Ligand-Promoted Palladium-Catalyzed Aerobic Oxidation Reactions

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ABSTRACT: Palladium-catalyzed aerobic oxidation reactions have been the focus of industrial application and extensive research efforts for nearly 60 years. A significant transition occurred in this field approximately 20 years ago, with the introduction of catalysts supported by ancillary ligands. The ligands play crucial roles in the reactions, including promotion of direct oxidation of palladium(0) by O_2, bypassing the typical requirement for Cu salts or related redox cocatalysts to facilitate oxidation of the reduced Pd catalyst; facilitation of key bond-breaking and bond-forming steps during substrate oxidation; and modulation of chemo-, regio-, or stereoselectivity of a reaction. The use of ligands has contributed to significant expansion of the scope of accessible aerobic oxidation reactions. Increased understanding of the role of ancillary ligands should promote the development of new synthetic transformations, enable improved control over the reaction selectivity, and improve catalyst activity and stability. This review surveys the different ligands that have been used to support palladium-catalyzed aerobic oxidation reactions and, where possible, describes mechanistic insights into the role played by the ancillary ligand.

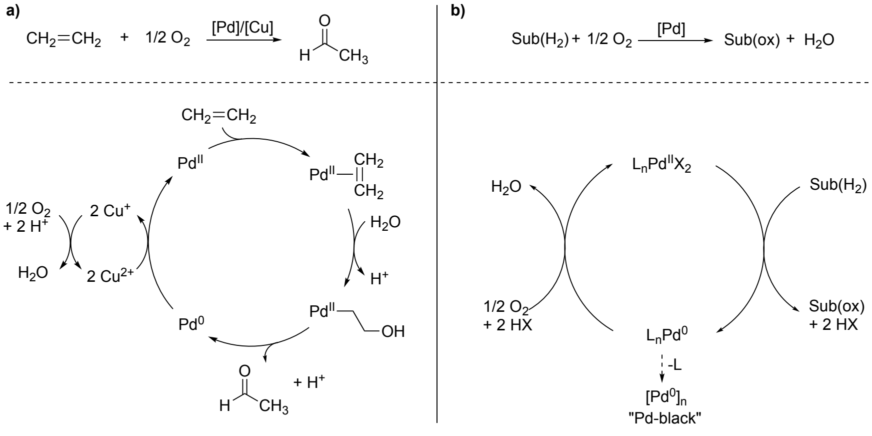
CONTENT

1. Introduction

The selective oxidation of organic molecules provides the basis for streamlined conversion of simple precursors into value-added products.[1] Among the different classes of reactions in organic chemistry, oxidations are notoriously challenging because they often exhibit poor selectivity and/or generate significant quantities of unwanted byproducts derived from the stoichiometric oxidants. In this context, development of liquid-phase aerobic oxidation reactions that exhibit broad scope and high selectivity, including chemo-, regio-, and/or stereoselectivity, could have a major impact on the synthesis of pharmaceuticals, agrochemicals, and fine chemicals.

Palladium-catalyzed aerobic oxidation reactions trace their origin to the Wacker process, which was discovered in the late 1950s[2-4] and, at one point, was responsible for an annual production of over one billion pounds of acetaldehyde from ethylene and water.[5] Many features of the catalytic mechanism have been investigated and debated,[6,7] but the overall process consists of Pd^{II}-mediated oxidative coupling of ethylene and water, followed by aerobic reoxidation of Pd^0 to Pd^{II}, mediated by Cu salts (Scheme 1a). Palladium-catalyzed oxidation reactions were the focus of considerable development in the decades following discovery of the Wacker Process, with the majority of these efforts focused on oxidative alkene functionalization.[8-12] The reported transformations typically employ simple palladium salts, such as $PdCl_2$ or $Pd(OAc)_2$, as the catalyst, and use cocatalytic or stoichiometric oxidants, such as Cu^{II} salts or benzoquinone, in combination with (or instead of) O_2 as the terminal oxidant.[8-13]

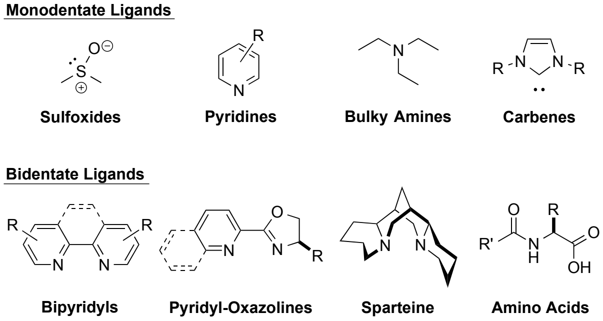
Scheme 1. Overview of the catalytic mechanism of the Wacker Process (a) and a general representation of ligand-supported palladium-catalyzed aerobic oxidation reactions (b).



In the mid-1990s, studies by Larock[14] and Hiemstra[15] showed that $Pd(OAc)_2$ in DMSO could promote intramolecular Wacker-type cyclizations of alkenes in the absence of a redox-active cocatalyst to support aerobic oxidation of the Pd catalyst. Although earlier precedents of direct dioxygen-coupled Pd-catalyzed oxidation reactions had been reported,[16-19] the diversity of reactions that proved to be compatible with these reaction conditions (see Section 3 below), and the role of the coordinating DMSO solvent evident from this work, drew attention to broader possibilities for the use of ancillary ligands to support aerobic catalytic oxidation reactions with homogeneous Pd catalysts. Shortly thereafter, Uemura,[20] Sheldon,[21] and Enichem[22] demonstrated the use of pyridine and phenanthroline-based nitrogen ligands in direct palladium-catalyzed aerobic oxidations. Collectively, these results ushered in a new era for the field of Pd-catalyzed aerobic oxidation catalysis, generically depicted in Scheme 1b, wherein ancillary ligands are used to modulate catalyst stability, activity and selectivity (including enantioselectivity). As a result, palladium-catalyzed oxidations have become more amenable to systematic modulation and optimization. Over the past two decades, the types of transformations achieved by homogeneous Pd oxidation catalysis have been extended to many other reactions, including alkene functionalizations,[23 - 31] alcohol oxidations,[32 - 35] dehydrogenation of C–C bonds,[36 - 38] oxidative C–H functionalizations,[39-43] among others.

The relatively recent emergence of ligand-supported Pd oxidation catalysts contrasts the historically prominent role of ligands in other areas of homogeneous catalysis, including palladium-catalyzed (non-oxidative) cross-coupling reactions. Cross-coupling reactions have benefited greatly from the development of new phosphine ligands that support catalytic turnover in various ways.[44-48] These ligands serve multiple roles, including stabilizing Pd^0, promoting oxidative addition and reductive elimination steps, and providing chiral scaffolds for asymmetric processes. Phosphine ligands are not expected to be compatible with aerobic oxidation reaction conditions, however, and ligand-supported Pd-catalyzed aerobic oxidation reactions have mostly relied on alternative ligand classes, such as sulfoxides, amines, pyridines, and carbene derivatives (Chart 1).

Chart 1. Representative ligand classes for Pd^{II} catalyzed aerobic oxidation reactions.



In this review, we survey the different classes of ligands that have been used to support Pd-catalyzed aerobic oxidation reactions. Where possible, we emphasize mechanistic features associated with the role of the ligand(s) on the reactions. In some cases, beneficial ligand effects simply arise from catalyst stabilization, enabling higher product yield and catalytic efficiency. In other cases, ligands contribute to specific substrate oxidation steps, including influencing regio- or stereoselectivity of aerobic oxidation reactions or promoting proton-shuttling events that facilitate substrate binding, bond-breaking and/or bond-forming steps. The oxidation of reduced Pd catalysts by O_2 is a key feature of all of the reactions described herein, and considerable insight has been gained into the fundamental reactivity of O_2 with ligand-supported Pd catalysts. Catalytically relevant insights from these studies are surveyed in the next section, with subsequent sections focusing on the different classes of ligands that have been used in ligand-supported Pd-catalyzed aerobic oxidation reactions. Solvent-based "ligands" are addressed first, followed by examples of discrete monodentate and bidentate ligands. Considerable advances have been made in this field since publication of the two most closely related reviews by Stahl in 2004[49] and by Gligorich and Sigman in 2009,[50] and the treatment here is somewhat different from these and other related reviews[23-43,51-55] owing to the emphasis on different ligand classes, rather than synthetic methodology and reaction scope.[56] Synthetic methods are presented as a means to highlight contributions of the ligands to catalytic reactivity.

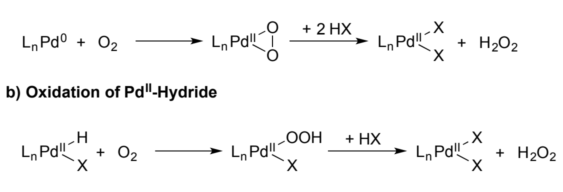
2. General mechanisms of ligand-supported O_2 activation

Pd^{II}-catalyzed oxidation reactions commonly feature high catalyst loading, and one of the principal origins of this limitation is catalyst decomposition into inactive Pd black (cf. Scheme 1b). Ancillary ligands that stabilize the Pd^0 intermediate and/or promote the reaction of Pd^0 with O_2 provide an approach to address this limitation, complementing the widespread use of cocatalysts or use of alternative stoichiometric oxidants (Cu^{II}, Ag^I, benzoquinone) to support Pd catalytic turnover. Kinetic and mechanistic studies of Pd-catalyzed aerobic oxidation reactions show that oxidation of Pd^0 (or other reduced Pd species) is typically not turnover-limiting.

Therefore, it has been difficult to gain direct insights into the reaction of O_2 with Pd catalysts under catalytic reaction conditions. Nevertheless, the reaction of O_2 with the Pd catalysts plays a crucial role in preventing catalyst decomposition. Several recent reviews have focused specifically on well-defined reactions of ligand-supported Pd (and other late-transition-metal) complexes with O_2,[57-59] but an overview of results in this area is provided here, in an effort to highlight mechanistic features relevant to the role of ligands in Pd-catalyzed aerobic oxidation reactions.

The product-forming step in Pd-catalyzed oxidation reactions consists of β-hydride elimination (e.g., Wacker-type oxidation of alkenes,[60] dehydrogenation reactions) or reductive elimination (e.g., biaryl coupling, allylic oxidation). These pathways afford Pd^{II}-hydride or a Pd^0 species, respectively, as the reduced form of the catalyst in the catalytic cycle. In principle, either species could undergo reaction with O_2 to regenerate the oxidized Pd^{II} catalyst (Scheme 2). Considerable mechanistic insight has been gained into these possible catalyst oxidation pathways through experimental and computational studies of well-defined Pd complexes supported by catalytically-relevant ligands. Appropriately designed ligands have also been shown to enable oxidation of Pd^{II} to Pd^{IV} by O_2,[61-64] but these ligands have not yet been incorporated in catalytic aerobic oxidation reactions.

Scheme 2. Two possible mechanisms for oxidation of reduced Pd-catalysts by O_2

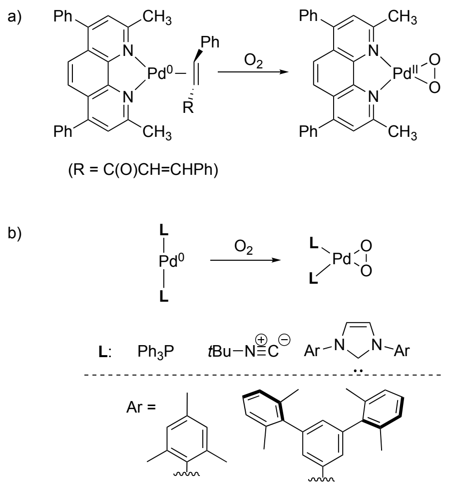


2.1 Reaction of O_2 with Pd^0 Species

The reaction of Pd^0 with O_2 to form an η^2-peroxo-Pd^{II} species was first reported by Wilke in 1967, using $Pd(PPh_3)_4$ as the Pd^0 source.[65] The resulting $(Ph_3P)_2Pd(\eta^2\text{-}O_2)$ complex was shown to decompose with concomitant formation of triphenylphosphine oxide, and, in the presence of excess PPh_3, catalytic conversion of PPh_3 to $OPPh_3$ was observed. Numerous other studies of late-transition-metal–O_2 adducts were performed during this period.[58,59,66,67] Most of the attention focused on oxygen-atom-transfer reactions; however, the nucleophilic character of these late-transition-metal peroxo species prevented their reactivity with many interesting substrates, such as non-activated alkenes and sulfides.

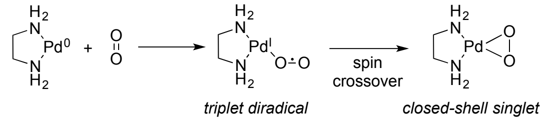
In 2001, Stahl and coworkers reported the reaction of O_2 with $(bc)Pd^0(dba)$ (bc = bathocuproine, dba = dibenzylideneacetone) (Scheme 3a).[68] Bathocuproine (bc) is a chelating nitrogen ligand that had been used by researchers at Enichem in efforts toward Pd-catalyzed production of hydrogen peroxide from O_2 and low-cost reductants (H_2, CO/H_2O, alcohols).[22,69-72] The rapid formation of $(bc)Pd(\eta^2\text{-}O_2)$ was shown to be kinetically competent to account for formation of H_2O_2 in the studies of Enichem. These observations and the associated mechanistic studies[73] represented the first direct link between $Pd(\eta^2\text{-}O_2)$ adducts and the emerging ligand-supported Pd-catalyzed aerobic oxidation reactions. Reactions of O_2 with bisligated Pd^0 complexes bearing ligands such as phosphines, isonitriles, or *N*-heterocyclic carbenes (NHCs) (Scheme 3b) are even more facile. For example, the groups of Stahl and Kawashima showed that the reaction of O_2 with NHC-ligated Pd^0 complexes occurs readily, even in the solid state.[74,75] This exceedingly rapid Pd-O_2 reactivity accounts for the difficulty in probing this step under catalytic conditions. This step is typically kinetically invisible, with other steps in the catalytic cycle controlling the turnover rate.

Scheme 3. Reaction between O_2 and well-defined Pd^0 to form Pd^{II} peroxo species

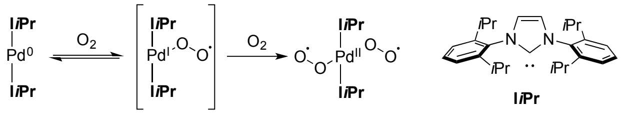


Density-functional-theory (DFT) studies have provided insights into the pathway for the spin-forbidden reaction of a ligated (singlet) Pd^0 species and triplet O_2. Using an ethylenediamine-ligated Pd^0 model system, Stahl and Landis showed that the initial interaction of dioxygen with Pd^0 forms an end-on triplet Pd^I-superoxo adduct that undergoes spin crossover to a singlet species prior to forming the second Pd–O bond (Scheme 4).[76] Subsequent studies showed that the reaction of Pd^0 with O_2 can be reversible, and O_2 dissociation is favored in non-polar solvents[77] or in the presence of electron-deficient alkenes, such as benzoquinone.[78,79] Direct experimental support for formation of Pd-superoxo species was later provided in a study by Hoff and coworkers using a Pd^0 complex bearing a sterically bulky NHC ligand (Scheme 5).[80] The reaction of $(IiPr)_2Pd^0$ with O_2 affords a bis(superoxo) adduct $(IiPr)_2Pd^{II}(\eta^1\text{-}O_2)_2$, presumably via a Pd^I monosuperoxo intermediate. The product structure was determined by X-ray crystallography and the biradical electronic structure of the bis(superoxo) was confirmed by magnetic susceptibility measurements, which indicating the presence of 1.8 unpaired electrons. With less sterically encumbered NHC ligands (e.g., IMes; cf. Scheme 3b), the monosuperoxo intermediate could undergo intersystem crossing and formation of a second Pd–O bond, resulting in the η^2-peroxo species. This pathway is supported by DFT computational studies.[77]

Scheme 4. Stepwise electron transfer between Pd^0 and O_2 to form Pd^{II} peroxide

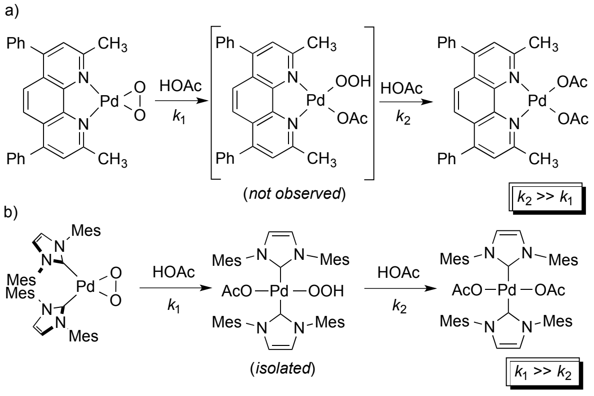


Scheme 5. Reaction between (I*i*Pr)Pd^0 and O_2 to form Pd-superoxo adduct



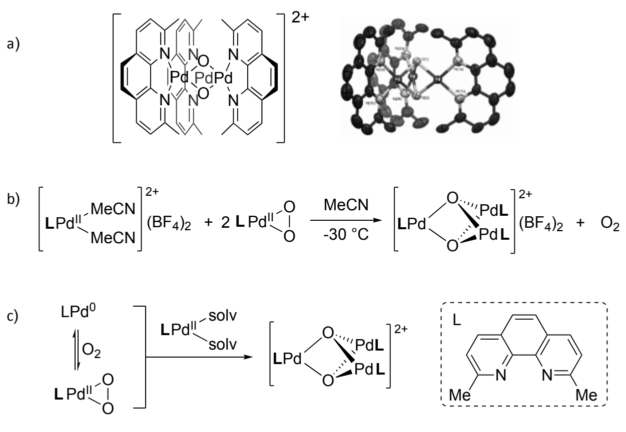
To complete the catalyst reoxidation steps in the catalytic cycle, Pd^{II}-peroxo species formed in the reaction between Pd^0 and O_2 could undergo a two-step protonolysis in the presence of Brønsted acids (HX) to form H_2O_2 and the corresponding L_2PdX_2 species that is the active catalyst for substrate oxidation. Experimental studies have shown that the relative rate of the sequential protonolysis steps is dependent on the nature of the ancillary ligand (Scheme 6). The Pd^{II}-hydroperoxide species was not observed when protonolysis was carried out with the bc-ligated peroxo complex, owing to more-rapid reaction of the Pd–OOH species with AcOH than the original peroxo complex, (bc)Pd(O_2).[68] In contrast, the hydroperoxo species derived from the first protonation of $(IMes)_2Pd(O_2)$ may be isolated and characterized.[74]

Scheme 6. Ligand effects on kinetics of protonolysis of Pd^{II}-peroxo species



Studies by Waymouth, Zare and coworkers provide a rare example of direct insight into Pd/O_2 reactivity in a catalytic reaction. Online ESI-MS studies of the oxidation of 1,2-propanediol, using a 2,9-dimethyl-1,10-phenanthroline (dmphen)/Pd catalyst system (see Section 5.1.1 below for further discussion), revealed formation of the oxo-bridged trinuclear complex $[(dmphen)_3Pd_3O_2]^{2+}$ (Scheme 7a).[81] Isotope labeling experiments with $^{18}O_2$ confirmed that the oxygen atoms in this complex come from O_2. The same species was prepared independently via the reaction of $[(dmphen)Pd(CH_3CN)_2]^{2+}$ with two equivalents of (dmphen)Pd(η^2-O_2) (Scheme 7b) and shown to be kinetically competent in the catalytic reaction. The mechanism for formation of the Pd_3O_2 species under catalytic conditions is proposed to follow a similar pathway (Scheme 7c). A subsequent study provided evidence for the involvement of the same $[(dmphen)_3Pd_3O_2]^{2+}$ species in H_2O_2 disproportionation, resulting in the net conversion of O_2 to water under the aerobic oxidation conditions.[82]

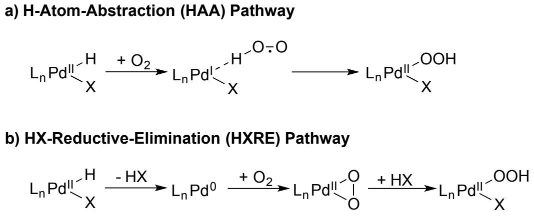
Scheme 7. Structure of (dmphen)$_3$Pd$_3$(μ_3-O)$_2$ determined by X-ray crystallography, its independent synthesis and proposed pathway of formation during catalysis (Scheme 7a was reprinted with permission from ref 81. Copyright 2014 John Wiley & Sons, Inc.)



2.2 Reaction of O$_2$ with Pd^{II}-hydride species

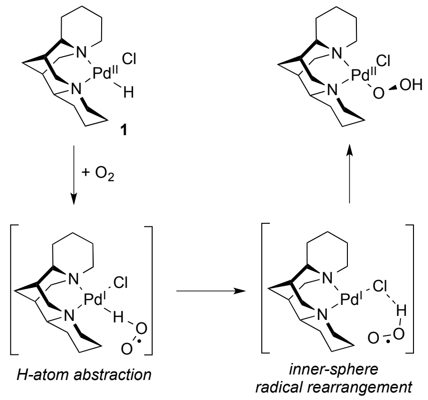
The reaction between Pd^{II}-hydride species and O$_2$ is an important consideration for aerobic oxidations that proceed via β-H elimination (e.g., alcohol oxidation, Wacker-type oxidation of alkenes and oxidative Heck reactions). Early studies of Pd-catalyzed aerobic oxidation reactions proposed O$_2$ insertion into a Pd^{II}-hydride as an important catalytic step,[83] but direct support or evidence for such reactivity was lacking. More recent studies have provided evidence for two viable mechanisms for conversion of a Pd^{II}–hydride into a Pd^{II}–hydroperoxide (Scheme 8): (a) an "H-atom-abstraction (HAA)" pathway initiated by O$_2$-mediated abstraction of a hydrogen atom (H·) and (b) and "H–X reductive elimination (HXRE)" pathway initiated by reductive elimination of a HX to afford a Pd^0 intermediate. The former pathway never generates zero-valent Pd in the mechanism, while the latter pathway is essentially identical to the Pd^0/O$_2$ reactivity described above, following reductive elimination of HX from the Pd^{II}–hydride species.

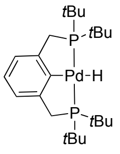
Scheme 8. Two possible pathways for catalyst reoxidation with Pd^{II}-hydride intermediates



Goddard and coworkers first postulated the HAA pathway in 2005 on the basis of a density function theory (DFT) computational study of O_2 reactivity with a (–)-sparteine (sp)-ligated Pd–H species **1** expected to form in aerobic alcohol oxidation reactions catalyzed by $(sp)Pd^{II}Cl_2$.[84] The DFT-based pathway (Scheme 9) features direct reaction of O_2 with the hydride ligand to afford a diradical Pd^{I}-hydroperoxyl intermediate, in which the hydroperoxyl species is only weakly associated with the Pd center. Subsequent rotation of the HO_2 fragment allows radical combination to afford the Pd^{II}-hydroperoxide product. An independent DFT study by Privalov and coworkers supported a similar pathway for the reaction of O_2 with a Pd^{II}–hydride species bearing a bidentate phenylpyridyl ligand.[85] Goldberg, Kemp[86] and coworkers reported the experimental observation of O_2 reaction with the PCP-pincer-ligated Pd^{II}–hydride complex **2** to afford the corresponding Pd^{II}–OOH species. A large KIE ($k_{\text{Pd-H}}/k_{\text{Pd-D}}$ = 5.8), first-order dependence on pO_2, and a subsequent computational study of the reaction in collaboration with Goddard and Oxgaard provided clear support for an H-atom abstraction pathway, in which the initial reaction with O_2 is the rate-limiting step.[87,88]

Scheme 9. Reaction of O_2 with palladium hydride via the H-atom-abstraction (HAA) pathway





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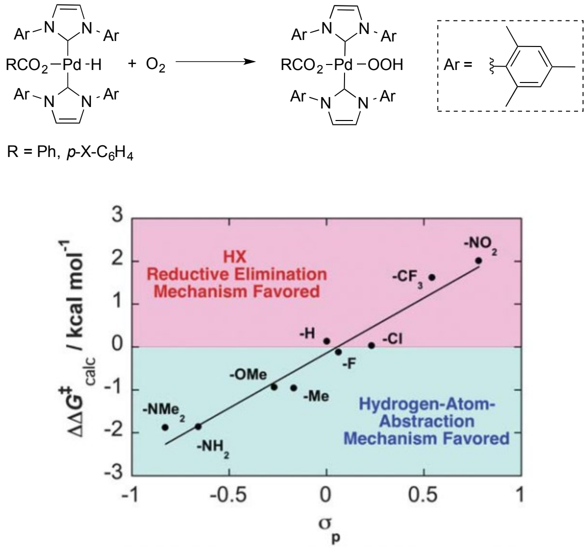
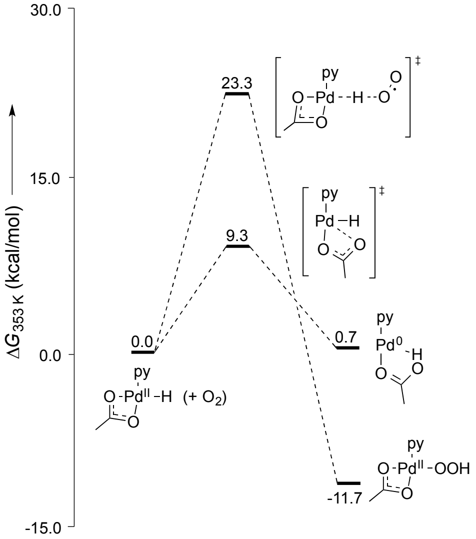
These observations were complemented by parallel studies by Stahl and coworkers with bis-NHC-ligated Pd^{II}-hydride complexes, which provided evidence for an H–X reductive-elimination (HXRE) pathway (X = carboxylate). [89 - 92] The reactivity of O_2 with $(NHC)_2Pd(H)(O_2CR)$ (R = Me, Ph, 4-$NO_2C_6H_4$) complexes was reported in 2006.[89] Kinetic studies of the reaction revealed a zero-order dependence on pO_2 and a negligible KIE ($k_{Pd\text{-}H}/k_{Pd\text{-}D}$ = 1.3).[91] These observations, together with a computational study,[90] revealed that the reaction is initiated by rate-limiting "reductive elimination" of carboxylic acid from the Pd^{II} center (i.e., deprotonation of the Pd^{II}–hydride by a carboxylate base). Subsequent oxygenation of the Pd^{0} species formed in this reaction and protonation of the Pd^{II}–peroxo complex (cf. Scheme 6b) proceed rapidly and are kinetically invisible. These initial studies provided clear support for the HXRE pathway, but the computational data suggested that the HXRE and HAA pathways are nearly isoenergetic. This insight prompted further work, which showed that minor variations of the electronic properties of the carboxylate ligand could shift the mechanism to favor the HAA pathway, as revealed by a first-order dependence on pO_2 and observation of a KIE ($k_{Pd\text{-}H}/k_{Pd\text{-}D}$ = 3.1).[93] Computational studies showed that the preferred mechanism changes from "HAA" to "HXRE" as the *para* substituent on the benzoate ligand shifts from electron-donating to electron-withdrawing (Scheme 10). This trend is rationalized by weakening of the Pd–H bond by more-electron-rich *trans* ligands (i.e., stronger *trans* influence; complex **2** is an extreme example of this principle) and by more-facile dissociation of electron-deficient carboxylates to release the base that contributes to the HXRE pathway. In an independent study, Stahl found that benzoquinone promotes reductive elimination of $PhCO_2$–H from *trans*-$(IMes)_2Pd(H)(O_2CPh)$, thereby enhancing the rate of aerobic oxidation of the Pd^{II}–H species. This observation has important implications for reactions that use quinone cocatalysts and, potentially, those that use electron-deficient alkene substrates.[94]

Scheme 10. Computed transition state energy difference of the HAA and HXRE pathways of O_2 insertion into $(IMe)_2Pd(H)(O_2CC_6H_4X)$ (Reprinted with permission from ref 93. Copyright 2011 The Royal Society of Chemistry.)



