Catalyst-Controlled Wacker-Type Oxidation: Facile Access to Functionalized Aldehydes

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Supporting Information

All metal salts and solvents were obtained from Sigman-Aldrich and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 500 Mhz, Varian 400 Mhz or a Varian 300 Mhz spectrometer. High-resolution mass spectra were provided by the California Institute of Technology Mass Spectrometry Facility using JEOL JMS-600H High Resolution Mass Spectrometer.

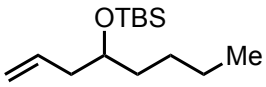
General Procedures

Procedure A for preparative scale (0.5 mmol) oxidation of alkenes (isolation):
$PdCl_2(PhCN)_2$ (0.05 mmol, 19.2 mg), $CuCl_2 \bullet 2H_2O$ (0.05 mmol, 8.5 mg) and $NaNO_2$ (0.025 mmol, 1.7 mg) were weighed into a 20 mL vial charged with a stir bar. The vial was sparged for 1 minute with oxygen (1 atm, balloon). Premixed and oxygen saturated *t*-BuOH (7.5 mL) and $MeNO_2$ (0.5 mL) was added followed by the alkene (0.5 mmol). The solution was saturated with oxygen by an additional 30 seconds of sparging. The reaction was then allowed to stir at room temperature (20-25ºC) for 4 h under 1 atm oxygen (balloon). Next, the reaction was quenched by addition to water (*ca*. 50mL) and extracted three times with dichloromethane (*ca*. 25 mL). The combined organic layers were subsequently washed with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed under reduced pressure and the desired aldehyde product was purified using flash chromatography (pentane/ether). The selectivity was calculated by ^{1}H NMR analysis of the unpurified reaction mixture. Long relaxation delays (d1=10) were applied due to the long T_1 of the aldehydic proton signal.

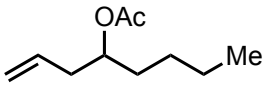
Procedure B for analytical scale (0.2 mmol) oxidation of alkenes (NMR analysis):
$PdCl_2(PhCN)_2$ (0.02 mmol, 7.7 mg), $CuCl_2 \bullet 2H_2O$ (0.02 mmol, 3.6 mg) and $NaNO_2$ (0.01 mmol, 0.7 mg) were weighed into a 8 mL vial charged with a stir bar. The vial was sparged for 1 minute with oxygen (1 atm, balloon). Premixed and oxygen saturated *t*-BuOH (3 mL) and $MeNO_2$ (0.2 mL) was added followed by the alkene (0.2 mmol). The solution was saturated with oxygen by an additional 15 seconds of sparging and then sealed under an atmosphere of oxygen. The reaction was then allowed to stir at room temperature (20-25ºC) for 4 h. Next, the reaction was quenched by addition to water (*ca*. 10mL) and extracted three times with dichloromethane (*ca*. 5 mL). The combined organic layers were subsequently washed with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. After volatiles were removed under reduced pressure, nitrobenzene was added as an internal standard. The resulting solution was subsequently subjected to ^{1}H NMR analysis to determine yield and selectivity.

Procedure for Tsuji–Wacker oxidations:
$PdCl_2$ (1.8 mg, 0.01 mmol) and CuCl (9.9 mg, 0.1 mmol) were weighed into a 8 mL vial. DMF (0.7 mL) and water (0.1 mL) were both added to the vial. The vial was sparged with oxygen (1 atm, balloon) for 3 minutes. The solution was stirred for another 1 h before alkene (0.1 mmol) was added. The reaction was stirred for at room temperature (20-25ºC). After 24 h, the reaction mixture was quenched by addition of water (*ca*. 10 mL) and extracted 3 times with dichloromethane (*ca*. 5 mL). The combined organic layers were subsequently washed with a saturated solution of LiCl(aq). After volatiles were removed under reduced pressure, nitrobenzene was added as an internal standard. The resulting solution was subsequently subjected to ^{1}H NMR analysis to determine yield and selectivity.

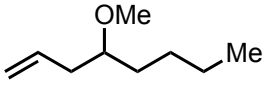
Characterization



***tert*-Butyldimethyl(oct-1-en-4-yloxy)silane:** Prepared according to the literature.[1] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.87 – 5.74 (m, 1H), 5.07 – 5.02 (m, 1H), 5.02 – 4.99 (m, 1H), 3.68 (p, *J* = 5.8 Hz, 1H), 2.29 – 2.14 (m, 2H), 1.50 – 1.21 (m, 6H). 0.89 (s, 9H), 0.88 (m, 3H), 0.05 (s, 6H). Spectral data were in accordance with the literature.[1]



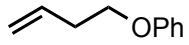
Oct-1-en-4-yl acetate: 4-Dimethylaminopyridine (122mg, 1 mmol) was weighed into a flask with a stir bar. Dichloromethane (10 mL), 1-octen-4-ol (1.54 mL, 10 mmol), acetic anhydride (1.9 mL, 20 mmol) was added to the vial and stirred overnight (10 hours). The reaction mixture was diluted with water (*ca.* 125 mL) and extracted with dichloromethane (*ca.* 50 mL x3) and the combined organics were washed with brine and subsequently dried over $MgSO_4$. Purification by column chromatography gave the desired compound (1.52g, 89% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.73 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.08 – 5.00 (m, 2H), 4.89 (ddd, *J* = 12.7, 6.6, 5.7 Hz, 1H), 2.34 – 2.22 (m, 2H), 2.01 (s, 3H), 1.59 – 1.47 (m, 2H), 1.45 – 1.17 (m, 4H), 0.96 – 0.81 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.71, 133.78, 117.47, 73.27, 38.62, 33.24, 27.43, 22.49, 21.17, 13.93. **HRMS** (EI+) calc'd for $C_7H_{13}O_2$ (M-CH_2CHCH_2) 129.0916, found 129.0917.



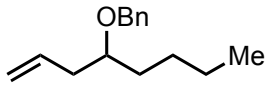
4-Methoxyoct-1-ene: NaH (60wt% dispersion in mineral oil, 600 mg, 15 mmol) was weighed into a flask with a stir bar. Tetrahydrofuran (10 mL) was added to the vial and

[1] *Org. Lett.* **2012**, *14,* 5728–5731

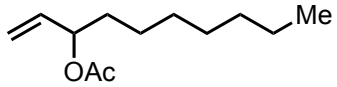
the mixture was cooled to 0 ºC. 1-Octen-4-ol (1.54 mL, 10 mmol) were added slowly to the suspension. MeI (0.75 mL, 12 mmol) was next added slowly to the reaction mixture. The reaction mixture was allowed to warm to room temperature and stirred overnight (*ca.* 10 h). The reaction mixture was diluted with water (*ca.* 125 mL) and extracted with diethyl ether (*ca.* 50 mL x3) and the combined organics were washed with brine and subsequently dried over $MgSO_4$. Purification by column chromatography gave the desired compound (1.01g, 71% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.06 (m, 2H), 3.34 (s, 3H), 3.20 (p, *J* = 5.9 Hz, 1H), 2.26 (m, 2H), 1.47 (m, 2H), 1.31 (m, 4H), 0.90 (m, 3H). Spectral data were in accordance with the literature.[2]



(but-3-en-1-yloxy)benzene: Prepared according to the literature.[3] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 6.97 – 6.92 (m, 1H), 6.92 – 6.90 (m, 2H), 5.95 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H), 5.20 – 5.09 (m, 2H), 4.03 (t, *J* = 6.7 Hz, 2H), 2.60 – 2.51 (m, 2H). Spectral data were in accordance with the literature.[3]



((oct-1-en-4-yloxy)methyl)benzene: NaH (60wt% dispersion in mineral oil, 600 mg, 15 mmol) was weighed into a flask with a stir bar. Tetrahydrofuran (10 mL) was added to the vial and the mixture was cooled to 0 ºC. 1-Octen-4-ol (1.54 mL, 10 mmol) was added slowly to the suspension. Benzyl bromide (1.4 mL, 12 mmol) was next added slowly to the reaction mixture. The reaction mixture was allowed to warm to room temperature and stirred overnight (*ca.* 10 h). The reaction mixture was diluted with water (*ca.* 125 mL) and extracted with diethyl ether (*ca.* 50 mL x3) and the combined organics were washed with brine and subsequently dried over $MgSO_4$. Purification by column chromatography gave the desired compound (1.48g, 68% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 4H), 7.33 – 7.27 (m, 1H), 5.89 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.21 – 5.06 (m, 2H), 4.60 (d, *J* = 15.0 Hz, 1H), 4.52 (d, *J* = 15.0 Hz, 1H), 3.47 (dq, *J* = 6.7, 5.6 Hz, 1H), 2.47 – 2.26 (m, 2H), 1.67 – 1.50 (m, 2H), 1.50 – 1.26 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.97, 135.12, 128.29, 127.72, 127.42, 116.79, 78.58, 70.89, 38.33, 33.52, 27.58, 22.81, 14.11. **HRMS** (EI+) calc'd for $C_{12}H_{17}O$ (M - CH_2CHCH_2) 177.1279, found 177.1284.



