A Simple Catalytic Mechanism for the Direct Coupling of α-Carbonyls with Functionalized Amines: A One-Step Synthesis of Plavix

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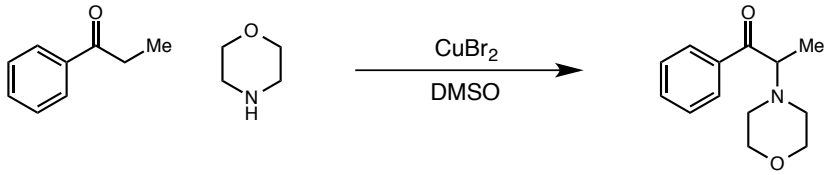
Supporting Information

1. General Information. Commercial reagents were purchased from Sigma Aldrich and purified prior to use following the guidelines of Perrin and Armarego.[1] All solvents were purified according to the method of Grubbs.[2] Organic solutions were concentrated under reduced pressure on a Buchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography according to the method of Still[3] on ICN 60 32-64 mesh silica gel 63. Thin-layer chromatography (TLC) was performed on Silicycle 250 mm silica gel F-254 plates. Visualization of the developed plates was performed by fluorescence quenching or by $KMnO_4$ and iodine stain.

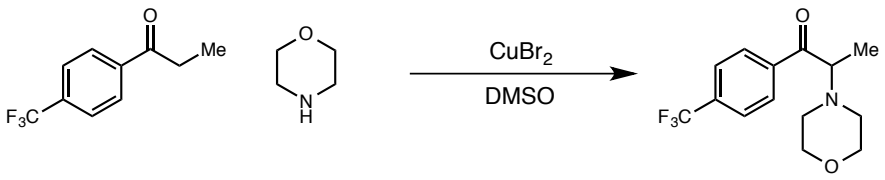
^{1}H NMR spectra was recorded on a Bruker 500 (500 MHz) or a Bruker 300 (5300 MHz) and are internally referenced to residual protio solvent signals ($CDCl_3$) at δ 7.27 ppm (^{1}H). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad), integration, coupling constant (Hz) and assignment. ^{13}C spectra were recorded on a Bruker 500 (126 MHz) and are referenced relative to $CDCl_3$ at δ 77.16 ppm. Data for ^{13}C NMR are reported in terms of chemical shift and multiplicity where appropriate. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of wavenumber of absorption (cm^{-1}). High Resolution Mass spectra were obtained from the Princeton University Mass Spectral Facility.

2. Experimental Data for Products of α-Amination



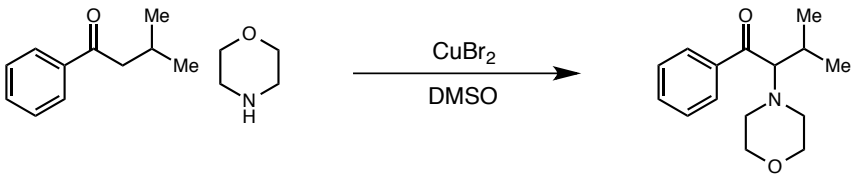
2-Morpholino-1-phenylpropan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.75 mL, 1.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv). The reaction was stirred at room temperature for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (152 mg, 93% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 6.9 Hz, 2H), 7.53 (m, 1H), 7.43 (m, 2H), 4.05 (q, J = 6.8 Hz, 1H),

3.66 (m, 4H), 2.60 (m, 2H), 2.53 (m, 2H), 1.28 (d, J = 6.8 Hz, 3H). ^{1}H NMR is consistent with the literature precedent.[4]



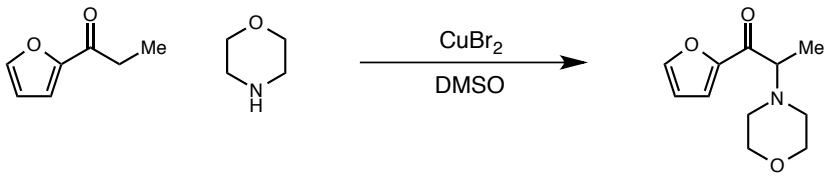
2-Morpholino-1-(4-(trifluoromethyl)phenyl)propan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.75 mL, 1.0 M with respect to the carbonyl component), and 1-(4-(trifluoromethyl)phenyl)propan-1-one (151 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv). The reaction was then stirred at 5 ^{o}C for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography the give tertiary amine (197 mg, 92% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 4.03 (q, J = 6.8 Hz, 1H), 3.64 (m, 4H), 2.56 (m ,4H), 1.27 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 199.1, 138.7, 134.1 (q, J = 32.7 Hz) 129.2, 125.4, 67.0, 65.3, 49.8, 10.4; HRMS (ESI-TOF) m/z calculated for $C_{14}H_{17}F_3NO_2$ $[M+H]^+$ 287.11331, found 245.11311, Δ 0.71 ppm; IR (film) 2961, 2855, 2824, 1691, 1453, 1409, 1320, 1254, 1220, 1166, 1110, 1065, 1016, 925, 853, 786, 696.

1-(4-Methoxyphenyl)-2-morpholinopropan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and 1-(4-methoxyphenyl)propan-1-one (122 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv). The reaction was then heated to 60 ^{o}C and stirred for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (145 mg, 78% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 3.95 (q, J = 7.0 Hz, 1H), 3.82 (s, 3H), 3.63 (m, 4H), 2.57 (m, 2H), 2.48 (m, 2H), 1.23 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz) δ 198.8, 163.4, 131.2, 129.8, 113.6, 67.2, 64.8, 55.4, 50.2, 12.1; HRMS (ESI-TOF) m/z calculated for $C_{14}H_{19}NO_3$ $[M+H]^+$ 249.13649, found 249.13665, Δ 0.62 ppm; IR (film) 2959, 1851, 1673, 1598, 1508, 1454, 1306, 1254, 1228, 1168, 1115, 1028, 926, 844, 785.



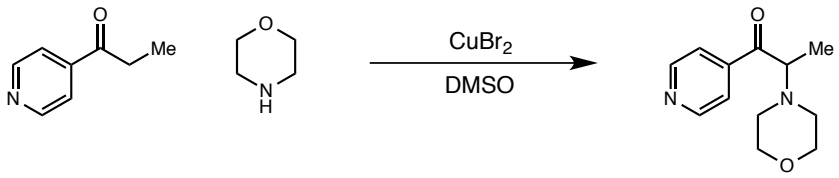
3-Methyl-2-morpholino-1-phenylbutan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.75 mL, 1.0 M with respect to the carbonyl component), and 3-methyl-1-phenylbutan-1-one (121 mg, 0.75 mmol, 1.0 equiv) was added. This was

stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv). The reaction was then heated to 50 ^{o}C and stirred for 12 hours, at which point morpholine was added (200 μL, 2.23 mmol, 3.0 equiv) and stirred at 50 ^{o}C for 12 hours. The crude reaction mixture was then loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (135 mg, 73% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (m, 2H), 7.51 (m, 1H), 7.47 (m, 2H) 3.80 (d, J = 10.0 Hz, 1H), 3.64 (m, 2H), 3.57 (m, 2H), 2.56 (m, 4H), 2.26 (m, 1H), 1.06 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz) δ 200.6, 139.4, 128.8, 127.9, 72.2, 67.7, 50.1, 26.6, 19.9, 19.8; HRMS (ESI-TOF) m/z calculated for $C_{15}H_{22}NO_2$ $[M+H]^+$ 247.15723, found 247.15673, Δ 2.01 ppm; IR (film) 2958, 2852, 1669, 1596, 1579, 1447, 1292, 1252, 1217, 1114, 1011, 916, 867, 843, 730, 712, 687.



1-(Furan-2-yl)-2-morpholinopropan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.75 mL, 1.0 M with respect to the carbonyl component), and 1-(furan-2-yl)propan-1-one (92 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv). The reaction was stirred for 12 hours at room temperature, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (133 mg, 85% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 1.8 Hz, 1H), 7.36 (d, J = 3.6 Hz, 1H), 6.49 (dd, J = 3.6, 1.8

Hz, 1H), 3.78 (q, J = 6.9 Hz, 1H), 3.64 (m, 4H), 2.57 (m, 2H), 2.47 (m, 2H), 1.24 (d, J = 6.9 Hz, 3H). ^{1}H NMR is consistent with literature precedent.[5]



2-Morpholino-1-(pyridin-4-yl)propan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.75 mL, 1.0 M with respect to the carbonyl component), and 1-(pyridin-4-yl)propan-1-one (101 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv). The reaction was stirred at 5 ^{o}C for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (164 mg, 82% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 6.1 Hz, 2H), 7.84 (d, J = 6.1 Hz, 2H), 3.99 (q, J = 6.8 Hz, 1H), 3.64 (m, 4H), 2.55 (m, 4H), 1.26 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 199.5, 150.8, 142.0, 121.8, 67.0, 65.2, 49.7, 10.0; HRMS (ESI-TOF) m/z calculated for $C_{12}H_{16}N_2O_2$ $[M+H]^+$ 220.12118, found 245.12044, Δ 3.35 ppm; IR (film) 2952, 2853, 1697, 1554, 1454, 1408, 1255, 1226, 1116, 930, 855, 771.

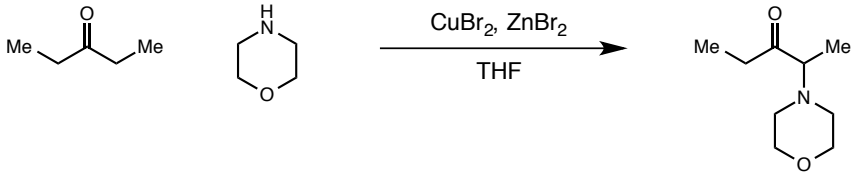
3-Morpholinobutan-2-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) and $ZnBr_2$ (40 mg, 0.18 mmol, 0.25 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the

carbonyl component), and butanone (54 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv) and placed under an atmosphere of oxygen. The reaction was stirred at room temperature for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (83 mg, 71% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (m, 2H), 3.00 (q, J = 6.9 Hz, 1H), 2.44 (m, 2H), 2.36 (m, 2H), 2.15 (s, 3H), 1.09, (d, J = 6.9 Hz; ^{13}C NMR (100 MHz) δ 210.9, 69.9, 67.1, 50.4, 26.5, 11.2; HRMS (ESI-TOF) m/z calculated for $C_8H_{16}NO_2$ $[M+H]^+$ 157.11028, found 157.11035, Δ 0.45 ppm; IR (film) 2960, 2853, 2818, 1713, 1453, 1353, 1264, 1252, 1232, 1147, 1114, 1068, 930, 917, 856, 731.

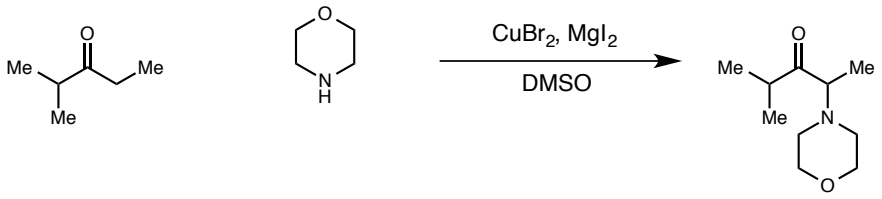
3-Morpholino-4-phenylbutan-2-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) and $NiBr_2$ (24 mg, 0.11 mmol, 0.15 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and 4-phenylbutan-2-one (110 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv) and placed under an atmosphere of oxygen. The reaction was stirred at room temperature for 18 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (106 mg, 61% Yield). ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.30 (m, 2H), 7.22 (m, 3H), 3.76 (m, 4H), 3.40 (dd, J = 9.5, 4.5 Hz), 1H), 2.99 (dd, J = 13.3, 9.5 Hz, 2H), 2.87 (dd, J = 13.3, 4.5 Hz, 1H), 2.69 (m, 4H), 2.08 (s, 3H); ^{13}C NMR (100 MHz) δ 208.5, 138.8, 129.3, 128.8, 126.3, 75.6, 67.3, 50.3, 31.3, 29.5; HRMS (ESI-TOF) m/z calculated for $C_{14}H_{19}NO_2$ $[M+H]^+$ 233.14158, found 245.14195, Δ 1.59 ppm; IR (film) 3028, 2957, 2852, 1713, 1602, 1494, 1453, 1351, 1290, 1248, 1134, 1120, 1009, 861, 736, 698.

3-Morpholinohex-5-en-2-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) and $NiBr_2$ (24 mg, 0.11 mmol, 0.15 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and hex-5-en-2-one (73 mg, .75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv) and placed under an atmosphere of oxygen. The reaction was stirred at room temperature for 18 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (86 mg, 63% Yield). ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddr, J = 17.1, 10.1, 7.0 Hz, 1H), 5.12 (m, 2H), 3.75 (m, 4H), 3.08 (dd, J = 8.5, 5.5 Hz, 1H), 2.64 (m, 2H), 2.52 (m, 4H), 2.19 (s, 3H); ^{13}C NMR (100 MHz) δ 209.1, 134.5, 117.5, 74.2, 67.2, 50.6, 30.5, 28.4; HRMS (ESI-TOF) m/z calculated for $C_{10}H_{17}NO_2$ $[M+H]^+$ 184.13375, found 184.13380, Δ 0.26 ppm; IR (film) 2959, 2853, 1714, 1640, 1452, 1353, 1291, 1248, 1141, 1170, 1117, 977, 911, 875, 862.

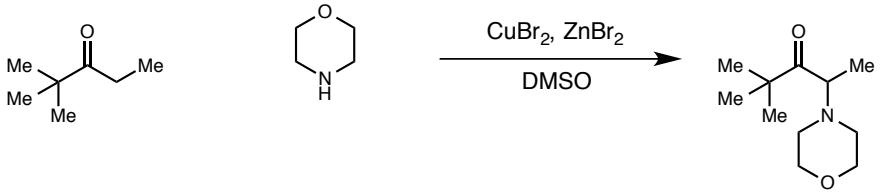


2-Morpholinopentan-3-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) and $ZnBr_2$ (16 mg, 0.07 mmol, 0.10 equiv) were dissolved in THF (0.12 mL, 6.0 M with respect to the carbonyl component), and pentan-3-one (64 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv) and sodium iodide (112 mg, 0.75 mmol, 1.0 equiv). The reaction was then placed under an atmosphere of oxygen and stirred at 10 ^{o}C for 12 hours. The crude reaction mixture was then loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (64 mg, 50% Yield). - ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (m, 4H), 3.06 (q, J = 6.9 Hz, 1H), 2.52 (t, J = 7.3 Hz, 2H), 2.45 (m, 2H), 2.37 (m, 2H), 1.08 (d, J = 6.9 Hz, 3H), 0.98 (t, J = 7.3 H, 3H). ^{1}H NMR is consistent with literature precedent.[6]



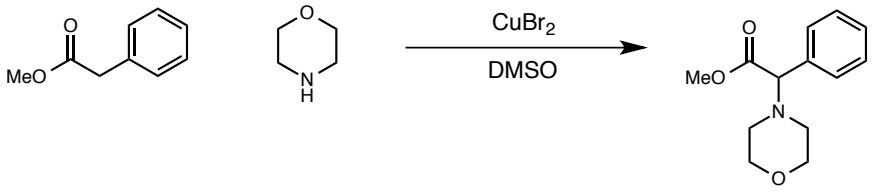
2-Methyl-4-morpholinopentan-3-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) and MgI_2 (51 mg, 0.19 mmol, 0.25 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and 2-methylpentan-3-one (75 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of

morpholine (200 μL, 2.23 mmol, 3.0 equiv) and placed under an atmosphere of oxygen. The reaction was stirred at room temperature for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (58 mg, 41% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (m, 4H), 3.31 (q, J = 7.0 Hz, 1H), 2.0 (hept, J = 7.0 Hz, 1H), 2.55 (m, 2H), 2.47(m, 2H), 1.12 (d, J = 7.0 Hz, 3H), 1.08 (d, J 7.0 = Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz) δ 215.5, 67.1, 50.2, 37.6, 29.7, 18.9, 18.5, 10.6; HRMS (ESI-TOF) m/z calculated for $C_{10}H_{20}NO_2$ $[M+H]^+$ 185.14171, found 185.14171, Δ 0.73 ppm; IR (film) 2965, 2933, 2853, 1711, 1453, 1379, 1326, 1290, 1251, 1147, 1116, 1001, 939, 854.



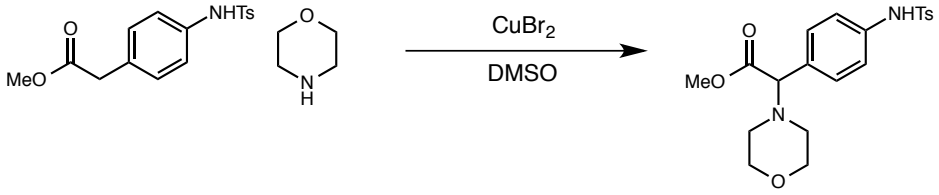
2,2-Dimethyl-4-morpholinopentan-3-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) and $NiBr_2$ (40 mg, 0.19 mmol, 0.25 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and 2,2-dimethylpentan-3-one (85 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv) and placed under an atmosphere of oxygen. The reaction was stirred at 60 ^{o}C for 12 hours, at which point morpholine (200 μL, 2.23 mmol, 3.0 equiv) was added again. The reaction was stirred at 60 ^{o}C for another 12 hours, before another addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv). This was stirred at 60 ^{o}C for another 12 hours, before the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the

tertiary amine (111 mg, 75% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (m, 5H), 2.63 (m, 2H), 2.49 (m, 2H), 1.19 (s, 9H); ^{13}C NMR (100 MHz) δ 214.8, 67.1, 61.9, 49.7, 44.0, 26.7, 11.0; HRMS (ESI-TOF) m/z calculated for $C_{11}H_{21}NO_2$ $[M+H]^+$ 200.16505, found 245.16447, Δ 2.89 ppm; IR (film) 2958, 2853, 1702, 1479, 1453, 1363, 1326, 1289, 1254, 1200, 1143, 1117, 1046, 990, 933, 857, 793.



