Published in final edited form as:

Angew Chem Int Ed Engl. 2017 March 20; 56(13): 3605–3610. doi:10.1002/anie.201700345.

Observation of Palladium(I) in Aerobic Oxidation Catalysis

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Abstract

Pd^{II}-catalyzed oxidation reactions exhibit broad utility in organic synthesis; however, they often feature high catalyst loading and low turnover numbers relative to non-oxidative cross-coupling reactions. Insights into the fate of the Pd catalyst during turnover could help to address this limitation. Here, we report the identification and characterization of a dimeric Pd^I species in two prototypical Pd-catalyzed aerobic oxidation reactions: allylic C–H acetoxylation of terminal alkenes and intramolecular aza-Wacker cyclization. Both reactions employ 4,5-diazafluoren-9-one (DAF) as an ancillary ligand. The dimeric Pd^I complex, [Pd^I(μ-DAF)(OAc)]₂, which features two bridging DAF ligands and two terminal acetate ligands, has been characterized by several spectroscopic methods, as well as single-crystal X-ray crystallography. The origin of this Pd^I complex and its implications for catalytic reactivity are discussed.

Graphical abstract

Catalyst Entanglement: Catalyst dimerization is observed in both the aerobic Pd-catalyzed allylic C–H acetoxylation and aza-Wacker cyclization. A novel Pd^I species is rigorously characterized in catalysis. This report has implications for Pd catalyst design and presents insights into catalyst deactivation.

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^bSupporting information for this article is given via a link at the end of the document.

Keywords

Palladium; Aerobic; Oxidation; Catalysis; Wacker

The development of new Pd-catalyzed oxidation reactions has been the focus of extensive research in recent years.^[1] Reactions that proceed via a Pd^{II}/Pd⁰ cycle are appealing because they are often compatible with the use of O₂ as the terminal oxidant.^[2] Prominent examples include the Wacker process,^[3] alcohol oxidation,^[4] Wacker-type cyclization^[5] and the Fujiwara-Moritani (dehydrogenative/oxidative Heck) reaction.^[6] The majority of Pd-catalyzed aerobic oxidations proceed through a catalytic cycle wherein Pd^{II} mediates substrate oxidation and Pd⁰ is reoxidized by O₂ (Scheme 1).^[7] The Pd⁰ intermediate in this cycle is metastable and susceptible to decomposition via aggregation into Pd nanoparticles and/or bulk metallic Pd. Use of ancillary ligands can help to prevent catalyst decomposition and/or promote reoxidation of Pd⁰ by O₂, thereby avoiding a requirement for undesirable oxidants, such as stoichiometric Cu^{II}, Ag^I, or benzoquinone (BQ). Nevertheless, the ligand-modulated aerobic oxidation reactions often feature high catalyst loading and low turnover numbers. The basis for this limitation is poorly understood, and efforts to overcome this issue are complicated by limited understanding of catalyst speciation under aerobic oxidation conditions. Here, we report the first observation of a Pd^I intermediate in ligand-modulated Pd-catalyzed oxidation reactions and assess its role in the catalytic mechanism.

Allylic C–H acetoxylation of alkenes and aza-Wacker reactions are two prototypical Pd-catalyzed aerobic oxidation reactions.^[8] In previous studies of these reactions, we found that 4,5-diazafluoren-9-one (DAF) is especially effective in promoting aerobic catalytic turnover [Eqs. (1) and (2)]^[9,10] and that DAF adopts diverse coordination modes, including κ^1 , κ^2 , and bimetallic bridging (μ) ligation, under the catalytic conditions.^[11,12]

Our initial mechanistic studies of DAF/Pd(OAc)₂-catalyzed allylic acetoxylation revealed unusual kinetic behavior. The reaction time course exhibits two kinetic phases: an initial burst of product formation, followed by slower steady-state behavior (Figure 1). The initial color of

(1)

the reaction mixture changes rapidly from a yellow solution to a deep red color upon addition of allyl benzene to a solution of the catalyst. When the beginning of the acetoxylation reaction was monitored by ^1H NMR spectroscopy (3:1 dioxane- d_8 /AcOD- d_4), new DAF ligand peaks appeared during the burst phase, consistent with the formation of a symmetrical DAF-ligated Pd species. This new DAF species had well-dispersed ^1H chemical shifts (*o*-/*m*-/*p*-CH ^1H δ = 8.83, 7.54 and 8.21 ppm) and a ^{15}N chemical shift of 217 ppm (Figure S2).

