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Reaction of O_2 with [(−)-Sparteine]Pd(H)Cl: Evidence for an Intramolecular $[H-L]^+$ "Reductive Elimination" Pathway

Nattawan Decharin, Brian V. Popp,[†] and Shannon S. Stahl*

Department of Chemistry, University of Wisconsin—Madison, 1101 University Avenue, Madison, Wisconsin 53706, United States

Supporting Information

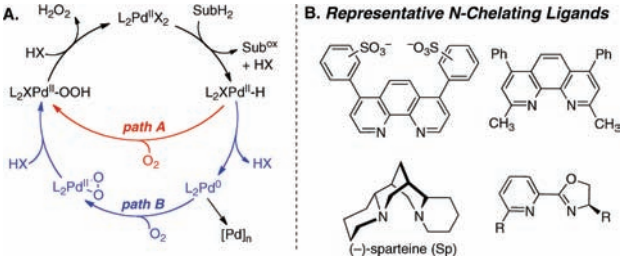
ABSTRACT: (Sp)$PdCl_2$ [Sp = (−)-sparteine] catalyzes a number of different aerobic oxidation reactions, and reaction of O_2 with a Pd^{II}−hydride intermediate, (Sp)Pd(H)Cl (**1**), is a key step in the proposed catalytic mechanism. Previous computational studies suggest that O_2 inserts into the Pd^{II}−H bond, initiated by abstraction of the hydrogen atom by O_2. Experimental and computational results obtained in the present study challenge this conclusion. Oxygenation of in-situ-generated (Sp)Pd(H)Cl exhibits a zero-order dependence on $[O_2]$. This result is inconsistent with a bimolecular H-atom-abstraction pathway, and DFT computational studies identify a novel "reductive elimination" mechanism, in which the chelating nitrogen ligand undergoes intramolecular deprotonation of the Pd^{II}−hydride. The relevance of this mechanism to other Pd^{II} oxidation catalysts with chelating nitrogen ligands is evaluated.

Pd-catalyzed aerobic oxidation reactions have expanded significantly over the past decade, and these advances are closely linked to the identification of oxidatively stable ancillary ligands that promote these reactions.[1] These ligands play a key role in stabilizing the reduced Pd catalyst formed upon substrate oxidation and promoting its reaction with molecular oxygen. The mechanism of catalyst oxidation by O_2 has been the focus of considerable recent study by us[2] and others.[3] For catalytic reactions that proceed via Pd^{II}−hydride intermediates, two mechanistic pathways appear to be viable (Scheme 1A): direct reaction of O_2 with the Pd−H bond via a hydrogen-atom-abstraction pathway (HAA, path A) and a pathway initiated by H−X reductive elimination from Pd^{II}, followed by a reaction of O_2 with Pd^0 (HXRE, path B). Insights from recent experimental and computational studies suggest that all catalyst systems with labile monodentate ligands (e.g., pyridine, Et_3N, DMSO) strongly favor the HXRE pathway.[4] Many catalysts feature chelating nitrogen ligands, however (Scheme 1B), and previous computational studies of the reaction of O_2 with (Sp)Pd(H)Cl (**1**) [Sp = (−)-sparteine] support an HAA mechanism.[3a,d,5] Here, we present experimental data that are incompatible with an HAA mechanism, together with DFT computational studies that reveal a novel "reductive elimination" pathway for aerobic oxidation of **1**. These and additional results presented herein suggest that no existing Pd catalysts undergo aerobic oxidation via the HAA pathway.