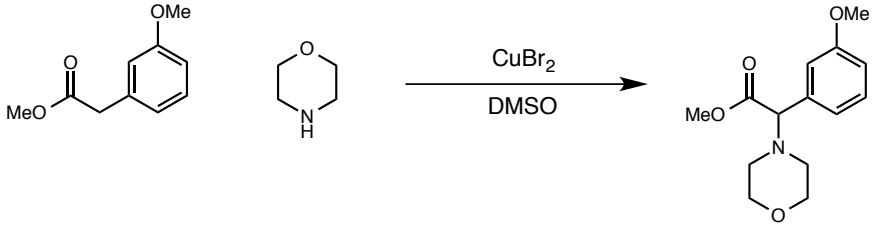
Methyl 2-morpholino-2-phenylacetate: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and methyl 2-phenylacetate (112 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv). The reaction was stirred at 50 ^{o}C for 12 hours, at which point morpholine (200 μL, 2.23 mmol, 3.0 equiv) was added again. The reaction was stirred at 50 ^{o}C for another 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (142 mg, 81% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.33 (m, 3H), 3.96 (s, 3H), 3.72 (t, J = 4.7 Hz, 4H), 3.67 (s, 3H), 2.43 (t, J = 4.7 Hz, 4H). ^{1}H NMR is consistent with literature precedent.[7]

Methyl 2-(4-bromophenyl)-2-morpholinoacetate: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and methyl 2-(4-bromophenyl)acetate (171 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv). The reaction was stirred at 50 ^{o}C for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (213 mg, 91% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 3.91 (s, 1H), 3.68 (t, J = 5.0 Hz, 4H), 3.63 (s, 3H), 2.40 (t, J = 5.0 Hz, 4H). ^{1}H NMR is consistent with literature precedent.[8]



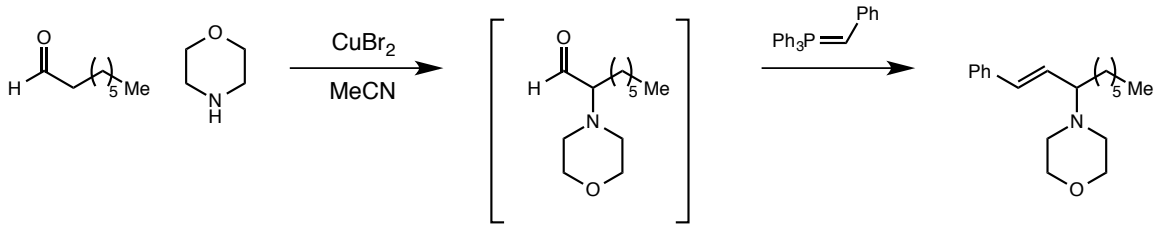
Methyl 2-(4-((4-methylphenyl)sulfonamido)phenyl)-2-morpholinoacetate: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.24 mL, 3.0 M with respect to the carbonyl component), and methyl 2-(4-((4-methylphenyl)sulfonamido)phenyl)acetate (238 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv), and placed under an atmosphere of oxygen. The reaction was stirred at 70 ^{o}C for 12 hours,

after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (211 mg, 70% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 8.5 Hz, 2H), 6.61 (br, 1H), 3.89 (s, 1H), 3.69 (t, J = 4.6 Hz, 4H), 3.66 (s, 3H), 2.38 (s, 3H), 2.36 (m, 4H); ^{13}C NMR (100 MHz) δ 169.0, 141.6, 134.3, 133.6, 129.5, 127.3, 127.2, 124.7, 118.3, 71.1, 64.2, 49.7, 49.0, 19.1; HRMS (ESI-TOF) m/z calculated for $C20H24N_2O_5S$ $[M+H]^+$ 404.14059, found 404.13996, Δ 1.56 ppm; IR (film) 3257, 2954, 2856, 1737, 1611, 1598, 1510, 1452, 1329, 1157, 1115, 1091, 1020, 910, 879, 814, 728, 662.



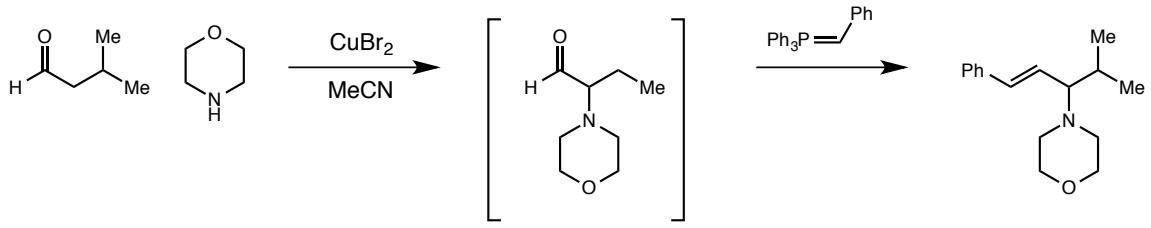
Methyl 2-(3-methoxyphenyl)-2-morpholinoacetate: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and methyl 2-(3-methoxyphenyl)acetate (134 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 μL, 2.23 mmol, 3.0 equiv). The reaction was stirred at 50 ^{o}C for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (140 mg, 71% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 8.1 Hz, 1H), 7.27 (m, 2H), 7.12 (m, 1H), 4.19 (s, 1H), 4.07 (s, 3H), 3.99 (m, 4H), 3.94 (s, 3H), 2.71 (m, 4H); ^{13}C NMR (100 MHz) δ 171.6, 159.8, 136.7, 129.6, 121.3, 114.2, 114.0, 74.5, 66.8, 55.4, 55.2, 51.7;

HRMS (ESI-TOF) m/z calculated for $C_{14}H_{20}NO_4$ $[M+H]^+$ 265.13141, found 265.13155, Δ 0.53 ppm; IR (film) 2954, 2838, 1742, 1599, 1585, 1489, 1450, 1435, 1259, 1197, 1149, 1114, 1022, 876, 781, 745, 693.



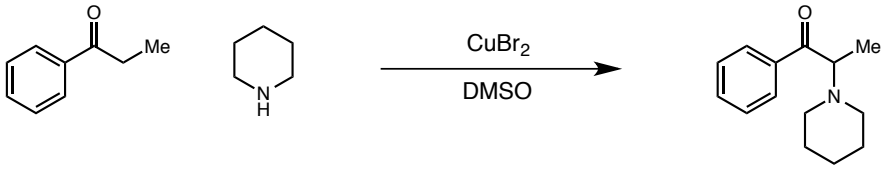
(*E*)-4-(1-Phenylnon-1-en-3-yl)morpholine: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in MeCN (1.5 mL, 0.5 M with respect to the carbonyl component), and octanal (96 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (100 μL, 1.12 mmol, 1.5 equiv). The reaction was stirred at room temperature for 6 hours. The reaction mixture was then added to a 0.3 M solution of the wittig reagent (16.75 mL, 5.03 mmol, 6.75 equiv) under a atmosphere of nitrogen. The reaction was stirred for 16 hours, and then quenched with a saturated aqueous solution of ammonium chloride. The organics were extracted three times with DCM, dried with $MgSO_4$, and filtered. The solution was concentrated and purified by column chromatography to give the tertiary amine (161 mg, 75% Yield, 3:1 *E*:*Z*.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m,2H), 7.33 (m, 2H), 7.24 (m, 1H), 6.43 (d, J = 15.9 Hz, 1H), 6.09 (dd, J = 15.9, 9.1 Hz, 1H), 3.68 (m, 4H), 2.83 (td, J = 9.1, 4.2 Hz, 1H), 2.58 (m, 4H), 1.74 (m, 1H), 1.49 (m, 1H), 1.28 (m, 8H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz) δ 136.9, 132.8, 129.9, 128.6, 127.4, 126.3, 68.5, 67.3, 50.7, 31.9, 31.8, 29.5, 26.3, 22.7, 14.2; HRMS (ESI-TOF) m/z calculated for $C_{19}H_{29}NO$ $[M+H]^+$

287.22491, found 287.22491, Δ 1.15 ppm; IR (film) 2954, 2926, 2853, 2811, 1494, 1456, 1267, 1117, 968, 865, 747, 692.

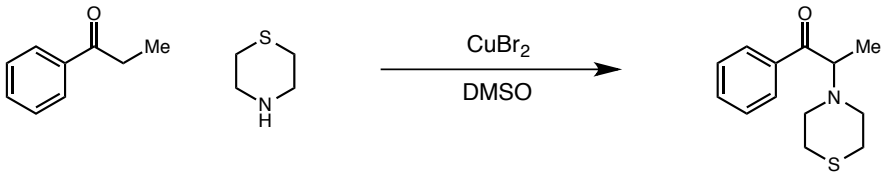


(*E*)-4-(4-Methyl-1-phenylpent-1-en-3-yl)morpholine: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in MeCN (1.5 mL, 0.5 M with respect to the carbonyl component), and isovaleraldehyde (64 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (100 μL, 1.12 mmol, 1.5 equiv). The reaction was stirred at room temperature for 5 hours. The reaction mixture was then added to a then added a 0.3 M solution of the wittig reagent (16.75 mL, 5.03 mmol, 4.5 equiv). The reaction was stirred for 16 hours, and then quenched with a saturated aqueous solution of ammonium chloride. The organics were extracted three times with DCM, dried with $MgSO_4$, and filtered. The solution was concentrated and purified by column chromatography to give the tertiary amine (122 mg, 67% Yield, 6:1 *E*:*Z*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.35 (m, 2H), 7.25 (m, 1H), 6.41 (d, J = 16.0 Hz, 1H), 6.08 (dd, J = 16.0, 9.5 Hz), 3.77 (m, 4H), 2.63 (m, 2H), 2.51 (dd, J = 9.5, 7.2 Hz, 1H), 2.48 (m, 2H), 2.1 (m, 1H), 0.97 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 137.2, 133.8, 128.6, 128.1, 127.5, 126.4, 74.5, 67.5, 50.8, 28.2, 20.5, 18.4; HRMS (ESI-TOF) m/z calculated for $C_{16}H_{23}NO$ $[M+H]^+$ 245.17796, found

245.17785, Δ 0.48 ppm; IR (film) 3026, 2955, 2851, 2807, 1599, 1494, 1449, 1384, 1365, 1285, 1268, 1253, 1139, 1116, 1070, 1030, 1008, 971, 877, 747, 692.

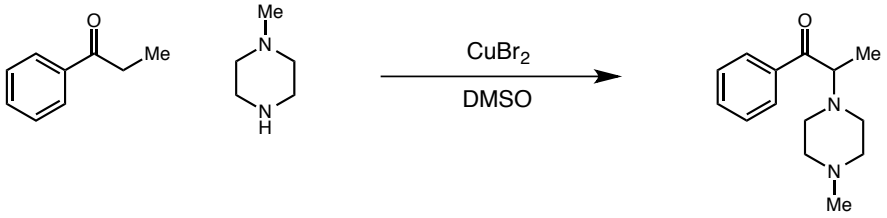


1-Phenyl-2-(piperidin-1-yl)propan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of piperidine (148 μL, 1.49 mmol, 2.0 equiv). The reaction was stirred for 12 hours at room temperature, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (142 mg, 88% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (m, 2H), 7.52(m, 1H), 7.44 (m, 2H), 4.06 (q, J = 6.8 Hz, 1H), 2.55 (m, 4H), 1.54 (m, 4H), 1.42 (m, 2H), 1.26 (d, J = 6.8 Hz, 3H); ^{1}H NMR is consistent with literature precedent.[5]



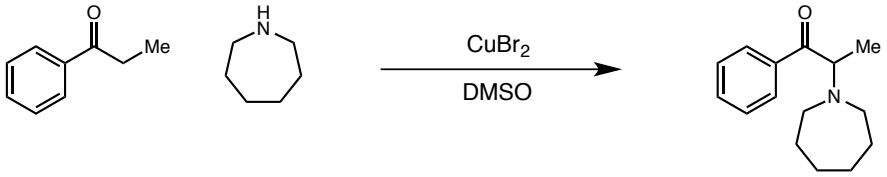
1-Phenyl-2-thiomorpholinopropan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.37 mL, 2.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of thiomorpholine (149 μL, 1.49 mmol,

2.0 equiv). The reaction was stirred for 12 hours at 50 ^{o}C, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (153 mg, 87% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 4.15 (q, J = 6.8 Hz, 1H), 2.92 (m, 4H), 2.67 (m, 4H), 1.25 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 200.1, 136.2, 133.0, 128.9, 128.4, 65.2, 51.6, 28.4, 9.9; HRMS (ESI-TOF) m/z calculated for $C_{13}H_{18}NOS$ $[M+H]^+$ 235.10305, found 235.10266, Δ 1.79 ppm; IR (film) 2909, 2819, 1683, 1596, 1447, 1231, 1209, 1183, 1122, 980, 958, 907, 741, 693.

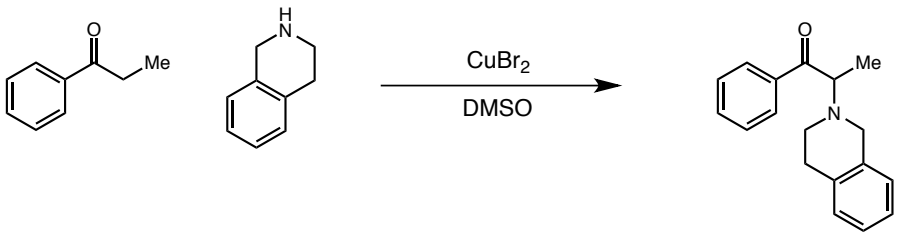


2-(4-Methylpiperazin-1-yl)-1-phenylpropan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of 1-methylpiperazine (165 μL, 1.49 mmol, 2.0 equiv). The reaction was stirred for 12 hours at room temperature, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (130 mg, 75% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 4.07 (q, J = 6.8 Hz, 1H), 2.70 (m, 4H), 2.49 (m, 2H), 2.26 (s, 3H), 1.28 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 200.5, 136.2, 133.0, 128.9, 128.4, 64.5, 55.3, 46.0, 11.7; HRMS (ESI-TOF) m/z calculated for C14H20N_2O $[M+H]^+$ 232.15756, found 245.15727, Δ 1.28 ppm; IR (film)

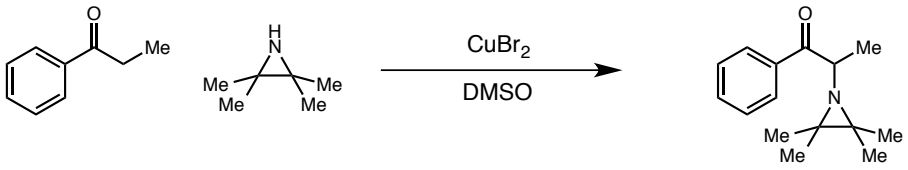
2935, 2794, 1682, 1597, 1448, 1373, 1284, 1231, 1170, 1146, 1013, 922, 812, 746, 702, 687.



2-(Azepan-1-yl)-1-phenylpropan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of azepane (269 μL, 2.23 mmol, 3.0 equiv). The reaction was stirred at room temperature for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (141 mg, 82% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 4.27 (q, J = 6.6 Hz, 1H), 2.72 (t, J = 5.6 Hz), 1.71 (m, 2H), 1.54 (m, 6H), 1.25 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 201.0, 136.6, 132.7, 129.0, 128.2, 64.6, 51.5, 29.4, 27.1, 10.0; HRMS (ESI-TOF) m/z calculated for $C_{15}H_{22}NO_2$ $[M+H]^+$ 231.16231, found 231.16197, Δ 1.49 ppm; IR (film) 2925, 2852, 1684, 1597, 1580, 1448, 1393, 1368, 1330, 1262, 1220, 1175, 1138, 1110, 1007, 969, 899, 728, 691.

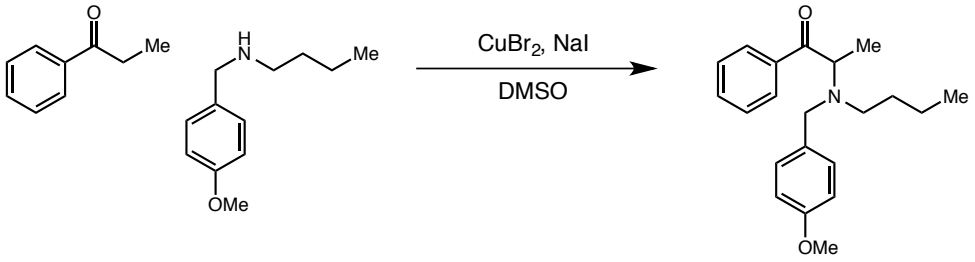


2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-1-phenylpropan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of 1,2,3,4-tetrahydroisoquinoline (189 μL, 1.49 mmol, 2.0 equiv). The reaction was stirred for 12 hours at room temperature, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (178 mg, 90% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 7.15 (m, 4H), 4.32 (q, J = 6.8 Hz, 1H), 3.90 (d, J = 14.8 Hz, 1H), 3.81 (d, J = 14.8 Hz, 1H), 2.91 (m, 4H), 1.39 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 200.6, 136.2, 134.9, 134.5, 133.0, 128.9, 128.8, 128.5, 126.6, 126.0, 125.6, 65.3, 52.1, 47.2, 29.7, 11.3; HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}NO$ $[M+H]^+$ 265.14666, found 245.14704, Δ 1.42 ppm; IR (film) 3063, 2977, 2920, 2805, 1681, 1596, 1447, 1388, 1222, 1153, 1107, 971, 922, 710, 699.



1-Phenyl-2-(2,2,3,3-tetramethylaziridin-1-yl)propan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of 2,2,3,3-tetramethylaziridine (148 mg, 1.49 mmol, 2.0 equiv). The reaction was stirred for 8 hours

at 40 °C, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (122 mg, 71% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94, (m, 2H) 7.48 (m, 1H), 7.38 (m, 2H), 3.82 (q, J = 7.0 Hz, 1H), 1.34 (d, J = 7.0 Hz, 3H), 1.21 (s, 3H), 1.16 (m, 6H), 0.90 (s, 3H); ^{13}C NMR (100 MHz) δ 201.8, 135.6, 132.8, 128.7, 128.5, 57.9, 41.9, 41.0, 24.5, 23.2, 20.53, 15.2, 14.7; HRMS (ESI-TOF) m/z calculated for $C_{15}H_{22}NO$ $[M+H]^+$ 231.16231, found 232.16260, Δ 1.25 ppm; IR (film) 3065, 2998, 2942, 1693, 1673, 1448, 1377, 1274, 1206, 1156, 970, 697.



2-(Butyl(4-methoxybenzyl)amino)-1-phenylpropan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) and NaI (56 mg, 0.37 mmol, 0.5 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of *N*-(4-methoxybenzyl)butan-1-amine (360 mg, 1.86 mmol, 2.5 equiv). The reaction was stirred for 12 hours at 60 °C, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (179 mg, 74% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.53 (m, 1H), 7.39 (m, 2H), 7.10 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 4.34 (q, J = 6.6 Hz, 1H), 3.80 (s, 3H), 3.65 (d, J = 13.5 Hz, 1H) 3.45 (d, J = 13.5 Hz, 1H), 2.52

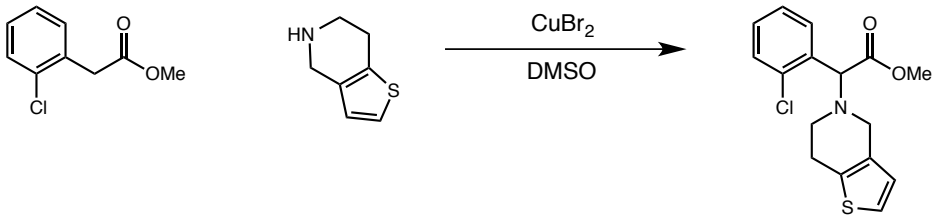
(m, 2H), 1.45 (m, 2H), 1.26 (d, J = 6.6 Hz, 3H), 1.24 (m, 2H), 0.77 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz) δ 202.0, 158.7, 136.9, 132.5, 131.7, 130.4, 128.9, 128.0, 113.5, 58.6, 55.3, 54.4, 49.7, 30.5, 20.2, 14.0, 8.3; HRMS (ESI-TOF) m/z calculated for $C_{21}H_{27}NO_2$ $[M+H]^+$ 326.20418, found 326.20456, Δ 1.17 ppm; IR (film) 2959, 2934, 2873, 2836, 2175, 2085, 1990, 1913, 1680, 1601, 1543, 1513, 1450, 1377, 1304, 1248, 1177, 1112, 1069, 1025, 832, 790, 716, 672, 656.

