Thermodynamic-Kinetic Comparison of Palladium(II)-Mediated Alcohol and Hydroquinone Oxidation

*David L. Bruns, Shannon S. Stahl**

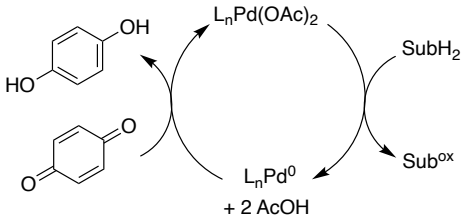
Department of Chemistry, University of Wisconsin-Madison, 1101 University Avenue
Madison, WI, 53706, United States

Abstract: Palladium(II) catalysts promote oxidative dehydrogenation and dehydrogenative coupling of many organic molecules. Oxidations of alcohols to aldehydes or ketones are prominent examples. Hydroquinone (H_2Q) oxidation to benzoquinone (BQ) is conceptually related to alcohol oxidation, but it is significantly more challenging thermodynamically. The BQ/H_2Q redox potential is sufficiently high that BQ is often used as an oxidant in Pd-catalyzed oxidation reactions. A recent report (*J. Am Chem. Soc.* **2020**, *142*, 19678-19688) showed that certain ancillary ligands can raise the $Pd^{II/0}$ redox potential sufficiently to reverse this reactivity, enabling (L)$Pd^{II}(OAc)_2$ to oxidize hydroquinone to benzoquinone. Here, we investigate the oxidation of *tert*-butylhydroquinone ($^tBuH_2Q$) and 4-fluorobenzyl alcohol ($^{4F}BnOH$), mediated by (bc)$Pd(OAc)_2$ (bc = bathocuproine). Although alcohol oxidation is thermodynamically favored over H_2Q oxidation by more than 400 mV, the oxidation of $^tBuH_2Q$ proceeds several orders of magnitude faster than $^{4F}BnOH$ oxidation. Kinetic and mechanistic studies reveal that these reactions feature different rate-limiting steps. Alcohol oxidation proceeds via rate-limiting β-hydride elimination from a Pd^{II}–alkoxide intermediate, while H_2Q oxidation features rate-limiting isomerization from an O-to-C-bound Pd^{II}–hydroquinonate species. The enhanced rate of H_2Q oxidation reflects the kinetic facility of O–H relative to C–H bond cleavage.

Introduction

Palladium(II)-catalyzed oxidation reactions are a versatile class of reactions in organic chemistry that enable diverse transformations, including alcohol oxidation, oxidative coupling of alkenes with heteroatom nucleophiles, oxidative C–C coupling reactions, among others. [1–15] These reactions typically feature two redox half-reactions, consisting of Pd^{II}-mediated substrate oxidation and reoxidation of Pd^{0} to Pd^{II} by various oxidants,[16] including O_2[17] and benzoquinone (BQ) (Scheme 1).[18,19] Ancillary ligands, such as amines and mono- and bidentate pyridine derivatives, are increasingly common in Pd-catalyzed oxidation reactions. These ligands can influence both redox half-reactions, for example, by stabilizing the Pd catalyst, enhancing the rate of catalyst reoxidation, or modulating the chemo-, regio-, or stereoselectivity of substrate oxidation.[15]

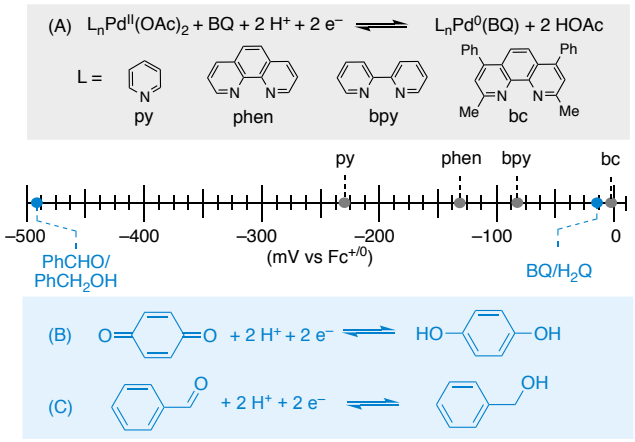
Scheme 1. Redox Half Reactions in Pd-catalyzed Oxidations with Benzoquinone as the Oxidant.



