

Mechanism of Catalytic Oxidation of Styrenes with Hydrogen Peroxide in the Presence of Cationic Palladium(II) Complexes

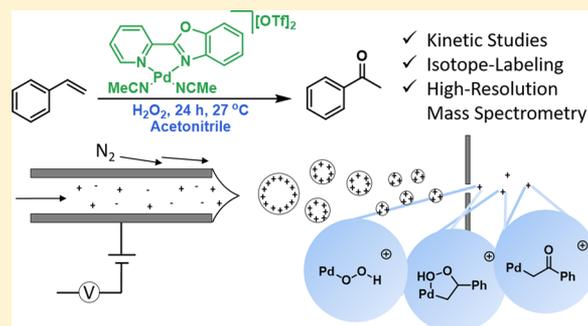
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Supporting Information

ABSTRACT: Kinetic studies, isotope labeling, and in situ high-resolution mass spectrometry are used to elucidate the mechanism for the catalytic oxidation of styrenes using aqueous hydrogen peroxide (H_2O_2) and the cationic palladium(II) compound, $[(\text{PBO})\text{Pd}(\text{NCMe})_2][\text{OTf}]_2$ (PBO = 2-(pyridin-2-yl)benzoxazole). Previous studies have shown that this reaction yields acetophenones with high selectivity. We find that H_2O_2 binds to Pd(II) followed by styrene binding to generate a Pd-alkylperoxide that liberates acetophenone by at least two competitive processes, one of which involves a palladium enolate intermediate that has not been previously observed in olefin oxidation reactions. We suggest that acetophenone is formed from the palladium enolate intermediate by protonation from H_2O_2 . We replaced hydrogen peroxide with *t*-butyl hydroperoxide and found that, although the palladium enolate intermediate was observed, it was not on the major product-generating pathway, indicating that the form of the oxidant plays a key role in the reaction mechanism.



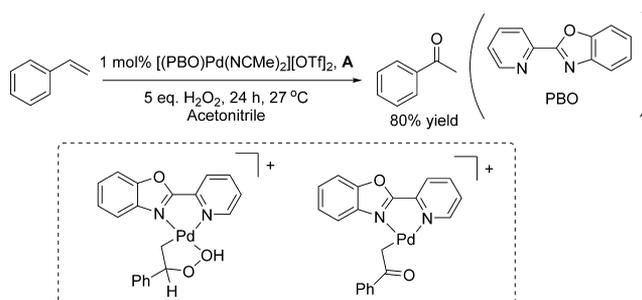
INTRODUCTION

The catalytic oxidation of alkenes provides an expedient synthesis of carbonyl compounds. Despite recent advances,^{1–3} many challenges remain. The Wacker process for aerobic oxidation of ethylene to acetaldehyde with palladium chloride/copper chloride is a textbook example of industrial oxidation of an alkene;⁴ however, this catalyst system is typically less effective for alkenes other than ethylene.^{5,6} Efforts to replace the copper salts with other electron-transfer mediators to facilitate the reoxidation of Pd(0) have been met with some success,^{7–24} as have efforts to employ alternative oxidants.^{25–28}

Direct aerobic oxidations of alkenes in the absence of mediators are also known,^{29–38} but for the oxidation of styrenes,^{33,34} these systems typically require high loadings of Pd catalyst (5–10 mol %) and lengthy reaction times. The Muldoon group recently reported efficient catalytic oxidation of styrenes with hydrogen peroxide (H_2O_2) in the presence of cationic Pd complexes ligated with 2-(pyridin-2-yl)benzoxazole (PBO), $[(\text{PBO})\text{Pd}(\text{NCMe})_2][\text{OTf}]_2$ (A, Scheme 1).³⁹ While this catalyst is selective for styrenyl substrates, aliphatic terminal alkenes are isomerized rapidly and give low yields of their corresponding 2-ketones.³⁹ Internal alkenes do not undergo oxidation under these conditions.

Hydrogen peroxide is an attractive oxidant,⁴⁰ it is inexpensive, degrades only to O_2 and H_2O , and has been utilized industrially for the production of pharmaceuticals⁴¹ as well as large scale commodity chemicals such as propylene oxide.⁴² While the use of aqueous H_2O_2 for Wacker-type

Scheme 1. Oxidation of Styrene with H_2O_2 ³⁹



oxidations dates to the 1960s,⁴³ considerably less is known regarding the mechanism of alkene oxidations mediated by H_2O_2 ^{44,45} relative to those employing O_2 ,^{46–49} or alkyl hydroperoxides.^{50–54} Herein we describe kinetic investigations, isotope labeling studies, and in situ high-resolution mass spectrometry^{55–57} of Pd(II)/ H_2O_2 catalyzed oxidation of styrenes. These studies provide clear evidence for a mechanism involving the initial formation of a Pd-hydroperoxide intermediate^{50,54} which reacts with styrene to generate a Pd-alkylperoxide intermediate that liberates acetophenone by at least two competitive processes, one of which involves an unusual palladium enolate intermediate (Scheme 1).

Received: May 25, 2017

Published: August 29, 2017

RESULTS

Kinetic Studies. The catalytic oxidation of styrene with H_2O_2 (5 equiv relative to styrene) in ambient air in the presence of $[(\text{PBO})\text{Pd}(\text{NCMe})_2][\text{OTf}]_2$, **A**, affords acetophenone in 80% yield after 24 h (Scheme 1).³⁹ The kinetics were analyzed by monitoring the concentrations as a function of time by gas chromatography. The initial rates were determined by monitoring the concentration of styrene up to 10–15% conversion. These experiments reveal that the initial rates exhibited a linear dependence on both $[\text{styrene}]$ and $[\text{Pd}]$ (Figure 1).

