



Trinuclear Pd₃O₂ Intermediate in Aerobic Oxidation Catalysis**

Andrew J. Ingram, Diego Solis-Ibarra, Richard N. Zare,* and Robert M. Waymouth*

Abstract: The activation of O₂ is a key step in selective catalytic aerobic oxidation reactions mediated by transition metals. The bridging trinuclear palladium species, [(LPd^{II})₃(μ³-O)₂]²⁺ (L = 2,9-dimethylphenanthroline), was identified during the [LPd(OAc)]₂(OTf)₂-catalyzed aerobic oxidation of 1,2-propanediol. Independent synthesis, structural characterization, and catalytic studies of the trinuclear compound show that it is a product of oxygen activation by reduced palladium species and is a competent intermediate in the catalytic aerobic oxidation of alcohols. The formation and catalytic activity of the trinuclear Pd₃O₂ species illuminates a multinuclear pathway for aerobic oxidation reactions catalyzed by Pd complexes.

Selective oxidation reactions are critical to all aerobic organisms and are among the most useful chemical transformations on an industrial scale.^[1–5] Air is convenient, thermodynamically potent, and readily available as a terminal oxidant; however, high rates and selectivity require a catalyst to bind and activate O₂. If reduced to water, oxygen is a 4-electron oxidant, but most desired oxidations are 2-electron oxidations (alkanes to alcohols, alcohols to carbonyls, olefins to epoxides, etc.). Moreover, partially reduced oxygen species are typically more reactive and potent oxidants than O₂ itself: a major challenge for selective oxidation reactions in air or O₂.^[1–6]

Mechanistic studies of the reactions of oxygen with transition metal compounds have illuminated many of the pathways for O₂ activation with reduced metal centers,^[4,5,7–11] as well as strategies for circumventing undesired free-radical auto-oxidation reactions.^[2,5] Herein, we report a new pathway

for O₂ activation by reduced palladium complexes, thereby providing new insights into strategies for selective aerobic oxidation catalysis.

Palladium catalysts are an important class of oxidation catalysts for both commodity and fine chemical intermediates.^[9,12–18] Experimental and theoretical investigations have illuminated several pathways for the activation of O₂ by reduced Pd complexes (Figure 1), the role of ligand environment, and η²-peroxo and hydroperoxy intermediates in the reoxidation of LPd⁰ or LPd-H⁺ with O₂.^[7,9,10,19]

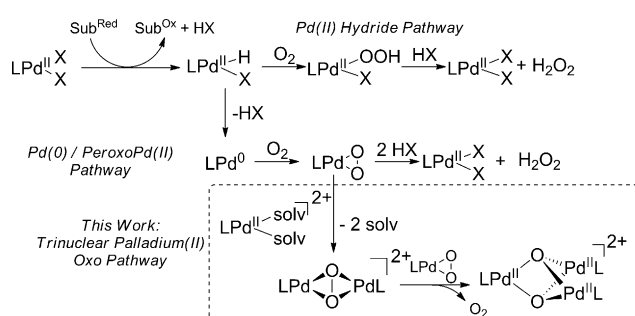


Figure 1. Pathways for the aerobic oxidation of LPd complexes.^[9,10]

Herein, we describe the discovery, identification, and isolation of a trinuclear [(LPd)₃(μ³-O)₂]²⁺ compound (**1**; L = neocuproine = 2,9-dimethylphenanthroline) that illuminates an additional pathway for O₂ activation with Pd complexes (Figure 1). The formation of the trinuclear complex **1** was detected by electrospray ionization mass spectrometry (ESI-MS) during the aerobic oxidation of vicinal diols catalyzed by [LPd(OAc)]₂(OTf)₂ (**2**₂(OTf)₂).^[20–22] Synthetic, mechanistic, and catalytic studies provide key insights into the role of multinuclear Pd complexes during aerobic oxidation catalysis.

