The Allyl Intermediate in Regioselective and Enantioselective Iridium-Catalyzed Asymmetric Allylic Substitution Reactions

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Supporting information

General Section

General Procedures. All reactions were conducted in flame or oven-dried round-bottomed flasks fitted with rubber septa under a positive pressure of argon or nitrogen, or in 1-gram vials sealed with a screw cap fitted with PTFE silicon septum under an atmosphere of Argon, unless otherwise stated. Air- and moisture-sensitive reagents were transferred via syringe, or were handled in a argon-filled drybox (Innovative Technologies, Newburyport, Massachusetts) equipped with an oxygen sensor (working oxygen level <1 ppm) and low-temperature refrigeration unit (–35 °C). Organic solutions were concentrated by rotary evaporation at 23–35 °C. Flash-column chromatography was performed as described by Still et. al.[1] employing silica gel (40–63 μm particle size) purchased from Silicycle. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm). TLC plates were visualized by exposure to ultraviolet light (UV) or submersion in aqueous potassium permanganate solution ($KMnO_4$), followed by brief heating by a heat gun (175 °C, 3–5 s).

Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran and benzene were deoxygenated by sparging with argon and then were purified according to the method of Pangborn et al.[2] Both enantiomers of **1** were synthesized according to procedures described in he literature[3]. (E)-but-2-enyl methyl carbonate was synthesized by the reaction of corresponding allylic alcohol with methyl chloroformate in the presence of pyridine. Sodium 2-methylpentanoate was prepared by the reaction of 2-methylpentanoic acid with NaOH in THF and drying the solid under vacuum at 100 °C overnight after removing the volatile materials. Aniline, *N*-ethylaniline, benzylamine, and 1,2,3,4-tetrahydroquinoline were all dried over KOH, distilled under reduced pressure and freeze pump thawed before transferring into the drybox. Sodium dibenzylmalonate and sodium dimethylmalonate were prepared by the reaction of 1 equiv of the corresponding malonate with 1 equiv NaH in THF or THF-d_8 directly before use. Lithium phenolate, lithium benzoate and lithium 3-(dimethylamino)phenolate were

all prepared by 1 equiv of the corresponding alcohol with 1 equiv of a 2.5 molar solution of n-butyllithium in hexanes at 0 °C.

Instrumentation. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 500 MHz at 22 °C. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26; THF, δ 1.73, 3.58). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, coupling constant in Hertz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz at 22 °C. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$, δ 77.0). Two-dimensional COSY (Correlation Spectroscopy) and Heteronuclear Multiple Quantum Coherence (HMQC) were recorded at 500 MHz at 22 °C. Gas chromatography was performed using an HP 6890 series gas chromatograph equipped with an HP-5 column (25 m, 0.2 mm I.D., 0.33 μm film). GC/MS analysis were performed on an Agilent 6890N GC equipped with a 5973 MS and an HP-5ms column (30 m x 0.25 mm ID x 0.25 μm film). HPLC analyses were carried out on a Waters chromatography system (1525 binary pump, 717+ autosampler, 2487 dual wavelength detector). Elemental analyses were obtained at the University of Illinois Microanalysis Laboratory. High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory.

Synthetic Procedures

Products of reactions of 2a: All of the products of stoichiometric reactions of **2a** were bought from commercial sources with following exceptions. N-allylbenzylamine[4] and N-allyl-N-ethylaniline[5] were prepared according to previously published methods. Allyl 2-methylpentanoate was made by refluxing sodium 2-methylpentanoate with allyl bromide in acetonitrile.

GC retention times of linear products of reactions of 2b: The GC retention times for all linear products were obtained by reacting 1 equiv crotyl chloride with the respective nucleophiles for 1 hour at 50 °C and running GC on crude reaction mixtures.

Preparation of complex 2a: In a 20 mL glass vial containing a magnetic stirbar, 400.0 mg of complex **1** (0.4617 mmol was dissolved in 10.0 mL of C_6H_6, and 37.5 μL (0.460 mmol) of allyl chloride were added to the resulting solution while stirring. After 5-15 min 115.6 mg of AgOTf (0.4499 mmol) dissolved in 3.0 mL of THF was added to the stirring solution. The AgCl, which precipitated, was removed by filtration through a 0.2 μm syringe filter. The resulting solution was concentrated to about 10 mL and allowed to stand at room temperature. After 24 h, the solid was isolated by removing the mother liquor with a pipette and washing the resulting crystals with benzene to give 290 mg of **2a** (55% yield). Complex **2a** crystallized with two molecules of benzene. Anal. Calc. for $C_{60}H_{58}F_3O_5IrNPS$: C, 60.79; H, 4.93; N 1.18. Found: C, 60.77; H, 4.90; N, 1.35. ^{1}H NMR (500 MHz, THF) δ 8.33 (m, 2H), 8.05 (m, 4H), 7.51 (m, 4H), 7.30 (m, 10H), 7.14 (d, J = 7.4, 2H), 5.22 (m, 1H), 4.63 (m, 1H), 4.22 (app, t, J = 6.9, 1H), 4.13 (m, 1H), 4.00 (m, 1H), 3.87 (m, 3H), 3.54 (m, 1H), 3.31 (m, 1H), 3.14 (app, t, J = 7.9, 1H), 2.87 (m, 1H), 2.71 (d, J = 12.0, 1H), 2.31 (m, 2H), 2.11 (m, 1H), 1.74 (m, 1H), 1.63 (m, 2H), 1.44 (m, 1H), 1.08 (t, J = 11.7, 1H), 0.59 (d, J = 7.4, 3H). ^{31}P NMR (202 MHz, THF) δ 124.99.

Preparation of complex 2b: In a 20 mL glass vial containing a magnetic stirbar, 118 mg of complex **1** (0.136 mmol) was dissolved in 5.0 mL of C_6H_6, and 18.8 μL (0.193 mmol) of crotyl chloride was added to the resulting solution while stiring. After 5-15 min, 46.6 mg of $AgSbF_6$ (0.136 mmol) dissolved in 2.0 mL of THF was added to the stirring solution. The AgCl, which precipitated, was removed by filtration through a 0.2 μm syringe filter. The resulting solution was concentrated to about 5 mL and allowed to stand at room temperature. After 48 h, the solid was isolated by removing the mother liquor with a pipette and washing the resulting crystals with benzene to give 60 mg (35% yield) of **2b**. Complex **2b** crystallized with two molecules of benzene. In THF solution, **2b** exists as two isomers in a ratio of 97/3. Anal. Calc. for $C_{60}H_{60}F_6O_2IrNPSb$: C, 56.03; H, 4.70; N 1.09. Found: C, 55.89; H, 4.78; N, 1.34. ^{1}H NMR (500 MHz, THF) 8.36 (d, J = 8.9, 1H), 8.27 (d, J = 8.9, 1H), 8.10 (m, J = 4.5, 2H), 8.01 (d, J = 8.9, 1H), 7.86 (d, J = 8.8, 1H), 7.55 (m, 2H), 7.36 (m, 24H), 7.16 (d, J = 7.0, 2H), 5.12 (m, 1H), 4.73 (m, 1H), 4.35 (m, 1H), 4.22 (m, 1H), 3.88 (m, 2H), 3.28 (m, 2H), 3.17 (m, 1H), 2.94 (m, 2H), 2.42 (m, 1H), 2.32 (m, 1H), 2.10 (m,

2H), 1.89 (m, 1H), 1.84 (m, 3H), 1.69 (m, 1H), 1.59 (m, 2H), 1.13 (t, J = 12.25, 1H), 0.56 (d, J = 7.4, 3H). 31P NMR (202 MHz, THF) δ 128.55 (minor), 124.93 (major) in a ratio of 97/3.

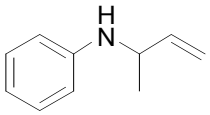
General procedure for stoichiometric reactions of 2a: Complex **2a** (20.0 mg, 0.0169 mmol) and Si_2Me_6 (1.0 μL) were dissolved in 0.4 mL of THF-d_8. A ^{1}H-NMR spectrum was acquired. To this solution was added the combination of a primary or secondary amine and triethylamine, an alkali metal alkoxide, sodium 2-methylpentanoate, or an alkali metal malonate as nucleophile. Reactions of the primary amines were conducted with 5.0 equiv of the primary amine and 1.2 equiv of the tertiary amine; the other reactions were conducted with 1.2 equiv of the nucleophile. The resulting mixture was stirred for 5 min. A solution of PPh_3 (4.9 mg, 0.019 mmol) in 0.1 mL of THF-d_8 was then added, at which point the solution turned yellow. A second ^{1}H-NMR spectrum was acquired, and the yields of the organic product were determined by integration of the two ^{1}H-NMR spectra vs the Si_2Me_6 internal standard. The identity of the allylation products was confirmed by comparing the GC retention times with commercially available material or independently synthesized products.

