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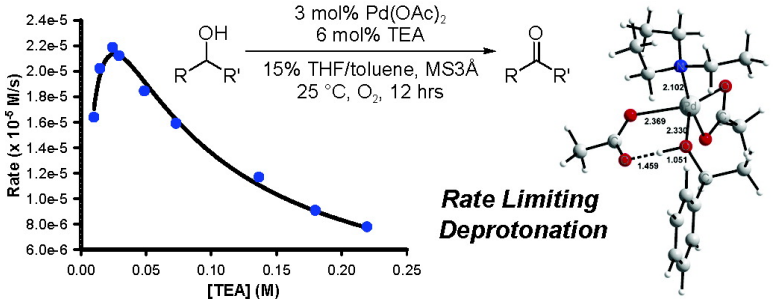

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Using Mechanistic and Computational Studies To Explain Ligand Effects in the Palladium-Catalyzed Aerobic Oxidation of Alcohols

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Abstract: The experimental and computational mechanistic details of the $Pd(OAc)_2$/TEA-catalyzed aerobic alcohol oxidation system are disclosed. Measurement of various kinetic isotope effects and the activation parameters as well as rate law derivation support rate-limiting deprotonation of the palladium-coordinated alcohol. Rate-limiting deprotonation of the alcohol is contrary to the majority of related kinetic studies for Pd-catalyzed aerobic oxidation of alcohols, which propose rate-limiting β-hydride elimination. This difference in the rate-limiting step is supported by the computational model, which predicts the activation energy for deprotonation is 3 kcal/mol higher than the activation energy for β-hydride elimination. The computational features of the similar $Pd(OAc)_2$/pyridine system were also elucidated. Details of the study illustrate that the use of TEA results in an active catalyst that has only one ligand bound to the Pd, resulting in a significant lowering of the activation energy for β-hydride elimination and, therefore, a catalyst that is active at room temperature.

Introduction

The report by Uemura and co-workers[1] of ligand-accelerated catalysis in a Pd-catalyzed aerobic oxidation of an alcohol has stimulated intense investigation into ligand-modulated Pd(II) catalysis.[2−4] Specifically, Uemura found that the addition of tertiary amines, especially pyridine, afforded an effective catalyst system for the aerobic alcohol oxidation at 80 °C. To improve on this system, we found through empirical screening that a closely related system, in which triethylamine (TEA) is substituted for pyridine, can be rendered active at room temperature. $Pd(OAc)_2$/TEA has proven particularly useful in the aerobic oxidation of a broad scope of functionalized substrates.[5] Of principle consideration, it was found that the use of pyridine as an additive resulted in no oxidation under these mild conditions. While the switch from pyridine to triethylamine appears subtle, the considerable difference in catalytic activity raises an important question about ligand effects in the Pd(II)-catalyzed aerobic alcohol oxidations and potentially in the broader context of Pd catalysis. Therefore, we have undertaken an experimental and computational study[6] to elucidate the mechanistic details of the $Pd(OAc)_2$/TEA-catalyzed aerobic alcohol oxidation. Herein, we present these results and a comparison to the recent elegant mechanistic study by Stahl and co-workers of the Pd-$(OAc)_2$/pyridine system[7] to provide a deeper fundamental

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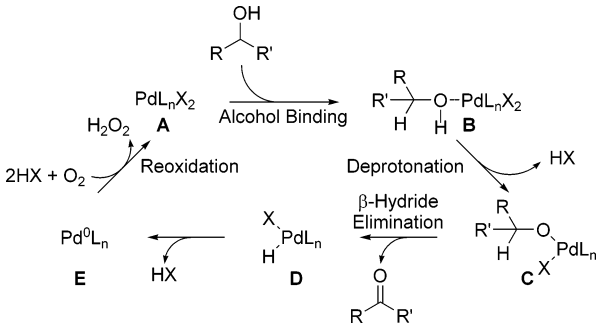
(6) For computational studies performed on this system, see refs 7b, 8g, 8h, and 8j.

Scheme 1. General Proposed Mechanism for the Pd-Catalyzed Aerobic Alcohol Oxidation



understanding of ligand effects in Pd(II)-catalyzed aerobic alcohol oxidations.

Kinetic Studies

Kinetic Studies. Through mechanistic studies of Pd-catalyzed aerobic alcohol oxidations, a generally accepted mechanism has been proposed (Scheme 1).[8] Starting with a Pd(II) catalyst, the alcohol binds to form a Pd-bound alcohol species (**B**). This is followed by deprotonation of the Pd-bound alcohol to form a Pd-alkoxide (**C**), which then undergoes β-hydride elimination to form the product and a Pd-hydride species (**D**). The Pd-hydride reductively eliminates 1 equiv of HX to form Pd(0) (**E**), followed by reoxidation with molecular oxygen and 2 equiv of acid to re-form the active catalyst and hydrogen peroxide.

β-Hydride elimination has been proposed to be the rate-limiting step in the majority of oxidation systems studied to date. This includes the systems derived from $Pd(OAc)_2$/pyridine, $Pd(PhenS)(OAc)_2$,[9] $Pd((-)\text{-sparteine})Cl_2$ at high base, and $Pd(IiPr)(OAc)_2(H_2O)$[10] with added acid. There are two exceptions to this: Larock's system, $Pd(OAc)_2$/DMSO, in which rate-limiting Pd(0) reoxidation is proposed and the $Pd((-)\text{-sparteine})Cl_2$ system under low base conditions in which rate-limiting alcohol deprotonation is proposed. Due to the similarities to the $Pd(OAc)_2$/pyridine system, it was initially hypothesized that the rate-limiting step for the $Pd(OAc)_2$/TEA system would also be β-hydride elimination.

To initiate the kinetic study, the reaction order for each reagent was determined. The dependence of oxidation rate on [*sec*-phenethyl alcohol] (0.09 to 0.32 M) showed a nonlinear dependence which fits to an equation describing simple saturation (Figure 1). The dependence of oxidation rate on [catalyst], with a constant $Pd(OAc)_2$/TEA ratio, was found to be first order in the range 0.006−0.014 M (Figure 2). Together, these data

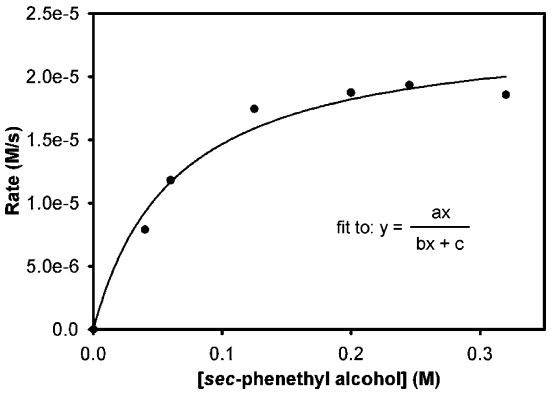


Figure 1. Rate dependence on [*sec*-phenethyl alcohol] at room temperature. Conditions: 0.09−032 M *sec*-phenethyl alcohol, 0.005 M $Pd(OAc)_2$, 0.01 M TEA, 15% THF/toluene, Na_2SO_4, and a balloon charged with O_2.

