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Published on Web 05/17/2003

Mechanistic Investigations of the Palladium-Catalyzed Aerobic Oxidative Kinetic Resolution of Secondary Alcohols Using (−)-Sparteine

Jaime A. Mueller and Matthew S. Sigman*

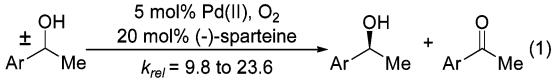
Contribution from the Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112

Received January 21, 2003; E-mail: sigman@chem.utah.edu

Abstract: The mechanistic details of the Pd(II)/(−)-sparteine-catalyzed aerobic oxidative kinetic resolution of secondary alcohols were elucidated, and the origin of asymmetric induction was determined. Saturation kinetics were observed for rate dependence on [(−)-sparteine]. First-order rate dependencies were observed for both the Pd((−)-sparteine)Cl_2 concentration and the alcohol concentration at high and low [(−)-sparteine]. The oxidation rate was inhibited by addition of (−)-sparteine HCl. At low [(−)-sparteine], Pd-alkoxide formation is proposed to be rate limiting, while at high [(−)-sparteine], β-hydride elimination is proposed to be rate determining. These conclusions are consistent with the measured kinetic isotope effect of $k_H/k_D = 1.31 \pm 0.04$ and a Hammett ρ value of -1.41 ± 0.15 at high [(−)-sparteine]. Calculated activation parameters agree with the change in the rate-limiting step by increasing [(−)-sparteine] with $\Delta H^{\ddagger} = 11.55 \pm 0.65$ kcal/mol, $\Delta S^{\ddagger} = -24.5 \pm 2.0$ eu at low [(−)-sparteine], and $\Delta H^{\ddagger} = 20.25 \pm 0.89$ kcal/mol, $\Delta S^{\ddagger} = -5.4 \pm 2.7$ eu at high [(−)-sparteine]. At high [(−)-sparteine], the selectivity is influenced by both a thermodynamic difference in the stability of the diastereomeric Pd-alkoxides formed and a kinetic β-hydride elimination to maximize asymmetric induction. At low [(−)-sparteine], the selectivity is influenced by kinetic deprotonation, resulting in lower k_{rel} values. A key, nonintuitive discovery is that (−)-sparteine plays a dual role in this oxidative kinetic resolution of secondary alcohols as a chiral ligand on palladium and as an exogenous chiral base.

Introduction

Pd(II)-catalyzed oxidations have broad utility in organic synthesis. An excellent example is the Wacker oxidation[1] employed in industry to generate millions of tons of carbonyl compounds from olefins per year. One of the unique features of the Wacker oxidation is the use of molecular oxygen as the terminal oxidant. Molecular oxygen can be considered an ideal terminal oxidant due to availability and environmentally benign byproducts produced in the oxidation manifold. In the development of simple, cost efficient oxidations, Pd(II)-catalyzed aerobic oxidations have been extended to more diverse reaction types including amination of olefins,[2] acetoxylation,[3] and transformations of *tert*-cyclobutanols.[4] Of the Pd(II)-catalyzed aerobic oxidations, the simple conversion of alcohols to ketones and aldehydes has garnered the most attention. Aerobic oxidation of alcohols using Pd(II) catalysts was first reported by Schwartz and Blackburn in 1977.[5] Subsequent efforts have extended the substrate scope, efficiency, and utility of Pd(II)-catalyzed aerobic oxidation of alcohols.[6]



(1)

Recently, our research group[7] and Stoltz et al.[8] simultaneously reported adaptations of Pd(II)-catalyzed aerobic oxidation of alcohols[6e,g] to kinetic resolution as a simple method to access enantiomerically enriched secondary alcohols (eq 1). In our reported kinetic resolution, the optimized system employs 5 mol % Pd(II) catalyst and 20 mol % (−)-sparteine, a commercially

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(3) Ebitani, K.; Choi, K. M.; Mizugaki, T.; Kaneda, K. *Langmuir* **2002**, *18*, 1849.
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(6) For examples of Pd(II)-catalyzed aerobic oxidations, see: (a) Schultz, M. J.; Park, C. C.; Sigman, M. S. *Chem. Commun.* **2002**, 3034. (b) Kakiuchi, N.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 6620. (c) Hallman, K.; Moberg, C. *Adv. Synth. Catal.* **2001**, *343*, 260. (d) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636. (e) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750. (f) Ebitani, K.; Fujie, Y.; Kaneda, K. *Langmuir* **1999**, *15*, 3557. (g) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **1998**, *39*, 6011. (h) Aït-Mohand, S.; Muzart, J. *J. Mol. Catal. A* **1998**, *129*, 135. (i) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185. (j) Kaneda, K.; Fujie, Y.; Ebitani, K. *Tetrahedron Lett.* **1997**, *38*, 9023. (k) Kaneda, K.; Fujii, M.; Morioka, K. *J. Org. Chem.* **1996**, *61*, 4502. (l) Aiet-Mohand, S.; Henin, F.; Muzart, J. *Tetrahedron Lett.* **1995**, *36*, 2473. (m) Gómez-Bengoa, E.; Noheda, P.; Echavarren, A. M. *Tetrahedron Lett.* **1994**, *35*, 7097. (n) Blackburn, T. F.; Schwartz, J. *J. Chem. Soc., Chem. Commun.* **1977**, 157.
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10.1021/ja034262n CCC: $25.00

available diamine natural product, to oxidatively resolve various racemic benzylic alcohols giving k_{rel}[9] values ranging from 9.8 to 23.6 and enantiomeric excess values up to 99%.[10,11] The transformation is performed at mild temperatures, 60−65 °C, in 1,2-dichloroethane solvent, with a balloon pressure of molecular oxygen.[12]

While the Pd(II)/(−)-sparteine-catalyzed aerobic oxidative kinetic resolution provides a useful synthetic method to access enantiomerically enriched secondary alcohols, there are limitations. The major drawback of this protocol is the use of (−)-sparteine as the chiral agent. Since it is widely available only as a single enantiomer, just one enantiomer of enriched alcohol is directly accessible.[13,14] Additionally, structural changes to (−)-sparteine for enhancement of selectivity and reactivity of the catalyst are difficult to envision.[15] Therefore, an improved catalyst system requires replacement of (−)-sparteine with a chiral agent available in both antipodes that can also be manipulated to allow for systematic variations of structure. Successfully replacing (−)-sparteine as the chiral agent requires a clear understanding of how it affects the reactivity and the selectivity of the reaction. Accordingly, we sought to elucidate the precise role(s) of (−)-sparteine and the other reagents in Pd(II)/(−)-sparteine oxidative kinetic resolution to provide a platform for the development of an improved catalytic system.

Various mechanisms have been proposed for Pd(II)-catalyzed oxidations of alcohols, but have had little evidence to support them, until recently.[16,17] Based on the Wacker oxidation, as well as other Pd(II)-catalyzed oxidation processes, a plausible mechanism can be considered. The basic steps include binding of the alcohol to the catalyst, β-hydride elimination from a Pd-alkoxide species, and catalyst regeneration.[18] Herein, we disclose the mechanistic details of the reaction prior to catalyst turnover, including the origin of asymmetric induction, the clarification of the active catalyst, and the specific role of each additive.[19,20]

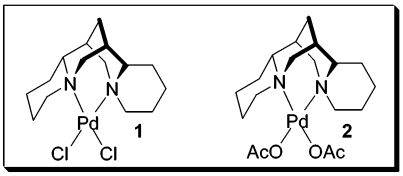
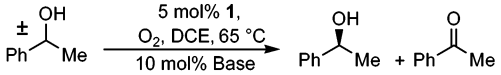


Figure 1. Structures of Pd((−)-sparteine)Cl_2 and Pd((−)-sparteine)$(OAc)_2$.

Table 1. Base Screen for Pd-Catalyzed Oxidative Kinetic Resolution of Alcohols



entry	base	% conv. (% ee)[a]	k_{rel}[b]
a	no base	0.0 (N.A.)	N.A.
b	(−)-sparteine	51.5 (82.4)	20.1
c	Hunig's base	28.0 (23.0)	5.1
d	Cs_2CO_3	52.9 (53.8)	4.7
e	KO*t*-Bu	14.0 (11.7)	6.9

[a] Conversion determined using internal standard. [b] Conversion <10% gives inaccurate k_{rel} values.