Complementary observations were made with the Pd-catalyzed aza-Wacker cyclization of (*Z*)-4-hexenyltosylamide. At 5 mol% catalyst loading, the reaction time course again exhibits two-phase kinetic behavior in which a burst of product formation is followed by a slower steady-state rate (Figure 2). Moreover, analysis of the aza-Wacker reaction by NMR spectroscopy in CDCl_3 ^[13] revealed formation of a new symmetrical DAF species at early stages of the reaction. The ^1H and ^{15}N chemical shifts are similar to those observed in the acetoxylation reaction, with differences likely arising from the different reaction solvents (*o*-/*m*-/*p*-CH ^1H δ 8.71, 7.49 and 8.15 ppm and ^{15}N δ 219 ppm; see Figure S5).

Further studies of the aza-Wacker reaction yielded valuable insights. The initial rate of the reaction exhibited a nearly linear dependence on [Pd] at low catalyst loading, but shifted abruptly to a zero-order dependence at [Pd] = 2.5 mM (Figure 3A). This behavior implicated the onset of gas-liquid mass transport limitations at [DAF/Pd(OAc)₂] = 2.5 mM, and O₂ pressure-dependence data support this hypothesis. The rate exhibits no dependence on $p\text{O}_2$ at low [DAF/Pd(OAc)₂] (0.5 mM) but a linear dependence at high [DAF/Pd(OAc)₂] (5 mM) (Figure 3B). Changes in the mixing technique (stirring versus orbital agitation) and use of different reaction vessels under otherwise identical conditions resulted in different rates. The rate plateau correlates with a color change from yellow to deep red and rapid precipitation of the Pd catalyst as a red solid.^[14]

The NMR data for the new DAF-ligated Pd species observed in the catalytic reactions do not match the data for any previously characterized DAF/Pd(OAc)₂ species.^[10,11] For example, the *ortho* and *para* protons of mononuclear κ^2 -DAF-ligated Pd^{II} complexes overlap,^[10] while the corresponding peaks of the new species are well resolved ($\delta > 0.5$ ppm). Dimeric Pd^{II} species with bridging DAF ligands have similarly well resolved chemical shifts for the *ortho* and *para* protons; however, the *o*-CH chemical shifts appear much further downfield (δ 9.9–10.6 ppm) than those in the new species (δ 8.6–8.7 ppm). The downfield ^{15}N chemical shift of DAF in the new species, detected by ^1H - ^{15}N HMBC (δ 217–219 ppm), more closely resembles that of the dimeric Pd^{II} complex [Pd(μ -DAF)(κ^1 -OPiv)₂]₂ (^{15}N δ 218 ppm) than those of mononuclear (κ^2 -DAF)Pd^{II} complexes (^{15}N δ 199–213 ppm).

The prominent color change associated with formation of the new Pd species facilitated monitoring of the reactions by UV-visible spectroscopy. Early stages of the acetoxylation reaction (Figure 4A) revealed the appearance of an absorbance at $\lambda_{\text{max}} = 475$ nm. The aza-Wacker reaction exhibited similar UV-visible spectroscopic features, again showing appearance of an absorption band with $\lambda_{\text{max}} = 475$ nm upon addition of (*Z*)-4-hexenyltosylamide to a toluene solution DAF/Pd(OAc)₂ (Figure 4B). The absorbance maximized at 1 min and then decayed as red precipitate formed in the cuvette. Collectively,

the NMR and UV-visible spectroscopic data obtained from the two different reactions suggest that the same species is forming in both reactions, with the minor differences attributed to the different solvents used in the reactions.

