Electronic Supplementary Material (ESI) for Chemical Communications.

Supporting Information

Transition metal free ether coupling and hydroamidation enabling efficient synthesis of congested heterocycles.

*Goki Hirata, Yusuke Shimoharai, Taisei Shimada, Takashi Nishikata**

Graduate School of Science and Engineering,Yamaguchi University, Ube, Yamaguchi, 755-8611, Japan

Corresponding Author: nisikata@yamaguchi-u.ac.jp

Table of Contents

1. General Procedures S2
2. Reactions with diastereo-enriched tert-alkyl bromide S21
3. Applications S25
4. Spectral charts for compounds S27

1. General Information

All reactions were carried out under nitrogen (99.95%) atmosphere. For TLC analyses precoated Kieselgel 60 F254 plates (Merck, 0.25 mm thick) were used; for column chromatography Silica *Flash*® P60 (SiliCycle, 40-63 μm) was used. Visualization was accomplished by UV light (254 nm), ^{1}H and ^{13}C NMR spectra were obtained using a JEOL 400 MHz NMR spectrometer. Chemical shifts for 1H NMR were described in parts per million (chloroform as an internal standard δ = 7.26) in $CDCl_3$, unless otherwise noted. Chemical shifts for ^{13}C NMR were expressed in parts per million in $CDCl_3$ as an internal standard (δ= 77.16), unless otherwise noted. High resolution mass analyses were obtained using ACQUITY UPLC/ TOF-MS for ESI. Anhydrous toluene and dichloromethane were purchased from Kanto Chemical Co., Ltd. Other chemicals were purchased from TCI, Aldrich and Wako and directly used from the bottles. Copper iodide (first grade; Lot. No. H28682K) was purchased from Kishida chemicals Co., Ltd. Cs_2CO_3 was provided by Iwatani.

1. General procedure

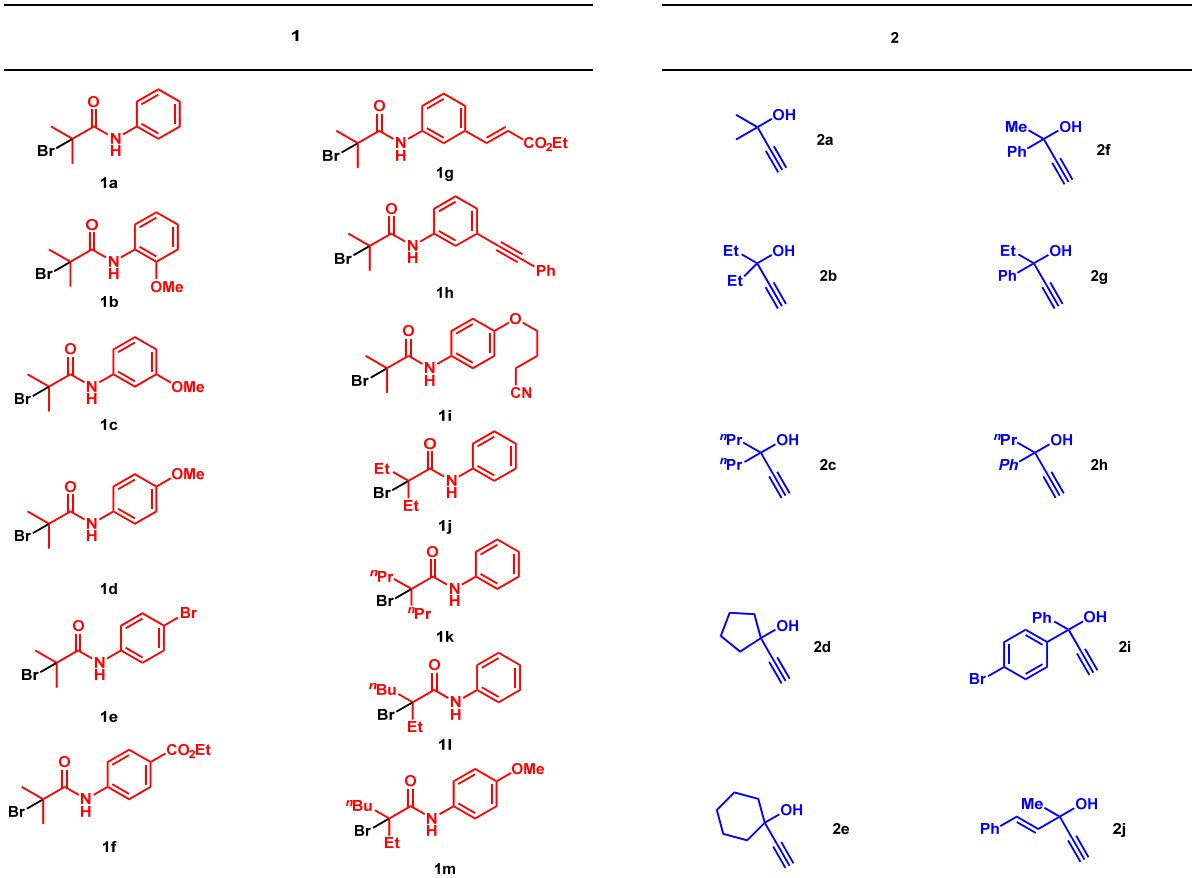


Figure 1. Starting materials.

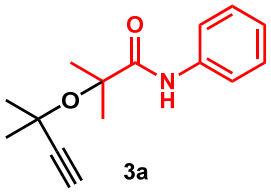
General procedure for the synthesis of ethers 3.

Substrate **1** (0.50 mmol), alcohol **2** (1.50 mmol, 3.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.0 equiv) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), dried THF (0.25 mL) was added by syringe and the resulting mixture was vigorously stirred under nitrogen atmosphere for 24 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the product **3**.

General procedure for the synthesis of cyclic ethers 4.

Substrate **1** (0.50 mmol), alcohol **2** (1.50 mmol, 3.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.0 equiv) K_3PO_4 (212.3 mg, 1.00 mmol, 2.0 equiv) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), dried MeCN (0.125mL) and Hexane (0.125mL) were added by syringe and the resulting mixture was vigorously stirred under nitrogen atmosphere for 24 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the product **4**.

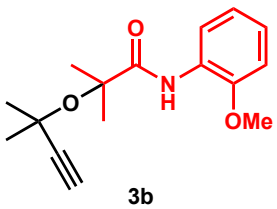
2-methyl-2-((2-methylbut-3-yn-2-yl)oxy)-N-phenylpropanamide (3a)



3a

Following the general procedure above, using **1a** (121.4 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (325.7 mg, 1.00 mmol, 1.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3a** (92.6 mg, 75%); IR (neat) ν: 3402, 3288, 2983, 2106, 1685, 1595, 1520,1439, 1132 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.62 (s, 6H), 1.65 (s, 6H), 2.49 (s, 6H), 7.10 (t, J = 7.52 Hz, 1H), 7.34 (t, J = 8.10 Hz, 2H), 7.54 (d, J = 7.90 Hz, 2H), 8.37 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 26.6, 32.6, 69.3, 75., 80.0, 85.3, 119.5, 124.1, 129.1, 137.9, 174.8; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{15}H_{20}O_2N$ 246.1494, found 246.1494.

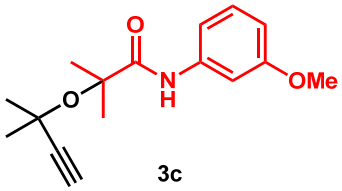
***N*-(2-methoxyphenyl)-2-methyl-2-((2-methylbut-3-yn-2-yl)oxy)propanamide (3b)**



3b

Following the general procedure above, using **1b** (138.0 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (332.9 mg, 1.00 mmol, 1.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3b** (116.8 mg, 85%); IR (neat) ν: 3402, 3287, 2983, 2107, 1685, 1518, 1132 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.63 (s, 6H), 1.64 (s, 6H), 2.46 (s, 6H), 3.90 (s, 3H), 6.89 (dd, *J* = 1.3 and 8.0 Hz, 1H), 6.96 (dt, *J* = 1.3 and 7.6 Hz, 1H), 7.04 (dt, *J* = 1.7 and 7.7 Hz, 1H), 8.43 (dd, *J* = 1.7 and 7.8 Hz, 1H), 9.10 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 26.6, 32.0, 55.5, 69.0, 74.9, 79.8, 85.3, 109.8, 118.9, 121.0, 123.2, 127.6, 147.8, 174.6; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{16}H_{22}O_3N$ 276.1600, found 276.1601.

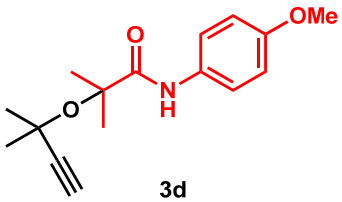
***N*-(3-methoxyphenyl)-2-methyl-2-((2-methylbut-3-yn-2-yl)oxy)propanamide (3c)**



3c

Following the general procedure above, using **1c** (136.0 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (163.3 mg, 0.50 mmol, 1.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3c** (98.6 mg, 72%); IR (neat) ν: 3403, 3303, 2983, 2249, 1687, 1604, 1523, 1132 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.62 (s, 6H), 1.64 (s, 6H), 2.50 (s, 1H), 3.82 (s, 3H), 6.66 (dd, *J* = 2.5 and 8.4 Hz, 1H), 6.95 (dd, *J* = 1.9 and 8.0 Hz, 1H), 7.22 (t, *J* = 8.1 Hz, 1H), 7.39 (t, *J* = 2.2 Hz, 1H), 8.38 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 26.6, 32.5, 55.3, 69.3, 75.2, 80.0, 85.1, 104.9, 110.0, 111.5, 129.7, 139.1, 160.3, 174.8; HRMS (EI-MS) m/z [M+H^+] $C_{16}H_{22}O_3N$ 276.1600, found 276.1600.

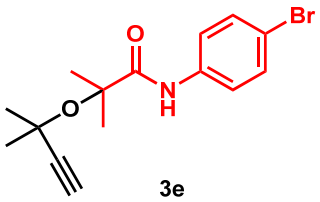
***N*-(4-methoxyphenyl)-2-methyl-2-((2-methylbut-3-yn-2-yl)oxy)propanamide (3d)**



3d

Following the general procedure above, using **1d** (136.2 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (244.4 mg, 0.75 mmol, 1.5 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3d** (93.3 mg, 68%); IR (neat) ν: 3407, 3302, 2984, 2248, 1682, 1512, 1244, 1132 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.62 (s, 6H), 1.64 (s, 6H), 2.50 (s, 1H), 3.79 (s, 3H), 6.87 (d, *J* = 9.0 Hz, 2H), 8.97 (d, *J* = 8.9 Hz, 2H), 8.26 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 26.6, 32.6, 55.5, 69.2, 75.1, 79.9, 85.3, 114.2, 121.2, 131.1, 156.2, 174.5; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{16}H_{22}O_3N$ 276.1600, found 276.1600.

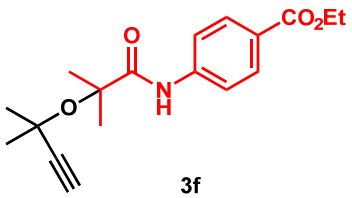
***N*-(4-bromophenyl)-2-methyl-2-((2-methylbut-3-yn-2-yl)oxy)propanamide (3e)**



3e

Following the general procedure above, using **1e** (160.6 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (244.6 mg, 0.75 mmol, 1.5 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3e** (115 mg, 68%); IR (neat) ν: 3370, 3294, 2981, 2108, 1684, 1502, 1392, 1131, 1008 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.61 (s, 6H), 1.63 (s, 6H), 2.48 (s, 1H), 7.44 (s, 4H), 8.37 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 26.6, 32.6, 69.4, 75.3, 80.0, 85.1, 116.5, 121.2, 132.0, 137.0, 174.9; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{15}H_{19}O_2NBr$ 324.0599, found 324.0600.

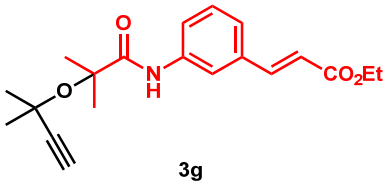
ethyl 4-(2-methyl-2-((2-methylbut-3-yn-2-yl)oxy)propanamido)benzoate (3f)



3f

Following the general procedure above, using **1f** (158.5 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (329.4 mg, 1.01 mmol, 2.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3f** (72.0 mg, 45 %); IR (neat) ν: 3342, 3279, 2989, 2110, 1688, 1516, 1271, 1101 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.39 (t, *J* = 7.2 Hz, 3H), 1.63 (s, 6H), 1.65 (s, 6H), 2.48 (s, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.7 Hz, 2H), 8.55 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 14.4, 26.5, 32.5, 60.9, 59.4, 75.4, 80.0, 84.9, 118.5, 125.7, 130.9, 141.9, 166.2, 175.1; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{18}H_{24}O_4N$ 318.1705, found 318.1704.

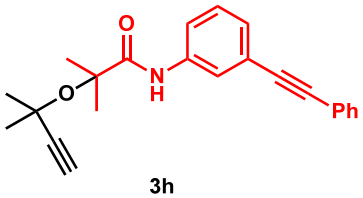
ethyl (E)-3-(3-(2-methyl-2-((2-methylbut-3-yn-2-yl)oxy)propanamido)phenyl)acrylate (3g)



3g

Following the general procedure above, using **1g** (175.1 mg, 0.51 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (327.8 mg, 1.01 mmol, 2.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3g** (112.5 mg, 64%); IR (neat) ν: 3342, 3279, 2989, 2110, 1688, 1516, 1271, 1101 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.33 (t, *J* = 7.2 Hz, 3H), 1.63 (s, 6H), 1.65 (s, 6H), 2.49 (s, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 6.46

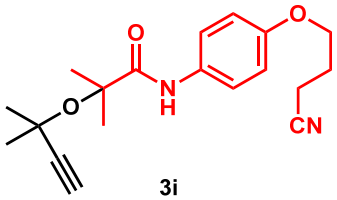
(d, J = 16.0 Hz, 1H), 7.27 (d, J = 5.1 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 16.0 Hz, 1H), 7.81 (s, 1H), 8.42 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 14.3, 26.5, 32.5, 60.5, 69.3, 75.3, 79.9, 85.1, 118.6, 118.9, 121.1, 123.8, 129.5, 135.4, 138.4, 144.2, 166.9, 175.0; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{20}H_{26}O_4N$ 344.1862, found 344.1862.



3h

Following the general procedure above, using **1h** (171.1 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (249.6 mg, 0.75 mmol, 1.5 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3h** (139.6 mg, 81%); IR (neat) ν: 3350, 3312, 2992, 2111, 1675, 1602, 1527, 1491, 1135 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.63 (s, 6H), 1.65 (s, 6H), 2.51 (s, 1H), 7.28-7.35 (m, 5H), 7.51-7.53 (m, 2H), 7.54 (d, J = 7.9 Hz, 1H), 7.72 (s, 1H), 8.40 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 26.6, 32.6, 69.4, 75.3, 80.0, 85.1, 89.1, 89.6, 119.5, 122.3, 123.2, 124.1, 127.3, 128.4, 129.1, 131.7, 137.9, 174.9; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{23}H_{24}O_2N$ 346.1807, found 346.1807.

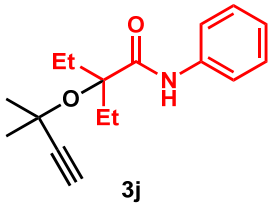
***N*-(4-(3-cyanopropoxy)phenyl)-2-methyl-2-((2-methylbut-3-yn-2-yl)oxy)propanamide (3i)**



3i

Following the general procedure above, using **1i** (162.7 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (244.2 mg, 0.75 mmol, 1.5 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3i** (113.0 mg, 69%); IR (neat) ν: 3402, 3286, 2983, 2246, 2106, 1678, 1509, 1230, 1132 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.62 (s, 6H), 1.64 (s, 6H), 2.13 (quint, J = 6.3 Hz, 2H), 2.50 (s, 1H), 2.59 (t, J = 7.0 Hz, 2H), 3.79 (s, 3H), 4.06 (t, J = 5.5 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 7.46 (d, J = 9.0 Hz, 2H), 8.28 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 14.1, 25.4, 26.5, 32.4, 65.5, 69.1, 75.0, 79.8, 85.2, 114.8, 119.2, 121.1, 131.5, 154.8, 174.4; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{19}H_{25}O_3N_2$ 329.1865, found 329.1865.

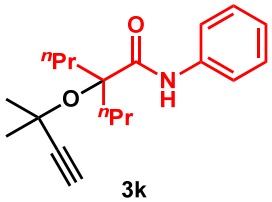
2-ethyl-2-((2-methylbut-3-yn-2-yl)oxy)-N-phenylbutanamide (3j)



3j

Following the general procedure above, using **1j** (143.7 mg, 0.53 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (346.3 mg, 1.06 mmol, 2.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3j** (107.0 mg, 74%); IR (neat) ν: 3390, 3278, 2984, 2105, 1671, 1529, 1436, 1124 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.94 (t, *J* = 7.1 Hz, 6H), 1.66 (s, 6H), 2.05-1.98 (m, 2H), 2.27-2.20 (m, 2H), 2.51 (s, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H), 8.53 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 8.6, 28.6, 32.9, 68.9, 74.4, 86.0, 87.0, 119.6, 124.0, 129.0, 137.7, 172.8; HRMS (EI-MS) m/z [$M+H^+$] Calcd for $C_{17}H_{24}O_2N$ 274.1807, found 274.1807.

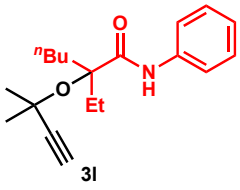
2-((2-methylbut-3-yn-2-yl)oxy)-N-phenyl-2-propylpentanamide (3k)



3k

Following the general procedure above, using **1k** (150.6 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.51 mmol, 3.0 equiv) and Cs_2CO_3 (328.9 mg, 1.01 mmol, 2.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3k** (115.0 mg, 76%); IR (neat) ν: 3309, 2959, 2111, 1667, 1519, 1437, 1128 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.89 (t, *J* = 7.8 Hz, 6H), 1.32-1.24 (m, 2H), 1.52-1.44 (m, 2H), 1.64 (s, 6H), 1.95-1.89 (m, 2H), 2.17-2.11 (m, 2H), 2.51 (s, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 8.55 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 14.1, 17.2, 32.9, 38.6, 68.9, 74.1, 86.3, 100.0, 119.6, 124.1, 129.1, 137.7, 173.0; HRMS (EI-MS) m/z [$M+H^+$] Calcd for $C_{19}H_{28}O_2N$ 302.2120, found 302.2120.

2-ethyl-2-((2-methylbut-3-yn-2-yl)oxy)-*N*-phenylhexanamide (3l)

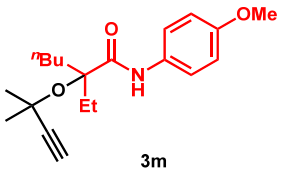


3l

Following the general procedure above, using **1l** (149.1 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.5 mmol, 3.0 equiv) and Cs_2CO_3 (246.7 mg, 0.75 mmol, 1.5 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3l** (121.0 mg, 80%); IR (neat) ν: 3308, 2955, 2104, 1665, 1593, 1516, 1437, 1125 cm^{-1}. ^1H NMR

($CDCl_3$) δ: 0.88 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), 1.21-1.33 (m, 3H), 1.39-1.47 (m, 1H), 1.65 (s, 6H), 1.91-2.05 (m, 2H), 2.13-2.27 (m, 2H), 2.50 (s, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 7.3 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 8.55 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 8.6, 14.1, 22.9, 26.0, 28.9, 32.9, 33.0, 35.9, 68.9, 74.3, 86.2, 86.7, 119.6, 124.1, 129.0, 137.7, 172.9; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{19}H_{28}O_2N$ 302.2120, found 302.2121.

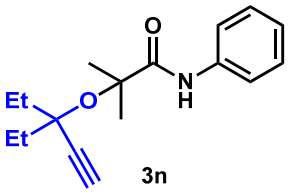
2-ethyl-*N*-(4-methoxyphenyl)-2-((2-methylbut-3-yn-2-yl)oxy)hexanamide (3m)



3m

Following the general procedure above, using **1m** (167.0 mg, 0.51 mmol), alcohol **2a** (0.15 mL, 1.51 mmol, 3.0 equiv) and Cs_2CO_3 (331.9 mg, 1.02 mmol, 2.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3m** (132.6 mg, 79%); IR (neat) ν: 3264, 3310, 2959, 2101, 1659, 1508, 1230, 1125 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), 1.19-1.33 (m, 3H), 1.39-1.48 (m, 1H), 1.64 (s, 6H), 1.90-2.04 (m, 2H), 2.13-2.27 (m, 2H), 2.50 (s, 1H), 3.79 (s, 3H), 6.87 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 9.0 Hz, 2H), 8.42 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 8.7, 14.1, 22.9, 26.1, 29.0, 32.9, 33.0, 36.0, 55.6, 68.8, 74.2, 86.3, 86.6, 114.2, 121.3, 131.0, 156.2, 172.6; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{20}H_{30}O_3N$ 332.2226, found 332.2226.

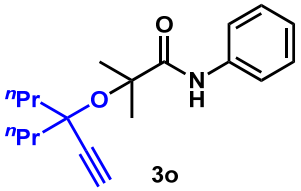
2-((3-ethylpent-1-yn-3-yl)oxy)-2-methyl-N-phenylpropanamide (3n)



3n

Following the general procedure above, using **1a** (121.1 mg, 0.50 mmol), alcohol **2b** (167.0 mg, 1.49 mmol, 3.0 equiv) and Cs_2CO_3 (325.6 mg, 1.00 mmol, 1.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3n** (85.1 mg, 62%); IR (neat) ν: 3390, 3295, 2974, 2937, 2104, 1685, 1518, 1438 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.04 (t, J = 7.2 Hz, 6H), 1.67 (s, 6H), 1.91-1.78 (s, 4H), 2.54 (s, 1H), 7.10 (t, J = 7.4 Hz, 1H), 7.33 (t, J = 8.5 Hz, 2H), 7.55 (d, J = 8.7 Hz, 2H), 8.50 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 8.6, 26.4, 33.5, 76.0, 76.7, 80.0, 84.1, 119.4, 124.0, 129.1, 137.9, 174.8; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{17}H_{24}O_2N$ 274.1807, found 274.1807.

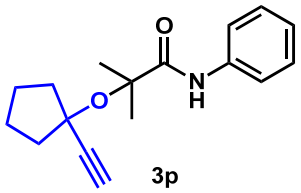
2-((4-ethynylheptan-4-yl)oxy)-2-methyl-N-phenylpropanamide (3o)



3o

Following the general procedure above, using **1a** (121.1 mg, 0.50 mmol), alcohol **2o** (209.2 mg, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (325.2 mg, 1.00 mmol, 1.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3o** (86.5 mg, 57%); IR (neat) ν: 3391, 3301, 2959, 2872, 2103, 1685, 1518, 1438 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.98 (t, *J* = 7.5 Hz, 6H), 1.55-1.46 (m, 4H), 1.66 (s, 6H), 1.84-1.73 (m, 4H), 2.52 (s, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 8.49 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 14.3, 17.6, 26.4, 43.7, 75.2, 76.5, 80.1, 84.5, 119.4, 124.0, 129.1, 138.0, 174.8; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{19}H_{28}O_2N$ 302.2120, found 302.2121.

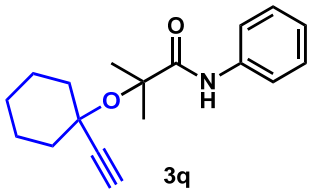
2-((1-ethynylcyclopentyl)oxy)-2-methyl-N-phenylpropanamide (3p)



3p

Following the general procedure above, using **1a** (120.9 mg, 0.50 mmol), alcohol **2p** (167.2 mg, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 1.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3p** (85.3 mg, 63%); IR (neat) ν: 3401, 3301, 2958, 2246, 2106, 1685, 1520, 1439 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.63 (s, 6H), 1.84-1.75 (m, 4H), 2.07-2.03 (m, 2H), 2.16-2.11 (m, 2H), 2.52 (s, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 8.40 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 23.2, 26.4, 43.3, 76.0, 78.7, 79.7, 85.0, 119.6, 124.0, 129.0, 137.9, 174.9; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{17}H_{22}O_2N$ 272.1651, found 272.1651.

2-((1-ethynylcyclohexyl)oxy)-2-methyl-N-phenylpropanamide (3q)

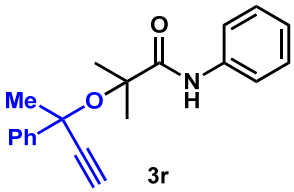


3q

Following the general procedure above, using **1a** (121.0 mg, 0.50 mmol), alcohol **2q** (0.19 mL, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (326.1 mg, 1.00 mmol, 1.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3q** (108.3 mg, 76 %); IR (neat) ν: 3401, 3295, 2932, 2857, 1940, 1685, 1517, 1438, 1049 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.30-1.23 (m, 1H), 1.61-1.54 (m, 3H), 1.64 (s, 6H), 1.76-1.68 (m, 4H), 2.05-2.01 (m, 2H), 2.57 (s, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 8.44 (brs, 1H). ^{13}C

NMR ($CDCl_3$) δ: 23.1, 25.1, 26.9, 40.8, 73.3, 77.9, 79.9, 83.7, 119.5, 124.0, 129.1, 138.0, 175.0; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{18}H_{24}O_2N$ 286.1807, found 286.1807.

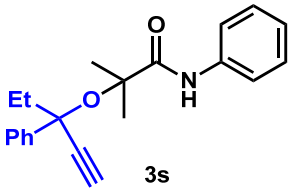
2-methyl-N-phenyl-2-((2-phenylbut-3-yn-2-yl)oxy)propanamide (3r)



3r

Following the general procedure above, using **1a** (121.1 mg, 0.50 mmol), alcohol **2r** (219.4 mg, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (325.2 mg, 1.00 mmol, 1.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3r** (97.6 mg, 63%); IR (neat) ν: 3394, 3211, 2977, 2100, 1676, 1524, 1056 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.34 (s, 3H), 1.54 (s, 3H), 1.85 (s, 3H), 2.78 (s, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.39-7.30 (m, 5H), 7.52 (t, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 8.52 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 23.7, 29.1, 36.6, 74.2, 78.9, 80.7, 82.8, 119.6, 124.0, 125.2, 127.9, 128.4, 129.1, 137.9, 145.3, 174.7; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{20}H_{22}O_2N$ 308.1651, found 308.1651.

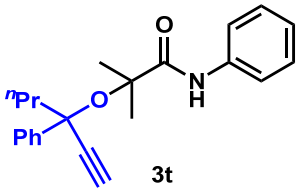
2-methyl-N-phenyl-2-((3-phenylpent-1-yn-3-yl)oxy)propanamide (3s)



3s

Following the general procedure above, using **1a** (121.1 mg, 0.50 mmol), alcohol **2s** (250.0 mg, 1.56 mmol, 3.0 equiv) and Cs_2CO_3 (325.7 mg, 1.00 mmol, 1.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3s** (119.9 mg, 74%); IR (neat) ν: 3400, 3217, 2967, 2920, 2101, 1682, 1507, 1438 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 0.99 (t, *J* = 7.0 Hz, 3H), 1.31 (s, 3H), 1.51 (s, 3H), 1.97-1.91 (m, 1H), 2.17-2.10 (m, 1H), 2.79 (s, 1H), 7.11 (t, *J* = 7.3 Hz, 1H), 7.38-7.29 (m, 5H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 8.58 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 9.5, 23.5, 29.5, 41.0, 78.3, 79.7, 80.6, 81.6, 119.4, 124.0, 125.8, 127.8, 128.2, 129.1, 138.0, 144.1, 174.7; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{21}H_{24}O_2N$ 322.1807, found 322.1807.

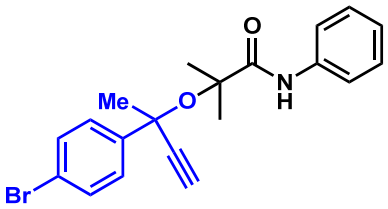
2-methyl-N-phenyl-2-((3-phenylhex-1-yn-3-yl)oxy)propanamide (3t)



3t

Following the general procedure above, using **1a** (121.2 mg, 0.50 mmol), alcohol **2o** (260.5 mg, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 1.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3t** (114.7 mg, 68%); IR (neat) ν: 3389, 3235, 2959, 2872, 2103, 1688, 1503, 1435 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.92 (t, *J* = 7.33 Hz, 3H), 1.30 (s, 3H), 1.25-1.34 (m, 1H), 1.50 (s, 3H), 1.63-1.55 (m, 1H), 1.89-1.83 (m, 1H), 2.10-2.04 (m, 1H), 2.78 (s, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.38-7.29 (m, 5H), 7.55 (t, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 8.57 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 14.0, 18.4, 23.5, 29.6, 50.3, 77.8, 79.6, 80.7, 82.0, 119.5, 124.0, 125.8, 127.8, 128.3, 129.1, 138.0, 144.5, 174.8; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{22}H_{26}O_2N$ 336.1964, found 336.1965.

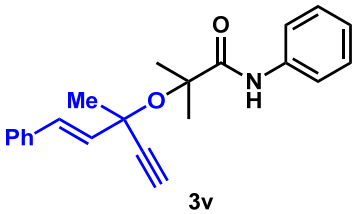
2-((2-(4-bromophenyl)but-3-yn-2-yl)oxy)-2-methyl-N-phenylpropanamide (3u)



3u

Following the general procedure above, using **1a** (120.9 mg, 0.50 mmol), alcohol **2u** (357.8 mg, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 1.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3u** (121.0 mg, 63%); IR (neat) ν: 3402, 3291, 2981, 2930, 2246, 2109, 1685, 1519, 1483, 1437 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.32 (s, 3H), 1.52 (s, 3H), 1.81 (s, 3H), 2.79 (s, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 2H), 7.55-7.49 (m, 6H), 8.44 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 23.6, 29.4, 36.5, 73.8, 79.3, 80.8, 82.2, 119.6, 121.9, 124.2, 127.1, 129.1, 131.6, 137.8, 144.6, 174.5; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{20}H_{21}O_2NBr$ 386.0756, found 386.0756.

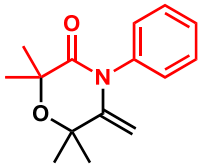
***(E)*-2-methyl-2-((3-methyl-1-phenylpent-1-en-4-yn-3-yl)oxy)-N-phenylpropanamide (3v)**



3v

Following the general procedure above, using **1a** (121.4 mg, 0.50 mmol), alcohol **2v** (259.1 mg, 1.50 mmol, 3.0 equiv) and Cs_2CO_3 (325.5 mg, 1.00 mmol, 1.0 equiv), and dried THF (0.25 mL) at 20 °C, yielded the product **3v** (87.2 mg, 50%); IR (neat) ν: 3397, 3298, 2982, 2928, 2247, 2110, 1685, 1520, 1483 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.62 (s, 3H), 1.63 (s, 3H), 1.75 (s, 3H), 2.75 (s, 1H), 6.29 (d, *J* = 16.0 Hz, 1H), 6.88 (d, *J* = 16.0 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.41-7.28 (m, 7H), 7.54 (d, *J* = 7.6 Hz, 2H), 8.45 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ: 25.7, 27.8, 33.2, 72.7, 78.5, 80.8, 82.5, 119.6, 124.1, 128.8, 133.3, 136.1, 137.9, 174.7; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{22}H_{24}O_2N$ 334.1807, found 334.1807.

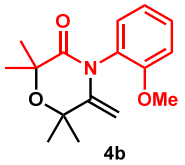
2,2,6,6-tetramethyl-5-methylene-4-phenylmorpholin-3-one (4a)



4a

Following the general procedure above, using **1a** (121.1 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) , K_3PO_4 (212.3 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 20 °C, yielded the product **4a** (90.6 mg, 74 %); IR (neat) ν: 2984, 2244, 1685, 1630, 1378, 1190, 1145, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.52 (s, 6H), 1.56 (s, 6H), 4.00 (d, *J* = 1.8 Hz, 1H), 4.48 (d, *J* = 1.8 Hz, 1H), 7.17 (dd, *J* = 1.2 and 7.5 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 27.8, 28.5, 72.7, 75.7, 94.9, 127.8, 128.1, 129.5, 139.5, 151.7, 172.4; HRMS (EI-MS) m/z [$M+H^+$] Calcd for $C_{15}H_{20}O_2N$ 246.1494, found 246.1494.

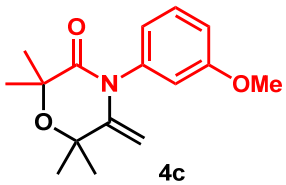
4-(2-methoxyphenyl)-2,2,6,6-tetramethyl-5-methylenemorpholin-3-one (4b)



4b

Following the general procedure above, using **1b** (151.7 mg, 0.55 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) , K_3PO_4 (543.2 mg, 2.56 mmol, 5.0 equiv) and Cs_2CO_3 (824.3 mg, 2.53 mmol, 5.0 equiv), and dried MeCN (0.25 mL) and Hexane (0.25 mL) at 20 °C, yielded the product **4b** (117.1 mg, 76 %); IR (neat) ν: 2982, 1672, 1632, 1500, 1381, 1114 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.52 (s, 3H), 1.53 (s, 3H), 1.54 (s, 3H), 1.56 (s, 3H), 3.89 (d, *J* = 1.7 Hz, 1H), 4.34 (d, *J* = 1.7 Hz, 1H),6.98-7.03 (m, 2H), 7.08 (dd, *J* = 1.8 and 7.7 Hz, 1H), 7.32-7.36 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 28.0, 28.23, 28.29, 28.7, 55.7, 72.8, 75.9, 92.3, 112.4, 121.2, 127.7, 129.64, 129.66, 150.8, 155.3, 172.3; HRMS (EI-MS) m/z [$M+H^+$] Calcd for $C_{16}H_{22}O_3N$ 276.1600, found 276.1600.

4-(3-methoxyphenyl)-2,2,6,6-tetramethyl-5-methylenemorpholin-3-one (4c)

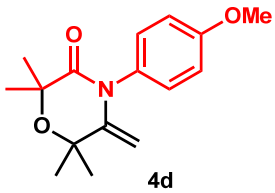


4c

Following the general procedure above, using **1c** (138.1 mg, 0.51 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) , K_3PO_4 (217.9 mg, 1.03 mmol, 2.0 equiv) and Cs_2CO_3 (332.8 mg, 1.02 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 20 °C, yielded the product **4c** (98.8 mg, 71%); IR (neat) ν: 2981, 1685, 1602, 1630, 1485, 1377, 1308, 1188, 1144 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.51 (s, 6H),

1.54 (s, 6H), 4.05 (d, J = 1.7 Hz, 1H), 4.47 (d, J = 1.7 Hz, 1H), 6.69 (t, J = 8.1 Hz, 1H), 6.76 (dd, J = 1.3 and 8.1 Hz, 1H), 6.88 (dd, J = 2.1 and 8.7 Hz, 1H), 7.35 (t, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 27.8, 28.5, 55.4, 72.7, 75.7, 95.0, 113.5, 113.9, 120.3, 130.3, 140.5, 151.4, 160.5, 172.3; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{16}H_{22}O_3N$ 276.1600, found 276.1600.

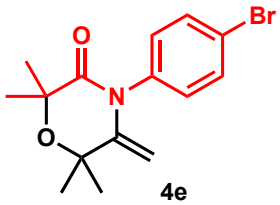
4-(4-methoxyphenyl)-2,2,6,6-tetramethyl-5-methylenemorpholin-3-one (**4d**)



4d

Following the general procedure above, using **1d** (138.0 mg, 0.51 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) , K_3PO_4 (212.2 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (332.9 mg, 1.02 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 20 °C, yielded the product **4d** (91.6 mg, 66%); IR (neat) ν: 2980, 1667, 1627, 1508, 1378, 1244, 1147, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.51 (s, 6H), 1.54 (s, 6H), 4.01 (d, J = 1.7 Hz, 1H), 4.45 (d, J = 1.7 Hz, 1H), 6.69 (t, J = 8.1 Hz, 1H), 6.76 (dd, J = 1.3 and 8.1 Hz, 1H), 6.95 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 27.8, 28.5, 55.5, 72.6, 75.7, 94.5, 114.8, 129.0, 132.0, 151.9, 158.9, 172.6; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{16}H_{22}O_3N$ 276.1600, found 276.1601.

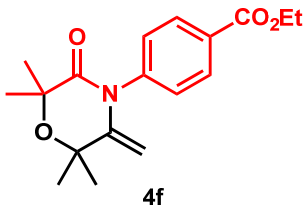
4-(4-bromophenyl)-2,2,6,6-tetramethyl-5-methylenemorpholin-3-one (**4e**)



4e

Following the general procedure above, using **1e** (158.9 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) , K_3PO_4 (217.9 mg, 1.03 mmol, 2.0 equiv) and Cs_2CO_3 (338.3 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 20 °C, yielded the product **4e** (112.1 mg, 70%); IR (neat) ν: 2980, 1680, 1629, 1485, 1305, 1188, 1151, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.50 (s, 6H), 1.53 (s, 6H), 4.01 (d, J = 1.9 Hz, 1H), 4.50 (d, J = 1.9 Hz, 1H), 7.05 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H). δ: 1.40 (t, J = 7.2 Hz, 3H), 1.51 (s, 6H), 1.55 (s, 6H), 4.02 (d, J = 1.9 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 4.50 (d, J = 1.9 Hz, 1H), 7.26 (d, J = 8.7 Hz, 2H), 8.11 (d, J = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 27.7, 28.5, 72.7, 75.7, 95.3, 121.6, 129.8, 132.8, 138.5, 151.5, 172.3; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{15}H_{19}O_2NBr$ 324.0599, found 324.0599.

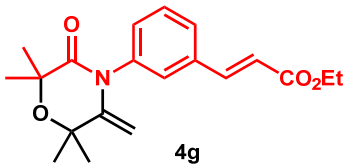
ethyl 4-(2,2,6,6-tetramethyl-3-methylene-5-oxomorpholino)benzoate (4f)



4f

Following the general procedure above, using **1f** (159.8 mg, 0.51 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) , K_3PO_4 (214.2 mg, 1.01 mmol, 2.0 equiv) and Cs_2CO_3 (325.5 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 20 °C, yielded the product **4f** (54.9 mg, 34%); IR (neat) ν: 2975, 1717, 1693, 1627, 1372, 1268, 1197, 1017cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.40 (t, *J* = 7.2 Hz, 3H), 1.51 (s, 6H), 1.55 (s, 6H), 4.02 (d, *J* = 1.9 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.50 (d, *J* = 1.9 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 8.11 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 14.4, 27.6, 28.4, 61.2, 72.8, 75.7, 95.8, 128.0, 129.7, 130.9, 143.6, 151.4, 165.8, 172.2; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{18}H_{24}O_4N$ 318.1705, found 318.1705.

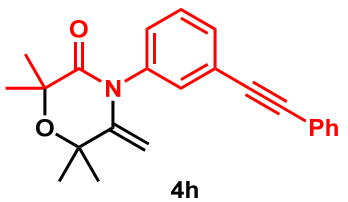
ethyl (E)-3-(3-(2,2,6,6-tetramethyl-3-methylene-5-oxomorpholino)phenyl)acrylate (4g)



4g

Following the general procedure above, using **1g** (179.5 mg, 0.53 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) , K_3PO_4 (214.6 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (326.8 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 20 °C, yielded the product **4g** (125.6 mg, 69%); IR (neat) ν: 2982, 1700, 1633, 1378, 1164, 1023 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, *J* = 7.2 Hz, 3H), 1.52 (s, 6H), 1.56 (s, 6H), 4.01 (d, *J* = 1.9 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.49 (d, *J* = 1.9 Hz, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 7.19 (dt, *J* = 1.8 and 7.7 Hz, 1H), 7.32 (s, 1H), 7.45-7.51 (m, 2H), 7.66 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 14.4, 26.6, 27.8, 28.5, 32.6, 60.7, 72.7, 75.7, 95.2, 127.5, 127.6, 129.8, 130.1, 136.1, 140.1, 143.5, 151.5, 166.7, 172.4; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{20}H_{26}O_4N$ 344.1862, found 344.1862.

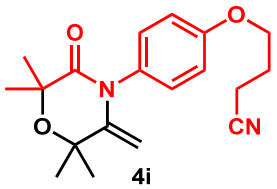
2,2,6,6-tetramethyl-5-methylene-4-(3-(phenylethynyl)phenyl)morpholin-3-one (4h)



4h

Following the general procedure above, using **1h** (171.0 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv) , K_3PO_4 (214.7 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (330.3 mg, 1.01 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 20 °C, yielded the product **4h** (120.4 mg, 70%); IR (neat) ν: 2975, 1678, 1627, 1310, 1188, 1148 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.52 (s, 6H), 1.56 (s, 6H), 4.05 (d, *J* = 1.9 Hz, 1H), 4.51 (d, *J* = 1.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.34-7.35 (m, 4H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.50-7.53 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 27.8, 28.5, 72.7, 75.8, 88.4, 90.5, 95.3, 123.0, 124.9, 128.2, 128.5, 128.6, 129.6, 131.1, 131.3, 131.7, 139.6, 151.4, 172.4; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{23}H_{24}O_2N$ 346.1807, found 346.1807.

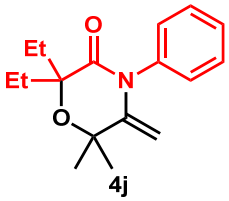
4-(4-(2,2,6,6-tetramethyl-3-methylene-5-oxomorpholino)phenoxy)butanenitrile (4i)



4i

Following the general procedure above, using **1i** (162.6 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv), K_3PO_4 (211.9 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (325.4 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 20 °C, yielded the product **4i** (111.3 mg,, 68%); IR (neat) ν: 2983, 2246, 1630, 1508, 1242, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.51 (s, 6H), 1.54 (s, 6H), 2.15 (quint, *J* = 6.4 Hz, 2H), 2.61 (t, *J* = 7.1 Hz, 2H), 4.01 (d, *J* = 1.6 Hz, 1H), 4.09 (t, *J* = 5.7 Hz, 2H), 4.46 (d, *J* = 1.6 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 7.08 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 14.1, 25.4, 27.8, 28.4, 65.5, 72.5, 75.6, 94.5, 115.3, 119.2, 129.1, 132.4, 151.7, 157.6, 172.5; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{19}H_{25}O_3N_2$ 329.1865, found 329.1865.

2,2-diethyl-6,6-dimethyl-5-methylene-4-phenylmorpholin-3-one (4j)

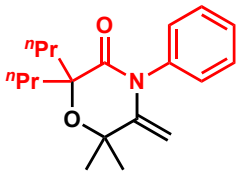


4j

Following the general procedure above, using **1j** (135.1 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv), K_3PO_4 (212.3 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 20 °C, yielded the product **4j** (91.1 mg,, 64%); IR (neat) ν: 2975, 1683, 1629, 1377, 1146 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.98 (t, *J* = 7.5 Hz, 6H), 1.57 (s, 6H), 1.87-1.82 (m, 4H), 3.96 (d, *J* = 1.7 Hz, 1H), 4.47 (d, *J* = 1.7 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 8.0, 14.2, 22.7, 28.4, 31.1, 31.7, 72.3, 80.7,

94.9, 127.9, 128.1, 129.6, 139.6, 151.5, 171.5; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{17}H_{24}O_2N$ 274.1807, found 274.1807.

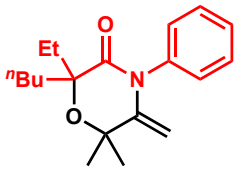
6,6-dimethyl-5-methylene-4-phenyl-2,2-dipropylmorpholin-3-one (4k)



4k

Following the general procedure above, using **1k** (149.1 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv), K_3PO_4 (212.3 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 20 °C, yielded the product **4k** (110.1 mg,, 73%); IR (neat) ν: 2985, 2871, 1670, 1626, 1318, 1146 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 0.92 (t, *J* = 7.1 Hz, 6H), 1.51-1.37 (m, 4H), 1.55 (s, 6H), 1.80-1.76 (m, 4H), 3.96 (d, *J* = 1.7 Hz, 1H), 4.46 (d, *J* = 1.7 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 14.2, 14.5, 16.9, 22.7, 28.4, 31.7, 41.1, 72.3, 80.4, 94.8, 127.9, 128.1, 129.6, 189.6, 151.5, 171.6; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{19}H_{28}O_2N$ 302.2120, found 302.2120.

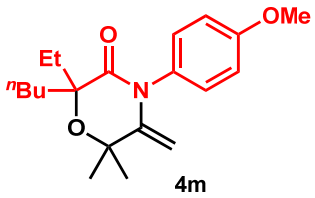
2-butyl-2-ethyl-6,6-dimethyl-5-methylene-4-phenylmorpholin-3-one (4l)



4l

Following the general procedure above, using **1l** (154.4 mg, 0.52 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv), K_3PO_4 (215.8 mg, 1.02 mmol, 2.0 equiv) and Cs_2CO_3 (326.0 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 20 °C, yielded the product **4l** (119.0 mg,, 76%); IR (neat) ν: 2957, 1694, 1629, 1378, 1167 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 0.91 (t, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H), 1.28-1.46 (m, 4H), 1.55 (s, 6H), 1.74-1.89 (m, 4H), 3.96 (d, *J* = 1.8 Hz, 1H), 4.46 (d, *J* = 1.8 Hz, 1H), 7.16 (dd, *J* = 1.1 and 8.3 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ:8.0, 14.2, 23.1, 25.6, 28.43, 28.48, 31.48, 38.0, 72.4, 80.5, 94.8, 127.8, 128.1, 129.5, 139.6, 151.5, 171.5; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{19}H_{28}O_2N$ 302.2120, found 302.2120.

