Enantioselective Iridium-Catalyzed Allylic Alkylation Reactions of Masked Acyl Cyanide Equivalents

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Table of Contents

Materials and Methods

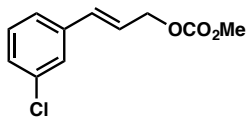
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Commercially obtained reagents were used as received. Chemicals were purchased from Sigma Aldrich/Strem/Alfa Aesar/Oakwood Chemicals and used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Glove box manipulations were performed under a nitrogen atmosphere. Thin-layer chromatography (TLC) and preparatory TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, $KMnO_4$ or *p*-anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak IC column (4.6 mm x 25 cm) or a Chiralpak AD column (4.6 mm x 25 cm), both obtained from Daicel Chemical Industries,

Ltd. with visualization at 210 nm. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing a Chiralpak IC-3 column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 210 nm. ^{1}H NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual $CDCl_3$ (δ 77.16 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). Some reported spectra include minor solvent impurities of benzene (δ 7.36 ppm), water (δ 1.56 ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments. IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm pathlength cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent).

List of Abbreviations: ee – enantiomeric excess, HPLC – high-performance liquid chromatography, SFC – supercritical fluid chromatography, TLC – thin-layer chromatography, EtOAc – ethyl acetate, THF – tetrahydrofuran, MeOH – methanol, Et_2O – diethyl ether, TBD – 1,5,7-triazabicyclo[4.4.0]dec-5-ene, cod – *cis,cis*-1,5-cyclooctadiene, DIBAL – diisobutylaluminium hydride, MAC – masked acyl cyanide

Preparation of Known Compounds: Previously reported methods were used to prepare ligand (*S,S*$_a$)-**3**[1] as well as starting materials **1a–c**[2], **2**[3], **5a**[3], **5b**[3], **5c**[4], **5d**[5], **5h**[1b], **5i**[5], **5j**[6], **5k**[7], **5l**[4].

General Procedure for the Synthesis of Electrophiles

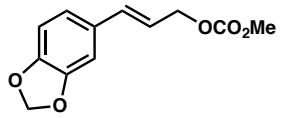


(*E*)-3-(3-Chlorophenyl)allyl methyl carbonate (5e). To a solution of methyl (*E*)-3-(3-chlorophenl)prop-2-enoate[8] (1.4 g, 7.0 mmol, 1 equiv) in Et_2O (28 mL) at –78 °C was added DIBAL (3.0 g, 21 mmol, 3 equiv) dropwise. The resulting reaction mixture was stirred at –78 °C for 2.5 h, whereupon the reaction was quenched with a saturated aqueous Rochelle's salt solution (10 mL). The cooling bath was then removed and the reaction was stirred for 18 h at ambient temperature. The aqueous layer was extracted

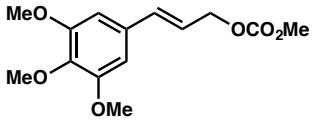
with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure.

The crude material was then dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. Pyridine (1.7 mL, 21 mmol, 3 equiv) was added followed by methyl chloroformate (0.81 mL, 11 mmol, 1.5 equiv) dropwise. The resulting solution was allowed to warm to ambient temperature and stirred for 18 h. The reaction was quenched with the addition of 1 M HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (5% EtOAc/hexanes) to give carbonate **5e** as a colorless oil (1.0 g, 63% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 1H), 7.30 – 7.23 (m, 3H), 6.69 – 6.60 (m, 1H), 6.32 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.81 (dd, *J* = 6.3, 1.4 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 138.0, 134.7, 133.2, 130.0, 128.3, 126.7, 125.0, 124.2, 68.1, 55.1; IR (Neat Film, NaCl) 3010, 2956, 2856, 1748, 1594, 1567, 1442, 1377, 1261, 1091, 1078, 962, 791, 777, 682 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{11}H_{11}ClO_3$ $[M]^+$: 226.0397, found 226.0398.

Spectroscopic Data for the Synthesis of Electrophiles



(*E*)-3-(Benzo[*d*][1,3]dioxol-5-yl)allyl methyl carbonate (5f). Carbonate **5f** was prepared from methyl (*2E*)-3-(1,3-benzodioxol-5-yl)acrylate[9] according to the general procedure and isolated by silica gel flash column chromatography (5% EtOAc/hexanes) as a colorless solid (0.79 g, 48% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 1.6 Hz, 1H), 6.83 (ddd, *J* = 7.9, 1.6, 0.5 Hz, 1H), 6.79 – 6.73 (m, 1H), 6.60 (dt, *J* = 15.7, 1.3 Hz, 1H), 6.12 (dt, *J* = 15.7, 6.6 Hz, 1H), 5.96 (s, 2H), 4.76 (dd, *J* = 6.6, 1.3 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 148.2, 147.9, 134.9, 130.6, 121.8, 120.7, 108.4, 106.0, 101.3, 68.7, 55.0; IR (Neat Film, NaCl) 3003, 2956, 2895, 2781, 1747, 1504, 1491, 1446, 1384, 1355, 1252, 1194, 1126, 1103, 1039, 933, 863, 791 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{12}O_5$ $[M]^+$: 236.0685, found 236.0674.



(*E*)-Methyl (3-(3,4,5-trimethoxyphenyl)allyl) carbonate (5g). Carbonate **5g** was prepared from methyl 3,4,5-trimethoxycinnamate[10] according to the general procedure and isolated by silica gel flash column chromatography (5% EtOAc/hexanes) as a colorless oil (1.2 g, 65% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 – 6.56 (m, 3H), 6.21 (dt, *J* = 15.8, 6.5 Hz, 1H), 4.78 (dd, *J* = 6.5, 1.3 Hz, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 3.81

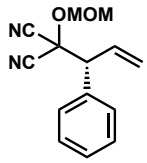
(s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 153.4, 138.4, 135.0, 131.8, 122.0, 103.9, 68.5, 61.1, 56.2, 55.0; IR (Neat Film, NaCl) 2999, 2956, 2840, 1748, 1583, 1508, 1452, 1420, 1339, 1265, 1128, 1010, 941, 850, 792 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{18}O_6$ $[M]^+$: 282.1103, found 282.1114.

General Procedure for Optimization Reactions (Table 1)

In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added $[Ir(cod)Cl]_2$ (1.3 mg, 0.0020 mmol, 2 mol %), ligand **3** (1.8 mg, 0.0040 mmol, 4 mol %), TBD (1.4 mg, 0.010 mmol, 10 mol%), and THF (0.5 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with LiBr (17 mg, 0.20 mmol, 200 mol %), MAC nucleophile **1** (0.20 mmol), and THF (0.25 mL). The pre-formed catalyst solution (vial A) was then transferred to vial B followed by 0.25 mL of a solution of cinnamyl carbonate **2** (0.4 M in THF). The vial was sealed and stirred at the specified temperature. After 18 or 48 h, the vial was removed from the glove box and filtered through a pad of silica, rinsing with EtOAc. The crude mixture was concentrated and 1,2,4,5-tetrachloro-3-nitrobenzene (0.10 mmol in 0.5 mL $CDCl_3$) was added. The NMR yield (measured in reference to 1,2,4,5-tetrachloro-3-nitrobenzene δ 7.74 ppm (s, 1H)) was determined by ^{1}H NMR analysis of the crude mixture. The residue was purified by preparatory TLC (15% EtOAc/hexanes) to afford product **4**, which was analyzed by chiral HPLC (1% IPA, 1.0 mL/min, Chiralpak IC column, λ = 210 nm).

General Procedure for the Ir-Catalyzed Allylic Alkylation

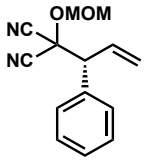
Please note that the absolute configuration of product **4c** was assigned by conversion to (*R*)-2-phenylbutanoic acid.[11] All other products (**6a–l**) were assigned by analogy. For respective HPLC and SFC conditions, please refer to Table S1.



(*R*)-2-(Methoxymethoxy)-2-(1-phenylallyl)malononitrile (4c). In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added $[Ir(cod)Cl]_2$ (2.7 mg, 0.0040 mmol, 2 mol %), ligand **3** (3.7 mg, 0.0080 mmol, 4 mol %), TBD (2.8 mg, 0.020 mmol, 10 mol %), and THF (1 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with LiBr (35 mg, 0.40 mmol, 200 mol %), MAC nucleophile **1c** (50 mg, 0.40 mmol, 200 mol %), and THF (0.5 mL). The pre-formed catalyst solution (vial A) was then transferred to vial B followed by a solution of cinnamyl carbonate **2** (38 mg, 0.20 mmol, 100 mol %) in THF (0.5 mL). The vial was sealed and stirred at 60 °C. After 18 h, the vial was removed from the glove box and filtered through a pad of silica, rinsing with EtOAc. The crude mixture was concentrated and the resulting residue was purified by silica gel flash column chromatography (10%

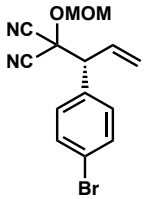
EtOAc/hexanes) to give the product **4c** as a colorless oil (41 mg, 85% yield): 95% ee; $[\alpha]_D^{25}$ –41.3 (*c* 2.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.32 (m, 5H), 6.29 (ddd, *J* = 16.9, 10.3, 8.6 Hz, 1H), 5.53 – 5.38 (m, 2H), 5.06 – 4.94 (m, 2H), 3.97 – 3.91 (m, 1H), 3.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4, 131.5, 129.6, 129.1, 128.9, 122.7, 112.7, 112.7, 96.5, 69.9, 58.4, 57.4; IR (Neat Film, NaCl) 3065, 3033, 2961, 2904, 2851, 2244, 1750, 1496, 1455, 1420, 1267, 1217, 1164, 1109, 1053, 1033, 967, 940, 791, 732, 700 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{15}N_2O_2$ $[M+H]^+$: 243.1131, found 243.1134; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 12.831, minor = 17.466.

Procedure for the Preparatory Scale Reaction



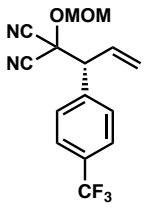
(*R*)-2-(Methoxymethoxy)-2-(1-phenylallyl)malononitrile (4c). In a nitrogen-filled glove box, a solution of $[Ir(cod)Cl]_2$ (106 mg, 0.16 mmol, 2 mol %), ligand **3** (145 mg, 0.32 mmol, 4 mol %), TBD (110 mg, 0.79 mmol, 10 mol %) in THF (20 mL) was stirred at 25 °C. After 10 minutes, the catalyst mixture was added to a mixture of LiBr (0.69 g, 7.9 mmol, 200 mol %), MAC nucleophile **1c** (1 g, 7.9 mmol, 200 mol %), and THF (20 mL) followed by cinnamyl carbonate **2** (0.76 g, 4.0 mmol, 100 mol %). The flask was removed from the glove box and stirred at 60 °C. After 18 h, the crude reaction mixture was concentrated and the resulting residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to give the product **4c** as a colorless oil (0.82 g, 86% yield): 95% ee, spectroscopic data vide supra.

Spectroscopic Data for the Ir-Catalyzed Allylic Alkylation Products

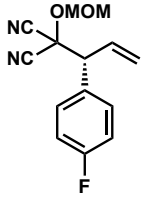


(*R*)-2-(1-(4-Bromophenyl)allyl)-2-(methoxymethoxy)malononitrile (6a). Product **6a** was prepared according to the general procedure and isolated by silica gel flash column chromatography (10% EtOAc/hexanes) to give a colorless oil (60 mg, 94% yield): 96% ee; $[\alpha]_D^{25}$ –44.3 (*c* 3.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 2H), 7.32 – 7.28 (m, 2H), 6.23 (ddd, *J* = 16.9, 10.3, 8.6 Hz, 1H), 5.55 – 5.38 (m, 2H), 5.05 – 4.96 (m, 2H), 3.92 (d, *J* = 8.6 Hz, 1H), 3.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.4, 132.1, 131.3, 130.9, 123.4, 123.2, 112.6, 112.5, 96.6, 69.5, 57.8, 57.5; IR (Neat Film, NaCl) 3013, 2934, 2242, 1488, 1404, 1274, 1216, 1163, 1108, 1034, 1010, 967, 939, 826,

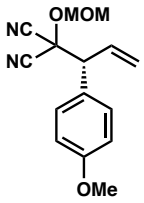
762 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{13}BrO_2N_2$ $[M]^+$: 320.0160, found 320.0155; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 15.852, minor = 11.623.



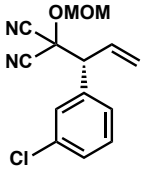
(*R*)-2-(Methoxymethoxy)-2-(1-(4-(trifluoromethyl)phenyl)allyl)malononitrile (6b). Product **6b** was prepared according to the general procedure and isolated by preparatory TLC (5% EtOAc/hexanes, plate eluted three times) to give a pale yellow oil (36 mg, 58% yield): 96% ee; $[\alpha]_D^{25}$ –25.2 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 6.27 (ddd, *J* = 16.9, 10.3, 8.7 Hz, 1H), 5.57 – 5.41 (m, 2H), 5.09 – 4.96 (m, 2H), 4.02 (d, *J* = 8.7 Hz, 1H), 3.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 131.5, 131.1, 130.6, 130.2, 125.9 (q, *J* = 3.9 Hz), 125.3, 123.6, 122.6, 112.5, 112.4, 96.7, 69.4, 58.0, 57.6; IR (Neat Film, NaCl) 2962, 2906, 2835, 2245, 1751, 1618, 1445, 1417, 1445, 1417, 1327, 1269, 1218, 1166, 1127, 1069, 943, 840, 792 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{15}H_{12}F_3N_2O_2$ $[(M+H)–H_2]^–$: 309.0851, found 309.0849; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 10.681, minor = 8.223.



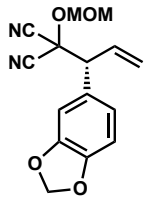
(*R*)-2-(1-(4-Fluorophenyl)allyl)-2-(methoxymethoxy)malononitrile (6c). Product **6c** was prepared according to the general procedure and isolated by preparatory TLC (9% EtOAc/hexanes, plate eluted two times) to give a colorless oil (37 mg, 69% yield): 96% ee; $[\alpha]_D^{25}$ –35.9 (*c* 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.32 (m, 2H), 7.15 – 7.02 (m, 2H), 6.25 (ddd, *J* = 16.9, 10.3, 8.5 Hz, 1H), 5.57 – 5.35 (m, 2H), 5.11 – 4.94 (m, 2H), 3.95 (d, *J* = 8.5 Hz, 1H), 3.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 161.9, 131.5, 131.4, 131.2, 130.2 (d, *J* = 3.5 Hz), 122.9, 116.1, 115.9, 112.7, 112.6, 96.6, 69.8 (d, *J* = 1.6 Hz), 57.5 (d, *J* = 9.2 Hz); IR (Neat Film, NaCl) 3085, 2964, 2847, 2242, 1606, 1511, 1415, 1281, 1230, 1164, 1108, 1053, 968, 940, 798, 766 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{14}H_{14}N_2O_2F$ $[M+H]^+$: 261.1039, found 261.1033; HPLC conditions: 1% IPA, 1 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 11.712, minor = 8.971.



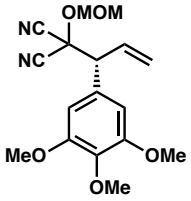
(*R*)-2-(Methoxymethoxy)-2-(1-(4-methoxyphenyl)allyl)malononitrile (6d). Product **6d** was prepared according to the general procedure and isolated by silica gel flash column chromatography (5–10% EtOAc/hexanes) to give a colorless oil (52 mg, 95% yield): 95% ee; $[\alpha]_D^{25}$ –51.8 (*c* 2.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.26 (ddd, *J* = 16.9, 10.3, 8.5 Hz, 1H), 5.61 – 5.34 (m, 2H), 5.08 – 4.94 (m, 2H), 3.91 (d, *J* = 8.5 Hz, 1H), 3.82 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 131.7, 130.8, 126.3, 122.3, 114.3, 112.82, 112.78, 96.5, 70.1, 57.6, 57.4, 55.4; IR (Neat Film, NaCl) 3005, 2962, 2939, 2905, 2838, 2244, 2052, 1890, 1610, 1584, 15112, 1459, 1305, 1252, 1216, 1182, 1162, 1107, 1031, 937, 834, 783, 765, 625 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{17}N_2O_3$ $[M+H]^+$: 273.1239, found 273.1227; SFC conditions: 3% IPA, 3.5 mL/min, Chiralpak IC-3 column, λ = 210 nm, t_R (min): major = 6.831, minor = 5.267.



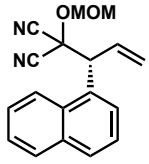
(*R*)-2-(1-(3-Chlorophenyl)allyl)-2-(methoxymethoxy)malononitrile (6e). Product **6e** was prepared according to the general procedure and isolated by silica gel flash column chromatography (10% EtOAc/hexanes) to give a colorless oil (47 mg, 85% yield): 92% ee; $[\alpha]_D^{25}$ –38.5 (*c* 2.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.28 (m, 4H), 6.23 (ddd, *J* = 16.9, 10.3, 8.7 Hz, 1H), 5.57 – 5.40 (m, 2H), 5.08 – 4.97 (m, 2H), 3.92 (d, *J* = 8.7 Hz, 1H), 3.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 134.7, 130.8, 130.2, 129.9, 129.3, 127.8, 123.3, 112.6, 112.4, 96.6, 69.5, 57.9, 57.5; IR (Neat Film, NaCl) 3069, 2962, 2849, 2832, 2244, 1751, 1596, 1576, 1478, 1436, 1418, 1277, 1217, 1164, 1109, 111055, 1032, 967, 940, 884, 797, 760, 730, 713, 690 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{14}H_{14}N_2O_2Cl$ $[M+H]^+$: 277.0744, found 277.0715; SFC conditions: 3% IPA, 3.5 mL/min, Chiralpak IC-3 column, λ = 210 nm, t_R (min): major = 3.846, minor = 3.428.



(*R*)-2-(1-(Benzo[*d*][1,3]dioxol-5-yl)allyl)-2-(methoxymethoxy)malononitrile (6f). Product **6f** was prepared according to the general procedure and isolated by silica gel flash column chromatography (5–10% EtOAc/hexanes) to give a colorless oil (51 mg, 90% yield): 96% ee; $[\alpha]_D^{25}$ –40.6 (*c* 3.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 – 6.78 (m, 3H), 6.20 (ddd, *J* = 16.9, 10.3, 8.5 Hz, 1H), 5.99 (s, 2H), 5.51 – 5.37 (m, 2H), 5.03 (d, *J* = 1.4 Hz, 2H), 3.86 (d, *J* = 8.5 Hz, 1H), 3.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 148.1, 131.5, 127.9, 123.5, 122.5, 112.7, 109.7, 108.7, 101.5, 96.6, 70.0, 58.1, 57.5; IR (Neat Film, NaCl) 3081, 2972, 2902, 2352, 1505, 1488, 1446, 1368, 1251, 1238, 1164, 1108, 1039, 967, 934, 864, 817, 800, 763 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{15}H_{15}N_2O_4$ $[M+H]^+$: 287.1032, found 287.1039; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 24.142, minor = 19.686.

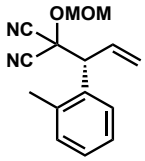


(*R*)-2-(Methoxymethoxy)-2-(1-(3,4,5-trimethoxyphenyl)allyl)malononitrile (6g). Product **6g** was prepared according to the general procedure and isolated by silica gel flash column chromatography (20% EtOAc/hexanes) to give a colorless oil (54 mg, 81% yield): 98% ee; $[\alpha]_D^{25}$ –28.2 (*c* 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 2H), 6.23 (ddd, *J* = 16.8, 10.3, 8.5 Hz, 1H), 5.55 – 5.35 (m, 2H), 5.11 – 4.94 (m, 2H), 3.87 (m, 7H), 3.85 (s, 3H), 3.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 138.5, 131.3, 129.7, 122.6, 112.8, 112.7, 106.6, 96.5, 69.9, 61.0, 58.5, 57.5, 56.3; IR (Neat Film, NaCl) 2941, 2840, 244, 1591, 1509, 1463, 1418, 1333, 1245, 1163, 1127, 1034, 1007, 950, 925, 840, 771, 719 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{21}N_2O_5$ $[M+H]^+$: 333.1450, found 333.1450; HPLC conditions: 7% IPA, 1.0 mL/min, Chiralpak AD column, λ = 210 nm, t_R (min): major = 17.062, minor = 12.809.