We recently reported an experimental and computational study of the influence of ancillary ligands on the $Pd^{II/0}$ redox potential.[20] This study was made possible by the unexpected finding that certain ligands, such as bathocuproine (bc), increase the $Pd^{II/0}$ potential sufficiently to allow oxidation of hydroquinone (H_2Q) by $(L)Pd^{II}(OAc)_2$, inverting the typical redox reactivity between $Pd^{II/0}$ and BQ/H_2Q.[21–23] Analysis of equilibria between $(L)Pd^{II}(OAc)_2/H_2Q$ and $(L)Pd^{0}(BQ)$/2 AcOH provided the basis for determination of formal redox potentials for various $(L)Pd^{II}(OAc)_2$

complexes (Scheme 2A) relative to potentials associated with the BQ/H_2Q and PhCHO/$PhCH_2OH$ redox reactions (Scheme 2B and 2C).[20,24,25]

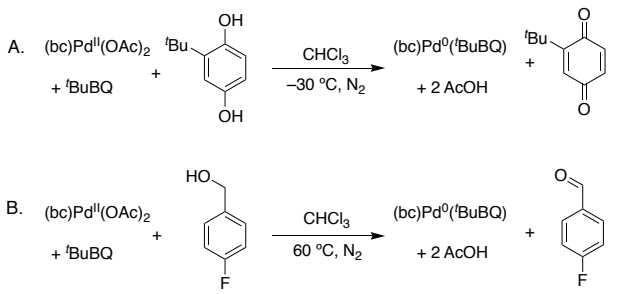
Scheme 2. Comparison of Redox Potentials for $Pd^{II/0}$, BQ/H_2Q, and PhCHO/$PhCH_2OH$.



Observation of (bc)$Pd(OAc)_2$-mediated oxidation of hydroquinone provides a unique opportunity to compare thermodynamic-kinetic relationships between oxidative dehydrogenation of H_2Q and alcohols. The redox potential for BQ/H_2Q is ~400-500 mV higher than that of PhCHO/$PhCH_2OH$ (Scheme 2),[25] but qualitative observations revealed that H_2Q oxidation is much more rapid than $PhCH_2OH$ oxidation. This contra-thermodynamic kinetic behavior prompted us to pursue a quantitative comparison of the relative rates and probe the mechanisms of these two conceptually similar dehydrogenation reactions. Here, we report an investigation of stoichiometric oxidation of *tert*-butylhydroquinone (^{t}BuH_2Q) to *tert*-butylbenzoquinone (^{t}BuBQ) and 4-fluorobenzyl alcohol (^{4F}BnOH) to 4-fluorobenzaldehyde, mediated by (bc)$Pd(OAc)_2$ (Scheme 3). Both reactions are conducted in the presence of *tert*-butylbenzoquinone (^{t}BuBQ) to ensure that they have identical $Pd^{II/0}$ reagents/products, [(bc)$Pd(OAc)_2$]/[(bc)Pd^0(BQ)]. This study of stoichiometric alcohol oxidation by Pd^{II} complements multiple mechanistic studies of *catalytic*

alcohol oxidation with Pd^{II} catalysts,[6,26–33] while mechanistic studies of Pd^{II}-mediated oxidation of hydroquinone in the absence of a secondary oxidant are unprecedented.[22]

Scheme 3. (bc)Pd(OAc)$_2$-Mediated Oxidation of ^{t}BuH$_2$Q and ^{4F}BnOH.



