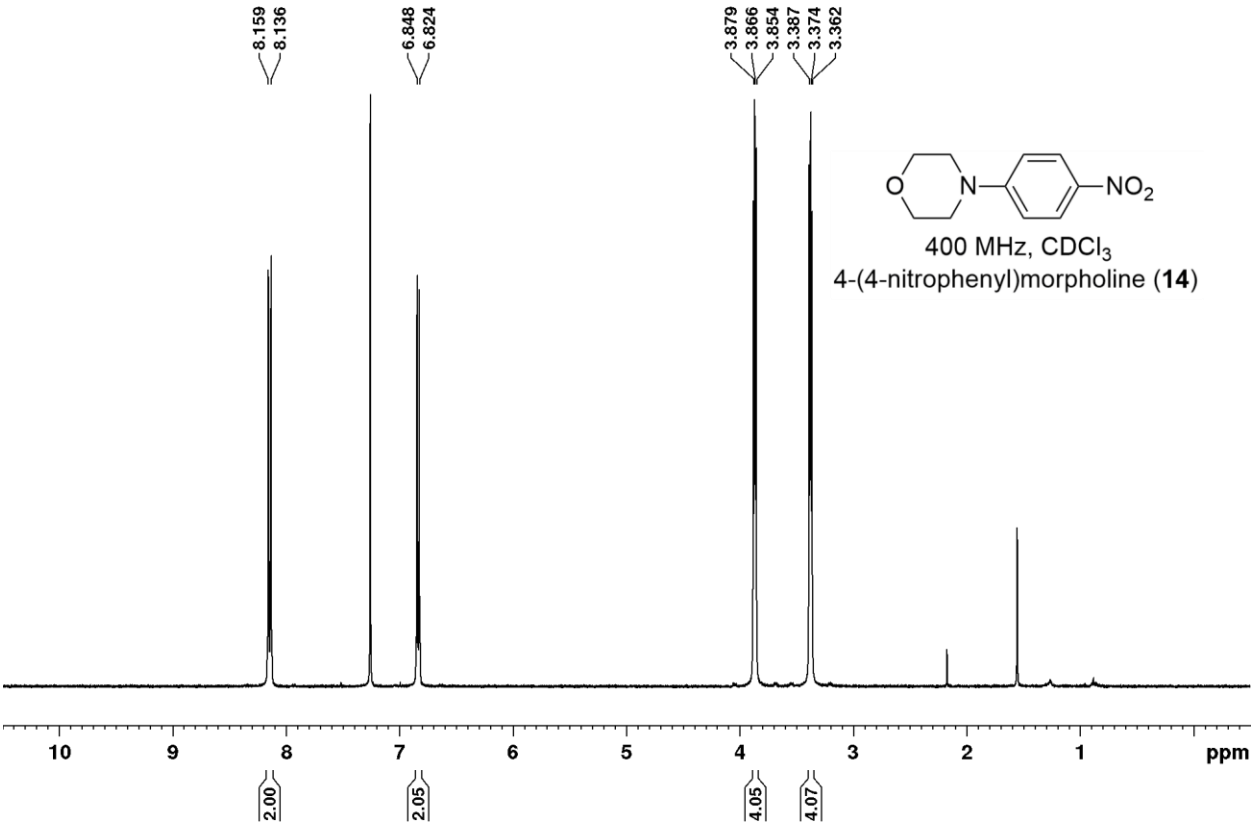

7.356
7.353
7.349
7.342
7.334
7.332
7.317
7.290
7.284
7.275
7.265
7.260
5.719
4.448
4.434
2.225
2.207
2.187
1.692
1.673
1.655
1.617
1.340
1.308
1.296
1.270
1.258
1.240
0.892
0.875
0.858
O
NHBn
6
400 MHz, CDCl3
N-benzyloctanamide (11)
10
9
8
7
6
5
4
3
2
1
ppm
5.58
1.01
2.01
1.96
2.32
8.18
3.00

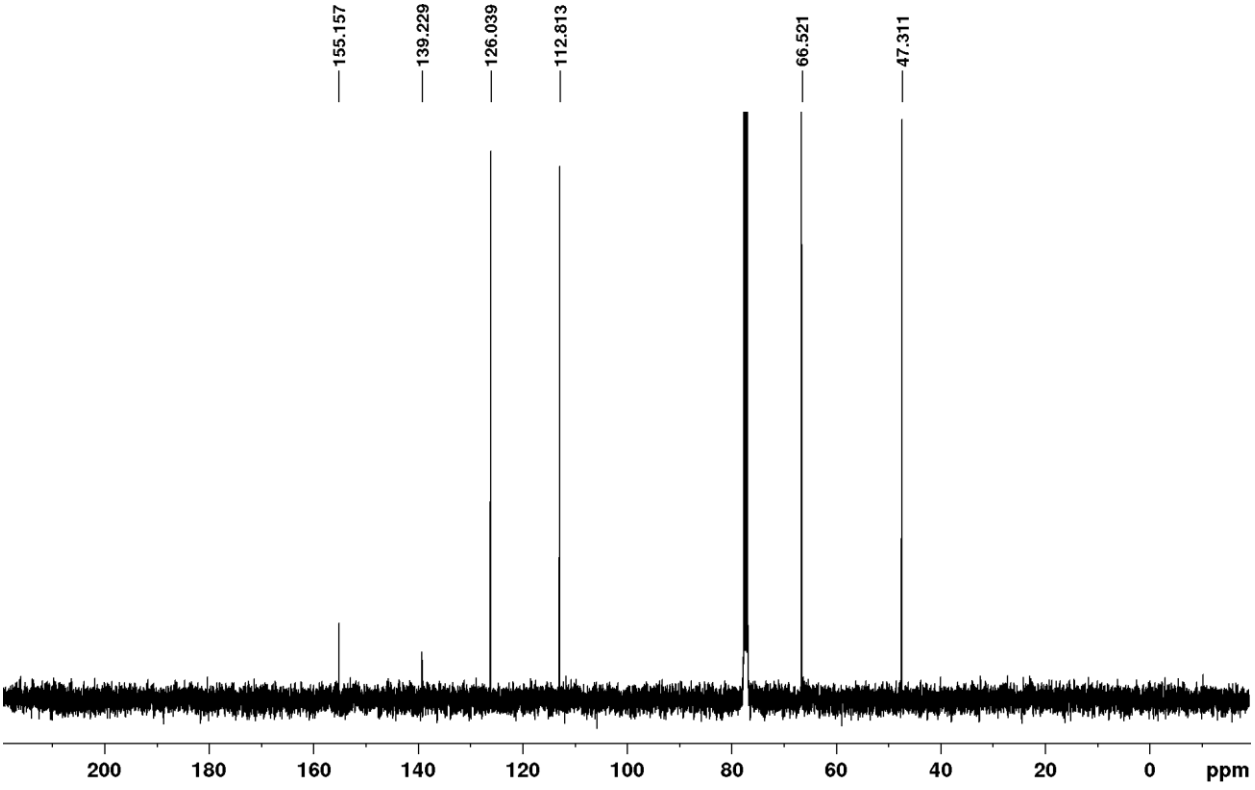

173.087
138.580
128.848
127.974
127.638
43.728
36.974
31.821
29.409
29.136
25.910
22.730
14.199
200
180
160
140
120
100
80
60
40
20
0
ppm