Dec-1-en-3-yl acetate: prepared according to the literature.[4] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.82 – 5.72 (m, 1H), 5.26 – 5.19 (m, 2H), 5.14 (dt, *J* = 10.4, 1.2 Hz, 1H), 2.05 (s, 3H), 1.72 – 1.52 (m, 2H), 1.36 – 1.23 (m, 10H), 0.90 (d, *J*=12.5 Hz, 3H). Spectral data were in accordance with the literature.[4]

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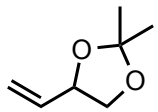
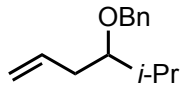
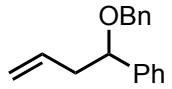
[2] *J. Org. Chem.* **2000**, *65*, 6254–6256
[3] *J. Org. Chem.* **2009**, *74*, 2854–2857
[4] *J. Organomet. Chem.* **2009**, *694,* 551-560



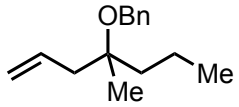
2,2-Dimethyl-4-vinyl-1,3-dioxolane: prepared according to the literature.[5] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.36 (m, 1H), 5.22 (ddd, *J* = 10.3, 1.5, 0.8 Hz, 1H), 4.50 (dtd, *J* = 7.3, 6.7, 6.3, 0.9 Hz, 1H), 4.11 (dd, *J* = 8.1, 6.2 Hz, 1H), 3.60 (t, *J* = 7.9 Hz, 1H), 1.41 (d, *J* = 10.5 Hz, 6H). Spectral data were in accordance with the literature.[5]



(((2-methylhex-5-en-3-yl)oxy)methyl)benzene: prepared according to literature.[6] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 4H), 7.30 – 7.24 (m, 1H), 5.89 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.10 (ddt, *J* = 17.1, 2.2, 1.5 Hz, 1H), 5.05 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 4.58 (d, *J* = 10 Hz, 1H), 4.50 (d, *J* = 10 Hz, 1H), 3.20 (dt, *J* = 6.2, 5.5 Hz, 1H), 2.31 (ddd, *J* = 7.3, 5.8, 1.3 Hz, 2H), 1.95 – 1.80 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H). Spectral data were in accordance with the literature.[6]



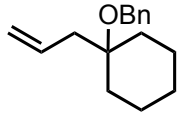
(1-(benzyloxy)but-3-en-1-yl)benzene: prepared according to literature.[7] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 10H), 5.78 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.07 – 5.00 (m, 2H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.37 (dd, *J* = 7.6, 5.8 Hz, 1H), 4.27 (m, 1H), 2.65 (dddt, *J* = 14.4, 7.7, 6.9, 1.3 Hz, 1H), 2.44 (dddt, *J* = 14.2, 7.1, 5.8, 1.3 Hz, 1H). Spectral data were in accordance with the literature.[7]



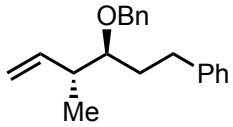
(((4-methylhept-1-en-4-yl)oxy)methyl)benzene: NaH (60wt% dispersion in mineral oil, 600 mg, 15 mmol) was weighed into a flask with a stir bar. Dimethylacetamide (10 mL) was added to the vial and the mixture was cooled to 0 ºC. 4-Methylhept-1-en-4-ol (1.28 g, 10 mmol) was added slowly to the suspension. Benzyl bromide (1.4 mL, 12 mmol) was next added slowly to the reaction mixture. The reaction mixture was allowed to warm to room temperature and stirred overnight (*ca.* 10 h). The reaction mixture was diluted with water (*ca.* 125 mL) and extracted with diethyl ether (*ca.* 50 mL x3) and the combined organics were washed with brine and subsequently dried over $MgSO_4$. Purification by column chromatography gave the desired compound (1.29 g, 59% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.22 (m, 5H), 5.97 – 5.83 (m, 1H), 5.14 – 5.06 (m, 2H), 4.44 (s, 2H), 2.43 – 2.29 (m, 2H), 1.62 – 1.49 (m, 2H), 1.48 – 1.36 (m, 2H), 1.22 (s,

[5] *Tetrahedron: Asymmetry* **1996**, *7*, 3593
[6] *Tetrahedron* **2011**, *67*, 5621-5629.
[7] *Org. Lett.* **2010** , *12*, 2488-2491

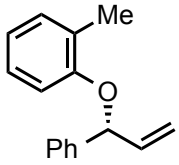
3H), 0.94 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.75, 134.63, 128.22, 127.26, 127.04, 117.18, 76.86, 63.23, 42.95, 40.42, 23.26, 16.71, 14.65. **HRMS** (EI+) calc'd for $C_{12}H_{17}O$ (M - CH_2CHCH_2) 177.1279, found 177.1283.



(((1-allylcyclohexyl)oxy)methyl)benzene: Prepared according to the literature.[6] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.36 – 7.31 (m, 2H), 7.28 – 7.23 (m, 1H), 5.98 – 5.80 (m, 1H), 5.12 – 5.04 (m, 2H), 4.42 (s, 2H), 2.34 (dt, J = 7.2, 1.3 Hz, 2H), 1.87 – 1.81 (m, 2H), 1.69 – 1.56 (m, 3H), 1.50 – 1.43 (m, 2H), 1.42 – 1.32 (m, 2H), 1.32 – 1.20 (m, 1H). Spectral data were in accordance with the literature.[6]



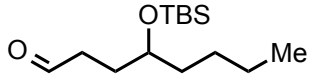
(*trans*-3-(benzyloxy)-4-methylhex-5-en-1-yl)benzene: NaH (60 wt% dispersion in mineral oil, 600 mg, 15 mmol) was weighed into a flask with a stir bar. Dimethylacetamide (10 mL) was added to the vial and the mixture was cooled to 0 ºC. *trans*-4-methyl-1-phenylhex-5-en-3-ol (1.9 g, 10 mmol) was added slowly to the suspension. Benzyl bromide (1.4 mL, 12 mmol) was next added slowly to the reaction mixture. The reaction mixture was allowed to warm to room temperature and stirred overnight (*ca*. 10 h). The reaction mixture was diluted with water (*ca*. 125 mL) and extracted with diethyl ether (*ca*. 50 mL x3) and the combined organics were washed with brine and subsequently dried over $MgSO_4$. Purification by column chromatography gave the desired compound (1.47 g, 52% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.13 (m, 10H), 5.88 – 5.76 (m, 1H), 5.12 – 5.01 (m, 2H), 4.62 (d, J = 10.1, 1H), 4.52 (d, J = 10.1 1H), 3.35 (dt, J = 8.4, 4.3 Hz, 1H), 2.84 – 2.76 (m, 1H), 2.60 (ddd, J = 13.9, 9.8, 6.7 Hz, 2H), 1.88–1.70 (m, 2H), 1.05 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.45, 140.79, 138.87, 128.42, 128.33, 128.31, 127.81, 127.50, 125.69, 114.64, 82.11, 71.73, 40.16, 32.46, 32.23, 14.50. **HRMS** (EI+) calc'd for $C_{20}H_{24}O$ (M+) 280.1827, found 280.1818.



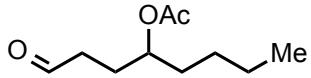
(*R*)-1-phenyl-1-(2-methylphenoxy)-2-propene: prepared according to the literature.[8] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.41 (m, 2H), 7.40 – 7.34 (m, 2H), 7.31 – 7.27 (m, 1H), 7.16 – 7.13 (m, 1H), 7.05 (tdd, J = 8.0, 1.5, 0.9 Hz, 1H), 6.86 – 6.80 (m, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.10 (ddd, J = 17.1, 10.4, 5.8, Hz, 1H), 5.65 (d, J = 5.8 Hz, 1H), 5.38 (d, J = 17.3, Hz, 1H), 5.24 (dq, J = 10.4, 1.2 Hz, 1H), 2.33 (s, 3H). Spectral data were in accordance with the literature.[8] $[\alpha]_D$ = -7.6 (c 0.94, $CHCl_3$), which is in accordance with

[8] *J. Am. Chem. Soc.* **2003,** *125*, 3426–3427

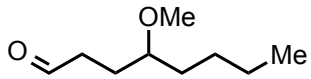
literature values.[8] HPLC analysis indicated an enantiomeric excess of 95% [Chiralcel® OJ-H column, eluting with 99.9:0.1 hexane/*i*-PrOH, 0.7 mL/min, 220 nm; (*S*) enantiomer t_R, 16.2, (*R*) enantiomer t_R 16.7 min].