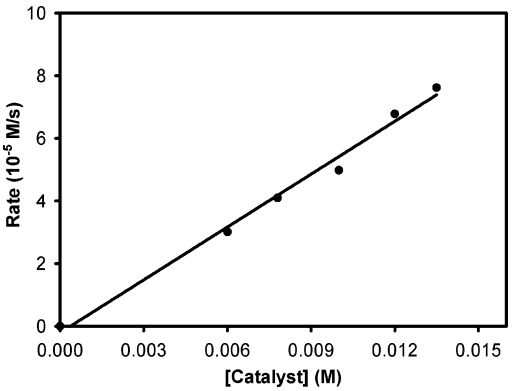


Figure 2. Dependence of reaction rate on [$Pd(OAc)_2$/TEA] at room temperature. Conditions: 0.3 M *sec*-phenethyl alcohol, 0.006−0.014 M $Pd(OAc)_2$, 0.012−0.28 M TEA, 15% THF/toluene, Na_2SO_4, and a balloon charged with O_2.

support a rate-limiting step in which both catalyst and alcohol are involved and, therefore, rule out the reoxidation of Pd(0) as rate determining. Since the observed saturation kinetics in [alcohol] point toward a pre-equilibrium between catalyst and substrate, it is unlikely that alcohol binding is rate determining. Thus, the initial kinetic studies point toward either rate-limiting alcohol deprotonation or β-hydride elimination.

Measuring the dependence of oxidation rate on [TEA] reveals an intriguing relationship. Initial addition of TEA increases oxidation rate, while high concentrations of TEA show an inhibitory effect on the rate of oxidation (Figure 3).[11] This finding is similar to Stahl's report on the [pyridine] dependence on oxidation rate in the $Pd(OAc)_2$/pyridine system.[7] To further understand the effect of added TEA, an NMR study was undertaken. An ^1H NMR spectrum of the reaction mixture, without alcohol present, shows three Pd species present: $Pd(OAc)_2$, $Pd(OAc)_2(TEA)$, and $Pd(OAc)_2(TEA)_2$ (eq 1). This is in contrast to the addition of pyridine to $Pd(OAc)_2$, which results in a single observable species, attributed to $Pd(OAc)_2(pyridine)_2$ (eq 2).

$$\underset{\mathbf{1}}{Pd(OAc)_2} \rightleftharpoons \underset{\mathbf{2}}{Pd(OAc)_2(TEA)} \rightleftharpoons \underset{\mathbf{3}}{Pd(OAc)_2(TEA)_2} \quad (1)$$

$$\underset{\mathbf{1}}{Pd(OAc)_2} \rightleftharpoons \underset{\mathbf{4}}{Pd(OAc)_2(pyridine)_2} \quad (2)$$

During the initial optimization of the $Pd(OAc)_2$/TEA system, using a solvent mixture of THF/toluene provided for the ideal

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(9) PhenS = bathophenanthroline disulfonate, see ref 3e.

(10) IiPr = 1,3-Bis(2,6-diisopropylphenyl)-2,3-dihydro-1*H*-imidazole, see ref 3h.

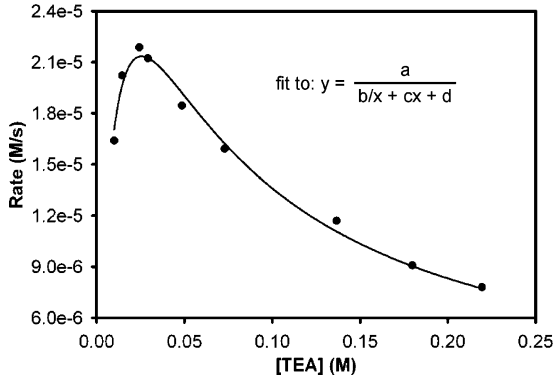


Figure 3. Dependence of reaction rate on triethylamine concentration at room temperature. Conditions: 0.4 M *sec*-phenethyl alcohol, 0.005 M Pd(OAc)$_2$, 0.01−0.22 M TEA, 15% THF/toluene, Na_2SO_4, and a balloon charged with O_2.

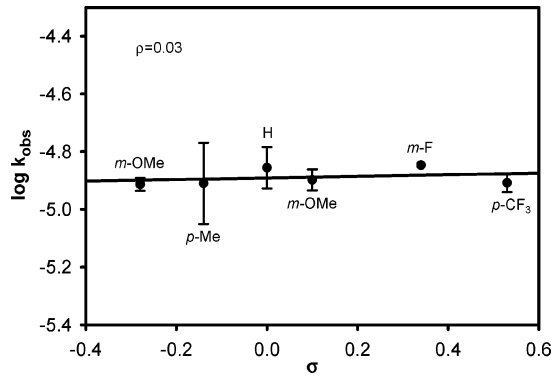
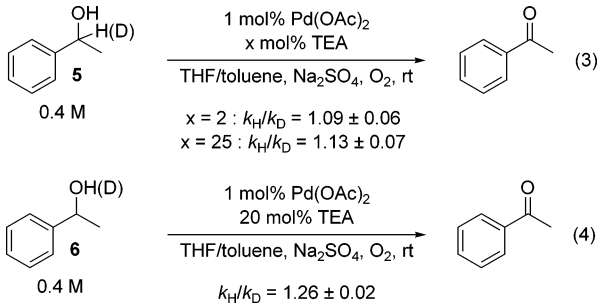


Figure 4. Log k_{obs} vs σ of benzyl alcohols at room temperature. Conditions: 0.4 M alcohol, 0.004 M Pd(OAc)$_2$, 0.008 M TEA in THF/toluene with Na_2SO_4 under a balloon of O_2.

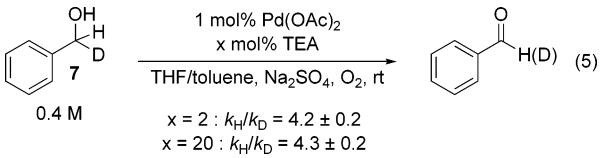
combination of oxidation rate and turnover number. Considering the pre-equilibrium observed for TEA and Pd(OAc)$_2$, it may be possible that THF is participating in a similar process. To probe this possibility, the reaction dependence on [THF] was measured, and it was found that there is no dependence of initial oxidation rate on [THF] from 0.074 to 1.85 M (1−15% THF/toluene). This supports a hypothesis that THF is important for long-term catalyst stability by presumably supporting Pd(0) species before or during reoxidation and that THF is not involved in another pre-equilibrium.