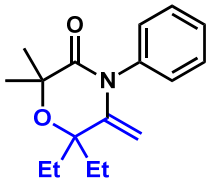
2-butyl-2-ethyl-4-(4-methoxyphenyl)-6,6-dimethyl-5-methylenemorpholin-3-one (4m)



4m

Following the general procedure above, using **1m** (162.4 mg, 0.50 mmol), alcohol **2a** (0.15 mL, 1.50 mmol, 3.0 equiv), K_3PO_4 (214.7 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (335.5 mg, 1.03 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 20 °C, yielded the product **4m** (122.6 mg,, 75%); IR (neat) ν: 2956, 1680, 1628, 1508, 1293, 1243, 1145, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.90 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H), 1.29-1.45 (m, 4H), 1.54 (s, 6H), 1.76-1.87 (m, 4H), 3.82 (s, 3H), 3.97 (d, J = 1.7 Hz, 1H), 4.43 (d, J = 1.7 Hz, 1H), 6.95 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ:8.0, 14.2, 23.1, 25.6, 28.4, 28.5, 31.5, 38.0, 55.5, 72.3, 80.5, 94.4, 114.8, 129.1, 132.1, 151.7, 158.9, 171.7; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{20}H_{30}O_3N$ 332.2226, found 332.2226.

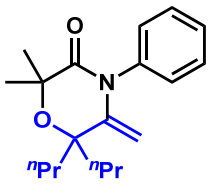
6,6-diethyl-2,2-dimethyl-5-methylene-4-phenylmorpholin-3-one (4n)



4n

Following the general procedure above, using **1a** (121.1 mg, 0.50 mmol), alcohol **2b** (168.3 mg, 1.50 mmol, 3.0 equiv), K_3PO_4 (212.3 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 50 °C, yielded the product **4n** (93.3 mg,, 68%); IR (neat) ν: 2971, 2937, 1686, 1626, 1181 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.97 (t, J = 7.4 Hz, 6H), 1.51 (s, 6H), 1.85-1.72 (m, 4H), 4.12 (d, J = 1.6 Hz, 1H), 4.36 (d, J = 1.6 Hz, 1H), 7.14 (d, J = 8.5 Hz, 2H), 7.35 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 8.2, 14.3, 21.14, 22.7, 27.8, 30.0, 31.7, 60.4, 75.2, 77.9, 96.9, 127.9, 128.3, 129.6, 139.5, 148.6, 171.2, 172.4; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{17}H_{24}O_2N$ 274.1807, found 274.1807.

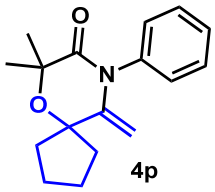
2,2-dimethyl-5-methylene-4-phenyl-6,6-dipropylmorpholin-3-one (4o)



4o

Following the general procedure above, using **1a** (121.1 mg, 0.50 mmol), alcohol **2c** (210.3 mg, 1.50 mmol, 3.0 equiv), K_3PO_4 (212.3 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 50 °C, yielded the product **4o** (107.1 mg,, 71%); IR (neat) ν: 2958, 2872, 1685, 1630, 1378 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.97 (t, J = 7.2 Hz, 6H), 1.48-1.36 (m, 4H), 1.50 (s, 6H), 1.78-1.66 (m, 4H), 4.09 (d, J = 1.8 Hz, 1H), 4.36 (d, J = 1.7 Hz, 1H), 7.12 (d, J = 8.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 14.6, 17.2, 27.9, 40.4, 75.2, 96.7, 127.9, 128.2, 129.7, 139.6, 149.2, 172.4; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{19}H_{28}O_2N$ 302.2120, found 302.2120.

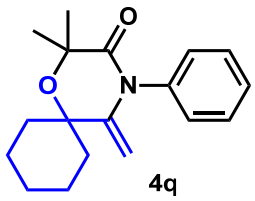
7,7-dimethyl-10-methylene-9-phenyl-6-oxa-9-azaspiro[4.5]decan-8-one (4p)



4p

Following the general procedure above, using **1a** (121.1 mg, 0.50 mmol), alcohol **2d** (165.2 mg, 1.50 mmol, 3.0 equiv), K_3PO_4 (212.3 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 50 °C, yielded the product **4n** (99.9 mg,, 73%); IR (neat) ν: 1617, 1373, 1156, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.52 (s, 6H), 1.75-1.68 (m, 2H), 1.93-1.87 (m, 2H), 2.06-1.98 (m, 4H), 4.01 (d, J = 1.6 Hz, 1H), 4.43 (d, J = 1.6 Hz, 1H), 7.16 (d, J = 8.2 Hz, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 23.1, 27.8, 38.5, 76.4, 83.7, 94.6, 127.9, 128.2, 129.6, 139.5, 150.3, 172.7; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{17}H_{22}O_2N$ 272.1651, found 272.1651.

2,2-dimethyl-5-methylene-4-phenyl-1-oxa-4-azaspiro[5.5]undecan-3-one (4q)

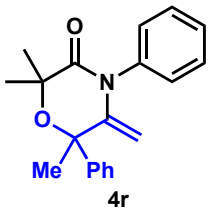


4q

Following the general procedure above, using **1a** (123.5 mg, 0.51 mmol), alcohol **2e** (193.5 mg, 1.56 mmol, 3.0 equiv), K_3PO_4 (214.6 mg, 1.01 mmol, 2.0 equiv) and Cs_2CO_3 (335.4 mg, 1.03 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 50 °C, yielded the product **4q** (129.1 mg,, 89%); IR (neat) ν: 2941, 1673, 1628, 1377, 1170, 1019 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.24-1.31 (m, 1H), 1.51 (s, 6H), 1.57-1.64 (m, 4H), 1.64-1.83 (m, 3H), 1.99-2.02 (m, 2H), 4.06 (d, J = 1.6 Hz, 1H), 4.52 (d, J = 1.6 Hz, 1H), 7.16 (d, J = 7.5 Hz, 2H), 7.32 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 21.8, 25.9, 27.8, 36.2, 73.1, 75.6, 96.0, 127.7, 128.1, 129.5, 139.8, 152.2, 172.4; HRMS (EI-MS) m/z [M+H^+] Calcd

for $C_{18}H_{24}O_2N$ 286.1807, found 286.1807.

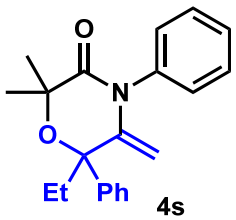
2,2,6-trimethyl-5-methylene-4,6-diphenylmorpholin-3-one (4r)



4r

Following the general procedure above, using **1a** (121.1 mg, 0.50 mmol), alcohol **2f** (219.3 mg, 1.50 mmol, 3.0 equiv), K_3PO_4 (212.3 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 25 °C, yielded the product **4r** (92.2 mg,, 60%); IR (neat) ν: 2986, 2936, 1685, 1627, 1379, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.49 (s, 3H), 1.62 (s, 3H), 1.79 (s, 3H), 4.36 (s, 1H), 4.71 (s, 1H), 6.95 (d, J = 7.3 Hz, 2H), 7.31 (d, J = 7.3 Hz, 2H), 7.38 (t, J = 7.5 Hz, 4H), 7.57 (d, J = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 26.4, 28.4, 29.6, 76.7, 77.8, 98.9, 126.0, 127.8, 127.8, 128.0, 128.3, 129.6, 139.3, 144.5, 149.7, 172.0; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{20}H_{22}O_2N$ 308.1651, found 308.1651.

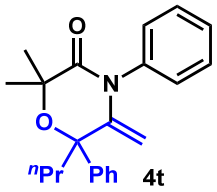
6-ethyl-2,2-dimethyl-5-methylene-4,6-diphenylmorpholin-3-one (4s)



4s

Following the general procedure above, using **1a** (123.1 mg, 0.51 mmol), alcohol **2g** (243.1 mg, 1.52 mmol, 3.0 equiv), K_3PO_4 (531.8 mg, 2.50 mmol, 5.0 equiv) and Cs_2CO_3 (814.7 mg, 2.50 mmol, 5.0 equiv), and dried MeCN (0.25 mL) and Hexane (0.25 mL) at 25 °C, yielded the product **4s** (116.5 mg, 71%); IR (neat) ν: 2981, 1684, 1633, 1489, 1380, 1252, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.92 (t, J = 7.2 Hz, 3H), 1.57 (s, 3H), 1.61 (s, 3H), 2.05-2.11 (m, 2H), 4.40 (d, J = 1.7 Hz, 1H), 4.77 (d, J = 1.7 Hz, 1H), 6.82 (dd, J = 1.0 and 8.0 Hz, 2H), 7.26-7.38 (m, 6H), 7.52 (dd, J = 1.1 and 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 8.2, 26.2, 27.8, 33.9, 76.3, 80.4, 99.6, 126.2, 127.5, 127.7, 127.8, 128.2, 129.5, 139.5, 143.6, 149.2, 171.8; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{21}H_{24}O_2N$ 322.1807, found 322.1807.

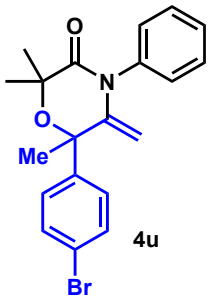
2,2-dimethyl-5-methylene-4,6-diphenyl-6-propylmorpholin-3-one (4t)



4t

Following the general procedure above, using **1a** (122.9 mg, 0.50 mmol), alcohol **2h** (265.1 mg, 1.52 mmol, 3.0 equiv), K_3PO_4 (532.6 mg, 2.51 mmol, 5.0 equiv) and Cs_2CO_3 (819.5 mg, 2.51 mmol, 5.0 equiv), and dried MeCN (0.25 mL) and Hexane (0.25 mL) at 25 °C, yielded the product **4t** (115.8 mg, 68%); IR (neat) ν: 2959, 1685, 1631, 1379, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.90 (t, *J* = 7.4 Hz, 3H), 1.20-1.29 (m, 1H), 1.57 (s, 3H), 1.61 (s, 3H), 1.5601.63 (m, 1H), 1.96-2.07 (m, 2H), 4.39 (s, 1H), 4.78 (s, 1H), 6.81 (d, *J* = 7.9 Hz, 2H), 7.27-7.37 (m, 6H), 7.52 (d, *J* = 7.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 14.5, 17.0, 26.2, 27.8, 43.4, 76.3, 80.3, 99.7, 126.2, 127.5, 127.7, 127.8, 128.2, 129.5, 139.5, 143.8, 149.4, 171.8; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{22}H_{26}O_2N$ 336.1964, found 336.1964.

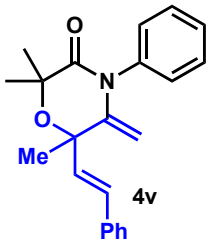
6-(4-bromophenyl)-2,2-dimethyl-5-methylene-4,6-diphenylmorpholin-3-one (4u)



4u

Following the general procedure above, using **1a** (121.1 mg, 0.50 mmol), alcohol **2i** (337.6 mg, 1.50 mmol, 3.0 equiv), K_3PO_4 (212.3 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 25 °C, yielded the product **4u** (134.0 mg,, 69%); IR (neat) ν: 2985, 2935, 1691, 1628, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.49 (s, 3H), 1.61 (s, 3H), 1.75 (s, 3H), 4.37 (d, *J* = 1.9 Hz, 1H), 4.70 (d, *J* = 1.9 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H) 7.45 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 26.4, 28.3, 29.6, 77.6, 99.2, 121.8, 127.8, 127.9, 128.1, 129.7, 131.5, 139.1, 143.8, 149.3, 171.8; HRMS (EI-MS) m/z [M+H$^+$] Calcd for $C_{20}H_{21}O_2NBr$ 386.0756, found 386.0756.

***(E)*-2,2,6-trimethyl-5-methylene-4-phenyl-6-styrylmorpholin-3-one (4v)**

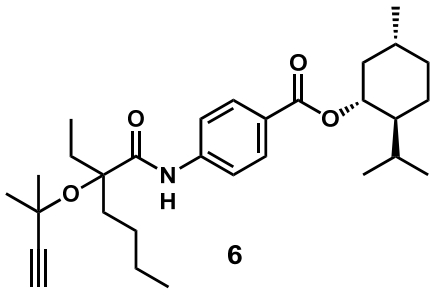


4v

Following the general procedure above, using **1a** (121.1 mg, 0.50 mmol), alcohol **2j** (258.3 mg, 1.50 mmol, 3.0 equiv), K_3PO_4 (212.3 mg, 1.00 mmol, 2.0 equiv) and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.0 equiv), and dried MeCN (0.125 mL) and Hexane (0.125 mL) at 25 °C, yielded the product **4v** (92.2 mg,, 55%); IR (neat) ν: 2983, 2933, 1685, 1628, 1378, 1178 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.58 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 4.20 (s, 1H), 4.57 (s, 1H), 6.35 (d, *J* = 15.8 Hz, 1H), 6.71 (d, *J* = 15.8 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H) 7.48-7.27 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 27.0, 27.6, 28.5, 75.6, 76.5, 96.9, 126.7, 128.1, 128.1, 128.2, 128.8, 129.6, 129.7, 133.8, 136.4, 139.2, 149.1, 172.1; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{22}H_{24}O_2N$ 334.1807, found 334.1807.

2. Reactions with diastereo-enriched tert-alkyl bromide

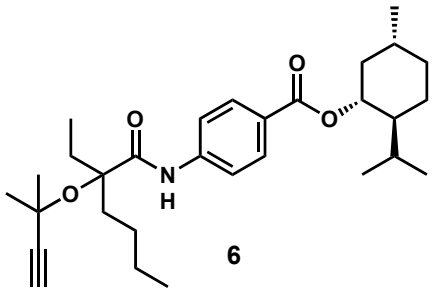
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 4-(2-ethyl-2-((2-methylbut-3-yn-2-yl)oxy)hexanamido)benzoate (6)



6

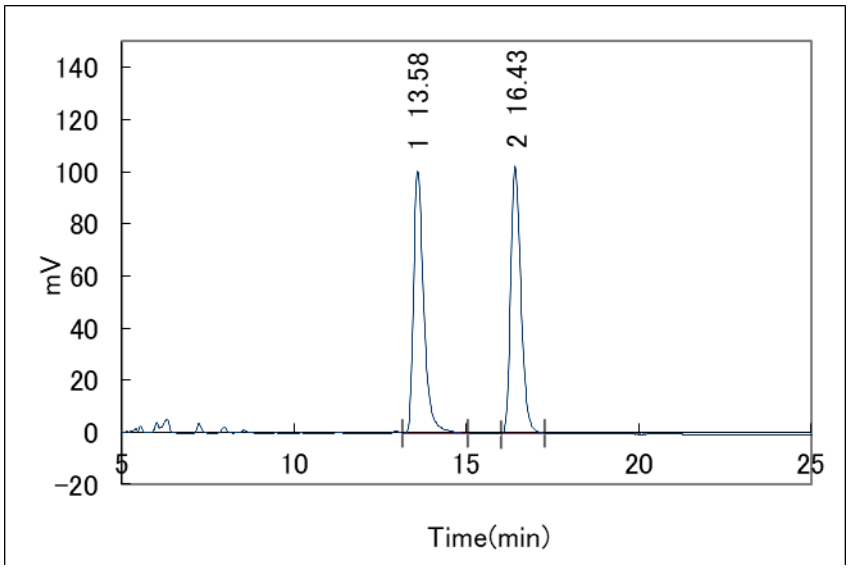
Following the general procedure above, using **5** (120.3 mg, 0.25 mmol, 1.0 equiv), alcohol **2a** (0.08 mL, 0.75 mmol, 3.0 equiv) and Cs_2CO_3 (122.2 mg, 0.38 mmol, 1.5 equiv), and dried THF (0.50 mL) at 20 °C, yielded the product **6** (81.3 mg, 0.17 mmol, 67%, dr = 15:85)), clear oil; **IR** (neat) ν: 3373, 2954, 1697, 1516, 1267, 1109, 768 cm^{-1}. **^1H NMR** ($CDCl_3$) δ: 0.79 (d, *J* = 6.3 Hz, 3H), 0.87-0.96 (m, 14H), 1.06-1.17 (m, 2H), 1.21-1.34 (m, 3H), 1.38-1.47 (m, 1H), 1.52-1.55 (m, 2H), 1.65 (s, 6H), 1.71-1.73 (m, 2H), 1.90-2.05 (m, 3H), 2.10-2.27 (m, 3H), 2.50 (s, 1H), 4.91 (dt, *J* = 4.6 and10.6 Hz, 1H), 7.63 (d, *J* = 9.8 Hz, 2H), 8.02 (d, *J* = 8.9 Hz, 2H), 8.68 (brs, 1H). **^{13}C NMR** ($CDCl_3$) δ: 8.6, 14.1, 16.6, 20.8, 22.1, 22.9, 23.7, 26.0, 26.6, 28.8, 31.5, 32.92, 32.97, 34.4, 35.8, 41.1, 47.4, 69.1, 74.7, 74.7, 85.9, 86.7, 118.7, 126.1, 130.9, 141.7, 165.7, 173.4; Colorless oil. Optical rotation $[\alpha]^{25}_D$ = –24.56 (c 1.13, $CHCl_3$); HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{30}H_{46}O_4N$ 484.3427, found 484.3427.

Chiral HPLC profiles for 6



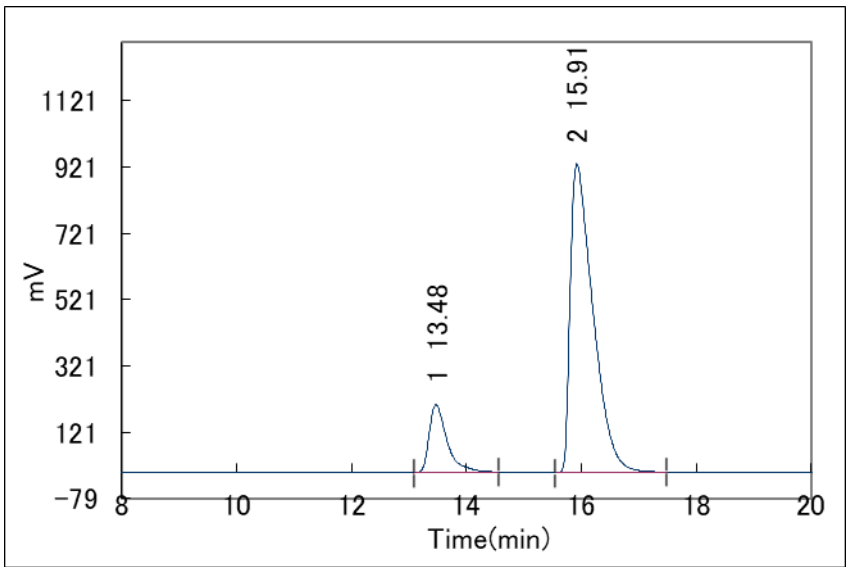
6

(a)



Retention time (min)	Area(%)
13.58	49.7412
16.43	50.2588

(b)

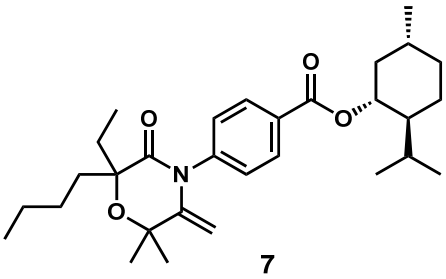


Retention time (min)	Area(%)
13.48	14.7845
15.91	85.2155

Figure 2 Chiral HPLC profiles of (a) diastereomeric mixture and (b) first-eluted diastereomer of **5** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/2-propanol = 97/3 as an eluent, monitored at 254 nm).

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl

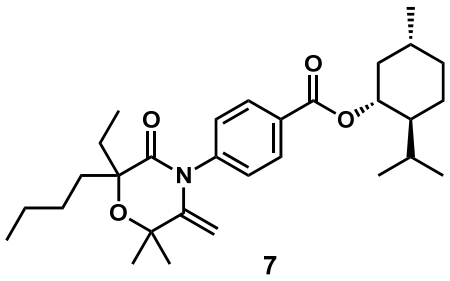
4-(2-butyl-2-ethyl-6,6-dimethyl-5-methylene-3-oxomorpholino)benzoate (7)



7

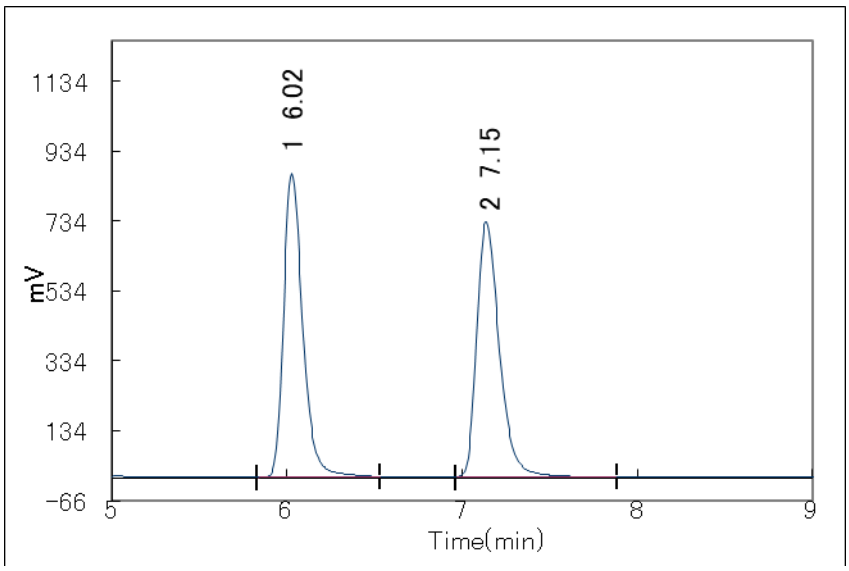
Following the general procedure above, using **5** (126.3 mg, 0.26 mmol), alcohol **2a** (0.08 mL, 0.75 mmol, 3.0 equiv), K_3PO_4 (106.13 mg, 0.50 mmol, 2.0 equiv) and Cs_2CO_3 (162.91 mg, 0.50 mmol, 2.0 equiv), and dried MeCN (0.25 mL) and Hexane (0.25 mL) at 20 °C or 40 °C, yielded the product **7** (71.4 mg, 0.14 mmol, 56%, dr = 92:8 at 20 °C), (70%, dr = 14:86 at 40 °C), clear oil; **IR** (neat) ν: 2929, 1686, 1631, 1265, 1095, 765, 697 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 0.78 (d, *J* = 7.5 Hz, 3H), 0.89-0.97 (m, 13H), 1.06-1.16 (m, 2H), 1.28-1.45 (m, 5H), 1.52-1.53 (m, 1H), 1.55 (s, 6H), 1.71-1.74 (m, 2H), 1.76-1.81 (m, 2H), 1.82-1.88 (m, 2H), 1.89-1.96 (m, 1H), 2.10-2.13 (m, 1H), 3.99 (d, *J* = 1.9 Hz, 1H), 4.51 (d, *J* = 2.0 Hz, 1H), 4.93 (dt, *J* = 4.7 Hz, 11.2 Hz, 1H), 7.25 (d, *J* = 8.9 Hz, 2H), 8.11 (d, *J* = 8.9 Hz, 2H). **^{13}C NMR** ($CDCl_3$) δ: 8.01, 8.03, 14.2, 16.6, 20.9, 22.1, 23.1, 23.7, 25.7, 26.63, 26.65, 28.3, 28.40, 28.45, 28.45, 31.33, 31.38, 31.5, 34.4, 37.85, 37.89, 41.0, 47.3, 72.5, 75.2, 80.7, 95.7, 128.1, 130.2, 131.0, 143.7, 151.3, 165.4, 171.5; Colorless oil. Optical rotation $[\alpha]^{25}_D$ = –3.51 (c 1.10, $CHCl_3$); HRMS (EI-MS) m/z [$M+H^+$] Calcd for $C_{30}H_{46}O_4N$ 484.3427, found 484.3428.

Chiral HPLC profiles for 7



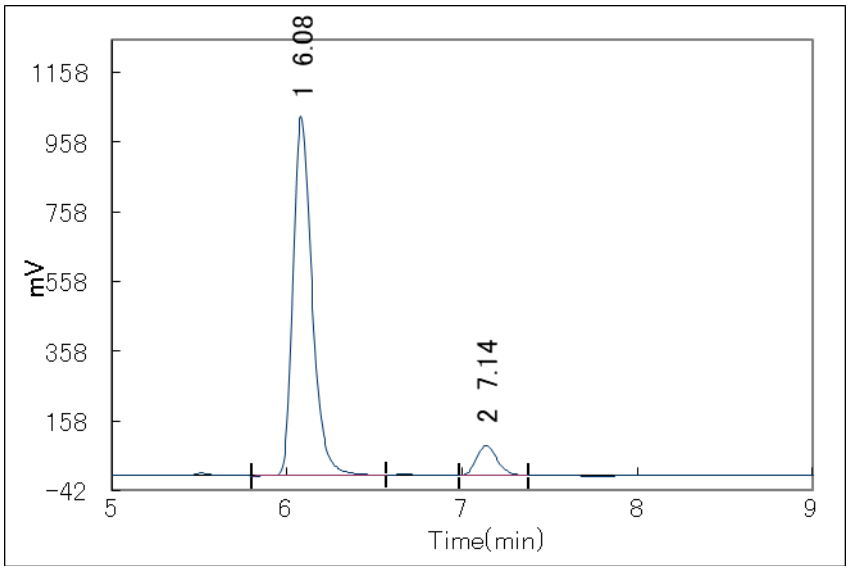
7

(a)



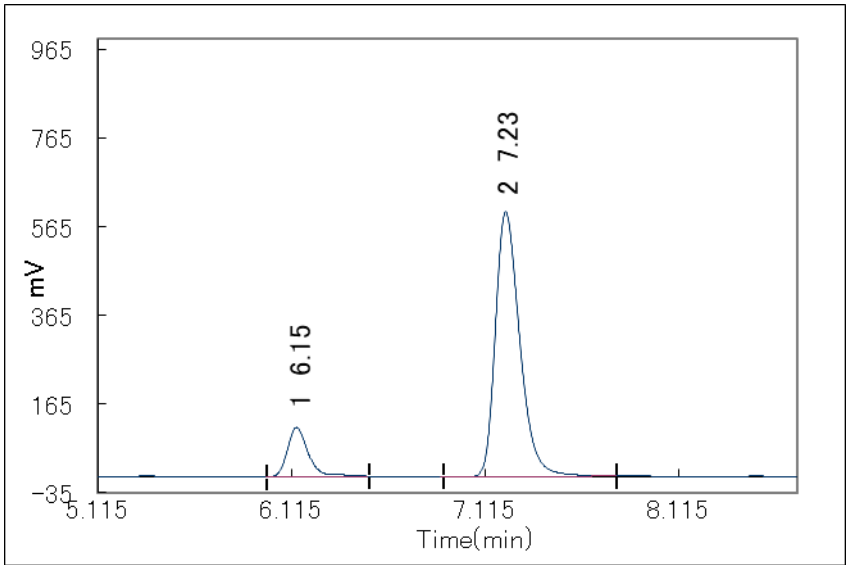
Retention time (min)	Area(%)
6.02	50.0714
7.15	49.9286

(b)



Retention time (min)	Area(%)
6.08	91.6537
7.14	8.3463

(c)

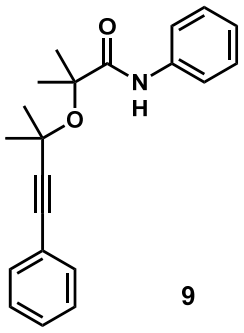


Retention time (min)	Area(%)
6.15	13.5996
7.23	86.4004

Figure 3 Chiral HPLC profiles of (a) diastereomeric mixture, (b) first-eluted diastereomer and (c) second-eluted diastereomer of **5** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/2-propanol = 97/3 as an eluent, monitored at 254 nm).

3. Applications

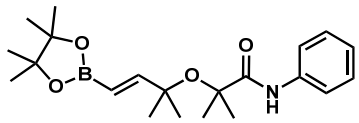
2-methyl-2-((2-methyl-4-phenylbut-3-yn-2-yl)oxy)-N-phenylpropanamide (9)



9

3a (152.2 mg, 0.62 mmol, 1.1 equiv), Iodobenzene **8** (114.1 mg, 0.56 mmol, 1.0 equiv), $PdCl_2(PPh_3)$ (9.9 mg, 2.5 mol%), and CuI (4.6 mg, 2.5 mol%) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), dried Et_3N (1.0 ml) was added by syringe and the resulting mixture stirred under nitrogen atmosphere for 20 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash column chromatography, eluting hexane/EtOAc to afford the product **9** (164.1 mg, 0.51 mmol, 82%); **IR** (neat) ν: 3368, 2975, 1674, 1436, 1128, 989, 753, 689 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 1.68 (s, 6H), 1.70 (s, 6H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.17-7.25 (m, 5H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 8.43 (brs, 1H). **^{13}C NMR** ($CDCl_3$) δ: 26.7, 32.8, 70.0, 79.9, 86.9, 90.4, 119.5, 122.4, 123.9, 128.2, 128.3, 129.0, 131.6, 138.1, 175.0; Brown solid. Melting point 89-91 °C; HRMS (EI-MS) m/z [M+H^+] Calcd for $C_{21}H_{24}O_2N$ 322.1807, found 322.1807.

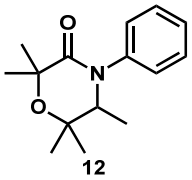
2-methyl-2-((2-methyl-4-phenylbut-3-yn-2-yl)oxy)-N-phenylpropanamide (11)



11

A flask was charged with $RuHCl(CO)(PPh_3)_3$ (15.8 mg, 3.0 mol%) and toluene (0.5 ml) under a nitrogen flow. After pinacol borane (4,4,5,5-Tetramethyl-1,3,2-dioxaborolane) **10** (0.4 ml, 2.8 mmol, 5.0 equiv) and terminal alkyne **3a** (132.1 mg, 0.54 mmol, 1.0 equiv) in toluene (0.5 ml) were added, the mixture was stirred at room temperature for 6 h. The reaction mixture was extracted with EtOAc, the extract was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography, eluting hexane/EtOAc to afford the product **11** (131.6 mg, 0.35 mmol, 65%); **IR** (neat) ν: 3380, 2977, 1689, 1520, 1345, 1321, 1127, 692 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 1.25 (s, 12H), 1.41 (s, 6H), 1.50 (s, 6H), 5.55 (d, *J* = 17.5 Hz, 1H), 6.77 (d, *J* = 18.6 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 7.1 Hz, 2H), 8.62 (brs, 1H). **^{13}C NMR** ($CDCl_3$) δ: 24.8, 27.2, 28.5, 77.9, 79.3, 83.4, 119.4, 124.1, 129.1, 137.8, 160.0, 175.2. HRMS (EI-MS) m/z [$M+H^+$] Calcd for $C_{21}H_{33}O_4NB$ 374.2503, found 374.2503.

2,2,5,6,6-pentamethyl-4-phenylmorpholin-3-one (12)

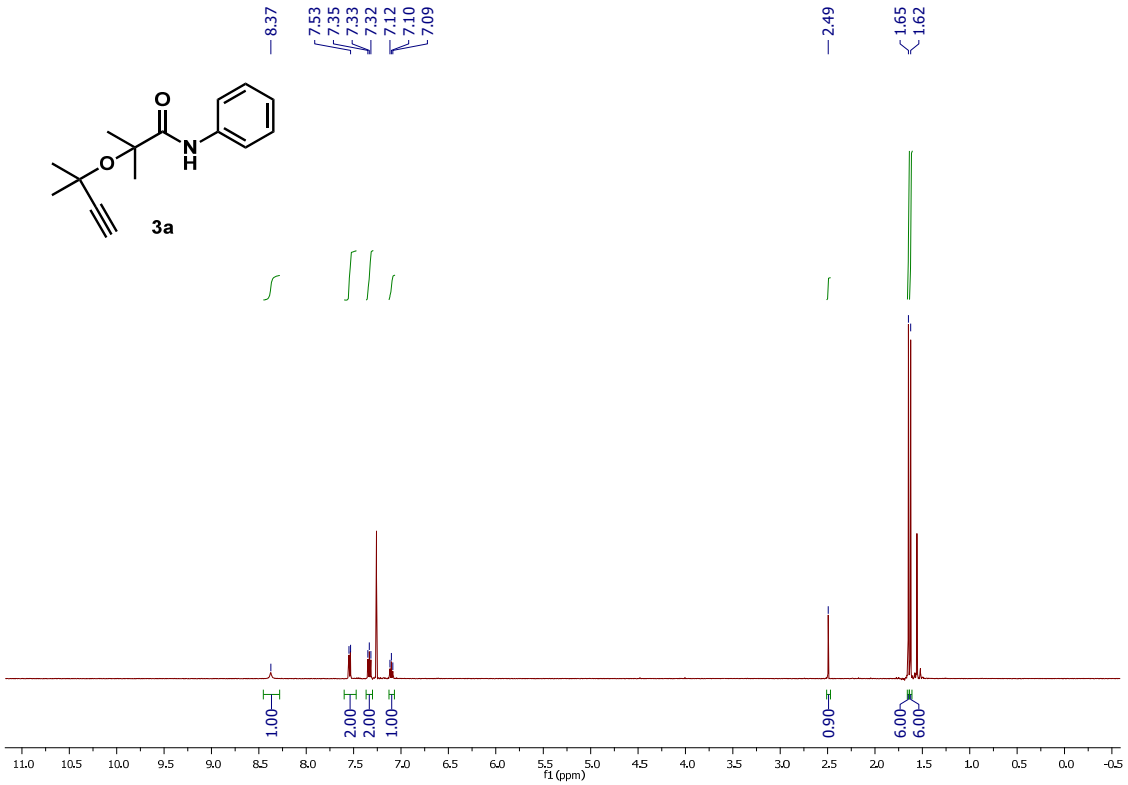


12

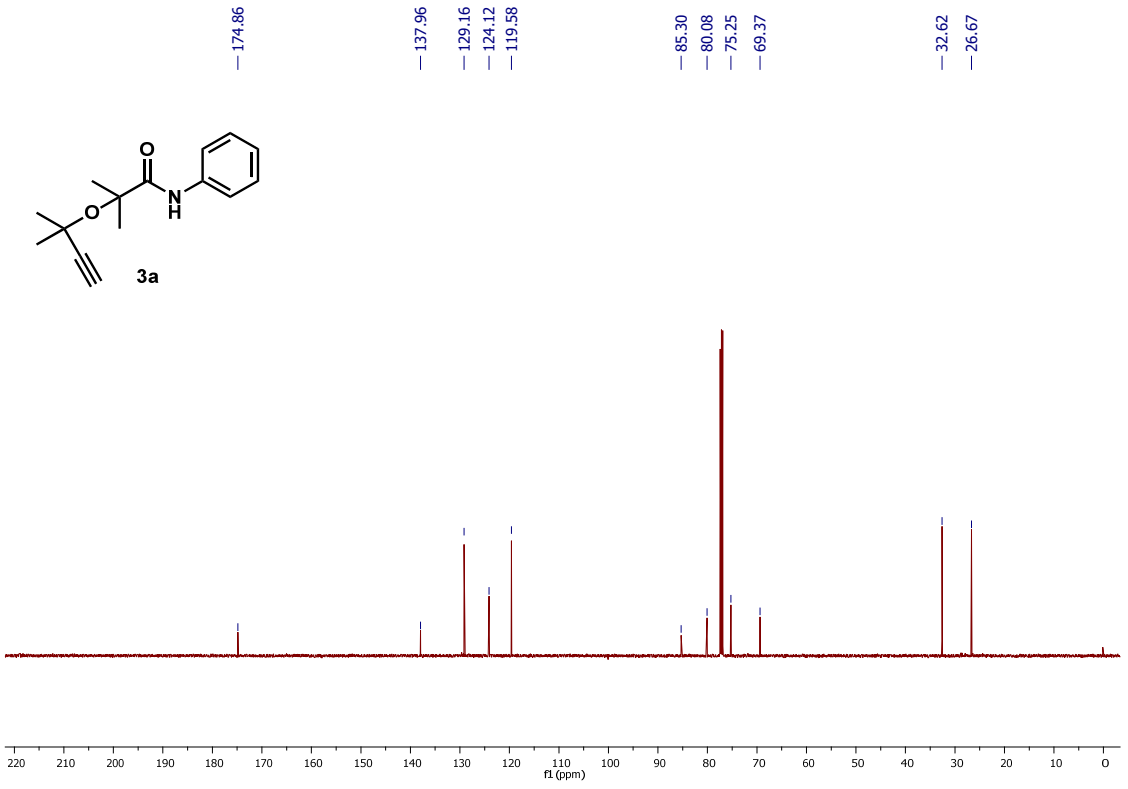
A mixture of **4a** (124.2 mg, 0.51 mmol) and Pd/C 5% (2.7 mg, 0.5 mol%) in EtOH (1 mL) was vigorously stirred during 24 hours under H_2 gas atmosphere. After this time, the contents of the flask were filtered through the plug of celite, and then concentrated by rotary evaporation. The residue was purified by flash column chromatography, eluting hexane/EtOAc to afford the product **12** (120.0 mg, 0.49 mmol, 96%); **IR** (neat) ν: 2973, 1646, 1430, 1160, 1018 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 1.26 (s, 3H), 1.28 (d, *J* = 6.6 Hz, 3H), 1.53 (s, 3H), 1.56 (s, 3H), 1.58 (s, 3H), 3.58 (q, *J* = 6.6 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H). **^{13}C NMR** ($CDCl_3$) δ: 15.3, 26.1, 26.6, 28.3, 30.3, 64.5, 72.5, 75.5, 127.3, 127.4, 129.3, 141.5, 172.5; White solid. Melting point 99-102°C; HRMS (EI-MS) m/z [$M+H^+$] Calcd for $C_{15}H_{22}O_2N$ 248.1651, found 248.1651.

4. Spectral charts for new compounds

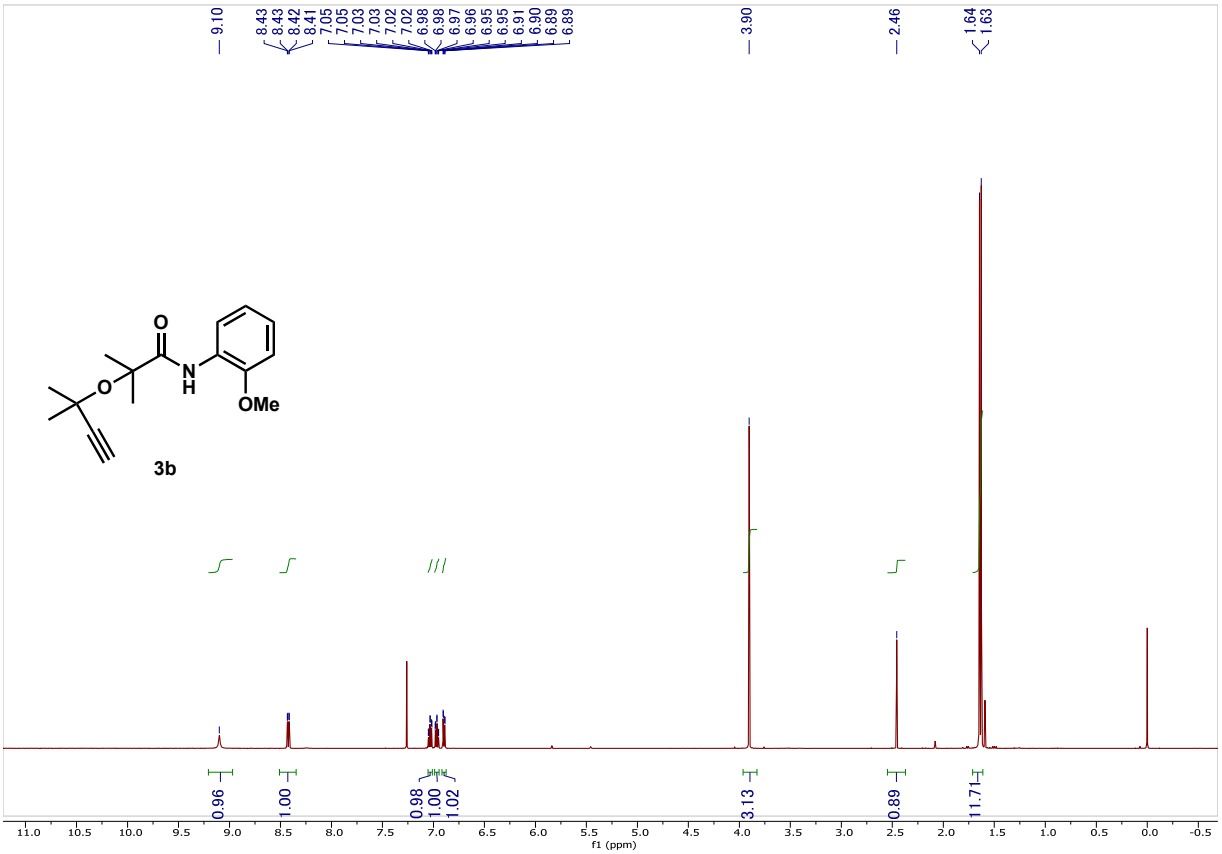
^{1}H NMR (500 MHz, $CDCl_3$)



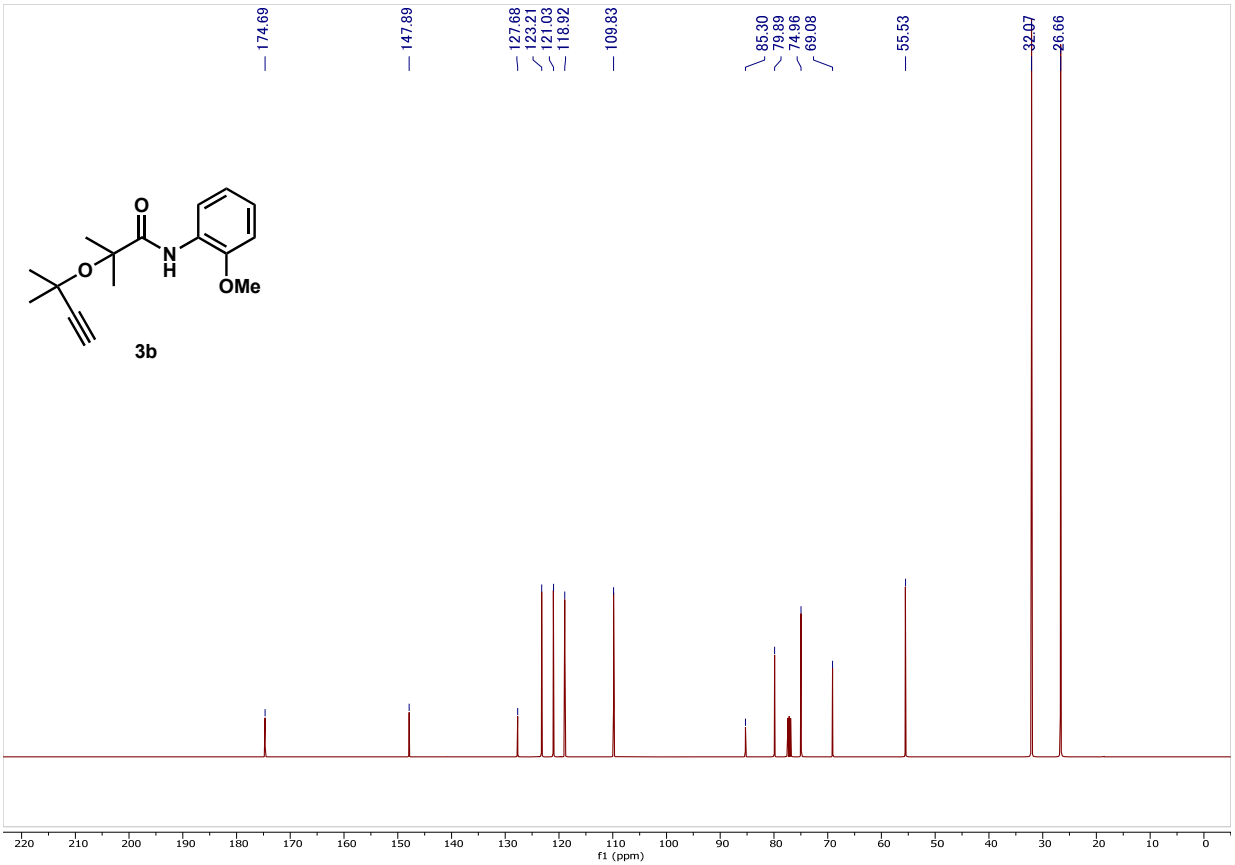
^{13}C NMR (125 MHz, $CDCl_3$)