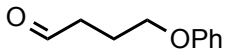
4-((*tert*-butyldimethylsilyl)oxy)octanal (table 1, entry 1): 98.6 mg (76% yield) obtained using procedure A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.7 Hz, 1H), 3.71 (tt, *J* = 6.2, 4.5 Hz, 1H), 2.49 (td, *J* = 7.5, 1.7 Hz, 2H), 1.89 – 1.80 (m, 1H), 1.71 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.51 – 1.34 (m, 2H), 1.35 – 1.20 (m, 4H), 0.88, (m, 3H), 0.87 (s, 9H), 0.04 (d, *J* = 4.1 Hz, 6H). Spectral data were in accordance with the literature.[9]



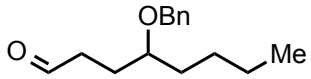
1-oxooctan-4-yl acetate (table 1, entry 2): 70.8 mg (76% yield) obtained using procedure A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.4 Hz, 1H), 4.89 (dddd, *J* = 8.2, 7.3, 5.4, 4.0 Hz, 1H), 2.48 (ddt, *J* = 8.2, 6.7, 1.3 Hz, 2H), 2.04 (s, 3H), 1.99 – 1.90 (m, 1H), 1.88 – 1.79 (m, 1H), 1.63 – 1.46 (m, 2H), 1.36 – 1.23 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.47, 170.82, 73.33, 39.96, 33.83, 27.40, 26.36, 22.50, 21.15, 13.94. **HRMS** (EI+) calc'd for $C_8H_{15}O_2$ (M - CH_3CO) 143.1072, found 143.1109



4-methoxyoctanal (table 1, entry 3): 71% obtained using procedure B.



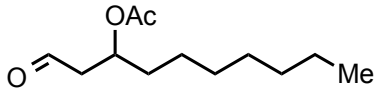
4-phenoxybutanal (table 1, entry 4): 72.0 mg (88% yield) obtained using procedure A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.85 (t, *J* = 1.4 Hz, 1H), 7.32 – 7.24 (m, 2H), 6.95 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.88 (dt, *J* = 7.8, 1.0 Hz, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 2.68 (td, *J* = 7.1, 1.3 Hz, 2H), 2.13 (tt, *J* = 7.0, 6.0 Hz, 2H). Spectral data were in accordance with the literature.[10]



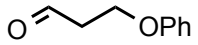
4-(benzyloxy)octanal (table 1, entry 5): 99.9 mg (85% yield) obtained using procedure A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.7 Hz, 1H), 7.40 – 7.26 (m, 5H), 4.54 – 4.50 (m, 1H), 4.45 – 4.41 (m, 1H), 3.41 (dtd, *J* = 7.3, 6.0, 4.1 Hz, 1H), 2.52 (ddt, *J* = 7.4, 6.9, 1.6 Hz, 2H), 1.92 (dddd, *J* = 14.5, 7.6, 6.9, 4.1 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.62 (dtd, *J* = 13.6, 5.8, 4.7 Hz, 1H), 1.52 – 1.42 (m, 1H), 1.33 (ttd, *J* = 6.0, 4.2, 3.2, 2.0 Hz, 4H), 0.91 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.55, 138.57, 128.36,

[9] *Org. Lett.* **2012**, *14*, 5728
[10] *Angew. Chem. Int. Ed.* **2010**, *49*, 4047

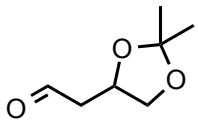
127.83, 127.57, 77.91, 70.87, 40.00, 33.34, 27.42, 26.28, 22.84, 14.06. **HRMS** (EI+) calc'd for $C_{15}H_{22}O_2$ (M+) 234.1620, found 234.1632.



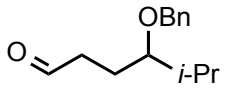
1-oxodecan-3-yl acetate (table 1, entry 6): 75% obtained using procedure B.



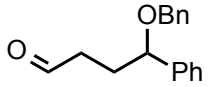
3-phenoxypropanal (table 1, entry 7): 61.3 mg (82% yield) obtained using procedure A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.7 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.00 – 6.95 (m, 1H), 6.93 – 6.90 (m, 2H), 4.32 (t, *J* = 6.1 Hz, 2H), 2.91 (td, *J* = 6.1, 1.6 Hz, 2H). Spectral data were in accordance with the literature.[11]



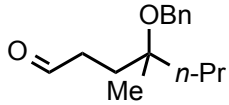
2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (table 1, entry 8): 64% yield obtained using procedure B.



4-(benzyloxy)-5-methylhexanal (table 2, entry 1): 88.1 mg (80% yield) obtained using procedure A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.66 (t, *J* = 1.7 Hz, 1H), 7.30 – 7.17 (m, 5H), 4.46 (d, *J* = 12.5, 1H), 4.34 (d, *J* = 12.5 1H), 3.11 (ddd, *J* = 8.6, 5.4, 3.4 Hz, 1H), 2.43 (m, 2H), 1.90 (dtd, *J* = 13.7, 6.9, 5.4 Hz, 1H), 1.78 (m, 1H), 1.70 (m, 1H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.68, 138.60, 128.35, 127.85, 127.57, 83.14, 71.64, 40.39, 30.27, 22.49, 18.72, 17.30. **HRMS** (EI+) calc'd for $C_{14}H_{20}O_2$ (M+) 220.1463, found 220.1466.



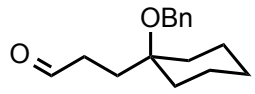
4-(benzyloxy)-4-phenylbutanal (table 2, entry 2): 94.1 mg (74% yield) obtained using procedure A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.6 Hz, 1H), 7.35 (m, 10H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.37 (dd, *J* = 8.3, 4.8 Hz, 1H), 4.25 (d, *J* = 11.7 Hz, 1H), 2.54 (m, 2H), 2.14 (ddt, *J* = 14.2, 8.4, 7.1 Hz, 1H), 2.04 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.21, 141.55, 138.18, 128.60, 128.38, 127.87, 127.81, 127.62, 126.63, 80.20, 70.52, 40.46, 30.91. **HRMS** (EI+) calc'd for $C_{11}H_{13}O_2$ (M - C_6H_5) 177.0916, found 177.0956.



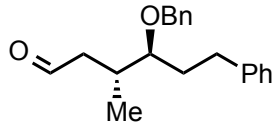
4-(benzyloxy)-4-methylheptanal (table 2, entry 3): 90.2 mg (77% yield) obtained using procedure A except $NaNO_2$ is replaced with $AgNO_2$ and the reaction is allowed to

[11] *Tetrahedron: Asymmetry* **1999**, *10*, 3939

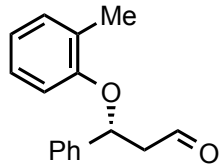
proceed for 24 h. Isolated as an inseparable mixture of aldehyde and ketone (9:1). Spectral data reported for aldehyde product (major). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.6 Hz, 1H), 7.35 – 7.31 (m, 4H), 7.28 – 7.24 (m, 1H), 4.37 (s, 2H), 2.55 (ddt, *J* = 8.4, 6.7, 1.6 Hz, 2H), 1.99 – 1.92 (m, 1H), 1.89 – 1.80 (m, 1H), 1.60 – 1.50 (m, 2H), 1.43 – 1.35 (m, 2H), 1.23 (s, 3H), 0.95 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.66, 139.36, 128.30, 127.23, 127.19, 76.23, 63.25, 40.66, 38.73, 30.32, 23.02, 17.04, 14.69. **HRMS** (EI+) calc'd for $C_{13}H_{19}O$ (M - CH_2CHO) 191.1436, found 191.1444.



3-(1-(benzyloxy)cyclohexyl)propanal: 94.8 mg (77% yield) obtained using procedure A except $NaNO_2$ is replaced with $AgNO_2$ and the reaction is allowed to proceed for 24 h. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.81 (t, *J* = 1.4 Hz, 1H), 7.38 – 7.32 (m, 4H), 7.29 – 7.24 (m, 1H), 4.35 – 4.29 (s, 2H), 2.54 (ddd, *J* = 9.1, 6.5, 1.5 Hz, 2H), 1.87 (m, 4H), 1.63 (m, 3H), 1.48 (m, 2H), 1.32 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.58, 139.30, 128.31, 127.23, 127.18, 74.77, 62.24, 37.90, 34.45, 28.51, 25.85, 21.92. **HRMS** (EI+) calc'd for $C_{16}H_{22}O_2$ (M+) 246.1620, found 246.1618.

