Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Clickable coupling of carboxylic acids and amines at room temperature mediated by SO_2F_2: A significant breakthrough for the construction of amides and peptide linkages

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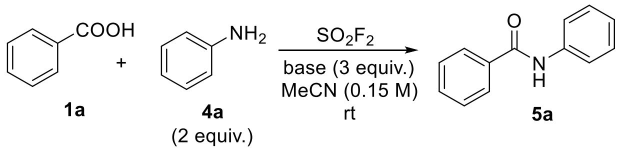
1. General considerations

All reactions were carried out under an air atmosphere. Unless otherwise specified, NMR spectra were recorded in $CDCl_3$ on a 500 MHz (for ^1H), 471 MHz (for ^{19}F), and 126 MHz (for ^{13}C) spectrometer. All chemical shifts were reported in ppm relative to TMS (^1H NMR, 0 ppm) and $CFCl_3$ (^{19}F NMR, 0 ppm) as internal standards. The HPLC experiments were carried out on a Waters e2695 instrument (column: J&K, RP-C18, 5 μm, 4.6 × 150 mm), and the yields of the products were determined by using the corresponding pure compounds as the external standards. Enantiomeric excesses were determined on HPLC using Chiralcel OD or IC column with UV detector. Optical rotations were measured on a Roudolph Autopl IV. Melting points of the products were measured on a micro melting point apparatus (SGW X-4) and uncorrected. High resolution mass spectra (HRMS) were obtained on an Agilent 1260-6221 TOF mass spectrometry. Reagents used in the reactions were all purchased from commercial sources and used without further purification.

2. Screening the optimized conditions for amidation reaction of 1a with 4a

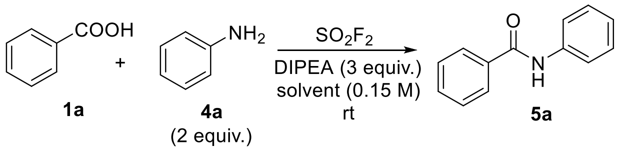
Table 1 The amidation reaction of **1a** with **4a** in the presence of different bases.[a]



Entry	Base	Yield (**5a**, %)[b]
1	DIPEA	82
2	Et_3N	81
3	DBU	<1
4	DBN	<1
5	TMEDA	54
6	DMAP	46
7	DABCO	32
8	proton sponge	<1
9	K_2CO_3	26
10	Na_2CO_3	<1
11	K_3PO_4	13
12	Na_3PO_4	<1
13	KOAc	9
14	NaOAc	<1
15	Cs_2CO_3	47
16	$NaHCO_3$	<1

[a] General conditions: a mixture of benzoic acid (**1a**, 0.3 mmol), aniline (**4a**, 0.6 mmol) and base (0.9 mmol, 3 equiv) in MeCN (reaction diluted to 0.15 M) under SO_2F_2 atmosphere (balloon) was stirred at room temperature for 5 h. [b] The yield was determined by HPLC using *N*-phenylbenzamide (**5a**, t_R = 3.807 min, λ_{max} = 263.0 nm, water/methanol = 30 : 70 (v/v)) as the external standard.

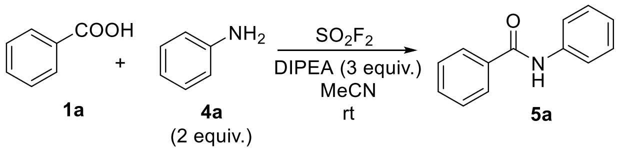
Table 2 The amidation reaction of **1a** with **4a** in the presence of different solvents.[a]



Entry	Solvent	Yield (**5a**, %)[b]
1	MeCN	82
2	dioxane	59
3	toluene	67
4	THF	19
5	acetone	24
6	DMF	20
7	DMSO	26
8	NMP	45
9	DCM	36

[a] General conditions: a mixture of benzoic acid (**1a**, 0.3 mmol), aniline (**4a**, 0.6 mmol) and DIPEA (0.9 mmol, 3 equiv) in solvent (reaction diluted to 0.15 M) under SO_2F_2 atmosphere (balloon) was stirred at room temperature for 5 h. [b] The yield was determined by HPLC using *N*-phenylbenzamide (**5a**, t_R = 3.807 min, λ_{max} = 263.0 nm, water/methanol = 30 : 70 (v/v)) as the external standard.

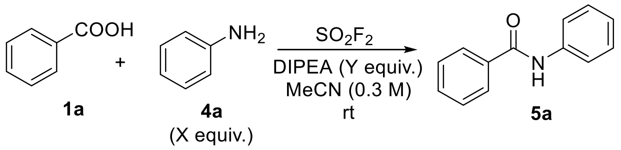
Table 3 The amidation reaction of **1a** with **4a** at different reaction concentrations.[a]



Entry	Concentration (mol/L)	Yield (**5a**, %)[b]
1	0.15	82
2	0.2	85
3	0.3	94
4	0.4	94
5	0.5	95
6	0.6	93
7	1.0	91

[a] General conditions: a mixture of benzoic acid (**1a**, 0.3 mmol), aniline (**4a**, 0.6 mmol) and DIPEA (0.9 mmol, 3 equiv) in MeCN (reaction diluted to the specified concentration) under SO_2F_2 atmosphere (balloon) was stirred at room temperature for 5 h. [b] The yield was determined by HPLC using *N*-phenylbenzamide (**5a**, t_R = 3.807 min, λ_{max} = 263.0 nm, water/methanol = 30 : 70 (v/v)) as the external standard.

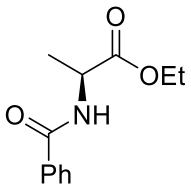
Table 4 Screening the loading of **4a** and DIPEA.[a]



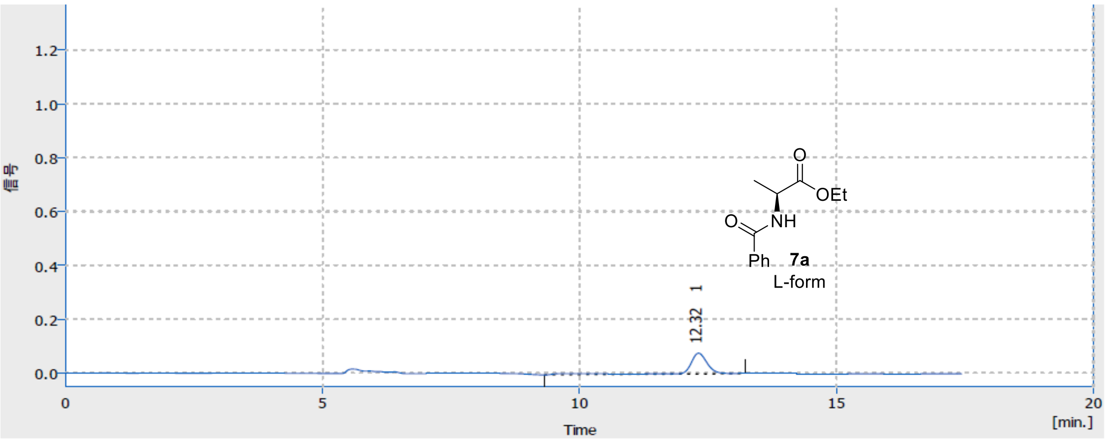
Entry	X (equiv)	Y (equiv)	Yield (**5a**, %)[b]
1	2	0	<1
2	2	1	61
3	2	2	88
4	2	3	94
5	2	4	94
6	2	5	92
7	1.5	3	90
8	1.2	3	84

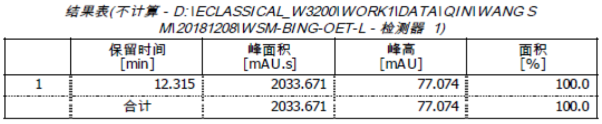
[a] General conditions: a mixture of benzoic acid (**1a**, 0.3 mmol), aniline (**4a**, 0.6 mmol) and DIPEA (0.9 mmol, 3 equiv) in MeCN (reaction diluted to 0.3 M) under SO_2F_2 atmosphere (balloon) was stirred at room temperature for 5 h. b: The yield was determined by HPLC using *N*-phenylbenzamide (**5a**, t_R = 3.807 min, λ_{max} = 263.0 nm, water/methanol = 30 : 70 (v/v)) as the external standard.

3. Enantiopurity of the Amino Acid Amides 7a-7m

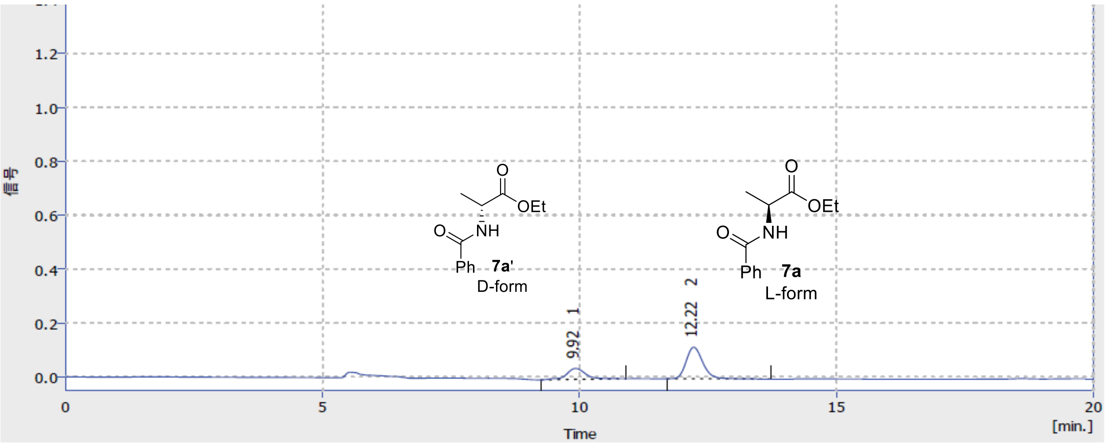


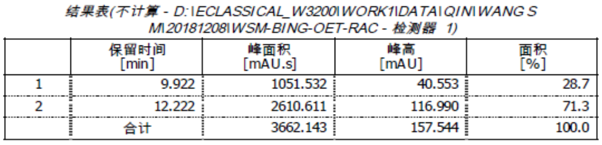
Ethyl benzoyl-L-alaninate (**7a**).[1] >99% ee was determined by chiral HPLC (chiralcel OD-H, n-hexane/2-propanol = 80/20, 0.5 mL/min, 254 nm). t_R = 9.92 min (minor) and 12.32 min (major). Authentic samples were independently prepared from L- and D-amino acids and their mixture was used as reference racemate.




结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S
M\20181208\WSM-BING-OET-L - 检测器 1)

	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	12.315	2033.671	77.074	100.0
	合计	2033.671	77.074	100.0

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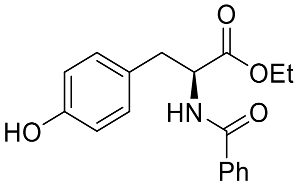
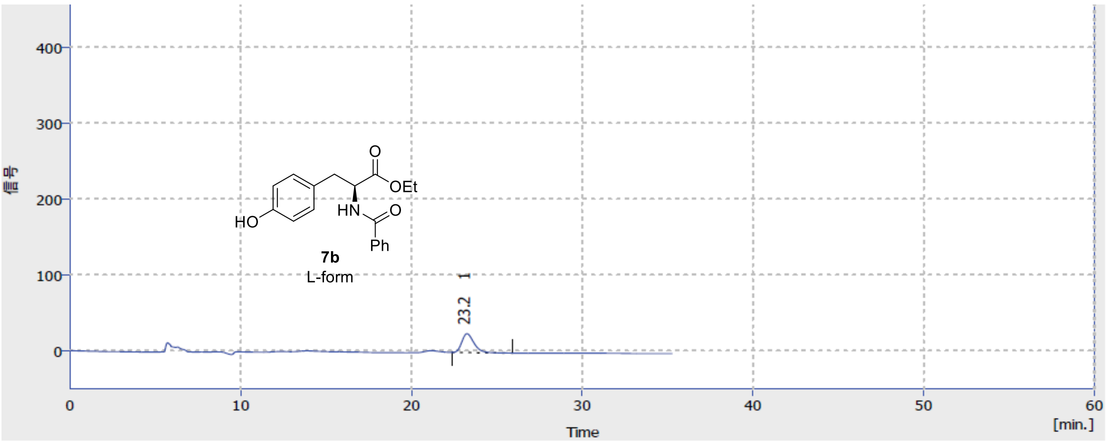
M\20181208\WSM-BING-OET-RAC - 检测器 1)

	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	9.922	1051.532	40.553	28.7
2	12.222	2610.611	116.990	71.3
	合计	3662.143	157.544	100.0



Ethyl benzoyl-L-tyrosinate (**7b**).[2] >99% ee was determined by chiral HPLC (chiralcel OD-H, n-hexane/2-propanol = 80/20, 0.5 mL/min, 254 nm). t_R = 14.79 min (minor) and 23.29 min (major). Authentic samples were independently prepared from L- and D-amino acids and their mixture was used as reference racemate.



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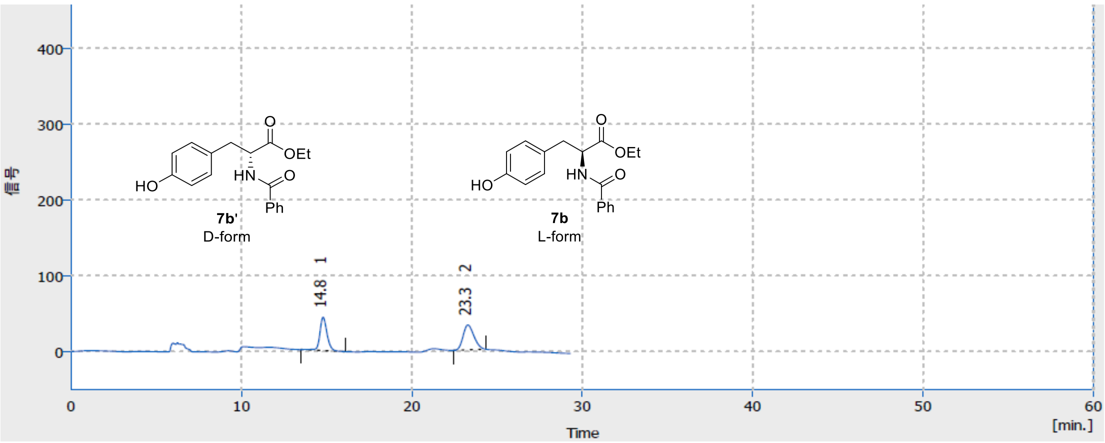
	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	23.247	1231.974	24.919	100.0
	合计	1231.974	24.919	100.0



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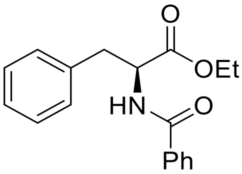
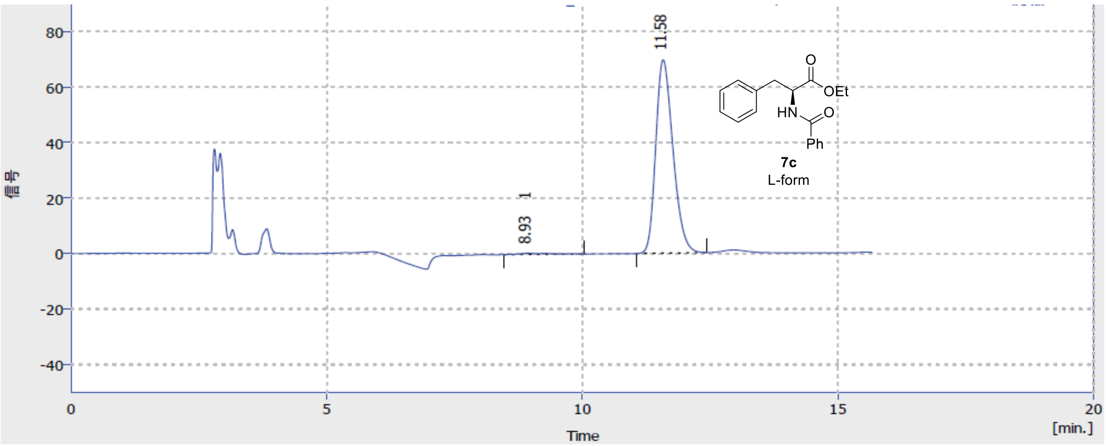
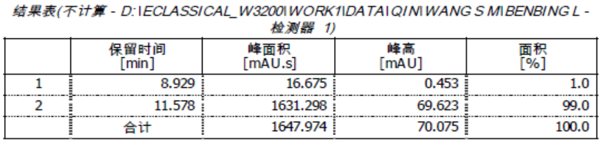
	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	14.788	1287.437	43.977	47.0
2	23.290	1453.636	32.855	53.0
	合计	2741.073	76.832	100.0



Ethyl benzoyl-L-phenylalaninate (**7c**).[1] 98% ee was determined by chiral HPLC (chiralcel OD-H, n-hexane/2-propanol = 90/10, 1.0 mL/min, 254 nm). t_R = 8.93 min (minor) and 11.58 min (major). Authentic samples were independently prepared from L- and D-amino acids and their mixture was used as reference racemate.

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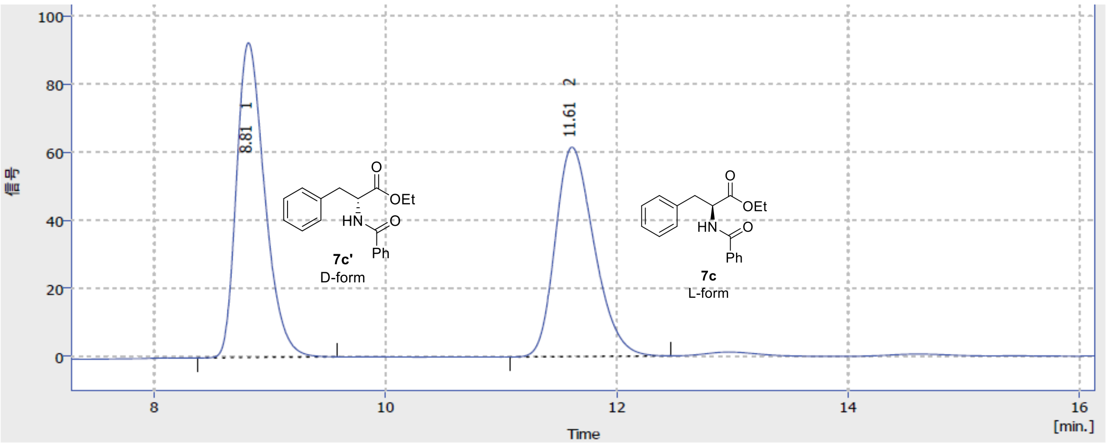
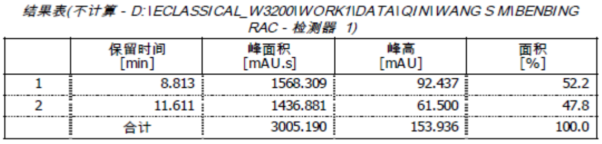
	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	8.929	16.675	0.453	1.0
2	11.578	1631.298	69.623	99.0
	合计	1647.974	70.075	100.0

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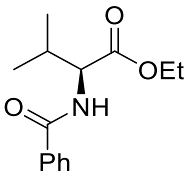
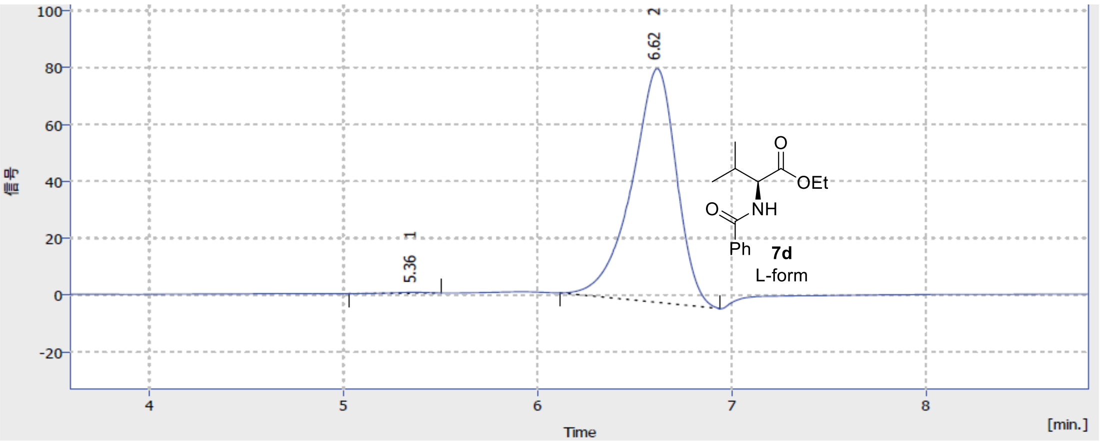
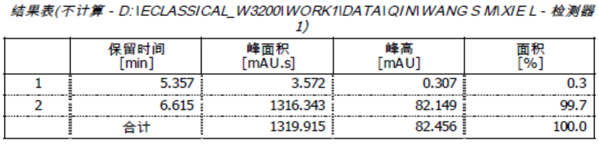
	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	8.813	1568.309	92.437	52.2
2	11.611	1436.881	61.500	47.8
	合计	3005.190	153.936	100.0



Ethyl benzoyl-L-valinate (**7d**).[3] 99% ee was determined by chiral HPLC (chiralcel OD-H, n-hexane/2-propanol = 90/10, 1.0 mL/min, 254 nm). t_R = 5.36 min (minor) and 6.62 min (major). Authentic samples were independently prepared from L- and D-amino acids and their mixture was used as reference racemate.

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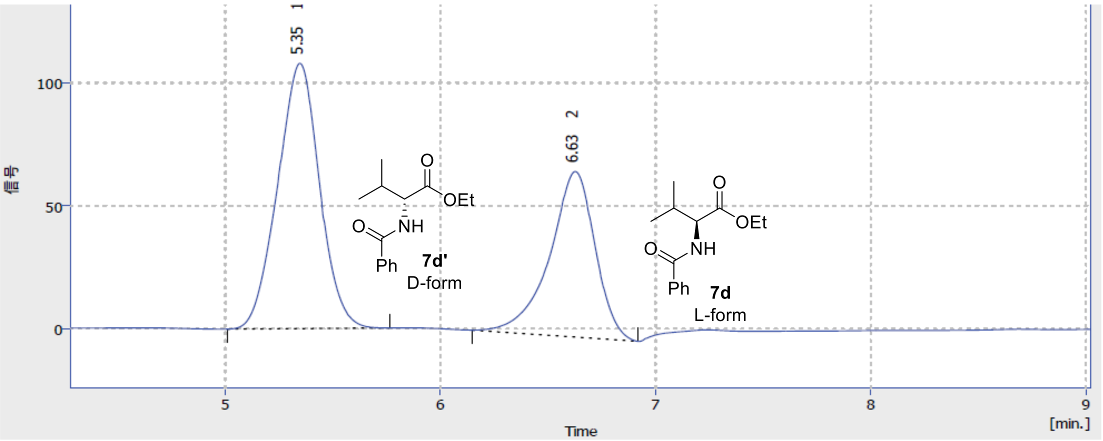
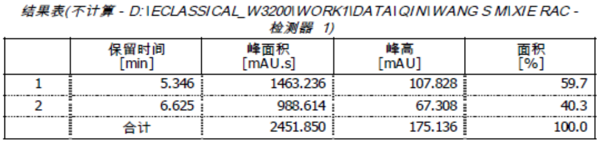
	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	5.357	3.572	0.307	0.3
2	6.615	1316.343	82.149	99.7
	合计	1319.915	82.456	100.0

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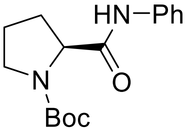
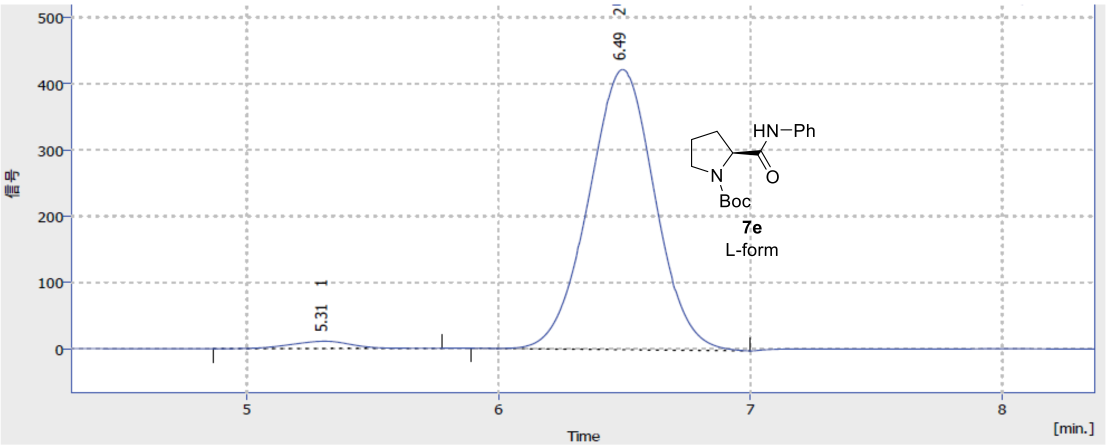
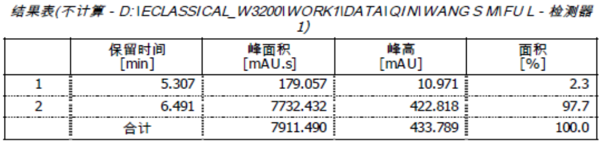
	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	5.346	1463.236	107.828	59.7
2	6.625	988.614	67.308	40.3
	合计	2451.850	175.136	100.0



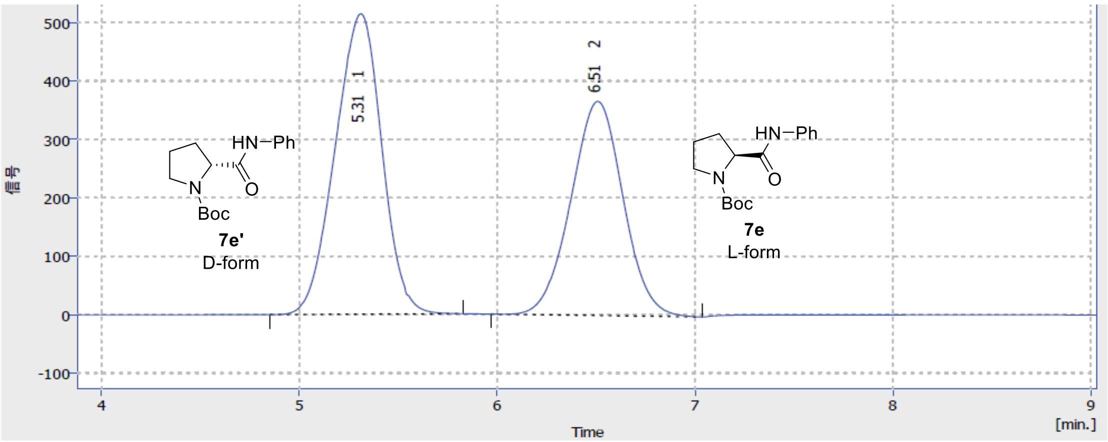
Tert-butyl (S)-2-(phenylcarbamoyl)pyrrolidine-1-carboxylate (**7e**).[4] 95% ee was determined by chiral HPLC (chiralcel OD-H, n-hexane/2-propanol = 90/10, 1.0 mL/min, 254 nm). t_R = 5.31 min. (minor) and 6.49 min. (major). Authentic samples were independently prepared from L- and D-amino acids and their mixture was used as reference racemate.

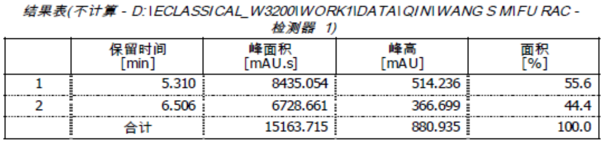




结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S M\FU L - 检测器 1)

	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	5.307	179.057	10.971	2.3
2	6.491	7732.432	422.818	97.7
	合计	7911.490	433.789	100.0





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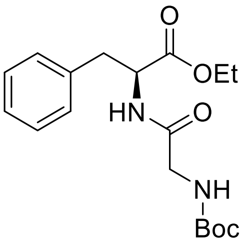
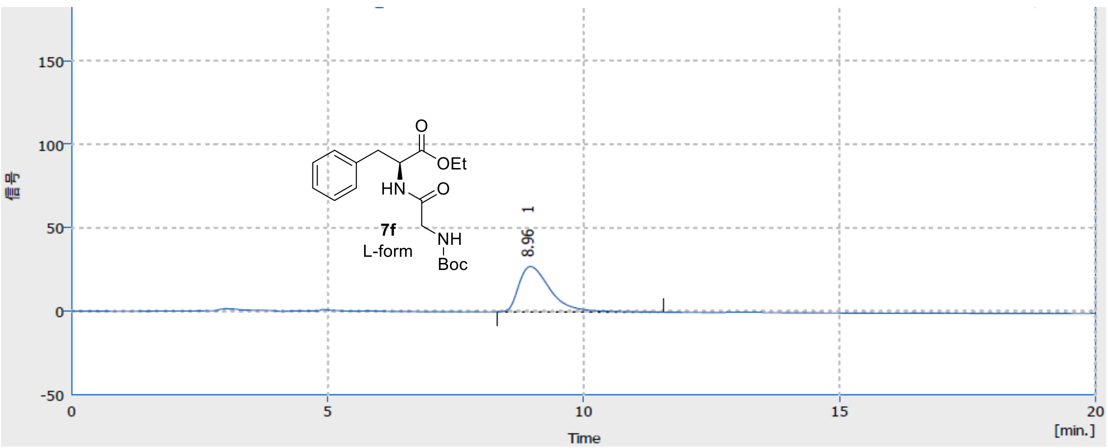
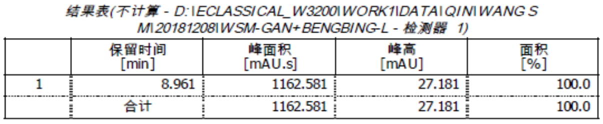
	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	5.310	8435.054	514.236	55.6
2	6.506	6728.661	366.699	44.4
	合计	15163.715	880.935	100.0



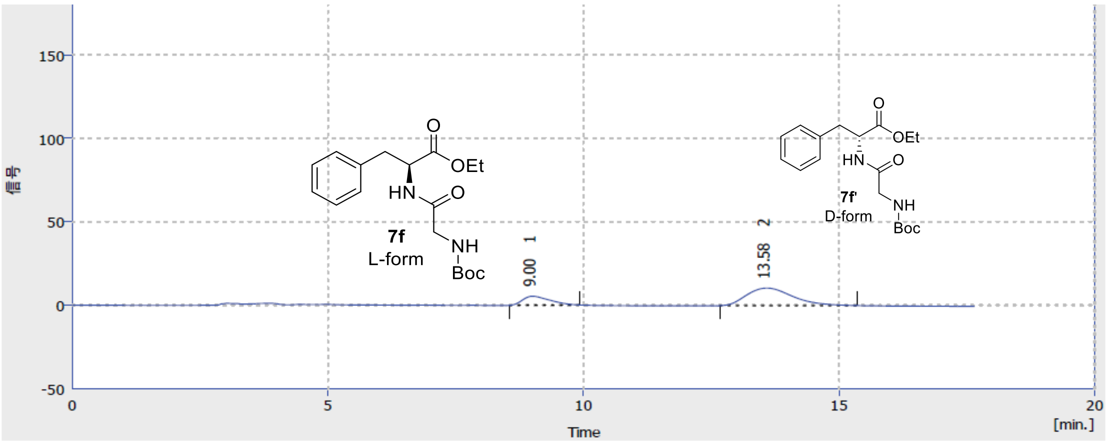
Ethyl (tert-butoxycarbonyl)glycyl-L-phenylalaninate (**7f**).[5] >99% ee was determined by chiral HPLC (chiralcel IC, n-hexane/2-propanol = 80/20, 1.0 mL/min, 254 nm). t_R = 8.96 min (major) and 13.58 min (minor). Authentic samples were independently prepared from L- and D-amino acids and their mixture was used as reference racemate.

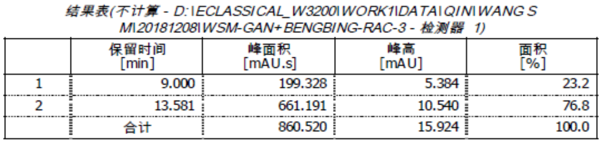




结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S M\20181208\WSM-GAN+BENGBING-L - 检测器 1)

	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	8.961	1162.581	27.181	100.0
	合计	1162.581	27.181	100.0





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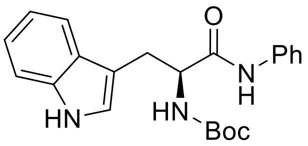
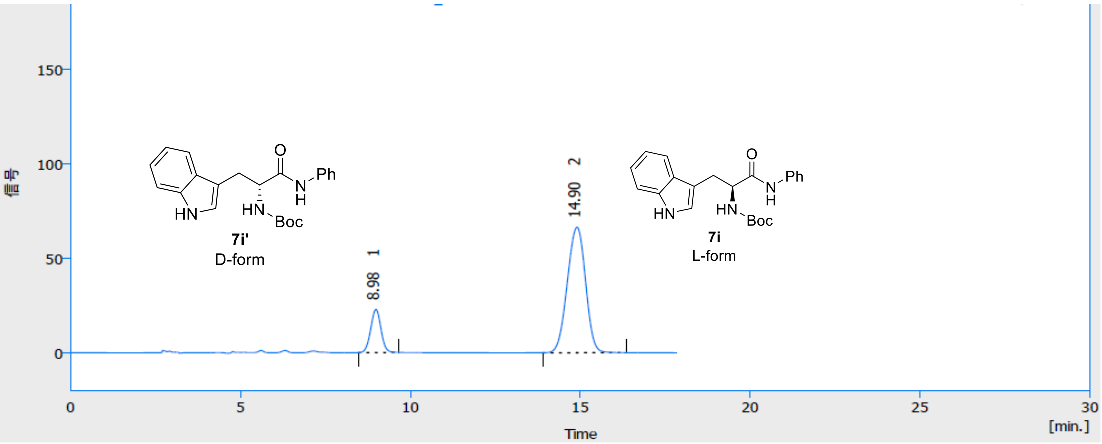
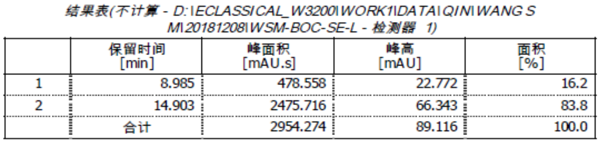
	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	9.000	199.328	5.384	23.2
2	13.581	661.191	10.540	76.8
	合计	860.520	15.924	100.0

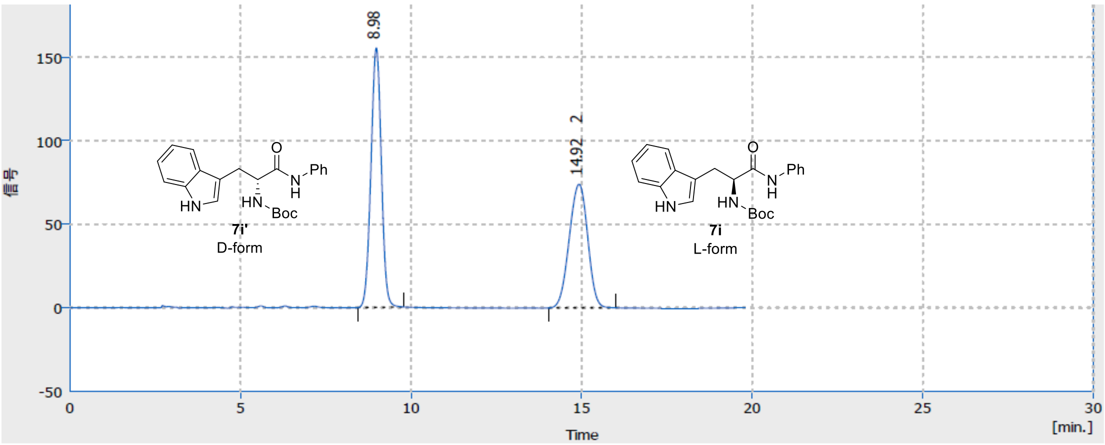


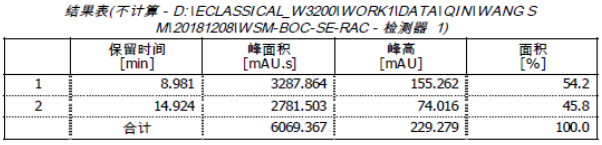
Tert-butyl-(3-(1H-indol-3-yl)-1-oxo-1-(phenylamino)propan-2-yl)carbamate (**7i**).[4] Petroleum ether / ethyl acetate = 2 : 1 (v /v) as eluent for column chromatography. White solid, 322.6 mg, 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.95 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.98 (s, 1H), 5.39 (s, 1H), 4.63 (s, 1H), 3.30 (d, *J* = 31.0 Hz, 2H), 1.42 (s, 9H). $[\alpha]_D^{25}$ = -26.3 (c = 0.10, $CHCl_3$). 68% ee was determined by chiral HPLC (chiralcel IA, n-hexane/2-propanol = 80/20, 1.0 mL/min, 254 nm). t_R = 8.98 min (major) and 14.90 min (minor). Authentic samples were independently prepared from L- and D-amino acids and their mixture was used as reference racemate.



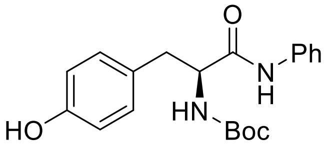

结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S M\20181208\WSM-BOC-SE-L - 检测器 1)

	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	8.985	478.558	22.772	16.2
2	14.903	2475.716	66.343	83.8
	合计	2954.274	89.116	100.0

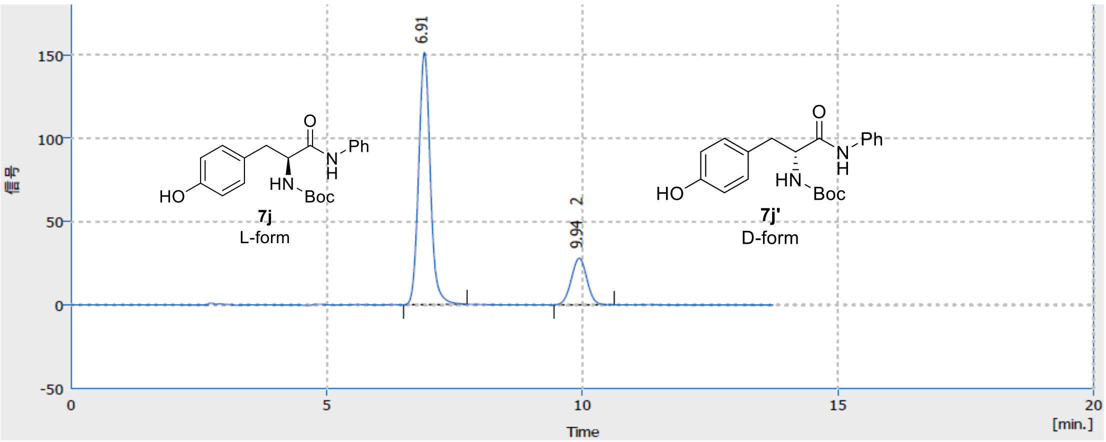



结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S M\20181208\WSM-BOC-SE-RAC - 检测器 1)

	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	8.981	3287.864	155.262	54.2
2	14.924	2781.503	74.016	45.8
	合计	6069.367	229.279	100.0

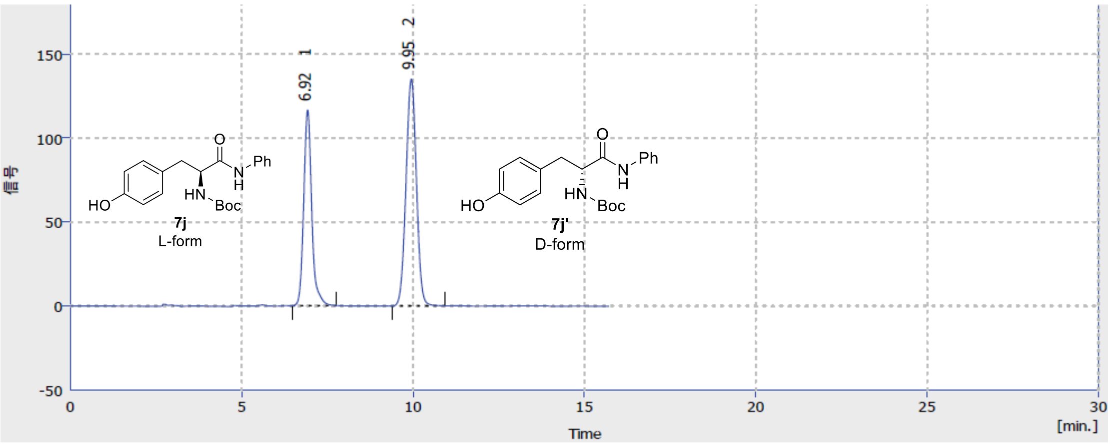


Tert-butyl-(3-(4-hydroxyphenyl)-1-oxo-1-(phenylamino)propan-2-yl)carbamate (**7j**).[4] Petroleum ether / ethyl acetate = 2 : 1 (v /v) as eluent for column chromatography. White solid, 352.9 mg, 99% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.39 (d, *J* = 7.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.31-7.26 (m, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 7.2 Hz, 1H), 5.40 (d, *J* = 8.0 Hz, 1H), 4.57 (s, 1H), 3.29-3.16 (m, 1H), 3.08 (dd, *J* = 13.6, 7.1 Hz, 1H), 1.39 (s, 9H). $[\alpha]_D^{25}$ = -61.4 (c = 0.10, $CHCl_3$). 60% ee was determined by chiral HPLC (chiralcel IA, n-hexane/2-propanol = 80/20, 1.0 mL/min, 254 nm). t_R = 6.91 min (major) and 9.94 min (minor). Authentic samples were independently prepared from L- and D-amino acids and their mixture was used as reference racemate.



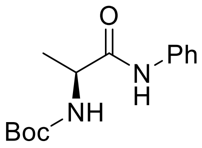
结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S M\20181208\WSM-BOC-LAO-L - 检测器 1)

	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	6.910	2392.661	151.121	80.2
2	9.937	592.146	27.973	19.8
	合计	2984.807	179.094	100.0

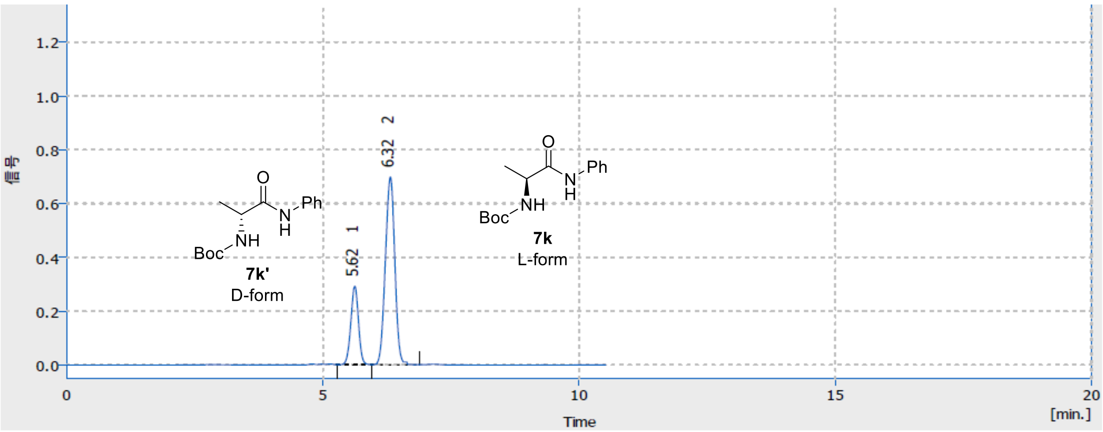


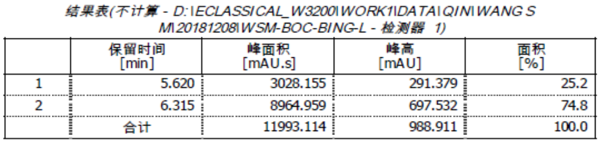
结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S M\20181208\WSM-BOC-LAO-RAC - 检测器 1)

	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	6.923	1902.427	116.497	40.0
2	9.948	2857.365	135.060	60.0
	合计	4759.792	251.557	100.0



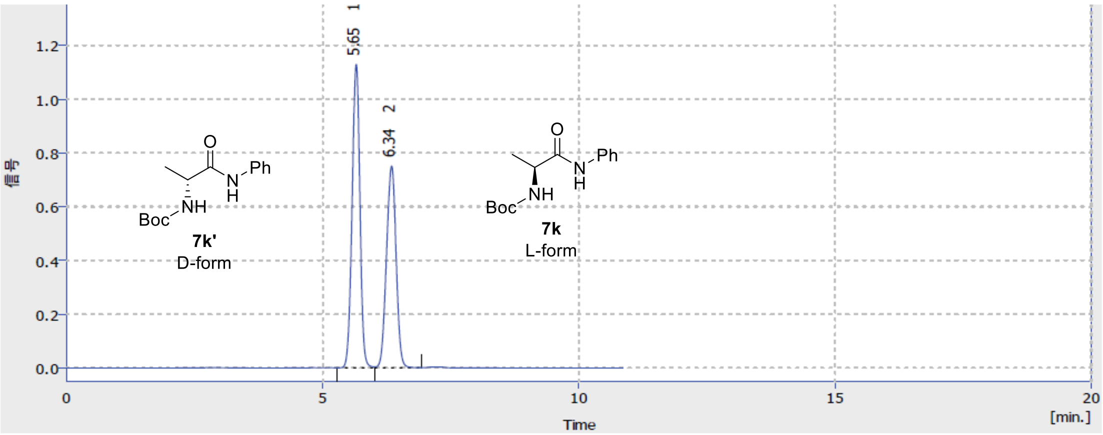
Tert-butyl-(1-oxo-1-(phenylamino)propan-2-yl)carbamate (**7k**).[4] Petroleum ether / ethyl acetate = 3 : 1 (v /v) as eluent for column chromatography. White solid, 259.0 mg, 98% yield. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.75 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.29 (t, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.10-7.04 (m, 1H), 5.41 (d, *J* = 5.2 Hz, 1H), 4.40 (s, 1H), 1.45 (s, 9H), 1.43 (d, *J* = 7.1 Hz, 3H). $[\alpha]_D^{25}$ = +12.6 (c = 0.10, MeOH). 50% ee was determined by chiral HPLC (chiralcel IA, n-hexane/2-propanol = 80/20, 1.0 mL/min, 254 nm). t$_R$ = 5.62 min (minor) and 6.32 min (major). Authentic samples were independently prepared from L- and D-amino acids and their mixture was used as reference racemate.

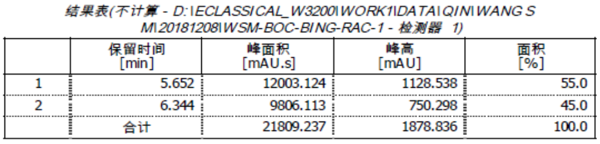




结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S M\20181208\WSM-BOC-BING-L - 检测器 1)

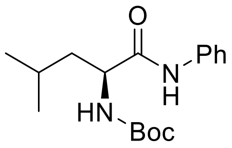
	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	5.620	3028.155	291.379	25.2
2	6.315	8964.959	697.532	74.8
	合计	11993.114	988.911	100.0



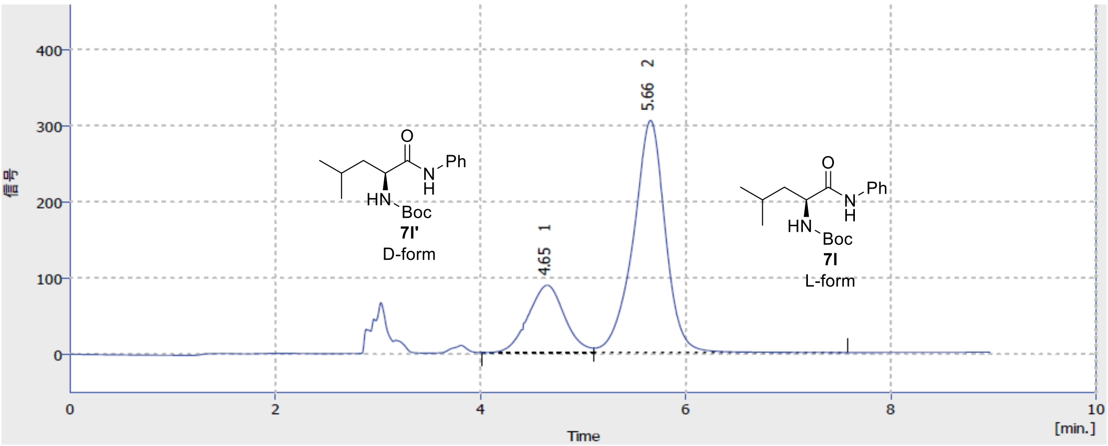


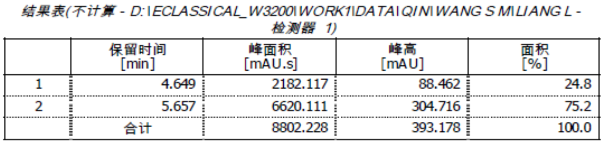
结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S M\20181208\WSM-BOC-BING-RAC-1 - 检测器 1)

	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	5.652	12003.124	1128.538	55.0
2	6.344	9806.113	750.298	45.0
	合计	21809.237	1878.836	100.0



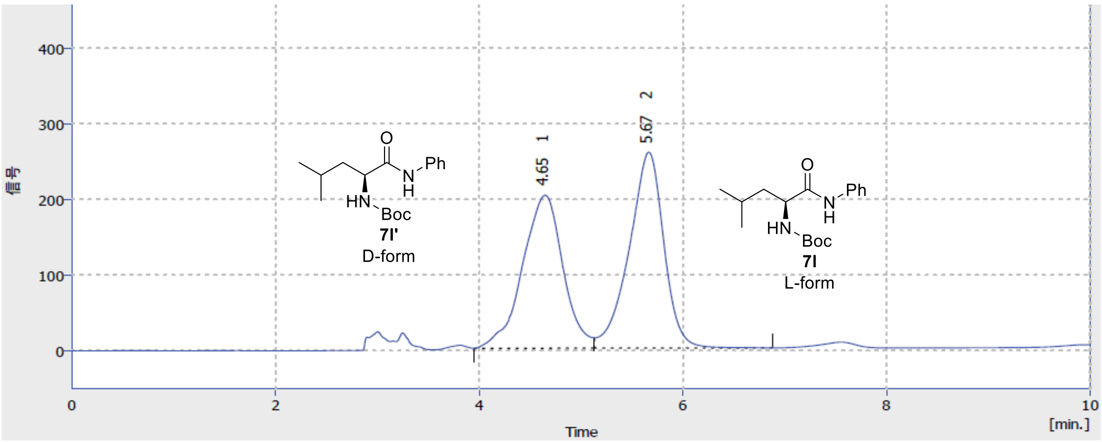
Tert-butyl-(4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)carbamate (**7l**). [4] Petroleum ether / ethyl acetate = 2 : 1 (v /v) as eluent for column chromatography. White solid, 281.9 mg, 92% yield. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.92 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.9 Hz, 2H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 4.13 (dd, *J* = 13.7, 9.0 Hz, 1H), 1.67-1.62 (m, 1H), 1.56-1.50 (m, 1H), 1.44 (dd, *J* = 8.3, 5.6 Hz, 1H), 1.38 (s, 9H), 0.89 (dd, *J* = 6.3, 4.2 Hz, 6H). $[\alpha]_D^{25}$ = +36.6 (c = 0.10, MeOH). 50% ee was determined by chiral HPLC (chiralcel IA, n-hexane/2-propanol = 80/20, 1.0 mL/min, 254 nm). t$_R$ = 4.65 min (minor) and 5.66 min (major). Authentic samples were independently prepared from L- and D-amino acids and their mixture was used as reference racemate.