The cationic Pd^{II} catalyst **2**₂(OTf)₂ catalyzes the selective oxidation of primary and secondary aliphatic alcohols,^[20–23] vicinal diols,^[21] polyols,^[22] and carbohydrates.^[24] For vicinal diols and polyols, room temperature oxidation with **2**₂(OTf)₂ is chemoselective to afford the α-hydroxyketones.^[21,22] Air or benzoquinone can be used as terminal oxidants; in the presence of air or O₂, competitive oxidation of the ligand limits the number of turnovers to approximately 15.^[20] With benzoquinone, more than 500 turnovers can be realized.^[22]

ESI-MS is a powerful technique for illuminating the speciation of intermediates in catalytic reactions.^[25–28] Unexpected species can be identified and characterized from reaction mixtures and their roles interrogated.^[26,27] We have previously reported a desorption electrospray ionization (DESI)-MS study of the oxidation of 1,2-propanediol by **2**₂(OTf)₂ at millisecond timescales.^[22] In the present study, we employed the longer timescales (minutes to hours) accessed

[*] A. J. Ingram, Dr. D. Solis-Ibarra, Prof. R. N. Zare, Prof. R. M. Waymouth
Department of Chemistry, Stanford University
333 Campus Drive, Stanford, CA 94305-5080 (USA)
E-mail: zare@stanford.edu
waymouth@stanford.edu

[**] R.M.W. acknowledges support from the Department of Energy (DE-FG02-10ER16198). R.N.Z. gratefully acknowledges the financial support from a subcontract with the University of Utah (Agreement no. 10029173-S2) for which the Air Force Office of Scientific Research (Grant FA9550-12-1-0481) is the prime sponsor. A.J.I. is grateful for a Robert M. Bass and Anne T. Bass Stanford Graduate Fellowship, a National Science Foundation Graduate Research Fellowship, and a Center for Molecular Analysis and Design Graduate Fellowship. We thank Wilson Ho for providing the **2**₂(OTf)₂ used in this work and Stephen R. Lynch for assisting with the diffusion NMR experiments. We are grateful to E. I. Solomon and J. W. Ginsbach for the gift of the ¹⁸O₂ used in these experiments. We also acknowledge Kevin Chung, T. Daniel P. Stack, and Hemamala Karunadasa for fruitful discussions.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201400134>.

by electrospray ionization (ESI) to identify species formed during the catalytic aerobic oxidation of 1,2-propanediol with $2_2(\text{OTf})_2$.

Aerobic oxidation of a 0.14 M solution of 1,2-propanediol in MeCN was carried out at room temperature under air with 7 mM $2_2(\text{OTf})_2$ (10 mol% Pd) and monitored by sampling diluted aliquots at various time points with ESI-MS.^[29] Analysis of the resulting mass spectra revealed a doubly charged species at m/z 486.9995 (m/z reported for ^{106}Pd isotopologues), which we assign as the trinuclear dication $[(\text{LPd}^{\text{II}})_3(\mu^3\text{-O})_2]^{2+}$ (**1**; Figure 2). Also detected were a number

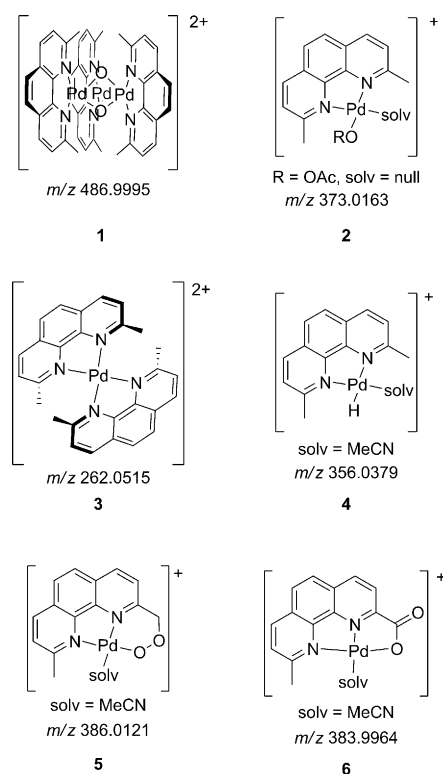
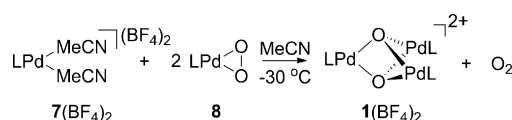


Figure 2. Representative species detected by mass spectrometry and their proposed structures.