$Pd(OAc)_2$/py (py = pyridine) catalyst systems have been widely used in ligand-supported aerobic oxidation reactions (see Sections 4.3-4.5 below). Well-defined py-ligated Pd^0 or Pd^{II}–H complexes have not been reported, so experimental studies of their reactions with O_2 are not available. Nevertheless, the experimental and computational studies described above provided a foundation for computational studies of analogous O_2 reactions with relevant py-ligated complexes, such as *trans*-$(py)_2Pd(H)(OAc)$. The reaction of this complex with O_2 was probed computationally by the groups of Goddard[95] and Stahl,[96] and both studies showed that the HXRE pathway is favored over the HAA pathway. In the study by Popp and Stahl, examination of multiple different mechanistic possibilities revealed that pathways involving formation of Pd^{III}- or Pd^{IV}-O_2 adducts are strongly disfavored. Furthermore, the lability of the monodentate pyridine ligands dramatically favors reductive elimination of AcO–H from Pd^{II} via a three coordinate intermediate. The resulting py-ligated Pd^0 species then undergoes facile oxidation by O_2. This pathway was calculated to proceed with an activation free energy ~14 kcal/mol lower than the most favorable HAA pathway (Scheme 11).[96] The results of this study prompted the authors to conclude that all Pd^{II}–hydride intermediates with monodentate L-type ligands and basic X-type ligands or additives (the latter being present in the vast majority of catalysts) will be susceptible to very facile reductive elimination of H–X to afford Pd^0. This feature suggests that no formal distinction exists between the two catalyst reoxidation classes shown in Scheme 2, since both will proceed via Pd^0 intermediates that undergo reaction with O_2.

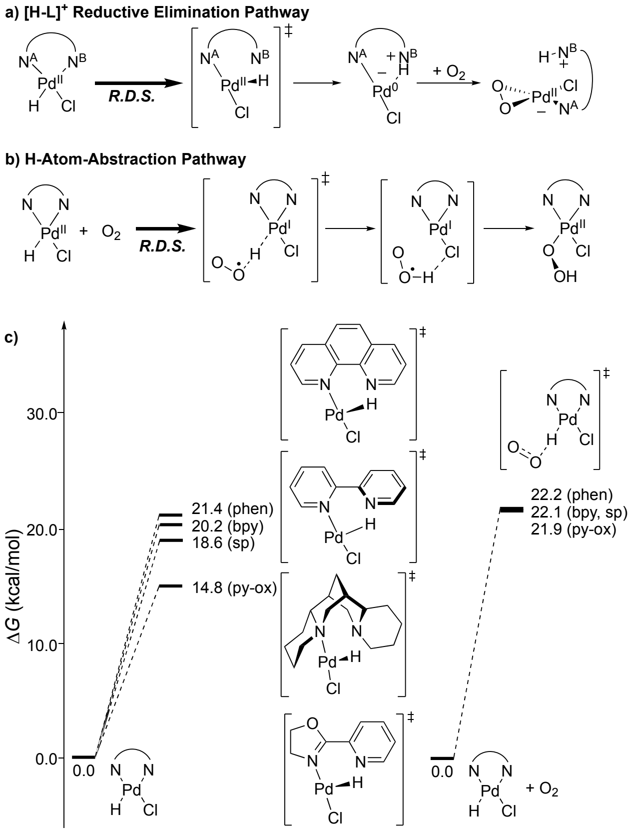
Scheme 11. Computed energies comparing the HAA and HXRE pathways for the reaction of O_2 with (py)Pd(H)(κ^2-OAc)



In 2011, Stahl and coworkers reassessed the reaction of (sp)Pd(H)(Cl) with O_2 in a combined experimental/computational study.[97] Kinetic studies showed a zero-order dependence on pO_2, which is inconsistent with rate-limiting H-atom abstraction, which was proposed on the basis of the previous DFT computations. Subsequent DFT studies revealed a new "$[H–L]^+$ reductive elimination" pathway, in which the nitrogen atom of the chelating ligand *trans* to the hydride dissociated and promotes intramolecular deprotonation of the hydride ligand to form a zwitterionic Pd^0 product (Scheme 12a). Dissociation of one arm of the chelating ligand is promoted by the strong *trans* influence of the hydride ligand. Additional computational study of other Pd^{II}–hydride complexes with bidentate ligands, including phenanthroline (phen), 2,2'-bipyridine (bpy), and pyridine-oxazoline (py-ox) showed that the $[H–L]^+$ reductive elimination pathway is favored over the H-atom-abstraction pathway in all cases, although the energy difference is < 1 kcal/mol with phen as the ancillary ligand. If the chloride ligand is replaced by a carboxylate anionic ligand, the H–X reductive elimination pathway is strongly favored,[97,98]and a deprotonation/reductive-elimination pathway is also favored in the presence of exogenous 3°

amine (e.g., if excess (–)-sparteine is used).[99] These observations, together with the analysis of monodentate ligand effects described above, suggests that all Pd^{II}-catalyzed aerobic oxidation reactions reported to date are likely to undergo catalyst oxidation via the intermediacy of Pd^0. Although the hydrogen-atom-abstraction pathway is energetically competitive or favored with certain model complexes, this pathway does not presently appear to be favored in catalytic processes. The fundamental insights gained from this work, however, could have implications for other catalytic aerobic oxidations, such as those involving Rh, Ir or other transition-metal catalysts.

Scheme 12. [H-L]$^+$ reductive elimination promoted by (–)-sparteine and other bidentate ligands

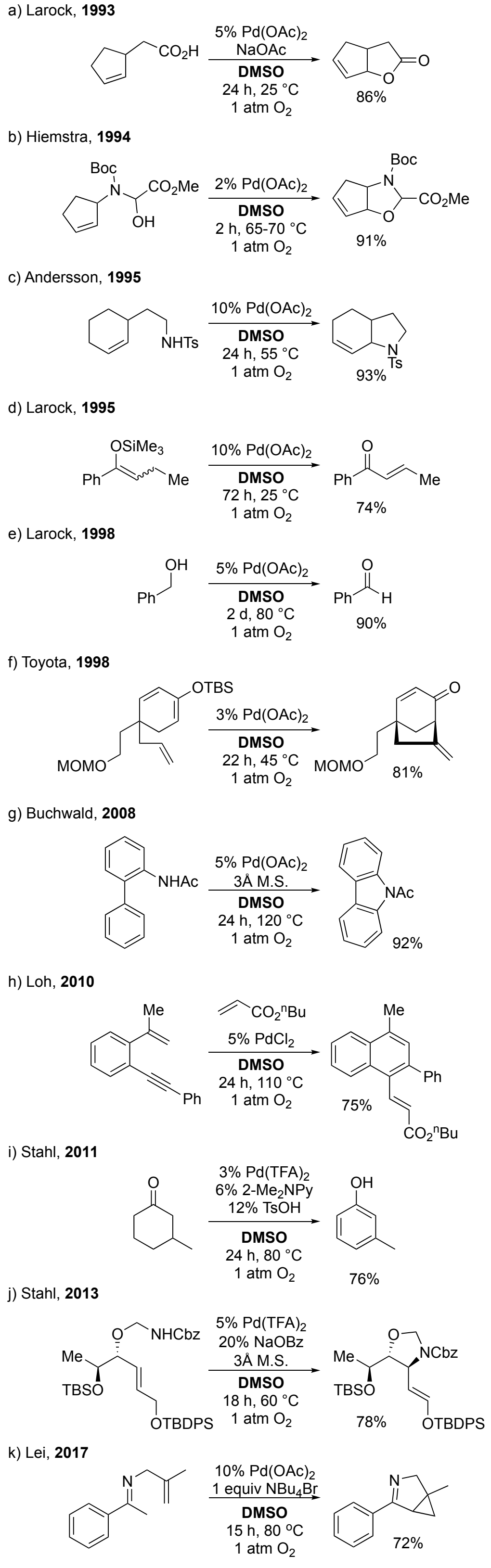


3. Solvent-based ligand systems and soluble nanoparticles

In the years following the discovery of the Wacker process, many Pd-catalyzed oxidation reactions used Cu^{II} salts and other stoichiometric oxidants to promote catalytic turnover. Meanwhile, Bäckvall and others have demonstrated the utility of multi-step redox cycles, employing benzoquinone, macrocyclic metal complexes and other "electron-transfer-mediators" as a means to promote catalytic turnover with O_2 as the terminal oxidant.[13] In the majority of these cases, the Pd catalyst consisted of a simple Pd^{II} salt, such as $PdCl_2$, $Pd(OAc)_2$, or $Pd(TFA)_2$ (TFA = O_2CCF_3). In the 1990s, several groups, including Larock,[14,100,101] Hiemstra[15,102] and Andersson/Bäckvall[103 - 105] demonstrated that $Pd(OAc)_2$ in dimethylsufoxide (DMSO) as the solvent is an effective catalyst system for aerobic Wacker-type oxidative cyclization reactions of alkenes. The noteworthy feature of these catalyst systems is the lack of requirement for a redox cocatalyst or stoichiometric oxidant other than O_2. Although DMSO is present in solvent-level quantities, these results provided compelling indication that ligand-supported catalysis could provide an alternative to cocatalyst-supported Pd-catalyzed aerobic oxidation reactions.

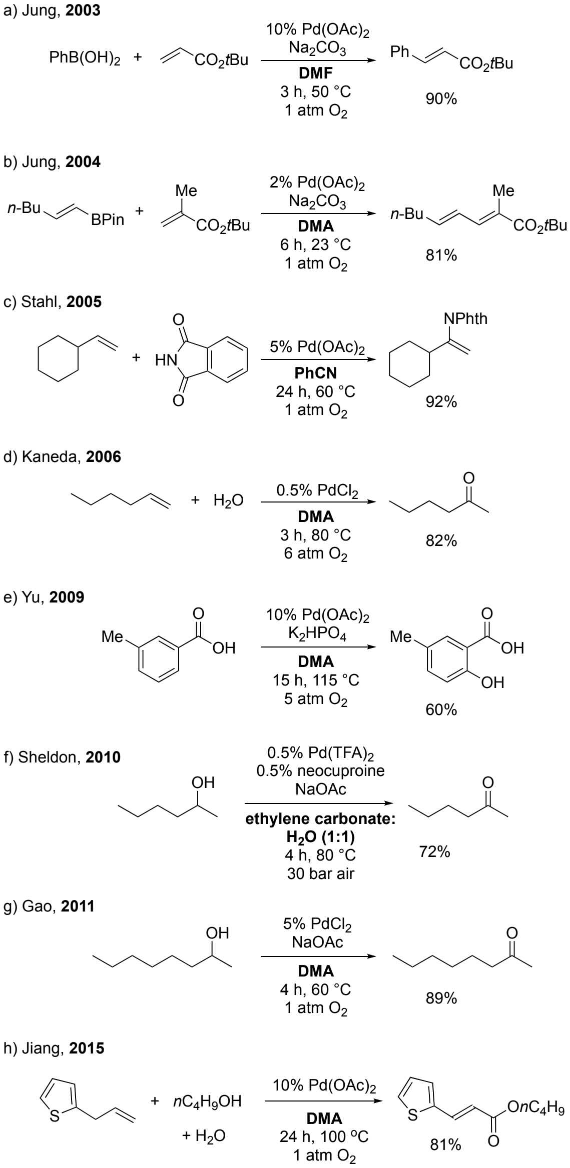
Pd^{II}/DMSO catalyst systems have proven to be effective for a wide range of chemical transformations, representative examples of which are shown in Scheme 13. A variety of oxygen and nitrogen nucleophiles reacted with 1,2-disubstituted alkenes to form five- and six-membered heterocycles (Scheme 13a-c).[14,15,100– 106] Larock and Kraus reported similar conditions for catalytic Saegusa-Ito oxidation of silyl enol ethers to α,β-unsaturated carbonyls (Scheme 13d),[107] and Larock used a $Pd(OAc)_2$/DMSO catalyst for oxidation of primary or secondary benzylic and allylic alcohols to the corresponding aldehydes and ketones (Scheme 13e).[108 -110] Toyota and coworkers, as well as others, developed diverse cycloalkenylation reactions with silylenol ether and other carbon based nucleophiles (Scheme 13f).[23, 111 - 119] More recently, Buchwald and coworkers demonstrated an aerobic intramolecular aryl C–H amination reaction for the synthesis of carbazoles (Scheme 13g),[120,121] Feng and Loh reported a bisolefination of alkynes in the synthesis of naphthalenes (Scheme 13h),[122] Stahl and coworkers reported dehydrogenations of cyclohexanones to phenols (Scheme 13i)[123] and diastereoselective aza-Wacker cyclization reactions for the synthesis of substituted heterocycles (Scheme 13j),[124,125] and Lei and coworkers reported oxidative annulation for the synthesis of bicyclic systems (Scheme 13k).[126]

Scheme 13. Representative examples of Pd-catalyzed aerobic oxidation reactions employing dimethylsulfoxide as the solvent.



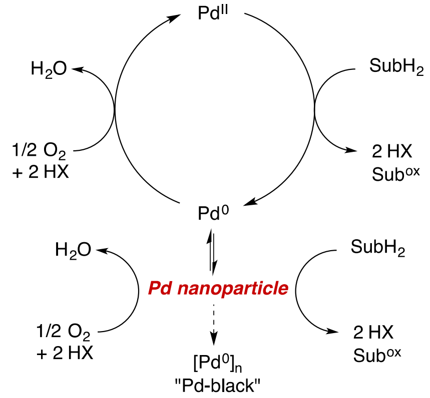
In addition to DMSO, other polar coordinating solvents, such as *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), and benzonitrile (PhCN), have proven to be effective in promoting direct dioxygen-coupled turnover (Scheme 14). Examples include oxidative Heck reactions in DMF[127] and DMA[128] (Scheme 14a, 14b), intermolecular oxidative amidation of alkenes in benzonitrile (Scheme 14c),[129,130] Wacker oxidation of alkenes in DMA (Scheme 14d),[131-133] C–H oxygenations of benzoic acids in DMA (Scheme 14e),[134] alcohol oxidation in 1:1 ethylene carbonate:water (Scheme 14f)[135] or DMA (Scheme 14g)[136] and allylic C–H oxidation in DMA (Scheme 14h).[137]

Scheme 14. Representative examples of Pd-catalyzed aerobic oxidation employing polar coordinating solvents other than DMSO



The use of a coordinating solvent in the reactions in Schemes 13 and 14 would seem to benefit catalysis by providing a high concentration of "ligand" that can stabilize Pd^0 and support its oxidation by O_2. However, an alternative possibility is that such solvents stabilize soluble nanoparticles that form under the reaction conditions and serve as an active catalyst species (Scheme 15).[138,139] Hiemstra and coworkers reported that the $Pd(OAc)_2$/DMSO catalyst system generates nanoparticles in a Wacker-type cyclization of *N*-hydroxymethyl carbamates (cf. Scheme 13b).[140] The nanoparticles were identified by transition electron microscopy (TEM), and the particles could be isolated and reused without loss of catalytic activity. In contrast, Stahl and coworkers showed that Pd particles formed in $Pd(OAc)_2$/DMSO catalyzed alcohol oxidation are inactive,[109,110] while Sheldon[135] and Gao[136] showed that nanoparticles formed during the oxidation of alcohols in ethylene carbonate and DMA, respectively, retain activity (cf. Schemes 14f and 14g). Collectively, these reports suggest that palladium nanoparticles are prevalent species in aerobic oxidation reactions carried out in polar coordinating solvents; however, the activity and/or precise role of nanoparticles could vary for different reactions. Kaneda analyzed the $PdCl_2$/DMA catalyst by EXAFS following the Wacker oxidation reaction in Scheme 14d and detected monomeric Pd^{II} with no evidence of Pd–Pd bonds in solution.[131] These findings contrast with those of Gao and coworkers in their study of a very similar catalyst system. These observations, together with the contrasting observations of Hiemstra and Stahl with the $Pd(OAc)_2$/DMSO catalyst system, suggest that the formation or activity of nanoparticles may be sensitive to the identity of the substrate or other variations in the reaction conditions. In any case, it can be difficult to establish the precise role of soluble nanoparticles in a catalytic mechanism. As has been considered extensively in Pd-catalyzed cross-coupling reactions,[138, 141 - 144] Pd nanoparticles could provide a reservoir of stabilized Pd^0 species in equilibrium with active monomeric species, or they could be the active form of the catalyst (Scheme 15).

Scheme 15. Possible participation of soluble palladium nanoparticles in aerobic oxidation catalysis.



The distinction between monomeric and nanoparticle catalysts may provide a basis for controlling or altering the reaction selectivity. A mechanistic investigation by Stahl revealed that the (2-Me$_2$Npy)Pd(TFA)$_2$/TsOH/DMSO (2-Me$_2$Npy = 2-dimethylaminopyridine) catalyst system for dehydrogenation of cyclohexanone to phenol involves the formation of soluble nanoparticles (cf. Scheme 13i).[145] The results showed that a monomeric catalyst species mediated initial dehydrogenation of cyclohexanone to cyclohexenone, while the dehydrogenation of the enone intermediate to phenol involved a nanoparticle catalyst generated *in situ*. Control experiments showed that the 2-Me$_2$Npy additive does not serve as a ligand, and the authors postulated that the 2-Me$_2$Npy and TsOH catalyst components form an ammonium salt that could stabilize the nanoparticles.[146 - 151] Alternative catalyst systems that disfavor nanoparticle formation show distinct dehydrogenation selectivity, mediating dehydrogenation of cyclohexanones to cyclohexenones without subsequent oxidation to phenol (see example discussed in Section 4.1).[152,153]

Overall, the examples discussed in this section illustrate the broad utility of Pd^{II} catalysts dissolved in polar coordinating solvents and their ability to support direct dioxygen-coupled turnover. These catalyst systems exhibit mechanistic complexities, and the use of coordinating solvent as the ligand limits the ability to tune catalyst properties in the manner elaborated below for catalyst systems that employ discrete, catalytic quantities of an ancillary ligand.

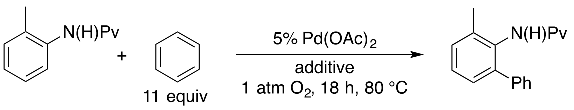
4. Monodentate ligands

4.1 Sulfoxide and Thioether Ligands

4.1.1 Dimethylsulfoxide (DMSO)

In addition to the use of DMSO as a coordinating solvent, DMSO has also been used as an effective ancillary ligand for Pd to promote aerobic oxidation reactions in solvents other than DMSO. In 2008, Buchwald reported aerobic C–H coupling between anilides and arenes with a $Pd(OAc)_2$ catalyst (Scheme 16).[154] Addition of trifluoroacetic acid (TFAH) enhanced reactivity, but inactive Pd black was observed. The addition of both TFAH and catalytic quantities of DMSO prevented catalyst decomposition and enabled efficient coupling of various electron-rich and electron-deficient anilides and arenes.

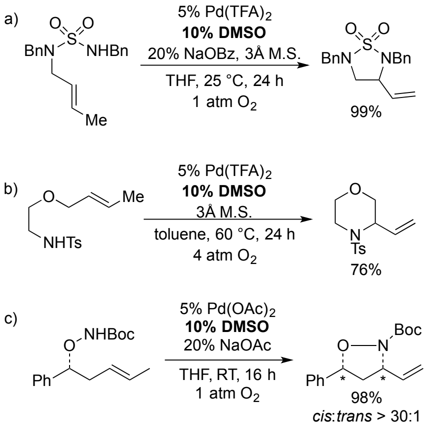
Scheme 16. DMSO-supported aryl C–H coupling between anilides and arenes.



Additive	Conv (%)	Yield (%)
none	8	3
5 equiv TFAH	66	64
5 equiv TFAH, 10 mol% DMSO	**91**	**87**

In 2010, Stahl reported diastereoselective synthesis of 1,2-diamine derivatives via aza-Wacker cyclization of allylic sulfamides (Scheme 17a).[155] A $(DMSO)_2Pd(TFA)_2$ catalyst was particularly effective for this transformation, and it was noted that the catalyst retains excellent activity and stability at ambient temperature. The (DMSO)$_2$Pd(TFA)$_2$ catalyst was also employed in aza-Wacker cyclizations to generate six- and seven-membered heterocycles (Scheme 17b).[156] These transformations were more challenging than the related syntheses of five-membered heterocycles, and elevated temperature (60 °C) was necessary to promote the reaction. In order to mitigate formation of Pd black at this temperature, the reactions were performed at increased pressure of O$_2$ (4 atm) as a means to increase the rate of Pd^0 reoxidation relative to decomposition. Kočovský employed a related (DMSO)$_2$Pd(OAc)$_2$ catalyst system in a diastereoselective aza-Wacker cyclization that affords *cis*-oxazolines (Scheme 17c).[157]

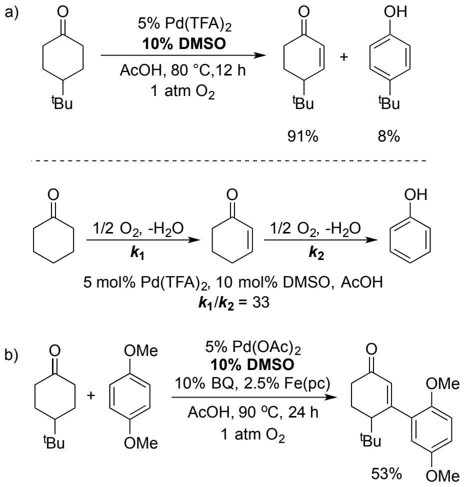
Scheme 17. DMSO supported aza-Wacker cyclization reactions.



In 2011, Stahl reported application of a (DMSO)$_2$Pd(TFA)$_2$ catalyst system to aerobic dehydrogenation of cyclic ketones (Scheme 18a).[152] The catalyst oxidizes 2-, 3- and 4-substituted cyclohexanones to the corresponding enones in high yield. The observed selectivity for a single dehydrogenation to afford the enone, rather than double dehydrogenation to form the phenol, distinguishes this system from the prior report using the (2-Me$_2$NPyr)Pd(TFA)$_2$/TsOH/DMSO catalyst system noted above (cf. Scheme 13i). Bäckvall and coworkers showed that

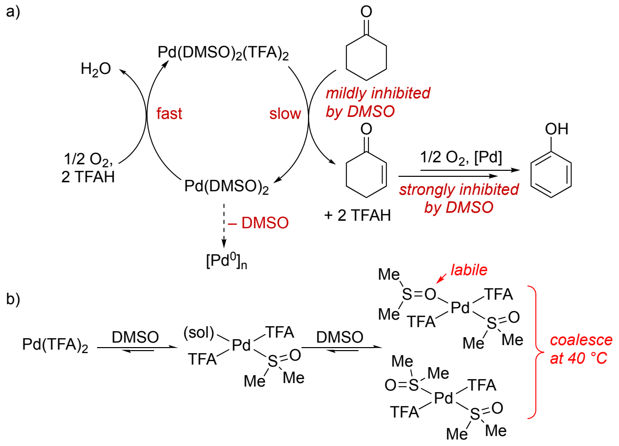
$(DMSO)_2Pd(OAc)_2$-catalyzed dehydrogenation of cyclohexanone could be carried out in tandem with dehydrogenative coupling between the resulting enone and an electron-rich arene reaction to afford 4-alkyl-3-aryl-2-cyclohexanones (Scheme 18b).[158] In this case, aerobic catalytic turnover benefited from the use of benzoquinone/Fe(phthalocyanine) [BQ/Fe(pc)] as a cocatalyst system.

Scheme 18. DMSO supported dehydrogenation of cyclic ketones to enones.



Mechanistic studies of $(DMSO)_2Pd(TFA)_2$-catalyzed dehydrogenation of cyclohexanone were conducted by Stahl and coworkers.[153] These studies showed that conversion of the ketone to the enone proceeds 33-fold faster than the conversion of the enone to the phenol, accounting for the selective formation of enone in these reactions. A first-order rate dependence on both the catalyst and substrate was observed, together with a zero-order dependence on O_2. Increasing [DMSO] had minimal influence on the rate, and significant quantities of Pd black were produced in the absence of DMSO. Collectively, these results indicated substrate oxidation was turnover limiting and that DMSO plays an important role in stabilizing the Pd catalyst (Scheme 19a).