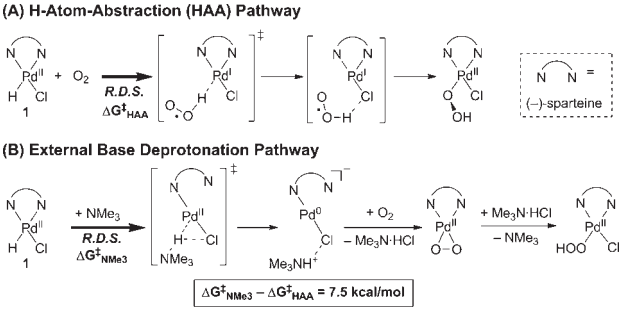
The reaction of (Sp)Pd(H)Cl with O_2 has been the focus of two previous computational studies by Goddard and coworkers.[3a,d] The first study identified the unprecedented HAA pathway as a possible mechanism for O_2 "insertion" into a Pd−H bond (Scheme 2A).[3a] The second study showed that an alternative mechanism, initiated by deprotonation of the Pd−H, has a significantly higher activation energy relative to the HAA pathway (Scheme 2B; $\Delta\Delta G^{\ddagger}$ = 7.5 kcal/mol).[3d,6] These results have not been confirmed experimentally. In principle, these two mechanisms could be distinguished on the basis of their kinetic dependence on $[O_2]$: the HAA pathway predicts a first-order dependence, whereas the deprotonation mechanism predicts a zero-order dependence. This possibility prompted us to pursue the synthesis of **1**.

We examined a number of methods for the preparation of **1**, including the reaction of (Sp)$PdCl_2$ with various Si−, B−, and Sn−hydride reagents,[7] β-hydride elimination from in-situ-generated Pd−formate and alkoxide derivatives,[8] and addition

Scheme 1. Possible Mechanisms for the Oxidation of Pd−H Species by Dioxygen and Representative Catalyst Systems with *N*-Chelating Ligands



Scheme 2. Two Proposed Mechanistic Pathways for O_2 Insertion into Pd−Hydride Bond of (Sp)Pd(H)Cl Complex[3a,d]



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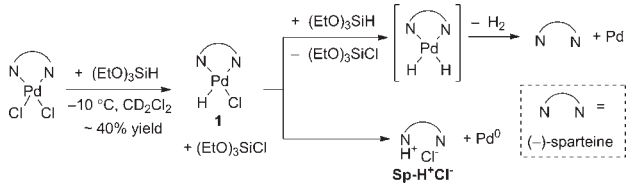
Scheme 3. Synthesis of (Sp)Pd(H)Cl and Proposed Decomposition Pathways under the Reaction Conditions



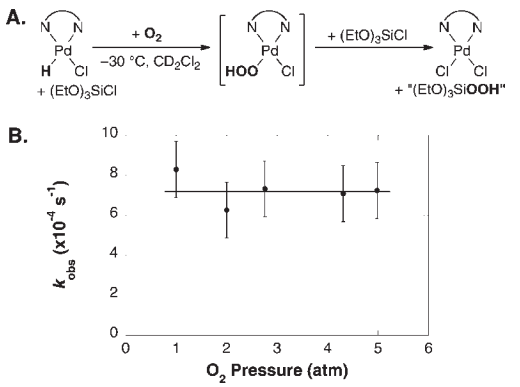


Figure 1. (A) Proposed pathway for oxygenation of in-situ-generated (Sp)Pd(H)Cl. (B) Oxygen-pressure effects on the oxygenation reactions, demonstrating zero-order kinetics. Reaction conditions: [Pd−H] = 0.53−0.92 mM, pO_2 = 1.0−5.0 atm (9.0−45 mM of dissolved O_2), CD_2Cl_2, −30 °C, 600 μL. Error bars reflect standard deviations based on independently prepared samples of the Pd^{II}−H.

of HCl to Pd^0 sources in the presence of (−)-sparteine.[9] With many of these methods, a common major Pd−H species was evident by ^{1}H NMR spectroscopy at reduced temperatures (≤ −35 °C); however, the complex was thermally unstable, and efforts to isolate the complex were unsuccessful. The instability of this Pd−H species is not entirely surprising. No mononuclear, nitrogen-chelated Pd−H complexes have been reported in the literature, and **1** has never been observed under catalytic conditions.

