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Supporting Information

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Aldehyde-Selective Wacker-Type Oxidation of Unbiased Alkenes Enabled by a Nitrite Co-Catalyst**

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Materials and methods

$PdCl_2(PhCN)_2$, $CuCl_2*2H_2O$, $AgNO_2$, anhydrous ^{t}BuOH and $MeNO_2$ were obtained from Sigma-Aldrich and were used as provided. All other materials were either obtained from commercial sources or prepared using literature methods. ^{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. GC-MS data was provided through the California Institute of Technology Mass Spectrometry Facility using HP 5970 series MSD with HP 5890 GC. Gas chromatography data was obtained using an Agilent 6850 FID gas chromatograph equipped with a HP-5 (5%-phenyl)-methylpolysiloxane capillary column (Agilent). Response factors relative to tridecane were collected for 1-dodecene, dodecanal and 2-dodecanone following literature procedures.[1]

General procedures

Procedure (A) for larger-scale (0.5 mmol) oxidation of aliphatic alkenes (isolation): $PdCl_2(PhCN)_2$ (0.06 mmol, 0.023 g), $CuCl_2*2H_2O$ (0.06 mmol, 0.0102 g) and $AgNO_2$ (0.03 mmol, 0.0046 g) were weighed into a 20 mL vial charged with a stir bar. The vial was sparged for 2 minutes 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) were added in that order via syringe. The solution was saturated with oxygen by an additional 45 seconds of sparging. The reaction was then allowed to stir at room temperature for 6 hours. 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). Selectivity was determined from ^{1}H NMR analysis of the unpurified mixture.

Procedure (B) for smaller-scale (0.2 mmol) oxidation of 1-dodecene (GC analysis): $PdCl_2(PhCN)_2$ (0.024 mmol, 0.0092 g), $CuCl_{2*}2H_2O$ (0.024 mmol, 0.0041 g) and $AgNO_2$ (0.012 mmol, 0.0018 g) were weighed into a 2 dram screw-cap vial charged with a stir bar. The vial was sparged for 45 seconds with oxygen (1 atm, balloon) then subsequently tridecane (0.00246 mmol, 6 μL), *t*-BuOH (3 mL), $MeNO_2$ (0.2 mL) and 1-dodecene (0.2 mmol, 44.4 µL) were added in that order via syringe. The solution was saturated with oxygen by an additional 45 seconds of sparging. The reaction was then allowed to stir at room temperature for 6 hours. Next, an aliquot (*ca*. 0.2 mL) was injected into a 2 mL vial containing an estimated 1 mL of premixed EtOAc/pyridine solution (3:1) to quench the reaction. The resulting solution was subsequently subjected to GC analysis to determine yield and selectivity.

Procedure (C) for small-scale (0.2mmol) oxidation of alkenes (NMR analysis): $PdCl_2(PhCN)_2$ (0.024 mmol, 0.0092 g), $CuCl_{2*}2H_2O$ (0.024 mmol, 0.0041 g) and $AgNO_2$ (0.012 mmol, 0.0018 g) were weighed into a 2 dram screw-cap vial charged with a stir bar. The vial was sparged for 45 seconds with oxygen (1 atm, balloon) then subsequently *t*-BuOH (3 mL), $MeNO_2$ (0.2 mL) and alkene (0.2 mmol) were added in that order via syringe. The solution was saturated with oxygen

[1] Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740–5745.

by an additional 45 seconds of sparging. The reaction was then allowed to stir at room temperature for 6 hours. Next, the reaction mixture was diluted with water (*ca*. 20 mL) and subsequently extracted three times with $CDCl_3$, dried with Na_2SO_4 and concentrated under reduced pressure for ^1H NMR analysis. Immediately prior to NMR analysis nitrobenzene was added as an internal standard. The resulting solution was subsequently subjected to ^1H NMR analysis to determine yield and selectivity.

Optimization of the nitrite additive

All entries produced following procedure B with the noted modifications.

