Ligand-Modulated Palladium-Catalyzed Aerobic Alcohol Oxidations

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ABSTRACT
The discovery and investigation of ligand-modulated Pd-catalyzed aerobic alcohol oxidations is documented. The project has evolved from a simple empirical discovery that (−)-sparteine, in combination with Pd^{II} salts, facilitates the aerobic oxidative kinetic resolution of secondary alcohols to an in-depth physical organic investigation that has provided key insights into how new, more effective catalysts can be designed. Mechanistic investigations, the substrate scope for the catalysts developed, and implications to oxidation catalysis are discussed.

Introduction

Palladium-catalyzed reactions have revolutionized the approach to and the synthesis of natural products, materials, and pharmaceuticals. This impact has primarily arisen from the use of Pd-catalyzed cross-coupling reactions, through which a seemingly endless combination of C−C, C−N, C−S, and C−O bonds can be formed.[1] However, the single most important palladium-catalyzed reaction historically, in terms of industrial applications, is not a cross-coupling reaction but rather an oxidation. The Wacker oxidation transforms an olefin into a carbonyl compound using the combination of Pd^{II}/Cu^{II} with O_2 as the terminal oxidant and has been extensively used in the production of acetaldehyde from ethylene.[2] While significant research effort has been focused on the Wacker oxidation, the synthetic potential of other Pd-catalyzed oxidation reactions has not been realized.

A possible reason for the relative dearth of well-developed Pd-catalyzed oxidation reactions has been an inability to identify a general and practical oxidant. This is principally attributable to the mechanistic complexities associated with both the oxidation of the substrate by Pd^{II} and the reoxidation of Pd^0 by the terminal oxidant.[3] While many terminal oxidants have been used in Pd-catalyzed oxidations, ranging from Cu^{II} salts to organic oxidants such as benzoquinone, clearly, the most advantageous is the direct use of molecular oxygen. This is in part due to the environmentally benign and inexpensive nature of using O_2. In 1999, only a few examples using molecular oxygen, with no co-oxidant, in a Pd^{II}-catalyzed oxidation had been reported.[3] Of these, a particularly interesting example was Uemura and co-workers' report of an aerobic alcohol oxidation reaction using $Pd(OAc)_2$ and pyridine where ligand-accelerated catalysis was observed.[4−6]

Inspired by their findings, we set out to explore and understand the fundamental role(s) of ligands in Pd-catalyzed aerobic alcohol oxidations,[7] with the synthetic goal of developing general and enantioselective methods. As additional motivation, we believed that understanding the precise mechanistic features of ligand-modulated oxidative catalysis could have a profound effect in the discovery and development of new Pd-catalyzed oxidative processes. As described in this Account, the selection of the ligand on Pd is crucial in developing robust and active aerobic alcohol oxidation catalysts. However, without mechanistic insight into the role of the ligand and other added reagents in catalysis, the development of the most effective catalysts would have most likely been overlooked.

Aerobic Oxidative Kinetic Resolution of Alcohols

We initiated our program with a simple question: Would replacing pyridine with a chiral additive confer asymmetry to Uemura and co-workers' oxidation, resulting in a kinetic resolution of secondary alcohols?[8] Therefore, chiral pyridines were designed and synthesized for evaluation in the oxidative kinetic resolution of secondary alcohols.[9,10] As can be seen from the initial ligand evaluation, pyridines were a poor template for asymmetric catalysis (Table 1). Rather, the most promising result was observed using the chiral diamine, (−)-sparteine, with a k_{rel} value of 2.6. Initial optimization led to a significantly enhanced k_{rel} value up to 17.5 in the kinetic resolution of *sec*-phenethyl alcohol using either $PdCl_2$ or $Pd(OAc)_2$ with (−)-sparteine.[9,11,12] It is interesting to note that Uemura et al. reported that only systems derived from $Pd(OAc)_2$ lead to effective catalysis (vide infra).

While the initial conditions were successful for benzylic substrates, further optimization by our group and Stoltz's group lead to a more general method (Table 2).[13−15] Replacement of 1,2-dichloroethane with *tert*-butanol as the solvent created an improved catalyst system that is effective not only for benzylic alcohols but also for allylic and aliphatic alcohols (entries 1−5). Applying this methodology to the oxidative desymmetrization of 1,3-*meso*-diols has also been accomplished, delivering β-keto alcohols in good yield and enantioselectivity.[14] A mild protocol has been reported by Stoltz and co-workers in which the use of $CHCl_3$ as a solvent allows reactions to

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David Jensen graduated from the University of Tennessee at Chattanooga with a B.S. in chemistry in 1999 where he did research with Prof. Robert Mebane. He received a Ph.D. in chemistry from the University of Utah in 2004 under the supervision of Prof. Matthew Sigman. He currently works for Fuji Hunt Photographic Chemicals in Dayton, TN.

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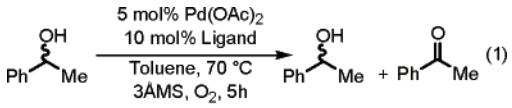
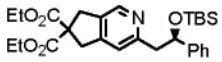
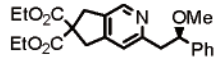
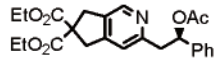
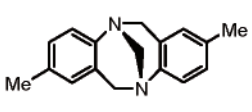
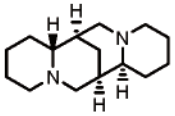
Table 1. Initial Evaluation of Ligands in the Palladium-Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols



Entry	Ligand	%Conversion	k_{rel}
a		82	<1.1
b		34	<1.1
c		62	<1.1
d	(S)-Nicotine	70	<1.1
e	Quinine (OTBS)	72	1.4
f	(+)-Tröger's Base	84	1.1
g	(-)-Sparteine	14	2.6