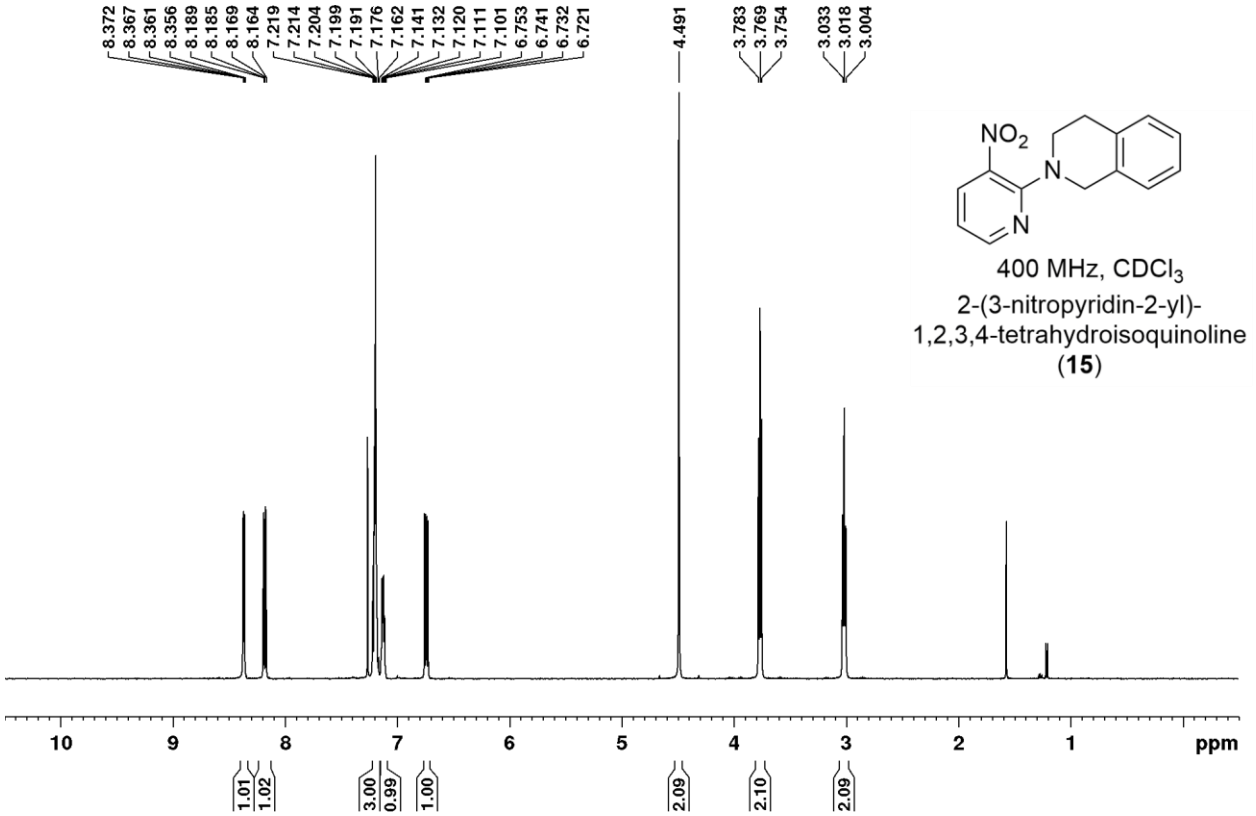

7.213
7.207
7.192
7.182
7.173
7.169
7.158
7.152
7.144
7.130
7.121
7.107
4.757
3.869
3.854
3.839
2.903
2.887
2.872
1.323
O
N
400 MHz, CDCl3
1-(3,4-dihydroisoquinolin-2(1H)-yl)-2,2-dimethylpropan-1-one
(12)
10
9
8
7
6
5
4
3
2
1
ppm
3.99
2.05
2.03
2.04
9.07

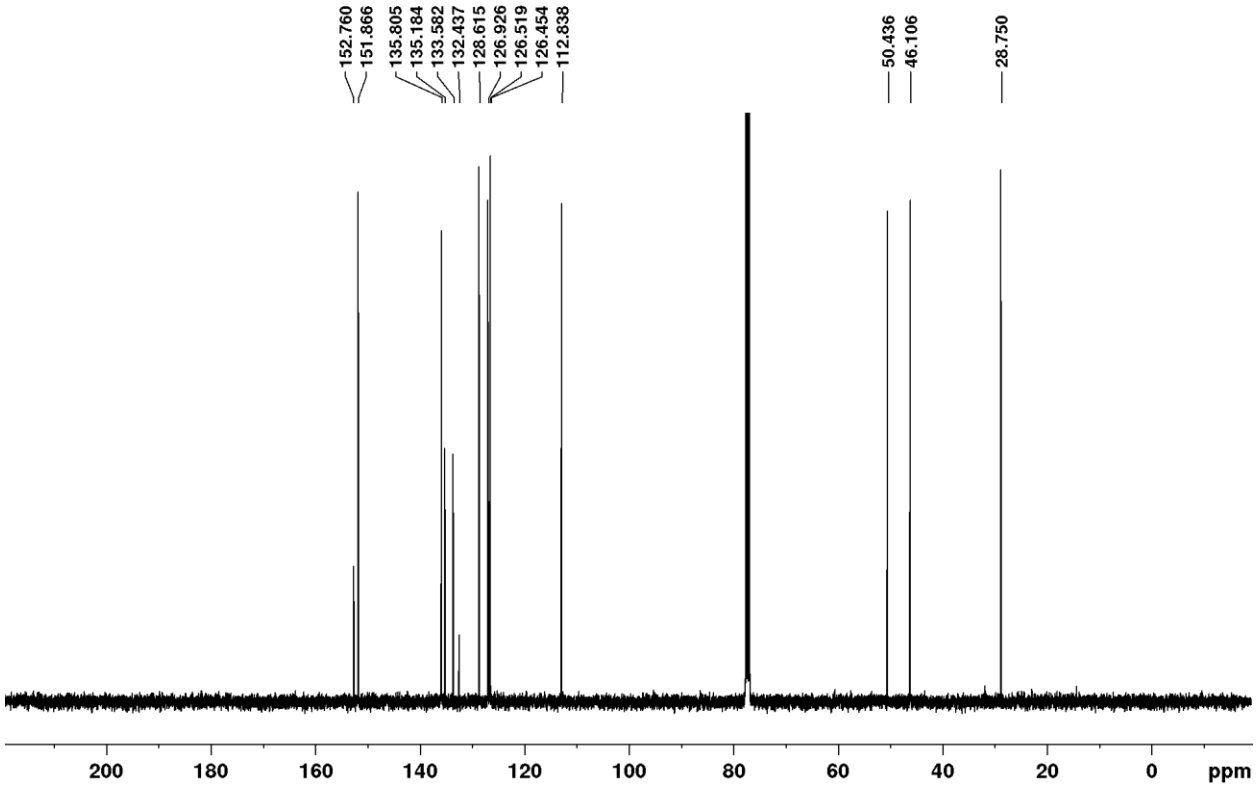

176.848
134.542
133.744
128.839
126.686
126.474
126.456
47.575
43.542
38.968
29.128
28.486
200
180
160
140
120
100
80
60
40
20
0
ppm

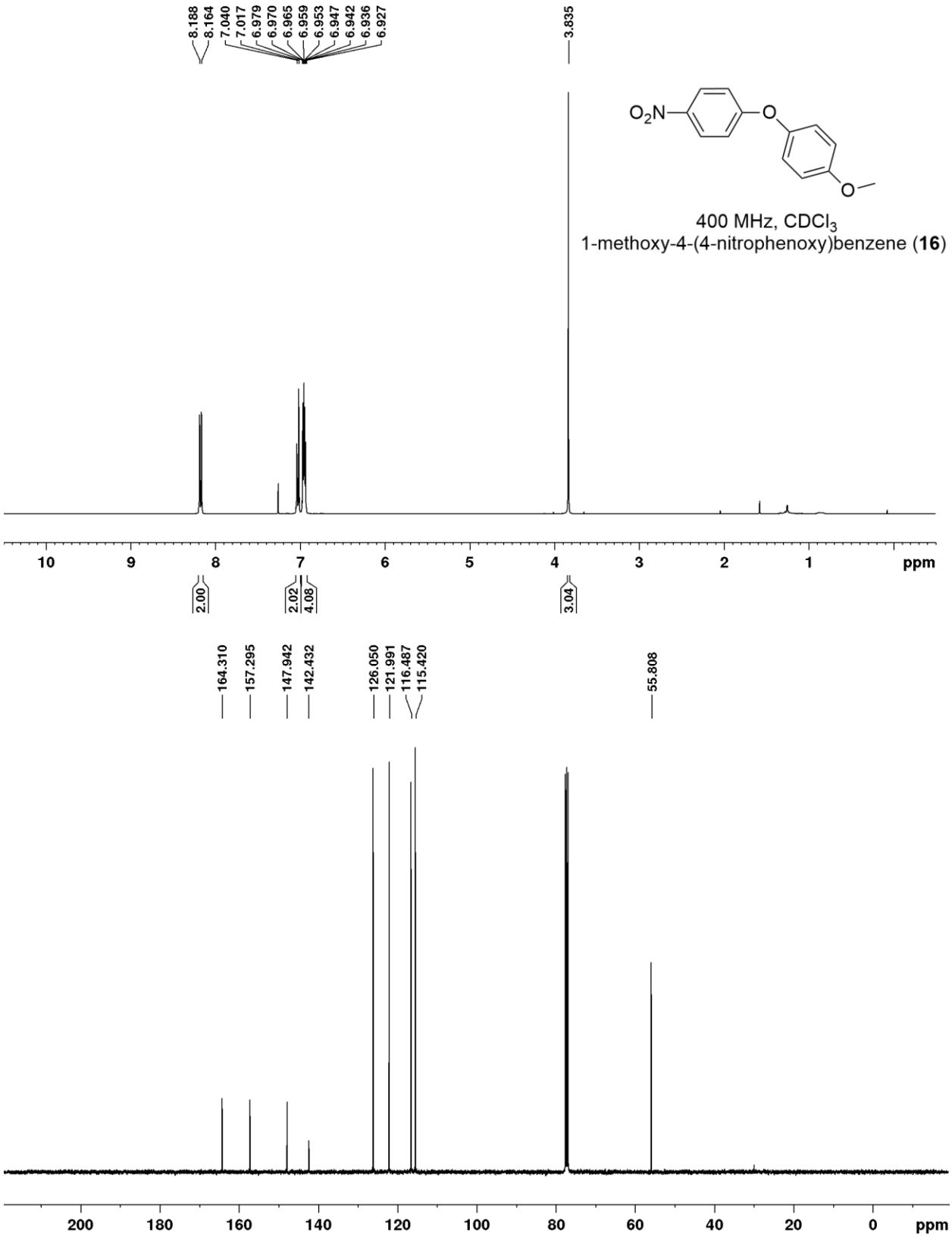

8.688
8.681
8.224
8.218
8.201
8.194
7.091
7.068
3.264
3.254
3.240
1.767
1.751
1.739
1.732
1.720
1.705
1.692
1.679
O2N
N
NO2
400 MHz, CDCl3
1-(2,4-dinitrophenyl)piperidine (13)
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.05
1.09
4.03
6.05
149.927
137.628
128.235
124.162
119.235
52.035
25.609
23.701
200
180
160
140
120
100
80
60
40
20
0
ppm