Scheme 19. Summary of mechanistic observations on the kinetics (a) and ground-state speciation (b) of Pd/DMSO-catalyzed dehydrogenation of cyclohexanone



To help elucidate the origin of the chemoselectivity for enone formation, oxidation of cyclohexenone to phenol by the $(DMSO)_2Pd(TFA)_2$ catalyst was also studied. In this case, DMSO inhibited dehydrogenation relative to ligand-free conditions. An induction period was observed at the start of the reaction when DMSO was present but not under ligand-free conditions. The length of the induction period was directly dependent on [DMSO], with higher [DMSO] leading to a longer induction period. The induction period provided evidence for in situ conversion of the catalyst into a more active species, resembling features that had been observed with the $(2\text{-}Me_2Npy)Pd(TFA)_2$/TsOH/DMSO catalyst system, for which dissolved nanoparticles were shown to be the active catalyst for cyclohexenone dehydrogenation.[145] The DMSO ligand inhibits nanoparticle formation with the $Pd(TFA)_2$/DMSO catalyst system and the corresponding nanoparticle-catalyzed dehydrogenation of the enone, thereby enabling chemoselective monodehydrogenation of the ketone to the enone.

DMSO exhibits unique coordination properties as a ligand for Pd and other transition metals, as it is capable of binding through either the *S*- or *O*-lone pair (and, occasionally, both at once).[159, 160] Early solid-state characterization of $(DMSO)_2Pd(TFA)_2$ revealed a *trans*-(*S*-

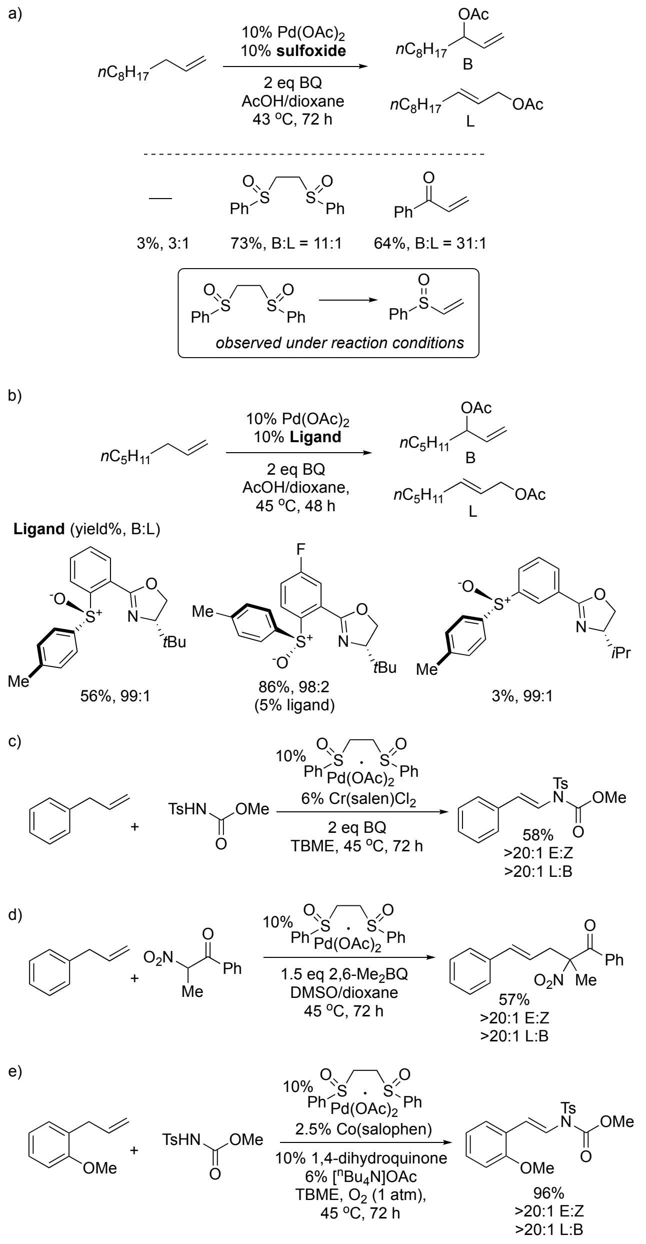
DMSO)(*O*-DMSO)Pd(TFA)$_2$ complex.[161] Recent NMR characterization of the Pd(TFA)$_2$/DMSO catalyst system demonstrated that both *S*- and *O*-bound DMSO ligands are present in solution (Scheme 19b).[162] In addition, the study revealed that DMSO is a rather labile ligand for Pd^{II} at standard reaction temperatures (50–80 °C) and *O*-bound DMSO is more labile than its *S*-bound analog. Ligand lability should facilitate substrate binding in these aerobic oxidation reactions and is a feature evident in many of the catalyst systems discussed below.

4.1.2 Other Sulfoxide Ligands

White and coworkers have shown that bis(sulfoxide) ligands support a number of allylic C–H oxidation reactions.[163-167] An early application of this type, featuring bis(phenylsulfinyl)ethane as the ligand and benzoquinone as the oxidant, exhibits unique selectivity for the branched acetoxylation product (Scheme 20a),[164] contrasting many literature precedents that generate the linear allylic oxidation product (cf. Scheme 51 and 55f in Section 5.1.2). Preliminary studies showed that the bis(sulfoxide) ligand is converted to vinyl sulfoxide under the reaction conditions (Scheme 20a), but little insight is available into the origin of branched vs. linear selectivity. Branched-selective acetoxylation has also been accomplished with a class of oxazoline-sulfoxide ligands developed by Itami and Liu (Scheme 20b).[168] No enantioselectivity was observed in these reactions.

Bis(sulfoxide) ligands have also been used in Pd-catalyzed allylic amination[165] and alkylation[166] reactions (Scheme 20c-d), resulting in the formation of linear products. Whereas the majority of bis(sulfoxide)-supported reactions employ benzoquinone as the stoichiometric oxidant, recent work from White achieved aerobic allylic amination in the presence of catalytic quinone and Co(salophen) (Scheme 20e).[167]

Scheme 20. Use of sulfoxide-based ligands in Pd-catalyzed C–H oxidation reactions

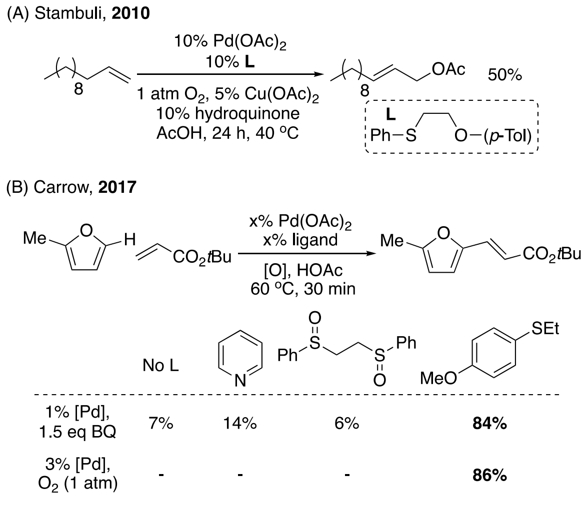


4.1.3 Thioether Ligands

Thioethers represent another class of ligands that have been demonstrated to support Pd-catalyzed C–H oxidation reactions. In 2010, Stambuli and coworkers showed that aryl-alkyl sulfide ligands support allylic acetoxylation of terminal alkyl olefins and allyl benzene derivatives. Most examples used BQ as the stoichiometric oxidant (Scheme 21A), but use of O_2 in combination with $Cu(OAc)_2$ (5 mol%) was also shown to be effective. Use of a related aryl-alkyl sulfoxide ligand led to Wacker-type vinylic acetoxylation under the same conditions.[169] The same research group later showed that other types of thioether ligands, including tetrahydrothiophene and bidentate thioethers, could support similar reactivity with BQ as the oxidant.[170] Use of diaryl thioether ligands led to mixtures of allylic and vinylic oxidation products.

More recently, Carrow and coworkers showed that thioethers are effective ligands for Fujiwara-Moritani-type oxidative olefination of heteroarenes with BQ as the oxidant. Thioethers outperformed sulfoxides and other ligands commonly used in Pd oxidation catalysis (Scheme 21B).[171] Kinetic studies revealed an inverse 1st-order dependence on [NaOAc] and led to the proposal that the thioether promotes dissociation of an acetate from Pd^{II} to induce a cationic pathway. The optimal ligand also enabled efficient olefination of 2-methylfuran and *N*-methyl indole under aerobic conditions with >80% yields (cf. Scheme 21B).

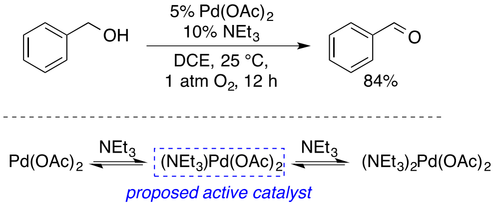
Scheme 21. Thioether-supported C–H Oxidations



4.2 Triethylamine

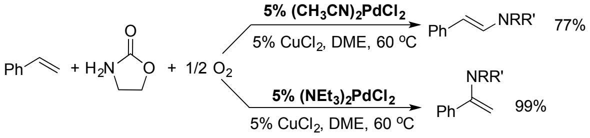
In 2002, Sigman reported a triethylamine-ligated Pd^{II} catalyst system for aerobic oxidation of benzylic, allylic and aliphatic alcohols at room temperature (Scheme 22).[172-175] This system provided milder conditions for substrate oxidation than previously reported palladium catalysts, such as Uemura's Pd(OAc)$_2$/py system,[20] which required elevated temperature (80 °C) for efficient reactivity (cf. Section 4.3.1). Measuring the initial rate of the reaction as a function of [NEt$_3$] revealed that stoichiometries of ≤1.5:1 NEt$_3$:Pd(OAc)$_2$ promoted substrate oxidation, while rate inhibition was observed beyond NEt$_3$:Pd(OAc)$_2$ ratios of 1.5:1. NMR spectroscopic studies revealed that solutions of NEt$_3$ and Pd(OAc)$_2$ produced an equilibrium between free Pd(OAc)$_2$, free NEt$_3$ and the *mono*- and *bis*-NEt$_3$-ligated Pd(OAc)$_2$ complexes. Mechanistic studies showed that the turnover-limiting step of the catalytic reaction is deprotonation of a Pd-coordinated alcohol, which contrast most other Pd-catalyzed alcohol oxidation reactions, for which β-hydride elimination is turnover-limiting.[173] The incomplete formation of the saturated (NEt$_3$)$_2$Pd(OAc)$_2$ complex demonstrated that NEt$_3$ is more labile than pyridine as a ligand for Pd^{II}, and low-energy access to a mono-NEt$_3$ Pd^{II} species was proposed to account for the facile β-hydride elimination and good catalytic activity at room temperature.

Scheme 22. Triethylamine-supported alcohol oxidation.



In 2003, Stahl and coworkers reported an intermolecular aza-Wacker reaction between styrene and amides where the regioselectivity is controlled by the catalyst: $(MeCN)_2PdCl_2$ led to the anti-Markovnikov product whereas $(NEt_3)_2PdCl_2$ led to the Markovnikov product (Scheme 23).[176] Although NEt_3 was shown to coordinate to $PdCl_2$ under the reaction conditions, the site-selectivity and enhanced catalytic rate with $(NEt_3)_2PdCl_2$ could be reproduced by a catalyst system consisting of $(MeCN)_2PdCl_2$ and $(NBu_4)OAc$. The latter observation suggested that the effect of the NEt_3 may be attributed to its role as Brønsted base, rather than as a ligand. Mechanistic studies showed how Brønsted bases contribute to kinetically controlled formation of the Markovnikov regioisomer, while the thermodynamically favored anti-Markovnikov product is formed in the absence of base. The role of other ligands as Brønsted bases in Pd-catalyzed oxidation reactions is evident in other catalyst systems described below [e.g., (–)-sparteine; cf. Section 5.2.1].

Scheme 23. Effect of triethylamine on the regioselectivity of oxidative amidation

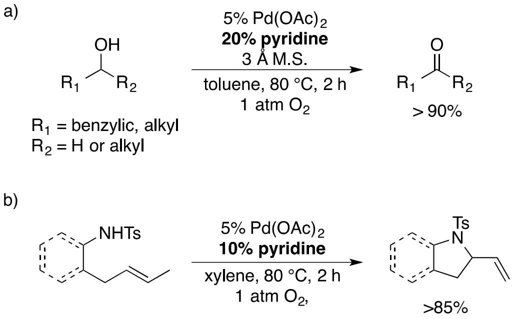


4.3. Pyridine derivatives

4.3.1. Pyridine (py)

In 1998, Uemura reported a $(py)_2Pd(OAc)_2$ catalyst for the aerobic oxidation of primary and secondary alcohols (Scheme 24a).[20,177] Stahl then showed that a related $(py)_2Pd(OAc)_2$ catalyst system was effective for aza-Wacker cyclizations of γ-alkenyl sulfonamides (Scheme 24b),[178] and analogous Wacker-type cyclizations were reported by Stoltz and Yang shortly thereafter (see further discussion below).[179,180]

Scheme 24. Pyridine supported a) alcohol oxidation and b) aza-Wacker cyclization.



A mechanistic study of the $(py)_2Pd(OAc)_2$ catalyst system for alcohol oxidation revealed that pyridine influenced both the substrate oxidation and catalyst reoxidation half reactions of the catalytic cycle.[181,182] In the absence of pyridine, no catalytic turnover was observed; the catalyst performed a stoichiometric oxidation of the substrate followed by immediate precipitation of metallic Pd. Inclusion of pyridine caused the initial rate to increase until a 1:1 py:Pd stoichiometry was reached, after which additional pyridine inhibited the reaction (Figure 1). NMR spectroscopic investigations revealed that a 2:1 py:$Pd(OAc)_2$ mixture forms a well-defined *trans*-$(py)_2Pd(OAc)_2$ complex in solution. A monoligated species is not observed, contrasting the results with NEt_3 ligand, noted above.

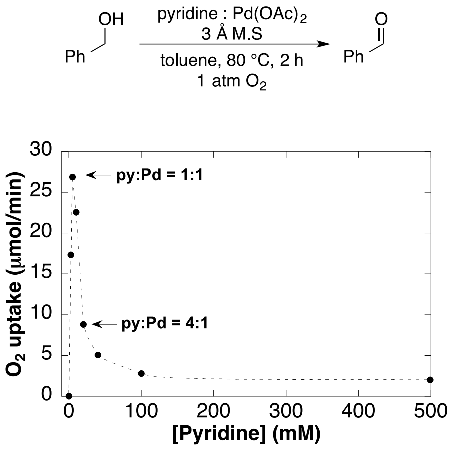
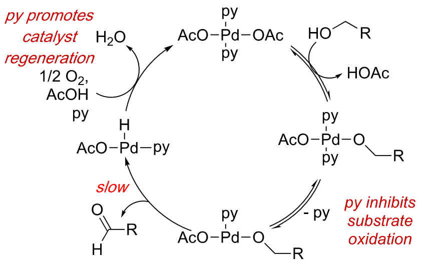


Figure 1. Dependence of the initial rate on pyridine concentration with the [Pd(OAc)$_2$] held constant. Conditions: [Pd(OAc)$_2$]) 5.0 mM, [pyridine]) 0-500 mM, [alcohol]) 0.10 M, initial pO$_2$) 700 Torr, 10 mL of toluene, 80 °C.

The substrate displayed saturation kinetics, and a kinetic isotope effect (KIE) was evident for a $PhCD_2OH$ substrate. The initial rate of the reaction was also observed to be zeroth order in the oxygen pressure. These and other data supported a catalytic cycle in which β-hydride elimination from a Pd^{II} alkoxide is turnover-limiting (Scheme 25). The optimal py:Pd ratio of 1:1 and strong inhibition at high [py] was attributed to the requirement of ligand dissociation to form the three-coordinate (py)Pd(OAc)(alkoxide) species prior to β-hydride elimination. The results show that a low py:Pd ratio favors catalytic activity, while elevated py:Pd ratios enhance catalyst stability (Scheme 25). The optimal synthetic catalyst system represents a balance between these competing effects. Many related insights were obtained from a mechanistic study of aza-Wacker cyclizations catalyzed by $(py)_2Pd(OAc)_2$,[183] and a similar kinetic benefit of 1:1 py:Pd ratio has also been identified in Pd-catalyzed acetoxylation of benzene with $PhI(OAc)_2$ as the oxidant.[184]

Scheme 25. Summary of mechanistic observations in $(py)_2Pd(OAc)_2$ catalyzed alcohol oxidation.



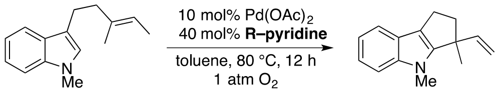
Summary of kinetic data

- * Saturation in [Pd/py]
- * Saturation in [RCH_2OH]
- * KIE obs. for $PhCD_2OH$
- * 0-order in pO_2
- * max rate @ 1:1 py:Pd

4.3.2. Electron-deficient pyridines

Stoltz reported an oxidative annulation of indoles catalyzed by ethyl nicotinate ([3-CO_2Et]-py)-ligated $Pd(OAc)_2$.[185, 186] Substituted pyridines with electron-donating and -withdrawing functional groups were screened, and a correlation was observed between the pK_a of the pyridinium (pyH^+) ligand and the conversion of substrate (Scheme 26). Electron-deficient pyridine ligands promoted the reaction, but if the ligand was too electron deficient, low yields and formation of Pd black was observed. Ethyl nicotinate [pK_a (pyH^+) = 3.35] was found to provide the ideal balance between catalyst reactivity and stability. Oestreich[187] and Buchwald[188] reported similar observations in the development of related Wacker-type alkene functionalization/arene annulation reactions, wherein ethyl nicotinate was found to be a superior ligand to more electron-rich pyridyl and bipyridyl derivatives.

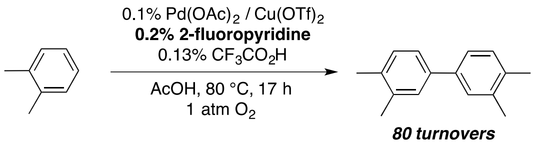
Scheme 26. Identification of an electronically tuned, pyridine-supported catalyst for the oxidative annulation of indoles.

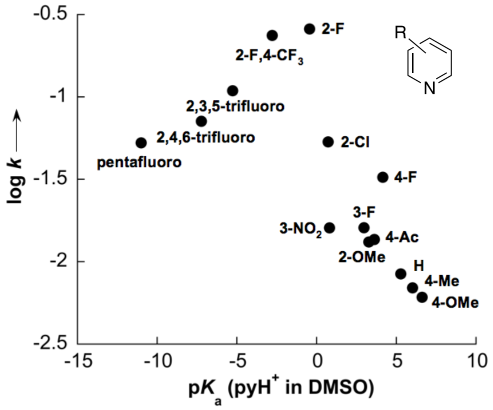


R	pK_a (pyrH^+)	Conversion (%)
4-MeO	6.47	3
H	5.25	23
3-CO_2Et	**3.35**	**76**
3-CN	1.39	55
3,5-di-Cl	0.90	22

An analogous trend in pyridine electronics and catalytic efficiency was also observed by Stahl in the oxidative homocoupling of *o*-xylene.[189] In this case, the optimized catalyst system consisted of $Pd(OAc)_2$, 2-fluoropyridine (2-Fpy), and catalytic quantities of TFAH and $Cu(OTf)_2$ (Scheme 27). A series of electron-rich and electron-deficient pyridine ligands were screened during catalyst optimization, and the rate of product formation was correlated to the pK_a of the corresponding pyridinium. For ligands with pyridinium pK_a values between ~7 – -0.44, the less coordinating pyridine ligands (i.e., more acidic pyH^+) led to enhanced reactivity. For ligands with pK_a (pyH^+) < -0.44, the opposite trend was observed (Scheme 27). 2-Fluoropyridine [pK_a (pyH^+) = -0.44] was identified as the optimal ligand. NMR studies of $Pd(TFA)_2$/pyridine mixtures revealed that ligands with pK_a (pyH^+) < -0.44 coordinate less effectively to $Pd(TFA)_2$, and that the Pd^{II} species likely exist as carboxylate bridged aggregates. Thus, weakly coordinated ligands that can break up these aggregates are capable of forming electrophilic mononuclear Pd^{II} species that promote C–H activation, which was shown to be the turnover-limiting step of the reaction.[190] More basic pyridines coordinate well to Pd^{II} but attenuate the electrophilicity of the $(py'_2)PdX_2$ catalyst and decrease activity. Neutral-donor ligand effects were shown to be complemented by effects of the anionic ligand. A nearly 50-fold rate enhancement observed with the inclusion of $Cu(OTf)_2$ as a cocatalyst was shown to arise from anionic ligand exchange with the Pd^{II} catalyst, resulting in formation of a $(2F\text{-}py)_2Pd(OAc)(OTf)$ as the active catalyst.[191] When testing other metal triflates as cocatalysts, even higher turnover rates were observed with $Fe(OTf)_3$. The mechanistic basis for this observation has not yet been determined.

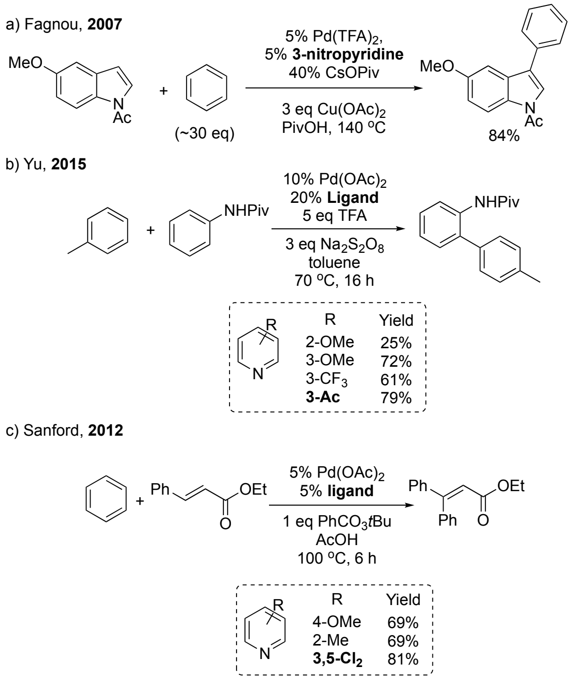
Scheme 27. 2-Fluoropyridine as the optimal pyridine-based ligands in the oxidative coupling of *o*-xylene (Reprinted with permission from ref 189. Copyright 2010 John Wiley & Sons, Inc.)





In addition to aerobic oxidations, electron-deficient pyridine ligands have been shown to be effective in Pd-catalyzed oxidations using alternate stoichiometric oxidants. Examples include the use of 3-nitropyridine in the oxidative cross-coupling between indole and arene,[192] 3-acetylpyridine in oxidative biaryl cross-coupling,[193] and 3,5-dichloropyridine in oxidative Heck coupling (Scheme 28).[194]

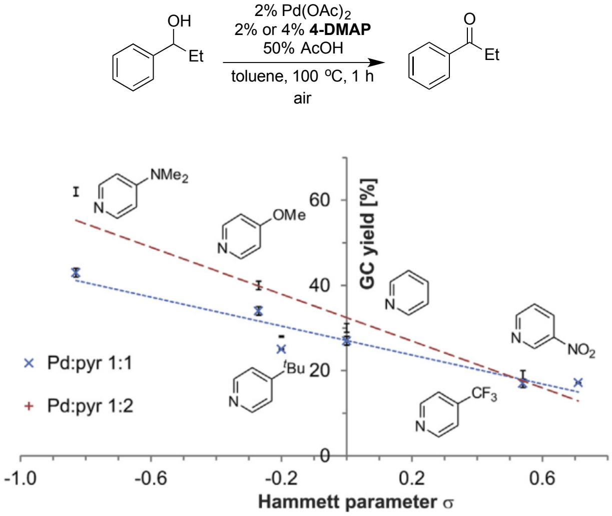
Scheme 28. Pd-catalyzed non-aerobic oxidations promoted by electron-deficient pyridines



4.3.3. 4-Dimethylaminopyridine (DMAP)

An interesting trend in pyridine electronics, distinct from the studies noted above, was reported by Emmert in 2013.[195] A Hammett plot for air oxidation of 1-phenylpropanol versus the substituent on the pyridine ligand reveals a negative correlation, with 4-DMAP as the optimal ligand. The authors attribute this trend to the ability of electron-rich pyridines to help prevent catalyst decomposition, which is more problematic when air (rather than pure O_2) is used as the oxidant. Consistent with this hypothesis, Pd black was observed with 4-CF_3- and 3-nitro pyridines, but not with 4-methoxy and 4-dimethylamino pyridines.

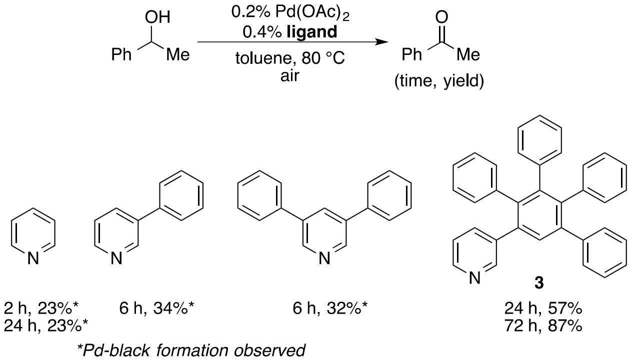
Scheme 29. Electron-rich pyridine-promoted alcohol oxidation. (Reprinted with permission from ref 195. Copyright 2013 Elsevier Ltd.)