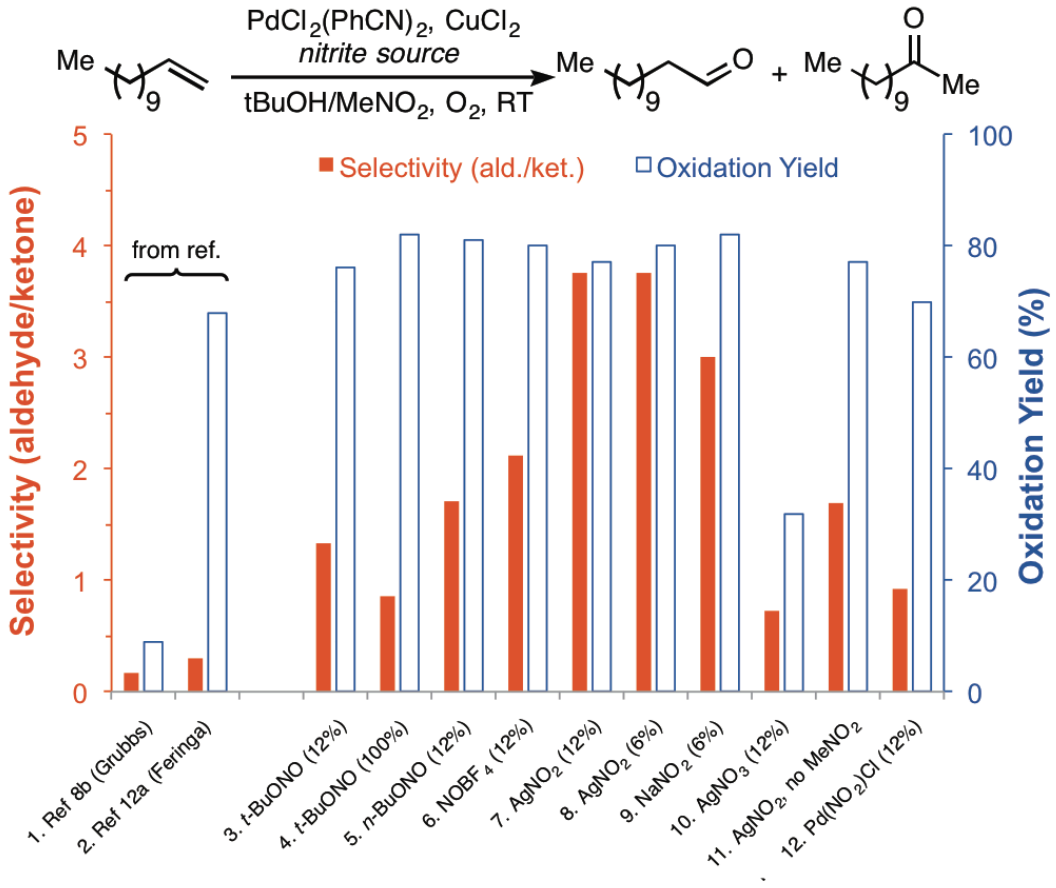


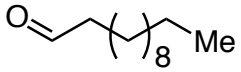
Table S1. Nitrite sources

entry	Nitrite source	Overall yield (aldehyde yield)	aldehyde/ketone (% selectivity)
1	Ref 8b (Grubbs)	9 (<1)	.16 (14)
2	Ref 12a (Feringa)	68 (12)	.22 (18)
3	*tert*-BuONO	76 (43)	1.3 (57)
4	*tert*-BuONO[a]	82 (38)	.85 (46)
5	*n*-BuONO	81 (51)	1.7 (63)
6	$NOBF_4$	80 (54)	2.1 (68)
7	$AgNO_2$	77 (61)	3.8 (79)
8	$AgNO_2$[b]	80 (63)	3.8 (79)
9	$NaNO_2$[b]	82 (62)	3 (75)
10	$AgNO_3$	32(13)	.72 (42)
11	$AgNO_2$[c]	77 (49)	1.7 (63)
12	$PdNO_2Cl(MeCN)_2$[d]	70 (34)	.9 (48)

[a]1 equiv *tert*-BuONO used instead of 12%. [b]6% nitrite used [c]$MeNO_2$ was omitted and reaction run at 30 ºC. [d]No $PdCl_2(PhCN)_2$

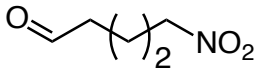
Substrate Scope

In all cases, the selectivity was calculated by ratio of the aldehydic proton signal to the most clear signal from the methyl ketone (usually the methyl). Long relaxation delays (d1=15) were applied due to the long t1 of the aldehydic proton signal.

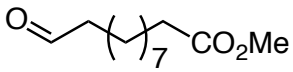


Dodecanal (table 1, entry 1): 63% aldehyde yield obtained using procedure B.

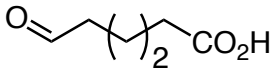
Dodecanal (table 1, entry 2): 56 mg (61% yield) obtained using procedure A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.9 Hz, 1H), 2.43 (td, *J* = 7.4, 1.9 Hz, 2H), 1.64 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.49 – 1.18 (m, 16H), 0.97 – 0.77 (t, *J* = 6.8, 3H). Spectral data were in accordance with a commercial sample.