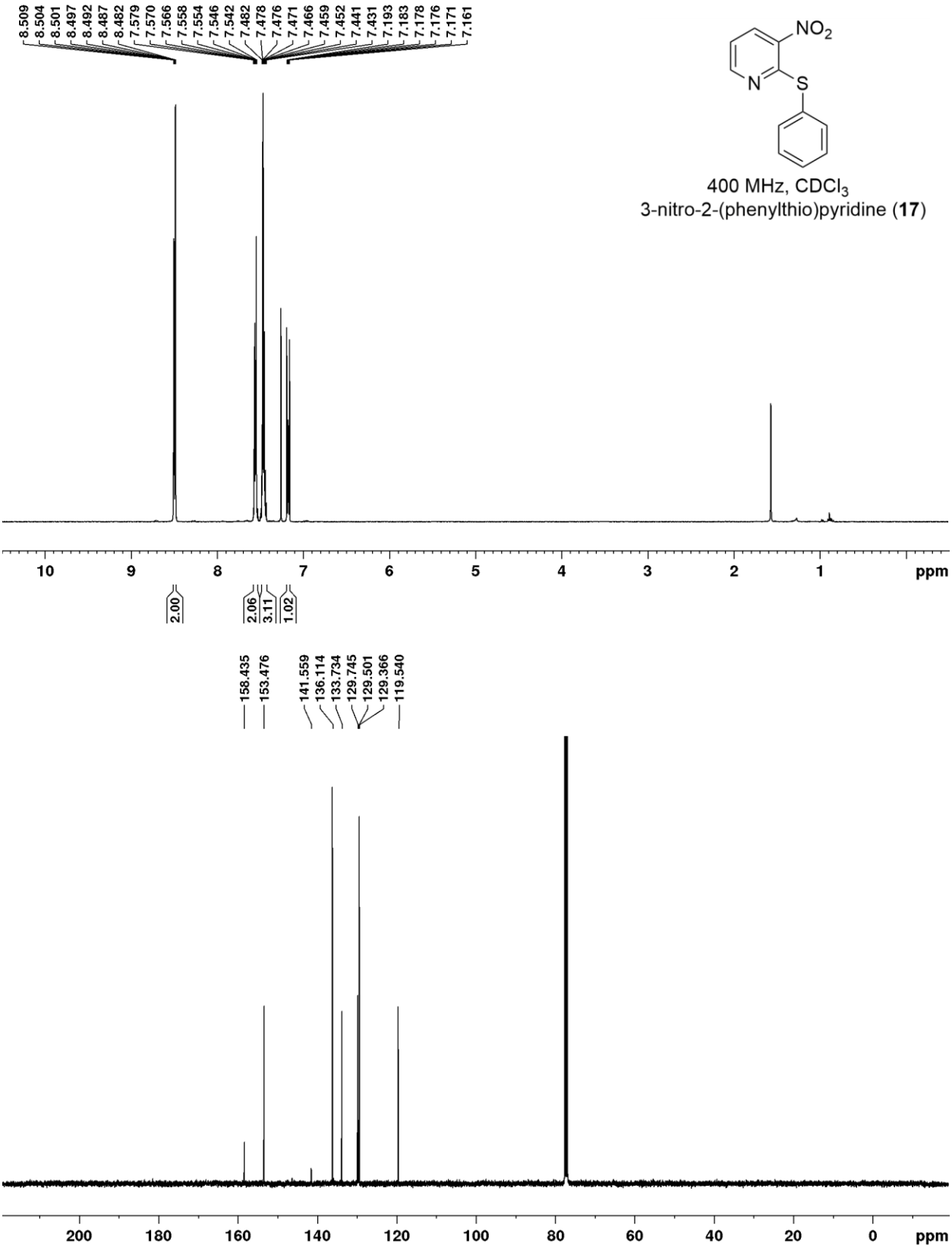

8.159
8.136
6.848
6.824
3.879
3.866
3.854
3.387
3.374
3.362
O
N
NO2
400 MHz, CDCl3
4-(4-nitrophenyl)morpholine (14)
10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.05
4.05
4.07

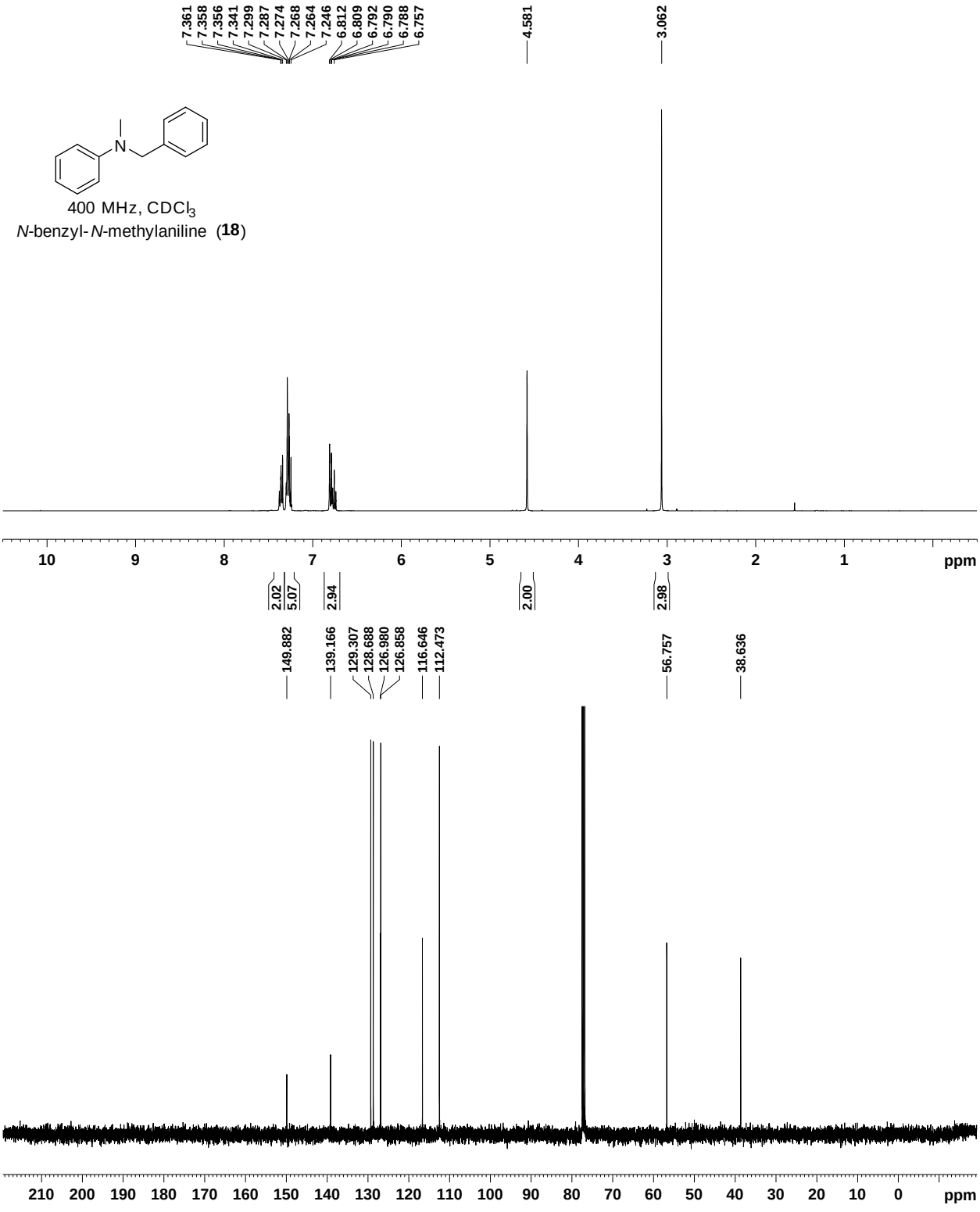

155.157
139.229
126.039
112.813
66.521
47.311
200
180
160
140
120
100
80
60
40
20
0
ppm