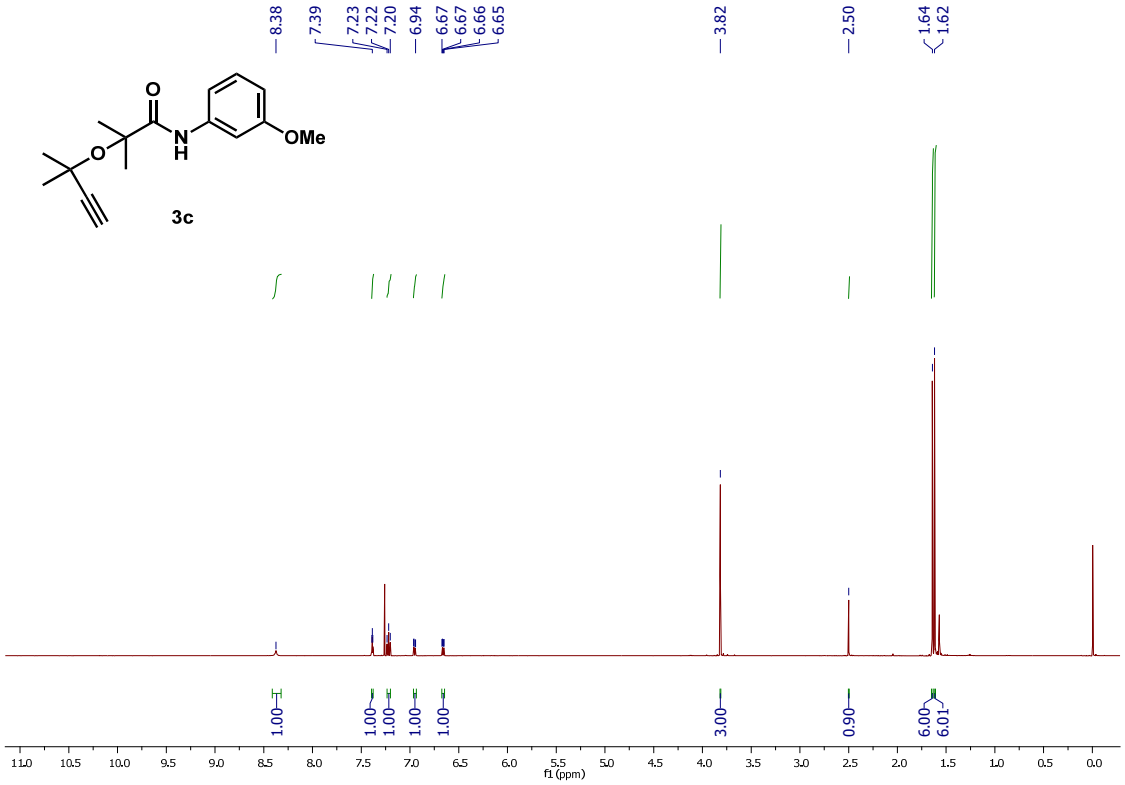
^{1}H NMR (500 MHz, $CDCl_3$)



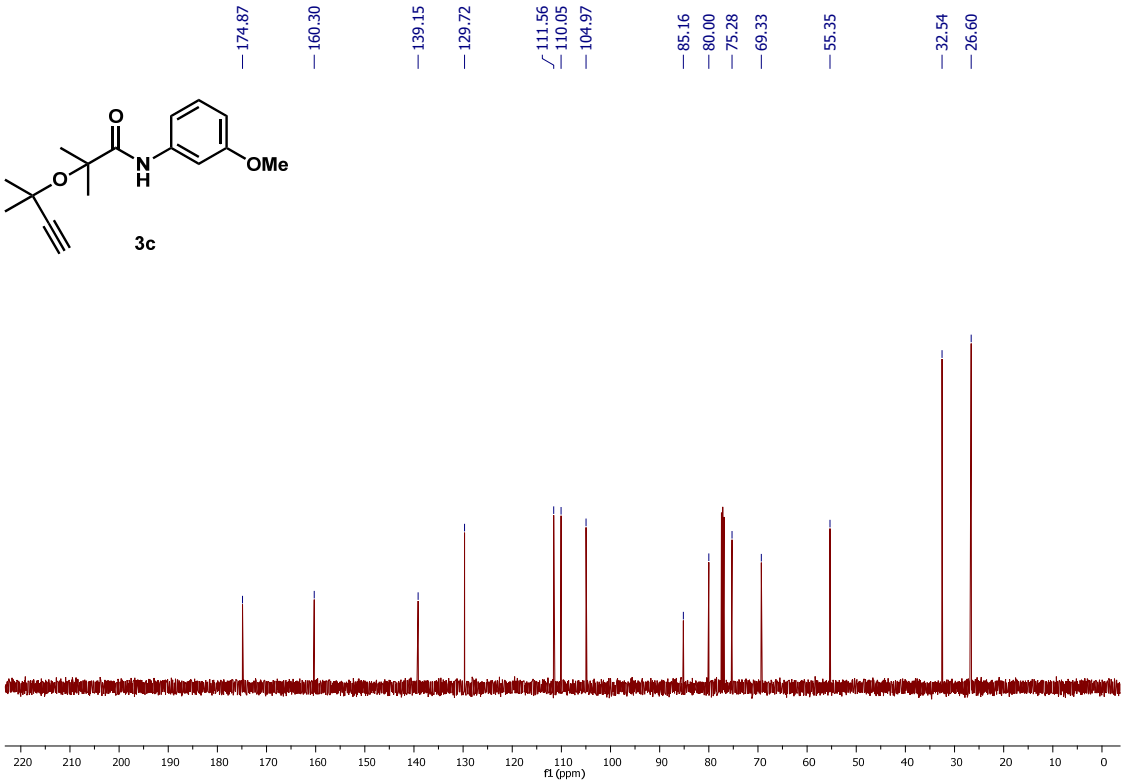
^{13}C NMR (125 MHz, $CDCl_3$)



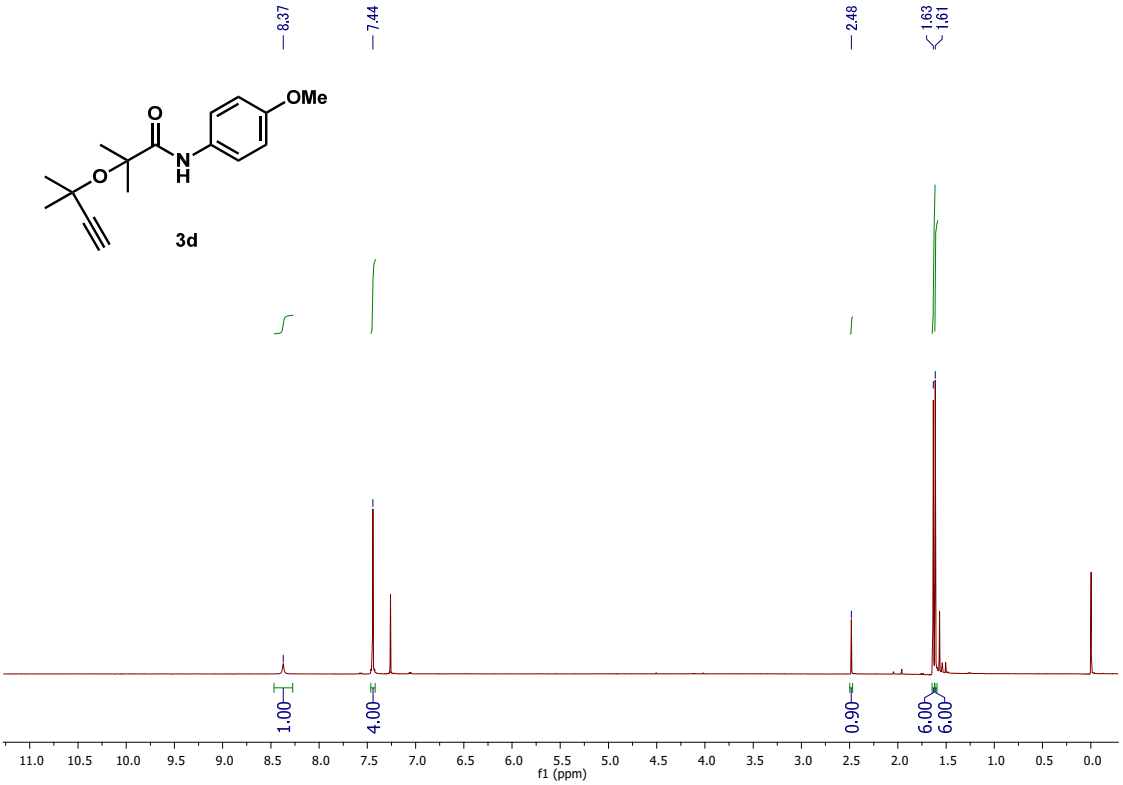
^{1}H NMR (500 MHz, $CDCl_3$)



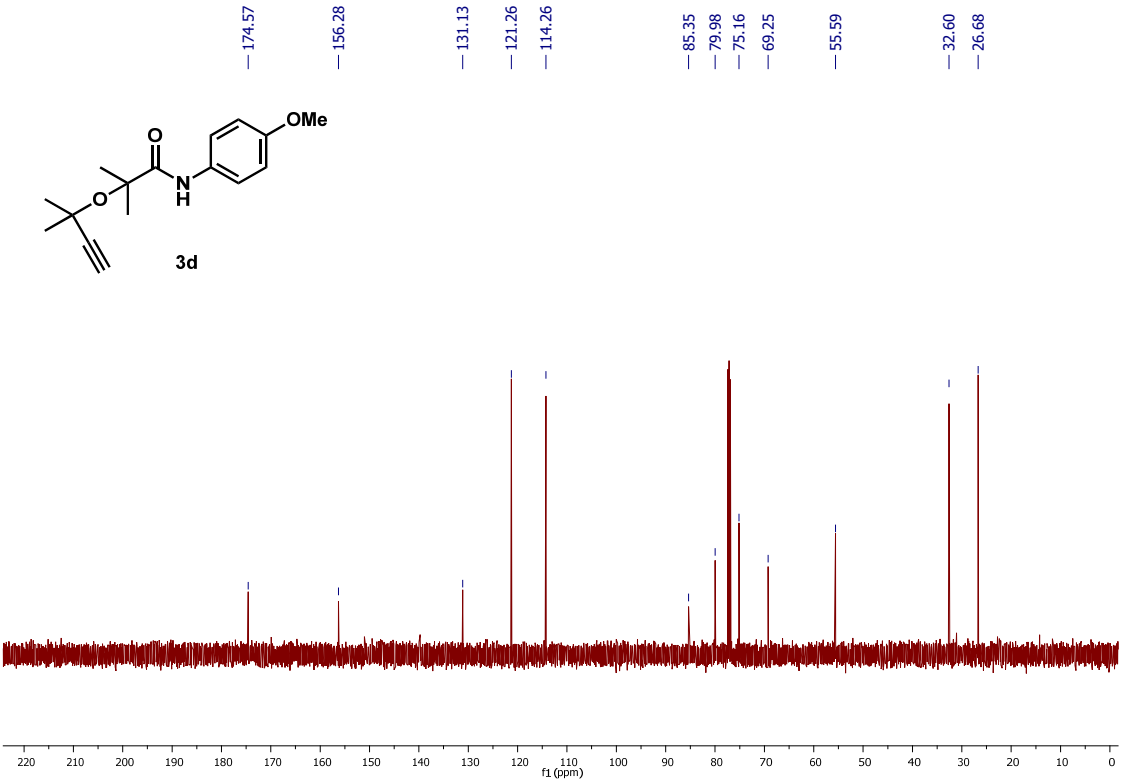
^{13}C NMR (125 MHz, $CDCl_3$)



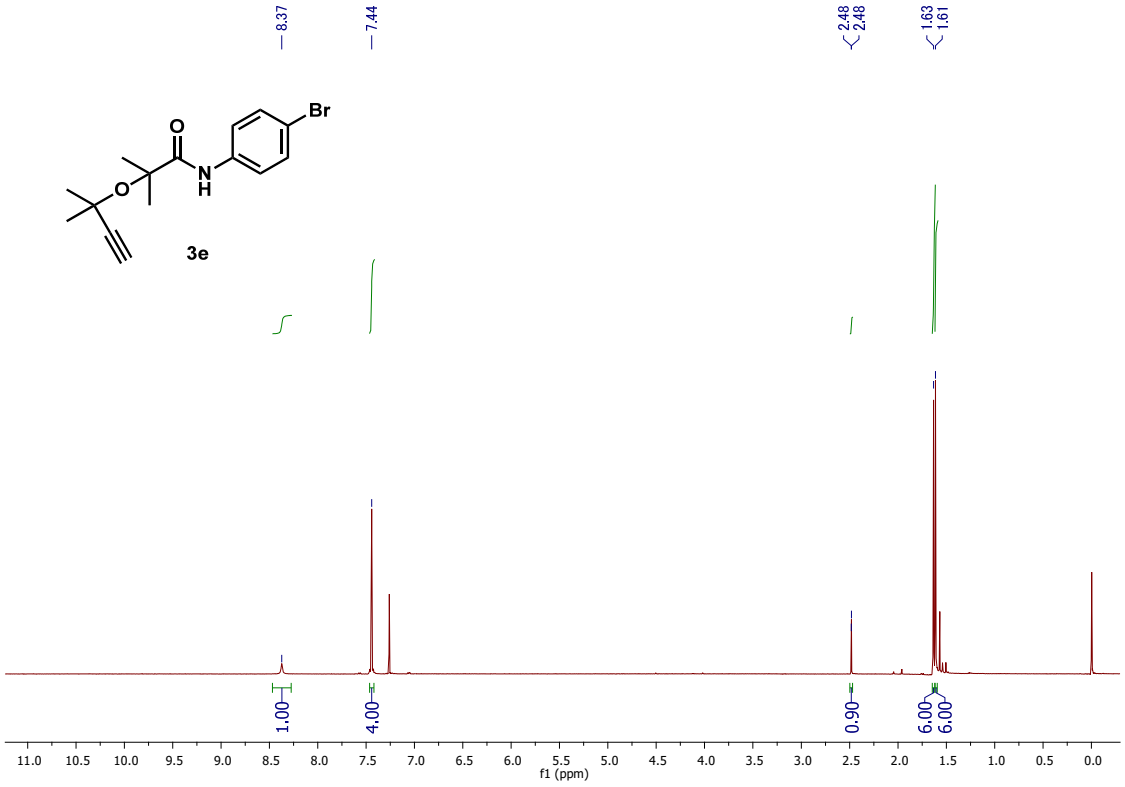
^{1}H NMR (500 MHz, $CDCl_3$)



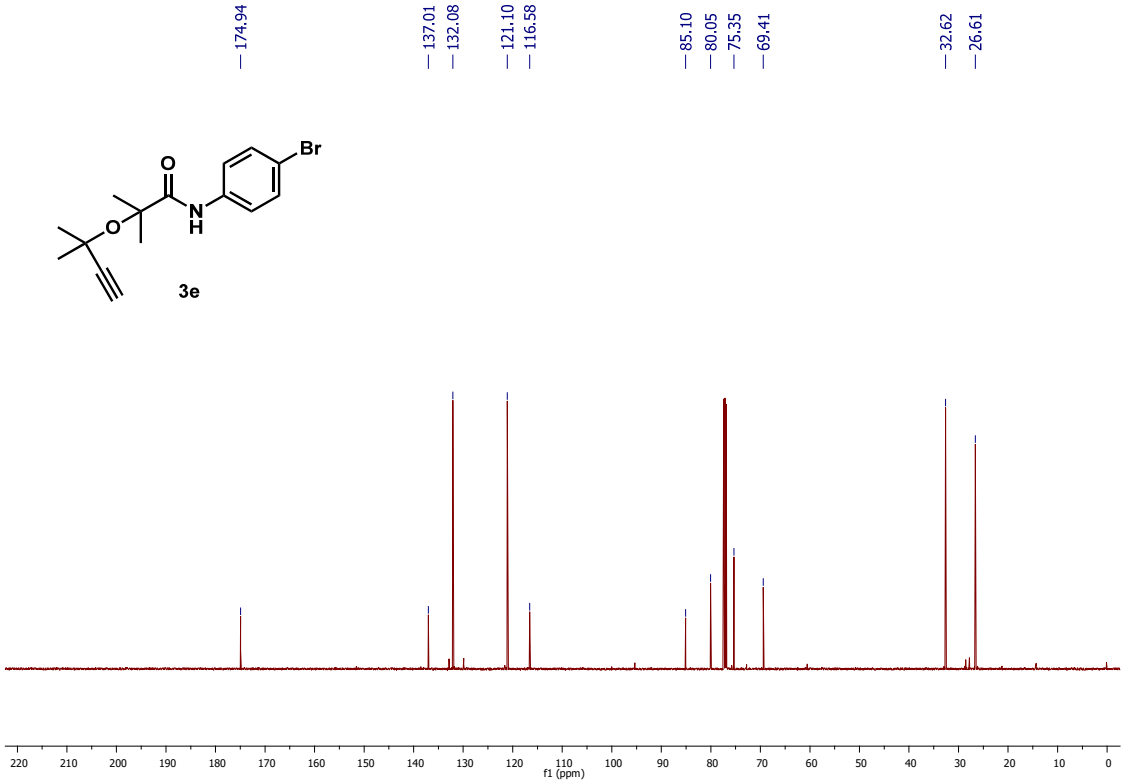
^{13}C NMR (125 MHz, $CDCl_3$)



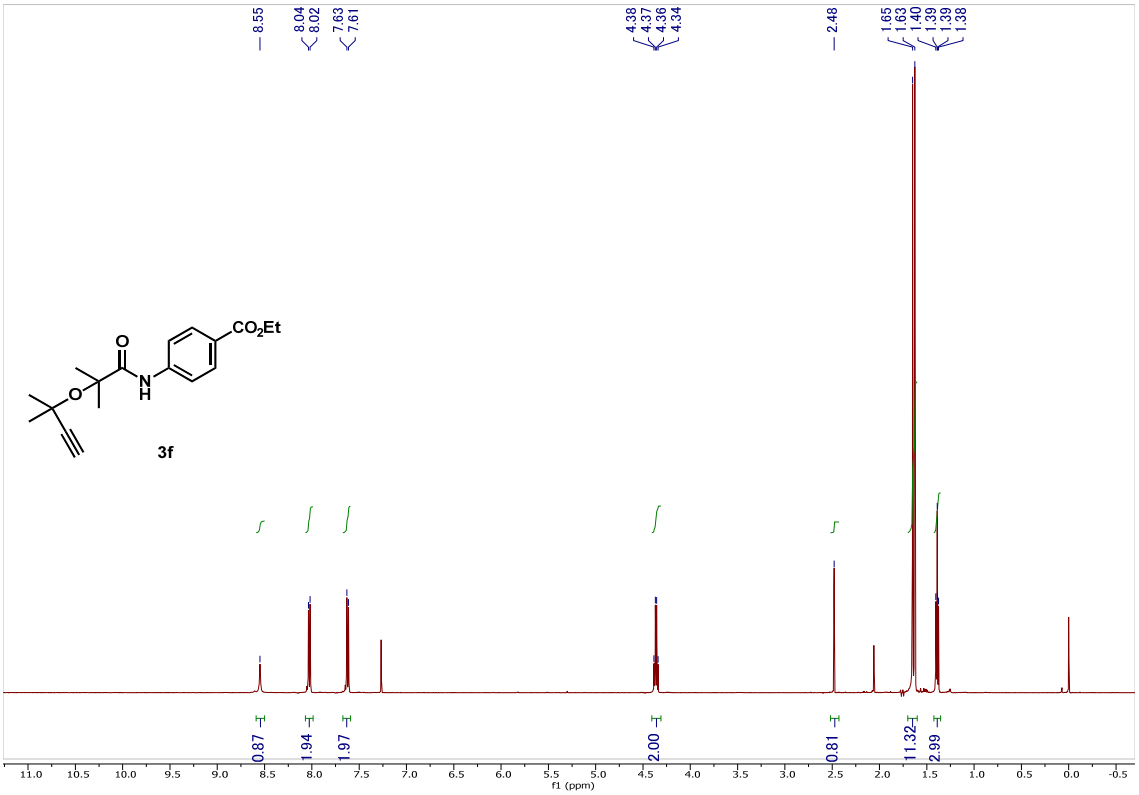
^{1}H NMR (500 MHz, $CDCl_3$)



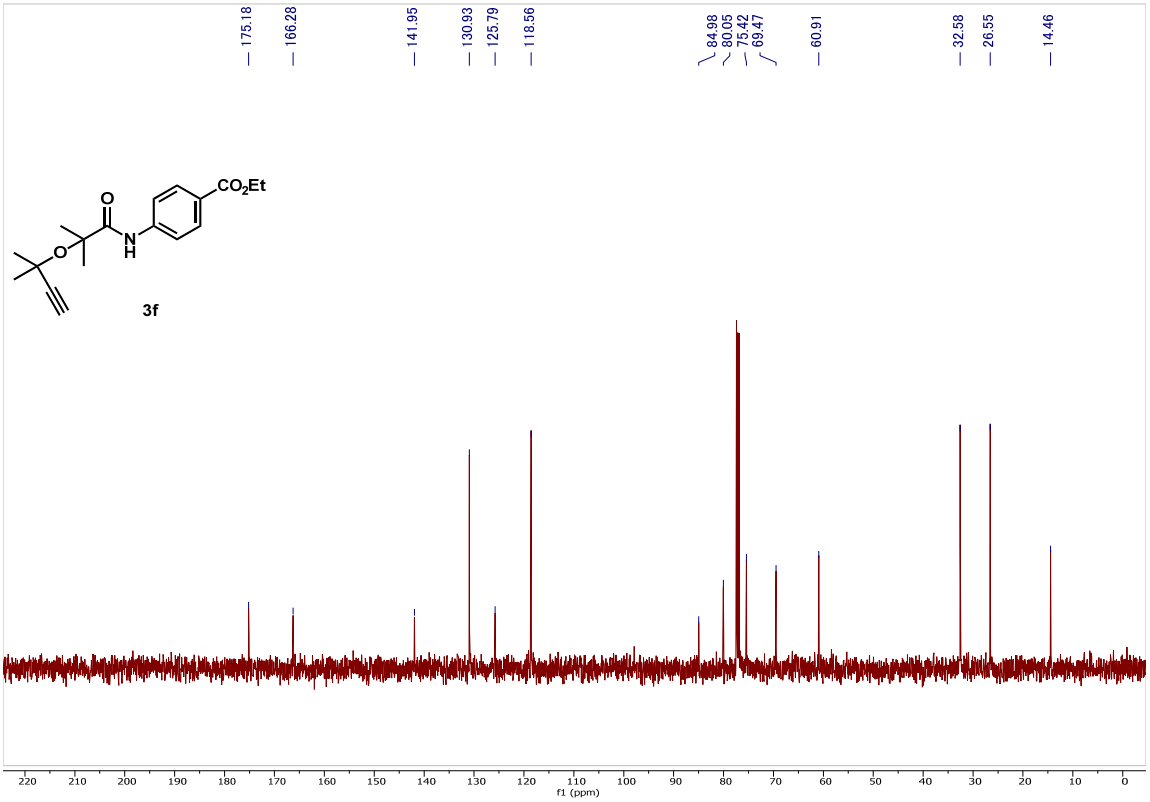
^{13}C NMR (125 MHz, $CDCl_3$)



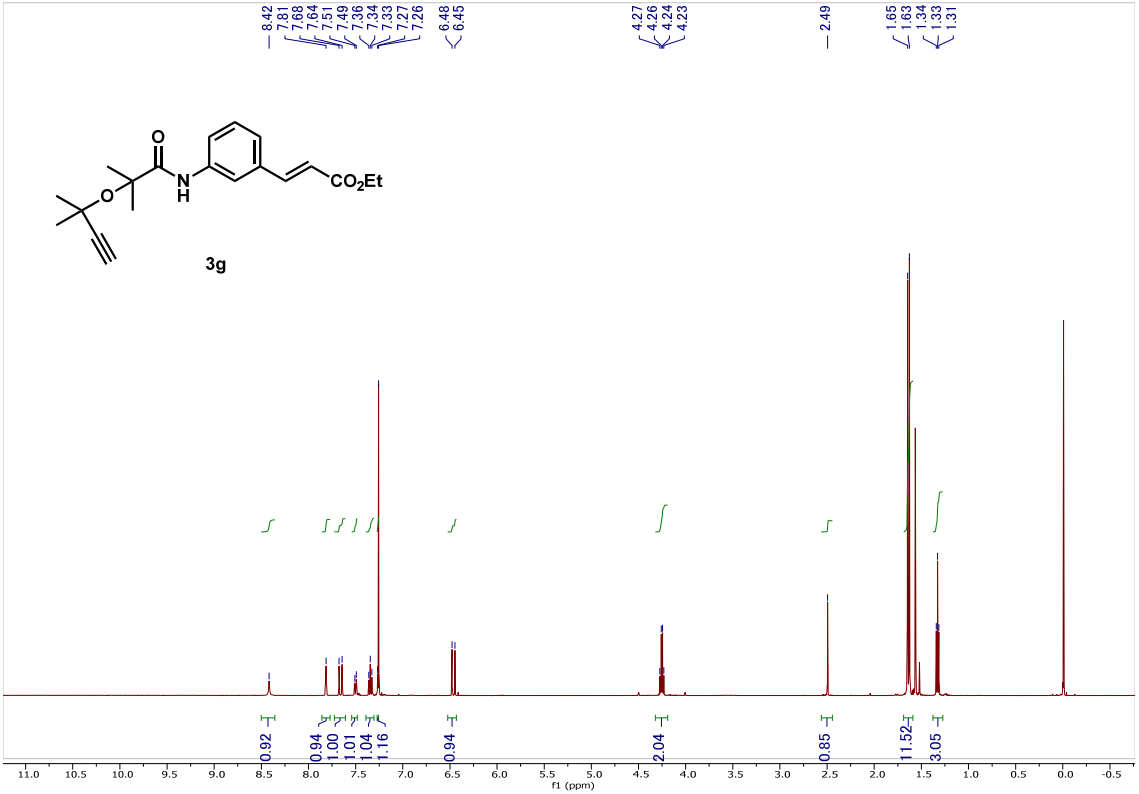
^{1}H NMR (500 MHz, $CDCl_3$)



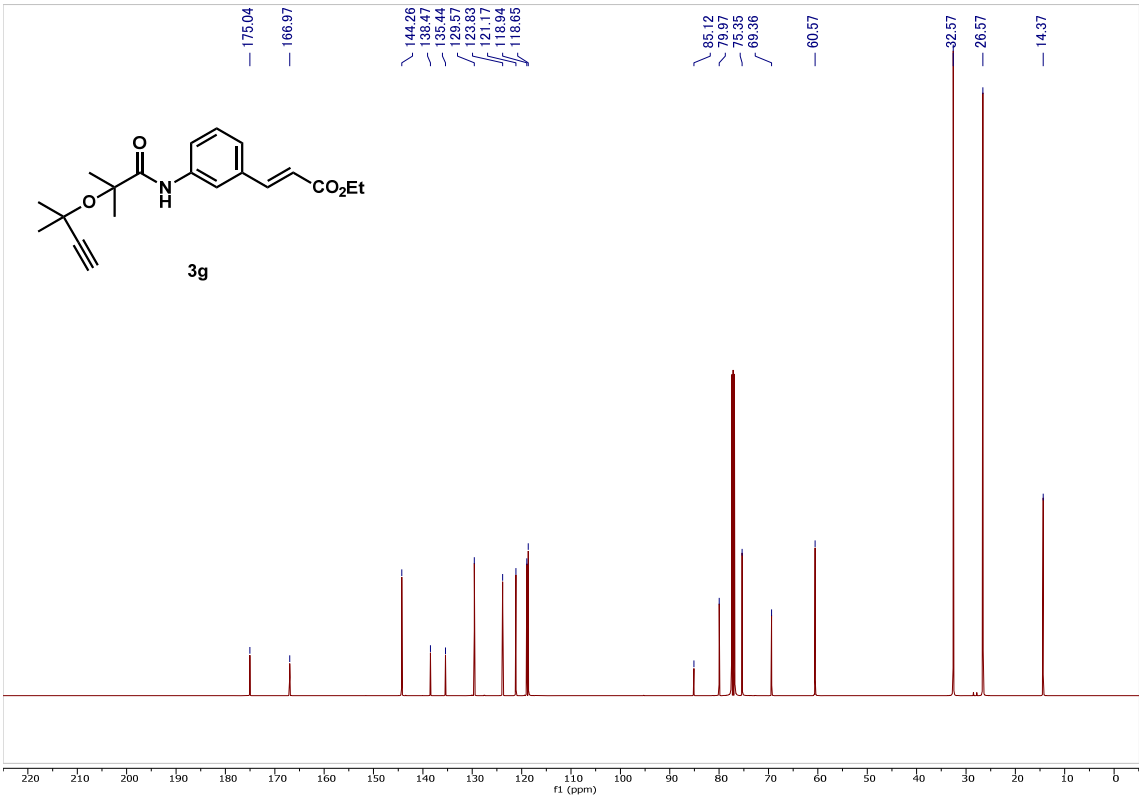
^{13}C NMR (125 MHz, $CDCl_3$)



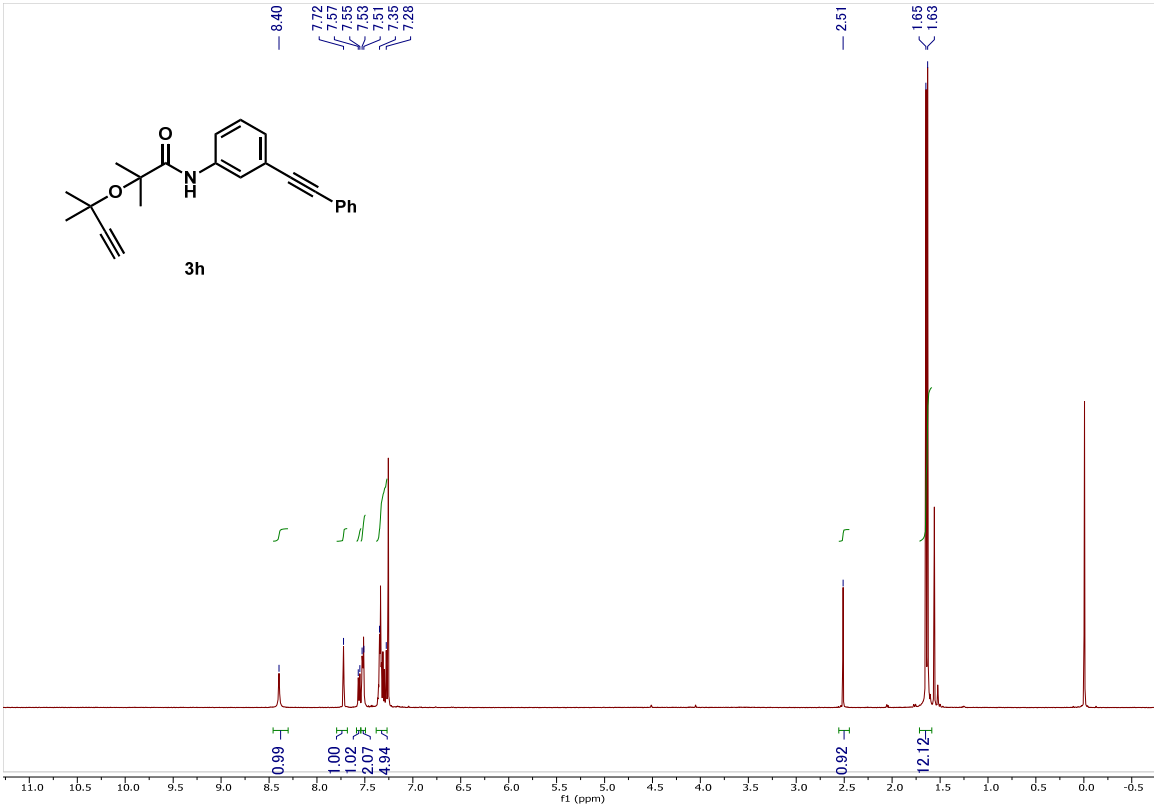
^{1}H NMR (500 MHz, $CDCl_3$)



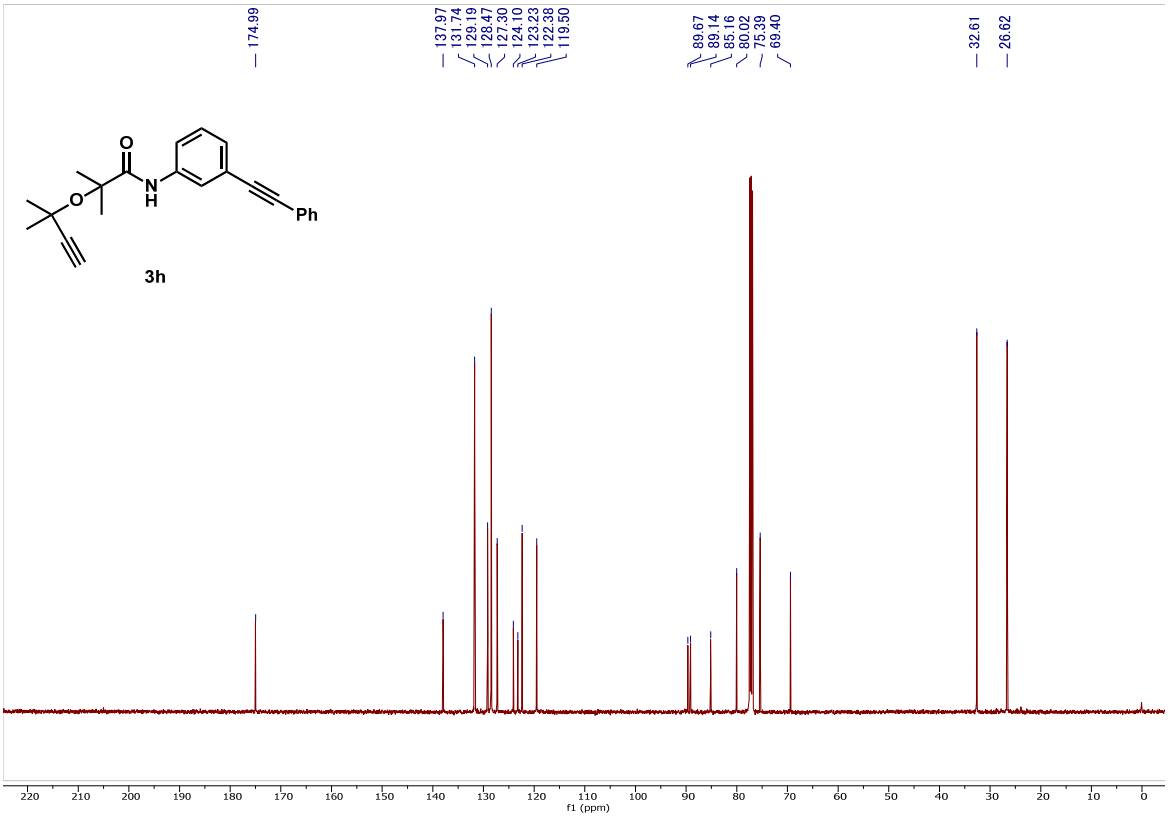
^{13}C NMR (125 MHz, $CDCl_3$)



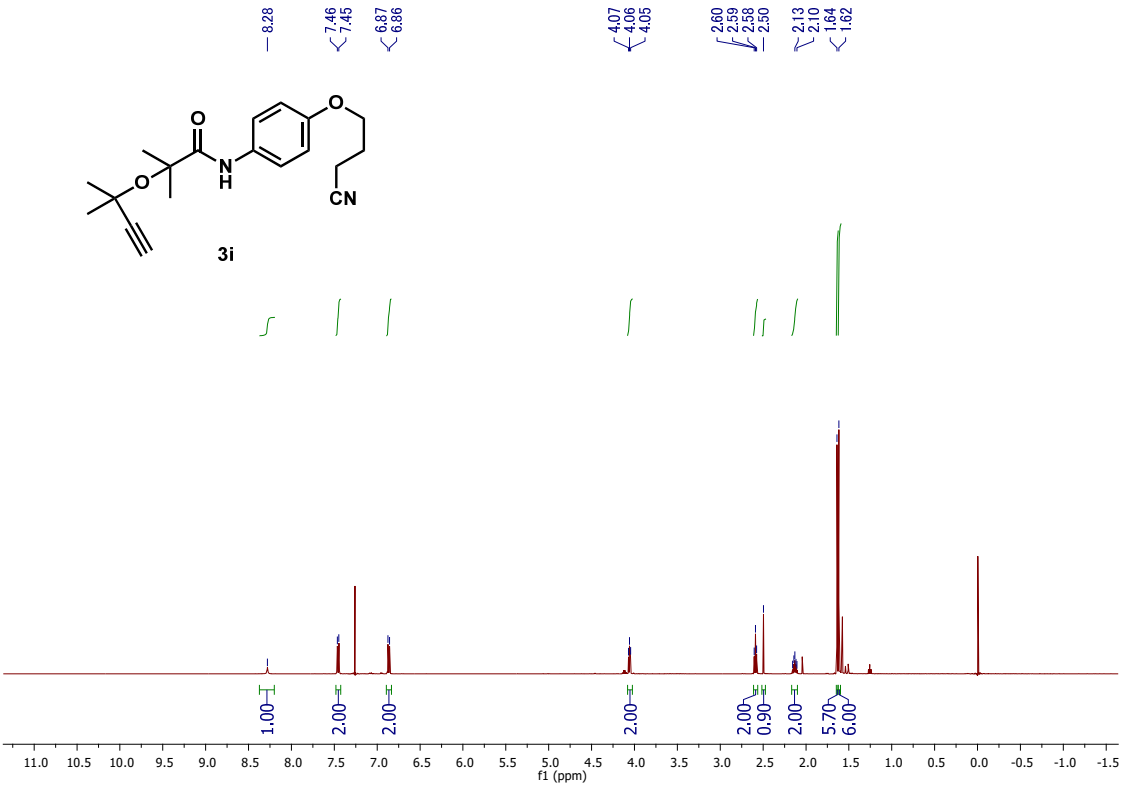
^{1}H NMR (500 MHz, $CDCl_3$)



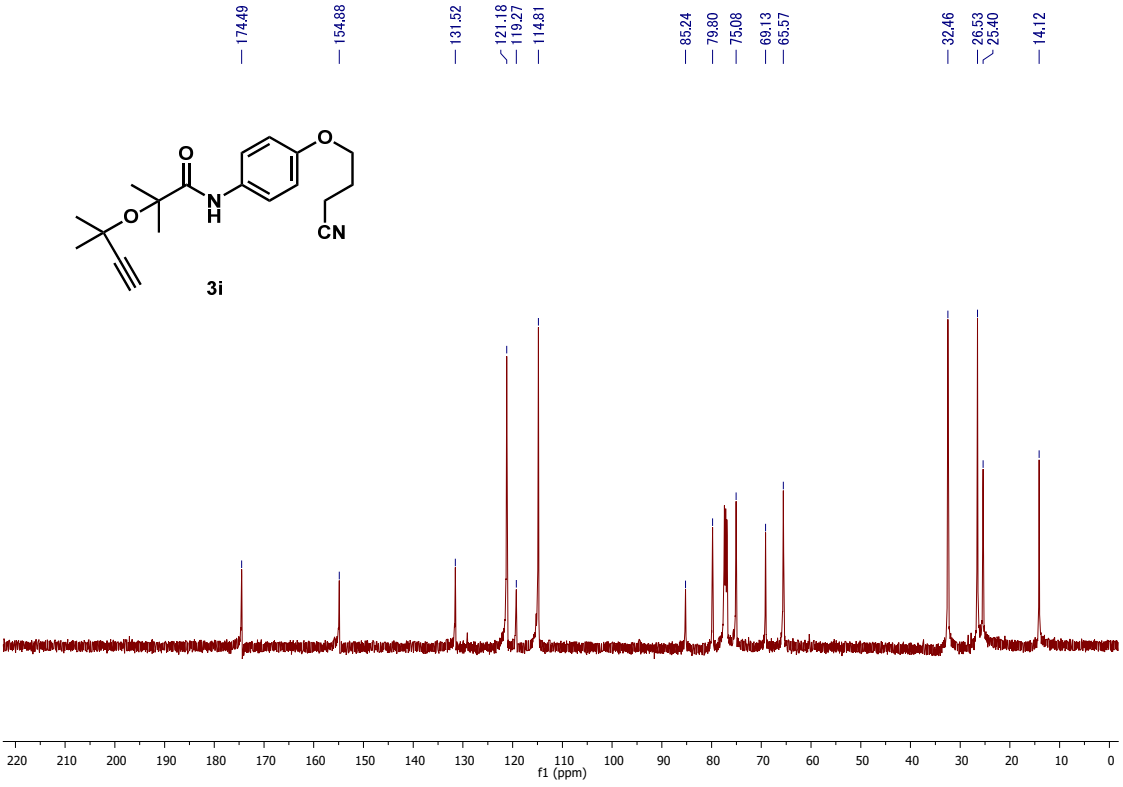
^{13}C NMR (125 MHz, $CDCl_3$)



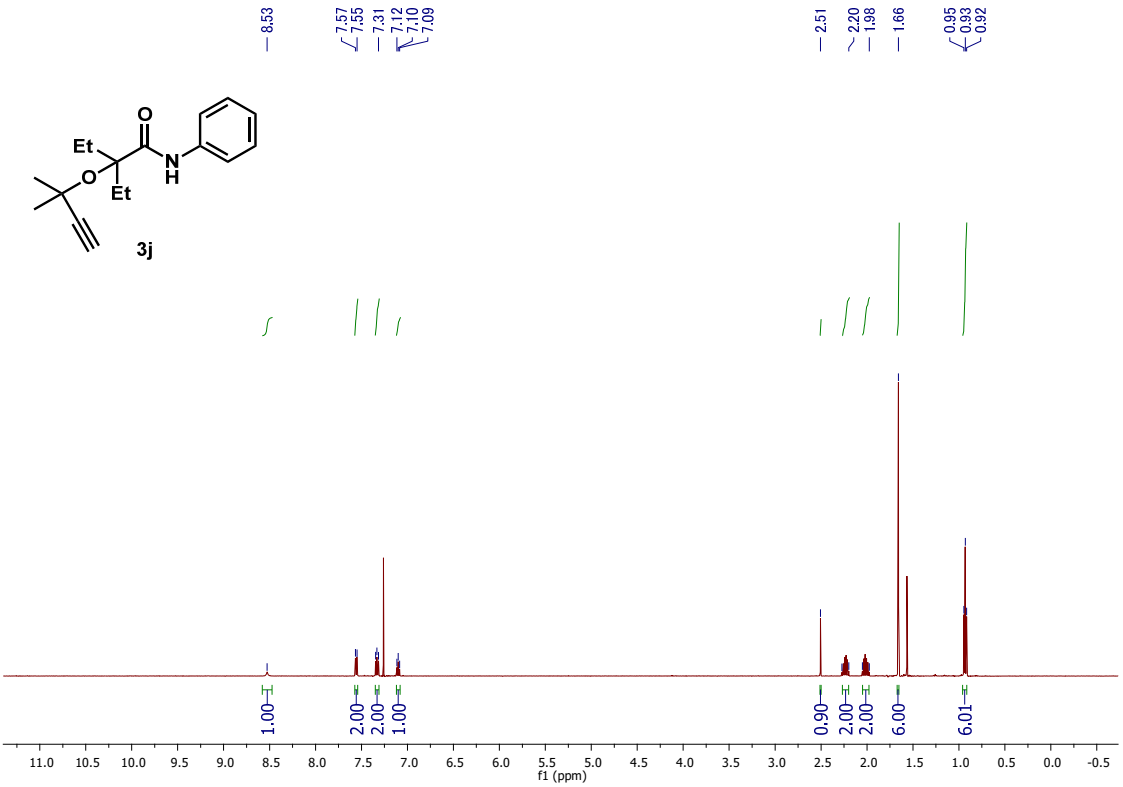
^{1}H NMR (500 MHz, $CDCl_3$)



