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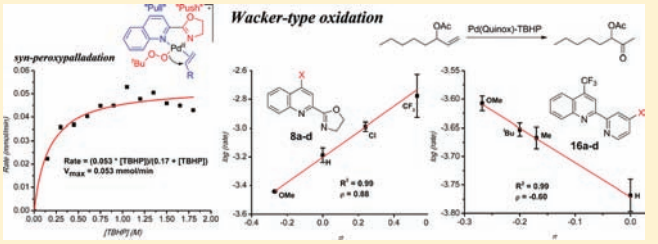
On the Mechanism of the Palladium-Catalyzed *tert*-Butylhydroperoxide-Mediated Wacker-Type Oxidation of Alkenes Using Quinoline-2-Oxazoline Ligands

Brian W. Michel, Laura D. Steffens, and Matthew S. Sigman*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112, United States

Supporting Information

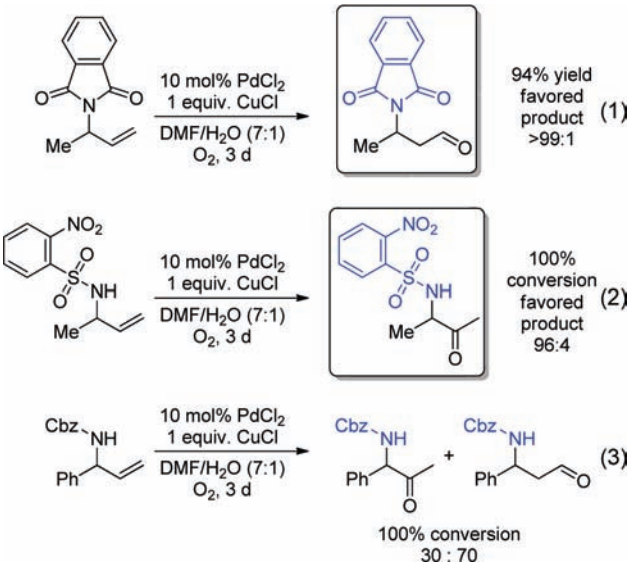
ABSTRACT: The mechanism of the *tert*-butylhydroperoxide-mediated, Pd(Quinox)-catalyzed Wacker-type oxidation was investigated to evaluate the hypothesis that a selective catalyst-controlled oxidation could be achieved by rendering the palladium coordinatively saturated using a bidentate amine ligand. The unique role of the Quinox ligand framework was probed via systematic ligand modifications. The modified ligands were evaluated through quantitative Hammett analysis, which supports a "push−pull" relationship between the electronically asymmetric quinoline and oxazoline ligand modules.



INTRODUCTION

The Wacker oxidation under Tsuji's modified conditions provides the means for a facile conversion of a variety of terminal olefins to methyl ketones.[1−4] Despite the simplicity and general functional group tolerance of this method, substrates bearing proximal heteroatoms are well-documented to provide mixtures of Markovnikov (ketone) and anti-Markovnikov (aldehyde) products in a generally unpredictable distribution.[5−8] It has been proposed that the anti-Markovnikov products arise from a secondary coordination of the adjacent Lewis-basic group, which disfavors Markovnikov oxypalladation (Figure 1a). This substrate control is highlighted by the recent work by Feringa and co-workers,[6] where allylic phthalimide-containing substrates provide high selectivity for the aldehyde product (eq 1). In contrast, substrates bearing a nosyl-protected allylic amine provide predominately the ketone product (eq 2). Further, some protecting groups, such as Cbz, provide mixtures of ketone and aldehyde (eq 3).

In addition to the empirical observation that the Wacker oxidation is under substrate control, the precise nature of oxypalladation (*syn* vs *anti*) has been a topic of considerable debate for >45 years.[9−16] It has been shown that the nature of oxypalladation can be dependent on [Cl^-] or other ligands such as organic oxidants like benzoquinone used in the redox manifold. A key mischievous participant in the Wacker oxidation is copper. Hosokawa and co-workers have isolated heterobimetallic Pd−Cu species, which can participate in the transfer of an oxygen atom to an olefin providing a methyl ketone, indicating that copper has a greater role than simply facilitating the reoxidation of Pd(0) to Pd(II).[17,18] In this regard, we have recently published an experimental and computational mechanistic investigation of a copper-free ligand-modulated Wacker oxidation,[19,20] where it was proposed, in agreement with other computational studies,[16,21,22] that oxypalladation proceeds through a hydrogen-bonded network of three water molecules (Figure 1b). Ultimately, to solve the problem of selective oxidation in substrates bearing proximal heteroatoms, the nature of oxypalladation is expected to be crucial; therefore, a mechanistically well-defined system is necessary.



In a system distinct from the classic Wacker oxidation, Mimoun and others have reported methods which are proposed to proceed through peroxometal species of platinum,[23] rhodium,[24,25] or palladium,[26−32] via either direct activation

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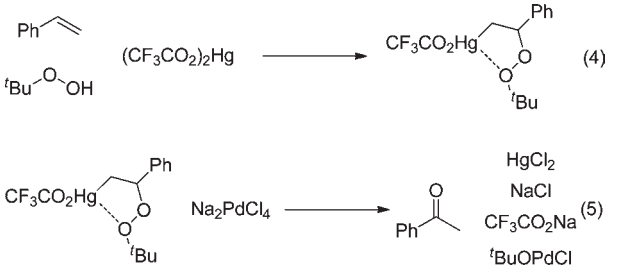
of molecular oxygen or the use of hydro- and alkylperoxides. Of particular relevance to our system was a series of *tert*-butylperoxidepalladium(II) carboxylate complexes for the stoichiometric oxidation of terminal olefins to methyl ketones.[28] These complexes were isolable as tetrameric units of the formula $[RCO_2PdOO^tBu]_4$ (R = CH_3, CCl_3, CF_3, C_5F_{11}), and their structures were confirmed by X-ray crystallography. With the exception of the R = CH_3 complex, these reagents were found to stoichiometrically convert 1-hexene to 2-hexanone. Notable characteristics of this oxidation are the following: (1) the rate of oxidation increases as a function of the electron-withdrawing ability of the carboxylate; (2) no palladium metal precipitate was observed; (3) only methyl ketones were observed as products; (4) *tert*-butanol is formed in the same stoichiometry as ketone product; and (5) σ-donor ligands such as pyridine, HMPA, 2,2′-bipyridine, and Ph_3P inhibit the reaction and decompose the complexes.

