JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Subscriber access provided by Universitaetsbibliothek | Johann Christian Senckenberg

Article

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

Wilson Ho, Kevin Chung, Andrew J. Ingram, and Robert M. Waymouth

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b11372 • Publication Date (Web): 15 Dec 2017

Downloaded from http://pubs.acs.org on December 15, 2017

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

ACS Publications

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036
Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

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

Wilson C. Ho,[a] Kevin Chung,[a,b] Andrew J. Ingram,[a,c] and Robert M. Waymouth*[a]

[a]*Department of Chemistry, Stanford University, Stanford, California 94306, United States*
[b]*Formosa Plastics Corporation, 201 Formosa Drive, Point Comfort, Texas 77978, United States*
[c]*James R. Randall Research Center, Archer Daniels Midland Company, Decatur, Illinois 62521, United States*

Abstract

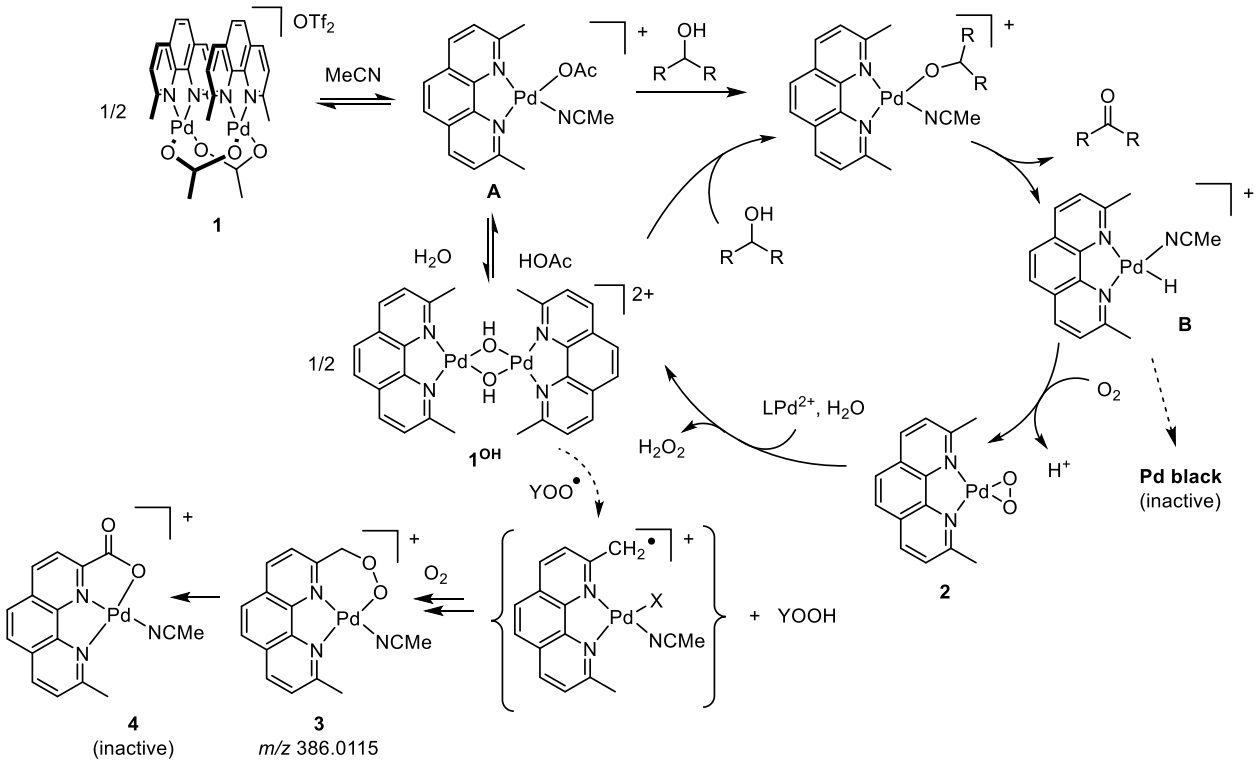
The palladium complex [(neocuproine)Pd(μ-OAc)]$_2$[OTf]$_2$ (**1**, neocuproine = 2,9-dimethyl-1,10-phenanthroline) is an effective catalyst precursor for the selective oxidation of primary and secondary alcohols, vicinal diols, polyols, and carbohydrates. Both air and benzoquinone can be used as terminal oxidants, but aerobic oxidations are accompanied by oxidative degradation of the neocuproine ligand, thus necessitating high Pd loadings. Several strategies to improve aerobic catalyst lifetimes were devised, guided by mechanistic studies of catalyst deactivation. These studies implicate a radical autoxidation mechanism initiated by H-atom abstraction from the neocuproine ligand. Ligand modifications designed to retard H-atom abstractions as well as the addition of sacrificial H-atom donors increase catalyst lifetimes and lead to higher turnover numbers (TON) under aerobic conditions. Additional investigations revealed that the addition of benzylic hydroperoxides or styrene lead to significant increases in TON as well. Mechanistic studies suggest that benzylic hydroperoxides function as H-atom donors and that styrene is effective at intercepting Pd hydrides. These strategies enabled the selective aerobic oxidation of polyols on preparative scales using as little as 0.25 mol% Pd, a major improvement over previous work.

Introduction

Selective oxidations are among the most important reactions for the synthesis of fine and commodity chemicals.[1-3] Air is a convenient terminal oxidant due to its abundance and high oxidation potential.[4-6] Aerobic oxidations catalyzed by Pd have been known for decades, but interest in them was reinvigorated by studies demonstrating that in appropriate ligation environments, Pd(0) can be readily re-oxidized by O_2.[3, 7-11] This has enabled new strategies for the selective catalytic aerobic oxidation of alcohols.[12-13]

The dimeric complex [(neocuproine)Pd(μ-OAc)]$_2$[OTf]$_2$ (**1**) has proven to be a highly chemoselective aerobic alcohol oxidation catalyst precursor that operates at room temperature.[14-16] Catalytic oxidation of α,ω-diols to lactones[17] with **1** provides an expedient synthesis of monomers for ring-opening polymerization.[18-19] This catalyst exhibits high selectivity for the oxidation of secondary alcohols in vicinal diols[15-16, 20] and carbohydrates[10, 21-23] to generate α-hydroxyketones. α-Hydroxyketones appear in numerous synthetic targets and can serve as versatile intermediates for further modification.[24-29] The selective oxidation of alcohols in unprotected polyhydroxylated substrates and carbohydrates provides an alternative to multi-step protection and deprotection strategies.[23, 30]

While air or O_2 is a convenient and readily available oxidant, there are significant challenges associated with using O_2 in a selective manner due to its redox stoichiometry. As O_2 is a 4-electron oxidant, the generation of highly reactive partially reduced oxygen species can lead to competitive non-selective autoxidation pathways.[4-5] In the case of **1**, catalysis under aerobic conditions causes oxidative degradation of the methyl groups on the neocuproine ligand, eventually leading to the inactive complex **4** (Scheme **1**). For this reason 1,4-benzoquinone (BQ) is occasionally employed as the terminal oxidant instead of dioxygen, but removal of the reduced hydroquinone complicates product isolation. Modified phenanthroline-based ligands designed to be more resistant to oxidation were previously synthesized and tested, but their use only improved the TON slightly.[31-32] Another major catalyst deactivation pathway is the formation of Pd(0) aggregates, *i.e.*, "Pd black." Guided by mechanistic knowledge of these deactivation pathways, herein we describe several strategies to improve catalyst lifetimes and turnover numbers (TON = moles product/mole Pd) from ~35 to >300 at room temperature.



Scheme 1. Mechanism of alcohol oxidation by Pd complex **1** and its proposed deactivation pathways. YOO• represents a reactive partially reduced oxygen species. Only one pathway for Pd reoxidation is shown; others may be operative.

Herein we present evidence implicating that H-atom abstraction (HAA) of a benzylic hydrogen from the neocuproine ligand initiates a radical autoxidation process that degrades the ligand (Scheme 1), and we accordingly designed strategies to suppress this pathway and increase TON. Traditional H-atom donors such as phenols are effective additives for this purpose, as are benzylic hydroperoxides. The oxidative degradation of ligands under aerobic conditions has historically been a challenge for Pd catalysis, and so this work is of broad relevance to the field.[7]

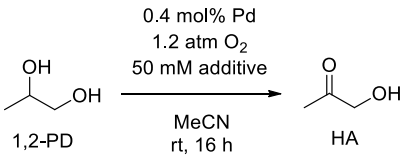
The other approach to improve TON focused on preventing Pd black formation. Styrene was found to be highly effective for this purpose, and its mechanism of action is more complex than simply binding to Pd(0) species as an olefin. We present evidence that styrene provides another pathway for Pd hydride **B** to be converted back into active catalyst without going through Pd(0). Styrene is converted to a benzylic hydroperoxide in the process, which in turn can also act as an H-atom donor to further improve TON. The synthetic utility of these TON enhancing strategies was demonstrated in the preparative scale aerobic oxidations of several polyol substrates. In each case the high chemoselectivity of catalyst **1** was retained.

Results and Discussion

Pathways for Oxidative Ligand Degradation. Prior mechanistic investigations combined with *in situ* Electrospray Ionization Mass Spectrometry (ESI-MS)[33-34] revealed several oxidized Pd intermediates that form during the catalytic aerobic oxidation of alcohols or disproportionation of hydrogen peroxide.[33] Ions corresponding to the Pd alkylperoxo complex **3** were identified as a key intermediate in the formation of the Pd carboxylate **4** (Scheme 1) which had been previously isolated[14] and shown to be inactive for catalytic alcohol oxidation. These observations spawned the hypothesis that oxidative degradation of the ligand was initiated by hydrogen atom abstraction of a benzylic C-H bond mediated by reactive peroxide species; subsequent trapping of the resultant benzylic radical by O_2 could explain the formation of **3**. This hypothesis was supported by isotope labeling experiments which revealed that both oxygens in **3** were derived from O_2.[33] Related pathways have been proposed from metal hydroperoxo compounds for both Ni and Pd complexes.[35-40]

Addition of Phenolic Additives to Mitigate Oxidative Degradation. Guided by the hypothesis that hydrogen atom abstraction is a key step in the oxidative degradation of **1**, we investigated whether the addition of sacrificial hydrogen atom donors would inhibit this pathway and lead to higher turnover numbers. Phenols are used as H-atom donors or antioxidants in a wide variety of reactions,[41-43] so several phenols were tested as additives in alcohol oxidations with catalyst **1**.[22] The phenols were screened at a concentration of 50 mM in the oxidation of 1,2-propanediol ($[1,2\text{-PD}]_0$ = 0.25 M) with Pd complex **1** ($[Pd]_0 = 2\times[\mathbf{1}]_0$ = 1.0 mM) in acetonitrile under 1.2 atm O_2 (Table 1). After 16 h the yield of hydroxyacetone (HA) was assessed by GC-FID with an internal standard to assess the number of catalytic turnovers (TON = mmol HA / mmol Pd). Low Pd loadings and long reaction times were employed to ensure that the maximal TON of the catalyst had been reached. For small scale reactions throughout this work, the standard deviation for yields between repeated experiments is ±3%.

