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Diazafluorenone-Promoted Oxidation Catalysis: Insights into the Role of Bidentate Ligands in Pd-Catalyzed Aerobic Aza-Wacker Reactions

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Abstract

2,2'-Bipyridine (bpy), 1,10-phenanthroline (phen) and related bidentate ligands often inhibit homogeneous Pd-catalyzed aerobic oxidation reactions; however, certain derivatives, such as 4,5-diazafluoren-9-one (DAF), can promote catalysis. In order to gain insight into this divergent ligand behavior, eight different bpy- and phen-derived chelating ligands have been evaluated in Pd(OAc)₂-catalyzed oxidative cyclization of (*E*)-4-hexenyltosylamide. Two of the ligands, DAF and 6,6'-dimethyl-2,2'-bipyridine (6,6'-Me₂bpy), support efficient catalytic turnover, while the others strongly inhibit the reaction. DAF is especially effective and is the only ligand that exhibits “ligand-accelerated catalysis”. Evidence suggests that the utility of DAF and 6,6'-Me₂bpy originates from the ability of these ligands to access κ^1 -coordination modes via dissociation of one of the pyridyl rings. This hemilabile character is directly observed by NMR spectroscopy upon adding one equivalent of pyridine to solutions of 1:1 L/Pd(OAc)₂ (L = DAF and 6,6'-Me₂bpy), and is further supported by an X-ray crystal structure of Pd(py)(κ^1 -DAF)OAc₂. DFT computational studies illuminate the influence of three different chelating ligands [DAF, 6,6'-Me₂bpy, and 2,9-dimethyl-1,10-phenanthroline (2,9-Me₂phen)] on the energetics of the aza-Wacker reaction pathway. The results show that DAF and 6,6'-Me₂bpy destabilize the corresponding ground-state Pd(N-N)(OAc)₂ complexes, while stabilizing the rate-limiting transition state for alkene insertion into a Pd–N bond. Interconversion between κ^2 - and κ^1 -coordination modes facilitate access to open coordination sites at the Pd^{II} center. The insights from these studies introduce new ligand concepts that could promote numerous other classes of Pd-catalyzed aerobic oxidation reaction.

Graphical Abstract

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Supporting Information. Experimental and computational details, NMR spectra and crystallography reports are available free of charge via the Internet at <http://pubs.acs.org>.

Keywords

palladium; aerobic; oxidation; catalysis; mechanism; Wacker; diazafluorenone

Introduction

The discovery of ligand-modulated palladium(II) catalysts has played a major role in the growth of homogeneous palladium-catalyzed aerobic oxidation reactions over the past 15+ years.^{1, 2} Ancillary ligands often provide the basis for dioxygen-coupled catalytic turnover without requiring cocatalysts or other stoichiometric oxidants, such as benzoquinone or Cu^{II} salts. Synthetic and mechanistic studies of these reactions highlight multiple roles of the ligands in this chemistry (Scheme 1). The ligands play a crucial role in stabilizing the catalyst³ and promoting reoxidation of Pd⁰ by O₂ (Scheme 1: *a* and *c*).^{4,5} Ligands also enable control over reaction selectivity, prominent examples of which include kinetic resolution of secondary alcohols,⁶ and regio-⁷ and enantioselective⁸ oxidative Heck reactions. But, the role of ligands is not always beneficial. Ligands often inhibit catalytic turnover or slow the rate by attenuating the electrophilicity of the Pd^{II} center and/or occupying open coordination sites needed for substrate oxidation. The characteristics of ligands that contribute to favorable, rather than deleterious, effects are not well understood, and insights into such factors could have a major impact on the field.⁹

