Rhodium catalyzed asymmetric hydrogenation of α,β-unsaturated carbonyl compounds via a thiourea hydrogen bonding

Supporting Information

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Content

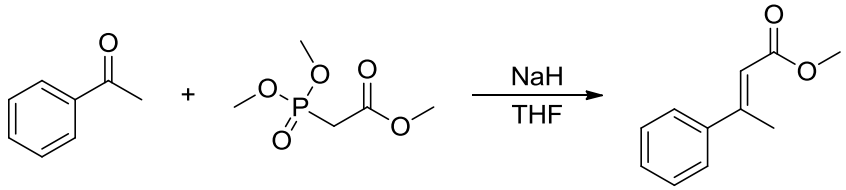
1. General Information.

All the reactions dealing with air- or moisture- sensitive compounds were carried out in a dry reaction vessel under nitrogen protection or in the nitrogen-filled glove box. Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers without further purification. THF was dried with sodium chips and indicated by benzophenone. Other anhydrous solvents were purchased from Sigma-Aldrich and transferred by syringe. Purification of products was carried out by chromatography using silica gel from ACROS (0.06-0.20 mm). Thin layer chromatography was carried out using silica gel plates from Merk (GF254). $[Rh(COD)Cl]_2$ and other metal precursors were purchased from Heraeus.

^1H NMR, ^{13}C NMR spectra were recorded on a Bruker Avance (400 MHz) spectrometer or on a Varian VNMRS 500 MHz spectrometer with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in parts per million e (ppm, δ scale) downfield from TMS at 0.00 ppm and referenced to the $CDCl_3$ at 7.26 ppm for ^1H NMR or 77.0 ppm for ^{13}C NMR. Data is reported as: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz) and signal area integration in natural numbers. ^{13}C NMR analyses were ran with decoupling. Enantiomeric excess values were determined with Agilent 1100 Series HPLC instrument. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P–2000 polarimeter at 589 nm.

2. Substrate synthesis.

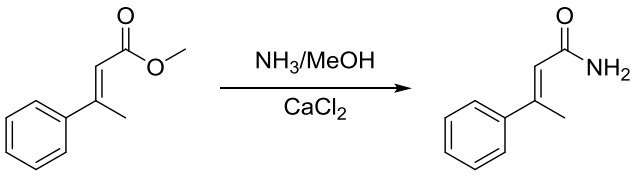
2.1 Typical procedure for the synthesis of α,β-unsaturated esters[1].



3

To a suspension of sodium hydride (60% dispersion in mineral oil, 10 mmol) in dry THF (20 mL) trimethyl phosphonoacetate (10 mmol) was added dropwise at 0 ºC under argon atmosphere. After 30 min, the appropriate ketones (8 mmol) was added dropwise at the same temperature. The reaction mixture was then allowed to warm to room temperature and stirred under reflux for 24 h. After the mixture cooling in an ice bath, saturated aqueous ammonium chloride solution (20 mL) was then added dropwise. The aqueous phase was extracted with diethyl ether (2 x 50mL) and the combined organic phase was washed with brine (50mL), dried over sodium sulfate, and concentrated *in vacuo*. Flash chromatography (hexanes/ethyl acetate, 95:5) yielded ester as a clear oil with 60-80% yields.

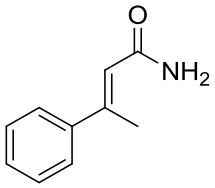
2.2 Typical procedure for the synthesis of α,β-unsaturated amides.



3a **1a**

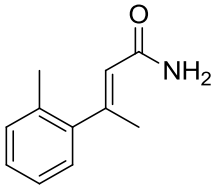
A schlenk tube was charged with α,β-unsaturated ester (5.0 mmol), anhydrous calcium chloride (2 eq.). The tube was protected under nitrogen and ammonia in methanol solution (7N, 10 eq.) was added. The tube was sealed and heated at 100 ºC. After stirring for 24h, the mixture was cooled to room temperature. Solvent was evaporated *in vacuo*. The residue was dissolved in 30ml water and extracted with dichloromethane (50ml×2). The combined organic layer was dried over sodium sulfate and concentrated. After purification by flash chromatography, α,β-unsaturated amide was obtain.

(*E*)-3-phenylbut-2-enamide **1a**



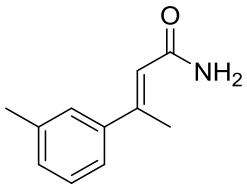
White soild; 0.53 g, 66 % yield; m.p. = 116-117 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 2H), 7.37-7.35 (m, 3H), 6.08 (d, *J* = 1.1 Hz, 1H), 5.81 (br, 1H), 5.62 (br, 1H), 2.56 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.92, 152.52, 142.52, 128.70, 128.50, 126.20, 118.74, 17.74; *m*/*z* (ESI–MS) 163.21 $[M + H]^+$.

(E)-3-(o-tolyl)but-2-enamide **1b**



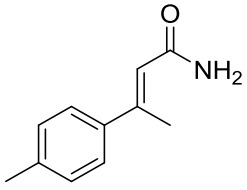
White soild; 0.37 g, 42 % yield; m.p. = 92-94 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.12 (m, 3H), 7.07-7.06 (m, 1H), 5.70 (d, *J* = 1.3 Hz, 1H), 5.63 (br, 1H), 5.46 (br, 1H), 2.44 (d, *J* = 1.3 Hz, 3H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.47, 155.46, 144.08, 133.95, 130.38, 127.57, 127.14, 125.74, 120.50, 20.38, 19.65; *m*/*z* (ESI–MS) 176.72 $[M + H]^+$.

(*E*)-3-(m-tolyl)but-2-enamide **1c**



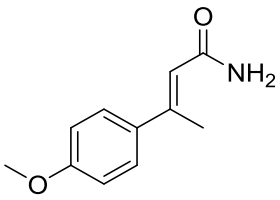
White solid; 0.55 g, 63 % yield; m.p. = 79-83 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 6.97 (m, 4H), 6.06 (s, 1H), 5.85 (br, 1H), 5.62 (br, 1H), 2.54 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.03, 152.64, 142.57, 138.09, 129.43, 128.38, 126.92, 123.33, 118.59, 21.45, 17.76; *m*/*z* (ESI–MS) 176.73 $[M + H]^+$.

(*E*)-3-(p-tolyl)but-2-enamide **1d**



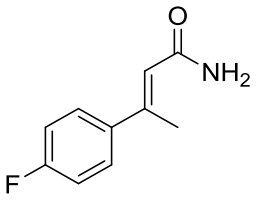
White solid; 0.61 g, 70 % yield; m.p. = 123-126 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 6.06 (d, J = 1.2 Hz, 1H), 5.61 (br, 2H), 2.55 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.87, 152.51, 139.56, 138.80, 129.19, 126.10, 117.81, 21.16, 17.63; (ESI–MS) 176.83 $[M + H]^+$.

(*E*)-3-(4-methoxyphenyl)but-2-enamide **1e**



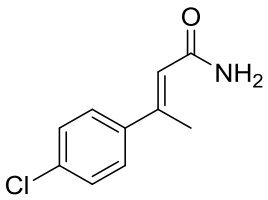
White soild; 0.61 g, 64 % yield; m.p. = 134-136 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 5.7 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.04 (d, *J* = 1.0 Hz, 1H), 5.48 (br, 2H), 3.83 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.86, 160.20, 152.05, 134.68, 127.48, 116.89, 113.85, 55.34, 17.50; *m*/*z* (ESI–MS) 192.71 $[M + H]^+$.

(*E*)-3-(4-fluorophenyl)but-2-enamide **1f**



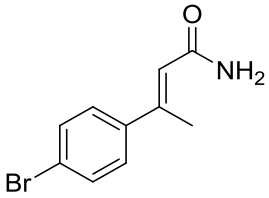
White soild; 0.64 g, 51 % yield; m.p. = 145-155 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.8, 5.6 Hz, 2H), 7.05 (t, *J* = 8.4 Hz, 2H), 6.03 (s, 1H), 5.56 (br, 2H), 2.54 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.53, 164.28, 161.81, 151.41, 138.53, 127.95 (d, *J* = 8.2 Hz), 118.58, 115.41 (d, *J* = 21.5 Hz), 17.78; *m*/*z* (ESI–MS) 180.45 $[M + H]^+$.

(*E*)-3-(4-chlorophenyl)but-2-enamide **1g**



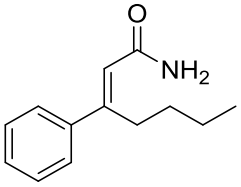
White soild; 0.60 g, 61 % yield; m.p. = 146-156 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.29 (m, 4H), 6.05 (d, *J* = 1.2 Hz, 1H), 5.52 (br, 2H), 2.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.31, 151.23, 140.88, 134.69, 128.68, 127.50, 118.95, 17.64; *m*/*z* (ESI–MS) 196.55, 198.30 $[M + H]^+$.

(*E*)-3-(4-bromophenyl)but-2-enamide **1h**



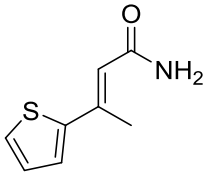
White soild; 0.78 g, 65 % yield; m.p. = 151-159 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.44 (m, 2H), 7.38 – 7.27 (m, 2H), 6.06 (d, *J* = 1.2 Hz, 1H), 5.61 (br, 2H), 2.53 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.44, 151.25, 141.34, 131.65, 127.81, 122.88, 119.03, 17.59; *m*/*z* (ESI–MS) 240.92, 242.81 $[M + H]^+$.

(*E*)-3-phenylhept-2-enamide **1i**



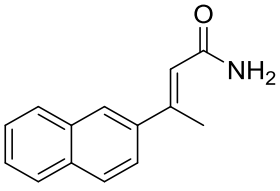
White soild; 0.34 g, 33 % yield; m.p. = 56-58 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.16 (m, 5H), 5.87 (s, 1H), 5.44 (br, 1H), 4.92 (br, 1H), 2.41 (t, *J* = 6.6 Hz, 2H), 1.34 (m, 4H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.64, 153.45, 139.45, 128.85, 128.28, 127.37, 121.62, 40.02, 29.37, 22.16, 13.79; *m*/*z* (ESI–MS) 205.41 $[M + H]^+$.

(*E*)-3-(thiophen-2-yl)but-2-enamide **1j**



White soild; 0.39 g, 47 % yield; m.p. = 125-126 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 4.0 Hz, 2H), 7.04 (dd, *J* = 5.0, 3.8 Hz, 1H), 6.20 (d, *J* = 1.2 Hz, 1H), 5.43 (br, 2H), 2.61 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.25, 145.79, 145.34, 127.90, 126.36 , 126.28, 115.67, 17.08; *m*/*z* (ESI–MS) 168.78 $[M + H]^+$.

(*E*)-3-(naphthalen-2-yl)but-2-enamide **1k**



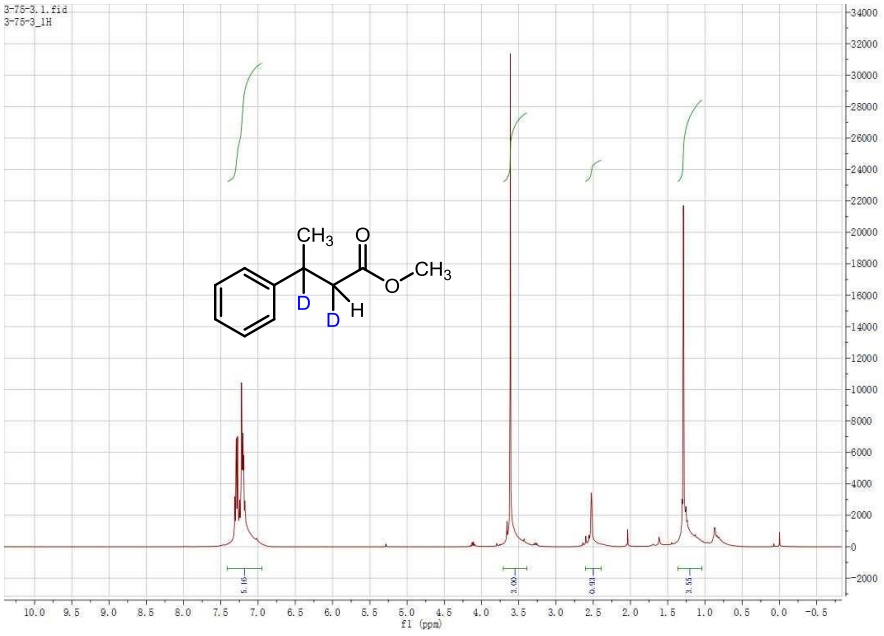
White soild; 0.58 g, 55 % yield; m.p. = 147-156 ºC; ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.4 Hz, 1H), 7.89 – 7.81 (m, 3H), 7.57 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.55 – 7.46 (m, 2H), 6.22 (d, *J* = 1.3 Hz, 1H), 5.56 (br, 2H), 2.68 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.69, 152.40, 139.67, 133.37, 133.20, 128.41, 128.15, 127.60, 126.57, 126.51, 125.68, 123.96, 118.99, 17.75; *m/z* (ESI–MS) 213.26 $[M + H]^+$.

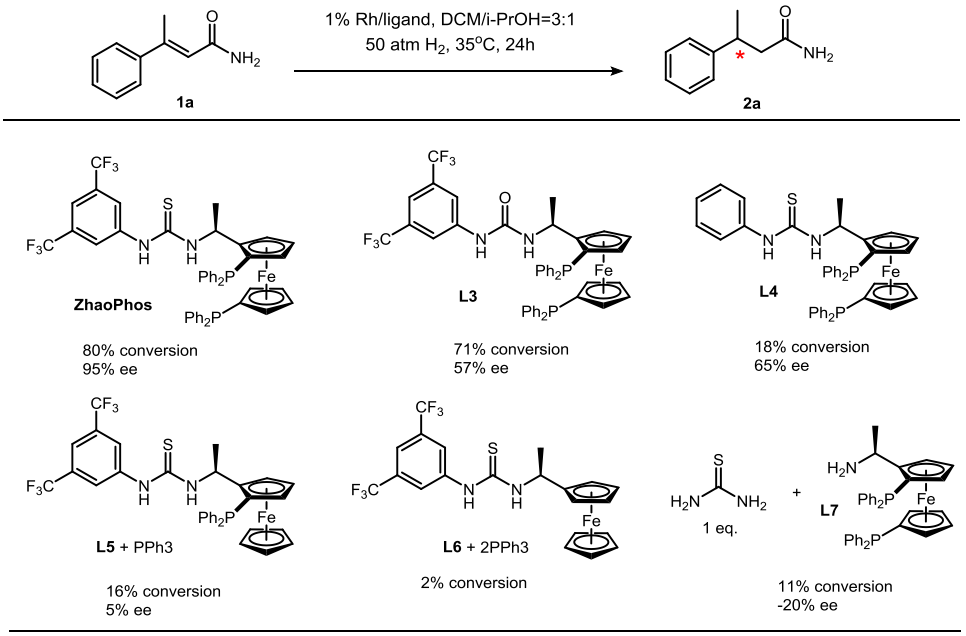
3. General procedure for asymmetric hydrogenation.

In the nitrogen-filled glovebox, solution of $[Rh(COD)Cl]_2$ (4.9 mg, 0.01 mmol) and ligand (2.1 eq.) in 5.0 ml anhydrous solvent was stirred at room temperature for 30 min. A specified volume of the resulting solution (0.5 ml, 1% Rh catalyst) was transferred by syringe to a Score-Break ampule charged with substrate solution (0.2 mmol in 0.5 ml). The ampule was placed into an autoclave, which was then charged with 50 atm H_2. The autoclave was stirred at desired temperature for the indicated period of time. After release of hydrogen gas, the resulting mixture was concentrated under vacuum. The residue passed through a silica plug to remove metal complex and then was concentrated under reduced pressure. The crude product was analysed by ^1H NMR to determine the conversion. The enantiomeric excess was determined by GC or HPLC analysis. Absolute configuration was assigned according to literatures[2].

4. Isotope labeling experiment result.



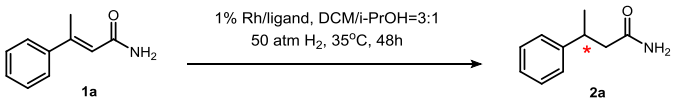
5. Control experiments and evaluation of each unit of ZhaoPhos.

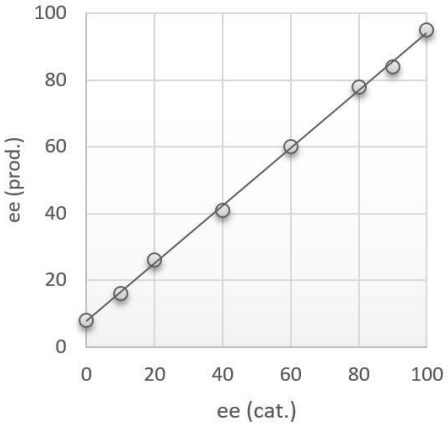


We synthesized a series of analogues of **ZhaoPhos** and conducted control experiments to evaluate the collaboration manner of each unit of **ZhaoPhos**. Urea bisphosphine ligand **L3** only gives both lower conversion and ee. Compared to H (**L6**), more electron-withdrawing trifluoromethyl group at 3- and 5- position on the phenyl ring increases the enantioselectivity, which is probably due to the stronger acidity of N-H proton on the thiourea. Furthermore, monophosphine ligand **L5** and the mixture of ferrocene-thiourea compound **L6** with triphenylphosphine can hardly catalyzed the hydrogenation reaction. On the other hand, the mixture of thiourea molecule and bisphosphine-Ugi's amine **L7** failed to show catalytic activity. These results (**ZhaoPhos** vs **L5 or L6** with PPh_3 and **L7**/thiourea) demonstrate the importance of a covalent incorporation of bisphosphine moiety and thiourea. The idea of secondary offers an alternative strategy for asymmetric hydrogenation.

6. Result of nonlinear effect study.

Table S2. Nonlinear effects for Rh/ZhaoPhos catalyzed asymmetric hydrogenation of 1a.

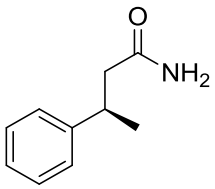




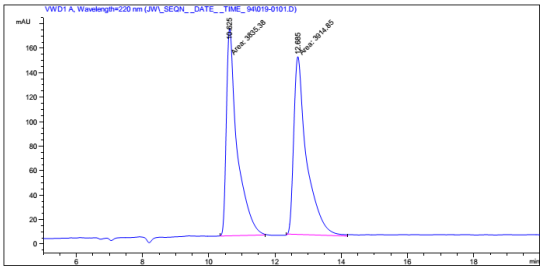
Entry	ee of ZhaoPhos	conversion	ee
1	0	> 95 %	8%
2	10%		16%
3	20%		26%
4	40%		41%
5	60%		60%
6	80%		78%
7	90%		84%
8	100%		95%

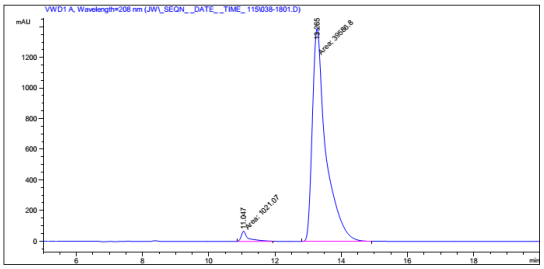
7. Characterization data for chiral carbonyl compounds.

(*R*)-3-phenylbutanamide **2a**



White solid; m.p. = 69-71 ºC; 31.6 mg, yield: 97%, 95% ee; $[\alpha]_D^{22}$ = -29.0 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1 mL/min; UV detection at 220 nm; t_R = 11.0 min (minor), 13.3 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H), 7.26 – 7.18 (m, 3H), 5.67 (br, 1H), 5.39 (br, 1H), 3.27 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.47 (m, 2H), 1.32 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.31, 145.77, 128.65, 126.76, 126.51, 44.80, 36.78, 21.77; *m/z* (ESI–MS) 164.0 [M + H]+.

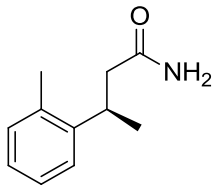




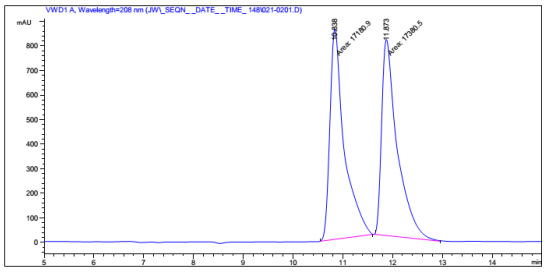
Signal 1: VWD1 A, Wavelength=208 nm

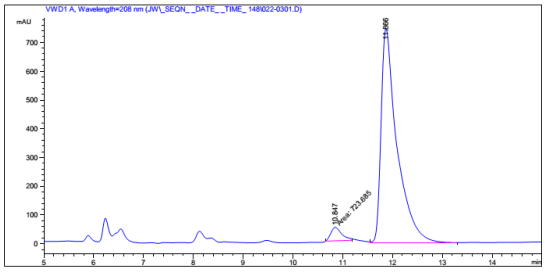
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.047	MM	0.2554	1021.06512	66.63529	2.5145
2	13.265	MM	0.4733	3.95868e4	1394.06787	97.4855
Totals :				4.06078e4	1460.70316	

(*R*)-3-(o-tolyl)butanamide **2b**



White solid; m.p. = 104-105 ºC; 7.1 mg, yield: 20%, 92% ee; $[\alpha]_D^{22}$ = -29.5 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1 mL/min; UV detection at 208 nm; t_R = 10.8 min (minor), 11.8 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.10 (m, 4H), 5.58 (br, 1H), 5.31 (br, 1H), 3.55 (d, *J* = 7.4 Hz, 1H), 2.52 (m, 1H), 2.48 – 2.30 (m, 4H), 1.28 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.29, 143.97, 135.54, 130.63, 126.36, 126.17, 124.95, 43.98, 31.72, 21.37, 19.51; *m/z* (ESI–MS) 179.27 $[M + H]^+$.

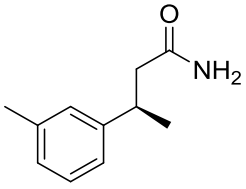




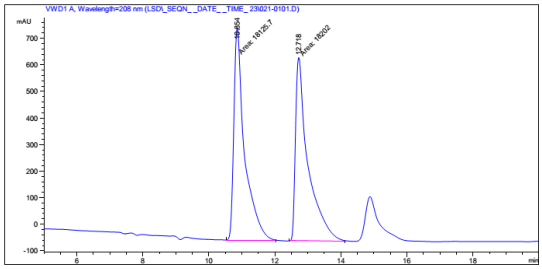
Signal 1: VWD1 A, Wavelength=208 nm

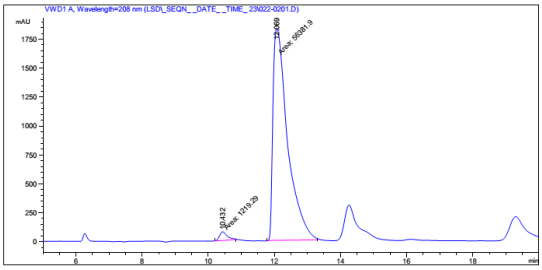
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.847	MM	0.2567	723.68524	46.98661	4.1734
2	11.866	VV	0.3183	1.66168e4	745.33368	95.8266
Totals :				1.73405e4	792.32029	

(*R*)-3-(m-tolyl)butanamide **2c**



White solid; m.p. = 61-64 ºC; 33.8 mg, yield: 95%, 96% ee; $[\alpha]_D^{22}$ = -30.0 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1 mL/min; UV detection at 208 nm; t_R = 10.4 min (minor), 12.1 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 1H), 7.03 (m, 3H), 5.64 (br, 1H), 5.34 (br, 1H), 3.23 (d, *J* = 7.2 Hz, 1H), 2.45 (m, 2H), 2.33 (s, 3H), 1.31 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.23, 145.74, 138.23, 128.55, 127.61, 127.28, 123.68, 44.82, 36.75, 21.86, 21.48; *m/z* (ESI–MS) 179.27 $[M + H]^+$.

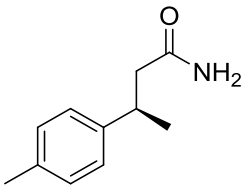




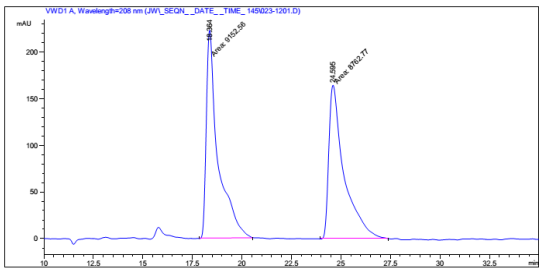
Signal 1: VWD1 A, Wavelength=208 nm

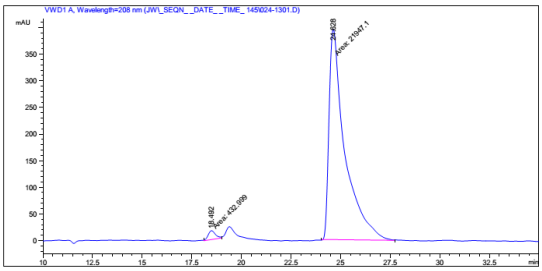
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.432	MM	0.2711	1219.29370	74.94867	2.1168
2	12.069	MM	0.5128	5.63819e4	1832.54810	97.8832
Totals :				5.76012e4	1907.49677	

(*R*)-3-(p-tolyl)butanamide **2d**



White solid; m.p. = 113-114 ºC; 34.5 mg, yield: 97%, 96% ee; $[\alpha]_D^{22}$ = -30.7 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 97:3; flow rate = 1 mL/min; UV detection at 208 nm; t_R = 18.5 min (minor), 24.6 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.07 (m, 4H), 5.54 (br, 1H), 5.30 (br, 1H), 3.23 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.57 – 2.37 (m, 2H), 2.32 (d, *J* = 6.8 Hz, 3H), 1.31 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.21, 142.72, 136.03, 129.33, 126.62, 44.91, 36.41, 21.92, 20.99; *m/z* (ESI–MS) 179.37 $[M + H]^+$.

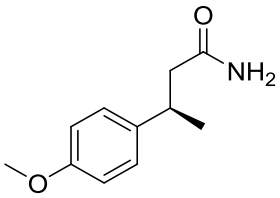




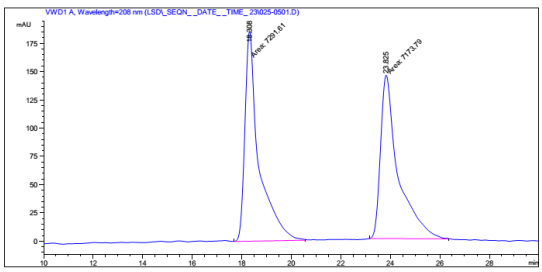
Signal 1: VWD1 A, Wavelength=208 nm

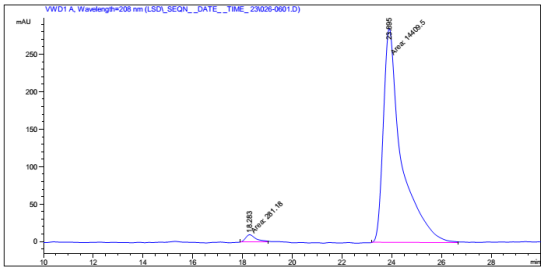
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	18.492	MM	0.4319	432.99863	16.70848	1.9347
2	24.628	MM	0.9252	2.19471e4	395.35178	98.0653
Totals :				2.23801e4	412.06025	

(*R*)-3-(4-methoxyphenyl)butanamide **2e**



White solid; m.p. = 106-108 ºC; 37.8 mg, yield: 96%, 96% ee; $[\alpha]_D^{22}$ = -26.1 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1 mL/min; UV detection at 208 nm; t_R = 18.3 min (minor), 23.9 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.04 (m, 2H), 6.96 – 6.76 (m, 2H), 5.57 (br, 1H), 5.31 (br, 1H), 3.78 (s, 3H), 3.23 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.44 (m, 2H), 1.30 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.24, 158.15, 137.81, 127.68, 114.01, 55.25, 45.09, 36.02, 21.99; *m/z* (ESI–MS) 194.77 $[M + H]^+$.

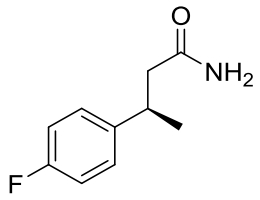




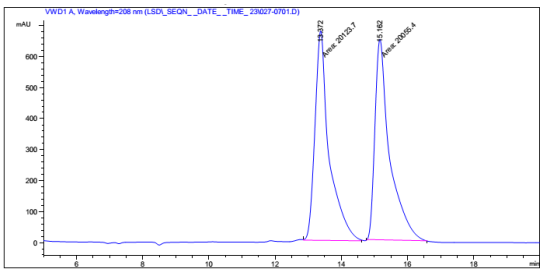
Signal 1: VWD1 A, Wavelength=208 nm

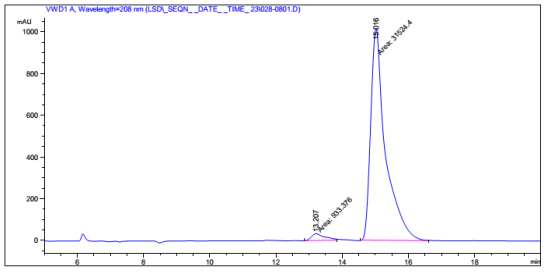
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	18.283	MM	0.4871	281.18048	9.61995	1.9140
2	23.895	MM	0.8411	1.44095e4	285.51715	98.0860
Totals :				1.46907e4	295.13710	

(*R*)-3-(4-fluorophenyl)butanamide **2f**



White solid; m.p. = 73-75 ºC; 32.9 mg, yield: 91%, 94% ee; $[\alpha]_D^{22}$ = -30.5 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1 mL/min; UV detection at 208 nm; t_R = 13.2 min (minor), 15.0 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 2H), 7.07 – 6.87 (m, 2H), 5.79 (br, 1H), 5.42 (br, 1H), 3.28 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.63 – 2.29 (m, 2H), 1.30 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.01, 161.45 (d, *J* = 244.2 Hz), 141.43 (d, *J* = 3.2 Hz), 128.17 (d, *J* = 7.8 Hz), 115.34 (d, *J* = 21.1 Hz), 44.89, 36.02, 21.85; *m/z* (ESI–MS) 182.62 $[M + H]^+$.

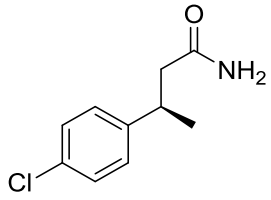




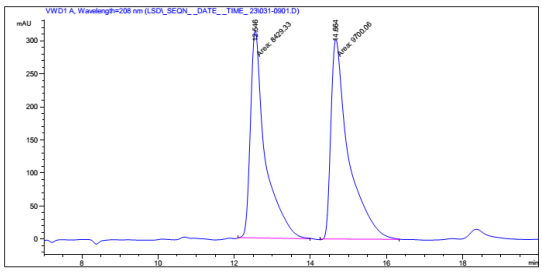
Signal 1: VWD1 A, Wavelength=208 nm

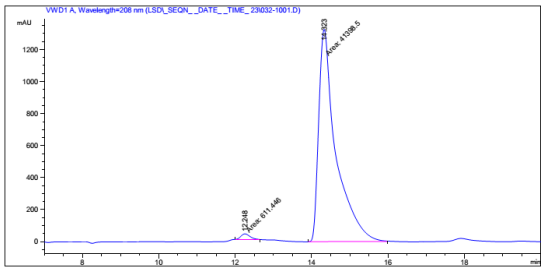
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.207	MM	0.4721	933.37561	32.95427	2.8757
2	15.016	MM	0.5176	3.15244e4	1015.01727	97.1243
Totals :				3.24578e4	1047.97154	

(*R*)-3-(4-chlorophenyl)butanamide **2g**



White solid; m.p. = 96-97 ºC; 37.8 mg, yield: 95%, 95% ee; $[\alpha]_D^{22}$ = -31.6 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1 mL/min; UV detection at 208 nm; t_R = 12.3 min (minor), 14.3 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.07 (m, 4H), 5.38 (d, *J* = 74.5 Hz, 2H), 3.29 (dd, *J* = 14.3, 7.1 Hz, 1H), 2.43 (m, 2H), 1.31 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.56, 144.23, 132.13, 128.72, 128.17, 44.65, 36.14, 21.66; *m/z* (ESI–MS) 199.45, 201.76 $[M + H]^+$.