From these observations, Mimoun proposes the mechanism shown in Scheme 1, where *tert*-butylperoxidepalladium(II) carboxylate complex **A** initially coordinates the olefin to give **B**. Next, peroxymetalation gives the pseudopalladacyclic species **C**, which can decompose with heterolytic O−O bond cleavage to give the methyl ketone product and *tert*-butoxypalladium species **D**. In the absence of excess *tert*-butylhydroperoxide (TBHP), a second olefin will substitute for *tert*-butanol, leading to the π-allyl complex **E**. However, in the presence of excess TBHP, this system was rendered catalytic. Unfortunately, the details of the catalytic system have not been disclosed.[33]

The source of the oxygen atom incorporated into the product has been further queried by isotopic labeling studies performed by Mimoun and co-workers,[26] and recently in a similar system from our laboratory (Figure 2a).[34] Specifically, the reaction was performed with anhydrous TBHP[35] in the presence of $^{18}OH_2$, and monitoring of the isotopic incorporation demonstrated that TBHP is the main source of oxygen in the product (Figure 2b). Additionally, it was determined that the hydrogen atoms from the substrate are conserved in the product, which was probed via the oxidation of α-deuteriostyrene.

To further support this mechanism, Mimoun and co-workers prepared the stable mercurial *tert*-butylperoxide styrene adduct, which has been shown to have a pseudometallocyclic structure similar to that proposed in the analogous palladium intermediate (eq 4).[36,37] This mercurial peroxy complex can undergo transmetalation with palladium to presumably form the unstable peroxypalladium species, which decomposes to provide acetophenone (eq 5). The evidence provided by Mimoun and co-workers, along with similarities of the proposed intermediates to related closed peroxometallic adducts,[38,39] strongly suggests an inner coordination sphere *syn*-palladation mechanism.



Initial Hypothesis. As an ongoing goal of our research to development ligand-modulated Pd(II)-catalyzed alkene functionalization reactions,[4,20,34,40−46] we were interested in developing catalysts for the Wacker oxidation of classically challenging substrates such as allylic alcohol derivatives.[47] Our initial hypothesis thus was to design a catalyst that utilizes an alkyl peroxide and the proposed *syn*-peroxypalladation mechanism. Specifically, if secondary substrate coordination is blocked with a bidentate ligand (Figure 1c), the substrate should exhibit exclusive Markonikov

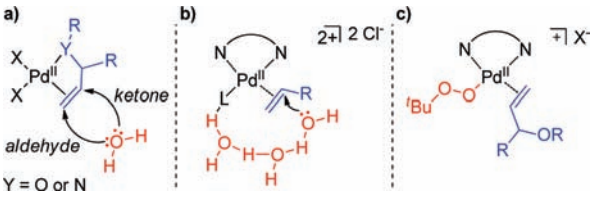


Figure 1. (a) Proximal Lewis-basic groups proposed to chelate to palladium resulting in mixtures of products. (b) Oxypalladation may occur through a hydrogen-bonding network of three water molecules. (c) Hypothesized coordinatively saturated palladium complex with anionic *tert*-butylperoxide ligand.

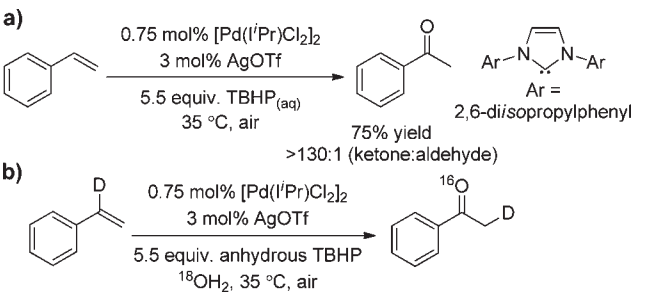
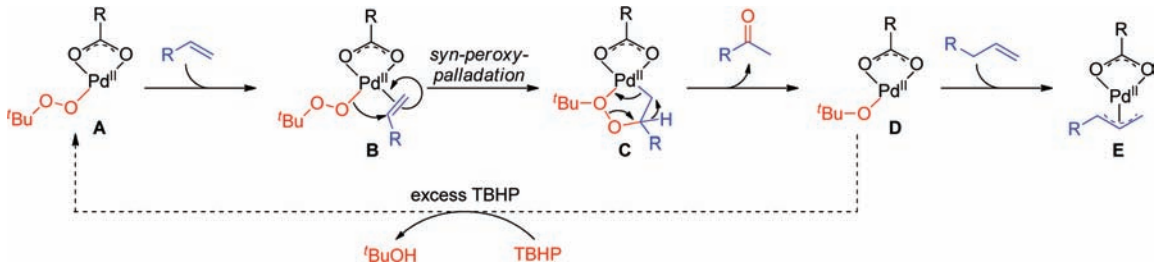


Figure 2. (a) Previously reported oxidation of styrenes using TBHP as the terminal oxidant. (b) Reaction performed with anhydrous TBHP and $^{18}OH_2$ shows that the rate of ^{18}O incorporation in the product under the reaction conditions is the same as the rate of washing ^{18}O into the product via hydrate formation. Use of α-deuteriostyrene shows that the hydrogen atoms in the substrate are maintained in the product.

