Similarities between the reactions of dioxygen and alkenes with palladium(0): Relevance to the use of benzoquinone and molecular oxygen as stoichiometric oxidants in palladium-catalyzed oxidation reactions

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Abstract

Bathocuproine-coordinated palladium(0) complexes, (bc)Pd^0(alkene) (bc = 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline) undergo facile oxygenation in the presence of molecular oxygen to produce the η^2-peroxopalladium(II) complex, (bc)Pd^{II}(O$_2$). The same Pd(0)-alkene complexes undergo self- and cross-exchange reactions with exogenous alkenes. Mechanistic studies highlight distinct similarities between the oxygenation and alkene-substitution reactions: kinetic studies reveal that both reactions proceed via an *associative* addition/substitution pathway, and electronic effects reveal that the transition states for both reactions feature removal of electron density from (i.e., oxidation of) the palladium(0) center. These results have important implications for the reactivity of dioxygen and benzoquinone (an electron-deficient alkene) as stoichiometric oxidants in palladium-catalyzed oxidation reactions.
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1. Introduction

Palladium(II) complexes are remarkably versatile reagents for the selective oxidation of organic molecules. Because of the high cost of palladium, significant effort has focused on the development of palladium-catalyzed reactions that use an inexpensive stoichiometric oxidant [1–3]. The most prominent Pd-catalyzed oxidation reaction is the Wacker process, which converts ethylene to acetaldehyde (Eq. (1)) with a PdCl$_2$ catalyst, a CuCl$_2$ cocatalyst and molecular oxygen as the stoichiometric oxidant [4]. Despite the success of this reaction, the aqueous reaction conditions employed in this industrial process are not amenable to the oxidation of many organic substrates. Consequently, most of the palladium-mediated oxidation reactions reported in the literature do not use O$_2$ as the terminal oxidant, but use stoichiometric palladium(II) or catalytic palladium in combination with alternate stoichiometric oxidants such as copper salts or benzoquinone. The added reagent cost, decreased atom economy, and more-complicated product isolation associated with these reactions limits large-scale applications. Alternate cocatalysts such as polyoxometallates and macrocyclic metal complexes have been identified that facilitate dioxygen-coupled catalytic turnover, but these, too, face limitations [5,6]:

$$CH_2{=}CH_2 \ + \ 1/2\ O_2 \ \xrightarrow[\text{H}_2\text{O}]{\text{[Pd]/[Cu]}} \ H_3C{-}\overset{\displaystyle O}{\underset{}{C}}{-}H \qquad (1)$$
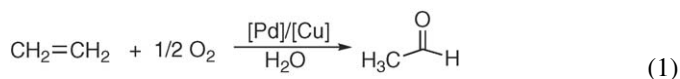
Since the mid-1990s, a number of groups have reported palladium-catalyzed oxidation reactions that proceed effectively with dioxygen in the absence of redox-active cocatalysts and other stoichiometric oxidants [7–15]. A simplified catalytic cycle for these reactions (Scheme 1) consists of the two key steps: (1) palladium(II)-mediated oxidation of the organic substrate followed by (2) regeneration of the oxidized catalyst by molecular oxygen. Collectively, these reactions are among the most diverse class of aerobic oxidation reactions known.

Despite these advances, reoxidation of palladium(0) during catalytic turnover remains a critical challenge. Inefficient reaction of dioxygen with the reduced form of the catalyst, L$_n$Pd^0 (Scheme 1), results in catalyst decomposition via aggregation of palladium(0) into bulk metal (e.g., palladium black). In a large number of empirical catalyst development studies, ben-

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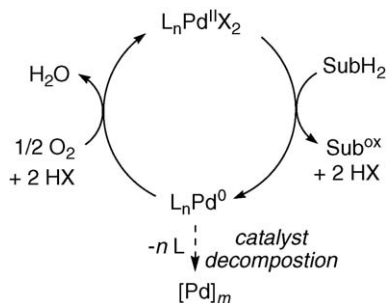
Scheme 1. Simplified catalytic cycle for palladium-catalyzed aerobic oxidation reactions.

zoquinone (BQ) is found to be a more effective stoichiometric oxidant than molecular oxygen [2,3,16,17]. In our recent study of alkene oxidative amination, however, dioxygen proved to be superior [18].