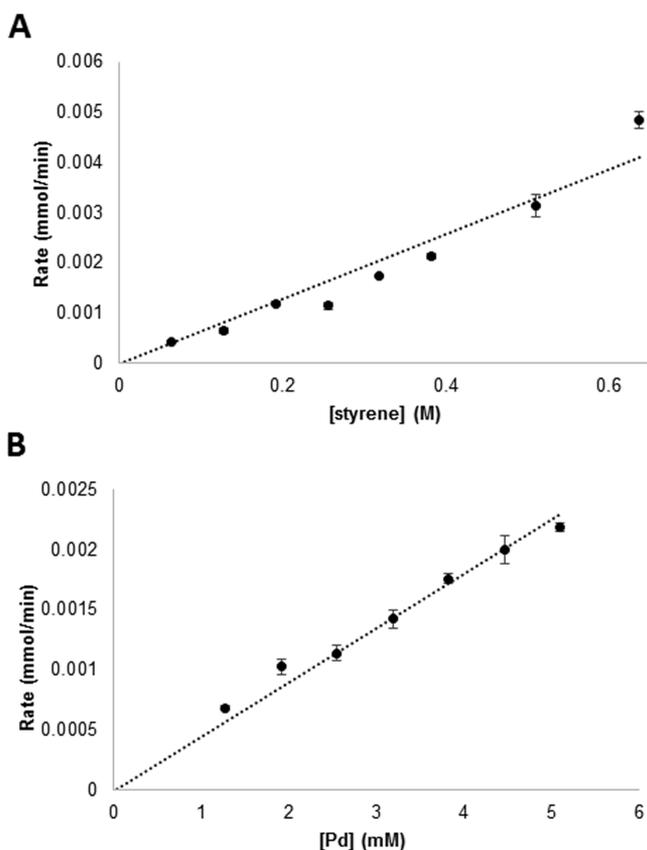


Figure 1. Initial rates for the oxidation of styrene by **A** with H_2O_2 . (A) Initial rates vs $[\text{styrene}]$ (conditions: 2.55 mM **A**, 1.275 M H_2O_2 , 2.534 M H_2O , MeCN, total volume 4.33 mL). (B) Initial rates vs $[\text{Pd}]$. (conditions: 0.255 M styrene, 1.275 M H_2O_2 , 2.534 M H_2O , MeCN, total volume 4.33 mL). Error bars represent one standard deviation for three replicate runs.

The initial rates exhibited saturation behavior with the concentration of hydrogen peroxide; for $[\text{H}_2\text{O}_2] \leq 0.3$ M (approximately 1.2 equiv of H_2O_2 relative to styrene), the rate increases linearly with $[\text{H}_2\text{O}_2]$, after which the rate is independent of peroxide concentration (Figure 2). The initial rates exhibited a similar saturation behavior with the concentration of water, exhibiting a linear increase in rate for $[\text{H}_2\text{O}] \leq 2.5$ M, but the initial rates do not change significantly at higher $[\text{H}_2\text{O}]$. Control experiments reveal that oxidation of styrene under similar conditions in the absence of H_2O_2 affords a 24% yield of acetophenone (Scheme 2),³⁹ indicating that aerobic Wacker oxidation of styrene can also occur under these conditions and may be responsible for some fraction of the acetophenone generated, even in the presence of H_2O_2 .

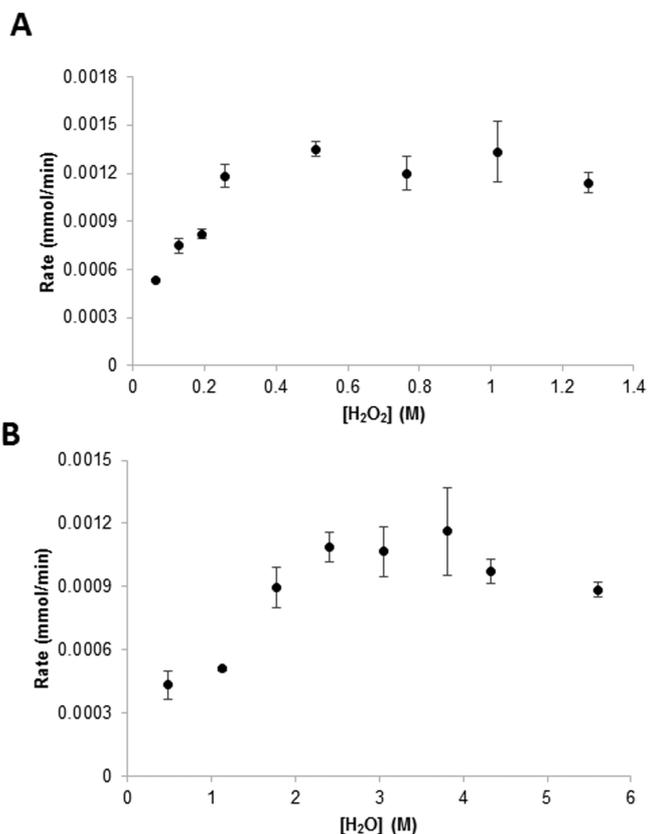
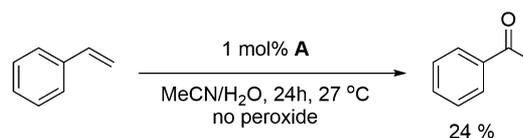


Figure 2. Initial rates for the oxidation of styrene by **A** as a function of $[\text{H}_2\text{O}_2]$ and $[\text{H}_2\text{O}]$. (A) Conditions: 0.255 M styrene, 2.55 mM **A**, 2.534 M H_2O , MeCN, total volume 4.33 mL. (B) Conditions: 0.255 M styrene, 2.55 mM **A**, 1.275 M H_2O_2 , MeCN, total volume 4.33 mL. Error bars represent one standard deviation for three replicate runs.

Scheme 2. Product Formation via Aerobic Wacker Oxidation



The initial rates for a range of substituted styrenes were investigated to probe the influence of electronic effects on the rate of styrene oxidation (Figure 3). These data revealed a

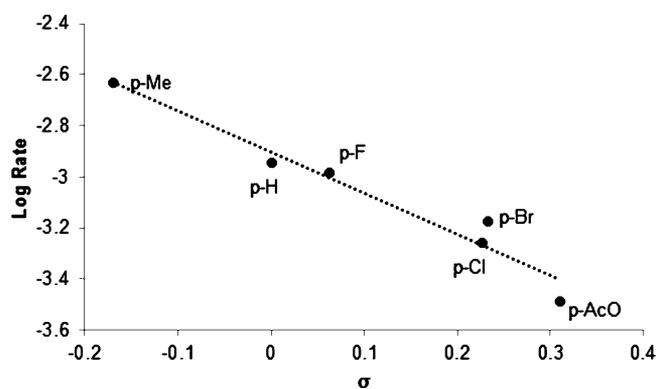


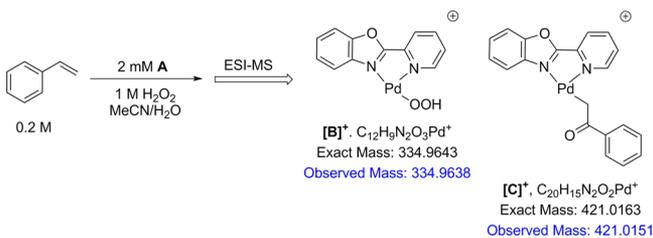
Figure 3. Hammett plot for substituted styrenes (conditions: 0.255 M styrene, 2.55 mM **A**, 2.534 M H_2O , 1.275 M H_2O_2 , MeCN, total volume 4.33 mL).