Hammett Correlation. To probe the nature of the transition state, the rate of oxidation of several benzyl alcohol derivatives was measured. The experiment was performed at high concentration of alcohol (0.4 M) to ensure saturation with the hope of solely evaluating the rate-limiting step. A linear free energy relationship was observed with a calculated ρ-value of 0.03 (Figure 4). This ρ-value varies dramatically from the previously measured values for the Pd((−)-sparteine)Cl$_2$ at high base ($\rho = -1.41$, $\rho^+ = -1.0$)[8e] and the Pd(IiPr)(OAc)$_2$(H$_2$O) ($\rho = -0.48$)[8h] oxidation systems, which all had negative ρ-values, implicating rate-limiting β-hydride elimination. This change in ρ-value indicates that the rate-limiting step for the oxidation with the TEA system is different from these other oxidations.

Activation Parameters. To gain additional understanding, the activation parameters were determined by measuring the rate of oxidation of *sec*-phenethyl alcohol from 23 to 47 °C with $\Delta G^{\ddagger} = 20.8 \pm 0.6$ at 25 °C, $\Delta H^{\ddagger} = 10.0 \pm 0.5$, and $\Delta S^{\ddagger} = -36 \pm 2$. The small $\Delta H^{\ddagger}$ and large negative $\Delta S^{\ddagger}$ values compare favorably with the Pd((−)-sparteine)Cl$_2$ at low base,[8e] where $\Delta H^{\ddagger} = 11.5 \pm 0.7$ and $\Delta S^{\ddagger} = -24.5 \pm 2$ for the oxidation of benzyl alcohol. Under these conditions, rate-limiting deprotonation from a bound alcohol was proposed. In addition, the enthalpy and entropy of activation differ significantly from both the Pd((−)-sparteine)Cl$_2$ system at high base[8e] ($\Delta H^{\ddagger} = 20.3 \pm 0.9$ and $\Delta S^{\ddagger} = -5.4 \pm 2.7$ for the oxidation of benzyl alcohol) and the Pd(IiPr)(OAc)$_2$(H$_2$O) system[8h] ($\Delta H^{\ddagger} = 20.1 \pm 0.5$ and $\Delta S^{\ddagger} = -3.5 \pm 1.6$ for the oxidation of *sec*-phenethyl alcohol), which both have proposed rate-limiting β-hydride elimination.



Kinetic Isotope Effects. Considering the unique nature of the rate dependence on [TEA], the KIE was measured at two limiting TEA concentrations for the oxidation of *sec*-phenethyl alcohol. At high [TEA], the KIE was measured to be 1.13 ± 0.07, and at low [TEA], the KIE was measured to be 1.09 ± 0.06 (eq 3). These KIEs are within error of each other, supporting no change in rate-determining step at differing [TEA]. Additionally, the KIEs are small compared to the observed KIEs for other Pd-catalyzed aerobic alcohol oxidation systems such as the Pd(OAc)$_2$/pyridine[7] (KIE = 1.5 ± 0.3 for benzyl alcohol), the Pd(IiPr)(OAc)$_2$(H$_2$O)[8h] (KIE = 5.5 ± 0.1 for *sec*-phenethyl alcohol), the Pd((−)-sparteine)Cl$_2$ at high base[8e] (KIE = 1.31 ± 0.04 for *sec*-phenethyl alcohol), and the Pd(PhenS)(OAc)$_2$[8c] (KIE = 1.4 for *sec*-phenethyl alcohol) systems, which all propose rate-limiting β-hydride elimination. This suggests the rate-determining step for this system is deprotonation of the Pd-bound alcohol instead of β-hydride elimination. To further investigate this possibility, the oxidation rates of both *sec*-phenethyl alcohol and *sec*-phenethylalcoh(d-ol), **6**, were measured (eq 4). A KIE of 1.26 ± 0.02 is observed, providing further evidence that deprotonation of the Pd-bound alcohol is the rate-determining step.

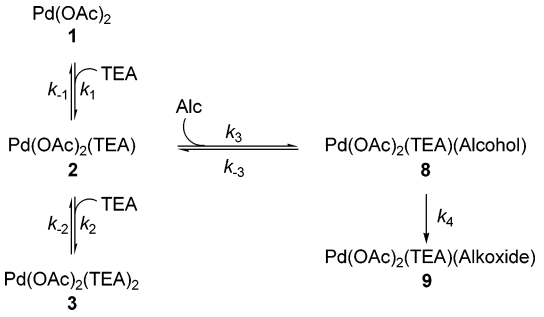


After establishing that alcohol deprotonation is most likely the rate-determining step, we chose to probe the nature of β-hydride elimination by measuring the intrinsic KIE using alcohol **7**. Since the substrate has both a C−H and C−D bond, the kinetic consequence of C−H(D) breakage via β-hydride elimination can be measured by the incorporation of H/D into

(11) Upon discovering this dependence on oxidation rate on [TEA], the alcohol dependence was measured at high [TEA] (Pd:TEA = 1:20) and saturation kinetics were observed as well.

product. Thus, a KIE of β-hydride elimination can be elucidated even though it is post rate limiting. Using alcohol **7**, it was found that the intrinsic KIE is 4.2 ± 0.2 and 4.3 ± 0.2 at low and high [TEA], respectively (eq 5).[12] This intrinsic isotope effect is large relative to other KIEs measured for related systems except for that measured using the $Pd(IiPr)(OAc)_2(H_2O)$[8h] oxidation system (KIE = 5.5 ± 0.1). In the case of $Pd(IiPr)(OAc)_2(H_2O)$, it was proposed that the KIE was large due to the presence of a readily available coordination site leading to greater C−H bond breakage in the β-hydride elimination transition state (vide infra). By analogy, the large intrinsic isotope effect supports a mechanism wherein only one TEA is bound to the Pd to afford an accessible coordination site prior to β-hydride elimination.

Scheme 2. Revised Proposed Mechanism of the $Pd(OAc)_2$/TEA Oxidation System



Revised Mechanism and Rate Law Derivation. The kinetic studies support, contrary to our initial hypothesis, that deprotonation of the Pd-bound alcohol is the rate-determining step. Additionally, the pre-equilibrium of TEA with $Pd(OAc)_2$ and the inhibition of the oxidation rate at high [TEA] implicate the active catalyst contains only one TEA molecule. Therefore, a revised, detailed mechanism is proposed wherein complex **2** is the active catalyst that binds the alcohol prior to deprotonation (Scheme 2). Inhibition by TEA occurs through the pre-equilibrium shifting toward **3** at high TEA concentrations. Initial acceleration by addition of small amounts of TEA can be explained by shifting the equilibrium toward **2** from **1**. Last, saturation can be accounted for by a buildup of intermediate **8** prior to rate-limiting deprotonation.

$$\text{rate} = \frac{K_{eq3}k_4[\text{Alc}][\text{Pdt}]}{\left(\frac{1}{K_{eq1}[\text{TEA}]}\right) + 1 + K_{eq2}[\text{TEA}] + K_{eq3}[\text{Alc}]} \quad (6)$$

To verify this mechanistic model, a rate law was derived (eq 6). The derived rate law qualitatively describes the analysis outlined above. However, a quantitative model can be obtained by fitting the derived rate law to the observed dependence of oxidation rate on [TEA] (Figure 3). This nonlinear fit is an excellent model for the observed data and allows for the extraction of all rate and equilibrium constants for this oxidation reaction (Table 1). The relative magnitude of these constants agree well with the kinetic model. The rate constants show that K_{eq2} is much larger than K_{eq1}, which agrees with the NMR data showing **3** as the dominant species in the pre-equilibrium (Table 1). K_{eq3} is an order of magnitude smaller than K_{eq2}, which accounts for saturation in [alcohol].