2-(Allyl(4-methoxybenzyl)amino)-1-phenylpropan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) and NaI (56 mg, 0.37 mmol, 0.5 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of *N*-(4-methoxybenzyl)prop-2-en-1-amine (330 mg, 1.86 mmol, 2.5 equiv). The reaction was stirred for 12 hours at 60 ^{o}C, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (161 mg, 70% Yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 7.5 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.40 (t, 7.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 5.79 (m, 1H), 5.16 (dd, J = 23.5 Hz, 10.0 Hz, 2H), 4.42 (q, J = 7.0 Hz, 1H), 3.78 (s, 3H), 3.65 (d, J = 14.0 Hz, 1H), 3.45 (d, J = 14.0 Hz, 1H), 3.19 (dd, J = 14.0, 5.5 Hz, 1H), 3.06 (dd, J = 14.0, 8.0 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H); ^{13}C NMR

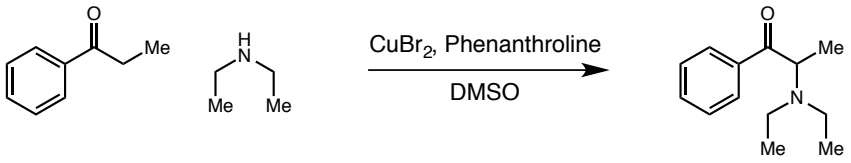
(100 MHz) δ 202.0, 158.7, 136.9, 136.6, 132.6, 131.4, 130.2, 129.0, 128.1, 117.6, 113.5, 58.1, 55.3, 53.6, 53.3, 8.7; HRMS (ESI-TOF) m/z calculated for $C_{20}H_{23}NO_2$ $[M+H]^+$ 309.17288, found 309.16637, Δ 21.05 ppm; IR (film) 2937, 2837, 2048, 1960, 1901, 1680, 1601, 1512, 1448, 1378, 1303, 1246, 1178, 1111, 1069, 1026, 991, 932, 831, 759, 718.

2-(Benzyl(2,2-dimethoxyethyl)amino)-1-phenylpropan-1-one: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) and NaI (56 mg, 0.37 mmol, 0.5 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of *N*-benzyl-2,2-dimethoxyethan-1-amine (330 mg, 1.86 mmol, 2.5 equiv). The reaction was stirred for 12 hours at 60 ^oC, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (181 mg, 74% Yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (m, 2H), 7.60 (m, 1H), 7.46 (m, 2H), 7.31 (m, 3H), 7.19 (m, 2H), 4.53 (q, J = 6.7 Hz, 1H), 4.19 (t, J = 5.3 Hz, 1H), 3.80 (d, J = 13.6 Hz, 1H), 3.67 (d, J = 13.6 Hz, 1H), 3.32 (s, 3H), 3.14 (s, 3H), 2.81 (m, 2H), 1.34 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz) δ 202.0, 139.6, 136.7, 132.7, 129.2, 128.2, 128.1, 127.2, 104.7, 59.9, 56.0, 54.5, 53.2, 52.6, 9.7; HRMS (ESI-TOF) m/z calculated for $C_{20}H_{25}NO_3$ $[M+H]^+$ 327.18344, found 327.18299, Δ 1.38

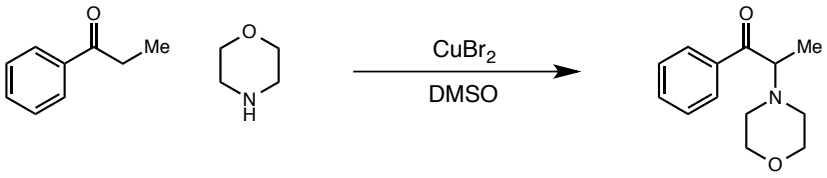
ppm; IR (film) 3066, 3027, 2934, 2832, 2201, 2178, 2052, 2008, 1961, 1682, 1597, 1581, 1494, 1448, 1374, 1227, 1124, 1075, 1027, 971, 927, 829, 739, 696.



Methyl-2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetate: $CuBr_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.37 mL, 2.0 M with respect to the carbonyl component), and methyl 2-(2-chlorophenyl)acetate (148 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (311 mg, 2.23 mmol, 3.0 equiv). The reaction was placed under an atmosphere of oxygen and stirred at room temperature for 24 hours, after which the crude reaction mixture was loaded directly onto a Biotage KP-NH snap column and purified by column chromatography to give the tertiary amine (209 mg, 87% Yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, J = 8.0, 1.0 Hz, 1H), 7.41 (dd, J = 8.0, 1.6 Hz, 1H), 7.25 (m, 2H), 7.00 (d, J = 4.0 Hz, 1H), 6.61 (d, J = 4.0 Hz, 1H), 4.85 (s, 1H), 3.70 (d, J = 12.0 Hz, 1H), 3.64 (s, 3H), 3.57 (d, J = 12.0 Hz, 1H), 2.82 (s, 4H); ^{1}H NMR is consistent with the literature precedent.[9]



2-(Benzyl(2,2-dimethoxyethyl)amino)-1-phenylpropan-1-one: $CuBr_2$ (32 mg, 0.14 mmol, 0.2 equiv) and phenanthroline (30 mg, 0.16 mmol, 0.22 equiv) were dissolved in DMSO (0.75 mL, 1.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of diethylamine (154 μL, 1.49 mmol, 2.0 equiv). The reaction was placed under an atmosphere of oxygen, and the reaction flask was sealed. The reaction was stirred for 90 minutes at 35 ^{o}C, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (122 mg, 80% Yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (m, 2H), 7.57 (m, 3H), 4.38(q, J = 7.0 Hz, 1H), 2.72 (m, 4H), 1.25 (d, J = 7.0 Hz, 3H), 1.03 (t, J = 7.0 Hz, 6H); ^{1}H NMR is consistent with the literature precedent.[10]



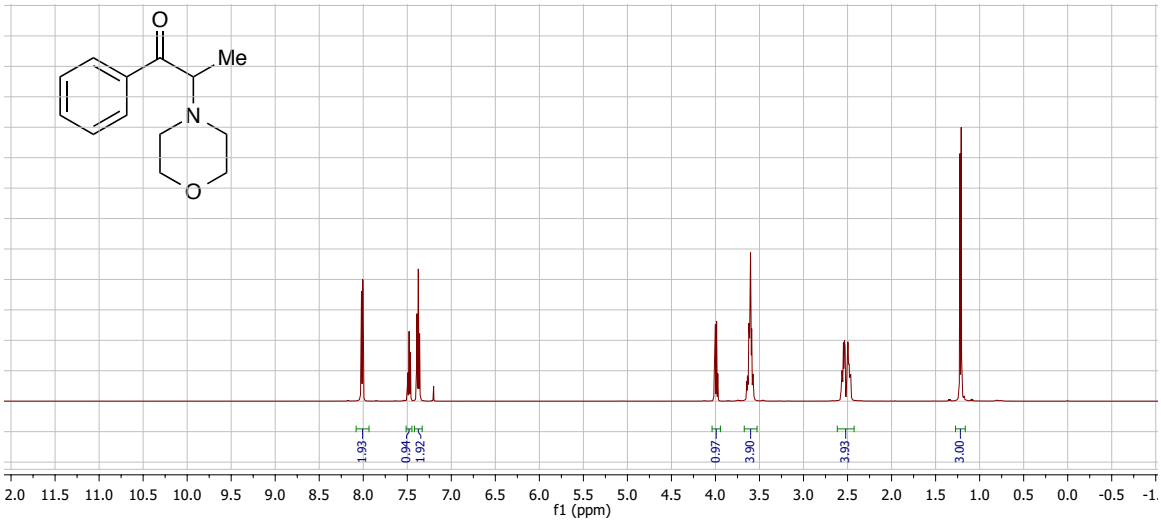
2-Morpholino-1-phenylpropan-1-one: $CuBr_2$ (800 mg, 3.72 mmol, 0.1 equiv) was dissolved in DMSO (37.25 mL, 1.0 M with respect to the carbonyl component), and propiophenone (5.0 g, 37.25 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (10 mL, 111.50 mmol, 3.0 equiv). The reaction was stirred at room temperature for 12 hours, after which the crude reaction mixture was diluted with brine (200 mL), and extracted with EtOAc until TLC analysis

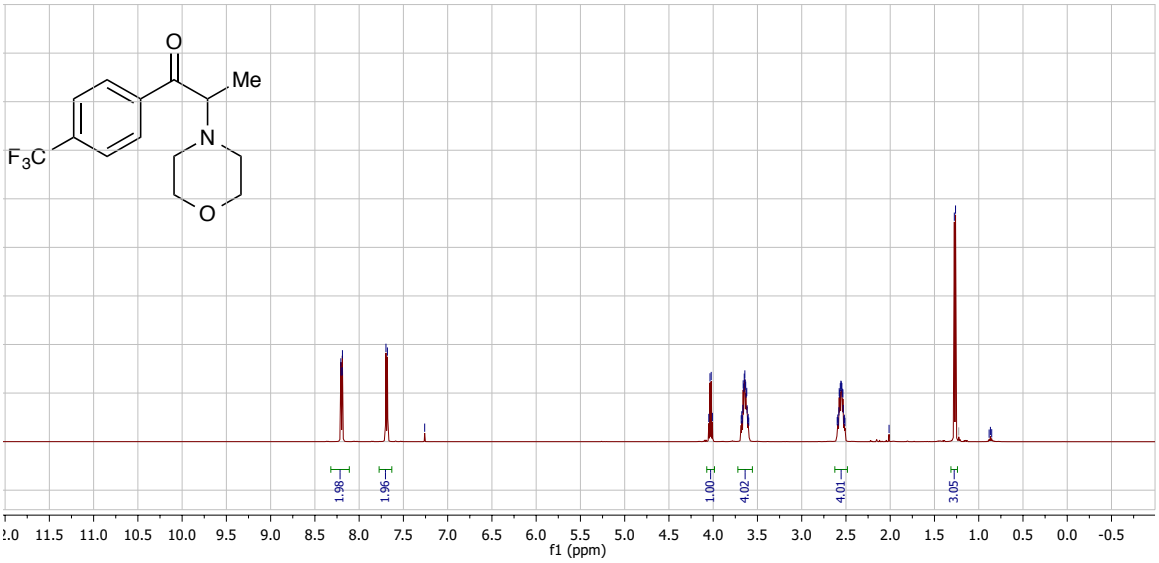
showed no product in the aqueous phase (7X200 mL). The organic layers were dried with $MgSO_4$, filtered, concentrated and purified by column chromatography to give the tertiary amine (7.1 g, 87% Yield).

References:

1. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed, Pergamon Press, Oxford, 1988
2. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Trimmers, F. J. *Organometallics,* **1996**, *15*, 1518
3. Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923
4. Stas, S.; Abbaspour Tehrani, K. *Synthesis*, **2007**, 433.
5. Lamani, M.; Prabhu, K. R. *Chem. Eur. J.*, **2012**, 14638.
6. Hoffman, R. V.; Jankowski, B. C.; Carr, C. S.; Duesler, E. N. *J. Org. Chem.*, **1986**, 130.
7. Miura, T.; Morimoto, M.; Murakami, M. *Org. Lett.*, **2012**, 5214
8. Hansen, S. R.; Spangler, J. E.; Hansen, J. H.; Davies, H. M. L. *Org. Lett.*, **2012**, 4626.
9. Aillaud, I.; Haurena, C.; Le Gall, E.; Martens, T.; Ricci, G. *Molecules*, **2010**, 8144.
10. Welle, F.; Verevkin, S. P.; Keller, M.; Beckhaus, H. D.; Ruechardt, C. *Chem. Ber*, **1994**, 697