benzoquinone (BQ)
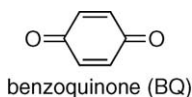
Recently, we have been investigating reactions between well-defined palladium(0) complexes and molecular oxygen [19,20]. In the course of this work, we identified distinct mechanistic similarities between the reactions of dioxygen and electron-deficient alkenes with palladium(0) complexes [21,22]. These observations belie the unique electronic structures of the two substrates: dioxygen – a ground-state triplet and alkenes – closed-shell singlets (Fig. 1). These results captured our attention because benzoquinone is an electron-deficient alkene. Hence, further characterization of these reactions may provide insights into the relative effectiveness of dioxygen versus benzoquinone as stoichiometric oxidants in palladium-catalyzed oxidation reactions. Herein, we lay the foundation for this future work by summarizing our mechanistic studies of oxygenation and alkene substitution reactions of $(bc)Pd^0(alkene)$ complexes (bc = bathocuproine: 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline).

2. Results and discussion

2.1. Oxygenation of $(bc)Pd^0(alkene)$ complexes [19]

Our initial studies of palladium(0) oxygenation focused on Pd(0) complexes coordinated by bathocuproine (bc), a phenanthroline derivative employed in catalytic reactions devel-

oped by researchers at Enichem [23,24]. (bc)Pd(dba), **1**, (dba = dibenzylideneacetone) is readily prepared from bc and Pd_2dba_3, and this complex reacts in CH_2Cl_2 with molecular oxygen at ambient pressure and temperature to produce the η^2-peroxo species, $(bc)Pd(O_2)$, **2** (Eq. (2)) [19]. The Pd–O bonds undergo rapid and quantitative protonolysis in the presence of two equivalents of acetic acid to yield $(bc)Pd(OAc)_2$ and hydrogen peroxide (Eq. (3)).

(2)

(3)
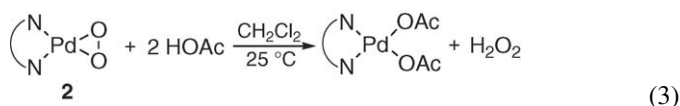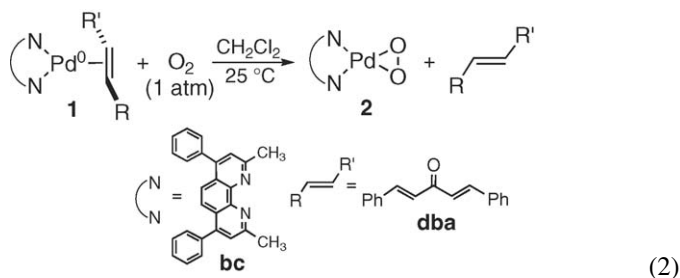
Kinetic studies reveal that the oxygenation of **1** (Eq. (2)) exhibits a first-order dependence on the oxygen pressure and a zero-order dependence on dba concentration (Fig. 2). The lack of inhibition at elevated [dba] indicates that dba dissociation does not precede the reaction of O_2 with the palladium center. The temperature dependence of the reaction was also examined (Fig. 3), analysis of the data using the Eyring equation reveals activation parameters consistent with an *associative* oxygenation mechanism ($\Delta H^{\ddagger} = 8.5(2.0)$ kcal/mol, $\Delta S^{\ddagger} = -43(7)$ eu).

Addition of *p*-X-*trans*-β-nitrostyrene derivatives (ns^X, X = OCH_3, CH_3, H, Br, CF_3) to **1** results in displacement of dba and formation of the nitrostyrene complexes, $(bc)Pd(ns^X)$ $\mathbf{3^X}$ (Eq. (4)). Access to this series of palladium(0)-alkene adducts enabled us to investigate electronic effects of palladium(0) oxygenation (Eq. (5)). Kinetic studies revealed that the more electron-rich analogs react more rapidly than those bearing electron-withdrawing substituents. A Hammett plot derived from the corresponding pseudo-first order rate constants reveals a relatively good correlation for the σ parameter with a negative slope of $\rho = -1.2$ (Fig. 4). This result is consistent with the formal description of this reaction as an oxidative addition of O_2 to the Pd(0) to form an η^2-peroxopalladium(II) product. The more electron-rich metal center with the MeO-substituted
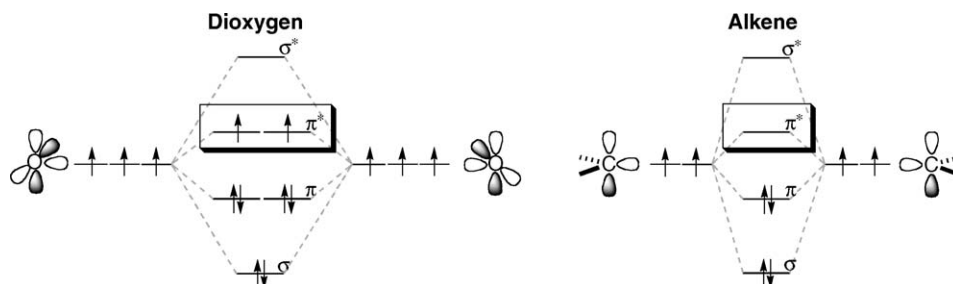

