N-Heterocyclic Carbene-Catalyzed Conjugate Additions of Alcohols

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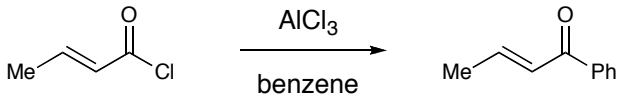
Supporting Information

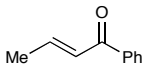
General Information

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring. Toluene, dichloromethane, and benzene were purified by passage through a bed of activated alumina.[1] Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[2] Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and *p*-anisaldehyde stain or potassium permangenate stain followed by heating. Infrared spectra were recorded on a Bruker Tensor 37 FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Varian Inova 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C-NMR spectra were recorded on a Varian Inova 500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra data were obtained on a Hewlett-Packard/Agilent 5972-A GC-MSD system with electron impact (EI) ionization source and Agilent 6210 TOF LC/MS (ESI).

Procedure for the Synthesis of 1



To a flame-dried, one-neck, 100-mL round bottom flask equipped with magnetic stirring bar, rubber septum, and N_2 inlet was added $AlCl_3$ (5.5 g, 41.1 mmol). Benzene (20 mL, 1.6 M) was added to the solid through a syringe and stirred vigorously. Crotonyl chloride[3] (3.1 mL, 32.1 mmol) was added to the solution through a syringe in a dropwise fashion over 10 min. The reaction stirred under a N_2 atmosphere. After 20 min, the solution was poured into an 500-mL Erlenmeyer flask, equipped with magnetic stirring bar, containing a solution of 100 mL ice and 50 mL 2 M HCl. The resulting mixture was poured into a separatory funnel and extracted with two 50-mL portions of Et_2O. The organic phase was washed with one 30-mL portion of 4 M NaOH. The organic phase was dried over $MgSO_4$, filtered and concentrated by rotary evaporator. The unpurified mixture was purified by distillation (84 °C, 0.7 mmHg) to afford the resulting enone (2.53 g, 54% yield) as a clear, colorless oil.



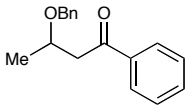
(*E*)-1-phenylbut-2-en-1-one: Analytical data for **1**: IR (film) 3060, 3031, 2972, 2939, 1670, 1624, 1296, 1220 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.92 (m, 2H), 7.57-7.54 (m, 1H),

1. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometal.* **1996**, *15*, 1518-1520.
2. Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals;* 3rd Ed., Pergamon Press, Oxford. 1988.
3. Freshly distilled over CaH_2.

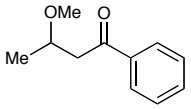
7.48-7.45 (m, 2H), 7.08 (dq, *J* = 15.3, 6.9 Hz, 1H), 6.91 (dq, *J* = 15.3, 1.6 Hz, 1H), 2.00 (dd, *J* = 6.9, 1.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 145.1, 137.9, 132.6, 128.5 (2x), 127.5, 18.6; LRMS (EI): Mass calcd for $C_{10}H_{10}O$ $[M]^+$, 146. Found $[M]^+$, 146.

General Procedure for the NHC-Catalyzed Conjugate Addition of Alcohols

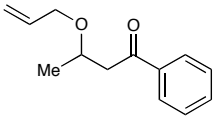
To an oven-dried 2-dram vial equipped with magnetic stirring bar was added azolium salt **A** (7 mg, 0.02 mmol) and LiCl (17 mg, 0.4 mmol) under inert atmosphere in a dry-box. The vial was sealed with a screw cap which was equipped with a teflon septum. Under N_2 atmosphere, THF (0.40 mL, 1 M) was added. The reaction was cooled to –78 °C in a CO_2/acetone bath and *n*-BuLi (8 μL, 0.02 mmol, 2.49 M in hexanes) was added through a syringe. The reaction was allowed to warm to 20 °C by removing the vial from the dry ice/acetone bath. After 5 min, the solvent was removed under vacuum and the vial was back-filled with N_2. A mixture of ketone (0.4 mmol), alcohol, and toluene (0.40 mL, 1 M) was added to the vial through a cannula. The reaction stirred under N_2 atmosphere at 20 °C until the consumption of the ketone was observed. Upon completion of the reaction, the mixture was diluted with EtOAc and filtered through a small pad of SiO_2. The material was concentrated and the residue was purified by flash column chromatography with 10% EtOAc in Hexanes unless stated otherwise to afford the corresponding β-alkoxy ketone.



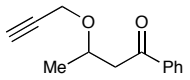
3-(benzyloxy)-1-phenylbutan-1-one (2): Prepared according to general procedure using (*E*)-1-phenylbut-2-en-1-one (58 mg, 0.4 mmol) and benzyl alcohol (124 μL, 1.2 mmol) to afford 91 mg (89%) of **2** as a yellow oil after 12 h. Analytical data for **2**: IR (film) 3086, 3030, 2971, 2871, 1685, 1450, 1371, 1211 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.58-7.55 (m, 1H), 7.48-7.45 (m, 2H), 7.30-7.25 (m, 5H), 4.59 (d, *J* = 11.5, Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.23 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 3.42 (dd, *J* = 16.1, 6.5 Hz, 1H), 3.00 (dd, *J* = 16.1, 6.1 Hz, 1H), 1.33 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 138.5, 137.2, 133.1, 128.6, 128.3, 128.2, 127.7, 127.5, 72.0, 71.0, 45.9, 20.2; LRMS (ESI): Mass calcd for $C_{17}H_{18}O_2$ $[M+Na]^+$, 277. Found $[M+Na]^+$, 277.



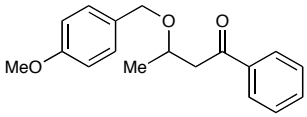
3-methoxy-1-phenylbutan-1-one (3): Prepared according to general procedure using (*E*)-1-phenylbut-2-en-1-one (58 mg, 0.4 mmol) and methanol (81 μL, 2.0 mmol) to afford 56 mg (79%) of **3** as a yellow oil after 12 hr. Analytical data for **3**: IR (film) 3062, 2974, 2932, 2823, 1685, 1449, 1217 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.58-7.55 (m, 1H), 7.48-7.45 (m, 2H), 4.00 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 3.35 (s, 3H), 2.34 (dd, *J* = 16.2, 6.5 Hz, 1H), 2.92 (d, *J* = 16.2, 6.1 Hz, 1H), 1.26 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 137.2, 133.1, 128.6, 128.1, 73.5, 56.5, 45.4, 19.8; LRMS (ESI): Mass calcd for $C_{11}H_{14}O_2$ $[M+H]^+$, 179. Found $[M+H]^+$, 179.



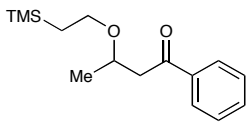
3-(allyloxy)-1-phenylbutan-1-one (4): Prepared according to general using (*E*)-1-phenylbut-2-en-1-one (58 mg, 0.4 mmol) and allyl alcohol (136 μL, 2.0 mmol) to afford 64 mg (78%) of **4** as a light yellow oil after 12 hr. Analytical data for **4**: IR (film) 3064, 2973, 2931, 2870, 1742, 1686, 1449, 1212 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.96 (m, 2H), 7.58-7.55 (m, 1H), 7.48-7.45 (m, 2H), 5.88 (dddd, *J* = 17.2, 10.5, 5.6, 5.6 Hz, 1H), 5.23 (dddd, *J* = 17.2, 1.7, 1.7, 1.7 Hz, 1H), 5.13 (dddd, *J* = 10.4, 1.4, 1.4, 1.4 Hz, 1H), 4.15 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 4.06 (dddd, *J* = 12.6, 5.6, 1.4, 1.4 Hz, 1H), 3.96 (dddd, *J* = 12.6, 5.6, 1.4, 1.4 Hz, 1H), 3.37 (dd, *J* = 16.2, 6.3 Hz, 1H), 2.95 (dd, *J* = 16.2, 6.2 Hz, 1H), 1.28 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 137.2, 135.0, 133.1, 128.5, 128.2, 116.7, 71.7, 69.9, 45.8, 20.2; LRMS (ESI): Mass calcd for $C_{13}H_{16}O_2$ $[M+H]^+$, 205. Found $[M+H]^+$, 205.



1-phenyl-3-(prop-2-ynyloxy)butan-1-one (5): Prepared according to general using (*E*)-1-phenylbut-2-en-1-one (58 mg, 0.4 mmol) and propargyl alcohol (115 μL, 2.0 mmol) to afford 69 mg (85%) of **5** as a clear oil after 12 hr. Analytical data for **5**: IR (film) 3293, 3062, 2973, 2932, 2906, 2858, 2115, 1684, 1597, 1449, 1083 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.58-7.55 (m, 1H), 7.48-7.45 (m, 2H), 4.31 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 4.23 (dd, *J* = 15.7, 2.4 Hz, 1H), 4.17 (dd, *J* = 15.7, 2.4 Hz, 1H), 3.40 (dd, *J* = 16.5, 6.2 Hz, 1H), 2.98 (dd, *J* = 16.5, 6.3 Hz, 1H), 2.39 (dd, *J* = 2.4, 2.4 Hz, 1H), 1.31 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 137.0, 133.2, 128.6, 128.2, 80.1, 74.0, 71.6, 56.2, 45.7, 20.0; LRMS (ESI): Mass calcd for $C_{13}H_{14}O_2$ $[M+Na]^+$, 225. Found $[M+Na]^+$, 225.

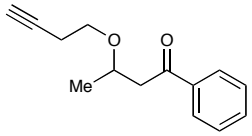


3-(4-methoxybenzyloxy)-1-phenylbutan-1-one (6): Prepared according to general procedure using (*E*)-1-phenylbut-2-en-1-one (58 mg, 0.4 mmol) and *p*-methoxybenzyl alcohol (166 mg, 1.2 mmol) to afford 92 mg (81%) of **6** as a yellow oil after 6 hr. Analytical data for **6**: IR (film) 3062, 3033, 2969, 2933, 2869, 1684, 1514, 1248 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.58-7.55 (m, 1H), 7.47-7.44 (m, 2H), 7.22-7.20 (m, 2H), 6.85-6.83 (m, 2H), 4.53 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 11.1 Hz, 1H), 4.23 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 3.78 (s, 3H), 3.40 (dd, *J* = 16.1, 6.5 Hz, 1H), 2.97 (dd, *J* = 16.1, 6.1 Hz, 1H), 1.31 (d, *J* = 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 159.1, 137.1, 133.1, 130.7, 129.3, 128.6, 113.8, 71.7, 70.7, 55.3, 46.0, 20.3; LRMS (ESI): Mass calcd for $C_{18}H_{20}O_3$ $[M+Na]^+$, 307. Found $[M+Na]^+$, 307.

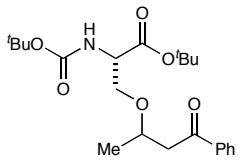


1-phenyl-3-(2-(trimethylsilyl)ethoxy)butan-1-one (7): Prepared according to general procedure using (*E*)-1-phenylbut-2-en-1-one (58 mg, 0.4 mmol) and 2-(trimethylsilyl)ethanol (287 μL, 2.0 mmol) to afford 84 mg (80%) of **7** as a yellow oil after 20 hr. Analytical data for **7**: IR (film)

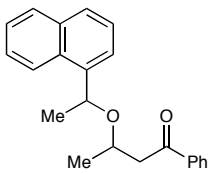
3063, 2954, 2894, 1687, 1449, 1248, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.58-7.55 (m, 1H), 7.48-7.45 (m, 2H), 4.07 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 3.61-3.56 (m, 1H), 3.49-3.43 (m, 1H), 3.33 (dd, *J* = 16.1, 6.2 Hz, 1H), 2.92 (dd, *J* = 16.1, 6.2 Hz, 1H), 1.25 (d, *J* = 6.1 Hz, 3H), 0.87 (d, *J* = 8.2 Hz, 1H), 0.86 (d, *J* = 8.2 Hz, 1H), -0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 137.7, 133.0, 128.5, 128.2, 71.6, 65.9, 45.8, 20.4, 18.4, -1.4; LRMS (ESI): Mass calcd for $C_{15}H_{24}O_2Si$ $[M+Na]^+$, 287. Found $[M+Na]^+$, 287.



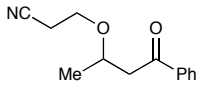
3-(but-3-ynyloxy)-1-phenylbutan-1-one (8): Prepared according to general procedure using (*E*)-1-phenylbut-2-en-1-one (58 mg, 0.4 mmol) and 3-butyn-1-ol (151 μL, 2.0 mmol) to afford 65 mg (75%) of **8** as a yellow oil after 20 h. Analytical data for **8**: IR (film) 3297, 3062, 2972, 2930, 2873, 2120, 1685, 1598, 1273, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.58-7.55 (m, 1H), 7.48-7.45 (m, 2H), 4.16 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 3.66 (ddd, *J* = 9.1, 7.1, 7.1 Hz, 1H), 3.54 (ddd, *J* = 9.1, 7.0, 7.0 Hz, 1H), 3.36 (dd, *J* = 16.3, 6.5 Hz, 1H), 2.93 (dd, *J* = 16.3, 6.0 Hz, 1H), 2.42-2.38 (m, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.28 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 137.2, 133.1, 128.5, 128.2, 81.4, 72.4, 69.4, 67.0, 45.7, 20.2, 20.1; LRMS (ESI): Mass calcd for $C_{14}H_{16}O_2$ $[M+H]^+$, 217. Found $[M+H]^+$, 217.