3. NMR Spectra for Reported Compounds

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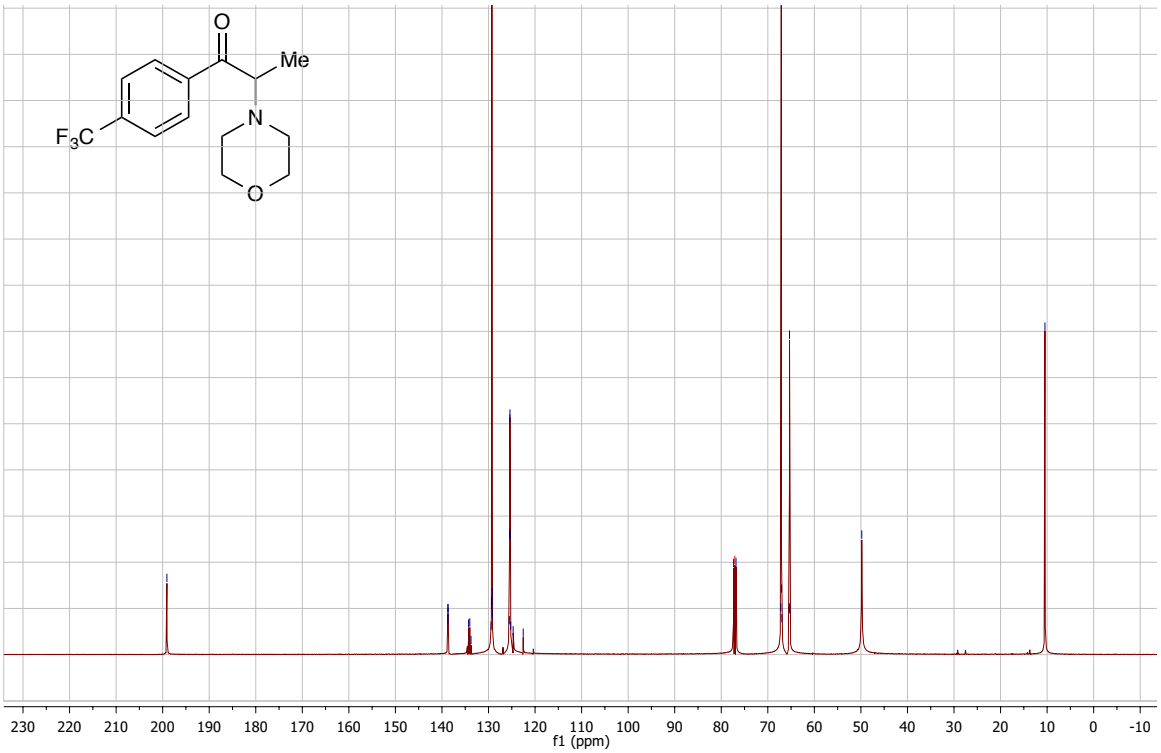
4.02
4.01
3.05
f1 (ppm)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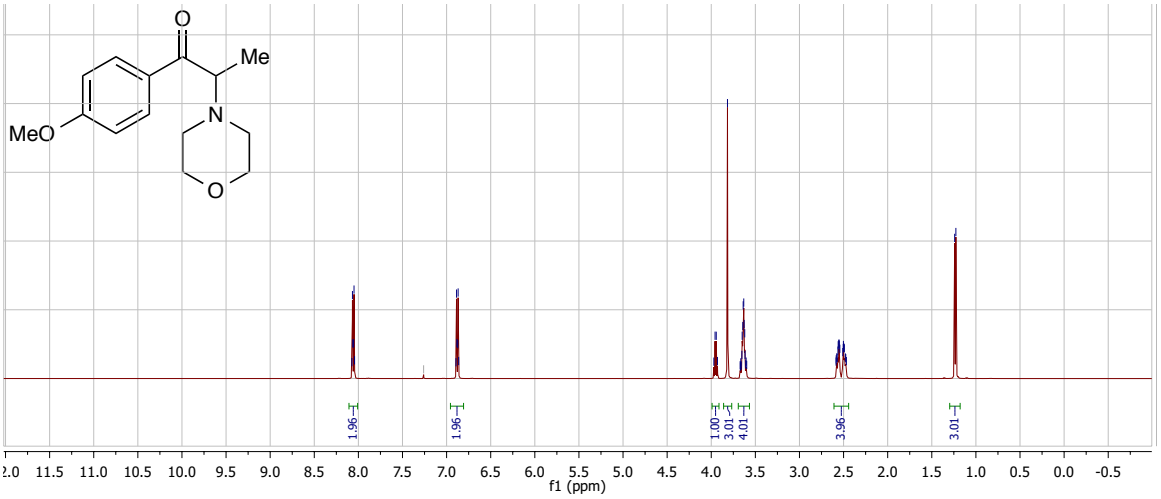
Me
N
F3C
O
f1 (ppm)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1.00
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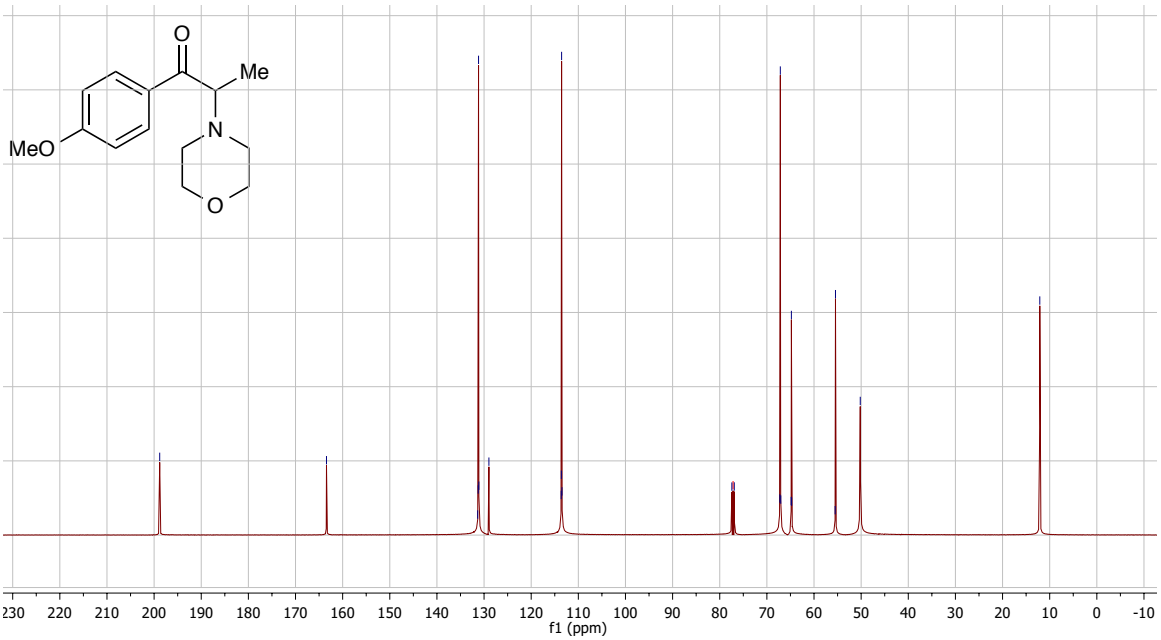
3.01
f1 (ppm)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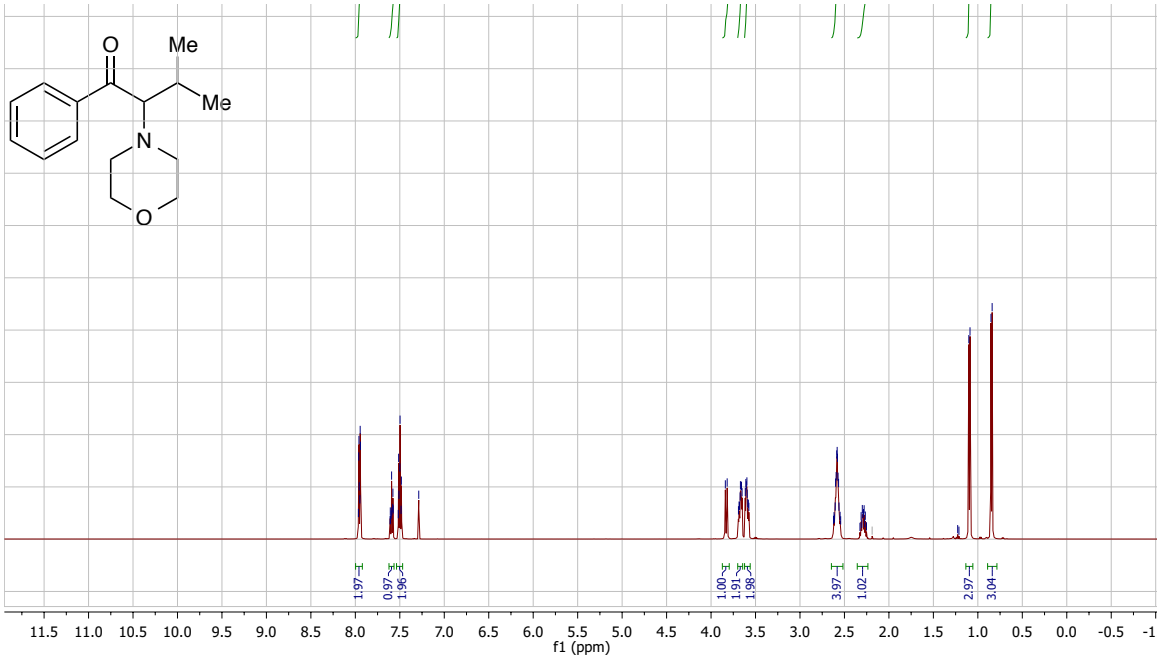
MeO
N
O
f1 (ppm)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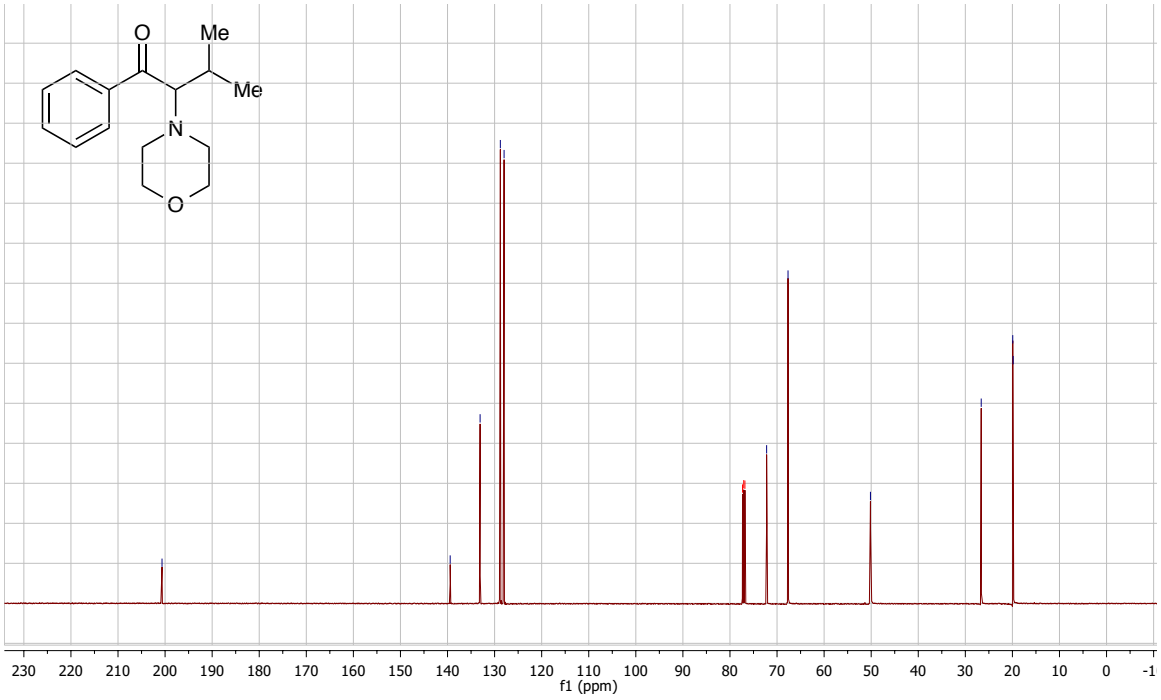
Me
Me
N
O
1.97
0.97
1.96
1.00
1.91
1.98
3.97
1.02
2.97
3.04
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)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Me
Me
N
O
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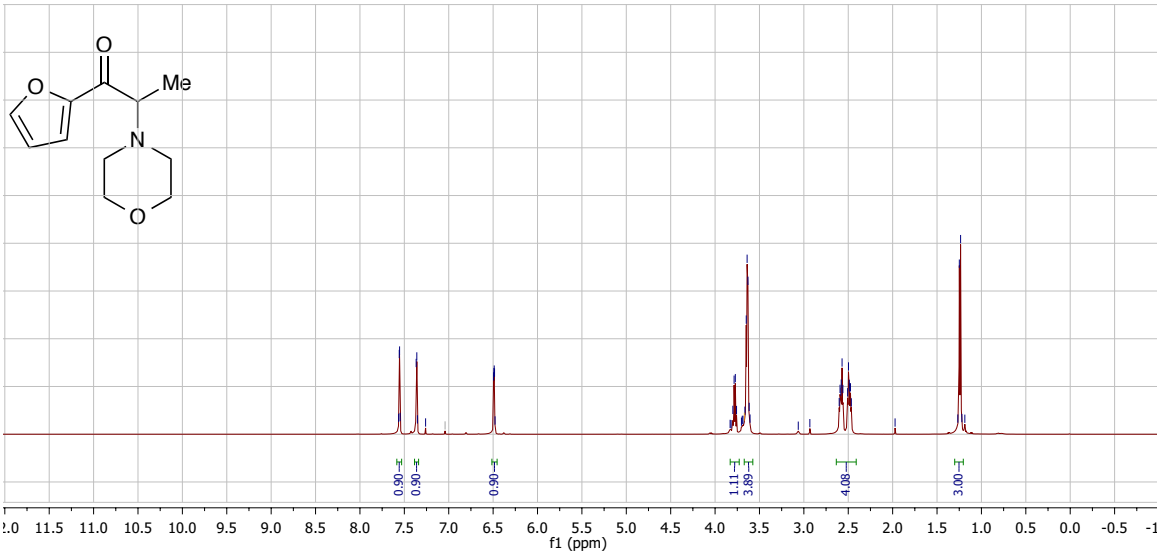
f1 (ppm)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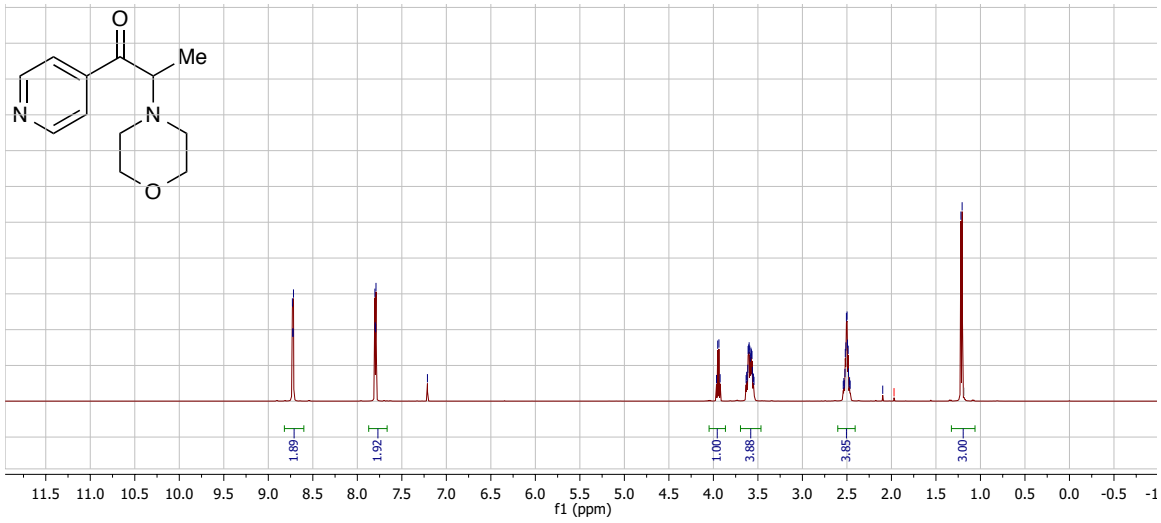
3.00
f1 (ppm)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N
O
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3.85
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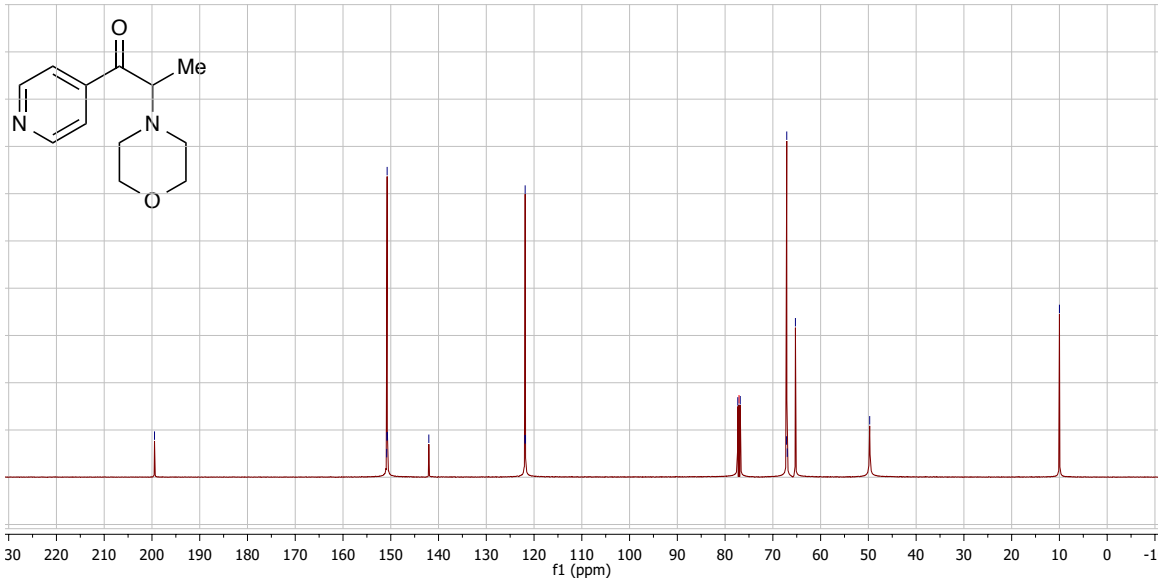
f1 (ppm)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N
N
O
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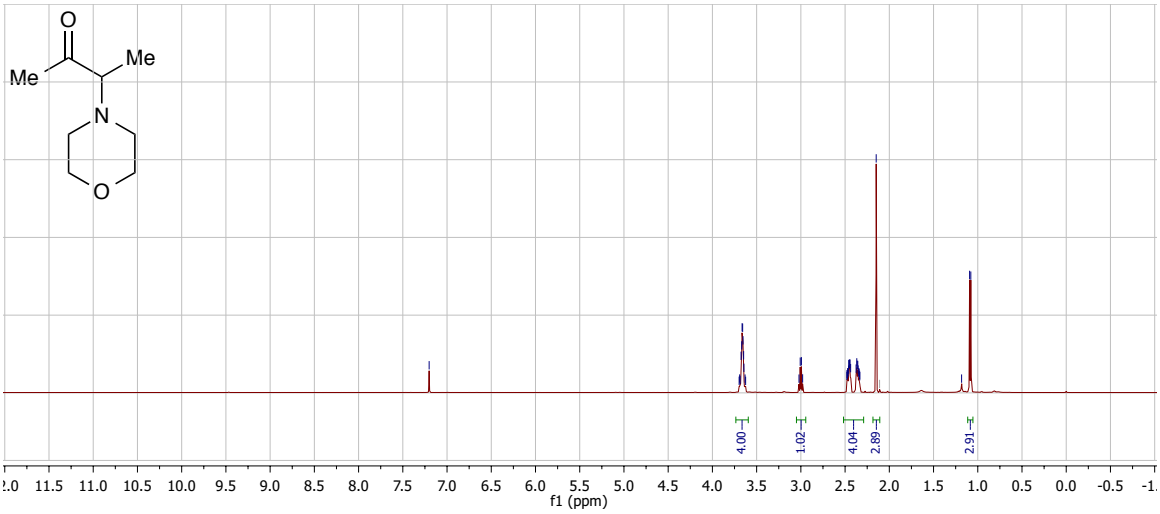
f1 (ppm)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Me
N
O
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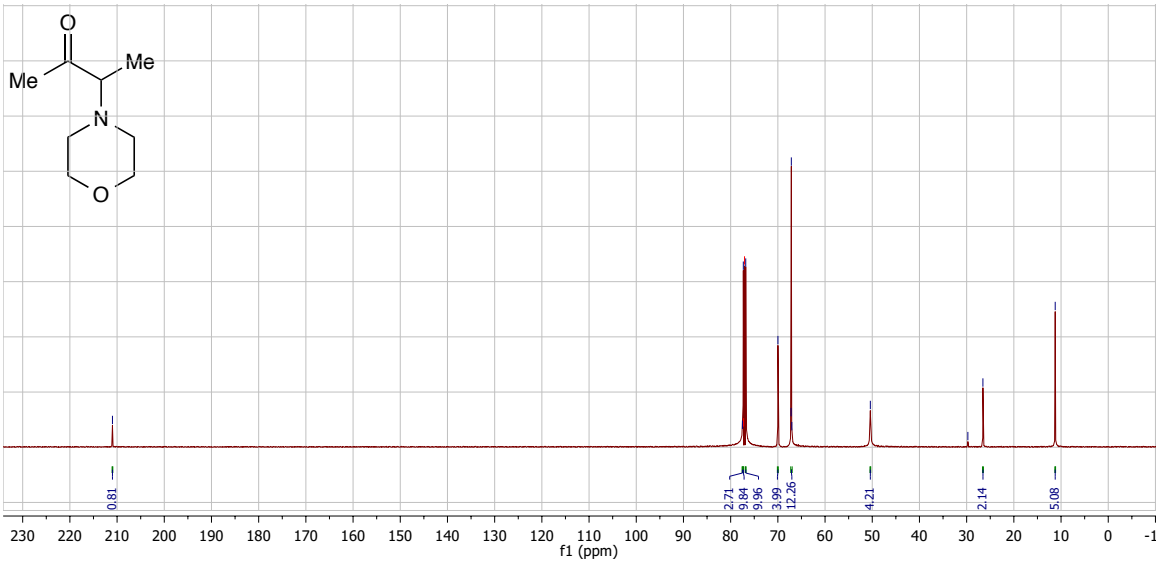
4.04
2.89
2.91
f1 (ppm)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Me
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4.21
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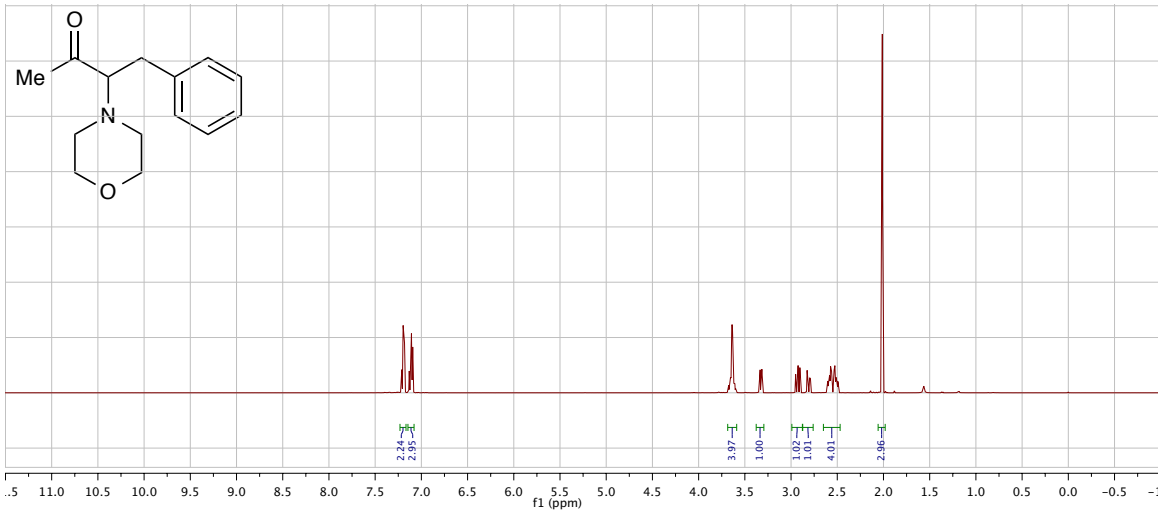
5.08
f1 (ppm)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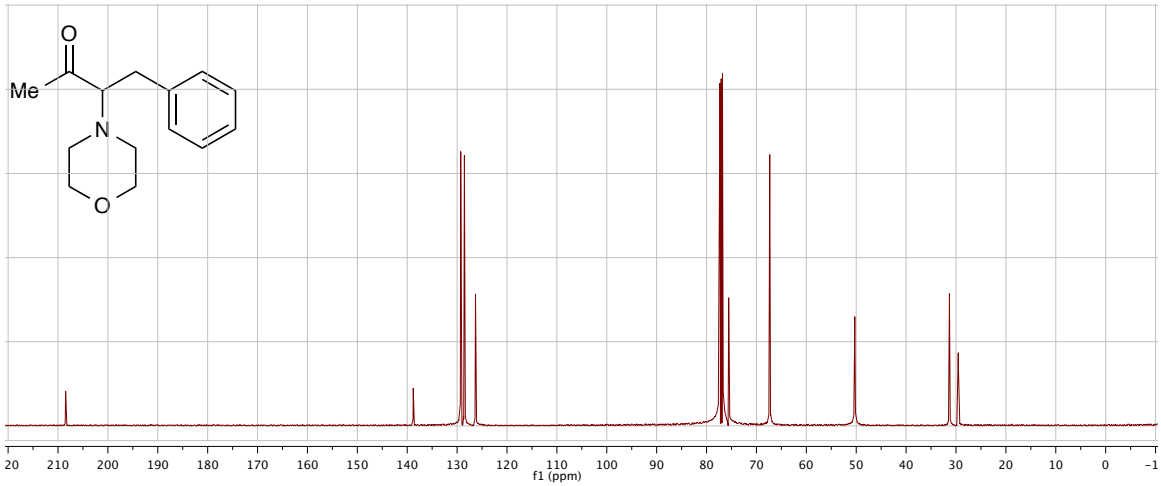
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N
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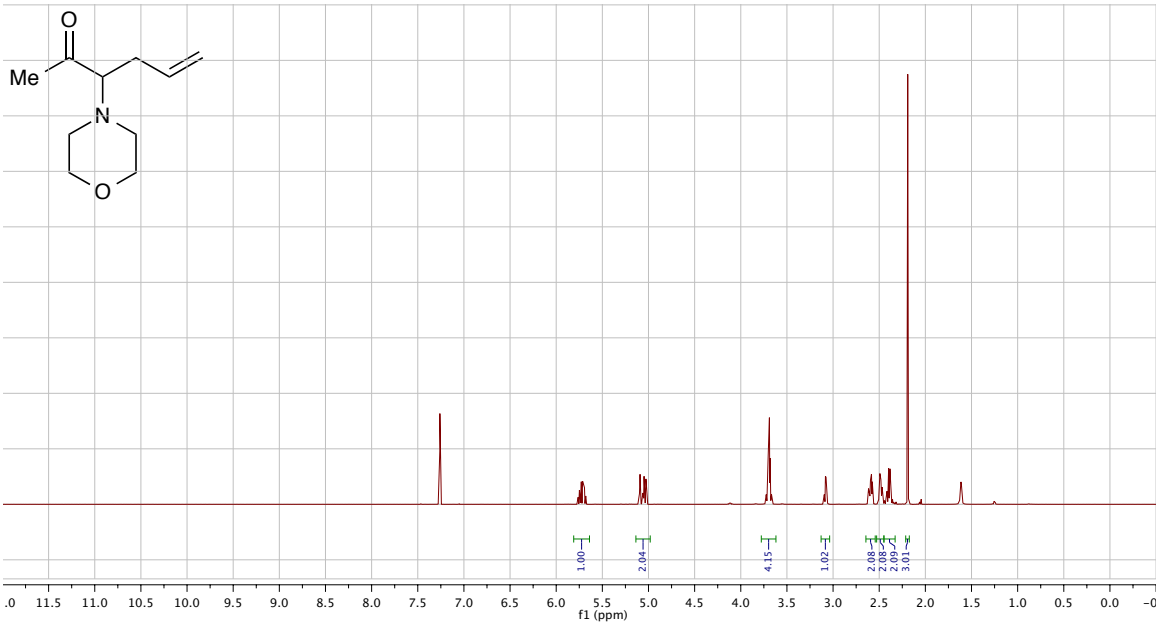
f1 (ppm)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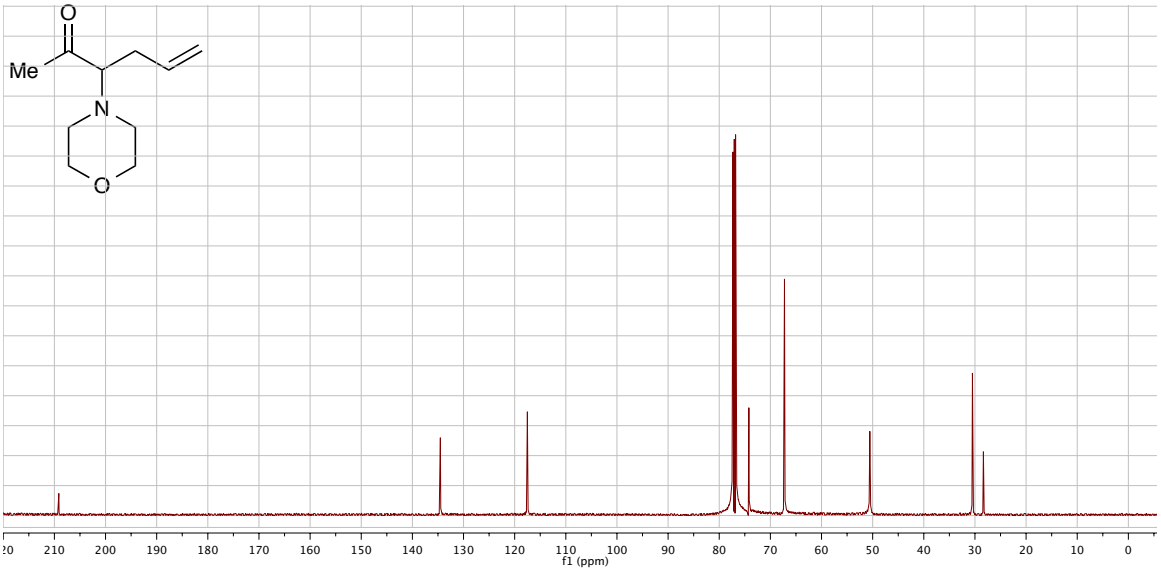
3.01
f1 (ppm)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N
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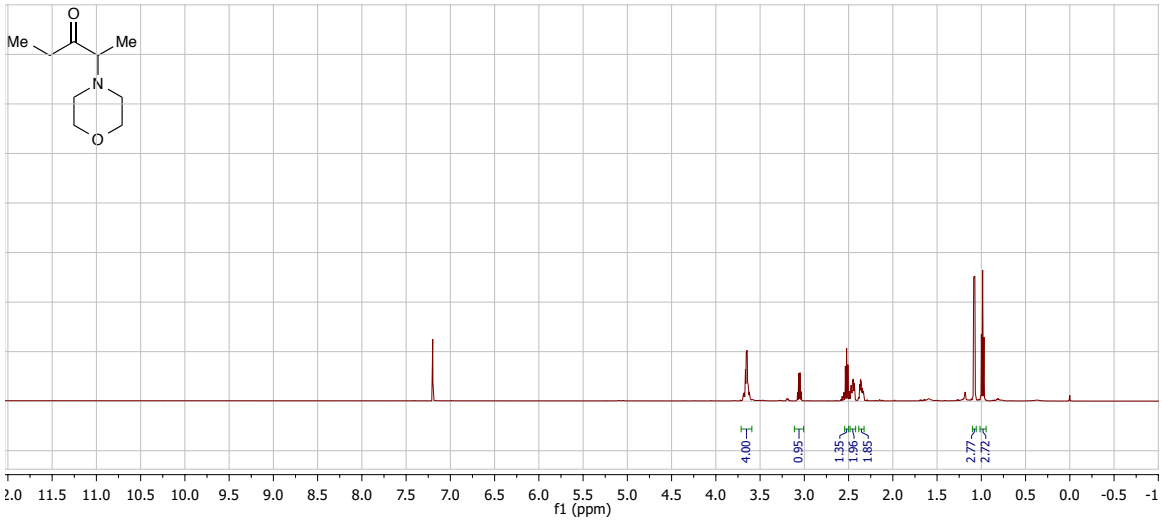
