Pd-Catalyzed Aerobic Oxidation Reactions: Strategies to Increase Catalyst Lifetimes

Supporting Information

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Materials and Methods

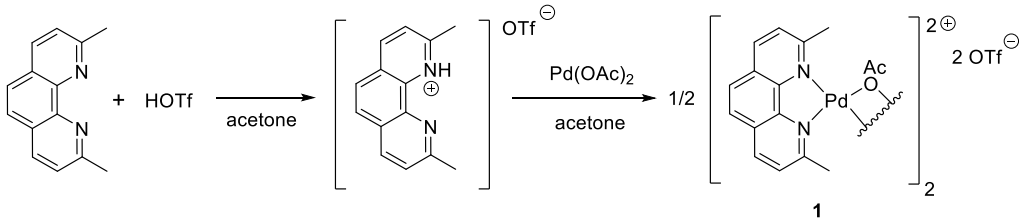
Unless otherwise specified, solvents were purchased from Fisher Scientific and reagents from Sigma-Aldrich. HPLC grade acetonitrile was used for all reactions. The reagent grade ethylbenzene that was used in most reactions came from Sigma-Aldrich and had been stored under ambient conditions, containing 90 mM of the hydroperoxide **9** when first analyzed. It was then stored at –20 °C in the dark. Purified ethylbenzene was obtained by refluxing the reagent grade EtPh over Na/benzophenone for several hours followed by vacuum transfer.

Methyl α-D-xylopyranoside was purchased from Carbosynth. ReagentPlus grade styrene from Sigma-Aldrich, which contains 50 ppm 4-*tert*-butylcatechol as a stabilizer, was stored at –20 °C in the dark. Deuterated NMR solvents were purchased from Cambridge Isotope Laboratories. Most experiments did not require dry solvents or substrates, but when necessary the liquids were dried over 3Å molecular sieves and filtered through oven-dried syringe filters. The syringe filters were made of PVDF and had a pore size of 0.22 μm. 1,4-Benzoquinone was purified by either sublimation or recrystallization from hexanes. Unless otherwise noted all other reagents were used without further purification. Silica gel chromatography (SGC) solvents were all ACS grade or better. In general, TLC plates were stained with $KMnO_4$.

NMR spectra were recorded on the following Varian instruments: an Inova 300 MHz, Mercury 400 MHz, Oxford 400 MHz, Inova 500 MHz, and Oxford 600 MHz. The time between successive scans (at + d1) was 14 seconds at minimum, which was confirmed to be sufficiently long for accurate quantification of all relevant compounds. GC-FID analyses were carried out on a Shimadzu GC-2014 with an Agilent J&W DB-WAX column (PEG-based); GC-MS on an Agilent 5975C with an Agilent J&W DB-5 column ((5%-phenyl)-methylpolysiloxane) with EI ionization; and ESI-MS on a Thermo Fisher LTQ-Orbitrap XL (100,000 resolution at m/z = 400).

Synthetic Procedures

[(bathocuproine)Pd(η^2-O_2)] (**2a**), [(d_6-neocuproine)Pd(μ-OAc)]$_2$[OTf]$_2$ (***d*$_{12}$-1**),[1] and 2,9-diethyl-1,10-phenanthroline[2] were prepared as previously reported.



[(neocuproine)Pd(μ-OAc)]$_2$[OTf]$_2$ (1). Compared to the previously reported procedure,[3] the one presented here uses half as much neocuproine and provides a method for purifying the crude product. Triflic acid (1.75 mL, 19.8 mmol) was added to a stirred solution of neocuproine (4.12 g, 19.8 mmol) in acetone (80 mL, ACS grade). The solution initially became dark red and then

turned light orange after several minutes, by which point some white precipitate had formed. After 30 min, Et_2O (225 mL) was added to precipitate a white solid, which was collected by filtration, washed with Et_2O, and dried *in vacuo* (white fluffy powder, 6.23 g, 17.4 mmol, 88% yield). This compound, [H-neocuproine][OTf], was characterized by ^{1}H-NMR in CD_3CN: δ 8.74 (d, *J* = 8.6 Hz, 2H), 8.12 (s, 2H), 7.94 (d, *J* = 8.4 Hz, 2H), 3.01 (s, 6H).

[H-neocuproine][OTf] (2.87 g, 8.02 mmol) was added in two equal portions, 30 minutes apart, to a stirred solution of $Pd(OAc)_2$ (1.80 g, 8.02 mmol, purchased from Strem Chemicals) in acetone (160 mL, ACS grade, dried over $MgSO_4$ then distilled). After 16 h, an orange precipitate had formed and the reaction solution was red/orange. The precipitate was collected by filtration, washed with Et_2O, and dried *in vacuo* (dull orange powder, 2.36 g, 2.26 mmol **1**, 56% yield). The mother liquor, which was not mixed with the Et_2O washings, was concentrated *in vacuo* down to 40 mL and acetic acid (0.5 mL) was added. After stirring overnight, a second crop of **1** had precipitated and was collected as before (dull orange powder, 0.649 g, 0.621 mmol **1**, 15% yield).

The catalyst can be further purified as follows: the first crop of **1** was dissolved in a mixture of MeCN (60 mL) and acetic acid (1.5 mL). After stirring for 1 h, the cloudy solution was filtered through a glass frit and then through syringe filters. Et_2O (325 mL) was added to the filtrate to precipitate an orange solid, which was collected by filtration, washed with Et_2O, and dried *in vacuo* (fine bright orange powder, 2.17 g, 2.07 mmol **1**, 52% yield). ^{1}H-NMR (CD_3CN) and mass spectrometry characterizations matched published data and indicated high purity product.

Isolation of Biphenol 6 from an Aerobic Reaction Mixture. Octyl β-D-glucopyranoside (87 mg, 0.30 mmol), Pd catalyst **1** (4.5 mg, 0.0043 mmol), and 2,6-di-*tert*-butylphenol (30.4 mg, 0.15 mmol) were dissolved in acetonitrile (3 mL) in a 20 mL septum-capped vial. The vial was purged with O_2 and the reaction was stirred at 50 °C for 22 h, repurging with O_2 at *t* = 1, 3, and 5 h. The reaction mixture was evaporated *in vacuo* and subjected to SGC (0-75% EtOAc in hexanes). A yellow compound was isolated, redissolved in acetonitrile, and subjected to SGC again (10% EtOAc in hexanes). Evaporation of the relevant fractions yielded a yellow oil (6 mg, 0.015 mmol, 20% yield). ^{1}H-NMR (400 MHz, CD_3CN): δ 7.32 (s, 4H), 5.45 (s, 2H), 1.45 (s, 36H). ^{13}C-NMR (126 MHz, CD_3CN): δ 153.7, 138.5, 134.7, 124.5, 35.2, 30.5. These spectra were in agreement with the literature.[4]

2,9-dimethyl-5-nitro-1,10-phenanthroline (7). A modified version of the procedure detailed by Strömberg was used.[5] Neocuproine (2.0 g, 9.6 mmol) was dissolved in oleum (9.2 mL). Concentrated nitric acid (4.8 mL) was added and the reaction was refluxed for 30 min. The solution was then cooled and very carefully neutralized with 30 wt% NaOH (aq). Dilute nitric acid was added to precipitate out the product, which was collected by filtration and dried *in vacuo*. The precipitate was triturated with chloroform and filtered two times. The filtrates were evaporated *in vacuo* and purified by SGC (100% EtOAc) to yield a flaky white solid (440 mg, 1.74 mmol, 18% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.94 (d, *J* = 8.8 Hz, 1H), 8.62 (s, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 7.66 (dd, *J* = 17.5, 8.5 Hz, 2H), 3.01 (dd, *J* = 6.7, 1.3 Hz, 6H). This spectrum was in agreement with the literature.[4]

2,9-dimethyl-1,10-phenanthroline-5,6-dione (8). A modified version of the procedure detailed by Beaudoin was used.[6] Neocuproine (520 mg, 2.5 mmol), potassium bromide (3.0 g) concentrated nitric acid (5 mL), and concentrated sulfuric acid (10 mL) were refluxed at 80 °C for 4 h. Then the mixture was cooled and sodium bicarbonate (17 g) was added. The solution was extracted with dichloromethane (3x100 mL), dried with magnesium sulfate, and evaporated *in vacuo* to obtain brown chunks. After washing these chunks with hexanes, light brown flakes were obtained (3.64 mg, 0.0152 mmol, 0.6% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 2.86 (s, 6H). This spectrum is in agreement with the literature.

1-phenylethyl hydroperoxide (9). One batch was prepared from 1-phenylethanol and H_2O_2 according to the procedure by Woerpel.[7] ^{1}H-NMR (400 MHz, CD_3CN): δ 9.40 (s, 1H, OO*H*), 7.39-7.28 (m, 5H), 4.96 (q, *J* = 6.6 Hz, 1H), 1.39 (q, *J* = 6.6 Hz, 3H).

Another batch was isolated from a 23-year-old bottle of EtPh (Mallinckrodt) that had accumulated 0.44 M **9**. EtPh (100 mL, containing 44 mmol **9**) was vacuum transferred at 25 °C from one flask to another. A yellow liquid (5.48 g) remained in the source flask, and a portion of this liquid (2.0 g) was subjected to SGC (15% EtOAc in hexanes) to give a faintly yellow liquid (1.05 g, 7.62 mmol, 47% yield relative to the amount subjected to SGC). The ^{1}H-NMR spectrum in CD_3CN was the same as above, and the spectrum in $CDCl_3$ matches that reported by Woerpel.

Both batches of **9** provide the same TON improvement in aerobic alcohol oxidations with Pd catalyst **1**.

methyl α-D-xylo-hexopyranosid-3-ulose (10). We previously reported the procedure for this experiment and additional product characterization data in ref.[8] ^{1}H-NMR (500 MHz, CD_3CN): δ 5.00 (d, *J* = 4.2 Hz, 1H), 4.36-4.31 (m, 2H), 4.02 (dd, *J* = 8.0, 10.2 Hz, 1H), 3.61 (d, *J* = 5.7 Hz, 1H), 3.52 (d, *J* = 8.5 Hz, 1H), 3.47 (t, *J* = 10.4 Hz, 1H), 3.34 (s, 3H). ^{13}C-NMR (126 MHz, CD_3CN): δ 207.0, 118.6, 104.0, 76.1, 73.0, 65.2, 55.9. HRMS calc'd for $[C_6H_{10}O_5 + Na]^+$: *m*/*z* =185.04204, found 185.04151 (ESI+).

hydroxyacetone (HA). 1,2-propanediol (7.35 mL, 100 mmol, 1 eq), styrene (2.86 mL, 25 mmol, 0.25 eq), and dimethyl sulfone (235 mg, 2.5 mmol) were dissolved in 100 mL of 1:1 (v/v) MeCN/EtPh (reagent grade, $[\mathbf{9}]_0$ = 45 mM in the total reaction mixture) in a 3-neck round bottom flask. The middle neck was equipped with a reflux condenser cooled by a water recirculator and the other two necks were sealed with rubber septa. Air was first saturated with MeCN vapors by bubbling it through acetonitrile in a separate flask, and then bubbled into the reaction solution through a needle through one of the septa. Reaction aliquots were taken through the other septum.

Stirring was initiated, the reaction was heated to 30 °C, and **1** was added (43.6 mg, 0.042 mmol, 0.083 mol% Pd) as a solution in ~1 mL MeCN; the later two portions of Pd were also added in this manner. The reaction solution became yellow. At *t* = 0.75 h, the temperature was increased to 40 °C. At *t* = 1 h, **1** was added (0.083 mol% Pd), causing the reaction solution to become orange. At *t* = 1.75 h, the temperature was increased to 50 °C. At *t* = 6.25, 8.75, 11.25, and 15.25 h, styrene was added (0.10, 0.25, 0.15, and 0.5 eq, respectively). Also at *t* = 11.25 h, **1** was added

(0.083 mol% Pd). In total, 1.25 eq styrene and 0.25 mol% Pd were employed. Reaction aliquots were taken periodically, diluted into CD_3CN, and analyzed by ^{1}H-NMR. It was later concluded that such numerous additions of Pd and styrene are not required for the reaction to proceed well.

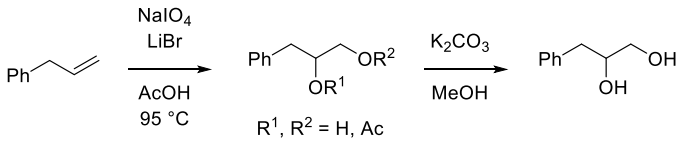
At *t* = 22.75 h, the reaction was stopped and the reaction mixture was concentrated *in vacuo* until most of the MeCN was removed. The remaining orange solution (61.17 g) contained mostly EtPh by mass; a portion of this crude mixture (11.89 g) was diluted with 10% EtOAc in hexanes and subjected to SGC (10-60% EtOAc in hexanes). Concentration *in vacuo* of the relevant fractions yielded the desired product as a faintly yellow liquid (0.455 g, 6.14 mmol, 32% yield). A significant portion of the product was lost due to co-evaporation with the EtOAc. ^{1}H-NMR (400 MHz, CD_3CN): δ 4.14 (apparent doublet, *J* = 5.1 Hz, 2H), 3.15 (t, *J* = 5.4 Hz, 1H, O*H*), 2.07 (t, *J* = 0.5 Hz, 3H). This spectrum matches that of an authentic sample from Sigma-Aldrich.

Oxidation of Glycerol. Glycerol (2.30 g, 25.0 mmol, 1 eq), styrene (2.86 mL, 25.0 mmol, 1 eq), and dimethyl sulfone (58.8 mg, 0.625 mmol) were dissolved in 85 mL MeCN in a 250 mL Erlenmeyer flask at room temperature. Stirring was initiated and **1** was added (26.1 mg, 0.025 mmol, 0.2 mol% Pd) as a solution in ~1 mL MeCN; the second portion of Pd was also added in this manner. The Erlenmeyer flask was kept open to the air. MeCN was occasionally added to replace evaporated solvent. At *t* = 8.5 h, **1** was added (0.1 mol% Pd). At *t* = 18 and 43 h, styrene was added (0.65 and 0.45 eq, respectively). In total, 2.1 eq styrene and 0.3 mol% Pd were employed. Reaction aliquots were taken periodically, diluted into CD_3CN, and analyzed by ^{1}H-NMR; the peak used to track glycerol concentration was at δ 3.42 (dd, *J* = 11.2, 6.1 Hz, 2H) and the peak for dihydroxyacetone was at δ 4.24 (s, 4H). The reaction was stopped at *t* = 72 h. A few attempts were made at purification, but the yields were not satisfactory.

***p*-dioxanone.** Diethylene glycol (0.949 mL, 10 mmol, 1 eq), styrene (1.15 mL, 10 mmol, 1 eq), and dimethyl sulfone (70.6 mg, 0.75 mmol) were dissolved in 33 mL MeCN in a 3-neck round bottom flask. The same setup as described above was used.

Stirring was initiated, the reaction was heated to 30 °C, and **1** was added (26.14 mg, 0.025 mmol, 0.5 mol% Pd) as a solution in ~1 mL MeCN; the later three portions of Pd were also added in this manner. The reaction solution became orange. The temperature was steadily increased to 50 °C over 3.25 h. At *t* = 4 h, styrene was added (1 eq). At *t* = 5 h, **1** was added (0.25 mol% Pd). At *t* = 6.5 h, styrene (0.75 eq) and **1** (0.5 mol% Pd) were added. At *t* = 10 h, styrene (0.75 eq) and **1** (0.25 mol% Pd) were added. In total, 3.5 eq styrene and 1.5 mol% Pd were employed. Reaction aliquots were taken periodically, diluted into CD_3CN, and analyzed by ^{1}H-NMR.

