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An Experimentally Derived Model for Stereoselectivity in the Aerobic Oxidative Kinetic Resolution of Secondary Alcohols by (Sparteine)$PdCl_2$

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Palladium-catalyzed aerobic oxidation of alcohols has a rich history that began with the first example by Schwartz in 1977.[1,2] Recently, enantioselective aerobic oxidation of secondary alcohols by Pd and (−)-sparteine (sp) has emerged as a powerful method for the preparation of enantioenriched alcohols by kinetic resolution.[3−5] While numerous improvements to oxidative kinetic resolution (OKR) have been made[3b,c] and the mechanism has been analyzed using kinetics,[6] there have been no reports detailing a structural model for asymmetric induction by sp in these reactions. Herein, we describe experiments that probe the origins of stereoselectivity in the oxidation and present a nonintuitive model for the absolute stereochemical outcome. This model is based on the reactivity and solid-state structures of (sp)Pd^{II} complexes, including the first reported structure of a chiral Pd(II) alkoxide relevant to this problem.

The oxidation of alcohols to carbonyl compounds most likely involves associative alcohol substitution on Pd, deprotonation of the resulting Pd·ROH complex by base to form a Pd alkoxide, and β-hydride elimination to the carbonyl.[8] For the kinetic resolution of 2° alcohols by (sp)$PdCl_2$, sp, and O_2, Sigman has shown that β-hydride elimination is rate determining and that the observed enantioselectivity results from a combination of the energy barriers for the elimination and the thermodynamic stability of the alkoxide complexes.[6] In this analysis sp was treated as if it mimicked a C_2 symmetric ligand.[9] It is well accepted that C_2 symmetric ligands quaternize the space around a transition metal to achieve asymmetric induction via equivalent hemispheres in the catalyst framework (Figure 1),[10] but the hemispheres of (sp)-ligated Pd are clearly nonequivalent (e.g., Cl^1 vs Cl^2 in **1**, Figure 1). Thus, to probe the structural origin of stereoselection in the OKR, we chose to address the extent to which the C_1 symmetric sp exhibits C_2 symmetry when bound to $PdCl_2$.

To experimentally test whether the C_1 symmetric sp ligand behaved as such (i.e., *not* as a C_2 mimic), complex **1** was treated with $AgSbF_6$ in the presence of pyridine. It was anticipated that if sp mimicked a C_2 symmetric ligand, two cationic pyridyl complexes (**2** and **3**) would be isolated (Scheme 1). In the event, one major complex was observed by ^1H and ^{13}C NMR. Analysis of a single crystal by X-ray diffraction revealed complex **2**.[11]

Intrigued by this observation, we turned to 2-mesityl pyridine to probe the steric environment of the other quadrants. Under identical conditions, we again observed one major product out of four possible, indicating that not only had substitution occurred on a single site of the Pd, but that there was also an atropisomeric preference about the Pd−pyridyl bond. X-ray crystallographic analysis showed that Cl^1 had been substituted as in **2** and that the mesityl group resided exclusively in quadrant **IV** (**4**, Scheme 2). These ligand substitution experiments provide convincing evidence that *sparteine does not mimic a C_2 symmetric ligand when bound to $PdCl_2$.*

To better understand the early stages of the OKR, we set out to synthesize a relevant alkoxide complex. Numerous Pd alkoxides

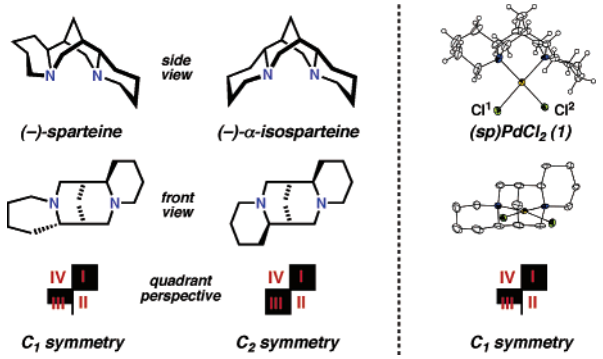
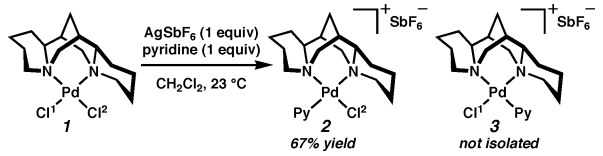
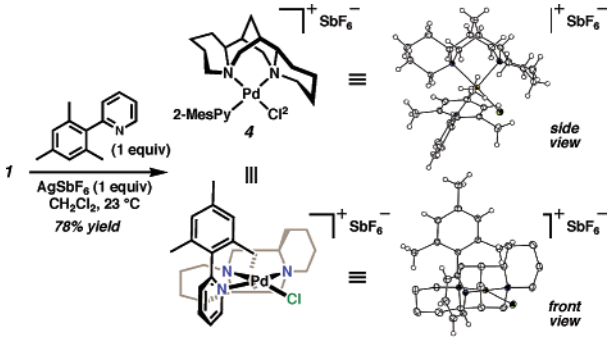


Figure 1.[7] Three perspectives of (−)-sparteine, (−)-α-isosparteine, and (sp)$PdCl_2$ showing the C_1- and C_2 symmetry of these ligands and the quaternization effect around the metal center.