f1 (ppm)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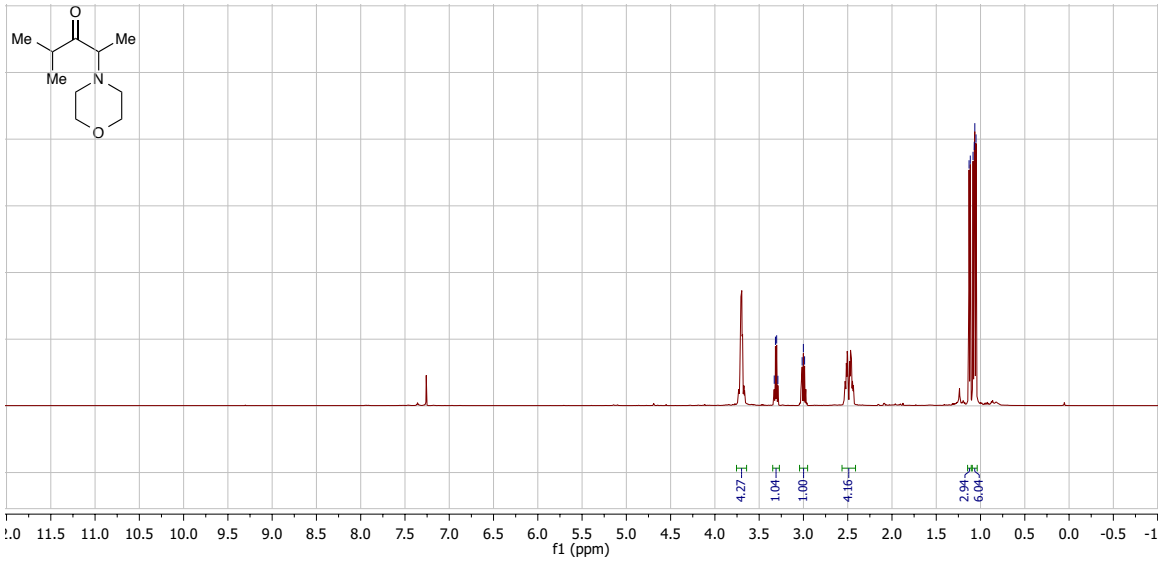
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Me
Me
N
O
O
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1.00
4.16
2.94
6.04
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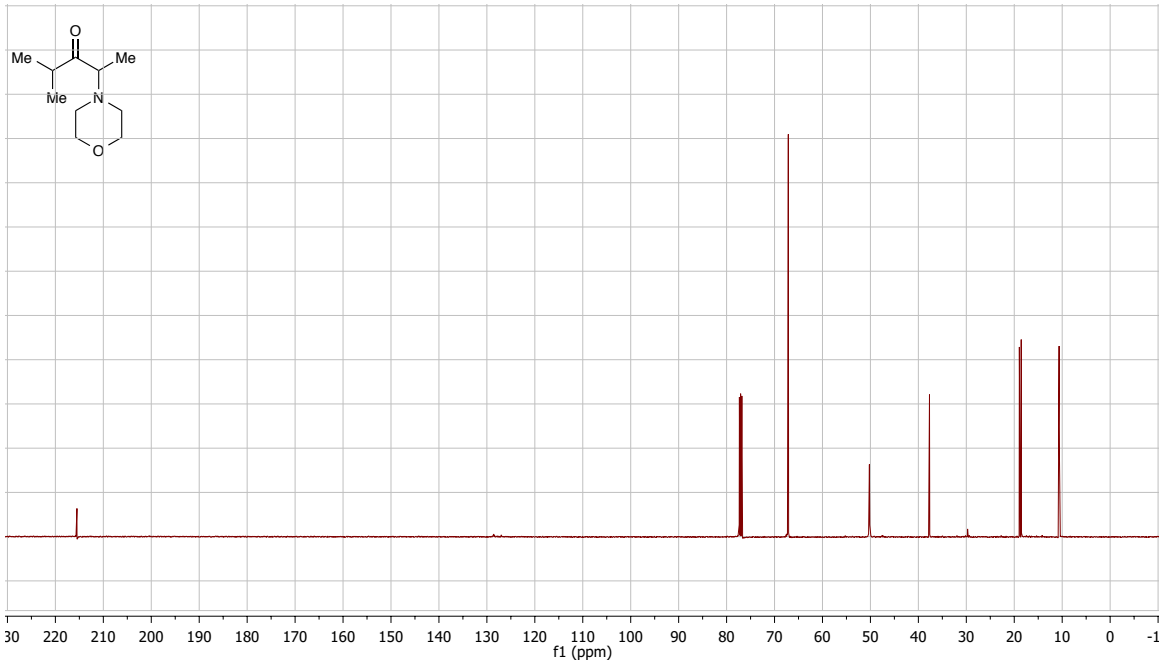
f1 (ppm)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Me
Me
N
O
O
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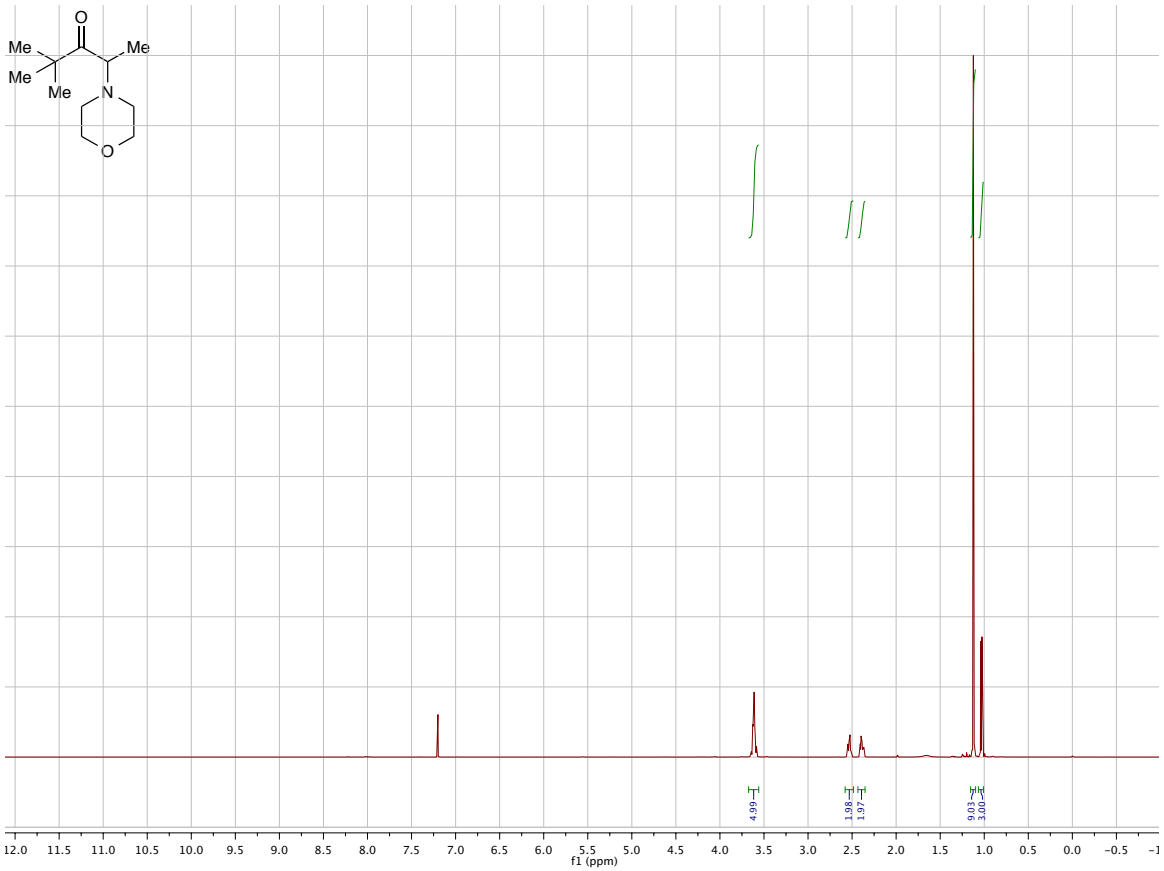
f1 (ppm)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Me
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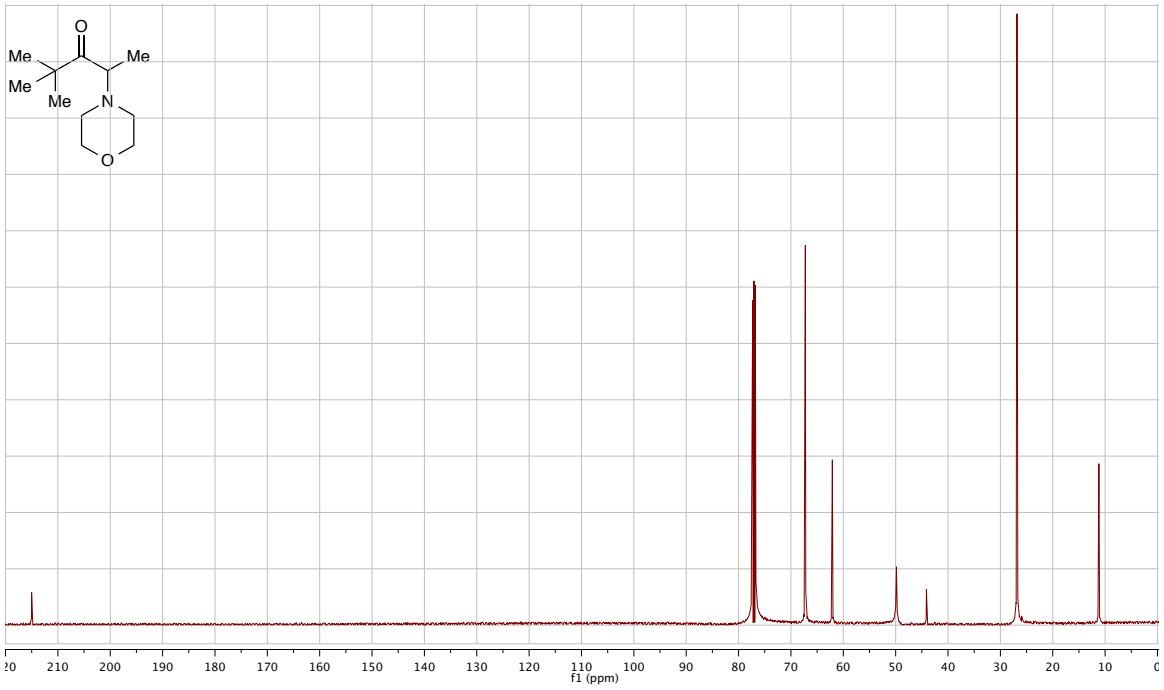
1.97
9.03
3.00
f1 (ppm)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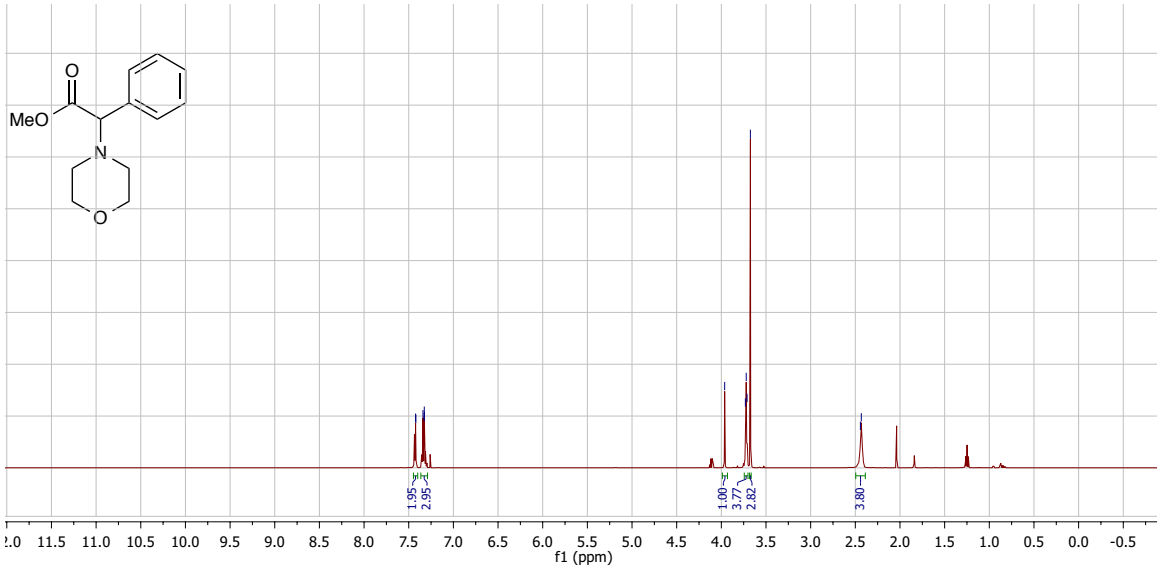
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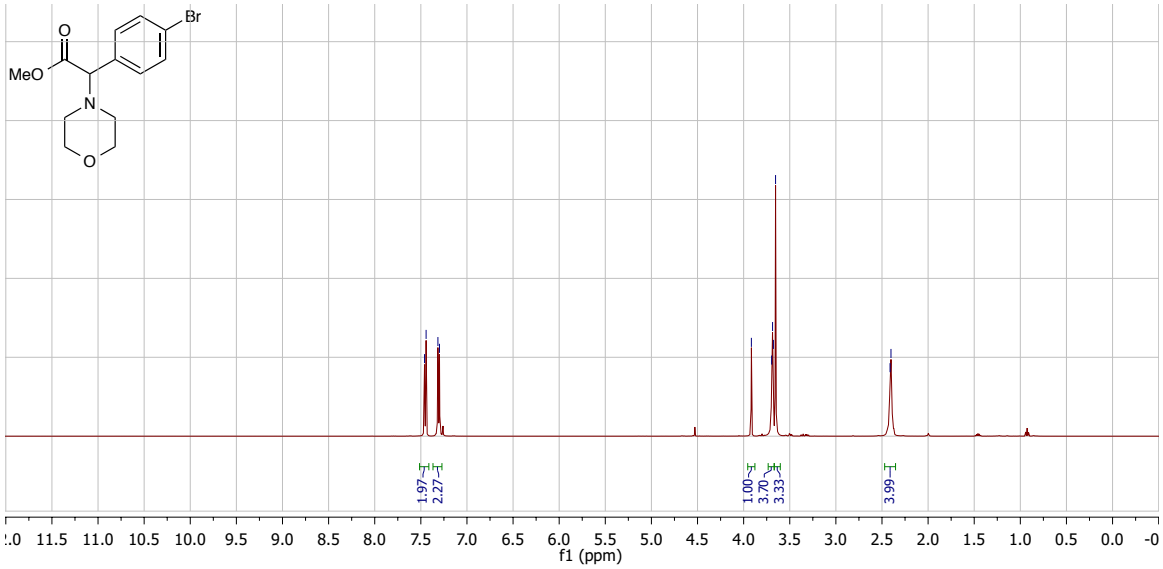
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O
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3.70
3.33
3.99
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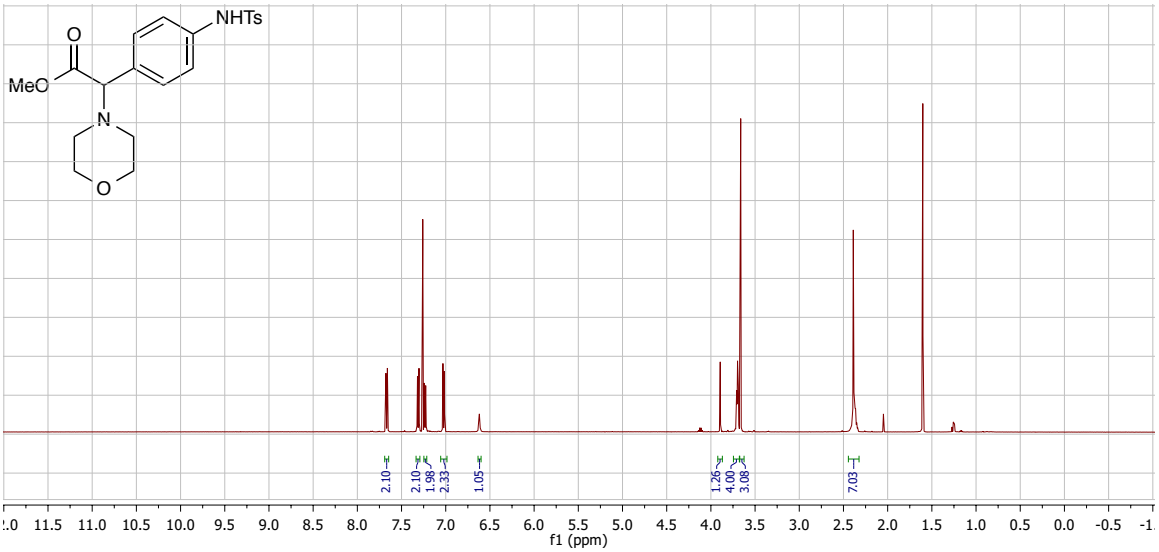
f1 (ppm)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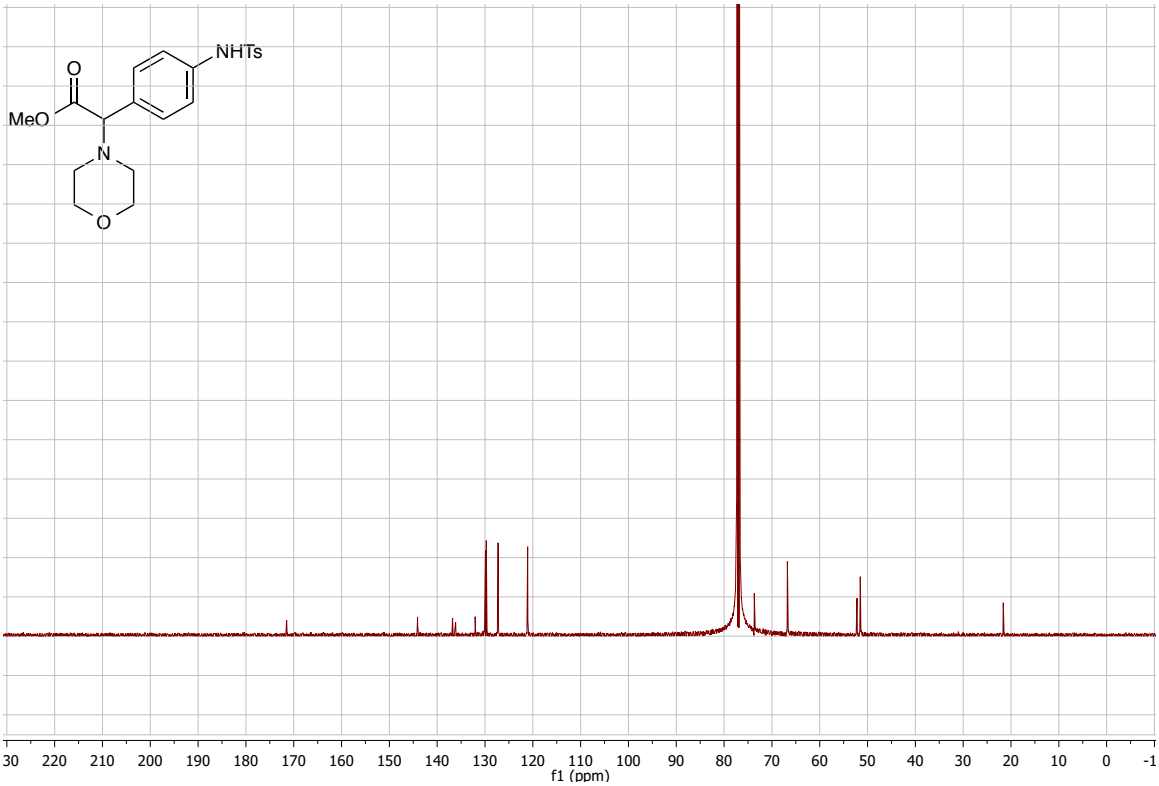
3.08
7.03
f1 (ppm)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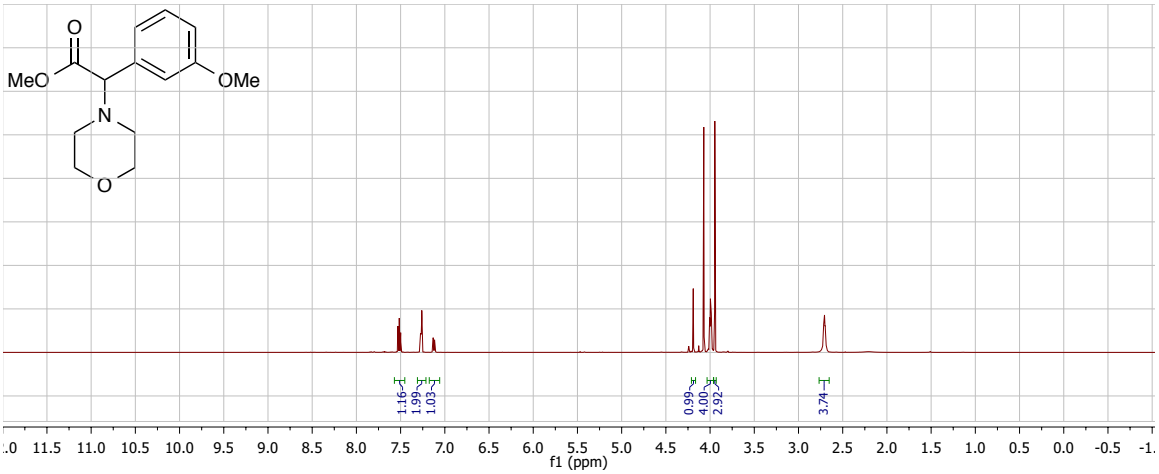
MeO
N
O
f1 (ppm)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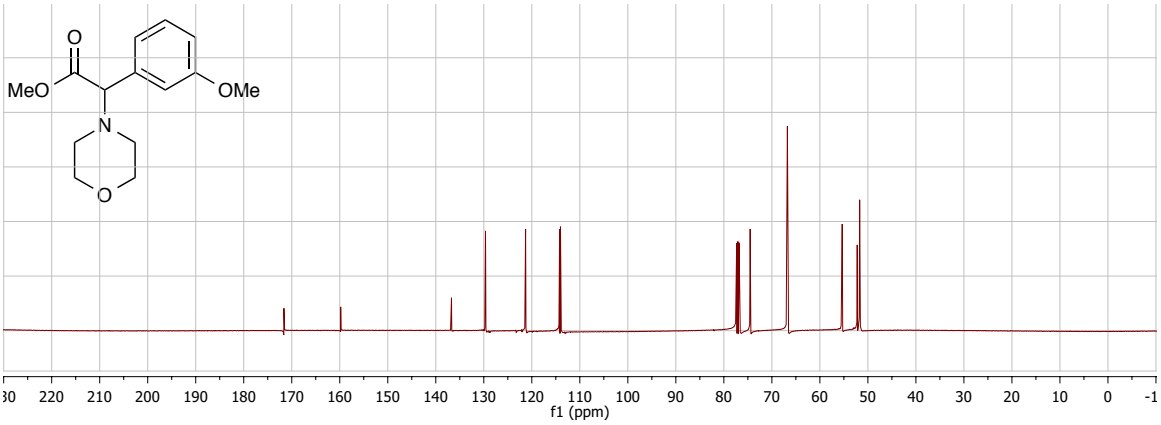
O
MeO
OMe
N
O
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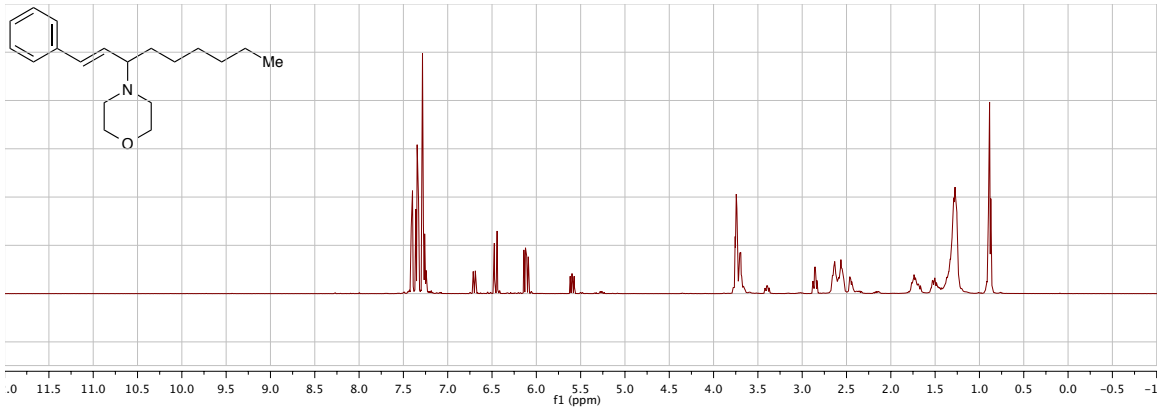
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N
O
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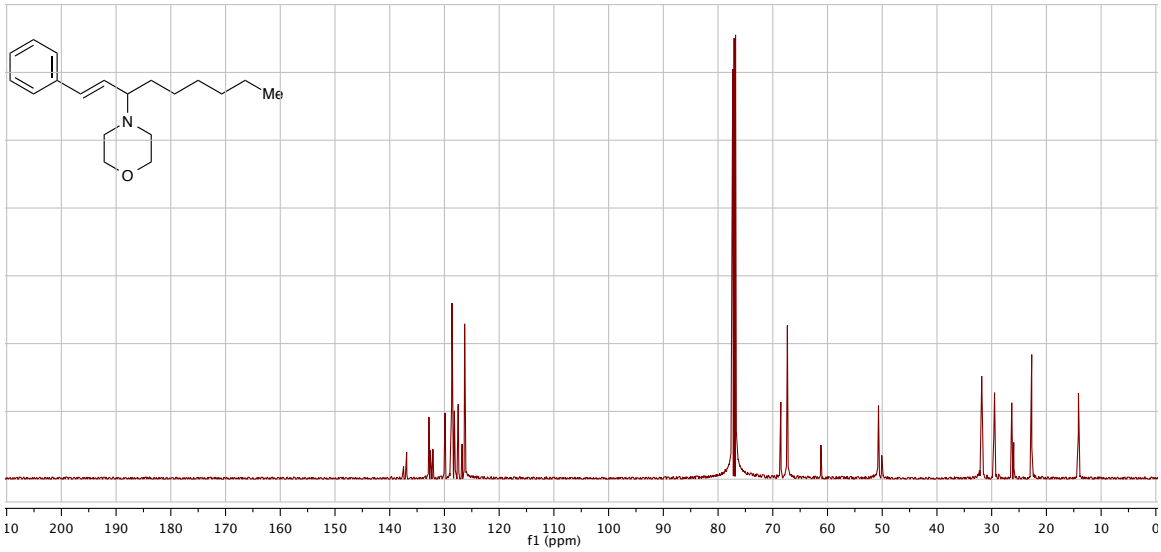
f1 (ppm)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O
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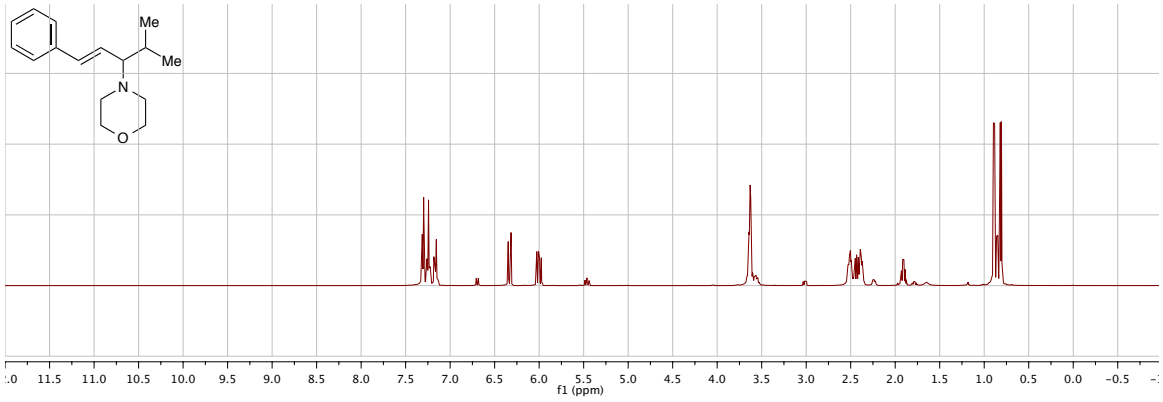
f1 (ppm)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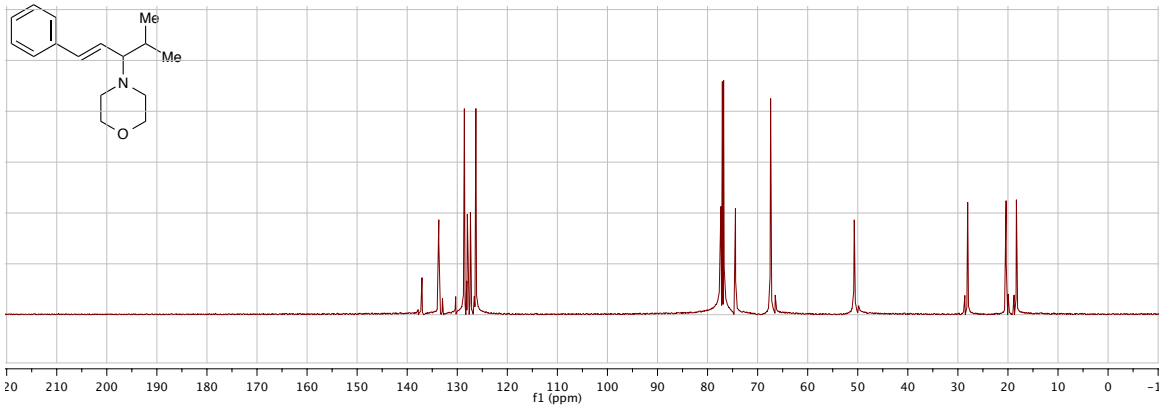
Me
N
O
f1 (ppm)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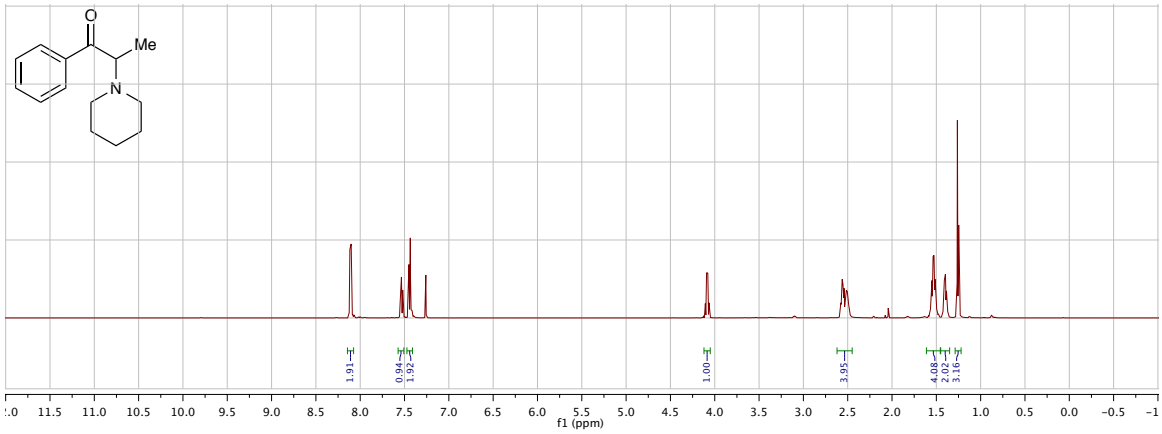
Me
N
O
f1 (ppm)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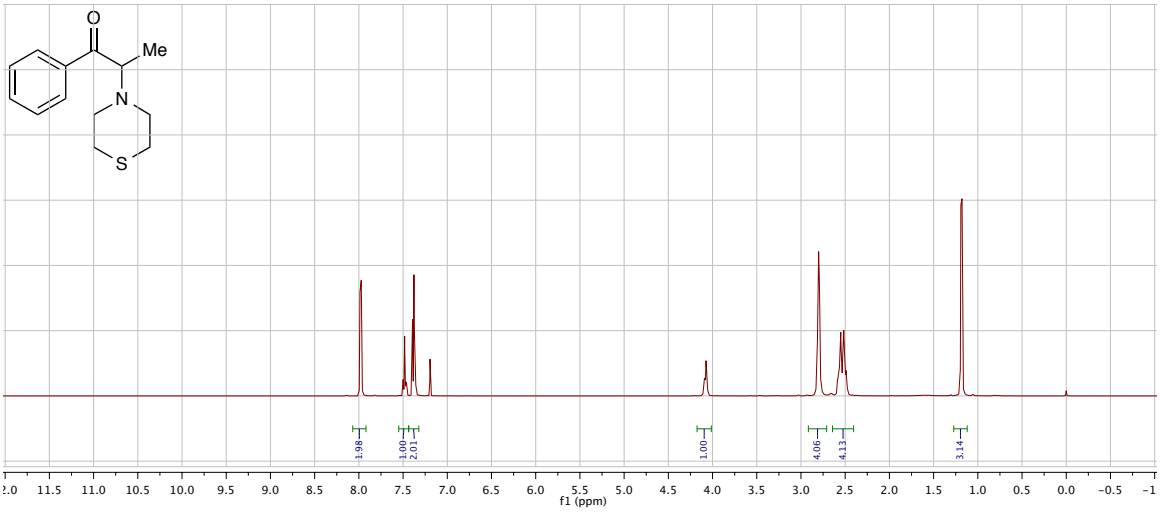
3.16
f1 (ppm)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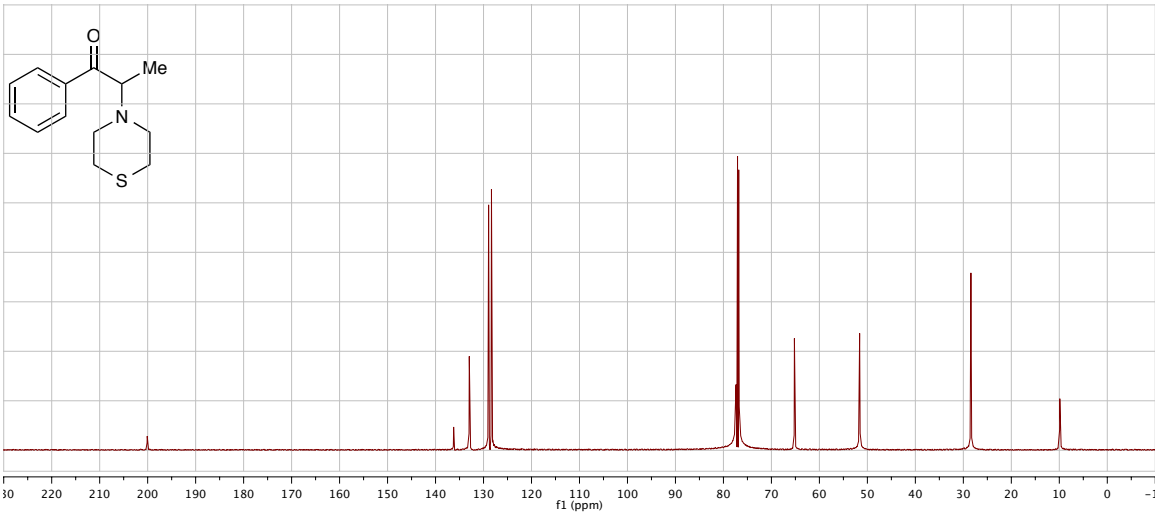
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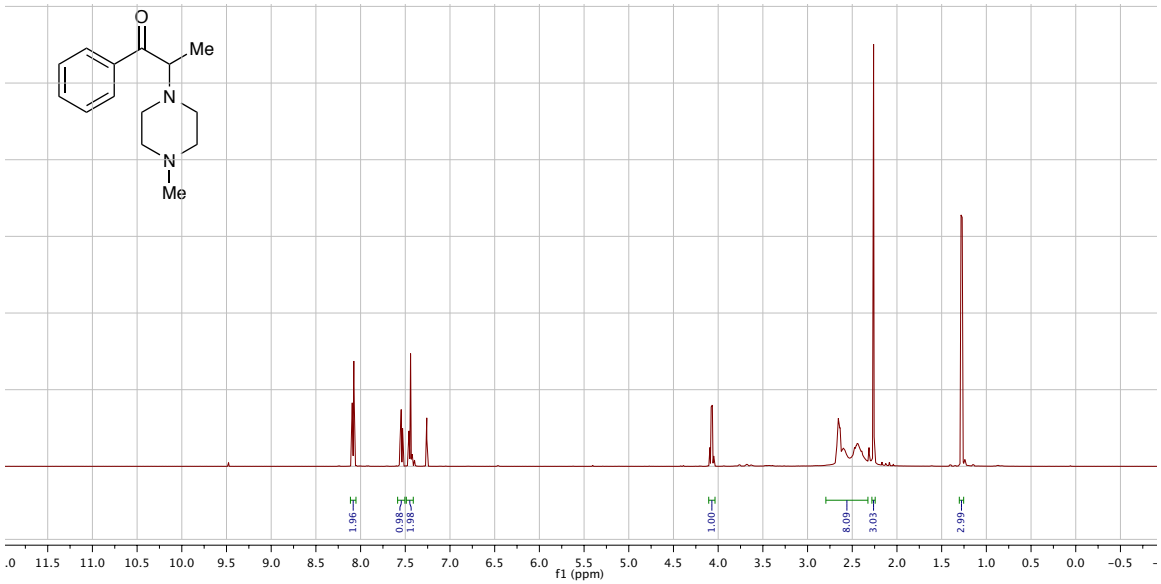
Me
N
S
f1 (ppm)