Pyridine (py)-based ligands are widely used in Pd-catalyzed aerobic oxidation reactions.^{1,2} In one of the earliest examples, Uemura and coworkers reported that Pd(OAc)₂/py (1:4 ratio) is a highly effective catalyst for aerobic alcohol oxidation (eq 1).¹⁰ Upon finding that a similar catalyst system, Pd(OAc)₂/py (1:2 ratio), mediates efficient intramolecular oxidative amination of alkenes (eq 2; aza-Wacker reactions),¹¹ we undertook mechanistic studies of these reactions to gain insight into the ligand effects.^{5c,12} In the alcohol oxidation reaction, Pd(OAc)₂ shows no catalytic turnover in the absence of pyridine. The initial catalytic rate maximizes at 1:1 Pd(OAc)₂/py; however, catalyst decomposition into Pd black limits the total turnover numbers. The catalyst is less active but more stable at higher [py], and the optimized 1:4 Pd(OAc)₂/py catalyst system represents the compromise between catalyst activity and stability that achieves the highest synthetic yields.^{10b} Related pyridine effects were observed for the aza-Wacker reaction, with the optimal balance observed with a 1:2 Pd(OAc)₂/py catalyst system.^{12c,13}

(1)

(2)

Bidentate ligands, such as 2,2'-bipyridine (bpy) and phenanthroline (phen), are appealing ligands to consider for Pd-catalyzed aerobic oxidation reactions because their chelating ability should enhance the stability of Pd⁰ and promote its oxidation by O₂ (cf. Scheme 1). But, bpy and phen strongly inhibit the reactions shown in eqs 1 and 2,^{10,14} and similar inhibitory effects have been observed in numerous other reactions.^{15,16} In an investigation of aerobic acetoxylation of allylic C–H bonds,¹⁷ we observed negligible catalytic activity with Pd(OAc)₂, both in the absence of an ancillary ligand and in the presence of pyridine or numerous bpy and phen ligand derivatives (eq 3). The sole exception was 4,5-diazafluoren-9-one (DAF). DAF/Pd(OAc)₂ proved to be an effective catalyst for aerobic allylic C–H acetoxylation of allyl benzene and numerous other terminal alkene substrates. Subsequent studies have shown that DAF is uniquely effective in a number of other Pd-catalyzed aerobic oxidation reactions, including oxidative C–C and C–O coupling reactions with arenes,¹⁸ α,β-dehydrogenation of cyclic ketones,¹⁹ oxidative Heck reactions,²⁰ and also various non-aerobic oxidation reactions.²¹

(3)

The basis for the unique effect of DAF in eq 3 and the other reactions is not well understood. In a recently completed study,²² we characterized *six* different complexes, including both monomeric and dimeric species, that are simultaneously present in a 1:1 mixture of DAF and Pd(OAc)₂ (Chart 1). The complex coordination chemistry of DAF²³ sharply contrasts the behavior of other bidentate ligands, such as bpy and phen, which form 1:1 adducts as the sole structure in solution. The unique ligand behavior of DAF correlates with the unique catalytic behavior noted above, but the mechanistic basis for the catalytic effects has not been established.

In an effort to gain further insights into the role of DAF, we decided to revisit the reactivity of bidentate ligands in Pd-catalyzed aza-Wacker reactions. This reaction class is one of the most extensively studied among Pd-catalyzed aerobic oxidations, with efforts leading to the identification of numerous catalyst systems, synthetic applications, and mechanistic insights.^{24,25} These precedents provide an excellent framework for the investigation of

ligand contributions to reactivity. Here, we show that whereas most bidentate ligands strongly inhibit catalytic turnover, both DAF and 6,6'-dimethyl-2,2'-bipyridine (6,6'-Me₂bpy) support reactivity. Only DAF, however, exceeds the utility of pyridine and exhibits “ligand accelerated catalysis”. Kinetic, spectroscopic, X-ray crystallographic, and DFT computational studies show that DAF and 6,6'-Me₂bpy exhibit hemilabile behavior in solution. The collective data provide valuable insights into ligand properties that promote efficient catalytic turnover and have broad implications for the field of Pd-catalyzed aerobic oxidation, as well as other catalytic applications.