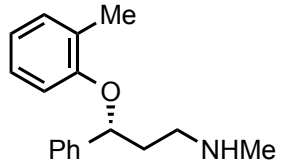


***trans*-4-(benzyloxy)-3-methyl-6-phenylhexanal:** 96.3 mg (65% yield) obtained using procedure A except $NaNO_2$ is replaced with $AgNO_2$ and the reaction is allowed to proceed for 24 h. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.72 (t, *J* = 2.1 Hz, 1H), 7.38 – 7.14 (m, 10H), 4.55 – 4.48 (m, 2H), 3.26 (td, *J* = 6.1, 4.3 Hz, 1H), 2.77 (ddd, *J* = 13.7, 9.9, 6.0 Hz, 1H), 2.66 (ddd, *J* = 13.8, 10.0, 6.7 Hz, 1H), 2.50 – 2.43 (m, 2H), 2.34 – 2.26 (m, 1H), 1.90 – 1.81 (m, 2H), 1.00 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.07, 142.18, 138.39, 128.43, 128.39, 128.34, 127.92, 127.66, 125.86, 82.08, 71.66, 47.86, 32.27, 31.27, 31.06, 16.36. **HRMS** (EI+) calc'd for $C_{20}H_{24}O_2$ (M+) 296.1776, found 296.1778.



(*R*)-3-phenyl-3-(*2*-methylphenoxy)propanal: 85.3 mg (71% yield) obtained using procedure A except $NaNO_2$ is replaced with $AgNO_2$. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.88 (dd, *J* = 2.5, 1.6 Hz, 1H), 7.41 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 7.13 (ddd, *J* = 7.4, 1.7, 0.9 Hz, 1H), 6.98 (td, *J* = 8.1, 1.7 Hz, 1H), 6.82 (td, *J* = 7.4, 1.1 Hz, 1H), 6.65 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.72 (dd, *J* = 8.6, 4.2 Hz, 1H), 3.15 (ddd, *J* = 16.6, 8.6, 2.6 Hz, 1H), 2.88 (ddd, *J* = 16.6, 4.2, 1.6 Hz, 1H), 2.28 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.83, 155.38, 140.36, 130.77, 128.91, 128.06, 127.16, 126.58, 125.67, 120.88, 112.88, 74.88, 51.91, 16.42. **HRMS** (EI+) calc'd for $C_{16}H_{16}O_2$ (M+) 240.1150, found 240.1155.

$[\alpha]_D$ = -10.1 (c 0.48, $CHCl_3$). Enantiomeric excess checked by derivatization to atomoxetine (*vide infra*).



(*R*)-3-phenyl-3-(*2*-methylphenoxy)propanal was derivatized to atomoxetine by treatment of the aldehyde with excess $NaBH_3CN$ (*ca*. 3 equiv) and methylamine hydrochloride (*ca*. 50 equiv) to provided a crude mixture (37% yield of atomoxetine according to ^{1}H NMR analysis), which was purified by preparatory thin layer chromatography for characterization and determination of enantiomeric excess. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 4H), 7.27 – 7.22 (m, 1H), 7.12 (ddd, *J* = 7.3, 1.7, 0.9 Hz, 1H), 6.98 – 6.92 (m, 1H), 6.78 (td, *J* = 7.4, 1.1 Hz, 1H), 6.62 – 6.58 (m, 1H), 5.28 (dd, *J* = 8.3, 4.4 Hz, 1H), 2.90 – 2.80 (m, 2H), 2.47 (s, 3H), 2.32 (s, 3H), 2.30 – 2.19 (m, 1H), 2.11 (dtd, *J* = 14.2, 7.3, 4.5 Hz, 1H). Spectral data were in accordance with the literature.[12] $[\alpha]_D$ = -31.6 (c 0.10, $CHCl_3$), which is in accordance with literature values.[12] SFC analysis indicated an enantiomeric excess of 94% [Chiralcel® OD-H column, eluting with 20% MeOH, 2.5 mL/min, 220 nm; (*S*) enantiomer t_R, 3.95, (*R*) enantiomer t_R 5.4 min].

Intramolecular competition experiments

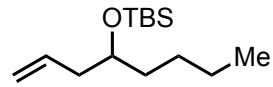
Each initial rate measurement was made in duplicate and the values averaged. The following procedure was used: $PdCl_2(PhCN)_2$ (0.02 mmol, 7.7 mg), $CuCl_2$•$2H_2O$ (0.02 mmol, 3.6 mg) and $NaNO_2$ (0.01 mmol, 0.7 mg) were weighed into a 8 mL vial charged with a stir bar. The vial was sparged for 1 minute with oxygen (1 atm, balloon). Premixed and oxygen saturated *t*-BuOH (3 mL) and $MeNO_2$ (0.2 mL) was added followed by the addition of pre-mixed alkenes (0.1 mmol of each alkene). The solution was saturated with oxygen by an additional 10 seconds of sparging. The reaction was then allowed to stir at room temperature (20-25ºC) for 10 minutes. Next, the reaction was quenched by addition of pyridine (5 μL) and then water (10mL) and extracted three times with dichloromethane (*ca*. 5 mL). The combined organic layers were subsequently washed with a saturated solution of $NaHCO_3$ (*ca.* 5 mL) and dried over Na_2SO_4. The resulting solution was subjected to ^{1}H NMR analysis to determine relative rates. Benzonitrile signals were used as an internal standard to confirm that conversion was <15% in each case.

The selectivity of each substrate under the nitrite-modified Wacker was independently measured using procedure B.

[12] *Tetrahedron: Asymmetry* **2013**, *24*, 913 - 918

^{1}H-NMR spectra

ZKW-IV-10-E1



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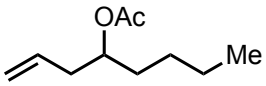

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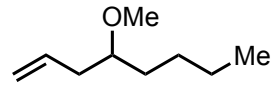

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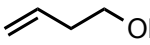

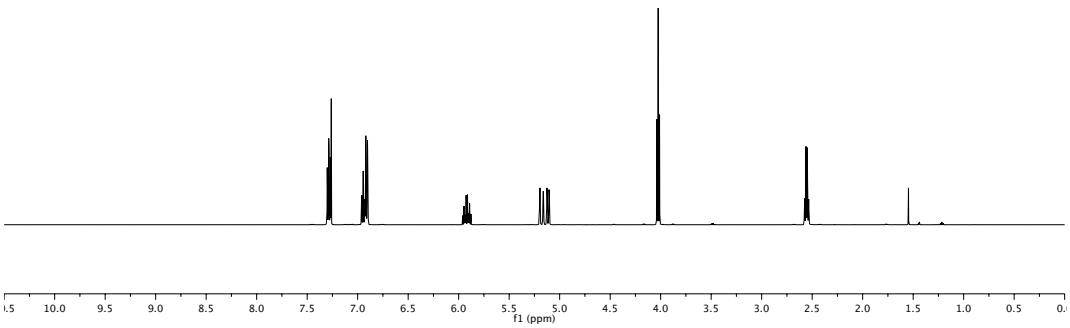

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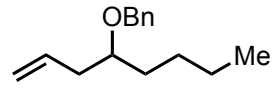
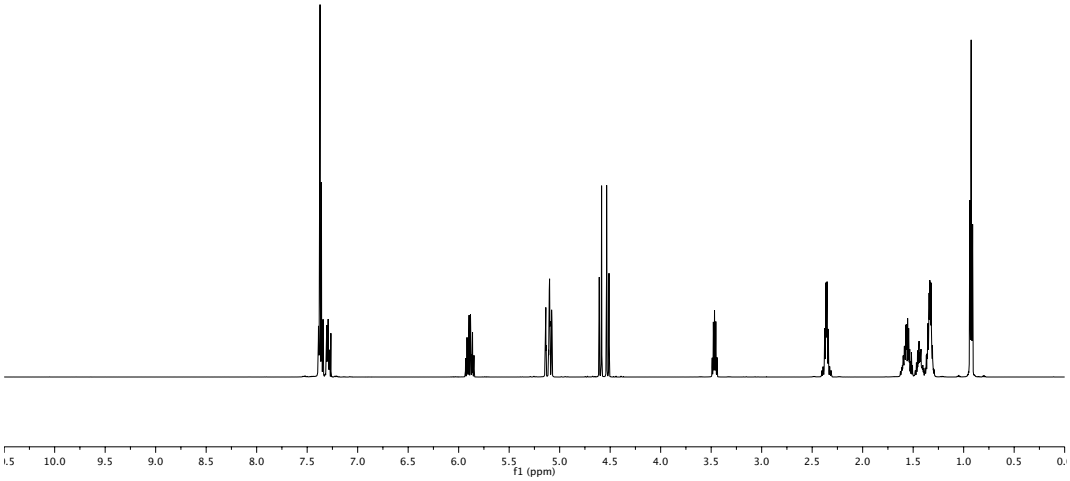
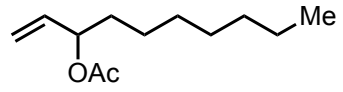
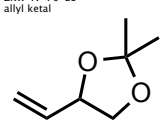