Scheme 1. Mechanism Proposed by Mimoun



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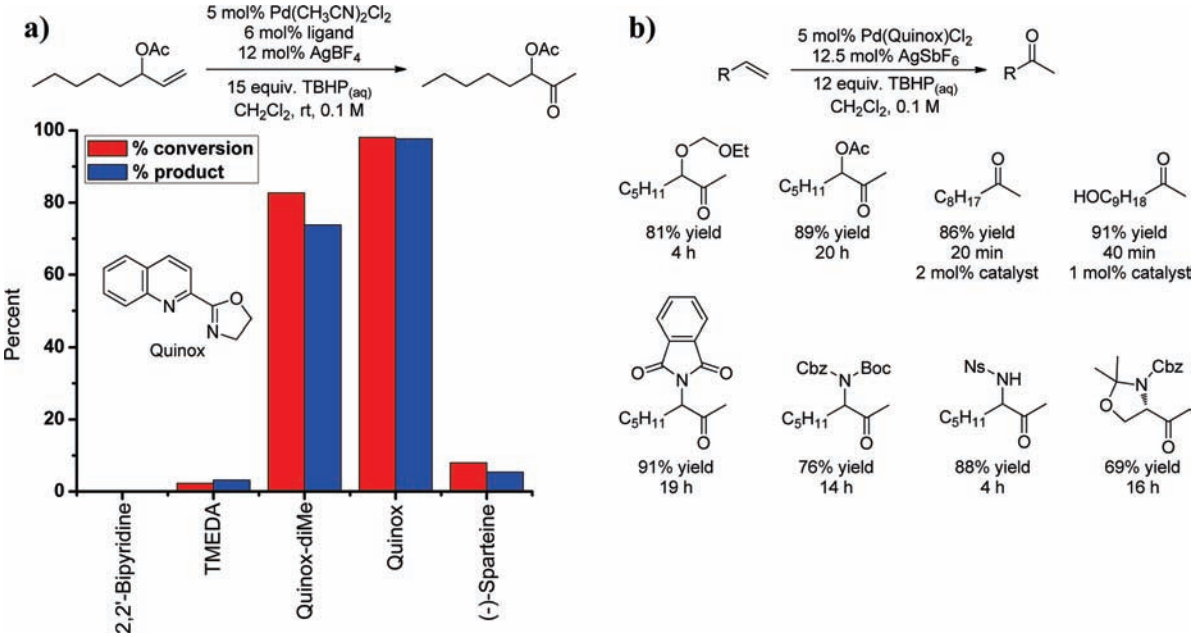

Figure 3. (a) Evaluation of bidentate amine ligands for the TBHP-mediated Wacker-type oxidation. (b) Summary of substrate scope.

selectivity, based on the results of Mimoun. While we were skeptical due to the loss of reactivity observed by Mimoun and co-workers in the presence of σ-donor ligands,[28] related ligand-modulated systems have been reported by Uemura[30] and our group,[34] where a peroxide is presumably the nucleophile. Therefore, several common bidentate amine ligands were evaluated and found to provide little to no product and sluggish rates of reaction in our initial screening.[40] However, ligands with the quinoline-2-oxazoline (Quinox) structure led to rapid consumption of substrate and significant and selective ketone formation (Figure 3a). Empirical optimization yielded a general, highly active Wacker-type oxidation catalyst system, which can convert diverse terminal olefin substrates bearing proximal heteroatoms to their corresponding methyl ketone products (Figure 3b).[41] Considering the synthetic utility of this Wacker oxidation and its uniqueness as compared to the prior accounts by Mimoun and the diverse examples of the Tsuji–Wacker oxidation,[3] a mechanistic investigation was initiated with a particular focus of gaining further insight into the origin of selectivity and the underlying features of the Quinox ligand scaffold essential for catalysis. Herein, based on kinetic analysis, we report evidence for a *syn*-peroxypalladation. Additionally, an investigation into the particular effectiveness of the Quinox ligand reveals that an electronic disparity of the electron-poor quinoline ring as compared to the electron-rich oxazoline is required for efficient catalysis.

RESULTS AND DISCUSSION

Kinetic Experiments. Although the general mechanism suggested by Mimoun for TBHP-mediated Wacker oxidations has been supported by various studies discussed above, additional reasonable mechanistic possibilities are depicted in Scheme 2. In a mechanism analogous to the one proposed by Mimoun, a dicationic palladium species **F**, which is formed in situ by treatment of Pd(Quinox)Cl_2 with a Ag salt, pre-coordinates a TBHP molecule to provide the cationic intermediate **G**. Subsequent coordination of the olefin to give **H** and *syn*-peroxypalladation leads to the pseudopalladacyclic species **I**, which can undergo heterolytic cleavage of the O–O bond with a concomitant 1,2-hydride shift to give product and the *tert*-butoxypalladium species **J**. Intermediate **G** can be regenerated via exchange with another equivalent of TBHP. It should be noted that Pd does not change formal oxidation states during this process.

Alternatively, initial olefin coordination to **F** could lead to intermediate **K**. From **K**, there are two plausible pathways. In one case, TBHP would coordinate to **K** to give the familiar intermediate **H**, which would follow the previously described pathway through **I** and **J**, ultimately returning to **K** through ligand exchange. A second possibility from **K** would be an intermolecular *trans*-peroxypalladation providing **L**, which would need to subsequently reorganize to give intermediate **I**. This pathway would again proceed through **J**.