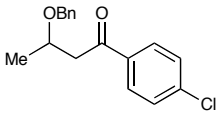
(2*S*)-*tert*-butyl 2-(*tert*-butoxycarbonylamino)-3-(4-oxo-4-phenylbutan-2-yloxy)propanoate (9): Prepared according to general procedure using (*E*)-1-phenylbut-2-en-1-one (58 mg, 0.4 mmol) and (*S*)-*N*-Boc serine t-butyl ester (526 mg, 2.0 mmol) and 1 mL CH_2Cl_2 to afford 132 mg (81%) of **9** as a light yellow oil containing a diastereomeric mixture in the ration of 1.1:1 after 48 hr. Methylene chloride was used in place of toluene due to insolubility of the amino acid in toluene. Analytical data for **9**: IR (film) 3445, 3365, 3062, 2977, 2932, 2877, 1717, 1687, 1598, 1499, 1450, 1368 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96-7.92 (m, 4H), 7.59-7.55 (m, 2H), 7.49-7.44 (m, 4H), 5.29 (d, *J* = 8.3 Hz, 1H), 5.23 (d, *J* = 8.8 Hz, 1H), 5.0 (bs), 4.25-4.21 (m, 2H), 4.11-4.06 (m, 1H), 4.07-4.03 (m, 1H), 3.95 (dd, *J* = 9.0, 2.7 Hz, 1H), 3.90 (bs), 3.82 (dd, *J* = 9.3, 3.1 Hz, 1H), 3.55 (dd, *J* = 9.0, 2.8 Hz, 1H), 3.32 (dd, *J* = 16.5, 6.8 Hz, 1H), 3.28 (dd, *J* = 16.6, 6.5 Hz, 1H), 2.90 (dd, *J* = 13.3, 5.6 Hz, 1H), 2.87 (dd, *J* = 12.9, 5.6 Hz, 1H), 1.44 (s, 9H), 1.44 (s, 9H), 1.43 (s, 9H), 1.39 (s, 9H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.23 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) d 198.7, 198.1, 169.7, 169.6, 155.6, 155.5, 137.2, 137.1, 133.18, 133.15, 128.59, 128.56, 128.2, 129.1, 81.8, 81.6, 79.6, 79.5, 72.9, 72.4, 69.2, 68.9, 54.6, 54.5, 45.51, 45.48, 28.3 (2x), 28.0, 27.9, 19.8, 19.7; LRMS (ESI): Mass calcd for $C_{22}H_{33}NO_6$ $[M+Na]^+$, 430. Found $[M+Na]^+$, 430.



3-(1-(naphthalen-1-yl)ethoxy)-1-phenylbutan-1-one (10): To an oven-dried 1-dram vial equipped with magnetic stirring bar was added azolium salt **A** (7 mg, 0.02 mmol), LiCl (17 mg, 0.4 mmol), and 50 mg 4 Å MS. The vial was sealed with a screw cap equipped with a teflon septum and a N_2 inlet. The vial was cooled to –78 °C in a CO_2/acetone bath. *n*-BuLi (8 μL, 0.02 mmol, 2.49 M in hexanes) was added through a syringe. After 5 min, the reaction was warmed to 20 °C and solvent removed under reduced pressure. A mixture of (*E*)-1-phenylbut-2-en-1-one (59 mg, 0.4 mmol) and 1-(naphthalen-1-yl)ethanol (344, 2.0 mmol) in toluene (400 μL, 1 M) was added to the carbene through a cannula. After 48 h, the reaction was filtered through a pad of SiO_2 with EtOAc as an eluent. The mixture was purified by flash column chromatography with a mixture of cold 10% EtOAc in Hex to afford 95 mg (75%) of **10** as a mixture of diastereomers in the ratio of 1.2:1. Analytical data for **10**: IR (film) 3059, 2974, 2929, 2903, 1717, 1683, 1653, 1596, 1448, 1372 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17-8.15 (m, 2H), 7.97-7.96 (m, 2H), 7.87-7.84 (m, 2H), 7.78-7.72 (m, 4H), 7.58-7.55 (m, 2H), 7.50-7.43 (m, 9H), 7.40-7.33 (m, 3H), 5.32 (q, *J* = 6.5 Hz, 1H, minor), 5.28 (q, *J* = 6.5 Hz, 1H, major), 4.16 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H, major), 4.04 (ddq, *J* = 6.3, 6.3, 6.3 Hz, 1H, minor), 3.48 (dd, *J* = 15.6, 6.3 Hz, 1H, major), 3.32 (dd, *J* = 15.5, 5.5 Hz, 1H, minor), 2.98 (dd, *J* = 15.3, 6.8 Hz, 1H, major), 2.97 (dd, *J* = 15.4, 8.3 Hz, 1H, minor), 1.59 (d, *J* = 6.6 Hz, 3H, minor), 1.51 (d, *J* = 6.5 Hz, 3H, major), 1.32 (d, *J* = 6.0 Hz, 3H, minor), 1.16 (d, *J* = 6.2 Hz, 3H, major); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 198.5, 140.1, 139.5, 137.3, 137.0, 133.9, 133.1, 132.9, 130.6, 130.5, 128.9, 128.8, 128.560, 128.4, 128.3 (2x), 128.2, 127.8, 127.7, 125.8, 125.7, 125.43, 125.37, 125.36, 123.9, 123.8, 123.5, 123.3, 74.2, 72.8, 71.0, 69.8, 46.7, 45.9, 24.1, 23.6, 21.6, 20.0; LRMS (ESI): Mass calcd for $C_{22}H_{22}O_2$ $[M+Na]^+$, 341. Found $[M+Na]^+$, 341.

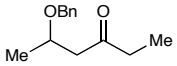


3-(4-oxo-4-phenylbutan-2-yloxy)propanenitrile (11): Prepared according to general procedure using (*E*)-1-phenylbut-2-en-1-one (59 mg, 0.4 mmol) and 2-cyanoethanol (82 μL, 1.2 mmol) to afford 77 mg (89 %) of **11** as a colorless oil after 18 h. Analytical data for **11**: IR (film) 3062, 2972, 2931, 2880, 2251, 1685, 1597, 1449, 1375, 1343, 1299, 1213, 1136, 1104, 1001 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (dt, *J* = 8.2, 1.5 Hz, 2H), 7.59-7.56 (m, 1H), 7.49-7.46 (m, 2H), 4.17 (dq, *J* = 12.3, 6.2 Hz, 1H), 3.76 (dt, *J* = 9.4, 6.6 Hz, 1H), 3.64 (dt, *J* = 9.4, 6.2 Hz, 1H), 3.37 (dd, *J* = 16.6, 7.1 Hz, 1H), 2.93 (dd, *J* = 16.6, 5.2 Hz, 1H), 2.55-2.52 (m, 2H), 1.30 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 137.2, 133.4, 128.8, 128.3, 118.1, 72.7, 63.7, 45.7, 20.1, 19.3; LRMS (ESI): Mass calcd for $C_{13}H_{15}NO_2$ $[M+H]^+$, 218. Found $[M+H]^+$, 218.

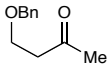


3-(benzyloxy)-1-(4-chlorophenyl)butan-1-one (12): Prepared according to general procedure using (*E*)-1-(4-chlorophenyl)but-2-en-1-one (90 mg, 0.5 mmol) and benzyl alcohol (258 μL, 2.5 mmol) to afford 105 mg (73 %) of **12** as a colorless oil after 16 h. Analytical data for **12**: IR (film) 3064, 3031, 2972, 2930, 2901, 2870, 1685, 1589, 1400, 1209, 1103, 1053 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.7 Hz, 2H), 7.31-7.25 (m, 5H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.20 (ddq, *J* = 6.2 Hz, 1H), 3.38 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.93 (dd, *J* = 16.0, 5.8 Hz, 1H), 1.32 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz,

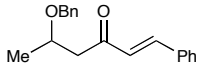
$CDCl_3$) δ 197.7, 139.6, 138.5, 135.7, 129.8, 129.0, 128.5, 127.8, 127.7, 72.1, 71.2, 46.0, 20.3; LRMS (ESI): Mass calcd for $C_{17}H_{17}ClO_2$ $[M+H]^+$, 289. Found $[M+H]^+$, 289.



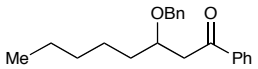
5-(benzyloxy)hexan-3-one (13): Prepared according to general procedure using (*E*)-hex-4-en-3-one (46 μL, 0.4 mmol) and benzyl alcohol (124 μL, 1.2 mmol) to afford 68 mg (82 %) of **13** as a colorless oil after 16 h. Analytical data for **13**: IR (film) 2973, 2934, 2878, 1714, 1454, 1375, 1131, 1095, 1063, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.08-4.02 (m, 1H), 2.78 (dd, *J* = 15.7, 7.4 Hz, 1H), 2.48-2.42 (m, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.04 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.3, 138.6, 128.5, 127.7, 71.9, 71.0, 49.7, 37.3, 20.1, 7.7; LRMS (ESI): Mass calcd for $C_{13}H_{18}O_2$ $[M+H]^+$, 207. Found $[M+H]^+$, 207.



4-(benzyloxy)butan-2-one (14): Prepared according to general procedure using but-3-en-2-one (33 μL, 0.4 mmol) and benzyl alcohol (41 μL, 0.4 mmol) to afford 35 mg (50 %) of **14** as a colorless oil after 16 h. Analytical data for **14**: IR (film) 3088, 3064, 3031, 3005, 2903, 2867, 1715, 1454, 1365, 1170, 1084, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 4.51 (s, 2H), 3.74 (t, *J* = 6.3 Hz, 2H), 2.72 (t, *J* = 6.3 Hz, 2H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.4, 138.2, 128.6, 127.9, 127.8, 73.4, 65.4, 43.9, 30.7; LRMS (ESI): Mass calcd for $C_{11}H_{14}O_2$ $[M+H]^+$, 179. Found $[M+H]^+$, 179.

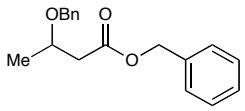


(*E*)-5-(benzyloxy)-1-phenylhex-1-en-3-one (17): Prepared according to general procedure using (1*E*,4*E*)-1-phenylhexa-1,4-dien-3-one (17 mg, 0.1 mmol) and benzyl alcohol (52 μL, 0.5 mmol) to afford 23 mg (82 %) of **17** as a colorless oil after 18 h. Analytical data for **17**: IR (film) 3062, 3030, 2970, 2928, 2871, 1718, 1688, 1660, 1629, 1606, 1451, 1375, 1339, 1312, 1276, 1201, 1182, 1129,1090, 1070, 978 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55-7.49 (m, 3H), 7.37-7.35 (m, 3H), 7.29-7.21 (m, 5H), 6.74 (d, *J* = 16.2 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.11 (ddq, *J* = 6.3 Hz, 1H), 3.05 (dd, *J* = 15.4, 6.9 Hz, 1H), 2.93 (dd, *J* = 15.4, 5.7 Hz, 1H), 1.27 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 143.2, 138.6, 134.6, 130.6, 129.1, 128.5, 127.8, 127.7, 126.9, 72.2, 71.1, 48.2, 20.3; LRMS (ESI): Mass calcd for $C_{19}H_{20}O_2$ $[M+H]^+$, 281. Found $[M+H]^+$, 281.

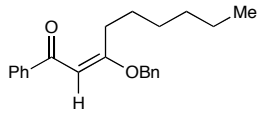


3-(benzyloxy)-1-phenyloctan-1-one (16): Prepared according to general procedure using (*E*)-1-phenyloct-2-en-1-one (81 mg, 0.4 mmol) and benzyl alcohol (0.4 mL) as solvent to afford 87 mg (70 %) of **16** as a colorless oil after 28 h. Analytical data for **16**: IR (film) 3087, 3063, 3032, 2956, 2930, 2859, 1679, 1620, 1598, 1449, 1376, 1353, 1305, 1282, 1214, 1180, 1093, 1068, 1027, 1001 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.58-7.55 (m, 1H), 7.47-7.44 (m, 2H), 7.30-7.24 (m, 5H), 4.53 (s, 2H), 4.15-4.10 (m, 1H), 3.37 (dd, *J* = 16.1, 6.9 Hz, 1H), 3.00 (dd, *J* = 16.1, 5.4 Hz, 1H), 1.69-1.56 (m, 2H), 1.50-1.36 (m, 2H), 1.33-1.26 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 138.7, 137.5, 133.2, 128.7,

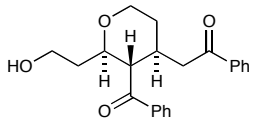
128.4, 128.4, 128.0, 127.6, 76.2, 72.0, 44.0, 35.0, 32.0, 25.1, 22.8; LRMS (ESI): Mass calcd for $C_{21}H_{26}O_2$ $[M+H]^+$, 311. Found $[M+H]^+$, 311.