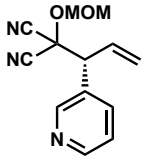


(*R*)-2-(Methoxymethoxy)-2-(1-(naphthalen-1-yl)allyl)malononitrile (6h). Product **6h** was prepared according to the general procedure and isolated by preparatory TLC (9%

Et_2O/hexanes, plate eluted two times) to give a colorless oil (24 mg, 41% yield): 92% ee; $[\alpha]_D^{25}$ –30.9 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.95 – 7.86 (m, 2H), 7.81 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.60 (ddd, *J* = 8.6, 6.8, 1.5 Hz, 1H), 7.57 – 7.49 (m, 2H), 6.38 (ddd, *J* = 16.7, 10.3, 8.2 Hz, 1H), 5.57 – 5.43 (m, 2H), 5.05 – 4.92 (m, 3H), 3.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.1, 132.2, 132.1, 130.8, 129.6, 129.3, 126.9, 126.6, 126.1, 125.3, 122.8, 122.7, 113.10, 112.72, 96.5, 70.1, 57.5, 51.6; IR (Neat Film, NaCl) 3051, 2960, 2926, 2851, 2244, 1708, 1398, 1215, 1162, 1106, 1030, 960, 925, 783 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{17}N_2O_2$ $[M+H]^+$: 293.1290, found 293.1263; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 15.134, minor = 10.197.

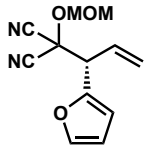


(*R*)-2-(Methoxymethoxy)-2-(1-(*o*-tolyl)allyl)malononitrile (6i). Product **6i** was prepared according to the general procedure and isolated by silica gel flash column chromatography (5% EtOAc/hexanes) to give a colorless oil (33 mg, 65% yield): 89% ee; $[\alpha]_D^{25}$ –68.7 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.48 (m, 1H), 7.28 – 7.19 (m, 3H), 6.22 (ddd, *J* = 16.9, 10.2, 8.2 Hz, 1H), 5.50 – 5.35 (m, 2H), 5.06 – 4.98 (m, 2H), 4.34 (dd, *J* = 8.2, 1.0 Hz, 1H), 3.45 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 133.1, 132.0, 131.2, 128.6, 128.1, 126.6, 122.5, 113.0, 112.8, 96.5, 69.8, 57.5, 53.0, 20.3; IR (Neat Film, NaCl) 3023, 2958, 2360, 2243, 1748, 1640, 1603, 1489, 1445, 1382, 1264, 1164, 1109, 1034, 943, 846, 792, 748, 654 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{17}N_2O_2$ $[M+H]^+$: 257.1290, found 257.1280; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 16.719, minor = 9.761.

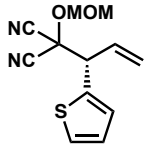


(*R*)-2-(Methoxymethoxy)-2-(1-(pyridin-3-yl)allyl)malononitrile (6j). Product **6j** was prepared according to the general procedure and isolated by silica gel flash column chromatography (25% acetone/hexanes) to give a pale yellow oil (36 mg, 74% yield): 90% ee; $[\alpha]_D^{25}$ –30.8 (*c* 2.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, *J* = 4.7, 1.7 Hz, 2H), 7.78 (dddd, *J* = 8.0, 2.3, 1.6, 0.5 Hz, 1H), 7.35 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 6.27 (ddd, *J* = 16.9, 10.3, 8.7 Hz, 1H), 5.63 – 5.39 (m, 2H), 5.06 – 4.97 (m, 2H), 4.00 (d, *J* = 8.7 Hz, 1H), 3.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1, 150.4, 136.7, 130.4, 130.3, 123.8, 123.7, 112.5, 112.3, 96.7, 69.4, 57.5, 56.0; IR (Neat Film, NaCl) 2963, 2943, 2905, 2833, 2244, 1751, 1718, 1590, 1577, 1480, 1419, 1430, 1271, 1217, 1164, 1109, 2055, 1028, 970, 941, 848, 817, 756, 714 cm^{-1}; HRMS (FAB+) *m/z* calc'd for

$C_{13}H_{14}N_3O_2$ $[M+H]^+$: 244.1086, found 244.1083; HPLC conditions: 20% IPA, 1.0 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 13.161, minor = 23.457.



(*R*)-2-(1-(Furan-2-yl)allyl)-2-(methoxymethoxy)malononitrile (6k). Product **6k** was prepared according to the general procedure and isolated by silica gel flash column chromatography (10% EtOAc/hexanes) to give a colorless oil (34 mg, 73% yield): 96% ee; $[\alpha]_D^{25}$ –44.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 6.53 – 6.34 (m, 2H), 6.14 (dddd, *J* = 16.9, 10.2, 8.5, 0.8 Hz, 1H), 5.58 – 5.43 (m, 2H), 5.10 – 4.94 (m, 2H), 4.16 (d, *J* = 8.5 Hz, 1H), 3.48 (d, *J* = 0.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 143.5, 129.1, 123.5, 112.4, 112.3, 111.0, 110.4, 96.6, 68.9, 57.5, 52.4; IR (Neat Film, NaCl) 3125, 2091, 2964, 2942, 2905, 2833, 2245, 1499, 1444, 14222, 1270, 1217, 1164, 1109, 1030, 922, 797, 743 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{12}H_{13}N_2O_3$ $[M+H]^+$: 233.0926, found 233.0948; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 13.297, minor = 10.761.

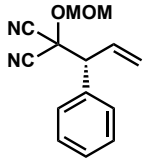
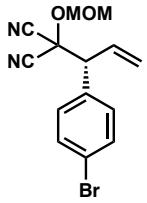
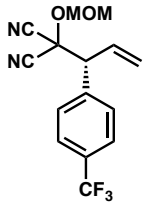
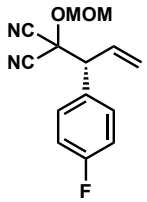
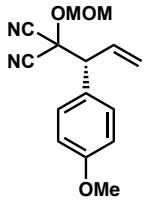
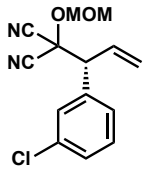


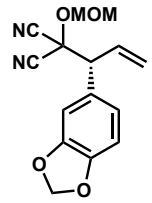
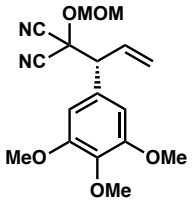
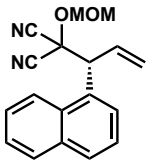
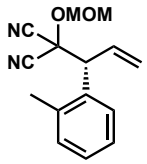
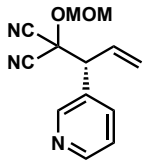
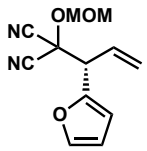
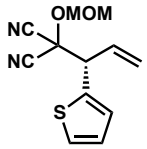
(*S*)-2-(Methoxymethoxy)-2-(1-(thiophen-2-yl)allyl)malononitrile (6l). Product **6l** was prepared according to the general procedure and isolated by silica gel flash column chromatography (10% EtOAc/hexanes) to give a colorless oil (49 mg, 98% yield): 93% ee; $[\alpha]_D^{25}$ –40.3 (*c* 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.20 (ddd, *J* = 3.6, 1.2, 0.7 Hz, 1H), 7.08 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.21 (ddd, *J* = 16.8, 10.2, 8.6 Hz, 1H), 5.59 – 5.48 (m, 2H), 5.09 (d, *J* = 1.7 Hz, 2H), 4.31 (dd, *J* = 8.6, 0.8 Hz, 1H), 3.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 131.3, 128.3, 127.1, 126.9, 123.0, 112.5, 112.4, 96.7, 69.8, 57.6, 54.0; IR (Neat Film, NaCl) 3090, 2963, 2904, 2833, 2245, 2079, 1639, 1433k 1365, 1270, 1238, 1216, 1162, 1108, 1029, 922, 856, 839, 704 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{12}H_{13}N_2O_2S$ $[M+H]^+$: 249.0698, found 249.0703; SFC conditions: 3% IPA, 3.5 mL/min, Chiralpak IC-3 column, λ = 210 nm, t_R (min): major = 5.289, minor = 4.010.

Determination of Enantiomeric Excess

Please note racemic products were synthesized using racemic **3**.

Table S1: Determination of Enantiomeric Excess

Entry	Product	Assay Conditions	Retention time of major isomer (min)	Retention time of minor isomer (min)	%ee
1		HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min	12.831	17.466	95
2		HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min	15.852	11.623	96
3		HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min	10.681	8.223	96
4		HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min	11.712	8.971	96
5		SFC Chiralpak IC-3 3% IPA isocratic, 3.5 mL/min	6.831	5.267	95
6		SFC Chiralpak IC-3 3% IPA isocratic, 3.5 mL/min	3.846	3.428	92

Entry	Product	Assay Conditions	Retention time of major isomer (min)	Retention time of minor isomer (min)	%ee
7		HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min	24.142	19.686	96
8		HPLC Chiralpak AD 7% IPA isocratic, 1 mL/min	17.062	12.809	98
9		HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min	15.134	10.197	92
10		HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min	16.719	9.761	89
11		HPLC Chiralpak IC 20% IPA isocratic, 1 mL/min	13.161	23.457	90
12		HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min	13.297	10.761	96
13		SFC Chiralpak IC-3 3% IPA isocratic, 3.5 mL/min	5.289	4.010	93

[1] (a) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Synthesis* **2009**, 2076–2082; (b) Liu, W.-B.; Zheng, C.; Zhuo, C.-X.; Dai, L.-X.; You, S.-L. *J. Am. Chem. Soc.* **2012**, *134*, 4812–4821.
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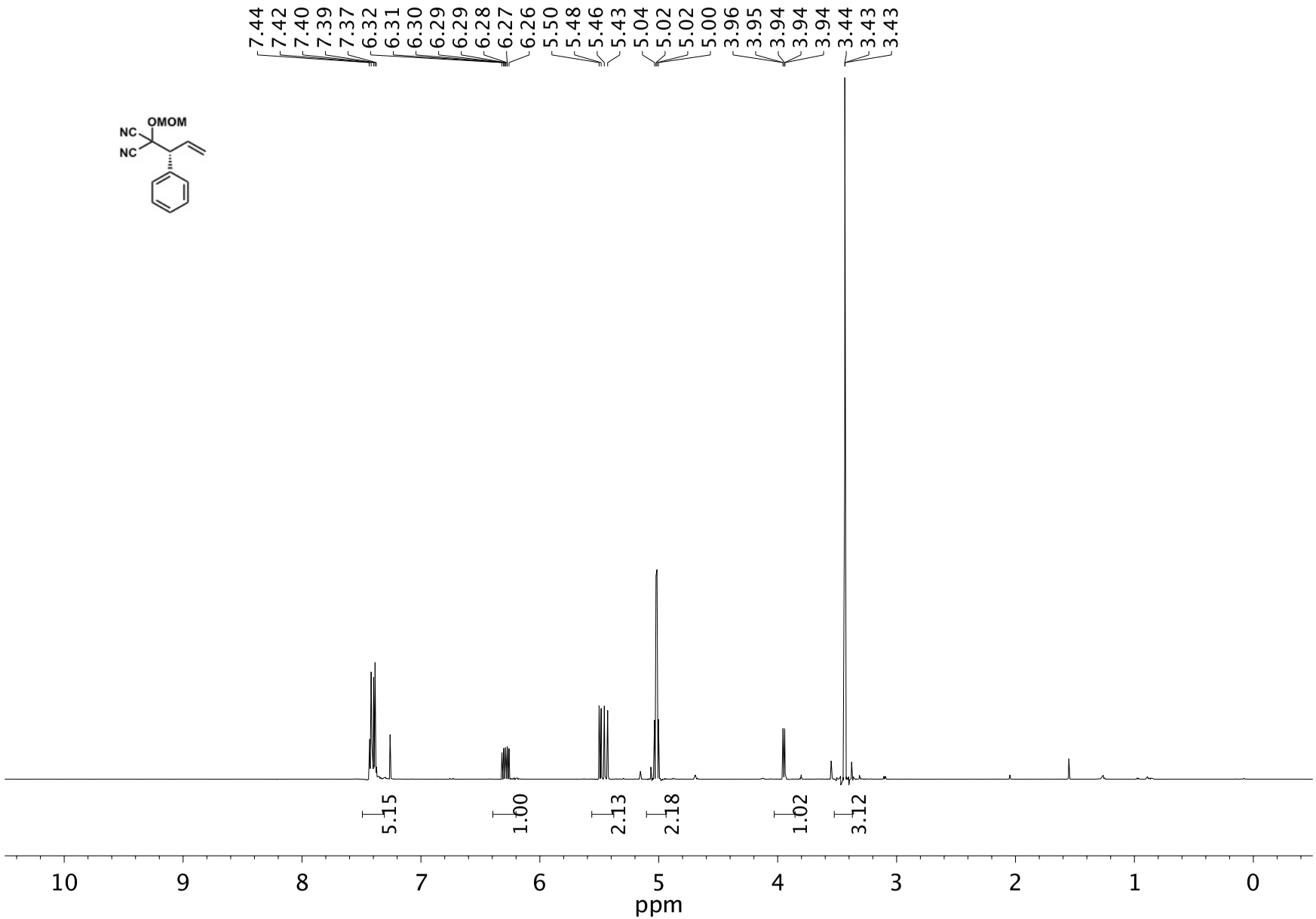
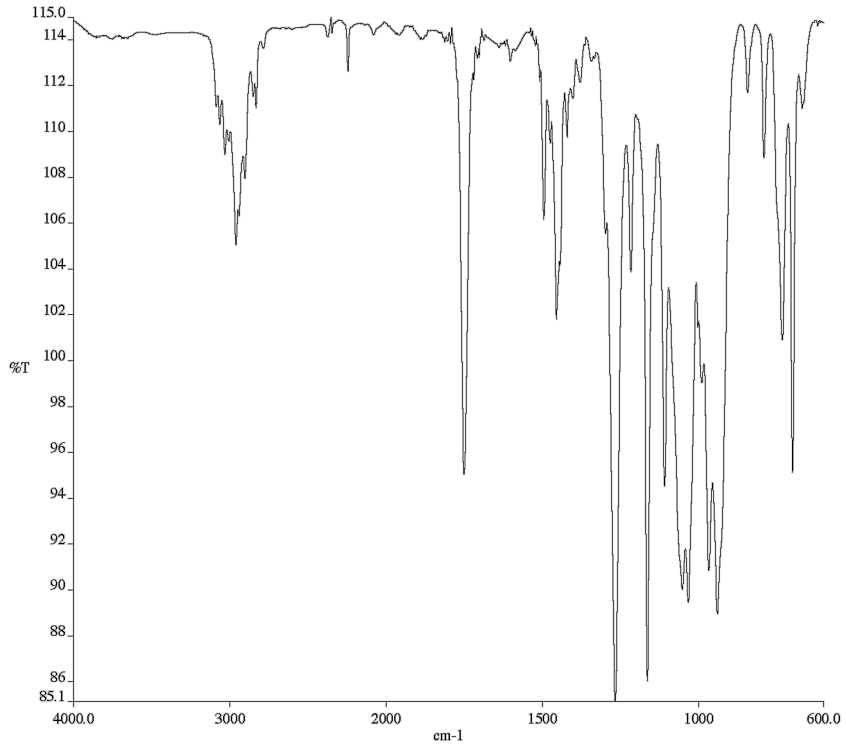
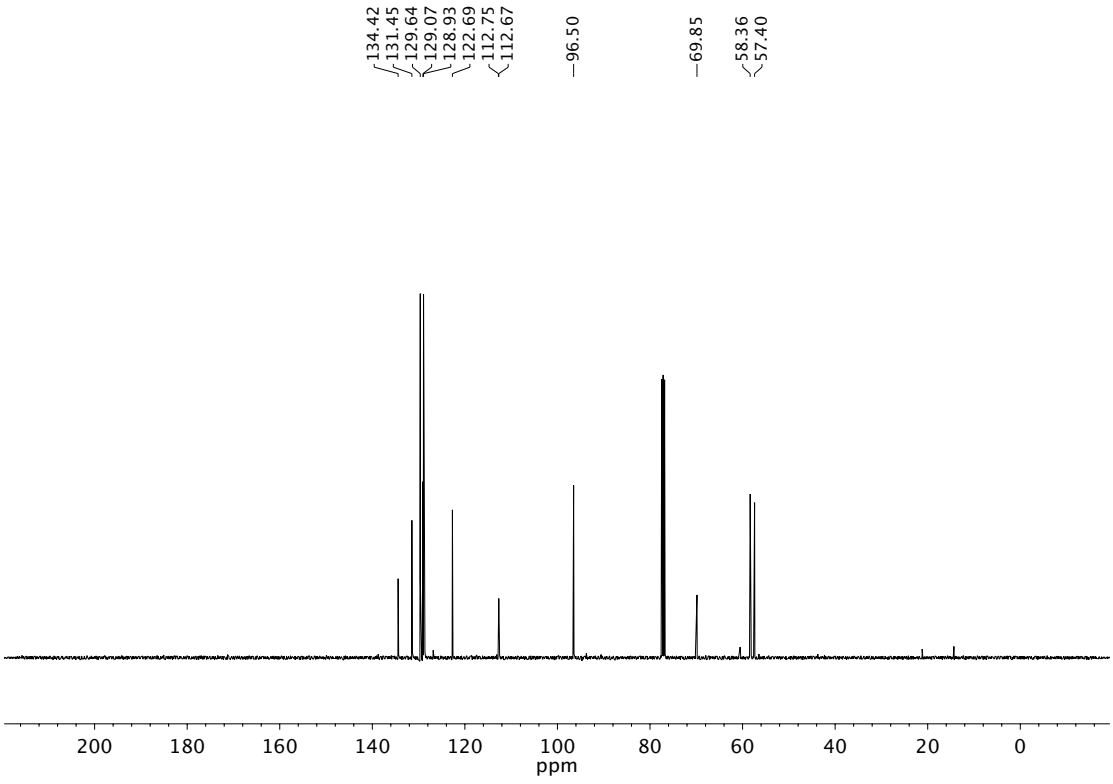
[11] Li, W.; Wang, J.; Hu, X.; Shen, K.; Wang, W.; Chu, Y.; Lin, L. Liu, X.; Feng, X. *J. Am. Chem. Soc.* **2010**, *132*, 8532–8533.



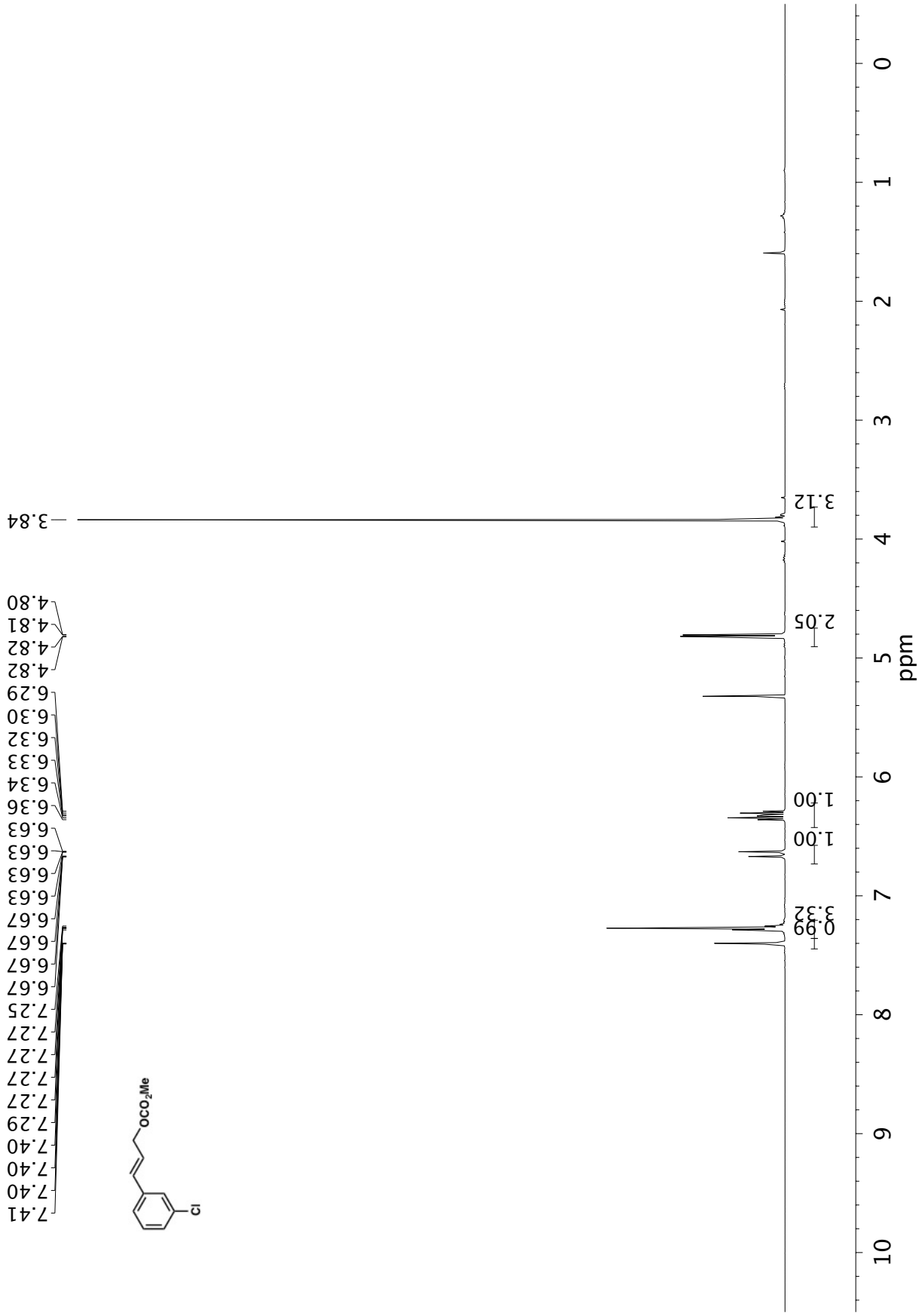
^{1}H NMR (400 MHz, $CDCl_3$) of compound **4c**.