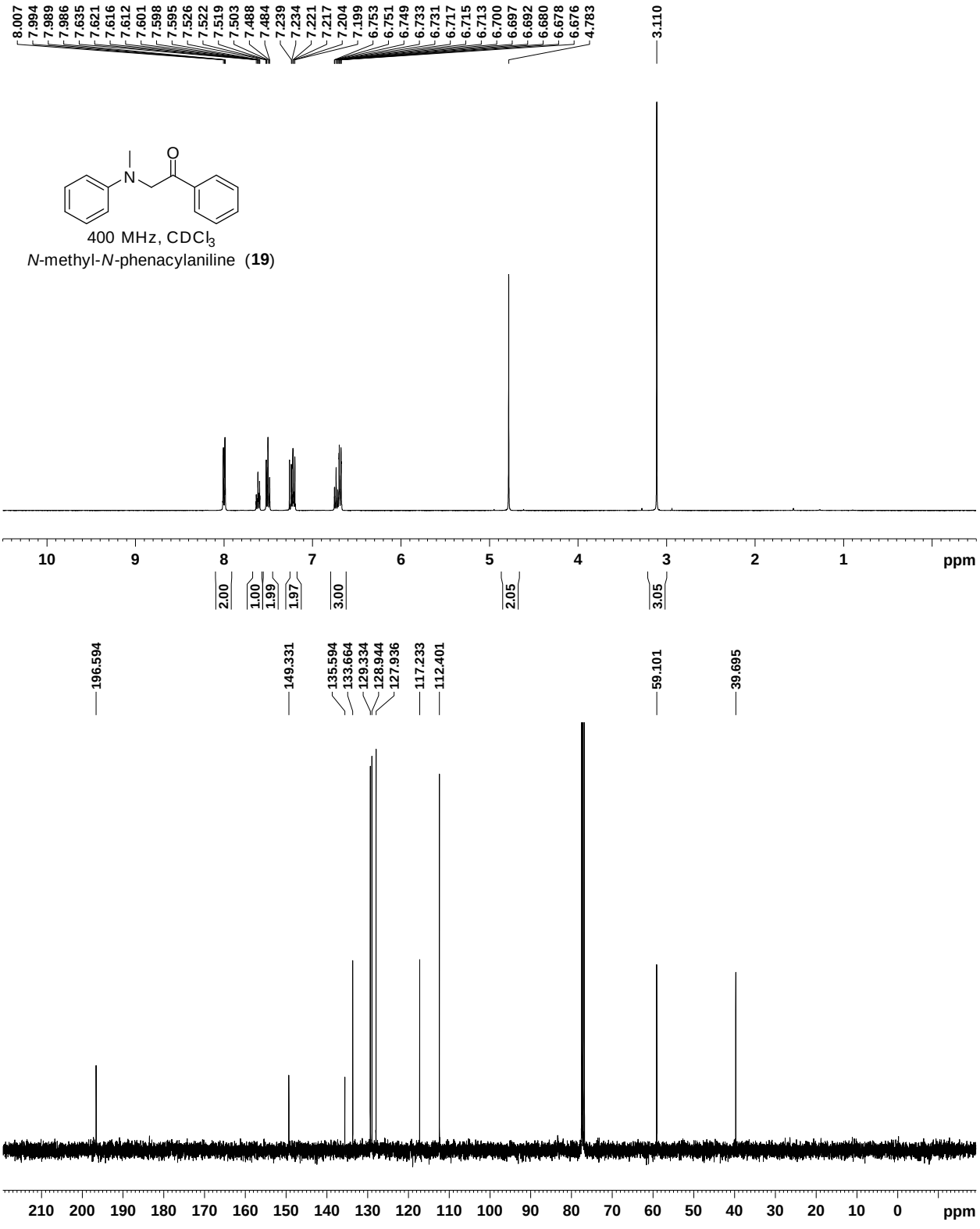

8.372
8.367
8.361
8.356
8.189
8.185
8.169
8.164
7.219
7.214
7.204
7.199
7.191
7.176
7.162
7.141
7.132
7.120
7.111
7.101
6.753
6.741
6.732
6.721
4.491
3.783
3.769
3.754
3.033
3.018
3.004
NO2
N
N
400 MHz, CDCl3
2-(3-nitropyridin-2-yl)-
1,2,3,4-tetrahydroisoquinoline
(15)
10
9
8
7
6
5
4
3
2
1
ppm
1.01
1.02
3.00
0.99
1.00
2.09
2.10
2.09

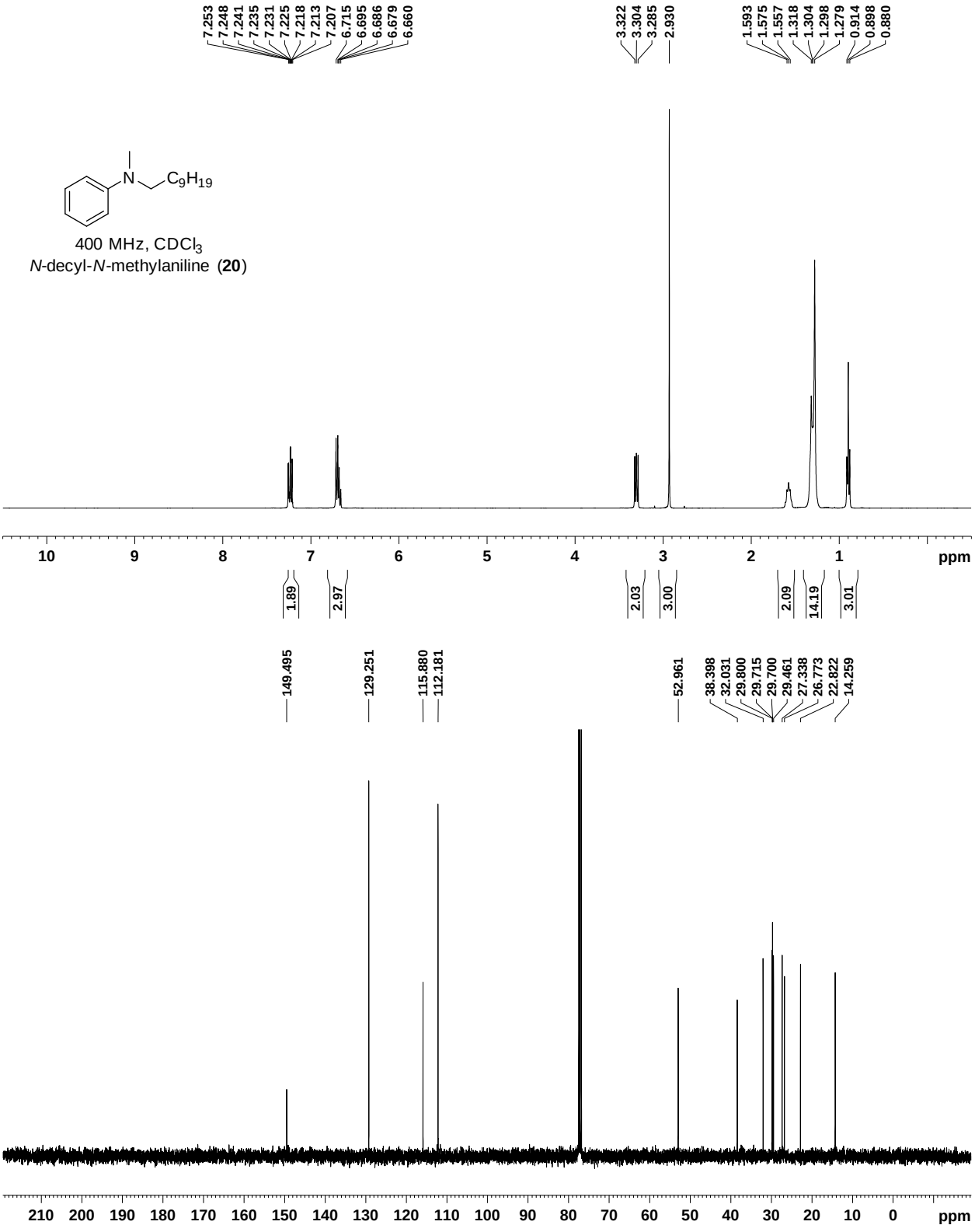

152.760
151.866
135.805
135.184
133.582
132.437
128.615
126.926
126.519
126.454
112.838
50.436
46.106
28.750
200
180
160
140
120
100
80
60
40
20
0
ppm

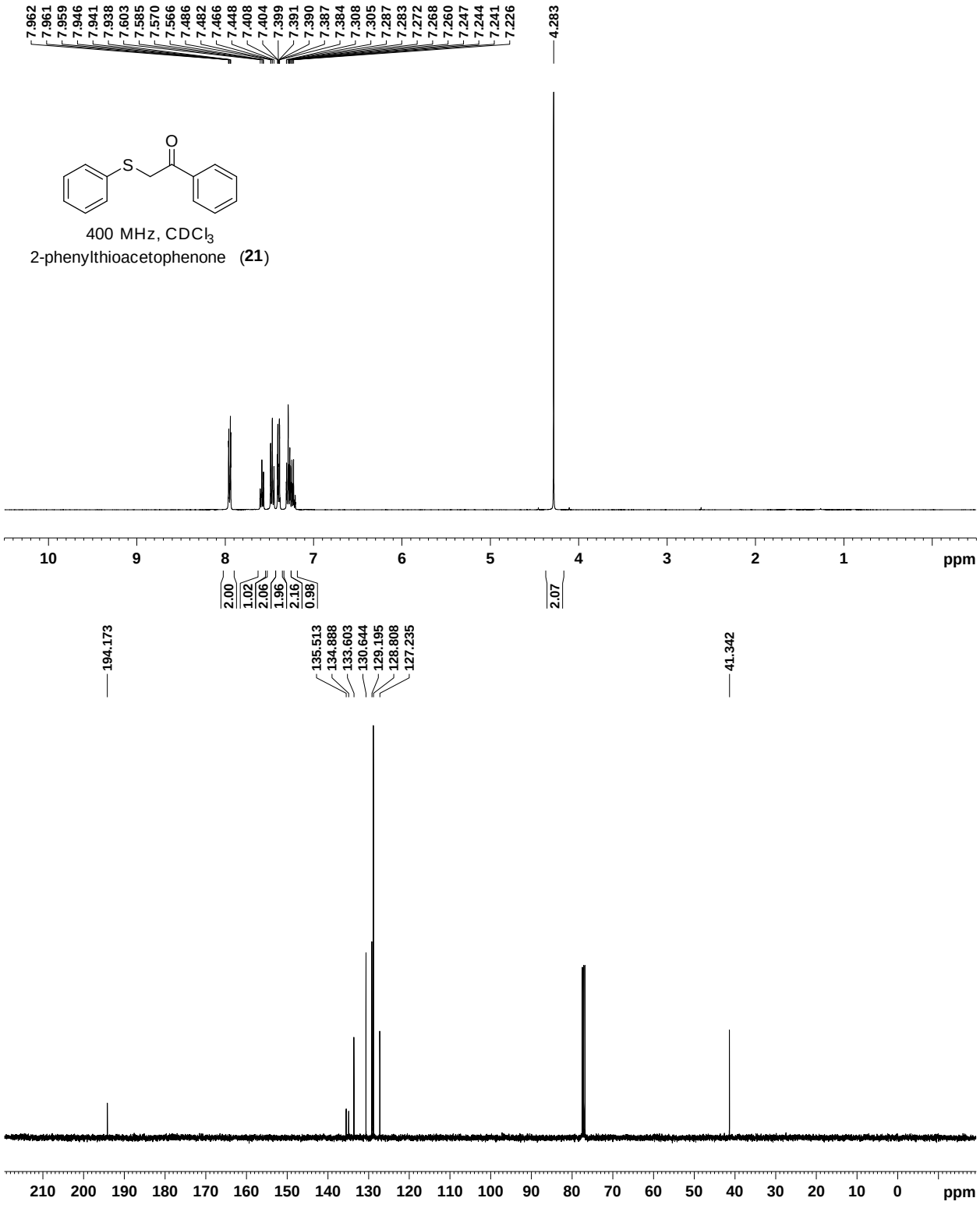

8.188
8.164
7.040
7.017
6.979
6.970
6.965
6.959
6.953
6.947
6.942
6.936
6.927
3.835
O2N
O
O
400 MHz, CDCl3
1-methoxy-4-(4-nitrophenoxy)benzene (16)
10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.02
4.08
3.04
164.310
157.295
147.942
142.432
126.050
121.991
116.487
115.420
55.808
200
180
160
140
120
100
80
60
40
20
0
ppm