Results and Discussion

In our reported Pd(II)/(−)sparteine-catalyzed oxidative kinetic resolution, the catalyst was formed in situ from the appropriate Pd(II) source and (−)-sparteine. To investigate the nature of the active catalyst structure, complexes were prepared using Pd-$(OAc)_2$ and a $PdCl_2$ source. Single crystals were obtained for each Pd-complex. X-ray analysis revealed (−)-sparteine binds bidentate to one side of a slightly distorted square planar Pd in both cases (Figure 1).[7,21] To determine if **1** is active in the catalysis, it was submitted to the standard oxidation reaction conditions without exogenous (−)-sparteine.[22] Surprisingly, no alcohol oxidation or decomposition was observed (Table 1, entry a). However, upon addition of 10 mol % exogenous (−)-sparteine, the catalytic activity was reestablished, and k_{rel} values were measured similar to those in the in situ method (Table 1, entry b). This observation suggests that exogenous (−)-sparteine is necessary for oxidation.

A possible role of exogenous (−)-sparteine is as a Brønsted base to form Pd-alkoxide **B** from bound alcohol **A** (Scheme 1). A simple test of this hypothesis is to evaluate the effectiveness of other exogenous bases in the oxidative kinetic resolution. Thus, several bases were tested under the standard conditions (Table 1). All bases examined yielded a catalytic oxidation. With the addition of cesium carbonate, a slightly enhanced conversion as compared to (−)-sparteine was observed; however, (−)-

(9) The k_{rel} was calculated using $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$ where C is the conversion and ee is the enantiomeric excess. For an excellent discussion of kinetic resolutions, see: Kagan, H. B.; Fiaud, J. C. Kinetic Resolution. *Top. Stereochem.* **1988**, *18*, 249.

(10) Alcohols can be resolved by other methods. For catalytic acylation, see: (a) Lin, M.-H.; RajanBabu, T. V. *Org. Lett.* **2002**, *4*, 1607. (b) Vedejs, E.; MacKay, J. A. *Org. Lett.* **2001**, *3*, 535. (c) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496. (d) Bellemine-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009. (e) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638. (f) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813. (g) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, 265. (h) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629. (i) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794. (j) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. (k) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169. For epoxidation approach: (l) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. Using benzoylation: (m) Iwata, T.; Miyake, Y.; Nishibayashi, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, *13*, 1548.

(11) For recent oxidative approaches, see: (a) Masutani, K.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 5119. (b) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291. (c) Gross, Z.; Ini, S. *Org Lett.* **1999**, *1*, 2077. (d) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288. (e) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org Chem.* **1996**, *61*, 1194.

(12) When this transformation is run in open air, significant catalyst decomposition is observed.

(13) A total synthesis of (+)-sparteine was reported recently, but it is not yet practical, see: Smith, B. T.; Wendt, J. A.; Aube, J. *Org. Lett.* **2002**, *4*, 2577−2579.

(14) This Pd(II)/(−)-sparteine-catalyzed OKR has been reported in the synthesis of pharmaceuticals where they used a Mitsunobu inversion to access the other needed enantiomer of alcohol, see: Ali, I. S.; Sudalai, A. *Tetrahedron Lett.* **2002**, *43*, 5435.

(15) Sparteine analogues have been synthesized and proven to access the other enantiomer of product with lower k_{rel} values, see: Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870.

(16) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *Org. Lett.* **2002**, *4*, 4179.

(17) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Adv. Synth. Catal.* **2002**, *344*, 355.

(18) Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202.

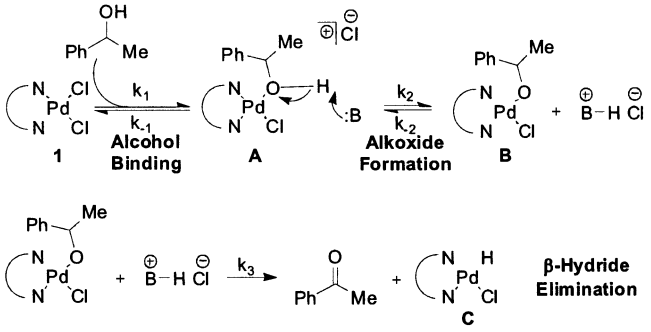
(19) For a study of Pd(II)-catalyzed oxidation of alcohols in DMSO with rate-limiting catalyst turnover, see: Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766.

(20) For mechanistic insight into the oxygenation of Pd(0)/bathocuproine, see: Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188.

(21) See Supporting Information for Pd((−)-sparteine)$(OAc)_2$ X-ray crystal analysis.

(22) Standard conditions for this experiment include 0.25 M *sec*-phenethyl alcohol, 5 mol % **1**, and 10 mol % base in 1 mL of 1,2-dichloroethane (DCE) under balloon pressure of O_2, at 65 °C.

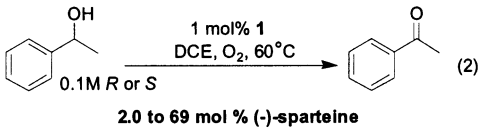
Scheme 1. Pd(II)-Catalyzed Oxidation of Alcohols



sparteine gives considerably higher k_{rel} values than the other bases tested. These results reinforce the proposal that a Brønsted base is needed for catalysis. Furthermore, the selectivity is dependent on the nature of the exogenous base, indicating (−)-sparteine could have an additional role as a chiral Brønsted base in an asymmetric deprotonation.

A revised mechanism is proposed that includes roles for (−)-sparteine as both a chiral ligand on palladium and a chiral Brønsted base (Scheme 1). After alcohol binding to the Pd((−)-sparteine)Cl_2 catalyst (**1**), exogenous (−)-sparteine deprotonates the bound alcohol (**A**) to form the Pd-alkoxide species (**B**). The Pd-alkoxide undergoes β-hydride elimination to release the ketone product and generate the Pd-hydride catalytic species (**C**) that is recycled by oxygen.

Mechanism Elucidation. Each step of the proposed mechanism involves a single Pd-species. If this proposed mechanism is plausible, a first-order dependence in Pd[(−)-sparteine]Cl_2 concentration should be observed. Thus, the dependence of oxidation rate on Pd[(−)-sparteine]Cl_2 concentration was evaluated from 0.5 to 5 mM (0.5−5 mol %), and a first-order dependence was observed.[23] Unless specified, for all kinetic studies, initial rates were measured, and single enantiomers of *sec*-phenethyl alcohol were utilized to avoid complications associated with competitive binding.[24]



(2)

To probe the role(s) of exogenous (−)-sparteine, the rate dependence on the concentration of (−)-sparteine (0.002−0.069 M, 2−69 mol %) was assessed (eq 2). For oxidation of each enantiomer of alcohol, a nonlinear relationship of rate to [(−)-sparteine] was observed (Figure 2). The data were fit using nonlinear least squares to an equation describing saturation with excellent agreement.[25]

The first-order (−)-sparteine dependence at low [(−)-sparteine] suggests deprotonation of the Pd-bound alcohol (**A**) is rate limiting. If this is the case, according to the proposed mechanism, a first-order dependence should be observed in

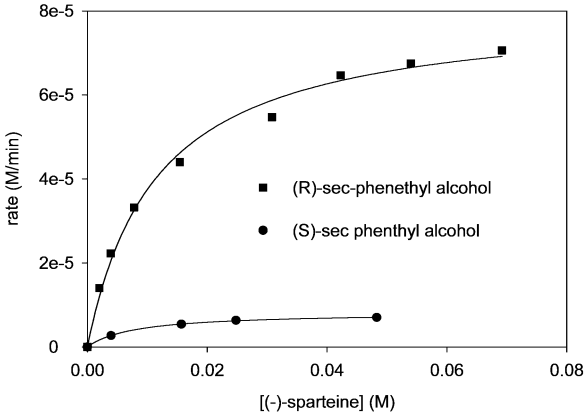


Figure 2. Rate dependence of *sec*-phenethyl alcohol oxidation on [(−)-sparteine].