of previously proposed^[20,21] or detected intermediates^[22] and/or inactive products of ligand oxidation.^[20] Representative ions are shown in Figure 2 (see the Supporting Information for complete assignments). Comparisons of the exact masses and relative intensities of the observed ions to simulated isotope patterns revealed a molecular formula of $[\text{C}_{42}\text{H}_{36}\text{N}_6\text{O}_2\text{Pd}_3]^{2+}$ for **1**. This composition corresponds to three neocuproine ligands, three Pd centers, and two oxygen atoms. Performing the alcohol oxidation in 9:1 MeCN/ H_2^{16}O solvent under $^{18}\text{O}_2$ yielded ions shifted by four mass units and centered about m/z 489.0042 ($z = 2$); a result consistent with the molecular formula $[\text{C}_{42}\text{H}_{36}\text{N}_6^{18}\text{O}_2\text{Pd}_3]^{2+}$. When the reaction was carried out under air ($^{16}\text{O}_2$) in 9:1 MeCN/ H_2^{18}O solvent, the species detected corresponded to $[\text{C}_{42}\text{H}_{36}\text{N}_6^{16}\text{O}_2\text{Pd}_3]^{2+}$ (see Table S1 in the Supporting Information for the isotope-labeling data for compounds **1**, **5**, and **6**). These data demonstrate that the oxygen atoms in **1** are derived from O_2 .



Scheme 1. Synthesis of $1(\text{BF}_4)_2$.

We devised an independent synthesis of $1(\text{BF}_4)_2$ to confirm its structure and characterize its reactivity (Scheme 1).^[29] The addition of a pale yellow MeCN solution of $[\text{LPd}(\text{MeCN})_2](\text{BF}_4)_2$ (**7**(BF_4)₂), to a brown MeCN slurry containing 1.8 equivalents of the η^2 -peroxo $\text{LPd}(\text{O}_2)$ (**8**)^[30] under anhydrous conditions and under nitrogen at -30°C resulted in gas evolution; after stirring for 90 min at -30°C , a bright orange solution containing **1**(BF_4)₂ as the major product was obtained. The complex is unstable in this solution at room temperature but can be precipitated with cold Et_2O and isolated as an orange powder in 87% yield. ESI-MS of this compound shows the same envelope of peaks about m/z 486.9995. ^1H NMR spectra are consistent with a diamagnetic compound in a symmetric neocuproine environment. Solid phase IR shows no major stretches above 600 cm^{-1} other than those of metallated neocuproine and BF_4^- . The stoichiometry of this reaction was confirmed by performing the reaction with an excess of **7**(BF_4)₂, where 2 equivalents of **8** were converted into **1** for each equivalent of **7** consumed.

The crystal structure of **1** is shown in Figure 3. The Pd_3O_2 core is evenly spaced with approximately 120° between Pd atoms, and the neocuproine ligands are bent slightly out of the

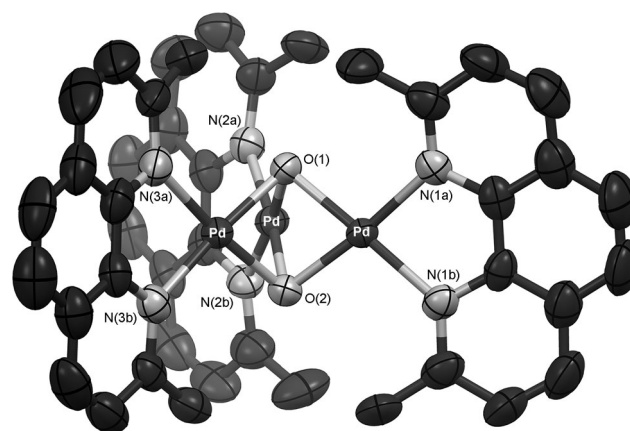


Figure 3. Crystal Structure of $1(\text{BF}_4)_2$ (O, N light gray (labeled); Pd medium gray (labeled); and C dark gray; H atoms, solvent, and counter ions omitted for clarity; thermal ellipsoids set at the 90% probability level).