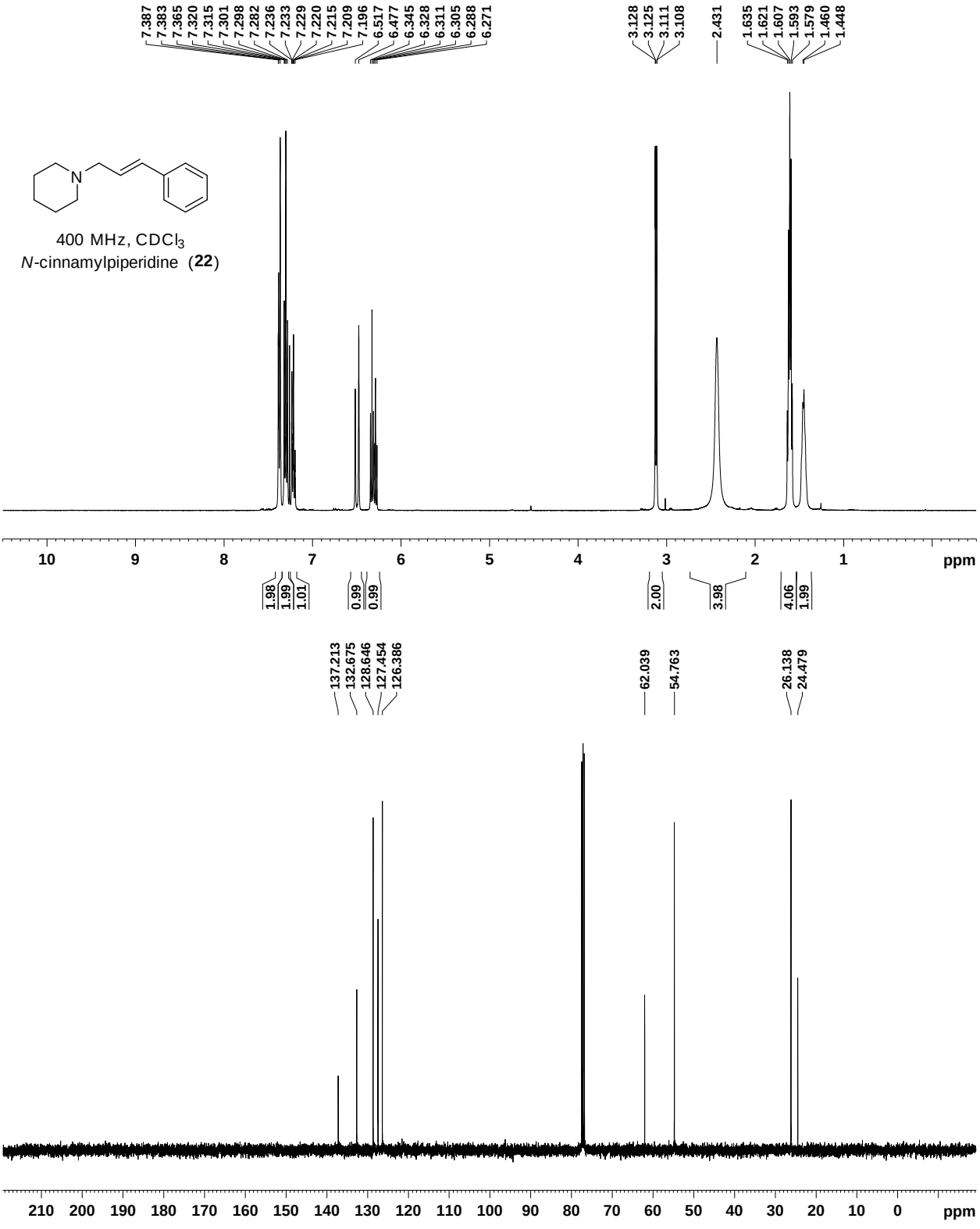

8.509
8.504
8.501
8.497
8.492
8.487
8.482
7.579
7.570
7.566
7.558
7.554
7.546
7.542
7.482
7.478
7.476
7.471
7.466
7.459
7.452
7.441
7.431
7.193
7.183
7.178
7.176
7.171
7.161
NO2
N
S
400 MHz, CDCl3
3-nitro-2-(phenylthio)pyridine (17)
10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.06
3.11
1.02
158.435
153.476
141.559
136.114
133.734
129.745
129.501
129.366
119.540
200
180
160
140
120
100
80
60
40
20
0
ppm

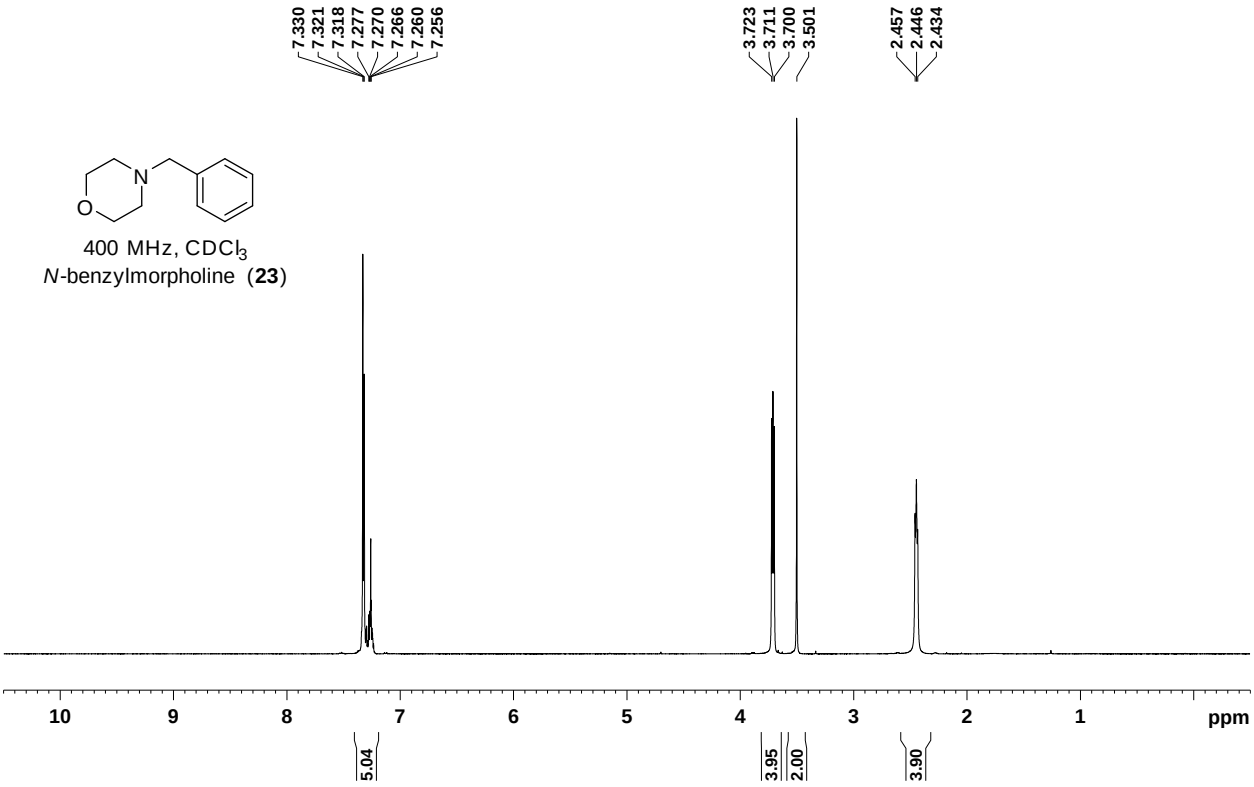

7.361
7.358
7.356
7.341
7.299
7.287
7.274
7.268
7.264
7.246
6.812
6.809
6.792
6.790
6.788
6.757
4.581
3.062
N
400 MHz, CDCl3
N-benzyl-N-methylaniline (18)
10 9 8 7 6 5 4 3 2 1 ppm
2.02
5.07
2.94
2.00
2.98
149.882
139.166
129.307
128.688
126.980
126.858
116.646
112.473
56.757
38.636
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