Table 2. Influence on Rate-Limiting Step

entry	dominant term	rate expression	rate-limiting step
1	k_3	k_1[A][catalyst]	alcohol binding
2	k_1[A]	k_3[catalyst]	β-hydride elimination
3	k_{-2}[BHCl]	k_1k_3[A][catalyst]/k_{-2}[BHCl]	β-hydride elimination
4	none	k_1k_3[A][catalyst]/ k_1[A] + k_3 + k_{-2}[BHCl]	β-hydride elimination

alcohol concentration. The observed saturation kinetics implicate another step, either alcohol binding, β-hydride elimination, or Pd(II) regeneration with O_2, becomes rate limiting at high [(−)-sparteine]. Probing the dependence on alcohol concentration should distinguish these possibilities. A rate dependence on alcohol concentration should be observed for either rate-limiting alcohol binding or β-hydride elimination but not for Pd(II) regeneration with O_2. At both low and saturating (−)-sparteine conditions,[26] a first-order [alcohol] dependence was observed within the concentration range from 0.02 to 0.2 M. These results confirm rate-limiting alkoxide formation at low [(−)-sparteine] and eliminate Pd(II) regeneration with O_2 as rate determining at high [(−)-sparteine].

$$\text{rate} = \frac{k_3k_2k_1\,[\text{Catalyst}]_{\text{Total}}\,[\text{A}][(-)\text{-sparteine}]}{k_2[(-)\text{-sparteine}]\,(k_1[\text{A}] + k_3 + k_{-2}[\text{BHCl}]) + k_{-1}k_3 + k_{-1}k_2[\text{BHCl}]} \quad (3)$$

[A] = [alcohol], [BHCl] = [(-)-sparteine HCl]

A rate law was derived to describe the overall catalytic process and to provide assistance in the differentiation of the two possible rate-limiting scenarios at high [(−)-sparteine]: alcohol binding and β-hydride elimination (eq 3, where [A] is [alcohol] and [BHCl] is [(−)-sparteine HCl]).[27] At saturation, the denominator of the derived rate law can be simplified to include only terms associated with k_2[(−)-sparteine] (k_3, k_1[A], and k_{-2}[BHCl]). Depending on which of these terms dominate, different mechanistic possibilities arise (Table 2). If the rate constant associated with β-hydride elimination, k_3, is large, alcohol binding will be rate limiting at high [(−)-sparteine] (entry 1). In contrast, β-hydride elimination becomes rate determining at high [(−)-sparteine] for the remaining possibilities (entries 2−4). If the term associated with alcohol binding, k_1[A], is dominant, the rate expression simplifies to k_3[catalyst], implying a simultaneous alcohol saturation event should be

(23) See Supporting Information for the plots and data analysis.
(24) Four reactions were analyzed simultaneously under the same reaction conditions (oxygen atmosphere and temperature fluctuations). See Supporting Information for apparatus. Conditions were slowed from the optimized synthetic conditions to enable the hand sampling of all four reactions.
(25) Fit to: $k_{obs} = k'[(-)\text{-sparteine}]/(k'' + [(-)\text{-sparteine}])$. For the Michaelis−Menten equation, see: Walsh, C. *Enzymatic Reaction Mechanisms*; W. H. Freeman and Company: New York, 1979.
(26) In these studies, 4 mol % (−)-sparteine is used as low base concentration conditions, and 50 mol % is used as saturating conditions.
(27) For derivation of the rate law, see Supporting Information.

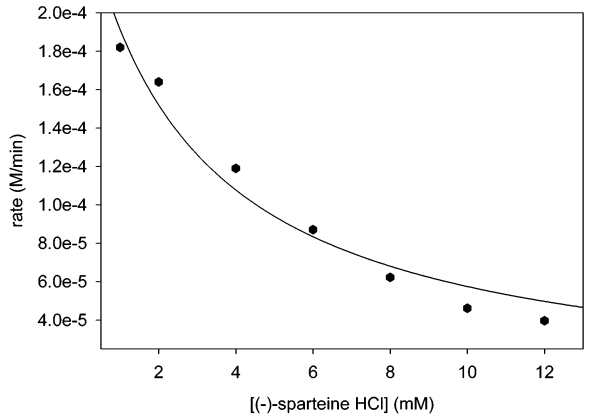


Figure 3. Rate inhibition by (−)-sparteine HCl.

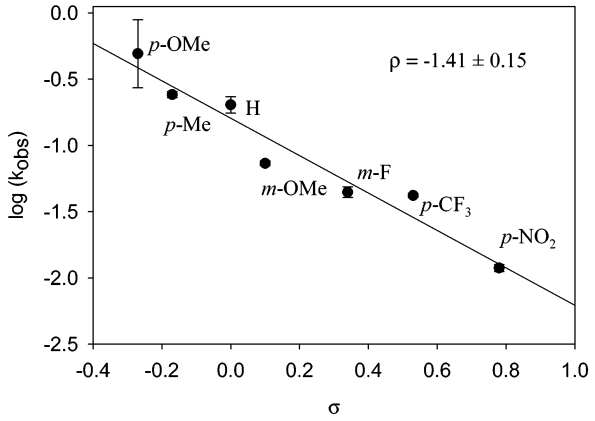
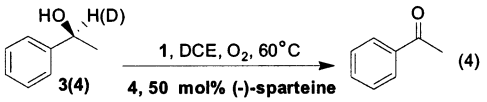


Figure 4. Benzyl alcohol oxidation Hammett plot at high [(−)-sparteine].

observed upon saturation in [(−)-sparteine]. However, saturation in alcohol was not observed over the range of alcohol concentration evaluated. On the basis of these observations, two situations remain in which β-hydride elimination can limit the rate: (1) when the term associated with reprotonation of the bound alkoxide, k_{-2}[BHCl], is dominant or (2) when a combination of terms dominates. In both cases, at high [(−)-sparteine], the rate of oxidation is inversely proportional to [(−)-sparteine HCl]. Therefore, evaluation of [(−)-sparteine HCl] dependence can distinguish between alcohol binding and β-hydride elimination becoming rate determining at high [(−)-sparteine]. If alcohol binding becomes rate limiting, the addition of (−)-sparteine HCl should not influence the reaction rate (entry 1), but if β-hydride elimination becomes rate limiting, adding (−)-sparteine HCl should inhibit the reaction.

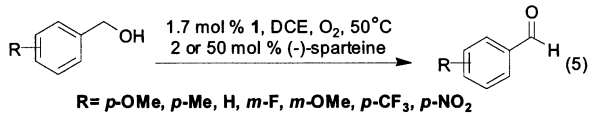
Reaction rates were measured with added (−)-sparteine HCl from 0.001 to 0.012 M (1−12 mol %). A significant retardation of rate was seen upon increase of [(−)-sparteine HCl] (Figure 3). Nonlinear least-squares analysis was used to fit the data to a simplified derived rate law with good agreement.[28] The observed inhibition is consistent with β-hydride elimination becoming rate limiting at high [(−)-sparteine].

Kinetic Isotope Effect. On account of only small amounts of (−)-sparteine-HCl presumably being present under normal reaction conditions, there is a possibility that the addition of (−)-sparteine-HCl may perturb the reaction mechanism. Thus, the kinetic isotope effect (KIE) at the β-position of the alcohol was investigated to unambiguously differentiate between alcohol binding and β-hydride elimination. If β-hydride elimination does indeed become the rate-limiting step at high [(−)-sparteine], substituting the β-hydrogen of *sec*-phenethyl alcohol (**3**) for deuterium (**4**) and measuring k_H/k_D should show a primary isotope effect. At low [(−)-sparteine], when deprotonation is rate limiting, no kinetic isotope effect should be observed.