linear free energy relationship between the logarithm of the rate vs the Hammett σ parameter. This plot yields a negative slope with $\rho = -1.61$, indicating slower rates for more electron-deficient styrenes.

Mass Spectrometry and Isotope Labeling. To provide insight on the nature of catalytic intermediates and the speciation of Pd species during the catalytic reaction, we utilized high-resolution electrospray mass spectrometry (ESI-MS), combined with isotope-labeling studies to monitor the catalytic oxidation of styrene with $[(\text{PBO})\text{Pd}(\text{NCMe})_2][\text{OTf}]_2$, **A**. Analysis of catalytic reactions by ESI-MS techniques coupled with other mechanistic tools and kinetic studies can provide valuable insights into complex catalytic mechanisms.^{48,55,58–61} We have recently used ESI-MS to investigate the mechanisms of aerobic Pd(II) catalysis for alcohol oxidation^{56,62} and H_2O_2 disproportionation.⁵⁷

Oxidations of 0.2 M styrene in ambient air with 1 M H_2O_2 in the presence of 2 mM **A** in MeCN/ H_2O were investigated by taking aliquots and diluting them directly before analyzing the reaction mixture by ESI-MS (Scheme 3). Immediately, an

Scheme 3. Ions Observed from ESI-MS



envelope of peaks centered at 334.9638 m/z is observed at reaction times as short as 1 min—corresponding to the Pd-hydroperoxide species $[(\text{PBO})\text{Pd}-\text{OOH}]^+$, **[B]⁺**. This ion appears early in the reaction and is observed throughout the reaction. At early reaction times, another envelope of peaks is evident at 469.4429 m/z but is not present after tens of minutes and later reaction times. This ion is formulated as the trimeric $[\text{PBO}_3\text{Pd}_3\text{O}_2]^{2+}$, an ion analogous to that observed and characterized in O_2 or H_2O_2 mediated oxidations with cationic Pd neocuproine complexes.^{56,57}

After 1 h of reaction, the major observed species is an ion at 421.0151 m/z , corresponding to the formula $[\text{PBOPd}-\text{CH}_2\text{COPh}]^+$, **[C]⁺**, which we assign as a Pd-enolate.⁶³ This ion remains the dominant species throughout the reaction. This was an unexpected observation, as such a species has rarely been observed or postulated in Wacker-type reactions of styrene. To more fully characterize this ion, collision induced dissociation (CID) mass spectrometry was carried out and revealed daughter ions that have lost either CO or CH_2CO , which agrees with a Pd-enolate ion.⁶³ ESI-MS of analogous reactions using 4-fluorostyrene and 3-nitrostyrene gave ions at 439.0051 m/z and 465.9989 m/z , respectively, consistent with corresponding palladium enolates. When the product acetophenone was subjected to the typical catalytic conditions in the absence of styrene, no ions corresponding to the Pd-enolate could be observed, implying that these ions are not derived from acetophenone.

Attempts to independently prepare the proposed $[\text{PBOPd}-\text{CH}_2\text{COPh}][\text{OTf}]$ were unsuccessful. However, the analogous 1,10-phenanthroline (phen) complex, $[(\text{phen})\text{Pd}-\text{CH}_2\text{COPh}(\text{NCMe})][\text{OTf}]$ (**phen-C**), was successfully syn-

thesized and characterized. The ^1H and ^{13}C NMR spectra of this compound are consistent with its formulation as a C-bound enolate.⁶³ The ESI-MS of **phen-C** afforded an envelope of ions centered at 405.0219 m/z corresponding to $[(\text{phen})\text{Pd}-\text{CH}_2\text{COPh}]^+$; furthermore, the CID spectrum had the same pattern of daughter peaks as those observed from **[C]⁺**, providing indirect evidence that the enolate **[C]⁺** is C-bound and not O-bound.⁶³ Treatment of a CD_3CN solution of this enolate with 1 M D_2O_2 afforded acetophenone in 5% yield, 91% of which was d_1 -acetophenone. When an analogous reaction was carried out with H_2O_2 and analyzed by ESI-MS, the ion corresponding to $[(\text{phen})\text{Pd}-\text{OOH}]^+$ was observed; these results indicate that the C-bound enolates can be protonated by H_2O_2 to afford acetophenone, although this process is not very efficient with the phen ligand (phen had been previously shown to be a poor ligand for the catalytic oxidation of styrene³⁹).