Table 1. Calculated Rate Constants

	K_{eq1} (M^{-1})	K_{eq2} (M^{-1})	K_{eq3} (M^{-1})	k_4 (s^{-1})
value	1.4 ± 0.2	1070 ± 85	121 ± 24	0.009 ± 0.003

Theoretical Studies

Using kinetic studies, we found by switching the ligand in the Pd-catalyzed aerobic oxidation of alcohols from pyridine to TEA, the rate-determining step changes from β-hydride elimination to deprotonation of the alcohol. Interpretation of the kinetic data led to the proposal that this change in rate-determining step may be due to the number of ligands on Pd during the reaction course (one versus two). To gain further insight into the difference between one and two ligands on Pd as well as a more precise identification of the relevant intermediates and transition states, computational studies were undertaken.

Technical Details. The calculations of the intermediates for catalytic alcohol oxidation were performed as follows. First, geometry optimizations of all intermediate complexes and transition states were carried out using the B3LYP functional[13] with the lacvp*/6-31G(d) basis set.[14,15] All degrees of freedom were optimized, and only positive vibrational frequencies were obtained at the optimized geometries. Transition states obtained were characterized by the presence of exactly one imaginary vibrational frequency along the appropriate normal mode.

In the second step, B3LYP energies were evaluated for the optimized geometry using a larger triple-ζ basis, lacv3p*+/6-311+G(d), with additional diffuse and polarization functions. All computations were performed with the Jaguar v4.0 suite of ab initio quantum chemistry programs.[16] Solvent (toluene) was represented with the following parameters: $\epsilon = 2.379$ and probe radius $r_p = 2.762$ Å. Gas-phase-optimized structures were used in the solvation calculations within the self-consistent reaction field model as implemented in the Jaguar computational package.[17]

Finally, complete thermochemical analysis and additional transition state searches were performed with the Gaussian 98[18] computational package within the restricted DFT/B3LYP level of theory and with the LanL2DZ[14] basis set. The structures of the intermediate complexes and transition states were reoptimized with this basis set prior to the computation of harmonic vibrational frequencies at the B3LYP/LanL2DZ level.[19]

Thermochemical Analysis of the Reaction Pathway. Since the kinetic studies indicate the number of ligands on Pd during

(12) One possibility that cannot be ruled out in the current study is direct transfer of the hydride from the palladium alkoxide to the acetate ligand.

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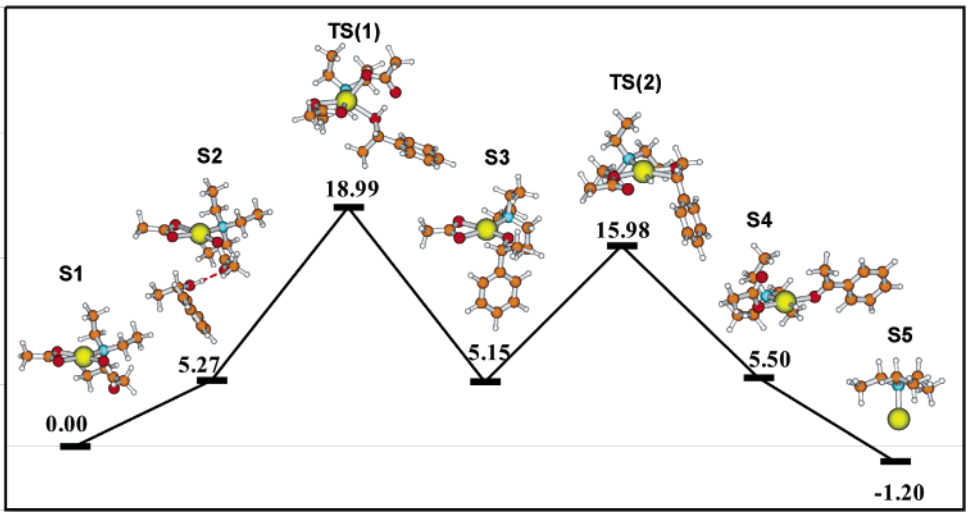

Figure 5. Complete Gibbs free energy profile of 1-*sec*-phenethyl oxidation catalyzed by $Pd(OAc)_2(TEA)$. All energies are in kcal/mol. **S1** through **S5** enumerate intermediate complexes, while **TS(1)** and **TS(2)** refer to deprotonation and β-hydride elimination transition states, respectively.

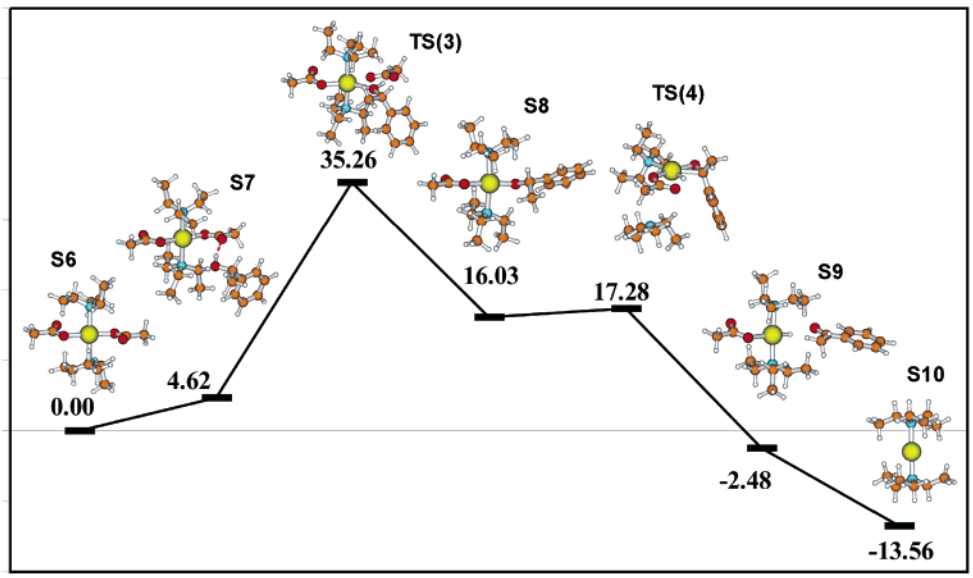

Figure 6. Complete Gibbs free energy profile of 1-*sec*-phenethyl oxidation catalyzed by $Pd(OAc)_2(TEA)_2$. All energies are in kcal/mol. **S6** through **S10** enumerate intermediate complexes, while **TS(3)** and **TS(4)** refer to deprotonation and β-hydride elimination transition states, respectively.

the oxidation could affect the rate-limiting step, the reaction pathway was analyzed under three separate conditions: (1) with no TEA bound to Pd, (2) with one TEA bound to Pd, and (3) with two TEAs bound to Pd. The results of these studies are also directly compared to the $Pd(OAc)_2$/pyridine system to help elucidate key differences between the two oxidation systems.