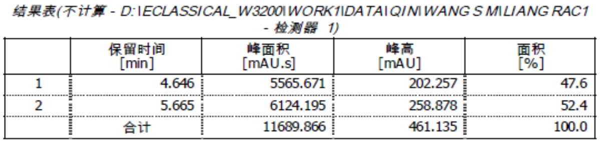




结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S M\LIANG L - 检测器 1)

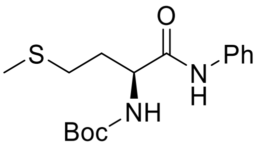
	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	4.649	2182.117	88.462	24.8
2	5.657	6620.111	304.716	75.2
	合计	8802.228	393.178	100.0



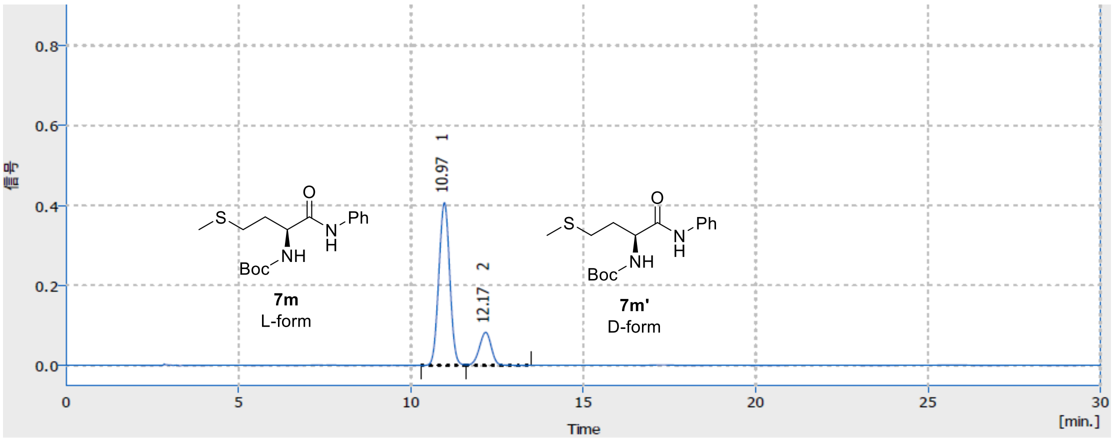


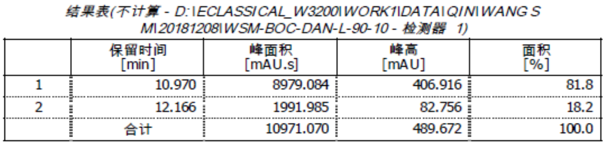
结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S M\LIANG RAC1 - 检测器 1)

	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	4.646	5565.671	202.257	47.6
2	5.665	6124.195	258.878	52.4
	合计	11689.866	461.135	100.0



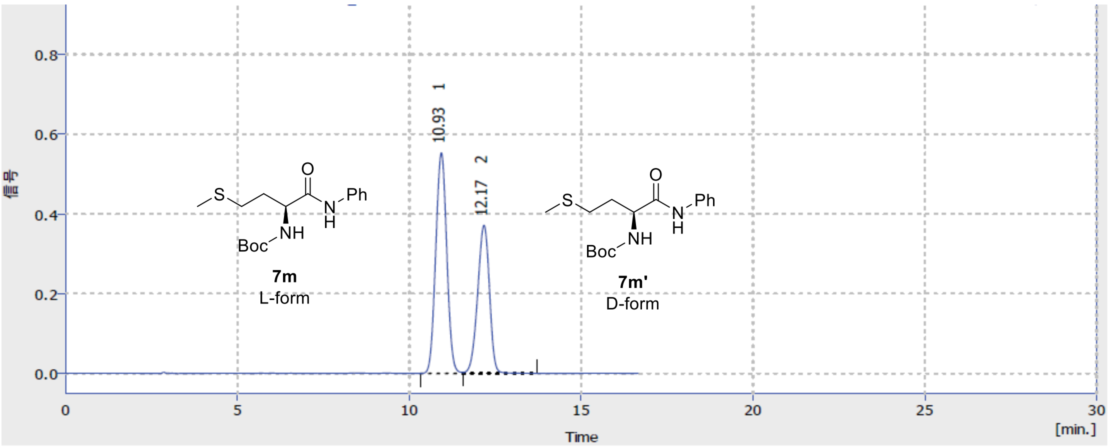
Tert-butyl-(4-(methylthio)-1-oxo-1-(phenylamino)butan-2-yl)carbamate (**7m**). [4] Petroleum ether / ethyl acetate = 3 : 1 (v /v) as eluent for column chromatography. White solid, 269.3 mg, 83% yield. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.63 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.29 (t, *J* = 6.5 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 5.50 (d, *J* = 0.5 Hz, 1H), 4.47 (s, 1H), 2.61 (dd, *J* = 12.4, 6.6 Hz, 2H), 2.18 (td, *J* = 13.5, 6.7 Hz, 1H), 2.10 (s, 3H), 2.01 (dd, *J* = 14.3, 7.0 Hz, 1H), 1.44 (s, 9H). $[\alpha]_D^{25}$ = -5.9 (c = 0.10, MeOH). 64% ee was determined by chiral HPLC (chiralcel IA, n-hexane/2-propanol = 90/10, 1.0 mL/min, 254 nm). t_R = 10.97 min (major) and 12.17 min (minor). Authentic samples were independently prepared from L- and D-amino acids and their mixture was used as reference racemate.

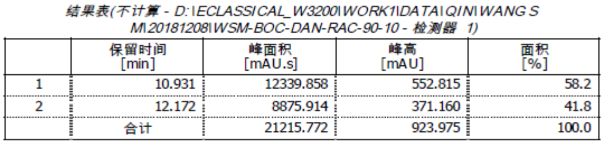




结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S M\20181208\WSM-BOC-DAN-L-90-10 - 检测器 1)

	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	10.970	8979.084	406.916	81.8
2	12.166	1991.985	82.756	18.2
	合计	10971.070	489.672	100.0





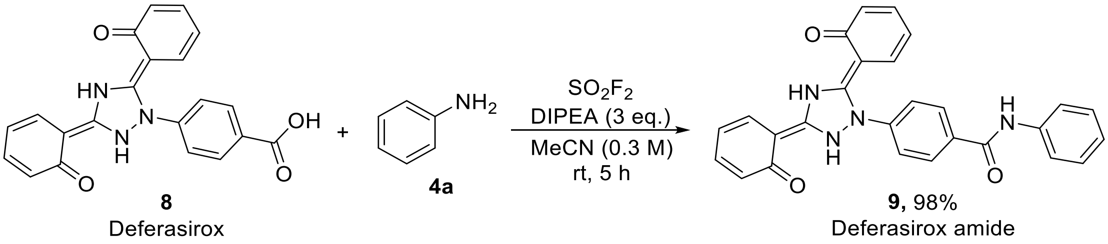
结果表(不计算 - D:\ECLASSICAL_W3200\WORK1\DATA\QIN\WANG S M\20181208\WSM-BOC-DAN-RAC-90-10 - 检测器 1)

	保留时间 [min]	峰面积 [mAU.s]	峰高 [mAU]	面积 [%]
1	10.931	12339.858	552.815	58.2
2	12.172	8875.914	371.160	41.8
	合计	21215.772	923.975	100.0

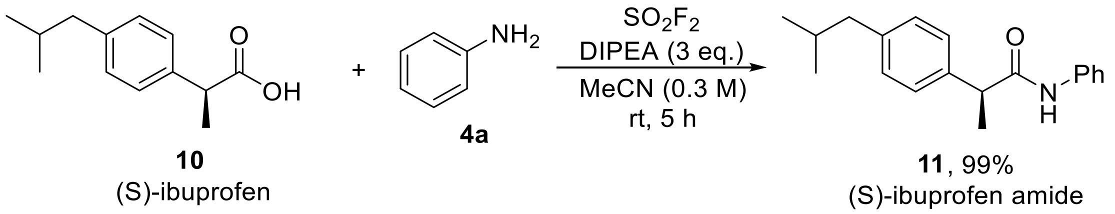
4. General procedures for the gram scale reactions

Carboxylic acid (**1**, 1.0 equiv), amine (**4**, 2.0 equiv), DIPEA (3.0 equiv) and MeCN (reaction mixture was diluted to 0.3 M) were added to an oven-dried 100 mL round bottom flask equipped with a stirring bar and covered with a rubber stopper. Sulfuryl fluoride gas was introduced into the stirred reaction mixture by slowly bubbling from a balloon. The reaction mixture was stirred at room temperature for 5 h. After the reaction was completed, 1 M aqueous HCl solution (3 × 20 mL) was added to remove the excess amine and the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The extracts were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the desired product.

5. Procedures for the synthesis of compound 9, 11, 14 and 17.



Deferasirox (**8**, 1.0 mmol, 1.0 equiv), aniline (**4a**, 2.0 mmol, 2.0 equiv), DIPEA (3.0 mmol, 3.0 equiv) and MeCN (reaction mixture was diluted to 0.3 M) were added to an oven-dried 25 mL reaction flask equipped with a stirring bar and covered with a rubber stopper. Sulfuryl fluoride gas was introduced into the stirred reaction mixture by slowly bubbling from a balloon. The reaction mixture was stirred at room temperature for 5 h. After the reaction was completed, the reaction mixture was directly concentrated under vacuum. The residue was purified by column chromatography on silica gel using petroleum ether / ethyl acetate = 1 : 1 (v /v) as eluents to give amide **9** in 98% yield.

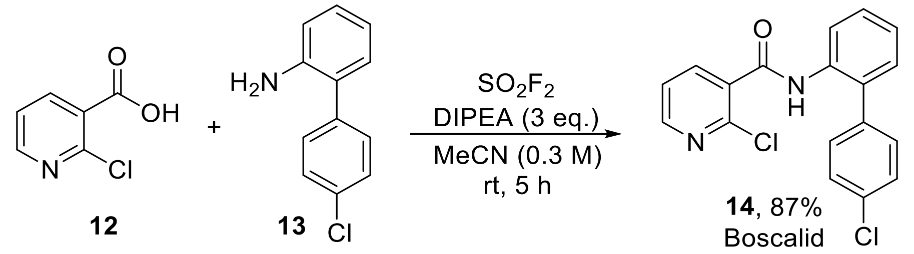


10
(S)-ibuprofen

4a

11, 99%
(S)-ibuprofen amide

(S)-ibuprofen (**10**, 1.0 mmol, 1.0 equiv), aniline (**4a**, 2.0 mmol, 2.0 equiv), DIPEA (3.0 mmol, 3.0 equiv) and MeCN (reaction mixture was diluted to 0.3 M) were added to an oven-dried 25 mL reaction flask equipped with a stirring bar and covered with a rubber stopper. Sulfuryl fluoride gas was introduced into the stirred reaction mixture by slowly bubbling from a balloon. The reaction mixture was stirred at room temperature for 5 h. After the reaction was completed, 1 M aqueous HCl solution (10 mL) was added to remove the excess amine and the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The extracts were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether / ethyl acetate = 2 : 1 (v /v) as eluents to give amide **11** in 99% yield.

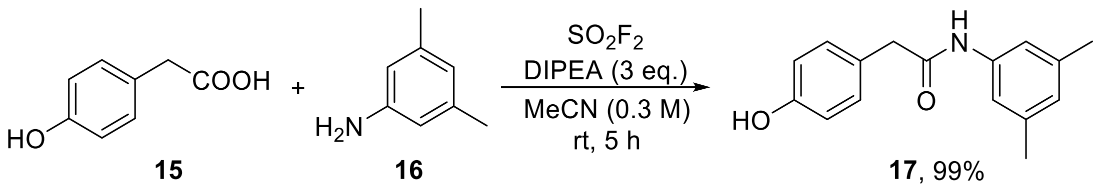


12

13

14, 87%
Boscalid

2-Chloronicotinic acid (**12**, 1.0 mmol, 1.0 equiv), 4'-chloro-[1,1'-biphenyl]-2-amine (**13**, 2.0 mmol, 2.0 equiv), DIPEA (3.0 mmol, 3.0 equiv) and MeCN (reaction mixture was diluted to 0.3 M) were added to an oven-dried 25 mL reaction flask equipped with a stirring bar and covered with a rubber stopper. Sulfuryl fluoride gas was introduced into the stirred reaction mixture by slowly bubbling from a balloon. The reaction mixture was stirred at room temperature for 5 h. After the reaction was completed, the reaction mixture was directly concentrated under vacuum. The residue was purified by column chromatography on silica gel using petroleum ether / ethyl acetate = 1 : 1 (v /v) as eluents to give amide **14** in 87% yield.



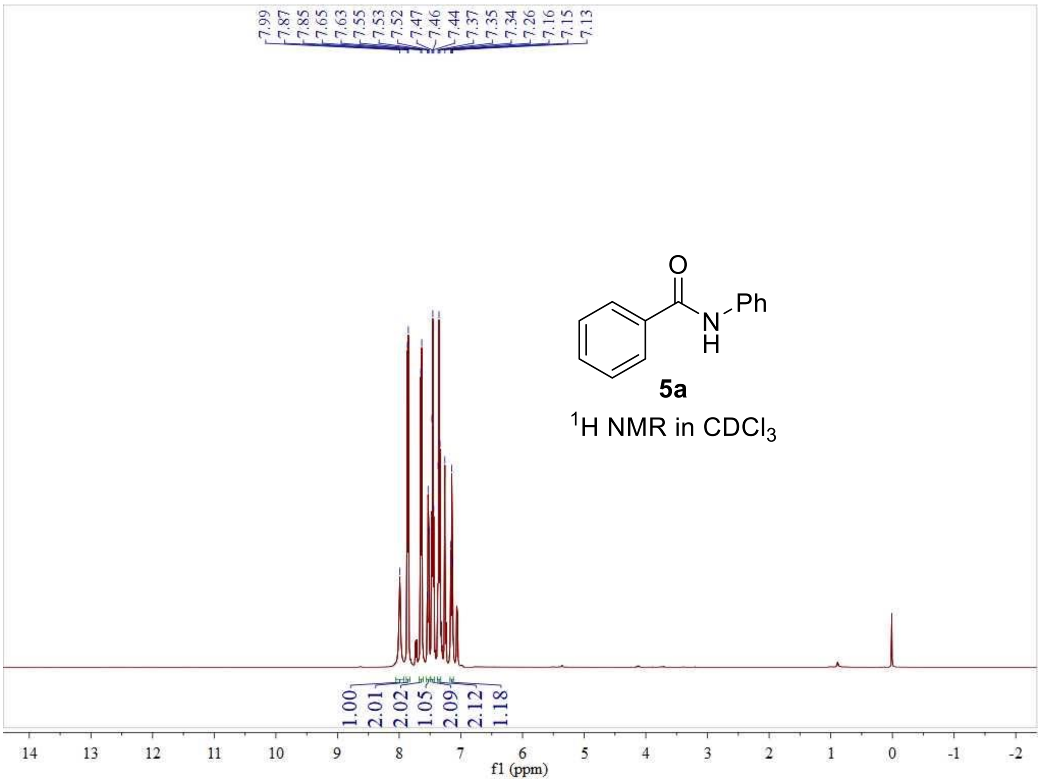
15

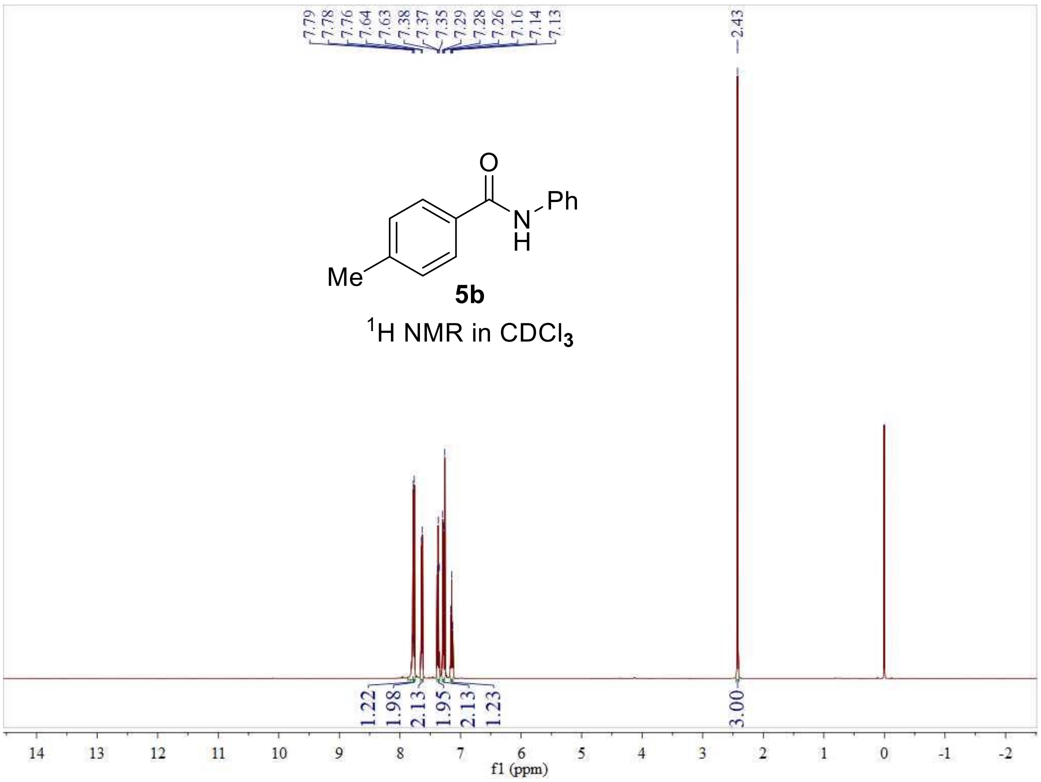
16

17, 99%

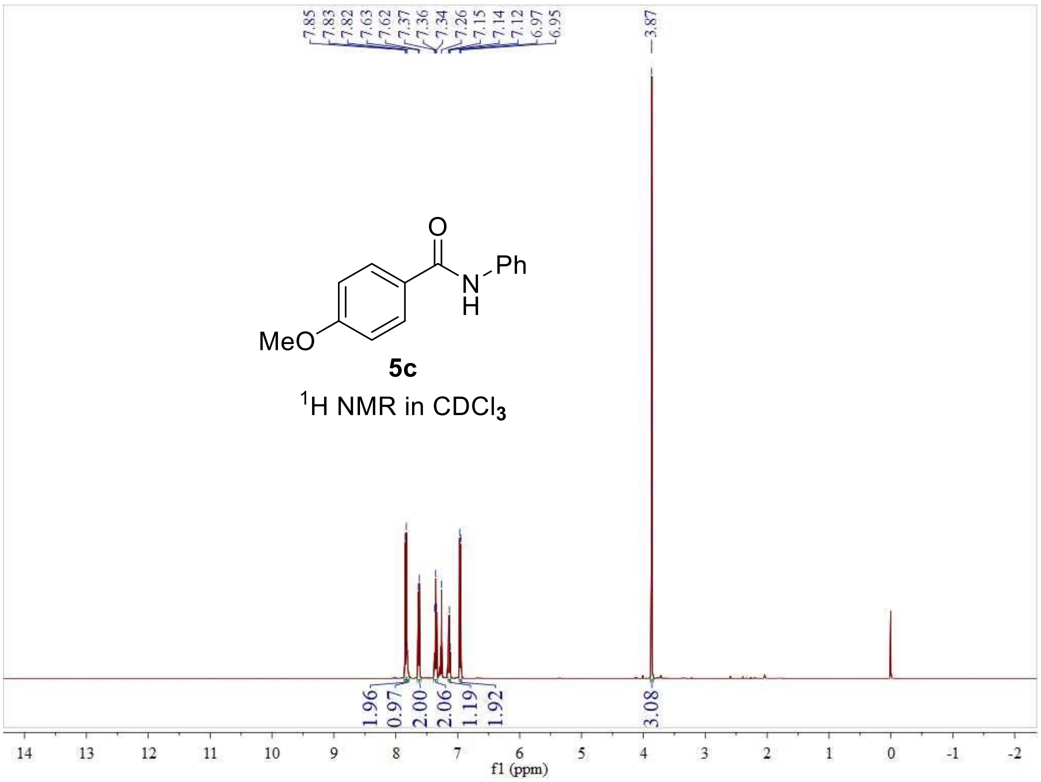
2-(4-hydroxyphenyl)acetic acid (**15**, 1.0 mmol, 1.0 equiv), 3,5-dimethylaniline (**16**, 2.0 mmol, 2.0 equiv), DIPEA (3.0 mmol, 3.0 equiv) and MeCN (reaction mixture was diluted to 0.3 M) were added to an oven-dried 25 mL reaction flask equipped with a stirring bar and covered with a rubber stopper. Sulfuryl fluoride gas was introduced into the stirred reaction mixture by slowly bubbling from a balloon. The reaction mixture was stirred at room temperature for 5 h. After the reaction was completed, 1 M aqueous HCl solution (10 mL) was added to remove the excess amine and the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The extracts were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether / ethyl acetate = 2 : 1 (v /v) as eluents to give amide **17** in 99% yield.

6. NMR spectra of 5, 6, 7, 9, 11, 14 and 17

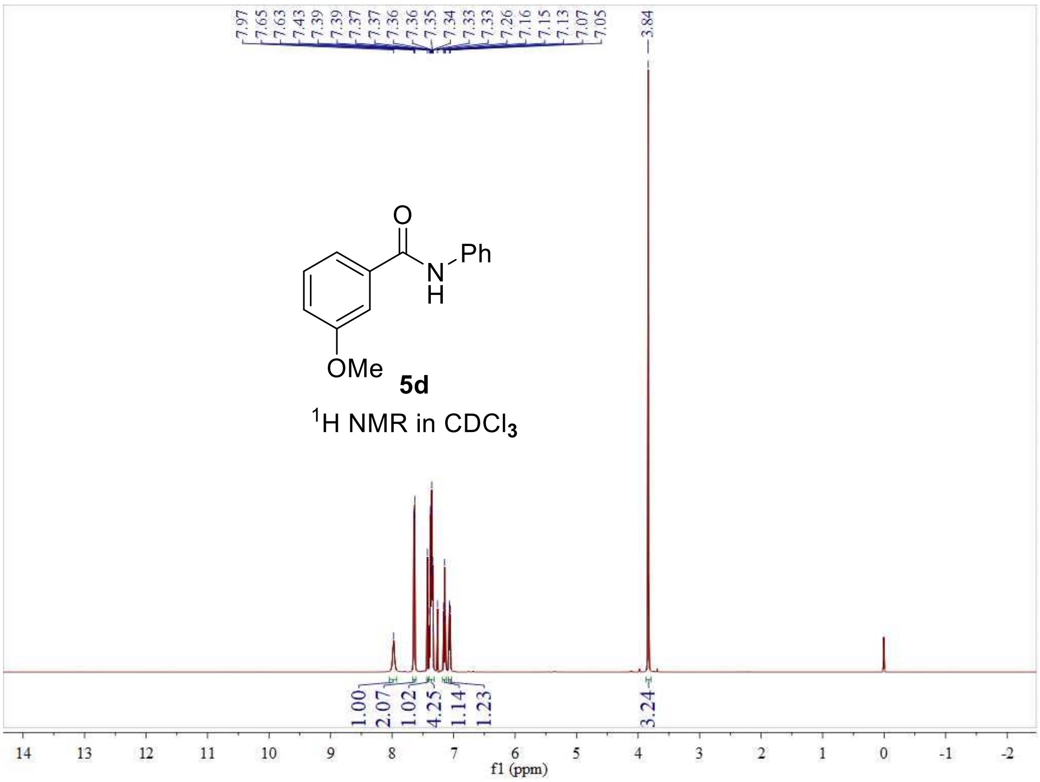



5b

^{1}H NMR in $CDCl_3$

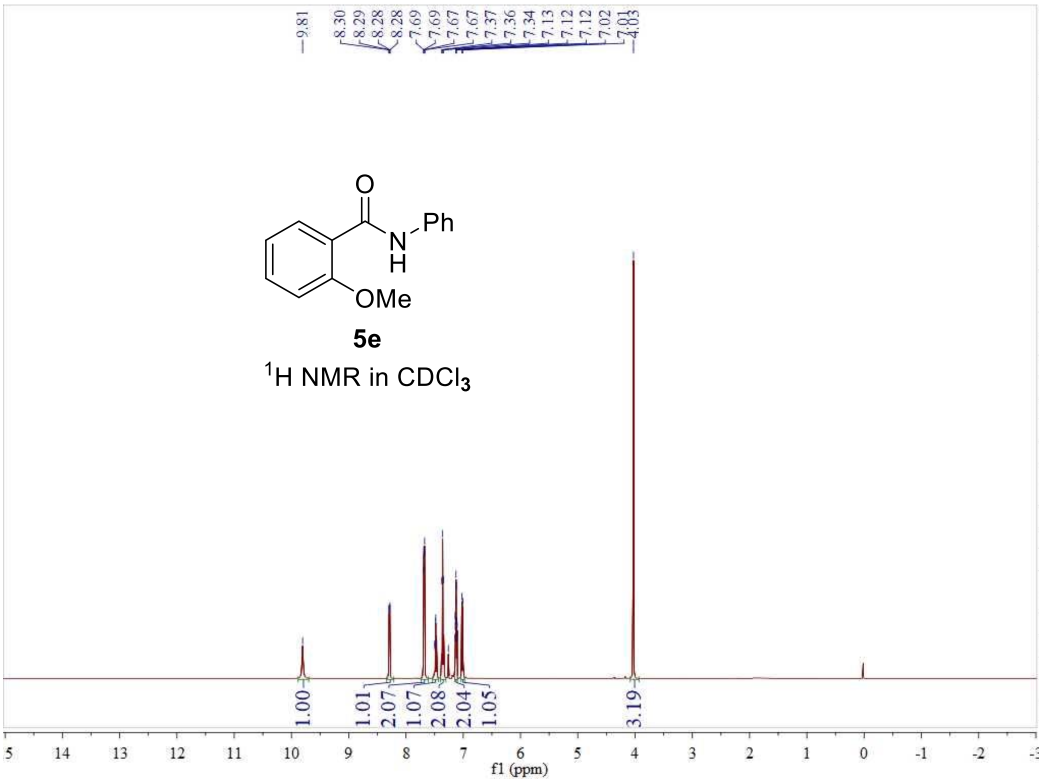

5c

^{1}H NMR in $CDCl_3$



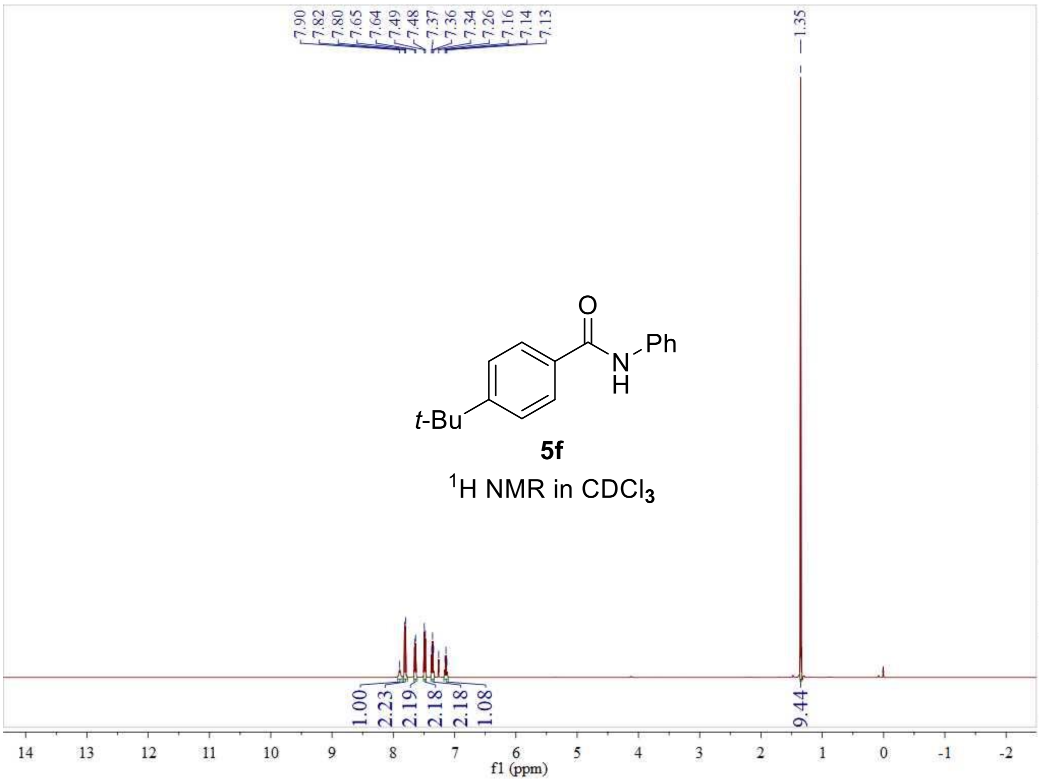
5d

^{1}H NMR in $CDCl_3$



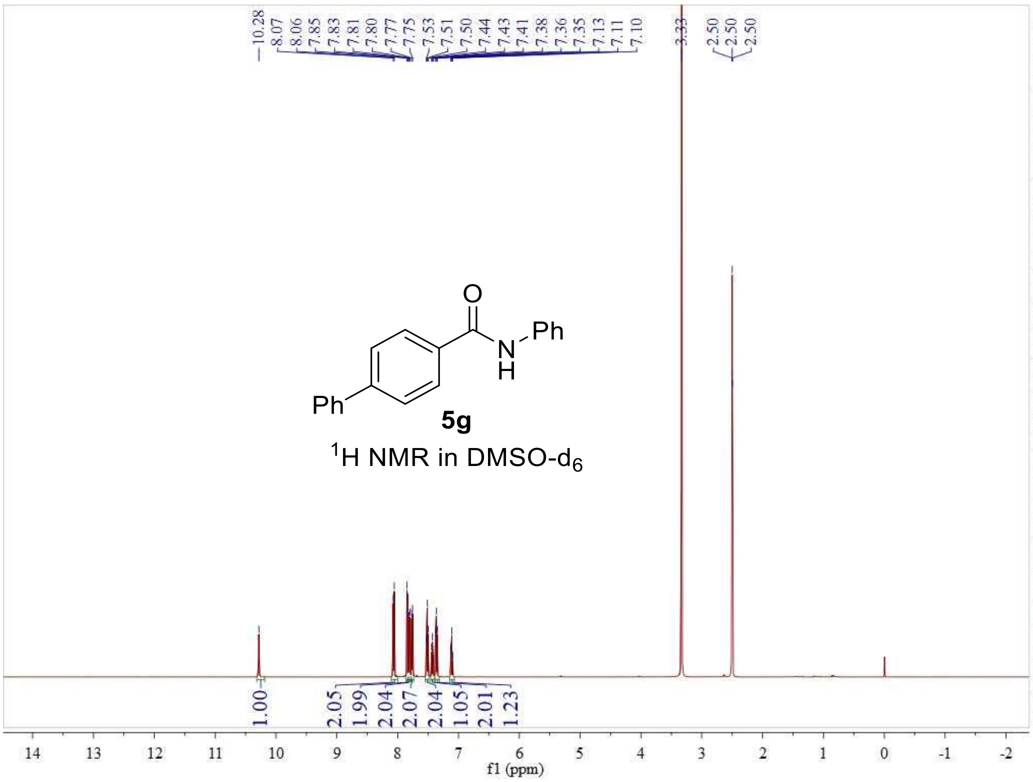
5e

^{1}H NMR in $CDCl_3$



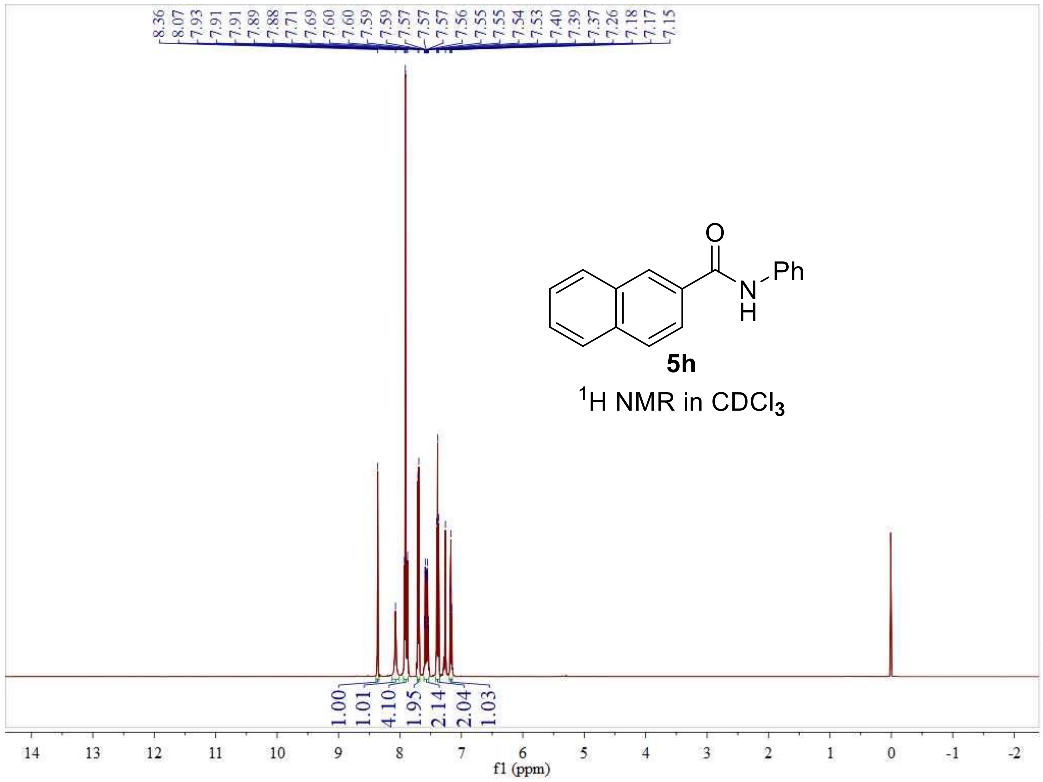
5f

^{1}H NMR in CDCl$_3$



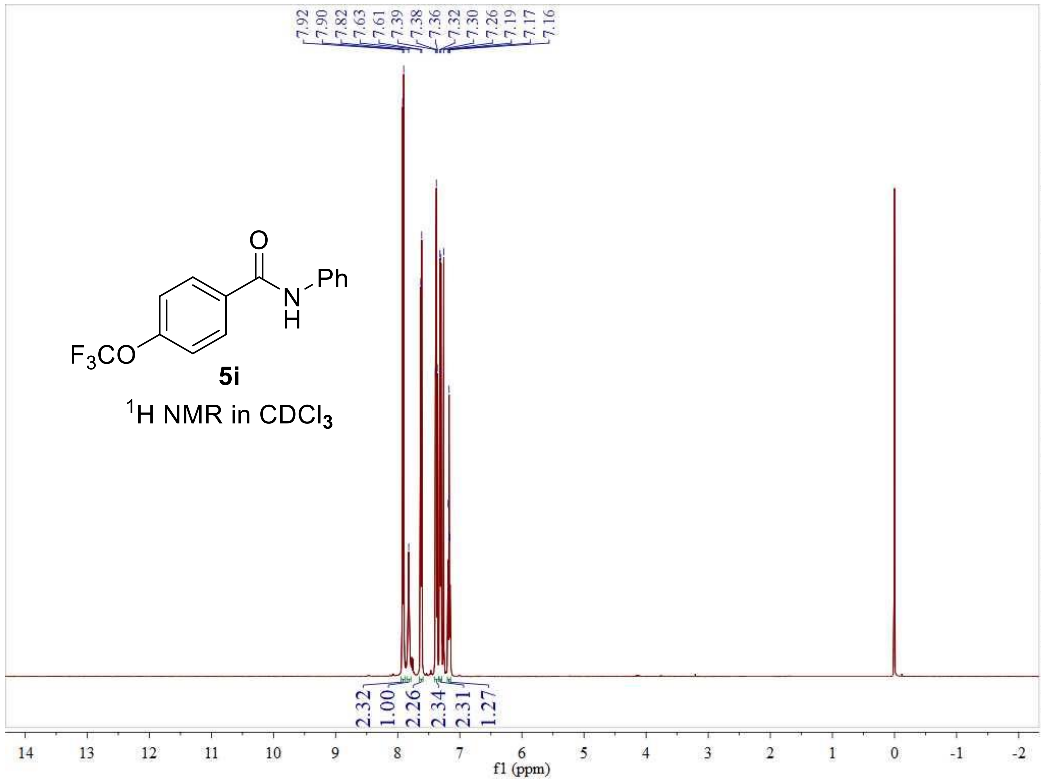
5g

^{1}H NMR in DMSO-d$_6$



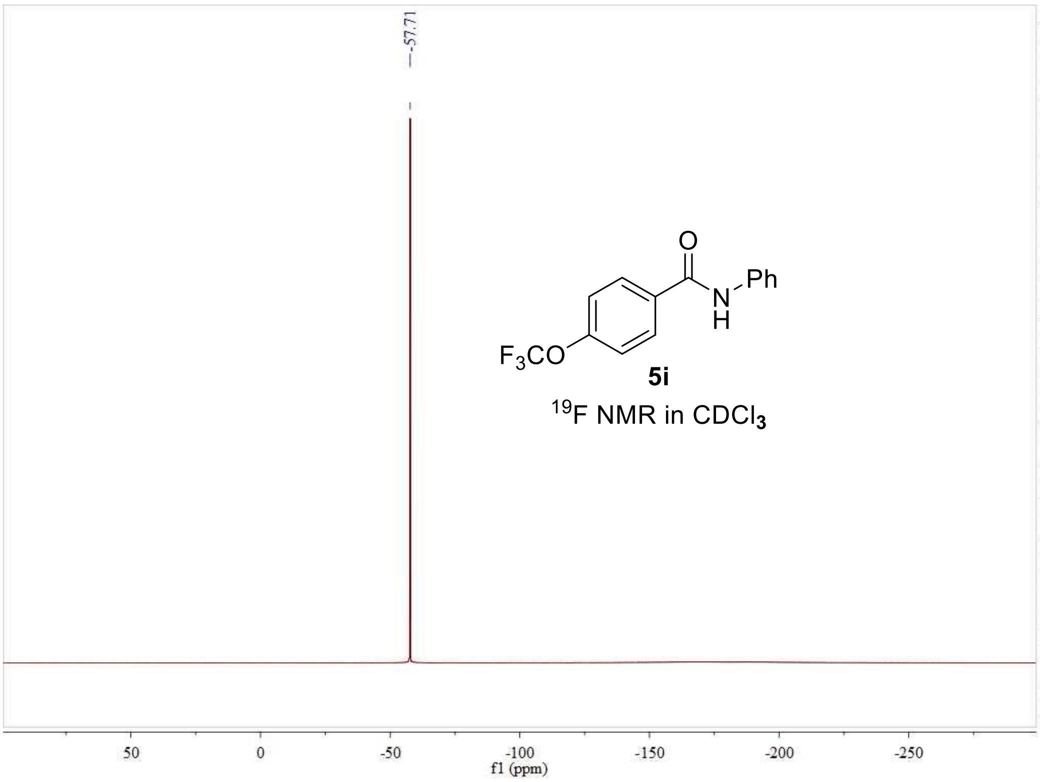
5h

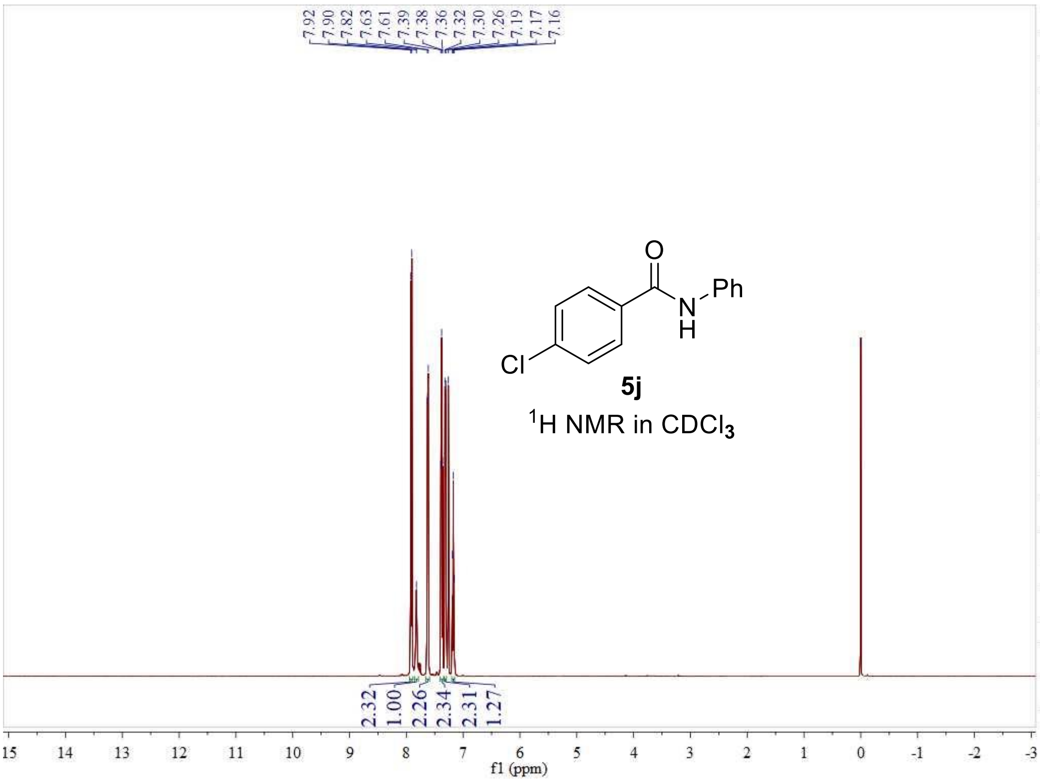
^{1}H NMR in $CDCl_3$

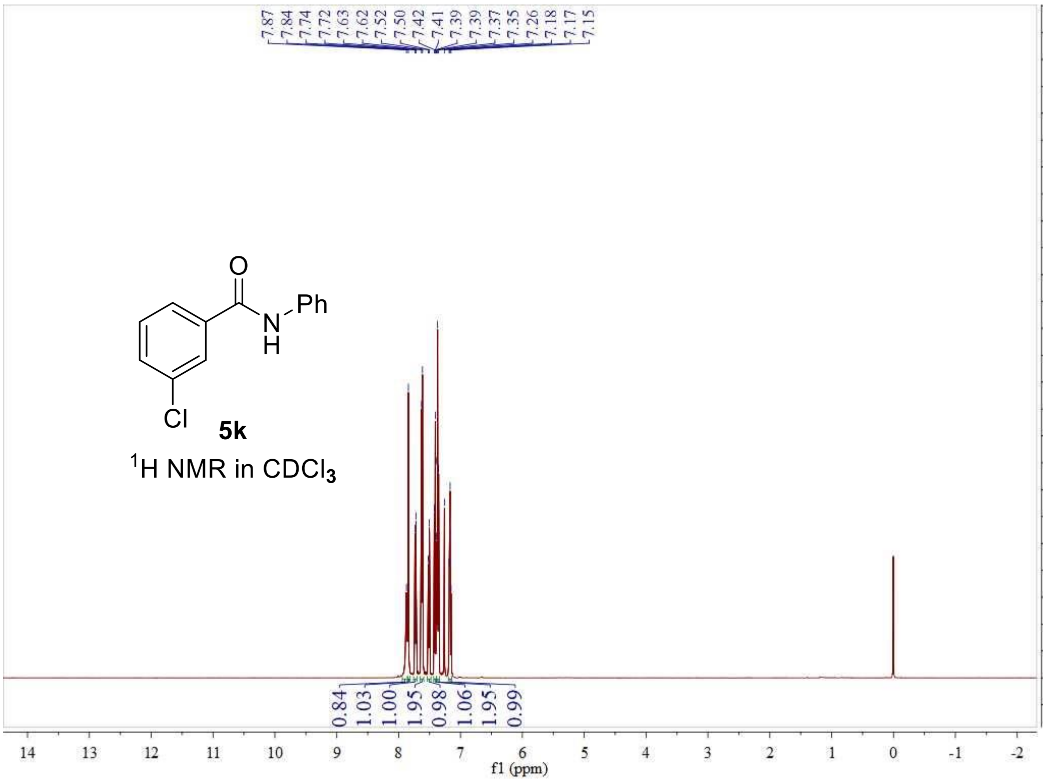


5i

^{1}H NMR in $CDCl_3$

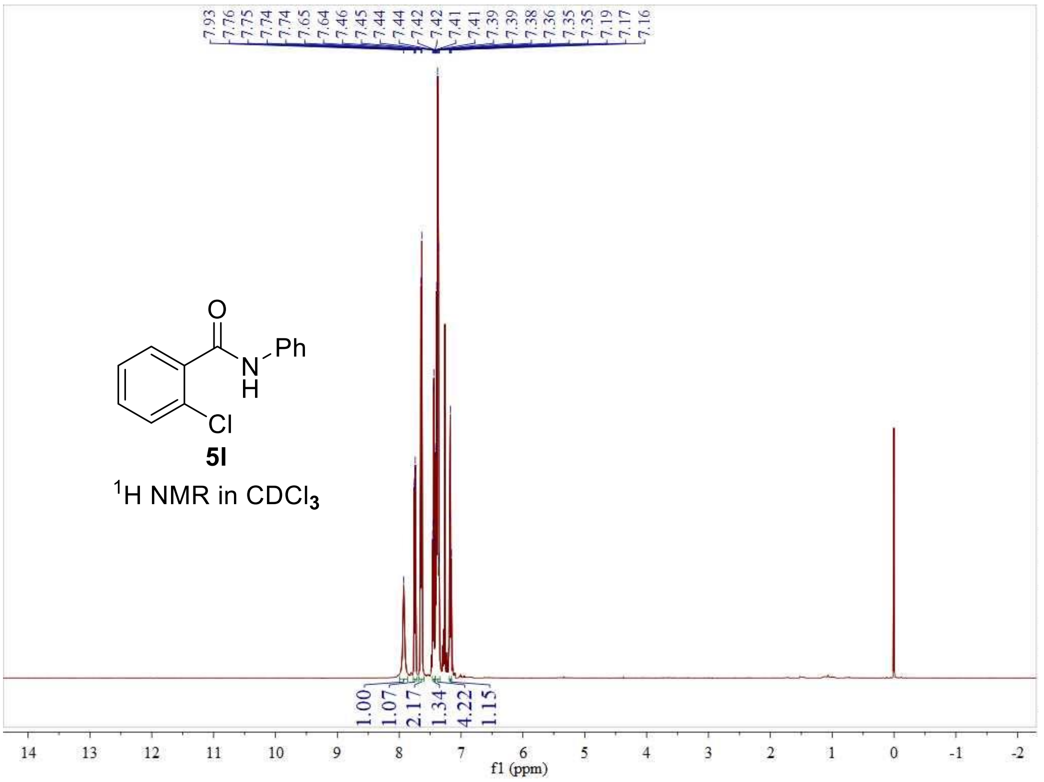

-57.71
O
N
H
Ph
F3CO
5i
19F NMR in CDCl3
50
0
-50
-100
-150
-200
-250
f1 (ppm)


7.92
7.90
7.82
7.63
7.61
7.39
7.38
7.36
7.32
7.30
7.26
7.19
7.17
7.16
O
N
H
Ph
Cl
5j
1H NMR in CDCl3
2.32
1.00
2.26
2.34
2.31
1.27
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)