Results and Discussion

Comparison of Ligand Effects on Pd-Catalyzed Aerobic Aza-Wacker Reactivity

4-Alkenyltosylamides (cf. eq 2) have been widely used for the development of new Pd catalyst systems²⁶ and characterization of catalytic mechanisms.²⁷ Therefore, *cis*-4-hexenyltosylamide (**1**) was chosen to assess the influence of bidentate ligands on aerobic aza-Wacker reactivity. A broad series of bpy and phen derivatives were evaluated in this reaction at 50 °C under conditions similar to those described previously with the Pd(OAc)₂/py-catalyst system (Table 1). Ligand-free Pd(OAc)₂ and the Pd(OAc)₂/py were included for comparison.²⁸ The ligand-free conditions (entry 1) give a moderate product yield, but poor mass balance. By-products were not fully characterized, but sulfonyl imine and its aldehyde hydrolysis product are detected. In contrast, Pd(OAc)₂/py catalyzes clean conversion to the pyrrolidine product in 86% yield (entry 2).¹¹ Use of four different phen derivatives, 4,4'-tBu₂bpy, and bipyrimidine (entries 3–8) resulted in nearly complete inhibition of the reaction (yield = 10%). Use of 2,2'-dipyridyl ketone and 6-Mebpy resulted led to a moderate yield (26% and 38%, respectively; entries 9 and 10), however, and the yield improved considerably upon use of 6,6'-Me₂bpy (81%, entry 11). The best results were observed with 9,9-dimethyl-4,5-diazafluorene (Me₂DAF) and DAF, which led to near-quantitative yield (92% and 97%, respectively; entries 12 and 13). The relative effects of 6,6'-Me₂bpy and the DAF derivatives were further analyzed at room temperature. Under these conditions, Me₂DAF and DAF proved to be quite effective, again affording excellent yield (92% and 97%, respectively), whereas a considerably lower yield was observed with 6,6'-Me₂bpy (40%). That all reactions except the ligand-free reaction exhibited excellent mass balance highlights the beneficial effect of ligands on reaction chemoselectivity. A number of traditional bidentate ligands strongly inhibit catalytic reactivity, but this preliminary screen also shows that certain bidentate ligands, specifically, 6,6'-Me₂bpy, Me₂DAF and DAF, match or exceed the performance of pyridine.

Reaction time-course studies performed with selected ligands at 50 °C provided further insight into the ligand effects. Reactions with DAF, 6,6'-Me₂bpy and the structurally related 2,9-Me₂phen ligand were compared to the ligand-free and Pd(OAc)₂/py-catalyzed reactions (Figure 1).²⁹ The latter benchmark reactions exhibit similar rates of substrate consumption, and the reaction with 6,6'-Me₂bpy is only moderately slower. The impact of the moderately slower rates observed with pyridine and 6,6'-Me₂bpy relative to the ligand-free conditions is offset by the improved mass balance/reaction selectivity observed in the presence of these ligands, as manifested in the product yields obtained from the reactions (cf. Table 1). 2,9-

Me₂phen almost completely inhibits of the reaction, while the reaction with DAF is significantly faster than all of the other reactions. DAF enables complete conversion to the pyrrolidine product in approximately 1 h, with excellent mass balance.

Next, the influence of Pd(OAc)₂:ligand stoichiometry on the catalytic reaction was evaluated (Figure 2). The pyridine data (Figure 2A) resemble those obtained previously under slightly different conditions.^{11c} A modest increase in rate is observed from 0–1 equiv of pyridine with respect to Pd(OAc)₂. Beyond this stoichiometry, additional pyridine exhibits an inhibitory effect until it reaches a non-zero plateau at high [py]. The bidentate ligands 6,6'-Me₂bpy and 2,9-Me₂phen inhibit Pd(OAc)₂ in direct proportion to their stoichiometry with respect to Pd(OAc)₂ (Figures 2B and 2C); however, 2,9-Me₂phen completely inhibits the reaction at 1 equiv of ligand relative to Pd(OAc)₂, while 6,6'-Me₂bpy/Pd(OAc)₂ retains moderate catalytic activity beyond 1:1 stoichiometry. The behavior of DAF is unique. No inhibitory effect is observed, even with a large excess of DAF (Figure 2D). This type of ligand-acceleration effect with a neutral-donor ligand is, to our knowledge, unprecedented in Pd-catalyzed aerobic oxidations.