PdO_2 planes. The O–O distance (2.393 Å) suggests there is no O–O bond. The average Pd–Pd distance is 2.824 Å. The methyl groups of the neocuproine ligands are positioned above and below the Pd-oxo^[31–33] core and are in close contact, with an average C–C distance between the methyl groups of 3.64 Å. This structure is related to known Cu_3O_2 , Ni_3O_2 , Pd_3S_2 and Pt_3O_2 analogues.^[34–36] Gas-phase DFT calculations are consistent with the solid-state structure and diamagnetism of **1** (see the Supporting Information). Diffu-

sion NMR experiments were performed to determine the Stokes radius of **1** and to confirm its structure in solution.^[29] The diffusion coefficient for **1** in [D₃]MeCN at -10°C was $(0.541 \pm 0.087) \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$. Assuming that the shape of **1** can be approximated as a sphere, this yields a radius of $(7.0 \pm 1.1) \text{ \AA}$, a value in good agreement with the crystal structure of **1**, in which the outermost hydrogen atoms lie between 5 and 8 Å from the center of the molecule.

A series of mass spectrometry and catalysis experiments were performed to assess the role of **1** in catalytic alcohol oxidations with the dimeric precursor **2**₂(OTf)₂. The speciation of the Pd compounds was monitored during the oxidation of 0.14 M 1,2-propanediol catalyzed by **2**₂(OTf)₂ (7 mM, 10 mol % Pd) in MeCN by measuring the ESI-MS of diluted aliquots at various time points (species that showed significant variation during catalysis are plotted in Figure 4,

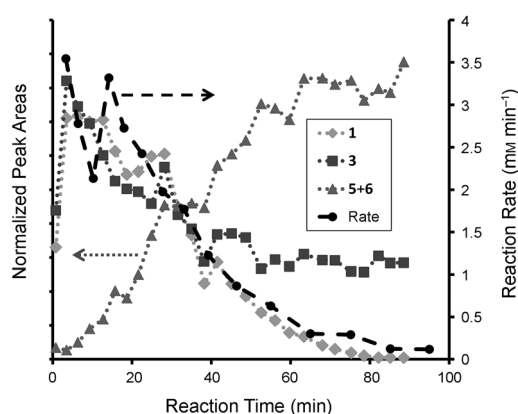


Figure 4. ESI-MS reaction monitoring. [Pd] for each sample = 0.2 mM, ESI potential = 2.0 kV. Intensities for each time point are normalized to the total ion current at that time point. Peaks areas for related species are summed and plotted against the left axis. The rate of 1,2-propanediol conversion (black circles), measured between two time points, is plotted against the right axis. Lines connecting data points are provided merely to illustrate the trends in the data.

others are described and plotted in Figure S4). An independent reaction was carried out under identical conditions except that the aliquots were passed through silica plugs and analyzed by gas chromatography with flame ionization detection (GC-FID) to measure the rate of 1,2-propanediol oxidation. As shown in Figure 4, the appearance and decay of the trinuclear compound **1** correlate with the rate of 1,2-propanediol consumption. While this correlation is only qualitative, given the challenges in quantifying complex mixtures by ESI-MS, the data nevertheless imply that **1** is associated with the catalytic oxidation reaction in MeCN. To assess whether **1** might have been formed during the ESI ionization process, a similar monitoring experiment was carried out with nano-electrospray ionization (nanospray) MS^[37] and provided similar results to those from the ESI-MS experiments (see the Supporting Information). Because ionization by nanospray occurs ca. 10^3 times faster than by ESI,^[38,39] the observation of similar species in both the ESI-MS and nanospray-MS implies that **1** and the other Pd species

observed are present in the reaction mixture rather than being generated in the course of microdroplet evaporation.