5-Nitropentanal (table 1, entry 3): 46 mg (70%) obtained using procedure A. **^{1}H NMR** (400 MHz, CDCl3) δ 9.78 (t, *J* = 1.1 Hz, 1H), 4.40 (t, *J* = 6.8 Hz, 2H), 2.54 (td, *J* = 7.1, 1.1 Hz, 2H), 2.09 – 2.00 (m, 2H), 1.77 – 1.68 (m, 2H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.84, 75.17, 42.78, 26.57, 18.74. **HRMS** (EI+) calcd for $C_4H_8O_2N$ (M - CHO) 102.0555, found 102.0560

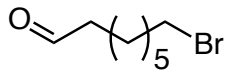


Methyl 11-oxoundecanoate (table 1, entry 4): 63 mg (59% yield) obtained using procedure A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.9 Hz, 1H), 3.56 (s, 3H), 2.40 (td, *J* = 7.4, 1.9 Hz, 2H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.73 – 1.48 (m, 4H), 1.34 – 1.20 (s, 10H). Spectral data were in accordance with the literature.[22]

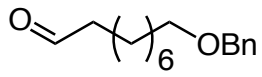


7-oxoheptanoic acid (table 1, entry 5): 51% aldehyde yield obtained using procedure C with the following modifications: work up was conducted by initial dilution with 0.5M HCl instead of water and mestiylene was added as an internal standard instead of nitrobenzene.

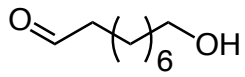
[2] Gorczynski, M. J.; Smitherman, P. K.; Akiyama, T. E.; Wood, H. B.; Berger, J. P.; King, S. B.; Morrow, C. S. *J. Med. Chem.* **2009**, *52*, 4631–4639.



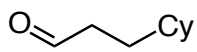
8-Bromooctanal (table 1, entry 6): 67 mg (65% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) 9.76 (t, *J* = 1.8 Hz, 1H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.42 (td, *J* = 7.3, 1.8 Hz, 2H), 1.83 (p, *J* = 6.8 Hz, 2H), 1.62 (m, 2H), 1.42 (m, 2H), 1.34 (m, *J* = 5.1, 3.7 Hz, 4H). Spectral data were in accordance with the literature.[3]



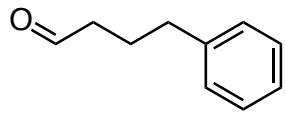
9-(Benzyloxy)nonanal (table 1, entry 7): 73 mg (59% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.9 Hz, 1H), 7.39 – 7.27 (m, 5H), 4.50 (s, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 2.53 – 2.31 (td, *J* = 7.4, 1.9 Hz, 2H), 1.70 – 1.53 (m, 4H), 1.42 – 1.22 (m, 8H). Spectral data were in accordance with the literature.[4]



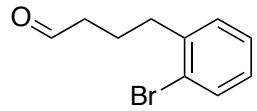
9-Hydroxynonanal (table 1, entry 8): 36 mg (45% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.8 Hz, 1H), 3.64 (t, *J* = 5.6 Hz, 2H), 2.43 (td, *J* = 7.4, 1.9 Hz, 2H), 1.69 - 1.24 (m, 12H). Spectral data were in accordance with the literature.[5]



3-Cyclohexylpropanal (table 1, entry 9): 60% aldehyde yield obtained using procedure C.

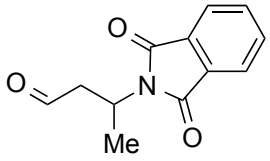


4-Phenylbutanal (table 1, entry 10): 51 mg (69% yield)**. ^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.6 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.24 – 7.15 (m, 3H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.46 (td, *J* = 7.3, 1.6 Hz, 2H), 1.97 (p, *J* = 7.4 Hz, 2H). Spectral data were in accordance with the literature.[6]

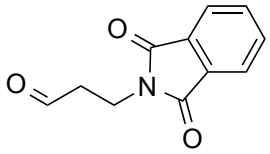


4-(2-bromophenyl)butanal (table 1, entry 11): 64% aldehyde yield obtained using procedure C.

