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Dual Role of (−)-Sparteine in the Palladium-Catalyzed Aerobic Oxidative Kinetic Resolution of Secondary Alcohols

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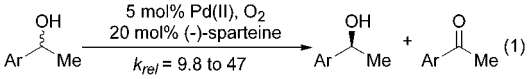
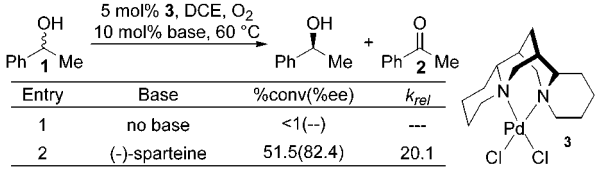
Pd(II)-catalyzed aerobic oxidations are a powerful class of transformations for organic synthesis.[1,2] An excellent example is the simple oxidation of alcohols,[3,4] which provides a practical alternative to high oxidation state metal-mediated oxidation. The development of improved catalysts for Pd(II)-catalyzed aerobic alcohol oxidations would benefit from an understanding of the two distinct processes involved: (a) formation of a palladium alkoxide followed by β-hydride elimination and (b) regeneration of the catalyst using molecular oxygen.[5] Details of the metal-catalyzed alcohol oxidation sequence and the precise role of additives are poorly understood.



(1)

We,[6] as well as Ferreira and Stoltz,[7] discovered that the combination of a Pd(II) salt and (−)-sparteine effectively catalyzes the aerobic oxidative kinetic resolution of secondary alcohols (eq 1). This reaction gives moderate to good k_{rel} values for various benzylic alcohols. A key observation from our study is that the isolated Pd((−)-sparteine)Cl_2 complex **3** is incompetent as a catalyst without additional (−)-sparteine (Figure 1). Herein we report a mechanistic study identifying the role of added (−)-sparteine as an exogenous base, which controls both the reactivity and enantioselectivity of the catalytic process.



Entry	Base	%conv(%ee)	k_{rel}
1	no base	<1(--)	---
2	(-)-sparteine	51.5(82.4)	20.1

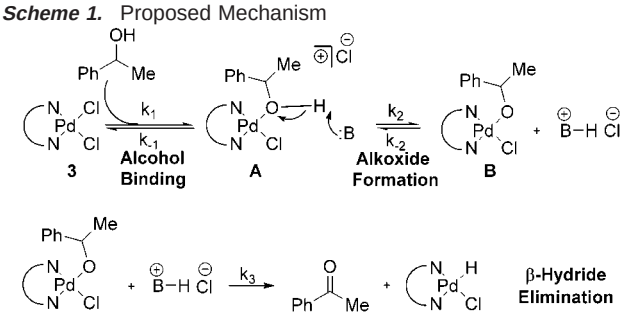
Figure 1. Dependence on exogenous base.

The empirical observation that (−)-sparteine is necessary for catalysis implicates a base-promoted pathway in the mechanism. In the generally accepted mechanism for the Pd(II)-catalyzed oxidation of alcohols,[8] a palladium alkoxide **B** is formed after alcohol binding, followed by β-hydride elimination[9] of **B** to yield a ketone product (Scheme 1). A base may be necessary to deprotonate the bound alcohol **A**, considering that Cl^- is a poor base. We sought to clarify the role of added (−)-sparteine as an exogenous base by determining the kinetic dependence.

For the kinetic studies, single enantiomers of alcohol **1** were used to avoid complications associated with competitive binding of enantiomers. Initial kinetic experiments did not give a clear indication of reaction order, suggesting a complex kinetic scenario. Therefore, initial rate kinetics were selected as a means to elucidate the kinetic dependence on [(−)-sparteine].

Using 1 mol % of **3** at 60 °C,[10] the dependence of exogenous [(−)-sparteine] was measured for both enantiomers of **1**. Over a

Scheme 1. Proposed Mechanism



35-fold change in [(−)-sparteine] (0.002−0.069 mM, 2−69 mol %), a nonlinear relationship between [(−)-sparteine] and the reaction rate was observed (Figure 2). Fitting each curve to an equation describing saturation[11,12] shows excellent agreement. Additionally, a first-order dependence on [**3**] was observed.

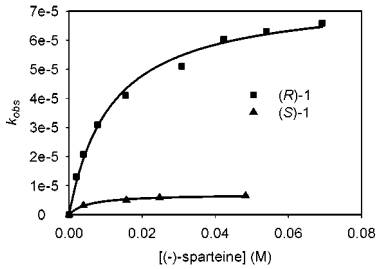


Figure 2. Rate dependence on [(−)-sparteine].

The first-order (−)-sparteine dependence at low [(−)-sparteine] suggests that deprotonation is rate-limiting under these conditions. The observed saturation kinetics suggests that another step, either alcohol binding, β-hydride elimination, or Pd(II) regeneration with O_2, becomes rate-limiting.[13] Probing the dependence on [alcohol] should distinguish these possibilities. A dependence on [alcohol] should be observed for either rate-limiting alcohol binding or β-hydride elimination but not for Pd(II) regeneration with O_2.[14] Under both low and saturating (−)-sparteine conditions,[15] a first-order [alcohol] dependence was observed in the concentration range of 0.02−0.2 M, ruling out Pd(II) regeneration with O_2 as rate-limiting. While an observed saturation in alcohol would be expected for rate-limiting β-hydride elimination, kinetic measurements at higher alcohol concentrations proved difficult due to catalyst decomposition and inconclusive kinetic measurements.