Upon evaluation, a negligible kinetic isotope effect of 1.04 ± 0.06 was measured at low [(−)-sparteine] (eq 4), consistent with rate-limiting deprotonation. A KIE of 1.31 ± 0.04 was measured at high [(−)-sparteine]. This value is consistent with KIE values measured for other processes, implicating β-hydride elimination as rate determining including a KIE of 1.4 ± 0.1 reported for the decomposition of *trans*-[Pd(CH_2-CD_3)$_2$($PMePh_2$)$_2$],[29,30] a KIE of 1.3 ± 0.1 recently reported by Stahl et al. in evaluating Uemura's Pd(II)/pyridine-catalyzed oxidation of benzyl alcohol (at 0.1 M alcohol),[16] and a KIE of 1.4 reported by Sheldon et al. for the Pd(II)/bathophenanthroline disulfonate-catalyzed oxidation of *sec*-phenethyl alcohol.[17]

Hammett Studies. To continue to characterize the unusual change in the rate-determining step by increasing [(−)-sparteine], Hammett plots were constructed by measuring the rate of oxidation of various substituted benzylic alcohols at high and low [(−)-sparteine] (eq 5).[31] These experiments were



accomplished using in situ IR to monitor the rate of appearance of the carbonyl absorbance of the corresponding aldehyde products. At high [(−)-sparteine], the initial rates of product appearance were plotted against their σ and σ^+ values (Figures 4 and 5).[32] The calculated ρ and ρ^+ values, −1.41 ± 0.15 and −1.00 ± 0.13, respectively, indicate that substituents influence the rate through both induction and resonance. The negative ρ value signifies a positive charge buildup in the transition state consistent with β-hydride elimination being rate limiting at high [(−)-sparteine]. The negative ρ^+ value specifies that direct resonance donation stabilizes the positive charge buildup at the benzylic center during rate-limiting β-hydride elimination at high [(−)-sparteine]. The same benzylic alcohols were also oxidized at low [(−)-sparteine].[33] When the Hammett plot was constructed with the calculated k_{obs} values, no correlation was

(28) The data were fit to $k_{obs} = k'/(k'' + [(-)\text{-sparteine HCl}])$, where k' and k'' are constants. See Supporting Information for the statistical analysis.

(29) Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 6457.
(30) KIEs on other d^8 metals have been reported in which β-hydride elimination has been implicated as the rate-determining step, see: (a) Evans, J.; Schwarts, J.; Urquhart, P. W. *J. Organomet. Chem.* **1974**, *81*, C37. (b) Ikariya, T.; Yamamoto, A. *Organomet. Chem.* **1976**, *120*, 257.
(31) These experiments were performed using in situ IR to measure the initial rates of formation of the aldehyde products. The initial absorbencies were measured and converted to concentration of aldehyde product using the Beer−Lambert relationship. Low [(−)-sparteine] is 2 mol % for studies using in situ IR.
(32) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; p 144.
(33) For these studies, 2 mol % (−)-sparteine is used for low base concentration conditions, and 50 mol % (−)-sparteine is used for saturation conditions.

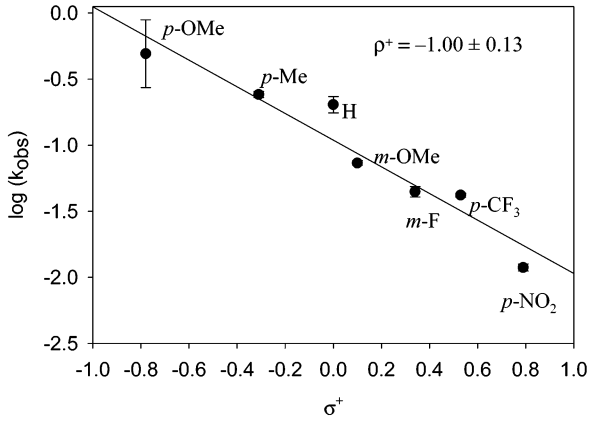


Figure 5. Benzyl alcohol oxidation Hammett plot with σ^+ values at high [(−)-sparteine].

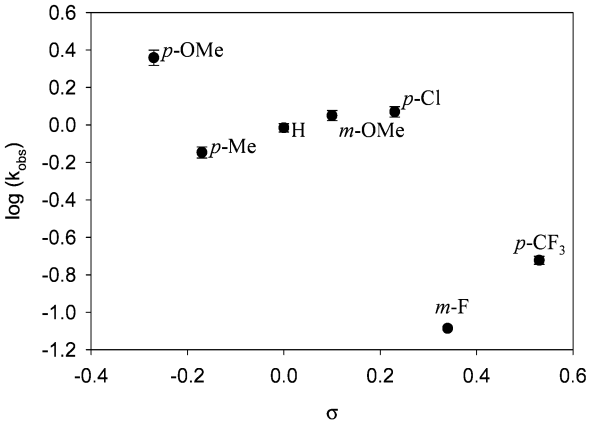


Figure 6. Benzyl alcohol oxidation Hammett plot at low [(−)-sparteine].

observed (Figure 6).[34] This illustrates at low [(−)-sparteine] that the transition state does not change consistently with substituent changes on the phenyl ring.

Eyring Studies. Further characterization of the rate-limiting step as a function of [(−)-sparteine] was achieved by measuring the activation parameters at high and low [(−)-sparteine] for benzyl alcohol oxidation (Figure 7).[35] At low concentrations of (−)-sparteine, the $\Delta H^{\ddagger}$ was measured to be 11.55 ± 0.65 kcal/mol (Table 3). This relatively low activation energy is consistent with deprotonation being rate limiting. The $\Delta S^{\ddagger}$ was measured to be −24.5 ± 2.0 eu. This large negative value is consistent with the bimolecular nature of intermolecular deprotonation. At high [(−)-sparteine], the $\Delta H^{\ddagger}$ is considerably higher at 20.25 ± 0.89 kcal/mol. This increased value is congruent with rate-limiting β-hydride elimination due to the higher energy required to break a C−H bond. The $\Delta S^{\ddagger}$ at high [(−)-sparteine] was measured to be −5.4 ± 2.7 eu, a value significantly larger than that observed at low [(−)-sparteine]. This is consistent with the unimolecularity of β-hydride elimination versus the bimolecularity of deprotonation. It is notable that both the entropy and the enthalpy of activation play a crucial role in [(−)-sparteine] causing a significant change in rate-limiting events.

Other Mechanistic Possibilities. Thus far, all evidence supports a mechanism that consists of rate-limiting deprotonation

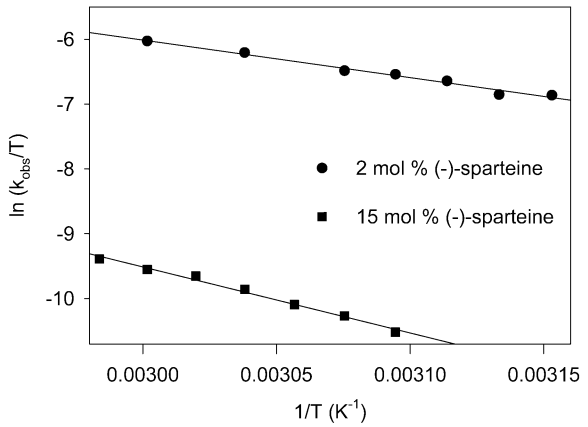


Figure 7. Eyring plots of benzyl alcohol oxidation at high and low [(−)-sparteine].

Table 3. Activation Parameters for Benzyl Alcohol Oxidation

activation parameters	2 mol % (–)-sparteine	15 mol % (–)-sparteine
$\Delta G^{\ddagger}$ at 60 °C	19.71 ± 0.94 kcal/mol	22.04 ± 1.26 kcal/mol
$\Delta H^{\ddagger}$	11.55 ± 0.65 kcal/mol	20.25 ± 0.89 kcal/mol
$\Delta S^{\ddagger}$	−24.5 ± 2.0 eu	−5.4 ± 2.7 eu

at low [(−)-sparteine] and rate-limiting β-hydride elimination at high [(−)-sparteine]. Other mechanistic scenarios can be considered for this system that may show saturation in (−)-sparteine. One possibility entails preactivation of the alcohol through hydrogen bonding to (−)-sparteine, followed by catalyst coordination and deprotonation.[36] For this case, saturation in alcohol should be seen simultaneous with saturation in (−)-sparteine. Also, if it is assumed that preactivation is rate limiting at low [(−)-sparteine], there should be no dependence on [Pd((−)-sparteine)Cl_2]. This possible scenario is effectively ruled out by the observation of a first-order rate dependence on [Pd((−)-sparteine)Cl_2] as well as no observed saturation in alcohol over the concentration range evaluated.