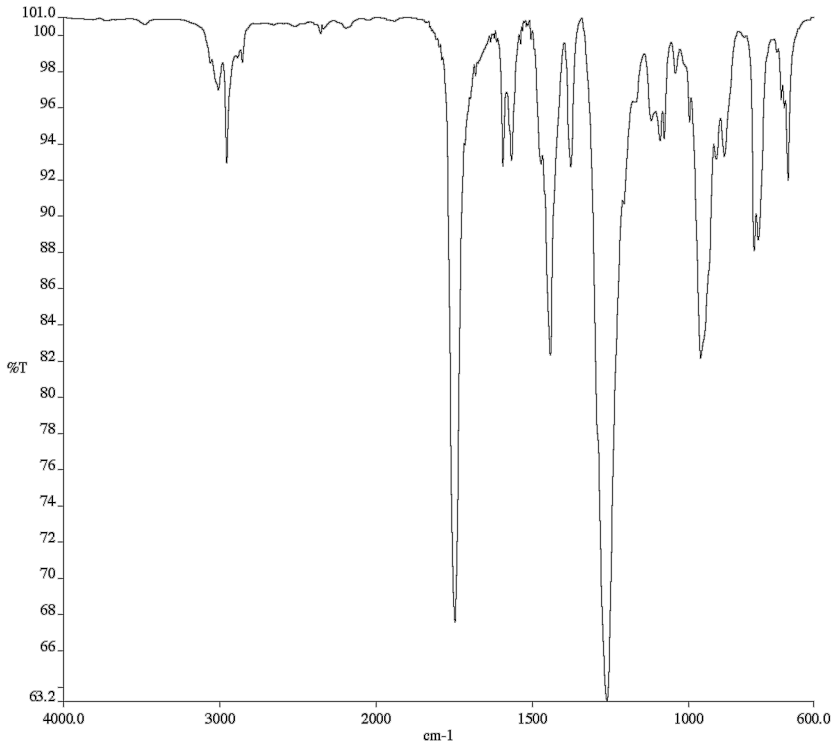
Infrared spectrum (Thin Film, NaCl) of compound **4c**.



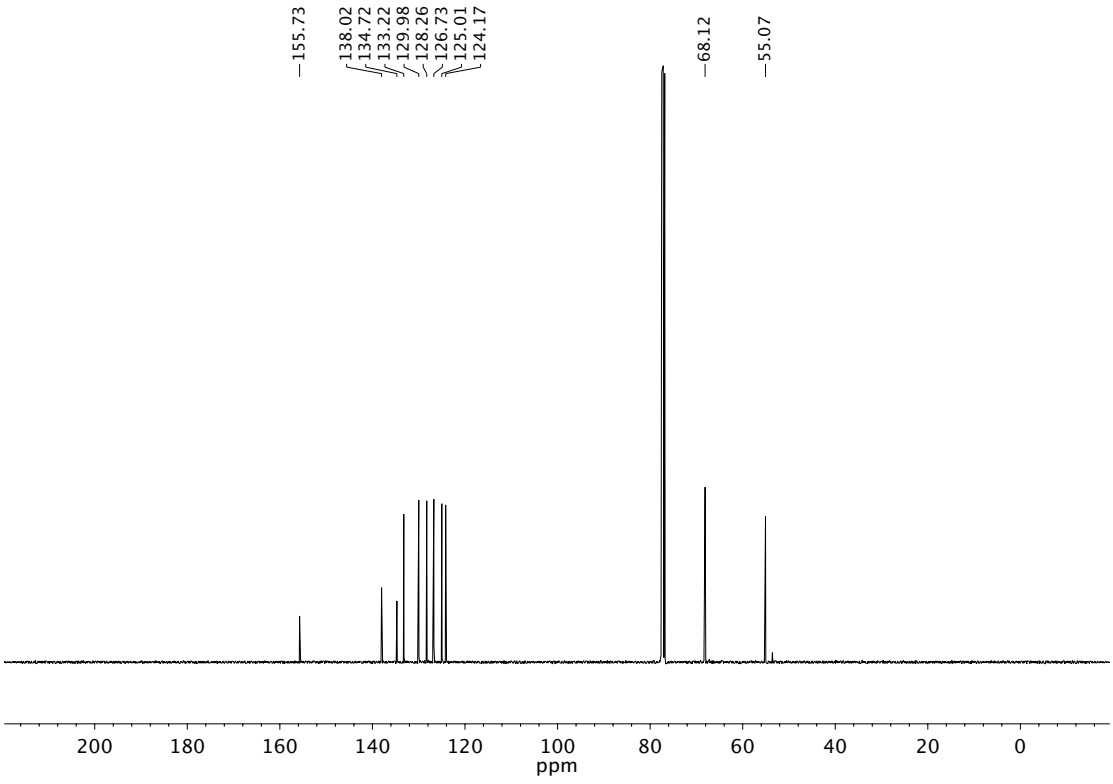
^{13}C NMR (101 MHz, $CDCl_3$) of compound **4c**.



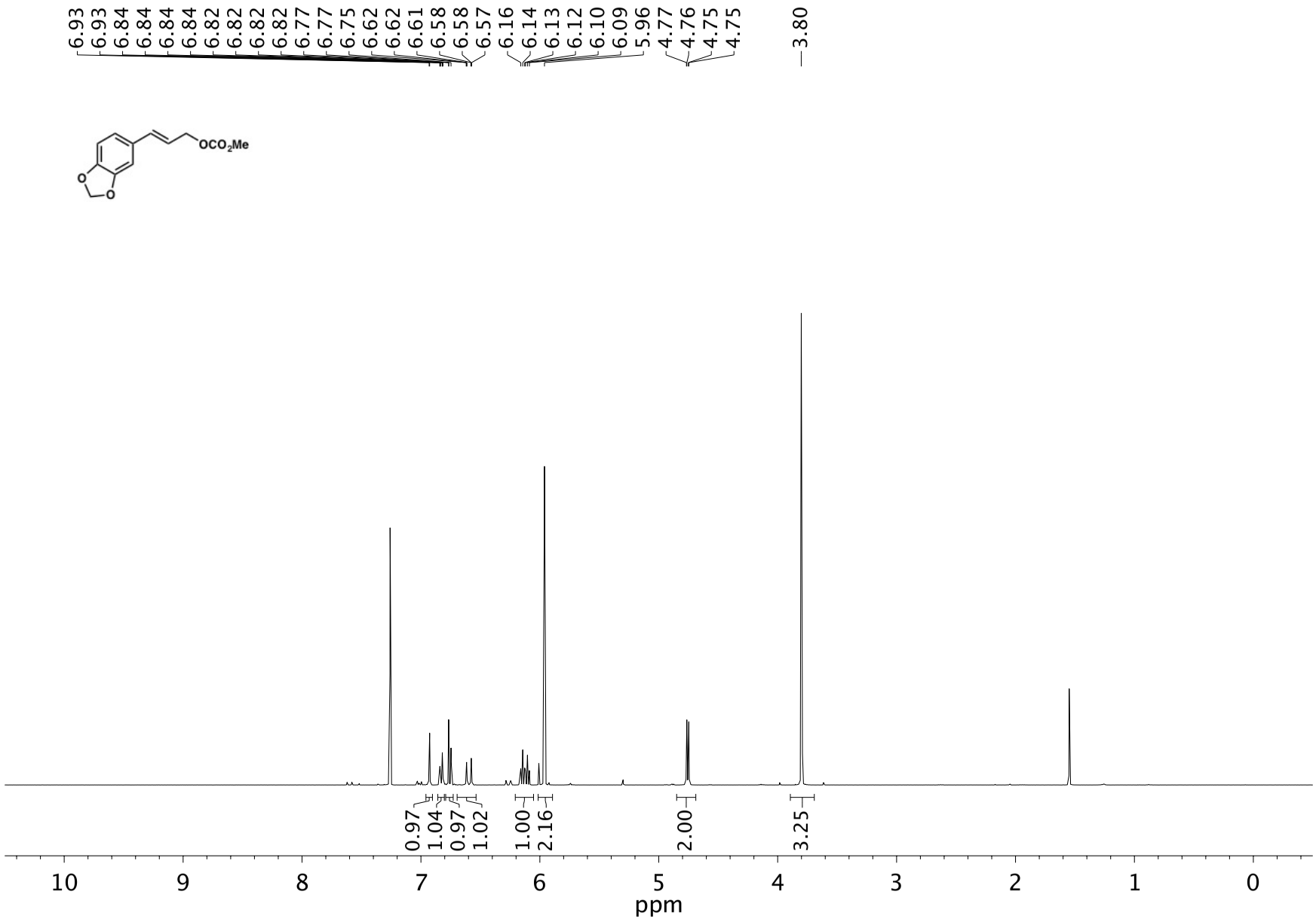
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5e**.



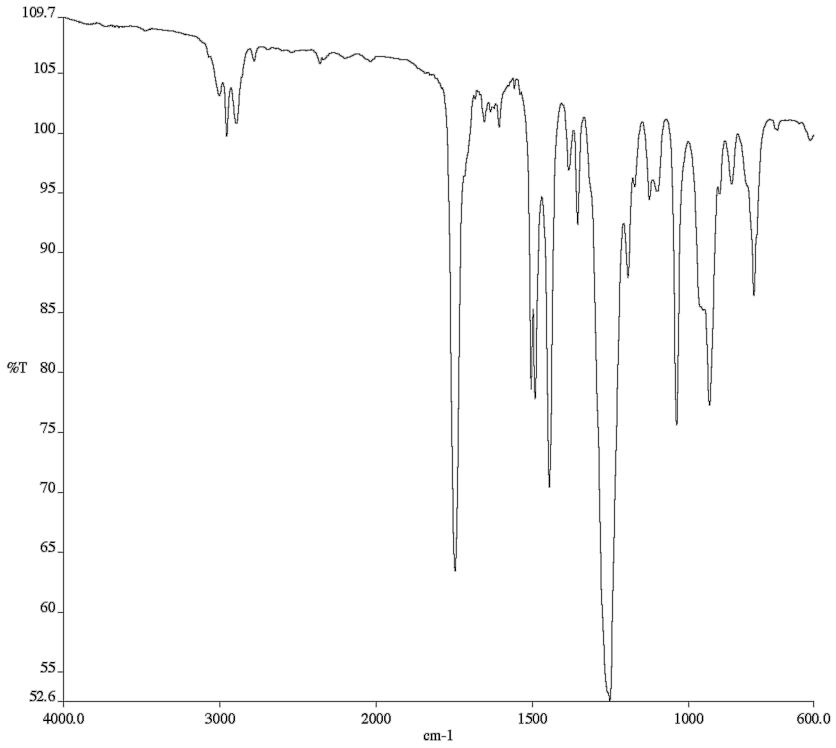
Infrared spectrum (Thin Film, NaCl) of compound **5e**.



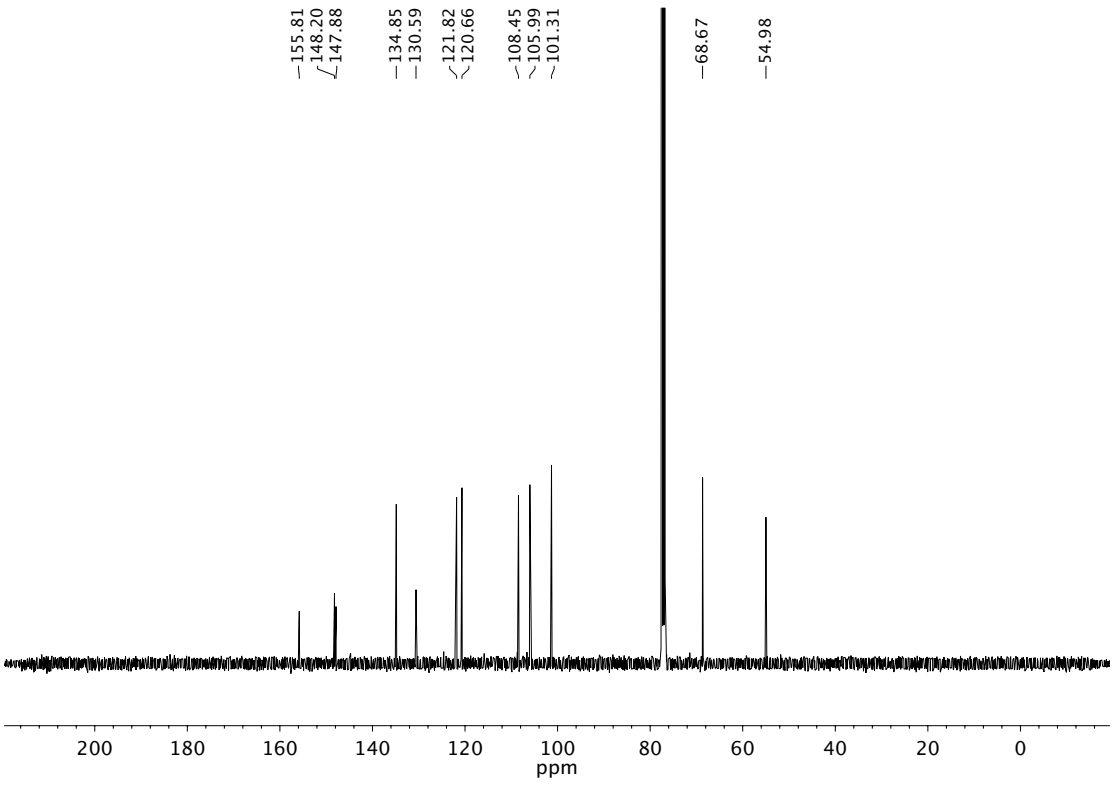
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5e**.



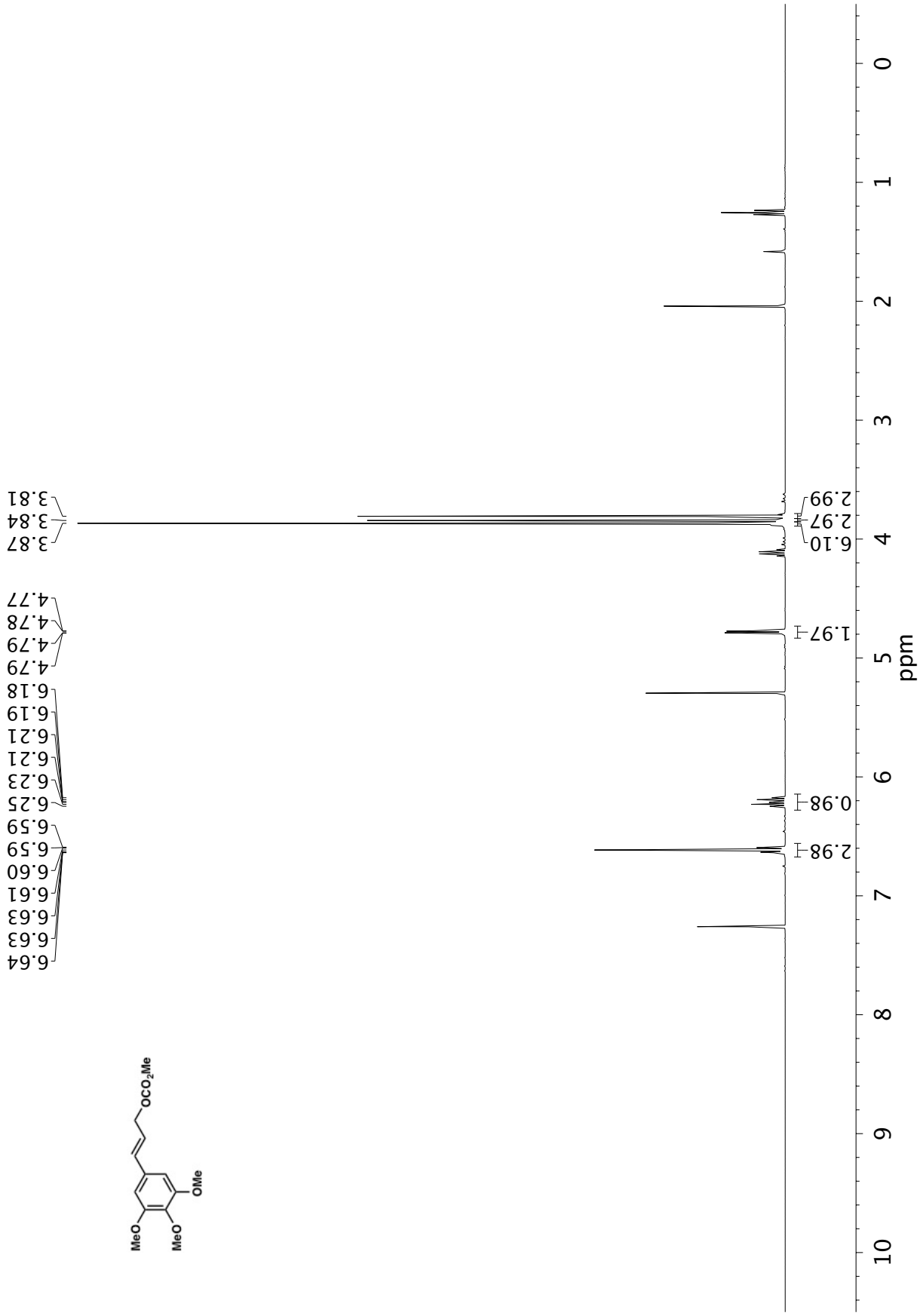
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5f**.



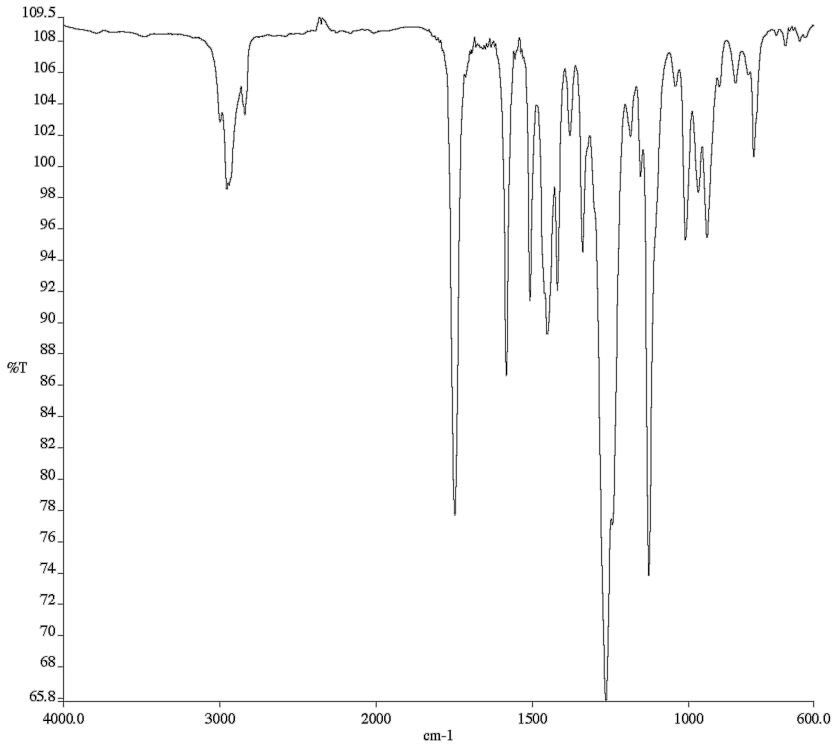
Infrared spectrum (Thin Film, NaCl) of compound **5f**.