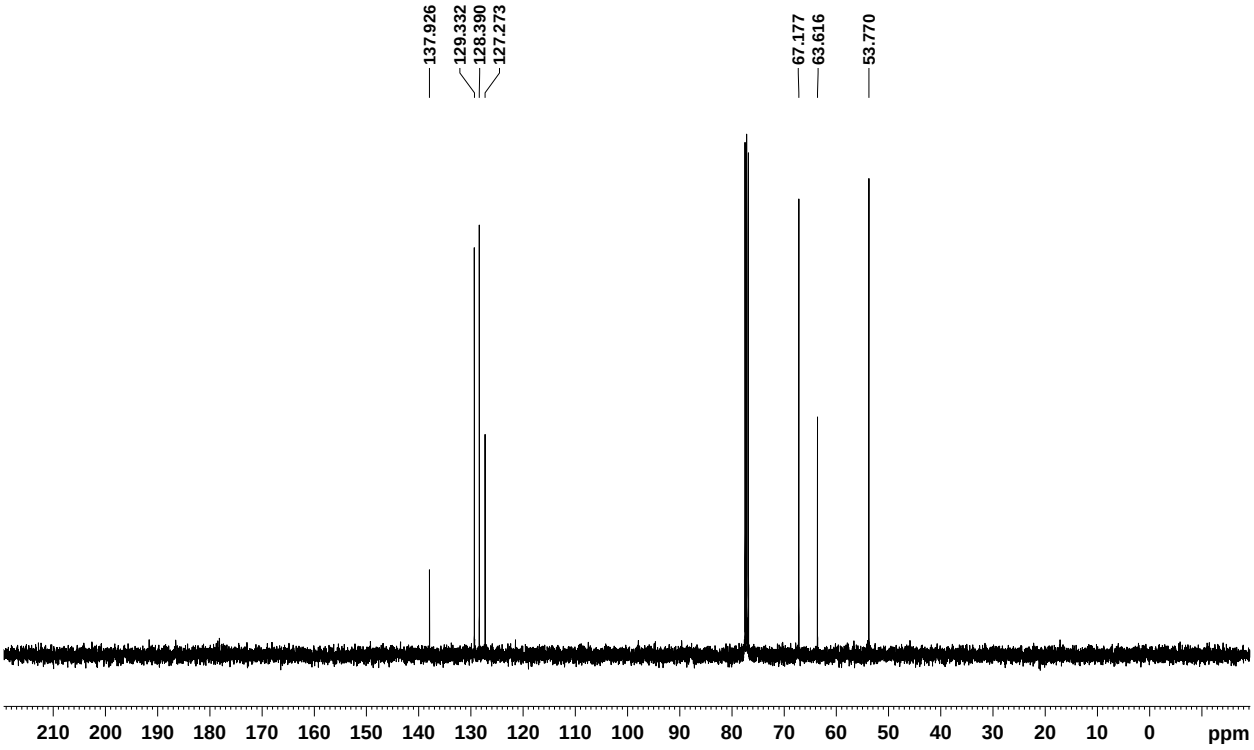

8.007
7.994
7.989
7.986
7.635
7.621
7.616
7.612
7.601
7.598
7.595
7.526
7.522
7.519
7.503
7.488
7.484
7.239
7.234
7.221
7.217
7.204
7.199
6.753
6.751
6.749
6.733
6.731
6.717
6.715
6.713
6.700
6.697
6.692
6.680
6.678
6.676
4.783
3.110
O
N
400 MHz, CDCl3
N-methyl-N-phenacylaniline (19)
10
9
8
7
6
5
4
3
2
1
ppm
2.00
1.00
1.99
1.97
3.00
2.05
3.05
196.594
149.331
135.594
133.664
129.334
128.944
127.936
117.233
112.401
59.101
39.695
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

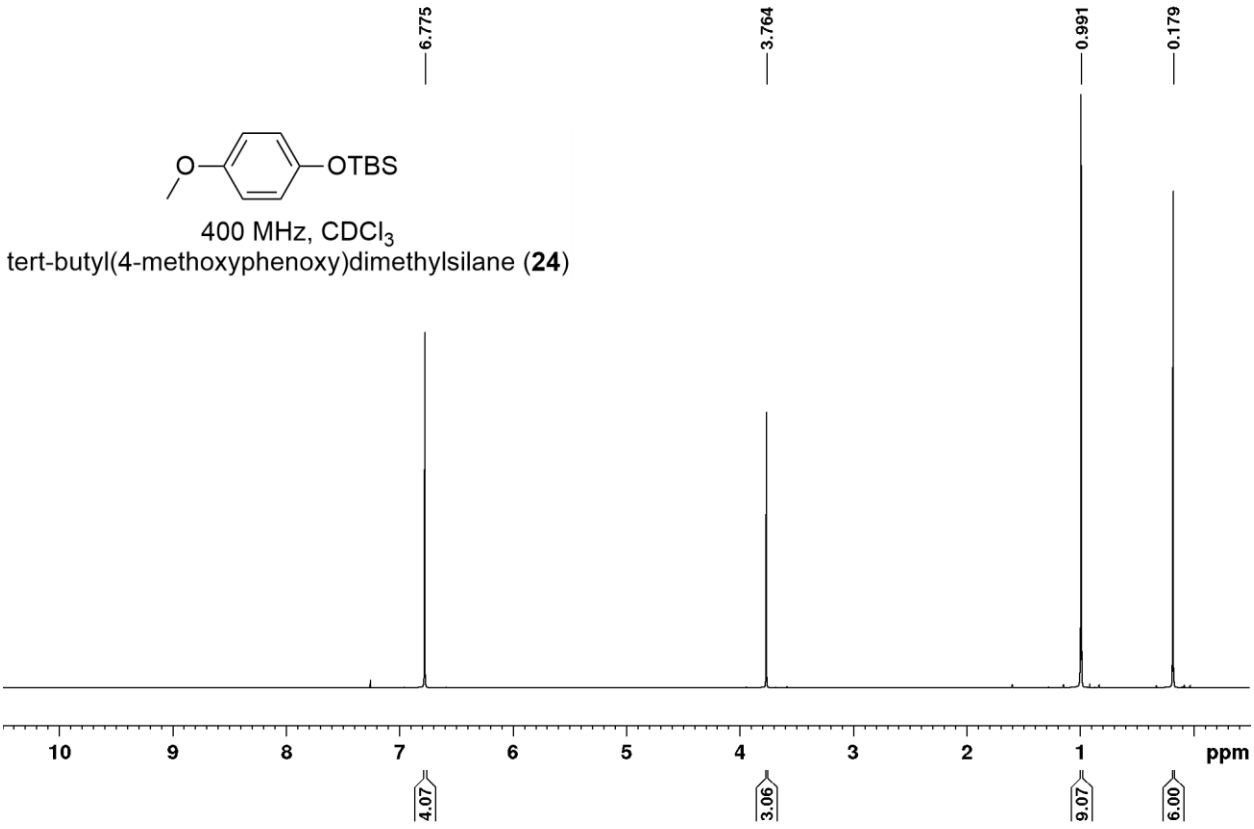

7.253
7.248
7.241
7.235
7.231
7.225
7.218
7.213
7.207
6.715
6.695
6.686
6.679
6.660
3.322
3.304
3.285
2.930
1.593
1.575
1.557
1.318
1.304
1.298
1.279
0.914
0.898
0.880
N
C9H19
400 MHz, CDCl3
N-decyl-N-methylaniline (20)
10
9
8
7
6
5
4
3
2
1
ppm
1.89
2.97
2.03
3.00
2.09
14.19
3.01
149.495
129.251
115.880
112.181
52.961
38.398
32.031
29.800
29.715
29.700
29.461
27.338
26.773
22.822
14.259
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