4.3.4. Sterically encumbered pyridines

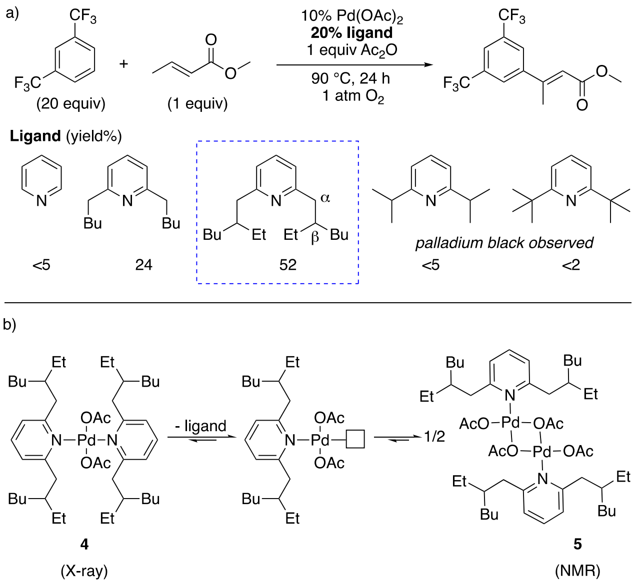
In 2004, Tsuji studied the effect of pyridine derivatives in the air oxidation of alcohols, and reported that 2,3,4,5-tetraphenyl substituted pyridine ligand **3** enabled high turnover numbers (Scheme 30).[196] Pyridine, 3-phenylpyridine and 3,5-diphenylpyridine gave low yields of alcohol oxidation, and the catalyst decomposed via Pd black formation under these conditions. Ligand **3** leads to a sterically encumbered Pd-complex, and the authors postulated that this feature prevents the formation of oligomeric Pd precursors to aggregated Pd black. A MALDI-TOF mass spectrometric analysis of the pyridyl ligand/Pd catalyst systems supported this claim, indicating that oligomers formed more readily in the presence of pyridine, 3-phenylpyridine and 3,5-diphenylpyridine than with ligand **3**.[197]

Scheme 30. Bulky pyridine ligand suppresses Pd black formation in air oxidation of alcohols.



In 2009, Yu reported an aerobic palladium-catalyzed method for *meta*-selective C–H olefination of electron-deficient arenes (Scheme 31a).[198] A series of 2,6-dialkyl-pyridine ligands were tested, and the yield of the reaction was sensitive to the size of the alkyl group. Unhindered pyridine ligands inhibited the reaction while very bulky ligands led to the formation of Pd black. The highest reactivity was achieved with a substitution pattern consisting of a methylene and methine group in the alpha and beta positions, respectively, in the 2-position of the pyridine. X-Ray crystallographic characterization of a Pd and ligand mixture identified *bis*-ligated $Pd(OAc)_2$ monomer **4** (Scheme 31b), which had slightly longer Pd–N bonds compared with the corresponding $(py)_2Pd(OAc)_2$ complex. Subsequent NMR spectroscopic analysis revealed that this monomer rapidly dissociates an equivalent of the ligand to form a *mono*-ligated $Pd(OAc)_2$ complex that was assigned as dimeric structure **5**. These findings suggest that the steric bulk of the *ortho* substituents on the pyridine ligand increases the lability of the ligand, resembling conclusions from Sigman's reports on triethylamine as a sterically hindered amine ligand. The 2,6-dialkyl-pyridine ligand and triethylamine likely stabilize Pd^0 by forming the *bis*-ligated adduct (cf. Scheme 22), as the Pd^0 species have a reduced coordination number and a larger atomic radius capable of accommodating longer Pd–ligand bonds.

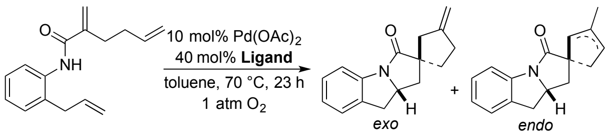
Scheme 31. 2,6-Dialkyl-pyridine supported aryl C–H olefination reactions.



4.4 Quinoline derivatives

In 2009, Yang and coworkers reported a tandem Wacker-type cyclization to afford a polycyclic system. It was found that among a range of pyridine-based ligands, quinoline and isoquinoline show high selectivity for the exocyclic olefin product, while the other ligands led to significant quantities of the endocyclic isomer (Scheme 32).[199] The authors attributed the byproducts to isomerization of the *exo* product *via* iterative reinsertion/β-H elimination, and they suggested that the quinoline and isoquinoline suppress this process. A noteworthy trend is that the conjugate acids of the three ligands giving the highest yields have very similar p*K*a values. Such correlation between catalytic activity and ligand basicity is reminiscent of previous discussion on ethyl nicotinate and 2-fluoropyridine (cf. Section 4.3.2).

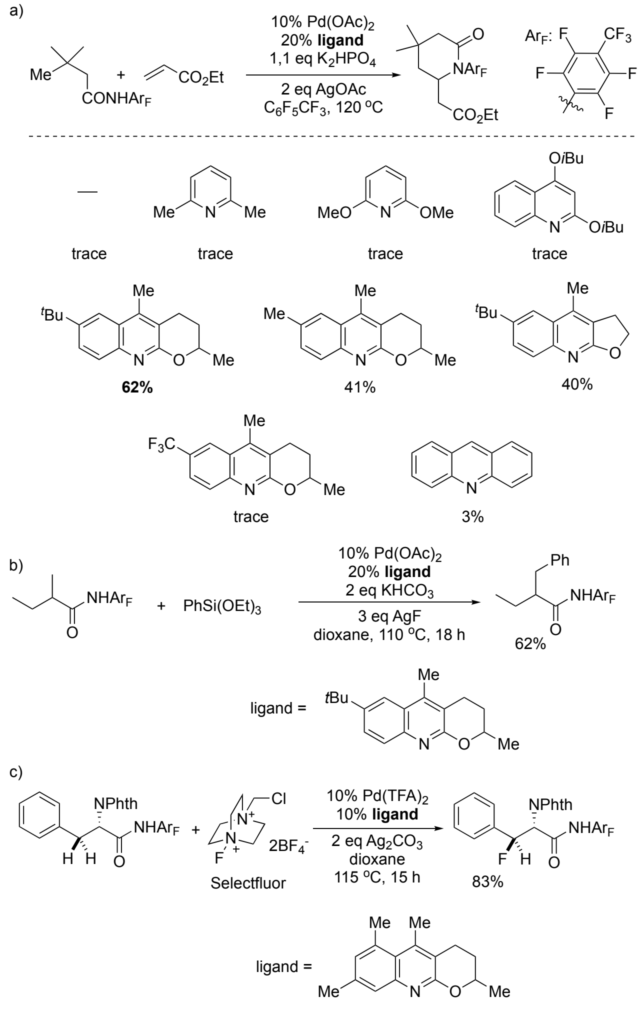
Scheme 32. Effects of quinoline in Wacker-type cyclization



Ligand	pK_a (LH$^+$)	*exo*+*endo* (%)	*exo*:*endo*
quinoxaline	0.60	39	1:1.4
8-methylquinoline	4.60	26	1:3.2
quinoline	4.85	70	4.2:1
isoquinoline	5.14	76	5.6:1
pyridine	5.14	56	1.5:1
acridine	5.60	24	1:6.3

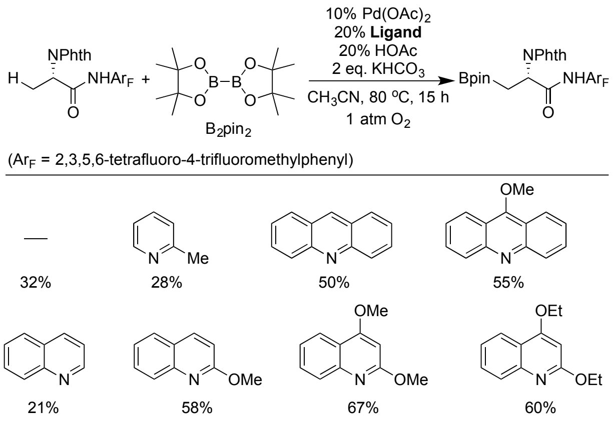
Quinoline derivatives have been shown by Yu and coworkers to be effective ligands in a number of oxidative C–H functionalization reactions, albeit often using an oxidant other than O$_2$. In 2014, Yu and coworkers reported a Heck-type oxidative cyclization reaction with AgOAc as the oxidant that featured a dihydropyran-fused quinoline as the optimal ligand. The ligand screening data revealed that electron-rich pyridine and quinolines are inactive, while the tetrahydrofuran-fused and electron-deficient variants of the optimal ligand are also less effective (Scheme 33a).[200] This same ligand class has been used in oxidative C–H/C–Si coupling and electrophilic fluorination reactions, again using Ag^I-based oxidants (Scheme 33b, c).[201,202]

Scheme 33. Representative C–H oxidations promoted by dihydropyran-fused quinoline ligands



In 2016, Yu and coworkers reported Pd-catalyzed aerobic oxidative borylation of the β-C–H bond of *N*-fluoroaryl carboxamides. Various pyridine-, quinoline- and acridine-based ligands were tested, and the best ligands were quinolines bearing 2- and 4-alkoxy groups (Scheme 34).[203] With the optimal 2,4-dimethoxyquinoline ligand, the reaction proceeded with 1% $Pd(OAc)_2$ to the product in 53% yield. An independent-rate comparison of protio and deuterio substrates revealed a KIE (k_H/k_D = 3.3), indicating that C–H cleavage is the turnover-limiting step in the reaction.

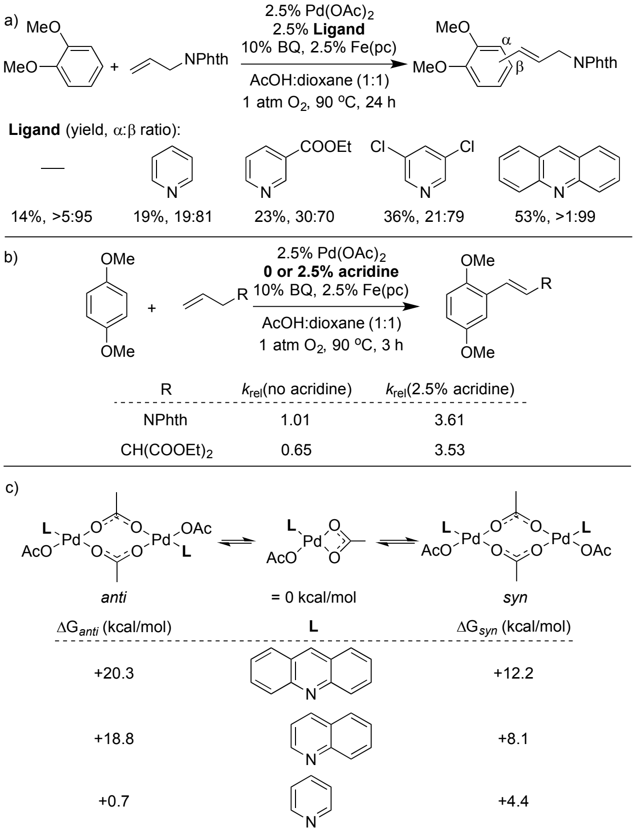
Scheme 34. 2,4-Dimethoxyquinoline-promoted C–H borylation



4.5 Acridine

Bäckvall reported the use of acridine as an ancillary ligand in an oxidative Heck reaction between arenes and electronically unbiased alkenes. Use of a Pd(OAc)$_2$/acridine catalyst system led to much higher aryl C–H regioselectivity comparing to pyridine-based ligands, an outcome attributed to steric effects (Scheme 35a).[204] Initial rate measurements indicated that the reaction proceeds 3-5 times faster with acridine than in the absence of ligand (Scheme 35b). A recent computational study by Emmert has provided insights into the effect of acridine.[205] The relative energies of monomeric and dimeric Pd(OAc)$_2$-acridine complexes indicate that the monomer is strongly favored, while for pyridine, the $\Delta\Delta G$ between monomer and dimer is minor (Scheme 35c). It is conceivable that the tendency of acridine to form a Pd monomer with a hemilabile κ^2-OAc ligand can facilitate important catalytic steps such as substrate binding.

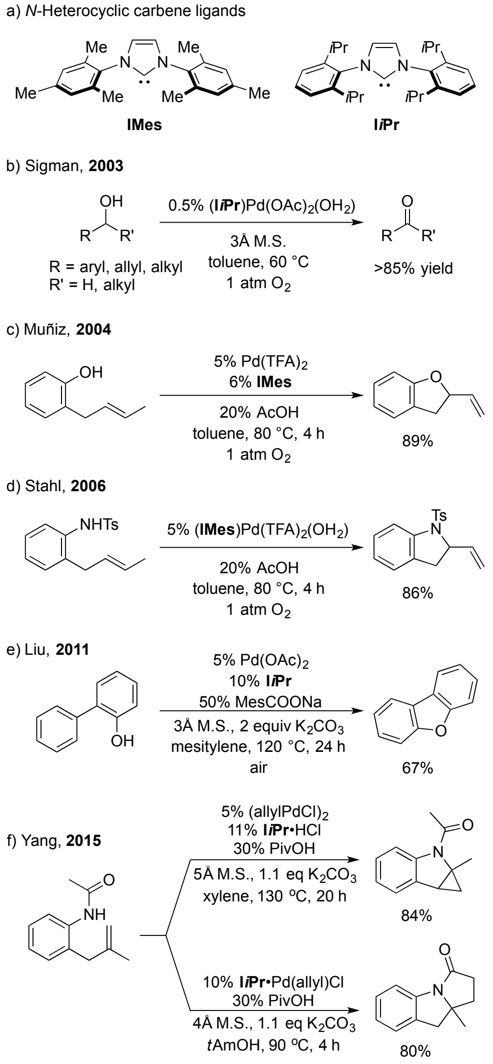
Scheme 35. Effects of acridine on the regioselectivity and initial rate of oxidative Heck reactions and Pd speciation



4.6. *N*-Heterocyclic carbenes (NHC)

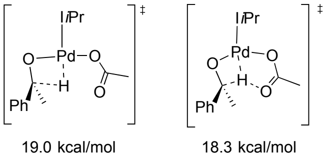
N-heterocyclic carbene (NHC) derivatives have been shown to be oxidatively stable ligands capable of supporting palladium-catalyzed aerobic oxidation reactions (IMes and I*i*Pr; Scheme 36a). In 2003, Sigman reported an (I*i*Pr)Pd(OAc)$_2$ catalyst for alcohol oxidation (Scheme 36b).[206] Muñiz and Stahl reported IMes-supported catalysts for Wacker-type cyclization reactions (Scheme 36c-d),[207-209] Liu reported an I*i*Pr-supported catalyst for intramolecular aryl C–H oxidation of 2-phenylphenols to benzofurans (Scheme 36e),[210] and Yang reported I*i*Pr-supported catalysts for tandem aminoalkylation via C–H functionalization, where two different types of tricylic compounds can be obtained by a switch of reaction condition (Scheme 36f).[211]

Scheme 36. Representative Pd-catalyzed aerobic oxidation reactions employing NHC-based ligands.



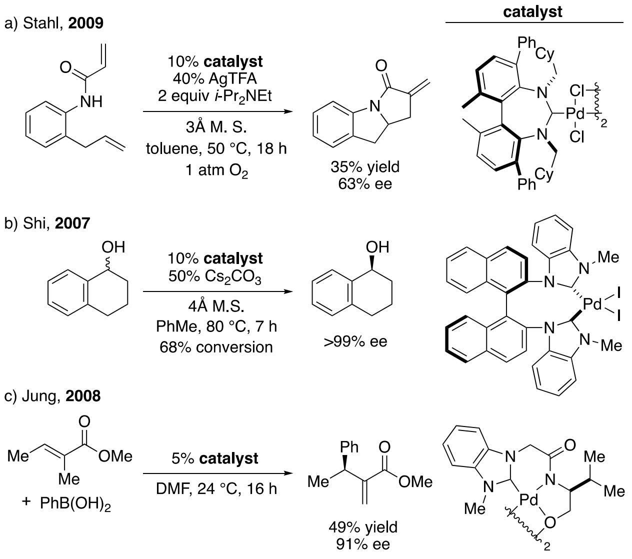
In 2004, Sigman and coworkers conducted a mechanistic study of the Pd(NHC)-catalyzed alcohol oxidation.[212] The study revealed an unusually large primary KIE (5.5 ± 0.1) and a negative Hammett correlation with a series of substituted benzyl alcohols (ρ = -0.48 ± 0.04), both of which supported β-H elimination from a (I*i*Pr)Pd^{II}-(OAc)(alkoxide) intermediate as the turnover-limiting step. To account for the large KIE, they also proposed an alternative reaction pathway, which involves direct β-H elimination to the OAc counterion to form Pd^0 ("reductive" β-H elimination). Subsequent DFT computational studies by Goddard provided evidence for a unique "reductive" β-H elimination pathway for this step, in which the β-hydrogen of the alkoxide ligand undergoes direct transfer to the acetate ligand to generate AcOH, Pd^0, and the aldehyde without formation of a discrete Pd^{II}–hydride intermediate.[213] The barrier for reductive β-H elimination, 18.3 kcal/mol, was calculated to 0.7 kcal/mol lower than the traditional β-H elimination pathway (Scheme 37). The traditional mechanism is disfavored by the strong *trans* influence of the NHC ligand, which thermodynamically disfavors placement of another strong-field ligand in the *trans* position.

Scheme 37. Transition states for traditional- and "reductive" β-H elimination pathway



Several efforts have targeted the use of chiral NHC ligands in catalytic asymmetric processes (Scheme 38). Seven-membered NHC derivatives were used for aza-Wacker annulation reactions, but only modest yield and selectivity were obtained (Scheme 38a).[214] A chelating chiral bis-NHC ligand proved effective in the kinetic resolution of secondary alcohols (Scheme 38b)[215] and oxidative Heck reactions (Scheme 38c).[216] In general, nitrogenous bidentate ligands, such as (–)-sparteine and pyridine-oxazoline derivatives have proven to be more effective for enantioselective Pd-catalyzed oxidation reactions (cf. Section 5.2).

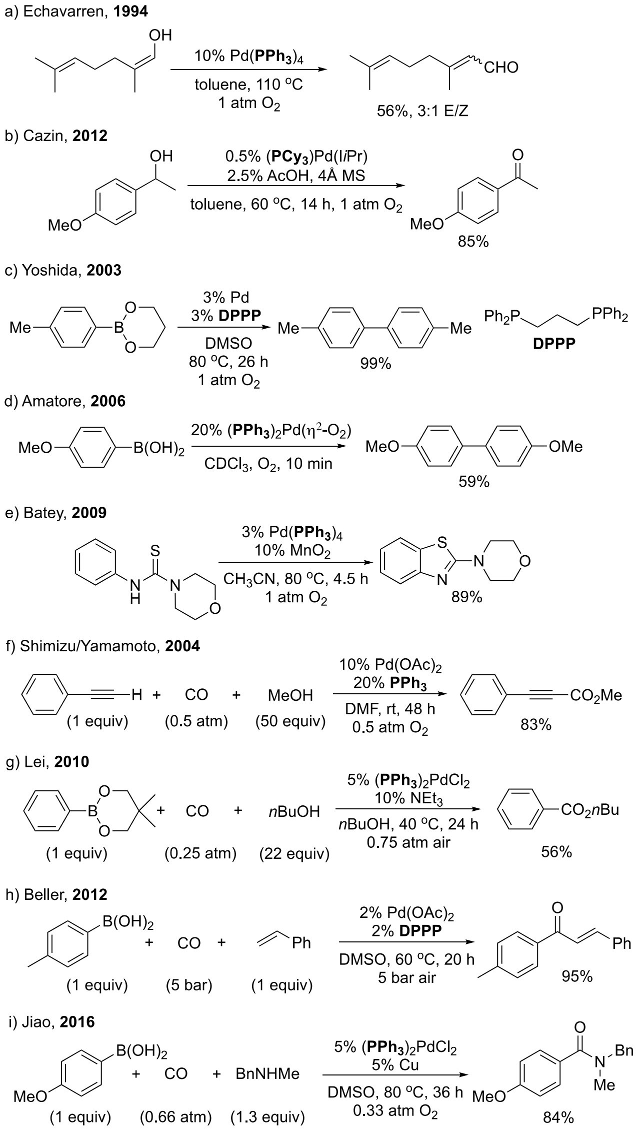
Scheme 38. NHC-supported asymmetric oxidation reactions.



4.7. Phosphine ligands

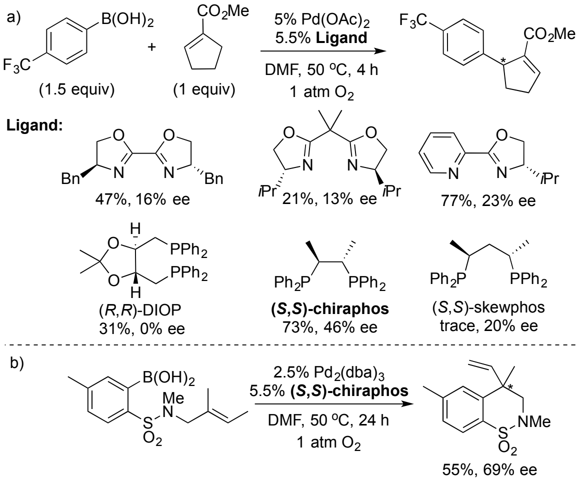
The instability of phosphines under oxidizing conditions would seem to limit their utility in Pd-catalyzed aerobic oxidations. For example, as noted above, $Pd(PPh_3)_4$ rapidly catalyzes the oxidation of Ph_3P to $Ph_3P{=}O$.[65,217] Nevertheless, Pd/phosphine catalyst systems have been used in numerous Pd-catalyzed aerobic oxidations, albeit often without direct assessment of the stability of the phosphine under the catalytic reaction conditions. Representative applications include alcohol oxidation (Scheme 39a-b),[218,219] homocoupling of arylboronic esters and acids (Scheme 39c-d),[220,221] oxidative C–S formation (Scheme 39e),[222] and oxidative carbonylation with CO (Scheme 39f-i).[223-226] In many cases, phosphine-ligated complexes are employed as precatalysts, and direct evidence for the superior performance of phosphines over nitrogen-based ligands is very rare.

Scheme 39. Representative phosphine supported Pd-catalyzed aerobic oxidations.



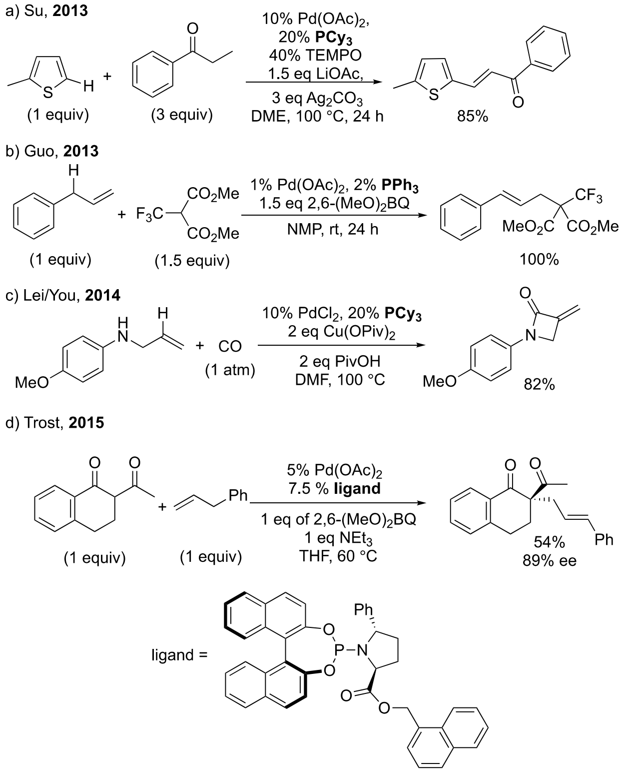
Chiral diphosphines have been used with Pd in asymmetric oxidation reactions.[227,228] In 2005, Mikami reported an oxidative Heck reaction between arylboronic acids and cyclopentyl carboxylates (Scheme 40a). Use of (*S*,*S*)-chiraphos led to much higher ee than box, pybox and other phosphine ligands. The same ligand was subsequently applied to an intramolecular oxidative Heck reaction to form benzo-fused heterocycles (Scheme 40b). While the stability of ligand under the reaction conditions was not analyzed, observation of enantioselectivity provides support for involvement of the chiral ligand in the catalytic reaction. This issue warrants further investigation, however. Diphosphine monoxides have been used as effective chiral ligands for Pd-catalyzed coupling reactions, in some cases leading to higher enantioselectivity than the corresponding diphosphine (e.g., in Mirozoki-Heck coupling[229, 230] and Buchwald-Hartwig coupling[231]). In another case, in-situ formation of a Xantphos[232] derived mono-oxide ligand leads to an effective Pd catalyst system, further demonstrating that that (partial) oxidation of phosphine ligands is not necessarily deleterious to catalytic reactivity.

Scheme 40. Diphosphine-supported asymmetric oxidation reactions



Phosphine ligands have also been employed in Pd-catalyzed oxidations that use stoichiometric oxidants other than O_2 (e.g., Cu^{II}, Ag^{I}, BQ). For example, Su and coworkers noted that in the heteroarene C–H olefination with ketones, using PCy_3 reduces the amount of thiophene homocoupling byproduct (Scheme 41a), which was attributed to the formation of an electron-rich (Cy_3P)Pd center that disfavors aryl-aryl coupling.[233] Pd/PPh_3 has been used in allylic C–H alkylation with a quinone oxidant (Scheme 41b).[234] Oxidative C–H/N–H carbonylation of amines to form β-lactams has been achieved with PCy_3 as the ligand and $Cu(OPiv)_2$ as the oxidant (Scheme 41c).[235] Asymmetric allylation of 1,3-diketones has been achieved with a new class of non-C_2-symmetric phosphoramidite ligands derived from pyroglutamic acid using a stoichiometric quinone oxidant (Scheme 41d).[236] Similar to the aerobic oxidation reactions, insights into the stability and/or fate of the phosphine ligands in these reactions have not been reported.