At *t* = 16.75 h, the reaction was stopped and the reaction mixture was concentrated *in vacuo* to an orange oil, which was subjected to SGC (5-50% EtOAc in hexanes) to give a yellow oil (0.795 g) containing the desired lactone and oligomeric side products. Subsequent sublimation at 28 °C yielded the product as a white powder (601 mg, 5.88 mmol, 59% yield). This powder, being highly hygroscopic, was recovered in a moisture-free glovebox after the sublimation. The ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum matches that of an authentic sample synthesized according to ref.[9] ^{1}H-NMR (400 MHz, CD_3CN): δ 4.42 (m, 2H), 4.29 (s, 2H), 3.83 (m, 2H).



3-phenyl-1,2-propanediol. The following procedure was adapted from Sudalai.[10] Allylbenzene (3.98 mL, 30 mmol), $NaIO_4$ (1.93 g, 9.0 mmol), and LiBr (0.521 g, 6.0 mmol) were stirred in glacial acetic acid (50 mL) at 95 °C for 22 h. After letting the reaction cool down to room temperature, water (100 mL) was added and the mixture was extracted with EtOAc (3 x 200 mL). The organic layers were combined, concentrated *in vacuo* down to ~150 mL, washed with saturated aqueous $Na_2S_2O_3$ (100 mL), saturated aqueous $NaHCO_3$ (75 mL), and water (75 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give an orange liquid.

To this liquid was added K_2CO_3 (6.22 g, 45 mmol) and MeOH (200 mL). After 48 h of stirring, the reaction mixture was concentrated *in vacuo*. Water (100 mL) was added and the mixture was extracted with EtOAc (3 x 200 mL). The organic layers were combined, concentrated *in vacuo* down to ~250 mL, washed with brine (100 mL) and water (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give an orange liquid. This crude product was first purified by SGC (50-70% EtOAc in hexanes) to give a light yellow oil, and then vacuum distilled at 70 °C to give a clear oil (1.84 g, 12.1 mmol, 40% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.37-7.28 (m, 2H), 7.28-7.18 (m, 3H), 3.94 (m, 1H), 3.66 (m, 1H), 3.50 (m, 1H), 2.81-2.71 (m, 2H), 2.39 (m, 1H, O*H*), 2.34 (m, 1H, O*H*). This spectrum was in agreement with the literature.[11]

1-hydroxy-3-phenyl-2-propanone (11). *Room Temperature Oxidation:* 3-phenyl-1,2-propanediol (0.750 g, 4.93 mmol, 1 eq), styrene (0.847 mL, 7.39 mmol, 1.5 eq), and dimethyl sulfone (46.4 mg, 0.493 mmol) were dissolved in 16 mL of 1:1 (v/v) MeCN/EtPh (reagent grade, $[\mathbf{9}]_0$ < 5 mM in the total reaction mixture) in a 125 mL Erlenmeyer flask. Stirring was initiated and **1** was added (10.3 mg, 9.86 μmol, 0.4 mol% Pd) as a solution in ~1 mL MeCN. The Erlenmeyer flask was left open to the air during the reaction. MeCN had to be added once to make up for evaporation.

At t = 37.5 h, the reaction was stopped and the reaction mixture was concentrated *in vacuo* to a yellow oil, which was subjected to SGC (20-30% EtOAc in hexanes) to yield slightly impure white crystals (0.627 g). A portion of these crystals (0.377 g) was recrystallized from 4:1 pentane/THF (40 °C to –16 °C) to provide shiny white flakes (0.267 g, 1.77 mmol, 60% yield). Recrystallization of the mother liquor gave a second crop of product (0.053 g, 0.35 mmol, 12% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38-7.20 (m, 5H), 4.29 (d, J = 4.3 Hz, 2H), 3.73 (s, 2H), 3.01 (t, J = 4.7 Hz, 1H, O*H*). This spectrum was in agreement with the literature.[12]

50 °C Oxidation: 3-phenyl-1,2-propanediol (0.750 g, 4.93 mmol, 1 eq), styrene (0.751 mL, 6.56 mmol, 1.33 eq), and dimethyl sulfone (46.4 mg, 0.493 mmol) were dissolved in 12 mL of 1:1 (v/v) MeCN/EtPh (reagent grade, $[\mathbf{9}]_0$ < 5 mM in the total reaction mixture) in a 2-neck flask. A balloon filled with O_2 was attached to one neck, and the other neck was sealed with a septum. The latter would be used for the addition of reagents and the taking of aliquots for reaction monitoring. After warming to 30 °C, the reaction mixture was stirred for 30 min to allow the solution to absorb O_2. Then catalyst **1** was added (6.44 mg, 6.16 μmol, 0.25 mol% Pd) as a solution in ~1 mL MeCN. The temperature was steadily increased to 50 °C over 2 h.

At *t* = 15 h, the reaction was stopped and the same work-up as above was carried out. The entire reaction was subjected to SGC and recrystallization (only one crop), which yielded shiny white flakes (0.504 g, 3.35 mmol, 68% yield).

***N*-Boc 2-morpholinone (12).** *N*-Boc diethanolamine (4.11 g, 20 mmol, 1 eq), styrene (4.58 mL, 40 mmol, 2 eq), and dimethyl sulfone (141 mg, 1.50 mmol) were dissolved in 60 mL MeCN in a 3-neck round bottom flask. The same setup as described above for hydroxyacetone was used.

Stirring was initiated, the reaction was heated to 30 °C, and **1** was added (52.3 mg, 0.05 mmol, 0.5 mol% Pd) as a solution in ~1 mL MeCN; the later two portions of Pd were also added in this manner. The temperature was steadily increased to 50 °C over 2 h. At *t* = 7.5 h, **1** was added (0.5 mol% Pd). At *t* = 13.5 h, styrene was added (1 eq). At *t* = 21.75 h, styrene (0.5 eq) and **1** were added (0.25 mol% Pd). In total, 3.5 eq styrene and 1.25 mol% Pd were employed. Reaction aliquots were taken periodically, diluted into CD_3CN, and analyzed by ^{1}H-NMR.

At *t* = 30 h, the reaction was stopped and the reaction mixture was concentrated *in vacuo* to an orange oil, which was subjected to SGC (10-50% EtOAc in hexanes) to provide an impure yellow oil. Recrystallization from 3:1 hexanes/THF (50 °C to –16 °C) produced several white crystalline masses, which were pulverized, filtered, washed with cold 3:1 hexanes/THF, and dried *in vacuo*. Fine white crystals were obtained (1.956 g, 9.72 mmol, 49% yield). Recrystallization of the mother liquor gave a second crop of product (0.196 g, 0.97 mmol, 4.9% yield). The ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum was in agreement with the literature.[9]

General Procedures for Small Scale Reactions

All additions of Pd catalyst **1** were from stock solutions in acetonitrile that were prepared the same day. As a highly representative example, the Pd catalyst (~5 mg) was weighed directly into a 1/2-dram vial using a Shimadzu AUW120D balance, and the precise mass of **1** would be recorded to the closest 0.01 mg. Then acetonitrile (~1 mL) would be added to this vial using a Gilson PIPETMAN P1000. The micropipette was confirmed to be able to accurately and precisely measure such volumes of acetonitrile: when set to 1000 μL, the micropipette dispensed 787 ± 5 mg of pure MeCN over 6 trials while the expected mass of 1000 μL MeCN is 786 mg based on the reference density of 0.786 g/mL at 25 °C (Sigma-Aldrich). After capping the vial and shaking vigorously, a clear orange catalyst stock solution would be obtained. The desired amount of this solution would be added to the reaction mixture via a Gilson PIPETMAN P200. If there were 5.00 mg catalyst in 1000 μL MeCN and the goal were to add 0.5 mol% Pd to a reaction containing 0.1 mmol alcohol and one ignores the effect of the dissolved Pd on the stock solution's volume, (0.1 mmol × (0.5% / 2) × (1045.58 g/mol) / 5.00 mg) × 1000 μL = 52.3 μL of the stock solution should be added. The micropipette was confirmed to be able to accurately and precisely measure such volumes of acetonitrile: when set to 50.0 μL, the micropipette dispensed 38.9 ± 1.1 mg of pure MeCN over 6 trials while the expected mass of 50.0 μL MeCN is 39.3 mg.

For ^{1}H-NMR analysis, reaction aliquots (typically 50-100 μL) were diluted into CD_3CN (0.5 mL). For GC-FID analysis, reaction aliquots (typically 50 μL) were eluted through silica plugs with MeCN (~1.5 mL) to remove the Pd before injection into the instrument. Control

experiments verified that all the relevant organic compounds elute quantitatively off the silica. Dimethyl sulfone, biphenyl, and naphthalene were used as internal standards (the latter two mainly for GC-FID). Calibration curves were performed for hydroxyacetone, 1,2-propanediol, acetophenone, and dimethyl sulfone, indicating relative molar FID sensitivities of 0.801, 1.115, 3.805, and 1.000, respectively. The molar sensitivities for other compounds were estimated using the Effective Carbon Number method detailed by Willis relative to acetophenone.[13] Retention times were verified using authentic samples that were either commercially available or synthesized according to previous procedures.[9]

Method A (Tables 3-4, default method unless otherwise specified): The reaction solution was prepared in a 20 mL vial charged with a magnetic stir bar. After the addition of Pd catalyst, the vial was purged with O_2 for 45 seconds (20 mL contains ~0.8 mmol O_2 at 1 atm at room temperature), capped, and then warmed for 15 seconds in a lukewarm (~30 °C) water bath to counteract evaporative cooling. If the reaction temperature was >35 °C, PTFE-coated silicone caps were used and the vial-cap junction was wrapped in electrical tape; otherwise polypropylene caps were used and the vial-cap junction was wrapped in Parafilm M. All the vials in the reaction set were placed into a room temperature water or oil bath while stirring was initiated. The bath temperature was then increased to the desired value. No water or oil bath was used for reactions conducted at room temperature.

Method B (Table 2): The reaction solution was prepared in a 1 dram vial charged with a magnetic stir bar. The Pd catalyst was added and the reaction was stirred open-capped at room temperature. After 3-6 h the vials were capped to prevent excessive evaporation.

Method C (Table 1): The reaction solution was prepared in a 2 dram vial charged with a magnetic stir bar. All the vials in the reaction set were placed open-capped into a metal reactor. The Pd catalyst was added and stirring was initiated at room temperature. The reactor was sealed and pressurized to 1.2 atm O_2. All the reactions share the same headspace, but control reactions without additives were always conducted in each set to confirm that cross-contamination between the vials was not occurring.

^{1}H-NMR Resonances for Reaction Monitoring

The following resonances were verified using authentic samples that were either commercially available, synthesized in this work, or synthesized according to previous procedures.[9]

1,2-propanediol: (CD_3CN) δ 3.71 (dqd, *J* = 6.8, 6.3, 4.1 Hz, 1H), 3.38 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.29 (dd, *J* = 11.3, 6.8 Hz, 1H), 2.82 (d, *J* = 4.4 Hz, 1H, O*H*), 2.75 (dd, *J* = 6.2, 5.6 Hz, 1H, O*H*), 1.04 (d, *J* = 6.3 Hz, 3H).
hydroxyacetone: (CD_3CN) δ 4.14 (apparent doublet, *J* = 5.1 Hz, 2H), 3.15 (t, *J* = 5.4 Hz, 1H, O*H*), 2.07 (t, *J* = 0.5 Hz, 3H).
dimethyl sulfone: (CD_3CN) δ 2.91 (s, 6H).
acetophenone: (CD_3CN, partial) δ 2.55 (s, 3H).
1-phenylethanol: (CD_3CN, partial) δ 4.78 (q, *J* = 6.5 Hz, 1H), 1.37 (d, *J* = 6.5 Hz, 3H).
benzaldehyde: (CD_3CN, partial) δ 10.00 (s, 1H).

styrene: (CD_3CN, partial) δ 6.76 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.81 (dd, *J* = 17.7, 1.1 Hz, 1H), 5.26 (dd, *J* = 11.0, 1.1 Hz, 1H).

1-phenylethyl hydroperoxide (**9**): (CD_3CN, partial) δ 4.96 (q, *J* = 6.6 Hz, 1H), 1.39 (d, *J* = 6.6 Hz, 3H).

diethylene glycol (DEG): (CD_3CN) δ 3.62-3.55 (m, 4H), 3.52-3.46 (m, 4H), 2.93 (t, *J* = 5.8 Hz, 2H, O*H*).

1,4-dioxan-2-ol (lactol of DEG): (CD_3CN, partial) δ 4.71 (dd, *J* = 6.1, 2.3 Hz, 1H), 3.23 (dd, *J* = 11.4, 6.1 Hz, 1H).

p-dioxanone: (CD_3CN) δ 4.42 (m, 2H), 4.29 (s, 2H), 3.83 (m, 2H).

2,6-diisopropylphenol (**5**): (400 MHz, CD_3CN) δ 7.03 (apparent doublet, *J* = 7.6 Hz, 2H), 6.84 (apparent triplet, *J* = 7.6 Hz, 1H), 5.97 (s, 1H, O*H*), 3.21 (hept, *J* = 6.9 Hz, 2H), 1.19 (d, *J* = 6.9 Hz, 12H).

Representative GC Trace for Reaction Monitoring

Heating Rate (°C/min)	Until Temp (°C)	Hold Time (min)
---	80	0
15	200	4

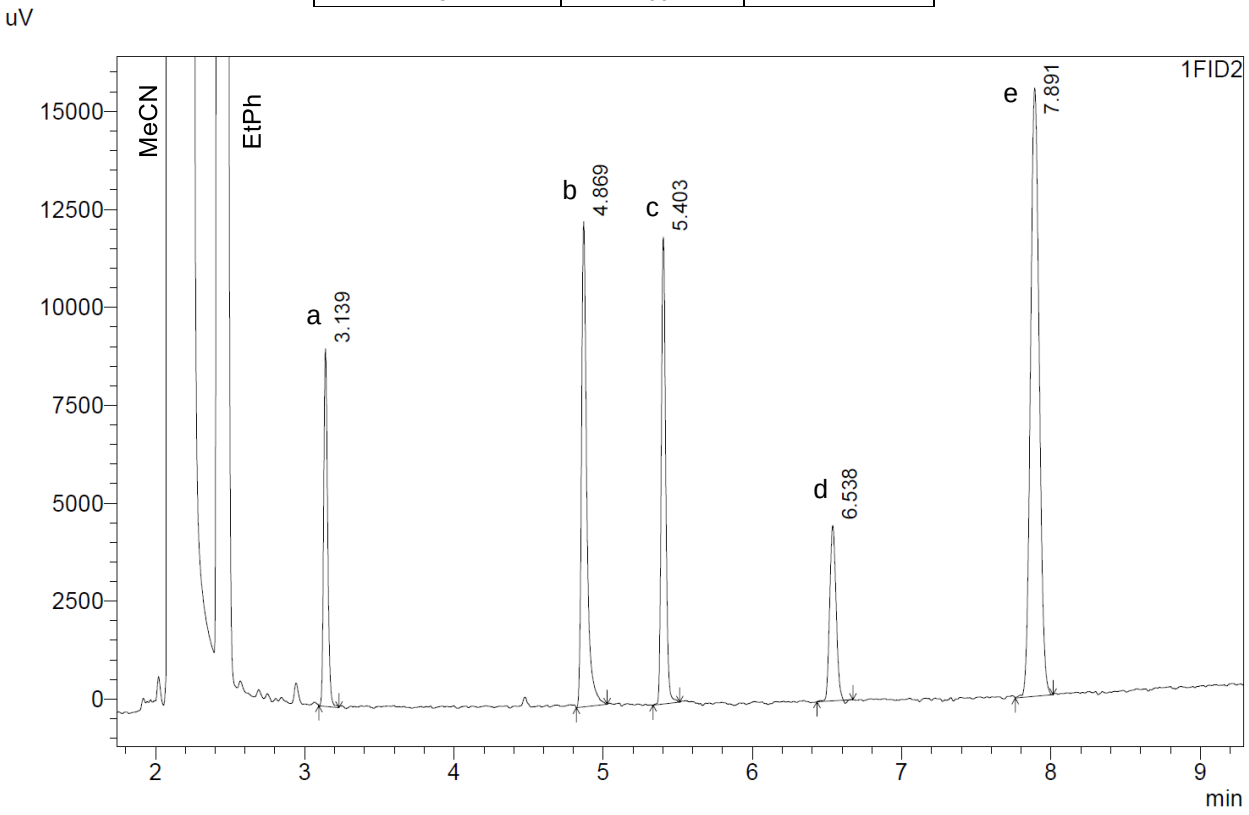
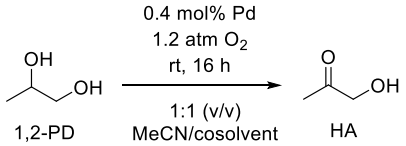


Figure S1. GC trace of an aerobic oxidation of 1,2-propanediol with cosolvent EtPh. Reaction conditions: 0.1 M 1,2-propanediol, 0.5 mM Pd (0.5 mol%), 1 mL 1:1 (v/v) MeCN/EtPh ([**9**] = 49 mM in the total reaction solution), 28 °C, 1 atm O_2, 26 h, Method A. a = hydroxyacetone, b = 1,2-propanediol, c = acetophenone, d = 1-phenylethanol, e = biphenyl. GC carrier gas = helium.