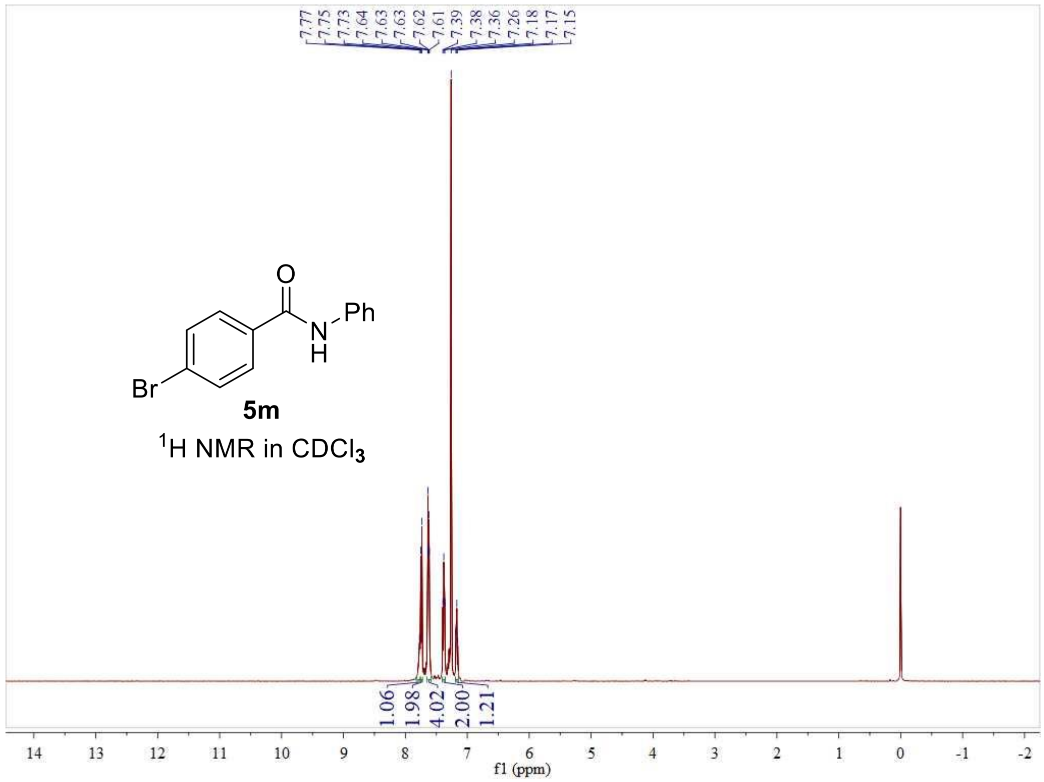
5k

^{1}H NMR in $CDCl_3$

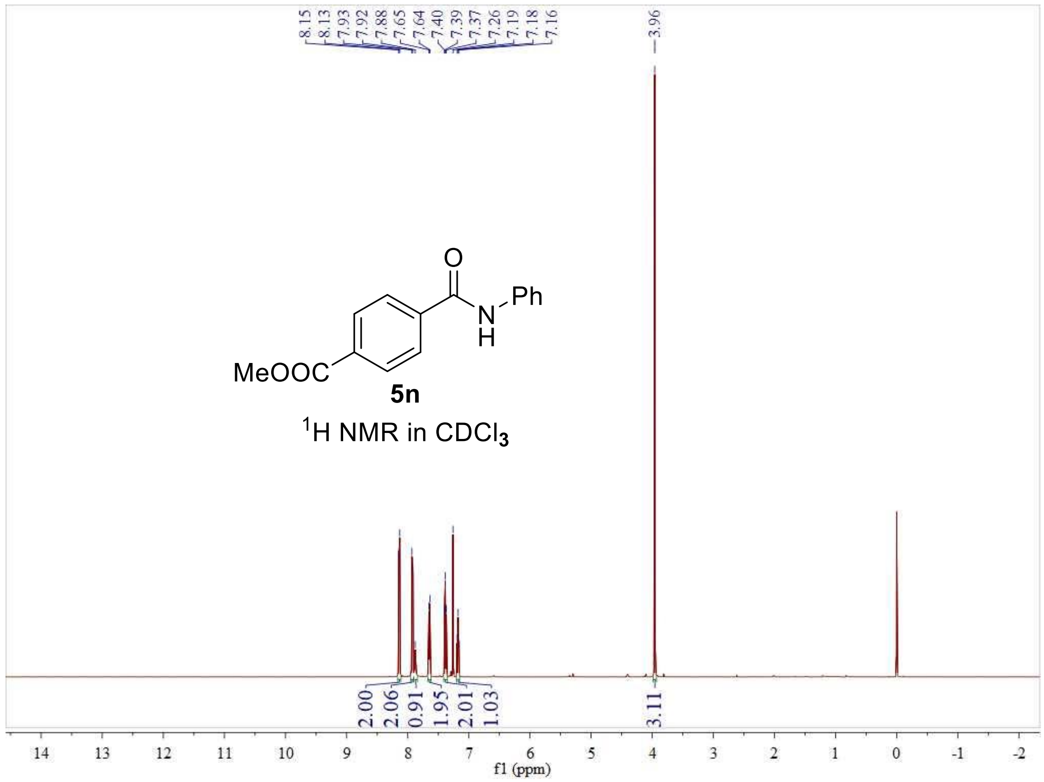


5l

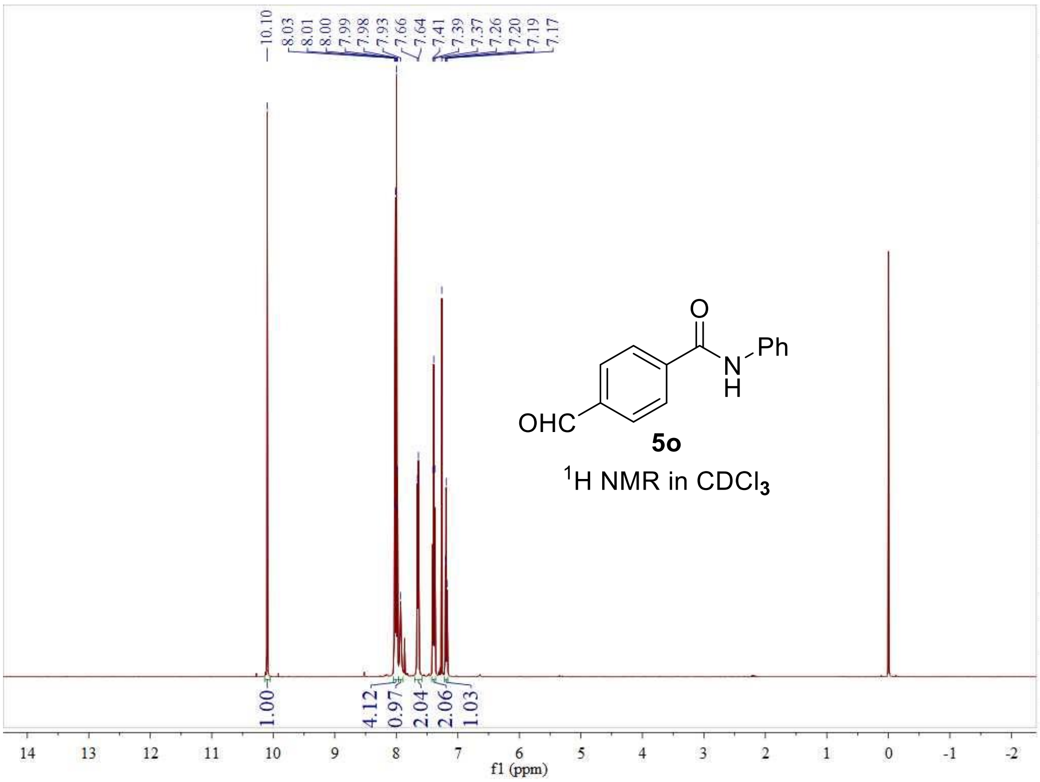
^{1}H NMR in $CDCl_3$


5m

^{1}H NMR in $CDCl_3$


5n

^{1}H NMR in $CDCl_3$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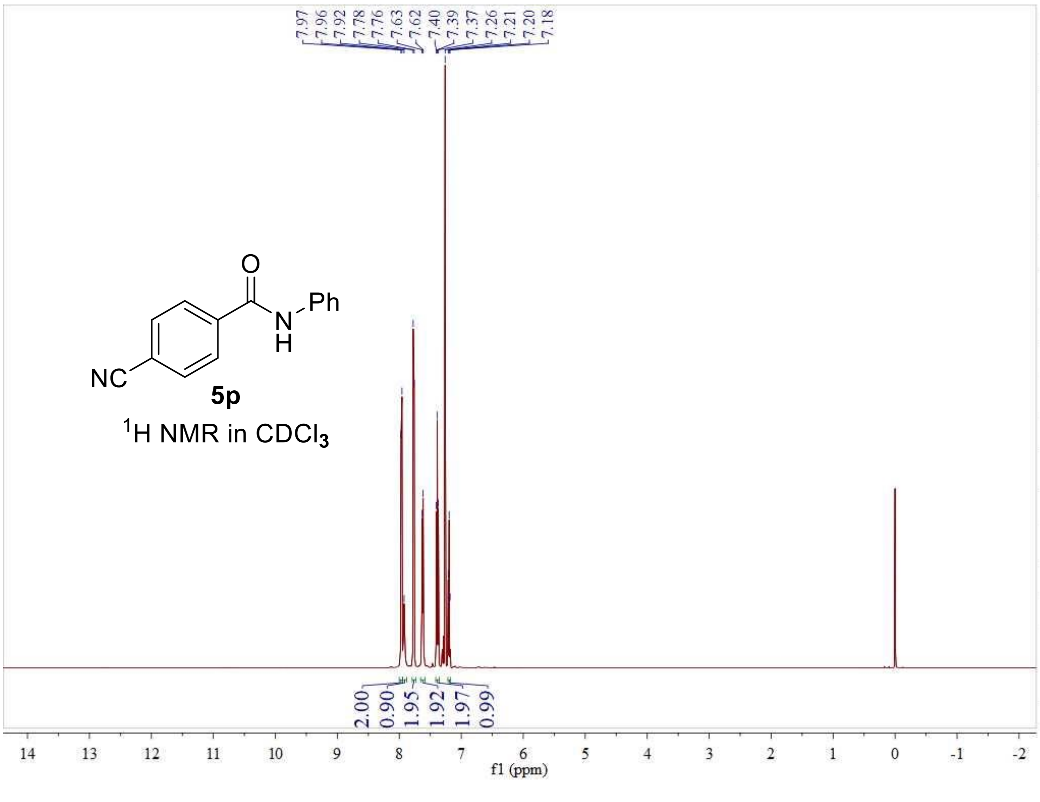
8.03
8.01
8.00
7.99
7.98
7.93
7.66
7.64
7.41
7.39
7.37
7.26
7.20
7.19
7.17
O
N
H
Ph
OHC
5o
1H NMR in CDCl3
1.00
4.12
0.97
2.04
2.06
1.03
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)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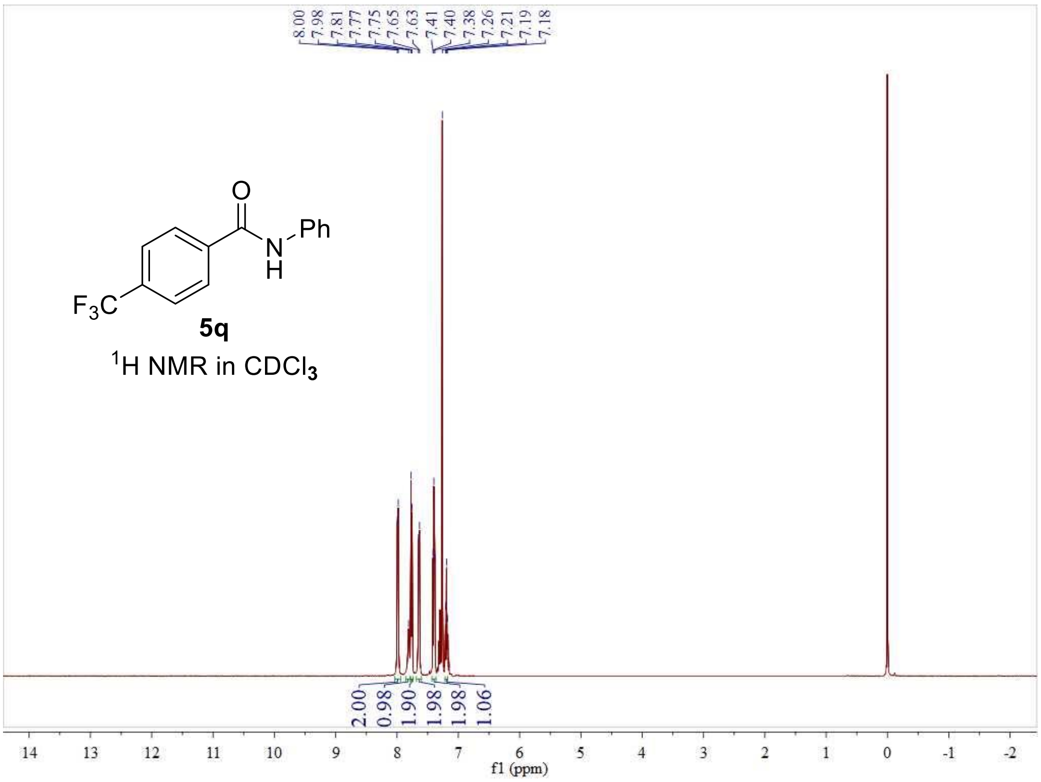
7.96
7.92
7.78
7.76
7.63
7.62
7.40
7.39
7.37
7.26
7.21
7.20
7.18
O
N
H
Ph
NC
5p
1H NMR in CDCl3
2.00
0.90
1.95
1.92
1.97
0.99
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)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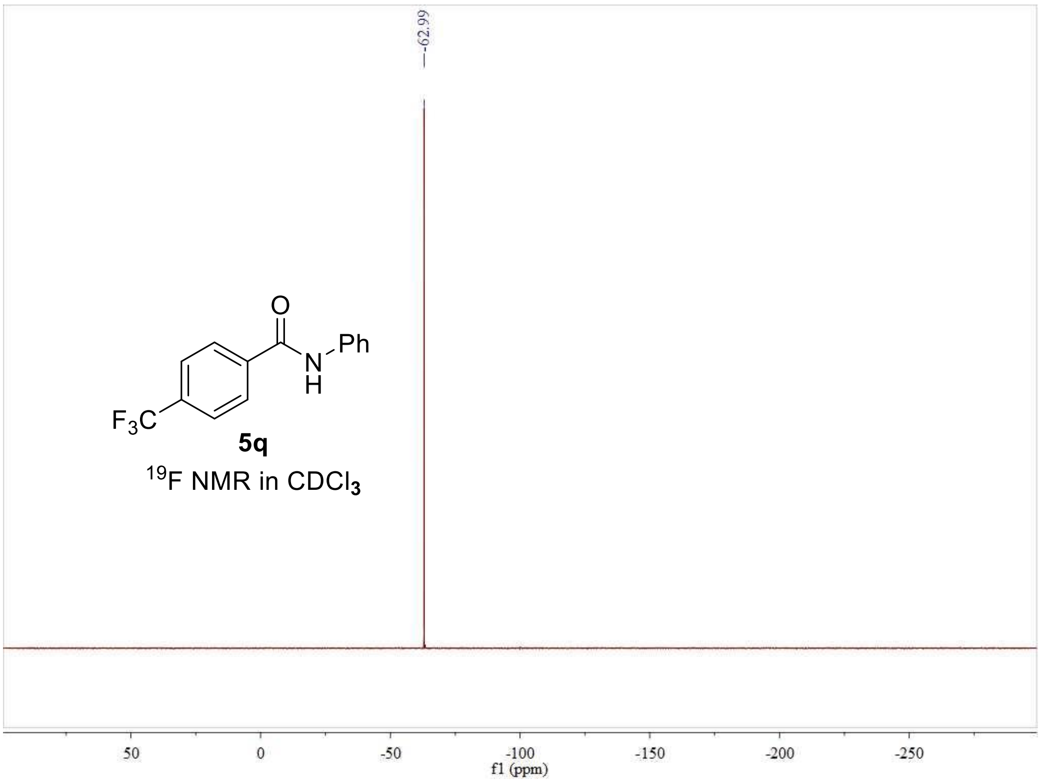
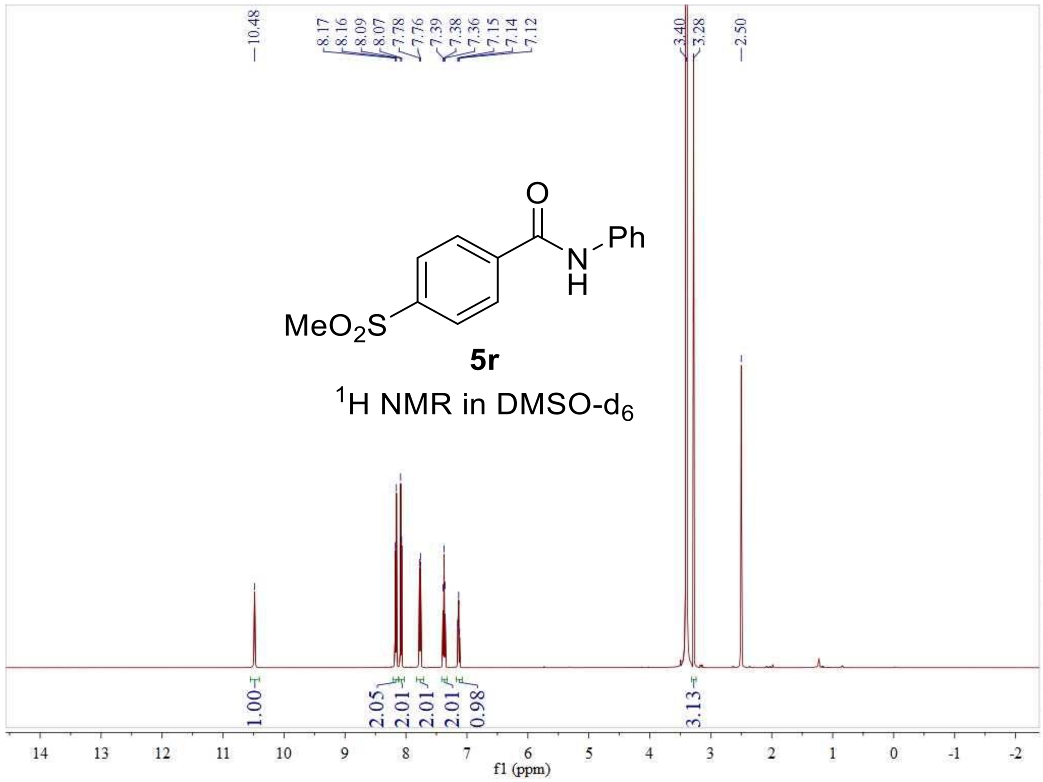
7.98
7.81
7.77
7.75
7.65
7.63
7.41
7.40
7.38
7.26
7.21
7.19
7.18
O
N
H
Ph
F3C
5q
¹H NMR in CDCl3
2.00
0.98
1.90
1.98
1.98
1.06
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


-62.99
O
N
H
Ph
F3C
5q
¹⁹F NMR in CDCl3
50
0
-50
-100
-150
-200
-250
f1 (ppm)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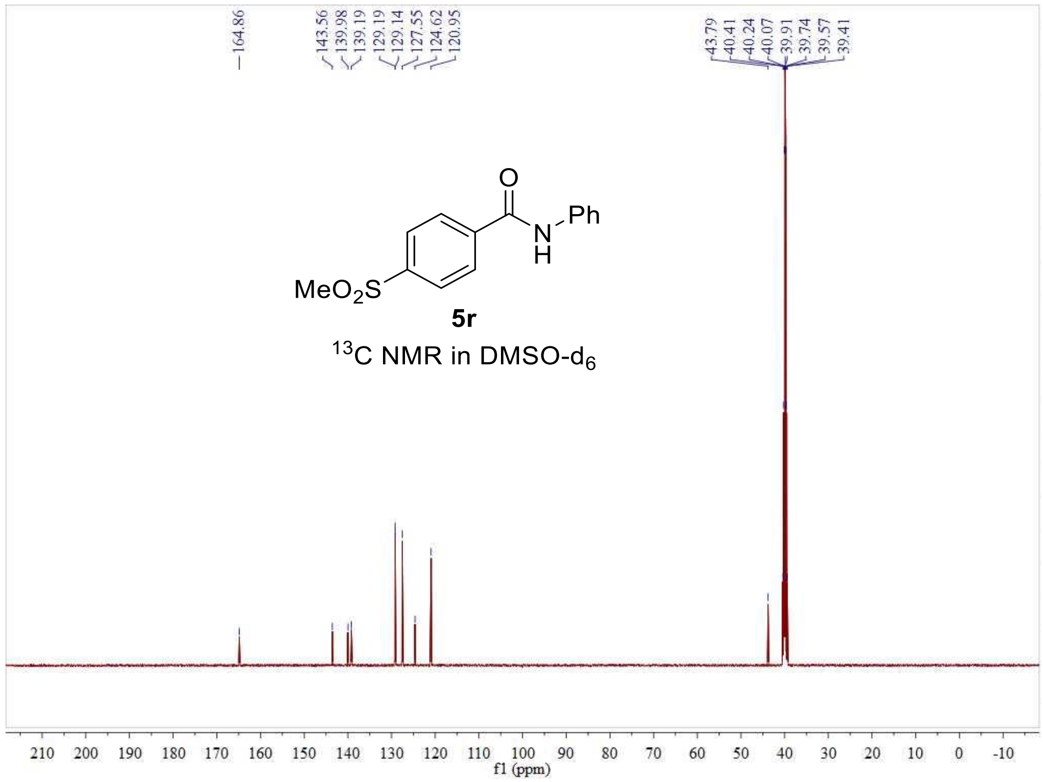
8.17
8.16
8.09
8.07
7.78
7.76
7.39
7.38
7.36
7.15
7.14
7.12
3.40
3.28
2.50
O
N
H
Ph
MeO2S
5r
1H NMR in DMSO-d6
1.00
2.05
2.01
2.01
2.01
0.98
3.13
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)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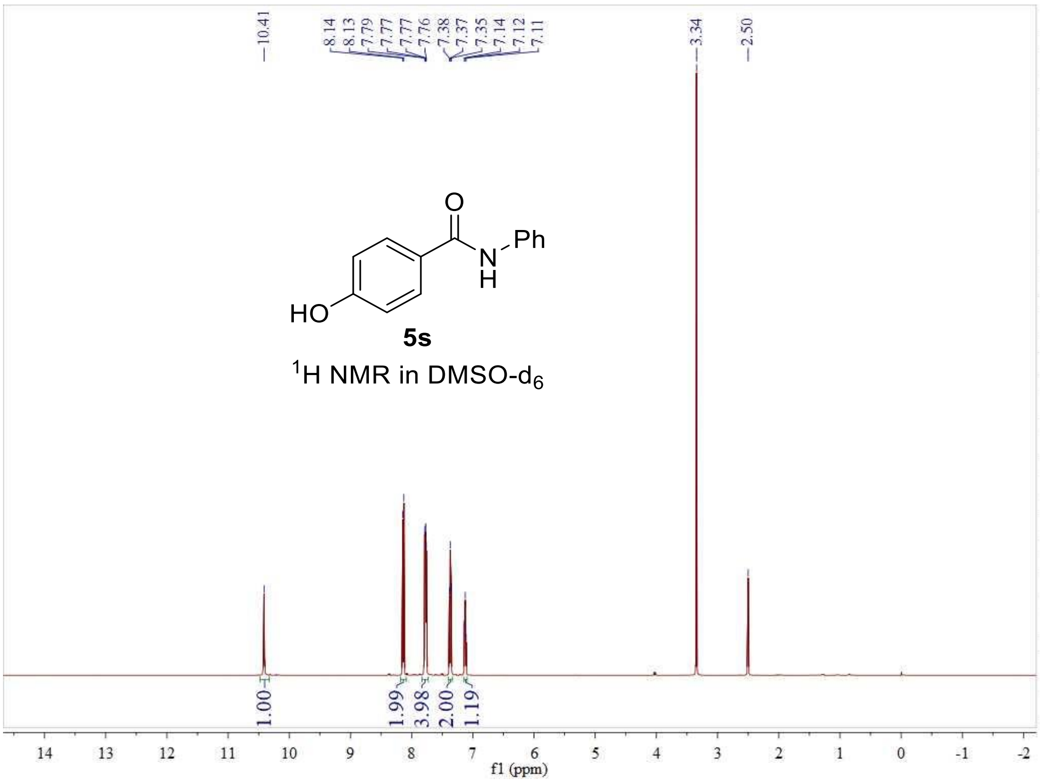
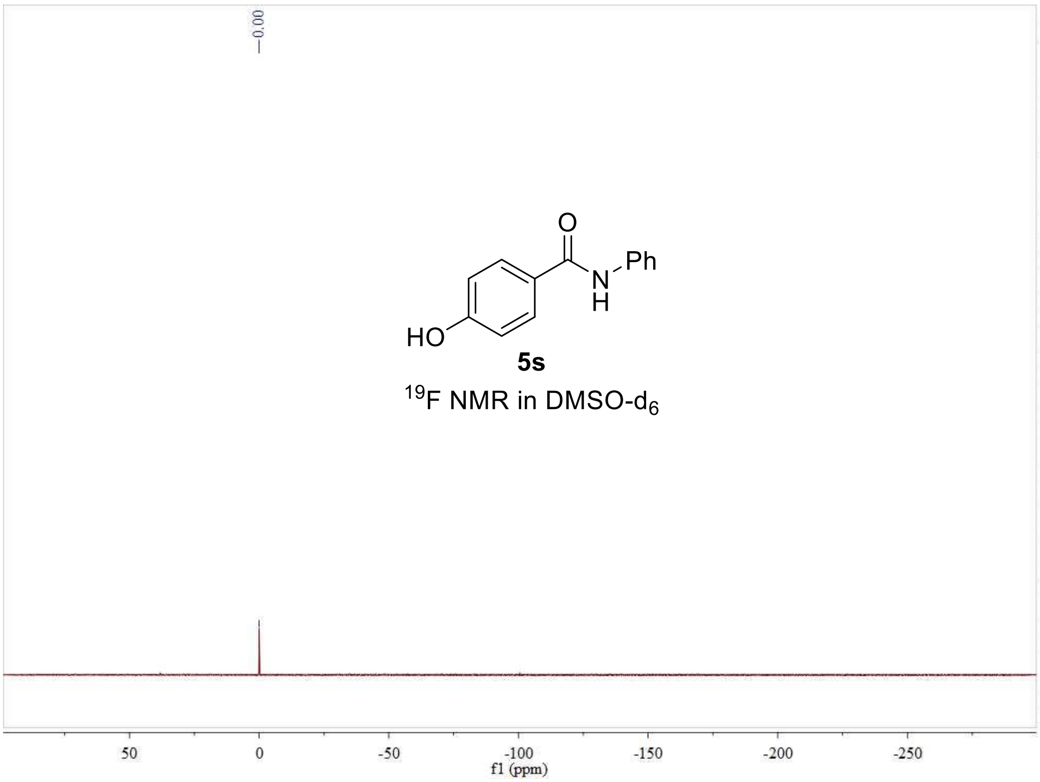
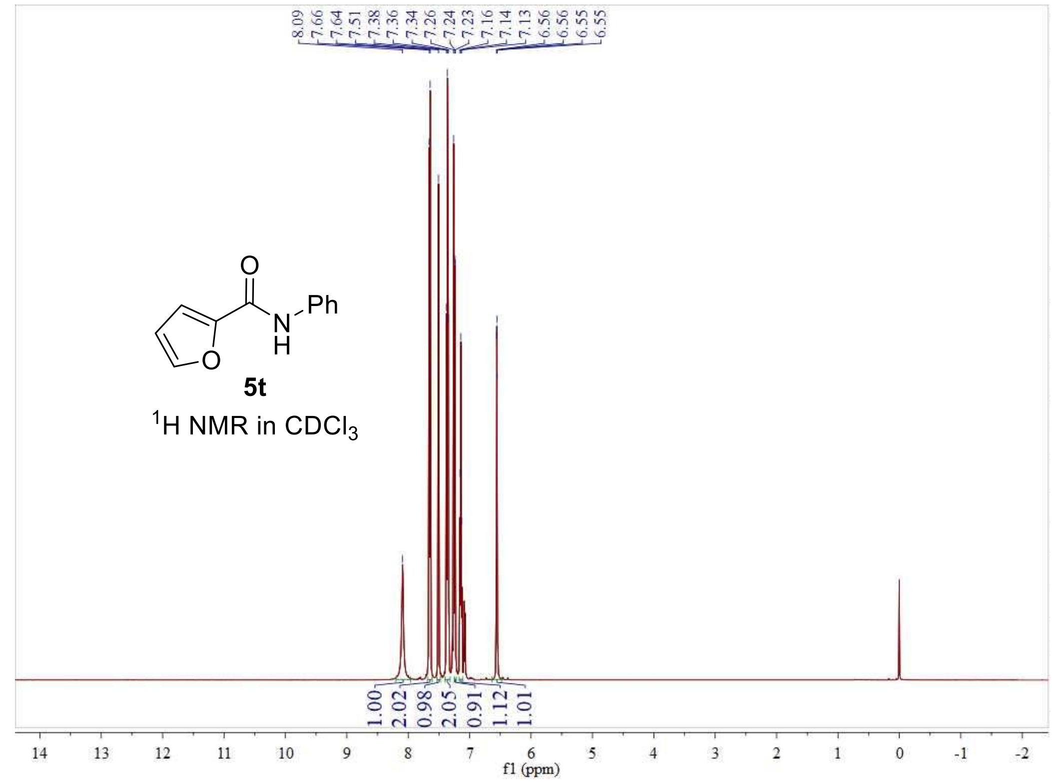
143.56
139.98
139.19
129.19
129.14
127.55
124.62
120.95
43.79
40.41
40.24
40.07
39.91
39.74
39.57
39.41
O
N
H
Ph
MeO2S
5r
13C NMR in DMSO-d6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

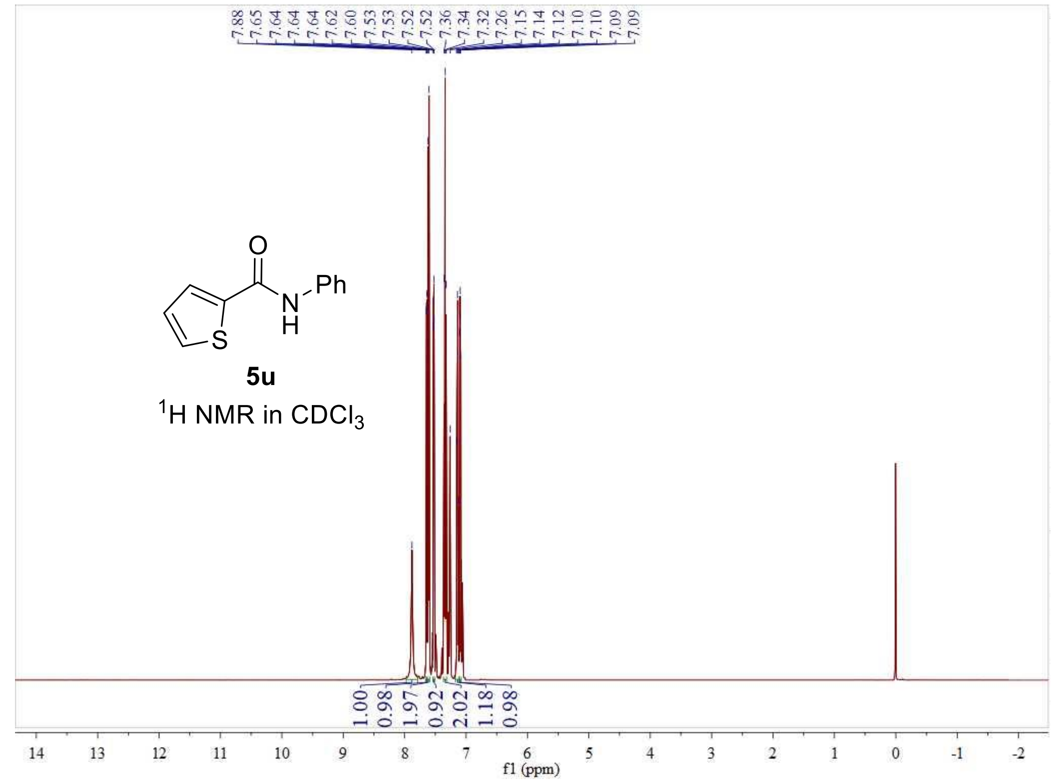

10.41
8.14
8.13
7.79
7.77
7.77
7.76
7.38
7.37
7.35
7.14
7.12
7.11
3.34
2.50
O
N
H
Ph
HO
5s
^{1}H NMR in DMSO-d$_6$
1.00
1.99
3.98
2.00
1.19
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


0.00
O
N
H
Ph
HO
5s
^{19}F NMR in DMSO-d$_6$
50
0
-50
-100
-150
-200
-250
f1 (ppm)



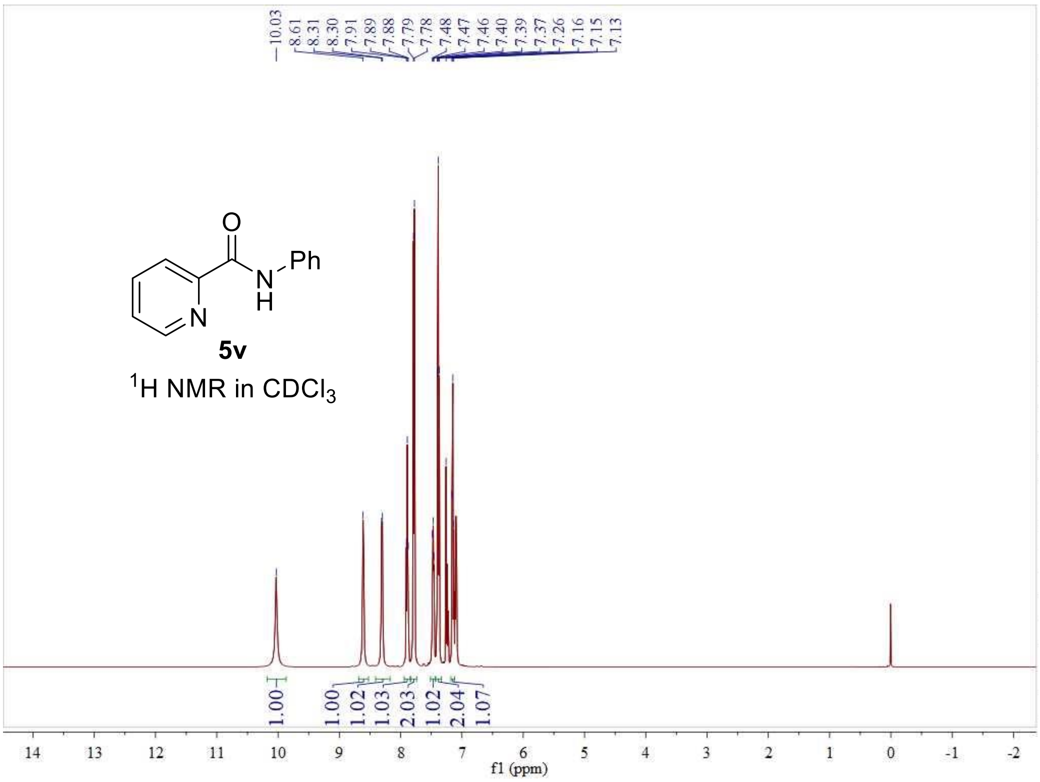
5t

^{1}H NMR in CDCl$_3$



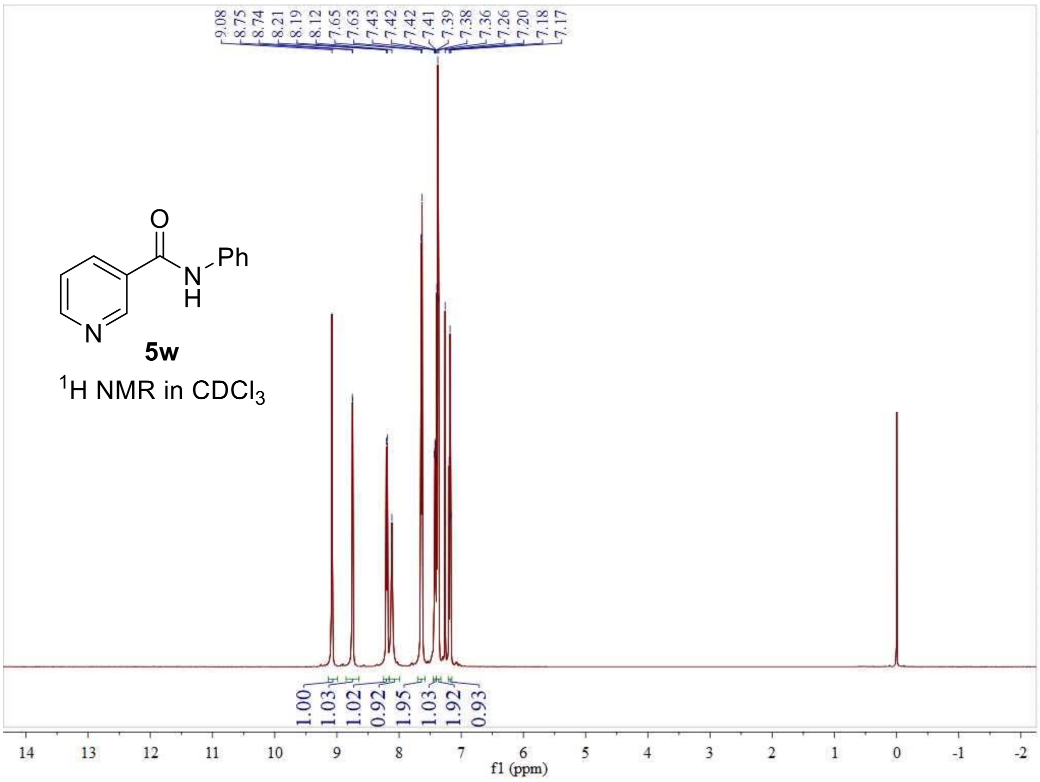
5u

^{1}H NMR in CDCl$_3$



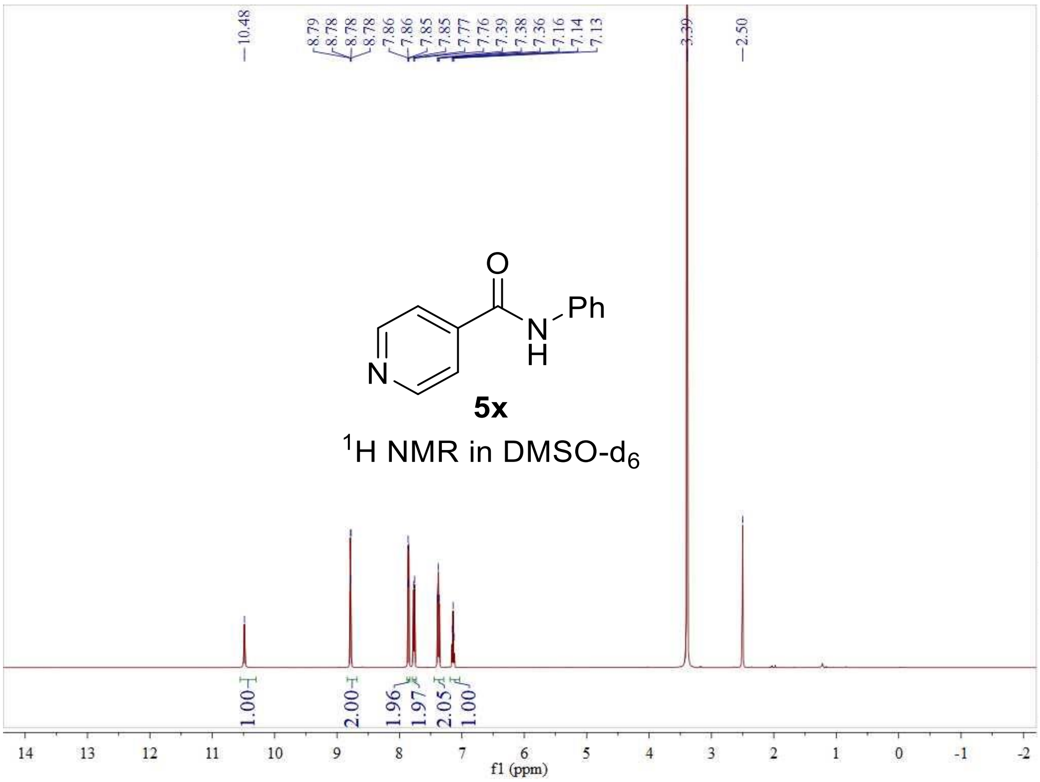
5v

^{1}H NMR in CDCl$_3$



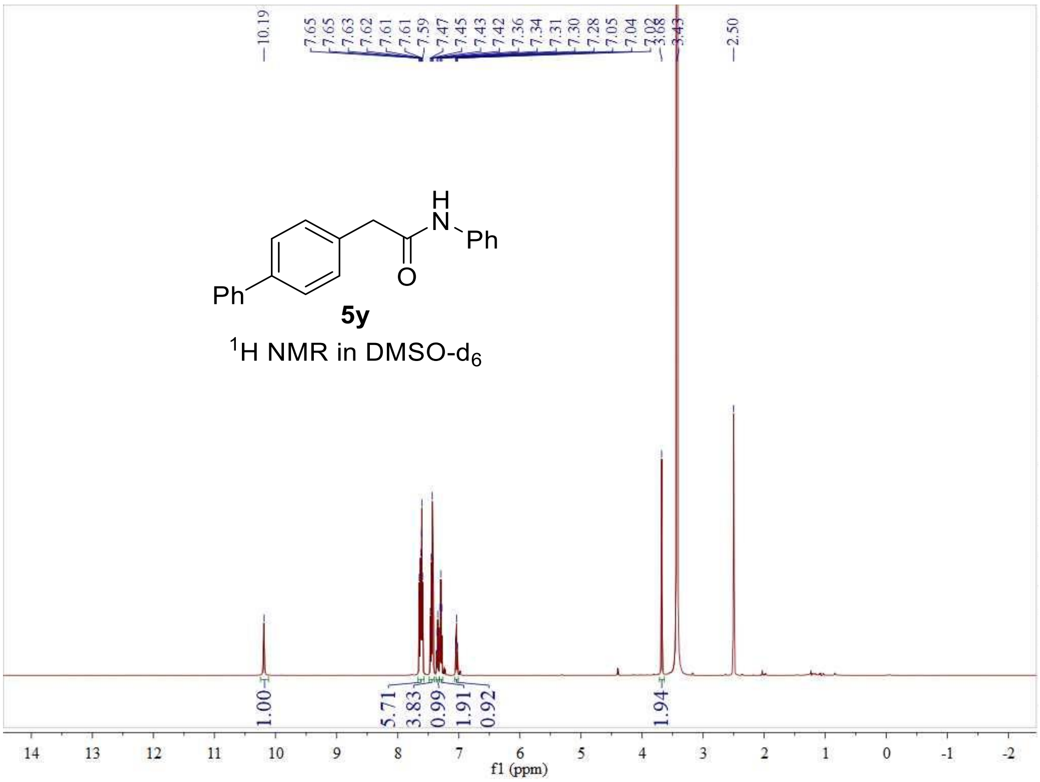
5w

^{1}H NMR in CDCl$_3$



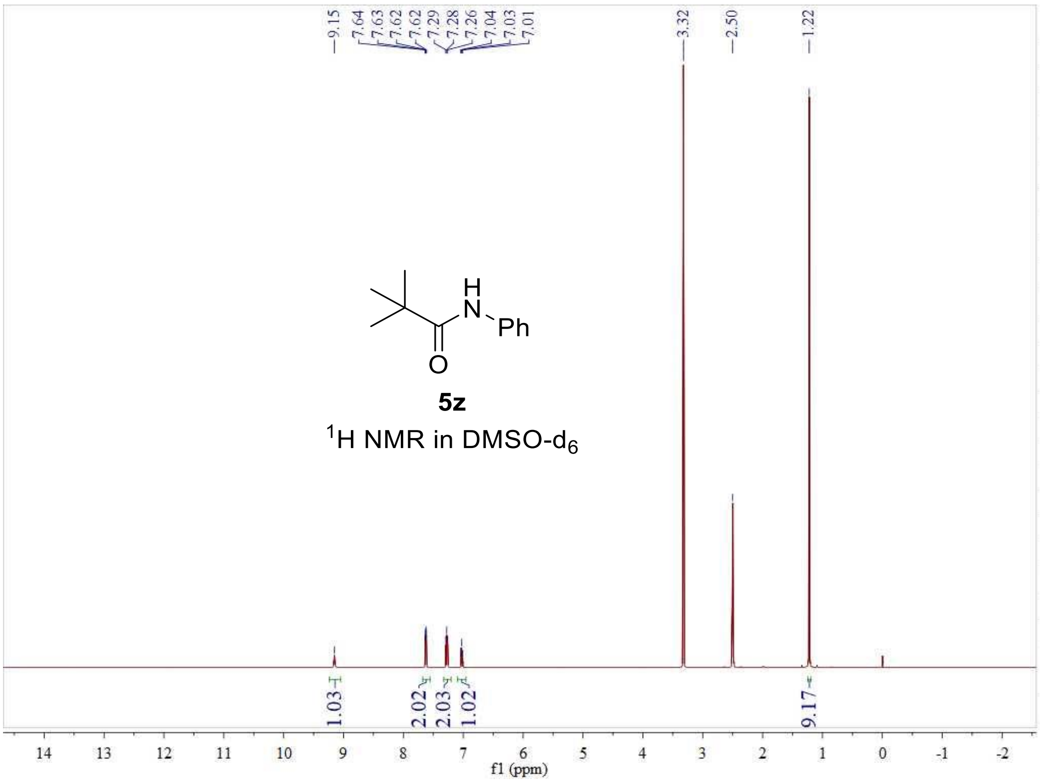
5x

^{1}H NMR in DMSO-d$_6$

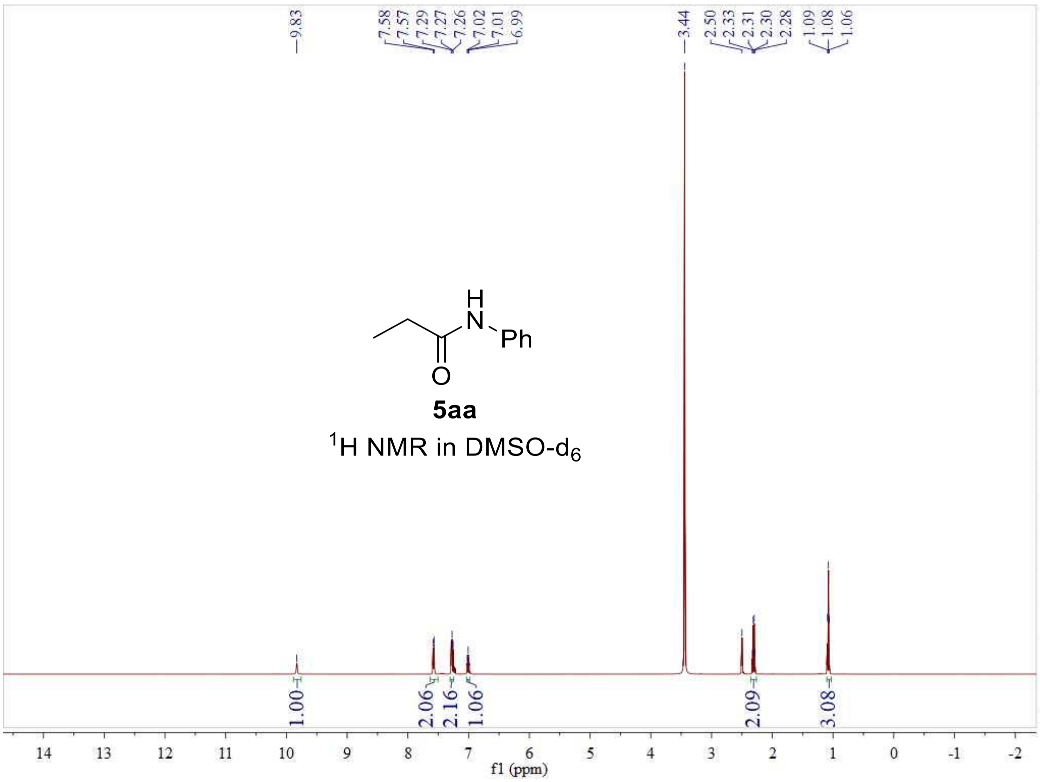


5y

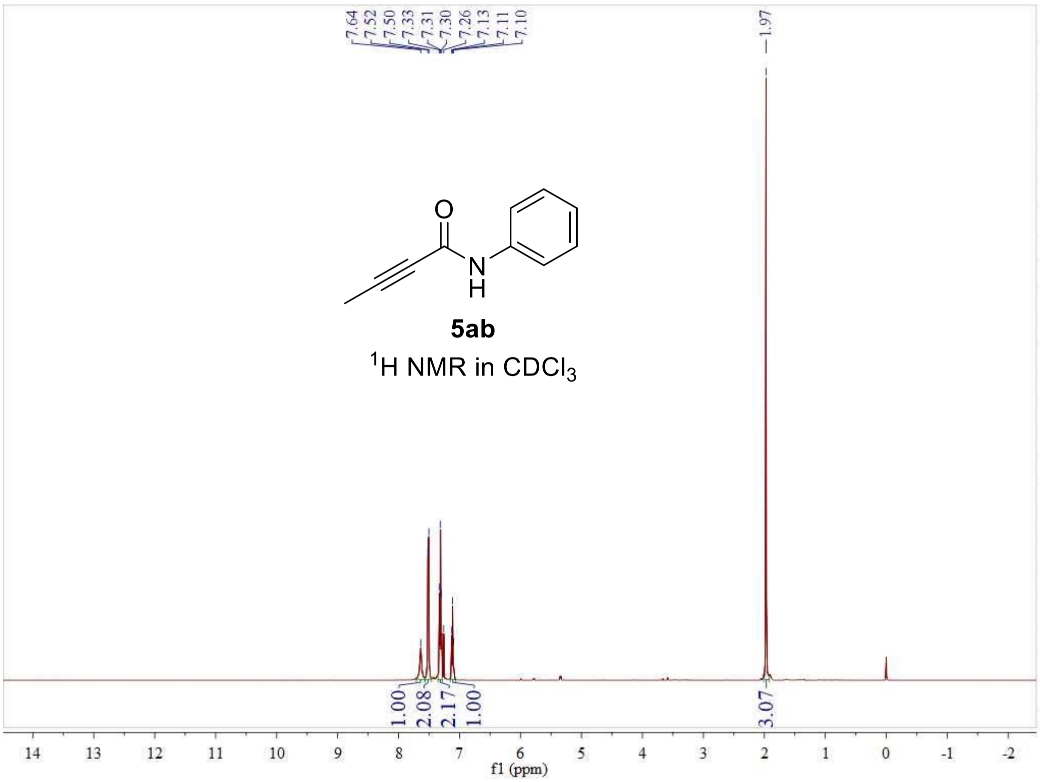
^{1}H NMR in DMSO-d$_6$

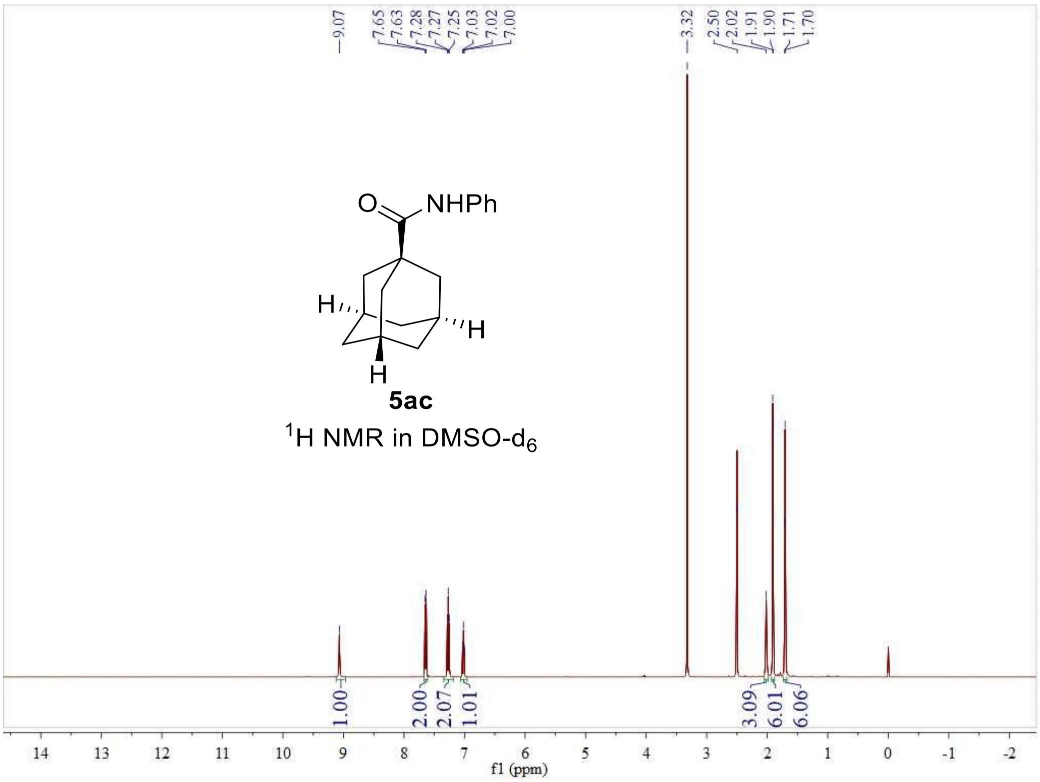

5z

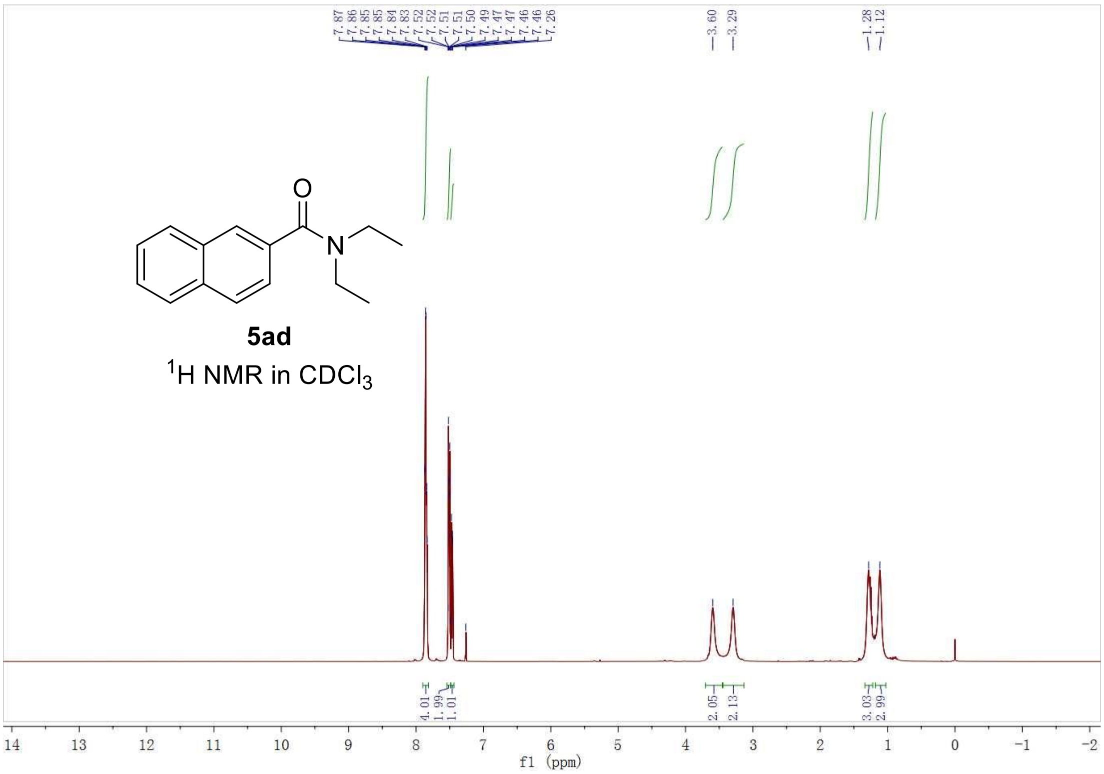
^{1}H NMR in DMSO-d_6


5aa

^{1}H NMR in DMSO-d_6

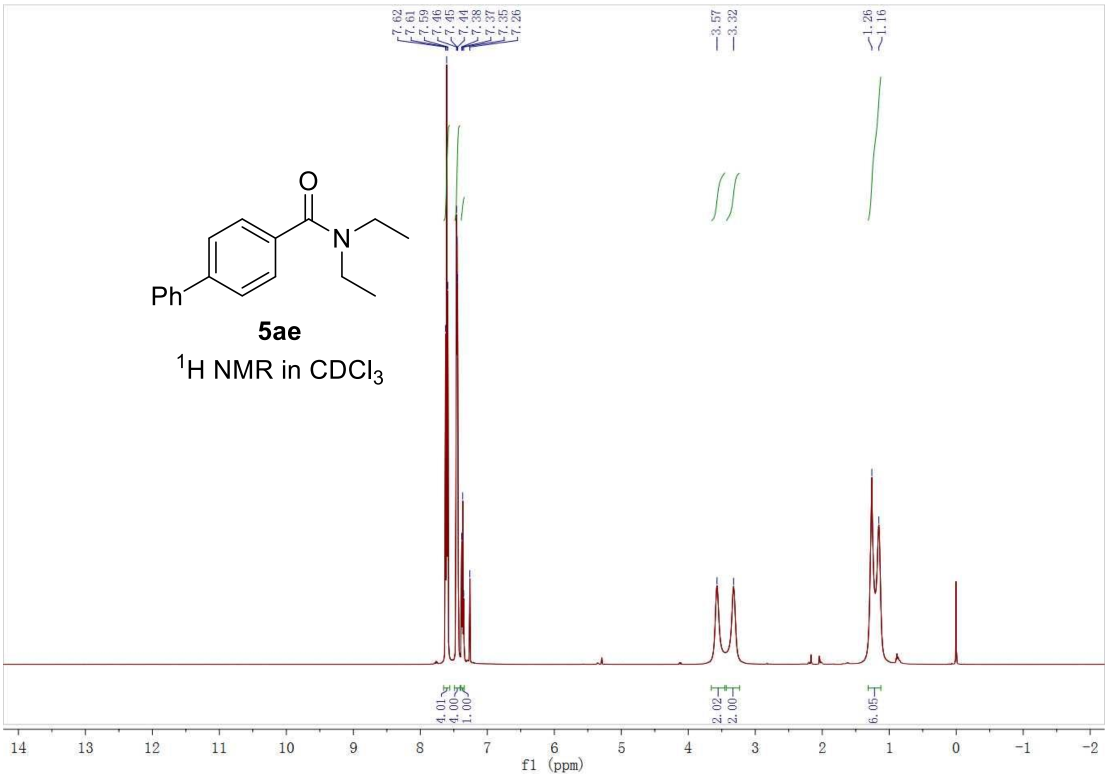

7.64
7.52
7.50
7.33
7.31
7.30
7.26
7.13
7.11
7.10
1.97
O
N
H
5ab
^{1}H NMR in CDCl$_3$
1.00
2.08
2.17
1.00
3.07
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)


9.07
7.65
7.63
7.28
7.27
7.25
7.03
7.02
7.00
3.32
2.50
2.02
1.91
1.90
1.71
1.70
O
NHPh
H
H
H
5ac
^{1}H NMR in DMSO-d$_6$
1.00
2.00
2.07
1.01
3.09
6.01
6.06
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)