Overview of Reaction Pathway. The Gibbs free energy profile for the conditions with one TEA bound to the Pd shows two distinct transition states, with alcohol deprotonation being slightly higher in energy then β-hydride elimination (Figure 5). However, with two molecules of TEA bound to Pd there is a large increase in the energy of the transition state for deprotonation while the β-hydride elimination step remains relatively the same (Figure 6). Interestingly, the first intermediate in the energy profiles for both processes show the alcohol initially hydrogen bonding to the carbonyl oxygen of the acetate ligand (**S2** and **S7**). While this species was not clearly observable in NMR experiments, Stahl proposed a similar species for the Pd-$(OAc)_2$/pyridine system which was observed via ^{1}H NMR.[7] Additionally, Privalov and co-workers have identified via computation related intermediates for various aerobic alcohol oxidations.[8j]

The energy profile with one TEA bound to Pd is in good agreement with the kinetic studies performed. Even though the deprotonation and β-hydride elimination transition states are close in energy, the prediction that deprotonation is higher in energy than β-hydride elimination agrees with the experimentally determined rate-limiting step. This is showcased by the relative energetics of the highest barrier, deprotonation, being in good agreement with an experimental $\Delta G^{\ddagger} = 20.8 \pm 0.6$ kcal/mol and a computationally predicted $\Delta G^{\ddagger} = 19$ kcal/mol.

Alcohol Binding. Examining the specific details of individual intermediates and transition states and comparison to the experimental data provide a more detailed understanding of this reaction. As a first step, the relative energies of the three pre-equilibrium species observed via ^{1}H NMR were calculated and were qualitatively similar to those calculated using the derived rate law fit of the [TEA] dependence.

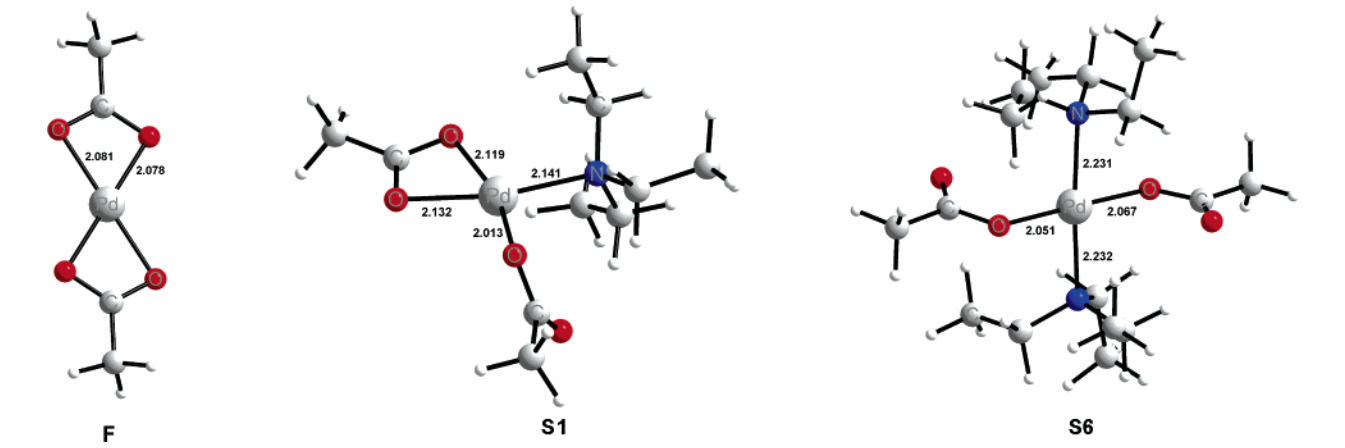

Figure 7. Optimized structures of Pd species from eq 1. All distances are in Å.

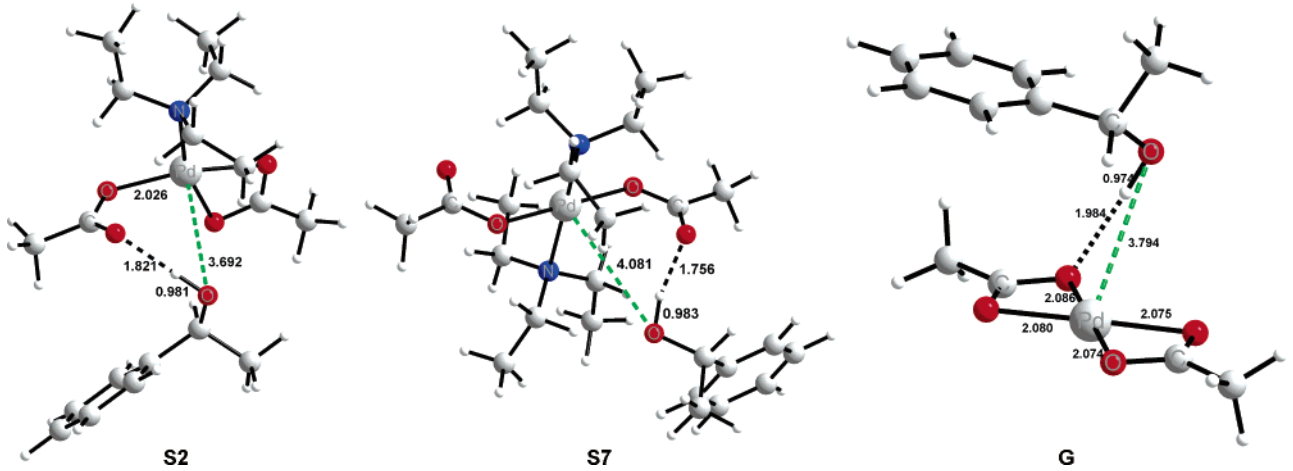

Figure 8. Coordination of *sec*-phenethyl alcohol to $Pd(OAc)_2(TEA)$ (**S2**), and $Pd(OAc)_2(TEA)_2$ complex (**S7**) and $Pd(OAc)_2$ (**G**). All distances are in Å. Dashed black line indicates OH bond from alcohol to OAc. Dashed green line indicates Pd−O distance.