(+)-Troger's Base

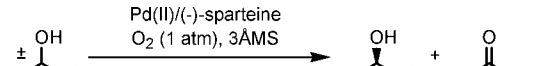

(-)-Sparteine

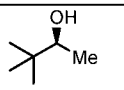
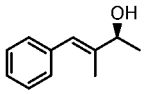
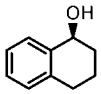
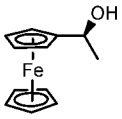
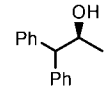
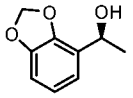
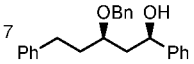
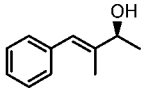
be performed at ambient temperature and air to be utilized as the source of O_2 (entries 6−8 in Table 2).[16]

While our initial goal of developing an asymmetric catalytic aerobic oxidation was met, several aspects were either unexpected or bothersome. The foremost issue centered on using (−)-sparteine as the chiral additive. Because of the difficulty in preparing analogues and accessing its enantiomer, (−)-sparteine is not a desirable ligand template. Additionally, through the last several years, evaluation of a significant number of alternative chiral diamine ligands has not only proved futile in terms of asymmetric induction but also for catalytic activity. This is a result that has been difficult for us to understand, especially the lack of catalytic activity. The other significant issue, which has been resolved, is why did a $PdCl_2$-based system promote catalysis with (−)-sparteine and not with pyridine as a ligand?

To explore the latter question and to begin unravelling the mechanistic complexity of this system, Pd[(−)-sparteine]Cl_2 was isolated and evaluated as a catalyst for the oxidative kinetic resolution of *sec*-phenethyl alcohol (Table 3).[9] We were initially surprised to find the isolated complex to be catalytically incompetent under reaction conditions similar to those used in the kinetic resolution (entry 1). However, the addition of 10 mol % of exogenous (−)-sparteine re-established normal catalytic activity and enantioselectivity (entry 3). Other exogenous bases also facilitate the oxidation reaction, but the k_{rel} values are significantly lower (entries 4−6).[17] In contrast, isolated Pd[(−)-sparteine](OAc)$_2$ is catalytically active, albeit with a diminished rate and low enantioselectivity (entry 2). These observations allude to the importance of a Brønsted base in the oxidation reaction and explain why $Pd(OAc)_2$ is the most effective catalyst in Uemura and co-workers' system, where the acetate counterion most likely acts as a base.

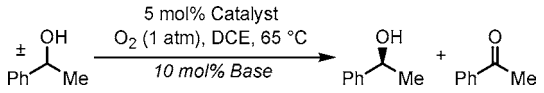
Table 2. Optimal Conditions Using ^{t}BuOH (Sigman) and $CHCl_3$ (Stoltz) Solvents for the Pd^{II}/(−)-Sparteine-Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols



Entry	Product	Solvent	Time(Temp)	%ee(k_{rel})	yield(%)
1		^{t}BuOH[a]	24h (65 °C)	92.2(15.7)	37
2		^{t}BuOH[a]	24h (65 °C)	98.3(11.9)	30
3		^{t}BuOH[a]	24h (65 °C)	99.1(20.2)	35
4		^{t}BuOH[a]	24h (65 °C)	99.3(16.1)	33
5		^{t}BuOH[a]	24h (65 °C)	96.6(18.3)	38
6		$CHCl_3$[b]	12h (40 °C)	95(29)	45
7		$CHCl_3$[b]	72h (40 °C)	99(32)	42.5
8		$CHCl_3$[b]	48h (23 °C)	99(18)	37.5

[a] Conditions: 5 mol % Pd[(−)-sparteine]Cl_2 and 20 mol % (−)-sparteine (10 mmol scale). [b] Pd(nbd)Cl_2 (5 mol %), (−)-sparteine (12 mol %), and Cs_2CO_3 (40 mol %).

Table 3. Effect of Exogenous Base



entry	catalyst	base	conversion (%)	k_{rel}
1	Pd[(−)-sparteine]Cl_2	no base	<5 (ND)	ND
2	Pd[(−)-sparteine](OAc)$_2$	no base	35	1.4
3	Pd[(−)-sparteine]Cl_2	(−)-sparteine	52	20.1
4	Pd[(−)-sparteine]Cl_2	(^{i}Pr)NEt	28	5.1
5	Pd[(−)-sparteine]Cl_2	Cs_2CO_3	53	4.7
6	Pd[(−)-sparteine]Cl_2	KO^{t}Bu	14	6.9

These observations prompted us to explore the mechanism in more detail. Kinetic experiments have revealed a remarkably complex catalytic system, wherein both rate and enantioselectivity are affected by the concentration of exogenous (−)-sparteine and its conjugate acid, (−)-sparteine-HCl (Figure 1). Saturation kinetics were observed in [(−)-sparteine] and attributed to a change in the rate-determining step from deprotonation of the bound alcohol to β-hydride elimination. This analysis was supported by the measurement of kinetic isotope effects, activation parameters, and substrate electronic effects.[17,18]