Ligand Coordination Properties and Relative Binding Strength

As noted in the Introduction, DAF forms six nearly isoenergetic coordination compounds upon reaction with Pd(OAc)₂ (cf. Chart 1).²² This unusual coordination chemistry was the focus of a recent study and was attributed to structural distortions of DAF relative to traditional bpy and phen ligands (Figure 3). Meanwhile, 6,6'-Me₂bpy and 2,9-Me₂phen also show unusual coordination behavior resulting from the steric clash between the methyl groups and other ligands in the square plane. An X-ray crystal obtained for Pd(6,6'-Me₂bpy)(OAc)₂ (Figure 4A) highlights the distorted coordination geometry of this complex. The plane of the 6,6'-Me₂bpy ligand lies at a 33° angle with respect to the Pd^{II} square plane, which reduces the steric interaction between the two ligand methyl groups and the acetate ligands. Similar structural behavior has been reported previously for Pd(2,9-Me₂phen)(OAc)₂, in which the phen ligand bends out of the square plane by 34°. ³⁰ One difference is evident between the 6,6'-Me₂bpy and 2,9-Me₂phen ligands: the 6,6'-Me₂bpy ligand exhibits an unfavorable steric interaction between the hydrogen atoms in the 3 and 3' positions (Figure 4B), whereas the phenanthroline ligand has a covalent C=C bond in this position. This feature is believed to destabilize the binding of 6,6'-Me₂bpy relative to 2,9-Me₂phen, as elaborated below.

An effort was made to assess the relative binding strength among 4,4'-tBu₂bpy, 2,9-Me₂phen, 6,6'-Me₂bpy, and DAF as ligands. Each of these ligands was combined with Pd(OAc)₂ in a 1:1 ratio in CDCl₃, and variable quantities of pyridine (0.5–5 equiv) were then added to these solutions (see Supporting Information, Figures S4–S7).³¹ The different mixtures were analyzed by ¹H NMR spectroscopy and, in all cases except with DAF, the sole species observed in solution were the Pd(N–N)(OAc)₂ adduct and *trans*-Pd(py)₂(OAc)₂. Mixtures of Pd(OAc)₂, the N–N ligand, and pyridine in 1:1:2 ratios provide a diagnostic assessment of the relative binding strengths of the different ligands (Table 2). With 4,4'-tBu₂bpy, negligible quantities of the pyridine complex were observed (< 3%). With 2,9-

Me₂phen, the bidentate ligand complex was favored 5:1 over the pyridine adduct, while an approximately inverted ratio (1:4.3) was observed with 6,6'-Me₂bpy.

The DAF mixture was complicated at room temperature, but negligible contribution from the simple κ^2 -DAF complex was evident. Broadened peaks implicated dynamic exchange processes, and the solution was cooled to $-35\text{ }^\circ\text{C}$ to facilitate characterization of the species in solution. Two major species were present: Pd(py)₂(OAc)₂ and a new species, which was characterized by 1D and 2D NMR spectroscopic methods (including 1D TOCSY, 1D ROESY, ¹H-¹³C HSQC, ¹H-¹³C HMBC, and ¹H-¹⁵N HMBC methods; see Supporting Information for details, Figures S8–S14). This species was identified as Pd(κ^1 -DAF)(py)(OAc)₂ and was present in a 1:5.4 ratio relative to Pd(py)₂(OAc)₂. The identity of this complex was further established by X-ray crystallography (Figure 5).³²