Scheme 41. Examples of non-aerobic Pd-catalyzed oxidation reactions supported by phosphine ligands



5. Bidentate ligands

Many Pd-catalyzed aerobic oxidation reactions that employ monodentate ligands exhibit limited catalytic stability and low turnover numbers. Bidentate ligands offer the potential to enhance catalyst stability, but they also inhibit many of the oxidation reactions described above. The chelating ligand disfavors dissociation of an L-type-ligand, which often provides the basis for substrate entry into the Pd coordination sphere. Furthermore, dissociation of an anionic ligand generates an ion pair that is energetically disfavored in non-polar solvents. Thus, bidentate ligands such as bpy and 1,10-phenanthroline (phen) are typically only effective in polar solvents (e.g., DMSO, DMF) and/or at high temperatures (100-200 °C) that allow for dissociation of an anionic ligand. Several structurally modified bidentate ligands have been identified that bypass these limitations, however, and bidentate ligands are among the important ligand classes used in Pd-catalyzed aerobic oxidation reactions.

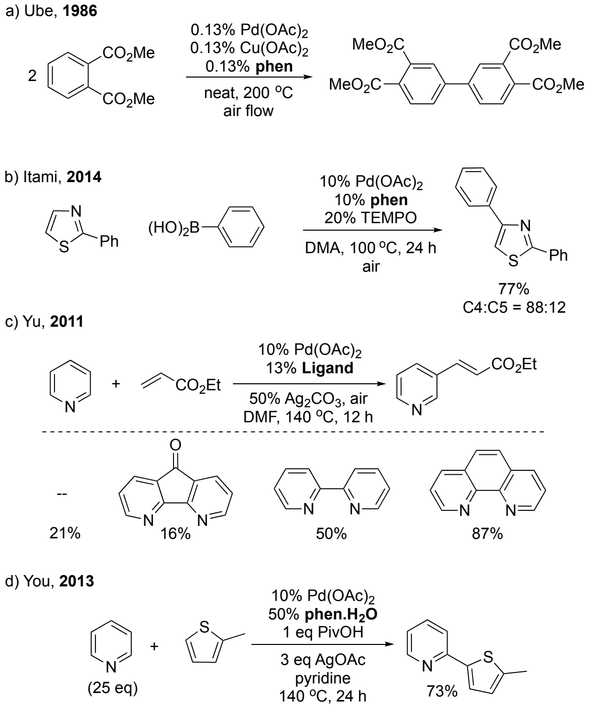
5.1. Bipyridyl derivatives

The parent 2,2'-bipyridyl (bpy) ligand class has rarely been identified as an optimal ligand in Pd-catalyzed aerobic oxidation reactions; however, examples have been reported. Applications of bpy-supported Pd catalysts include oxidative homocoupling of simple arenes[237] and aza-Wacker cyclization.[238] As elaborated below, however, modified bpy and 1,10-phenanthroline derivatives exhibit improved performance in these and many other transformations.

5.1.1. 1,10-Phenanthroline derivatives

In the 1980s, Ube Industries (Japan) developed a process for Pd-catalyzed aerobic C–H/C–H homocoupling of dimethyl phthalate as a key step in the preparation of the monomeric precursor to Upilex, a high-performance polyimide resin.[237,239-242] The parent 1,10-phenanthroline (phen) ligand is crucial to achieve high regioselectivity for the 3,4,3',4'-substituted product (Scheme 42a).[239,241,242] In the absence of phen, the ratio of desired product to the 2,3,3',4'-substituted isomer drops from 10:1 to 1:5.[239]

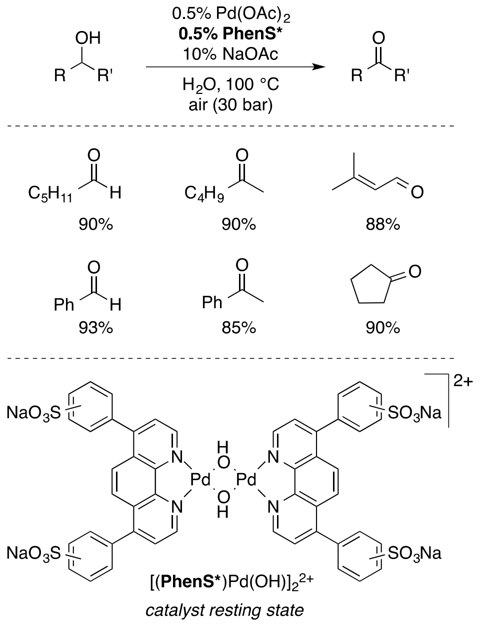
Scheme 42. Phen-supported Pd-catalyzed oxidative functionalization of aromatic C–H bonds



More recently, several reports have described use of the parent phen ligand in Pd-catalyzed methods for oxidative functionalization of heteroarene C–H bonds (Scheme 42b-d). These examples employ polar solvents that presumably support formation of a cationic $[(\text{phen})\text{PdX}]^+$ species that is capable of promoting C–H activation. Itami and coworkers reported Pd/phen-catalyzed oxidative coupling of thiazoles and aryl boronic acids (Scheme 42b).[243] The groups of Yu[244] and You[245] employed Pd/phen-based catalysts in combination with stoichiometric Ag-based oxidants for C–H functionalization of pyridine (Scheme 42c-d). Use of phen as a chelating ancillary ligand may play an important role in avoiding *N*-coordination of the pyridine substrate; however, specific insights into the role of the ligand were not provided in these studies.

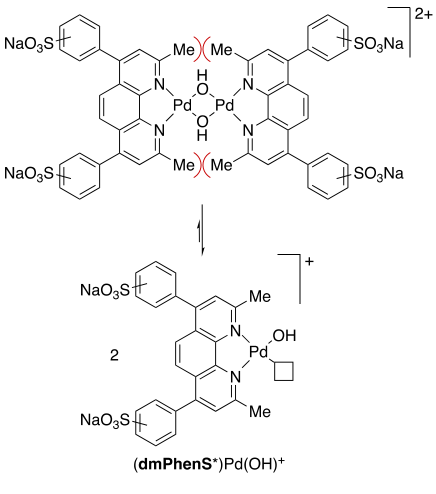
In 1998, Sheldon and coworkers showed that use of the water-soluble bathophenanthroline disulfonate ligand (PhenS*) provided the basis for a Cu and chloride-free Wacker reaction, enabling conversion of a series of terminal alkenes to the corresponding methyl ketones.[21] Shortly thereafter, they demonstrated that a similar catalyst system enabled efficient aerobic alcohol oxidation (Scheme 43).[246 - 248] A variety of secondary alcohols and activated (i.e., benzylic, allylic) primary alcohols were oxidized in good yield and selectivity with low catalyst loading in water as the solvent. Use of cocatalytic 2,2,6,6-tetramethylpiperidinyl-*N*-oxyl was needed to prevent overoxidation of unactivated primary alcohols to the corresponding carboxylic acid, presumably due to background autoxidation of the aldehyde. Kinetic studies revealed a half-order [Pd] dependence, suggesting that a dimeric species $[(\text{PhenS*})\text{Pd(OH)}]_2^{2+}$ was the catalyst resting state.[247] Bimolecular reaction of the alcohol substrate with this dimer to afford a mononuclear Pd^{II}–alkoxide was proposed as the turnover-limiting step.

Scheme 43. Bathophenanthroline disulfonate supported alcohol oxidations.

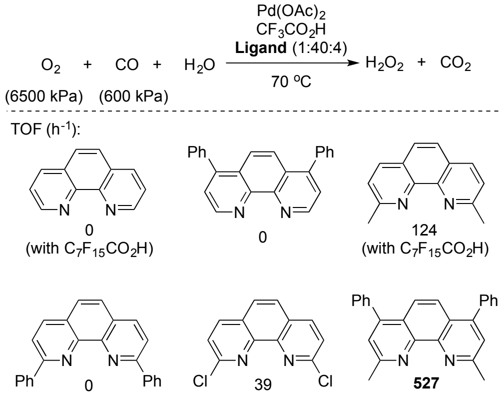


Sheldon and coworkers hypothesized that modifications to the ligand structure that would favor a monomeric catalyst resting state would improve catalysis. They employed a sterically encumbered derivative of the PhenS* ligand bearing methyl groups at the positions *ortho* to the phenanthroline nitrogen atoms (dmPhenS*) to disfavor formation of the dimeric species and favor formation of the active monomeric catalyst (Scheme 44). Catalytic activity for oxidation of 2-hexanol tripled with this modified catalyst, from a TOF of 49 h^{-1} with PhenS* as the ligand to 150 h^{-1} with dmPhenS* as the ligand.[249] Subsequent studies showed that the even further improvements could be achieved by using the non-sulfonated 2,9-dimethylphenthroline (dmphen or neocuproine) ligand in combination with $Pd(OAc)_2$ and performing the reaction in water/DMSO solvent mixtures. Process optimization enabled turnover frequencies of 1800 h^{-1} for the oxidation of 2-octanol.[250] The beneficial effects of the dmphen ligand resemble the observations of researchers at Enichem in the late 1990s in studies of the Pd-catalyzed conversion of O_2 to H_2O_2 with various sacrificial reductants (H_2, CO/H_2O, alcohols).[22,69] A series of patents and publications on this topic showed that bathocuproine (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline) was the most effective ligand from among a series of phenanthroline derivatives (Scheme 45).

Scheme 44. Ligand methyl groups favor formation of active monomeric catalyst.

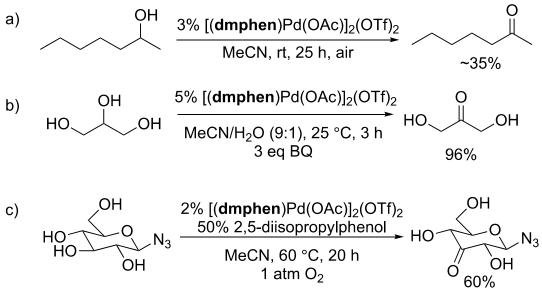


Scheme 45. Effectiveness of phenthroline derivatives in Pd-catalyzed O_2 reduction



Following the reports of Sheldon, Waymouth and coworkers prepared a well-defined [(dmphen)Pd(OAc)]$_2$(OTf)$_2$ catalyst for the aerobic oxidation of various alcohols.[81,82, 251-255] Replacement of one of the acetate ligands in Sheldon's dmphen/Pd(OAc)$_2$ catalyst system with a trifluoromethanesulfonate led to substantially enhance activity, enabling oxidation of 2-heptanol at room temperature under air (Scheme 46a).[251] The bis(acetate)- and bis(triflate) analogs of the catalyst exhibited poor activity under the same conditions. The utility of the mixed anionic ligands was attributed to the beneficial effect of a labile OTf anion for substrate binding and a basic OAc ligand for substrate deprotonation. The reaction exhibited a fast initial rate (TOF = 78 h^{-1}), but then slowed as a result of catalyst decomposition (see below for further discussion).

Scheme 46. Cationic-(dmphen)Pd supported alcohol oxidations.



Subsequent studies showed that this catalyst system mediates unusually chemoselective oxidation of polyols[252,254] and carbohydrates[255] with high efficiency (as low as 1% Pd) and up to 99% selectivity for secondary alcohols (Scheme 46b-c). Many of the reactions are more effective with benzoquinone as the oxidant, but use of O_2 was also demonstrated. Mechanistic studies provided insights into the origin of fast rates and chemoselectivity in 1,2-diol oxidation. Formation of Pd-alkoxide is the rate-limiting step in the oxidation of simple alcohols, but this step is promoted by chelation of the diol. Formation of a primary alkoxide is favored over the secondary alkoxide for 1,2-diols, but the species can interconvert, and β-H elimination is favored for the secondary alkoxide. DFT calculations show a 4 kcal/mol preference for the ketone-forming pathway vs. the aldehyde-forming pathway.[254] Studies of catalyst decomposition showed that the (dmphen)Pd-based catalysts can undergo oxidation of the CH_3 arm of the ligand (Figure 2).[81,82,251] These observations inspired the development of improved catalyst systems by the groups of Waymouth and Minnaard, including addition of phenolic radical traps (cf. Scheme 46c) [255] and the replacement of the ligand CH_3 group with CF_3[253] or CD_3[256], all of which led to enhanced catalyst stability and catalytic performance.

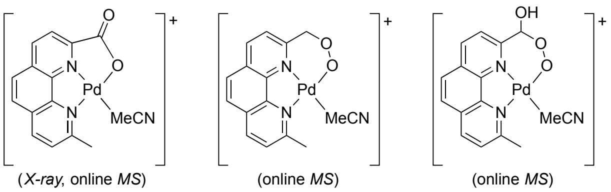
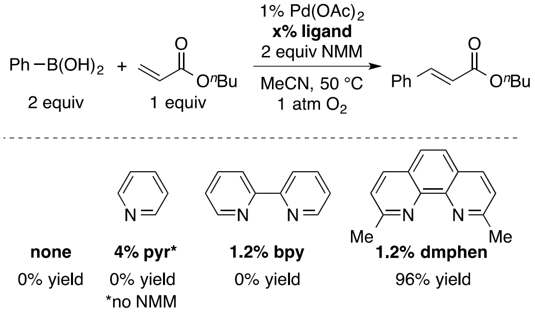


Figure 2. Products of oxidative decomposition of (dmphen)Pd

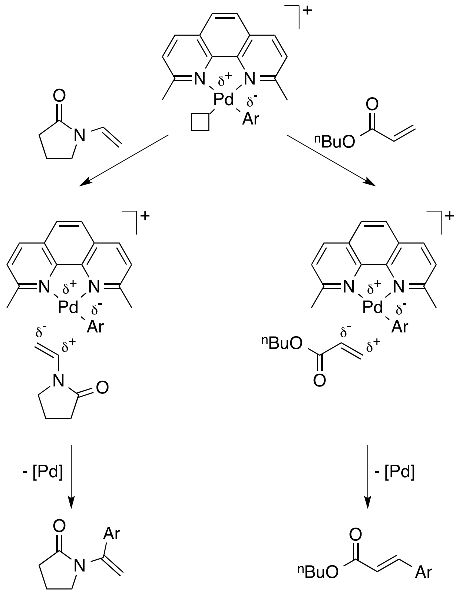
Oxidative Heck-type coupling is another reaction class in which dmphen has been shown to be a highly efficient ligand. Larhed reported that dmphen promotes aerobic oxidative Heck reactions in *N*-methylmorpholine (NMM) (Scheme 47).[257] The authors found that simple acrylates, enones or styrenes underwent efficient coupling with aryl boronic acids under aerobic conditions. The reactions employ dmphen as the ligand; without ligand or with pyridine or 2,2'-bipyridine, no product was obtained.

Scheme 47. Dmphen supported oxidative Heck reactions.



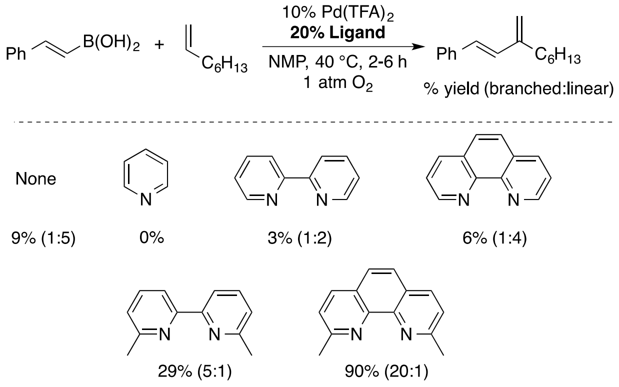
The regioselectivity of Heck reactions is an important issue, as migratory insertion of terminal alkenes into Pd–C bonds can give rise to either branched or linear products. Studies by Larhed[258-260] and Jung[261] on aerobic oxidative Heck reactions with dmphen demonstrated that electron rich alkenes give rise to branched products, while electron deficient alkenes give rise to linear products (Scheme 48). These findings are consistent with observations in non-oxidative Heck coupling reactions, which show that a bidentate neutral donor ligand enforces a cationic $[(L_2)Pd(Ar)(alkene)]^+$ intermediate that promotes Markovnikov selectivity.[262,263]

Scheme 48. Substrate controlled (Markovnikov) selectivity in Heck reactions.



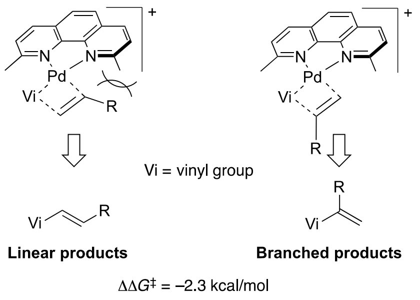
In 2012, Stahl reported a (dmphen)Pd(TFA)$_2$ system that achieved catalyst-controlled regioselectivity in oxidative Heck reactions between vinylboronic acids and electronically unbiased terminal olefins to afford branched 1,3-dienes (Scheme 49).[264] Dmphen was found to be the most active ligand and enforced the highest selectivity for branched products, yielding synthetically useful substituted 1,3-dienes. Analogous results were later reported with arylboronic acids coupling partners, which led to selective formation of α-branched styrenes.[265]

Scheme 49. Dmphen-controlled branched selectivity in Heck reactions



DFT computational studies indicated that a steric interaction between the olefin and the methyl group of the dmphen ligand in the [Pd(dmphen)(vinyl)(olefin)]$^+$ complex disfavors formation of the linear product (Scheme 50). These studies showed how the steric properties of the dmphen ligand enhance the electronic effects favoring Markovnikov-selective migratory insertion of an electronically unbiased alkenes into a Pd–C bond.

Scheme 50. Influence of dmphen ligand sterics on the regioselectivity of oxidative Heck reactions.



The dmphen ligand represents an early important example of how modification of the phen ligand framework is a crucial contributor to catalytic activity. The steric interaction between the methyl group and the neighboring ligand destabilizes an inactive dimeric resting state (Sheldon) or promotes a branched-selective alkene-insertion step in the oxidative Heck reaction (Stahl). The influence of the methyl-group steric effects is evident from the X-ray structure of (dmphen)Pd(OAc)$_2$ (Figure 3). The interaction between the ligand methyl group and acetate causes significant distortion of the dmphen ligand out of the square plane of the Pd^{II} coordination sphere.[266] Analogous steric interactions that contribute to reaction outcomes with (–)-sparteine and oxazoline-based chiral ligands will be highlighted below.

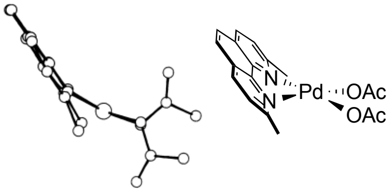
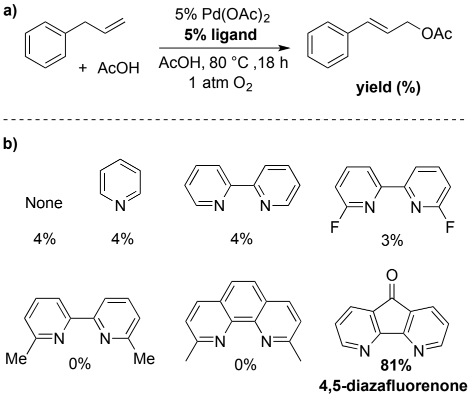


Figure 3. X-ray crystallographic structure and illustration of (dmphen)Pd(OAc)$_2$, showing the bending of the dmphen ligand with respect to the ligand donor atom square plane (Reprinted with permission from ref 266. Copyright 1994 The Royal Society of Chemistry.)

5.1.2. 4, 5-Diazafluorenone (DAF)

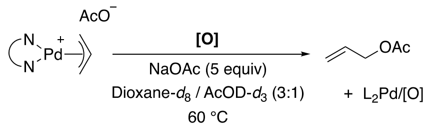
In 2010, Stahl and coworkers showed that 4,5-diazafluorenone (DAF) enables allylic C–H acetoxylation of terminal olefins to proceed with O_2 as the oxidant (Scheme 51).[267] A screen of common pyridine-based ligands highlighted the unique effectiveness of the diazafluorene ligand scaffold; use of pyridine and various bidentate ligands led to negligible reactivity.

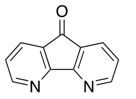
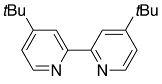
Scheme 51. 4,5-Diazafluorenone-supported allylic acetoxylation reactions.



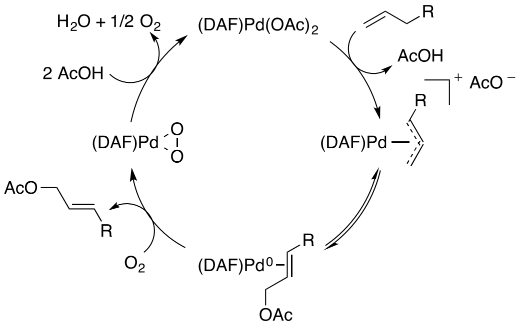
Stoichiometric reactions of a DAF-ligated π-allyl–Pd^{II} complex and a *t*Bu$_2$bpy-ligated π-allyl–Pd^{II} complex showed that reductive elimination of allyl acetate readily occurred from the DAF-ligated complex, while the *t*Bu$_2$bpy-ligated π-allyl–Pd^{II} complex was unreactive unless benzoquinone was added to promote reductive elimination (Scheme 52). These results provide evidence that DAF is capable of promoting reductive elimination of allyl acetate under aerobic conditions (i.e., in the absence of benzoquinone). Additional mechanistic investigations revealed that reductive elimination is reversible, but that O_2 is able to trap the Pd^0-alkene adduct, resulting in release of the allyl acetate product and reoxidation of the Pd catalyst (Scheme 53).

Scheme 52. Ligand effects on reductive elimination of allyl acetate from $[(N\sim N)Pd(\pi\text{-allyl})]^+$ complexes.



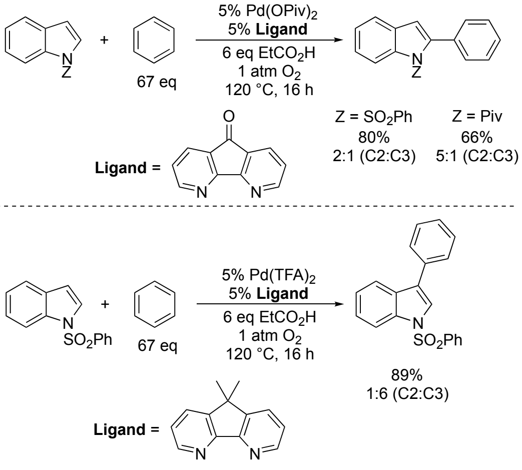
 ligand	yield of allyl acetate	
	2 equiv benzoquinone	3 atm O_2
	88% (1 h)	90% (1 h)
	88% (24 h)	0% (24 h)

Scheme 53. Proposed catalytic mechanism for DAF-promoted aerobic allylic acetoxylation.



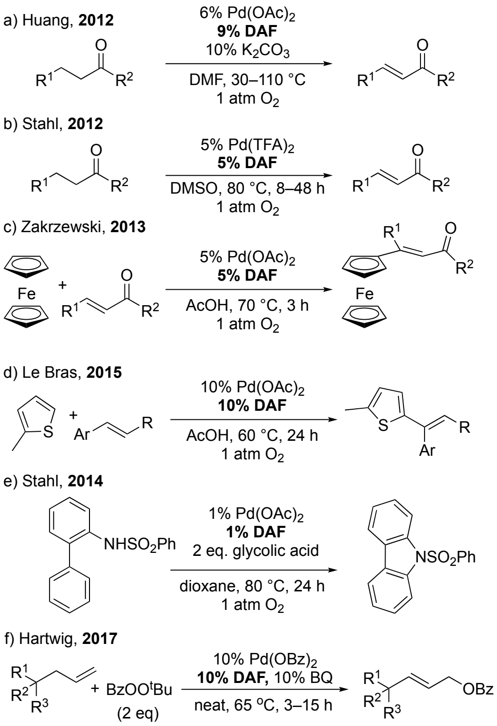
Subsequent studies have shown that DAF-ligated Pd^{II} catalysts are effective in a number of other aerobic oxidation reactions. Stahl reported aerobic oxidative coupling of indoles and benzene using DAF and Me_2DAF as ligands (Scheme 54).[268] The diazafluorene-based ligands were found to be the most active among a number of mono- and bidentate ligands screened, and the regioselectivity of the reaction (C2 versus C3 arylation) was governed by the identity of the Pd^{II} salt and ligand. Prior studies by Fagnou and coworkers had demonstrated that stoichiometric AgOAc or $Cu(OAc)_2$ oxidant could be used to achieve regioselective C2 versus C3 indole/arene coupling, respectively.[192,269] This more recent work highlights the ability to achieve catalyst-controlled indole arylation with O_2 as the oxidant.

Scheme 54. Catalyst-controlled aerobic C–H/C–H oxidative cross-coupling with diazafluorene-based ligands.



The groups of Huang [270] and Stahl [271] reported (DAF)Pd^{II} catalyst systems for dehydrogenation of linear and cyclic ketones and aldehydes to the corresponding α,β-unsaturated carbonyl compounds. In each of the methods, other mono- and bidentate ligands were found to inhibit the reaction or to be inferior to DAF. The Huang method used Pd(OAc)$_2$ in DMF as the solvent (Scheme 55a) while the Stahl method used Pd(TFA)$_2$ in DMSO (Scheme 55b). The groups of Zakrzewski[272] and Le Bras[273] used (DAF)Pd^{II} catalysts in Fujiwara-Moritani-type dehydrogenative coupling reactions (Scheme 55c-d). Stahl reported a DAF-promoted oxidative C–N coupling to form carbazoles (Scheme 55e).[274] Hartwig and coworkers recently adapted the Stahl allylic acetoxylation condition to achieve a non-aerobic allylic benzoyloxylation using two equivalents BzOO*t*Bu as the oxidant (Scheme 55f).[275,276]

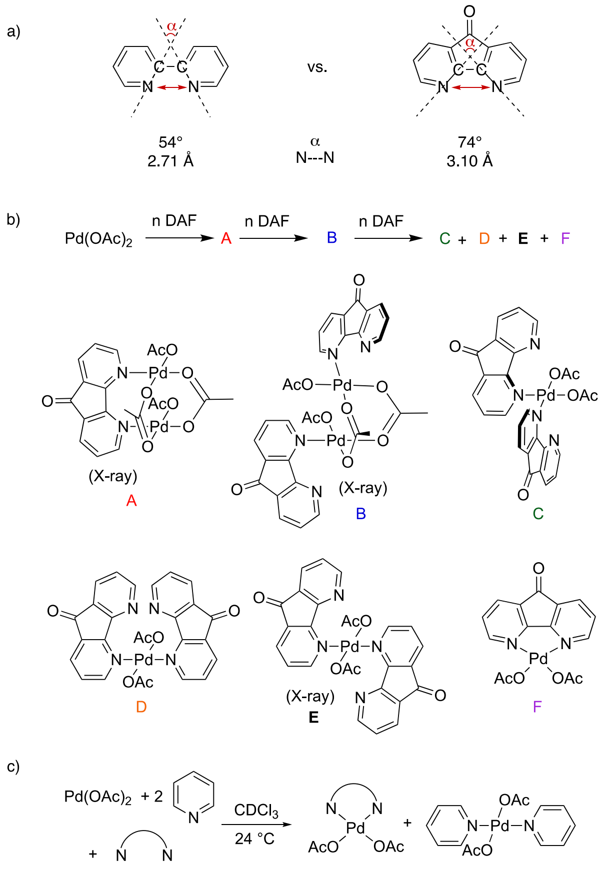
Scheme 55. Examples of 4,5-diazafluorenone (DAF)-supported Pd-catalyzed aerobic oxidation reactions.