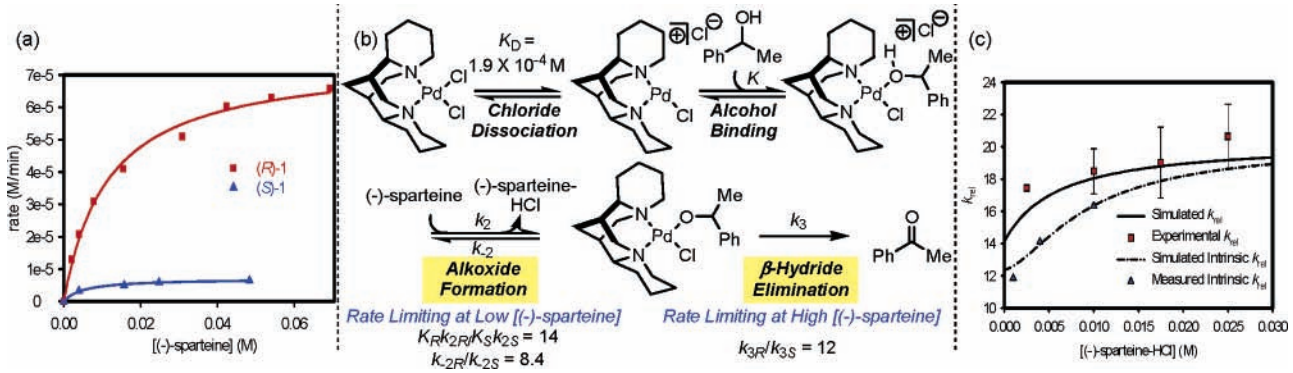


FIGURE 1. (a) Rate dependence on [(−)-sparteine]. (b) Proposed mechanism and mechanistic details for the Pd[(−)-sparteine]Cl_2-catalyzed oxidative kinetic resolution of secondary alcohols. (c) Effect of [(−)-sparteine-HCl)] on both the intrinsic k_{rel} and experimental k_{rel} (racemate). Simulated data derived from extracted microscopic rate constants are also pictured.

More recent computational studies by Goddard, Stoltz, and co-workers are also in agreement.[19]

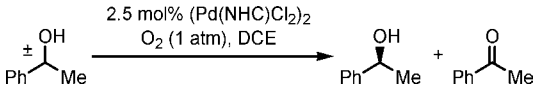
While kinetic resolutions can be synthetically limited, they provide an excellent opportunity to study how both kinetic and thermodynamic processes influence asymmetric catalysis. Separation of these two factors can be accomplished by comparing the ratio of oxidation rates for each individual enantiomer (intrinsic k_{rel}, a purely kinetic phenomenon) to the k_{rel} measured with both enantiomers present (the racemate) and competing for the same active catalyst. At high [(−)-sparteine], where β-hydride elimination is rate-limiting, a significant difference of the intrinsic k_{rel} (∼11) compared to the experimental k_{rel} (∼25) using the racemate is observed.[18] Only recently have we been able to reconcile this difference. Two factors play simultaneous roles promoting the enhancement in k_{rel}: (1) [sparteine-HCl] in the kinetic resolution is controlled by alkoxide formation (Kk_2), where the deprotonation of the *R* enantiomer is 14 times faster, and (2) the rate of the palladium alkoxide reprotonation (k_{-2}) versus the rate of β-hydride elimination (k_3) is faster for the slower oxidizing enantiomer (k_{-2}/k_3, where R/S is 0.69).[20] This leads to an overall slowing of the *S*-enantiomer oxidation rate. As one raises the [sparteine-HCl], the intrinsic k_{rel} and racemate k_{rel} plateau at approximately the same k_{rel} value (Figure 1c). This finding explains why exogenous (−)-sparteine can be replaced with significant amounts of an achiral base, e.g., sodium carbonate, to effect the oxidative kinetic resolution with similar k_{rel} values.[21] Overall, an underlying mechanistic theme is that, while the ligand is central to induce asymmetric catalysis, simple acid/base chemistry can control the rate of product formation.

In considering why (−)-sparteine is "special" for Pd-catalyzed oxidative kinetic resolutions, Stoltz and Trend found the C_1 symmetry of (−)-sparteine promotes a diastereoselective chloride substitution.[22] The models that they developed are also in agreement with a faster oxidation of the *R* enantiomer of the alcohol. However, what is still unclear is why other C_1 or C_2 symmetric diamines do not provide nearly as active or selective catalysis.[23] One notable observation is that Pd[(−)-sparteine]Cl_2 readily dissociates a chloride ion in dichloroethane (∼35% under reaction conditions), and even considering the cationic nature of the catalyst, the alcohol substrate does not bind with a high affinity ($K < 1$).[20] While we have not measured the dissociation constant for other diamine-containing complexes, the greater catalytic activity of Pd-[(−)-sparteine]Cl_2 compared to other diamines may be attributed to its ability to dissociate a chloride. This observation is influencing how we approach other Pd^{II}-catalyzed oxidative processes.

Application of Mechanistic Studies. The mechanistic studies suggested a unique strategy for catalyst development. Because these studies showed that the acid/base in the reaction and the ligand on Pd play crucial roles in Pd-catalyzed oxidative kinetic resolution, we hoped to develop a system using ligands and/or bases other than (−)-sparteine. Pd complexes with N-heterocyclic carbene (NHC) ligands were chosen to study these approaches. NHC ligands were selected because both achiral and chiral NHC ligands can be synthesized in a modular fashion and the NHC should act as a strong ligand to stabilize both Pd^{II} and Pd^0 intermediates.[24]