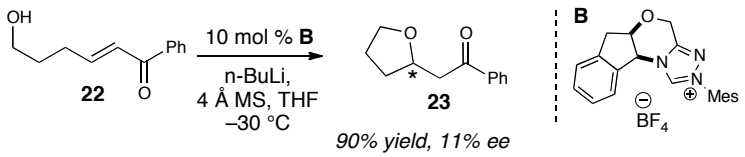
benzyl 3-(benzyloxy)butanoate (15): Prepared according to general procedure using (*E*)-benzyl but-2-enoate (71 mg, 0.4 mmol) and benzyl alcohol (0.4 mL) as solvent to afford 67 mg (60 %) of **15** as a colorless oil after 28 h. Analytical data for **15**: IR (film) 3089, 3065, 3033, 2973, 2932, 2874, 1735, 1497, 1455, 1379, 1360, 1343, 1298, 1259, 1175, 1136, 1087, 1054, 1001 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.26 (m, 10H), 5.16-5.10 (m, 2H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.07-4.01 (m, 1H), 2.71 (dd, *J* = 15.1, 7.5 Hz, 1H), 2.50 (dd, *J* = 15.1, 5.5 Hz, 1H), 1.27 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 138.6, 136.0, 128.7, 128.5, 128.4, 128.3, 127.8, 127.7, 72.1, 71.0, 66.4, 42.2, 20.0; LRMS (ESI): Mass calcd for $C_{18}H_{20}O_3$ $[M+H]^+$, 285. Found $[M+H]^+$, 285.



(*E*)-3-(benzyloxy)-1-phenylnon-2-en-1-one (19): Prepared according to general procedure using 1-phenylnon-2-yn-1-one (86 mg, 0.4 mmol) benzyl alcohol (201 μL, 2.0 mmol) to afford 100 mg (78%) of **19** as a colorless oil after 8 h. Analytical data for **19**: IR (film) 3064, 3032, 2955, 2929, 2858, 1656, 1598, 1454, 1280, 1195 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85-7.84 (m, 2H), 7.52-7.49 (m, 1H), 7.45-7.36 (m, 7H), 6.20 (m, 1H), 5.00 (s, 2H), 2.90 (dd, *J* = 7.8, 7.8 Hz, 2H), 1.70-1.64 (m, 2H), 1.43-1.37 (m, 2H), 1.32-1.26 (m, 4H), 0.89-0.86 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 177.3, 140.4, 135.6, 131.7, 128.7, 128.33, 128.31, 127.7, 127.5, 97.1, 70.2, 33.1, 31.7, 29.3, 27.6, 22.6, 14.1; LRMS (ESI): Mass calcd for $C_{22}H_{26}O_2$ $[M+H]^+$, 323. Found $[M+H]^+$, 323.



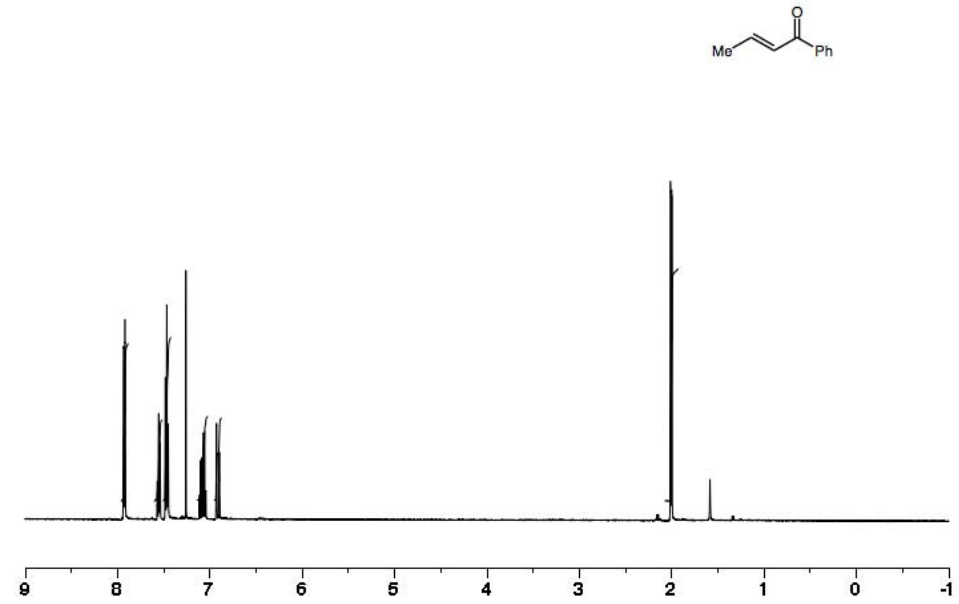
2-(3-benzoyl-2-(2-hydroxyethyl)tetrahydro-2*H*-pyran-4-yl)-1-phenylethanone (21): Prepared according to general procedure using (*E*)-5-hydroxy-1-phenylpent-2-en-1-one (71 mg, 0.4 mmol) to afford 59 mg (83 %) of **21** as a colorless oil after 72 h. Analytical data for **21**: IR (film) 3442, 2945, 2853, 1671, 1580, 1365, 1290, 1214, 1129, 1105, 1075, 1049, 1001, 976 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03-8.02 (m, 2H), 7.79-7.77 (m, 2H), 7.63-7.60 (m, 1H), 7.54-7.50 (m, 3H), 7.42-7.39 (m, 2H), 4.05 (ddd, *J* = 11.5, 4.6, 1.5 Hz, 1H), 3.80 (ddd, *J* = 9.6, 2.5, 2.5 Hz, 1H), 3.72-3.50 (m, 3H), 3.55 (dd, *J* = 10.5, 9.6 Hz, 1H), 2.87 (dd, *J* = 15.3, 3.1 Hz, 1H), 2.82-2.74 (m, 1H), 2.66-2.61 (m, 2H), 1.81 (dddd, *J* = 13.5, 3.7, 3.7, 1.9 Hz, 1H), 1.71-1.64 (m, 1H), 1.59-1.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 198.2, 138.2, 136.6, 133.9, 133.3, 129.1, 128.7, 128.4, 128.1, 81.0, 67.8, 61.5, 53.6, 43.1, 36.5, 36.0, 30.8; LRMS (ESI): Mass calcd for $C_{22}H_{24}O_4$ $[M+Na]^+$, 375. Found $[M+Na]^+$, 375.

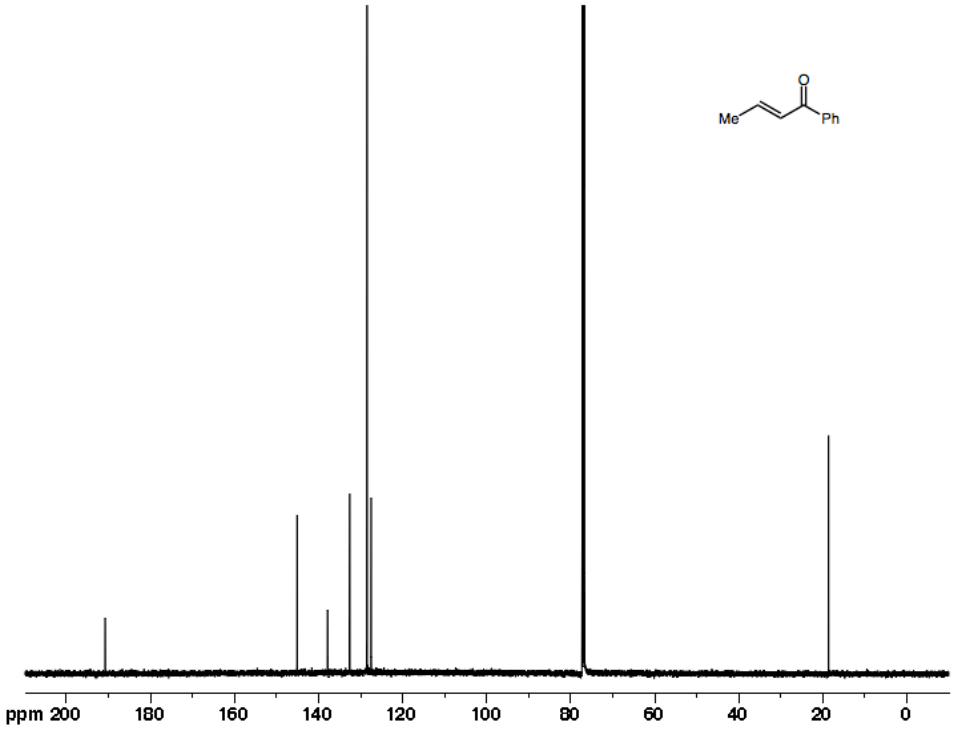


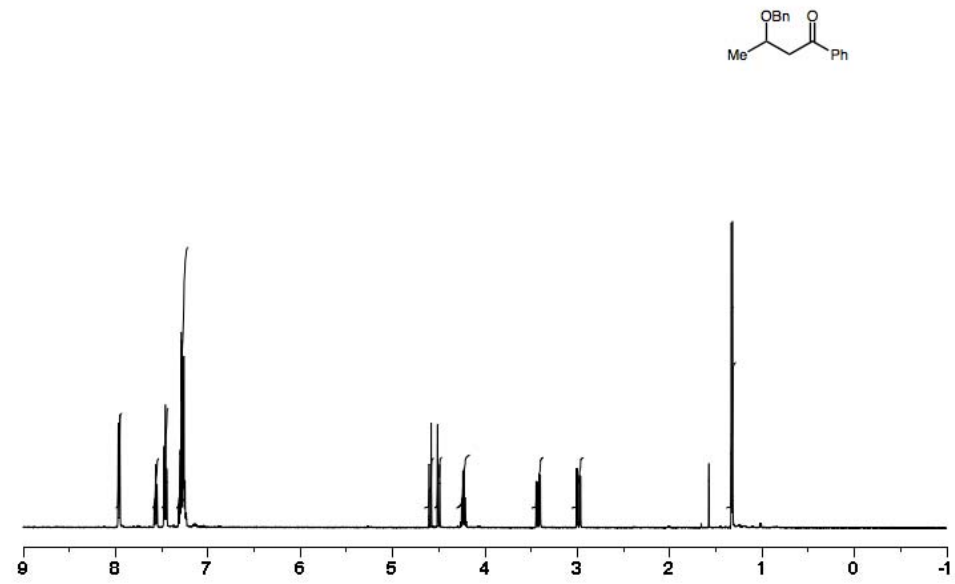
2-(3-benzoyl-2-(2-hydroxyethyl)tetrahydro-2*H*-pyran-4-yl)-1-phenylethanone (23): To an oven-dried 1-dram vial equipped with magnetic stirring bar, screw cap, teflon septum, and N_2 inlet was added azolium salt **B**[4] (6 mg, 0.015 mmol) and 4 Å molecular sieves (50 mg). THF (300 μL) was added through a syringe and the vial was cooled to –78 °C in a CO_2/acetone bath. After 5 min, *n*-BuLi (2.5 M hexanes, 4 μL, 0.01 mmol) was added through a syringe. The solution was allowed to stir for 5 min and then removed from the CO_2/acetone bath. After 10 min, vial cooled to –78 °C in a CO_2/acetone bath. A solution of (*E*)-6-hydroxy-1-phenylhex-2-en-1-one (**22**, 30 mg, 0.15 mmol) in THF (300 μL) was added to the vial through a cannula. The flask was then warmed to –30 °C for 12 h. The material was filtered through a small pad of SiO_2 with Et_2O as an eluent. The mixture was concentrated and purified by column chromatography with 5% EtOAc in Hexanes as an eluent to afford 27 mg (90 %) of **23** as a colorless oil with 11% enantiomeric excess. Analytical data for **23**: IR (film) 3061, 3028, 2973, 2872, 1684, 1596, 1448, 1382, 1210 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98-7.96 (m, 2H), 7.58-7.50 (m, 1H), 7.48-7.45 (m, 2H), 4.41 (dddd, *J* = 6.8, 6.8, 6.8, 6.8 Hz, 1H), 3.90 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1H), 3.76 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1H), 3.40 (dd, *J* = 16.3, 6.1 Hz, 1H), 3.06 (dd, *J* = 16.3, 6.7 Hz, 1H), 2.20 (dddd, *J* = 19.8, 6.2, 6.2, 6.2 Hz, 1H), 1.96 -1.90 (m, 2H), 1.57 (dddd, *J* = 20.1, 7.9, 7.9, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 137.0, 133.1, 128.6, 128.2, 75.4, 67.8, 44.6, 31.6, 25.6; LRMS (ESI): Mass calcd for $C_{12}H_{14}O_2$ $[M+Na]^+$, 213. Found $[M+Na]^+$, 213. Enantiomeric ratio was measured by HPLC ((S,S) Whelk-O1, 5% IPA/Hexanes, 1 mL/min, Rt_1 = 20.2, Rt_2 = 24.8).

[4] He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418-8420.