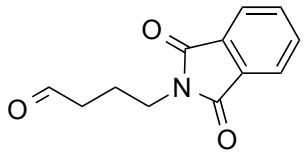
[3] Clyne, D.; Weiler, L. *Tetrahedron* **1999**, *55*, 13659–13682.
[4] Raghavan, S.; Krishnaiah, V. *J. Org. Chem.* **2010**, *75*, 748–761.
[5] Nagano, Y.; Orita, A.; Otera, J. *Tetrahedron* **2002**, *58*, 8211–8217.
[6] Ghosh, A. K.; Nicponski, D. R. *Org. Lett.* **2011**, *13*, 4328–4331.



3-(1,3-dioxoisoindolin-2-yl)butanal (figure 3, entry 1): 86mg (79% yield) obtained using procedure A. **^{1}H NMR** (500 MHz, CDCl3) δ 9.75 (t, *J* = 1.3 Hz, 1H), 7.85 – 7.79 (m, 2H), 7.74 – 7.68 (m, 2H), 4.97 – 4.86 (m, 1H), 3.31 (ddd, *J* = 18.0, 8.2, 1.4 Hz, 1H), 3.01 (ddd, *J* = 18.0, 6.2, 1.1 Hz, 1H), 1.50 (d, *J* = 7.0 Hz, 3H). Spectra data were in accordance with the literature.[7]



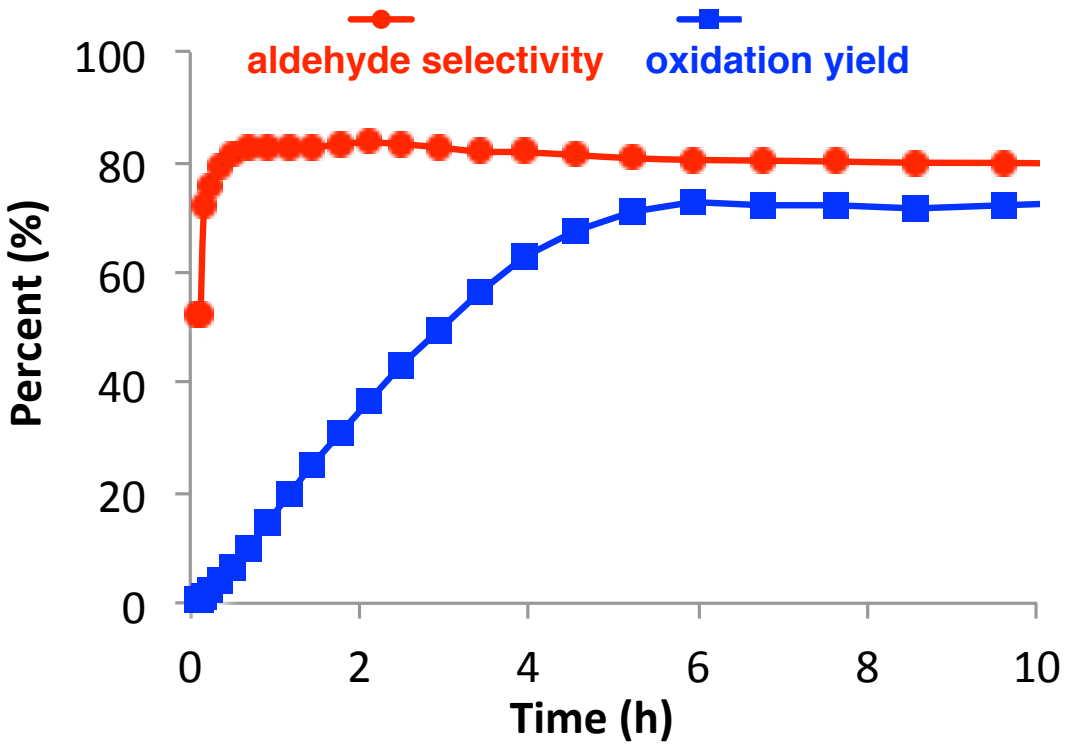
3-(1,3-dioxoisoindolin-2-yl)propanal (figure 3, entry 2): 76mg (75% yield) obtained using procedure A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.82 (t, *J* = 1.4 Hz, 1H), 7.87 – 7.82 (m, 2H), 7.74 – 7.71 (m, 2H), 4.04 (t, *J* = 7.0 Hz, 2H), 2.88 (td, *J* = 7.0, 1.4 Hz, 2H). Spectra data were in accordance with the literature.[8]



4-(1,3-dioxoisoindolin-2-yl)butanal 84mg (77% yield) obtained using procedure A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.2 Hz, 1H), 7.86 – 7.82 (m, 2H), 7.75 – 7.70 (m, 2H), 3.74 (t, *J* = 6.8 Hz, 2H), 2.54 (td, *J* = 7.3, 1.2 Hz, 2H), 2.02 (p, *J* = 7.0 Hz, 2H). Spectra data were in accordance with the literature.[8]