To exclude some of these plausible mechanisms, the initial rates of reaction were monitored (to ~10–15% conversion/product formation, which is typically >5 turnovers of the catalyst) to determine the reaction order for all involved reactants under synthetically relevant conditions. It was found that the reaction was first order in [Pd(Quinox)-$(SbF_6)_2$] and [olefin], whereas [TBHP] showed saturation kinetics (Figure 4a–c).[48] These results logically support a mechanism with initial reversible coordination of TBHP prior to substrate binding. Specifically, increasing [THBP] results in a faster rate, until a certain point, where increasing [TBHP] leads to no further acceleration of the reaction. The observation of saturation in [TBHP] and first order in [alkene] contradicts the mechanisms that invoke initial alkene coordination prior to TBHP involvement. If the alkene coordinates prior to TBHP involvement, then it should be possible to reach a point at which increasing [alkene] no longer increases the rate (a build up of an intermediate similar to **F**). However, since saturation was observed for [TBHP] and not observed over the practical ranges of [alkene] used in these experiments, it is likely that TBHP coordination occurs before coordination of the alkene.[49] It should be noted that, in contrast to our previously reported system for the oxidation of styrenes using *N*-heterocyclic carbene

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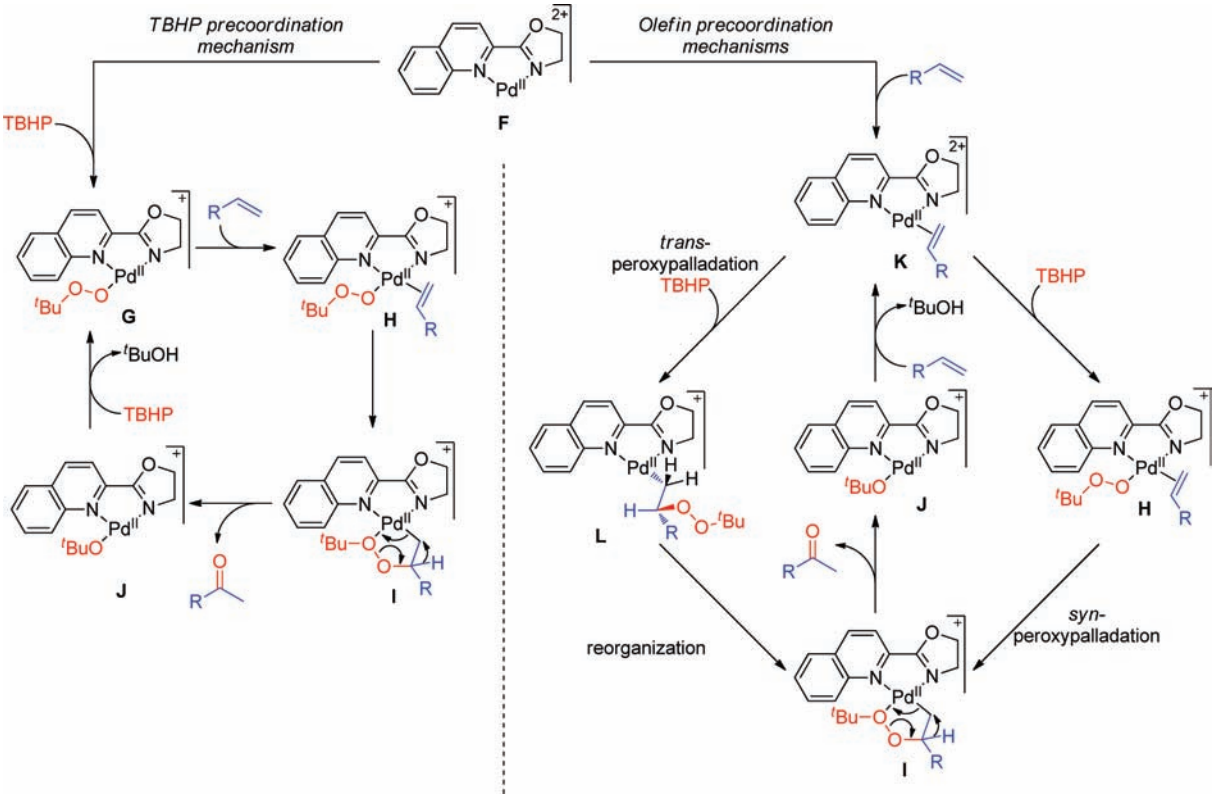
Scheme 2. Possible Mechanisms



ligands, this system was found to have no dependence on [water] (Figure 4d). Importantly, >0.25 M water is required for successful catalysis, where possible roles are solubilizing reagent(s) and/or stabilizing the highly electrophilic palladium as ligands. Additionally, proton-transfer steps have been omitted from the present discussion. Mimoun and co-workers observed formation of the *tert*-butylperoxide palladium complex (PPT), with no O−H stretch observable by IR.[28] Therefore, it is likely that deprotonation is facile to give intermediate **G** in our similar system.[50]

Based on the observed initial rates, olefin coordination or subsequent peroxypalladation are possible turnover-limiting steps. As expected, at high [TBHP], derived rate laws are indistinguishable.[51] A cationic complex with the composition of **G** was identified by MS analysis (in the absence of alkene),[51] which lends credence to the initial association of TBHP prior to alkene coordination.

As many of the intermediates are cationic in nature, the Lewis acidity of the catalyst was examined by counterion metathesis with different silver salts in the oxidation of 4-methylstyrene. Plotting initial rate versus pK_a of the conjugate acid for each non-coordinating counterion (Figure 5a),[52] the resulting linear free energy relationship gives a slope of −0.04 over a wide range of pK_a values, indicating that the counterion has a modest effect on initial rate. Not surprisingly, based on possible turnover-limiting alkene binding, the most electrophilic catalyst containing the most non-coordinating counterion, SbF_6^-, leads to the highest initial rates. It should be noted that the use of a slight excess of the silver salt is to ensure that there are at least two equivalents relative to palladium. The reaction shows no change in initial rates when using excess silver salt as compared to using precisely 2.0 equiv.[51]

Considering the effect of the counterion, one may anticipate that a good Lewis base, like the ketone product, may act as a competitive inhibitor in the reaction. Indeed, even though the empirical rate suggests a pseudo-first-order reaction, the log alkene consumption versus time is not linear after ∼30% conversion, consistent with secondary processes influencing catalysis.[53] To probe this, 4-methylstyrene was oxidized in the presence of exogenous acetophenone. As more acetophenone was added, the observed initial rate was found to decrease (Figure 5b); however, the magnitude of this inhibition is minor relative to the overall rate of reaction. Even when [inhibitor] is 10 times [substrate], the rate is only modestly decreased (∼33%), which indicates that the product is a relatively poor inhibitor and that some other secondary process must be responsible for the catalyst deactivation.