General procedures for stoichiometric reactions of 2b: Complex **2b** (20.0 mg, 0.0156 mmol) and Si_2Me_6 (1.0 μL) were dissolved in 0.4 mL of THF-d_8. A ^{1}H-NMR spectrum was acquired. To this solution was added a combination of a primary amine and triethylamine, 1,2,3,4-tetrahydroquinoline and *tert*-butylmethylcarbonate, or an alkali metal alkoxide. Reactions of the primary amines were conducted with 5.0 equiv of the primary amine and 1.2 equiv of the tertiary amine; the other reactions were conducted with 1.2 equiv of the nucleophile. The resulting solution was stirred for 5 min, and a solution of PPh_3 (8.1 mg, 0.032 mmol) in THF-d_8 was added to the stirred solution. A second ^{1}H-NMR spectrum was acquired, and the yields of the organic product were determined by integration of the two ^{1}H-NMR spectra versus the Si_2Me_6 internal standard. The crude reaction was concentrated under vacuum. The product was isolated by preparative TLC, eluting with 20:1 hexanes:ethyl acetate in all cases, except for the isolation of *N*-benzyl but-3-en-2-amine, which was isolated by elution with 3:1 hexanes:acetone. Formation of the allylation products was confirmed by comparing the GC retention times with products prepared independently by catalytic reactions described in the next procedure. Branched-to-linear ratios were measured by GC prior to purification by TLC, and enantiomeric excesses of samples purified by TLC were obtained by chiral HPLC or with chiral lanthanide shift reagents using the same conditions determined for the products obtained by the catalytic reactions. The major enantiomer was always found to correspond to the major enantiomer obtained using **1(R,R,R)** catalyst.

General procedures for catalytic reactions using trans-crotyl methyl carbonate: Methyl crotyl carbonate (130 mg, 1.00 mmol) was dissolved in 2 mL of THF. To this solution was added the nucleophile (1.20 mmol), followed by complex **1** (34.7 mg, 0.0400 mmol). The solution was stirred for 30 min. The volatile materials from the crude reaction solution were evaporated under vacuum. Mesitylene 7.0 μL (0.050 mmol) and $CDCl_3$ were added. A ^{1}H-NMR spectrum was acquired, and the yield was determined by integration of the signals due to the organic product versus the mesitylene standard. The chloroform solvent was then evaporated, and the product was isolated by silica-gel chromatography as described for the individual products. Branched-to-linear ratios were measured by GC. Enantioselectivities were determined by chiral HPLC of the products isolated after chromatography, or with chiral lanthanide shift reagents. The retention times of the enantiomeric products were determined from racemic mixtures obtained by mixing the products of separate catalytic reactions conducted with the two enantiomers of **1**. The yields, enantioselectivities and branched-to-linear ratios for each reaction are given in Table S1.

Conditions for Isolation and spectral data of the organic products prepared by the catalytic reactions.

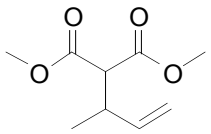
***N*-(but-3-en-2-yl)aniline**



The reaction was conducted according to the general procedure. The product was purified by silica gel chromatography, eluting with 9:1 (hexane:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (dd, J = 7.3, 7.6, 2H), 6.70 (t, J = 7.3, 1H), 6.63 (d, J = 7.6, 2H), 5.84 (ddd, J = 5.6, 10.3, 17.2, 1H), 5.23 (dd, J = 1.4, 17.2, 1H), 5.09 (dd, J = 1.4, 10.3, 1H), 3.99 (dq, J = 5.6, 6.7 1H), 3.63 (br, 1H) 1.32 (d, J = 6.7, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.30, 141.35, 129.10, 117.07, 114.08, 113.31, 51.00, 21.61. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{10}H_{14}N$, 148.1126; found, 148.1122. HPLC conditions: Daicel CHIRALCEL OJ-H (0.46 cm x 25 cm); hexane/2-propanol =99.5/0.5; flow rate

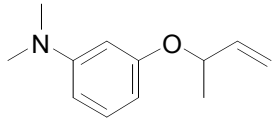
= 1 mL/min; detection wave length = 220 nm; TR = 17.1 (major), 20.3 (minor) min. $[\alpha]_D^{RT}$ = –1.6 (*c* 0.2, $CHCl_3$), (*S*)-(-)-*N*-(but-3-en-2-yl)aniline.

Dimethyl 2-(but-3-en-2-yl)malonate



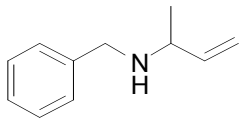
The reaction was conducted according to the general procedure. The crude product was passed through a fritted glass filter packed with Celite layered on silica gel and eluted with 20 ml of EtOAc. The solvents were removed under reduced pressure, and the product was purified by silica gel chromatography, eluting with 9:1 (hexane:EtOAc). ^{1}H NMR (499 MHz, $CDCl_3$) δ 5.77 (ddd, J = 8.0, 10.3, 17.2, 1H), 5.09 (d, J = 17.1, 1H), 5.01 (d, J = 10.3, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.32 (d, J = 8.9, 1H), 2.95 (m, 1H), 1.10 (d, J = 6.8, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.42, 168.36, 139.49, 115.24, 57.28, 52.10, 52.00, 37.89, 17.67. The enantiomeric excess was determined by GC: Chiraldex γ-CDTA 30 m column, 50-100 °C, 1 °/min, 90 kPa H_2, *t*R = 37.3 (minor) min, *t*R = 37.6 (major) min. $[\alpha]^{21}_D$ = -18.8 (*c* 1.25, $CHCl_3$), (*S*)-(-) Dimethyl 2-(but-3-en-2-yl)malonate.

3-(but-3-en-2-yloxy)-N,N-dimethylaniline



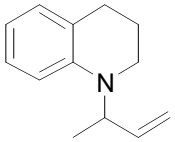
The reaction was conducted according to the general procedure. The product was purified by silica gel chromatography, eluting with 9:1 (hexane:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (dd, J = 4.4, 12.1, 1H), 6.33 (m, 3H), 5.94 (ddd, J = 5.8, 10.6, 17.3, 1H), 5.28 (app. dt, J = 1.3, 17.3, 1H), 5.16 (app. dt, J = 1.3, 10.6, 1H), 4.81 (dq, J = 5.8, 6.4 1H), 2.94 (s, 6H), 1.43 (d, J = 6.4, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.01, 151.99, 139.58, 129.51, 115.28, 105.73, 103.53, 101.16, 74.32, 40.58, 21.30. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{12}H_{18}NO$, 192.1388; found, 192.1386. HPLC conditions: Daicel CHIRALCEL OD-H (0.46 cm x 25 cm); hexane/2-propanol =99.5/0.5; flow rate = 1 mL/min; detection wave length = 220 nm; TR = 29.4 (major), 39.4 (minor) min.

N-benzylbut-3-en-2-amine



The reaction was conducted according to the general procedure. The product was purified by silica gel chromatography eluting with 3:1 (hexane:acetone). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 4H), 7.24 (m, 1H), 5.72 (ddd, J = 7.7, 10.2, 17.2, 1H), 5.13 (d, J = 17.2, 1H), 5.09 (d, J = 10.2, 1H), 3.81 (d, J = 13.1, 1H), 3.69 (d, J = 13.1, 1H), 3.22 (dq, J = 7.7, 6.5, 1H), 1.41 (br, 1H), 1.18 (d, J = 6.5, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.50, 140.78, 128.37, 128.14, 126.81, 114.73, 56.01, 51.35, 21.78. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{11}H_{16}N$, 162.1283; found, 162.1276. Daicel CHIRALCEL AD-H (0.46 cm x 25 cm); hexane/2-propanol/diethylamine = 99.75/0.24/0.01; flow rate = 0.5 mL/min; detection wave length = 220 nm; TR = 12.5 (minor), 13.3 (major) min.