[7] B. Weiner, A. Baeza, T. Jerphagnon, B. Feringa, *J. Am. Chem. Soc.* **2009**, *131*, 9473–9474.
[8] C. Chaoxian, Y. Shichao, C. Bonan, Z. Xumu *Chem. Eur. J.* **2012**, *32*, 9992 - 9998

Reaction Profile



Procedure B was followed. Time points were collected with a Freeslate (formly symyx) at the given times and quenched with a 3:1 mixture of EtOAc and pyridine, followed by GC analysis using tridecane as an internal standard. Reaction temperature is further maintained at 20 ºC throughout the course of the reaction. After GC analysis, the data was processed and graphed using Microsoft Excel.

^{18}O-Labeling study

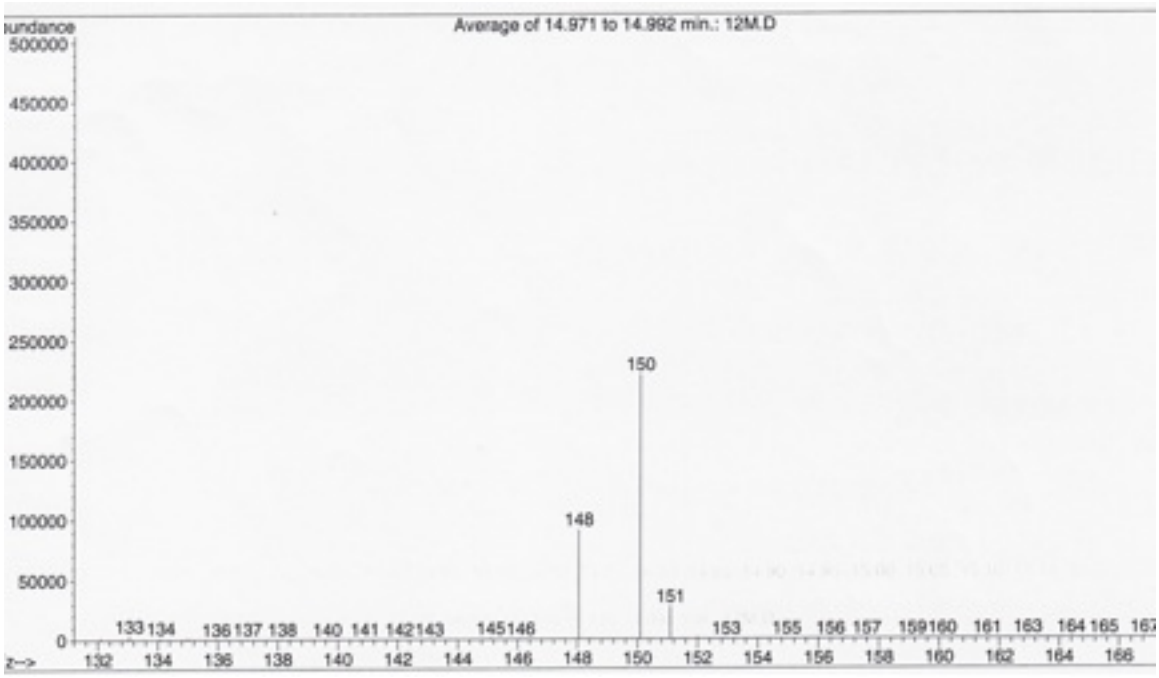
Labeling Experiment Procedure:

In a drybox under a nitrogen atmosphere, 1 mg (0.013 mmol) $Na^{15}N^{18}O_2$ (90% ^{18}O, 95% ^{15}N specified by Sigma-Aldrich) was weighed into a 2 mL vial, followed by the addition of 5.2 mg $PdCl_2(PhCN)_2$ (0.013 mmol) and 1.8 mg anhydrous $CuCl_2$ (0.013 mmol). 200 μL of pre-mixed dry *t*-BuOH and $MeNO_2$ (15:1) was then added, followed by vigourously agitation for one minute. Following agitation, 2 μL (0.013 mmol) 4-phenyl-1-butene was added. The reaction mixture was stirred for 12 min at room temperature. An aliquot of the mixture 100 μL was then rapidly taken out of the drybox and quenched by addition into 1 mL dry pyridine, immediately followed by freezing in liquid nitrogen. The sample was kept at -178 ºC and was allowed to warm to room temperature directly before injection into the GC-MS.