Catalyst Stability Studies. Over the course of the reaction, Pd(Quinox)-TBHP is deactivated, so that catalyst reuse has not been feasible. Unfortunately, due to the insolubility of the precatalyst Pd(Quinox)Cl_2 and instability of other species, in situ NMR analysis of the catalytic system limited our ability to extract meaningful information. Therefore, ligand modification studies are the primary focus of the investigation into the nature and fate of the catalyst. While the exact nature of catalyst deactivation remains elusive, two possibilities were probed via ligand modification: ligand oxidation or hydrolysis under the reaction conditions. One possibility is that the oxazoline ring of **1** can undergo oxidation to provide the quinoline-oxazole **2**. To address the possibility of oxazoline oxidation, ligands **2** and **3** were synthesized (Scheme 3), where **2** could be the result of

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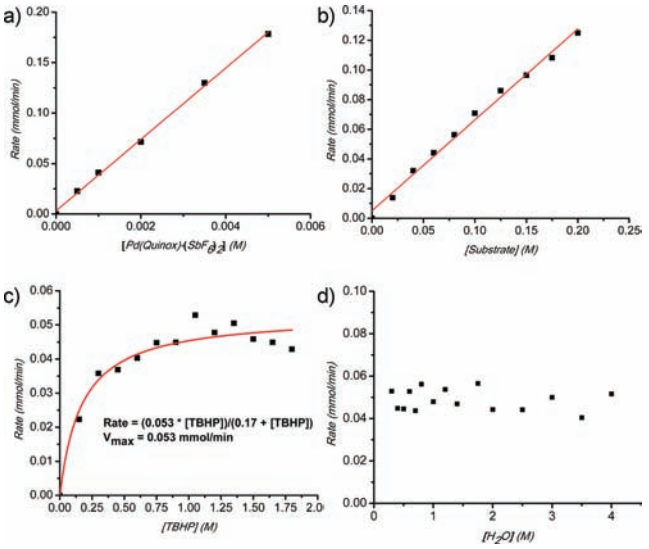

Figure 4. Initial rates to determine dependencies. (a) Conditions: [Pd(Quinox)Cl_2] = 0 to 5 × 10^{-3} M; [$AgSbF_6$] = 2.5 × [Pd(Quinox)Cl_2]; aqueous [TBHP] = 1.2 M; [alkene] = 0.05 M; CH_2Cl_2; rt. (b) Conditions: [Pd(Quinox)Cl_2] = 2 × 10^{-3} M; [$AgSbF_6$] = 5 × 10^{-3} M; aqueous [TBHP] = 3.0 M; [alkene] = 0 to 0.2 M; CH_2Cl_2; rt. (c) Conditions: [Pd(Quinox)Cl_2] = 2 × 10^{-3} M; [$AgSbF_6$] = 5 × 10^{-3} M; anhydrous [TBHP] = 0 to 1.80 M; [H_2O] = 2.5 M; [alkene] = 0.045 M; CH_2Cl_2; rt. (d) Conditions: [Pd(Quinox)Cl_2] = 2 × 10^{-3} M; [$AgSbF_6$] = 5 × 10^{-3} M; anhydrous [TBHP] = 1.2 M; [H_2O] = 0.3 − 4.0 M; [alkene] = 0.05 M; CH_2Cl_2; rt.

oxazoline ring oxidation, while **3** should not be able to undergo oxidation of the oxazoline ring. These ligands were evaluated and compared with Quinox (Table 1). The quinoline-2-oxazole was prepared via a Stille cross-coupling of 2-bromoquinoline **4** with the known stannane **5**.[54] The Quinox analogue **3** was synthesized through the amide and cyclized with $BF_3 \cdot Et_2O$. Both **2** and **3** were able to act as competent ligands but did not show any significant change in TON. This indicates that oxidation of the oxazoline moiety to the oxazole is inconsequential, should it occur during the course of the reaction. Another alternative could be hydrolysis of the oxazoline **1** to the amide **6**, which is not a competent catalyst. This possibility is not supported by the observation that **2**, which should be less prone to hydrolysis due to the aromatic nature of the oxazole ring, does not exhibit an enhanced TON. Mimoun and co-workers observed the formation of Pd-π-allyl dimers which resulted in insoluble precipitates. Additionally, μ-hydroxo or other bridging dimers could be formed over the course of the reaction. These dimers may be catalytically deactivated, incompetent, or insoluble in the reaction media.[55] Unfortunately, MS analysis for π-allyl species or bridging dimers was inconclusive.