Selected NMR Spectra



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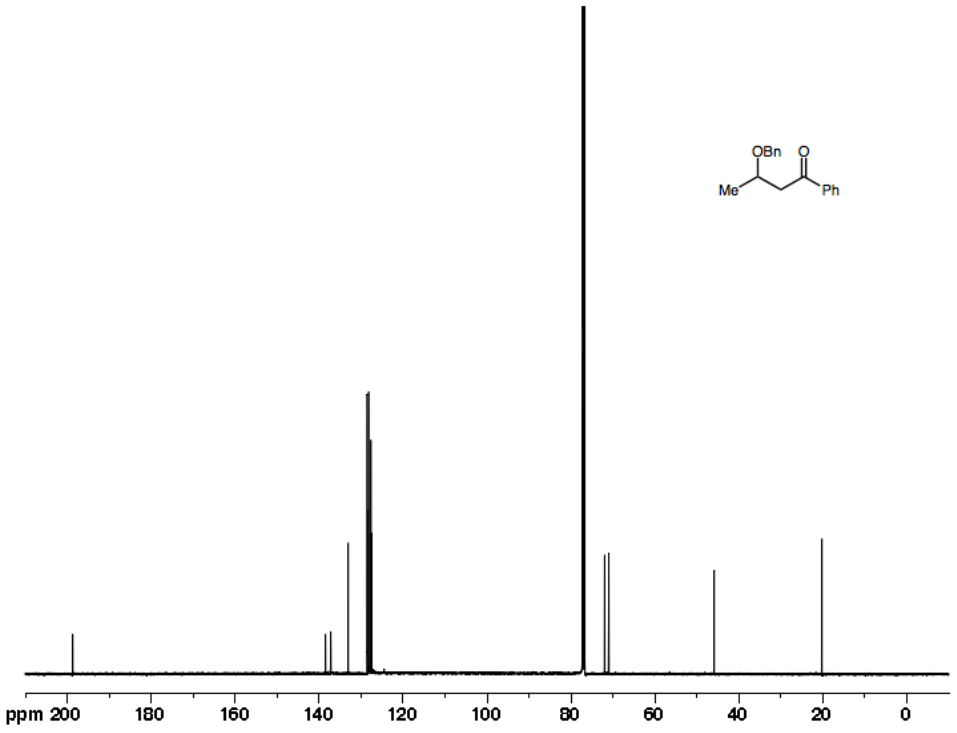
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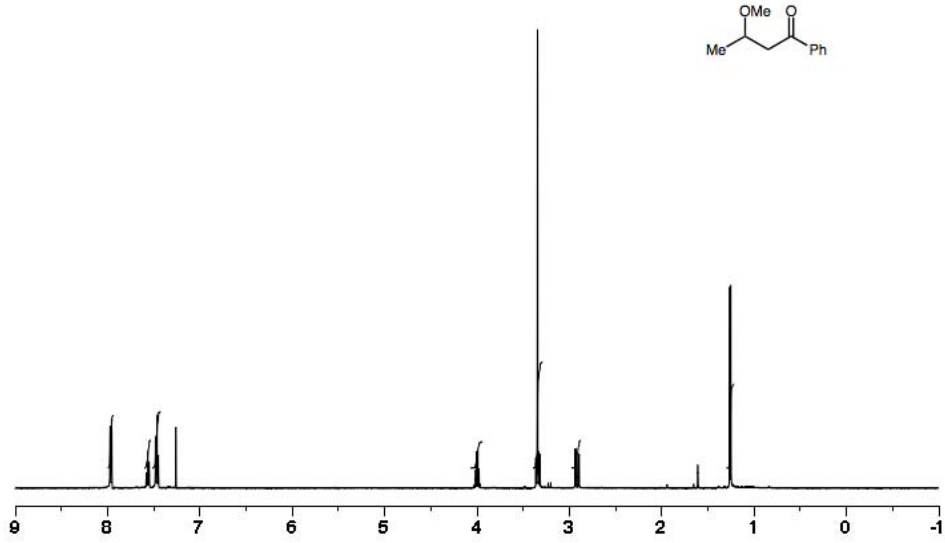
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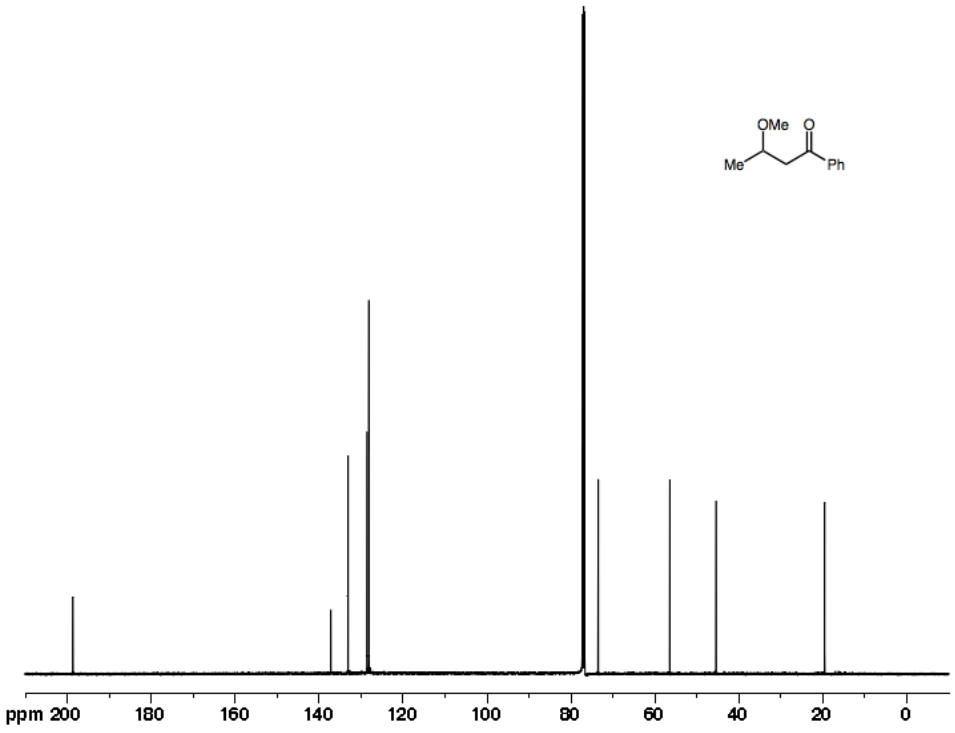
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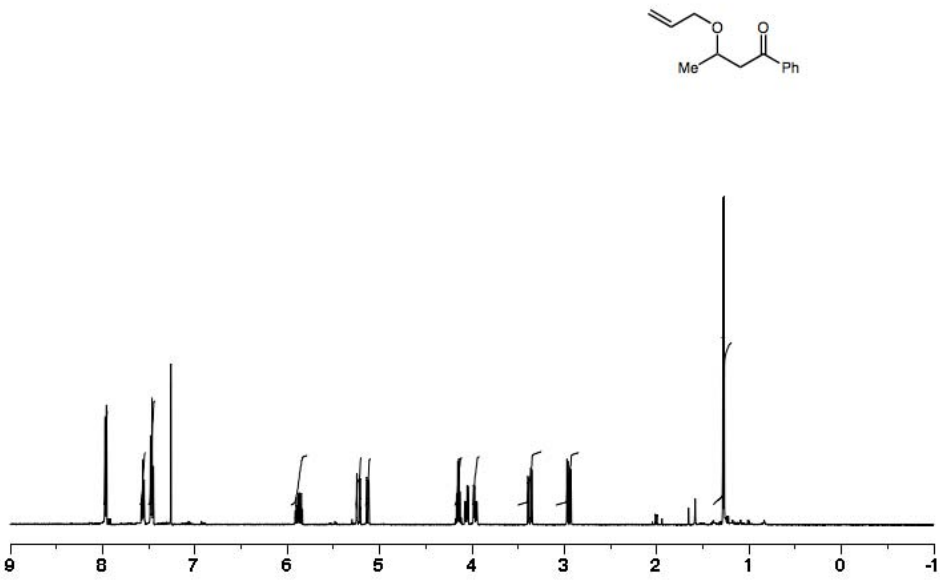
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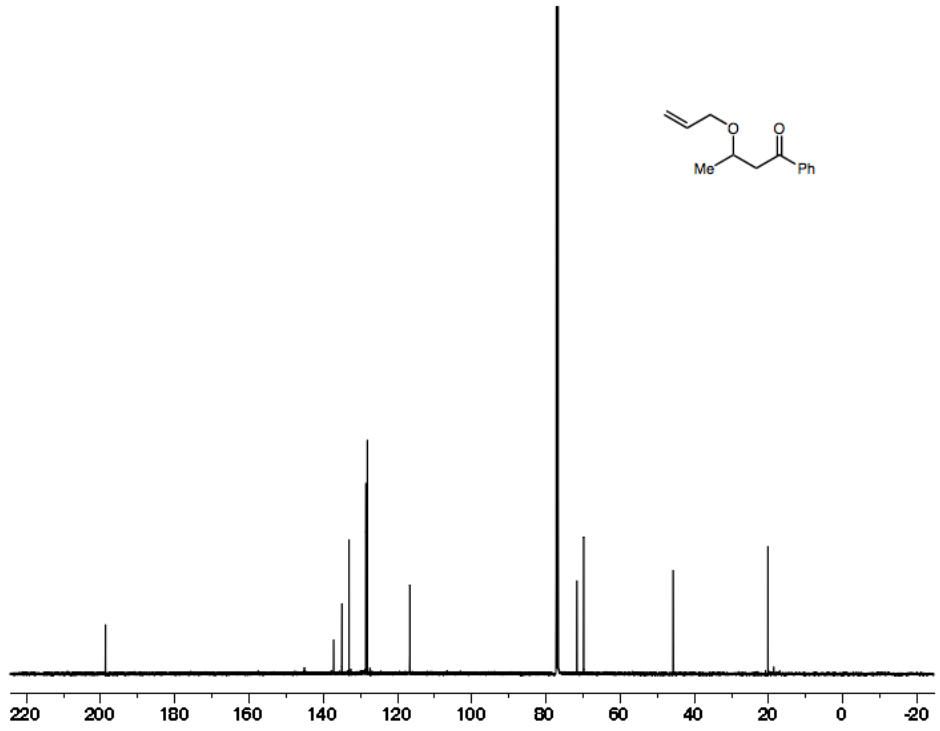
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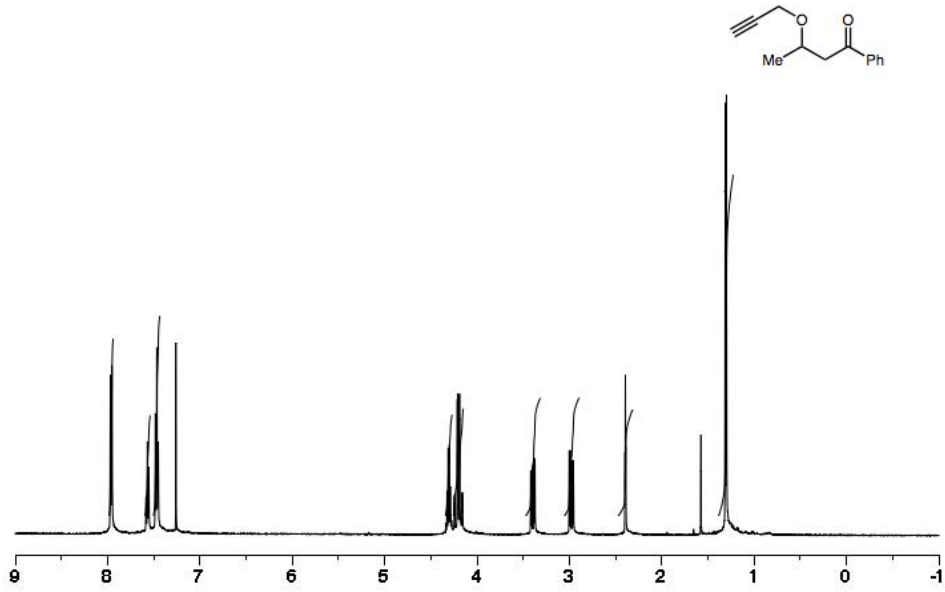
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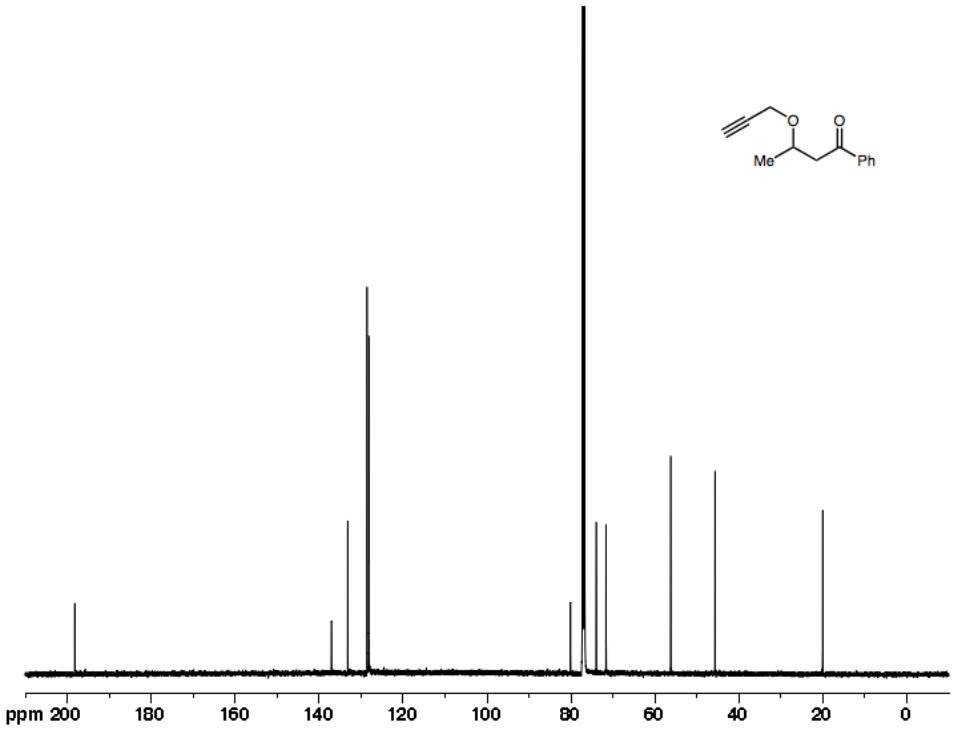