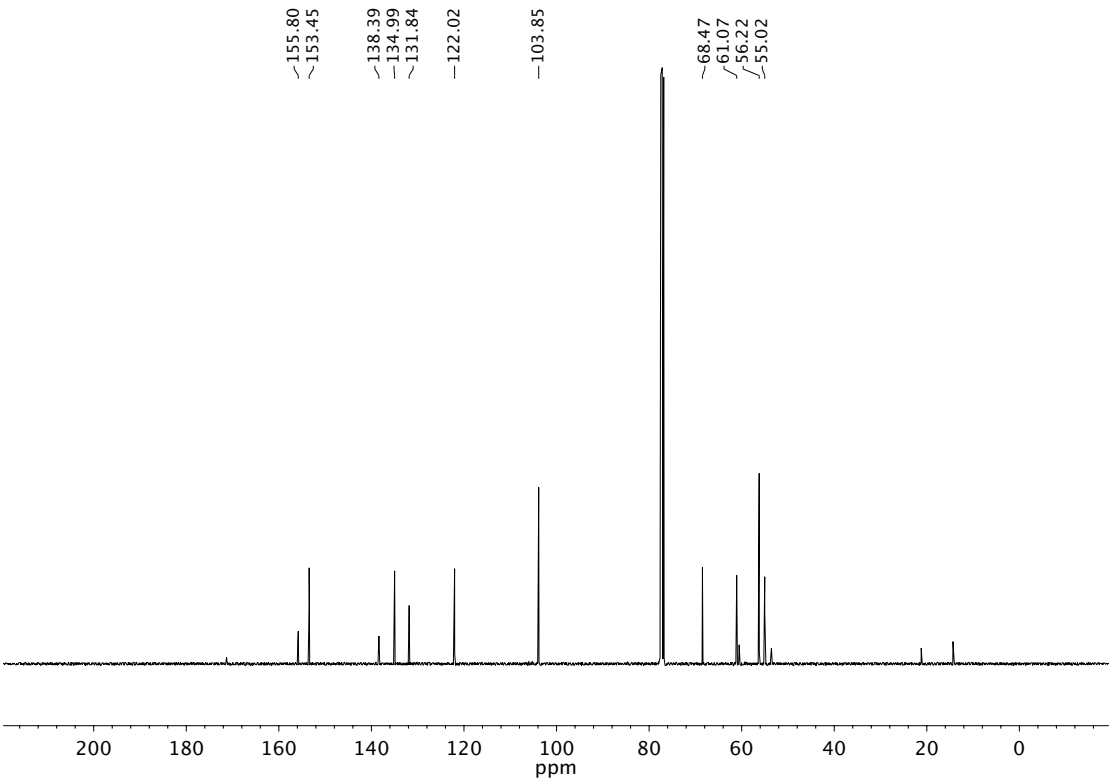
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5f**.



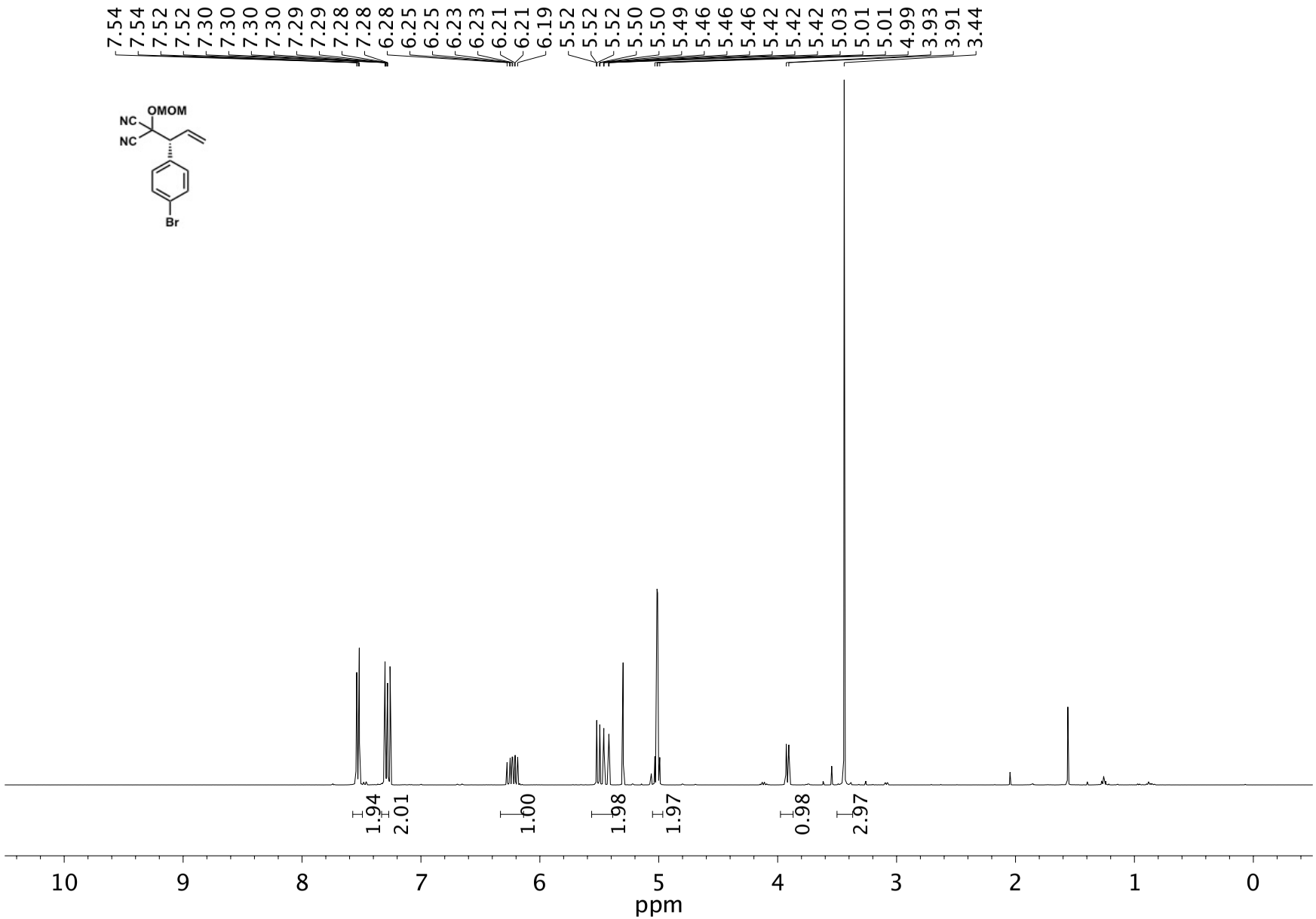
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5g**.



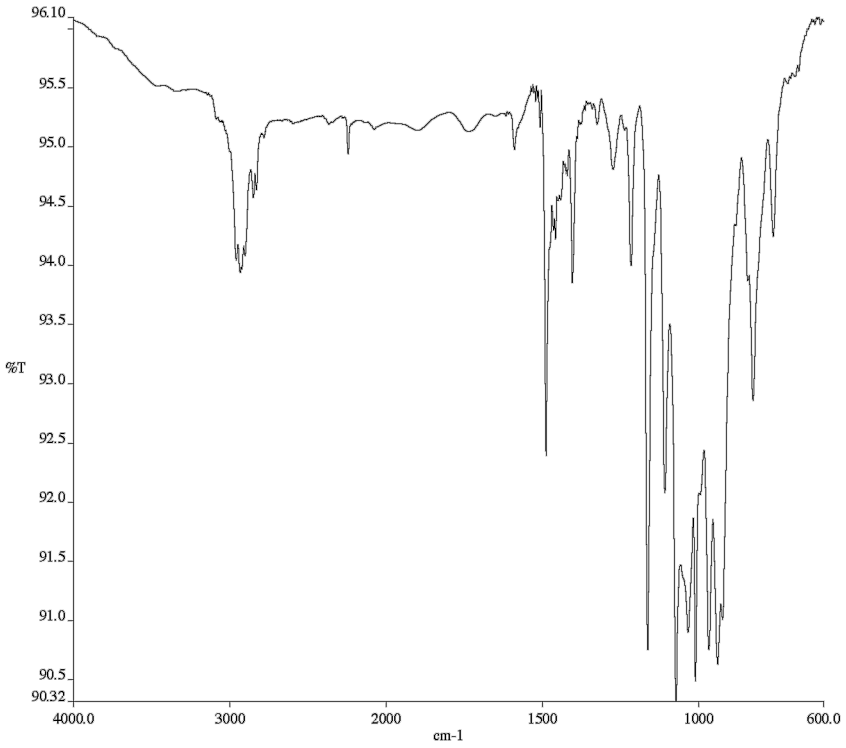
Infrared spectrum (Thin Film, NaCl) of compound **5g**.



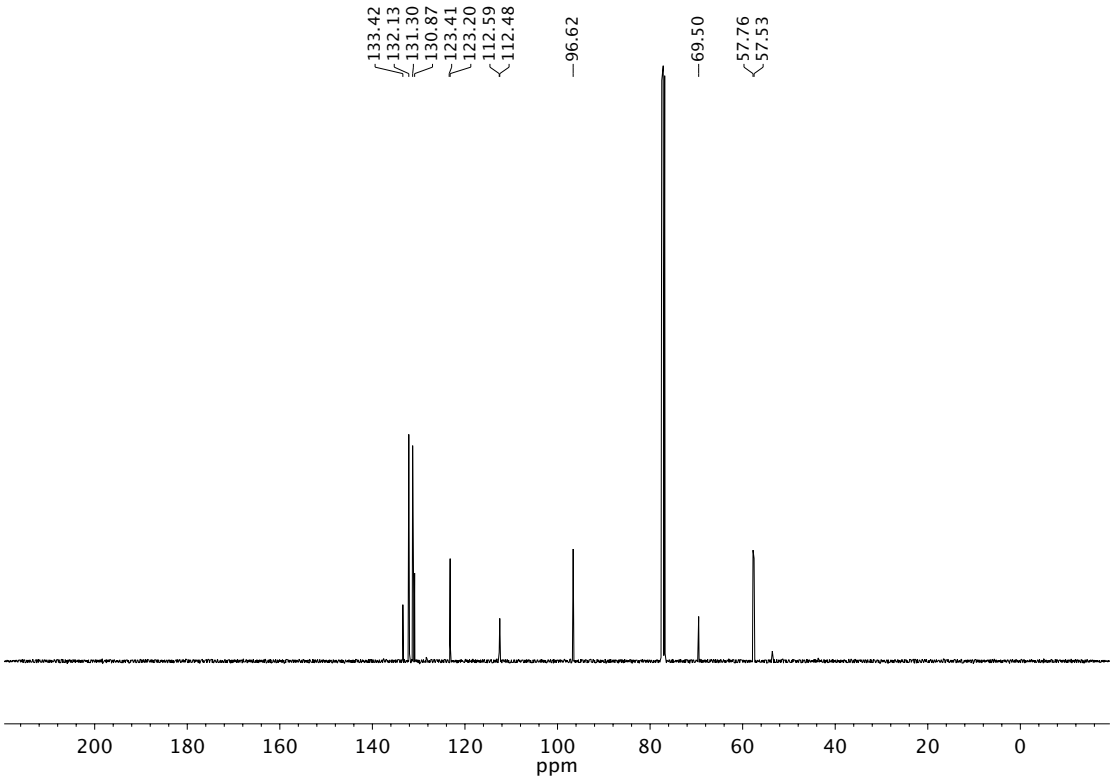
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5g**.



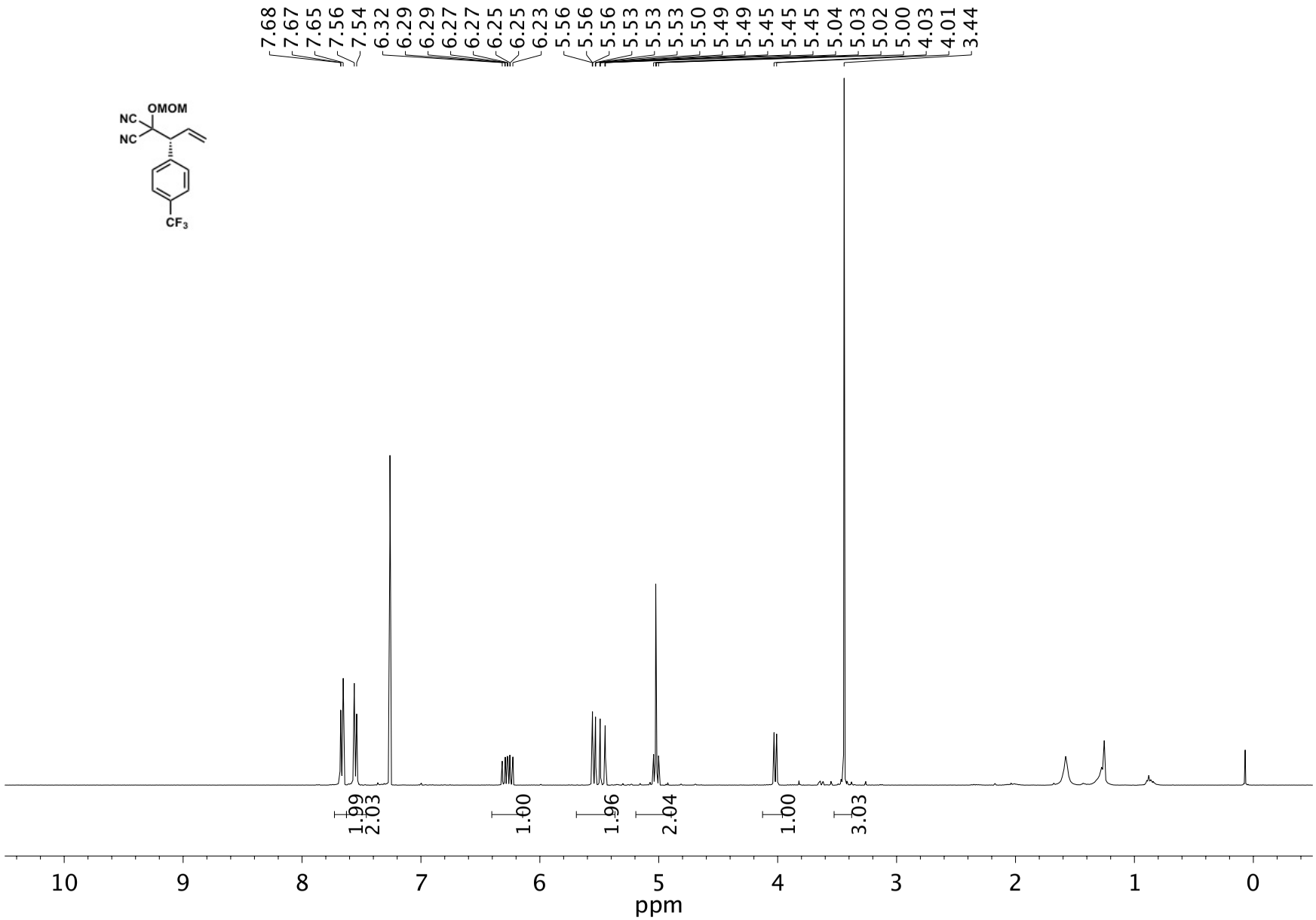
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6a**.



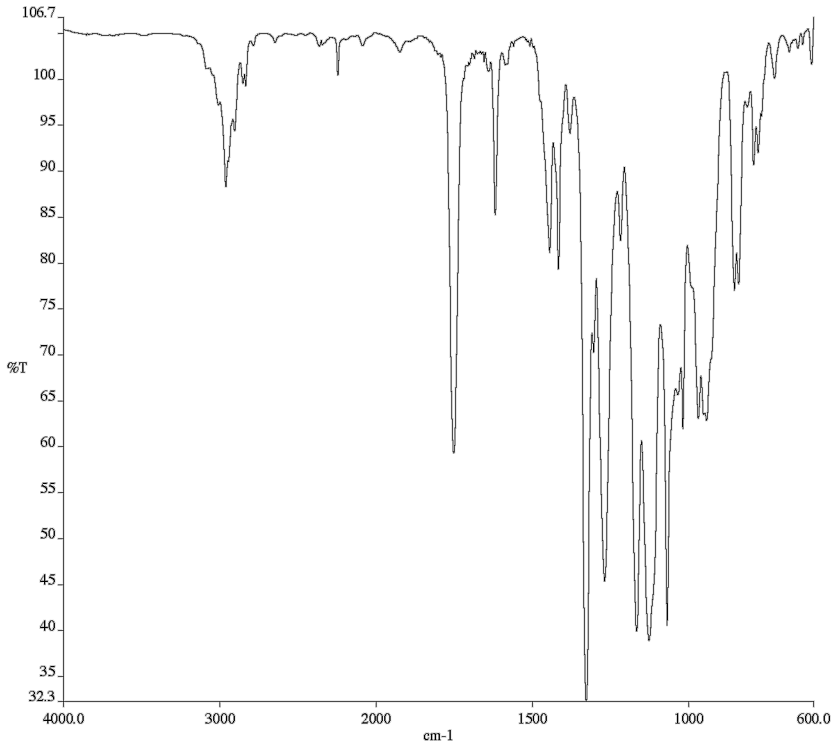
Infrared spectrum (Thin Film, NaCl) of compound **6a**.



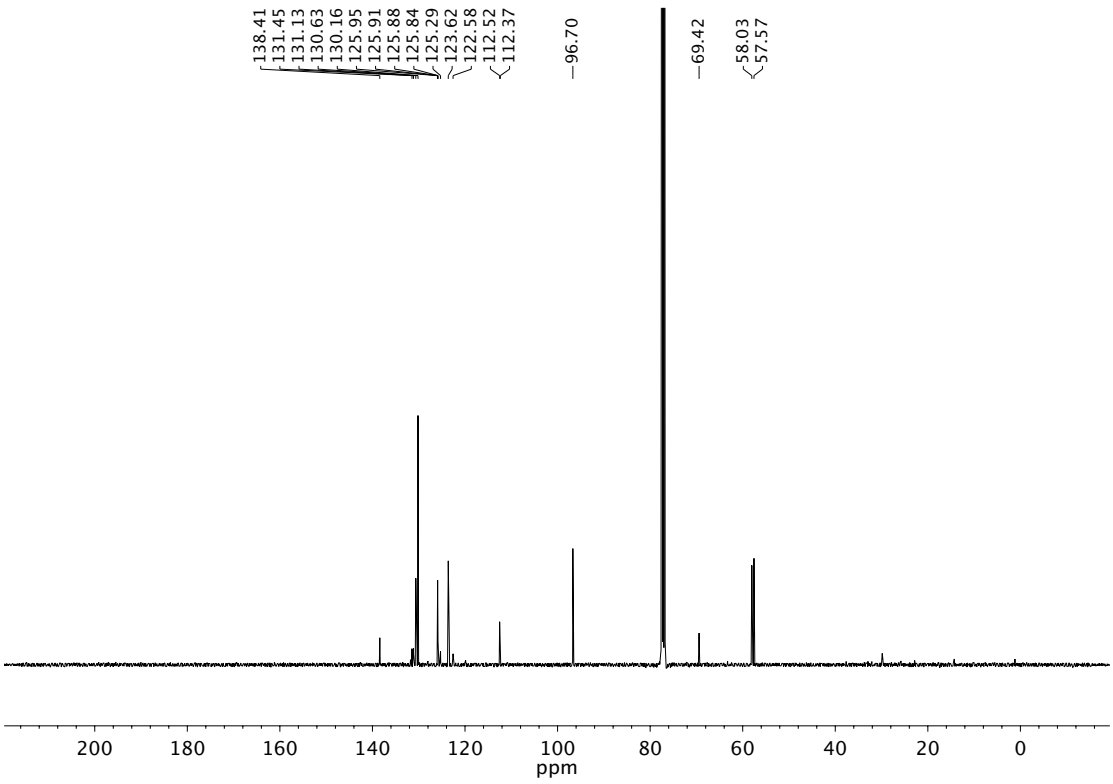
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6a**.



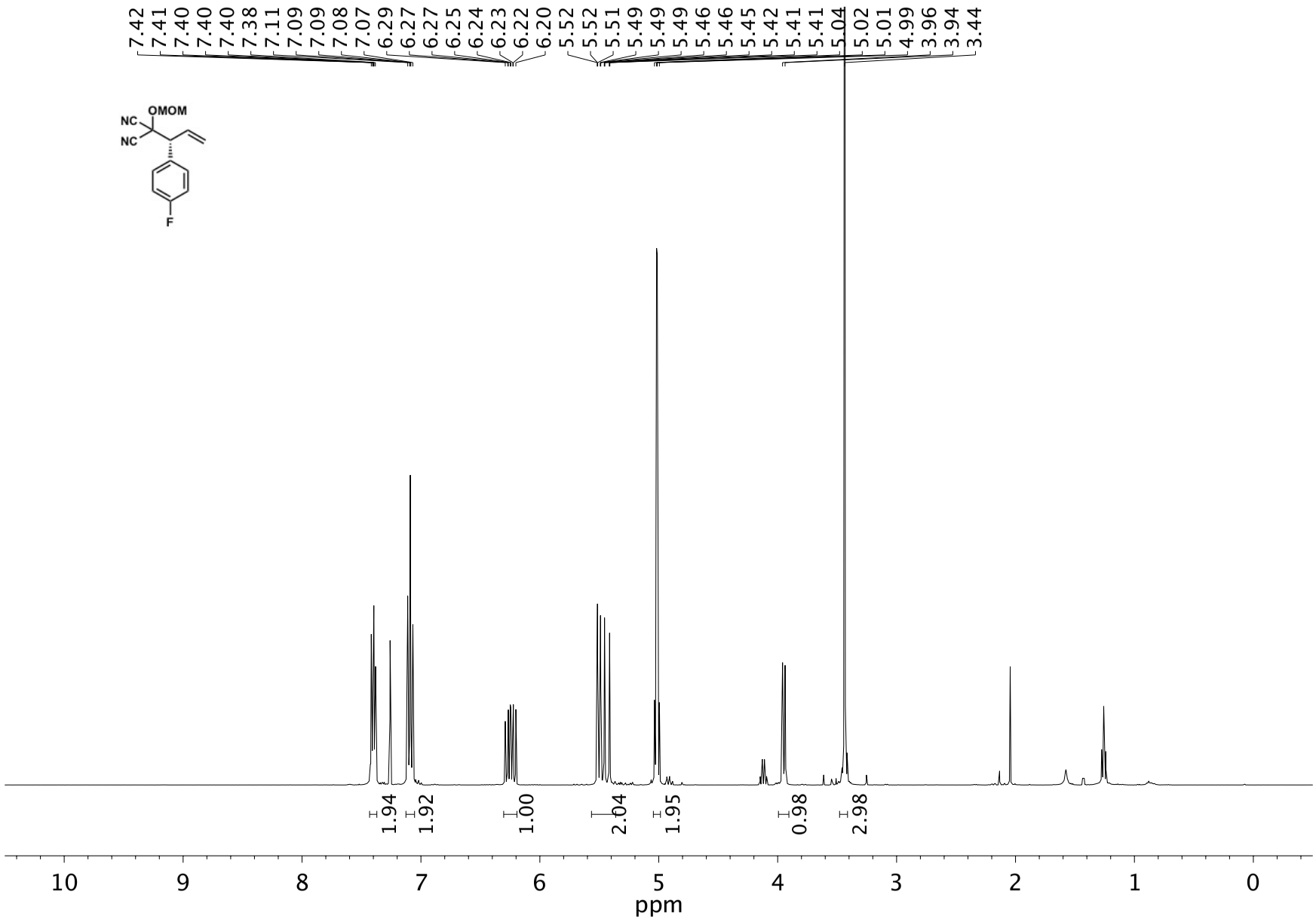
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6b**.