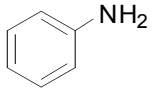
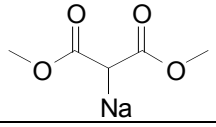
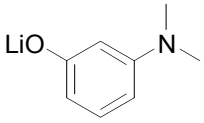
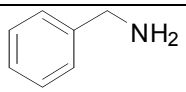
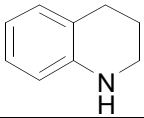
1-(but-3-en-2-yl)-1,2,3,4-tetrahydroquinoline



The reaction was conducted according to the general procedure. The product was purified by silica gel chromatography, eluting with 9:1 (hexane:EtOAc). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.10 (t, J = 7.0, 1H), 7.01 (d, J = 7.3, 1H), 6.73 (d, J = 8.3, 1H), 6.62 (t, J = 7.3, 1H), 5.96 (ddd, J = 4.1, 10.2, 17.7, 1H), 5.23 (m, 1H), 5.20 (m, 1H), 4.55 (dq, J = 4.1, 6.8, 1H), 3.20 (m, 2H), 2.80 (t, J = 6.4, 2H), 1.96 (m, 2H), 1.35 (d, J = 6.8, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.09, 139.02, 129.19, 126.96, 123.08, 115.46, 114.83, 110.79, 53.19, 41.98, 28.45, 22.38, 15.21. $[MH]^+$ calcd for $C_{13}H_{18}N$, 188.1439; found, 188.1437. Daicel CHIRALCEL OJ-H (0.46 cm x 25 cm); hexane/2-

propanol =99.75/0.25; flow rate = 0.5 mL/min; detection wave length = 220 nm; TR = 11.9 (major), 14.5 (minor) min.

Table S1. Yields and selectivities for the reaction of methyl crotyl carbonate with different nucleophiles catalyzed by **1**.

Nu	cat.	yield(%)	b:l	ee(%)	time(h)
	4%	52	97:3	94	0.5
	4%	83	93:7	91	0.5
	4%	60	99:1	92	0.5
	4%	94	95:5	98	0.5
	4%	100%	9:1	94	0.5

Crystal Structure and NMR Data

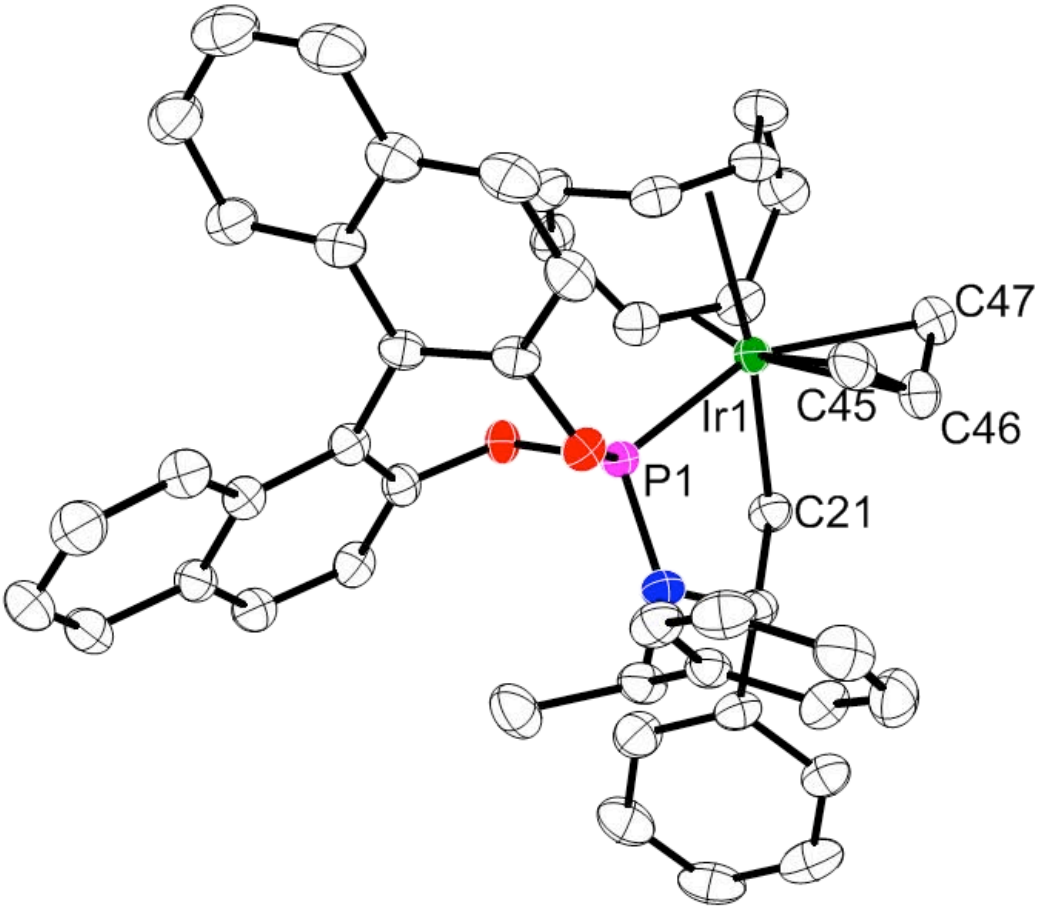
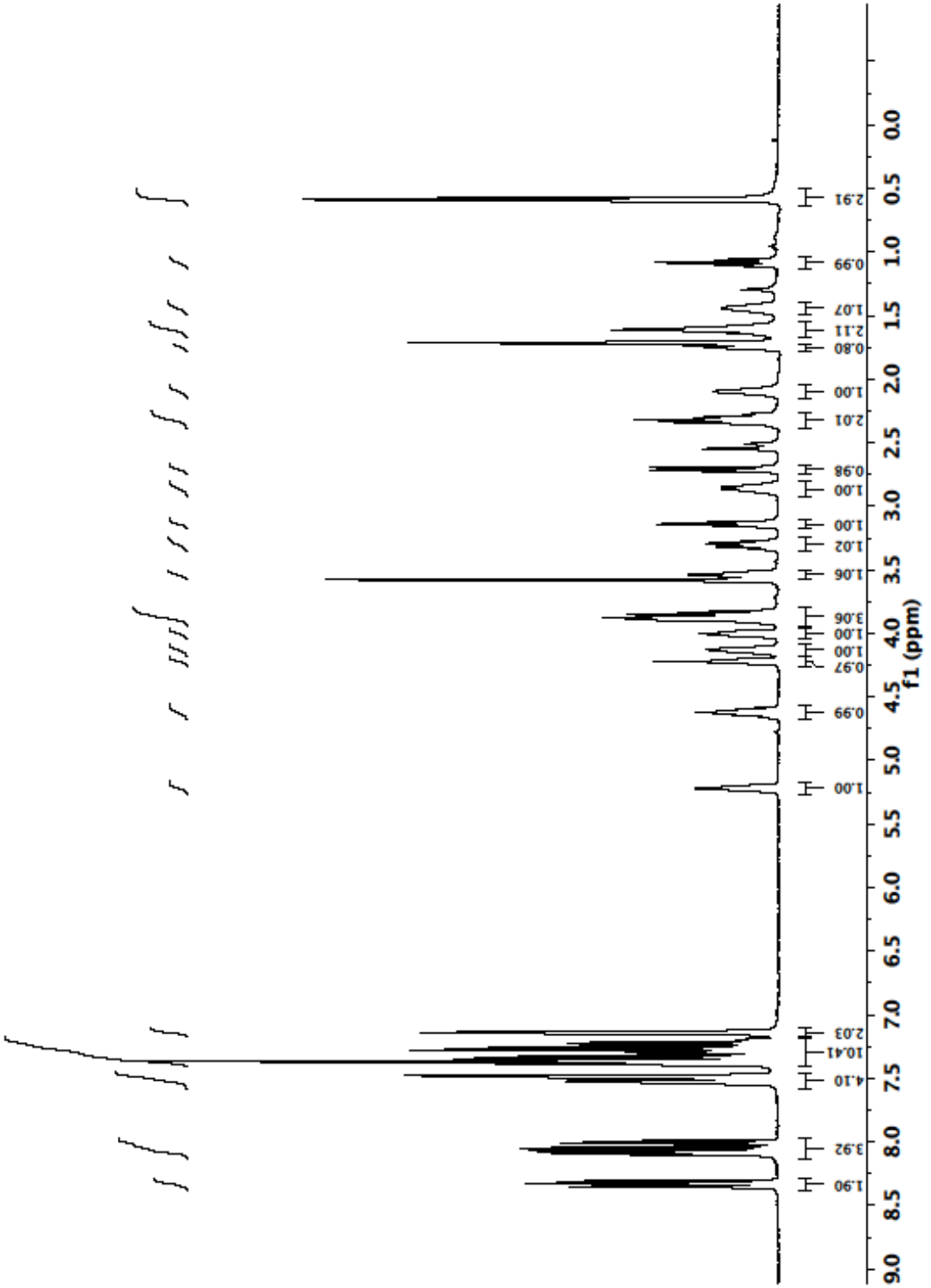