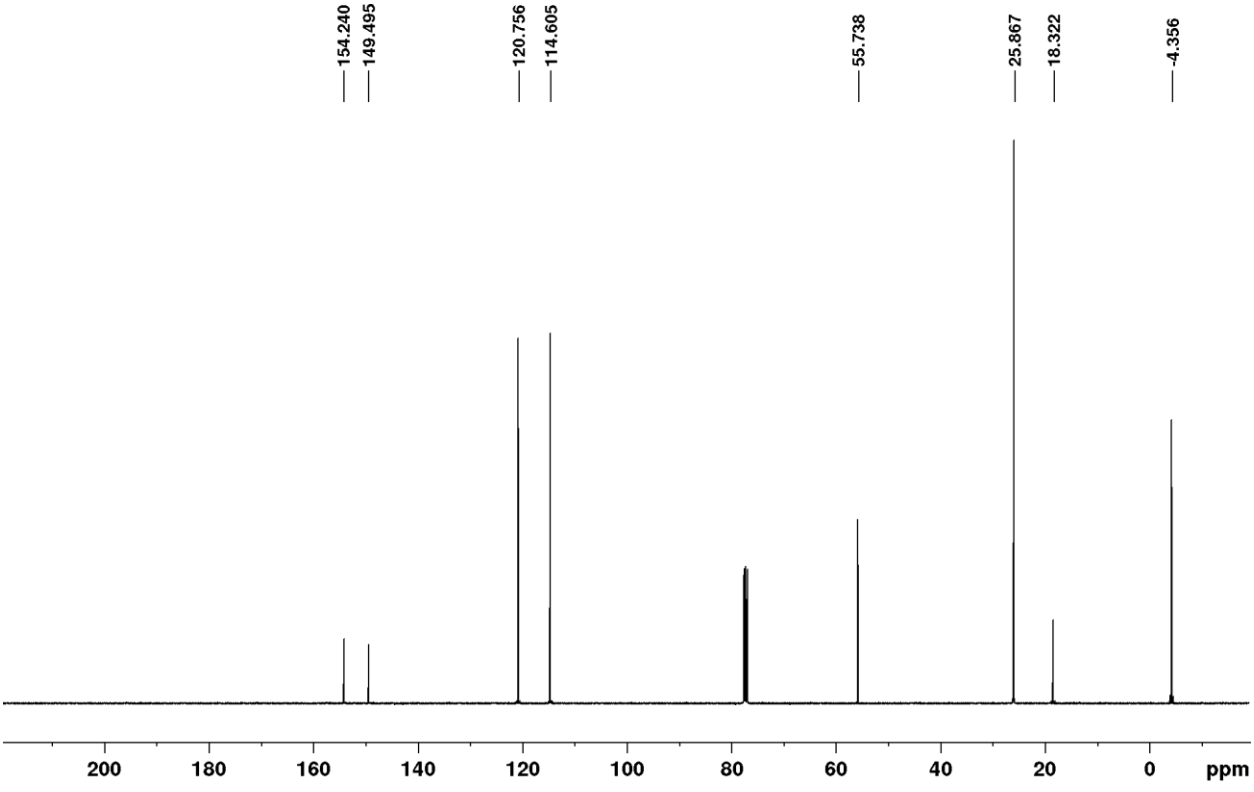

7.962
7.961
7.959
7.946
7.941
7.938
7.603
7.585
7.570
7.566
7.486
7.482
7.466
7.448
7.408
7.404
7.399
7.391
7.390
7.387
7.384
7.308
7.305
7.287
7.283
7.272
7.268
7.260
7.247
7.244
7.241
7.226
4.283
O
S
400 MHz, CDCl3
2-phenylthioacetophenone (21)
10 9 8 7 6 5 4 3 2 1 ppm
2.00
1.02
2.06
1.96
2.16
0.98
2.07
194.173
135.513
134.888
133.603
130.644
129.195
128.808
127.235
41.342
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

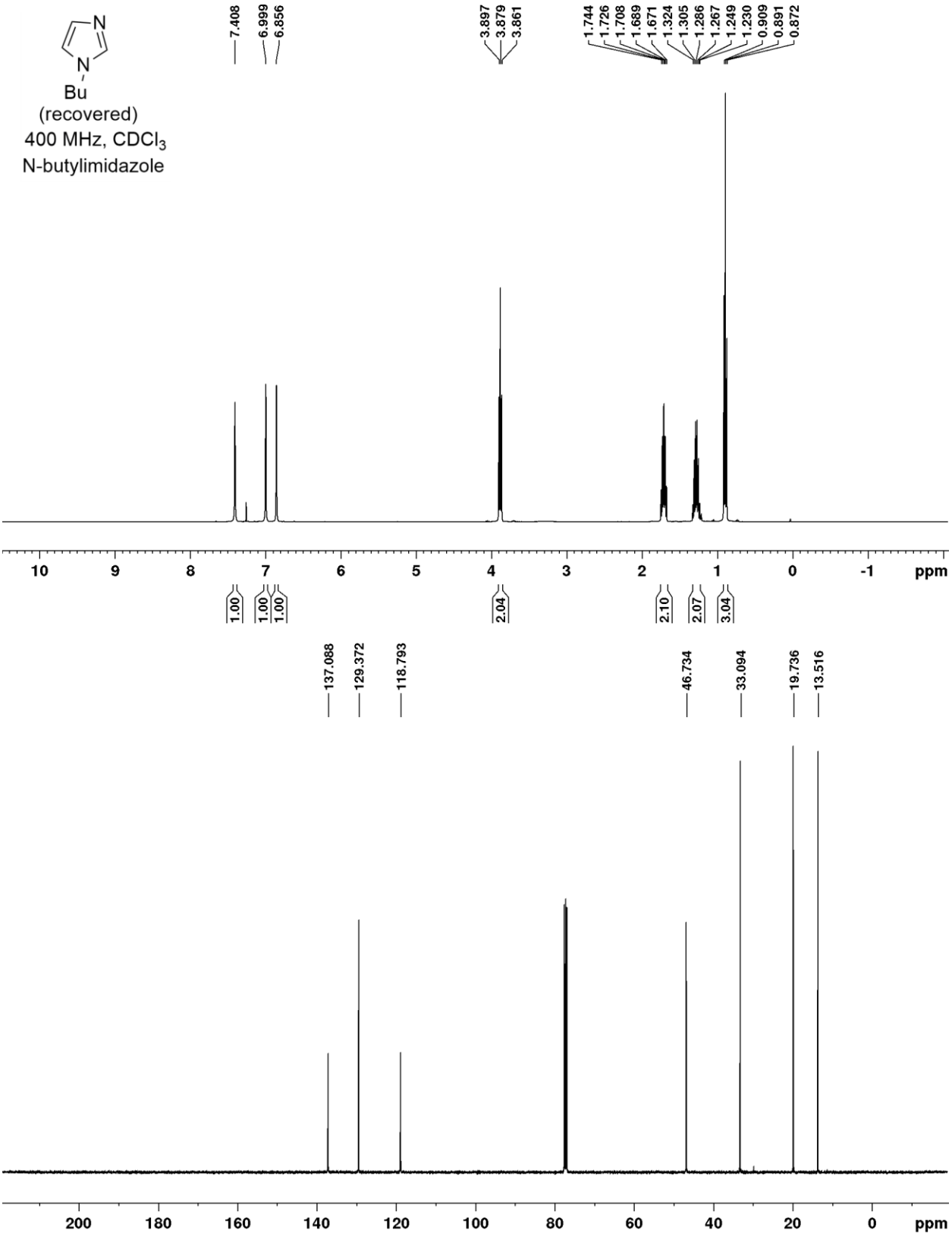

7.387
7.383
7.365
7.320
7.315
7.301
7.298
7.282
7.236
7.233
7.229
7.220
7.215
7.209
7.196
6.517
6.477
6.345
6.328
6.311
6.305
6.288
6.271
3.128
3.125
3.111
3.108
2.431
1.635
1.621
1.607
1.593
1.579
1.460
1.448
400 MHz, CDCl3
N-cinnamylpiperidine (22)
10
9
8
7
6
5
4
3
2
1
ppm
1.98
1.99
1.01
0.99
0.99
2.00
3.98
4.06
1.99
137.213
132.675
128.646
127.454
126.386
62.039
54.763
26.138
24.479
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

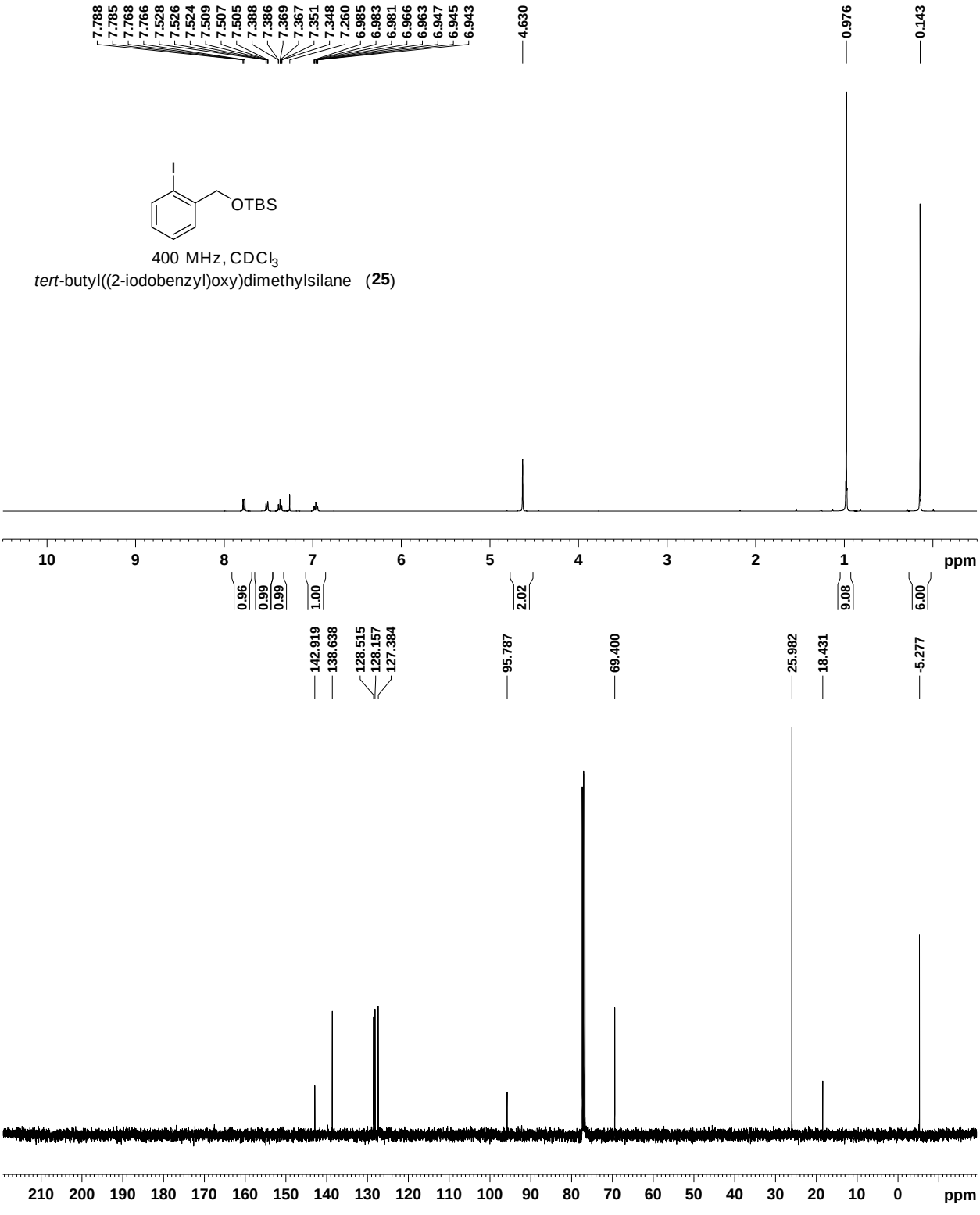

7.330
7.321
7.318
7.277
7.270
7.266
7.260
7.256
3.723
3.711
3.700
3.501
2.457
2.446
2.434
O
N
400 MHz, CDCl3
N-benzylmorpholine (23)
10
9
8
7
6
5
4
3
2
1
ppm
5.04
3.95
2.00
3.90