Cosolvent Screens

Table S1. Alkylbenzene cosolvent TON experiments



Cosolvent	Yield (GC)[a]	TON[b]
None	13%	32
cymene	17%	42
cumene	25%	63
toluene	26%	64
p-xylene	27%	69
diethylbenzene[c]	33%	82
ethylbenzene	34%	84
1,4-diisopropylbenzene	35%	88

Conditions: 0.25 M 1,2-propanediol, 1.0 mM Pd (0.4 mol%), 2 mL 1:1 (v/v) MeCN/cosolvent, rt, 1.2 atm O_2, 16 h, Method C. Reactions done in duplicate. [a]Yield of HA, as measured by GC-FID with biphenyl and naphthalene internal standards. [b]TON = (mmol HA produced)/(mmol Pd). [c]Mixture of isomers.

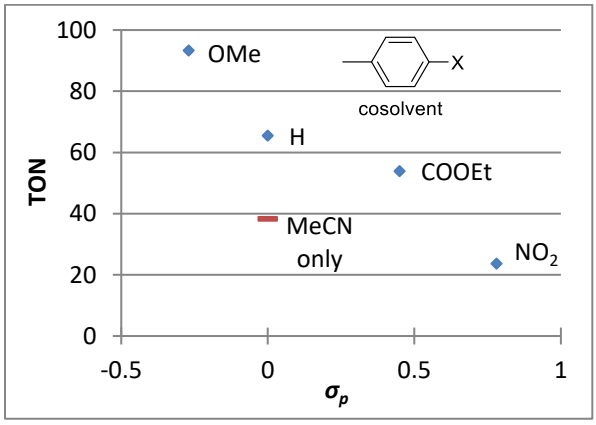


Figure S2. Dependence of TON on Hammett parameter[14] σ_p for *p*-substituted toluene cosolvents. Conditions: 0.5 M 1,2-PD, 2.5 mM Pd (0.5 mol%), 1 mL 1:1 (v/v) MeCN/cosolvent, rt, air, 25 h, Method B, vials capped after 6 h. Reactions done in duplicate. TON = (mmol HA produced)/(mmol Pd), as measured by GC-FID with dimethyl sulfone as the internal standard.

An alkylbenzene cosolvent that is more susceptible to H-atom abstraction (HAA) is expected to provide greater TON improvement for several reasons: (i) the cosolvent itself is a better H-atom donor, (ii) the alkyl hydroperoxide it generates is likely to be a better H-atom donor since it is the same C-H bond in both molecules that is susceptible to HAA, and (iii) the cosolvent autoxidizes more readily, meaning that higher quantities of alkyl hydroperoxides are likely to have formed during aerobic storage.

Since the concentrations of alkyl hydroperoxides were not measured in the above cosolvent screens, definitive conclusions cannot be drawn from these data. Nonetheless, it was satisfying to see the negative correlation between TON and σ_p in Figure S2 since electron deficient toluenes are known to be less susceptible to HAA.

Investigations with Alkyl Hydroperoxides

A pure sample of hydroperoxide **9** was synthesized by treatment of 1-phenylethanol with H_2O_2 under acidic conditions as detailed above. **9** could also be isolated from reagent grade EtPh by concentration *in vacuo* followed by silica gel chromatography. Adding either batch of **9** to distilled EtPh reproduced the same TON improvement as observed when reagent grade EtPh with an equivalent concentration of **9** is used as a cosolvent. A control experiment verified that adding low concentrations of acetophenone and 1-phenylethanol (8 mM of each in the total reaction solution[15]) to reactions with distilled EtPh cosolvent do not affect TON (Table S5, entry 6). Figure S3 shows the effect of varying the concentrations of **9** on TON, from which it is apparent that increasing [**9**] beyond ~20 mM provides little additional benefit to TON.

In toluene, benzyl hydroperoxide (formed from autoxidation during storage) was found to have the same effect on TON as **9** in EtPh. Two batches of toluene were identified with different concentrations of [BnOOH]: 0 mM and 3 mM. The former batch of toluene yielded a low TON of 44 that was very close to that obtained with distilled EtPh, while the latter batch gave a higher TON of 66. Furthermore, adding 6 mM **9** into the total reaction solution with the [BnOOH] = 0 mM batch of toluene as the cosolvent produced a TON of 65, which is very close to that obtained from the same concentration of **9** in distilled EtPh (TON = 64).
These experiments, along with those described in the main text, establish conclusively that the hydroperoxides formed from alkylbenzene autoxidation provide a significant benefit to aerobic TON.

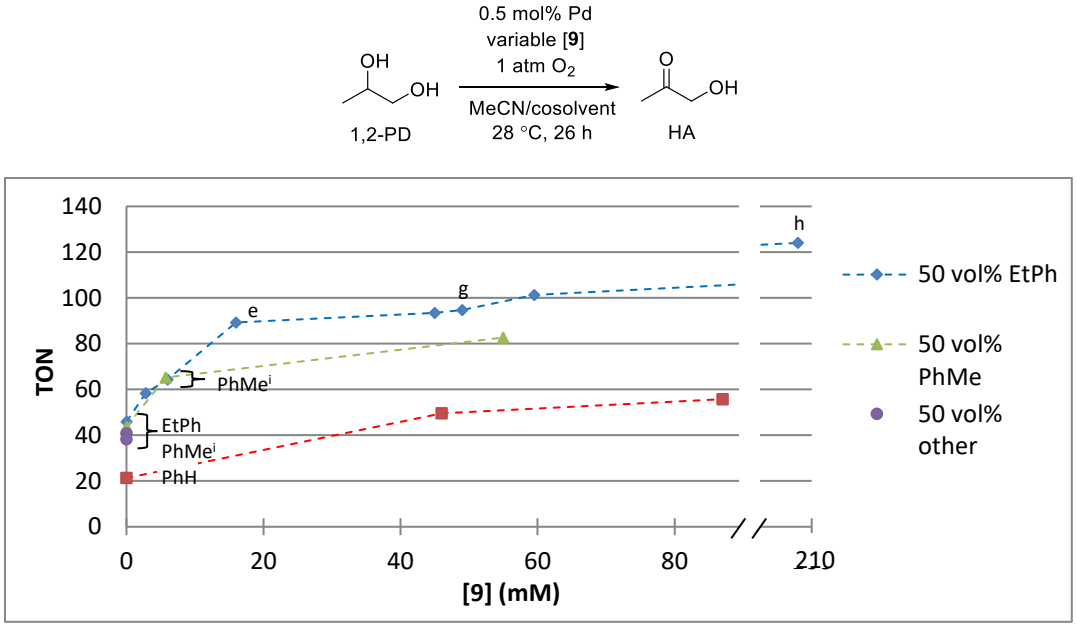


Figure S3. Dependence of TON on [**9**] in various cosolvent mixtures. The dashed lines are meant only to guide the eye. Refer to the notes in Table S2.

Table S2. Tabular form of Figure S3 with additional data

Cosolvent[a]	[9][b]	Yield (NMR)[c]	TON[d]
EtPh	0	23%	46
EtPh	3	29%	58
EtPh	6	32%	64
EtPh[e]	16	45%	89
EtPh	45	47%	93
EtPh[f,k]	47	46%	92
EtPh[g]	49	47%	95
EtPh	60	51%	101
EtPh[h]	208	62%	124
PhMe[i]	0	22%	44
PhMe[j,k]	0	33%	66
PhMe[i]	6	33%	65
PhMe[i]	55	41%	83
PhH	0	20%	41
Ph*t*Bu	0	19%	38
MeCN	0	11%	21
MeCN	46	25%	50
MeCN	87	28%	56

Conditions: 0.1 M 1,2-PD, 0.5 mM Pd (0.5 mol%), 1:1 (v/v) MeCN/cosolvent, 28 °C, 1 atm O_2, 26 h. Reactions done in at least duplicate. [a]By default, the EtPh was distilled while the other cosolvents were not. [b][**9**] is calculated relative to the total reaction solution volume. The added **9** was synthesized from 1-

phenylethanol and H_2O_2 by default. [c]Yield of HA as measured by ^{1}H-NMR with dimethyl sulfone as the internal standard. [d]TON = (mmol HA produced)/(mmol Pd)×(scaling factor, see note g). [e]Distilled EtPh allowed to autoxidize on the benchtop for 6 weeks. [f]**9** isolated from reagent grade EtPh. [g]Reagent grade EtPh with no additional **9** from the same batch that the distilled EtPh was purified from; used as a standard to multiplicatively scale TON values between sets of reaction runs. [h]Reagent grade EtPh with additional **9** isolated from reagent grade EtPh. [i]Toluene batch with [BnOOH] = 0 mM. [j]Toluene batch with [BnOOH] = 3 mM. [k]Not depicted in Figure S3.

Since **9**, acetophenone, and 1-phenylethanol are produced by EtPh autoxidation under ambient conditions, it was necessary to check whether their formation qualified as evidence for H-atom abstractions originating from Pd-catalyzed alcohol oxidation. Solutions of **9** in 1:1 (v/v) MeCN/EtPh did not generate acetophenone in the presence of 1,2-propanediol after 24 h at ambient temperature; similarly solutions of **9** in the presence of Pd catalyst **1** (but no 1,2-PD) did not generate acetophenone after 24 h. When stored on the benchtop for 4 days under an air headspace, neat distilled EtPh produced <1 mM **9**. These results sharply contrast with, as a representative example, an oxidation of 1,2-propanediol in MeCN/EtPh with 0.5 mol% Pd conducted for 26 h where initially [**9**] = 49 mM in the total reaction solution and at the end [**9**] = 24 mM with [**9**] + [acetophenone] + [1-phenylethanol] = 71 mM.[16] These data conclusively show that the greatly accelerated formation of these byproducts in total and decomposition of **9** are attributable to the intermediates of Pd-catalyzed alcohol oxidation.

Estimations of TOF

For the experiments under ambient air, the reaction solution was prepared in a 20 mL vial charged with a magnetic stir bar. The vial, which remained uncapped throughout the reaction, was heated to 28 °C and stirring was initiated. The Pd catalyst was added and reaction aliquots were taken every 5 min for 1 h.

For the experiments under pure O_2, the reaction solution was prepared in a 100 mL Schlenk flask charged with a magnetic stir bar. The flask was sealed with a septum, heated to 28 °C, purged with O_2, and then equipped with a balloon of O_2. The reaction solution was stirred for 45 min before the Pd catalyst was added through the septum. Reaction aliquots were taken through the septum.

The turnover frequencies (TOF = moles HA/mole Pd•h) were estimated from the linear portion of the concentration vs. time plots. Later in the reaction the rate begins to decay, presumably due to catalyst degradation and/or decreasing substrate concentration. Some representative examples of the time point data are shown below. For the 50 °C experiments, the TOF was estimated from the initial rate.

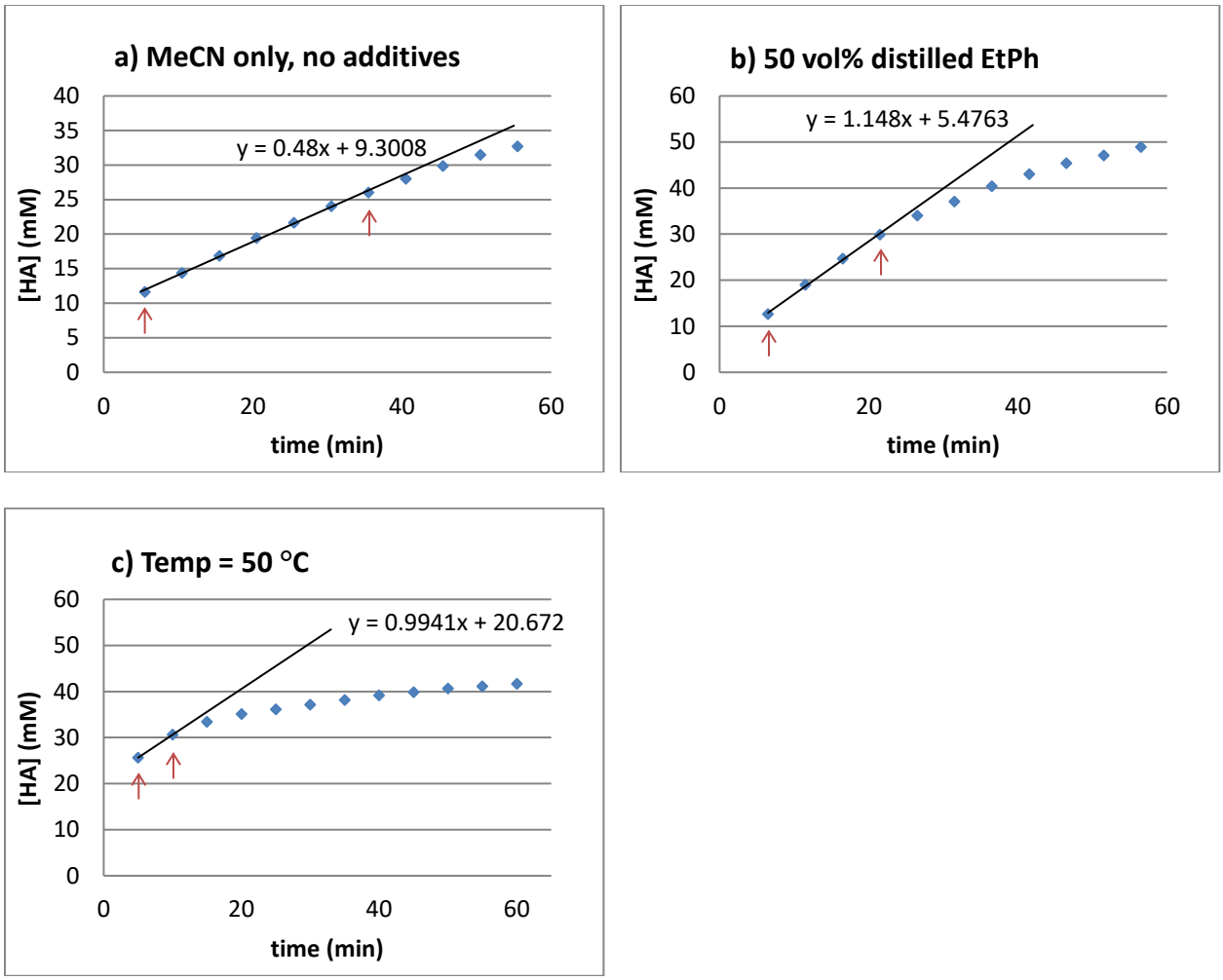


Figure S4. Examples of data used to calculate estimated TOF. The arrows mark the first and last time points used for linear regression.