Table 1. Influence of phenolic additives on the catalytic oxidation of 1,2-propanediol

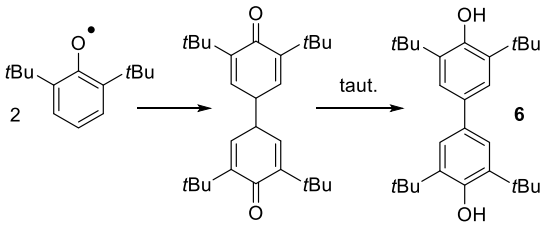


Entry	Additive	Yield (GC)[a]	TON[b]
1	None	12%	31
2	2,6-*i*Pr$_2$-phenol (**5**)	27%	67
3	2,6-*t*Bu$_2$-phenol	14%	36
4	2,4,6-*t*Bu$_3$-phenol (25 mM)	21%	52
5	(50 mM)	23%	57
6	(100 mM)	21%	53
7	2,6-*i*Pr$_2$-aniline	11%	28

Conditions: 0.25 M 1,2-propanediol, 1.0 mM Pd (0.4 mol%), 50 mM additive, 2 mL MeCN, rt, 16 h. Reactions done in duplicate. The reactions were carried out in a sealed metal reactor with a shared headspace of 1.2 atm O_2. [a]Yield of HA, as measured by GC-FID with either biphenyl or naphthalene internal standards. [b]TON = (mmol HA)/(mmol Pd).

The addition of phenols led to an improvement in the yield of hydroxyacetone generated, corresponding to an increase in turnover number from 31 to as high as TON = 67 in the case of 2,6-diisopropylphenol (**5**, Table 1, entry 2). For 2,4,6-tri-*tert*-butylphenol, varying the additive concentration from 25 mM to 100 mM had little effect on TON. Addition of 2,6-diispropylaniline[44] did not result in an increase in yield relative to that observed in the absence of additive (Table 1, entry 1 vs. 7).

During the aerobic oxidation of the sugar octyl β-D-glucopyranoside[21] with 2,6-di-*tert*-butylphenol at 50 °C, the biphenol **6** was observed by ^{1}H-NMR and was subsequently isolated and characterized (4.5% yield relative to initial phenol loading). The formation of biphenol **6** is consistent with the intermediacy of phenoxy radicals during the reaction (Scheme 2),[45] thus supporting that the phenols act as sacrificial H-atom donors. Control experiments in the presence of alcohol substrate but no Pd catalyst verified that none of the biphenol is formed after 21 h at 50 °C.



Scheme 2. Coupling of phenoxy radicals to produce an isolable biphenol

Analysis of the reaction stoichiometry reveals that the increase in the moles of alcohols oxidized exceeds the moles of phenol consumed. For example, in the oxidation of 1,2-propanediol (0.1 mmol) at room temperature, 4 μmol of the phenol **5** was consumed while the

conversion of 1,2-propanediol increased by 30 μmol over the control reaction with no additives. This suggests that phenol is able to enhance Pd catalyst lifetimes without being consumed on every turnover.

Kinetic experiments (see Supporting Information) showed that the addition of phenols had a negligible effect on the rate of the aerobic oxidation of 1,2-propanediol. Phenols also had no effect on the yield of hydroxyacetone when benzoquinone was used as the terminal oxidant in the absence of O_2. These results suggest that phenols likely do not serve other roles in improving aerobic TON.

Ligand Modifications. Previous investigations revealed that the methyl substituents at the 2,9-positions of phenanthroline are critical for the room temperature activity of these phen-based Pd complexes,[31] but are also a liability. The cationic Pd phenanthroline complexes lacking 2,9-substituents are inactive at room temperature (Table 2, entry 1), which we have attributed to the stability of the μ-hydroxo complexes analogous to $\mathbf{1^{OH}}$ (Scheme 1).[31] Previous attempts to generate more oxidatively-resistant ligands by the introduction of CF_3 groups led to only modest improvements in the turnover numbers.[31] The 2,9-diethyl-1,10-phenanthroline ligand was also ineffective (Table 2, entry 8), revealing that the catalytic activity is quite sensitive to steric effects.

In an effort to generate Pd complexes that might be more resistant to hydrogen atom abstraction, several modified neocuproine ligands were investigated, including d_6-neocuproine (which bears perdeuterated methyl groups),[32-33] 2,9-dimethyl-5-nitro-1,10-phenanthroline (**7**), and 2,9-dimethyl-1,10-phenanthroline-5,6-dione (**8**). If hydrogen atom abstraction were the key step in oxidative catalyst degradation, then complexes bearing the deuterated ligand should exhibit longer lifetimes due to the deuterium isotope effect.[46] Similarly, ligands **7** and **8** were investigated because toluenes bearing electron-withdrawing substituents are known to undergo slower rates of hydrogen atom abstraction.[47]

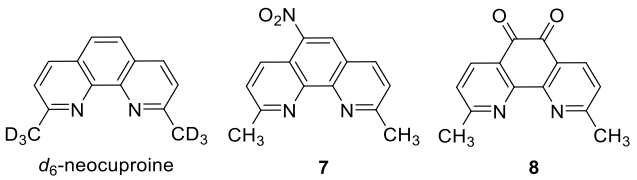


Chart 1. Modified neocuproine ligands

These new ligands were tested in the aerobic oxidation of 1,2-propanediol in MeCN utilizing the isolated complexes $[(L)Pd(OAc)]_2[OTf]_2$ and/or the complexes prepared *in situ*.[31] Oxidation of 1,2-propanediol with the Pd complex $\boldsymbol{d_{12}}$**-1**, derived from the d_6-neocuproine ligand, led to higher yields of hydroxyacetone, corresponding to a 60% increase in the turnover number from TON = 35 to TON = 56 (Table 2, entries 2-5). Similar results were recently reported by de Vries and Minnaard.[32] The NO_2-substituted neocuproine ligand **7** afforded a similar increase in TON, whereas the diketone ligand **8** was inactive for the aerobic oxidation of 1,2-propanediol.

Table 2. Influence of ligands on the catalytic oxidation of 1,2-propanediol

Entry	Ligand	Catalyst Prep.	Yield (GC)	TON
1	phen	isolated	<1%	<2
2[c]	neoc	isolated	18%	36
3[c]	neoc	*in situ*[a]	17%	34
4	d_6-neoc	isolated	29%	58
5	d_6-neoc	*in situ*[a]	27%	54
6[c]	**7**	*in situ*[b]	29%	59
7	**8**	*in situ*[b]	<1%	<2
8	2,9-Et_2-phen	*in situ*[b]	<1%	<2

Conditions: 0.25 M 1,2-propanediol, 1.25 mM Pd (0.5 mol%), 1 mL MeCN, rt, air, 24 h. The vials were open-capped for the initial 6 h. [a]Catalyst prepared *in situ* by reacting a 2:1:1 mixture of ligand / $Pd(OAc)_2$ / $[Pd(MeCN)_4][BF_4]_2$ for 1 h prior to reaction. [b]Components complexed for 24 hours prior to reaction. [c]Reaction done in duplicate.

Cosolvents with Benzylic C-H Bonds. We also investigated whether solvents containing weak C-H bonds might serve as sacrificial hydrogen atom donors to increase catalyst lifetimes. The influence of aromatic cosolvents, including those bearing benzylic C-H bonds, was investigated on the aerobic oxidation of 1,2-propanediol with Pd complex **1** (Table 3). These experiments were carried out at a lower concentration of 1,2-propanediol (0.1 M) than those reported in Table 1; under these conditions, the yield and turnover number of the control reaction were slightly lower (TON = 21, Table 3, entry 1) than those observed at the higher concentration (TON = 31, Table 1, entry 1).

Table 3. Influence of cosolvents on the catalytic oxidation of 1,2-propanediol

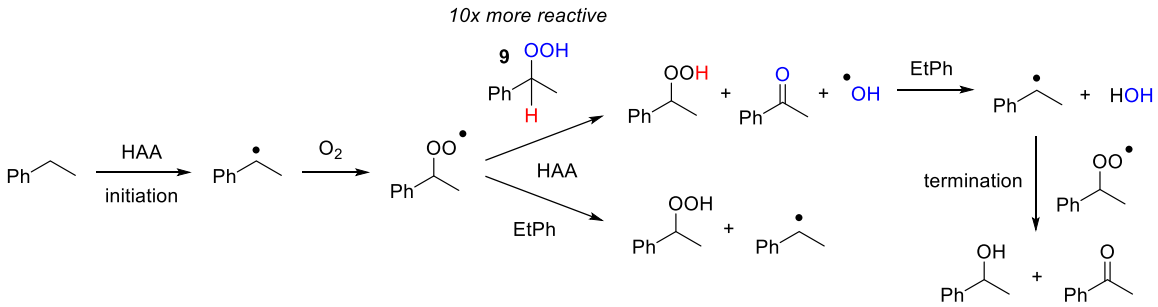
Entry	Cosolvent[a]	[9][b] (mM)	Yield (NMR)[c]	TON
1	MeCN	0	11%	21
2	EtPh[d]	0	23%	46
3	PhMe	0	22%	44
4	PhH	0	20%	41
5	*t*BuPh	0	19%	38
6	EtPh[e]	45	47%	93
7	EtPh[f]	47	46%	92
8	EtPh[g]	16	45%	89
9	MeCN	46	25%	50
10	MeCN[h]	0	23%	47

Conditions: 0.1 M 1,2-propanediol, 0.5 mM Pd (0.5 mol%), 1 mL 1:1 (v/v) MeCN/cosolvent, 28 °C, 1 atm O_2, 26 h. Reactions done in duplicate. [a]Unless otherwise specified, the cosolvents were used from commercial sources without further purification. The PhMe contained negligible amounts of toluene hydroperoxide. [b]Concentrations based on the total reaction volume. [c]Yield of HA, as measured by ^{1}H-NMR with dimethyl sulfone as the internal standard. [d]EtPh distilled from Na/benzophenone. [e]Reagent grade EtPh containing 90 mM **9**. [f]Distilled EtPh combined with pure sample of **9**. [g]Distilled EtPh allowed to autoxidize on the benchtop for 6 weeks. [h]50 mM dihydroanthracene added to total reaction volume.