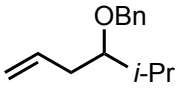
ZKW-III-109p
OAc

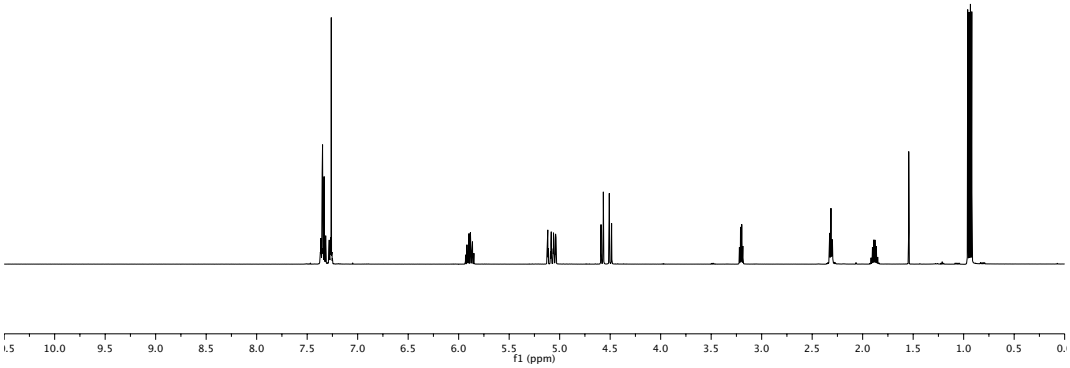


ZKW-IV-70-E1
allyl ketal

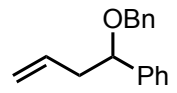


KS_II_29_PureOBn
(Pure isolated product)

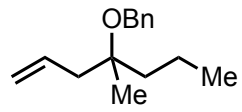


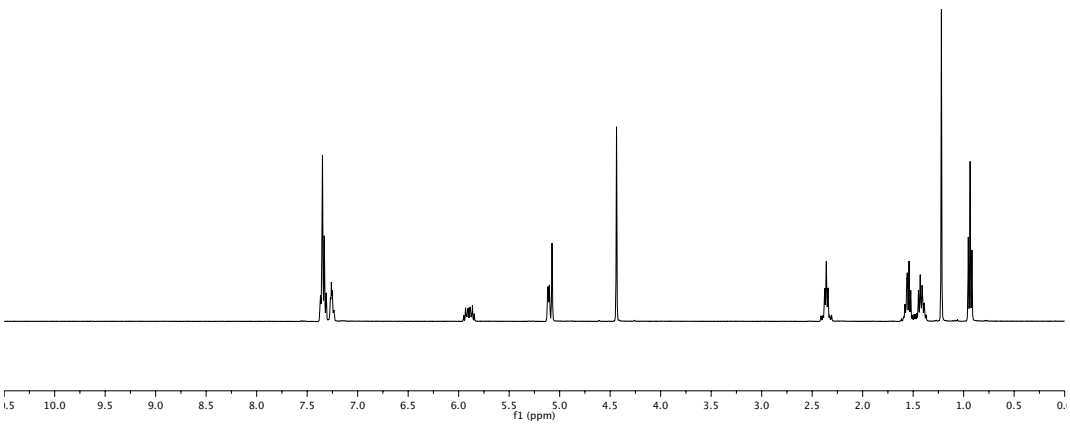


KS_II_39_OBnVial



ZKW-IV-70-E2





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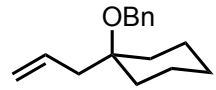
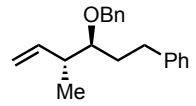
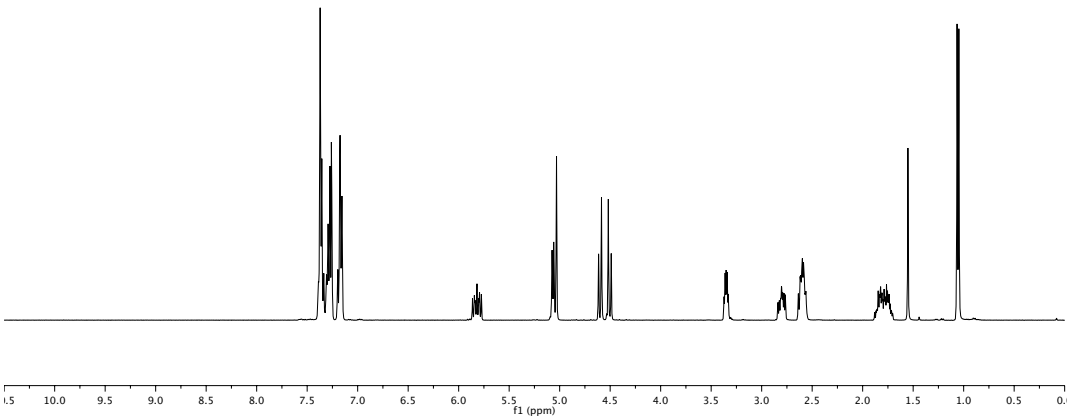
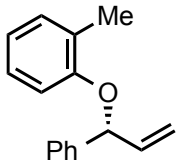


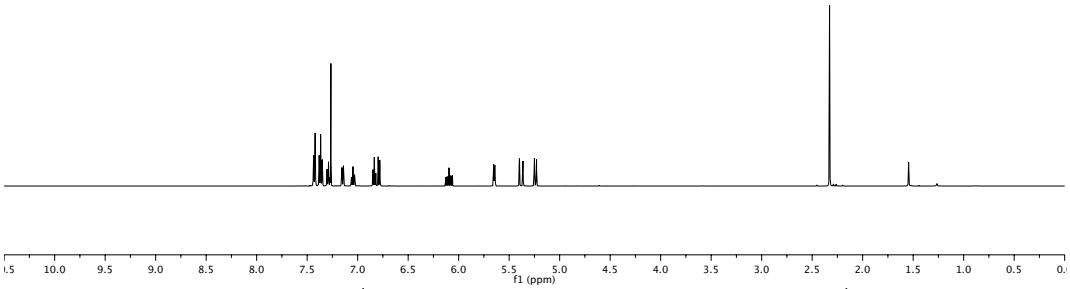
ZKW-IV-70-E3
crotylation benzyl



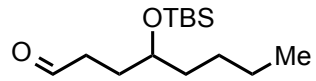


ZKW-IV-35p





ZKW-III-183pA-DRY



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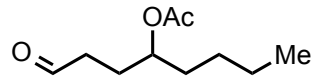

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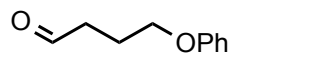
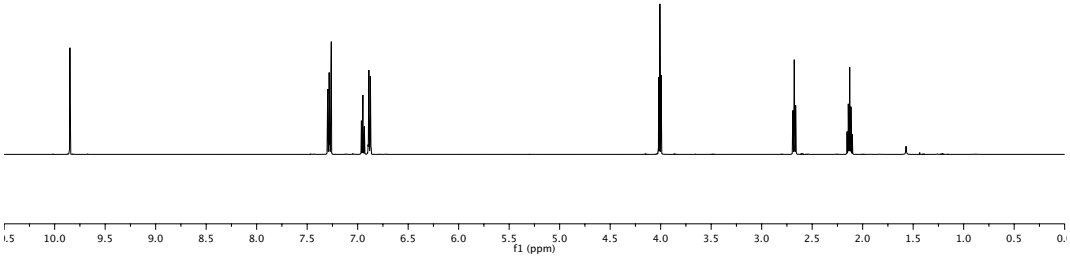
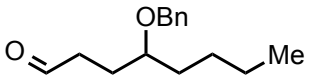
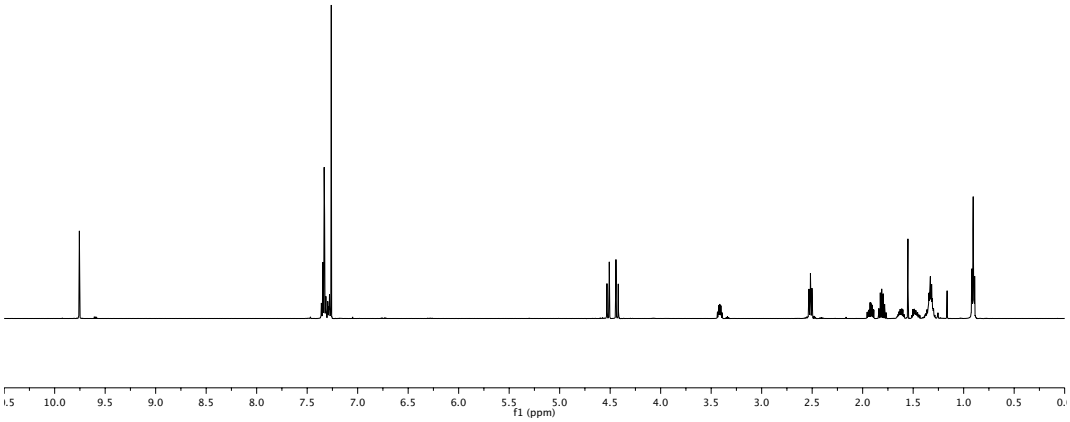