When the acetoxylation reaction was performed at room temperature, crystals suitable for single crystal X-ray diffraction (XRD) analysis were obtained from the red reaction mixture (see Experimental Details and Supporting Information). XRD analysis of the red crystals revealed a Pd^I dimer with two bridging DAF ligands and a κ^1 -acetate ligand capping each of the Pd centers (Figure 4). The Pd–Pd distance of 2.4764(7) Å is consistent with the presence of a bond between the two metals.^[15] The 78.04(4)° dihedral angle between the planes of the two coordinated DAF ligands presumably allows Pd–N bonding to be maximized while allowing the Pd centers to optimize Pd–Pd bonding. The acetate ligands exhibit a *syn* relationship, in which the carbonyl groups are oriented in the same direction. The [Pd^I(μ -DAF)(OAc)]₂ complex co-crystallizes with one equivalent of dioxane and two equivalents of acetic acid (not shown in Figure 5), with the latter hydrogen bonding to the coordinated acetate ligands. This structure is an unusual example of a Pd^I dimer that does not have a bridging anionic (e.g., halide, allyl) or carbonyl ligand.^[16,17]

The dimeric structure of the [Pd^I(μ -DAF)(OAc)]₂ complex was anticipated to be responsible for the UV-visible absorption band at 475 nm. But, to probe the origin of this feature, time-dependent density functional theory (TD-DFT) calculations were carried out. The calculations revealed an excitation at 497 nm, which is in good agreement with the experimental value. Electronic structural analysis of this transition show that it arises from excitation of an electron in the Pd–Pd σ bond as the HOMO into π^* orbitals associated with the DAF ligand (Figure 6). The calculations predict an extinction coefficient of $\epsilon = 0.99 \text{ mM}^{-1} \cdot \text{cm}^{-1}$, which is consistent with the experimental value from UV-visible titrations: $\epsilon_{475 \text{ nm}} = 1.44 \text{ mM}^{-1} \text{ cm}^{-1}$ (see Figure S11 in the Supporting Information).

Formation of the Pd^I dimer may be rationalized by a reaction sequence involving oxidation of the substrate by Pd^{II}, followed by rapid reaction of the resulting Pd⁰ intermediate with another equivalent of the Pd^{II} catalyst. To probe this mechanism of Pd^I formation, we performed the allylic acetoxylation and aza-Wacker reactions under anaerobic conditions [Eqs. (3) and (4)]. In both cases, approximately 50% yield of product was observed with respect to the original [Pd]. This result indicates that the Pd^{II} species reacts much faster with Pd⁰ than with the substrate, resulting in formation of the Pd^I dimer. As an additional control experiment, Pd(OAc)₂ and 0.5 equivalents of Pd₂dba₃ were combined with 2 equivalents of DAF (DAF: Pd_{total} = 1) in acetonitrile [Eq. (5)]. The dimeric Pd^I complex [Pd(μ -DAF)(OAc)]₂ formed rapidly and was isolated in 94% yield from this reaction. The NMR and UV-visible spectroscopic properties of this compound are identical to observed from the catalytic reactions.

(3)

(4)

(5)

Additional control experiments demonstrate that the Pd^{I} dimer is a kinetically competent precatalyst for the the acetoxylation reaction. No kinetic burst is observed, and the reaction time course matches the steady-state profile of the reaction initiated with $\text{DAF}/\text{Pd}(\text{OAc})_2$ as the pre-catalyst (see Figure S12 in the Supporting Information). Furthermore the Pd^{I} dimer reacts with O_2 in AcOH /dioxane to afford a product mixture that is spectroscopically indistinguishable from a 1:1 solution of DAF and $\text{Pd}(\text{OAc})_2$ (see [Eq. (6)] and Figure S13 in the Supporting Information). The insolubility of the Pd^{I} dimer in toluene precluded kinetic competency tests for the aza-Wacker reaction.