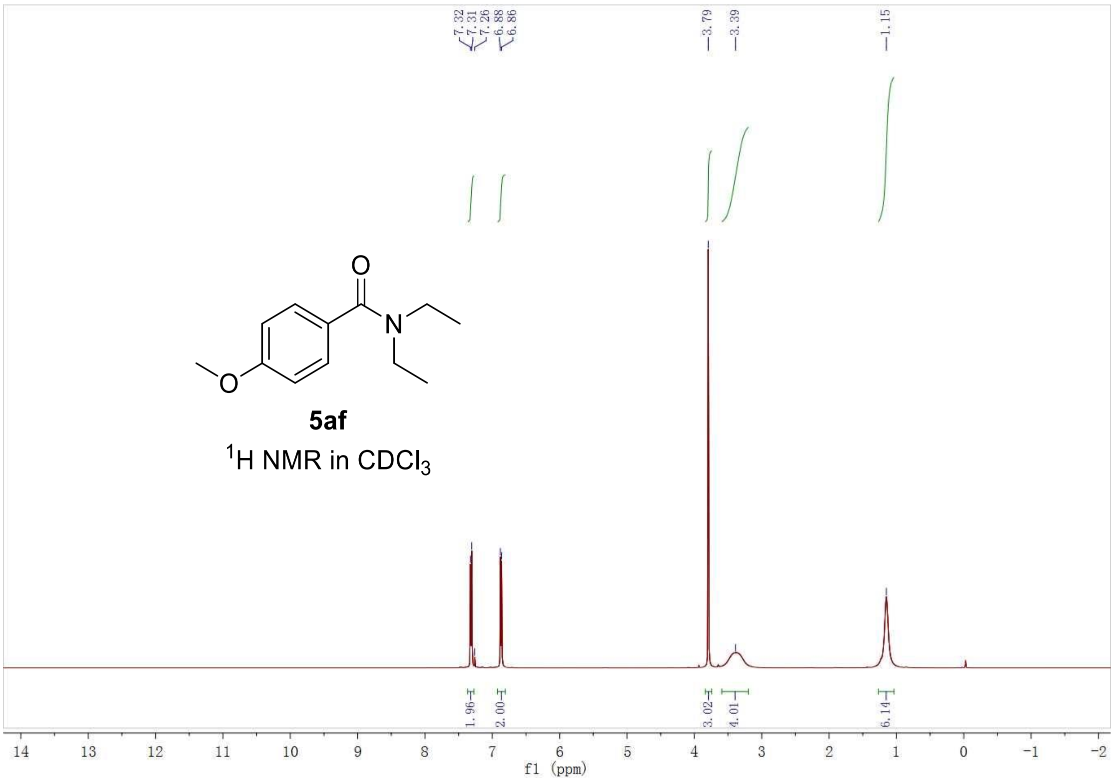
5ad

^{1}H NMR in $CDCl_3$



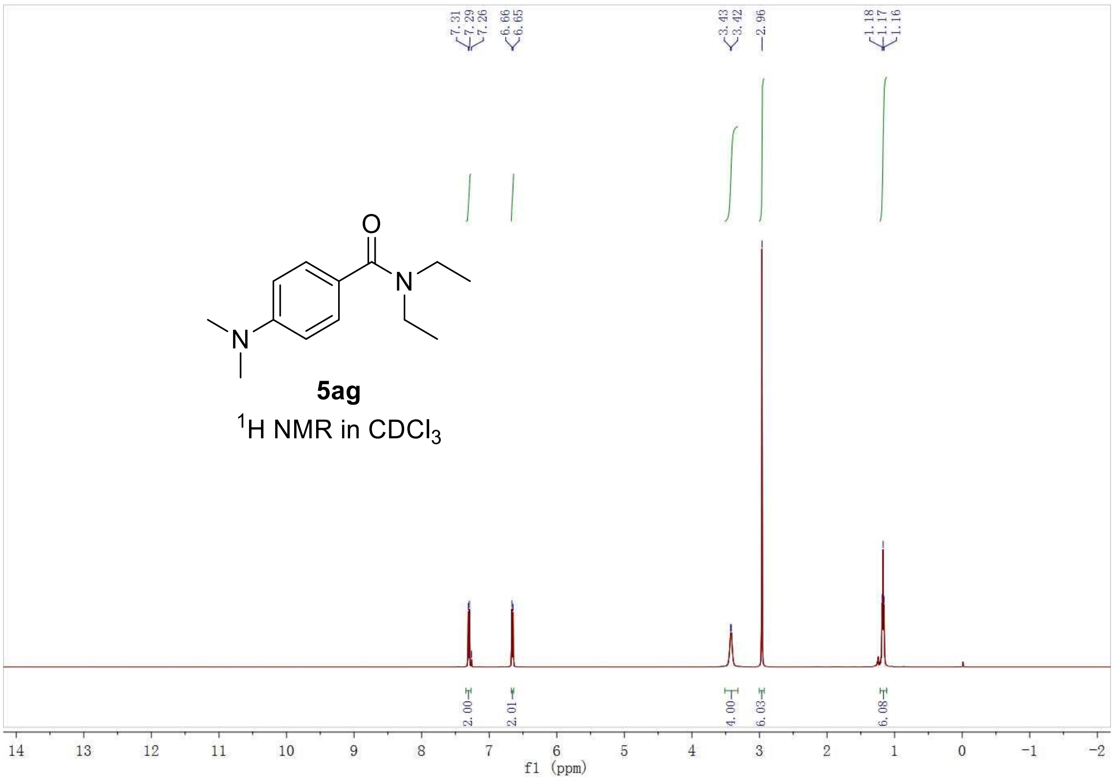
5ae

^{1}H NMR in $CDCl_3$



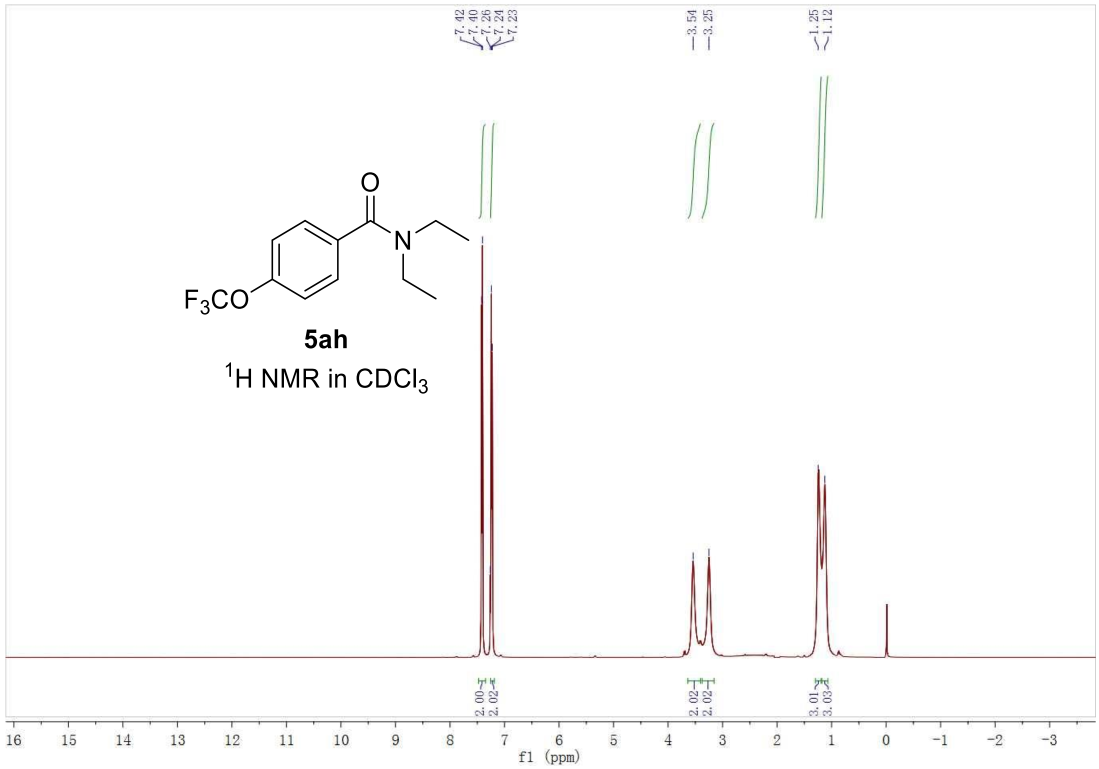
5af

^{1}H NMR in CDCl$_3$



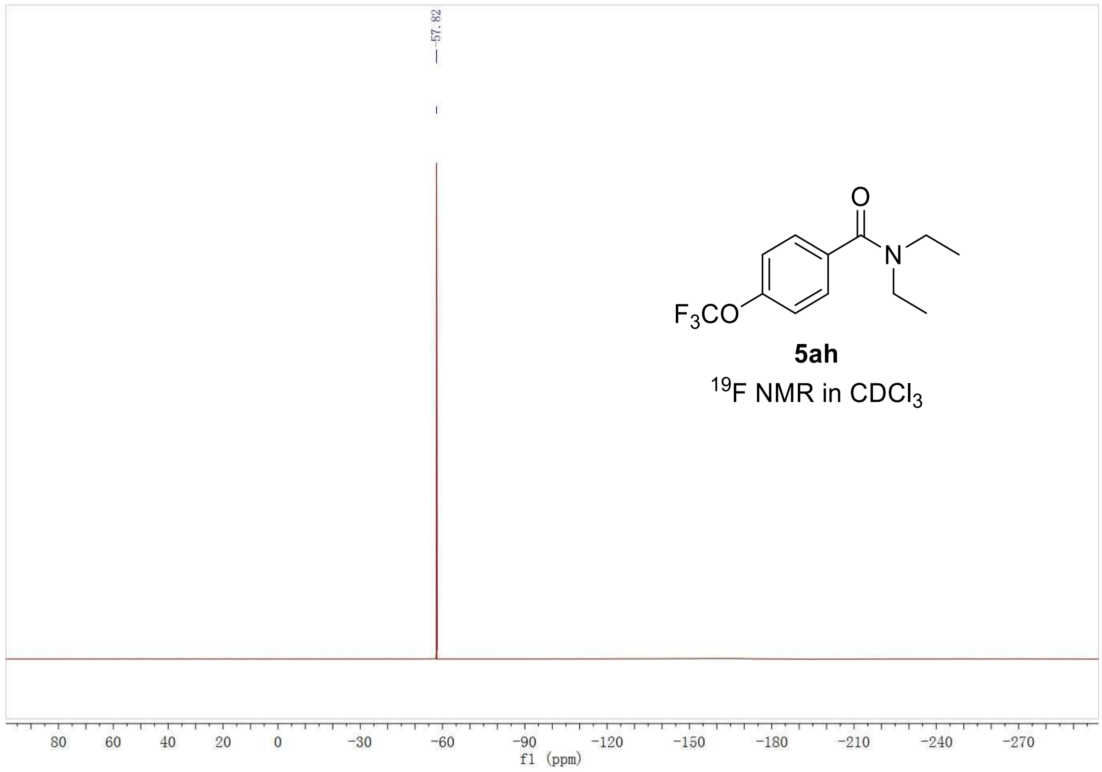
5ag

^{1}H NMR in CDCl$_3$



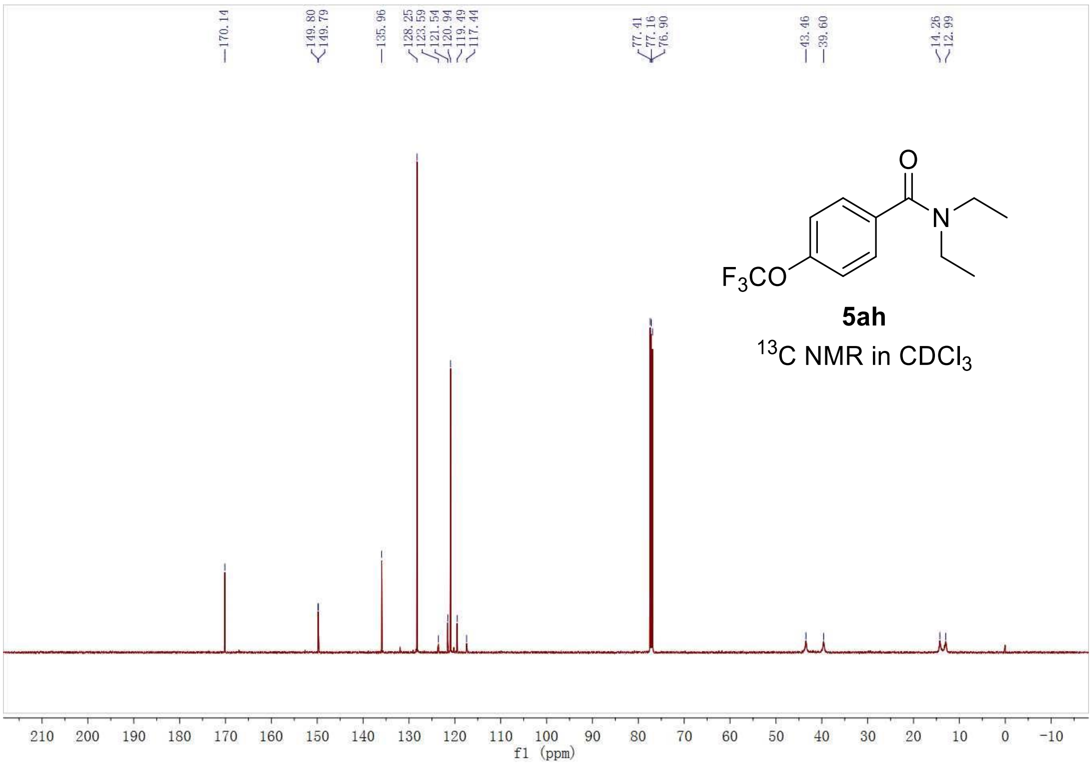
5ah

^{1}H NMR in CDCl$_3$



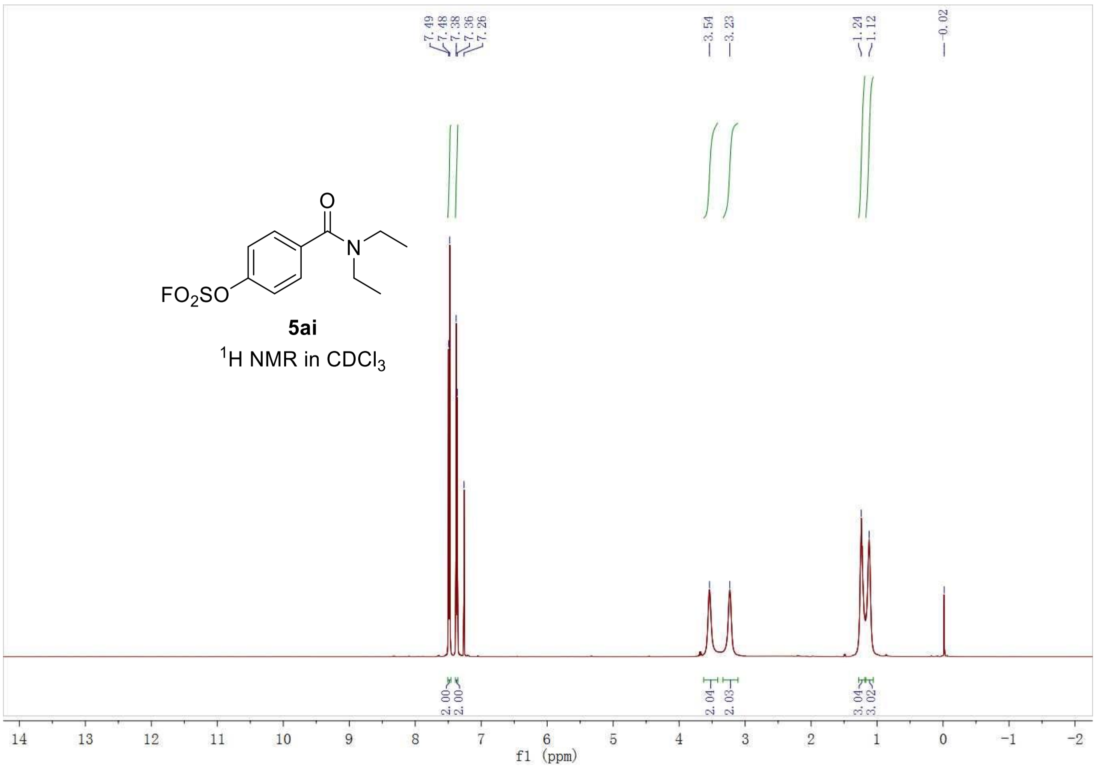
5ah

^{19}F NMR in CDCl$_3$



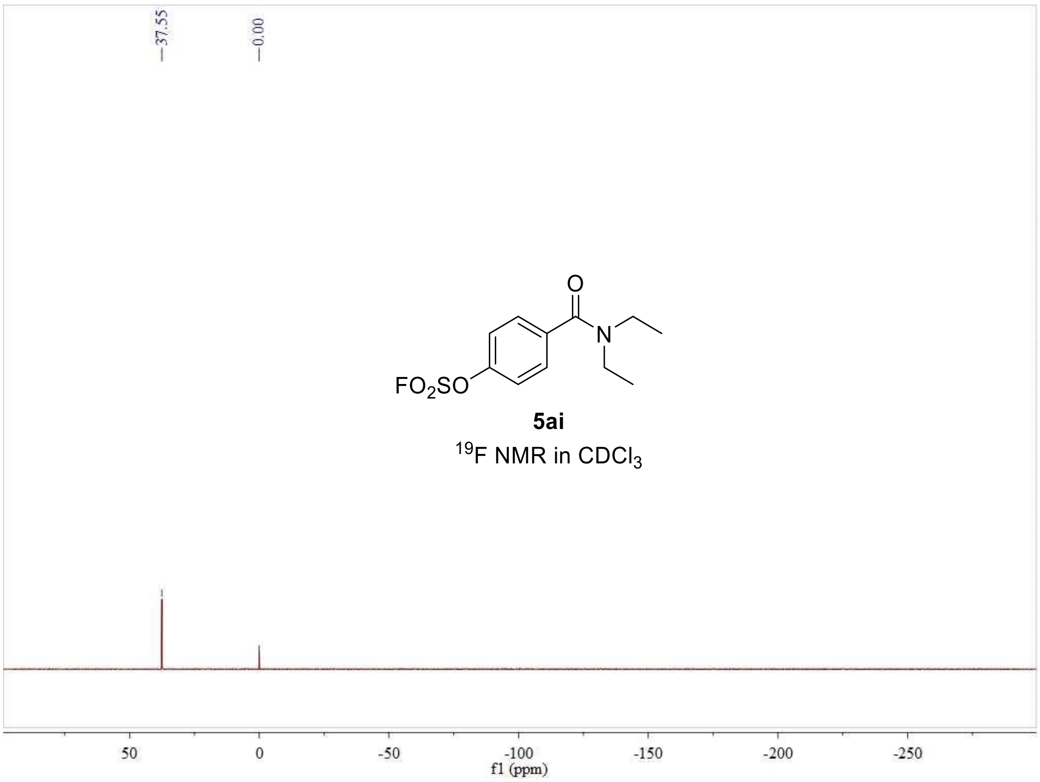
5ah

^{13}C NMR in CDCl$_3$

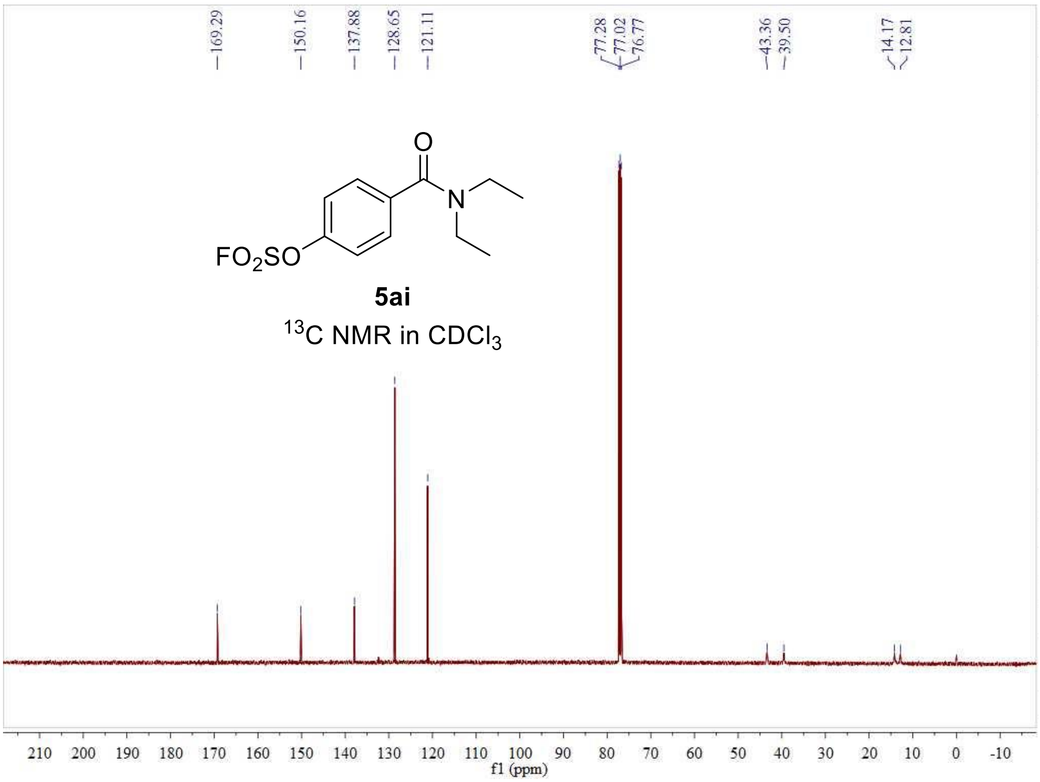


5ai

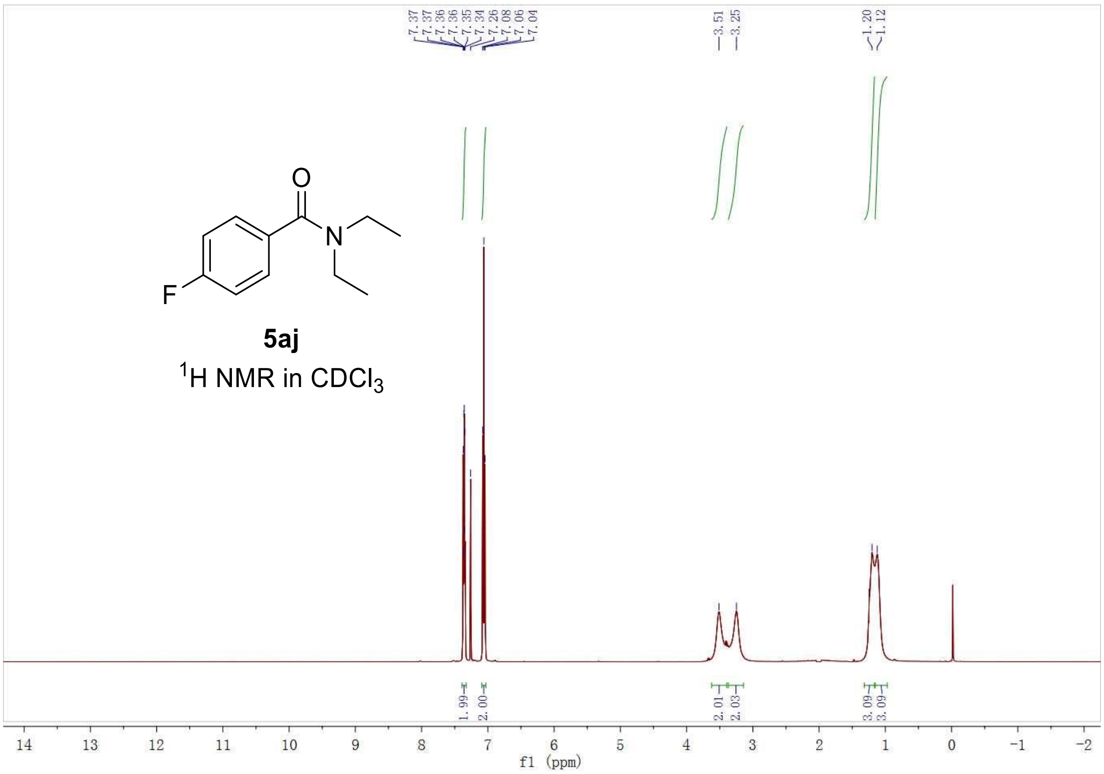
^{1}H NMR in CDCl$_3$



37.55
0.00
FO$_2$SO
O
N
5ai
^{19}F NMR in CDCl$_3$
50
0
-50
-100
-150
-200
-250
f1 (ppm)

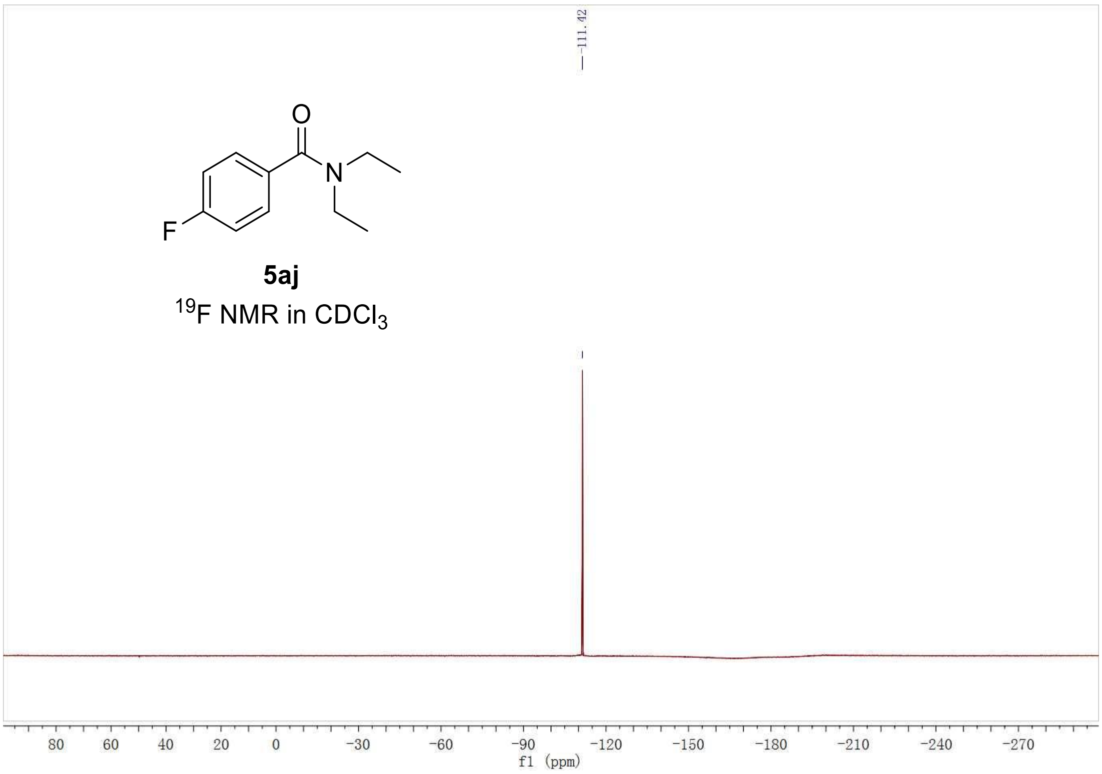


169.29
150.16
137.88
128.65
121.11
77.28
77.02
76.77
43.36
39.50
14.17
12.81
FO$_2$SO
O
N
5ai
^{13}C NMR in CDCl$_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