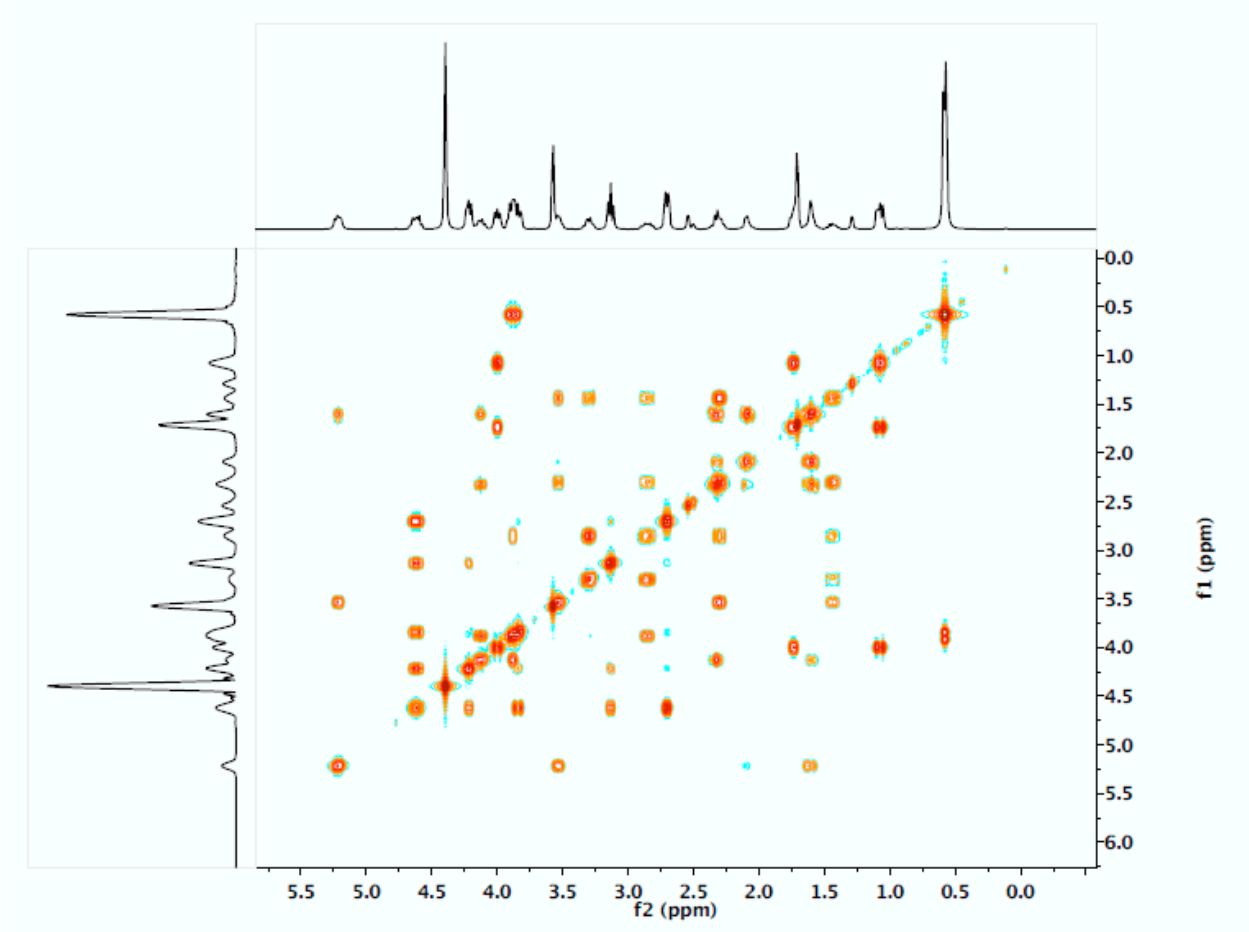
Figure S1. ORTEP digram of **2a** at 35% ellipsoids.

1D and 2D NMR data for 2a and 2b and the products of catalytic reactions.

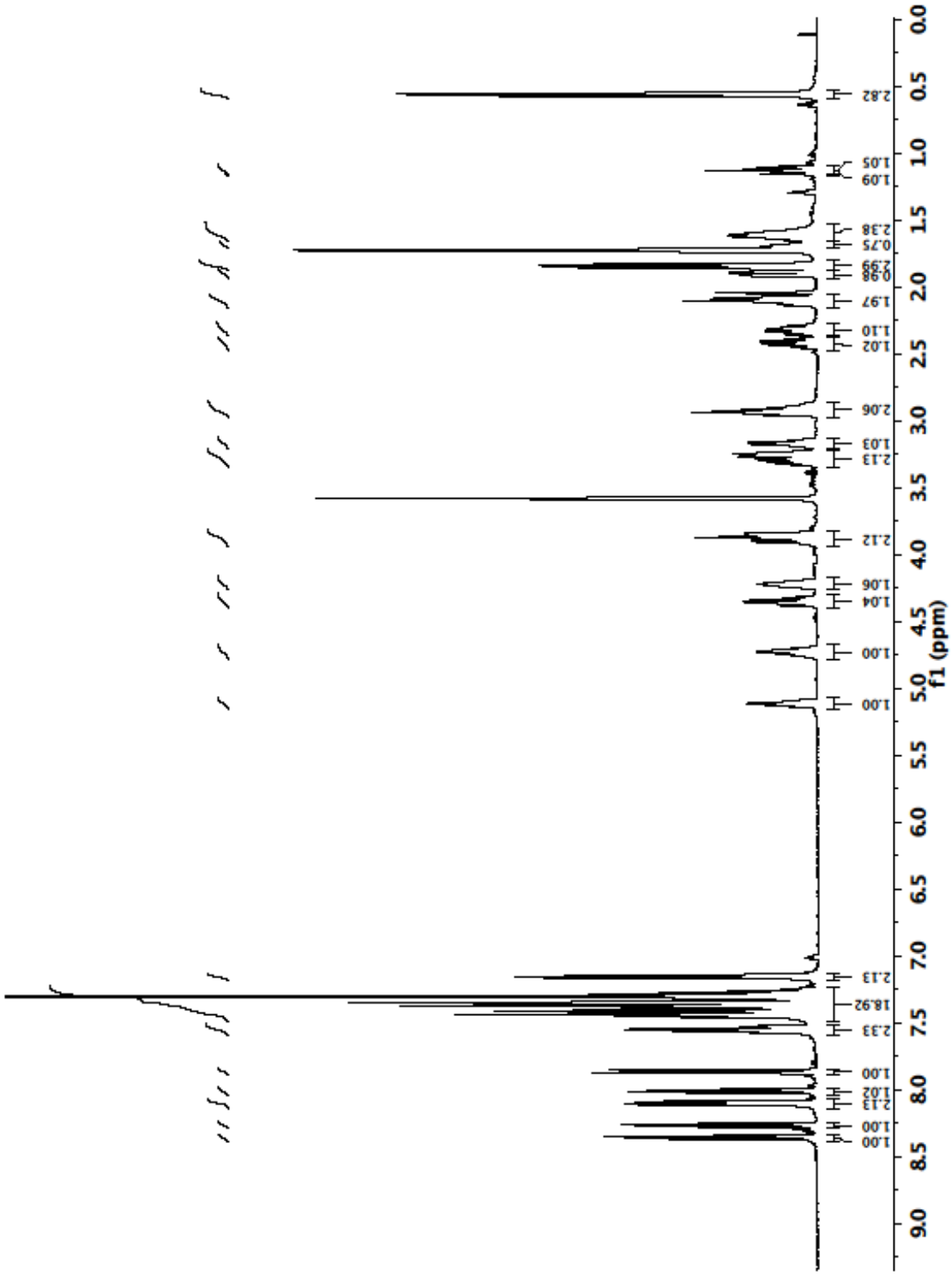
^{1}H-NMR spectrum of **2a**



gCOSY of **2a**


5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
f1 (ppm)