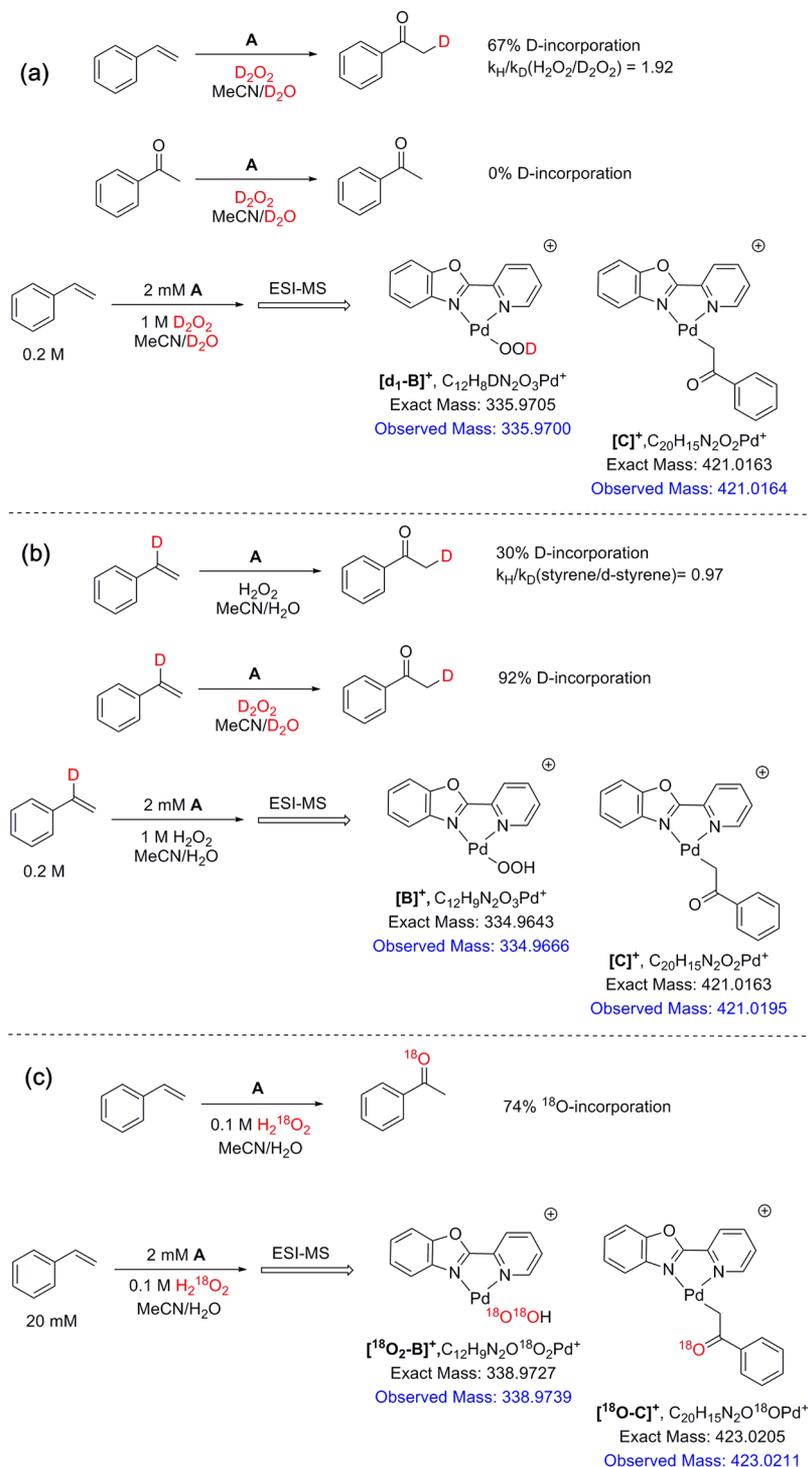
To provide further information on the processes that lead to the Pd-enolate ion and its role in the oxidation reaction, a series of isotope labeling studies was carried out. The catalytic oxidation of 0.2 M styrene with 1 M D_2O_2 (approximately 98% D-labeled) in MeCN/ D_2O catalyzed by 2 mM **A** afforded a mixture of d_1 -acetophenone (67%) and acetophenone (33%) (Scheme 4a). Kinetic experiments revealed a primary kinetic isotope effect of $k_{\text{H}}/k_{\text{D}}$ ($\text{H}_2\text{O}_2/\text{D}_2\text{O}_2$) = 1.92. A control experiment under the same D_2O_2 conditions with acetophenone instead of styrene yielded no d_1 -acetophenone, indicating that d_1 -acetophenone is not derived from the product acetophenone. When the reaction of styrene with D_2O_2 was monitored by ESI-MS, two overlapping ion envelopes centered at 334.9656 m/z and 335.9700 m/z were observed, corresponding to a mixture of **[B]⁺** and $[\text{PBOPd}-\text{OOD}]^+$, $[\text{d}_1\text{-B}]^+$. However, the ion corresponding to the Pd-enolate was observed at 421.0164 m/z , indicating that the enolate generated under these conditions contains no deuterium. These observations suggest that d_1 -acetophenone likely arises from deuterolysis of the C-bound Pd-enolate.

Catalytic oxidation of 0.2 M α -D-styrene with 1 M H_2O_2 and 2 mM **A** in MeCN/ H_2O leads to a mixture of d_1 -acetophenone (30%) and unlabeled acetophenone (70%) (Scheme 4b). Kinetic studies revealed a negligible kinetic isotope effect, $k_{\text{H}}/k_{\text{D}} = 0.97$ (styrene vs α -D-styrene). In contrast, when the oxidation of α -D-styrene was carried out in $\text{D}_2\text{O}_2/\text{D}_2\text{O}$, over 92% of the acetophenone was deuterated (Scheme 4b). When this reaction was monitored by ESI-MS, the undeuterated enolate **[C]⁺** was observed, indicating that the Pd-enolate derived from α -D-styrene lost its deuterium atom.

When the catalytic oxidation of 20 mM styrene with 2 mM **A** was carried out with ^{18}O -labeled hydrogen peroxide (0.1 M $\text{H}_2^{18}\text{O}_2$) in MeCN/ H_2O , GCMS analysis revealed that 74% of the acetophenone product is ^{18}O labeled (Scheme 4c). The ESI-MS of this reaction revealed ions at 338.9739 m/z corresponding to the palladium hydroperoxide containing two ^{18}O atoms, $[\text{PBO}_2\text{-B}]^+$. The ion corresponding to the palladium enolate shifts to 423.0211 m/z , $[\text{PBO-C}]^+$, which indicates that the oxygen in the enolate is derived from the labeled hydrogen peroxide. When an analogous experiment was carried out with unlabeled H_2O_2 in labeled H_2^{18}O water, the ion corresponding to the Pd-enolate did not incorporate the ^{18}O from water (see the Supporting Information).