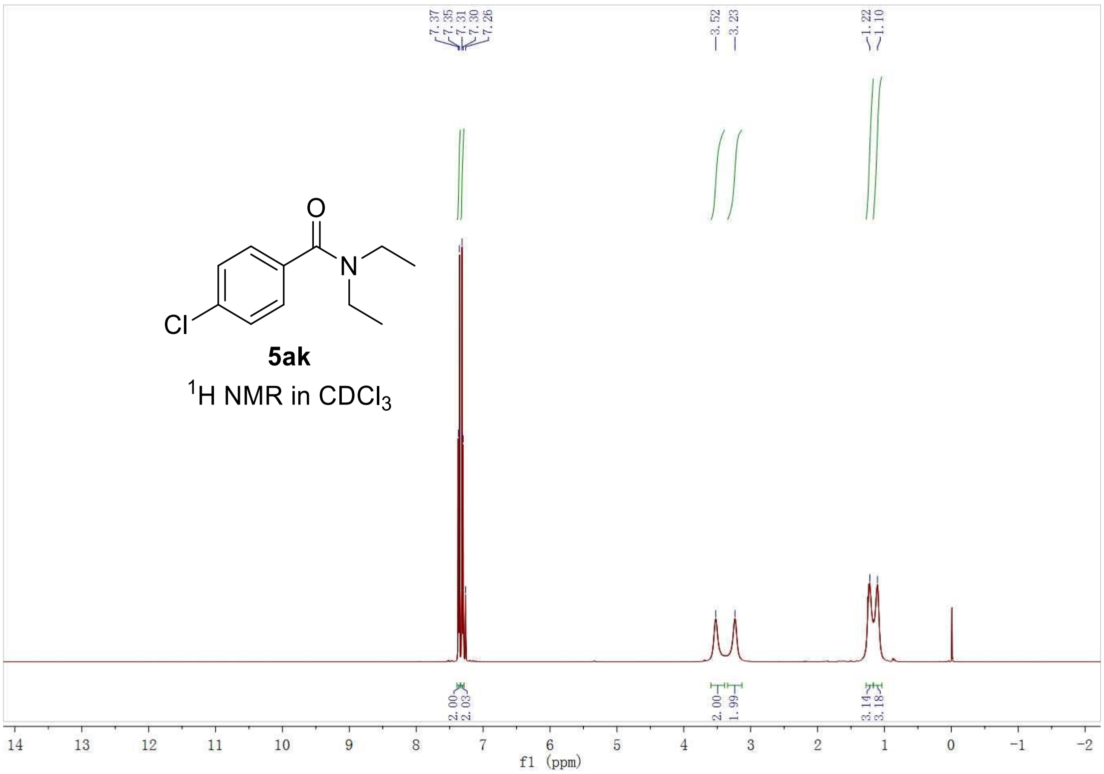
5aj

^{1}H NMR in CDCl$_3$



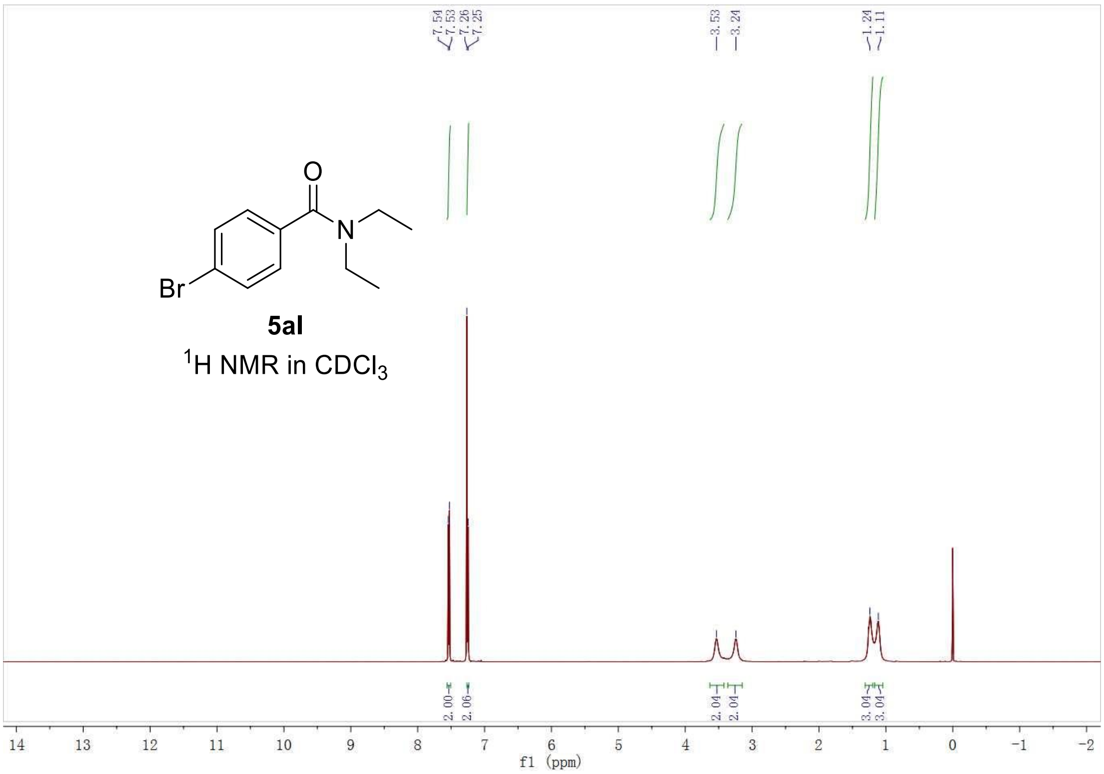
5aj

^{19}F NMR in CDCl$_3$



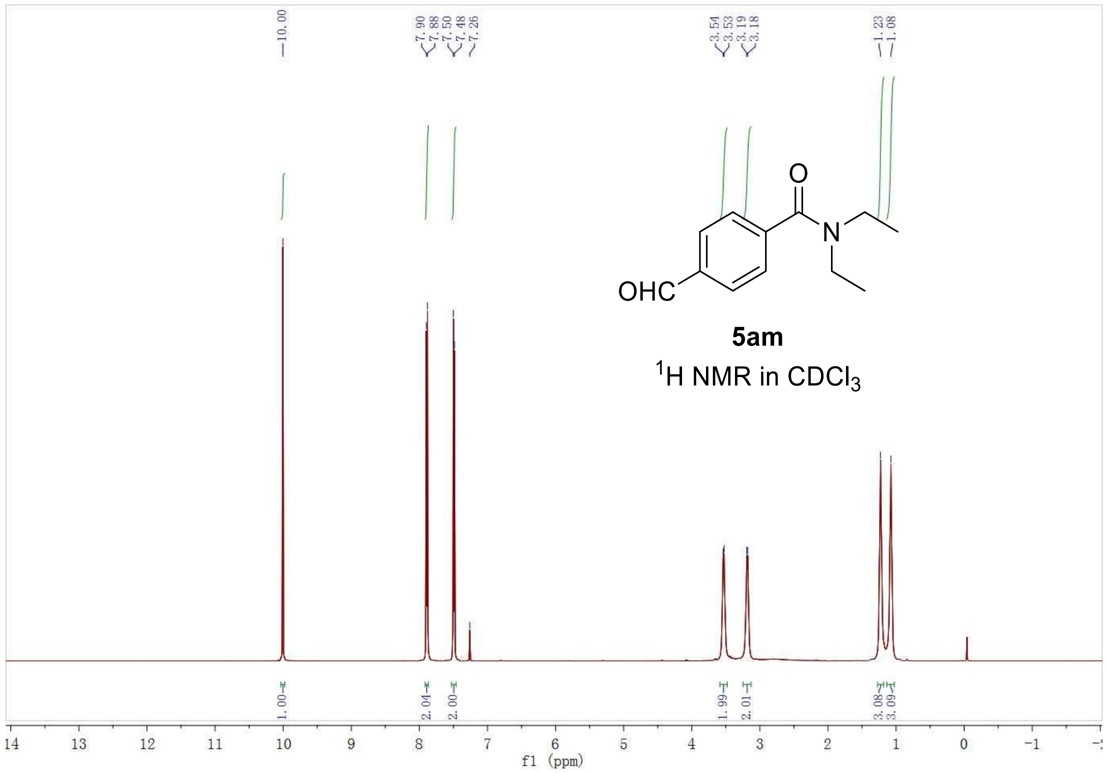
5ak

^{1}H NMR in $CDCl_3$



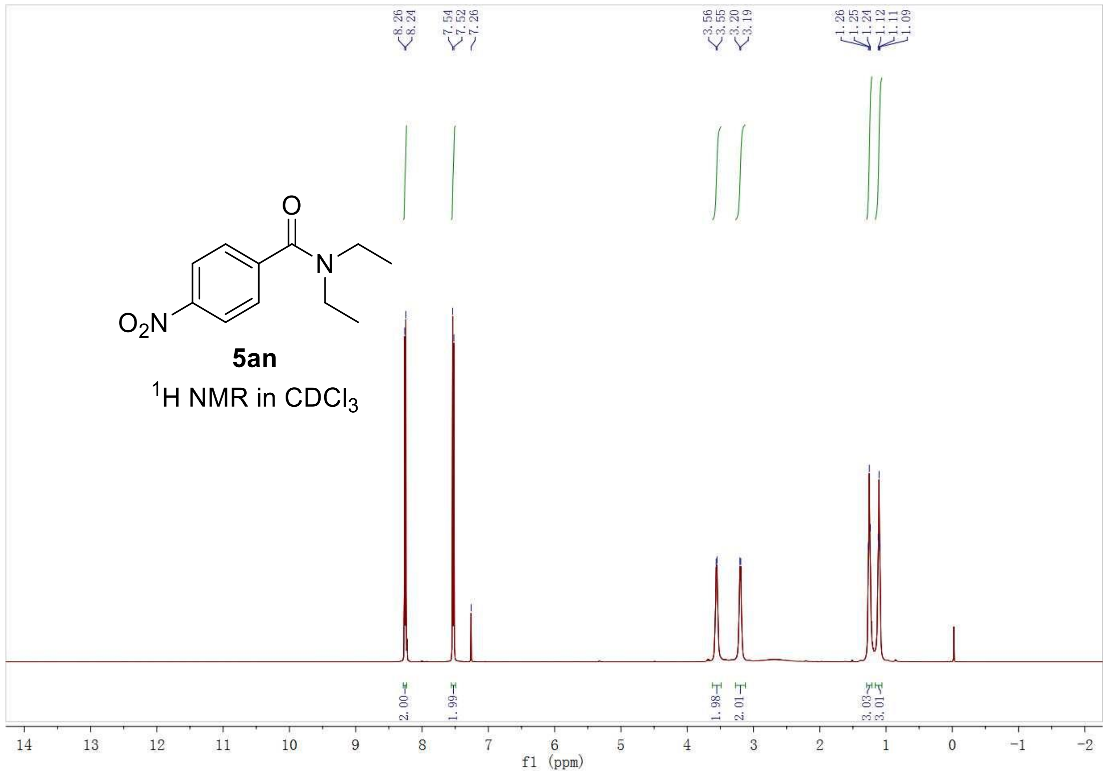
5al

^{1}H NMR in $CDCl_3$



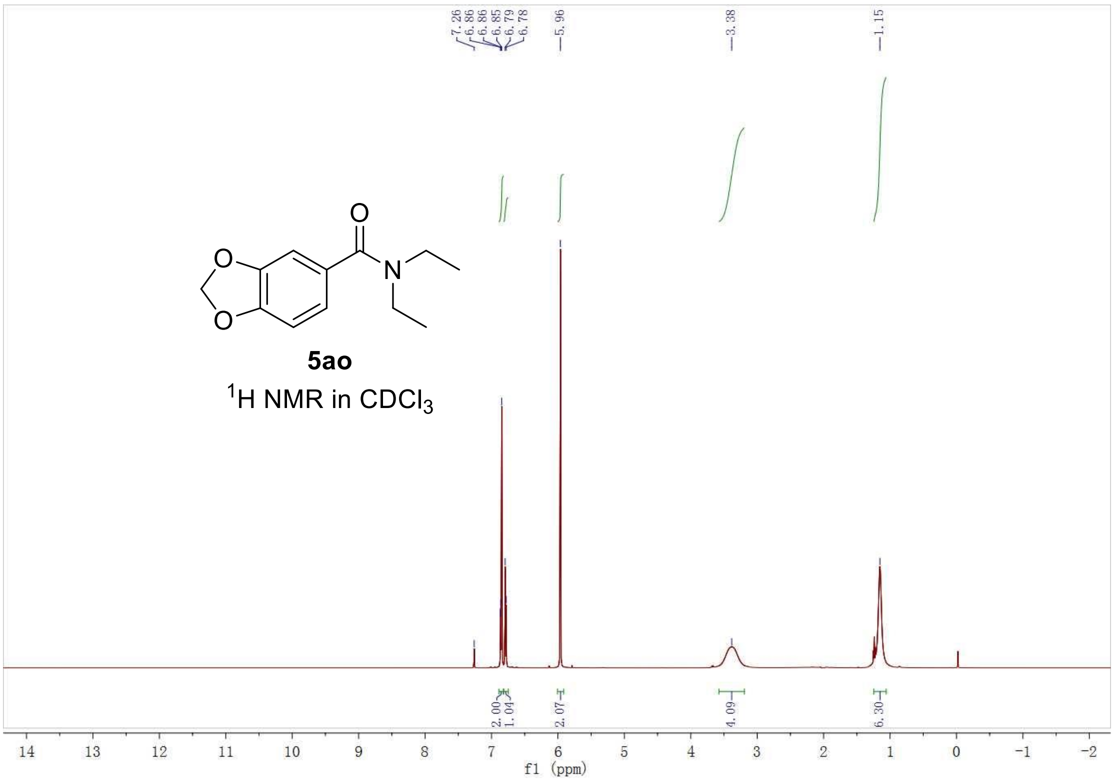
5am

^{1}H NMR in $CDCl_3$



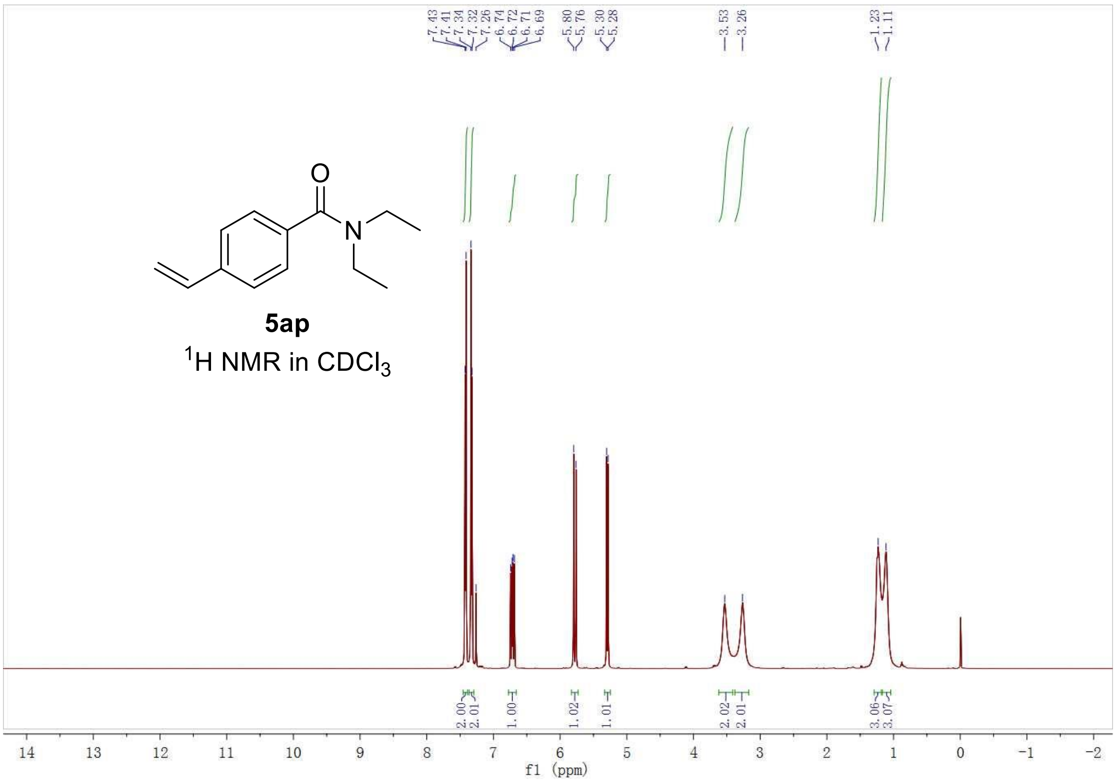
5an

^{1}H NMR in $CDCl_3$



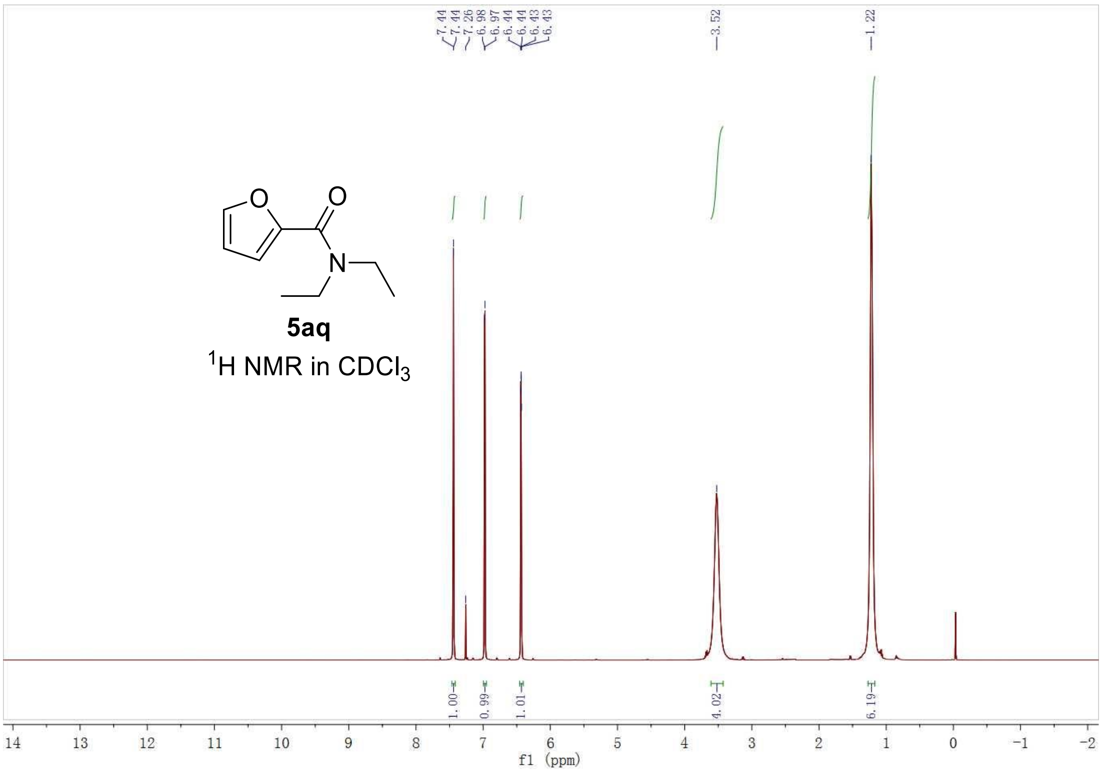
5ao

^{1}H NMR in $CDCl_3$

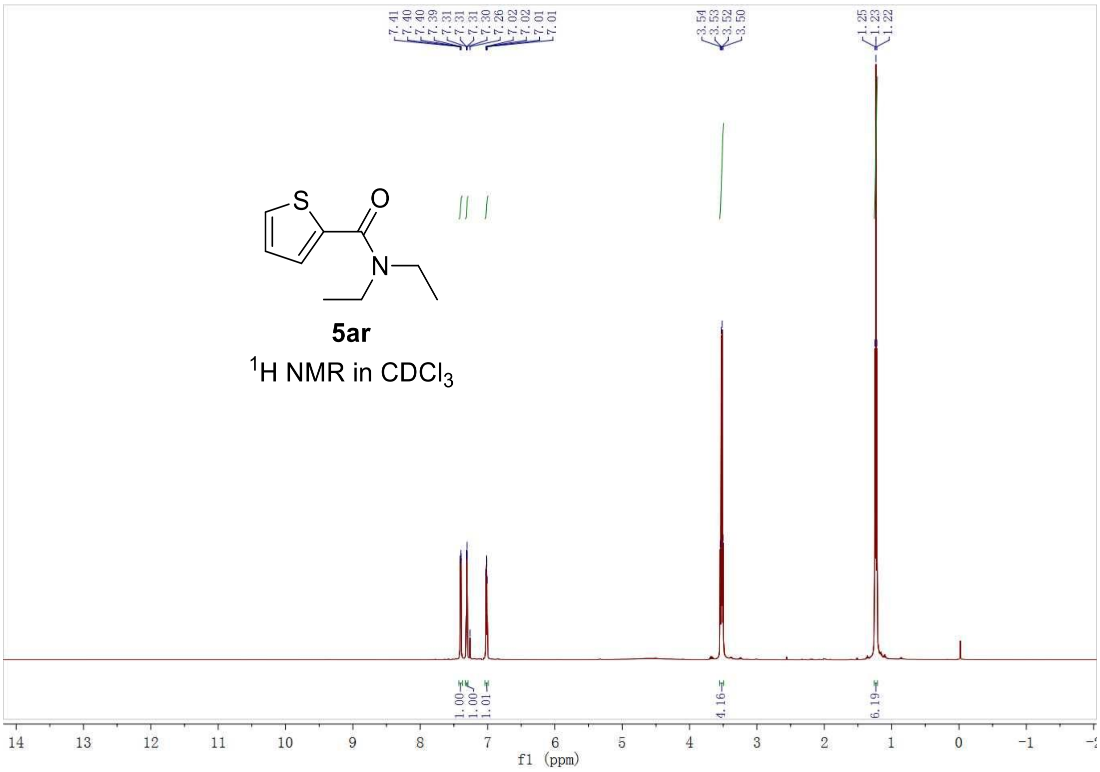


5ap

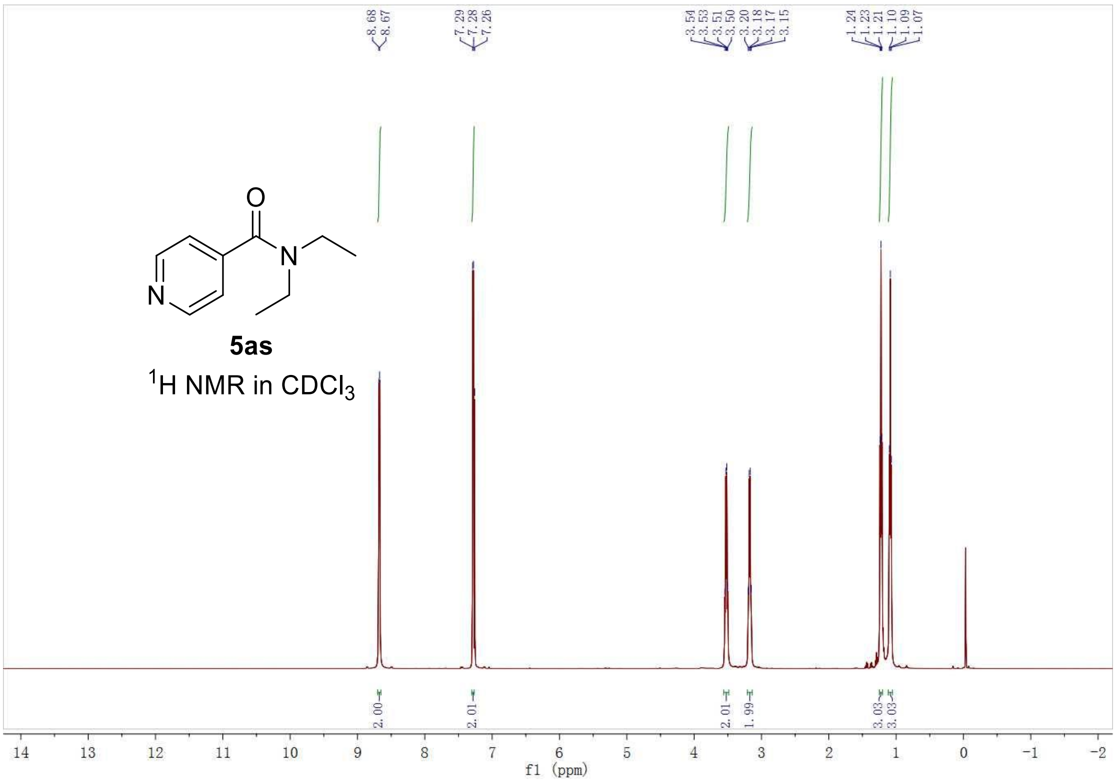
^{1}H NMR in $CDCl_3$


5aq

^{1}H NMR in CDCl$_3$

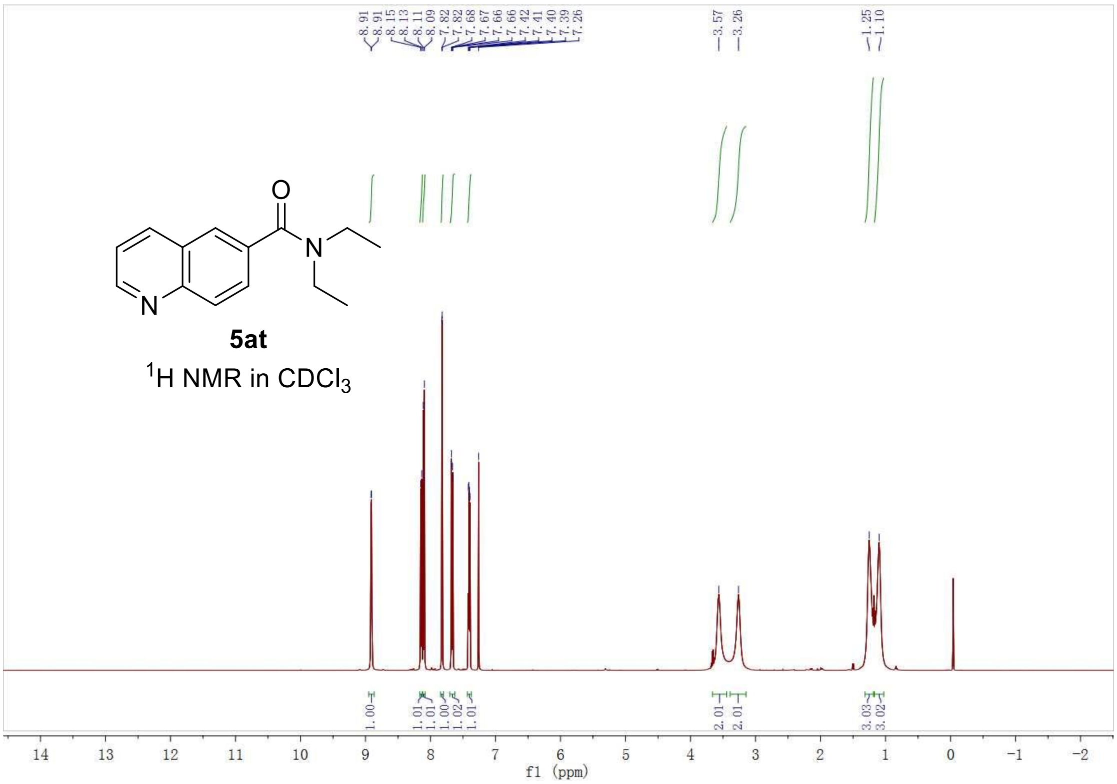

5ar

^{1}H NMR in CDCl$_3$



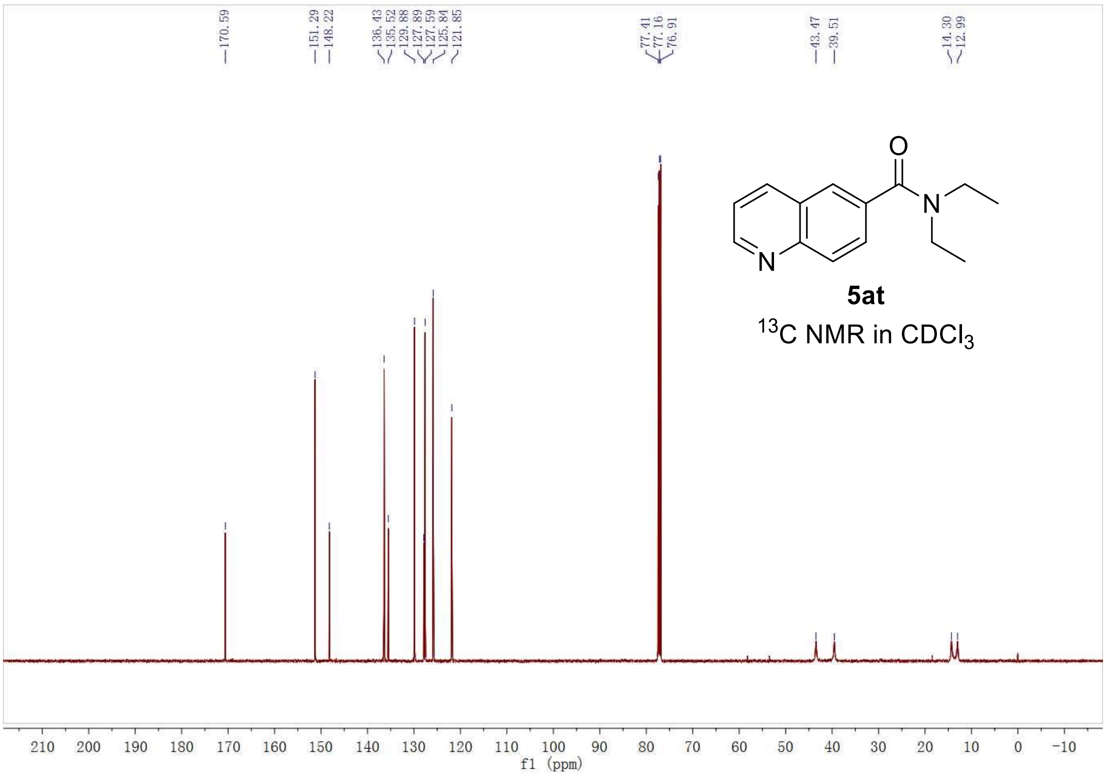
5as

^{1}H NMR in $CDCl_3$



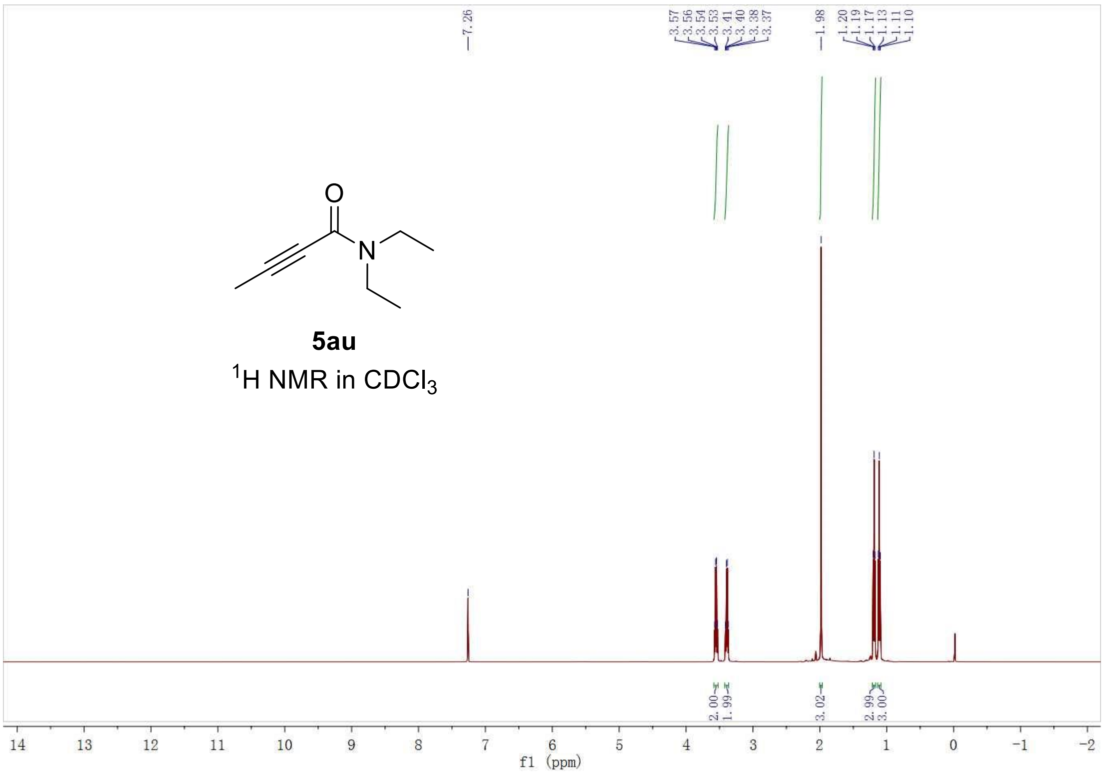
5at

^{1}H NMR in $CDCl_3$



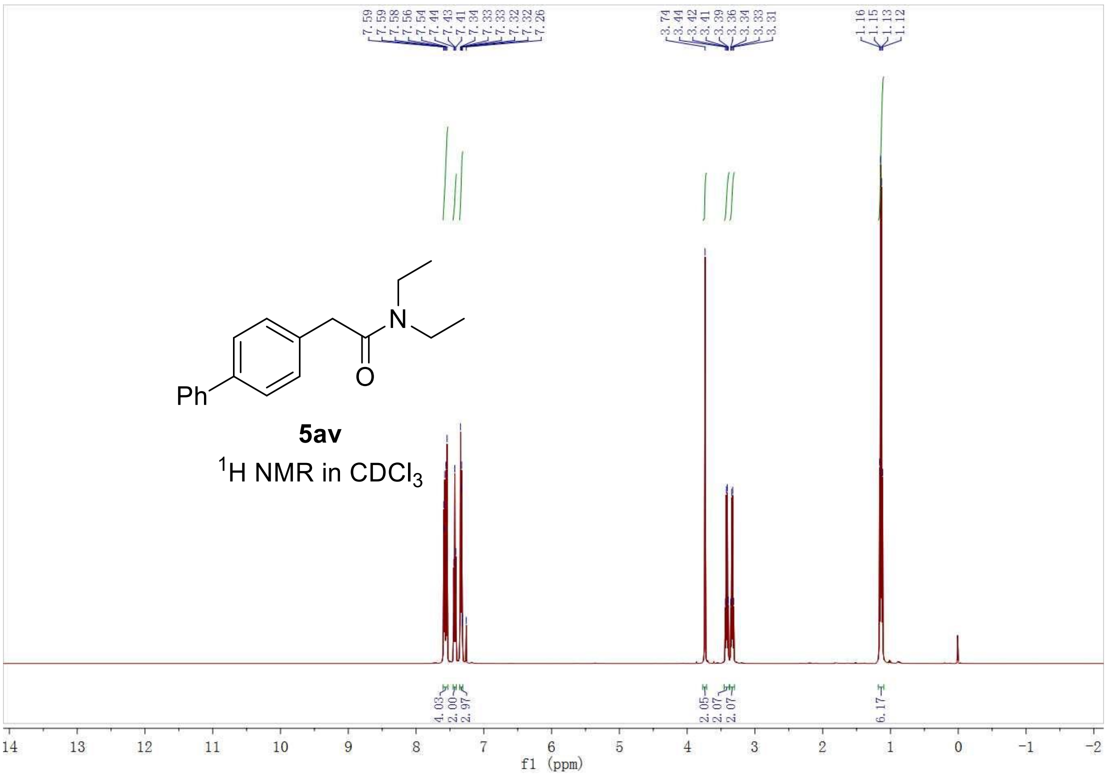
5at

^{13}C NMR in $CDCl_3$



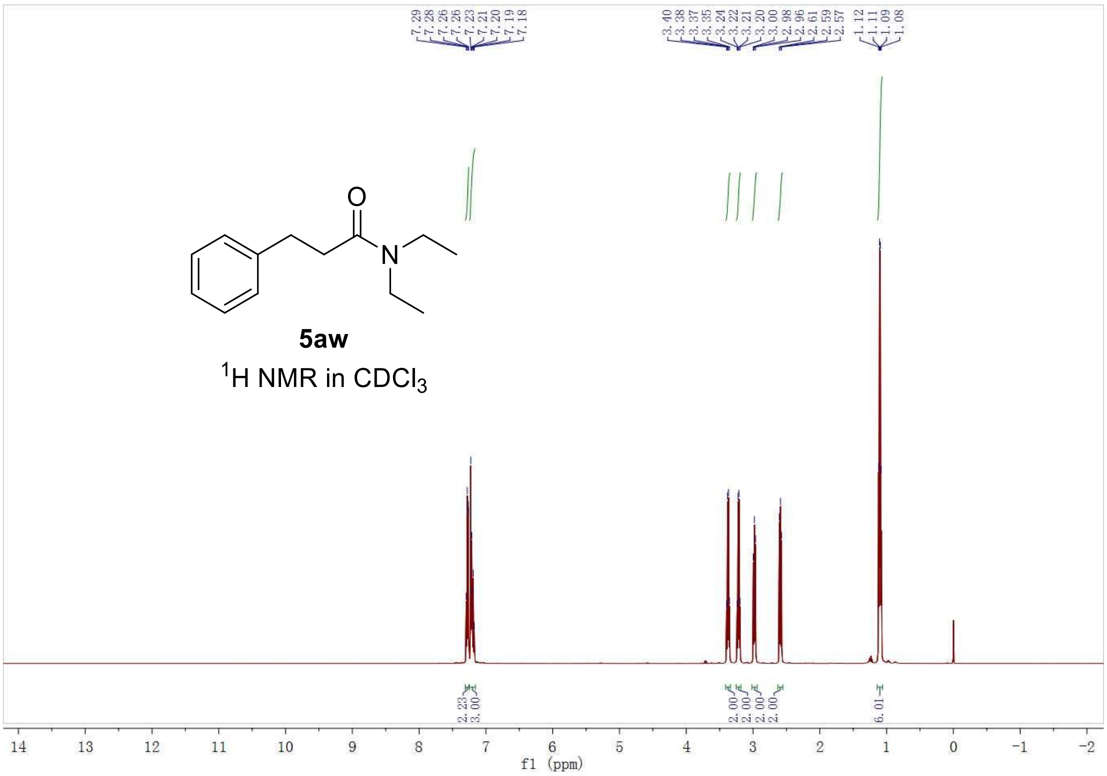
5au

^{1}H NMR in $CDCl_3$



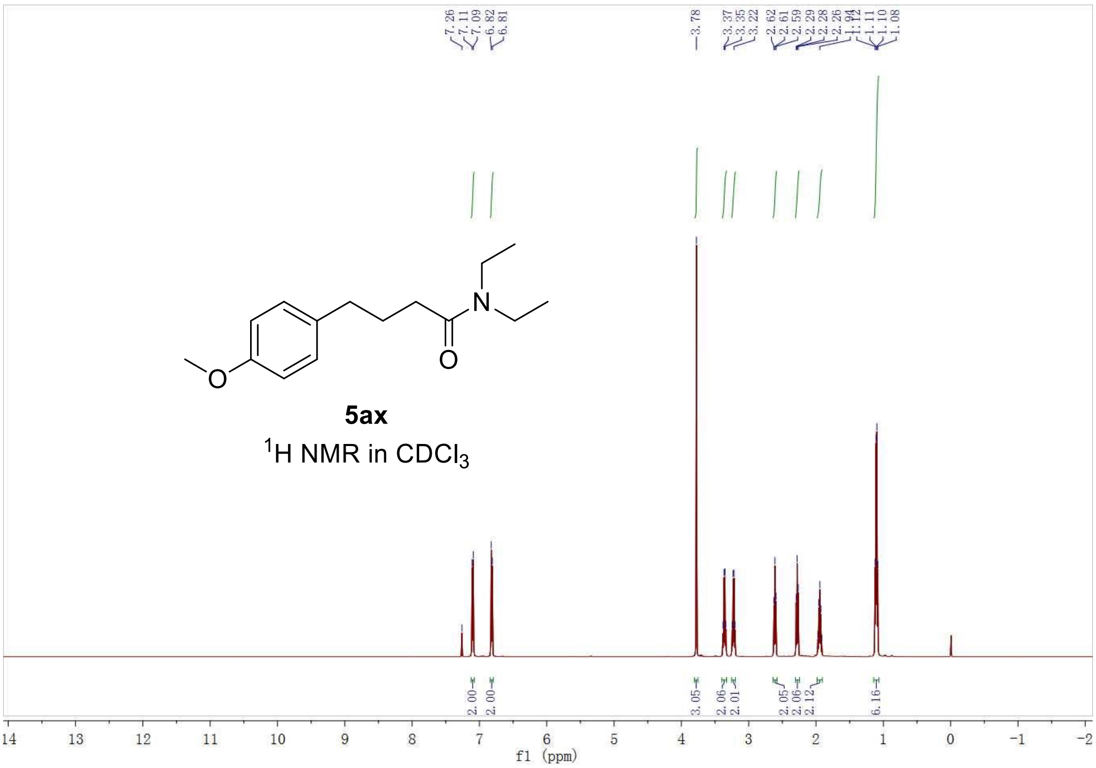
5av

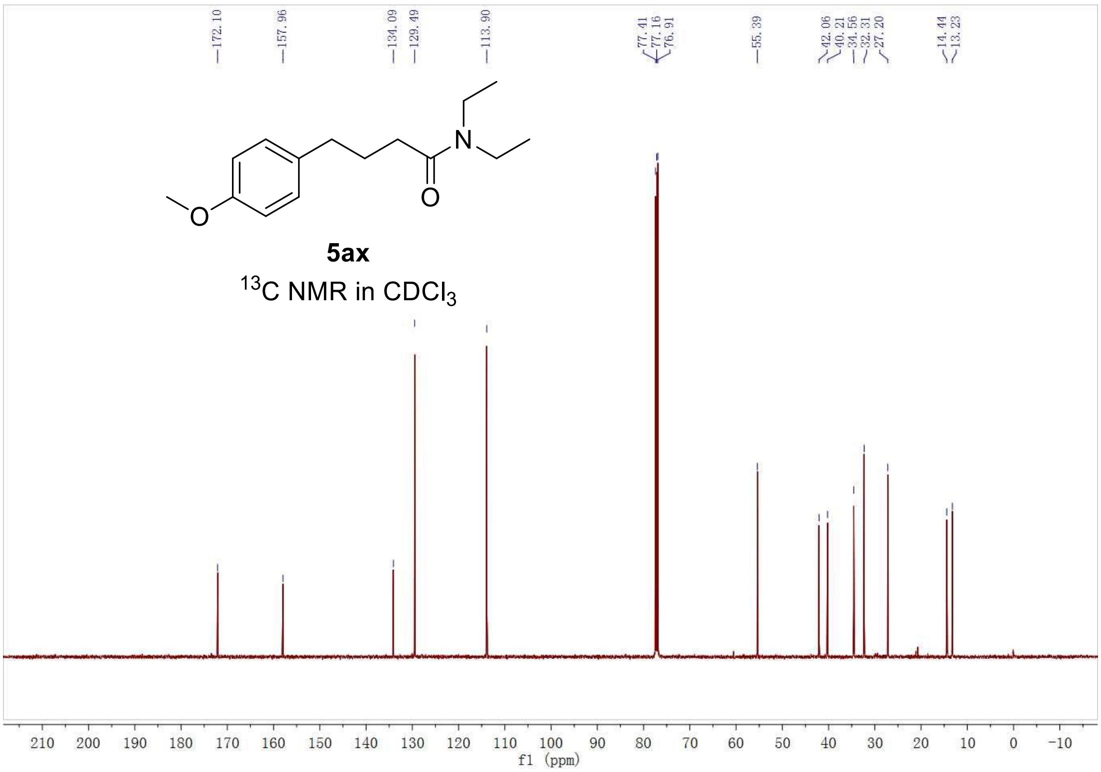
^{1}H NMR in CDCl$_3$

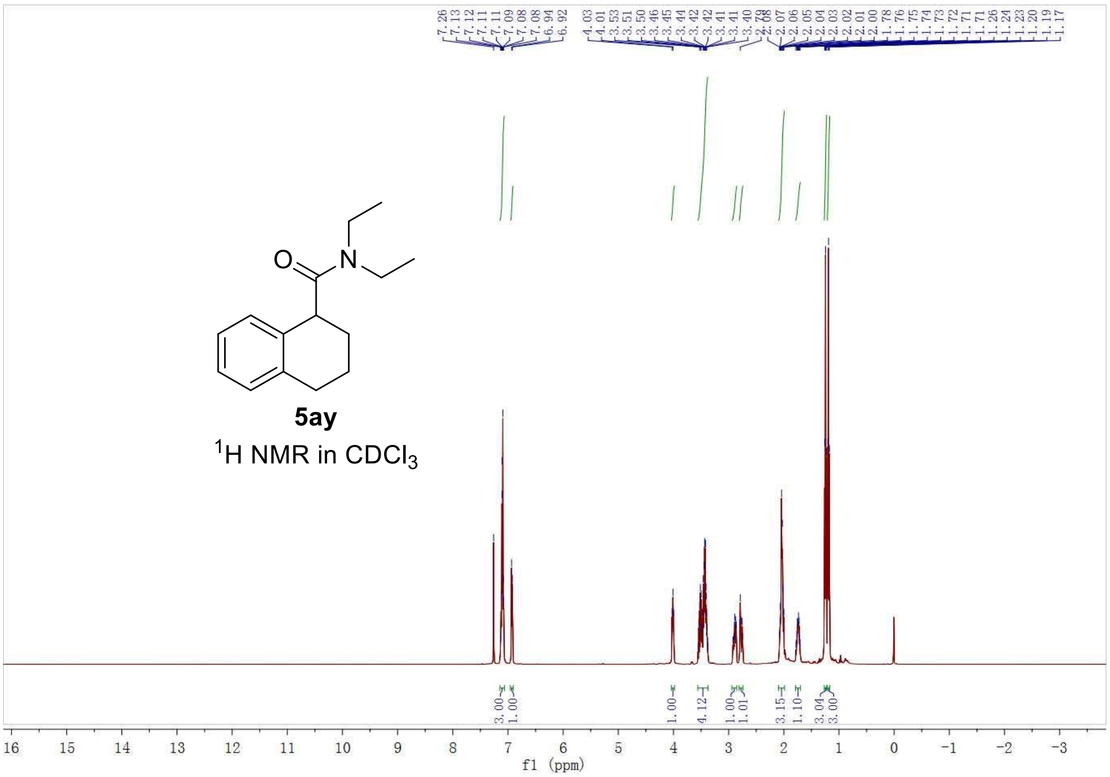


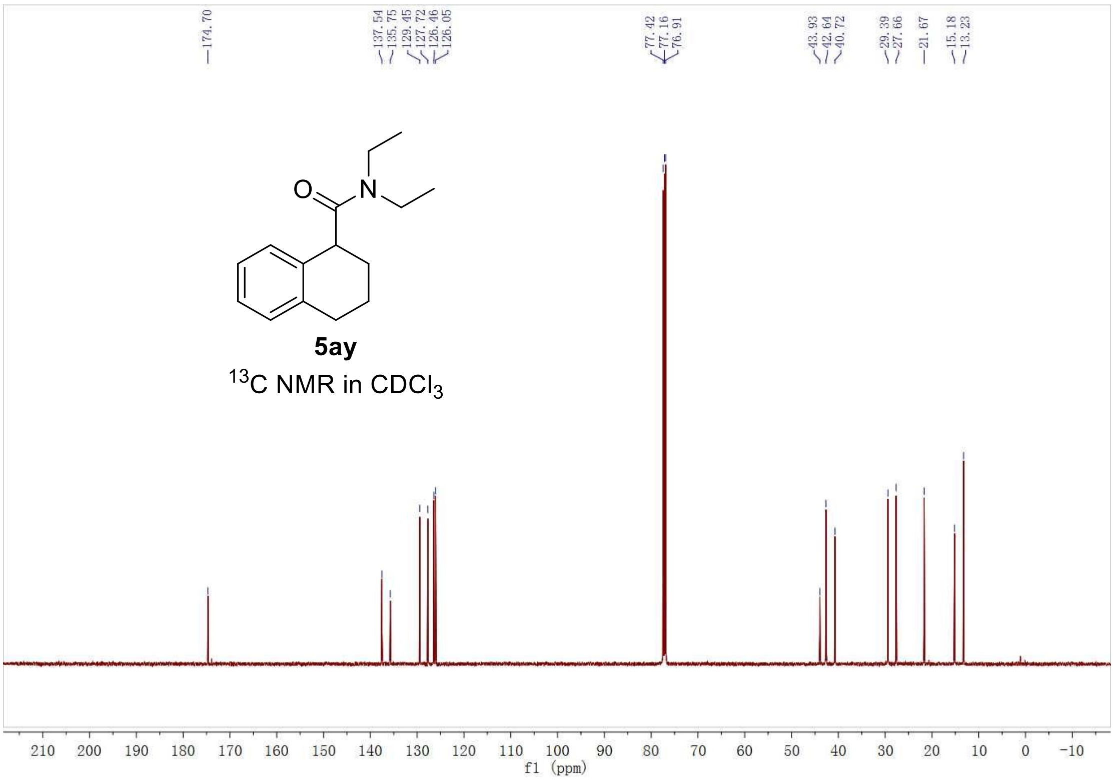
5aw

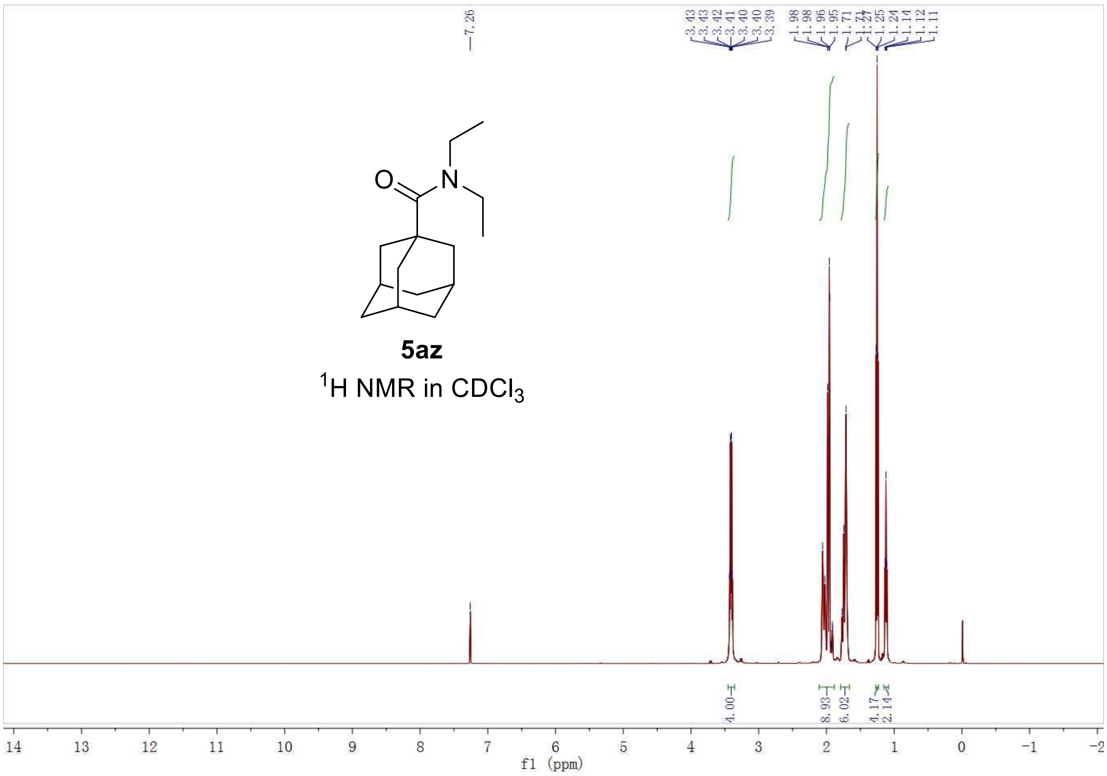
^{1}H NMR in CDCl$_3$


5ax
^{1}H NMR in CDCl$_3$

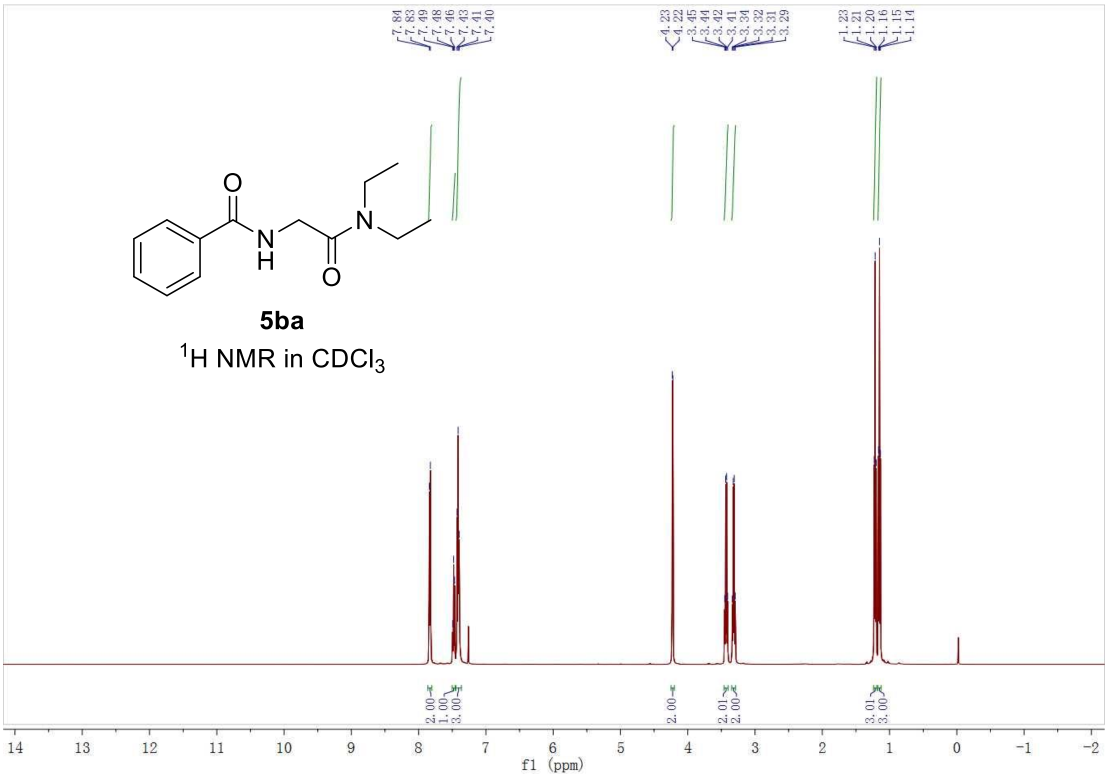

5ax
^{13}C NMR in CDCl$_3$


7.26
7.13
7.12
7.11
7.11
7.09
7.08
7.08
6.94
6.92
4.03
4.01
3.53
3.51
3.50
3.46
3.45
3.44
3.42
3.42
3.41
3.41
3.40
2.79
2.08
2.07
2.06
2.05
2.04
2.03
2.02
2.01
2.00
1.78
1.76
1.75
1.74
1.73
1.72
1.71
1.71
1.26
1.24
1.23
1.20
1.19
1.17
O
N
5ay
^{1}H NMR in CDCl$_3$
3.00
1.00
1.00
4.12
1.00
1.01
3.15
1.10
3.04
3.00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
−3
f1 (ppm)

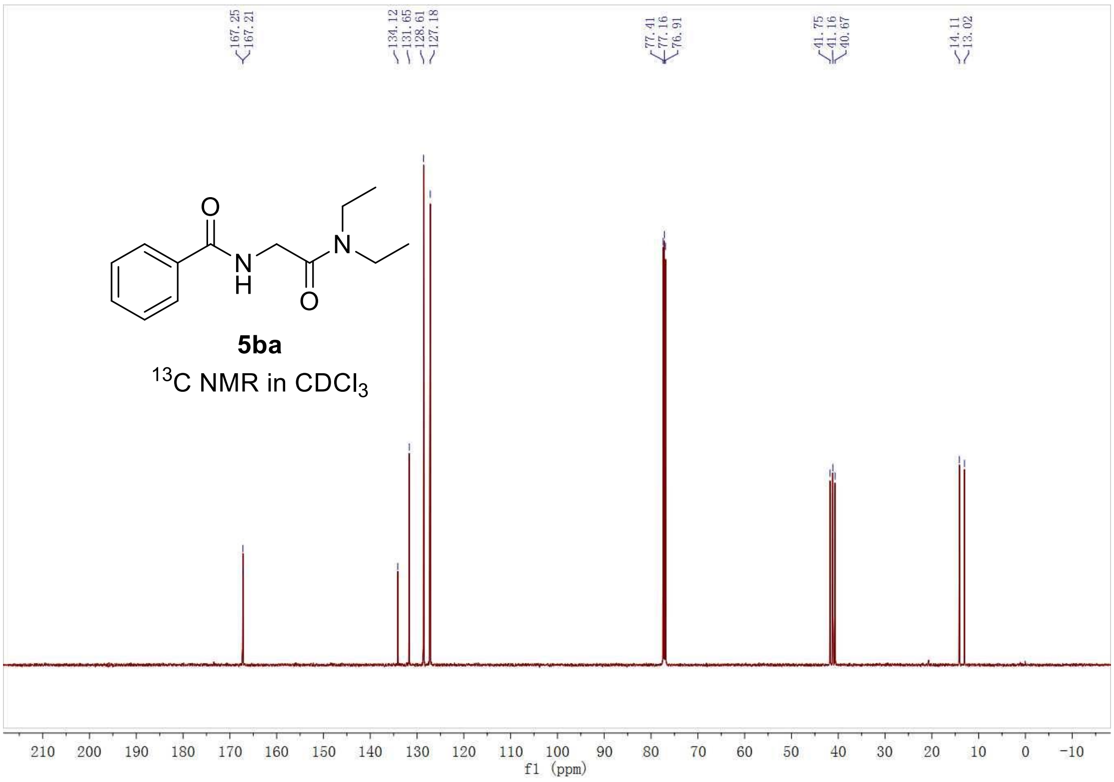

174.70
137.54
135.75
129.45
127.72
126.46
126.05
77.42
77.16
76.91
43.93
42.64
40.72
29.39
27.66
21.67
15.18
13.23
O
N
5ay
^{13}C NMR in CDCl$_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)