The room-temperature mixtures of Pd(OAc)₂, 6,6'-Me₂bpy and pyridine also showed some evidence for dynamic behavior, reflected by changes in the chemical shift of peaks associated with the 6,6'-Me₂bpy as a function of the amount of pyridine in solution. As noted in Table 2, pyridine coordination is favored over coordination of 6,6'-Me₂bpy, and when pyridine was added to a solution of Pd(6,6'-Me₂bpy)(OAc)₂ at $-70\text{ }^\circ\text{C}$, an intermediate species was detected. Upon warming a solution of this species, it converted into a simple mixture of Pd(6,6'-Me₂bpy)(OAc)₂ and Pd(py)₂(OAc)₂. NMR analysis of the intermediate showed evidence of dynamic exchange processes, even at $-90\text{ }^\circ\text{C}$, which prevented heteronuclear 2D NMR characterization similar to that used with Pd(κ^1 -DAF)(py)(OAc)₂. Nevertheless, ¹H 1D TOCSY, EXSY and ROESY experiments (Figures S15–S16), in combination with integration of the 1D ¹H NMR spectrum, revealed a 6,6'-Me₂bpy ligand with two inequivalent rings (Figure 6). Through-space interactions between the 6,6'-Me₂bpy, pyridine and two acetate ligands, and the integrations the respective peaks support a structure consisting of *trans*-Pd(κ^1 -6,6'-Me₂bpy)(py)(κ^1 -OAc)₂ (Figure 6). To our knowledge, this direct observation of reversible κ^1 coordination for 6,6'-Me₂bpy is unprecedented. No evidence for dynamic exchange processes were evident in the pyridine titration studies of 2,9-Me₂phen/Pd(OAc)₂ mixtures.

To summarize, the pyridine titration studies suggest the ligand binding strength of the different bidentate ligands follows the trend 4,4'-^tBu₂bpy > 2,9-Me₂phen > 6,6'-Me₂bpy ~ DAF. This trend inversely correlates with the relative yields and rates observed with these ligands in the aza-Wacker reaction (Table 1 and Figure 1). 4,4'-^tBu₂bpy and 2,9-Me₂phen form static, strongly-bound 1:1 adducts with Pd(OAc)₂, and both strongly inhibit the catalytic reaction. In contrast, 6,6'-Me₂bpy exhibits dynamic behavior in the presence of a monodentate donor ligand (pyridine), with transient formation of a κ^1 -ligated bpy adduct, while DAF exhibits dynamic interconversion between κ^2 - and κ^1 -coordination modes, even in the absence of a donor ligand (cf. Chart 1). The correlation between this bidentate ligand behavior and the respective catalytic activity supported by these ligands will be explored further below.

Assessment of Ligand Effects on the Aza-Wacker Reaction Mechanism

Pd(OAc)₂/pyridine-catalyzed oxidative cyclization of 4-hexenyltosylamide has been the focus of previous mechanistic study and a simplified mechanism is depicted in Scheme 2.

The reaction involves displacement of pyridine and an acetate ligand (as AcOH) to afford an alkene/amidate–Pd^{II} chelate, followed by insertion of the alkene into the Pd^{II}–N bond in a “*cis*-amidopalladation” reaction. Subsequent β-hydride elimination from the resulting alkyl–Pd^{II} species affords the vinyl-pyrrolidine product, and the Pd^{II}-hydride is then reoxidized by O₂ in a multistep process via a Pd⁰ intermediate.

Amidopalladation of alkenes can proceed via a *cis* or *trans* pathway, depending on the identity of the catalyst or reaction conditions.²⁴ Insight into the stereochemical course of the aza-Wacker reactions catalyzed by Pd(OAc)₂/6,6'-Me₂bpy and Pd(OAc)₂/DAF reaction was obtained by using the stereospecifically labeled cyclopentene-*d*₁ derivative **I** (Scheme 3).³³ The bicyclic product **II**, which arises from *cis*-amidopalladation of the alkene, was observed as the sole product of both reactions (72% and 98%, respectively). This outcome is consistent with a mechanism similar to the Pd(OAc)₂/pyridine-catalyzed pathway in Scheme 2.

Density functional theory (DFT) methods were used to explore the aza-Wacker reaction pathway with three different ligands, 2,9-Me₂phen, 6,6'-Me₂bpy, and DAF. The calculations show that these ligands vary considerably in their binding strength to Pd(OAc)₂, consistent with the experimental results describe above (cf. Table 2). The bidentate ligand complexes range from strongly favored for 2,9-Me₂phen (−7.1 kcal/mol) to nearly isoergic for 6,6'-Me₂bpy (−1.4 kcal/mol) and DAF (−1.8 kcal/mol) (Scheme 4). For comparison, *trans*-Pd(py)₂(OAc)₂ has a calculated energy of (−8.1 kcal/mol), and coordination of the traditional bpy ligand 4,4'-tBu₂bpy, which lack steric features or structural distortions that would disfavor binding, is strongly favored ($G^\circ = -15.8$ kcal/mol).