^{1}H-NMR of **2b**


f1 (ppm)
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1.5
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2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
2.82
1.09
1.05
0.75
2.38
0.98
2.99
1.97
1.02
1.10
2.06
1.03
2.13
2.12
1.04
1.06
1.00
1.00
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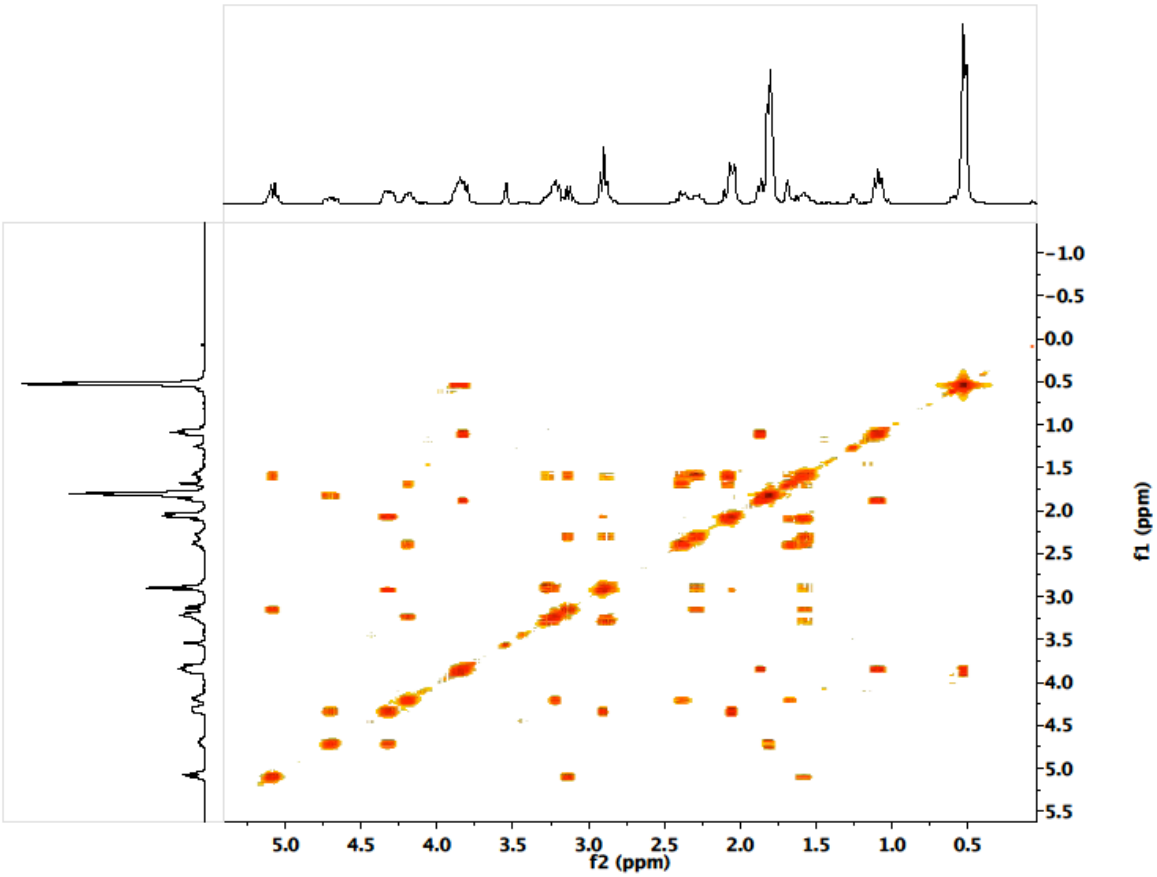
2.33
1.00
1.02
2.13
1.00
1.00

gCOSY of **2a**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-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
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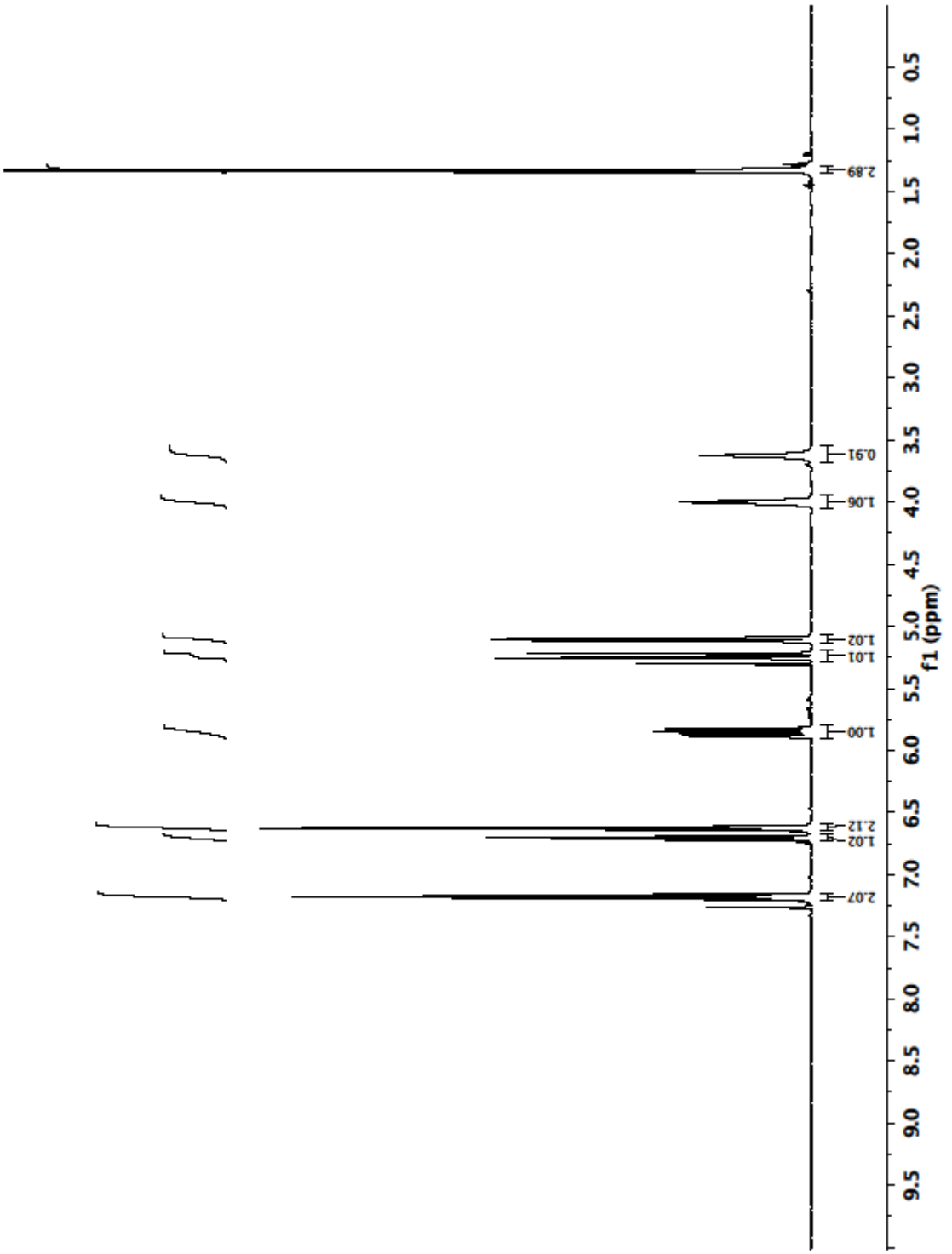
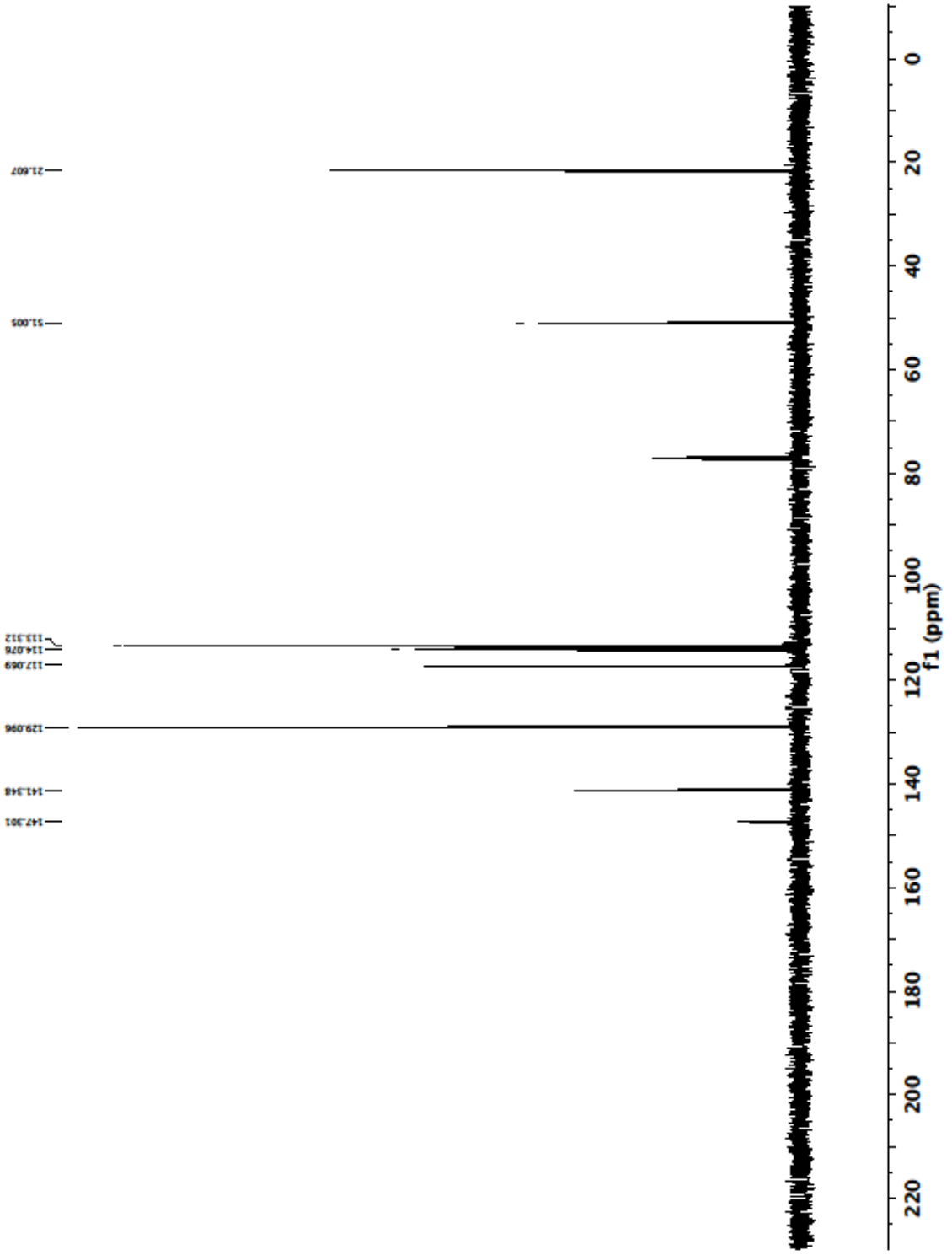
5.0
5.5
f1 (ppm)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