Results and Discussion

Kinetic investigation of (bc)Pd(OAc)$_2$-mediated hydroquinone oxidation. We initiated our investigation with a kinetic analysis of (bc)Pd(OAc)$_2$-mediated oxidation of ^{t}BuH$_2$Q at -30 °C in chloroform by UV-visible spectroscopy (monitoring appearance of an absorption band at 420 nM; see Figure S7 in the Supporting Information). This hydroquinone derivative was used instead of the parent H$_2$Q because of its higher solubility in chloroform. The reaction forms the known complex, (bc)Pd^0(^{t}BuBQ).[20] The concentration of (bc)Pd(OAc)$_2$ was varied from 0.25-1.25 mM, with [^{t}BuH$_2$Q] fixed at 4 mM and [^{t}BuBQ] at 1 mM. Then, [^{t}BuH$_2$Q] was varied from 1-10 mM, with [(bc)Pd(OAc)$_2$] and [^{t}BuBQ] fixed at 1 mM each. Comparison of the initial rates under each of these conditions revealed a first-order dependence on [(bc)Pd(OAc)$_2$] and [^{t}BuH$_2$Q] (Figures 1a and 1b). The reaction was unaffected by changes to [^{t}BuBQ] over a range of 1-8 mM concentration (See Supporting Information, Figure S9). No deuterium kinetic isotope effect was evident from independent rate measurements with ^{t}BuH$_2$Q and ^{t}BuD$_2$Q (k_H/k_D = 1.0 ± 0.2, Figure 1c; care was

taken to avoid O–D exchange with sources of "H" in the glassware; see section 8 in the Supporting Information for details).

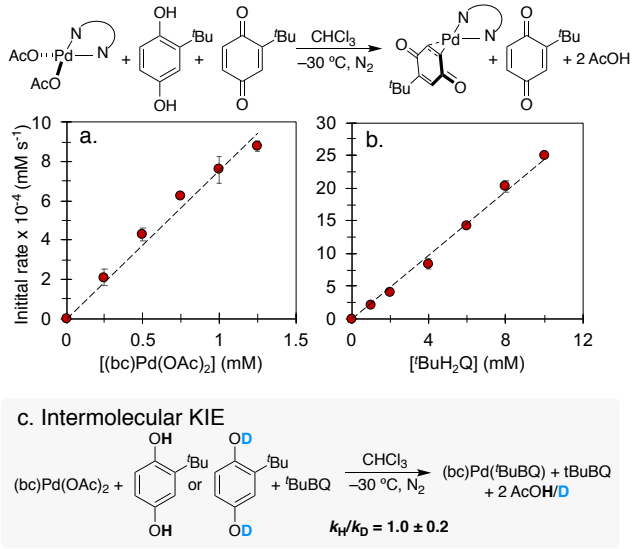


Figure 1. Kinetic analysis of (bc)Pd(OAc)$_2$-mediated oxidation of ^{t}BuH$_2$Q, including (a) [(bc)Pd(OAc)$_2$] dependence, (b) [^{t}BuH$_2$Q] dependence, and (c) kinetic isotope effect obtained via independent rate measurement. See sections 7 and 8 in the Supporting Information for experimental details.

Kinetic investigation of (bc)Pd(OAc)$_2$-mediated alcohol oxidation. Similar kinetic analysis was conducted for (bc)Pd(OAc)$_2$-mediated oxidation of ^{4F}BnOH. Use of this substrate facilitated analysis of the reaction by ^{19}F NMR spectroscopy, although most kinetic data were acquired by UPLC analysis of reaction aliquots. The concentration of (bc)Pd(OAc)$_2$ was varied from 2-12 mM, [^{4F}BnOH] and [^{t}BuBQ] fixed at 40 mM and 10 mM. Then, [^{4F}BnOH] was varied from 10-160 mM, while fixing [(bc)Pd(OAc)$_2$] and [^{t}BuBQ] at 10 mM each. Comparison of the initial rates under each of these conditions revealed a first-order dependence on [(bc)Pd(OAc)$_2$] and [^{4F}BnOH] (Figures 2a and 2b). The reaction was unaffected by changes to [^{t}BuBQ] (see Supporting Information, Figure S3). A deuterium kinetic isotope effect of $k_H/k_D = 2.0 \pm 0.3$ was observed from the comparison of independent rates measured with ^{4F}BnOH and ^{4F}PhCD$_2$OH as the substrate. An intramolecular kinetic isotope of $k_H/k_D = 2.8 \pm 0.3$ was obtained from oxidation of ^{4F}PhC(H)(D)OH

(Figure 2c and 2d). These KIEs are similar to those observed for Pd-catalyzed alcohol oxidation with bc-ligated Pd catalysts.[26] Hammett analysis of 4-substituted benzyl alcohols revealed that the reaction is slightly faster with more electron-rich alcohols (ρ = –0.33) (see Figure S6 in the Supporting Information).