(*Z*)-4-Hexenylmethanesulfonamide was the used as the substrate to assess aza-Wacker reaction pathways (Scheme 4). Formation of a Pd^{II}-amidate via proton-coupled displacement of an acetate ligand (i.e., with loss of AcOH) is uphill by approx. 9 kcal/mol for the 2,9-Me₂phen and 6,6'-Me₂bpy complexes, but only by 2.3 kcal/mol for the DAF complex. This difference reflects steric effects of the methyl groups in 2,9-Me₂phen and 6,6'-Me₂bpy, which disfavor binding of the larger mesylamide group relative to acetate. Coordination of the alkene to afford a chelated alkene/amidate structure requires dissociation of another ligand from Pd^{II}. Loss of acetate to afford a cationic complex is energetically costly in a non-polar solvent, such as toluene. For example, formation of the DAF complex [Pd(DAF)(alkene/amidate)]⁺OAc[−] (**D'**) is calculated to have an energy of 29.0 kcal/mol (Figure 7). The experimental evidence for κ²/κ¹ interconversion of DAF and 6,6'-Me₂bpy (cf. Figures 5 and 6) prompted us to consider an alternative pathway involving dissociation of one of the pyridyl rings of the chelating ligand (i.e., **C** → **D**). This step is especially accessible with DAF. The alkene/amidate–Pd^{II} chelate lies at 7.2 kcal/mol, which is only 9 kcal/mol higher in energy than the initial Pd(OAc)₂/DAF complex. And, the subsequent transition state for alkene insertion into the Pd–N bond (**E**) (i.e., *cis*-amidopalladation of the alkene) is at 18.6 kcal/mol ($G^\ddagger = 20.4$ kcal/mol relative to Pd(DAF)(OAc)₂). The analogous transition state with 6,6'-Me₂bpy is higher in energy (25.8 kcal/mol), but still quite accessible. The absolute energies of the 2,9-Me₂phen and 6,6'-Me₂bpy transition states differ by less than 2 kcal/mol; however, Pd(2,9-Me₂phen)OAc₂ has significant ground-state stability that results in a very high net activation energy ($G^\ddagger = 34.6$ kcal/mol) and accounts for the inhibitory effect of

this ligand. For comparison, the previously reported computational study of the $\text{Pd}(\text{py})_2(\text{OAc})_2$ -catalyzed reaction revealed a net activation energy for the reaction of 24.6 kcal/mol,^{12c} which is higher than that of the DAF-based reaction, but lower than that of the reactions with 6,6'-Me₂bpy and 2,9-Me₂phen. The relative calculated activation-energies for the different ligands align with the relative experimental ligand-reactivity trends shown in Figure 1 and highlight the importance of both ground-state and transition-state ligand effects on the reaction.

Subsequent β -hydride elimination from the Pd-alkyl intermediate **F** is lower in energy than the amidopalladation step. The preferred pathway identified for this process features a concerted “reductive β -hydride elimination” step in which the β -hydrogen of alkyl ligand is transferred directly to the free oxygen of the carboxylate ligand, resulting in formation of a Pd⁰ product with a bound AcOH ligand (**H**), rather than a Pd^{II}-hydride species. A similar pathway was identified previously for a Pd-catalyzed alcohol oxidation reaction.³⁴ Loss of the AcOH ligand from this complex is energetically favorable, and subsequent oxidation of the resulting Pd(N~N)(alkene) complex is expected to be very facile, on the basis of prior studies of this reaction.^{5a,e,35}

Conclusions and Implications for Aerobic Oxidation Catalysis

The results presented above add another Pd-catalyzed aerobic oxidation method to the growing number of reactions that benefit from the use of DAF as an ancillary ligand. In the present case, DAF is the only bidentate bpy/phen-type ligand among numerous examples that supports efficient catalytic turnover at room temperature. Perhaps more importantly, the results described here provide some of the first clear insights into the unique ability of DAF to promote these reactions.