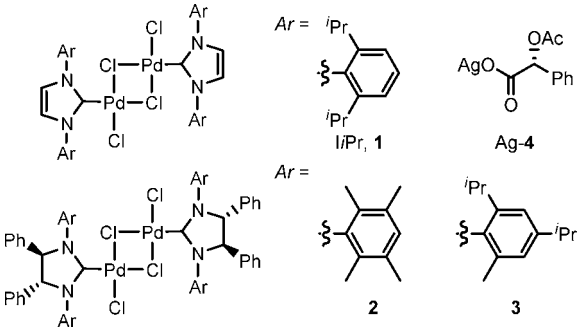
An achiral $(Pd(NHC)Cl_2)_2$ complex in combination with exogenous (−)-sparteine catalyzes the oxidative kinetic resolution of *sec*-phenethyl alcohol (entry 1 in Table 4).[25] To determine the possibility of "matched" and "mismatched" diastereomeric interactions between a chiral ligand and a chiral base, both enantiomers of **2** were evaluated for oxidative kinetic resolution using (−)-sparteine as the base (entries 2 and 3). A significantly higher k_{rel} value of 11.8 was observed for the *S*,*S* catalyst. The observation of higher selectivity for one enantiomer of the ligand showcases an approach in which a "matched" chiral ligand and chiral base pair can act in concert to enhance the oxidative kinetic resolution. To further demonstrate the potential of this approach, (−)-sparteine was replaced with carboxylate bases (entries 4−8). While the initial experiments did not give exceptional k_{rel} values, they do show that both chiral carbene ligands and chiral carboxylate bases can influence the oxidative kinetic resolution of alcohols.[8,26] As of yet, we have not identified a combination that promotes a highly effective oxidative kinetic resolution.

Table 4. Alternative Ligands and Bases in the Pd-Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols



entry	$(Pd(NHC)Cl_2)_2$	base[a]	% conversion (% ee)	k_{rel}
1	**1**	(−)-sparteine	64.7 (96.0)	11.6
2	(*R*,*R*)-**2**	(−)-sparteine	39.7 (36.4)	4.5
3	(*S*,*S*)-**2**	(−)-sparteine	34.6 (42.0)	11.8
4	(*S*,*S*)-**2**	AgOAc	34.5 (10.2)	1.6
5	(*R*,*R*)-**3**	AgOAc	34.0 (23.2)	3.3
6	**1**	Ag-(*S*)-**4**	57.0 (29.9)	2.1
7	(*R*,*R*)-**3**	Ag-(*S*)-**4**	39.8 (27.6)	3.2
8	(*R*,*R*)-**3**	Ag-(*R*)-**4**	48.5 (17.8)	1.7

[a] (−)-Sparteine (15 mol %) and Ag salt (10%) generally used. The reaction temperature was generally between 50 and 65 °C.



New Catalysts for General Alcohol Oxidation

$Pd(OAc)_2$/Triethylamine (TEA) Catalyzed Aerobic Alcohol Oxidation. A parallel goal of our research program was the development of mild aerobic alcohol oxidation methods amenable to complex molecule synthesis. When we initiated this program, all Pd-catalyzed aerobic alcohol oxidations suffered from the use of high temperatures, increased pressures of O_2, and/or impractical catalyst loadings. Several observations early in the development of the Pd-catalyzed oxidative kinetic resolution led us to discover a ligand that promotes catalysis at ambient temperature: (1) in general, monodentate nitrogen-based ligands displayed the best rates for alcohol oxidation (entries a, d, e, and f versus entries b, c, and g in Table 1), and (2) specifically, use of Tröger's base as an additive gave similar rates of oxidation to the use of pyridine, under Uemura and co-workers' conditions.[4,5] This latter observation was somewhat surprising, considering the significant structural difference of Tröger's base compared to pyridine. On the basis of these observations, our simple hypothesis was that a *single* dative nitrogenous ligand on Pd was necessary to facilitate the oxidation and, therefore, dissociation of a ligand must play an important role. Thus, simple monodentate amine ligands were examined with $Pd(OAc)_2$ for alcohol oxidation at *room* temperature. Moderately bulky tertiary amines, such as triethylamine and Tröger's base, were shown to facilitate Pd-catalyzed alcohol oxidation (Figure 2).[27] Upon optimization, catalytic $Pd(OAc)_2$/TEA has proven useful for the oxidation of a broad scope of alcohols and is one of the simplest aerobic alcohol oxidations available to the synthetic chemist.[28]

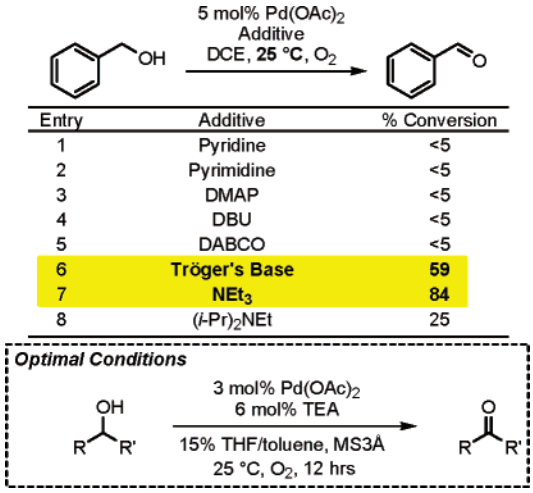


FIGURE 2. Identification and optimal conditions for the TEA/$Pd(OAc)_2$-catalyzed aerobic alcohol oxidation at room temperature.

Additionally, the use of Pd(II) with TEA has been effective in other aerobic oxidation reactions.[29]

At first glance, both the approach and the discovery of the $Pd(OAc)_2$/TEA system does not seem remarkably different from Uemura and co-workers' ($Pd(OAc)_2$/pyridine). However, if one considers that the addition of pyridine to $Pd(OAc)_2$ at ambient temperature does not lead to catalysis but, at 80 °C, pyridine is a superior additive to TEA, it seemed prudent to gain a fundamental understanding of these systems. Stahl and co-workers have reported an elegant study on the mechanistic aspects of Uemura and co-workers' system.[30,31] For the purposes of this discussion, three findings are important to highlight: (1) excess pyridine is required to avoid decomposition of the palladium catalyst, (2) the acetate counterion is proposed to hydrogen bond to the alcohol prior to deprotonation, and (3) β-hydride elimination is rate-limiting, which requires the dissociation of a pyridine ligand (pyridine inhibits the reaction).

