Micro-flow heteroatom alkylation via TfOH-mediated rapid in situ generation of carbocations and subsequent nucleophile addition

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Note added after publication: This file replaces the supporting information originally published on 29th January 2024, as there was an error within the mass spectrometry data for compound 2s on page S19. This does not affect the results and conclusions of the paper.

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1. General techniques

NMR spectra were recorded on a JEOL-ECS400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) or JEOL-ECZ400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) instrument in the indicated solvent. Chemical shifts were reported in units of parts per million (ppm) relative to tetramethylsilane (0.000 ppm) in $CDCl_3$ for ^{1}H NMR and $CDCl_3$ (77.16 ppm) for ^{13}C NMR. Multiplicities were reported by using the following abbreviations: s; singlet, d; doublet, dd; double doublet, ddd; double double doublet, t; triplet, tt; triple triplet, q; quartet, sep; septet, m; multiplet, br; broad *J*; coupling constants in Hertz (Hz). IR spectra were recorded on a JASCO FT/IR-4100 Fourier Transform Infrared Spectrophotometer. Only the strongest and/or structurally important peaks were reported as the IR data are given in cm^{-1}. High-resolution mass spectra (HRMS) were obtained on a Bruker Daltonics Compact in the electrospray ionization–time of light (ESI-TOF) method. Gel permeation chromatography (GPC) for purification was performed on Japan Analytical Industry Model LaboACE LC-5060 (recycling preparative HPLC) on a Japan Analytical Industry Model UV-2564 LA ultraviolet detector and RI-700 LA refractive index detector with a polystyrene gel column (JAIGEL-2HR, 20 mm × 600 mm), using chloroform as a solvent (10 mL/min). Column chromatography was performed on Silica Gel PSQ 60B purchased from Fuji Silysia Chemical LTD. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light, visualized by *p*-anisaldehyde, ceric sulfate solution, 10% ethanolic phosphomolybdic acid. THF was dried by a Glass Contour Solvent dispensing system (Nikko Hansen & Co., Ltd.). CH_3CN was dried by molecular sieves 3A. Other solvents and reagents were purchased from commercial suppliers (FUJIFILM Wako Pure Chemical, Kanto Chemical, Sigma-Aldrich, and Tokyo Chemical Industry) and used without further purification.

2. Micro-flow reactor setup

Stainless steel T-shape (inner diameter: 0.250 mm, 0.500 mm, or 1.00 mm) and V-shape mixers (inner diameter: 0.250 mm) were purchased from Sanko Seiki Co. Ltd. The front and side view of the T-shape and V-shape mixer is shown in **Figure S-1**. Teflon® tubes (inner diameter: 0.800 or 0.500 mm were purchased from Senshu Scientific Co., Ltd. PEEK fittings, PEEK unions, stainless steel tubes, stainless steel fittings, and stainless steel unions (inner diameter: 0.800 mm) were purchased from GL Science Inc. Solutions were introduced to a micro-flow system with syringe pumps (Harvard PHD ULTRA) equipped gastight syringes (SGE 10 mL or 50 mL). The gastight syringes and the Teflon tubes were connected with joints purchased from Flon Industry Co., Ltd.

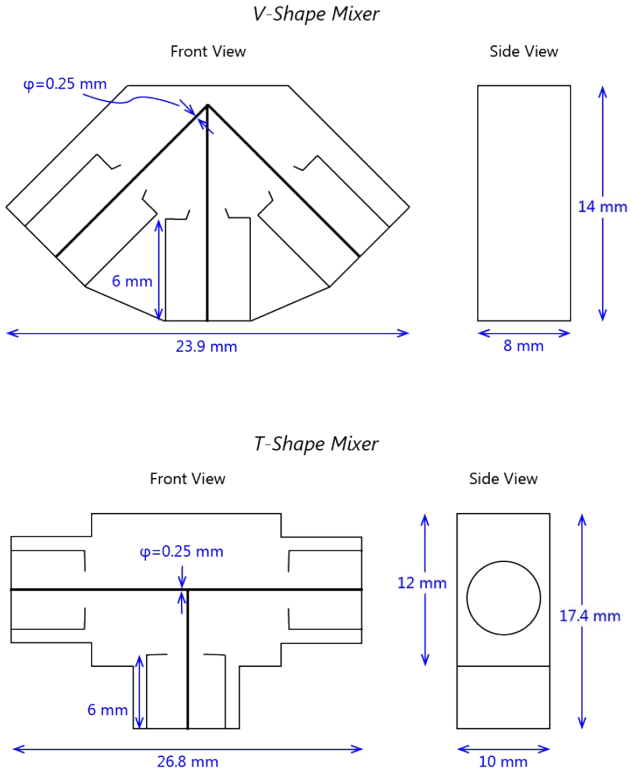


Figure S-1. T- and V-shape mixers used in this study.

The employed micro-flow system is shown in **Figure S-2**. The gastight syringes and the 1st and 2nd V-shape mixers were connected with the Teflon tubes and stainless-steel tubes (for controlling the temperature of solutions). The 1st and 2nd V-shape mixers were connected with reaction tube 1 (Teflon tube). The 2nd V-shape mixer was connected with the reaction tube 2 (Teflon tube). These mixers and reaction tubes were immersed in a water bath.

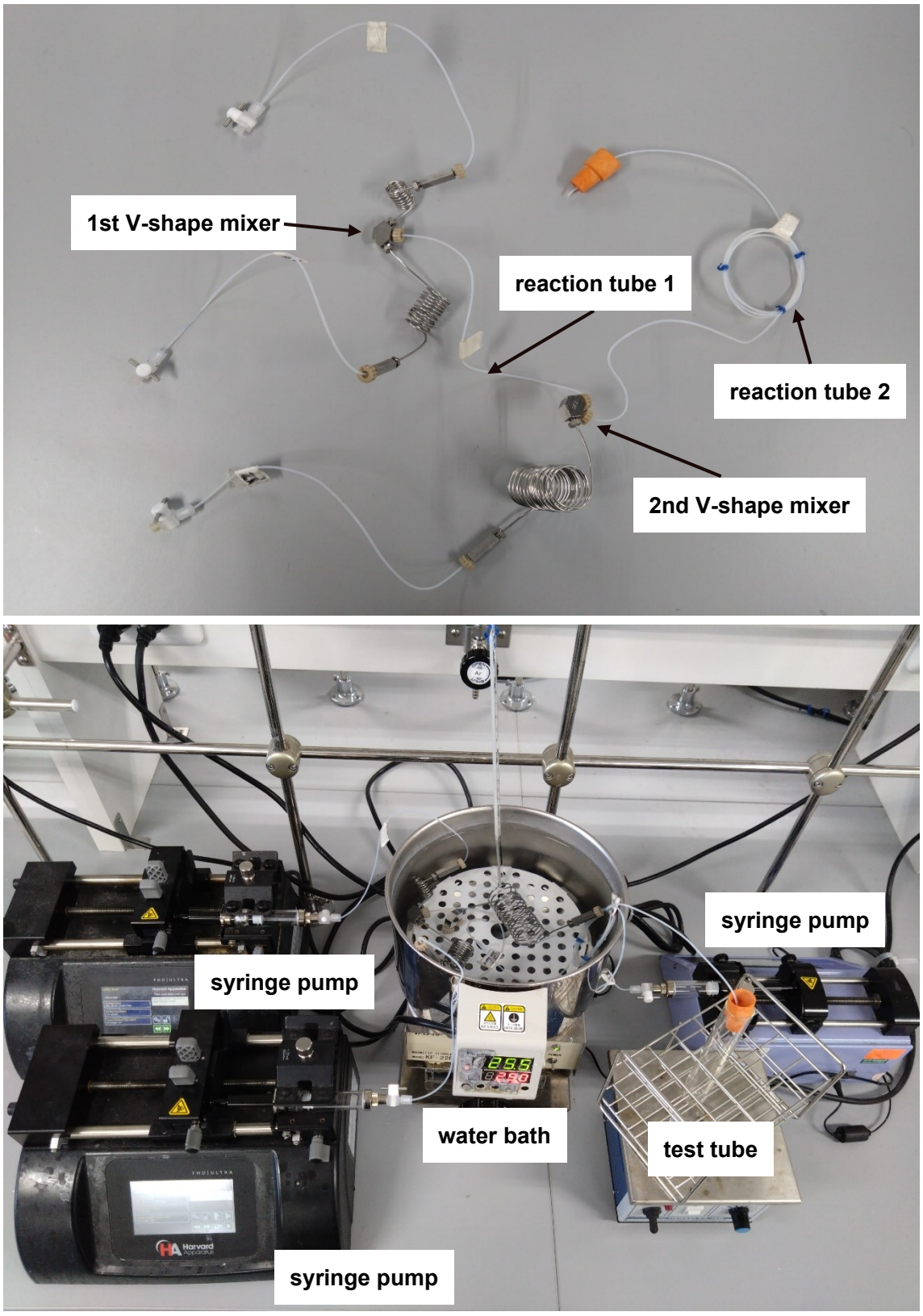
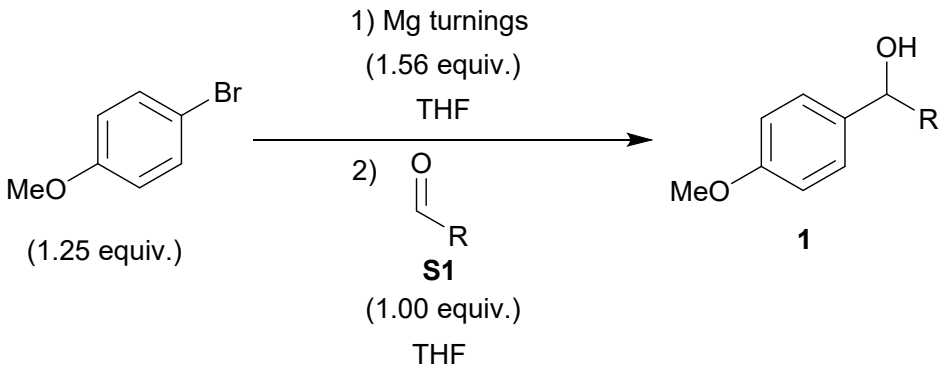


Figure S-2. Micro-flow reactor setup

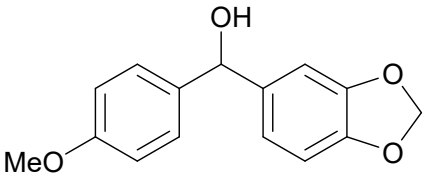
3. General procedure for the synthesis of alcohols[S1]



A suspension of Mg turnings (11.3 mmol, 1.56 equiv.) and several pieces of iodine in dry THF (32 mL) were stirred at room temperature for 10 min. To the resultant mixture, 4-bromoanisole (9.00 mmol, 1.25 equiv.) was added slowly at room temperature, and the resultant mixture was stirred at 40 ℃ for 1 h. After cooling to 0 ℃, aldehyde **S1** (7.20 mmol, 1.00 equiv.) was added slowly to the reaction mixture, and it was stirred at room temperature for 12 h. The reaction was quenched by addition of sat. NH_4Cl aq. and extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

***α*-(4-Methoxyphenyl)-1,3-benzodioxole-5-methanol (1b)**

According to the general procedure for the synthesis of alcohols using 3,4-methylenedioxybenzaldehyde **S1a** (1.08 g, 7.20 mmol, 1.00 equiv.), the crude product was purified by column chromatography on silica gel (hexane/EtOAc = 10:1 to 5:1) to give *α*-(4-methoxyphenyl)-1,3-benzodioxole-5-methanol (**1b**) (1.17 g, 4.53 mmol, 63%).

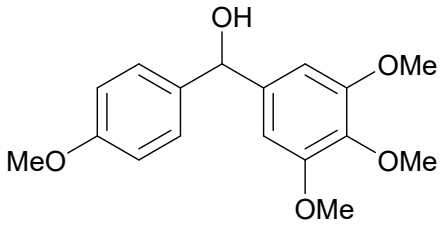


colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.27 (m, 2H), 6.89-6.83 (m, 4H), 6.76 (dd, J = 2.8, 8.8 Hz, 1H), 5.93 (s, 2H), 5.73 (d, J = 3.2 Hz, 1H), 3.79 (s, 3H), 2.08 (d, J = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 147.9, 147.0, 138.4, 136.3, 127.8, 120.0, 114.0, 108.2, 107.2, 101.1, 75.7, 55.4.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in previous literature[S2].

(4-Methoxyphenyl)(3,4,5-trimethoxyphenyl)methanol (1c)

According to the general procedure for the synthesis of alcohols using 3,4,5-trimethoxybenzaldehyde **S1b** (1.77 g, 7.20 mmol, 1.00 equiv.), the crude product was purified by recrystallization to give (4-methoxyphenyl)(3,4,5-trimethoxyphenyl)methanol (**1c**) (1.27 g, 5.10 mmol, 71%).



white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.28 (m, 2H), 6.89-6.87 (m, 2H), 6.60 (s, 2H), 5.73 (d, J = 3.6 Hz, 1H), 3.83 (s, 9H), 3.80 (s, 3H), 2.23 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 153.4, 139.8, 137.2, 136.0, 128.0, 114.0, 103.5, 76.0, 61.0, 56.2, 55.4.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in previous literature[S3].

4. Optimization of reaction conditions

4.1. Examination of Brønsted acids, bases, solvents, and reaction times in micro-flow nucleophilic substitution

A solution of 4,4'-dimethoxybenzhydrol (**1a**) (**C** M, 1.00 equiv.) in **solvent** (flow rate: 2.40 mL/min) and a solution of **Brønsted acid** (0.188 M, 1.50 equiv.) in CH_3CN (flow rate: 4.80 mL/min) were introduced to 1st V-shape mixer at **D** ℃ with syringe pumps. The resultant mixture was passed through reaction tube 1 **(**inner diameter: 0.500 mm (entries 1-14, 16-24), or 0.800 mm (entry 15), reaction time: **A** s) at **D** ℃. The resultant mixture and a solution of piperidine (0.0625 M, 1.00 equiv.) and **base** (0.0625 M, 1.00 equiv.) in **solvent** (flow rate: 9.60 mL/min) were introduced to the 2nd V-shape mixer at **D** ℃ with syringe pumps. The resultant mixture was passed through reaction tube 2 (inner diameter: 0.500 mm (entries 1-16, 18-24), or 0.800 mm (entry 17), reaction time: **B** s) at **D** ℃. After being eluted for *ca.* 25 s to reach a steady state, the resultant mixture was poured into a test tube containing sat. $NaHCO_3$ aq. (5 mL) and EtOAc (5 mL) for 30 s at room temperature. The reaction mixture was extracted with EtOAc (5 mL) twice. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Yields were determined by ^{1}H NMR analysis using dimethyl sulfone as an internal standard.

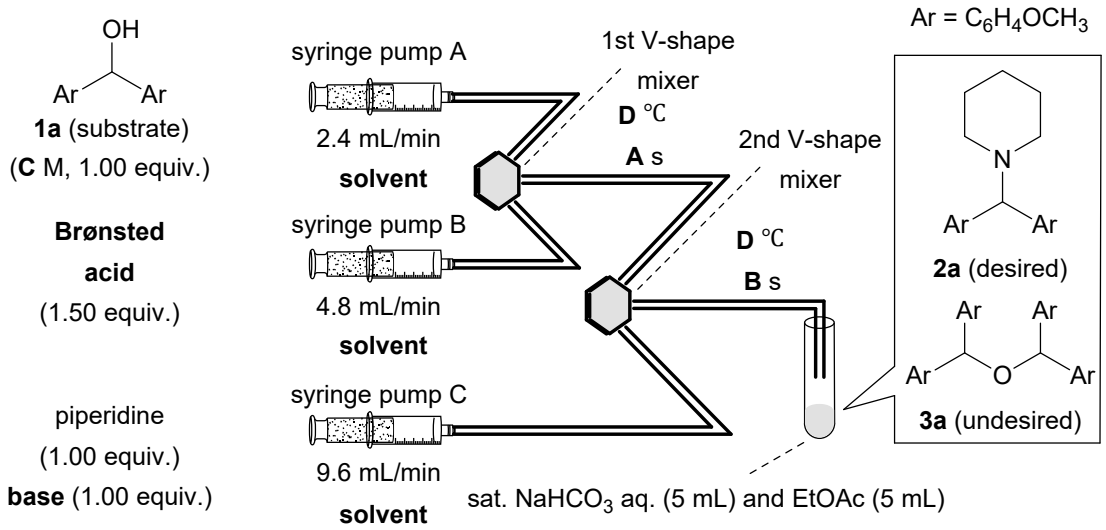


Table S-1

entry	**A** [s]	**B** [s]	**C** [M]	**D** [℃]	**Brønsted acid** (pK_a[a])	**base** (pK_aH[b])	**solvent**	yield [%][c]		
								2a	**1a**	**3a**
1	0.10	1.0	0.250	25	TFA (12.7) [S4]	DBU (24.3) [S7]	CH_3CN	<1	93	2

2	0.10	1.0	0.250	25	TCA (10.6) [S4]	DBU (24.3)	CH_3CN	4	92	2
3	0.10	1.0	0.250	25	HCl[f] (10.3) [S5]	DBU (24.3)	CH_3CN	44	48	2
4	0.10	1.0	0.250	25	H_2SO_4 (8.7) [S6]	DBU (24.3)	CH_3CN	5	32	56
5	0.10	1.0	0.250	25	HBr[g] (5.5) [S5]	DBU (24.3)	CH_3CN	70	22	2
6	0.10	1.0	0.250	25	HI[h] (2.8) [S5]	DBU (24.3)	CH_3CN	74	13	2
7[d]	0.10	1.0	0.250	25	TfOH (0.7) [S5]	DBU (24.3)	CH_3CN	85	7	4
8[d]	0.10	1.0	0.250	25	TfOH (0.7)	TMG (23.4) [S7]	CH_3CN	84	7	3
9[d]	0.10	1.0	0.250	25	TfOH (0.7)	*i*-Pr_2NEt (18.1) [S8]	CH_3CN	81	8	11
10[d]	0.10	1.0	0.250	25	TfOH (0.7)	NMe_3 (17.6) [S7]	CH_3CN	<1	21	19
11[d]	0.10	1.0	0.250	25	TfOH (0.7)	DBU (24.3)	CH_3CN	85	7	4
12[d, e]	0.50	1.0	0.250	25	TfOH (0.7)	DBU (24.3)	CH_3CN	91 ±1	6	3± 1
13[d]	1.0	1.0	0.250	25	TfOH (0.7)	DBU (24.3)	CH_3CN	84	6	3
14[d]	5.0	1.0	0.250	25	TfOH (0.7)	DBU (24.3)	CH_3CN	81	5	1
15[d]	10	1.0	0.250	25	TfOH (0.7)	DBU (24.3)	CH_3CN	77	5	1
16[d]	0.50	5.0	0.250	25	TfOH (0.7)	DBU (24.3)	CH_3CN	90	6	4
17[d]	0.50	10	0.250	25	TfOH (0.7)	DBU (24.3)	CH_3CN	91	7	4
18[d]	0.5	1.0	0.125	25	TfOH (0.7)	DBU (24.3)	CH_3CN	88	8	4
19[d]	0.5	1.0	0.500	25	TfOH (0.7)	DBU (24.3)	CH_3CN	77	11	9
20[d]	0.5	1.0	0.250	0	TfOH (0.7)	DBU (24.3)	CH_3CN	80	5	6
21[d]	0.5	1.0	0.250	40	TfOH (0.7)	DBU (24.3)	CH_3CN	81	8	2
22[d]	0.5	1.0	0.250	25	TfOH (0.7)	DBU (24.3)	acetone	9	10	73

23[d]	0.5	1.0	0.250	25	TfOH (0.7)	DBU (24.3)	CH_2Cl_2	28	14	55
24[d]	0.5	1.0	0.250	25	TfOH (0.7)	DBU (24.3)	THF[n]	2	4	84

[a]The pK_a in CH_3CN. [b]The pK_a of conjugated acids in CH_3CN. [c]Yields were determined by ^{1}H NMR analysis using dimethyl sulfone as an internal standard. [d]A trace amounts of 4,4′-dimethoxybenzophenone (**6a**) and 4,4'-dimethoxydiphenylmethane (**7a**) were generated. [e] Three independent experiments were performed. [f]Aqueous solution of HCl (36 w/w%) was used. [g]Aqueous solution of HBr (47 w/w%) was used. [h]Aqueous solution of HI (57 w/w%) was used. TFA = Trifluoroacetic acid. TCA = Trichloroacetic acid. TfOH = trifluoromethanesulfonic acid. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. TMG = 1,1,3,3-Tetramethylguanidine. THF = Tetrahydrofuran.