137.926
129.332
128.390
127.273
67.177
63.616
53.770
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


6.775
3.764
0.991
0.179
O
OTBS
400 MHz, CDCl3
tert-butyl(4-methoxyphenoxy)dimethylsilane (24)
10
9
8
7
6
5
4
3
2
1
ppm
4.07
3.06
9.07
6.00

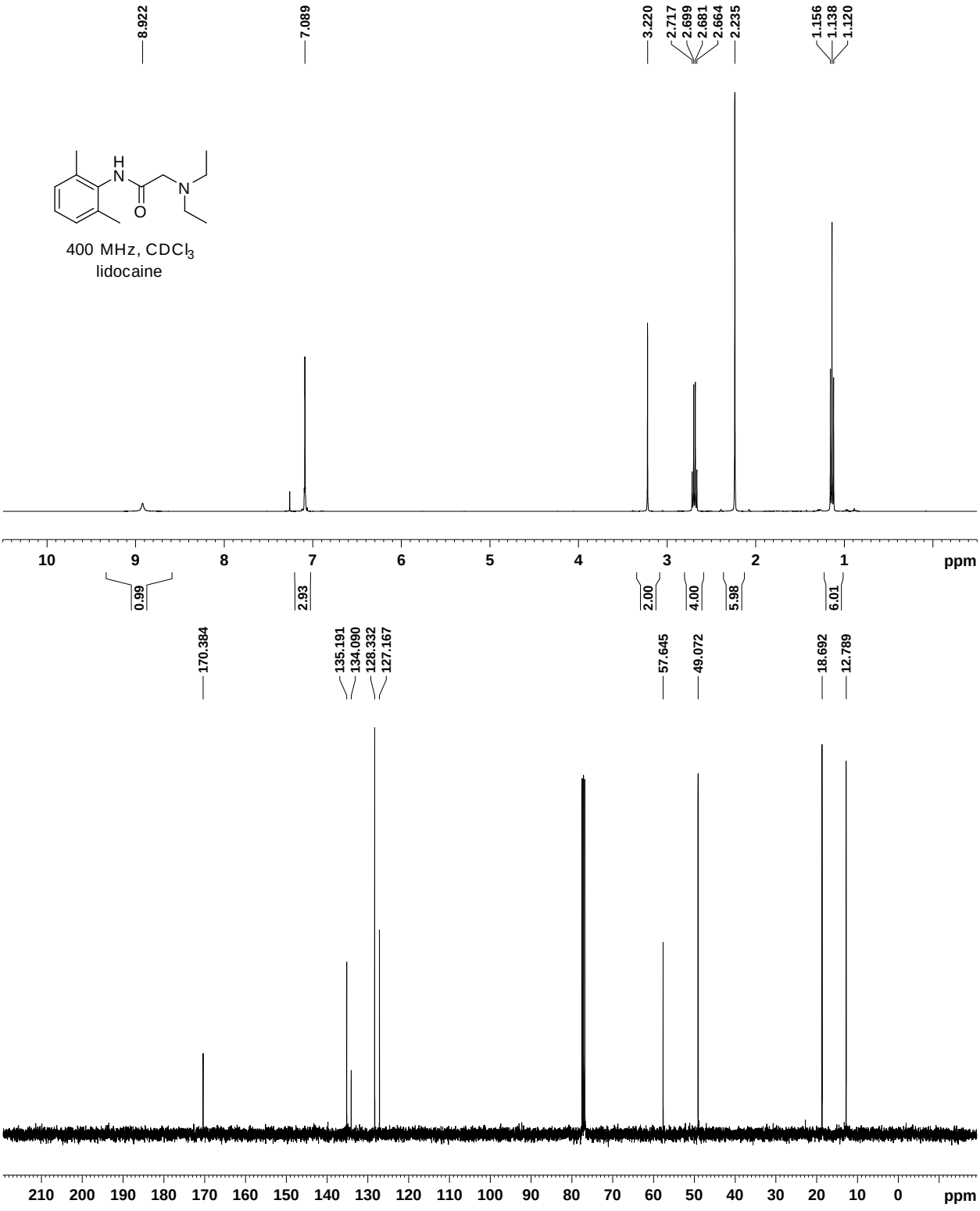

154.240
149.495
120.756
114.605
55.738
25.867
18.322
-4.356
200
180
160
140
120
100
80
60
40
20
0
ppm

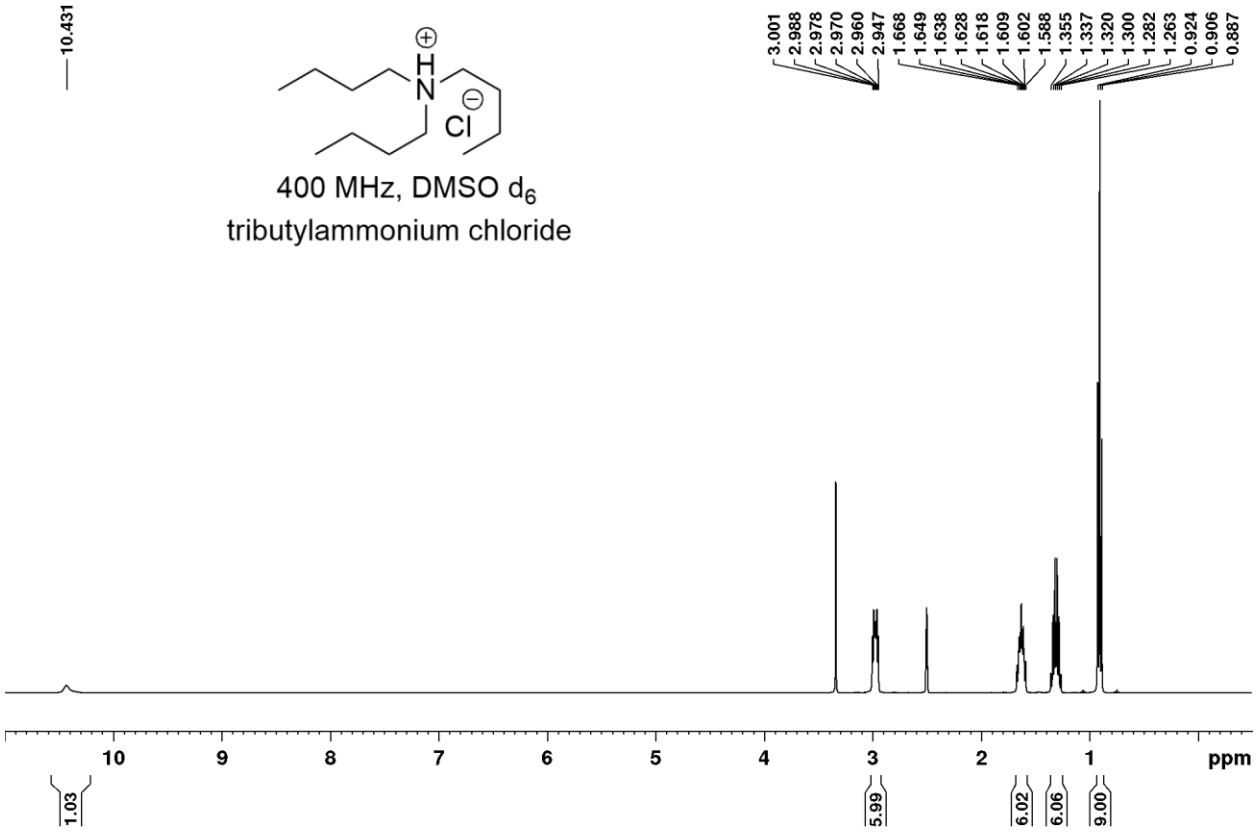

Bu
(recovered)
400 MHz, CDCl3
N-butylimidazole
7.408
6.999
6.856
3.897
3.879
3.861
1.744
1.726
1.708
1.689
1.671
1.324
1.305
1.286
1.267
1.249
1.230
0.909
0.891
0.872
ppm
1.00
1.00
1.00
2.04
2.10
2.07
3.04
137.088
129.372
118.793
46.734
33.094
19.736
13.516
ppm



400 MHz, $CDCl_3$

tert-butyl((2-iodobenzyl)oxy)dimethylsilane (**25**)


8.922
7.089
3.220
2.717
2.699
2.681
2.664
2.235
1.156
1.138
1.120
400 MHz, CDCl3
lidocaine
ppm
0.99
2.93
2.00
4.00
5.98
6.01
170.384
135.191
134.090
128.332
127.167
57.645
49.072
18.692
12.789
ppm


10.431
3.001
2.988
2.978
2.970
2.960
2.947
1.668
1.649
1.638
1.628
1.618
1.609
1.602
1.588
1.355
1.337
1.320
1.300
1.282
1.263
0.924
0.906
0.887
H
N
Cl
400 MHz, DMSO d6
tributylammonium chloride
10
9
8
7
6
5
4
3
2
1
ppm
1.03
5.99
6.02
6.06
9.00

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