O
Me
N
N
Me
1.96
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1.98
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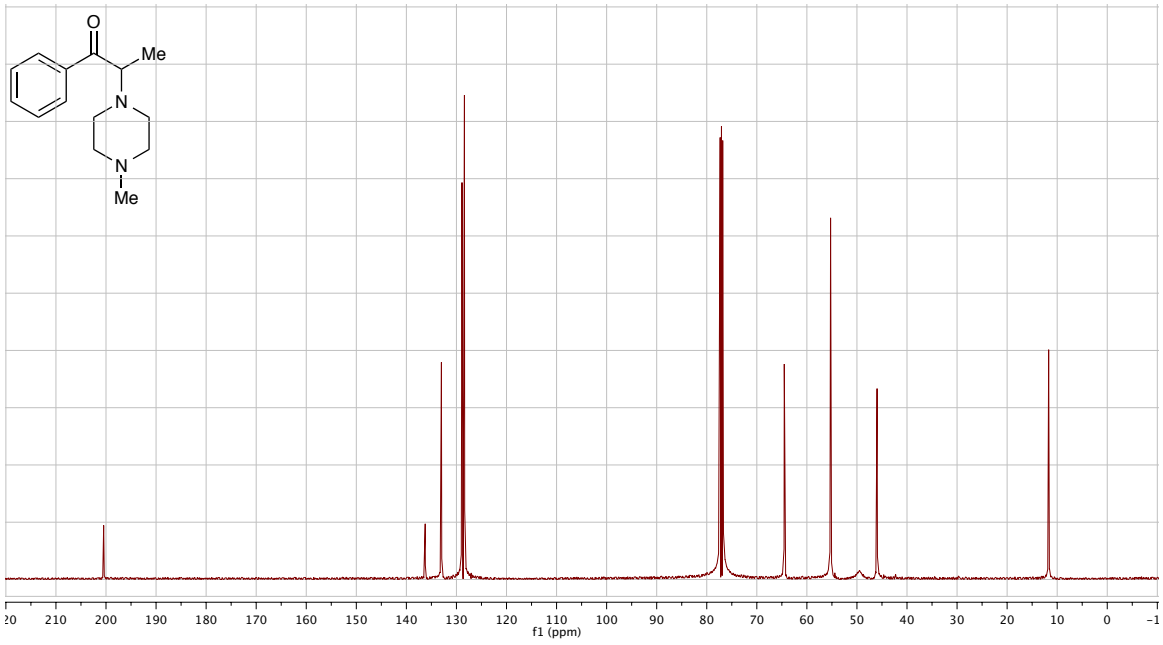
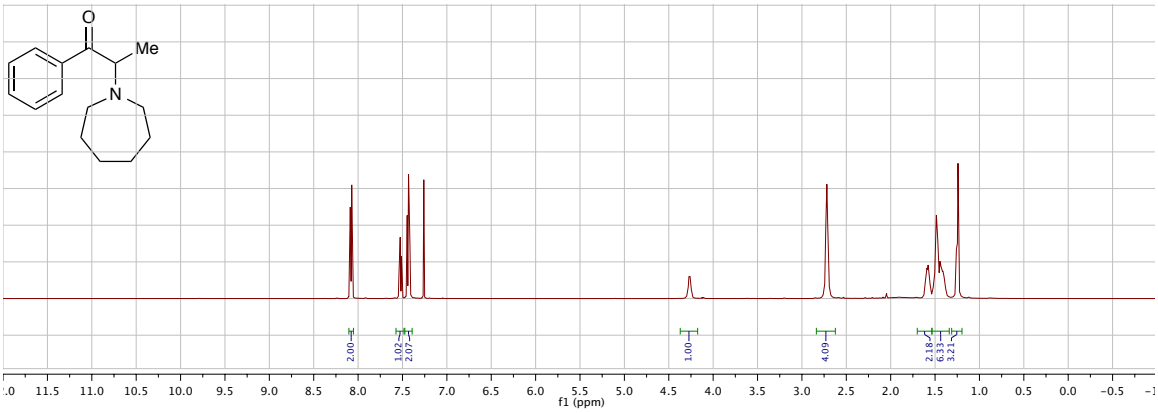
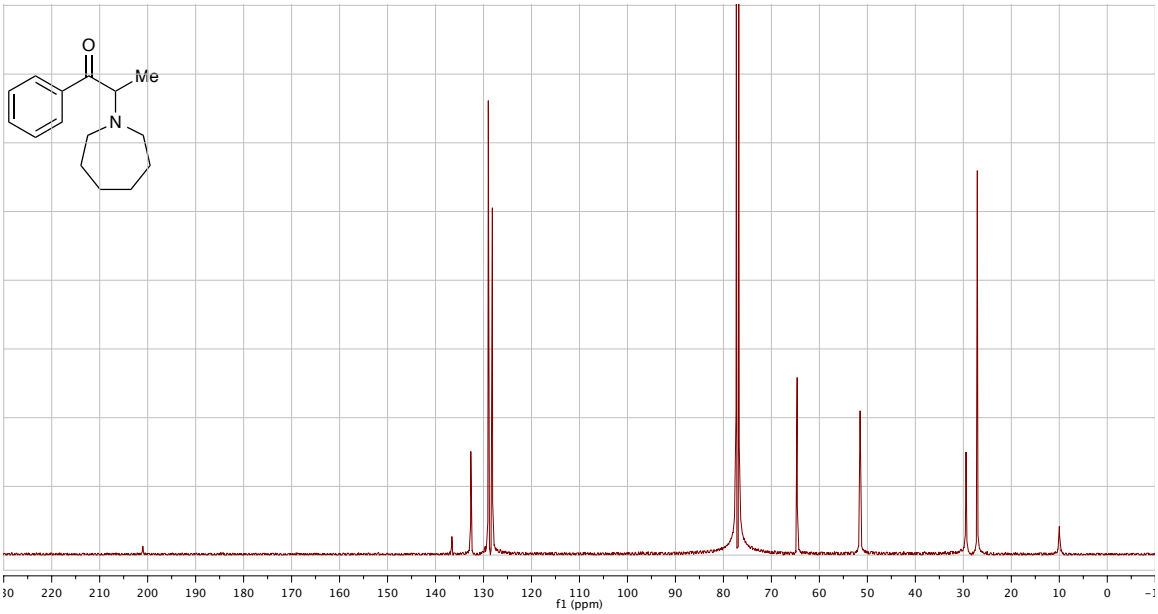
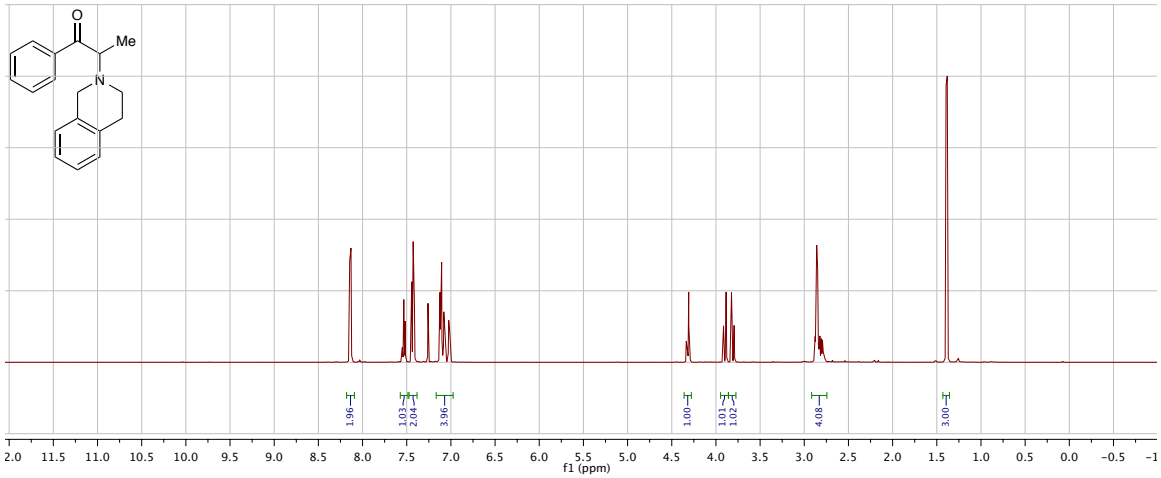
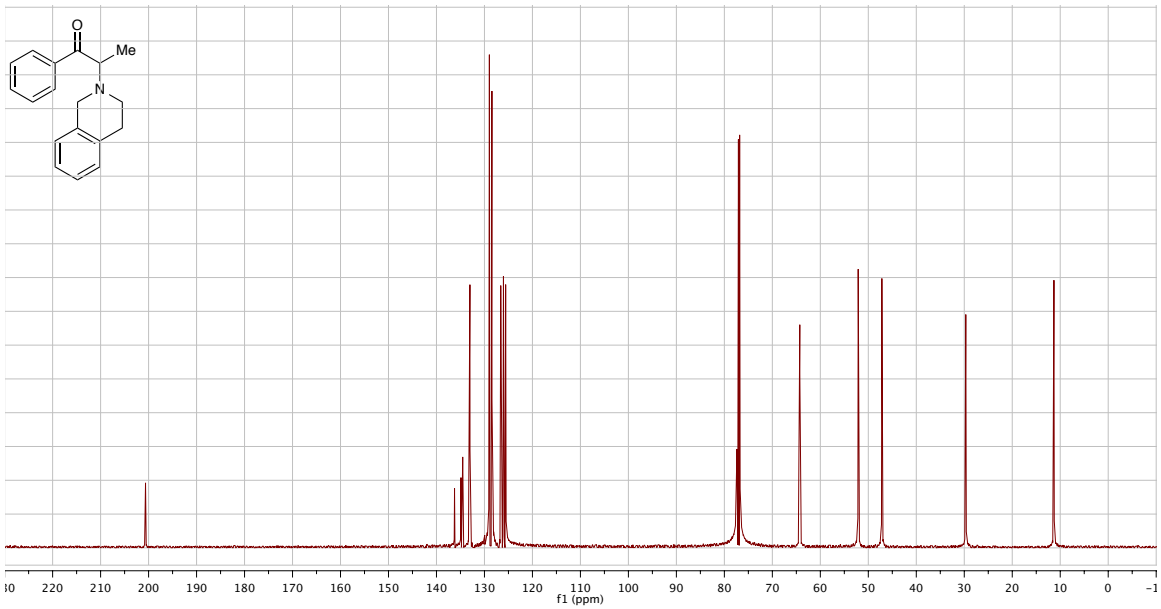
8.09
3.03
2.99
f1 (ppm)