Additionally, two possible pathways can be considered involving the coordination of a second (−)-sparteine onto the catalyst that may account for saturation in (−)-sparteine. The first scenario entails coordination of a second (−)-sparteine to [Pd((−)-sparteine)Cl_2], followed by alcohol coordination and deprotonation to form the Pd-alkoxide. In this case, at low [(−)-sparteine], there should be no dependence on alcohol concentration. Thus, it is effectively ruled out due to the observed alcohol concentration dependence under these conditions.[37] The second possibility is coordination of a second (−)-sparteine after alcohol coordination followed by intramolecular deprotonation by (−)-sparteine. This scenario seems unlikely due to the structurally large nature of (−)-sparteine, and upon alcohol coordination, the resulting complex would be dicationic. Therefore, the original mechanistic proposal (Scheme 1) is the most compatible with kinetic data presented.

Origin of Enantioselectivity. Key considerations for the development of new catalysts are the influence on enantioselectivity of the change in rate-limiting steps from deprotonation

(34) *p*-Nitrobenzyl alcohol formed the aldehyde initially, but then formed another side product. Because of the determination of the rate by aldehyde formation, this substrate was not used for the Hammett plot at low [(−)-sparteine].

(35) For oxidations using benzyl alcohol, 15 mol % (−)-sparteine is suitable for saturation.

(36) (−)-Sparteine has been used to thermodynamically resolve tertiary acetylenic alcohols, see: Toda, F.; Tanaka, K.; Ueda, H.; Oshima, T. *J. Chem. Soc., Chem. Commun.* **1983**, 743.

(37) For this scenario, a second-order dependence in [(−)-sparteine] should be observed at low [(−)-sparteine]. Additionally, NMR experiments showed no evidence of another species other than Pd[(−)-sparteine]Cl_2.

Table 4. Intrinsic k_{rel} and Racemate k_{rel} Values at High and Low [(−)-Sparteine]

(–)-sparteine (mol %)	rate (*R*) (M/min)	rate (*S*) (M/min)	intrinsic k_{rel}	racemate k_{rel}
4	1.91×10^{-5}	3.11×10^{-6}	6.1	7.6 ± 2.0
50	7.51×10^{-5}	7.11×10^{-6}	11	25 ± 4.6

to β-hydride elimination and the overall origin of asymmetric induction. Three steps which could possibly influence the selectivity of the Pd-catalyzed aerobic oxidative kinetic resolution are (1) alcohol binding, (2) alkoxide formation, and/or (3) β-hydride elimination (see Scheme 1). Catalyst turnover by oxygen does not presumably involve the alcohol; therefore, it should not influence selectivity. At low [(−)-sparteine], possible influences on selectivity are thermodynamic binding and kinetic deprotonation. At high [(−)-sparteine], thermodynamic binding, thermodynamic deprotonation, and kinetic β-hydride elimination can affect selectivity.

An apparent discrepancy is revealed when the intrinsic k_{rel} values, calculated from the relative oxidation rates for each enantiomer of *sec*-phenethyl alcohol, are compared to the k_{rel} values calculated from oxidative kinetic resolution of the racemic alcohol at both high and low [(−)-sparteine] (Figure 2). The intrinsic k_{rel} values arise from asymmetric discrimination due to the kinetic steps alone because a single enantiomer is used in these experiments. At low [(−)-sparteine], the intrinsic k_{rel} is 6.1, solely due to the selectivity of kinetic deprotonation (Table 4). At high [(−)-sparteine], the intrinsic k_{rel} value is 11 and is only attributable to the selectivity of kinetic β-hydride elimination. Unlike the intrinsic k_{rel} values, the k_{rel} values calculated from the Pd-catalyzed oxidative kinetic resolution of *sec*-phenethyl alcohol at both high and low [(−)-sparteine] can include thermodynamic events in addition to the known kinetic contributions (Table 4). At low [(−)-sparteine], the racemate k_{rel} value is 7.6, within error of the intrinsic k_{rel} value of 6.1. This implies that, at low [(−)-sparteine], deprotonation is enantiodetermining and alcohol binding does not play a significant role in asymmetric induction. In contrast, the racemate k_{rel} increases to 25 at high [(−)-sparteine], a value 2.3 times higher than the intrinsic k_{rel} value of 11. This increase in selectivity can be explained by a thermodynamic difference in stability between the diastereomeric alkoxide species, $\Delta\Delta G_f$, formed prior to kinetic β-hydride elimination (Figure 8). A difference of 0.52 kcal/mol between the diastereomeric alkoxides with the *R*-alkoxide being favored corresponds to a selectivity factor of 2.3. When the $\Delta\Delta G_f$ (0.52 kcal/mol) is added to $\Delta\Delta G^{\ddagger}$ associated with kinetic β-hydride elimination (1.59 kcal/mol, $k_{rel} = 11$), the total difference in free energy is 2.11 kcal/mol corresponding to the ultimately calculated k_{rel} value of 25. In this system, the k_{rel} value is not only defined by $\Delta\Delta G^{\ddagger}$, the difference in $\Delta G_R^{\ddagger}$ and $\Delta G_S^{\ddagger}$, but it is also influenced by $\Delta\Delta G_f$, thus providing a supplementary source of selectivity from the difference in the zero point energies of the diastereomeric alkoxides. Therefore, the k_{rel} or selectivity is a combination of $\Delta\Delta G^{\ddagger}$ and $\Delta\Delta G_f$ in accordance with the Curtin−Hammett principle.[38,39] These experiments implicate that the optimal selectivity is achieved at high [(−)-sparteine] when there is both a selective kinetic component attributable to rate-limiting β-hydride elimination and a selective thermodynamic component due to the difference in stability of the diastereomeric alkoxide complexes formed.

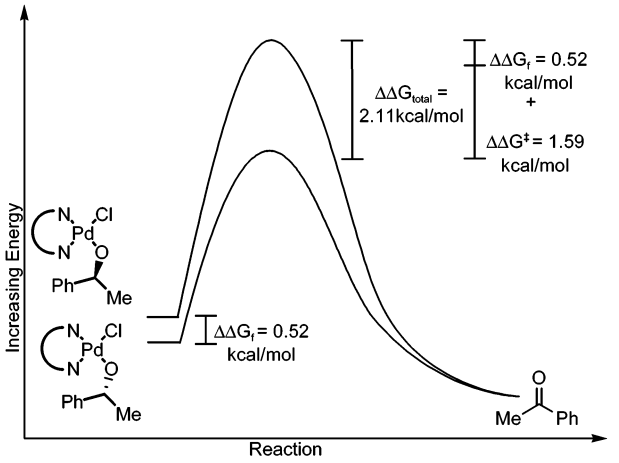
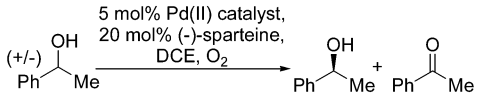


Figure 8. Reaction coordinate of oxidative kinetic resolution.

Table 5. Activation Parameters for *sec*-Phenethyl Alcohol Oxidation

activation parameters	(*R*)-*sec*-phenethyl alcohol	(*S*)-*sec*-phenethyl alcohol
$\Delta G^{\ddagger}$ at 60 °C	22.48 ± 0.64 kcal/mol	23.77 ± 2.55 kcal/mol
$\Delta H^{\ddagger}$	16.76 ± 0.45 kcal/mol	14.31 ± 1.79 kcal/mol
$\Delta S^{\ddagger}$	-17.1 ± 1.4 eu	-28.4 ± 5.4 eu

Table 6. Oxidative Kinetic Resolution Changing Pd Catalyst Counterion



Pd(II) catalyst	k_{rel} value
Pd((−)-sparteine)Cl_2	17.5
Pd((−)-sparteine)$(OAc)_2$	13.0

Additionally, the activation parameters for each enantiomer of *sec*-phenethyl alcohol were determined at high [(−)-sparteine] (Table 5). Eyring plots were constructed by measuring the rates of reaction over a temperature range from 30 to 65 °C. These data indicate selectivity is entropically derived due to the significant difference in $\Delta\Delta S^{\ddagger}$ of 11.3 eu. Qualitatively, the free energy of the transition state of the *R*-alkoxide is smaller than that of the *S*-alkoxide, consistent with the proposed model. Unfortunately, the margins of error are too great to draw specific conclusions.