ZKW-III-175-pA





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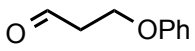
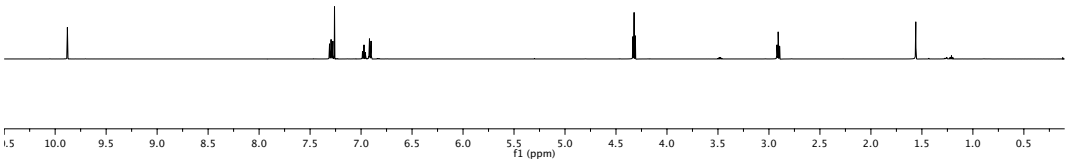
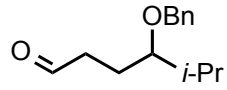
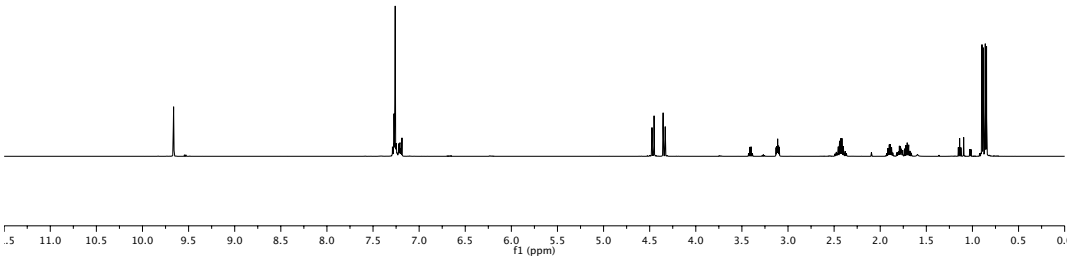