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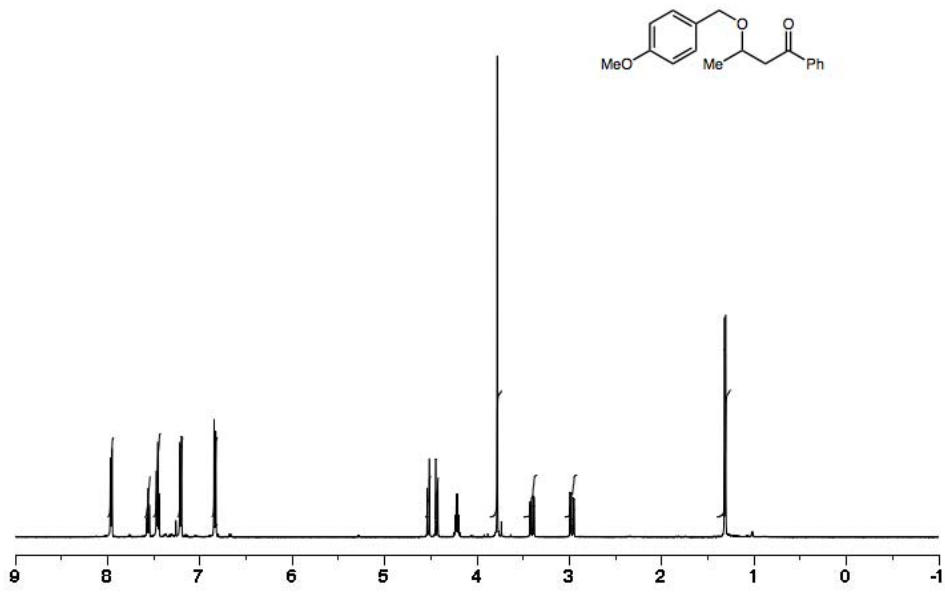
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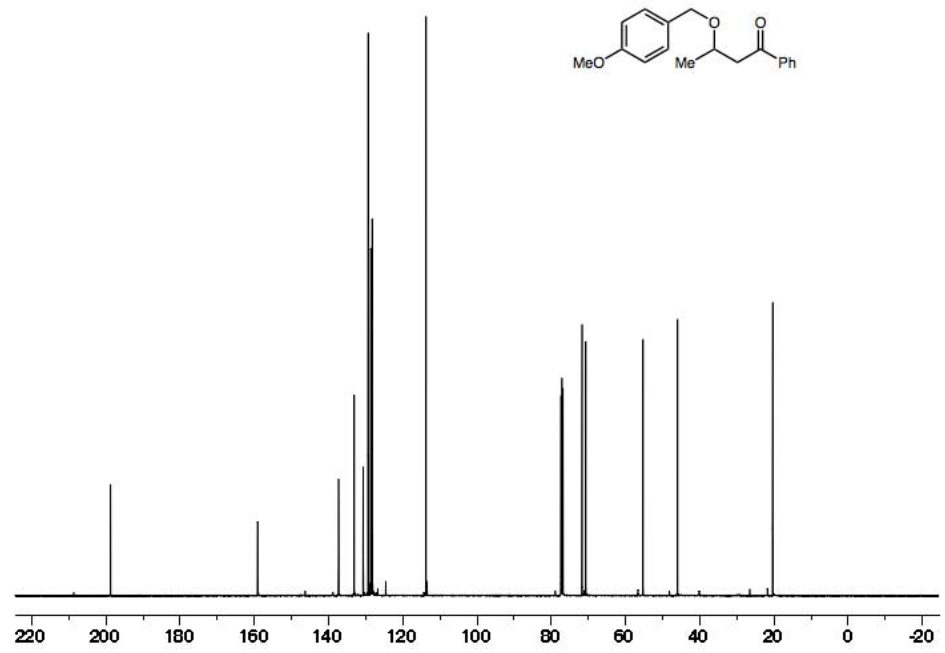
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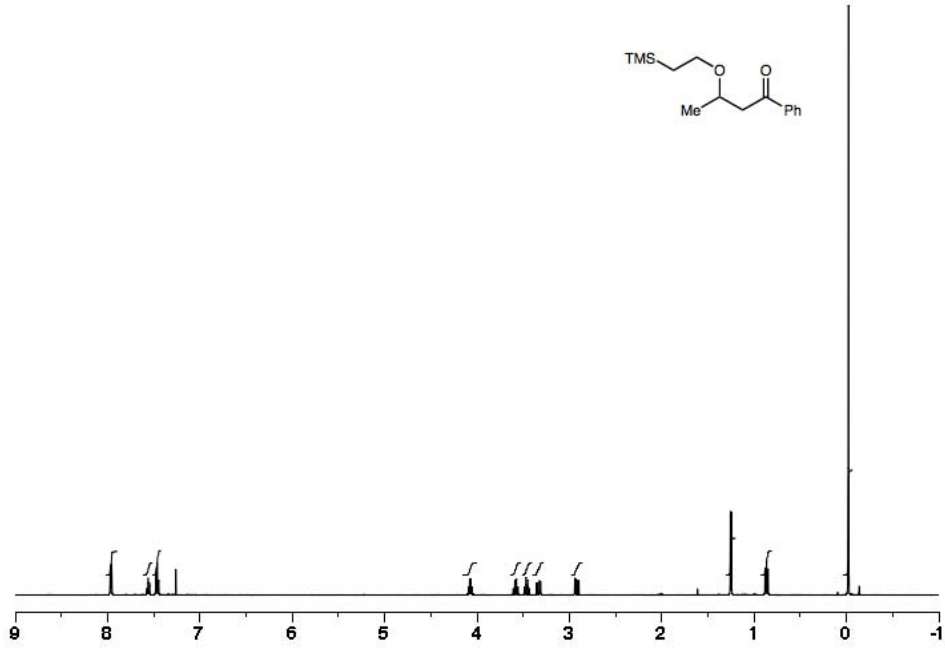
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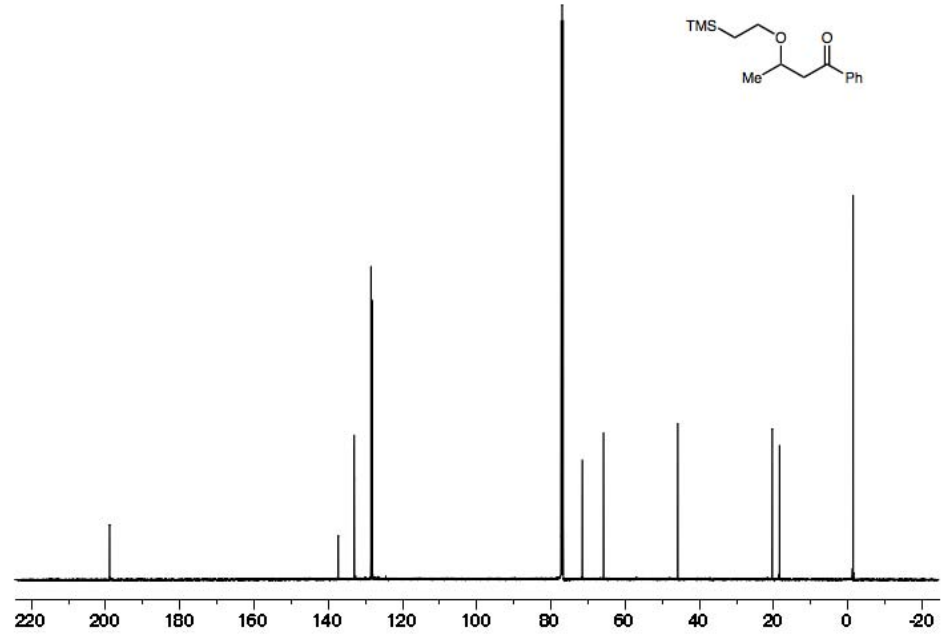
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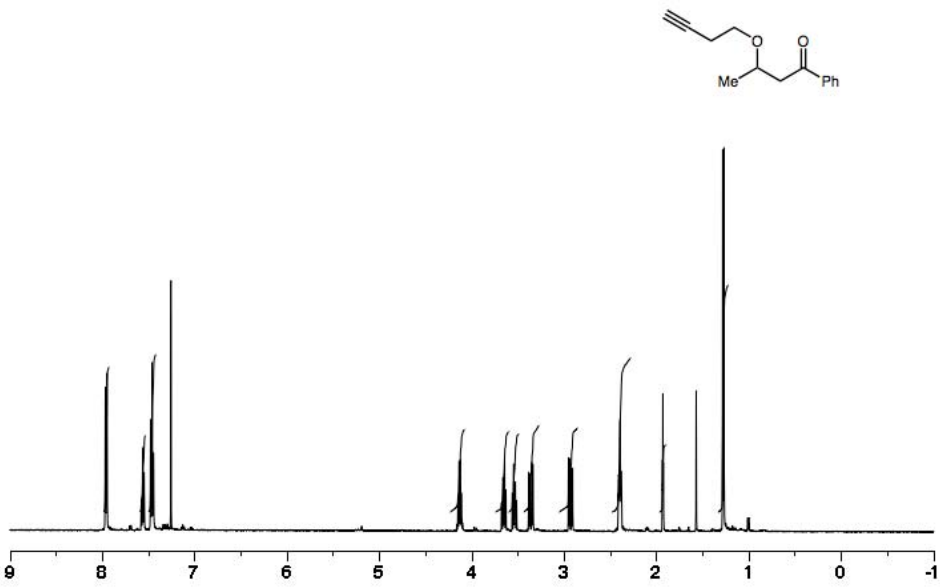
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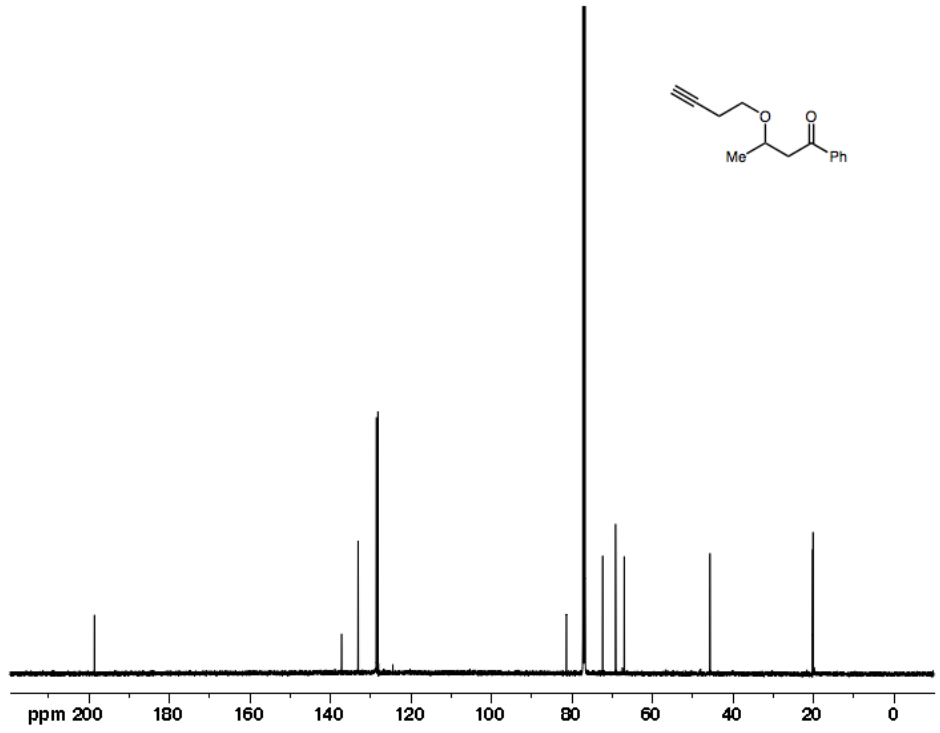