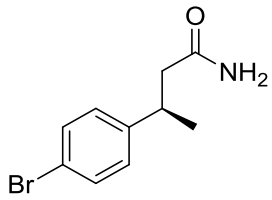




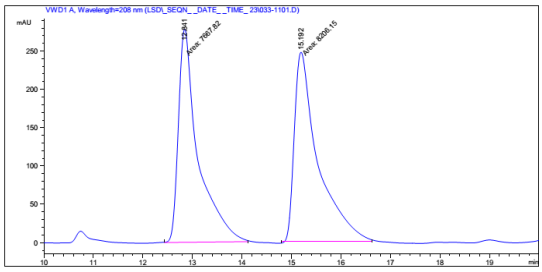
Signal 1: VWD1 A, Wavelength=208 nm

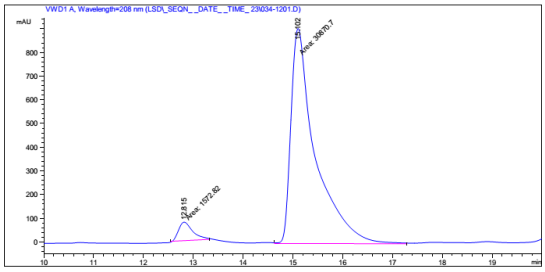
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.248	MM	0.2833	611.44568	35.96681	1.4555
2	14.323	MM	0.5203	4.13985e4	1326.08508	98.5445
Totals :				4.20100e4	1362.05190	

(*R*)-3-(4-bromophenyl)butanamide **2h**



White solid; m.p. = 93-94 ºC; 29.6 mg, yield: 61%, 90% ee; $[\alpha]_D^{22}$ = -28.0 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1 mL/min; UV detection at 208 nm; t_R = 12.8 min (minor), 15.1 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.11 (m, 2H), 5.49 (br, 2H), 3.26 (dd, *J* = 14.1, 7.0 Hz, 1H), 2.50 – 2.36 (m, 2H), 1.30 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.68, 144.78, 131.67, 128.58, 120.15, 44.56, 36.19, 21.61; *m/z* (ESI–MS) 243.08, 244.56 $[M + H]^+$.

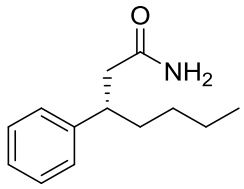




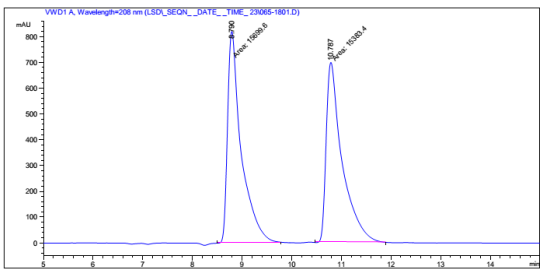
Signal 1: VWD1 A, Wavelength=208 nm

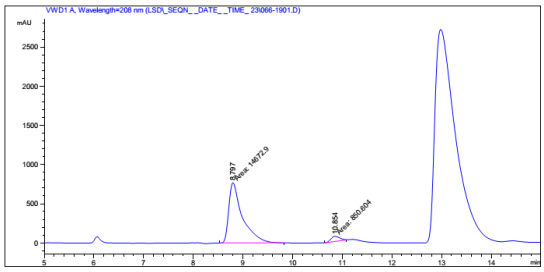
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.815	MM	0.3324	1572.82239	78.86093	4.8479
2	15.102	MM	0.5667	3.08707e4	907.83868	95.1521
Totals :				3.24435e4	986.69962	

(*S*)-3-phenylheptanamide **2i**



White solid; m.p. = 65-68 ºC; 12.6 mg, yield: 31%, 89% ee; $[\alpha]_D^{22}$ = 12.1 (c = 0.1, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1 mL/min; UV detection at 208 nm; t_R = 8.8 min (major), 10.9 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.25 – 7.13 (m, 3H), 5.33 (br, *J* = 95.1 Hz, 2H), 3.06 (m, 1H), 2.48 (m, 2H), 1.76 – 1.55 (m, 2H), 1.34 – 1.03 (m, 4H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.19, 144.30, 128.58, 127.45, 126.50, 43.83, 42.64, 35.97, 29.54, 22.57, 13.90; *m/z* (ESI–MS) 205.19 $[M + H]^+$.

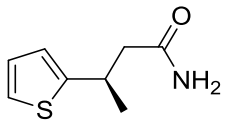




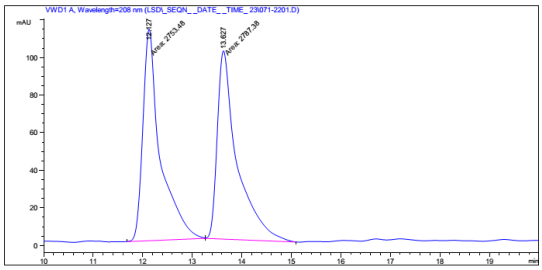
Signal 1: VWD1 A, Wavelength=208 nm

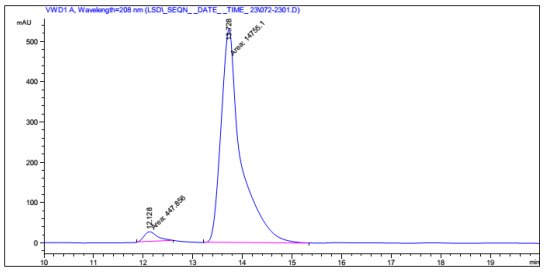
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.797	MM	0.3178	1.46729e4	769.49799	94.5205
2	10.854	MM	0.2111	850.60370	67.15005	5.4795
Totals :				1.55235e4	836.64803	

(*R*)-3-(thiophen-2-yl)butanamide **2j**



White solid; m.p. = 79-82 ºC; 31.9 mg yield: 94%, 94% ee; $[\alpha]_D^{22}$ = -27.1 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1 mL/min; UV detection at 208 nm; t_R = 12.1 min (minor), 13.7 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (m, 1H), 7.00 – 6.80 (m, 2H), 5.47 (br, 2H), 3.62 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.65 – 2.54 (m, 1H), 2.46 (m, 1H), 1.41 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.50 (s), 149.81 (s), 126.72 (s), 123.19, 123.04, 45.67, 32.32, 22.68; *m/z* (ESI–MS) 170.81 [M + H]$^+$.

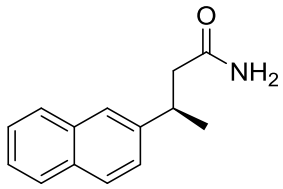




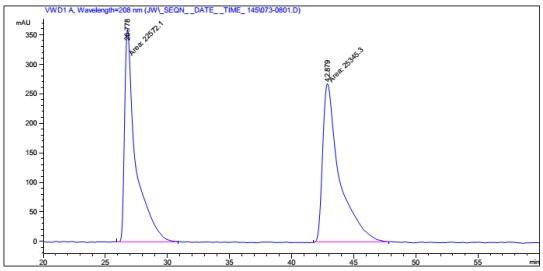
Signal 1: VWD1 A, Wavelength=208 nm

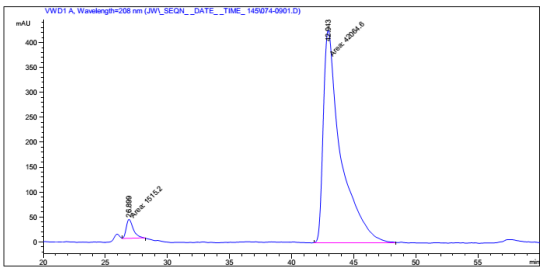
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.128	MM	0.3104	447.85587	24.04399	2.9458
2	13.728	MM	0.4641	1.47551e4	529.89001	97.0542
Totals :				1.52030e4	553.93401	

(*R*)-3-(naphthalen-2-yl)butanamide **2k**



White solid; m.p. = 104-105 ºC; 41.5 mg, yield: 98%, 93% ee; $[\alpha]_D^{22}$ = -24.1 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 97:3; flow rate = 1 mL/min; UV detection at 208 nm; t_R = 26.9 min (minor), 42.9 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.74 (m, 3H), 7.66 (s, 1H), 7.54 – 7.34 (m, 3H), 5.48 (br, 2H), 3.44 (dd, *J* = 14.2, 7.1 Hz, 1H), 2.54 (m, 2H), 1.40 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.20, 143.15, 133.57, 132.34, 128.33, 127.65, 127.60, 126.09 , 125.50, 125.35, 125.06, 44.78, 36.90, 21.76; *m/z* (ESI–MS) 213.29 [M + H]$^+$.

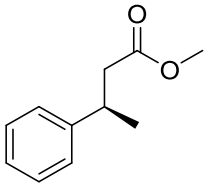




Signal 1: VWD1 A, Wavelength=208 nm

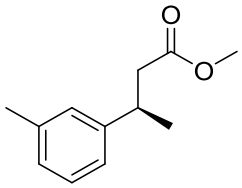
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	26.899	MM	0.6631	1515.20068	38.08642	3.4768
2	42.943	MM	1.6392	4.20646e4	427.68735	96.5232
Totals :				4.35798e4	465.77377	

(*R*)-methyl 3-phenylbutanoate **4a**

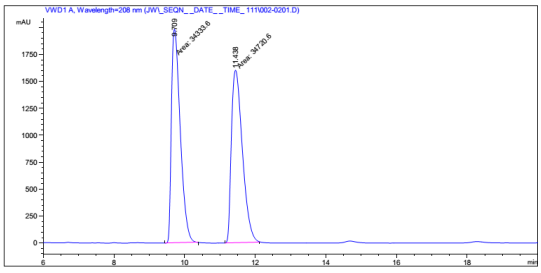


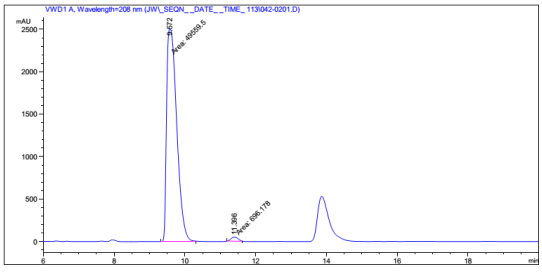
Colorless liquid; 34.5 mg, yield: 97%, 96% ee; $[\alpha]_D^{22}$ = -27.3 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak OJ-H column, hexane: isopropanol = 98:2; flow rate = 1.0 mL/min; UV detection at 208 nm; t_R = 14.0 min (major), 17.3 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 3.62 (s, 3H), 3.28 (dd, *J* = 14.9, 7.1 Hz, 1H), 2.59 (qd, *J* = 15.2, 7.6 Hz, 2H), 1.30 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.85, 145.72, 128.52, 126.72, 126.42, 51.50, 42.75, 36.44, 21.78.

(*R*)-methyl 3-(m-tolyl)butanoate **4b**



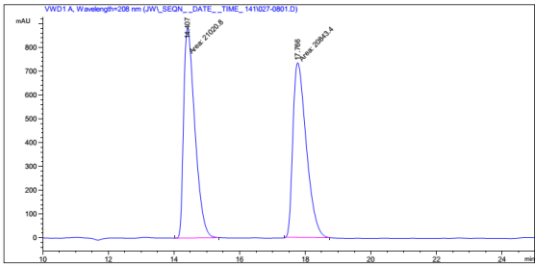
Colorless liquid; 34.9 mg, yeld: 91%, 97% ee; $[\alpha]_D^{22}$ = -16.1 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak OJ-H column, hexane: isopropanol = 98:2; flow rate = 1.0 mL/min; UV detection at 208 nm; t_R = 9.6 min (major), 11.4 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 1H), 7.02 (m, 3H), 3.63 (s, 3H), 3.24 (dd, *J* = 15.1, 7.0 Hz, 1H), 2.57 (m, 2H), 2.33 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.94, 145.72, 138.05, 128.42, 127.55, 127.18, 123.68, 51.51, 42.75, 36.36, 21.79, 21.49.

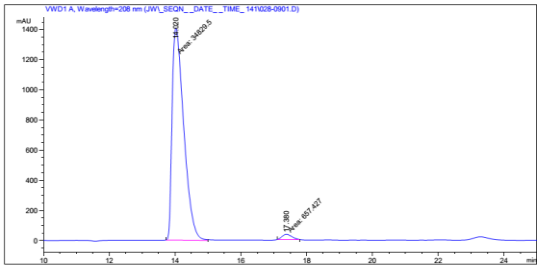




Signal 1: VWD1 A, Wavelength=208 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.572	MM	0.3292	4.95595e4	2508.79517	98.6147
2	11.396	MM	0.2350	696.17810	49.37650	1.3853
Totals :				5.02556e4	2558.17166	

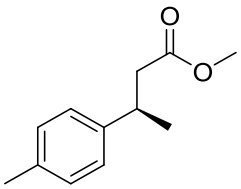




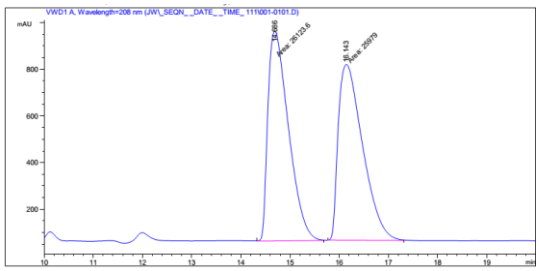
Signal 1: VWD1 A, Wavelength=208 nm

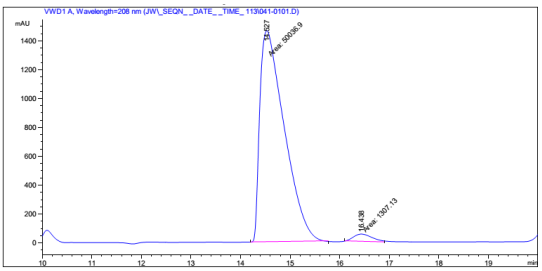
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.020	MM	0.4127	3.48295e4	1406.67395	98.1474
2	17.380	MM	0.3325	657.42725	32.95865	1.8526
Totals :				3.54869e4	1439.63260	

(*R*)-methyl 3-(p-tolyl)butanoate **4c**



Colorless liquid; 37.2 mg, yield: 97%, 95% ee; $[\alpha]_D^{22}$ = -16.8 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak OJ-H column, hexane: isopropanol = 98:2; flow rate = 1.0 mL/min; UV detection at 208 nm; t_R = 14.5 min (major), 16.4 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 4H), 3.62 (s, 3H), 3.25 (m, 1H), 2.57 (m, 2H), 2.31 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.94, 142.72, 135.90, 129.20, 126.58, 51.50, 42.84, 36.03, 21.88, 21.01.

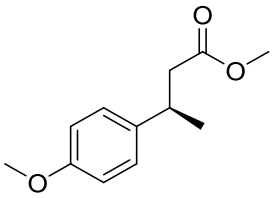




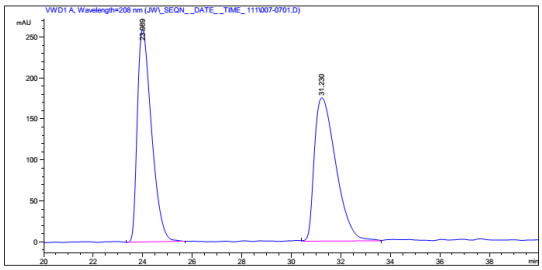
Signal 1: VWD1 A, Wavelength=208 nm

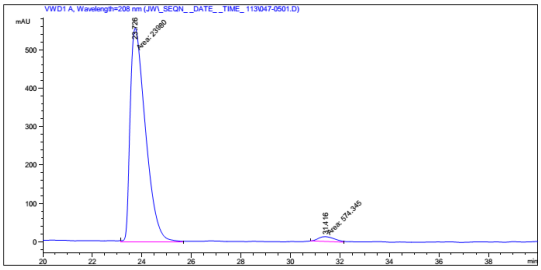
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.527	MM	0.5704	5.00369e4	1462.16687	97.4542
2	16.438	MM	0.4320	1307.13208	50.42678	2.5458
Totals :				5.13440e4	1512.59365	

(*R*)-methyl 3-(4-methoxyphenyl)butanoate **4d**



Colorless liquid; 40.7 mg yield: 98%, 95% ee; $[\alpha]_D^{22}$ = -12.4 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak OJ-H column, hexane: isopropanol = 98:2; flow rate = 1.0 mL/min; UV detection at 208 nm; t_R = 23.7 min (major), 31.4 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.08 (m, 2H), 6.91 – 6.79 (m, 2H), 3.78 (s, 3H), 3.62 (s, 3H), 3.23 (m, 1H), 2.55 (m, 2H), 1.27 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.93, 158.08, 137.81, 127.63, 113.86, 77.36, 77.04, 76.72, 55.24, 51.49, 43.01, 35.66, 21.96.

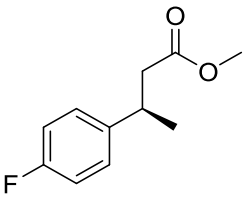




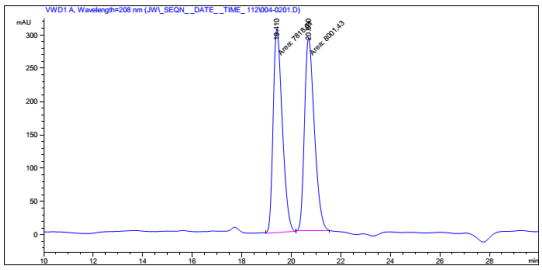
Signal 1: VWD1 A, Wavelength=208 nm

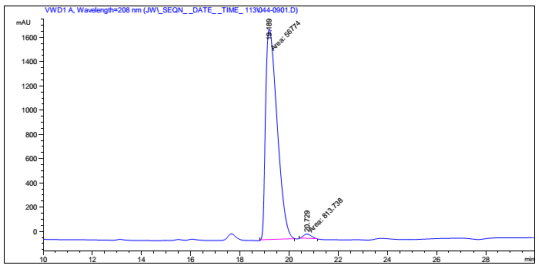
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	23.726	MM	0.7174	2.39800e4	557.07166	97.6609
2	31.416	MM	0.7644	574.34534	12.52320	2.3391
Totals :				2.45544e4	569.59486	

(*R*)-methyl 3-(4-fluorophenyl)butanoate **4e**



Colorless liquid; 37.2 mg, yield: 95%, 97% ee; $[\alpha]_D^{22}$ = -10.9 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak OJ-H column, hexane: isopropanol = 99:1; flow rate = 0.6 mL/min; UV detection at 208 nm; t_R = 19.2 min (major), 20.7 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.14 (m, 2H), 7.03 – 6.93 (m, 2H), 3.62 (d, *J* = 6.9 Hz, 3H), 3.27 (dd, *J* = 14.5, 7.2 Hz, 1H), 2.66 – 2.48 (m, 2H), 1.28 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.65, 161.45 (d, *J* = 244.1 Hz), 141.32, 128.12 (d, *J* = 7.8 Hz), 115.25 (d, *J* = 21.1 Hz), 51.53, 42.85, 35.78, 21.96.

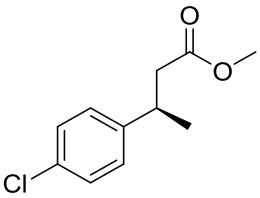




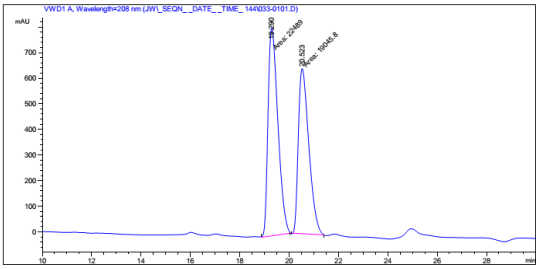
Signal 1: VWD1 A, Wavelength=208 nm

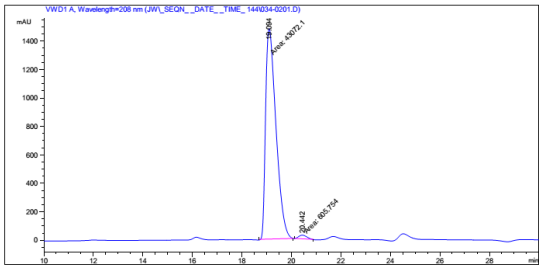
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	19.189	MM	0.5451	5.67740e4	1736.04346	98.5870
2	20.729	MM	0.3745	813.73761	36.21154	1.4130
Totals :				5.75878e4	1772.25499	

(*R*)-methyl 3-(4-chlorophenyl)butanoate **4f**



Colorless liquid; 41.1 mg, yield: 97%, 97% ee; $[\alpha]_D^{22}$ = -12.7 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak OJ-H column, hexane: isopropanol = 99:1; flow rate = 0.6 mL/min; UV detection at 208 nm; t_R = 19.1 min (major), 20.4 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.19 (m, 2H), 3.62 (s, 3H), 3.28 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.59 (m, 2H), 1.30 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.86, 145.71, 128.52, 126.72, 126.43, 51.51, 42.75, 36.44, 21.78.

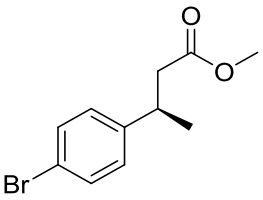




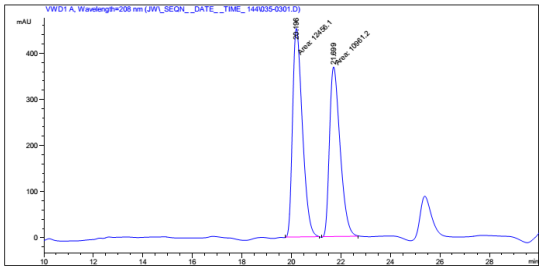
Signal 1: VWD1 A, Wavelength=208 nm

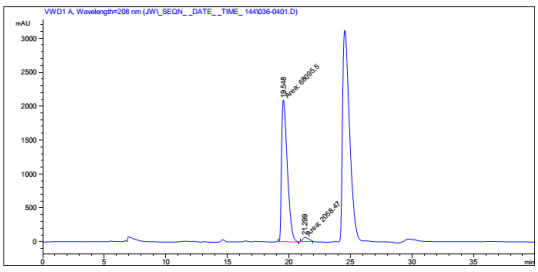
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	19.094	MM	0.4844	4.30721e4	1482.00610	98.6131
2	20.442	MM	0.3806	605.75427	26.52571	1.3869
Totals :				4.36778e4	1508.53181	

(*R*)-methyl 3-(4-bromophenyl)butanoate **4g**



White solid; 26.2 mg, yield: 51%, 94% ee; $[\alpha]_D^{22}$ = -16.5 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak OJ-H column, hexane: isopropanol = 99:1; flow rate = 0.6 mL/min; UV detection at 208 nm; t_R = 19.5 min (major), 21.3 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.21 (m, 2H), 3.62 (s, 3H), 3.28 (dd, *J* = 14.6, 7.2 Hz, 1H), 2.59 (m, 2H), 1.30 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.93, 145.72, 128.54, 126.75, 126.44, 51.62, 42.79, 36.46, 21.82.

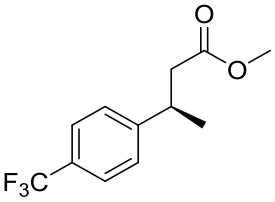




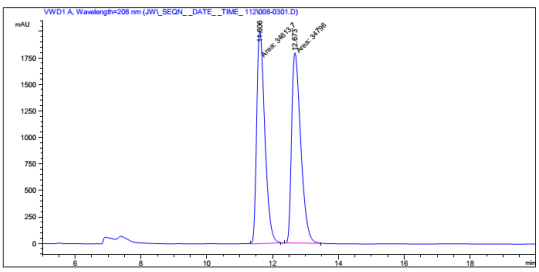
Signal 1: VWD1 A, Wavelength=208 nm

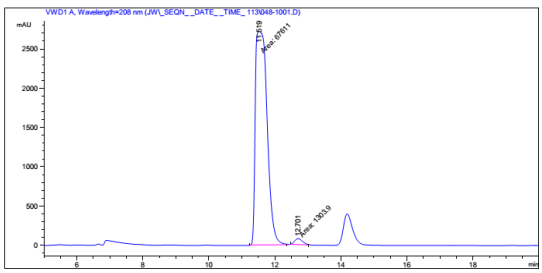
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	19.548	MM	0.5434	6.80955e4	2088.56860	97.0658
2	21.299	MM	0.5588	2058.47192	61.39164	2.9342
Totals :				7.01540e4	2149.96024	

(*R*)-methyl 3-(4-(trifluoromethyl)phenyl)butanoate **4h**



Colorless liquid; 47.7 mg, yield: 97%, 96% ee; $[\alpha]_D^{22}$ = -12.2 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak OJ-H column, hexane: isopropanol = 99:1; flow rate = 0.6 mL/min; UV detection at 208 nm; t_R = 11.5 min (major), 12.7 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.34 (m, 2H), 3.62 (s, 3H), 3.35 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.69 – 2.53 (m, 2H), 1.31 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.37, 149.71, 128.77 (dd, *J* = 65.3, 33.1 Hz), 127.14, 125.49 (q, *J* = 3.7 Hz), 51.61, 42.27, 36.29, 21.71.

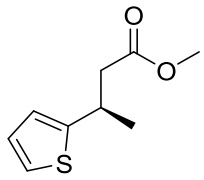




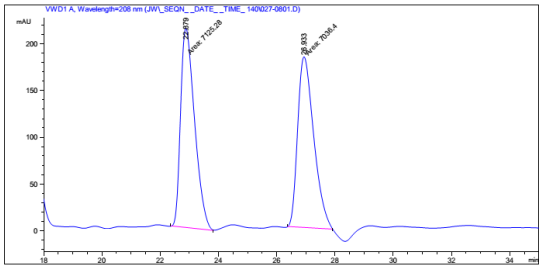
Signal 1: VWD1 A, Wavelength=208 nm

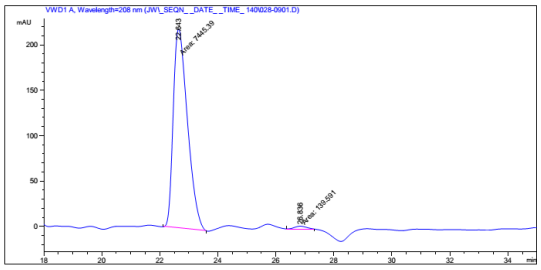
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.519	MM	0.4144	6.76110e4	2719.33838	98.1080
2	12.701	MM	0.2798	1303.90015	77.66666	1.8920
Totals :				6.89149e4	2797.00504	

(*R*)-methyl 3-(thiophen-2-yl)butanoate **4i**



Colorless liquid; 35.0 mg, yield: 95%, 96% ee; $[\alpha]_D^{22}$ = -7.2 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak OJ-H column, hexane: isopropanol = 99:1; flow rate = 0.6 mL/min; UV detection at 208 nm; t_R = 22.6 min (major), 26.8 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (m, 1H), 7.00 – 6.70 (m, 2H), 3.78 – 3.52 (m, 4H), 2.63 (m, 2H), 1.38 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.37, 149.64, 126.61, 122.99, 122.88, 51.63, 43.67, 31.96, 22.63.

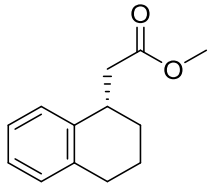




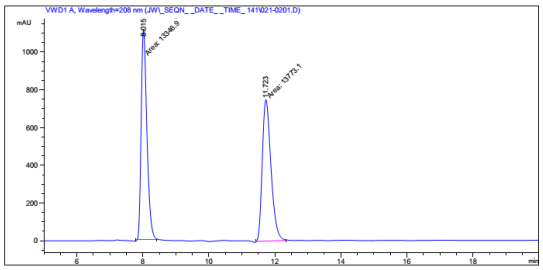
Signal 1: VWD1 A, Wavelength=208 nm

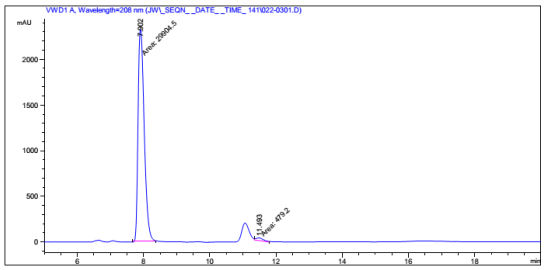
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	22.643	MM	0.5665	7445.38916	219.05545	98.1596
2	26.836	MM	0.5814	139.59059	4.00129	1.8404
Totals :				7584.97975	223.05674	

(*S*)-methyl 2-(1,2,3,4-tetrahydronaphthalen-1-yl)acetate **4j**



Colorless liquid; 29.3 mg, yield: 72%, 96% ee; $[\alpha]_D^{22}$ = 2.1 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak OJ-H column, hexane: isopropanol = 98:2; flow rate = 1.0 mL/min; UV detection at 208 nm; t_R = 7.9 min (major), 11.5 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.01 (m, 4H), 3.71 (s, 3H), 3.35 (m, 1H), 2.84 – 2.66 (m, 3H), 2.60 – 2.49 (m, 1H), 1.95 – 1.64 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.29, 139.24, 137.15, 129.31, 128.27, 126.05, 125.84, 51.61, 41.83, 34.55, 29.53, 28.12, 19.48.

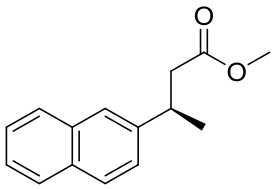




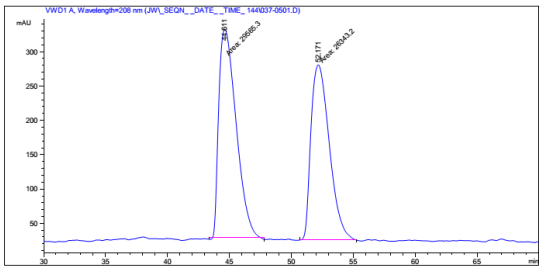
Signal 1: VWD1 A, Wavelength=208 nm

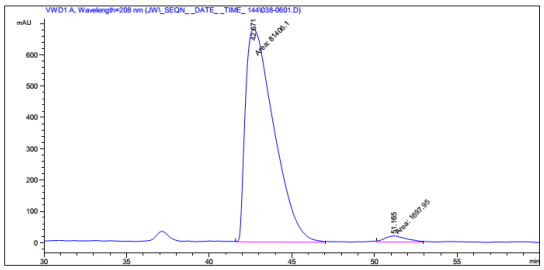
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.902	MM	0.2148	2.99045e4	2319.95996	98.4228
2	11.493	MM	0.2709	479.19977	29.47843	1.5772
Totals :				3.03837e4	2349.43839	

(*R*)-methyl 3-(naphthalen-2-yl)butanoate **4k**



White solid; 44.2 mg, yield: 97%, 96% ee; $[\alpha]_D^{22}$ = -19.1 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak OJ-H column, hexane: isopropanol = 99:1; flow rate = 1 mL/min; UV detection at 208 nm; t_R = 42.7 min (major), 51.2 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.75 (m, 3H), 7.65 (s, 1H), 7.52 – 7.33 (m, 3H), 3.61 (s, 3H), 3.45 (dd, *J* = 14.7, 7.2 Hz, 1H), 2.68 (m, 2H), 1.38 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.83, 143.17, 133.59, 132.35, 128.19, 127.68, 127.61, 126.00, 125.48, 125.42, 124.94, 51.55, 42.68, 36.57, 21.82.