Table S3. Estimated TOF in aerobic oxidations

Conditions	TOF[a] (h^{-1})
MeCN only	11
Pure O_2 headspace[b]	13
Temp = 50 °C	26
50 mM **5**[c]	12
Catalyst = $\boldsymbol{d_{12}}$**-1**	11
50 vol% distilled EtPh	27
50 vol% EtPh[d]	26
0.5 M styrene	9.4

Conditions: 0.1 M 1,2-PD, 2.5 mM Pd (2.5 mol%), 3 mL MeCN, 28 °C, air, 1 h. Reactions done in duplicate. [a]Estimated turnover frequency (= Δ(mmol HA) / (mmol Pd)(Δ*t*)) as measured by GC-FID with

biphenyl as the internal standard. [b]9 mL MeCN. [c]HA yield measured by ^{1}H-NMR with dimethyl sulfone as the internal standard. [d]Reagent grade EtPh; $[\mathbf{9}]_0$ = 45 mM in the total reaction solution.

Anaerobic Experiments

All liquid reagents were dried and degassed before use. Solid reagents were dried *in vacuo*. 1,4-benzoquinone (BQ), being sublimable, was subjected to vacuum for a shorter period of time. The reactions were prepared in a water- and O_2-free glovebox with an N_2 atmosphere. The reaction solution, including the BQ, was prepared in a 20 mL vial charged with a magnetic stir bar. Then Pd catalyst **1** was added. The reaction was stirred at room temperature.

In the reaction with hydroperoxide **9** as the terminal oxidant, the solution became dark within the first 2 min and Pd black was visible at the end.

Table S4. Anaerobic TON experiments

Terminal Oxidant	Additives	mol% Pd	time (h)	Yield (NMR)[a]	TON[b]
2 eq BQ	---	0.5	29.5	38%	75
2 eq BQ	50 mM **5**	0.5	29.5	37%	73
1 eq **9**	---	9.6	15	33%	3.5

Conditions: 0.1 M 1,2-propanediol, Pd catalyst **1**, 1 mL MeCN or CD_3CN, rt, anaerobic N_2 atmosphere. Reactions done in duplicate. [a]Yield of HA as measured by ^{1}H-NMR with dimethyl sulfone as the internal standard. [b]TON = (mmol HA produced)/(mmol Pd).

Pd Black Experiments

A solution of 1,2-propanediol (1 M) and dimethyl sulfone (0.025 M) in MeCN (3 mL) was prepared in a 20 mL vial. While stirring, catalyst **1** (2 mol% Pd) was added as a solution in 0.4 mL MeCN. The vial remained uncapped while the reaction occurred. At t = 40 min, the dark reaction solution was filtered through 0.2 μm Nylon filter paper. The stir bar and vial were rinsed with 1 mL MeCN, and these washings were passed through the same filter paper. The filtrate was transferred to a new vial with a new stir bar and stirring was initiated. The filter paper and stir bar both had small amounts of Pd black on them, and were both placed into the old vial. A copy of the starting solution (1,2-PD and dimethyl sulfone in 3 mL MeCN) was prepared and added to this vial. Stirring was initiated. Immediately prior to filtration (t = 40 min) the parent reaction had achieved 23% yield of hydroxyacetone by ^{1}H-NMR. At t = 4.5 h, the filtrate and filter cake reactions achieved 51% and 0% yields of HA, respectively.

At the end (t = 16.5 h) of a similar reaction in which 0.5 M 1,2-PD and 3 mol% Pd were used, significantly larger amounts of Pd black were visible, including the presence of a dark ring on the sides of the vial. The reaction was filtered as described above, and a fresh solution of 1,2-PD (0.25 M) and dimethyl sulfone (0.025 M) in MeCN (3 mL) was added to the old vial containing the filter paper and old stir bar. After 18 h of stirring, no hydroxyacetone was detected in the new reaction solution.

The above results demonstrate that isolable Pd black is catalytically inactive for alcohol oxidation. However, Pd nanoclusters, which are much smaller than 0.2 μm and mix homogeneously into solutions, cannot yet be ruled out as active or resting state catalysts.

Additional Experiments

Table S5. Experiments referenced in the main text or SI whose details are not shown elsewhere

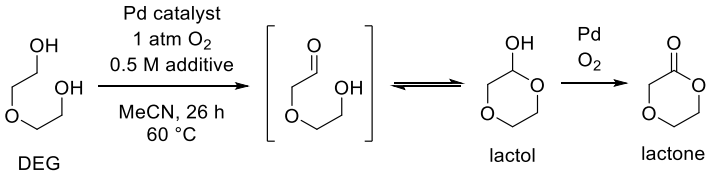
Entry	Substrate	mol% Pd	Solvent[a]	Temp (°C)	Time (h)	Conditions	Yield[b]	TON	Method	Notes
1	0.1 M 1,2-PD	0.5	1 mL MeCN	28	27.5		11%	21	A	16 μmol diol conversion
2			Repeat.				11%	21	A	15 μmol diol conv
3	0.1 M 1,2-PD	0.5	1 mL MeCN	28	24	50 mM 2,6-*i*Pr$_2$-phenol	32%	64	A	46 μmol diol conv, 4 μmol phenol conv
4	0.1 M 1,2-PD	1	0.9 mL MeCN	50	21	50 mM 2,6-*t*Bu$_2$-phenol	81.5%[d]	81.5	A	7 μmol phenol conv
5	0.1 M 1,2-PD	none	0.9 mL MeCN	50	21	50 mM 2,6-*t*Bu$_2$-phenol	0%	---	A	0 μmol phenol conv
6	0.1 M 1,2-PD	0.5	1 mL MeCN/ distilled EtPh	28	27.5	8 mM acetophenone, 8 mM 1-phenylethanol	23%	45	A	
7			Repeat.				24%	48	A	
8	none	0.5 μmol	1 mL MeCN/EtPh	28	27.5				A	Initially, [**9**] = 71 mM, [acetophenone] = 2 mM. At the end, [**9**] = 71 mM, [acetophenone] = 11 mM.
9			Repeat.						A	Initially, [**9**] = 71 mM, [acetophenone] = 2 mM. At the end, [**9**] = 68 mM, [acetophenone] = 9 mM.
10	0.1 M 1,2-PD	none	1 mL MeCN/EtPh	28	27.5				A	Initially, [**9**] = 71 mM, [acetophenone] = 2 mM. At the end, [**9**] = 82 mM, [acetophenone] = 4 mM.
11			Repeat.						A	Initially, [**9**] = 71 mM, [acetophenone] = 2 mM. At the end, [**9**] = 82 mM, [acetophenone] = 3 mM.
12	0.1 M DEG	1	1 mL MeCN	60	26	0.5 M distilled styrene	24% (lactol) 62%[c] (lactone)	142 (total)	A	
13	0.1 M 1,2-PD	0.5	1 mL MeCN	28	26	0.5 M styrene	22%	44	A	At the end, [**9**] = 14 mM, [acetophenone] = 3 mM, [1-phenylethanol] = 8 mM.
14	0.1 M 1,2-PD	0.5	1 mL MeCN	28	26	0.5 M styrene, 45 mM **9**	51%	101	A	At the end, [**9**] = 55 mM, [acetophenone] = 14 mM, [1-phenylethanol] = 6 mM.
15	0.1 M 1,2-PD	0.5	1 mL MeCN	28	26	45 mM **9**	23%[d]	47	A	At the end, [**9**] = 22 mM, [acetophenone] = 16 mM, [1-phenylethanol] = 5 mM.
16	0.5 M 1,2-PD	0.25	2 mL MeCN/EtPh	rt	72	0.5 M styrene	84%	334	C	Initially, [**9**] = 45 mM.

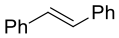
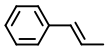
17			Repeat.				89%	355	C	Initially, [**9**] = 45 mM.
18			Repeat.				89%	354	C	Initially, [**9**] = 45 mM.
19	0.197 M 1,2-PD	0.75	1 mL CD_3CN	28	26		22%	30	A	Initially [H_2O] = 38 mM. At the end, [H_2O] = 78 mM, [HA] = 44 mM.
20			Repeat.				22%	30	A	Initially [H_2O] = 38 mM. At the end, [H_2O] = 81 mM, [HA] = 44 mM.
21	0.194 M 1,2-PD	0.75	1 mL CD_3CN	28	26	0.5 M styrene	84%	111	A	Initially [H_2O] = 36 mM. At the end, [H_2O] = 80 mM, [HA] = 162 mM, [acetophenone] = 48 mM.
22			Repeat.				84%	112	A	Initially [H_2O] = 36 mM. At the end, [H_2O] = 87 mM, [HA] = 163 mM, [acetophenone] = 54 mM.
23	0.1 M 1,2-PD	0.5	1 mL MeCN	28	26	50 mM 9,10-dihydro-anthracene (DHA)	22%	44	A	8.4 μmol DHA conv
24			Repeat.				25%	50	A	5.6 μmol DHA conv

By default, reagents were not dried or distilled prior to use. [a]1:1 (v/v) ratio for binary mixtures of solvents. Reagent grade EtPh was used by default. [b]Yield of product determined by either ^{1}H-NMR or GC-FID with respect to an internal standard (in most cases, dimethyl sulfone for NMR and biphenyl for GC). Unless otherwise specified, the product is the α-hydroxyketone. [c]Each lactone produced counts as two turnovers. [d]Yield and TON multiplicatively scaled to the EtPh control reaction used in Table S2.

Initial Studies with Olefins

Table S6. Olefinic Additive TON Experiments



Entry	mol% Pd	Additive	Yield (NMR)[a]		TON (NMR)
1	0.5	None	lactol lactone	6% 0%	13
2[b]	1.0	maleic anhydride	lactol lactone	11% 0%	11
3	1.0	1-octene	lactol lactone	16% 1%	17
4	1.0	acrylonitrile	lactol lactone	32% 2%	36
5	1.0	methyl acrylate	lactol lactone	31% 3%	36
6	1.0	styrene	lactol lactone	44% 54%	151
7[c]	1.0	 *trans*-stilbene	lactol lactone	14% 1%	15
8	2.6	 α-Me-styrene	lactol lactone	28% 2%	12
9	2.6	 *trans*-β-Me-styrene	lactol lactone	56% 20%	38
10[c]	1.0	4-*t*Bu-styrene	lactol lactone	44% 44%	133
11[c]	1.0	4-Cl-styrene	lactol lactone	42% 47%	137
12[c]	1.0	4-F-styrene	lactol lactone	40% 50%	140
13	1.0	4-Me-styrene	lactol lactone	32% 61%	153

Conditions: 0.1 M diethylene glycol, 0.5 M additive, 1 mL MeCN, 60 °C, 1 atm O_2, 26 h. [a]Yield measured by ^{1}H-NMR with dimethyl sulfone as the internal standard. Each lactone produced counts as two turnovers. [b]32 h reaction time. [c]37 h reaction time.

Negligible Effect of Stabilizers in Commercial Styrene

The commercial styrene that was used for the initial reaction screen contained 50 ppm 4-*tert*-butylcatechol as a stabilizer. To remove these trace amounts of catechol, the styrene was vacuum distilled after stirring over CaH_2 for several days at room temperature. The distilled styrene provided the same TON improvement as before. Unless otherwise specified, all reactions were conducted using non-distilled styrene for convenience and to avoid polymerization problems.

Monitoring Styrene Byproduct Formation over Time

Glycerol is selectively oxidized to dihydroxyacetone by Pd catalyst **1**, and one such aerobic oxidation with styrene was monitored over time at room temperature by ^{1}H-NMR. Figure S5 illustrates that the consumption of styrene correlates 1:1 with that of glycerol, which is the same result as observed with 1,2-propanediol described in the main text. At 17 h the ratio [**9**] : [acetophenone] : [1-phenylethanol] : [benzaldehyde] = 95 : 5 : 0 : 0, while at 57 h it was 73 : 13 : 12 : 2. These data support that, initially, styrene is converted almost exclusively into **9**.

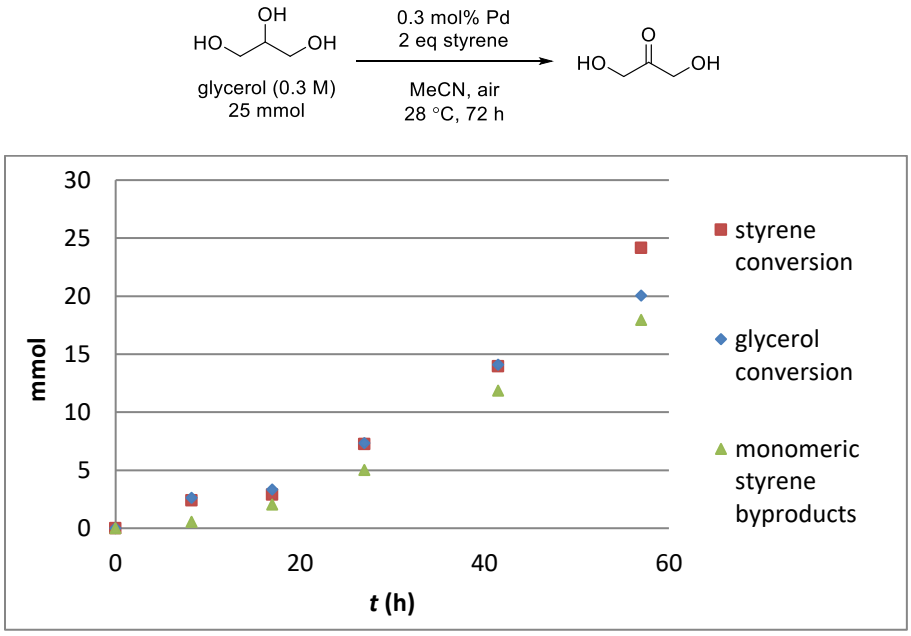
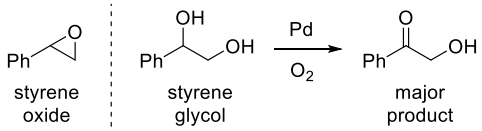


Figure S5. Reaction monitoring over time during a large scale aerobic oxidation of glycerol with styrene. Conditions: 0.3 M glycerol, 0.3 mol% Pd total, 2.1 eq styrene total, 85 mL MeCN, 28 °C, air. The Pd and styrene were added in several portions over time. Molar quantities determined by ^{1}H-NMR with dimethyl sulfone as the internal standard. The monomeric styrene byproducts are **9**, acetophenone, 1-phenylethanol, and benzaldehyde.

Ruling Out Styrene Oxide and Styrene Glycol as Intermediates



Styrene oxide (250 μmol) was added to an oxidation of DEG (100 μmol) at 60 °C with 2.7 μmol Pd in 1 mL CD_3CN under 1 atm O_2. Dimethyl sulfone was used as the internal standard. After 26 h, ^{1}H-NMR analysis indicated that 22 μmol of the epoxide was consumed and minimal amounts of benzaldehyde and acetophenone were produced (0.9 and 0.1 μmol, respectively). Styrene oxide did not appreciably benefit the TON for DEG oxidation (29 μmol lactol, 3 μmol lactone, TON_{total} = 13). Conducting the same reaction in the presence of 100 μmol styrene only increased the consumption of the epoxide by 6 μmol. Styrene oxide is not an observed byproduct in the Pd-catalyzed alcohol oxidations conducted with styrene, and these results demonstrate its stability under catalytic conditions. Thus it is not a reasonable intermediate in the styrene mechanism.