To assess the chemical and kinetic competence of **1** as an intermediate in the catalytic oxidation reaction, the isolated complex **1**(BF₄)₂ was investigated for its activity in the catalytic oxidation of 1,2-propanediol at room temperature. Oxidation of 1,2-propanediol (0.3 M, MeCN) occurred readily under 1 atm of air in the presence of 0.83 mM of **1**(BF₄)₂ (2.5 mM Pd, 0.83 % loading). The initial rate of alcohol oxidation and TON (TON = mmol diol consumed/mmol Pd, see Table S2) with **1**(BF₄)₂ [$\text{rate}_i = (0.77 \pm 0.08) \times 10^{-1} \text{ mmol min}^{-1}$] are lower than those with **2**₂(BF₄)₂ [$\text{rate}_i = (6.06 \pm 0.26) \times 10^{-1} \text{ mmol min}^{-1}$] under similar conditions.^[40] Furthermore, a significant amount of a black precipitate, likely Pd black, formed during catalysis with **1**(BF₄)₂, thus suggesting that LPd⁰ oxidation was not efficient under these conditions. By contrast, no Pd black is observed for the oxidation of 1,2-propanediol with **2**₂(BF₄)₂ under these conditions. The addition of 3 equiv of HOAc relative to **1** led to an increase in the initial rate and TON [$\text{rate} = (0.98 \pm 0.11) \times 10^{-1} \text{ mmol min}^{-1}$] of diol oxidation with **1**, however the activity was lower than that of **2**₂(BF₄)₂ and Pd black still formed. By contrast, when a 2:1 cocatalytic mixture of **1**(BF₄)₂ and [LPd(MeCN)₂](BF₄)₂ (**7**(BF₄)₂) was used (0.55 mM **1**(BF₄)₂, 0.83 mM **7**(BF₄)₂, 2.5 mM total Pd.), the initial rate of 1,2-propanediol conversion and TON per Pd atom [$\text{rate} = (5.84 \pm 0.23) \times 10^{-1} \text{ mmol min}^{-1}$] were indistinguishable to those for **2**₂(BF₄)₂ at the same Pd loading.^[41] Under these conditions, the formation of Pd black was significantly reduced (see the Supporting Information). This result suggests that some amount of LPd^{II} with exchangeable ligands is required for efficient oxidation of LPd⁰ when **1** is used as a catalyst precursor.

The catalytic activity of **1**(BF₄)₂ in combination with **7**(BF₄)₂ indicates that the trinuclear Pd₃O₂ complex **1**(BF₄)₂ is both a chemically and kinetically competent intermediate in the catalytic oxidation of 1,2-propanediol. That both **1**(BF₄)₂ and **7**(BF₄)₂ are needed to achieve a similar rate to that achieved with the cationic dimer **2**₂(BF₄)₂ implies that the efficient activation and reduction of O₂ to H₂O is facilitated by the cooperative behavior of multiple Pd centers.^[11,34,42]

In Figure 5, we present a mechanistic hypothesis in which the Pd₃O₂ complex **1** liberates the catalytically active μ -OH compound **9**^[15,20] and [LPd^{II}]²⁺ (**7**) in the presence of acid. Oxidation of the alcohol would generate [LPd-H]⁺ and subsequently the η^2 -peroxo Pd complex LPd(O₂) (**8**).^[30] Regeneration of the Pd₃O₂ complex **1** could occur in a manner similar to that utilized in its synthesis (Scheme 1), where coupling of the peroxo complex **8** with [LPd^{II}]²⁺ (**7**) generates the proposed dicationic μ -peroxo **10**, which reacts with another unit of **8**, thereby displacing O₂ in order to form **1** (see the Supporting Information for DFT calculations).^[43] Alternatively, **10** might also be generated from hydrogen peroxide generated from protonolysis of peroxo **8**.^[30] That complex **1** can be formed in aprotic solvents indicates that hydrogen peroxide is not necessary to generate **10** or **1**, but these intermediates may be relevant to the proposed disproportionation of hydrogen peroxide.^[45,46]

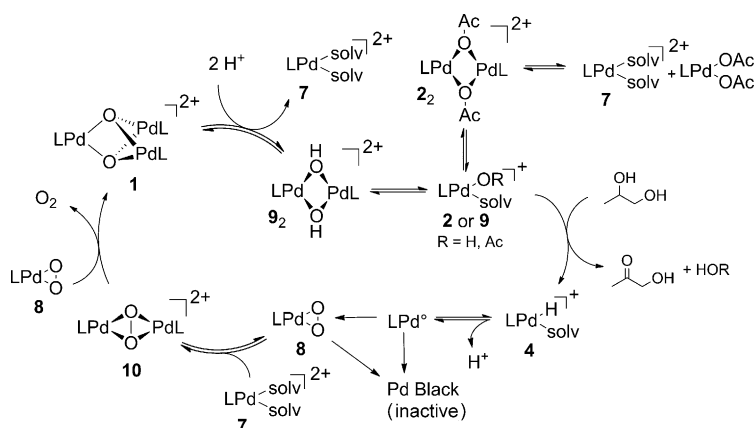


Figure 5. Proposed multinuclear catalytic mechanism.