Counterion Effect. In the development of Pd-catalyzed oxidative kinetic resolution of secondary alcohols, it was observed that the k_{rel} values when using Pd((−)-sparteine)Cl_2 were consistently higher than those measured when using Pd((−)-sparteine)$(OAc)_2$ (Table 6). The difference between these precatalysts is the counterion: chloride versus acetate. Studying this intriguing effect could lead to a better understanding of the role of the counterion in oxidative kinetic resolution. Thus, the dependence of k_{rel} on [(−)-sparteine] was investigated using Pd[(−)-sparteine]$(OAc)_2$. A pronounced enhancement of k_{rel} was observed as [(−)-sparteine] was increased from 0 to 50 mol % (Figure 9). Of note is the observation of catalysis (35% conversion in 22 h) and a measurable k_{rel} value of 1.4 in the

(38) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111.
(39) For a manifestation of the Curtin-Hammett principle in which the minor diastereomeric adduct gives rise to the major enantiomer of product, see: Halpern, J. *Science* **1982**, *217*, 401.

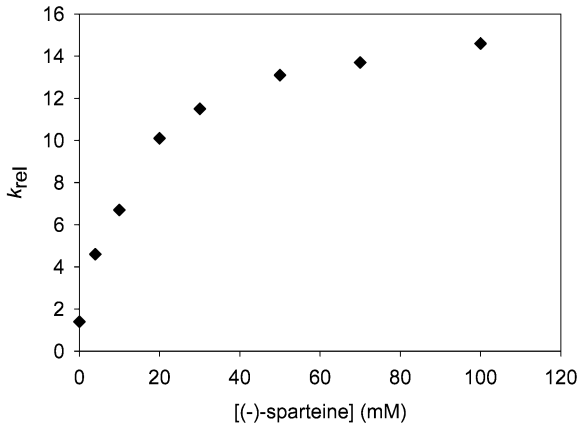


Figure 9. Selectivity dependence on [(−)-sparteine] using Pd((−)-sparteine)$(OAc)_2$.

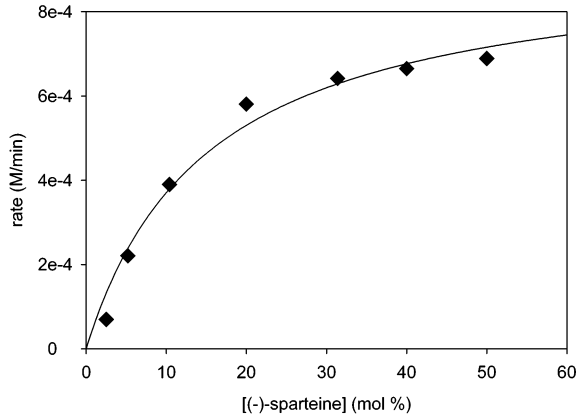


Figure 10. Rate dependence of *sec*-phenethyl alcohol oxidation on [(−)-sparteine] in *tert*-butyl alcohol.

absence of exogenous (−)-sparteine. Recall in the initial studies that Pd[(−)-sparteine]Cl_2 was found to be incompetent without additive (−)-sparteine. These results implicate that acetate can compete with (−)-sparteine as a Brønsted base through a much less selective pathway and only when significant levels of exogenous (−)-sparteine exist can an effective kinetic resolution result. Therefore, the difference in counterions is directly related to their basicity given that chloride is a poor Brønsted base and its use limits any nonselective pathways.[40]

Oxidative Kinetic Resolutions in *tert*-Butyl Alcohol Solvent. Using 1,2-dichloroethane as the solvent, we found that the oxidative kinetic resolution of aliphatic substrates, such as 3,3-dimethyl-2-butanol, proceeds with significantly lower k_{rel} values than the oxidative kinetic resolution of benzylic substrates. When the solvent is switched to *tert*-butyl alcohol, the k_{rel} for the oxidative kinetic resolution of 3,3-dimethyl-2-butanol increases from 7.6 to 17.4.[41] Such a dramatic change in enantioselectivity brings into question whether the solvent change also causes a change in mechanism. Thus, the dependence of the oxidation rate on [(−)-sparteine] was determined in *tert*-butyl alcohol (Figure 10). As observed in 1,2-dichloroethane, a nonlinear relationship of rate to [(−)-sparteine] was obtained and fit using a nonlinear least squares to an equation describing saturation with good agreement. This is reasonable initial evidence that there are no significant changes in mechanism when the solvent is changed from 1,2-dichloroethane to *tert*-butanol. While a precise explanation for the increase in k_{rel} values by switching to *tert*-butyl alcohol solvent is unclear, a simple solvent polarity argument may be made in which *tert*-butyl alcohol more readily supports any cationic intermediates.

Conclusions

The mechanistic details for the Pd-catalyzed aerobic oxidative kinetic resolution of secondary alcohols have been elucidated. Saturation kinetics were observed for the dependence of oxidation rate on (−)-sparteine concentration. At low [(−)-sparteine], when the dependence on [(−)-sparteine] is first order, deprotonation is proposed to be rate determining due to a first-order dependence in both alcohol concentration and Pd((−)-sparteine)Cl_2 concentration. At saturation, when the dependence on [(−)-sparteine] is zero order, KIE experiments, [(−)-sparteine HCl] inhibition, and Hammett correlations support β-hydride elimination being the rate-limiting step. These overall observations are further supported by the measurement of activation parameters at high and low [(−)-sparteine].

The origin of asymmetric induction was also elucidated under both conditions. At low [(−)-sparteine], it was found that the intrinsic k_{rel} was experimentally equivalent to the calculated racemate k_{rel}, indicating that deprotonation is both enantio- and rate determining. In contrast, the intrinsic and racemate k_{rel} values were significantly different at high [(−)-sparteine]. This discrepancy is proposed to arise from both selective kinetic β-hydride elimination and a thermodynamic difference in the stability of the diastereomeric alkoxides formed in the reaction.

A key, nonintuitive discovery from this investigation is (−)-sparteine plays a dual role in the oxidative kinetic resolution of secondary alcohols as a chiral ligand on palladium and as a chiral Brønsted base. This insight has led to new catalysts for oxidative kinetic resolution in which chiral carbene ligands successfully replace (−)-sparteine.[42] Further studies are ongoing regarding replacement of (−)-sparteine as the chiral base using information acquired from these investigations.

Experimental Section

General. All reagents, unless specified, were bought from commercial sources and used without further purification. It was necessary to purify (*R*)-(+)-*sec*-phenethyl alcohol purchased from Alpha Aesar by flash chromatography (20% ethyl acetate/hexanes) and distillation. (−)-Sparteine was prepared by dissolving (−)-sparteine hydrogensulfate pentahydrate salt in water, adding sodium hydroxide pellets until the pH > 10, and extracting the free-base product with ether (three times). The extract was dried over sodium sulfate and filtered, and the solvent was removed in vacuo. 1,2-Dichloroethane (DCE) and trimethylsilyl chloride (TMSCl) were distilled from calcium hydride. Methanol was distilled from potassium carbonate. Unless otherwise specified, analysis of reactions was performed using GC equipped with a chiral column (autosampling 6890 GC fitted with a Hewlett-Packard HP Chiral 20% permethylated β-cyclodextrin column (0.25 μm film thickness, 30 m length, phase ratio 320) using a 2.0 mL/min hydrogen flow rate). Tetradecane was used as an internal standard. A 120 °C constant temperature program for 9.5 min was used to separate (*R*)-(+)- from (*S*)-(−)-*sec*-phenethyl alcohol and the internal standard. In situ IR was used to analyze reactions for certain experiments (ASI ReactIR 1000). A three-neck jacketed apparatus equipped with a condenser, an O_2-

(40) Upon comparing the pK_a values, we found that acetate (pK_a of 12.3 in DMSO) can function as a base much more readily than chloride (pK_a = 1.8 in DMSO).

(41) Benzylic alcohols also resolve with good k_{rel} values using *tert*-butyl alcohol as a solvent. Mandal, S. K.; Jensen, D. R.; Pugsley, J. P.; Sigman, M. S. *J. Org. Chem.* **2003**, ASAP.