Styrene glycol (100 μmol) was oxidized in the presence of styrene (100 μmol) at 60 °C with 2.9 μmol Pd in 1 mL CD_3CN under 1 atm O_2. Dimethyl sulfone was used as the internal standard. After 26 h, ^{1}H-NMR analysis indicated that the major product by far originating from the glycol was the α-hydroxyketone (65 μmol yield out of 79 μmol conversion). This product is not observed in other Pd-catalyzed alcohol oxidations conducted with styrene. The amount of styrene consumed (26 μmol) was sufficient to account for the benzaldehyde, acetophenone, and 1-phenylethanol produced as well (7, 9, and 3 μmol, respectively). Therefore styrene glycol is not a reasonable intermediate in the styrene mechanism.

^{1}H-NMR Quantification of Water

The following method was used to quantify the water in entries 19-22 of Table S5. These reactions were conducted in CD_3CN so that they could be directly analyzed by ^{1}H-NMR. The concentration of dimethyl sulfone was known to be 25 mM. As there are alcohols in the reaction solution, one must assess the effect of proton exchange on the OH peak integrations if ^{1}H-NMR is to be used to quantify water content.

Figure S6 shows the ^{1}H-NMR spectra for the styrene-containing reaction from entry 21 at t = 0 (before Pd addition) and 26 h. The 6H peak from dimethyl sulfone has been set to have an area of 6.00 in both spectra. In the t = 0 spectrum it is clear that the water peak at δ 2.23 is well separated from the alcohol peaks of 1,2-propanediol at δ 2.85 and 2.79. There is negligible error in the peak areas due to exchange as evidenced by each alcohol peak having the same area as the 1H alkyl CH peak at δ 3.71 (7.78 and 7.68 vs. 7.76).

In the t = 26 h spectrum, the OH peaks of all types are significantly broader due to a higher concentration of exchangeable protons being present, but they are still well separated in chemical shift. Peak fitting procedures (MestReNova) were used to quantify the area under these broad peaks, and as shown in the figure the quality of the fits is very high. This reaction had proceeded to full conversion, so the main sources of exchangeable protons in this spectrum are water, hydroxyacetone, and hydroperoxide **9**. The area of the hydroxyacetone 1H alcohol peak at δ 3.22 is close to 1/3 of the area of the 3H methyl peak at δ 2.08 (6.97 vs. 19.40 / 3 = 6.47). The area of the 1H hydroperoxide peak from **9** at δ 9.47 is very close to the area of the 1H alkyl CH peak at δ 4.99 (4.82 vs. 4.98). Thus the error in the peak areas due to exchange, while greater here than in the t = 0 spectrum, is not severe enough to invalidate the large reduction in water produced relative to hydroxyacetone formed that occurs when styrene additive is used.

Solvent	CD_3CN	Number of Scans	4	Spectrometer Freq. (MHz)	399.72
Temperature (°C)	25	Relaxation Delay (s)	6	Acquired Size (points)	33632
Pulse Sequence	s2pul	Acquisition Time (s)	8	Spectral Size (points)	65536

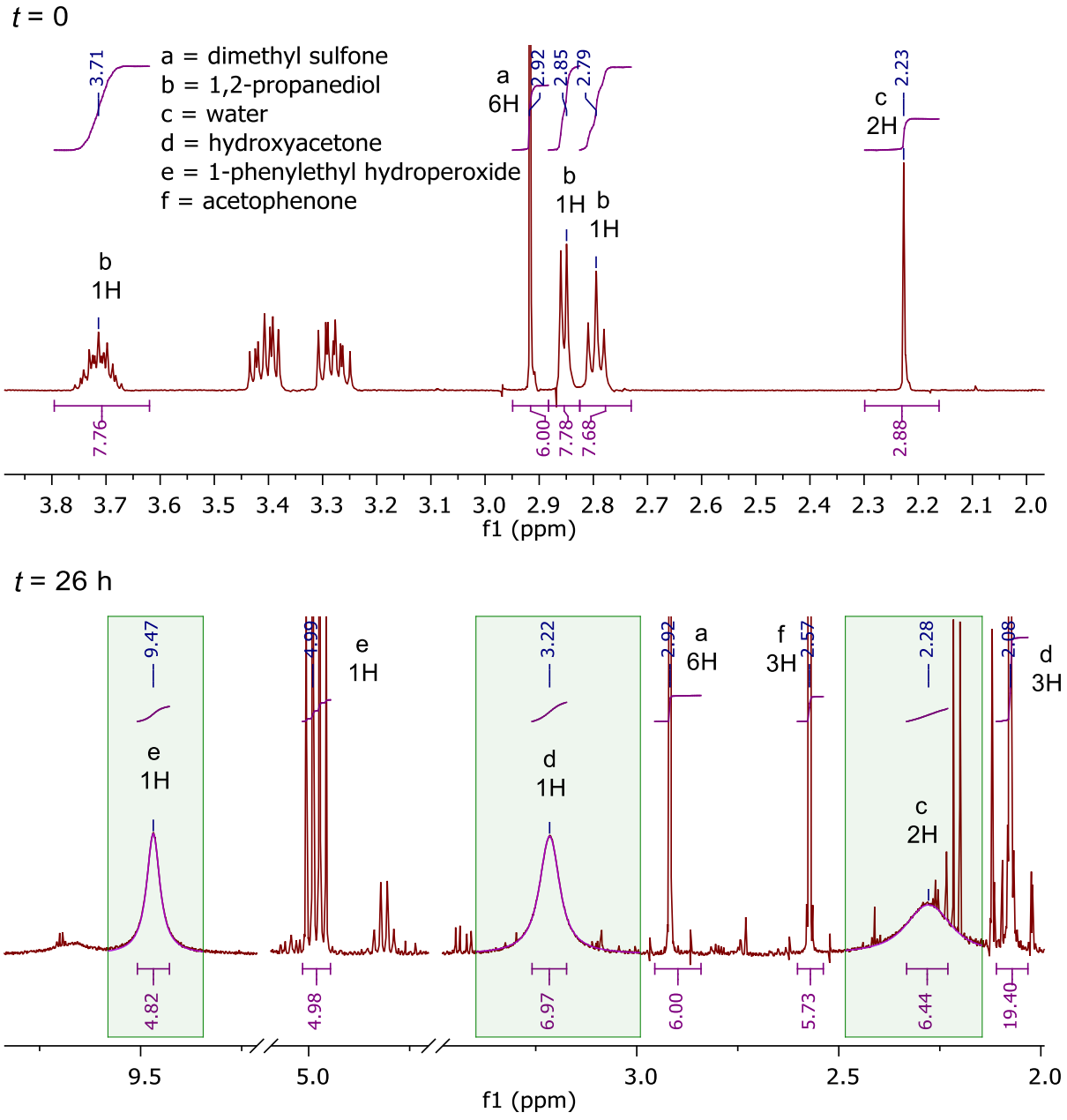


Figure S6. Examples of ^{1}H-NMR spectra used to quantify water. Conditions: 0.194 M 1,2-PD, 0.75 mol% Pd, 0.5 M styrene, 25 mM dimethyl sulfone, 1 mL CD_3CN, 28 °C, 1 atm O_2, 26 h. The magenta curves are the simulated peaks. If an integral is inside the green peak fitting region, its listed area reflects the total area under the simulated peak; the bounds as drawn do not matter.

Isotopic Labeling Experiments

Table S7. Summary of isotopic labeling experiments

Entry	Substrate	mol% Pd	Solvent[a]	Temp (°C)	Time (h)	Conditions	Method[b]	Analysis
1	0.1 M 1,2-PD	1	1 mL dry MeCN/EtPh[c]	60	32 h	0.5 M $H_2{}^{18}O$	A	GC-MS
2	0.1 M 1,2-PD	1	1 mL dry MeCN	rt	28 h	0.5 M styrene, 0.5 M $H_2{}^{18}O$	A	GC-MS
3	0.25 M 1,2-PD	0.5	2 mL dry MeCN/EtPh[d]	60	26 h	1 atm $^{18}O_2$	see below	GC-MS
4	0.05 M 1,2-PD	2.5	1 mL dry MeCN	60	32 h	0.5 M styrene, 0.5 atm 3:7 (v/v) $^{18}O_2/N_2$	see below	GC-MS
5	0.5 M d_8-*i*PrOD	0.5	1 mL MeCN	28	26 h	0.5 M styrene	A	^{1}H-NMR, ^{2}H-NMR, GC-MS
6	0.5M *i*PrOH	0.5	1 mL dry MeCN	28	26 h	0.5 M styrene, 1.5 M D_2O	A	^{1}H-NMR, ^{2}H-NMR, GC-MS

[a]If dry solvents were employed, the other reagents and glassware were dried before use as well. [b]Method A was used with vials with PTFE-coated silicone caps, which served as septa through which air-free reagents could be transferred. [c]Reagent grade EtPh; $[\mathbf{9}]_0 = 2$ mM in the total reaction solution. By the end, 14 mM acetophenone and 11 mM 1-phenylethanol were detected by GC with biphenyl as an internal standard. [d]Distilled EtPh.

For the experiment with $^{18}O_2$ and cosolvent EtPh (entry 3), an evacuated Schlenk flask was first filled with $^{18}O_2$ at room temperature. The reaction solution was prepared in a separate vial using degassed reagents under N_2 and then transferred to the Schlenk flask through a septum. After stirring for 45 min to dissolve $^{18}O_2$ into solution, a solution of Pd catalyst **1** in MeCN was added to the reaction mixture through the septum. The punctures in the septum were covered with multiple layers of Parafilm M and the flask was slowly heated to the desired reaction temperature.

For the experiment with $^{18}O_2$ and styrene (entry 4), $^{18}O_2/N_2$ (3:7, v/v) was first condensed into a Schlenk flask cooled by liquid nitrogen. The flask was allowed to warm to room temperature. The rest of the procedure was the same as above. The GC-MS analysis of this reaction is shown below as a representative example. The retention times for the assigned peaks are consistent with those from authentic samples.

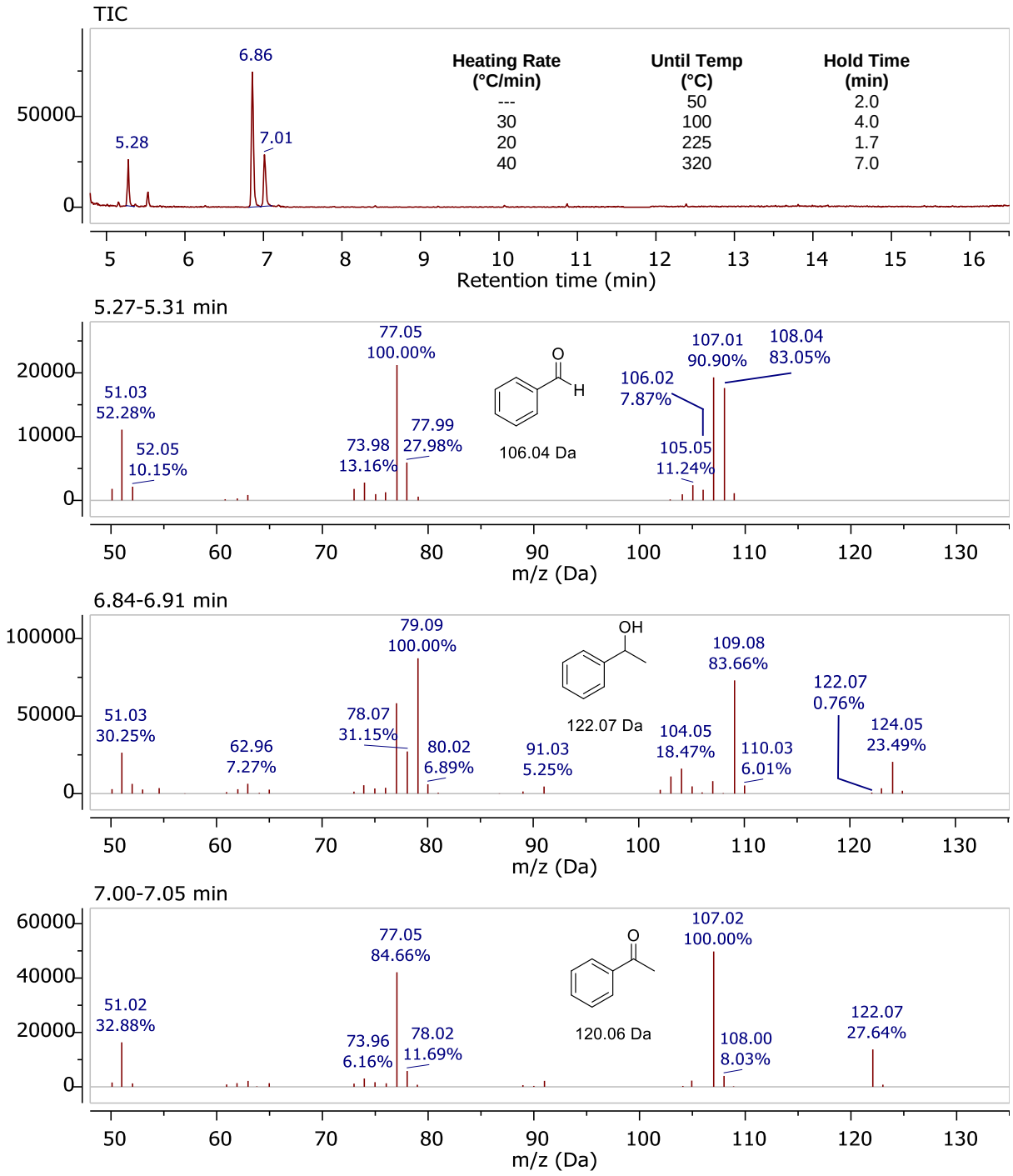


Figure S7. GC-MS analysis of the oxidation of 1,2-PD with $^{18}O_2$ and styrene (Table S7, entry 4). GC carrier gas = helium. Note that benzaldehyde produces $[M]^+$ and $[M–H]^+$ peaks of similar intensity.

Isotopic labeling ratios can be determined from GC-MS data by least-squares fitting of horizontally offset copies of the peak pattern found in the undeuterated compound.

As shown below, hydroperoxide **9** produces a very weak molecular ion peak at *m*/*z* = 138 in the GC-MS. Hence, the *m*/*z* = 105 peak, which corresponds to a loss of OOH, was used as the basis for determining its isotopic labeling ratios.