5az

^{1}H NMR in CDCl$_3$

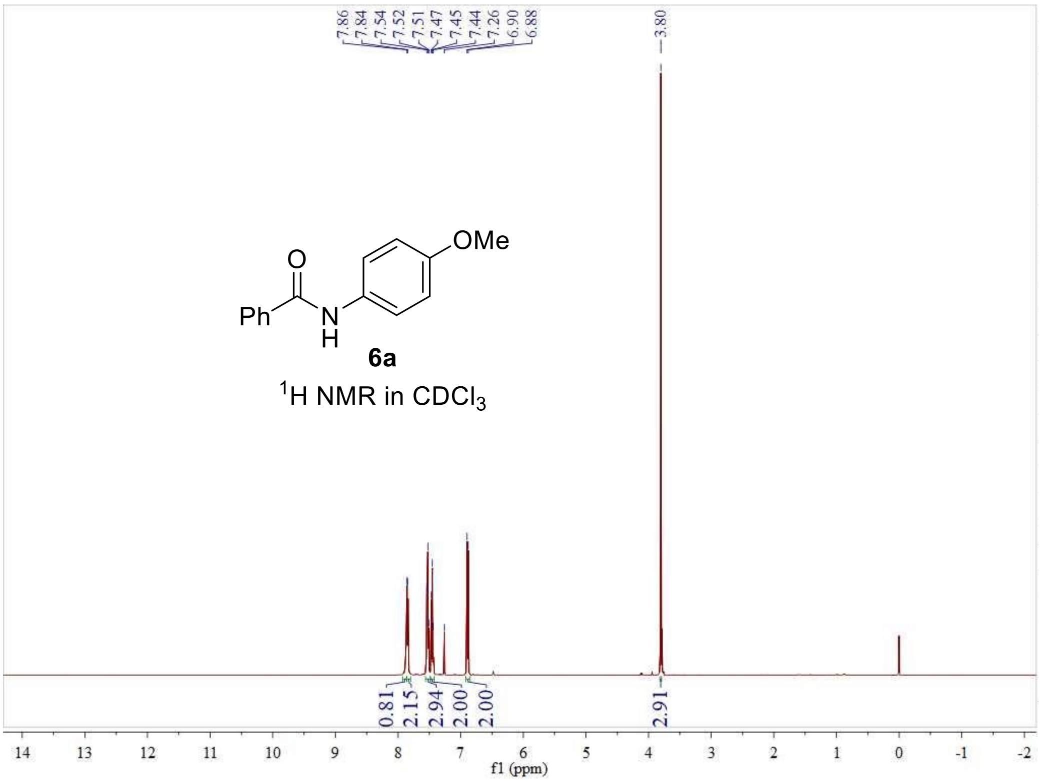

5ba

^{1}H NMR in CDCl$_3$



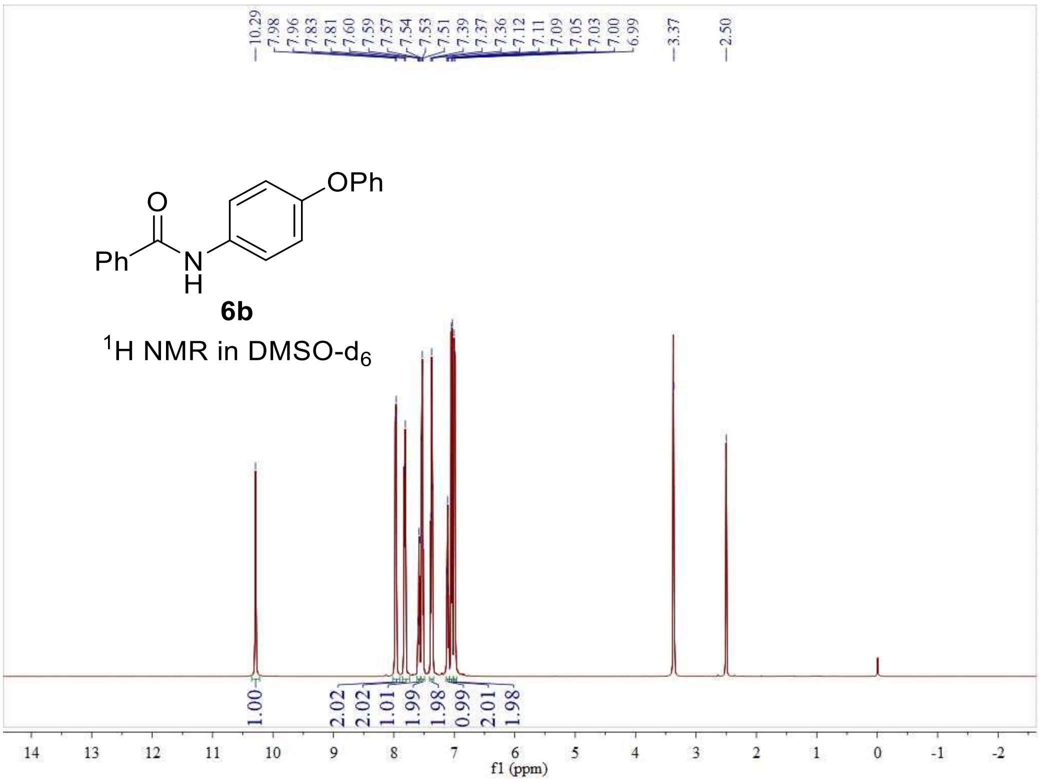
5ba

^{13}C NMR in CDCl$_3$



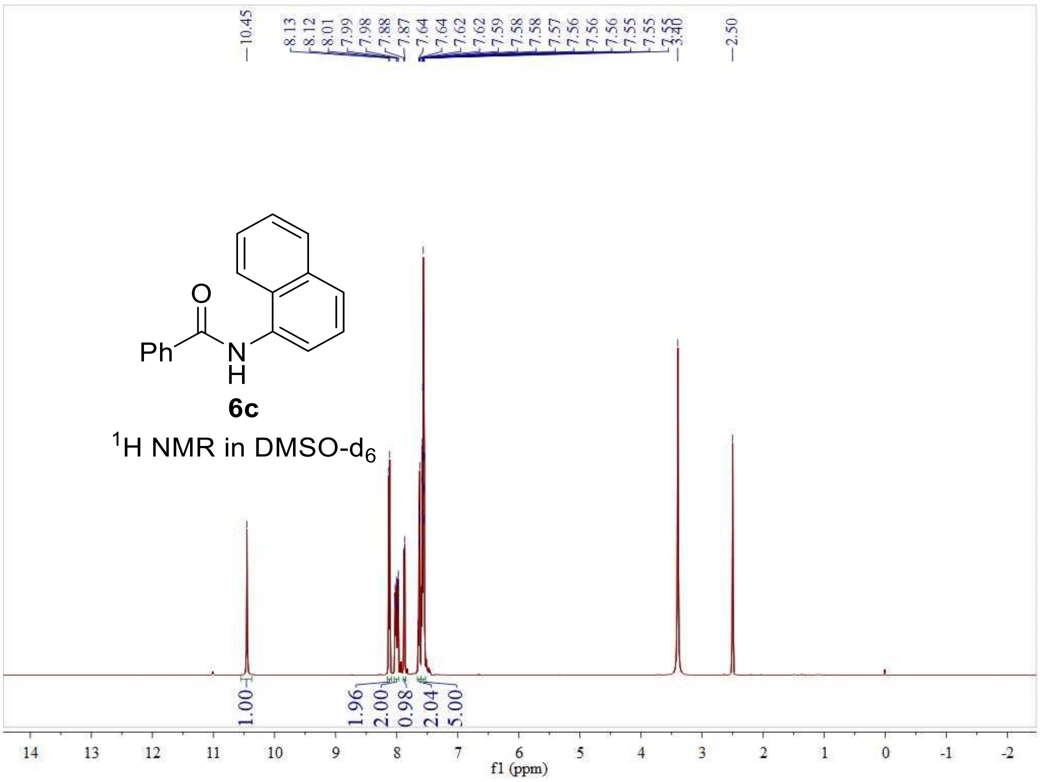
6a

^{1}H NMR in CDCl$_3$



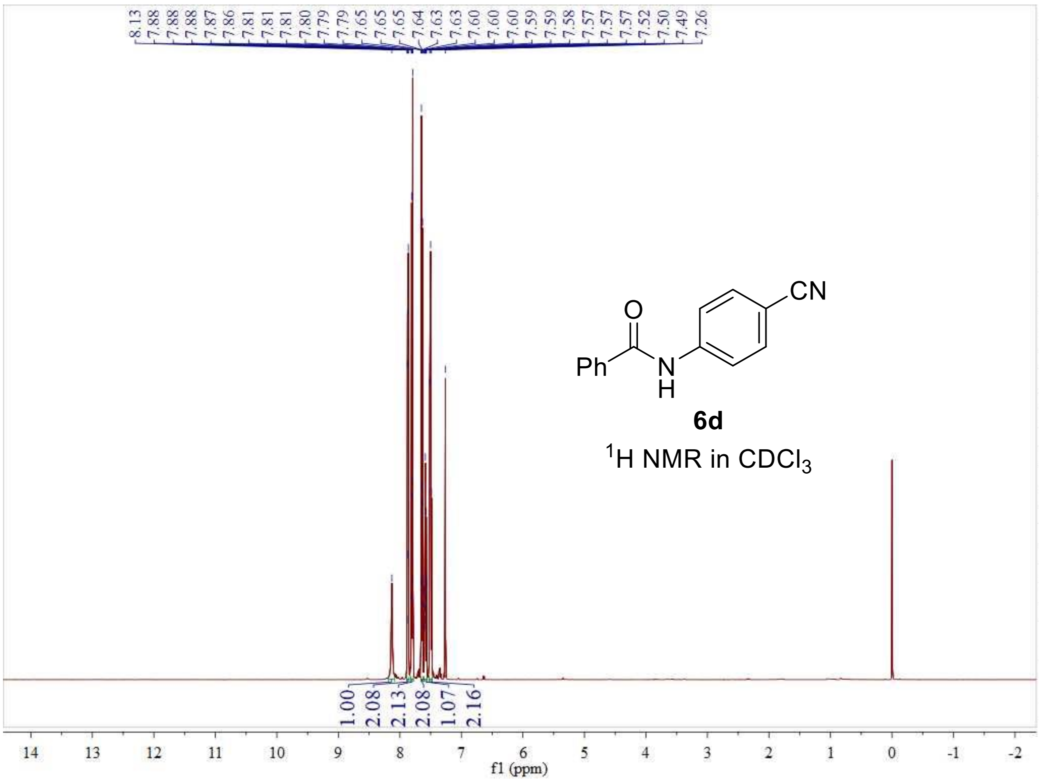
6b

^{1}H NMR in DMSO-d_6



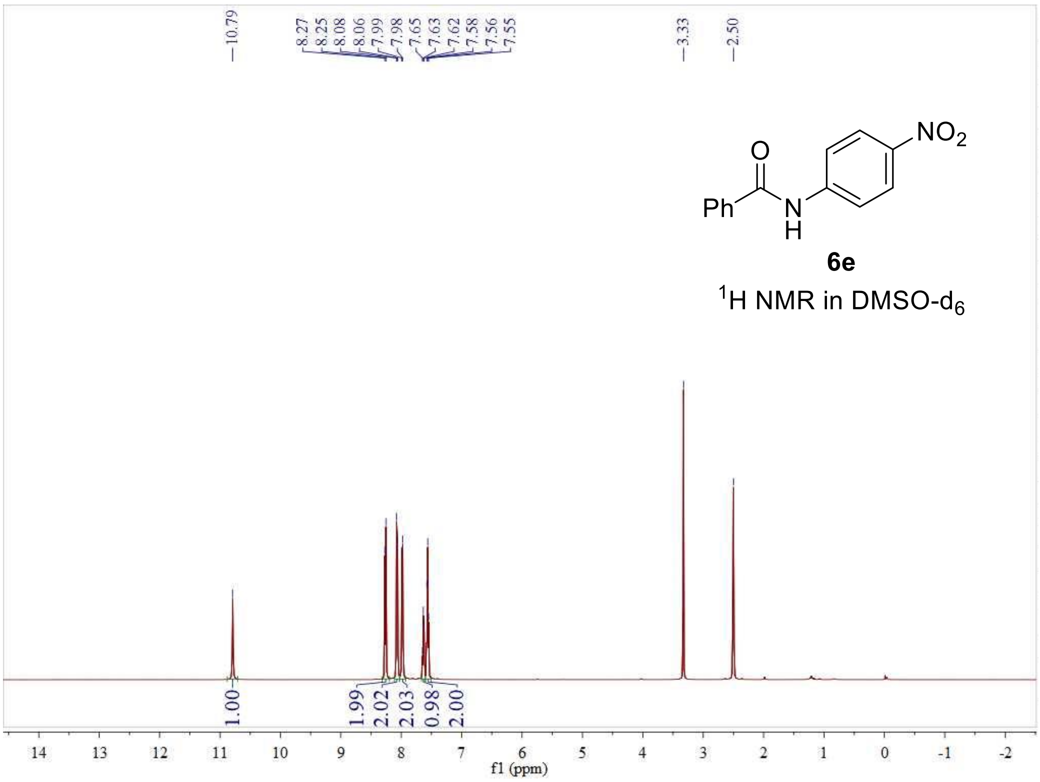
6c

^{1}H NMR in DMSO-d_6



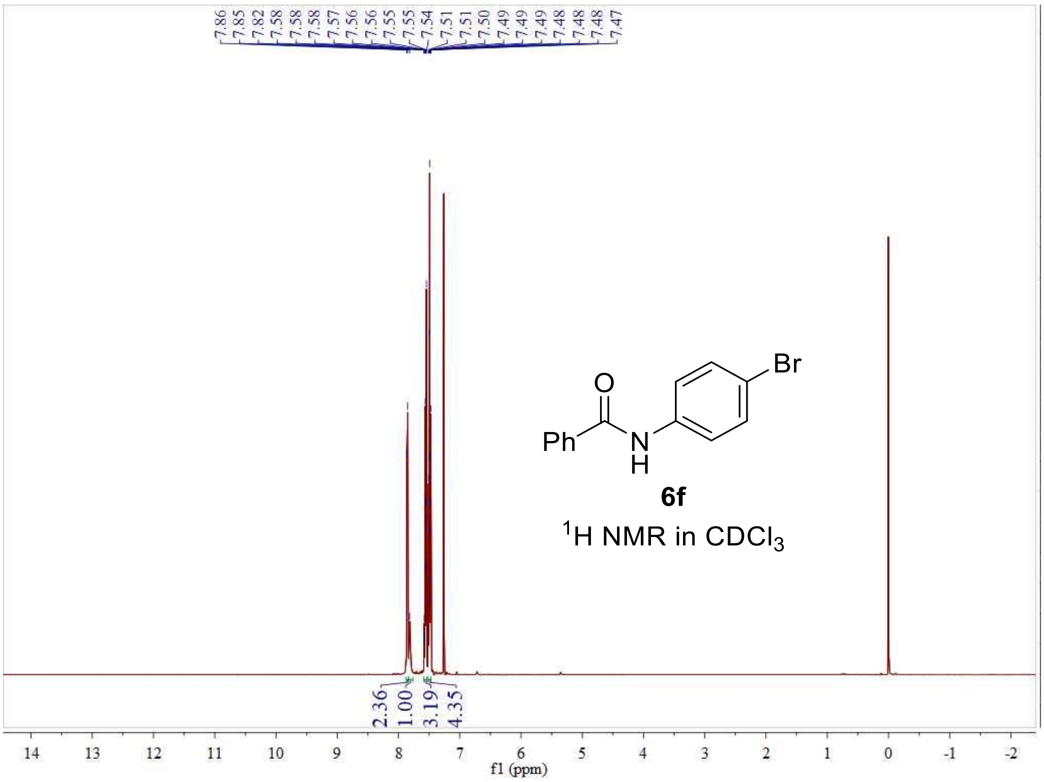
6d

^{1}H NMR in $CDCl_3$



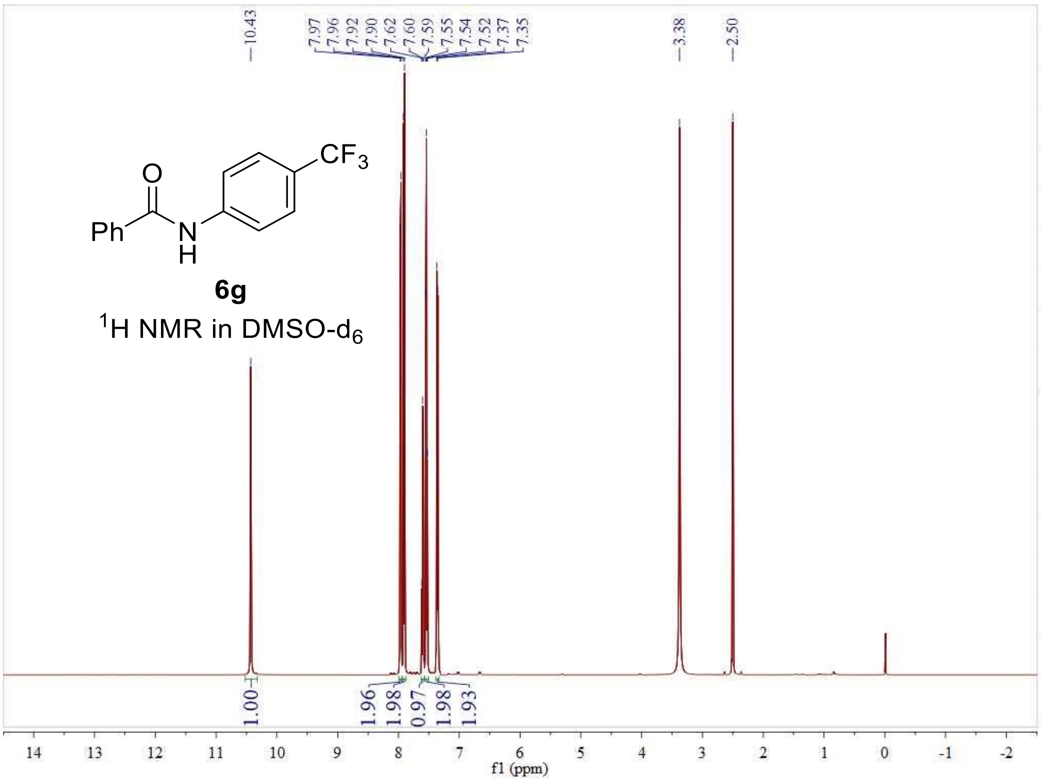
6e

^{1}H NMR in DMSO-d_6



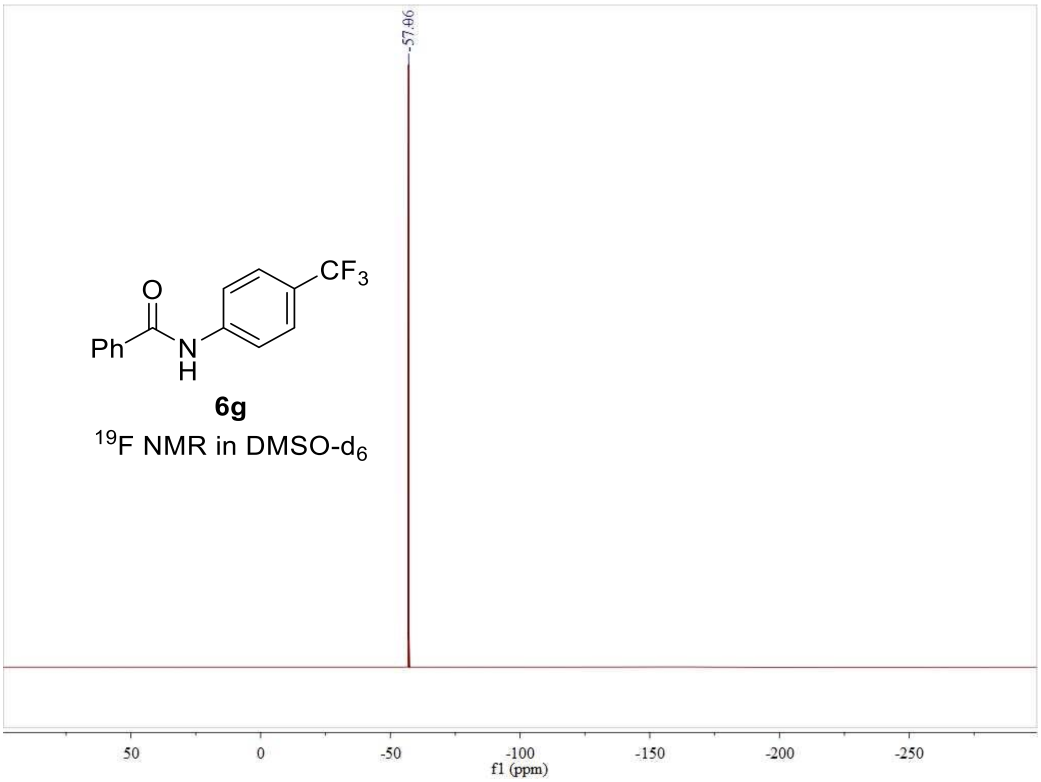
6f

^{1}H NMR in $CDCl_3$



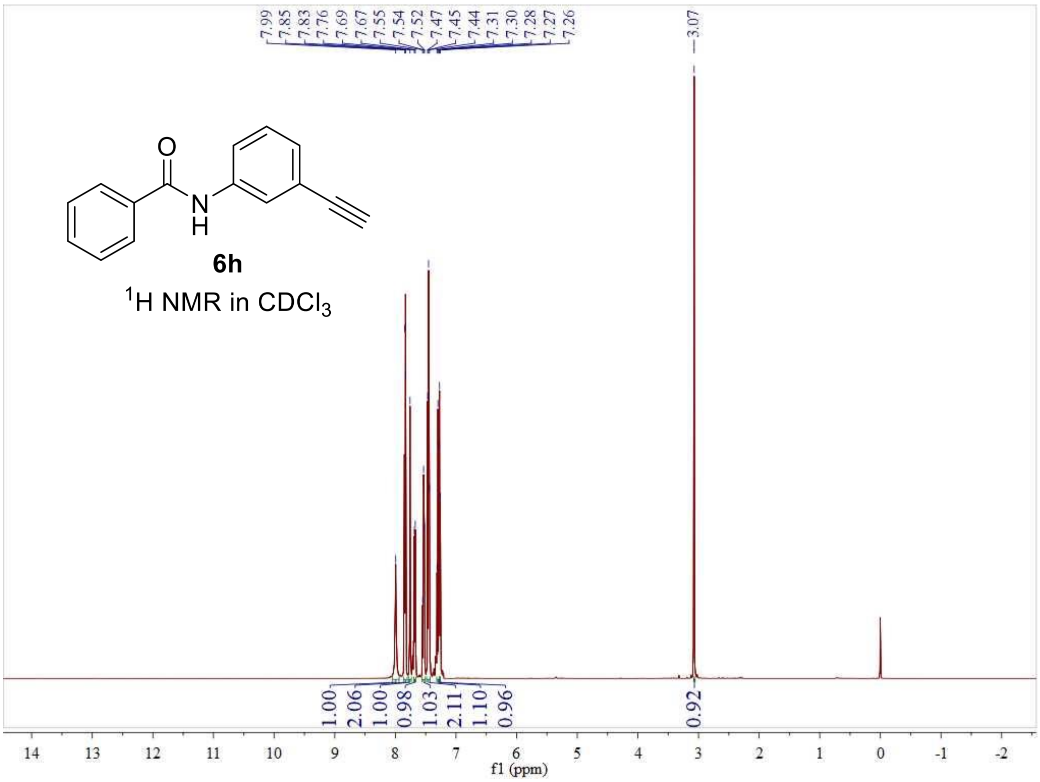
6g

^{1}H NMR in DMSO-d_6



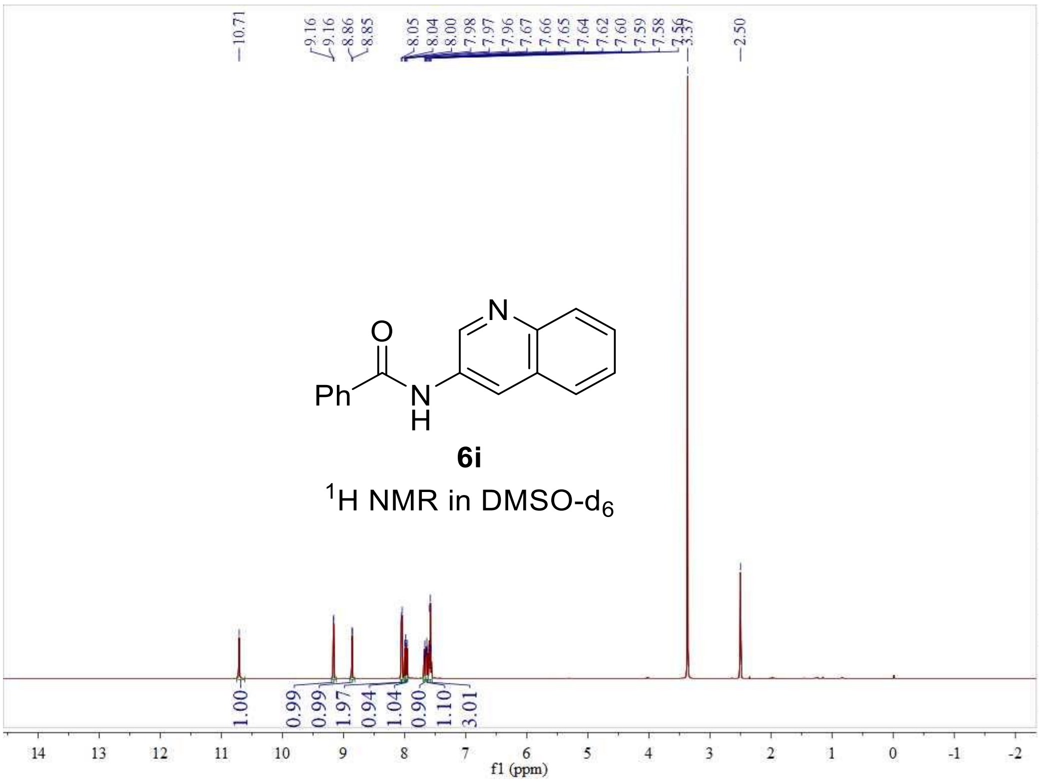
6g

^{19}F NMR in DMSO-d_6



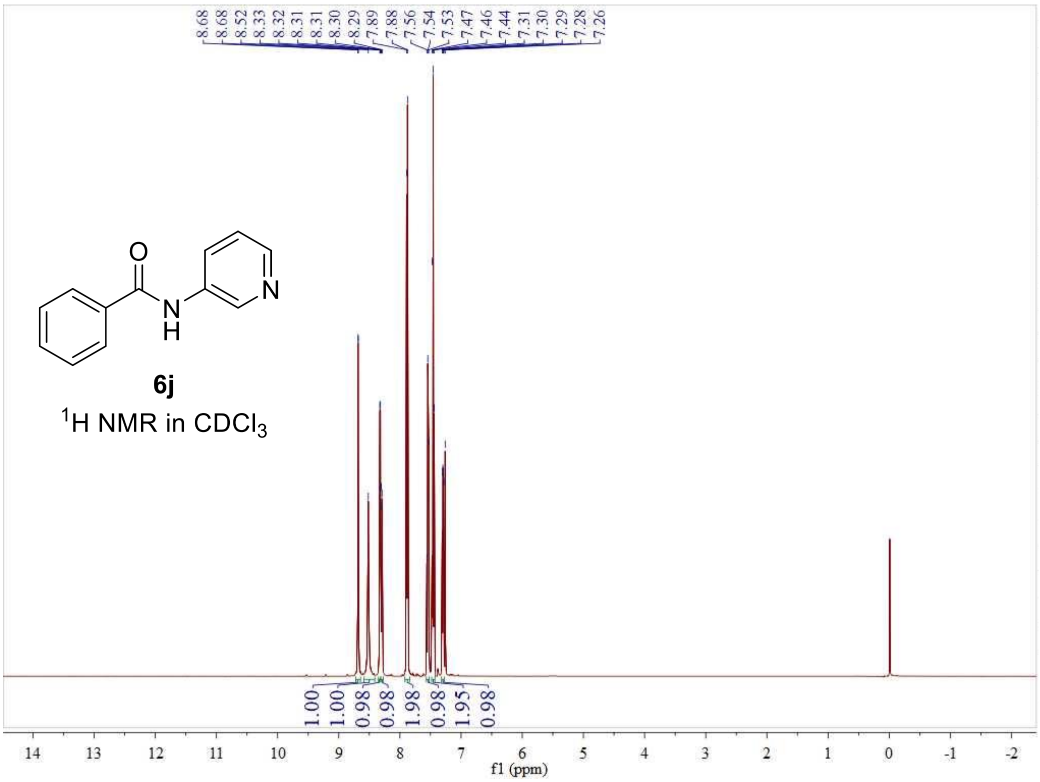
6h

^{1}H NMR in CDCl$_3$



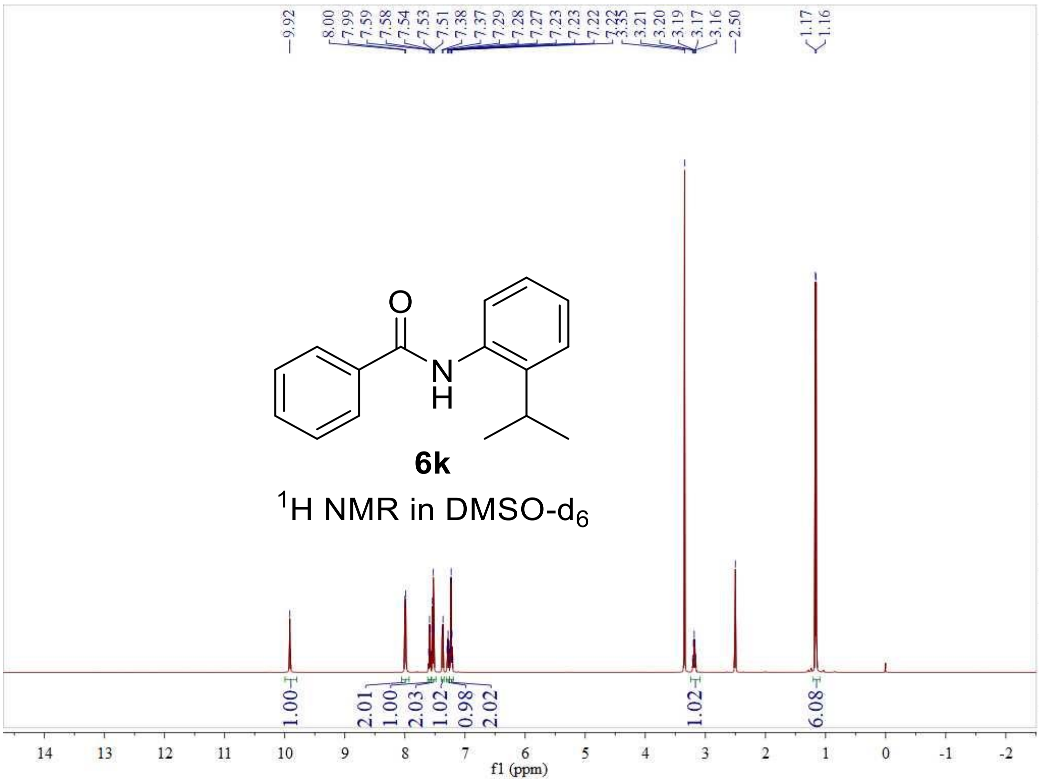
6i

^{1}H NMR in DMSO-d_6

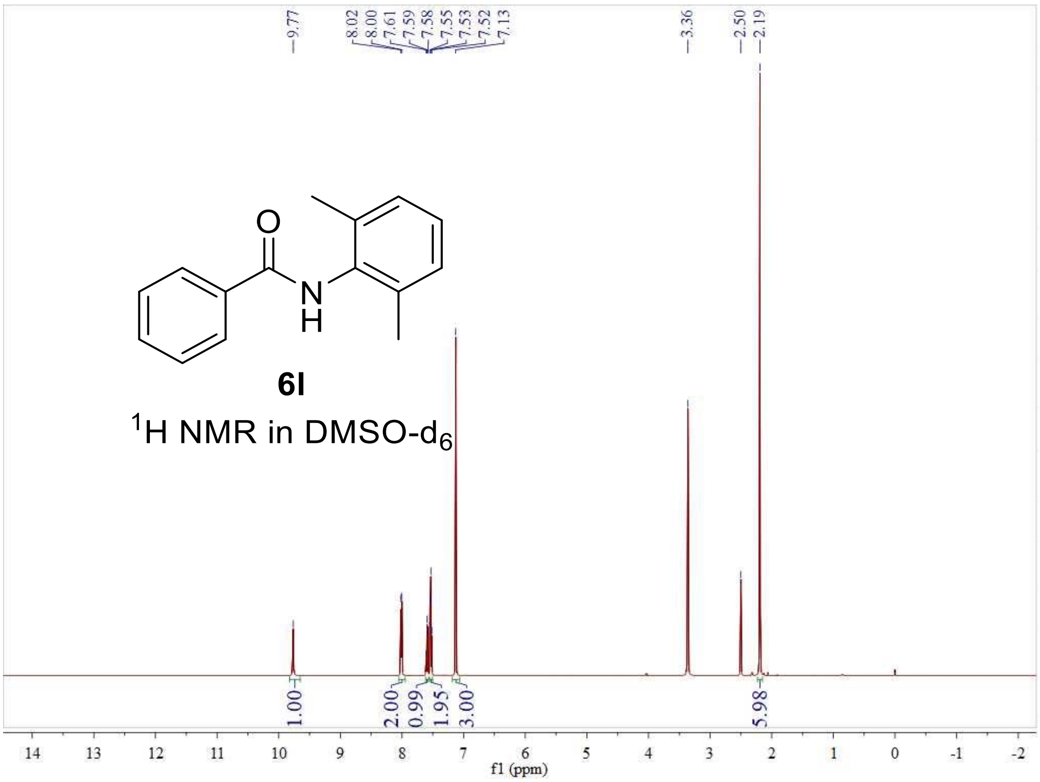


6j

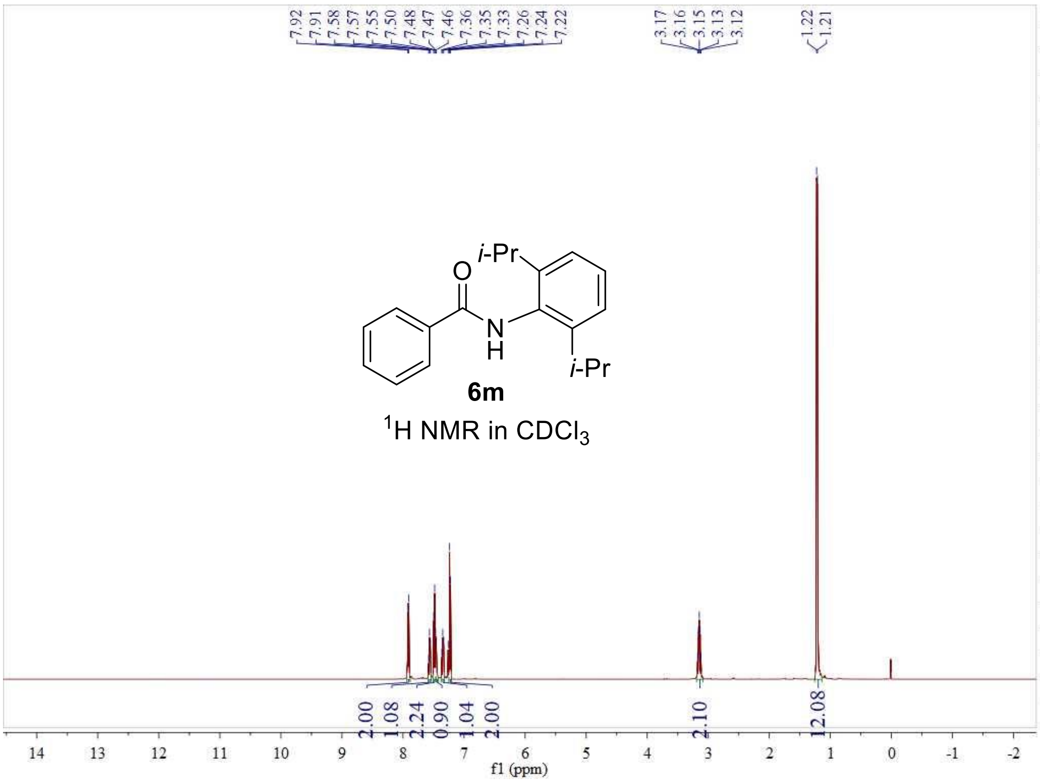
^{1}H NMR in $CDCl_3$


6k

^{1}H NMR in DMSO-d_6

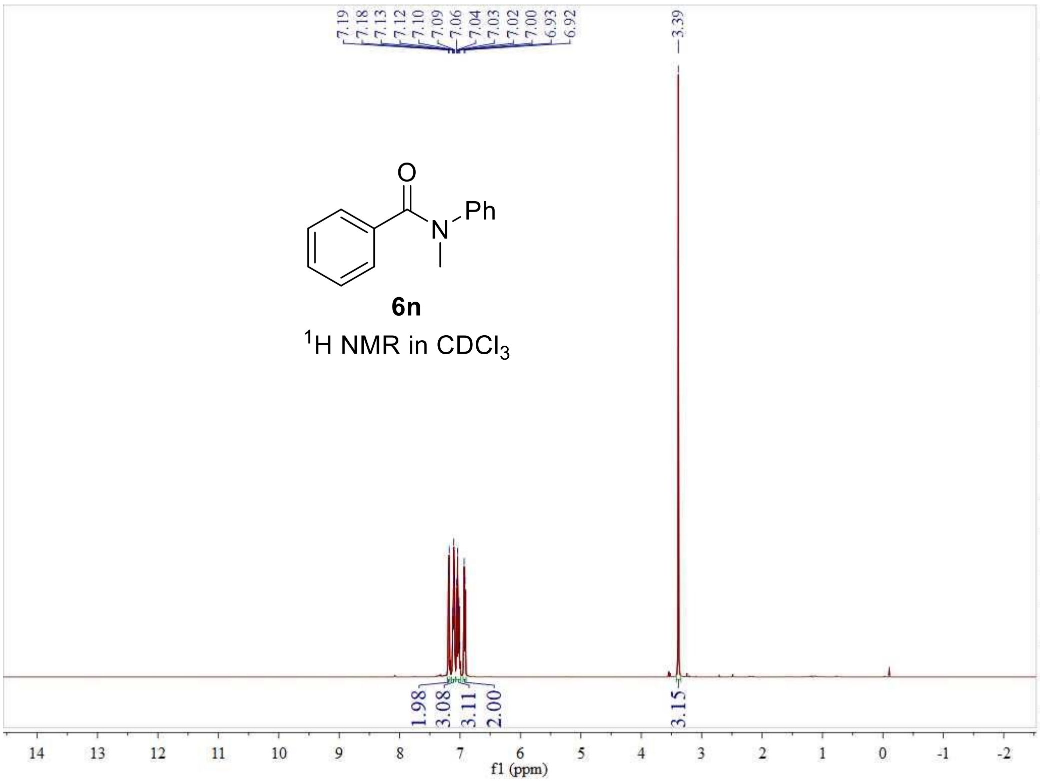

6l

^{1}H NMR in DMSO-d_6



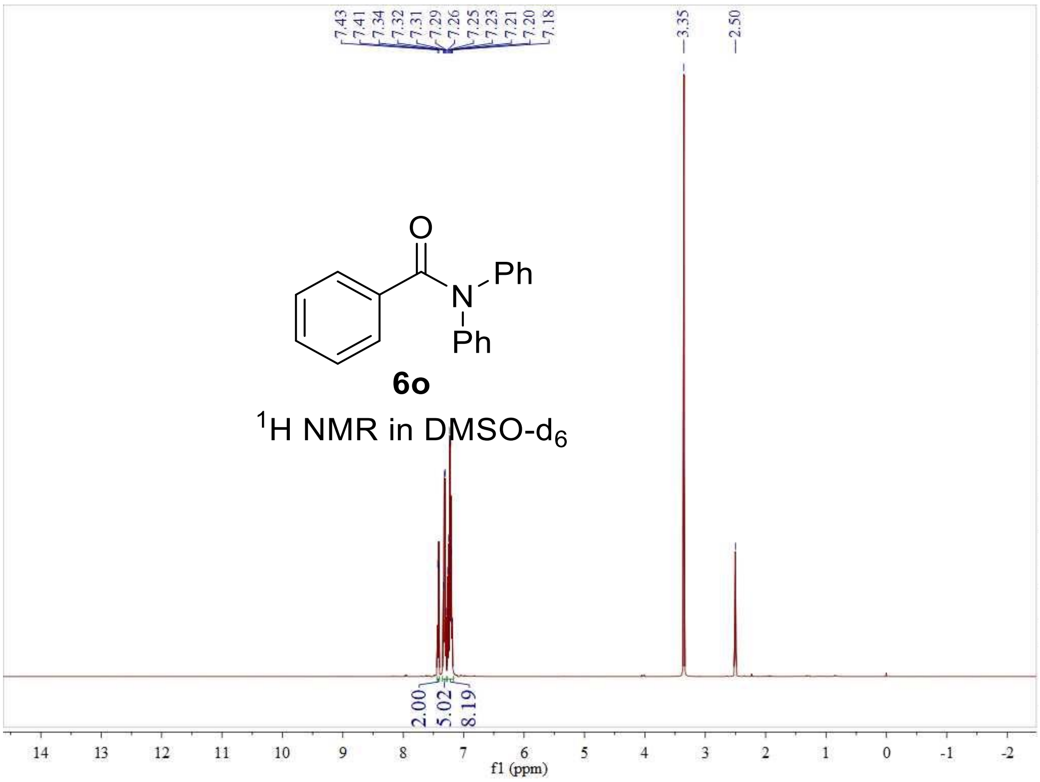
6m

^{1}H NMR in CDCl$_3$



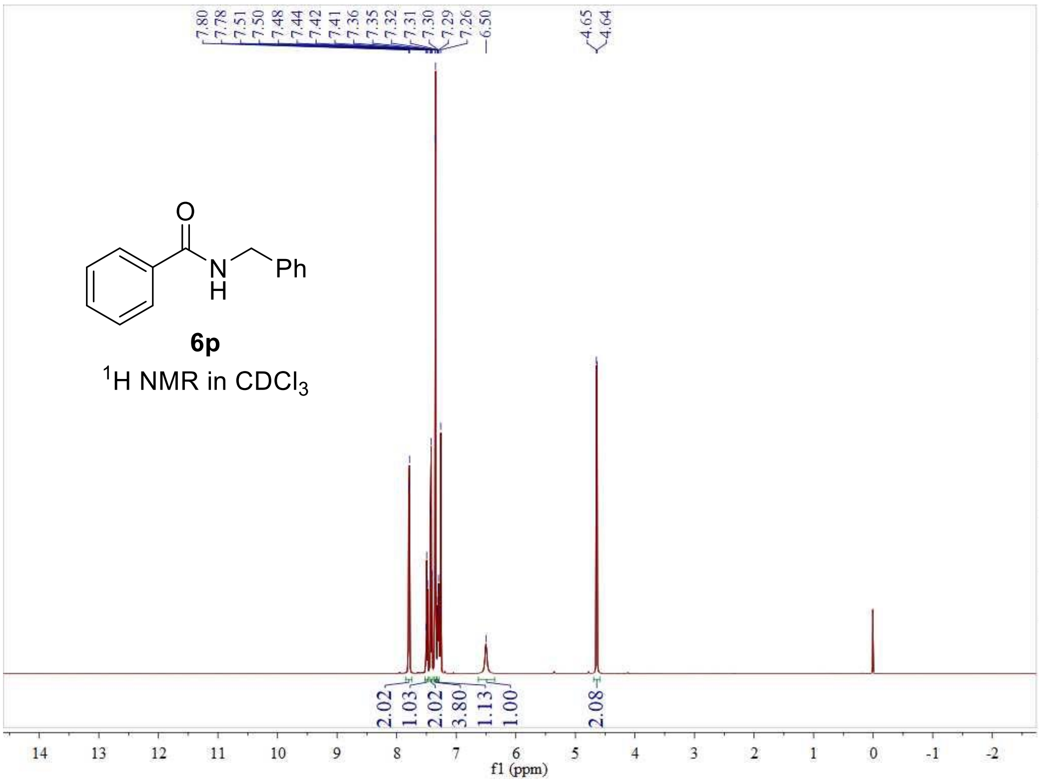
6n

^{1}H NMR in CDCl$_3$



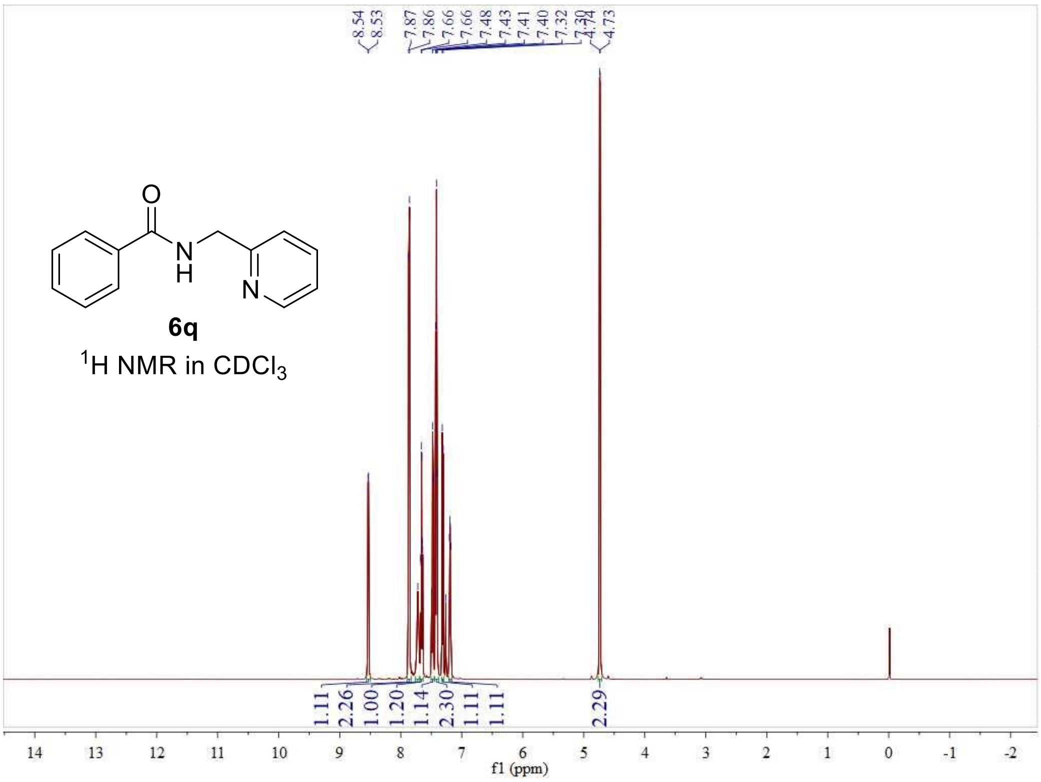
6o

^{1}H NMR in DMSO-d$_6$



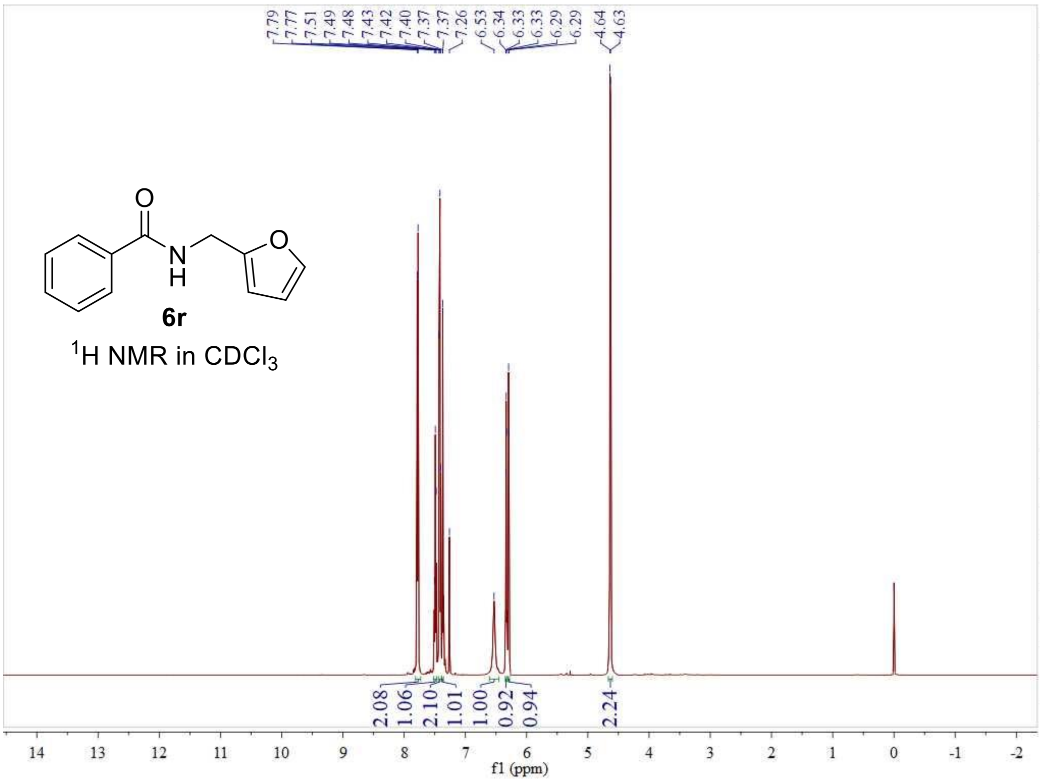
6p

^{1}H NMR in CDCl$_3$



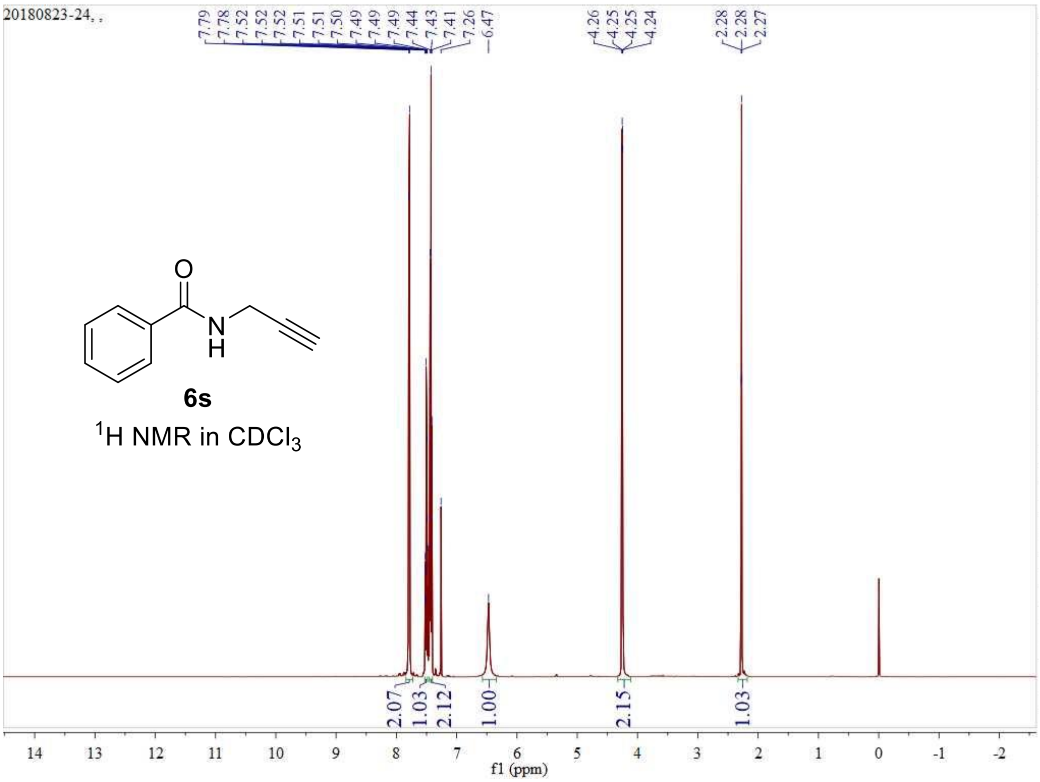
6q

^{1}H NMR in CDCl$_3$



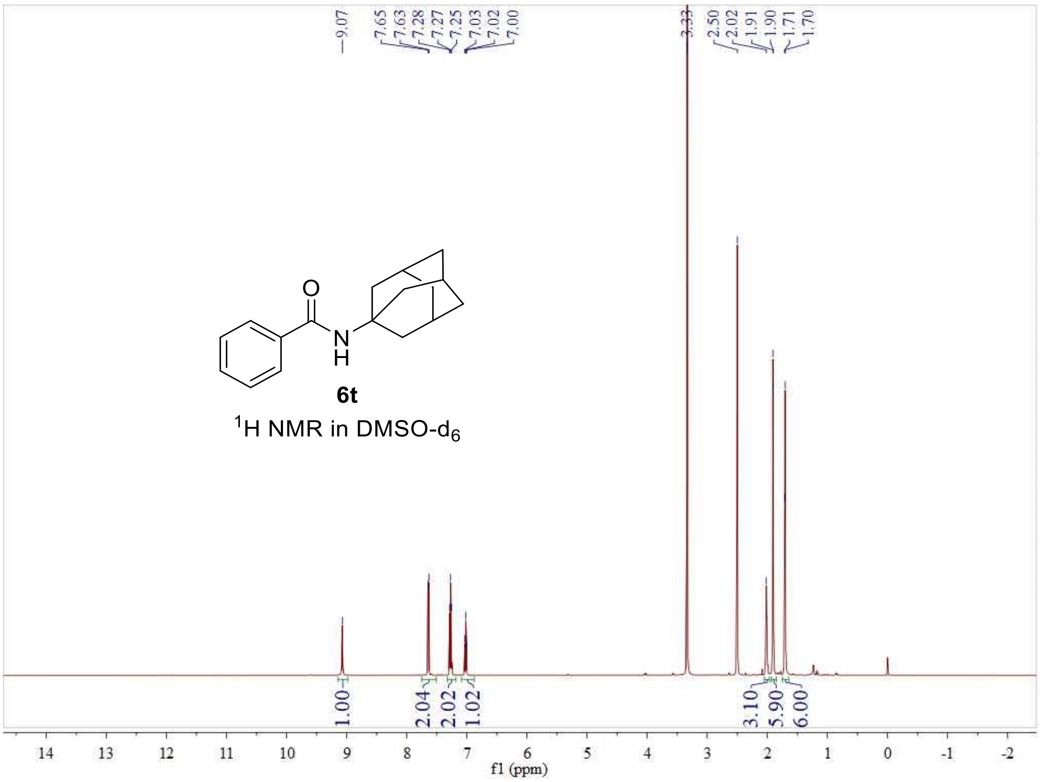
6r

^{1}H NMR in CDCl$_3$



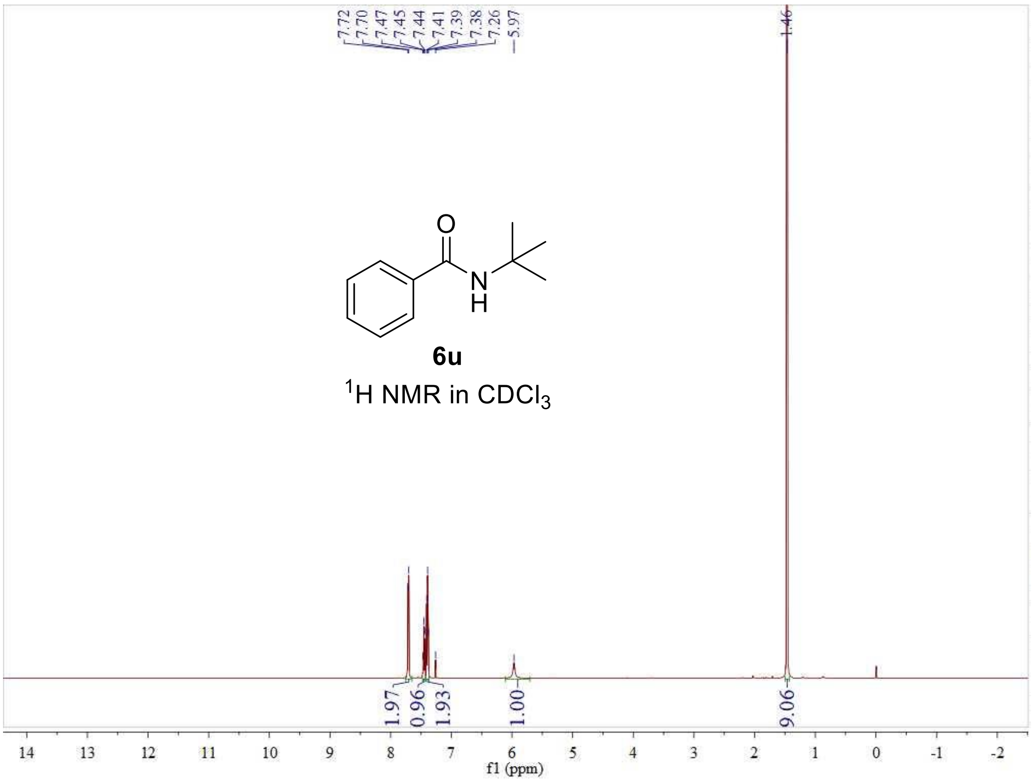
6s

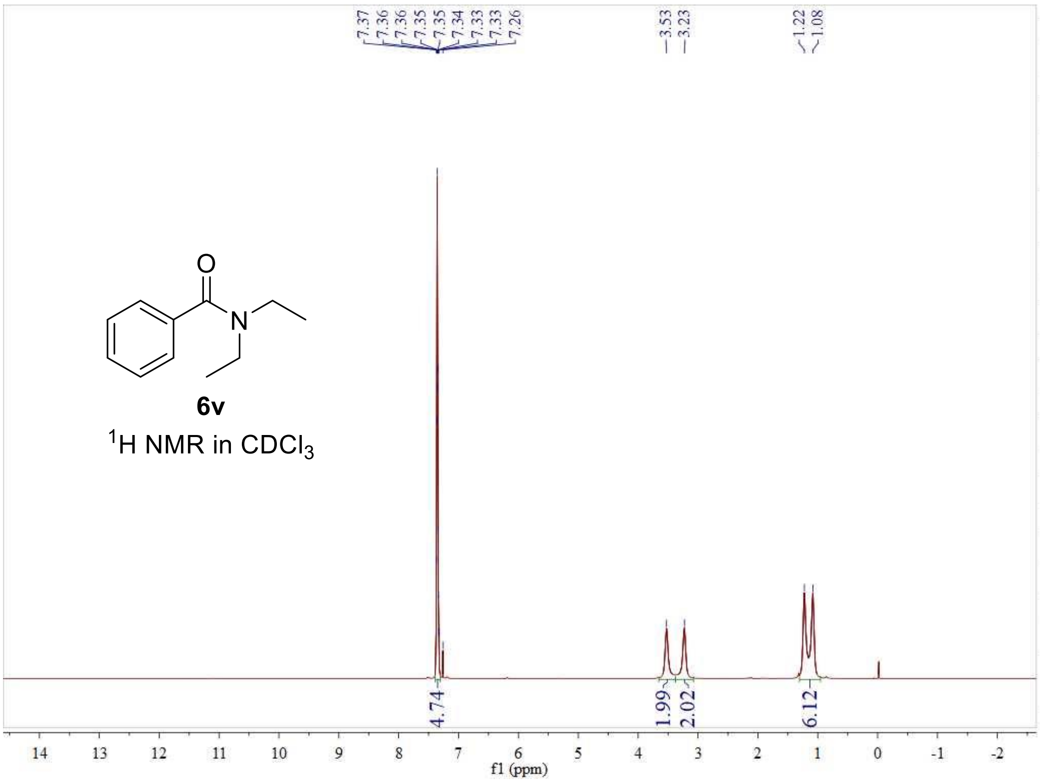
^{1}H NMR in $CDCl_3$

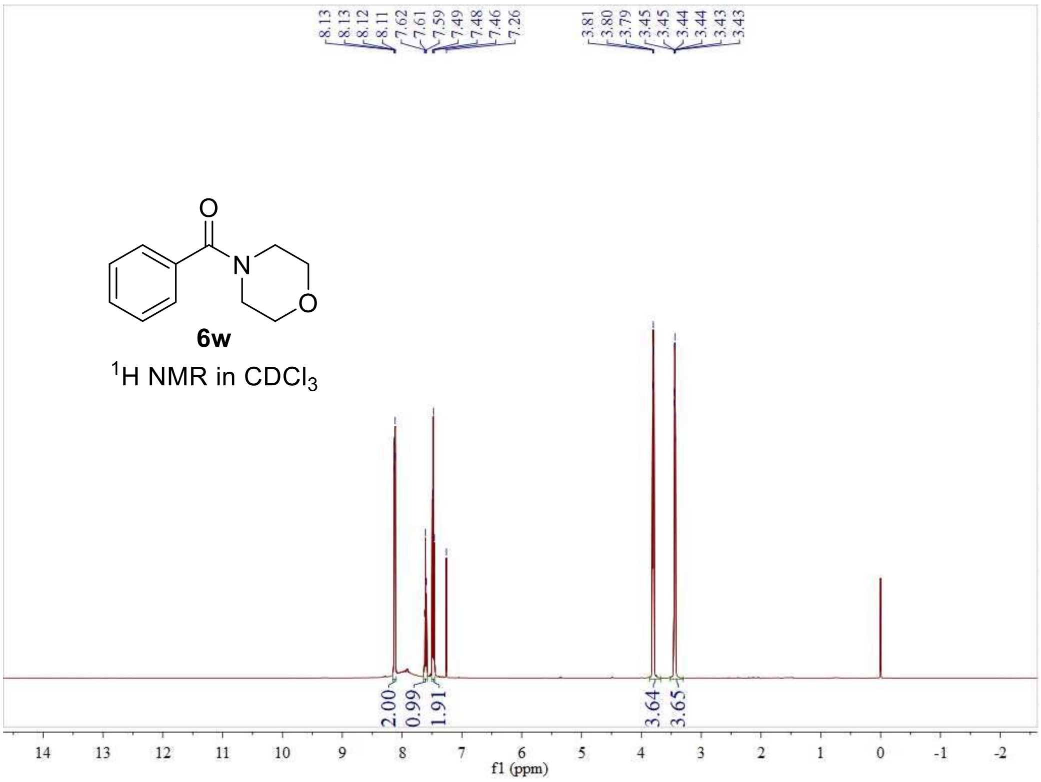


6t

^{1}H NMR in DMSO-d_6

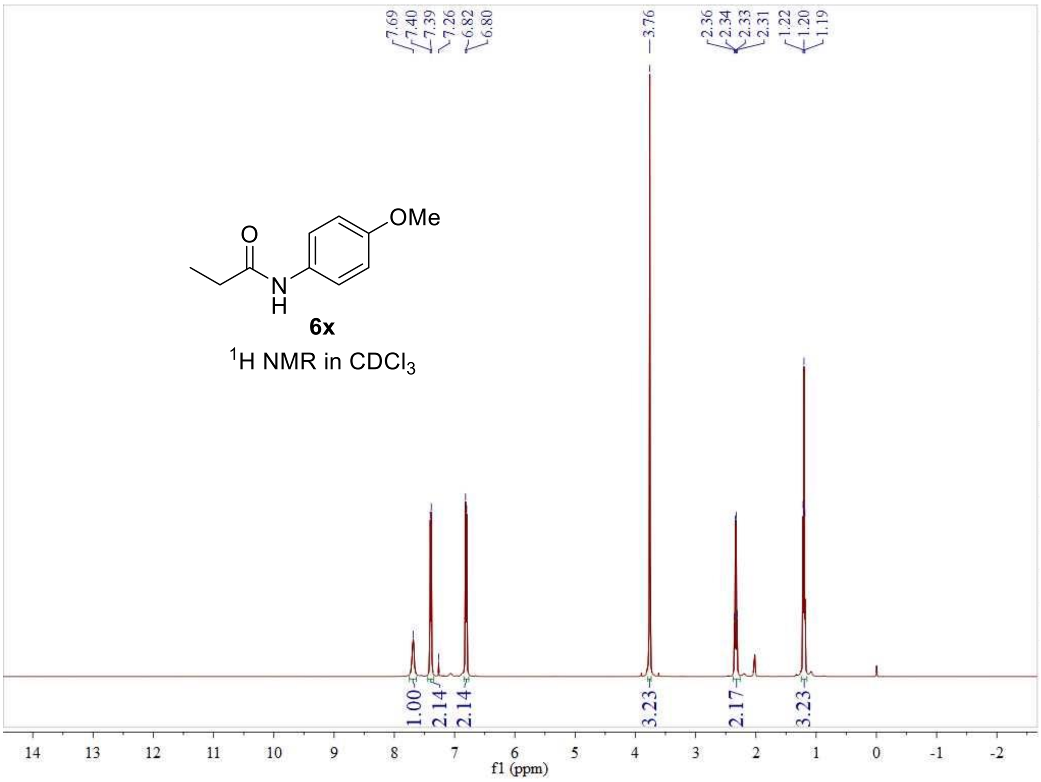

7.72
7.70
7.47
7.45
7.44
7.41
7.39
7.38
7.26
5.97
1.46
6u
^{1}H NMR in CDCl$_3$
1.97
0.96
1.93
1.00
9.06
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.26
3.53
3.23
1.22
1.08
6v
^{1}H NMR in CDCl$_3$
4.74
1.99
2.02
6.12
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)