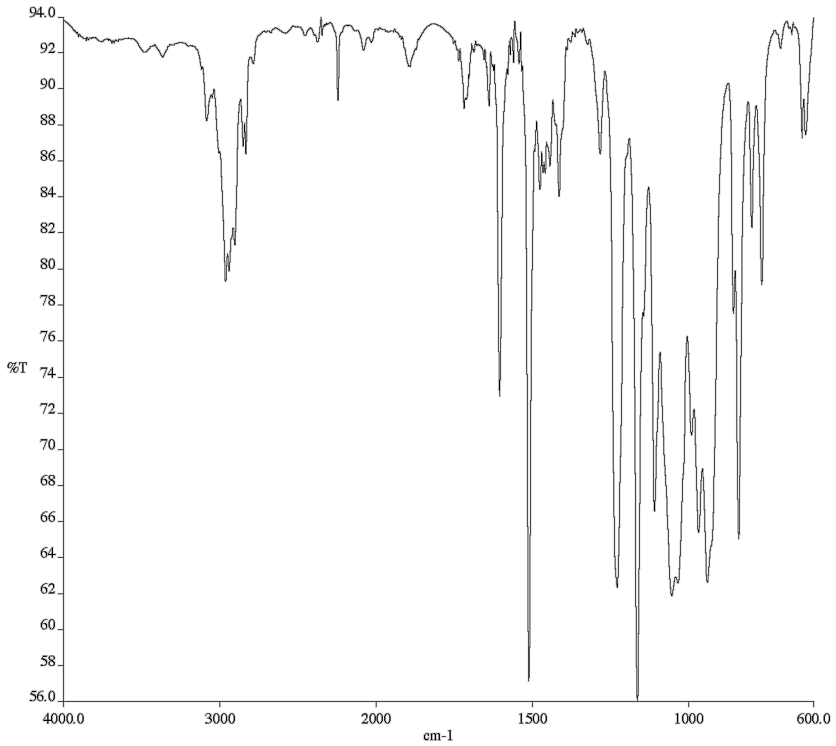
Infrared spectrum (Thin Film, NaCl) of compound **6b**.



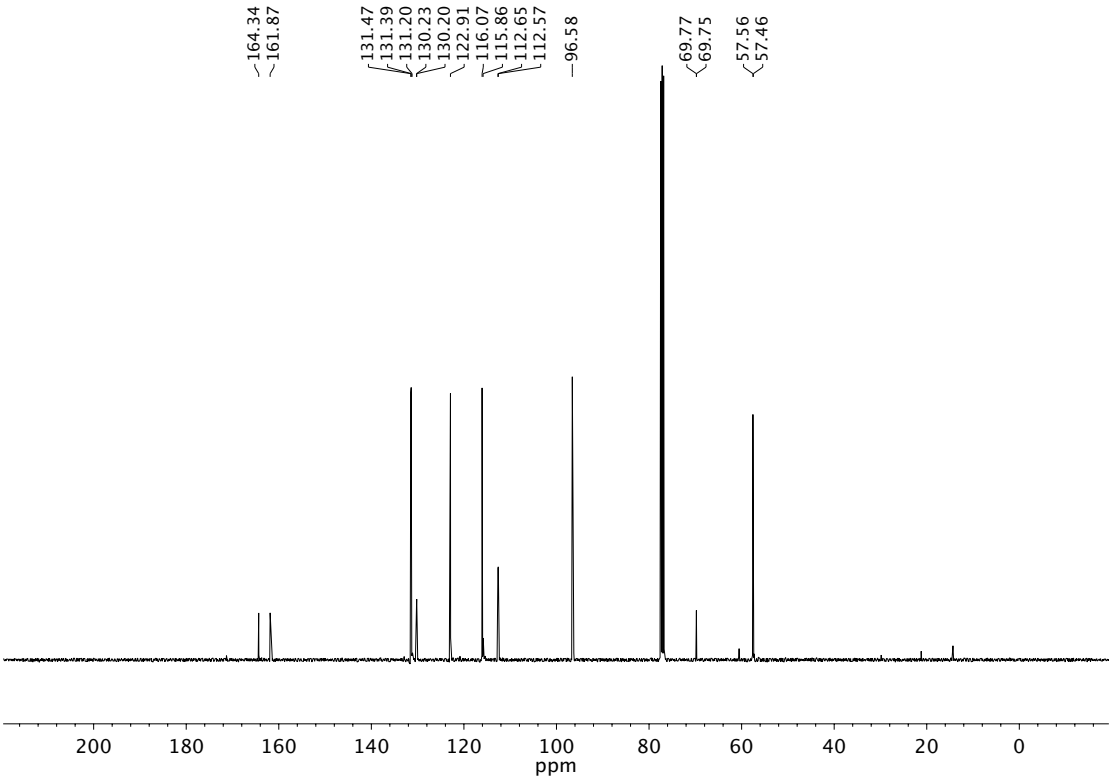
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6b**.



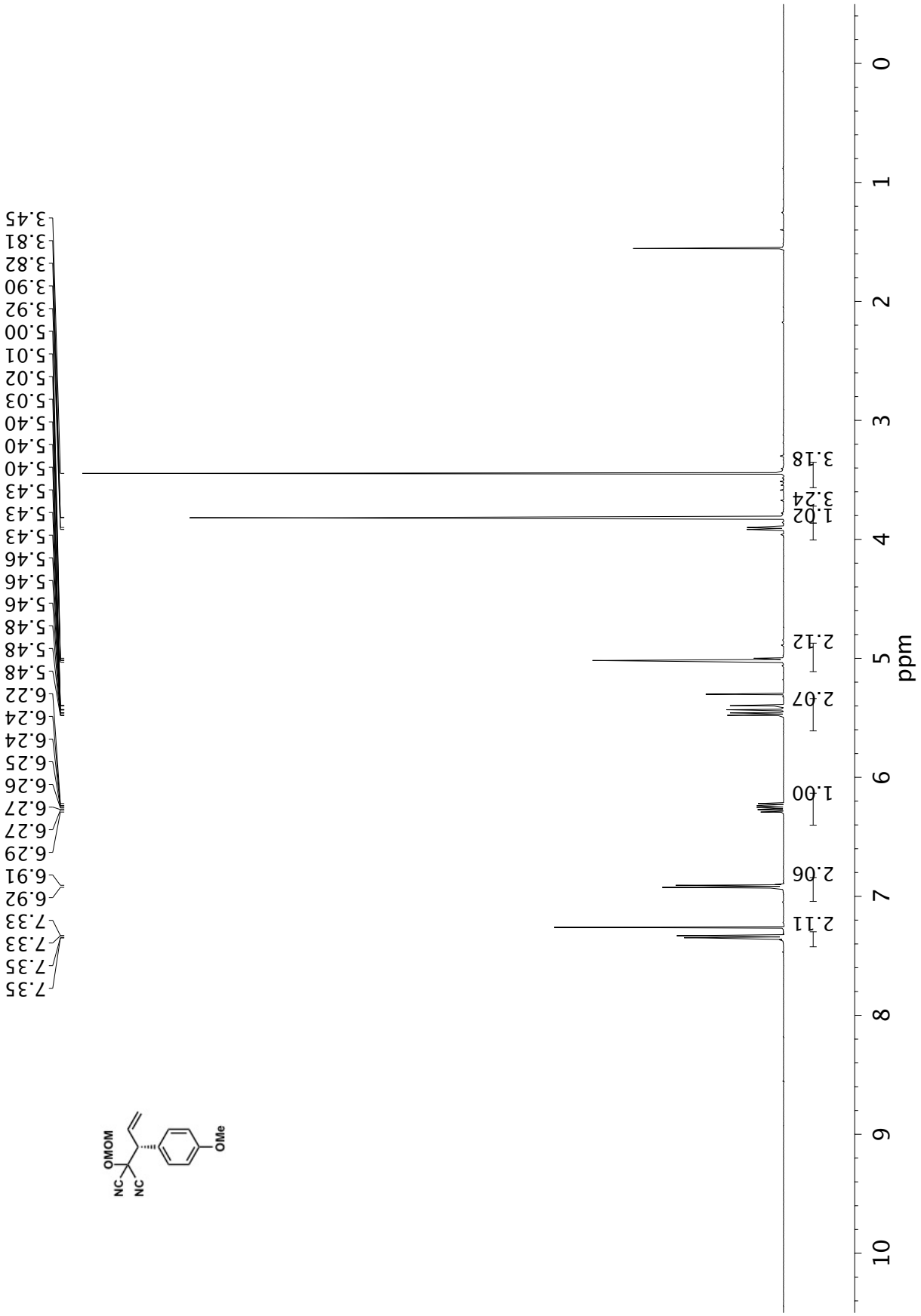
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6c**.



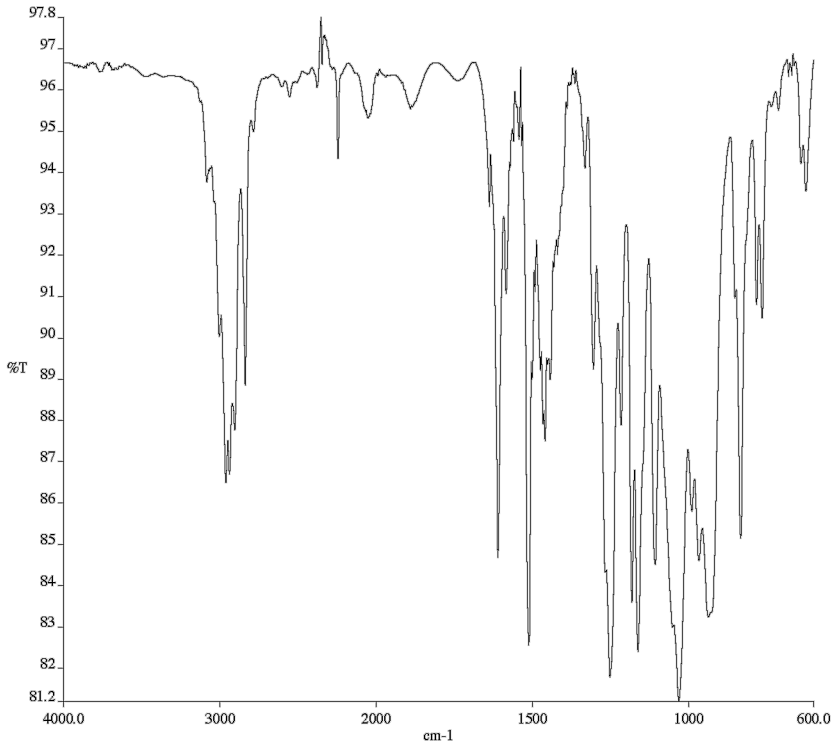
Infrared spectrum (Thin Film, NaCl) of compound **6c**.



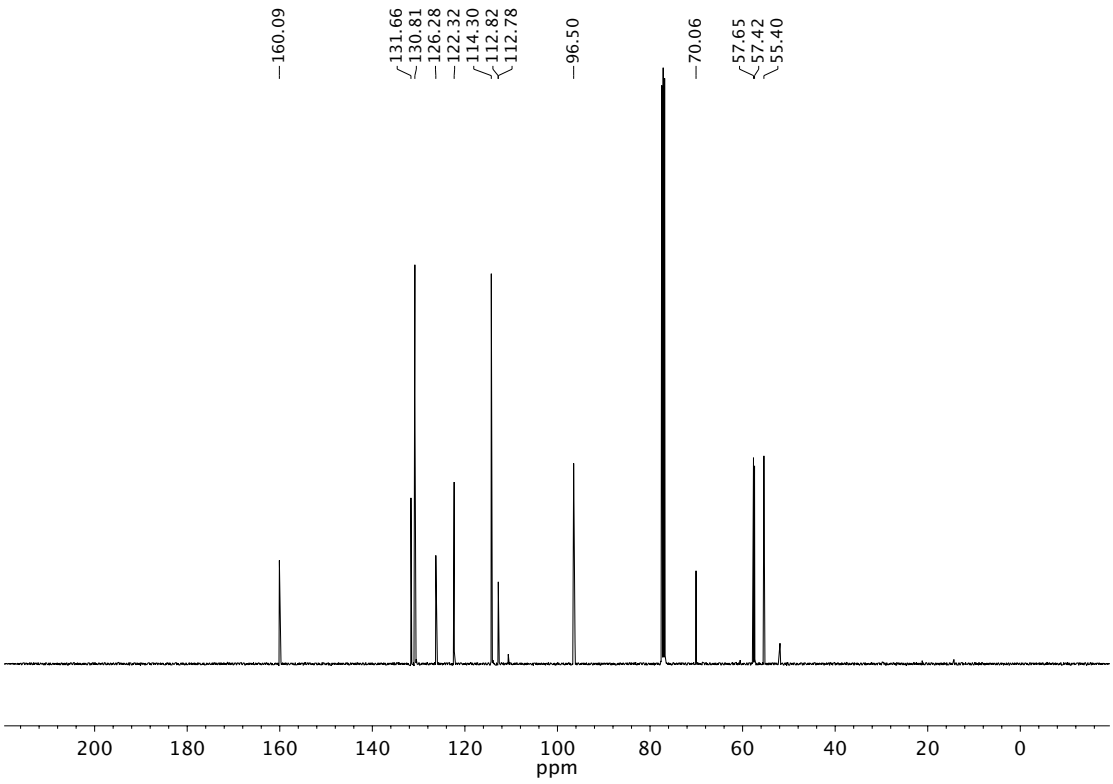
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6c**.



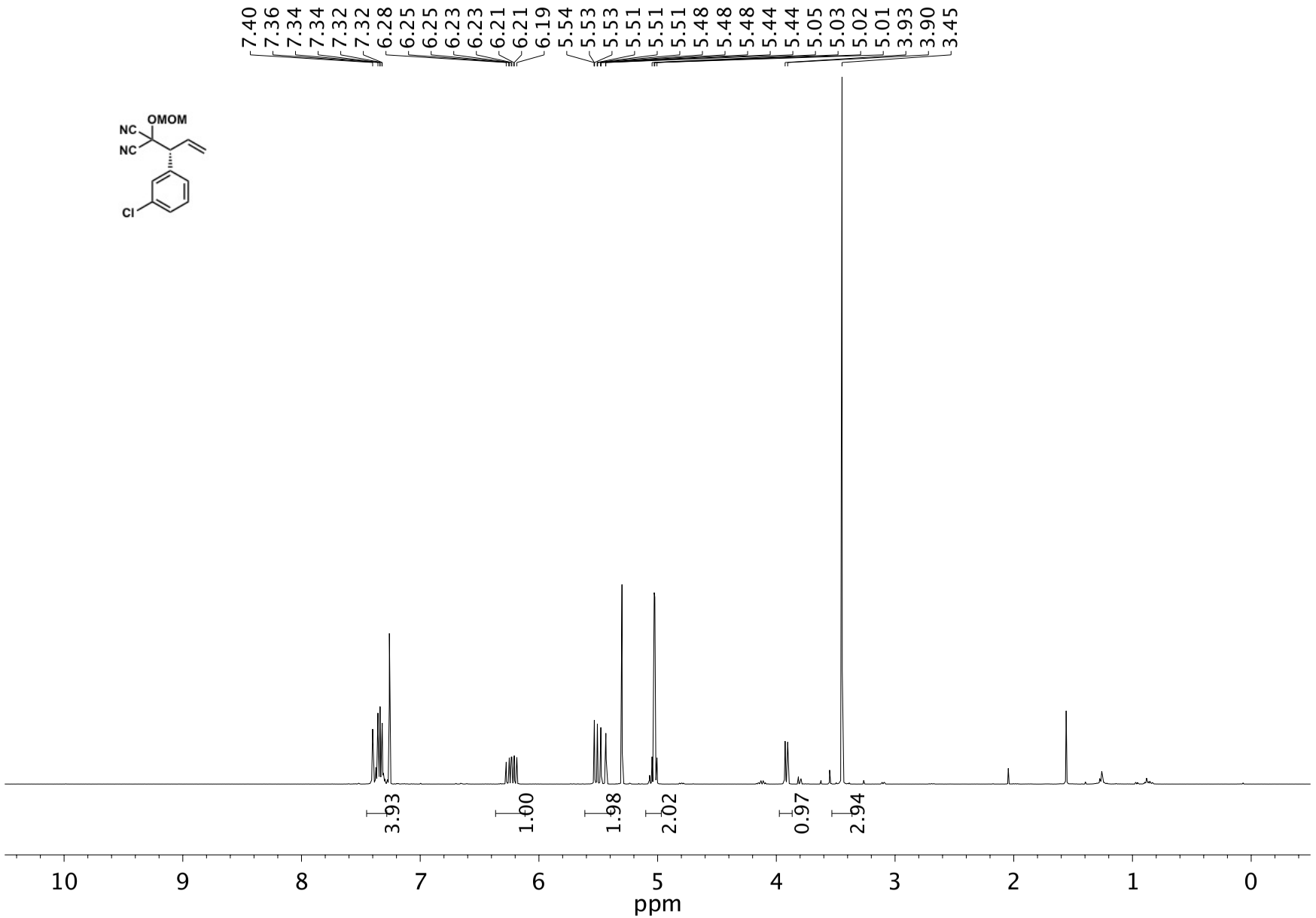
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6d**.



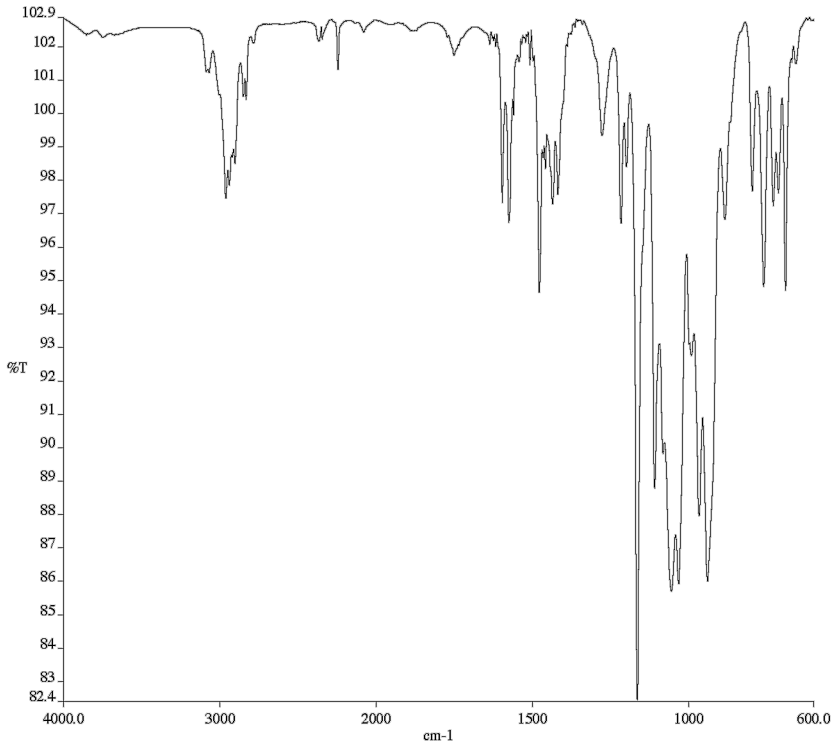
Infrared spectrum (Thin Film, NaCl) of compound **6d**.