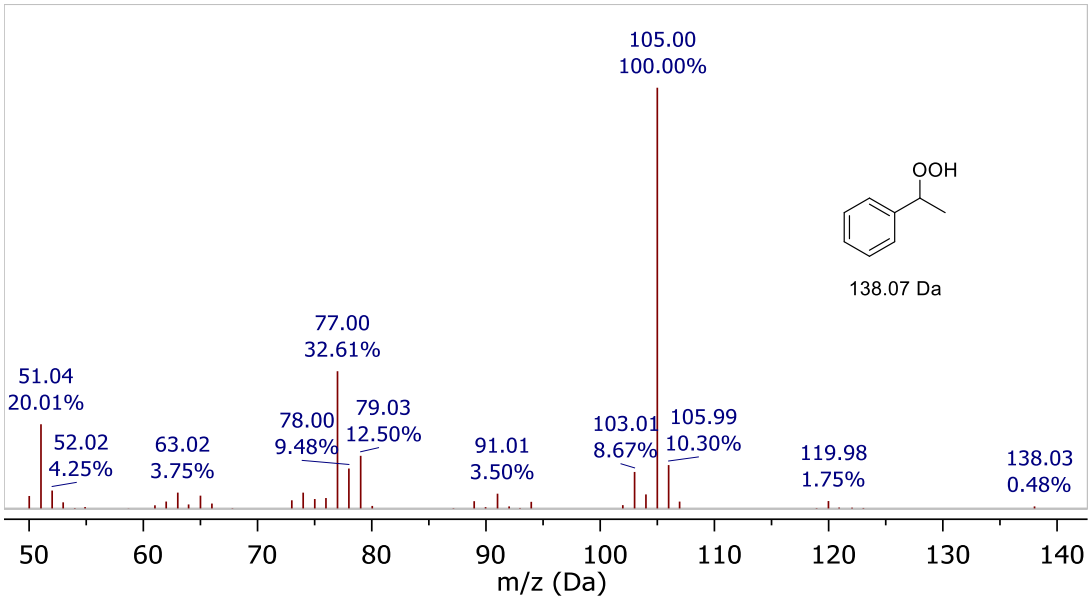


Figure S8. GC-MS mass spectrum of hydroperoxide **9**

For the deuteration experiments with styrene (Table S7, entries 5-6), the isotopic labeling conclusions were drawn from an interpolation of different analytical techniques. All deuteration was assumed to occur at non-aromatic carbons. The GC-MS data revealed the relative proportions of the isotopologues for acetophenone and **9**.

Dimethyl sulfone (25 μmol) was employed as an internal standard for ^{1}H-NMR. In the ^{1}H-NMR spectrum, acetophenone has a 3H singlet at δ 2.57, and there is a 1:1:1 triplet at δ 2.55 that arises from d_1- and, presumably, d_2-acetophenone. The corresponding peak in the ^{2}H-NMR appears at δ 2.60 (referenced such that the CD_3CN peak is at δ 1.96) and is partially overlapped, but its area can be determined from peak fitting procedures (MestReNova v10.0.0). Correlating the areas under the 1:1:1 triplet at δ 2.55 in the ^{1}H-NMR and the singlet at δ 2.60 in the ^{2}H-NMR, taking into account the 90:10 ratio of d_1:d_2-acetophenone determined by GC-MS, allows one to relate ^{2}H-NMR integral areas to absolute amounts. The feasibility of this calculation was verified by adding known amounts of MeCN and d_6-benzene to the NMR samples and re-acquiring the spectra.

Solvent	CD_3CN	Number of Scans	8
Temperature (°C)	29	Relaxation Delay (s)	6
Nucleus	^1H	Acquisition Time (s)	8
Acquired Size (points)	48000	Spectrometer Freq. (MHz)	499.75
Spectral Size (points)	65536	Pulse Sequence	s2pul

Solvent	MeCN	Number of Scans	8
Temperature (°C)	29	Relaxation Delay (s)	6
Nucleus	^1H	Acquisition Time (s)	8
Acquired Size (points)	15343	Spectrometer Freq. (MHz)	76.72
Spectral Size (points)	32768	Pulse Sequence	s2pul

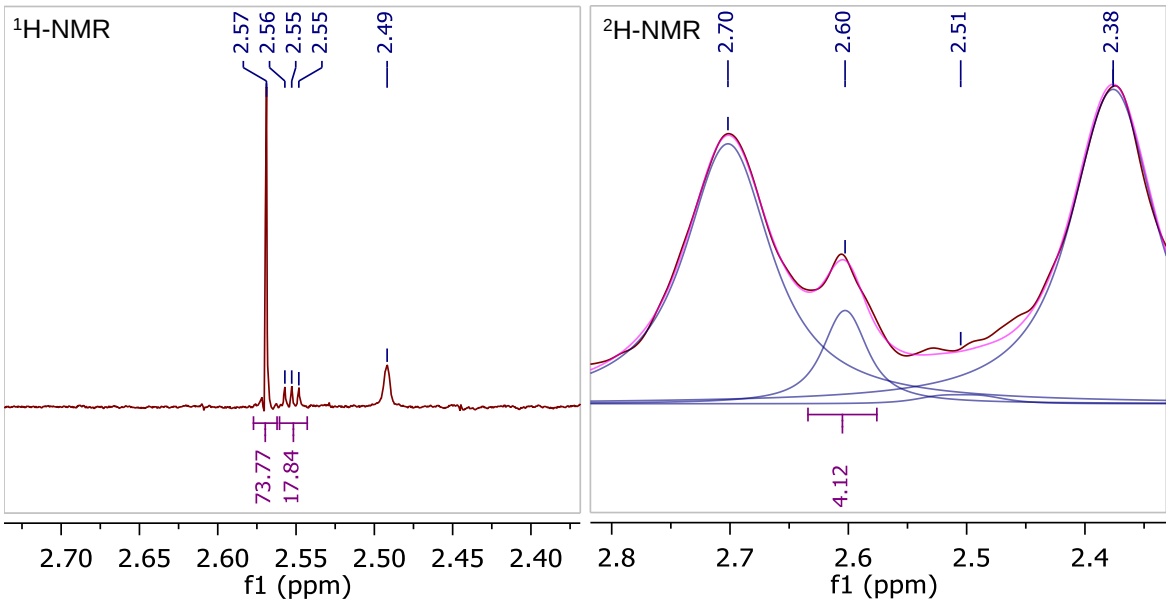


Figure S9. ^1H- and ^2H-NMR spectra focused on the acetophenone methyl peaks in the oxidation of d_8-isopropanol with styrene (Table S7, entry 5). In the ^2H-NMR spectrum, the results of peak fitting are shown where blue = individual simulated peaks and magenta = sum of simulated peaks. The integral for the δ 2.60 peak is reflective of the entire theoretical area under that simulated peak.

Styrene did not produce a peak in the GC-MS analyses, so its extent of deuteration was instead determined from the olefin peaks in the ^1H-NMR that came from d_1- and d_2-styrene. Assuming that all the styrene is singly deuterated gives a lower bound on the proportion of styrene that contains at least one deuterium.

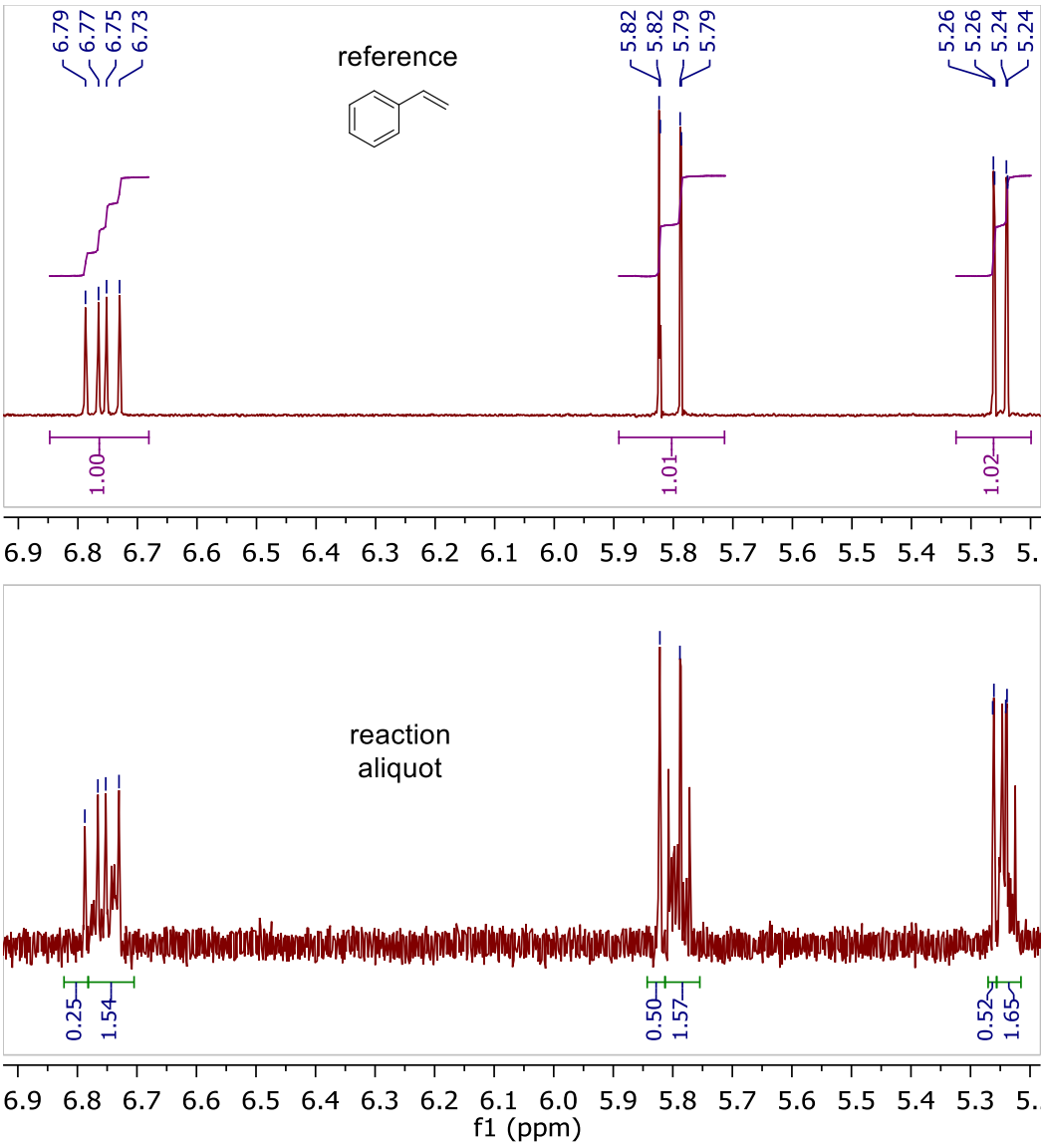


Figure S10. ^{1}H-NMR spectra focused on the olefin peaks of styrene. Top: a reference spectrum of undeuterated styrene. Bottom: a reaction aliquot (Table S7, entry 5) that contains a mixture of deuterated and undeuterated styrene. Each of the undeuterated styrene resonances has downfield peak(s) that can be cleanly integrated.

H-atom Abstraction Experiment with (bathocuproine)PdO_2 and 9,10-Dihydroanthracene

The following experiments were prepared in a moisture- and O_2-free glovebox with an N_2 atmosphere. All solvents were dried before use. Solution A consisted of (bathocuproine)PdO_2 (6.0 mg, 0.012 mmol) dissolved in CD_2Cl_2 (0.35 mL), and Solution B consisted of 9,10-dihydroanthracene (4.3 mg, 0.024 mmol) and dimethyl sulfone (2.3 mg, 0.024 mmol) dissolved in CD_3CN (0.7 mL). Reaction 1 was prepared by thoroughly mixing 0.35 mL each of Solutions A and B in a J. Young tube. Reaction 2, a Pd-free control, was similarly prepared with 0.35 mL CD_2Cl_2 and 0.35 mL Solution B. The J. Young tubes were sealed and allowed to sit at room

temperature. ^{1}H-NMR spectra were taken at *t* = 5 min, 2.5 h, and 6.5 h. Initially orange/brown, the solution in Reaction 1 became browner over time. Reaction 2 remained clear throughout. After 6.5 h, significant decomposition of (bathocuproine)Pd(O_2) was observed in Reaction 1, but anthracene was not produced and 9,10-dihydroanthracene was not consumed in either reaction.

Solvent	CD_3CN / CD_2Cl_2	Number of Scans	16	Spectrometer Freq. (MHz)	399.72
Temperature (°C)	25	Relaxation Delay (s)	12	Acquired Size (points)	51282
Pulse Sequence	s2pul	Acquisition Time (s)	8	Spectral Size (points)	65536

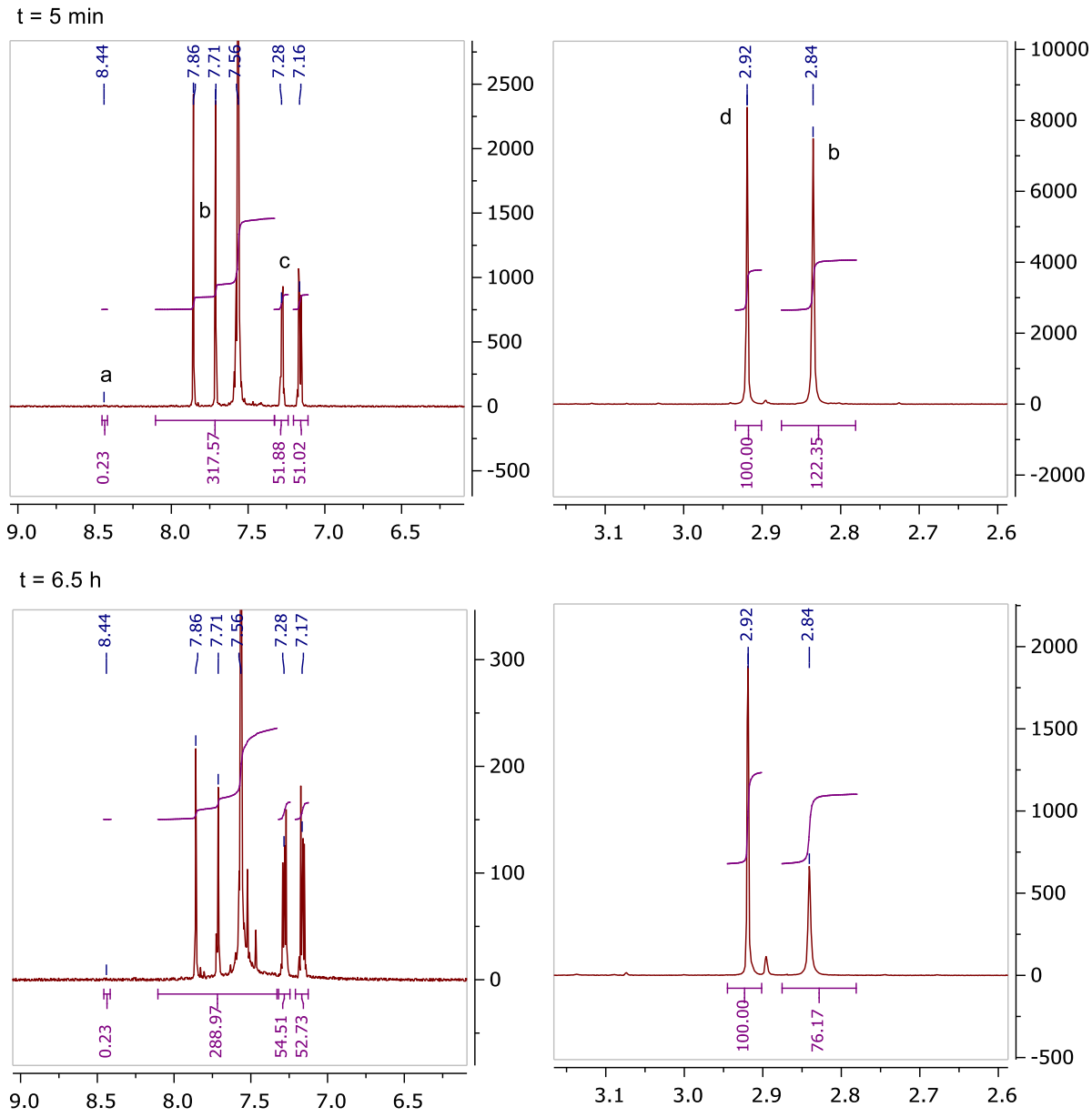


Figure S11. ^{1}H-NMR spectra of the reaction between (bathocuproine)Pd(O_2) and 9,10-dihydro-anthracene. a = anthracene, b = (bathocuproine)Pd(O_2), c = 9,10-dihydroanthracene, d = dimethyl sulfone. The very small amount of anthracene observed was a starting impurity in the 9,10-dihydroanthracene. The decomposition of (bathocuproine)Pd(O_2) over time is evidenced by both the decrease in area under the δ 2.84 singlet and the broadening of the δ 7.56 multiplet.