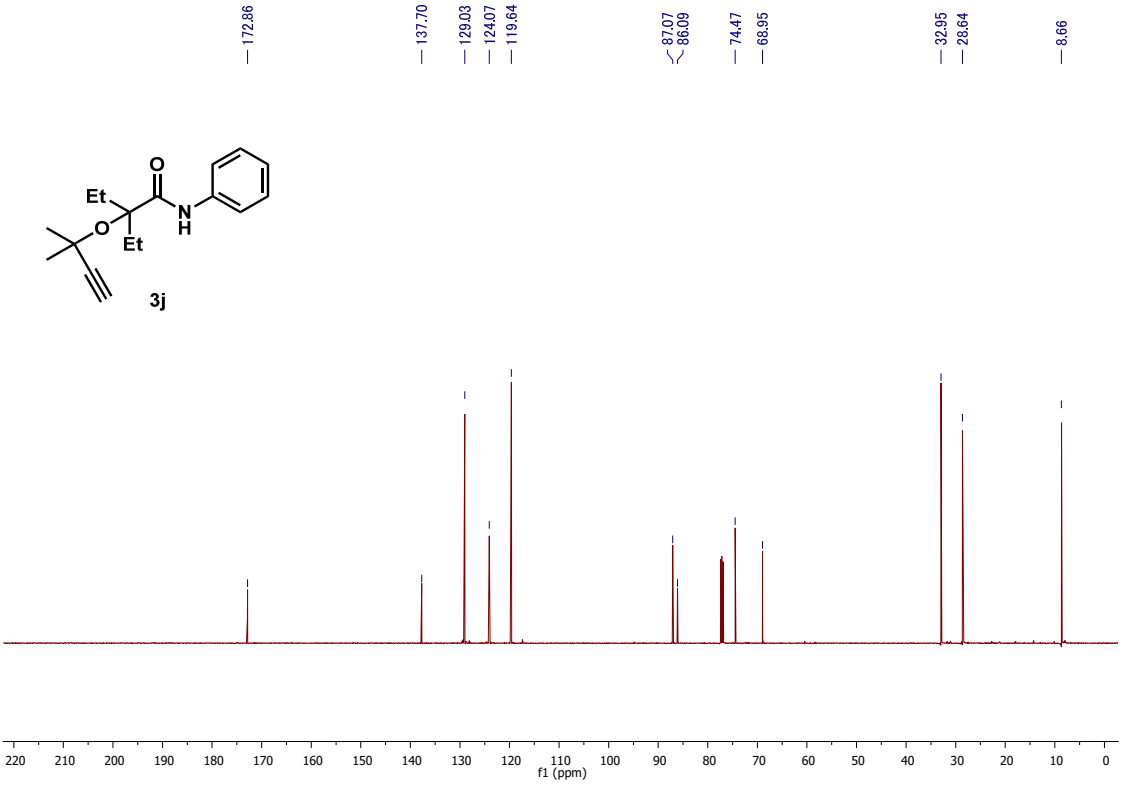
^{13}C NMR (125 MHz, $CDCl_3$)



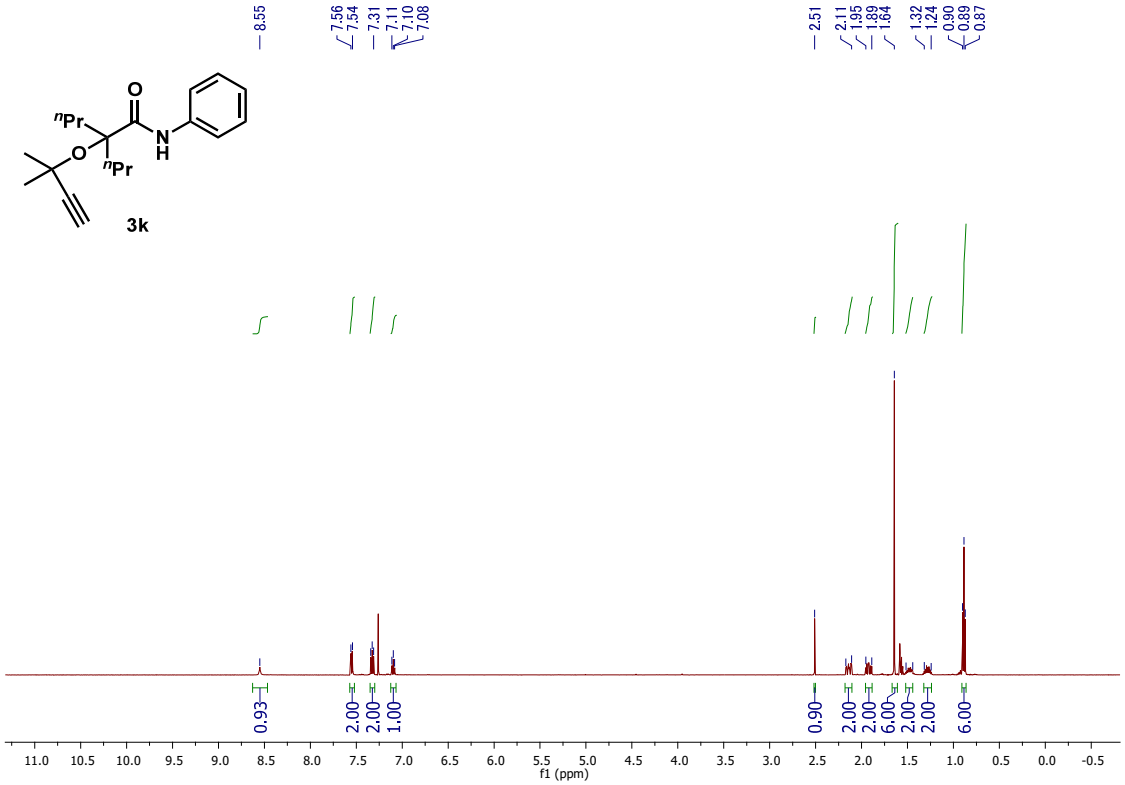
^{1}H NMR (500 MHz, $CDCl_3$)



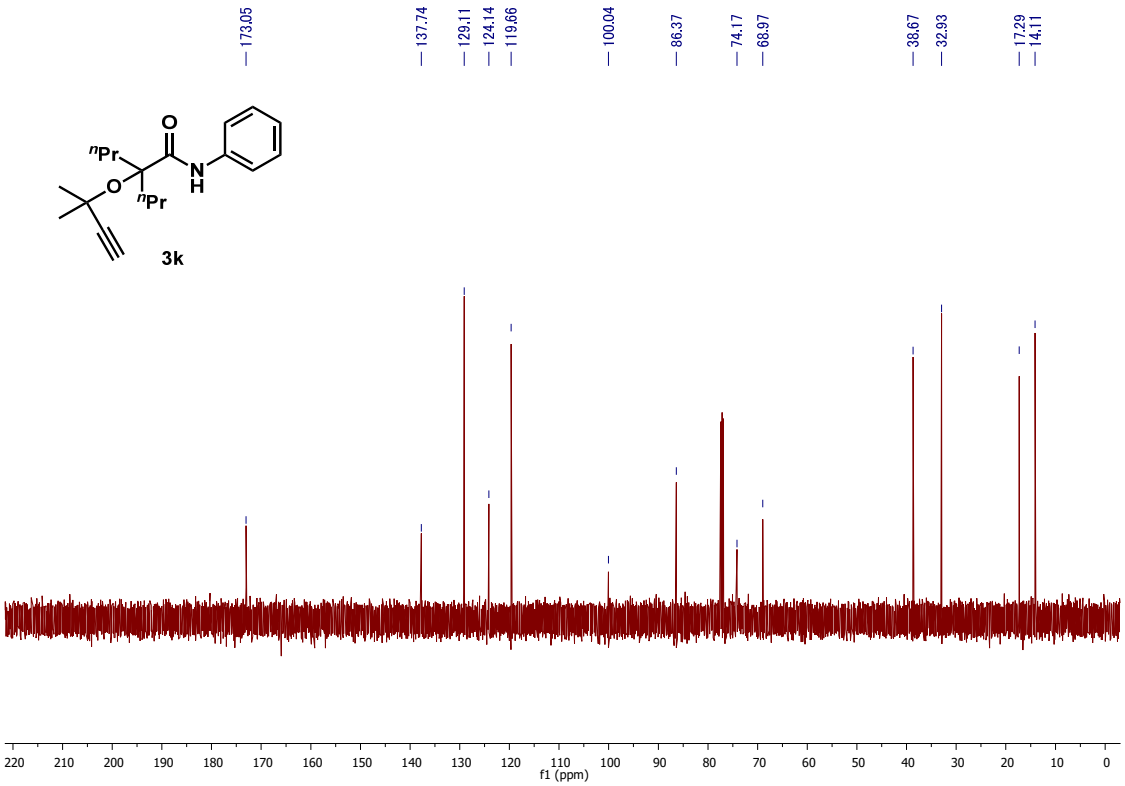
^{13}C NMR (125 MHz, $CDCl_3$)



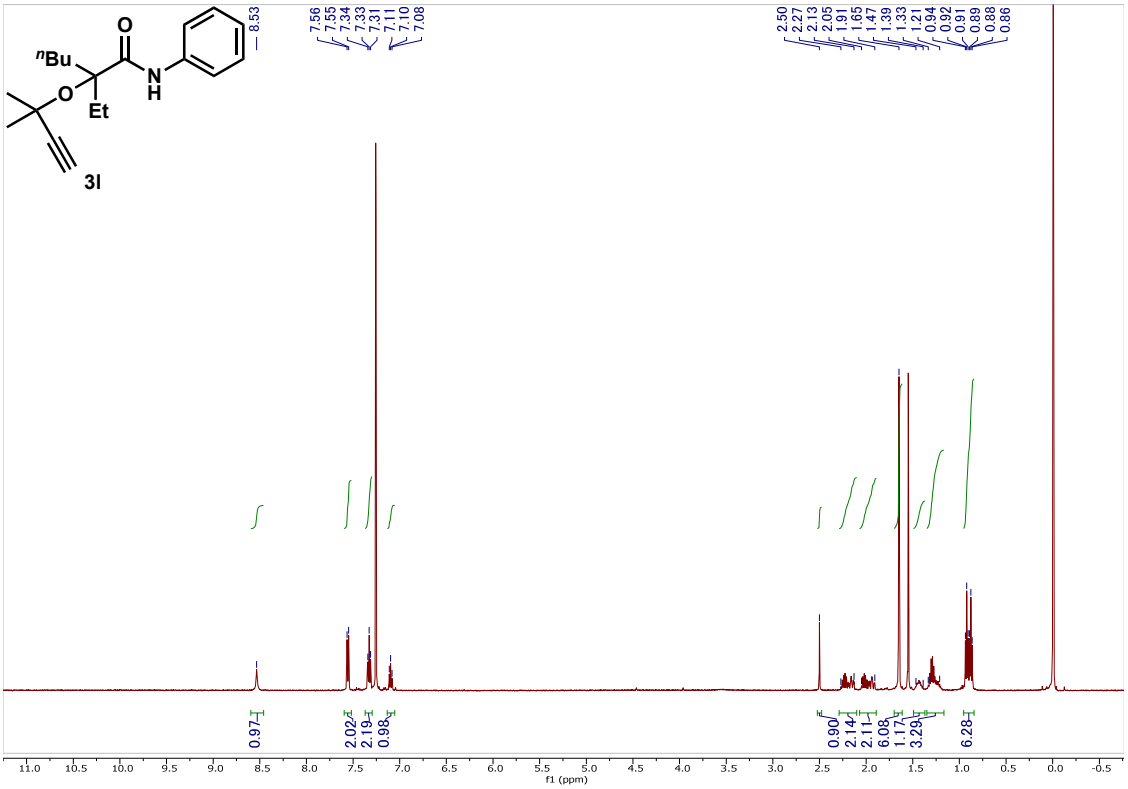
^{1}H NMR (500 MHz, $CDCl_3$)



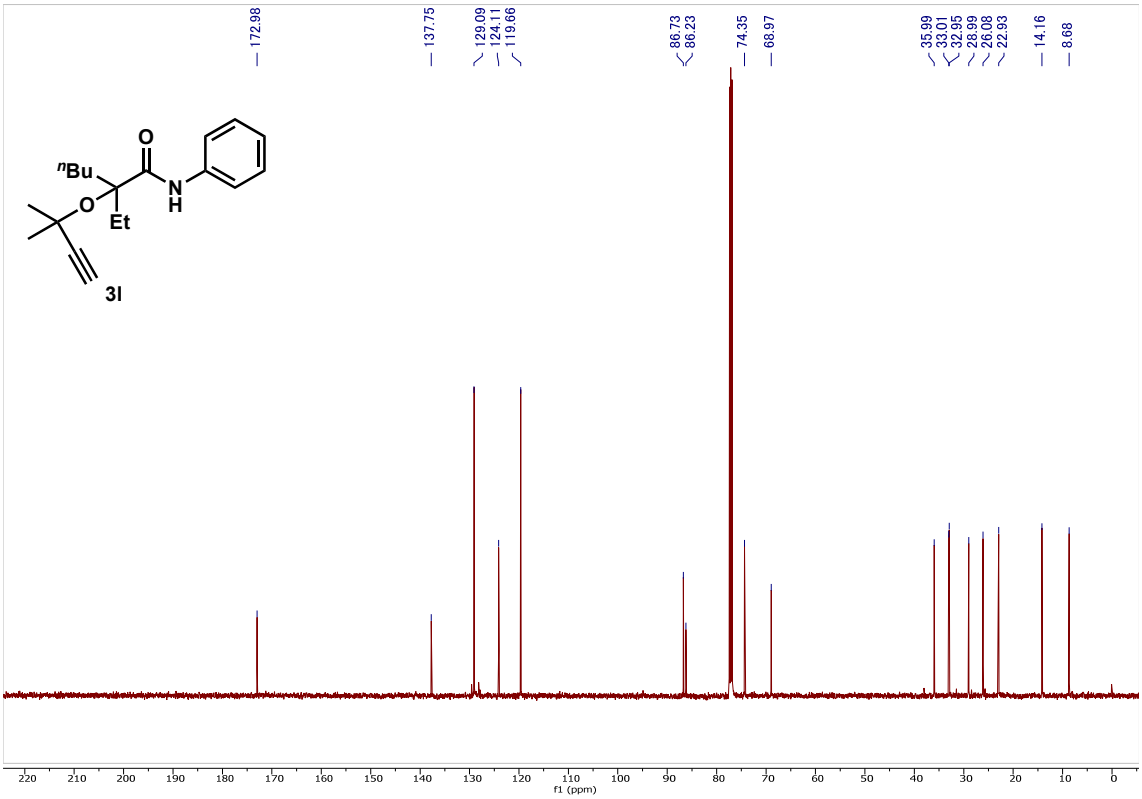
^{13}C NMR (125 MHz, $CDCl_3$)



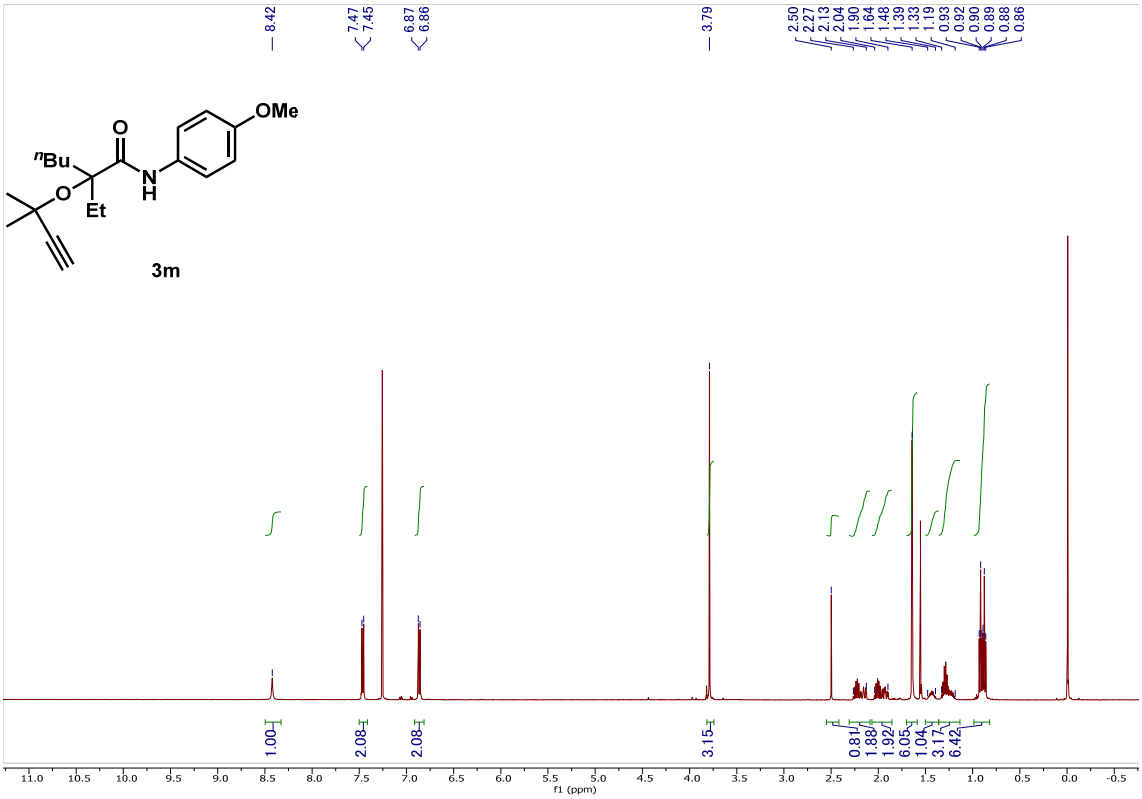
^{1}H NMR (500 MHz, $CDCl_3$)



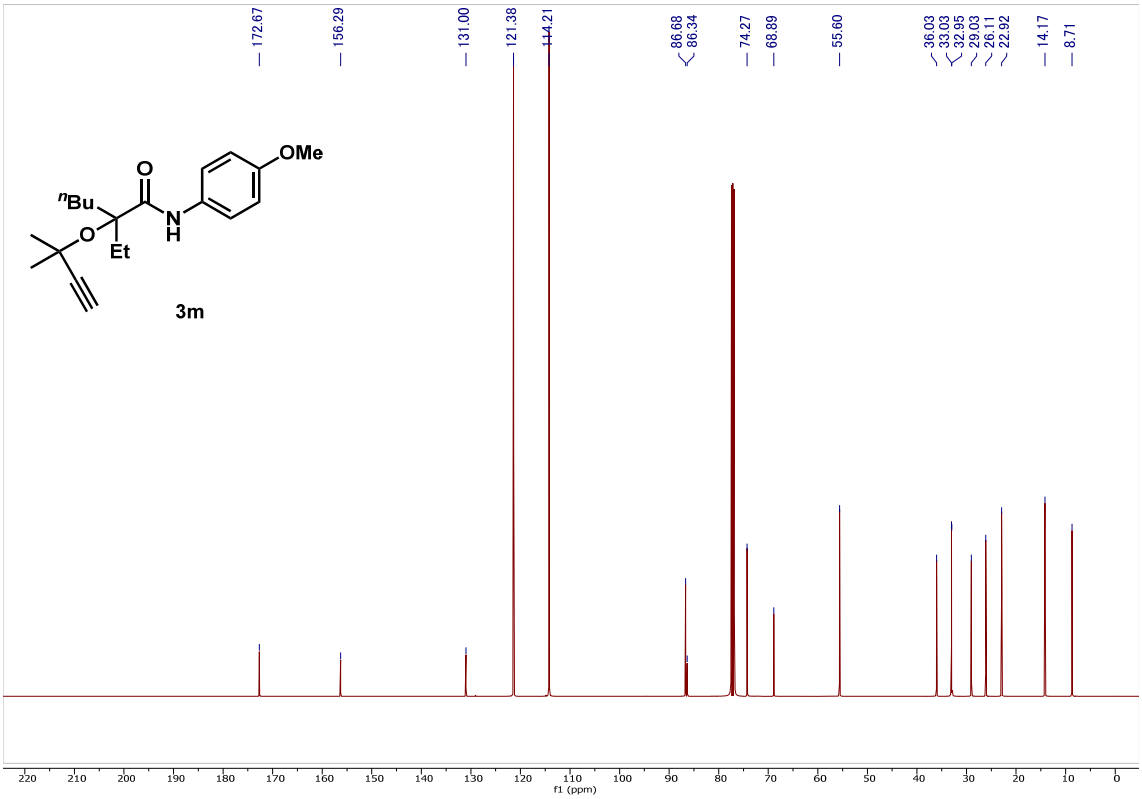
^{13}C NMR (125 MHz, $CDCl_3$)



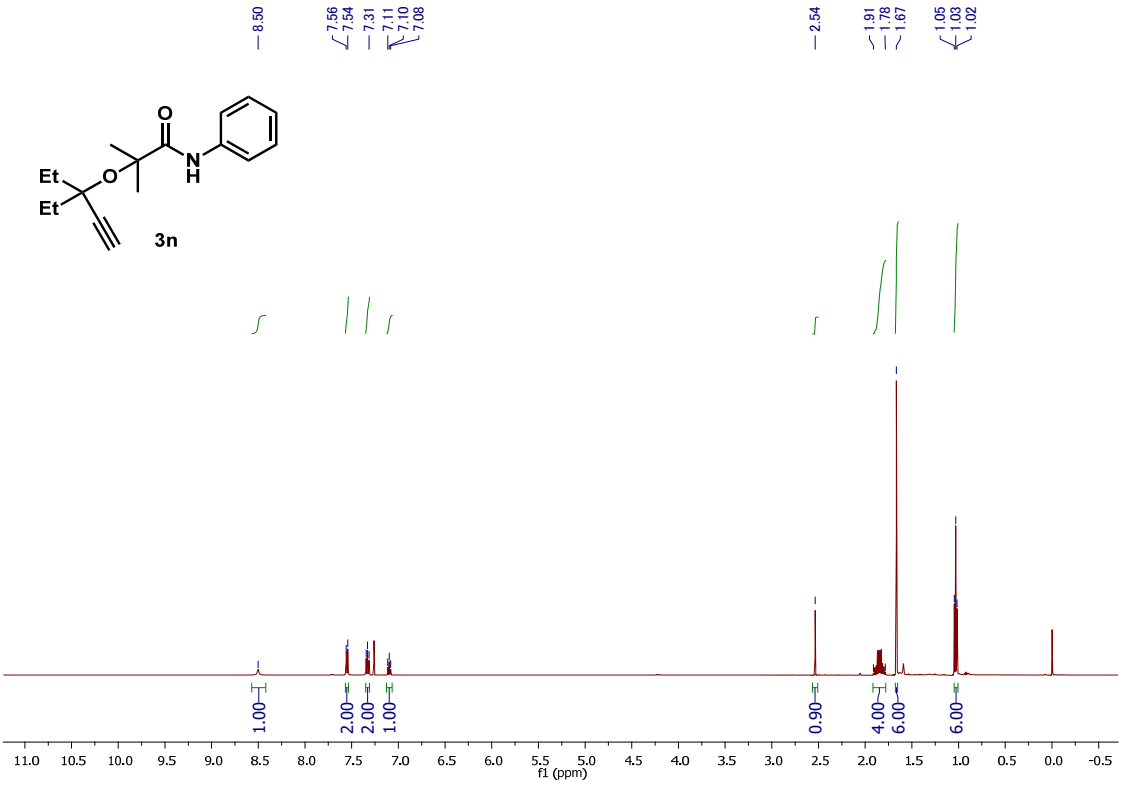
^{1}H NMR (500 MHz, $CDCl_3$)



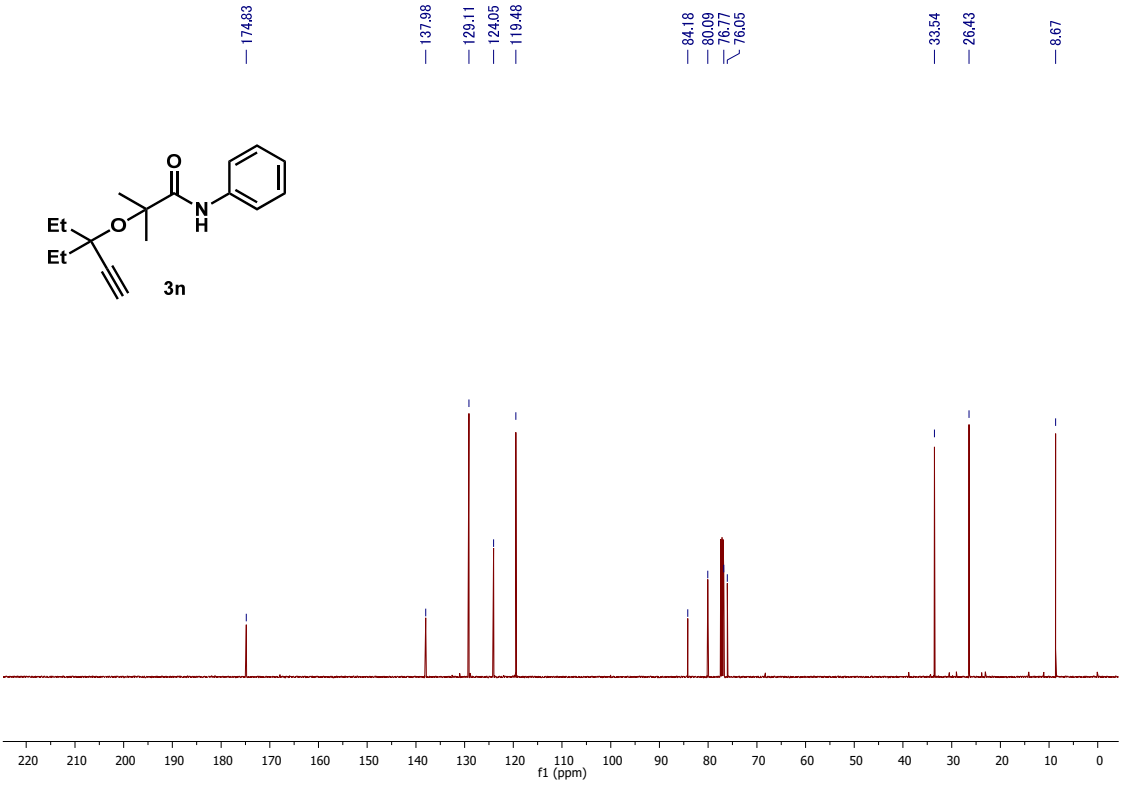
^{13}C NMR (125 MHz, $CDCl_3$)



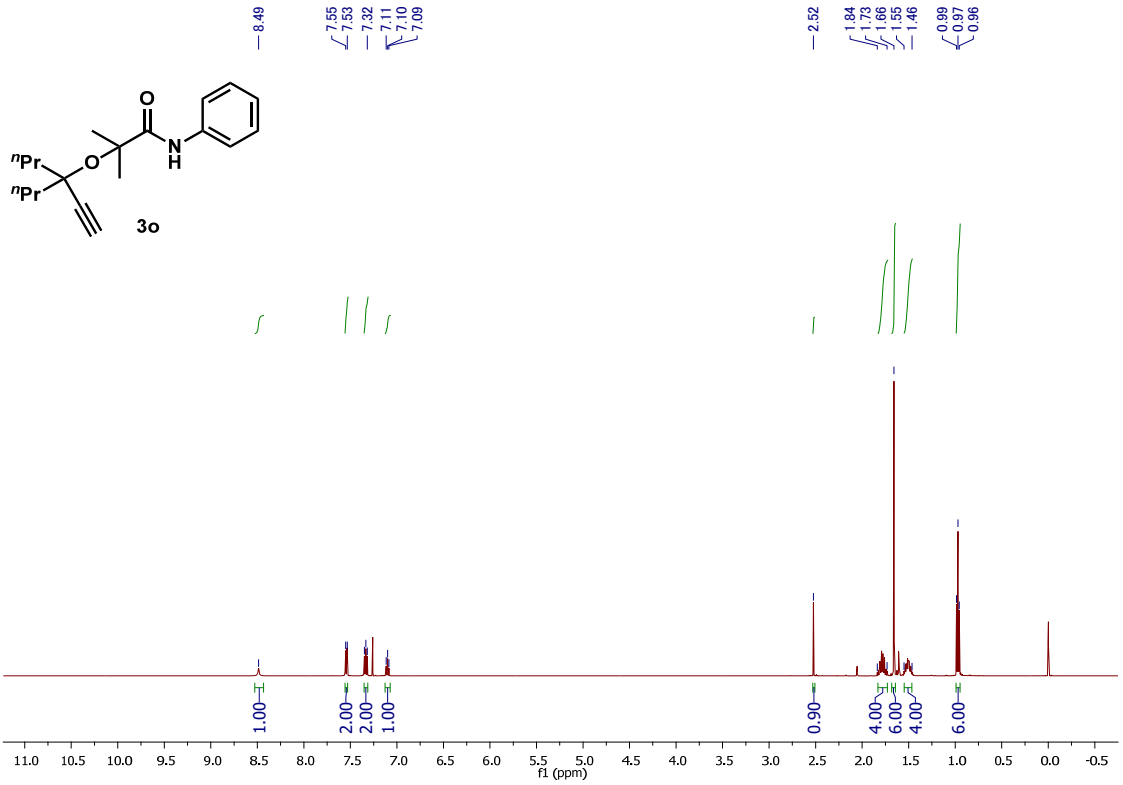
^{1}H NMR (500 MHz, $CDCl_3$)



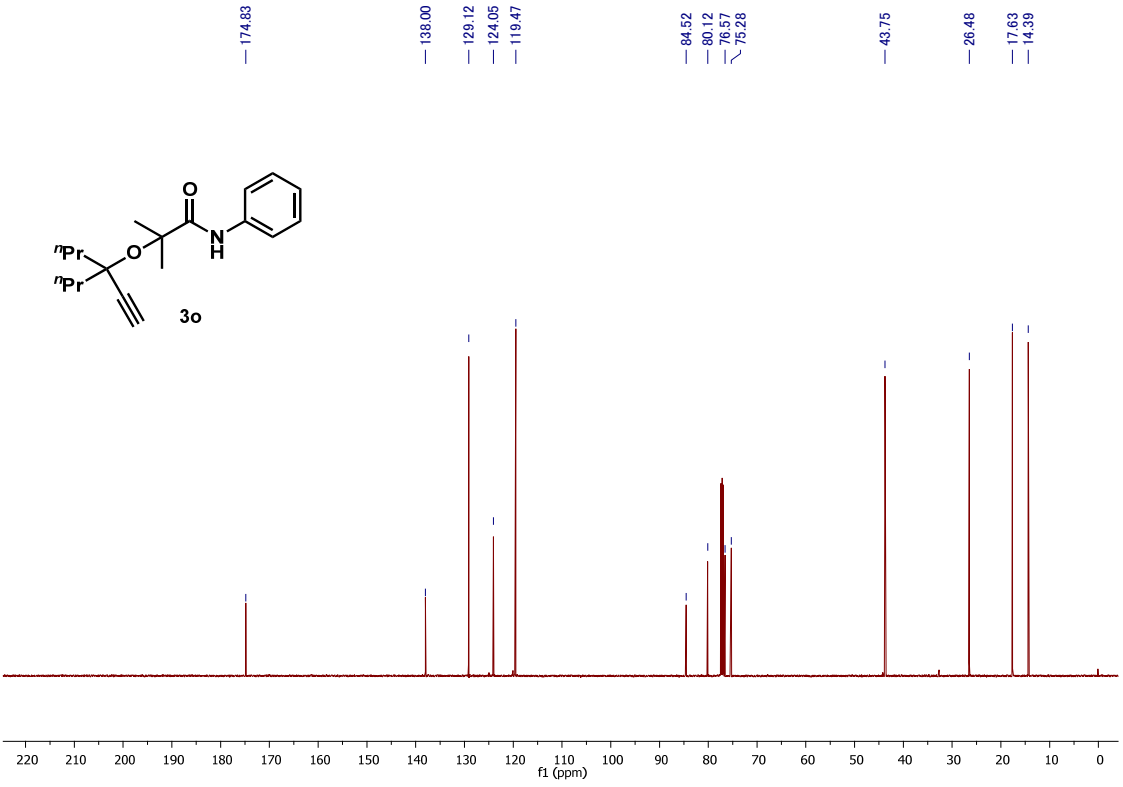
^{13}C NMR (125 MHz, $CDCl_3$)



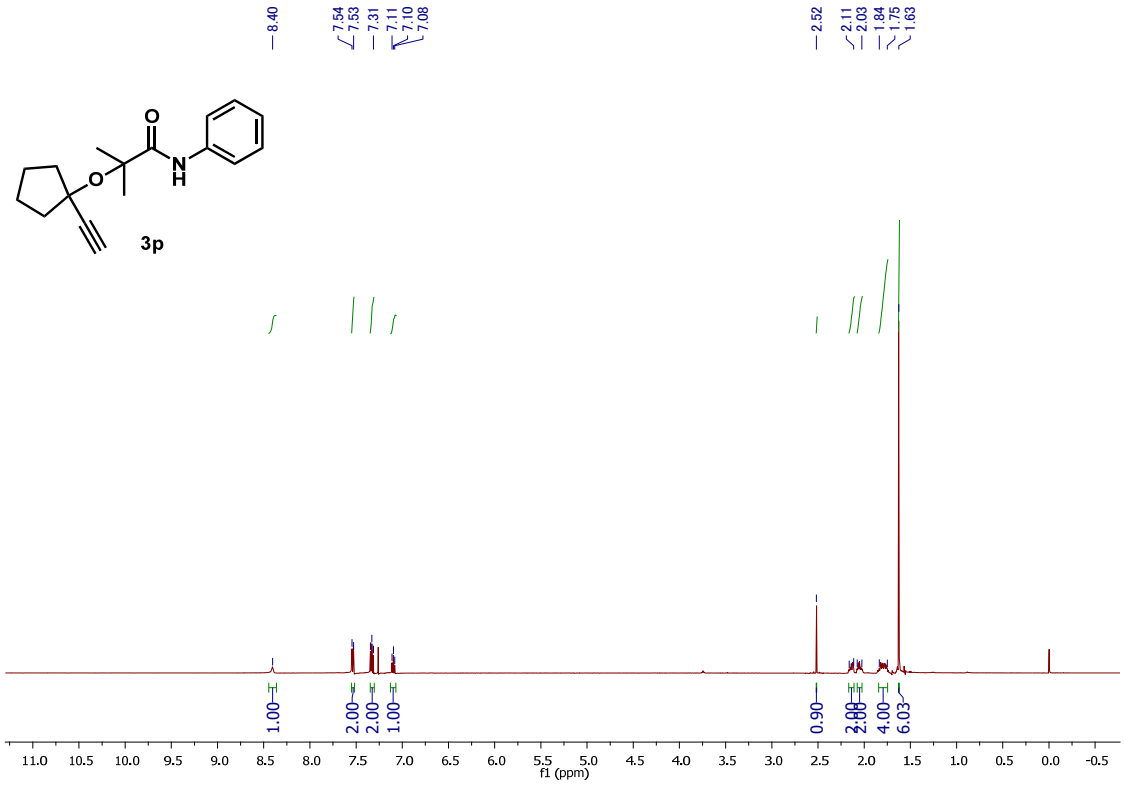
^{1}H NMR (500 MHz, $CDCl_3$)



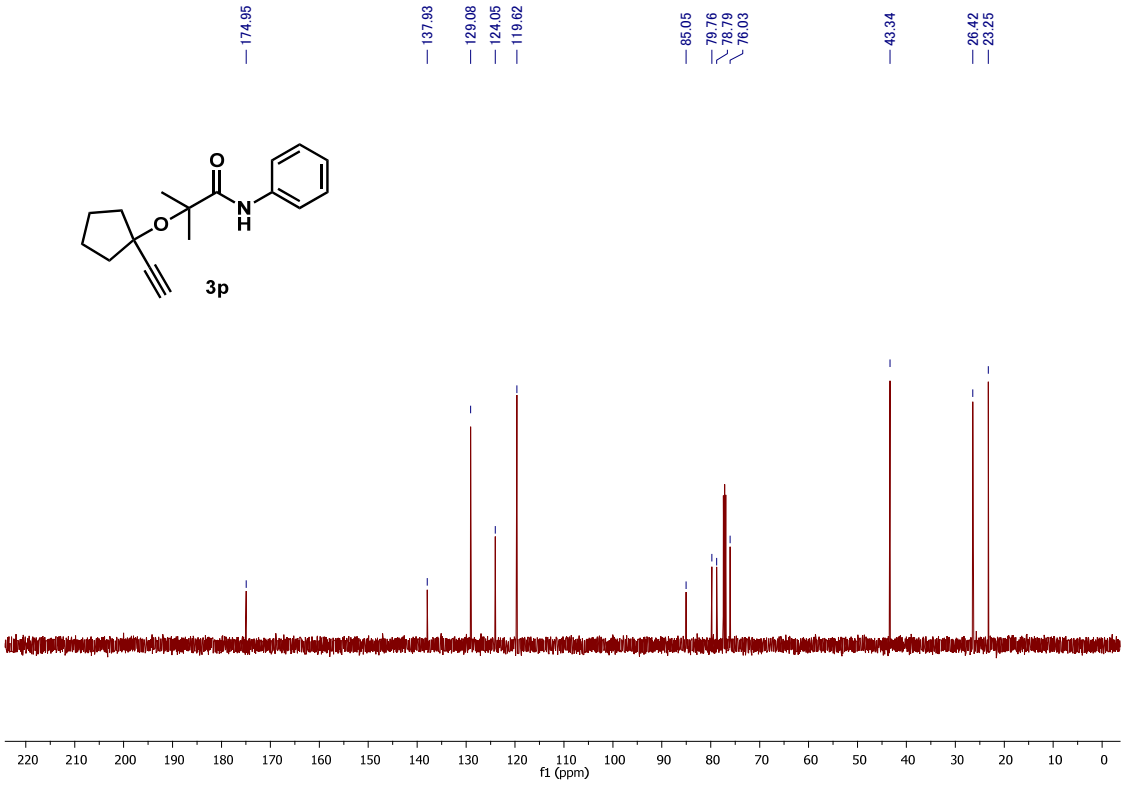
^{13}C NMR (125 MHz, $CDCl_3$)



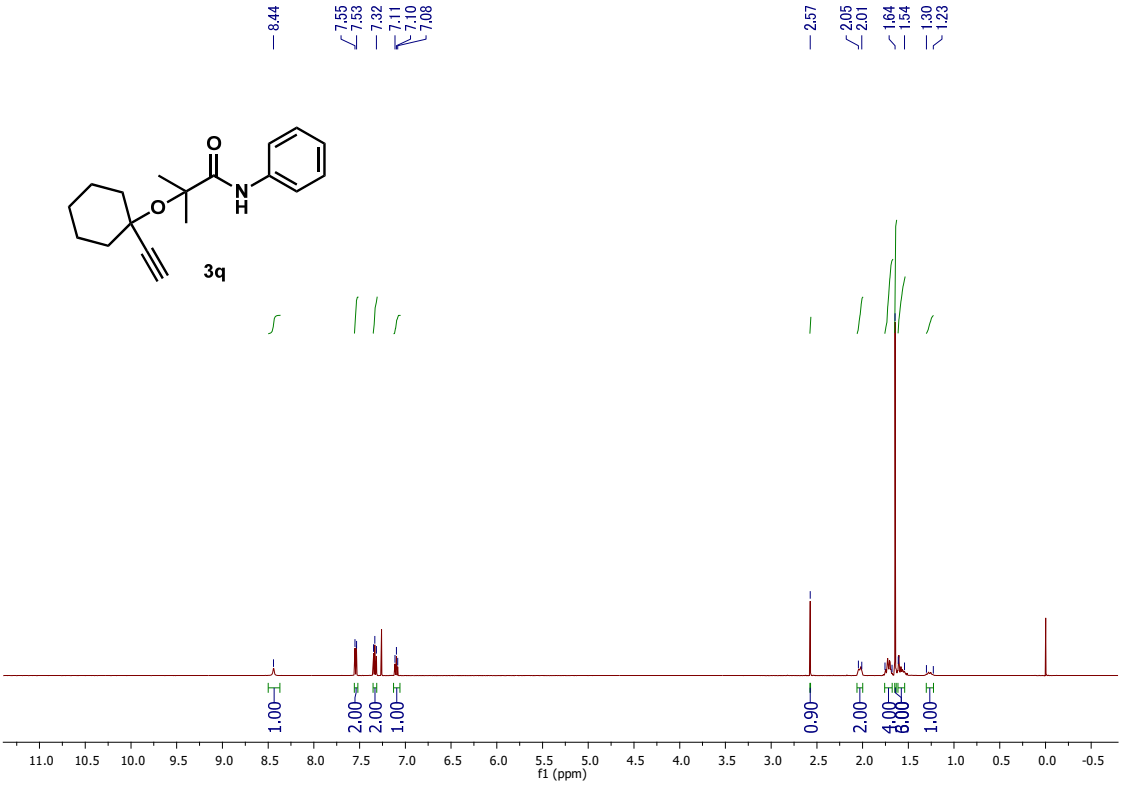
^{1}H NMR (500 MHz, $CDCl_3$)



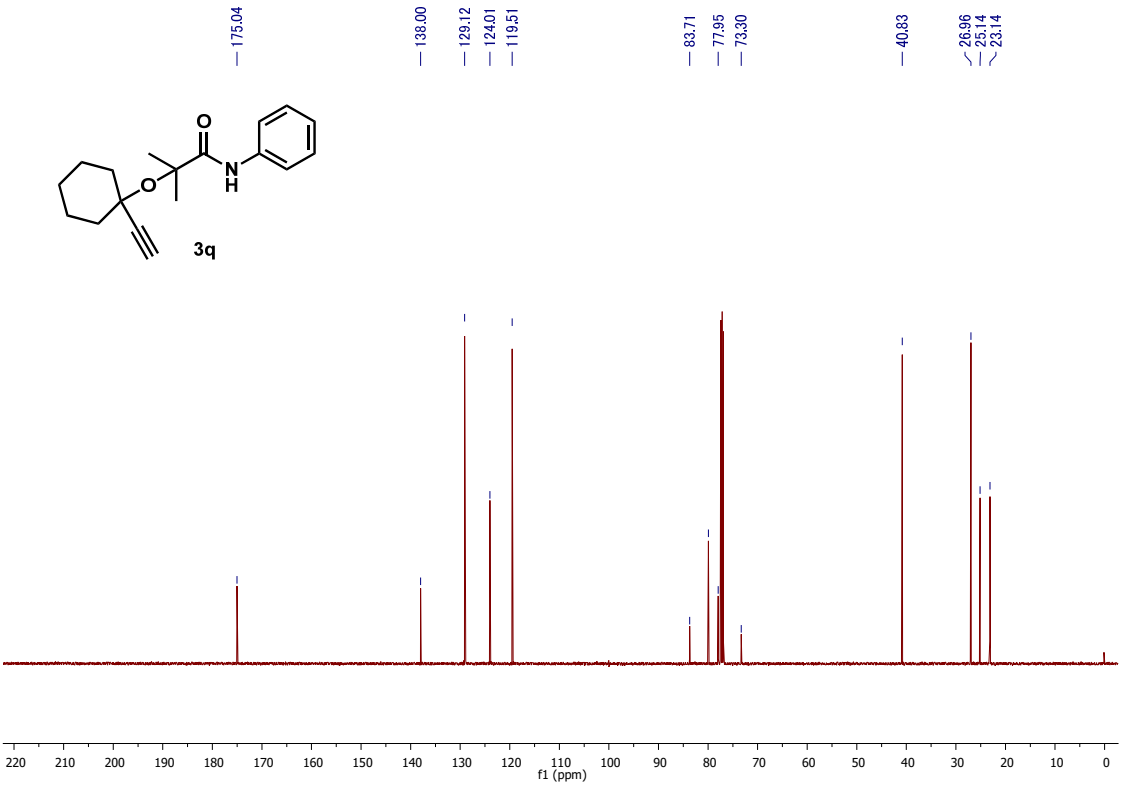
^{13}C NMR (125 MHz, $CDCl_3$)



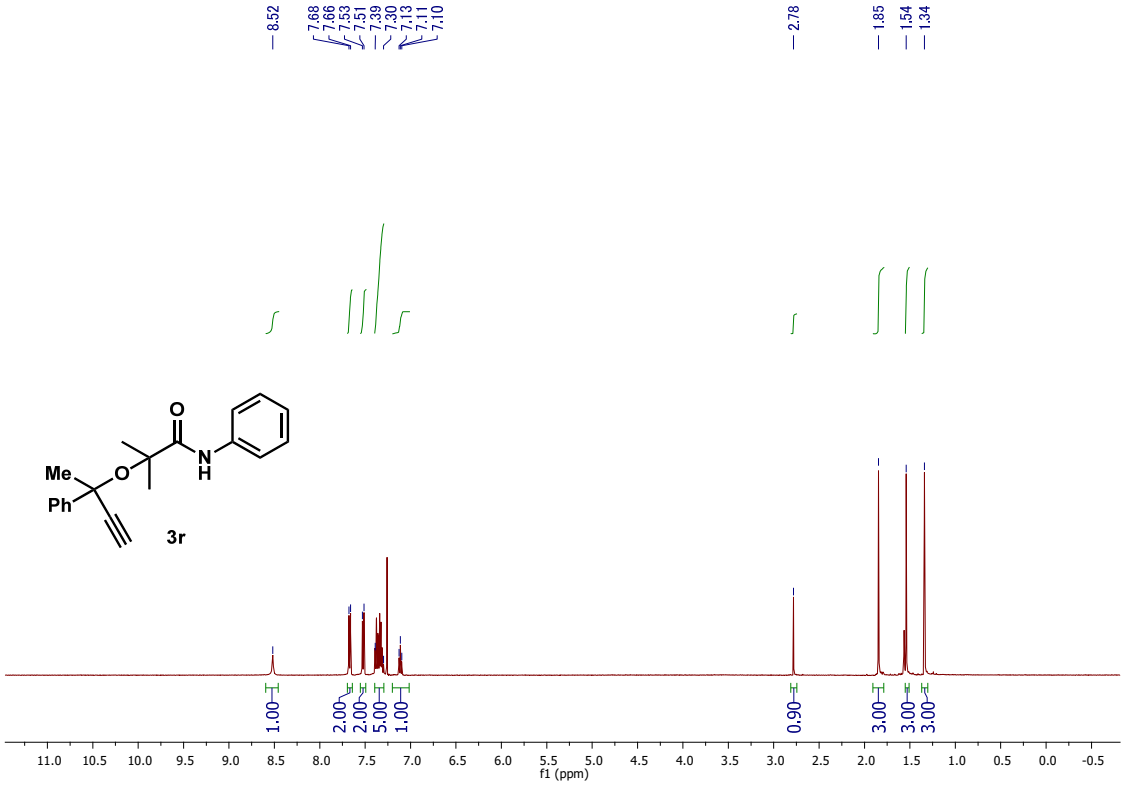
^{1}H NMR (500 MHz, $CDCl_3$)