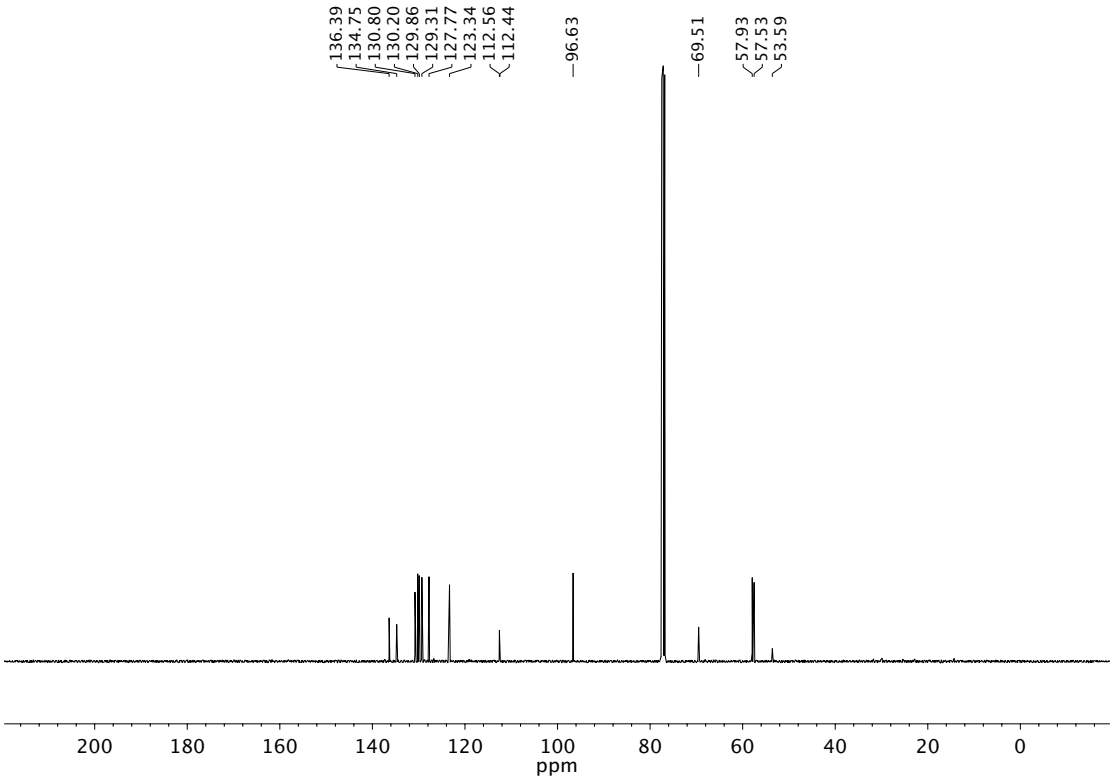
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6d**.



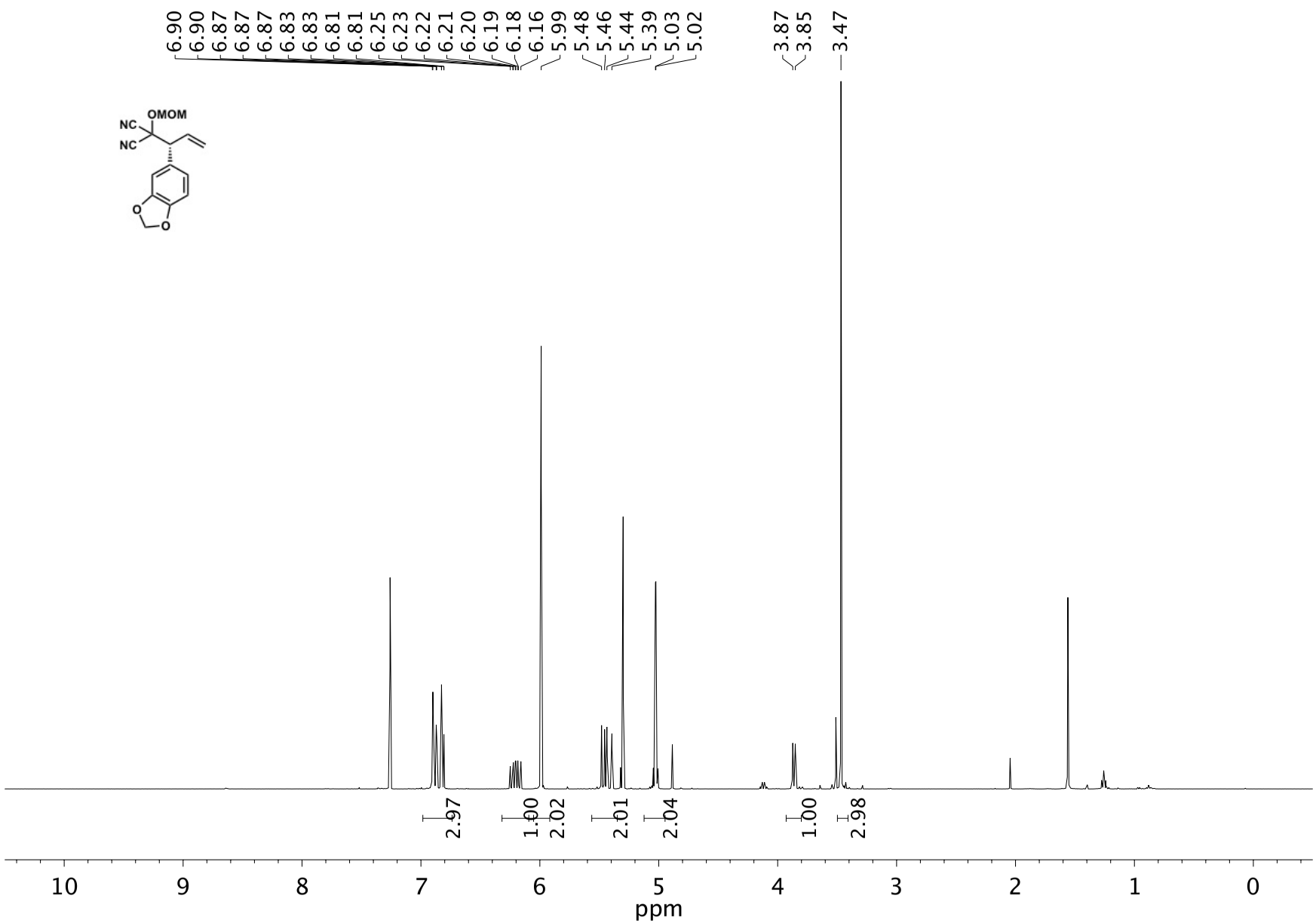
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6e**.



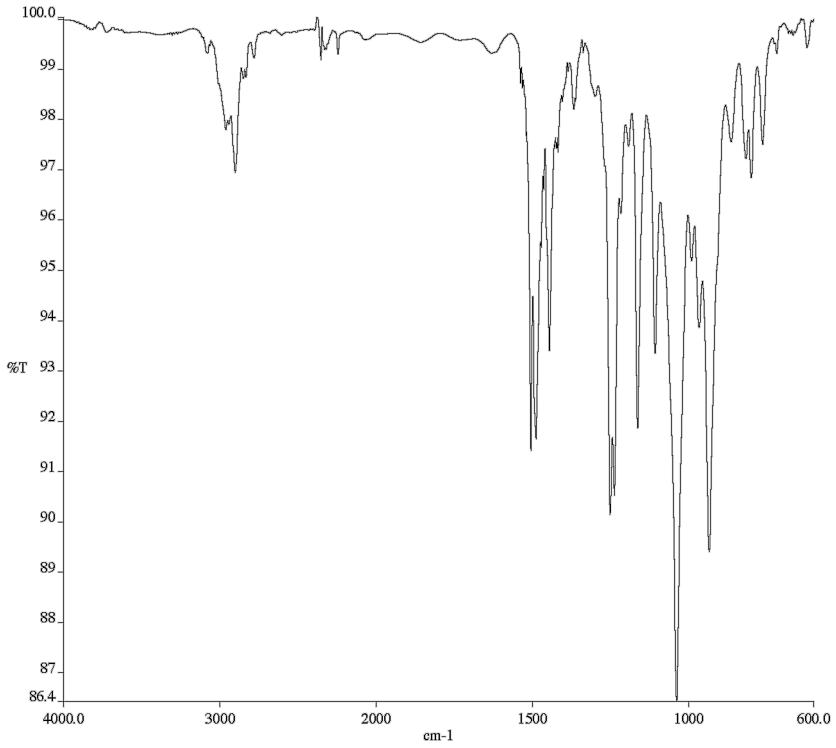
Infrared spectrum (Thin Film, NaCl) of compound **6e**.



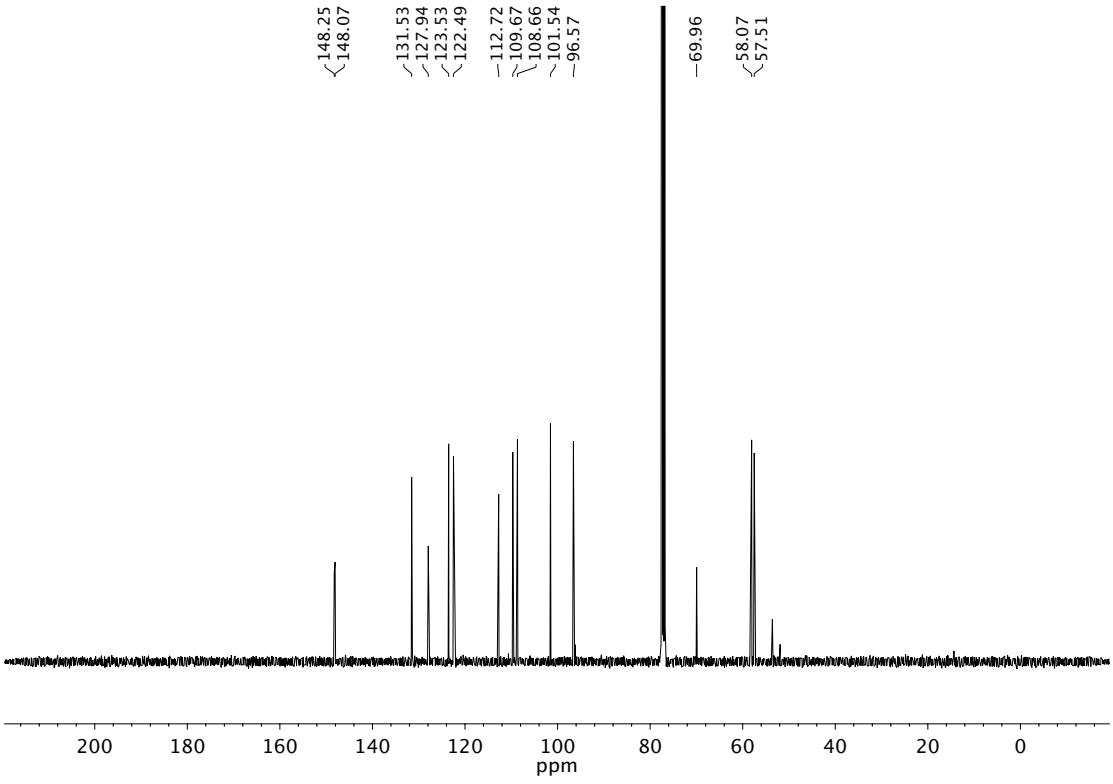
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6e**.



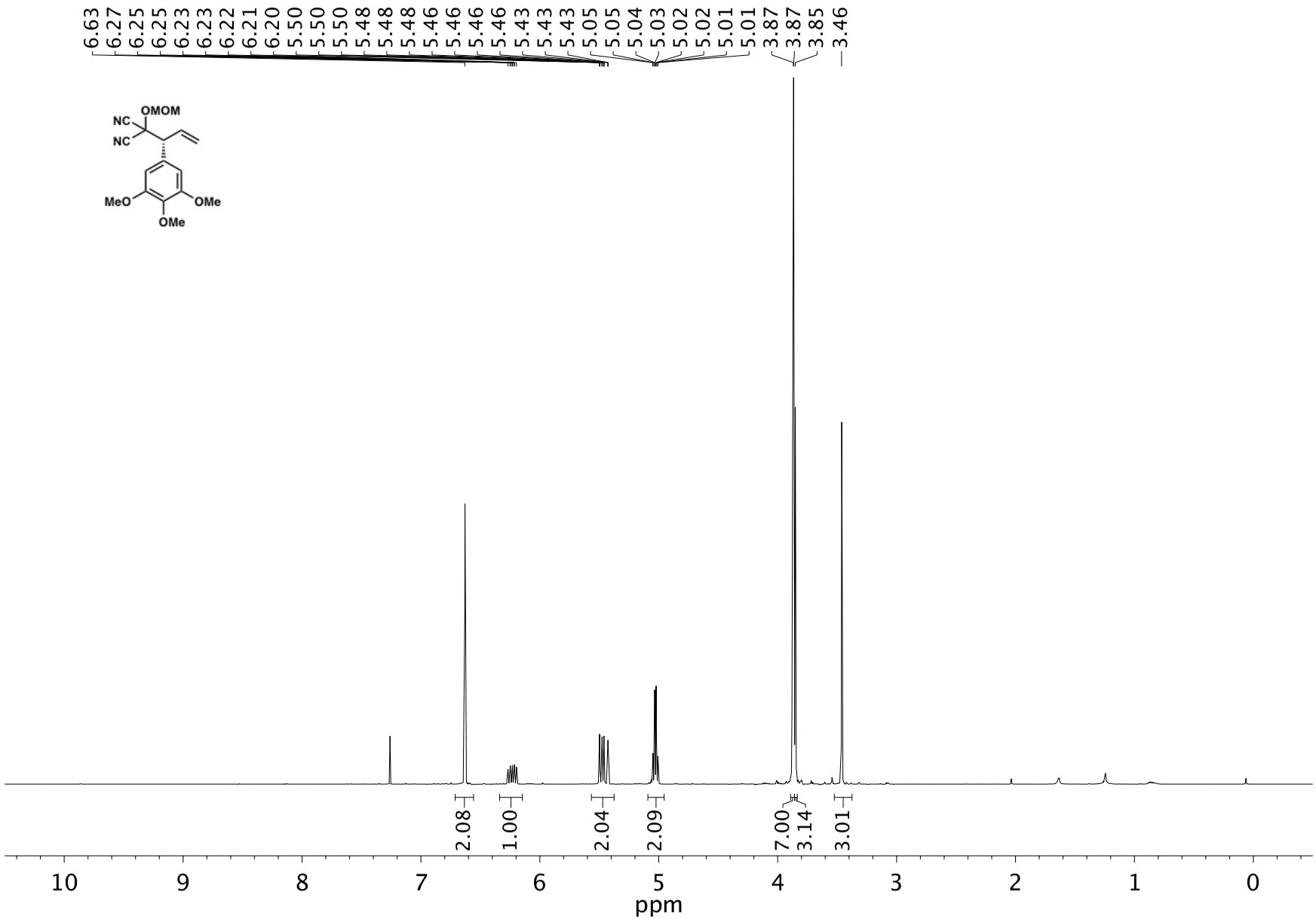
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6f**.



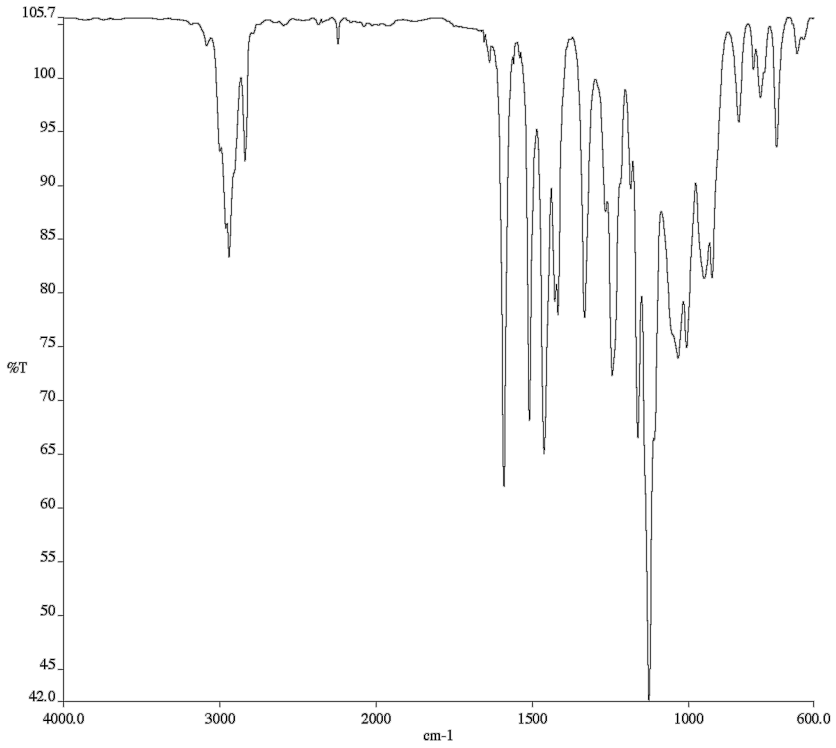
Infrared spectrum (Thin Film, NaCl) of compound **6f**.



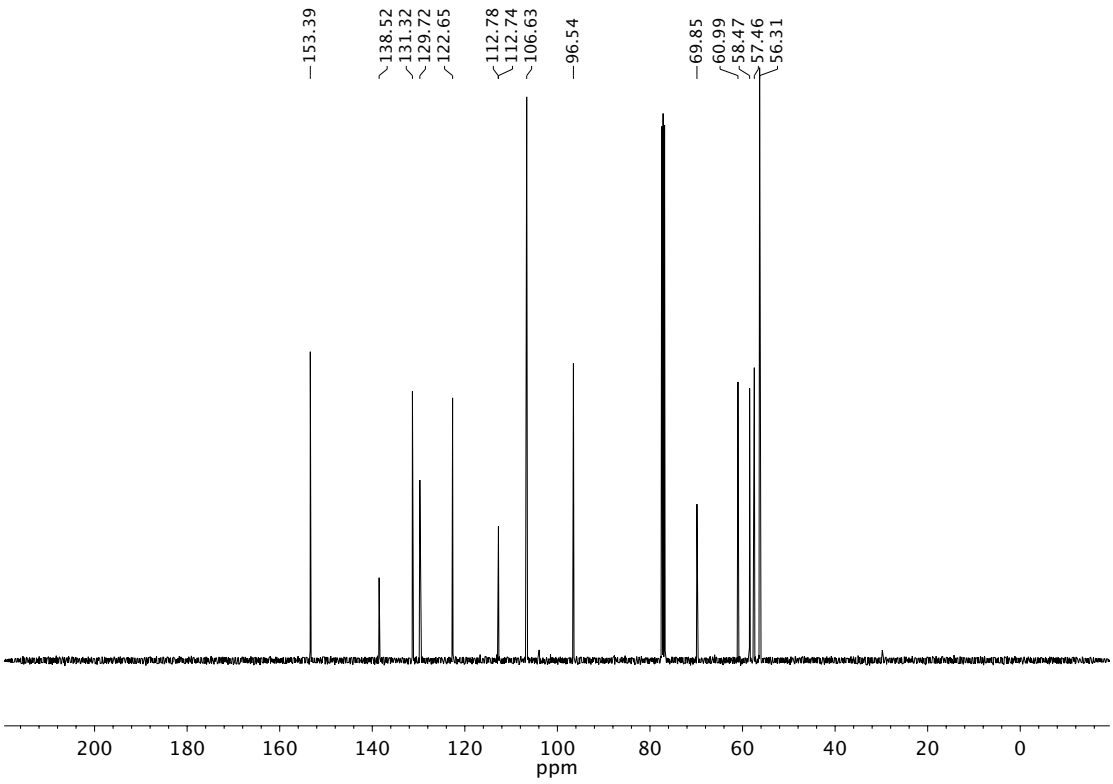
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6f**.