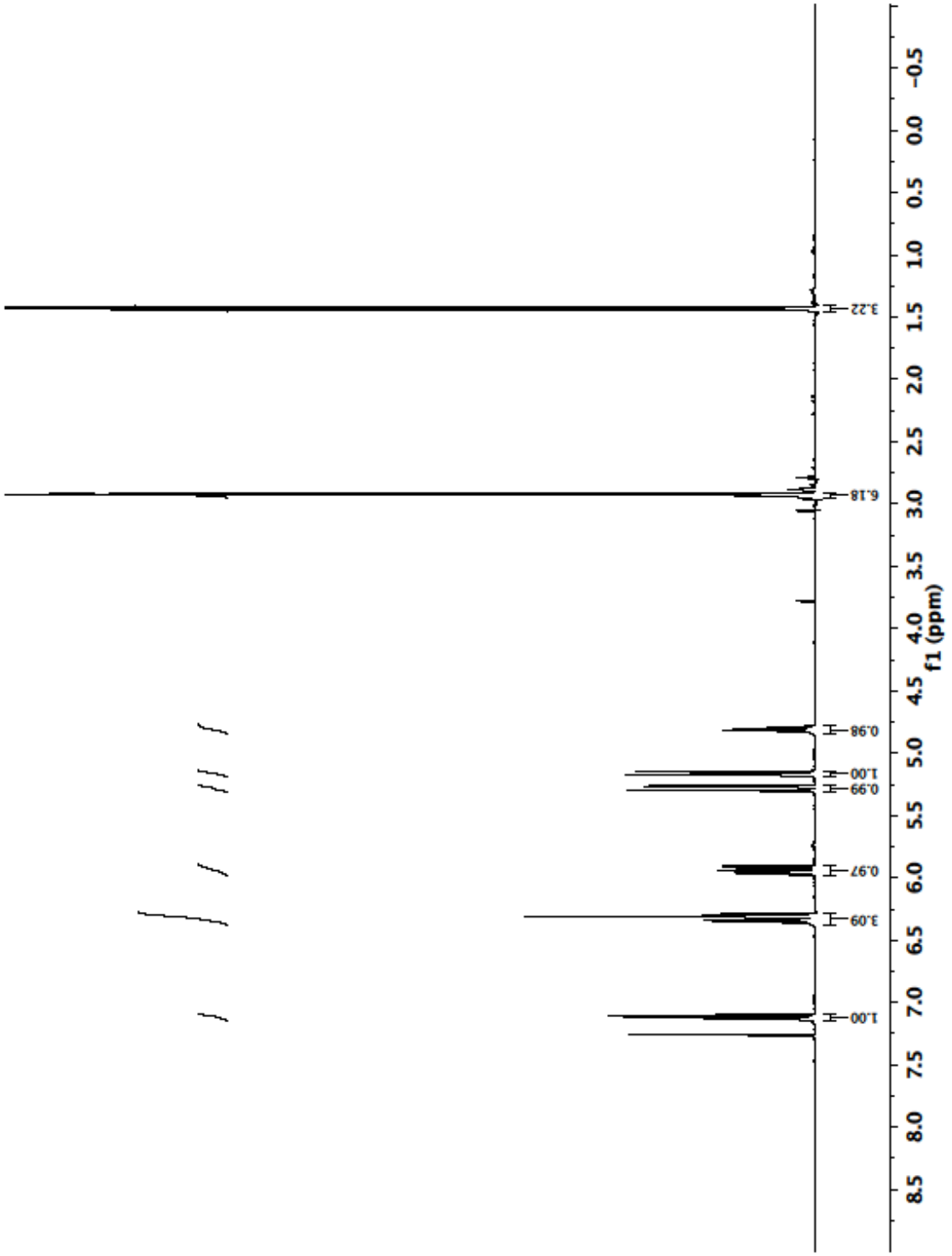
***N*-(but-3-en-2-yl)aniline**
^{1}H-NMR



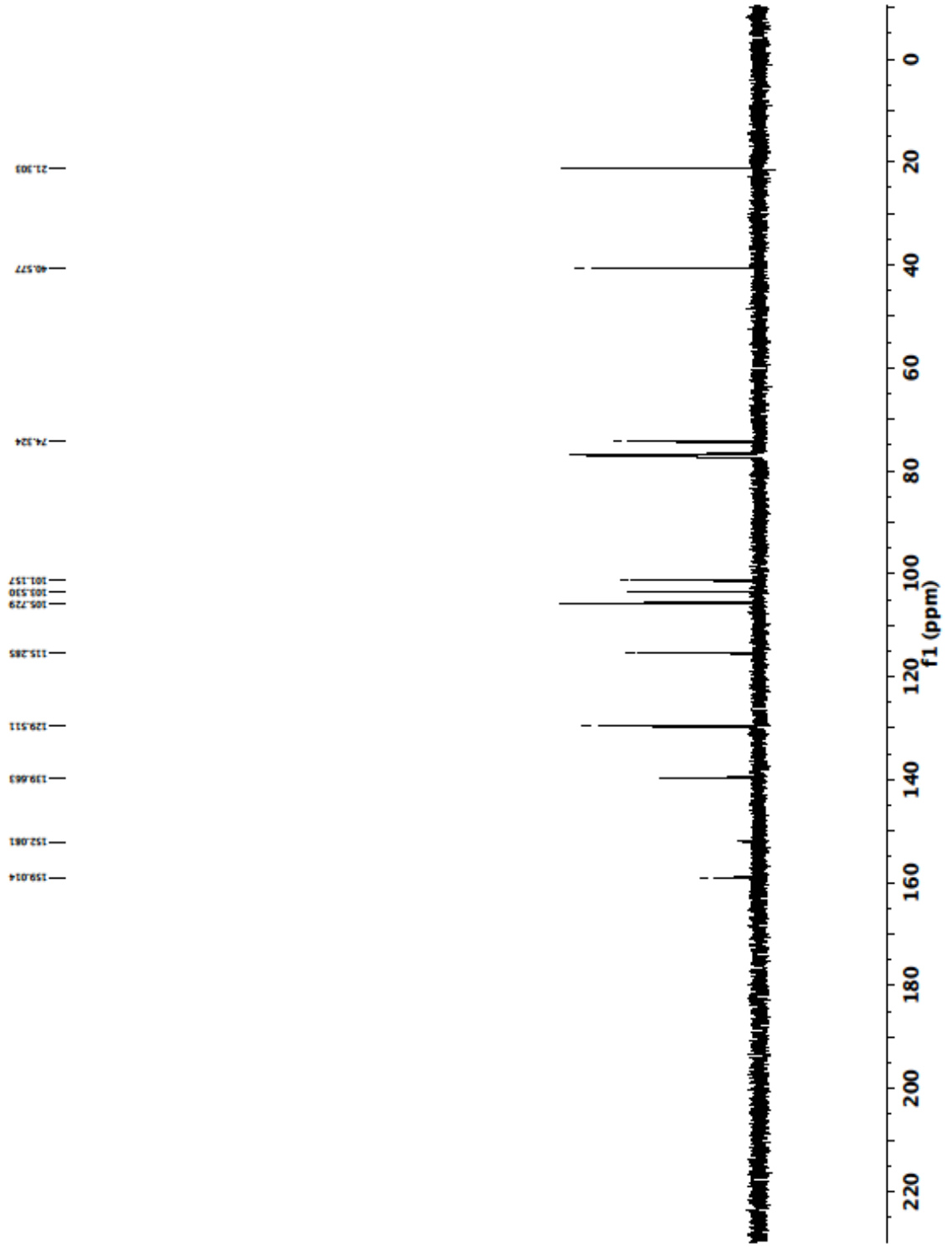
^{13}C-NMR


21.607
51.005
113.312
114.076
117.069
129.096
141.348
147.301
0
20
40
60
80
100
120
140
160
180
200
220
f1 (ppm)