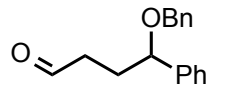


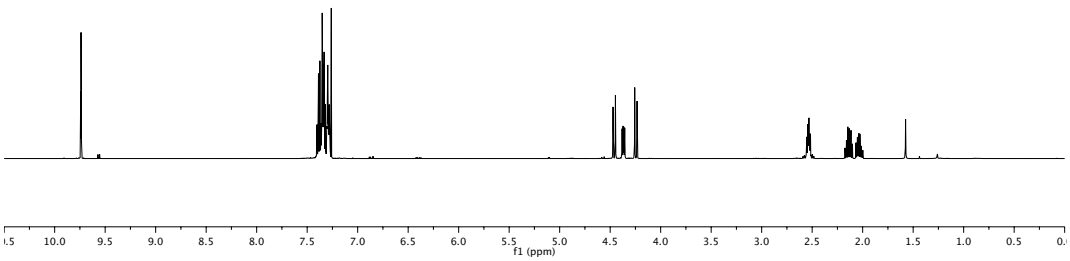
KS_II_59_pA



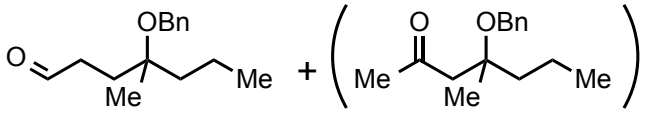


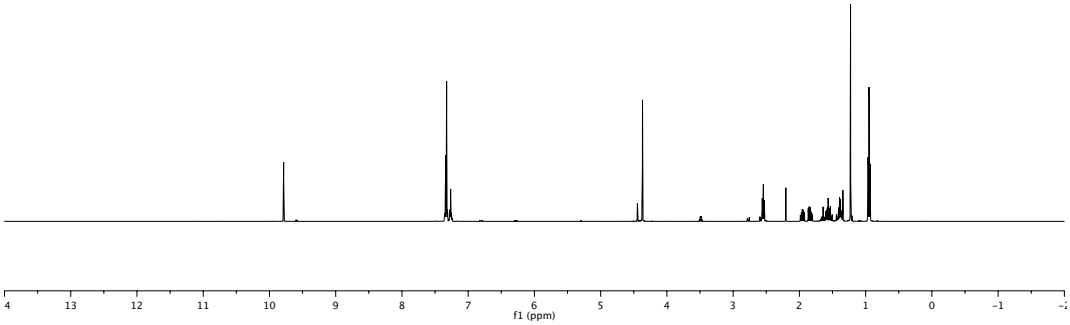
KS_II_53_pA



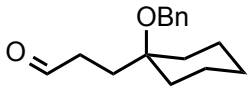


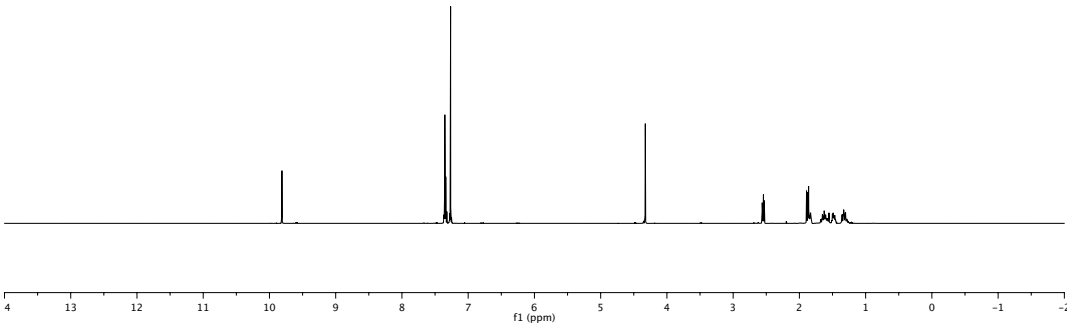
KS_II_71_v1_pA



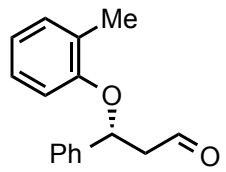


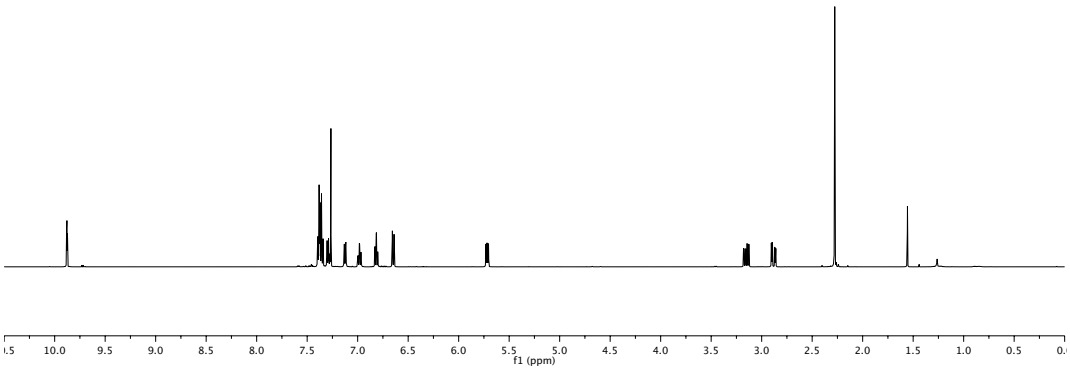
KS_II_95_v1_pA



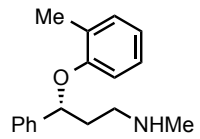


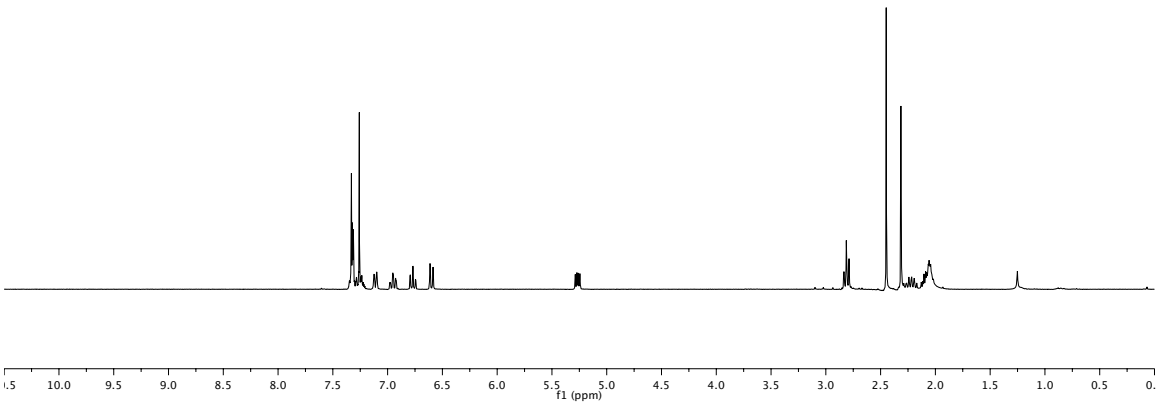
ZKW-IV-79pC





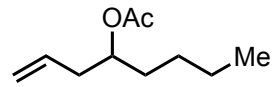
ZKW-IV-91p2

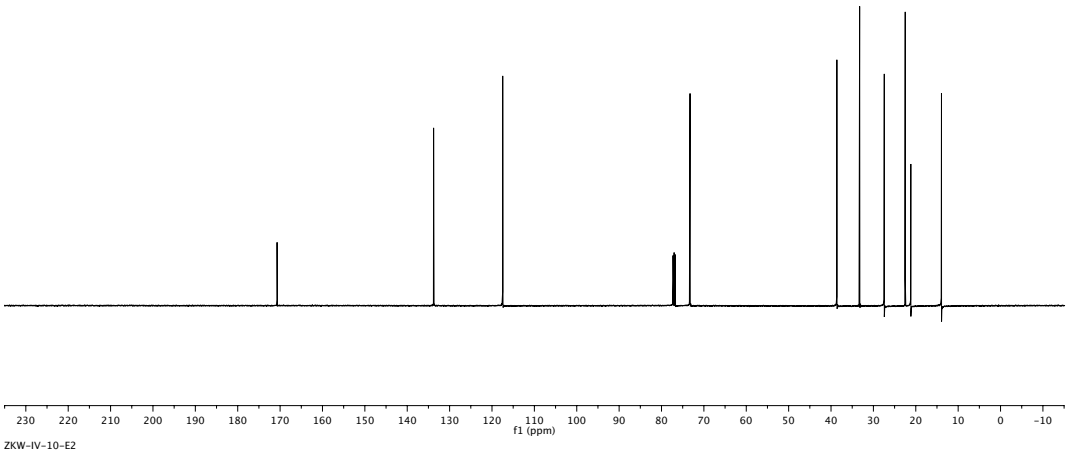




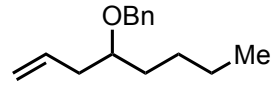
^{13}C-NMR spectra

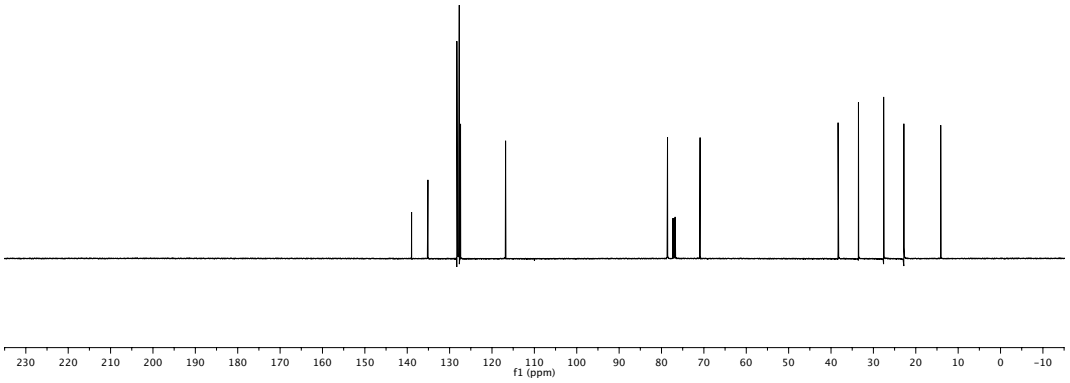
ZKW-IV-10-E3



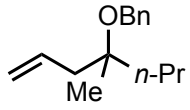


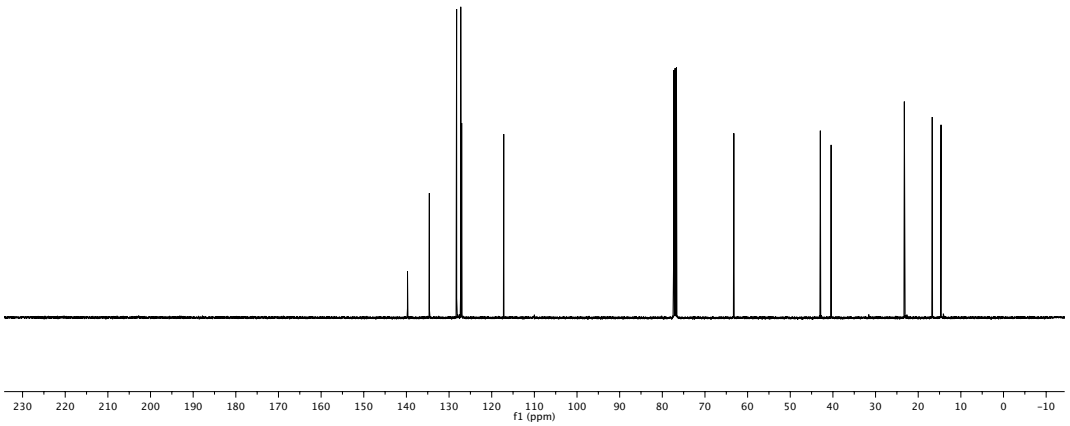
ZKW-IV-10-E2





ZKW-IV-70-E2





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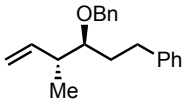
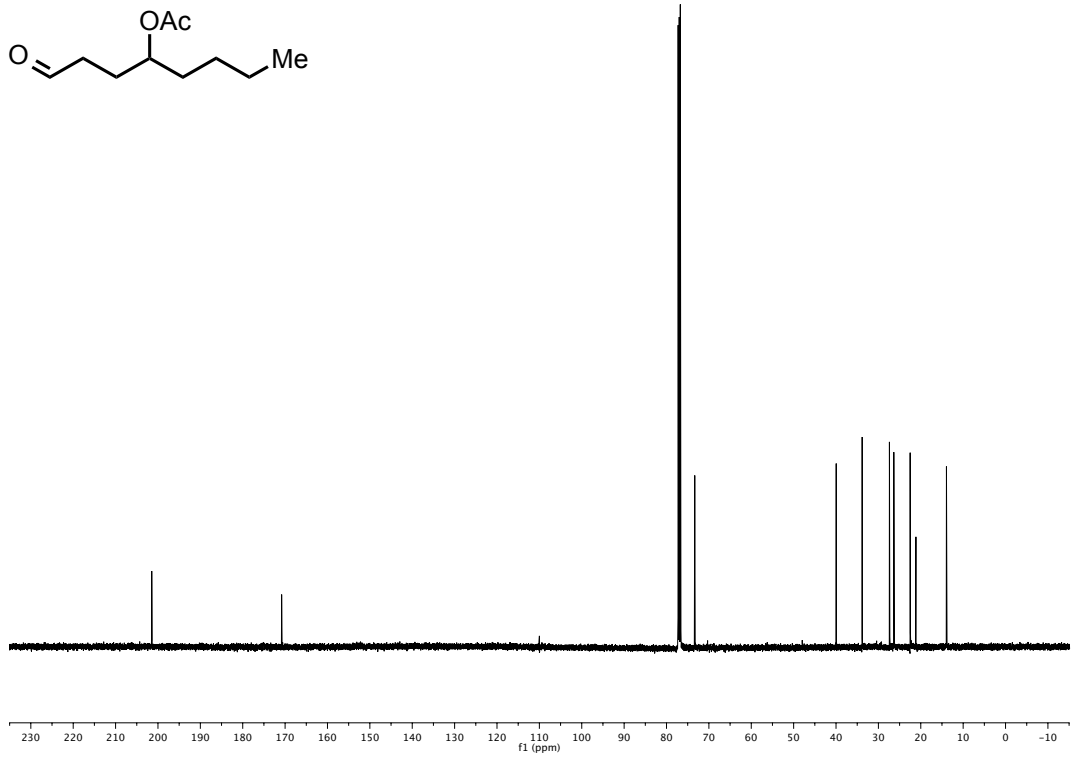
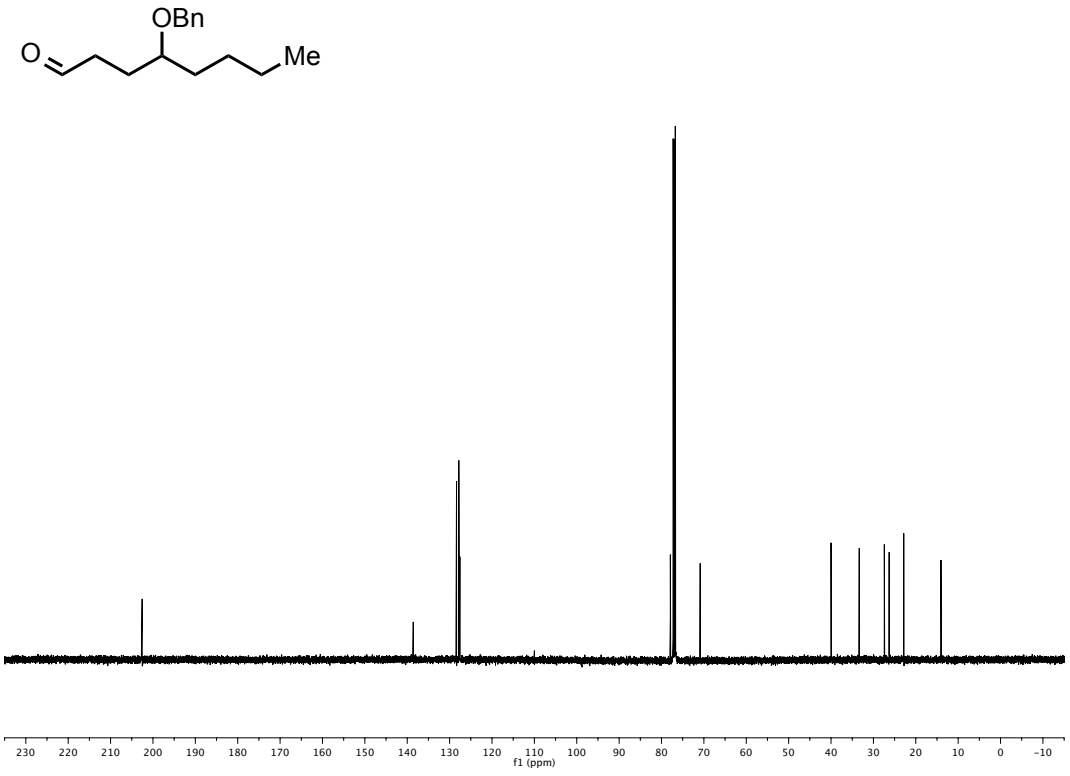