(6)

The collective observations above provide clear evidence for a palladium(I) intermediate in these Pd -catalyzed aerobic oxidation reactions, and they show that the Pd^{I} species arises from comproportionation of Pd^0 and Pd^{II} (left equilibrium, Scheme 2). These results may be compared to the involvement of Pd^{I} species in carbonylation^[18] and cross-coupling reactions.^[19,20] For example, dimeric Pd^{I} complexes have been used as pre-catalysts or observed as intermediates in diverse cross-coupling reactions.^[19,21] We speculate that O_2 reacts with the reversibly generated Pd^0 species; however, direct reaction of O_2 with the Pd^{I} dimer cannot be excluded and will be the focus of future studies.^[22]

These results have several implications for catalysis. On one hand, the Pd^{I} dimer appears to be an off-cycle species that slows catalytic turnover. This behavior is evident in the aza-Wacker reaction. The Pd^{I} dimer is not only off-cycle in this reaction, but it precipitates from the reaction mixture, thereby removing some of the Pd catalyst from solution. At sufficiently low catalyst concentration, oxidation of Pd^0 by O_2 can outcompete the bimolecular Pd^{I} dimer formation and accounts for the observed steady-state turnover (cf. Figure 3). In the allylic acetoxylation reaction, involvement of the Pd^{I} dimer is somewhat different. The Pd^{I} dimer is soluble under these reaction conditions, and it is a kinetically competent source of

the active catalyst. The kinetic burst in this reaction (cf. Figure 1) indicates that the DAF/ $\text{Pd}(\text{OAc})_2$ pre-catalyst is more active than the Pd^{I} dimer; however, we speculated that formation of Pd^{I} has a net beneficial effect that partly accounts for the unique effectiveness of DAF as a ligand that promotes aerobic allylic acetoxylation. Specifically, the ability of DAF to promote comproportionation of Pd^0 and Pd^{II} into Pd^{I} by serving as a stabilizing bridging ligand could help to prevent aggregation of Pd^0 into inactive metallic Pd .^[23]

The results described herein provide an important foundation for future efforts to probe the role and reactivity of Pd^{I} species in diverse Pd -catalyzed aerobic oxidation reactions. We anticipate that such efforts will contribute to the development of new highly effective ligands and practical catalyst systems.