Among the synthetic routes evaluated, the most promising result was obtained from the reaction of excess $(EtO)_3SiH$ (10 equiv) with (Sp)$PdCl_2$ in CD_2Cl_2 at −10 °C (Scheme 3). Over 25 min, the reaction turned from yellow to dark brown, and a single Pd−hydride complex was formed in 40% yield by ^{1}H NMR spectroscopy (δ_{Pd-H} = −25.97 ppm).[10] The Pd−H complex decomposes if it is maintained at the reaction temperature, and it appears to have at least two accessible decomposition pathways (Scheme 3): (1) formation of H_2, evident by the emergence of a peak in the ^{1}H NMR spectrum at 4.59 ppm,[11] and (2) formation of the protonated sparteine ligand (Sp-H^+) and Pd black, formally arising from N_{Sp}−H "reductive elimination" and aggregation of the Pd^0 byproduct. The former decomposition pathway is especially evident when hydride reagents are used, and it may proceed via a Pd^{II}−dihydride intermediate (top pathway, Scheme 3).

The difficulties in isolating **1** prompted us to investigate the O_2 reactivity of the Pd^{II}−H complex in situ. When the reaction mixture, containing ∼40% yield of Pd^{II}−H, was exposed to an atmosphere of O_2, the solution changed color from dark brown to yellow, and a ^{1}H NMR spectrum of the product solution revealed (Sp)$PdCl_2$ as the predominant product (Figure S1). A plausible explanation for this observation is

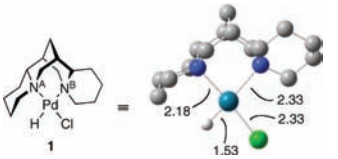


Figure 2. Ball-and-stick illustrations of (Sp)Pd(H)Cl with key metrics.

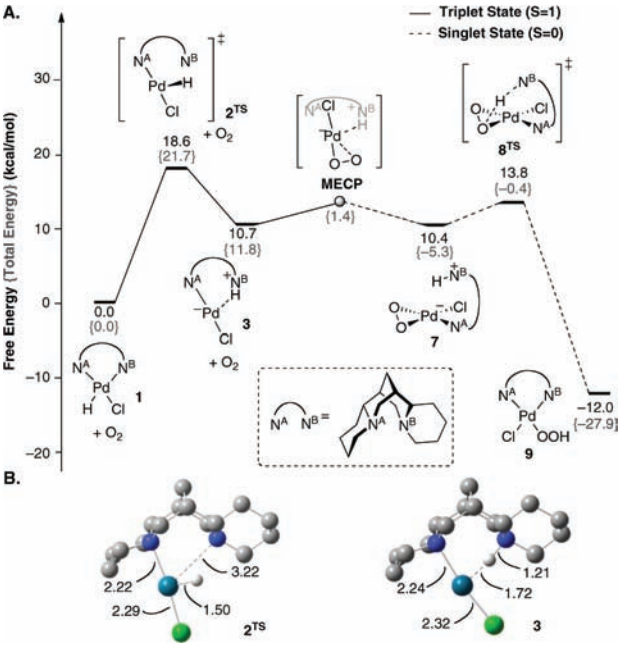


Figure 3. Computed reaction coordinate for oxygenation of **1** initiated by H-ligand reductive-elimination (HLRE). (A) Reaction profile for the HLRE, oxygenation, and protonolysis steps in toluene solvent. See Supporting Information for complete reaction coordinate. (B) Ball-and-stick illustrations with key metrics for the complexes $\mathbf{2}^{TS}$ and **3**.

that the Pd^{II}−H reacts with O_2 to afford a Pd−hydroperoxide that undergoes rapid reaction with $(EtO)_3SiCl$ present in the reaction mixture to afford (Sp)$PdCl_2$ and $(EtO)_3SiOOH$ (Figure 1A). It was possible to monitor the kinetics of the O_2 reactivity by ^{1}H NMR spectroscopy at −30 °C ($t_{1/2} \approx 20$ min),[12] and increasing the O_2 pressure from 1 to 5 atm exhibited no effect on the reaction rate (Figure 1B).