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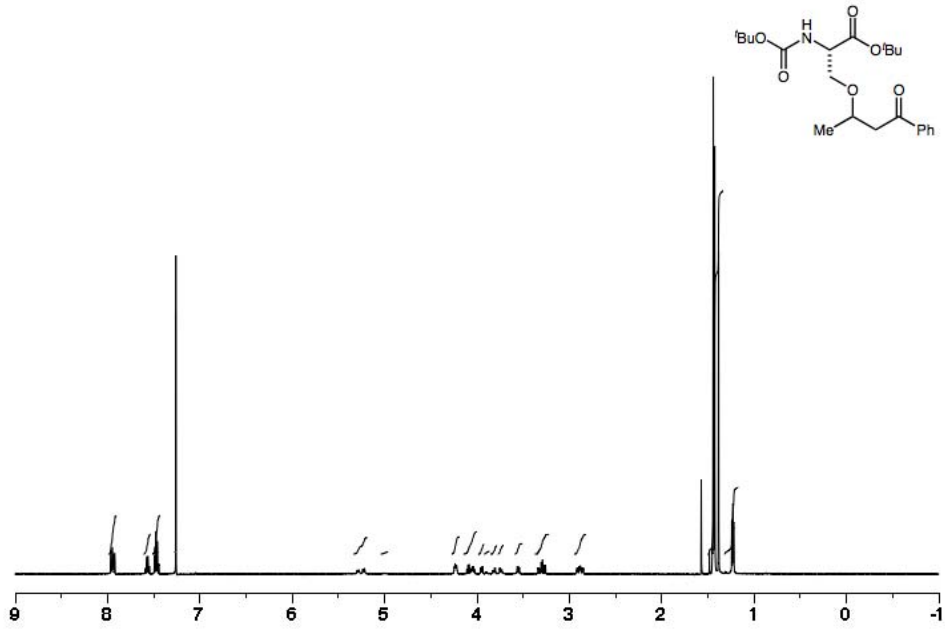
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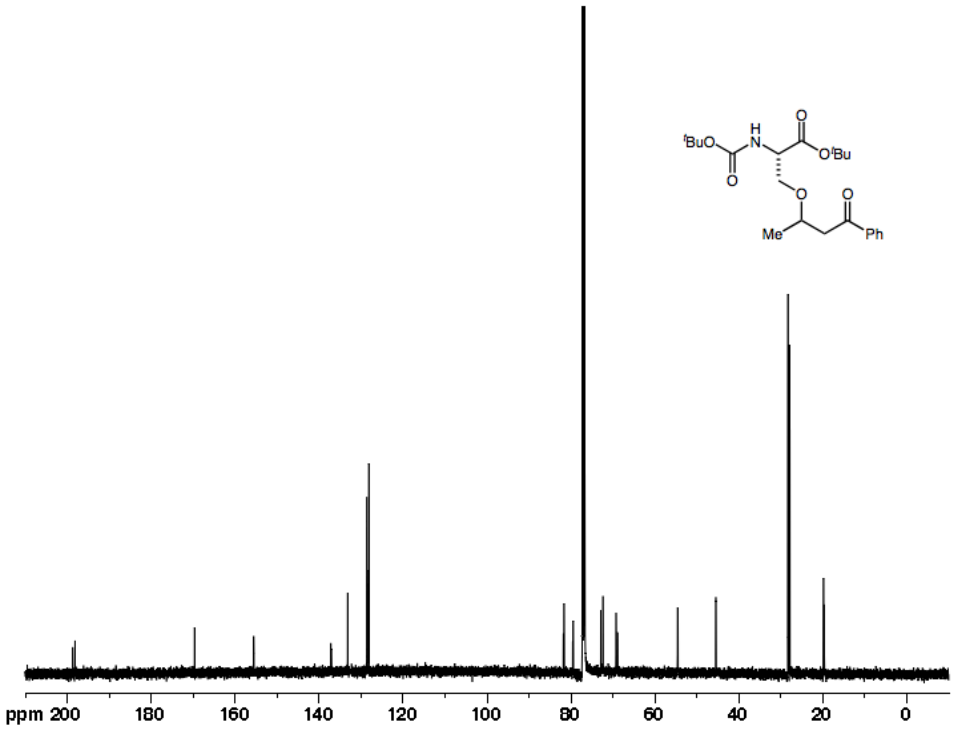
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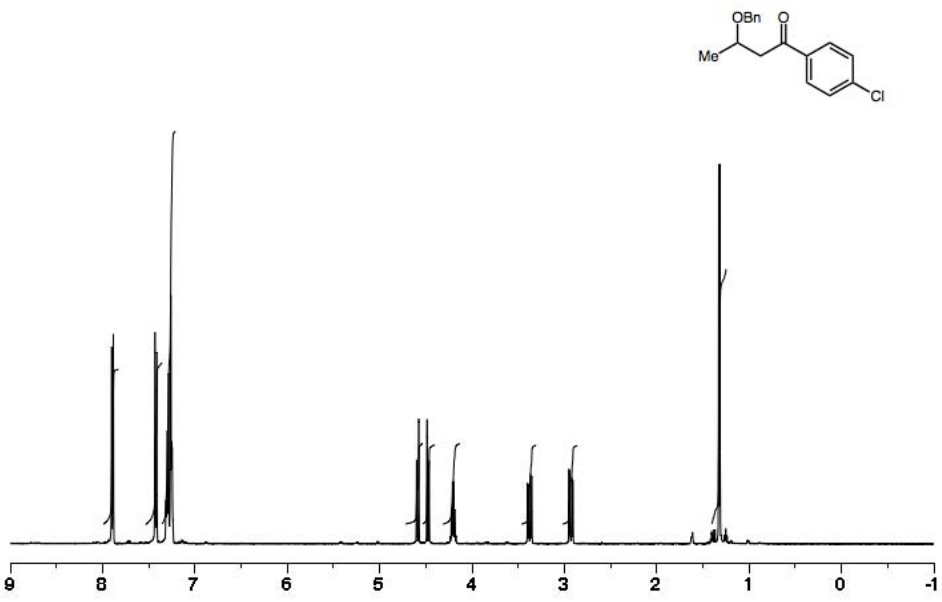
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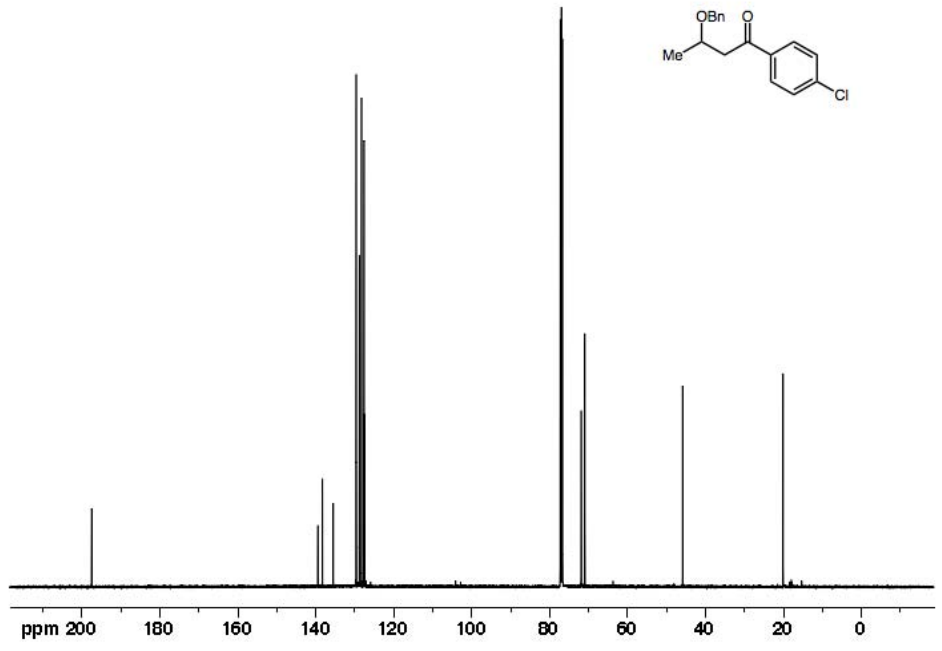
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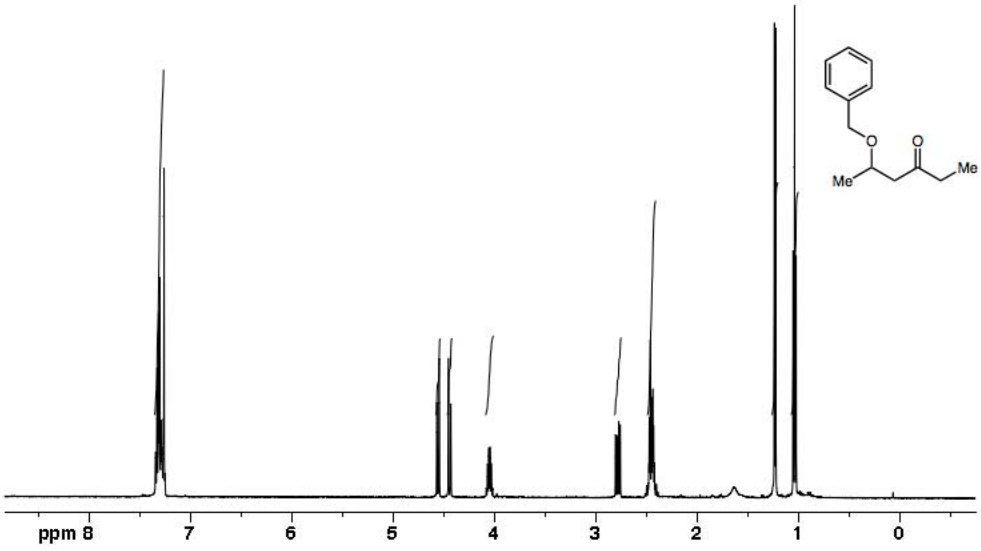
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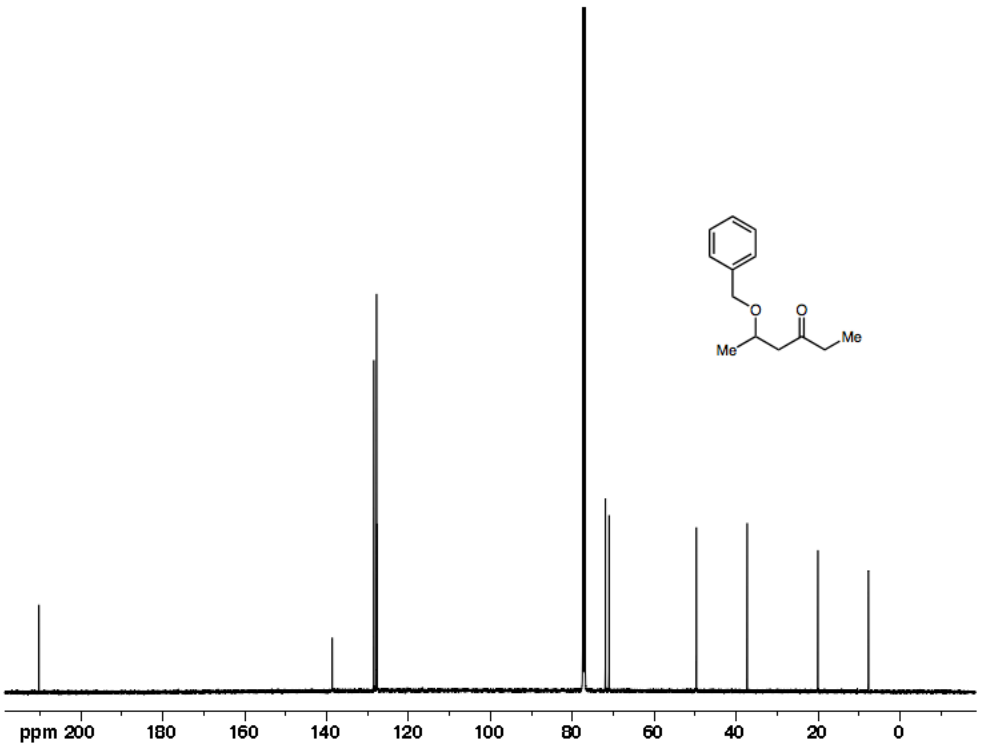
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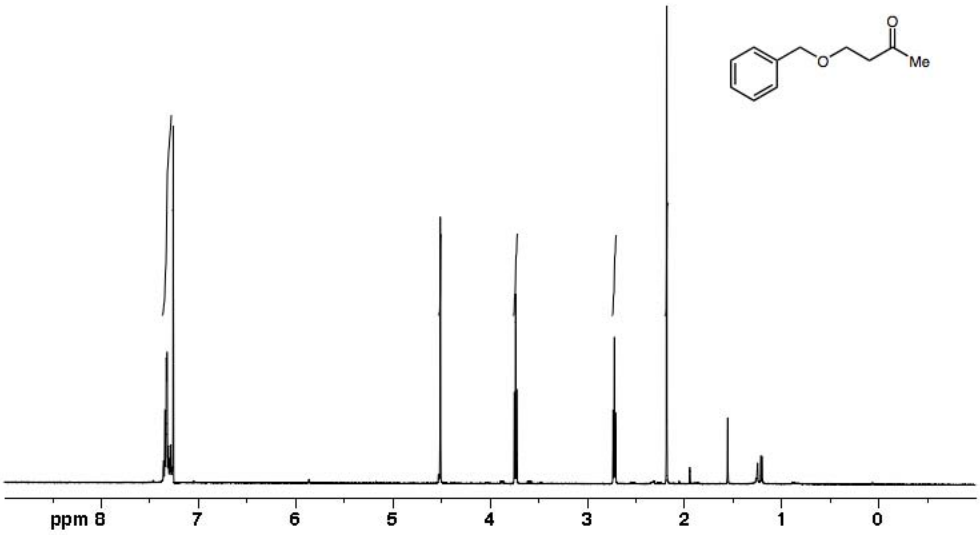