(42) Jensen, D. R.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 63.

filled balloon, and a Schlenk sidearm was utilized for these kinetic experiments.

Standard solutions were prepared for use in kinetic experiments. A standard solution of (−)-sparteine was prepared by adding the desired amount of (−)-sparteine to a 2 mL volumetric flask and diluting with DCE to 2 mL. A 0.0123 M standard solution of Pd ((−)-sparteine)Cl_2 was prepared in situ by adding 12.8 mg of $Pd(MeCN)_2Cl_2$ (1 equiv, 0.0494 mmol) and 300 μL of 0.1822 M (−)-sparteine solution (1.1 equiv, 0.0547 mmol) to a 4 mL volumetric flask. DCE was used to dilute to 4 mL. The NMR spectrum of the catalyst solution prepared in the described manner is identical to the NMR spectrum of recrystallized Pd((−)-sparteine)Cl_2 (see Supporting Information). Standard solutions of the alcohols were prepared by adding *sec*-phenethyl alcohol and 0.1 mol equiv of tetradecane (internal standard) to a 2 mL volumetric flask and diluting to volume with freshly distilled DCE. The concentrations of the alcohols were determined by UV−vis spectroscopy (HP 8452A diode array spectrophotometer).

Recrystallization of Pd((−)-sparteine)$(OAc)_2$. In a vial were dissolved $PdOAc_2$ (1.0 equiv) and (−)-sparteine (1.1 equiv) in 1,2-dichloroethane. To this was added hexanes. The solvent volume was reduced, and the vial was placed in a jar containing hexanes. A single yellow crystal suitable for X-ray diffraction was obtained after 1 week. See Supporting Information for X-ray analysis.

External Base Screen. In a 5 mL round-bottom flask was dissolved 4.1 mg (0.01 mmol, 0.05 equiv) of Pd((−)-sparteine)Cl_2 in 0.5 mL of DCE. To this, 0.02 mmol, 0.1 equiv, of external base was added. The reaction flask was attached to a condenser, and the system was evacuated of air and refilled with oxygen from a balloon. The evacuation and refill was repeated three times. The flask was placed in a 65 °C constant temperature oil bath. To this, 24 μL (0.20 mmol, 1.0 equiv) of the alcohol in 0.5 mL of DCE was added with a small amount of tetradecane as internal standard, and a small sample was saved as a time zero reference. An aliquot (∼0.1 mL) was taken from the reaction via syringe and quenched by diluting in a methanol/dichloromethane solution. Conversion was measured relative to the tetradecane internal standard. The k_{rel} was then calculated.

Standard Kinetic Protocol. Four kinetic experiments were performed simultaneously. In each 10 mL Schlenk tube, equipped with a stir bar, the desired amounts of Pd((−)-sparteine)Cl_2 (0.001 mmol, 0.01 equiv) solution and excess (−)-sparteine were added and brought to a volume of 0.5 mL by addition of DCE. Condensers were attached to the Schlenk tubes to prevent loss of solvent. When the apparatus was assembled with the four Schlenk tubes attached, it was evacuated of air by water aspiration and filled with oxygen from a balloon. This process was repeated three times. After the four reactions were allowed to stir for 30 min while heating in a 60 ± 0.1 °C oil bath, 0.5 mL of *sec*-phenethyl alcohol (0.1 mmol, 1 equiv) solution, containing tetradecane as internal standard (0.01 mmol, 0.1 equiv), was syringed into each reaction vessel. A small sample of alcohol solution was retained as a time zero reference. Aliquots (25−50 μL) were syringed out as the reactions progressed and quenched with 1 mL of 2% TFA in methanol. The aliquots were analyzed by GC, and the reactions were followed to 5−15% conversion to determine the initial rates. This protocol was used for [Pd((−)-sparteine)Cl_2] dependence, [(−)-sparteine] dependence, [alcohol] dependence, and [(−)-sparteine HCl] dependence.

Preparation of (−)-Sparteine HCl. To a 10 mL round-bottom flask was added 1.5 mL of DCE. To this were added 110 mg of (−)-sparteine (0.5 mmol, 1 equiv), 21 μL of methanol (0.55 mmol, 1.1 equiv), and 58.5 μL of trimethylsilyl chloride (0.46 mmol, 0.98 equiv). This mixture was stirred for 5 min, and the solvent was removed in vacuo. A white precipitate formed upon removal of the solvent (97% yield). ^{1}H NMR (300 MHz $(CD_3)_2SO$): δ 10.99 (s, 1H), 4.00 (dd, J = 13.0 Hz, 2H), 3.84−2.77 (m, 10H), 2.71−1.15 (m, 14H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ 17.61, 22.13, 23.01, 23.13, 24.26, 25.87, 28.43, 32.20, 32.26, 46.21, 52.18, 55.21, 60.10, 61.40, 65.02.

KIE Studies. Preparation of (*S*)-α-D-*sec*-Phenethyl Alcohol. To a 100 mL round bottom flask was added 12.85 mL of methanol. To this was added 3 mL of acetophenone (25.7 mmol, 1 equiv) by syringe. Sodium borodeuteride, 1.19 g (28.3 mmol, 1.1 equiv), was added over 20 min while the mixture was stirred under nitrogen at 0 °C. After 2 h, the reaction was worked up by concentrating in vacuo, partitioning between water and dichloromethane, and extracting into dichloromethane three times. The resulting oil was further purified by bulb-to-bulb distillation. A 78% yield was obtained. Purity was determined by GC equipped with a chiral column to be >99% with 93% deuterium incorporation by GC mass spectroscopy.

The racemic deuterated product was then subjected to an oxidative kinetic resolution to obtain the (*S*)-(−)-enantiomer of α-D-*sec*-phenethyl alcohol. To a 50 mL Schlenk flask was added 274 mg of $Pd(OAc)_2$ (1.22 mmol, 0.1 equiv). To this were added 840 μL of (−)-sparteine (3.66 mmol, 0.3 equiv) and 16 mL of DCE. The flask was fitted with a condenser and a balloon filled with oxygen. The reaction vessel was evacuated and filled with oxygen from the balloon three times and allowed to stir at 60 ± 0.1 °C for 30 min. A solution of 1.5 g of α-D-*sec*-phenethyl alcohol (12.2 mmol, 1 equiv) and 335 μL of tetradecane (1.22 mmol, 0.1 equiv) in 6 mL of DCE was then added by syringe. After 3 days, the reaction was concentrated by water aspiration and purified by column chromatography (20% ethyl acetate/hexanes). The deuterated alcohol was further purified by bulb-to-bulb distillation to yield 235 mg of clear oil (15% yield). The isolated material was determined to be >99% ee.

Standard solutions of (*S*)-α-D-*sec*-phenethyl alcohol and (*S*)-α-*sec*-phenethyl alcohol were made up with 1 equiv alcohol and 0.1 equiv of tetradecane in DCE. The molarity of these solutions was confirmed by UV−vis. The absorbance was recorded at 270 nm at various concentrations of *sec*-phenethyl alcohol to construct a calibration curve.

To each of four 10 mL Schlenk tubes was added 81 μL of 0.0123 M Pd((−)-sparteine)Cl_2 solution (0.001 mmol, 0.01 equiv). To two reaction flasks were added 19 μL of 0.2122 M (−)-sparteine solution (0.004 mmol, 0.04 equiv) and 400 μL of freshly distilled DCE to bring the reaction volume to 0.5 mL. To the other two Schlenk tubes were added 235 μL of 0.2122 M (−)-sparteine solution (0.05 mmol, 0.5 equiv) and 184 μL of freshly distilled DCE to bring the reaction volume to 0.5 mL. The four reactions were allowed to stir under oxygen at 60 ± 0.1 °C for 30 min, and 500 μL of either (*S*)-*sec*-phenethyl alcohol or (*S*)-α-D-*sec*-phenethyl alcohol solution (0.1 mmol, 1 equiv) was added to each reaction so that both substrates were reacted at both (−)-sparteine concentrations (4 mol %, 50 mol %). Aliquots (25−50 μL) were syringed out as the reactions progressed, quenched with 1 mL of 2% TFA in methanol, and analyzed by GC. The disappearance of substrate was plotted against time for each substrate at each concentration. The rate was calculated for each reaction. k_D values were corrected for incomplete deuterium incorporation[43] (93%). The ratios of k_H/k_D were calculated for each set of experiments. At 4 mol % (−)-sparteine, these reactions were run in quadruplicate, while at 50 mol % (−)-sparteine, they were run in triplicate.