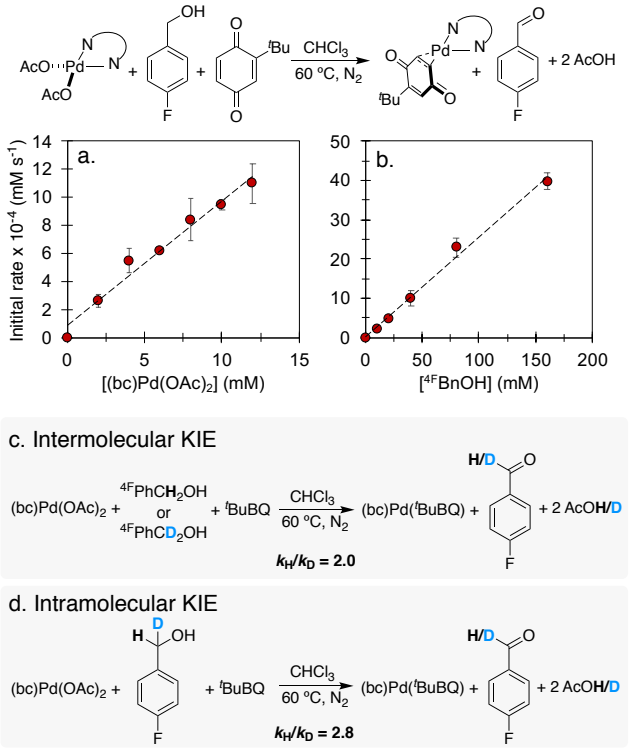


Figure 2. Kinetic analysis of (bc)Pd(OAc)$_2$-mediated oxidation of ^{4F}BnOH, including (a) [(bc)Pd(OAc)$_2$] dependence (b) [^{4F}BnOH] dependence, and kinetic isotopic effects determined by (c) independent rate measurements of ^{4F}BnOH and ^{4F}PhCD$_2$OH and (d) an intramolecular competition experiment with ^{4F}PhC(H)(D)OH. See sections 2 and 3 in the Supporting Information for experimental details.

Carboxylate electronic and steric effects and temperature analysis of hydroquinone and alcohol oxidation rates. A series of bc-supported Pd carboxylate complexes, (bc)Pd(O$_2$CR)$_2$, were used to probe steric and electronic effects for oxidation of ^{t}BuH$_2$Q and ^{4F}BnOH. The carboxylate ligands included 4-trifluoromethylbenzoate, benzoate, 4-*tert*-butylbenzoate, acetate,

and pivalate. Electronic parameters correspond to the pK_a values of the conjugate acids of the carboxylates, which range from 10.1 to 12.6 (DMSO values).[34–37] Relative steric effects were assessed by using a proxy value corresponding to the percent buried volume reported for PR_3 groups (R = ^{4CF3}Ph, Ph, $^{4t\text{Bu}}$Ph, Me, ^{t}Bu) at 2 Å in (R_3P)AuCl complexes.[38,39]

Initial rates of ^{t}BuH$_2$Q oxidation were obtained with the different (bc)Pd$(O_2CR)_2$ complexes. A plot of log(rate) versus carboxylate pK_a values revealed a slope of 0.06 with a poor correlation (R^2 = 0.04) (Figure 3a), indicating the rate is not strongly correlated with the basicity of the carboxylate ligand. A relatively good correlation was observed, however, between log(rate) versus the buried volume parameter for the carboxylate ligands (R^2 = 0.86) (Figure 3b), indicating that the rate of ^{t}BuH$_2$Q oxidation by (bc)Pd$(O_2CR)_2$ is sensitive to the steric profile of the carboxylate ligand.

An analogous set of experiments was performed for ^{4F}BnOH oxidation. In this case, the Brønsted plot exhibits a much better correlation (R^2 = 0.99) with a positive slope (0.37) (Figure 3c), indicating that the reaction is promoted by more basic carboxylate ligands. On the other hand, the corresponding assessment of steric effects (Figure 3d) exhibits a very poor correlation (R^2 = 0.02), indicating that steric effects of the carboxylate ligand play little role in ^{4F}BnOH oxidation.