These experiments revealed a modest influence of aromatic cosolvents on the yields of hydroxyacetone generated (Table 3, entries 1-5). Catalytic oxidation of 1,2-propanediol with Pd complex **1** (0.5 mol% Pd) in a 50/50 (v/v) mixture of acetonitrile and ethylbenzene (distilled over Na/benzophenone) afforded a 23% yield of hydroxyacetone (TON = 46), approximately twice that observed in pure acetonitrile. Similar increases were observed for benzene, toluene, and *tert*-butylbenzene, indicating that aromatic cosolvents have a modest but reproducible effect on catalyst lifetimes. The use of purified ethylbenzene (EtPh) led to a modest increase in the reaction rate relative to that observed in MeCN (see Supporting Information).

A larger effect on TON was observed when reagent grade ethylbenzene was employed as a cosolvent. Under these conditions (Table 3, entry 6) the yield of hydroxyacetone increased to 47%, corresponding to TON = 93. This dramatic effect was traced to the presence of 1-phenylethyl hydroperoxide **9** present in the unpurified ethylbenzene (approx. 90 mM in 100 vol% EtPh). Appreciable amounts of **9** form in EtPh during storage under air. The role of **9** as a beneficial additive was established by the addition of an independently prepared sample of the hydroperoxide **9** to distilled EtPh; when this mixture was used as a cosolvent, the yields and TON matched that observed when reagent grade EtPh was used as a cosolvent (Table 3, entry 7). Moreover, when the aerobic oxidation of 1,2-propanediol was carried out in acetonitrile with 46 mM of the hydroperoxide **9** but without another cosolvent, the yield of hydroxyacetone increased, affording TON = 50 (Table 3, entry 9). This increase was similar to that observed when 50 mM 9,10-dihydroanthracene, a benzylic H-atom donor, was added to the reaction carried out in MeCN (Table 3, entry 10).

When reagent grade EtPh containing hydroperoxide **9** was used as a cosolvent for the aerobic oxidation of 1,2-propanediol, ^{1}H-NMR and GC-FID analyses of the reaction mixtures revealed the presence of acetophenone, 1-phenylethanol, and **9** (approx. 15-40 mM each, and always totaling more than $[\mathbf{9}]_0$ = 45 mM). These products are characteristic of the well-established mechanism for the radical autoxidation of ethylbenzene (Scheme 3)[48] and the reactivity of alkylperoxides.[49-50] In contrast, if distilled EtPh was used as the cosolvent in the oxidation of 1,2-propanediol, much lower concentrations of acetophenone, 1-phenylethanol, and **9** were detected during the reaction (approx. 2 mM total).



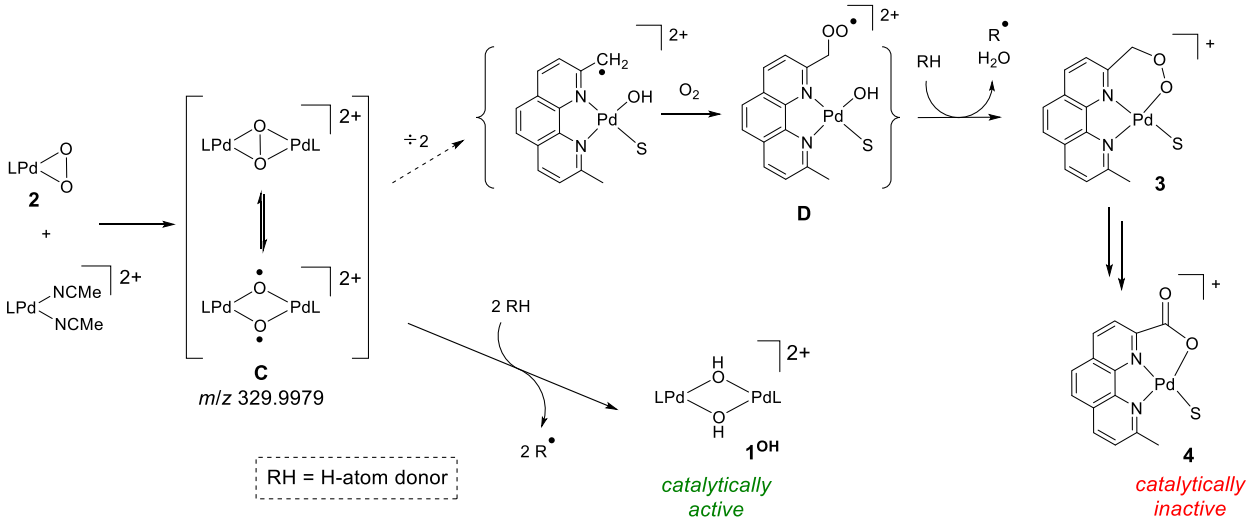
Scheme 3. Mechanism of EtPh autoxidation

^{18}O-labeling experiments were carried out to confirm that the oxygen atoms in the acetophenone and 1-phenylethanol byproducts come from O_2. When the oxidation of 1,2-propanediol was carried out under an $^{18}O_2$ atmosphere in 1:1 (v/v) distilled EtPh/MeCN, analysis of the reaction mixture by GC-MS revealed that 100% of the 1-phenylethanol and 82% of the acetophenone was labeled with ^{18}O. In contrast, for the analogous reaction carried out with air

($^{16}O_2$) in the presence of 0.5 M $H_2{}^{18}O$, no ^{18}O was detected in the 1-phenylethanol and only 5% ^{18}O incorporation was detected in the acetophenone.

These experiments indicate that the dramatic increase in the turnover numbers observed in the aerobic oxidation of 1,2-propanediol in the presence of reagent grade ethylbenzene (Table 3, entry 6) is due to: (i) the beneficial effect of aromatic cosolvents, and (ii) the presence of the hydroperoxide **9**. As Hermans et al. had previously highlighted the key role of **9** as an H-atom donor in the EtPh autoxidation mechanism,[48] these results lead to the rather surprising suggestion that the hydroperoxide **9** extends the lifetime of the Pd catalyst **1** by functioning as an efficient sacrificial hydrogen atom donor. Anaerobic experiments indicated that although **9** can function as a terminal oxidant for this reaction, it performs substantially worse than O_2.

Proposed Ligand Degradation Mechanism. The nature of the partially reduced oxygen species responsible for ligand degradation cannot be unambiguously established. Prior mechanistic studies[33] revealed a complicated reaction network involving multiple pathways for both alcohol oxidation and hydrogen peroxide disproportionation catalyzed by Pd complex **1**. One plausible reactive oxygen species is the binuclear Pd peroxo complex **C** (Scheme 4) that was previously identified by ESI-MS[33] and is generated from the neutral Pd peroxo **2** and the dication $[LPd(MeCN)_2]^{2+}$. DFT calculations of this species indicate that the μ-peroxo and diradical structures are both feasible. This complex is expected to be highly reactive toward hydrogen atom abstraction from the benzylic C-H bond of the neocuproine ligand based on analogy to similar μ-peroxo Cu,[51-54] Pd/Cu[55] and Ni complexes.[39-40]



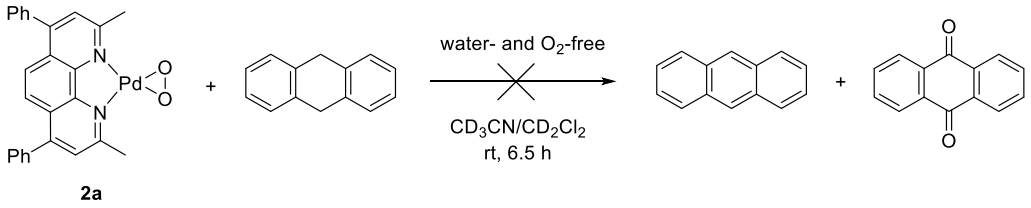
Scheme 4. Possible mechanism for oxidative degradation of Pd catalyst **1**

Hydrogen atom abstraction from a ligand methyl group would generate a benzylic radical, which would be expected to react rapidly with dioxygen to generate the peroxyl intermediate **D** (Scheme 4). In the presence of another suitable hydrogen atom donor – which could even be another molecule of catalyst – the peroxyl **D** would react to form the Pd benzylperoxo **3**, which we have implicated as a key intermediate on the path to the catalytically inactive carboxylate **4**. We propose that the beneficial effect of sacrificial hydrogen atom donors is due, in part, to their ability to quench partially reduced reactive oxygen species, such as in the

conversion of reactive intermediate **C** to the μ-hydroxo complex $\mathbf{1}^{\mathbf{OH}}$, which we have previously shown to be a chemically and kinetically competent catalytic species.[14, 33]

Several experiments indicate that the mononuclear Pd peroxo **2** is not likely to be responsible for ligand degradation. This complex can be isolated[33-34, 56] and is stable in solution for days. In addition, when the related (bathocuproine)Pd(O_2) (bathocuproine = 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline) complex **2a** was mixed with 9,10-dihydroanthracene in 1:1 (v/v) CD_3CN/CD_2Cl_2 under moisture- and O_2-free conditions, no anthracene or anthraquinone was produced even after 6.5 h at room temperature (Scheme 5).[57-58] This latter result suggests that the peroxo **2** is incapable of abstracting C-H bonds even as weak as 76 kcal/mol (*cf.* 87 kcal/mol for the benzylic C-H in 2-methylpyridine).[59]

The trinuclear species $[(neoc)_3Pd_3O_2]^{2+}$ is another intermediate that has been implicated in the catalytic cycle, and our studies have shown that it can be converted to $[(neoc)Pd(OAc)]^+$ in high yield.[33-34] The fact that this trinuclear species is isolable and stable in CD_3CN for days suggests that it is unlikely to be responsible for ligand degradation.



Scheme 5. (bathocuproine)Pd(O_2) is unreactive toward dihydroanthracene.

Preventing Pd Black – Olefinic Additives. For **1** and many other Pd complexes, the competitive precipitation of Pd black is another significant means of catalyst degradation. Pd black formation is typically observed in aerobic alcohol oxidations with catalyst **1** when the diol concentration (>0.3 M), Pd loading (>5 mM), or temperature (>40 °C) is sufficiently high. To identify additives that might bind to and stabilize Pd(0) intermediates, we screened several olefins in aerobic alcohol oxidations at elevated temperature (see Supporting Information). Initial results revealed that styrene was particularly effective at increasing turnover numbers (Table 4).

Catalytic aerobic oxidation of 1,2-propanediol ($[1,2\text{-PD}]_0$ = 0.1 M) with complex **1** (0.5 mol% Pd) at 25°C in acetonitrile affords a 10% yield of hydroxyacetone, corresponding to TON = 21. However, in the presence of 0.5 M styrene, the yield of hydroxyacetone increases to 22%, corresponding to TON = 44 (Table 4, entry 2). The positive effect of styrene was more pronounced at higher substrate concentrations ($[1,2\text{-PD}]_0$ = 0.2 M in entries 3-4, TON increases from 32 to 111) and temperatures (60 °C in entries 9-10, TON increases from 22 to 227). At 60 °C, signficant amounts of Pd black are formed in the absence of styrene, but almost none forms in its presence.