Unique Nature of Quinox. While the kinetic evidence gathered supports the proposed mechanism of TBHP pre-coordination, followed by olefin coordination and subsequent *syn*-peroxymetalation, the question remains as to why the Quinox structure is required for catalysis. In the initial optimization, similar ligands in terms of chelate size and general electronic structure, such as 2,2′-bipyridine (BIPY), were found to be ineffective (Figure 3a). This is in agreement with Mimoun's stoichiometric work with *tert*-butylperoxidepalladium(II)carboxylate complexes, where σ-donor ligands such as pyridine, BIPY, HMPA, and Ph_3P were all observed to prevent methyl ketone

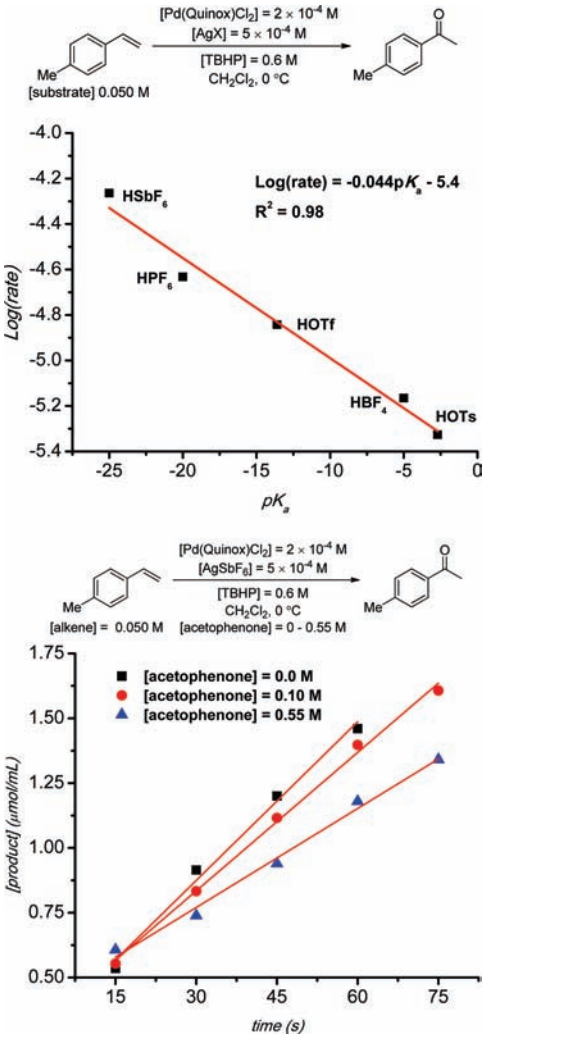

Figure 5. (a) Plot of the log of the rate as a function of counterion conjugate acid pK_a. (b) Evaluation of inhibitor concentration on initial rate of reaction.

product formation.[28] Therefore, it is interesting that the Quinox-ligated palladium complexes lead to effective catalysis.

One hypothesis is that the electronically asymmetric nature of Quinox is responsible for the success of the system; specifically, the quinoline ring acts as a relatively electron-poor ligand as compared to the relatively electron-rich oxazoline moiety. This electronic disparity should lead to a well-defined coordination sphere **H**, where anionic *tert*-butylperoxide should prefer to bind *trans* to the oxazoline and the more electrophilic site, *trans* to the quinoline, should bind the alkene (Figure 6a). However, it is prudent to consider the alternative possibility (**N**), where the *tert*-butylperoxide binds *trans* to the quinoline and the olefin binds *trans* to the oxazoline (Figure 6b).

To gain insight into the coordination sphere of the Pd(Quinox) system, electronic variance in the substrate and ligand was investigated. In the olefin coordination step (**G** → **H**), a more electron-rich olefin should lead to an increase in rate of reaction based on the proposed mechanism. The initial rates of product formation for electronically disparate styrene derivatives were measured, and a Hammett plot was constructed (Figure 7). A ρ value of −1.29 was observed when fitting the plot from

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Scheme 3. Synthesis of Quinoline-2-oxazole (2) and Quinoline-2-(5,5-dimethyloxazoline) (3)

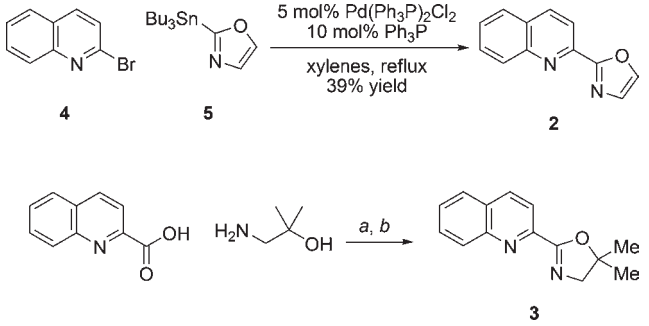
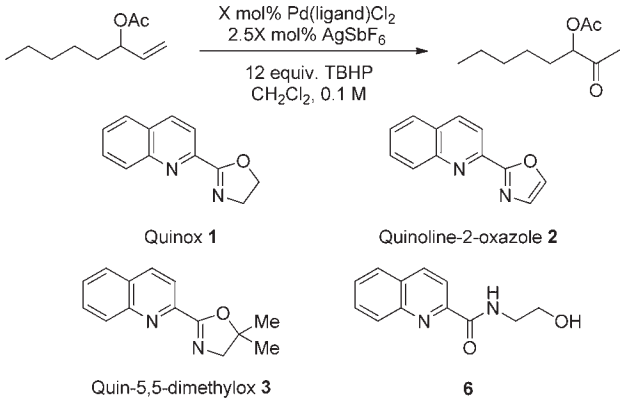


Table 1. Evaluation of Ligands for Insight into Catalyst Deactivation



ligand	X (mol % cat.)	time (h)	% conv[a]	% prod[b]	TON[c]
1	5.0	16	97	93	19
1	1.0	16	78	43	43
2	5.0	3	95	86	17
2	1.0	16	54	42	42
3	5.0	16	>99	97	19
3	1.0	16	74	43	43
6	5.0	24	5	0.4	0.1

[a] % conversions calculated by GC integrations, comparing peak areas to 10 wt % dodecane internal standard. [b] % product calculated by GC integrations and corrected by an independently determined response factor. [c] Turnover number (TON) = mmol of product/mmol of catalyst.