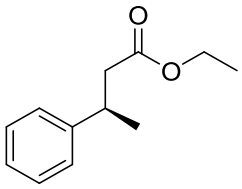




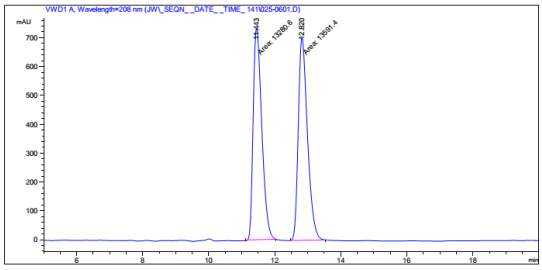
Signal 1: VWD1 A, Wavelength=208 nm

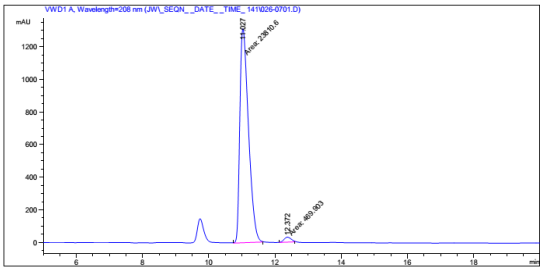
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	42.671	MM	1.9949	8.14061e4	680.13202	97.9568
2	51.165	MM	1.5042	1697.95483	18.81376	2.0432
Totals :				8.31041e4	698.94578	

(*R*)-ethyl 3-phenylbutanoate **4l**



Colorless liquid; 31.1 mg, yield: 81%, 95% ee; $[\alpha]_D^{22}$ = -9.0 (c = 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralpak OJ-H column, hexane: isopropanol = 98:2; flow rate = 1.0 mL/min; UV detection at 208 nm; t_R = 11.0 min (major), 12.4 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.12 (m, 5H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.36 – 3.17 (m, 1H), 2.57 (m, 2H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.41, 145.76, 128.48, 126.78, 126.39, 60.27, 43.01, 36.53, 21.82, 14.18.

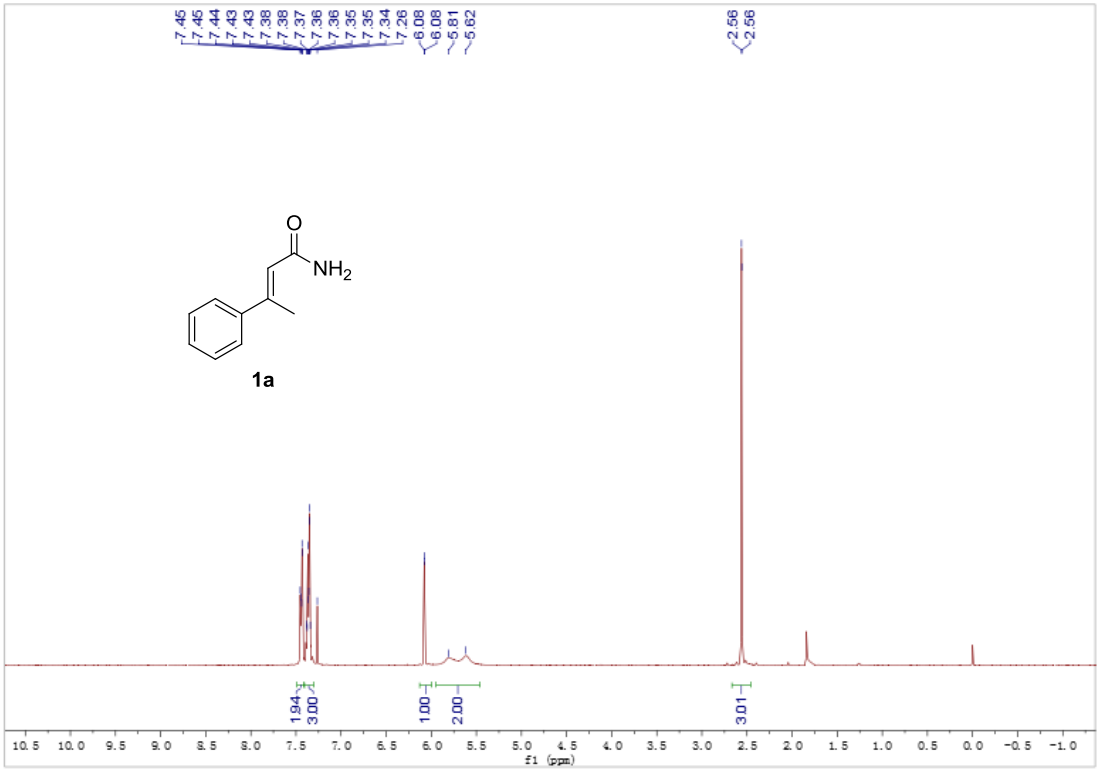


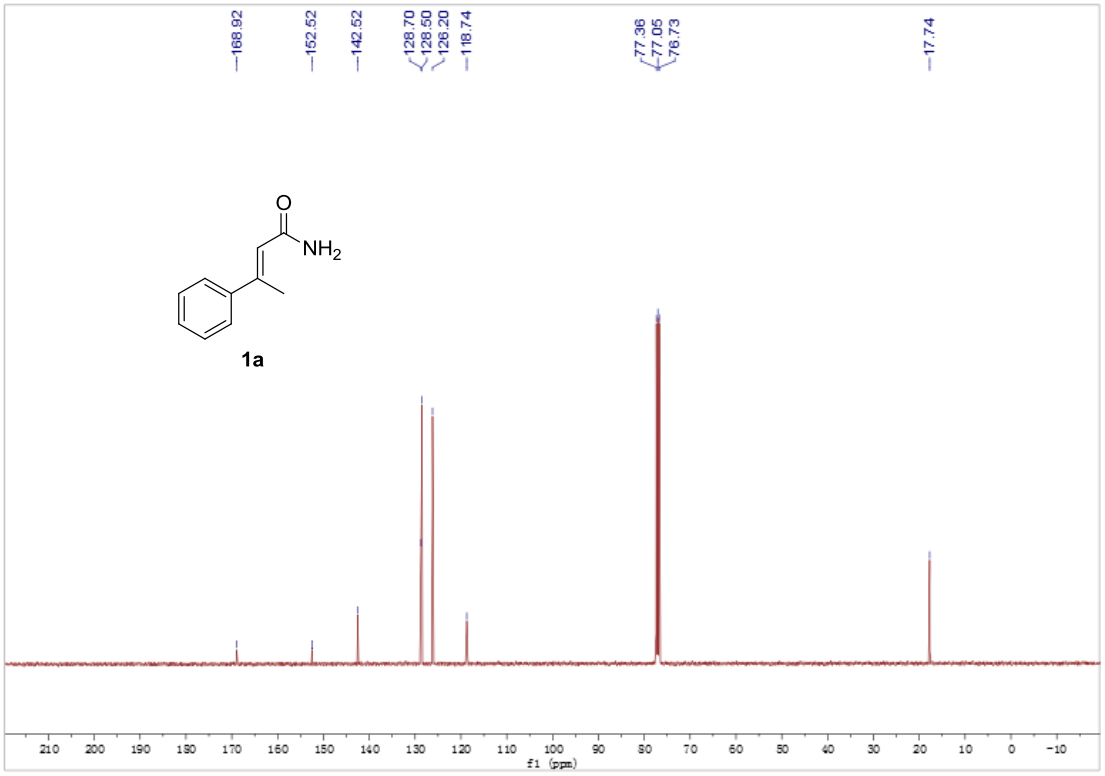


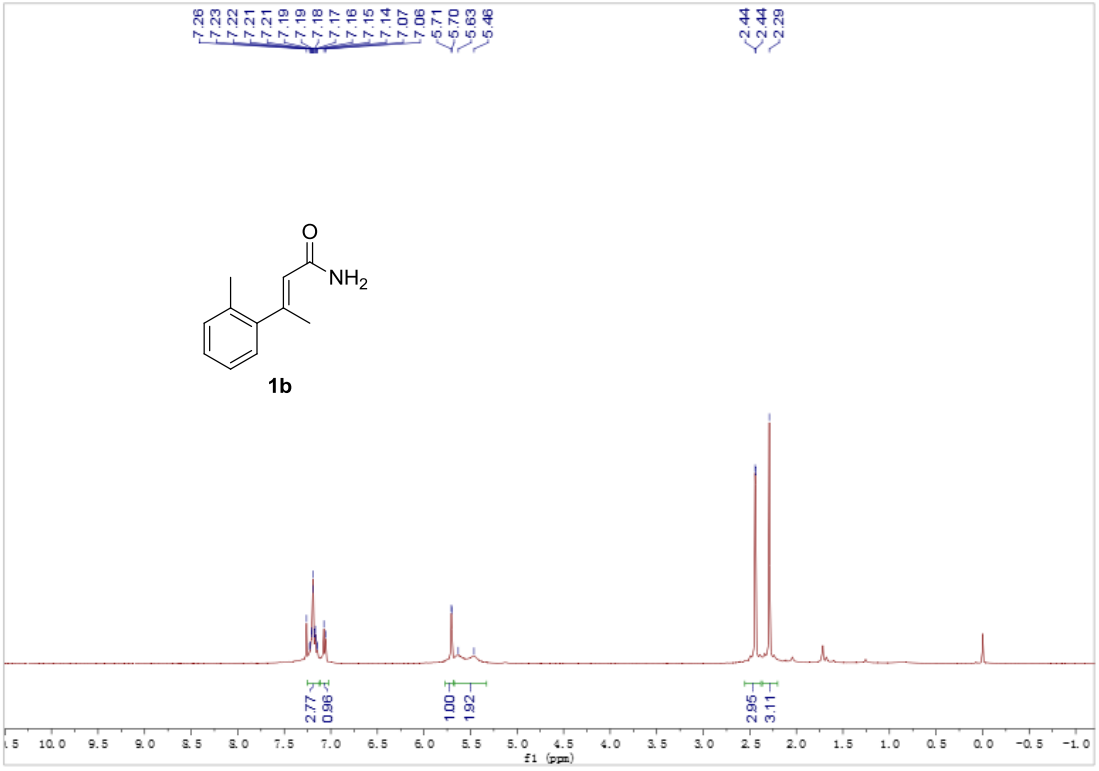
Signal 1: VWD1 A, Wavelength=208 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.027	MM	0.3023	2.38106e4	1312.65613	98.0647
2	12.372	MM	0.2540	469.90295	30.83426	1.9353
Totals :				2.42805e4	1343.49039	

8. NMR spectrum.




168.92
152.52
142.52
128.70
128.50
126.20
118.74
77.36
77.05
76.73
17.74
O
NH2
1a
f1 (ppm)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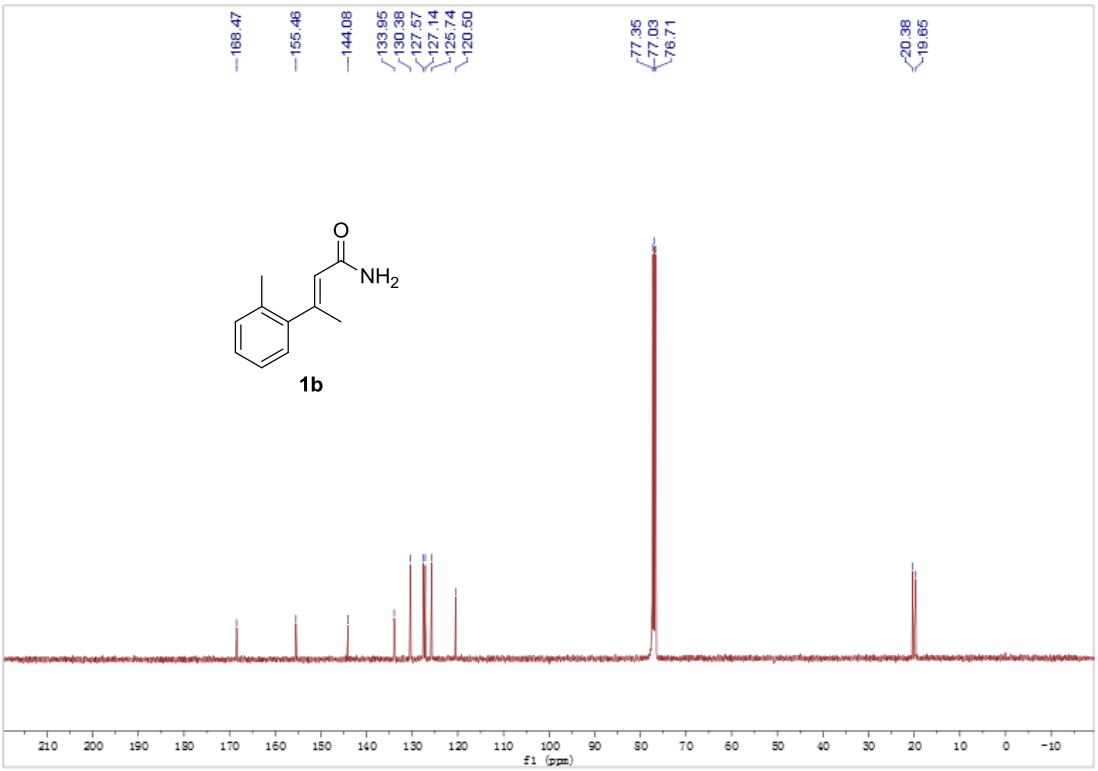
7.23
7.22
7.21
7.21
7.19
7.18
7.17
7.16
7.15
7.14
7.07
7.06
5.71
5.70
5.63
5.46
2.44
2.44
2.29
O
NH2
1b
2.77
0.96
1.00
1.92
2.95
3.11
f1 (ppm)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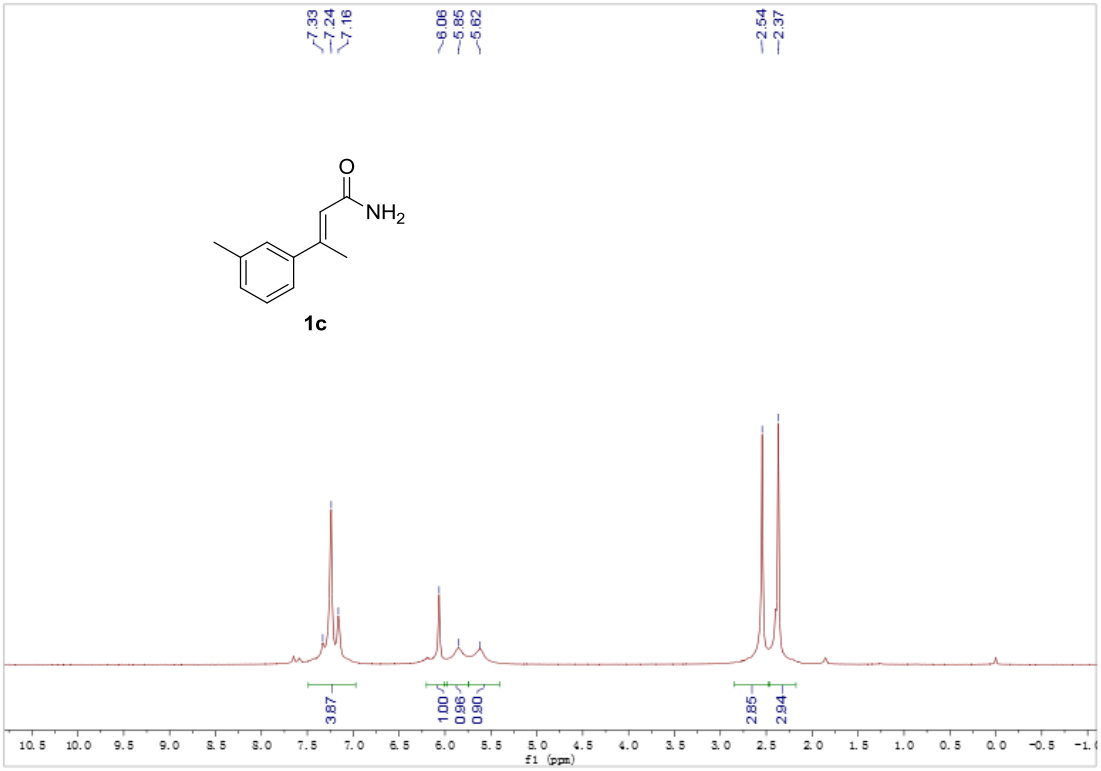
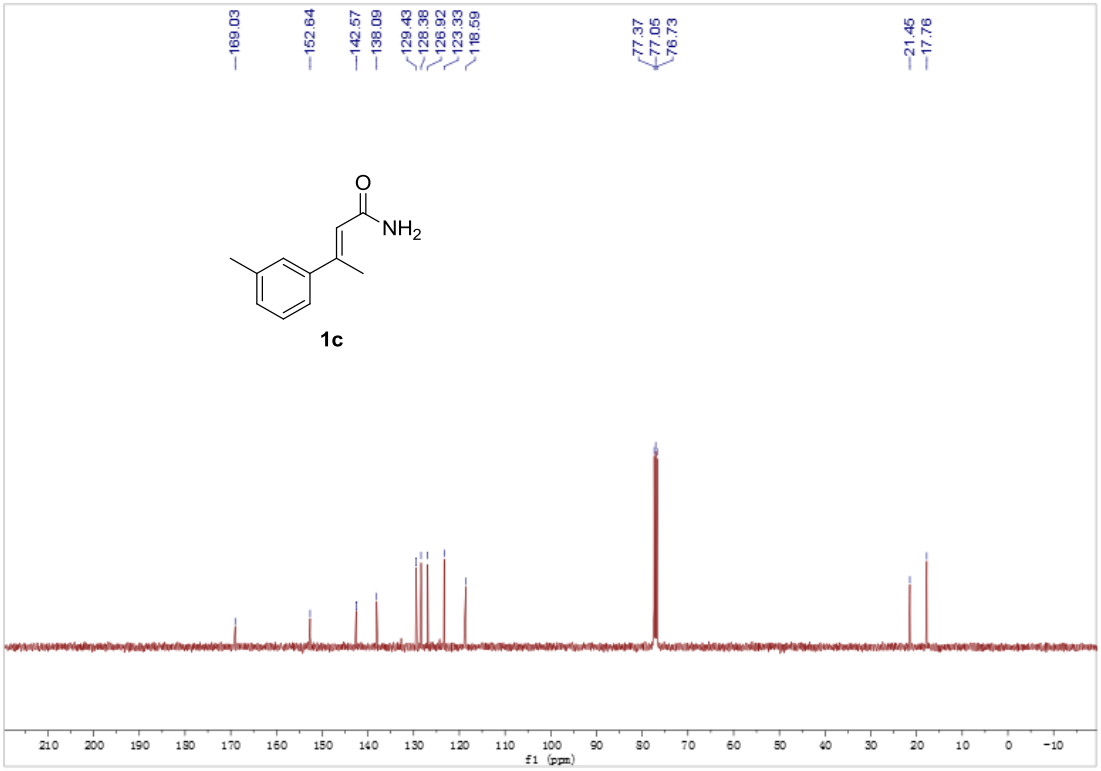
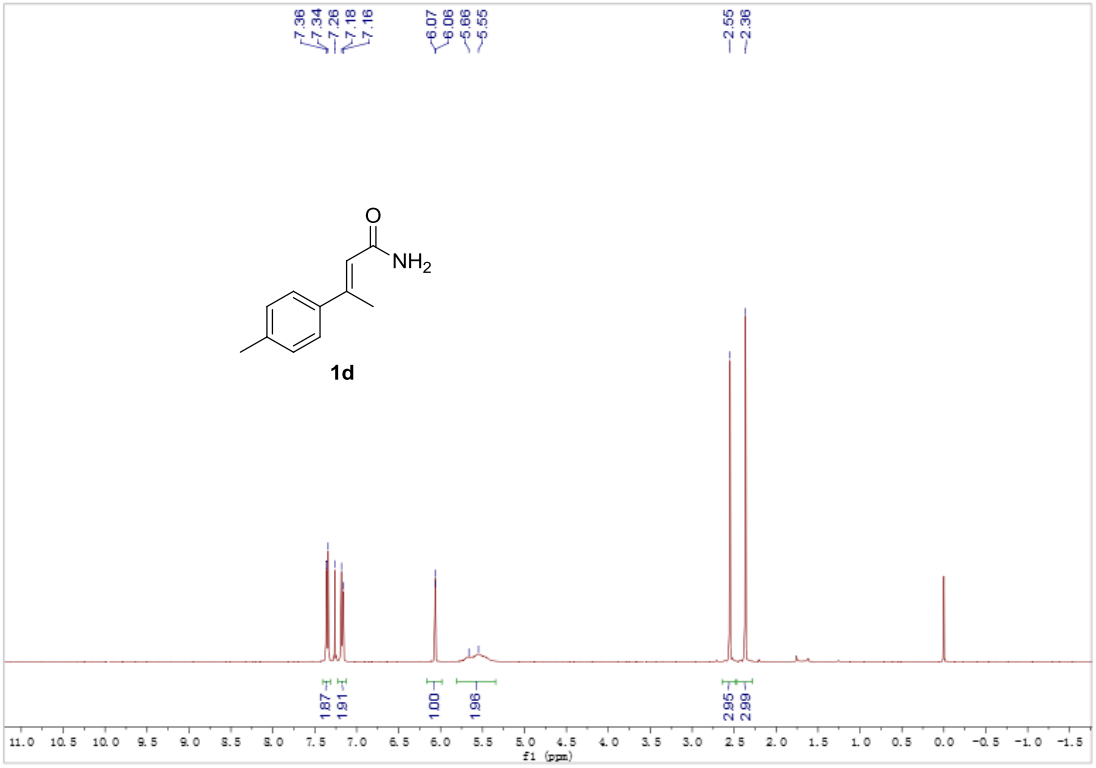
155.46
144.08
133.95
130.38
127.57
127.14
125.74
120.50
77.35
77.03
76.71
20.38
19.65
O
NH2
1b
f1 (ppm)


7.33
7.24
7.16
6.06
5.85
5.62
2.54
2.37
O
NH2
1c
3.87
1.00
0.96
0.90
2.85
2.94
f1 (ppm)