Interpretation of this result is subject to a number of caveats associated with the complexity of the reaction mixture and lack of full characterization of **1** or the Pd−hydroperoxide intermediate. Conservatively, however, the data indicate that a sparteine-coordinated Pd−hydride species undergoes a reaction that is induced by the presence of O_2 but is independent of the [O_2]. While this conclusion lacks mechanistic certainty, the data are not consistent with an HAA mechanism, which should exhibit a first-order dependence on [O_2].

Previous studies of the reactions between O_2 and well-defined (albeit catalytically unreactive) Pd−hydride complexes demonstrate close agreement between experimental and computational results.[2b,c,e,3b,3c] The discrepancy between the experimental and computational results noted above suggests that a mechanism different from those shown in Scheme 2 might be involved. In order to examine this possibility, we decided to reinvestigate the reaction of **1** with O_2 using DFT computational methods.[13]

Analysis of the ground-state structure of **1** reveals that the two Pd−N bonds differ in length by 0.15 Å, with the longer one *trans* to the hydride ligand (Figure 2). This observation, together with the formation of Sp-H$^+$ observed experimentally (cf. bottom pathway, Scheme 3), raised the possibility that sparteine could serve as an internal base upon dissociation of the amine ligand *trans* to the hydride ligand. This mechanism would be analogous to the deprotonation pathway noted in Scheme 2B, but it would avoid the entropic cost associated with a bimolecular reaction.[3d]

A transition state for dissociation of the N^B amine of sparteine was identified computationally (**2**^{TS}, Figure 3). The imaginary frequency associated with this step includes both Pd−N^B bond lengthening and rotation of the sparteine ligand about the Pd−N^A bond. The rotation enables the basic N^B atom to approach the hydride ligand, and deprotonation of the hydride ligand by the N^B amine occurs, yielding the zwitterionic Pd^0 product **3** (Figure 3). The calculated free-energy barrier for this concerted process is 18.6 kcal/mol (Figure 3A). The Pd−H bond distance in **3** is 1.72 Å, and the Pd--H−N interaction is best described as a hydrogen bond between a Lewis-basic Pd^0 center and an acidic H−N$_{Sp}$ fragment.[14] Natural charge analysis suggests the deprotonation can be described formally as an N−H "reductive elimination" reaction in which the Pd center starts with a +0.36 charge and ends with a −0.15 charge. The H atom simultaneously shifts from having slight hydridic character (−0.054 charge) in **1** to protic character (+0.32 charge) in **3**. By analogy to the HXRE nomenclature employed when the reductive elimination step involves an anionic X-type ligand, we assign the name HLRE to the present reaction, reflecting the involvement of a neutral L-type ligand in the reaction.

Aerobic oxidation of the zwitterionic intermediate **3** proceeds via an oxygenation/protonolysis sequence in which all of the calculated intermediates and transition states are lower in energy than **2**^{TS} (Figures 3A and S3). These results indicate that the HLRE step is rate-limiting, and oxygenation of **1** by this mechanism should exhibit a zero-order dependence on [O_2]. Reinvestigation of the HAA mechanism, using the same computational package and methods employed for the HLRE study, revealed that the HLRE mechanism is more favorable than the HAA pathway: $\Delta G^{\ddagger}_{HLRE} - \Delta G^{\ddagger}_{HAA} = -3.5$ kcal/mol).[15] The experimental free energy of activation (cf. Figure 1), $\Delta G^{\ddagger}_{expt} \approx$ 18 kcal/mol, and the calculated barrier for the HLRE pathway are in good agreement,[16] and we propose that aerobic oxidation of (Sp)Pd(H)Cl proceeds via this novel HLRE mechanism.