Whether there are zero, one, or two triethylamines bound to Pd, the alcohol first binds to the acetate through a hydrogen bond. When no ligand is bound to the Pd, the weakest alcohol binding is observed with a 1.964 Å acetate O−H bond distance due to the inability of the acetate carbonyl to dissociate from the palladium (Figure 8, **G**). The hydrogen bonding of the alcohol to the acetate carbonyl is similar whether there is one (1.821 Å) or two TEAs (1.756 Å) bound to the Pd. However, in the complex with two TEAs bound, the alcohol oxygen is further away from the Pd presumably due to steric interactions (**S2** and **S7**). Additionally, nonpolar solvent does not provide sufficient dielectric screening that might weaken this long-range interaction responsible for hydrogen bonding between substrate and OAc.

An alternative pathway to coordinate the alcohol to Pd is direct metal−substrate coordination, which requires substantial reorganization of the first coordination sphere of Pd. Species that follow this pathway have been identified. As an example, $Pd(OAc)_2(TEA)_2$(substrate) leads to dissociation of one TEA to the second coordination sphere. However, these alternative complexes are considerably less stable (energy difference is 5 kcal/mol or more) than those pictured in Figure 8.

Deprotonation. Comparison of the hydrogen-bonded alcohol-catalyst intermediates with the transition state structures and the resulting Pd-alkoxide intermediates provides detailed insight into the mechanism of the deprotonation step. This deprotonation requires the alcohol to enter the first coordination sphere of Pd followed by an intramolecular deprotonation (Figure 9). An intramolecular deprotonation of a Pd-bound alcohol has also been proposed in the aerobic oxidation of alcohols in the $Pd(IiPr)(OAc)_2(H_2O)$ and palladaheterocycle/pyridine system.[8h,j] Ligands clearly have a significant impact on the energy required for this coordination. With one TEA bound to the Pd, this binding has an activation energy of 19 kcal/mol. However, in the case of two TEAs bound to the Pd, the amplified steric crowding results in the activation energy increasing dramatically to 36 kcal/mol. The steric crowding also results in much longer Pd−O (alcohol) bond lengths, 3.056 Å opposed to 2.33 Å when only one TEA is bound to the Pd (Figure 9). These data strongly support the hypothesis that only one TEA is bound to the Pd in the alcohol oxidation sequence, consistent with the kinetic model proposed. In contrast, the transition state for deprotonation has been identified with the Pd species with no ligand present, leading to the lowest barrier for deprotonation of 10 kcal/mol.

Another plausible mechanism for the deprotonation step for the two TEA bound model is dissociation of the one TEA to the second coordination sphere with one TEA remaining bound (Figure 9, **H**). The transition state for this pathway is 12 kcal/mol lower than with two TEAs directly bound to the Pd, but it is still 3.5 kcal/mol higher than the transition state with only one TEA bound to the Pd. Therefore, it seems like an unlikely reaction path.

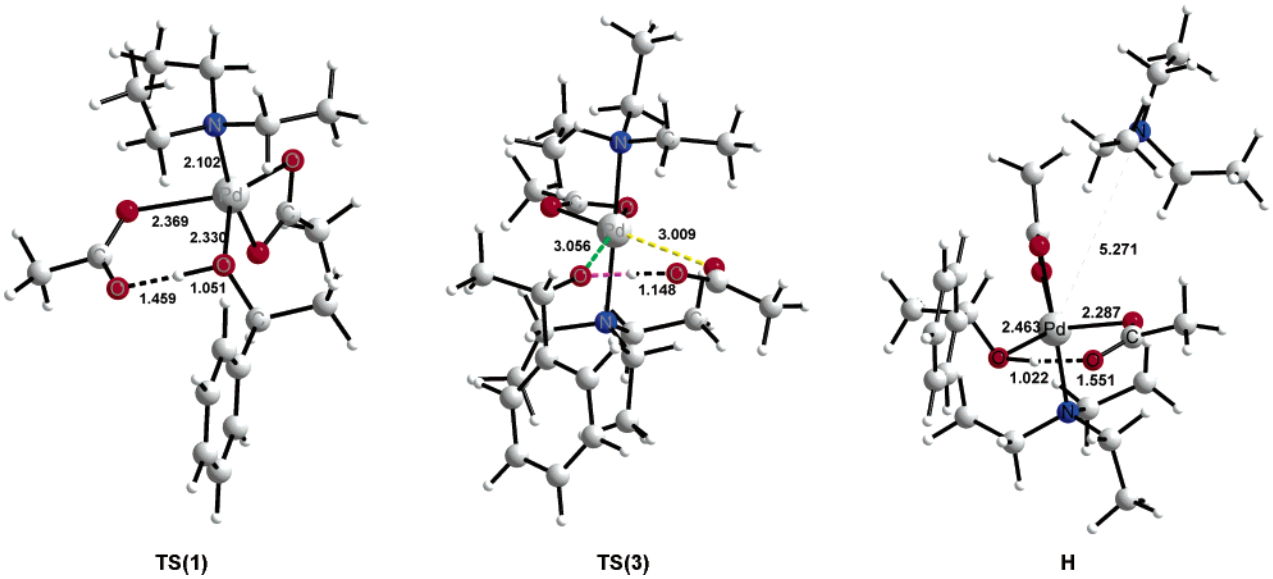

Figure 9. Transition states for the first deprotonation. **TS(1)**: Dashed black line indicates OH bond between AcO and OH on the substrate. **TS(3)**: Dashed purple line indicates elongated OH bond (1.316 Å) of the substrate. **H**: Dashed black line indicates OH bond of 1.551 Å, while thin dashed black line indicates Pd−TEA distance.

Since KIEs were used in the kinetic studies to confirm the rate-limiting step of the reaction, a comparison of the experimentally derived and the computationally calculated KIEs would provide further verification of the reaction mechanism. Thermochemical data for both the precursors and transition states (Figures 8 and 9) allow for the possibility of computing the KIE. The finding that there was no significant KIE for the β-hydrogen in substrate **5** (KIE of 1.09 ± 0.06) agrees within error with the computed KIE of 1.1. Additionally, the experimentally found KIE of 1.26 ± 0.02 in the oxidation of labeled *sec*-phenethyl alcohol-O-H(D) leads to the conclusion that deprotonation of the Pd-bound alcohol is the rate-limiting step. Again, a calculated KIE of 1.37 agrees well with the experimentally derived KIE. The major source of this kinetic isotope effect results from the movement of the substrate toward the Pd and a small elongation of the O−H bond in the transition state.