169.03
152.64
142.57
138.09
129.43
128.38
126.92
123.33
118.59
77.37
77.05
76.73
21.45
17.76
O
NH2
1c
f1 (ppm)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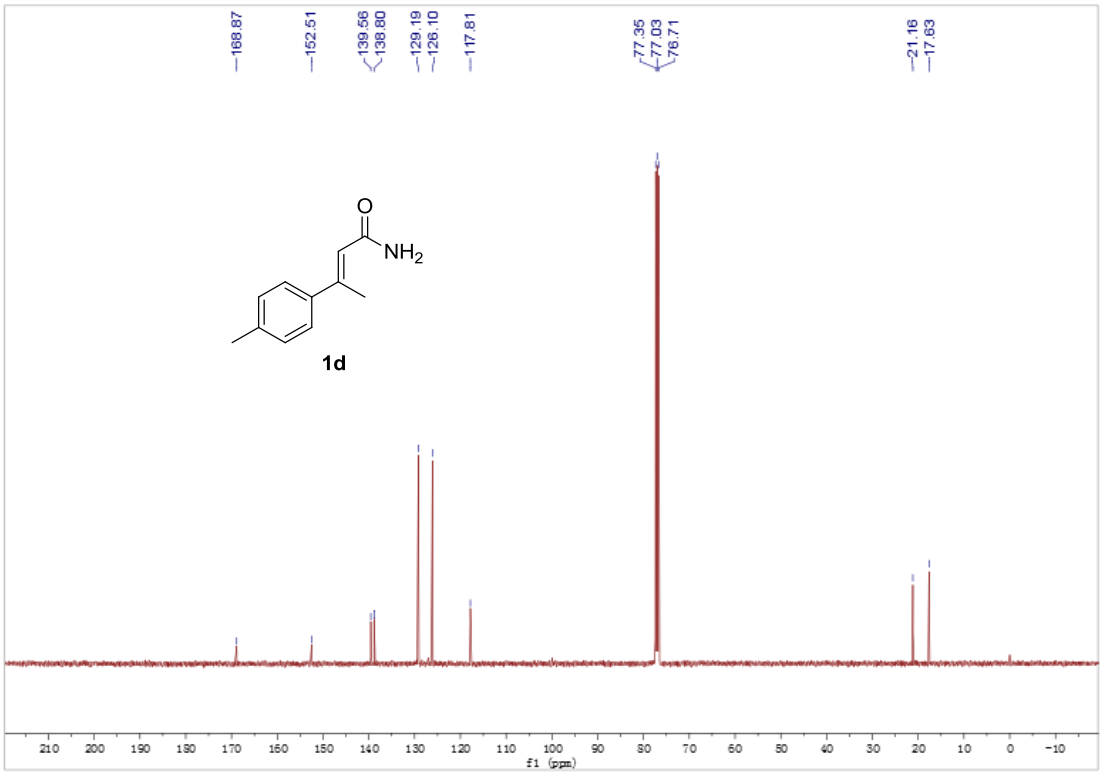
7.34
7.28
7.18
7.16
6.07
6.06
5.66
5.55
2.55
2.36
O
NH2
1d
1.87
1.91
1.00
1.96
2.95
2.99
f1 (ppm)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152.51
139.56
138.80
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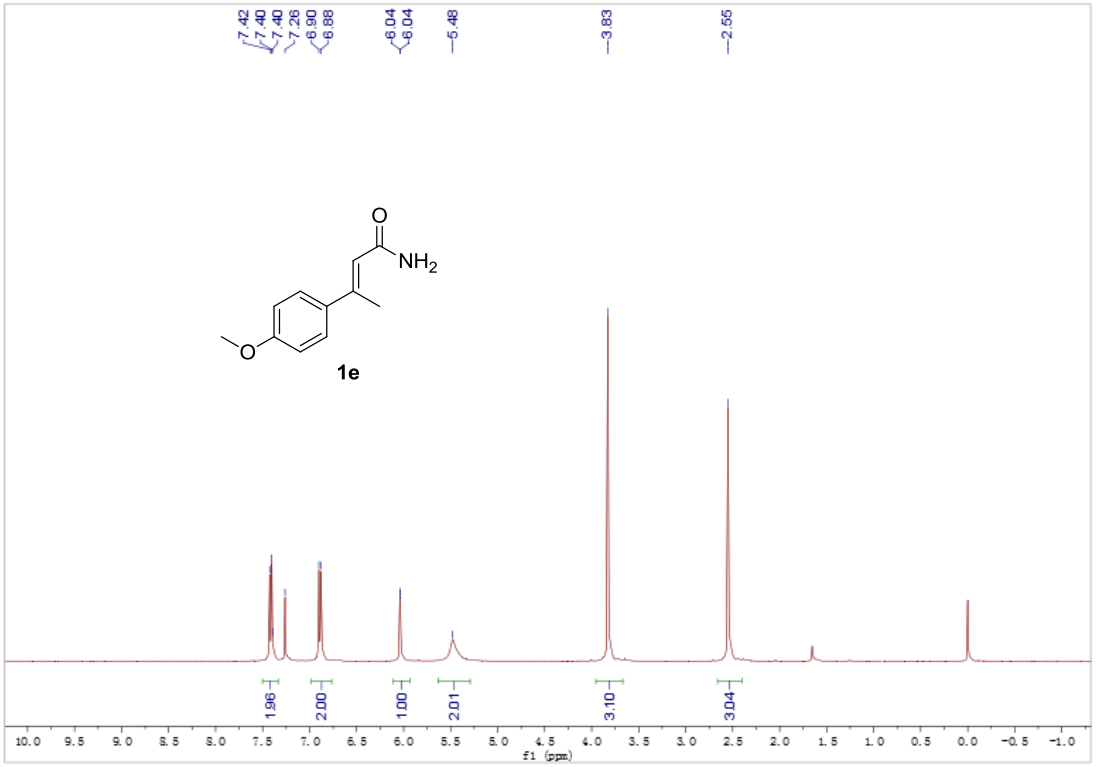
117.81
77.35
77.03
76.71
21.16
17.63
O
NH2
1d
f1 (ppm)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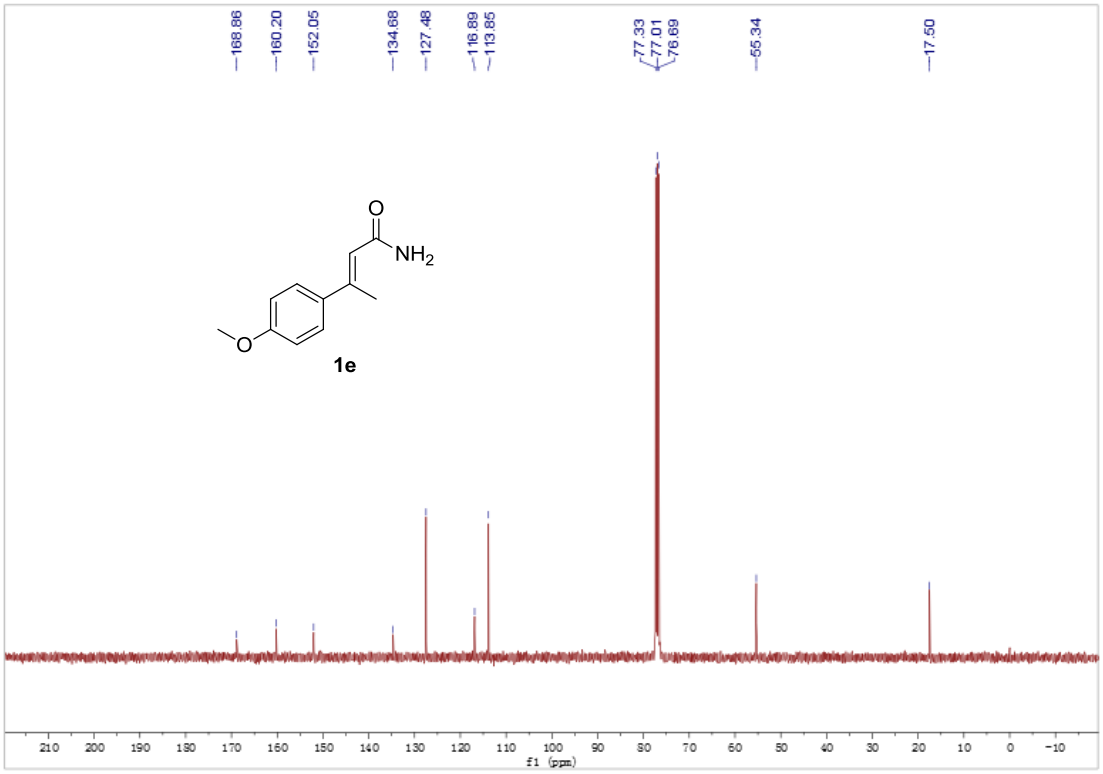
7.40
7.40
7.26
6.90
6.88
6.04
6.04
5.48
3.83
2.55
O
NH2
O
1e
1.96
2.00
1.00
2.01
3.10
3.04
f1 (ppm)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134.68
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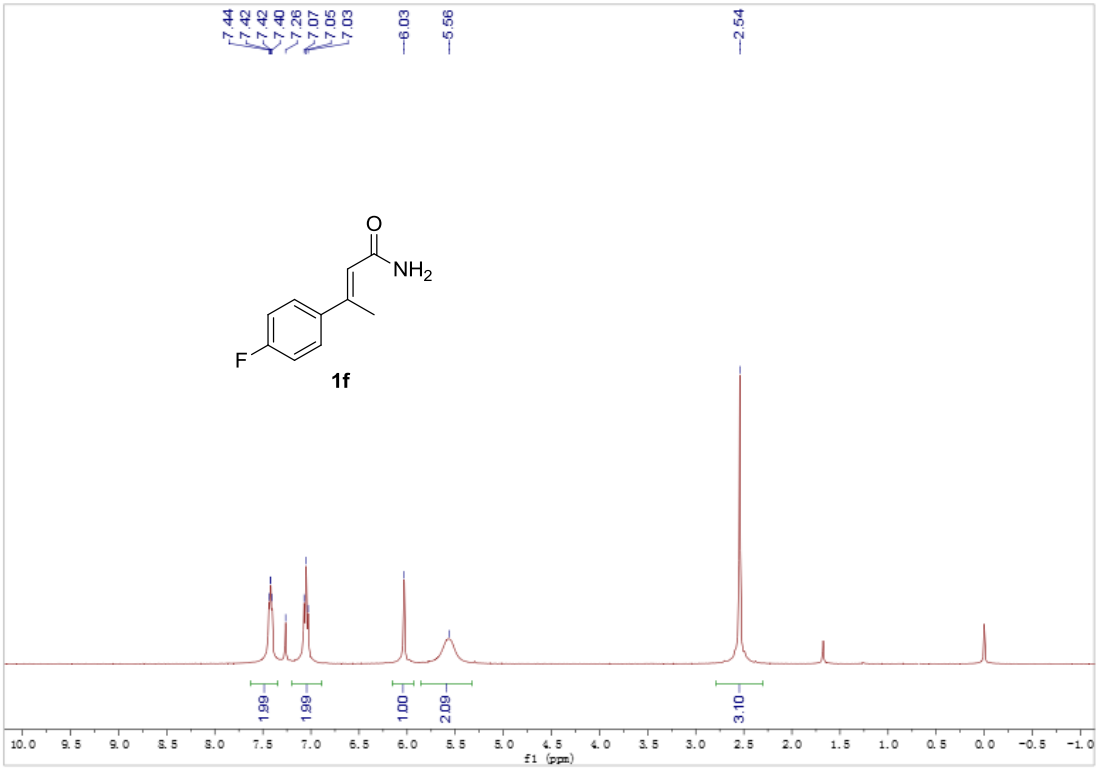
113.85
77.33
77.01
76.69
55.34
17.50
O
NH2
O
1e
f1 (ppm)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7.42
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7.40
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7.07
7.05
7.03
6.03
5.56
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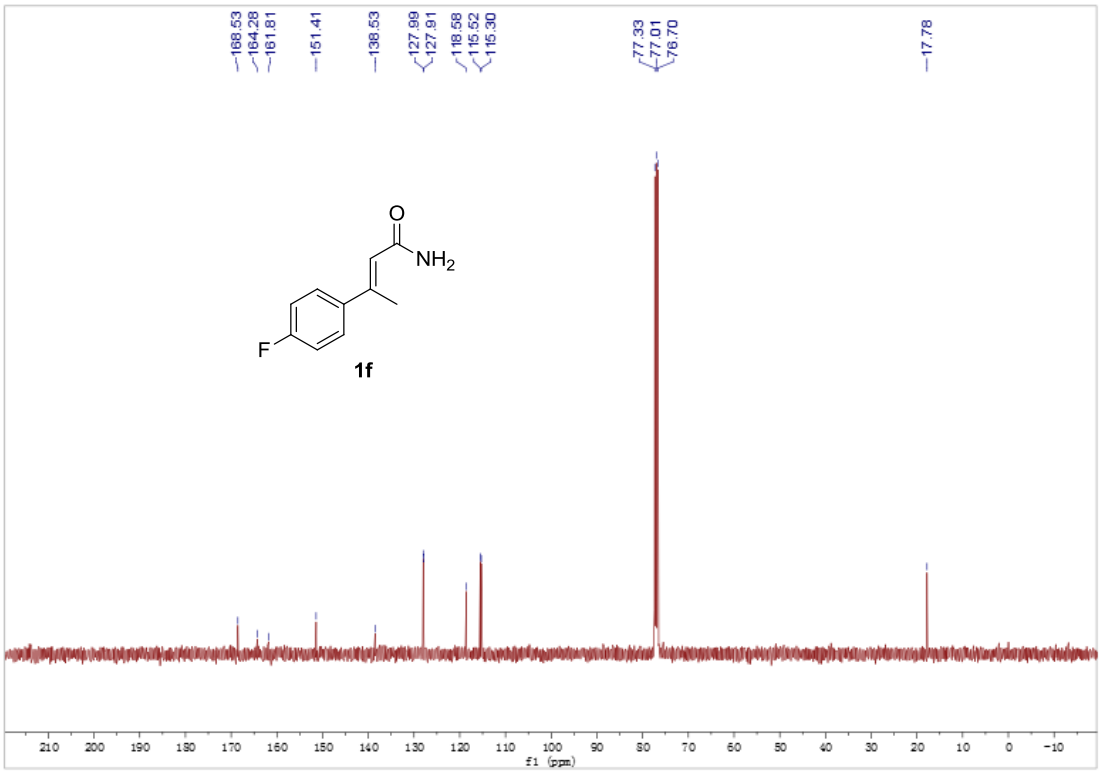
O
NH2
F
1f
1.99
1.99
1.00
2.09
3.10
f1 (ppm)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138.53
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77.01
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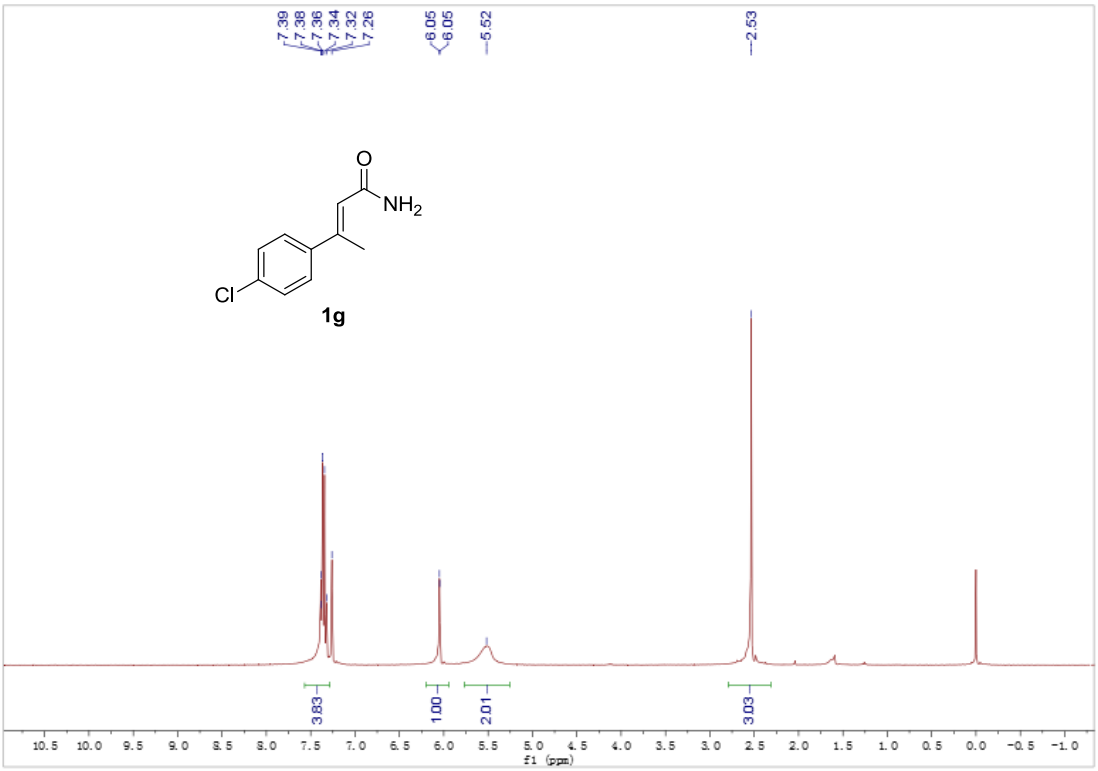
17.78
O
NH2
F
1f
f1 (ppm)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7.34
7.32
7.26
6.05
6.05
5.52
2.53
O
NH2
Cl
1g
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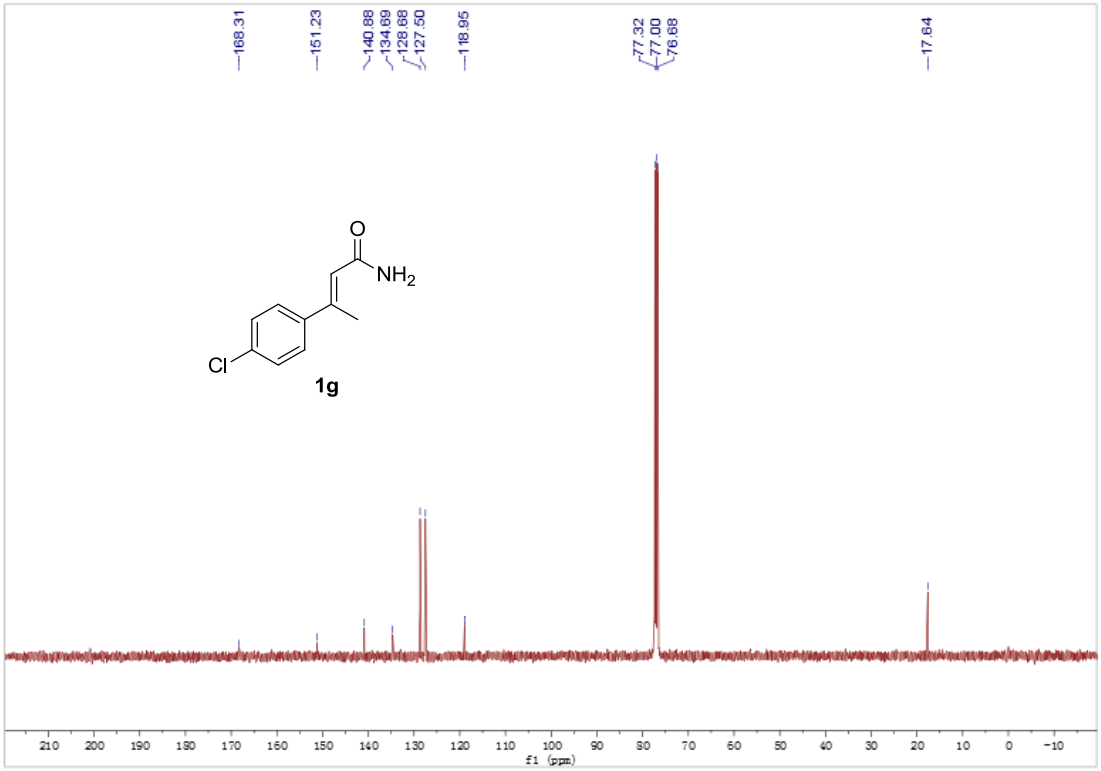
1.00
2.01
3.03
f1 (ppm)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76.68
17.64
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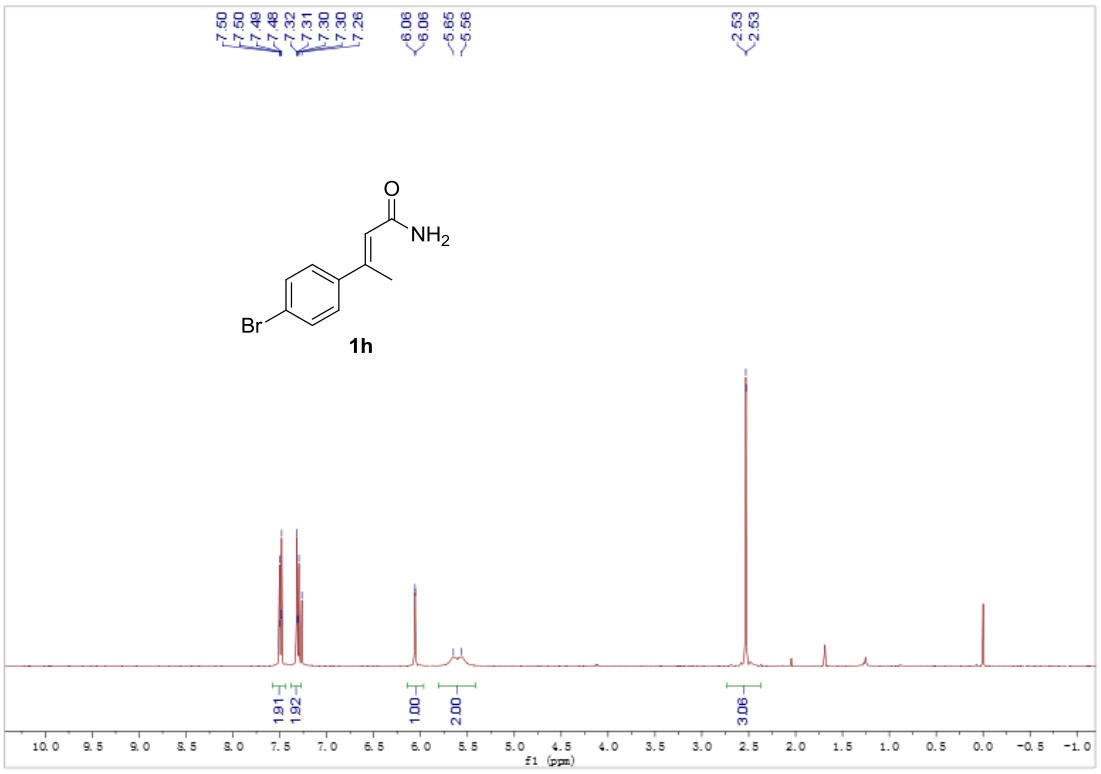
NH2
Cl
1g
f1 (ppm)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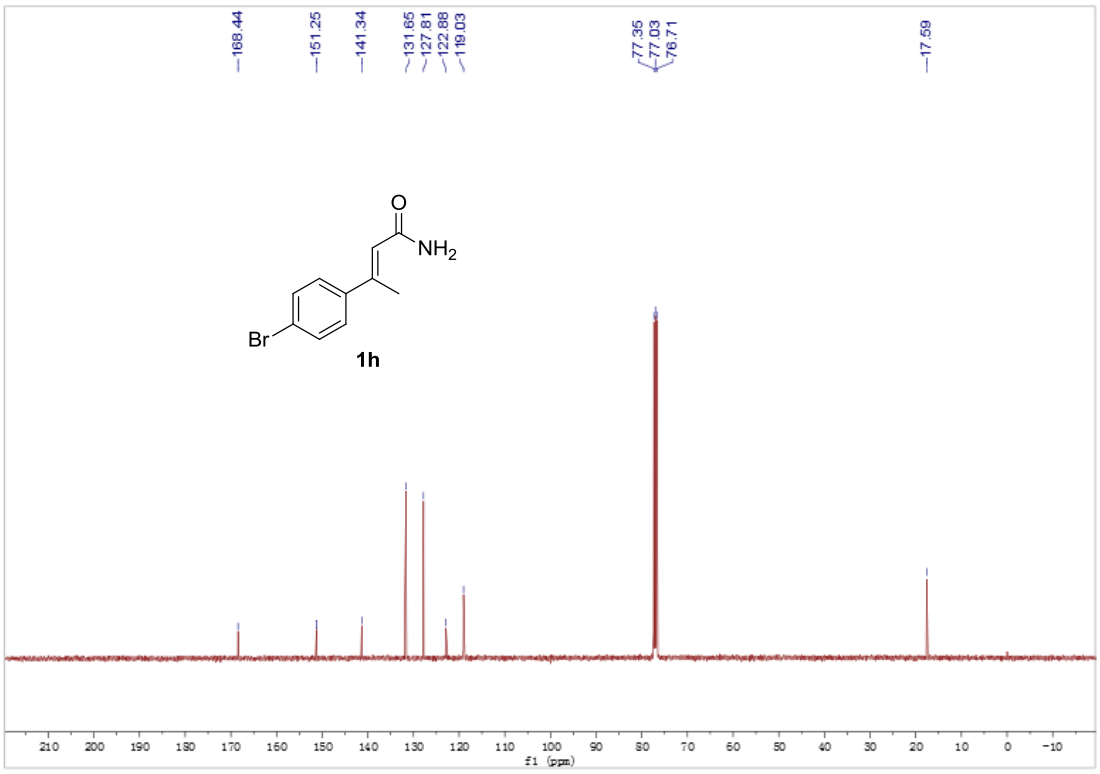
7.30
7.26
6.06
6.06
5.65
5.56
2.53
2.53
O
NH2
Br
1h
1.91
1.92
1.00
2.00
3.06
f1 (ppm)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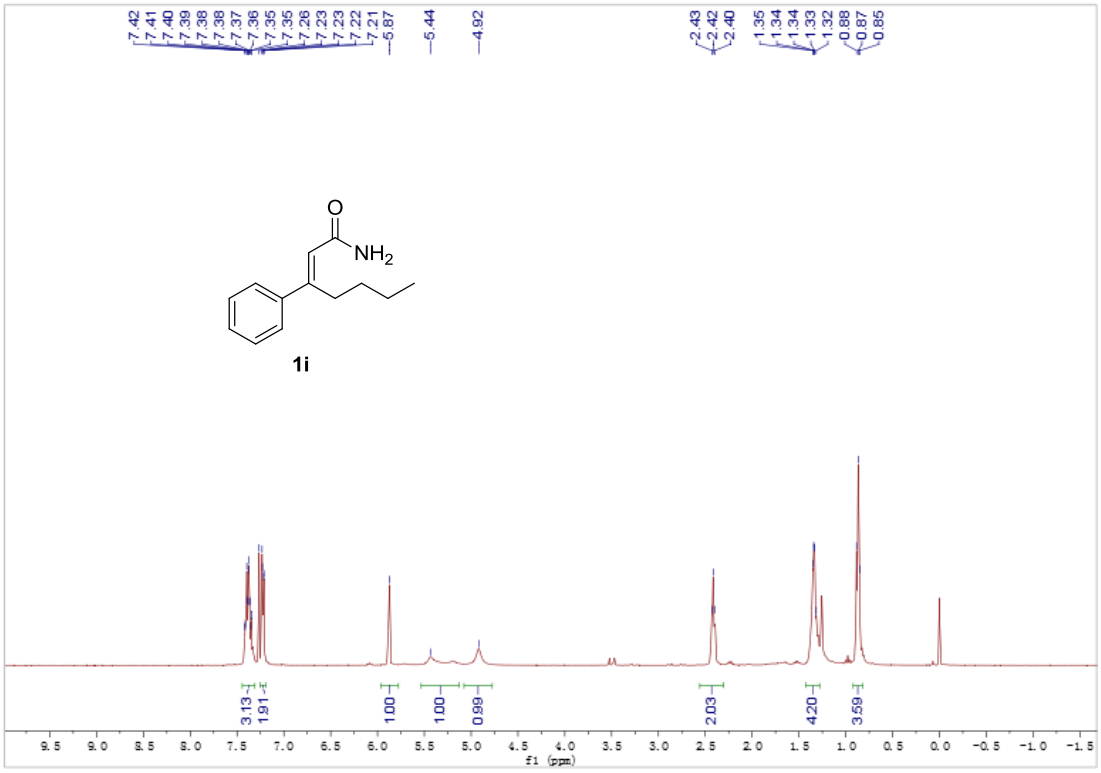
Br
1h
f1 (ppm)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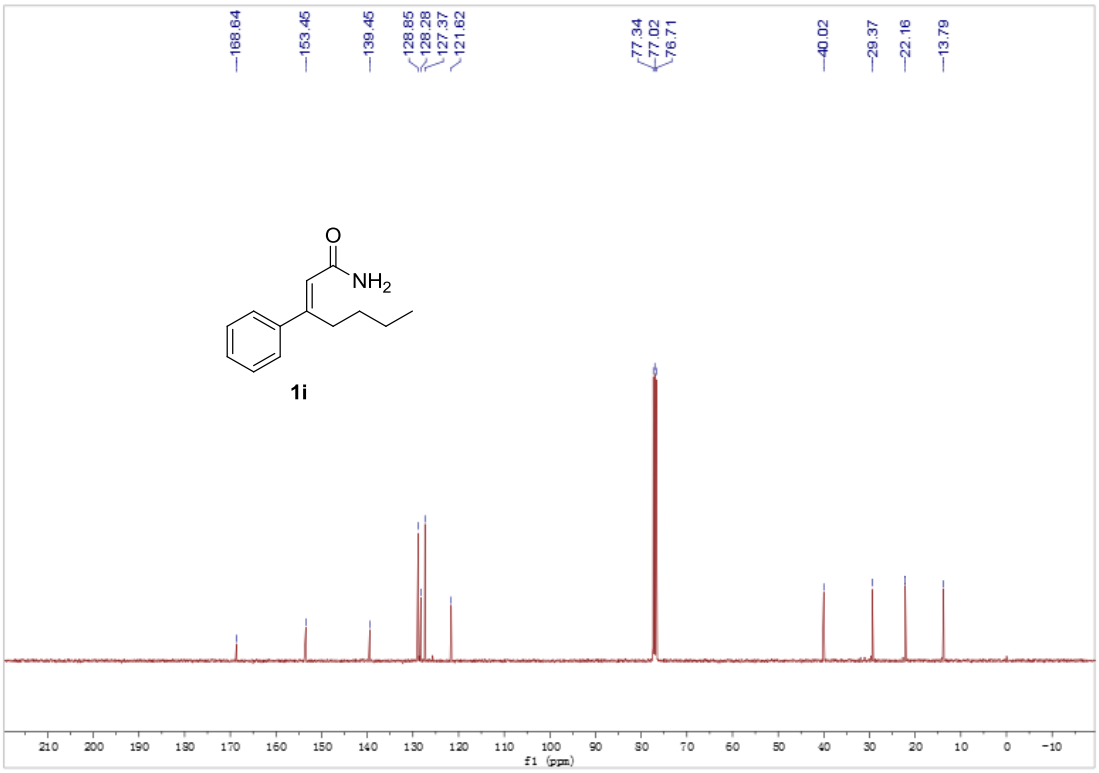
7.23
7.22
7.21
6.87
5.44
4.92
2.43
2.42
2.40
1.35
1.34
1.34
1.33
1.32
0.88
0.87
0.85
O
NH2
1i
3.13
1.91
1.00
1.00
0.99
2.03
4.20
3.59
f1 (ppm)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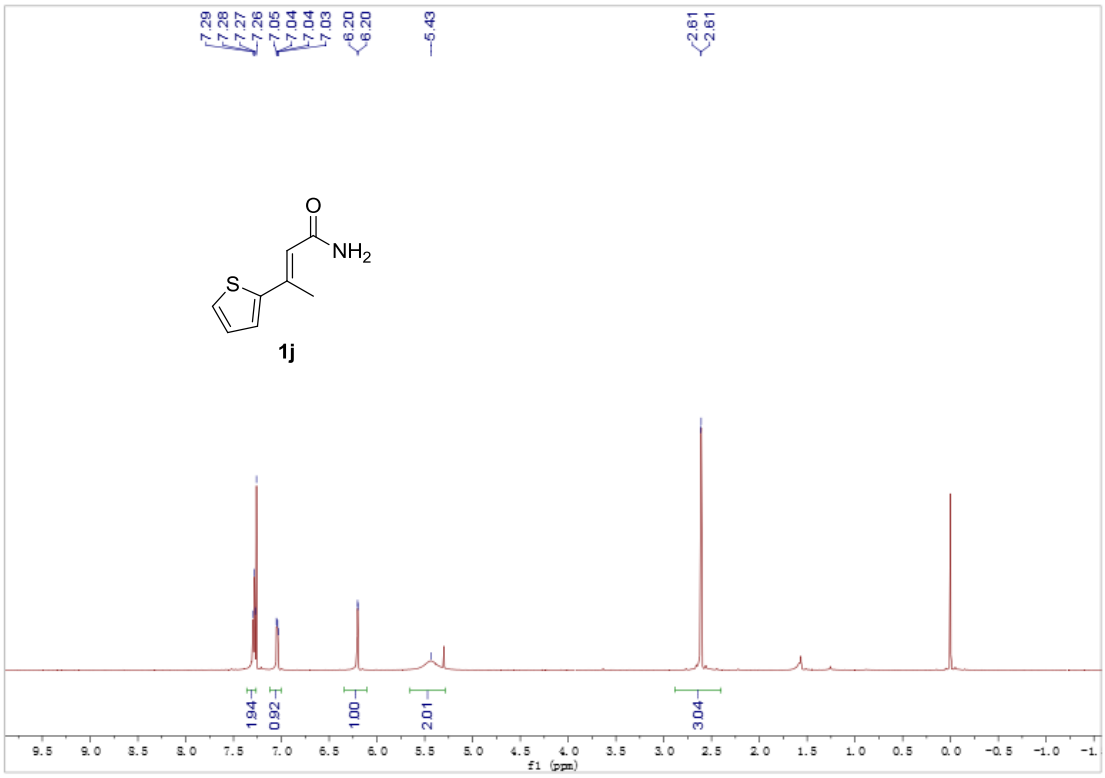
76.71
40.02
29.37
22.16
13.79
O
NH2
1i
f1 (ppm)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7.03
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6.20
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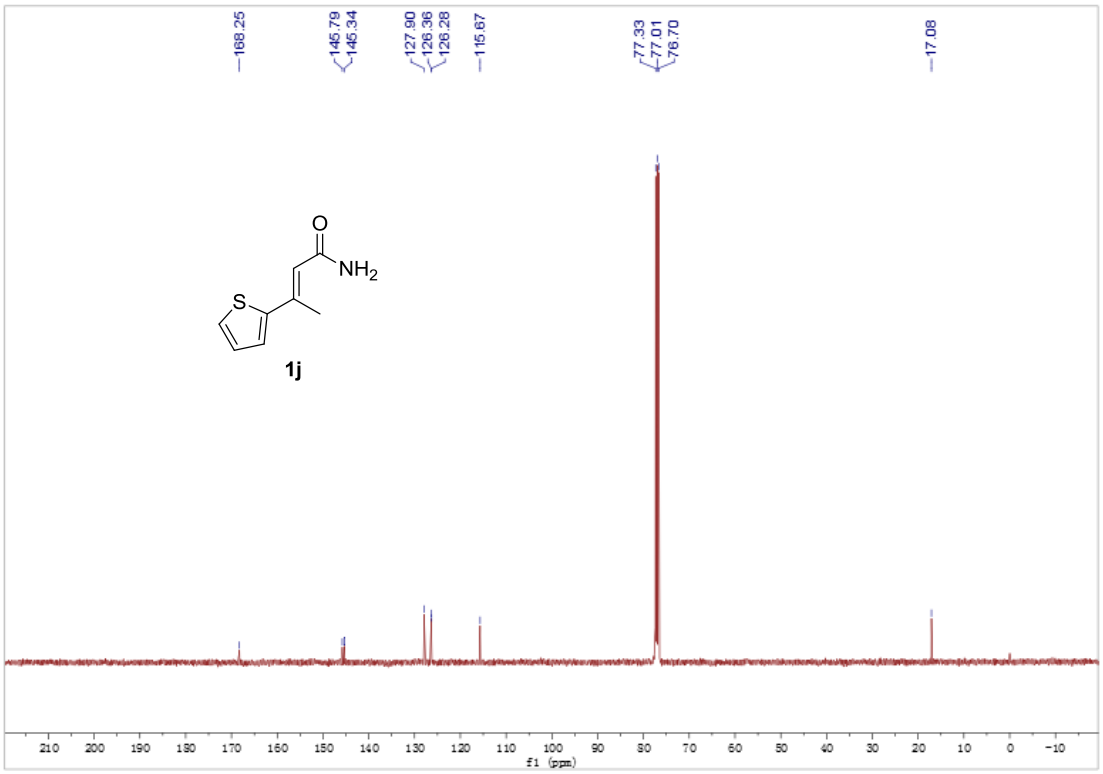
O
NH2
S
1j
1.94
0.92
1.00
2.01
3.04
f1 (ppm)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76.70
17.08
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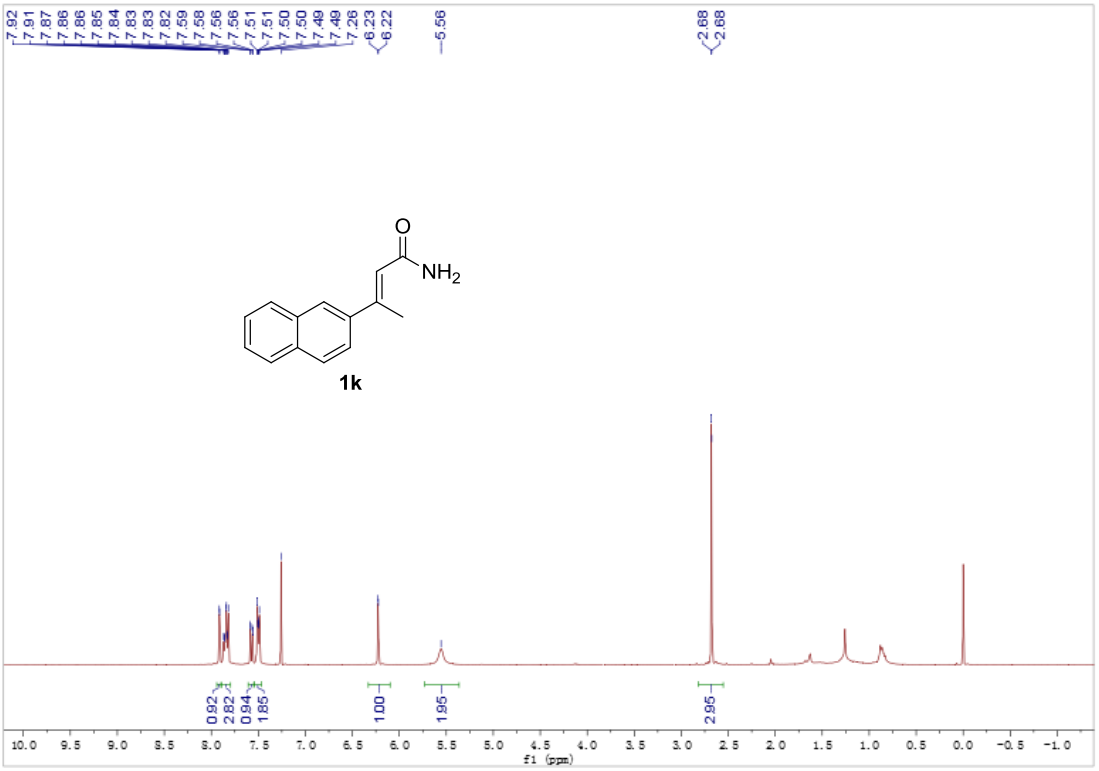
NH2
S
1j
f1 (ppm)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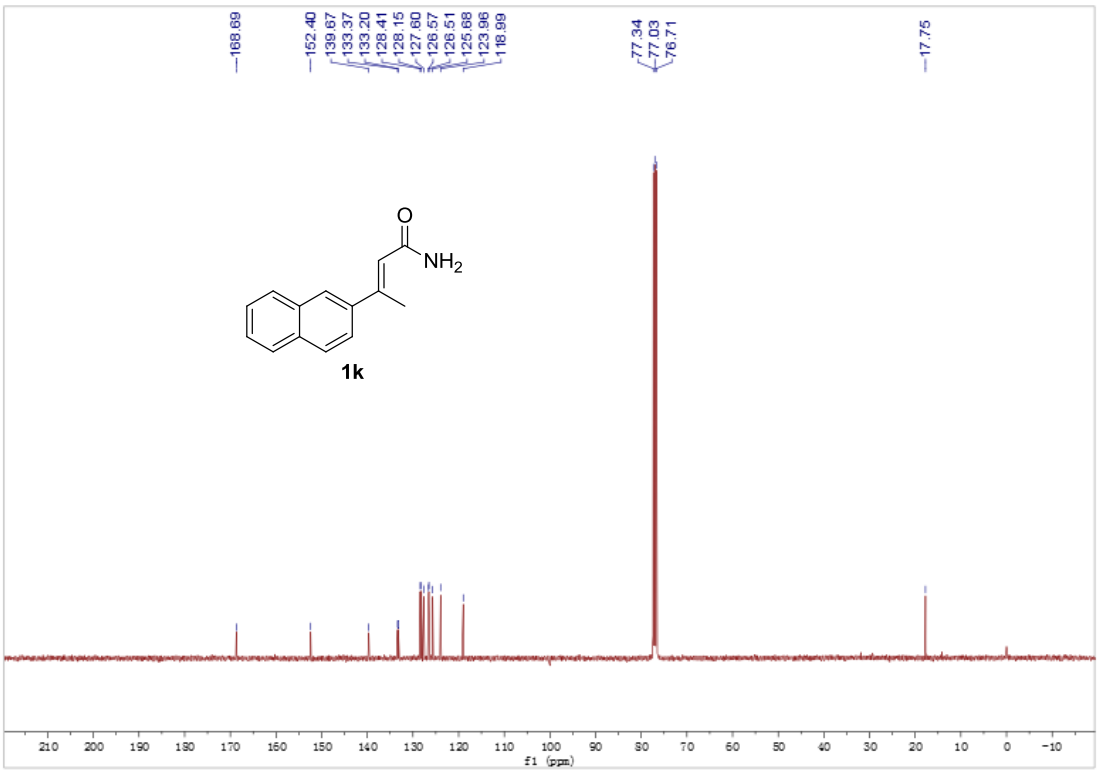
7.56
7.51
7.51
7.50
7.50
7.49
7.49
7.26
6.23
6.22
5.56
2.68
2.68
O
NH2
1k
0.92
2.82
0.94
1.85
1.00
1.95
2.95
f1 (ppm)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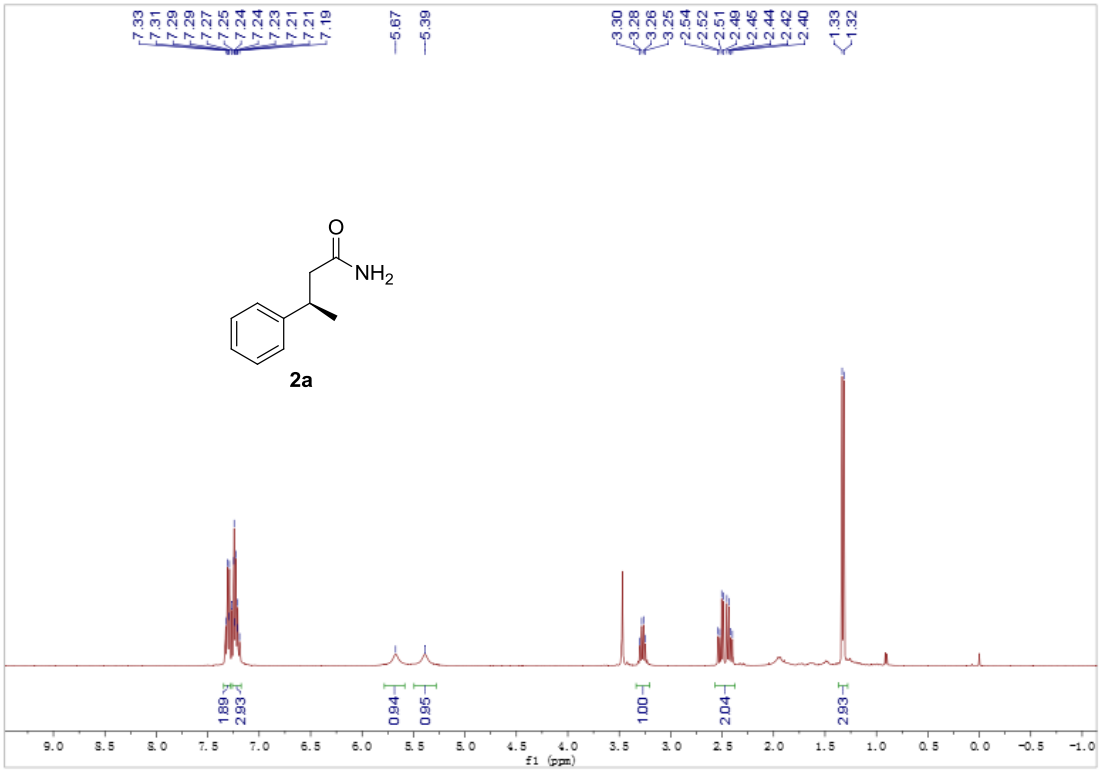
17.75
O
NH2
1k
f1 (ppm)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7.21
7.19
5.67
5.39
3.30
3.28
3.26
3.25
2.54
2.52
2.51
2.49
2.45
2.44
2.42
2.40
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NH2
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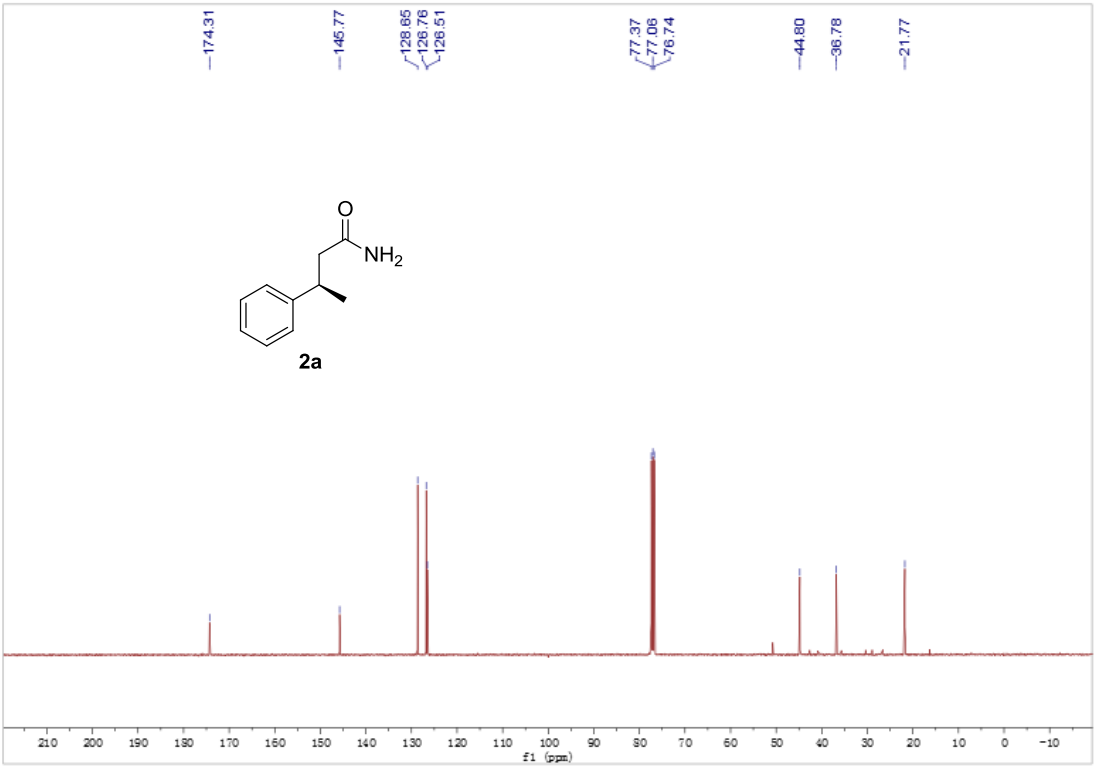
0.95
1.00
2.04
2.93
f1 (ppm)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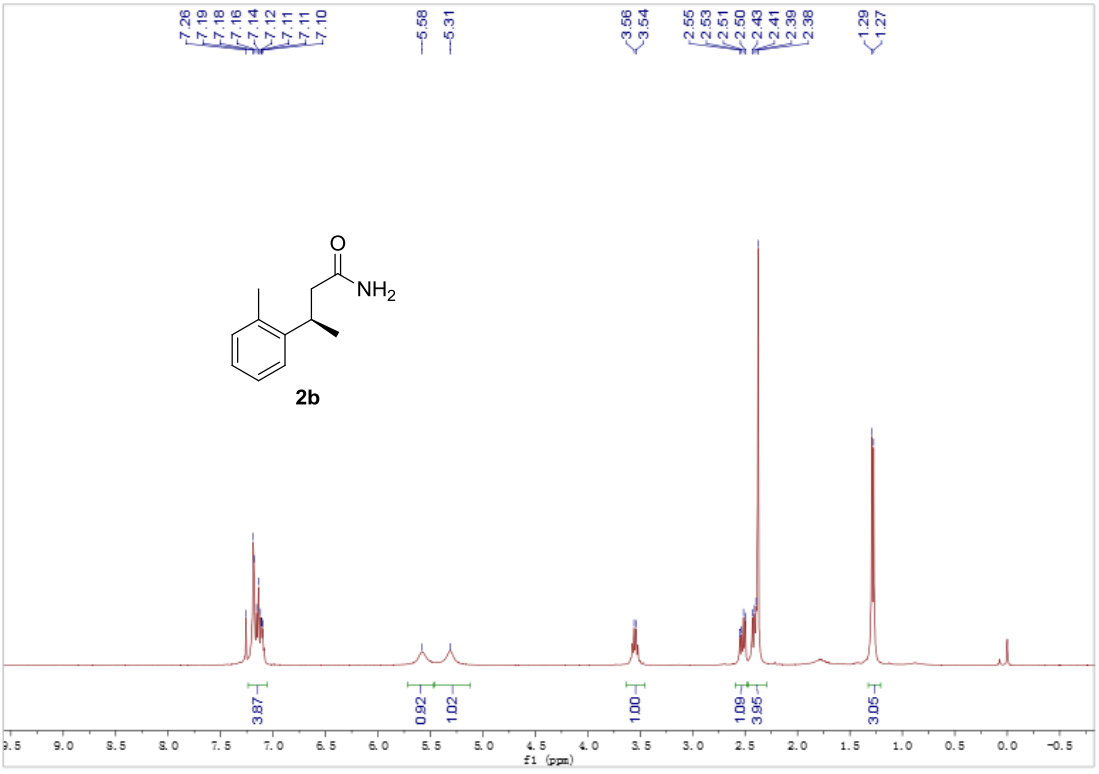
77.06
76.74
44.80
36.78
21.77
O
NH2
2a
f1 (ppm)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5.31
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2.55
2.53
2.51
2.50
2.43
2.41
2.39
2.38
1.29
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O
NH2
2b
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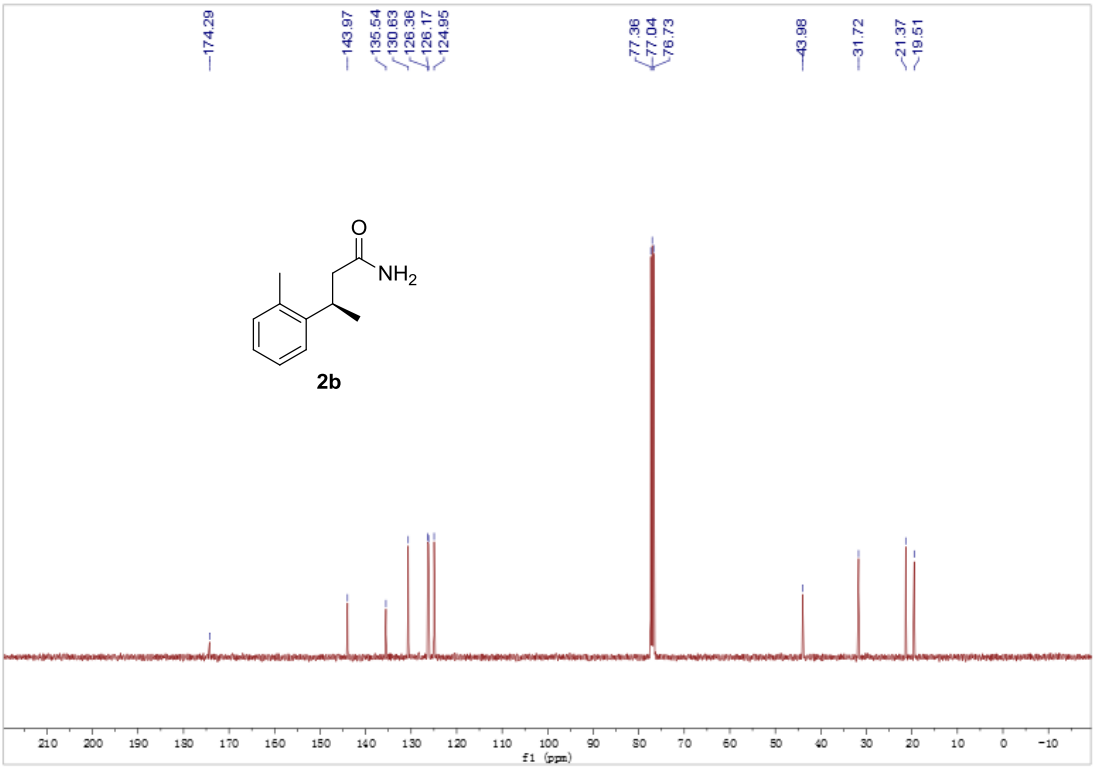
1.09
3.95
3.05
f1 (ppm)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126.36
126.17
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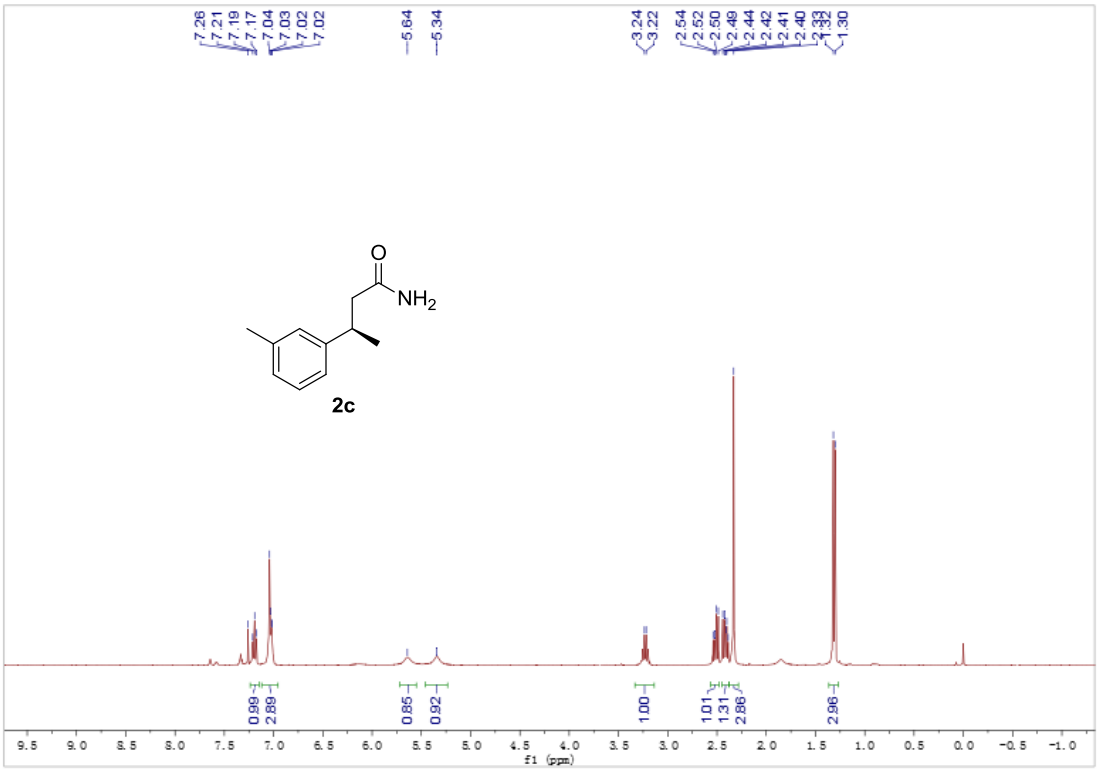
77.04
76.73
43.98
31.72
21.37
19.51
O
NH2
2b
f1 (ppm)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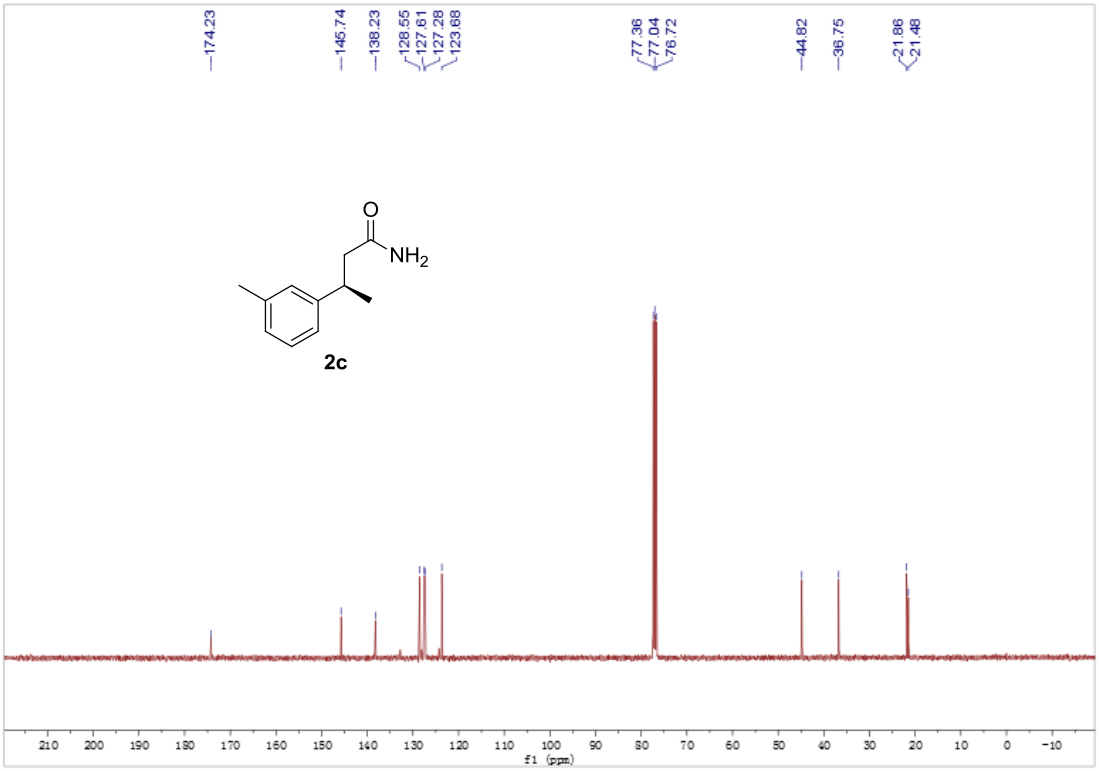
7.17
7.04
7.03
7.02
7.02
5.64
5.34
3.24
3.22
2.54
2.52
2.50
2.49
2.44
2.42
2.41
2.40
1.33
1.30
O
NH2
2c
0.99
2.89
0.85
0.92
1.00
1.01
1.31
2.86
2.96
f1 (ppm)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77.04
76.72
44.82
36.75
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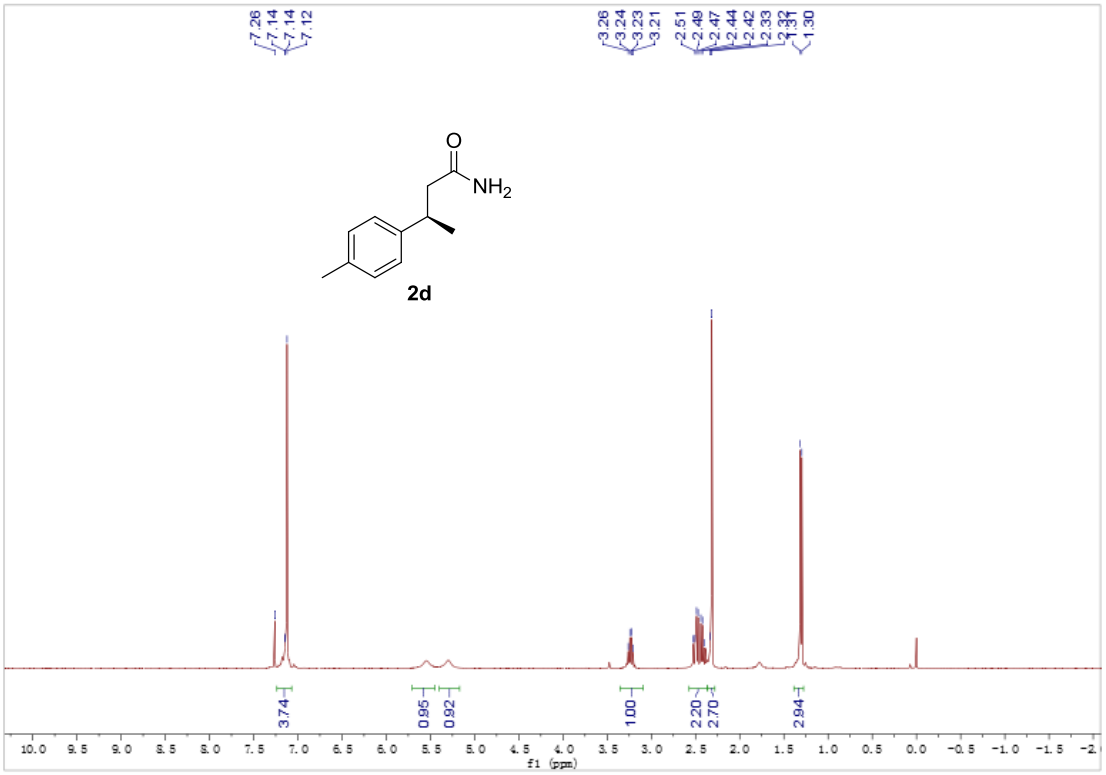
21.48
O
NH2
2c
f1 (ppm)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2.47
2.44
2.42
2.33
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2d
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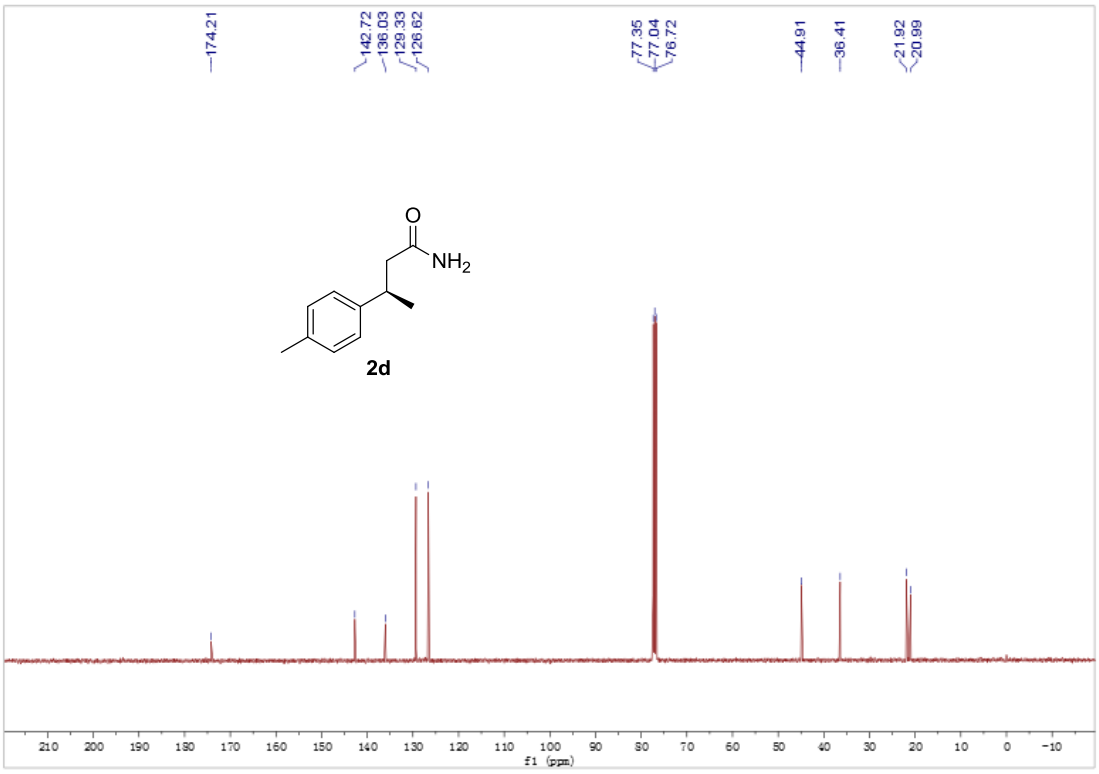
2.94
f1 (ppm)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76.72
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20.99
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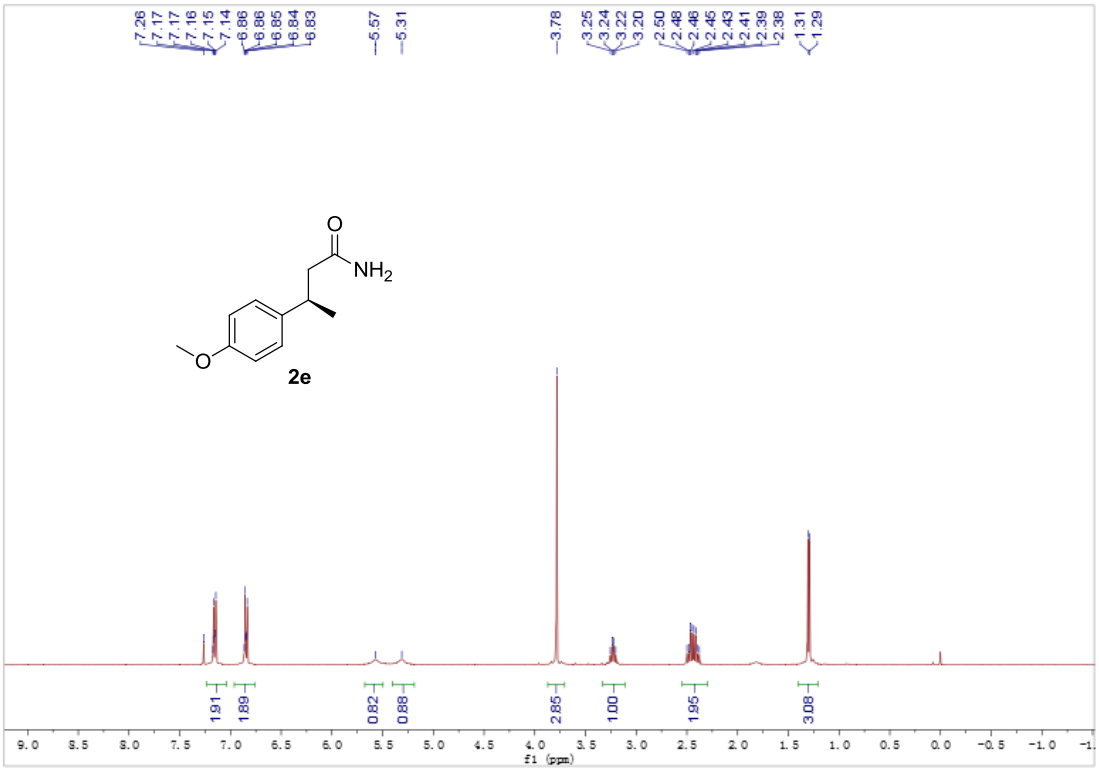
NH2
2d
f1 (ppm)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3.24
3.22
3.20
2.50
2.48
2.46
2.45
2.43
2.41
2.39
2.38
1.31
1.29
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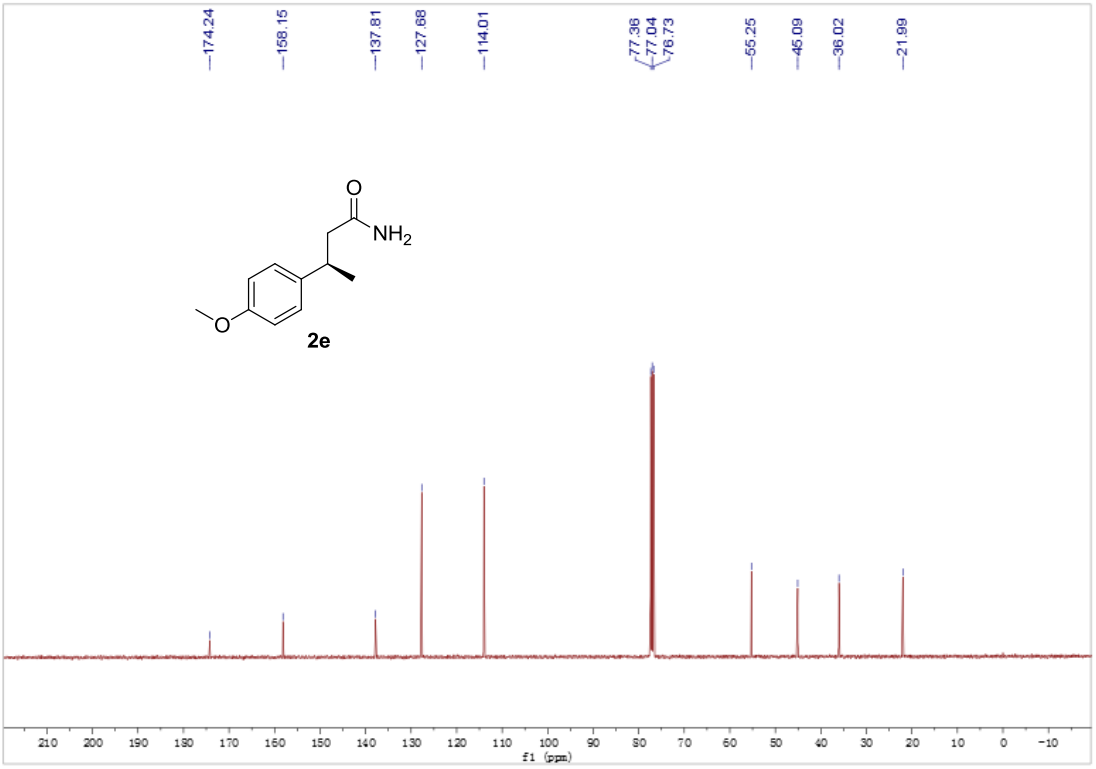
f1 (ppm)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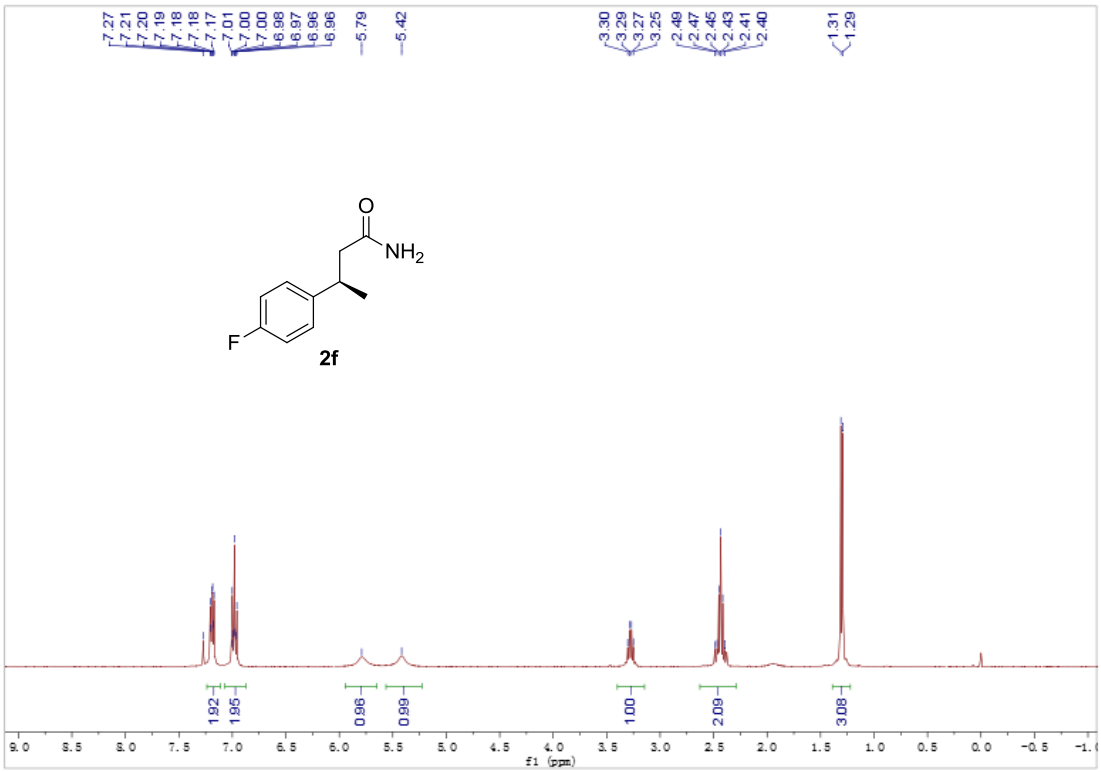
36.02
21.99
O
NH2
O
2e
f1 (ppm)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7.00
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6.96
6.96
5.79
5.42
3.30
3.29
3.27
3.25
2.49
2.47
2.45
2.43
2.41
2.40
1.31
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O
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F
2f
1.92
1.95
0.96
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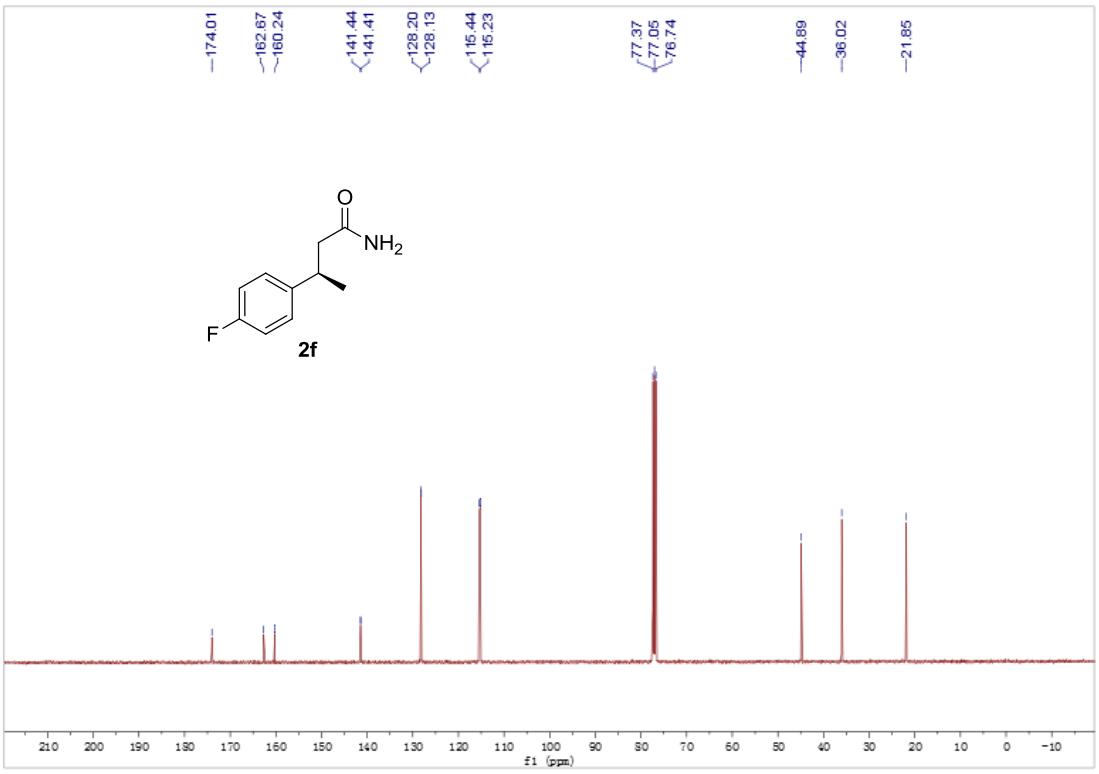
1.00
2.09
3.08
f1 (ppm)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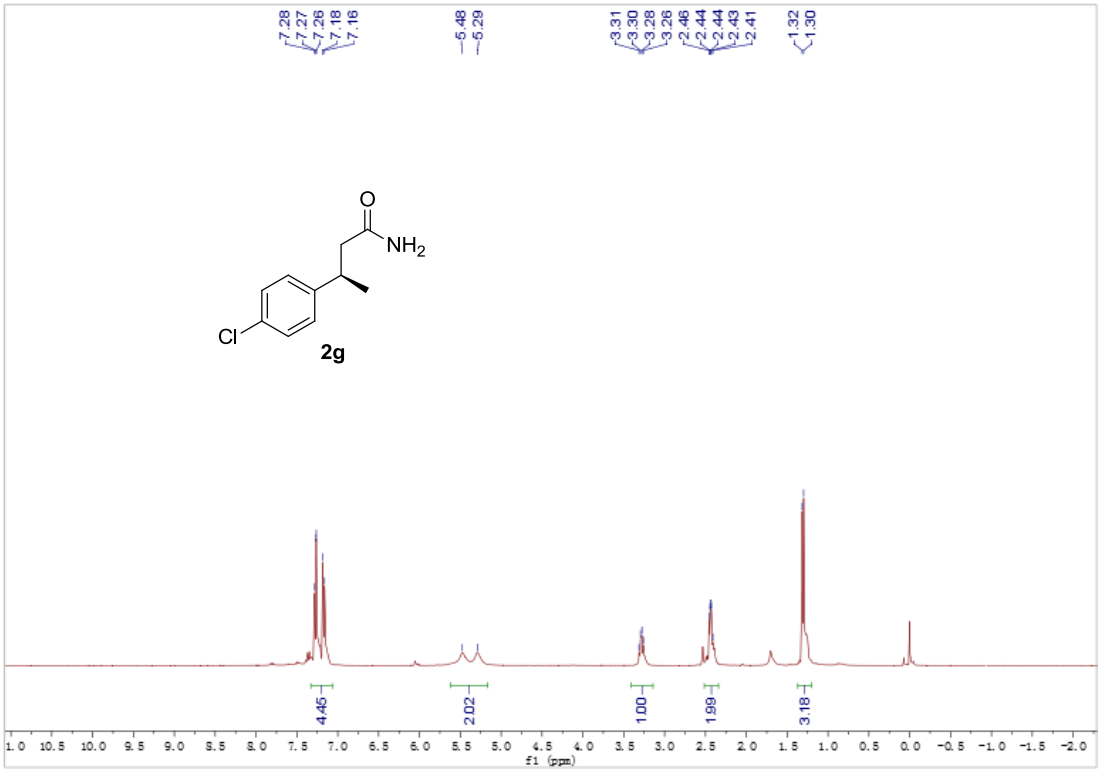
O
NH2
F
2f
f1 (ppm)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2.44
2.44
2.43
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Cl
2g
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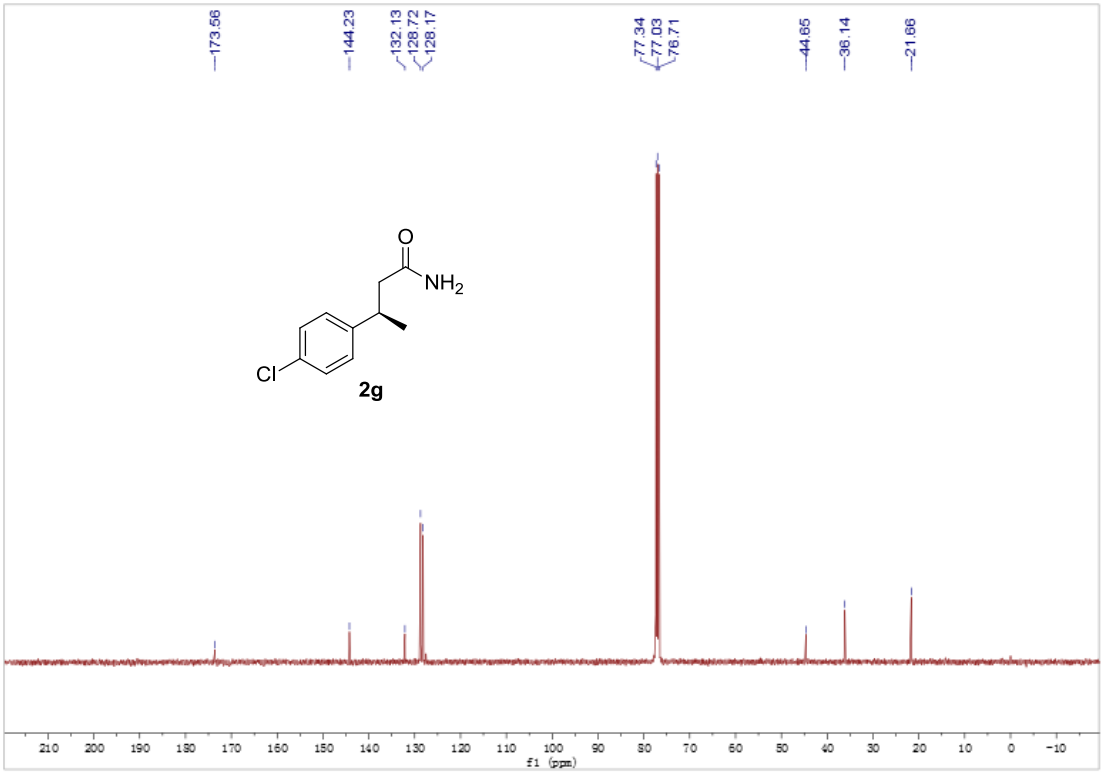
1.00
1.99
3.18
f1 (ppm)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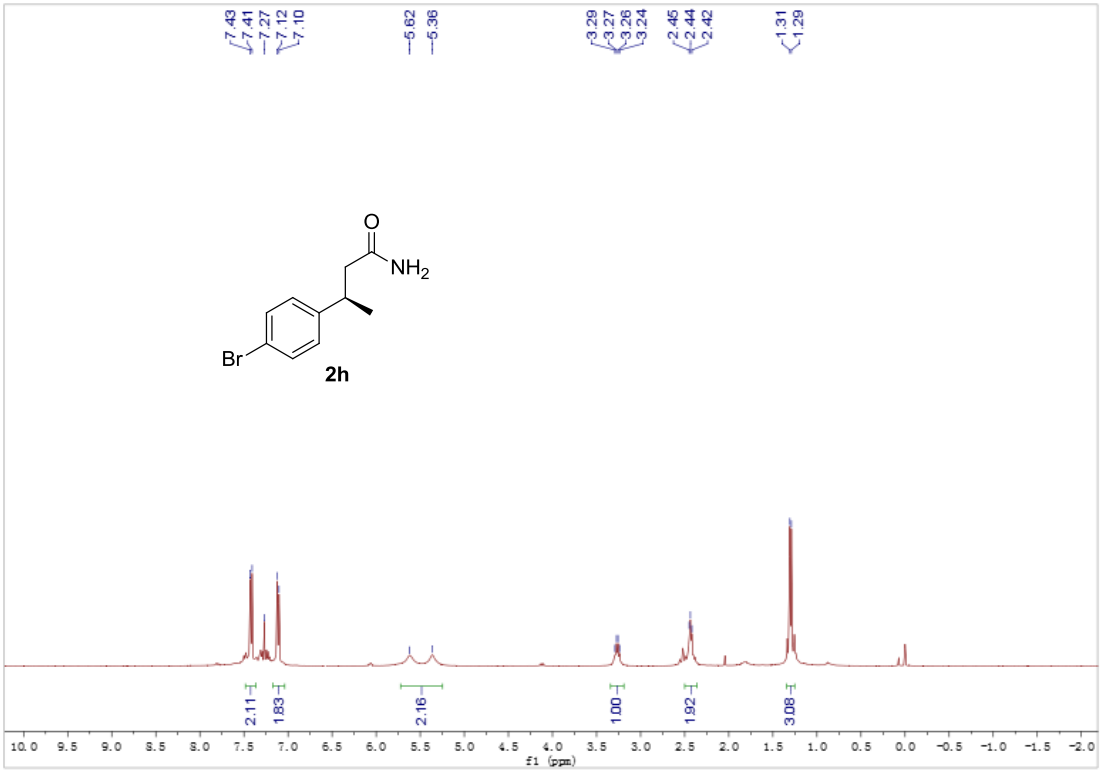
Cl
2g
f1 (ppm)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3.24
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2.44
2.42
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1.29
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Br
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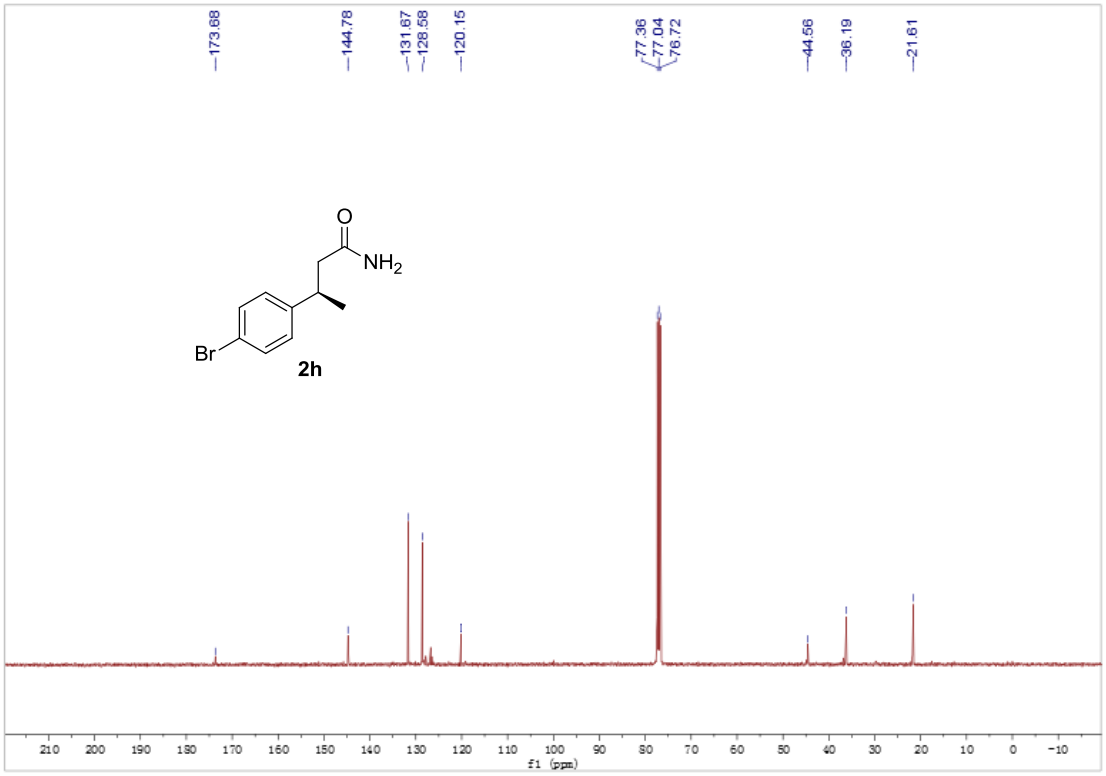
1.83
2.16
1.00
1.92
3.08
f1 (ppm)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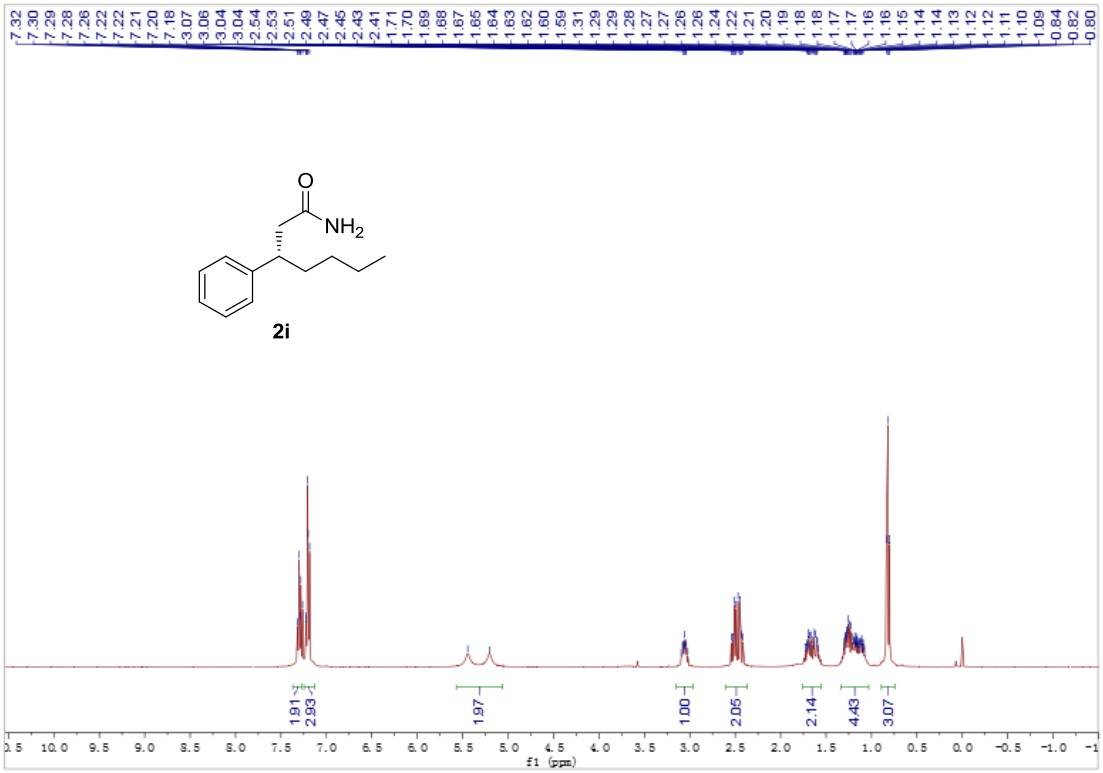
Br
2h
f1 (ppm)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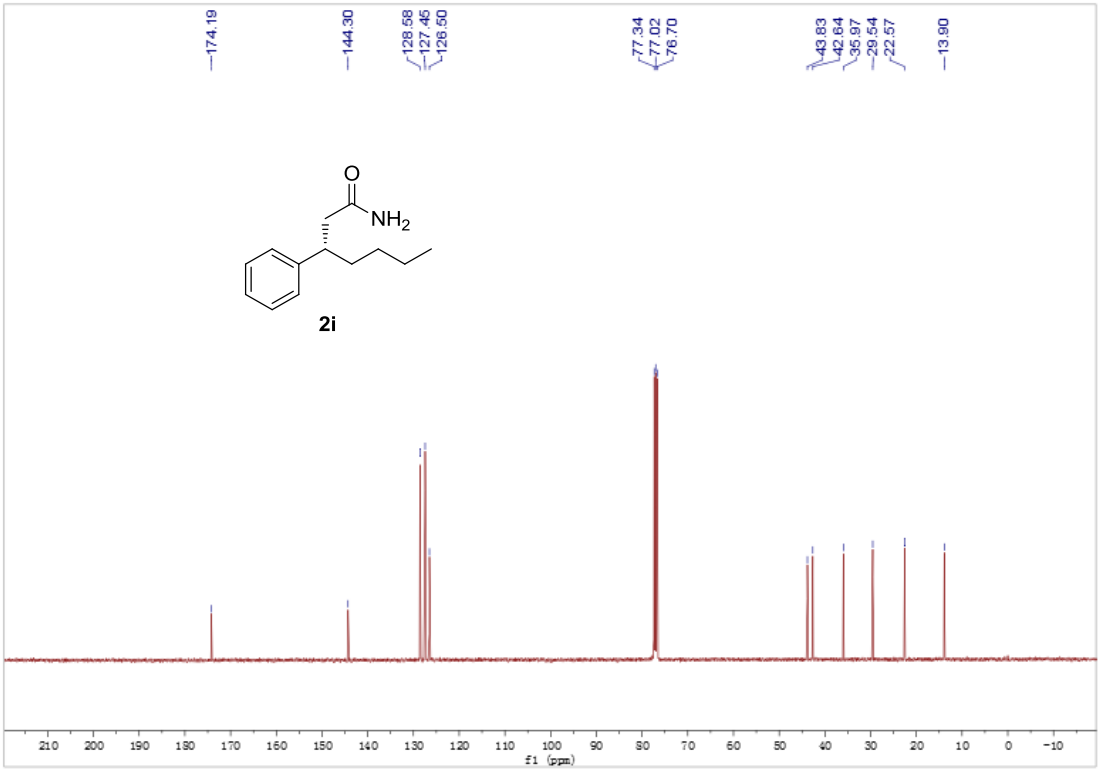
3.07
f1 (ppm)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13.90
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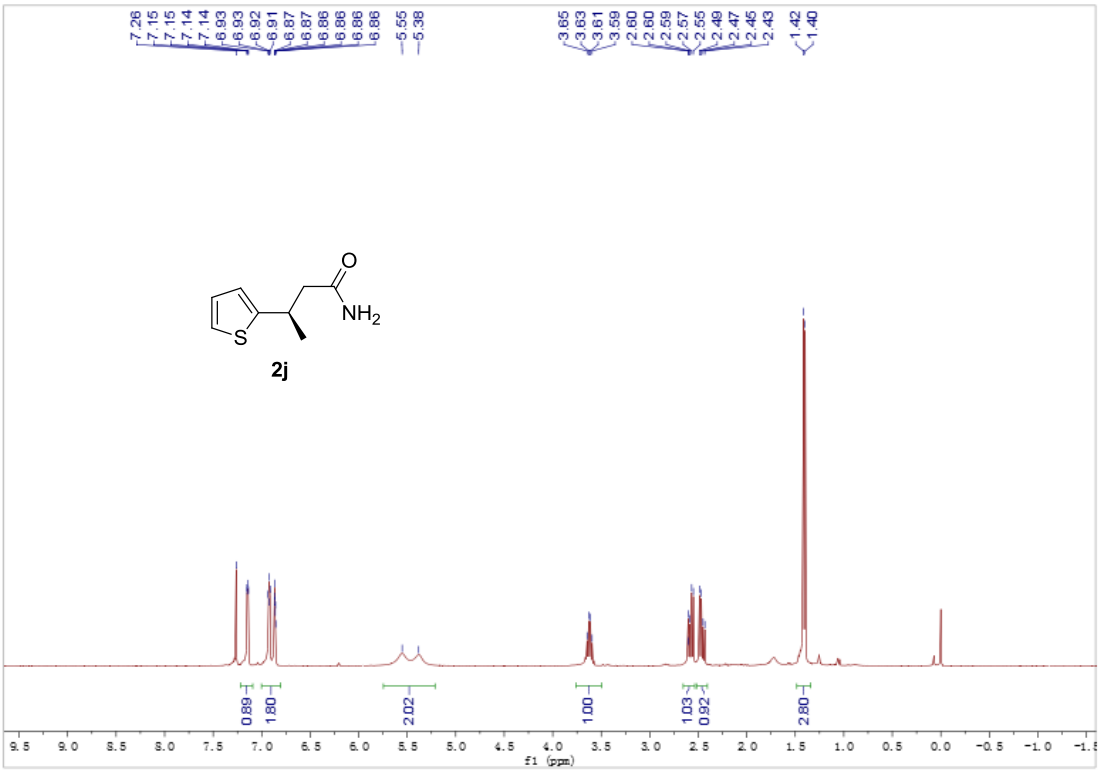
2i
f1 (ppm)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2.59
2.57
2.55
2.49
2.47
2.45
2.43
1.42
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S
2j
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2.02
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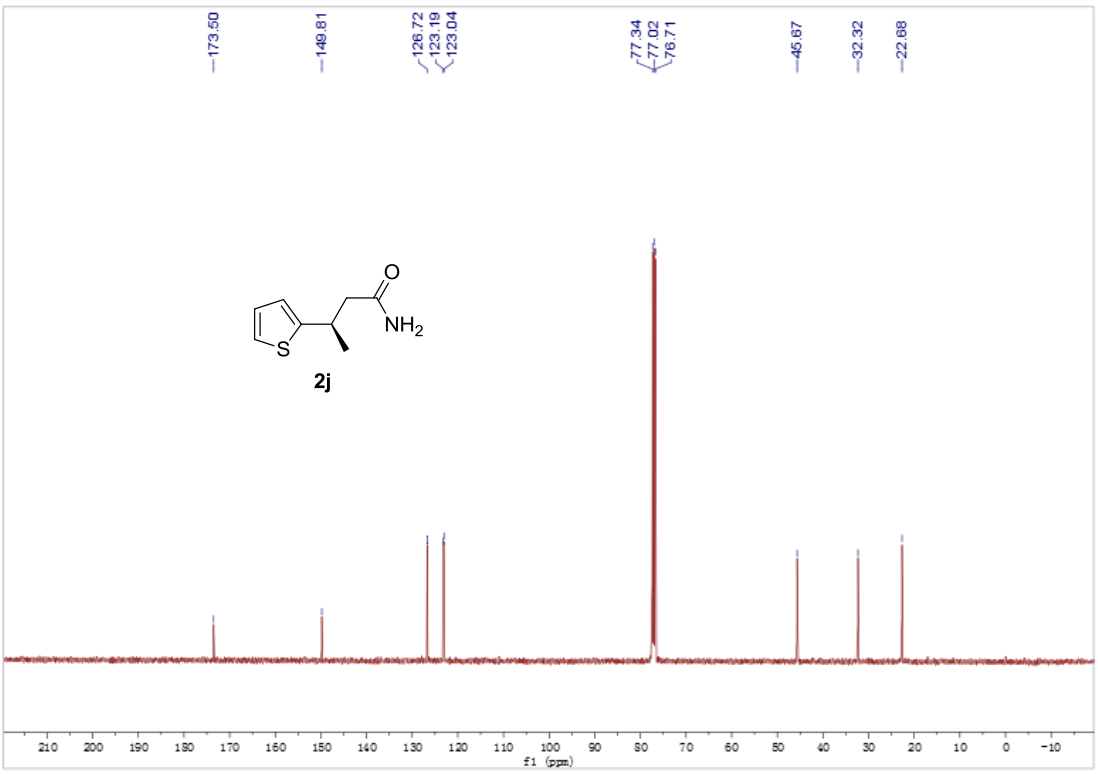
1.03
0.92
2.80
f1 (ppm)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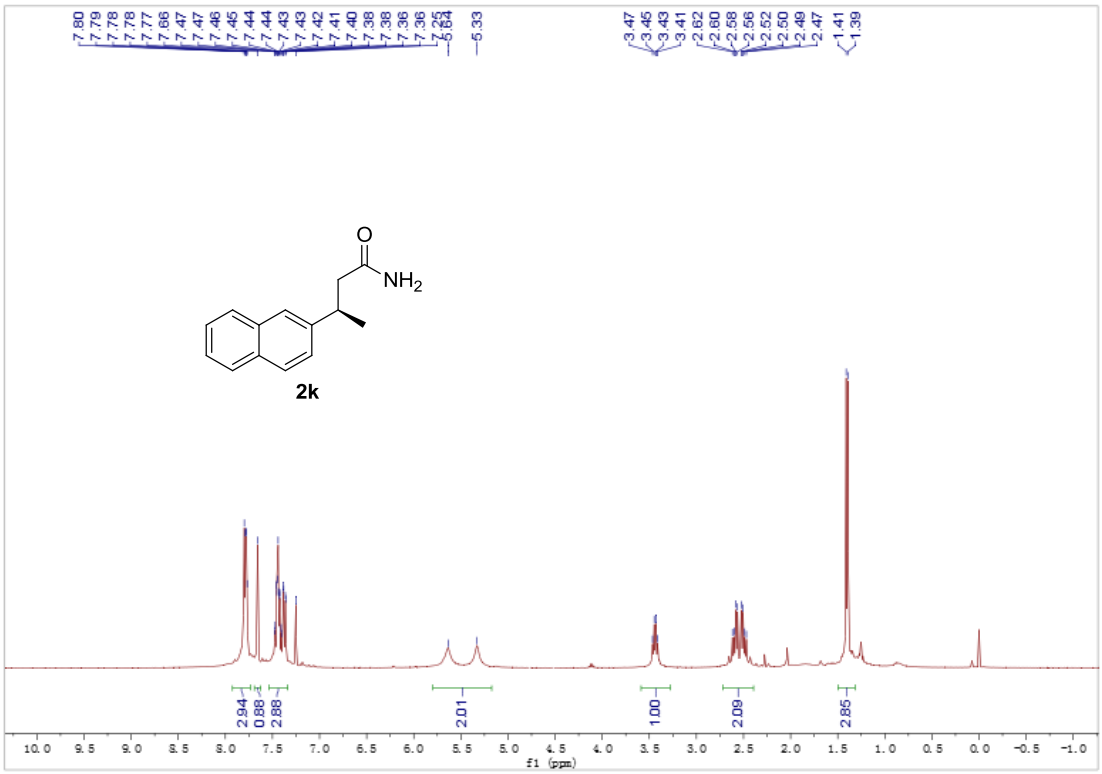
S
f1 (ppm)