Performing the oxidation in the presence of both styrene (0.5 M) and 50 vol% reagent grade ethylbenzene at room temperature for 72 h under 1.2 atm O_2 achieved an impressive average TON of 354. At room temperature, these turnover numbers are among the highest reported for a Pd aerobic alcohol oxidation catalyst.[60-61] Similar enhancements in TON were observed for other substrates (see "Preparative Scale Oxidations" below). Some styrenic additives with substituents on the phenyl ring also provided TON improvements. In contrast, styrenic additives with substituents on the olefin such as α-methylstyrene, β-methylstyrene, or *trans*-stilbene had negligible effect on the catalytic reaction or TON.

Table 4. Influence of styrene on the catalytic oxidation of 1,2-propanediol

Entry	$[1,2\text{-PD}]_0$ (M)	mol% Pd	Additives	Yield (GC)	TON
1	0.1	0.5	none	10%	21
2	0.1	0.5	0.5 M styrene	22%	43
3	0.2	0.75	none	24%	32
4	0.2	0.75	0.5 M styrene	83%	111
5	0.1	0.5	46 mM **9**	25%	50
6	0.1	0.5	0.5 M styrene 45 mM **9**	51%	101
7	0.5	0.25	none	14%	57
8[a]	0.5	0.25	0.5 M styrene 50 vol% EtPh[b]	89%	354
9[c]	0.1	0.5	none	11%	22
10[c]	0.1	0.25	0.5 M styrene	57%	227

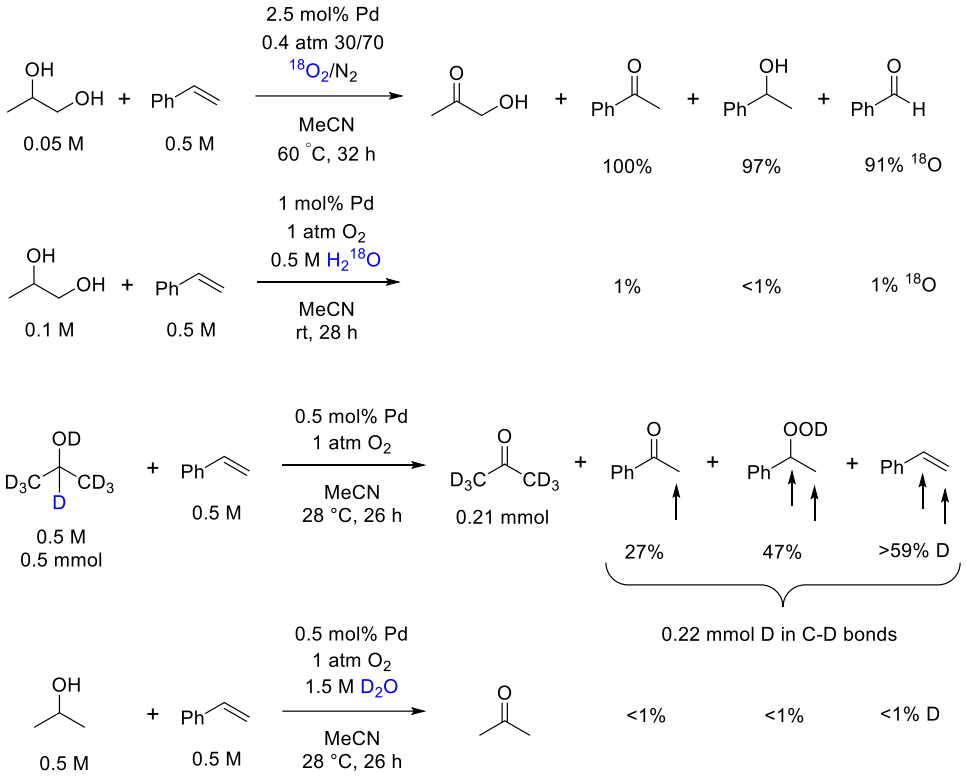
Conditions: 1 mL MeCN, 28 °C, 1 atm O_2, 26 h. Reactions done in duplicate. [a]72 hours, 2 mL total solvent. [b]Reagent grade, which contained 90 mM **9** in 100 vol% EtPh. [c]60° C.

Control experiments confirmed that the presence of 4-*tert*-butylcatechol, a stabilizer in commercial styrene present at approx. 50 ppm concentration, was not responsible for the increased yields at these concentrations. GC-FID and ^{1}H-NMR analyses of the reactions carried out with styrene by gas chromatography revealed the formation of the hydroperoxide **9**, acetophenone, 1-phenylethanol, benzaldehyde, and various oligomers as the byproducts of styrene. According to gel permeation chromatography, the oligostyrenes were of low molecular weight (M_n < 1000).

Styrene Additives: Mechanistic Investigations. Isotopic labeling experiments were carried out to assess the fate of styrene additives in the catalytic oxidation of 1,2-propanediol and isopropanol (Scheme 6). Analyses of styrene-derived coproducts generated from 1,2-propanediol oxidations conducted in MeCN with isotopically labeled $^{18}O_2$ by GC-MS revealed that the acetophenone, 1-phenylethanol, and benzaldehyde each contained >90% ^{18}O incorporation, indicating that the oxygen atoms in these monomeric styrene byproducts all come from dioxygen. In contrast, when the reaction was carried out in the presence of air ($^{16}O_2$) and 0.5 M $H_2{}^{18}O$, these byproducts exhibited minimal ^{18}O incorporation.

Oxidation of d_8-isopropanol under analogous conditions in the presence of styrene revealed that a significant amount of deuterium was incorporated onto the non-aromatic carbons

of hydroperoxide **9**, acetophenone, and the remaining styrene, and that this amount of deuterium corresponds closely to the amount of d_6-acetone generated. Control reactions with D_2O and proteo-isopropanol led to minimal deuterium incorporation on those carbons, demonstrating that the deuterium comes from the methine C-D of d_8-isopropanol. These results strongly imply that the deuteration of styrene and its byproducts is mediated by palladium hydride species.



Scheme 6. Isotopic labeling experiments with styrene. For the deuterium labeling experiments, the percentages indicate what fraction of the compound present at the end contains at least one deuterium in the positions marked with arrows.

These results suggest that styrene plays multiple roles in enhancing the lifetime of Pd complex **1**. We propose that styrene is converted primarily to hydroperoxide **9** via a Pd-mediated mechanism. Control experiments with styrene glycol and styrene oxide ruled them out as potential intermediates (see Supporting Information). ^{1}H-NMR monitoring of the reaction over time indicated that styrene is consumed at the same rate as that of the alcohol substrate (Figure 1), which implies that styrene reacts quantitatively with a catalytic intermediate, most likely the Pd hydride. These timepoint data suggest that acetophenone and 1-phenylethanol arise from the decomposition of **9** because their concentrations do not become significant until very late into the reaction. For instance, at t = 17 h the ratio [**9**] : [acetophenone] : [1-phenylethanol] = 90 : 7 : 3, while at 51 h the ratio was 74 : 11 : 14.[62]

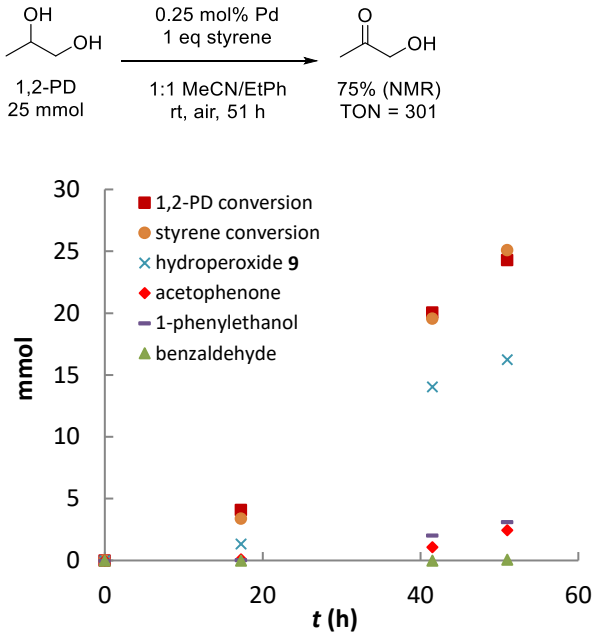
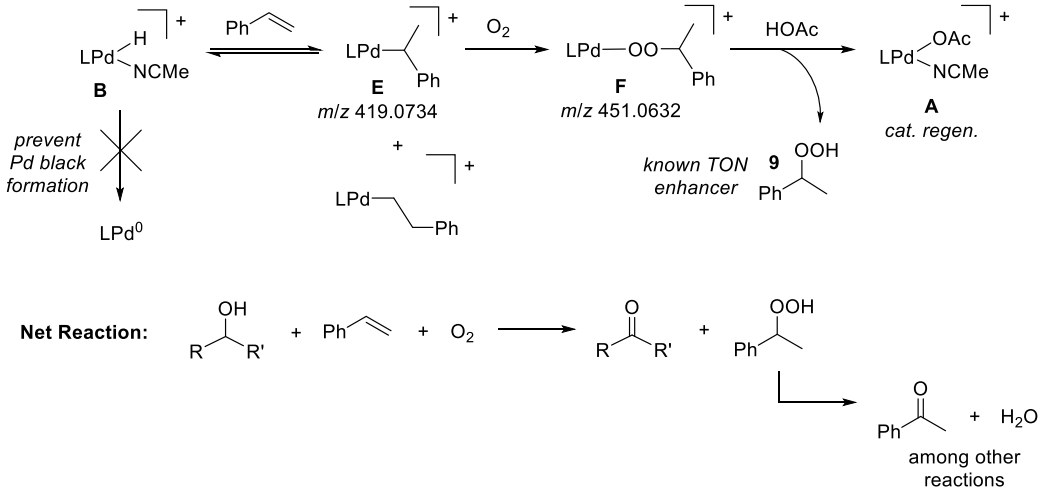


Figure 1. Reaction monitoring of a large scale aerobic oxidation of 1,2-propanediol with styrene. Conditions: 0.5 M 1,2-propanediol, 0.25 mol% Pd, 0.5 M styrene, 50 mL 1:1 (v/v) MeCN/EtPh (reagent grade, $[\mathbf{9}]_0 < 5$ mM in the total reaction mixture), rt, air, 51 h. Molar quantities determined by ^{1}H-NMR with dimethyl sulfone as the internal standard. Very similar data are also observed when a different substrate (glycerol) is used in 100 vol% MeCN (see Supporting Information).