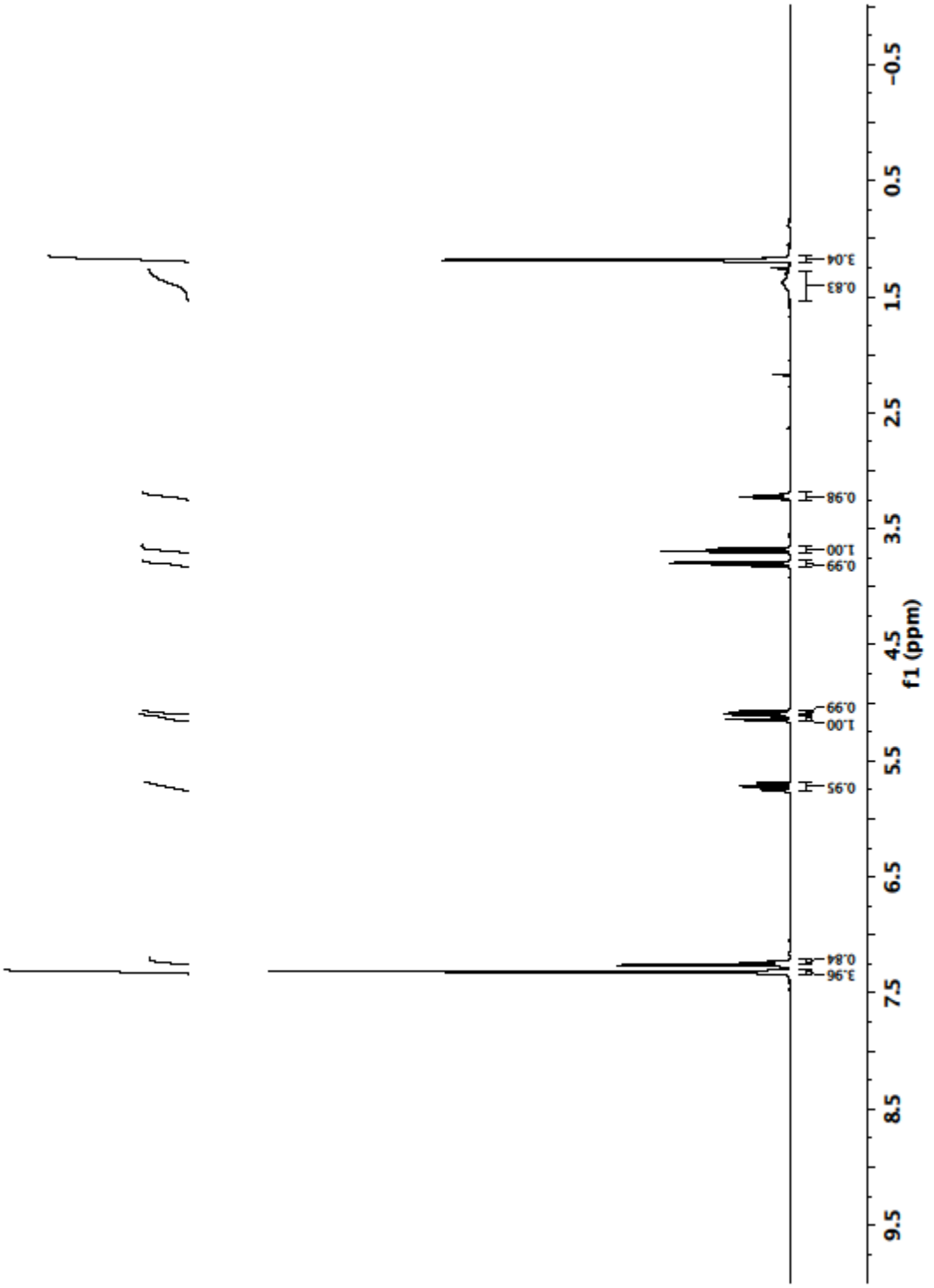
3-(but-3-en-2-yloxy)-N,N-dimethylaniline
^{1}H-NMR



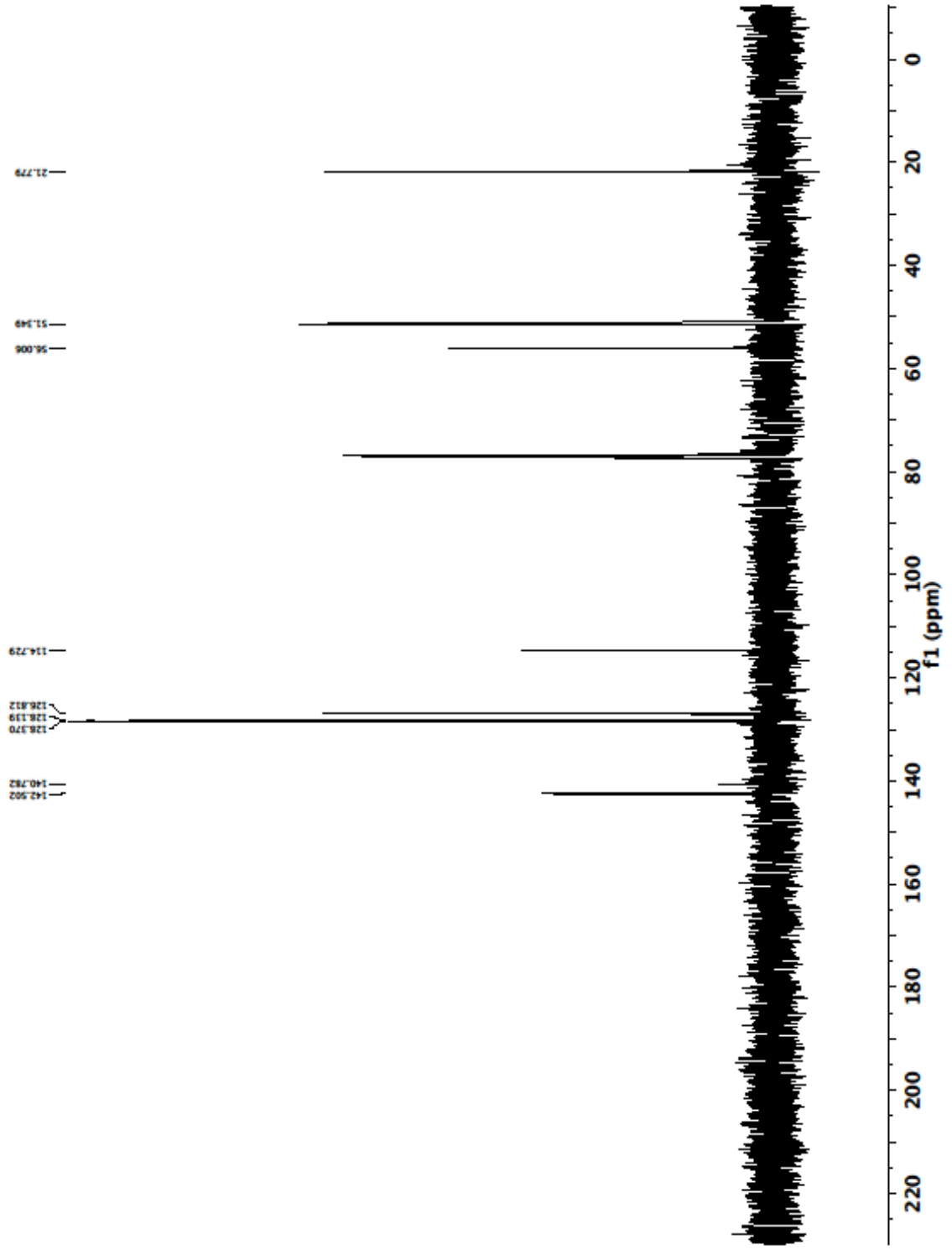
^{13}C-NMR


21.303
40.577
74.324
101.157
103.530
105.729
115.285
129.511
139.663
152.061
159.014
0
20
40
60
80
100
120
140
160
180
200
220
f1 (ppm)