According to this mechanism, the dicationic $[LPd^{II}]^{2+}$ (**7**) plays a key role in reacting with the peroxo complex **8** to generate **10**. This hypothesis is related to that proposed for O_2 activation by multinuclear copper complexes,^[11] where the second Pd center facilitates the activation of the O–O bond in **10** to form the trinuclear μ^3 -oxo complex **1**. The species responsible for ligand oxidation to form the inactive species **5** and **6** are not yet clear but may be associated with intermediates **8** or **10**. The mechanism by which **1** forms from **8** and **7** warrants further investigation; nevertheless, the observation that significant concentrations of the catalytically active Pd_3O_2 complex **1** form during the aerobic oxidation of alcohols with cationic Pd catalysts highlights the potential role of multinuclear μ -oxo Pd complexes in aerobic oxidation reactions.

In summary, the trinuclear Pd_3O_2 complex **1** is generated in the course of aerobic alcohol oxidation by cationic neocuproine Pd complexes. This compound was shown to be a chemically and kinetically competent intermediate in catalytic alcohol oxidation reactions. The indication that multinuclear Pd complexes are involved in the activation of O_2 presents a new mechanistic hypothesis for aerobic Pd oxidation reactions.

Received: January 7, 2014
Revised: February 2, 2014
Published online: April 7, 2014

Keywords: aerobic oxidation · homogeneous catalysis · mass spectrometry · palladium · reaction mechanisms

- [1] F. Cavani, J. H. Teles, *ChemSusChem* **2009**, *2*, 508.
[2] T. Punniyamurthy, S. Velusamy, J. Iqbal, *Chem. Rev.* **2005**, *105*, 2329.
[3] J. R. Monnier, *Appl. Catal. A* **2001**, *221*, 73.
[4] "Catalysis by Metal Complexes": L. I. Simándi, *Advances in Catalytic Activation of Dioxygen by Metal Complexes*, Kluwer, Dordrecht, **2002**.
[5] L. Que, W. B. Tolman, *Nature* **2008**, *455*, 333.
[6] B. N. Ames, M. K. Shigenaga, T. M. Hagen, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 7915.
[7] L. Boisvert, K. I. Goldberg, *Acc. Chem. Res.* **2012**, *45*, 899.
[8] Z. Shi, C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3381.