Efforts to investigate the influence of radical traps or hydrogen atom donors on the oxidation of styrene with H_2O_2 were ambiguous. Addition of TEMPO or TEMPOH

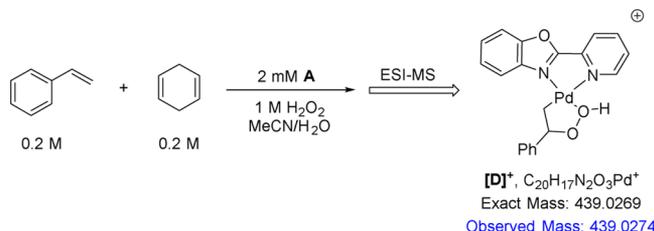
Scheme 4. Isotope-Labeling Studies



(TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) completely shut down the reaction, and was thus not informative. The addition of 1 equiv (relative to styrene) of 1,4-cyclohexadiene (CHD) to a styrene oxidation reaction with H₂O₂ resulted in a decrease in rate but exhibited a similar selectivity to those carried out with D₂O₂ or α -D-styrene in the absence of CHD. We were encouraged to look at this reaction by ESI-MS to assess if the lower rates observed in the presence of CHD might enable observation of short-lived intermediates that might not otherwise be detectable. Analysis of the reaction of 0.2 M

styrene and 2 M H₂O₂ in MeCN catalyzed by 2 mM A in the presence of 0.2 M CHD revealed an envelope of ions at 439.0274 *m/z* in low relative abundance at early time points (Scheme 5). This ion corresponds to the formula [PBOPdCH₂CH(OOH)Ph]⁺, [D]⁺, corresponding to a Pd-alkylperoxide, an intermediate which had been previously proposed by Mimoun^{44,50} and Sigman^{51,54} in peroxide-mediated oxidations of olefins. Other intermediates with CHD coordinated to the Pd center were also observed (see the Supporting Information).

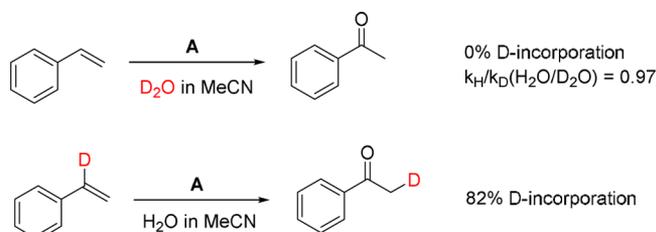
Scheme 5. Ions Observed from ESI-MS with CHD Additive



In an effort to identify short-lived intermediates, alternative electrospray techniques were employed. Desorption electrospray ionization (DESI) MS is a useful technique for observing species that form on the microsecond time scale.^{64,65} For these experiments, an acetonitrile solution of the Pd precursor A was deposited on a porous Teflon sheet and allowed to dry. A solution of styrene and H_2O_2 in MeCN was then sprayed onto it using an ESI source, and the secondary microdroplets generated were analyzed by MS. One of the first ions observed was the Pd–OOH ion $[\text{B}]^+$; subsequently, ions corresponding to the Pd-enolate $[\text{C}]^+$ grew in slowly over about a minute. These experiments suggest that the hydroperoxide $[\text{B}]^+$ is formed rapidly upon contact of hydrogen peroxide with the cationic Pd precursor A. These experiments were corroborated utilizing a theta capillary nanoESI experiment. In this technique, two solutions are simultaneously sprayed from two barrels of a single capillary with an $\sim 2 \mu\text{m}$ tip, resulting in mixing just prior to formation of the primary droplets. Depending on the distance of the spray from the mass spectrometer, this technique results in mixing times on the order of 10–1000 μs .^{66–68} When separate MeCN solutions of A and styrene mixed with H_2O_2 were sprayed through the theta capillary, the predominant ion observed (other than the precursor $[(\text{PBO})\text{Pd}(\text{NCMe})_2]^{2+}$) was that corresponding to $[\text{B}]^+$. Ions corresponding to the palladium enolate were not observed under these conditions, from which we conclude that the Pd-hydroperoxide is formed prior to the Pd-enolate.

Aerobic Wacker Oxidation. As prior studies³⁹ had suggested that some fraction of the acetophenone produced when styrene is oxidized with H_2O_2 in air may derive from a competitive aerobic Wacker reaction (Scheme 2, 24% after 24 h in air vs 80% with H_2O_2), we carried out several experiments to monitor the oxidation of styrene in air in the absence of hydrogen peroxide (Scheme 6). When 0.2 M styrene was

Scheme 6. Aerobic Wacker Isotope Labeling Studies



oxidized in air in 4 M D_2O (in MeCN) with 2 mM A, analysis of the resulting acetophenone revealed undetectable amounts of deuterium incorporation. In contrast, for α -D-styrene under similar conditions, 82% of the acetophenone was labeled.

When these reactions were analyzed by ESI-MS, at early reaction time points, the mass spectrum was similar to that of $[(\text{PBO})\text{Pd}(\text{NCMe})_2][\text{OTf}]_2$ in wet MeCN. However, after 1 h,

the peak at 421.0179 m/z (corresponding to Pd-enolate) began to grow in, albeit in a much lower relative abundance than that observed in the presence of H_2O_2 . This peak was also present when D_2O was used instead of H_2O .

Other Peroxide Oxidants. The observation of the Pd-enolate intermediate was unexpected, as this intermediate had not been commonly invoked in Wacker-type oxidations.¹ To assess the generality of this observation and the potential role of Pd-enolates in other olefin oxidation reactions, we investigated the oxidation of styrene with *t*-butyl hydroperoxide (TBHP) under conditions analogous to those reported by Sigman.^{52,54}

When the catalytic oxidation of α -D-styrene with (Quinox)- $\text{PdCl}_2/\text{AgSbF}_6$ (Quinox = 2-(4,5-dihydro-2-oxazolyl)-quinolone) was carried out in CH_2Cl_2 with TBHP (70% solution in water), analysis of the reaction mixture revealed that 98% of acetophenone generated was monodeuterated.

When the oxidation of styrene with TBHP was monitored by ESI-MS, two major species were observed after 15 min: an ion at 497.1047 m/z and one at 423.0322 m/z (see the Supporting Information). The former corresponds to the formula $[(\text{Quinox})\text{Pd}-\text{CH}_2\text{CH}(\text{OOtBu})\text{Ph}]^+$, $[\text{E}]^+$, and the latter to $[(\text{Quinox})\text{Pd}-\text{CH}_2\text{COPh}]^+$, $[\text{F}]^+$ (Scheme 7). The CID spectrum of $[\text{E}]^+$ (Figure S42) shows, instead of loss of styrene, fragmentation peaks consistent with O–O bond cleavage to produce $[\text{F}]^+$ as well as loss of the *t*-butyl group. This fragmentation pattern is most consistent with a palladium alkylperoxide, rather than a palladium peroxide with a coordinated styrene. When the same reaction was carried out with α -D-styrene, analysis of the mass spectra revealed ions corresponding to the Pd-alkylperoxide $[(\text{Quinox})\text{Pd}-\text{CH}_2\text{CD}(\text{OOtBu})\text{Ph}]^+$, $[\text{d}_1\text{-E}]^+$, containing one deuterium; in contrast, the ion corresponding to the Pd-enolate did not contain a deuterium label. Both Sigman⁵⁴ and Mimoun⁴⁴ had proposed that alkylperoxides are key intermediates in the peroxide-mediated oxidations of olefins. The results of the in situ mass spectroscopy measurements are fully consistent with this hypothesis.