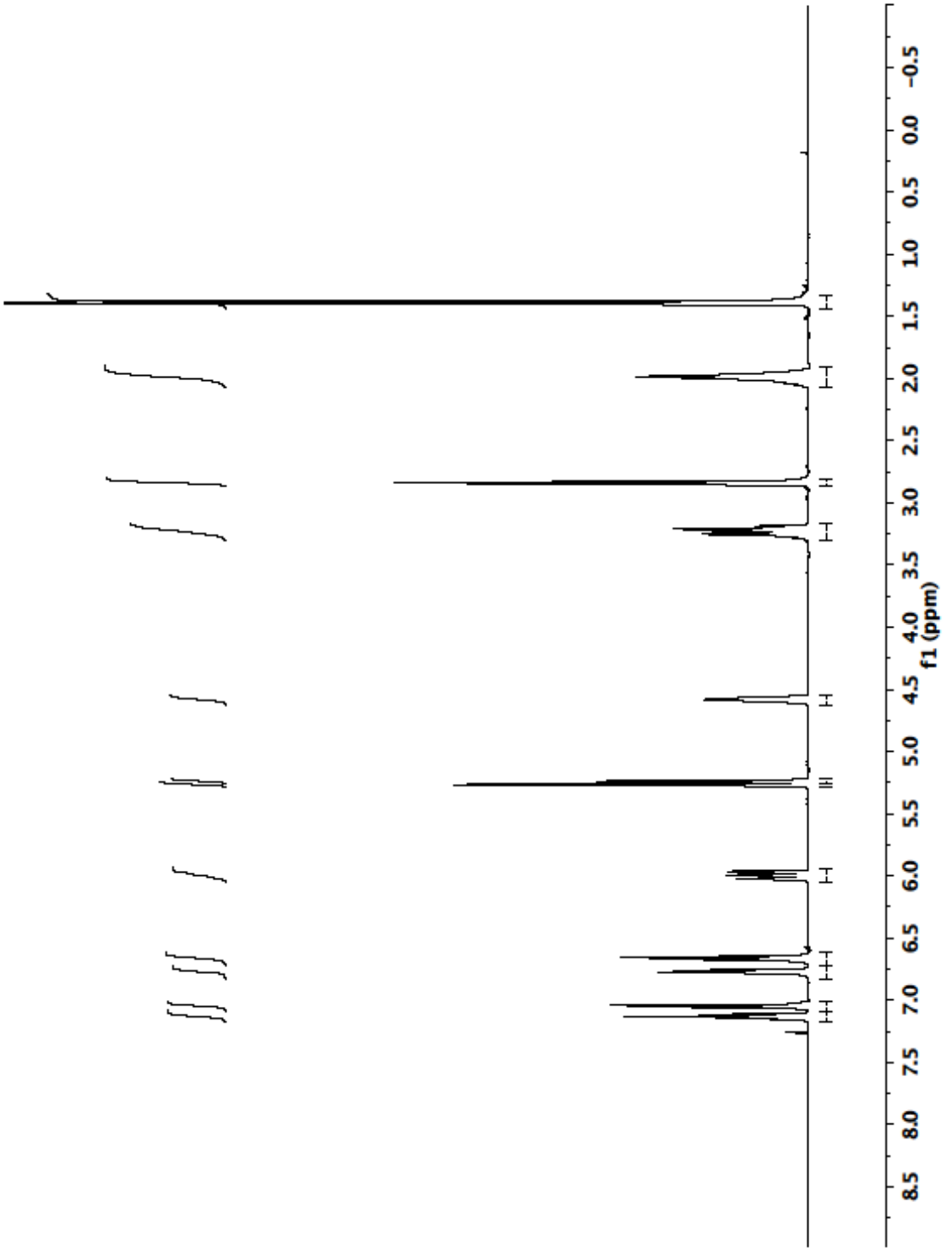
N-benzylbut-3-en-2-amine
^{1}H-NMR



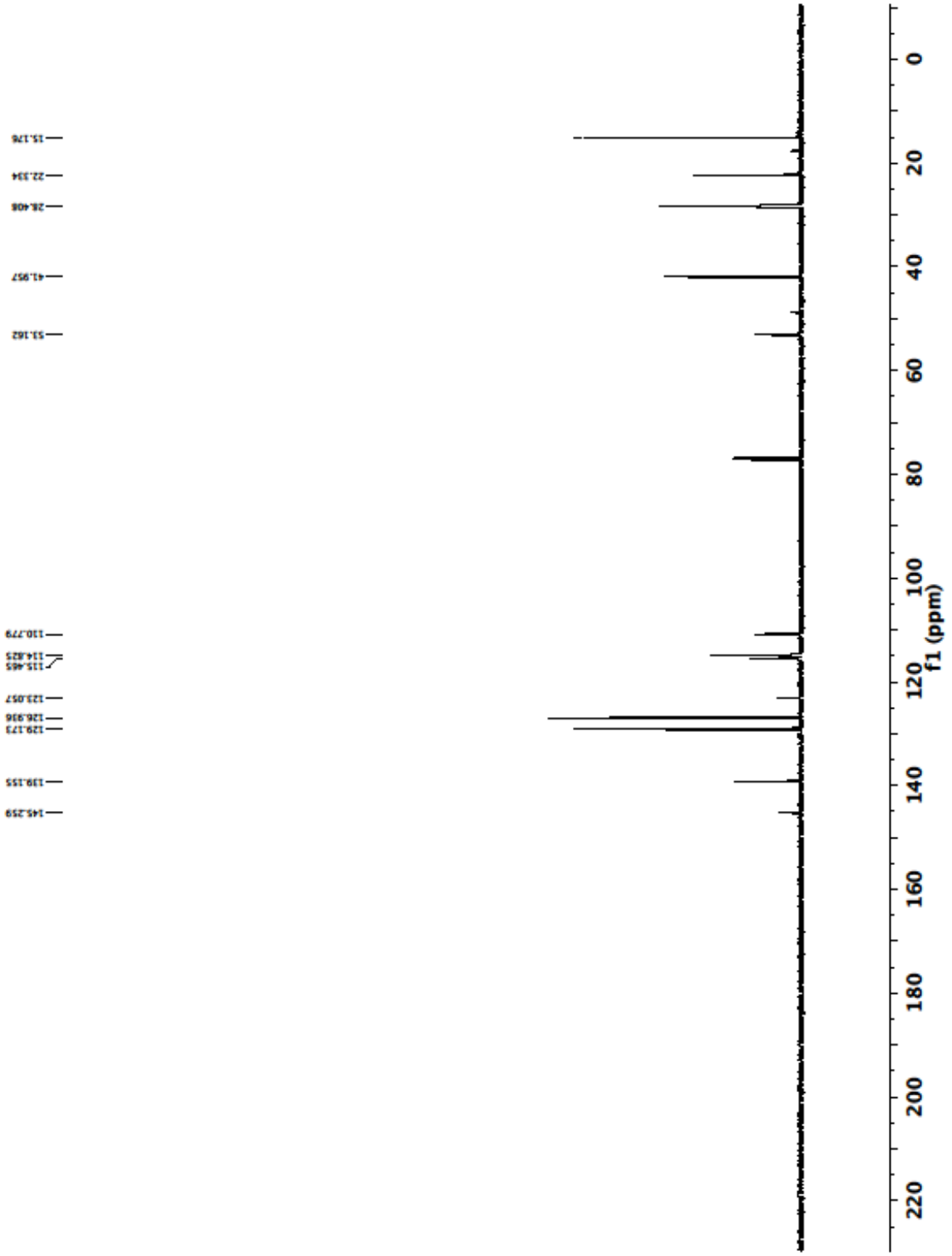
^{13}C-NMR


21.779
51.349
56.006
114.729
126.812
126.139
126.370
140.782
142.502
0
20
40
60
80
100
120
140
160
180
200
220
f1 (ppm)

1-(but-3-en-2-yl)-1,2,3,4-tetrahydroquinoline
^{1}H-NMR



^{13}C-NMR


15.176
22.334
28.408
41.957
53.162
110.779
114.825
115.465
123.057
126.936
129.173
139.155
145.259
0
20
40
60
80
100
120
140
160
180
200
220
f1 (ppm)

Bibliography

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