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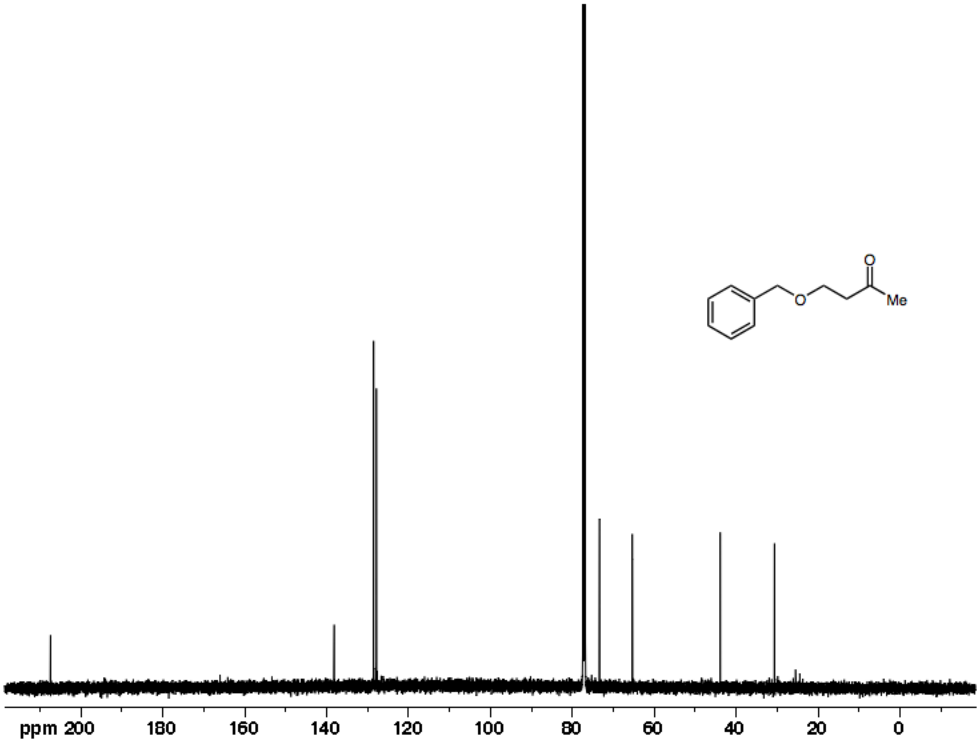
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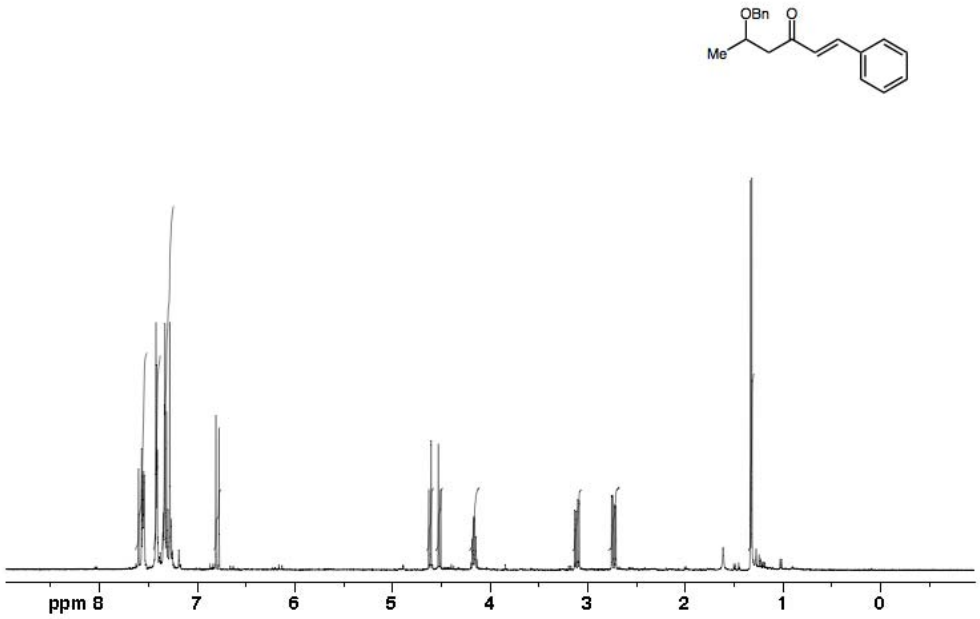
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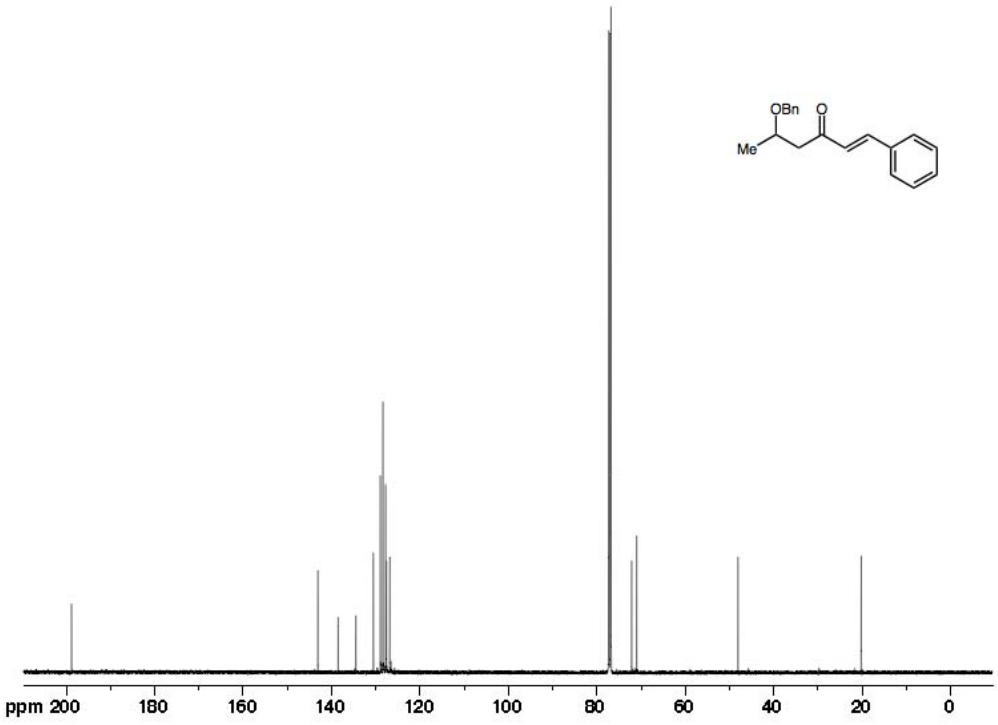
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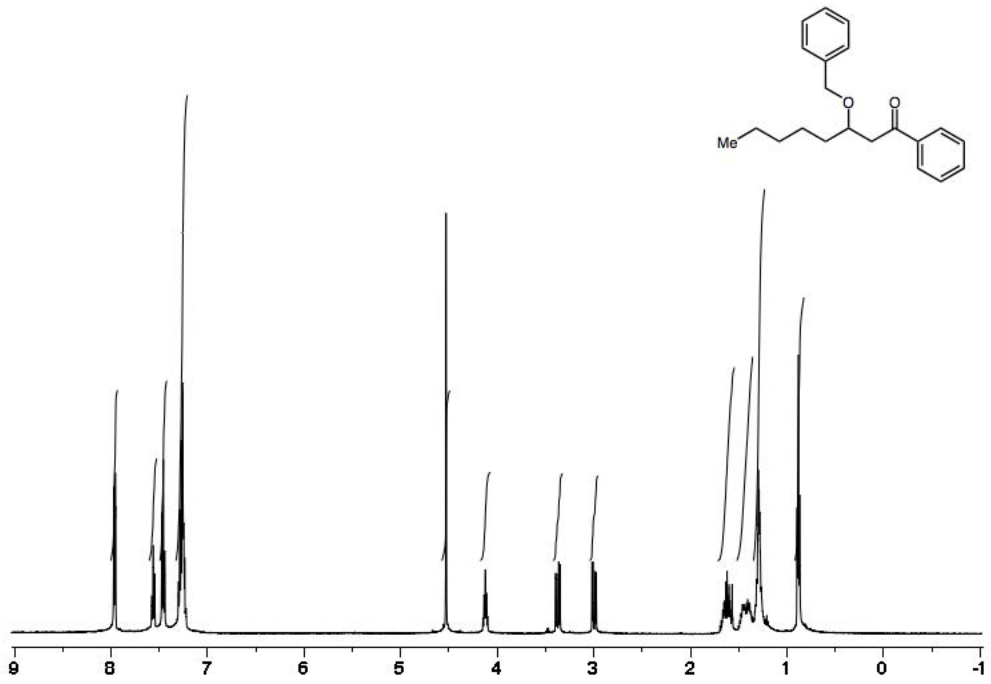
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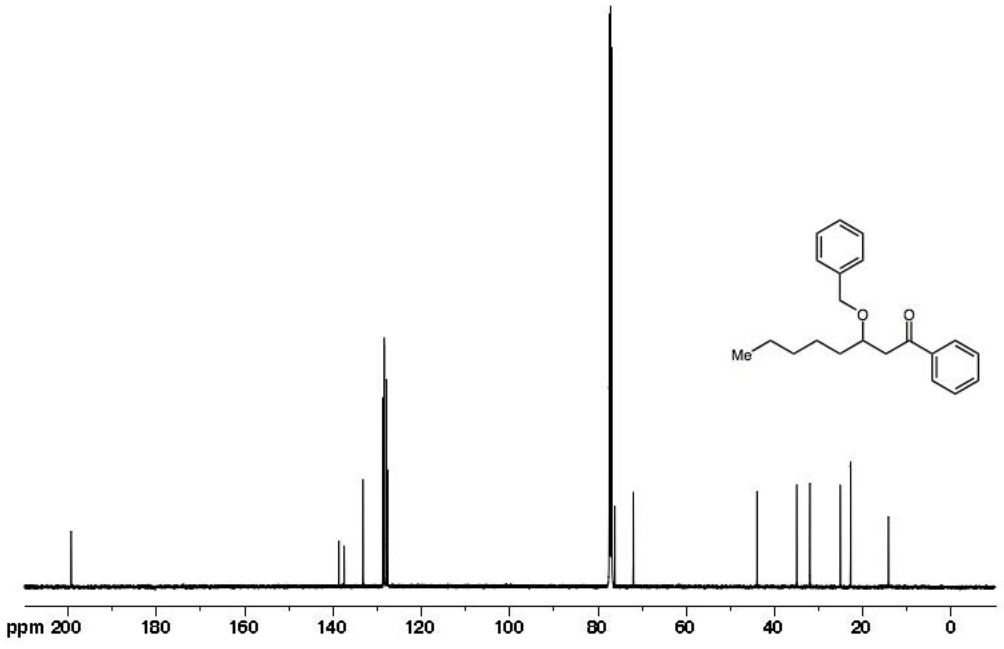
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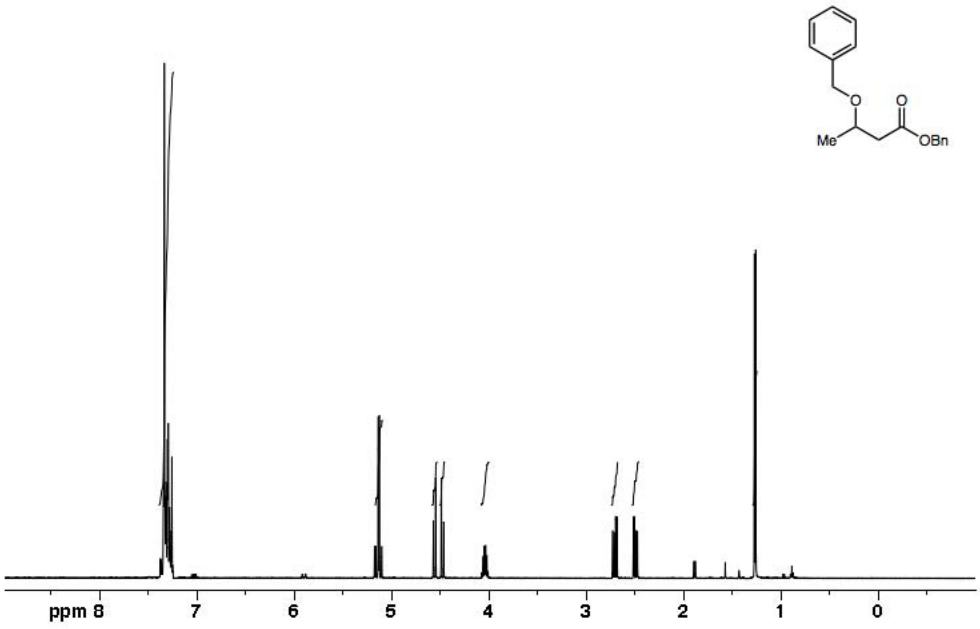
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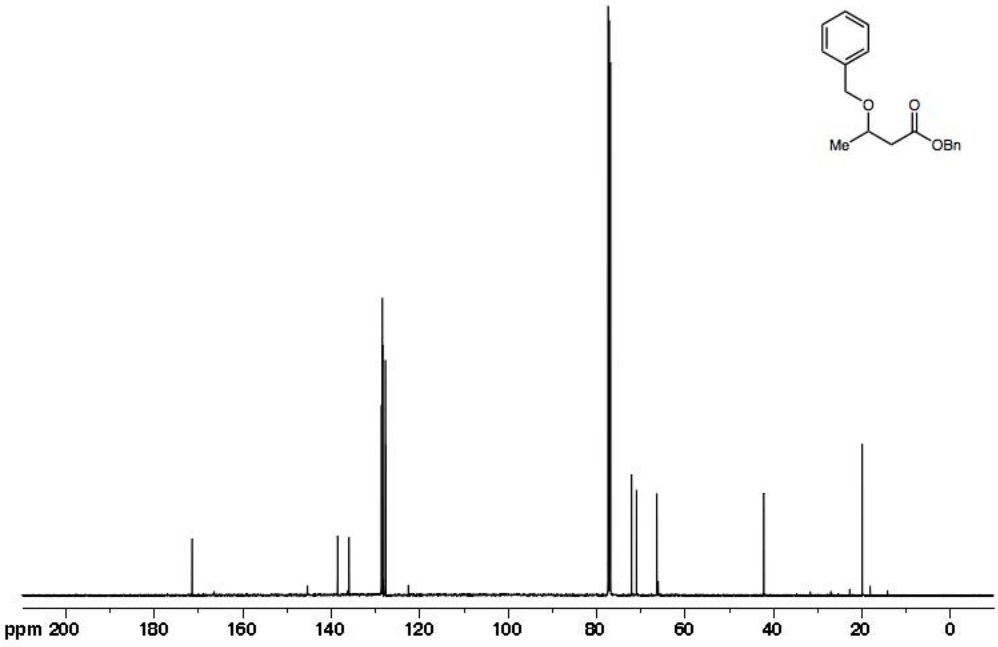