The results noted above show that the DAF is a versatile ligand for palladium-catalyzed aerobic oxidations. The structure of DAF exhibits several important differences relative to traditional bpy and phen ligand frameworks. The DAF carbonyl group that bridges the 3,3' positions of bpy increases the distance between the two nitrogen atoms and alters the orientation of the nitrogen lone pairs (Scheme 56a). These differences cause DAF to coordinate to transition metals less effectively than bpy and accounts for diverse coordination modes observed in DAF-transition-metal complexes.[277] In 1998, Elsevier and coworkers reported the crystal structures of several (DAF)Pd^0-quinone complexes in which DAF coordinated to Pd as κ^1 monodentate ligand or as a bridging ligand.[278] Stahl and coworkers recently reported an extensive investigation of the coordination chemistry of DAF with Pd(OAc)$_2$, elucidating both solution-phase and solid state structures.[279,280] Ligand titration studies showed the progressive formation of DAF/Pd(OAc)$_2$

complexes with diverse DAF coordination modes, including κ^1, κ^2 and μ (bridging) modes (Scheme 56b). Facile interchange between these coordination modes was proposed to be crucial to promote important steps in catalysis (e.g., substrate binding, Pd^0 stabilization). NMR spectroscopic studies analyzed the coordinating ability of DAF and other common bidentate nitrogen ligands, in competition with pyridine. The results showed that traditional bpy/phen type bidentate ligands coordinate more strongly than pyridine, while the sterically-demanding 6,6'-dimethylbipyridine (dmbpy) and DAF coordinate more weakly than pyridine (Scheme 56c).

Scheme 56. (a) Geometric distinction between bpy and DAF coordination frameworks; (b) Diverse coordination modes of DAF; (c) comparison of DAF and other ligands in coordinating ability

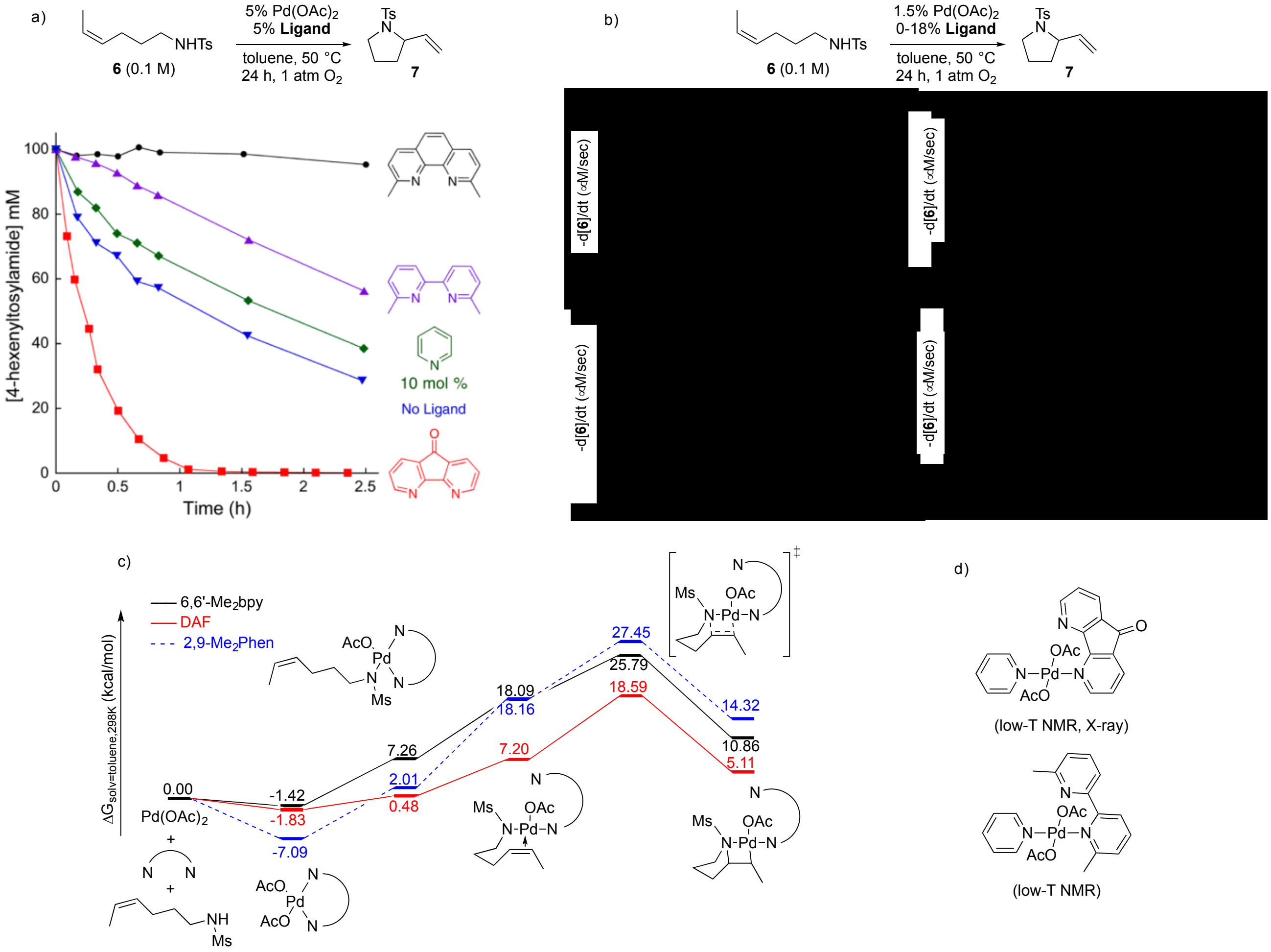


Ligand	(N~N)Pd(OAc)$_2$: Pd(py)$_2$(OAc)$_2$
4,4'-*t*Bu$_2$bpy	40 : 1
2,9-Me$_2$phen	5 : 1
6,6'-Me$_2$bpy	1 : 4.3
DAF	1 : 5.4[a]

[a] The DAF ligated species is Pd(κ^1-DAF)(py)(OAc)$_2$

Valuable insights into the influence of DAF on catalysis were obtained from a comparative study of different ligands in a Pd-catalyzed aza-Wacker reaction (Scheme 57).[280] Analysis of reaction time courses show that only DAF accelerates the rate of the catalytic reaction (Scheme 58a). As another important metric for "ligand accelerated catalysis", only DAF shows no inhibitory effect with the addition of more ligand to the reaction mixture (Scheme 57b). Pyridine enhances the rate at low concentrations (up to py:Pd = 1:1), after which it inhibits, and dmbpy and dmphen inhibit the reaction up to a 1:1 L:Pd ratio. The dmbpy ligand is noteworthy in that it supports catalysis at a dmbpy:Pd ratio of ≥ 1:1, contrasting the effect of dmphen, which completely inhibits the reaction at a dmphen:Pd ratio of ≥ 1:1. These observations may be rationalized on the basis of the mechanism supported by experimental and DFT computational studies, in which the preferred pathway involves dissociation of one nitrogen atom of the bidentate ligand to allow coordination of the olefin prior to C–N bond formation (Scheme 57c). Direct evidence for κ^2–κ^1 interconversion of DAF and dmbpy ligands was obtained from low-temperature NMR spectroscopic studies, upon adding 1 equiv of pyridine to solutions of these ligands and $Pd(OAc)_2$, and the $Pd(\kappa^1\text{-DAF})(py)(OAc)_2$ complex was characterized by X-ray crystallography (Scheme 57d). The beneficial effect of DAF arises from a minimal ligand binding effect on the ground state energy relative to unbound $Pd(OAc)_2$ and a significant lowering of the transition-state energy of aminopalladation, owing to facile κ^2–κ^1 interconversion. In contrast, dmphen significantly stabilizes the ground state (7.09 kcal/mol) and has a much higher transition-state energy. This result highlights the importance of both ground-state and transition-state effects of ligands on catalytic reactions.

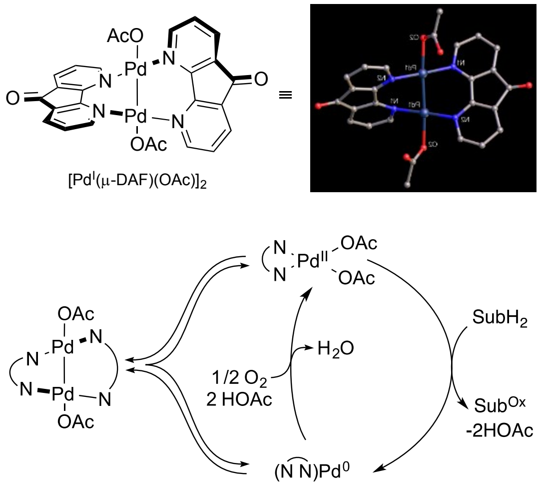
Scheme 57. Comparison of DAF with common ligands in their effects on reaction time course (a), reaction rate (b) and computed reaction energy diagram (c). Structures of Pd(κ^1-L)(py)(OAc)$_2$ (L=DAF, 6,6'-Me$_2$bpy) characterized in solution (d). (Reprinted with permission from ref 280. Copyright 2016 American Chemical Society.)



[redacted]

Finally, a recent study of two Pd(OAc)$_2$/DAF-catalyzed aerobic oxidation reactions by Stahl and coworkers, allylic C–H acetoxylation and intramolecular aza-Wacker, revealed in situ formation of a DAF-ligated dimeric Pd$^{\mathrm{I}}$ species under the catalytic reaction conditions (Scheme 58).[281] Formation of this species was rationalized by reaction of (DAF)Pd^0, formed upon substrate oxidation, with a resting-state (DAF)Pd(OAc)$_2$ species. This intermediate could have beneficial or deleterious consequences for the reaction: it could benefit the reaction by diverting unstable Pd^{0} species into a more-stable off-cycle Pd^{I} species, or it could hinder catalytic turnover by diverting the active catalyst into an inactive off-cycle species. More studies will be needed to probe the influence of this unusual species and to determine whether formation of Pd^{I} is a common phenomenon in aerobic oxidation reactions.

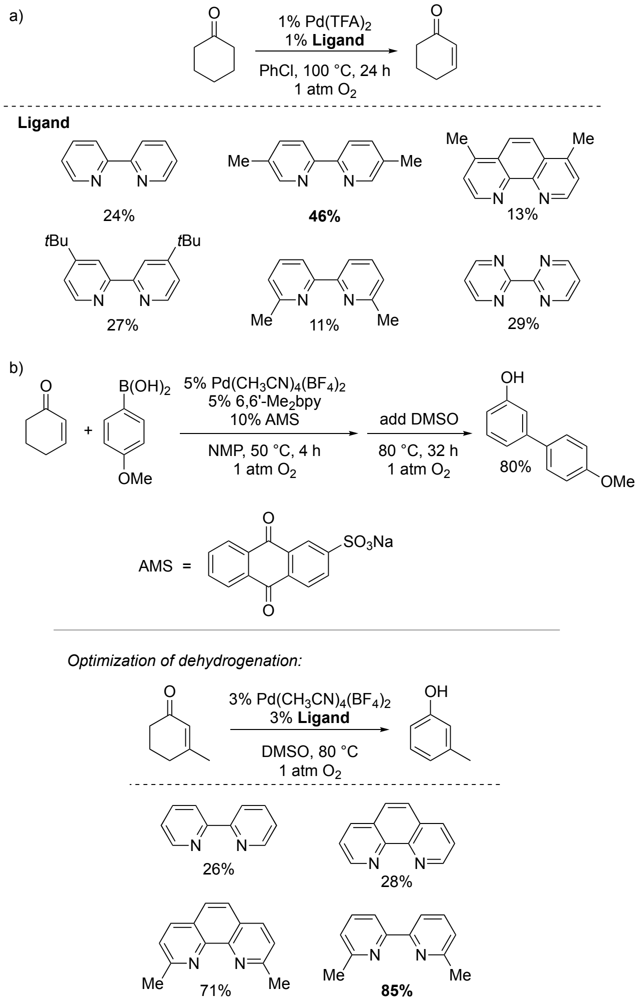
Scheme 58. DAF-ligated dimeric Pd^{I} species generated in allylic C–H acetoxylation and intramolecular aza-Wacker reactions. (Reprinted with permission from ref 281. Copyright 2017 John Wiley & Sons, Inc.)



5.1.3 Additional achiral chelating nitrogen Ligands

Other chelating nitrogen ligands have shown beneficial effects on aerobic oxidation reactions. In 2007, Tsuji and coworkers noted 5,5'-dimethylbipyridine performed the best among a number of bidentate nitrogen ligands in the dehydrogenation of cyclohexanone to cyclohexenone (Scheme 59a).[282] Inclusion of molecular sieves and allowing the reaction to proceed longer (48 h) led to an 84% yield of cyclohexenone. In 2013, Stahl and coworkers reported a sequential oxidative Heck/dehydrogenation reaction to afford *meta*-substituted phenols.[283] In the optimization of the dehydrogenation step, 6,6'-dimethylbipyridine (dmbpy) proved to be the optimal ligand (Scheme 59b). The beneficial effects of this ligand may arise from the ability of the dmbpy ligand to undergo more-facile κ^2–κ^1 interconversion, as described above (cf. Scheme 57c,d).[280]

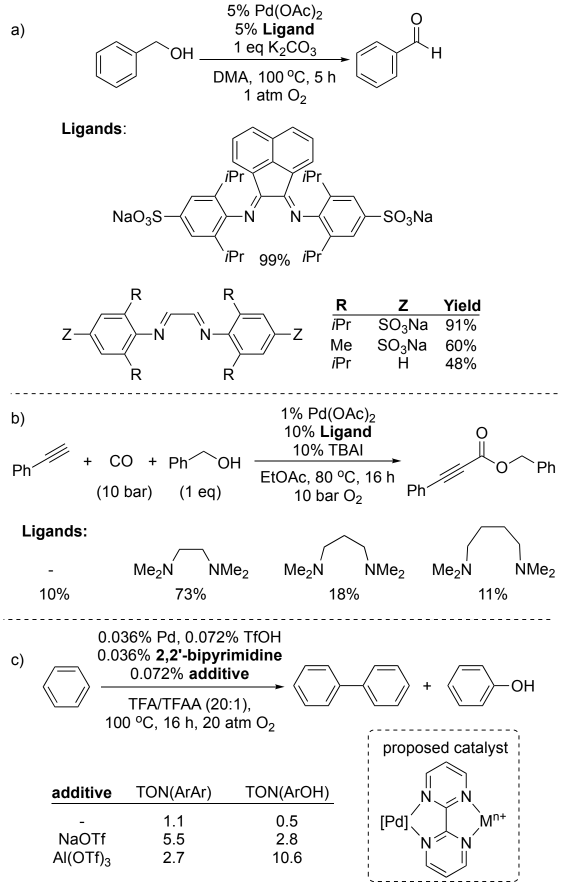
Scheme 59. Substituted-bpy-supported aerobic oxidations.



Diamines and diimines have also been used as ligands in Pd-catalyzed aerobic oxidations. In 2008, Sun investigated the effect of various α-diimine ligands in oxidation of benzyl alcohol. The optimal ligand featured a bis(aryl)acetenaphthenequinonediimine (BIAN) backbone and 4-sulfonate/2,6-diisopropyl substituents on the *N*-aryl groups (Scheme 60a).[284] In 2016, Muldoon and coworkers reported an oxidative alkoxycarbonylation reaction catalyzed by Pd/TMEDA.[285] Replacing the ethylene spacer in TMEDA with the corresponding three-carbon or four-carbon equivalents dramatically decreases the yield from 73% to less than 20% (Scheme 60b), suggesting that chelation of Pd is important for the reaction.

2,2'-Bipyrimidine typically is capable of bridging two metal centers, and this property has been implicated in Pd-catalyzed oxidation reaction. In 2009, Bercaw and Labinger reported a Pd/bpym catalyst system for allylic acetoxylation with stoichiometric benzoquinone as the oxidant. The optimal L:Pd ratio of 0.5:1 observed for this reaction was proposed to arise from a dimeric Pd species that serves as the active form of the catalyst.[286] In 2013, Yin and coworkers reported aerobic oxidative coupling of benzene to biphenyl using a Pd^{II}/Al^{3+}/bpym system (Scheme 60c).[287] The catalyst was proposed to feature the Lewis acidic Al^{3+} center coordinated backside of a (bpym)Pd(OAc)$_2$ species, thereby creating a more electron-deficient Pd center that would be more efficient in arene C–H activation.[288-290]

Scheme 60. Diimine, diamine and bipyrimidine-promoted aerobic oxidations



R	Z	Yield
*i*Pr	SO_3Na	91%
Me	SO_3Na	60%
*i*Pr	H	48%

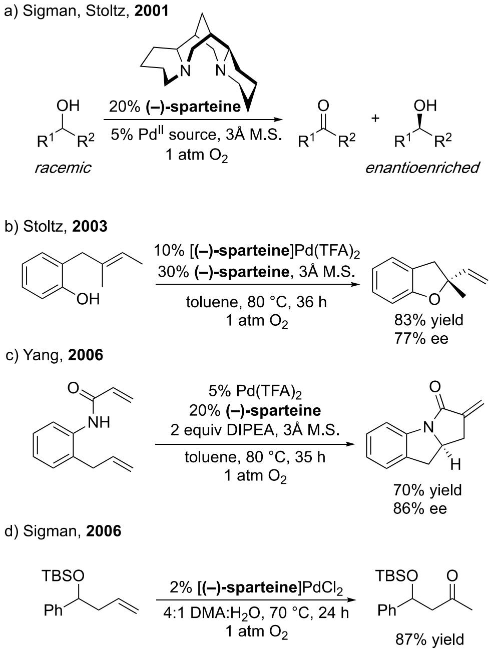
additive	TON(ArAr)	TON(ArOH)
-	1.1	0.5
NaOTf	5.5	2.8
$Al(OTf)_3$	2.7	10.6

5.2. Chiral bidentate ligands for asymmetric catalysis

5.2.1. (–)-Sparteine (sp)

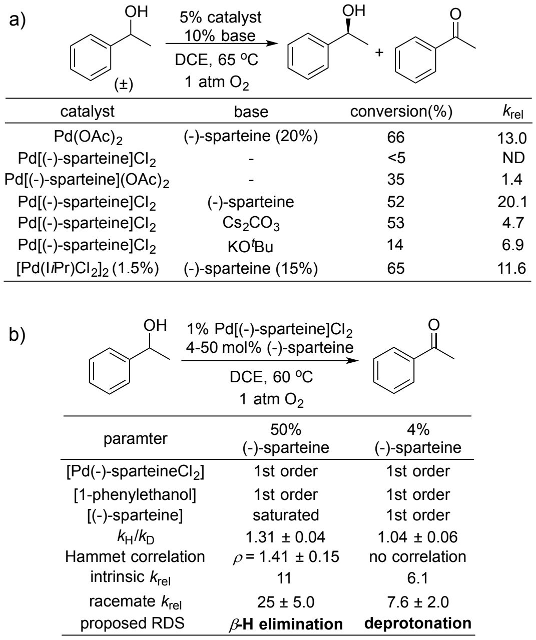
(–)-Sparteine (sp) is an alkaloid natural product that has been widely used as a chiral ligand and Brønsted base in many enantioselective reactions. Early examples of Pd/sparteine in asymmetric catalysis included non-oxidative allylic alkylation reactions, but only moderate enantioselectivity was observed (20-85% *ee*).[291, 292] In 2001, the research groups of Sigman and Stoltz independently reported that (–)-sparteine could promote palladium-catalyzed oxidative kinetic resolution of secondary alcohols (Scheme 61a).[293,294] In subsequent years, (–)-sparteine was used to support asymmetric Wacker-type cyclization reactions (Scheme 61b, c)[179,295,296] and Wacker oxidation of terminal alkenes (Scheme 61d).[297]

Scheme 61. (–)-Sparteine supported Pd-catalyzed aerobic oxidation reactions.



The groups of Sigman[298-303] and Stoltz[304-312] performed extensive synthetic and mechanistic studies of the kinetic resolution of secondary alcohols.[34] In the initial reports, an optimal sparteine:Pd ratio of 4:1 was identified.[293] This unusual ligand loading was shown to arise from sparteine acting as an exogenous base that deprotonates the secondary alcohol, in addition to serving as an ancillary ligand (Scheme 62a).[298] Subsequent studies showed that enantioselectivity could also be achieved by using a Pd^{II} salt and (–)-sparteine in combination with an achiral ligand[299] or an achiral base[300,304] (Scheme 62a). These observations highlighted the dual role of sp as a chiral ligand and Brønsted base. In 2003, Sigman and coworkers reported kinetic studies of this reaction.[298,302] The reaction rate exhibits saturation kinetics in [sp]. At low [sp], no isotope effects were observed with α-d_1-alcohol while at high [sp], a KIE of 1.3 was observed. Meanwhile, the reaction is 1st-order in [alcohol] at both low and high [sp]. These results led to a proposed switch in the rate-limiting step from alcohol deprotonation to β-H elimination upon increasing [sp] (Scheme 62b). Later findings provided a mathematical model showing how multiple factors contributed to the overall enantioselectivity, including competitive binding of the enantiomers of alcohol to Pd and the relative rate of β-H elimination and reprotonation of diastereomeric Pd-alkoxides with (–)-sparteine▪HCl.[302] The sparteine ligand was also shown to promote dissociation of a chloride ligand from the (sp)$PdCl_2$ complex, even in the non-polar solvent DCE (35% dissociation determined by conductivity test).[302] This property was proposed to facilitate substrate binding, thereby enabling good catalytic activity relative to other diamine ligands.

Scheme 62. Demonstration of the role of sparteine as an exogenous base and summary of kinetic observations of (sparteine)Pd-catalyzed oxidative kinetic resolution



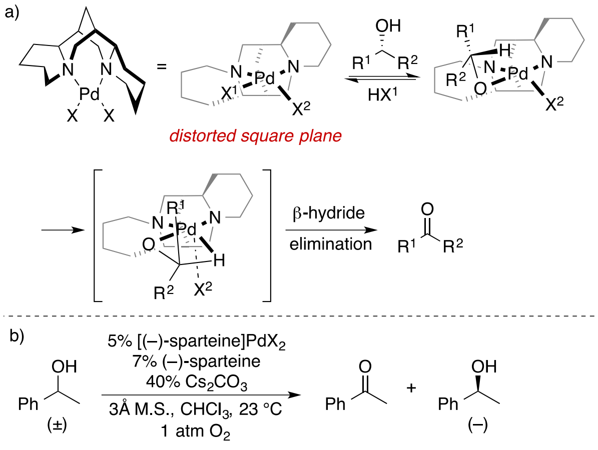
catalyst	base	conversion(%)	k_{rel}
$Pd(OAc)_2$	(-)-sparteine (20%)	66	13.0
Pd[(-)-sparteine]Cl_2	-	<5	ND
Pd[(-)-sparteine]$(OAc)_2$	-	35	1.4
Pd[(-)-sparteine]Cl_2	(-)-sparteine	52	20.1
Pd[(-)-sparteine]Cl_2	Cs_2CO_3	53	4.7
Pd[(-)-sparteine]Cl_2	KO^tBu	14	6.9
$[Pd(I^iPr)Cl_2]_2$ (1.5%)	(-)-sparteine (15%)	65	11.6

paramter	50% (-)-sparteine	4% (-)-sparteine
[Pd(-)-sparteineCl_2]	1st order	1st order
[1-phenylethanol]	1st order	1st order
[(-)-sparteine]	saturated	1st order
k_H/k_D	1.31 ± 0.04	1.04 ± 0.06
Hammet correlation	ρ = 1.41 ± 0.15	no correlation
intrinsic k_{rel}	11	6.1
racemate k_{rel}	25 ± 5.0	7.6 ± 2.0
proposed RDS	**β-H elimination**	**deprotonation**

Stoltz and coworkers demonstrated the importance of the X-type ligand of the Pd catalyst in determining the overall enantioselectivity. X-ray crystallographic analysis of (sp)PdX_2

complexes showed that the C_1-symmetric chiral sparteine ligand distorts the Pd^{II} coordination sphere, shifting one of the anionic ligands (typically chloride) out of the square plane[311]In the proposed mechanism, the alcohol coordinates to the more sterically accessible position, displacing the in-plane X^1 ligand, while the more distorted X^2 ligand is displaced later during β-H elimination (Scheme 63a). The distorted square planar conformation was proposed to accelerate the rate of alcohol oxidation by mimicking the transition state of β-hydride elimination, which had been previously probed by DFT studies.[307] To test this hypothesis, Stoltz and coworkers compared (sp)PdX_2 catalysts where X = Cl or Br. The larger bromide ion resulted in complexes with more distorted square planar conformations and led to a substantial rate enhancement, while maintaining good selectivity in the kinetic resolution reaction (Scheme 63b).[309]

Scheme 63. Sparteine promoted kinetic resolution of alcohols exhibits a rate enhancement due to a distorted square planar conformation at palladium

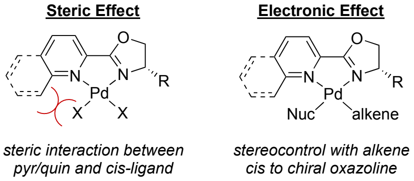


X	time (h)	% conv.	%ee alcohol
Cl	48	60	99
Br	4	56	86

5.2.2. Pyridine-oxazoline (pyrox) and quinoline-oxazoline (quinox)

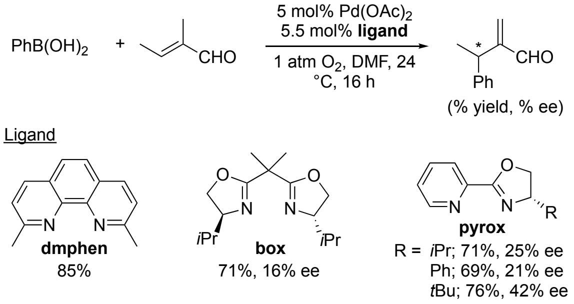
Pyridine-oxazoline (pyrox) and quinoline-oxazoline (quinox) ligands have emerged as a common ligand class in asymmetric aerobic oxidation reactions. This ligand class is especially appealing because either enantiomer of the chiral oxazoline moiety is readily synthesized from the corresponding amino acid. The quinox and pyrox ligand frameworks have steric bulk adjacent to the chelating nitrogen atoms, similar to the dmphen and sparteine ligands discussed above. The substituents in these positions cause distortions in the square-planar coordination environments, leading to ground-state destabilization of the Pd^{II} complexes relative to those with traditional unsubstituted bpy or phen ligands (Scheme 64, left). [266,313,314] Additionally, the two different nitrogen heterocycles quinox and pyrox ligands create an electronically unsymmetrical coordination environment owing to the stronger *trans* influence of the oxazoline relative to the pyridine ligand. This feature favors the binding strong-field substrate ligands, such as alkenes, *trans* to the quinoline (or pyridine) and adjacent to the chiral oxazoline, thereby contributing to the high level of stereocontrol observed in the reactions described below.