2j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5.84
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2.62
2.60
2.58
2.56
2.52
2.50
2.49
2.47
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2.88
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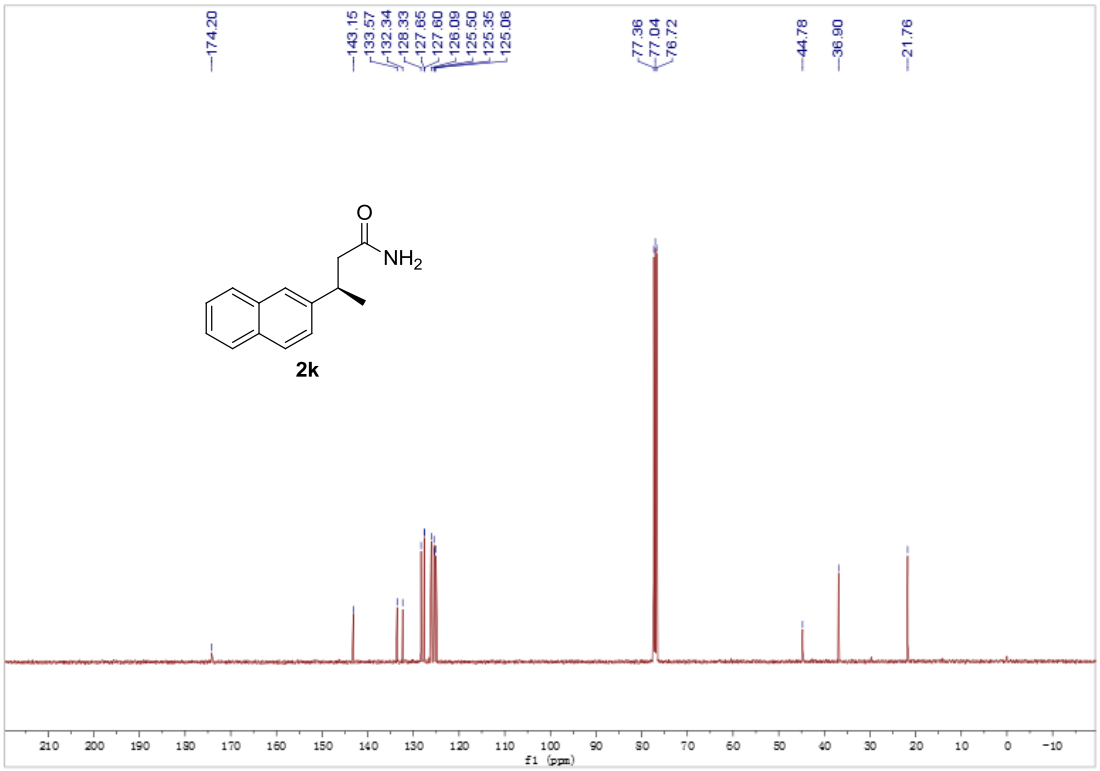
2.85
f1 (ppm)