***β*-Hydride Elimination.** Once the Pd-alkoxide is formed, β-hydride elimination follows, resulting in a second transition state for the reaction (Figure 10). In the case with two TEAs bound to Pd, all attempts to locate a transition state with both ligands directly coordinated to Pd failed, presumably due to steric crowding. However, transition states could be found with one TEA bound or with one TEA bound and a second TEA in the second coordination sphere. In both instances, the Pd−O (alcohol) bond has lengthened about 0.1 Å from the Pd-alkoxide precursor. In the case with one TEA bound to Pd, one of the acetate carbonyl oxygens has dissociated to open a coordination site for delivery of the β-hydride. With one TEA bound to the Pd, the Pd−H bond and the C−H bond are nearly equal in length. However, when one TEA is coordinated and one TEA is in the second coordination sphere, the Pd−H bond distance is significantly shorter than the C−H bond length (0.42 Å), indicating more C−H bond breakage in the transition state. This difference is interesting since both of these species are similar in energy (ca. 1 kcal/mol difference). The computed KIEs using substrate **5** for transition states involving one or two TEA molecules were 5.3 and 5.7, respectively. Once again, these data

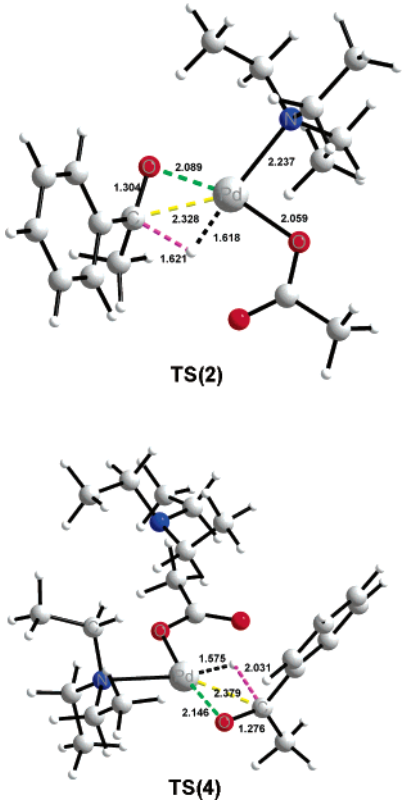

Figure 10. β-Hydride elimination transition states within one- (**TS(2)**) and two-TEA (**TS(4)**) models. All distances are in Å.

are in strong agreement with the experimentally determined intrinsic KIE of 4.3 ± 0.2.

To further understand the role of ligands in the Pd-catalyzed aerobic oxidation of alcohols, the transition state for β-hydride elimination of $Pd(OAc)_2$ with no added ligand was evaluated (see Figure 11). Interestingly, the activation energy for this step was 35 kcal/mol. This is much larger than the activation energy with one TEA bound and is surprising because it was assumed that the barrier would be low due to an accessible coordination

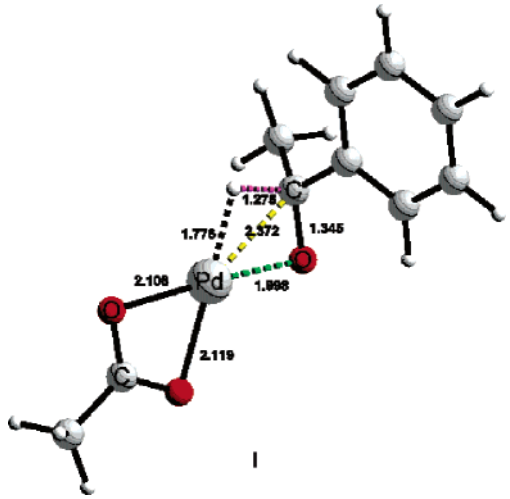

Figure 11. β-Hydride elimination of $Pd(OAc)_2$ with no added ligand. All bond distances are in Å.

site for β-hydride elimination. This shows that although TEA does increase the activation energy of the deprotonation step, it significantly decreases the activation energy of β-hydride elimination. Of additional consideration, this oxidation reaction does not proceed effectively without the use of ligands where they have been implicated in supporting Pd(0) species during reoxidation to Pd(II) by molecular oxygen. Without ligands to support Pd(0), Pd-metal often precipitates out of the reaction mixture and the oxidation terminates.

Comparison with Uemura's Pyridine System. While the kinetic and computational studies so far have shown the importance of having one TEA bound to the Pd, the question still remains: why is $Pd(OAc)_2$/TEA active at room temperature and $Pd(OAc)_2$/pyridine not? One key difference is a change in rate-limiting step from β-hydride elimination to deprotonation when switching from pyridine to TEA. To further understand this kinetic information, a computational study was performed on the $Pd(OAc)_2$/pyridine system.

For this system, Stahl has proposed that the alcohol binds in a similar way by hydrogen bonding to the acetate ligand. Once again, systems with one and two pyridines were examined. For the deprotonation step with only one pyridine bound to the Pd, no transition state could be located. During attempts to locate this transition state it was found that as the alcohol approaches the Pd, acetate ligand is freely protonated and there was no significant energy barrier.

In contrast to having one pyridine bound to the Pd, a transition state can be found for the kinetically relevant path where two pyridines are bound to Pd (Figure 12, **J**). The activation energy for this step is 23 kcal/mol, which is similar to the calculated activation energy with the $Pd(OAc)_2$/TEA system (19 kcal/mol). Also, the geometrical parameters between $Pd(OAc)_2$ with one TEA bound and $Pd(OAc)_2$ with two pyridines bound are quite similar. This indicates that one TEA is sterically similar to two pyridines in the transition state for deprotonation. Additionally, this result is in agreement with Stahl's observation of saturation in [alcohol] and a proposed binding of the alcohol to the ligand prior to deprotonation.[7]

When examining the β-hydride elimination transition state for the $Pd(OAc)_2$/pyridine system, the difference between TEA and pyridine becomes much more obvious. While the activation

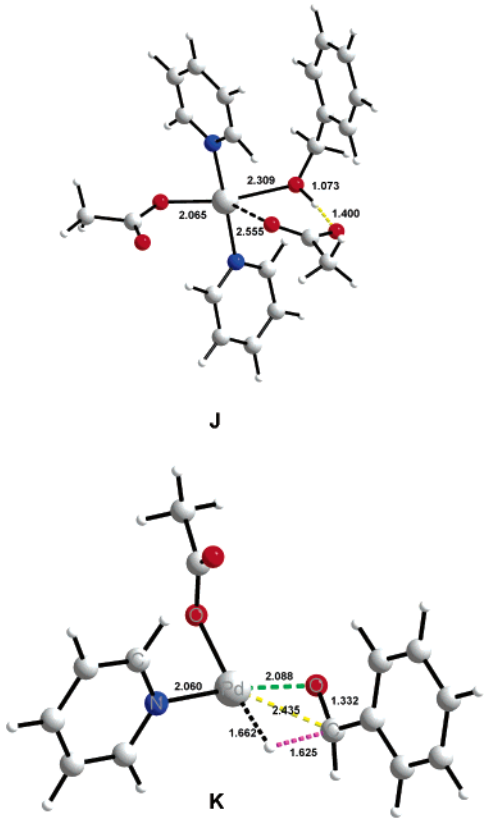

Figure 12. **J**: First deprotonation state for the $Pd(OAc)_2(pyridine)_2$ system. **K**: β-hydride elimination step for the $Pd(OAc)_2(pyridine)$.