The observation of significant incorporation of deuterium into the styrene byproducts from the oxidation of d_8-isopropanol indicates that styrene is also effective at intercepting palladium hydrides, which provides a potential alternative pathway for the aerobic regeneration of the catalyst that avoids Pd(0) intermediates. A plausible mechanism is provided in Scheme 7, wherein reversible insertion of styrene into the Pd-H (or Pd-D in the case of d_8-isopropanol oxidation) bond would generate the secondary benzylic Pd alkyl **E**.[63] Insertion of dioxygen could then give rise to the Pd alkylperoxo **F**,[64-67] which upon exchange with a proton source would regenerate the catalyst while producing hydroperoxide **9**. The insertion of O_2 into Pd-alkyl bonds is rare, but has been observed in other contexts.[64-67] The primary hydroperoxide $PhCH_2CH_2OOH$ and its decomposition products are not observed, suggesting that either dioxygen inserts preferentially into the benzylic Pd-alkyl or that the olefin insertion/de-insertion equilibrium strongly favors the benzylic isomer.[68-69] The reversibility of olefin insertion for both Pd alkyl isomers is evidenced by the observed deuteration of styrene at both the α and β positions (Scheme 6). The benzylic isomer may be stabilized by a π-benzyl interaction with the metal. That α- and β-methylstyrene and *trans*-stilbene are unreactive under similar conditions might indicate that these additives are less reactive toward Pd hydrides.



Scheme 7. Proposed mechanisms for TON enhancement by styrene

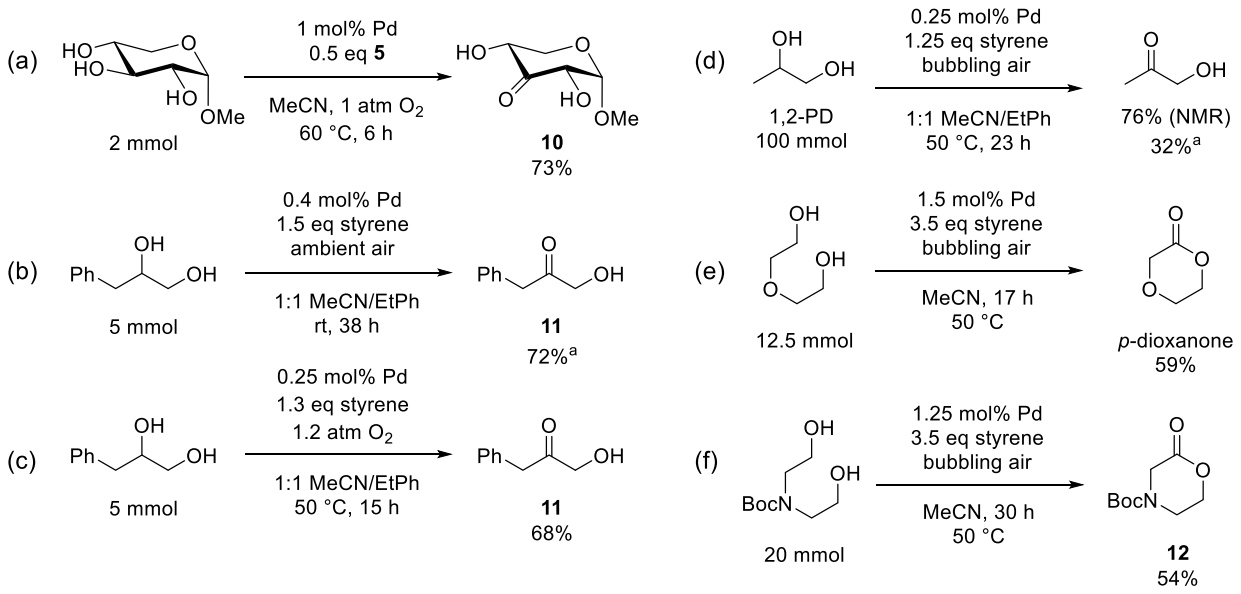
In support of this mechanism, electrospray ionization mass spectrometry (ESI-MS) of reaction aliquots revealed ions consistent with Pd alkyl **E** (*m*/*z* 419.0734) and Pd alkylperoxo **F** (*m*/*z* 451.0632). One implication of this mechanism is that hydroperoxide **9** is produced instead of water, at least until **9** itself decomposes over time to acetophenone and water. Consistent with this prediction, in the aerobic oxidation of 1,2-propanediol monitored by ^{1}H-NMR, the ratio of water produced to hydroxyacetone was found to be 0.94, while in the presence of styrene this ratio decreased to 0.29. Furthermore, in the latter case the ratio of water produced to acetophenone was 0.93.

Preparative Scale Oxidations. The synthetic utility of these strategies for mitigating catalyst deactivation was assessed in several preparative scale reactions (Scheme 8). Catalytic oxidation of methyl α-D-xylopyranoside (328 mg, 2 mmol, Scheme 8a),[22] carried out in the presence of 1 atm of O_2 with 1 mol% Pd and 0.5 eq phenol **5** in MeCN at 60 °C for 6 h, occurred selectively at the C3-position to afford a 73% isolated yield of the 3-ketose **10** following silica gel chromatography. In contrast, oxidation of analogous pyranosides with benzoquinone as the terminal oxidant[21] or with the deuterated catalyst ***d*$_{12}$-1** required 6 mol% Pd under aerobic conditions.[32] A key advantage of these phenolic additives is that they can be used in substoichiometric amounts and are converted into a small number of well-defined byproducts.

Catalytic oxidation of 3-phenyl-1,2-propanediol (5 mmol, 0.75 g, Scheme 8b) with 0.4 mol% Pd and 1.5 eq styrene in 1:1 (v/v) MeCN/EtPh (reagent grade, $[\mathbf{9}]_0 < 5$ mM in the total reaction mixture) at room temperature for 37 h to give the α-hydroxyketone **11** in 72% isolated yield following chromatography and recrystallization. Notably this reaction was conducted in an uncovered Erlenmeyer flask and was very simple to set up. With the same substrate, increasing the temperature to 50 °C enabled significant reductions in both reaction time (15 h) and Pd loading (0.25 mol%) with only a minor decrease in isolated yield (68%).

Aerobic oxidation of 1,2-propanediol (7.61 g, 100 mmol, Scheme 8d) at 50 °C with catalyst **1** (0.25 mol% Pd) and 1.25 eq styrene in 1:1 (v/v) MeCN/EtPh (reagent grade, $[\mathbf{9}]_0 = 45$ mM in the total reaction mixture) afforded a 76% NMR yield (TON = 303) of hydroxyacetone by analysis of the crude reaction mixture. Hydroxyacetone is polar enough to be separated from the styrene oligomers by silica gel chromatography alone. However, due to its volatility, concentration *in vacuo* of the relevant fractions gave only 32% isolated yield.

The aerobic oxidative lactonization of diethylene glycol[15] (1.06 g, 12.5 mmol, Scheme 8e) was carried out with 1.5 mol% Pd and 3.5 eq styrene in MeCN at 50 °C to afford *p*-dioxanone in 59% isolated yield following chromatography and vacuum sublimation at room temperature. This is a significant improvement over our previously reported procedure,[15] which required Pd loadings of 11 mol% to achieve a similar isolated yield (65%). The oxidative lactonization of *N*-Boc diethanolamine[15, 18] in the presence of 1.25 mol% Pd and 3.5 eq styrene afforded a 54% isolated yield of the morpholinone **12** after chromatography and recrystallization (Scheme 8f). While this yield is lower than that reported previously (76%), the much lower Pd loading (1.25% vs. 20%) facilitated product work-up.



Scheme 8. Preparative scale aerobic oxidations. Isolated yields after purification are given. [a]Scaled relative to the portion of the crude subjected to purification.

Conclusion

The major deactivation pathways for Pd catalyst **1** under aerobic conditions, namely oxidative degradation of the ligand and Pd black formation, were mitigated with several complementary approaches, achieving >10 fold improvements in turnover number. A radical-based mechanism for ligand degradation was proposed that is initiated by H-atom abstraction from a ligand methyl group by a reactive oxygen species on Pd. This insight informed the choice of alternate ligands or phenol or styrene additives to increase the catalyst lifetimes. Styrene was identified as a potent additive for the prevention of Pd black, and its novel mechanism of action was elucidated.

Employing these techniques in preparative scale reactions allowed the catalyst loadings to be reduced to <1 mol% Pd, a considerable advance over prior studies which required 5-10% Pd loadings to reach high conversion. The high chemoselectivities of catalyst **1** were retained, and the desired products could be isolated from the reaction mixtures using standard methods. These studies reveal that the addition of sacrificial H-atom donors such as phenols are effective in catalytic aerobic oxidation reactions. An unexpected discovery was that benzylic hydroperoxides like **9** are also effective at increasing catalyst lifetimes.

The use of styrenes as additives revealed a novel process for mitigating the formation of Pd black, which we propose is a consequence of intercepting reactive Pd hydrides. The addition of styrene is useful in those cases where product separation from the oligomers is straightforward, but the use of a stoichiometric additive is not an ideal solution, and moreover the styrene byproducts cannot be separated from non-polar compounds by chromatography alone. Nevertheless, these studies reveal that strategies to intercept reactive cationic Pd hydrides, which are readily deprotonated to Pd(0), might be profitably investigated as a means to mitigate the formation of Pd black in many Pd-catalyzed reactions.

Associated Content

Experimental procedures, characterization data, and turnover number data are available in the Supporting Information via the Internet.

Author Information

Corresponding Author
waymouth@stanford.edu
Notes
The authors declare no competing financial interest.

Acknowledgements

We acknowledge support from the Department of Energy (Office of Basic Energy Science, Catalysis Science Program, Award DE-SC0018168). We thank Katherine L. Walker and Prof. Richard N. Zare for the ESI-MS experiments with styrene. W.C.H. is grateful for a Benchmark Stanford Graduate Fellowship. K.C. is grateful for a Stanford Graduate Fellowship. A.J.I is grateful for a Robert N. and Anne T. Bass Stanford Graduate Fellowship, an NSF Graduate Research Fellowship, and a Stanford Center for Molecular Analysis and Design Fellowship.