Fig. 1. Molecular-orbital representations of dioxygen and alkenes illustrating their unique electronic structures.
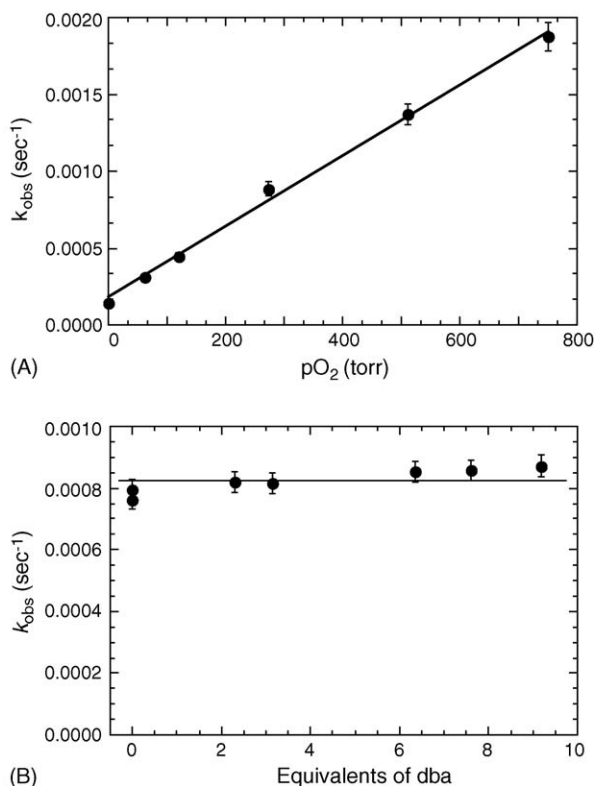
(4)

(5)

Fig. 2. Kinetic data for the oxygenation of **1** (Eq. (2)), obtained by monitoring the reaction via UV–vis spectroscopy at 425 nm. (A) Oxygen-pressure dependence. The non-zero intercept arises from a background decomposition reaction of **1**. (B) Dibenzylideneacetone concentration dependence of Eq. (2).
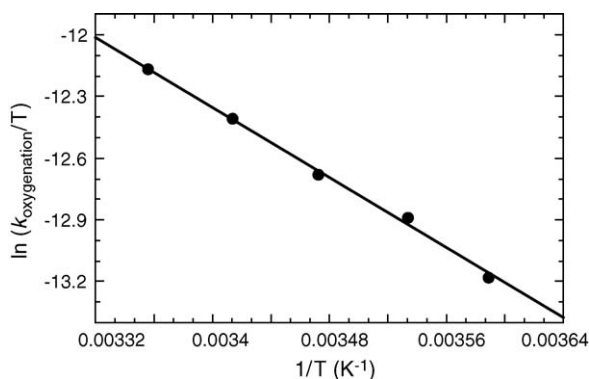