energies for the deprotonation step were similar, the activation energies for β-hydride elimination are extremely different. As was the case for the $Pd(OAc)_2$/TEA system, only one pyridine is bound in the β-hydride elimination transition state, which has been supported by Stahl's kinetic studies.[7] However, the activation energy for this step is 31 kcal/mol, double that of the same step in the $Pd(OAc)_2$/TEA system and 12 kcal/mol more than rate-limiting deprotonation for the $Pd(OAc)_2$/TEA system. Additionally, the calculated kinetic isotope effect for β-hydride elimination is 3.15, which is in fair agreement with Stahl's reported KIEs of 1.5 ± 0.3 for the oxidation of benzyl alcohol (H_2 vs D_2) and an intrinsic isotope effect of 2.6 ± 0.2 for the oxidation of benzyl alcohol.

Examining the transition state for β-hydride elimination reveals that the Pd−H bond is more than 0.04 Å longer than the corresponding transition state for the $Pd(OAc)_2$/TEA system (Figure 12, **K**). This implies an earlier transition state with less C−H bond breakage, which could explain the lower observed and calculated KIEs. Another significant difference between the two systems is the Pd−N bond length with the different ligands (pyridine−Pd = 2.060 Å and TEA−Pd = 2.374 Å). The Pd−pyridine bond is much shorter in the optimized complexes than the corresponding Pd−TEA bond, which indicates that pyridine is a stronger ligand for the palladium presumably due to π-back-bonding from the Pd and steric interactions of TEA with the other ligands on the complex.

Mechanistic and Electronic Requirements for Efficient β-Hydride Elimination. The ability to directly compare two similar systems allows for further analysis of what is needed for efficient β-hydride elimination from a Pd-alkoxide. Classic requirements include (a) a coplanar conformation of the Pd−

O−C−H unit to allow the β-hydride to approach the metal center and (b) an open coordination site adjacent to the alkoxide that can accept the H^- into an empty d-orbital. In both cases, the computational models for $Pd(OAc)_2$/pyridine and TEA systems contain an open coordination site adjacent to the alkoxide in the β-hydride elimination transition state. Initially, this does not provide an explanation pertaining to the large difference in activation energies for this step. However, a more detailed examination of the preceding Pd-alkoxide intermediates sheds some light on this issue. In the TEA system, both kinetic and computational studies support a Pd-alkoxide intermediate that contains a single TEA coordinated to Pd. In contrast, two pyridines are bound to the Pd prior to rate-limiting β-hydride elimination. Therefore, the difference in the relative activation energies for β-hydride elimination results from the need to dissociate a pyridine to open the necessary coordination site. Supporting this hypothesis, Stahl has reported a Hammett correlation exists with respect to the electronics of the pyridine derivatives. The use of electron-rich pyridines (stronger σ-donors) results in a slower oxidation rate than electron-deficient pyridines. This experimental evidence strongly supports the idea that dissociation of a pyridine from the Pd causes a significant increase in activation energy for β-hydride elimination as compared to TEA as a ligand.

Another effect that changing the ligand can influence is the electronic nature of the β-hydride elimination process. Like much of transition metal catalysis, the Pd catalyst must serve dual and opposing roles for effective β-hydride elimination. First, Pd has to act as a Lewis acid in order to accept the electrons (act as an electrophile) associated with the β-hydride. This would require an electron-deficient Pd(II) center. The opposing role of Pd is to contribute electron density (act as a nucleophile) into the σ^* of the C−H bond in order to facilitate the breakage of this bond. This duality can be seen within these systems. The pyridine can act as a σ-donor and a π-acid, whereas TEA can act only as a σ-donor. Using the above analysis, the TEA system is more apt to donate electron density into the σ^* of the C−H bond, lowering the transition state energy necessary to abstract the hydride.[20] While it is difficult to differentiate the energetics of ligand dissociation from the other factors influencing β-hydride elimination, this type of electronic bias certainly plays a role in catalytic systems such as these.

Overall Mechanistic Implications and Conclusions

Switching from a relatively small, strongly coordinating ligand (pyridine) to a more sterically hindered, labile ligand (TEA) has a tremendous impact on the oxidation rate of the Pd-catalyzed oxidation of alcohols. While initially this empirical observation was somewhat perplexing, kinetic and computational models have provided strong evidence for the inherent reactivity differences. When using TEA, a pre-equilibrium exists between free $Pd(OAc)_2$, $Pd(OAc)_2$(TEA), and $Pd(OAc)_2(TEA)_2$. Kinetic experiments support that TEA inhibits the reaction prior to alcohol binding through this equilibrium wherein the active species is $Pd(OAc)_2$(TEA). After alcohol binding, rate-limiting deprotonation occurs, as supported by the derived rate law, activation parameters, and KIE experiments. In contrast, Stahl and co-workers have proposed rate-limiting β-hydride elimination for the use of pyridine wherein ligand inhibition occurs after alkoxide formation, prior to β-hydride elimination.

Computational studies agree very well with both kinetic studies and allow for a more precise understanding of these kinetic differences. The use of either pyridine or TEA as ligands for this reaction results in an increase in the activation energy for the deprotonation of the alcohol compared to a ligandless system. However, the use of TEA results in a significantly lower activation energy for β-hydride elimination than with no ligand or with pyridine, which clearly shows why a change in rate-limiting step is observed. The lowering of the transition state energy for β-hydride elimination was not predicted and leads to more direct insight into the factors that control this fundamental step in organometallic chemistry.

Designing new catalysts for this and related reactions involving β-hydride elimination is clearly a balancing act in which selection of ligands can lead to unanticipated mechanistic differences. This study showcases why both experimental and computational studies are necessary to provide a clearer and detailed picture of the fundamental processes occurring. Current work is focused on applying this combined method to elucidate mechanistic details for related Pd(II)-catalyzed processes and using this information to enhance catalyst performance.

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Supporting Information Available: Experimental procedures, graphs, data tables for the kinetic study, and complete ref 17 are provided. Also provided are the coordinates, energies, and structural parameters of optimized complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The pyridine has higher *average Hartree−Fock local ionization energy* than the TEA ligand by almost 30 kcal/mol. Therefore Pd-TEA complexes with already electron-deficient Pd(II) should be more active than Pd−pyridine complexes in breaking of the C−H bond due to the more labile electronic density on the TEA ligand. For the computation of the average Hartree−Fock local ionization energy see: Brink., T. *J. Phys. Chem. A* **1997**, *101*, 3408−3415.