2k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77.04
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21.76
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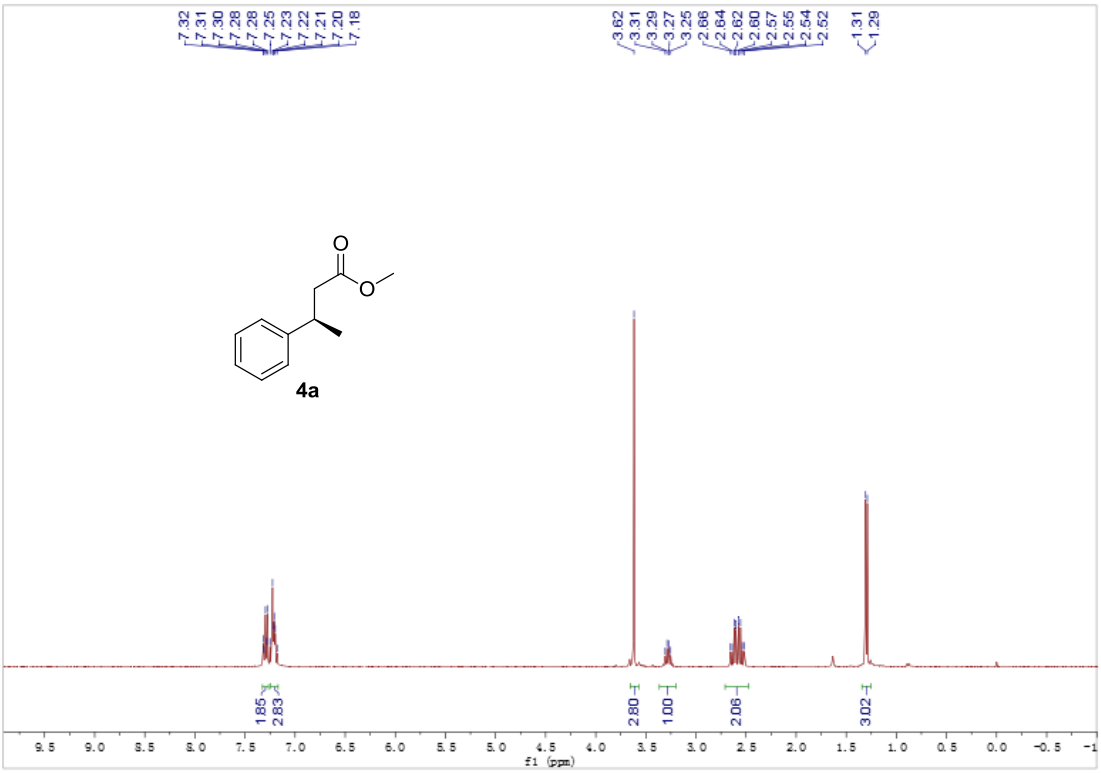
2k
f1 (ppm)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3.29
3.27
3.25
2.66
2.64
2.62
2.60
2.57
2.55
2.54
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O
O
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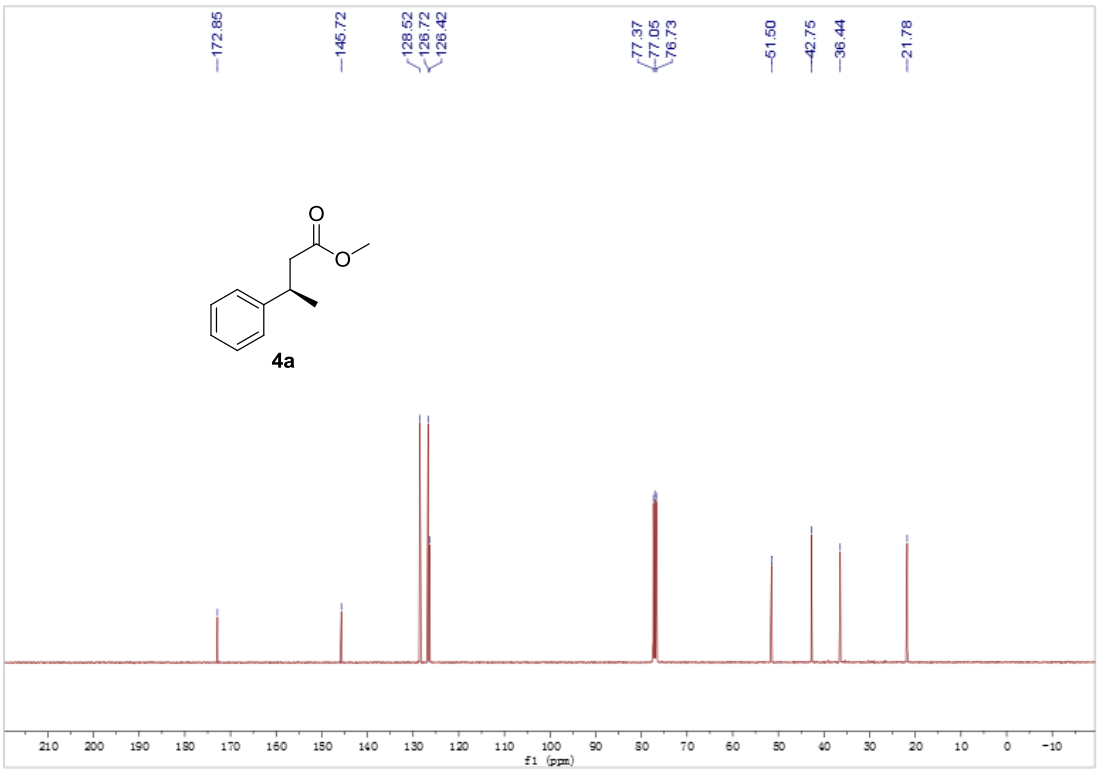
2.83
2.80
1.00
2.06
3.02
f1 (ppm)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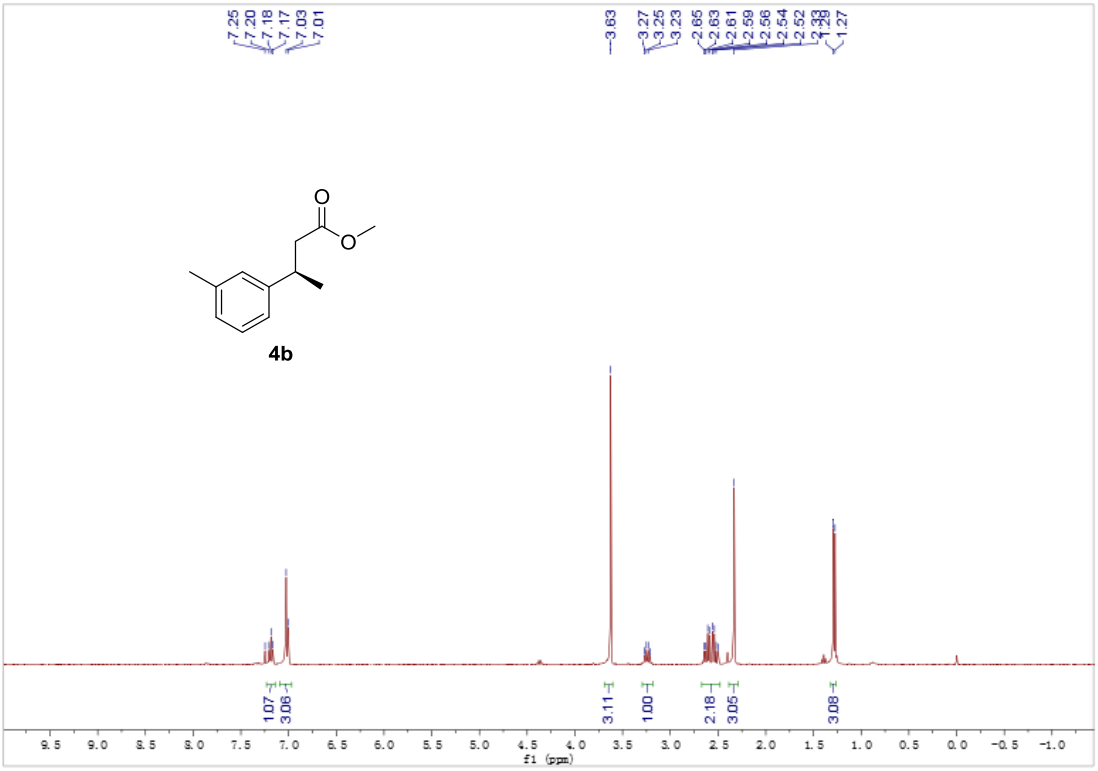
42.75
36.44
21.78
O
O
4a
f1 (ppm)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2.61
2.59
2.56
2.54
2.52
2.33
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O
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3.06
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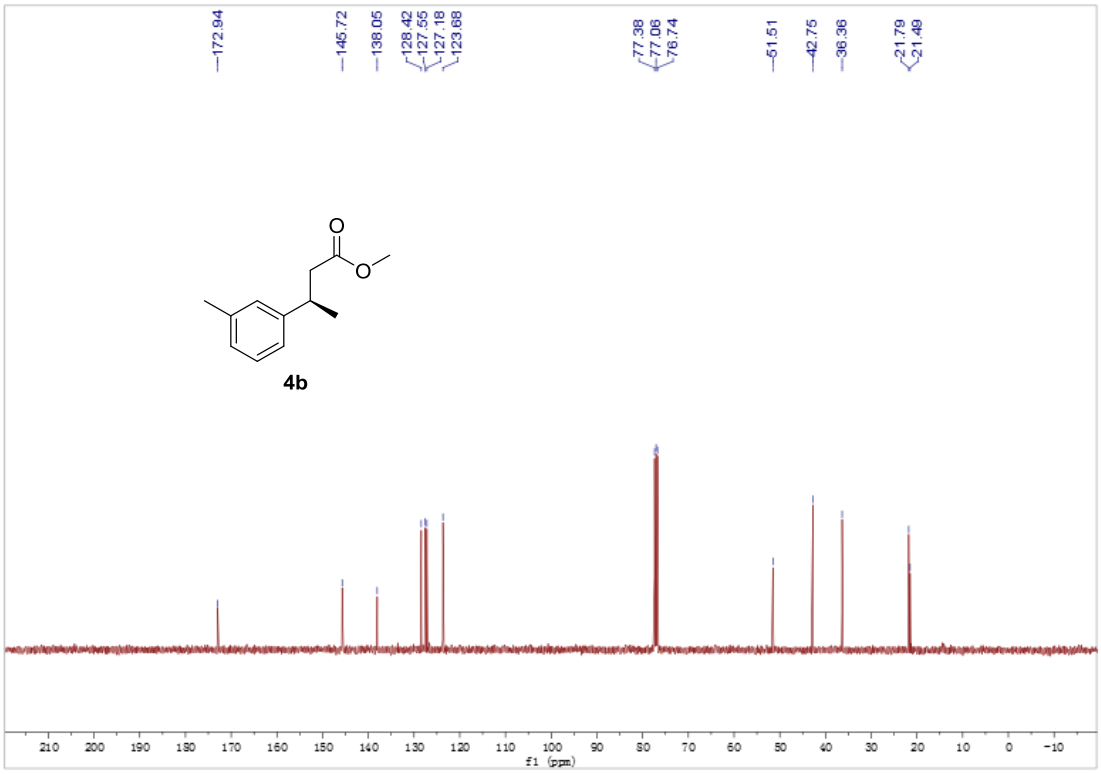
3.05
3.08
f1 (ppm)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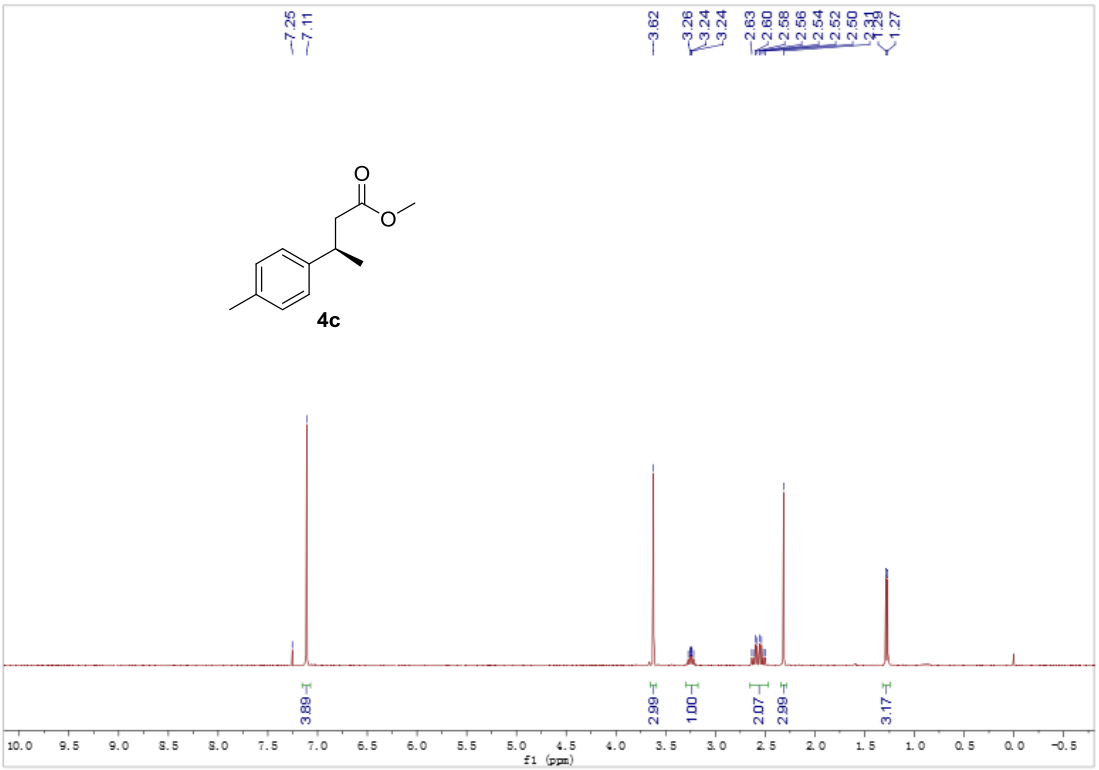
36.36
21.79
21.49
4b
f1 (ppm)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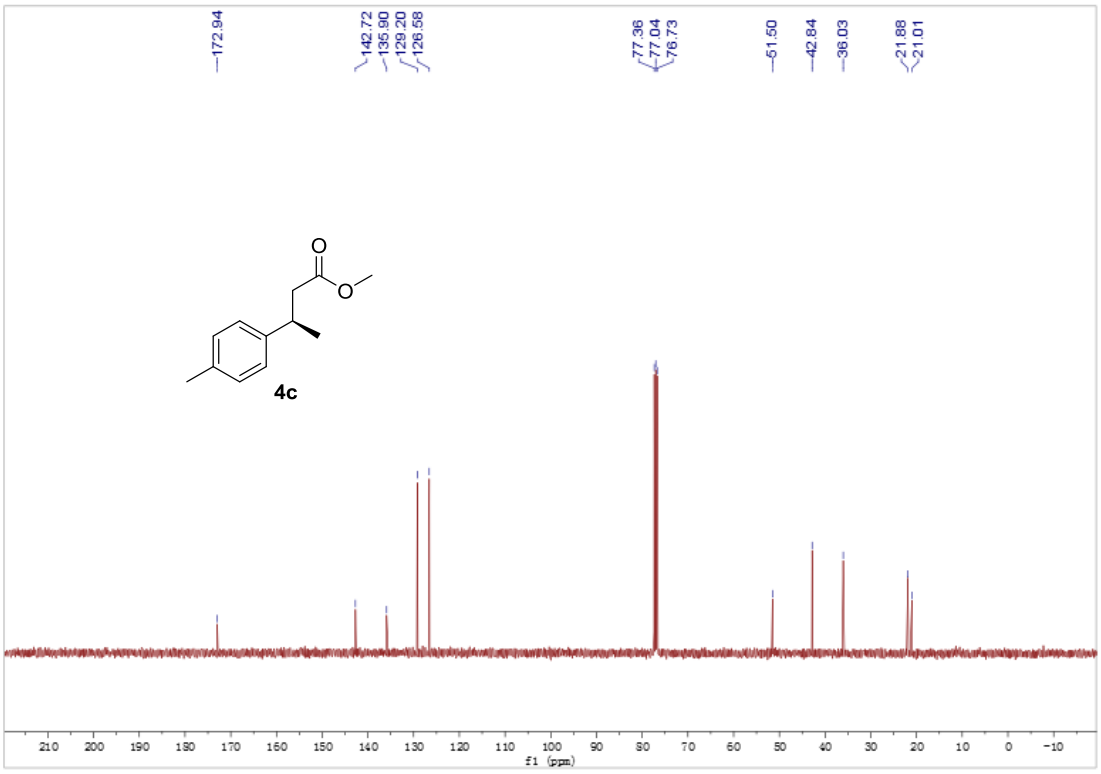
f1 (ppm)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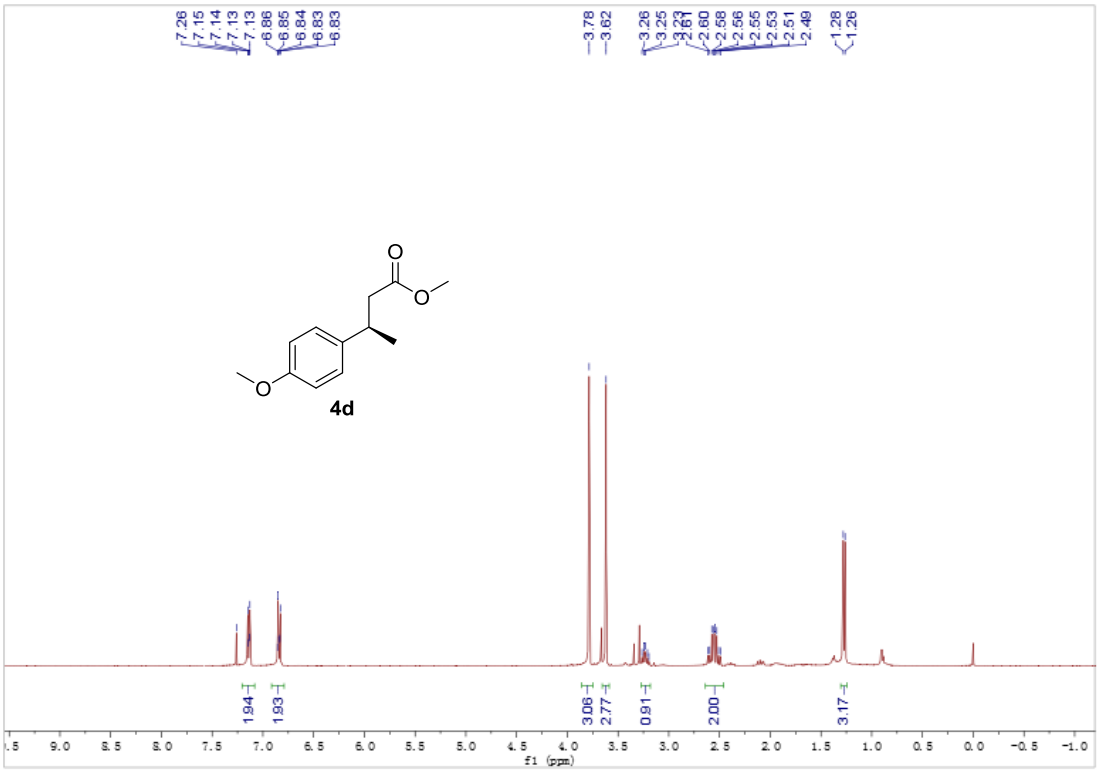
O
4c
f1 (ppm)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2.53
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2.49
1.28
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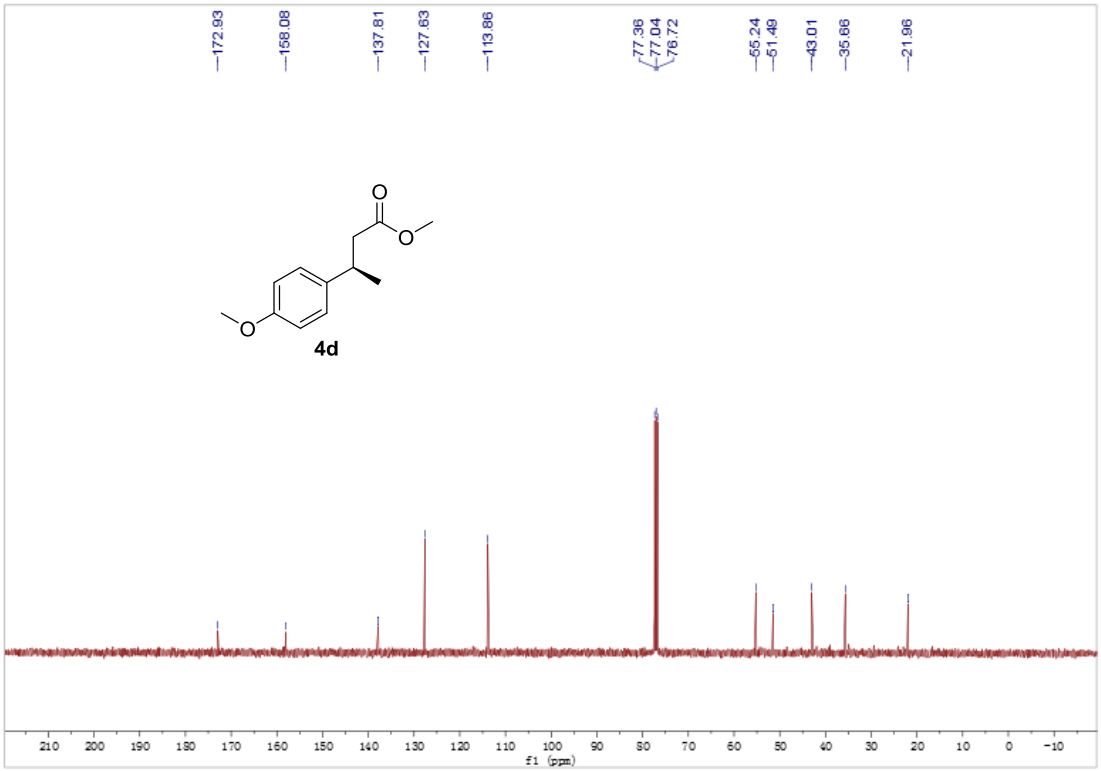
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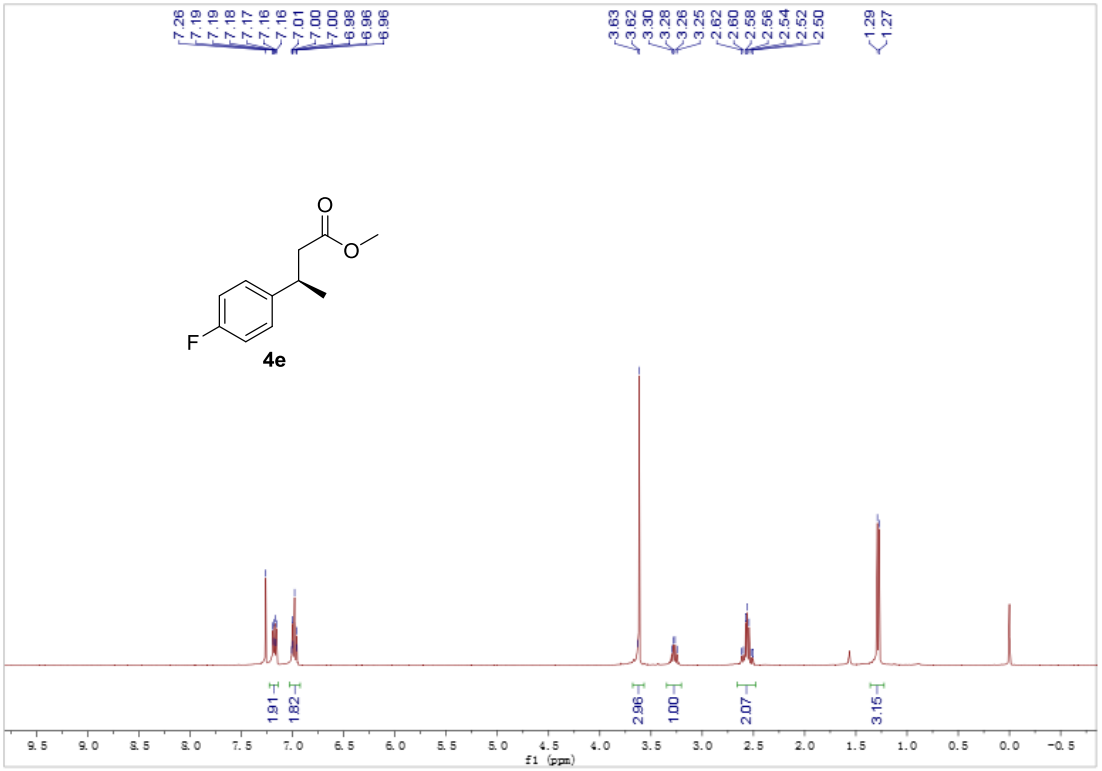
O
O
4d
f1 (ppm)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2.60
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2.50
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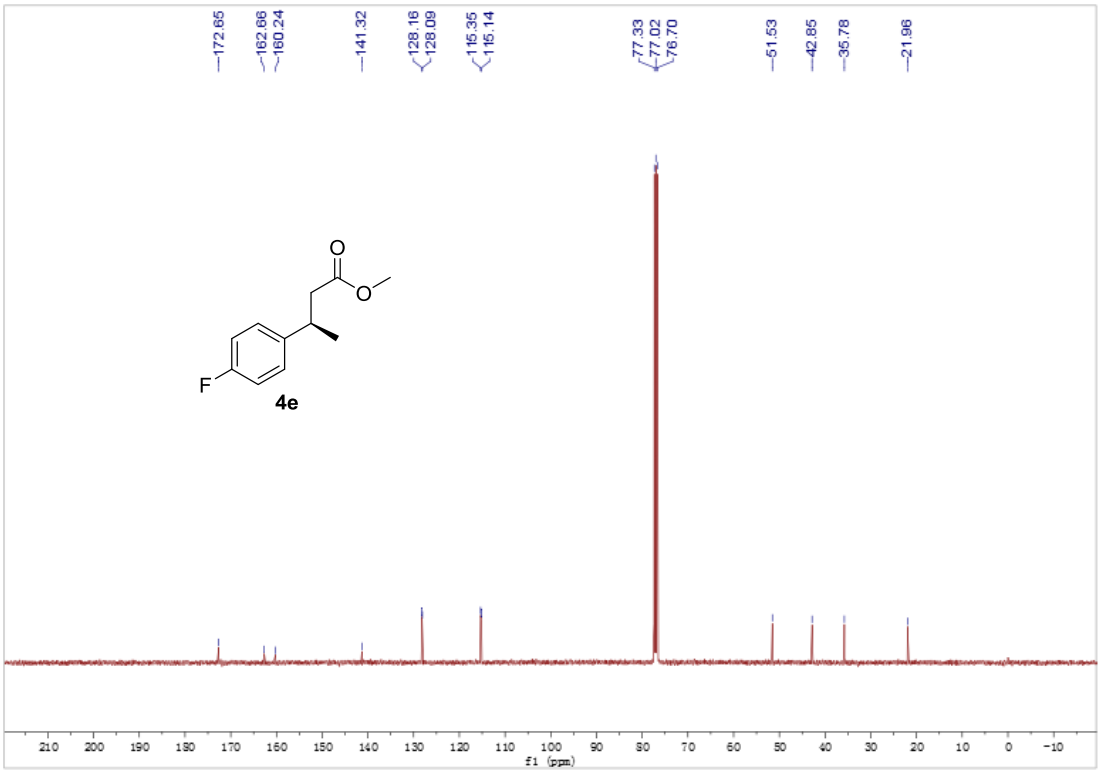
f1 (ppm)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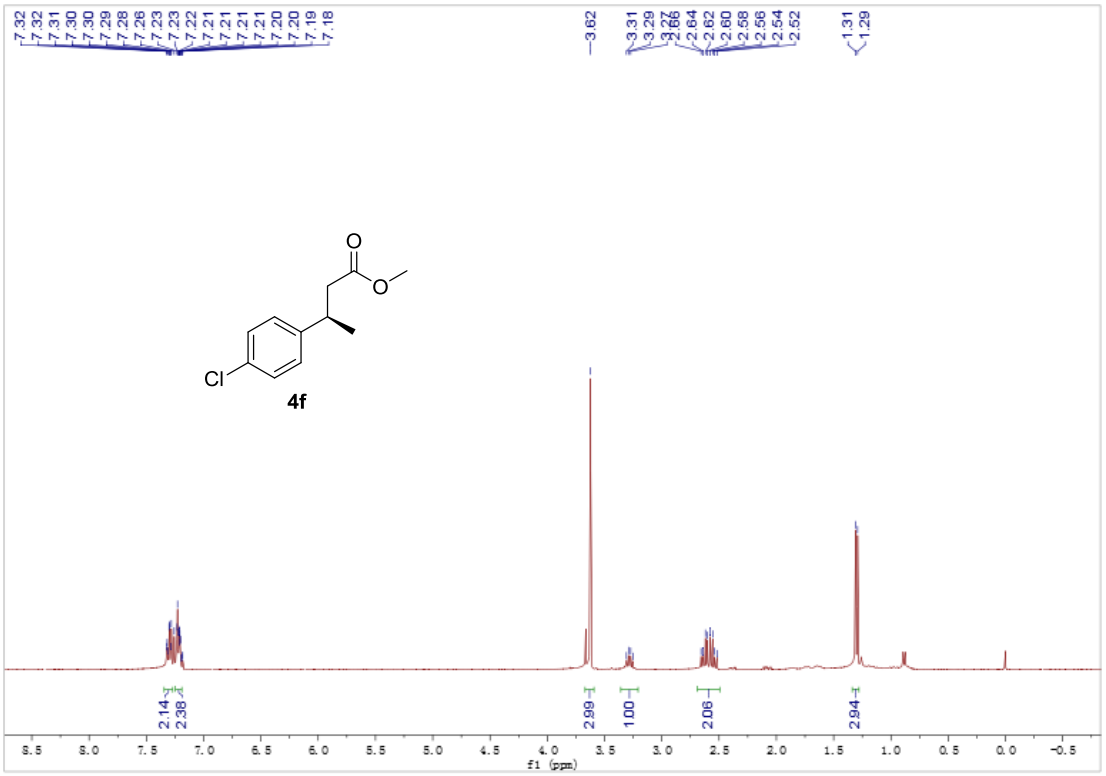
21.96
O
O
F
4e
f1 (ppm)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2.52
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O
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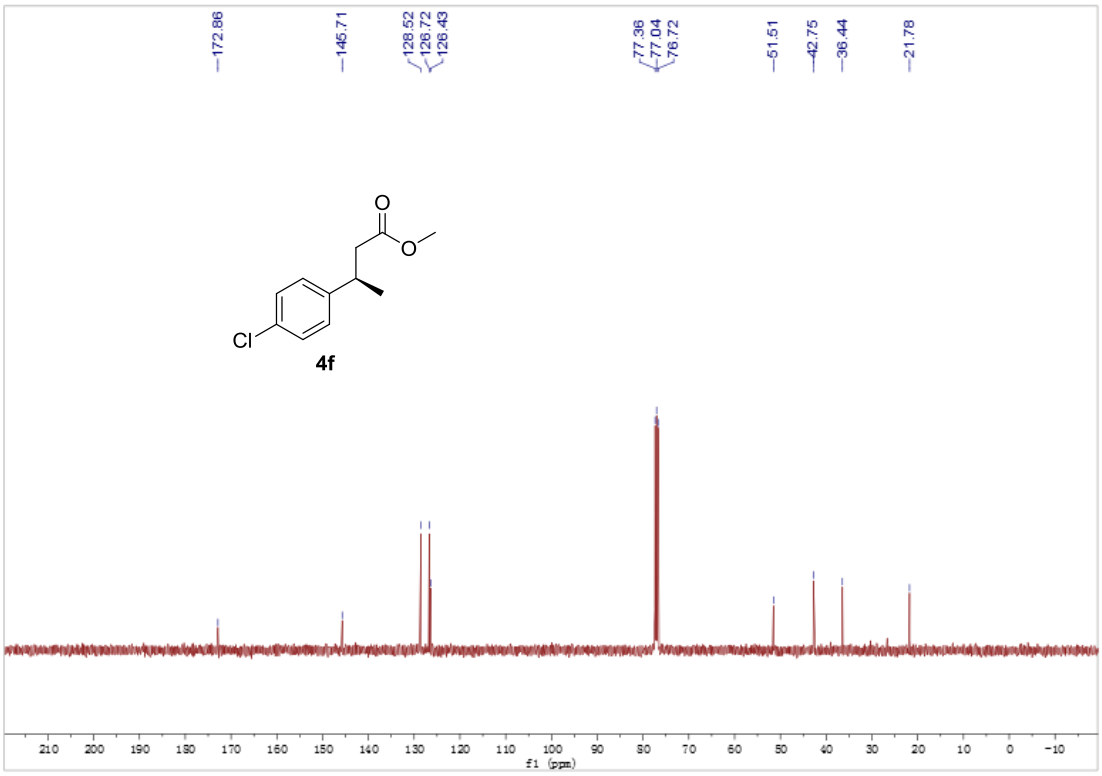
2.94
f1 (ppm)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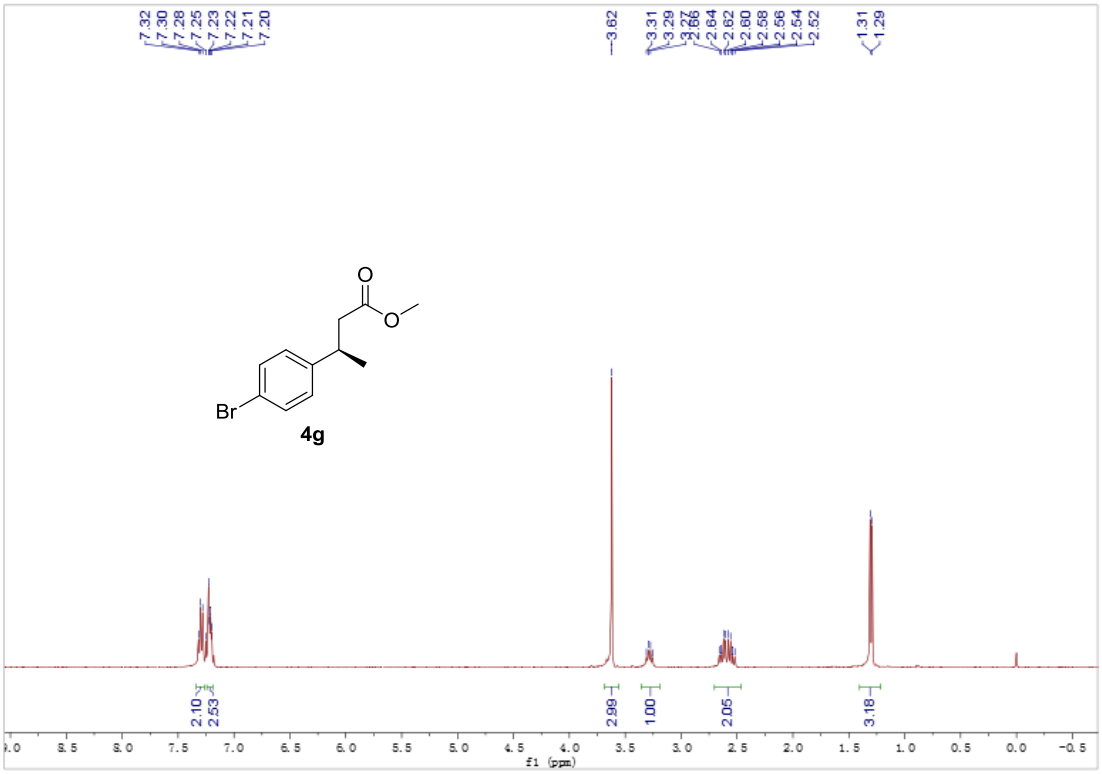
O
Cl
4f
f1 (ppm)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2.58
2.56
2.54
2.52
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1.00
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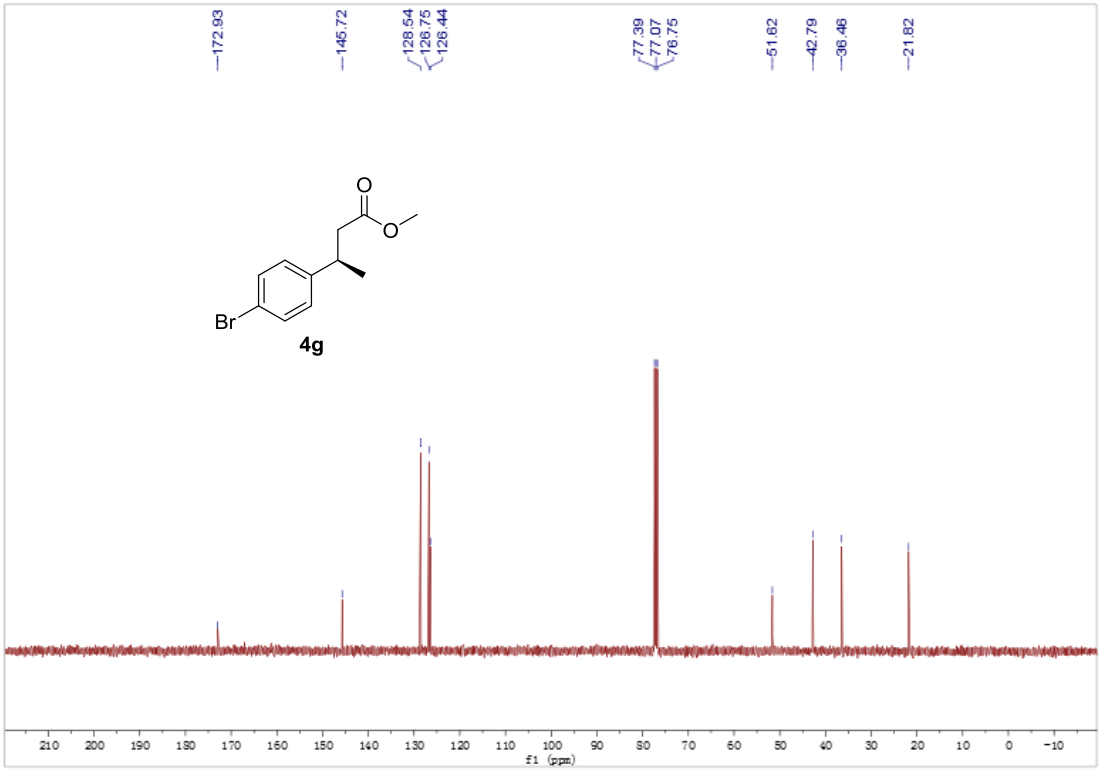
f1 (ppm)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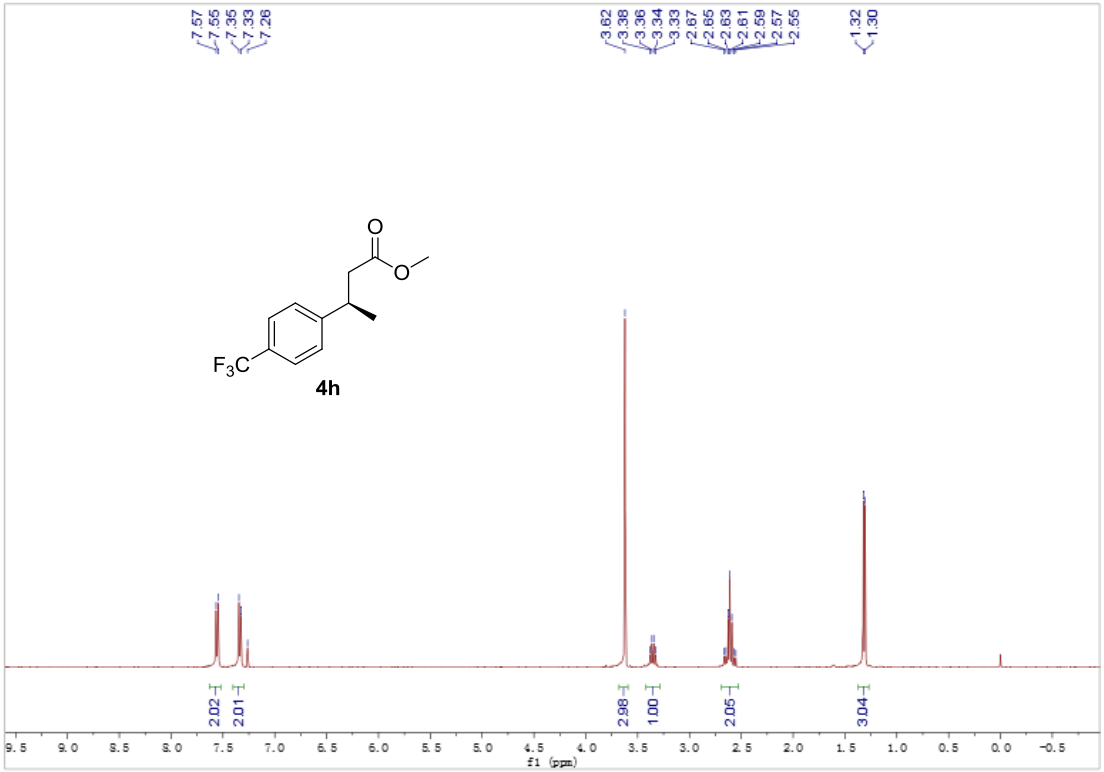
Br
4g
f1 (ppm)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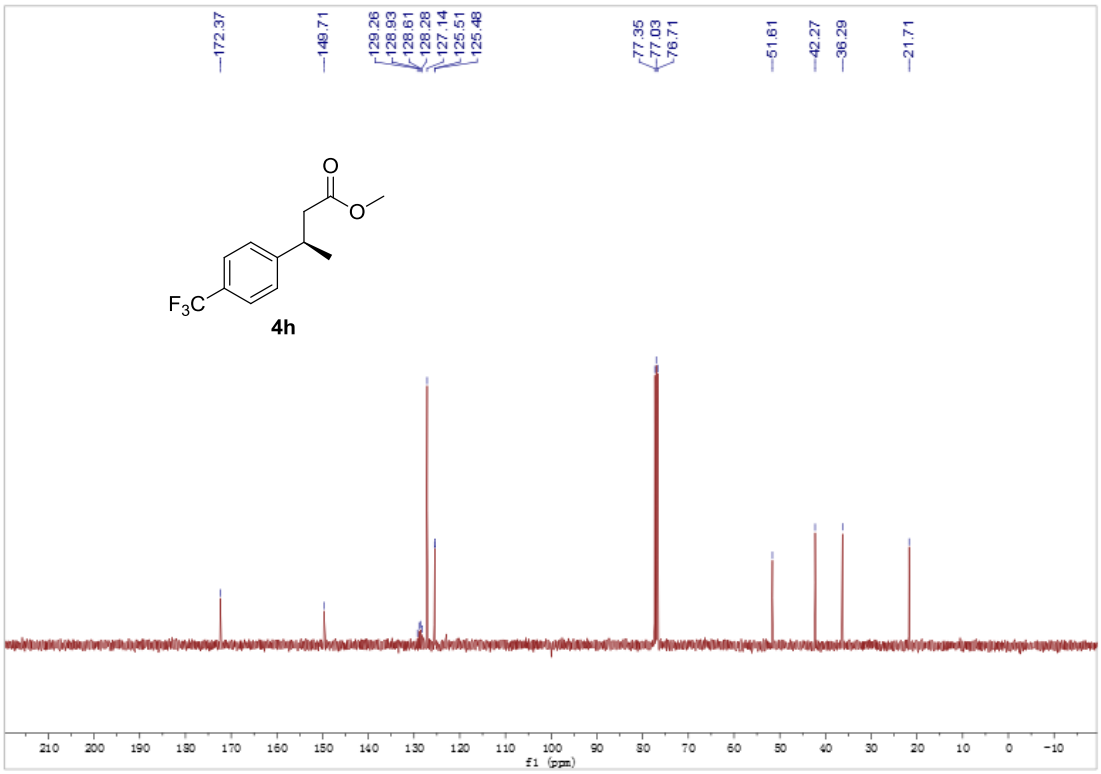
2.55
1.32
1.30
O
O
F3C
4h
2.02
2.01
2.98
1.00
2.05
3.04
f1 (ppm)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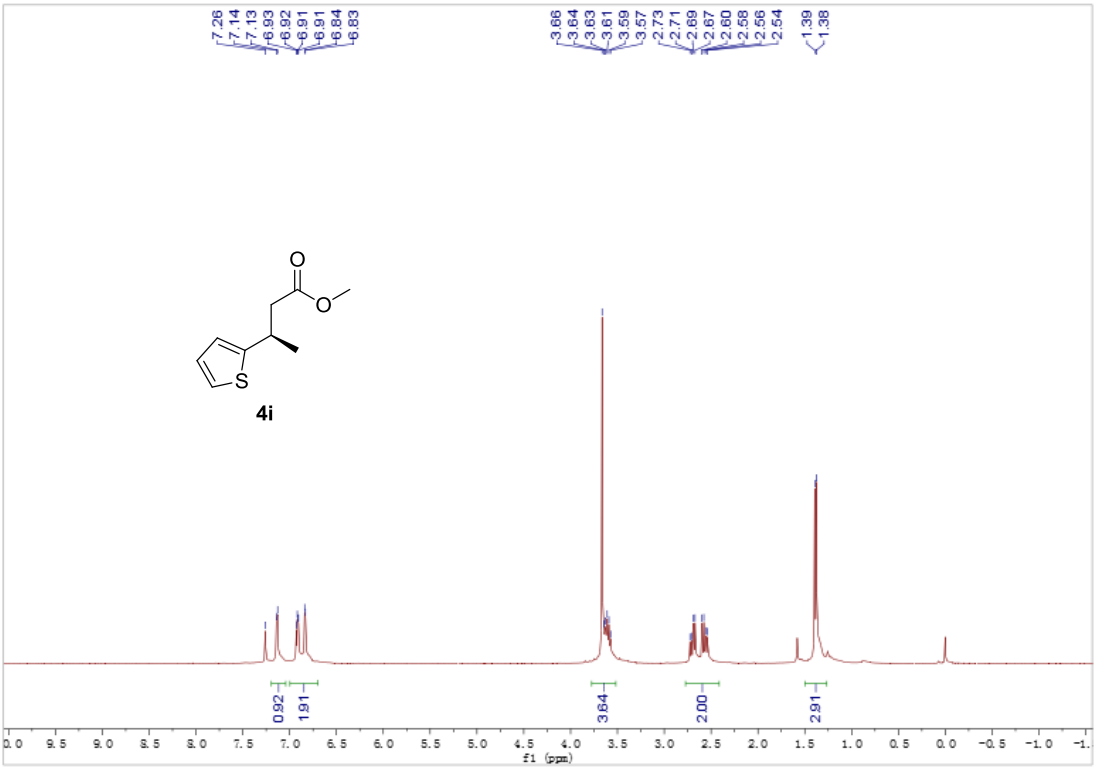
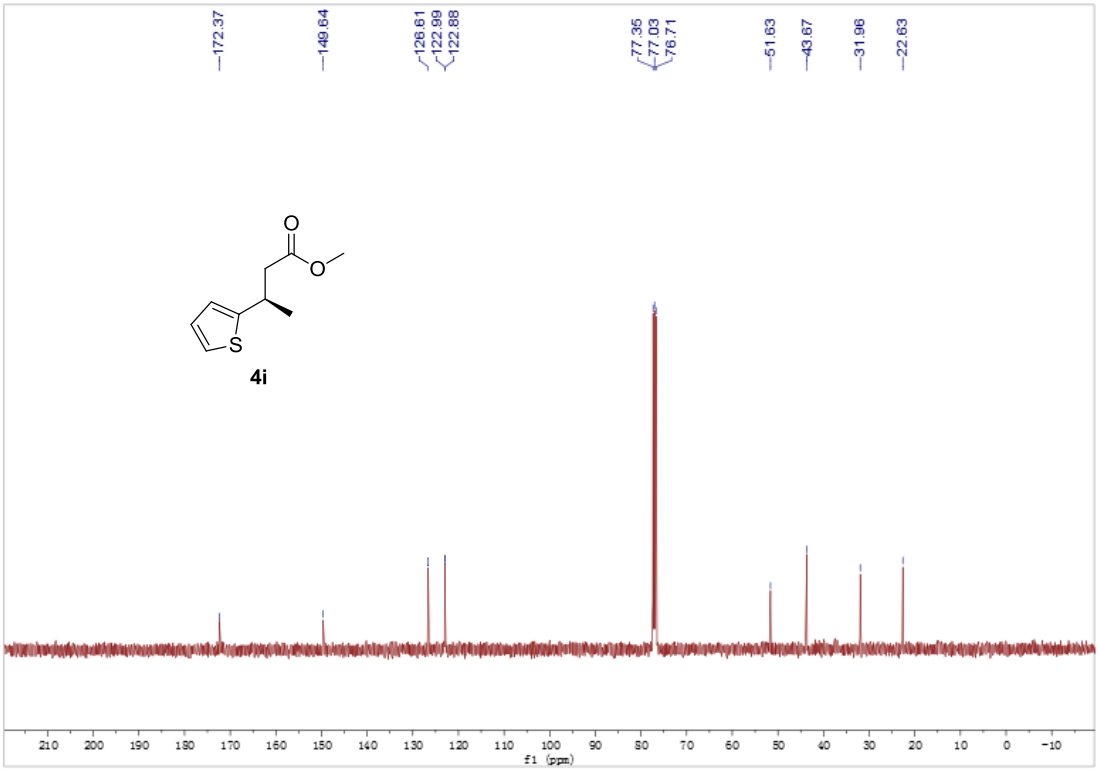
149.71
129.26
128.93
128.61
128.28
127.14
125.51
125.48
77.35
77.03
76.71
51.61
42.27
36.29
21.71
O
O
F3C
4h
f1 (ppm)