References

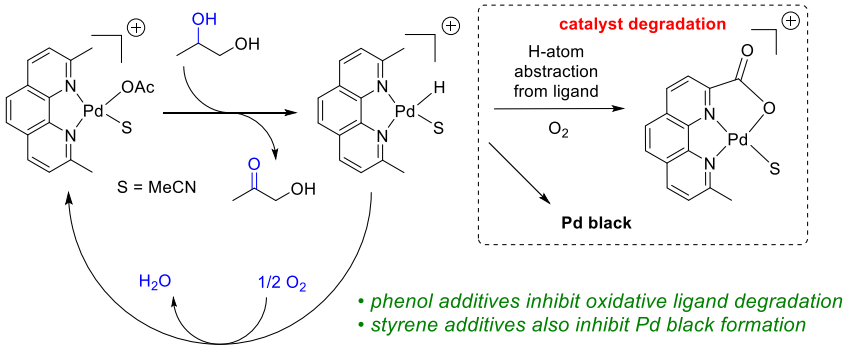
1. *Modern Oxidation Methods*, 2nd ed.; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, Germany, 2010; pp xi-xii, 147-240.
2. Cavani, F.; Teles, J. H. *ChemSusChem* **2009,** *2* (6), 508-534.
3. Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009,** (26), 3854-3867.
4. Parmeggiani, C.; Cardona, F. *Green Chem.* **2012,** *14* (3), 547-564.
5. Schultz, M. J.; Sigman, M. S. *Tetrahedron* **2006,** *62* (35), 8227-8241.
6. Muzart, J. *Tetrahedron* **2003,** *59* (31), 5789-5816.
7. Stahl, S. S. *Science* **2005,** *309* (5742), 1824-1826.
8. Arends, I. W. C. E.; Sheldon, R. A. Modern Oxidation of Alcohols using Environmentally Benign Oxidants. In *Modern Oxidation Methods*, 2nd ed.; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, Germany, 2010; pp 147-185.
9. Durndell, L. J.; Lee, A. F.; Bailie, D. S.; Muldoon, M. J. Selective Palladium-Catalysed Aerobic Oxidation of Alcohols. In *Transition Metal Catalysis in Aerobic Alcohol Oxidation*;

Cardona, F.; Parmeggiani, C., Eds.; The Royal Society of Chemistry: Cambridge, United Kingdom, 2015; Vol. 28, pp 92-132.
10. Eisink, N. N. H. M.; Minnaard, A. J.; Witte, M. D. *Synthesis* **2017,** *49* (04), 822-829.
11. Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. *Chem. Rev.* **2017**, doi: 10.1021.acs.chemrev.7b00334.
12. Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem. Int. Ed.* **2003,** *42* (32), 3810-3813.
13. Ebner, D. C.; Trend, R. M.; Genet, C.; McGrath, M. J.; O'Brien, P.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2008,** *47* (34), 6367-6370.
14. Conley, N. R.; Labios, L. A.; Pearson, D. M.; McCrory, C. C. L.; Waymouth, R. M. *Organometallics* **2007,** *26* (23), 5447-5453.
15. Chung, K.; Banik, S. M.; De Crisci, A. G.; Pearson, D. M.; Blake, T. R.; Olsson, J. V.; Ingram, A. J.; Zare, R. N.; Waymouth, R. M. *J. Am. Chem. Soc.* **2013,** *135* (20), 7593-7602.
16. Painter, R. M.; Pearson, D. M.; Waymouth, R. M. *Angew. Chem. Int. Ed.* **2010,** *49* (49), 9456-9459.
17. Xie, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2015,** *137* (11), 3767-3770.
18. Blake, T. R.; Waymouth, R. M. *J. Am. Chem. Soc.* **2014,** *136* (26), 9252-9255.
19. McKinlay, C. J.; Vargas, J. R.; Blake, T. R.; Hardy, J. W.; Kanada, M.; Contag, C. H.; Wender, P. A.; Waymouth, R. M. *Proc. Natl. Acad. Sci. U. S. A.* **2017,** *114* (4), E448-E456.
20. De Crisci, A. G.; Chung, K.; Oliver, A. G.; Solis-Ibarra, D.; Waymouth, R. M. *Organometallics* **2013,** *32* (7), 2257-2266.
21. Jäger, M.; Hartmann, M.; de Vries, J. G.; Minnaard, A. J. *Angew. Chem. Int. Ed.* **2013,** *52* (30), 7809. In this paper benzoquinone-type terminal oxidants were used exclusively instead of O_2.
22. Chung, K.; Waymouth, R. M. *ACS Catalysis* **2016,** *6* (7), 4653-4659.
23. Eisink, N.; Witte, M. D.; Minnaard, A. J. *ACS Catalysis* **2017,** *7* (2), 1438-1445.
24. Hoyos, P.; Sinisterra, J.-V.; Molinari, F.; Alcántara, A. R.; Domínguez de María, P. *Acc. Chem. Res.* **2010,** *43* (2), 288-299.
25. Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem. Int. Ed.* **2004,** *43* (9), 1109-1112.
26. Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001,** *123* (14), 3367-3368.
27. Plietker, B. *J. Org. Chem.* **2004,** *69* (24), 8287-8296.
28. Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2004,** *43* (9), 1112-1115.
29. Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992,** *92* (5), 919-934.
30. Stick, R. V. *Carbohydrates: The Sweet Molecules of Life*; Academic Press: London, 2001; pp 37-65.
31. Pearson, D. M.; Conley, N. R.; Waymouth, R. M. *Organometallics* **2011,** *30* (6), 1445-1453.
32. Armenise, N.; Tahiri, N.; Eisink, N. N. H. M.; Denis, M.; Jager, M.; De Vries, J. G.; Witte, M. D.; Minnaard, A. J. *Chem. Commun.* **2016,** *52* (10), 2189-2191.
33. Ingram, A. J.; Walker, K. L.; Zare, R. N.; Waymouth, R. M. *J. Am. Chem. Soc.* **2015,** *137* (42), 13632-13646.
34. Ingram, A. J.; Solis-Ibarra, D.; Zare, R. N.; Waymouth, R. M. *Angew. Chem.* **2014,** *126* (22), 5754-5758.
35. Nam, W. *Acc. Chem. Res.* **2007,** *40* (7), 522-531.
36. Ray, K.; Pfaff, F. F.; Wang, B.; Nam, W. *J. Am. Chem. Soc.* **2014,** *136* (40), 13942-13958.

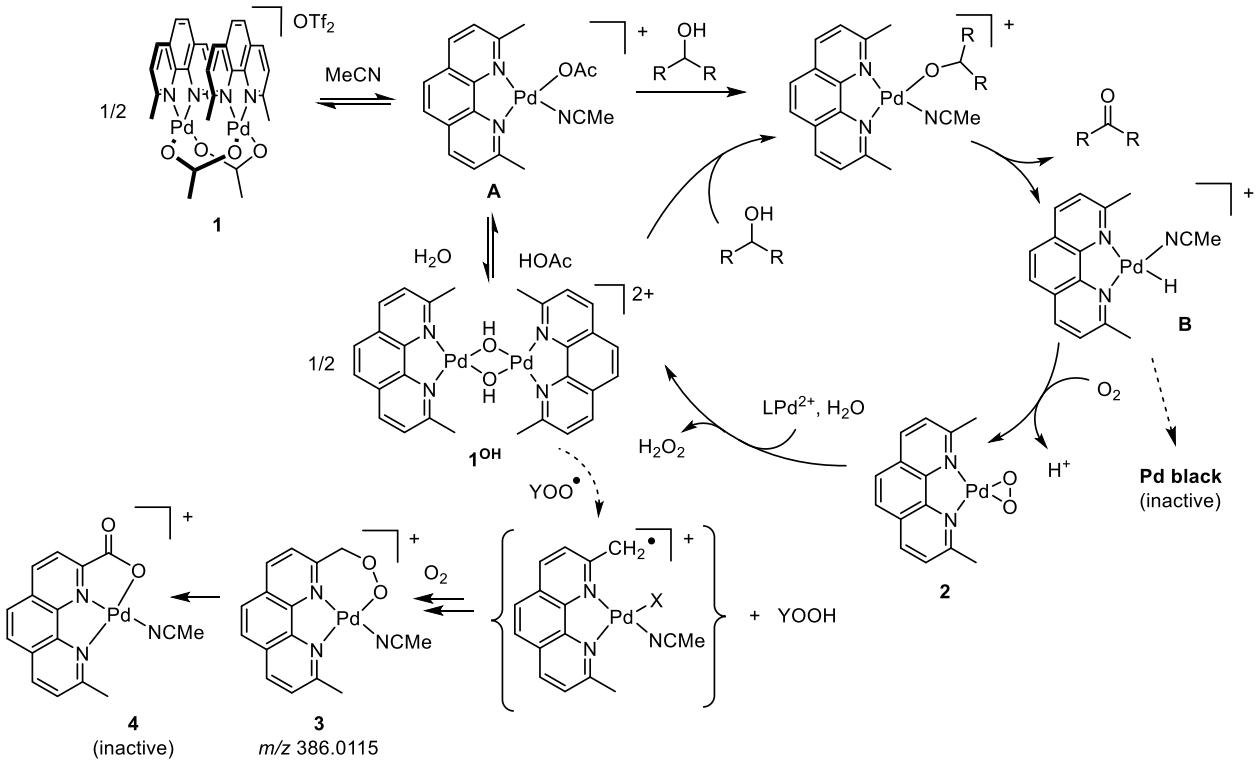
37. Konnick, M. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008,** *130* (17), 5753-5762.
38. Kujime, M.; Hikichi, S.; Akita, M. *Dalton Trans.* **2003,** (18), 3506-3515.
39. Cho, J.; Furutachi, H.; Fujinami, S.; Suzuki, M. *Angew. Chem. Int. Ed.* **2004,** *43* (25), 3300-3303.
40. Cho, J.; Furutachi, H.; Fujinami, S.; Tosha, T.; Ohtsu, H.; Ikeda, O.; Suzuki, A.; Nomura, M.; Uruga, T.; Tanida, H.; Kawai, T.; Tanaka, K.; Kitagawa, T.; Suzuki, M. *Inorg. Chem.* **2006,** *45* (7), 2873-2885.
41. Ingold, K. U.; Pratt, D. A. *Chem. Rev.* **2014,** *114* (18), 9022-9046.
42. Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1981,** *103* (21), 6472-6477.
43. Warren, J. J.; Tronic, T. A.; Mayer, J. M. *Chem. Rev.* **2010,** *110* (12), 6961-7001.
44. BDE measurements for similar compounds have been made before. Jonsson, M.; Lind, J.; Merényi, G.; Eriksen, T. E. *J. Chem. Soc. Perkin Trans. 2* **1995**, 61-65 reported the BDE for the N-H bond in 2,4-Me_2-aniline to be 88.0 kcal/mol and Lucarini, M.; Pedrielli, P.; Pedulli, G. F. *J. Org. Chem.* **1996**, *61*, 9259-9263 reported the BDE for the O-H bond in 2,6-*t*Bu_2-phenol to be 82.8 kcal/mol.
45. Omura, K. *J. Org. Chem.* **1991,** *56* (3), 921-927.
46. Beaudoin, D. S.; Obare, S. O. *Tetrahedron Lett.* **2008,** *49* (42), 6054-6057.
47. Howard, J. A.; Chenier, J. H. B. *J. Am. Chem. Soc.* **1973,** *95* (9), 3054-3055.
48. Hermans, I.; Peeters, J.; Jacobs, P. A. *J. Org. Chem.* **2007,** *72* (8), 3057-3064.
49. Kornblum, N.; Delamare, H. E. *J. Am. Chem. Soc.* **1951,** *73* (2), 880-881.
50. Kelly, D. R.; Bansal, H.; Morgan, J. J. G. *Tetrahedron Lett.* **2002,** *43* (51), 9331-9333.
51. Halfen, J. A.; Mahapatra, S.; Wilkinson, E. C.; Kaderli, S.; Young, V. G.; Que, L.; Zuberbühler, A. D.; Tolman, W. B. *Science* **1996,** *271* (5254), 1397-1400.
52. Lucas, H. R.; Li, L.; Sarjeant, A. A. N.; Vance, M. A.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2009,** *131* (9), 3230-3245.
53. Cole, A. P.; Mahadevan, V.; Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. *Inorg. Chem.* **2005,** *44* (21), 7345-7364.
54. Kang, P.; Bobyr, E.; Dustman, J.; Hodgson, K. O.; Hedman, B.; Solomon, E. I.; Stack, T. D. P. *Inorg. Chem.* **2010,** *49* (23), 11030-11038.
55. Kujime, M.; Hikichi, S.; Akita, M. *Chem. Lett.* **2003,** *32* (6), 486-487.
56. Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001,** *123* (29), 7188-7189.
57. Tezuka, M.; Ohkatsu, Y.; Osa, T. *Bull. Chem. Soc. Jpn.* **1975,** *48* (5), 1471-1474.
58. Dhar, D.; Yee, G. M.; Markle, T. F.; Mayer, J. M.; Tolman, W. B. *Chem. Sci.* **2017,** *8* (2), 1075-1085.
59. Luo, Y.-R. *Comprehensive Handbook of Chemical Bond Energies*; CRC Press: Boca Raton, Florida, 2007; pp 51, 114.
60. Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005,** *70* (9), 3343. Homogeneous catalyst.
61. Dun, R.; Wang, X.; Tan, M.; Huang, Z.; Huang, X.; Ding, W.; Lu, X. *ACS Catalysis* **2013,** *3* (12), 3063. Heterogeneous catalyst.
62. It is also possible that the acetophenone and 1-phenylethanol are formed from species **F** via a peroxide-mediated Wacker-type mechanism as a minor pathway. See Michel, B. W.; Steffens, L. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133* (21), 8317-8325.
63. Ittel, S. D.; Johnson, L. K.; Brookhart, M. *Chem. Rev.* **2000,** *100* (4), 1169-1204.