X = AcO through X = Me; however, a faster rate than predicted was observed for 4-methoxystyrene. This could indicate a change in mechanism or turnover-limiting step for highly electron-releasing substituents on the alkene. It is interesting to note that, when the Hammett plot was constructed using the σ_ρ^+ value for 4-methoxystyrene, a linear relationship was observed with an almost identical slope (ρ = 1.33). These results indicate a Lewis-acid/Lewis-base interaction between the cationic palladium and the alkene, conceivably *trans* to the quinoline ring.

To further probe a *trans* relationship between the alkene and the quinoline ring, a series of electronically distinct 4-substituted quinoline oxazolines were synthesized through various routes, as depicted

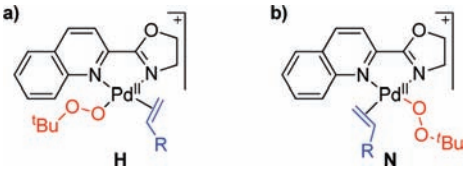


Figure 6. (a) Proposed coordination model of the penultimate intermediate prior to oxypalladation. (b) Alternative possible coordination model of the penultimate intermediate prior to oxypalladation.

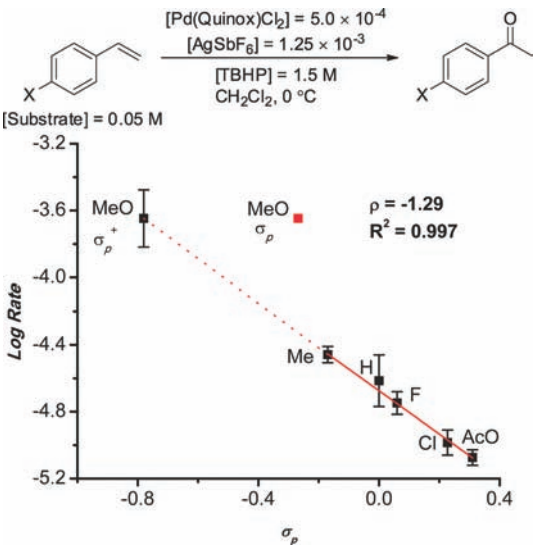


Figure 7. Hammett analysis of electronically disparate styrenes. For 4-methoxystyrene the σ_ρ^+ value provides a good linear fit, which is nearly identical to a plot with that substrate omitted. The σ_ρ value for 4-methoxystyrene is also plotted to highlight its deviation from linearity.

in Scheme 4. As we have previously reported for the synthesis of Quinox, an Anderson coupling with 2-chloroethylamine, followed by a solvent switch and basification, leads to facile formation of the Quinox ligands (**8a** and **8b**) from the commercially available quinaldic acids (X = H, **7a**; OMe, **7b**).[41] For the synthesis of the trifluoromethyl analogue **8c**, a reported procedure was followed to give access to 2-bromo-4-trifluoromethylquinoline **10**;[56,57] however, in our hands the lithium−halogen exchange and subsequent quenching with CO_2 (and other electrophiles) was ineffective, and despite exhaustive attempts, none of the carboxylic acid **7c** was obtained. Alternatively, it was found that the electron-deficient 2-bromoquinoline was an excellent partner for cross-coupling with Pd(0), where carbonylation was achieved yielding the methyl ester **11**.[58] Subsequent saponification provided the requisite acid **7c**, which led to the desired 4-CF_3-Quinox **8c**. An alternative method was utilized to obtain the 4-Cl-Quinox derivative **8d**. Urea hydrogen peroxide in the presence of trifluoroacetic anhydride converted 4-chloroquinoline **12** to *N*-oxide **13**,[59] which was reacted with benzoyl chloride and silver cyanide to provide the 2-carbonitrile-4-chloroquinoline **14** in excellent yield.[60] Basic and anhydrous methanol affords the methyl imidate **15**, which can subsequently be converted to 4-Cl-Quinox **8d** by treatment with ethanolamine.[61]

Using the isolated palladium(II) complexes of these quinoline derivatives, the initial rates were measured. By plotting the log of the observed initial rates as a function of Hammett σ_p values, a linear free energy relationship with ρ = 0.88 (Figure 8a) is

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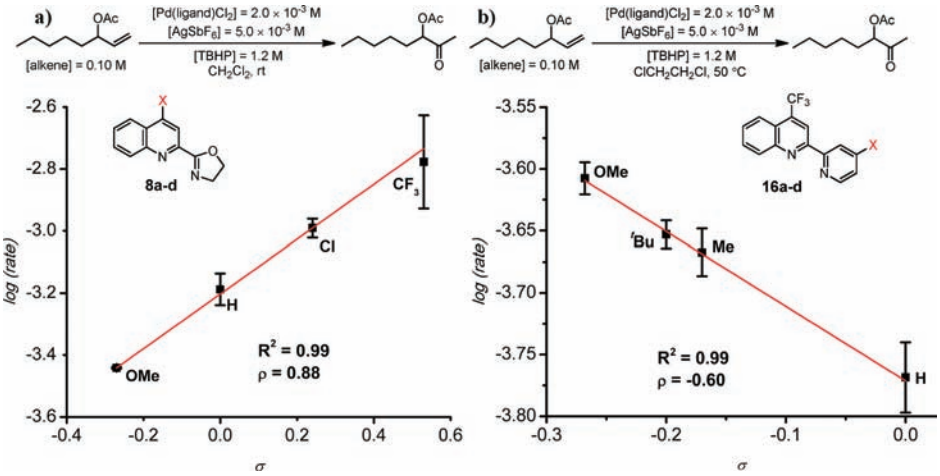
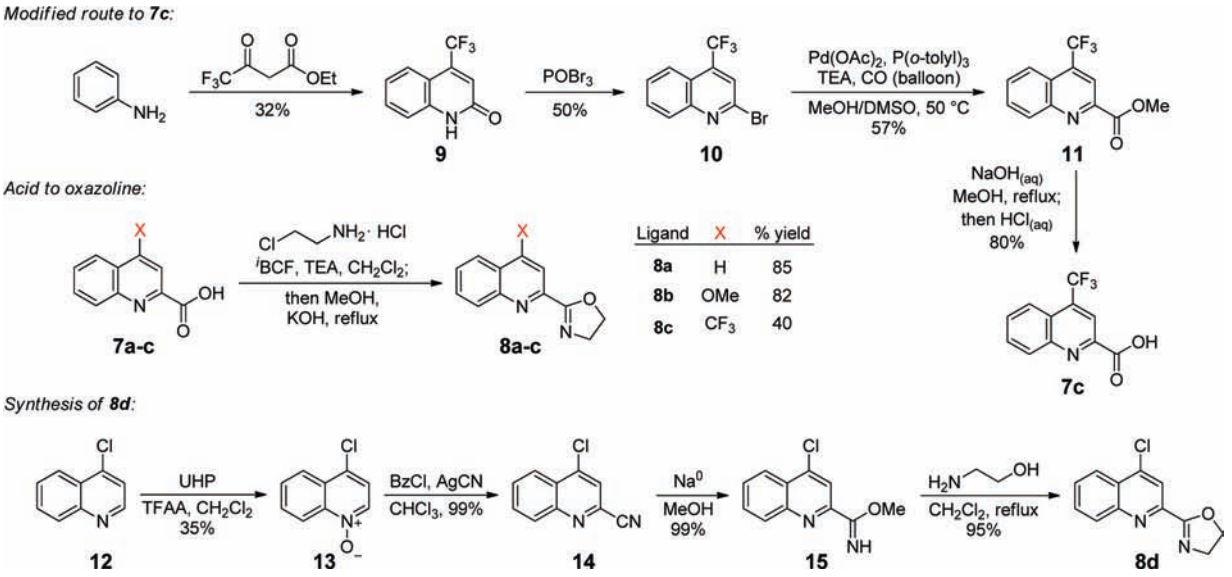