4.2. Examination of 1st mixer and 2nd mixer for micro-flow nucleophilic substitution

A solution of 4,4'-dimethoxybenzhydrol (**1a**) (0.250 M, 1.00 equiv.) in CH_3CN (flow rate: 2.40 mL/min) and a solution of TfOH (0.188 M, 1.50 equiv.) in CH_3CN (flow rate: 4.80 mL/min) were introduced to **1st mixer** at 25 ℃ with syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.500 mm, length: 306 mm, volume: 60 μL, reaction time: 0.50 s) at 25 ℃. The resultant mixture and a solution of piperidine (0.0625 M, 1.00 equiv.) and DBU (0.0625 M, 1.00 equiv.) in CH_3CN (flow rate: 9.60 mL/min) were introduced to the **2nd mixer** at 25 ℃ with syringe pumps. The resultant mixture was passed through reaction tube 2 (inner diameter: 0.500 mm, length: 1,427 mm, volume: 280 μL, reaction time: 1.0 s) at 25 ℃. After being eluted for *ca.* 25 s to reach a steady state, the resultant mixture was poured into a test tube containing sat. $NaHCO_3$ aq. (5 mL) and EtOAc (5 mL) for 30 s at room temperature. The reaction mixture was extracted with EtOAc (5 mL) twice. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Yields were determined by ^{1}H NMR analysis using dimethyl sulfone as an internal standard.

According to a report, the mixing efficiency of the mixer in the microflow synthesis is superior with a V-shape compared to a T-shape [S9], and a smaller inner diameter is also preferable [S10]. Our examination of the shape of a mixer and the inner diameter revealed that as the mixing efficiency decreased, the yield of the target product 2a also decreased (entries 1-5).

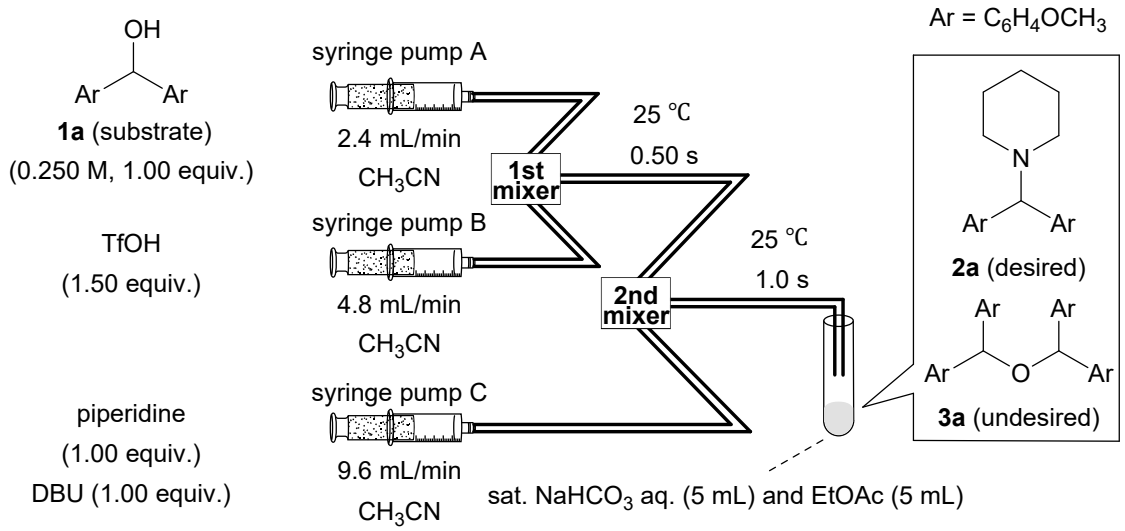


Table S-2

entry	1st mixer	inner diameter (mm)	2nd mixer	inner diameter (mm)	NMR yield [%] 2a (desired)	1a (sub)	3a (undesired)
1	V shape	0.25	V shape	0.25	91	6	3
2	V shape	0.25	T shape	0.25	81	9	4
3	V shape	0.25	T shape	0.50	76	19	5
4	V shape	0.25	T shape	1.0	61	25	13
5	T shape	1.0	V shape	0.25	83	6	3

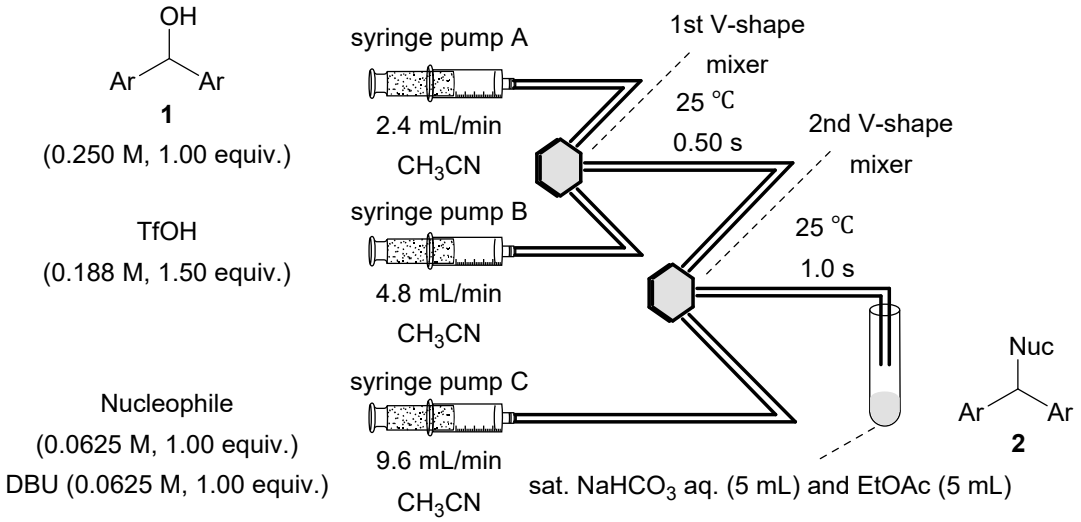
4.3. Procedure for synthesis of 2a using a batch reactor

(Quantities of compounds, solvents, and temperature were identical to those of flow condition.)

To a vigorously stirred (magnetic stirrer, 1,000 rpm.) solution of 4,4'-dimethoxybenzhydrol (**1a**) (0.250 M, 1.00 equiv.) in CH_3CN (1.20 mL), a solution of TfOH (0.188 M, 1.50 equiv.) in CH_3CN (2.40 mL) was added to the reaction mixture in one portion at 25 ℃ under an argon atmosphere. After being stirred for 10 s at 25 ℃, the resultant mixture was added to the reaction mixture in one portion at 25 ℃ to a vigorously stirred (magnetic stirrer, 1,000 rpm.) solution of piperidine (0.0625 M, 1.00 equiv.) and DBU (0.0625 M, 1.00 equiv.) in CH_3CN (4.80 mL). After being stirred for 10 s at 25 ℃, sat. $NaHCO_3$ aq. (5 mL) and EtOAc (5 mL) was added to the reaction mixture in one portion at 25 ℃ (Under the flow condition, activation and nucleophilic substitution were carried out at 0.50 s and 1.0 s respectively. However, under batch conditions, it was impossible to operate the reaction within 10 s. Thus, the reaction time was extended to 10 s.). The reaction mixture was extracted with EtOAc (5 mL) twice. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Yields were determined

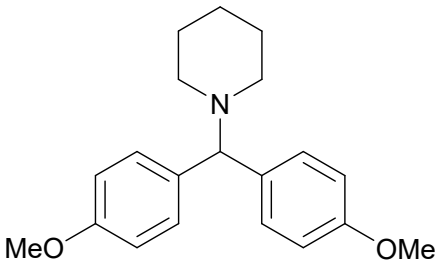
by ^{1}H NMR analysis using dimethyl sulfone as an internal standard. Three independent experiments were performed.

5. Typical procedure for a micro-flow nucleophilic substitution



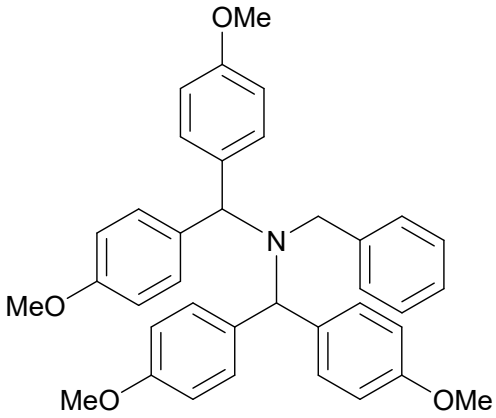
A solution of **alcohol 1** (0.250 M, 1.00 equiv.) in CH_3CN (flow rate: 2.40 mL/min) and a solution of TfOH (0.188 M, 1.50 equiv.) in CH_3CN (flow rate: 4.80 mL/min) were introduced to 1st V-shape mixer at 25 ℃ with syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.500 mm, length: 306 mm, volume: 60 μL, reaction time: 0.50 s) at 25 ℃. The resultant mixture and a solution of **nucleophile** (0.0625 M, 1.00 equiv.) and DBU (0.0625 M, 1.00 equiv.) in CH_3CN (flow rate: 9.60 mL/min) were introduced to the 2nd V-shape mixer at 25 ℃ with syringe pumps. The resultant mixture was passed through reaction tube 2 (inner diameter: 0.500 mm, length: 1,427 mm, volume: 280 μL, reaction time: 1.0 s) at 25 ℃. After being eluted for *ca.* 25 s to reach a steady state, the resultant mixture was poured into a test tube containing sat. $NaHCO_3$ aq. (5 mL) and EtOAc (5 mL) for 30 s at room temperature. The reaction mixture was extracted with EtOAc (5 mL) twice. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

1-(Bis(4-methoxyphenyl)methyl)piperidine (2a)



Purification method: PTLC (1%NEt_3 in EtOAc: hexane = 1: 2) / column chromatography on silica gel (hexane: EtOAc = 10:1 to 5:1) (scaled-up synthesis)
78.6 mg, 0.252 mmol, 84%
1.11 g, 3.54 mmol, 70% (scaled-up synthesis, the resultant mixture was collected for 255 s)
yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 4H), 6.82-6.79 (m, 4H), 4.14 (s, 1H), 3.75 (s, 6H), 2.29 (brs, 4H), 1.55 (tt, *J* = 5.2, 5.2 Hz, 4H), 1.44-1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 135.8, 129.0, 113.8, 75.3, 55.3, 53.2, 26.4, 24.9.
Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in previous literature[S9].

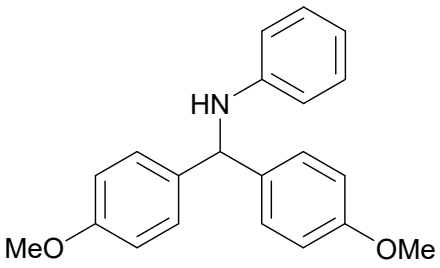
***N*-Benzyl-*N*-(bis(4-methoxyphenyl)methyl)-1,1-bis(4-methoxyphenyl)methanamine (2b)**



Purification method: PTLC (5%NEt_3 in EtOAc: hexane = 1: 4)
78.3 mg, 0.140 mmol, 93%
colorless oil; IR (neat): 2835, 1608, 1508, 1459, 1300, 1246, 1173, 1034, 824, 734, 567 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.19 (m, 8H), 6.95-6.93 (m, 3H), 6.83-6.81 (m, 2H), 6.76-6.73 (m, 8H), 4.96 (s, 2H), 3.83 (s, 2H), 3.76 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 142.9,

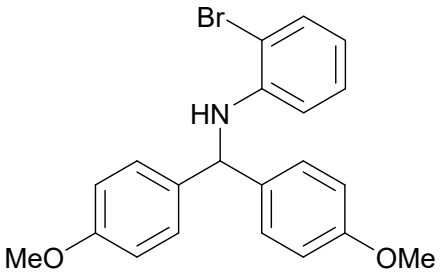
134.1, 130.5, 127.7, 127.3, 125.3, 113.4, 69.0, 55.3, 52.8; HRMS (ESI-TOF): calcd. for $C_{37}H_{37}NO_4$ ([M+Na]$^+$): 582.2615, found 582.2615.

***N*-(Bis(4-methoxyphenyl)methyl)aniline (2c)**



Purification method: PTLC (EtOAc: hexane = 1: 4, twice)
69.2 mg, 0.217 mmol, 72%
colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.23 (m, 4H), 7.13-7.09 (m, 2H), 6.87-6.83 (m, 4H), 6.68 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.54-6.52 (m, 2H), 5.41 (s, 1H), 4.15 (brs, 1H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 147.6, 135.5, 129.2, 128.6, 117.6, 114.1, 113.6, 61.8, 55.4. Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in previous literature[S9].

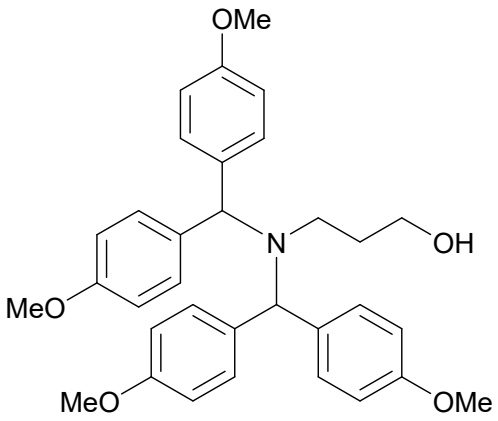
***N*-(Bis(4-methoxyphenyl)methyl)-2-bromo-aniline (2d)**



Purification method: PTLC (EtOAc: hexane = 1: 4, twice)
81.6 mg, 0.205 mmol, 68%
yellow oil; IR (neat): 3410, 2828, 1591, 1458, 1300, 1173, 1033, 818, 743, 574 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.25-7.21 (m, 4H), 7.03-6.99 (m, 1H), 6.87-6.83 (m, 4H), 6.53 (ddd, *J* = 1.2, 8.0, 8.0 Hz, 1H), 6.45 (dd, *J* = 1.2, 8.4 Hz, 1H), 5.46 (d, *J* = 4.4 Hz, 1H), 4.84 (d, *J* = 4.4 Hz, 1H), 3.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 144.2, 134.8, 132.3, 128.5, 128.4, 118.1, 114.2, 112.9, 109.9, 61.6, 55.4; HRMS (ESI-TOF): calcd. for

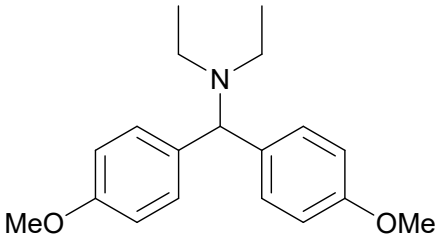
$C_{21}H_{20}NO_2Br$ ([M+Na]$^+$): 420.0570, found 420.0568.

3-(Bis(bis)(4-mehoxyphenyl)methyl)amino)propan-1-ol (2e)



Purification method: PTLC (5%NEt_3 in EtOAc: hexane = 1: 4)
32.1 mg, 0.0608mmol, 41%
colorless oil; IR (neat): 2952, 1608, 1508, 1460, 1300, 1245, 1173, 1033, 822, 569 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 8H), 6.85-6.82 (m, 8H), 4.95 (s, 2H), 3.78 (s, 12H), 3.10 (brs, 2H), 2.82-2.78 (m, 2H), 0.99-0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 134.8, 130.1, 113.7, 68.2, 61.6, 55.3, 45.1, 32.5; HRMS (ESI-TOF): calcd. for $C_{33}H_{37}NO_5$ ([M+Na]$^+$): 550.2564, found 550.2564.

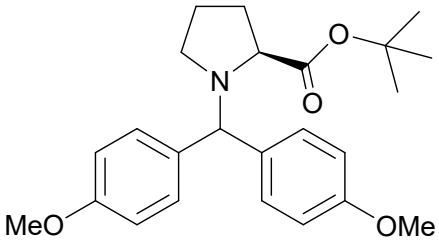
1-(Bis(4-methoxyphenyl)methyl)diethylamine (2g)



Purification method: PTLC (5%NEt_3 in EtOAc: hexane = 1: 1)
73.5 mg, 0.245 mmol, 82%
colorless oil; IR (neat): 2967, 1608, 1508, 1457, 1244, 1173, 1036, 819 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.29 (m, 4H), 6.81-6.79 (m, 4H), 4.62 (s, 1H), 3.76 (s, 6H), 2.53 (q, J = 6.8 Hz, 4H), 0.96 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 136.0, 129.1, 113.7, 69.8,

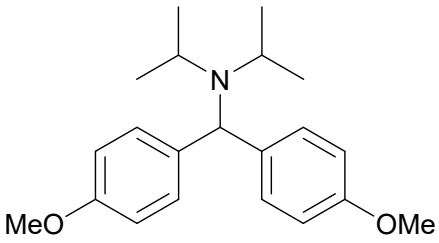
55.3, 42.9, 11.3; HRMS (ESI-TOF): calcd. for $C_{19}H_{25}NO_2$ ([M+Na]$^+$): 322.1777, found 322.1777.