Labeling Experiment Analysis:

The level of incorporation was determined by the counts of m/z 150, 151 divided by the total counts (of m/z 148, 149, 150, 151). This % incorporation (73%) was then subsequently adjusted by the initial purity of the ^{18}O-label (90%) to determine the percentage of ^{18}O transferred from the nitrite salt (81%).

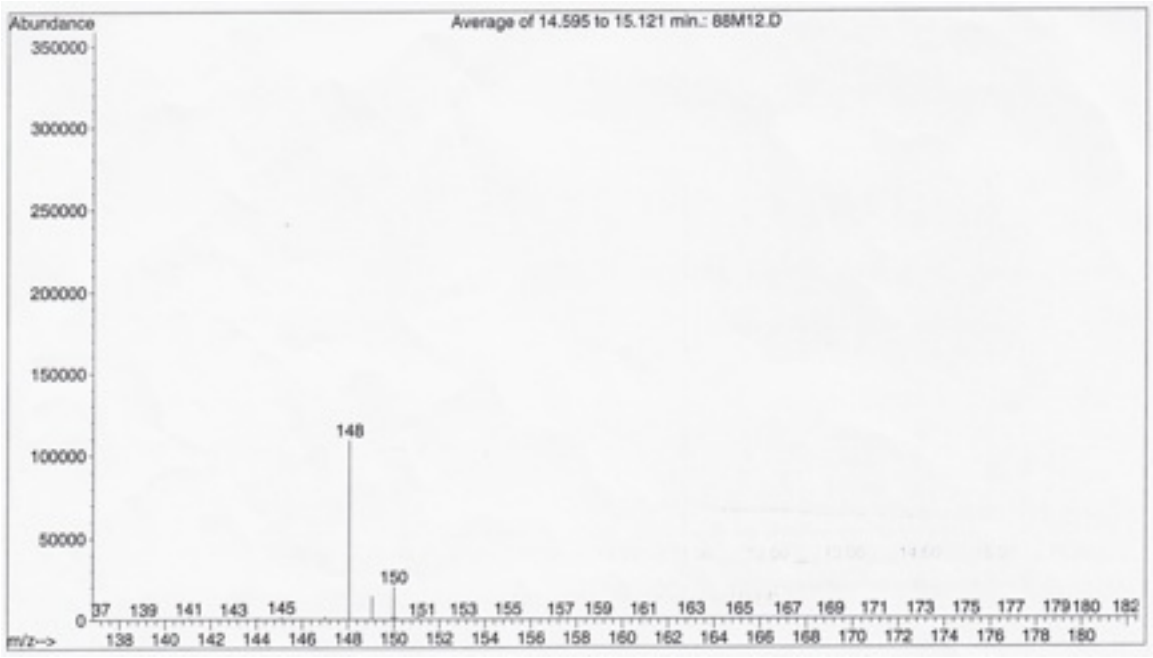
Mass spectrum of 18O-enriched 4-phenylbutanal:



Control Experiment:

The product aldehyde (4-phenylbutanal) was subjected to the same reaction conditions and subsequent analysis as described above for the labeling experiment. The % ^{18}O transfer was thus determined to be 18%.

Mass spectrum of 4-phenylbutanal subjected to the 18O-labeling conditions (control):



Discussion:

The reaction was not allowed to reach completion because residual water can rapidly exchange with the aldehyde signal by formation of a transient hemiacetal. This exchange would be expected to dilute the isotopic label. Thus, we suspect the 19% dilution of isotopic label can be accounted for by exchange of the aldehydic oxygen atom. The reaction yield was estimated by ^{1}H NMR analysis (using benzonitrile as an internal standard) on an unlabeled sample prepared by the same protocol. Yield of aldehyde was estimated to be 35% from this analogous reaction.