To differentiate whether alcohol binding or β-hydride elimination becomes rate-limiting under saturation conditions, the dependence of [(−)-sparteine-HCl] was investigated. If alcohol binding becomes rate-limiting (formation of **A**), increasing [(−)-sparteine-HCl] should have little effect on the observed rate. In contrast, adding (−)-sparteine-HCl should inhibit the reaction if β-hydride elimination becomes rate-limiting according to the derived rate law.[16] In the event, a significant retardation in the rate was observed by

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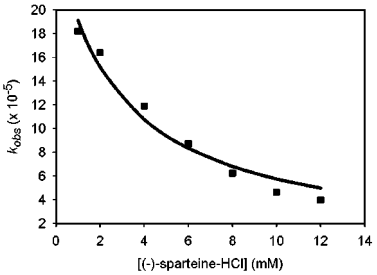
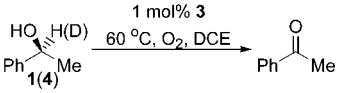


Figure 3. Dependence on [(−)-sparteine-HCl].

adding (−)-sparteine-HCl (Figure 3).[17] This is consistent with β-hydride elimination becoming rate-limiting under (−)-sparteine saturation conditions.

Another experiment to examine rate-limiting β-hydride elimination under saturation conditions is the determination of relative rates for (*S*)-**1** versus that for (*S*)-**4**.[18] Using low [(−)-sparteine], in which deprotonation is rate-limiting, no kinetic isotope effect (KIE) would be expected. However, if β-hydride elimination becomes rate-limiting under saturating (−)-sparteine, a primary KIE is predicted. In the experiment, no appreciable KIE was observed under low [(−)-sparteine] (Figure 4). In contrast, a KIE of 1.31 ± 0.04 was measured under saturation conditions. This small primary KIE is similar to a previously measured KIE of 1.4 ± 0.1 for the decomposition of *trans*-$[Pd(CH_2CD_3)_2(PMePh_2)_2]$ in which β-hydride elimination has been implicated as the rate-limiting step.[19,20] Considering these experiments, rate-limiting β-hydride elimination under saturation is most consistent.



(-)-sparteine	k_H/k_D
4 mol%	1.04 ± 0.06
50 mol%	1.31 ± 0.04

Figure 4. Kinetic isotope effects.

Another consideration is the influence on enantioselectivity of the change in rate-limiting steps from deprotonation to β-hydride elimination. Using low [(−)-sparteine], the k_{rel} value[21] for racemic **1** is 7.6 (Table 1). However, under saturation conditions, the observed k_{rel} value increases to 25. This increase in k_{rel} suggests a change in enantioselectivity-influencing steps. Comparing these k_{rel} values for the racemate to the relative rates measured from the single enantiomer kinetic experiments presented in Figure 1 (intrinsic k_{rel}) provides insight into the origin of enantioselectivity. At 4 mol % (−)-sparteine, the intrinsic k_{rel} is 6.1, a value comparable to that for the racemate within experimental error and consistent with a kinetic deprotonation being responsible for the observed enantioselectivity. In contrast, base saturation conditions reveal an intrinsic k_{rel} of 11, approximately half the observed k_{rel} for the racemate. The disparity is best explained by the combination of a kinetic β-hydride elimination coupled with a thermodynamic difference between the diastereotopic alkoxides **B**, a demonstration of the Curtin−Hammett principle.[22] Therefore, the intrinsic k_{rel} measurement, in which **B** arises from a single enantiomer of alcohol **1**, does not account for thermodynamic differences in alkoxide stability.

In conclusion, (−)-sparteine plays a dual role in the oxidative kinetic resolution of alcohols, as a ligand on palladium and an exogenous base. Higher concentrations of exogenous (−)-sparteine allow β-hydride elimination to become rate-limiting. The enantioselective events are additionally controlled by (−)-sparteine in which high concentrations afford a more selective kinetic resolution. These results show that the exogenous base and the ligand on palladium play vital roles in Pd-catalyzed aerobic oxidations and provide a foundation for the development of second-generation catalysts for the oxidative kinetic resolution.

Table 1. Effect of (−)-Sparteine Concentration on k_{rel}

(–)-sparteine (mol %)	k_{obs} *R*-(**1**)	k_{obs} *S*-(**1**)	intrinsic k_{rel}	racemate k_{rel}[c]
4[a]	1.9×10^{-5}	3.1×10^{-6}	6.1	7.6 ± 2.0
50[b]	7.5×10^{-5}	7.1×10^{-6}	11	25 ± 4.6

[a] Rates extrapolated from the fitted curves in Figure 1. [b] Rates are the calculated V_{max} from each fitted curve. [c] Average of multiple experiments.

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Note Added after ASAP: Equation in ref 16 in ASAP version (6/20/02) contained errors. Final Web and print versions are correct.

Supporting Information Available: Experimental procedures and kinetic data are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) In these studies, 4 mol % (−)-sparteine is used for low base concentration conditions and 50 mol % for saturation conditions.
(16) $$\text{rate} = \frac{k_3k_2k_1[\mathbf{1}][\mathbf{3}][(-)\text{-sparteine}]}{k_2[(-)\text{-sparteine}](k_1[\mathbf{1}] + k_3 + k_{-2}[\text{BHCl}]) + k_{-1}(k_3 + k_2[\text{BHCl}])}$$
(17) Fit to $k_{obs} = k'/(k'' + [(-)\text{-sparteine-HCl}])$ where k' and k'' are constants.
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