Scheme 64. Pyrox and quinox ligands distort the square planar geometry at palladium and provide electronic asymmetry through the pyridyl and oxazoline coordination.



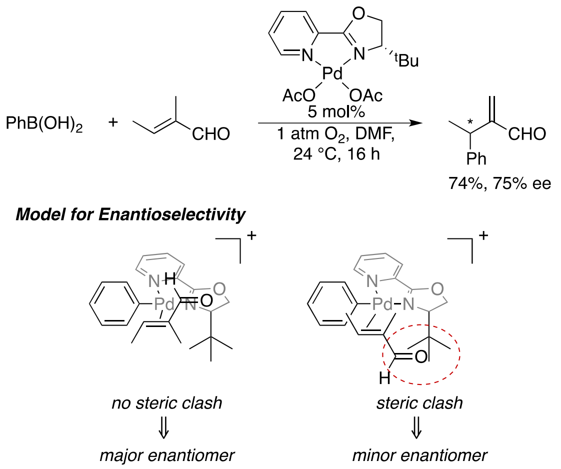
In 2007, Jung reported an aerobic palladium-catalyzed asymmetric Heck coupling between arylboronic acids and electron-deficient olefins (Scheme 65).[315] Upon observing good reactivity with dmphen as the ligand, the authors tested enantioselectivity with chiral *bis*-oxazoline (box) and pyrox ligands. Relatively good yields were obtained with a number of ligands, but the highest enantioselectivity was obtained with *t*Bu-substituted pyrox ligand.

Scheme 65. Ligand-promoted asymmetric oxidative Heck reactions.



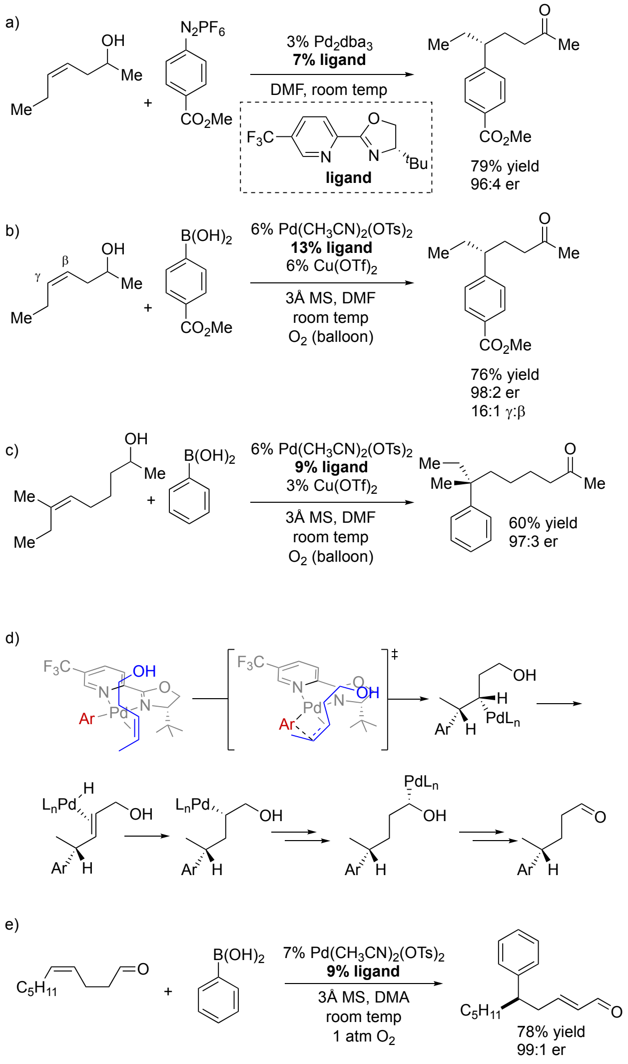
The moderate levels of enantioselectivity (≤ 42% ee) was attributed to inefficient complexation of the ligand, allowing for a non-selective background reaction. Pre-formation of the catalyst enabled ee values of >70% to be obtained (Scheme 66). The carbopalladation transition state was proposed to occur from a cationic Pd complex and enantioselectivity was attributed to the steric interaction between the olefin and the *tert*-butyl group on the oxazoline.

Scheme 66. Pyrox-promoted asymmetric oxidative Heck reactions.



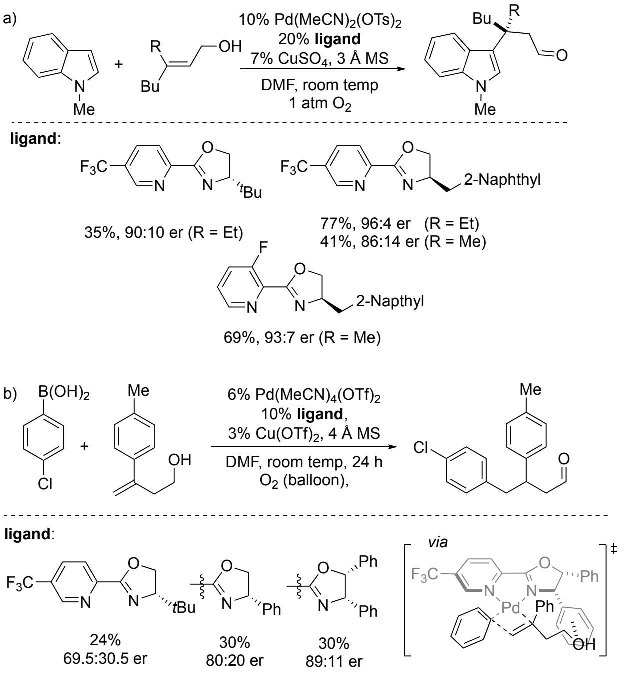
In 2012, Sigman reported non-oxidative asymmetric Heck reactions that incorporate "redox-relay" migration of the alkene functionality to generate a carbonyl group from a remote alcohol group, yielding a new stereogenic center at the site of C–C bond formation (Scheme 67a).[316] A multidimensional parameter-based optimization strategy was used to identify the optimal electron-deficient pyridine-oxazoline ligand for these reactions.[317,318] A similar approach was then used in aerobic oxidative coupling reactions with arylboronic acids (Scheme 67b).[319] Later, trisubstituted alkenyl alcohols were shown to be effective reaction partners in asymmetric oxidative Heck reactions, enabling generation of quaternary carbon centers with excellent enantioselectivity (Scheme 67c).[320] Experimental[321] and computational[322] mechanistic studies led to a model for stereocontrol in which the alkene binds *cis* to the oxazoline, and the *tert*-butyl group directs facial selectivity during migratory insertion of the alkene (Scheme 67d). A series of β-hydride-elimination/alkene-insertion events allows migration of the Pd center along the alkyl chain. The electrophilicity of the Pd-center, which is enhanced by the relatively electron deficient trifluoromethyl-substituted pyrox ligand, disfavors dissociation of the alkene adduct prior to re-insertion of the Pd–H species. This relay process is driven by the stabilizing effect that the electron-withdrawing alcohol functional group has on the Pd-alkyl species as it moves down the alkyl chain, and the process terminates when the Pd-alkoxide species undergoes β-hydride elimination and releases the carbonyl product. When an aldehyde is already present in the starting material, the pyrox-promoted redox-relay reaction affords the α,β-unsaturated aldehyde product (Scheme 67e). [323]

Scheme 67. Pyrox-promoted asymmetric redox-relay Heck reactions.



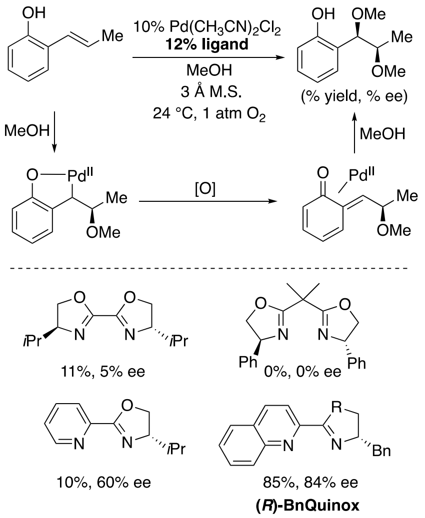
Sigman and coworkers have developed several new pyrox-based ligands using structure-enantioselectivity correlations. For example, the presence of a 2-naphthylmethyl group on the oxazoline side chain led to increased yield and enantioselectivity for the coupling between *N*-methyl indole and a trisubstituted alkenyl alcohol (Scheme 68a).[324] A ligand structure-enantioselectivity study led to discovery of the optimal ligand with a 5-F substituent on the pyridine ring. With 1,1-disubstituted homoallylic alcohols, phenyl groups on the oxazole fragment of the pyrox ligand proved crucial to enable good enantioselectivity. These observations were attributed to π-stacking or lone-pair/π interactions between the ligand aryl group and the aryl or alcohol motifs in the substrate (Scheme 68b).[325]

Scheme 68. Redox-relay Heck arylation supported by modified pyrox ligands



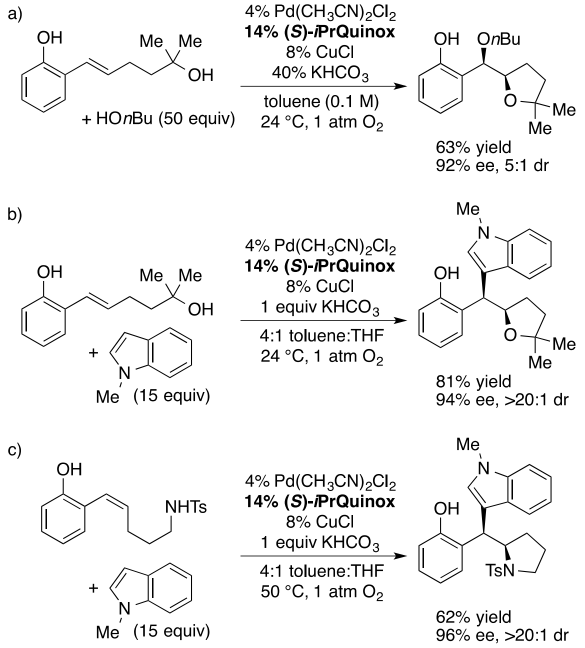
In 2007, Sigman reported an asymmetric Wacker-type dialkoxylation of *ortho*-vinyl phenols.[326] A quinone methide species, formed after initial oxypalladation of the alkene, undergoes diastereoselective nucleophilic attack by a second equivalent of alcohol (Scheme 69). The enantioselective variant of the reaction was realized by using a chiral quinox ligand. Other ligands, including various bioxazoline (biox), bisoxazoline (box) and pyrox ligands, were screened but resulted in lower yield or enantioselectivity.

Scheme 69. Quinox-supported asymmetric dialkoxylation of *ortho*-vinyl phenols.



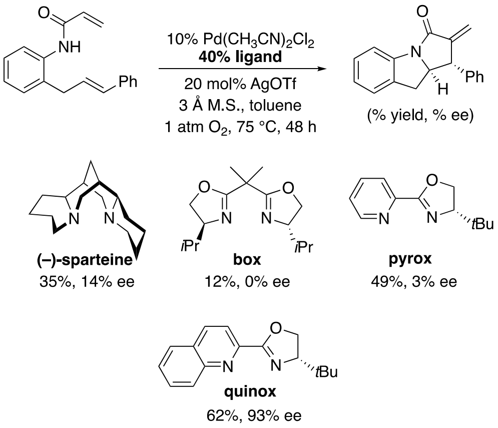
The authors noted that in the absence of quinox, using $CuCl_2$ as cocatalyst can promote catalytic turnover.[327] However, addition of $CuCl_2$ with the quinox-ligated Pd^{II} catalyst system eroded enantioselectivity and had negligible effect on turnover numbers, presumably due to competitive binding of the chiral ligand to Cu^{II}. This finding indirectly indicates that the bidentate quinox ligand is able to stabilize the Pd^0 species and promote its reoxidation in the absence of a redox cocatalyst. Avoiding the Cu cocatalyst allows for well-defined, selective asymmetric catalysis. Subsequent studies by Sigman and coworkers expanded the scope of these transformations by initiating the reaction via intramolecular Wacker-type cyclization reaction to enable addition of different nucleophiles across the alkene, including alcohol (Scheme 70a), indole (Scheme 70b), and amine derivatives (Scheme 70c).[328-330] These studies revealed that copper cocatalysts could provide a beneficial effect on reactivity without degrading the enantioselectivity if sufficient quantities of chiral ligand were employed to bind both palladium and copper species. Mechanistic experiments established that ligand exchange between palladium and copper is fast under these conditions, and kinetic studies provided evidence for the involvement of copper in substrate oxidation steps.[331] The role of copper in these reactions is thus more complicated than in traditional mechanistic manifolds for Pd/Cu-cocatalyzed aerobic oxidation reactions, wherein copper is simply a redox cocatalyst that mediates aerobic oxidation of Pd^0 to Pd^{II}.

Scheme 70. Quinox-supported asymmetric difunctionalization of *ortho*-vinyl phenols.



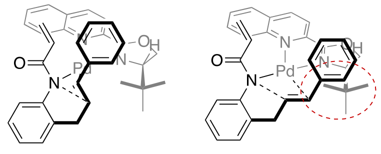
In 2009, Yang reported an improved catalyst system for the asymmetric aza-Wacker cyclization/annulation of *ortho*-allyl anilides.[332] The previously-reported Pd/sparteine catalyst (cf. Scheme 61c), led to poor results with these internal-alkene-containing substrates. Further screening efforts showed that bisoxazoline and pyrox ligands are also ineffective, but quinox ligands provided moderate yield and good *ee* (Scheme 71).

Scheme 71. Quinox-supported asymmetric aza-Wacker cyclization/annulation reaction.



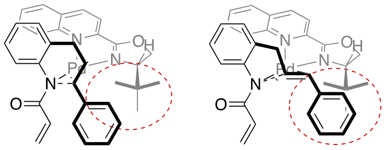
A variety of substrates were investigated and each exhibited modest to good yield and ≥80% *ee*. The absolute configuration of one of the products was determined by X-ray crystallography and the outcome indicated that the reaction proceeded via a sequence of *cis*-amidopalladation of the internal alkene, followed by *cis*-carbopalladation of the terminal alkene. A stereochemical model was proposed in which the alkene coordinates *trans* to the quinoline moiety and therefore experiences the full effect of the chiral steric group on the oxazoline ligand (Scheme 72). This steric interaction favors one of four possible alkene orientations, which undergoes amidopalladation to afford the observed enantiomeric product.

Scheme 72. Stereochemical model for enantioselective *cis*-amidopalladation of the alkene.



Major Enantiomer
Favored TS

Minor Enantiomer
Disfavored TS



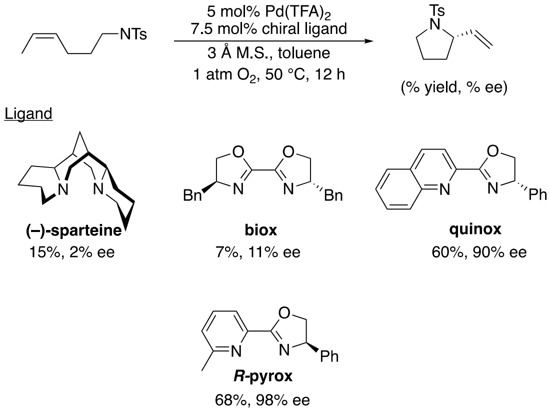
Minor Enantiomer
Disfavored TS

Major Enantiomer
Disfavored TS

Sigman and coworkers conducted systematic Hammett studies to gain insights into the coordination environment on the Pd-quinox complex in the context of Wacker oxidation with *tert*-butylhydroperoxide as the oxidant.[333] Faster reaction rate was observed with more electron-rich alkene substrates ($\rho = -1.29$) and more electron-deficient quinoline fragments ($\rho = 0.88$) of the quinox ligand. By comparison, electronic variation of the pyridine fragment of a pyridine-quinoline ligand (to mimic the oxazoline in quinox) revealed a negative correlation ($\rho = -0.60$). Collectively, these data led the authors to suggest that the preferred configuration of the (quinox)Pd(alkene)(X) intermediate features the alkene coordinated *trans* to the quinoline ring.

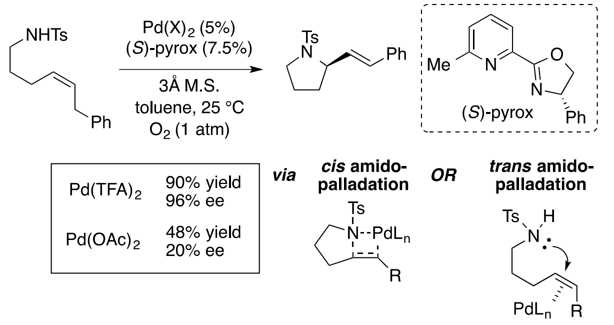
In 2011, Stahl reported a related pyrox-promoted asymmetric aza-Wacker cyclization reaction with γ-alkenyl sulfonamides to produce pyrrolidines.[334,335] Biox and (–)-sparteine ligands resulted in poor yield and enantioselectivity while quinox and pyrox ligands provided moderate-to-good yield and good-to-excellent enantioselectivity (Scheme 73). Pyrox ligands proved superior to the quinox ligands, giving >95% *ee* and improved yields at ambient temperatures.

Scheme 73. Enantioselective aza-Wacker cyclization reactions.



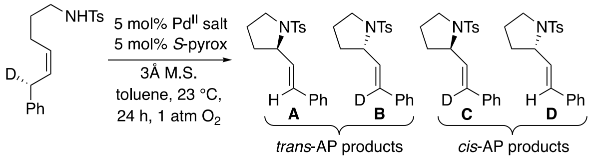
During the course of these studies, it was noted that the enantioselectivity of the aza-Wacker cyclization reaction was dramatically influenced by the identity of the Pd^{II} salt employed. Use of $Pd(TFA)_2$ enabled high *ee* and yield, whereas use of $Pd(OAc)_2$ led to significantly reduced *ee* and yield (Scheme 74).

Scheme 74. Divergent stereochemical mechanisms for enantioselective aza-Wacker cyclizations.



The distinct outcomes with $Pd(TFA)_2$ and $Pd(OAc)_2$ were proposed to arise from different mechanisms for the key amidopalladation steps, and a mechanistic study was carried out to probe the stereochemical course of amidopalladation.[336] A chiral, enantiopure deuterated substrate was used to probe the *cis* vs *trans* amidopalladation pathway (Table 1). Diminished enantioselectivity with Pd(OAc)$_2$ correlated with a switch in the predominant stereochemical pathway from *trans*- to *cis*-amidopalladation (entries 1-2), and both Pd(TFA)$_2$ and Pd(OAc)$_2$ favored the *cis*-amidopalladation pathway when the reaction was performed in the absence of ancillary ligand (entries 3-4). These results illustrate the ability of the neutral and ionic ligands to control both the relative and absolute stereochemical pathway in Pd^{II}-catalyzed (Wacker-type) alkene functionalization.

Table 1. Determination of the stereochemical course of amidopalladation in enantioselective aza-Wacker cyclization reactions.



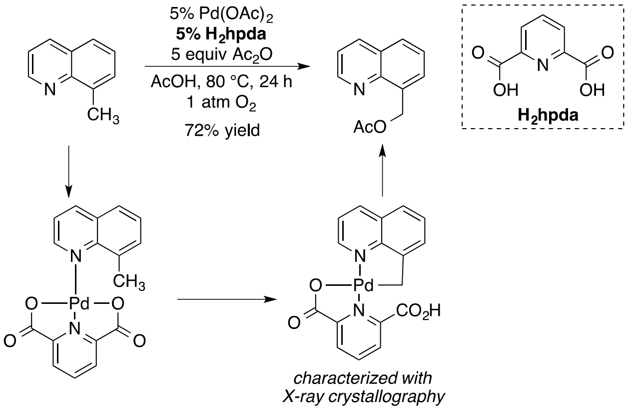
entry	PdX$_2$ (5%)	ligand (7.5%)	% yield	% ee	**A** : **B** : **C** : **D**	*trans* : *cis* -AP
1	Pd(TFA)$_2$	(*S*)-pyrox	90	96	91 : 0 : 7 : 2	>9 : 1
2	Pd(OAc)$_2$	(*S*)-pyrox	48	20	9 : 1 : 51 : 39	1 : 9
3	Pd(TFA)$_2$	none	55	0	8 : 8 : 42 : 42	1 : 6
4	Pd(OAc)$_2$	none	15	0	3 : 3 : 47 : 47	<1 : 9

5.3 Bidentate LX Ligands

In addition to L$_2$-type bidentate ligands in which both coordinating atoms are neutral donors, LX-type ligands, incorporating both neutral and anionic donor groups, have also been used as effective ligand classes in aerobic Pd-catalyzed oxidation reactions. An important feature provided by the LX ligand structure is that the anionic fragment can participate in key catalytic steps involving proton transfer, such as activation of substrate C–H and/or N–H bonds.

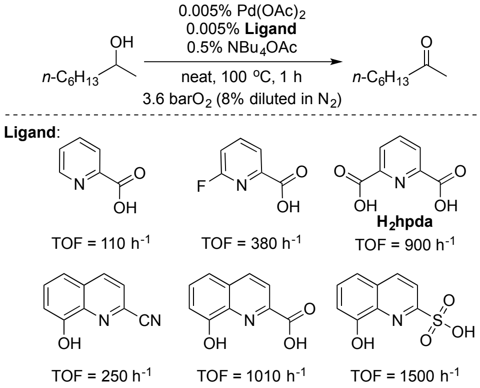
In 2008, Vedernikov reported a method for sp^3 C–H acetoxylation of 8-methyl quinolines in the presence of dipicolinic acid (H_2hpda) as the ligand (Scheme 75).[337] In the absence of ligand, the reactions gave only trace product. The intermediate complex that resulted from C–H activation of 8-methylquinoline was characterized by X-ray crystallography. Stoichiometric, kinetic and computational studies provided evidence for a mechanism in which one of the chelating carboxylates of the H_2hpda ligand facilitates C–H activation of 8-methylquinoline by a cyclometallation-deprotonation pathway.[338]

Scheme 75. Dipicolinic acid supported C–H acetoxylation.