Our kinetic and computational studies of the $Pd(OAc)_2$/TEA catalyst uncovers features analogous to (1) and (2).[32] However, with TEA, deprotonation of the Pd-bound alcohol is proposed to be rate-limiting based on several kinetic experiments (Figure 3). Additionally, an unusual "up/down" rate dependence on [TEA] is measured. At low concentrations of [TEA], a rate enhancement is observed; however, an inverse first-order dependence on [TEA] is observed as the [TEA] is increased. Considering that a pre-equilibrium of three species is observed by NMR (Figure 3b),[27] these data are consistent with only a single TEA on the active catalyst, initial formation of $Pd(OAc)_2$(TEA) enhancing the rate at low [TEA], and inhibition of the oxidation occurring at high [TEA] via the formation of $Pd(OAc)_2(TEA)_2$. The derived rate law used to describe this scenario can be fit with excellent agreement to the observed dependence of the oxidation rate on [TEA] (Figure 3a). Considering that $Pd(OAc)_2(pyridine)_2$ is the resting state in the analogous system, it was believed that an equilibrium amount of $Pd(OAc)_2$(TEA) facilitates the reaction at lower temperatures. A computational comparison of pyridine versus TEA as the ligand shows a

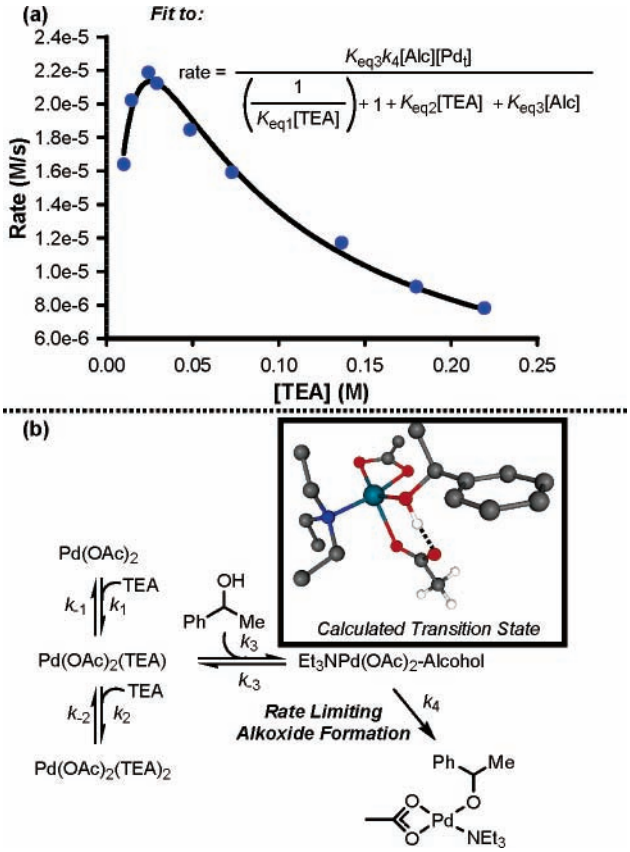


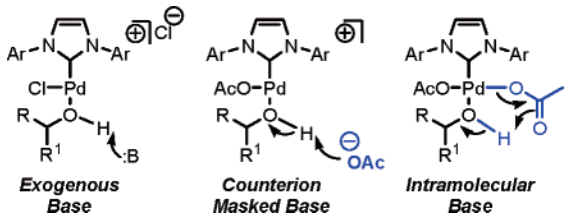
FIGURE 3. (a) Rate dependence on [TEA]. (b) Rate-limiting alkoxide formation with a single TEA ligand.

significantly higher barrier for β-hydride elimination when pyridine is used. This is presumably because pyridine, a strong ligand, is unable to readily dissociate from Pd^{II}. Overall, these studies highlight that the presence of only one dative ligand on palladium promotes the oxidation, but excess ligand is always necessary for a competent catalytic system to avoid catalyst decomposition.

Pd(IiPr)(OAc)$_2$(H$_2$O)-Catalyzed Aerobic Alcohol Oxidation. Our next goal was to design a Pd complex that oxidizes alcohols at lower concentrations of both catalyst and O_2. The mechanistic studies of Pd-catalyzed alcohol oxidations described above provided a foundation in which ligand and base selection were deemed crucial. In considering a ligand, two conflicting issues had to be addressed. A single dative ligand on Pd is proposed to give the most efficient catalysis by lowering the barrier to β-hydride elimination. However, use of TEA, which was our most active system, requires excess TEA (at least 2 equiv) to prevent catalyst decomposition. The use of pyridine also shows similar features. Therefore, a monodentate ligand that does not diminish the ability of Pd^{II} to catalyze the alcohol oxidation and can stabilize Pd^0 intermediates from decomposition was desired. We again looked to NHC−Pd complexes that we had previously shown to remain on Pd during catalysis while promoting alcohol oxidation, albeit slowly, with added (−)-sparteine as the base.[25]

The next stage was selecting a base for which carboxylate bases seemed reasonable. Carboxylates are in a similar

Scheme 1. Design of a New Catalyst for Palladium-Catalyzed Aerobic Alcohol Oxidations



pK_a range to amine bases (in DMSO),[33] and several observations at the time suggested acetate acts as a base in Pd-catalyzed oxidations. For example, Uemura et al. found that the acetate counterion on Pd was necessary for effective catalysis.[5] Additionally, Pd[(−)-sparteine](OAc)$_2$ is a competent oxidation catalyst in the absence of added base.[17] These observations allude to acetate acting as both an anionic ligand and base in this chemistry. Another appealing feature is that acetate as a ligand could facilitate an intramolecular deprotonation (Scheme 1). We believed this would enhance the rate of deprotonation and simultaneously provide an accessible coordination site for β-hydride elimination. Significantly, recent experimental and computational work supports these assertions for various Pd-catalyzed aerobic alcohol oxidations.[31,34,35]