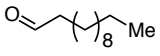
Labeling was also observed (to a lesser extent ~60%) in the ketone product. However, it has been previously shown with ^{18}O-labeled nitrite that palladium can transfer oxygen from nitrite in a ketone selective Wacker-type oxidation.[9]

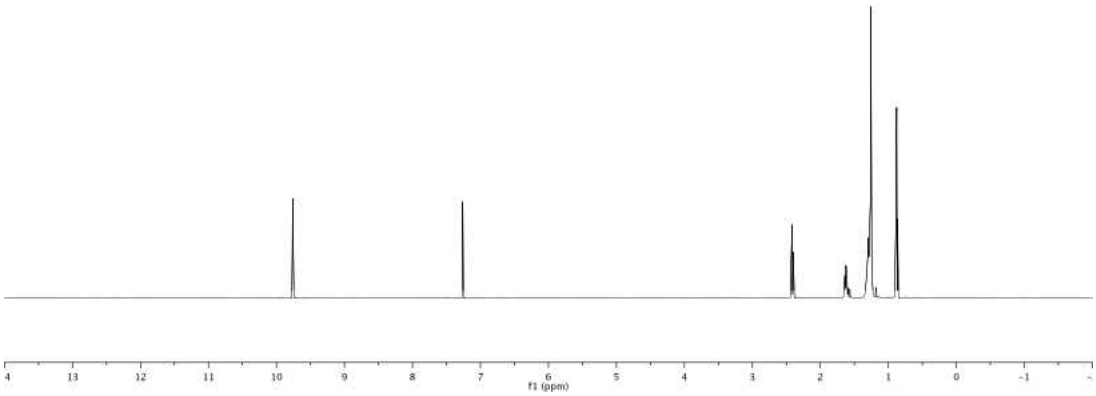
4-Phenylbutene was selected as the substrate for its prominent molecular ion. The molecular ion for 1-dodecanal was challenging to obtain reproducibly.

[9] Andrews, M. A.; Kelly, K. P. *J. Am. Chem. Soc* **1981**, *103*, 2894–2896.

^{1}H-NMR Spectra

BM-262_dry





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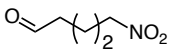

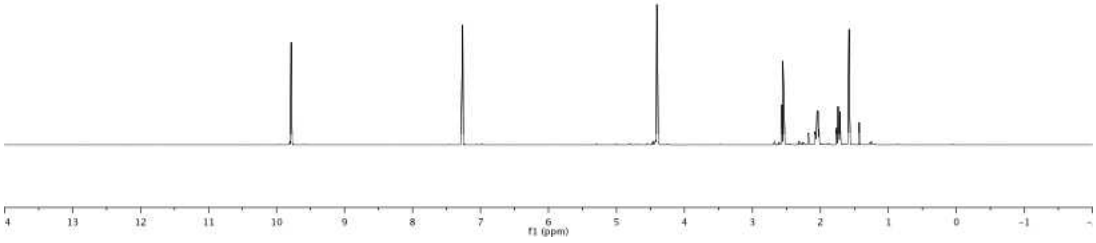

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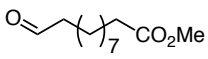
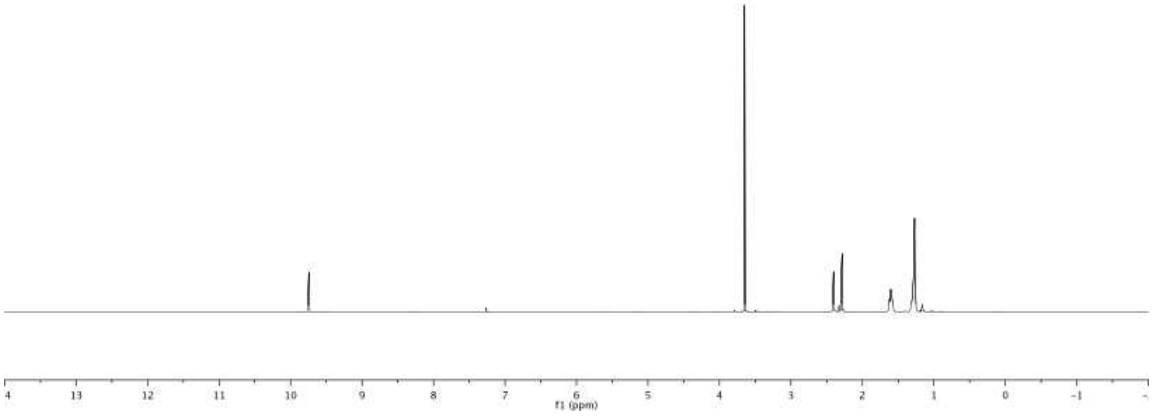
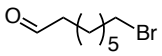
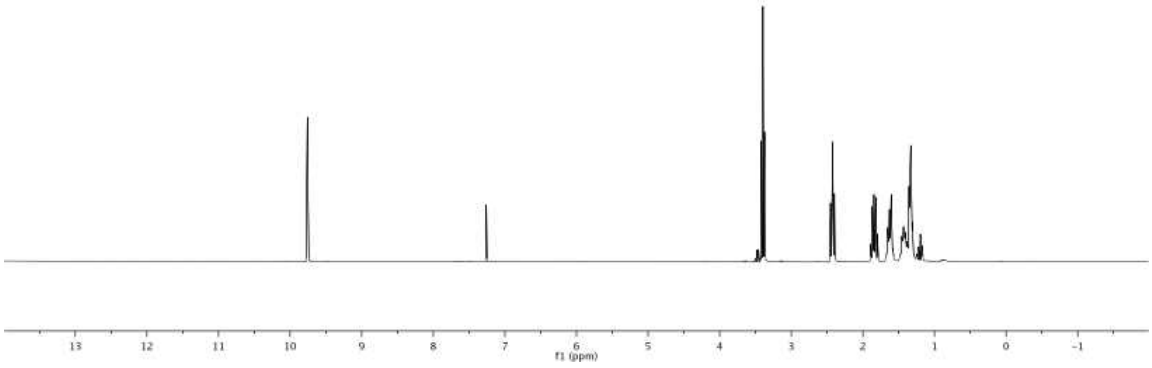