Fig. 3. Eyring plot for the oxygenation of **1** in CD_2Cl_2 under pseudo-first-order conditions from 278 to 303 K.
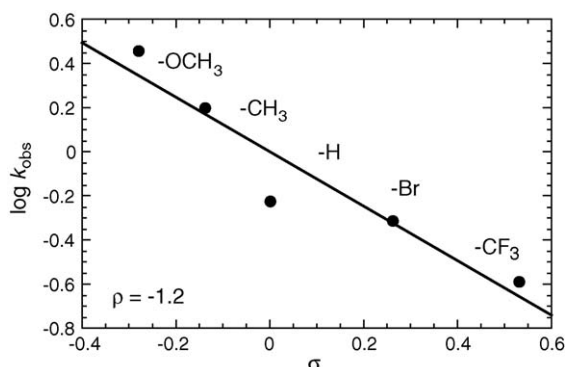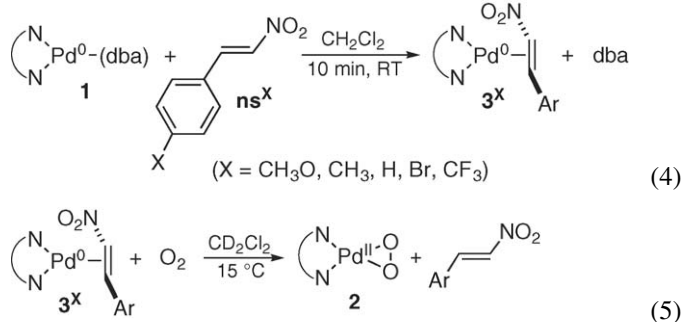

Fig. 4. Hammett plot for the oxygenation of 3^X (Eq. (5)).

alkene should be more susceptible to oxidation.

These mechanistic results for the oxygenation of (bc)Pd(alkene) complexes can be compared to two related chemical transformations: (1) the reaction of aryl halides with $L_2Pd(dba)$ complexes and (2) alkene exchange reactions of other $L_2Pd(alkene)$ complexes. The reactions of both aryl halides and dioxygen with palladium(0) formally correspond to oxidative addition reactions. Nevertheless, studies of aryl halide oxidative addition to $L_2Pd(dba)$ (L = phosphine) reveal that the reaction favors a *dissociative* mechanism [25]. The addition of exogenous dba to these reactions significantly inhibits the rate. This result contrasts the *associative* oxygenation pathway described above. Prior studies of alkene exchange (i.e., substitution) reactions at palladium(0) suggested that these reactions exhibit significant similarities to the oxygenation of **1** [26–29]. If correct, this correlation suggests that, despite the electronic structural distinctions between the substrates, dioxygen might be considered a "heteroatomic alkene" with respect to its reactivity with palladium(0). In order to probe this correlation directly, we decided to investigate alkene exchange reactions with palladium(0) complexes identical to those employed in the palladium(0) oxygenation studies.

2.2. Alkene substitution at palladium(0)-alkene complexes [21,22]

Our studies of alkene exchange at palladium(0) (Eq. (6)) began with the alkene self-exchange reaction between ns^{CF_3} and (bc)Pd(ns^{CF_3}), 3^{CF_3}, which was readily investigated via measurement of ^1H NMR spectroscopic line-broadening of the bound alkene resonances. This experiment established a first order dependence on the concentration of free ns^{CF_3} (Fig. 5). An Eyring analysis of the temperature dependence on the exchange reaction rate yielded a large, negative entropy of activation (−24(3) eu) (Fig. 6). These results indicate that alkene exchange with these complexes proceeds via an *associative* mechanism.

(6)
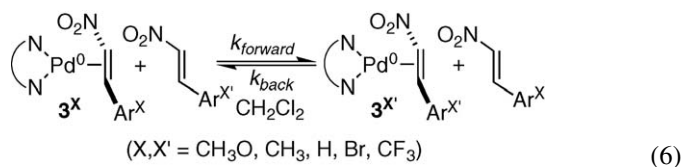
Electronic effects on the rate of alkene substitution were determined by monitoring the cross-exchange reaction of different nitrostyrene derivatives, ns^X (X = OCH_3, H, Br, CF_3) with
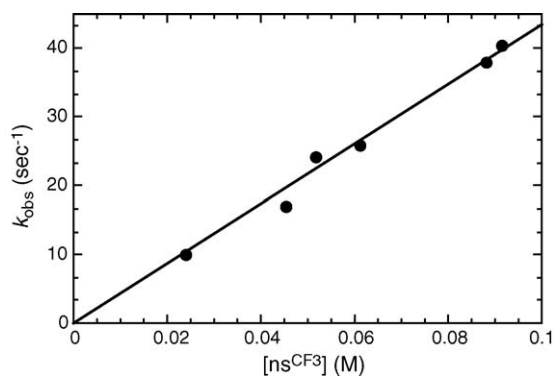
Fig. 5. First-order alkene concentration dependence on the alkene self-exchange rate between $(bc)Pd(ns^{CF_3})$ and ns^{CF_3}.
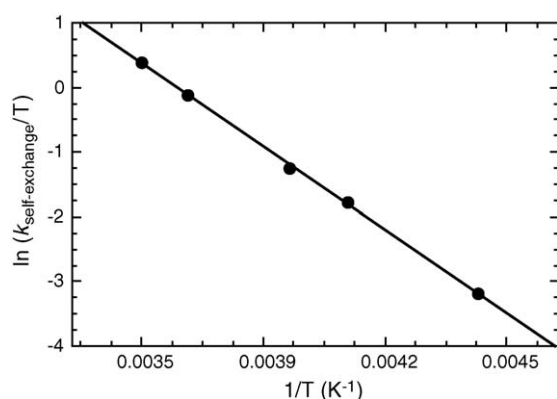