Figure 8. (a) Linear free energy relationship observed for plotting the log(rate) for a series of 4-substituted Quinox ligands **8a**−**d** as a function of Hammett σ_p values. (b) Linear free energy relationship observed for plotting the log(rate) for a series of ligands **16a**−**d** as a function of Hammett σ_p values.

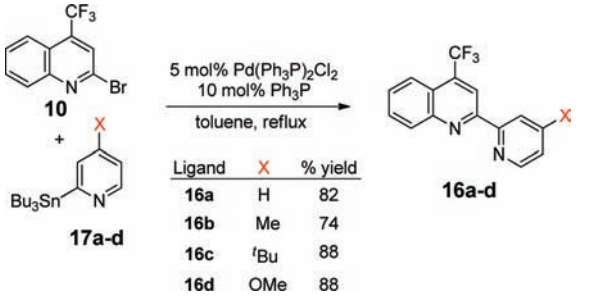
Scheme 4. Synthesis of 4-Substituted Quinox Ligands



observed, which implies that a more electron-poor palladium center reacts faster with the alkene. These data are consistent with the Hammett correlation for the electronic nature of the alkene and further support the proposed *trans* coordination of the alkene with the quinoline moiety.[62]

Since a systematic evaluation of oxazoline electronic parameters is difficult to envision, a series of quinoline-2-pyridyl ligands were synthesized to probe the "electron-rich" ligating group (Scheme 5). To ensure that the quinoline ring was the "electron-poor" module, the 4-trifluoromethylquinoline moiety was utilized. Ligands **16a**−**d** were easily prepared via a Stille cross-coupling reaction between 2-bromo-4-trifluoromethylquinoline **10** and the respective stannanes **17a**−**d**.[63] The 2-stannylpyridines **17a**−**d** were either commercially available or prepared via a reported directed lithiation procedure.[64,65] It was found that, while these ligands proved less active in modulating catalysis, considerable conversion and product formation were observed at 50 °C with 3-acetoxyoct-1-ene. Therefore, under

Scheme 5. Stille Cross-Coupling Preparation of 4-Quinoline-2-(4-pyridyl) Ligands



slightly modified reaction conditions, the initial rates were measured, and the log of the initial rates was plotted as a function of Hammett σ_p values (Figure 8b). Again, a linear free energy

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relationship is observed, with a ρ value of opposite sign and similar magnitude (−0.60). Accordingly, upon modification of the more electron-donating portion of the ligand, greater electron-donating ability leads to increased rate of reaction. This further supports coordination of the anionic *tert*-butylperoxide *trans* to the more donating portion of the ligand (i.e., the oxazoline). Should the coordination environment exist as it is depicted in **N**, then the trends in the ligand Hammett studies would be expected to be opposite of what is observed.

CONCLUSION

In conclusion, the proposed mechanism for the TBHP-mediated Wacker-type oxidation of olefins was supported by initial rate kinetics. Saturation in TBHP is in concert with *syn*-peroxypalladation by *tert*-butylperoxide, which agrees with the analogous mechanism proposed by Mimoun and co-workers. The electrophilicity of the catalyst was found to have a direct influence on reactivity, as indicated by a linear free energy relationship between the rate of reaction and the pK_a of the counterions' conjugate acids. Product inhibition was observed; however, this effect was negligible even in the presence of a large excess of ketone inhibitor. The initial hypothesis has been supported, in that a well-defined oxypalladation mechanism in conjunction with a suitable ligand for blocking secondary substrate coordination leads to a selective Wacker-type oxidation. It was found that an electronic disparity between the two modules of the ligand (i.e., the quinoline and the oxazoline) was a necessary characteristic for efficient catalysis. In this regard, analysis of substrate reactivity and ligand modification was used to support the "push−pull" hypothesis through quantitative Hammett analyses. The more complete understanding of this mechanism, and specifically the requirements for an electronically asymmetric ligand design, should benefit our endeavors to rationally develop new alkene functionalization reactions.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, kinetic data, and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
sigman@chem.utah.edu

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