- [9] S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480; *Angew. Chem. Int. Ed.* **2004**, *43*, 3400.
[10] K. M. Gligorich, M. S. Sigman, *Angew. Chem.* **2006**, *118*, 6764; *Angew. Chem. Int. Ed.* **2006**, *45*, 6612.
[11] E. I. Solomon, J. W. Ginsbach, D. E. Heppner, M. T. Kieber-Emmons, C. H. Kjaergaard, P. J. Smets, L. Tian, J. S. Woertink, *Faraday Discuss.* **2011**, *148*, 11.
[12] B. M. Stoltz, *Chem. Lett.* **2004**, *33*, 362.
[13] K. M. Gligorich, M. S. Sigman, *Chem. Commun.* **2009**, 3854.
[14] C. N. Cornell, M. S. Sigman, *Inorg. Chem.* **2007**, *46*, 1903.
[15] R. A. Sheldon, I. W. C. E. Arends, G.-J. ten Brink, A. Dijkman, *Acc. Chem. Res.* **2002**, *35*, 774.
[16] X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.
[17] R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981.
[18] C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215.
[19] J. M. Keith, R. J. Nielsen, J. Ongaard, W. A. Goddard, *J. Am. Chem. Soc.* **2005**, *127*, 13172.
[20] N. R. Conley, L. A. Labios, D. M. Pearson, C. C. L. McCrory, R. M. Waymouth, *Organometallics* **2007**, *26*, 5447.
[21] R. M. Painter, D. M. Pearson, R. M. Waymouth, *Angew. Chem.* **2010**, *122*, 9646; *Angew. Chem. Int. Ed.* **2010**, *49*, 9456.
[22] K. Chung, S. M. Banik, A. G. De Crisci, D. M. Pearson, T. R. Blake, J. V. Olsson, A. J. Ingram, R. N. Zare, R. M. Waymouth, *J. Am. Chem. Soc.* **2013**, *135*, 7593.
[23] D. M. Pearson, N. R. Conley, R. M. Waymouth, *Organometallics* **2011**, *30*, 1445.
[24] M. Jäger, M. Hartmann, J. G. de Vries, A. J. Minnaard, *Angew. Chem.* **2013**, *125*, 7963; *Angew. Chem. Int. Ed.* **2013**, *52*, 7809.
[25] M. N. Eberlin, *Eur. J. Mass Spectrom.* **2007**, *13*, 19.
[26] *Reactive Intermediates: MS Investigations in Solution* (Ed.: L. S. Santos), Wiley-VCH, Weinheim, **2010**.
[27] K. L. Vikse, Z. Ahmadi, C. C. Manning, D. A. Harrington, J. S. McIndoe, *Angew. Chem.* **2011**, *123*, 8454; *Angew. Chem. Int. Ed.* **2011**, *50*, 8304.
[28] D. Schröder, *Acc. Chem. Res.* **2012**, *45*, 1521.
[29] See the Supporting Information for experimental procedures.
[30] S. S. Stahl, J. L. Thorman, R. C. Nelson, M. A. Kozee, *J. Am. Chem. Soc.* **2001**, *123*, 7188.
[31] T. Hosokawa, M. Takano, S. Murahashi, *J. Am. Chem. Soc.* **1996**, *118*, 3990.
[32] Y. Zhang, R. J. Puddephatt, L. Manojlović-Muir, K. W. Muir, *Chem. Commun.* **1996**, 2599.
[33] A. Singh, P. R. Sharp, *Dalton Trans.* **2005**, 2080.
[34] L. M. Mirica, X. Ottenwaelder, T. D. P. Stack, *Chem. Rev.* **2004**, *104*, 1013.
[35] A. Singh, U. Anandhi, M. A. Cinellu, P. R. Sharp, *Dalton Trans.* **2008**, 2314.
[36] V. K. Jain, L. Jain, *Coord. Chem. Rev.* **2010**, *254*, 2848.
[37] M. S. Wilm, M. Mann, *Int. J. Mass Spectrom. Ion Processes* **1994**, *136*, 167.
[38] A. Wortmann, A. Kistler-Momotova, R. Zenobi, M. C. Heine, O. Wilhelm, S. E. Pratsinis, *J. Am. Soc. Mass Spectrom.* **2007**, *18*, 385.
[39] M. Girod, E. Moyano, D. I. Campbell, R. G. Cooks, *Chem. Sci.* **2011**, *2*, 501.
[40] The rates of diol oxidation with $2_2(BF_4)_2$ or $2_2(OTf)_2$ were indistinguishable under the conditions employed, thus indicating that the nature of the anion (OTf to BF_4) does not influence the catalytic reactivity.
[41] The rate of diol oxidation with a mixture of $1(BF_4)_2$ and $7(BF_4)_2$ did not change upon the addition of 1 equiv (relative to Pd) of acetic acid (Table S2).

- [42] J. T. York, A. Llobet, C. J. Cramer, W. B. Tolman, *J. Am. Chem. Soc.* **2007**, *129*, 7990.
- [43] The displacement of O₂ from **8** in the formation of **1** is likely an associative process since O₂ does not readily dissociate from **8** (Ref. [44]).
- [44] B. V. Popp, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 2804.
- [45] B. A. Steinhoff, S. R. Fix, S. S. Stahl, *J. Am. Chem. Soc.* **2002**, *124*, 766.
- [46] We have been unable to detect hydrogen peroxide in aerobic alcohol oxidations catalyzed by [LPd(OAc)]₂OTf₂ (**2**, (OTf)₂) at room temperature (Ref. [20]), but we cannot rule out that it is rapidly disproportionated under these conditions.
-