Hammett Studies. To the reaction apparatus attached to the in situ IR probe was added 133 μL of Pd((−)-sparteine)Cl_2 (0.00504 mmol, 0.0168 equiv) standard solution (0.0365 M in DCE). To this were added 34 μL of (−)-sparteine (0.148 mmol, 0.5 equiv) and 533 μL of DCE for high base conditions. A 50 ± 0.1 °C oil bath was elevated to immerse the reaction vessel. The apparatus was evacuated of air by water aspiration and refilled with oxygen from the balloon three times. Next, 300 μL of alcohol solution (0.3 mmol of substrate alcohol) was added to begin the reaction. The reactions were monitored using in situ IR to measure the appearance of the carbonyl stretch band for each aldehyde product. For low base conditions, the same procedure was followed except 45 μL of 0.133 M (−)-sparteine solution (0.006 mmol, 0.02 equiv) was added with 522 μL of DCE. Rates from 5% to 7.5%

(43) Lewis, E. S.; Funderburk, L. *J. Am. Chem. Soc.* **1967**, *89*, 2322.

conversion were measured. The data were plotted log k_{obs} versus σ (or σ^+); see Supporting Information for data and Sigma Plot analysis.

Eyring Studies. Benzyl Alcohol Oxidation. To the reaction apparatus attached to the in situ IR probe was added 133 μL of Pd((−)-sparteine)Cl_2 (0.00504 mmol, 0.0168 equiv) standard solution (0.0365 M in DCE). To this were added 34 μL of (−)-sparteine (0.148 mmol, 0.5 equiv) and 533 μL of DCE for high base conditions. An oil bath, varied in temperature from 30 to 65 ± 0.1 °C, was elevated to immerse the reaction vessel. The apparatus was evacuated of air by water aspiration and refilled with oxygen from the balloon three times. Next, 300 μL of alcohol solution (0.3 mmol of substrate alcohol in DCE) was added to begin the reaction. The reactions were monitored using in situ IR to measure the appearance of the carbonyl stretch band for benzaldehyde at 1706.1 cm^{-1}. For low base conditions, the same procedure was followed except 45 μL of 0.133 M (−)-sparteine solution (0.006 mmol, 0.02 equiv) was added with 522 μL of DCE. Rates from 5 to 7.5% conversion were measured for benzyl alcohol. The data were plotted ln(k_{obs}/T) versus 1/T. See Supporting Information for data and Sigma Plot analysis.

***sec*-Phenethyl Alcohol Oxidation.** To the apparatus was added 26 μL of Pd((−)-sparteine)Cl_2 (0.001 mmol, 0.010 equiv) standard solution (0.0365 M in DCE). To this were added 11.5 μL of (−)-sparteine (0.050 mmol, 0.5 equiv) and 662 μL of DCE for high base conditions. An oil bath, varied in temperature from 30 to 65 ± 0.1 °C, was elevated to immerse the reaction vessel. The apparatus was evacuated of air by aspiration and refilled with oxygen from the balloon three times. Next, 300 μL of alcohol solution (0.3 mmol of (*R*)- or (*S*)-*sec*-phenethyl alcohol in DCE) was added. The reactions were monitored using in situ IR to measure the appearance of the carbonyl stretch band for acetophenone at 1686.8 cm^{-1}. Rates from 3% to 8% conversion were measured for (*R*)-*sec*-phenethyl alcohol and (*S*)-*sec*-phenethyl alcohol. The data were plotted ln(k_{obs}/T) versus 1/T. See Supporting Information for data and Sigma Plot analysis.

Oxidative Kinetic Resolutions with Pd((−)-sparteine)Cl_2. To 10 mL Schlenk tubes was added 81 μL of 0.0123 M Pd((−)-sparteine)Cl_2 solution (0.001 mmol, 0.01 equiv). To one reaction flask were added 7.5 μL of (−)-sparteine solution (0.004 mmol, 0.04 equiv) and 411 μL of freshly distilled DCE to bring the reaction volume to 0.5 mL. To the other Schlenk tube were added 97 μL of (−)-sparteine solution (0.05 mmol, 0.5 equiv) and 322 μL of freshly distilled DCE to bring the reaction volume to 0.5 mL. The flasks were evacuated by water aspiration and filled with oxygen from the balloon three times. The reactions had been stirred under oxygen at 60 ± 0.1 °C for 30 min, and 0.5 mL of *sec*-phenethyl alcohol solution (0.1 mmol, 1 equiv), containing tetradecane as internal standard, was syringed into each reaction. Aliquots (25−50 μL) were syringed out as the reactions progressed, quenched with 1 mL of 2% TFA in methanol, and analyzed by GC. Samples were taken every 12 h, and relative rates were calculated as a function of conversion and enantiomeric excess at each time.

Oxidative Kinetic Resolutions with Pd((−)-sparteine)$(OAc)_2$. To a 10 mL Schlenk tube was added 80 μL of 0.05 M Pd((−)-sparteine)$(OAc)_2$ solution (0.004 mmol, 0.05 equiv). To this were added 25 μL of 0.326 M (−)-sparteine solution (0.00815 mmol, 0.1 equiv) and 195 μL of freshly distilled DCE to bring the reaction volume to 300 μL. This was repeated for the three other reactions for each run, keeping the amount of catalyst constant while varying the amount of (−)-sparteine from 0.0 to 0.04 mmol (0.0−0.5 equiv) and adding DCE to a total volume of 300 μL. The apparatus with flasks attached was evacuated by water aspiration and filled with oxygen from the balloon. This process was repeated three times. After the reactions had been stirred under oxygen at 60 ± 0.1 °C for 30 min, 100 μL of *sec*-phenethyl alcohol solution (0.08 mmol, 1 equiv with 0.008 mmol, 0.1 equiv of tetradecane standard) was syringed into each reaction. Aliquots (25−50 μL) were syringed out as the reactions progressed, quenched with 1 mL of 2% TFA in methanol, and analyzed by GC. Samples were taken after 22 h, and the relative rates were calculated as a function of conversion and enantiomeric excess.

[(−)-Sparteine] Dependence in *tert*-Butyl Alcohol. To the apparatus was added 5.1 mg of Pd((−)-sparteine)Cl_2 (0.0123 mmol, 0.05 equiv). To this were added 11.5 μL of (−)-sparteine (0.05 mmol, 0.2 equiv), 958 μL of *tert*-butyl alcohol, and 25 mg of 3 Å activated MS. For other reactions, [(−)-sparteine] was varied from 2.5 to 50 mol % (0.005−0.125 mmol, 0.025−0.5 equiv), adding *tert*-butyl alcohol to bring the reaction volume to 0.97 mL. A 65 ± 0.1 °C oil bath was elevated to immerse the reaction vessel. The apparatus was evacuated of air by water aspiration and refilled with oxygen from a balloon three times. Next, 30 μL of alcohol (*R*)-*sec*-phenethyl alcohol (0.25 mmol) was added. The reactions were monitored using in situ IR to measure the appearance of the carbonyl stretch band for acetophenone at 1683.0 cm^{-1}. Rates from 3% to 8% conversion were measured.

Acknowledgment. This work was supported by the National Institutes of Health (NIGMS #RO1 GM63540) and supported by a Research Innovation Award sponsored by the Research Corporation. We would like to thank the University of Utah Research Foundation, Merck Research, Rohm and Haas Research, and Invenux Inc. for partial support of this research. We thank the donors of the Petroleum Research Fund, administered by the ACS, for partial support of this research (PRF#37536-G1). We thank Johnson Matthey for supplies of various palladium salts. We also thank David R. Jensen, Professor Joel Harris, and Professor Gary Keck for insightful discussions. The X-ray crystal structure analysis was performed by Atta Arif.

Supporting Information Available: Statistical analyses, rate tables, rate law derivation, X-ray crystallography analysis, and NMR spectra (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA034262N