Relevant ^{1}H-NMR resonances in 1:1 (v/v) CD_3CN/CD_2Cl_2 are listed below.

(bathocuproine)Pd(O_2): δ 7.86 (s, 2H), 7.71 (s, 2H), 7.57-7.51 (m, 10H), 2.84 (s, 6H).
anthracene: δ 8.44 (s, 2H), 8.00 (m, 4H), 7.45 (m, 4H).
9,10-dihydroanthracene: δ 7.28 (m, 4H), 7.16 (m, 4H), 3.91 (s, 4H).

Characterization of Styrene Oligomers

A reaction aliquot was taken at the end of a preparative scale oxidation of DEG with styrene, eluted through a silica plug with MeCN, diluted with THF, and then analyzed by gel permeation chromatography (GPC) on a Viscotek GPCMax VE-2001 with two Waters Styragel columns (300 mm by 7.7 mm) and a Viscotek S3580 refractive index detector. THF was used as the carrier solvent at 35°C at a flow rate of 1 mL/min. Molecular weight calibrations were carried out using monodisperse polystyrene samples ranging from M_p = 500 to 275,000. The GPC data shown below clearly indicated the presence of small oligomers with MW < 1000. The GPC trace of an analogous reaction without styrene did not contain any large peaks before the solvent peak region.

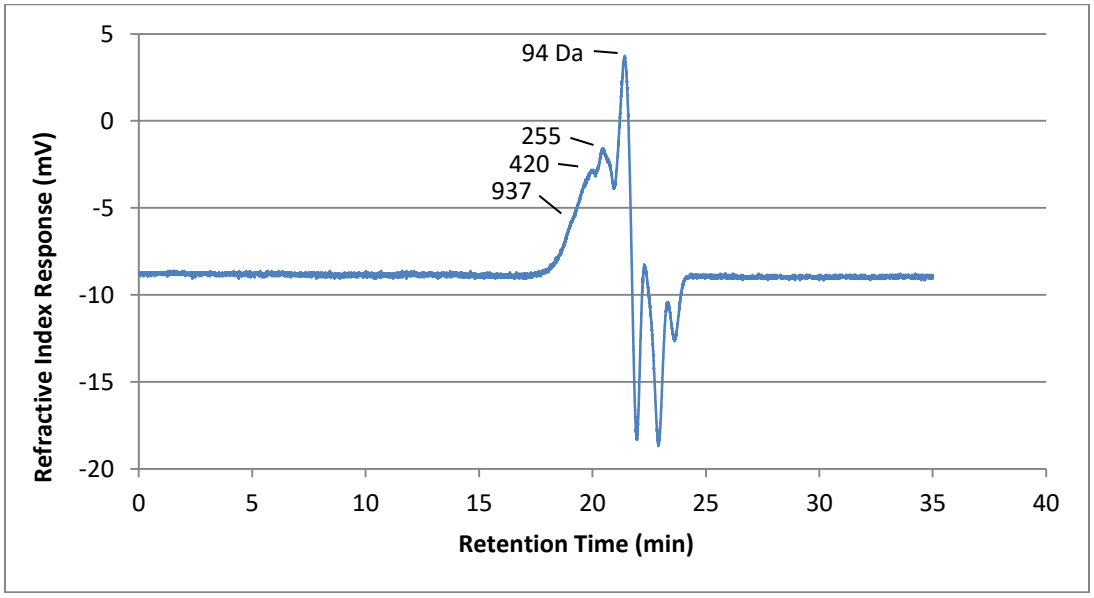


Figure S12. GPC trace of a reaction aliquot containing styrene oligomers

Silica gel chromatography (40% EtOAc in hexanes) of the reaction mixture from a preparative scale oxidation of DEG with styrene provided, separately from the lactone product, a yellow oil that contained mostly styrene oligomers and a small amount of monomeric byproducts. The broad resonances in the δ 5.5-3.8 region of the ^{1}H-NMR spectrum are consistent with a polyperoxide structure, though other oxygen-containing motifs such as alcohols or ethers could also be responsible for these downfield shifts.

Solvent	CD_3CN	Number of Scans	8	Spectrometer Freq. (MHz)	399.72
Temperature (°C)	25	Relaxation Delay (s)	6	Acquired Size (points)	51282
Pulse Sequence	s2pul	Acquisition Time (s)	8	Spectral Size (points)	65536

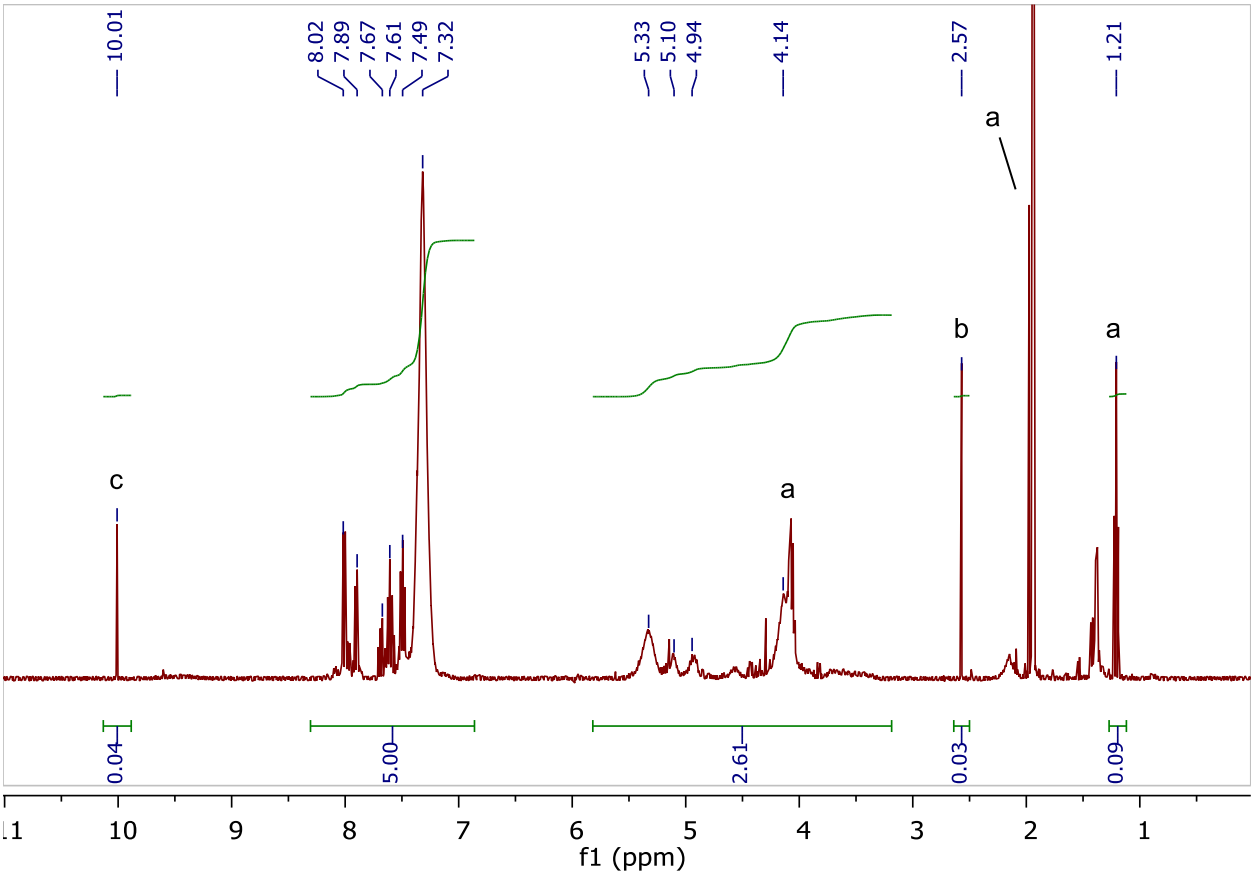


Figure S13. ^{1}H-NMR spectrum of styrene oligomers. a = EtOAc, b = acetophenone, c = benzaldehyde.

ESI-MS of an Aerobic Oxidation Containing Styrene

Optima grade acetonitrile from Fisher Scientific was used for these experiments. 1,2-propanediol (7.35 μL, 0.1 mmol) and styrene (11.5 μL, 0.1 mmol) were dissolved in MeCN (10 mL). 1 mL of this solution was transferred to a 20 mL vial. Pd catalyst **1** was added (2.61 mg, 0.0025 mmol, 50 mol% Pd relative to the diol) from a 5 mM stock solution in MeCN and the reaction mixture was vortexed briefly. A reaction aliquot was taken at approximately t = 1 min, diluted 1000x with MeCN, and injected into the ESI-MS instrument. The instrument calibration was checked by analyzing a solution of pure **1** (calc'd m/z for $[(neoc)Pd(OAc)]^+$ = 373.0163 (exact), 373.0169 (MNova prediction); obs'd 373.0173).

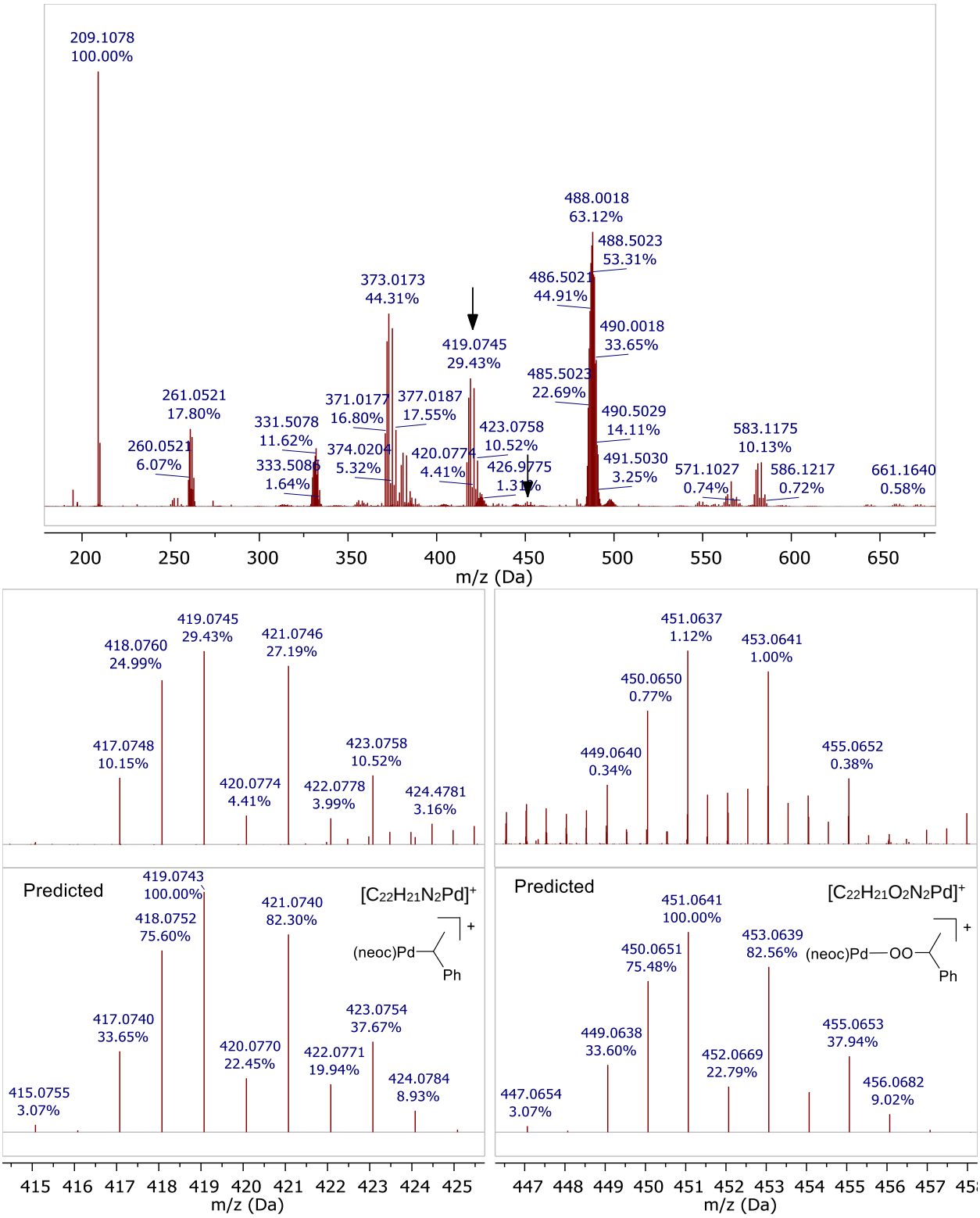


Figure S14. ESI-MS data consistent with proposed intermediates in the styrene mechanism. See refs[1, 3, 9] for the assignment of other major mass peaks. The predicted spectra were generated by MNova software.

Example of a TLC Plate for Aerobic Oxidations Containing Styrene

A TLC plate to analyze the end of two small scale reactions with styrene additive are shown below. The plate was developed in 75% EtOAc/hexanes and visualized with a $KMnO_4$ stain. The TLC plate illustrates that hydroxyacetone (the product of Reaction 1) is more polar than *N*-Boc 2-morpholinone (**12**, the product of Reaction 2) by a decent amount. The spot for morpholinone **12** is somewhat close to the acetophenone/hydroperoxide **9** spot, but preparative scale chromatography shows that it is not these compounds that co-elute with **12** but rather a mixture of styrene oligomers. The oligomers are not easily visible on the TLC plate, but on the preparative scale it has been empirically determined that the oligomers smear along the silica until sufficiently polar eluents are used. Hydroxyacetone is polar enough to be separated from the styrene byproducts by chromatography alone.