To test these hypotheses, the complex Pd(IiPr)(OAc)$_2$(H$_2$O) was synthesized and evaluated for alcohol oxidation.[36] Our initial result was rewarding, where at 50 °C *sec*-phenethyl alcohol was converted to acetophenone in 2 h with 5 mol % Pd. To put this in perspective, Uemura and co-workers' conditions require 80 °C for the same result. We then focused on lowering the catalyst loading, which proved to be difficult. As an example, evaluating side-by-side reactions under identical conditions led to inconsistent substrate conversion, which we attributed to catalyst decomposition. The proposed mechanism that guided our optimization efforts is pictured in Figure 4a.[37] We thought the instability of Pd^0 complexes was the crux of the problem, and if the oxygenation process was promoted or the resting state was changed to a palladium hydride, a more consistent oxidation reaction would result. To accomplish this, small amounts of acetic acid (HOAc) were added, resulting in a successful use of lower catalyst loadings (0.5 mol %) (Figure 4b).[36] Using these conditions, a variety of alcohols were oxidized and, with an activated substrate, 1000 turnovers can be accomplished, a significant achievement considering that this is a homogeneous aerobic oxidation. Additionally, when the acetic acid concentration is increased, the reaction can be carried out open to the ambient atmosphere, with air providing the source of O_2, a considerable practical improvement over other Pd-catalyzed alcohol oxidations (Figure 4b). A diverse set of substrates have also been oxidized using this catalytic system,[28] and the catalyst system has been applied in a multicatalytic transformation of alcohols to olefins.[38]

Several questions inspired us to study the mechanism of this catalytic system. The key question was whether the

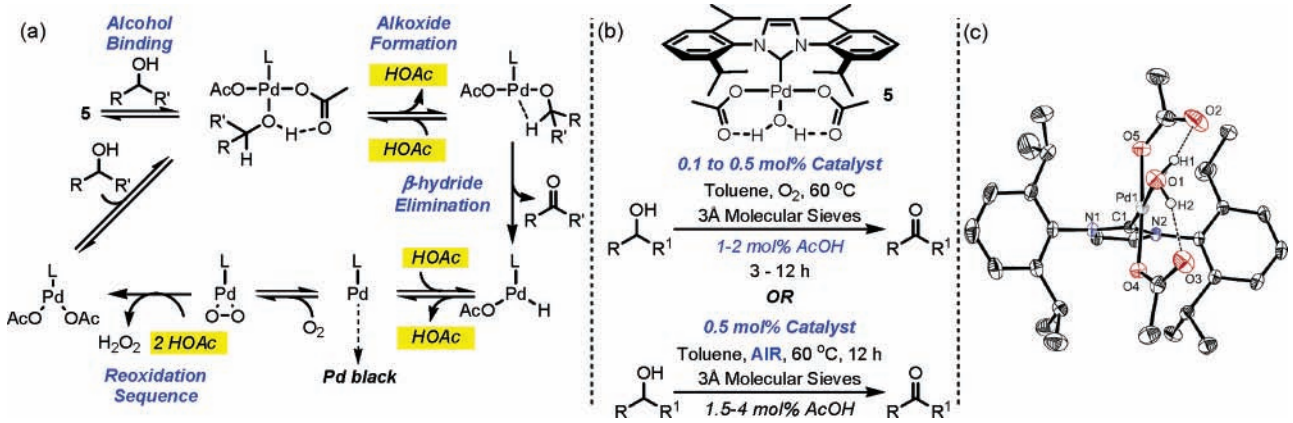


FIGURE 4. (a) Proposed mechanism using Pd(IiPr)$(OAc)_2(H_2O)$ as the catalyst. (b) Optimized oxidation conditions. (c) ORTEP of Pd(IiPr)-$(OAc)_2(H_2O)$.

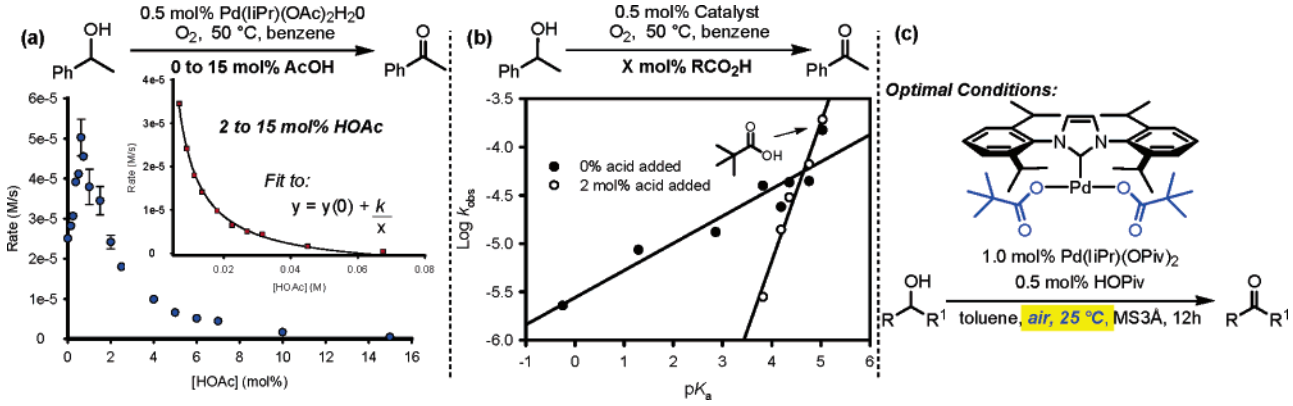


FIGURE 5. (a) Rate dependence on [HOAc]. (b) Effect of counterion and added acid pK_a on the oxidation rate. (c) Optimized oxidation conditions using pivalate/pivalic acid in place of acetate.