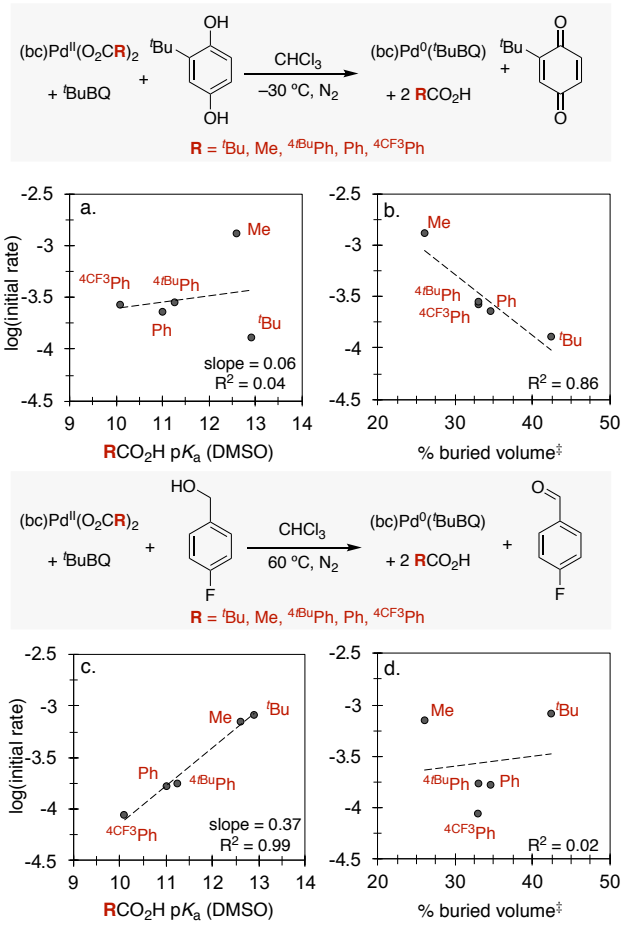


Figure 3. Rate dependence of ^{4F}BnOH oxidation by (bc)Pd(O_2CR)$_2$ on (a) pK_a (DMSO) of RCO_2H and (b) on percent buried volume. Rate dependence of ^{t}BuH_2Q oxidation by (bc)Pd(O_2CR)$_2$ on (c) pK_a (DMSO) of RCO_2H and (d) on percent buried volume. ‡Percent buried volume values obtained from PR_3 ligands (see text for details).

The studies described thus far have employed different temperatures for investigation of ^{t}BuH_2Q and ^{4F}BnOH oxidation reactions, -30 °C and 60 °C, respectively. These different temperatures highlight the faster rate of ^{t}BuH_2Q oxidation. In order to permit quantitative comparison at a single temperature, both reactions were analyzed over a range of temperatures, from -40 – 0 °C for ^{t}BuH_2Q and +30 – +60 °C for ^{4F}BnOH. The resulting data were then subjected to Eyring analysis to obtain activation free energies at 298 K: $\Delta G^{\ddagger}_{tBuH2Q}$(298 K) = 17.1 kcal/mol and $\Delta G^{\ddagger}_{4FBnOH}$(298 K) = 23.1 kcal/mol. The values, which quantify the kinetic facility of ^{t}BuH_2Q

over ^{4F}BnOH oxidation may be compared to the overall reaction free energies of reaction with (bc)Pd(OAc)$_2$, which strongly favor ^{4F}BnOH over ^{t}BuH$_2$Q oxidation: $\Delta G°_{tBuH2Q}$(298 K) = –2.9 kcal/mol[20] and $\Delta G°_{4FBnOH}$(298 K) = approx. –22 kcal/mol (the latter estimated from the difference in reported reduction potentials of ^{t}BuBQ and benzaldehyde[24,25]). Both sets of energetic values are depicted in the energy diagram in Figure 4.