Scheme 1



Scheme 2[7]



have been characterized, but few bear β-hydrogens.[11] A meaningful steric model for the prototypical OKR substrate 1-phenylethanol is α-(trifluoromethyl)benzyl alcohol **5**,[12a,b] in particular **(+)-5**, which corresponds to the more reactive enantiomer in the resolution. Treatment of complex **1** with the sodium alkoxide of (+)-**5** produced a major product that was crystallized and shown to be alkoxide complex **6** by X-ray analysis (Scheme 3). A single isomer is observed, and again substitution of Cl^1 occurs. The phenyl moiety is located in quadrant **IV** in an orientation similar to that of the mesityl group of complex **4**. Moreover, alkoxide **6** contains a distorted square plane in which the benzylic C−H bond points toward the Pd center and the chloride is displaced toward open quadrant **II** (15.4° out of plane).[13,14]

On the basis of the reactivity of (sp)$PdCl_2$ (**1**) and the structures of **2**, **4**, and **6**, we propose a general model for asymmetric induction in the Pd-catalyzed OKR of secondary alcohols. Upon reaction of

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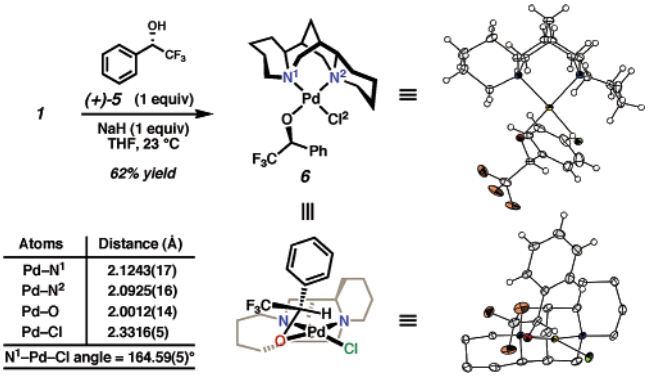
Scheme 3[7]



complex **1** with a racemic alcohol, Cl^1 is substituted preferentially over Cl^2 to form two diastereomeric Pd alkoxides (Figure 2, **7** and **8**), which could reprotonate and dissociate or undergo β-hydride elimination. The unsaturated moiety (R_L) resides in open quadrant **IV**. The position of R_L in quadrant **IV** of reacting diastereomer **8** situates the benzylic C−H bond opposite the oblique Pd−Cl bond, as observed in structure **6**. The same orientation of R_L in quadrant **IV** of the less reactive diastereomer **7** requires that the C−H bond point away from Pd. The transition state for β-hydride elimination (i.e., **9**) is expected to involve a cationic Pd species with four-coordinate square planar geometry,[15] although calculations have shown that Cl^- remains closely associated below the square plane.[16] In structure **6**, and **8** by analogy, the reactive C−H bond is poised to achieve the conformation for elimination via **9** after displacement of Cl^2 into quadrant **II**. This sequence of events minimizes potential steric interactions en route to ketone. In contrast, achievement of a similar conformation by diastereomer **7** would entail destabilizing interactions between R_L and quadrant **III** or between Cl^2 and quadrant **I** (Figure 2). A closely associated Cl^- could further disfavor the diastereomeric transition state (arising from **7**) by steric crowding with R_L. Thus, diastereomer **8** reacts to form ketone, while **7** protolytically dissociates to result in the observed enantiomer of resolved alcohol. This model predicts the absolute stereochemical outcome of every (sp)$PdCl_2$-catalyzed OKR performed to date.

On the basis of this model, we wondered about the behavior of the C_2 symmetric ligand (−)-α-isosparteine (isosp) (Figure 1).[17] Both anionic Cl ligands of (isosp)$PdCl_2$ are in an environment identical to that of Cl^2 in (sp)$PdCl_2$.[18] Attempted resolutions of 1-phenylethanol with (isosp)$PdCl_2$ led to a value for k_{rel} of only 4.7 after 72 h.[19,11] Unlike many asymmetric reactions in which a C_2 symmetric ligand leads to a more selective process,[10] these results support the unusual conclusion that a C_1 symmetric ligand can be better for the OKR.[20] Further, the poor selectivity and low reactivity of (isosp)$PdCl_2$ provide additional support for the relevance of this model to the OKR (i.e., reactivity only at Cl^1).

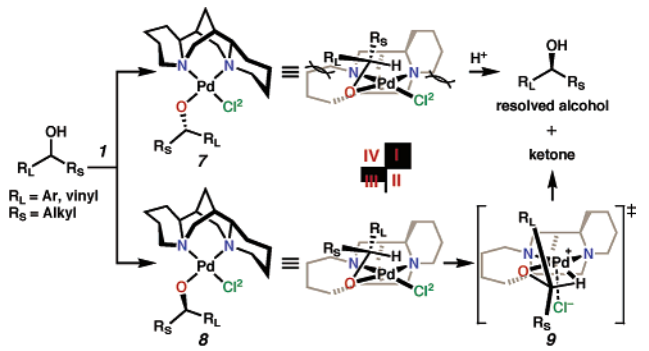


Figure 2. Model for stereoselectivity in the Pd-catalyzed aerobic oxidative kinetic resolution using (sp)$PdCl_2$.

In conclusion, we have developed a model for the stereoselectivity in the Pd-catalyzed aerobic oxidative kinetic resolution. The model is based on coordination complexes and general reactivity trends of (sp)$PdCl_2$. The first solid-state structure of a nonracemic chiral palladium alkoxide is presented and further exhibits the subtle steric influences of the ligand sparteine. Utilization of this model to develop new ligands for the asymmetric oxidation of organic substrates as well as investigation of complex **6** and derivatives to further probe the mechanism is currently underway. Finally, our findings may have general implications on the role of sparteine in other processes.

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Supporting Information Available: Experimental details and characterization data for all new compounds. X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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