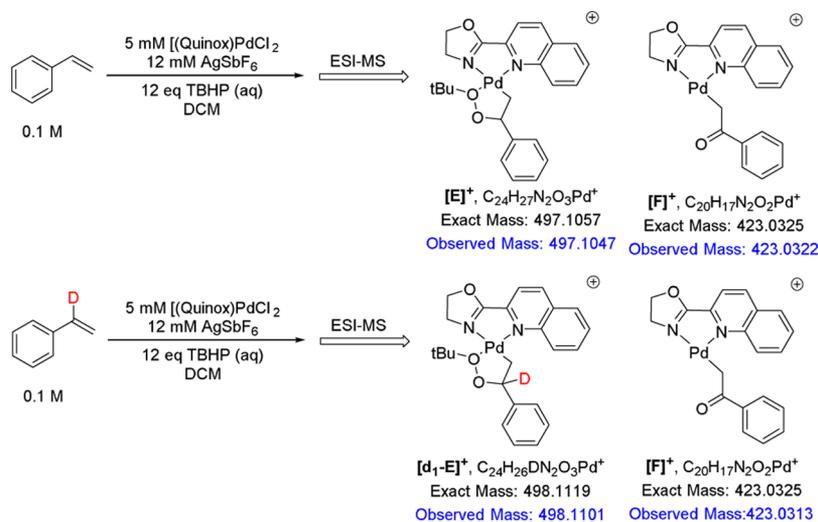
Analogous experiments were carried out with $[(\text{PBO})\text{Pd}(\text{NCMe})_2][\text{OTf}]_2$, A, in an effort to assess the role of both the ligand and the oxidant on the distribution of deuterium in the products. Oxidation of α -D-styrene with TBHP in the presence of A afforded 60% yield of acetophenone after 1 h where 98% of the acetophenone was deuterated (Scheme 8). Analysis of a reaction with perprotio styrene by ESI-MS revealed ions corresponding to the Pd-tertbutylperoxide, $[\text{G}]^+$ (391.0289 m/z), the Pd-alkylperoxide, $[\text{H}]^+$ (495.0918 m/z), and the Pd-enolate, $[\text{C}]^+$ (421.0189 m/z).

These latter experiments are informative as they clearly indicate that, with the same ligand system (PBO), the nature of the oxidant has a significant influence on the fate of the deuterium derived from α -D-styrene and on the observed intermediates by ESI-MS. When H_2O_2 is used as the oxidant, only 30% of the resulting acetophenone is labeled with deuterium, whereas, when TBHP is the oxidant, 98% of the acetophenone is labeled.

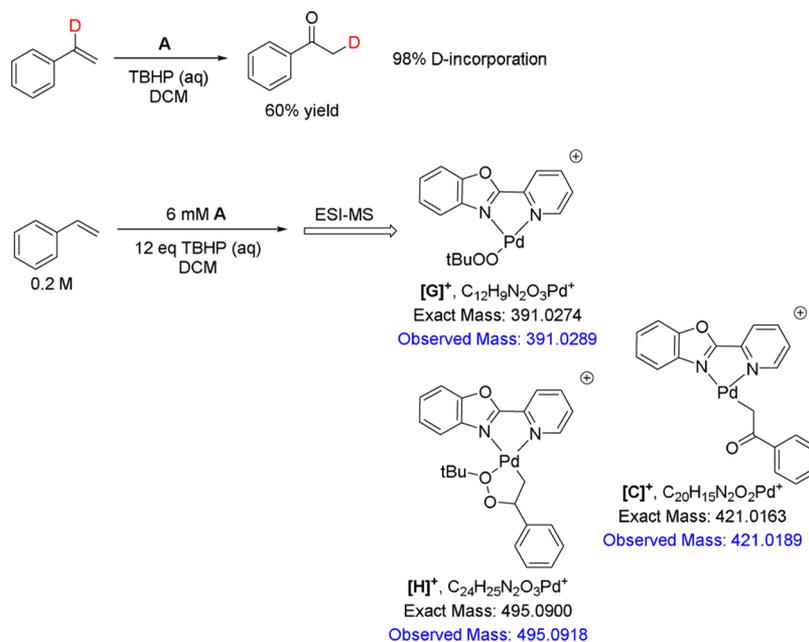
DISCUSSION

The results of this study indicate that the catalytic oxidation of styrene with $[(\text{PBO})\text{Pd}(\text{NCMe})_2][\text{OTf}]_2$, A, and H_2O_2 as the terminal oxidant proceeds by several competitive pathways (Scheme 9, represented with α -D-styrene), including a competitive oxidation pathway mediated by O_2 (aerobic Wacker reaction). In the following, we will describe the