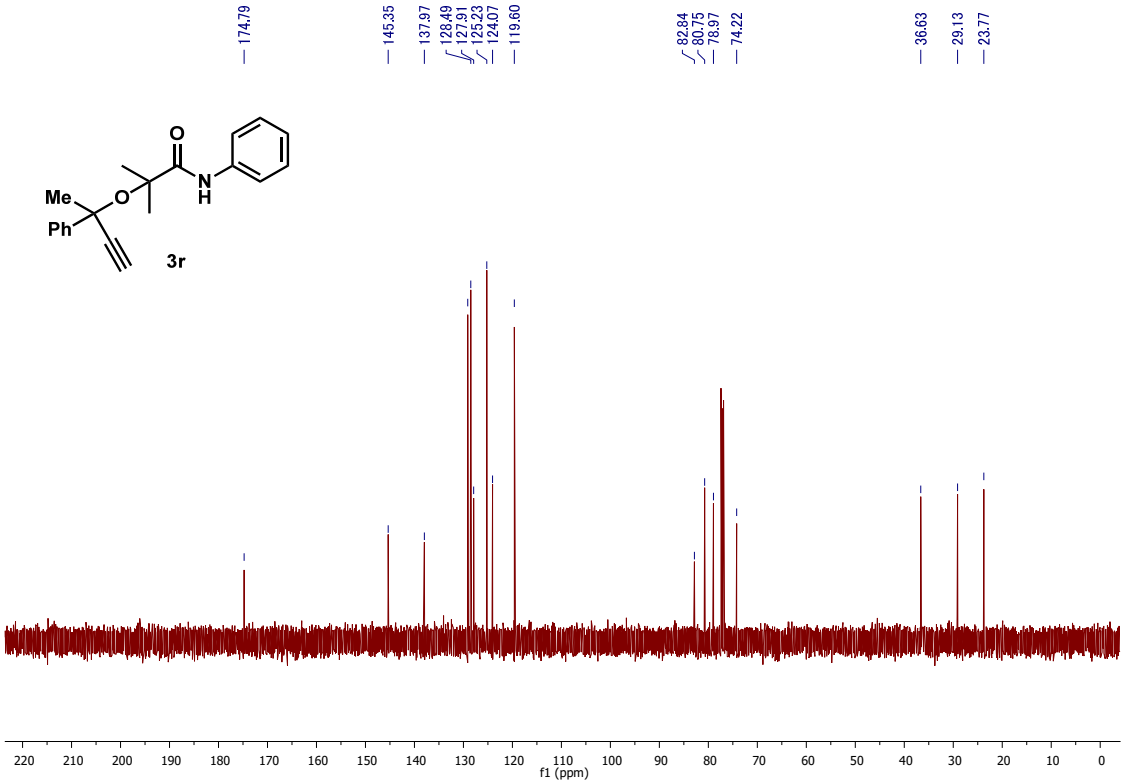
^{13}C NMR (125 MHz, $CDCl_3$)



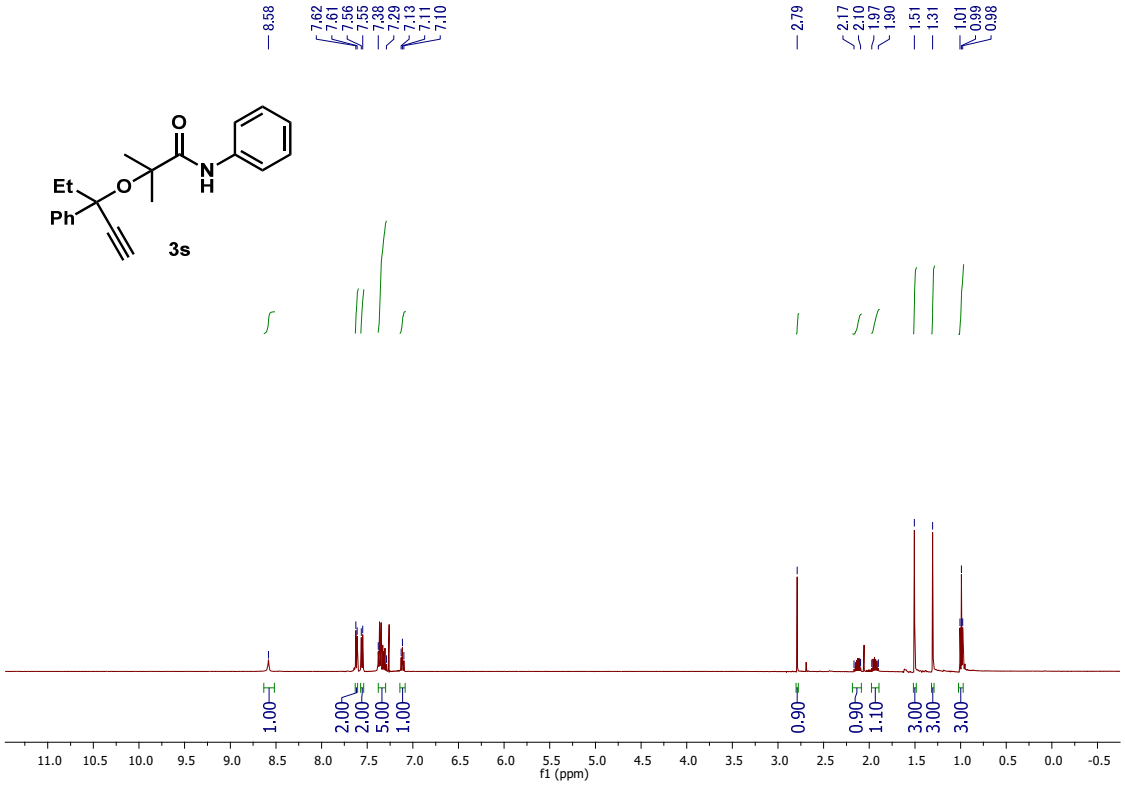
^{1}H NMR (500 MHz, $CDCl_3$)



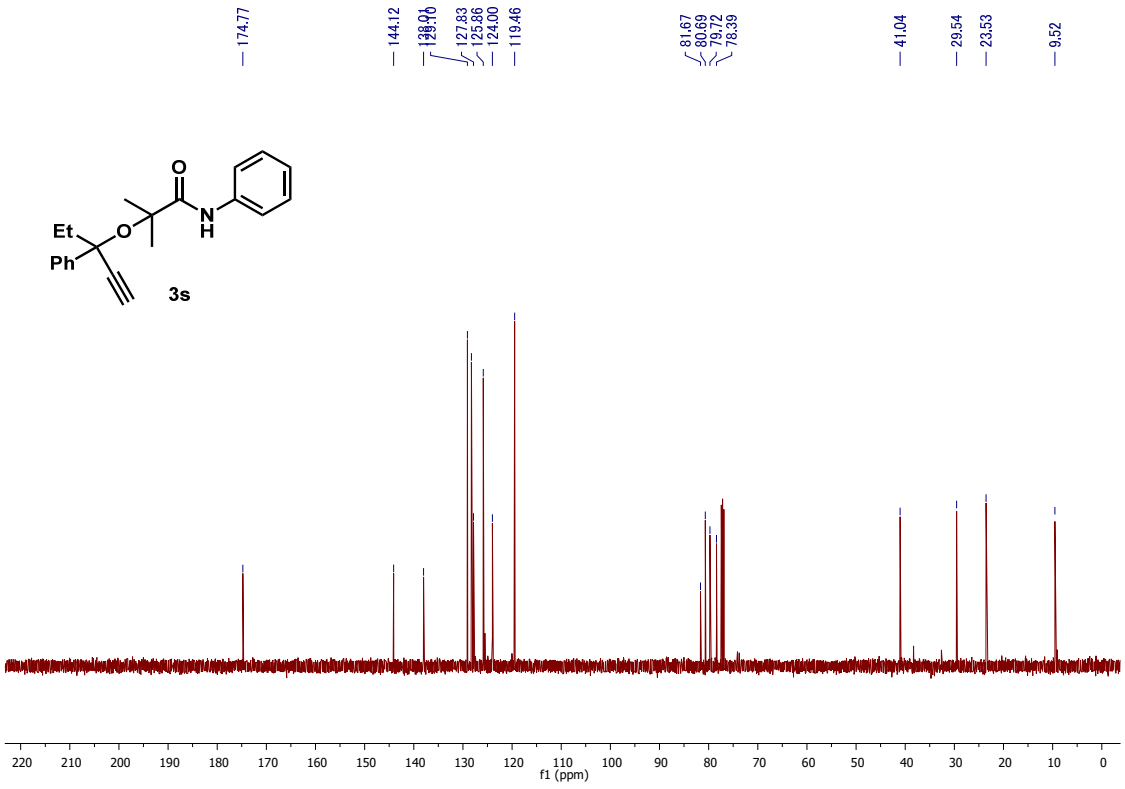
^{13}C NMR (125 MHz, $CDCl_3$)



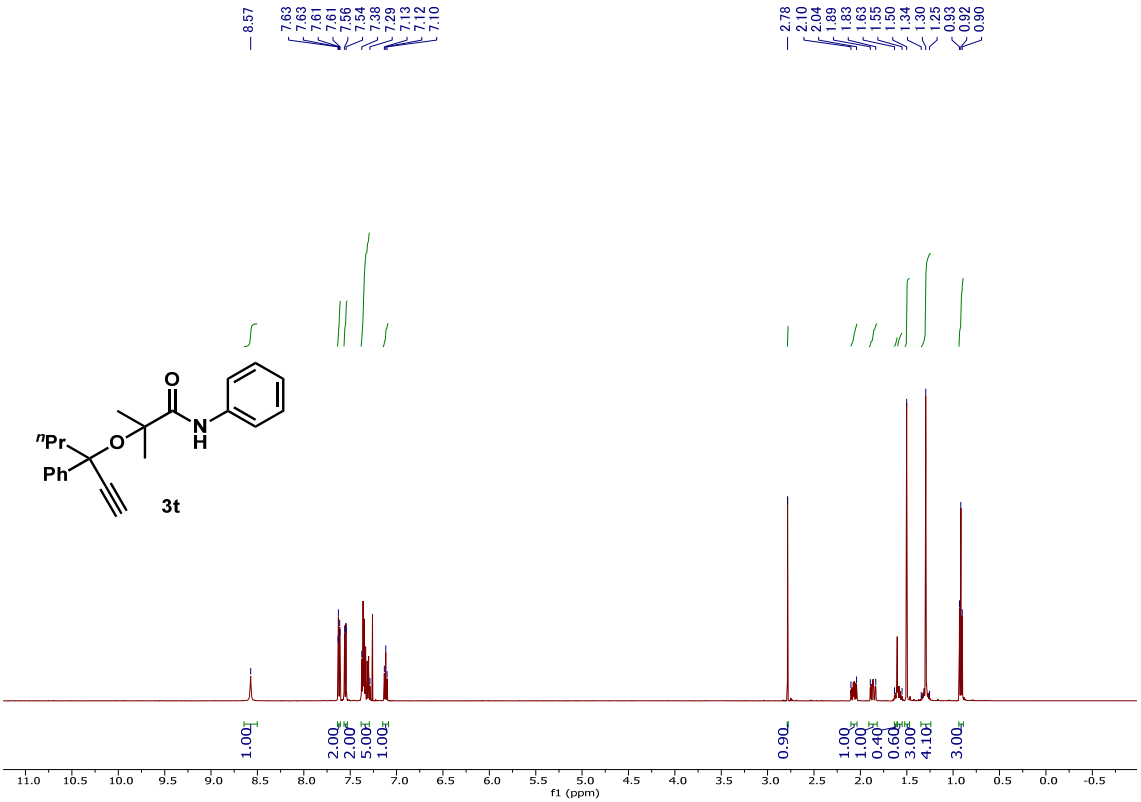
^{1}H NMR (500 MHz, $CDCl_3$)



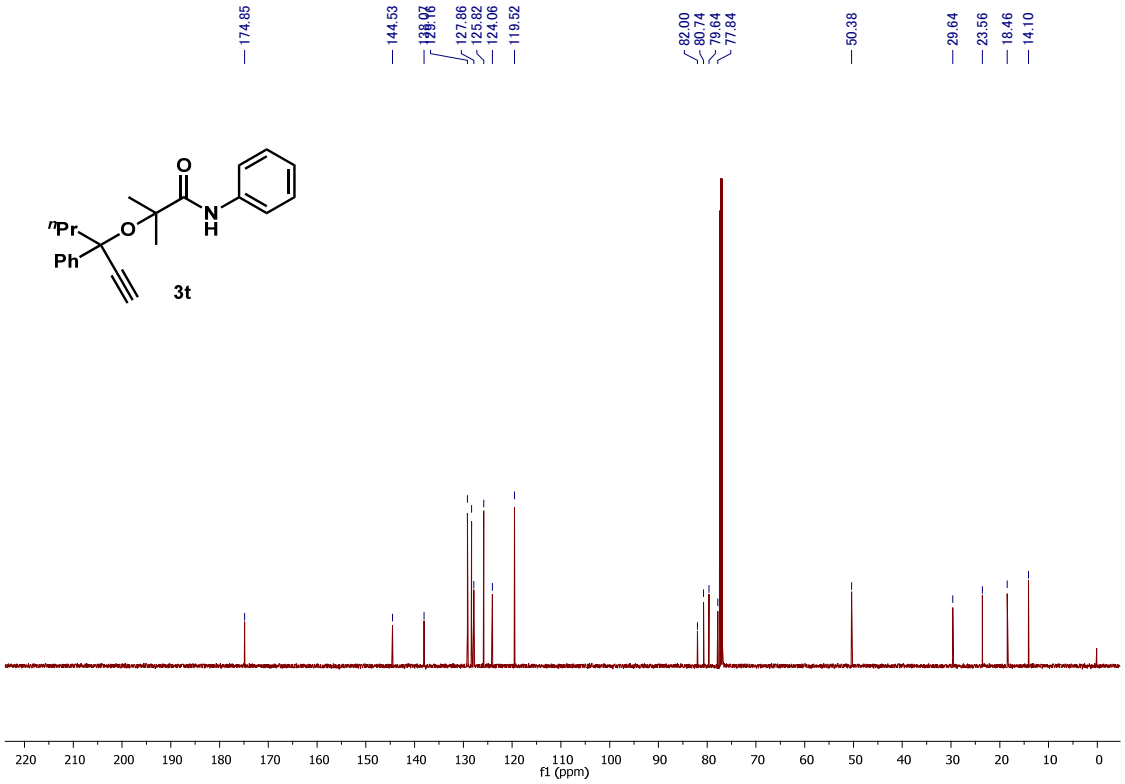
^{13}C NMR (125 MHz, $CDCl_3$)



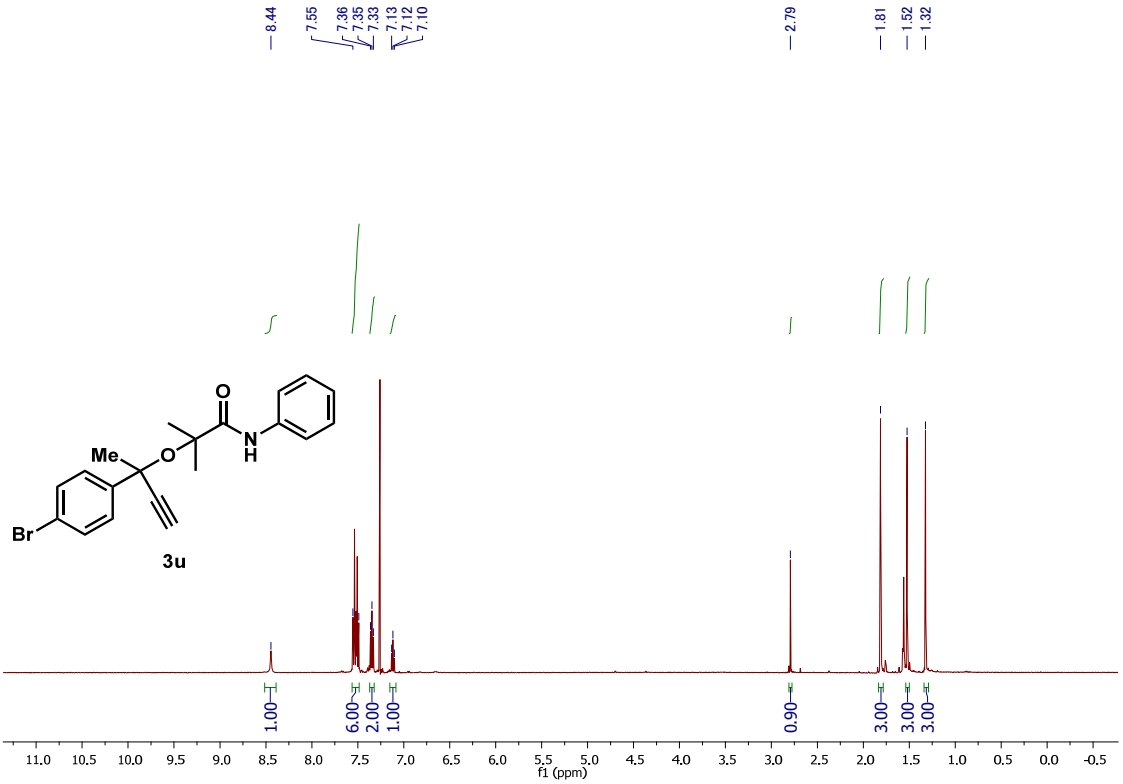
^{1}H NMR (500 MHz, $CDCl_3$)



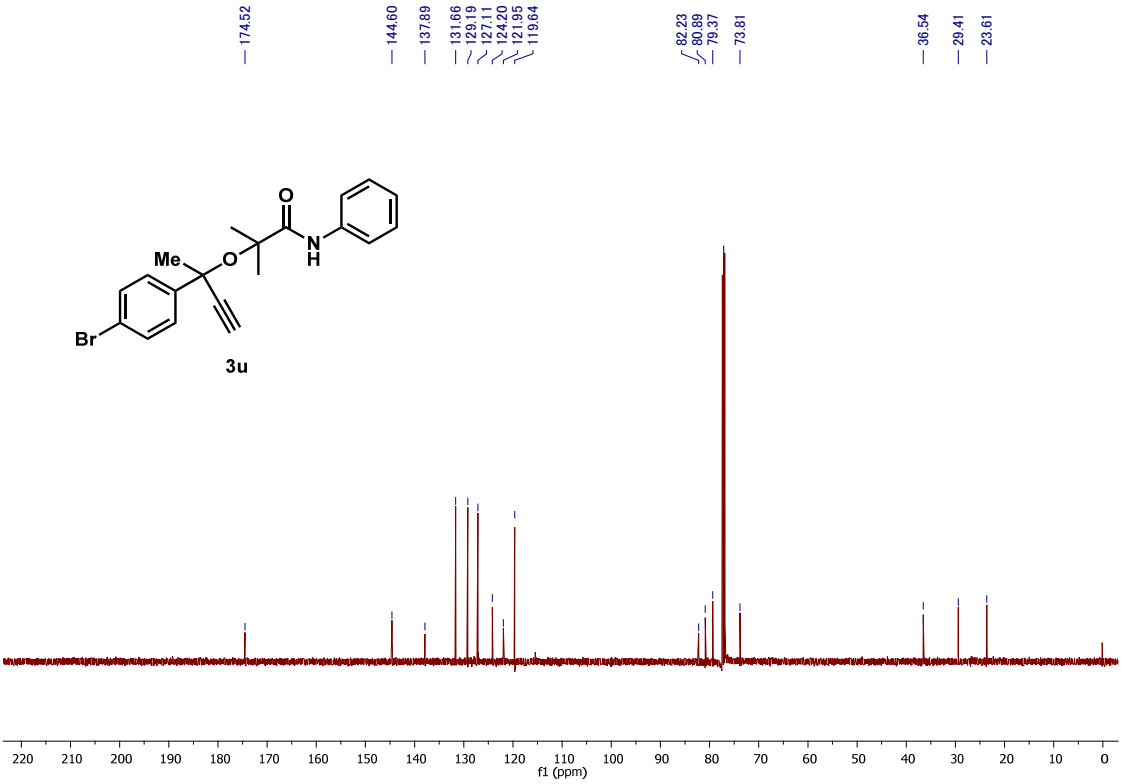
^{13}C NMR (125 MHz, $CDCl_3$)



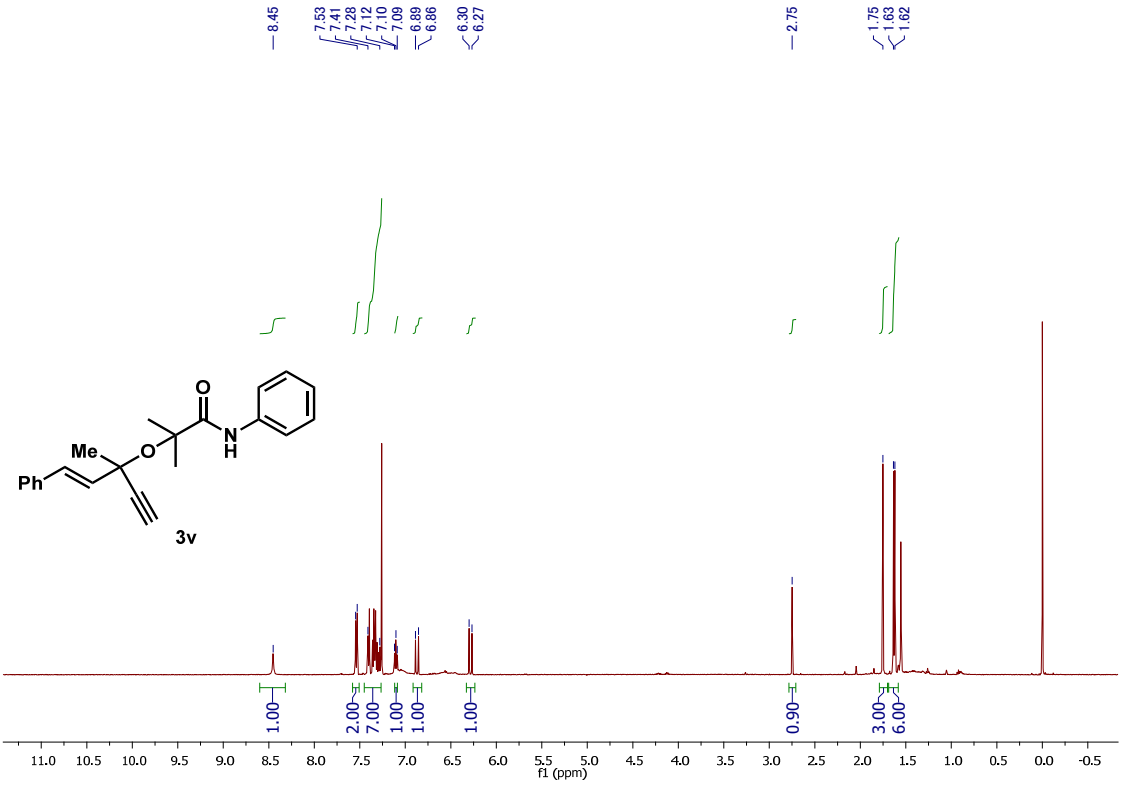
^{1}H NMR (500 MHz, $CDCl_3$)



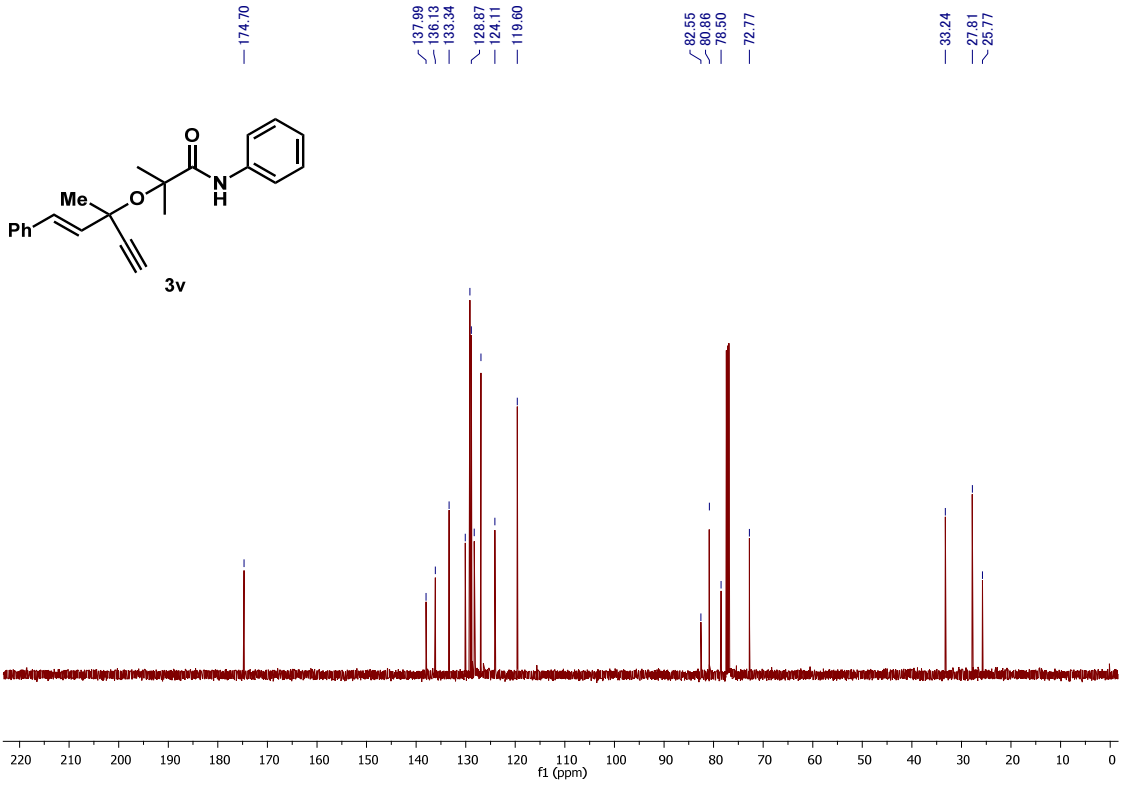
^{13}C NMR (125 MHz, $CDCl_3$)



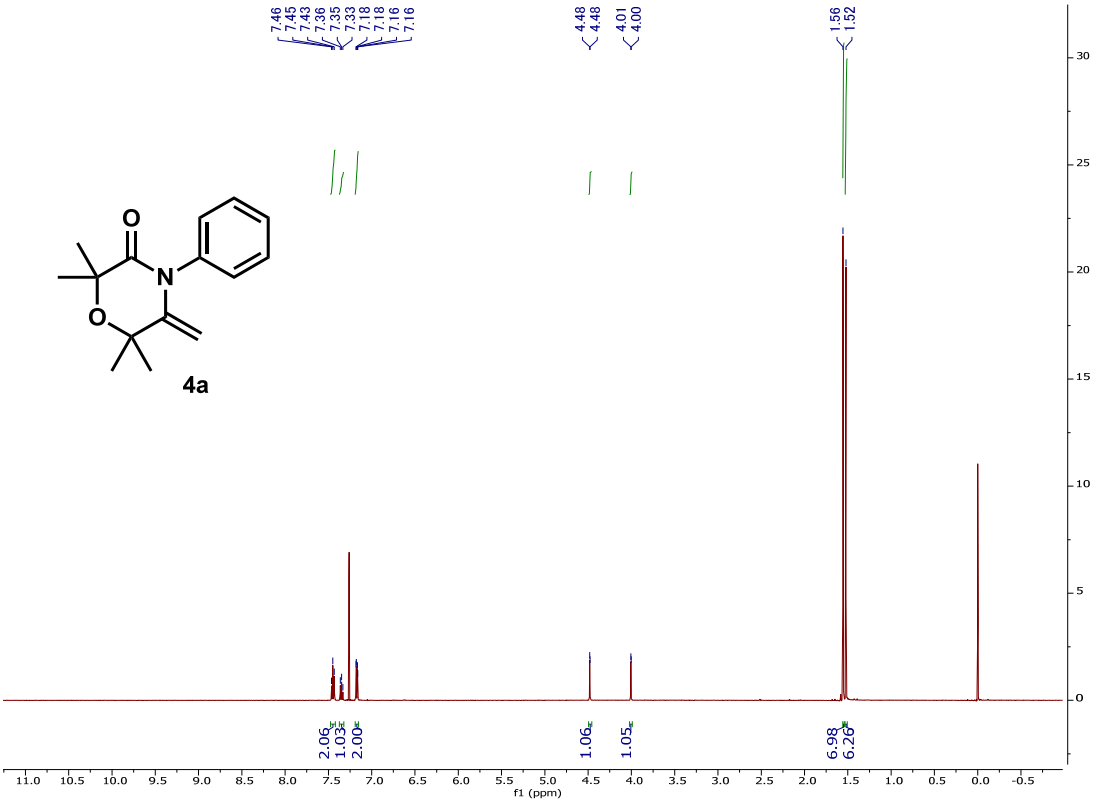
^{1}H NMR (500 MHz, $CDCl_3$)



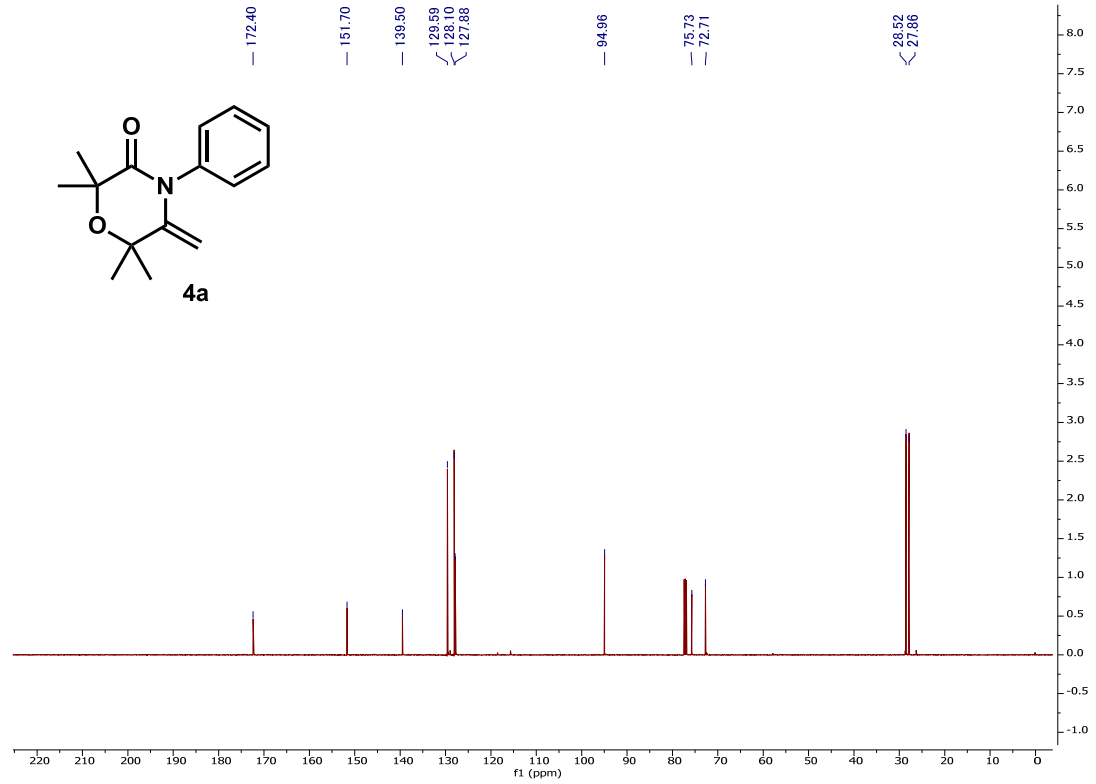
^{13}C NMR (125 MHz, $CDCl_3$)



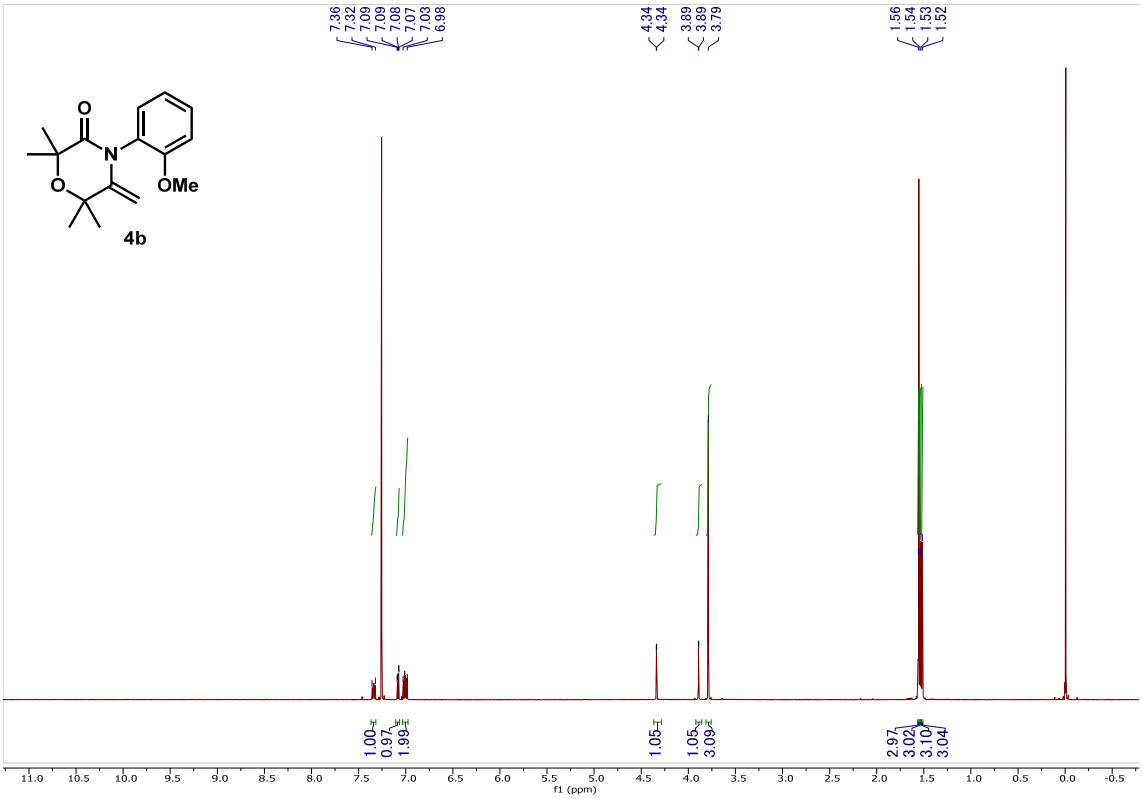
^{1}H NMR (500 MHz, $CDCl_3$)



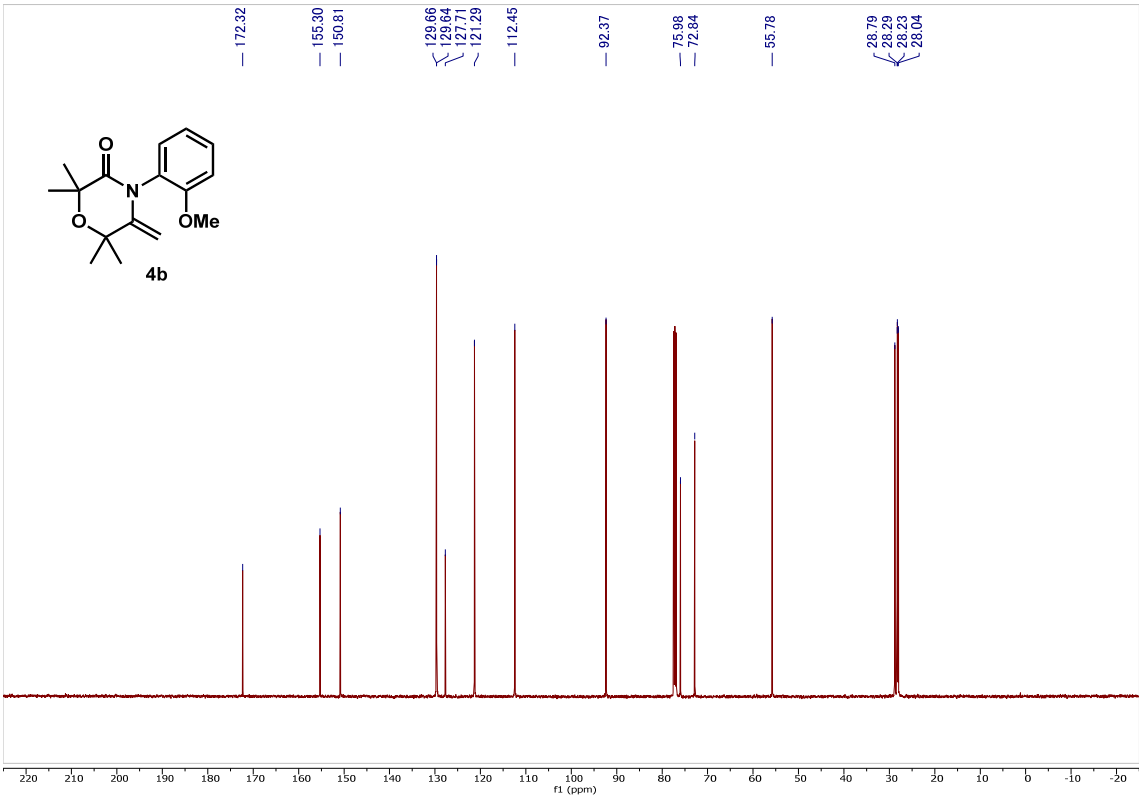
^{13}C NMR (125 MHz, $CDCl_3$)



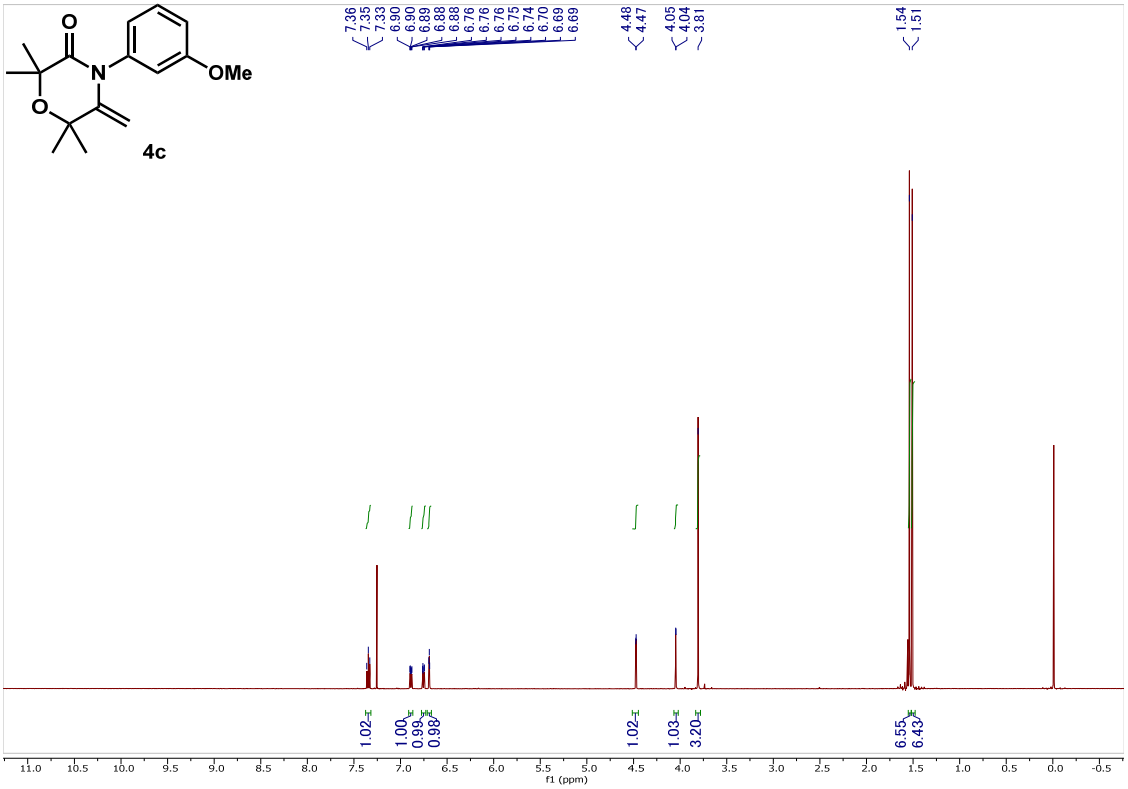
^{1}H NMR (500 MHz, $CDCl_3$)



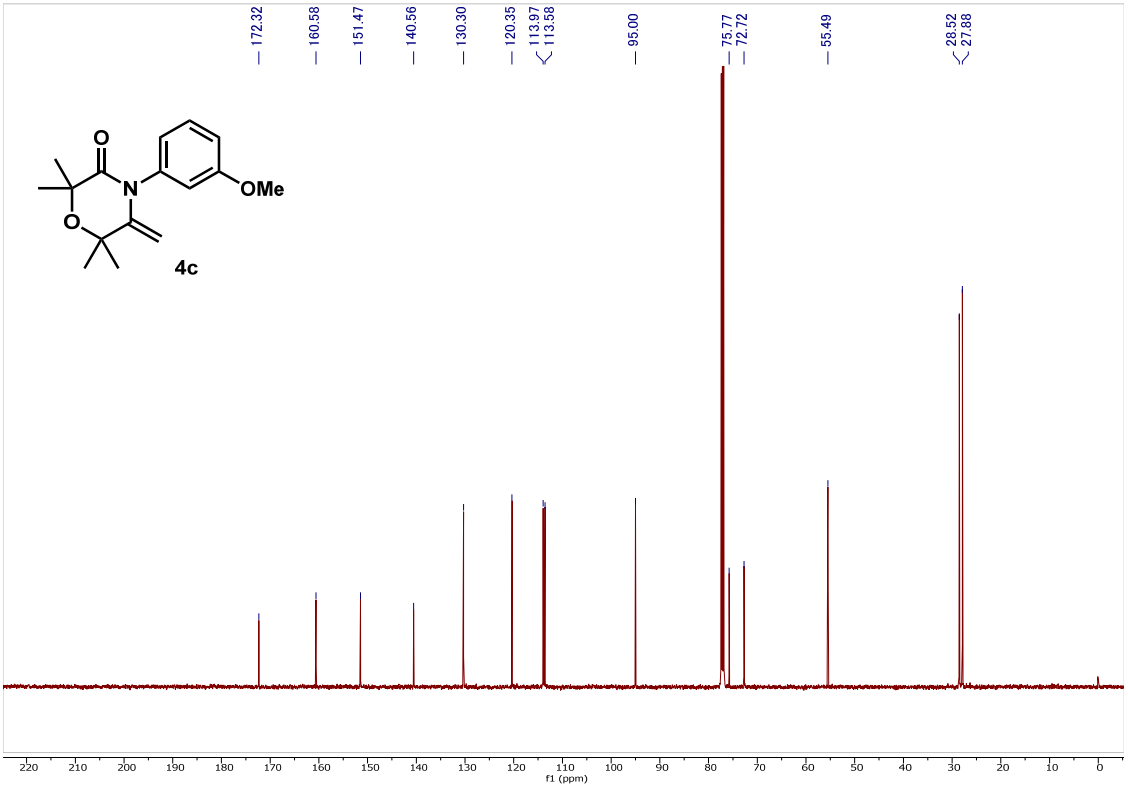
^{13}C NMR (125 MHz, $CDCl_3$)



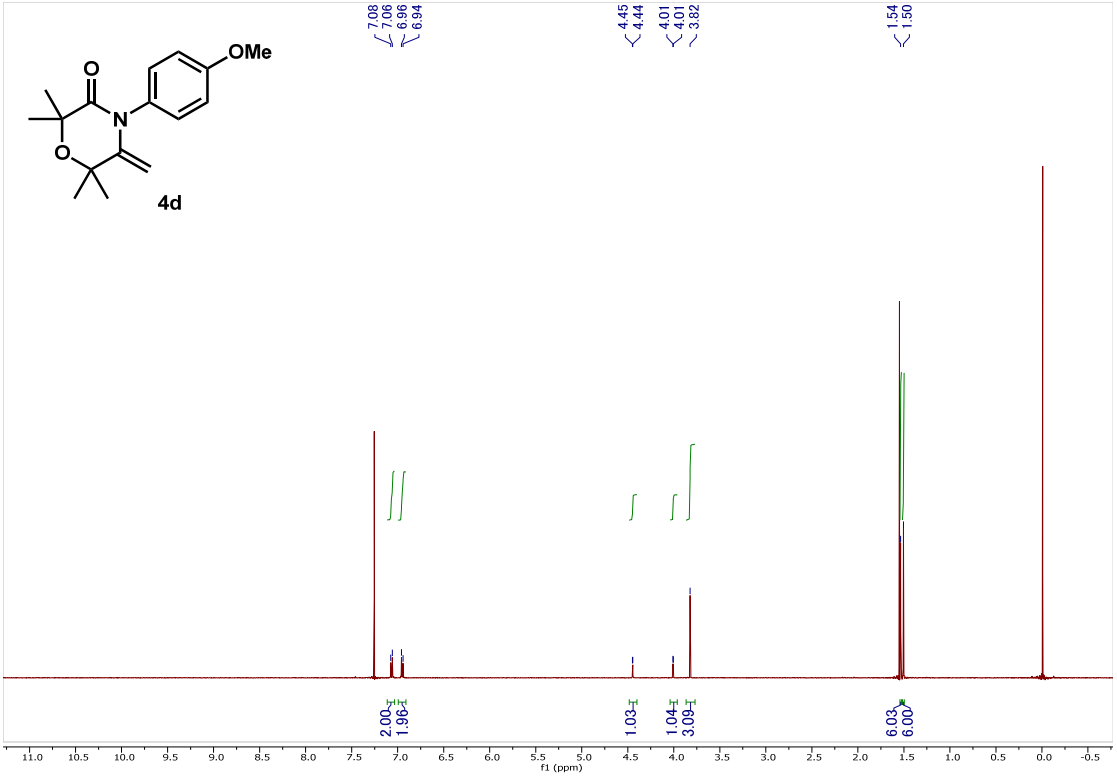
^{1}H NMR (500 MHz, $CDCl_3$)