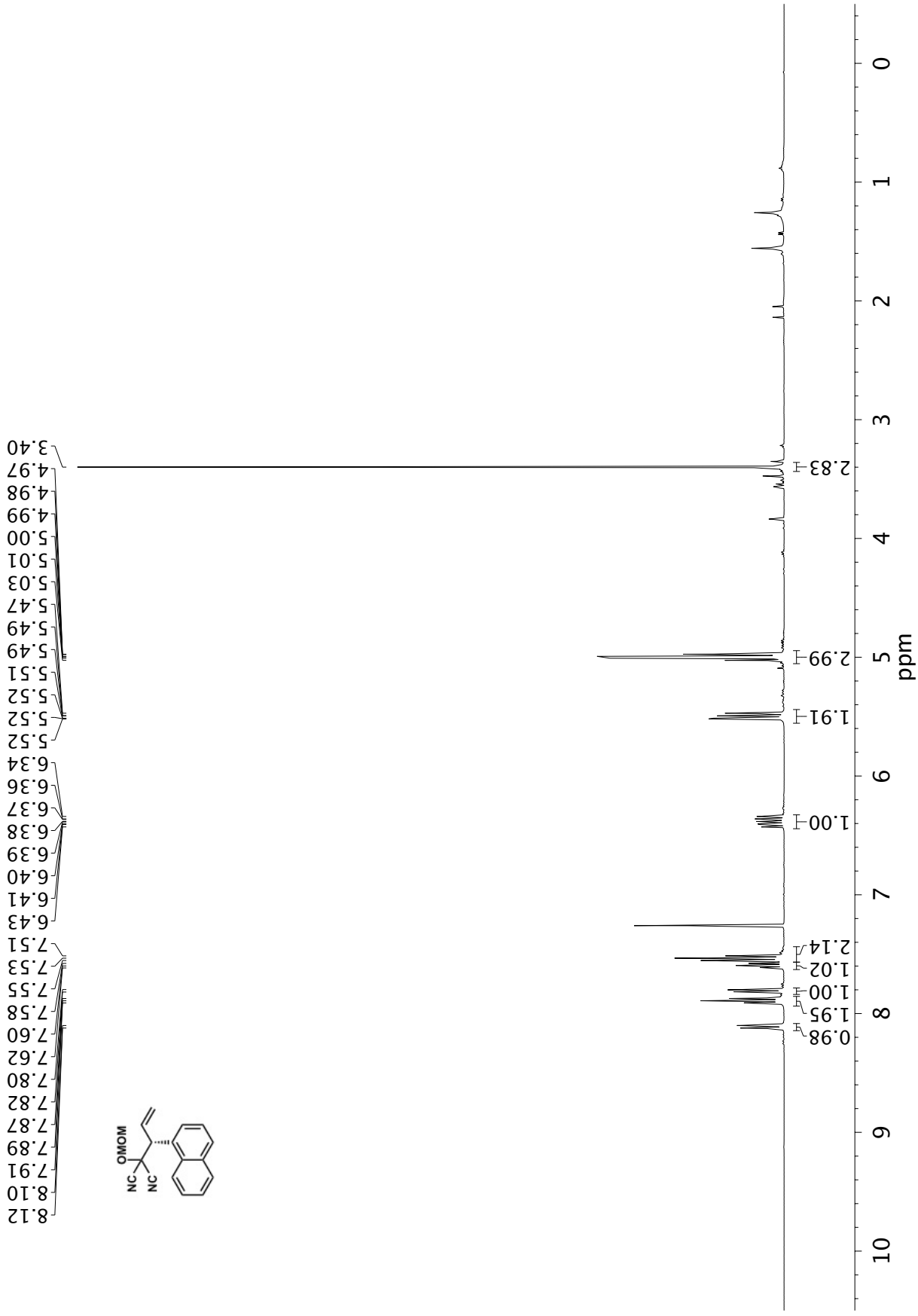
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6g**.



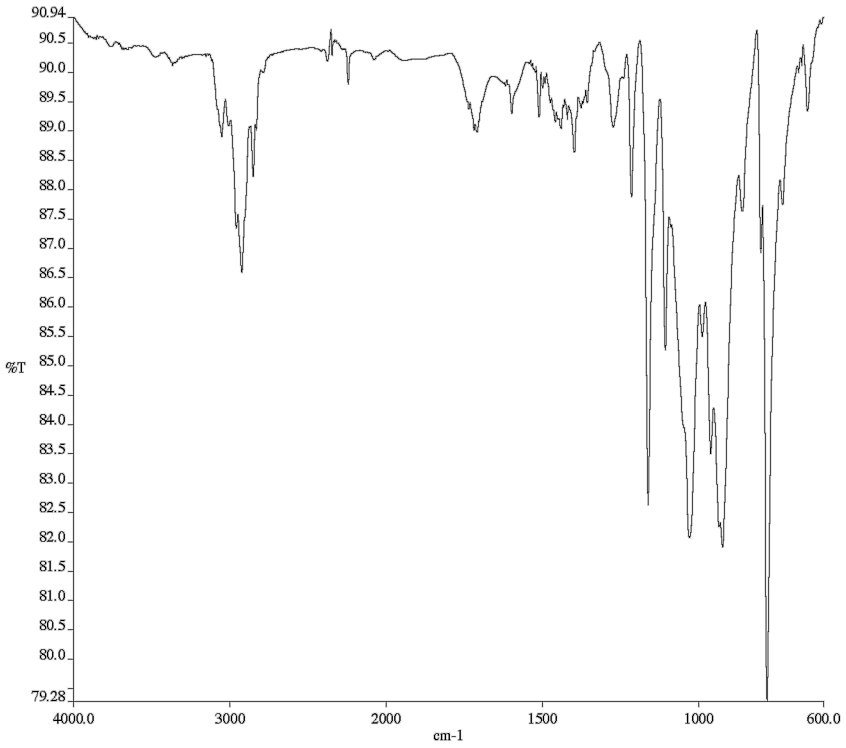
Infrared spectrum (Thin Film, NaCl) of compound **6g**.



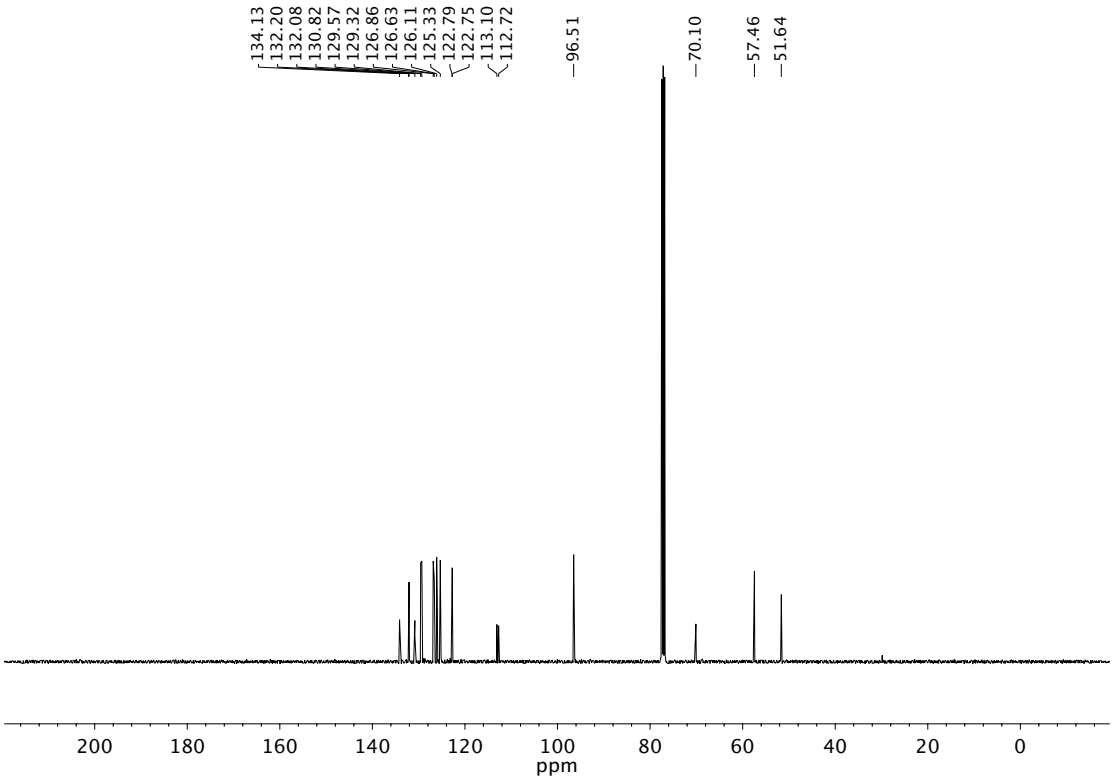
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6g**.



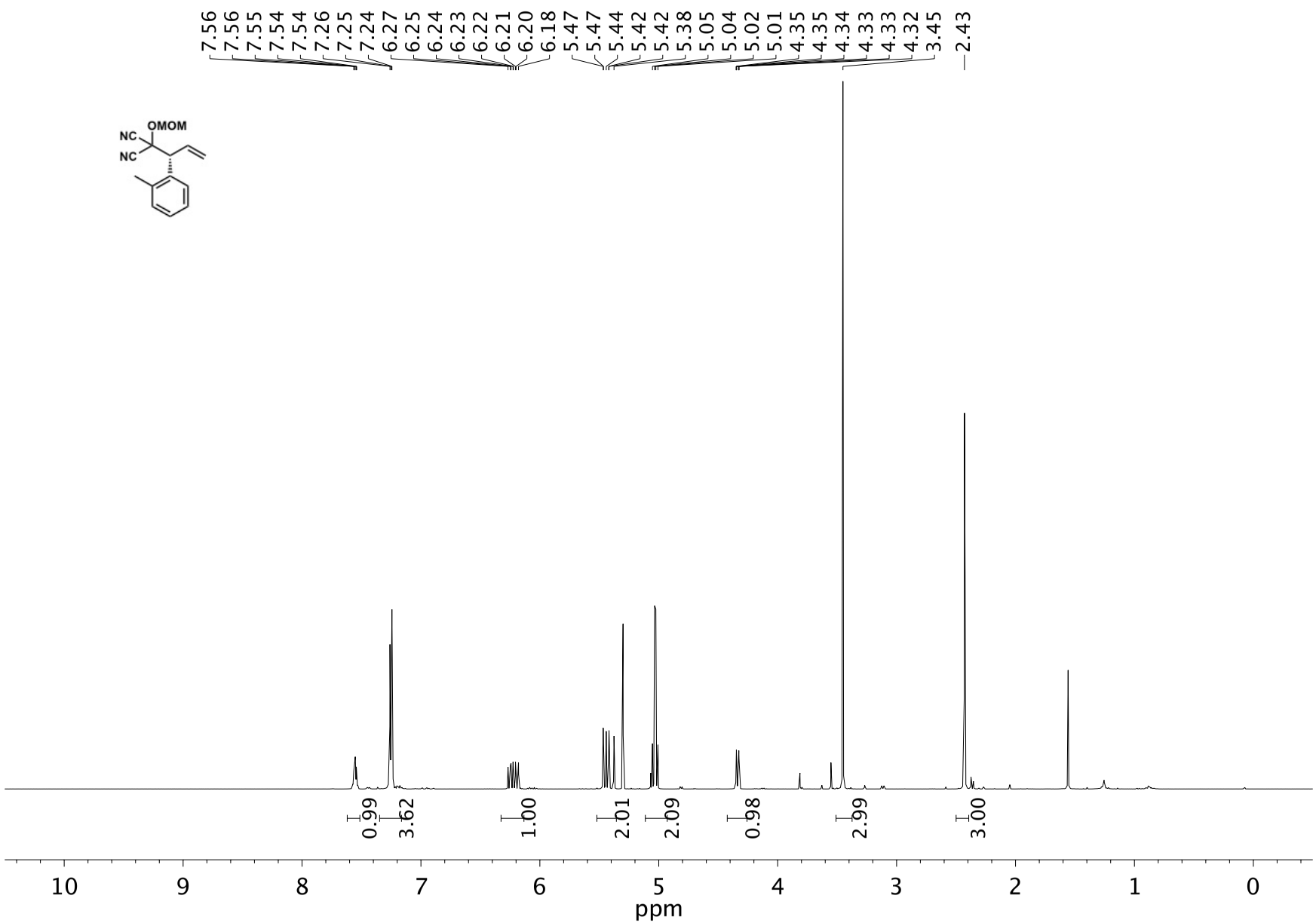
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6h**.



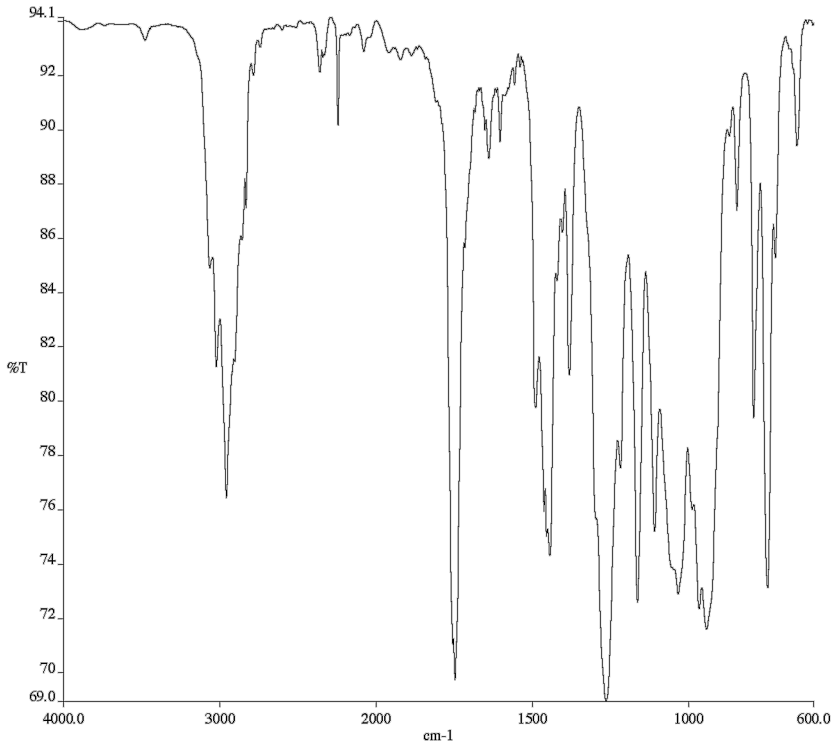
Infrared spectrum (Thin Film, NaCl) of compound **6h**.



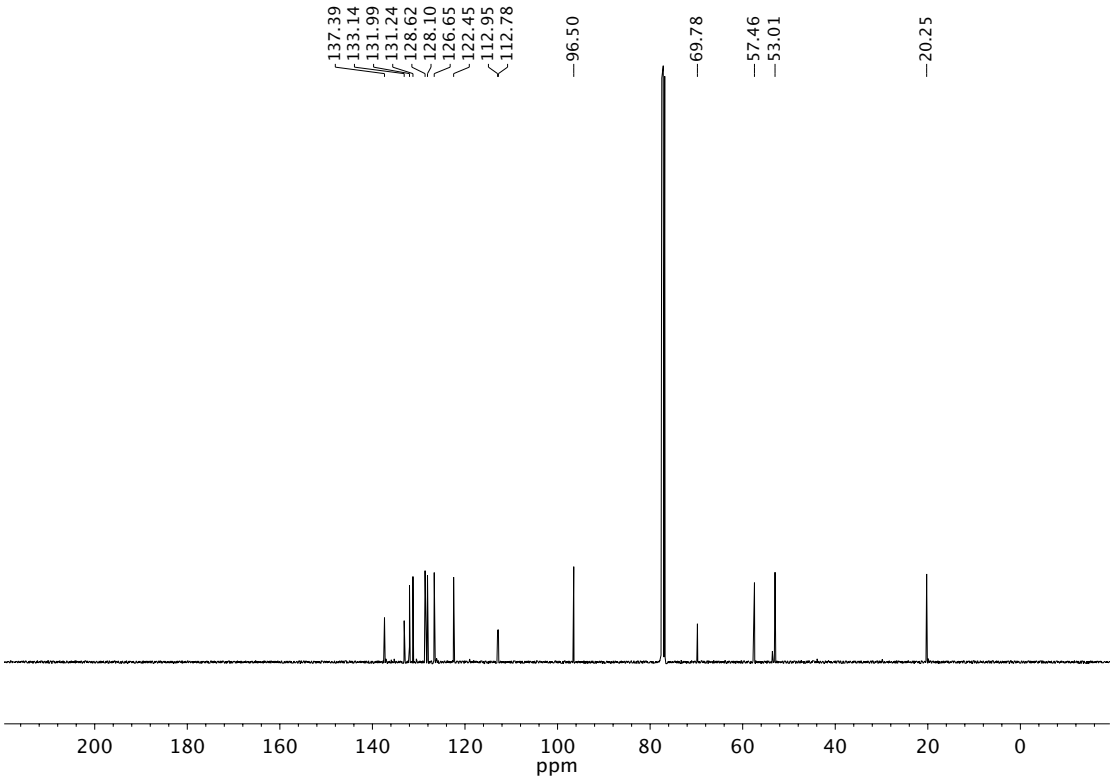
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6h**.



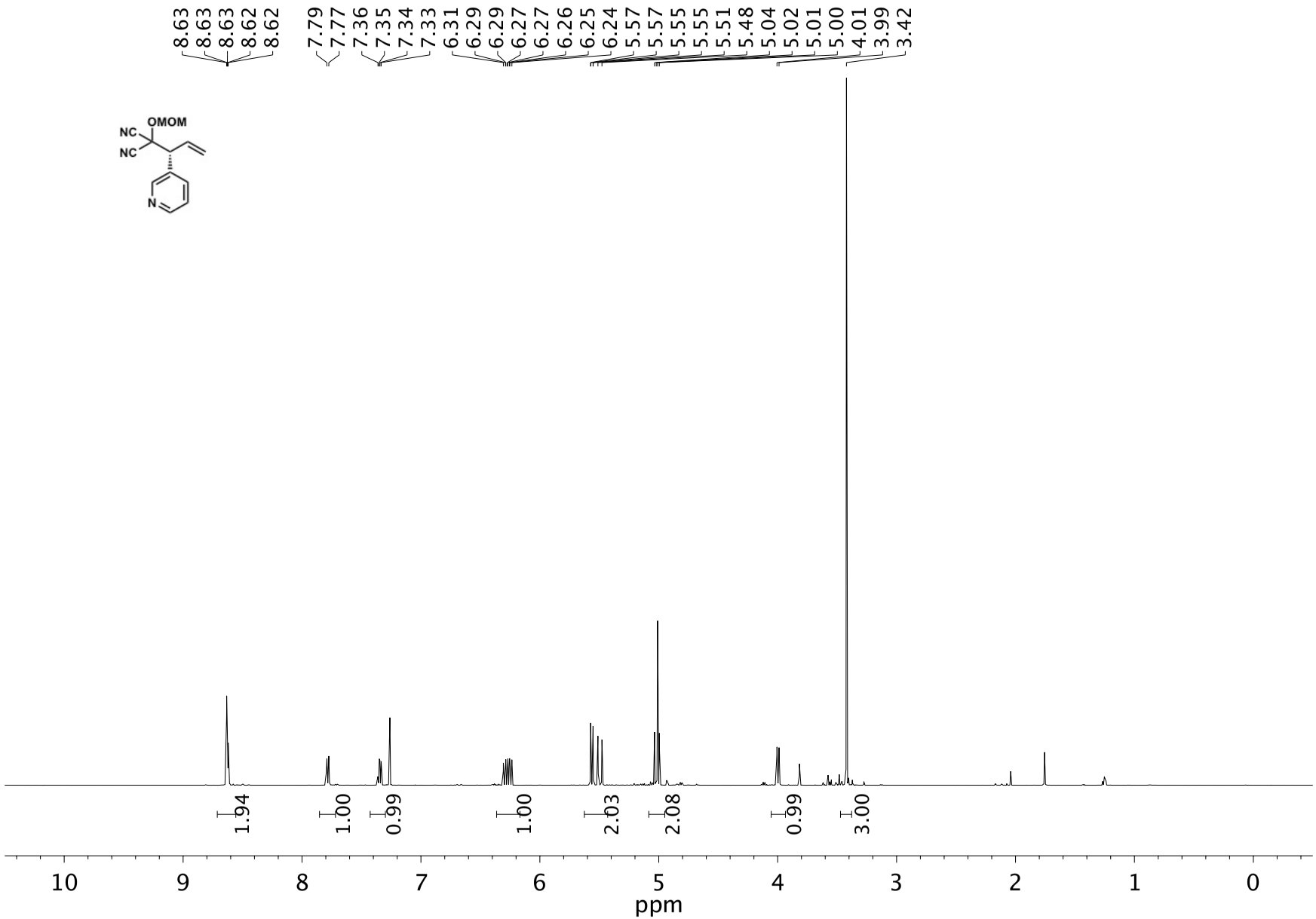
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6i**.



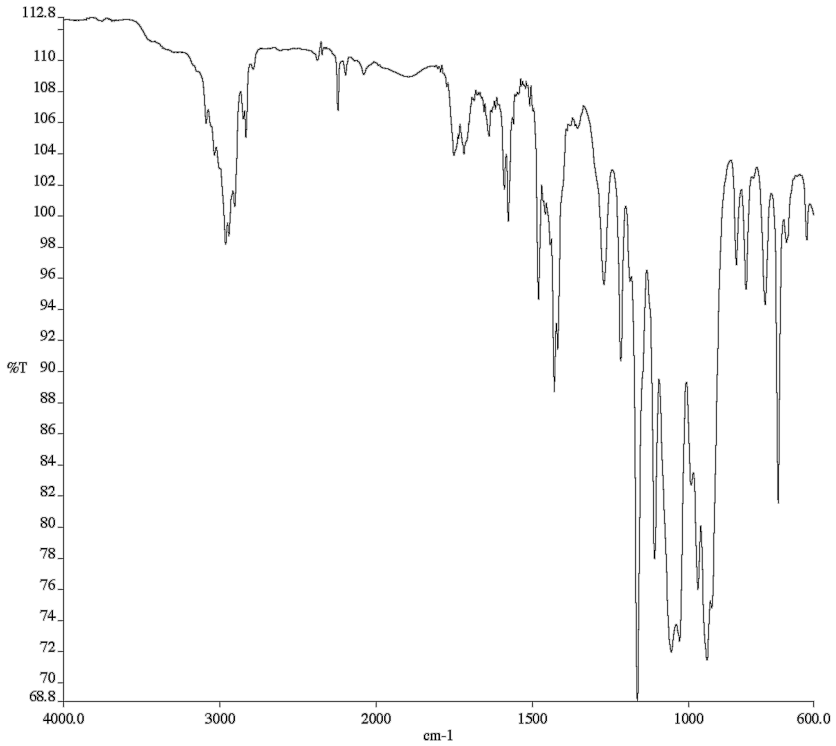
Infrared spectrum (Thin Film, NaCl) of compound **6i**.