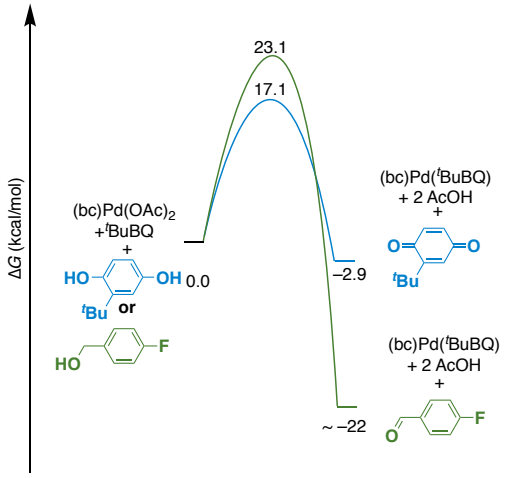
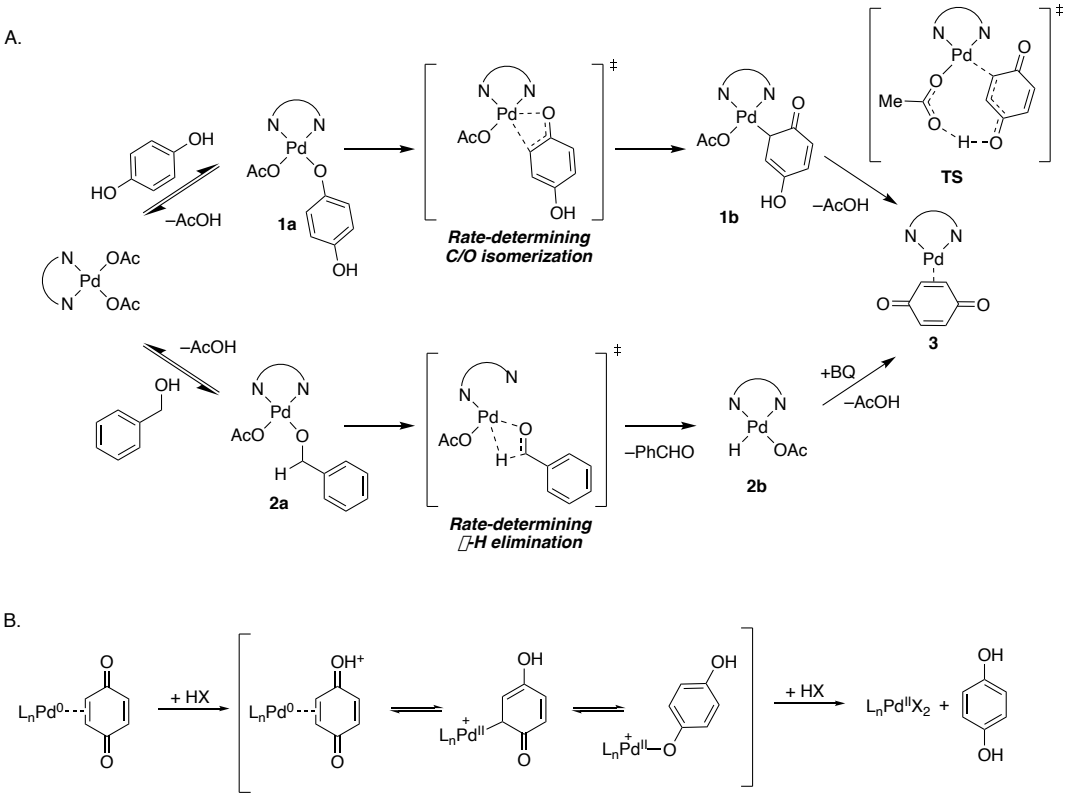


Figure 4. Free energy diagram for (bc)Pd(OAc)$_2$-mediated oxidation of ^{4F}BnOH and ^{t}BuH$_2$Q.

Mechanistic analysis. The kinetic data elaborated above provide a foundation for understanding the origin of the contra-thermodynamic outcome depicted in Figure 4. The data reveal both similarities and differences between (bc)Pd(OAc)$_2$-mediated oxidation of ^{t}BuH$_2$Q and ^{4F}BnOH. Both reactions feature a first-order dependence on [(bc)Pd(OAc)$_2$] and [substrate], but they exhibit different KIEs and show different electronic and steric effects. Mechanisms that rationalize these observations are depicted in Scheme 4A.