7.26
7.14
7.13
6.93
6.92
6.91
6.91
6.84
6.83
3.66
3.64
3.63
3.61
3.59
3.57
2.73
2.71
2.69
2.67
2.60
2.58
2.56
2.54
1.39
1.38
O
O
S
4i
0.92
1.91
3.64
2.00
2.91
f1 (ppm)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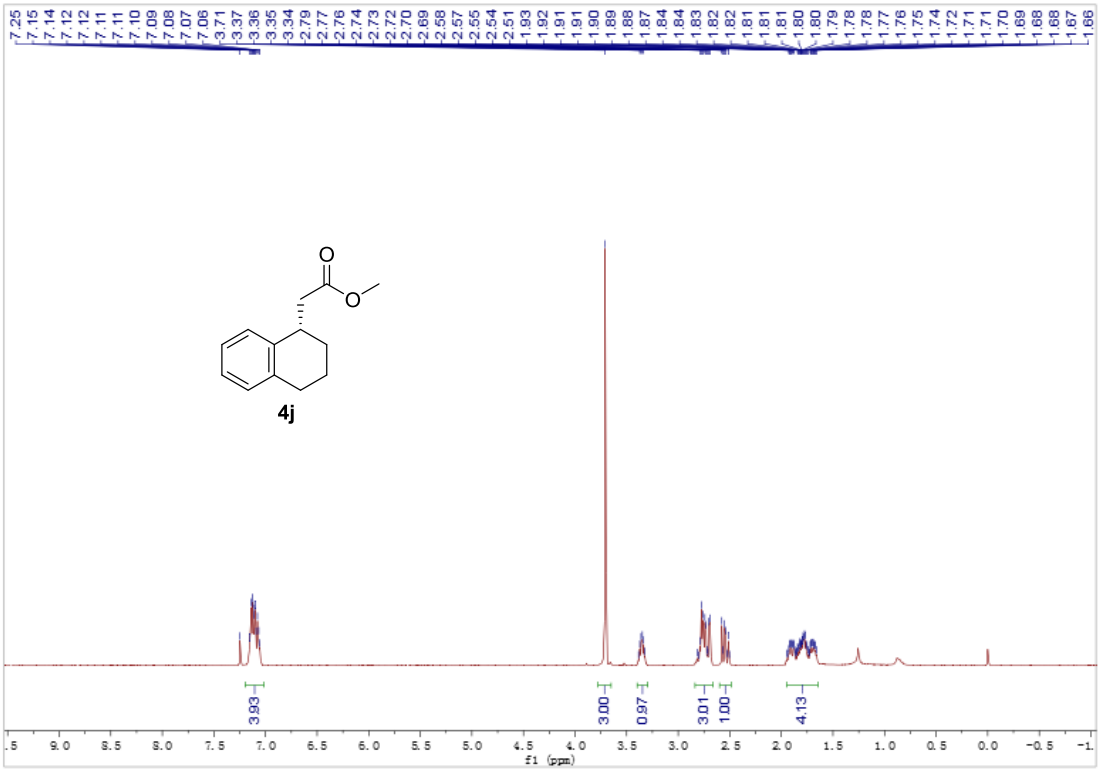
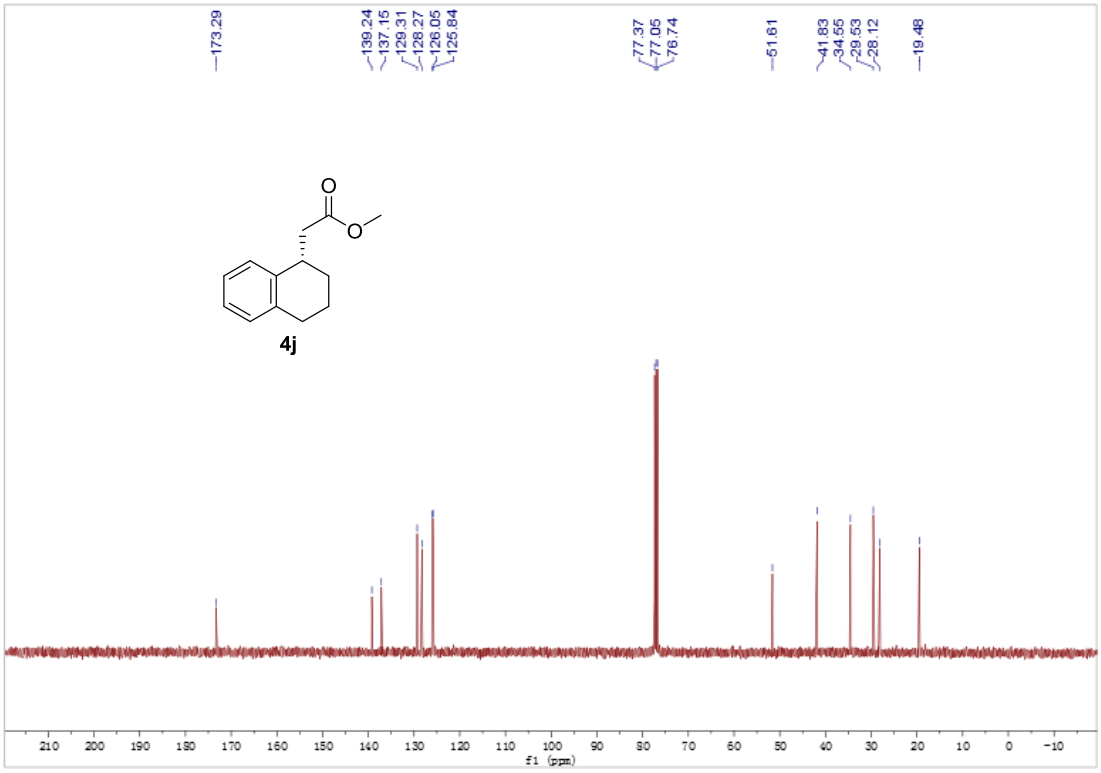
149.64
126.61
122.99
122.88
77.35
77.03
76.71
51.63
43.67
31.96
22.63
O
O
S
4i
f1 (ppm)