***tert*-Butyl (bis(4-methoxyphenyl)methyl)prolinate (2h)**



Purification method: PTLC (5%NEt_3 in EtOAc: hexane = 1: 4)
81.9 mg, 0.206 mmol, 69% (2.00 eq. of DBU was used.)
yellow oil; IR (neat): 2972, 1723, 1608, 1509, 1245, 1146, 1035, 821 cm^{-1}; $[\alpha]^{23}_D$ = -41.4 (c 0.79, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.80-6.79 (m, 2H), 6.78-6.77 (m, 2H), 4.81 (s, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.38-3.36 (m, 1H), 2.95-2.90 (m, 1H), 2.66-2.60 (m, 1H), 2.12-2.06 (m, 1H), 1.93-1.79 (m, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 158.5, 158.4, 136.6, 135.8, 129.1, 128.8, 113.73, 113.72, 80.0, 70.3, 63.3, 55.3, 51.4, 30.2, 28.1, 23.5; HRMS (ESI-TOF): calcd. for $C_{24}H_{31}NO_4$ ([M+Na]$^+$): 420.2145, found 420.2145.

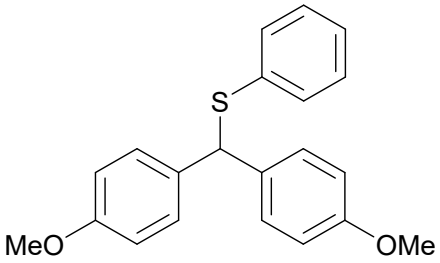
***N*-(Bis(4-methoxyphenyl)methyl)butan-2-amine (2i)**



Purification method: PTLC (5%NEt_3 in EtOAc: hexane = 1: 4)
53.9 mg, 0.165 mmol, 55%
yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.22 (m, 4H), 6.80-6.78 (m, 4H), 5.16 (s, 1H), 3.78 (s, 6H), 3.27 (sep, *J* = 6.4 Hz, 2H), 0.98 (d, *J* = 6.4 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 137.9, 130.2, 113.2, 62.4, 55.3, 46.4, 22.7.
Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in previous

literature[S9].

(Bis(4-methoxyphenyl)methyl)(phenyl)sulfane (2j)



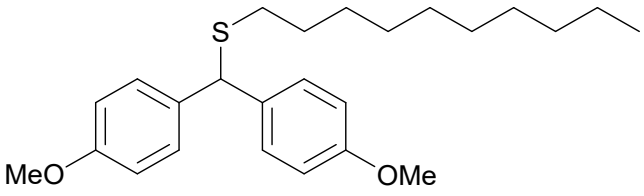
Purification method: PTLC (EtOAc: hexane = 1: 2)

87.4 mg, 0.260 mmol, 87%

white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.30 (m, 4H), 7.23-7.12 (m, 5H), 6.84-6.81 (m, 4H), 5.49 (s, 1H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 136.6, 133.4, 130.3, 129.5, 128.8, 126.4, 114.0, 56.1, 55.3.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in previous literature[S9].

(Bis(4-methoxyphenyl)methyl)decanthiolate (2k)

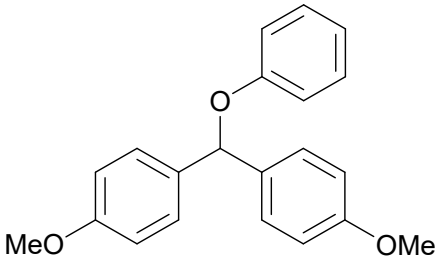


Purification method: PTLC (EtOAc: hexane = 1: 2)

75.1 mg, 0.187 mmol, 62%

yellow oil; IR (neat): 2925, 2853, 1608, 1508,1457, 1248, 1173,1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.30 (m, 4H), 6.85-6.81 (m, 4H), 5.07 (s, 1H), 3.78 (s, 6H), 2.35 (t, J = 7.2 Hz, 2H), 1.53 (tt, J = 7.2, 7.2 Hz, 2H), 1.33-1.23 (m, 14H), 0.88 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 134.1, 129.4, 113.9, 55.3, 52.9, 32.4, 32.0, 29.7, 29.6, 29.4, 29.3, 29.2, 29.0, 22.8, 14.3; HRMS (ESI-TOF): calcd. for $C_{25}H_{36}O_2S$ ($[M+Na]^+$): 423.2328, found 423.2326.

(Bis(4-methoxyphenyl)methyl)phenol (2l)

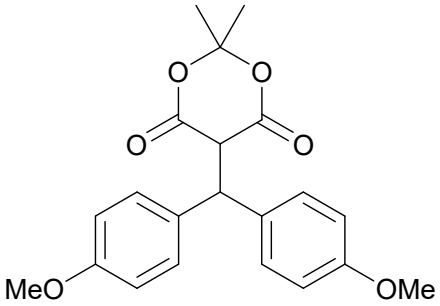


Purification method: PTLC (EtOAc: hexane = 1: 4, twice)

40.6 mg, 0.127 mmol, 42% (2.00 eq. of DBU was used.)

yellow oil; IR (neat): 1608, 1300, 1173, 1032, 816, 753, 690, 573 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.29 (m, 4H), 7.22-7.18 (m, 2H), 6.94-6.85 (m, 7H), 6.14 (s, 1H), 3.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 158.3, 133.8, 129.4, 128.3, 121.0, 116.3, 114.1, 81.0, 55.4; HRMS (ESI-TOF): calcd. for $C_{21}H_{20}O_3$ ($[M+Na]^+$): 343.1305, found 343.1305.

5-(Bis(4-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2n)



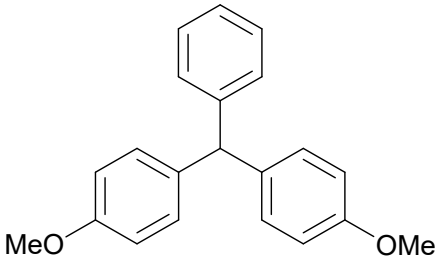
Purification method: GPC

53.4 mg, 0.144 mmol, 48% (2.00 eq. of DBU was used . The resultant mixture was poured into a test tube containing 1M HCl aq. (5 mL) and EtOAc (5 mL) instead of sat. $NaHCO_3$ aq. (5 mL) and EtOAc (5 mL).)

yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.21 (m, 4H), 6.85-6.81 (m, 4H), 5.28 (d, J = 2.8 Hz, 1H), 4.25 (d, J = 2.8 Hz, 1H), 3.78 (s, 6H), 1.73 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 158.6, 132.5, 130.4, 113.8, 105.2, 55.3, 51.5, 48.0, 28.4, 27.8.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in previous literature[S10].

4,4'-(Phenylmethylene)bis(methoxybenzene) (2o)



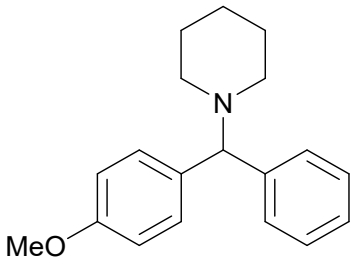
Purification method: PTLC (EtOAc: hexane = 1: 4)

70.2 mg, 0.231 mmol, 77%

white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H, f), 7.18 (t, *J* = 7.2 Hz, 1H), 7.11-7.09 (m, 2H), 7.02-6.99 (m, 4H), 6.83-6.80 (m, 4H), 5.44 (s, 1H), 3.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 144.7, 136.6, 130.4, 129.4, 128.4, 126.3, 113.8, 55.34, 55.30.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in previous literature[S11].

1-Phenyl-(4-methoxyphenyl)-methyl-piperidine (2r)



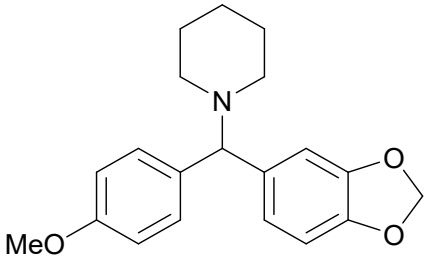
Purification method: PTLC (5%NEt_3 in EtOAc: hexane = 1: 4)

22.6 mg, 0.0803 mmol, 27%

white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (m, 2H), 7.30-7.23 (m, 4H), 7.17-7.13 (m, 1H), 6.81-6.79 (m, 2H), 4.18 (s, 1H), 3.75 (s, 3H), 2.30 (brs, 4H), 1.55 (tt, *J* = 5.6, 5.6 Hz, 4H), 1.44-1.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 143.8, 135.5, 129.2, 128.4, 128.0, 126.7, 113.8, 76.1, 55.3, 53.2, 26.4, 24.9.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in previous literature[S12].

1-((3,4-Methylenedioxyphenyl)-(4-methoxyphenyl)methylene)piperidine (2s)

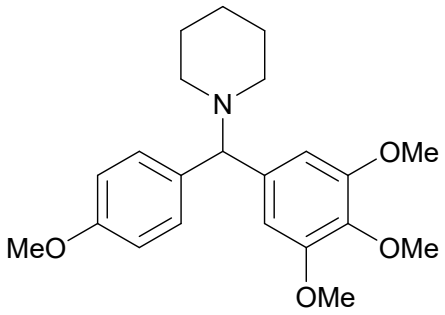


Purification method: PTLC (5%NEt_3 in EtOAc: hexane = 1: 4)

81.9 mg, 0.252 mmol, 84%

colorless oil; IR (neat): 2930, 2361, 1506, 1483, 1440, 1244, 1038, 934 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.25 (m, 2H), 6.93 (d, *J* = 1.2 Hz, 1H), 6.82-6.79 (m, 3H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.89-5.87 (m, 2H), 4.08 (s, 1H), 3.75 (s, 3H), 2.28 (brs, 4H), 1.54 (tt, *J* = 6.0, 6.0 Hz, 4H), 1.44-1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 147.8, 146.2, 138.0, 135.6, 128.9, 121.0, 113.8, 108.1, 108.0, 100.9, 75.7, 55.3, 53.2, 26.4, 24.9; HRMS (ESI-TOF): calcd. for $C_{20}H_{23}NO_3$ ($[M+Na]^+$): 348.1570, found 348.1570.

1-((4-Methoxyphenyl)(3,4,5-trimethoxyphenyl)methyl)piperidine (2t)



Purification method: PTLC (5%NEt_3 in EtOAc: hexane = 1: 4)

81.9 mg, 0.219 mmol, 73%

colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30-7.29 (m, 2H, c), 6.83-6.81 (m, 2H), 6.65 (s, 2H), 4.08 (s, 1H), 3.83 (s, 6H), 3.79 (s, 3H), 3.76 (s, 3H), 2.30-2.29 (m, 4H), 1.55 (tt, *J* = 6.0, 6.0 Hz, 4H), 1.44-1.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 153.1, 139.6, 136.5, 135.1, 129.1, 113.7, 104.6, 76.2, 60.9, 56.2, 55.3, 53.2, 26.4, 24.8.

Spectral data of ^1H NMR and ^{13}C NMR were well consistent with those reported in previous literature[S3].

6. References

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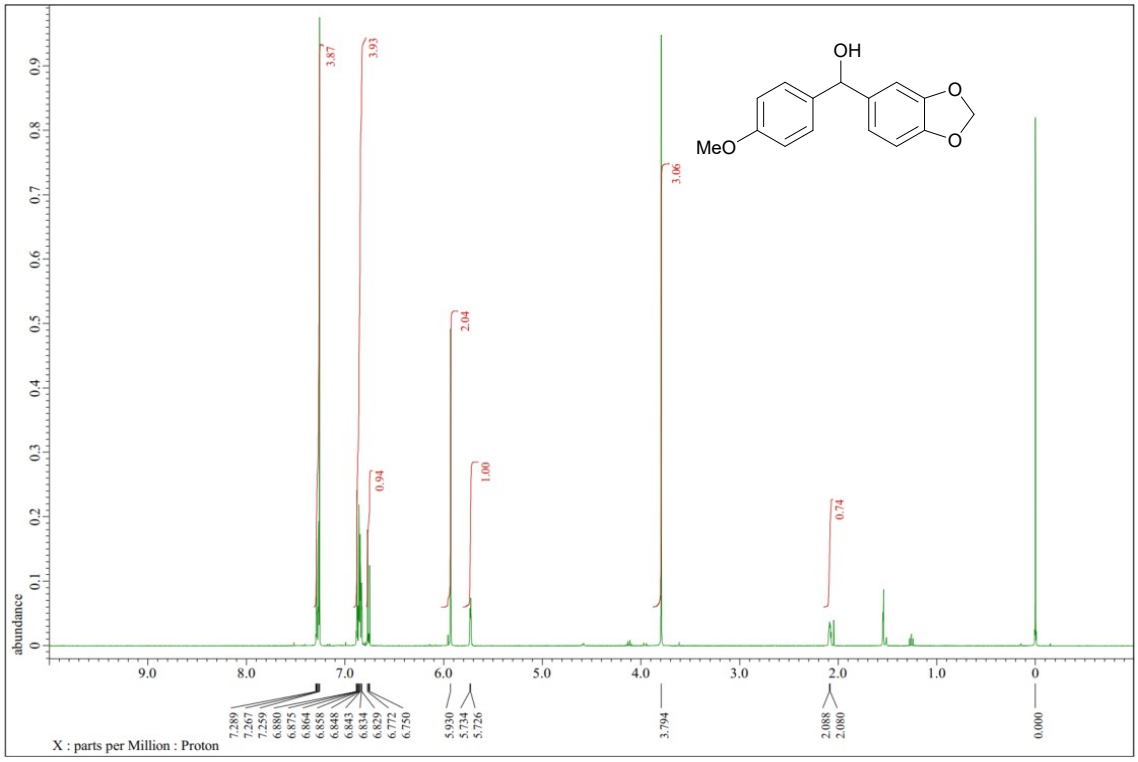
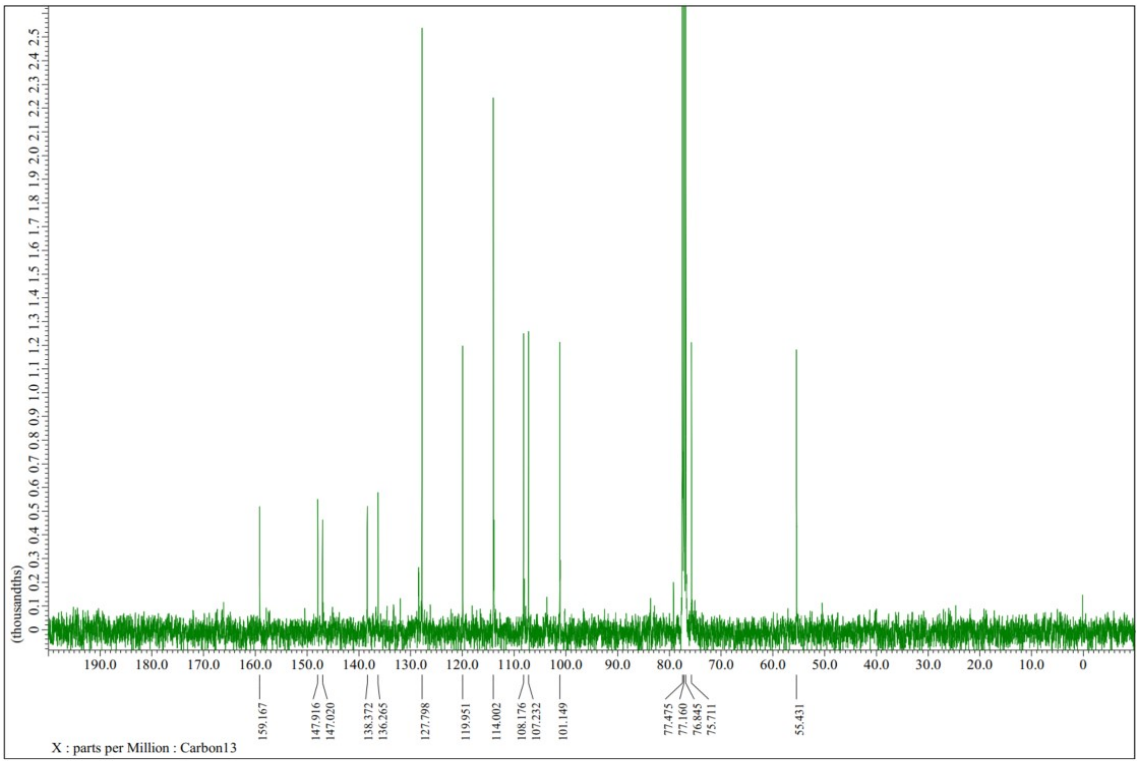
7. NMR chart

α-(4-Methoxyphenyl)-1,3-benzodioxole-5-methanol (1b)

(^{1}H NMR, 400 MHz, $CDCl_3$)

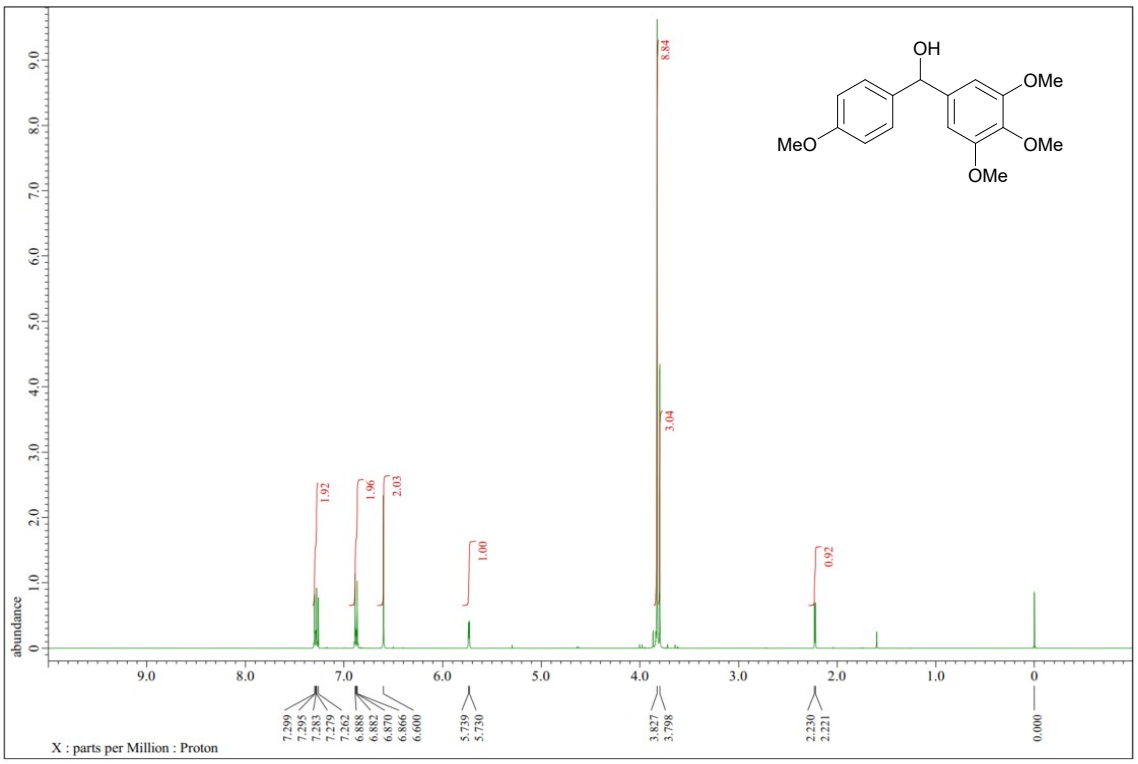


(^{13}C NMR, 100 MHz, $CDCl_3$)