Experimental Details

Acetoxylation time course data was acquired using 0.27 M allylbenzene, 54 mM NaOAc , 13.5 mM $\text{DAF/Pd}(\text{OAc})_2$ in 3:1 Dioxane/ AcOH with 1 atm O_2 and 80 °C in a 48-well custom built orbital mixer at 50 rpm. Yields were assayed by sampling the reaction mixture via syringe, quenching with 0.1 M pyridine in EtOAc and analyzed using gas chromatography. Initial NMR acetoxylation speciation experiments were performed by using 67 mM allylbenzene (5 eq. relative to Pd) in a solvent mixture of 3:1 $\text{AcOD}-d_4/1,4$ -dioxane- d_8 with 3.2 atm O_2 at 40 °C. O_2 was condensed into an J-Young as previously described.^[24] Amidation time course data was acquired with 0.1 M (Z)-4-hexenyltosylamide, 5 mM $\text{DAF/Pd}(\text{OAc})_2$ in toluene with 1 atm O_2 and at 24 °C. 1,3,5-Trimethoxybenzene was used as an internal standard. Reactions were processed by filtering the mixture through silica, washing with EtOAc and removing the solvent by vacuum centrifugation. The resulting concentrate was dissolved in CDCl_3 and analyzed by ^1H NMR spectroscopy. Gas uptake kinetics were performed in the same manner as previously reported.^[25] $[(\text{Z})\text{-4-hexenyltosylamide}] = 0.1 \text{ M}$, $[\text{DAF/Pd}(\text{OAc})_2]$ varied accordingly, 3 mL toluene, $p(\text{O}_2) = 730 \text{ Torr}$. UV-visible experiments were performed in a 1 mm cuvette using a Cary 60 spectrometer. $\text{DAF/Pd}(\text{OAc})_2$ concentrations were kept the same for a direct comparison. The acetoxylation reaction mixture from the UV-visible experiment was subjected to vapour diffusion with pentane at 4 °C for two days to obtain red crystals suitable for XRD analysis. For the DFT studies, geometries were optimized via unrestricted DFT using the CAM-B3LYP functional, LANL2TZ(f) basis set and effective core potential for palladium and 6-31g(d) basis set for all other atoms using Gaussian09. TD-DFT calculations were performed using the CAM-B3LYP functional at the optimized geometries, employing the same basis set for palladium and the 6-311G(2df,p) basis set for other atoms. The SMD continuum solvation model was used to model the effects of dioxane. The computed extinction coefficient for the Pd^{I} dimer was estimated by viewing the predicted UV-visible spectrum in Gaussview using a 1 cm^{-1} gaussian fit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Drs. Paul White and Damian Hruszkewycz for insightful discussions and Professor Thomas Brunold for his help in performing TD-DFT computations. We are grateful to the NIH (R01 GM067173 and R01 GM100143) for financial support of this work. Scott McCann is grateful for support from the NIH (F31-GM116443). The NSF provided partial support for the computational resources (CHE-0840494). NMR spectroscopic instrumentation was partially funded by the NSF (CHE-1048642, CHE-0342998, CHE-9208463, S10 RR13866-01).

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Figure 1. A 20 h time course of DAF/Pd-catalyzed allylic acetoxylation of allyl benzene and expansion of the burst phase observed during the first 30 min of the reaction at 80 °C.

Figure 2. A 5 h time course of DAF/Pd-catalyzed aza-Wacker and expansion of the burst phase observed during the first 30 min of the reaction at 24 °C.

Figure 3.

Catalyst and O₂ dependence on the aza-Wacker cyclization reaction. A. Catalyst dependence [DAF/Pd(OAc)₂] = 2 mM – 10 mM B. O₂ dependence with [DAF/Pd(OAc)₂] at 5 mM and 0.5 mM. All reaction performed with [(*Z*)-4-hexenyltosylamide] = 0.1 M and 730 torr O₂ and reactions monitored by O₂ gas consumption.

Figure 4.

UV-visible spectra of an aza-Wacker and acetoxylation at room temperature under air. A. First 120 min of UV-visible time course 5 mM DAF/ $\text{Pd}(\text{OAc})_2$ in 3:1 Dioxane/ AcOH with 0.27 M allylbenzene. B. First 60 s of UV-visible time course of a reaction of 5 mM DAF/ $\text{Pd}(\text{OAc})_2$ in toluene with 0.1 M (*Z*)-4-hexenyltosylamide.

Figure 5.

Two views of the structure of $[\text{Pd}^{\text{I}}(\mu\text{-DAF})(\text{OAc})_2]$. H-atoms, two AcOH molecules and dioxane are omitted for clarity. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Pd1–Pd1 2.4764(7), Pd1–O2 2.2136(2), Pd1–N1 2.022(2), Pd1–N2 2.044(2). N1–Pd1–Pd1ⁱ–N2ⁱ 52.549(7). Symmetry code (i): 1–x, y, 1.5–z.

Figure 6.

Calculated TD-DFT excitation that correspond to the observed 475 nm absorbance of $[\text{Pd}^{\text{I}}(\mu\text{-DAF})(\text{OAc})_2]$. Excitation from the Pd HOMO to different ligand antibonding orbitals (MLCT).

Scheme 1.

Simplified Catalytic Cycle for Homogeneous Pd-Catalyzed Aerobic Oxidation Reactions.

Scheme 2.
 Pd^0 Pathways in DAF-Promoted Reactions