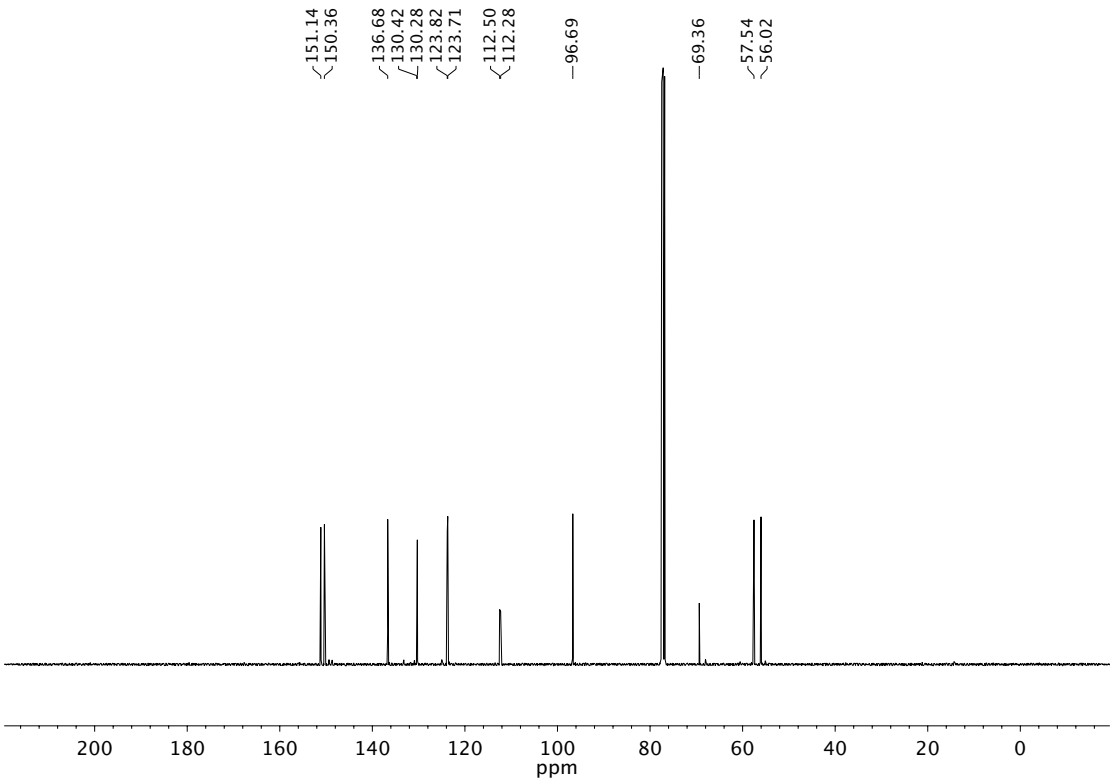
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6i**.



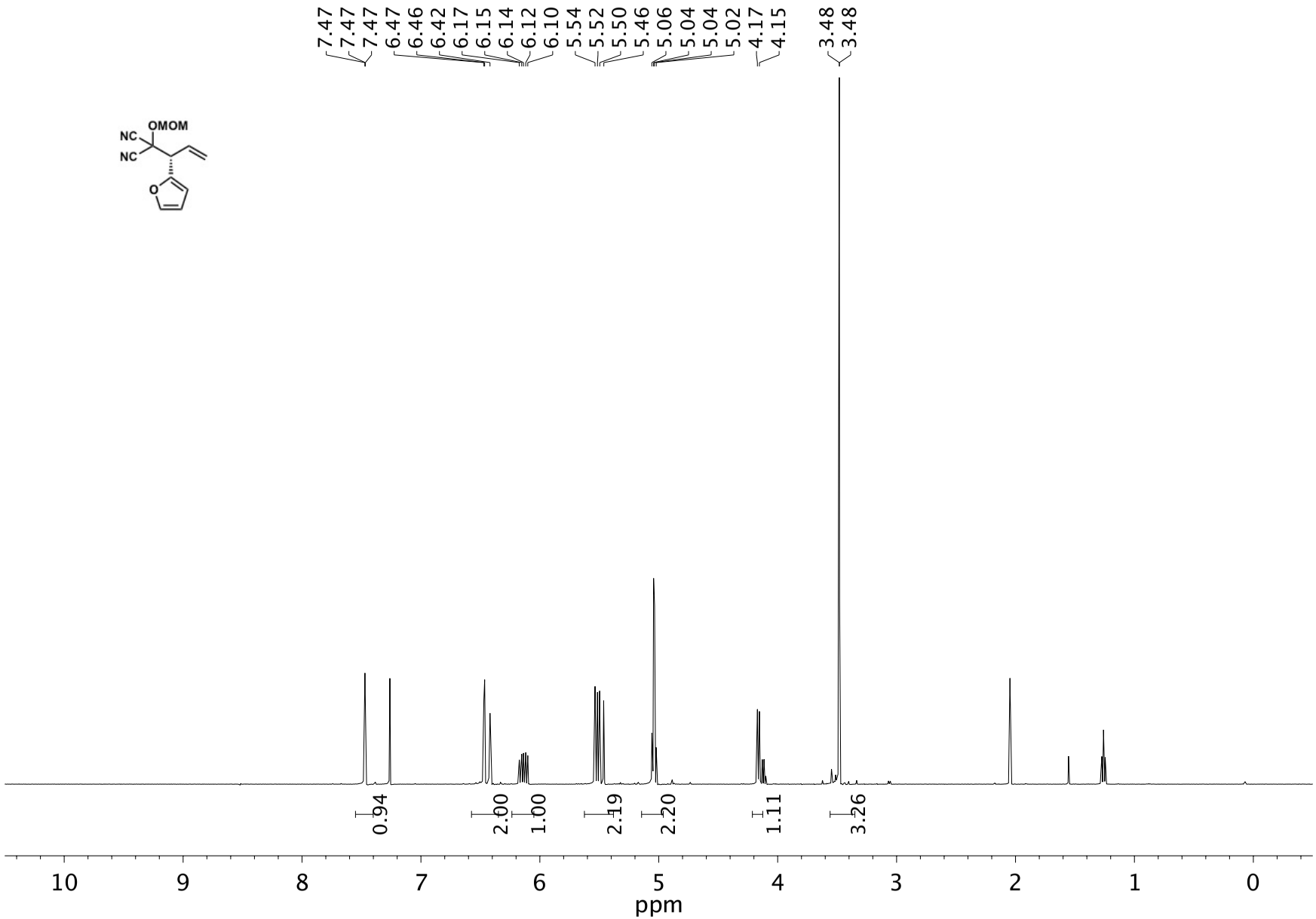
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6j**.



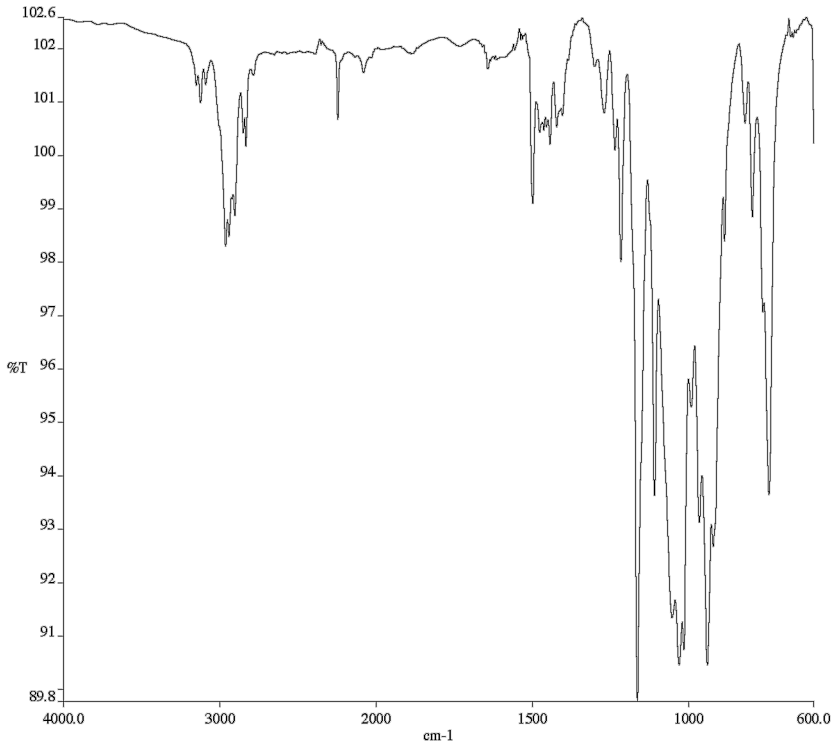
Infrared spectrum (Thin Film, NaCl) of compound **6j**.



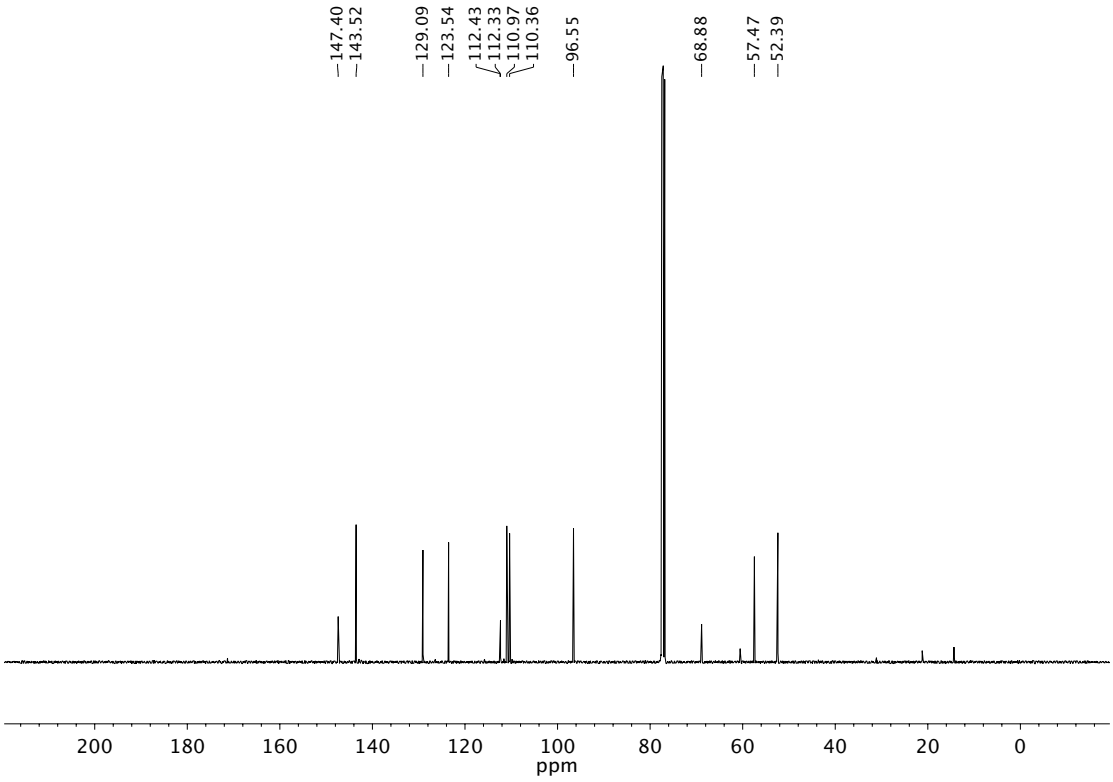
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6j**.



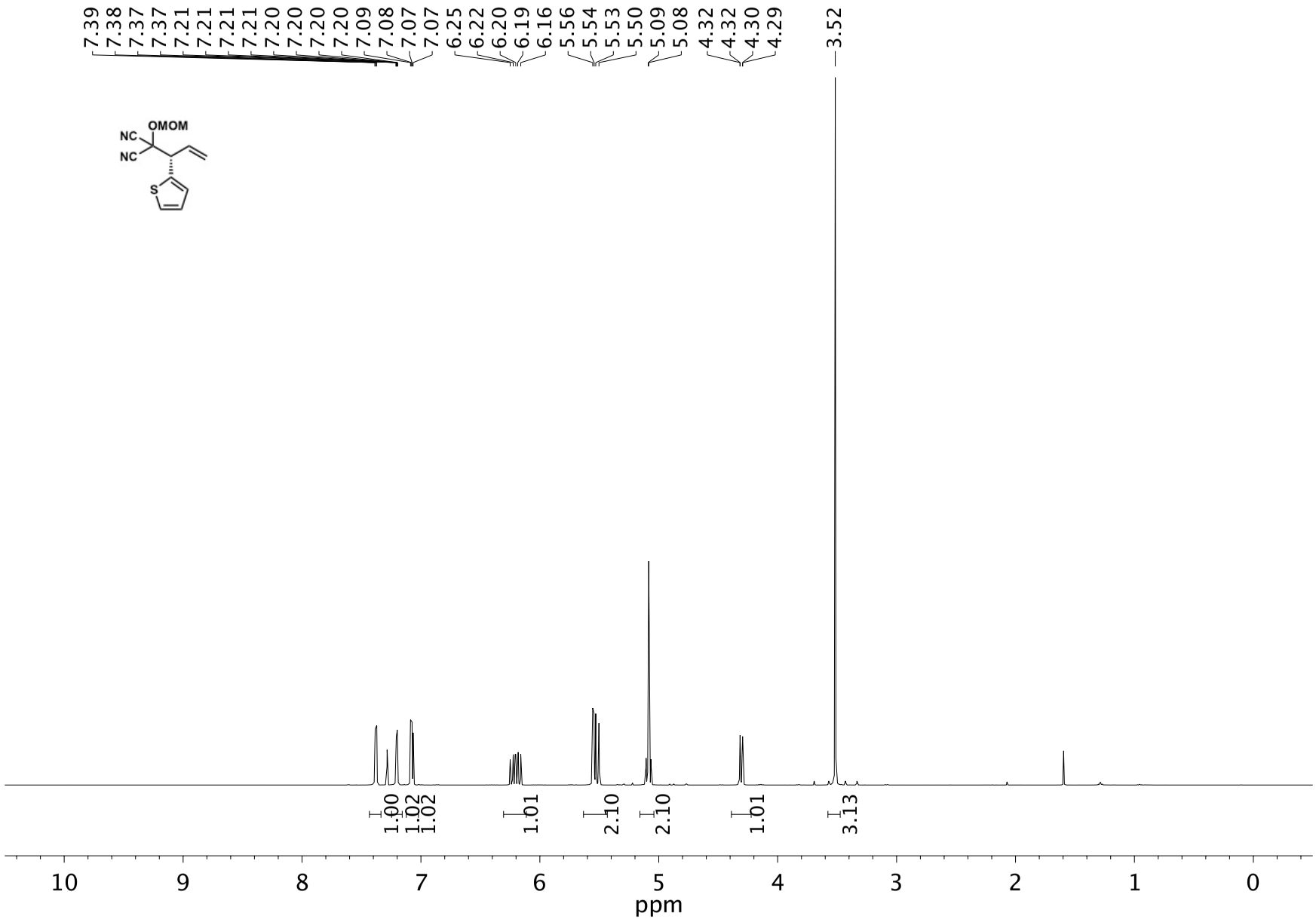
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6k**.



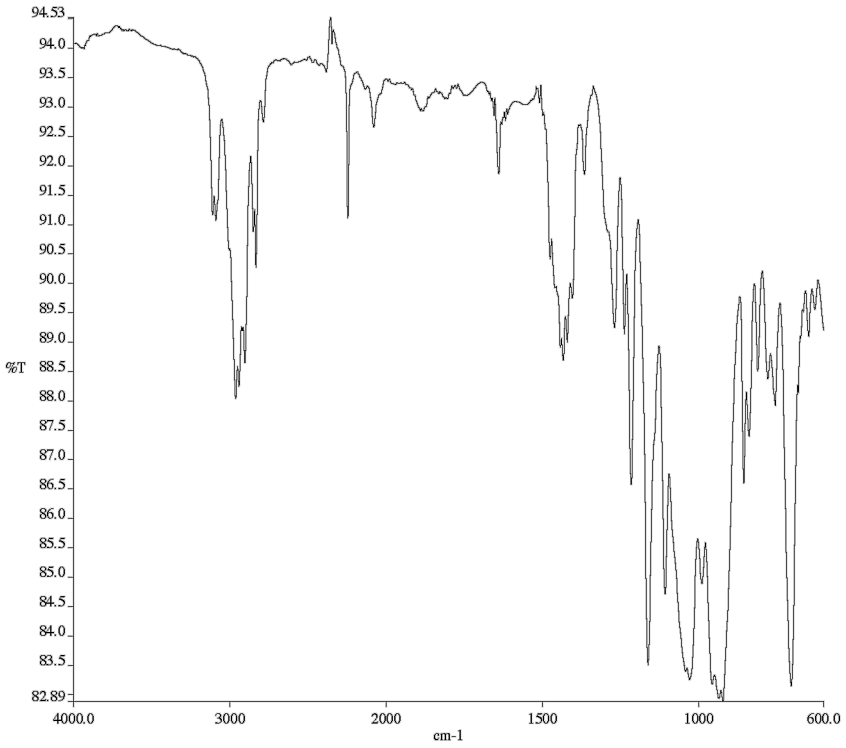
Infrared spectrum (Thin Film, NaCl) of compound **6k**.



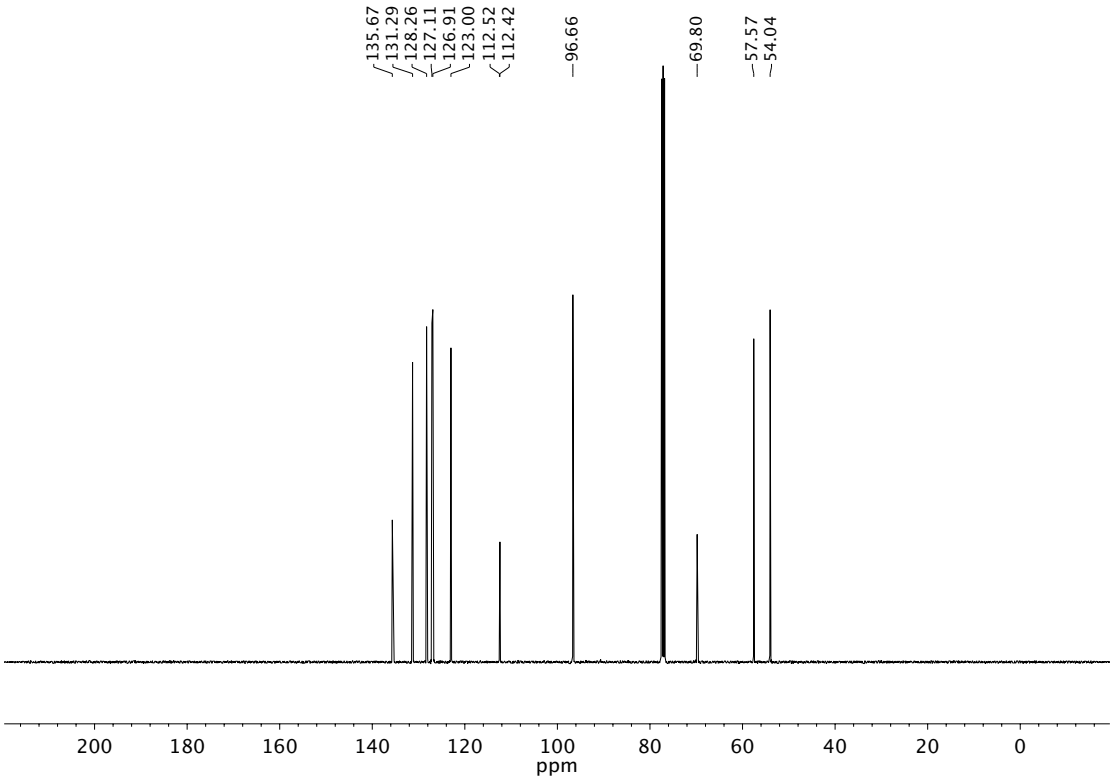
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6k**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **6l**.



Infrared spectrum (Thin Film, NaCl) of compound **6l**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **6l**.