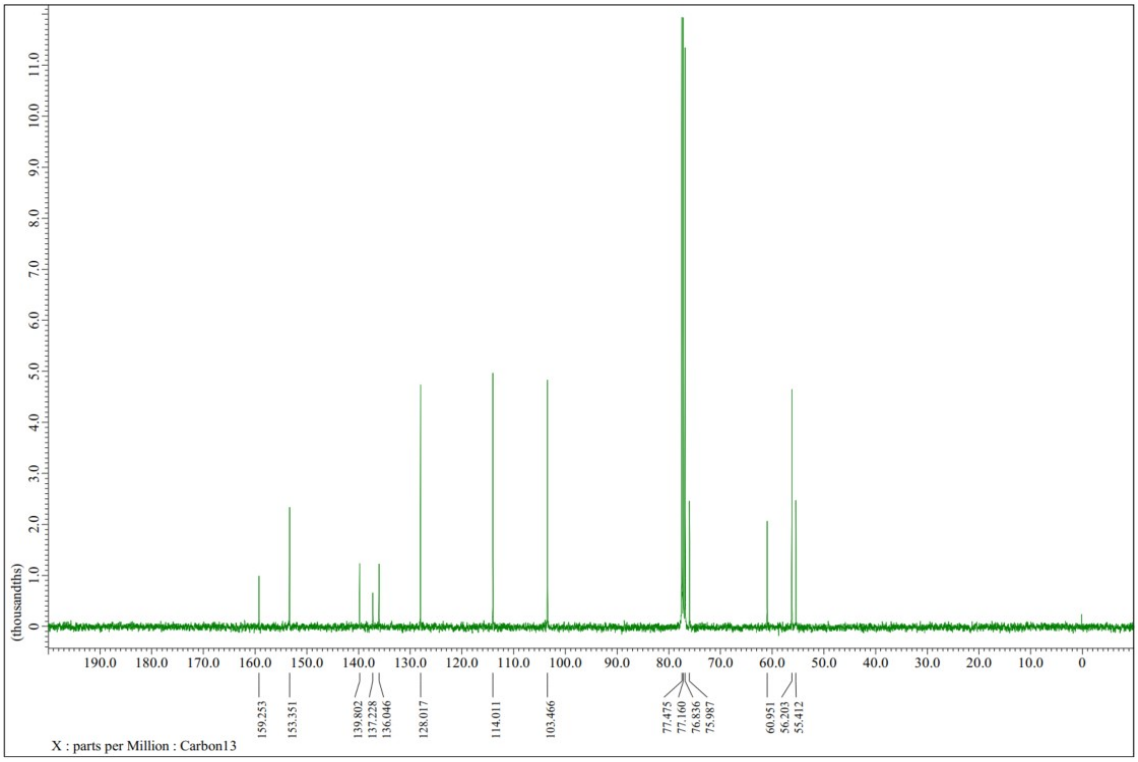


(4-Methoxyphenyl)(3,4,5-trimethoxyphenyl)methanol (1c)

(^{1}H NMR, 400 MHz, $CDCl_3$)

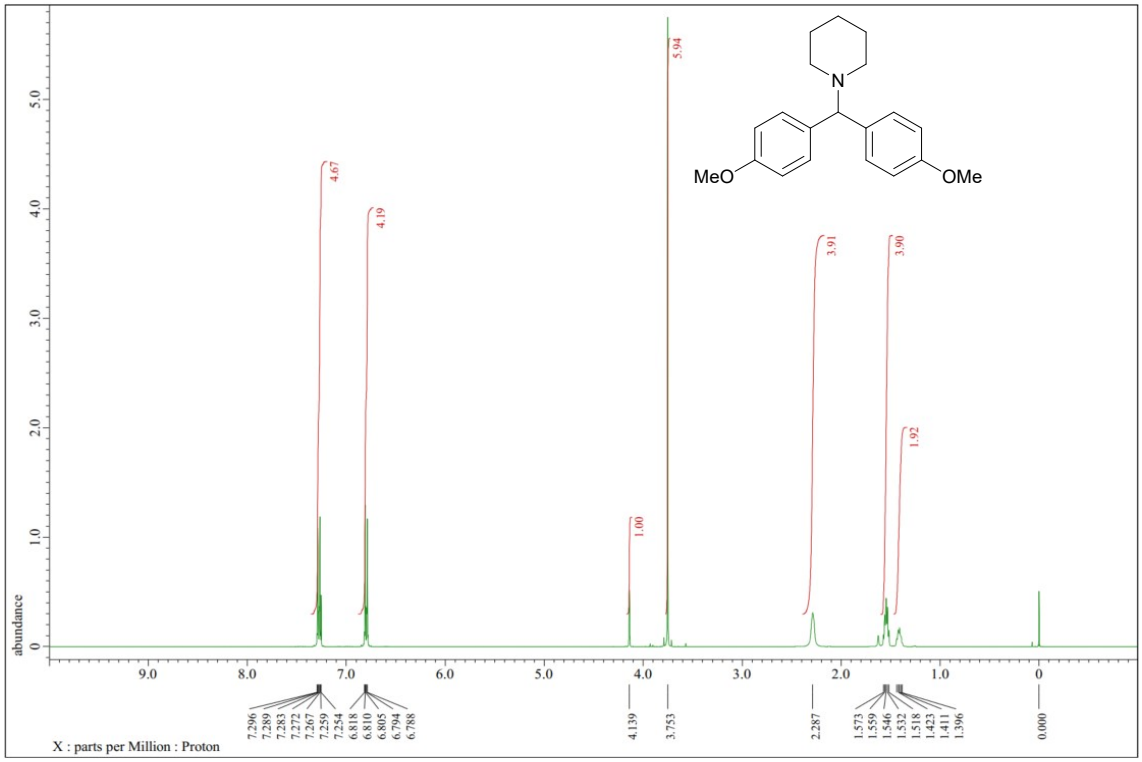


(^{13}C NMR, 100 MHz, $CDCl_3$)

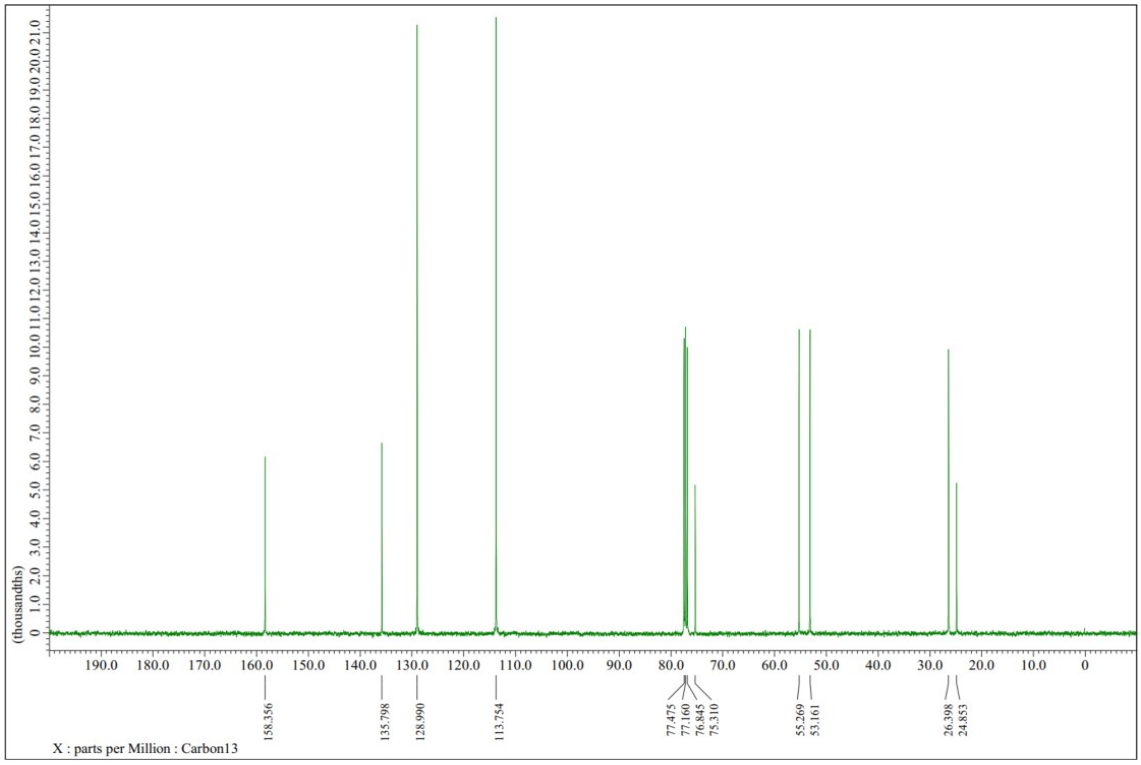


1-(Bis(4-methoxyphenyl)methyl)piperidine (2a)

(^{1}H NMR, 400 MHz, $CDCl_3$)

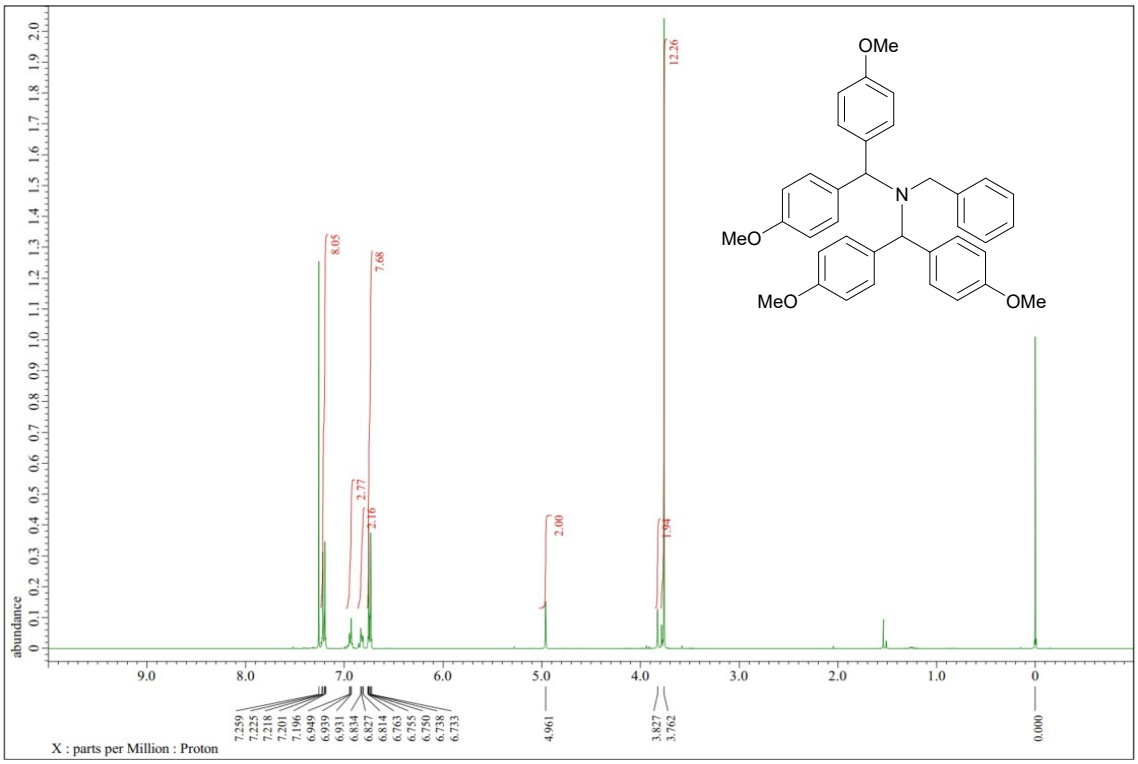


(^{13}C NMR, 100 MHz, $CDCl_3$)

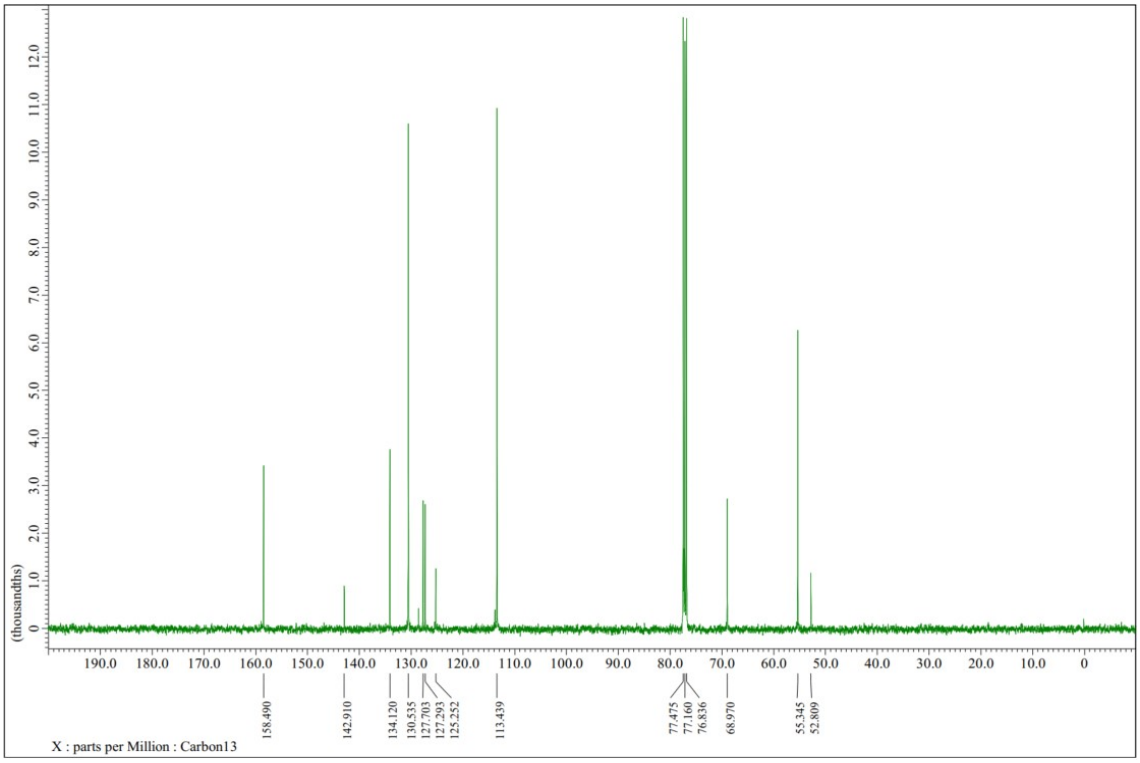


***N*-Benzyl-*N*-(bis(4-methoxyphenyl)methyl)-1,1-bis(4-methoxyphenyl)methanamine (2b)**

(^{1}H NMR, 400 MHz, $CDCl_3$)

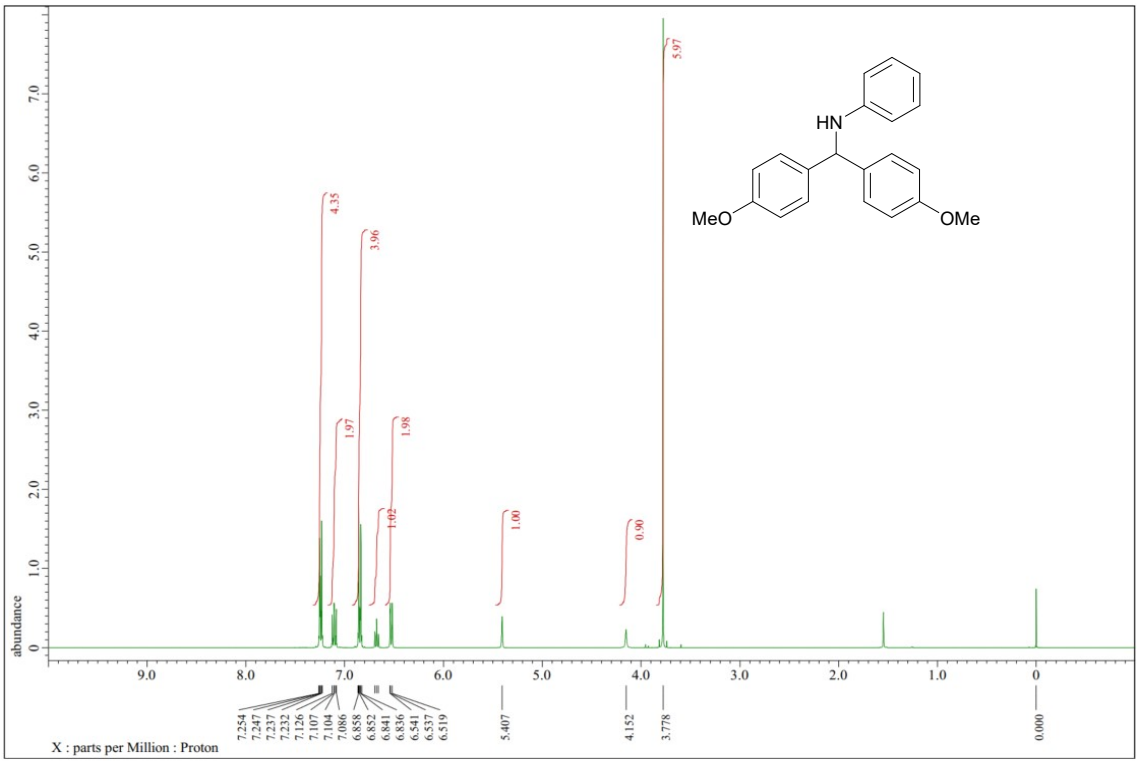


(^{13}C NMR, 100 MHz, $CDCl_3$)