Fig. 7. Hammett plot reflecting the electronic effect on ligand substitution of ns^{CH_3} from 3^{CH_3} by ns^X.

Fig. 6. Eyring plot for the degenerate exchange of ns^{CF_3} at 3^{CF_3} from 224 to 286 K. The activation parameters obtained from this analysis are $\Delta H^{\ddagger} = 7.3(1.0)$ kcal/mol, $\Delta S^{\ddagger} = -24(3)$ eu, and $\Delta G^{\ddagger} = 14.5$ kcal/mol at 300 K.

overlap that occurs in the transition state of these reactions (Fig. 8) [21,22].

2.3. The relationship between Pd(0) oxygenation and alkene exchange at Pd(0)

In our study of alkene exchange at palladium(0) centers, we also investigated the reaction via density functional theory to assess the orbital overlap that occurs in the transition state [22]. Specifically, we probed ethylene self-exchange at $(en)Pd(C_2H_4)$ (en = ethylenediimine). As the Natural Bond Orbital plot indicates (Fig. 9A), the primary interaction between palladium(0) and the alkene involves donation from a doubly occupied d-orbital on the palladium center into the empty π^* orbital of the incoming alkene. This observation is noteworthy because it suggests that approach of the alkene results in withdrawal of electron density from (i.e., oxidation of) the reduced palladium center. The net alkene-exchange reaction (Eq. (6)) does not represent a redox reaction. The corresponding orbital picture for the oxygenation of palladium(0) is shown in Fig. 9B. In this case, the π^* orbital of the incoming dioxygen molecule possesses a single unpaired electron. The implications of this orbital occupancy in the case of dioxygen have not yet been fully elucidated. The data presented above, which reveal significant similarities between alkene exchange and palladium(0) oxygenation, imply that the effects might be quite subtle.