ZKW-IV-71-E2p1



ZKW-III-175-pA



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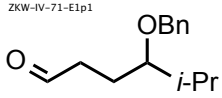
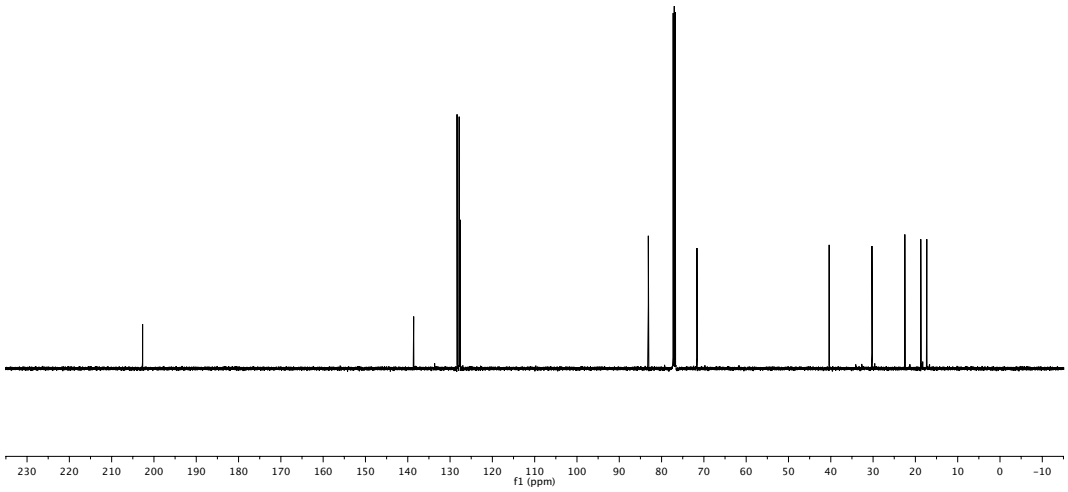
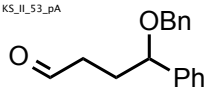
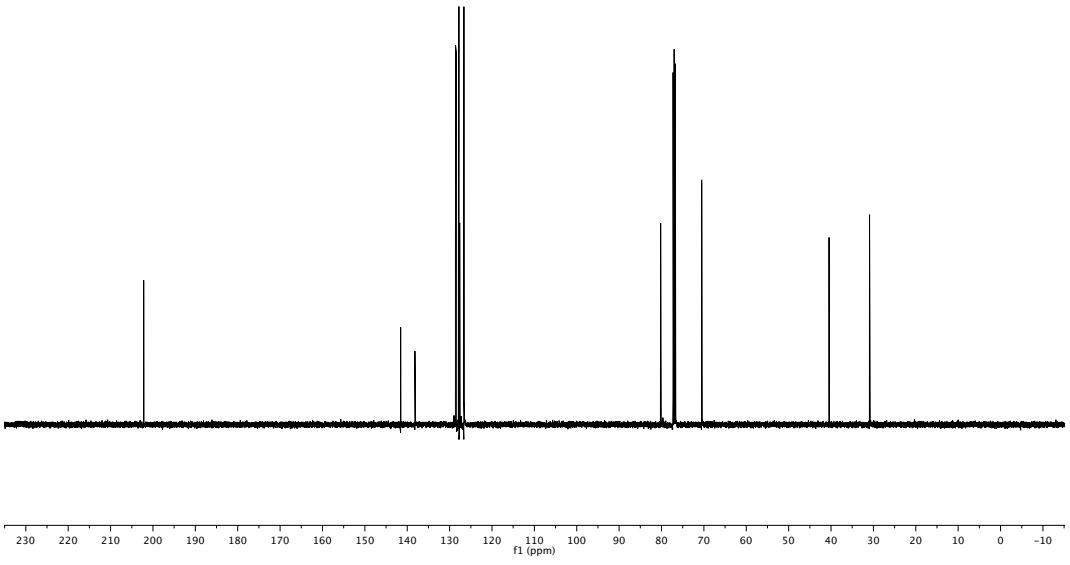


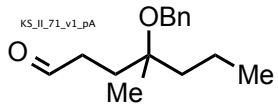


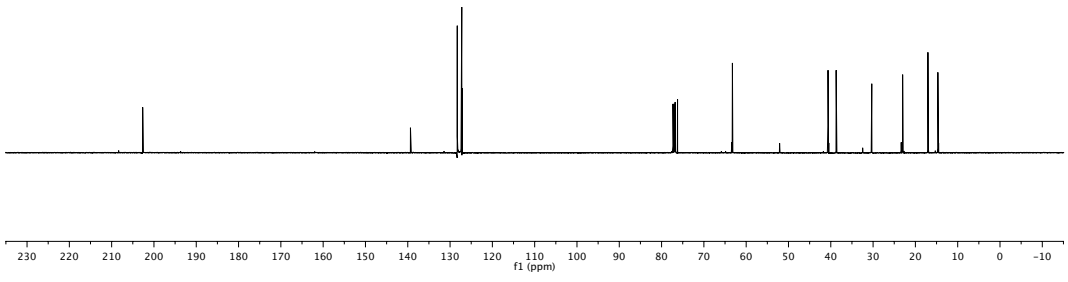
KS_II_53_pA



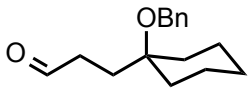


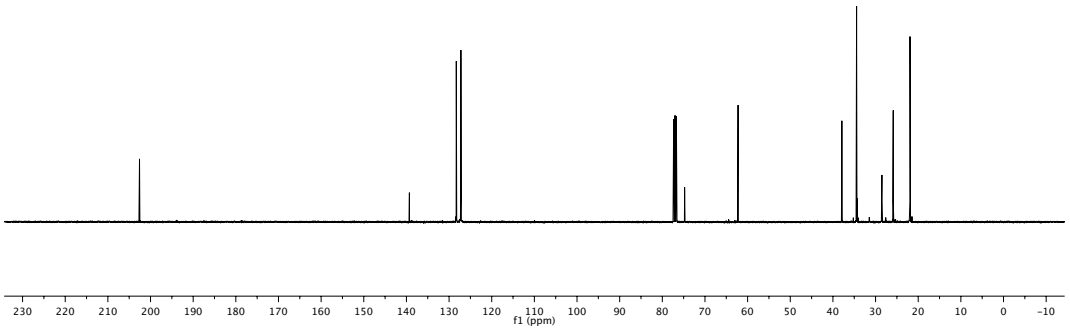
KS_II_71_v1_pA





KS_III_17_1





ZKW-IV-79p-atoCHO