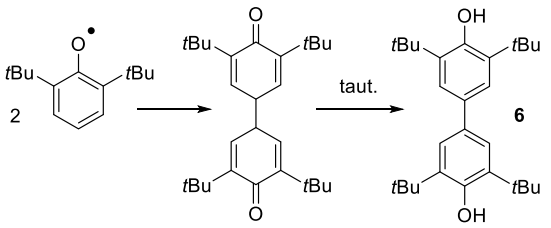
64. Boisvert, L.; Denney, M. C.; Hanson, S. K.; Goldberg, K. I. *J. Am. Chem. Soc.* **2009,** *131* (43), 15802-15814.
65. Grice, K. A.; Goldberg, K. I. *Organometallics* **2009,** *28* (4), 953-955.
66. See the references in Scheuermann, M. L.; Goldberg, K. I. *Chem. – Eur. J.* **2014**, *20*, 14556-14568 to find examples of transformations proposed to involve O_2 insertion into Pd(II)-alkyls and observed examples of O_2 insertion into Pt(II)-alkyls.
67. Petersen, A. R.; Taylor, R. A.; Vicente-Hernández, I.; Mallender, P. R.; Olley, H.; White, A. J. P.; Britovsek, G. J. P. *J. Am. Chem. Soc.* **2014,** *136* (40), 14089-14099.
68. Gligorich, K. M.; Cummings, S. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2007,** *129* (46), 14193-14195.
69. Podhajsky, S. M.; Sigman, M. S. *Organometallics* **2007,** *26* (23), 5680-5686.

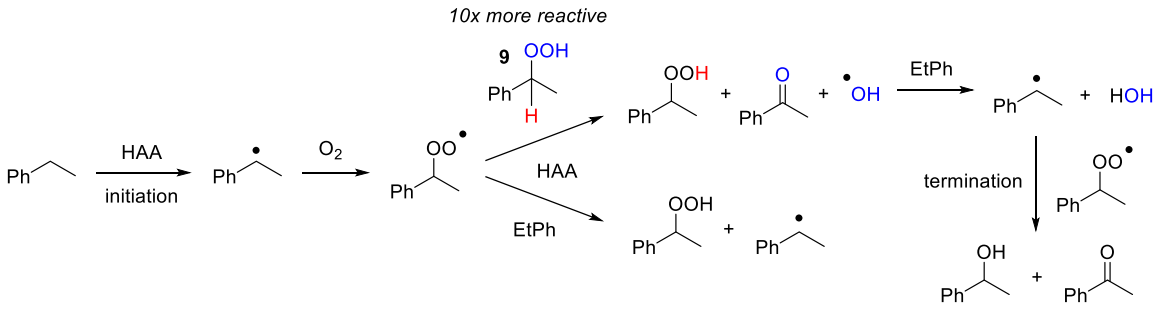
TOC Graphic:

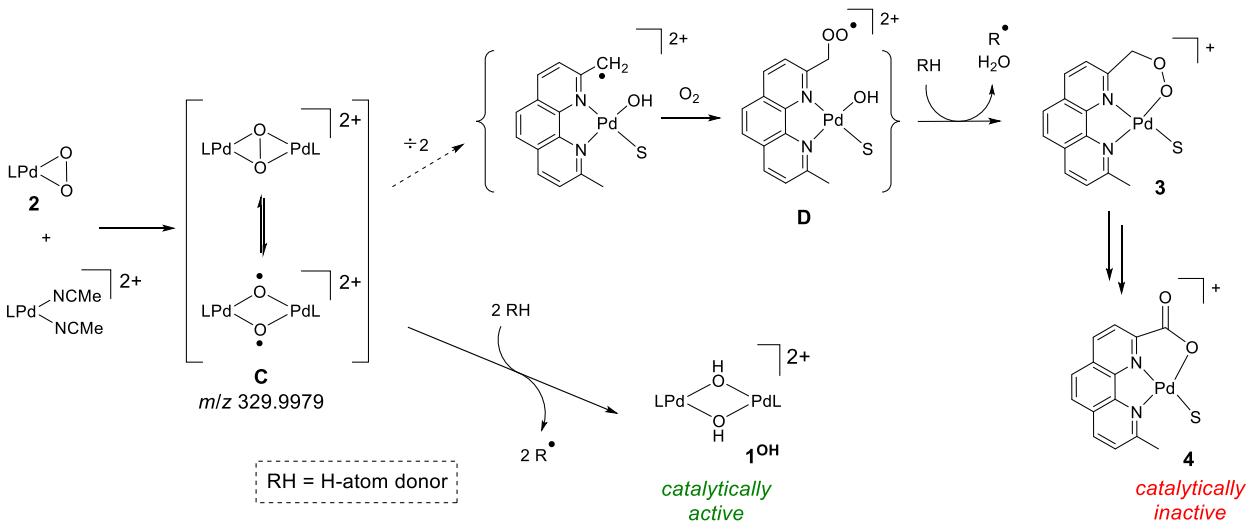


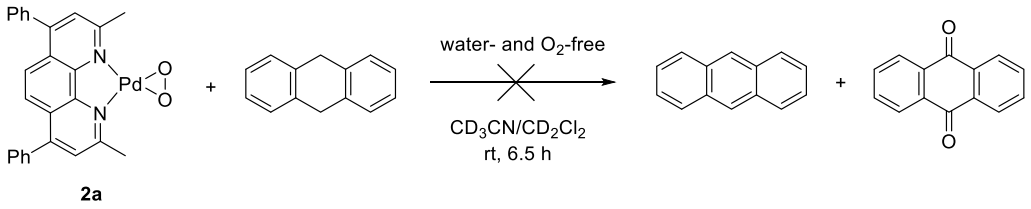
- *phenol additives inhibit oxidative ligand degradation*
- *styrene additives also inhibit Pd black formation*


OTf2
1/2
MeCN
OAc
NCMe
Pd
A
OH
R
R
H2O
HOAc
2+
1OH
LPd2+, H2O
H2O2
YOO•
O2
H+
Pd black
(inactive)
B
2
CH2•
X
+ YOOH
4
(inactive)
3
m/z 386.0115