hypotheses used for the catalyst design were responsible for the excellent catalytic activity. We should note at the outset that we did not anticipate that additional HOAc would be required for consistent catalysis. Evidence for acetate acting as an internal base was afforded through X-ray crystal structural analysis of Pd(IiPr)$(OAc)_2(H_2O)$ (Figure 4c).[36] In the complex, the water molecule is not only coordinated to the Pd atom but is also hydrogen-bound to both of the acetate ligands. This hydrogen bonding can be considered a mimic of the proposed intramolecular deprotonation. Because of the fast nature of the deprotonation reaction, we were unable to kinetically differentiate between an intra- or intermolecular deprotonation. However, recent computational studies reported by Privalov and co-workers support an intramolecular process.[35]

Kinetic characterization of this system initially revealed a relatively simple mechanistic model, where deprotonation is fast and β-hydride elimination is rate-limiting.[39] One question that we still wanted to address was the role(s) of added acetic acid. When the dependence on [HOAc] was evaluated, we observed a more complicated mechanistic scenario (Figure 5a). Under standard reaction conditions (>2 mol % acetic acid), an anticipated inverse first-order dependence was observed. This is consistent with inhibition caused by reprotonation of the palladium alkoxide (see Figure 4a). In contrast, at lower concentrations of acid (<2 mol %), an "up/down" dependence is observed, which, upon further investigation, was proposed to arise from rate-influencing protonation of a palladium peroxy species.[40] Consistent with this, lowering the $[O_2]$ leads to significantly greater catalyst decomposition. The underlying discovery is that regeneration of the active catalyst is slower than the rate of alcohol oxidation without added acid and leads to catalyst decomposition. The main role of acetic acid under standard conditions is to slow the overall process, mainly through reprotonation of the alkoxide. A balance between the relative rate of alcohol oxidation and the relative rate of Pd-catalyst regeneration is maintained thereby avoiding catalyst decomposition. A new catalyst design would strive to either enhance the rate of catalyst regeneration or slow the rate of decomposition.[41]

The role of the acid is not limited to controlling the rate-limiting events. Evaluation of the nature of the carboxylate and the added acid reveals that more basic counterions and weaker added acids afford enhanced catalysis (Figure 5b). As an example, we were able to develop a pivalate-based system that is operative at room temperature using 1 mol % catalyst and air as the O_2 source (Figure 5c). While these conditions are the mildest to date, the scope of this process is limited as compared to the TEA/$Pd(OAc)_2$ and Pd(IiPr)$(OAc)_2(H_2O)$ systems.[28]

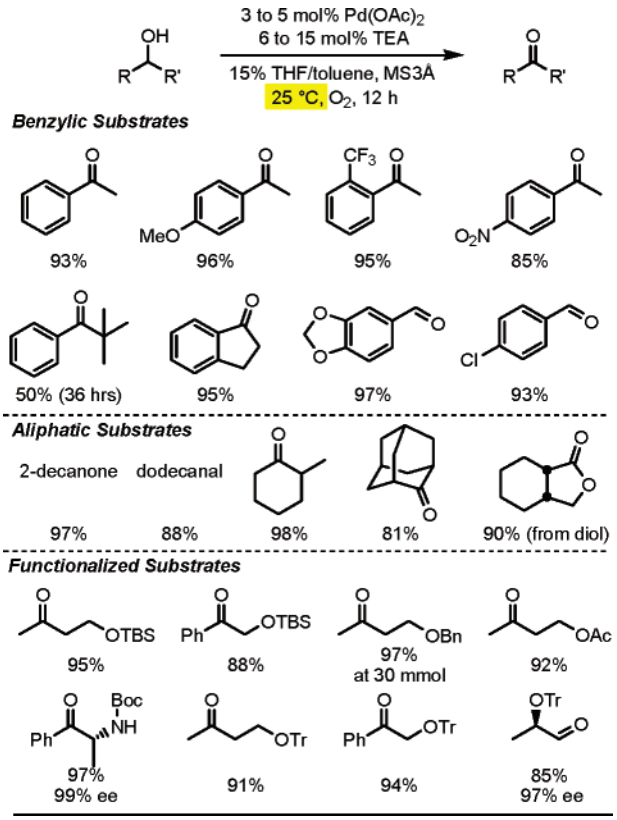


FIGURE 6. Selected products from aerobic alcohol oxidation using catalytic TEA/Pd(OAc)$_2$ and O_2.

Overview and Outlook

Our two main goals outlined in the Introduction were to elucidate the mechanistic features of palladium oxidation catalysis and develop synthetically useful aerobic alcohol oxidations. Success in the latter is easier to evaluate in which we have developed several variants of both enantioselective and general oxidation methods. The simplicity of the oxidative kinetic resolution using (−)-sparteine makes this system an attractive method for the synthesis of highly enantiomerically enriched, readily accessible alcohols.[15] However, even with a precise understanding of the kinetic factors that control enantioselectivity, we and others have been unable to identify other chiral ligands that achieve high enantioselectivity.