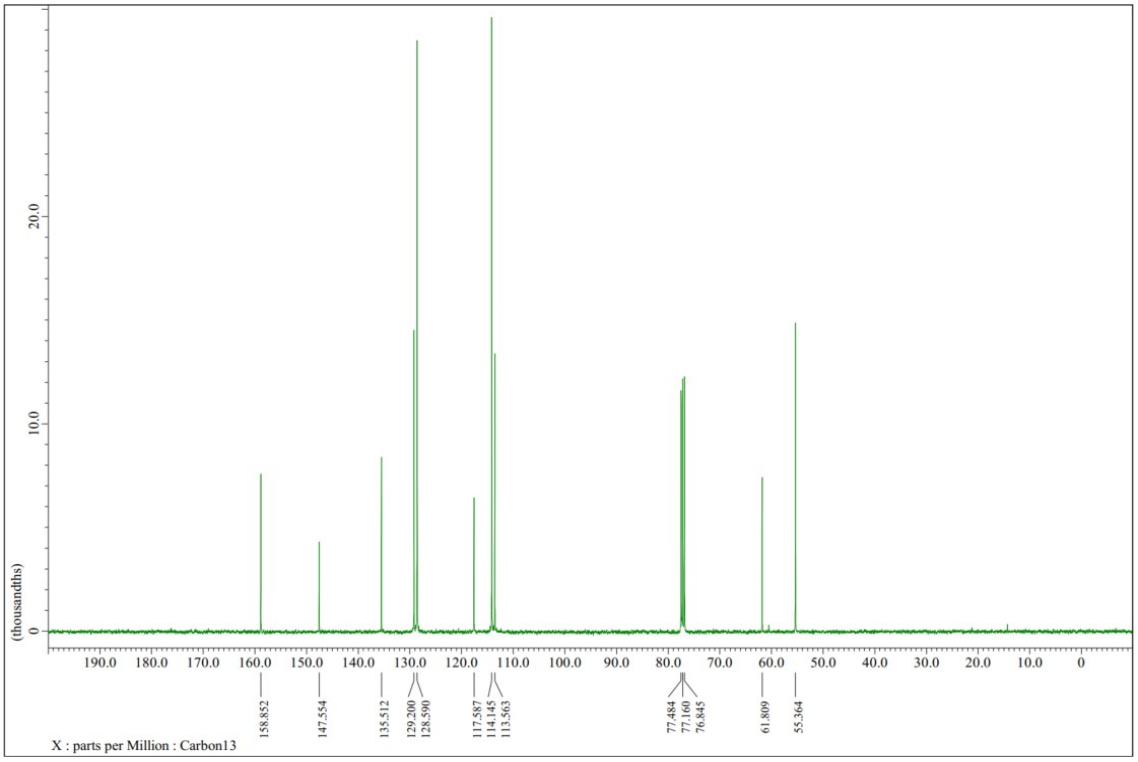


***N*-(Bis(4-methoxyphenyl)methyl)aniline (2c)**

(^{1}H NMR, 400 MHz, $CDCl_3$)

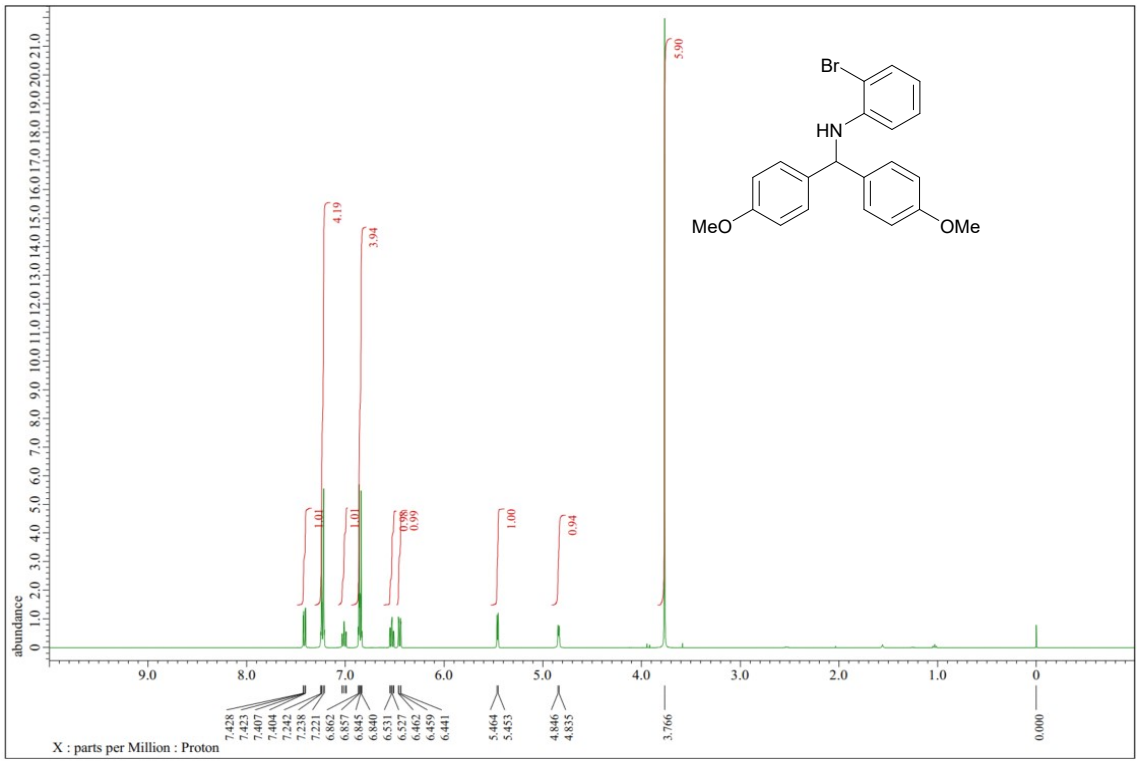


(^{13}C NMR, 100 MHz, $CDCl_3$)

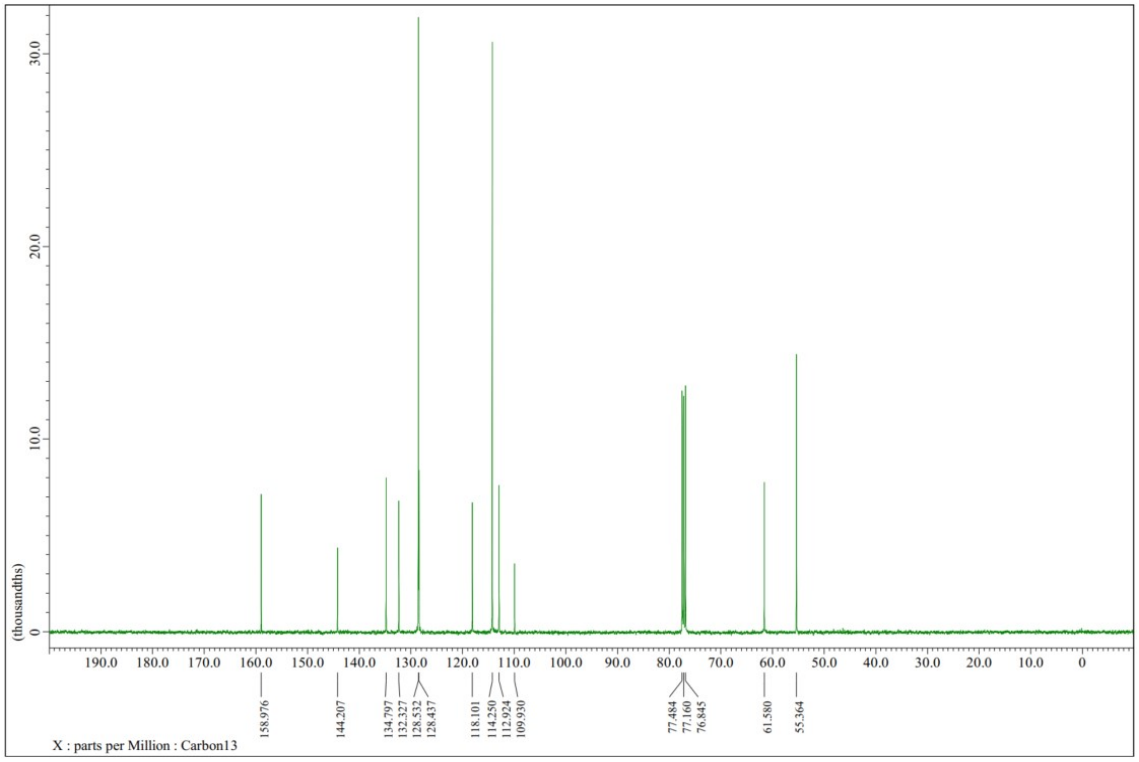


***N*-(Bis(4-methoxyphenyl)methyl)-2-bromo-aniline (2d)**

(^{1}H NMR, 400 MHz, $CDCl_3$)

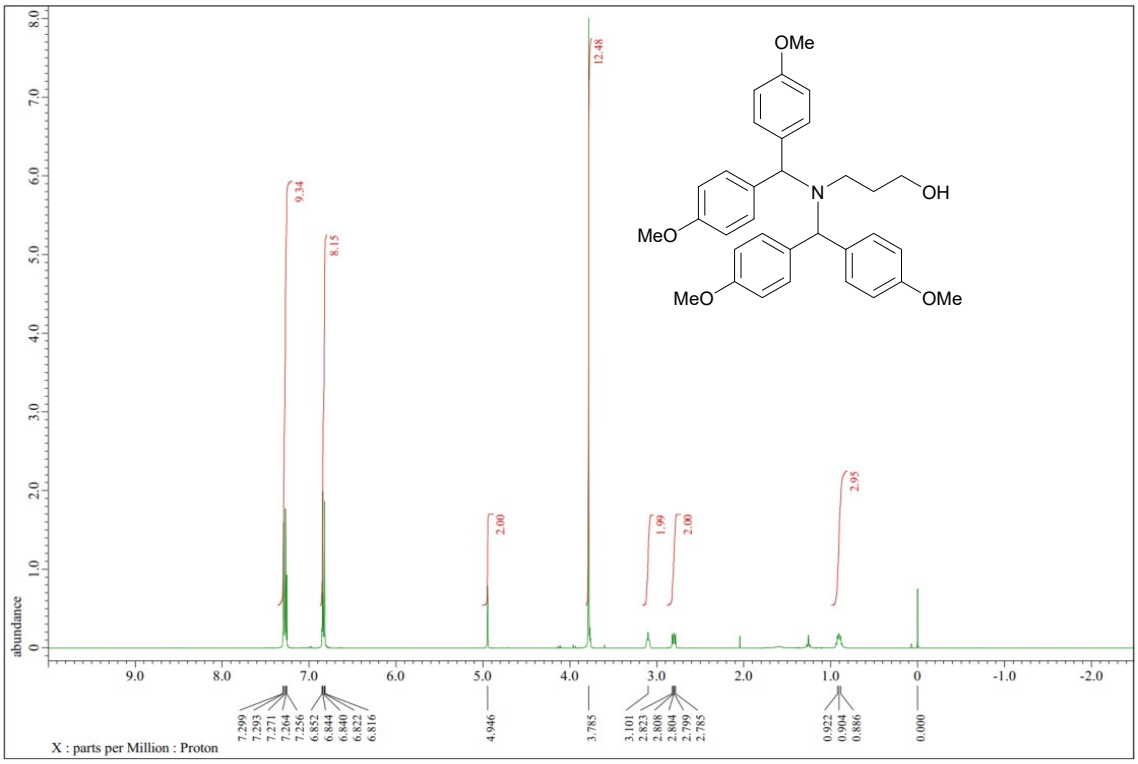


(^{13}C NMR, 100 MHz, $CDCl_3$)

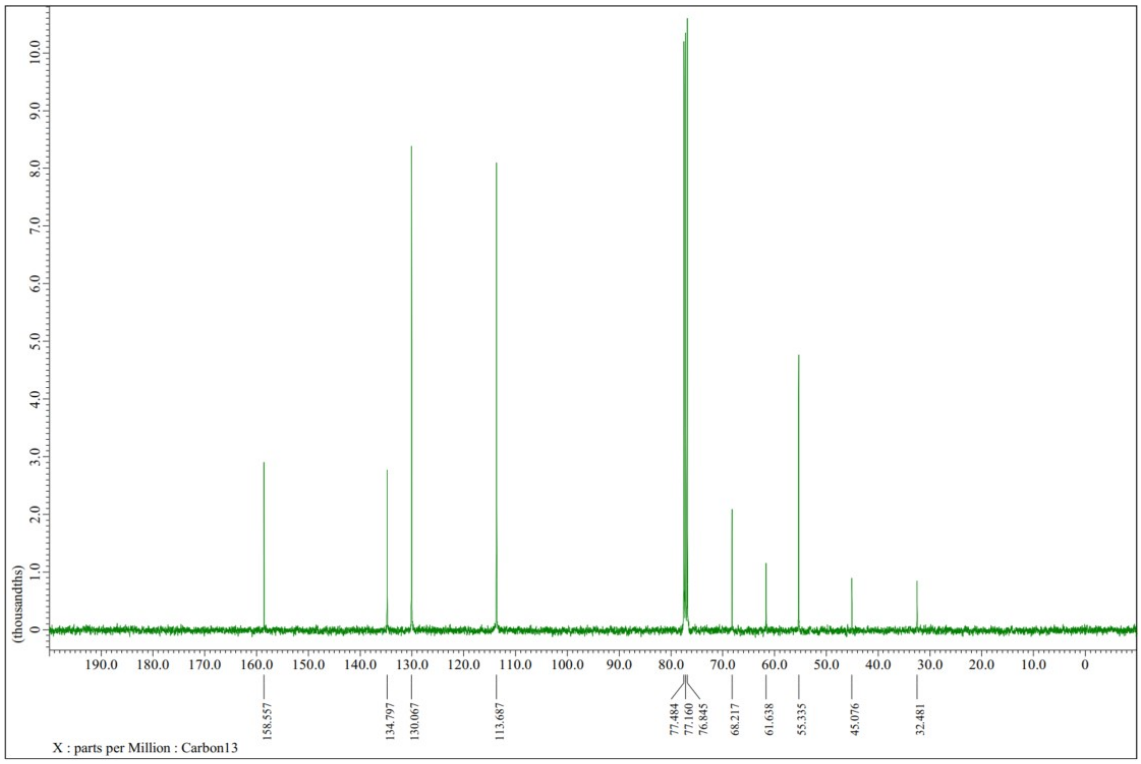


3-(Bis(bis)(4-mehoxyphenyl)methyl)amino)propan-1-ol (2e)

(^{1}H NMR, 400 MHz, $CDCl_3$)

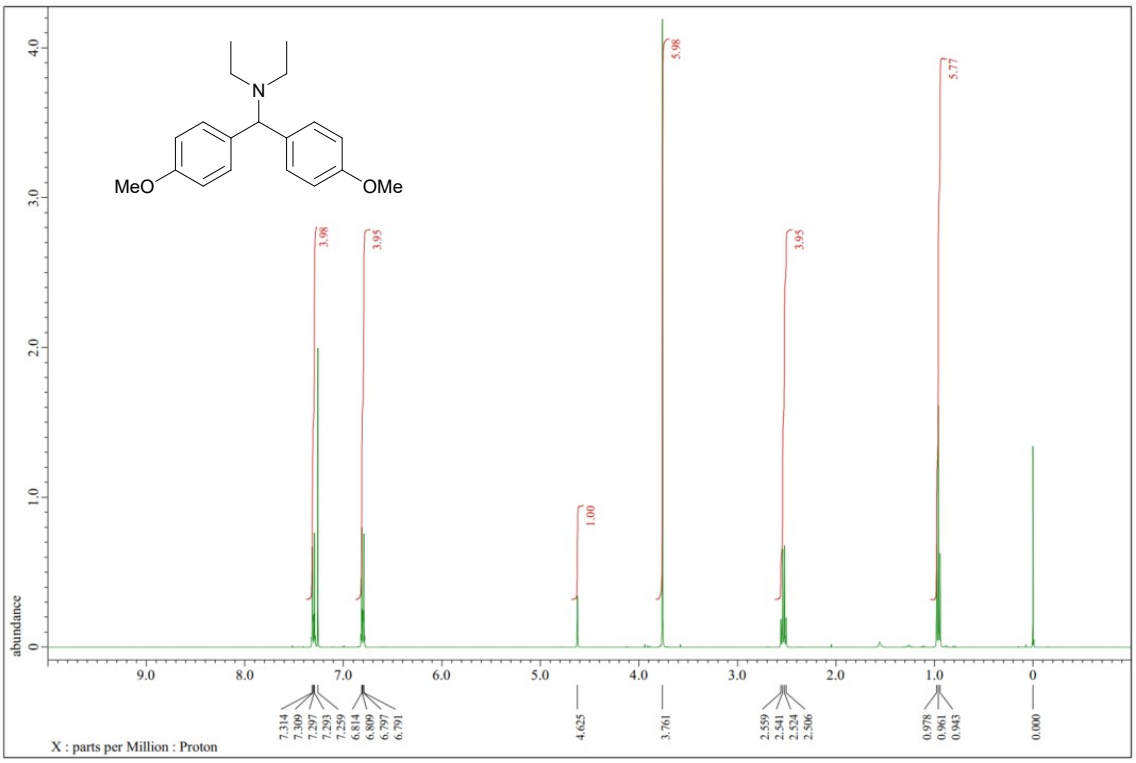


(^{13}C NMR, 100 MHz, $CDCl_3$)

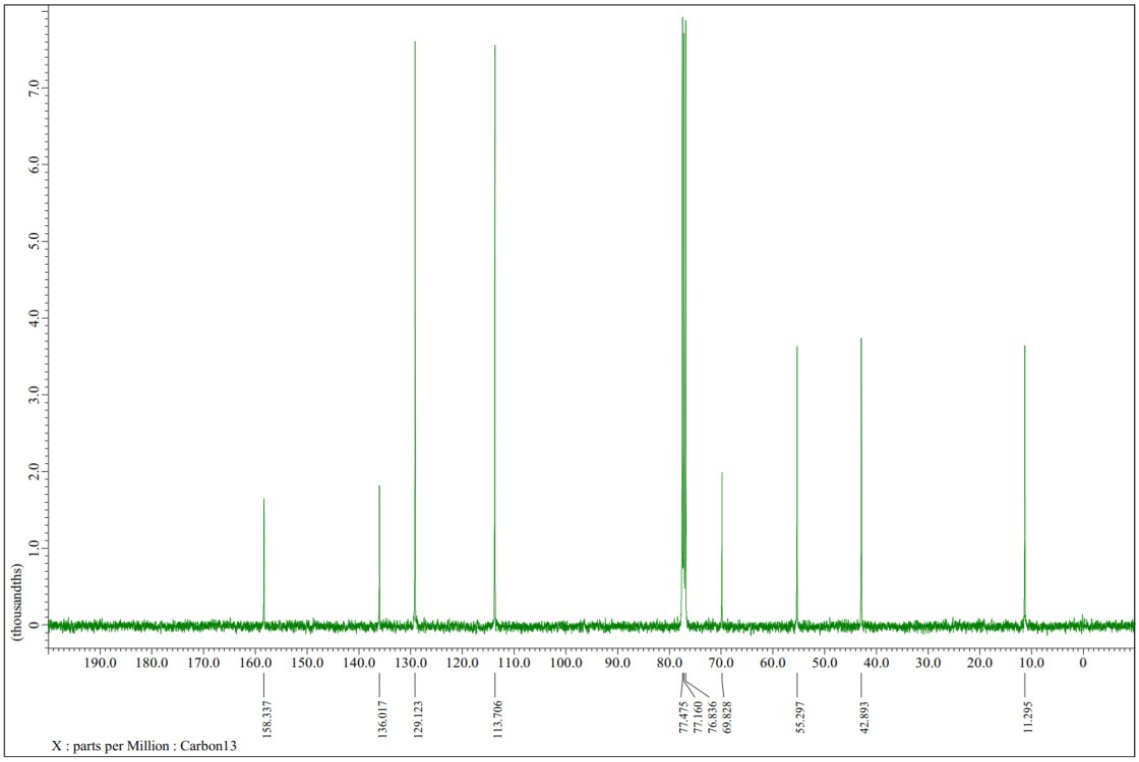


1-(Bis(4-methoxyphenyl)methyl)diethylamine (2g)