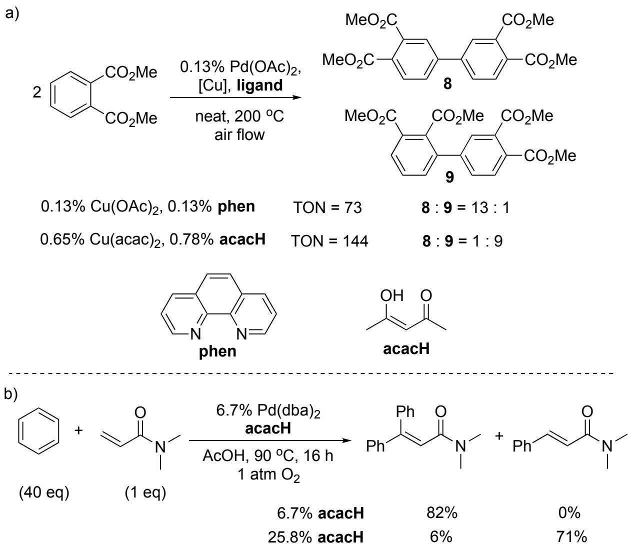
In 2010, Muldoon and coworkers surveyed numerous pyridine and quinoline-based LX and LX_2 ligands for their activity in Pd-catalyzed aerobic oxidation of 2-octanol. H_2hpda supported the highest catalytic activity among all the pyridine ligands tested, but ligands derived from 8-hydroxyquinoline bearing 2-carboxylic acid and 2-sulfonic acid groups exhibited even better performance, with catalyst activities of >1000 turnovers per hour (Scheme 76).[339] Analogous observations were later reported by Cámpora and coworkers.[340] Replacing the carboxylic acid group in the optimal ligands with other electron-withdrawing groups such as fluoro or cyano groups dramatically decreased the turnover frequency. The acidic groups on the ligand were proposed to participate in proton shuttling or hydrogen bonding in key catalytic steps. The optimal sulfonic-acid-substituted ligand was later shown to support oxidation of a range of secondary aliphatic alcohols.[341]

Scheme 76. 8-hydroxyquinoline-2-sulfonic acid-supported aerobic alcohol oxidation



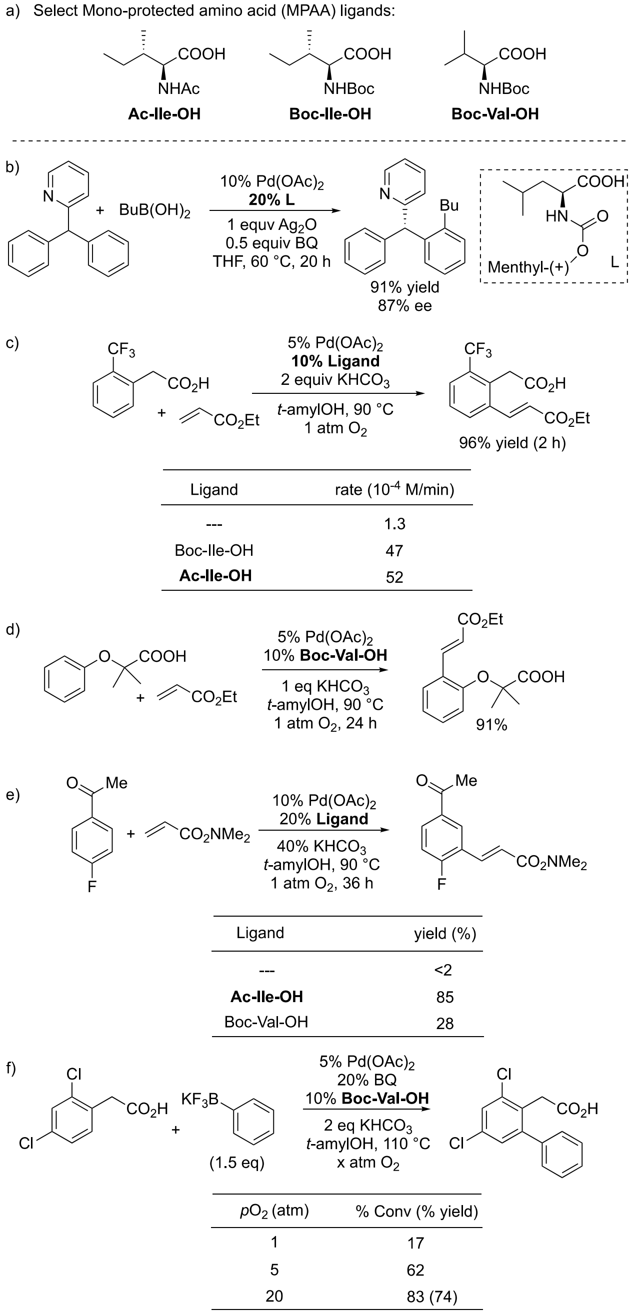
Acetoacetone (acacH) has been used as an additive in aerobic oxidations and has been proposed to participate as an LX ligand. In the 1980s, researchers from Ube Industries investigated the oxidative homocoupling of dimethyl phthalate and found that addition of acac leads to a switch in regioselectivity, favoring formation of the unsymmetrical 2,3,3',4'-tetramethyl biphenyltetracarboxylate (Scheme 77a, cf. Scheme 42a).[240,242] In 2013, Obora and coworkers reported an oxidative Heck reaction with a Pd/acac catalyst system. Either monoarylated or diarylated product were obtained in high yields, depending on the acacH:Pd ratio from 1:1 to 4:1 (Scheme 77b).[342] The origin of selectivity effects was not determined in these cases, but, in the latter example, high [acac] could inhibit catalytic activity and thereby minimize arylation of the sterically more-encumbered monoarylated intermediate.

Scheme 77. Effects of acetoacetone on aerobic C–C coupling reactions



In 2008, Yu introduced mono-protected amino acids (MPAAs) as an effective ligand class for Pd-catalyzed C–H functionalization (Scheme 78a).[343] The first report of MPAA/Pd-catalyzed C–H functionalization involved desymmetrization of diphenyl(2-pyridyl)methane via directed C–H alkylation with alkyl boronic acids (Scheme 78b). This report represented a major advance over work by Solokov and coworkers decades earlier showing that amino-acid-derived carboxylates could promote stoichiometric cyclopalladation of an aminomethylferrocene derivative with moderate *ee*.[344,345] Over the past decade, MPAA ligands have been applied to a diverse array of C–H functionalization reactions, as summarized in two recent reviews by Engle[346] and Yu.[56] Many of these reactions consist of oxidation methods, and, while most use stoichiometric Ag^I salts, BQ, or related stoichiometric oxidants (cf. Scheme 78b), a number of examples have been demonstrated with O_2.[347-361] The first aerobic example, reported by Yu and coworkers, featured a Fujiwara-Moritani-type dehydrogenative coupling of phenylacetic acid derivatives and acrylates (Scheme 78c).[347] Subsequent aerobic examples included olefination of various arenes with different directing groups, including aryl ethers with pendant carboxylic acids (Scheme 78d)[351] or pyridylmethyl groups,[352] *N,N*-dimethylaminomethylferrocenes,[353,354] phenylglycine and mandelic acid derivatives,[355] and phenethylamine derivatives.[356] Non-directed C–H olefination of electron-deficient arenes and pyridines (Scheme 78e),[357] benzofurans[358] and polyfluoroarenes[359] have also been achieved. Most Pd/MPAA-catalyzed reactions compatible with O_2 consist of C–H olefinations; however, two examples of directed C–H arylation with aryl boronic reagents have been reported, the first by Yu and coworkers (Scheme 78f)[360] and a later example by You and coworkers.[361] In the former case, use of a BQ cocatalyst was important to stabilize the Pd catalyst, and higher pressures of O_2 led to significantly increased conversion (Scheme 78f). These observations contrast to analogous olefination reactions, which do not require BQ and achieve high turnover numbers in the presence of low O_2 pressure (air or 1 atm O_2), and they suggest that the alkene substrate in olefination reactions (typically, an acrylate or related electron-deficient alkene) plays an important role in stabilizing Pd^0 by acting as an ancillary ligand or otherwise facilitating catalyst reoxidation by O_2.[94]

Scheme 78. Mono-protected amino acids and representative Pd/MPAA-catalyzed C–H oxidation reactions



Ligand	rate (10^{-4} M/min)
---	1.3
Boc-Ile-OH	47
Ac-Ile-OH	52

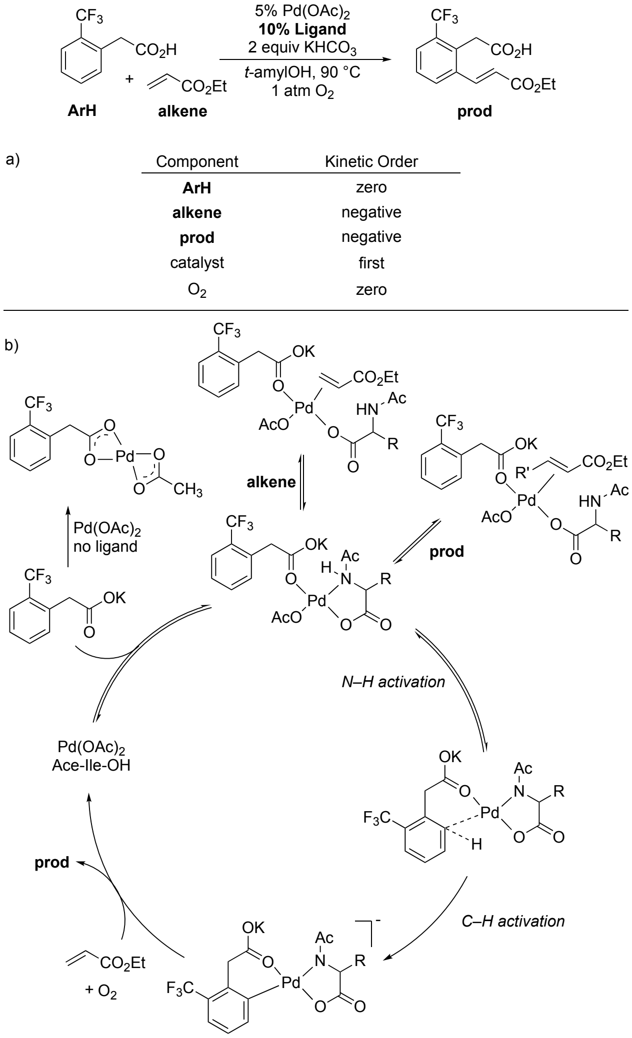
Ligand	yield (%)
---	<2
Ac-Ile-OH	85
Boc-Val-OH	28

pO_2 (atm)	% Conv (% yield)
1	17
5	62
20	83 (74)

Insights into the beneficial effect of MPAA ligands have been gained from kinetic and computational studies. Initial studies focused on the C–H olefination of phenylacetic acid derivatives, which used Ac-Ile-OH as the optimal ligand. In 2010, Yu and coworkers noted that addition of Ac-Ile-OH to the reaction significantly enhanced the rate (cf. Scheme 78c).[348] Competition studies revealed that the relative reactivity of 6-CH_3- and 6-CF_3-substituted phenylacetic acid derivatives and the magnitude of the kinetic isotope effect obtained from parent and perdeutero- *o*-tolylacetic acid differed significantly in the presence and absence of Ac-Ile-OH. These data indicated that the MPAA ligand has a significant influence on the C–H activation step.

In 2012, Blackmond and coworkers reported a thorough mechanistic study of this reaction.[362] Kinetic data revealed a rate law for the olefination reaction that is first-order in [Pd], zeroth-order in phenylacetic acid and O_2, and negative order in [olefin] and [product] (Scheme 79a). NMR spectroscopic data indicated that both MPAA and the phenylacetic acid substrate coordinate to Pd in the resting-state of the catalyst. Substrate and product alkenes coordinate reversibly to Pd to form off-cycle reservoirs of the catalyst. These results, together with KIE data,[348] led to a mechanistic proposal in which the active catalyst is generated by alkene dissociation from substrate- and/or product-bound MPAA-ligated Pd^{II} species, followed by turnover-limiting C–H activation (Scheme 79b).[362] Coordination of the MPAA ligand to Pd was proposed to prevent formation of inactive Pd^{II} mixed carboxylate species. A parallel computational study by Musaev, Yu and coworkers of a related MPAA-promoted reaction accounted for the proposal that the ligand N–H bond is deprotonated prior to aryl C–H activation.[363] Recent mass-spectrometry data has provided evidence for MPAA ligation to the Pd catalyst resting state.[364]

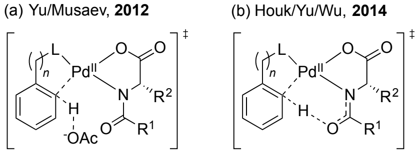
Scheme 79. Proposed mechanism for amino acid supported aryl C–H olefination reactions



Component	Kinetic Order
ArH	zero
alkene	negative
prod	negative
catalyst	first
O_2	zero

The mechanistic features of Pd/MPAA-mediated C–H cleavage have been the subject of considerable recent study by DFT computational methods. In the aforementioned study by Musaev and Yu,[363] the C–H cleavage step was proposed to involve an external carboxylate as the base (Scheme 80a). A more recent computational study by Houk, Yu, Wu and coworkers of a related MPAA-promoted aryl C–H functionalization method proposed that the *N*-acyl fragment in the amino acid ligand participates as an internal base in a concerted-metalation-deprotonation of the aryl C–H bond (Scheme 80b).[365] This proposal suggests the amino acid ligand facilitates the key C–H activation step while remaining bound to the Pd center. The authors noted that the *N*-acyl (amidate) fragment has higher basicity than acetate, which could account for the rate enhancement observed in these reactions relative to a simple Pd(OAc)$_2$ catalyst. The preferred pathway, internal versus external deprotonation, could potentially depend on the specific reaction conditions, substrate or other features of the reaction. For example Musaev has recently noted the role of the basicity of the carbonyl group of the MPAA ligand and non-covalent interactions between the Pd/MPAA species and free anions in solution[366] as factors that could contribute to a preferred pathway.

Scheme 80. Proposed transition states for Pd/MPAA-mediated C–H activation

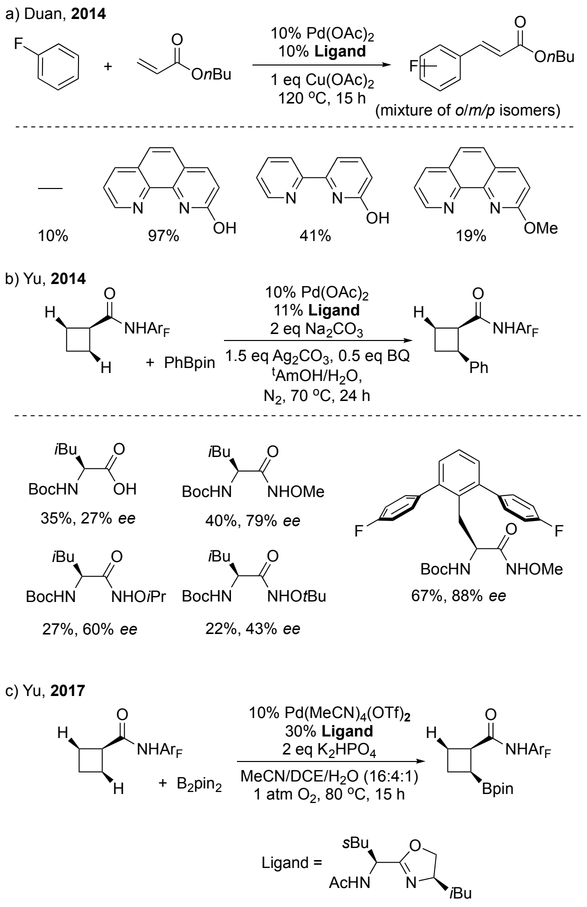


The above studies suggest that MPAA ligands could serve as LX- or as X$_2$-type ligands. The preferred binding mode during catalysis is conceivably influenced by factors such as whether the substrate binds to Pd with a neutral or anionic directing group or the polarity of solvent. For example, the ability of the amino acid ligand to bind as a dianionic (X$_2$) ligand opens coordination sites for weakly binding neutral substrates, such as nitriles, which have been used as directing groups in remote functionalization reactions.[367-369] Facile interchange between different protonated states and participation in proton shuttling between the ligand and substrate probably contribute to the success of MPAA ligands in Pd-catalyzed C–H activation reactions.

A few other LX-type ligands have been shown to be effective in Pd-catalyzed aerobic oxidation reactions. Duan and coworkers observed the unique effect of 2-hydroxy-1,10-

phenathroline on the oxidative Heck coupling between fluorobenzene and acrylate (Scheme 81a),[370] whereas the bpy and 2-methoxy analogs are less effective. Yu and coworkers reported that replacing MPAA with mono-protected amino *O*-methyl hydroxamic acid (MPAHA) derivatives as the ligand, presumably causing stronger coordination with Pd^{II}, led to an increase in enantioselectivity in asymmetric β-arylation of cyclic carboxamides (Scheme 81b).[371] The related β-borylation reaction has also been developed using acetyl-protected aminomethyl oxazoline (APAO) as ligand, another MPAA analog (Scheme 81c).[372]

Scheme 81. Oxidations supported by 2-hydroxyphenanthroline, MPAHA and APAO

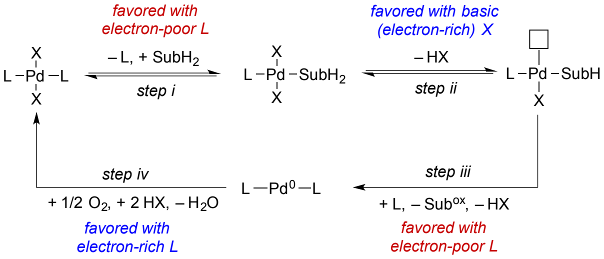


6. Conclusions and Outlook

The content presented above highlights the diverse array of ligands that have been shown to influence Pd-catalyzed aerobic oxidations. Many of these ligands have been identified empirically; however, mechanistic studies are increasingly providing insights into the origin of certain ligand effects, and several trends have begun to emerge that could contribute to the use and/or design of ligands for new aerobic Pd catalysis.

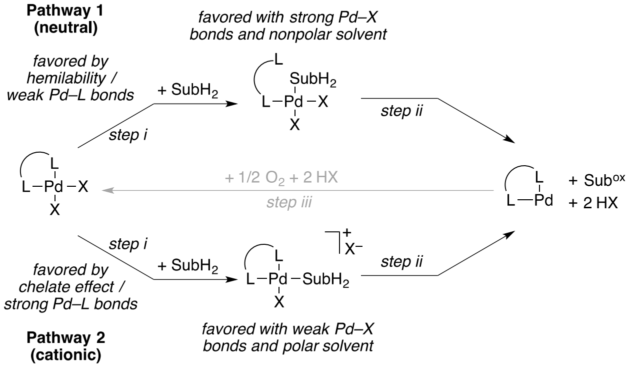
The beneficial effect of monodentate neutral donor ligands in palladium-catalyzed aerobic oxidation reactions is controlled by several competing considerations, as illustrated in Scheme 82. Substrate activation at Pd^{II}, especially with monodentate ancillary ligands, is typically initiated by displacement or dissociation of a neutral ancillary ligand (*step i*), and this ligand-substitution reaction is more facile when the ligand is weakly coordinating. The coordinating ability of the ancillary ligand may be influenced by electronic effects (as with electron-deficient pyridines) or through steric effects (as with 2,6-dialkylpyridines, quinolines, and acridine versus pyridine). A basic (electron-rich) X-type ligand often participates in deprotonation of the substrate to generate a key intermediate, as in the formation of Pd^{II}–alkoxide or Pd^{II}–aryl species en route to alcohol oxidation or C–H functionalization (*step ii*). Substrate oxidation (*step iii*) is also promoted by electron-poor L-type ligands, as more-electrophilic Pd^{II} centers facilitate the transfer of electron density from the substrate to the metal center, thereby promoting key steps, such as nucleophilic addition to alkenes, β-hydride elimination and reductive elimination. Meanwhile, catalyst stability and reoxidation by O_2 tends to benefit from stabilization of Pd^0 by more-electronic rich ligands that increase the electron density on Pd^0 (*step iv*). Catalyst decomposition by aggregation of Pd^0 into metallic Pd is among the most significant challenges in the development of aerobic oxidation methods and could account for the prevalence of examples that employ coordinating solvents or relatively strongly coordinating (and oxidatively stable) pyridine and carbene ligands.

Scheme 82. Overview of the contributions of monodentate ligands for Pd catalysts in aerobic oxidation reactions.



Optimal bidentate (L2-type) ancillary ligands for palladium-catalyzed aerobic oxidation reactions exhibit characteristics that are somewhat different from the monodentate ligands (Scheme 83), and two general pathways are relevant. In pathway 1, substrate coordination (*step i*) involves partial dissociation of the ligand and forms a neutral Pd^{II}-substrate species that leads to substrate oxidation (*step ii*). Bidentate ligands that are susceptible to hemilability, such as diazafluorenone and 6,6'-dimethylbipyridine, allow substrate oxidation to proceed in non-polar solvents via pathway 1. In pathway 2, substrate coordination (*step i*) requires dissociation of an X-type ligand and leads to formation of a cationic Pd^{II} species that mediates substrate oxidation. Strong chelation favors pathway 2 and is likely involved with bidentate ligands such as 2,9-dimethylphenanthroline. At least one weakly coordinating (i.e., non-basic) X-type ligand and/or polar solvents will facilitate the formation of the cationic intermediate. In both pathways, the bidentate ligand is able to support reoxidation of Pd^0 by molecular oxygen and thereby enhance catalyst stability.

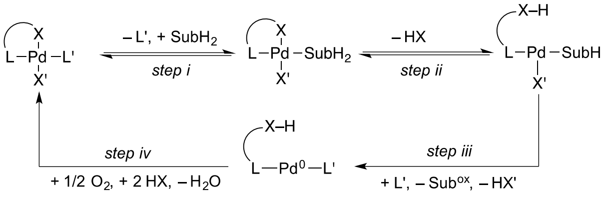
Scheme 83. Overview of the contributions of of bidentate ligands for Pd catalysts in aerobic oxidation reactions.



Bidentate ligands are appealing in efforts to control of reaction selectivity, including regio and stereoselectivity. The bidentate ligand framework provides a rigid steric (and potentially chiral) scaffold around the Pd center, as demonstrated in examples of bidentate ligands that promote highly regioselective reactions (e.g., dmphen, in regioselective oxidative Heck coupling) or enantioselective reactions (e.g., with pyridyl-oxazolines in oxidative Heck and Wacker-type reactions with alkenes).

Bidentate L–X ligands exhibit unique characteristics relative to both mono- and bidentate neutral donor ligands (Scheme 84). These ligands chelate Pd, but substrate binding (*step i*) does not necessarily require generation of a charged species or perturbation of the chelating ligand. The substrate could undergo displacement of a labile L-type ligand (L' in Scheme 84). Furthermore, the X-type ligand could contribute to proton transfer steps during substrate activation (*step ii*), as has been implicated for MPAA ligands. Although the reactivity of O_2 with LX-ligated Pd^0 complexes has not been studied directly, it is plausible that the pendant protonated ligand could contribute to catalyst reoxidation (*step iv*), similar to the manner in which acetic acid has been proposed to play a role with the $(py)_2Pd(OAc)_2$ catalyst system, on the basis of DFT calculations.[96]

Scheme 84. Overview of the possible contributions of bidentate L–X ligands for Pd catalysts in aerobic oxidation reactions.



The discovery of new ancillary ligands that promote Pd-catalyzed aerobic oxidation reactions accounts for much of the recent progress in the field. Whether the ligands are monodentate or bidentate, neutral or anionic, ligands have been shown to contribute significantly to the stability, activity and selectivity of the Pd catalysts. The examples presented above demonstrate the diverse roles of ancillary ligands and illuminate some of the important considerations that could contribute to the design of new ligands. Further advances in ligand discovery and design will undoubtedly play a key role in future progress in this field.

While ancillary ligands largely contribute to catalyst stability, several other factors relevant to catalyst decomposition and/or reoxidation are worth considering. For example, different solvents can influence the kinetics of formation and/or the stability of Pd-nanoparticles (cf. Section 3).[138,140-144] Certain polar solvents (e.g., NMP, dioxane) have been shown to promote reductive decomposition of Pd^{II}-aryl intermediates to form Pd^0.[373] Organic substrates or products, such as electron-deficient alkenes in oxidative Heck reactions, may also contribute to catalyst stability by serving as ligands for Pd^0.

Another important, but often overlooked issue relates to O_2 solubility and gas-liquid mass transfer in the reaction solvent. Aerobic oxidation of Pd^0 is a kinetically facile step, as revealed by the observation that the rates of Pd-catalyzed aerobic oxidation reactions usually exhibit a zeroth-order dependence on O_2. Nevertheless, the chemical reaction can deplete the dissolved O_2

faster than it can be replenished via gas-liquid mass transfer, and thereby contributes to background catalyst decomposition. Such mass-transfer effects have been probed for alcohol oxidation in DMSO, an organic solvent with particularly low O_2 solubility (approx. 3 mM at 1 atm O_2).[110] Use of higher pressures of O_2 provides a means to offset this limitation, but this approach must be considered within the context of safety hazards associated with mixtures of oxygen gas and organic solvents/reagents.[374] Such concerns may be partly addressed by diluting O_2 with an inert gas, such as N_2. The growing development of continuous-flow reaction technology provides a means to achieve safe implementation of high-pressure aerobic oxidation reactions on larger scale.[375-378] Such practical strategies may be leveraged in the ongoing development of new ligand-supported Pd catalyst systems for aerobic oxidation of organic molecules.

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Biographies

Dian Wang was raised in Hefei, China. He obtained a BS in chemistry from Peking University in 2011, and he obtained his PhD in organic chemistry at the University of Wisconsin-Madison in 2017. His graduate work with Professor Shannon Stahl focused on palladium-catalyzed aerobic C–H oxidations. He will conduct postdoctoral research with Professor Robert Knowles at Princeton University.

Adam B. Weinstein obtained a BS in chemical biology from UC Berkeley in 2007 and a PhD in organic chemistry from the University of Wisconsin-Madison in 2014. His graduate work was conducted in the labs of Professor Shannon Stahl, where he studied palladium catalyzed aerobic oxidation reactions. He then studied rhodium catalyzed C–H functionalization reactions as an NIH postdoctoral fellow with Professor Jonathan Ellman at Yale University. In 2017, Adam joined the process chemistry team at Gilead Sciences in Foster City, CA.

Paul B. White was raised in Dallas, TX, and received his B.S. degree in 2008 from Trinity University, San Antonio. His doctoral studies were carried out with Professor Shannon S. Stahl at the University of Wisconsin-Madison and focused on mechanisms of aerobic Pd-catalyzed C–N bond-forming reactions. After completing his Ph.D. in 2013, he joined the solid-state NMR group of Professor Mei Hong as a postdoc at Iowa State University and Massachusetts Institute of Technology, where he investigated the dynamics and structural properties of partially hydrated plant cell walls and NHN low-barrier hydrogen bonds by solid-state NMR spectroscopy. In 2015, he joined Radboud University, The Netherlands where he runs an NMR facility within the Institute of Molecules and Materials.

Shannon S. Stahl was an undergraduate at the University of Illinois at Urbana-Champaign, and a graduate student at Caltech (PhD, 1997), where he worked with with Professor John Bercaw. He was an NSF postdoctoral fellow with Professor Stephen Lippard at Massachusetts Institute of Technology from 1997–1999. He is currently a Professor of Chemistry at the University of Wisconsin-Madison, where he began his independent career in 1999. His research group specializes in catalysis, with an emphasis on aerobic oxidation reactions and oxygen chemistry related to energy conversion.

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