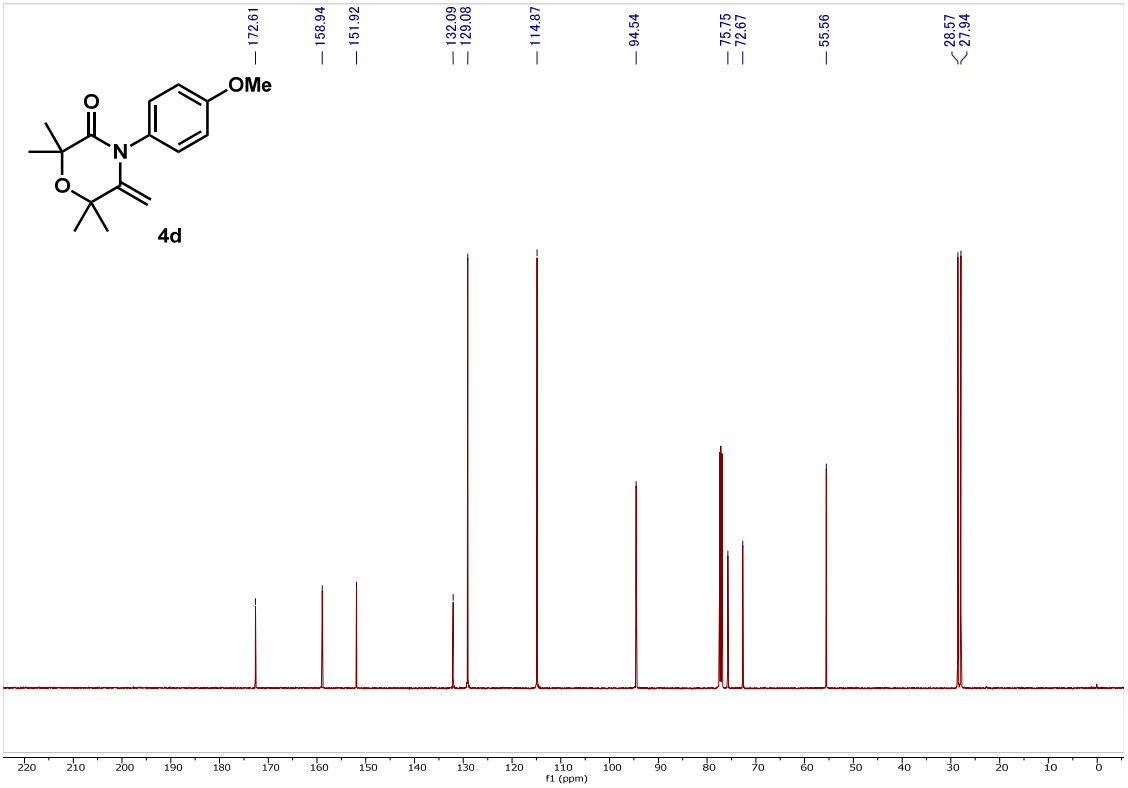
^{13}C NMR (125 MHz, $CDCl_3$)



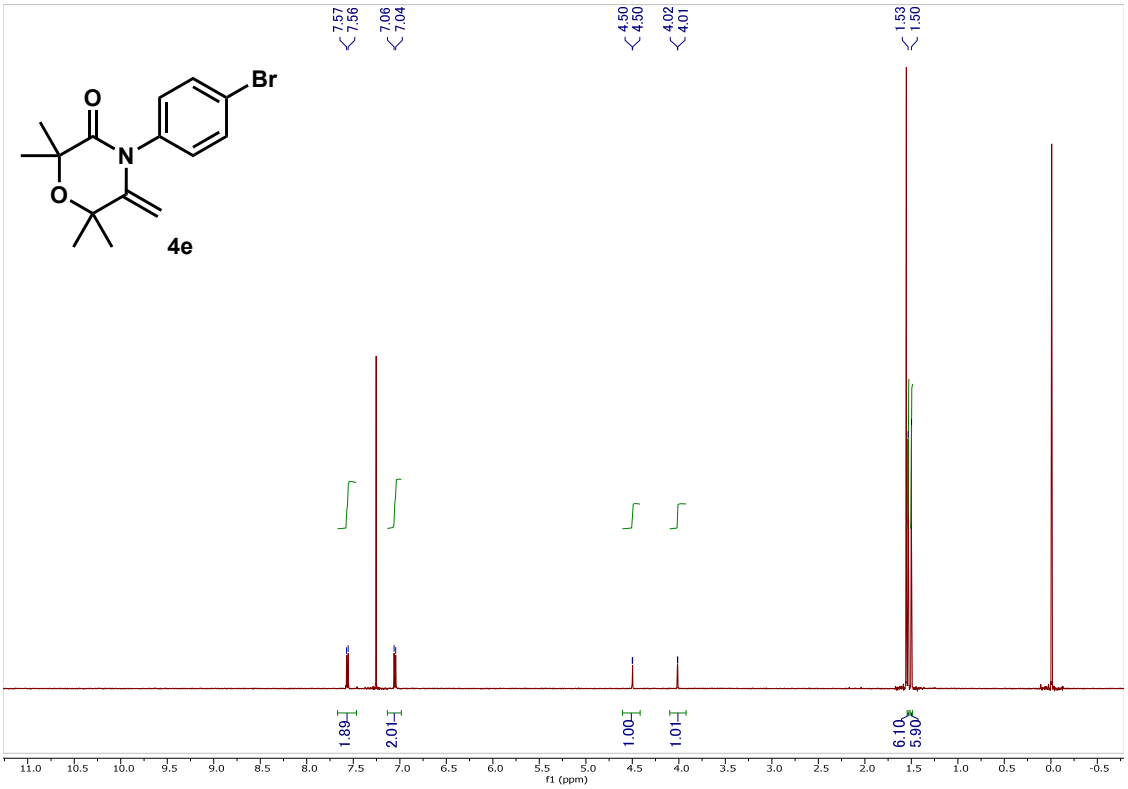
^{1}H NMR (500 MHz, $CDCl_3$)



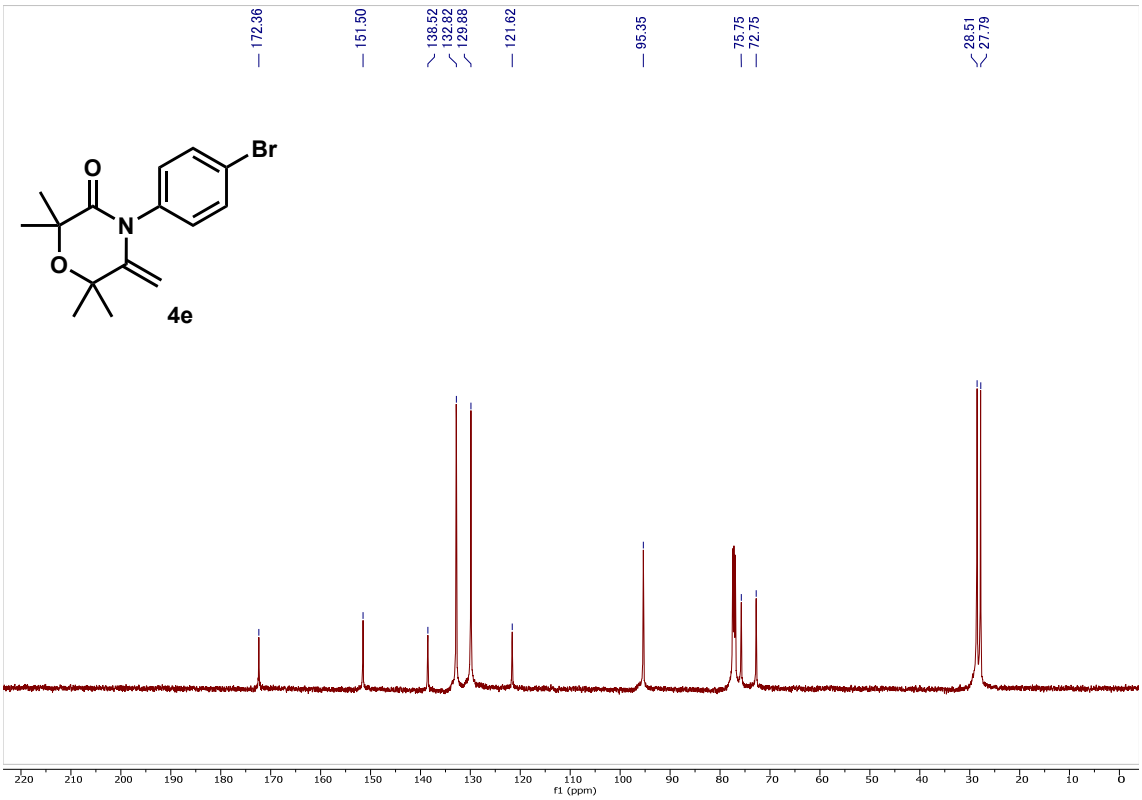
^{13}C NMR (125 MHz, $CDCl_3$)



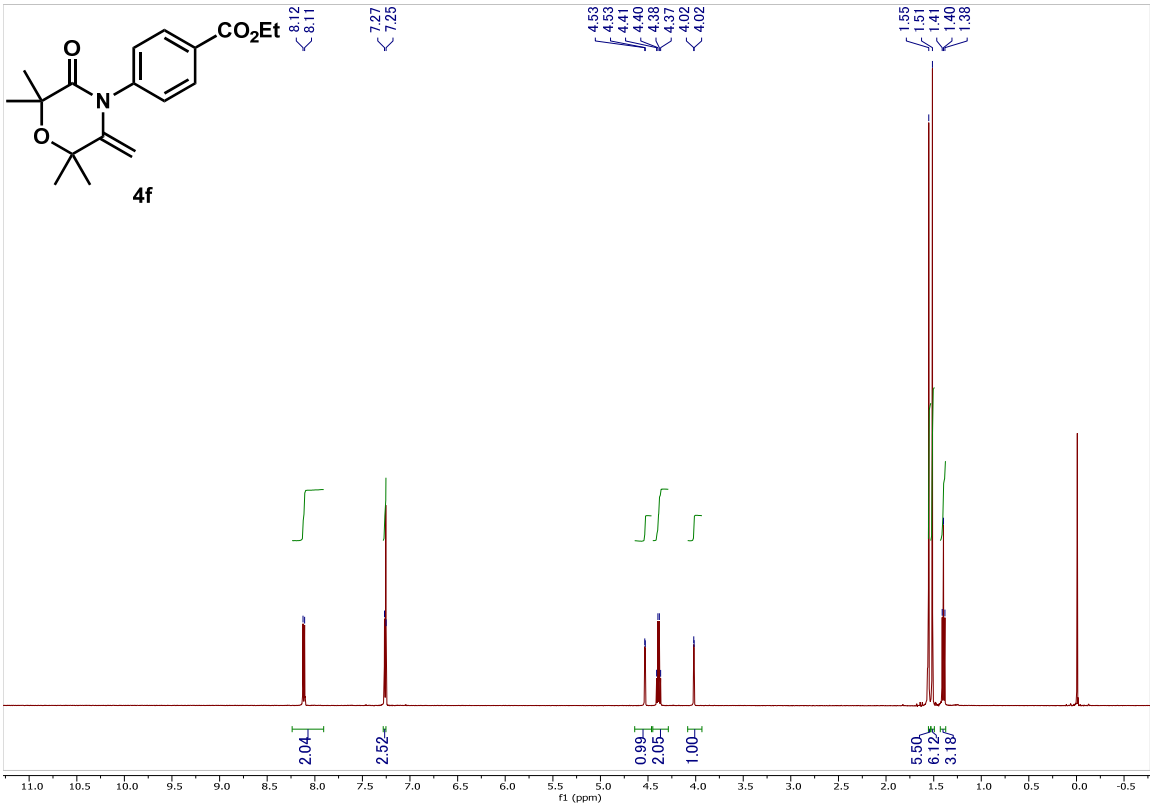
^{1}H NMR (500 MHz, $CDCl_3$)



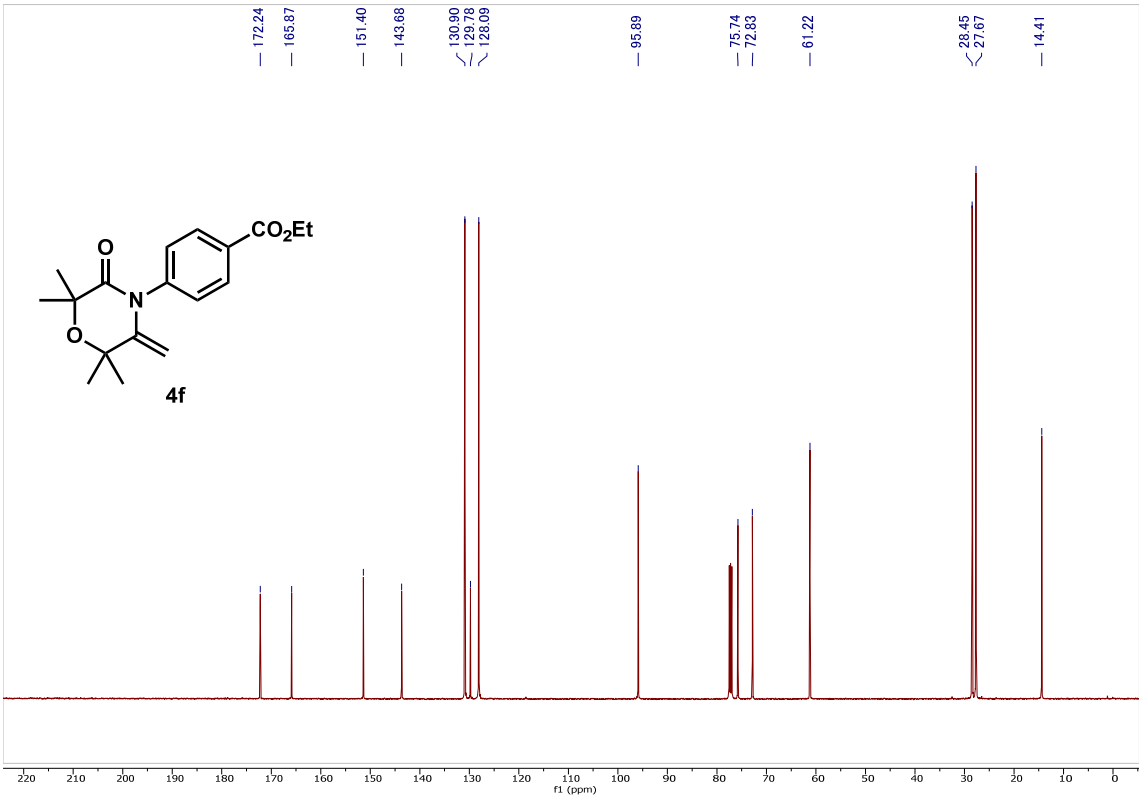
^{13}C NMR (125 MHz, $CDCl_3$)



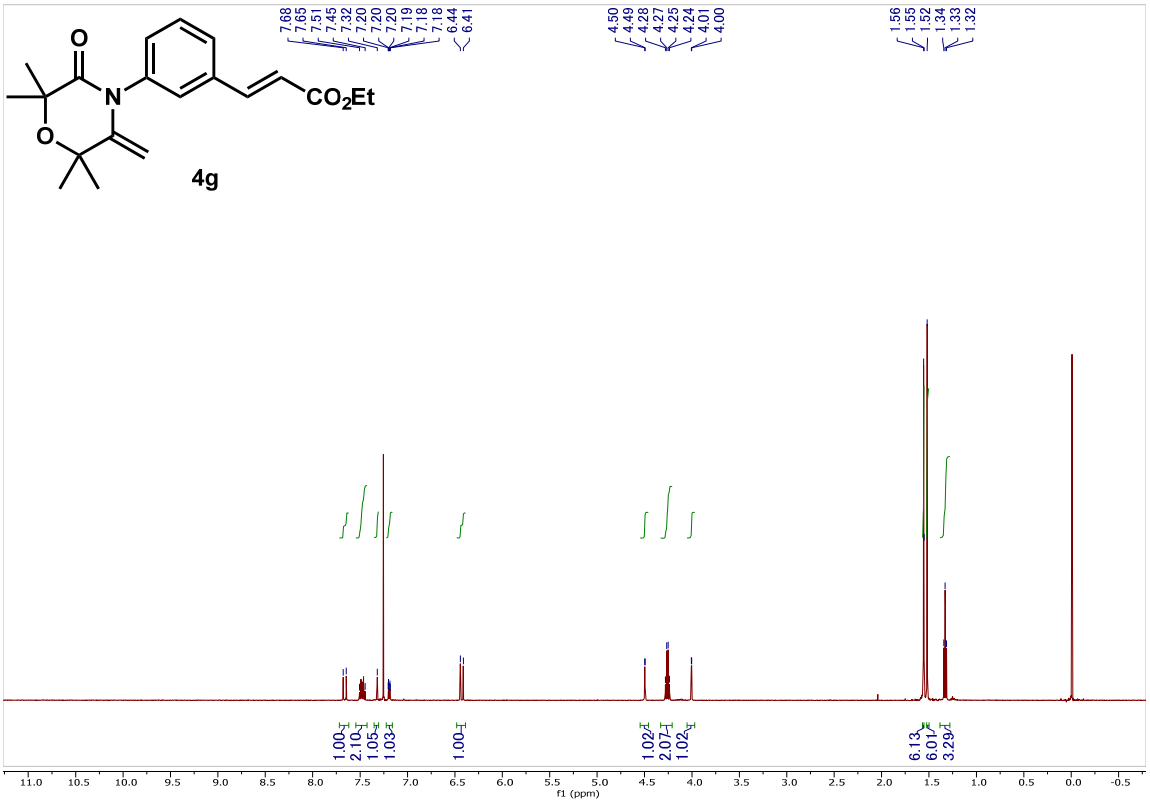
^{1}H NMR (500 MHz, $CDCl_3$)



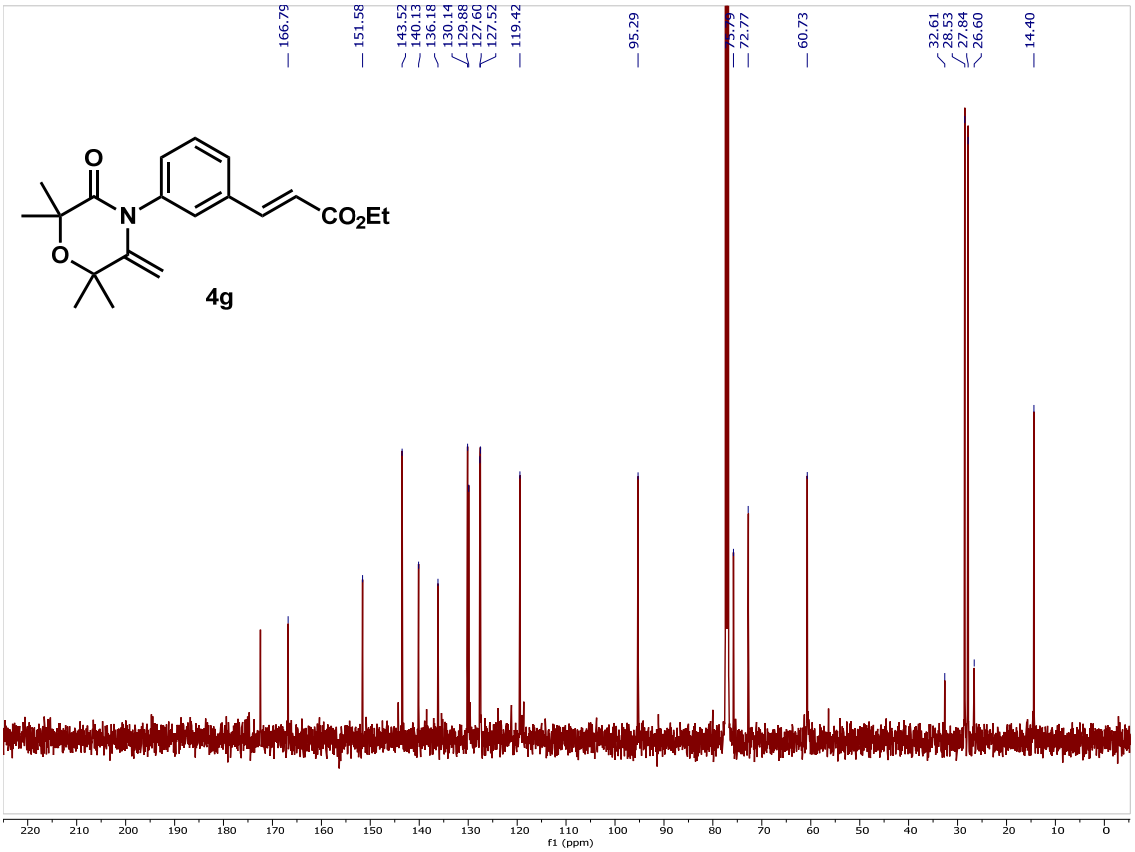
^{13}C NMR (125 MHz, $CDCl_3$)



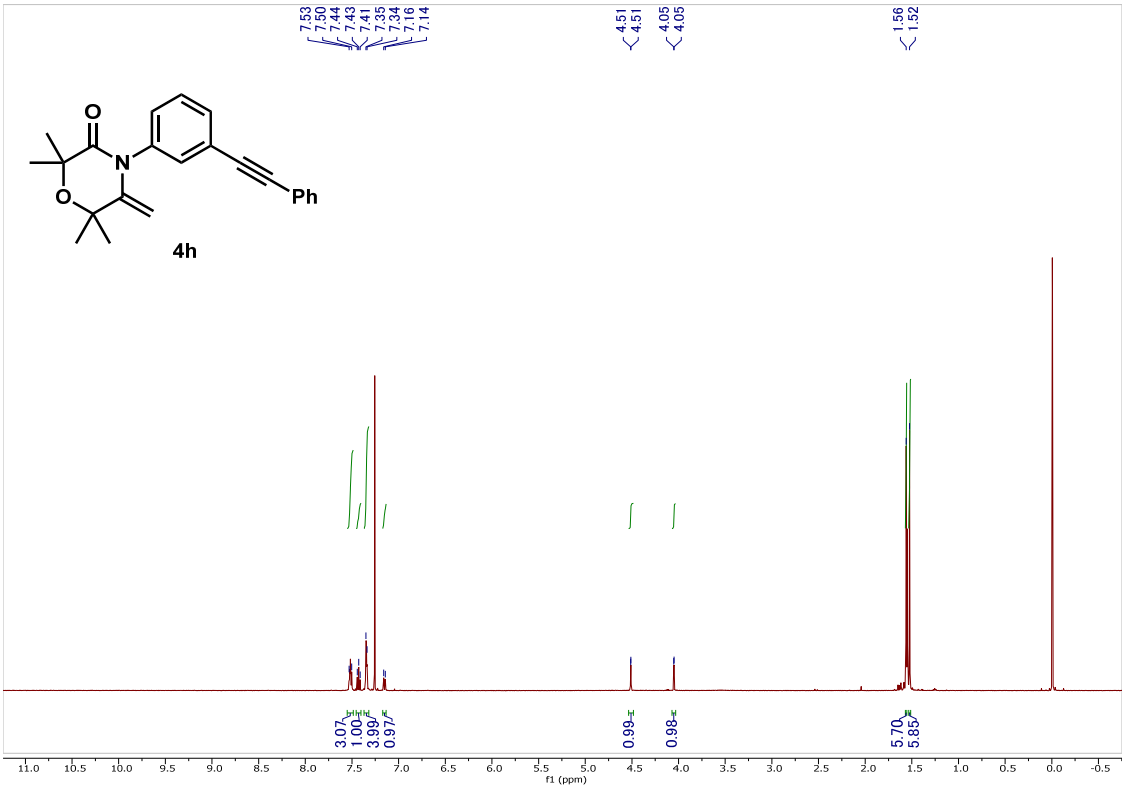
^{1}H NMR (500 MHz, $CDCl_3$)



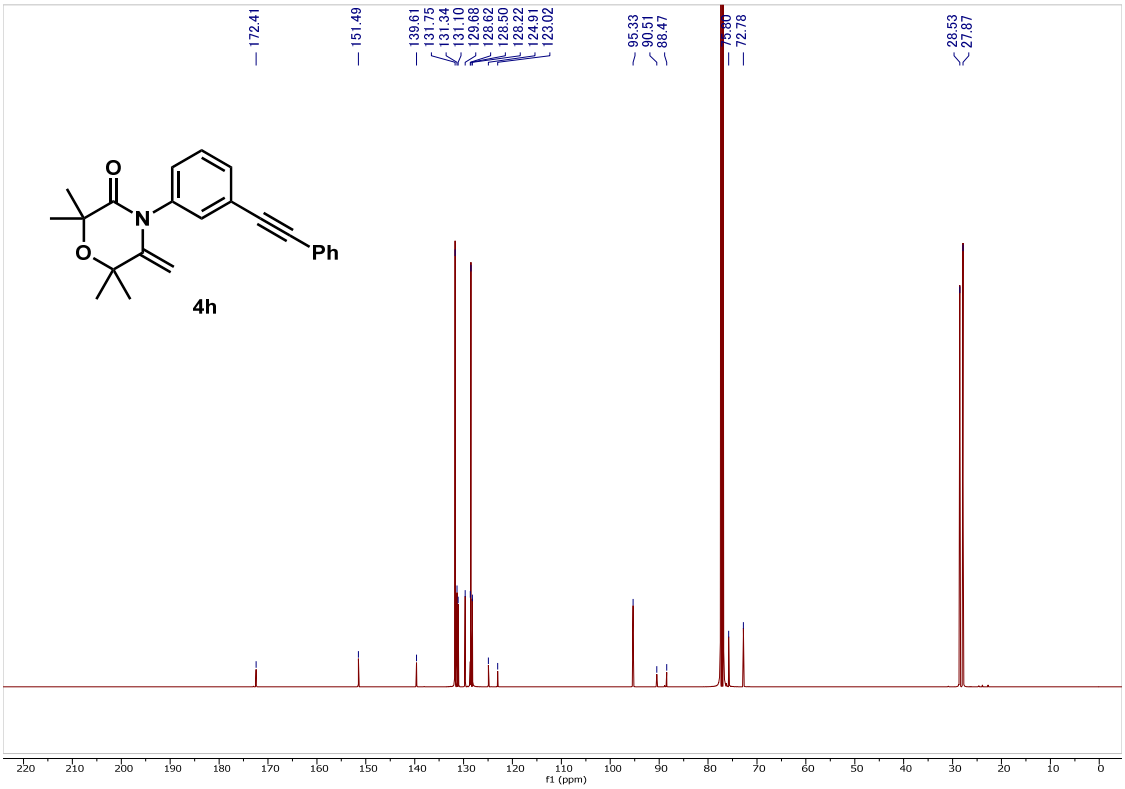
^{13}C NMR (125 MHz, $CDCl_3$)



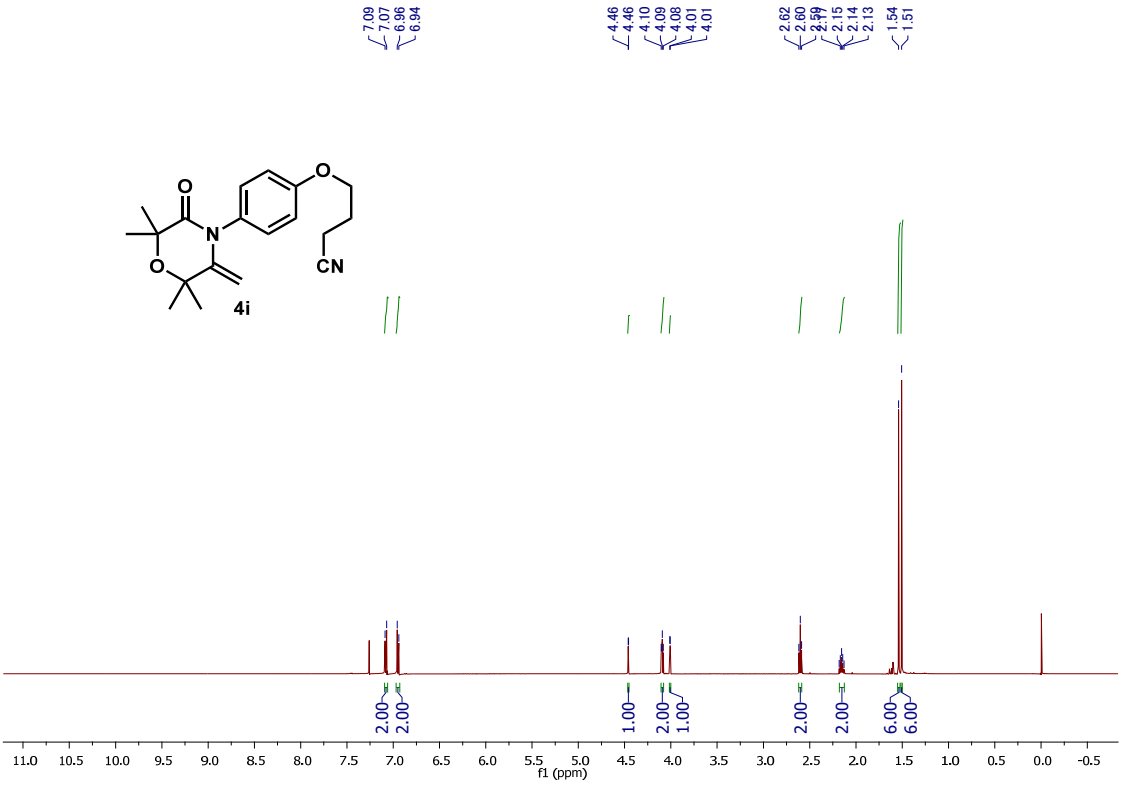
^{1}H NMR (500 MHz, $CDCl_3$)



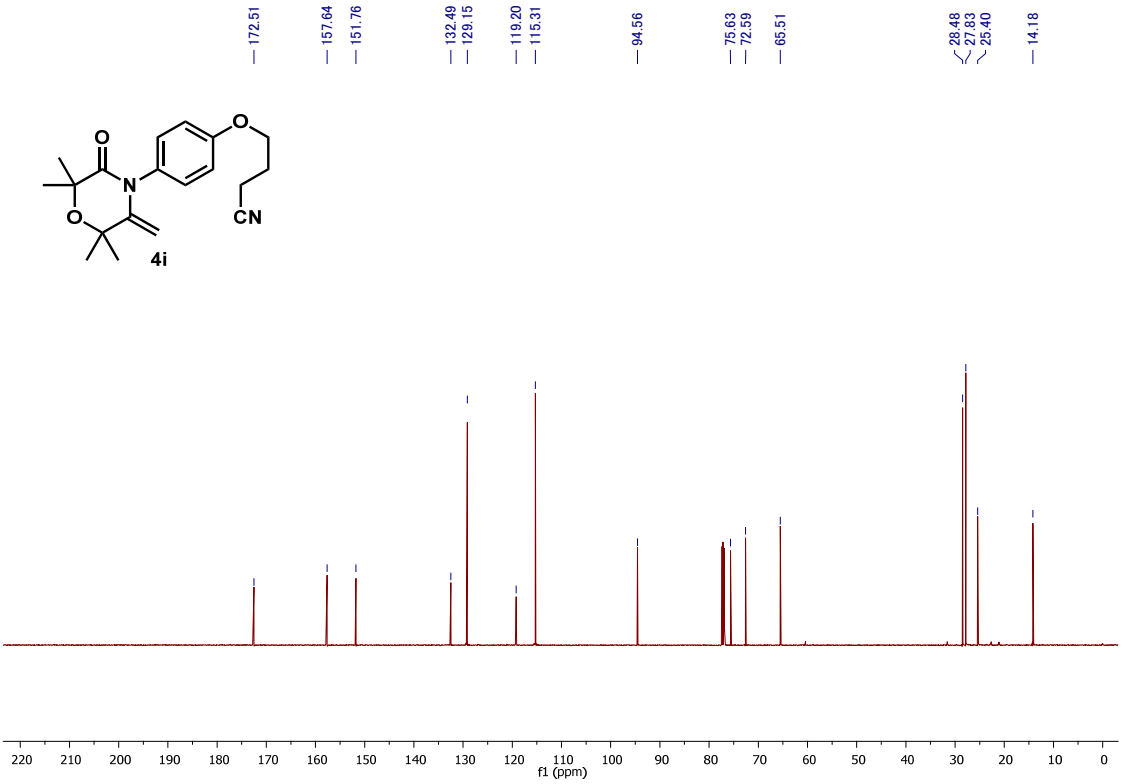
^{13}C NMR (125 MHz, $CDCl_3$)



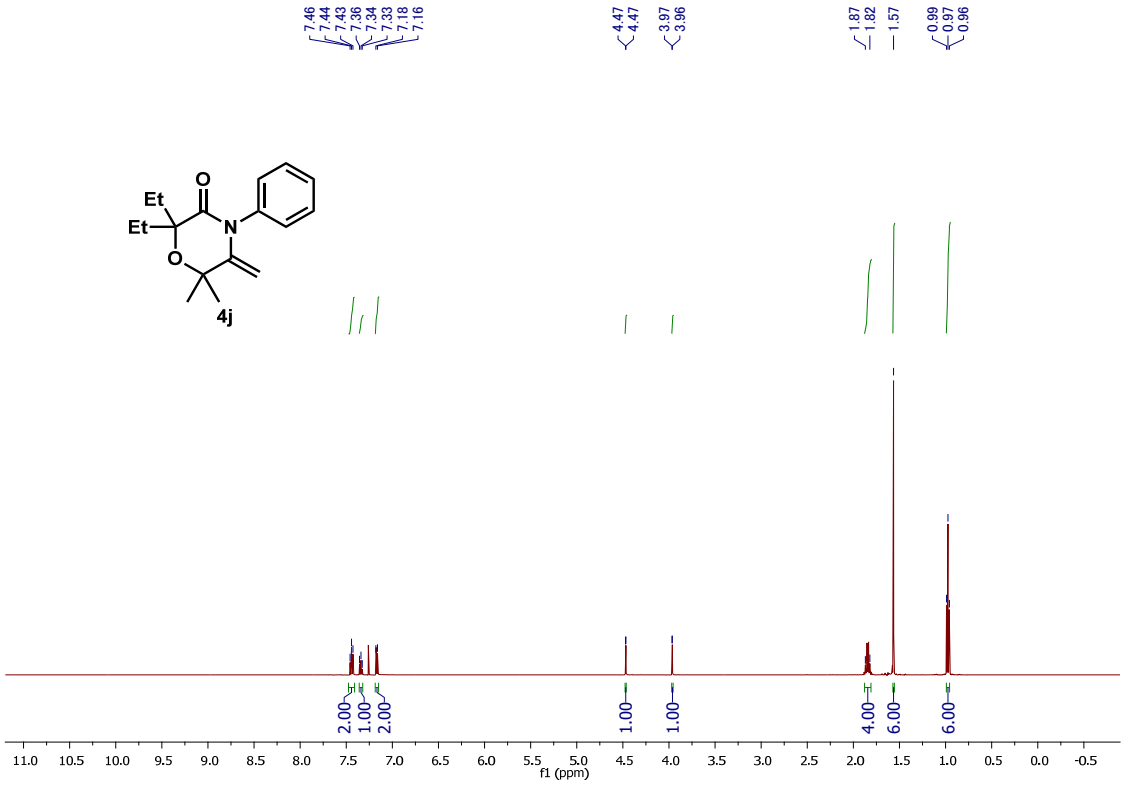
^{1}H NMR (500 MHz, $CDCl_3$)



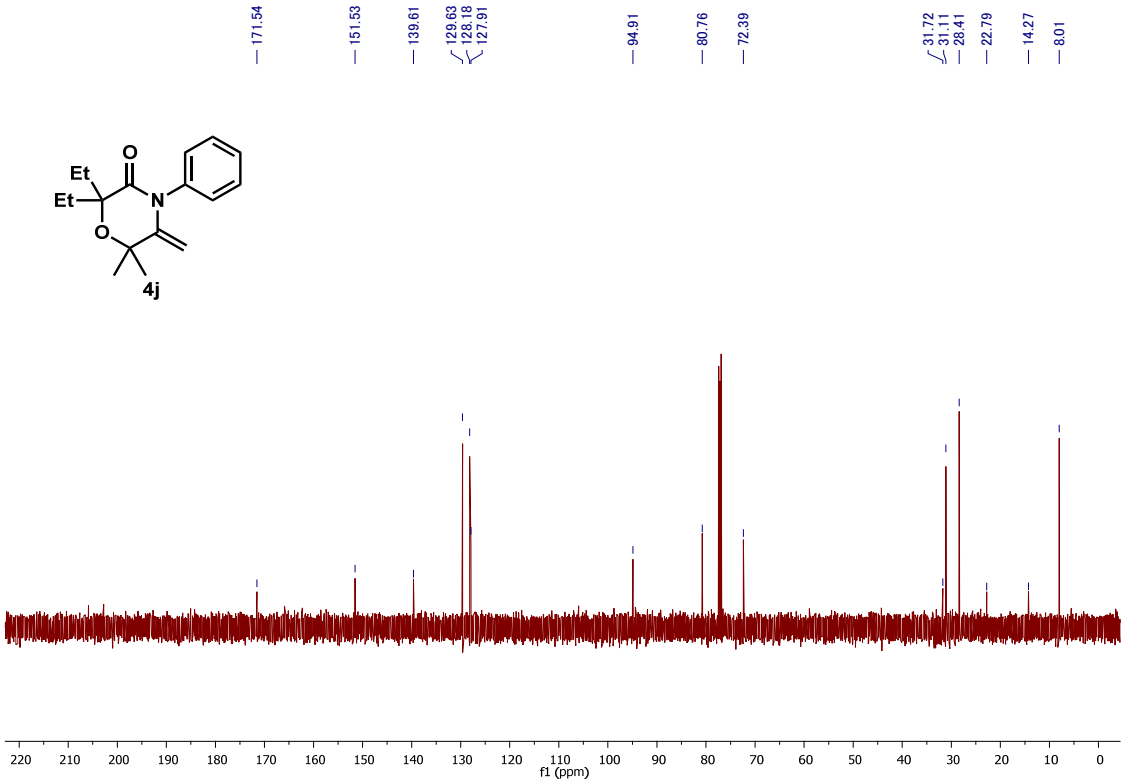
^{13}C NMR (125 MHz, $CDCl_3$)



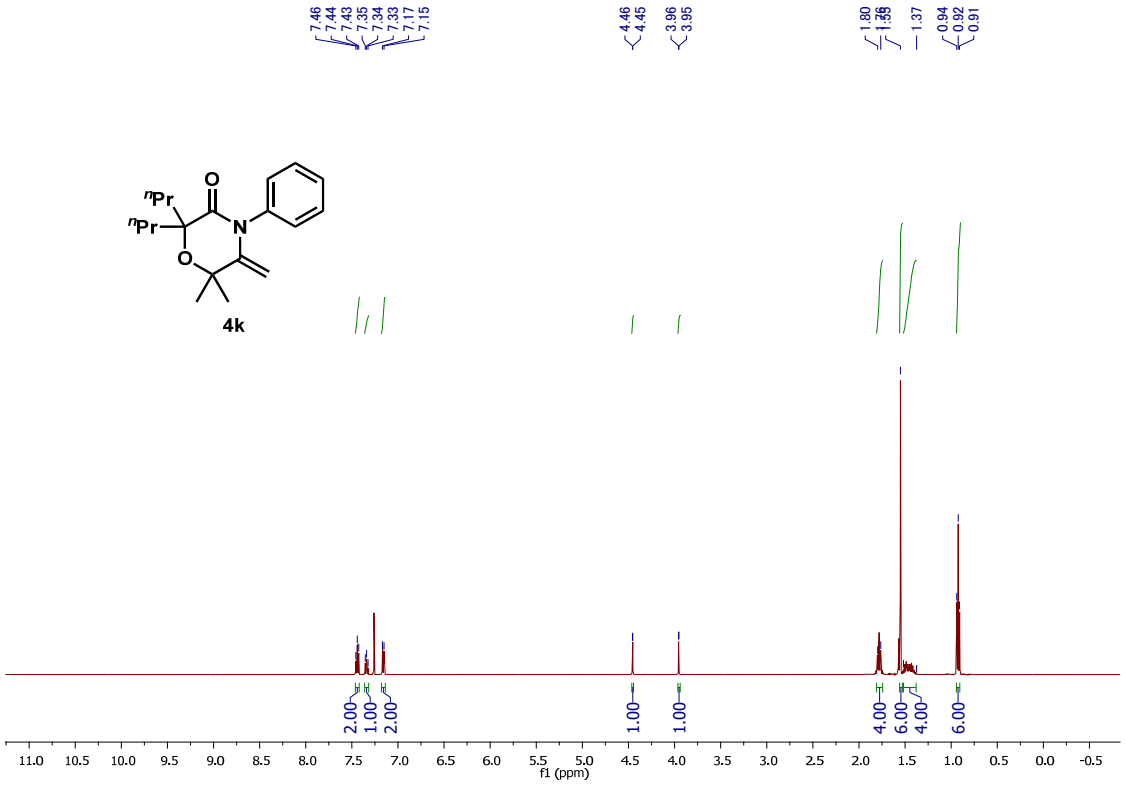
^{1}H NMR (500 MHz, $CDCl_3$)



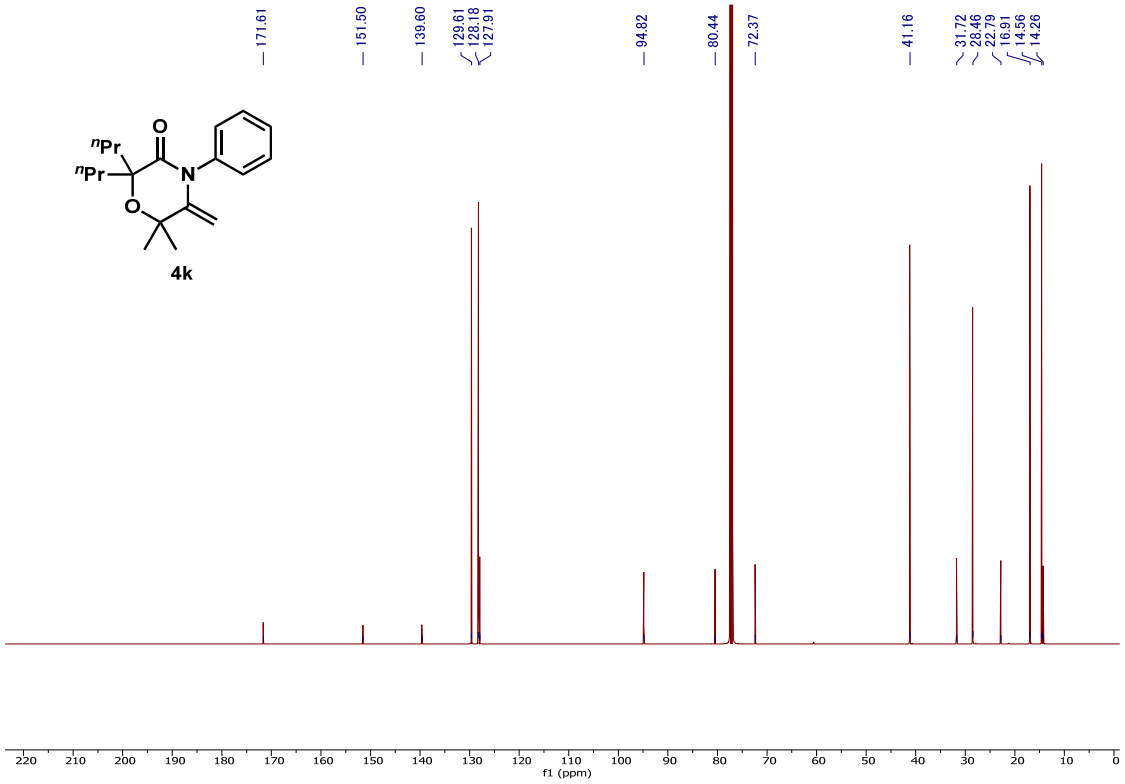
^{13}C NMR (125 MHz, $CDCl_3$)