The unusual coordination properties of DAF, evident in Chart 1²² and elsewhere,²³ reflect the structural differences of DAF relative traditional bpy- and phen-type ligands that make it a non-ideal chelating ligand (cf. Figure 3). Coordination of DAF to Pd^{II} as a bidentate ligand requires a distortion of the DAF ligand, and the resulting strain raises the ground-state energy of the catalyst. This strain contributes to the low-energy interconversion between κ^2/κ^1 ligand-coordination modes, which then facilitates binding of the alkene substrate to Pd^{II} and lowers the transition-state energy of the rate-limiting *cis*-amidopalladation step. The reaction pathway in Scheme 4 highlights the synergistic participation of the basic X-type ligand (acetate), which undergoes proton-coupled exchange with the N–H group of the amide substrate (i.e., N–H activation), and a neutral L-type ligand (one of the pyridyl rings of DAF) that is readily displaced to enable activation of the neutral alkene.

There are aspects of the “ligand acceleration” effect that remain unclear, but the salient point is that DAF does not bind as strongly to Pd(OAc)₂ as does pyridine or traditional bidentate ligands. This point is highlighted in Table 2 and appears again in the computational studies (Scheme 4). More-stable catalyst ground states contribute to higher net activation barriers in the catalytic reaction.

Similar ligand effects are expected to play important roles in other Pd-catalyzed aerobic oxidations, which typically require coordination of both X- and L-type substrate fragments at the Pd^{II} center. For example, α,β -dehydrogenation of ketones,¹⁹ oxidative Heck (i.e., aryl-C–H/alkene) coupling²⁰ and allylic C–H oxidation reactions^{17,21} have been promoted by DAF as an ancillary ligand. Each of these reactions resemble the aza-Wacker reaction in that they feature steps that require simultaneous access to L- and X-type ligand sites by the substrate(s) and/or involve carboxylate-mediated activation of a substrate that is coordinated to Pd^{II} as a neutral donor ligand (Figure 8). Each of these reactions is expected to benefit from the strain-induced hemilability of the DAF ligand, which provide low-energy access to an open L-type coordinate site at Pd^{II}.

Collectively, the insight gained from this study illuminate features of DAF that make it especially effective in many Pd-catalyzed aerobic oxidation reactions. Current efforts are being directed toward the intentional design and testing of new ligands with similar features that could prove to be even more effective than DAF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Kinetic time courses of the oxidative cyclization of **1**. Conditions: 5 mol % Pd(OAc)₂ (3.4 mg, 15 μmoles), ligand (2,9-Me₂phen, 6,6'-Me₂bpy, DAF = 5 mol % 15 μmoles; pyridine: 10 mol % 30 μmoles), **1** (76 mg, 300 μmoles, 0.1 M), 50 °C, 1 atm O₂, toluene (3 mL), int. std. = 1,3,5-trimethoxybenzene. The reaction was followed for 2.5 hours for with data collected every 5 min for DAF, and the other ligands were followed with data collected every 10 min for the first 50 min and every hour for two more hours.

Figure 2.

Kinetic dependence of the initial rate of the oxidation of **1** on [ligand]. Conditions were as followed: [Substrate] = 0.1 M, [Pd(OAc)₂] = 1.5 mM, 3 mL, $p\text{O}_2$ = 730 torr, toluene (3 mL).

(A) [DAF] = 0–18 mM, 27 °C. (B) [Pyridine] = 0–18 mM 50 °C. (C) [6,6'-Me₂bpy] = 0–4.5 mM, 50 °C. (D) [2,9-Me₂phen] = 0–4.5 mM, 50 °C.

Figure 3.
Comparison of uncoordinated bpy and DAF ligands, highlighting the structural distortion of DAF.