(^{1}H NMR, 400 MHz, $CDCl_3$)

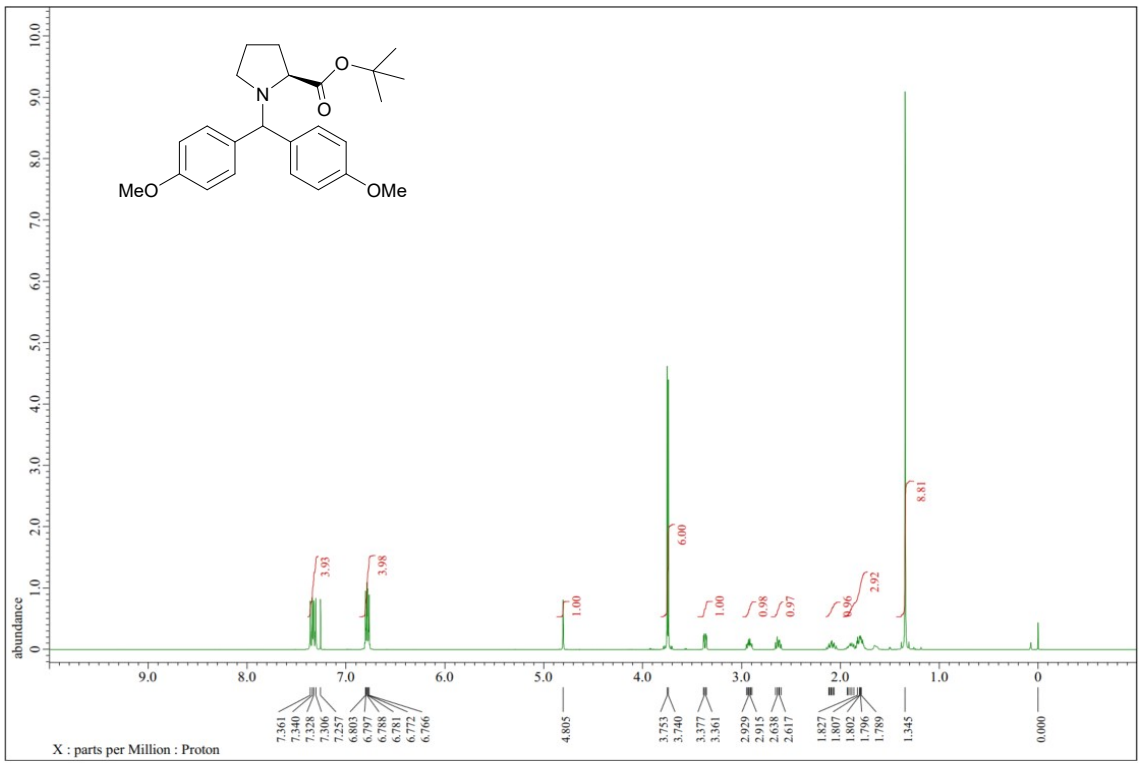


(^{13}C NMR, 100 MHz, $CDCl_3$)

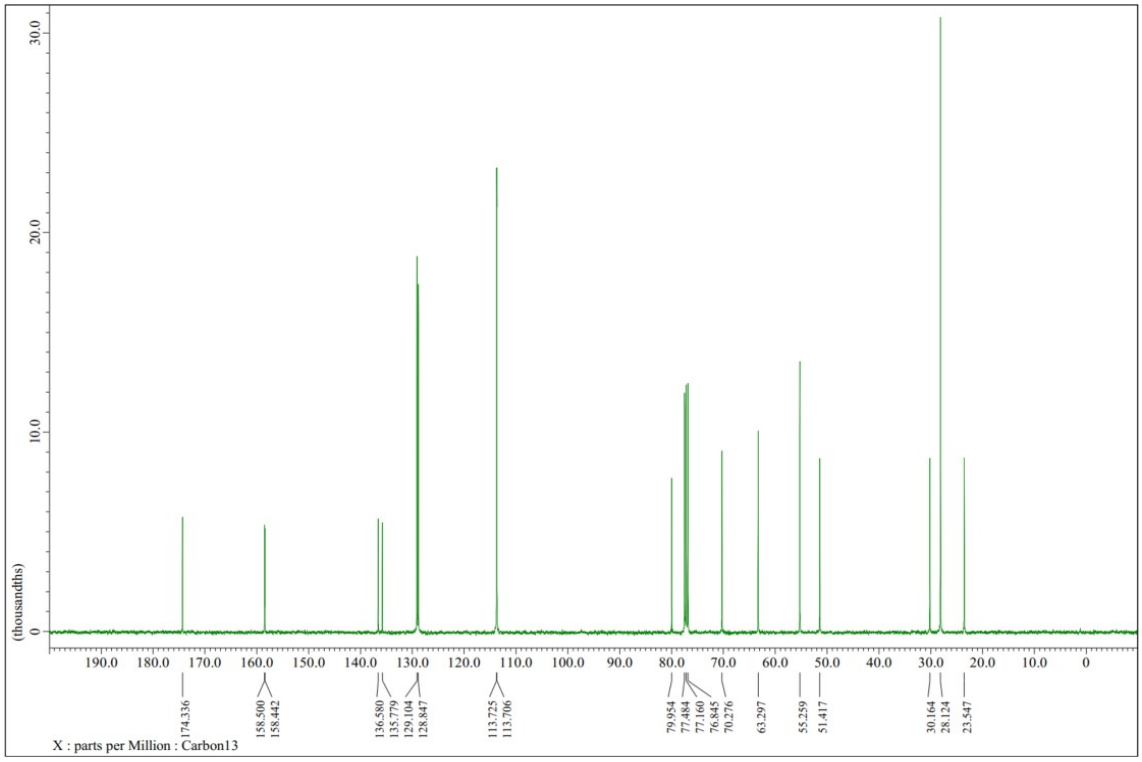


***tert*-Butyl (bis(4-methoxyphenyl)methyl)prolinate (2h)**

(^{1}H NMR, 400 MHz, $CDCl_3$)

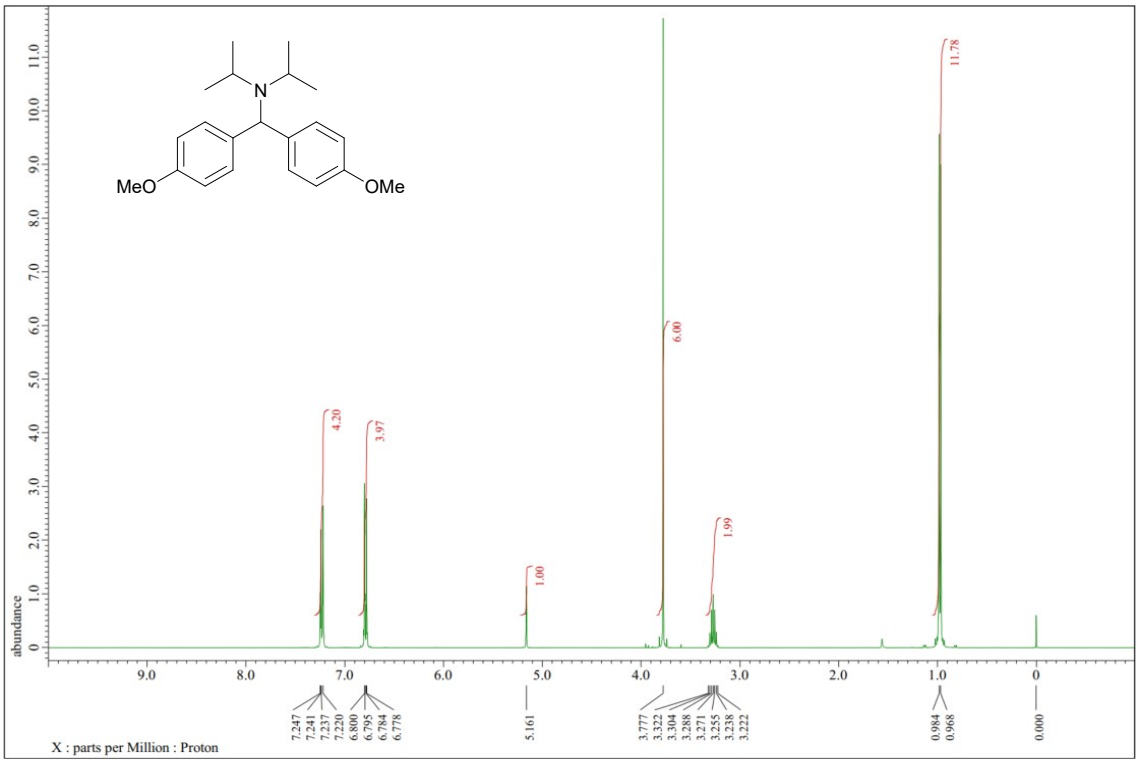


(^{13}C NMR, 100 MHz, $CDCl_3$)

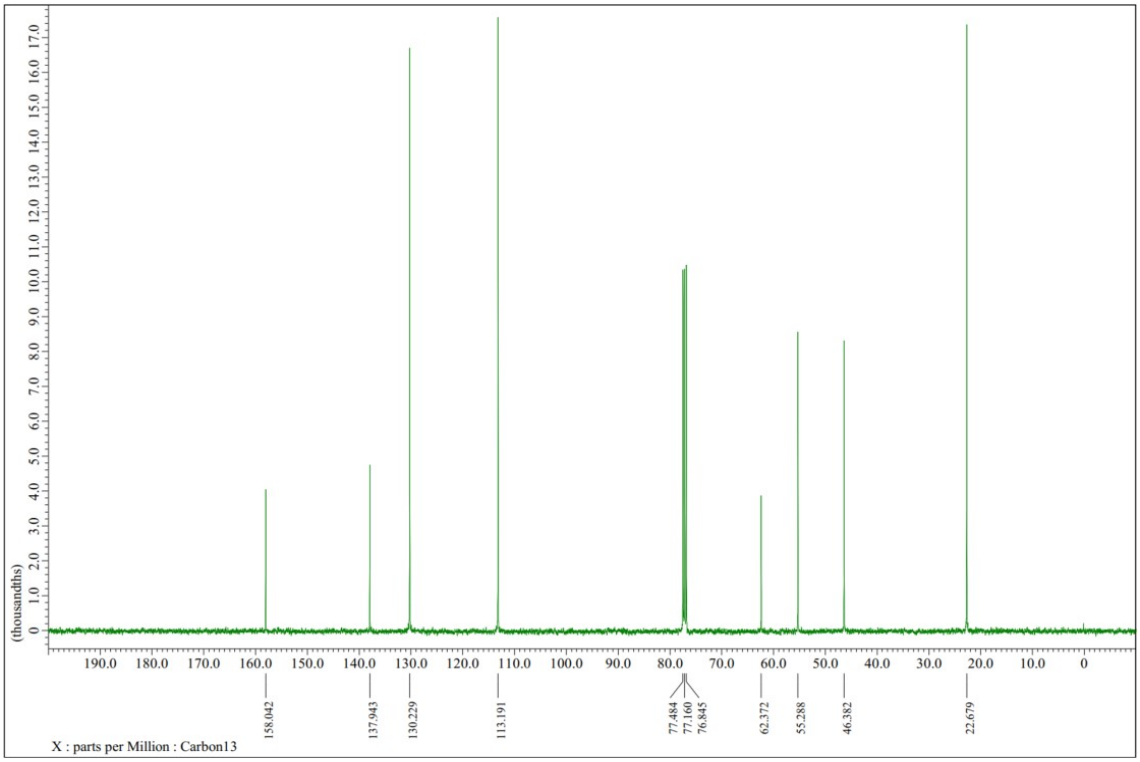


***N*-(Bis(4-methoxyphenyl)methyl)butan-2-amine (2i)**

(^{1}H NMR, 400 MHz, $CDCl_3$)

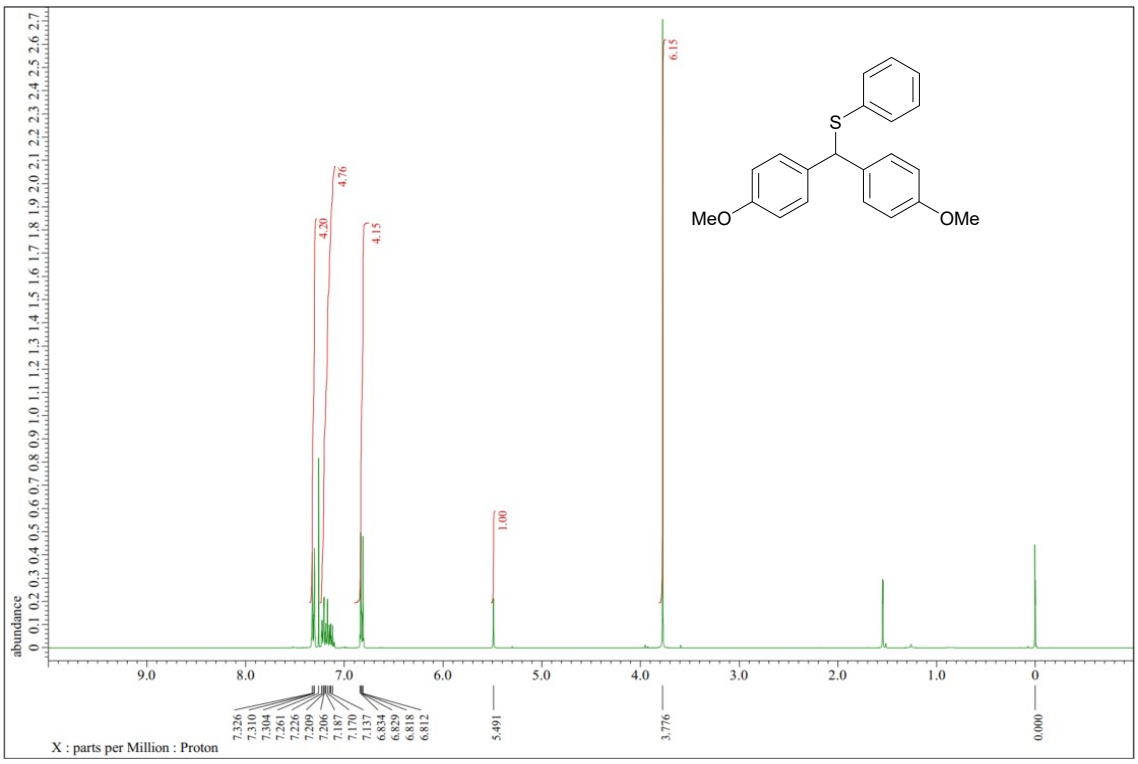


(^{13}C NMR, 100 MHz, $CDCl_3$)

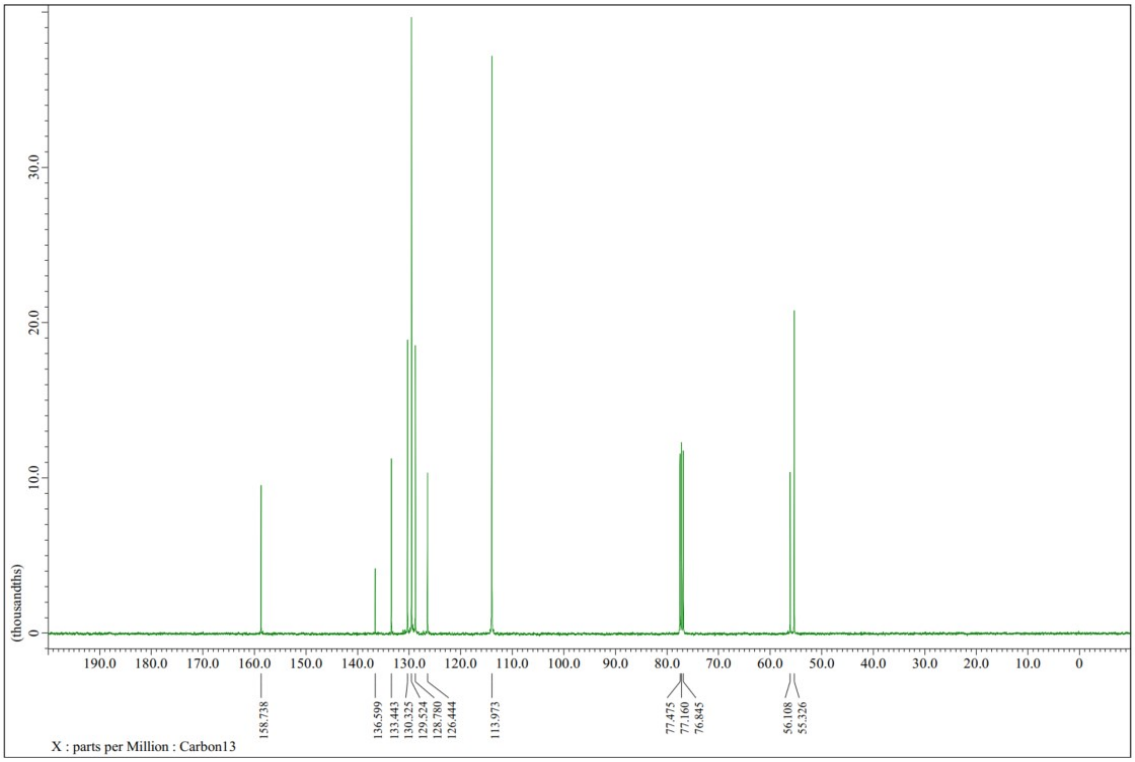


(Bis(4-methoxyphenyl)methyl)(phenyl)sulfane (2j)

(^{1}H NMR, 400 MHz, $CDCl_3$)