7.25
7.15
7.14
7.12
7.12
7.11
7.11
7.10
7.09
7.08
7.07
7.06
3.71
3.37
3.36
3.35
3.34
2.79
2.77
2.76
2.74
2.73
2.72
2.70
2.69
2.58
2.57
2.55
2.54
2.51
1.93
1.92
1.91
1.91
1.90
1.89
1.88
1.87
1.84
1.84
1.83
1.82
1.82
1.81
1.81
1.81
1.80
1.80
1.79
1.78
1.78
1.77
1.76
1.75
1.74
1.72
1.71
1.71
1.70
1.69
1.68
1.68
1.67
1.66
O
O
4j
3.93
3.00
0.97
3.01
1.00
4.13
f1 (ppm)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137.15
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128.27
126.05
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77.05
76.74
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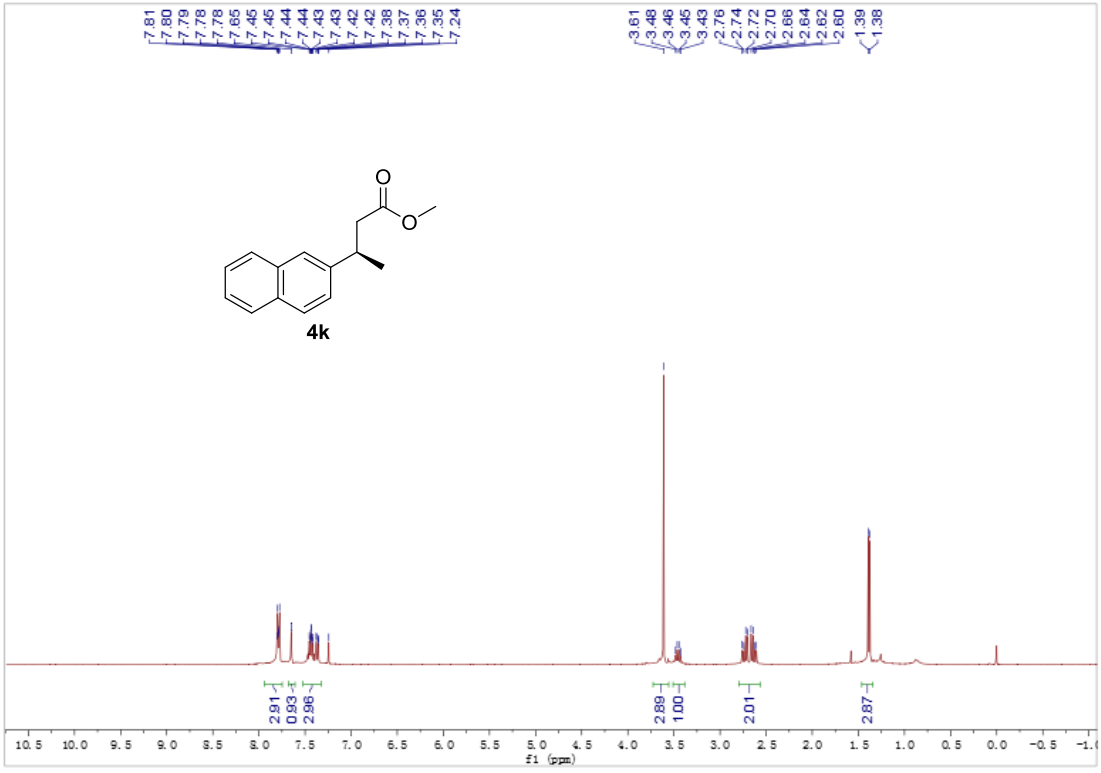
29.53
28.12
19.48
4j
f1 (ppm)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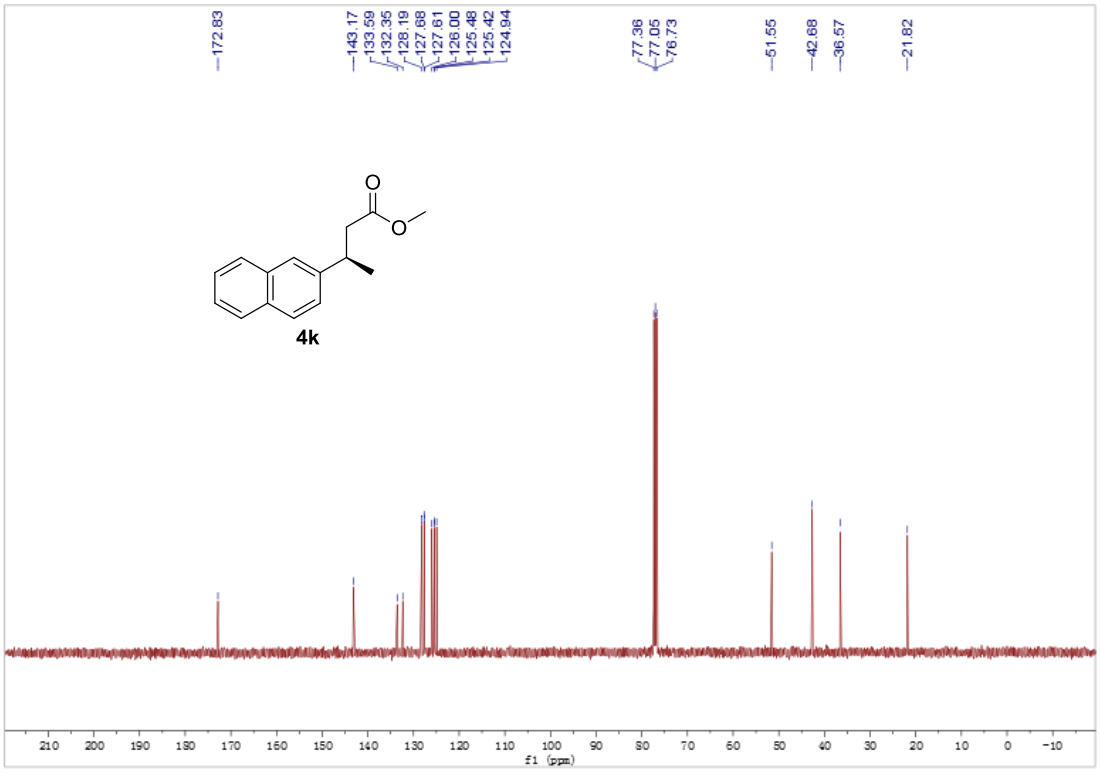
7.80
7.79
7.78
7.78
7.65
7.45
7.44
7.44
7.43
7.43
7.42
7.42
7.38
7.37
7.36
7.35
7.24
3.61
3.48
3.46
3.45
3.43
2.76
2.74
2.72
2.70
2.66
2.64
2.62
2.60
1.39
1.38
4k
2.91
0.93
2.96
2.89
1.00
2.01
2.87
f1 (ppm)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127.68
127.61
126.00
125.48
125.42
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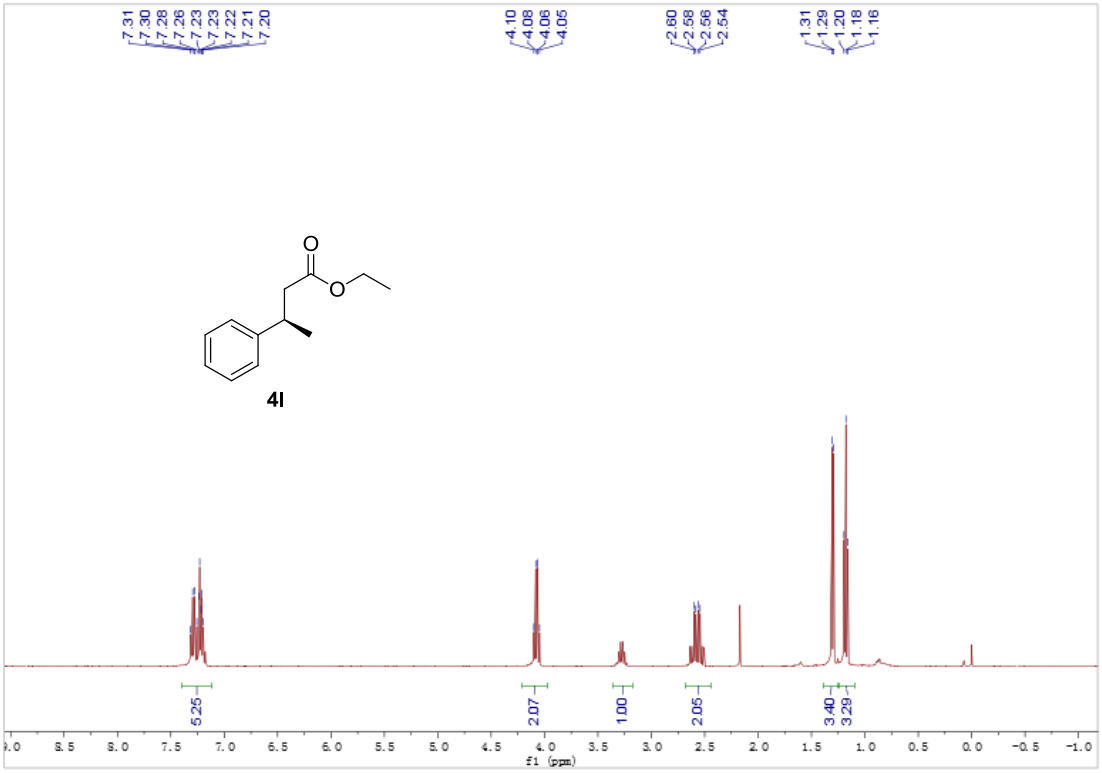
77.36
77.05
76.73
51.55
42.68
36.57
21.82
4k
f1 (ppm)


7.31
7.30
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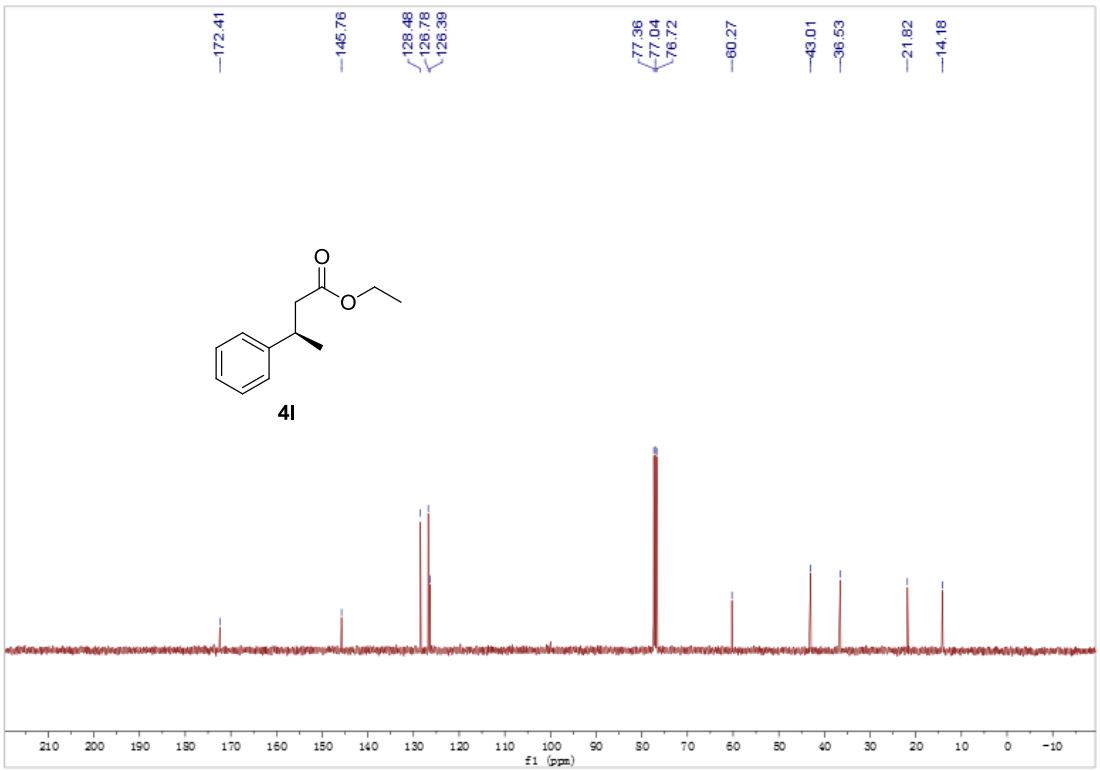
7.26
7.23
7.22
7.21
7.20
4.10
4.08
4.06
4.05
2.60
2.58
2.56
2.54
1.31
1.29
1.20
1.18
1.16
4l
5.25
2.07
1.00
2.05
3.40
3.29
f1 (ppm)



Reference:

[1] R. Wu, M. G. Beauchamps, J. M. Laquidara, J. R. Sowa, *Angewandte Chemie International Edition* **2012**, *51*, 2106-2110.

[2] (a) W. Tang, W. Wang, X. Zhang, *Angewandte Chemie International Edition* **2003**, *42*, 943-946; (b) S. Oi, A. Taira, Y. Honma, Y. Inoue, *Organic Letters* **2003**, *5*, 97-99.