A. Crystal Structure of Pd(6,6'-Me₂bpy)(OAc)₂. **B. Steric Interactions Formed Upon Chelation to Pd(OAc)₂** **Figure 4.**

X-ray crystal structure of Pd(6,6'-Me₂bpy)(OAc)₂ depicting the steric effects of the methyl groups that causes bending of the 6,6'-Me₂bpy ligand out of the Pd^{II} square plane by 27°. (A; the molecular representation of the crystal structure is drawn with 50% thermal ellipsoids and the hydrogen atoms are omitted for clarity). Illustration of the steric clash between the 3 and 3' hydrogen atoms of the 6,6'-Me₂bpy ligand (B).

A. Species observed from mixtures of Pd(OAc)₂, DAF and pyridine. **B.** X-ray crystal structure of Pd(κ^1 -DAF)(py)(OAc)₂. **Figure 5.**

Observation of a mixed DAF/pyridine intermediate, **8**, characterized by NMR spectroscopy (A) and X-ray crystallography (B). Molecular diagram of the crystal is drawn with 50% probability ellipsoids and all H atoms are omitted for clarity.

Figure 6.

Observation of a mixed 6,6'-Me₂bpy/pyridine intermediate, β , characterized by NMR spectroscopy at -70°C (ns = 8, ds = 2, d1 = 20 s). The integrations of the aromatic and aliphatic protons are consistent with *trans*-Pd(κ^1 -6,6'-Me₂bpy)(py)(OAc)₂. Correlations within and between ligands were made with 1D TOCSY and ROESY experiments at -70°C (See Supporting Information, Figures S15–S16).

Figure 7.
DAF complex $[\text{Pd}(\text{DAF})(\text{alkene/amidate})]^+\text{OAc}^-$ (**D'**).

Figure 8.

Representative transition-state structures in Pd-catalyzed aerobic oxidation reactions that feature substrate coordination to Pd^{II} in L- and X-type ligand sites and/or involvement of carboxylate-mediated activation of a substrate that is coordinated to Pd^{II} as a neutral donor ligand.

Scheme 1.

Simplified Mechanism and Overview of Ligand Effects in Pd-Catalyzed Aerobic Oxidation Reactions.

Scheme 2. Mechanism of Pd(OAc)_2 /Pyridine-Catalyzed Aza-Wacker Cyclization.

Scheme 3.

Assessment of *cis*- vs. *trans*-Amidopalladation (AP) Pathway with Pd(OAc)₂/6,6'-Me₂bpy and Pd(OAc)₂/DAF Catalyst Systems.

Scheme 4.
Aza-Wacker Reaction Pathway and Energetics for DAF, 6,6'-Me₂bpy and 2,9-Me₂phen

Chart 1.
Structures Present in a 1:1 Solution of DAF and Pd(OAc)₂.²²

Table 1Assessment of Bidentate Ligands on Oxidative Amidation^a

Entry	Ligand	Yield ^b	Entry	Ligand	Yield ^b
1	None	66%	9		26%
2	10 mol%	86%	10		38%

3	R ₁ = R ₂ = H	3%			
4	R ₁ = Me, R ₂ = H	9%			
5	R ₁ = H, R ₂ = Ph	1%			
6	R ₁ = Me, R ₂ = Ph	7%			
7		1%	11		81% 40% (24 °C)
8		2%	12		92% 92% (24 °C)
			13		97% 97% (24 °C)

^aConditions: substrate (75 μmol, 0.1 M), Pd(OAc)₂ (3.75 μmol), O₂ (1 atm), toluene (0.75 mL), 50 °C, 24 h.^bYield determined by ¹H NMR spectroscopy, int. std. = PhSiMe₃.

Table 2

Relative Ligand Binding Strength of Bidentate Ligands Relative to Pyridine.

Ligand	(N~N)Pd(OAc) ₂ : Pd(py) ₂ (OAc) ₂	
4,4'-tBu ₂ bpy	40 : 1	
2,9-Me ₂ phen	5 : 1	
6,6'-Me ₂ bpy	1 : 4.3	
DAF	1 : 5.4 ^a	

^aThe DAF ligated species is Pd(κ^1 -DAF)(py)(OAc)₂, not Pd(κ^2 -DAF)(OAc)₂.

See Figure 5 and text for details