Scheme 4. Proposed Mechanisms for (A) Hydroquinone and Benzyl Alcohol Oxidation Mediated by (bc)Pd(OAc)$_2$ and (B) Oxidation of Pd^0 by Benzoquinone in the Presence of Acid[21]



Oxidation of ^{t}BuH$_2$Q by (bc)Pd(OAc)$_2$ (Scheme 4A, top) is proposed to begin with formation of a Pd^{II}-(*O*-hydroquinonate) species **1a** via proton-coupled ligand exchange[30] between acetate and ^{t}BuH$_2$Q, followed by rate-limiting isomerization to the Pd^{II}-(*C*-hydroquinonate) species **1b**. These steps rationalize (a) the rate law, with a first order dependence on [Pd] and [^{t}BuH$_2$Q], and (b) the lack of a primary kinetic isotope effect, since H/D reactivity is incorporated in an equilibrium step expected to have negligible equilibrium isotope effect. The lack of systematic correlation between the rate and carboxylate pK_a suggests proton transfer steps are not involved in the rate-limiting step, while the carboxylate steric influence, favoring less sterically hindered carboxylates, is rationalized by rate-limiting isomerization of the hydroquinonate to the more hindered *C*-bound isomer **1b**. The reaction concludes with an intramolecular redox reaction involving proton transfer from the phenolic O–H of **1b** to the carboxylate, coupled to two-electron transfer to Pd. This step

forms the (bc)Pd^0(BQ) product **3**. This mechanism corresponds to the microscopic reverse of the mechanism proposed by Bäckvall for acid-promoted oxidation of well-defined Pd^0(BQ) complexes (Scheme 4B).[21]

The oxidation of ^{4F}BnOH (Scheme 4A, bottom) is similarly proposed to begin with proton-coupled exchange of ^{4F}BnOH with acetate at (bc)$Pd(OAc)_2$ to generate Pd-alkoxide **1b**. The kinetic isotope effect data, however, suggest that β-hydride elimination to generate Pd^{II}-hydride **2b** is rate-limiting. The electronic dependence on the carboxylate ligand suggests that formation of the Pd^{II}-alkoxide **2a** also contributes the reaction rate.[6] Subsequent loss (formally, reductive elimination) of acetic acid from **2b** in the presence of ^{t}BuBQ forms the Pd-quinone product **3**. The kinetic facility of this step,[40] enhanced further by the ability of quinones to promote H–O_2CR reductive elimination from Pd^{II}(H)(O_2CR) complexes,[41] rationalizes the zero-order dependence of the reaction rate on [^{t}BuBQ].

To summarize, ^{4F}BnOH oxidation has a significantly higher kinetic barrier than ^{t}BuH_2Q oxidation, even though the net reaction of ^{4F}BnOH is more favorable by approximately 20 kcal/mol. At least two factors support faster rates of ^{t}BuH_2Q oxidation. The first step in both reactions involves proton-coupled ligand substitution between the substrate and a carboxylate ligand, and H_2Q is significantly more acidic than benzyl alcohol (aqueous pK_a value of H_2Q is ~5 units lower than the pK_a of benzyl alcohol).[42,43] Thus, the pre-equilibrium formation of a Pd^{II}-hydroquinonate intermediate will be strongly favored relative to formation of a Pd^{II}-alkoxide. The difference in relative rates, however, ultimately arises from the difference in relative energies of the rate-limiting transition states. The data indicate that the transition state for hydroquinonate isomerization is lower in energy than the transition state for Pd^{II}-alkoxide β-hydride elimination. Net hydride transfer from the hydroquinonate intermediate, involving proton transfer to

carboxylate and two-electron transfer to Pd, is sufficiently facile that it proceeds after the rate-limiting isomerization step. This step is undoubtedly facilitated by the polarity of the O–H bond of the hydroquinonate, which facilitates proton transfer, relative to cleavage of the C–H bond involved in β-hydride elimination from the alkoxide.[44]