In order to probe the generality of the HLRE pathway, we performed analogous calculations with three other commonly used bidentate nitrogen ligands: phenanthroline (phen), bipyridine (bpy), and pyridine-oxazoline (py-ox). A slight difference observed in the HLRE mechanism with these three ligands relative to (−)-sparteine was the presence of a stepwise, rather than concerted, ligand dissociation/deprotonation pathway. The highest barrier for the pathway was associated with ligand dissociation.[17] A comparison between the rate-limiting transition-state energies for the HLRE and HAA mechanisms with each of these ligands reveals that the HLRE mechanism is always lower in energy (Figure 4), although the difference is relatively small with the phen and bpy ligands ($\Delta\Delta G^{\ddagger} \approx 1-2$ kcal/mol). Despite the relative small energy differences, however, these observations reveal the potential for these "ancillary" ligands to participate directly in reactions at the Pd center.

The mechanisms depicted in Figure 4 feature Pd−hydride complexes with chloride as the second anionic ligand; however, the (Sp)PdCl$_2$ catalyst system is unusual in its use of chloride.

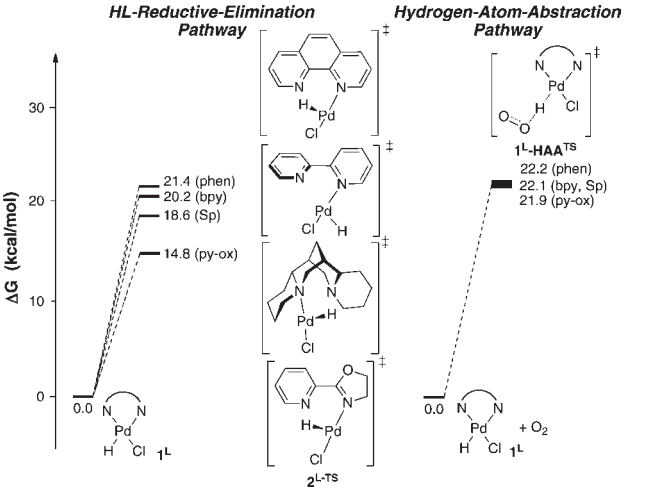


Figure 4. Comparison of the rate-limiting transition-state energies for the HLRE and HAA mechanisms for O_2 insertion into a Pd−H bond with four different bidentate nitrogen ligands. Full reaction coordinates are provided in the Supporting Information.

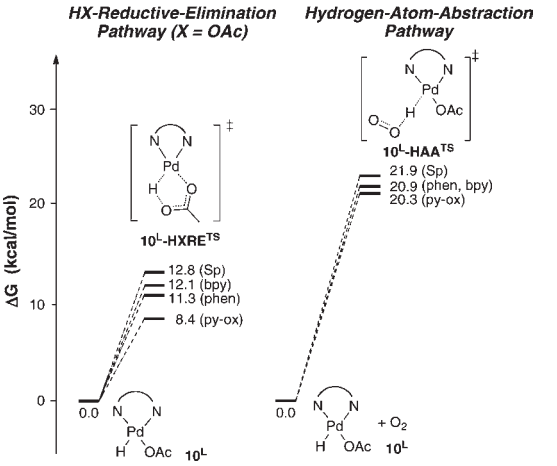


Figure 5. Comparison of the rate-limiting transition-state energies for the HXRE (X = OAc) and HAA mechanisms for O_2 insertion into a Pd−H bond with four different bidentate nitrogen ligands.