Concerning general alcohol oxidations, our hope has been to develop aerobic oxidative methods that are applicable beyond simple substrates. This Account has not focused on this point, but the alcohol substrate scope of these aerobic oxidations is the broadest to date and selected examples are pictured in Figure 6.[28] The use of TEA/Pd(OAc)$_2$ is the simplest and mildest catalyst available, while Pd(IiPr)(OAc)$_2$(H$_2$O) (not pictured) provides the ability to use both low catalyst loadings and low concentrations of O_2. This is highlighted by the fact that <5% O_2 can be used with no observed catalyst decomposition when 7 mol % acetic acid is added to the reaction.[39]

We also have made considerable progress in elucidating the mechanistic features of Pd-catalyzed aerobic alcohol oxidations. Table 5 contains a compilation of the mechanistic parameters of the systems that we have developed and studied.[17,18,32,39] While these systems are kinetically complex, the guiding principles for catalyst design are rather simple; a single monodentate dative ligand on Pd facilitates β-hydride elimination, and a base is necessary for deprotonation of the Pd-bound alcohol. The difference in reactivity between Pd(OAc)$_2$/pyridine and Pd(OAc)$_2$/TEA highlights the former where Pd(OAc)$_2$(TEA) is the proposed active catalyst species. Additionally, changing from pyridine to TEA as the ligand leads to an unanticipated change in the rate-limiting step from β-hydride elimination to alcohol deprotonation. Computationally, the barrier for β-hydride elimination is considerably higher in energy using pyridine, which is attributed to a required dissociation of a pyridine ligand. The importance of a base is highlighted by exogenous (−)-sparteine being necessary for oxidative kinetic resolution using Pd[(−)-sparteine]Cl$_2$. Increasing [(−)-sparteine] changes the rate-limiting step from deprotonation to β-hydride elimination. This concentration effect is further supported by the differences in $\Delta G^{\ddagger}$, where deprotonation has a significantly lower barrier. It is a rather exciting discovery that simple acid/base chemistry can play such an integral role in a C−H-bond-breaking organometallic process.

These findings and analyses led to the design of a well-defined complex, Pd(IiPr)(OAc)$_2$(H$_2$O), which initially performed inconsistently. However, with the insight garnered from previous studies and the knowledge of potential pitfalls in the design, we anticipated catalysis could be modulated with the addition of HOAc. When HOAc of differing amounts was added, both high turnover numbers can be achieved (up to 1000) and O_2 can be effectively replaced with ambient air pressure.[36] It is difficult to know whether one would have tested this catalyst empirically,

Table 5. Compilation of Mechanistic Information for Developed Systems

catalyst	alcohol dependence	KIE	Hammett correlation	$\Delta H^{\ddagger}$(kcal/mol)[a]	$\Delta S^{\ddagger}$(eu)	$\Delta G^{\ddagger}$(kcal/mol)	rate-limiting step
TEA/Pd(OAc)$_2$	saturation	1.10 ± 0.07[b] 1.26 ± 0.02[c] 4.2 ± 0.2[d]	$\rho = 0.03$	10.0 ± 0.5	−36 ± 2	20.8 at 25 °C 22.0 at 60 °C	deprotonation
(IiPr)Pd(OAc)$_2$-H$_2$O 2 mol % AcOH	first order	5.5 ± 0.07[b]	$\rho = -0.48 \pm 0.04$	21.1 ± 0.5	−3.5 ± 0.6	21.1 at 25 °C 21.3 at 60 °C	β-hydride elimination
Pd[(−)-sparteine]Cl$_2$ low base	first order	1.04 ± 0.06[b]	ND	11.6 ± 0.7	−24.5 ± 2.0	18.9 at 25 °C 19.7 at 60 °C	deprotonation
Pd[(−)-sparteine]Cl$_2$ high base	first order	1.31 ± 0.04[b]	$\rho = -1.4 \pm 0.2$ $\rho^{+} = -1.0 \pm 0.1$	20.3 ± 0.9	−5.4 ± 2.7	20.8 at 25 °C 22.0 at 60 °C	β-hydride elimination

[a] Activation parameters measured for either *sec*-phenethyl alcohol or benzyl alcohol. [b] Oxidation of PhCH/D(OH)CH$_3$. [c] Oxidation of PhCH(OH/D)CH$_3$. [d] Oxidation of PhCHDOH.

but analysis of the mechanistic studies provided an excellent framework to facilitate its discovery.

In conclusion, the catalyst is asked to do much in oxidative catalysis: act as an electrophilic metal center during substrate oxidation and as a nucleophilic metal center during catalyst regeneration by O_2. Using this simplistic analysis, a highly donating ligand, such as the NHC, was envisioned to facilitate catalyst regeneration and potentially slow substrate oxidation. Qualitatively, this is observed in that excess ligand is not necessary with a NHC ligand but is required for effective catalysis with TEA. Conversely, a more donating ligand should slow β-hydride elimination. As anticipated, a higher barrier of 21.1 kcal/mol at 25 °C (measured) for β-hydride elimination is observed with the NHC ligand, compared to 16 kcal/mol at 25 °C (calculated) observed with TEA as the ligand. As we start to evaluate new Pd-catalyzed oxidations that are not focused on alcohol oxidations, we can use much of the mechanistic insight presented herein to guide our choice of ligand/conditions. However, the question of why one oxidant or ligand works for one transformation and not for a closely related transformation still exemplifies how early we are in the understanding and development of oxidative catalysis.[42] As was illustrated in this Account, we believe mechanistic investigation will be a key contributor to exploiting the powerful nature of Pd oxidation catalysis.

I have been blessed with a highly talented and motivated group of co-workers who I am indebted to for their contributions to this work. Special thanks goes to David Jensen, Jaime Mueller, Mitchell Schultz, Jacob Pugsley, Sunil Mandal, Candace Park, Christopher Goller, and Steven Hamilton. I also thank my collaborators Professors Timo Privalov and Bert Chandler for their contributions and insightful discussions. This project has received generous support from the National Institutes of Health, the Petroleum Research Fund, and the University of Utah. M. S. S. thanks the Research Corporation and the Dreyfus Foundation for fellowships as well as support from Merck Research Labs, Pfizer Global Research, and Rohm and Haas Research. We also thank Johnson Matthey for supplies of various palladium salts.

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