Conclusions

The mechanistic studies of (bc)Pd(OAc)$_2$-mediated oxidation of ^{4F}BnOH and ^{t}BuH$_2$Q outlined above illuminate the kinetic and thermodynamic relationships between these reactions. The oxidation of ^{4F}BnOH is approximately 20 kcal/mol more favorable than the oxidation of ^{t}BuH$_2$Q. Nonetheless, the activation energy for ^{4F}BnOH oxidation is substantially higher than that for ^{t}BuH$_2$Q oxidation ($\Delta\Delta G^{\ddagger}$ = 6 kcal/mol), resulting in ^{t}BuH$_2$Q oxidation proceeding several orders of magnitude faster than ^{4F}BnOH oxidation at room temperature. Mechanistic data provide insights into the different rate-limiting steps for these reactions, which feature β-hydride elimination for ^{4F}BnOH oxidation and isomerization from an *O*-to-*C*-bound hydroquinonate in ^{t}BuH$_2$Q oxidation. This study represents the first mechanistic analysis of hydroquinone by Pd^{II} complexes, and it was made possible by the identification of ancillary ligands that increasing the Pd$^{II/0}$ redox potential sufficiently to support oxidation of hydroquinones.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website: Experimental details and compound characterization data (PDF).

AUTHOR INFORMATION

Corresponding Author

Shannon S. Stahl – Department of Chemistry, University of Wisconsin−Madison, Madison, Wisconsin 53706, United States; orcid.org/0000-0002-9000-7665; Email: stahl@chem.wisc.edu

Authors

David L. Bruns – Department of Chemistry, University of Wisconsin−Madison, Madison, Wisconsin 53706, United States; orcid.org/0000-0003-2455-502X

Notes

The authors declare no competing financial interests.

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22. An earlier precedent features Pd^{II}-mediated oxidation of hydroquinone in the absence of a secondary oxidant, although the thermodynamics are likely influenced by the formation of

metallic Pd as the final product. See the following: Coe, J. S.; Rispoli, P. L. Kinetics of the Oxidation of Benzene-1,4-Diol by Palladium(II) Compounds in Aqueous Solution. *J. Chem. Soc.*, *Dalton. Trans.* **1976**, 2215-2218.

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25. The estimated standard potential for benzyl alcohol oxidation under the present conditions is deduced from the difference between previously reported standard potentials for PhCHO/$PhCH_2OH$ and BQ/H_2Q. Although this estimate is imperfect, any errors (e.g., due to relative differences in solvation energy) are expected to be relatively minor and will not alter the analysis here. See the following references: (a) Wang, Y.; Gonell, S.; Mathiyazhagan, U. R.; Liu, Y.; Wang, D.; Miller, A. J. M.; Meyer, T. J. Simultaneous Electrosynthesis of Syngas and an Aldehyde from CO_2 and an Alcohol by Molecular Electrocatalysis. *ACS Appl. Energy Mater*. **2019**, *2*, 97-101. (b) Nutting, J. E.; Gerken, J. B.; Stamoulis, A. G.; Bruns, D. L.; Stahl, S. S. "How Should I Think about Voltage? What is Overpotential?": Establishing an Organic Chemistry Intuition for Electrochemistry. *J. Org. Chem.* **2021**, *86*, 15875-15885.
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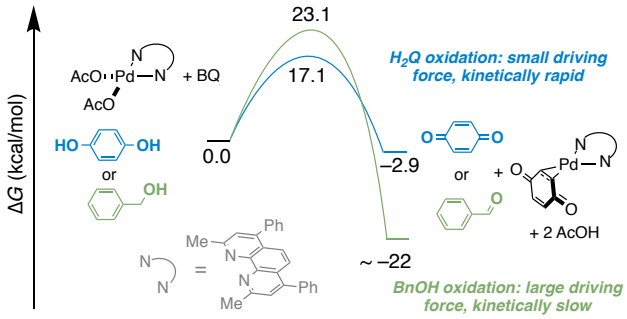
TOC Graphic


ΔG (kcal/mol)
23.1
17.1
0.0
–2.9
~ –22
+ BQ
+ 2 AcOH
or
or
H2Q oxidation: small driving force, kinetically rapid
BnOH oxidation: large driving force, kinetically slow