The vast majority of nitrogen-ligated Pd catalysts for aerobic oxidation reactions feature carboxylates as the anionic ligands. We have previously highlighted the ability of acetate and other carboxylate ligands to undergo intramolecular deprotonation of Pd−hydrides, formally H−O_2CR reductive elimination from the Pd^{II} center.[2b−e] Calculation of the rate-limiting transition states for this HXRE pathway for (N−N)Pd(H)OAc complexes (**10**^{L}) reveals that this mechanism is strongly favored[18] relative to the HAA mechanism ($\Delta\Delta G^{\ddagger}$ = 8.8−11.9 kcal/mol) (Figure 5). This mechanism is also significantly favored relative to the HLRE mechanism with Pd−chloride complexes ($\Delta\Delta G^{\ddagger}$ = 6.4−10.1 kcal/mol). The carboxylate HXRE pathway benefits energetically from the ability of the carboxylate ligand to retain partial bonding to the Pd center as it participates in the deprotonation step. In contrast, the bidentate nitrogen ligands must fully dissociate one of the nitrogen atoms before they can interact with the hydride ligand.

These observations have clear implications for Pd-catalyzed aerobic oxidation reactions. Pd^{II}−hydride intermediates in

Pd-catalyzed aerobic oxidation reactions are elusive, and insights into their reactivity are limited by the lack of direct investigations. Nevertheless, experimental and computational studies of well-defined model systems suggested that nearly all catalyst systems undergo oxidation by O_2 via a Pd^0 intermediate. The $(Sp)PdCl_2$ catalyst system appeared to be the sole exception. The present work, however, provides evidence for a previously unrecognized mechanism in which the chelating nitrogen ligand participates in intramolecular deprotonation of the hydride ligand, resulting in the formation of a Pd^0 species. This mechanism exhibits many features in common with the previously characterized HX reductive elimination pathway. In both pathways, one portion of the ligand remains coordinated to the Pd center while a remote site deprotonates the Pd−H. The intramolecular nature of this process avoids the unfavorable entropy associated with a bimolecular reaction. The hydrogen-atom-abstraction pathway remains an intriguing pathway for O_2 insertion into a Pd−H bond, but we are not aware of any aerobic oxidation reactions in which it represents a viable pathway for catalyst oxidation.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, computational methods and results, detailed DFT reaction coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
stahl@chem.wisc.edu

Present Addresses
[†]Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

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■ REFERENCES

(1) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (b) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854–3867.

(2) (a) Konnick, M. M.; Gandhi, B. A.; Guzei, I. A.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2904–2907. (b) Popp, B. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 4410–4422. (c) Konnick, M. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 5753–5762. (d) Popp, B. V.; Stahl, S. S. *Chem. Eur. J.* **2009**, *15*, 2915–2922. (e) Konnick, M. M.; Decharin, N.; Popp, B. V.; Stahl, S. S. *Chem. Sci.* **2011**, *2*, 326–330.

(3) For leading references, see: (a) Keith, J. M.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A., III *J. Am. Chem. Soc.* **2005**, *127*, 13172–13179. (b) Denney, M. C.; Smythe, N. A.; Cetto, K. L.; Kemp, R. A.; Goldberg, K. I. *J. Am. Chem. Soc.* **2006**, *128*, 2508–2509. (c) Keith, J. M.; Muller, R. P.; Kemp, R. A.; Goldberg, K. I.; Goddard, W. A., III; Oxgaard, J. *Inorg. Chem.* **2006**, *45*, 9631–9633. (d) Keith, J. M.; Goddard, W. A., III; Oxgaard, J. *J. Am. Chem. Soc.* **2007**, *129*, 10361–10369. (e) Keith, J. M.; Goddard, W. A., III *J. Am. Chem. Soc.* **2009**, *131*, 1416–1425.

(4) For justification of this claim, see refs 2c and 2d and discussion therein.

(5) Application of (−)-sparteine as an ancillary ligand for Pd-catalyzed aerobic oxidation reactions was first reported by the groups of Sigman and Stoltz in the context of alcohol oxidation: (a) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475–7476. (b) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725–7726.