Scheme 7. Ions Observed from ESI-MS for the Quinox/TBHP System



Scheme 8. PBOPd with TBHP Deuterium Labeling

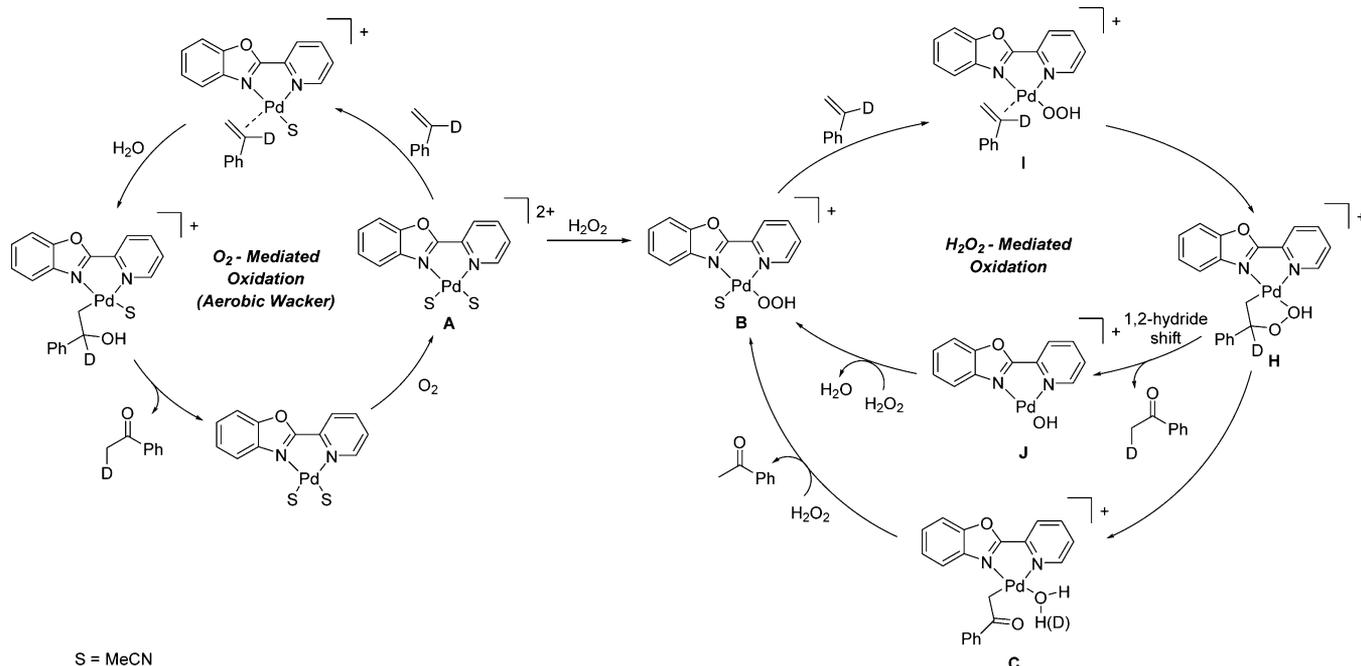


cumulative evidence obtained from kinetic measurements, isotope labeling, and in situ mass spectrometry that is consistent with this proposal.

Experimental data from DESI and theta capillary nanoESI provide compelling evidence that the initial intermediate formed within microseconds upon reaction of **A** with H₂O₂ is the Pd–OOH intermediate **B**. Mimoun^{44,50} and others^{69,70} had previously proposed the formation of a Pd–OOR intermediate as a first step in olefin oxidation reactions by hydrogen peroxide or alkyl hydroperoxides.^{51,54} This hypothesis that intermediate **B** is the first step of the mechanism is also supported by the first order kinetics observed with [Pd], the saturation-type kinetics observed with H₂O₂, and the kinetic isotope effect (H₂O₂/D₂O₂) of 1.92. Pd-hydroperoxide species can be generated from aerobic pathways, either from the direct reaction of molecular oxygen with Pd–H species or via protonation of Pd-peroxo species.^{1,71–75} The use of labeled H₂¹⁸O₂ and the observation of subsequent ¹⁸O-incorporation in Pd–OOH (**B**)

is strong evidence that this Pd-hydroperoxide is the result of direct reaction of the Pd catalyst with H₂O₂.

The reaction of intermediate **B** with styrene is proposed to generate the alkylperoxide intermediate **H** (Scheme 9); related intermediates have been proposed by both Mimoun⁴⁴ and Sigman.^{44,51,54} This is consistent with linear kinetics plots obtained with varying styrene concentration. Although this intermediate was not observed directly by ESI under the typical reaction conditions, an ion at 439.0274 *m/z* corresponding to the alkylhydroperoxide [(PBO)PdCH₂CH(OOH)Ph]⁺, [**D**]⁺, was observed in the oxidation of styrene with H₂O₂ in the presence of 1,4-cyclohexadiene. Moreover, when the oxidation of styrene was carried out with TBHP as the terminal oxidant, ions corresponding to the alkylperoxide [(L)Pd–CH₂CH–(OOtBu)Ph]⁺ were observed with Pd complexes ligated by both the Quinox and PBO. Collision-induced dissociation (CID) performed on this intermediate **H** shows that the

Scheme 9. Proposed Pathways for the Oxidation of α -D-Styrene with H_2O_2 to Generate Acetophenone

structure of this intermediate is indeed the Pd-alkylperoxide rather than simply the styrene-bound Pd–OOH species I.

The deuterium labeling studies strongly imply that the oxidation of styrene with H_2O_2 generates acetophenone by at least three competitive pathways (Scheme 9). Control experiments (Scheme 2) indicate that, in the absence of H_2O_2 , acetophenone is formed in 24% yield after 24 h by an aerobic Wacker reaction mediated by O_2 and H_2O .^{47,76–78} The degree to which the aerobic Wacker competes with the H_2O_2 -mediated oxidation is not clear, but the fact that 74% of the acetophenone is ^{18}O -labeled when styrene is oxidized with $\text{H}_2^{18}\text{O}_2$ (Scheme 4c) suggests that some of the acetophenone may be generated by the aerobic Wacker pathway as the water present is ^{16}O . However, the ^{16}O -labeled acetophenone could also come from an oxygen exchange between the ^{18}O -labeled acetophenone and the H_2^{16}O .⁷⁹

For the H_2O_2 -mediated oxidation, the labeling and mass spectrometry data imply two additional pathways: one that generates acetophenone by a 1,2-hydride shift from the Pd-alkylhydroperoxide^{44,51,54} and another pathway that generates acetophenone by the protonolysis of the novel Pd-enolate intermediate. Mimoun and Sigman had previously proposed a related 1,2-hydride shift to account for the formation of d_1 -acetophenone from the oxidation of α -D-styrene with TBHP. That approximately 30% of d_1 -acetophenone is observed in the oxidation of α -D-styrene with H_2O_2 with A is consistent with a 1,2-hydride shift mechanism. However, some fraction of the d_1 -acetophenone could come from the competitive background aerobic Wacker mechanism.