$(bc)Pd(ns^{CH_3})$ by UV–vis spectroscopy. The Hammett plot in this case reveals a *positive* slope, reflecting the fact that electron-deficient alkenes react more rapidly than electron-rich analogs with the palladium(0) (Fig. 7). This trend contrasts the electronic dependence of traditional associative ligand substitution reactions, which proceed more rapidly with more electron-rich (i.e., nucleophilic) incoming ligands [30]. We have designated this unique class of reactions "inverse-electron-demand" ligand substitution reactions because of the inverted HOMO–LUMO
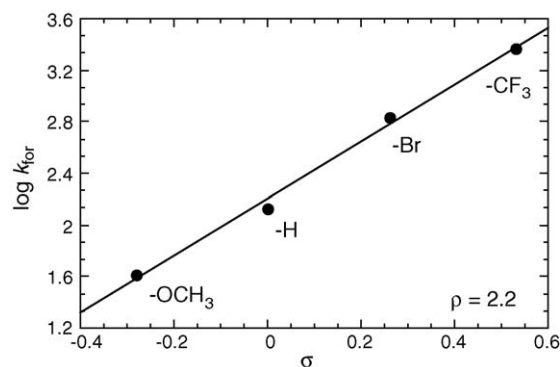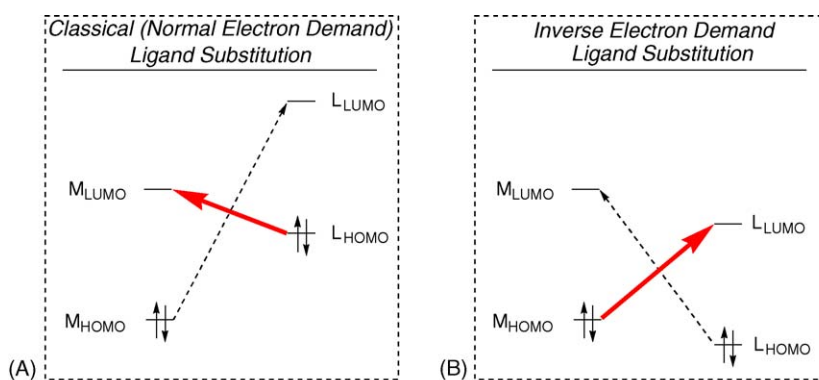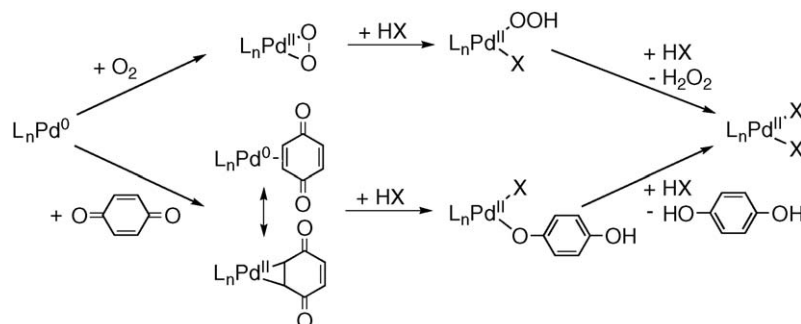

Fig. 8. Qualitative molecular orbital representations of normal- and inverse-electron demand associative ligand substitution reactions.

Scheme 2. Mechanistic relationship between the oxidation of palladium(0) by molecular oxygen and benzoquinone.
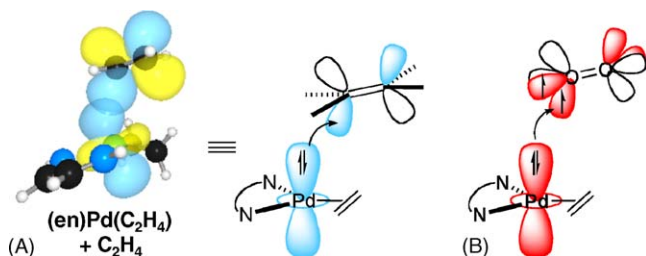

Fig. 9. (A) DFT-derived transition state structure (Natural Bond Orbital plot) for associative ethylene substitution at a ethylenediimine (en)-coordinated palladium(0)-ethylene complex. This structure, illustrating the inverse-electron-demand character of the ligand substitution reaction, is also depicted in the adjacent line drawing. (B) Orbital picture for palladium(0) oxygenation if the reaction proceeds by a pathway analogous to alkene substitution.

3. Conclusion and analysis

The studies outlined herein highlight the mechanistic resemblance between reactions of electron-deficient alkenes and dioxygen with palladium(0). Specifically, both substrates react with (bc)Pd(alkene) complexes, **1** and **3**^{X}, via an *associative* mechanism. This feature was anticipated for alkene substitution, but the associative oxidative addition of O_2 contrasts a dissociative oxidative addition pathway for aryl halide reactions with Pd(0). Secondly, electronic effects evident in the alkene exchange and oxygenation reactions reveal that both substrates react via an *oxidative* pathway in which the substrate extracts electron density from the d^{10} Pd(0) center in the transition state. This observation was expected for the oxygenation reaction, which involves the net oxidation of Pd(0) to Pd(II); however, alkene exchange is formally redox-neutral, and in virtually all other characterized examples of associative ligand substitution, the metal center participates as an electrophile or recipient of electron density.

We noted above the critical importance of efficient reactivity between palladium(0) and the oxidant during catalytic turnover (Scheme 1). These results outlined herein provide an important starting point for our ongoing studies designed to elucidate the mechanistic relationship between dioxygen and benzoquinone as oxidants in palladium-catalyzed oxidation reactions. As indicated in Scheme 2, the respective reactions of these reagents with palladium(0) represent only the first of several mechanistically related steps involved in regeneration of the palladium(II) species during catalytic turnover.

Acknowledgement

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