BM-266_CCB





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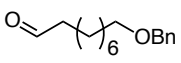
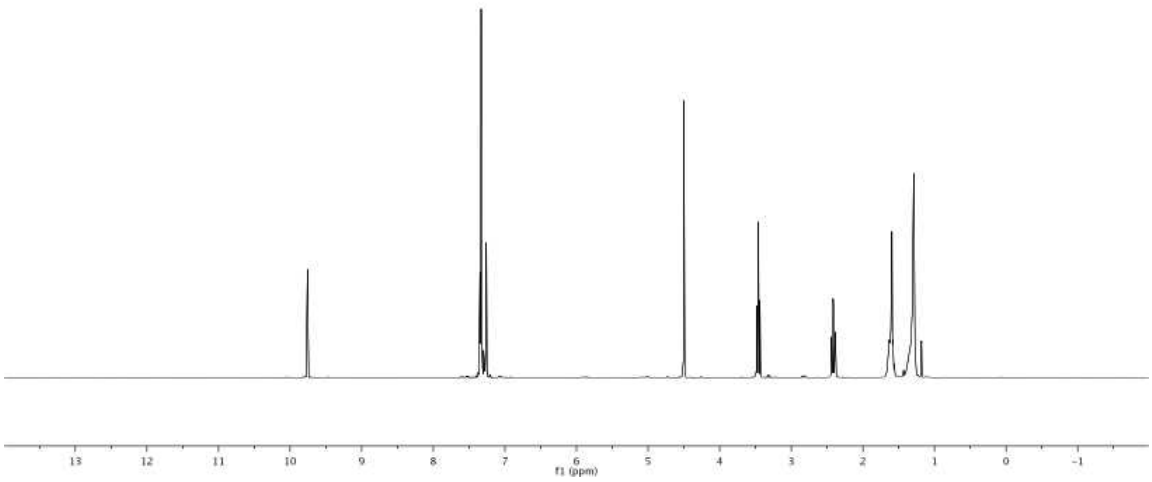
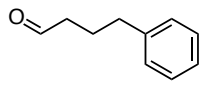
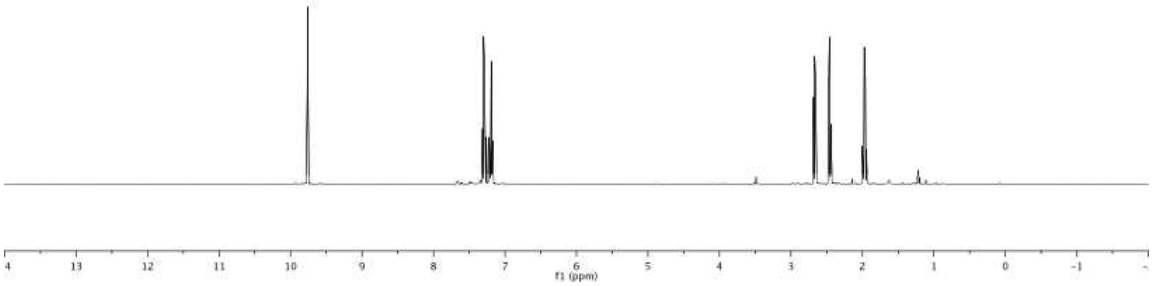
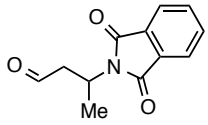




BM-269_CC







ZKW-III-279pA-DRY