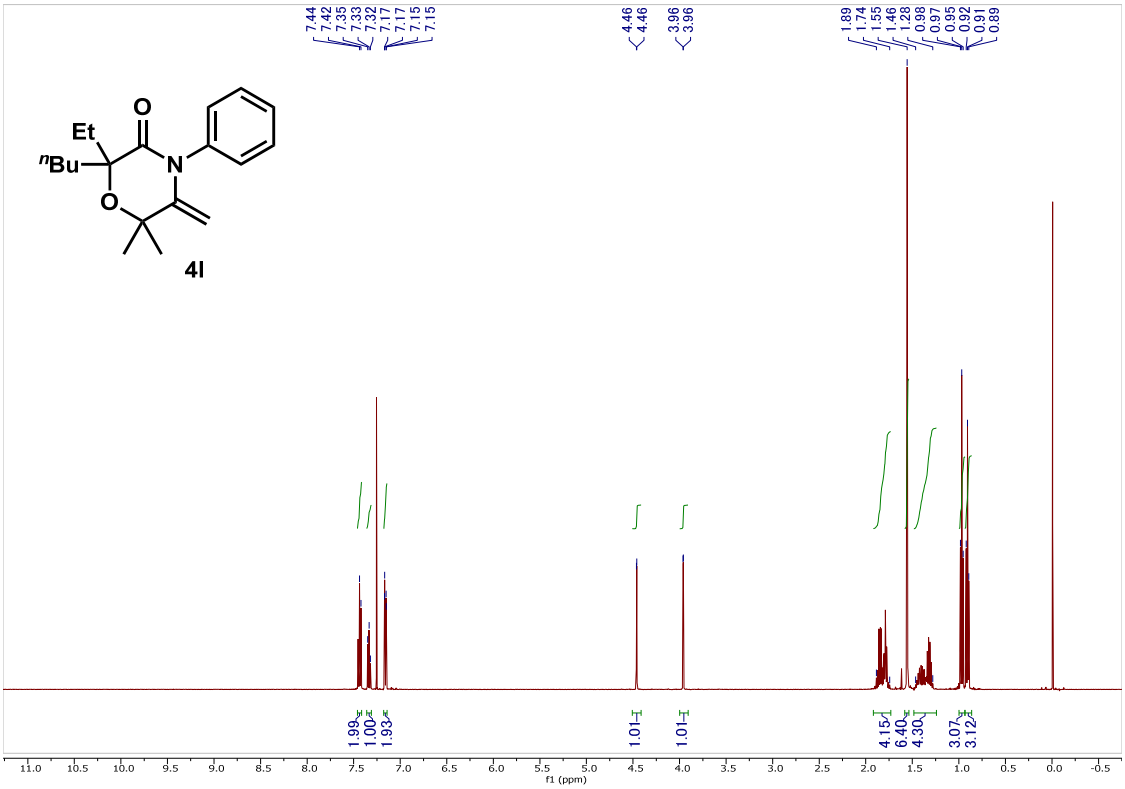
^{1}H NMR (500 MHz, $CDCl_3$)



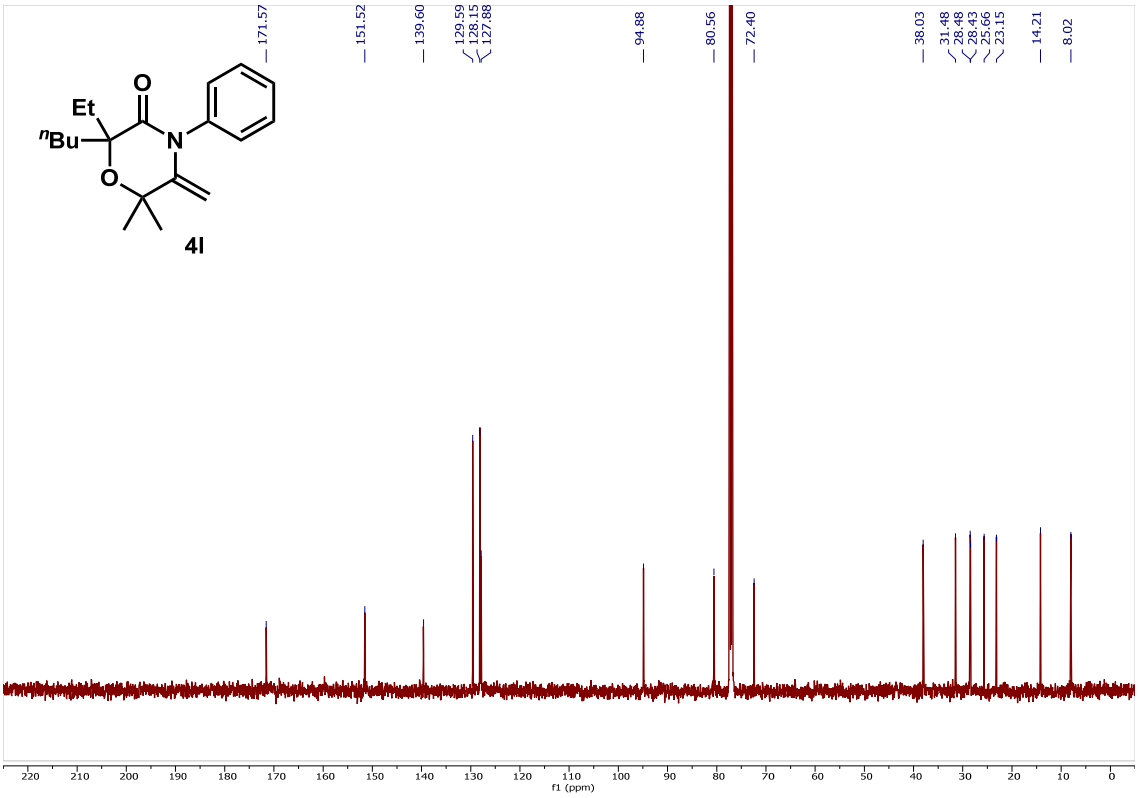
^{13}C NMR (125 MHz, $CDCl_3$)



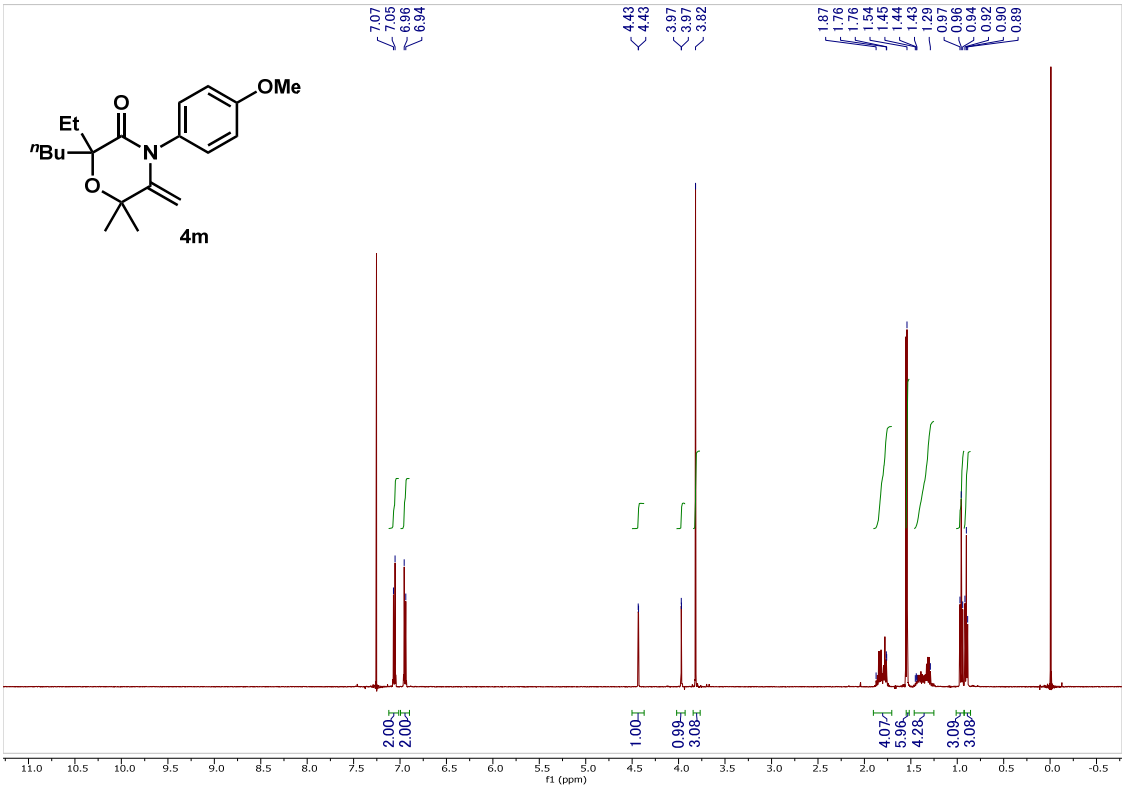
^{1}H NMR (500 MHz, $CDCl_3$)



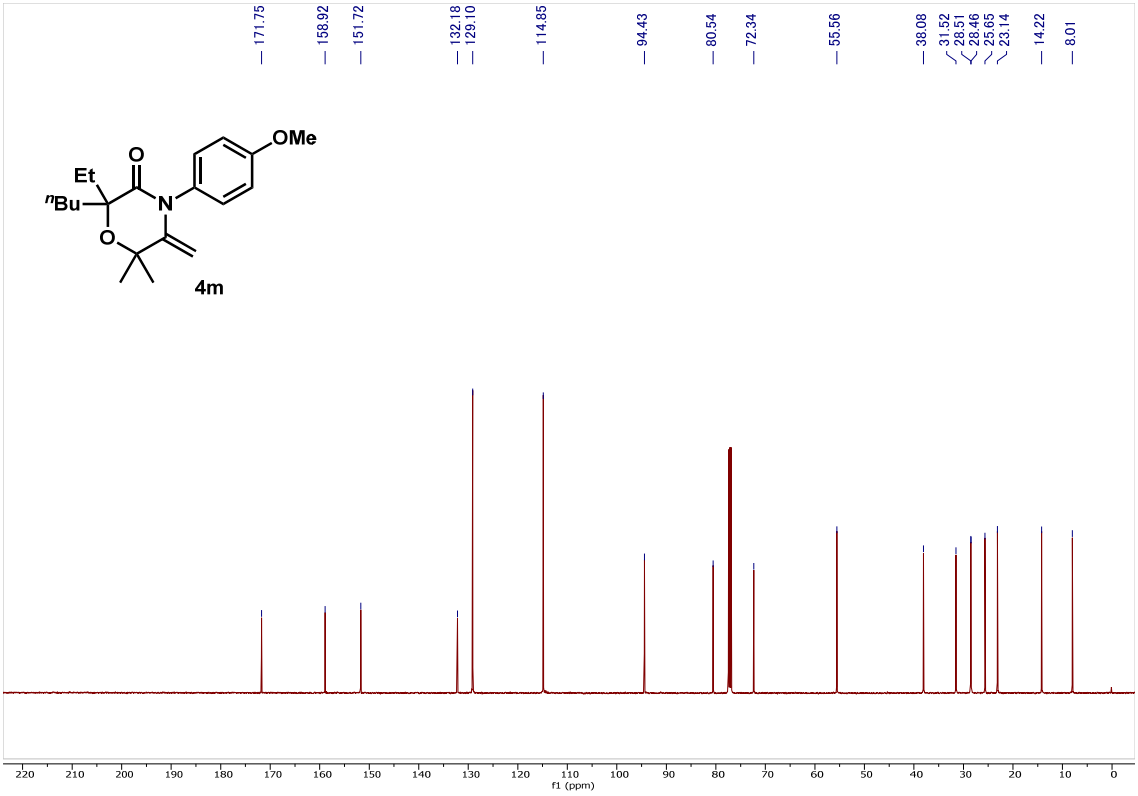
^{13}C NMR (125 MHz, $CDCl_3$)



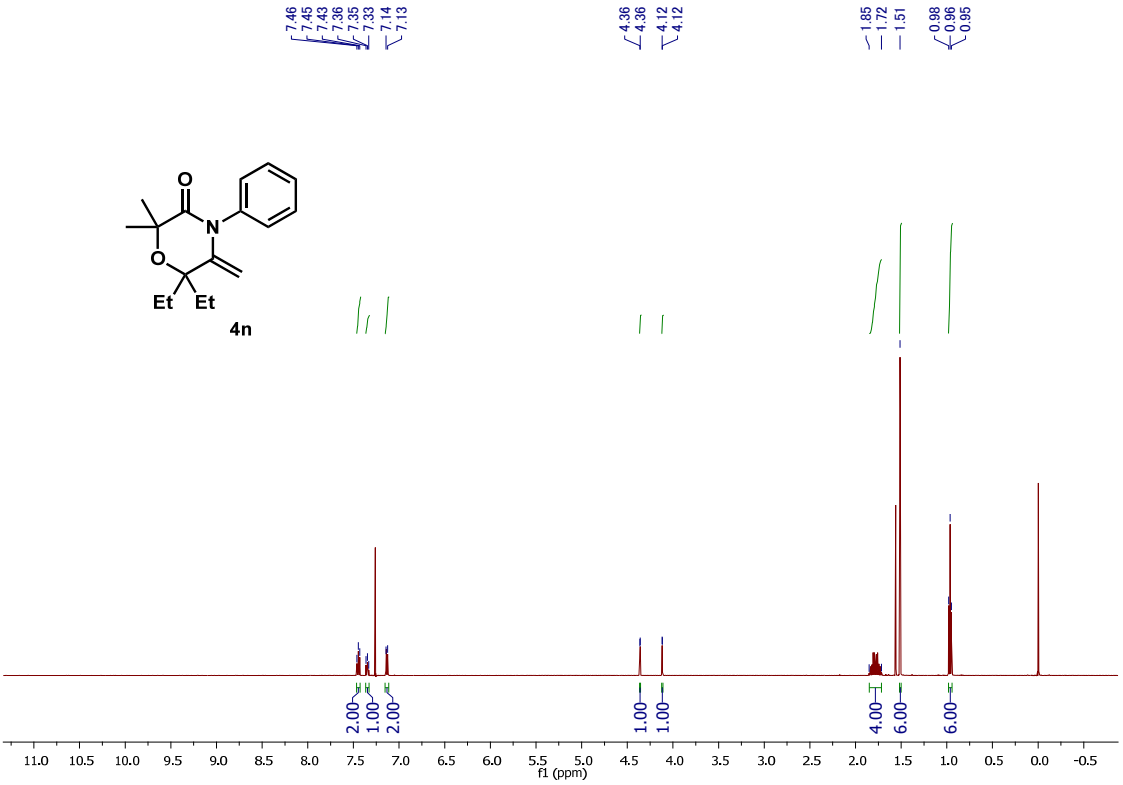
^{1}H NMR (500 MHz, $CDCl_3$)



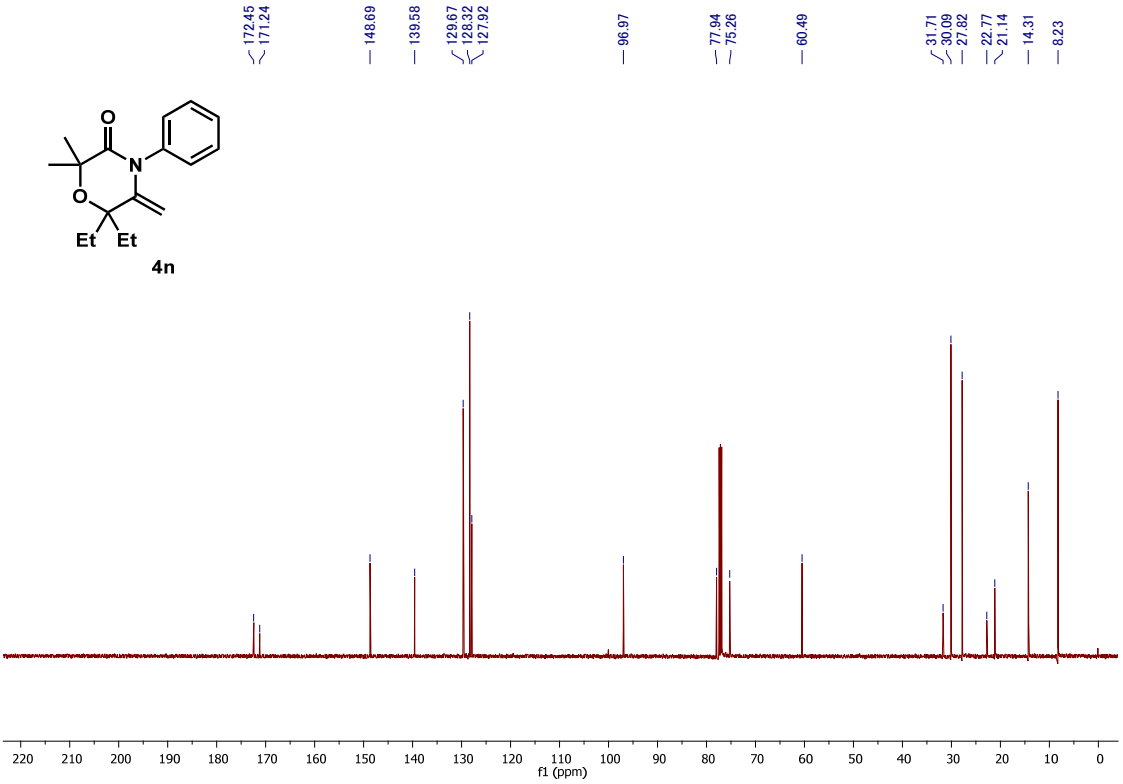
^{13}C NMR (125 MHz, $CDCl_3$)



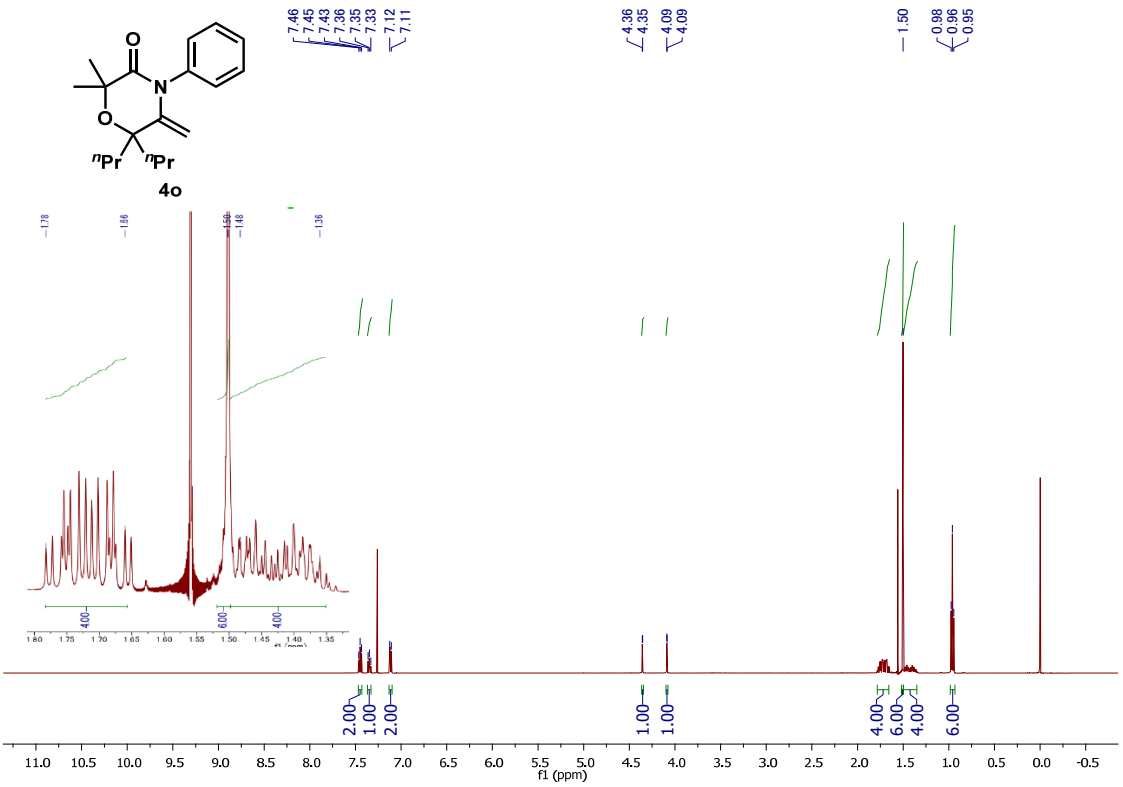
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

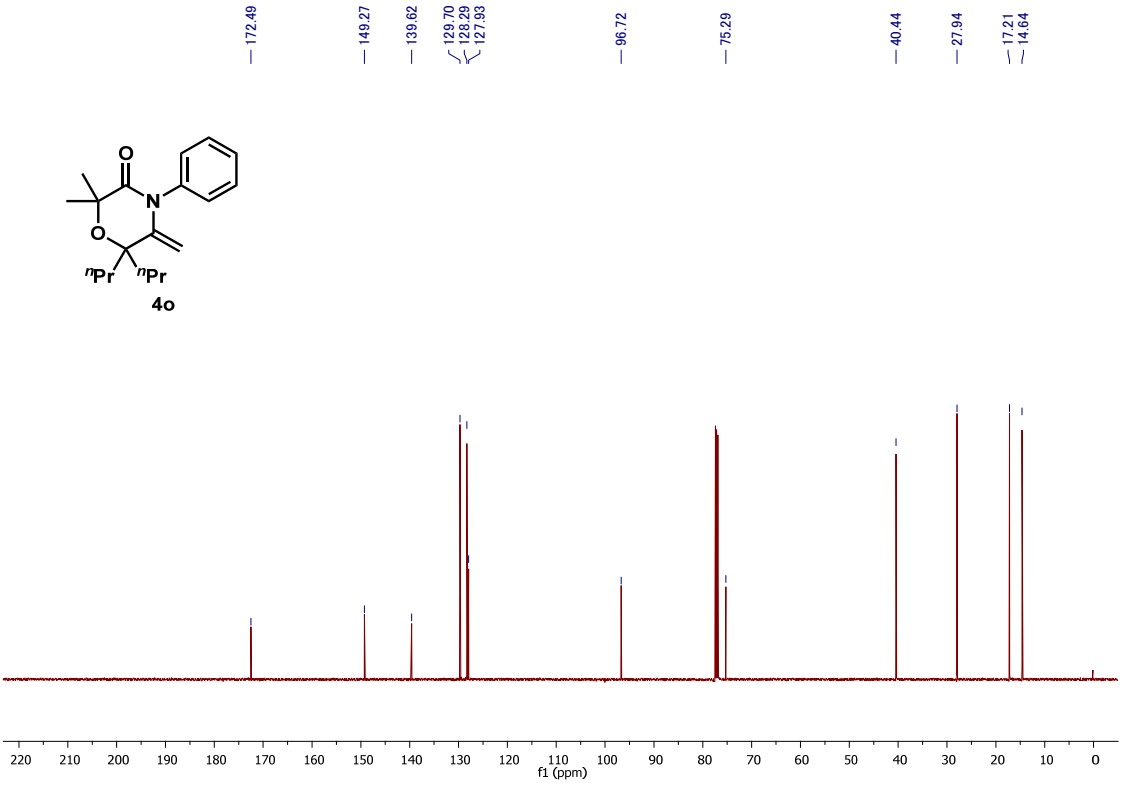


^{1}H NMR (500 MHz, $CDCl_3$)



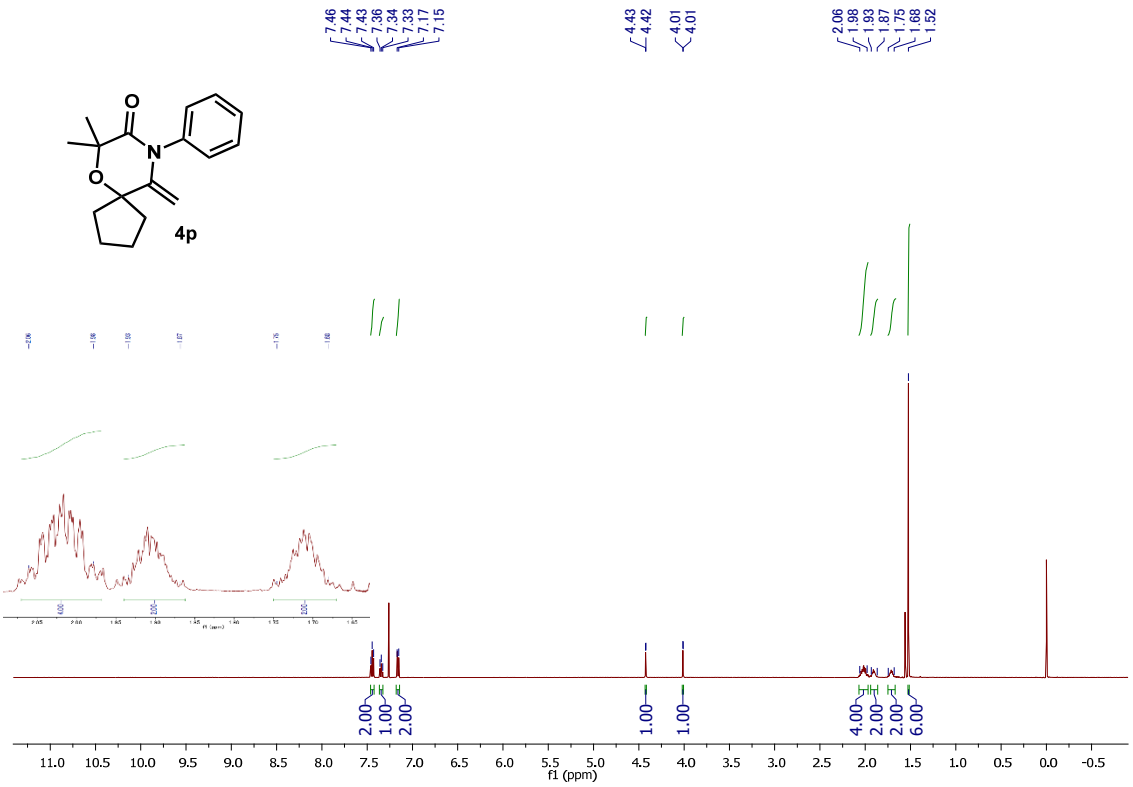
4o

^{13}C NMR (125 MHz, $CDCl_3$)

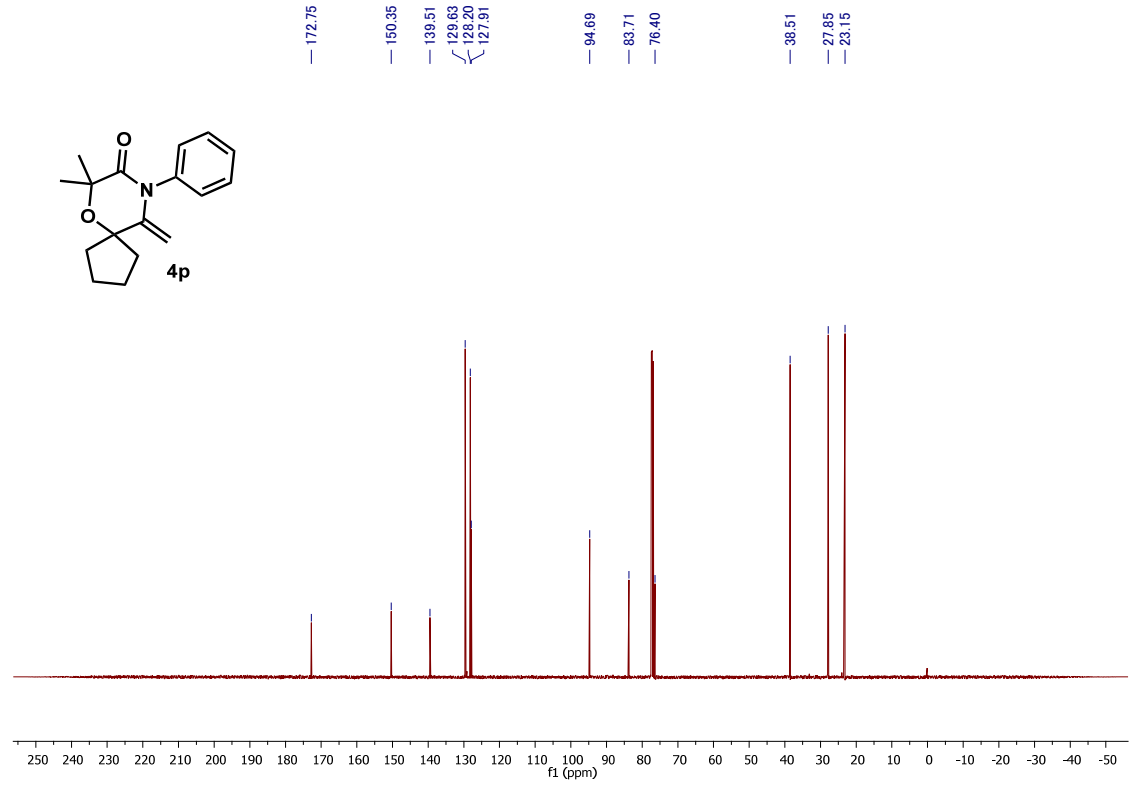


4o

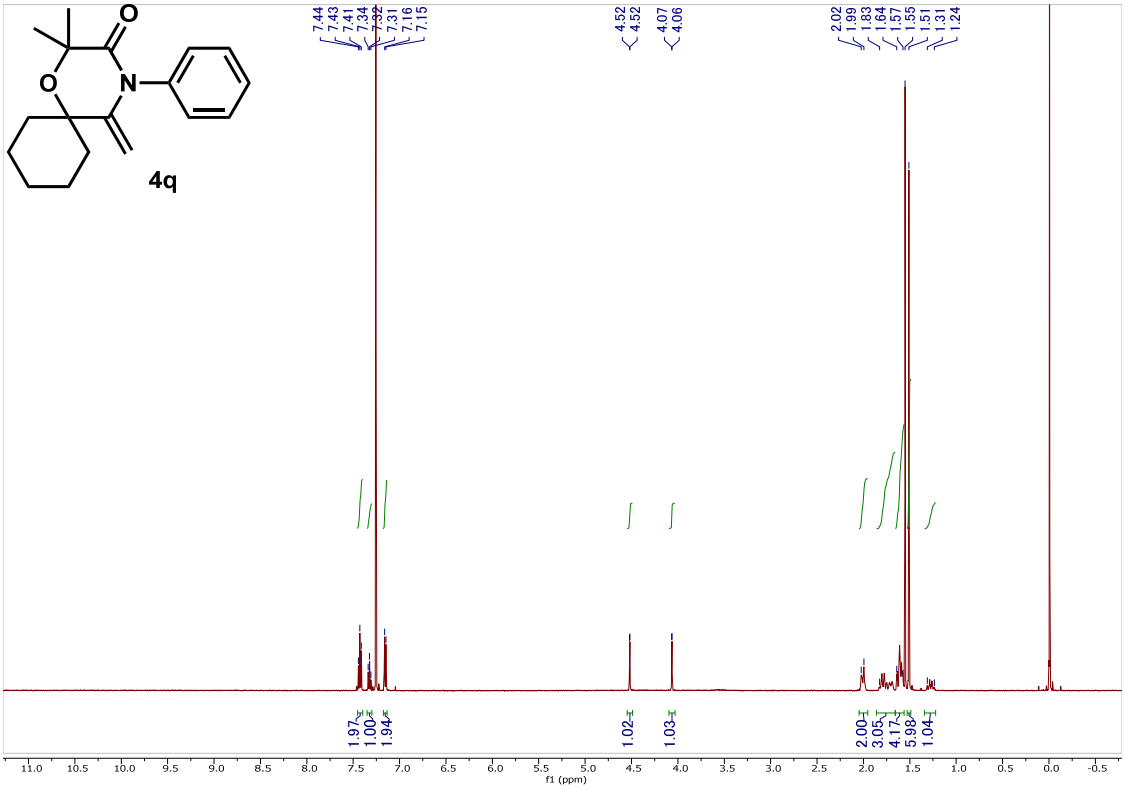
^{1}H NMR (500 MHz, $CDCl_3$)



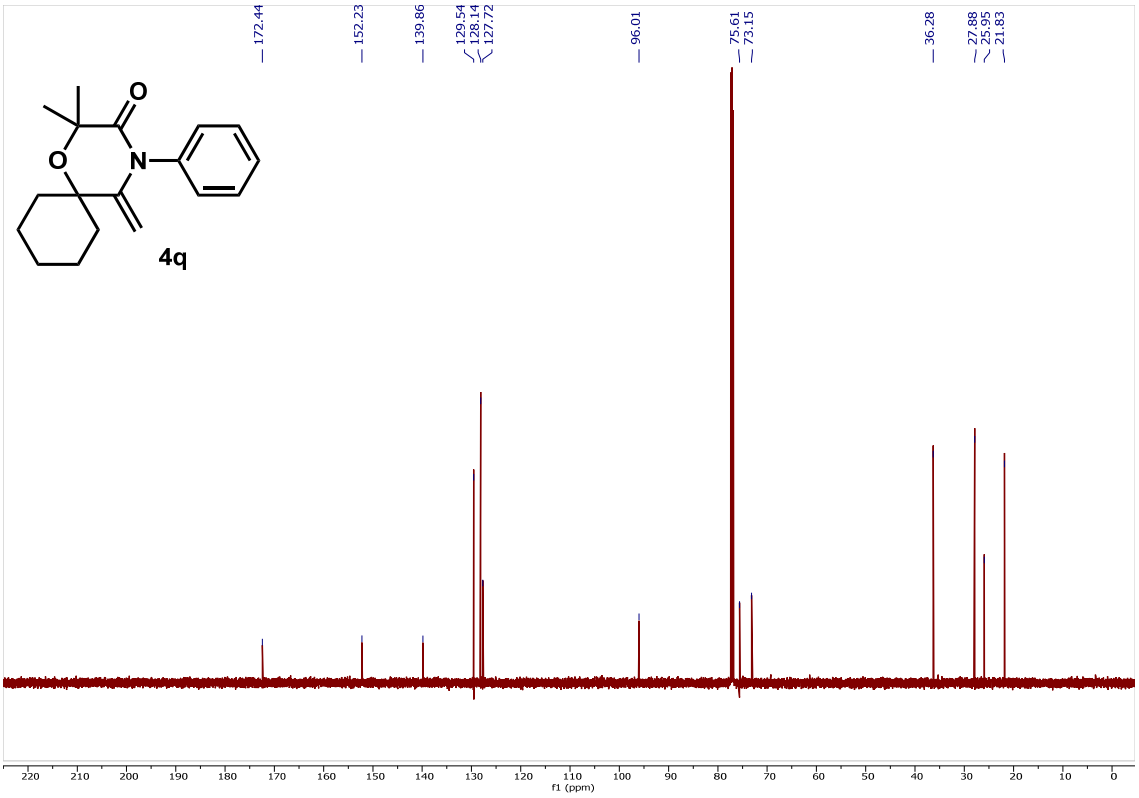
^{13}C NMR (125 MHz, $CDCl_3$)



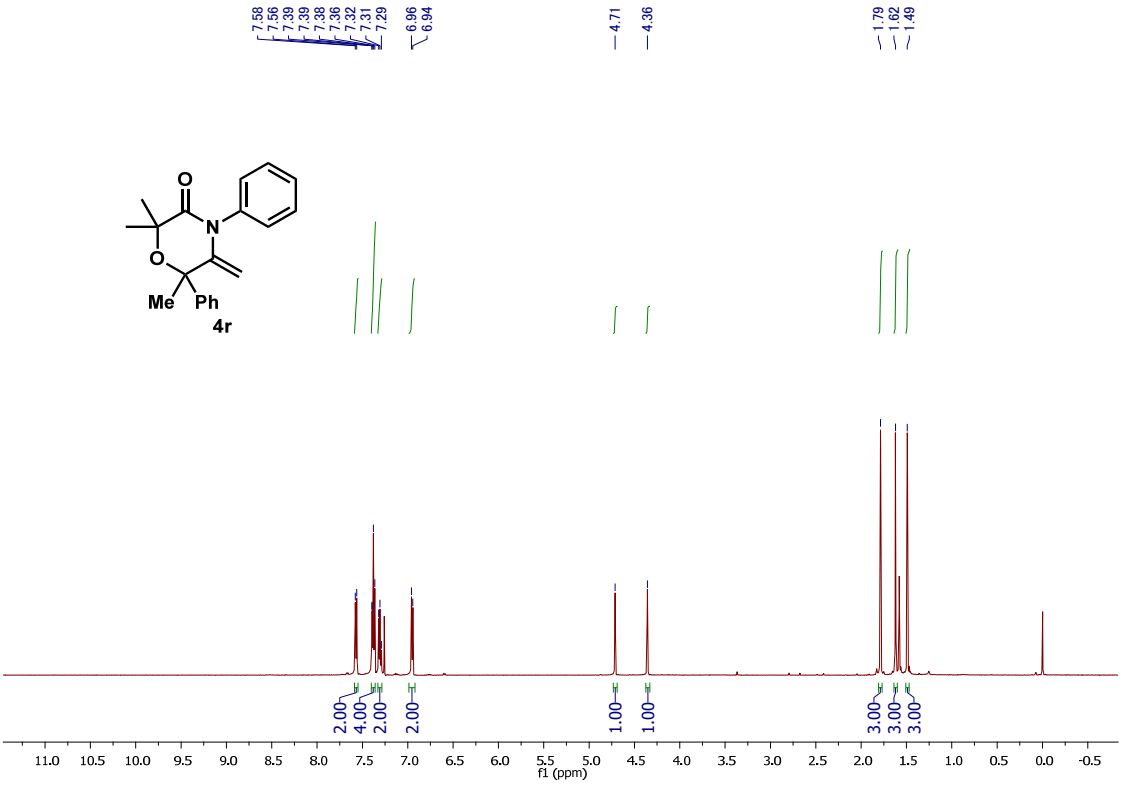
^{1}H NMR (500 MHz, $CDCl_3$)



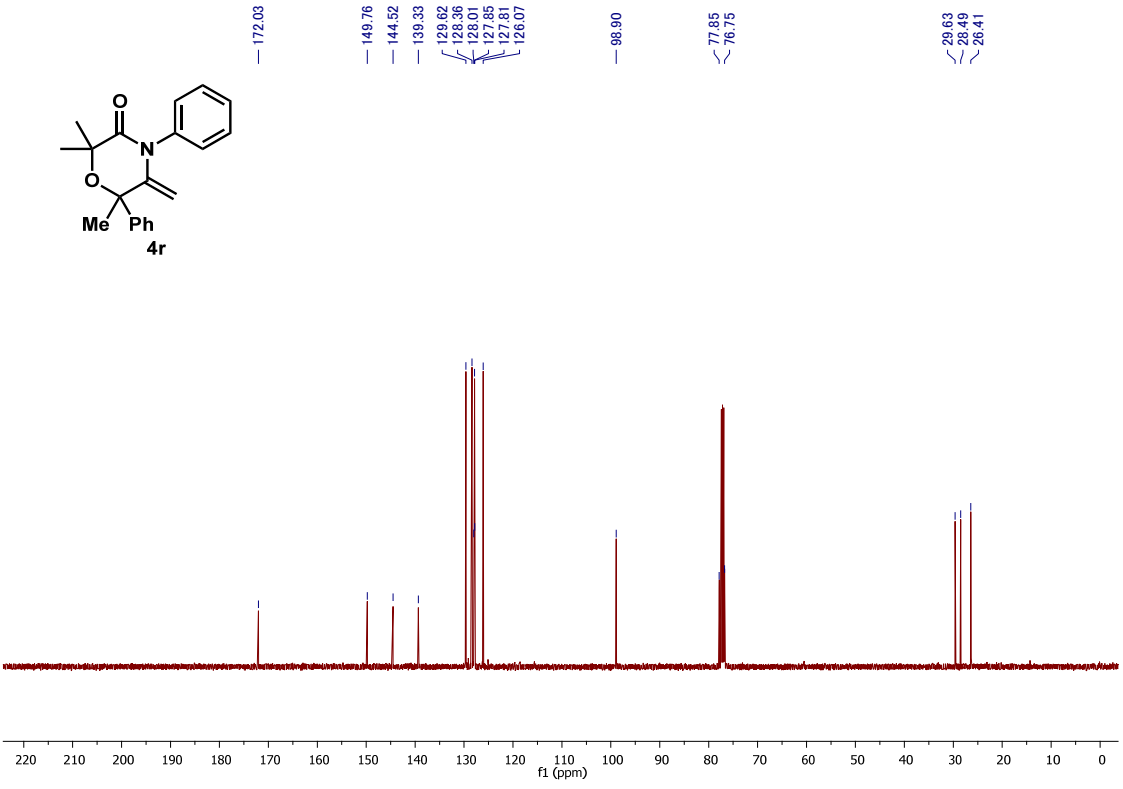
^{13}C NMR (125 MHz, $CDCl_3$)



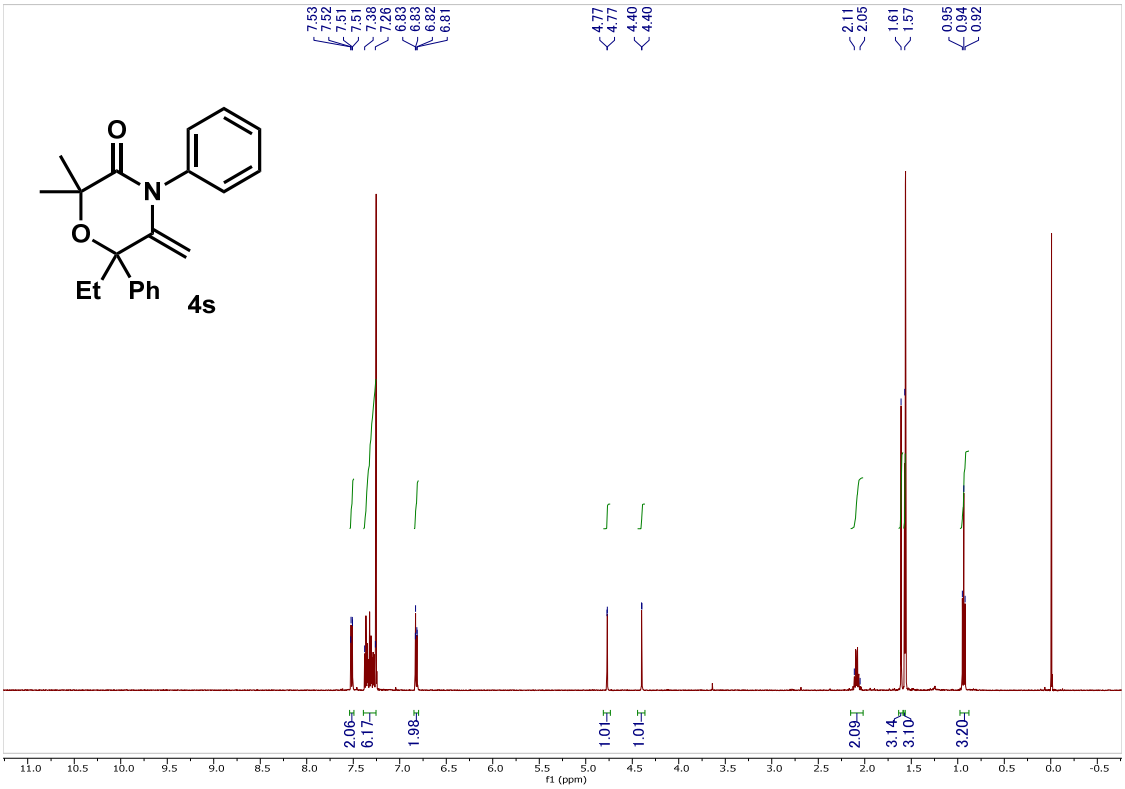
^{1}H NMR (500 MHz, $CDCl_3$)