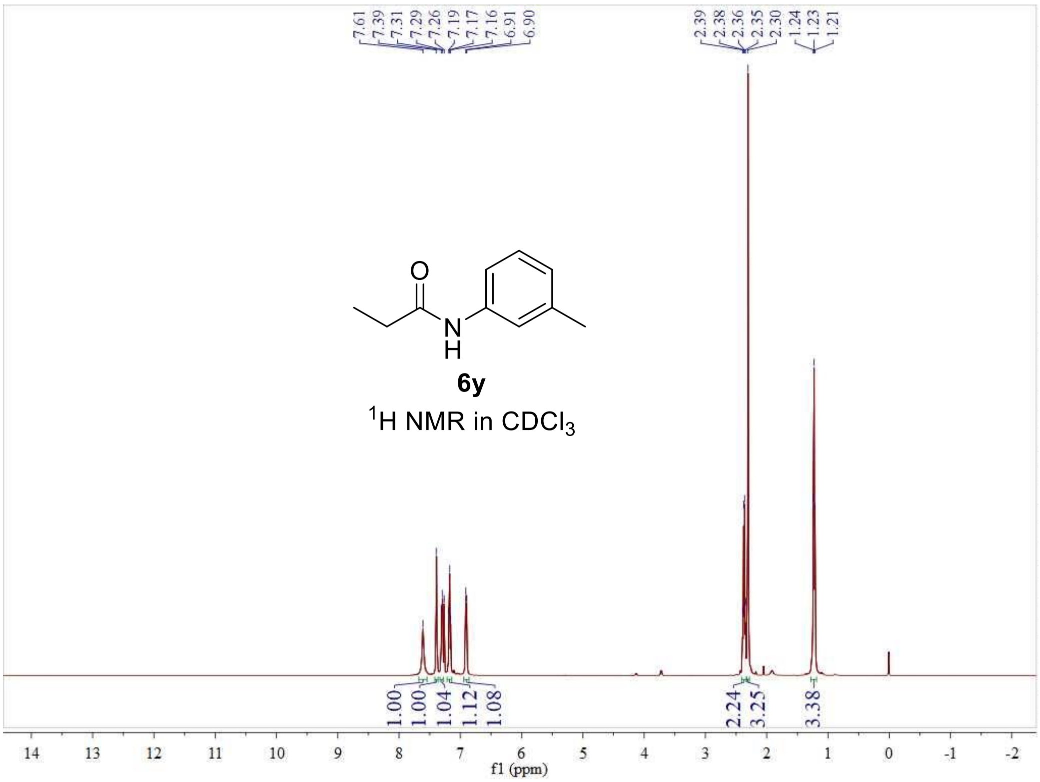
6w

^{1}H NMR in $CDCl_3$



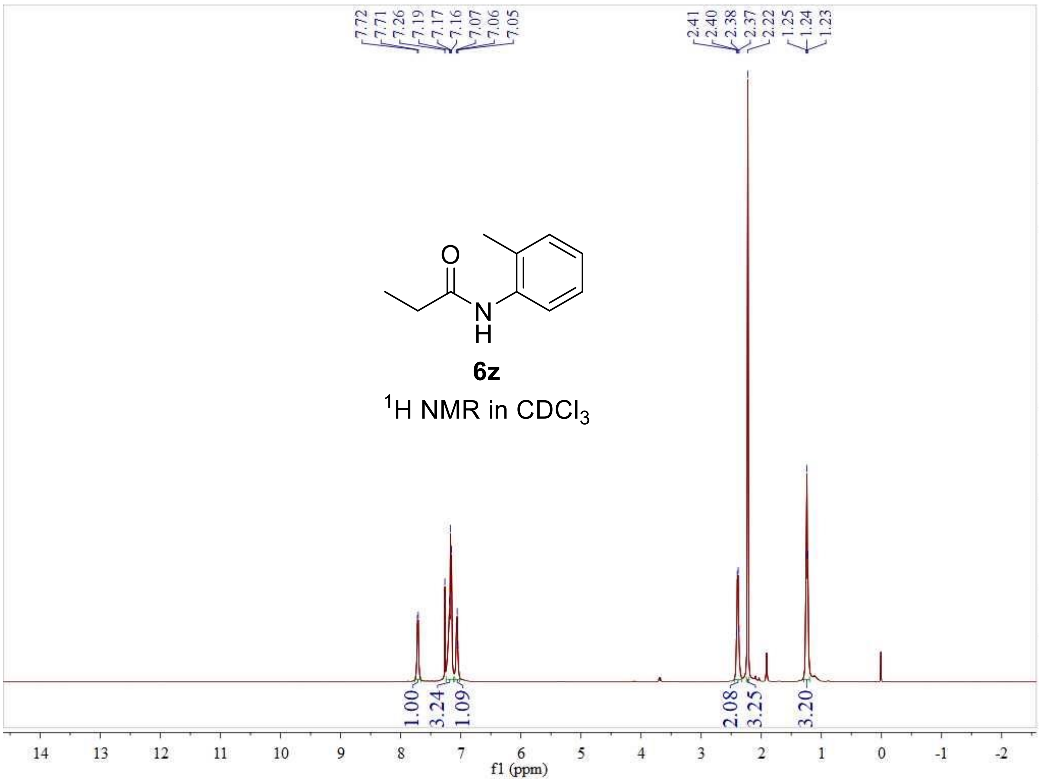
6x

^{1}H NMR in $CDCl_3$



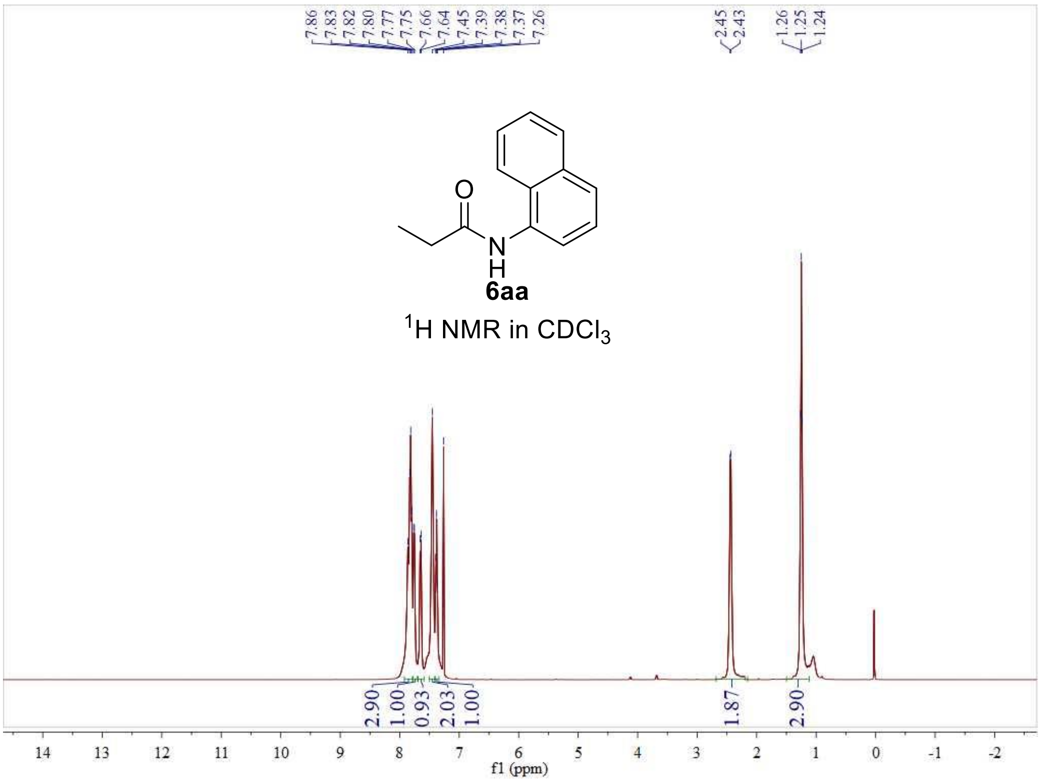
6y

^{1}H NMR in CDCl$_3$



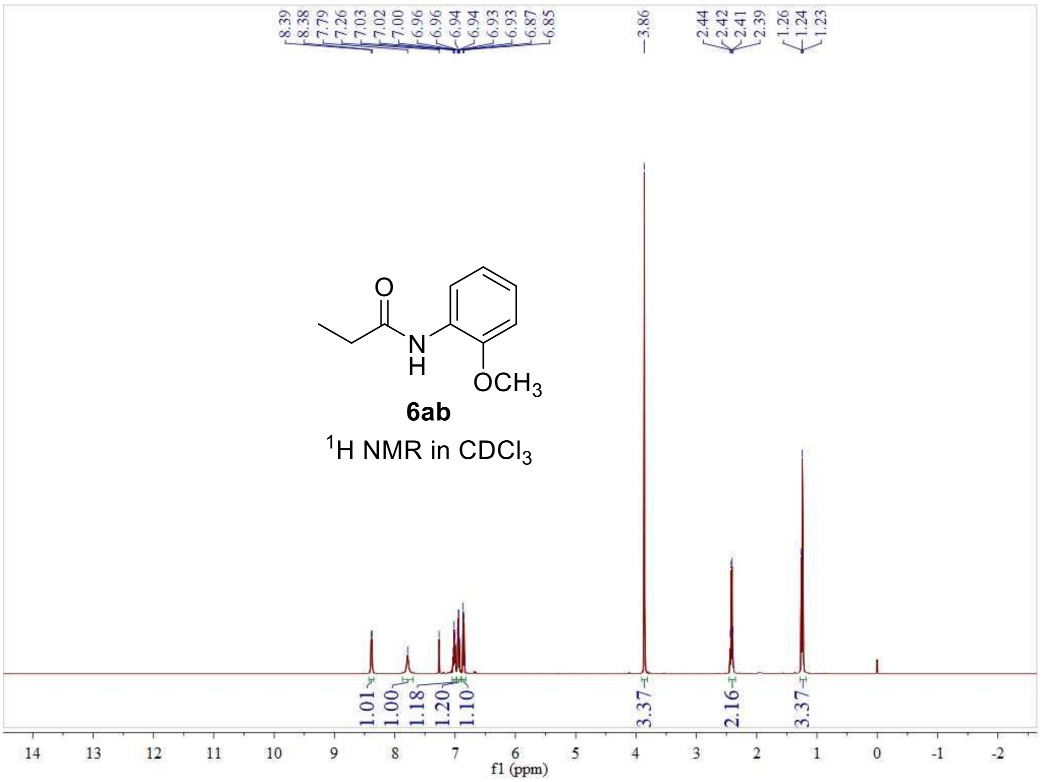
6z

^{1}H NMR in CDCl$_3$



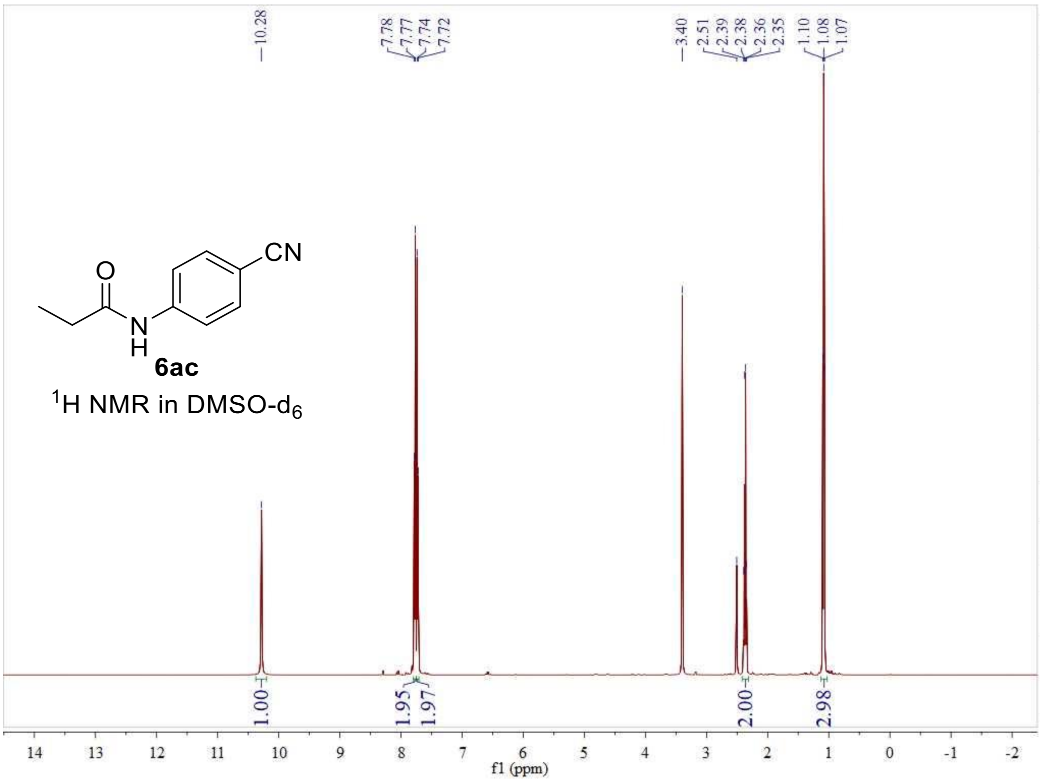
6aa

^{1}H NMR in CDCl$_3$



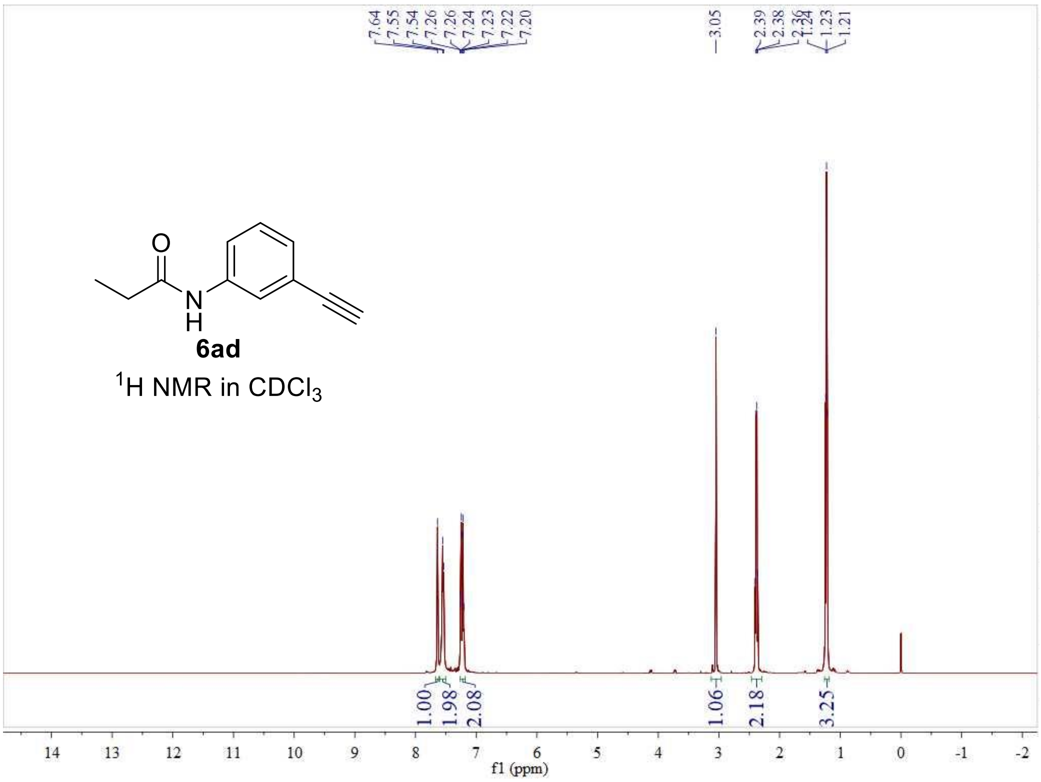
6ab

^{1}H NMR in CDCl$_3$



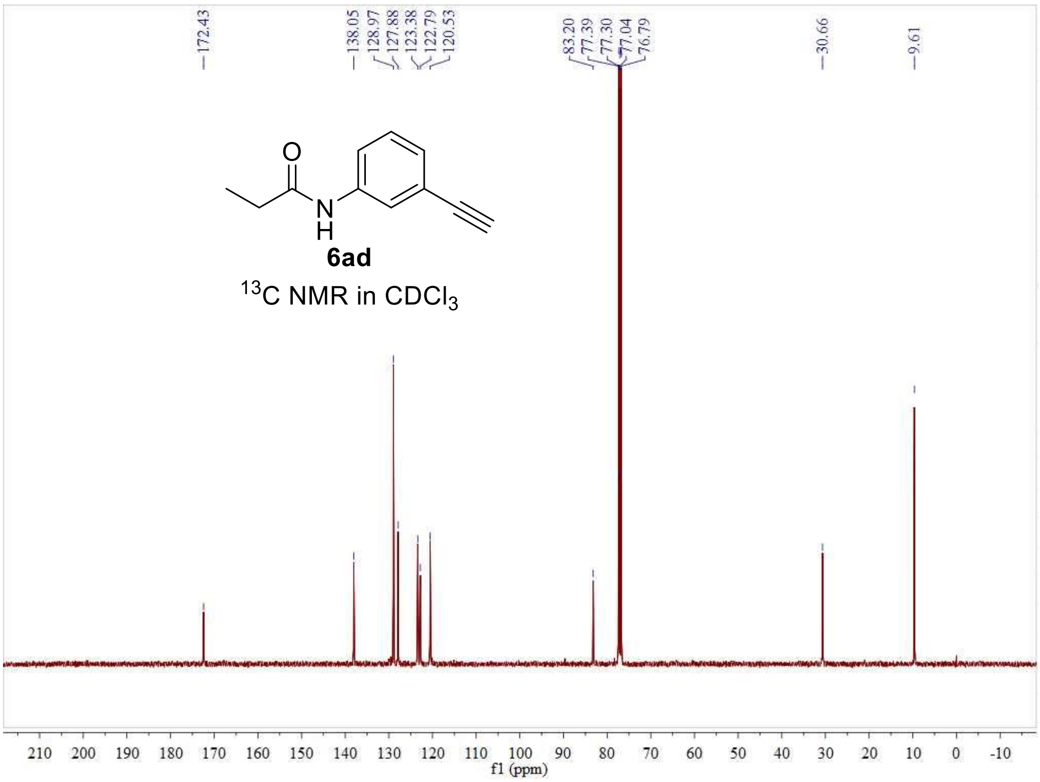
6ac

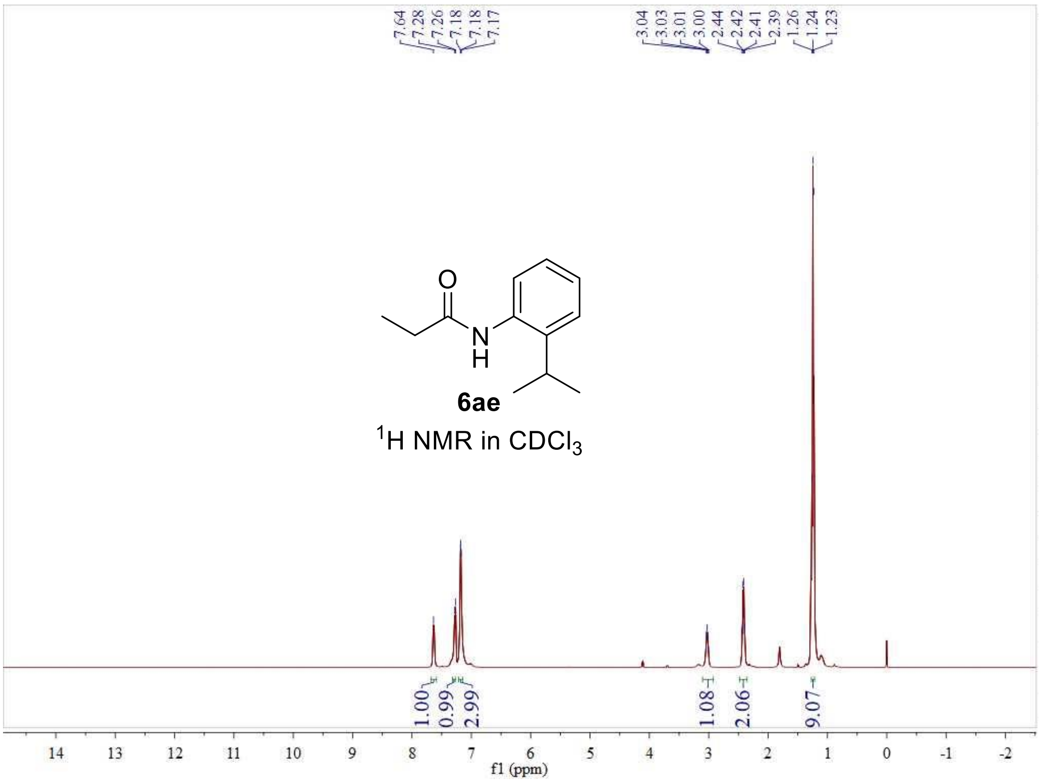
^{1}H NMR in DMSO-d_6

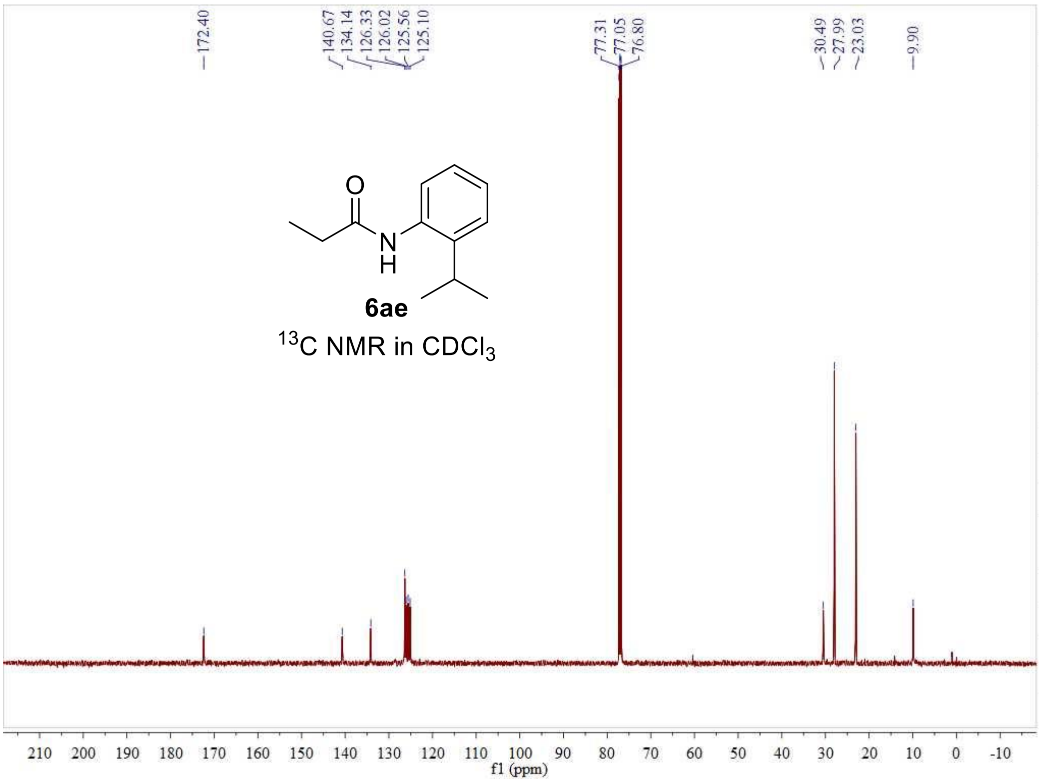


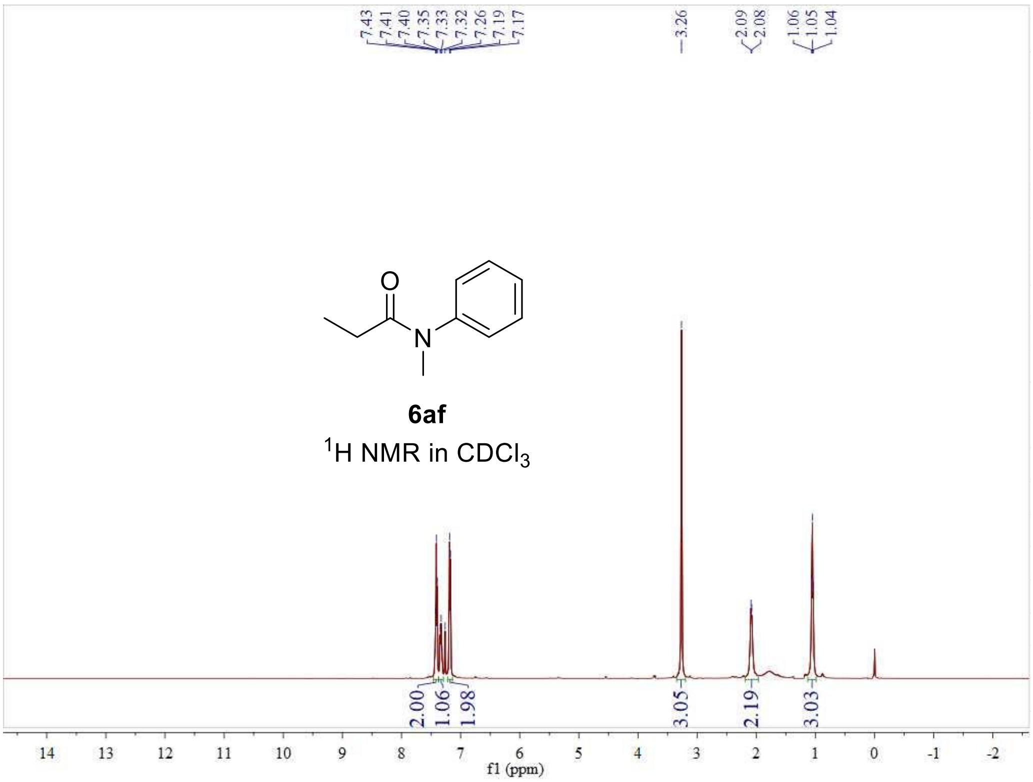
6ad

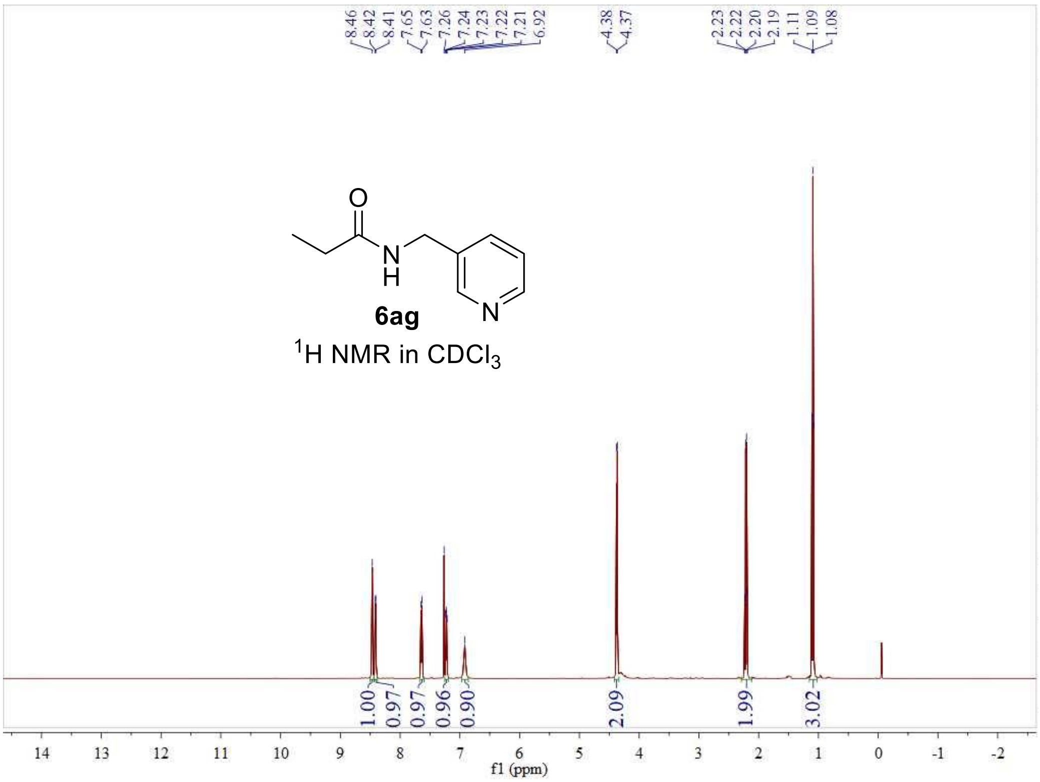
^{1}H NMR in CDCl$_3$


172.43
138.05
128.97
127.88
123.38
122.79
120.53
83.20
77.39
77.30
77.04
76.79
30.66
9.61
O
N
H
6ad
^{13}C NMR in CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.64
7.28
7.26
7.18
7.18
7.17
3.04
3.03
3.01
3.00
2.44
2.42
2.41
2.39
1.26
1.24
1.23
O
N
H
6ae
^{1}H NMR in CDCl$_3$
1.00
0.99
2.99
1.08
2.06
9.07
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)

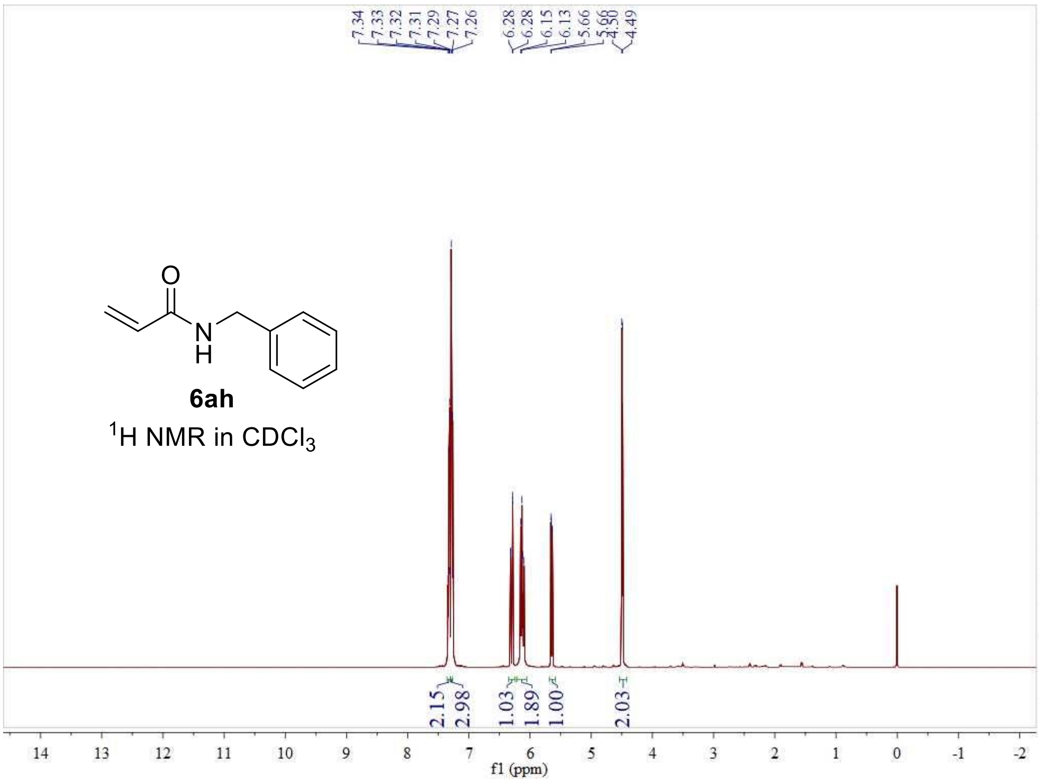

172.40
140.67
134.14
126.33
126.02
125.56
125.10
77.31
77.05
76.80
30.49
27.99
23.03
9.90
O
N
H
6ae
^{13}C NMR in CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.43
7.41
7.40
7.35
7.33
7.32
7.26
7.19
7.17
3.26
2.09
2.08
1.06
1.05
1.04
O
N
6af
^{1}H NMR in CDCl$_3$
2.00
1.06
1.98
3.05
2.19
3.03
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)



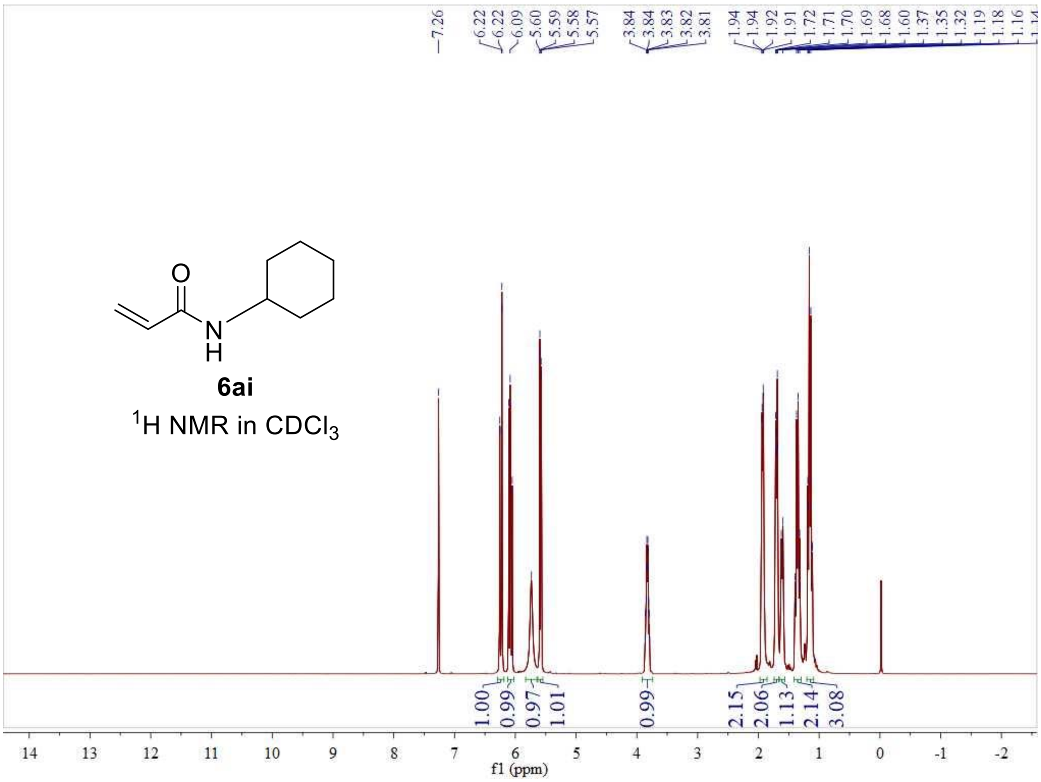
6ag

^{1}H NMR in CDCl$_3$



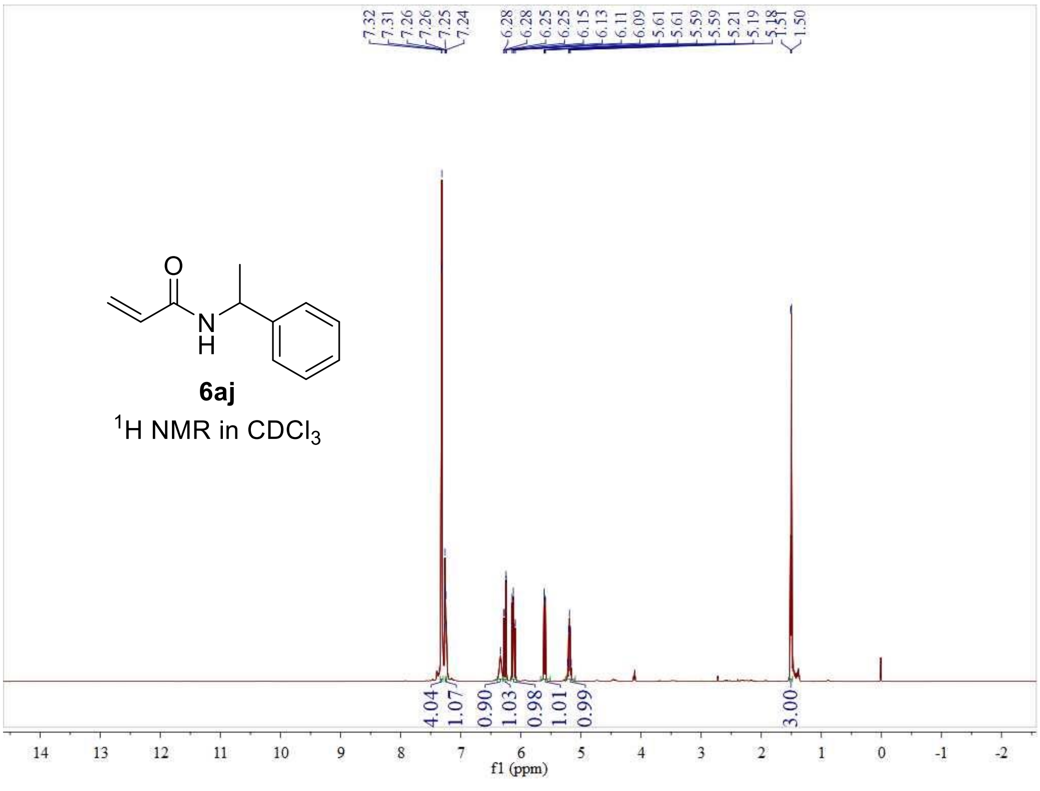
6ah

^{1}H NMR in CDCl$_3$



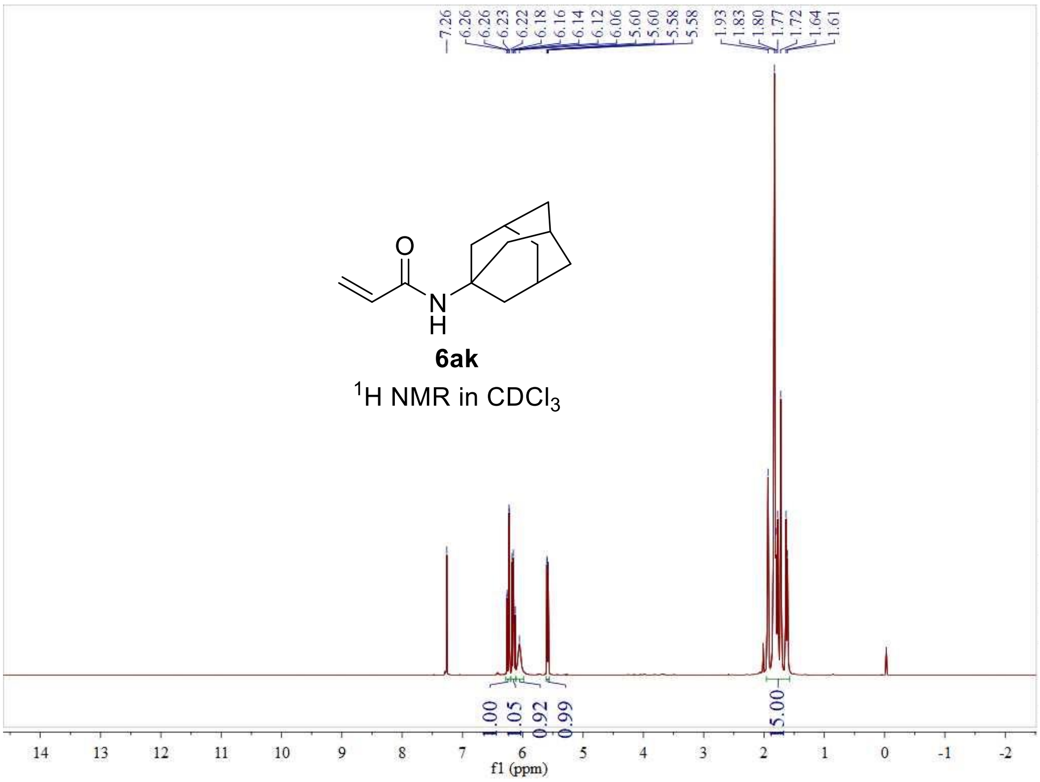
6ai

^{1}H NMR in CDCl$_3$

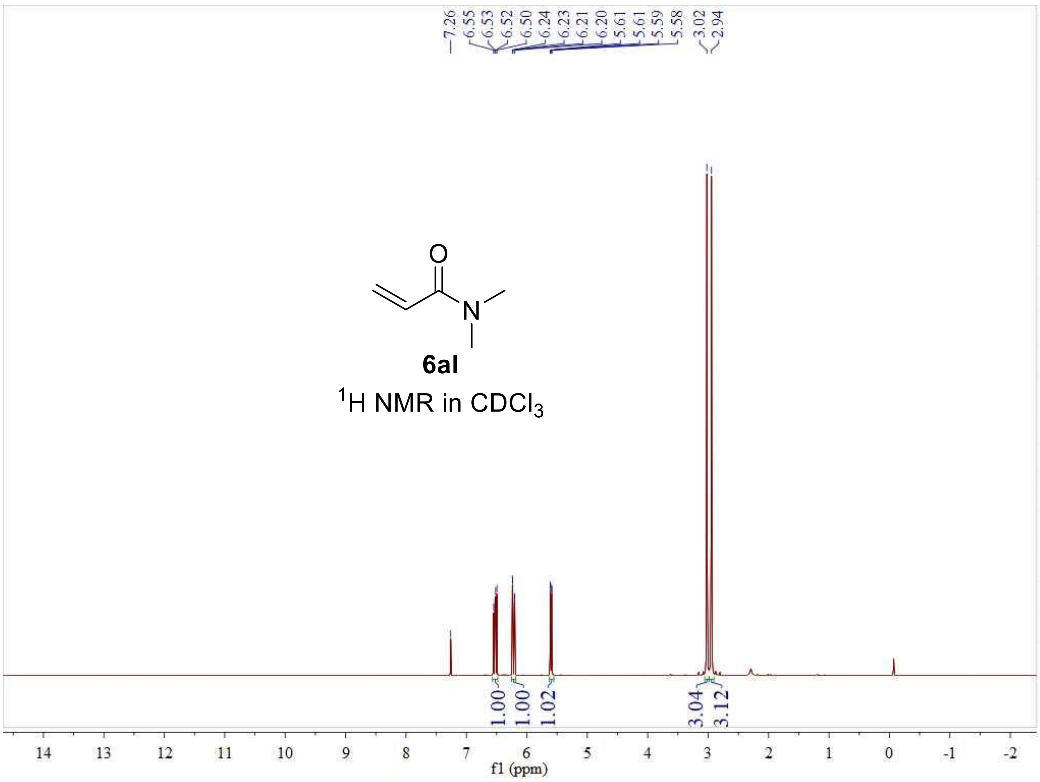


6aj

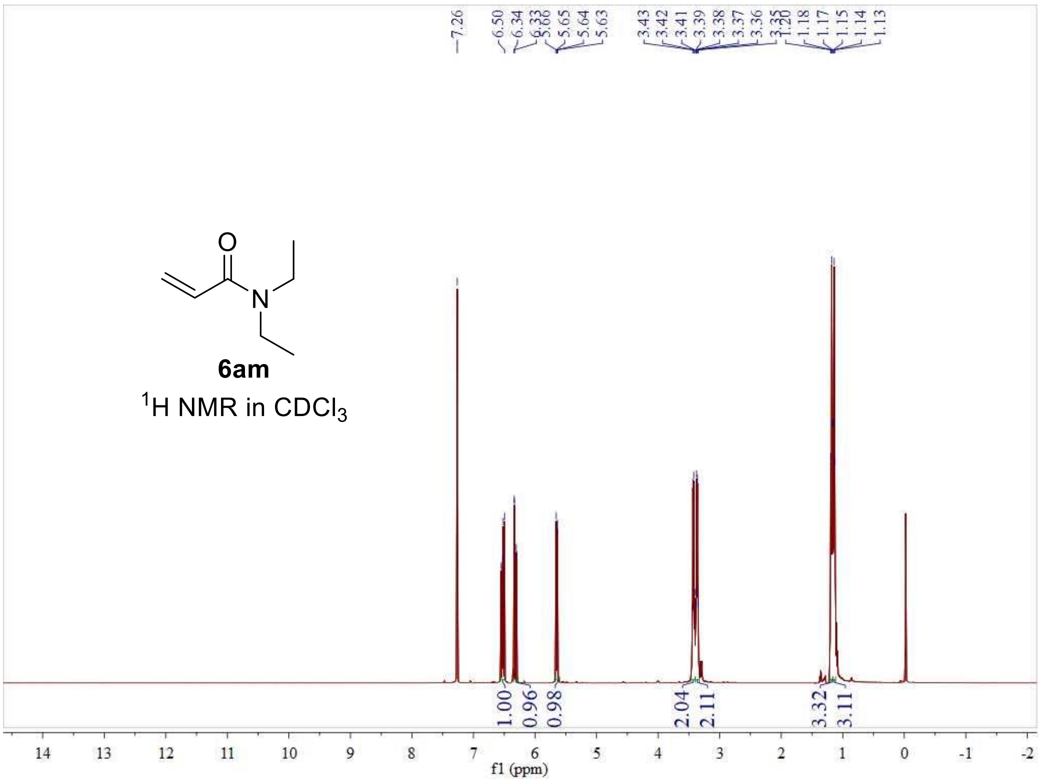
^{1}H NMR in CDCl$_3$


6ak

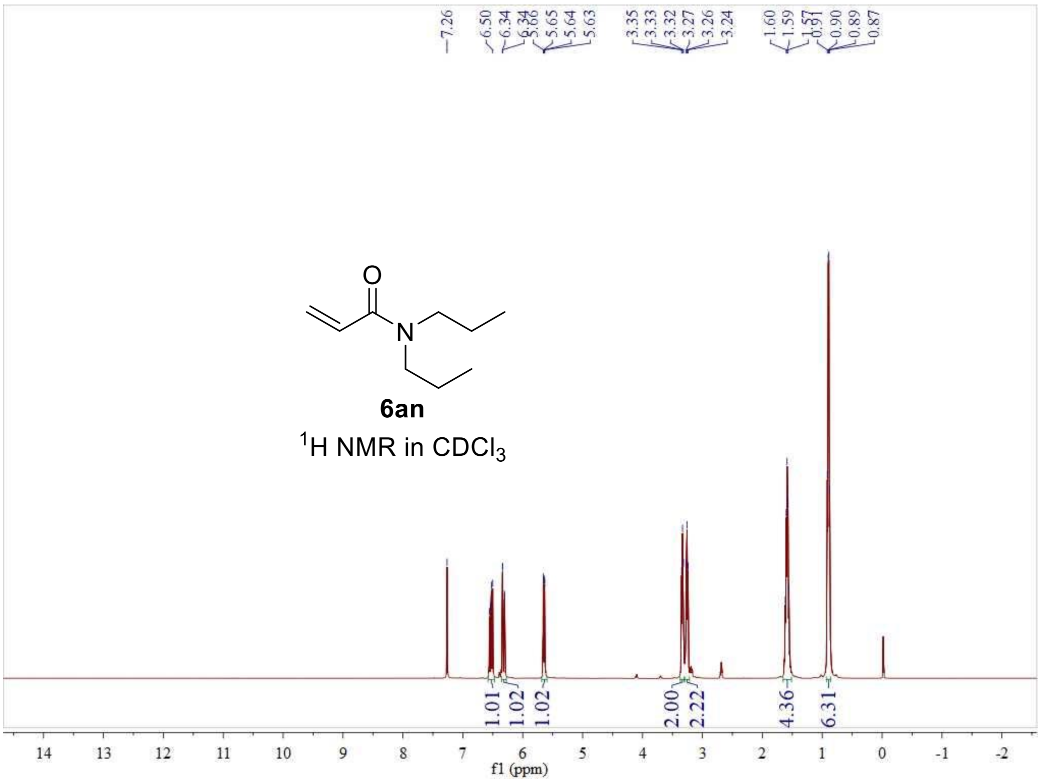
^{1}H NMR in CDCl$_3$


6al

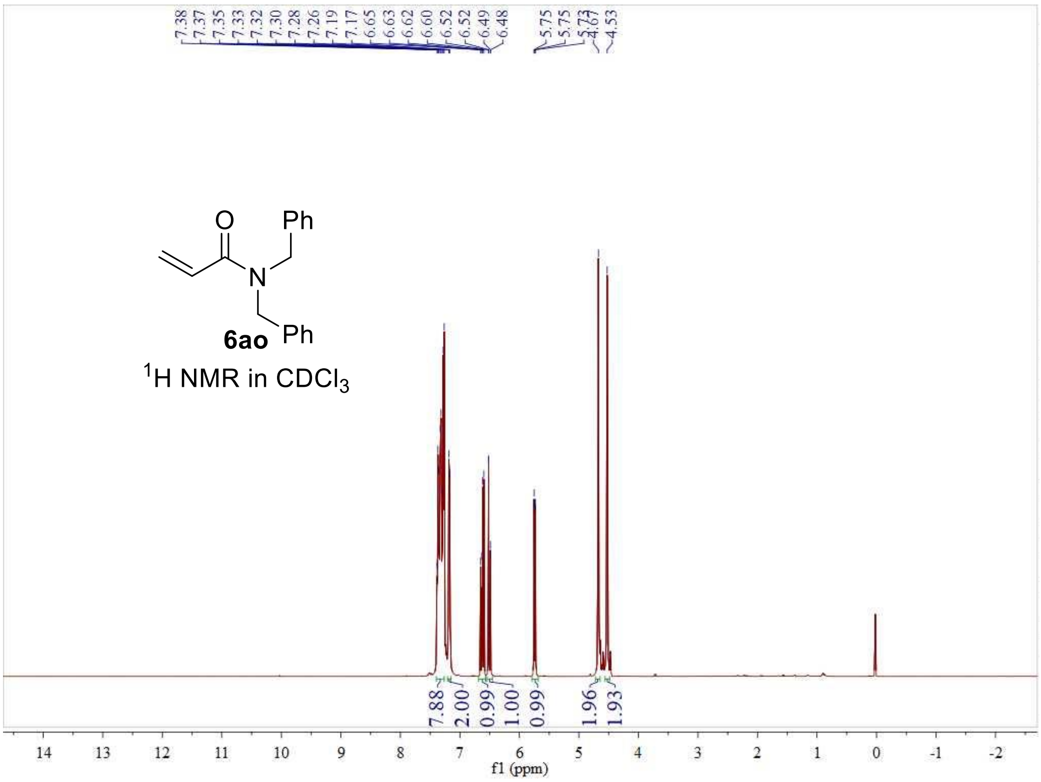
^{1}H NMR in CDCl$_3$


6am

^{1}H NMR in CDCl$_3$


6an

^{1}H NMR in CDCl$_3$


7.38
7.37
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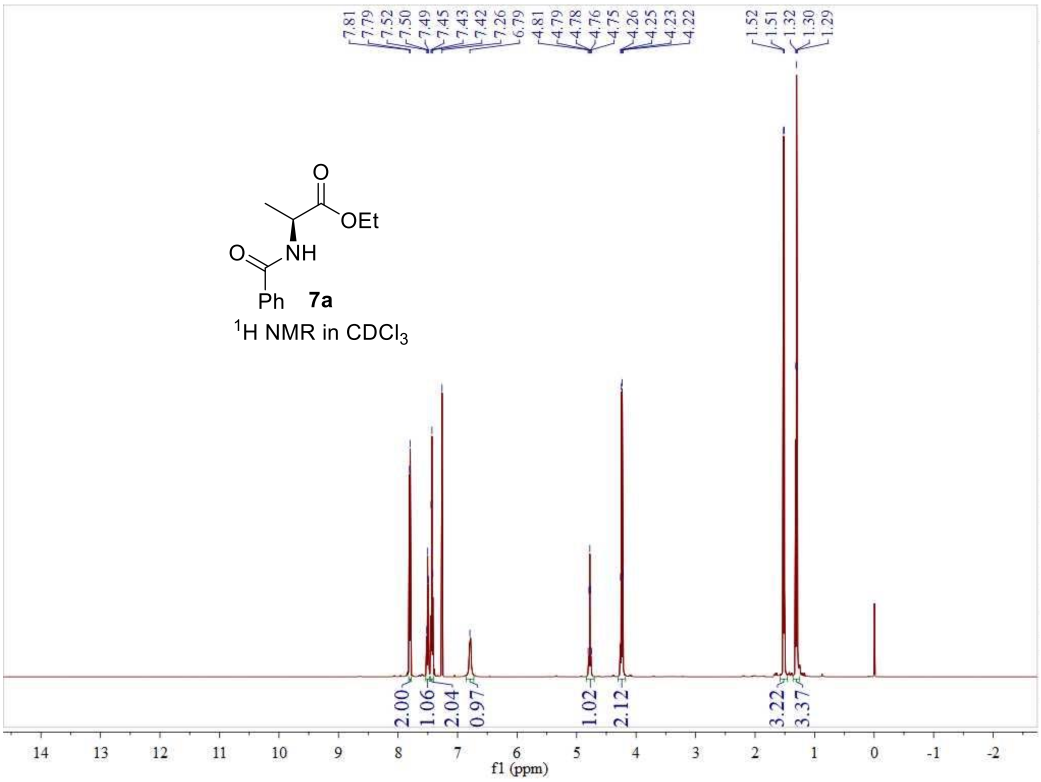
7.33
7.32
7.30
7.28
7.26
7.19
7.17
6.65
6.63
6.62
6.60
6.52
6.52
6.49
6.48
5.75
5.75
5.73
4.67
4.53
O
Ph
N
6ao
Ph
^{1}H NMR in CDCl$_3$
7.88
2.00
0.99
1.00
0.99
1.96
1.93
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)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7.52
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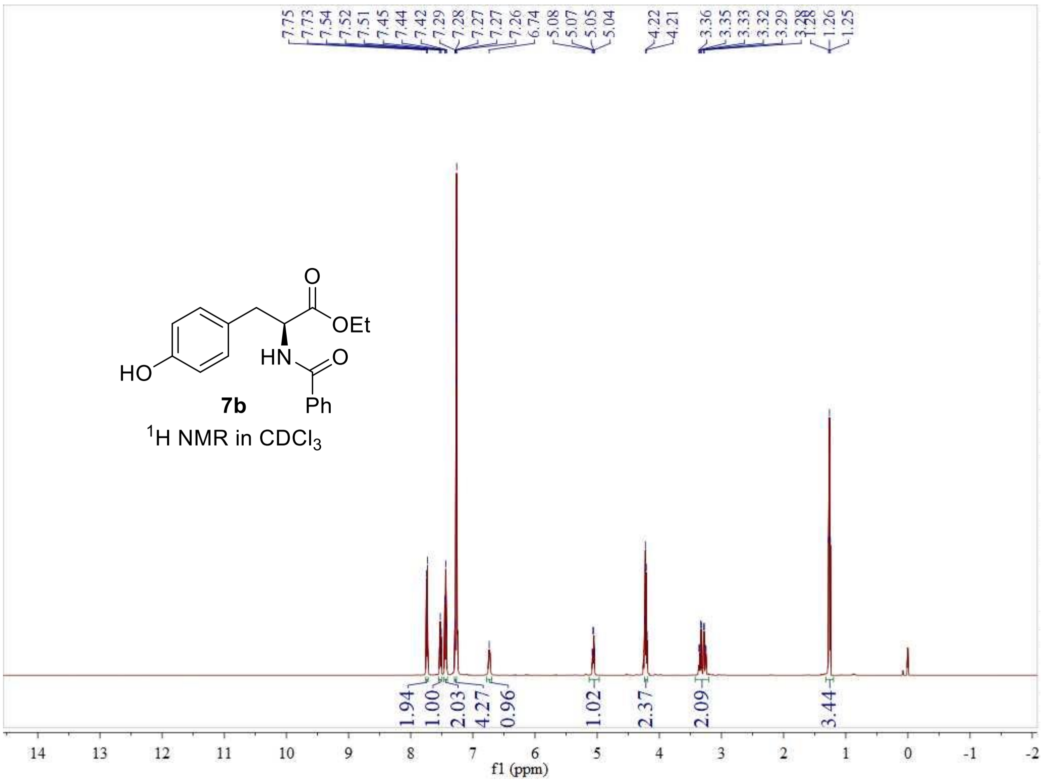
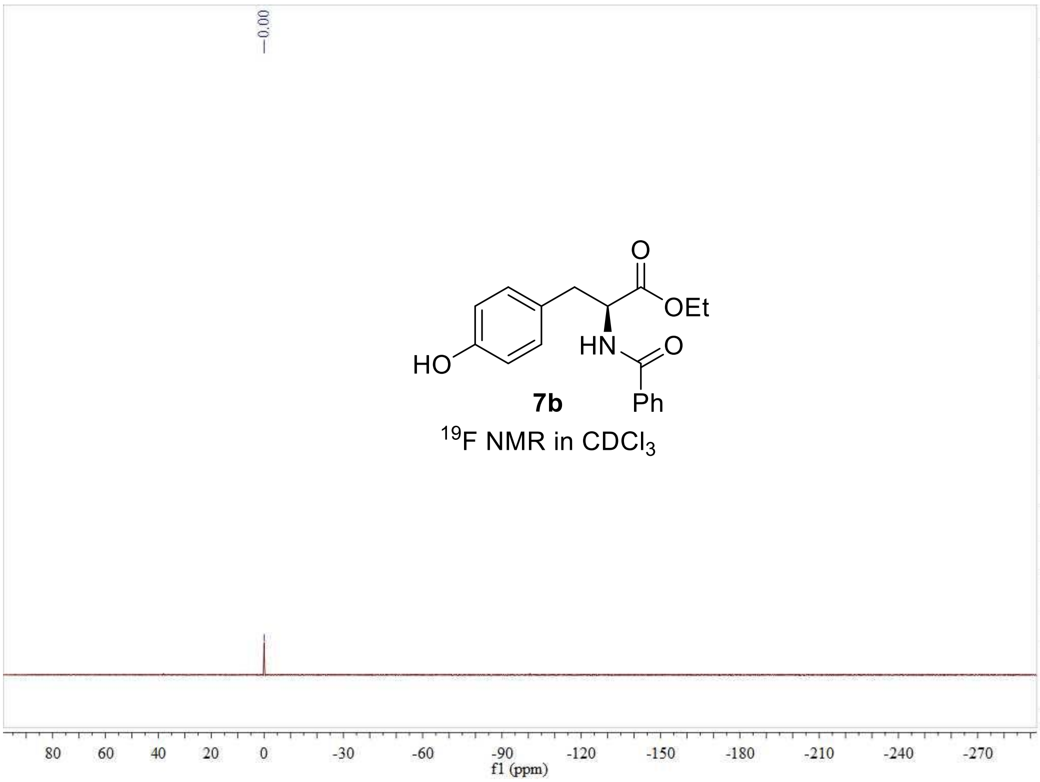
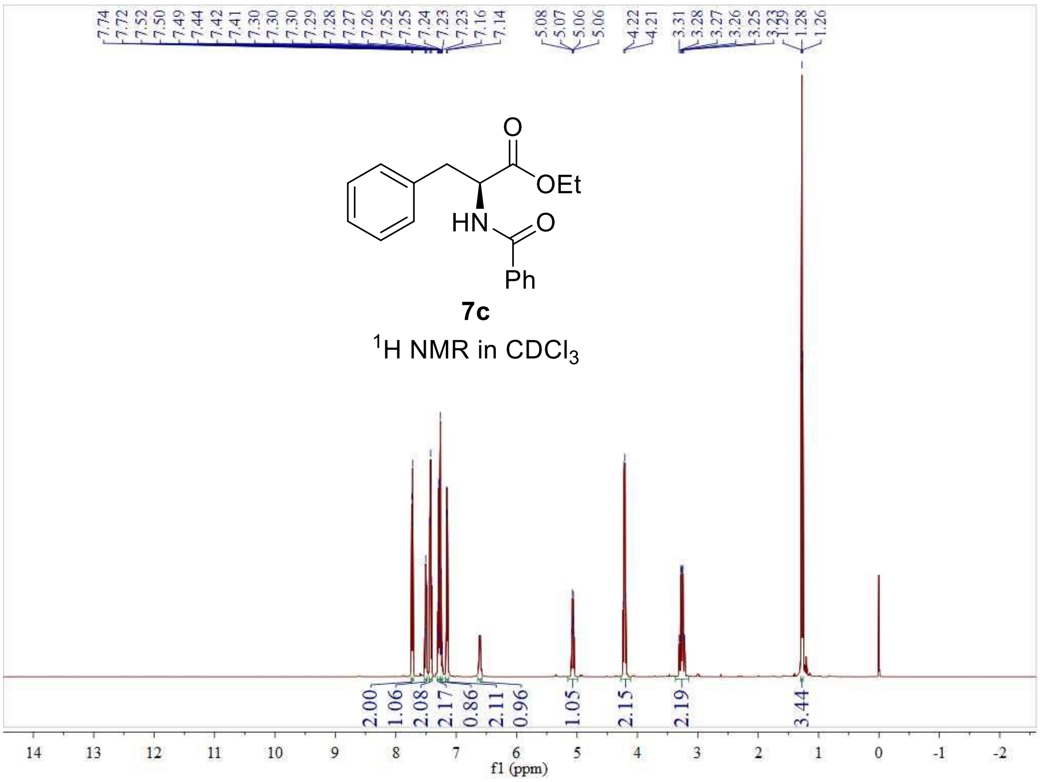
7.49
7.45
7.43
7.42
7.26
6.79
4.81
4.79
4.78
4.76
4.75
4.26
4.25
4.23
4.22
1.52
1.51
1.32
1.30
1.29
O
OEt
O
NH
Ph
7a
^{1}H NMR in CDCl$_3$
2.00
1.06
2.04
0.97
1.02
2.12
3.22
3.37
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

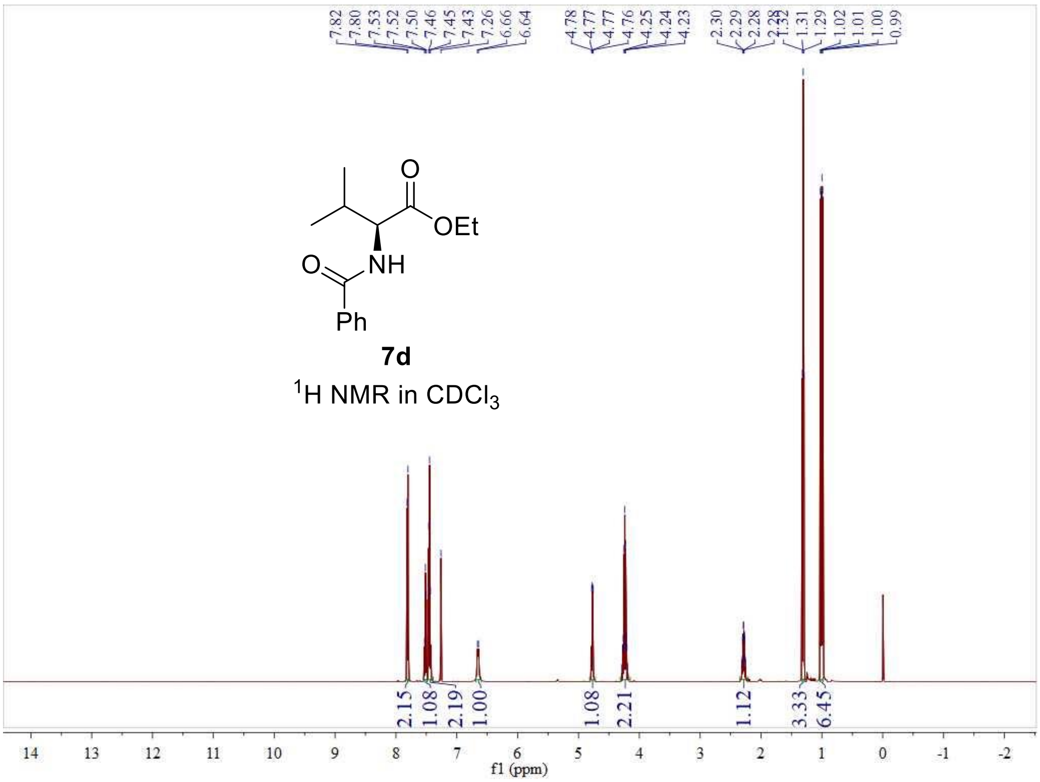

7.75
7.73
7.54
7.52
7.51
7.45
7.44
7.42
7.29
7.28
7.27
7.27
7.26
6.74
5.08
5.07
5.05
5.04
4.22
4.21
3.36
3.35
3.33
3.32
3.29
3.28
1.28
1.26
1.25
O
OEt
HN
O
HO
Ph
7b
1H NMR in CDCl3
1.94
1.00
2.03
4.27
0.96
1.02
2.37
2.09
3.44
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