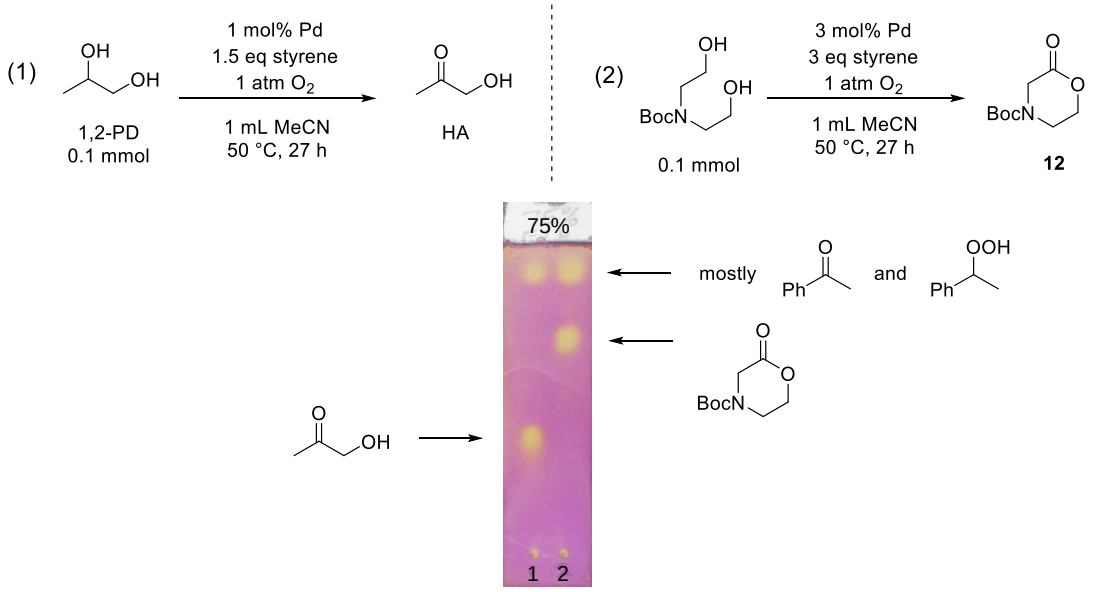
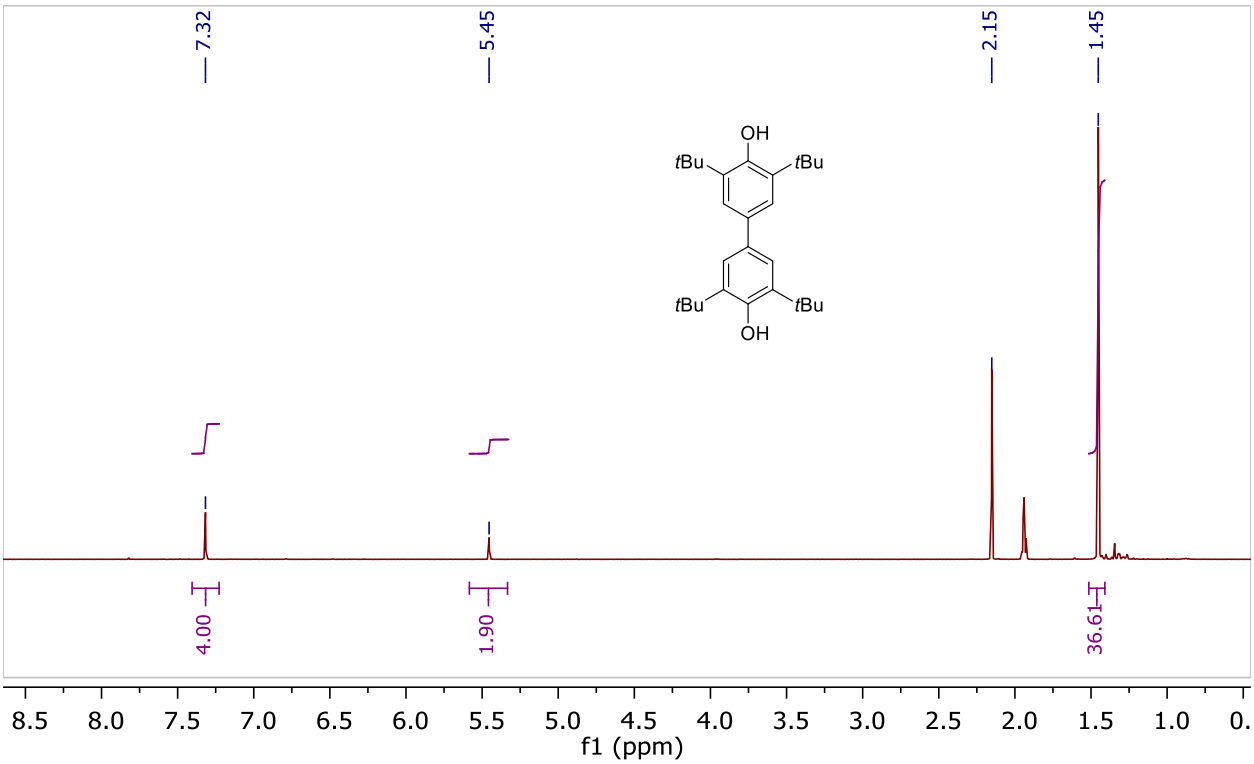


Figure S15. Representative TLC (thin layer chromatography; silica gel) plate for two aerobic oxidations with styrene additives.

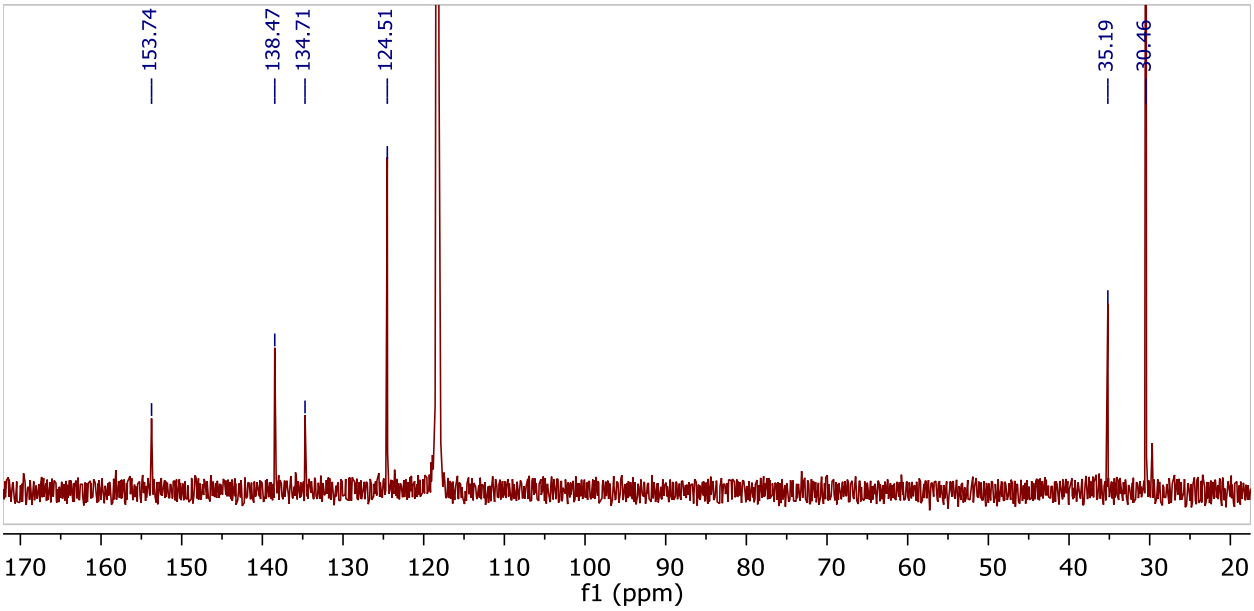
Spectra for Selected Compounds

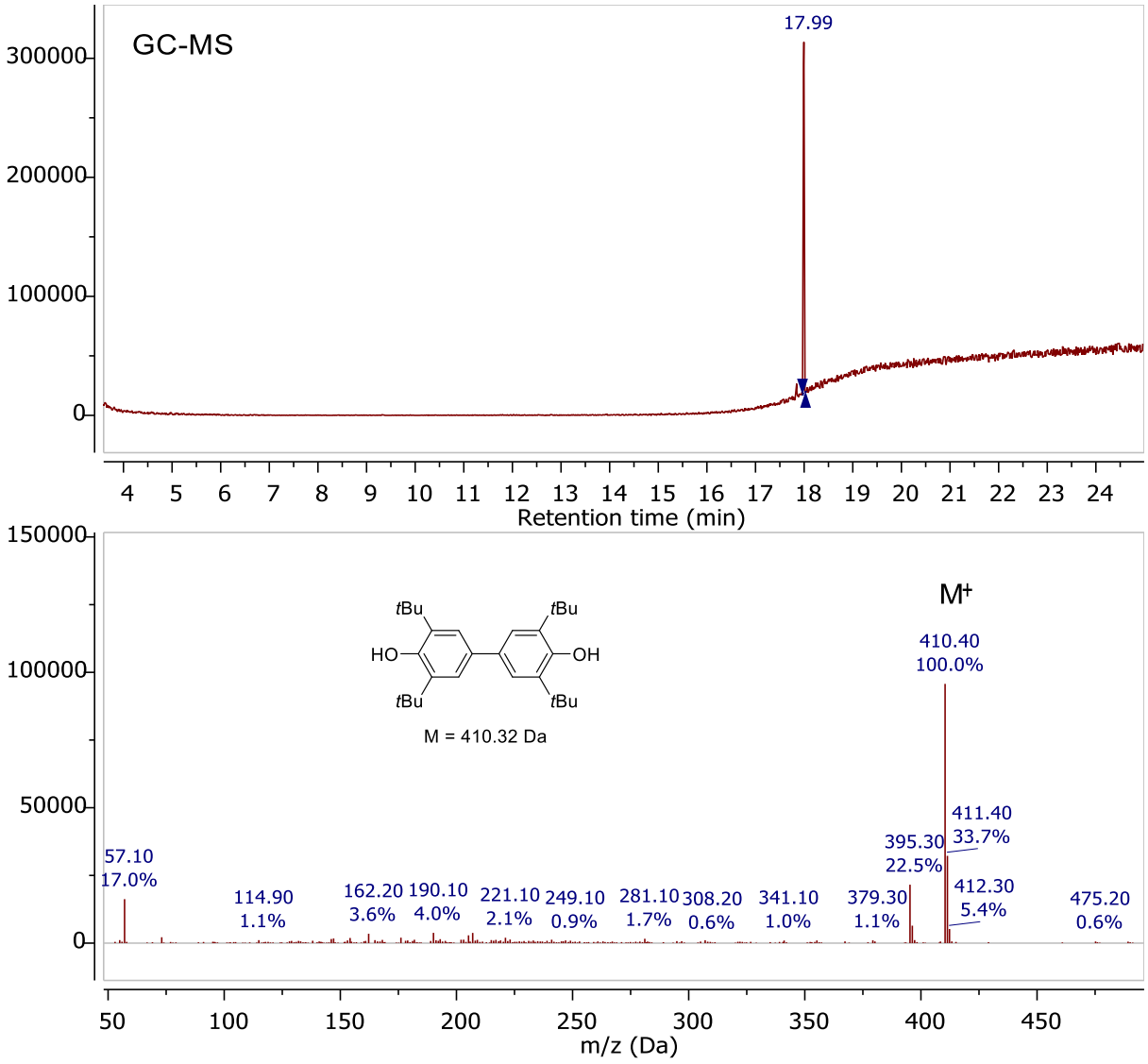
4,4′-dihydroxy-3,3′,5,5′-tetra-*tert*-butylbiphenyl (6)

Solvent	CD_3CN	Number of Scans	24	Spectrometer Freq. (MHz)	399.72	Pulse Sequence	s2pul
Temperature (°C)	20	Relaxation Delay (s)	0.5	Acquired Size (points)	22422	Solvent residual set to	
Nucleus	^1H	Acquisition Time (s)	4	Spectral Size (points)	32768	1.94 ppm	



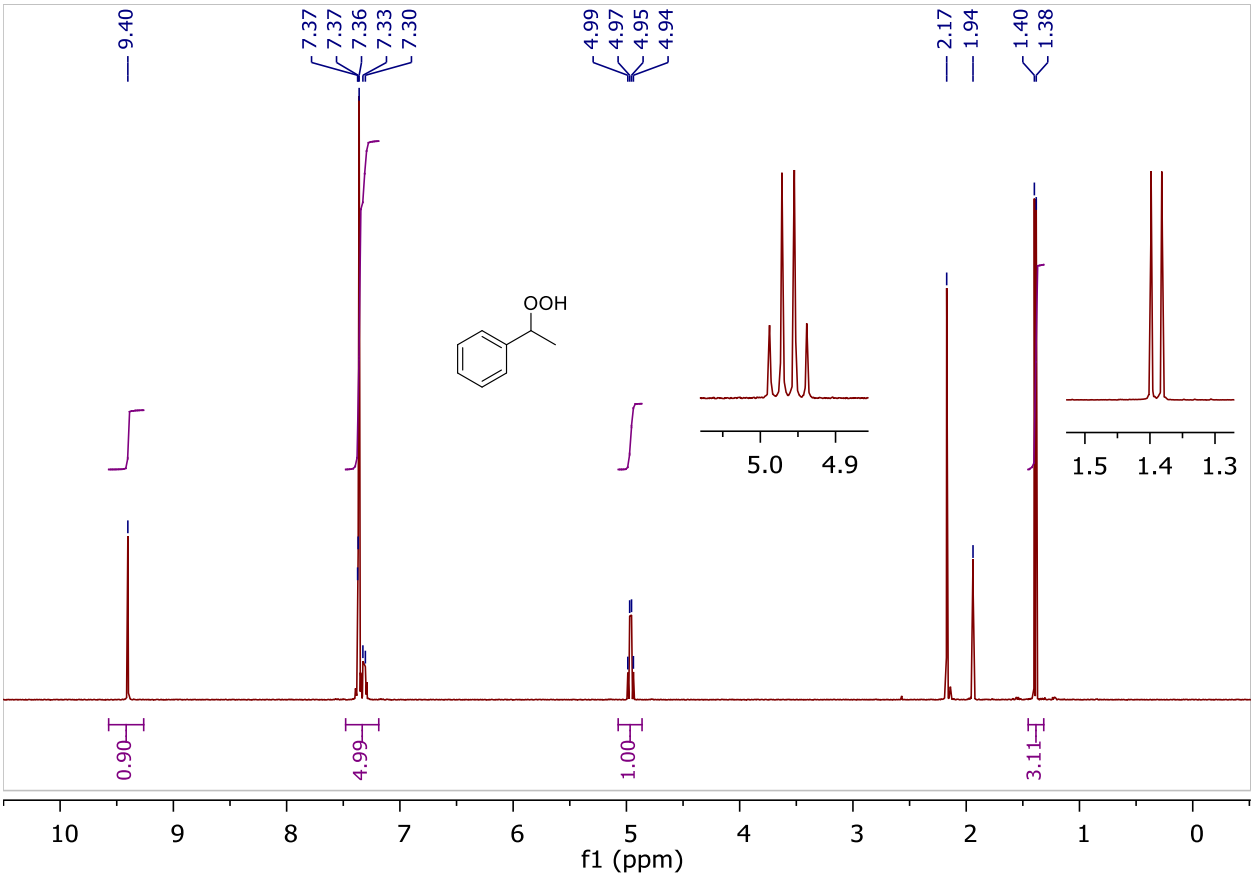
Solvent	CD_3CN	Number of Scans	1652	Spectrometer Freq. (MHz)	125.67	Pulse Sequence	s2pul
Temperature (°C)	29	Relaxation Delay (s)	0.5	Acquired Size (points)	49508	Solvent residual set to	
Nucleus	^{13}C	Acquisition Time (s)	1.5	Spectral Size (points)	65536	118.26 ppm	




GC-MS
17.99
300000
200000
100000
0
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Retention time (min)
150000
100000
50000
0
tBu
tBu
HO
OH
tBu
tBu
M = 410.32 Da
M+
410.40
100.0%
411.40
33.7%
395.30
22.5%
412.30
5.4%
57.10
17.0%
114.90
1.1%
162.20
3.6%
190.10
4.0%
221.10
2.1%
249.10
0.9%
281.10
1.7%
308.20
0.6%
341.10
1.0%
379.30
1.1%
475.20
0.6%
50 100 150 200 250 300 350 400 450
m/z (Da)

1-phenylethyl hydroperoxide (9)

Solvent	CD_3CN	Number of Scans	8	Spectrometer Freq. (MHz)	399.72	Pulse Sequence	s2pul
Temperature (°C)	22	Relaxation Delay (s)	6	Acquired Size (points)	44843		
Nucleus	^1H	Acquisition Time (s)	8	Spectral Size (points)	65536		



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15. These concentrations are higher than those commonly found in benchtop EtPh (<1 mM), but lower than those observed at the end of an alcohol oxidation reaction (>15 mM, measured with respect to the total reaction solution volume) when such cosolvents are used.
16. Same reaction conditions as used in Figure S3. At t = 0, [acetophenone] = [1-phenylethanol] = 0 mM. At t = 26 h, [acetophenone] = 24 mM, [1-phenylethanol] = 23 mM, and [HA] = 41 mM.