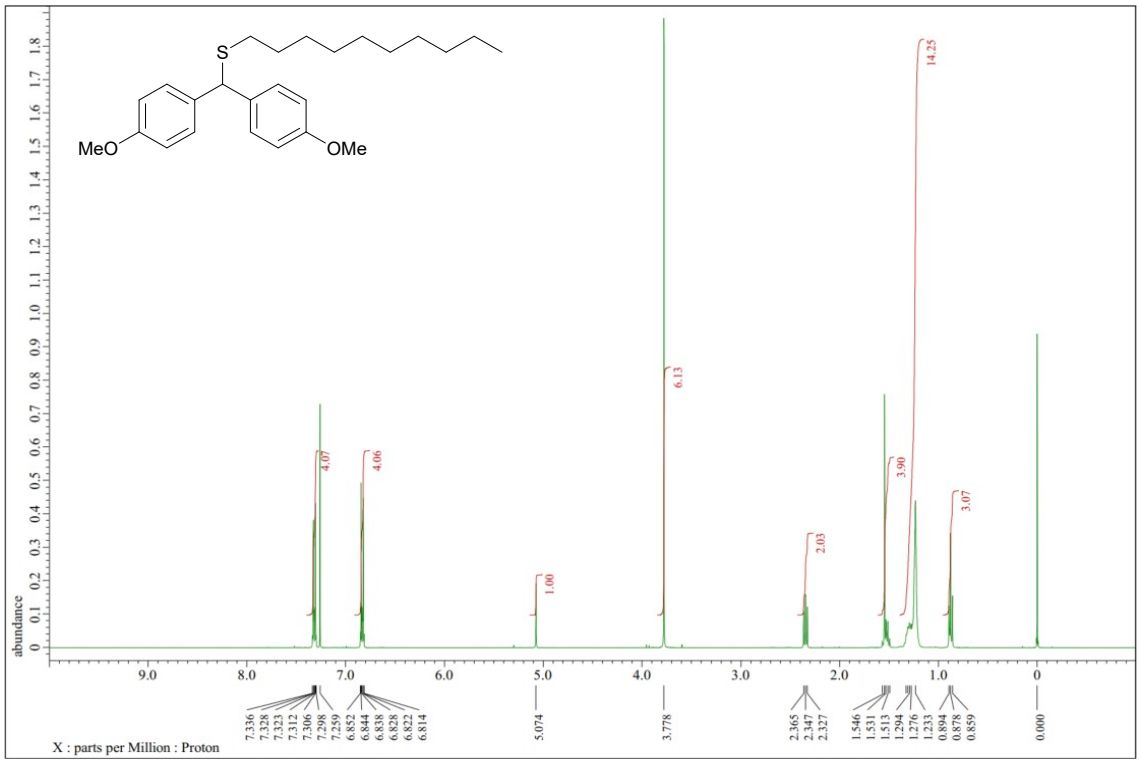


(^{13}C NMR, 100 MHz, $CDCl_3$)

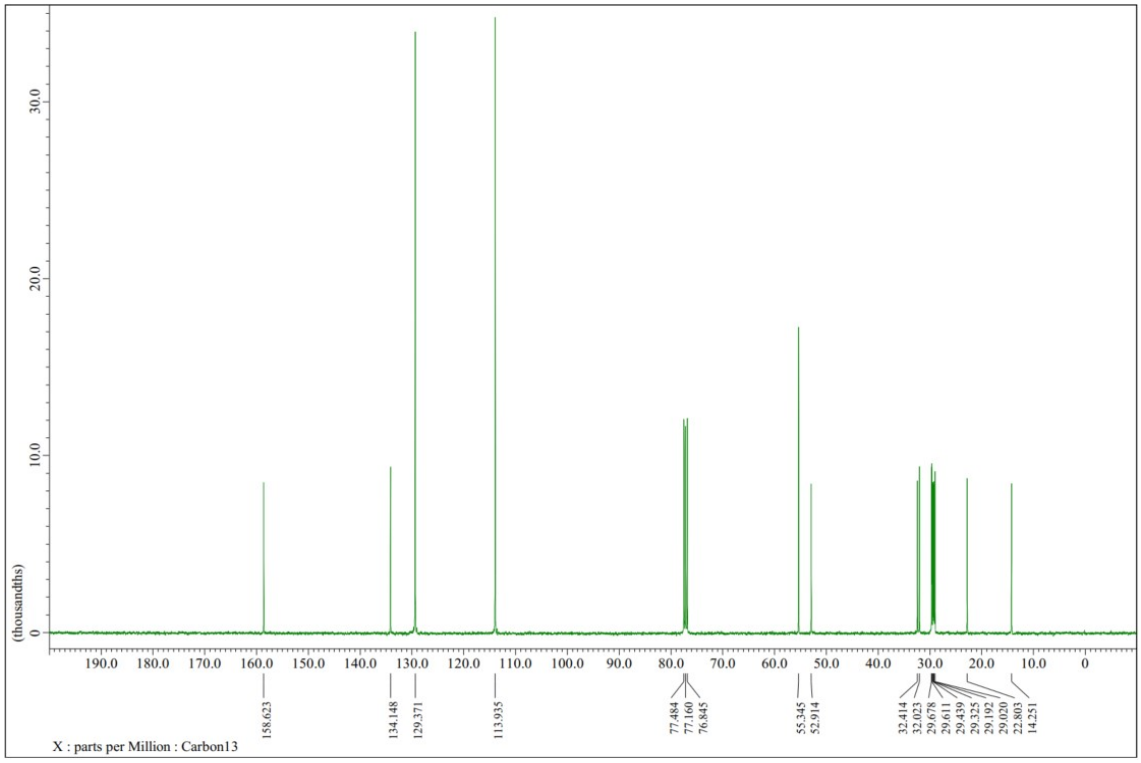


(Bis(4-methoxyphenyl)methyl)decanthiolate (2k)

(^{1}H NMR, 400 MHz, $CDCl_3$)

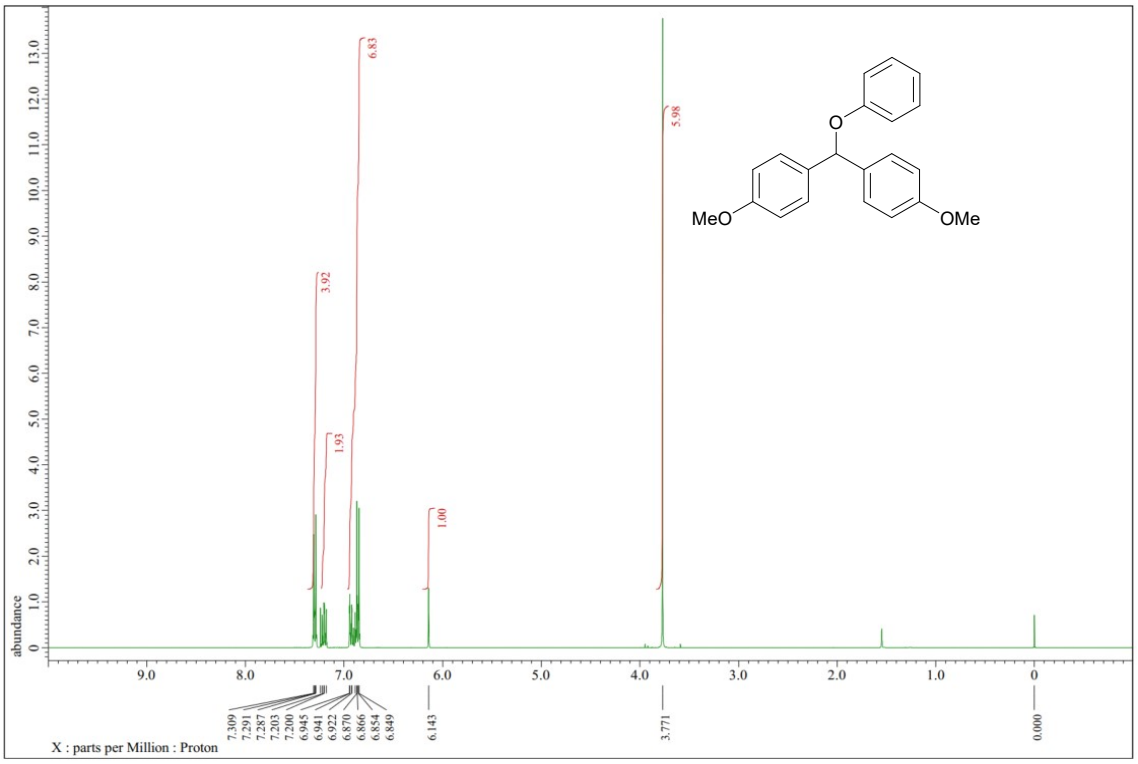


(^{13}C NMR, 100 MHz, $CDCl_3$)

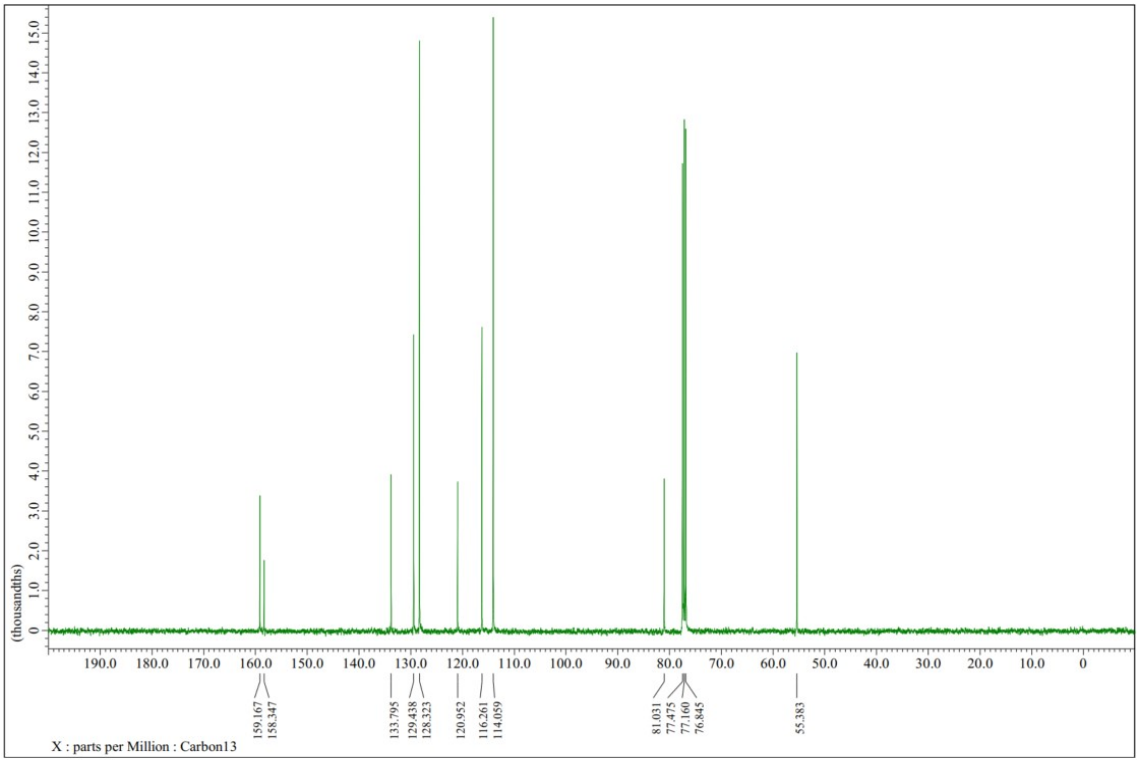


(Bis(4-methoxyphenyl)methyl)phenol (2l)

(^{1}H NMR, 400 MHz, $CDCl_3$)

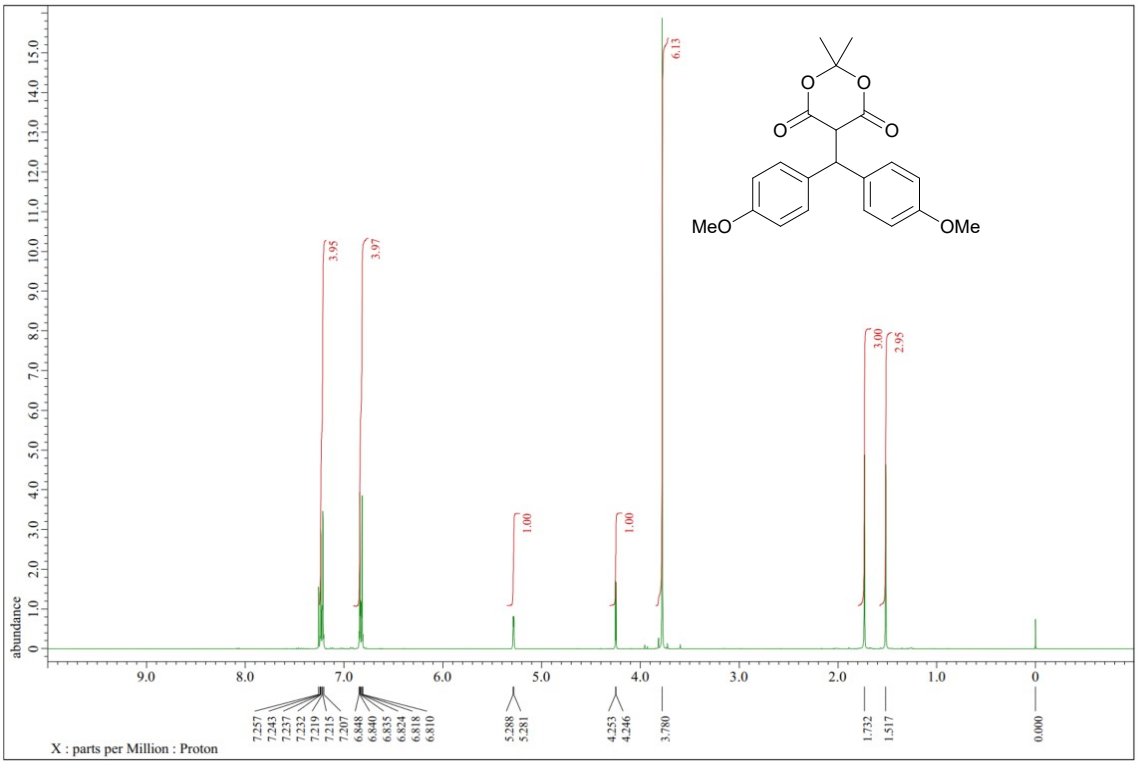


(^{13}C NMR, 100 MHz, $CDCl_3$)

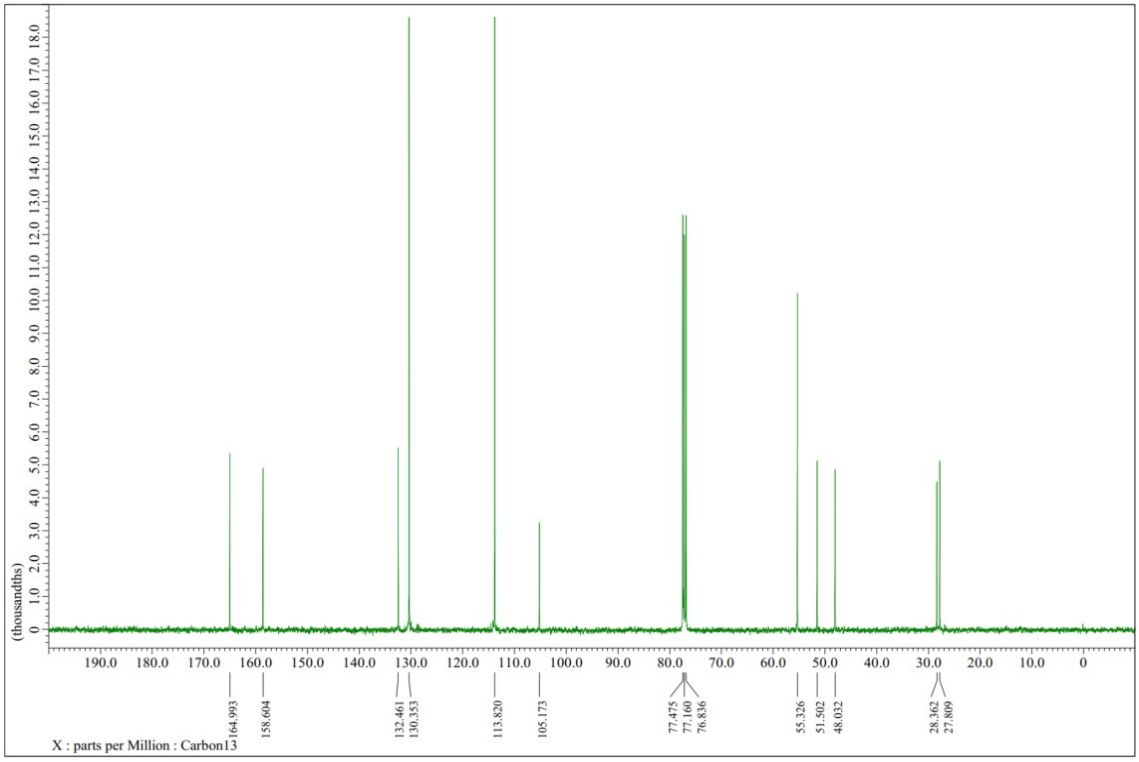


5-(Bis(4-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2n)

(^{1}H NMR, 400 MHz, $CDCl_3$)

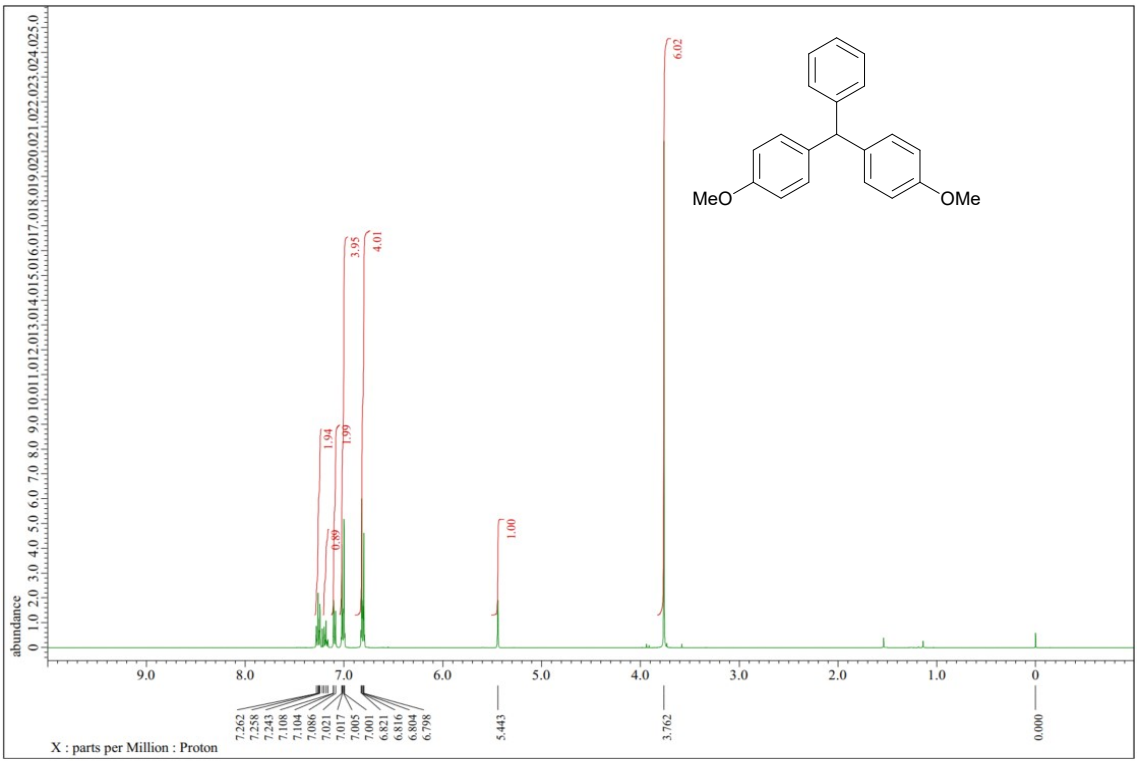


(^{13}C NMR, 100 MHz, $CDCl_3$)