0.00
O
OEt
HN
O
HO
Ph
7b
19F NMR in CDCl3
80
60
40
20
0
-30
-60
-90
-120
-150
-180
-210
-240
-270
f1 (ppm)



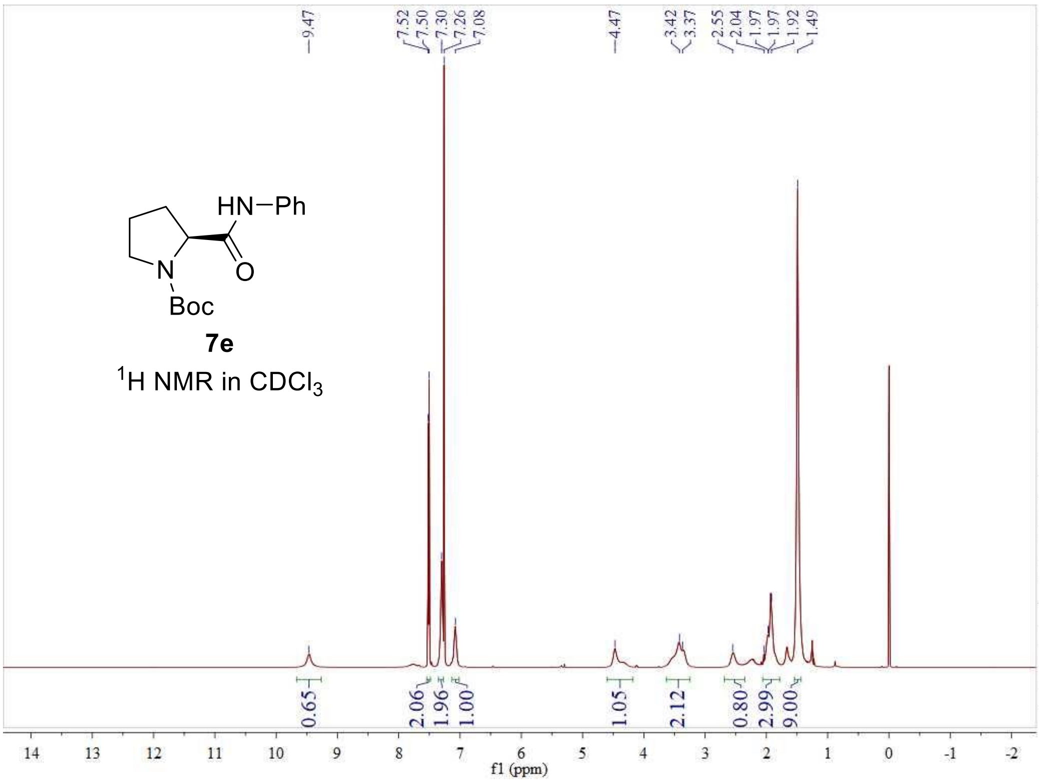
7c

^{1}H NMR in CDCl$_3$



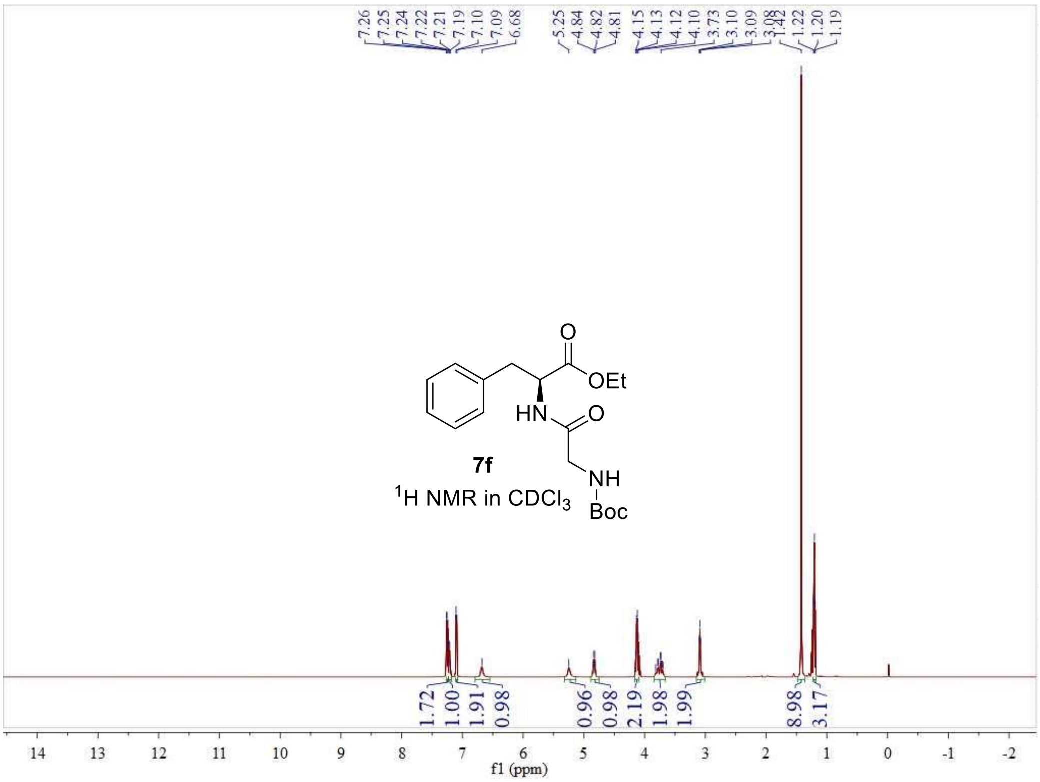
7d

^{1}H NMR in CDCl$_3$



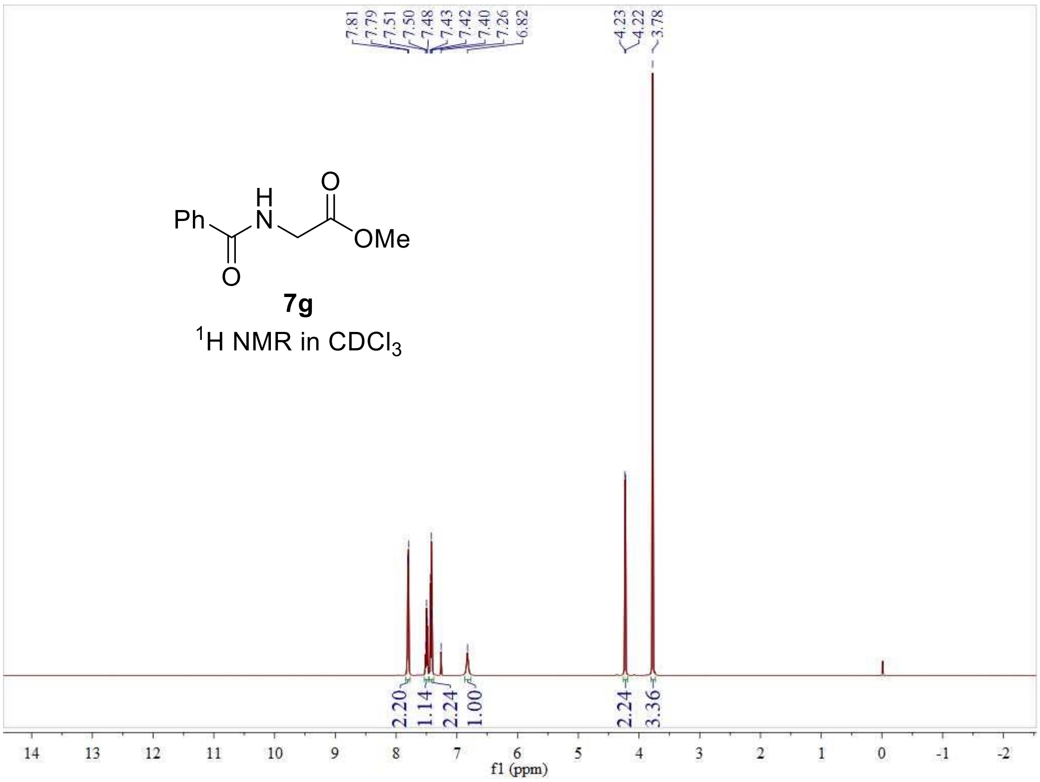
7e

^{1}H NMR in $CDCl_3$



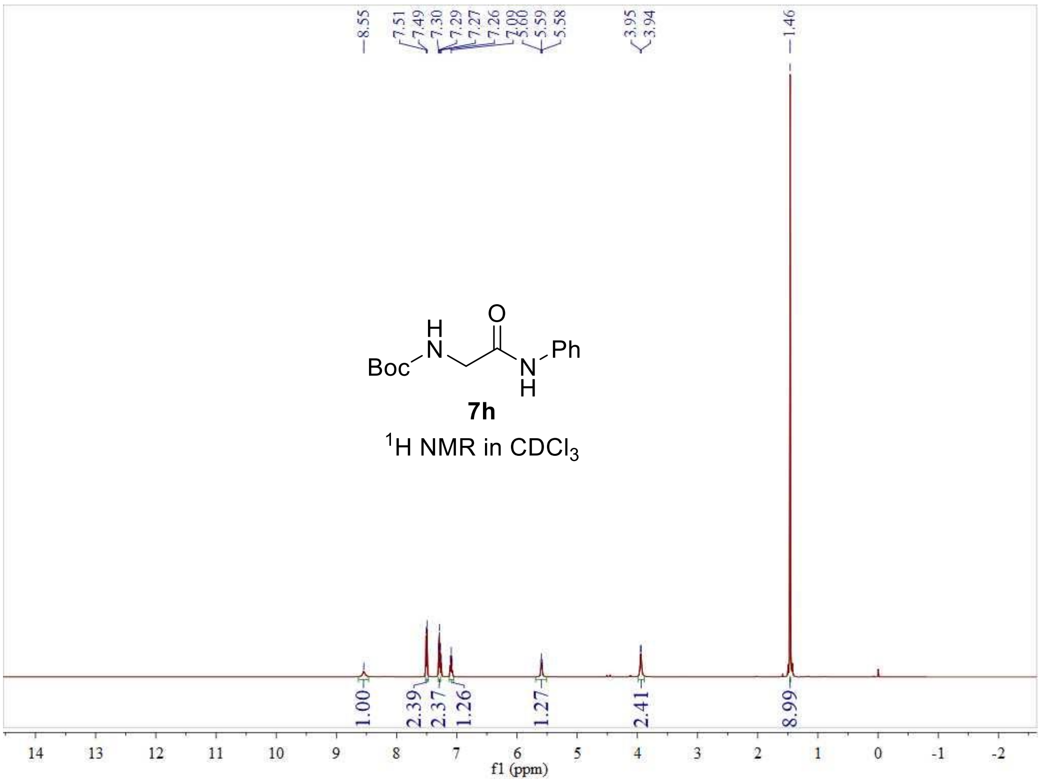
7f

^{1}H NMR in $CDCl_3$



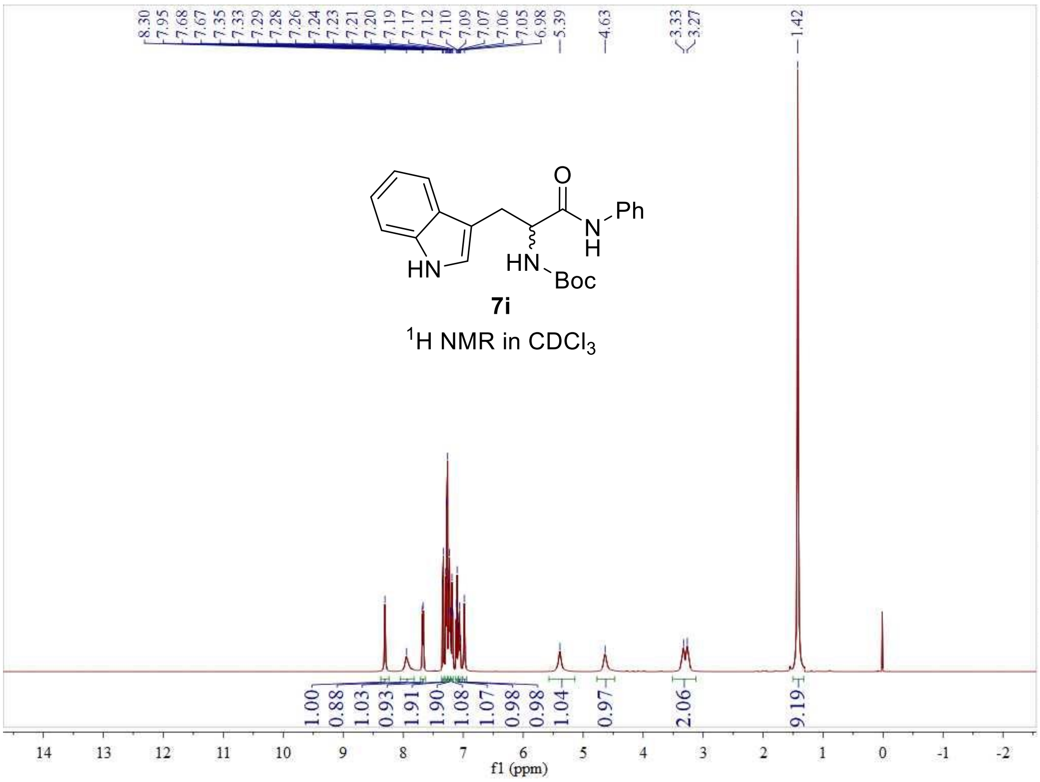
7g

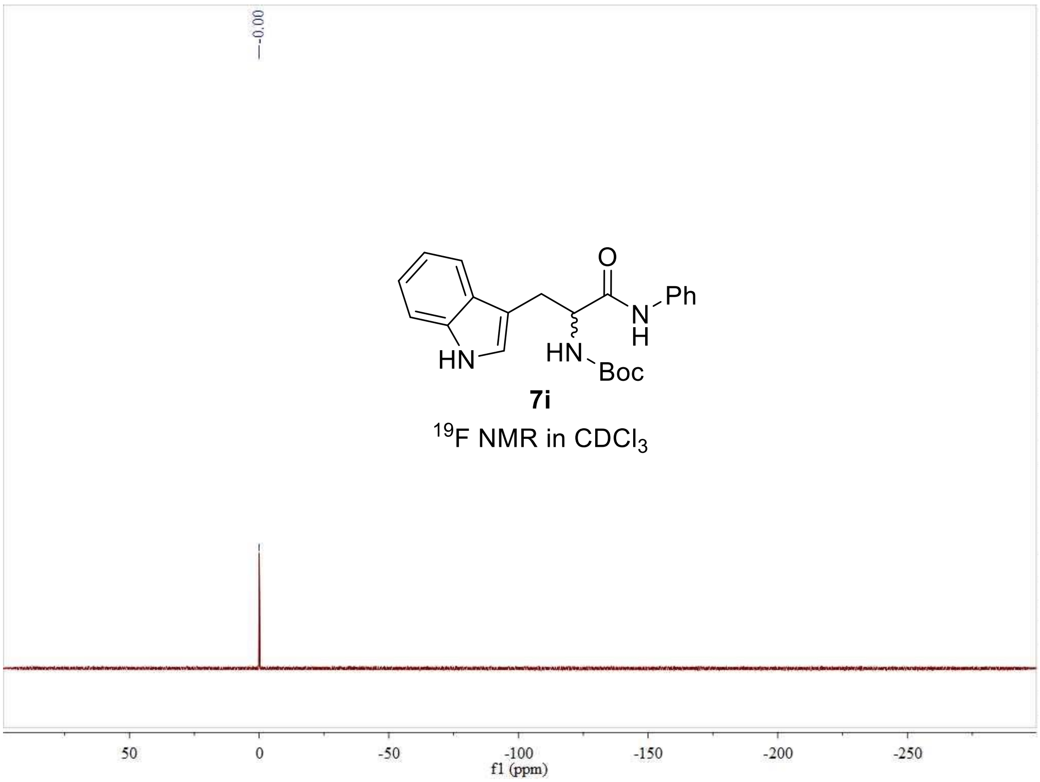
^{1}H NMR in CDCl$_3$

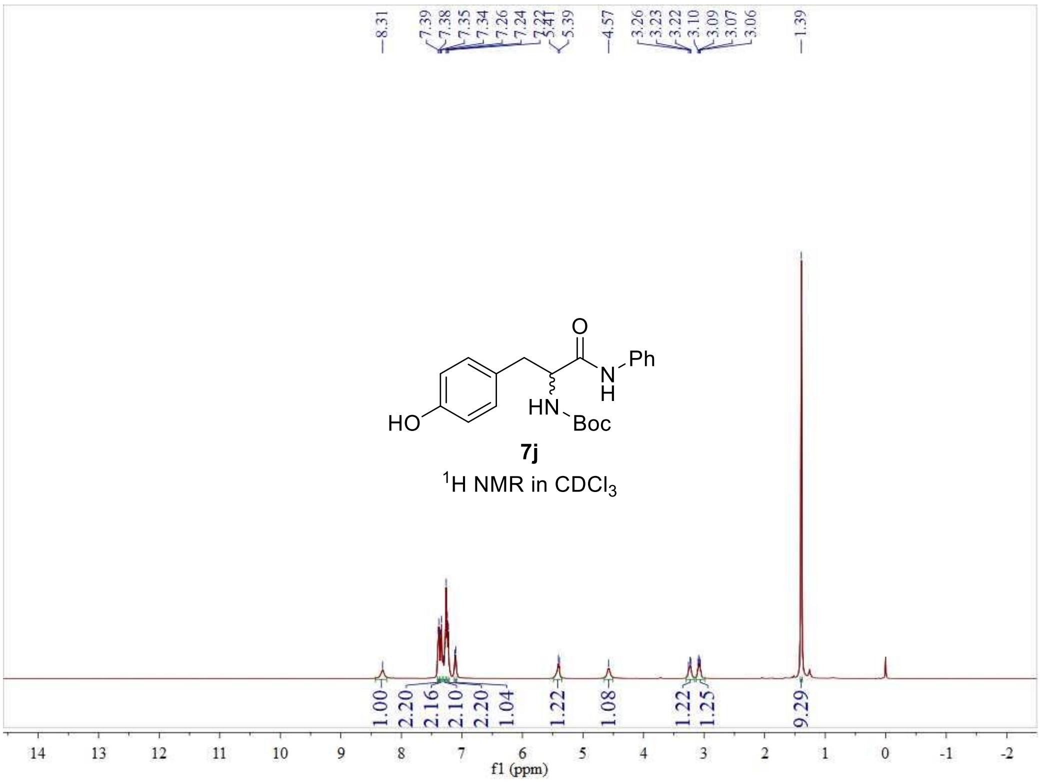


7h

^{1}H NMR in CDCl$_3$

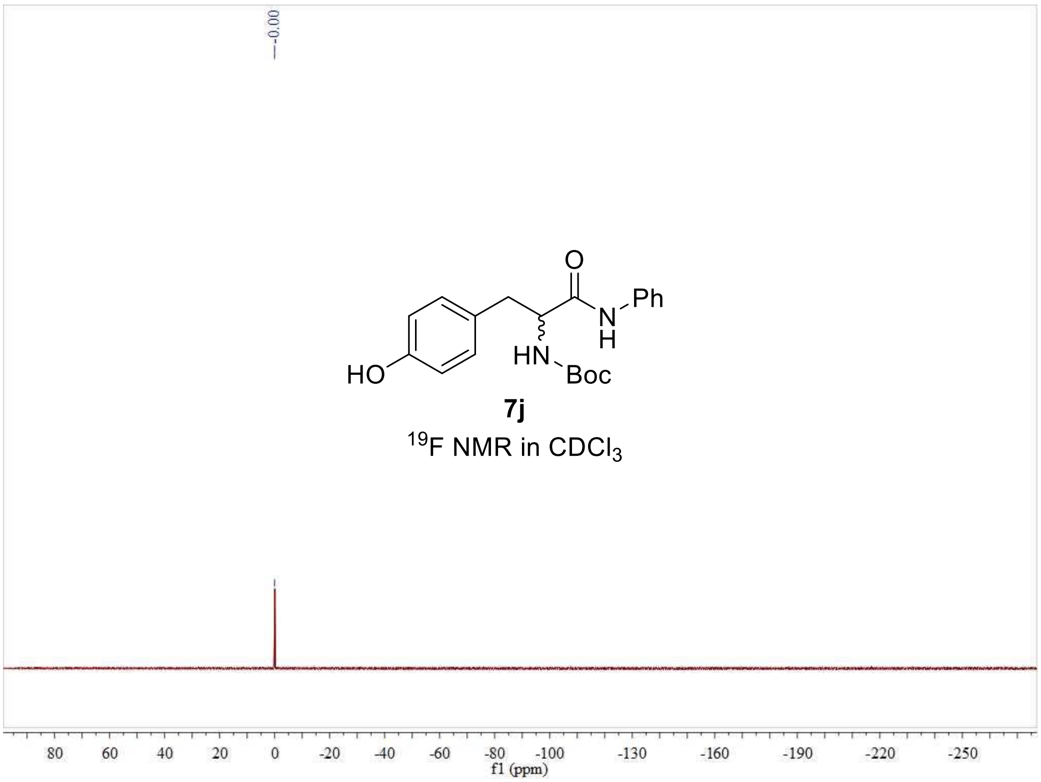

8.30
7.95
7.68
7.67
7.35
7.33
7.29
7.28
7.26
7.24
7.23
7.21
7.20
7.19
7.17
7.12
7.10
7.09
7.07
7.06
7.05
6.98
5.39
4.63
3.33
3.27
1.42
O
N
Ph
H
HN
HN
Boc
7i
1H NMR in CDCl3
1.00
0.88
1.03
0.93
1.91
1.90
1.08
1.07
0.98
0.98
1.04
0.97
2.06
9.19
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


0.00
O
N
Ph
H
HN
HN
Boc
7i
19F NMR in CDCl3
50
0
-50
-100
-150
-200
-250
f1 (ppm)



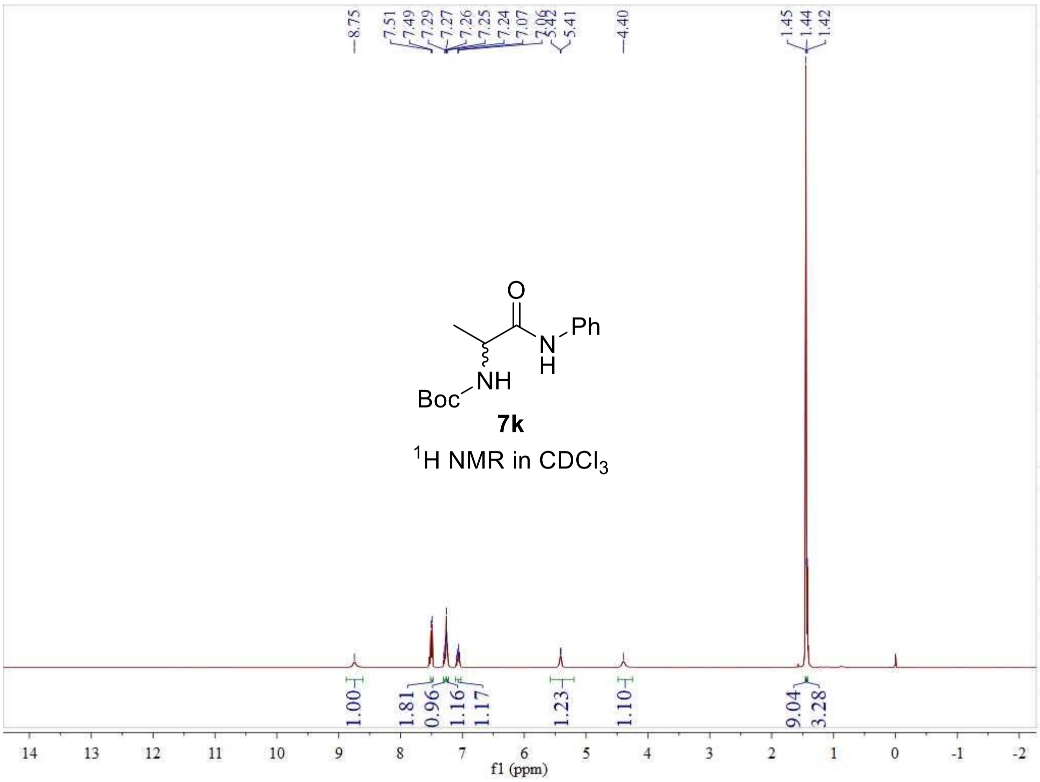
7j

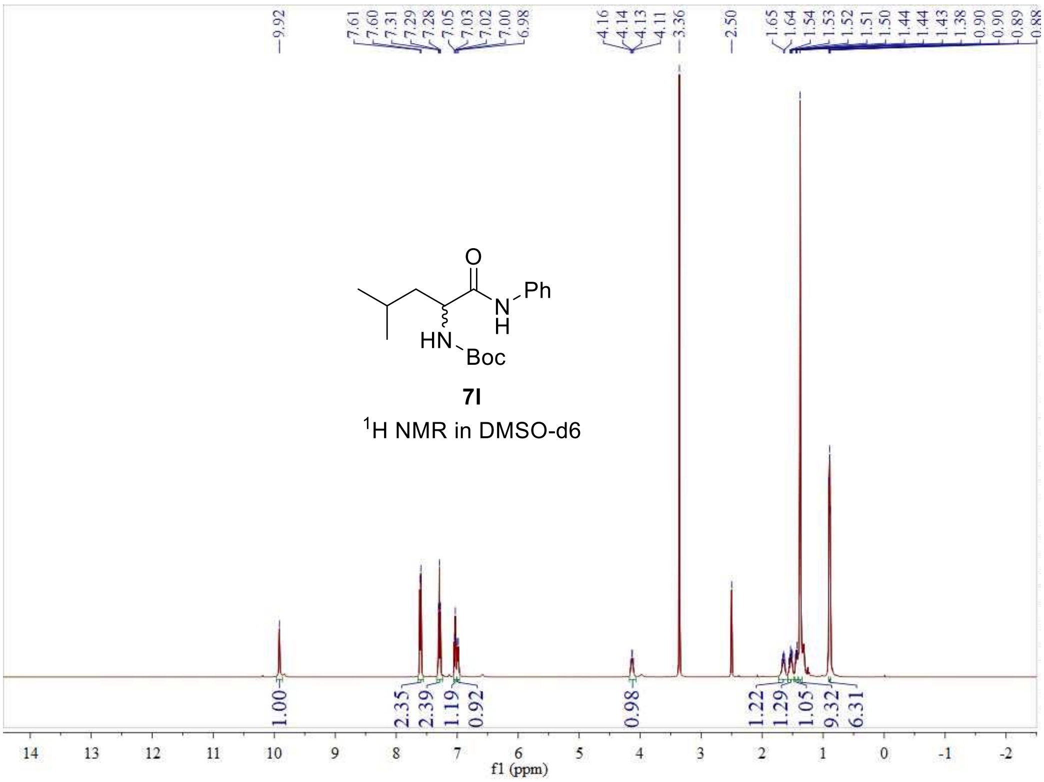
^{1}H NMR in $CDCl_3$

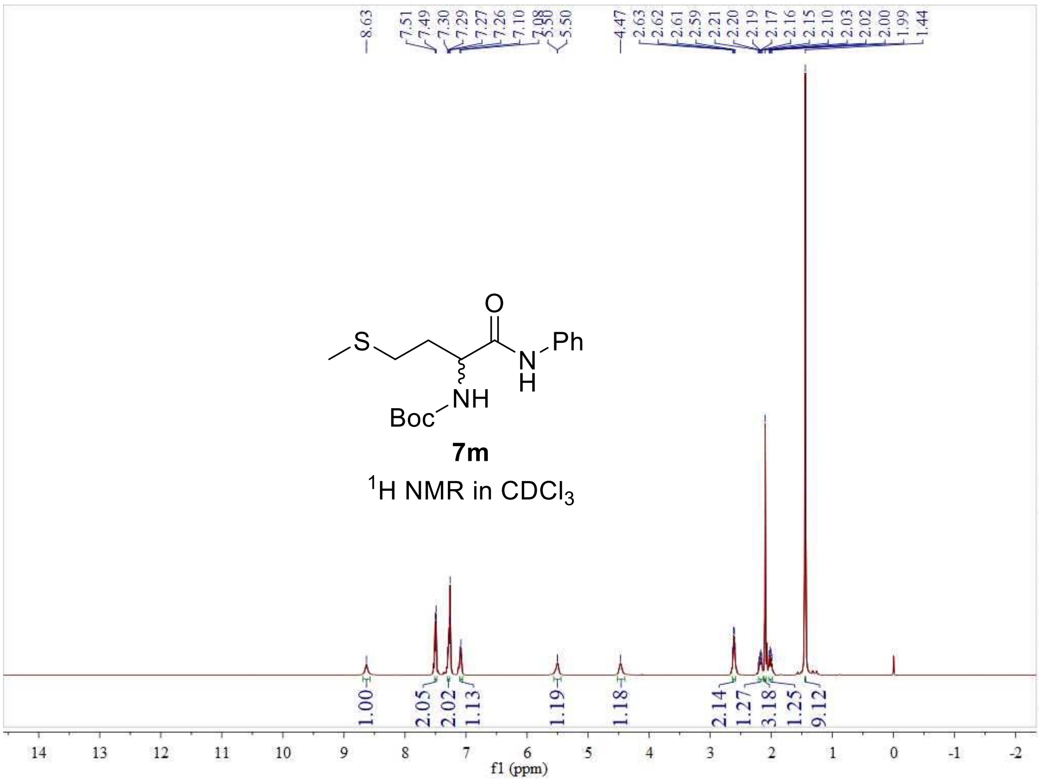


7j

^{19}F NMR in $CDCl_3$

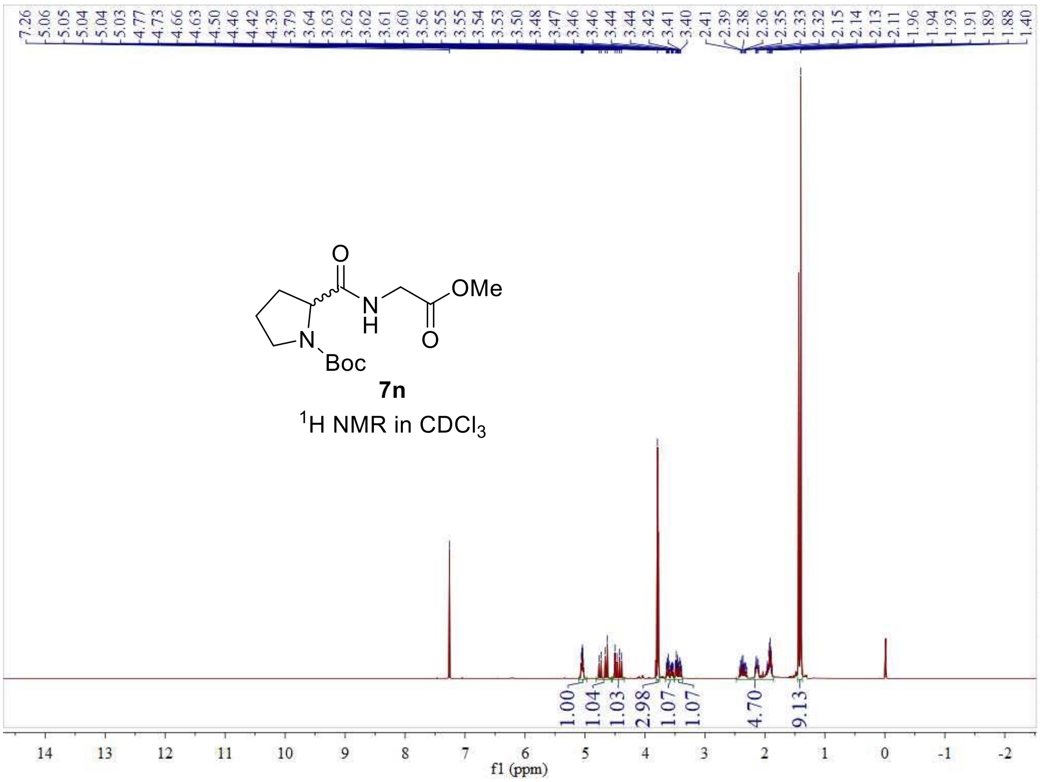

8.75
7.51
7.49
7.29
7.27
7.26
7.25
7.24
7.07
7.06
5.42
5.41
4.40
1.45
1.44
1.42
O
N
Ph
H
NH
Boc
7k
1H NMR in CDCl3
1.00
1.81
0.96
1.16
1.17
1.23
1.10
9.04
3.28
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


9.92
7.61
7.60
7.31
7.29
7.28
7.05
7.03
7.02
7.00
6.98
4.16
4.14
4.13
4.11
3.36
2.50
1.65
1.64
1.54
1.53
1.52
1.51
1.50
1.44
1.44
1.43
1.38
0.90
0.90
0.89
0.88
O
N
Ph
H
HN
Boc
7l
1H NMR in DMSO-d6
1.00
2.35
2.39
1.19
0.92
0.98
1.22
1.29
1.05
9.32
6.31
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)



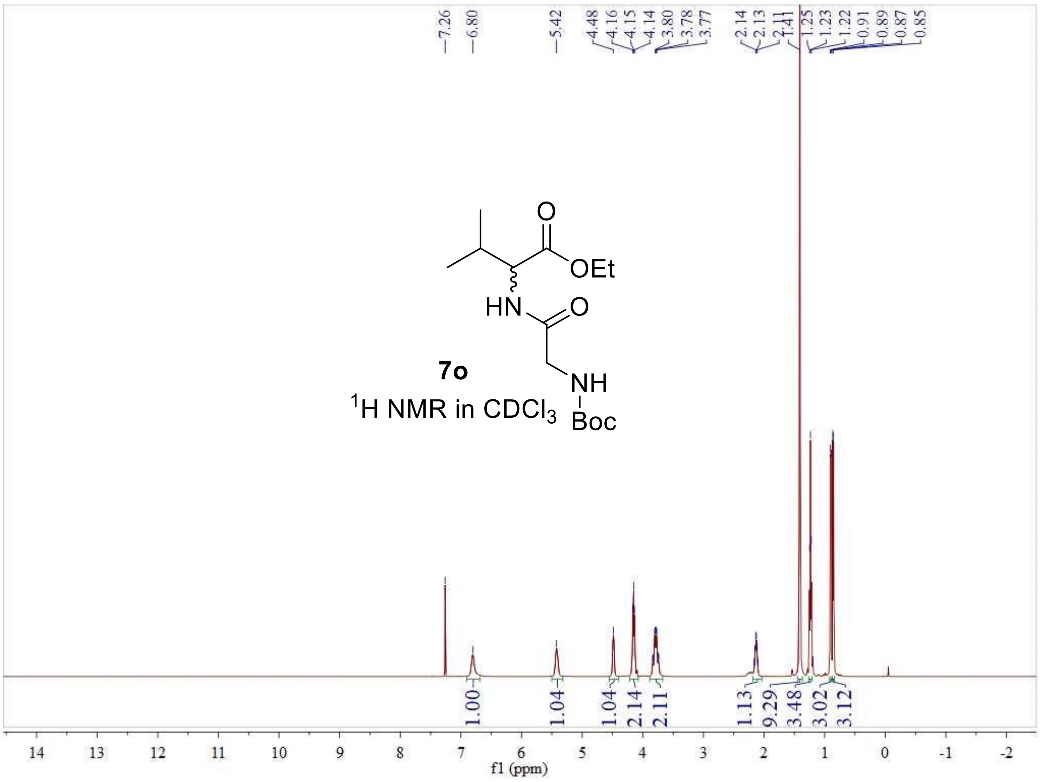
7m

^{1}H NMR in CDCl$_3$

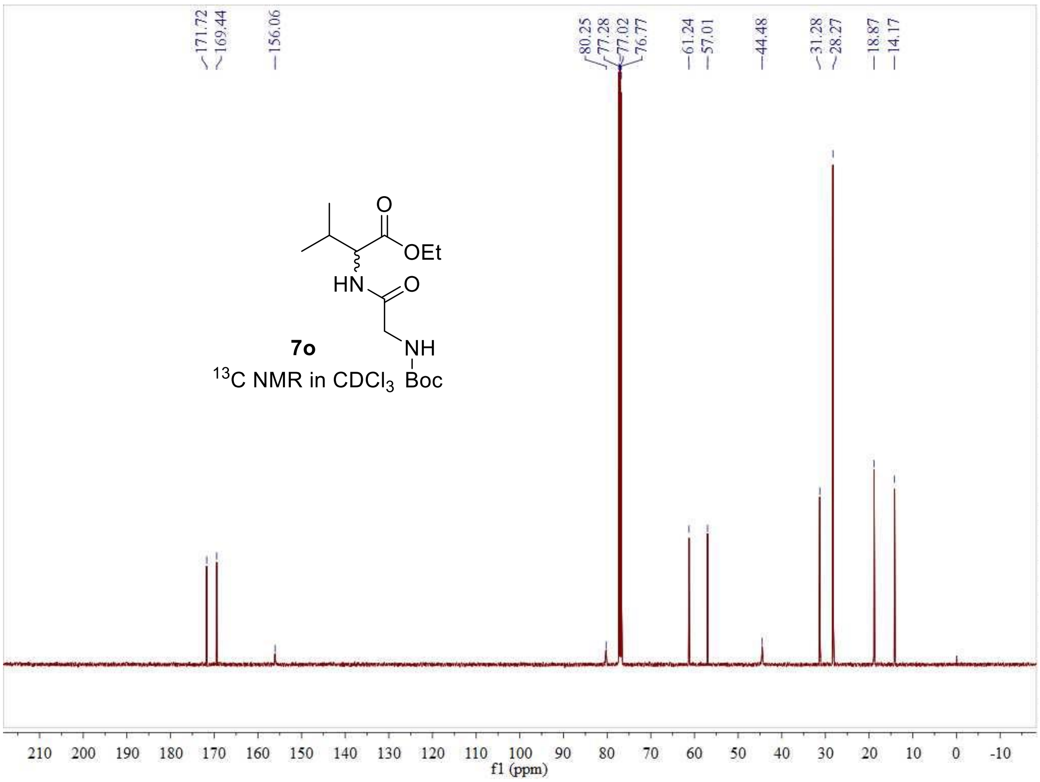


7n

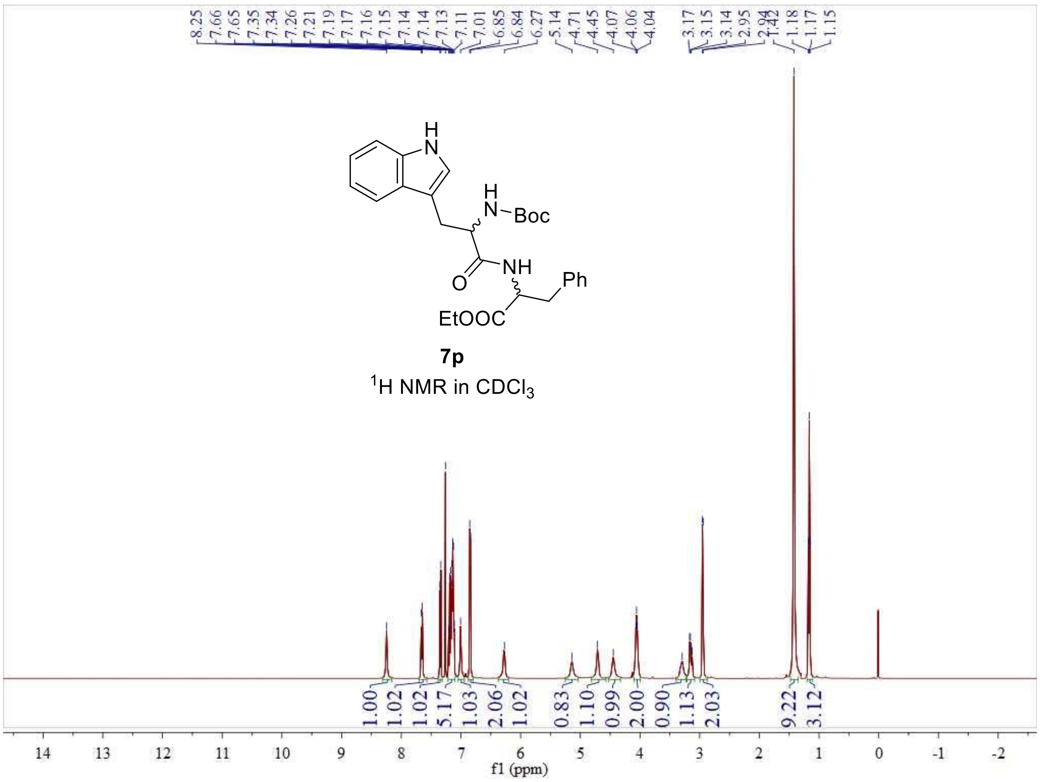
^{1}H NMR in CDCl$_3$


7o

^{1}H NMR in CDCl$_3$

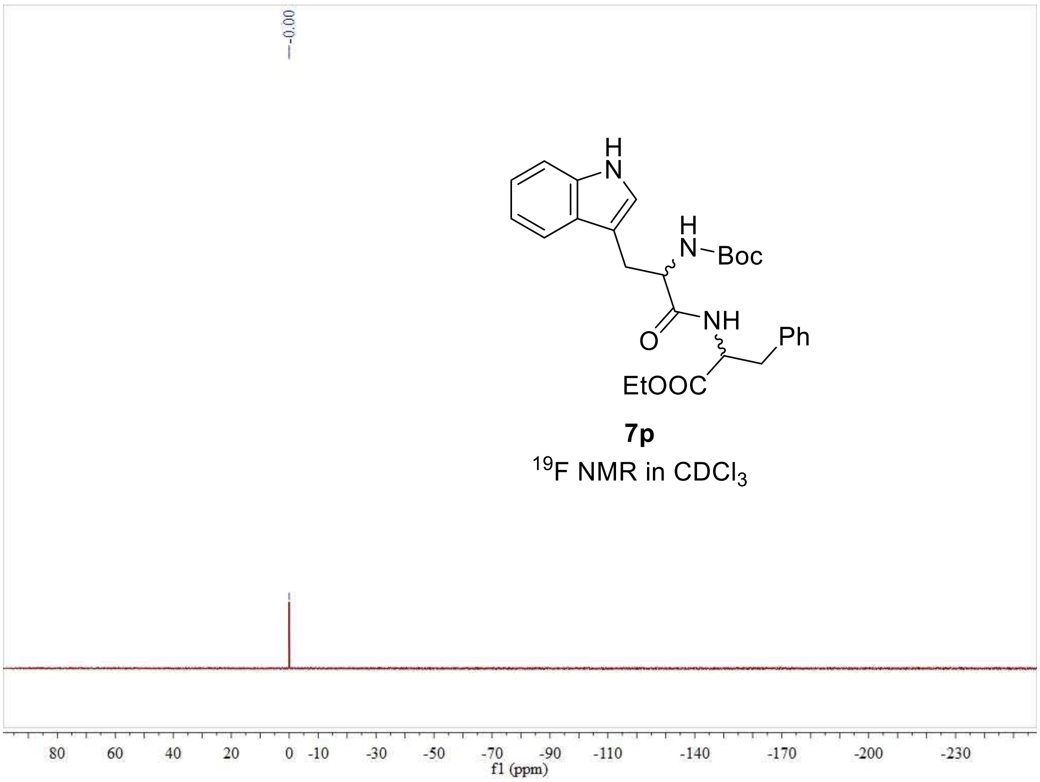

7o

^{13}C NMR in CDCl$_3$



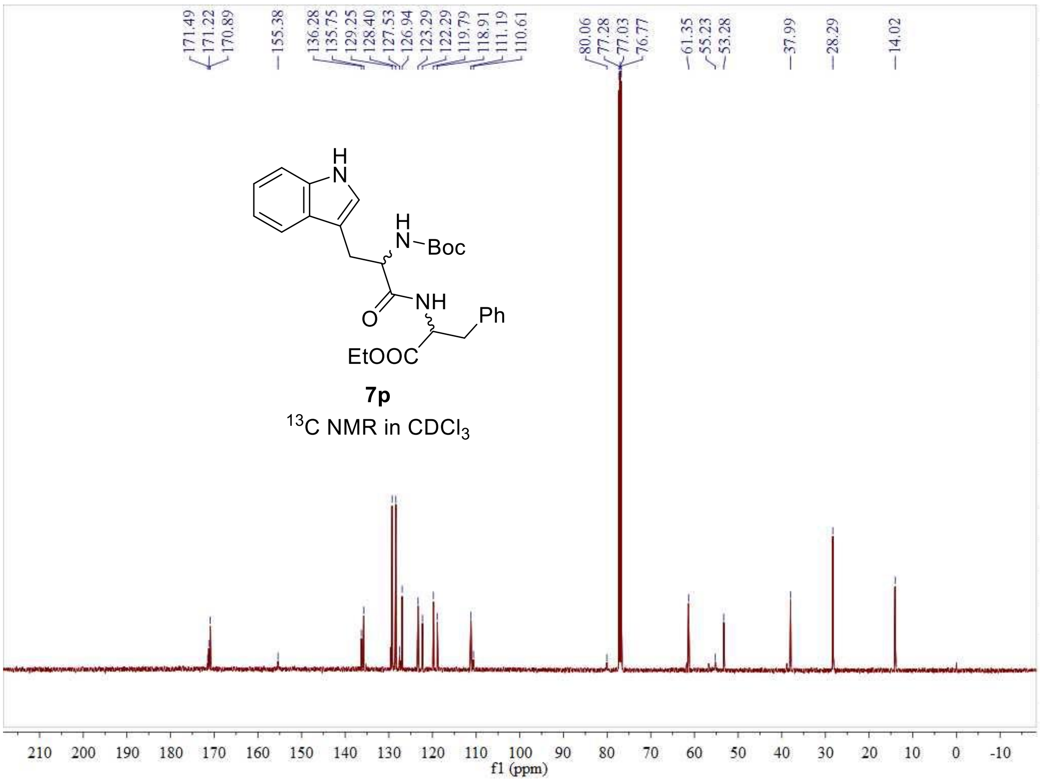
7p

^{1}H NMR in CDCl$_3$



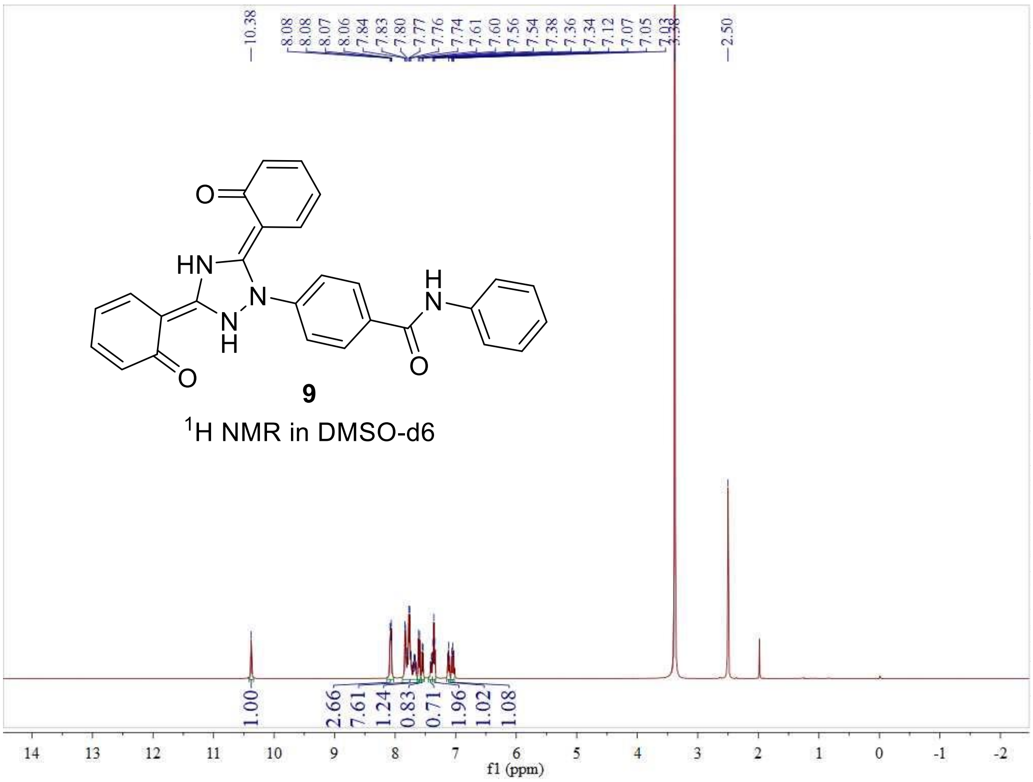
7p

^{19}F NMR in CDCl$_3$



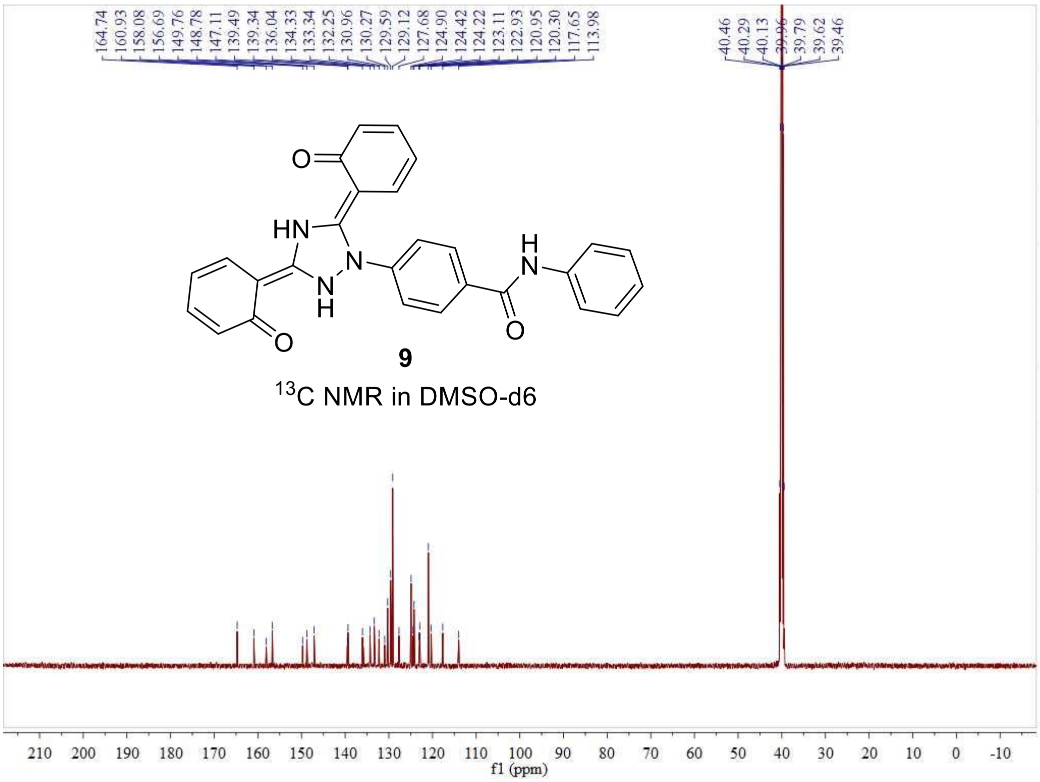
7p

^{13}C NMR in $CDCl_3$

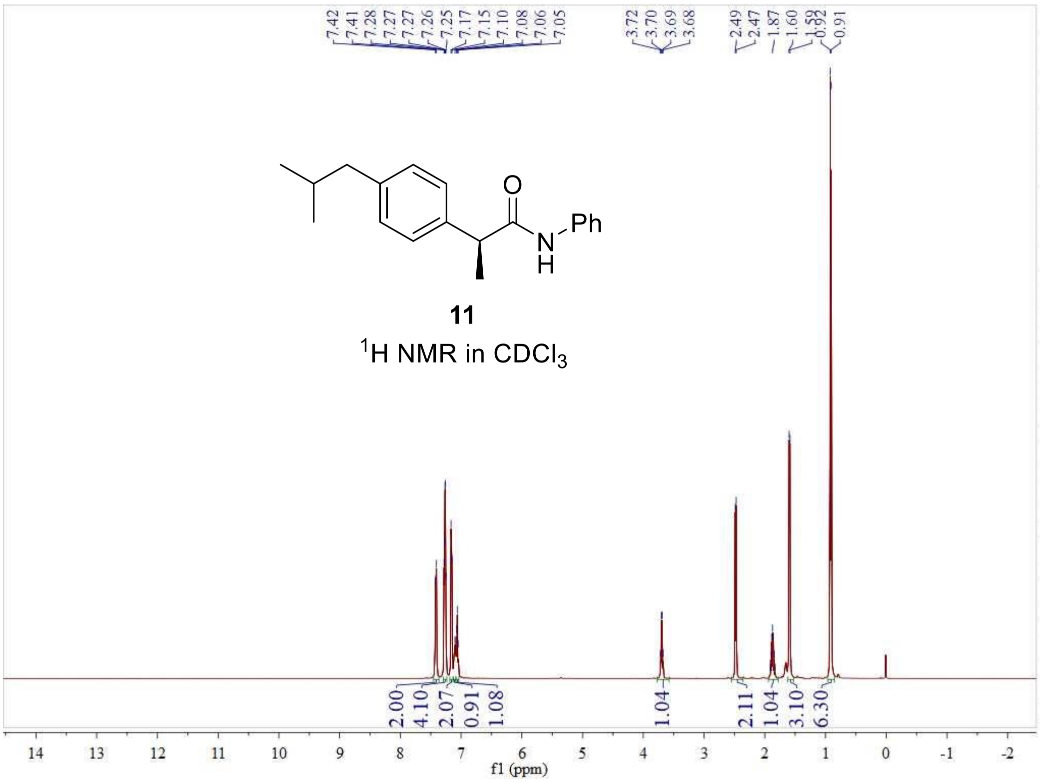


9

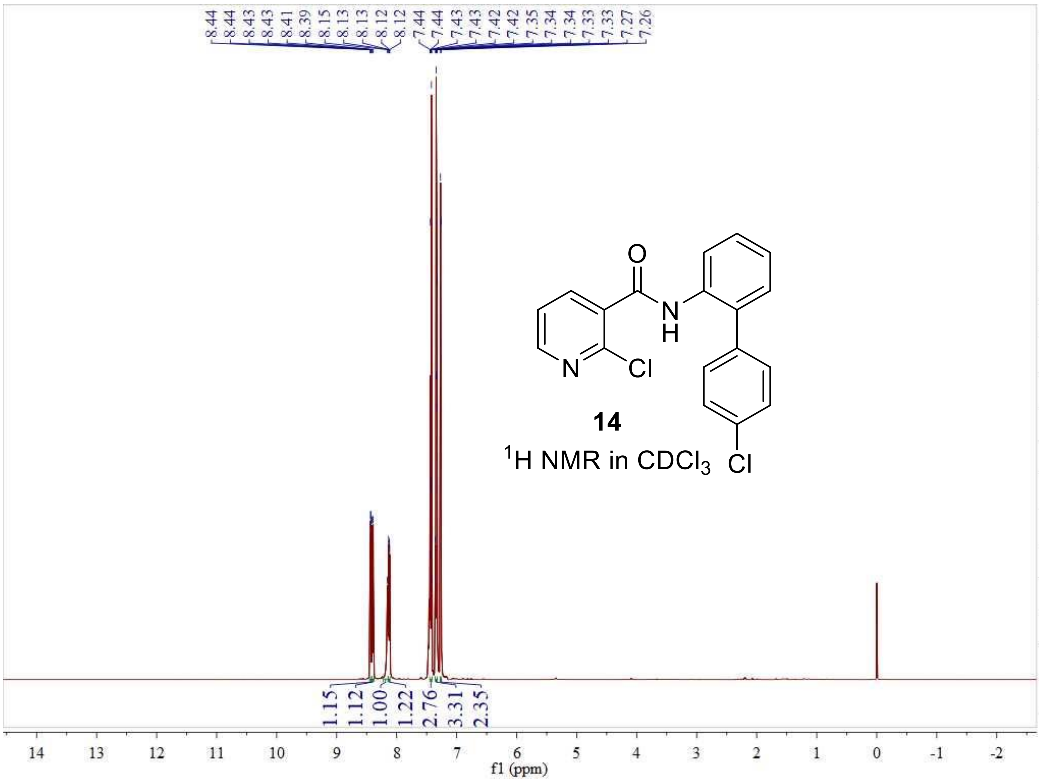
^{1}H NMR in DMSO-d6


9

^{13}C NMR in DMSO-d6

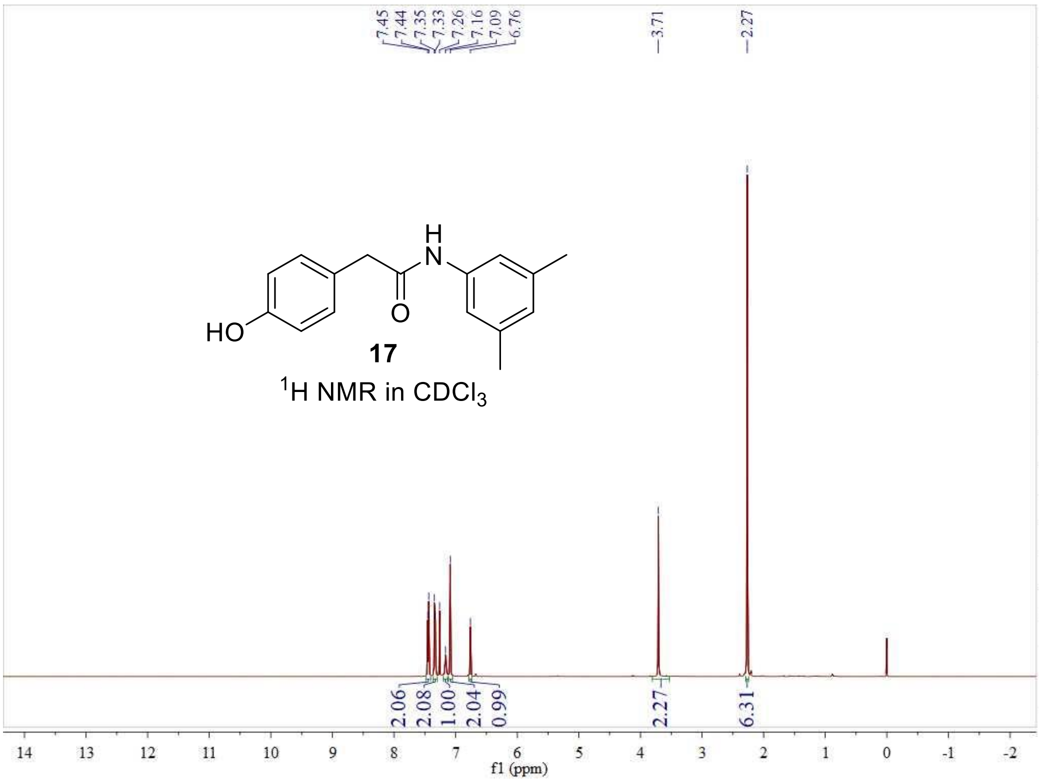

11

^{1}H NMR in CDCl$_3$



14

^{1}H NMR in $CDCl_3$



17

^{1}H NMR in $CDCl_3$

7. References

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2009, *46*, 7224.

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