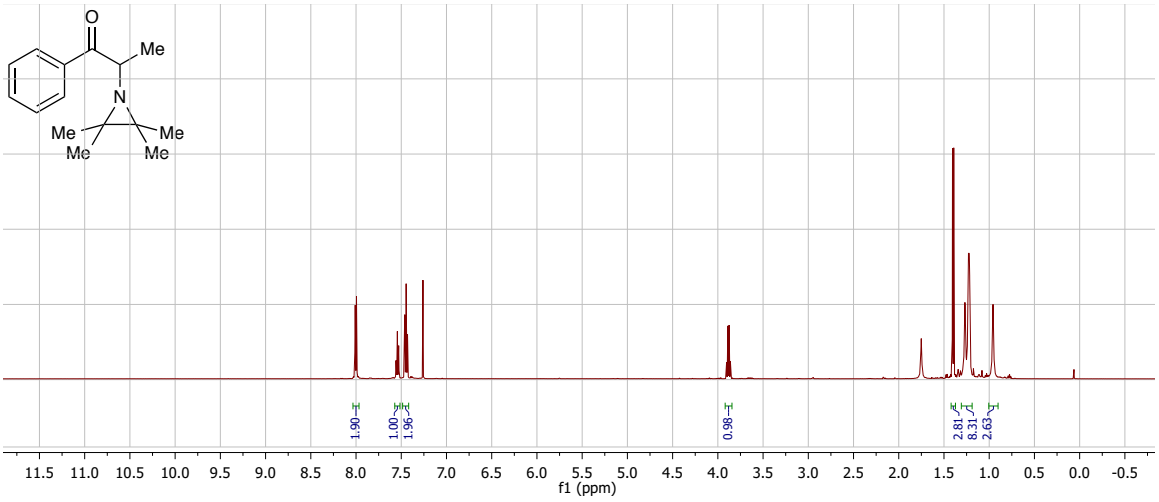

O
Me
N
N
Me
f1 (ppm)