(6) Direct H−Cl reductive elimination was calculated to be highly unfavorable, so an external amine base was invoked to catalyze the transformation. See ref 3d for details.

(7) Reaction of L_2PdCl_2 with hydride donor reagents: (a) Brooks, E. H.; Glockling, F. *Chem. Commun.* **1965**, 510. (b) Moulton, C. J.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1976**, 1020–1024. (c) Saito, T.; Munakata, H.; Imoto, H. *Inorg. Synth.* **1977**, *17*, 83–88. (d) Imoto, H.; Moriyama, H.; Saito, T.; Sasaki, Y. *J. Organomet. Chem.* **1976**, *120*, 453–460. (e) Moriyama, H.; Saito, T.; Sasaki, Y. *Chem. Lett.* **1976**, 175–176. (f) Reger, D. L.; Garza, D. G. *Organometallics* **1993**, *12*, 554–558. (g) Fryzuk, M. D.; Lloyd, B. R.; Clentsmith, G. K. B.; Rettig, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 4332–4334. (h) Reference 3b. (i) Nguyen, D. H.; Laurenczy, G.; Urrutigoïty, M.; Kalck, P. *Eur. J. Inorg. Chem.* **2005**, *2005*, 4215–4225.

(8) β-Hydride elimination from Pd−alkyl, −alkoxide, and −formate complexes: (a) Hosokawa, T.; Maitlis, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 3238–3240. (b) Goel, A. B.; Goel, S. *Inorg. Chim. Acta* **1980**, *45*, L85–L86. (c) Clegg, W.; Eastham, G. R.; Elsegood, M. R. J.; Heaton, B. T.; Iggo, J. A.; Tooze, R. P.; Whyman, R.; Zacchini, S. *J. Chem. Soc., Dalton Trans.* **2002**, 3300–3308. (d) Johansson, R.; Wendt, O. F. *Organometallics* **2007**, *26*, 2426–2430.

(9) Oxidative addition of an H^+ source to an L_2Pd^0: (a) Ozawa, F.; Ito, T.; Nakamura, Y.; Yamamoto, A. *J. Organomet. Chem.* **1979**, *168*, 375–391. (b) Seligson, A. L.; Cowan, R. L.; Trogler, W. C. *Inorg. Chem.* **1991**, *30*, 3371–3381.

(10) The large upfield signal of Pd−H resonances is common: Grushin, V. V. *Chem. Rev.* **1996**, *96*, 2011–2034.

(11) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176–2179.

(12) Background decomposition of (Sp)Pd(H)Cl at this temperature is >7-fold slower than the O_2-induced reaction, and the decomposition reaction does not afford $(Sp)PdCl_2$ as the product. These considerations suggest that the background process should have little effect on the observed oxygenation kinetics.

(13) All computations were performed with the Gaussian 03 program. Geometry optimizations were performed using the B3LYP functional with the Stuttgart RSC 1997 ECP basis set for Pd and 6-31+G(d) for all other atoms. At the calculated stationary points, solvation-corrected single-point energy calculations (toluene solvent at 298 K) were carried out with the Pd basis detailed above and the 6-311+G(d,p) basis for all other atoms. See Supporting Information for details.

(14) Falvello, L. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 10045–10047.

(15) The calculated HAA transition state, employing our DFT methods, is 22.1 kcal/mol relative to $(Sp)Pd(H)Cl + O_2$.

(16) The extent of agreement between the experimental and calculated barriers is almost certainly fortuitous, considering the typical errors associated with DFT calculations (∼3−5 kcal/mol). See, for example: Siegbahn, P. E. M. *J. Biol. Inorg. Chem.* **2006**, *11*, 695–701.

(17) See Supporting Information for the full energy diagrams.

(18) The HXRE pathway from (Sp)Pd(H)OAc system has been previously studied: Keith, J. M. Palladium Mediated Activation of Molecular Oxygen. Ph.D. Thesis, California Institute of Technology, 2008.