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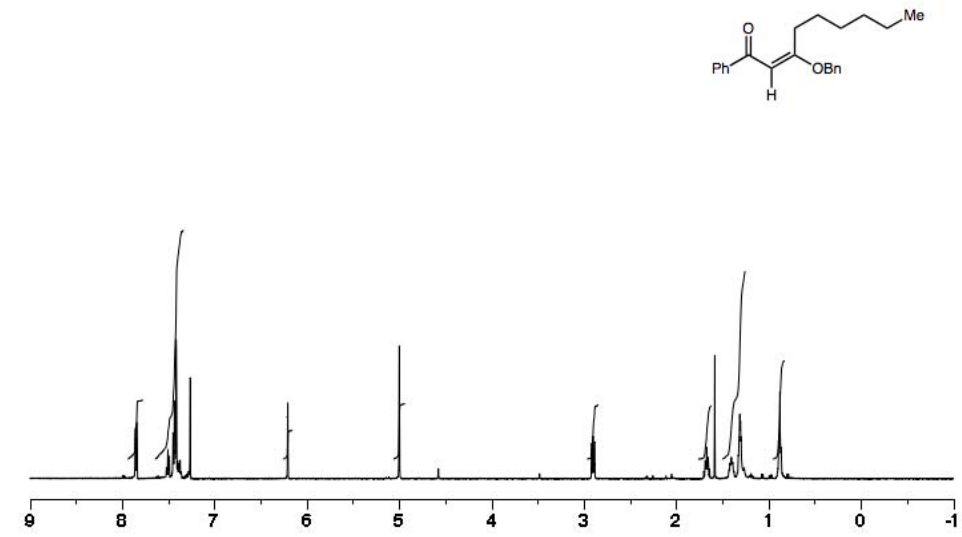
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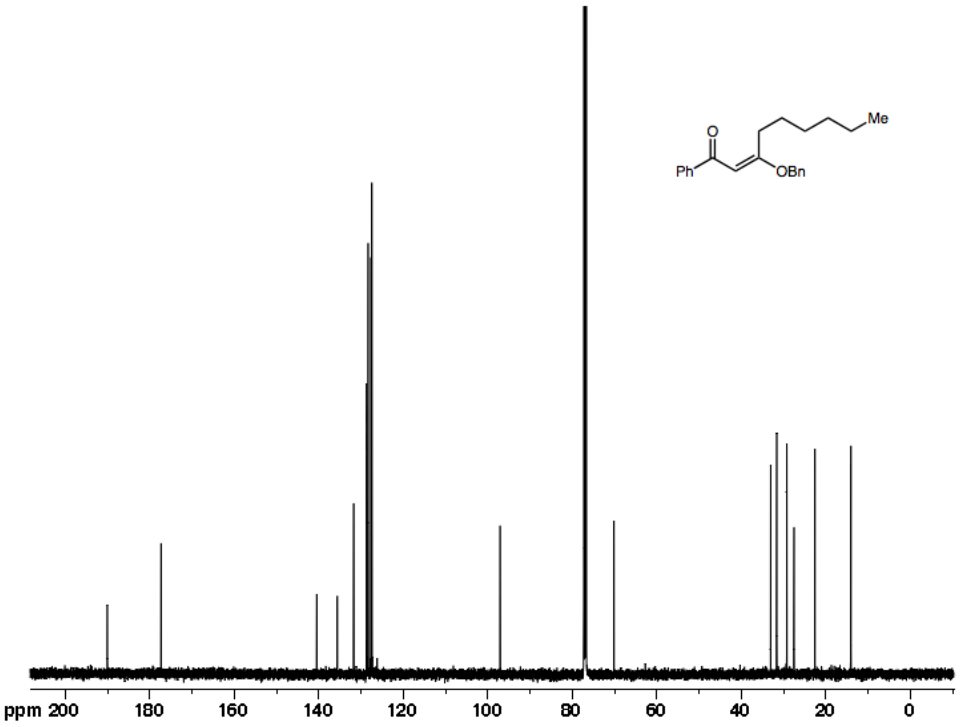
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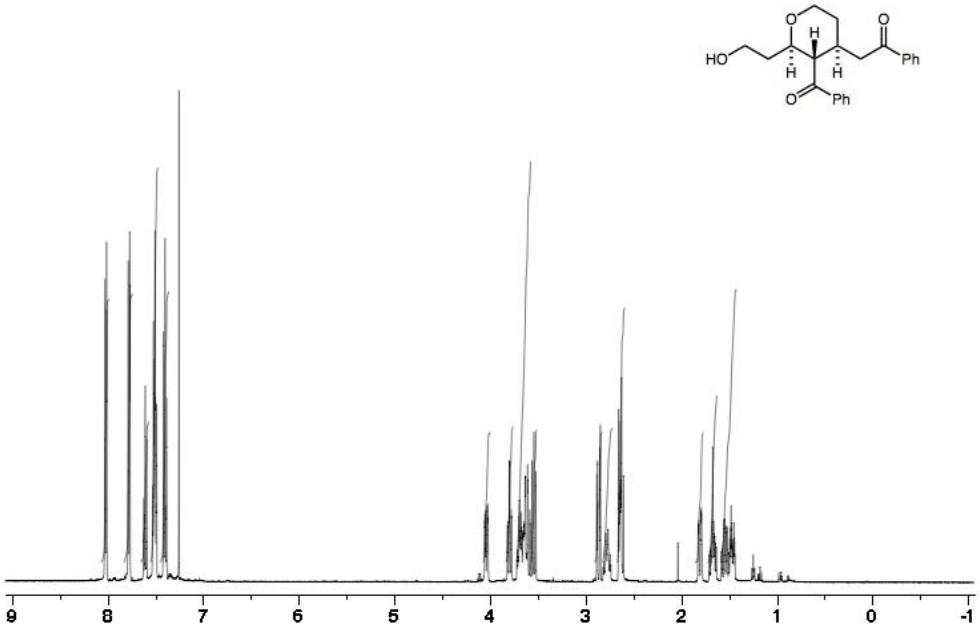
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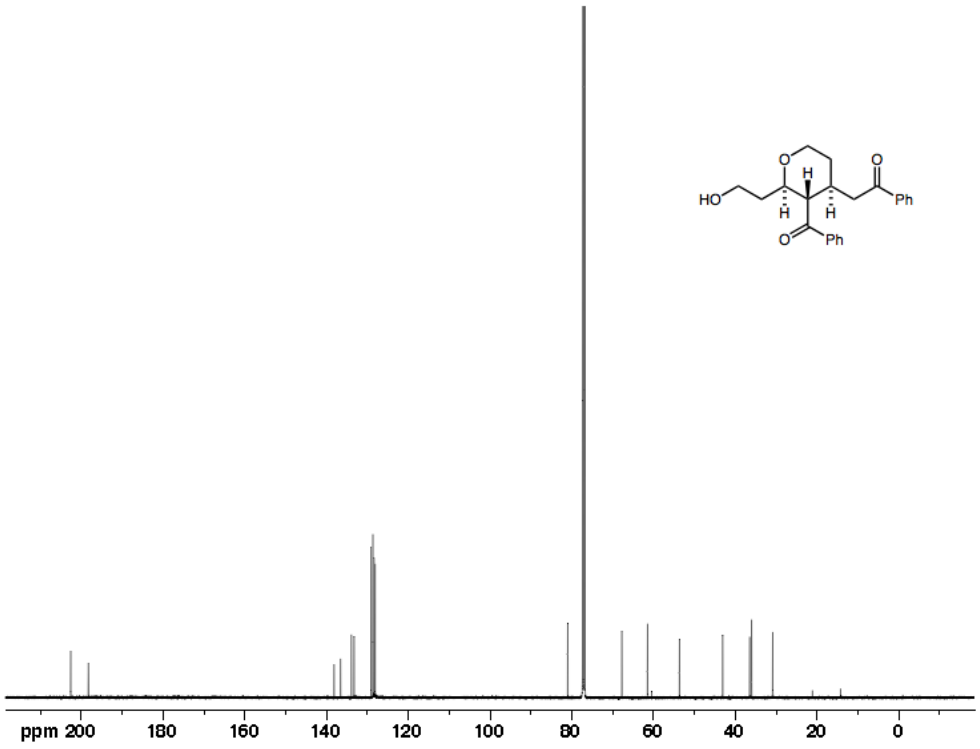
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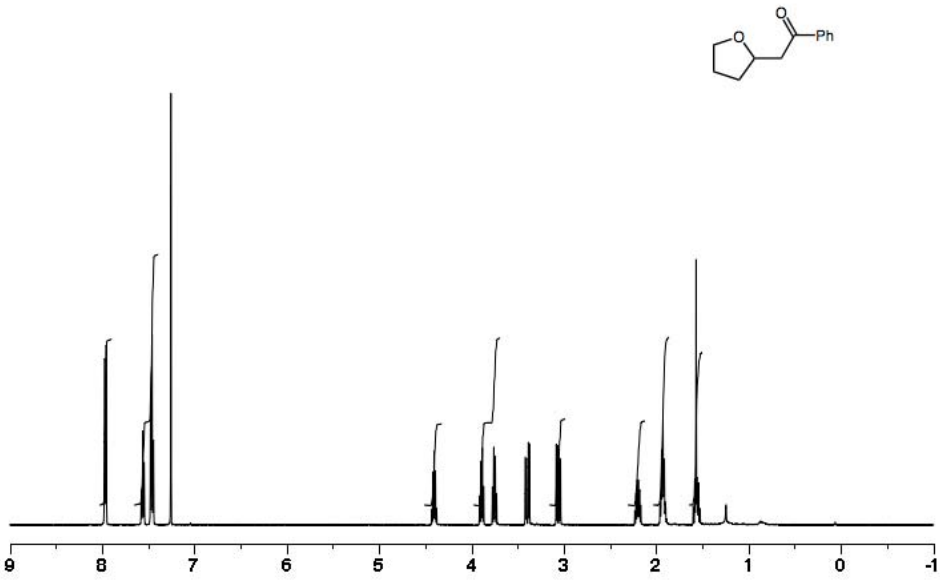
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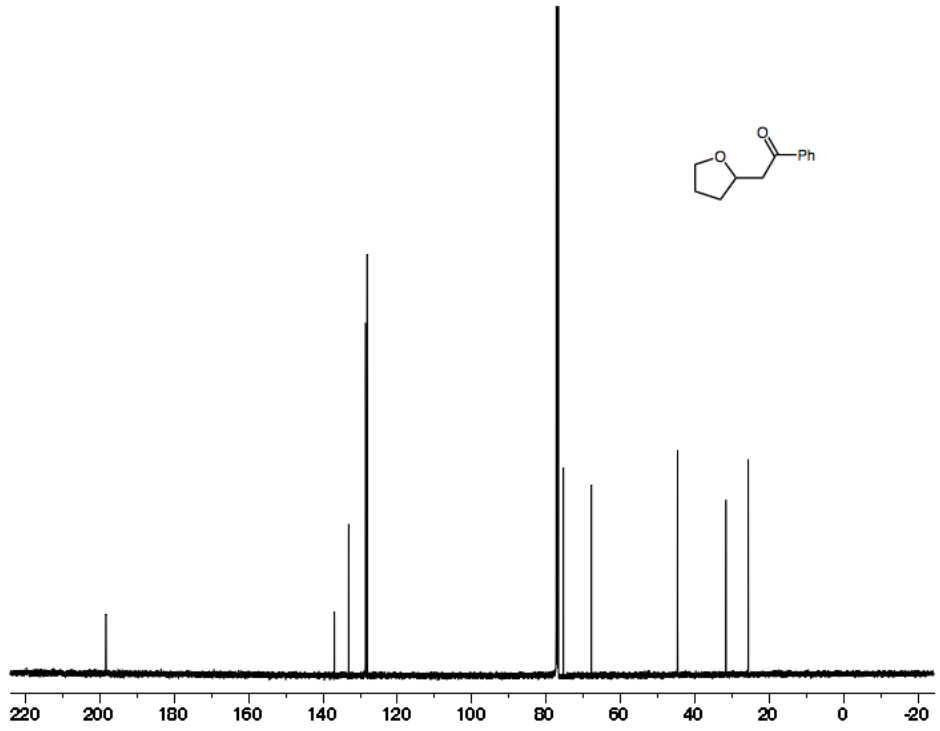
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