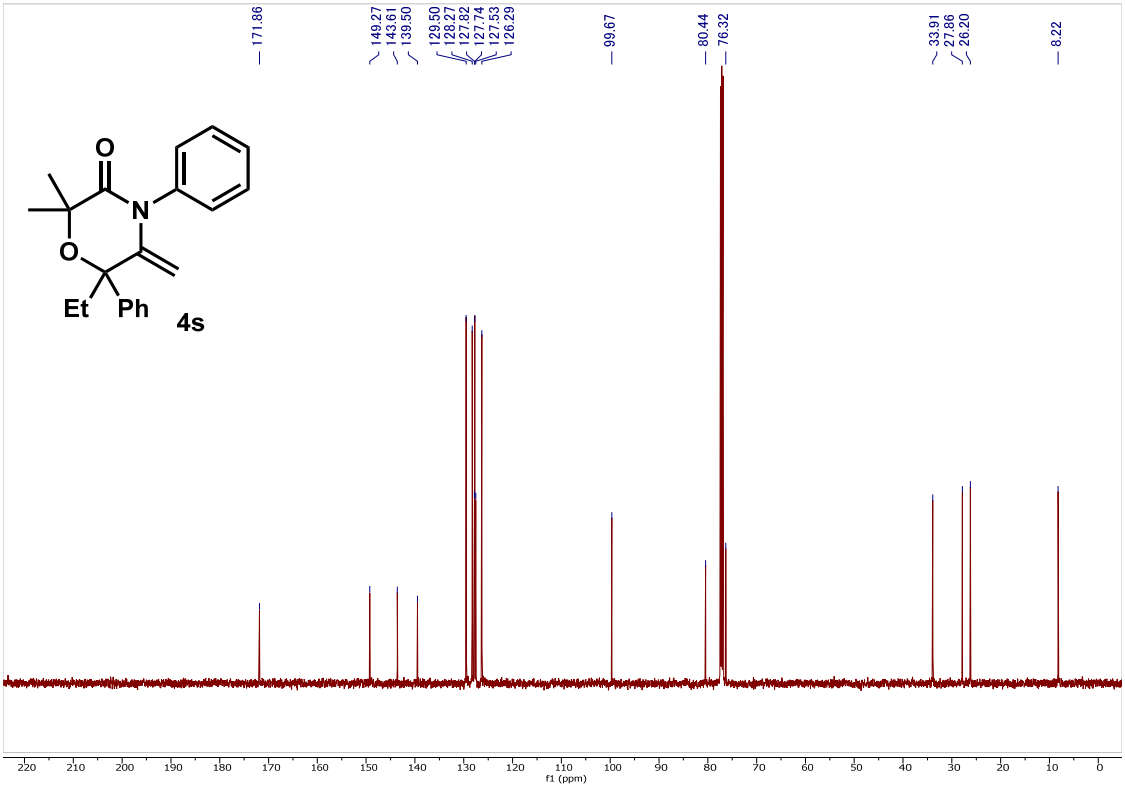
^{13}C NMR (125 MHz, $CDCl_3$)



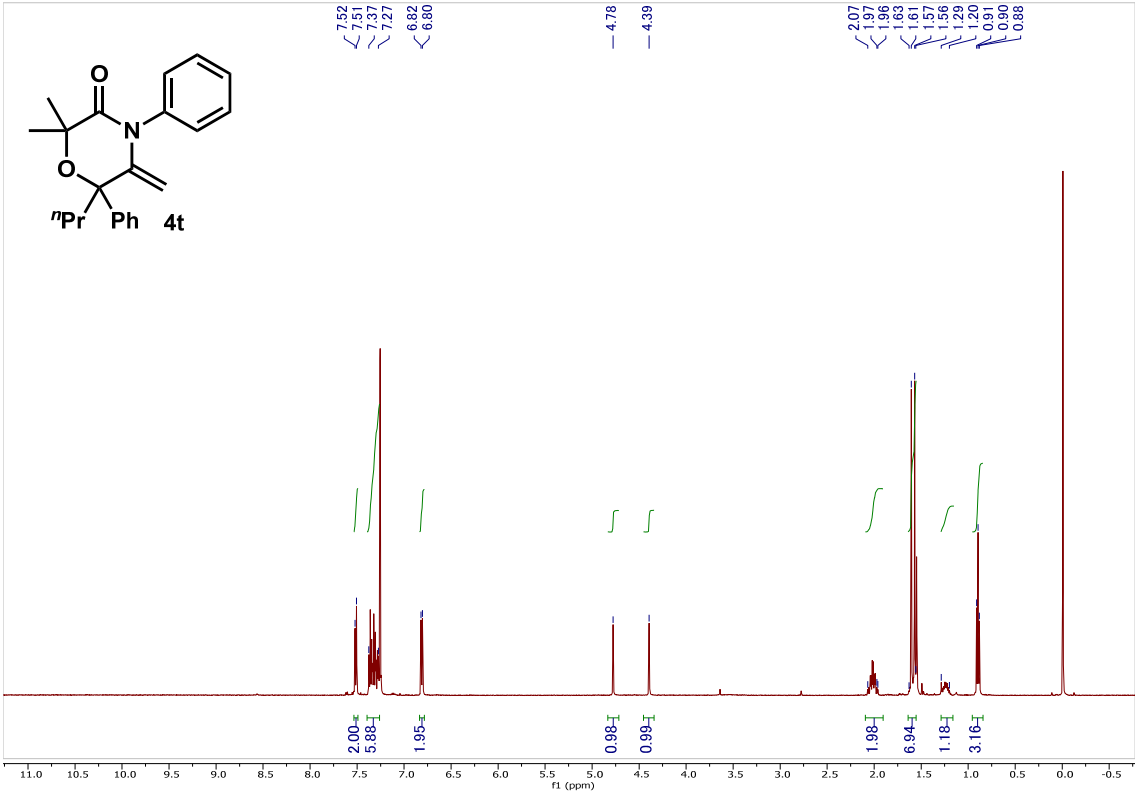
^{1}H NMR (500 MHz, $CDCl_3$)



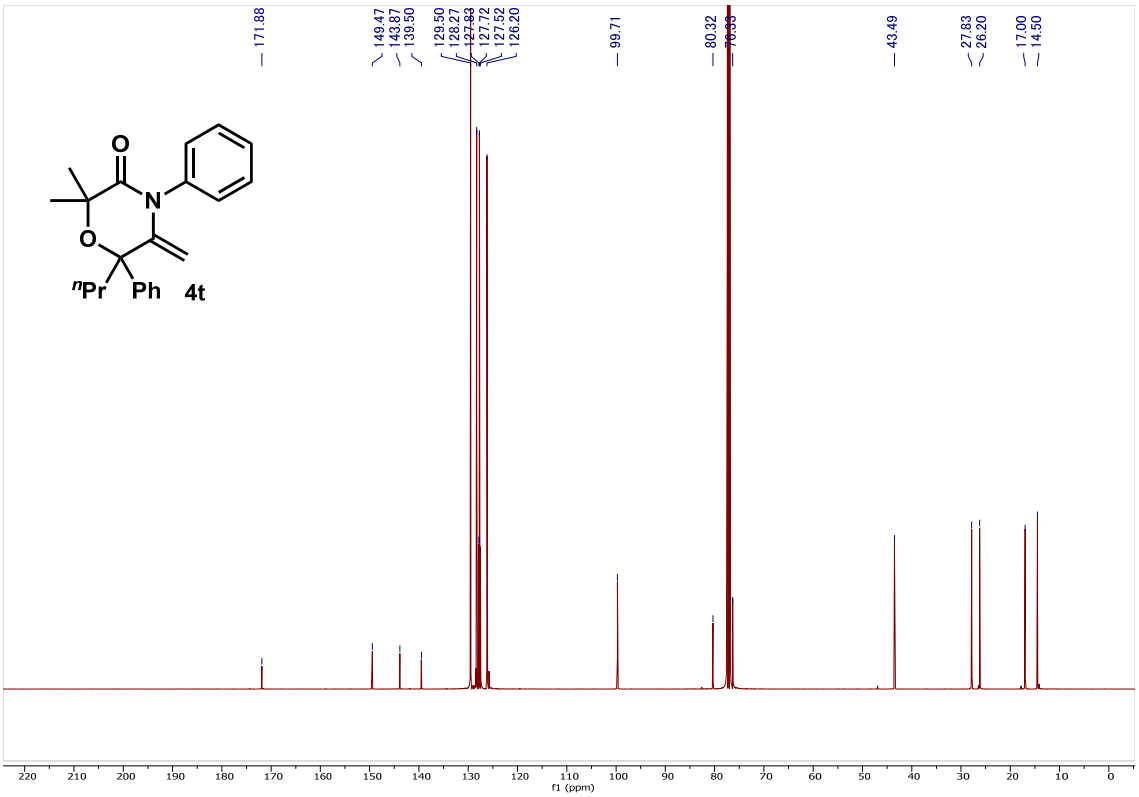
^{13}C NMR (125 MHz, $CDCl_3$)



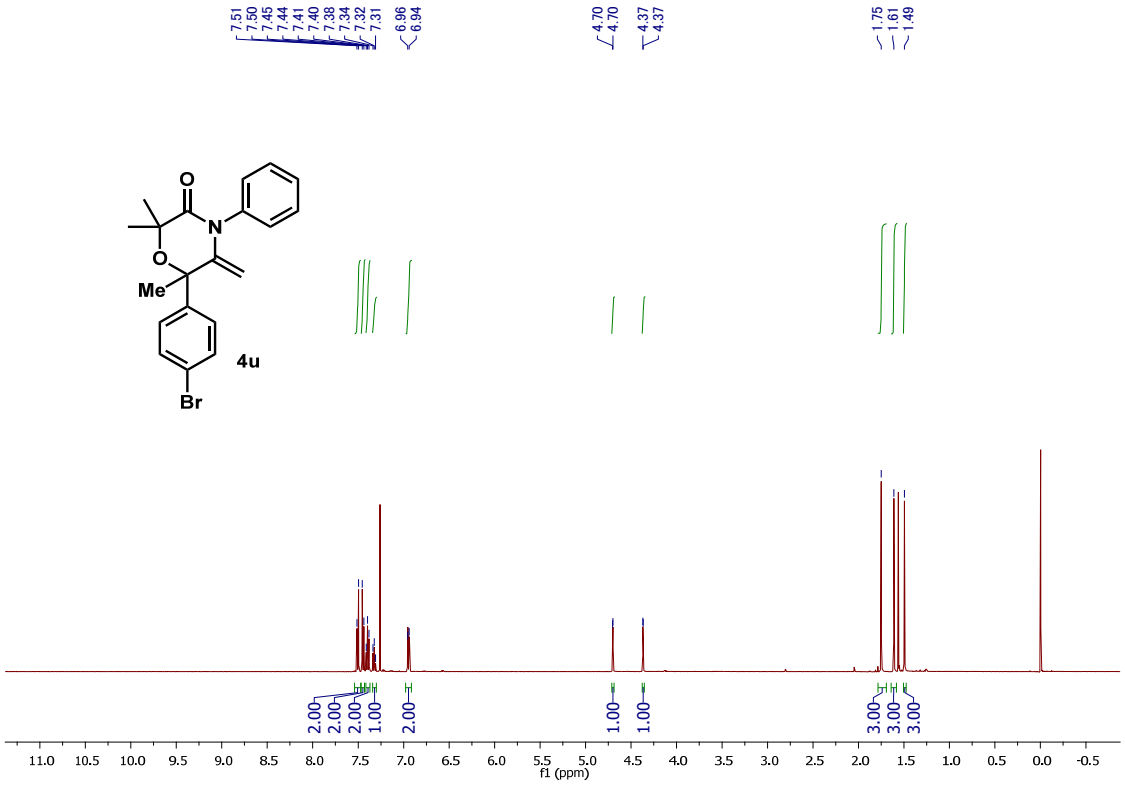
^{1}H NMR (500 MHz, $CDCl_3$)



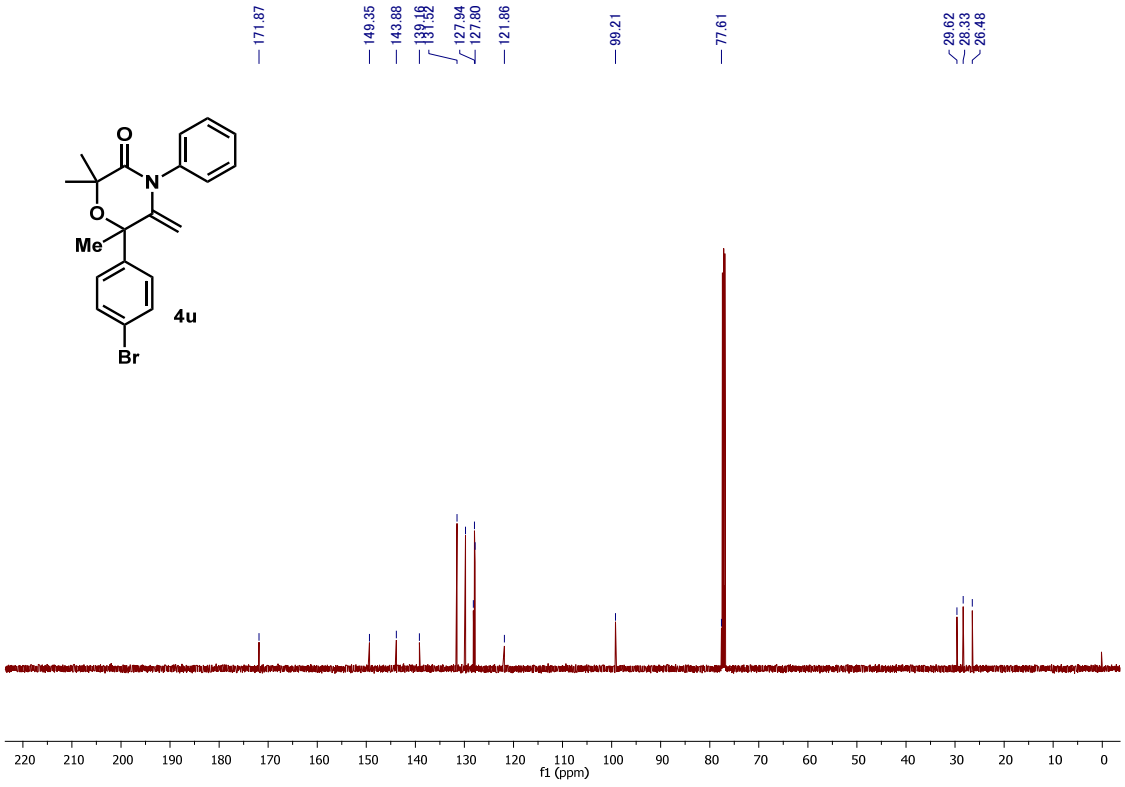
^{13}C NMR (125 MHz, $CDCl_3$)



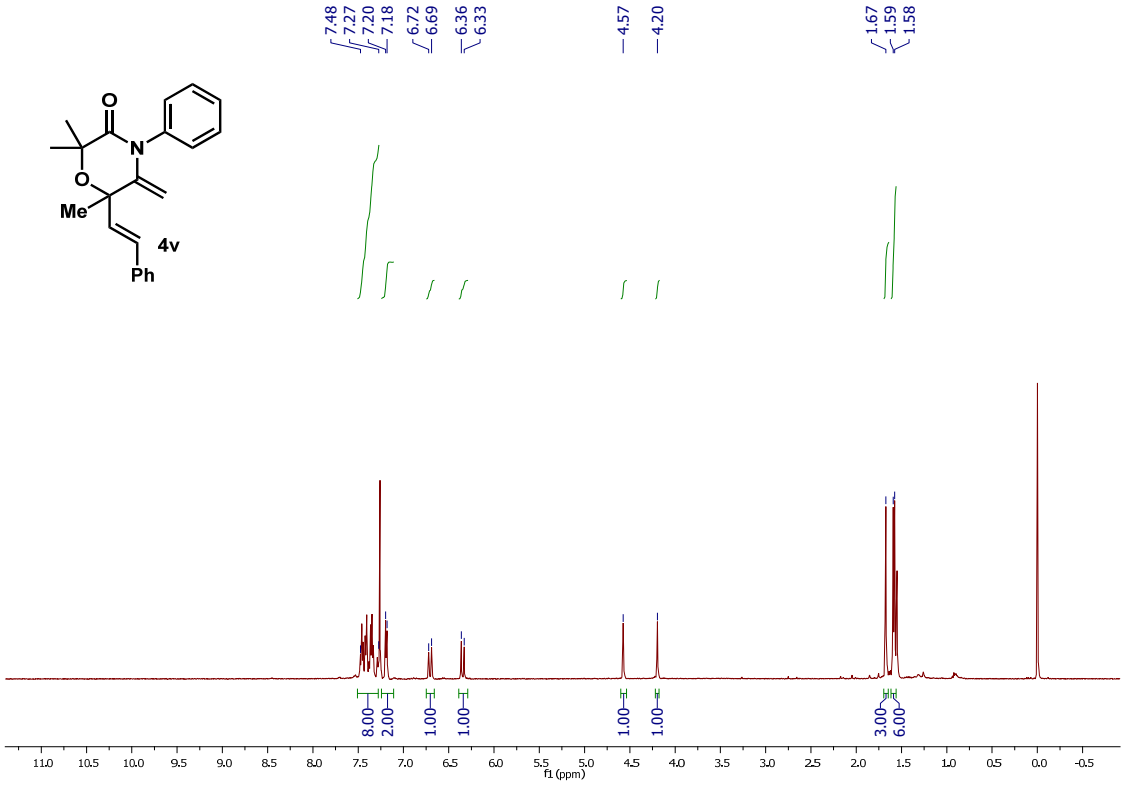
^{1}H NMR (500 MHz, $CDCl_3$)



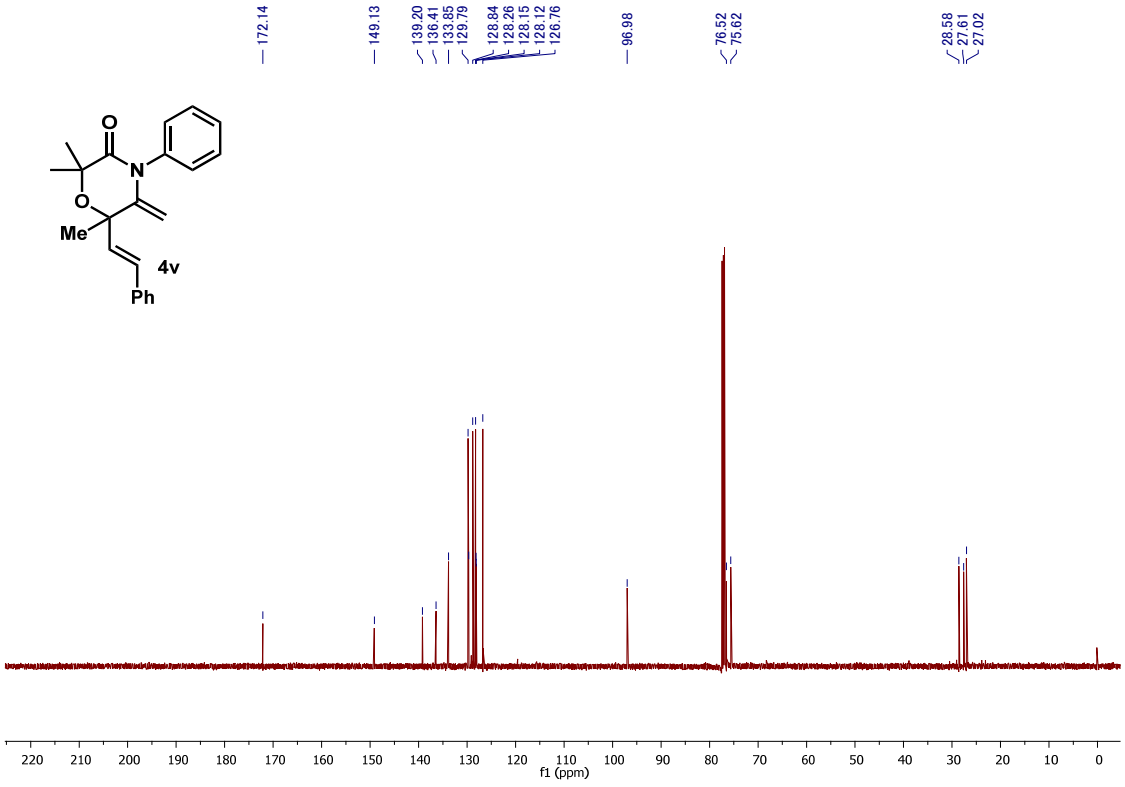
^{13}C NMR (125 MHz, $CDCl_3$)



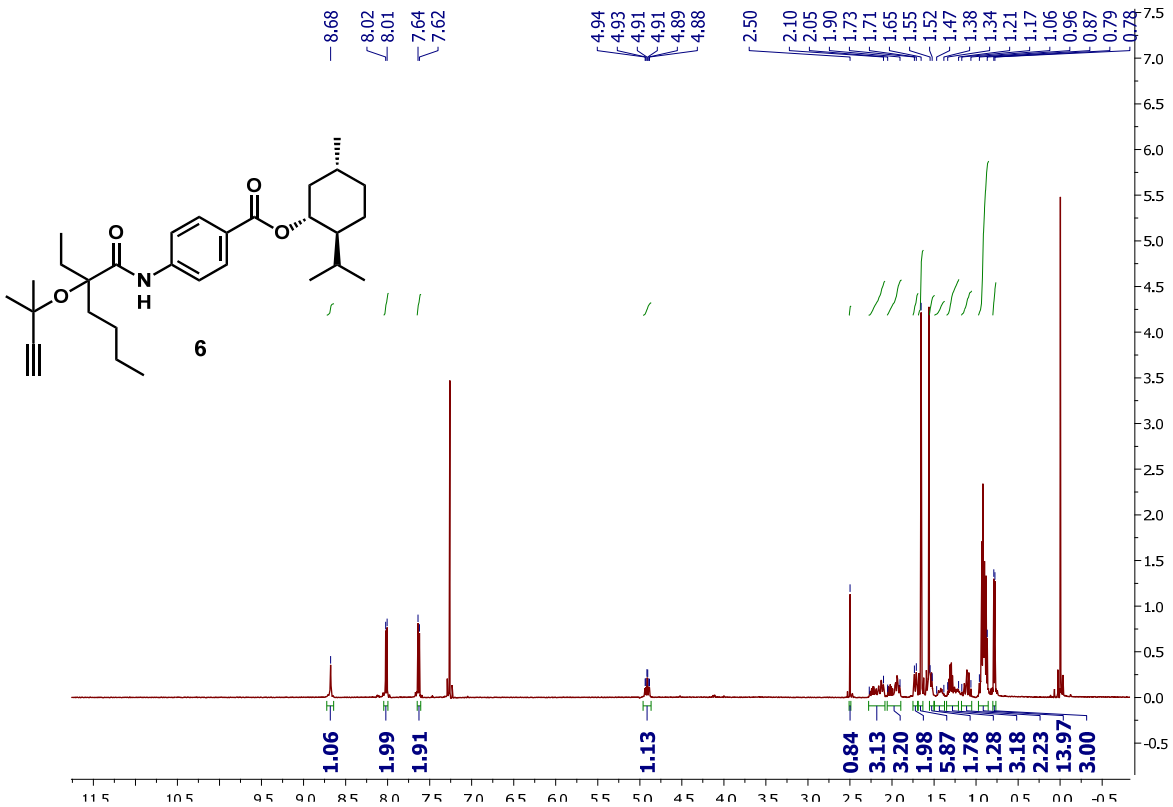
^{1}H NMR (500 MHz, $CDCl_3$)



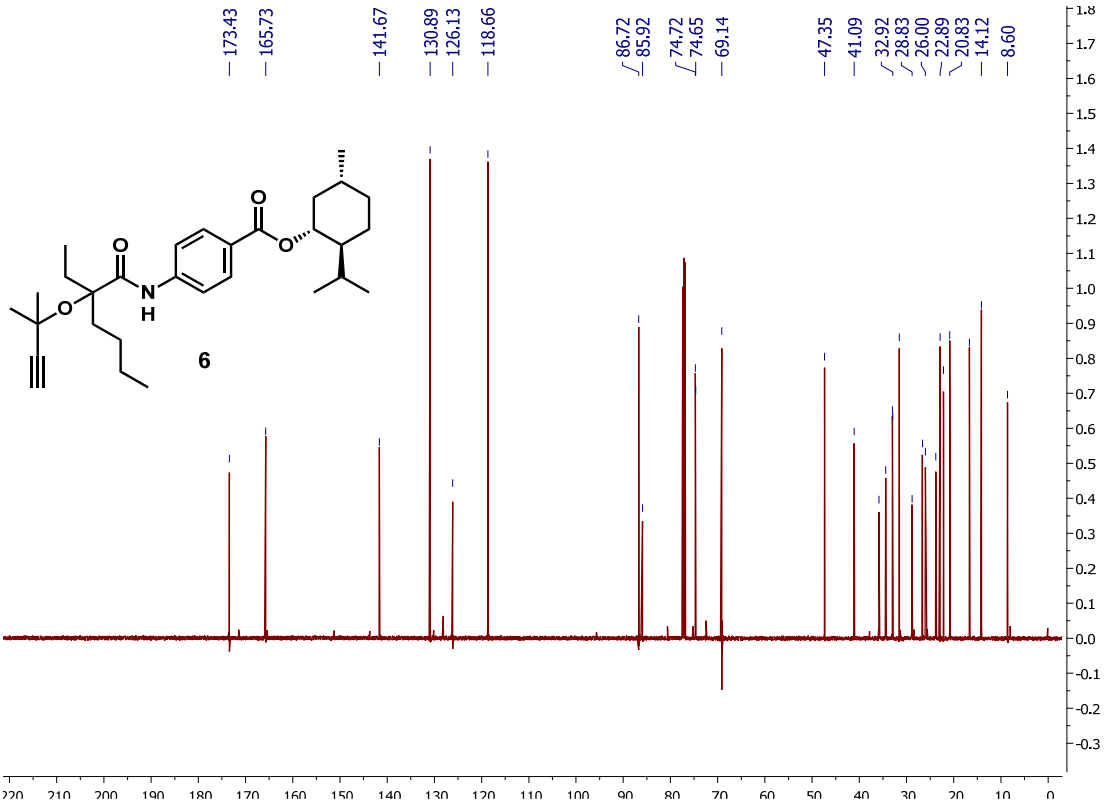
^{13}C NMR (125 MHz, $CDCl_3$)



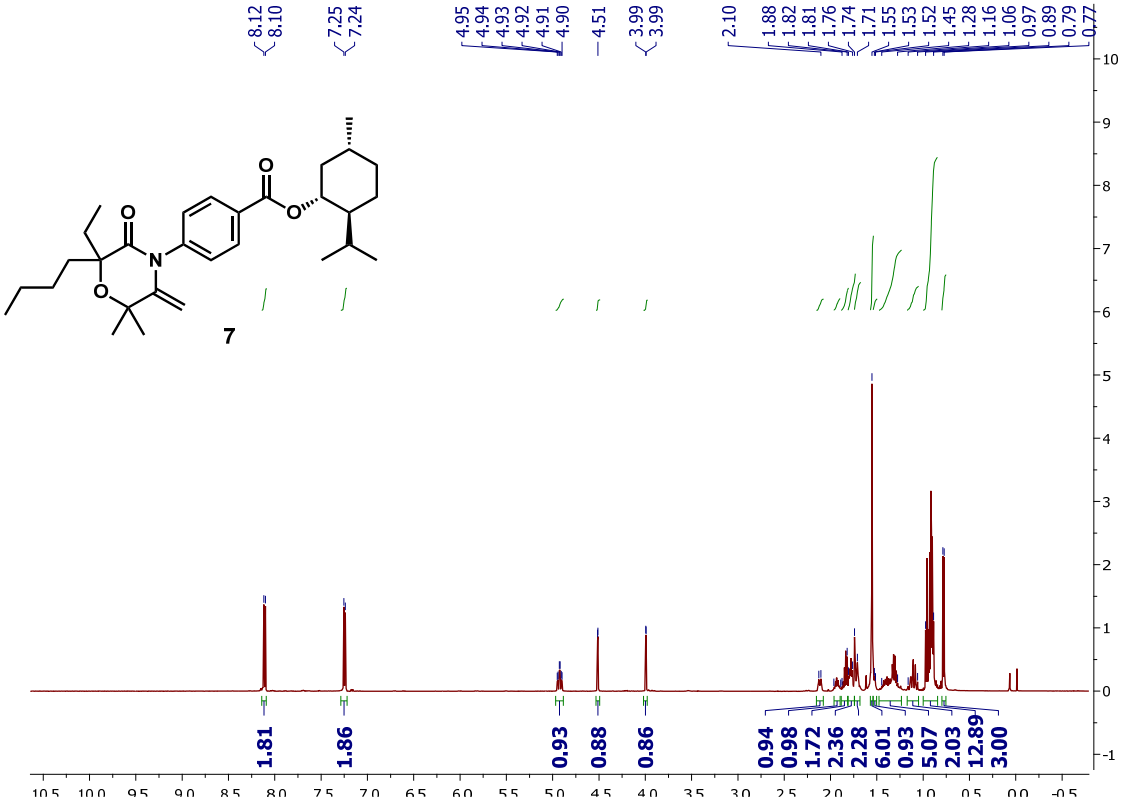
^{1}H NMR (500 MHz, $CDCl_3$)



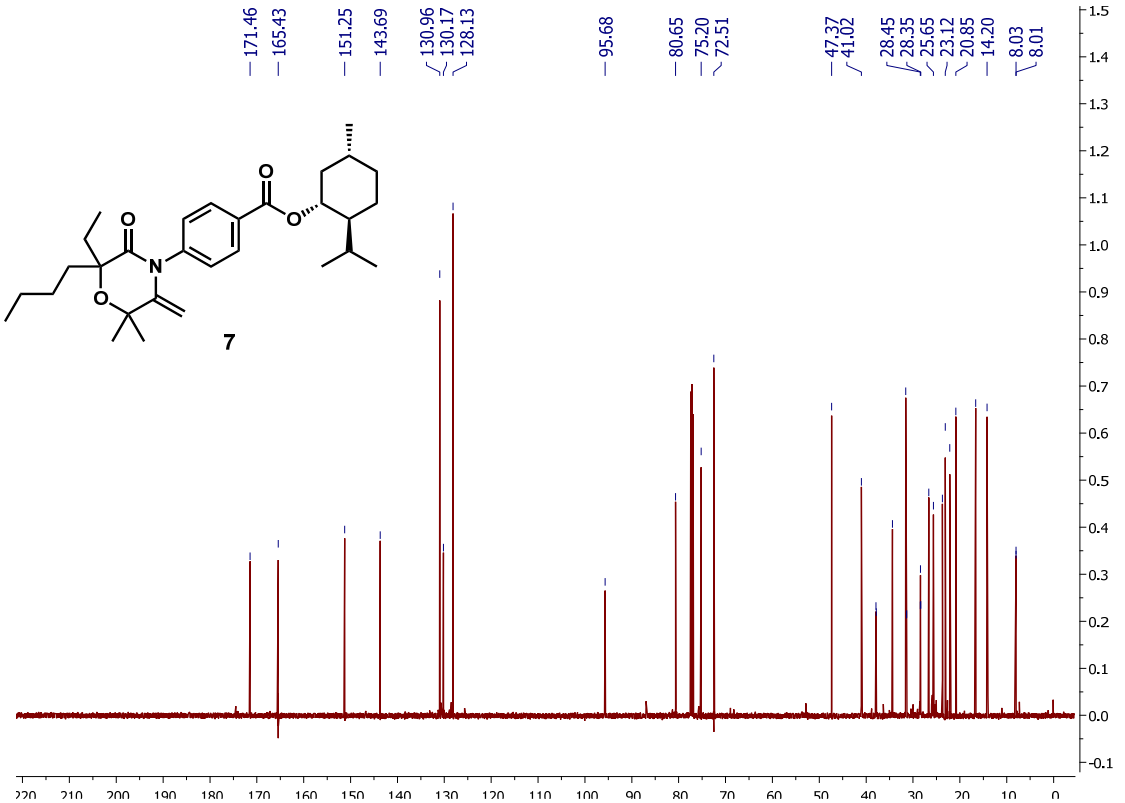
^{13}C NMR (125 MHz, $CDCl_3$)



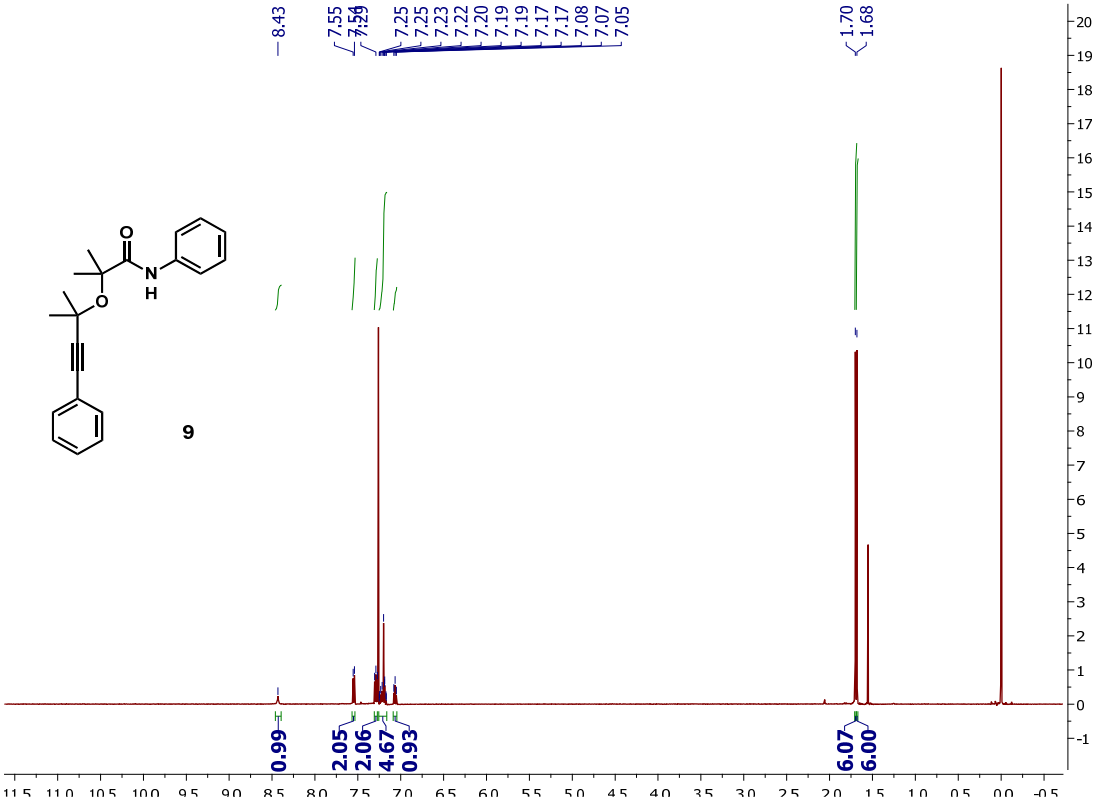
^{1}H NMR (500 MHz, $CDCl_3$)



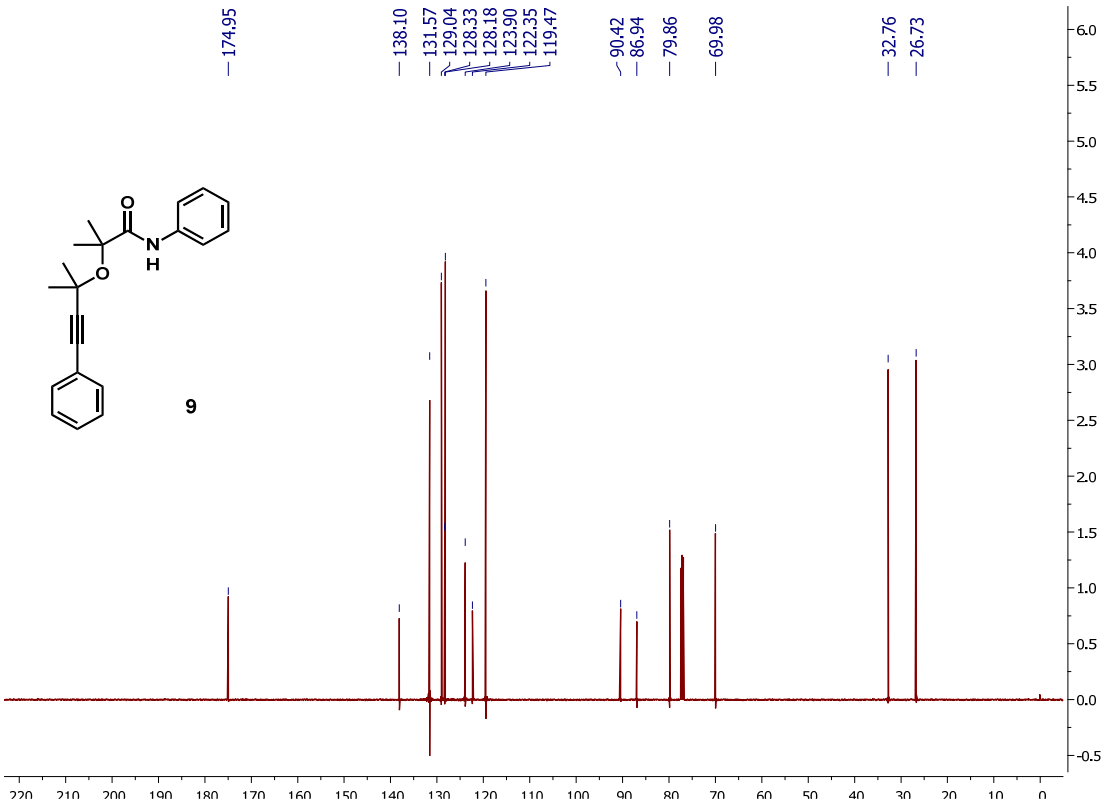
^{13}C NMR (125 MHz, $CDCl_3$)



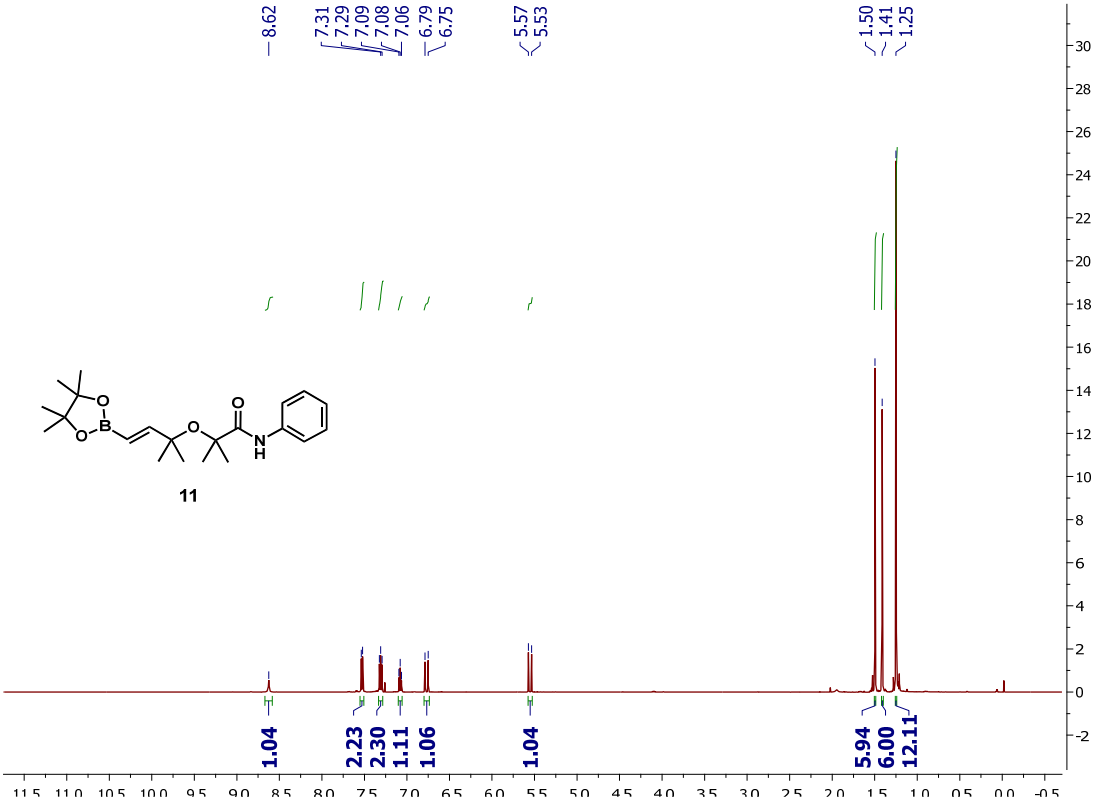
^{1}H NMR (500 MHz, $CDCl_3$)



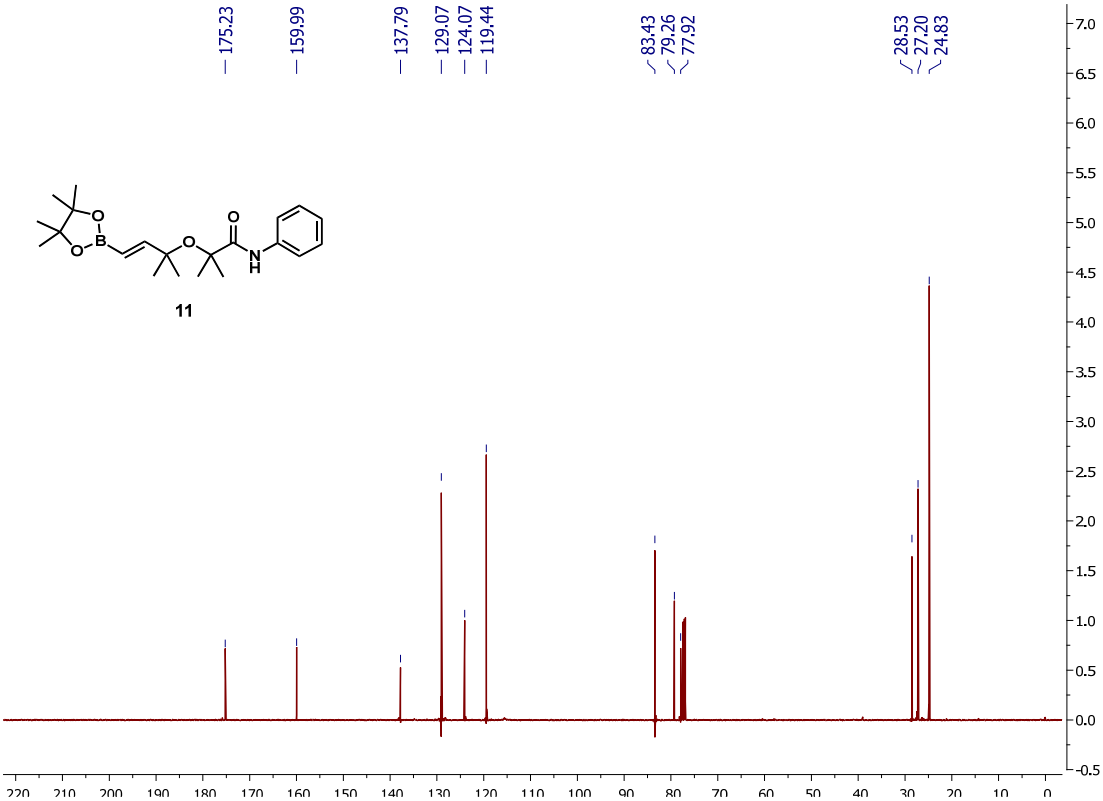
^{13}C NMR (125 MHz, $CDCl_3$)



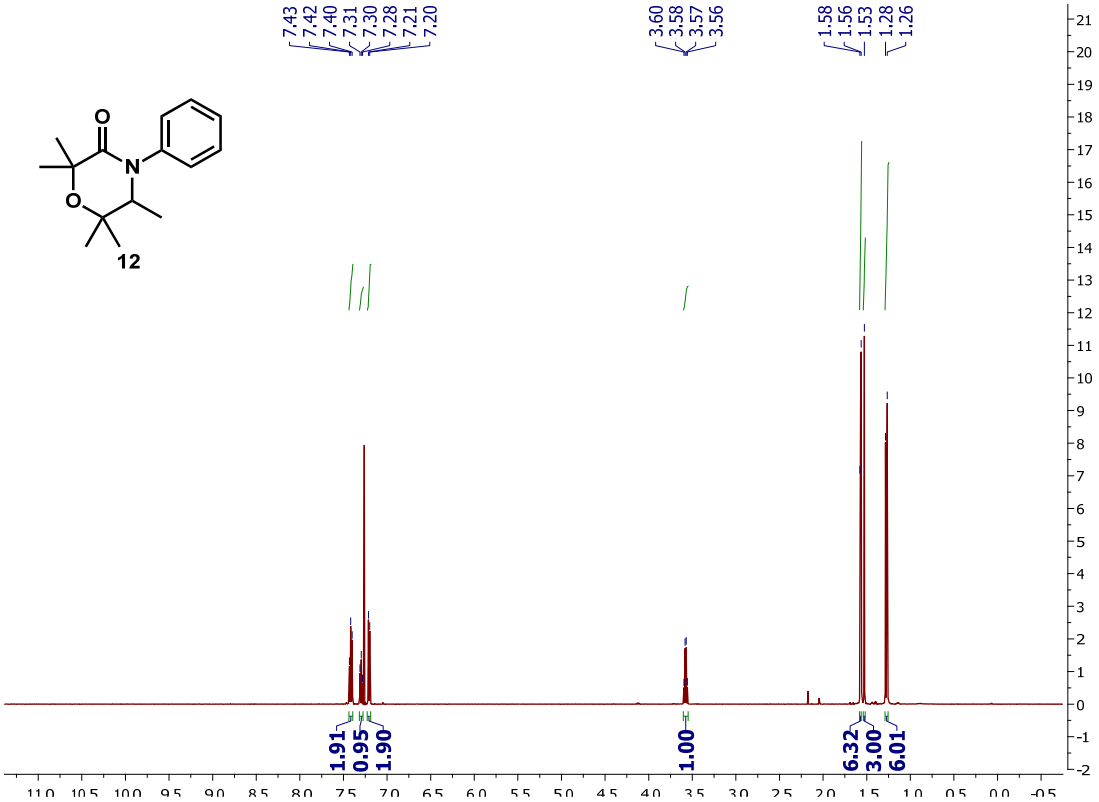
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)