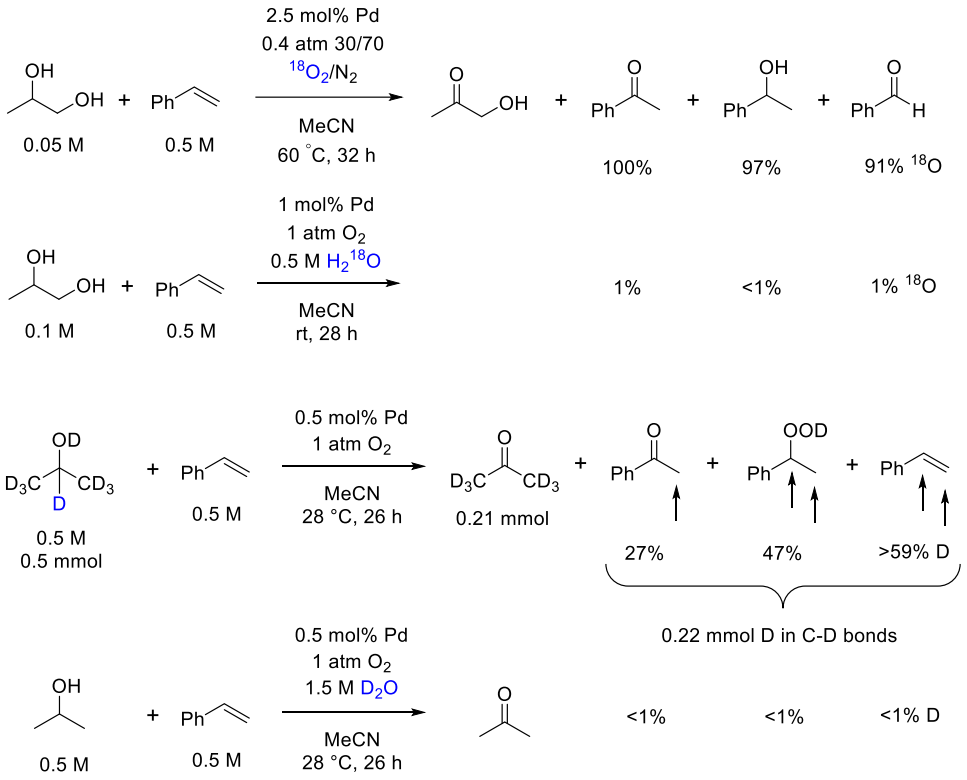

O
tBu
tBu
2
O
tBu
tBu
tBu
tBu
O
taut.
OH
tBu
tBu
6
tBu
tBu
OH

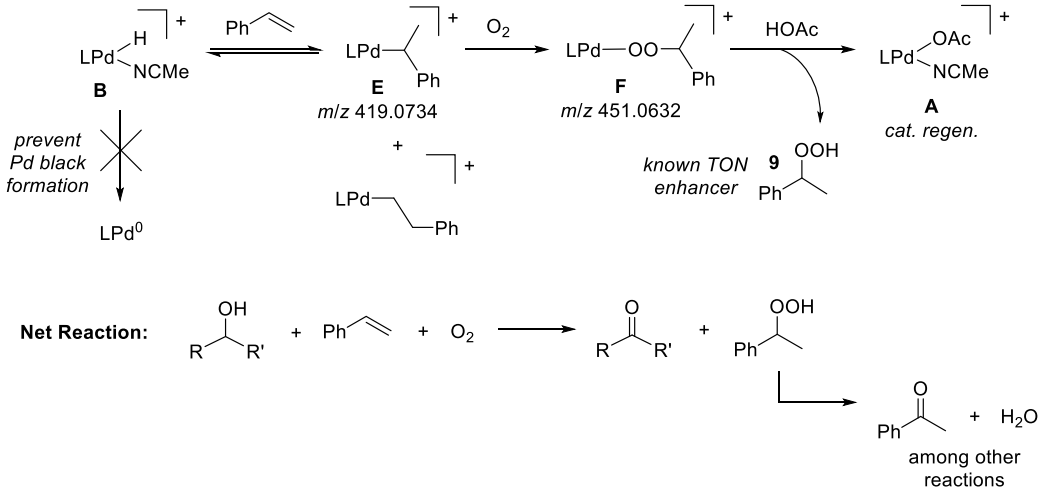

10x more reactive
9
OOH
Ph
H
HAA
initiation
O_2
OO
HAA
EtPh
OOH
O
OH
EtPh
HOH
termination
OO
OH
O


LPd
O
O
2
+
LPd
NCMe
NCMe
2+
LPd
O
O
PdL
2+
LPd
O
O
PdL
2+
C
m/z 329.9979
÷2
CH2
OH
Pd
S
N
N
2+
O2
OO
OH
Pd
S
2+
D
RH
R
H2O
O
O
Pd
S
3
+
2 RH
2 R
H
O
O
H
LPd
PdL
2+
1OH
catalytically active
O
O
Pd
S
4
+
catalytically inactive
RH = H-atom donor

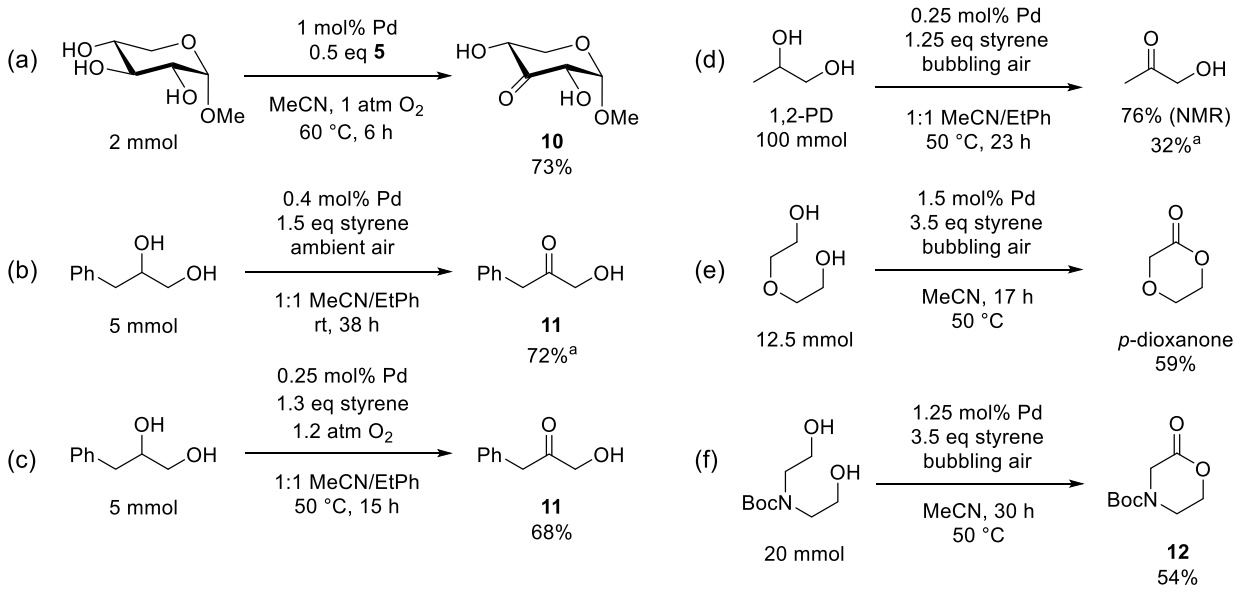


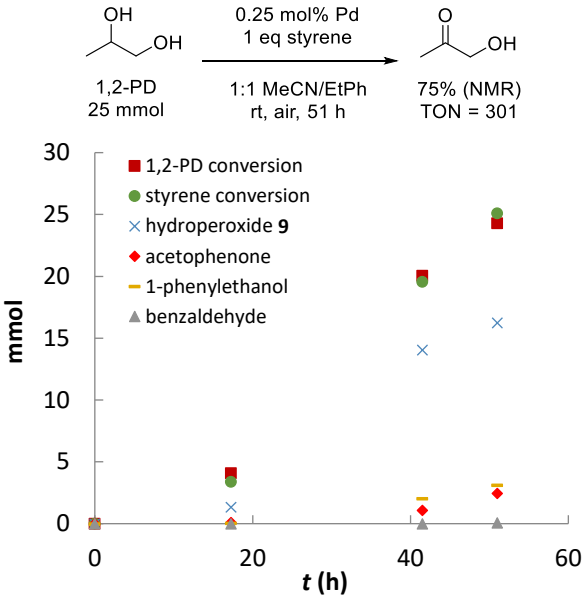
2a

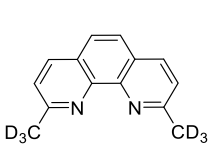

2.5 mol% Pd
0.4 atm 30/70
18O2/N2
MeCN
60 °C, 32 h
0.05 M
0.5 M
100%
97%
91% 18O
1 mol% Pd
1 atm O2
0.5 M H2 18O
MeCN
rt, 28 h
0.1 M
0.5 M
1%
<1%
1% 18O
0.5 mol% Pd
1 atm O2
MeCN
28 °C, 26 h
0.5 M
0.5 mmol
0.5 M
0.21 mmol
27%
47%
>59% D
0.22 mmol D in C-D bonds
0.5 mol% Pd
1 atm O2
1.5 M D2O
MeCN
28 °C, 26 h
0.5 M
0.5 M
<1%
<1%
<1% D


LPd
H
NCMe
B
Ph
E
m/z 419.0734
O2
F
m/z 451.0632
HOAc
A
cat. regen.
OAc
prevent
Pd black
formation
LPd0
known TON
enhancer
9
OOH
Ph

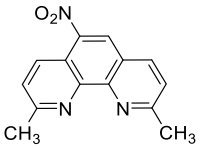
Net Reaction:
OH
R
R'
Ph
O2
O
OOH
H2O
among other
reactions


(a)
HO
HO
HO
O
OMe
2 mmol
1 mol% Pd
0.5 eq 5
MeCN, 1 atm O2
60 °C, 6 h
HO
O
O
HO
OMe
10
73%
(b)
OH
Ph
OH
5 mmol
0.4 mol% Pd
1.5 eq styrene
ambient air
1:1 MeCN/EtPh
rt, 38 h
O
Ph
OH
11
72%a
(c)
OH
Ph
OH
5 mmol
0.25 mol% Pd
1.3 eq styrene
1.2 atm O2
1:1 MeCN/EtPh
50 °C, 15 h
O
Ph
OH
11
68%
(d)
OH
OH
1,2-PD
100 mmol
0.25 mol% Pd
1.25 eq styrene
bubbling air
1:1 MeCN/EtPh
50 °C, 23 h
O
OH
76% (NMR)
32%a
(e)
OH
OH
O
12.5 mmol
1.5 mol% Pd
3.5 eq styrene
bubbling air
MeCN, 17 h
50 °C
O
O
O
p-dioxanone
59%
(f)
OH
OH
BocN
20 mmol
1.25 mol% Pd
3.5 eq styrene
bubbling air
MeCN, 30 h
50 °C
O
O
BocN
12
54%

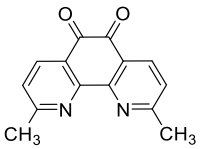

OH
OH
1,2-PD
25 mmol
0.25 mol% Pd
1 eq styrene
1:1 MeCN/EtPh
rt, air, 51 h
O
OH
75% (NMR)
TON = 301
1,2-PD conversion
styrene conversion
hydroperoxide 9
acetophenone
1-phenylethanol
benzaldehyde
mmol
t (h)
0
5
10
15
20
25
30
0
20
40
60



d_6-neocuproine

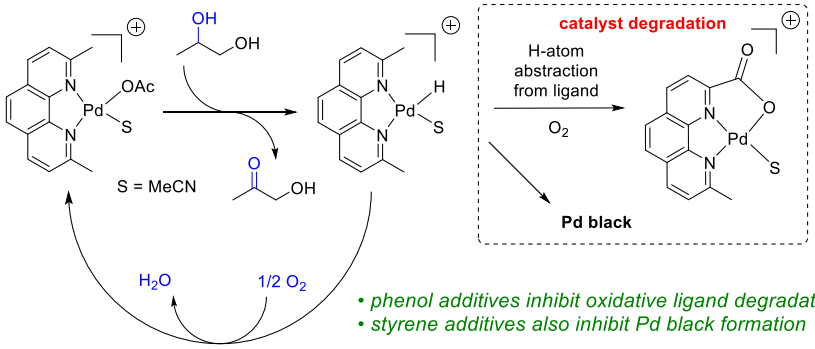


7



8


0.4 mol% Pd
1.2 atm O2
50 mM additive
OH
OH
1,2-PD
MeCN
rt, 16 h
O
OH
HA



- *phenol additives inhibit oxidative ligand degradation*
- *styrene additives also inhibit Pd black formation*