The observation that a significant percentage (approximately 70%) of the acetophenone generated from α -D-styrene is unlabeled and that a similar percentage (approximately 67%) of styrene is deuterated upon oxidation by D_2O_2 suggests that another competitive pathway must exist for the formation of acetophenone. We propose that this pathway involves the Pd C-bound enolate. The ESI-MS data reveals that ions corresponding to the Pd-enolate C are among the most

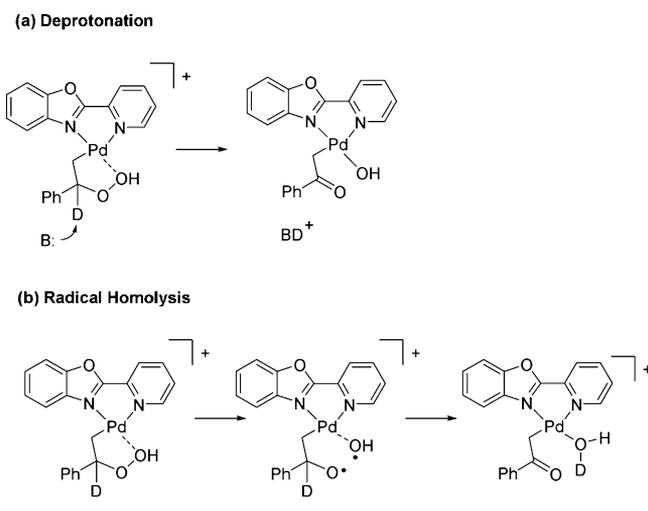
abundant ions observed, and the independent synthesis of an analogous compound with a 1,10-phenanthroline ligand is consistent with its formulation as a carbon-bound enolate.^{63,80}

When the oxidation of α -D-styrene was monitored by ESI-MS, the ion corresponding to the enolate C contained no deuterium, which is consistent with the observation that approximately 70% of the acetophenone generated from α -D-styrene contains no deuterium. When unlabeled styrene is oxidized with D_2O_2 , the ion corresponding to the enolate C likewise contains no deuterium, although approximately 67% of the resulting acetophenone contains one deuterium. This latter observation could be explained by the protonolysis of the enolate by D_2O_2 (Scheme 9). The lack of an observable KIE for the oxidation of α -D-styrene/styrene is consistent with the loss of the deuterium label prior to Pd-enolate decomposition.

The proposed rearrangement of the Pd-alkylhydroperoxide to the Pd-enolate is preceded in the chemistry of alkylperoxides.^{81–83} Alkylperoxides bearing α -hydrogen atoms are known to cleave to ketones by the Kornblum–DeLaMare rearrangement;^{81–83} both heterolytic^{82,83} and homolytic⁸⁴ mechanisms for this rearrangement are preceded. Shown in Scheme 10 are two possible mechanisms for the formation of the Pd-enolate from the Pd-alkylhydroperoxide intermediate: one involving deprotonation facilitated by the coordination of the hydroperoxide to the cationic Pd center^{81–83} and another involving hydrogen-atom abstraction of the α -H(D) and homolysis of the O–O bond.⁸⁴ Although either of these processes could account for the loss of the deuterium label when using α -D-styrene as a substrate (Scheme 4b), our data to date do not allow us to distinguish between these two possibilities.

The observation of a Pd-enolate in these H_2O_2 -mediated oxidations was unexpected, as such species are rarely invoked in the oxidation of olefins by Pd. While we were unable to prepare this species independently with the PBO ligand, the isotope-labeling and ESI data provide compelling, if indirect, support for the intermediacy of carbon-bound Pd-enolates in the H_2O_2 -

Scheme 10. Two Potential Mechanisms for Pd-Enolate Formation from a Pd-Alkylperoxide



mediated oxidation of styrene with $[(\text{PBO})\text{Pd}(\text{NCMe})_2][\text{OTf}]_2$, **A**, and therefore provide new insights on oxidation mechanisms of olefins with peroxides.

While Pd-enolate intermediates were also observed in the oxidation of styrenes with the alkylperoxide TBHP using either $[(\text{PBO})\text{Pd}(\text{NCMe})_2][\text{OTf}]_2$ (Scheme 8) or the (Quinox)-PdCl₂ system⁵⁴ (Scheme 7), the observation that 98% of the acetophenone was deuterated with α -D-styrene implies that the enolate pathway is only a minor contributor when TBHP is used as the oxidant, irrespective of the diimine ligand. These results suggest that the different reactivities between the two peroxide oxidants can be rationalized by the different reactivities of the Pd-alkylperoxide intermediates $[(\text{L})\text{Pd}-\text{CH}_2\text{CH}(\text{OOR})\text{Ph}]^+$ (R = tBu vs H).

CONCLUSIONS

In summary, a new mechanism involving Pd-enolate intermediates is proposed for the oxidation of styrenes with H₂O₂ and catalysts derived from the cationic complex $[(\text{PBO})\text{Pd}(\text{NCMe})_2][\text{OTf}]_2$. Kinetic investigations, isotope labeling studies, and in situ high-resolution mass spectrometry provide evidence for a mechanism involving the initial formation of a Pd-hydroperoxide intermediate. This species reacts with styrene to generate a Pd-alkylhydroperoxide that liberates acetophenone by at least two competitive processes, one of which involves an unusual palladium enolate intermediate. Mechanistic and labeling studies indicate that oxidation pathways involving these novel palladium enolate intermediates are competitive with 1,2-hydride migration pathways with H₂O₂, whereas, with *t*-butyl hydroperoxide, the 1,2-hydride mechanism dominates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05413.

Detailed kinetic procedure, data, and analysis, syntheses and NMR spectra, experimental ESI-MS spectra, and computed ESI-MS for comparison (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge support from the Department of Energy (Office of Basic Energy Science, Catalysis Science Program, Award DE-SC0005430, R.M.W.), the Air Force Office of Scientific Research (Grant FA-9550-16-1-0113, R.N.Z.), and the Department of Employment and Learning (DEL), Northern Ireland and Queen's University Ionic Liquids Laboratories (M.J.M. and L.M.D.). K.L.W. acknowledges the Center for Molecular Analysis and Design (CMAD, Stanford) for a fellowship and the National Science Foundation Graduate Research Fellowship Program for support (GRFP). K.L.W. would like to thank Erik Jansson for help with the theta capillary experiments. L.M.D. would like to thank the US-UK Fulbright Commission for a fellowship.

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