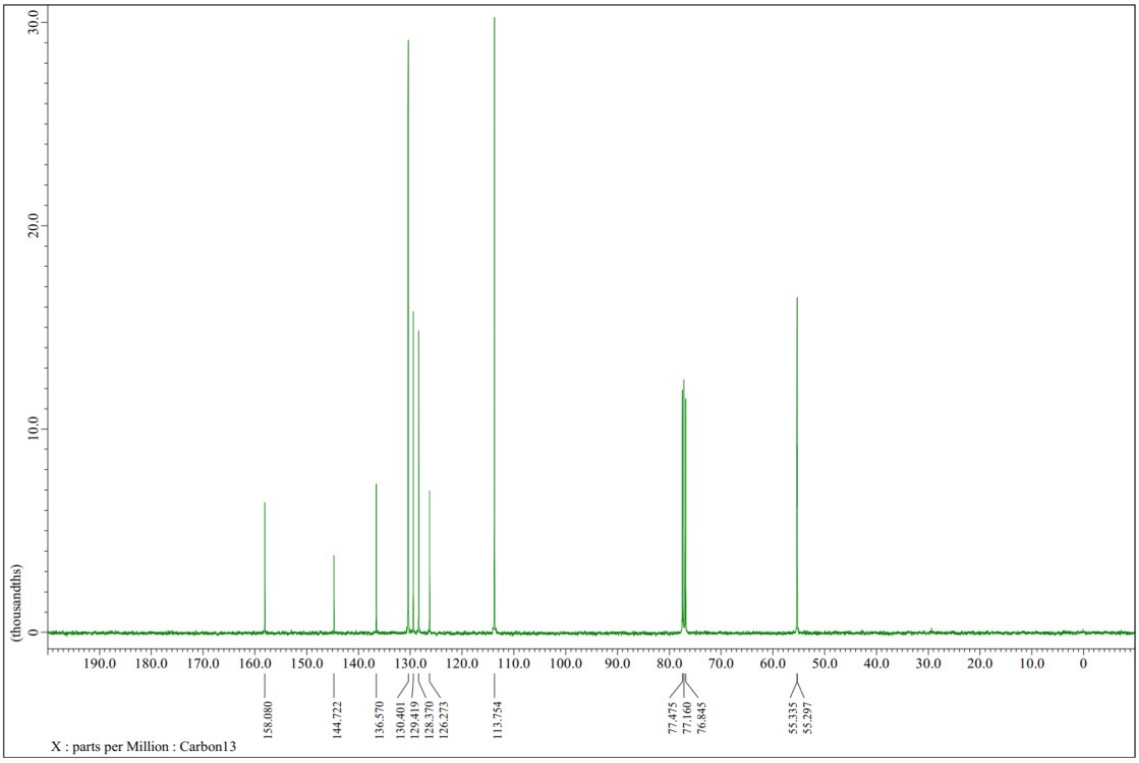


4,4'-(Phenylmethylene)bis(methoxybenzene) (2o)

(^{1}H NMR, 400 MHz, $CDCl_3$)

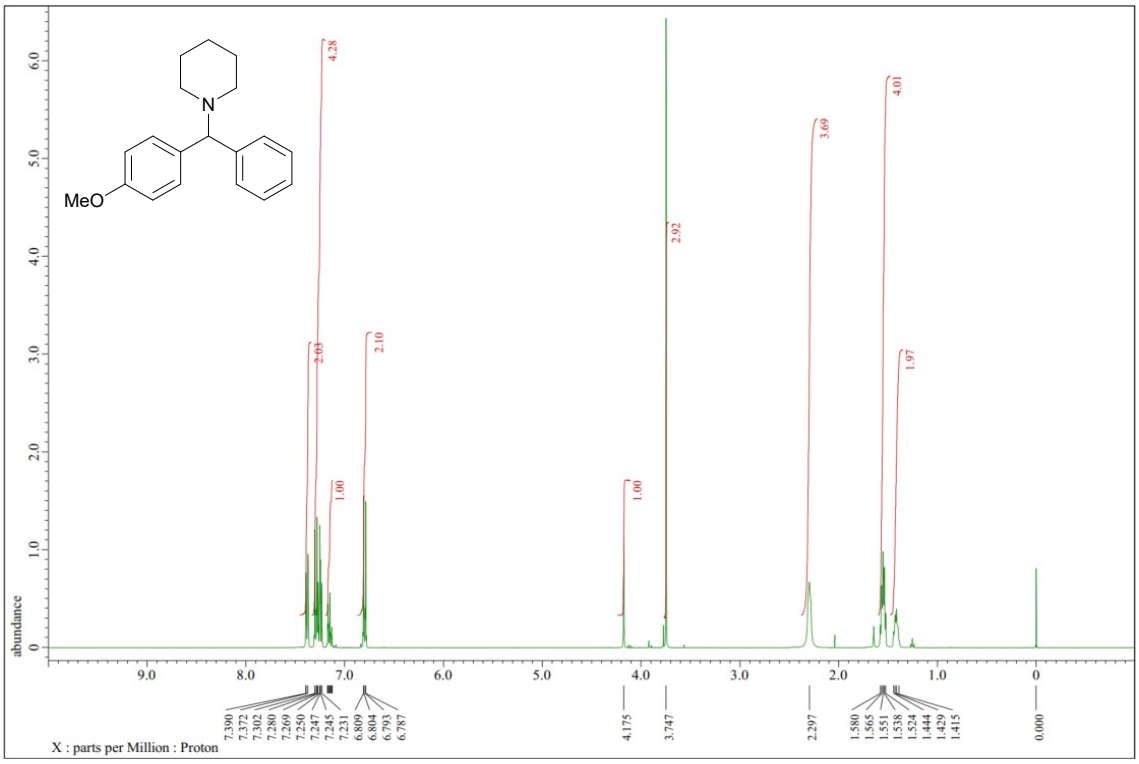


(^{13}C NMR, 100 MHz, $CDCl_3$)

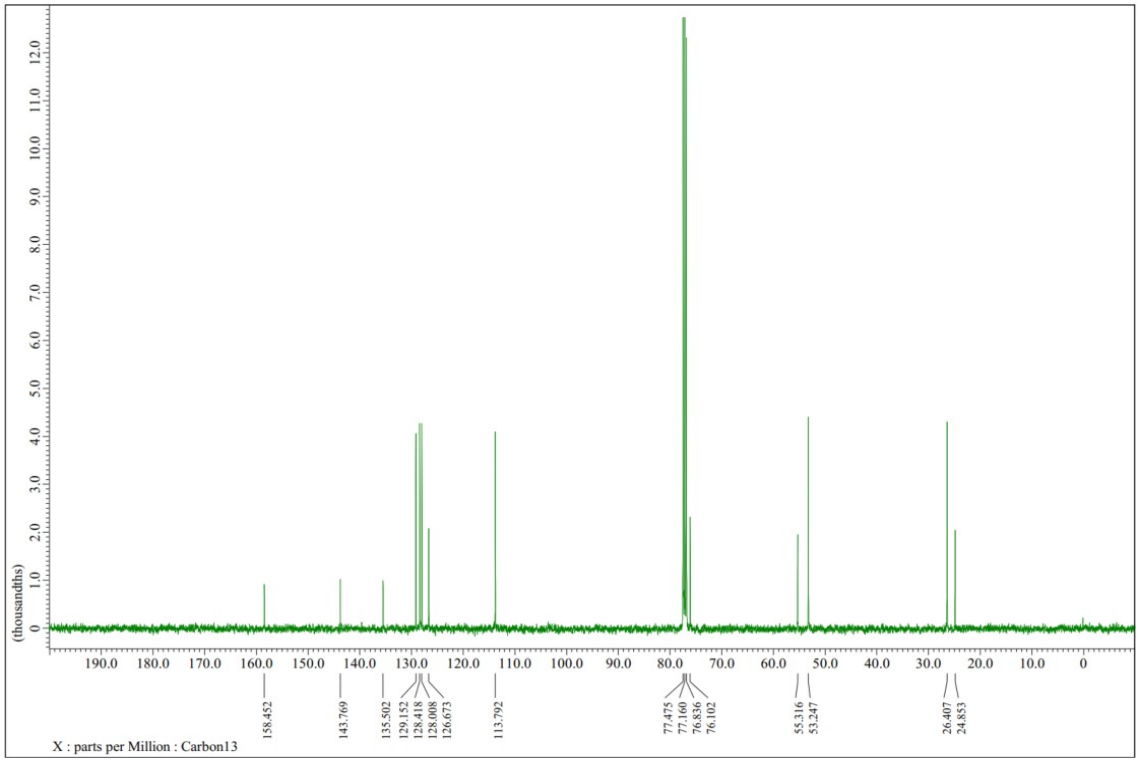


1-Phenyl-(4-methoxyphenyl)-methyl-piperidine (2r)

(^{1}H NMR, 400 MHz, $CDCl_3$)

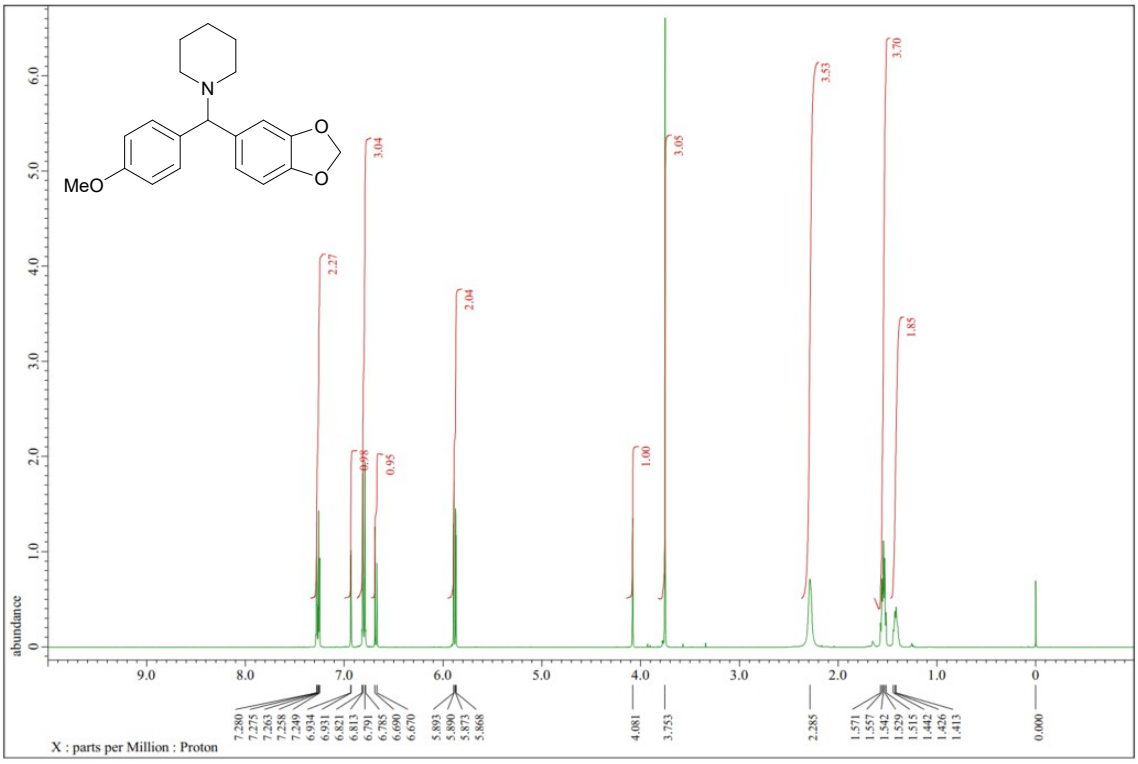


(^{13}C NMR, 100 MHz, $CDCl_3$)

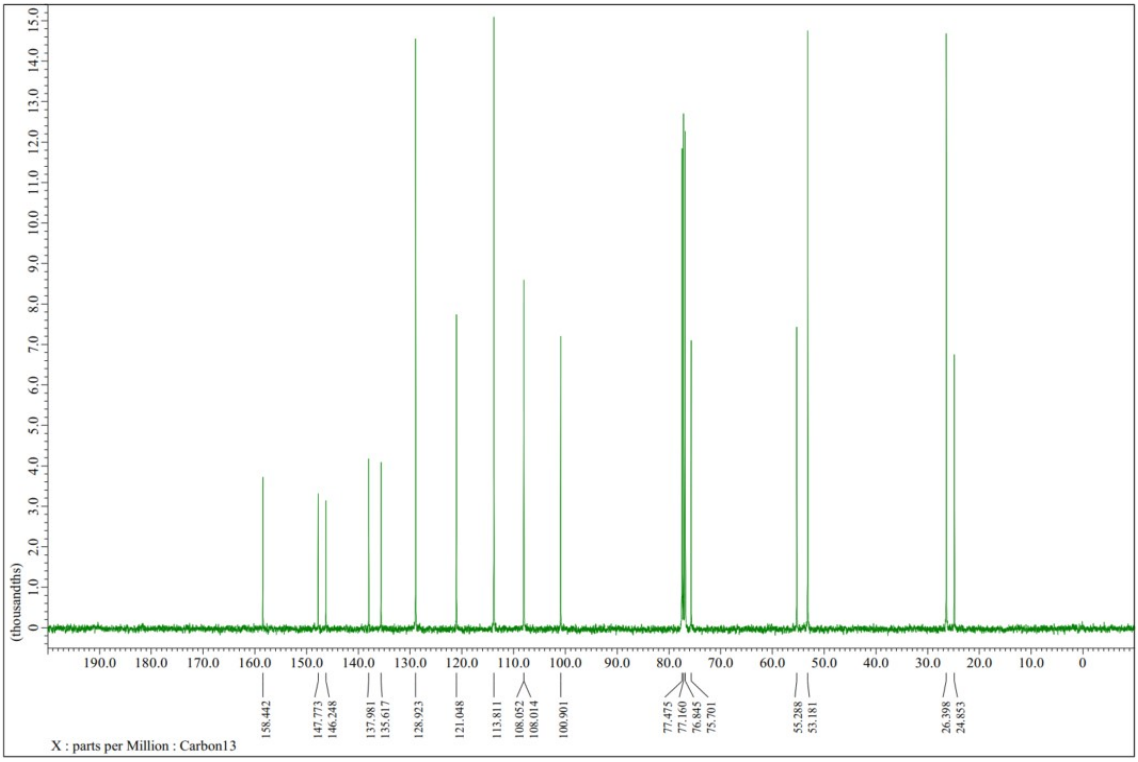


1-((3,4-Methylenedioxyphenyl)-(4-methoxyphenyl)methylene)piperidine (2s)

(^{1}H NMR, 400 MHz, $CDCl_3$)

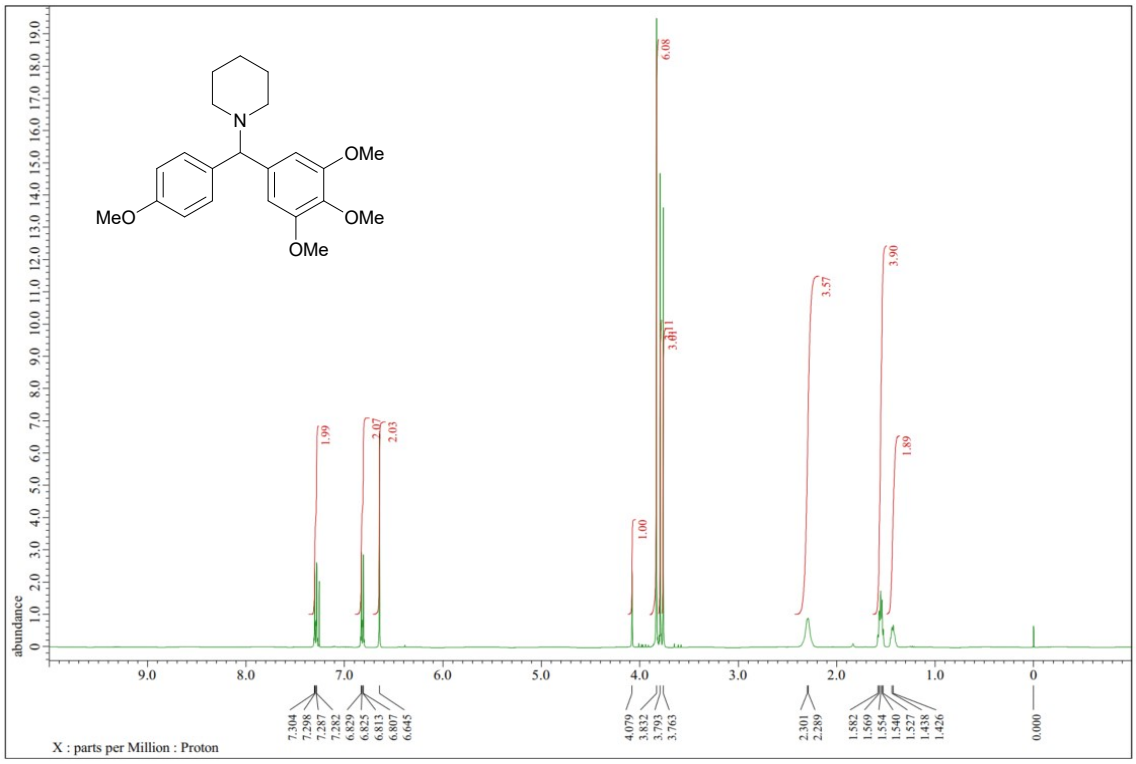


(^{13}C NMR, 100 MHz, $CDCl_3$)



1-((4-Methoxyphenyl)(3,4,5-trimethoxyphenyl)methyl)piperidine (2t)

(^{1}H NMR, 400 MHz, $CDCl_3$)



(^{13}C NMR, 100 MHz, $CDCl_3$)