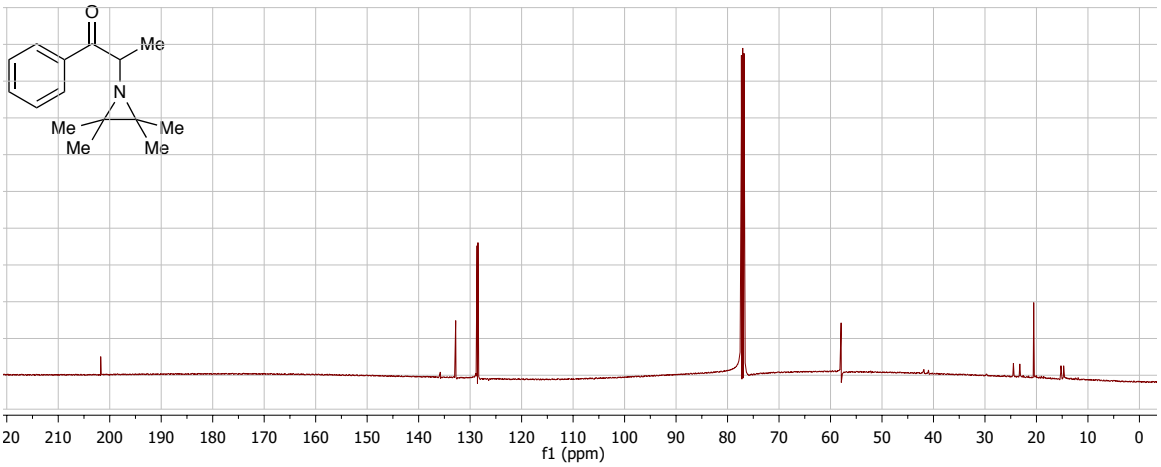

O
Me
N
2.00
1.02
2.07
1.00
4.09
2.18
6.33
3.21
f1 (ppm)

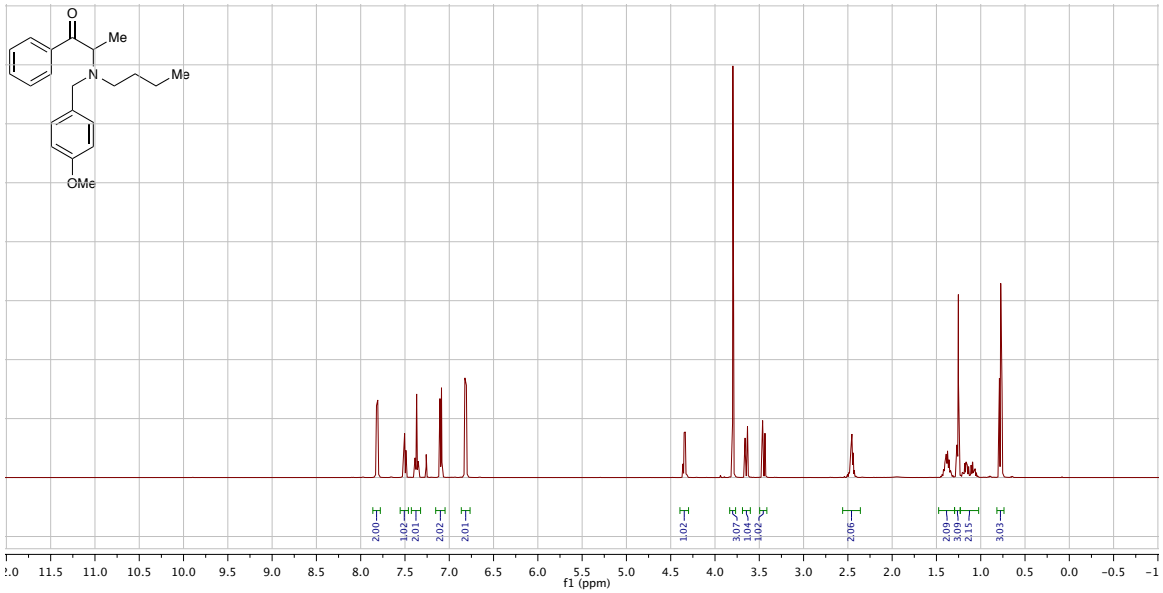

O
Me
N
f1 (ppm)

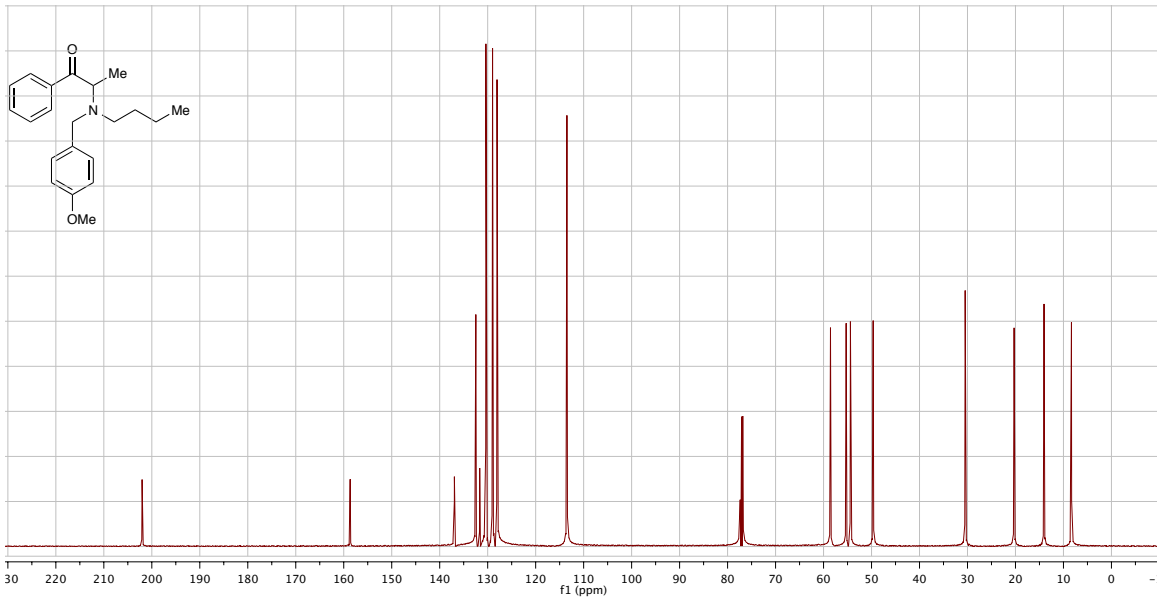

O
Me
N
1.96
1.03
2.04
3.96
1.00
1.01
1.02
4.08
3.00
f1 (ppm)

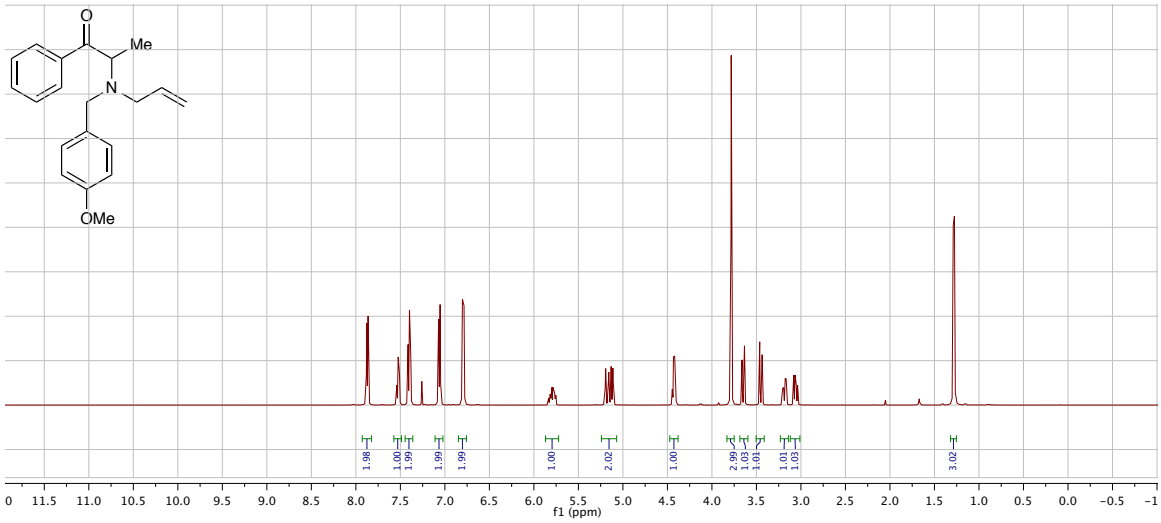

O
Me
N
f1 (ppm)

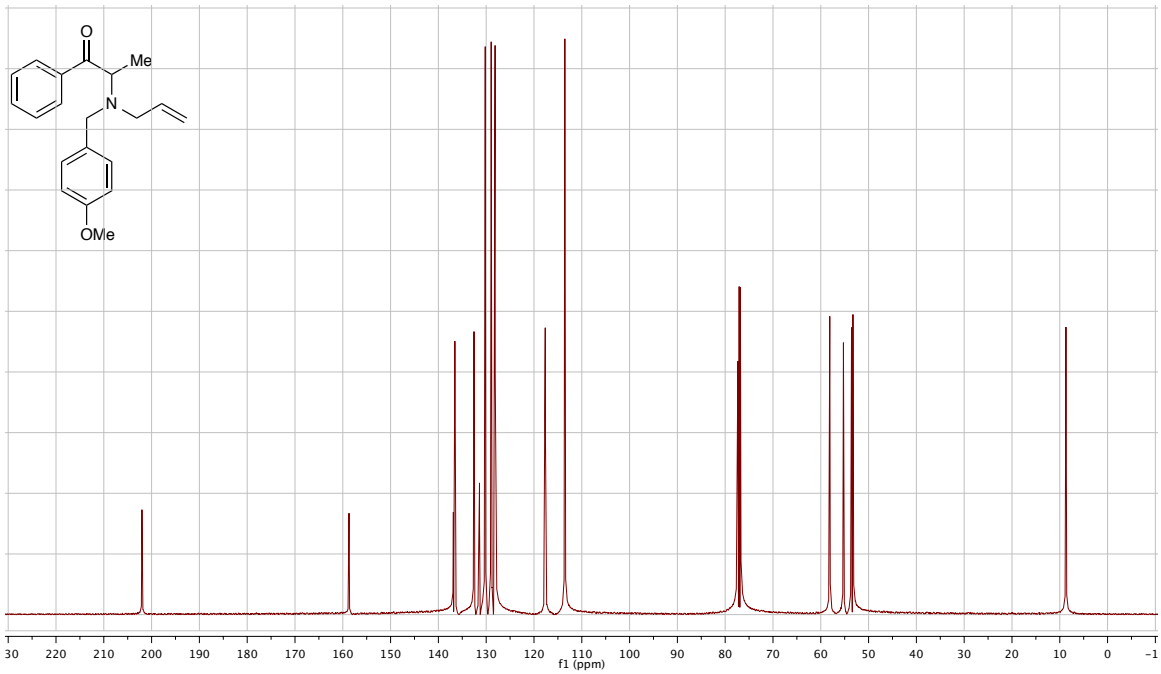

O
Me
N
Me
Me
Me
Me
1.90
1.00
1.96
0.98
2.81
8.31
2.63
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

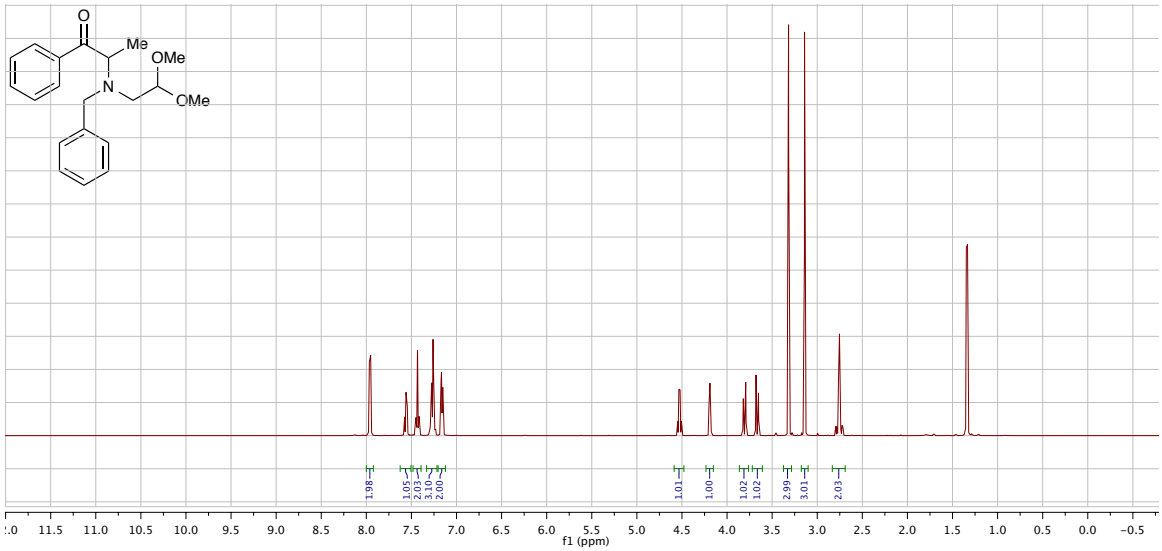

O
Me
N
Me
Me
Me
Me
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

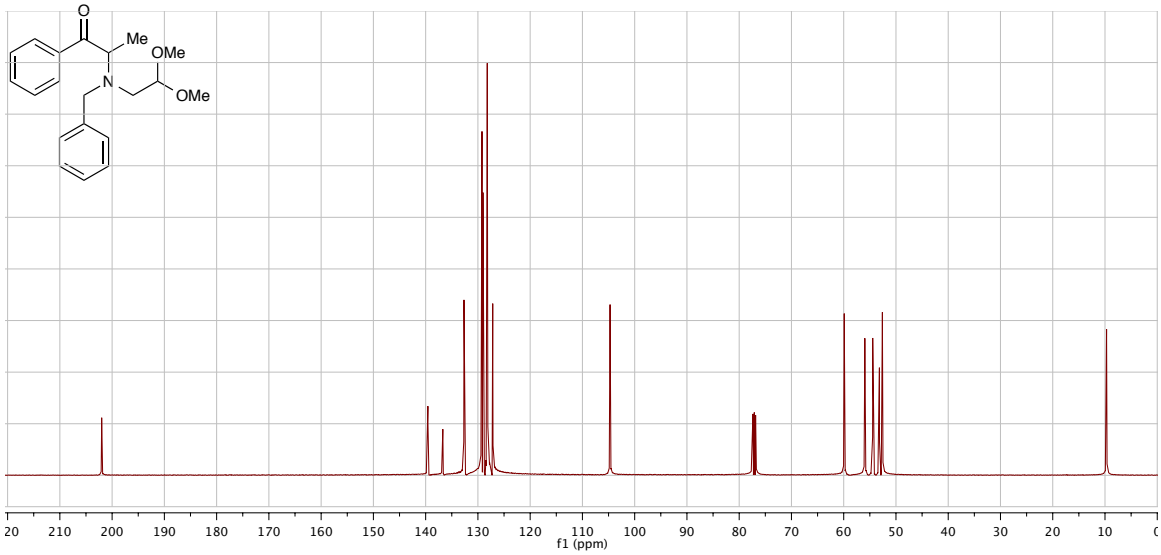

O
Me
N
Me
OMe
2.00
1.02
2.01
2.02
2.01
1.02
3.07
1.04
1.04
2.06
2.09
3.09
2.15
3.03
f1 (ppm)

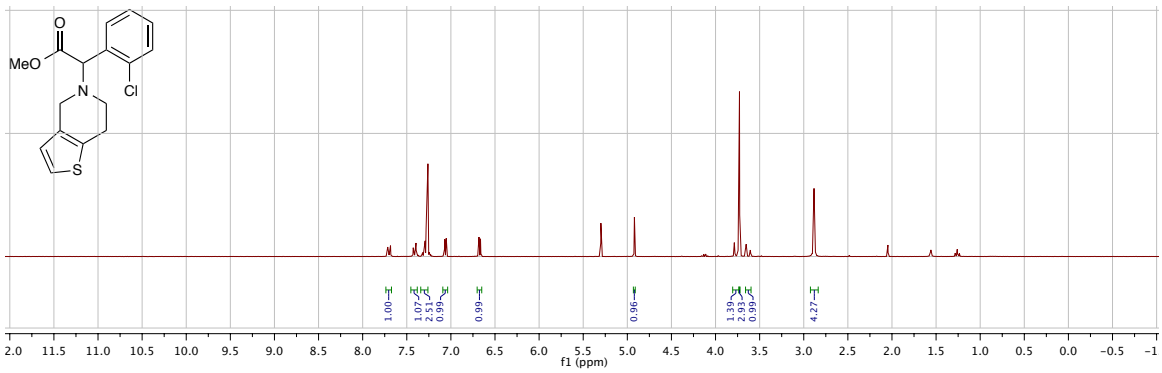

O
Me
N
Me
OMe
f1 (ppm)

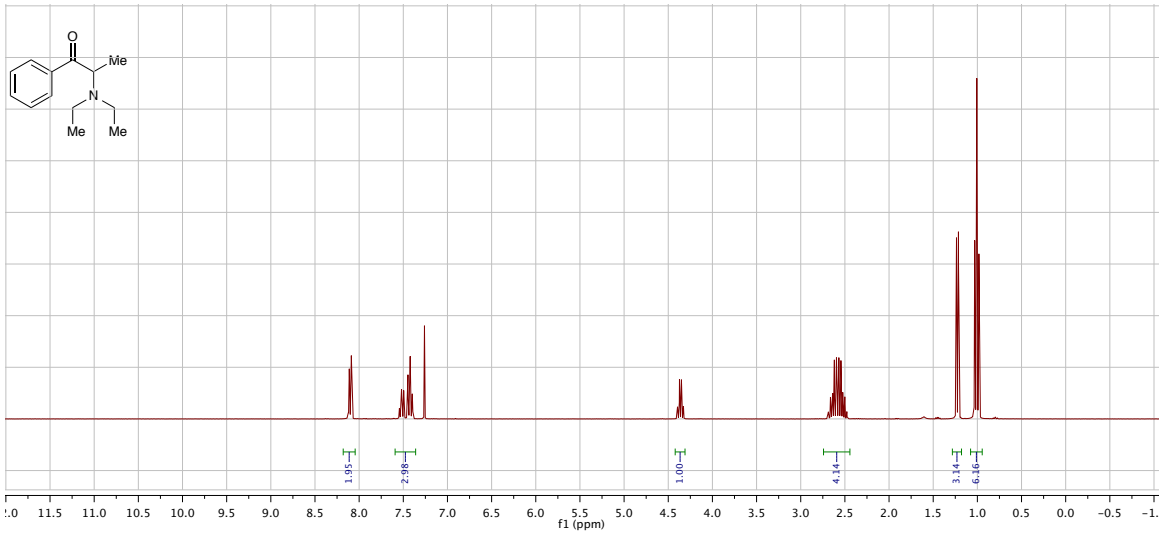

O
Me
N
OMe
1.98
1.00
1.99
1.99
1.99
1.00
2.02
1.00
2.99
3.03
1.04
1.01
1.03
3.02
f1 (ppm)


O
Me
N
OMe
f1 (ppm)


O
Me
OMe
N
OMe
1.98
1.05
2.03
3.10
2.00
1.01
1.00
1.02
1.02
2.99
3.01
2.03
f1 (ppm)


O
Me
OMe
N
OMe
f1 (ppm)


O
MeO
N
Cl
S
1.00
1.07
2.51
0.99
0.99
0.96
1.39
2.93
0.99
4.27
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1
f1 (ppm)


O
Me
N
Me
Me
1.95
2.98
1.00
4.14
3.14
6.46
f1 (ppm)